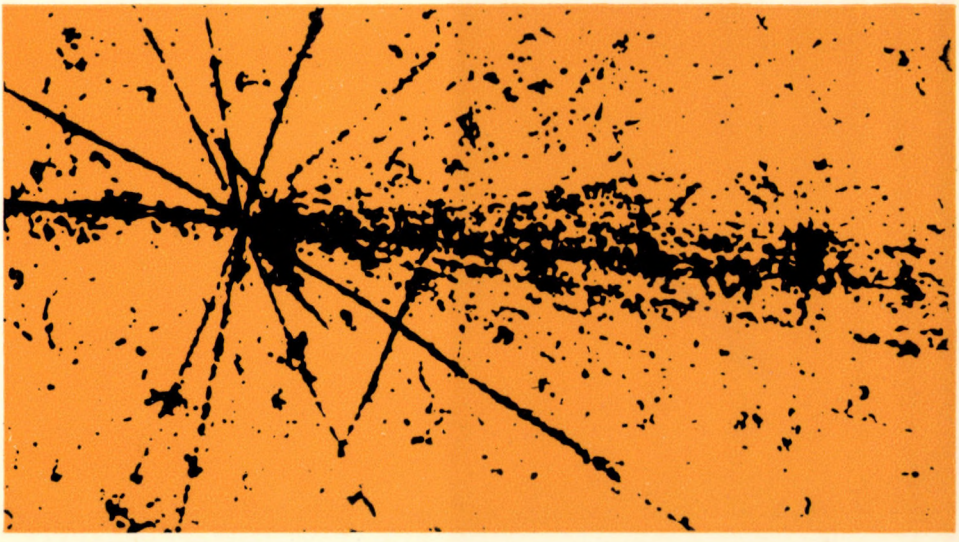
RADIOMETRISCHE TITRATIONEN

T. BRAUN UND J. TÖLGYESSY



T. BRAUN–J. TÖLGYESSY

RADIOMETRISCHE TITRATIONEN

Die in vielen Zeitschriften verstreut erschienenen und daher schwierig zugänglichen Daten über radiometrische Titrationen sind in diesem Buche monographieartig zusammengefaßt. Die Verfasser geben darüber hinaus auch eine systematische Übersicht der charakteristischen Merkmale dieses Gebietes der radioanalytischen Chemie sowie ihrer jüngsten Entwicklungen. Die Vor- und Nachteile der radiometrischen Endpunktsbestimmung und die Möglichkeiten ihrer Anwendung in Verbindung mit den in der Titrimetrie verwendeten verschiedenen Reaktionstypen werden besprochen. Im Rahmen eines tabellarischen Anhanges wurden in der vorliegenden deutschen Ausgabe auch die seit der englisch erschienenen Fassung veröffentlichten neuesten Ergebnisse verarbeitet.

AKADÉMIAI KIADÓ

VERLAG DER UNGARISCHEN AKADEMIE DER WISSENSCHAFTEN

BUDAPEST

Braun – Tölgyessy

Radiometrische Titrationen

Radiometrische Titrationen

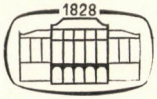
Dr. Tibor Braun

Institut für Anorganische und Analytische Chemie
der Eötvös Loránd Universität
Budapest, Ungarn

und

Doz. Dr.-Ing. habil. Juraj Tölgyessy

Institut für Radiochemie und Strahlungschemie
der Slowakischen Technischen Hochschule
Bratislava, Tschechoslowakei



Akadémiai Kiadó, Budapest 1968

Titel der Originalausgabe:
Radiometric Titration
Akadémiai Kiadó, Budapest

Aus dem Englischen übertragen

von

Tibor Wein

© Akadémiai Kiadó, Budapest 1968

Gemeinschaftsausgabe des Akadémiai Kiadó, Budapest und
des S. Hirzel Verlags, Stuttgart

Printed in Hungary

Inhalt

Symbole und Abkürzungen VII

1. Einführung 1

1.1. Literatur 1

2. Radiometrische Endpunktanzeige 3

2.1. Problem 3
2.2. Historischer Rückblick 5
2.3. Literatur 6

3. Radiometrische Fällungstitrationen 7

3.1. Einführung 7
3.2. Theoretische Grundlagen der Methode 11
3.3. Bestimmung des Endpunktes 15
3.4. Methoden der Abtrennung des Niederschlages und Technik der Titration 21
3.4.1. Filtration 21
3.4.1.1. Diskontinuierliche Titration 21
3.4.1.2. Kontinuierliche, automatische Titration 25
3.4.2. Zentrifugen-Methode 29
3.4.3. Flotationsmethode 30
3.5. Bestimmung mehrerer Komponenten nebeneinander 32
3.5.1. Bestimmung von zwei Komponenten nebeneinander 32
3.5.2. Bestimmung vondrei Komponenten nebeneinan der 37
3.6. Spezielle radiometrische Titrationen 37
3.6.1. Titrationen in nichtwäßrigen Medien 38
3.6.2. Auf Absorption und Rückstreuung von e^--Strahlen beruhende Fällungstitrationen 40
3.6.2.1. Auf der Rückstreuung der e^--Strahlung beruhende Titrationen 40
3.6.2.2. Auf der Absorption der e^--Strahlung beruhende Titrationen 44
3.6.3. Radiocoulometrische Titrationen 45
3.7. Verschiedene Anwendungsmöglichkeiten der Fällungstitrationen . . . 48
3.7.1. Bestimmung der Zusammensetzung von Verbindungen 48
3.7.2. Untersuchung der Mitfällung 50
3.7.3. Bestimmung der Löslichkeit und des Löslichkeitsproduktes . . 52
3.7.4. Bestimmung der spezifischen Aktivität radioaktiver Präparate 54
3.8. Praktische Anwendungen 56
3.8.1. Radiometrische Fällungstitration 56
3.8.1.1. Anorganische Stoffe 56
3.8.1.2. Organische Stoffe 66
3.9. Literatur 69

4. Radiometrische Komplexbildungstitrationen 73

4.1. Einführung 73
4.2. Trennung durch Lösungsmittelextraktion 73
4.2.1. Prinzip der Methode 73
4.2.2. Direkt-Titrationen 74
4.2.2.1. Titration einer Komponente 80
4.2.2.2. Titration von zwei Komponenten 83
4.2.2.3. Titration von drei Komponenten 83
4.2.3. Indirekte Titrationen 84
4.2.4. Theoretische Grundlagen 85
4.2.5. Einrichtungen und Technik 92
4.2.5.1. Halbautomatischer Titrierapparat nach Spitzy 93
4.2.5.2. Halbautomatischer Titrierapparat von Duncan und Thomas 95
4.2.5.3. Halbautomatischer Titrierapparat von Braun und Kőrös 96
4.3. Endpunktbestimmung unter Anwendung fester Indikatoren 96
4.3.1. Prinzip der Methode 96
4.3.2. Typen der Titrationen: direkte, indirekte und Rücktitration . . 99
4.3.3. Anwendung fester radioaktiver Kryptonate 102
4.3.4. Titrierapparate und Technik der Titrationen 103
4.4. Endpunktbestimmung durch Trennung mit Ionenaustauschern 107
4.5. Endpunktbestimmung durch papierchromatographische Trennung . . 109
4.6. Endpunktbestimmung durch fokussierenden Ionenaustausch 112
4.6.1. Typen der Titration 113
4.6.2. Apparat und Methode der Titration 115
4.7. Radiometrische Komplexbildungstitrationen 116
4.8. Literatur 121

5. Radiometrische Redox-Titrationen 123

5.1. Problem der Endpunktbestimmung 123
5.2. Endpunktbestimmung mit festen Indikatoren 123
5.3. Endpunktbestimmung durch Lösungsmittelextraktion 124
5.4. Endpunktbestimmung mit Amalgamen 124
5.5. Literatur 126

6. Addendum zur deutschen Ausgabe 127

6.1. Literatur 134
Appendix 136
Sachregister 137
Namenregister 142

Symbole und Abkürzungen

1. a = Massenabsorptionskoeffizient
2. A = Konstante
3. a_l = spezifische Radioaktivität
4. a_s = spezifische Radioaktivität einer festen Phase
5. B = "Untergrund"-Aktivität einer Lösung
6. ϑ = theoretischer Titrationsfehler
7. E_{max} = Energiemaximum der e^--Strahlung
8. ε = Dielektrizitätskonstante des Mediums
9. γ = Konzentration einer Lösung (N)
10. $\overline{HL}$ = Komponente HL in einer organischen Phase
11. Ipm = Impulse pro Minute
12. k = Proportionalitätskonstante oder Korrektionsfaktor
13. K = Dissoziationskonstante oder Stabilitätskonstante
14. K_a = Säure-Dissoziationskonstante
15. L_{AB} = Löslichkeitsprodukt des schwerlöslichen Niederschlages AB
16. m = zugegebene bekannte Menge eines Trägers
17. m_x = die zu bestimmende Menge eines Trägers
18. M = Molarität einer Lösung
19. μ = linearer Absorptionskoeffizient
20. μg = Mikrogramm (10^{-6}g)
21. N = Normalität einer Lösung
22. P_{HL} = Verteilungskoeffizient der Komponente HL zwischen zwei unmischbaren Lösungen
23. ϱ = Dichte des absorbierenden Mediums
24. V = Volumen der Lösung
25. v_{ex} = zur Erreichung des Endpunktes benötigtes Volumen der Maßlösung
26. v_E = theoretischer Lösungsverbrauch
27. $V_{äqu}$ = zur Erreichung des Äquivalenzpunktes benötigtes Volumen der Maßlösung

137 Quaternary bases 367
138 Tetraphenylborates of bases 368
139 Bases in the presence of either 'acidic' —SH or =S groups 369
140 Sulphates, ethanesulphonates, *p*-toluenesulphonates, phosphates and nitrates of bases 370

25. DETERMINATION OF MIXTURES OF NITROGENOUS BASES OR MIXTURES OF BASE HYDROCHLORIDES 374

141 Amine mixtures in differentiating solvents 374
142 Salicylaldehyde, method I 377
143 Salicylaldehyde, method II 378
144 Acetylacetone method 378
145 Phthalic anhydride method 380
146 Acetic anhydride method 380
147 Photometric titration of primary amines in the presence of secondary and tertiary amines 382
148 Determination of amine mixtures by the combined method 383
149 Distillation methods 384
150 Determination of hydrochlorides of tertiary amines in the presence of hydrochlorides of acetylatable amines 386

26. DETERMINATION OF CARBONYL GROUPS 388

151 Identification of aldehydes and ketones 388
152 Determination of carbonyl groups 389

27. DETERMINATION OF MULTIPLE BONDS: APPLICATION OF MERCURY(II) ACETATE REAGENT. APPLICATION OF BROMINE IN ACETIC ACID OR 0·1 N HYDROGEN BROMIDE IN ACETIC ACID 395

153 Internal double bond in terminal or *cis*-positions 395
154 Acyl cyclopropylamines with mercury(II) acetate in methanol 398
155 Double bonds with 0·1 N bromine solution in acetic acid 398
156 Oxiran oxygen (α-epoxide group) 400
157 Acetylenic hydrogen 401

28. DETERMINATION OF ELEMENTARY SULPHUR AND ORGANIC COMPOUNDS CONTAINING SULPHUR. APPLICATION OF SILVER NITRATE IN PYRIDINE REAGENT 403

158 Elementary sulphur in non-aqueous media 403
159 Organic sulphoxides 404
160 Alkane thiols (mercaptans). Applications of silver nitrate in pyridine 404
161 Titration with perchloric acid of alkyl xanthogenates, S-alkyl- and S-benzyl-thiuronium derivatives and dialkyl-*p*-bromophenacyl sulphonium compounds 406

29. REDOX TITRATION IN NON-AQUEOUS MEDIA 409

162 Determination of ascorbic acid in non-aqueous media 410
163 Semimicro determination of phenylhydrazine, hydroxylamine and compounds containing carbonyl group with copper(II) acetate 411
164 Determination of alkyl xanthogenates (xanthates) with cerium(IV) ammonium nitrate 412
165 Determination of rubber in vegetable matter 413

30. TITRATIONS WITH COMPLEX FORMATION IN NON-AQUEOUS MEDIA 415

166 Alkylaluminium compounds 415
167 Diels–Alder-active dienes and aromatic hydrocarbons 416

1. Einführung

Über die Anwendung radioaktiver Isotope in der analytischen Chemie berichtet heute schon eine reichhaltige Literatur. Außer zahlreichen Originalmitteilungen wurden über dieses Thema im vergangenen Jahrzehnt auch mehrere Monographien und zusammenfassende Arbeiten veröffentlicht [2, 3, 4, 7, 10, 12, 13, 14, 15, 16, 17, 18], die sich jedoch nur auf beschränktem Raum mit den radiometrischen Titrationen beschäftigen. Zwar wird diese Methode der Endpunktanzeige in den zitierten Publikationen in großen Zügen ausnahmslos beschrieben, doch hat man sich dabei bisher immer damit begnügt, über frühere Ergebnisse kurz und unvollständig zu berichten.

Auch in den allgemein anerkannten Handbüchern werden gewöhnlich nur die in den Jahren 1941 und 1950 erschienenen grundlegenden Publikationen von LANGER zitiert [8, 9], ohne auf weitere, später veröffentlichte Ergebnisse einzugehen [5, 6].

In der vorliegenden Monographie über die Endpunktanzeige mit Hilfe radiometrischer Verfahren lag es den Autoren hauptsächlich daran, dem interessierten Fachmann eine einheitliche und ausführliche Zusammenstellung der in der Literatur an sehr vielen Stellen verstreut veröffentlichten zahlreichen Informationen in die Hand zu geben.

Mit der Zusammentragung und Auswertung der aus der Literatur verfügbaren Daten soll ein Beitrag zur Kenntnis und weiteren Verbreitung der radiometrischen Titrationen geleistet werden nachdem bereits die Arbeiten [1, 17] einen ersten Überblick gegeben und auf die Bedeutung der radiometrischen Indikationsmethoden hingewiesen haben. Im Anschluß an die einheitliche und ausführliche Beschreibung der bisherigen Erkenntnisse wird versucht, die charakteristischen Wesenszüge der radiometrischen Titrationen hervorzuheben und gleichzeitig auch auf die wahrscheinlichsten Entwicklungsrichtungen aufmerksam zu machen.

1.1 Literatur

[1] BRAUN, T. und TÖLGYESSY, J.: Talanta, *11*, 1277 (1964)

[2] BRODA, E.: Radioactive Isotopes in Biochemistry, Elsevier, New York (1960)

[3] BRODA, E. und SCHÖNFELD, T.: in Handbuch der mikrochemischen Methoden, *II*, Springer Verlag, Wien (1955)

[4] BRODA, E. und SCHÖNFELD, T.: Chim. e Ind. (Milano), *37*, 548 (1955)

[5] CHARLOT, G.: Les méthodes de la chimie analytique, Masson et Cie, Paris (1961)

31. DETERMINATION OF THE ALKOXYL GROUP, CARBAMIC ACID ESTERS, SUBSTITUTED PHOSPHINES, ORGANOSILICON COMPOUNDS 419

168 The alkoxyl group 419
169 Carbamic acid esters 421
170 Substituted phosphines 422
171 Organosilicon compounds 422

References 425

Author index 445

Subject index 455

[6] HAISSINSKY, M.: La chimie nucléaire et ses applications, Masson et Cie, Paris (1957)
[7] LAMBIE, D. A.: Techniques for the Use of Radioisotopes in Analysis, E. and F. N. Spon Ltd., London (1964)
[8] LANGER, A.: J. Phys. Chem., *45*, 639 (1941)
[9] LANGER, A.: Analyt. Chem., *22*, 1288 (1950).
[10] LEDDICOTTE, G. W.: Analyt. Chem., *34*, 143R (1962)
[11] LEDDICOTTE, G. W. und REYNOLDS, S. A.: Analyt. Chem., *36*, 419R (1964)
[12] MEINKE, W. W.: Analyt. Chem., *28*, 736 (1956)
[13] MEINKE, W. W.: Analyt. Chem., *30*, 686 (1958)
[14] MEINKE, W. W.: Analyt. Chem., *32*, 104R (1960)
[15] MIKHEEWA, L. und MIKHEEW, N. B.: Radioaktive Isotope in der analytischen Chemie, Akademie-Verlag, Berlin (1962)
[16] MOSES, A. F.: Nuclear Techniques in Analytical Chemistry, Pergamon Press, Oxford (1964)
[17] REYNOLDS, S. A. und LEDDICOTTE, G. W.: Nucleonics, *21*, Nr. 8, 128 (1963)
[18] SCHÖNFELD, T. und BRODA, E.: Atompraxis, *3*, 294 (1957)

Preface to Hungarian Edition

One of the oldest and probably most widespread analytical methods is volumetric analysis. It is well known that determinations in non-aqueous media can be regarded as a rebirth of classical titrimetry. The modern method, however, dates back as far as the experiments of Folin and Flanders who in 1912 titrated water-insoluble carboxylic acids with sodium methoxide in chloroform, benzene or ethanol and demonstrated that the determination was precise and the colour change of the indicator sharp.

On the other hand, later studies on the use of non-aqueous techniques made it necessary time and again to evaluate the theoretical determinations obtained. The aim of this small book is to draw attention to the very many possibilities provided for research workers and for other analytical chemists by non-aqueous titrimetry. While the properties of the only solvent in the domain of aqueous determinations — i.e. water — set a limit to the extension of this field, the range of solvents employable in non-aqueous titrations — benzene, acetone, acetic acid, pyridine etc. — make possible many which formerly were not practicable.

I have not attempted to attain completeness either in the theoretical treatment or in the literature cited but I hope that by careful selection of the data, useful information can be obtained from the growing literature on non-aqueous titrations and that, at the same time, the chemist working in industrial laboratories on routine analysis will be assisted.

Budapest, August, 1959 I. Gy.

2. Radiometrische Endpunktanzeige

2.1. Problem

Bei den radiometrischen Titrationen ist die Radioaktivität jene »Eigenschaft« der Lösung, deren Änderungen zur Feststellung des Endpunktes verfolgt werden. Unter gleichbleibenden Versuchsbedingungen ist die Größe der Radioaktivität der Konzentration der markierten Komponente proportional. Während der Titrationsreaktion ändert sich die Konzentration der miteinander reagierenden Komponenten und dies zieht eine proportionale Änderung ihrer Radioaktivität nach sich. Folgerichtig ist es möglich, den Endpunkt der Reaktion auf Grund der Änderungen der Radioaktivität festzustellen. Oft wird der Endpunkt der Reaktion durch graphische Darstellung der Änderungen der Radioaktivität als Funktion der zugegebenen Menge der Maßlösung ermittelt. Da zwischen der Radioaktivität und der Konzentration der markierten Komponente ein linearer Zusammenhang besteht, ist die Titrationskurve gleichfalls linear. Der Schnittpunkt der beiden linearen Abschnitte der Titrationskurve liefert den Endpunkt.

Vergleicht man die radiometrische Endpunktbestimmung mit anderen, bisher angewandten Indikationsmethoden, so wird eines der wesentlichsten Merkmale der radiometrischen Methode sofort klar: Es ist allein die Radioaktivität der gewählten Komponente, die gemessen wird, alle übrigen Komponenten bleiben in dieser Hinsicht völlig unberücksichtigt. Dies ist notwendig, zumal sich ja die Gesamt-Aktivität des Systems während der Titration nicht ändert. Hieraus folgt, daß der Endpunkt nur dann festgestellt werden kann, wenn die Möglichkeit besteht, die Aktivität der betreffenden Komponente getrennt zu messen. Die radiometrischen Titrationen sind also *Trennungs-Titrationen*. Den markierten Reaktionspartner während des Titrationsprozesses auf irgendeine Weise zu isolieren, um seine Radioaktivität getrennt messen zu können, ist eine der Hauptaufgaben, die für diese Art der Endpunktanzeige gelöst werden muß. In der Regel wird dieses Problem mit Hilfe des sog. »Phasenüberganges« überwunden, bei dem die markierte Komponente während der Titration allmählich quantitativ in eine andere Phase übergeht (Fällung oder Auflösung; Extraktion mit einem nicht mischbaren Lösungsmittel). Verfolgt wird dabei die Radioaktivität einer der Phasen.

Bei Fällungsreaktionen ist der Phasenübergang von vornherein gegeben. Hierin liegt auch die Erklärung dafür, warum die radiometrische Endpunktbestimmung meistens in Verbindung mit diesem Titrationstyp angewandt wurde [2]. Bei allen übrigen Typen von Titrationsreaktionen (Komplexbildung, Redox-Reaktionen) beinhaltet die Methode als solche die Isolie-

rung nicht. Für sie muß eine zusätzliche Operation sorgen, wie z. B. Lösungsmittelextraktion, Ionenaustausch usw.

Die Notwendigkeit der Trennung ist ein Nachteil der radiometrischen Titrationen gegenüber anderen Indikationsverfahren. Die Titrationen werden etwas langwierig und manchmal unbequem, da Trennungen und Aktivitätsmessungen wiederholt durchgeführt werden müssen.

Eine kontinuierliche Titration ist nur dann möglich, wenn auch die Trennung in einer kontinuierlichen Operation durchgeführt werden kann. Hierzu bietet sich in der Praxis nur selten Gelegenheit. Es sei bemerkt, daß der Einsatz kontinuierlich arbeitender Zentrifugen die Durchführung der auf Niederschlagsbildung beruhenden radiometrischen Titrationen wahrscheinlich erleichtern würde; jedoch ist uns bisher nichts über Versuche dieser Art bekannt geworden. Offensichtlich ist dieses Problem eng mit der Frage einer möglichen Automatisierung des Titrationsprozesses verbunden.

Im Vergleich zu konventionellen Methoden der Endpunktanzeige liegt der Vorzug der radiometrischen Titrationen hauptsächlich in ihrer Empfindlichkeit. Dies folgt aus der Natur der radioaktiven Markierung. Bei Anwendung genügend hoher spezifischer Aktivitäten können auch außergewöhnlich geringe Stoffmengen bestimmt werden.

Der Wert der durch die Titration verfolgten Eigenschaft (d. h. der Radioaktivität) läßt sich durch Zugabe von trägerfreien Isotopen (d. h. durch Änderung der spezifischen Aktivität) noch vor der Titration nach Belieben einstellen.

Es bedarf wohl keiner besonderen Erklärung, daß die Vorteile dieser Möglichkeit besonders im Bereich der niedrigen Konzentrationen groß sind. Bei anderen instrumentellen Methoden der Endpunktanzeige, wie z. B. die photometrischen oder konduktometrischen Verfahren, bei denen die gemessene Eigenschaft eine lineare Funktion der Konzentration ist, werden während der Titration sowohl die gemessene Eigenschaft als auch deren Änderungen umso weniger deutlich, je weiter man in den Bereich niedriger Konzentrationen eindringt. Ebenso wird es auch immer schwerer, die Stelle des Endpunktes auf der Titrationskurve genau zu bestimmen. Im Gegensatz dazu ist es bei den radiometrischen Titrationen möglich, die Radioaktivität und ihre Änderung im gewünschten Maße einzustellen. Bei den radiometrischen Fällungstitrationen, mit denen bisher die meisten Erfolge erzielt werden konnten, liegen die zu bestimmenden Mengen in der Größenordnung von ca. 1 mg und der relative Fehler der Methoden (Variationskoeffizient) beträgt im allgemeinen ± 3–4%. Der relative Fehler der zur Bestimmung von Stoffmengen in der Größenordnung von einigen μg mit Dithizon und Phasentrennung durch Lösungsmittelextraktion durchgeführten Titrationen, bei denen in der Regel höhere spezifische Aktivitäten verwendet werden, beträgt weniger als $\pm 1\%$.

Die in der Literatur näher beschriebenen Apparate mit Geiger–Müller- oder Szintillationszählern können für die radiometrischen Titrationen ohne

Preface to English Edition

The five or six years which have passed since the issue of the first Hungarian edition have proved repeatedly that determinations in non-aqueous media are nowadays a valuable aid in the everyday work of research and quality-control laboratories in organic chemistry and in the pharmaceutical industry. The new English edition is considerably enlarged compared with the first Hungarian edition both in its theoretical content and in the procedures described. It contains thirty-one chapters instead of twenty, and, to meet the wishes and comply with the advice of colleagues working in the field of practical analysis, many more illustrations are included than in the original edition. I hope that these will provide ample practical assistance to those interested in this field of chemistry.

From the theoretical aspect, especially in the case of acid–base theories, I have retained the original format founded on historical development. However, I must emphasize that the evolution of acid–base theories cannot be considered to be completed and progress may still have some surprises in store. That, however, will only intensify and enrich the theory as well as the practice of non-aqueous titrimetry.

Budapest, September, 1966 I. Gy.

jede Modifizierung angewandt werden. Im allgemeinen lassen sich die für die Titrationen und Messungen vorzugsweise verwendeten Einrichtungen in den Laboratorien selbst herstellen. Die von den verschiedenen Autoren konstruierten und verwendeten Einrichtungen sollen später eingehend beschrieben werden. Soweit bekannt, sind bisher keine, speziell den Zwecken der radiometrischen Titrationen dienende Instrumente auf den Markt gebracht worden. Was die Messung der Radioaktivität anbelangt, steht der vollen Automatisierung der Titrationen nichts im Wege. Die Schwierigkeiten liegen – wie bereits erwähnt wurde – in der Automatisierung der Trennungsprozesse. Darauf ist es zurückzuführen, daß in dieser Hinsicht bisher keine befriedigenden Ergebnisse erzielt werden konnten. Trotzdem dürfen jene automatischen und halbautomatischen Einrichtungen, über die bisher berichtet wurde, und die später noch besprochen werden sollen, als erste und vielversprechende Versuche auf diesem Gebiet betrachtet werden.

Man kann die radiometrischen Titrationen in heterogenen, gefärbten, trüben, korrosiven oder nichtwäßrigen Systemen durchführen, zumal ja diese Umstände auf die Radioaktivität keinen Einfluß nehmen. Das gleiche gilt auch für die Temperatur.

2.2. Historischer Rückblick

Als Erfinder der radiometrischen Endpunktanzeige gilt LANGER; sie wird erstmalig in seiner im Jahre 1940 patentierten Erfindung erwähnt [5]. In dieser Patentschrift wird das Prinzip der radiometrischen Fällungstitrationen und ein Instrument beschrieben, das sich zur Trennung der Filtration bedient. Ausführlichere Beschreibungen der Methode veröffentlichte LANGER in zwei späteren Publikationen, die 1941 [6] bzw. 1950 [7] erschienen sind. Die erste beschrieb die auf der Fällung von ^{32}P-markiertem Phosphat beruhenden radiometrischen Titrationen, während die zweite über die Einführung des ^{105}Ag als Indikator in die Radio-Argentometrie berichtete. Eine weitere wichtige Entwicklung war die Einführung der Phasentrennung durch Zentrifugieren [8].

Die auf Komplexbildung beruhenden Titrationen, in Verbindung mit Lösungsmittelextraktion, wurden — fast gleichzeitig — von KORENMAN und Mitarb. [9] sowie von DUNCAN und THOMAS [4] empfohlen. Die genannten Autoren schlugen auch die Verwendung von Nichtisotop-Indikatoren zur Markierung vor. Einen weiteren Fortschritt bedeutete die Einführung der festen Indikatoren, mit deren Hilfe die Radio-Komplexometrie entstand [1].

Die ersten halbautomatischen radiometrischen Titrationseinrichtungen wurden 1958 von DUNCAN und THOMAS [3] und 1960 von SPITZY [10] konstruiert. Ein Jahr später beschrieben TÖLGYESSY und ŠAJTER [12] eine vollautomatische Einrichtung für die Durchführung von radiometrischen Fällungstitrationen.

Die Prinzipien und Techniken der radiometrischen Titrationen haben 1964 BRAUN und TÖLGYESSY [2] in einer zusammenfassenden Übersicht beschrieben. Die Monographie von TÖLGYESSY [11] ist ebenfalls diesem Thema gewidmet. Beachtliche Resultate auf dem Gebiete der Theorie und Praxis der radiometrischen Titrationen erzielten in der Sowjetunion ALIMARIN sowie KORENMAN und ihre Schulen, in Australien DUNCAN und THOMAS und in Österreich SPITZY.

2.3. Literatur

[1] BRAUN, T., MAXIM, I. und GALATEANU, I.: Nature, *182*, 936 (1958)
[2] BRAUN, T. und TÖLGYESSY, J.: Talanta, *11*, 1277 (1964)
[3] DUNCAN, J. F. und THOMAS, F. G.: J. Inorg. Nucl. Chem., *4*, 376 (1957)
[4] DUNCAN, J. F. und THOMAS, F. G.: Proc. Australian Atomic Energy Symp. Radioisotopes, Physical Sciences, 617 (1958)
[5] LANGER, A.: Radiometric Titration Method, U. S. Pat. 2, 367, 949 23 Nov., 1940
[6] LANGER, A.: J. Phys. Chem., *45*, 639 (1941)
[7] LANGER, A.: Analyt. Chem., *22*, 1288 (1950)
[8] KORENMAN, I. M., SEJANOWA, F. R., DEMINA, E. A. und SAPOSCHNIKOWA, M. I.: Zavod. Lab. *22*, 1143 (1956)
[9] KORENMAN, I. M., SEJANOWA, F. R., MESINA, H. M. und OSTASEWA, M. I.: Schur. Analit. Khim., *12*, 48 (1957)
[10] SPITZY, H.: Mikrochim. Acta, 789 (1960)
[11] TÖLGYESSY, J.: Radiometrické titrácie (Radiometrische Titrationen), Vydavatel'stvo SAV, Bratislava 1966
[12] TÖLGYESSY, J. und ŠAJTER, V.: Acta Chim. Hung., *26*, 179 (1961)

Chapter 1

Development of Acid–Base Concepts

Though 'acid' and 'base' are fundamental and long-standing concepts in chemistry they have never been unambiguously defined. Similarly, opinions concerning the definition of the 'strength' of acids and bases differ. In order to make titrations in non-aqueous media easier to understand it is necessary to outline briefly the evolution [325] of theories of acids and bases.

For a long time the importance of defining acids and bases has been obvious; 'tenir la définition des acides, c'est tenir la clef de la Chymie' (Guyton de Morveau, 1786). In the course of their development, theories on acids and bases have proved, repeatedly, to be inadequate for the interpretation of reactions taking place when titrations are made in non-aqueous media, especially as recent theoretical studies have opened new vistas for the application of non-aqueous titrations. It is not our concern to furnish an elaborate analysis of the various acid-base theories but we shall lay particular stress on the differences between the better-known theories.

1. Early Scientific Views on Acids

The first theory dates back to the seventeenth century. According to it, salts are derived from the interaction of acids and bases, which thereby 'disappear'. Boyle (1627–1691) pointed out the chemical contrast between acid and base, the experimental test of which is the reversible change in colour of tincture of violets when treated with acid and base; at that time acids were imagined as particles having needle-like points, which enabled them to penetrate into the pores of metals. These are essentially materialistic ideas, a premature formulation of the later donor-acceptor theories.

Lavoisier's oxygen theory (*Traité élémentaire de chimie*, 1789) was, until the commencement of the nineteenth century, widely held; according to it non-metallic elements are converted by burning to acids, i.e. to oxides: CO_2, SiO_2. For the clarification of the properties of acids Davy's experiments of 1816 were of great significance, when he proved chlorine to be an element and not a compound of oxygen;

3. Radiometrische Fällungstitrationen

3.1. Einführung

Bei den radiometrischen Fällungstitrationen wird der radioaktive Indikator während des Titriervorganges gefällt. Der Endpunkt kann auf Grund der Änderung der Radioaktivität in einer der Phasen festgestellt werden. In allen bisher beschriebenen Fällen war dies die flüssige Phase. Bei dieser Titrationsart wird einer der Fällungsbestandteile durch einen chemisch gleichartigen radioaktiven Zusatz markiert. Es kann dies die zu bestimmende Komponente oder auch derjenige Bestandteil der Titrierlösung sein, der die Fällung erzeugt. Eine dritte Möglichkeit eröffnet die gleichzeitige Markierung beider Komponenten. Man spricht allgemein von *isotoper Markierung*.

Die Wahl des entsprechenden Radionuclids, das als Indikator dient, muß unter Berücksichtigung der Art und Bedingungen der Bestimmung getroffen werden. Obwohl eine große Zahl von Radionucliden zugänglich ist, eignen sich doch nur verhältnismäßig wenige als Indikatoren. Die für diesen Zweck in Frage kommenden Radionuclide müssen die nachstehenden Forderungen erfüllen:

1. *Halbwertszeit.* Radionuclide mit zu langen oder zu kurzen Halbwertszeiten sind unbrauchbar. Die aktive Menge der letzteren nimmt rapid ab, was bei den im Titrationsprozeß gemessenen Aktivitätswerten als Korrektur berücksichtigt werden muß. Radionuclide mit extrem langen Halbwertszeiten hingegen emittieren meist eine Strahlung von geringer Energie. Eine hinreichend genaue Erfassung von Meßimpulsen ist in diesem Fall nur nach zeitraubender und oft schwieriger Anreicherung oder durch Vergrößerung der radioaktiven Indikatormenge möglich. Letzteres erweist sich jedoch als unvorteilhaft, da eine Erhöhung der Bestimmungsgrenzen parallel geht und eine Korrektur der Resultate erforderlich wird. Am besten geeignet sind die Radionuclide mit Halbwertszeiten von einer Woche bis zu einigen Monaten.

2. *Art und Energie der emittierten Strahlung.* Radionuclide mit α-Strahlung scheiden wegen der geringen Reichweite der Strahlung von vornherein aus, da bei den üblichen Messungen der Aktivitäten von flüssigen Phasen mit erheblichen Absorptionseffekten zu rechnen ist. Radionuklide mit der durchdringenden γ-Strahlung werden zwar durch Absorption nur wenig geschwächt, bedingen aber wegen der Strahlungsgefährdung besondere Schutzvorrichtungen und umständliche Arbeitstechniken. Als besonders geeignet haben sich Radionuclide mit irgendeiner e^-Strahlung ($E_{max} > 0{,}3$ MeV) erwiesen.

3. *Radiochemische Reinheit der radioaktiven Indikatoren.* Die als Indikatoren verwendeten Präparate müssen radiochemisch rein sein, d. h. sie dürfen keine fremde radioaktiven Nuclide enthalten. Die Reinheit kann mit physikalischen und mit chemischen Methoden geprüft werden. Die physikalischen Verfahren bestehen aus der Messung der Halbwertszeit und Ermittlung der Art und Energie der Strahlung. Die chemischen Methoden sind im wesentlichen die folgenden: Zu einer Lösung der zu

since hydrogen chloride consists of chlorine and hydrogen, it cannot contain oxygen. It follows from this that Davy's concept is contrary to Lavoisier's oxygen theory, according to which oxygen is the 'acid-engendering' element. Davy stated that 'acidity does not depend upon any particular elementary substance, but upon a particular arrangement of various substances'. The oxygen-free acids containing hydrogen discovered by Davy, e.g. HCl and HCN, were called 'hydrogen-acids' by Gay-Lussac. In non-aqueous titration terminology the term hydrogen-acid (H-acid) still finds use.

The main point of Berzelius' 'dualistic' hypothesis is the perception that atoms are linked to one another by electrical forces; though atoms possess both positive and negative charge, one charge type may be dominant, as a result of which compounds may be formed. Thus the properties of acids have no relation to a specific acid-bearing constituent but depend on the structure of the substance, and for almost every substance the acidic and the basic properties are characteristic. According to Berzelius – though he does not put this specifically – amphoterism is a general characteristic of any substance.

A later view according to which acid character depends on the presence of a specific particle – the H^+ ion – is, strictly speaking, a step back. This regress ensued when – contrary to the mainly mineralogical researches of Berzelius' time – scientific investigation in research laboratories become more and more concerned with processes in aqueous media [827].

Nowadays, anhydrides (oxides) such CO_2 and SiO_2, and H-acids, as well as L-acids (Lewis acids; $AlBr_3$, BF_3 etc.) are again all considered to be acids.

2. The Arrhenius–Ostwald Theory

Familiarity with experiments carried out in aqueous media makes the Arrhenius–Ostwald electrolytic dissociation theory (1887) easily comprehensible. According to this theory a compound can be looked upon as acid or base only when, in an aqueous medium, it yields through dissociation hydrogen or hydroxyl ions respectively; neutralization is an interaction of 'acid' and 'base', giving rise to water and a salt. From Arrhenius' theory it follows that the decisive proof of the interaction of an H-acid and an OH-base is the formation of an additional molecule of water and the formation of either a solid salt or one dissolved in water. Hence, the product of the interaction of acid and base is water: $H^+ + OH^- = H_2O$, this relation becoming the basis for the idea of neutrality from which the scale for pH values, determining acidity and alkalinity, is built up.

The inadequacy of Arrhenius' hypothesis is shown by the fact that, for instance, an acetone solution of ammonia is basic though no hydroxide ion is present. The study of reactions in non-aqueous media demonstrated the defects of the hypothesis, and led to the development of numerous new acid–base theories.

3. The Solvent Theory

In Europe Walden and his collaborators [855] and in the United States Franklin, Kraus, and later Audrieth became aware [21, 22, 239, 472] that not only water but other solvents may show autoprotolytic reactions. Formally, ammonia is e-

untersuchenden Probe werden solche stabile Elemente zugegeben, die im Präparat möglicherweise vorhanden sind. Dann werden diese Elemente mit analytischen Verfahren, z. B. durch Fällung, isoliert. Sind die Niederschläge nicht radioaktiv, so darf das betreffende Präparat als rein betrachtet werden. Im entgegengesetzten Fall bedarf es weiterer Untersuchungen. Es muß dann festgestellt werden, ob die Radioaktivität des Niederschlages auf Mitfällung oder nur auf Adsorption des betreffenden Radionuclids zurückzuführen ist.

4. *Chemische Form der Indikator-Präparate.* Der radioaktive Indikator muß meist in der gleichen chemischen Form zur Verfügung stehen, wie der zu bestimmende Stoff. Besonders nachdrücklich besteht diese Forderung bei Elementen mit mehreren Oxydationsstufen. Nicht weniger wichtig ist die entsprechende Wahl der Menge des zur Markierung verwendeten Präparate. Die beim Titrationsprozeß eintretende Verdünnung muß dabei berücksichtigt werden. Bei den Aktivitätsmessungen arbeitet man am besten im Bereich von 5000 bis 10 000 Ipm.*

In ihrer einfachsten Form können die radiometrischen Fällungstitrationen drei verschiedene Typen von Titrationskurven liefern. Der Kurvenverlauf hängt davon ab, ob die Maßlösung, die Prüflösung oder beide markiert sind.

(a) *Aktive Prüflösung und inaktive Maßlösung.* Die Aktivität der flüssigen Phase nimmt mit fortschreitender Titration und wachsender Menge des gebildeten Niederschlages ab. Im Endpunkt ist die verbleibende Aktivität der flüssigen Phase eine Funktion der Löslichkeit des Niederschlages (Abb. 3.1, *a*).

(b) *Inaktive Prüflösung und aktive Maßlösung.* Zu Beginn der Titration bestimmt die Löslichkeit des in der Titrationsreaktion gebildeten Niederschlages die Aktivität der Prüflösung. Diese Anfangs-Aktivität bleibt bis zum Endpunkt weitgehend konstant, um bei Überschreiten steil anzusteigen (Abb. 3.1, *b*).

(c) *Prüflösung und Maßlösung sind beide aktiv.* Die Aktivität der Prüflösung nimmt bis zum Endpunkt ab und beginnt dann zuzunehmen. Den Endpunkt zeigt das Minimum der Kurve an (Abb. 3.1, *c*).

In vielen Fällen steht dem zu bestimmenden Element kein entsprechendes Radioisotop zur Verfügung (z. B. im Falle von Kupfer, Nickel, Aluminium, Magnesium, Titan usw.). Zur Indikation des zu bestimmenden Elements kann in solchen Fällen häufig das Radioisotop eines anderen gleichartig reagierenden Elements verwendet werden. Man nennt diese Technik »*nichtisotope*« *Markierung.*

Die verwendeten nichtisotopen Indikatoren lassen sich in die beiden Gruppen der isomorphen und nichtisomorphen Indikatoren eingliedern.

(A) *Isomorphe Indikatoren.* In manchen Fällen ist es möglich, ein solches Radioisotop eines anderen Elements als Indikator zu verwenden, welches mit dem zu bestimmenden Element isomorph gefällt wird.

* Ipm = Impulse pro Minute (entsprechend der in der angelsächsischen Literatur allgemein üblichen Abkürzung c.p.m. = 'counts per minute').

qually a parent substance for some nitrogenous compounds, as water is of some containing oxygen. When examining the effects of solvents this roughly outlined interpretation may provide a useful, if limited, approach. When water is ionized to a small extent a hydroxonium ion (solvated proton) and a hydroxyl ion originate. Liquid ammonia is similarly ionized giving rise to an ammonium ion and an amide ion:

$$2\,H_2O \rightleftharpoons H_3O^+ + HO^-; \quad 2\,NH_3 \rightleftharpoons NH_4^+ + NH_2^-$$

In the above sense, as regards liquid ammonia, compounds increasing the concentration of NH_4^+ ions may be looked upon as acids, while bases increase the concentration of the NH_2^- ion. In anhydrous acetic acid the compound increasing the concentration of the acetacidium ion can be taken as an acid while that augmenting the concentration of the acetate may be considered to be a base:

$$2\,CH_3COOH \rightleftharpoons CH_3COOH_2^+ + CH_3COO^-$$

In many cases, however, this formal similarity goes deeper. For instance, ammonium salts ($NH_4^+Cl^-$), behave in liquid ammonia like acids, just as hydroxonium salts (H_3O^+ Cl^-) do in water. It follows, therefore, that the acid or base character of some compounds remains hidden in certain solvents, while in others it comes to the fore. A case in point is the behaviour of urea, which in water is a very weak base, in acetic acid is stronger, but in liquid ammonia possesses acid characteristics:

$$NH_2CONH_2 + H_2O \rightleftharpoons NH_2CONH_2 \ldots H^+ + OH^-$$

(OH^- = solvent anion)

$$NH_2CONH_2 + CH_3COOH \rightleftharpoons NH_2CONH_3^+ + CH_3COO^-$$

(CH_3COO^- = solvent anion)

$$NH_2CONH_2 + NH_3 \rightleftharpoons NH_2CONH^- + NH_4^+$$

(NH_4^+ = solvent cation).

This theory allows any solvent containing protons to be in principle capable of autoprotolysis, giving rise to solvated protons, the carrier of acid character, and solvent anions.

Parent Compound	*Solvated Proton + Solvent Anion*
Water	$H_3O^+ + OH^-$
Methanol	$CH_3OH_2^+ + CH_3O^-$
Ammonia	$NH_4^+ + NH_2^-$
Acetic acid	$CH_3COOH_2^+ + CH_3COO^-$

These acid–base theories can be classified in two ways, either by their constitutional or by their functional characteristics. According to the first criterion an acid is a hydrogen compound; according to the second at least one H^+ must be able to split off the acid. In this sense the same criterion can be applied to bases also; a base contains an

Zur radiometrischen Bestimmung von Zn^{2+} mit $(NH_4)_2[Hg(CNS)_4]$ als Titriermittel nutzten KORENMAN und Mitarb. [51] die isomorphe Mitfällung des Co^{2+} aus. Co^{2+} und Zn^{2+} werden gemeinsam gefällt; bei vollständiger Fällung des Zn^{2+} liegt auch Co^{2+} quantitativ im Niederschlag vor. Während der Titration nimmt die Aktivität der flüssigen Phase ab. Am Endpunkt besitzt die Aktivität einen konstanten Wert. bestimmt durch die Löslichkeit des Niederschlages (Abb. 3.2). Nach KORENMAN und Mitarb. stimmen die mit dem nichtisotopen Indikator (^{60}Co) erhaltenen Ergebnisse vollkommen mit jenen überein, die mit einem isotopen Indikator (^{65}Zn) erhalten wurden. Auf diese Weise konnten in 2 ml Lösung 0,3—1,0 mg Zink mit einem durchschnittlichen relativen Fehler von $\pm 5\%$ bestimmt werden.

Das gleiche Prinzip wird bei der radiometrischen Titration von Fluorid mit einer Lösung von Samariumnitrat angewandt, wobei diese auch Europium als nichtisotopen Indikator enthält [82].

(B) *Nichtisomorphe Indikatoren.* Man kann die nichtisotopen Indikatoren auch auf andere Weise anwenden. Eine der Möglichkeiten soll hier als praktisches Beispiel angeführt werden.

Bei der Fällung von Kaliumhexacyanoferrat(II) mit einer Cu^{2+}- und Zn^{2+} -Ionen enthaltenden Lösung scheidet sich zuerst der mit Cu^{2+} und erst dann der mit dem Zn^{2+} gebildete Niederschlag ab. Wird die mit ^{65}Zn markierte Prüflösung mit Kaliumhexacyanoferrat(II) titriert, so bewirkt die Ausscheidung des Kupfercyanoferrat(II)-Nieder-

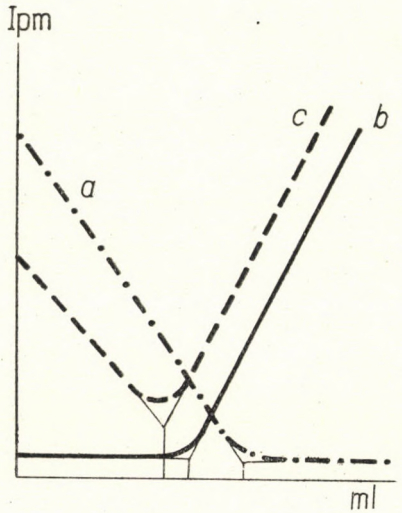


Abb. 3.1
Kurven radiometrischer Fällungstitrationen (*a* — Prüflösung aktiv, Maßlösung inaktiv; *b* — Prüflösung inaktiv, Maßlösung aktiv; *c* — beide Lösungen aktiv)

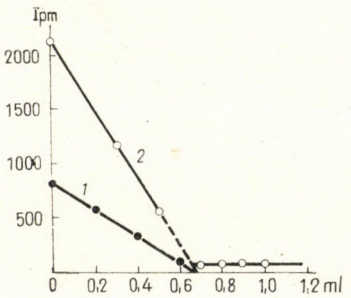


Abb. 3.2
Titration von Zink mit $(NH_4)_2[Hg(CNS)_4]$ als Maßlösung (*1* — Indikator: ^{65}Zn; *2* — Indikator ^{60}Co) (KORENMAN und Mitarb. [51])

OH-group, or an OH^- ion is dissociable. In the course of time the two criteria were found to be insufficient because with the advance of solvent theory it became manifest that acid–base interactions in liquid sulphur dioxide, as well as in liquid phosgene are also possible. In this case the acid analogue compound is free of protons; and the base analogue compound is free of hydroxyl ions:

$$2\,SO_2 \rightleftharpoons SO^{2+} + SO_3^{2-}$$

$$2\,COCl_2 \rightleftharpoons COCl^+ + COCl_3^-$$

4. Brönsted–Lowry's Protonic Theory

The proton, H^+, is unique among the cations, having no electron and with a sphere of action of radius 10^{-13} cm, whereas that of other ions is on the average 10^{-8} cm. Its mobility is very great compared with other ions; hence the hydrogen ion concentration of a solution is roughly proportional to its conductance, and in certain cases the H^+ concentration, the catalytic effect and the acid strength run parallel (Ostwald, 1884). The table below gives a clear idea of the above facts, the conductance and catalytic effect of hydrochloric acid being arbitrarily set as equal to 100:

Acid	K_{acid}	*Relative Conductance*	*Catalytic Effect on:*	
			Hydrolysis of Methyl Acetate	*Inversion of Saccharose*
Hydrochloric acid		100	100	100
Nitric acid		99·6	92	100
Sulphuric acid		65·1	73·9	73·2
Trichloroacetic acid	$1{\cdot}3 \times 10^{-1}$	62·3	68·2	75·4
Dichloroacetic acid	5×10^{-2}	25·3	23·0	27·1
Monochloroacetic acid	$1{\cdot}4 \times 10^{-3}$	4·9	4·3	4·8
Acetic acid	$1{\cdot}75 \times 10^{-5}$	0·42	0·35	0·4

The electrical field strength is considerable in the neighbourhood of the proton, hence the great affinity of hydrogen ions for particles possessing free electron pairs. Thus it is comprehensible that in water the solvated proton is the particle accentuating acidic character; the proportion of unsolvated protons is negligibly small. Since the proton-binding ability of particles with free electron pairs – be it a molecule of a solvent or a dissolved base – varies, the behaviour of acids, depending on the solvent, varies profoundly. This fact was disregarded for a long time because in acid–base titrations water was 'the solvent', though, in the great family of solvents, it is water which possesses remarkable properties: it has a nigh dielectric constant, water molecules are associated in a high degree, etc.

It is more than three decades since Brönsted and Lowry independently broke through what was until then a narrow interpretation of the acid–base theory [99, 522, 523].

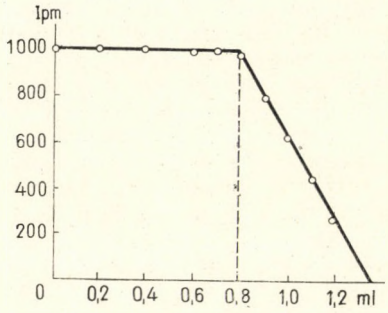


Abb. 3.3
Bestimmung von Zn und Cu nebeneinander unter Anwendung von ^{65}Zn als Indikator (KORENMAN und Mitarb. [51])

schlages zunächst keine Abnahme der Aktivität der Lösung. Sobald aber praktisch alle Cu^{2+}-Ionen verbraucht sind, beginnt die Ausscheidung des zinkhaltigen Niederschlages und damit die Abnahme der Aktivität der flüssigen Phase. Auf diese Weise kann also das Radioisotop des Zinks als Indikator zur Bestimmung von Kupfer verwendet werden [51] (Abb. 3.3). Bei der Durchführung der Bestimmung muß dafür Sorge getragen werden, daß die Prüflösung eine genügende Menge des radioaktiven Indikators und seines stabilen Isotops (als Träger) enthält, damit sich der Indikator als Niederschlag ausscheiden kann.

Bei dieser Technik ist eine unumgängliche Forderung, daß der nichtisotope Indikator (und sein Träger) mit dem Titriermittel einen schwerlöslichen Niederschlag bildet, dessen Löslichkeit jedoch größer sein muß, als die Löslichkeit des mit dem zu bestimmenden Element gebildeten Niederschlages.

Die auf die Genauigkeit Einfluß nehmenden Faktoren sind die gleichen wie bei den allgemeinen Fällungstitrationen z. B.: quantitativer Ablauf der Reaktion, Adsorption von Fremdionen durch den Niederschlag, Wert des Löslichkeitsproduktes, Konzentration der Ausgangslösungen, eventuelle Nebenreaktionen usw.

Die Empfindlichkeitsgrenze liegt im allgemeinen in der Größenordnung von 1 mg. Dieser Grenzwert wird durch das Löslichkeitsprodukt des während der Titration gebildeten Niederschlages bestimmt.

In letzter Zeit sind mehrere Methoden entwickelt worden, mit denen die Empfindlichkeit der Titrationen dieses Typs bedeutend erhöht werden konnte. So wurden u. a. Ionenaustauscher [20], Trennung durch sog. Kollektoren und Titrationen in nicht wäßrigen Medien [25] angewandt.

Die radiometrische Titration von Jodat mit einer mit ^{110m}Ag markierten Silbernitratlösung in stark verdünnten Lösungen ist wegen der nicht unerheblichen Löslichkeit des Silberjodats undurchführbar. Wird das Jodat aber vorher an einen in das System gebrachten Anionenaustauscher gebunden, so kann man selbst 10^{-4} M Lösungen noch titrieren. Der Niederschlag setzt sich dann auf der Oberfläche des Anionenaustauschers ab, an der die zu titrierenden Ionen konzentriert sind [20].

Die radiometrische Titration des Zirkoniums kann mit ^{32}P-markierter Phosphatlösung durchgeführt werden. Es lassen sich Zirkoniummengen in der Größenordnung von 1 mg zuverlässig titrieren [4]. Werden nun aber zum System nach der Zugabe der einzelnen Portionen der Titrierflüssigkeit jeweils auch äquivalente Mengen Silbernitrat- und Natriumjodatlösung aus zwei Büretten tropfenweise zugegeben, so spielt der gebildete Silberjodat-Niederschlag die Rolle eines Kollektors für das noch nicht ausgeschiedene Zirkoniumphosphat. Bei dieser Titrationstechnik sind sogar noch 10 μg Zr mit einem Variationskoeffizienten von $\pm 5\%$ bestimmbar [20].

Their definition has a functional character to some extent; accordingly, not only hydroxyl-containing compounds are bases, but all those compounds able to co-ordinate with a proton. For the sake of clarity the ideas characteristic of the protonic concept are enumerated as follows:

(a) The basis of the theory is that it establishes a reasonable connection between the notion of an acid, and of a base: an acid is a proton donor; a base, a proton acceptor. These terms hold good in the language of non-aqueous titration also:

S	$\rightleftarrows$	B^-	$+$	H^+
(Acid)	$\rightleftarrows$	(Base)	$+$	(Proton)
HCl	$\rightleftarrows$	Cl^-	$+$	H^+
NH_4^+	$\rightleftarrows$	NH_3	$+$	H^+
HCO_3^-	$\rightleftarrows$	CO_3^{2-}	$+$	H^+

It emphasizes, however, that a proton does not exist *per se* but only as a solvate.

(b) Brönsted drew a distinction between salt formation and neutralization reactions since, according to him, interaction of acid and base never leads to neutralization but in all cases new acids and new bases are formed:

S_1	$+$	B_2	$\rightleftarrows$	S_2	$+$	B_1
(Acid)		(Base)		(Acid)		(Base)
H_2O	$+$	H_2O	$\rightleftarrows$	H_3O^+	$+$	HO^-
HCl	$+$	H_2O	$\rightleftarrows$	H_3O^+	$+$	Cl^-
CH_3COOH	$+$	CH_3COOH	$\rightleftarrows$	$CH_2COOH_2^+$	$+$	CH_3COO^-
$HClO_4$	$+$	CH_3COOH	$\rightleftarrows$	$CH_3COOH_2^+$	$+$	ClO_4^-
$(C_6H_5)_3CH$	$+$	NH_2^-	$\rightleftarrows$	NH_3	$+$	$(C_6H_5)_3C^-$*
HBr	$+$	$H_2N-NH_3^+$	$\rightleftarrows$	$[H_3N-NH_3]^{2+}$	$+$	Br^-

The conjugate bases of the acids indicated in the first or third column above are the compounds (ions) listed in the fourth or second columns. The formation of a salt is not the characteristic acid–base interaction since salt formation can also be observed without an acid–base reaction:

$$N(CH_3)_3 + CH_3I = N(CH_3)_4I$$

(c) A compound of acidic character can release its proton only in the presence of a compound with a greater readiness to co-ordinate the proton (i.e. with a higher proton affinity) than the base with which the proton is linked. Brönsted disregards the effect of the solvent, though, depending on the specific features of the latter, the formation of a salt is influenced by the following states of equilibrium:

AH	$\rightleftarrows$	A^-	$+$	H^+
s	$+$	H^+	$\rightleftarrows$	sH^+
B	$+$	H^+	$\rightleftarrows$	BH^+

* In liquid ammonia with sodium amide: $NaNH_2 \rightleftarrows Na^+ + NH_2^-$.

Durch die Anwendung von nichtwäßrigen Lösungsmitteln, in denen der gebildete Niederschlag weniger löslich ist als in Wasser, kann die Empfindlichkeit noch weiter erhöht werden (siehe S. 38 uff.).

3.2. Theoretische Grundlagen der Methode

Bei den radiometrischen Fällungstitrationen wird die Menge der gesuchten Komponente auf Grund des zur vollständigen Fällung verbrauchten Volumens der Titrierlösung berechnet. Für titrimetrische Bestimmungen eignen sich nur solche Reaktionen, in denen ein Niederschlag von wohldefinierter Zusammensetzung gebildet wird, die Reaktion genügend schnell vor sich geht, der gebildete Niederschlag genügend schwerlöslich ist und für die ein isotoper oder nichtisotoper Indikator zur Ermittlung des Endpunktes der Reaktion gefunden werden kann.

Bisher haben sich nur wenige Arbeiten mit den theoretischen Problemen der radiometrischen Fällungstitrationen und der mathematischen Analyse der Titrationskurven beschäftigt [27, 43, 44, 45, 48, 101, 105, 111], obwohl die bei manchen radiometrischen Titrationen resultierenden Kurven mit Kurven anderer Indikationsmethoden übereinstimmen oder zumindest mit solchen in Korrelation stehen [36, 60, 69].

DUNCAN und THOMAS [27] haben als erste die Kurven der radiometrischen Fällungstitrationen mathematisch analysiert.

Wird eine Lösung die markiertes A^+ enthält, mit einer B^- enthaltenden Lösung titriert, wobei sich der schwerlösliche Niederschlag AB (mit dem Löslichkeitsprodukt L_{AB}) bildet,

$$A^+ + B^- \rightleftharpoons AB\downarrow, \tag{3.1}$$

so kann der Ablauf der Titration durch die Gleichung

$$L_{AB}\, v^2 + v v_0 \left(2L_{AB} - [B^-]_0\, [A^+]_0\, R\right) + \\ + v_0^2 \left\{L_{AB} + [A^+]_0^2\, R(1 - R)\right\} = 0 \tag{3.2}$$

ausgedrückt werden. Hier werden v ml einer Lösung der Ausgangskonzentration $[B^-]_0$ zu v_0 ml einer Lösung der Ausgangskonzentration $[A^+]_0$ zugegeben. Die Aktivität der letzteren Lösung ist a_0 Ipm und $R = a/a_0$, d. h. das Verhältnis der Gesamtaktivität der Lösung in jedem Zeitpunkte der Titration zur Ausgangs-Gesamtaktivität.

Ist der Wert von L_{AB} vernachlässigbar klein, so ergibt sich aus (3.2):

$$v = v_0 \frac{[A^+]_0}{[B^-]_0} (1 - R). \tag{3.3}$$

Der Ablauf der Titration kann durch Ermittlung von R für verschiedene Werte von v verfolgt werden. Die Bedingungen der Titration sollten so

where AH = the proton-donor acid – e.g. perchloric acid
s = the solvent molecule, e.g. acetic acid
B = the dissolved base, e.g. aniline
sH^+ = the 'onium ion formed with solvent ('lyonium ion' [68], e.g. $CH_3COOH_2^+$)
BH^+ = the base cation (cationic acid).

(d) An 'acid' may thus be a neutral molecule, a cation or an anion. All these are able to release a proton to the solvent or to the proton-co-ordinating base while giving rise, at the same time, to a hydroxonium ion (generally, to an 'onium ion):

Increasing acidic character ↓ / Increasing basic character ↑

$$\begin{array}{llllll} H_2O & + H_2O & \rightleftarrows & H_3O^+ & + HO^- \\ HCO_3^- & + H_2O & \rightleftarrows & H_3O^+ & + CO_3^{2-} \\ NH_4^+ & + H_2O & \rightleftarrows & H_3O^+ & + NH_3 \\ HCl & + H_2O & \rightleftarrows & H_3O^+ & + Cl^- \end{array}$$

The solvent molecule converted by protonation into a cation is termed a 'solvent cation' whether it be a water molecule or another solvent.

The inadequacy of Brönsted's theory is that in its original form it is only valid for proton-containing solvents and excludes the possibility that a hydrogen-free compound may act as an acid. His concept does not explain each and every salt-forming reaction since numerous salt-forming processes are known which occur in the absence of a proton-containing solvent, or a hydrogen ion dissociating compound: e.g.

$$\begin{array}{lll} CO_2 + CaO & \rightleftarrows & CaCO_3 \\ SiO_2 + Na_2O & \rightleftarrows & Na_2SiO_3 \\ AlCl_3 + C_5H_5N & \rightleftarrows & (C_5H_5N \,.\, AlCl_2)Cl \end{array}$$

5. Lewis' Electronic Theory

In Lewis' electronic theory also, acid and base are antagonistic though in a different sense from the proton theory [509, 528]. According to Lewis a distinction is drawn between constitutional criteria founded upon the material properties of the molecule, and functional ones based upon the reaction behaviour of the molecule, described by Lewis as phenomenological criteria.

(a) The neutralization reaction consists of the immediate formation of a co-ordinate covalent bond. The establishment of the bond is a primary process which, in a suitable solvent, may be followed by ionization, and possibly by dissociation:

Base	+ *Acid*	= *Product of neutralization*
R_3N	+ H^+	= R_3NH^+
R_3N	+ HCl	= $R_3N \,.\, HCl \longrightarrow R_3NH^+ + Cl^-$
R_3N	+ SO_2	= $R_3N \,.\, SO_2 \longrightarrow R_3NSO^{2+} + O^{2-}$
R_3N	+ BCl_3	= $R_3N \,.\, BCl_3$
$COCl_2$	+ $AlCl_3$	= $COCl_2 \,.\, AlCl_3 \longrightarrow COCl^+ + AlCl_4^-$
$2\,HCl$	+ $SnCl_4$	= $SnCl_4 \,.\, 2\,HCl$
$2\,NH_3$	+ Ag^+	= $Ag(NH_3)_2^+$

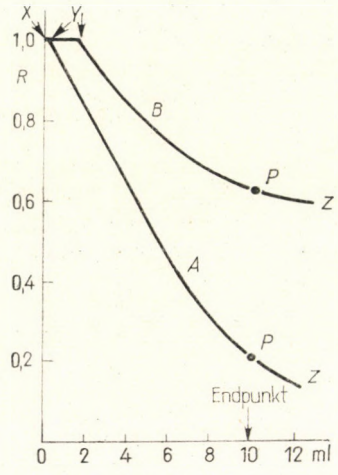


Abb. 3.4
Theoretische Kurve der radiometrischen Fällungstitration (DUNCAN und THOMAS [27]). ($[A^+]_0 = [B^-]_0 = 1$; $v_0 = 10$; Kurve A—$L_{AB} = 10^{-2}$; Kurve B—$L_{AB} = 10^{-1}$)

gewählt werden, daß die Voraussetzung zu (3.3) erfüllt ist. $[A^+]_0$ kann aus dem Wert von $[B^-]_0$ oder durch eine Berechnung erhalten werden, bei der nur eine Reihe von $[A^+]_0$, v- oder R-Werten verwendet wird (außer $v = 0$).

Die Voraussetzung der Vernachlässigung von L_{AB} (z. B. $L_{AB} < 10^{-6}$) war in allen über radiometrische Fällungstitrationen bisher erschienenen Arbeiten erfüllt [4, 17, 59, 80]. L_{AB} könnte auch dann noch vernachlässigt werden, wenn sein Wert viel größer ist (z. B. $\sim 10^{-2}$). Man erhält noch immer eine lineare Titrationskurve, wenn die Konzentrationen der Lösungen genügend hoch und die Werte von v und v_0 klein sind. Die Genauigkeit ist dann befriedigend, wenn die Volumina sehr genau mit einer Halbmikro-Technik abgemessen werden; die Empfindlichkeit jedoch wäre nicht hoch.

Abb. 3.4 zeigt die theoretisch zu erwartenden Kurven, wenn L_{AB} nicht vernachlässigbar ist. Der Kurvenverlauf ist anfangs horizontal ($R = 1$). Solange sich kein Niederschlag ausscheidet, können auch keine Werte $R < 1$ erhalten werden. Obgleich die Kurve nach Beginn der Fällung ohne Knickpunkte stetig abfällt, kann bei bekannten Werten von L_{AB} und $[B^-]_0$ ein Wert für $[A^+]_0$ berechnet werden. Hierzu können zwei verschiedene Auswertemethoden herangezogen werden:

1. Die Werte R und v eines beliebigen Punktes im Kurvenbereich Y bis Z werden in die Gleichungen (3.2) eingesetzt. Man löst die entstehende $[A^+]_0$-quadratische Gleichung.
2. Einfacher ist die Berechnung von $[A^+]_0$ durch Einsetzten von v für den Punkt Y, der durch die eben beginnende Fällung charakterisiert ist, in das Löslichkeitsprodukt:

$$L_{AB} = \frac{v_0}{v_0 + v} \cdot [A^+]_0 \cdot \frac{v}{v_0 + v} \cdot [B^+]_0 \,. \tag{3.4}$$

Theoretisch folgt der für Y maßgebende v-Wert aus (3.4) zu:

$$\frac{v}{v_0} = \left(\frac{1}{2}\,\eta - 1\right) - \sqrt{\eta\left(\frac{1}{4}\,\eta - 1\right)} \tag{3.5}$$

mit

$$\eta = \frac{[A^+]_0 \cdot [B^-]_0}{L_{AB}} \,. \tag{3.6}$$

Für große η ($L_{AB} \to 0$) sind in den Klammern von (3.5) Eins-Glieder vernachläßigbar und es folgt $v = 0$, d. h. die Fällung beginnt sofort nach Zugabe des ersten Tropfens der Titrierlösung.

$$C_5H_5N + AsCl_3 = C_5H_5N \cdot AsCl_3 \rightarrow [C_5H_5NAsCl_2]^+ + Cl^-$$
$$(C_2H_5)_2O + SO_3 = (C_2H_5)_2O \cdot SO_3$$
$$ROH + Al(OR)_3 = ROH \cdot Al(OR)_3 \rightarrow H^+ + [Al(OR)_4]^-$$
$$(C_6H_5)_2CO + SOCl_2 = [(C_6H_5)_2CO \cdot SOCl)]^+Cl^-$$



$$O - C_6H_5 \pm AlCl_3 = [C_6H_5O.AlCl_3]^- [CH_3CO]^+$$
$$2\,CH_3CN + 2\,AlCl_3 = [CH_3CN.AlCl_2.NCCH_3]^+ + AlCl_4^-$$

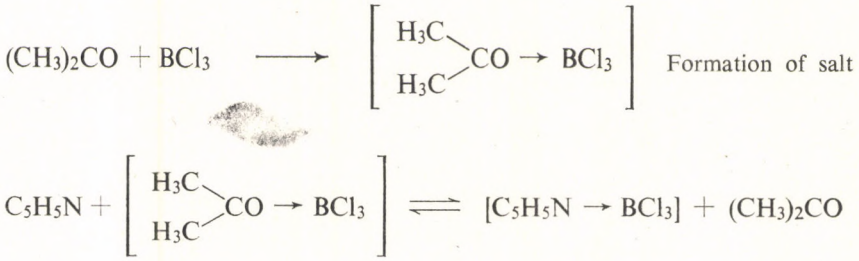
(b) Acids and bases bring about reversible colour changes with indicators.

(c) Any kind of acid can be reciprocally titrated with a suitable base, usually in the presence of an appropriate indicator. For the reaction the presence of protons is not essential: crystal violet, following the addition of pyridine in water, or in acetic acid, or in benzene gives the solution a 'basic' (violet) colour but gives an 'acidic' (yellow-green) colour in all three solvents when boron trichloride is added:

$$Cl_3B + NC_5H_5 = Cl_3B \leftarrow NC_5H_5$$
(Acid) + (Base) (Product of neutralization)

(d) Displacement of a weaker acid (base) by a stronger one is recognized: e.g.

$$NH_3 + H_3O^+ \longrightarrow NH_4^+ + H_2O$$



In the Lewis sense every experimentally demonstrable acid–base process can be explained by a simple and universally valid constitutional stipulation: an acid is co-ordinatively unsaturated and is therefore able to accept an electron pair through formation of a co-ordinate covalent bond. A base may be characterized by the presence of a sharable electron pair. Thus an acid, as well as a base, is characterized by the electronic configuration. The tendency to form 'onium salts (ammonium, oxonium, sulphonium, carbenium) is a sign of basicity even if no hydrogen ion is needed in order to form the latter.

$$N(CH_3)_3 + CH_3I = {}^+N(CH_3)_4I^-$$

Lewis' theory explains the behaviour of acids and bases irrespective of the solvent, and also in proton-free systems. Through Lewis' concept the interaction of 'acidic' and 'basic' oxides, as well as numerous processes in organic chemistry, become particularly comprehensible; in fact, more so than with the aid of many other

Setzt man in die Gleichung (3.5) für L_{AB} Werte von 10^{-2} bzw. 10^{-1} ein, und nimmt an, daß $[A^+]_0 = [B^-]_0 = 1$ ist, so erhält man für v/v_0 im Punkt Y die Werte 0,012 bzw. 0,12 (siehe Abb. 3.4).

Wenn die Maßlösung aktiv ist, so gelten die obigen Gleichungen, wenn die Symbole die folgende Bedeutung haben: Ein Volumen v_0 der Lösung von A^+ wird aus einer Bürette zu einem Volumen v der Lösung von B^- zugegeben. R hat die gleiche Bedeutung wie oben. a_0 ist hingegen nicht mehr konstant, sondern bedeutet den Wert der zugegebenen Aktivität im variablen Volumen v_0. Für den Fall $L_{AB} = 0$ lautet die Gleichung (3.3) daher

$$v_0 = \frac{v \cdot [B^-]_0}{[A^+]_0 (1 - R)} . \tag{3.7}$$

Nach dem Endpunkt, in welchem $a_{A^+} = 0$ ist, nimmt die gemessene Aktivität mit v_0 linear zu, d. h.

$$v_0 = \frac{v \cdot [B^-]_0}{[A^+]_0} .$$

Auf der Basis der Analogie mit den amperometrischen Titrationen [69] haben JESENÁK und TÖLGYESSY [43, 44, 101, 111] die Theorie der radiometrischen Fällungstitrationen entwickelt. Die Beziehung zwischen der Konzentration von A^+ und der zugegebenen Menge der Titrierlösung wurde durch die Gleichung (3.8) ausgedrückt:

$$\gamma^2 - \frac{\gamma_0 v_0 - c_0 v}{v_0 + v} \gamma - L_{AB} = 0 , \tag{3.8}$$

γ_0 = Ausgangskonzentration von A^+ (N)
γ = Konzentration von A^+ während der Titration (N)
c_0 = Konzentration der Maßlösung B^- (N)
v_0 und v (Liter).

Bei den einfachsten Fällen der radiometrischen Titrationen können drei verschiedene Typen von Titrationskurven erhalten werden. Ihr Verlauf hängt davon ab, ob die Prüflösung, die Maßlösung oder beide aktiv sind.

(a) *Prüflösung aktiv, Maßlösung inaktiv.* Die Radioaktivität der Lösung ist der Konzentration direkt proportional, d. h. $\gamma_0 = k \cdot I_0$. I bzw. I_0 bedeutet die in einem festgelegten Volumen an Lösung gemessene Aktivität in Ipm, k ist eine volumenabhängige Proportionalitätskonstante. Durch Einsetzen in die Gleichung (3.8) folgt:

$$I^2 - \frac{k I_0 v_0 - c_0 v}{k(v_0 + v)} I - \frac{L_{AB}}{k^2} = 0 . \tag{3.9}$$

Abb. 3.5 zeigt die mit (3.9) erhaltene theoretische Titrationskurve; die Parameter sind gleichfalls in der Abb. angegeben.

theories. This concept is undoubtedly a fundamental one. However, it is in danger, as has happened with many earlier theories, of being misapplied to chemical phenomena to which Lewis never meant it to apply.

According to Brönsted an acid is a proton donor, a base is a proton acceptor; on the other hand in Lewis' concept an acid is an electron acceptor and a base an electron donor. These two concepts, however, are only apparently antagonistic.

Usanovich in his uniform acid–base theory made a reasonable attempt to bring together the two concepts.

In titrations performed in non-aqueous media, electron-deficient acids, not containing a proton, are desirably named as Lewis-acids (L-acids) e.g.:

$$AlCl_3,\ FeCl_3,\ BCl_3,\ (CH_3)_3B,\ AsCl_3$$

Boron trifluoride (or trichloride) generates carbon dioxide from an acetone-carbon tetrachloride suspension of calcium carbonate.

It follows from this classification that a cation of inert gas structure, e.g. NH_4^+, cannot be looked upon as acid. Neither can hydrogen chloride be taken as an acid because it may be produced from the interaction of an electron acceptor particle and an electron donor particle:

$$Cl^- + H_3O^+ \rightleftharpoons HCl + H_2O$$

Hydrogen chloride is not an electron-deficient compound but possesses three lone electron pairs; H : $\dot{\underset{\cdot\cdot}{\text{Cl}}}$: – in this sense it ought to be considered a base.

L-acids are likewise differentiated from H-acids because chemical reactions based upon electron transfer often require considerable activation energy while those based upon prototropic reactions do not [52, 510].

Their catalytic effect is one of the most characteristic properties of acids. Its investigation contributed greatly to the development of our ideas concerning acids and bases. The comprehensive validity of Lewis' acid–base concept was restricted in connection with the catalytic effect of the Lewis acids BF_3, $AlCl_3$, $TiCl_4$. Polányi and his co-workers showed (1947) that Lewis acids are not able to catalyze the polymerization of isobutene if the co-reactants are completely purified, and that polymerization is initiated by traces of H-acid (cf. p. 213 in [231]),

$$BF_3 + H_2O \rightarrow [BF_3OH]^-\ H^+$$

In practice the empirical order of Lewis acids favouring this polymerization is:

$$BF_3 > AlBr_3 > AlCl_3 > TiCl_4 > BCl_3 > SnCl_4 > H_2SO_4$$

However, Lewis himself emphasizes that strength in acids and bases does not only depend on the solvent but also on the reference base or acid. According to the classical interpretation NH_3 is a weaker base than OH^- but when compared with an Ag^+ ion of Lewis-acid character the order undergoes a change, since AgOH dissociates while $[Ag(NH_3)_2]^+$ remains a stable complex.

Thus it is practicable to distinguish between proton-donor H-acids (Brönsted-acids), and electron-acceptor L-acids (Lewis-acids). (For a comparison of Brönsted's and Lewis' acid–base theories see also: [833]).

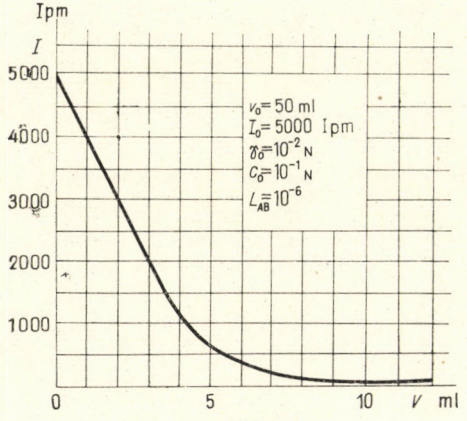


Abb. 3.5
Theoretische Kurve radiometrischer Titrationen (Prüflösung aktiv, Titriermittel inaktiv) (JESENÁK und TÖLGYESSY [43])

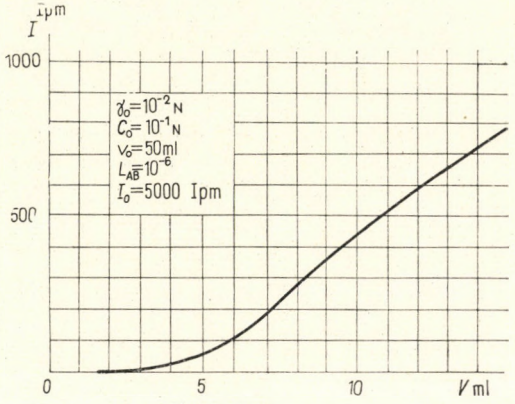


Abb. 3.6
Theoretische Kurve radiometrischer Titrationen(Prüflösung inaktiv, Titriermittel aktiv) (JESENÁK und TÖLGYESSY [43])

(b) *Prüflösung inaktiv, Maßlösung aktiv.* Durch Einsetzen von $\gamma_0 = k \cdot I_0$ in (3.9) ergibt sich:

$$I^2 + \frac{\gamma_0 v_0 - c_0 v}{k(v_0 + v)} I - \frac{L_{AB}}{k^2} = 0. \tag{3.10}$$

Die Titrationskurve zeigt Abb. 3.6.

(c) *Prüflösung und Maßlösung aktiv.* Den Endpunkt bestimmt das Minimum der Titrationskurve. Wenn

$$\gamma_0 = k_1 I_{1.0} ,$$
$$\gamma = k_1 I_1 ,$$
$$c = k_2 I_2 ,$$

so gilt für die während der Titration gemessene relative Aktivität (I):

$$2I = R\left(1 - \frac{k_1}{k_2}\right) + \left(R^2 + \frac{4L_{AB}}{k_1^2}\right)^{\frac{1}{2}} + \left[\left(\frac{k_1}{k_2} R\right)^2 + \frac{4L_{AB}}{k_2^2}\right]^{\frac{1}{2}}. \tag{3.11}$$

In dieser ist

$$R = \frac{k_1 I_{1.0} v_0 - c_0 v}{k_1 (v_0 + v)}. \tag{3.12}$$

Für bestimmte Fälle kann (3.11) wie folgt vereinfacht werden:

1. Ist $k_1 = k_2 = k$, d. h. entspricht das Verhältnis der Aktivität der

These examples make the deficiencies of Lewis' electronic concept obvious, and prompted some research workers to create a more comprehensive theory in order to eliminate the contradictions contained in Brönsted's and Lewis' theories.

We have now seen that on Arrhenius' hypothesis compounds are grouped into acids and bases according to structural and functional criteria. In Brönsted's theory they are classified partly according to their structural and partly by their functional properties. In the concept promulgated by Lewis, compounds are ranked into acids or bases decisively according to structural criteria. The functional acid–base theory advanced by Ebert and Konopik does not contain any structural criteria [201].

6. Ebert–Konopik's Acid–base Concept

In solvents liable to autoprotolysis (self-ionization) two sorts of acids and bases are distinguishable:

1. Donor-acid (S_D) releases a solvent-cation or some other acid, or forms with the solvent a solvent-cation.
2. Acceptor-acid (S_A) binds a solvent-anion or any other base.
3. Donor-base (B_D) releases a solvent-anion or some other base or forms with the solvent molecule a solvent-anion.
4. Acceptor-base (B_A) is able to bind solvent-cation or any other acid.

Compounds belonging to groups S_D and B_D are well known: H-acids, OH-bases. NH_3 belongs to group B_A. To the group S_A belongs e.g. PO_3^- which by binding a hydroxyl ion is converted into HPO_4^{2-}.

Five acid–base type reactions may occur in solvents liable to self-ionization:

$$S_D + B_D = \text{salt} + \text{solvent}, \text{ e.g.: } HCl + KOH = KCl + H_2O \quad (6.1)$$

$$S_D + B_A = \text{salt, e.g.: } HCl + NH_3 = NH_4^+Cl^- \quad (6.2)$$

$$S_A + B_D = \text{salt, e.g.: } Zn(OH)_2 + 2\,NaOH = 2\,Na^+[Zn(OH)_4]^{2-} \quad (6.3)$$

$$S_A + B_A = \text{solvent} + \text{salt, e.g.: } SO_2 + 2\,NH_3 + H_2O = (NH_4)_2^{2+}SO_3^{2-} \quad (6.4)$$

$$B_A + S_A = \text{salt, e.g.: } BCl_3 + N(CH_3)_3 = Cl_3B \,.\, N(CH_3)_3 \quad (6.5)$$

In inert solvents — hexane, carbon tetrachloride, benzene — only reactions of types (6.2) (6.3) and (6.5) take place.

Terms such as, for example, acceptor-acid, donor-base thereby become of current use in the field of non-aqueous titrations.

7. Gutmann–Lindqvist's Ionotropy Theory

According to Mandel four acid–base concepts are well known [545]:

1. Solvent theory
2. Proton theory
3. Cation–anion theory
4. Electronic theory (cf. [528])

Prüflösung und Maßlösung dem Verhältnis ihrer Konzentrationen, so gilt für I der Ausdruck:

(3.13)

$$I = \left(R^2 + \frac{4L_{AB}}{k^2}\right)^{\frac{1}{2}}.$$

Abb. 3.7 zeigt die bei diesen Bedingungen aufgenommene Titrationskurve.

2. Ist k_1 im Vergleich zu k_2 vernachlässigbar, d. h. ist die Aktivität der Prüflösung viel größer als die der Maßlösung, so geht (3.11) über in:

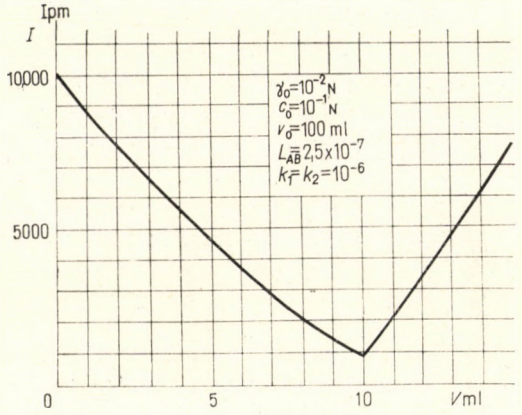


Abb. 3.7
Theoretische Kurve radiometrischer Titrationen (beide Lösungen aktiv) (JESENÁK und TÖLGYESSY [43])

(3.14)

$$2I \approx R + \left(R^2 + \frac{4L_{AB}}{k_1^2}\right)^{\frac{1}{2}}.$$

3. Wenn k_2 im Vergleich zu k_1 vernachlässigbar ist, so folgt aus (3.11):

(3.15)

$$2I \approx -\frac{k_1}{k_2}R + \left[\left(\frac{k_1}{k_2}R\right)^2 + \frac{4L_{AB}}{k_2^2}\right]^{\frac{1}{2}}.$$

Die bei den radiometrischen Fällungstitrationen in den meisten Fällen erhaltenen Titrationskurven können mit diesen Beziehungen beschrieben werden.

3.3. Bestimmung des Endpunktes

Bei den radiometrischen Fällungstitrationen wird die Funktion $I = f(v)$ verfolgt, in der I die Aktivität der Lösung über dem Niederschlag und v das zugegebene Volumen der Maßlösung bedeutet. Auf Grund der aufgenommenen Titrationskurve kann der Endpunkt graphisch bestimmt werden. Zur Aufstellung der Kurve werden auf der Ordinate die Volumina v der zugegebenen Maßlösung und auf der Abszisse die Aktivitäten der flüssigen Phase (in der Regel in Ipm) aufgetragen. Der Knickpunkt der Kurve zeigt den Endpunkt an.

Die Bestimmung des Endpunktes auf Grund einer Titrationskurve, zu deren Aufstellung sechs Werte notwendig sind, erfordert 40–50 Minuten. Die Schnelligkeit des Verfahrens hängt von der Natur und der Sedimentationsgeschwindigkeit des gebildeten Niederschlages ab.

Gutmann and Lindqvist's recent acid–base concept makes it possible to bring the first three theories into line with the proton transfer theory and in a wider sense with the ion transfer theory (ionotropy theory) [295, 296]. Some of Gurney's published work regarding the mechanism of proton transfer supports Gutmann and Lindqvist's ionotropy theory [294].

The acid–base properties of a molecule (or ion) become evident in the course of interaction with the solvent. The molecule possesses an acid character if it releases to the solvent molecule a positively charged particle. On the other hand, if it releases a negatively charged particle it possesses basic character. The converse also holds good: the solvent molecule releasing a negatively charged particle to the dissolved molecule of acid character, etc. In a more simplified and generalized way, the above describes:

(a) Cation transfer within the solvent molecule:

$$2\,sP \rightleftarrows sP_2^+ + s^-$$

1. Acidic interaction:

$$AP + sP \rightleftarrows sP_2^+ + A^-$$

2. Basic interaction:

$$B + sP \rightleftarrows BP^+ + s^-$$

(b) Anion transfer within the solvent molecule:

$$2\,sN \rightleftarrows sN_2^- + s^+$$

1. Acidic interaction:

$$A + sN \rightleftarrows AN^- + s^+$$

2. Basic interaction:

$$BN + sN \rightleftarrows B^+ + sN_2^-$$

where P = positively charged particle (proton, cation)
N = negatively charged particle (anion)
AP = donor-acid
B = acceptor-base
A = acceptor-acid
BN = donor-base
s = the solvent taking part in the ionotropic reaction.

Examples of 1 and 2 (in a) are the interaction of perchloric acid and a nitrogenous base with acetic acid as solvent. An example of (b) is

$$2\,AsCl_3 \rightleftarrows AsCl_2^+ + AsCl_4^-$$

In arsenic(III)chloride as solvent iron(III)chloride is the acceptor-acid 1 (in b), and tetramethylammonium chloride the donor-base 2 (in b)

$$FeCl_3 + (CH_3)_4N^+Cl^- \rightarrow (FeCl_4)^- \ {}^+N(CH_3)_4$$

Außer der etwas langwierigen graphischen Methode kann auch die Extrapolation aus zwei Punkten der Kurve herangezogen werden [1, 59, 99, 100, 101, 103]. Dieses Verfahren ist schnell und daher für Serienanalysen – unter den nachstehend angegebenen Bedingungen – besonders geeignet. Seine mathematische Analyse ist in der Literatur bereits beschrieben worden [43, 44, 105, 110, 111].

Bei der Titration einfach geladener, markierter Ionen mit einer inaktiven Maßlösung liefert die umgeformte Gleichung (3.8) die Abhängigkeit der Konzentration der markierten Ionen von den übrigen Parametern des Prozesses zu:

$$\gamma^2 (v_0 + v) - \gamma\gamma_0 v_0 + \gamma c_0 v - L_{AB} (v_0 + v) = 0 . \tag{3.16}$$

Mit $\gamma = k \cdot I$ und $\gamma_0 = k \cdot I_0$ geht (3.16) über in die Aktivitätsbeziehung:

$$\gamma_0^2 v_0 I^2 + \gamma_0^2 v I^2 - \gamma_0^2 v_0 I_0 I + \gamma_0 c_0 I_0 I v - L_{AB} I_0^2 v_0 - L_{AB} I_0^2 v = 0 . \tag{3.17}$$

Die Gültigkeit von Gleichung (3.17) erstreckt sich von der ersten Bildung bis zur eventuellen Auflösung des Niederschlages im Überschuß der Maßlösung. Ist die durch Zugabe der Maßlösung hervorgerufene Änderung des Volumens und ebenso auch das Löslichkeitsprodukt vernachlässigbar, d. h. ist

$$v_0 + v \approx v_0 \tag{3.18}$$

und

$$L_{AB} \approx 0 , \tag{3.19}$$

so gilt für die durch Gleichung (3.16) definierte Kurve der vereinfachte Zusammenhang:

$$I = I_0 \left(1 - \frac{c_0 v}{\gamma_0 \cdot v_0}\right) = I_0 - \frac{c_0 v}{k v_0} . \tag{3.20}$$

In der Literatur wird die Bestimmung des Endpunktes durch zwei Punkte der Titrationskurve empfohlen [3, 59], besonders mit Hilfe der Anfangsaktivität der markierten Lösung (I_0) und der Aktivität (I) der Lösung über dem Niederschlag, die nach der Zugabe eines bestimmten (zur Erreichung des Endpunktes nicht ausreichenden) Volumens der Maßlösungen (v) erhalten wird. Das zur Erreichung des Endpunktes notwendige Volumen der Maßlösung (v_{ex}) kann nach (3.21) berechnet werden:

$$v_{ex} = \frac{I_0}{I_0 - I} v \tag{3.21}$$

Beziehung (3.21) ist jedoch nur brauchbar, wenn die durch die Gleichungen (3.18) und (3.19) definierten Bedingungen erfüllt sind.

Experimental data concerning solvents with a non-protonic migrating cation are not available.

The transporting phenomenon in acid-base reactions is, in fact, the migration of ions (ionotropy) from one compound to the other. Depending on the movement of a cation or of an anion, a cationotropic or anionotropic solvosystem is spoken of [295, 296].

The best-known example of cationotropy is the migration of protons (proton-transfer). In a cationotropic solvosystem, the acid is the cation donor and the base the cation acceptor. On the other hand, in the anionotropic solvosystem the acid is the anion acceptor and the base the anion donor:

Cationotropic solvosystem

Proton donor	+	*Proton acceptor*	⇄	*Proton acceptor*	+	*Proton donor*
NH_3	+	NH_3	⇄	NH_2^-	+	NH_4^+
CH_3COOH	+	CH_3COOH	⇄	CH_3COO^-	+	$CH_3COOH_2^+$
$HClO_4$	+	CH_3COOH	⇄	ClO_4^-	+	$CH_3COOH_2^+$

Anionotropic solvosystem

Anion donor	+	*Anion acceptor*	⇄	*Anion acceptor*	+	*Anion donor*
SO_2	+	SO_2	⇄	SO^{2+}	+	SO_3^{2-}
CaO	+	CO_2	⇄	Ca^{2+}	+	CO_3^{2-}
$FeCl_3$	+	$AsCl_3$	⇄	$AsCl_2^+$	+	$FeCl_4^-$

In this way Brönsted's prototropic system reveals itself as special case of the cationotropic solvosystem. The Gutmann–Lindqvist theory is not contrary to the Lewis concept. It differs from Usanovich's acid–base concept in so far as the notion of ionotropy excludes all complex ions as migrating units as well as all oxidation-reduction processes. The question of the energy necessary for proton transfer will be discussed later in Chapter 2: Strength of acids.

The acid–base theories treated so far have not furnished a unified view of all modes of salt formation; moreover they consider the latter in certain cases as independent of acid–base reactions.

8. Usanovich's Acid–Base Theory

It is a characteristic feature of Usanovich's acid–base concept that an established idea such as that of salt formation is looked upon a typical consequence of acid–base reactions. The two cannot, therefore – according to Usanovich – be separated [269, 325, 825, 826, 827]. Thus

$$N(CH_3)_3 + CH_3I = [N(CH_3)_4]^+ I^-$$

is a typical acid–base reaction, the methyl iodide releasing a CH_3^+ cation to the trimethylamine base in the same way as in the reaction:

$$N(CH_3)_3 + HI = [N(CH_3)_3H]^+ I^-$$

Eine Untersuchung dieses Problems hat ergeben, daß die genannten Bedingungen nicht immer erfüllt sind und der hieraus resultierende Fehler dann auch nicht in jedem Falle vernachlässigt werden kann. Theoretisch ist dieser Fehler gegeben durch:

$$\vartheta = \frac{v_{ex} - v_E}{v_E} = \left(\frac{KI_0}{I_0 - I} - 1 \right), \tag{3.22}$$

v_E = theoretischer Verbrauch (Liter)
v_{ex} = durch Extrapolation bestimmter Verbrauch
K = Quotient v/v_E.

Wird I aus (3.17) in (3.22) eingesetzt, so ergibt sich

$$\vartheta = \frac{KI_0}{I_0 - \frac{1}{2}\left[\frac{kI_0 v_0 - c_0 v}{k(v_0 + v)} - \left(\frac{kI_0 - c_0 v}{k(v_0 + v)} + \frac{4L_{AB}}{k^2} \right)^{\frac{1}{2}} \right]}. \tag{3.23}$$

Zur Feststellung der praktischen Verwendbarkeit der abgeleiteten Zusammenhänge haben JESENÁK und TÖLGYESSY [44] eine mit ^{204}Tl markierte $3{,}0919 \times 10^{-2}$ N Lösung von Thallium(I)-Ionen mit 0,1 N Bromidlösung titriert. Der Endpunkt wurde nach drei verschiedenen Methoden bestimmt:

(a) gravimetrisch,

(b) mit der Extrapolationsmethode, auf Grund der gemessenen Aktivitätswerte,

(c) mit der Auflösung von (3.17).

Die Fehler der Extrapolationsmethode zeigten gute Übereinstimmung mit den auf Grund der Gleichung (3.23) berechneten (vgl. Abb. 3.8). Die in der Literatur [3, 59] angegebene Regel, das Volumen der zugegebenen Maßlösung so zu wählen, daß nach seiner Zugabe die Aktivität der Prüflösung auf die Hälfte des Ausgangswertes sinkt, ist demnach anfechtbar. Aus den oben genannten Gründen wird empfohlen [44], mit den Beziehungen

$$J = \frac{I}{I_0}; \quad V = \frac{v}{v_0} \tag{3.24}$$

und den Ansätzen

$$C_\gamma = \frac{\gamma_0}{(L_{AB})^{\frac{1}{2}}}; \quad C_c = \frac{c_0}{(L_{AB})^{\frac{1}{2}}} \tag{3.25}$$

zu arbeiten, um Gleichung (3.17) in *dimensionsloser* Form zu erhalten:

$$C_\gamma^2 [J^2 + VJ^2 - J] + C_c VJC_\gamma - (1 + V) = 0. \tag{3.26}$$

in which hydrogen iodide releases a proton (cationotropy). Alkyloxonium compounds are, for instance, alkyl cation donors.

The unusual and questionable inference of Usanovich's concept is that redox processes are also to be considered as acid–base reactions. E.g.: sodium 'base' releases an electron to chlorine 'acid' so that Na^+ cation acid and Cl^- anion base arise; the union of these leads to the formation of a salt.

According to Usanovich acids are substances able either to release a hydrogen ion or another cation, or to take up any other anion: in a wider sense acids are able to release electropositive particles and to take up electronegative ones. *Bases are all those compounds able to release electrons or an anion, or take up a proton or another cation.* Thus Usanovich unified the protonic and electronic concepts.

From the viewpoint of valence the character of a saturated compound may be changed by its co-ordination of ions. The co-ordination number of the central atom sets a limit to the co-ordinating tendency. As a consequence a compound is able to fulfil its acidic or basic function until it is saturated from a co-ordinative aspect. Co-ordinatively unsaturated electropositive atoms, molecules and ions behave as acids, but co-ordina tively unsaturated electronegative particles act like bases. So, for instance, the carbon dioxide molecule is an acid since its electropositive atom possesses a higher valence than the electronegative oxygen atom though both kinds of atoms are co-ordinatively unsaturated; and by gaining oxygen it is converted into a carbonate anion. The carbon is, however, co-ordinatively still unsaturated and can still take up an oxygen ion thus becoming converted into orthocarbonic acid anion. This ion, however, does not show any acidic character since the carbon has become co-ordinatively saturated. At the same time, its basic property becomes highly apparent because of its negative charge:

$$CO_2 \rightarrow CO_3^{2-} \rightarrow CO_4^{4-}$$

This essentially correct concept by Usanovich is logically founded on the classification of elements into acidic and basic elements. *The strength of bases and acids stands in inverse ratio to the strength of the conjugate acids and bases.* This may be illustrated quite simply in the case of elementary cationic acids and anionic bases. The lower the ionization potential of the metal the stronger the base, e.g.: $K - e = K^+$, that is to say, that metals display their basic function through releasing electrons; the higher the ionization potential the stronger the cationic acid. *Accordingly, strong acid corresponds to weak base, the converse also being true*:

$$\underset{\text{Strong acid}}{Cl} + e = \underset{\text{Weak base}}{Cl^-}; \qquad \underset{\text{Weak acid}}{K^+} + e = \underset{\text{Strong base}}{K}$$

It is a well-known phenomenon that in non-aqueous titrations, e.g. acetic acid is a 'weak acid' while the corresponding base – acetate ion – is a 'strong base'. Aniline is a weak base, but the cationic acid derived from it, the anilinium ion, as a result of proton gain, is a strong acid.

According to Usanovich, organic bases not able to release anions because they contain co-ordinatively unsaturated electronegative atoms (Ebert–Konopik acceptor-bases) undergo reciprocal polarization, prior to the formation of salt, e.g.:

$$\overset{\delta+\ \ \delta-\ \ \delta+\ \delta-}{C_5H_5N + AsCl_3} \rightarrow C_5H_5N \cdot AsCl_3 \rightarrow [C_5H_5N \,.\, AsCl_2]^+ + Cl^-$$

Zur Durchführung von Serienanalysen wird mit Hilfe der Gleichungen (3.24), (3.25) und (3.26) zuerst die Korrelation $C_\gamma - J$ für zwei oder drei Standard-Werte von V (V_1, V_2, V_3) berechnet und graphisch dargestellt (Abb. 3.9). Die den Werten V_1,V_2 und V_3 sowie den relativen Aktivitäten J_1, J_2 und J_3 entsprechenden Daten für C_γ und γ können dann aus den Kurven abgelesen werden (vgl. Abb. 3.9). Somit werden die Fehler der Extrapolationsmethode eliminiert.

Theoretisch setzt sich die als Funktion des Volumens der zugegebenen Maßlösung aufgenommene Aktivitätskurve der flüssigen Phase aus drei Abschnitten zusammen (Abb. 3.10), d. h. aus zwei Abschnitten der Verdünnungskurve *(a)* und dem Abschnitt der Niederschlagsbildung *(b)*. Der erste Abschnitt der Verdünnungskurve entspricht dem Zustand, in welchem noch kein Niederschlag gebildet wird. Der Schnittpunkt der Kurven bei V_1 zeigt den Beginn der Niederschlagsbildung an, während im Schnittpunkt V_2 die Auflösung des Niederschlags im Überschuß der Maßlösung beendet ist.

Der Kurvenabschnitt der Niederschlagsbildung entspricht dem gleichzeitigen Vorhandensein von Niederschlag und Lösung.

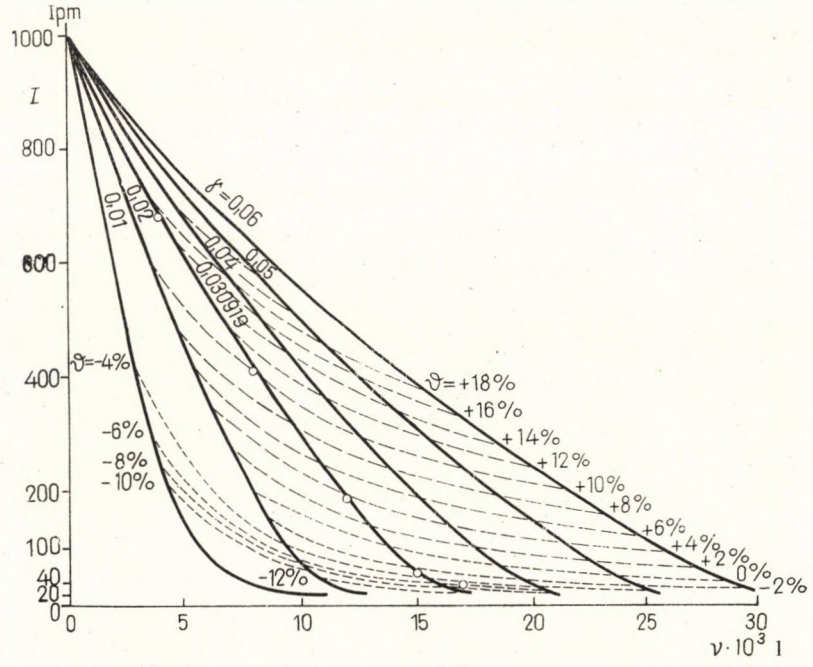


Abb. 3.8
Aktivitätskurven der Lösung als Funktion der zugegebenen Titriermittel-Menge und Kurven des theoretischen relativen Fehlers der Extrapolationsmethode (JESENÁK und TÖLGYESSY [44]). Die Kreise (o) zeigen die experimentellen Ergebnisse

Thus pyridine and arsenic trichloride form, by means of their induced dipoles, a bond between opposite charges, and after establishing the co-ordinate bond of the additive compound the chloride ion dissociates under the repelling effect of the negatively charged electron cloud of the nitrogen.

At this point a summary of the criteria used in Usanovich's acid-base concept seems desirable:

(a) Acid–base interaction may result other than from interaction between proton-containing substances. Proton-free acid–base equilibrium also exists.

(b) Compounds able to release cations or to take up anions may be regarded as acids. Compounds able to bind cations or release anions are bases.

(c) The acid–base function depends on the co-ordinative unsaturation of the atoms or ions in the chemical composition of the given compound.

(d) Acids are compounds in which co-ordinatively unsaturated electropositive atoms are present. *Lack* of co-ordinatively unsaturated electropositive atoms gives the compound a basic character.

(e) Since in the majority of compounds, co-ordinatively unsaturated atoms of both signs are both present, amphoterism can be considered to be a general property of polar compounds, though the amphoteric character does not exclude the predominance of either acidic or basic properties. The acidic or basic function depends on the co-reactant and the solvent.

From the above it must be concluded that acid–base concepts cannot be looked upon as a definitely settled problem. From the viewpoint of titrations in non-aqueous media, however, the development of acid–base concepts is of primary importance. In order to account for the phenomena observed with numerous compounds in the course of titrations in non-aqueous media, modern acid–base concepts are indispensable, even if the theoretical views are not unanimous.

Zur Ermittlung der Werte der verschiedenen Parameter für Fälle, in denen bestimmte Vereinfachungen der ursprünglichen Gleichung möglich sind, wurden die folgenden Symbole eingeführt [45, 105]:

$$\Gamma = \frac{\gamma_0}{c_0} \quad \text{und} \quad L = \frac{(L_{AB})^{\frac{1}{2}}}{c_0}, \tag{3.27}$$

mit denen die Gleichung

$$J^2\Gamma^2(1+V) + J\Gamma(V-\Gamma) - L^2(1+V) = 0 \tag{3.28}$$

aufgestellt werden kann.

Diese Gleichung wurde mit Hilfe des Elektronenrechners ZRA I für eine große Zahl der verschiedenen Parameter gelöst, wie z. B. für L von 10^{-1} bis 10^{-5}, für Γ von 1,00 bis 0,007 und für V von 2,00 bis 0,01.

Die zu diesen Daten gehörenden Werte von J und wurden nach (3.22) und (3.28) berechnet.

Aus den erhaltenen Ergebnissen (Abb. 3.11) geht hervor, daß die zu verschiedenen Γ-Werten gehörenden Kurven einander schneiden. Eine Auswertung der Titrationen kann dennoch nicht nur mit Hilfe eines einzigen Wertes der relativen Aktivität (J) vorgenommen werden. Weiter folgt, daß es für jeden Wert von V einen bestimmten Bereich von L-Werten gibt, bei

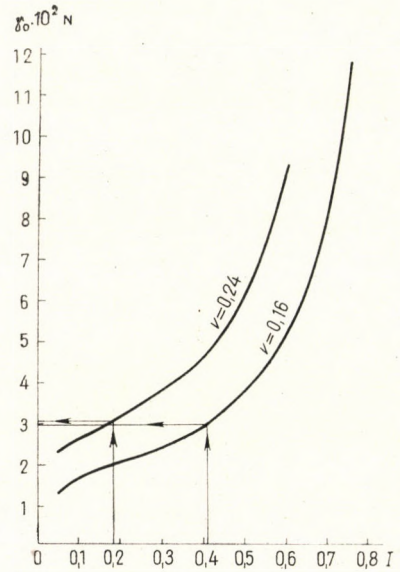


Abb. 3.9
Diagramm zur Auswertung der Titrationsergebnisse (JESENÁK und TÖLGYESSY [44])

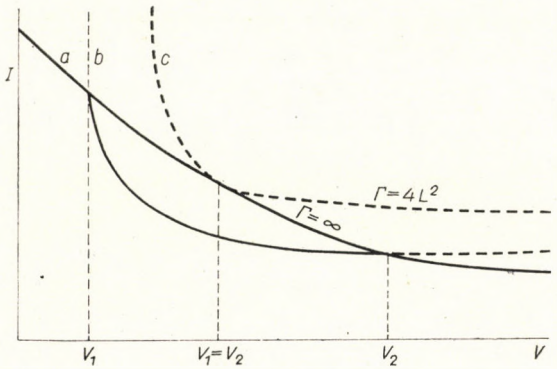


Abb. 3.10
Änderung der Aktivität der flüssigen Phase als Funktion der zugegebenen Titriermittel-Menge (TÖLGYESSY, JESENÁK und BRAUN [110])

Chapter 2

Strength of Acids

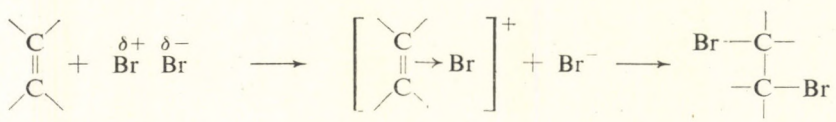
The 'strength' of acids is discussed in the relevant literature in detail, though a wholly satisfactory definition has not yet been given. The physico-chemical properties of acids are well known; the origin of these properties, however, is only partially known. The elucidation of the latter is the more difficult since in analytical and organic chemistry more and more solvents are available. For instance in titrations in non-aqueous media, nowadays, more than forty solvents are utilized.

In discussing titrations in non-aqueous media it seems advisable to obtain full details of the relative strengths of acids and bases, of their decrease or increase owing to the effect produced by the solvent and the titrant, and above all, of the effect of molecular structure. For this reason experiments to establish the order of the relative strength of acids are of invaluable importance, for instance, in the course of potentiometric titration on the basis of half-neutralization potential.

9. Ionization of Organic Compounds

The fission of compounds with covalent bonds into ions in non-aqueous media is now a familiar concept. Lapworth offered the opinion that most of the transformations in organic chemistry are preceded by slight electrolytic dissociation, that is, ionic intermediates arise. From many observations it can be concluded that some of the typical additive reactions of the olefinic bond are accomplished in two steps with the interposing of ionic intermediates (see: p. 206 in [653]).

The ionic intermediates can be considered as π-complexes, and in them the cationic part of the bromine dipole in the course of bromination is linked to the π-electronic system of the double bond [184]:



(cf. Chapter 27; Section 155).

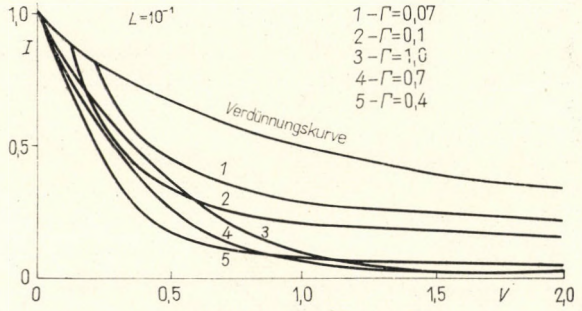


Abb. 3.11
Mit dem Elektronenrechner ZRA 1 erhaltene Titrationskurven (TÖLGYESSY, JESENÁK und BRAUN [110]).

denen die erhaltenen Daten auf Grund der nicht vereinfachten Gleichung berechnet werden müssen. Liegen die L-Werte hingegen unter bestimmten Grenzen, so können auch mehrere Titrationen mit ein und derselben Kurve ausgewertet werden, indem man ein bestimmtes Standard-Volumen des Titriermittels zugibt. Bei Serienbestimmungen ist es angezeigt, für die Auswertung der Messungen die für 2 oder 3 Standard-Werte von V aufgestellten Γ–J Kurven zu verwenden.

Beim Titrieren einer inaktiven Prüflösung mit einem markierten Titriermittel kann das zur Erreichung des Endpunktes notwendige Volumen der Maßlösung mit Hilfe der Gleichung (3.29) berechnet werden:

$$v_{ex} = \frac{v_1 I_2 - v_2 I_1}{I_2 - I_1} \tag{3.29}$$

Zuerst wird ein Überschuß der Maßlösung (v_1) zur Prüflösung zugegeben und die Aktivität des Reaktionsgemisches (I_1) bestimmt. Nach Zugabe einer zweiten Portion (v) der Maßlösung ($v_2 = v_1 + v$) wird die Aktivität des Systems (I_2) erneut gemessen.

Wird in diesem Fall die Extrapolationsmethode verwendet, so können gewisse Fehler auftreten. Es ist daher besser, zur Berechnung des Endpunktes zwei Werte zu nehmen, bei denen die relative Aktivität (J) nicht größer als 0,8 ist. Bei der Auswertung mit Hilfe von Gleichung (3.10) können genaue Ergebnisse erhalten werden [105].

Zur Endpunktbestimmung kann man auch auf folgende Weise vorgehen [61]: Man gibt eine überschüssige Menge der Maßlösung zum untersuchten System. Gleichzeitig wird das gleiche Volumen der markierten Titrierlösung auch zu einer aus destilliertem Wasser bestehenden Blindprobe zugegeben, d. h. man bestimmt die Aktivität der Maßlösung in der gleichen Verdünnung wie bei der Titration der Probe. Nachdem die Aktivitäten beider Lösungen bestimmt wurden, wird durch den Nullpunkt und den der Blindprobe entsprechenden Wert eine Gerade und parallel zu die-

Lewis and Langmuir showed that the covalent bond can be disrupted in two different ways, i. e. by forming ions of opposite charge (9.1), or two neutral radicals (9.2). The carbon atom is amphoteric: it may possess electrophilic, as well as nucleophilic properties. In liquid sulphur dioxide, hexaphenylethane splits into ions and the solution is, therefore, electrically conducting:

$$\underset{\text{Hexaphenylethane}}{(C_6H_5)_3C-C(C_6H_5)_3} \rightleftharpoons \underset{\substack{\text{Triphenylmethyl}\\\text{carbenium ion}}}{(C_6H_5)_3C^+} + \underset{\substack{\text{Triphenylmethyl}\\\text{carbanion}}}{(C_6H_5)_3C^-} \qquad (9.1)$$

Whereas in a non-ionizing solvent:

$$(C_6H_5)_3C-C(C_6H_5)_3 \rightleftharpoons \underset{\substack{\text{Triphenylmethyl}\\\text{radicals}}}{(C_6H_5)_3C\cdot} + \cdot C(C_6H_5)_3 \qquad (9.2)$$

From the viewpoint of acid–base interaction in triphenylmethane derivatives the carbinol bases, e.g. triphenylmethylcarbinol, are decidedly basic. With dry hydrogen chloride in benzene this gives a chloride:

$$(C_6H_5)_3C-OH + HCl = (C_6H_5)_3CCl + H_2O$$

Thus the reaction is similar to neutralization. The anionic character of the triphenylmethyl group is demonstrated by tetramethylammonium triphenylmethanate which as an electrolyte is ionized in all solvents:

$$(C_6H_5)_3C^- \ {}^+N(CH_3)_4$$

Conjugated organic compounds which conduct a current in solution in benzene containing trichloroacetic acid are also known, e.g. cyclopentadiene, β-carotene, vitamin A [861, 862].

The separation of ionic lattice-forming compounds into kinetically independent ions requires great energy which, at room-temperature, cannot result from thermal motion. The cause of the dissociation is that the ions interact with the solvent, when a considerable amount of energy is released.

Salts derived from organic cations or anions, in general, dissolve readily in organic solvents. (Thus, N-*o*-bromobenzyl-N-ethyl-N,N-dimethylammonium *p*-toluenesulphonate dissolves in dioxan; however, its tetraphenylborate does not [316].)

In a solvent with a small dielectric constant the effective size of the dissolved particles is generally greater than that of a simple solvated ion: the aggregates consist of a number of ions or of an ion and one or more un-ionized molecules.

In hydroxyl-containing solvents the formation of solvated ions is accompanied by that of oxonium ions (protolytic reaction):

$$HCl + CH_3OH \rightleftharpoons CH_3OH_2^+ + Cl^-$$

compare: $HCl + CH_3NH_2 \rightleftharpoons CH_3NH_3^+ + Cl^-$

ser eine zweite gezogen, die durch jenen Punkt geht, der dem im untersucht System gemessenen und auf das Gesamtvolumen der Lösung bezogenen Aktivitätswert entspricht. Der Schnittpunkt dieser Geraden mit der Abszisse gibt den Endpunkt an (Abb. 3.12).

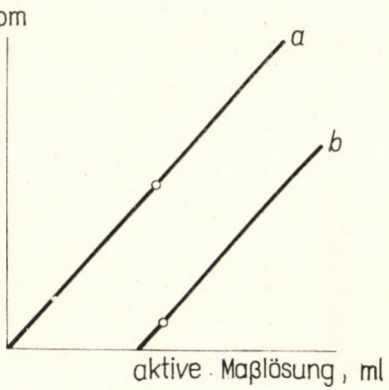


Abb. 3.12
Radiometrische Schnelltitration (*a* — Gerade der Verdünnung; *b* — mit überschüssigem Maßlösung erhaltene Gerade [61]).

Wird eine markierte Prüflösung mit einer gleichfalls markierten Maßlösung titriert, so kann der Endpunkt nach (3.21) oder (3.29) berechnet werden. Zu bemerken ist hierzu, daß man bei den so berechneten Werten einen nicht unerheblichen Fehler mit in Kauf nehmen muß. In der Praxis genügt es in den meisten Fällen, entweder die Maßlösung oder die Prüflösung zu markieren. Theoretisch ist auch die Markierung beider Lösungen möglich, nur wird dadurch die Auswertung erschwert.

3.4. Methoden der Abtrennung des Niederschlages und Technik der Titration

Radiometrische Titrationen können nur dann durchgeführt werden, wenn es gelingt, die verwendeten radioaktiven Reagenzien von den radioaktiven Reaktionsprodukten zu trennen. Diese Bedingung ist bei solchen Fällungsreaktionen erfüllt, bei denen der radioaktive Indikator aus der flüssigen in die feste Phase übergeführt wird. Zur Trennung der Phasen können die Filtration, Flotation oder das Zentrifugieren angewandt werden.

3.4.1. *Filtration*

Eines der am häufigsten verwendeten Verfahren der Phasentrennung ist die Filtration. Bei ihrer Anwendung können die Titrationen diskontinuierlich oder kontinuierlich durchgeführt werden.

3.4.1.1. *Diskontinuierliche Titration*

In den einfachsten Fällen kann man die gebildeten Niederschläge durch Filtration über ein Filterpapier aus der Lösung entfernen. Dieses Verfahrens haben sich z. B. MOELLER, TERRIL und SEAL [80] bei der Bestimmung von Chlorid in Wasser bedient.

The differences between organic and inorganic ionic reactions are not sharp, but show gradation [263]. The generation of intermediates by rupture of covalent bonds is sometimes a slow process. 'Acidic hydrogen' (ionizable hydrogen), characteristic of proton-donor acids, is essentially identical with the 'active hydrogen' of organic chemistry, though with the limitation that acidity is a favourable case for the mobility of the hydrogen; the value of the pK_{acid} may be as high as 30, but in such cases, the hydrogen atom is only slightly active:

Trichloroacetic acid	pK_{acid}	0·9
Phenol	pK_{acid}	9·9
α-Glucose [582]	pK_{acid}	12·44
Phenylacetylene	pK_{acid}	21
Triphenylmethane	pK_{acid}	33

By convention, the border between acidic hydrogen and active hydrogen has, from the empirical view-point, a pK_{acid} value of 10–12.

For the experimental determination of active hydrogen it is important that the reaction used should be irreversible. For other reasons, however, the determination of active hydrogen is a problem requiring great care (see: Chapter 19).

10. Hydrogen-containing Acids

The strength of hydrogen-containing acids is determined by their proton-donor capability; that of bases by their proton-accepting capability. Thus, for the determination of the degree of proton transfer one must take into account the interaction of two particles (the term 'particle' in this case meaning a kinetically independent molecule, atom or ion). The extent of proton transfer has, therefore, less importance. According to Fajans the solvation heat of a free proton is 232 kcal. per gram-atom [221]. Therefore, the ionization of an acid cannot be considered as proton 'emission' because it only takes place in the presence of a proton-acceptor base. The proton affinity of the latter, however, decreases with increasing number of free electron pairs; the stability of the completed octet causes an abrupt disappearance of proton affinity:

$$|\overline{CH_3}^- > |\overline{NH_2}^- > |\overline{\underline{O}H}^- > |\overline{\underline{F}}|^-$$

At the same time the proton affinity (base strength) also decreases in the following order:

$$O^{2-} > OH^- > OH_2 > OH_3^+ > OH_4^{2+}$$

The inherent acid and base strengths of acids and bases cannot be measured directly but can be determined only by comparison: (1) by interposition of a solvent capable of autoprotolysis; (2) in a neutral, proton-free solvent, when the addition of a reference acid or base is necessary, e.g. for the determination of the relative strengths of aromatic acids in benzene solution the reference base may be diphenylguanidine [173]; and (3) in the gaseous state; e.g. interaction of trimethylborane and trimethylamine (Lewis acid and base).

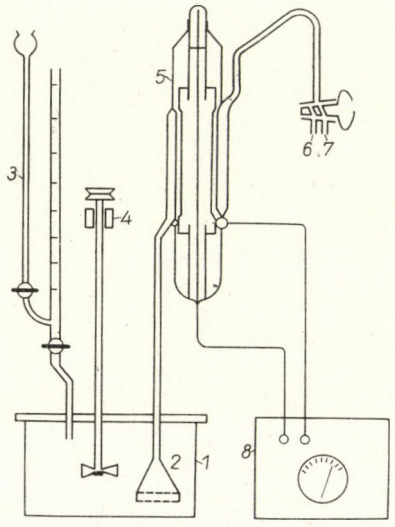


Abb. 3.13
Apparat für radiometrische Titrationen, nach LANGER (*1* — Titrationsgefäß; *2* — Saugvorrichtung; *3* — Bürette; *4* — Rührer; *5* — GM-Zähler für Flüssigkeiten; *6* — Lüftung; *7* — zur Pumpe; *8* — Impulszähler [58])

Eine geeignete Filtrationsvorrichtung hat LANGER [57, 58] beschrieben (Abb. 3.13). Bei den mit ihrer Hilfe durchgeführten Titrationen wird ein bestimmtes Volumen der Maßlösung zur Prüflösung zugegeben. Danach wird die flüssige Phase des Reaktionsgemisches in den Glasmantel eines GM-Zählrohres gesaugt und ihre Aktivität gemessen. Nach Rücklauf der Lösung in das Maßlösung ist eine weitere Portion der Titrierflüssigkeit zuzusetzen, und der Vorgang zu wiederholen.

Die in Abb. 3.14 gezeigte Vorrichtung verwendeten POLEWAJA, TSCHERNOWA und MIRKINA [85], während SIROTINA und ALIMARIN [94] mit der in Abb. 3.15 veranschaulichten Versuchsanordnung arbeiteten.

Die Verfasser selbst haben eine Vorrichtung zusammengestellt [101], die in Abb. 3.16 (Schema) bzw. 3.17 und 3.18 gezeigt ist.

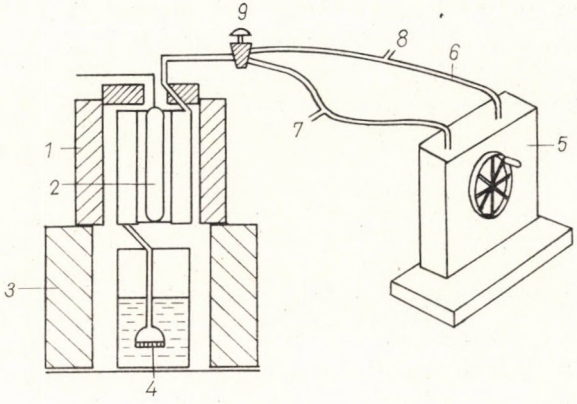


Abb. 3.14
Apparat für radiometrische Titrationen (POLEWAJA, TSCHERNOWA und MIRKINA [85]). (*1* und *3* — Bleiturm; *2* — GM-Zähler; *4* — Filter; *5* — mechanische Saugvorrichtung; *6* — Gummischlauch; *7*, *8* und *9* — Dreiweghähne)

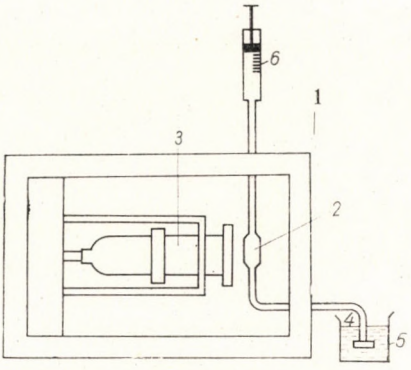


Abb. 3.15
Vorrichtung für radiometrische Titrationen (SIROTINA und ALIMARIN [94]). (*1* — Bleimantel; *2* — Glasbehälter; *3* — GM-Endfensterzählrohr; *4* — Filterscheibe; *5* — Titrationsgefäß; *6* — Spritze)

Ratios denoting the relative strengths of acids and bases: pK, H_0, H_+, H_-, PA* are founded on experiments with solvents most of which are liable to self-ionization.

11. Proton-transfer and Proton-transfer Energy

In Gutmann and Lindqvist's acid–base theory, in solvents liable to autoprotolysis the acidic character is the result of interaction between the solvent molecule and the dissolved acid molecule when, during the partial dissociation of the acid, ion transfer (proton transfer) ensues between the two interacting particles [295, 296].

(a) *Proton-transfer energy.* The energy necessary for the proton transfer (J) may define the acid effect and its strength (see: pp. 34, 64 and 105, in [294]; [544, 614]). When an acid AH is dissolved in a solvent capable of autoprotolysis there are two possibilities for the transfer of protons: between the solvent molecules, and between the acid and the solvent:

$$2\,s\mathrm{H} \rightleftarrows s\mathrm{H}_2^+ + s^-, \quad \text{or} \quad A\mathrm{H} + s\mathrm{H} \rightleftarrows A^- + s\mathrm{H}_2^+.$$

The probability of proton transfer from an acid molecule AH to a solvent molecule sH is proportional to

$$\exp(-J/kT),$$

where J = the proton-transfer energy
k = the Boltzmann constant
T = the absolute temperature.

The proton-transfer energy is given by

$$J = (-kT \times \log K_a) + (kT \times \log M)$$

where K_a = the Brönsted acid constant
M = the number of moles of solute in 1,000 g of solvent.

If the energy required for the proton transfer between dissolved acid and solvent is greater than that for transfer between the solvent molecules, $J \geqq J_\sigma$, then the $s\mathrm{H}_2^+$ concentration of the solvent cation in the solvent does not increase, and, therefore, the acid character of AH remains latent.

* pK_{acid} and pK_{base} are exponents of the acid and base dissociation constant, where $pK_{acid} = -\log K_{acid}$.

Hammett's acidity function, H_0, H_+, H_-, is the degree of a solvent's proton-donor capability towards electrically neutral, positively and negatively charged indicators. Izmaĭlov's universal acidity scale gives:

$$PA = -\log M_{\gamma\gamma_0}$$

where M = the concentration of the solution
γ = the activity coefficient of infinitely dilute water-free solution
γ_0 = quotient of the activity coefficient of the former and its aqueous solution [76, 179, 342, 413, 625].

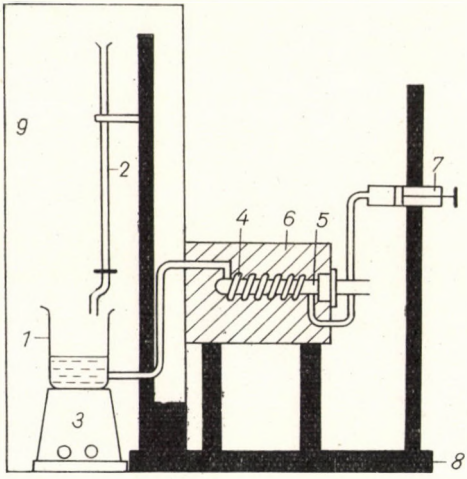


Abb. 3.16
Schema des radiometrischen Titrationsapparates nach TÖLGYESSY [101]

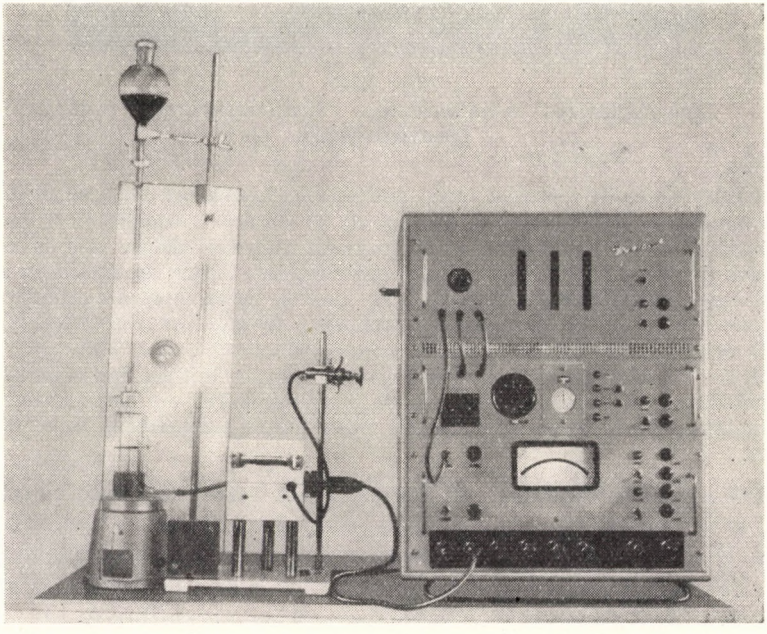


Abb. 3.17
Radiometrischer Titrationsapparat nach TÖLGYESSY [101]

On the other hand, if $J \leqq 0$, then in a given solvent the AH molecule will behave like a strong acid. The closer Gurney's acid function $X = 1 - J/J_\sigma$ approaches unity, the stronger the acid, and when the acid is very weak this function tends to zero.

Proton-transfer energy consists of two parts: (1) an intrinsic, specific part, and (2) one manifesting itself after dissociation in the course of various interactions with the solvent (dipole-interaction, H-bonding, dielectric constant effect, etc.). The first part depends only on the difference between the lowest quantum energy level of the ion (or molecule) before and after the proton transfer ('intrinsic' proton transfer) while the part based on interaction of the proton-transfer energy greatly depends on solvation. The equilibrium constant depends on whether the two parts have the same or opposed signs.

The division of proton transfer energy into two components is related to the grouping of hydrogen acids into *ionogen* type acids and *isoion* type acids [218]. Following proton transfer the number of charged particles in ionogenic acids increases, while that in isoionic acids remains unchanged before and after the interaction. In the latter case the proton-transfer energy, founded on solvent-soqute interaction, is smaller:

$$J = J_1 + J_2 ,$$

where J_1 = the 'intrinsic' proton transfer, independent of the temperature
J_2 = the result of various electrostatic interactions ('énergie interactionelle') deriving from particles after the proton transfer [545].

This depends on the temperature and is not a simple function of the dielectric constant of the solvent.

The weakness of the energy part (J_2) due to electrostatic interaction is characteristic of *isoionic* acids because, from the aspect of solvent-solute interaction, the condition *after* proton transfer has not undergone a considerable change in comparison with that before proton transfer. Therefore, the K_{acid} values of the isoionic and ionogenic acids change differently as a function of change in temperature.

(b) *The mechanism of proton transfer* is roughly as follows [546]: the transfer between the acid molecule and the solvent molecule begins with the formation of a hydrogen bond: $AH \ldots sH$. The migration of the proton proceeds in the $(AH \ldots sH)_{solv}$ complex until the H-bond ceases to exist. The dipole interaction of the $(AH \ldots sH)$ and the nascent $(A^-. sH_2^+)$ associations with the solvent is complex. The dissociation of the $(A^-. sH_2^+)_{solv}$ complex begins with the gradual separation of the particles and with solvation progressing, while $(A^-)_{solv}$ and $(sH_2^+)_{solv}$ arise:

where AH = the proton-containing acid
sH = the proton-containing solvent
A^- = the anion
sH_2^+ = the solvent-cation.

(c) *Types of proton transfer* [294, 887]:

1. $AH + B \rightleftarrows A^- + (BH)^+$.

Example:

$$HClO_4 + CH_3COOH \rightleftarrows ClO_4^- + CH_3COOH_2^+$$

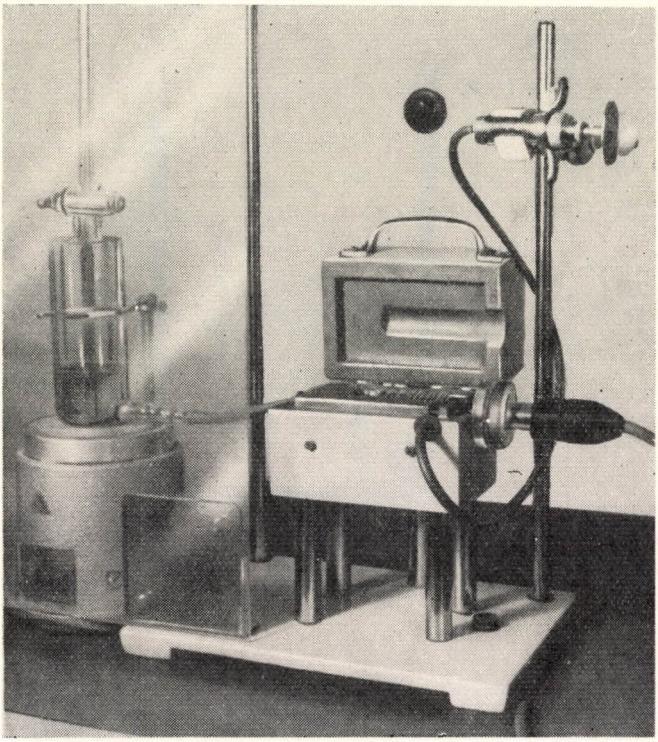


Abb. 3.18
Teilansicht des radiometrischen Titrationsapparats nach TÖLGYESSY [101]

Der GM-Zähler ist von einer innen mit Silicon überzogenen Glasrohrspirale *(4)* von 3 mm lichter Weite umgeben. Die Spirale ist mit dem Titriergefäß *(1)* und der Injektionsspritze *(7)* verbunden. Glasrohrspirale und GM-Zähler sind in einem Bleiblock *(6)* mit seitlichem Zugang untergebracht. Das Gestell des Bleiblocks sowie zwei Ständer, an denen die Mikrobürette *(2)* und die Injektionsspritze befestigt werden können, sind auf die gemeinsame Bodenplatte *(8)* montiert. Eine Schutzscheibe aus Plexiglas *(9)* ist vor der Titriereinrichtung angebracht. Das Titriergefäß faßt 150 ml. Ein mit einer Filterplatte versehenes Glasrohr, das mit der Spirale über einen Gummischlauch in Verbindung steht, ist in den unteren Teil des Titriergefäßes eingeschmolzen. Die Titration wird auf die oben bereits beschriebene Weise durchgeführt.

Wenn ein Gammastrahler als Indikator im Titrationsprozeß eingesetzt wird, so verwendet man zur Aktivitätsmessung vorzugsweise Szintillationszähler. Die schematische Darstellung einer solchen Versuchsanordnung zeigt Abb. 3.19 [81]. Die überstehende Lösung wird in eine Proberöhre gesaugt, die in der Meßöffnung eines Szintillationszählers untergebracht ist.

AYLWARD und Mitarb. [12] haben die im allgemeinen für amperometrische Titrationen verwendete Anordnung modifiziert und den radiometrischen

2. $(AH)^+ + B \rightleftarrows A + (BH)^+$

Example:

$$CH_3COOH_2^+ + R_3N \rightleftarrows CH_3COOH + R_3NH^+$$

3. $(AH)^- + B \rightleftarrows (BH)^+ + A^{2-}$

Example:

$$CH_2(COOH)COO^- + H_2NCH_2CH_2NH_2 \rightleftarrows CH_2(COO^-)_2^+ + [H_2NCH_2CH_2NH_3^+]$$

4. $AH + B^- \rightleftarrows A^- + BH$

Example:

$$C_6H_5COOH + CH_3O^- \rightleftarrows C_6H_5COO^- + CH_3OH$$

12. Acid–Base Dissociation Constants

In Brönsted and Lowry's protonic concept, acids are proton-donors and bases are proton-acceptors:

$$\text{Acid} \rightleftarrows \text{Base} + \text{Proton}$$

$$AH \rightleftarrows A^- + H^+$$

For proton transfer, however, the presence of a proton-acceptor base is indispensable. A solvent molecule capable of both receiving protons as well as releasing them, may act as a proton acceptor base. Such amphiprotic solvents, bearing the symbol sH, may be water, alcohols, carboxylic acids (formic acid, acetic acid, propionic acid):

$$AH + sH \rightleftarrows A^- + sH_2^+ \tag{12.1}$$

where sH_2^+ = the lyonium ion, formed in the course of proton acceptance, that is the solvated proton. The state of equilibrium is determined by the relative basicity of the sH and the A^- molecule or ion. The mass action law may be written for the state of equilibrium:

$$K = \frac{[A^-]\,[sH_2^+]}{[AH]\,[sH]}$$

Since in dilute solutions the quantity of the solvent can be considered to be practically constant, the dissociation constant of the acid AH may be written:

$$K_{\text{acid}} = \frac{[A^-]\,[sH_2^+]}{[AH]} \tag{12.2}$$

Acids whose equilibrium according to Eq. (12.1) is shifted considerably to the right are strong acids and at first approximation the acid constant is proportional to the basicity of the solvent. However, numerous other factors influence the equilibrium and there is no solvent which differs from water by its basicity alone.

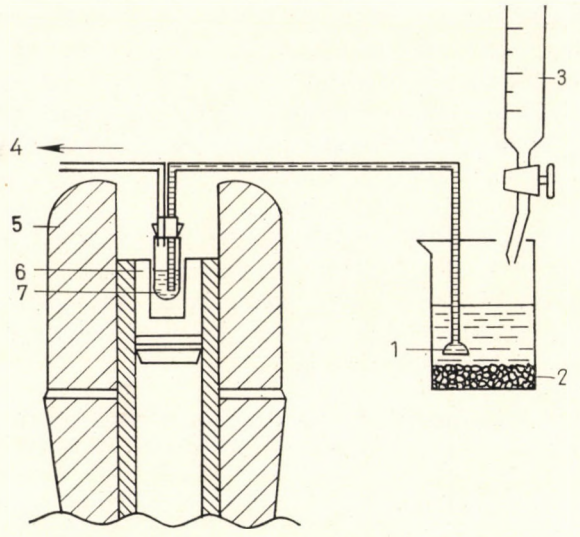


Abb. 3.19
Bei radiometrischen Titrationen angewandter hülsenförmiger Szintillator (Nuclear Chicago Corp. [81]). (*1* — Filter; *2* — Titrationsgefäß; *3* — Bürette; *4* — zur Pumpe; *5* — Bleiturm; *6* — Szintillator; *7* — flüssige Phase)

Titrationsbedingungen angepaßt. An Stelle der Quecksilbertropfelektrode tritt eine Filterröhre. Zur Bestimmung von Cu^{2+} mit ^3H-markierter Anthranilsäure wurde die markierte Maßlösung aus einer Mikrobürette in Portionen von 0,2–0,4 ml zugegeben. 3–5 mg der vom Niederschlag mit Hilfe der Filterröhre getrennten Lösung wurden in gewogene Ampullen übergeführt und die ^3H-Aktivitäten mit einer modifizierten [33] Wilzbach-Methode [121] gemessen.

Bei dieser Titrationstechnik kommt es durch die Zugabe der Maßlösung zu Volumenänderungen. Die gemessenen Aktivitäten müssen daher mit einem Korrektionsfaktor (3.30) korrigiert werden:

$$k = \frac{v_0 + v}{v_0} \tag{3.30}$$

Ein großer Nachteil der Filtrationsmethode liegt in der häufigen Verstopfung der Filter. Die Filtrationsdauer wird dadurch verlängert und ein häufiger Wechsel der Filterplatten notwendig.

3.4.1.2. *Kontinuierliche, automatische Titration*

Mit der Frage der Automatisierung der radiometrischen Fällungstitrationen haben sich bereits mehrere Autoren beschäftigt [27, 101, 112, 113].

An equilibrium constant similar to Eq. (12.2) can be also written for other conjugate acid–base systems. For instance, in the case of the charged A^- acceptor-base (e.g. benzoate anion) which co-ordinates a proton, the following interaction with a proton donor molecule leading to equilibrium can be written:

$$A^- + s\mathrm{H} \rightleftarrows A\mathrm{H} + s^-$$

where s^- may represent OH^-, CH_3O^-, CH_3COO^- ion, etc. (lyate ion). In this case the basicity constant is

$$K_{\text{base}} = \frac{[A\mathrm{H}]\,[s^-]}{[A^-]} \tag{12.3}$$

and, rearranged:

$$[A\mathrm{H}] = \frac{K_{\text{base}} \times [A^-]}{[s^-]} \tag{12.4}$$

The following relationship between the acid constant and base constant of the conjugated acid–base system becomes evident when the value corresponding to $[A\mathrm{H}]$ is substituted into Eq. (12.2):

$$K_{\text{acid}} = \frac{[s\mathrm{H}_2^+]\,[s^-]}{K_{\text{base}}} \tag{12.5}$$

In the case of water the product

$$[s\mathrm{H}_2^+] \times [s^-]$$

is the ionic product of water. Generalized for solvent molecules capable of prototropic interaction this can be denoted by:

$$[s\mathrm{H}_2^+] \times [s^-] = K_{\text{auto}} = K_{\text{acid}} \times K_{\text{base}} \tag{12.6}$$

and

$$K_{\text{base}} = \frac{K_{\text{auto}}}{K_{\text{acid}}}$$

Instead of K_{acid} and K_{base}, on the analogy of pH, the values of pK_{acid} and pK_{base} are much used, that is, the negative decadic logarithm of K_{acid} and K_{base} ($pK = -\log K$). In the case of water

$$pK_{\mathrm{H_2O}} = pK_{\text{acid}} + pK_{\text{base}}$$

or

$$pK_{\text{acid}} = 14 - pK_{\text{base}}$$

The autoprotolysis constant of acetic acid is:

$$K_{\text{auto}} = [\mathrm{CH_3COOH_2^+}]\,[\mathrm{CH_3COO^-}] = 2{\cdot}5 \times 10^{-13}$$ [677], see also: [102].

Eq. (12.6) illustrates the dependence of the acid and base constant on the autoprotolysis of the solvent. In 0·1 M acetic acid solution, theoretically the highest

Die erste Apparatur haben DUNCAN und THOMAS konstruiert [27]. Die Vorrichtung, die zur Durchführung von radiometrischen Titrationen mit Lösungsmittelextraktion mehrfach geändert wurde (vgl. Abb. 4.17 in Kapitel 4.2), ist auch für kontinuierliche Fällungstitrationen geeignet. Die genannten Autoren haben jedoch nur eine Skizze der empfohlenen Apparatur ohne ausführliche Beschreibung der Arbeitsweise oder der experimentellen Ergebnisse veröffentlicht.

TÖLGYESSY und ŠAJTER [101, 112] entwickelten eine Arbeitsmethode und einen Titrator, mit dem das Titriermittel automatisch dosiert und die Titrationskurve automatisch registriert werden kann. Die Arbeitsweise der Anordnung geht aus dem in Abb. 3.20 dargestellten Schema hervor, während Abb. 3.21 ihre Photographie zeigt.

Das mit der zu bestimmenden Komponente einen schwer löslichen Niederschlag liefernde Maßlösung wird mit konstanter Geschwindigkeit zur Prüflösung gegeben. Die mit Hilfe eines im Titriergefäß befindlichen Filters vom Niederschlag befreite Lösung wird mit einer Mikropumpe in dauernder Zirkulation gehalten. Die Lösung durchströmt dabei den Glasmantel eines GM-Zählers und gelangt von hier zurück in das Titriergefäß. Der Zähler ist mit einem Ratemeter verbunden. Eine Schreibvorrichtung registriert kontinuierlich die durch das Ratemeter angezeigte Aktivität.

Die registrierten Titrationskurven können nach zwei verschiedenen Methoden ausgewertet werden:

(a) Durch Bestimmung des Volumens eines Tropfens der Maßlösung und der Geschwindigkeit ihrer Zugabe.

(b) Durch Vergleich der erhaltenen Titrationskurve mit der Kurve eines Standards.

Bei der Auswertung der Titrationskurven nach (a) wird der Abstand zwischen dem Beginn der Zugabe der Maßlösung und dem Schnittpunkt der linearen Abschnitte der Kurve gemessen. Häufiger bedient man sich der zweiten Methode (b). In diesem Falle ist es nicht notwendig, die Konzentration der Maßlösung genau zu kennen. Die Vorrichtung wird mit Hilfe einer Probe von genau bekannter Konzentration geeicht. Bei den nachfolgenden, unter gleichen Bedingungen durchgeführten Bestimmungen ist es auf Grund der Proportionalität zwischen Punktabständen der Kurve und dem Gewicht des zu bestimmenden Stoffes einfach möglich, die unbekannte Konzentration zu berechnen.

An anderer Stelle [101, 113] berichten die gleichen Autoren über eine Methode, mit der automatische radiometrische Titrationen bis zum Endpunkt geführt werden können. Dieses Verfahren ist in erster Linie zur serienmäßigen Durchführung von Bestimmungen annähernd gleicher Stoffmengen geeignet. Zuerst wird mit einer hierzu geeigneten, charakteristischen Probe die ganze Titrationskurve aufgenommen, um die Radioaktivität der überstehenden Lösung im Endpunkt festzustellen. Die Titriertechnik ist im wesentlichen die gleiche, wie bei der oben beschriebenen automatischen Registrierung der Titrationskurven. Der einzige Unterschied liegt in der Messung der Radioaktivität der Lösung im Endpunkt. Beim Titrationsprozeß wird die zwischen der Zugabe der ersten Dosis des Titriermittels und der Erreichung des Endpunktes verstrichene Zeit mit einer elektrischen Stoppuhr gemessen, die mit Hilfe eines Ratemeters automatisch in Gang

lyonium ion concentration formed from a strong acid is 0·1 and the lowest, when a strong base is dissolved, may be $2{\cdot}5 \times 10^{-12}$. The concentration of the lyonium ion is similarly limited in formic acid to the range 0·1 to 6×10^{-6}, and in ethanol from 0·1 to 8×10^{-19}. The autoprotolysis constants of some solvents are:

Solvent	*Lyonium Ion*	*Lyate Ion*	pK_{auto}	*Reference*
Acetonitrile	$(CH_3CNH)^+$	CH_2CN^-	19·5	[689]
Sulphuric acid	$H_3SO_4^+$	HSO_4^-	3·0	[342]
Formic acid	$H.COOH_2^+$	$H.COO^-$	6·2	[343]
Acetic acid	$CH_3COOH_2^+$	CH_3COO^-	12·6	[677]
Methanol	$CH_3OH_2^+$	CH_3O^-	16·7	[342]
Ethanol	$C_2H_5OH_2^+$	$C_2H_5O^-$	19·1	[677]
Ammonia*	NH_4^+	NH_2^-	22	[677]

* at −33·4°C

Proton transfer tends to be towards the free electron pair of the dissolved base when proton acceptor bases (e.g. aniline) are dissolved in ampholytic solvents (e.g. acetic acid). The dissociation equilibrium may be represented by the following reaction:

$$B + s\mathrm{H} \rightleftarrows B\mathrm{H}^+ + s^-$$

and its dissociation constant by

$$K_{\text{base}} = \frac{[B\mathrm{H}^+]\,[s^-]}{[B]} \tag{12.7}$$

where s^- is e.g. the acetate ion.

Thus, in the course of proton acceptance a new acid is formed: the 'onium ion corresponding to the base being the stronger donor-acid, the weaker the corresponding acceptor base. The following relation shows the proton donor role of the 'onium ion (cationic acid):

$$B\mathrm{H}^+ + s\mathrm{H} \rightleftarrows B + s\mathrm{H}_2^+$$

$$K_{\text{acid}} = K_{B\mathrm{H}^+} = \frac{[s\mathrm{H}_2^+]\,[B]}{[B\mathrm{H}^+]} \tag{12.8}$$

where $s\mathrm{H}_2^+$ may represent the acetacidium ion and $s\mathrm{H}$ is acetic acid.

Table 4 (p. 61) gives information on the correlations between various notations such as K, pK, $K_{B\mathrm{H}^+}$, $pK_{B\mathrm{H}^+}$

Similar correlations as between Eqs. (12.2), (12.3), (12.7) and (12.8) are valid for any other ampholytic solvent, but the value of K_{auto} changes from solvent to solvent.

In the case of inert, aprotic solvents the above correlations do not hold (see: Section 16).

In non-aqueous media a factor must be taken into consideration which, in aqueous media, is of secondary importance, and that is the tendency of solvated ions to associate to form ion pairs and larger aggregates, especially in solvents with low dielectric constants. In this type of solvent ionic dissociation becomes insignificant compared with formation of ion pairs.

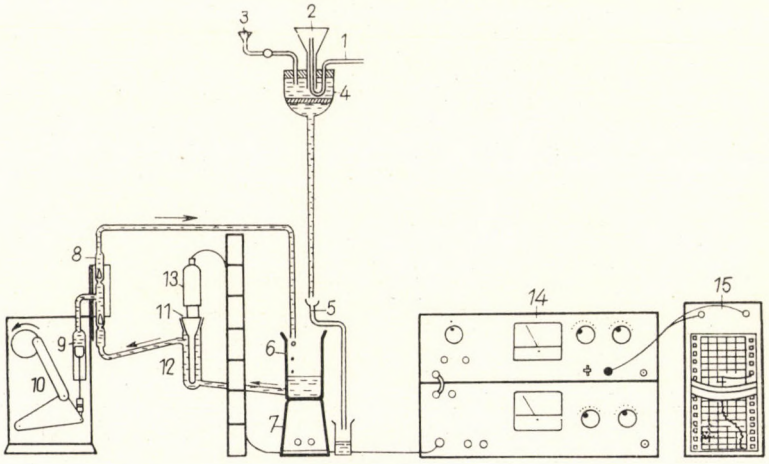


Abb. 3.20
Schema der automatischen Titrationsvorrichtung (TÖLGYESSY und ŠAJTER [112]). (*1* — Hilfsröhre, verbunden mit Saugvorrichtung, zum Auffüllen des Reservebehälters; *2* — Reservebehälter; *3* — Trichter; *4* — Behälter; *5* — Ausflußröhre; *6* — Titrationsgefäß mit eingebauter Glasfritte; *7* — elektromagnetischer Rührer; *8* — Quecksilber-Ventil; *9* — Injektionsspritze; *10* — Elektromotor mit Gelenk-Transmission; *11* — GM-Zähler; *12* — Glasmantel; *13* — Verstärkerkopf; *14* — Ratemeter mit Hochspannungs-Stromquelle; *15* — Registriergerät)

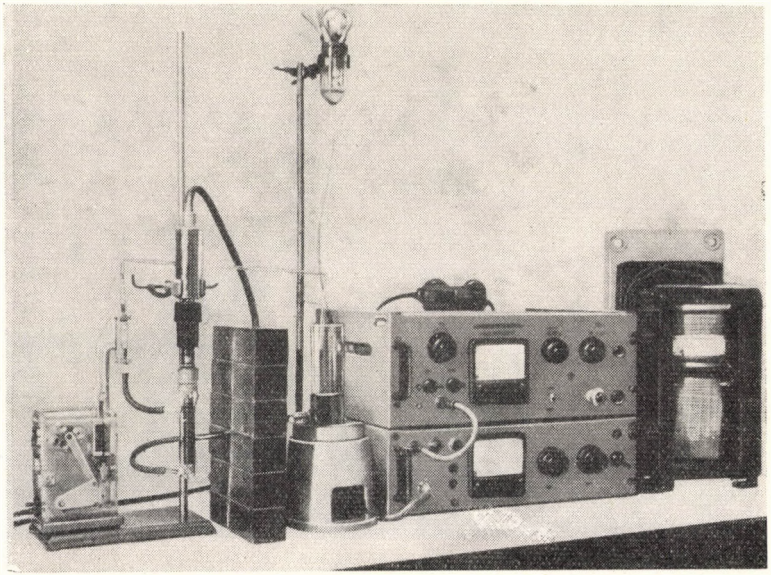


Abb. 3.21
Automatische Vorrichtung zur radiometrischen Titration (TÖLGYESSY und ŠAJTER [112])

In general, the K_{acid} value of acids depends on both the proton donor ability inherent in the acid, as well as on the proton acceptor ability of the solvent; e.g. in acetic acid K_{acid} cannot be considered as an absolute value of acid strength.

Besides the acid strength, the 'acidity' of the solution must also be taken into consideration. That is, the ionization of a given acid does not necessarily conform to the 'acidity' of its solution [350]. In the former example the acidity of the solution depends on the proton donor ability of the lyonium ion, in this case that of the acetacidium ion. If the solvent is changed, and e.g. isopropanol is used instead of acetic acid, not only does the value of K_{acid} change but so also does the 'acidity' of the solution. The proton donor ability of the acetacidium ion surpasses considerably that of the $(CH_3)_2CHOH_2^+$ ion.

Isopropanol possesses a greater basicity than acetic acid, and its dielectric constant is also twice that of latter; therefore, perchloric acid dissociates in isopropanol more readily, yet the 'acidity' of the acetic acid–perchloric acid solution is greater because of the greater proton-donor tendency of the acetacidium ion.

The absolute strength of acids and bases cannot be determined in solvents liable to autoprotolysis. In fact, even the relative order of their strength can only be established approximately by the use of equations. The strength of acids and bases depends not only on the strength of the reference base or acid but also on the dielectric constant of the medium, the autoprotolytic constant, and on less closely definable specific interactions.

13. Effect of Solvents on the Strength of Acids

In a proton-containing solvent the relative strength of acids depends on the solvent; the latter determining the energy required to remove a proton from a molecule or an ion to infinity [546]. The role of the solvent, however, is not a passive one. The acid and base character is closely related to the interaction of solute and solvent

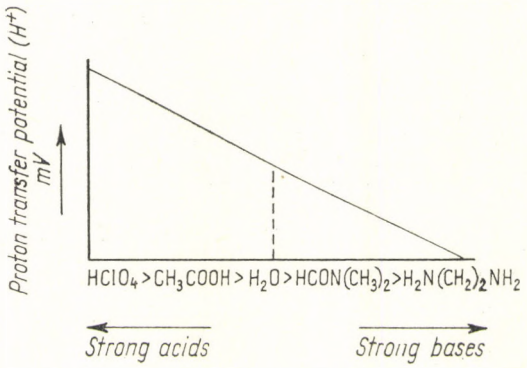


Fig. 1

[295, 296]. The effect of the solvent is due to its dielectric constant and prototropic property. *As a consequence the order of strengths of acids (and bases) can vary according to the solvent.*

The free energy of acids (and bases) varies from solvent to solvent, thus, the relative strengths of acids (and bases) in different solvents are not always the same [88, 103, 172, 763]. For instance, in chloroform and chlorobenzene the tertiary

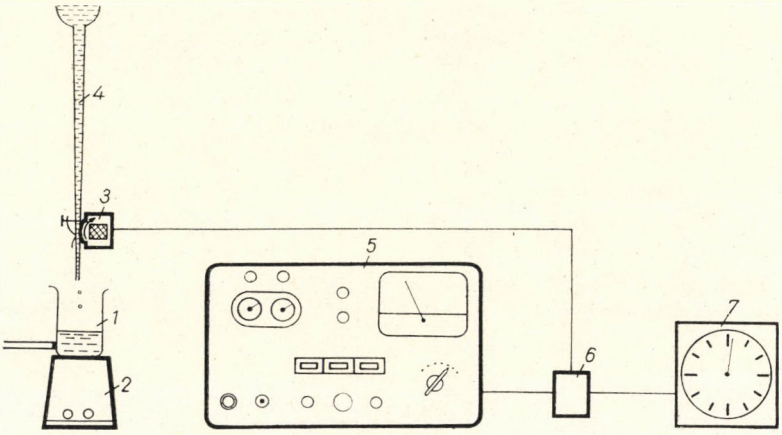


Abb. 3.22
Schema der radiometrischen Titrationsvorrichtung für die Durchführung von radiometrischen Titrationen bis zum Endpunkt (TÖLGYESSY und ŠAJTER [113]). (*1* — Titrationsgefäß; *2* — elektromagnetischer Rührer; *3* — elektromagnetisches Ventil; *4* — Polyäthylen-Röhre; *5* — Ratemeter; *6* — Relais; *7* — elektrische Stoppuhr)

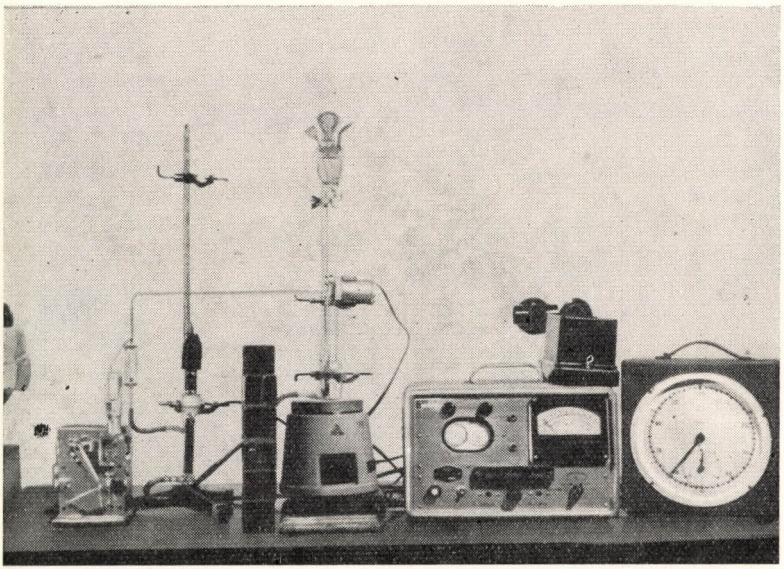


Abb. 3.23
Automatischer Apparat für die Durchführung von radiometrischen Titrationen bis zum Endpunkt (TÖLGYESSY und ŠAJTER [113])

amines are stronger, while in n-heptane, benzene and 1,4-dioxan the secondary amines are the stronger bases [849].

In a prototropic solvent the transporting phenomenon of neutralization is proton transfer (migration of protons). The proton-donor readiness of molecules and ions of acid type and the proton co-ordinating tendency of molecules of basic type are related to their molecular structure. In a given solvent the proton-donor or proton-

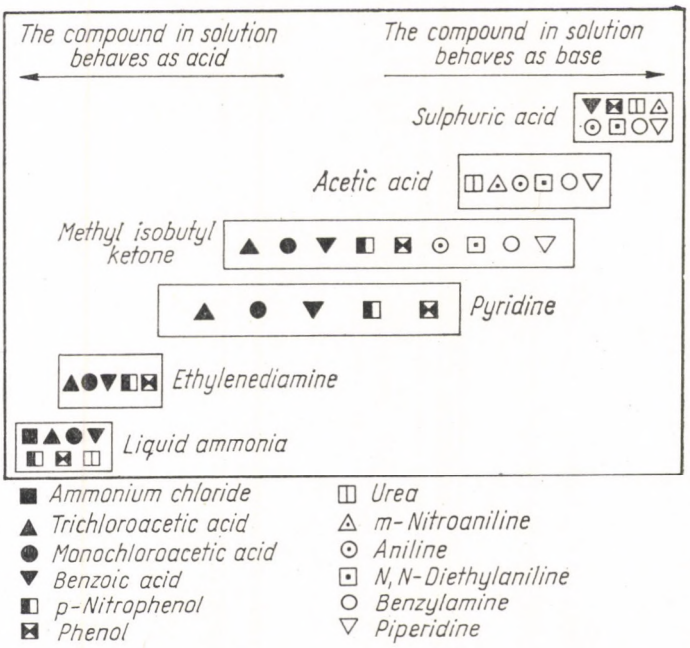


Fig. 2. Characteristic features of acids and bases (idealized scheme)

acceptor ability of polarized molecules decreases continuously from the strongest acid to the strongest base. Thus, an acidity scale results as a function of the proton transfer potential, comparable with the redox scale. In Fig. 1, by convention, water is the neutral compound: on the left of the figure the compounds act as proton donors towards those on the right-hand side with more efficiency, the further they are from each other, that is, the greater their proton transfer potential (cf. [847]). Perchloric acid is a strong acid in acetic acid but it is a still stronger acid in water; with perchloric acid, water behaves like a base; on the other hand, ethylenediamine forms an 'onium ion in water i.e. it is a proton acceptor.

The ability of molecules and ions to act as acids or bases depending on their structure is related to their 'intrinsic polarity'. Each solvent reveals the 'intrinsic polarity' of the dissolved molecule with a different efficiency. Monochloroacetic acid is a strong acid in pyridine but in acetic acid it no longer possesses acidic properties. Methylurea and guanidine behave in sulphuric acid as bases, but in liquid ammonia as acids (Fig. 2).

The order of relative acid strength of some compounds and ions in liquid ammonia [864] is as follows:

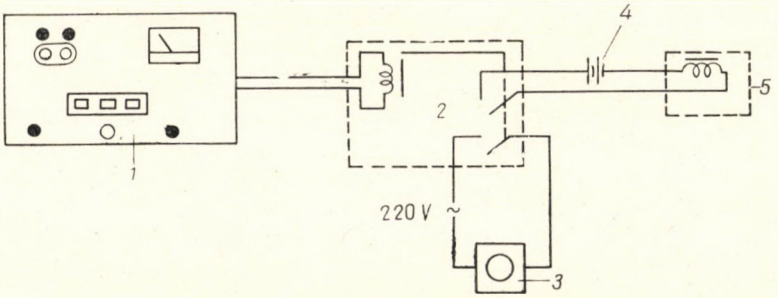


Abb. 3.24
Stromkreise der in Abb. 3.22 bzw. 3.23 gezeigten Vorrichtung (TÖLGYESSY und ŠAJTER [113]). (*1* — Ratemeter sowjetischer Herkunft, Typ TISS; *2* — elektromagnetisches Ventil; *3* — elektrische Stoppuhr; *4* — 24-V-Batterie; *5* — Relais

gesetzt und angehalten wird. Auf ähnliche Weise wird auch die Zugabe der Maßlösung geregelt. Sobald die Radioaktivität der überstehenden Lösung auf den am Ratemeter vorher eingestellten Endpunkt-Wert sinkt, wird die Zugabe der Maßlösung unterbrochen und die Stoppuhr angehalten. Das Schema der Vorrichtung ist aus Abb. 3.22 ersichtlich, ihre Photographie zeigt Abb. 3.23.

Die Dosiereinrichtung besteht aus einem dünnen Polyäthylenrohr *(4)* und einem elektromagnetisch arbeitendes Ventil *(3)*, das über Relais *(6)* durch ein Ratemeter *(5)* Typ TISS (UdSSR-Erzeugnis) gesteuert wird.

Das Schaltschema der Vorrichtung zeigt Abb. 3.24.

Wird die Maßlösung mit konstanter Geschwindigkeit zugegeben, so kann ihr Verbrauch auf Grund der verstrichenen Zeit berechnet werden. Wenn man zur Titration eine automatische Bürette oder andere kalibrierte Gefäße verwendet, so ist die Stoppuhr überflüssig, da das Volumen der verbrauchten Titrierlösung unmittelbar abgelesen werden kann.

Die Anwendung einer solchen automatischen Apparatur gestattet die Ausschaltung subjektiver Fehler, Genauigkeit und Schnelligkeit der Titration werden gesteigert. Eine Bestimmung dauert nicht länger als 8 Minuten. Mit häufiger Verstopfung der Filterplatte muß jedoch auch hier gerechnet werden.

3.4.2. *Zentrifugen-Methode*

KORENMAN und Mitarb. [51] bedienten sich als erste einer Zentrifuge zur Phasentrennung. Sie füllten gleiche Volumina der Prüflösung in mehrere Zentrifugenröhren und gaben verschiedene Mengen des Maßlösung zu den Lösungen. Dann wurden alle Röhren mit destilliertem Wasser auf ein gleiches Volumen aufgefüllt. Nach Abzentrifugieren des Niederschlages wurden aus der klaren Lösung jeweils 0,5 ml abpipettiert und tropfenweise auf einen Streifen Filterpapier gebracht. Die Aktivität der getrockneten

ammonium ion > guanidinium ion > thiourea > urea > guanidine <
thiourea anion > carbamide anion > guanidine anion > amide anion

In ammonia the amide ion is the solvent-anion.

A factor additional to those dependent on the molecular structure of the solute is the complex nature of the solvent. Some components of this complex factor are

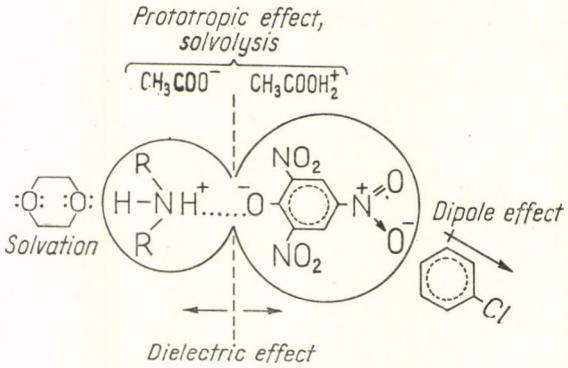


Fig. 3. The effect of solvent mixtures on dialkylammonium picrates. (Idealized scheme)

the solvation effect, the dielectric constant, and the prototropic effect (e.g. acidity or basicity of the solvent) (Fig. 3).

In a solvent with a stronger acidity than that of water the strength of acids weakens or vanishes while that of bases increases; the basicity of strong bases is levelled and that of weak or very weak bases is differentiated. In a solvent with a stronger basicity than water the strength of acids increases while that of bases becomes weaker or disappears.

In differentiating solvents with a low dielectric constant, such as e.g. isobutyl methyl ketone, both acids and bases can be titrated within certain limits.

Much of the usefulness of titrations performed in non-aqueous media depends on the fact that the relative strength of acids and bases can be altered from solvent

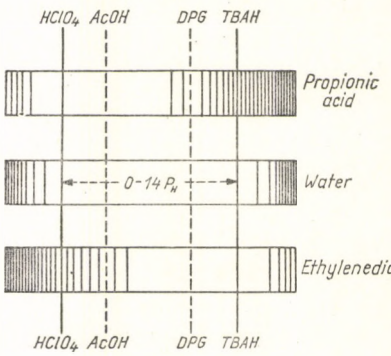


Fig. 4. Effect of solvent on the strength of acid or base. — *(AcOH)* Acetic acid, *(DPG)* Diphenylguanidine, *(TBAH)* Tetrabutylammonium hydroxide

to solvent. This is indicated in Fig. 4. The extreme range of acidic and basic solutions in water is symbolized by the right and left borders of the figure, for reactions which can no longer be denoted by pH. In propionic acid the number and strength of totally ionized acids decrease, contrary to bases whose number and strength increase.

Streifen wurde bestimmt und zur Aufstellung der Titrationskurve verwendet.

Die von verschiedenen Firmen gebauten, mit automatischem Probenwechsler versehenen Zähl- und Registrierinstrumente sind zur schnellen Durchführung der Zentrifugen-Methode vorzüglich geeignet. So verwendete z. B. TÖLGYESSY [104] die Einrichtung »Automat Frieseke und Hoepfner FH«. Die nach der obigen Methode erhaltenen kreisrunden Filterpapierscheiben wurden in die Vertiefungen des rotierenden Probenwechslers eingelegt und die Aktivitäten der Scheiben gemessen. Die graphische Darstellung der Meßwerte ergab die Titrationskurve.

Die Zentrifugen-Methode besitzt gegenüber der Filtrationsmethode einige Vorteile. Es entfallen die durch Verstopfung der Filter oder Durchlaufen insbesondere bei feinkörnigen Niederschlägen verursachten Schwierigkeiten. Da mit konstanten Volumina gearbeitet wird, sind Volumenkorrekturen nicht erforderlich. Der Zeitbedarf zur Ermittlung einer Titrationskurve aus etwa 6 Meßwerten liegt bei 25 Minuten.

Eine Spezialeinrichtung, mit einer sog. »dünnwandigen β-Zähler-Zentrifuge« stammt von SCOTT und DRISCOLL [91]. Der GM-Zähler befindet sich innerhalb der Zentrifugenröhre. Die Aktivität kann daher nach Abzentrifugieren des Niederschlages unmittelbar gemessen werden. Die Entfernung zwischen der Zentrifugierröhre und dem Zähler wurde so gewählt, daß die e^--Strahlung, die der an der Wand der Zentrifugenröhre abgesetzte Niederschlag emittiert, durch die Lösung vollständig absorbiert wird. Der Zähler mißt nur die Aktivität der Lösung. Die »Zähler-Zentrifuge« zeigt — in ihrer durch BERRY und SCOTT [15] angewandten Form — Abb. 3.25.

3.4.3. *Flotationsmethode*

BRAUN, GALATEANU und MAXIM haben zur Trennung der Phasen mit Erfolg die Flotation angewandt [18, 19, 76]. Ein flotierfähiges System

Tabelle 3.1

Phasentrennung durch Flotation

Flotationsmittel	$[MePy_4](SCN)_2$ worin Me =					Mercaptobenzthiazol-Komplex von					$Me[Hg(SCN)_4]$ worin Me =		
	Cu	Co	Ni	Cd	Zn	Cu	Ag	Bi	Cd	Au	Cu	Co	Zn
Diäthyläther	+	+	+	+	+	+	−	s	s	+	−	−	+
Tetrachlorkohlenstoff	+	+	+	+	+	+	−	+	s	+	−	−	+
n-Butanol	+	+	+	+	−	−	−	−	−	−	+	+	+
n-Amylalkohol	+	+	+	−+							−	−	+
n-Kresol-Tetrachlorkohlenstoff											−	−	−

+: Flotation; −: keine Flotation; s: Niederschlag löst sich

In ethylenediamine the number and strength of bases decrease, that of acids and acid analogues increase. The intermediate zone separating the very strong bases and acids from one another varies with the autoprotolysis of the solvent, its range being for water pH 0–14, for acetic acid pH 0–12·6 (ionic product $2{\cdot}5 \times \times 10^{-13}$), for formic acid pH 0–6·2 (ionic product $6{\cdot}3 \times 10^{-7}$).

In inert solvents this intermediate region may be considered infinite because solvent cations and solvent anions are not present. In such a solvent the strengths of acids and bases become apparent without interposition of the solvent. In solvents with low dielectric constant and lessened solvating power the formation of aggregates, ion-pairs, ion-dipoles and adducts considerably influences acid–base interaction.

14. Effect of the Solvating Properties of Solvents on the Strength of Acids

The ion-solvating power of the solvent is an important factor, its increase promoting and accelerating the formation of ions, and opposing their disappearance [402]. The effect is striking when a comparison is made between the acid constants of acids with different types of charge in solvents of differing basicity. The acid constants of aliphatic carboxylic acids are 10^5–10^6 times greater in water than in ethanol while those of substituted ammonium ions are only 10 times greater (p. 54 in [393]).

In water the reaction

$$R_3NH^+ + H_2O \rightleftarrows R_3N + H_3O^+$$

is shifted in the direction of the upper arrow, water being about 15–20 times stronger as a base than ethanol [84]:

$$R_3NH^+ + C_2H_5OH \rightleftarrows R_3N + C_2H_5OH_2^+$$

In the case of carboxylic acids, on the left of the reaction leading to equilibrium there are two neutral molecules while on the right there are two charged co-reactants. The formation of charged particles is promoted by the more powerfully solvating solvent:

$$R.\,COOH + H_2O \rightleftarrows R.\,COO^- + H_3O^+;$$

$$R.\,COOH + CH_3.\,CO.\,CH_3 \rightleftarrows R.\,COO^- + [CH_3.\,CO.\,CH_3]H^+$$

The solvating effect promoting ionization is also influenced by a possible resonance effect (Chapter 4; Section 27). The ionization constant of picric acid is roughly only 1,050 times greater in water than in ethanol because the charge of the picrate anion, owing to resonance, is dispersed over the molecule, and it is therefore not strongly solvated: its stability is scarcely modified when the solvating properties of the solvent undergo a change. In contrast, the charge of the carboxylate anion is only shared by two oxygen atoms, thus, e.g. monochloroacetic acid is 96,000 times stronger in water than in ethanol.

Electrically neutral acids are weaker in ethanol than in water; those charged positively vary to a slight degree [185]:

besteht im allgemeinen aus drei verschiedenen Phasen mit stärkeren Wechselwirkungskräften zwischen jeweils nur zwei Phasen. So können die in einer flüssigen Phase suspendierten Teilchen eines Feststoffes unter bestimmten Bedingungen durch feinverteilte, von unten einströmende Gasbläschen an die Oberfläche transportiert werden.

Bei den radiometrischen Fällungstitrationen liegt zunächst ein aus Niederschlag und wässeriger Lösung bestehendes Zweiphasensystem vor. Wird danach eine mit Wasser nicht mischbare organische Flüssigkeit zugesetzt, so erhält man durch intensives Schütteln oder Rühren eine nur kurzzeitig stabile Emulsion. Bei genügend großer Benetzbarkeit des Niederschlages durch die organische Phase (Flotationsmittel) haftet dieser an der Oberfläche des organischen Emulsionströpfchens. Bei Entmischung des ruhenden Systems wird der Niederschlag dadurch in die Grenzfläche der beiden flüssigen Phasen transportiert und von der wässerigen Phase weitgehend getrennt. Da einerseits die Rest-Aktivität der wässerigen Lösung gemessen werden soll und anderseits diese Messung für die obere Phase einfacher ist, wird zweckmäßig eine organische Flüssigkeit als Flotationsmittel gewählt, deren Dichte größer als diejenige der wässerigen Lösung ist.

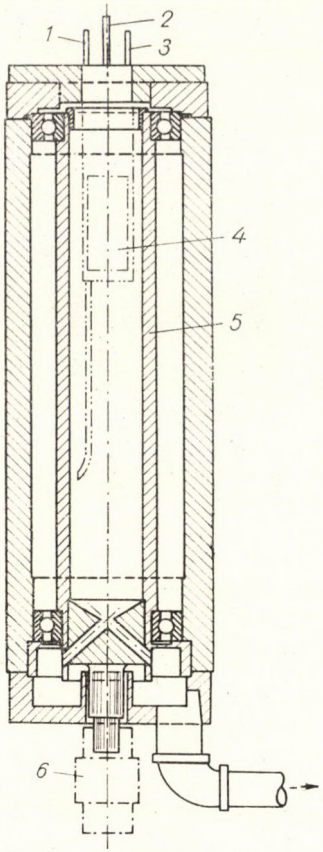


Abb. 3.25
Zentrifugen-Zähler (Scott und Driscoll [91]). (*1* — Wasserzuleitung; *2* — Gaszuleitung; *3* — Gasableitung; *4* — Zähler; *5* — untersuchte Lösung; *6* — Antriebsmotor)

Die Flotation des Niederschlages $[CoPy_4](SCN)_2$ in verschiedenen Flotationsmitteln zeigt Abb. 3.26. Bei Vorliegen geeigneter Flotationsmittel lassen sich ziemlich große Niederschlagsmengen von der wäßrigen Phase abtrennen.

Von den Autoren wurde die Flotations-Trennung der Niederschläge zahlreicher Kationen mit anorganischen und organischen Reagenzien untersucht. Einige der mit verschiedenen Flotationsmitteln erhaltenen experimentellen Ergebnisse bringt Tab. 3.1. So wurden z. B. Kobalt- und Nickelionen — in Gegenwart von ^{60}Co als Indikator — mit Kaliumthiocyanat titriert. Für die gebildeten Niederschläge, $[CoPy_4](SCN)_2$ und $[NiPy_4](SCN)_2$ wurde Tetrachlorkohlenstoff als Flotationsmittel eingesetzt.

Nach den Angaben dieser Autoren ist die Trennung durch Flotation viel einfacher, schneller und vollständiger als durch Zentrifugieren.

Compound	pK_{acid} *(In Water)*	pK_{acid} *(In Ethanol)*
Nitric acid		3·57
Picric acid	0·8	4·0
Trichloroacetic acid	0·7	5·46
Oxalic acid	1·3	6·58
Monochloroacetic acid	2·9	7·74
2,4-Dinitrophenol	3·9	7·74

Compound	pK_{BH^+} *(In Water)*	pK_{BH^+} *(In Ethanol)*
Anilinium ion	4·6	3·73
N,N-Dimethylanilinium ion	5·0	4·13
Pyridinium ion	5·3	4·33

The solvent with the stronger ion-solvating property promotes the formation of ions when electrically neutral molecules give rise to ion pairs:

$AH + s \rightleftarrows A^- + sH^+$ (two ions formed, AH = ionogen acid [218])

$BH^+ + s \rightleftarrows B + sH^+$ (number of ions remains unchanged, BH^+ = isoion acid [218]).

In reactions where charged particles are formed from neutral ones the dielectric medium promotes the formation and separation of ions. A solvent with a low

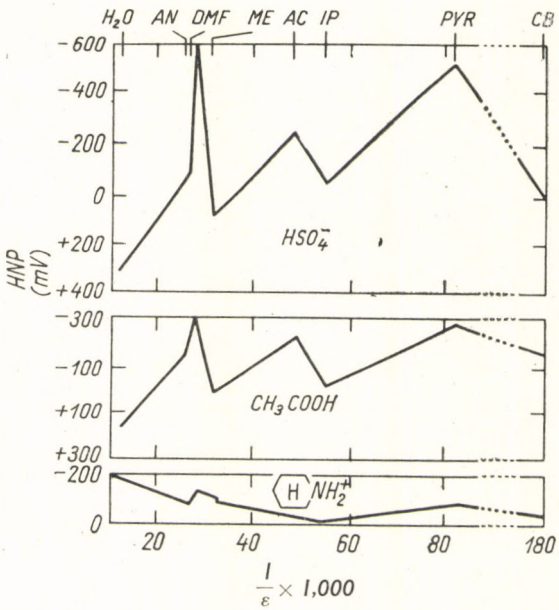


Fig. 5. Effect of the dielectric constant of solvents on the half-neutralization point according to Dahmen [168]. — *(AN)* Acetonitrile, *(DMF)* Dimethylformamide, *(ME)* Methanol, *(AC)* Acetone, *(IP)* Isopropanol, *(PYR)* Pyridine, *(CB)* Chlorobenzene

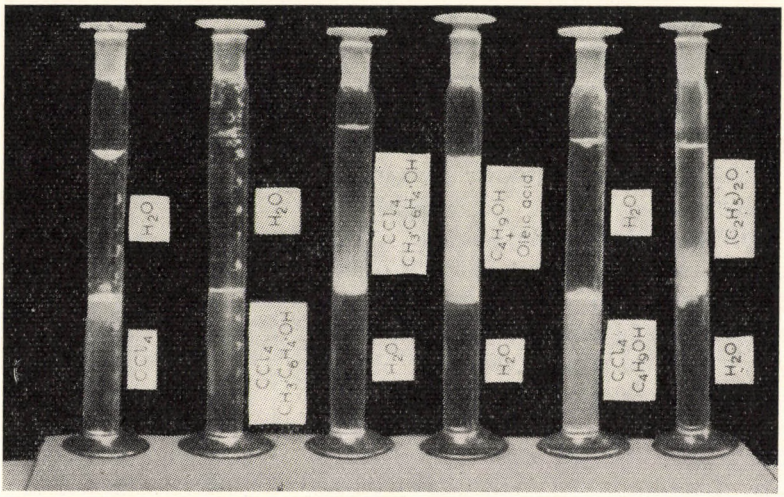


Abb. 3.26
Die Flotation des Niederschlages $[CoPy_4](SCN)_2$ in verschiedenen Flotationsmitteln (BRAUN [18])

3.5. Bestimmung mehrerer Komponenten nebeneinander

Ein Vorteil der radiometrischen Titrationen liegt in der Möglichkeit, parallel zwei Komponenten mit einer Titration bzw. zwei oder mehrere Komponenten mit zwei Titrationen zu bestimmen. Diese ist z. B. gegeben, wenn der Unterschied zwischen den Löslichkeitsprodukten der gebildeten Niederschläge genügend groß ist. Durch geeignete Wahl des (isotopen oder nichtisotopen) Indikators, entsprechender Einstellung des pH-Wertes usw. kommt man aber oft auch zum Ziel. Einige Beispiele für die Bestimmung von zwei oder drei Komponenten nebeneinander sind weiter unten angeführt. Selbstverständlich können mit diesen Beispielen nicht alle Möglichkeiten erfaßt werden. Durch Anwendung von Komplexbildnern oder Demaskierung, kombinierten Einsatz mehrerer radioaktiver Indikatoren oder entsprechende Variierung des pH-Wertes usw. können gleichfalls selektive Titrationen erzielt werden. Theoretische Überlegungen führen zu dem Schluß, daß es prinzipiell möglich ist, bis zu fünf Komponenten nebeneinander zu erfassen. Die Zahl der Fehlermöglichkeiten wächst in solchen Systemen selbstverständlich ungemein stark an. Daher sind Methoden für die gleichzeitige Bestimmung von mehr als drei Komponenten heute noch nicht von praktischer Bedeutung.

3.5.1. *Bestimmung von zwei Komponenten nebeneinander*

Wenn durch ein Titriermittel beide zu bestimmenden Komponenten gefällt werden, so ist es möglich, sie nebeneinander zu bestimmen. Durch Titration

dielectric constant prevents the generation of ions and promotes the formation of ion pairs and ion aggregates: e.g. acetic acid, acetonitrile, nitromethane, benzene etc.

In reactions with equally charged ions on both sides of the equation the effect of the dielectric constant of the medium is smaller. This is exemplified by the interaction of (1) benzoic acid and aniline, and (2) benzoic acid and the *salt* of *o*-nitrobenzoic acid in water and in ethanol (see: p. 205 in [380]):

1. $C_6H_5COOH + C_6H_5NH_2 \rightleftharpoons C_6H_5COO^- + C_6H_5NH_3^+$

2. $C_6H_5COOH + O_2N \cdot C_6H_4 \cdot COO^- \rightleftharpoons C_6H_5COO^- + O_2N \cdot C_6H_4 \cdot COOH$

Values of the equilibrium constants:

	In Ethanol, $\varepsilon = 25$	*In Water*, $\varepsilon = 80$	*Ratio*
1.	0·000015	2·7	180,000
2.	0·015	0·0095	0·6

In the potentiometric titration of acids the half-neutralization potential (h.n.p.) is roughly proportional to the ionization constant of the acids. The relationship between the h.n.p., the solvating ability of the solvent and the dielectric constant (ε) is not unambiguous [168]. Figure 5 illustrates the half-neutralization potential change of piperidinium ion, acetic acid and bisulphate anion as a function of the $1/\varepsilon$ value: the effect of the dielectric constant of the solvent is smallest in the case of cationic acids.

According to Wolf the relative strengths of uncharged acids remain constant, of those positively charged increase, and the relative strengths of negatively charged acids decrease if the dielectric constant of the solvent decreases [882].

15. Effect of Differentiating Solvents and of those not Analogous to Water on the Ionization and Solvation of Acids

The effect of solvents with differentiating properties is often unlike the solvating effect of solvents comparable with water. This becomes apparent e.g. by the considerable change in the differences between the strengths of acids of neighbouring dissociation constants, and further by the fact that anions formed in the course of prototropic reactions do not solvate; ion pairs and larger ion aggregates are formed, and other specific interactions may be observed which are not even definable in detail.

(a) *Ionization of acids in acetonitrile* [424]. The dielectric constant of acetonitrile, CH_3CN, is relatively high, higher even than that of methanol (Table 12, p. 110). As an amphiprotic solvent, it possesses very weak acidic and weak basic character, similar to that of acetone. In practice, however, it can be classed among the inert solvents. Polarographic measurements show its differentiating properties [138, 467].

Halogen hydracids ionize in acetonitrile in two ways, *nitrilium* and *imino* type ions, respectively, being formed.

mit dem markierten Titriermittel wird in einem aliquoten Teil der Prüflösung zunächst die gemeinsame Menge beider Komponenten bestimmt. Aus einem zweiten aliquoten Teil wird dann mit einem selektiven Reagens eine der Komponenten gefällt, und nach der Entfernung des Niederschlages (oder, wie später noch gezeigt werden soll, auch ohne diese Maßnahme) wird schließlich die andere Komponente mit dem markierten Titriermittel titriert. Eine einfache Berechnung ergibt die gesuchten Konzentrationen.

Sollen z. B. Zink und Blei nebeneinander bestimmt werden, so titriert man einen aliquoten Teil der Lösung mit ^{59}Fe-markiertem Kaliumhexacyanoferrat(II) und erhält so zunächst die Gesamtmenge von Zink und Blei. Aus einem zweiten aliquoten Volumen der Prüflösung wird nun das Blei mit Schwefelsäure gefällt und der Zinkgehalt durch radiometrische Titration bestimmt. Die Differenz ergibt den Bleigehalt [106].

Durch Abänderung des obigen Verfahrens können zwei verschiedene Oxydationsstufen eines Stoffes bestimmt werden, wenn eine mit dem markierten Maßlösung einen Niederschlag liefert. Man arbeitet hier ebenfalls mit zwei gleich großen aliquoten Volumina. Zuerst wird die Konzentration jener Komponente bestimmt, die mit dem Titriermittel einen Niederschlag liefert. Mit Hilfe einer geeigneten Redox-Reaktion wird dann im zweiten aliquoten Teil auch die andere Komponente in die Oxydationsstufe übergeführt, die den Niederschlag liefert, und die Gesamtmenge der beiden Komponenten bestimmt.

Ein Beispiel für die geschilderte Methode ist die Bestimmung von Jod und Jodid nebeneinander. Zunächst wird die Jodid-Konzentration durch Titration mit ^{204}Tl-markiertem Thallium(I)sulfat erfaßt. Dann wird das Jod im zweiten aliquoten Teil der Prüflösung mit Natriumthiosulfat zu Jodid reduziert und die Jodid-Gesamtkonzentration nach der gleichen Methode titriert [63, 65, 88].

Zwei Komponenten können weiterhin nebeneinander bestimmt werden, indem man beide Komponenten mit entsprechenden Radionucliden markiert und dann die Lösung mit einem selektiven, inaktiven Maßlösung titriert.

Zur Bestimmung von Sulfat und Jodid z. B. wird mit $^{131}I^-$ und $^{35}SO_4^{2-}$ markiert und dann mit Bariumchloridlösung titriert. Sulfat fällt aus, demzufolge sinkt die Aktivität der flüssigen Phase bis zum ersten Endpunkt, um dann konstant zu bleiben. Nachdem der erste Endpunkt erreicht wurde, titriert man mit Silbernitratlösung weiter. Jetzt fällt Jodid aus und die Aktivität der überstehenden Lösung sinkt wieder. Nach Erreichung des zweiten Endpunktes ist die Aktivität der Lösung nur mehr eine Funktion der Löslichkeit der beiden Niederschläge. Man verfolgt den Titrationsablauf graphisch und bestimmt die Endpunkte auf Grund der Titrationskurven (Abb. 3.27) [106].

Zwei Stoffe können nebeneinander mit Hilfe eines inaktiven Titriermittels auch dann bestimmt werden, wenn zwischen den Löslichkeitsprodukten der mit dem Titriermittel gebildeten Niederschläge ein genügend großer Unterschied besteht. Die Prüflösung wird für jene Komponente mit einem geeigneten Radionuclid markiert, die den leichter löslichen Nieder-

A nitrilium type interaction is shown by hydrogen chloride:

$$CH_3C{\equiv}N + HCl \rightleftarrows CH_3C{\equiv}N.\,HCl \rightleftarrows CH_3C{\equiv}NHCl \rightleftarrows CH_3C{\equiv}NH^+ + Cl^-_{solv} \quad (15.1a)$$

$$Cl^-_{solv} + HCl \rightleftarrows Cl(HCl)^-_{solv} \quad (15.1b)$$

Owing to the enhanced polarizability of hydrogen bromide and hydrogen iodide an imino-type interaction comes to the fore with these acids:

$$CH_3C{\equiv}N + HBr \rightleftarrows CH_3C{\equiv}\overset{+}{N}H\overset{-}{Br} \rightleftarrows CH_3\overset{+}{C}{=}NH\,.\,\overset{-}{Br} \quad (15.2a)$$

$$CH_3\overset{+}{C}{=}NH\,.\,\overset{-}{Br} + HBr \rightleftarrows CH_3\underset{\underset{Br}{|}}{C}{=}\overset{+}{N}H_2\overset{-}{Br} \rightleftarrows CH_3\underset{\underset{Br}{|}}{C}{=}NH_2^+ + Br^-_{solv} \quad (15.2b)$$

Heteroconjugation and homoconjugation in acetonitrile: see: [466]. Heteroconjugation is defined as the conjugation of an anion A^- with a hydrogen bond donor HR:

$$A^- + nHR \rightleftarrows A(HR)^-_n.$$

Homoconjugation: $A^- + nHA \rightleftarrows A(HA)^-_n$.

It is characteristic of acetonitrile that its proton acceptor property towards acids and acid analogues develops slowly as a function of time, and is not an instantaneous phenomenon as in the case of methanol (as regards ketones, propionitrile and benzonitrile see: [598]). Because of the slight polarity of the $-CH_3$ group, weeks are needed to reach the ionization equilibrium of picric acid, unlike solutions in acetophenone and benzonitrile, where, due to the π-electron system of the aromatic ring, considerable interaction is present.

The solvating and ionization-promoting ability of solvents is influenced by the electrophilic character of the radicals bonded to the polar group of the solvent molecule. With the increase in the electrophilicity of these radicals (R) the electron-donor property of the polar group of the solvent molecule decreases toward the dissolved acid, that is, the stability of the proton-solvent association weakens and by so doing the ionization of the acid decreases [281, 397, 494, 598]:

Solvent	ε (20°)	*Electrophilicity of the R Radicals Bonded to the* $-CO\,.\,CH_3$ *and* $-CN$ *Groups, respectively* [281, 397, 494]	*Ionization Constant of Picric Acid* $K \times 10^4$
Acetone	21·5	−1·40	1·38
Ethyl methyl ketone	17·8	−1·45	1·98
Acetophenone	18·1	+4·2	0·15
Propionitrile	27·0	−1·45	4·25
Benzonitrile	26·5	+4·2	1·02

schlag liefert. Die Endpunkte werden graphisch ermittelt, es ist aber auch möglich, sie rechnerisch zu bestimmen [100, 106].

Zur Berechnung der beiden Endpunkte sind drei Aktivitätsmessungen erforderlich. Den Verlauf der Titration zeigt Abb. 3.28. Die beiden Endpunkte werden unter Anwendung der Beziehungen (3.31) und (3.32) errechnet:

$$V_{1\text{äqu.}} = (V_2 - V_1)\frac{I_0 - I_1}{I_2 - I_1} + V_1\,, \tag{3.31}$$

$$V_{2\text{äqu.}} = (I_0 - F)\frac{V_1 - V_2}{I_2 - I_1} + V_{1\text{äqu.}} \tag{3.32}$$

Bei der praktischen Durchführung wird zuerst die Ausgangs-Aktivität der markierten Prüflösung (I_0) bestimmt. Nach Zugabe von V_2 ml der Maßlösung (die zur quantitativen Fällung der ersten Komponente ausreichen) wird die Aktivität der überstehenden Lösung (I_2) gemessen. Es werden nun v ml der Maßlösung zugegeben ($V_1 = V_2 + v$), gefolgt von einer erneuten Messung der Aktivität (I_1). F steht für die Aktivität der Lösung im zweiten Endpunkt.

Ein Beispiel ist die Bestimmung von Sulfid und Jodid nebeneinander. Die Prüflösung wird mit $^{131}I^-$ markiert, als Titriermittel dient Silbernitratlösung. Während der Zugabe der Maßlösung erfährt die Aktivität der flüssigen Phase so lange keine Änderung, wie noch Sulfid in der Lösung vorliegt. Nach der quantitativen Fällung des Sulfids beginnt die Ausscheidung des Jodids, die eine Abnahme der Aktivität der überstehenden Lösung nach sich zieht.

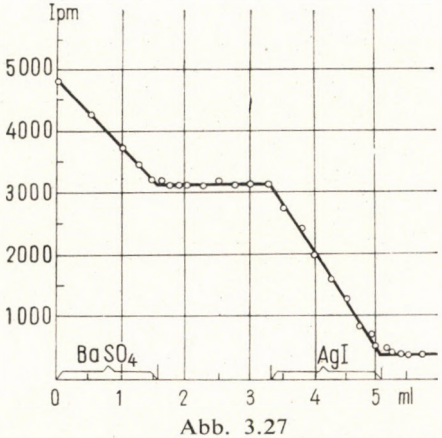


Abb. 3.27
Bestimmung von SO_4^{2-} und I^- nebeneinander, unter Anwendung von $BaCl_2$ und $AgNO_3$ Lösung als Titriermittel (TÖLGYESSY [106])

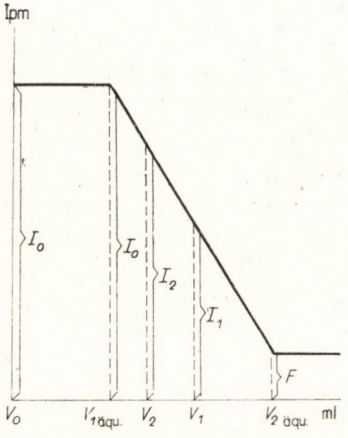


Abb. 3.28
Bei der Bestimmung von zwei Stoffen nebeneinander erhaltene radiometrische Titrationskurve (Titriermittel inaktiv) (TÖLGYESSY [106])

The above list shows the varying acid strength of picric acid, depending on the differentiating ability of the solvent.

Dulova and co-workers investigated the strength of different acids in acetophenone, cyclohexanone and cyclohexanol. These solvents possess, to a certain degree, differentiating properties; thus the pK difference between dichloroacetic acid and trichloroacetic acid in water is only 0·4 units, but in the solvents mentioned above it is nearly three times as much [194, 195, 196]:

	p$K(H_2O)$	Δ	pK(*Acetophenone*)	Δ	pK(*Cyclohexanone*)	Δ
Dichloroacetic acid	1·30	0·4	7·41	1·15	6·86	1·19
Trichloroacetic acid	0·9		6·26		5·66	

(b) *Ionization of sulphuric acid in nitromethane.* The specific interaction of differentiating solvents is also fairly well demonstrated by nitromethane. Though the dielectric constant of nitromethane, CH_3NO_2, does not differ considerably from that of methanol it does not solvate acids. In nitromethane with a nitroaniline-type indicator-base (B), sulphuric acid (AH) enters into the reactions:

1. in lower concentration

$$A\mathrm{H} + B \rightleftharpoons B\mathrm{H}^+ . A^-$$

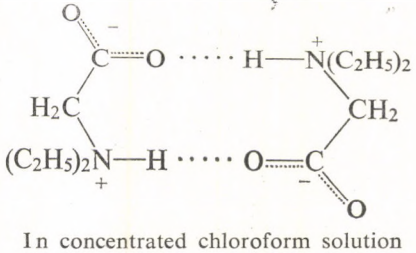
2. in concentrations above 0·1 M

$$3A\mathrm{H} + B \rightleftharpoons B\mathrm{H}^+ . A\,(A\mathrm{H})_2^-$$

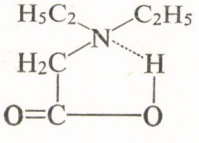
The free BH$^+$ ion and the ion pairs BH$^+$. A^- and BH$^+$. $A(A\mathrm{H})_2^-$ show the same light absorption [520]. The anion, formed in the course of proton transfer, must become 'solvated' by the acid molecule, and not by the solvent molecule, because nitromethane lacks solvating power.

In prototropic reactions of water-like solvents solvation of the anion is dominant, e.g. by means of the hydrogen-bond established between the mobile hydrogen of the solvent and the free electron-pair of the anion. The lack of readiness to establish an H-bond is one cause, to mention no other, for this 'un-water-like' property of nitromethane.

(c) *Solvation of amino-acids in chloroform and carbon tetrachloride* [34]. Amino-acids solvate in water as 'zwitterions'. In a solvent of low dielectric constant the amino and carboxyl groups solvate with or without proton transfer. In concentrated chloroform solution N,N-diethylglycine is present as a 'zwitterion-dimer', and in a more dilute solution or in carbon tetrachloride as an internally H-bonded monomer:



In concentrated chloroform solution



In dilute chloroform, or carbon tetrachloride solution

Man kann auch zwei Komponenten nebeneinander mit ein und demselben markierten Titriermittel erfassen, wenn sie mit dem Titriermittel bei verschiedenen pH-Werten Niederschläge liefern.

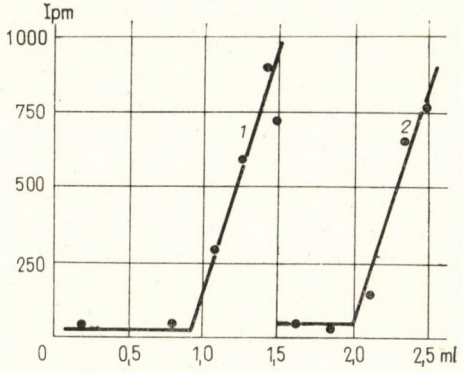


Abb. 3.29
Radiometrische Titration von Tl(III) und In(III) nebeneinander unter Anwendung von 0,05 N Natrium-1-dithiocarboxy-3-methyl-5-phenylpyrazolinat-Lösung (markiert mit ^{35}S) als Titriermittel (BUSEW und BYRKO [23]) (*1* — Titration von Tl; *2* — Titration von In)

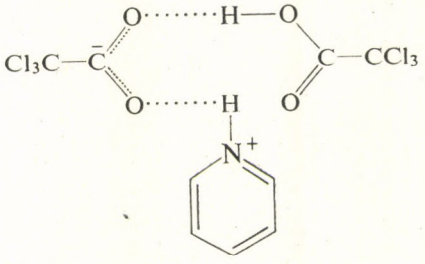
BUSEW und BYRKO [21, 23] bestimmten Thallium(III) und Indium (III) nebeneinander durch Titration mit 1-Dithiocarboxy-3-methyl-5-phenylpyrazolinat, das mit ^{35}S markiert war (Abb. 3.29). Zuerst fällt Thallium quantitativ bei pH = 14. Nach dem Endpunkt beginnt die Aktivität auf Zugabe weiterer Mengen der Maßlösung, zu steigen (Abb. 3.29, Kurve *1*). Der pH der Lösung wird nun auf 7 eingestellt und der Überschuß der Maßlösung bzw. weitere Portionen bewirken jetzt die Fällung des Indiums. Die Aktivität der Lösung bleibt unterdessen bei einem konstanten Wert, der von der Löslichkeit der Niederschläge abhängig ist. Nach erfolgter quantitativer Fällung des Indiums beginnt die Aktivität der Lösung wieder anzusteigen (Abb. 3.29, Kurve *2*).

Eine weitere Methode, zwei Komponenten nebeneinander unter Variierung des pH-Wertes zu bestimmen, ist folgende: Die sich bei höheren pH-Werten ausscheidenden Ionen werden mit einem geeigneten Radioisotop markiert und mit einem gleichfalls markierten Titriermittel titriert.

So können z. B. Thallium(III) (markiert mit ^{204}Tl) und Zink nebeneinander durch Titration mit 1-Dithiocarboxy-3-methyl-5-phenylpyrazolinat (markiert mit ^{35}S) bestimmt werden. Während der Zugabe der Maßlösung nimmt die Aktivität infolge der Bildung des wenig löslichen Thallium-Komplexes ab. Nach dem Endpunkt beginnt die Aktivität auf Zugabe weiterer Portionen des markierten Titriermittels wieder anzusteigen (vgl. Kurve *1* auf Abb. 3.30). Wird der pH-Wert nun gesenkt, so reagiert das überschüssige Titriermittel mit dem Zink und die Aktivität der Lösung stellt sich auf den durch die Löslichkeit der beiden Niederschläge bedingten Wert ein. Nach dem zweiten Endpunkt bewirken zusätzliche Mengen der Maßlösung dann wieder einen Anstieg der Aktivität (vgl. Kurve *2* auf Abb. 3.30) [21, 23].

Einen anderen Ablauf zeigen die Titrationskurven, wenn Zink (markiert mit ^{65}Zn) und Cadmium in ein und derselben Lösung mit dem wie oben markierten 1-Dithiocarboxy-3-methyl-5-phenylpyrazolinat titriert werden. Wie Abb. 3.31 (Kurve *1*) erkennen läßt, bleibt die Aktivität der Lösung während der Fällung des Cadmiums bei einem (dem ^{65}Zn entsprechenden) konstanten Wert. Nachdem alles Cadmium gefällt und der pH der Lösung auf 7 eingestellt ist, wird durch einen geringen Überschuß des Titriermittels auch bereits etwas Zink gefällt und die Radioaktivität der Lösung nimmt ab. Diese Abnahme setzt sich dann so lange fort, bis alles Zink im

(d) *Interaction of trichloroacetic acid and pyridine in chloroform* [33]. In the course of acid-base interaction the ion-pairs in an aprotic solvent are linked by a hydrogen-bond. In this case proton transfer takes place towards the basic nitrogen atom, and the H-bond to the anion is essentially of electrostatic type:

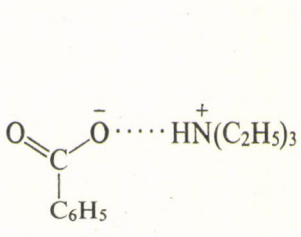


The kind of association is in this case:

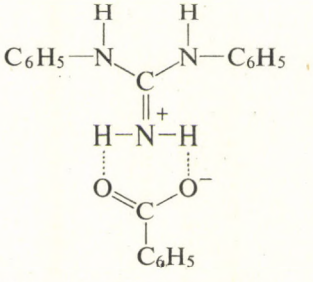
$$BH^+ . A(AH)^-$$

(cf. (b) in this section and Chapter 3; Section 23).

(e) *Association of the benzoate anion in benzene* [174]. Depending on the base, the benzoate anion may behave in different ways:



With triethylamine



With 1,3-diphenylguanidine

The three nitrogen atoms of the diphenylguanidinium ion are not all equivalent. The terminal nitrogen atoms are presumably in aniline-type resonance, and so oppose the guanidinium type resonance. The positive charge is very probably on the $=NH_2$ group, and therefore both hydrogen atoms interact with the two oxygen atoms of the benzoate anion.

In benzene, benzoic acid is a weaker acid towards triethylamine base than towards diphenylguanidine as base. Both oxygens of the carboxylate anion are bonded to the hydrogen, thus enhancing its acidic strength. The relative strength of benzoic acid, therefore, also depends on the reference base, though in this case both bases are of comparable strength: for triethylamine $pK_b = 3{\cdot}26$ and for 1,3-diphenylguanidine $pK_b = 4{\cdot}00$.

16. Determination of the Strength of Acids and of the 'Acidity' of Solutions

In a given solvent the strength of acids can be determined by the measurement of proton activity either by the electrometric or by the indicator method. However, a dis-

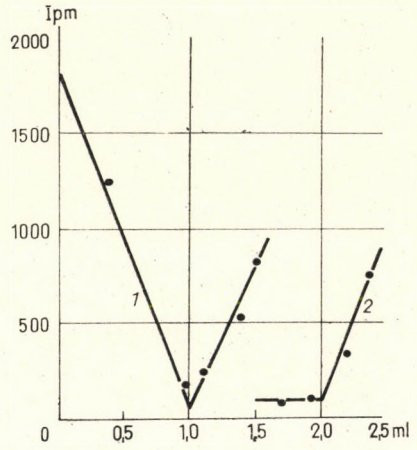


Abb. 3.30
Radiometrische Titration von Tl(III), markiert mit ^{204}Tl, in Gegenwart von Zn unter Anwendung von 0,05 N Natrium-1-dithiocarboxy-3-methyl-5-phenylpyrazolinat-Lösung (BUSEW und BYRKO [23]). (*1* — Titration von Tl; *2* — Titration von Zn)

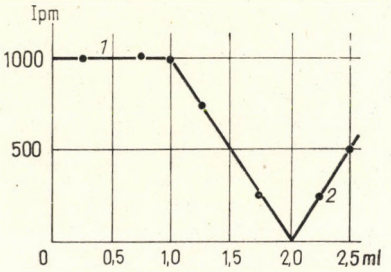


Abb. 3.31
Radiometrische Titration von Zn (markiert mit ^{65}Zn) in Gegenwart von Cd unter Anwendung von 0,05 N Natrium-1-dithiocarboxy-3-methyl-5-phenyl-pyrazolinat-Lösung (BUSEW und BYRKO [23]). (*1* — Titration von Cd; *2* — Titration von Zn)

Niederschlag vorliegt. Sobald dies der Fall ist, bewirkt eine überschüssige Menge der Maßlösung sogleich einen Anstieg der Aktivität (in diesem Falle ist es die e^--Aktivität des ^{35}S). Kurve *2* in Abb. 3.31 zeigt also die gemeinsame Menge von Cadmium und Zink [21, 23].

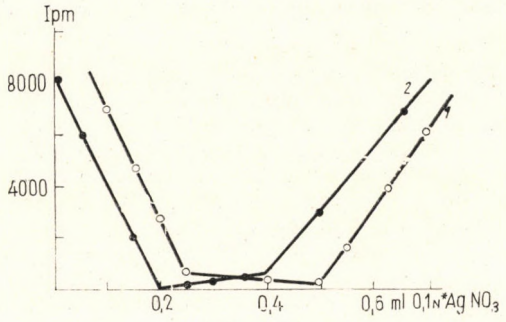
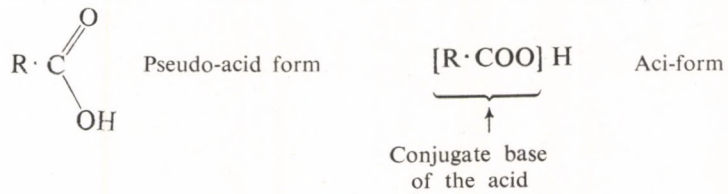


Abb. 3.32
Radiometrische Titration einer Mischung von Halogenidionen unter Anwendung von 0,1 N $AgNO_3$-Lösung (markiert mit ^{110m}Ag) (KIMURA und KAMETANI [47]). (*1* — 0,25 ml 0,1 N K*I-Lösung + 0,25 ml 0,1 N NaCl-Lösung; *2* — 0,2 ml 0,1 N K*I-Lösung + 0,2 ml 0,1 N KBr-Lösung + 0,2 ml 0,1 N NaCl-Lösung)

KIMURA und KAMETANI [47] haben die Unterschiede zwischen den Löslichkeitsprodukten der im Laufe der Titration gebildeten Niederschläge erfolgreich zur Bestimmung von Halogeniden ausgenutzt. Nach ihrer Methode wird jenes Halogenid markiert, welches den am wenigsten löslichen (sich also zuerst ausscheiden den) Niederschlag liefert. Die Prüflösung wird mit markierter Silbernitratlösung titriert.

So konnten Jodid (markiert mit ^{131}I) sowie Chlorid und Bromid mit ^{110m}Ag-markierter Silbernitrat-

tinction must be made between the proton activity of solution and its hydrogen-ion activity [39, 40, 728]. The latter, in particular, exhibits in each solvent capable of proton acceptance a different activity depending on the nature of the solvent molecule solvating the proton. In water hydroxonium ions, in acetic acid acetacidium ions, and in pyridine pyridinium ions are formed. By proton activity is to be understood the readiness with which the dissolved acid transfers its proton to the solvent molecule. The proton activity of the solvated proton, however, may still differ from that of the dissolved acid. This is closely connected with the basicity of the solvent. Hantzsch suggested [351] that the dissociation constant measured in water could not be an accurate measure of the strength of acids; acid strength and electrolytic dissociation do not always run parallel. The ultraviolet absorption spectrum of some acids in ethyl ether (behaving in this case as a weak acid) differs from the spectrum which they exhibit in a solvent in which the acid behaves as a strong acid. In the former case the absorption spectrum resembles that of the ester of the acid (pseudo-acid form), while in the latter case the spectrum is similar to the salt of the acid (aci-form). According to Brönsted's nomenclature, in this case, the spectrum of the compound's conjugate base, or conjugate acid form, may be observed:



(a) *Indicator method. Association equilibrium constant of substituted benzoic acids with 1,3-diphenylguanidine.* It is well known that indicators may be considered as acid–base systems, the absorption spectrum in the visible of the two components being different. In aqueous, as well as non-aqueous (liable to prototropic reaction) media the proton activity can be determined if the ratio of the acidic and basic forms of the indicator is known, e.g. by spectrophotometric measurement:

$$I + H^+ \rightleftarrows IH^+$$

The 'acid constant' of the indicator is defined as:

$$K^i_{\text{acid}} = \frac{[I]\,[H^+]}{[IH^+]} \quad \text{and} \quad (H^+) = K^i_{\text{acid}} \frac{[IH^+]}{[I]}$$

The K^i_{acid} value must be determined by another method and then the proton activity $[H^+]$ can be computed by absorptiometric measurement of the IH^+/I ratio. In non-aqueous media, however, the K^i_{acid} value of the indicator is not independent of the solvent, and further the ratio IH^+/I must be approximately unity.

The order of strength of various acids was investigated by Hantzsch by adding certain indicators to chloroform solutions of the acids and finding the maximum dilution at which the unequivocal change of the indicator to its aci-form could be observed. Thus the following sequence could be established:

$$HClO_4 > C_{10}H_{11}SO_3H > HCl > CCl_3COOH > CH_2ClCOOH > HCOOH >$$
$$CH_3COOH > C_2H_5COOH > C_8H_7COOH.$$

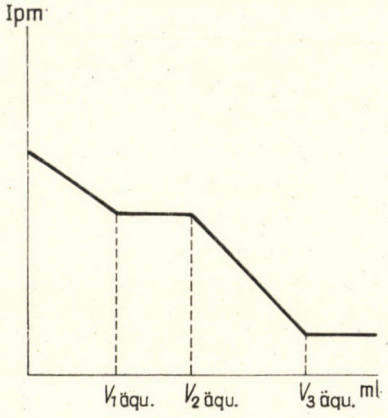


Abb. 3.33
Kurve der radiometrischen Titration von drei Komponenten nebeneinander

lösung erfaßt werden. Die Titrationskurven zeigt Abb. 3.32. Während der Titration fällt zuerst Jodid aus, demzufolge nimmt die Aktivität bis zum Endpunkt ab und bleibt dann während der Fällung des Chlorids und Bromids konstant. Nach dem zweiten Endpunkt beginnt die Aktivität auf Wirkung zusätzlicher Mengen des Titriermittels wieder anzusteigen.

3.5.2. *Bestimmung von drei Komponenten nebeneinander*

Drei Komponenten lassen sich durch radiometrische Titrationen nebeneinander bestimmen, wenn sie mit dem Titriermittel schwer lösliche Niederschläge liefern, deren Löslichkeitsprodukte in genügendem Maße verschieden sind. Als Radioindikatoren werden entsprechende Isotope jener beiden Komponenten verwendet, die den am meisten und am wenigsten löslichen Niederschlag liefern. Eine Titrationskurve dieses Typs ist in Abb. 3.33 gezeigt.

3.6. Spezielle radiometrische Titrationen

In den letzten Jahren haben sich zahlreiche Forschergruppen mit der Entwicklung neuer Methoden auf dem Gebiete der radiometrischen Fällungstitrationen beschäftigt, und zwar mit dem Ziel, ihr Anwendungsgebiet möglichst weit auszudehnen. Angesichts der relativ geringen Zahl erschienener Veröffentlichungen und der in diesen mitgeteilten experimentellen Ergebnisse, ist es heute noch schwierig, zum praktischen Wert der empfohlenen Methoden kritisch Stellung zu nehmen. Sicher ist aber, daß die in Vorschlag gebrachten Verfahren auf dem Gebiete der Kombination der radiometrischen Titrationen mit anderen physikalisch-chemischen Methoden überaus interessante Möglichkeiten eröffnen.

In chloroform and benzene even strong acids are ionized to only a small degree. Experience in organic chemistry, however, shows that in such solutions strong acids can bring about considerable effects. In organic solvents Lewis acids may be just as efficient as H-acids; therefore, proton activity is not involved but the interaction can be considered as affinity towards a lone electron pair.

Trémillion and co-workers [499, 819] measured the order of relative strengths of different acids and bases in acetic acid. Their method is fundamentally an indicator-spectrophotometric method. (See: (b) on p. 36: *The order of relative strengths of acids and bases in acetic acid.*)

Davis and Hetzer [173] determined the relative acidic strengths of mono-, di- and tri-substituted benzoic acid derivatives in benzene. In non-polar media the relative strengths of acids can be determined only by the addition of a reference base. For this purpose 1,3-diphenylguanidine was used by Davis and Hetzer, the indicator acid being tetrabromophenolphthalein ethyl ester. The acids under examination and the indicator acid reacted with the reference base in accordance with the following scheme:

$$B + I\mathrm{H} \rightleftarrows B\mathrm{H}I \tag{16.1}$$

or

$$B + A\mathrm{H} \rightleftarrows B\mathrm{H}A \tag{16.2}$$

where B = diphenylguanidine
$I\mathrm{H}$ = tetrabromophenolphthalein ethyl ester
$A\mathrm{H}$ = the substituted benzoic acid.

Thus, by this method the acid-base association equilibrium constant is determined:

$$K'_{\mathrm{ass}} = \frac{[B\mathrm{H}I]}{[B]\,[I\mathrm{H}]} \tag{16.3a}$$

$$K''_{\mathrm{ass}} = \frac{[B\mathrm{H}A]}{[B]\,[A\mathrm{H}]} \tag{16.3b}$$

$B\mathrm{H}I$ or $B\mathrm{H}A$ may be regarded as hydrogen-bonded salts possessing ion-pair character [172].

In acid-base equilibrium-state investigations performed in non-polar solvents, association-forming possibilities of a different character must also be taken into consideration, especially at higher concentrations. Measurements of freezing-point depression demonstrate e.g. the intermolecular association of diphenylguanidine by H-bonding; in 5×10^{-5} molar concentration this sort of association is negligible. Similarly it is also well known that carboxylic acids associate to form dimers and that equilibrium exists between the monomeric and the dimeric forms.

Davis and Hetzer's experiments are briefly outlined below:

Concentration of the reactants in benzene solution:

tetrabromophenolphthalein ethyl ester,

$C_{a'} = 5 \times 10^{-5}$ mol;

diphenylguanidine,

$C_b = nC_{a'}$

where $n = 0{\cdot}5\text{–}4$;

substituted benzoic acid,

$C_{a''} = {}_{n''}C_{a'}$

where $n'' = 0{\cdot}5\text{–}0{\cdot}6$

3.6.1. *Titrationen in nichtwäßrigen Medien*

In den letzten Jahren hat die erfolgreiche Entwicklung der Theorie der nichtwäßrigen Lösungen die ausgedehnte Anwendung der in nichtwäßrigen Medien durchgeführten Titrationen stark gefördert. Sie stellen heute bereits ein wichtiges Kapitel der titrimetrischen Analyse dar [32, 42, 54, 56, 83].

Nichtwäßrige Lösungsmittel werden vorwiegend zur titrimetrischen Bestimmung von Säuren und Basen verwendet. In weitaus geringerem Maße konnten bisher Fällungs-, Redox- und andere Reaktionen nutzbar gemacht werden. Dies ist in erster Linie auf die Schwierigkeit der Anwendung elektrochemischer und anderer Methoden der Endpunktanzeige in nichtwäßrigen Lösungsmitteln zurückzuführen. Die Einführung der radiometrischen Endpunktanzeige eröffnet auf diesem Gebiete daher unerwartete Möglichkeiten. Die relativ große Zahl der für solche Zwecke verwendbaren Radionuclide, die vollkommene Unabhängigkeit der Strahlungsintensität von der Natur des Lösungsmittels, und der zwischen der Intensität der Strahlung und der Konzentration bestehende lineare Zusammenhang macht es möglich, radioaktive Isotope in nichtwäßrigen Medien mannigfaltig anzuwenden.

Die theoretischen und praktischen Grundlagen der in nichtwäßrigen Medien durchgeführten radiometrischen Fällungstitrationen haben Tschernij, Wail und Ismajlow [25] ausgearbeitet.

Wenn an Stelle des Wassers ein Lösungsmittel verwendet wird, in welchem der Niederschlag weniger löslich ist, so wird es damit möglich, die Empfindlichkeit und Genauigkeit der Titration zu erhöhen.

In der Regel wird der Wert des Löslichkeitsproduktes mit abnehmender Dielektrizitätskonstante geringer nach (3.33):

$$\ln L = A - \frac{C}{\varepsilon} \tag{3.33}$$

ε = Dielektrizitätskonstante des Mediums

A und C = Konstanten.

Daher sind die Ergebnisse der Fällungstitrationen umso genauer, je niedriger der Wert der Dielektrizitätskonstante des angewandten Lösungsmittels ist. In einem nichtwäßrigen Lösungsmittel nimmt der Dissoziationsgrad der Elektrolyte in einem der Gleichung (3.34) entsprechenden Zusammenhang ab:

$$\ln K = a - \frac{C}{\varepsilon}, \tag{3.34}$$

a und C = Konstanten.

Für die Titration von Salzen durch Fällung in nichtwäßrigen Medien nebeneinander gibt es mehrere interessante Möglichkeiten. So kann ein Gemisch von Salzen, das Niederschläge mit unterschiedlichen Löslichkeitsprodukten liefert, analysiert werden. Ein Beispiel hierfür ist die Umsetzung:

$$M_1A_1 + M_2A_2 + 2\,RS \rightleftharpoons RA_1\downarrow + RA_2\downarrow + M_1S + M_2S. \tag{3.35}$$

For the experiments, preparation of solutions etc., measures were taken to minimize the atmospheric moisture content by making use of dry-boxes.

The absorption maximum of the diphenylguanidine–indicator complex is found at 540 mμ. On the addition of various substituted benzoic acids the light absorption decreases owing to a competitive acid interaction with the diphenylguanidine part (*B*) of the *IHB* complex.

A Beckman DU quartz spectrophotometer was used with absorption cells of 2·5 mm, 5·0 mm, 10 mm, and 20 mm thickness, and so selected that light transmittance was within the range 20—70%. The temperature was maintained at 25·0° ± 0·1°.

For calculating association constants the following formula may be used:

$$K''_{ass} = \frac{x - y}{y - [C_{a''} - (x - y)]},$$

where

$$x = \frac{C_{a'}}{L}(nL - Z)$$

and

$$y = \left(\frac{1}{K'_{ass}}\right)\left(\frac{Z}{L - Z}\right)$$

Z = absorbance of the solution at 540 mμ and 5 mm cell length
L = experimentally established limiting absorbance of *IHB*-complex at 5 mm cell length and in 5×10^{-5} concentration = 1·017;
value of K'_{ass} (*BHI*) at 25° = $2{\cdot}5 \times 10^5$.

The table below shows some of the experimental data obtained for *m*-nitrobenzoic acid:

$C_{a''}$	n	Z	K_{ass}
$5{\cdot}015 \times 10^{-5}$	1·0	0·1581	$6{\cdot}65 \times 10^6$
$10{\cdot}140 \times 10^{-5}$	2·0	0·2124	$6{\cdot}64 \times 10^6$
$20{\cdot}047 \times 10^{-5}$	4·0	0·3072	$6{\cdot}25 \times 10^6$

By these experiments it was shown that the reactivity of acids in benzene, as expressed by their equilibrium constant for association with a suitable reference base, can be correlated with their reactivity in aqueous media. This means that if the ionic dissociation constant in water is expressed by pK ($-\log K_{diss}$) values, the association constant (K_{ass}) shows inverse parallelism.

Thus the K_{diss} value of benzoic acid is $6{\cdot}30 \times 10^{-5}$ (pK 4·20) and its K_{ass} value with diphenylguanidine is 182,000 ($\log K_{ass} = 5{\cdot}26$). The stronger the acid in water, the smaller its pK value, and the stronger the same acid in benzene the greater its log K_{ass} value (see: Chapter 4; Section 25).

In aqueous media the fundamental acid–base reaction is followed by secondary phenomena: ionization, solvation, etc. In inert solvents various manifestations of hydrogen-bonding become prominent. For such reasons deviations from a linear relationship between the two equilibrium constants occur. For the understanding of these deviations experimental work on the position and effect of the substituents in benzoic acid is necessary.

The relative order of acidic strength of *meta*-substituted benzoic acids (with the exception of *m*-aminobenzoic acid) is identical in water, methanol, ethanol, n-propanol, n-butanol, ethylene glycol and benzene. In the case of *ortho*- and

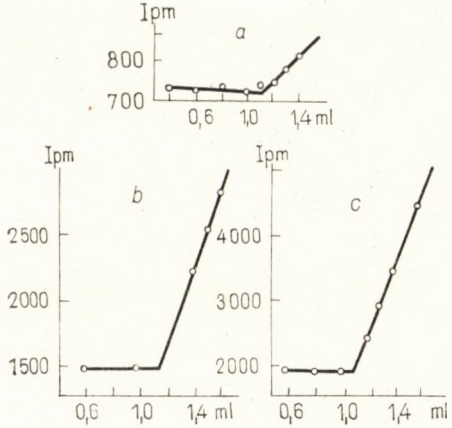


Abb. 3.34
Kurven von radiometrischen Titrationen in Methanol (TSCHERNIJ, WAYL und ISMAJLOW [25]). (*a* – 0,01 N CH_3COONa, 0,008 N $AgNO_3$; V_E = 1,16 ml; *b* – 0,01 N $(C_3H_7COO)_2Ca$, 0,0084 N $AgNO_3$; V_E = 1,15 ml; *c* – 0,0112 N C_6H_5COONa, 0,01 N $AgNO_3$; V_E = 1,13 ml)

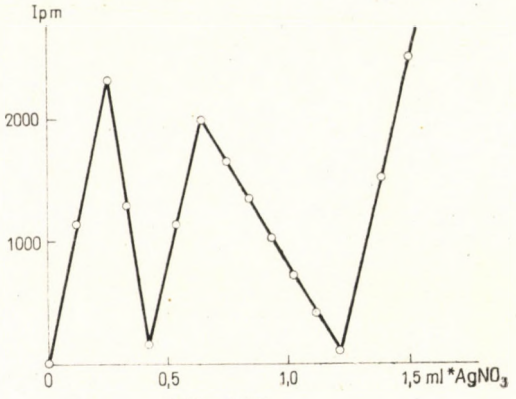


Abb. 3.35
Titrationskurve eines Gemisches von KBr + $(C_2H_5)_4NBr$ in acetonhaltigem Medium mit $*AgNO_3$ als Titriermittel (TSCHERNIJ, WAYL und ISMAJLOW [25])

Es können auch Verbindungen nebeneinander bestimmt werden, die den gleichen Niederschlag liefern:

$$(3.36) \qquad M_1A + M_2A + 2\,RS \rightleftharpoons 2\,RA^{\downarrow} + M_1S + M_2S.$$

Solche Titrationen können in unterschiedlichen Lösungsmitteln durchgeführt werden, d. h. in solchen, die zur Differenzierung des Dissoziationsgrades der Salze fähig sind, wie z. B. Aceton, Methyläthylketon usw. [41].

Viel schwieriger ist die Wahl der für die Titration von Säuren oder Basen geeigneten Lösungsmittel. Die Dissoziation der Säuren oder Basen wird nämlich nicht nur von der Solvatationsenergie der Ionen, sondern auch von der Energie des Protonenaustausches mit dem Lösungsmittel und anderen Faktoren, die ihrerseits wieder von der Natur der Säure (oder Base) und des Lösungsmittels abhängig sind, beeinflußt.

Wenn die betreffende Säure oder Base sowohl in wäßrigem als auch in nichtwäßrigem Medium ein starker Elektrolyt ist, so gelten die gleichen Auswahlbedingungen wie bei der Titration von Salzen, d. h. man arbeitet in Lösungsmitteln mit niedriger Dielektrizitätskonstante. Bei schwachen oder mäßig starken Säuren bzw. Basen muß deren unvollständige Dissoziation zusätzlich in Betracht gezogen werden.

para-substituted benzoic acids the inductive effect of the substituents is greatly affected by resonance effects, steric factors and the possible formation of H-bonds.

The heavy line on Fig. 6 gives a clear idea of the 'standard' behaviour of the *meta*-substituted benzoic acids when the K_{ass} value is represented as a function of the pK value in water. Acids above this line appear to be stronger in water or weaker in benzene.

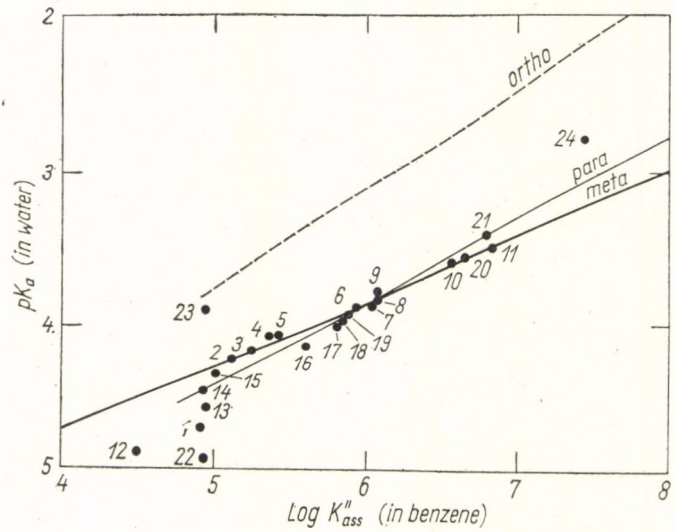


Fig. 6. Correlation between pK_a values of substituted benzoic acids and their association equilibrium constants (log K'') measured in benzene according to Davis and Hetzer [173]. — (*1*) *meta*-NH_2, (*2*) $-CH_3$, (*3*) Benzoic acid, (*4*) *meta*-OCH_3, (*5*) $-OH$, (*6*) $-F$, (*7*) $-I$, (*8*) $-Cl$, (*9*) $-Br$, (*10*) $-CN$, (*11*) $-NO_2$, (*12*) *para*-NH_2, (*13*) $-OH$, (*14*) $-OCH_3$, (*15*) $-CH_3$, (*16*) $-F$, (*17*) $-Cl$, (*18*) $-I$, (*19*) $-Br$, (*20*) $-CN$, (*21*) $-NO_2$, (*22*) *ortho*-NH_2, (*23*) $-CH_3$, (*24*) $-OH$

Meta-aminobenzoic acid falls below the line since its ionization constant in water does not represent accurately the strength of the acid (Fig. 6, (*1*)). Aminobenzoic acids have two ionization constants [456]:

Position of Substituent	*Potentiometric*		*Spectrophotometric*	
	pK_1	pK_2	pK_1	pK_2
ortho	2·05	4·95	2·14	4·80
meta	3·07	4·75	—	—
para	2·38	4·89	2·29	4·86

The inductive effect of the amino group and its resonance with the benzene ring is influenced by its interaction with water molecules. In water, *meta*-aminobenzoic acid is present in a zwitterion form [142].

Owing to zwitterion formation *m*-aminobenzoic acid does not dissolve in some inert solvents, e.g. *o*-nitrotoluene, chloro- and bromo-benzene [595]. Yet, when dissolved, for example, in

Bei Fällungstitration von Säuren können gute Ergebnisse in Lösungsmitteln von geringer Basizität und mit sehr kleiner Dielektrizitätskonstante erwartet werden (wie z. B. Äthanol/Benzol oder Äthanol/Tetrachlorkohlenstoff).

TSCHERNIJ, WAIL und ISMAJLOW [25] beschrieben eine Titrationsmethode für organische Säuren und ihre Salze. Sie titrierten in Methanol oder in einem Gemisch aus Methanol und Aceton (oder Dioxan) mit Silbernitrat (markiert mit ^{110m}Ag) als Titriermittel. Dioxan diente zur Herabsetzung der Dielektrizitätskonstante des Methanols, während die Zugabe von Methanol zum Aceton die Löslichkeit des Titriermittels im Lösungsmittelgemisch erhöht. Es wurde mit der Zentrifugen-Methode gearbeitet und der Endpunkt durch Extrapolieren ermittelt.

Calciumbutyrat, Natriumacetat und Natriumbenzoat wurden im Methanol als Medium titriert [25]. Die Löslichkeitsprodukte der Silbersalze der Butter-, Essig- und Benzoesäure in Wasser liegen bei ca. 10^{-3}–10^{-4} (g-Ion)^{2}l^{-1}. Die untersuchten Lösungen waren ungefähr 0,01 N und der relative Fehler betrug 1–2%. Um diese Ergebnisse in Wasser zu erhalten, hätte das Löslichkeitsprodukt ca. 10^{-8} (g-Ion)^{2}l^{-2} betragen müssen [124]. Die Titrationskurven der genannten Salze zeigt Abb. 3.34.

TSCHERNIJ und Mitarb. [25] titrierten Essigsäure, Buttersäure, Valeriansäure und Capronsäure in einem aus Methanol und Dioxan bestehenden, sowie einige quaternäre Ammoniumhalogenide in einem acetonhaltigen Medium. Abb. 3.35 zeigt die Titrationskurve eines Salzgemisches mit gemeinsamem Anion ($KBr + (C_2H_5)_4NBr$) in acetonhaltigem Medium. Ihrem Dissoziationsgrad entsprechend reagierten die Salze nacheinander. In ihrem Ablauf weicht diese Titrationskurve von der einer normalen radiometrischen Titration ab. Die Knickpunkte dürften auf die Ausscheidung von Silberbromid und höherer Komplexe, wie z. B. $KAgBr_2$, zurückzuführen sein.

3.6.2. *Auf Absorption und Rückstreuung von* e^-*-Strahlen beruhende Fällungstitrationen*

Bei Durchgang durch Materie verlieren die e^--Strahlen allmählich ihre Energie und werden zu Richtungsänderungen veranlaßt. Bei den auf der Absorption und Rückstreuung der e^--Strahlen beruhenden radiometrischen Titrationen macht man sich diese Erscheinungen zunutze [20, 109, 110, 119].

3.6.2.1. *Auf der Rückstreuung der* e^-*-Strahlung beruhende Titrationen*

Treffen e^--Strahlen auf ein Atom auf, so werden sie sowohl durch die Elektronenhülle als auch durch den Kern gestreut. Im Extremfall kann der Streuungswinkel bis zu 180° betragen. Mit wachsender Ordnungszahl nimmt der durch den Atomkern verursachte Anteil der Streuung erheblich zu. Bei Elementen mit hoher Ordnungszahl wird die durch die Elektronenhülle verursachte Streuung vernachlässigbar gering (beim Gold z. B. beträgt sie nur 1% der durch den Kern verursachten Streuung). Obiges bezieht sich jedoch nur auf die durch ein Atom eines bestimmten Elements verursachte Streuung. In der Praxis ist die Lage viel unübersichtlicher, da an die Stelle der einfachen eine mehrfache Streuung tritt. Je größer die untersuchte flüssige oder feste Schichtdicke wird, umso größer wird auch der Anteil der Rückstreuung, so lange, bis die Schichtdicke der halben

pyridine, acetonitrile, isobutyl methyl ketone, 2-nitropropane, nitrobenzene or dimethylformamide, its behaviour is that of a stronger acid, as compared to other acids in the same solvent. The ionization of *m*-aminobenzoic acid may be represented by the reaction

$$m\text{-}H_3\overset{+}{N}C_6H_4COO^- + s \rightleftarrows m\text{-}H_2NC_6H_4COO^- + sH^+$$

and that of *p*-aminobenzoic acid by:

$$p\text{-}H_2NC_6H_4COOH + s \rightleftarrows p\text{-}H_2NC_6H_4COO^- + sH^+$$

Thus, ionization is preceded by the separation of charges through the formation of the zwitterion. The effect of the dielectric constant of the solvent is less upon *m*-aminobenzoic acid than upon *p*-aminobenzoic acid. (See: Chapter 2; Section 2 and Fig. 5.) Further, with the decrease in the dielectric constant of the solvent the relative acid strength of *m*-aminobenzoic acid increases compared with other acids, since intramolecular 'ionization' has already taken place while in other acids ionization is the result of an intermolecular interaction between the dissolved acids and the solvent molecules; and this can be influenced in a positive direction by the increase of the dielectric constant and in a negative one by its decrease.

p-Aminobenzoic acid, however, may exhibit another very characteristic interaction e.g. with nitrobenzene. (See: Chapter 7; Section 44.)

In contrast with the *meta*-substituted benzoic acids, the correlation between pK and log K_{ass} values of *para*- and *ortho*-substituted benzoic acids deviates from the 'standard' behaviour. In the case of benzoic acids substituted by *para* halogen, the deviation is slight; benzoic acids, substituted by electron releasing groups ($-OH$, $-OCH_3$, $-NH_2$) are relatively stronger in benzene than in water; while *para*-substituted benzoic acids containing $-CN$ and $-NO_2$ groups are weaker in benzene than in water.

According to Davis and Hetzer the water-coordinating ability of $-CN$ and $-NO_2$ groups accentuates their acid strength effect by enhancing resonance with the ring. But hydration of the $-OH$, $-OCH_3$ and $-NH_2$ groups reduces their acid weakening effect by decreasing resonance with the ring (see: Chapter 4; Section 27). The aqueous pK values of *para*-substituted benzoic acids are apt to present a misleading picture concerning the intrinsic strength of these acids.

It is well known that the effect of substituents in close proximity to the $-COOH$ group is generally not predictable. In Fig. 6 the dotted line indicates that *ortho*-substituted benzoic acids (except *o*-aminobenzoic acid) fall above the 'standard' line, that is, they are strong in water and weak in benzene, respectively.

The dotted line in Fig. 6 illustrating the correlation between aqueous pK values and K_{ass} values in benzene is only a rough guide to indicate the order of acid strength of *ortho*-substituted benzoic acids.

o-Methoxybenzoic acid is by far the weakest in benzene (not even represented in Fig. 6), pK (in water) 4·09 and log K_{ass} (in benzene) 3·7. Its association with diphenylguanidine in benzene is opposed by the stability of the chelate structure when the proton of the carboxyl group is held by the fields of force of the oxygen atom of the methoxy group (H-bond). In water, however, the hydrogen-bonding of the solvent opposes the formation of a chelate structure and modifies the inductive effect of the methoxy group on the carboxyl group, as well as its resonance with the benzene ring. Hydration could increase the steric requirement of the methoxy group to such a degree that it would cause steric inhibition of the preferred coplanar arrangement of the carboxyl group with the ring.

maximalen Reichweite der gegebenen e^--Strahlen im betreffenden Stoff entspricht. Man nennt diesen Effekt dann Sättigungsrückstreuung.

Für eine gegebene e^--Strahlung ist die Wahrscheinlichkeit, daß die Streuung einen bestimmten Winkel überschreitet, dem Quadrat der Ordnungszahl der die Streuung verursachenden Atome und der Schichtdicke des aus ihnen bestehenden Stoffes proportional (die »Schichtdicke« wird hier in den Einheiten: »Zahl der Atome je cm^2« ausgedrückt). Bei einer gegebenen e^--Strahlung ist die Intensität der Rückstreuung demnach für die Natur des Stoffes kennzeichnend, vorausgesetzt, daß die untersuchten Schichtdicken größer sind als die halbe maximale Reichweite [55, 102, 103].

Die Intensität der rückgestreuten e^--Strahlung nimmt mit steigender Ordnungszahl und mit steigender Konzentration des Elements zu. Aus der Natur der Rückstreuung der e^--Strahlung folgt, daß eine analytische Verwendung nur bei solchen Zweikomponentensystemen möglich ist, bei denen zwischen *dem Grad* der Rückstreuung und der Zusammensetzung des untersuchten Stoffes ein funktioneller Zusammenhang besteht.

Es wurden einige Fällungstitrationen ausgearbeitet, die auf der Rückstreuung von e^--Strahlen beruhen [110, 119]. Die Titrationskurve zeigt die als Funktion des Volumens der zugegebenen Titrierlösung aufgenommene Intensität der rückgestreuten e^--Strahlung. Ebenso, wie bei den einfachen radiometrischen Titrationen, sind auch hier drei Typen möglich.

(a) *Prüflösung enthält Elemente höherer Ordnungszahl; Maßlösung mit einem oder mehreren Elementen niedriger Ordnungszahl.*

Ein Beispiel hierfür ist die Titration von Silber(I) mit Salzsäure. Während der Titration nimmt mit abnehmender Konzentration des Elements mit höherer Ordnungszahl (infolge von Ausfällung) die Intensität der aus der Lösung rückgestreuten e^--Strahlung ab. Nach dem Endpunkt zeigt die Intensität der rückgestreuten Strahlung einen geringen Anstieg.

(b) *Elemente niedriger Ordnungszahl in der Prüflösung; Maßlösung enthält Elemente höherer Ordnungszahl.*

Als Beispiel sei die Titration von Chlorid mit Silbernitrat erwähnt. Während der Titration nimmt die Intensität der rückgestreuten Strahlung schwach ab, bis der Endpunkt erreicht ist. Dann beginnt die Intensität stark anzusteigen.

(c) *Sowohl Prüflösung als auch Maßlösung enthalten Elemente höherer Ordnungszahl.*

Die Intensität der rückgestreuten e^--Strahlung nimmt bis zum Endpunkt ab, um dann anzusteigen.

Der Endpunkt kann auf Grund der verschiedenen Titrationskurven auf ähnliche Weise bestimmt werden wie bei den einfachen radiometrischen Titrationen.

Die Verfasser bedienten sich bei diesen Titrationen der konventionellen Filtrier- und Zentrifugiermethoden.

o-Hydroxybenzoic acid (salicylic acid) is so close to the 'standard' pK/log K_{ass} correlation, denoted in Fig. 6 by the heavy line, that it may be inferred that the salicylate anion is mainly present in the same chelated form which accounts for its enhanced acid strength in aqueous solution.

The behaviour of *o*-methylbenzoic acid (*o*-toluic acid) in benzene is also of interest. In benzene the methyl group does not sterically inhibit the resonance of the carboxyl group with the ring. In aqueous solution, however, the clustering of the water dipoles round the carboxyl group sterically inhibits the resonance of the carboxyl group in *o*-toluic acid with the ring. Hydration of the carboxyl group in electron releasing *ortho*-substituted benzoic acids in an aqueous medium contributes generally to steric inhibition of resonance; the latter would otherwise result in the diminution of acid strength.

Summarizing the above: the order of relative strength of benzoic acids containing substituents in the *meta*-position is the same in benzene, as it is in solvents liable to autoprotolysis.

As regards benzoic acids containing substituents in a *para*-position, solvation reduces or enhances the acid strength; therefore the order of their relative acid strength in benzene reflects intrinsic acidity more accurately than does the aqueous pK value.

With a change of solvent, even a change from water to a solvent 'similar to water', a reverse order of relative strengths of benzoic acids containing substituents in the *ortho*-position may be found. A carboxyl group in the *ortho*-position enhances acid strength in aqueous media because it solvates. Phthalic acid while remarkably strong in water is of 'standard' strength in benzene.

The formation of an intramolecular hydrogen bond decreases the strength of *ortho*-substituted benzoic acids in benzene (e.g. *o*-methoxybenzoic acid). The possibility of chelation decreases when an H-bond is established between solute and solvent.

The higher acidic strength of *o*-nitrobenzoic acids, measured in water, may be in part attributed to hydration.

The above indicates that acid strengths measured in water do not provide accurate evidence of the intrinsic strength of acids. In prototropic solvents the proton exists only in a solvated form. Water, however, is able not only to solvate the proton, but also the carboxyl group of the benzoic acid as well possibly as others of its substituents, and thus the electrostatic, resonance and steric effects also undergo change. These experiments and Izmaĭlov's thorough investigations on the change of acid strength dependent on the solvent [412] furnish evidence that no universally valid scale of acid strength exists independently of the solvent. In an inert solvent, the strength of acids is also influenced by the structure of the reference base [174]. In practice, however, and keeping in mind the structural and solvating factors, useful acidity scales can be constructed.

(b) *The order of relative strengths of acids and bases in acetic acid.* According to Kolthoff and co-workers, in a solvent of low dielectric constant e.g. in acetic acid, the separation of ionizable compounds into ions is of minor importance. The degree of acid-base interaction can be described by acidity and basicity scales, respectively. Proton-acceptor bases, listed in the order of their strength, may be classed on the basis of their interaction with the same acid, e.g. perchloric acid. On the analogy of pK, a p_{HClO_4} scale can be constructed and the same bases with hydrochloric acid enable another scale, that of p_{HCl} [819] to be set up.

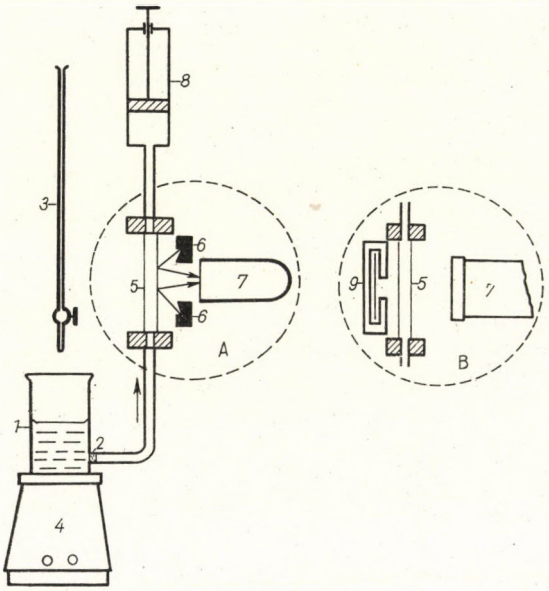


Abb. 3.36
Vorrichtung zur Durchführung der auf e^--Strahlen-Rückstreuung *(A)* und auf e^--Strahlen-Absorption *(B)* beruhenden radiometrischen Titrationen (Tölgyessy und Mitarb. [110]). (*1* — Titrationsgefäß; *2* — Glasfilter; *3* — Bürette; *4* — Rührer; *5* — Meßküvette; *6* — ringförmige e^--Strahlenquelle; *7* — GM-Zähler oder Szintillationszähler als Detektor; *8* — Injektionsspritze; *9* — geschlossene e^--Strahlenquelle)

Die Versuchseinrichtung ist in Abb. 3.36 (*A*) gezeigt. Sie besteht aus einem Becherglas als Titrationsgefäß, einer Bürette und einem Magnetrührer. In den unteren Teil des Becherglases ist eine Filterplatte eingeschmolzen, die zur Trennung der Lösung vom gebildeten Niederschlag dient. Gegenüber der aus Plexiglas bestehenden, mit Polyäthylen-Fenstern versehenen Meßküvette ist eine ringförmige e^--Strahlungquelle (^{204}Tl) angeordnet. Die durch die Lösung in der Meßküvette rückgestreute e^--Strahlung wird mit einem GM-Endfenster-Zählrohr gemessen. Alle Bauelemente in der Nähe des e^--Strahlendetektors bestehen aus Stoffen mit möglichst niedrigen Ordnungszahlen. Als solche eignen sich besonders Kunststoffe, wie Polyäthylen und Plexiglas.

Praktisch wird die Titration wie folgt durchgeführt: Man gibt eine bestimmte Menge der Maßlösung zur Prüflösung, läßt den gebildeten Niederschlag absetzen, saugt die klare Lösung durch die Filterplatte in die Meßküvette und mißt die Intensität der rückgestreuten Strahlung. Änderungen des Volumens werden als Korrektion berücksichtigt. Der Knickpunkt der Titrationskurve zeigt den Endpunkt an.

Bei der Zentrifugen-Methode werden verschiedene Mengen der Maßlösung zu gleichen Volumina der Prüflösung in mehreren Zentrifugenröhren zugegeben. Die Reaktionsgemische werden hierauf mit destilliertem Wasser auf ein gleiches Volumen aufgefüllt, und der Niederschlag wird abzentrifugiert. Dann werden gleiche Mengen aus dem Zentrifugat pipettiert und die Intensitäten der Rückstreuung der e^--Strahlung durch die Lösung in einer für diese Zwecke konstruierten Vorrichtung (Schema: siehe Abb. 3.37; Foto: Abb. 3.38) gemessen.

Abb. 3.39 zeigt die Titrationskurve von Silber(I) mit 0,1 N Salzsäure. Nach dem gleichen Verfahren haben die Verfasser Hexacyanoferrat(II) mit 0,1 N Bleinitratlösung bestimmt. Die Intensität der durch destilliertes Wasser — in der Küvette — rückgestreuten e^--Strahlung muß von der Rückstreuung durch die untersuchten Lösungen abgezogen werden.

The above also applies to prototropic reactions of acids with bases. To indicate the degree of proton transfer between hydrogen-acids and, for example, diphenylguanidine the acid strength-scale P_{DPG} can be constructed. As many basicity p_{AH} scales can be constructed as there are reference acids while the reverse is also true: every reference base represents the basis of another p_B acidic strength scale. Thus one scale, the pH scale, is not universal.

Brönsted's acid–base concept in the sense:

$$\text{Acid} \rightleftharpoons \text{Base} + H^+ ,$$

can also be extended to prototropic reactions in low-dielectric solvents. The customary process of proton transfer is, however, modified by an important factor: in solvents of low dielectric constant, ions can exist only in minute quantities because they mainly solvate as uncharged particles, associations and ion-pairs.

In acetic acid the dissociation constant of salts is roughly 10^{-6} or even somewhat smaller [102, 412]. The ionization of perchloric acid is $10^{-4{\cdot}85}$ [102]. Apart from some exceptions ionization phenomena can only be compared in solvents whose dielectric constant exceeds 40.

Among the various sorts of proton transfer the most important is when the *A*H acid molecule (perchloric acid, *p*-toluenesulphonic acid, hydrochloric acid, etc.) associates, simultaneously with the proton transfer, with some base *B* (amines, heterocyclic bases, acid amides) (see: Chapter 2; Section 11(c), [294, 887]):

$$AH + B \rightleftharpoons BHA \; ; \quad K = \frac{[B]\,[AH]}{[BHA]} ,$$

and the A^- anion base and the BH^+ 'onium acid form an ion pair since the solvent with small dielectric constant is not able to separate the charged ions permanently. The ionization constant of pyridinium perchlorate is only $10^{-6{\cdot}1}$.

Bases, depending on their strength, dissolve in acetic acid either as acetates or in the molecular form. Pyridine being a strong base in acetic acid, 80% of it is present in the $[C_5H_5NH^+]CH_3COO^-$ form, and 20% in the molecular form. Methyl yellow is 10% solvated as acetate and 90% in the molecular form. Urea is similarly a weak base, since it does not form an acetate in acetic acid.

The above also applies to acids. Perchloric acid is present in acetic acid as acetacidium perchlorate, $[CH_3COOH_2]^+ClO_4^-$, while trichloroacetic acid is dissolved in the molecular form.

When comparing the interaction of various bases with one and the same reference acid, e.g. perchloric acid, it can be seen that the association constant K and pK characterize the degree of base reference–acid interaction while a $BHClO_4$ complex is formed:

$$K = \frac{[B]}{[BHClO_4]}\,[HClO_4]$$

The pK values of various bases in comparison with perchloric acid can be represented on a *common scale.*

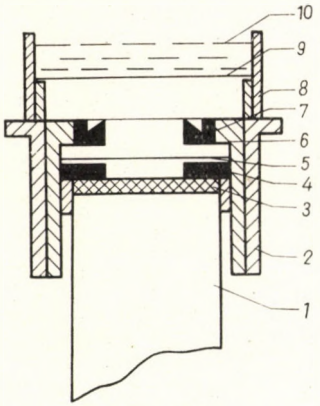


Abb. 3.37
Schema des Meßkopfes zur Bestimmung der Rückstreuung von e^--Strahlen (ŠARSUNOVA, KLAS und TÖLGYESSY; vgl. TÖLGYESSY [105]). (*1* — Szintillations-Verstärkerkopf; *2* — Gehäuse aus Plexiglas; *3* — e^--Szintillator; *4* — Bleikollimator; *5* — Absorber; *6* — Bleiring; *7* — Strahlenquelle, ^{204}Tl; *8* — Küvette; *9* — Polyäthylenfolie; *10* — Prüflösung)

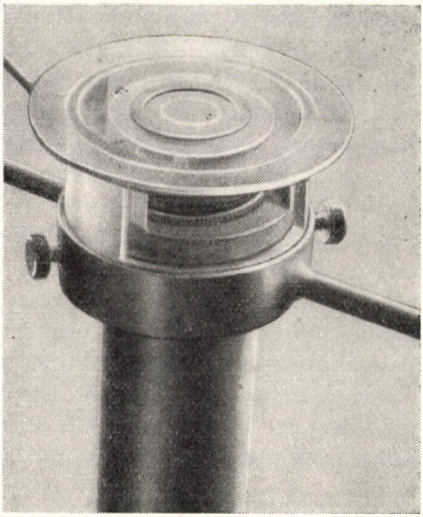


Abb. 3.38
Ansicht des Meßkopfes zur Bestimmung der Rückstreuung von e^--Strahlen (ŠARSUNOVA, KLAS und TÖLGYESSY; vgl. TÖLGYESSY [105])

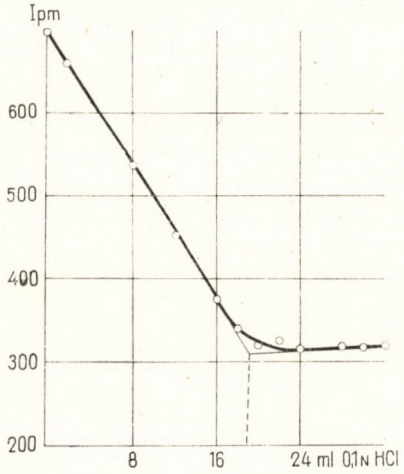


Abb. 3.39
Bei der auf e^--Strahlen-Rückstreuung beruhenden radiometrischen Titration von Ag mit 0,1 N HCl erhaltene Kurve (TÖLGYESSY und VARGA [119])

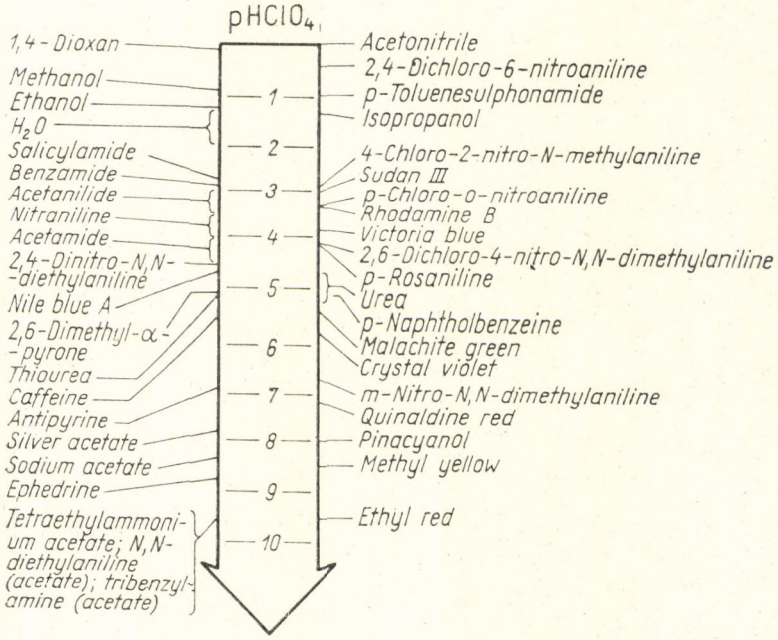


Fig. 7. Basicity scale $pHClO_4$ according to Trémillon [819]. See also: [101, 102, 388, 389, 390, 463, 499, 505, 763]

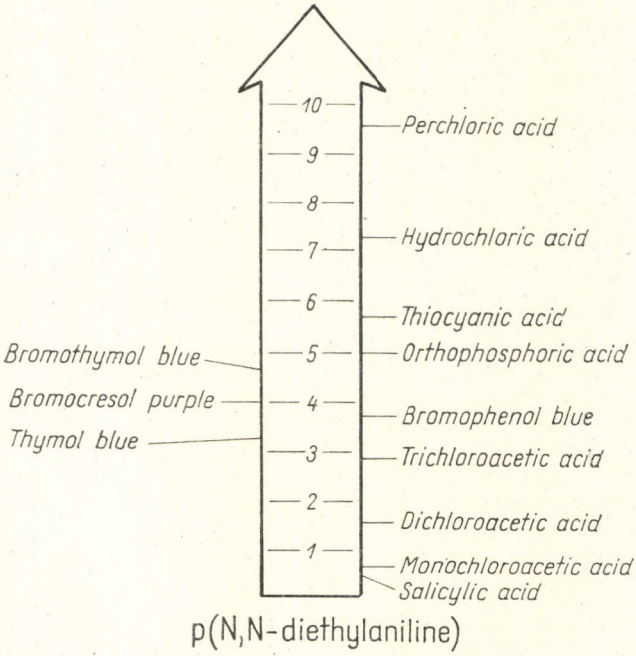


Fig. 8. Acidity scale p(N,N-diethylaniline) according to Trémillon [819]. See also: [102, 499]

Die auf der Rückstreuung der e^--Strahlung beruhenden radiometrischen Fällungstitrationen haben gegenüber den bisher erwähnten Methoden den Vorteil, daß sie mit einer geschlossenen Strahlenquelle arbeiten, die eine Strahlungsgefährdung erheblich reduzieren. Ebenso sind auch die Anwendung verschiedener radioaktiver Indikatoren überflüssig. Bei Verwendung der bereits erwähnten Methoden (vgl. S. 40) können diese Titrationen leicht automatisiert werden. Man kann die auf Rückstreuung der e^--Strahlung beruhenden radiometrischen Titrationen aber auch auf solche Reaktionen anwenden, die nicht mit Niederschlagsbildung einhergehen. Beispiele hierfür sind die Redox-Amalgam-Titrationen, die auf Lösungsmittelextraktion beruhenden Titrationen usw., bei denen also die Ausgangsstoffe von den Reaktionsprodukten getrennt werden können.

Ein wesentlicher Nachteil ist die geringe Empfindlichkeit (mehrere mg/Liter) der Methode und die Tatsache, daß sie nur die Bestimmung von Stoffen erlaubt, die Elemente mit höherer Ordnungszahl enthalten.

3.6.2.2. *Auf der Absorption der* e^-*-Strahlung beruhende Titrationen*

Da die e^--Strahlen zahlreiche Wechselwirkungseffekte mit der Materie zeigen, kann ihr Weg auch zickzack-förmige mehrfache Richtungsänderungen aufweisen. Die Geschwindigkeiten der Teilchen sind selbst in der Anfangsphase verschieden; daher lassen sich für die allgemeine Abnahme ihrer Intensität keine exakten Zusammenhänge ableiten. Es ist jedoch gelungen, auf empirischem Wege einige annähernde Zusammenhänge zu finden.

Eine dem Lambert–Beerschen Gesetz der Lichtabsorption ähnliche exponentielle Beziehung besitzt auch für die Absorption der e^--Strahlung annähernde Gültigkeit:

$$I = I_0 \exp\left[-\frac{\mu}{\varrho} R\right] = I_0 \exp\,(-aR), \tag{3.37}$$

I = Intensität der Strahlung nach ihrem Durchgang durch das Material
I_0 = Intensität der Strahlung vor dem Eintritt in das Material
μ = linearer Absorptionskoeffizient (cm^{-1})
a = Massenabsorptionskoeffizient ($cm^2\,g^{-1}$)
ϱ = Dichte des absorbierenden Mediums ($g\,cm^{-3}$)
R = Schichtdicke, ausgedrückt in Oberflächendichte ($g\,cm^{-2}$).

Der Massenabsorptionskoeffizient hängt nur in geringem Maße von der Natur des Stoffes ab. Wasserstoff absorbiert jedoch extrem stark (doppelt so stark wie Kohlenstoff). Daher wurde die Absorption der e^--Strahlen als Grundlage quantitativer Analysen bisher vorwiegend zur Bestimmung von Wasserstoff und in einigen Fällen des C : H-Verhältnisses in verschiedenen Stoffen verwendet. Es sind bisher nur wenige Arbeiten über die Absorption

This is the p_{HClO_4} basicity strength scale:

where $$[HClO_4] = 1$$

$$p_{HClO_4} = 0.$$

Such a basicity strength scale may also be set up with hydrochloric and other acids [819] (Fig. 7).

Comparing pK values of different acids with N,N-diethylaniline a similar scale can be established, though in a reverse sense: this is the $p_{(N,N\text{-diethylaniline})}$-scale [102, 499, 819] (Fig. 8).

When the various p_{AH} basicity scales are collated it may be seen that the position or order of widely different bases compared with each other, and, similarly

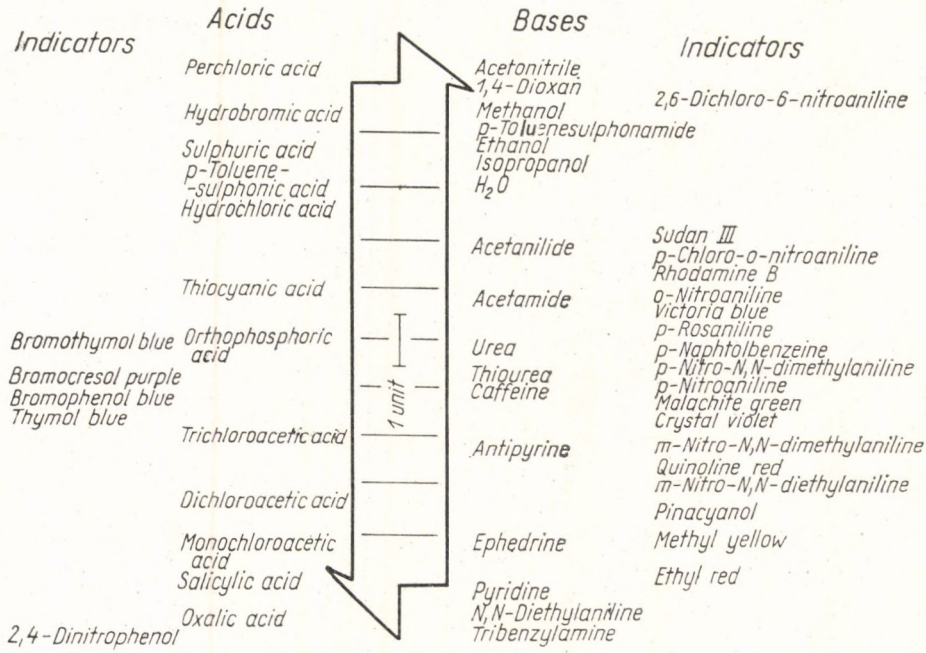


Fig. 9. 'Acidity' scale in acetic acid medium according to Trémillon [819]

the relative position of hydrogen acids on the p_B acidic scales are to a good approximation the same [819]. It follows from this that the various p_{AH} and p_B scales, respectively, may be united into one common 'acidity scale', valid in acetic acid medium, with the strength of acids increasing upwards, and of bases downwards. The p_K region is about 9·6 units (Fig. 9).

Concerning the practical value of the scale, it can be seen, at a glance, that every acid is capable of entering into reaction with a base ranked on a lower level of the scale, and every base is capable of entering into prototropic reaction with an acid placed on a higher level of the scale.

For the plotting of acid–base scales, and their experimental use, see: [499, 819]. Measurements were carried out by the Hammett–Deyrupp indicator–spectrophotometric method [342, 343].

von e^--Strahlen durch Lösungen bzw. über die quantitative Bestimmung schwerer Elemente in ihren Lösungen erschienen [102, 103].

Bisher wurden nur wenige Fällungstitrationen ausgearbeitet, die auf der Absorption von e^--Strahlen beruhen [107, 109, 110]. Bei solchen Titrationen muß entweder die Prüflösung oder das Titriermittel oder auch beide ein Element von höherer Ordnungszahl enthalten. In der Titrationskurve wird die gemessenen Strahlungsintensität (Logarithmus der Zahl der Impulse in der Zeiteinheit) als Funktion des Volumens der zugegebenen Maßlösung dargestellt. Solche Kurven zeigen im Vergleich zu jenen, die bei den auf Rückstreuung der e^--Strahlen beruhenden Titrationen erhalten werden, einen umgekehrten Ablauf.

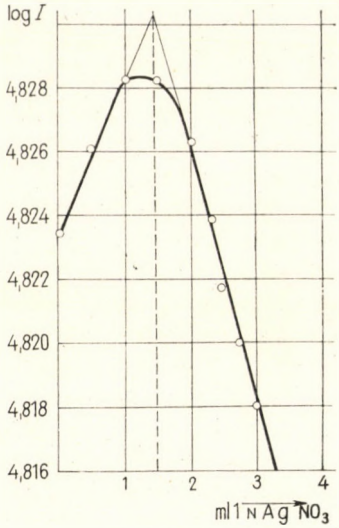


Abb. 3.40
Bei der auf e^--Strahlen-Absorption beruhenden radiometrischen Titration von Cl^- mit 1,0 N $AgNO_3$-Lösung erhaltene Kurve (TÖLGYESSY und DILLINGER; vgl. Tölgyessy [105])

Die konventionellen Methoden der Filtration und des Zentrifugierens können auch hier angewandt werden. Zur Durchführung der Filtrationsmethode diente die in Abb. 3.36 *(B)* gezeigte Vorrichtung. Auf der einen Seite der mit Polyäthylen-Fenstern versehenen Meßküvette aus Plexiglas wurde eine e^--Strahlenquelle, 1 mCi ^{90}Sr, angebracht, ihr gegenüber, auf der anderen Seite der Küvette, ein Szintillationszähler, der mit einer automatischen Registriervorrichtung in Verbindung stand. Während des Titrationsprozesses wurde die Intensität der e^--Strahlung, nach ihrem Durchgang durch die Prüflösung, gemessen. Eine bei der Titration von 25 ml einer Chlorid-Lösung mit 1 N Silbernitratlösung erhaltene Kurve ist in Abb. 3.40 gezeigt. Die Genauigkeit der Bestimmung ist $\pm$ 1,5%. Die Technik des Zentrifugierens ist die gleiche wie bei den oben bereits beschriebenen Methoden.

Die auf der Absorption der e^--Strahlung beruhenden Titrationen weisen die gleichen Vorteile wie die Rückstreuungs-Verfahren auf. Ihre Empfindlichkeit ist jedoch geringer, da der Massenabsorptionskoeffizient nur in geringem Maße von der Natur des Stoffes abhängig ist.

Auf Grund der genannten Tatsachen werden sich diese Titrationsverfahren in der Praxis wohl kaum auf breiter Basis durchsetzen können.

3.6.3. *Radiocoulometrische Titrationen*

Die Verschmelzung der theoretischen Grundlagen der coulometrischen und radiometrischen Titrationen hat zur Entwicklung der radiocoulometrischen

(c) *Correlation between half-neutralization potential* (h.n.p.) *and pK value.* Streuli used an electrometric method for determining the pK_{acid} values of substituted benzoic acid and phenol derivatives [780, 782]. The acidic character of substituted benzoic acids and phenols in pyridine can be determined from their pK_{acid} value in water when the molecular structure is taken into consideration: within a group of similar

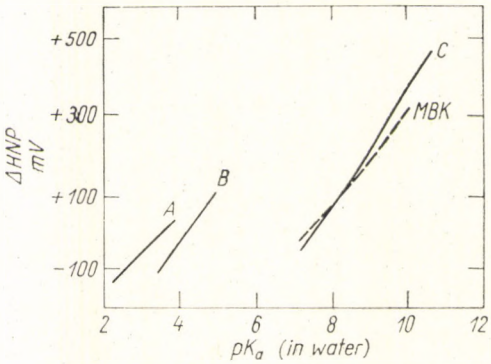


Fig. 10. Correlation between half-neutralization potential of substituted benzoic acids and phenols and their pK_a value measured in water according to Streuli and Miron [595,780, 782]. — *(A) ortho*-substituted benzoic acids (in pyridine), *(B) meta*- and *para*-substituted benzoic acids (in pyridine), *(C)* substituted phenols (in pyridine) and *(MBK)* substituted phenols (in methyl isobutyl ketone)

molecular structure, similar behaviour is to be expected when titrated potentiometrically. This applies, in particular, to the correlations between half-neutralization potential and pK_{acid}.

The acid strength of phenols in pyridine is increased to a relatively higher degree than that of carboxylic acids. Half-neutralization potential differences of phenols and acids can be measured by a similar method. A suitable electrode pair is glass

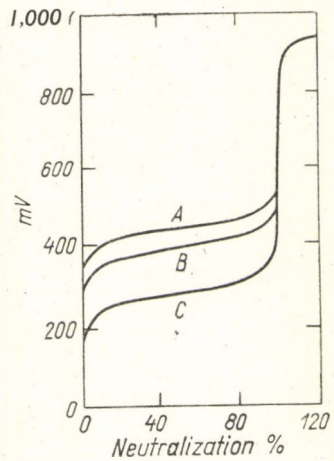


Fig. 11. Potentiometric curves of *o*-toluic acid *(A)*, benzoic acid *(B)*, and *p*-nitrobenzoic acid *(C)*, in pyridine standard solution: 0·1 *N TBAH;* according to Streuli and Miron [782]

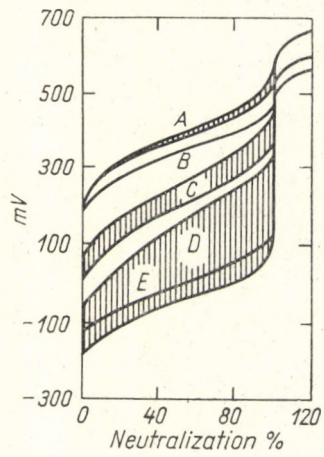


Fig. 12. Potentiometric curves of substituted phenols according to Streuli [780].— Solvent: pyridine. Titrant: 0·1 N Tetrabutylammonium hydroxide. *(A)* Cresols, *(B)* Phenol, *(C)* Chlorophenols, *(D)* Nitrophenols, *(E)* Benzoic acid

Titrationsmethoden geführt [107, 110]. Den bisher beschriebenen Methoden gegenüber weist dieses kombinierte Verfahren die folgenden Vorteile auf:

(a) Erhöhte Genauigkeit der Bestimmungen.

(b) Eliminierung der Schwierigkeiten, die Maßlösung genau und kontinuierlich zu dosieren. Das Titriermittel wird nicht aus einer Bürette zugegeben, sondern durch Elektrolyse in der Prüflösung selbst hergestellt.

(c) Beseitigung der mit der Herstellung, Einstellung und Lagerung instabiler Titriermittel verbundenen Schwierigkeiten.

(d) Korrekturen für Volumen-Änderungen entfallen.

Drei Typen radiocoulometrischer Fällungstitrationen sind bekannt geworden: Entweder die Prüflösung oder die verwendete Elektrode bzw. beide sind markiert.

1. *Prüflösung aktiv.* Ein Beispiel hierfür ist die Titration von ^{131}I-markiertem Jodid. Sie wird mit einer Silberelektrode durchgeführt, die auf elektrochemischem Wege Silberionen erzeugt. Mit fortschreitender Ausfällung des ^{131}I aus der Lösung nimmt deren Aktivität ab. Nach dem Endpunkt bleibt dann die Aktivität konstant.

2. *Prüflösung inaktiv.* Wird eine schwach aktivierte Silberplatte als Anode verwendet, so können Jodidionen mit elektrochemisch erzeugten $^{110m}Ag^+$-Ionen titriert werden. Bis zum Endpunkt bleibt die Aktivität der flüssigen Phase bei einem niedrigen Wert und steigt dann – mit Anwachsen der $^{110m}Ag^+$-Konzentration – steil an.

3. *Prüflösung und Elektrode aktiv.* In diesem Falle nimmt die Aktivität der flüssigen Phase bis zum Endpunkt ab, um dann anzusteigen.

Mit Hilfe der radiocoulometrischen Fällungstitrationen können zwei oder drei Komponenten nebeneinander bestimmt werden, vorausgesetzt, daß sie mit den elektrochemisch erzeugten Ionen Niederschläge liefern, deren Löslichkeitsprodukte genügend unterschiedlich sind.

Für die bei der Titration eines markierten Ions unter Anwendung einer inaktiven Elektrode erhaltene Kurve gilt die Gleichung:

$$I^2 - I\left(I_0 - \frac{At}{kV}\right) - \frac{L}{k^2} = 0 \tag{3.38}$$

I = Aktivität eines konstanten Volumens der Lösung während der Titration [Ipm],

I_0 = Ausgangs-Aktivität der markierten Prüflösung (Ipm)

V = Volumen der titrierten Lösung (Liter)

k = Verhältnis der Konzentration der markierten, titrierten Ionen zu ihrer Radioaktivität (d. h. $[A^+] = k \cdot I$) $\left[\frac{\text{g. Äqu. Min}}{\text{l. Ipm}}\right]$

L = Löslichkeitsprodukt der während der Titration gebildeten Verbindung $\left[\frac{(\text{g. Äqu.})^2}{\text{l}^2}\right]$

and methanolic calomel (see: Chapter 12; Section 67). Titrant: 0·1 N tetrabutylammonium hydroxide (see: Chapter 10; Section 57). For both groups of compounds the zero value of h.n.p. is the h.n.p. millivolt value of benzoic acid, measured the same day and under identical experimental conditions, and subtracted, together with its sign, from the h.n.p. millivolt value of the acid or phenol to be measured. If the h.n.p. value of the measured acid or phenol is smaller than that of benzoic acid – i.e. it is of negative sign – the former is stronger than benzoic acid.

Line *B* in Fig. 10 represents the pK_{acid} in water and Δ h.n.p. function in pyridine of *meta-* and *para*-substituted benzoic acids, except for *m*-aminobenzoic acid which contains in the crystalline state an NH_3^+ group, as shown by the infrared spectrum. Therefore, in a solvent of low dielectric constant it is probably the cationic acid that is titrated and not its ionized form,

$$[m\text{-}H_2N.C_6H_4.COO^-]\ H^+$$

Line *A* in Fig. 10 refers to *ortho*-substituted benzoic acids.

Acids on the left of the line representing acidic ratios measured in pyridine and water are weaker in pyridine; those on the right are stronger in pyridine than in water. Most of the *ortho*-substituted benzoic acids are weaker in pyridine than in water, exhibiting a decrease in the *ortho*-effect. However, *o*-hydroxy and *o*-aminobenzoic acid are stronger in pyridine than in water, probably because they are present in a stabilized anionic or cationic form.

Line *C* in Fig. 10 relates to substituted phenols.

A difference between phenols and benzoic acids is that in pyridine the strength of acids is influenced decisively by substituents, while the same does not apply to phenols.

In Fig. 11 potentiometric curves of some benzoic acid derivatives are illustrated, while in Fig. 12 those of some substituted phenols are shown. Tables 1, 2 and 3 give

Table 1

pK_{acid} VALUES IN WATER AND Δ h.n.p. VALUES IN PYRIDINE OF ORTHO-SUBSTITUTED BENZOIC ACIDS. $h.n.p._0$ = BENZOIC ACID [780, 782]

Acid	Δ h.n.p. mV	pK_{acid} [189]	*Calculated* pK_{acid}
Toluic acid	+ 44	3·91	4·05
Methoxybenzoic acid	+ 33	4·09	3·95
Chlorobenzoic acid	− 65	2·94	2·96
Bromobenzoic acid	− 77	2·86	2·84
Nitrobenzoic acid	−142	2·17	2·19

an abstract of pK_{acid} and Δ h.n.p. correlations of some better-known benzoic acid derivatives and phenol derivatives, respectively [780, 782].

To sum up: linear correlation between h.n.p. and pK_{acid} values in pyridine makes it possible to provide an approximate estimate of pK_{acid} values for benzoic acid and phenol derivatives. The accuracy in the case of phenols is 0·18 p*K*, and for *meta-* and *para*-substituted benzoic acids 0·1 p*K* unit [780, 782].

A = Konstante, die auch das elektrochemische Äquivalent enthält, $\left[\frac{\text{g. Äqu.}}{\text{Min.}}\right]$

t = Zeit [Min.].

Wenn der letzte Ausdruck in (3.38) vernachlässigt werden kann, so läßt sich die Titrationskurve mit zwei Geraden ausdrücken:

$$I - I_0 - \frac{At}{kV} \quad \text{und} \quad I = 0. \tag{3.39}$$

Sie stellen die Asymptoten der ursprünglichen Kurve (einer Hyperbel) dar. Die aus ihrem Schnittpunkt zur Zeitachse gezogene Normale ergibt den Endpunkt.

Radiocoulometrische Titrationen können diskontinuierlich und auch kontinuierlich durchgeführt werden.

Die Verfasser titrierten z. B. Jodid (markiert durch ^{131}I) mit Silber(I), das aus einer Silberelektrode elektrochemisch erzeugt wurde (40 ml Acetatpuffer, pH = 6,0, + 40 ml 2 N Kaliumnitratlösung + 20 ml der Kaliumjodid-Prüflösung markiert mit ^{131}I; zwei Silberelektroden, 10 mA).

Die bei der diskontinuierlichen Titration erhaltene Kurve ist in Abb. 3.41 gezeigt. Zu ihrer Aufnahme wurde die Aktivität der flüssigen Phase während der Titration mehrere Male gemessen.

Zur kontinuierlichen Durchführung radiocoulometrischer Fällungstitrationen haben die Verfasser ein automatisches Titrimeter entwickelt.

Abb. 3.42 zeigt das Schema der Vorrichtung, in der Jodid (markiert mit ^{131}I) mit coulometrisch erzeugten Silberionen titriert wurde. Für den kontinuierlichen Kreislauf der flüssigen Phase — durch die in das Titriergefäß eingeschmolzene Filterplatte in den Glasmantel eines GM-Zählrohres und von hier zurück in das Titriergefäß — sorgte eine Laboratoriums-Mikropumpe. Das GM-Zählrohr war mit einem Ratemeter verbunden und die gemessene Aktivität wurde laufend registriert. So wurde die Titrationskurve $a = f(t)$ — die Aktivität der flüssigen Phase als Funktion der Zeit — erhalten. Den 10-mA-Gleichstrom lieferte ein 12-V-Akkumulator. (Beschreibung des Stromstärkestabilisators siehe [86].)

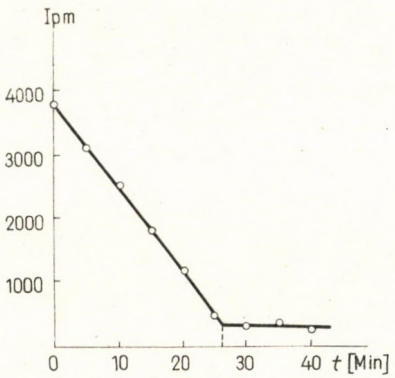


Abb. 3.41
Kurve der diskontinuierlichen radiocoulometrischen Titration von I^- (markiert mit ^{131}I) mit coulometrisch hergestelltem Ag^+. (TÖLGYESSY, JESENÁK und BRAUN [110])

Zur Auswertung der Zeit-Aktivitäts-Titrationskurven ist der Abstand zwischen dem Beginn der Titration und dem Schnittpunkt der linearen Abschnitte der Kurve zu ermitteln. Die weitere Auswertung erfolgt dann mit Hilfe einer der folgenden beiden Methoden:

Table 2

pK_{acid} VALUES IN WATER AND Δ h.n.p. VALUES IN PYRIDINE OF META- AND PARA-SUBSTITUTED BENZOIC ACIDS. h.n.p.$_0$ = BENZOIC ACID [780, 782]

Acid	Δ h.n.p. mV	pK_{acid} [189]	*Calculated* pK_{acid}
p-Aminobenzoic acid	+105	4·92	4·82
p-Hydroxybenzoic acid	+ 80	4·54	4·66
p-Methoxybenzoic acid	+ 45	4·47	4·44
m-Hydroxybenzoic acid	+ 23	4·08	4·30
m-Toluic acid	+ 16	4·27	4·25
p-Toluic acid	+ 3	4·37	4·17
m-Methoxybenzoic acid	− 5	4·09	4·20
p-Chlorobenzoic acid	− 25	3·98	3·99
p-Bromobenzoic acid	− 30	3·97	3·96
m-Chlorobenzoic acid	− 49	3·83	3·84
m-Bromobenzoic acid	− 63	3·81	3·75
m-Nitrobenzoic acid	− 97	3·49	3·53
p-Nitrobenzoic acid	−110	3·42	3·44

Table 3

pK_{acid} VALUES IN WATER AND Δ h.n.p. VALUES IN PYRIDINE OF SUBSTITUTED PHENOLS. h.n.p.$_0$ = BENZOIC ACID [780, 782]

Phenol	Δ h.n.p. mV	pK_{acid}	*Calculated* pK_{acid}
p-Aminophenol	+463	10·68	10·58
p-Methoxyphenol	+403	10·16	10·18
o-Aminophenol	+389	9·95	10·09
m-Cresol	+386	10·01	10·07
Phenol	+340	9·95	9·77
p-Cresol	+387	10·17	10·07
o-Cresol	+386	10·20	10·07
m-Methoxyphenol	+310	9·33	9·57
p-Chlorophenol	+248	9·38	9·16
m-Chlorophenol	+220	9·02	8·97
o-Chlorophenol	+190	8·48	8·77
m-Nitrophenol	+139	8·35	8·44
2,4-Dichlorophenol	+ 78	7·85	8·03
o-Nitrophenol	− 25	7·23	7·35
p-Nitrophenol	− 50	7·14	7·19

(d) *Hammett's H_0 acidity function.* According to classical concepts the degree of acidity in aqueous solutions is determined by the concentration of the hydroxonium ion. The laws of ionic equilibrium are only valid for very weak solutions and do not hold in more highly concentrated solutions. The concentration of the hydroxonium ion can be measured electrometrically or absorptiometrically but in some acid-catalyzed reactions the reaction velocity is not proportional to the concentration of the measured hydroxonium ion. In concentrated sulphuric acid (virtually free from

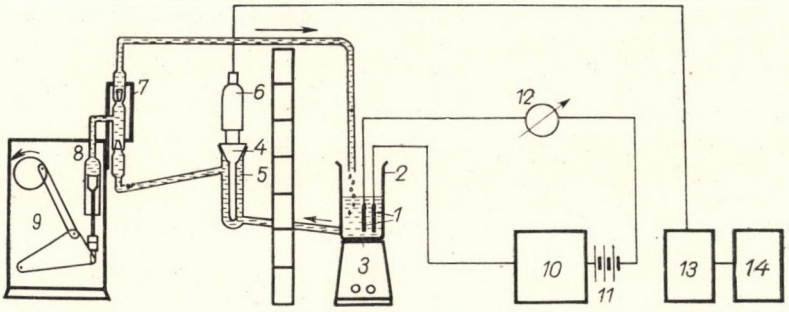


Abb. 3.42
Automatisches radiocoulometrisches Titrimeter (TÖLGYESSY, JESENÁK und BRAUN [110]). (*1* — Silberelektroden; *2* — Titrationsgefäß mit eingebauter Filtrierscheibe; *3* — elektromagnetischer Rührer; *4* — GM-Zähler; *5* — Glasmantel; *6* — Verstärkerkopf; *7* — Quecksilberventil; *8* — Injektionsspritze; *9* — Elektromotor mit Getriebe; *10* — Amperostat; *11* — Gleichstrombatterie; *12* — Amperometer; *13* — Ratemeter; *14* — Registrierapparat)

(a) Die zur Erreichung des Endpunktes notwendige Strommenge (Coulomb) kann auf Grund der Zeit und der Stromstärke berechnet werden.
(b) Zum gleichen Ergebnis gelangt man auch durch Vergleich der obigen Zeit mit der zur Titration eines Standards notwendigen Zeit.

3.7. Verschiedene Anwendungsmöglichkeiten der Fällungstitrationen

Die radiometrischen Fällungstitrationen wurden auch auf nicht direkt analytische Fragestellungen mit Erfolg angewandt: So z. B. zur Bestimmung der Zusammensetzung von Verbindungen, zur Untersuchung der Mitfällung, zur Ermittlung von Löslichkeitsprodukten und der spezifischen Aktivität radioaktiver Präparate. Die Zahl der hierüber erschienenen Arbeiten ist zwar noch ziemlich klein, doch dürften die bisher erzielten Erfolge zu weiteren Versuchen anregen.

3.7.1. *Bestimmung der Zusammensetzung von Verbindungen*

Zur Bestimmung der Zusammensetzung der im Laufe der Titrationen gebildeten Stoffe konnten die radiometrischen Titrationen in mehreren Fällen mit Erfolg eingesetzt werden.

SHINAGAWA, MATSUO und YOSHIDA [92] gelang es, die Zusammensetzung der Triphenyl-selenonium-tetrajodbismutat(III)-Komplexe zu klären. Zur Phasentrennung bedienten sie sich der Zentrifugen-Methode.

In Zentrifugenröhren wurden 25 ml einer mit 0,5 N HCl angesäuerten $1{,}09 \times 10^{-3}$ M $BiCl_3$-Lösung und 3,0 ml einer mit ^{131}I markierten 0,1 M KI-Lösung mit verschiedenen Volumina von $1{,}00 \times 10^{-2}$ M $(C_6H_5)_3SeCl$-Lösung vermischt. Nach Messung der Aktivität der flüssigen Phasen wurden die Titrationskurven auf Grund der erhalte-

water) the concentration of the hydroxonium ion is small and, in this sense, its acid strength ought to be likewise small; this, however, is not observed in practice.

Hammett and Deyrup's acidity function (H_0) seems in many cases to be more convenient for expressing the strength of concentrated acid solutions than pH, with which it is identical in very dilute solutions but not in concentrated solutions where it has other values [339, 340, 342, 625]. Their method is based on the ionization equilibria of a particular class of indicators, behaving in Brönsted's sense as uncharged bases.

When an indicator B is added to the aqueous solution of an acid of low concentration the equilibrium may be represented as follows:

$$B + H_3O^+ \rightleftharpoons BH^+ + H_2O$$

The indicator-constant, that is, the acid-constant of the conjugate acid BH^+ is:

$$pK_{BH^+} = \log \frac{[BH^+]}{[B]} + pH$$

By substituting pH by the symbol H_0 the indicator-constant becomes

$$pK_{BH^+} = \log \frac{[BH^+]}{[B]} + H_0 \text{ and } H_0 = pK_{BH^+} - \log \frac{[BH^+]}{[B]}$$

where B = the uncharged indicator-base, the pK_{BH^+} value of which is related to the value found in dilute aqueous solution by the *indirect* and stepwise method.

The pK_{BH^+} value of indicators with neither too large nor too small a $[BH^+]/[B]$ ratio (i.e. convenient for absorptiometric measurement), may be calculated by a joint absorptiometric and electrometric measurement. The relation between the ratio of the acidic and basic form of the indicator and light absorption (e.g. in sulphuric acid medium) is: [625] and [230]:

$$\frac{[BH^+]}{[B]} = \frac{\varepsilon_B - \varepsilon}{\varepsilon - \varepsilon_{BH^+}},$$

where εB = the molar extinction coefficient of the basic form only, at a given wavelength

ε_{BH^+} = the molar extinction coefficient of the solution containing only the acidic form

ε = the molar extinction coefficient of the solutions containing the partially ionized indicator.

For solutions of increasing concentration, Hammett used a series of indicators whose basicity decreased in stages. By this means the $[BH^+]/[B]$ ratio can be measured precisely (see: [230]). Values of these ratios have proved to be adequate for determinations carried out with intermittent measurements in the acid concentration range; and also for measurements in highly dilute solutions. Fig. 13 shows the process roughly outlined.

nen Werte aufgestellt (vgl. Abb. 3.43). Auf Grund des Endpunktes ergab das Verhältnis $[(C_6H_5)_3Se]^+$: Bi in der ausgeschiedenen Verbindung zu 1 : 1.

In der Lösung, zu der keine $(C_6H_5)_3SeCl$-Lösung zugegeben worden war, lag Bi : I im Verhältnis 1 : 11,1 vor und es schied sich kein Niederschlag aus. Die Ausgangsaktivität der Jodidlösung betrug 5841 Ipm (Ausgangspunkt der in Abb. 3.43 gezeigten Titrationskurve), die Aktivität des aktiven Jodids pro Mol demnach 5841 : 11,1 = 526. Am Endpunkt betrug die Aktivität 3744; die im Niederschlag vorliegende Jodid-Aktivität also 5841 — 3744 = 2097. Die Zahl der auf ein Mol Wismut entfallenden Mole Jodid ist also 2097/526 = 3,99, d. h. dem Niederschlag kommt die Zusammensetzung $(C_6H_5)_3SeBiI_4$ zu.

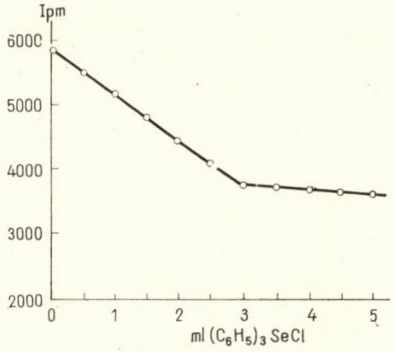


Abb. 3.43
Untersuchung der Zusammensetzung von Triphenylselenoniumjodobismuthit durch radiometrische Titration (SHINAGAWA, MATSUO und YOSHIDA [92])

ALIMARIN und GIBALO [5] untersuchten die Zusammensetzung des in der Reaktion zwischen Beryllium und Phosphat (markiert mit ^{32}P) gebildeten Niederschlages. Die mit Lösungen der gleichen molaren Konzentrationen (0,1 M; 0,005 M; 0,01 M) durchgeführten Titrationen zeigten, daß sich sowohl bei der direkten Titration als auch bei der Rücktitration ein Niederschlag der Zusammensetzung $Be_3(PO_4)_2$ bildet.

Die gleichen Autoren untersuchten auch die Zusammensetzung des in der Reaktion von Zirkonylchlorid mit Phosphorsäure gebildeten Niederschlages. Die mit Lösungen der oben erwähnten Konzentrationen unter verschiedenen Bedingungen durchgeführten Titrationen (z. B. wurde die Acidität der Lösung zwischen 0,5 und 2,5 N und die Konzentration der Stoffe zwischen 0,01 und 1,0 mg/ml variiert) zeigten, daß zur Fällung von einem Mol Zirkonylchlorid ein Mol Phosphorsäure benötigt wird. Der Niederschlag hat also die Zusammensetzung $ZrOHPO_4$.

BRADHURST, COLLER und DUNCAN [17] beschäftigten sich mit der Zusammensetzung von Silber- und Kobaltwolframat-Lösungen bei verschiedenen pH-Werten. Wie aus Abb. 3.44 hervorgeht, zeigt die Titrationskurve von Natriumwolframat mit Silbernitratlösung (markiert mit ^{110m}Ag) bei pH 6,2 bis 7,8 einen scharfen Knickpunkt. Das aus den Ergebnissen der bei verschiedenen pH-Werten durchgeführten Titrationen berechnete Ag : W-Verhältnis ist in Abb. 3.45 gezeigt. Wie man sieht, eignet sich diese Methode dazu, Aufschlüsse über die Zusammensetzung der in der Lösung vorhandenen verschiedenen Polywolframat-Ionen zu liefern.

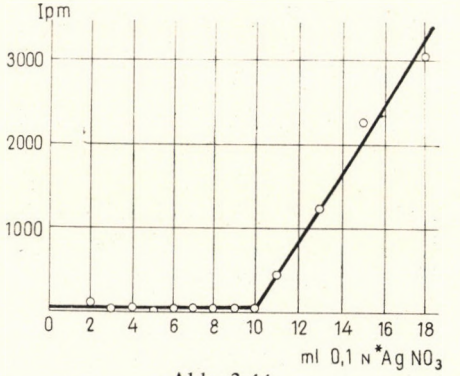


Abb. 3.44
Radiometrische Titration von 10 ml 0,1 N Natriumwolframatlösung mit 0,1 N $AgNO_3$-Lösung (markiert mit ^{110m}Ag) bei pH = 6,2–7,8 (BRADHURST, COLLER und DUNCAN [17])

Die Untersuchung der Zusammensetzung der Quecksilber-hexacyanoferrate(II) knüpft sich an die Namen BASIŃSKI, SZYMAŃSKI, KRYGER und ZAPALOWSKA [13]. Die Zusammensetzung der in der Reaktion von

For measurements with two uncharged indicator bases, B and C, in identical acid concentration the following relation can be used:

$$pK_{CH^+} - pK_{BH^+} = \log \frac{[CH^+]}{[C]} - \log \frac{[BH^+]}{[B]}$$

If the pK_{BH^+} value of indicator B is known, pK_{CH^+} can also be calculated. In Hammett's view, the above equation in which concentrations occur, remains valid in

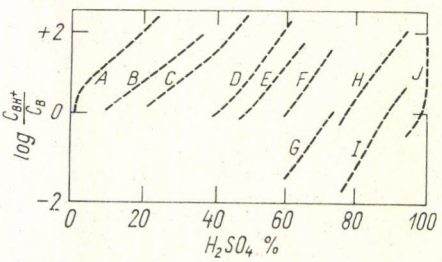


Fig. 13. Logarithms of ionization ratios of indicators in $H_2SO_4-H_2O$ (wt. %). Abridged from Hammett and Deyrup [342, 625]. —*(A)* *p*-Nitroaniline (pK_{BH^+} 0·99), *(B)* *o*-Nitroaniline (−0·25), *(C)* 4-Chloro-2-nitroaniline (−0·97), *(D)* *p*-Nitrodiphenylamine (−2·50), *(E)* 2,4-Dichloro-6-nitroaniline (−3·34), *(F)* 2,4-Dinitroaniline (−4·50), *(G)* 2-Benzoylnaphthalene (−6·04), *(H)* 6-Bromo-2,4-dinitroaniline (−6·71), *(I)* Anthraquinone (−8·26), *(J)* 2,4,6-Trinitroaniline (−9·41)

media of high acid concentration and with a large dielectric constant, where otherwise other factors ought to be taken into consideration.

Fig. 14 shows that the H_0 value increases faster in concentrated aqueous solutions of a strong acid than in concentrated aqueous solutions of a weak acid.

Thus an approach can be made experimentally to the H_0 value which is identical with the pH value only in very dilute solutions. The proton-donor ability of highly

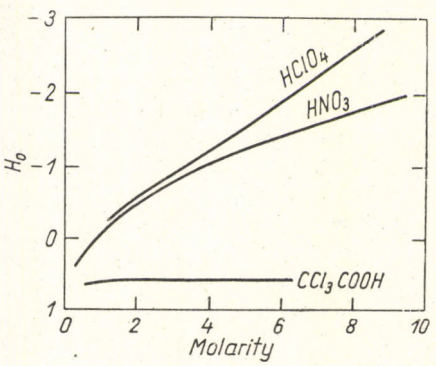


Fig. 14. Acidity function of moderately concentrated aqueous acid solutions, according to Hammett (abridged) [340]

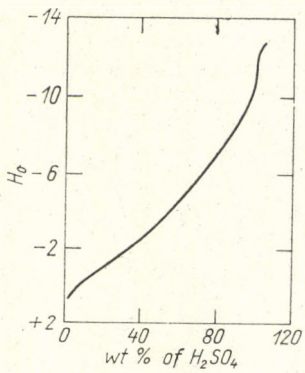


Fig. 15. Change of H_0 values in mixtures of sulphuric acid-water and sulphuric acid-sulphur trioxide according to Paul and Long [625]. See also: [82, 342]

acidic solutions towards uncharged indicators is expressed by H_0, defined as a negative logarithm. The greater the negative number, the 'more acidic' is the solution.

Bates and Schwarzenbach in a critical comment on Hammett's 'Acidity Function' reach the conclusion that the H_0 value substantially depends on the individual

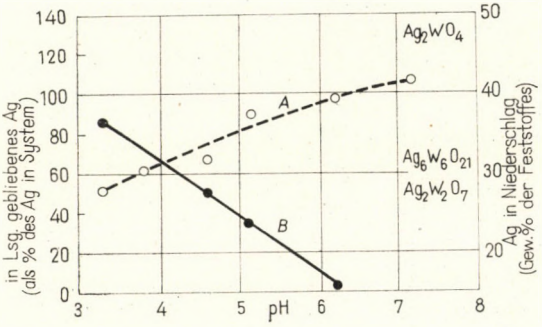


Abb. 3.45
Kurve *A* — Änderungen des Ag : W-Verhältnisses im Niederschlag; Kurve *B* — zurückgebliebenes Ag in %, bei verschiedenen pH-Werten (BRADHURST, COLLER und DUNCAN [17])

Hg^{2+} mit Alkalihexacyanoferraten(II) gebildeten Niederschläge ist ziemlich kompliziert. Die genannten Autoren titrierten Qecksilber(II)nitrat (markiert mit ^{203}Hg) mit Natrium-bzw. Lithiumhexacyanoferrat(II). Auf Grund des Ablaufes der Titrationskurven gelangten sie zu dem Ergebnis, daß die Zusammensetzung der gebildeten Verbindungen den allgemeinen Formeln $Me_2Hg[Fe(CN)_6] \cdot x\,Hg(NO_3)_2$ bzw. $Hg_2[Fe(CN)_6] \cdot y\,Hg(NO_3)_2$ entspricht (Me = = Alkalielement). Die tatsächliche Zusammensetzung hängt vom Verhältnis der in der Lösung befindlichen beiden Komponenten ab. Sie fanden außerdem, daß sich auch die Verbindungen $Hg_2[Fe(CN)_6]$ und $Li_2Hg[Fe(CN)_6]$ bilden. Im Zuge dieser Studien wurde auch Quecksilber(II)chlorid-Lösung (markiert mit ^{203}Hg) mit Kalium oder Lithiumhexacyanoferrat(II) titriert. Die Titrationskurven ließen erkennen, daß sich beim Vorliegen von überschüssigem Quecksilber(II)chlorid eine Reihe von Verbindungen der allgemeinen Formel $Hg_2[Fe(CN)_6] \cdot x\,HgCl_2$ bildet. Demnach existieren zahlreiche basische Quecksilber-hexacyanoferrate(II), die mit einander gemischte und Doppelsalze bilden können. In Abhängigkeit vom stöchiometrischen Verhältnis der beiden Komponenten erfährt die Zusammensetzung dieser Verbindungen eine allmähliche Änderung.

Die erwähnten wenigen Beispiele lassen deutlich erkennen, daß die radiometrischen Titrationen für die Ermittlung der Zusammensetzung von Verbindungen eine wertvolle Hilfe bedeuten können. Trotzdem hat man sich ihrer, sowohl auf diesem Gebiet, als auch bei anderen Untersuchungen, bisher nur in wenigen Fällen bedient.

3.7.2. *Untersuchung der Mitfällung*

Untersuchungen auf dem Gebiete der Mitfällung sind ganz besonders in der Kernchemie von großer Wichtigkeit. ALIMARIN und SIROTINA [7] waren die ersten, die die Anwendung radiometrischer Titrationen zum Studium

properties of the indicator used. Thus, the 'acidity function' is not useful for the measurement of solutions of low dielectric constant. This fact must be taken into consideration when acidity or basicity of indicators is determined in non-aqueous media [40]; cf. [84, 505].

In Fig. 15 the change of H_0 is shown as a function of sulphuric acid concentration, indicating values for 0–100% sulphuric acid and the H_0 value of sulphuric acid containing 31% by weight of SO_3 [82, 342, 625].

17. Comparison of the Strength of Acids in Various Solvents

For the examination of the degree of proton transfer, generally the amphiprotic solvent itself is employed as reference base or acid. The data in the literature for K_{acid} and K_{base} have been based on water as reference acid and reference base. Water is a very weak acid and base but many other solvents with similar amphoteric properties also exist: methanol, isopropanol, acetic acid, etc.

In a proton-accepting solvent, the dissolved acid enters into protolytic interaction with the molecules of the solvent, e.g.:

$$HClO_4 + CH_3COOH \rightleftharpoons CH_3COOH_2^+ ClO_4^-$$

$$(C_6H_5)_2NH_2^+ + CH_3COOH \rightleftharpoons CH_3COOH_2^+ \ldots HN(C_6H_5)_2$$

The degree of acid strength is shown by the shift of equilibrium in the direction of the upper arrow.

(a) Suitable choice of the solvent is essential for the comparison of K_{acid} values of acids. In a highly basic solvent the difference in the value of the dissociation constants of strong and medium acids is hardly noticeabln, because of the solvent levelling effect. A very acidic medium is also unsuitable: *p*-toluenesulphonic acid hardly dissociates in sulphuric acid and trichloroacetic acid is a weak acid in acetic acid. Solvents subject to slight autoprotolysis would be suitable for the comparison of the strength of acids but owing to their poor dielectric properties, electrolytes are only poorly solvated by them. For the electrometric comparison of acids, pyridine (cf. Section 16 (c)) *m*-cresol and n-butanol are convenient solvents. Their dielectric constants are respectively: $\varepsilon = 12{\cdot}5$, 13, 15·8. Among non-polar solvents benzene is suitable; as a reference base diphenylguanidine, and as indicator for the measurement of competitive equilibrium, tetrabromophenolphthalein ethyl ester is useful (cf. Section 16 (a)).

In very dilute solutions in butanol or *m*-cresol the values of the dissociation constant of some acids show a close agreement with those found in water.

In acetic acid the order of strength of acids is as follows:

perchloric acid > *hydrobromic acid* > *sulphuric acid* > *hydrochloric acid* > *nitric acid*
(cf. Fig. 9).

Owing to the low dielectric constant of acetic acid, its ionization constant values are dubious but conductivity measurements show the following values (with nitric acid as unity): perchloric acid 400, hydrobromic acid 160, sulphuric acid 30, hydrochloric

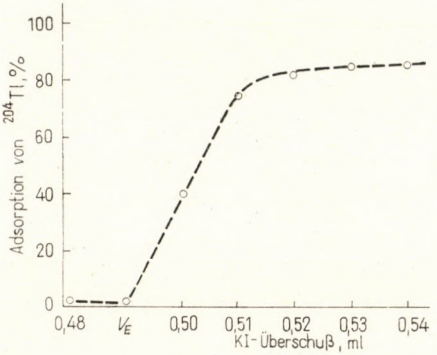


Abb. 3.46
Kurve der Adsorption von ^{204}Tl durch gefälltes AgI (ALIMARIN und SIROTINA [7])

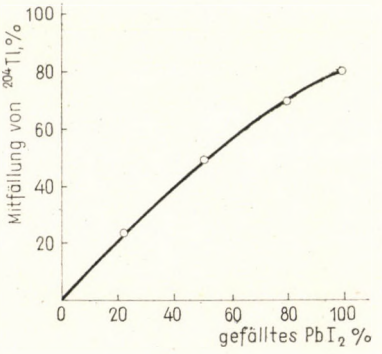


Abb. 3.47
Kurve der Mitfällung von ^{204}Tl mit PbI_2 (ALIMARIN und SIROTINA [7])

der Mitfällung in Vorschlag brachten. Sie untersuchten die Mitfällung von Silber, Thallium und Blei mit Jodid, Thiocyanat, Chromat und Sulfid unter Anwendung der radioaktiven Isotopen ^{204}Tl, ^{110m}Ag und ^{212}Pb.

Diese Versuche zeigten, daß die Mitfällung von Thallium mit Silberjodid auf Adsorption beruht. Sie beginnt dann, wenn in der Lösung ein geringer Jodid-Überschuß erscheint, d. h. nach der Erreichung des Endpunktes. Infolge der Jodid-Adsorption auf dem Silberjodid erhält die Oberfläche eine negative Ladung. Während der Titration bildet sich daher zuerst das weniger lösliche Silberjodid, dann folgt die Bildung des Thalliumjodid-Niederschlages. Die adsorbierte ^{204}Tl-Menge änderte sich bei der Zugabe von radioaktivem Thallium zu dem bereits gefällten Silberjodid nicht. Abb. 3.46 zeigt die Kurve der Adsorption von ^{204}Tl durch gefälltes Silberjodid (V_E für 5 mg Ag = 0,49 ml 0,1 N KJ). Unter Anwendung von ^{204}Tl als Indikator können auf diese Weise Thallium und Silber nebeneinander bestimmt werden.

Diese Mitfällung ist analog derjenigen von an Silberbromid (HAHN [37]).

Von anderer Natur ist die Mitfällung von Thallium (1–2 μg) mit Bleijodid. Die charakteristische Kurve zeigt Abb. 3.47. Bei 100%iger Fällung der Makro-Komponente (Pb) werden 80% der Mikro-Komponente (^{204}Tl) mitgefällt. Möglicherweise geht dies unter Bildung anomaler Mischkristalle vor sich. Aus den Ergebnissen folgt, daß das ^{204}Tl als nicht-isotoper Indikator zur radiometrischen Bestimmung von Blei durch Titration mit Kaliumjodid in saurem Medium geeignet ist.

Die Verfasser beobachteten eine ähnliche Erscheinung bei der Fällung von Bleisulfid in Gegenwart von ^{204}Tl in schwach saurem Medium. Auch hier werden mit 100% der Makro-Komponente (Pb) 80% der Mikro-Komponente (^{204}Tl) mitgefällt. Unter den gleichen Versuchsbedingungen ist es jedoch nicht möglich, Makromengen von Thallium auszufällen. In alkalischem Medium (Na_2CO_3 + NaOH) erreichte die Mitfällung von ^{204}Tl 75–80%, während die Menge der gefällten Makro-Komponente (Pb) nur 30–35% betrug.

Thallium(I)- und Silberchromat besitzen die gleiche Löslichkeit. Sind nur Mikromengen von Thallium vorhanden (1–2 μg), so werden diese mit dem Silberchromat quantitativ mitgefällt. Wahrscheinlich handelt es sich auch hier um die Bildung

acid 9, nitric acid 1. In Hammett and Deyrup's method (cf. Section 16 (d)) the order of strength of some acids in anhydrous acetic acid is the following:

methanedisulphonic acid > chloromethanedisulphonic acid > perchloric acid > chlorocarboxymethanesulphonic acid > chloromethane sulphonic acid > sulphuric acid > methanesulphonic acid > hydrochloric acid [625,763].

Owing to the levelling effect of water (see: Chapter 6; Section 38) perchloric acid, *p*-toluenesulphonic acid, sulphuric acid and hydrochloric acid are fairly similar in

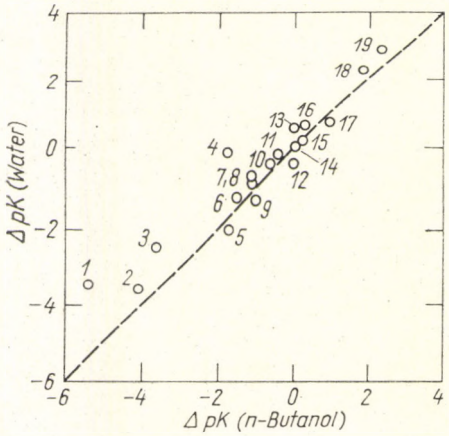


Fig. 16. Relative strength of acids in water and n-butanol compared with benzoic acid, according to Hammett [340]. – *(1)* 2,4,6-Trinitrophenol, *(2)* Trichloroacetic acid, *(3)* Maleic acid K_1, *(4)* 2,4-Dinitrophenol, *(5)* *o*-Nitrobenzoic acid, *(6)* *o*-Hydroxybenzoic acid, *(7)* *m*-Nitrobenzoic acid, *(8)* *p*-Nitrobenzoic acid, *(9)* *o*-Chlorobenzoic acid, *(10)* *m*-Chlorobenzoic acid, *(11)* *p*-Chlorobenzoic acid, *(12)* *o*-Toluic acid, *(13)* Acetic acid, *(14)* *m*-Toluic acid, *(15)* *p*-Toluic acid, *(16)* Butyric acid, *(17)* Trimethylacetic acid, *(18)* Maleic acid K_2, *(19)* *p*-Nitrophenol

strength. Nitric acid, however, proves to be weaker in ethanol, and perchloric acid stronger in acetic acid, both in comparison with hydrochloric acid.

Thus, even ethanol and acetic acid show a differentiating effect, although it is small. The above-mentioned acids, except for perchloric acid, are weak acids in acetone, acetonitrile, dioxan and nitromethane. For that reason, the base-content

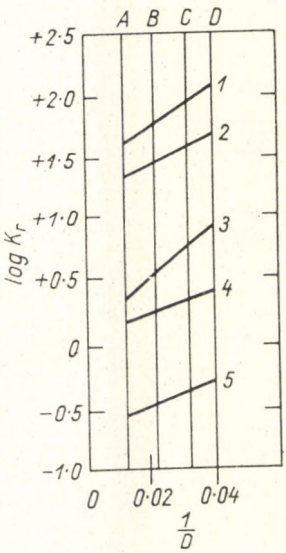


Fig. 17. Relative strength of acids in solvents of different dielectric constants according to Minnick and Kilpatrick [593]. — *(A)* Water, *(B)* Dioxan+water ($D = 45$), *(C)* Methanol, *(D)* Ethanol, dioxan+water ($D = 25$); *(1)* Cyanoacetic acid, *(2)* Monochloroacetic acid, *(3)* Glycolic acid, *(4)* *p*-Chlorobenzoic acid, *(5)* Acetic acid

anomaler Mischkristalle. Titriert man Makromengen von Silber und Thallium, so fällt zuerst das Thalliumchromat und dann das Silberchromat aus.

3.7.3. *Bestimmung der Löslichkeit und des Löslichkeitsproduktes*

Die radioaktive Indikation bietet eine Möglichkeit zur Untersuchung von Verteilungs-Erscheinungen (wie z. B. heterogene Gleichgewichte, gegenseitige Löslichkeit usw.). Auf Grund der Aktivitäten der aus den verschiedenen Phasen des untersuchten Systems entnommenen Proben können die Verteilungskoeffizienten der markierten Stoffe berechnet werden.

Mit Erfolg wird die radioaktive Indikation auch zur Bestimmung von Löslichkeiten herangezogen. Vorausgesetzt, daß sich das aktive und stabile Isotop eines Elements identisch verhält, d. h. der mengenmäßige Anteil des Isotops in der festen und flüssigen Phase gleich ist, kann die Löslichkeit $L(\text{mg} \cdot \text{ml}^{-1})$ mit Hilfe der Gleichung (3.40) berechnet werden:

$$L = \frac{a_l}{a_s} \tag{3.40}$$

a_l = spezifische Aktivität der flüssigen Phase, $[\text{Ipm} \cdot \text{ml}^{-1}]$
a_s = spezifische Aktivität der festen Phase $[\text{Ipm} \cdot \text{ml}^{-1}]$.

Verläßliche Ergebnisse erhält man jedoch nur dann, wenn das Gleichgewicht erreicht ist und die spezifische Aktivität der festen und flüssigen Phase mit der gleichen Methode bestimmt wird. Einige Nachteile hat jedoch auch diese Methode der radioaktiven Indikation:

(a) Es muß mehr Feststoff vorhanden sein, als im gegebenen Lösungsmittelvolumen löslich ist. Daher sind mg-Mengen des Feststoffes erforderlich.

(b) Es muß ein markierter Feststoff von hoher spezifische Aktivität und Reinheit hergestellt werden.

(c) Je geringer die Löslichkeit, umso niedriger ist auch die spezifische Aktivität der Lösung. Demzufolge sind größere Lösungsmittelmengen notwendig, die dann eingedampft werden müssen.

(d) Vor der Bestimmung der Aktivität muß der Feststoff von der Lösung vollständig getrennt werden.

(e) Zur Einstellung des Gleichgewichtes zwischen den beiden Phasen bedarf es in der Regel längerer Zeit [102, 103].

DUNCAN [26, 27] versuchte, diesen Schwierigkeiten durch radiometrische Titrationen zu begegnen. Das Prinzip seiner Methode war folgendes: Zu einem Volumen v einer Lösung, deren N^--Konzentration $[N^-]_0$ ist, wird das Volumen v_0 einer mit markierter M^+-Lösung der Konzentration $[M^+]_0$ und der Aktivität a_0 Ipm zugegeben. Nach Erreichung des Löslich-

of alkaloid sulphates, and the *p*-toluenesulphonates and ethanesulphonates of some organic bases can be titrated in some cases with perchloric acid in dioxan [123, 321].

In non-aqueous titration work the relative change of strength as a result of change of solvent, is important. An acid-base pair is brought into equilibrium with a standard acid–base pair $AH_0 - B_0$ and the state of equilibrium is determined. $AH_0 - B_0$ may

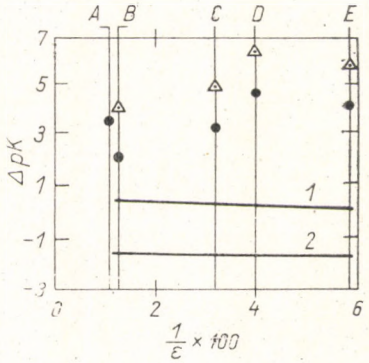


Fig. 18. ΔpK value of different acid pairs in solvents of different dielectric constant according to Izmaïlov and Mandel [412, 545]. —*(A)* Formamide, *(B)* Water, *(C)* Methanol, *(D)* Ethanol, *(E)* n-Butanol; *(1)* Acetic acid–benzoic acid, *(2)* Monochloroacetic acid—benzoic acid, (△) Acetic acid—picric acid, (•) Monochloroacetic acid–picric acid

be a lyonium-lyate pair formed from the solvent in the course of autoprotolysis: $sH^+ - s^-$. In this case the dissociation constants of the two acids are compared. The $AH_0 - B_0$ may also be an indicator system, in which case the ratio of IH^+/I is measured. Experience shows that the relative acid strengths of acids of identical

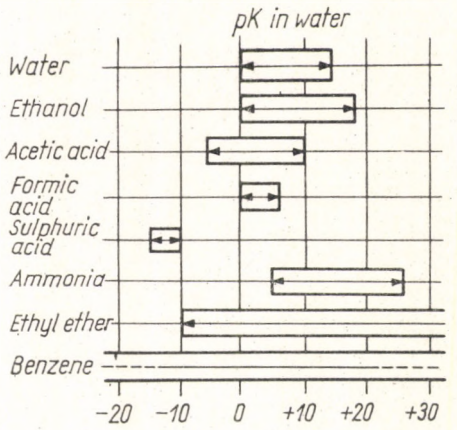


Fig. 19. 'p*K* -range' of solvents according to Bell [53]

charge type and similar structure are roughly independent of the solvent (cf. Section 16(a) and [173]).

Fig. 16 shows the relative acid strengths of some acids in water and in n-butanol compared with benzoic acid. If the strengths of the acids had been identical in both solvents the points would have been on the tangent [340].

(b) *Correlation of* K_{rel}, *and* Δ pK *with the dielectric constant* (ε) *of the solvent.* Acid strength, and thus also the pK_{acid} value are influenced by the intrinsic basicity of the solvent (Chapter 2; Sections 13 and 14). However, the comparison can be made so that, instead of the value of K_{acid}, the value of log K_{rel} is plotted against 1/D, where $K_{rel} = K/K_0$ and $\log K_{rel} = \log K/K_0$. Thus, K_{rel} is the ratio of the dissociation constants of the acid examined and the standard acid (e.g. benzoic acid) [593, 727, 873, 886].

keitsproduktes $L = [M^+] \cdot [N^-]$, in welchem $[M^+]$ und $[N^-]$ die Gleichgewichtskonzentrationen von M^+ und N^- sind, die den Niederschlag MN bilden, gilt:

$$Lv^2 + vv_0\{2L - [N^-]_0[M^+]_0 R\} + v_0^2\{L + [M^+]_0^2 R(1 - R)\} = 0\,, \tag{3.41}$$

a = Restaktivität von M^+ in der Lösung nach der Bildung des Niederschlages

$$R = a/a_0.$$

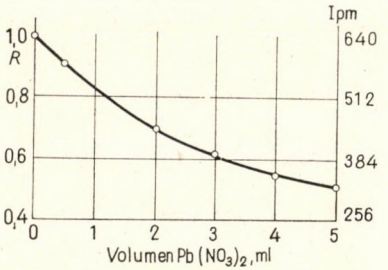


Abb. 3.48
Bestimmung der Löslichkeit von PbI_2 durch radiometrische Titration (DUNCAN [26]). (Titration von 5 ml 0,01 M KI, markiert mit ^{131}I, unter Anwendung von 0,005 M $Pb(NO_3)_2$-Lösung als Titriermittel)

Die Titrationskurve ergibt sich aus den Änderungen von R als Funktion der Änderungen von v (Abb. 3.48). Der Wert von L kann mit Hilfe der Gleichung (3.41) aus jedem Punkt der Kurve berechnet werden.

Für die allgemeine Reaktion

$$nM^{m+} + mN^{n-} = M_n N_m^{\downarrow}\,, \tag{3.42}$$

kann L wie folgt erhalten werden:

$$L = [M^{m+}]^n \cdot [N^{n-}]^m$$

$$L = \{[M_m^+]_0 Rv_0/v + v_0\}^n - \{(v[N^{n-}]_0) - (m/n)[M^{m+}]_0 v_0(1 - R)/(v + v_0)\}^m. \tag{3.43}$$

Unter der Annahme, daß $[M^{m+}]_0 = k[N^{n-}]_0$ ist, und daß äquivalente Mengen der Lösungen vermischt werden, d. h. $v = kv_0 m/n$ ist, ergibt sich für L:

$$L = \left(\frac{m}{n}\right)^m \left[R[N^{n-}]_0 \Big/ \left(\frac{m}{n} + \frac{1}{k}\right)\right]^{(m+n)}. \tag{3.44}$$

Fig. 17 illustrates these correlations. The K_{rel} value of five different acids changes linearly as a function of 1/D [593]. However, it is instructive to note that the gradients of the tangents differ, the dielectric effect being different from compound to compound.

Comparing acids of different charge and structure it becomes apparent that in some cases the dielectric constant and the intrinsic basicity exert an opposite, and in other cases a parallel effect on the strength of acids. So it would be inappropriate to merge the two concepts into one, into that of 'basicity of solvents' ([677]; p. 259). The correlation between log K_{rel} and Δ pK, respectively, and $1/\varepsilon$ is only valid for certain acid pairs, e.g.: acetic acid–benzoic acid (Fig. 18 line *1*), monochloroacetic acid–benzoic acid (Fig 18, line *2*); but in the case of acetic acid–picric acid (△) or monochloroacetic acid–picric acid (•) pairs the above correlation is no longer valid [412] [545].

(c) *Correlation between the possible* pK *range of solvents and* pK *values of acids (bases).* (See: Chapter 2; Section 12.) The pK values of an sH^+-s^- acid–base pair, characteristic for a given solvent, determine the possible pK range of the dissolved acid–base pair. When the lower pK value of the solvent is denoted by pK', and the upper one by pK'', and p$K <$ pK'', then the acid investigated is 'levelled' since it forms a solvent cation. When, however, for the base investigated p$K >$ pK' it is levelled due to the formation of a solvent anion. Figure 19 shows the approximative pK ranges of some solvents [53].

18. Proton-donor Properties of Very Weak Acids

A continuous transition exists between 'acidic hydrogen' and 'active hydrogen' as known to organic chemists (Chapter 2; Section 9). A weak acid is known, the K_{acid} value of which is only 10^{-21} (phenylacetylene). For the measurement of the strength of acids, in general an equilibrium measurement between two acids is needed:

$$\begin{array}{ccccccc} AH & + & B & \rightleftharpoons & A & + & BH \\ \text{Acid} & + & \text{Base} & \rightleftharpoons & \text{Base} & + & \text{Acid} \end{array}$$

In an equilibrium of such a character one of the acids or bases may be the solvent or solvent-anion. In the case of stronger acids, A can be satisfactorily determined, if the base B is at the same time the solvent molecule:

$$HClO_4 + CH_3OH \rightleftharpoons ClO_4^- + CH_3OH_2^+$$

In the case of very weak acids, however, the conjugate base of the solvent must be used instead of B for a measurable quantity of A to be formed from AH. The favourable shift of equilibrium depends upon the basicity of B (which must be very strong); that is the acid BH corresponding to the B-base must be very weak. Liquid ammonia may be used for the study of very weak acids [22] and ethylenediamine for their titration [176, 359, 601]. Recently tetramethylene sulphone (Sulfolan) has also been used [111, 498].

Even an acid as weak as *p,p'*-dihydroxydiphenylmethane shows two potentiometric inflections in ethylenediamine medium with tetrabutylammonium hydroxide (Chapter 18; Section 108 (b)).

Example of the interaction of a very weak acid:

$$HO.C_6H_4.CH_2.C_6H_4.OH + H_2N.(CH_2)_2.NH_2 \rightleftharpoons O.C_6H_4.CH_2.C_6H_4.O^- + {}^+H_3N.(CH_2)_2.NH_3^+$$

Für die Verbindung AB gilt:

$$L = \frac{1}{4}\,(R[\mathrm{M}^+]_0)^2 \tag{3.45}$$

Für die Verbindung AB_2 gilt:

$$L = \frac{1}{2}\,R^3[\mathrm{M}^{2+}]_0^3\,. \tag{3.46}$$

Bestimmung des Löslichkeitsproduktes: 5 ml einer Lösung, die eine bekannte Menge eines Ions enthält, werden mit einem bekannten Volumen einer Lösung vermischt, die das andere Ion in bekannter Konzentration enthält. Das Gemisch wird bis zur Einstellung des Gleichgewichtes zwischen Niederschlag und Lösung energisch gerührt. Ist $[\mathrm{M}^+]_0 = [\mathrm{N}^-]_0 > 100\,L^{1/2}$, so genügt es, 5–10 Minuten zu rühren. Man läßt den Niederschlag nun absetzen oder zentrifugiert das System. Nach erfolgter Sedimentation wird die Aktivität von 5 ml der klaren Lösung gemessen und mit der Aktivität von 5 ml der Ausgangslösung verglichen.

Mit dieser Methode bestimmte DUNCAN [26] das Löslichkeitsprodukt von PbI_2 mit Hilfe von ^{131}I. Die erhaltenen Werte von L waren: bei 18°C, $L = 0{,}97\times10^{-8}$ (g Ion)^{3}l^{-3}; bei 22°C, $L = 1{,}28\times10^{-8}$ (g Ion)^{3}l^{-3}. Auf Grund des Endpunktes der in Abb. 3.48 gezeigten Titrationskurve ergab sich für das Löslichkeitsprodukt bei 18°C $(0{,}88 \pm 0{,}20)\times10^{-8}$ (g Ion)^{3}l^{-3}. CASEY und ROBB [24] bestimmten das Löslichkeitsprodukt des $Cs_2[PtCl_6]$ in Wasser durch radiometrische Titration unter Anwendung von Cäsiumchlorid (markiert mit ^{137}Cs) als Titriermittel. Sie erhielten den Wert $(3{,}51 \pm 1{,}09)\times10^{-12}$ (g Ion)^{3}l^{-3}.

3.7.4. *Bestimmung der spezifischen Aktivität radioaktiver Präparate*

Die auf die Gewichts- oder Volumeneinheit bezogene Aktivität eines radioaktiven Präparates wird *spezifische Aktivität* genannt. Sie kann in mCi · g^{-1}, mCi · mg^{-1} oder mCi · ml^{-1} (absolute spezifische Aktivität) oder in Ipm · g^{-1}, Ipm · mg^{-1} bzw. Ipm · ml^{-1} (relative spezifische Aktivität) ausgedrückt werden.

Die Anwendung der radiometrischen Titrationen zur Bestimmung der spezifischen Aktivität radioaktiver Präparate haben KAMETANI, KIMURA und KATAOKA [46] empfohlen. Die Methode hat den Vorteil, daß sie keine Markierung der Prüflösung erfordert, zumal die Radioaktivität des untersuchten Stoffes gleichzeitig auch zur Indikation herangezogen wird. Man titriert mit einem inaktiven Titriermittel.

Der Ausgangspunkt der Kurve ergibt die tatsächliche Aktivität des Präparates, während seine Konzentration aus dem Endpunkt berechnet werden kann.

In liquid ammonia even hydrocarbons behave as proton donors towards sodium amide. Sodium amide dissociates in liquid ammonia, the resultant amide ion NH_2^- being the conjugate base of the solvent ammonia

$$2\,NH_3 \rightleftharpoons NH_2^+ + NH_2^-$$

Example of the interaction of an extremely weak acid:

$$(C_6H_5)_2CH_2 + NH_2^- \rightleftharpoons (C_6H_5)_2CH^- + NH_3$$

Diphenylmethane — Diphenylmethyl carbanion

Ammonium salts when dissolved in liquid ammonia show all the conventional properties of acids:

$$[NH_4]^+Cl^- + NaNH_2 \rightarrow NaCl + 2\,NH_3\,,$$

this being analogous to the reaction of hydrochloric acid with sodium hydroxide:

$$[H_3O]^+Cl^- + NaOH \rightarrow NaCl + 2\,OH_2$$

A solution of ammonium chloride in liquid ammonia dissolves metals with evolution of hydrogen and catalyzes many reactions as an acid; when suitable indicators are added a colour change occurs. Urea behaves in ammonia as an acid, though in acetic acid it is a base:

In ammonia:

$$CO(NH_2)_2 + (NH_2^-.\ NH_4^+) \rightleftharpoons CO(NH_2)NH^- + NH_3 + NH_4^+$$

Thus the concentration of the solvent cation is increased.

In acetic acid:

$$CO(NH_2)_2 + (CH_3COOH_2^+.\ CH_3COO^-) \rightleftharpoons CO(NH_2)NH_3^+ + CH_3COOH + CH_3COO^-$$

i.e. the concentration of the solvent anion is increased.

The autoprotolysis constant of ammonia is:

$$2\,NH_3 \rightleftharpoons NH_2^- + NH_4^+;\quad K_{auto} = \text{approx. } 10^{-22}$$

The proton affinity of amide ions is very great and, for this reason, even diphenylmethane is forced to undergo protolytic reactions.

Another procedure for studying extremely weak acids is founded on measuring the state of equilibrium between the acid to be tested and the conjugate base of the reference acid in ethyl ether, benzene or liquid ammonia, that is, in solvents of negligibly weak acidity. The conjugate base of the reference acid may be its alkali metal salt e.g. diphenylmethylsodium: [147], cf. p. 765 in [231].

$(C_6H_5)_2CH_2$	$(C_6H_5)_2CHNa$	$[C_6H_5.\,CH.\,C_6H_5]^-$
Diphenylmethane	Diphenylmethylsodium	Conjugate base of diphenylmethane

Die genannten Autoren bestimmten die spezifischen Aktivitäten von ^{65}Zn- und ^{237}U-Präparaten auf diese Weise. Für Zink wurde eine Kalium-hexacyanoferrat(II)-Lösung, für Uran Natriumhydroxyd- oder Dinatriumhydrophosphatlösung als Titriermittel verwendet. Zink wurde im Mikro-Maßstabe auch mit der auf Lösungsmittelextraktion beruhenden radiometrischen Titration bestimmt; als Titriermittel diente Dithizon, extrahiert wurde mit CCl_4. In beiden Fällen wurde das Meßinstrument mit Standard-^{65}Zn- und -^{237}U-Präparaten geeicht.

According to this classification the order of acid strength is as follows:
t-butanol ~ acetophenone > phenylacetylene ~ indene > diphenylamine > acetylene > aniline > triphenylmethane > diphenylmethane > ammonia > toluene > benzene [147, 884]. (See also: Chapter 4; Section 27, Table 10.)

Acetylene is a very weak acid but with silver nitrate or silver perchlorate in a suitable medium silver acetylide is formed and the acid is liberated. (See: Chapter 27; Section 157.)

The alcoholic hydroxyl group can be titrated in ethyl ether medium as an acid analogue, in the presence of etioporphyrin indicator, with triphenylmethylsodium [567]

$$(C_6H_5)_3C^-Na^+ + R.OH \rightleftarrows (C_6H_5)_3CH + R.ONa$$

Borneol and triphenylmethanol can be similarly titrated with phenylisopropylpotassium [896] and the active hydrogen of pyrrole derivatives with triphenylmethylsodium [150].

19. 'Onium Ions, Cationic Acids

'Onium ions play an important part in non-aqueous titration: molecules of amphiprotic solvents form 'onium ions by protonation. An example is the acetacidium ion: $CH_3COOH_2^+$.

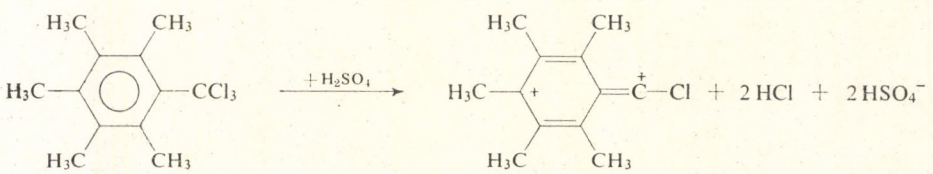
Nitrogenous bases are also converted into 'onium ions by protonation, e.g. anilinium ion: $C_6H_5NH_3^+$. In Brönsted's sense all these are cationic acids. The acid strength of cationic acids is in inverse ratio to the base strength of the conjugate bases. Acetic acid is so weak a base that the $K_{AcOH_2^+}$ value of the 'onium acid formed by it is $10^{6\cdot2}$ ($pK_{AcOH_2^+} = -6\cdot2$). On the other hand, N,N-diphenylguanidine is so strong a base that the acid strength of the diphenylguanidinium ion formed by it is only $pK_{BH^+} = 10\cdot00$ ($K = 10^{-10}$) [779].

All those compounds are here called 'onium compounds in which an atom possessing an unshared electron pair forms a co-ordinate bond and becomes saturated. (See: p. 40 in [231].)

(a) *Carbenium ions.* Triphenylmethane dyes are derivatives of the triphenylmethyl cation $(C_6H_5)_3C^+$, an important carbenium ion. Among the triphenylmethane dyes crystal violet is an indicator frequently used. In carbenium ions the co-ordination number of the carbon atom is one less than its valence. In the literature the term carbonium ion is much used for $[R_3C]^+$. The notation of the Bonn school seems to be more correct; in this the co-ordination number of '*onium*-complexes is greater by one, that of the '*enium*-complexes smaller by one than the valence of the central atom [17, 186]:

$[R_3NR]^+$	$[R_3C]^+$	$[R_3C]^-$	$[R_5C]$
Ammonium ion	Carbenium ion	Carbanion	True carbonium ion (Theoretically impossible)

A dicarbenium ion is also known: it is formed from trichloromethyl-pentamethylbenzene in concentrated sulphuric acid [363]:



3.8. Praktische Anwendungen

3.8.1. Radiometrische Fällungstitration

3.8.1.1. Anorganische Stoffe

(Falls nicht anders vermerkt, lagen Modell-Lösungen vor)

Bestimmte Komponente	Probe	Maßlösung	Prüflösung (markiert mit)	Maßlösung (markiert mit)	Bemerkung	Literatur
Ag^+	Legierungen	0,1–0,005 N HCl	^{110m}Ag	—	Medium: HNO_3	[84]
		0,1 N HCl	—	—	Bestimmungsmethode: e^--Strahlen-Rückstreuung	[119]
		0,1 N KI	—	^{131}I	Medium: HNO_3	[100, 118]
		0,1 N NaBr	^{105}Ag	—		[59]
		0,01 N KIO_3	^{110m}Ag	—		[14]
		0,1 N $K_3[Co(CN)_6]$	—	^{60}Co	Niederschlag: $Ag_3[Co(CN)_6]$	[98]
		0,01 M Na_2HPO_4	—	^{32}P		[58]
		0,025 M $K_4[Fe(CN)_6]$	—	^{59}Fe	Medium neutral oder schwach alkalisch; Niederschlag: $Ag_4[Fe(CN)_6]$	[104]
		0,1 M Phenyltetrazolin-5-thion	^{110m}Ag	—	NH_4Cl-NH_4OH-Puffer pH = 10,0	[96]
$Ag^+ + Pb^{2+}$		K_2CrO_4	^{110m}Ag	—	Erst Pb^{2+}, dann Ag^+ titriert	[14]
AsO_4^{3-}		0,1 N KI	—	^{131}I	Indirekte Titration (vgl. Best. von PO_4^{3-})	[100]
Ba^{2+}		0,1 N H_2SO_4	—	^{35}S	Medium neutral oder schwach sauer	[100]
		0,01 M Na_2HPO_4	—	^{32}P	NH_4OH-NH_4Cl-Puffer	[58]

Carbenium ions are acceptor acids, and the acetylium ion (acetyl cation) can also be considered as a carbenium ion: CH_3C^+O. It plays an important role in acetylation. Acetylium perchlorate, a salt, is also known:

$$\underset{\text{Acetyl chloride}}{H_3C-CO-Cl} + HClO_4 \rightarrow \underset{\text{Acetylium perchlorate}}{[H_3C-C{=}O]^+ClO_4^-} + HCl$$

The collective noun for carbenium ions of type $[R-CO]^+$ is oxacarbenium ion. An ion of this type is formed from 2,4,6-trimethylbenzoic acid in sulphuric acid solution (Chapter 3; Section 22 (b)).

(b) *Solvation of ammonium ions.* The basic strength of amines is considerably influenced by the solvation of ammonium ions [55, 629, 820]. (See: Chapter 3; Section 24.) The solvation energy of ammonium ions decreases with increasing number of alkyl substituents. The substitution of each hydrogen atom in the NH_4^+-ion reduces the solvation heat by the effect of one methyl group, that is, about 8 kcal [631]. In contrast with ammonium ions the solvation energy of free amines remains about the same. This greatly influences the equilibrium:

$$R_3NH^+ + A^- \rightleftharpoons AH + R_3N$$

Solvation of ammonium ions occurs in two ways: (1) the acidic hydrogen of the 'onium ion is solvated by the electron-rich parts of the solvent molecules, on the analogy of acid-base reactions, depending on the nucleophilic properties of the solvent molecules:



(2) the solvating effect due to the conventional polarization of solvent molecules. The heat of solvation for the first process is 10 kcal/mol; that of the second, 69 kcal/mol [8].

The equilibrium of the acid-base reaction of ethyl-, diethyl- and triethyl-amine (B) with 2,4-dinitrophenol (AH) depends on the solvating ability of the solvent [631]:

$$B + AH \rightleftharpoons BH^+A^-$$

Equilibrium constants for ion-pair formation are as follows:

Base	*Benzene* $\varepsilon = 2{\cdot}3$	*Dioxan* $\varepsilon = 2{\cdot}2$	*Chloroform* $\varepsilon = 4{\cdot}8$	*Chloro-benzene* $\varepsilon = 5{\cdot}6$	*Ethyl Acetate* $\varepsilon = 6{\cdot}3$
Ethylamine		4,900			65,500
Diethylamine	1,200	6,230	1,730	2,500	47,500
Triethylamine	2,940	1,460	15,800	9,680	11,900

Solvents containing basic oxygen atoms exhibit an enhanced solvation effect: e.g. dioxan, ethyl acetate. The electron-rich parts of the solvent molecule stabilize the ion pairs, probably by H-bonding. In the case of 'onium ions of tertiary amines this

Be^{2+}	Modell-Lösungen, Legierungen, Konzentrate	0,1 M $(NH_4)_2HPO_4$	—	^{32}P	Acetatpuffer, pH = 5,0–5,5; Niederschlag: NH_4BePO_4; Al, Fe, Cu, Mg, Pb, Cr, Ca, Mn und Ni mit ÄDTE maskiert	[5, 6, 35]
Br^-		0,1 N KI	—	^{131}I	Indirekte Titration (vgl. Best. von Cl^-)	[100]
		0,1 N $AgNO_3$	^{82}Br	^{105}Ag		[59]
	Arzneimittel-präparate	0,1 N $AgNO_3$	—	^{110m}Ag		[64, 114, 117]
Ca^{2+}	Arzneimittel-präparate	0,01 N Oxalsäure	^{45}Ca	—	Medium: NaOH, pH = 12,0	[63, 65, 90]
$Ca^{2+} + Pb^{2+}$		0,1 N $(NH_4)_2CO_3$	^{45}Ca	—	Erst Pb^{2+}, dann Ca^{2+} titriert	[106]
Cd^{2+}		0,1023 M $K_4[Fe(CN)_6]$	—	^{59}Fe	In Ggw. von überschüssigem K_2SO_4, in 0,5–2,0 N Säure scheiden sich aus: $5Cd_2[Fe(CN)_6] \cdot 4K_4[Fe(CN)_6]$	[34]
			^{115}Cd	^{59}Fe		
Ce^{3+}		0,025 M Cupferron	^{144}Ce	—	Prüflsg. enthält 3 g NaCl in 10 ml; Acetatpuffer (pH = 5,0); Hydroxylammoniumchlorid verhindert Oxydation zu Ce^{4+}; Niederschlag: $Ce(C_6H_5O_2N_2)_3$	[73]
		0,01–0,05 M 8-Oxychinolin	^{147}Pm	—	Prüflösung enthält K—Na-Tartarat (zur Verhinderung der Fällung von $Ce(OH)_3$), Hydroxylammoniumchlorid (zur Verhinderung der Oxydation zu Ce^{4+}) u. Ammoniumacetat Puffer (pH = 9,0). Niederschlag: $Ce(C_9H_6ON)_3$	[71]

cannot happen because H^+ is already hydrogen-bonded with the oxygen atom of the nitrophenoxide ion:

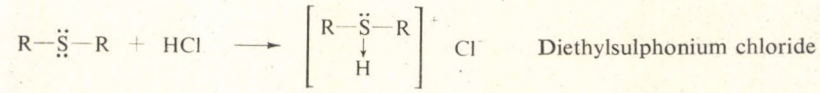
$$R_3N \ldots H^+ \ldots {}^-O-C_6H_3(NO_2)_2$$

(c) *Oxonium and sulphonium ions.* The oxygen and sulphur atoms are capable of co-ordinating to a proton through their free electron pairs, thus giving rise to oxonium and sulphonium ions. Perchloric acid monohydrate may be considered as hydroxonium perchlorate and is isomorphous with ammonium perchlorate:

$$[H_3O]^+ClO_4^-; \qquad [NH_4]^+ClO_4^-$$

Hydroxonium perchlorate forms a stable salt having a crystal lattice in which H_3O^+ and ClO_4^- alternate [63, 851]. (Regarding the electronic structure of acetacidium perchlorate see: Chapter 7; Section 44.)

Ethers, and to a greater extent thioethers, also are capable of forming 'onium compounds:



Diethylsulphonium chloride

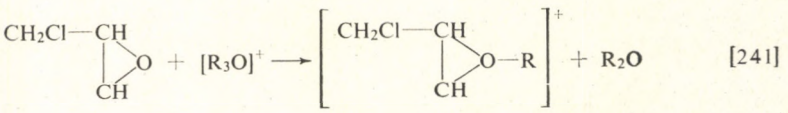
The 'onium-forming tendency of oxygen and sulphur atoms is less than that of nitrogen. The following are also oxonium salts:

$[(CH_3)_3O]^+ \ {}^-OOC.CH_3$	$[(CH_3)_3O]^+ \ {}^-OC_6H_3(NO_2)_3$
Trimethyloxonium acetate	Trimethyloxonium picrate

These can be considered as substituted H_3O^+ ions [572].

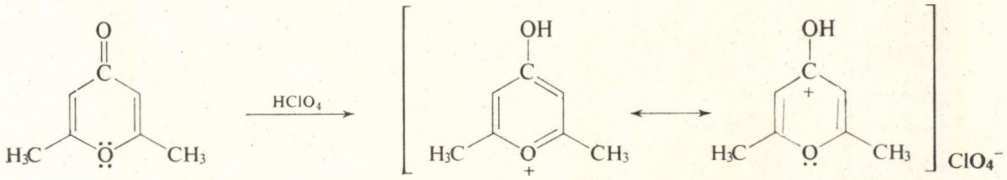
The trialkyloxonium ion is an acceptor acid towards the ion $[BF_4]^-$; otherwise it is an alkyl cation $[R]^+$ donor (cf.: [231] and Chapter 1; Section 8).

Heterocyclic oxonium compounds are also known, the hetero-atom being oxygen: e.g.

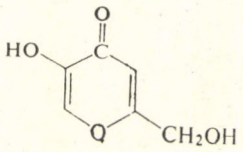


[241]

2,6-Dimethyl-γ-pyrone is a weak base and can be titrated with perchloric acid [148, 332]:



5-Hydroxy-2-(hydroxymethyl)-γ-pyrone (kojic acid) being a weak acid can be titrated with sodium methoxide [506]



Kojic acid, see: Chapter 18, Table 33.

Bestimmte Komponente	Probe	Maßlösung	Prüflösung (markiert mit)	Maßlösung (markiert mit)	Bemerkung	Literatur
Cl^-		0,001 N $AgNO_3$	^{36}Cl	—		[125]
		1,0 N $AgNO_3$	—	—	e^--Strahlen-Rückstreuung; geschlossene e^- Strahlenquelle, ^{90}Sr(1 mCi)	[109]
		0,1 N $AgNO_3$	—	^{105}Ag		[59]
	Wasser	0,01711 N $AgNO_3$	—	^{110m}Ag	Medium: HNO_3	[80]
	Arzneimittelpräparate	0,1 N $AgNO_3$	—	^{110m}Ag	Saures Medium	[114]
		0,1 N KI	—	^{131}I	Indirekte Titration (Fällung des Cl^- in HNO_3-Medium mit überschüssigem Ag^+; Ag^+-Überschuß nach Filtration mit KI titriert)	[100]
$Cl^- + I^-$, $Cl^- + I^- + Br^-$		0,001 N $AgNO_3$	^{36}Cl, ^{131}I	—	Medium: äthanolisch	[125]
CN^-		0,1 N KI	—	^{131}I	Indirekte Titration (vgl. Best. von Cl^-)	[100]
	Arzneimittelpräparate	0,1–0,01 N $AgNO_3$	—	^{110m}Ag	Medium neutral oder schwach alkalisch. Zwei Knickpunkte auf der Titrationskurve: 1. bei $[Ag(CN)_2]^-$-Endpunkt; 2. bei AgCN-Endpunkt	[14, 64, 97, 117]

(d) Negatively charged analogues of 'onium ions are also known, e.g. $[BH_4]^-$.

In the ammonium ion a proton is co-ordinated to the nitrogen atom while in the borohydride ion, a hydride ion is co-ordinated to boron:

$$NH_3 + H^+ = [NH_4]^+; \quad BH_3 + H^- = [BH_4]^-$$

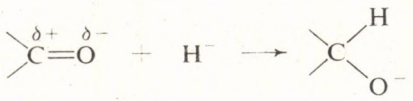
This type of ion exists in lithium aluminium hydride: $Li^+[AlH_4]^-$. Lithium aluminium hydride in tetrahydrofuran is a suitable titrant for the titration of very weak acids: e.g. alcohols and certain hydrocarbons ([391] and Chapter 19). When bases are titrated in acetic acid with perchloric acid the acetacidium ion is the proton donor, but when titrating very weak acids the tetrahydroaluminate $[AlH_4]^-$ ion is the proton acceptor, immediately evolving hydrogen:

$$H^+ + H^- = H_2$$

and

$$R-OH + 1/4\ LiAlH_4 = 1/4\ LiAl(OR)_4 + H_2$$

This reaction is irreversible and thus differs from the usual acid–base reactions. Recently lithium aluminium tetramide has been applied to the titration of alcohols [387]: its basicity is lower than that of the hydride. For this reason it is suitable for the titration of alcohols in the presence of carbonyl, ester and amide groups; the reduction of a carbonyl group by a hydride can be regarded as an irreversible reaction between a Lewis acid and a hydride base [383]:



Lewis acid + Base = Neutralization product

The structure of lithium aluminium amides has not yet been clarified (p. 123 in [383]).

Tetraalkyl borates are formed readily from a trialkyl borate and sodium alkoxide:

$$B(OR)_3 + RONa \rightarrow [B(OR)_4]^-Na^+$$

Sodium tetraphenylborate is a similar compound:

$$[B(C_6H_5)_4]^-Na^+$$

Its complexes, mainly insoluble in water, formed with alkaloids and quaternary bases can be titrated with perchloric acid in dioxan or in a mixture of acetic anhydride and methyl ethyl ketone [267, 316] (Chapter 24; Sections 134 and 138)

$$[R_4N]^+[B(C_6H_5)_4]^- + CH_3COOH_2^+ClO_4^- \rightarrow R_4N^+ClO_4^- + [B(C_6H_5)_4]H + CH_3COOH$$

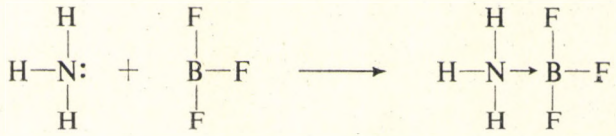
20. Lewis Acids

Regarding Lewis acids and Lewis' acid–base theory, see: Chapter 1. The determination of Lewis acids in non-aqueous media with nucleophilic bases and the interaction of nitrogenous bases with Lewis acids is, practically, of less importance than the analo-

Co^{2+}		0,004 M $K_4[Fe(CN)_6]$	^{60}Co	—	pH = 5,0–5,5 (Acetatpuffer), bei 60–70°C; Niederschlag: $5Co_2[Fe(CN)_6] \cdot \cdot K_4[Fe(CN)_6]$	[28, 29]
		KSCN	^{60}Co	—	In Ggw. von Pyridin bildet sich $[CoPy_4] \cdot (SCN)_2$; Phasentrennung durch Flotation	[19, 76]
CO_3^{2-}		0,025 M $K_4[Fe(CN)_6]$	—	^{59}Fe	Indirekte Titration (vgl. Best. von SO_4^{2-})	[104]
CrO_4^{2-}		0,025 M $K_4[Fe(CN)_6]$	—	^{59}Fe	Indirekte Titration (vgl. Best. von SO_4^{2-})	[104]
Cu^+		0,1 N KI	—	^{131}I		[118]
Cu^{2-}		0,025 M $K_4[Fe(CN)_6]$	—	^{59}Fe	Medium enthält Ammoniak. Reaktionsprodukt: $Cu_2[Fe(CN)_6]$	[104]
		0,17 M Na-Anthranilat	—	^{3}H		[11, 12]
F^-		0,1124–0,0202 M Lanthanid-Nitrate	—	^{154}Eu ^{152}mEu	Titration in Essigsäure, pH = = 2,0–2,5, bei 60–80°C; Best. von Na_2SiF_6 durch Titration des Destillats einer Willard–Winter-Trennung	[82]
Fe^{3+}		$C_6H_5SeO_2H$	^{59}Fe	—	Medium: HNO_3 oder HCl, pH = 1–2; Niederschlag: $Fe(C_6H_5SeO_2)_3$	[8]

gous reactions of hydrogen acids and N-containing bases. However, the investigations on Lewis acids are of great significance in organic chemistry (Friedel–Crafts reactions, acylation, sulphonation, etc.).

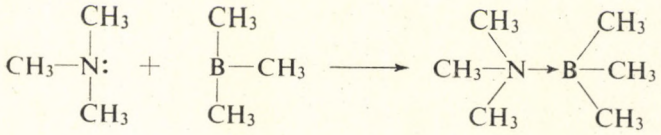
(a) *Examples of Lewis acid reactions.* A well-known interaction is the co-ordination of ammonia and boron trifluoride:



This reaction is rapid in dioxan, and may be followed by an indicator. As early as 1938 Lewis had titrated pyridine and similar bases in an organic solvent with boron trichloride and stannic chloride [509].

In organic chemistry there is a characteristic type of heterolytic (polar) reaction where the co-reactants are a Lewis acid (electrophilic reagent) and a Lewis base (nucleophilic reagent). The driving force of the process is the affinity of the electrophilic reagent for the free electron pair and that of the nucleophilic reagent for the electron-deficient particle:

Additive reaction:



Displacement reactions:

$$(CH_3)_3\overset{+}{N} \rightarrow \overset{-}{B}(CH_3)_3 + NH_3 \rightleftharpoons (CH_3)_3\overset{-}{B} \leftarrow \overset{+}{N}H_3 + N(CH_3)_3$$

$$(CH_3)_3\overset{+}{N} \rightarrow \overset{-}{B}(CH_3)_3 + BF_3 \rightleftharpoons (CH_3)_3\overset{+}{N} \rightarrow \overset{-}{B}F_3 + B(CH_3)_3$$

Lewis acids, such as, for instance, BF_3 and BCl_3 displace carbon dioxide from a suspension of sodium carbonate in acetone-carbon tetrachloride.

Similarly to the hydroxonium ion, BF_3 also reacts with the sulphate anion:

$$OH_3^+ + SO_4^{2-} \rightleftharpoons OH_2 + HSO_4^-$$

$$BF_3 + SO_4^{2-} \rightarrow [SO_4BF_3]^{2-}$$

Thus an analogy exists between the proton- and the Lewis-acid neutralization reactions.

Lewis acids, e.g. BF_3, $AlBr_3$, $TiCl_4$ interact with benzophenone, acetophenone, dipropyl ketone and aromatic nitro compounds [122, 261, 786]. In the case of ketones the electron donor 'basic' atom is the oxygen atom of the carbonyl group. In nitro compounds two theoretically indistinguishable electron-donor oxygen atoms are attached to the nitro group, though infrared spectral analysis renders it probable that only one oxygen atom forms a co-ordinate bond with $AlBr_3$.

Bestimmte Komponente	Probe	Maßlösung	Prüflösung (markiert mit)	Maßlösung (markiert mit)	Bemerkung	Literatur
$[Fe(CN)_6]^{4-}$		0,033 N $Pb(NO_3)_2$	^{59}Fe		Neutrales Medium, markiert mit $[Fe(CN)_6]^{4-}$	[100]
		0,1 N $Pb(NO_3)_2$			e^--Strahlen-Rückstreuung; geschlossene Strahlenquelle (^{204}Tl)	[119]
Hg_2^{2+}		0,1 N KI	–	^{131}I		[100]
I^-		0,1 N $AgNO_3$	^{131}I	–	Auch in Ggw. von Cl^-, Br^-, SCN^- oder CN^-	[100]
		0,001 N $AgNO_3$	^{131}I	–		[125]
		Ag^+	^{131}I	–	Radiocoulometrische Titration	[107, 110]
IO_3^-		0,025 M $K_4[Fe^5CN)_6]$	–	^{59}Fe	Indirekte Titration (vgl. Best. von SO_4^{2-})	[104]
		$AgNO_3$	–	^{110m}Ag		[14]
$I^- + I_2$	Arzneimittelpräparate	0,1 N Tl_2SO_4	–	^{204}Tl	Beschreibung der Methode auf Seite 33	[63, 65, 88]
$I^- + CrO_4^{2-}$		0,1 N $Pb(NO_3)_2$	^{131}I	–		[106]
Lu^{3+}		~ 0,025 M Cupferron	^{177}Lu	–	Titration in Acetatpuffer (pH = 5,0) in Ggw. von NaCl. Niederschlag: $Lu(C_6H_5O_2N_2)_3 \cdot NH_4C_6H_5O_2N_2$	[73]
		Oxalsäure	^{177}Lu	–	Medium: äthanolisch	[70]

Ashworth's monograph [20] contains an excellent compilation of Lewis acid-base titrations with halides of metals belonging to groups 2—8 of the periodic system.

(b) *Friedel–Crafts reactions* also take place owing to the catalytic effect of Lewis acids, e.g. $AlCl_3$, $AlBr_3$ etc. In the interaction of benzene, t-butyl chloride and $AlCl_3$, the carbenium ion is displaced by the Lewis acid from its covalent bond: subsequently the carbenium ion forms a π-complex with benzene, after which a proton is released. The proton then interacts with the complex ion $AlCl_4^-$. Hence the *apparent* order of acid strength is:

$$\text{Lewis acid} > \text{carbenium ion} > \text{benzene},$$

$$(CH_3)_3CCl + AlCl_3 \rightarrow (CH_3)_3C^+ + AlCl_4^-$$

$$(CH_3)_3C^+ + C_6H_6 \rightarrow (CH_3)_3C{-}C_6H_5 + H^+$$

$$AlCl_4^- + H^+ \rightarrow AlCl_3 + HCl$$

This representation of the above reactions is considerably simplified and does not take into account the occurrence of π-complexes [231].

Regarding the order of strength of Lewis acids see: [181, 365, 734].

(c) *Carbenium ions as Lewis acids.* From the theoretical viewpoint, in non-aqueous titration, the electron-deficient carbenium and oxacarbenium ions are also Lewis acids. (See: Section 19 (a).) The acetylium ion $(CH_3CO)^+$ plays an important part in acetylation. (See: Chapter 25; Section 150.)

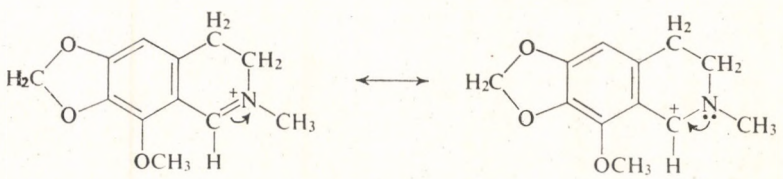
Acetyl perchlorate is formed from the interaction of acetyl chloride and silver perchlorate. This process is carried out in acetic anhydride, the solvent dissociating to an acetyl cation and an acetate ion [531]. (See: Chapter 7; Section 44.)

$$CH_3CO^+Cl^- + Ag^+ClO_4^- \rightleftharpoons CH_3CO^+ClO_4^- + AgCl$$

This reaction makes the existence of the acetylium ion (acetyl cation) very probable. In the case of an acetylium ion the concepts: Lewis acid (electron deficient particle), carbenium ion and acceptor acid are equivalent.

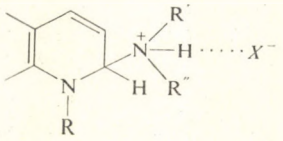
Heterocyclic quaternary ammonium salts can be represented by mesomeric forms. The quaternary ammonium ion in its carbenium form can be regarded as a Lewis acid, and as such enters into reaction with a Lewis base. The titration of cotarnine chloride with standard potassium cyanide solution in acetone-isopropanol is founded on this fact. The highly nucleophilic cyanide ion attacks the carbenium ion while a covalent bond is formed. The end-point of the titration can be detected either potentiometrically or visually [215]. A quaternary ammonium *base* cannot be titrated with cyanide. 2,4-Dinitrophenyl-6,7-dimethoxyisoquinolinium chloride can also be determined in a similar way [215].

Spectrophotometric investigations have shown that electron donors, such as butylamine, readily give reversible adducts in chloroform medium with, e.g., N-2,6-dichlorobenzyl-



Mg^{2+}	Modell-Lösungen Silikate	0,1–0,01 M Na_2HPO_4	–	^{32}P	Im Medium: NH_4OH-NH_4Cl; Niederschlag: $MgNH_4PO_4$	[58, 77, 78, 85]
MoO_4^{2-}		0,1 M $[Co(NH_3)_6]Cl_3$	–	^{60}Co	Medium äthanolisch oder Aceton, pH = 3–4; Niederschlag: $[Co(NH_3)_6]_3[Mo_7O_{24}]$	[123]
Nb^{3+}	Stahl	Cupferron	^{182}Ta	–		[9]
Nd^{3+}		~ 0,025 M Cupferron	^{147}Pm	–	Titration in Acetat-Puffer (pH ~ ~ 5), in Ggw. von NaCl. Niederschlag: $Nd(C_6H_5O_2N_2)_3$	[73]
		Oxalsäure	^{147}Nd	–	50–60°C	[70]
		0,01–0,05 M 8-Oxychinolin	^{147}Pm	–	vgl. Best. von Ce^{3+}	[71]
		~ $2{,}6\times10^{-3}$ M 5,7-Dichlor-8-Oxychinolin	^{147}Pm	–	Titration in Ggw. von K—Na-Tartarat und Acetat-Puffer (pH = 8,5)	[74]
		~ 1×10^{-3} M 5,7-Dibrom-8-Oxychinolin				
Ni^{2+}		KSCN	^{60}Co	–	Medium: Pyridin; Reaktionsprodukt: $[NiPy_4]\cdot(SCN)_2$; Phasentrennung durch Flotation	[19, 76]
		0,1 N $K_3[Co(CN)_6]$	–	^{60}Co	Niederschlag: $Ni_3[Co(CN)_6]_2$	[98]
Pb^{2+}		0,025 M $K_4[Fe(CN)_6]$	–	^{59}Fe	Medium neutral oder schwach sauer; Niederschlag: $Pb_2[Fe(CN)_6]$	[103, 104, 106]
		K_2CrO_4	^{204}Tl	–		[50, 52]
		Na_2HPO_4	–	^{32}P	Acetat-Puffer	[58]

quinolinium cation. When the concentration of butylamine is increased, the following type of adduct is formed [89]:



(For determination of acetyl chloride see: Chapter 16; Section 101.)

(d) *Reactions of Lewis acids in acetyl chloride* [626]. The high dipole moment of acetyl chloride, its properties and great reactivity make it probable that it splits to form an acetylium ion and a chloride ion (see: this section (c)):

$$CH_3COCl \rightleftarrows (CH_3CO)^+ + Cl^-$$

It is shown by conductivity measurements that in some cases acetyl chloride reacts as an ion-pair:

$$C_5H_5N \cdot CH_3COCl \rightleftarrows C_5H_5N \cdot (CH_3CO)^+ + Cl^-; \qquad (20.1)$$

$$2\,CH_3COCl + SnCl_4 \rightleftarrows SnCl_6^{2-} + 2\,(CH_3CO)^+ \qquad (20.2)$$

Lewis acid

$C_5H_5N \cdot CH_3COCl$ is the pyridine-acetyl chloride solvate.

In acetyl chloride solution, compounds increasing the concentration of $(CH_3CO)^+$ ion or Cl^- ion are acids or bases, respectively. Similarly, in acetic anhydride the reaction of $(CH_3CO)^+$ ions is acidic, while that of CH_3COO^- ions is basic. (See: Chapter 7; Section 44.)

Lewis acids, by forming complexes of higher co-ordination number, increase the concentration of the acetylium ion indirectly, by decreasing the concentration of the anion base Cl^-:

$$SnCl_4 + 2\,Cl^- \rightleftarrows SnCl_6^{2-}$$

since the product $[CH_3CO^+]\,[Cl^-]$ remains constant. For this reason Lewis acids are said to be solvo acids in acetyl chloride.

The concentration of the chloride ion from acetyl chloride is indirectly raised by tertiary nitrogenous bases, for example pyridine or quinoline, since they react with the acetylium ion: $(C_5H_5N) \cdot CH_3CO^+$ is formed. Owing to this solvolytic action the above bases are termed solvo bases. Quaternary ammonium chlorides are likewise basic, since they increase the concentration of the Cl^- ion. Quaternary compounds, e.g. benzyltrimethylammonium chloride, and Lewis acids form a neutral complex in the ratio of 2 : 1:

$$2\,(R_4N)\,Cl + SnCl_4 \rightarrow (R_4N)_2.SnCl_6 \quad \text{i.e.} \quad (R_4N)_2{}^{++}SnCl_6^{2-}$$

The Lewis acids $SnCl_4$, $TiCl_4$ are non-electrolytes, although their acetyl chloride solutions are better conductors than the solvent itself. The former neutral complexes exhibit maximum conductivity when more $SnCl_4$ is added, when complexes of 1 : 1 type are formed:

$$(R_4N)_2 \,.\, SnCl_6 + (CH_3CO)_2SnCl_6 \rightarrow$$

$$2\,R_4N \,.\, SnCl_6(CH_3CO) \rightleftarrows 2\,(CH_3CO)^+ + 2\,[R_4N \,.\, SnCl_6]^-$$

Regarding change of conductivity as a function of complex formation see: Chapter 5; Section 33.

The above solvolytic reactions explain the fact that titration can be performed in acetyl chloride even in the presence of crystal violet indicator. In this case the colour change of the indicator resembles that observed in acetic anhydride: in acetyl chloride it is blue, on addition of $TiCl_4$ or $SnCl_4$ it becomes deep yellow or yellow, and on adding quinoline it changes to violet.

(e) *Reaction of Lewis acids and bases in nitrobenzene* [379]. Pyridine and quinoline may be titrated conductometrically in nitrobenzene containing a measured quantity of boron tribromide

Bestimmte Komponente	Probe	Maßlösung	Prüflösung (markiert mit)	Maßlösung (markiert mit)	Bemerkung	Literatur
$Pb^{2+} + Zn^{2+}$		0,025 M $K_4[Fe(CN)_6]$	—	^{59}Fe	Medium neutral oder schwach sauer (vgl. S. 33)	[104, 106]
Pd^{2+}		0,1 N KI	—	^{131}I		[118]
		NaI	—	^{131}I	Medium: Pyridin; Niederschlag: $PdPy_2I_2$	[95]
		NaI	^{109}Pd	—	Medium: Pyridin; Niederschlag: $PdPy_2I_2$	[95]
		NH_4SCN	^{109}Pd	—	Medium: Pyridin; Niederschlag: $PdPy_2(SCN)_2$	[95]
		$K_2Cr_2O_7$	^{109}Pd	—	Medium: Pyridin; Niederschlag: $[PdPy_4](Cr_2O_7)$	[95]
PO_4^{3-}	Phosphorit	0,1 M $[Co(NH_3)_6]Cl_3$	—	^{60}Co	pH = 13 (1 N NaOH) Niederschlag: $[Co(NH_3)_6]PO_4 \cdot [Fe(CN)_6]^{3-,4-}$, $C_2O_4^{2-}$ stören	[123]
	Arzneimittelpräparate	0,1 N $AgNO_3$	—	^{110m}Ag	Borat-Puffer, pH = 9,0	[114]
		0,01 M $MgCl_2$	^{32}P	—	Medium enthält NH_4OH—NH_4Cl	[58]
		0,1 N KI	—	^{131}I	Indirekte Titration in neutralem Medium; Fällung von Ag_3PO_4 mit überschüssigem Ag^+; Ag^+ in Salpetersäure mit $K^{131}I$ titriert	[100]

(i.e. by a 'reversed titration' when the titrant, boron tribromide, is titrated with the solution of the compound to be estimated). As a result of this theoretically interesting method, which, however, requires great care in practice, it was found that initially BBr_3 interacts with the nitrobenzene and a complex is formed in the ratio of 1 : 1. This dissociates according to the following scheme:

$$2\,C_6H_5NO_2 \cdot BBr_3 \rightleftarrows [(C_6H_5NO_2)_2BBr_2]^+ + BBr_4^-$$

Pyridine and quinoline, being stronger bases, displace the weak base nitrobenzene from its complex:

$$C_6H_5NO_2 \cdot BBr_3 + :NC_5H_5 \longrightarrow C_6H_5NO_2 + C_5H_5N \rightarrow BBr_3$$

Dissociation of the pyridine-BBr_3 complex is greater than that of the solvent–BBr_3 complex. The above displacement reaction indicates an analogy with hydrogen acids: the titration of perchloric acid with pyridine in acetic acid may be represented as follows (without indicating charges):

$$CH_3COOH \cdot HClO_4 + NC_5H_5 \rightarrow CH_3COOH + C_5H_5NHClO_4$$

Pyridine being a stronger base displaces the weaker base, acetic acid, from the acetacidium perchlorate. (See: Chapter 1; Section 5 (d).)

(f) *Reactions of triethylaluminium with isoquinoline* [222, 833]. The Lewis acid triethylaluminium can be titrated in an inert solvent with 0·5 N isoquinoline as titrant. Addition of indicator is unnecessary since the complex is yellow in the ratio of 1 : 1, and red in that of 1 : 2:

$$\underset{\text{Lewis acid}}{(C_2H_5)_3Al} + \underset{\text{Base}}{:NC_9H_9} \rightarrow \underset{\text{Yellow complex}}{(C_2H_5)_3Al \leftarrow NC_9H_9} \xrightarrow{+\,:NC_9H_9} \underset{\text{Red complex}}{(C_2H_5)_3Al(NC_9H_9)_2}$$

The red complex is formed only when all the isoquinoline has been used up for the formation of the yellow complex.

Since the colour change is rather slow it is advisable to perform the titration by Hahn's method: 'Umkehrtitration' (reversed titration) [331]. (See: Chapter 30; Section 166 [222].)

(g) '*Acidity*' *of the joint acetic acid solution of Lewis acid and an H-acid* [711]. When tin(IV) chloride is dissolved in acetic acid a reaction product separates with evolution of heat; the complex $SnCl_4(CH_3COOH)_2$ is formed, exhibiting characteristic Brönsted acid properties [830]. This complex in solution is solvated by a third acetic acid molecule; the acetic acid is protonated by a proton from the complex, $SnCl_4(CH_3COOH)_3$, as it is formed and the conductivity of the solution increases.

$$SnCl_4(CH_3COOH)_3 \rightleftarrows [HSnCl_4(CH_3COO)_2]^- + CH_3COOH_2^+$$

By adding tin(IV) chloride to an acetic acid solution of a nitroaniline-type indicator, the ultraviolet spectrum of the indicator is gradually changed to the characteristic acid form of the indicator. In this sense, the acid $SnCl_4(CH_3COOH)_2$ in acetic acid is of a strength equal to or greater than sulphuric acid towards 4-chloro-2-nitroaniline.

21. Secondary Acids

In further developing his electronic theory [510], Lewis considered as an acid 'any substance one of whose atoms is capable of receiving into its valence or co-ordination shell the basic electron pair of another atom'. On this basis every compound is a

$[PtCl_6]^{2-}$		CsCl	—	^{137}Cs	Saures Medium; Niederschlag: $Cs_2[PtCl_6]$	[24]
SO_4^{2-}		0,1 N $BaCl_2$	^{35}S	—	Medium: wäßriges Aceton	[100]
	Arzneimittelpräparate	0,1–0,01 N $BaCl_2$	^{35}S	—	Medium: wäßriges Aceton	[63, 65, 90, 101]
	Wasser	$BaCl_2$	^{35}S	—	Medium: HCl	[80]
		0,1 M $[Co(NH_3)_6]Cl_3$	—	^{60}Co	Neutrales oder schwach saures acetonisch- oder äthanolisch-wäßriges Medium; Niederschlag: $[Co(NH_3)_6]SO_4Cl$	[123]
		0,025 M $K_4[Fe(CN)_6]$	—	^{59}Fe	Indirekte Titration, Fällung von $PbSO_4$ mit überschlüssigem Pb^{2+}, Rücktitration des Pb^{2+}-Überschusses mit markiertem $K_4[Fe(CN)_6]$	[104]
S^{2-}		0,025 M $K_4[Fe(CN)_6]$	—	^{59}Fe	Indirekte Titration (vgl. Best. von SO_4^{2-})	[104]
$S^{2-} + I^-$		0,1 N $AgNO_3$ in NH_4OH	^{131}I	—	vgl. S. 34	[100, 106]
SCN^-		0,1 N KI	—	^{131}I	Indirekte Titration (vgl. Best. von Cl^-)	[100]
SiO_2	Zement, Rohstoffe der Zementindustrie	$CaCl_2$	—	^{45}Ca	Fällung in Form von K_2SiF_6. Freisetzung des F^- bei pH = = 10–11, dann radiometrische Titration	[15]
		Ce—$Pr(NO_3)_3$		^{144}Ce ^{144}Pr		
$S_2O_3^{2-}$	Arzneimittelpräparate	0,1 N $AgNO_3$	—	^{110m}Ag	Acetat-Puffer	[114]

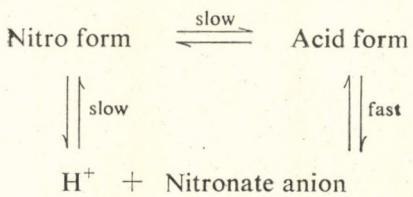
hypothetical acid or base, but with very divergent reactivity, particularly when the time factor is also taken into account. Numerous acids, when interacting with a base, do not require activation energy. These are primary acids. Secondary acids, on the other hand, require activation energy in the course of interaction. The idea of secondary acids is connected with Hantzsch's 'pseudo-acid' concept. (See: Chapter 2, Section 16 and also Section 15 (a).)

Nitroethane reacts only slowly with alkalies and the product, when neutralized with hydrochloric acid, only slowly approaches the conductivity value characteristic of sodium chloride. Mononitroalkanes are acidic substances which exist in tautomeric equilibria with their nitronic acids:



Nitro isomer; weakly acidic Enolic isomer; much more acidic

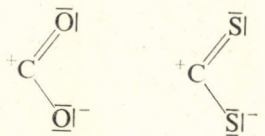
The equilibria of nitroalkanes, nitronic acids, and their ions are summarized in the following scheme:



(See: Chapter 7; Section 44.)

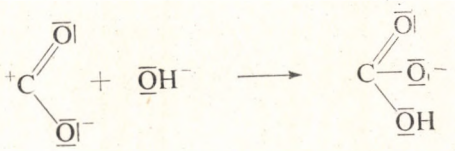
Hantzsch's 'pseudo-acid' theory was only concerned with tautomeric transformations in hydrogen acids. With his concept of secondary acids Lewis made a stride forward; this is demonstrated by the example of carbon dioxide; with its two double bonds it cannot be considered as an electron acceptor while the two double bonds are intact. Neutralization of carbon dioxide is a slow process; thus CO_2 is a secondary acid [510]. Carbon dioxide in ethanol solution at a temperature of $-60°$ reacts only very slowly with sodium ethoxide in dilute ethanol and this slow process can be followed by an indicator. When, however, prior to mixing, the solution is allowed to stand, the colour change of the indicator can be seen at once. This indicates that CO_2 at its lowest energy level does not possess an acid character. CO_2 can be titrated as an acid in acetone or pyridine media with sodium methoxide [71], and with tetrabutylammonium hydroxide in pyridine [168, 286].

Resonance forms of carbon dioxide and carbon disulphide include [628]:



Bestimmte Komponente	Probe	Maßlösung	Prüflösung (markiert mit)	Maßlösung (markiert mit)	Bemerkung	Literatur
$SO_4^{2-} + I^-$		0,1 N $BaCl_2$ 0,1 N $AgNO_3$	^{35}S ^{131}I	— —	Aufeinander folgende Titrationen (vgl. S. 33)	[100, 101, 106]
Ta^{5+}	Stahl	Cupferron	^{182}Tl	—		[9]
Th^{4+}	Konzentrate, Monazit-Sand	0,01 M Na_2HPO_4 0,1 N $Na_4P_2O_7$	— —	^{32}P ^{32}P	Acetat-Puffer Medium: 0,3 N HCl	[58] [79, 87]
Tl^+		0,1 N KI	^{204}Tl	—	Acetat-Puffer, pH = 4,0	[16, 35, 50, 52]
		0,05 M K_2CrO_4	^{204}Tl	—	Medium: NH_4OH	[6, 35]
		0,1 M $H_7[P(W_2O_7)_6]$	—	^{32}P	Medium: 0,5–1,0 N HNO_3 Niederschlag: $Tl_4H_3[P(W_2O_7)_6]$	[6, 35]
		~ 0,02 M $Na[B(C_6H_5)_4]$	— ^{204}Tl	—	Acetat-Puffer (pH = 5,0); Niederschlag: $Tl[B(C_6H_5)_4]$	[6, 35, 94]
Tl^{3+}		$[Co(NH_3)_6]Cl_3$	—	^{60}Co	Medium: HCl, pH = 3,0 Niederschlag: $[Co(NH_3)_6](TlCl_6)$	[49]
		Natrium-1-dithiocarboxy-3-methyl-5-phenyl-pyrazolinat $C_{11}H_{10}N_2S_2Na$	^{204}Tl	—	Niederschlag: $Tl(C_{11}H_{10}N_2S_2)_3$	[21]
$Tl^3 + In^{3+}$		$C_{11}H_{10}N_2S_2Na$	—	^{35}S	vgl. S. 35	[21, 23]
$Tl^{3+} + Zn^{2+}$		$C_{11}H_{10}N_2S_2Na$	—	^{35}S	vgl. S. 35	[21, 23]

Carbon dioxide, as a Lewis acid, enters into reaction with the OH^- ion of tetrabutylammonium hydroxide as a Lewis base and a bicarbonate ion is formed:



In this sense, organic acid chlorides, acid anhydrides and also triphenylmethyl cations are secondary acids (p. 242, in [677]). (See: Chapter 16; Sections 96, 101 and [828].)

UO_2^{2+}		0,1 M Na_2HPO_4	–	^{32}P	Acetat-Puffer	[58]
Y^{3+}		~ 0,023 M Cupferron	^{91}Y	–	Acetat-Puffer (pH = 6), 3 g NaCl in 10 ml Lsg.; Niederschlag: $Y(C_6H_5O_2N_2)_3 \cdot NH_4C_6H_5O_2N_2$	[72]
Zn^{2+}	Legierungen	0,0784 M	–	^{59}Fe	Medium: 1–2 N H_2SO_4, 1–3 g $(NH_4)_2SO_4$ in 10 ml Lsg. bei 50°C; Niederschlag: $K_2Zn_3[Fe(CN)_6]_3$	[34, 104]
		0,025 M	^{65}Zn	^{59}Fe		
		0,1023 M $K_4[Fe(CN)_6]$	^{65}Zn	–		
	Arzneimittelpräparate	0,025 M $K_4[Fe(CN)_6]$	^{65}Zn	–	Medium: HCl oder H_2SO_4, in Ggw. von $(NH_4)_2SO_4$, bei 50°C	[46, 51, 63, 101, 116]
		0,3 N $(NH_4)_2[Hg(CNS)_4]$	–	^{203}Hg	Medium: CH_3COOH	[50]
		$(NH_4)_2[Hg(CNS)_4]$	^{65}Zn	–		[51]
			^{60}Co	–	Mitfällung von radioaktivem Indikator mit Zn^{2+}	[50]
$Zn^{2+} + Cu^{2+}$	Legierungen	$K_4[Fe(CN)_6]$	^{65}Zn	–	Medium: HCl; Fällung erst von Cu^{2+}, dann von Zn^{2+}	[51]
		$(NH_4)_2[Hg(CNS)_4]$	^{60}Co	–	Fällung erst von Cu^{2+}, dann von Zn^{2+} (^{60}Co)	[50]
$Zn^{2+} + Cd^{2+}$		Natrium-1-dithiocarboxy-3-methyl-5-phenyl-pyrazolinat	^{65}Zn	–	Titration von Cd^{2+} bei pH = 14 ($Na_2C_4H_4O_6$ + NaOH), dann Zugabe von Essigsäure bis pH = 9 und Titration von Zn^{2+}	[21]
	Szintillatoren	wie oben	^{65}Zn	^{35}S	vgl. S. 35	[22, 23]
Zr^{4+}	Legierungen	0,01–0,1 M H_3PO_4	–	^{32}P	Medium: 0,5–2,5 N HCl	[4, 6, 35]

Chapter 3

Strength of Bases

22. Strength of Weak Bases

Base strength for weak bases can be expressed either by the strength of the conjugate acid or the reciprocal of the K_{BH^+} value, respectively, defined according to the following general equation (see: Chapter 2; Section 12):

$$K_{BH^+} = \frac{[sH_2^+]\,[B]}{[BH^+]}$$

The greater the acid constant of the conjugate acid the smaller its reciprocal value and the weaker the base. The acid constant of the anilinium ion is $10^{-4.58}$; it is therefore a stronger acid than acetic acid, with acid constant $10^{-4.76}$.

The correlation betwen the dissociation constant of bases K_{base} and their negative logarithms ($-\log K_{base} = pK_{base}$) is illustrated by Table 4.

(a) *In very acidic solvents water is a proton acceptor.* In formic acetic and propionic acids, water acts as a base. It is, therefore, an undesirable contaminant. The actual base strength of water differs according to the solvent:

$$H_2O + sH \rightleftharpoons H_3O^+ + s^- ,$$

where e.g. sH may represent ethanol or formic acid.

By analogy with the formula in Section 22, where BH^+ represents the 'onium ion (NH_4^+; H_3O^+), the acid constant of the conjugate acid of water is:

$$K_{H_3O^+} = \frac{[sH_2^+]\,[H_2O]}{[H_3O^+]}$$

Since $pK_{acid} = pK_{auto} - pK_{diss}$, the $pK_{H_3O^+}$ value of the conjugate acid of water can be determined experimentally, e.g. by the indicator method. The exponent of the dissociation constant of water in ethanol is 18·3 and in formic acid 4·8. Since in ethanol $pK_{H_3O^+} = 19{\cdot}1 - 18{\cdot}3 = 0{\cdot}8$ and in formic acid $pK_{H_3O^+} = 6{\cdot}2 - 4{\cdot}8 = 1{\cdot}2$, the hydroxonium ion is a stronger cationic acid in ethanol than in formic acid, and

3.8.1.2. Organische Stoffe

(Außer den Modellpräparaten Citronensäure und 8-Oxychinolin lagen Arzneimittelpräparate vor)

Bestimmter Stoff	Maßlösung	Prüflösung (markiert mit)	Maßlösung (markiert mit)	Bemerkung	Literatur
Amidopyrin	0,1–0,05 M $KBiI_4$	–	^{131}I	Acetatpuffer, pH = 4,0 bei 0°C, in Ggw. von KI und K_2SO_4	[66, 68]
Allobarbital, Barbital, Phenobarbital und ihre Na-Salze	0,1 N $AgNO_3$	–	^{110m}Ag	Medium: Pyridin, in Ggw. von Na_2CO_3	[89, 111]
Bromadal, Bromisoval	0,1 N $AgNO_3$	–	^{110m}Ag	Medium: H_2SO_4	[115]
Citronensäure, Citrate	0,1 N $AgNO_3$	–	^{110m}Ag		[115]
Ephedrin-hydrochlorid	0,01 N $AgNO_3$	–	^{110m}Ag	Medium: 0,7–0,8 N HNO_3	[93]
Emetin-hydrochlorid	0,1 N $AgNO_3$	–	^{110m}Ag		[115]
8-Oxychinolin	0,05 M $KBiI_4$	–	^{131}I	Medium: HCl, 0°C, in Ggw. von KI und K_2SO_4	[67, 68]
Hyoscyamin	0,1 M $KBiI_4$	–	^{131}I		[62, 64, 101]
Chinin	0,1–0,05 M $KBiI_4$	–	^{131}I	Medium: HCl; in Ggw. von KI und K_2SO_4	[62, 64, 66, 67, 68]
	0,01 M $H_7[P(W_2O_7)_6]$	–	^{32}P	Medium: HCl	[62, 64, 66, 67, 68]

Table 4

Increasing Base-strength	*Base*	K_{base}	pK_{base}	K_{BH^+}	pK_{BH^+}	$\frac{1}{K_{BH^+}}$	*Increasing Proton-Donor Ability of 'Onium Ion*
↑	2-Propylpyridine	10^{-3}	3·00	10^{-11}	11·00	10^{11}	↓
	1,2,3-Triphenylguanidine	$1{\cdot}26\times10^{-5}$	4·90	$7{\cdot}95\times10^{-10}$	9·10 [333]	$1{\cdot}26\times10^{9}$	
	N-Allylmorpholine	$1{\cdot}15\times10^{-7}$	6·94	$8{\cdot}71\times10^{-8}$	7·06 [333]	$1{\cdot}15\times10^{7}$	
	N,N-Dimethylaniline	$1{\cdot}15\times10^{-9}$	8·94	$8{\cdot}71\times10^{-6}$	5·06 [333]	$1{\cdot}15\times10^{5}$	
	Narceine	2×10^{-11} [497]	10·7	5×10^{-4}	3·3	2×10^{3}	
	Diphenylamine	$0{\cdot}71\times10^{-13}$	13·15	$1{\cdot}4\times10^{-1}$	0·85 [332]	7·09	

Chinin-hydrochlorid, Chinin-sulfat	0,1–0,01 N $AgNO_3$	—	^{110m}Ag	Medium: neutral oder schwach sauer	[93, 115]
Codein-phosphat, Codein-hydrochlorid	0,1–0,01 N $AgNO_3$	—	^{110m}Ag	Medium: NaOH	[93, 115]
Cocain-hydrochlorid	0,01 N $AgNO_3$	—	^{110m}Ag	Medium: HNO_3	[93]
Lobelin-hydrochlorid	0,1 N $AgNO_3$	—	^{110m}Ag		[115]
Morphin	0,1 M $KBiI_4$ 0,01 M $H_7[P(W_2O_7]_6$	— —	^{131}I ^{32}P	vgl. Best. von Chinin vgl. Best. von Chinin	[62, 64] [62, 64]
Morphin-hydrochlorid, Äthylmorphin-hydrochlorid	0,1 N $AgNO_3$	—	^{110m}Ag		[115]
Natrium-p-aminosalicylat	0,1 N $AgNO_3$	—	^{110m}Ag	Medium: äthanolisch pH = 7,0	[115]
Oxalsäure, Oxalate	0,1 N $AgNO_3$ 0,025 M $K_4[Fe(CN)_6]$	— —	^{110m}Ag ^{59}Fe	Medium: äthanolisch Indirekte Titration (vgl. Best. von SO_4^{2-})	[14, 97, 115] [104]
Papaverin-hydrochlorid	0,01 N $AgNO_3$	—	^{110m}Ag		[93, 115]
Pilocarpin-hydrochlorid	0,1 N $AgNO_3$	—	^{110m}Ag		[115]
Procain-hydrochlorid	0,1 N $AgNO_3$	—	^{110m}Ag	Saures Medium	[115]
Scopolamin-hydrochlorid	0,1 N $AgNO_3$	—	^{110}Ag		[115]

consequently water itself is a weaker base in ethanol than in formic acid ($10^{-0.8} > 10^{-1.2}$). Thus it becomes clear why acidic solvents have to be dehydrated prior to their use in the titration of very weak bases. (Chapter 8, Section 47.)

(b) *Ionization of very weak bases in sulphuric acid. (Sulphuric acid as solvent for the measurement of strength of basicity of very weak bases.)* Very weak bases can be investigated only by their interaction with very strong acids, and conversely, the strength of very weak acids can only be determined by their interaction with strong bases. (See: Chapter 2; Section 18.) The solvent itself can be such a strong acid, for example, sulphuric acid, in which ionization of weak bases can be determined either by measuring the freezing-point depression or spectrophotometrically [344, 349, 352, 818]. Apart from acetic acid, sulphuric acid is the most thoroughly tested solvent. Hantzsch did the pioneer work in this field (1907–1930). More accurate measurements were made by Hammett (1933–1937) and by Gillespie and Ingold (1946–1950) [271, 272]. Sulphuric acid as a solvent has the great advantage that, when ionic or non-ionic compounds are dissolved in it, the freezing-point depression over a very wide range is proportional to the concentration of the dissolved compounds, since the activity coefficient of the ions involved remains nearly constant up to an unusually high concentration. The ion-solvating ability of sulphuric acid is possibly the highest of all solvents.

Most molecules containing oxygen and nitrogen atoms (amines, ethers, ketones, aldehydes, alcohols and esters) are able to co-ordinate protons in sulphuric acid. Most of them exhibit twice the calculated freezing-point depression per mole thus indicating that the reaction $\rangle O + H_2SO_4 \rightarrow \rangle OH^+ + HSO_4^-$ has proceeded to completion:

$$C_2H_5OH + 2\,H_2SO_4 \rightarrow C_2H_5SO_4H + H_3O^+ + HSO_4^- \;;$$

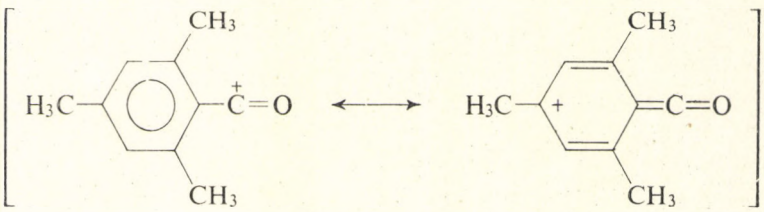
$$(C_2H_5)_2O + H_2SO_4 \rightarrow [(C_2H_5)_2OH]^+ + HSO_4^-$$

Numerous aliphatic and aromatic carboxylic acids add a proton and an acidium ion is formed, that is to say, they *behave as bases*. Formation of protonated acid molecules is only partial in the case of dichloroacetic acid, aliphatic and aromatic nitro compounds and sulphonic acids. In the course of proton transfer some compounds undergo an even more complicated process, e.g.

$$\underset{\text{Acetic anhydride}}{(CH_3CO)_2O} + 2\,H_2SO_4 \rightarrow \underset{\text{Acetyl cation}}{(CH_3CO)^+} + \underset{\text{Acetacidium ion}}{CH_3COOH_2^+} + 2\,HSO_4^-$$

In all these reactions the basic character of the oxygen atom, resulting from the free electron pair, is evident. In aromatic carboxylic acids, with a possible oxocarbenium form stabilized by resonance, four ions arise [611]:

$$2,4,6-(CH_3)_3C_6H_2-COOH + 2\,H_2SO_4 \rightarrow H_3O^+ + 2\,HSO_4^- +$$



Bestimmter Stoff	Maßlösung	Prüflösung (markiert mit)	Maßlösung (markiert mit)	Bemerkung	Literatur
Strychnin	0,1 M $KBiI_4$	—	^{131}I	vgl. Best. von Chinin	[62, 64]
	0,01 M $H_7[P(W_2O_7)_6]$	—	^{32}P	vgl. Best. von Chinin	[62, 64]
	K_2HgI_4	—	^{203}Hg		[93]
Strychnin-sulfat	0,01 N $AgNO_3$	—	^{110m}Ag		[93]
Theobromin	0,1 N $AgNO_3$	—	^{110m}Ag	Medium: NaOH	[89, 111]
Theophyllin, Aminophyllin	0,1 N $AgNO_3$	—	^{110m}Ag	Medium: NH_4OH	[89, 111]
Thiopental	0,1 N $AgNO_3$	—	^{110m}Ag	Medium: 1 M KNO_3	[89]

Triphenylmethylcarbinol in sulphuric acid yields a deep yellow solution and the freezing-point depression shows the formation of four ions:

$$(C_6H_5)_3C{-}OH + 2\,H_2SO_4 \rightarrow (C_6H_5)_3C^+ + H_3O^+ + 2\,HSO_4^-$$

This reaction is analogous to that of triphenylmethyl chloride with $AlCl_3$:

$$(C_6H_5)_3C{-}Cl + AlCl_3 \rightarrow (C_6H_5)_3C^+ + AlCl_4^-$$

The existence of the carbenium ion is proved by the isolation of triphenylmethylcarbenium perchlorate:

$$[(C_6H_5)_3C]^+ClO_4^-.$$

A sulphuric acid solution of 1,1-diphenylethylene likewise gives a yellow highly coloured solution; the hydrocarbon acts as a base and its conjugate acid is the carbenium ion:

$$(C_6H_5)_2C{=}CH_2 + H_2SO_4 \rightleftarrows (C_6H_5)\overset{+}{C}{-}CH_3 + HSO_4^-$$

Numerous nitrogen-containing compounds behave like electrolytes in sulphuric acid: nitroaniline, azobenzene, acetonitrile, benzamide, etc. Urea behaves as a diacidic base:

$$CO(NH_2)_2 + 2\,H_2SO_4 \rightleftarrows CO(NH_3)_2^{++} + 2\,HSO_4^-$$

A specific method for the spectrophotometric determination of the pK_{BH^+} value of very weak bases in sulphuric acid–water mixtures has been developed by Flexer, Hammett and Dingwall [230, 625]. If the H_0 value of the medium is known the pK_{BH^+} value can be calculated (see: Chapter 2; Section 16 (d)):

$$pK_{BH^+} = H_0 + \log \frac{\varepsilon_B - \varepsilon}{\varepsilon - \varepsilon_{BH^+}}$$

The following table illustrates the pK_{BH^+} value of some very weak bases. Urea is a weak base, benzoic acid an extremely weak base:

Base	pK_{BH^+}
p-Nitroaniline	+0·99 [625]
Urea	+0·4 [505]
Acetamide	+0·25 [279]
Acetonitrile	−4·3 [505]
1,4-Dioxan	−4·4 [505]
Acetic acid	−6·2 [279]
Benzoic acid	−7·38 [230]
2,4,6-Trinitroaniline	−9·41 [625]

The above table indicates that acetic acid is a very weak base and therefore its conjugate acid the acetacidium ion, must be a very strong acid.

23. Measurement of the Base Strength of Nitrogenous Organic Bases; Relationship between Half-neutralization Potential and pK Value

By the potentiometric titration of nitrogenous bases in acetic acid, acetic anhydride, nitromethane, acetonitrile, etc. the order of their relative base strengths can be determined. In many cases a numerical correlation becomes apparent between the

3.9. Literatur

[1] ALIMARIN, I. P.: Chem. Analyt. (Warschau), *2*, 297 (1957)
[2] ALIMARIN, I. P.: Proc. Internat. Conf. on the Peaceful Uses of Atomic Energy, Genf, *15*, 60 (1956)
[3] ALIMARIN, I. P. und GIBALO, I. M.: Sawod. Lab., *21*, 1022 (1955)
[4] ALIMARIN, I. P. und GIBALO, I. M.: Sawod. Lab., *22*, 635 (1956)
[5] ALIMARIN, I. P. und GIBALO, I. M.: Sawod. Lab., *23*, 412 (1957)
[6] ALIMARIN, I. P., GIBALO, I. M. und SIROTINA, I. A.: Internat. J. Appl. Radiation Isotopes, *2*, 117 (1957)
[7] ALIMARIN, I. P. und SIROTINA, I. A.: Shur. Neorg. Chim., *3*, 1709 (1958)
[8] ALIMARIN, I. P. und SOTNIKOW, W. S.: Trudy Kom. Analit. Chim., Akad. Nauk SSSR, *IX (XII)*, 213 (1958)
[9] AMANO, H.: Sci. Repts. Res. Inst. Tohoku Univ. Ser. A., *11*, 304 (1959)
[10] ARCHIBALD, E. H. und HALLERR, L. T.: J. Amer. Chem. Soc., *47*, 1314 (1925)
[11] AYLWARD, G. H., GARNETT, J. L., HAYES, J. W. und LAW, S. W.: Chem. and Ind., 560 (1960)
[12] AYLWARD, G. H., GARNETT, J. L., HAYES, J. W. und LAW, S. W.: J. Inorg. Nucl. Chem., *16*, 350 (1961)
[13] BASIŃSKI, A., SZYMAŃSKI, W., KRYGIER, A. und ZAPALOWSKA, G.: Roczniki Chem., *37*, 1345 (1963)
[14] BEBESEL, P. und SIRBU, I.: Rev. Chim. (Rumänien), *11*, 288 (1960)
[15] BERRY, D. S. und SCOTT, B. F.: Proceedings of the Sixth Conference on Analytical Chemistry in Nuclear Reactor Technology, Gatlinburg, Tenn., 9–11 Okt. 1962; TID – *7655*, 291; vgl. Nucl. Sci. Abstr., *17*, 40711 (1963)
[16] BLESCHINSKIJ, S. W. und ABRAMOWA, W. F.: Primenenie Mechenik Atomow v analit. Chim. (Verwendung radioaktiver Atome in der analytischen Chemie). Isd. Akad. Nauk SSSR. Inst. Geochim. i Analit. Chim. S. 37 (1955)
[17] BRADHURST, D. H., COLLER, B. A. W. und DUNCAN, J. F.: J. Inorg. Nucl. Chem., *4*, 379 (1957)
[18] BRAUN, T.: Chim. analyt., *46*, 61 (1964)
[19] BRAUN, T., GALATEANU, I. und MAXIM, I.: Technica Nucleara (Bukarest), *7*, 20 (1959)
[20] BRAUN, T. und TÖLGYESSY, J.: Talanta, *11*, 1277 (1964)
[21] BUSEW, A. I. und BYRKO, V. M.: Trudy Kom. Analit. Chim., Akad. Nauk SSSR, *IX (XI[)*, 200 (1958)
[22] BUSEW, A. I. und BYRKO, W. M.: Trudy chim. i chim. Technol., *3*, 52 (1960)
[23] BUSEW, A. I. und BYRKO, W. M.: Talanta, *8*, 492 (1961)
[24] CASEY, A. T. und ROBB, W.: Nature, *198*, 581 (1963)
[25] TSCHERNJI, V. S., WAIL, E. I. und ISMAJLOW, N. A.: Trudy Kom. Analit. Chim., Akad. Nauk SSSR, *XIII*, 445 (1963)
[26] DUNCAN, J. F.: J. Inorg. Nucl. Chem., *11*, 161 (1959)
[27] DUNCAN, J. F. und THOMAS, F. G.: Proc. Australian Atomic Energy Symposium, Radioisotopes Physical Sciences, 637 (1958)
[28] ERSITAWI, D. I., BROUCHEK, F. I. und TSCHITSIWADSE, T. A.: Trudy Grusinsk. Polit. Inst., *4*, 3 (1959)
[29] ERISTAWI, D. I., BROUCHEK, F. I. und TSCHITSIWADSE, T. A.: Shur. Analit. Chim., *14*, 631 (1959)
[30] ESCUE, R. B. und BULLOCH, P. N.: Regional Conclave of the Amer. Chem. Soc., New Orleans 10–12 Dez. (1953)
[31] ESCUE, R. B. und BULLOCH, P. N.: Analyt. Chem., *25*, 1932 (1953)
[32] FRITZ, J. S.: Acid-Base Titrations in Non-aqueous Solvents, G. F. Smith Chemical Co., Columbus, Ohio U. S. A. (1952)
[33] GARNETT, J. L. und LAW, S. W.: zit. in [12]

half-neutralization potential (h.n.p.) measured in the organic solvent and the aqueous pK value [146, 247, 333, 337, 778, 779, 838].

Bayles and Chetwyn, and also Pearson and Vogelsong performed spectrophotometric experiments on the equilibrium of nitrogenous bases with 2,4-dinitrophenol as a reference acid in solvents with differing dielectric constants and solvating ability [46, 631]. The strength of bases changes in a complicated way as a function of the dielectric constant and the solvation effect of the solvent. Investigations on the change of strength of bases caused by the solvation effect of the solvent and that caused by stereochemistry of the molecule often led to conflicting results [8, 96, 629, 631, 820].

(a) *The relative strengths of bases in acetic acid* are illustrated in Figs 20 and 21 [332, 337, 838]. The majority of potentiometric graphs show the customary S-shaped curve. For weak bases the starting point of the potentiometric curve is set higher on the ordinate; the steepness of the potential jump decreases gradually, as for instance, with acetoxime, urea and acetamide

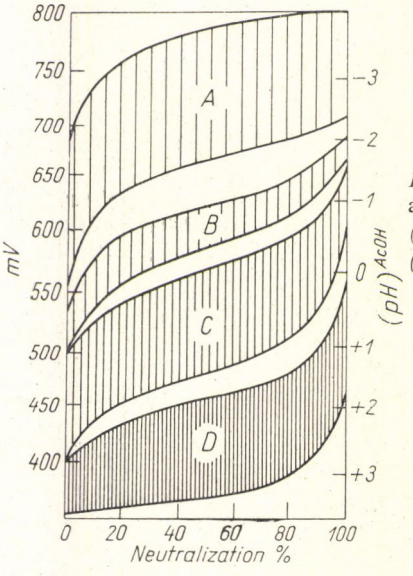


Fig. 20. Potentiometric curves of bases in acetic acid according to Hall [332, 337]. — *(A)* Very weak bases, *(B)* Weak bases, *(C)* Bases of medium strength, *(D)* Strong bases

(Fig. 20). When titrating very weak bases ($K_{base} \leqq 10^{-14}$) with 1 M perchloric acid in solutions of 0·05 M the proton activity shows a steep rise even when small amounts of titrant are added, but the point of inflection does not occur at all or, in the case of some weak bases, becomes flattened (between K_{base} 10^{-14} and 10^{-10}). In the case of medium-strength or strong bases the potentiometric curve rises evenly from the outset up to the point of inflection since on solvation an acetate ion is formed and this interacts with perchloric acid. Weak and very weak bases in acetic acid form acetic acid solvate and 'onium ion in varying proportions.

$$\text{Very weak bases: } R_2NH \ldots . HOOC . CH_3 \rightleftarrows R_2NH_2^+ . CH_3COO^-$$

$$\text{Weak bases: } R_2NH \ldots . HOOC . CH_3 \rightleftarrows R_2NH_2^+ . CH_3COO^-$$

The order of strength of bases, potentiometrically titrated with perchloric acid in acetic acid, is as follows: [332], Figs 20 and 21:

1. *In acetic acid the following very weak bases are not titratable:* propionitrile, 4-nitro-2,6-dichloroaniline, diacetylmonoxime, formanilide, diethyldiphenylurea, acetanilide, tribromoaniline, N-propylacetanilide, N-methylacetanilide, *o*-nitroaniline, phenylurea, acetamide.

2. *In acetic acid the following weak bases are inaccurately titratable: p*-nitrodimethylaniline, urea, methylurea, diphenylamine, 2,5-dichloraniline, *p*-nitroaniline (from $pK_{BH^+} \sim 0$ to pK_{BH^+} 2).

[34] GIBALO, I. M. und BYRKO, W. M.: Sawod. Lab., *24*, 281 (1958)
[35] GIBALO, I. M., SIROTINA, I. A. und ALIMARIN, I. P.: Isotopi i Islutschenja w Chimii (Isotope und Strahlung in der Chemie) Moskau, 178 (1958)
[36] GOLDMAN, J. A. und MEITES, L.: Analyt. Chim. Acta, *30*, 280 (1964)
[37] HAHN, O.: Z. angew. Chem., *40*, 871 (1930)
[38] ISMAJLOW, N. A.: Elektrochimija Rastworow (Elektrochemie von Lösungen), Isd. Charkow. Univ. (1959)
[39] ISMAJLOW, N. A. und TSCHERNIJ, W. S.: Shur. Fis. Chim., *24*, 129, 319 (1960)
[40] ISMAJLOW, N. A., KRASOWSKIJ, I. W., ALEXANDROW, W. W. und WAIL, E. I.: Dokl. Akad. Nauk SSSR, *74*, 91 (1950)
[41] ISMAJLOW, N. A. und WAIL, E. I.: Ukrain. Chim. Schur., *23*, 662 (1957)
[42] JASINSKI, T.: Analiza miareczkowa w srodowiskach niewodnych (Maßanalyse in nichtwäßrigen Medien), Panstwowe Wydawnictwo naukowe, Warschau (1956)
[43] JESENÁK, V. und TÖLGYESSY, J.: Acta Chim. Hung., *32*, 397 (1962)
[44] JESENÁK, V. und TÖLGYESSY, J.: Chem. Zvesti, *17*, 161 (1963)
[45] JESENÁK, V., TÖLGYESSY, J. und VALTYNI, J.: Atompraxis, *12*, 606 (1966)
[46] KAMETANI, F., KIMURA, K. und KATAOKA, A.: Nippon Genshiryoku Gakkaishi (J. At. Energy Soc. Japan), *4*, 373 (1962)
[47] KIMURA, K. und KAMETANI, F.: Japan Analyst., *10*, 1293 (1961)
[48] KLAS, J.: Chem. Zvesti, *19*, 689, 695 (1965)
[49] KOCH, J.: Kernenergie, *3*, 609 (1960)
[50] KORENMAN, I. M. und SEJANOWA, F. R.: Trudy Kom. Analit. Chim., Akad. Nauk SSSR, *IX (XII)*, 205 (1958)
[51] KORENMAN, I. M., SEJANOWA, F. R., DEMINA, E. A. und SAPOSCHNIKOWA, M. I.: Sawod. Lab., *22*, 1143 (1956)
[52] KORENMAN, I. M., SEJANOWA, F. R. und MULJANOW, P. W.: Trudy Chim. i Chim. Technol., *1*, 118 (1958)
[53] KORSCHUNOW, I. A. und BUDOW, T. M.: Trudy Chim. i Chim. Technol., *2*, 489 (1959)
[54] KRESCHKOW, A. P.: Supplement to PALIT, S. R., DAS, M. N. und SOMAYAYULU, G. R.: Nevodnoe titrovanie (Titrationen in nichtwäßrigen Medien), Goschimisdat, Moskau (1958)
[55] KRIVÁŇ, V.: Dissertation, Bratislava (1964)
[56] KUCHARSKÝ, J. und ŠAFAŘIK, L.: Titrations in Non-aqueous Solvents, Elsevier, Amsterdam (1965)
[57] LANGER, A.: Radiometric Titration Method. U. S. Pat. 2, 367, 949. 23 Nov., 1940
[58] LANGER, A.: J. Phys. Chem., *45*, 639 (1941)
[59] LANGER, A.: Analyt. Chem., *22*, 1288 (1950)
[60] LANGER, A. und STEVENSON, D. P.: Analyt. Chem., *14*, 770 (1942)
[61] Magkémia (Kernchemie), Tankönyvkiadó, Budapest (1963)
[62] MAJER, J., ŠARŠUNOVÁ, M. und TÖLGYESSY, J.: XVIIIe Congrès internat. des sci. pharm., Brüssel, Rep. *10*, 6–15 Sept. (1958)
[63] MAJER, J., ŠARŠUNOVÁ, M. und TÖLGYESSY, J.: XIX. Internat. Kongress der pharm. Wiss., Zürich, 6-10. Sept. (1959)
[64] MAJER, J., ŠARŠUNOVÁ, M. und TÖLGYESSY, J.: Pharmazie, *14*, 218 (1959)
[65] MAJER, J., ŠARŠUNOVÁ, M. und TÖLGYESSY, J.: Schweiz. Apoth. Ztg., *98*, 631 (1960)
[66] MAJER, J. und TÖLGYESSY, J.: Acta Facult. Pharm. Brunensis et Bratislavensis, *III*, 77 (1960)
[67] MAJER, J. und TÖLGYESSY, J.: XVIIIe Congrès internat. des sci. pharm., Brüssel, Rep. *9*, 6–15 Sept. (1958)
[68] MAJER, J., TÖLGYESSY, J. und SCHILLER, P.: Sb. Chemickej Fakulty SVŠT (Ber. der Abt. Chemie der Techn. Univ.), Bratislava, 21 (1960)

3. *Bases of medium strength:* acetoxime, 2,4-dichloroaniline, 2-nitro-4-chloroaniline, *m*-nitrodimethylaniline, *o*-bromoaniline, *o*-chloroaniline, antipyrine (from pK_{BH^+} 2 to 3·5).

4. *Strong bases:* *m*-chloroaniline, *m*-bromoaniline, *p*-nitrosodiphenylamine, semicarbazide, *p*-chloroaniline, *p*-bromoaniline, α-naphthylamine, *m*-toluidine, *m*-anisidine, *p*-anisidine, benzylaniline, *o*-toluidine, *p*-toluidine, methylaniline, *o*-anisidine, methyl-*o*-toluidine, quinoline, methyl-*p*-toluidine, ethylaniline, dimethylaniline, pyridine, dimethylamine, 2-picoline, diphenylguanidine, piperidine, diethylamine, triphenylguanidine, methyl-n-propylaniline, *p*-aminodimethylaniline, tri-n-butylamine, di-n-butylamine, guanidine, di-n-propylaniline, diethylaniline, triethanolamine, dimethyl-*o*-toluidine, diethyl-*p*-toluidine, triethylamine, diethyl-*o*-toluidine (above pK_{BH^+} 3·5).

For a correlation between base strength and molecular structure see: [334].

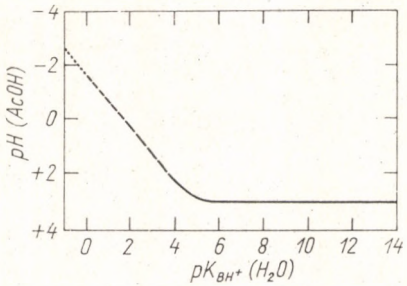


Fig. 21. Relative strength of bases in water and acetic acid according to Hall [332]. — $pH_{(AcOH)}$ is the 'pH' taken at the potentiometric titration midpoint. In acetic acid: (. . . . .) non-titratable very weak bases; (- - - - - -) only inaccurately titratable weak bases; (— — —) medium strength bases; (————) strong bases. Between pK_{BH^+} 4·5 and pK_{BH^+} 14 bases, in acetic acid, are levelled

(b) *The correlation between base strength and half neutralization potential* has been the subject of much research. Fig. 21 illustrates that a base the pK_{BH^+} value of which is 1–2 can only just be titrated potentiometrically (under favourable circumstances) in acetic acid; Fig. 22 shows that a linear relationship exists between the h.n.p. and p*K* values of bases with p*K* values from 9 to 13 [332, 838].

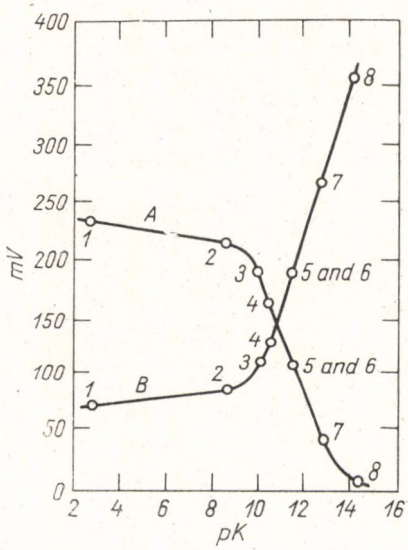


Fig. 22. Correlation between half-neutralization potential and p*K* value according to Veibel [838]. — *(A)* Potential jump between 9·5 and 11 ml on adding 0·1 N perchloric acid, *(B)* Half-neutralization potential; *(1)* Piperidine, *(2)* Pyridine, *(3)* *p*-Chloroaniline, *(4)* *m*-Chloroaniline, *(5)* *m*-Nitroaniline, *(6)* *o*-Chloroaniline, *(7)* *p*-Nitroaniline, *(8)* *o*-Nitroaniline

(c) *Correlation between base strength and half-neutralization potential in acetic anhydride.* According to Streuli's investigations a linear relationship exists between h.n.p. of nitrogen-containing bases and the pK_{BH^+} value of the conjugate acids of

[69] MAJER, VL.: Z. Elektrochem., *42*, 123 (1936)
[70] MARJANOW, B. M. und SEREBRENNIKOW, W. W.: Sb. Woprosy chim. kinetiki i reakcionnoi sposobnosti weshestw (Sammlung der Arbeiten über chemische Kinetik und Reaktivität), Isd. Tomsk. Gos. Univ., 256 (1962)
[71] MARJANOW, B. M. und SEREBRENNIKOW, W.W.: Sb. Waprosi chimii. Isd. Tomsk. Gos. Univ., 8 (1963)
[72] MARJANOW, B. M. und SEREBRENNIKOW, W. W.: Sb. Waprosi chimii, Isd. Tomsk. Gos. Univ., 195 (1963)
[73] MARJANOW, B. M. und SEREBRENNIKOW, W. W.: Radiochimija, *5*, 347 (1963)
[74] MARJANOW, B. M. und SEREBRENNIKOW, W. W.: Shur. Analit. Chim., *18*, 58 (1963)
[75] MATSUSHINA, I.: Koru Taru, *14*, 646 (1962), vgl. Chem. Abstr., *60*, 2334f (1964)
[76] MAXIM, I., BRAUN, T. und GALATEANU, I.: J. Inorg. Nucl. Chem., *10*, 166 (1959)
[77] MEVEL, N. und LACRUCHE, B.: 15th Internat. Congr. Pure and Appl. Chem., Lissabon, Paper V-20 (1956)
[78] MIKHEEWA, L. M. und MIKHEEW, N. B.: Radioaktiwnije isotopy v analititschewskoj chimii (Radioisotopen in der analytischen Chemie), Gosatomisdat, Moskau (1961)
[79] MOELLER, T. und SCHWEITZER, K.: Analyt. Chem., *20*, 1201 (1948)
[80] MOELLER, D. W., TERRIL, J. G. und SEAL, M. S.: Proc. Internat. Conf. on the Peaceful Uses of Atomic Energy, Genf, *15*, 49 (1956)
[81] Nuclear Chicago Corporation, Technical Bulletin, Nr. 6 (1959)
[82] ONSTOTT, E. J. und ELLIS, W. P.: Analyt. Chem. *28*, 393 (1956)
[83] PALIT, S. R., DAS, M. N. und SOMAYAJULU, G. R.: Non-aqueous titrations, Indian Assoc. for the Cultivation of Science, Calcutta (1954)
[84] PLOTNIKOV, V. I.: Sawod. Lab., *24*, 927 (1958)
[85] POLEWAJA, N. I., TSCHERNOWA, N. N. und MIRKINA, S. L.: Wschesojus. Nautsch. Issledowatel. Geol. Inst., Int. Sbornik, Nr. 1, 119 (1955)
[86] Proc. IRE, Australia, *19*, 175 (1958)
[87] RYABCHIKOV, D. I. und GOLBRAICH, E. K.: Analytical Chemistry of Thorium, Pergamon, Oxford (1963)
[88] ŠARŠUNOVÁ, M., MAJER, J. und TÖLGYESSY, J.: Česk. Farm. *8*, 567 (1959)
[89] ŠARŠUNOVÁ, M. und TÖLGYESSY, J.: Z. analyt. Chem. *196*, 107 (1963)
[90] ŠARŠUNOVÁ, M., TÖLGYESSY, J. und MAJER, J.: Česk. Farm., *9*, 68 (1960)
[91] SCOTT, F. B. und DRISCOLL, W. J.: Review of Isotopes in the Physical Sciences and Industry (Proceedings of the Conf. on the Uses of Radioisotopes in the Physical Sciences and Industry, gehalten durch die IAEA in Kopenhagen, 6–17. Sept., 1960) *II*, 339–349, IAEA, Wien (1962)
[92] SHINAGAWA, M., MATSUO, J. und YOSHIDA, M.: Japan Analyst., *4*, 139 (1955)
[93] SIRBU, I. und BEBESEL, P.: Rev. chim. (Rumänien), *10*, 641 (1959)
[94] SIROTINA, I. A. und ALIMARIN, I. P.: Shur. Analit. Chim., *12*, 367 (1957)
[95] SPACU, P. und VOICU, V.: Acad. Rep. Populare Romine, Studii Cercetari Chim., *10*, 305 (1962)
[96] STEVANČEVIĆ, D. B. und BLAGOJEVIĆ, O.: Bull. of the Inst. of Nuclear Sciences »Boris Kidrič«, *12*, 115 (1961)
[97] STRAUB, GY. und CSAPÓ, Z.: Acta Chim. Hung., *26*, 267 (1961)
[98] STÜRZER, U.: Kernenergie, *1*, 817 (1958)
[99] TÖLGYESSY, J.: Chem. Listy, *54*, 686 (1960)
[100] TÖLGYESSY, J.: Dissertation, Prag (1959)
[101] TÖLGYESSY, J.: Dissertation, Bratislava (1961)
[102] TÖLGYESSY, J.: Jadrové žiarenie v chemickej analýze (Die Kernstrahlung in der analytischen Chemie), SNTL, Prag, SVTL, Bratislava (1962)

these bases in acetic anhydride [778]. Neutral, uncharged bases are weaker in acetic anhydride than in water in comparison with negatively charged base-anions.

Numerous investigators have studied the use of acetic anhydride as a solvent [249, 288, 831]. A number of nitrogenous bases which cannot be titrated as bases in acetonitrile or acetic acid can be potentiometrically titrated in acetic anhydride.

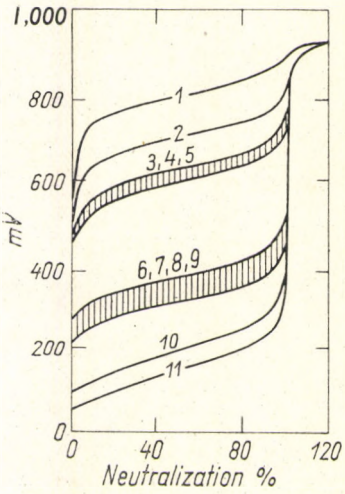


Fig. 23. Potentiometric curves of bases in acetic anhydride according to Streuli [778]. —*(1)* Acetanilide, pK_{BH^+} — 2·9 [505], *(2)* Acetamide pK_{BH^+} —0·48 [382], *(3)* Caffeine pK_{BH^+} 0·61 [497], *(4)* Urea pK_{BH^+} 0·50 [505], *(5)* Methylurea pK_{BH^+} 0·90 [332], *(6)* N,N-Dimethylaniline pK_{BH^+} 5·21 [778], *(7)* Quinoline pK_{BH^+} 5·06 [778], *(8)* Pyridine pK_{BH^+} 5·30 [332], *(9)* N,N-Diethylaniline pK_{BH^+} 6·52 [332], *(10)* N,N-Dimethylbenzylamine pK_{BH^+} 9·02 [497], *(11)* Tri-n-butylamine pK_{BH^+} 9·85 [332]

A disadvantage of the solvent is that it reacts with acetylatable amines and the resulting acid amides are of far weaker basicity.

For experiments in acetic anhydride, 0·05 N perchloric acid solution has proved to be a suitable titrant, prepared in a 1 : 1 acetic acid-acetic anhydride mixture [778]. For the potentiometric titration, a glass electrode and a silver–silver chloride reference electrode can be used. The latter is immersed in acetic anhydride previously saturated with silver chloride and lithium chloride (Chapter 12; Section 67). Fig. 23 illustrates potentiometric curves for 100 ml of 0·25 mM base solutions. It is apparent

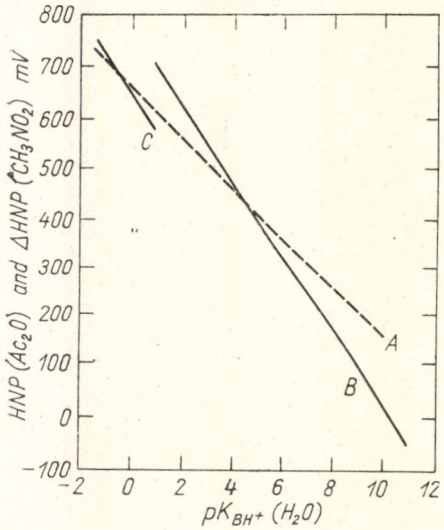


Fig. 24. Correlation between half-neutralization potential and base strength *(A)* in acetic anhydride and *(B, C)* in nitromethane, according to Streuli [778, 779]. See Tables 5 and 6

[103] TÖLGYESSY, J.: Magsugárzás a kémiai analízisben (Die Kernstrahlung in der analytischen Chemie), Műszaki Könyvkiadó, Budapest (1965)
[104] TÖLGYESSY, J.: Magyar Kém. Folyóirat *65*, 149 (1959)
[105] TÖLGYESSY, J.: Rádiometrické titrácie (Radiometrische Titrationen), SAV, Bratislava (1966)
[106] TÖLGYESSY, J.: Sb. Chemickej Fakulty SVŠT (Ber. d. Abt. Chemie d. Techn. Univ.), Bratislava, 3 (1960)
[107] TÖLGYESSY, J. und BRAUN, T.: Sb. III. Celostátni Rádiochem. Konf. Liblice u Mělnika (Berichte der III. Radiochemischen Konferenz in Liblice bei Mělnik, ČSSR), 330 (1964)
[108] TÖLGYESSY, J. und DILLINGER, P.: Chem. Zvesti, *17*, 439 (1963)
[109] TÖLGYESSY, J. und DILLINGER, P.: XX. Sjazd Chemikov (Berichte des XX. Chemischen Kongresses), Žilina, ČSSR, 9–12. Juli (1963)
[110] TÖLGYESSY, J., JESENÁK, V. und BRAUN, T.: Proc. of the IAEA Symp. on Radiochemical Methods of Analysis, *II*, 99, IAEA, Wien (1965)
[111] TÖLGYESSY, J., JESENÁK, V., und ŠARŠUNOVÁ, M.: Report of the Department of Chemistry, Technical University 24/03. 04 d, Bratislava (1963)
[112] TÖLGYESSY, J. und ŠAJTER, V.: Acta Chim. Hung., *26*, 217 (1961)
[113] Töund ŠLAGYESSY, J. JTER, V.: Chem. Zvesti, *16*, 217 (1962)
[114] TÖLGYESSY, J. und ŠARŠUNOVÁ, M.: Z. analyt. Chem., *195*, 429 (1963)
[115] TÖLGYESSY, J. und ŠARŠUNOVÁ, M.: Z. analyt. Chem., *196*, 192 (1963)
[116] TÖLGYESSY, J., ŠARŠUNOVÁ, M. und MAJER, J.: Česk. Farm., *8*, 565 (1959)
[117] TÖLGYESSY, J., ŠARŠUNOVÁ, M. und MAJER, J.: XVIIIe Congrès internat. des sci. pharm., Brüssel, 6–15. Sept. (1958)
[118] TÖLGYESSY, J. und SCHILLER, P.: Magyar Kém. Folyóirat, *63*, 269 (1957)
[119] TÖLGYESSY, J. und VARGA, S.: Chem. Zvesti, *17*, 779 (1963)
[120] WASKRESSENJSKIJ, S. A. und BACHTIMIROW, R. S.: Shur. Neorg. Chim., *2*, 942 (1957)
[121] WILZBACH, K. E., KAPLAN, L. und BROWN, W. G.: Science, *118*, 522 (1953)
[122] WILZBACH, K. E., VAN DYKEN, A. R. und KAPLAN, L.: Analyt. Chem., *26*, 880 (1954)
[123] JATSCHIMIRSKIJ, K. B. und ROSLJAKOWA, E. N.: Trudy Kom. Analit. Chim., Akad. Nauk. SSSR, *IX (XII)*, 194 (1958)
[124] JATSCHIMIRSKIJ, K. B. und ROSLJAKOWA, E. N.: Schur. Analit. Chim., *5*, 206 (1952)
[125] YOFFE, J., WELWART, Y. und TULER, W.: Bull. Res. Counc. of Israel (XXVIIth Sci. Meeting Israel Chem. Soc., Rehovoth, 10–11 Okt. 1960), *9A*, 253 (1960)

that the strength of bases is not levelled by acetic anhydride, and so differential titrations can be carried out. An abridged list of the values is shown in Table 5 [778]. Line *A* in Fig. 24 indicates the half-neutralization potential (h.n.p.) in acetic anhydride medium $(AcO)_2O$, as a function of the pK_{BH^+} value measured in water. Bases containing nitrogen hetero-atoms are found further from the line. It is noteworthy that triphenylphosphine, represented in Table 5, can be titrated in acetic anhydride while its nitrogen-containing analogue triphenylamine cannot, the latter being a very weak base, $pK = 16{\cdot}83$ [47]. Substituted phosphines can be titrated in nitromethane by perchloric acid. (See: Chapter 31, and [781].) Dimethyl sulphoxide $(CH_3)_2$ S:O is titratable as a base in acetic anhydride [878].

Table 5

H.n.p. VALUES OF BASES IN ACETIC ANHYDRIDE AND THEIR pK_{BH^+} VALUES IN WATER

Base	H.n.p.	pK_{BH^+} *(Literature)*	pK_{BH^+} *(Calculated)*
N,N-Dimethylbenzylamine	196	9·02	9·01
N,N-Diethylaniline	322	6·52	6·55
N-Ethyl-N-Methylaniline	358	5·99	5·85
N,N-Dimethylaniline	389	5·21	5·25
Dimethylsulphoxide	605		1·0
1-Methyl-2-pyrrolidinone	676		− 0·3
Triphenylphosphine	620		
Caffeine	633	0·61	0·49
Phenylurea	660	−0·30	−0·04

(d) *Correlation of base strength and h.n.p. in nitromethane* [333, 765, 779]. Nitromethane is an excellent solvent for the titration of weak or medium-strength organic bases. It is a solvent of very feeble acidic character so that no levelling is observed. The determination of bases with pK_{BH^+} value greater than 14 is rendered

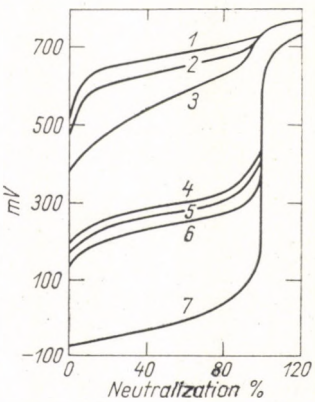


Fig. 25. Potentiometric curves of bases in nitromethane according to Streuli [779]. — *(1)* Diphenylamine, *(2)* N-Methylacetanilide, *(3)* Urea, *(4)* N-Ethyl-N-methylaniline, *(5)* Pyridine, *(6)* N,N-Diethylaniline, *(7)* N,N′-Diphenylguanidine (pK_{BH^+} 10·00 [332])

impracticable by traces of water. Streuli titrated 100 ml 0·25 mM nitromethane solutions of bases with 0·05 N perchloric acid in nitromethane. Some of the potentiometric curves are shown in Fig. 25 and some results in Table 6. Fig. 25 is interesting because it demonstrates that the 'steepness' of potentiometric plots between 20%

4. Radiometrische Komplexbildungstitrationen

4.1. Einführung

Das Schwierigste bei der radiometrischen Endpunktbestimmung im Falle von Komplexbildungsreaktionen ist die Trennung der Komponenten. Der Erfolg der Titration ist daher von der Wirksamkeit der Trennungsmethode abhängig. Zahlreiche Methoden zur Trennung sind beschrieben worden. Außer der – als ersten Trennungsmethode verwendeten – Lösungsmittelextraktion befaßt sich dieser Abschnitt mit der papierchromatographischen, der fokussierenden Ionenaustausch- und der unter Anwendung fester Indikatoren arbeitenden Methode.

Die Empfindlichkeit der radiometrischen Komplexbildungstitrationen hängt von jenen Faktoren ab, die auch in der konventionellen Komplexometrie ausschlaggebend mitwirken [13], nur kommt als einflußnehmender Faktor die Wirksamkeit der Trennungsmethode hinzu. In den nachfolgenden Kapiteln soll gezeigt werden, daß unter genau präzisierten Bedingungen noch Bestimmungen in 10^{-5}–10^{-6} M Lösungen möglich sind.

4.2. Trennung durch Lösungsmittelextraktion

4.2.1. *Prinzip der Methode*

Mit Dithizon werden Extraktionstitrationen praktisch seit der Einführung dieses Reagens in die quantitative Analyse durchgeführt [16]. Im allgemeinen wurden die wäßrigen Lösungen der in Spuren vorhandenen Metalle mit Lösungen von Dithizon in Chloroform oder Tetrachlorkohlenstoff titriert. Den Endpunkt zeigte das Erscheinen der grünen Farbe des Dithizons in der organischen Phase an. Die Empfindlichkeit dieser Methode liegt der der kolorimetrischen Dithizon-Verfahren nahe. Die Genauigkeit ist jedoch wesentlich geringer, zumal es visuell nicht möglich ist, den Endpunkt genügend genau festzustellen. Die mit Trennung durch Extraktion kombinierte radiometrische Endpunktbestimmung wurde durch KORENMAN und Mitarb. [19] sowie durch DUNCAN und THOMAS [11] eingeführt.

Man bedient sich solcher Systeme, in denen eine der Reaktions-Komponenten und zwar in den meisten Fällen das Reaktionsprodukt mit Hilfe eines, mit dem System nicht mischbaren Lösungsmittels extrahiert werden kann. Als Titriermittel für die Bestimmung von Metallionen werden in der Regel organische Reagenzien verwendet. Der gebildete, in Was-

and 80% neutralization are similar for diphenylamine, N-methylacetanilide, N-ethyl-N-methylaniline, pyridine, N,N-diethylaniline and N,N′-diphenylguanidine. In the case of those bases whose pK_{BH^+} value is < 8, 10% neutralization causes a potential jump of 11 ± 1 mV. In the case of urea, however, after neutralization a 23 mV potential jump is observed, i.e. the curve is 'steeper'. This type of curve is also typical of substituted urea derivatives, acid amides and monosubstituted acid amides.

'Steepness' of the section of the potentiometric curve leading to the point of inflexion can also be observed in the case of phenols in acetone or pyridine media, and is explained by H-bonding between the solvated molecules [258, 782].

Table 6

H.n.p. VALUES OF BASES IN NITROMETHANE AND THEIR pK_{BH^+} VALUES IN WATER (H.n.p.$_0$ = N,N′-DIPHENYLGUANIDINE)

Base	*Δ* H.n.p.	*Fig. 24*	pK_{BH^+} *(Literature)*	pK_{BH^+} *(Calculated)*
Piperidine	−47	*B*	11·09	10·72
Triethylamine	−69	*B*	10·64	11·01
2-Cyanoethylamine	204	*B*	7·86	7·49
bis-2-Cyanoethylamine	386	*B*	5·14	5·14
o-Phenylenediamine	412	*B*	4·52	4·81
2-Naphthylamine	490	*B*	4·11	3·80
Anthranilic acid	602	*B*	2·15	2·36
Diphenylamine	701	*B*	0·85	1·08
Methylurea	576	*C*	0·90	0·79
Urea	590	*C*	0·50	0·61
N-Methylacetanilide	663	*C*	−0·50	−0·34
Acetamide	691	*C*	−0·48	−0·70
Acetanilide	757	*C*	−0·9 [505]	−1·56

Lines *B* and *C* in Fig. 24 indicate the h.n.p. of amines, amides and urea derivatives in water as a function of pK_{BH^+} value. A zero value of h. n. p. measurements applies to N,N′-diphenylguanidine (cf. Chapter 2; Section 16 (c)). The position of the line for amines containing heteronitrogen, hydroxyl or $=N-\underset{|}{\overset{|}{C}}-O-$ group deviates from either lines *B* or *C*. Thus, quinoline, isoquinoline, pyridine, bis- and tris-(2-hydroxyethyl)amine are stronger bases in nitromethane than in water as compared with other amines.

(e) *Correlation between base strength and h.n.p. in acetonitrile.* A large number of solvents, scarcely or not at all liable to autoprotolysis, have been employed for the measurement of base strength, chiefly by making use of the indicator method. These solvents include benzene [172, 559b], chlorobenzene [54], acetonitrile [247, 333, 455], nitrobenzene [469], nitromethane (see: Section (d), and [333, 765], chloroform and carbon tetrachloride [35]).

According to Fritz, h.n.p. and base strength show linear correlation in acetonitrile. However, other solvents are also suitable for potentiometric measurements of h.n.p., such as the highly polar solvents, nitromethane and nitrobenzene (aceto-

ser wenig lösliche Komplex wird in eine organische Phase übergeführ. Der Endpunkt wird auf Grund der Verfolgung der Änderungen der Radioaktivität in einer der Phasen bestimmt.

4.2.2. *Direkt-Titrationen*

Theoretisch bestehen für die radiometrischen Direkt-Titrationen drei Möglichkeiten:

(a) *Bestimmung einer aktiven Komponente mit einem inaktiven Titriermittel.* Das zu bestimmende Element oder die Verbindung wird mit einem ihrer radioaktiven Isotopen markiert. Am besten und bequemsten ist die Anwendung eines trägerfreien Isotops. Ist die Menge des zur Markierung verwendeten Stoffes relativ gering, so entfällt bei der Berechnung der Ergebnisse eine Korrektur. Wird jedoch nicht trägerfrei gearbeitet, so muß die zur Prüflösung zugegebene Menge bekannt sein und im Ergebnis berücksichtigt werden.

Werden während der Titration die Änderungen der Radioaktivität der wäßrigen und organischen Phase verfolgt, so gelangt man zu den in Abb. 4.1 *a* gezeigten Kurven *1* und *2*.

(b) *Die Titration einer inaktiven Komponente mit einem aktiven Titriermittel* führt zu den in Abb. 4.1 *b* gezeigten Kurven *1* und *2*.

(c) Die Titrationskurven der *Bestimmung einer aktiven Komponente mit einem gleichfalls aktiven Titriermittel* ergeben die in Abb. 4.1 *c* gezeigten Kurven *1* und *2*.

Das unter (c) erwähnte Verfahren weist den beiden ersteren gegenüber keine Vorteile auf.

Wird die zu bestimmende Komponente mit ihrem radioaktiven Isotop markiert, so spricht man von *isotoper Markierung*. Zur *nichtisotopen Markierung* greift man, wenn kein entsprechendes radioaktives Isotop des zu bestimmenden Elements zur Verfügung steht. Man markiert dann mit dem Isotop eines fremden Elements.

Zwei Methoden sind für die nichtisotope Markierung bekannt:

(a) Das Isotop des zur Markierung verwendeten Elements bildet mit dem Titriermittel einen ähnlich extrahierbaren Komplex, und die Extraktions-Konstanten beider Komplexe (des gesuchten und zur Markierung verwendeten Elements) liegen in der gleichen Größenordnung. Beide Elemente werden gleichzeitig extrahiert und verhalten sich – was die Extraktion und Titration anbelangt – in jeder Hinsicht gleich.

(b) Zur Markierung wird ein entsprechendes Isotop eines Elements verwendet, das mit dem Titriermittel einen Komplex bildet, dessen Extraktionskonstante um mehrere Größenordnungen niedriger ist als die des zu bestimmenden Elements. Zu Beginn reagiert dann nur die zu bestimmende Komponente mit dem Titriermittel, und die gemessene Radioaktivität bleibt bei einem konstanten, hohen oder niedrigen, Wert (je nach dem, ob die

nitrile is also a polar solvent), of the moderately polar solvents ethyl acetate, and of the non-polar solvents ethylene chloride [333]. Hall jr. points out that among aromatic amines, *para-* and especially *ortho*-nitroaniline are too weakly basic to give sharp inflexions. Nitroaniline however, can be readily titrated. Pyrrolidine was the strongest base investigated. Methylamine and ethylamine perchlorate are precipitated in ethylene chloride.

The concentration of the amines used with the above five solvents was such that for 50–75 ml of solvent, 0·3 – 1·1 ml of 0·5 M perchloric acid in dioxan was required as titrant. Since the addition of so small an amount of titrant requires great care, Hall jr. used a 1 ml Gilmont microburette-pipette; the titrant was added in portions of 0·030 ml The Beckmann type electrodes were standardized in a di-isobutylamine perchlorate buffer solution.

The conclusion may be drawn that the relative strengths of bases are independent of the titrant, e.g. perchloric acid or *p*-toluenesulphonic acid; and to a first approximation it is also independent of the solvent. Thus, the strength of the base investigated is primarily a function of structure: electron-attracting groups (e.g. vinyl or phenyl groups) cause a marked reduction in base strength. The sequence of strengths of alkylamines in the above five types of solvents (and in water) is as follows:

$$NH_3 < RNH_2, R_2HN > R_3N$$

However, the 'ideal' order of base strength would be:

$$NH_3 < RNH_2 < R_2NH < R_3N$$

Deviations, e.g. in methanol and ethanol, may be attributed to H-bonded solvates established between ammonium ions and the hydroxyl group of the solvent. The ideal order cannot always be expected to be attained in inert solvents since H-bonding

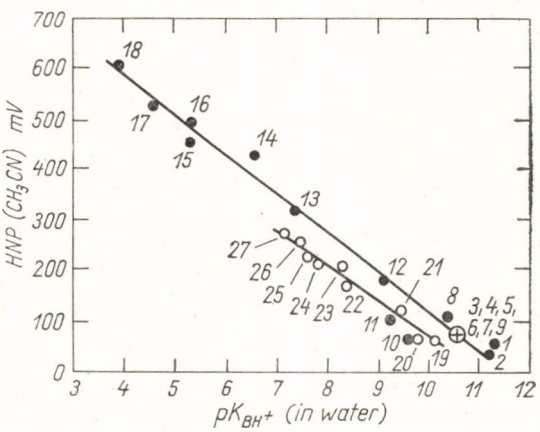


Fig. 26. Correlation between half-neutralization potential and base strength in acetonitrile according to Hall jr. [333]. – *(1)* Di-n-butylamine, *(2)* Piperidine, *(3)* Triethylamine, *(4)* Trimethylamine, *(5)* Methylamine, *(6)* Dimethylamine, *(7)* n-Butylamine, *(8)* iso-Butylamine, *(9)* N-Ethylpiperidine, *(10)* 1,3-Di-*o*-tolylguanidine, *(11)* Ammonia, *(12)* 1,2,3-Triphenylguanidine, *(13)* 2,6-Lutidine, *(14)* Diethylaniline, *(15)* *p*-Methoxyaniline, *(16)* *p*-Toluidine, *(17)* Aniline, *(18)* *p*-Bromoaniline, *(19)* Ethylenediamine, *(20)* Piperazine, *(21)* Ethanolamine, *(22)* Morpholine, *(23)* 1-Carbethoxypiperazine, *(24)* Benzoylpiperazine, *(25)* N-Ethylmorpholine, *(26)* 1-Tosylpiperazine, *(27)* N-Allylmorpholine

may also occur with other molecules, e.g. amine molecules, acid molecules or salt molecules (cf. [35, 172, 469, 559/b]). Base strength is determined by entropy changes as well as steric and solvation effects and the resulting effect on each amine may be different. The result of the experiments is represented in Fig. 26. The pK_{BH^+} values of 16 out of 18 monofunctional bases correspond with the values measured in water to

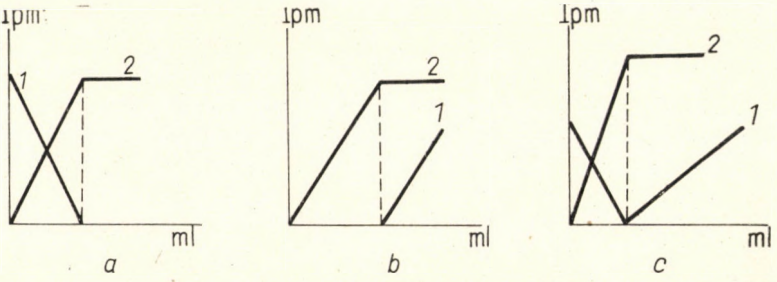


Abb. 4.1
Kurven von Direkt-Titrationen mit Phasentrennung durch Lösungsmittelextraktion (KORENMAN und Mitarb. [19]). (*1* — wäßrige Phase; *2* — organische Phase; *a* — Titration von radioaktiver Prüflösung mit inaktivem Titriermittel; *b* — Titration von inaktiver Prüflösung mit aktivem Titriermittel; *c* — beide Lösungen aktiv)

Radioaktivität in der wäßrigen oder in der organischen Phase gemessen wird). Ist die Gesamtmenge der zu bestimmenden Komponente verbraucht, setzt die Reaktion der zur Markierung verwendeten Komponente ein. Die Titrationskurve zeigt dies durch Abnahme oder Anstieg der Aktivität an.

In der erwähnten Fällen liegt das zur nichtisotopen Markierung verwendete Element immer in der gleichen Phase wie die zu bestimmende Komponente [11, 19] vor. In neuerer Zeit brachten BRAUN und KÖRÖS [3] eine Abwandlung der nichtisotopen Markierung in Vorschlag. Bei dieser befindet sich die zu bestimmende Komponente in der wäßrigen Phase, der nichtisotope Indikator, in Form eines mit einem Metallion gebildeten, gut löslichen Komplexes, in der organischen Phase. Während der Titration reagiert das Titriermittel zuerst mit der zu bestimmenden Komponente. Nachdem diese vollkommen verbraucht ist, wird das markierte Elemention durch das Titriermittel aus dem Komplex verdrängt. Hier zeigt die Titrationskurve einen scharfen Knickpunkt. Voraussetzung ist, daß das Titriermittel mit der zu bestimmenden Komponente einen genügend stabileren Komplex als mit dem zur Markierung verwendeten Element bildet. Zum anderen müssen die relativen Stabilitäten der mit dem Titriermittel einerseits und mit dem Komplexbildner in der organischen Phase andererseits gebildeten Komplexe des zur Markierung verwendeten Metalls so beschaffen sein, daß das markierte Metall durch das Titriermittel nur nach dem vollständigen Verbrauch des zu bestimmenden Elements komplexiert wird.

Bei den Direkt-Titrationen wird der Endpunkt in der Regel durch graphische Auswertung der Funktion

$$I = f(v)$$

bestimmt.

I = Radioaktivität der wäßrigen oder organischen Lösung (Ipm)

v = Volumen der zugegebenen Maßlösung (ml).

within $\pm$ 0·2 pK unit. The correlations show that the relative order of the strengths of bases in water is a useful check for titrations performed in non-aqueous media. Though the degree of solvation may vary this cannot cause very large discrepancies.

The strength of nine different bases possessing oxygen or nitrogen in close proximity to the amino group increases in organic solvents in comparison with their values in water. The function represented by the second line indicates, as a mean value, that the pK_{BH^+} value of the bases investigated agrees closely with the values measured in water to within $\pm$ 0·18 pK unit. Thus, piperazine is stronger in acetonitrile than in water (see Chapter 23; Section 123). It may be assumed that the electron-rich, polar groups of the molecules solvate the 'onium ions by internal H-bonding. This stabilizes the ions compared with those ions which do not possess such bonding (see: Chapter 2; Section 19).

The experiments of Hall jr., Streuli, Fritz and Veibel showed that measurement of half-neutralization potential and the relative strength of bases in water is a useful aid for the titration of bases. Solvation effects can cause small or large divergences. However, the pK_{BH^+} value determined by h.n.p. measurements deviates only occasionally by more than $\pm$ 0·5 pK unit. Deviations caused by temperature fluctuations during titrations may be neglected. The irreproducibility of glass electrode readings may lead to greater errors, though this can be eliminated by careful standardization. The lack of constant ionic strength can be a serious source of error, especially in solvents of low dielectric constant. In such solvents the degree of ionization changes to a greater extent with the concentration of the solution.

The graph of h.n.p. against pK_{BH^+} value measured in water indicates that the latter value depends primarily upon the effect of the substituents and only secondarily on the solvent. The order of basicity of alkylamines in water is as follows:

$$NH_3 < RNH_2 \text{ and } R_2NH > R_3N$$

In acetonitrile, ethyl acetate, nitrobenzene and nitromethane the order does not change. In chloroform and chlorobenzene, tertiary amines are stronger but in n-heptane, benzene and 1,4-dioxan secondary amines are stronger [849]. Owing to the electron-releasing effect of the alkyl groups the order would be expected to be as stated below:

$$NH_3 < RNH_2 < R_2NH < R_3N.$$

However, the result of experiments performed in methanol and ethanol is different. This may be attributed to the H-bonded stabilization of the ammonium ions formed during solvation. Neither can the above 'ideal' basicity order be expected in the case of inert solvents because alkylammonium ions establish a hydrogen bond with another amine molecule or acid molecule, respectively (cf. [35, 172, 469]). For the relationship between $pK_b(H_2O)$ of phenothiazines and sympathomimetic amines and h.n.p. values in acetone, acetonitrile, isopropanol and nitromethane, see: [125].

24. Influence of Solvation Effects on the Strength of Nitrogenous Bases; Association Effects

In the preceding chapter, change in the basicity order of alkylamines depending on the solvent has been discussed. This change was assigned to steric effects by Brown and his collaborators, but by others to solvation effects.

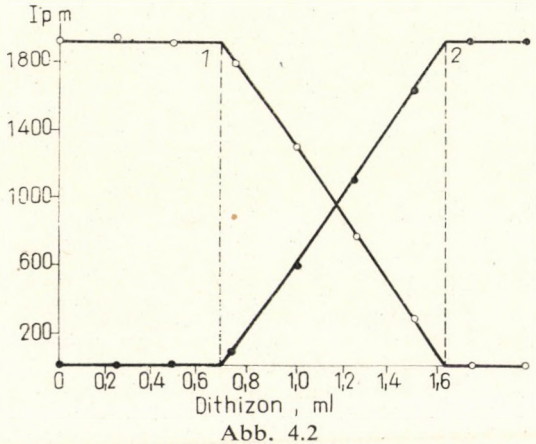


Abb. 4.2
Titration von Quecksilber und Zink (^{65}Zn) mit Dithizon als Titriermittel (KORENMAN und Mitarb. [19]). (*1* — Radioaktivität der wäßrigen Phase; *2* — Radioaktivität der organischen Phase)

Je nach dem, ob die Aktivität in der wäßrigen oder in der organischen Phase gemessen wird, zeigen die Kurven ein Maximum oder ein Minimum. Soll die Genauigkeit der Endpunktbestimmung noch gesteigert werden, so mißt man die Aktivität in beiden Phasen. Es ist dann bequemer, den Schnittpunkt der beiden Kurven aufzusuchen (Abb. 4.2).

KORENMAN und Mitarb. [19] empfehlen die rechnerische Ermittlung des Endpunkts. Wird die Radioaktivität der wäßrigen Phase gemessen, so kann man den Endpunkt mit Hilfe der Gleichung (4.1) berechnen:

$$v_{\text{äqu.}} = v_1 \cdot \frac{I_0}{I_0 - I_1} \tag{4.1}$$

$v_{\text{äqu.}}$ = zur Erreichung des Endpunktes notwendige Menge der Maßlösung (ml)

I_0 = Radioaktivität der wäßrigen Phase zu Beginn der Titration (Ipm)

I_1 = Radioaktivität des gleichen Volumens der wäßrigen Phase (Ipm) nach Zugabe von v_1 ml der Maßlösung ($v_1 < v_{\text{äqu.}}$).

Wird die Radioaktivität der organischen Phase bestimmt, so berechnet man den Endpunkt nach:

$$v_{\text{äqu.}} = v_1 \frac{I_0}{I_1} \tag{4.2}$$

$v_{\text{äqu.}}$, v_1 und I_0 = gleiche Bedeutung wie oben (4.1)

I_0 = Radioaktivität der organischen Phase (Ipm) nach Zugabe von v_1 ml der Maßlösung und Extraktion.

Eine neue und interessante Methode zur Auswertung der mit Trennung durch Extraktion kombinierten komplexometrischen Titrationen haben KUKULA und KŘIVÁNEK [24] ausgearbeitet. Ihr Verfahren zur Bestimmung der Menge der Trägerstoffe in radioaktiven Präparaten beruht auf der kombinierten Anwendung der radiometrischen Titration und der Isotopenverdünnungsanalyse. Zur Auswertung sind zwei Titrationen notwendig:

(a) The subject of Pearson and Vogelsong's spectrophotometric investigations was *the order of basicity of alkylamines against 2,4-dinitrophenol* [631]. Based on the equilibrium constants of ion-pair formation, the strongest bases in chloroform, chlorobenzene and dichloroethane are tertiary amines; in n-heptane, benzene and dioxan, secondary amines, and finally, in ethyl acetate primary amines are the strongest bases (cf. Chapter 2; Section 19 (b)).

In Brown's 'backstrain' theory it is noted that the valence angles in a tertiary amine are somewhat larger than would correspond with a normal tetrahedral configuration [96]. As a result of proton co-ordination the molecule is 'crowded' in a tetrahedral form. The greater the space-filling and electrostatic repelling force of the substituents on the nitrogen atom the more they oppose this strain. Thus in spite of the inductive effect of the electron-releasing substituents trimethylamine is a weaker base than methylamine. This of course, is an alternative argument to that based on solution effects (see above).

Moreover the experimental data prove that strengths of bases are not independent of the solvation effect of the solvent [219, 629, 631, 820]. The distribution ratio between water and organic solvent also indicates that the solvating and H-bonding tendencies may vary considerably in the alkylamines. The distribution rates for the methylamines, that is,

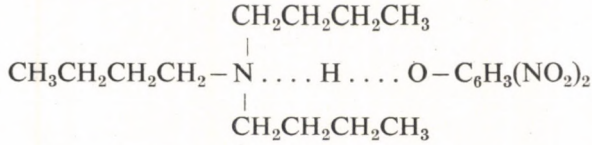
$$\frac{\text{amine concentration in water phase}}{\text{amine concentration in organic phase}}$$

is as follows:

Alkylamine	*In Carbon Tetrachloride*	*In Benzene*	*In Chlorobenzene*	*In Ethyl Ether*	*In Chloroform*
Ammonia	246	210	179	180	26
Methylamine	31·1	27·8	57·6	43·5	11·4
Dimethylamine	13·5	11·2	13·6	18·2	2·75
Trimethylamine	1·3	2·1	2·0	2·2	0·45

(See also: Chapter 5; Section 30.)

In chlorobenzene the order of basicity of n-butylamines is mono- < di- < tri-n-butylamine [46]. Thus, contrary to the theory based only on steric hindrance the order follows the influence of the increasing inductive effect of the number of substituents (see: Chapter 4; Section 27 (b)). According to the 'backstrain' theory, the steric effect ought to be striking in inert solvents, especially against 2,4-dinitrophenol. In chlorobenzene there are base–acid associations whereas in aqueous media the ions separate, so butylamines in chlorobenzene ought to show the reverse order to that determined in water. *All this indicates that steric hindrance cannot be looked upon as the sole factor, particularly not in aqueous media.*



Association in solutions of tri-n-butylamine and 2,4-dinitrophenol

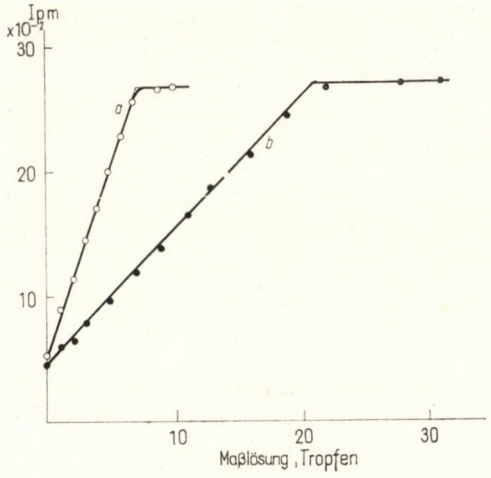


Abb. 4.3
Titration von Quecksilber mit Natrium-diäthyldithiocarbamat (KUKULA und KŘIVÁNEK [24]) unter Anwendung von zwei aliquoten Teilen (*a* — ursprüngliche Lösung; *b* — ursprüngliche Lösung und bekannte Menge Träger)

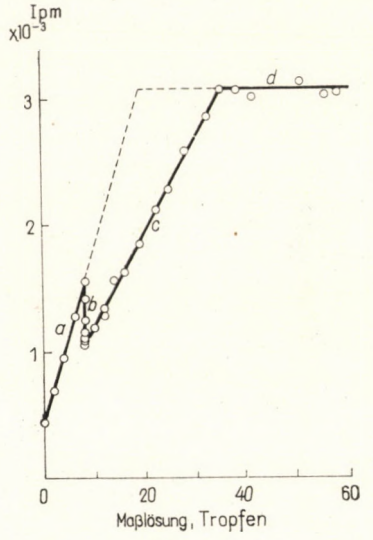


Abb. 4.4
Titration von Quecksilber mit Natrium-diäthyldithiocarbamat (KUKULA und KŘIVÁNEK [24]) unter Anwendung von nur einem aliquoten Teil (*a* — ursprüngliche Lösung; *b* — Zugabe einer bekannten Menge Träger; *c* — weitere Titration der ursprünglichen Lösung)

Zuerst wird die den zu bestimmenden Träger und das radioaktive Präparat enthaltende Lösung titriert und extrahiert. Dieser Titration folgt eine zweite Titration eines gleich großen aliquoten Teiles der Lösung, zu dem aber eine bekannte Menge des inaktiven Trägers zugegeben wurde.

Die Kurven der Titration einer ^{203}Hg und Hg-Träger enthaltenden Lösung mit Natrium-diäthyldithiocarbamat sind in Abb. 4.3 gezeigt.

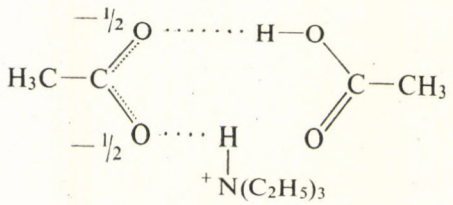
Die Bestimmung kann auch in ein und derselben Lösung durchgeführt werden, wenn man die bekannte Menge des Trägers während des Titrationsprozesses zur Lösung zugibt. Zur Gleichgewichtseinstellung wird mechanisch geschüttelt und dann die Titration fortgesetzt.

Die Kurven der auf diese Weise durchgeführten Titration einer ^{203}Hg und Hg-Träger enthaltenden Lösung mit Natrium-diäthyldithiocarbamat zeigt Abb. 4.4.

Durch Auswertung der Titrationskurven kann die Menge des jeweiligen Trägers (m_x) wie folgt ermittelt werden:

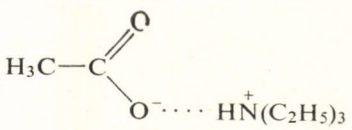
(b) *Association in inert solvents.* In the interaction of acetic acid and triethylamine in chloroform and carbon tetrachloride, respectively, the co-reactants undergo various types of association depending upon the concentration of the solution ([35, 36, 37] and Chapter 2; Section 15 (d)).

In carbon tetrachloride:



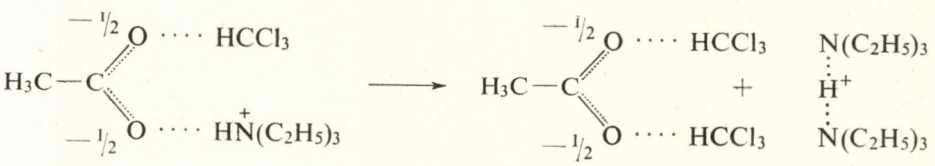
Type of association: $BH^+ \cdot A(AH)^-$

On addition of further triethylamine:



Type of association: $BH^+ \cdot A^-$

In chloroform:



Type of association: $BH^+ \,.\, A^- \,.$ solvent $\rightarrow B(BH^+) \,.\, A^- \,.$ 2 solvent.

The resonance form of the anion is stabilized by establishing an H-bond with the chloroform solvent molecule in such a way that distribution of the negative charge is delocalized equally over the oxygen atoms.

The above examples show that in the interaction of H-acid and acceptor base, in inert solvents, ion pairs are formed by H-bonding [33, 54, 171]. However, the degree of proton transfer may vary widely. Moreover, in the interaction of acids and bases proton transfer to the base is not necessary. If the base is transformed into 'onium ions the H-bond formed with an anion is essentially of an electrostatic character. Reaction products of weak acids and weak acceptor bases in non-polar solvents are simple H-bonded complexes: the proton remains in a covalent bond, and owing to electrostatic attraction, the amine is bonded to the 'acidic hydrogen'. Between these two extreme cases formal transitions also exist. Thus when pyridine is titrated with trifluoroacetic acid in chloroform at first a *B.* H*A* type complex in the ratio 1 : 1 is formed. The addition of further acid results in a $BH^+ \,.\, A(HA)^-$ type complex in the ratio 1 : 2:

(a) *Auf Grund des sich aus der Titrationskurve ergebenden Endpunktes.* Wenn m_x die zu bestimmende und m die zur Lösung zugegebene bekannte Menge des Trägers bedeutet, so ist:

$$m_x = m \frac{v_1}{v_2 - v_1}. \tag{4.3}$$

v_1 und v_2 = bis zur Erreichung der beiden Endpunkte verbrauchte Volumina der Maßlösung.

(b) Außer den Endpunkten können zu der mit Hilfe von (4.3) durchgeführten Berechnung auch zwei andere, willkürlich gewählte, dem gleichen Aktivitätswert entsprechende Punkte der Titrationskurven verwendet werden.

(c) Ähnlich kann man m_x auch unter Anwendung von zum gleichen Maßlösungsverbrauch gehörenden Aktivitätswerten auf beiden Titrationskurven, mit Hilfe der Gleichung (4.4) berechnen:

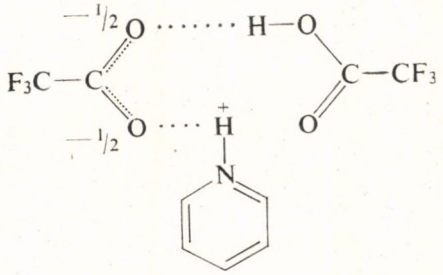
$$m_x = m \frac{I_2 - B}{I_1 - I_2} \tag{4.4}$$

I_1 und I_2 = bei gleichem Maßlösungsverbrauch gemessene Aktivitäten
B = »Untergrund«-Aktivität der wäßrigen Lösung vor der Titration

Im Gegensatz zur konventionellen volumetrischen Analyse, wird das Ergebnis nicht unbedingt auf Grund der Konzentration der Maßlösung, sondern vielmehr unter Ausnutzung der durch die Isotopenverdünnungsanalyse gebotenen Möglichkeiten berechnet. Die Konzentration der Maßlösung muß nicht genau bekannt sein, es ist nur – wie oben bereits gezeigt wurde – dafür zu sorgen, daß die Konzentration der Maßlösung während der Bestimmungsprozesse konstant bleibt. Dies bedeutet besonders im Falle der Extraktionstitrationen einen beachtlichen Vorteil, da sich bei diesen die Lösungen der als Titriermittel verwendeten organischen Reagenzien oft ziemlich rasch zersetzen, was ganz besonders für starke Verdünnungen gilt. Diesen Nachteil schaltet die Isotopenverdünnungsmethode aus.

Die Zahl der für die auf Extraktion beruhenden und mit direkter Titration mehrerer Komponenten nebeneinander zur Verfügung stehenden Methoden ist beachtlich. Am häufigsten werden verwendet: die nichtisotope Markierung in zwei oder drei gesuchte Komponenten enthaltenden Systemen, das unter Anwendung markierter Titriermittel verschiedener spezifischer Aktivitäten arbeitende Verfahren, die bei verschiedenen pH-Werten oder in Gegenwart von Markierungsmitteln durchgeführten Titrationen.

Die bei nichtisotoper Markierung sowie markierter Titriermittel verschiedener spezifischer Aktivitäten zur Bestimmung von einer bzw. von zwei oder drei Komponenten nebeneinander theoretisch möglichen Titrationskurven sind in Abb. 4.5 gezeigt. In dieser Abb. wurden alle theoretischen Möglichkeiten berücksichtigt.



Similarly, the reaction between a carboxylic acid of weaker proton donor properties and pyridine may be represented as follows:

$$R-C(:O)-O-H\ldots NC_5H_5 \rightleftharpoons R-C(:O)-O^- \ldots \overset{+}{H}NC_5H_5$$

Summarizing the above, the order of strengths of bases is, primarily, determined by structural characteristics. The order may vary from solvent to solvent. However, this deviation is not too significant when, taking into account structural characteristics, the value of the half-neutralization potential is compared to the pK_{BH^+} value measured in water.

Theories on the origin of different valumes for base strengths are often conflicting. This can be ascribed, among other things, to dissimilar experimental conditions – e.g. spectrophotometric determination of acid-base equilibrium, potentiometric titration or thermometric titration (cf. [236]).

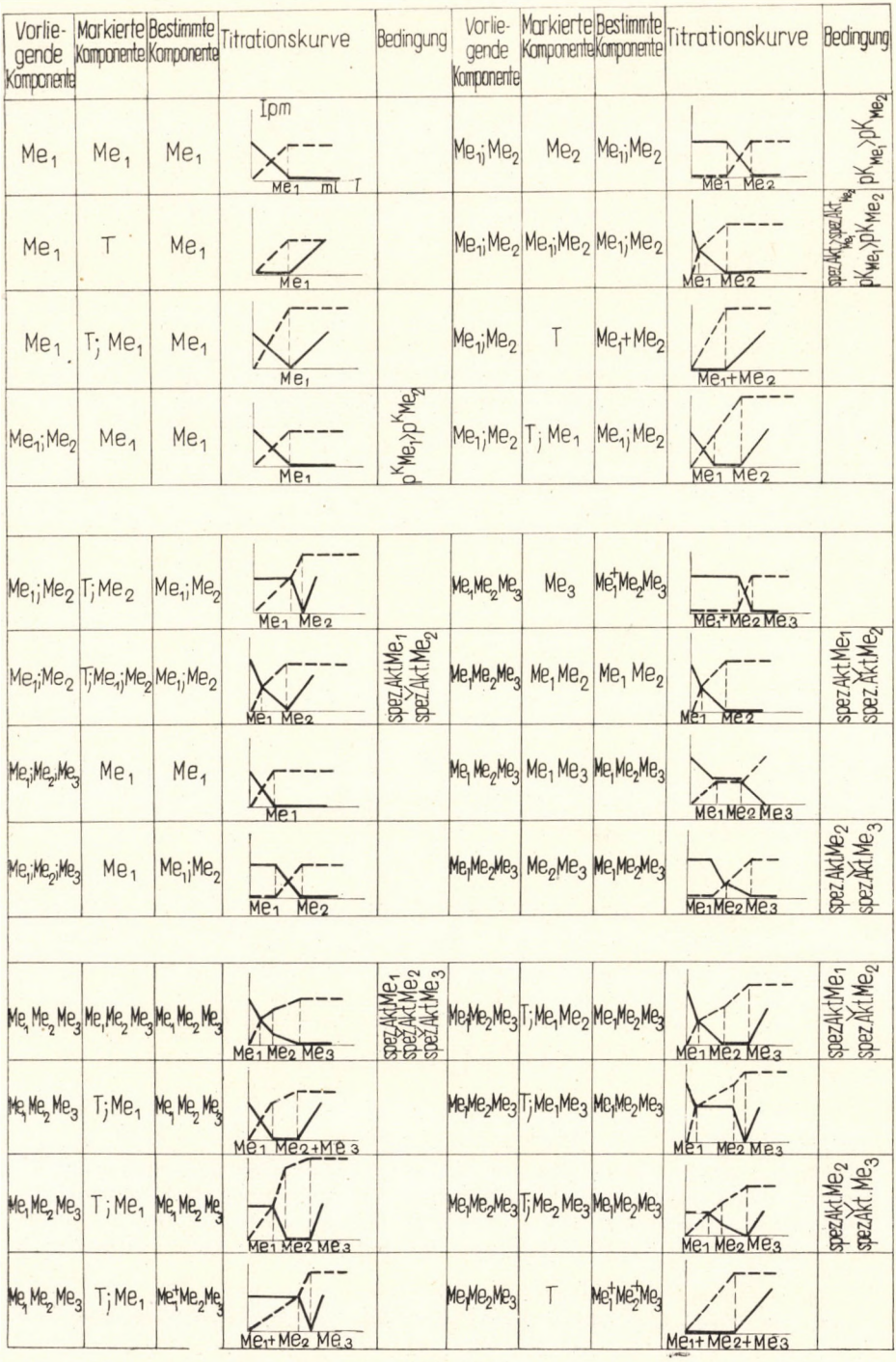


Abb. 4.5

Theoretische Kurven der auf Komplexbildung beruhenden und mit Phasentrennung durch Lösungsmittelextraktion durchgeführten radiometrischen Titrationen. Titration von einer, zwei und drei Komponenten nebeneinander, unter Anwendung von nichtisotoper Markierung, markierten Titriermitteln und verschiedenen spezifischen Aktivitäten

Chapter 4

Relationship between Acidity, Basicity and Molecular Structure

Correlations between acid and base strength and molecular structure have been applied frequently to the investigation of chemical bonds and electron shifts within the molecule.

Within one period of the periodic system the acidity of hydrides increases with their electronegativity:

$$HCH_3 < HNH_2 < HOH < HF$$

This change can be explained by the increasing nuclear charge, and the decreasing number of electropositive H-atoms bonded to the central atom. This also applies to cationic acids of the same charge type e.g.:

$$HNH_3^+ < HOH_2^+ < HFH^+$$

From these two orders of acidity the sequence of strength of the corresponding bases follows:

$$CH_3^- > NH_2^- > HO^- > F^- \text{ and } NH_3 > H_2O > HF$$

(cf. Chapter 1; Section 8).

The equilibrium state is determined by three factors: (1) potential energy, (2) kinetic energy, (3) entropy (probability) effects. Potential energy differences may arise from changes in bond energy due to resonance, electrophilic or nucleophilic effects of functional groups and the interaction of ions and dipoles. Changes in kinetic energy may be assigned to rotational and translational motions of the molecules or to vibrational and rotational motions within the molecule.

In many cases the factors causing changes in the equilibrium of the reaction cannot be determined experimentally. The study of structural changes in connection with acid-base equilibrium, however, throws light upon the fact that the displacement of the electron-cloud and the formation of a dipole may also cause a change in potential energy. It cannot be expected, however, that a theory taking into account only the molecular structure of acids and bases will always solve in each and every case the problems of acid or base strength without regard to the solvent. It proves more difficult to establish a regularity among organic compounds; therefore, correlations between molecular structure and acid and base strength will be outlined by some characteristic examples.

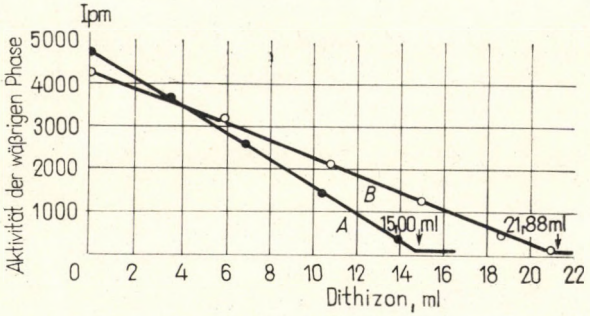


Abb. 4.6

Titration von Kobalt- und Quecksilber-Spuren (^{60}Co bzw. ^{203}Hg) mit Dithizon (DUNCAN und THOMAS [11]). (Ordinate: Ipm einer Prüflösung von 5 ml (Co) oder 0,5 ml nach Eindampfen zur Trockne (Hg). Abszisse Volumen der Dithizonlösung, $3{,}62 \times 10^{-5}$ M (Co); $1{,}84 \times 10^{-5}$ M (Hg). Kurve *A* — Co; Kurve *B* — Hg)

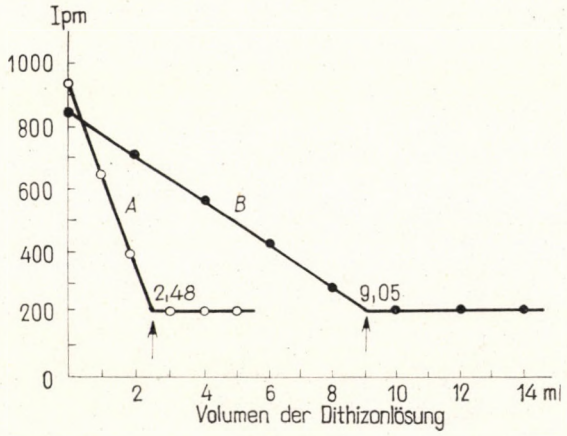


Abb. 4.7

Titrationskurven von Silber- und Zink-Spuren (^{110m}Ag bzw. ^{65}Zn) mit Dithizon (SPITZY [32]). (Ordinate: Aktivität der wäßrigen Phase. Abszisse: Volumen der (34,4 μM) Dithizon-Lösung. Kurve *A* — Ag; Kurve *B* — Zn)

4.2.2.1. *Titration einer Komponente*

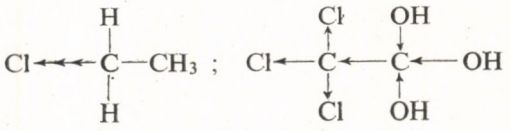
Zahlreiche Autoren haben Methoden für die Titration einer Komponente ausgearbeitet. DUNCAN und THOMAS [11] verwendeten Dithizonlösung als Titriermittel für Kobaltspuren (markiert mit ^{60}Co) und Quecksilber (markiert mit ^{203}Hg). Die durch Messung der Aktivität der wäßrigen Lösung erhaltenen Titrationskurven zeigt Abb. 4.6.

SPITZY [32] entwickelte eine Methode zur Titration von Spuren von Silber (markiert mit ^{110m}Ag) und Zink (markiert mit ^{65}Zn). Die erhaltenen Titrationskurven

25. Influence of Substituents, Inductive and Other Effects

Owing to the varying electron affinity of elements, in the case of the carbon to halogen bond, the valence electrons are displaced towards the halogen nucleus ('inequality of electron sharing' [628]). The electron attracting (electrophilic) group shares to a greater extent in the electron pair establishing the bond, while inducing a positive charge on the atom to which it is bonded. The unequal charge distribution leads to partial polarization of the molecule, e.g. $H_3C \rightarrow Cl$. The induced positive charge itself also exerts an electron attracting effect on the adjacent atoms, which in their turn 'relay' the inductive effect (*I* effect), though with diminishing efficiency.

The inductive effect of the 'key atom', chlorine, is transmitted along the carbon chain without diminution only by a conjugated system of double bonds (p. 201 in [206], p. 101 in [605]). The direction of displacement of the electrons, that is, the tendency of the electron cloud to accumulate is denoted by arrows:



Trichloroacetic acid hydrate

The electron attracting effect increases with the electropositivity of the electron attracting atom or group:

$$-SR_2^+ > -SR > -S^-; \qquad -NR_2H^+ > -NR_2 > NR^-$$

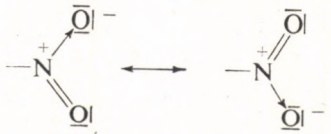
It increases likewise in elements with the same number of inner electronic shells with increase in nuclear charge:

$$-F > -OR > -NR_2 < -CR_3$$

and decreases with the increase in the number of inner electronic shells:

$$-F > -Cl > -Br > -I$$

Nitro groups, the nitrogen atom of which possesses a positive charge in both the major resonance forms, are relatively strong electrophilic groups:



Double or triple bonds likewise can bring about electron attracting effects:

$$-C{\equiv}CR > -CR{=}CR_2 > -CR_3$$

(a) *Effects of substituents on the strength of aliphatic carboxylic acids.* Lewis and Lucas gave the following interpretation of the electron attracting effect of substituents on the acid strength of carboxylic acids: in the Cl ← C bond of chloroacetic acid the centre of electron density of the valence electrons is displaced towards the

zeigt Abb. 4.7. KORENMAN und Mitarb. [19] beschrieben eine analoge Zinktitration mit Dithizon als Titriermittel. Die Ergebnisse wurden sowohl graphisch als auch rechnerisch ermittelt, die Übereinstimmung war gut. Die für Zink ausgearbeitete Methode wurde von SPITZY und DOSUDIL [33] auch zur Bestimmung von Zinkspuren in biologischem Material verwendet.

Ein Verfahren für die Titration von Palladium (markiert mit ^{109}Pd) wurde ausgearbeitet [31].

Palladium(II) wurde in Gegenwart von Pyridin mit Natriumjoid oder Ammoniumthiocyanat titriert. Die während der Titration gebildeten Komplexe $[PdPy_2]I_2$ bzw. $[PdPy_2](SCN)_2$ wurden mit Chloroform extrahiert und die Aktivität von 1 ml des Extraktes wurde nach Eindampfung zur Trockne gemessen. Notwendig ist ein pH-Wert >8,0, da die Chloroform-Lösung des Komplexes in neutralem oder saurem Medium — wie aus Abb. 4.8 hervorgeht — instabil ist.

Mit dem Ziel, eine Methode für die radiometrische Titration von Kobalt(II) mit Ammoniumthiocyanat zu entwickeln, haben IONESCU und GRIGORESCU-SABĂU [15] das System Kobalt-Pyridin-Thiocyanat zum Gegenstand eingehender Untersuchungen gemacht. Das im Laufe der Titration gebildete $[CoPy_2](SCN)_2$ wurde mit Chloroform extrahiert. Die Titrationskurve ist in Abb. 4.9 gezeigt.

Für die quantitative Bestimmung der inaktiven Träger in radioaktiven Eisen- (^{59}Fe) und Quecksilberpräparaten (^{203}Hg) haben KUKULA und KŘIVÁNEK [24] ein Verfahren empfohlen. Für Eisen verwendeten sie Cupferron, für Quecksilber Diäthyldithiocarbamat als Titriermittel. Die Quecksilber—Titrationskurven zeigen die Abb. 4.3 und 4.4.

BRAUN und KŐRÖS [3] entwickelten ein Verfahren für die Titration von Nickel mit Kaliumcyanid. Als Indikatoren verwendeten sie die Chloroform-Lösungen der

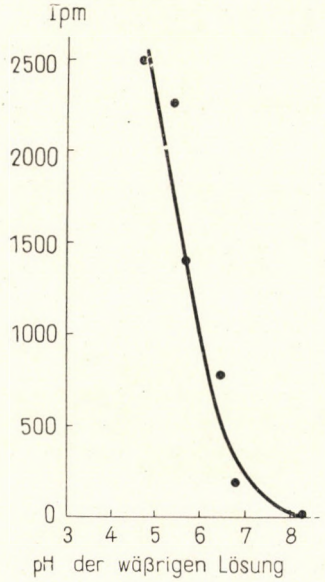


Abb. 4.8
Stabilität der chloroformischen Lösung von $^{109}PdPy_2I_2$ als Funktion des pH (SPACU und VOICU [31]). (Ordinate: Aktivität der wäßrigen Lösung)

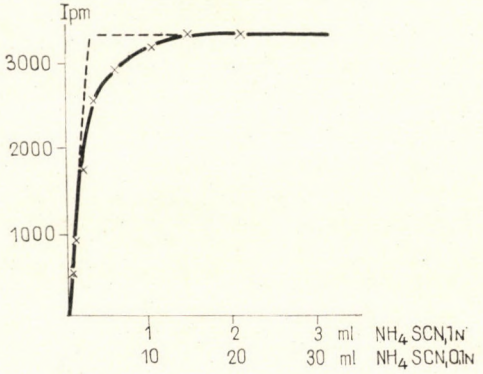
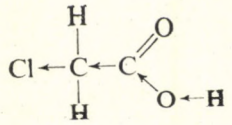


Abb. 4.9
Titration von Co (^{60}Co) in Pyridin mit NH_4SCN als Titriermittel (IONESCU und GRIGORESCU-SABĂU [15]). (Ordinate: Aktivität der chloroformischen Lösung)

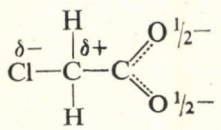
chlorine atom and becomes observable as a permanent dipole. This intramolecular dipole interaction also spreads to the neighbouring atoms:



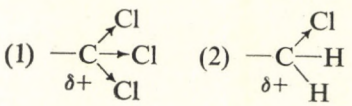
Inductive effect due to chlorine

As a consequence the electron density lessens on the carboxylic group, the proton co-ordinating forces diminish, and so the proton-donor readiness, that is, the acid strength, increases. Thermodynamic arguments based on entropy changes lead to similar conclusions.

In halogenated aliphatic acids the anion is stabilized by interaction of the Cl ← C dipole with the negative charge:



Trichloroacetic acid is 93 times stronger than monochloroacetic acid although the dipole moments of the groups $-CCl_3$ and $-\overset{|}{C}Cl$ are very similar. The field effect of the two groups is similar at a greater distance, but in a field commensurable with the dimensions of the dipole the charge distribution on the carbon atom is the more important factor; (1) possesses a greater positive charge on carbon than (2):



In acid-base equilibrium the atom carrying the labile proton has a relative electron deficit in the acid form and an electron surplus in the conjugate base form. Since the electron attracting group enhances the actual electron deficit, it increases the acid strength and lessens the proton co-ordinating ability of the anion base.

Branch and Calvin also discussed the influence of inductive effects on the strength of acids. On the basis of inductive constants, acid strength in acids of type X-CH_2COOH is enhanced ($-I$ effect), or decreased ($+I$ effect) in the following order, by the inductive effect of electrophilic or nucleophilic groups (p. 67 in [79]):

$$\left.\begin{array}{l} X = -SO_2R > -NH_3^+ > -NO_2 > -CN \\ > -F > -Cl > -COOH > -Br > \\ > -OCH_3 > -I > -OR > -SR > -C_6H_5 > -NR_2 \end{array}\right\} -I \text{ effect}$$

$$> H$$

$$> -C_2H_5 > -CH_3 > -C(CH_3)_3 > -COO^- \qquad +I \text{ effect}$$

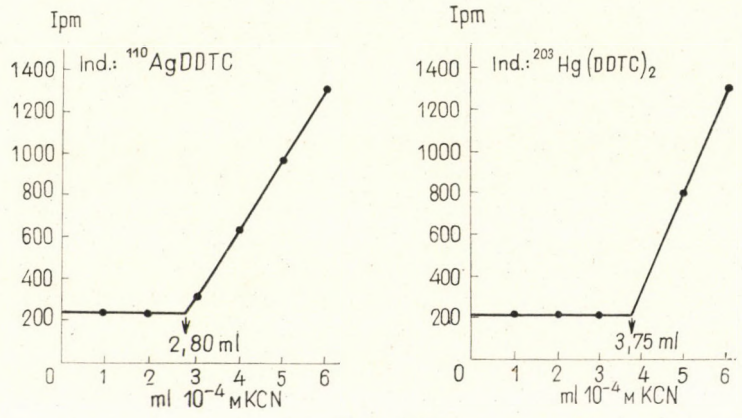


Abb. 4.10

Titration von Ni mit KCN in Gegenwart von ^{110m}AgDDTC und ^{203}Hg(DDTC)$_2$ (BRAUN und KŐRÖS [3]). (Ordinate: Aktivität der wäßrigen Lösung)

Diäthyldithiocarbamate von Silber (^{110m}Ag) und Quecksilber (^{203}Hg). Abb. 4.10 zeigt die Titrationskurven. Das Erscheinen von $^{110m}Ag^+$ oder $^{203}Hg^{2+}$ in der wäßrigen Phase auf Grund der Reaktionen

$$^{110m}AgDDTC_{CHCl_3} + 2\,CN^- \rightleftharpoons [^{110m}Ag(CN)_2]^-_{H_2O} + DDTC$$

$$^{203}Hg(DDTC)_{2\,CHCl_3} + 2CN^- \rightleftharpoons [^{203}Hg(CN)_2]_{H_2O} + 2\,DDTC$$

zeigt den Endpunkt an.
(DDTC = Diäthyldithiocarbamation)

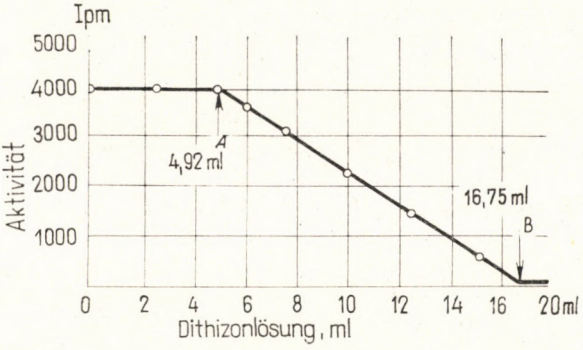


Abb. 4.11

Titration von Co und Zn mit Dithizon in Gegenwart von ^{60}Co (DUNCAN und THOMAS [11])

This static, permanent inductive effect is symbolized by Ingold as I_S; if valence electrons are more attracted by the key atom than they would be by an H-atom situated on the same carbon atom, i.e. if the key atom is more electronegative, $-I_S$ is the term used, while the term $+I_S$ is used if the key atom is more electropositive. The effect of the key atom decreases rapidly with the number of interposed carbon atoms. The effect of the substituents on the strength of bases follows logically in the opposite sense. (See: this Section: (f).)

The table below indicating pK_{acid} values of various halogenated aliphatic carboxylic acids shows the $-I$ effect as a function of (*A*) accumulation of electron attracting substituents and (*B*) distance from the $-COOH$ group:

A

CH_3COOH	4·76*				
FCH_2COOH	2·7**			$F_3C.COOH$	0·30
$ClCH_2COOH$	2·86*	$Cl_2CHCOOH$	1·30*	$Cl_3C.COOH$	0·89*
$BrCH_2COOH$	2·87*				
ICH_2COOH	3·0**				

B

$CH_3CH_2CHCl.COOH$	2·9**
$CH_3CHClCH_2.COOH$	4·1**
$CH_2ClCH_2CH_2.COOH$	4·5**

* [497]
** p. 68 in [393].

Table 7 indicates change of acid strength, in K_{acid} values, as a result of the effect of substituents X_1,X_2 and X_3 in carboxylic acids of the type $X_1X_2X_3C.COOH$ (cf. [83, 206, 693]). The α- and β-acetylenic carboxylic acids are stronger than saturated or olefinic acids as a consequence of the strong electron attracting effect of the acetylenic bond [189, 547]:

$R.C{\equiv}C.COOH$, pK_{acid} 2·23–2·66

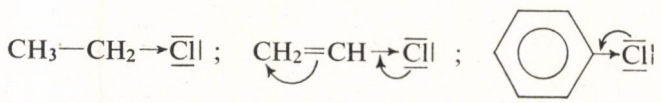
$R.C{\equiv}C.CH_2.COOH$, pK_{acid} 3·60–3·44

$R.C{\equiv}C-(CH_2)_n-COOH$, pK_{acid} 4·20–4·58

where R = alkyl or phenyl, and n = 2–4

Conjugation occurs between the π-electron system and the lone electron pair of the oxygen atom, i.e. the electron system exerts an attractive effect on the electron cloud of the COOH group, and thus the electron density on it decreases.

(b) *Aromatic rings* such as the phenyl group have electron attracting properties, that is, the electron sextet of the aromatic ring conjugates with an atom having a free electron pair. This is essentially a mesomeric effect (see later), and may be, in this sense, opposed to the inductive effect as illustrated by the following example:



2·03 *D* 1·66 *D* 1·55 *D*

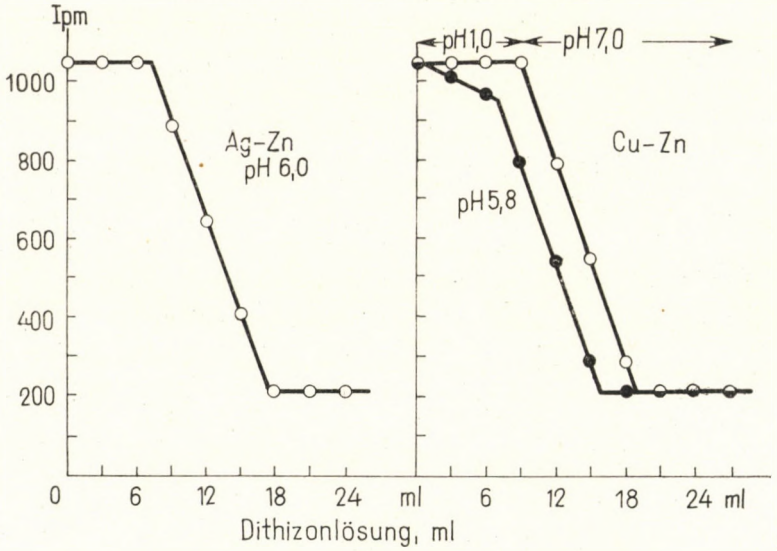


Abb. 4.12
Titration von Ag und Zn bzw. Cu und Zn mit Dithizon, mit und ohne Änderung des pH (nichtisotoper Indikator: ^{65}Zn) (SPITZY [32])

4.2.2.2. *Titration von zwei Komponenten*

Für die Titration von zwei Komponenten nebeneinander diente in erster Linie die nichtisotope Markierung.

DUNCAN und THOMAS [11] titrierten mit Dithizon Kobalt- und Zinkspuren nebeneinander; als nichtisotoper Indikator wurde ^{60}Co verwendet (Abb. 4.11).

Abb. 4.2 zeigt die Titration von Quecksilber- und Zinkspuren mit Dithizon in Gegenwart von ^{65}Zn als nichtisotopen Indikator [19]. Während der Titration wurde die Aktivität sowohl der wäßrigen, als auch der organischen Phase gemessen. Gleichfalls unter Anwendung von Dithizon als Titriermittel und von ^{65}Zn als nichtisotopen Indikator gelang es, Spuren von Silber und Zink nebeneinander zu titrieren [32]. Die Bestimmung von Kupfer- und Zinkspuren war jedoch nur mit Hilfe von zwei Titrationen bei verschiedenen pH-Werten, möglich. Kupfer wurde bei pH = 1,0 titriert und anschließend Zink bei pH = 7,0. Die Titrationskurven zeigt Abb. 4.12, aus der auch hervorgeht, daß man falsche Endpunkte erhält, wenn die Titrationen bei pH = 5,8 durchgeführt werden.

Mit Dithizon titrierten auch [12] Spuren von Blei und Kobalt bzw. Nickel und Kobalt (in beiden Fällen mit ^{60}Co als nichtisotopen Indikator).

4.2.2.3. *Titration von drei Komponenten*

Zwar gibt es – wie Abb. 4.5 erkennen läßt – etliche theoretisch mögliche Wege zur Titration von drei Komponenten nebeneinander, doch sind bisher nur sehr wenige, auch praktisch erprobte Bestimmungen beschrieben worden.

Table 7

EFFECT OF SUBSTITUENTS ON THE STRENGTH OF CARBOXYLIC ACIDS

Acids	*Substituents*			K_{acid} ($\times 10^5$)	*I Effect*	*Reference*
	X_1	X_2	X_3			
Malonic acid anion	$-COO^-$	$-H$	$-H$	0·20	+	[206]
Trimethylacetic acid	$-CH_3$	$-CH_3$	$-CH_3$	0·89	+	[497]
Propionic acid	$-CH_3$	$-H$	$-H$	1·35	+	[497]
Butyric acid	$-C_2H_5$	$-H$	$-H$	1·51	+	[497]
Acetic acid	$-H$	$-H$	$-H$	1·75	±	[497]
Phenylacetic acid	$-C_6H_5$	$-H$	$-H$	4·88	−	[497]
Diphenylacetic acid	$-C_6H_5$	$-C_6H_5$	$-H$	11·5	−	[497]
Glycolic acid	$-OH$	$-H$	$-H$	15·1	−	[497]
Monoiodoacetic acid	$-I$	$-H$	$-H$	100	−	[497]
Monobromoacetic acid	$-Br$	$-H$	$-H$	135	−	[497]
Monochloroacetic acid	$-Cl$	$-H$	$-H$	138	−	[497]
Malonic acid	$-COOH$	$-H$	$-H$	141	−	[497]
Monofluoroacetic acid	$-F$	$-H$	$-H$	200	−	see (p. 68 in [393])
Cyanoacetic acid	$-CN$	$-H$	$-H$	356	−	[206]
$^+NH_3.CH_2.COOH$	$-NH_3^+$	$-H$	$-H$	502	−	see (p. 68 in [393])
Nitroacetic acid	$-NO_2$	$-H$	$-H$	2,100	−	
Dichloroacetic acid	$-Cl$	$-Cl$	$-H$	5,000	−	[497]
Trichloroacetic acid	$-Cl$	$-Cl$	$-Cl$	13,000	−	[497]

Note: The above order should not be mistaken for the order of the inductive effect of electrophilic radicals. K_{acid} *values are derived from experiments in aqueous media and may change in each case depending on the solvent. Strength of acids is also determined by other effects.*

Introduction of the phenyl group into a molecule in general increases acid strength and decreases base strength. Phenylacetic acid and diphenylacetic acid are stronger than acetic acid; but aniline and diphenylamine are weaker bases than methylamine:

Acid	$K_{acid} \times 10^5$ [497]	*Base*	$K_{base} \times 10^8$ [497, 332]
Acetic acid	1·75	Methylamine	43,700
Phenylacetic acid	4·88	Aniline	0·0383
Diphenylacetic acid	11·5	Diphenylamine	0·0000071

(c) *Effect of substituents on the acidity of phenols and enols.* The acidic character of substituted phenols is increased by substituents in non-aqueous media in the following order [258]:

$$-NO_2 > -\overset{\overset{O}{\|}}{C}-H > -\overset{\overset{O}{\|}}{C}-R > -Cl > -Br > -C_6H_5$$

(See also: Chapter 17.)

The acidity of phenolic hydroxyl is decreased by the $-COOH$ group in the case of salicylic acid. Substituents containing unshared electron pairs ($-NO_2$, $-COOH$, $-CHO$) in the *ortho* position establish a hydrogen bond with phenolic hydroxyl,

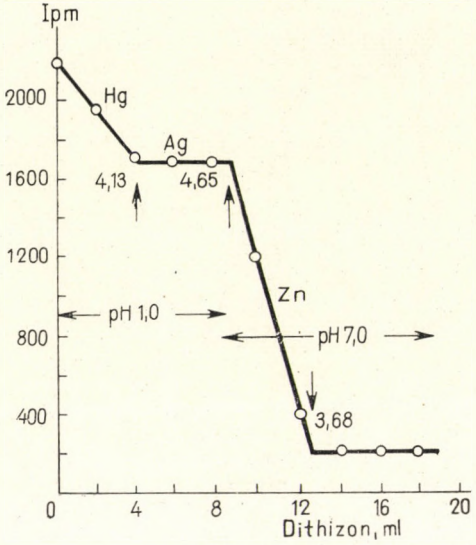


Abb. 4.13
Titration von Hg, Ag und Zn mit Dithizon (nichtisotope Indikatoren: ^{203}Hg und ^{65}Zn) unter Änderung des pH (SPITZY [32])

Quecksilber-, Silber- und Zinkspuren wurden mit Dithizon unter Anwendung von ^{203}Hg und ^{65}Zn als nichtisotope Indikatoren erfaßt [32] (Abb. 4.13). Der pH betrug für Quecksilber und Silber 1,0, für Zink 7,0, Quecksilber, Kupfer und Zink (Indikatoren: ^{203}Hg und ^{65}Zn) bzw. Silber, Kupfer und Cadmium (Indikatoren: ^{110m}Ag und ^{115}Cd) wurden nebeneinander titriert [18, 20].

4.2.3. *Indirekte Titrationen*

Die auf Extraktion beruhenden indirekten radiometrischen Titrationen werden vorwiegend dann angewandt, wenn die Reaktionsgeschwindigkeit zwischen der zu bestimmenden Komponente und dem Titriermittel gering ist.

Ein typisches Beispiel hierfür ist die Bestimmung von Palladium mit Dithizon [33]. Während der Titration verläuft die Reaktion nur langsam, in Gegenwart eines Überschusses an Dithizon jedoch schnell und quantitativ.

In einem 50-ml-Scheidetrichter mit Siliconüberzug werden 20 ml der Palladium enthaltenden Lösung mit einer überschüssigen Menge Dithizonlösung von bekannter Konzentration ausgeschüttelt. Die organische Phase (12 ml) wird in das Titriergefäß der beschriebenen halbautomatischen Titriervorrichtung übergeführt, in welches vorher ein bekanntes Volumen ^{110m}Ag enthaltender Lösung eingebracht wurde. Das Gemisch wird geschüttelt, wobei eine bestimmte Silbermenge mit dem durch das Palladium nicht gebundenen Dithizon reagiert. Die Lösung der Dithizonate wird nun abgelassen und der Silberüberschuß wird mit Dithizon radiometrisch titriert.

Ausgehend vom Prinzip der indirekten radiometrischen Titrationen, entwickelte SPITZY [32, 34] eine sogenannte Schnellmethode zur Bestimmung einer Komponente mit Hilfe einer einzigen Aktivitätsmessung. Die zu bestimmende Komponente wird mit einem bekannten Überschuß von Dithizonlösung extrahiert, hierauf ein bekannter Überschuß einer (im obigen Fall mit ^{65}Zn) markierten Standard-Lösung zum Extrakt zugegeben. Durch diese Standard-Lösung wird das überschüssige Dithizon quantitativ verbraucht. Abschließend wird die Rest-Aktivität der wäßrigen Lösung gemessen. Somit genügt eine einzige Aktivitätsmessung (*i*) für die Bestimmung des Dithizonverbrauches der gesuchten Komponente während alle anderen Werte nur einmal bestimmt und dann lediglich von Zeit zu Zeit kontrolliert werden müssen.

resulting in a change in the properties of both functional groups, e.g. the acidity of the carboxyl group is increased, that of the phenolic hydroxyl decreased, and the molecule dissolves more readily in polar solvents.

Enols and imides can be titrated as acid analogues with alkali metal methoxide or alkylammonium hydroxide (R . CH_2 . R′ and R . NH . R′ where the electrophilic groups R and R′ are: $-COR$, $-CONH_2$, $-CHO$, $-COOR$, $-CONHAr$). When, however, the electrophilic group is an amido- or imino group, titration is not always practicable [246]. So, for instance, hydantoin can be titrated in dimethylformamide as an acid analogue but acetylurea cannot be so titrated:

$HN-CH_2-CO-NH-CO$ (Hydantoin) $\qquad$ $CH_3-CO-NH-CO-NH_2$ (Acetylurea)

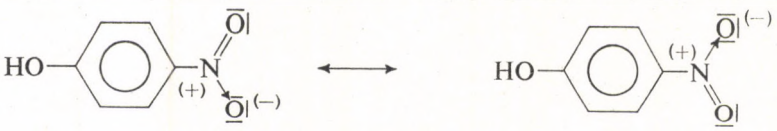
(d) The nitro group is one of the most effective electrophilic substituents (p. 248 in [863]): nitromethane is an 'acidic' solvent, $pK_{acid} = 10{\cdot}6$ [780]; phenolic compounds are converted into strong acids (*o*- and *p*-nitrophenol liberate carbon dioxide from sodium carbonate), on the other hand, nitroaniline is only soluble in concentrated mineral acids.

The powerful acid enhancing effect of the aromatic nitro group in *ortho* and *para* positions is due to its dipole moment, and sometimes, to steric effects or to its anion stabilizing through resonance (charge delocalization).

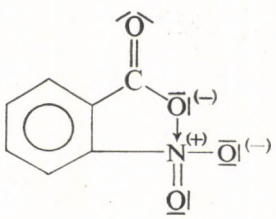
Table 8

DISSOCIATION CONSTANTS OF SUBSTITUTED BENZOIC ACIDS IN WATER ($\times 10^5$) AND ASSOCIATION CONSTANTS IN BENZENE ($\times 10^{-5}$). (ACCORDING TO DATA OF [173])

Substituent	*Ortho*		*Meta*		*Para*	
	K_{diss} *In Water*	K_{ass} *In Benzene*	K_{diss} *In Water*	K_{ass} *In Benzene*	K_{diss} *In Water*	K_{ass} *In Benzene*
CH_3	12·0	0·87	5·37	1·35	4·26	1·07
Cl	115·0	12·0	14·8	11·5	10·5	6·60
OH	106·0	282·0	8·32	2·24	2·63	0·88
NO_2	676·0	274·0	32·8	66·0	37·6	62·8
OCH_3	8·13	0·05	8·13	2·39	3·39	0·83
NH_2	1·12	0·88	1·78	0·85	1·29	0·28
CN	—		25·0	36·3	28·2	33·8



p-Nitrophenol, pK_{acid} 7.14 [780]



o-Nitrobenzoate anion

Die Menge der zu bestimmenden Komponente x wird berechnet nach:

$$x(\mu g) = \left[A - \frac{B[1 - (i/I)]}{C}\right] D ,$$

A = Volumen der Dithizonlösung (ml)
B = Menge des zugegebenen Zinks (^{65}Zn) (μg)
C = Konzentration des mit der Dithizonlösung äquivalenten Zinks ($\mu g\ ml^{-1}$)
D = Konzentration von x (μg/ml), äquivalent mit der Dithizonlösung
I = Ausgangs-Aktivität (Ipm)
i = Rest-Aktivität (Ipm)

Als Vorbedingung gilt, daß der Dithizonatkomplex des zu bestimmenden Elements stabiler ist, als der des Standardelementes. Nach dem geschilderten Prinzip wurden Spuren von Kupfer, Silber und Quecksilber bestimmt.

4.2.4. *Theoretische Grundlagen*

Mit den theoretischen Grundlagen der radiometrischen Extraktions-Titrationen beschäftigten sich DUNCAN und THOMAS [12].

Die in einer Ausgangskonzentration $[M^+]_0$ und in einem Ausgangsvolumen v_0 vorliegende aktive Komponente M^+ wird mit v ml der Lösung eines Komplexbildners HL der Konzentration $[HL]_0$ titriert. Während der Titration befinden sich x_{M^+} Mole von M^+ in der Lösung, entsprechend einer Gesamtaktivität von a_{M^+}. In diesem Falle gilt für den Gesamtverlauf der Titration:

(4.5) $$x_{M^+} = k a_{M^+} ,$$

k = Konstante

Hieraus folgt:

(4.6) $$[M^+] = \frac{x_{M^+}}{v_0 + v} = \frac{k a_{M^+}}{v_0 + v}$$

bzw.

(4.7) $$[M^+]_0 = \frac{x_{0M^+}}{v_0} = \frac{k a_{0M^+}}{v_0} ,$$

Index 0 bezeichnet die Ausgangs-Lösung von M^+.

Daher ist:

(4.8) $$\frac{[M^+]}{[M^+]_0} = \frac{a_{M^+}}{a_{0M^+}} \cdot \frac{v_0}{v_0 + v} = R \cdot \frac{v_0}{v_0 + v} ,$$

$R = a_{M^+}/a_{0M^+}$.

A nitro group in the *ortho* position also stabilizes the anion by displacing the electrons of the carboxylate anion in the field of force of the nitrogen; *o*-nitrobenzoic acid is about eighteen times stronger than *p*-nitrobenzoic acid (cf. [572]).

In Table 8 the dissociation constants of substituted benzoic acids in water ($\times 10^5$) and their association constants in benzene ($\times 10^{-5}$) are given. (See also: Chapter 2; Section 16 (a) and [173].)

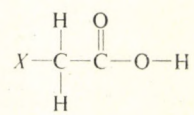
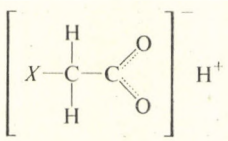
(e) The amino group possesses basic properties, being able to co-ordinate protons (nucleophilic substituent). Its inductive effect on the acid strength, however, is definitely of electrophilic type since the nuclear charge of the nitrogen atom is greater than that of the carbon atom (p. 248 in [863]). In amino acids, owing to the formation of the zwitterion, $^+H_3N-CH_2\,COO^-$, the $-I$ effect remains latent, but becomes apparent when for example the strength of anilinodiacetic acid is compared with that of 2-phenylglutaric acid. The former is about 3·5 times as strong an acid as the latter (p. 248 in [863]):

$C_6H_5N(CH_2COOH)_2$	$C_6H_5CH(CH_2COOH)_2$
Anilinodiacetic acid	2-Phenylglutaric acid
($K \times 10^5 = 270$)	($K \times 10^5 = 77$)

As another example, the pK_{acid} value of nitroguanidine is 12·20 but that of 1-amino-3-nitroguanidine is 10·60 (see: Chapter 20; Section 115).

(f) *The effect of substituents on the strength of nitrogenous bases.* The inductive effect of substituents on bases has the expected effect, in comparison with the foregoing examples dealing with acids. Substituents in $X_1X_2X_3N$ type bases are bonded directly to the proton acceptor atom possessing a free electron pair. Their effect is therefore direct and has, together with other effects, a substantial influence on the base strength.

In acids of the type $X_1X_2X_3C\,.\,COOH$ there are, in contrast, three (1) or four (2) interposed atoms between the electron pair shared by the hydrogen and oxygen and the atom or group (X) with the inductive effect:

(1)  or (2) 

Concerning the inductive effect of alkyl substituents in aliphatic amines see: [348].

On the pattern of Table 7, Table 9 systematizes the effect of substituents on the strength of bases on type $X_1X_2X_3N$.

26. Electrostatic Field Effect

Besides the inductive effect transmitted along the carbon chain an interaction through space also exists, e.g. between the dipoles associated with the carboxyl group or the carboxylate anion and the electronegative group [458, 869]. In halogenated aliphatic carboxylic acids the positive end of the C → Cl dipole is closer to the car-

Folgende Gleichgewichte kommen in Betracht:

$$\overline{HL} \rightleftharpoons HL \tag{4.9}$$

$$HL \rightleftharpoons H^+ + L^- \tag{4.10}$$

$$M^+ + L^- \rightleftharpoons ML \tag{4.11}$$

$$ML \rightleftharpoons \overline{ML} \tag{4.12}$$

Ein Symbol mit einem Strich darüber ($\bar{x}$) bedeutet, daß es sich um die Komponente in der organischen Phase handelt, ohne Strich (x) ist von der in der wäßrigen Phase vorliegenden Komponente die Rede.

Verteilungskoeffizient des Komplexbildners:

$$P_{HL} = \frac{[\overline{HL}]}{[HL]} \tag{4.13}$$

Verteilungskoeffizient des Komplexes:

$$P_{ML} = \frac{[\overline{ML}]}{[ML]} . \tag{4.14}$$

Säure-Dissoziationskonstante des Liganden:

$$K_a = \frac{[H^+][L^-]}{[HL]} \tag{4.15}$$

Stabilitätskonstante des Komplexes:

$$K = \frac{[ML]}{[M^+] + [L^-]} . \tag{4.16}$$

Sind die ungeladenen Komponenten nur im organischen Lösungsmittel löslich, so gilt, wie nachgewiesen werden kann:

$$v^2(KP_{ML}K_aR[\overline{HL}]_0) + vv_0\{KK_aR[P_{ML}(R-1)[M^+]_0 + [\overline{HL}]_0] +$$
$$+ P_{HL}[H^+](R-1)\} + v_0^2(R-1)\{KK_aR[M^+]_0 + [H^+] + K_a\} = 0 . \tag{4.17}$$

Zur Vereinfachung der Gleichung (4.17) kann angenommen werden:

(a) K und P_{ML} sind groß;

(b) $[\overline{HL}]_0$ und $[M^+]_0$ sind klein und von der gleichen Größenordnung (z. B. wie in verdünnten Lösungen);

(c) der pH der wäßrigen Lösung ist konstant und $[H^+] \ll KK_a[M^+]_0$ (z. B. die Menge des nach der Einstellung des Gleichgewichtes in der wäßrigen Phase verbleibenden HL ist vernachläßigbar gering);

(d) P_{ML} und P_{HL} sind größenordnungsmäßig gleich.

boxylate anion than is its negative end, resulting in the stabilization of the anion. The degree of stabilization depends on the magnitude of the dipole, on the distance between the carboxylate anion and the dipole, and finally, on the dielectric constant of the medium through which the interacting lines of force have to pass. The latter is called electrostatic interaction and, in certain cases, must be taken into account together with the inductive effect.

Table 9

EFFECT OF SUBSTITUENTS ON THE STRENGTH OF ORGANIC BASES

Base	*Substituents*			K_{base} ($\times 10^8$)	*I Effect*	*Reference*
	X_1	X_2	X_3			
Urea	NH_2-CO-	$-H$	$-H$	0·0000032	+	[779]
Diphenylamine	$-C_6H_5$	$-C_6H_5$	$-H$	0·0000071	+	[332]
1-Naphthylamine	$-C_{10}H_7$	$-H$	$-H$	0·00836	+	[332]
2-Naphthylamine	$-C_{10}H_7$	$-H$	$-H$	0·0129	+	[332]
Aniline	$-C_6H_5$	$-H$	$-H$	0·0383	+	[497]
Phenylhydrazine	$-NH-C_6H_5$	$-H$	$-H$	0·16	+	[497]
Hydroxylamine	$-OH$	$-H$	$-H$	1·07	+	[497]
Hydrazine	$-NH_2$	$-H$	$-H$	302	+	[497]
Ammonia	$-H$	$-H$	$-H$	1,790	±	
Benzylamine	$-CH_2-C_6H_5$	$-H$	$-H$	2,000	−	[497]
Trimethylamine	$-CH_3$	$-CH_3$	$-CH_3$	5,270	−	[497]
Ethylenediamine	$-CH_2CH_2NH_2$	$-H$	$-H$	8,510	−	[497]
Methylamine	$-CH_3$	$-H$	$-H$	43,700	−	[497]
Dimethylamine	$-CH_3$	$-CH_3$	$-H$	51,200	−	[497]
Ethylamine	$-C_2H_5$	$-H$	$-H$	56,000	−	[497]
Triethylamine	$-C_2H_5$	$-C_2H_5$	$-C_2H_5$	56,500	−	[497]
Diethylamine	$-C_2H_5$	$-C_2H_5$	$-H$	126,000	−	[497]

Note: The above order should not be mistaken for the order of the inductive effects of single substituents! K_{base} values are results of experiments in aqueous media and may change in each case, depending on the solvent. Strength of bases is also determined by other effects.

The carboxyl and also the $-COOC_2H_5$ and $-CONH_2$ groups have electron attracting properties. In the case of dicarboxylic acids, however, the $-COO^-$ ion decreases the acid strength of the second $-COOH$ group, since it is more difficult to split off a proton from a negatively charged ion than from a neutral molecule.

In symmetrical dicarboxylic acids the two carboxyl groups have equal chances to dissociate one proton. But the carboxylic acid anion, e.g. $HOOC.(CH_2)_n.COO^-$, has only one possibility of co-ordinating a proton. For the dissociation of the second proton the converse situation arises: there is one possibility for loss and two for co-ordination of a proton. On the ground of these simple probability considerations the first dissociation constant would be expected to be four times as great as the second. Actually the ratio is greater than $K' : K'' = 4$ because of the electrostatic field effect, especially in the case of two adjacent carboxyl groups (cf. p. 384 in [380]):

Gleichung (4.17) reduziert sich dann auf:

$$v = v_0 \frac{[M^+]_0}{[HL]_0} (1 - R) . \tag{4.18}$$

Man erhält bei der graphischen Darstellung von R (oder der Gesamt-Aktivität einer der Phasen) als Funktion von v eine Gerade. Bei Gültigkeit der Gleichung (4.18) kann man den Wert von $[M^+]_0$ aus $[HL]_0$ oder umgekehrt bestimmen. Eine einzige Serie von v- und R-Werten genügt für die Berechnung (sofern $v \neq v_0$).

Diese Methode ermöglicht auch die Ermittlung des statistischen Fehlers der Aktivitätsmessungen. Die Standard-Abweichung des aus v, v_0, $[M^+]_0$ und R bestimmten $[HL]_0$ ist:

$$\sigma_{[HL]_0} = \frac{v_0}{v} [M^+] \sigma_R \tag{4.19}$$

und

$$\sigma_R = \frac{a_{M^+}}{a_{0M^+}} \left\{ \frac{(\sigma a_{M^+})^2}{(a_{M^+})^2} + \frac{(\sigma a_{0M^+})^2}{(a_{M^+})^2} \right\}^{\frac{1}{2}} . \tag{4.20}$$

Ist die Extraktion von ML nicht quantitativ (d. h. sind P_{ML} oder K klein und $[H^+]$ signifikant) ergibt die Titration keine Gerade, sondern eine gekrümmte Linie. Sind jedoch K_a, $[H^+]$ und P_{HL} bekannt, so ist es möglich, die Werte von K, P_{ML} und $[M^+]_0$ auf Grund von drei Punkten einer solchen Kurve zu berechnen.

Ionen von Elementen, die kein entsprechendes radioaktives Isotop besitzen, können unter Anwendung bekannter Mengen eines anderen markierten Ions bestimmt werden. Ein Beispiel hierfür ist die Bestimmung von Zink als Dithizonat unter Anwendung von ^{60}Co. Vor der eigentlichen Extraktion der markierten Ionen werden die zu bestimmenden Ionen vorzugsweise mit einem Lösungsmittel extrahiert. Es ist aber auch möglich, die Menge des gesuchten Ions unter gleichzeitiger Extraktion des Indikators zu bestimmen. In diesem Falle sind die obigen Gleichungen auch gültig, nur müssen sich die Konzentrationswerte auf die zu bestimmenden und die zur Markierung verwendeten Stoffe gemeinsam beziehen.

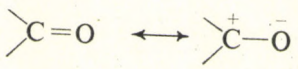
Beispiele hierfür sind die gemeinsamen Extraktionen von Kobalt und Blei bzw. Nickel mit Dithizon unter Anwendung von ^{60}Co als Indikator. Im ersteren Fall ergibt der Endpunkt der Extraktionskurve (Abb. 4.14) das der gemeinsamen Menge von Blei und Kobalt entsprechende Volumen der Maßlösung. Ist die Menge des angewandten Kobalts bekannt, so läßt sich diejenige des zu bestimmenden Stoffes einfach berechnen. Der Bleikomplex wird vor dem Kobaltkomplex extrahiert. Daher entspricht die Titrationskurve ABC nicht der erwarteten Geraden AC. Anderenfalls könnte man das Gesamtgewicht des Bleis und Kobalts aus den Werten von R und v aus jedem Punkt der Titrationskurve erhalten. Es ist aber sehr selten, daß zwei Metallkomplexe gemeinsam extrahiert werden.

FIRST (K') AND SECOND (K'') DISSOCIATION CONSTANTS OF CARBOXYLIC ACIDS. $K_{acid} \times 10^5$

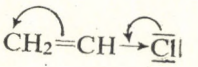
Acid	K'	K''	$K' : K''$	*Reference*
Oxalic acid	6,500	6·1	1,065	[497]
Malonic acid	139·7	0·08	1,750	[497]
Succinic acid	6·9	0·247	28	
Glutaric acid	4·5	0·38	12	(p. 384 in [380])

27. Effect of Mesomerism on the Strength of Acids and Bases

The different electron affinity of the di- or poly-atomic substituents on a double- or triple-bonded carbon-oxygen or carbon-nitrogen multiple bond produces unsymmetrical distribution of the π-electron density in the double bond; this state may be illustrated as a polar mesomeric structure ('Zwischenstufe': [16]):



In contrast with the displacement due to I effects in σ-bonds, the M effects produce displacement of the π-bonds. This permanent displacement of the π-electron system can lead to the total polarization of the molecule. The direction of the displacement is determined by the structure of the compound. The mesomeric effect may be ascribed to either of two causes, or perhaps to the joint effect of both; (1) the presence of heteronuclear π-electron orbitals $C \overset{\frown}{=} O$; (2) the expansion of the π-electron system, e.g. the overlap of an electron pair in a 'p' orbital with the π-system:

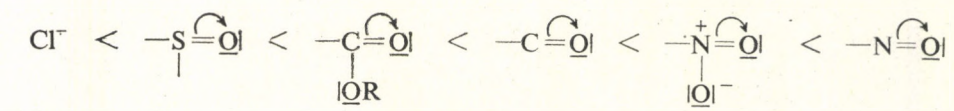


In the first case the effect is in the same direction as the I effect, in the second case an opposing effect results. (See: Section 25 (b)).

A distinction is made between electron releasing and electron attracting groups; each can be placed in sequence according to their effect. Electron releasing groups ($+M$) include:

carboxylate ion > amino > hydroxyl > methyl group

Electron attracting groups ($-M$) include:



Chloride Sulphoxide Carboxylic acid ester Carbonyl Nitro Nitroso

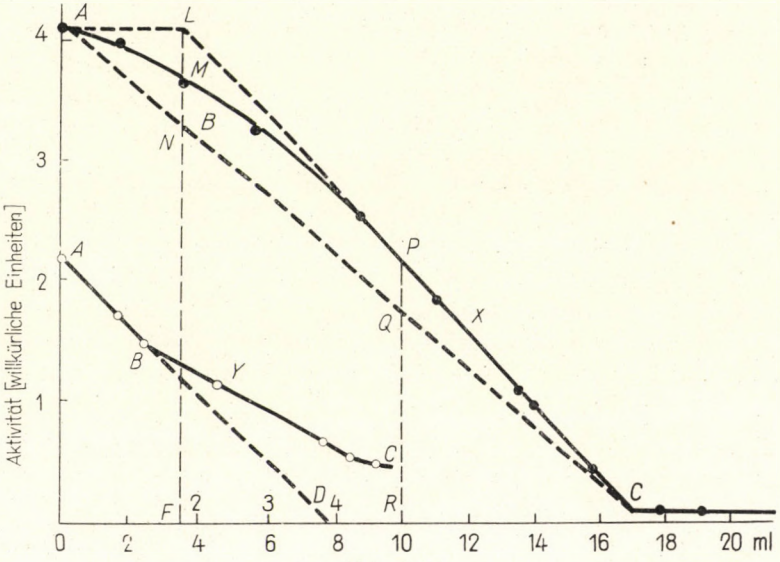


Abb. 4.14
Titration von Pb und Co sowie von Ni und Co mit Dithizon (DUNCAN und THOMAS [12]) (Kurve *X* — Pb und Co; Kurve *Y* — Ni und Co)

Um für einfach geladene Ionen eine solche theoretische Kurve zu erhalten, sollen die Volumina v_{J^+} und v_{M^+} der Lösung des Komplexbildners [HL], die zur Extraktion der beiden Ionen J^+ und M^+ benötigt werden, durch die gerade extrahierten Fraktionen der Ionen f_{J^+} und f_{M^+} ausgedrückt werden:

$$v_{J^+} = v_0 \frac{[J^+]_0}{[HL]_0} f_{J^+} . \tag{4.21}$$

Eine ähnliche Gleichung läßt sich auch für M^+ aufstellen. Ferner gilt:

$$v = \frac{v_0}{[HL]_0} ([M^+]_0 + [J^+]_0) f_T , \tag{4.22}$$

f_T = jene Fraktion der Gesamtmenge von M^+ und J^+ die gerade extrahiert wird.

Da aber

$$v = v_{J^+} + v_{M^+}$$

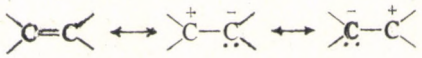
folgt:

$$f_{M^+} [M^+]_0 + f_{J^+} [J^+]_0 = f_T ([M^+]_0 + [J^+]_0) , \tag{4.23}$$

Bedeuten nun in Abb. 4.14 *X*, M^+ das zur Markierung verwendete Ion, $f_{M^+} = LM/LF$ und $f_T = LN/LF$, so sind beide Ausdrücke für jede Stellung von *L* am Abschnitt *AL* bekannt. Ebenso kann $[M^+]_0 + [J^+]_0 = [T]_0$

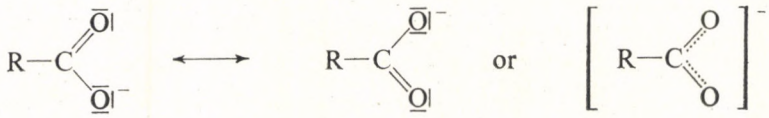
The 'mesomeric structure' has no well-defined physical existence under normal conditions; but such structures aid understanding of the molecular structure (p. 200 in [26]).

The electromeric effect (E) is important in unsaturated compounds: it symbolizes polarizability and not permanent polarization:



Concerning inductive (I_S), mesomeric (M), inductomeric (I_d) and electromeric (E) displacement of electrons see: (pp. 182—185 in [231]).

Theoretically the strength of every acid or base of unsaturated or aromatic type is influenced by an electron distribution which can be symbolized by the mesomeric structures. Consider the carboxylate anion, where the negative charge is dispersed and the inherent proton affinity diminishes (p. 258 in [605]):

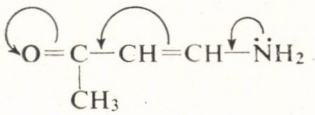


The above symbols illustrate the possibility of displacement of the two π-electrons towards one of the atoms, thus giving rise to a 'semi-polar' bond (Lowry and Sidgwick). These are actually resonance forms and possibly exist only as intermediate transition states during reaction (p. 376 in [380]).

The mesomeric (M) effect describes the charge distribution in a non-activated 'ground state' of the molecule, and is symbolized by the canonical resonance forms, as in the example:



The localization of the electrons and the direction of the displacement of the electron-cloud can also be represented by curved arrows:



The ionization of acids is reversible; the dissociation constant, therefore, depends both on the electron configuration of the acid and on that of the anion (pp. 246 and 258 in [863]).

The dissociation equilibrium constant:

$$K = \frac{\text{rate of formation of } H^+ \text{ ion from } R-OH \text{ molecule}}{\text{rate of co-ordination of } H^+ \text{ ion with } (R-O)^- \text{ ion}}$$

shows acid strength to be influenced by two factors independent of each other: (1) release of the proton, and (2) the stabilization of the anion by resonance.

auf Grund von Punkt *C* berechnet werden. Gleichung (4.23) läßt sich nun für die Berechnung sowohl von $[M^+]_0$ als auch von $[J^+]_0$ aus dem linearen Abschnitt von *PC* verwenden, für den $f_{J^+} = 1$ ist, indem man nach einer der folgenden beiden Methoden vorgeht:

(a) Die Extrapolation von *CP* auf *L*, auf dem Abschnitt *AL* ($f_{J^+} = 1$; $f_{M^+} = 0$) ergibt:

$$\frac{[J^+]_0}{[T]_0} = f_T = \frac{LN}{LF} = \frac{OF}{OC}, \tag{4.24}$$

d. h. $[J^+]_0$ und $[T]_0$ sind den Volumina *OF* und *OC* proportional.

(b) Für jeden Punkt *P* am linearen Abschnitt *PC* ($f_{J^+} = 1$) gilt:

$$f_{M^+}[M^+]_0 + [J^+]_0 = f_T[T]_0 .$$

zumal

$$[J^+]_0 = [T]_0 - [M^+]_0 ,$$

$$\frac{[M^+]_0}{[T]_0} = \frac{f_T - 1}{f_{M^+} - 1} = \frac{QR}{PR}, \tag{4.25}$$

d. h. $[M^+]_0$ kann auf Grund eines jeden Punktes auf Abschnitt *PC* und des Punktes *C* gefunden werden.

In Tab. 4.1 sind die auf Grund von Abb. 4.14 X, unter Anwendung der beschriebenen beiden Methoden berechneten Kobalt- und Bleigehalt-Werte zusammengestellt. Die Stöchiometrie der beiden Komplexe weicht ab ($CoDz_3$, $PbDz_2$). Trotzdem sind keine mathematischen Modifizierungen notwendig, vorausgesetzt, daß die Konzentrationsausdrücke in den obigen Gleichungen in äquivalenten Konzentrationen (bezogen auf $[\overline{HL}]_0$) angegeben sind.

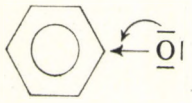
Tabelle 4.1

Auf Grund von Abb. 4.14 X gefundene Mengen von Blei und Kobalt

	Pb^{2+} (μg)	Co^{2+} (μg)
Aus Punkt *L*	$14{,}8_5$	$10{,}1_3$
Aus Punkt *P* bei 10 ml	$14{,}8_1$	$10{,}2_4$
Tatsächlich zugegeben	$15{,}0_3$	$10{,}1_3$

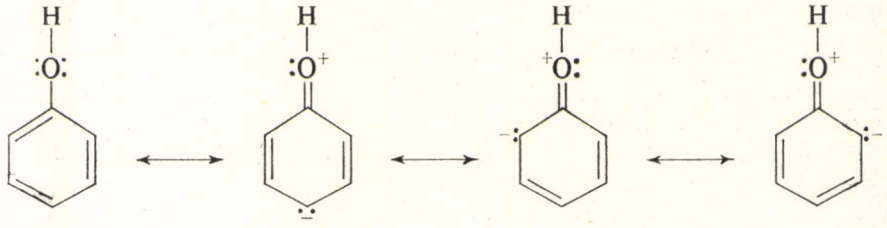
Es ist natürlich möglich, daß ein bestimmter Abschnitt der Extraktionskurve selbst dann linear ist, wenn keines der Elemente vollständig extrahiert wird. Die gefundenen Werte werden dann nicht entsprechend übereinstimmen. Um $[J^+]_0/[T]_0$ nach Methode (b) zu bestimmen, wird ein Extrapolationsverfahren notwendig, wobei der begrenzende Wert von $\frac{QR}{PR}$ ermittelt werden kann (wenn $P \rightarrow C$).

Phenols are in general stronger acids than alcohols; and aniline is a weaker base than methylamine. For phenols, as well as for aniline, strength of the acid or base is determined by resonance effects which can be symbolized by various structural formulae. These structural formulae do not represent compounds in any physical sense but only represent limiting cases where the electronic displacement is completed. The true state cannot be expressed either by the Kekulé formula, or by the quinonoid mesomeric structures shown below. E.g. in the phenoxide anion the negative charge releases electrons through the σ-bonds towards the aromatic ring and the electron pair moves towards the π-system:



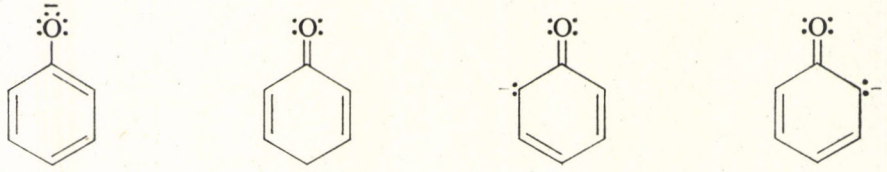
The quinonoid mesomeric forms involved are the following:*

Phenol:



a *b* *c* *d*

Phenoxide anion:



e *f* *g* *h*

In the forms *(b−d)* the positive part of the field of force of the dipole helps to eliminate the proton, while in the forms *(f−h)* the negative charge is distributed over the whole of the molecule; consequently the charge localized on the oxygen atom in the $C_6H_5O^-$ ion is smaller than in the alkoxide anion e.g. CH_3O^-. Thus phenol can be titrated with potassium methoxide:

$$C_6H_5OH + CH_3O^-K^+ = C_6H_5OK + CH_3OH$$

The basic character of the O-atom diminishes to such a degree that the phenol assumes the character of a weak acid. Phenol is able to stabilize the two lone electron pairs of the oxygen atom by eliminating a proton.

*Wheland and Pauling, *J. Am. Chem. Soc.* **57**, 2086 (1935).

Wird das zur Markierung verwendete Element vor dem inaktiven extrahiert (z. B. Nickel vor ^{60}Co, als Dithizonat, vgl. Abb. 4.14 *Y*), so ist die Konzentration des inaktiven Stoffes nicht bestimmbar, da die Extrapolation auf die Abszisse (*BC*) sehr ungenau ist. Ist jedoch die Anfangs-Änderung der Aktivität *AB* linear, so kann der Endpunkt für den inaktiven Stoff noch erhalten werden. Die Ungenauigkeit hängt dann vom Grad der Verunreinigung durch das inaktive Element ab. Daher entspricht — für Kobalt und Nickel — der Endpunkt der Extraktion von $CoDz_3$ 2,6$_4$ μg Kobalt, anstatt der tatsächlich zugegebenen Menge von 2,0 μg (Punkt *D*).

Die theoretischen Grundlagen der *substöchiometrischen Lösungsmittelextraktion* haben RŮŽIČKA und STARÝ [26] bis in Einzelheiten entwickelt. Da sich ihre Ergebnisse ohne jedwede Modifizierung auf die radiometrischen Extraktions-Titrationen übertragen lassen, sind nachstehend die sich auf die Berechnung des optimalen pH-Intervalls der Titration beziehenden theoretischen Bedingungen angeführt.

Metallionen (M) werden mit einem Komplexbildner (HL), der in diesem Falle eine schwache Säure ist, gemäß der Gleichung (4.26) titriert:

$$M + n[\overline{HL}] = [\overline{ML_n}] + nH. \tag{4.26}$$

Der Einfachheit halber sind die Ionenladungen ebenso wie in den nachfolgenden Ausführungen weggelassen.

Die Gleichgewichtskonstante (Extraktionskonstante) für (4.26) ist:

$$K = \frac{[\overline{ML_n}]\,[H]^n}{[M]\,[\overline{HL}]^n}\,. \tag{4.27}$$

Setzt man in Gleichung (4.27) die Gleichgewichts-Werte von $[\overline{ML_n}]$, $[\overline{HL}]$ und [M] sowie den bekannten Wert von *K* ein, so kann jener pH-Wert berechnet werden, bei dem sich, im Falle der nacheinander folgenden Maßlösung-Zugabe, gleiche Mengen von Metallionen extrahieren lassen.

Die Gleichgewichts-Konzentration des Komplexes, $[\overline{ML_n}]$ wird unter Berücksichtigung dessen berechnet, daß bei der Bildung von ML_n mehr als 99% des Titriermittels verbraucht werden, d. h.

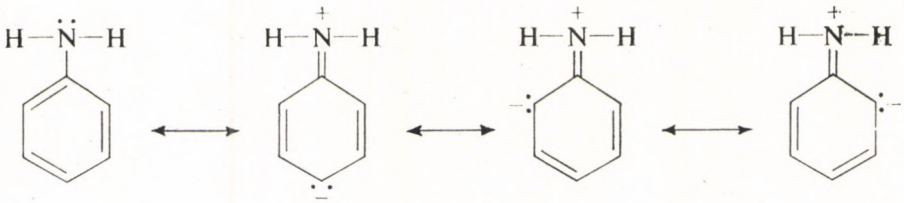
$$[\overline{ML_n}]\,\bar{v} \geq 0{,}99\,\frac{[\overline{HL}]_0}{n}\,\bar{v}\,, \tag{4.28}$$

$\bar{v}$ = Volumen der organischen Phase

$[\overline{HL}]_0$ = Ausgangs-Konzentration des Titriermittels in der organischen Phase.

Die Bedingung (4.28) bedeutet, daß während der Titration bei der Zugabe jeder einzelnen Portion des Titriermittels mehr als 99% der entsprechenden Metallionenmenge extrahiert werden.

The strength of aromatic bases is also influenced by mesomeric effects. So, for instance, the lone electron pair, responsible for the proton co-ordinating ability of aniline, is attracted from the nitrogen atom by the π-electron sextet of the aromatic ring ($+M$ effect). The resulting electron configuration can be approximately represented by the following resonance structures:



a *b* *c* *d*

In the quinonoid resonance forms of aniline *(b–d)* the N atom appears in the ammonium (immonium) form; thus its proton-binding ability lessens. The anilinium ion cannot stabilize in the quinonoid form because the octet of the nitrogen atom is complete and the quinonoid form can be attained only by elimination of the proton. For this reason aniline is a weaker base than methylamine. This effect is enhanced by substitution of two or three phenyl groups *(A)* or, by substitution in the aromatic ring of the aniline with a nitro group *(B)*:

A

Base	p*K*	*Reference*	*Base*	p*K*	*Reference*
Aniline	9·42	[334]	*p*-Toluidine	8·21	[334]
Diphenylamine	13·15	[334]	Di-*p*-tolylamine	11·77	[47]
Triphenylamine	16·83	[47]	Tri-*p*-tolylamine	15·33	[47]

B

Base	pK_{BH^+}	*Reference*	*Base*	pK_{BH^+}	*Reference*
Aniline	4·58		2,4-Dinitroaniline	−4·53	[625]
m-Nitroaniline	2·62	[333]	2,4,6-Trinitroaniline		
	2·50	[625]	(picramide)	−9·41	[625]
p-Nitroaniline	0·99	[625]			
o-Nitroaniline	−0·29	[625]			

In *m*-nitroaniline the effect of the nitro group asserts itself without the occurrence of comparable resonance forms. This can be ascribed to second-order effects (as regards picramide see also: Chapter 4; Section 28).

(a) *Effect of additional ionic resonance on the strength of heterocyclic bases* [2, 3, 4, 5]. In the synthesis of drugs and in chemotherapy, compounds containing heterocyclic nitrogen atoms are of great importance. It is obvious that compounds of this type can be titrated with perchloric acid; therefore, the relation of base strength to structure will now be discussed in more detail.

Die Gleichgewichts-Konzentration der Metallionen wird mit Hilfe der Gleichung (4.29) berechnet:

$$[M]v = [M]_0 v - \frac{[\overline{HL}]_0}{n} \bar{v} \tag{4.29}$$

v = Volumen der wäßrigen Lösung
$[M]_0$ = Ausgangskonzentration der Metallionen in dieser Phase.

Zur Berechnung der Gleichgewichts-Konzentration der Maßlösung wird der Ausdruck (4.30) verwendet:

$$[\overline{HL}]\bar{v} \leq 0{,}01\,[\overline{HL}]_0 v \tag{4.30}$$

Nach Lösung von (4.27–30) für $[H^+]$ ergeben sich die am besten geeigneten pH-Schwellenwerte mit Hilfe von:

$$pH \geq \frac{1}{n} \log \frac{[\overline{HL}]_0}{n} - \frac{1}{n} \log \left([M]_0 - \frac{[\overline{HL}]_0}{n} \frac{\bar{v}}{v} \right) - \frac{1}{n} \log K$$

$$- \log (0{,}001\,[\overline{HL}]_0). \tag{4.31}$$

Diese letztere Gleichung gilt nur dann, wenn die Dissoziation des Titriermittels in der organischen Phase vernachlässigt werden kann, d. h. wenn

$$v[L] < [\overline{HL}]\,\bar{v}\,. \tag{4.32}$$

Diese Bedingung ist erfüllt, sofern

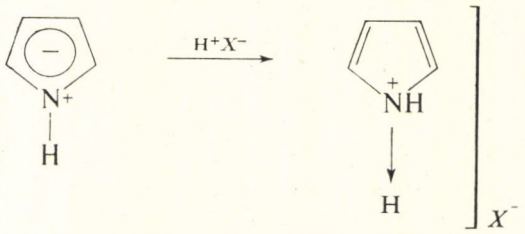
$$pH \leq pK_{HL} + \log q_{HL} + \log \frac{\bar{v}}{v}, \tag{4.33}$$

K_{HL} = Dissoziationskonstante des Titriermittels
q_{HL} = Verteilungskoeffizient.

Gemäß Gleichung (4.33) ist bei Titrationen mit der Dithizonlösung in Tetrachlorkohlenstoff die obere Grenze des pH-Schwellenwertes: $9 + \log \bar{v}/v$. Liegt der pH über diesem Wert, so ist die in Beziehung (4.28) ausgedrückte Bedingung nicht erfüllt, zumal infolge der Dissoziation ein erheblicher Anteil des Dithizons in die wäßrige Phase übergeht.

Gleichung (4.31) läßt deutlich erkennen, daß die untere Grenze des pH-Schwellenwertes durch die ersten beiden Ausdrücke auf der rechten Seite relativ wenig beeinflußt wird. Titriert man z. B. mit Dithizon derart, daß eine Portion des zugegebenen Titriermittels einem Zehntel der Gesamtmenge der zu titrierenden Kationen äquivalent ist, so ist die Summe der ersten beiden Ausdrücke $-\frac{1}{n}$. In viel größerem Maße wird die untere Grenze des pH-Schwellenwertes durch die beiden anderen Ausdrücke beeinflußt.

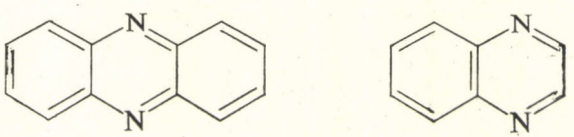
Pyrrole is a very feeble base since for the formation of the sextet required for aromaticity the unshared electron pair of the nitrogen atom is required, and it is just this, however, which is needed for the co-ordination of the proton. Pyrrole when dissolved in concentrated aqueous mineral acids is polymerized since this electron pair, on protonation, is removed from the electron sextet of the ring; and the molecule develops a diene character:



A different situation arises in the case of N-heterocyclic compounds containing a six-membered ring. In the pyridine ring the unshared electron pair of the nitrogen is not required to take part in the formation of the aromatic sextet. Thus, the nitrogen of pyridine is of distinctly nucleophilic character, and pyridine behaves as a cyclic tertiary amine of strong basicity.

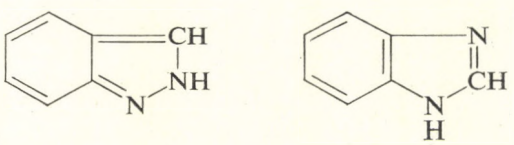


Detailed studies by Albert and his co-workers have been concerned with the change of base strength in heterocyclic bases as a function of the number of atoms forming the ring, and with the effect on base strength of a second nitrogen atom introduced into the ring. The effect of additional ionic resonance on heterocyclic bases is demonstrated by many experiments and measurements. Placing a second nitrogen atom in the skeleton of a pyridine ring causes a decrease in base strength. Phenazine and quinoxaline are weaker bases than acridine and quinoline, respectively.



Phenazine, pK_{BH^+} 1·2 Quinoxaline, $pK_{BH^+} \sim 0{\cdot}8$

Compounds containing a *pyrrole-type ring* acquire a basic character by insertion of a second nitrogen hetero-atom although the molecule otherwise has poorly basic properties. Indazole (benzpyrazole) and benzimidazole are stronger bases than pyrrole and indole, respectively.



Benzpyrazole, pK_{BH^+} 1·3 Benzimidazole, pK_{BH^+} 5·53

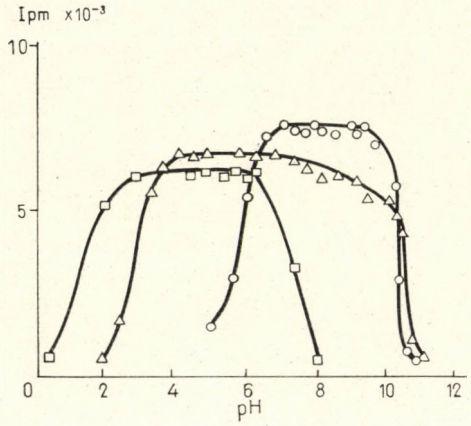


Abb. 4.15
Einfluß des pH auf die substöchiometrische Extraktion von Cu (□), Bi (△) und Zn (○) unter Anwendung von 10^{-5} M Dithizonlösung in Chloroform als Titriermittel (RŮŽIČKA und STARÝ [26])

Die Konzentration der zu bestimmenden Komponenten liegt bei den radiometrischen Extraktions-Titrationen in der Regel zwischen 10^{-5} und 10^{-8} M. Wenn also das Volumen der organischen Phase ein Zehntel des Volumens der wäßrigen Phase ausmacht, liegt die Konzentration des Titriermittels zwischen 10^{-4} und 10^{-7} M.

Daher läßt sich die Gleichung (4.31) wie folgt vereinfachen:

$$\text{pH} > -0{,}01 \log [\text{HL}]_0 - \frac{1}{n} \log K \,. \tag{4.34}$$

Abb. 4.15 zeigt die Extraktion von Kupfer, Wismut und Zink als Funktion des pH. Die Übereinstimmung zwischen den gemessenen und berechneten Werten ist gut.

4.2.5. *Einrichtungen und Technik*

Die radiometrischen Komplexbildungstitrationen werden in den meisten Fällen diskontinuierlich durchgeführt, d. h. der Zugabe jeder Portion des Titriermittels folgt jeweils eine Extraktion. Dieser folgt die Messung der Radioaktivität der wäßrigen oder der organischen Phase, dann wird wieder eine Portion der Titrierflüssigkeit zugegeben usw. Alldies muß man so viele Male wiederholen, wie Punkte zur Aufnahme der Titrationskurve benötigt werden.

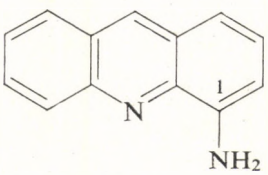
DUNCAN und THOMAS [11] führten diese Titrationen in Kolben mit eingeschliffenem Glasstopfen durch. Vor der Verwendung werden die Kolben zweimal mit destilliertem Wasser und dann mit einer Lösung von Dithizon in Tetrachlorkohlenstoff gespült. Zur Bildung einer wasserabweisenden Schicht — zur Herabsetzung der Adsorption — folgt schließlich eine Behandlung mit »Desicote«-Lösung.

Zu 6,5–10,0 ml der im Titrierkolben befindlichen und auf den gewünschten pH-Wert eingestellten Prüflösung wird aus einer Bürette Dithizon-Lösung in kleinen Portionen zugegeben. Nach Zugabe jeder Portion der Maßlösung wird der Kolben bis zur Erreichung des Extraktions-Gleichgewichtes geschüttelt und dann die Aktivität eines 5 ml betragenden aliquoten Teiles der wäßrigen Phase mit Hilfe eines GM-Flüssigkeitszählrohres gemessen. Anschließend wird der aliquote Teil aus dem — gleichfalls mit »Desicote« behandelten — Zählrohr in den Titrierkolben zurückgegossen. Der Titer der verwendeten Lösung von Dithizon in Tetrachlorkohlenstoff wird

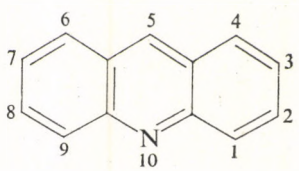
The base strength of saturated heterocyclic bases is similar to that of the corresponding aliphatic amines: pK_{BH+} = approx 10. Many investigations were needed, however, to determine the strength of unsaturated heterocyclic bases and to throw light upon the correlation between the latter and their molecular structure [2, 3].

The basicity of unsaturated heterocyclic bases differs from that of saturated bases in its origin. In the course of ionization of bases containing an aromatic ring the resonating system of electrons plays a considerable role in the change of energy content. The ionization constant, the measure of free energy change of ionization, also contains a factor related to change in resonance energy.

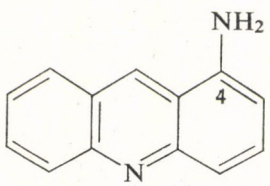
The result of an additional ionic resonance effect, contributing to the change of base strength, is shown by acridine. Acridine itself is a weak base and its strength is enhanced only to a small extent when an amino group is substituted in position 3 or 4. The basicity is decreased by substituting an NH_2-group in position 1, while amino groups in position 2 or 5 increase the basicity of the molecule because of the additional ionic resonance effect:



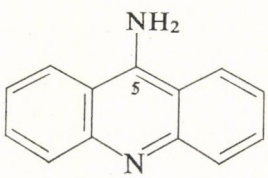
1-Aminoacridine pK_{BH+} 4·40



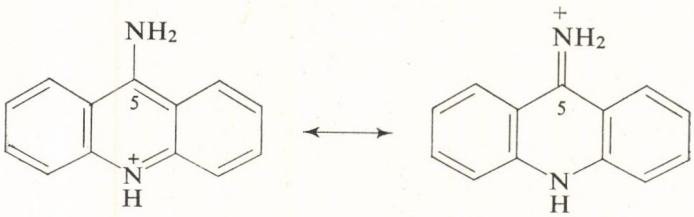
Acridine pK_{BH+} 5·60



4-Aminoacridine pK_{BH+} 6·04



5-Aminoacridine pK^{+} 9·99



Resonance forms of 5-aminoacridinium ion

unter Anwendung einer Silbernitratlösung von bekannter Konzentration oder spektrophotometrisch (durch Messung des Extinktionskoeffizienten bei 620 mμ) bestimmt.

KORENMAN und Mitarb. [19] verwendeten die folgende Methode.

In eine bestimmte Zahl von Zentrifugenröhren mit eingeschliffenem Glasstopfen (die Anzahl der Röhren entspricht der Zahl der zu bestimmenden Punkte auf der Titrationskurve) wird je 1 ml der Prüflösung und je 1 ml einer entsprechenden Pufferlösung pipettiert. Aus einer Bürette werden dann wachsende Volumina einer Lösung von Dithizon in Chloroform in die Zentrifugenröhren einlaufen gelassen. Anschließend wird das Flüssigkeitsvolumen in allen Röhren mit reinem Chloroform auf genau 2 ml ergänzt. Die Röhren werden 15 Minuten hindurch mechanisch geschüttelt und dann wird 2 Minuten hindurch zentrifugiert. Abschließend wird die Aktivität sowohl in der wäßrigen als auch in der organischen Phase gemessen.

Es liegen nur wenige Versuche vor, diesen Titrationsprozeß kontinuierlich zu gestalten, was offenbar auf die Natur der flüssig–flüssig-Extraktion zurückzuführen ist. Ähnliche Schwierigkeiten verursachte auch die Automatisierung der Titration

Halbautomatische Einrichtungen beschrieben mehrere Autoren. Das Problem der kontinuierlichen Titration konnte mit diesen zwar nicht vollständig gelöst werden, doch ist es mit ihrer Hilfe gelungen, die Bestimmungsprozesse einfacher zu gestalten und zu beschleunigen, weshalb sie an dieser Stelle auch ausführlich beschrieben werden sollen.

4.2.5.1. *Halbautomatischer Titrierapparat nach* SPITZY [32]

Bei der Entwicklung dieser Einrichtung wird von folgenden Überlegungen ausgegangen.

(a) Um die Verwendung eines Trenngefäßes mit großer Grenzfläche zwischen den beiden Phasen zu vermeiden, muß das Titriergefäß mit einem wirksamen Rührer versehen sein, der eine genügend intensive Vermischung gewährleistet.

(b) Zähler und Titriergefäß müssen so angeordnet sein, daß sie die Messung der Aktivität der *gesamten* wäßrigen Lösung gestatten.

(c) Die Überführung der wäßrigen Phase in ein zweites Gefäß (zur Messung der Aktivität) und auch die Zurückführung in das Titriergefäß, muß vermieden werden.

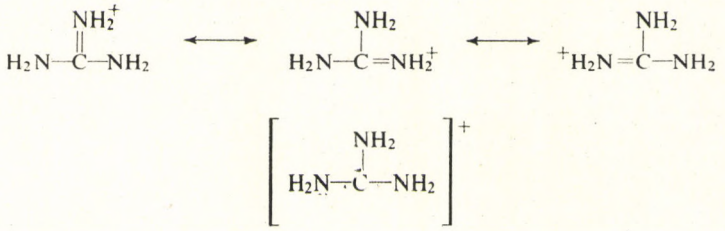
(d) Zur Beschleunigung des Titrationsprozesses muß ein automatisches Ablaßventil für die Trennung der organischen von der wäßrigen Phase sorgen.

Abb. 4.16 zeigt den Titrierapparat, der aus folgenden Teilen besteht:

1 — Gestell für Bürette und Rührer. Der mit Silicon überzogene, elektrisch betriebene Rührer läuft mit einer Drehzahl von 3000 U/Min.

2 — Mit GM-Zählrohren umgebenes Titrationsgefäß. Als solches wird ein 30 ml fassender Teflon-Becher oder ein mit Silicon überzogenes dünnwandiges Becherglas verwendet, um welches herum vier GM-Zähler (Philips 18505) in Kunststoffhaltern

The additional ionic resonance effect is clearly illustrated by the very strong base, guanidine (pK_{BH^+} 13·71). Three possible and equivalent structures correspond to the guanidinium ion, each of which possesses the cationic $=NH_2^+$group and the double bond: consequently it is a cation with a symmetrical electron structure:



The situation is similar in the case of acetamidine, though it is a weaker base because only two equivalent resonance forms are possible; pK_{BH^+} 12·52:



5-Aminoacridine is comparable to acetamidine, and 2,5-diaminoacridine to guanidine:

5-Aminoacridine	pK_{BH^+} 9·92	Acetamidine	pK_{BH^+} 12·52
2,5-Diaminoacridine	pK_{BH^+} 11·49	Guanidine	pK_{BH^+} 13·71

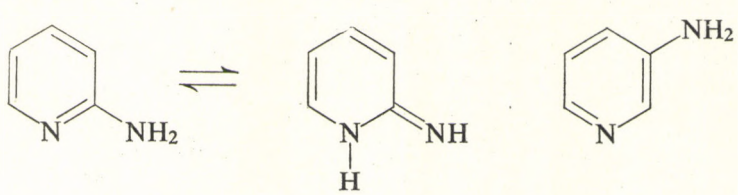
Removal of one or two benzene rings brings about only slight changes:

Acridine	pK_{BH^+}	5·60
Quinoline	pK_{BH^+}	4·94
Pyridine	pK_{BH^+}	5·23

In the case of pyridine and quinoline, the base strength is also only enhanced to a small extent when an amino group is substituted in position 3.

Analogously to 5-aminoacridine, 4-aminopyridine and 4-aminoquinoline are strong bases due to an additional resonance effect:

Base	pK_{BH^+}	*Base*	pK_{BH^+}
3-Aminopyridine	5·98	3-Aminoquinoline	4·95
4-Aminopyridine	9·17	4-Aminoquinoline	9·17
2-Aminopyridine	6·86	8-Aminoquinoline	3·99



a *b*

a = 2-Aminopyridine
b = 2-pyridonimide form

3-Aminopyridine
(behaves as aromatic amine)

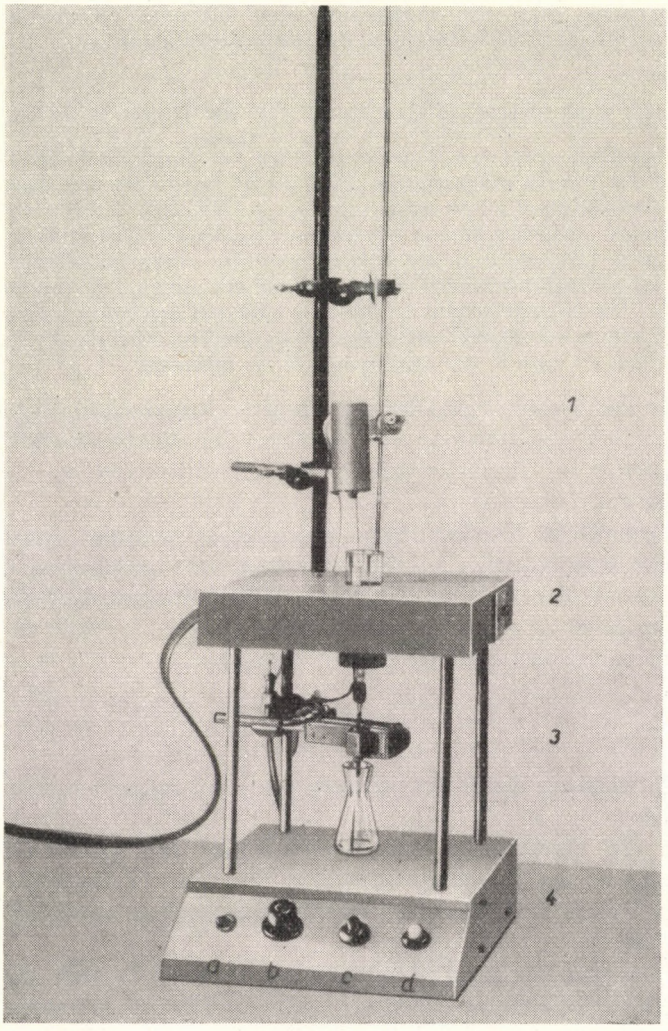
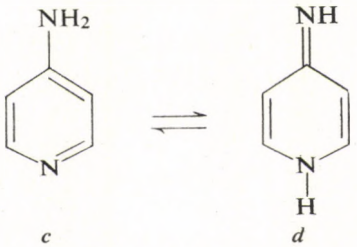


Abb. 4.16
Halbautomatischer Titrationsapparat mit Trennung durch Extraktion (SPITZY [32]). (*1* — Ständer mit Bürette und Rührer; *2* — Titrationsgefäß, umgeben von GM-Röhren; *3* — automatisches Ausflußventil; *4* — Schaltbrett)

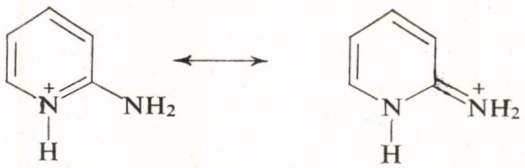
angeordnet sind. Die Zählrohre sind parallel geschaltet und können mit einem geeigneten Zählersystem verbunden sein. Diese geometrische Anordnung ist ungefähr 3,7mal wirksamer als nur ein GM-Zählrohr.

Zur Erleichterung der Entfernung der organischen Phase ist der Boden des Titrationsgefäßes keilförmig ausgebildet und endet in einer Glaskapillare mit zwei eingeschmolzenen Platindrähten in einer Entfernung von 3 mm voneinander.

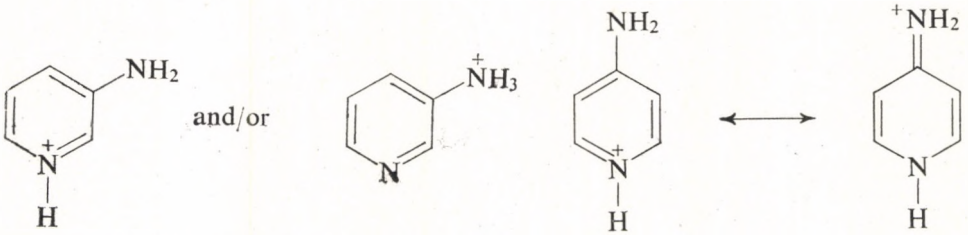


c *d*

c = 4-Aminopyridine
d = 4-pyridonimide form



2-Aminopyridinium ion



3-Aminopyridinium ion 4-Aminopyridinium ion

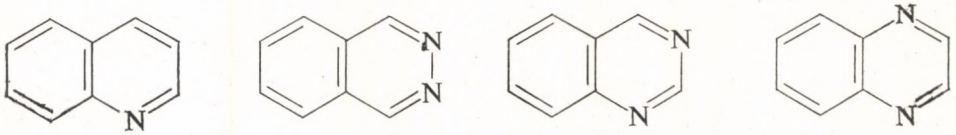
(See also: Chapter 23; Section 121 and [262, 732].)

In six-membered cyclic bases containing only one nitrogen atom, introducing a second nitrogen atom into the ring decreases base strength. The same applies also to fused heterocyclic compounds (quinoline, acridine):



Pyridine > Pyridazine (1,2-diazine) > Pyrimidine (1,3-diazine) > Pyrazine (1,4-diazine)

pK_{BH^+} 5·23 pK_{BH^+} 2·33 pK_{BH^+} 2·30 pK_{BH^+} 0·6



Quinoline > Phthalazine > Quinazoline > Quinoxaline

pK_{BH^+} 4·94 pK_{BH^+} 3·47 pK_{BH^+} 3·2 pK_{BH^+} ~ 0·8

3 — Automatisches Ablaßventil zur Beschleunigung des Titrierens. Das Ventil ist mit der Ausflußkapillare des Titrationsgefäßes verbunden. Es wird magnetisch durch einen Leitfähigkeitsmeß-Stromkreis über einen transistorisierten Verstärker gesteuert. Sobald die wäßrige Phase die in die Ausflußkapillare eingeschmolzenen Platindrähte erreicht, wird das Ventil geschlossen. Um es zu öffnen, muß der Knopf *d* am Schaltbrett 4 gedrückt werden. Dies erleichtert die Entleerung und Reinigung des Titrationsgefäßes.

4 — Schaltbrett, dahinter die elektrischen Einrichtungen. Auf der Frontplatte befindet sich der Schalter des Elektromotors *(a)*, der Drehzahlregler *(b)*, der Hauptschalter *(c)* und der Druckknopf zur Betätigung des Magnetventils *(d)*.

In das Titrationsgefaß werden 20 ml der — vorher auf den gewünschten pH-Wert eingestellten — Prüflösung gefüllt. Zu dieser werden aus einer Bürette gleiche Volumina der Titrierlösung dosiert (SPITZY z. B. arbeitete mit Dithizon in Tetrachlorkohlenstoff). Nach jeder Portion des Titriermittels wird so viel reines Lösungsmittel zugegeben, daß die organische Phase auf 5 ml ergänzt und das Volumen-Verhältnis der beiden Phasen somit konstant gehalten wird. Das Gemisch wird dann 2 Minuten lang intensiv gerührt.

Nachdem sich die beiden Phasen getrennt haben, wird die organische Lösung abgelassen. Zur vollständigen Entfernung der dithizonhaltigen Phase wird sodann mit 3 ml Tetrachlorkohlenstoff gerührt und nach Trennung der Phasen die untere Schicht ebenfalls abgelassen. Hierauf wird dann die Aktivität der gesamten wäßrigen Lösung 2 Minuten lang gemessen.

4.2.5.2. *Halbautomatischer Titrierapparat von* DUNCAN *und* THOMAS [12]

Diese — in Abb. 4.17 gezeigte — Einrichtung erleichtert die Durchführung der Titrationen dadurch besonders, daß sie die automatische Messung der

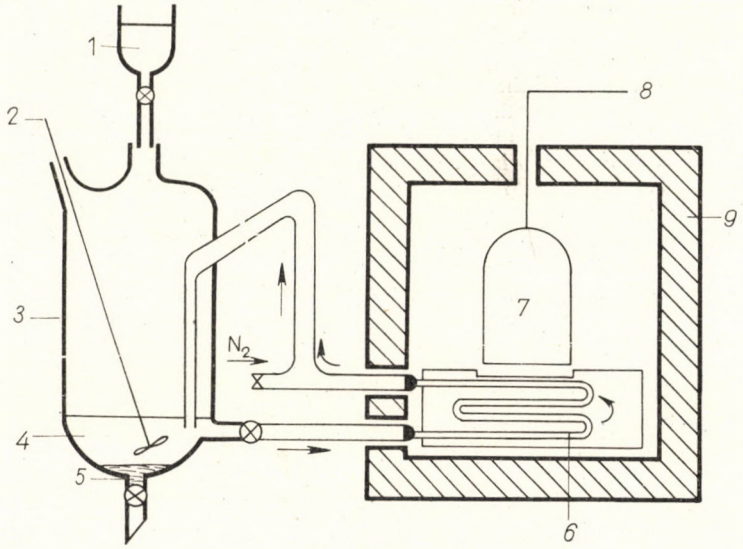
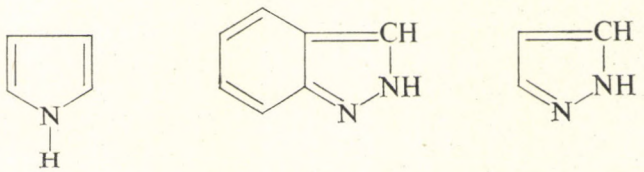


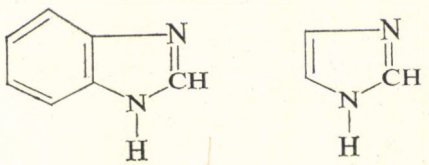
Abb. 4.17
Halbautomatischer Titrierapparat mit Trennung durch Extraktion (DUNCAN und THOMAS [12]). (*1* — Bürette; *2* — Rührer; *3* — Titrationsgefäß; *4* — wäßrige Schicht; *5* — CCl_4-Schicht; *6* — Glasrohrspirale; *7* — GM-Zählrohr; *8* — zum Zähler; *9* — Bleimantel)

Five-membered bases containing one nitrogen atom increase in base strength on introducing a second nitrogen atom into the ring:



Pyrrole < Indazole (benzpyrazole) < Pyrazole

pK_{BH^+} 0·4 pK_{BH^+} 1·3 pK_{BH^+} 2·53



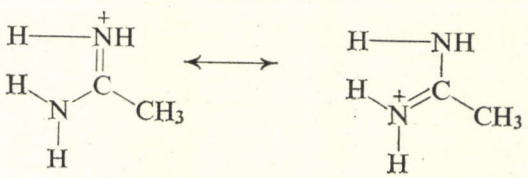
Benzimidazole < Imidazole (glyoxaline)

pK_{BH^+} 5·53 pK_{BH^+} 7·03

Thus a contrast between six-membered and five-membered systems becomes apparent. The additional ionic resonance effects due to the nitrogen atom introduced into the five-membered ring, enhance base strength:



Imidazolinium ion



Acetamidium ion

(b) *Combined M effect and I effect.* Great care is needed to decide the precise basic or acidic character of a compound on the basis of its structural formula. Thus, for instance, *p*-hydroxybenzoic acid is weaker than *m*-hydroxybenzoic acid since in the former the nucleophilic $-OH$ group is conjugated with the $-COOH$ group located in the *para* position ($+M$ effect). For this reason the electron density, and thus also the proton affinity of the carboxylate anion are enhanced.

Aktivität möglich macht. Zu bemerken ist jedoch, daß ihre Beschreibung in der Literatur ziemlich mangelhaft ist. Die Originalmitteilung enthält weder eine eingehende Beschreibung des Apparats noch eine solche seiner Funktion. Die automatische Messung der Aktivität der oberen Phase beruht auf ihrer kontinuierlichen Strömung unter einem GM-Zählrohr. Die Flüssigkeit wird, nach dem Prinzip der Mischgasheber mit Stickstoff in Strömung gehalten.

Leider haben sich die Autoren darauf beschränkt, lediglich zu erwähnen, daß dieser Apparat auf einfache Weise auch vollautomatisiert werden kann.

4.2.5.3. *Halbautomatischer Titrierapparat von* BRAUN *und* KŐRÖS [3]

Die Skizze dieser Vorrichtung zeigt Abb. 4.18. Sie ist zum Teil der von DUNCAN und THOMAS [12] beschriebenen ähnlich, ihr Anwendungsgebiet ist aber ein anderes. Während außerdem der Apparat von DUNCAN und THOMAS nur die Zirkulation der wäßrigen Phase ermöglicht, kann die Radioaktivität mit der neuen Vorrichtung sowohl in der wäßrigen als auch in der nichtwäßrigen Phase gemessen werden. Zu diesem Zweck wird die Flüssigkeit kontinuierlich unter einem Szintillationskristall durchgeleitet.

Als Detektor wird ein mit Blei abgeschirmter Universal-Detektor ungarischer Herkunft (Typ: Gamma) verwendet. An diesen sind die Titrations- und Zirkulationsvorrichtungen angeschlossen. Die Strömung der Flüssigkeit wird auch hier auf Grund des Prinzips der Mischgasheber bewirkt. Der wesentlichste Teil der Einrichtung ist das Titrationsgefäß *(1)*. Die Flüssigkeitsvolumina müssen so gewählt werden, daß die Phasengrenze zwischen die mit den Hähnen *(7)* und *(8)* versehenen Röhren zu liegen kommt. Der Extraktionsprozeß wird durch Mischen mit einem Luftstrom herbeigeführt, der mit Hilfe eines Gummiballons erzeugt und über die Röhre *(2)*, durch den Gasverteiler *(10)* in das System geleitet wird. Auf diese Weise können die beiden Phasen miteinander intensiv vermischt werden. Nach erfolgtem Vermischen läßt man die beiden Phasen sich trennen und setzt dann die Zirkulation in Gang. Je nach dem, ob die untere oder die obere Phase unter den Zähler geleitet werden soll, wird der Hahn *(7)* oder *(8)* geöffnet. Beim Öffnen des Hahnes *(7)* und Schließen des Hahnes *(8)* zirkuliert die untere (schwerere) Phase und umgekehrt. Die Zirkulation wird durch Anlegen eines schwachen Vakuums an das Rohrende *(12)* eingeleitet und dann durch Einblasen von Luft über Röhre *(5)* und Düse *(4)* in Gang gehalten. Das Röhrenpaar *(6)* führt unter dem Detektor hindurch. Die Titrierlösung wird durch das Schliffrohr *(13)* zugegeben, der Hahn *(9)* dient zum Ablassen der Flüssigkeit aus dem Röhrensystem.

4.3. Endpunktbestimmung unter Anwendung fester Indikatoren

4.3.1. *Prinzip der Methode*

BRAUN, MAXIM und GALATEANU [4, 5] entwickelten ein neues Verfahren für die radiometrischen Komplexbildungstitrationen. Es werden sogenannte feste Indikatoren angewandt.

It is well known that the hydroxyl group exerts a $-I$ effect: however, in this case the inductive effect is outweighed by the release of electrons towards the aromatic ring ($+M$ effect). In *m*-hydroxybenzoic acid the $+M$ effect is largely lacking at the $-CO_2H$ group, and the governing effect is the $-I$ effect of the $-OH$ group (see also: below (c)).

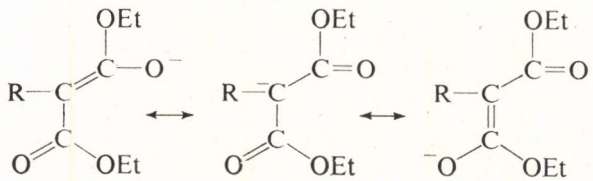
In the case of aromatic amines, e.g. aniline, the proton affinity of the $-NH_2$ group is smaller than in methylamine because of the electron withdrawing power of the ring. In benzylamine, owing to the CH_2 group interposed between the ring and the NH_2 group, the conjugation between the aromatic ring and the amino nitrogen is broken and thus benzylamine is a stronger base than aniline. In saturated aliphatic amines the orientation of the dipole is $R \rightarrow NH_2$, in aromatic amines $Ar \leftarrow NH_2$ [26]. In these systems an opposed mesomeric electric moment occurs which, in some cases, exceeds the electrostatic moment:

$$(\delta+)\ \text{alkyl} \longrightarrow NR_2\ (\delta-); \qquad (\delta-)\ \text{aryl} \longrightarrow \ddot{N}R_2\ (\delta+)$$

(c) *Stabilization due to resonance.* The stabilization due to resonance in acids and their conjugate bases is an important factor. On comparing the acidity of alcohols with that of aliphatic carboxylic acids it can be seen that the stronger acidic character of the latter is due to the stabilization of the carboxylate anion as a result of resonance. The two oxygen atoms in the anion possess equal though diminished proton-binding ability since the negative charge is more dispersed:



The enolate anion can also stabilize by resonance, which enhances acid strength (p. 442 in [346]). Diethyl malonate can be titrated as an acid in dimethylformamide or in a benzene–pyridine mixture. (Chapter 17, and [893].)



(d) *Effect of resonance forms and substituents on the strength of substituted benzoic acids* [79, 173, 189, 863]. A substituent influences the strength of a benzoic acid according to its electrophilic or nucleophilic nature and depending on the location of the $-COOH$ group. The substitution of a hydrogen atom of the benzene ring by a more powerful electrophile than hydrogen causes the electrons of the carboxyl O–H bond to become more localized on the oxygen atom, thus

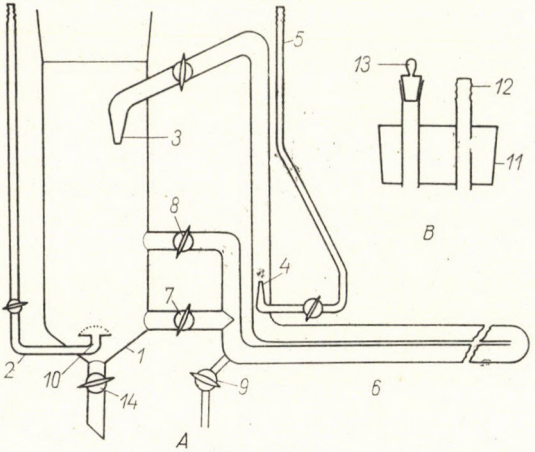


Abb. 4.18a
Halbautomatischer Titrierapparat mit Trennung durch Extraktion (BRAUN und KŐRÖS [3]). (*1* — Titrationsgefäß; *2* — Lufteinleitungsrohr für Misch-Luft; *3* — Rückleitungsrohr; *4* — Düse; *5* — Gaseinleitungsrohr; *6* — Doppel-Glasröhre unter dem Detektor; *7* und *8* — Hähne; *9* — Ablaßhahn; *10* — Düse zur Einleitung von Luft; *11* — Gummistopfen; *12* — Anschluß für Vakuum; *13* — Zuflußrohr; *14* — Ablaßhahn)

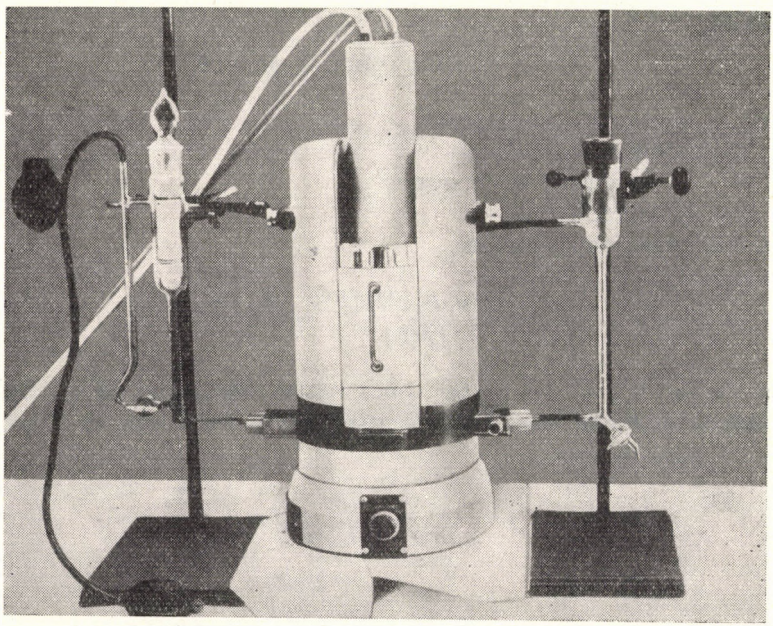
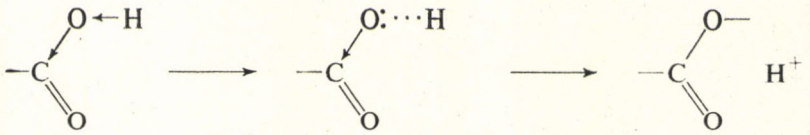


Abb. 4.18b
Fotografie des Titrierapparats

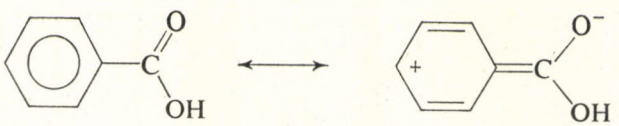
facilitating the mobility of the proton of the carboxyl group:



The effect of the substituent is transmitted both through the molecule and through space ('field effect'). Both effects operate in the same sense and diminish with increasing distance from the COOH group.

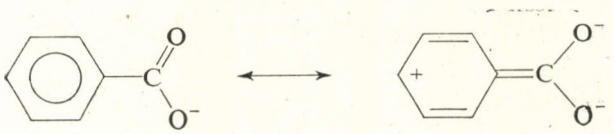
Acid	$K_{acid} \times 10^5$
$C_6H_5 . COOH$	6·30
$C_6H_5 . CH_2 . COOH$	4·88
$C_6H_5 . CH_2 . CH_2 . COOH$	2·19

Since other effects besides those mentioned above are involved, the strength of benzoic acid needs further explanation. There are various reasons for the K_{acid} value of benzoic acid being $6{\cdot}30 \times 10^{-5}$, and not more. For instance, benzoic acid is stabilized in an undissociated dipolar-ion form *(b)*: the stability of the benzoate anion is, at the same time, decreased by contributions from resonance forms *(c)* and *(d)*. In the resonance form *(d)* the negative charge density of the oxygen atoms is enhanced. Dissociation of the proton, that is, the development of acid characteristics is hindered to a certain extent.



a *b*

Resonance forms of benzoic acid



c *d*

Resonance forms of benzoate anion

This line of reasoning is supported by the fact that *ortho*-substituted benzoic acids (in aqueous media) are, independently of the substituent, stronger than benzoic acid itself. Such substituents, presumably, inhibit planar conformations and so decrease the possibility that structures *(b)* and *(d)* should be formed. (See: Table 8, except for *o*-aminobenzoic acid.)

Wenn eine Komponente M mit einem Komplexbildner L titriert und der Endpunkt radiometrisch angezeigt werden soll, muß während der Titration die Aktivität von M, von L oder von ML als Funktion der Konzentration des dosierten L getrennt verfolgt werden. Man kann den Endpunkt radiometrisch auch anzeigen, wenn man zu der die zu bestimmende Komponente M enthaltenden Lösung auch eine schwerlösliche feste Verbindung ($M_i B$) zugibt, deren markiertes Kation mit dem Komplexbildner L gleichfalls reagiert (fester Indikator).

Vorbedingung der Endpunktanzeige ist, daß die Komponente M_i während der Titration mit dem Chelatbildner L nur dann zu reagieren beginnt, wenn die zu titrierende Komponente M bereits vollständig verbraucht wurde. Den Eintritt der Komponente $^*M_i$ in den Komplex charakterisiert die folgende Lösungsreaktion:

$$^*M_i B + L \rightleftarrows {}^*M_i L + B\,.$$

Zur Endpunktanzeige kann also der Übergang eines radioaktiven Isotops aus der festen in die flüssige Phase verwertet werden, in dem man die Änderung der Löslichkeit eines markierten Niederschlages während der Titration in einem heterogenen System verfolgt.

Bei der Wahl des Indikatorniederschlages müssen die sowohl im Endpunkt als auch nach diesem bestehenden Gleichgewichte berücksichtigt werden. Die Gleichgewichte im Endpunkt veranschaulicht die folgende Gleichung:

$$^*M_i B + ML \rightleftarrows {}^*M_i L + M + B,$$

$^*M_i$ = markierte Komponente
B = Niederschlagsbildner
M = zu titrierende Komponente
L = Komplexbildner.

Die Gleichgewichtskonstante

$$K_1 = \frac{[^*M_i L]\,[M]\,[B]}{[ML]} = \frac{K_2' \cdot K_S'}{K_1'}$$

kann aus den K_1', K_2' und K_S' berechnet werden. Diese sind die scheinbaren Stabilitätskonstanten bzw. Löslichkeitsprodukte der folgenden Komplexe bzw. des Niederschlags:

$$ML \rightleftarrows M + L\,; \quad K_1' = \frac{[ML]}{[M']\,[L']} = \frac{K_1}{\alpha_{M(X)}\,\alpha_{L(A)}}$$

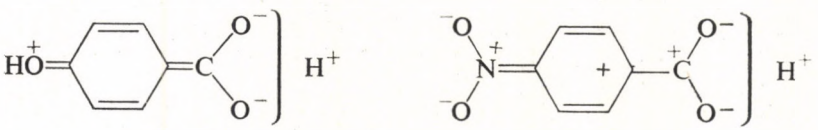
$$^*M_i L \rightleftarrows {}^*M_i + L\,; \quad K_2' = \frac{[^*M_i L]}{[^*M_i']\,[L]} = \frac{K_2}{\alpha_{M_i(X)}\,\alpha_{L(A)}}$$

$$\downarrow\ ^*M_i B \rightleftarrows {}^*M_i + B\,; \quad K_S = [^*M_i]\,[B]\,.$$

The acidity due to the effect transmitted in the resonance forms of benzoic acid or the benzoate anion may be either lessened or enhanced by substituents in the *ortho* or *para* position:

$-OH$, $-OCH_3$, $-NH_2$ } Electron releasing groups

$-NO_2$, $-CN$ } Electron attracting groups



e

Resonance form of *p*-hydroxybenzoic acid [173] Resonance form of *p*-nitrobenzoic acid

The above formulae show that the OH group in the *para* position enhances but the NO_2 group in a *para* position diminishes the resonance effect *(b)* and *(d)*. Structure *(e)* demonstrates that the resonance effect is *contrary* to the acid-strengthening inductive effects of the OH substituent ($-I$, $+M$ effects). Structure *(f)* indicates that the acid-strengthening inductive effect of the NO_2 group is *enhanced* by resonance ($-I$, $-M$ effects):

Acid	$K_{acid} \times 10^5$
p-Hydroxybenzoic acid	2·63 [173]
p-Nitrobenzoic acid	37·6 [173]
Ratio	1 : 14·3

A substituent in the *meta* position does not take part in substantial resonance interaction. Its influence, therefore, is almost entirely due to 'second-order' inductive effects.

Hydrogen-bonding also influences strength in *ortho*-substituted benzoic acids. In some cases it enhances, in others again it diminishes the acid character, dependent on the solvent (see: Chapter 2; Section 16 (a) and [173]). The acid strength of salicylic acid increases owing to the formation of a chelate ring between phenolic hydrogen and carboxyl oxygen. The anion is stabilized by the chelate ring and this applies to an even greater extent in, e.g., 2,6-dihydroxybenzoic acid (see also: Section 28 (c) of this Chapter, and [29, 81, 227]).

These examples give indications about the possibility of titrimetric determination of a given compound, acid or base, in relation to its structure.

(e) *Resonance forms and acidity of ketones, 1,3-diketones, pyrroles and cyclopentadiene.* In ketones, and to a far greater extent, in 1,3-diketones a hydrogen atom in the α-position has some acidic character (Table 10). The resonance hybrid of the anion resulting from elimination of the proton can be symbolized in the following way:

Zur erfolgreichen Titration muß der Wert von K_I möglichst klein sein, um die Verschiebung der Endpunkt-Reaktion in Richtung des unteren Pfeiles vernachlässigen zu können.

Nach dem Endpunkt muß das folgende Gleichgewicht berücksichtigt werden:

$$*M_i B + L \rightleftharpoons M_i L + B .$$

Die Gleichgewichtskonstante dieser Reaktion ist:

$$K_{II} = \frac{[*M_i L]\,[B]}{[L]} .$$

Die Symbole haben hier die gleiche Bedeutung wie oben.

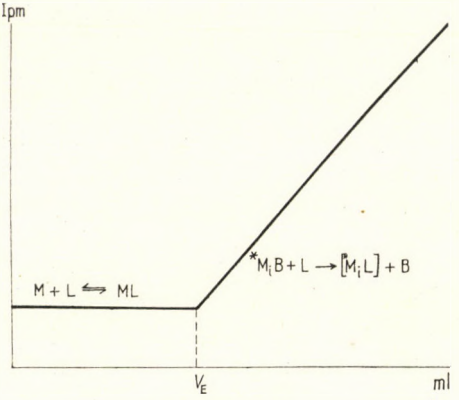


Abb. 4.19
Theoretische Titrationskurve der komplexometrischen Titration unter Anwendung eines festen Indikators

Zur eindeutigen Durchführung der Titration muß die Konstante K_{II} möglichst groß sein, damit die Lösung von $*M_i B$ mit dem Überschuß von L vollständig vor sich geht. Eine theoretische Titrationskurve zeigt Abb. 4.19.

4.3.2. *Typen der Titrationen: direkte, indirekte und Rücktitration*

Bei den Direkt-Titrationen werden die zu bestimmenden Ionen mit dem Komplexbildner in Gegenwart des entsprechenden festen Indikators unmittelbar titriert.

Eine Methode zur Direkt-Titration von Calcium, Magnesium und Strontium mit ÄDTE unter Anwendung von $^{110m}AgIO_3$ als festen Indikator wurde ausgearbeitet [5].

Die Funktion des $*AgIO_3$-Indikators beim Endpunkt der Calciumbestimmung z. B. wird durch das folgende Gleichgewicht geregelt:

$$\downarrow *AgIO_3 + CaY^{2-} \rightleftharpoons *AgY^{3-} + Ca^{2+} + IO_3^- .$$

Die Gleichgewichtskonstante ist:

$$K_I = \frac{[AgY^{3-}]\,[Ca^{2+}]\,[IO_3^-]}{[CaY^{2-}]} = \frac{K'_{AgY} \cdot K'_{S(AgIO_3)}}{K'_{CaY}} ,$$

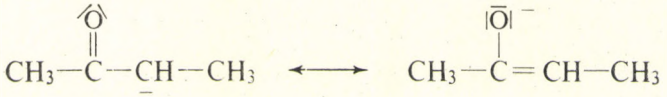
darin ist

$$K_{S(*AgIO_3)} = [*Ag^+]\,[IO_3^-] = 10^{-7{,}3}$$

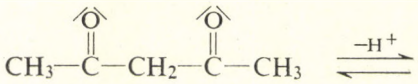
$$K'_{AgY} = \frac{K_{AgY}}{\alpha_{Ag(OH)}\,\alpha_{Y(H)}} \quad \text{und} \quad K'_{CaY} = \frac{K_{CaY}}{\alpha_{Ca(OH)}\,\alpha_{Y(H)}} .$$

Werden die Werte von K'_{AgY} und K'_{CaY} bei pH = 10 in die Formel der Konstanten K_I eingesetzt, so ergibt sich:

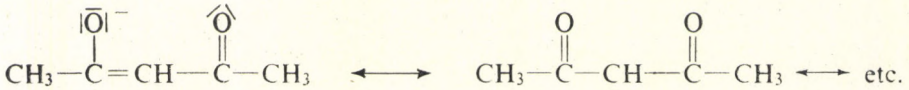
$$K_I \approx 10^{-10} .$$



Methyl ethyl ketone anion (very strong base)

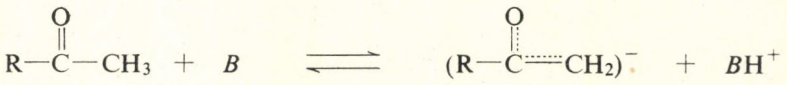


Acetylacetone (titratable in butylamine with sodium methoxide in the presence of thymol blue [246]



Acetylacetone anion; resonance forms

Keto-enol tautomerism can be considered as a migration of a proton within the molecule and thus it is understandable that as a consequence of the catalytic effect of a base *(B)* enolization starts with the formation of an enolate anion (cf. p. 368 in [380]):



The conjugate acid of acetone can also be represented by a resonance hybrid structure.



This structure lies between that of an oxonium ion and a carbenium ion (see: Chapter 2; Sections 19 (a) and (c). Regarding the conjugate base of acetone see: Table 10, and: Chapter 6; Section 36, and [380, 729].

In dibenzoylmethane and ω-nitroacetophenone the aci-form is stabilized by an intramolecular H-bond. In toluene solution the content of aci-form of ω-nitroacetophenone has been reported as about 10% (p. 233 in [745] and [744]), however, recent p.m.r. studies imply that it exists exclusively in the simple nitroketone form (T. Simmons et al. *J. Org. Chem.* 1966. **31,** 2400):

Der berechnete Wert zeigt, daß bei pH = 10 die Verschiebung des oberen Gleichgewichtes in Richtung des oberen Pfeiles vernachlässigt werden kann und sich demzufolge der $*AgIO_3$-Indikator bei der Titration mit ÄDTE so lange nicht in bemerkenswerter Menge löst, bis in der Lösung die zu titrierenden Ca^{2+}-Ionen vorliegen. Nach dem Endpunkt hat man es mit der folgenden Reaktion zu tun:

$$\downarrow *AgIO_3 + Y^{4-} \rightleftarrows *AgY^{3-} + IO_3^-$$

mit der Gleichgewichtskonstante:

$$K_{II} = \frac{[*AgY^{3-}]\,[IO_3^-]}{[Y^{4-}]} = K_S \cdot K'_{AgY}.$$

Wird in diese Gleichung der dem pH = 10 entsprechende Wert von K'_{AgY} eingesetzt, so ergibt sich

$$K_{II} \approx 1\,.$$

Dies bedeutet, daß sich das Gleichgewicht (der Lösungsreaktion) bei pH = 10 vollständig in Richtung des oberen Pfeiles verschiebt, d. h. der $*AgIO_3$-Niederschlag löst sich im Überschuß der ÄDTE vollständig auf.

Die beim Calcium erhaltenen Titrationskurven zeigt Abb. 4.20. Mit Erfolg ist diese Methode auch zur Titration von Kupfer und Zink mit ÄDTE (unter Anwendung des gleichen Indikators) einzusetzen [5, 14]. Auch zur Bestimmung des Kupfer-Gehaltes von Messing und Bronze wurde dieses Verfahren angewandt [14].

Unter Anwendung genannten Prinzips haben SPITZY und Mitarbeiter [38] die radiokomplexometrische Mikrotitration von Magnesium, Nickel, Zink, Kupfer und Blei unter Anwendung von festem Silberjodat als Indikator, ausgearbeitet.

Bei einer für Kupfer und Zink entwickelten vereinfachten Schnellmethode wird zuerst eine Suspension von $^{110m}AgIO_3$ enthaltende wäßrige Lösung bei pH = 10 mit

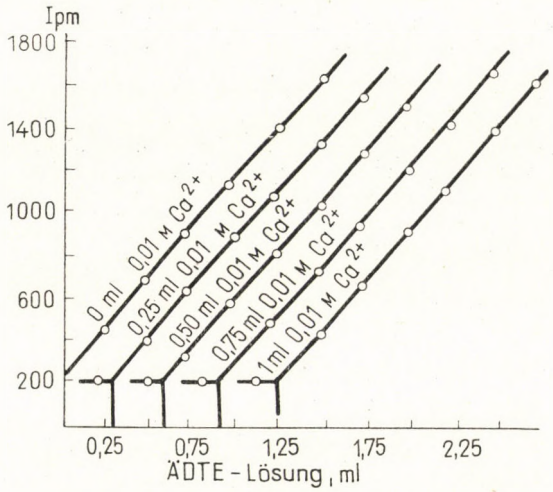


Abb. 4.20
Titration von Ca mit ÄDTE unter Anwendung von $^{110m}AgIO_3$ als festen Indikator (BRAUN, MAXIM und GALATEANU [5])

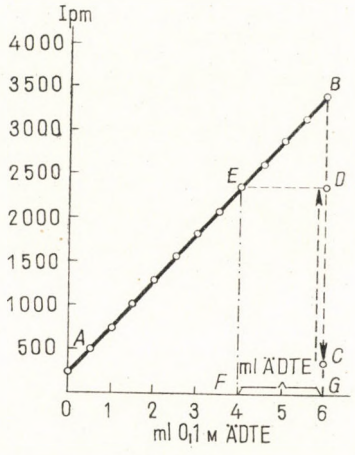
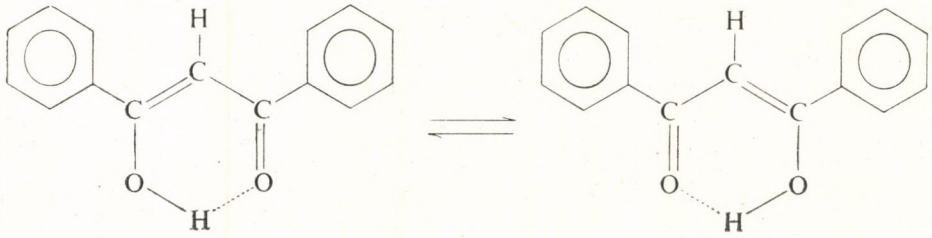
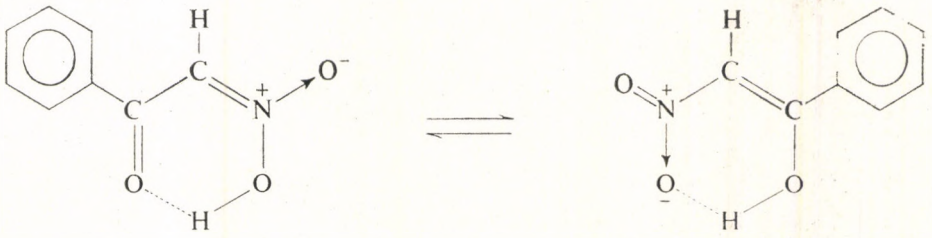


Abb. 4.21
Titration von Zn mit ÄDTE in Gegenwart von $^{110m}AgIO_3$ als festen Indikator (BRAUN [1])

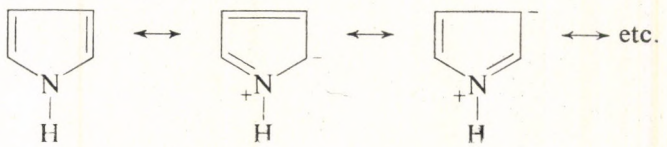


Dibenzoylmethane, aci-form
(Titratable with sodium methoxide in dimethylformamide in the presence of thymol blue [246])

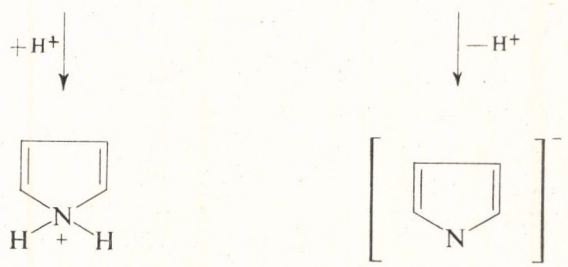


ω-Nitroacetophenone, aci-form

The combined effect of the aromatic ring and the possibility of resonance forms provide an explanation for the very low basicity of pyrrole, and for the acid character of cyclopentadiene which does not, however, contain enolic hydroxyl (p. 65 in [393] and p. 340 in [870]).



Pyrrole
(Very weak acid and base)
pK_a 16·5



Pyrrole cation
(Very strong acid)
pK_{BH^+} 0·4

Pyrrole anion
(Very strong base)

ÄDTE titriert und die Radioaktivität der Lösung gemessen [14]. Die Titrationskurve wird durch die in Abb. 4.21 gezeigte Gerade AB wiedergegeben. Die Reaktion geht nach der Gleichung

$$[H_2Y]^{2-} + {}^{110m}AgIO_3^{\downarrow} \rightleftarrows [{}^{110m}AgY]^{3-} + \\ + IO_3^- + 2\,H^+$$

vor sich. Dann wird der pH der Lösung auf 5 eingestellt und die Aktivität erneut gemessen. Nach dem Ansäuern sinkt die Aktivität von *B* auf *C* (Abb. 4.21). $^{110m}AgIO_3$ wird aus der Lösung (der umgekehrten Reaktion entsprechend) wieder gefällt.

Nun wird die das zu bestimmende Zink und Kupfer enthaltende Lösung zugegeben und der pH wieder auf 10 eingestellt, worauf folgende Umsetzungen stattfinden

(a) $[H_2Y]^{2-} + Zn^{2+} \rightleftarrows [ZnY]^{2-} + 2\,H^+$.

(b) Auflösung des $^{110m}AgIO_3$ in der restlichen ÄDTE.

Die Radioaktivität der Lösung steigt dann nur bis zum Wert *D*, da ein Teil der ÄDTE zum Komplexieren des Zinks oder Kupfers verbraucht wird (vgl. *ED* und *FG* auf Abb. 4.21).

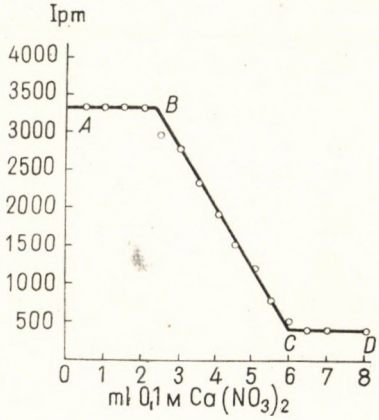


Abb. 4.22
Bestimmung von Al durch Rücktitration mit $Ca(NO_3)_2$ in Gegenwart von $^{110m}AgIO_3$ als festen Indikator (BRAUN [1])

Die radiokomplexometrische Bestimmung von Eisen in den Rohstoffen der Zement- und Baumaterialien-Industrie unter Verwendung von mit ^{91}Y markiertem Yttriumoxalat haben LIEBERMAN und Mitarb. beschrieben [25].

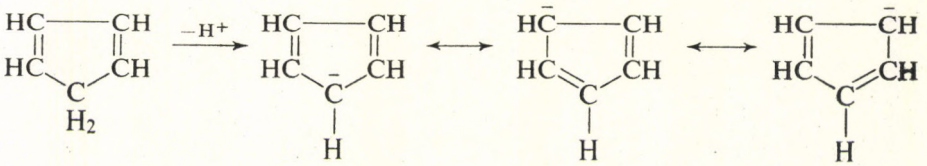
Bei den *indirekten Titrationen* wird die zu bestimmende Komponente mit Hilfe eines Ions gefällt, das nach der Isolierung und Auflösung des Niederschlages radiokomplexometrisch direkt titriert werden kann.

Zur Bestimmung von Natrium wird dieses zuerst als Natrium–Zink–Uranylacetat gefällt, der Niederschlag isoliert, aufgelöst und Zink in Gegenwart von Silberjodid, als festem Indikator, mit ÄDTE titriert [1]. Auf ähnliche Weise kann auch Wolfram, nach Fällung als Calciumwolframat, bestimmt werden; der Niederschlag wird aufgelöst und sein Calciumgehalt titrimetrisch erfaßt.

Feste Indikatoren können auch bei *Rücktitrationen* angewandt werden. Solche Bestimmungen führt man vorzugsweise dann durch, wenn die Reaktion zwischen den zu bestimmenden Ionen und dem Komplexbildner sehr langsam vor sich geht.

Zur Aluminiumbestimmung [1] wird zu einer Al^{3+} enthaltenden, auf pH = 3 eingestellten Lösung ein bekannter Überschuß von ÄDTE-Lösung zugegeben. Das Gemisch wird erwärmt, auf pH 9 gebracht und eine Suspension von markiertem Silberjodat eingetragen. Ein Teil der zugegebenen ÄDTE wird zur Komplexierung des Aluminiums verbraucht, der Rest löst den festen Indikator auf. Das System wird hierauf mit Standard-Calciumnitratlösung titriert und die Radioaktivität der Lösung nach Zugabe jeder Portion des Titriermittels gemessen.

Abb. 4.22 zeigt die erhaltene Titrationskurve. Im Abschnitt *AB* reagiert Ca^{2+} mit der überschüssigen ÄDTE, während im Abschnitt *BC* die Ca^{2+}-Ionen aus dem



Cyclopentadiene Cyclopentadienyl anion

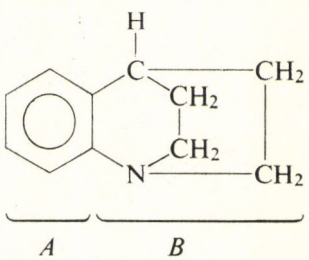
Finally it should be pointed out that aromatic compounds containing $-OH$, $=NH$, $\rangle CH$ groups are acid analogues though this cannot be considered as a general rule. The acid strength of more complex molecules is enhanced when the negative charge of the anion is not concentrated on a single atom alone but, as a result of electron redistribution, spreads over other atoms within the molecule ([53, 263, 567, 884]; Table 10).

28. Influence of Steric Hindrance on the Strength of Acids and Bases

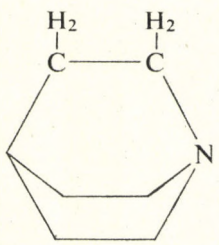
Dissociation of acids, strength of bases and salt formation are influenced by the steric requirements of the substituents and their steric arrangement within the molecule.

(a) *Steric hindrance effects on resonance.*

Steric hindrance is important from the viewpoint of resonance effects. In this context, characteristic examples are benzoquinuclidine [867] and N,N-dimethylpicramide and acid analogues, e.g. 3,5-dimethylphenol, 3,5-dimethyl-4-cyanophenol and 3,5-dimethyl-4-nitrophenol.



Benzoquinuclidine, pK 6·21



Quinuclidine pK 3·35

Benzoquinuclidine is a stronger base than dialkylaniline derivatives and phenylpiperidine:

Dimethylaniline,	pK 8·94
Diethylaniline,	pK 7·44
N-Phenylpiperidine,	pK 8·80

Its enhanced base strength cannot be attributed to the bicyclic system *(B)* since quinuclidine itself is a weaker base than piperidine (pK 2·80). It may be assumed that in the case of benzoquinuclidine the formation of resonance forms decreasing base strength is influenced by steric effects: carbon atoms directly bonded to the nitrogen atom cannot be co-planar with the aromatic ring, so that the possibility of resonance forms resulting in a base weakening effect lessens. So it is comprehen-

ÄDTE-Silberkomplex Ag^+-Ionen in Freiheit setzen, die durch das in der Lösung befindliche Jodat gefällt werden. Demzufolge nimmt die Radioaktivität der Lösung ab. Nachdem alles Ag^+ gefällt ist, bleibt die Radioaktivität der Lösung konstant (Abschnitt *CD*), da das Ca^{2+} nicht fähig ist, Al^{3+} aus dem ÄDTE-Komplex zu verdrängen.

Während der Titration spielen sich die folgenden Reaktionen ab:

$$[H_2Y]^{2-} + Ca^{2+} \rightleftarrows [CaY]^{2-} + 2\,H^+ \quad (AB)$$

$$[^{110m}AgY]^{3-} + Ca^{2+} \rightleftarrows [CaY]^{2-} + {}^{110m}Ag^+$$

$$^{110m}Ag^+ + IO_3^- \rightleftarrows {}^{110m}AgIO_3 \quad (BC).$$

4.3.3. *Anwendung fester radioaktiver Kryptonate*

Eines der neuesten Anwendungsgebiete der radioaktiven Kryptonate (d. s. feste Stoffe, die das radioaktive Nuclid ^{85}Kr enthalten) wurde von CHLECK [8, 9] beschrieben. Es gelang ihm, diese Stoffe zur Endpunktbestimmung bei radiometrischen Titrationen zu verwenden. ^{85}Kr wurde in verschiedene Feststoffe (u. a. Elemente, anorganische und organische Verbindungen, Legierungen, Gläser) eingeführt. Zur Herstellung dieser »Kryptonate« wurden zwei verschiedene Methoden verwendet:

(a) Beschuß des Trägers mit beschleunigten Kryptonionen bei niederen Drücken.

(b) Diffusion von gasförmigem Krypton in feste Stoffe.

Die hergestellten Kryptonate enthalten ^{85}Kr in den Oberflächenschichten der Feststoffe konzentriert. Sie zeigen selbst bei höheren Temperaturen relativ hohe Stabilität.

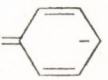
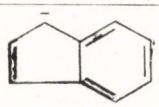
Eine wesentliche Eigenschaft der Kryptonate ist, daß bei Abtragung oder beim Abbau ihrer Oberflächen – unabhängig davon, ob dies auf chemischem oder physikalischem Wege geschieht – das radioaktive Krypton in einer der Zerstörung der Oberfläche proportionalen Menge frei wird.

Die Anwendung der radioaktiven Kryptonate zur Endpunktanzeige beruht auf der Umsetzung des Titriermittelüberschusses mit dem Kryptonat. Sie zerstört seine Oberfläche und führt so zur Freisetzung von gasförmigem radioaktivem Krypton, das von den übrigen Komponenten des Systems leicht abgetrennt werden kann. Eine solche Reaktion eignet sich zur Endpunktanzeige aber nur dann, wenn das betreffende Kryptonat wohl mit dem Titriermittel, nicht aber mit der Prüflösung reagiert.

^{65}Zn-Kryptonat wird als Indikator zur Titration von Fluorid mit Thoriumnitrat verwendet [8]. Nachdem das Fluorid verbraucht ist, hydrolysiert überschüssiges Thoriumnitrat und die gebildeten Wasserstoffionen reagieren mit dem Kryptonat. Gut auswertbare Endpunkte werden herab bis zu Konzentrationen von 10^{-4} N erhalten und 2 μg Fluorid/ml sind noch zu bestimmen. Da der Endpunkt nicht stöchiometrisch ist, wird er mit Hilfe einer Eichkurve (Abb. 4.23) ermittelt.

Table 10

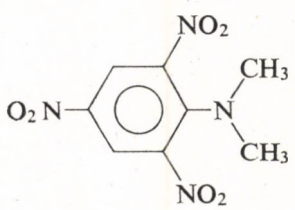
EXTREMELY WEAK ACIDS POSSESSING MOBILE HYDROGEN (PSEUDO ACIDS)

Compound	pK_{acid}	*Structure of Conjugate Base*	*Comments*
Ammonia	~ 36		
Diphenylmethane	~ 35		
Triphenylmethane	~ 33	$(C_6H_5)_2C=$  , etc.	The negative charge can also be on an *ortho* C atom
Aniline	27		
Acetylene	26		
Diphenylamine	23		
Indene	21		The negative charge can be on C_1 or C_3
Phenylacetylene	21	$C_6H_5C{\equiv}C^-$	
Acetone	19	$(CH_3CO\ CH_2)^-$	The enol content of acetone is $2{\cdot}5\times10^{-4}$ % [729] [380]
Acetophenone	19	$(C_6H_5CO\ CH_2)^-$	
t-Butanol	19	$(CH_3)_3C-O^-$	
Benzyl alcohol	18		
Pyrrole	16·5		See: Chapter 4; Section 27 (e)
Methanol	16—17		
Ethyl malonate	12·9		See: Chapter 4; Section 27 (c). In the case of sodium salts the carbanion form is probable
Acetylacetone	9·03*		See: Chapter 4; Section 27 (e)

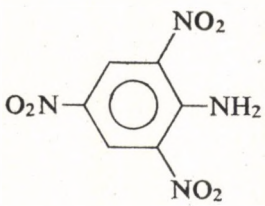
* Maroni and Calmon, *Bull. soc. chim. France* **1964,** 519.

sible for quinuclidine to be the strongest base, followed in order by benzoquinuclidine, while dialkylaniline derivatives, owing to the occurrence of resonance forms, are of lower base strength.

Example: N,N-dimethylpicramide:



K_{base} 2×10^{-19}



K_{base} $5{\cdot}16\times10^{-24}$

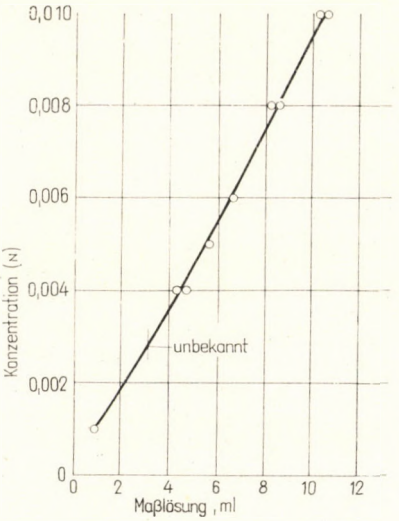


Abb. 4.23
Titration von NaF mit $Th(NO_3)_4$ unter Anwendung von ^{65}Zn-Kryptonat als festen Indikator (CHLECK [8])

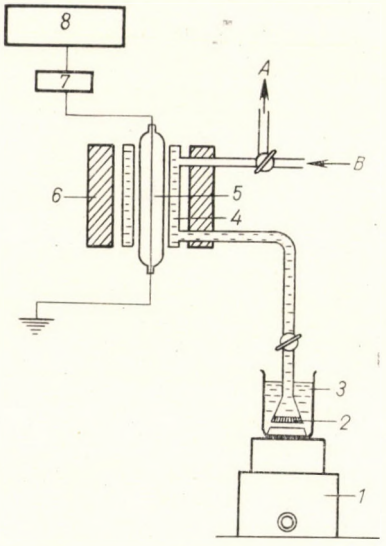


Abb. 4.24
Vorrichtung zur Durchführung radiokomplexometrischer Titrationen unter Anwendung von festen Indikatoren und Trennung durch Filtration (BRAUN [1]). (*1* — Rührer; *2* — Saugrohr mit Glasfilter; *3* — Titrationsgefäß; *4* — Glasmantel; *5* — GM-Zählrohr; *6* — Bleimantel; *7* Vorverstärker; *8* — Zähler; *A* — Luft; *B* — Vakuum)

4.3.4. *Titrierapparate und Technik der Titrationen*

Die bei Anwendung von festen Indikatoren eingesetzten Titrationsapparate weichen nur wenig von den zu radiometrischen Titrationen allgemein verwendeten ab. Wird der feste Indikator in Form einer Suspension eingesetzt, so kann die Phasentrennung durch Filtration, Zentrifugieren oder Flotation vorgenommen werden.

Zur Trennung durch Filtration wird der in Abb. 4.24 gezeigte Apparat [1], bzw. eine Vorrichtung [25] nach Abb. 4.25 verwendet. Zur Trennung durch Flotation dient die durch Abb. 4.26 veranschaulichte Einrichtung [1].

Wie die Trennung, ist auch die Titration als solche diskontinuierlich. Diese Diskontinuität ist der größte Nachteil und stellt der Automatisierung schwere Hindernisse in den Weg. Er kann jedoch überwunden werden, wenn man den festen Indikator auf einem Träger fixiert.

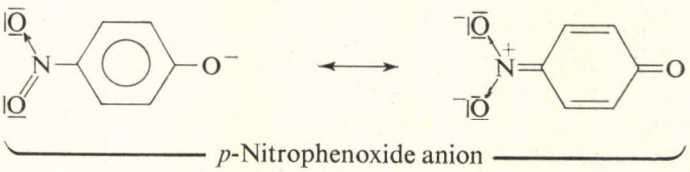
Chromatographisches Filterpapier hat sich als Träger bestens bewährt [3, 6]. Der Niederschlag wird auf den Fasern des Filterpapiers frisch gefällt und die erhaltenen Niederschlag-Membranen werden, in einen geeigneten Rahmen gespannt, einfach in

N,N-Dimethylpicramide is about forty thousand times as strong a base as picramide (2,4,6-trinitroaniline). Introducing the two methyl groups obviously does not account for this large difference because dimethylaniline is only 3·3 times stronger than aniline. Nitro groups in the *ortho* position prevent the dimethylamino group being co-planar with the ring [88].

Methyl substitution in positions 3 and 5 decreases the acidity of phenol by 0·19, of *p*-hydroxyphenyl cyanide by 0·26, and of *p*-nitrophenol by 1·11 p*K* units [871]:

Acid Analogue	p*K*
Phenol	9·99
3,5-Dimethylphenol	10·18
p-Hydroxyphenyl cyanide	7·95
3,5-Dimethyl-4-cyanophenol	8·21
p-Nitrophenol	7·14
3,5-Dimethyl-4-nitrophenol	8·25

The *p*-nitrophenoxide anion is stabilized by its quinonoid mesomeric form and the nitro group is co-planar with the quinonoid ring. The formation of the coplanar form is hindered by methyl substitution in the *ortho* positions and the resonance of the nitrophenoxide anion with the ring is inhibited (Fig. 27):



Electron density on the oxygen atom of 3,5-dimethyl-4-nitrophenoxide increases, so enhancing its proton affinity, and decreasing its acid strength [871].

The situation is different in the case of 3,5-dimethyl substitution of a ring containing a CN group. Methyl substitution only slightly decreases acid strength owing to the linear structure of the $-C{=}N$ group, and the anion is stabilized by resonance.

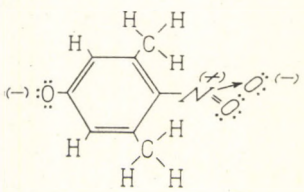


Fig. 27. 3,5-Dimethyl-4-nitrophenoxide anion

(b) *Backstrain theory.* Brown and his collaborators have discussed in some detail the problem of a steric effect of a character different from that previously discussed, but which also influences the strength of organic bases [94, 95, 96, 97, 98].

Alkyl groups are electron releasing, so the nitrogen atom of methylamine is more nucleophilic than the nitrogen of ammonia. Dimethylamine, however, is only slightly

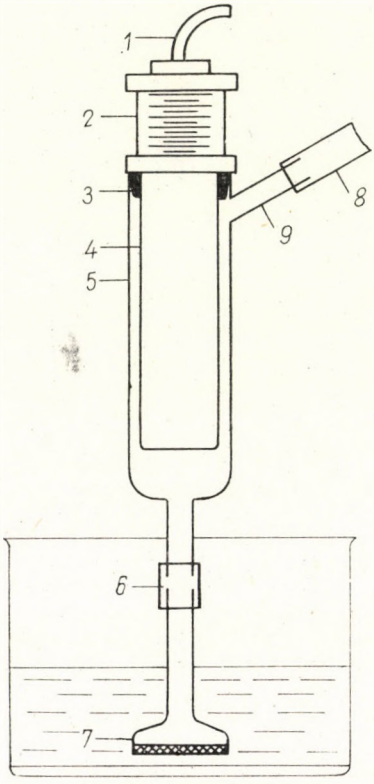


Abb. 4.25
Apparat zur Durchführung radiokomplexometrischer Titrationen unter Anwendung von festen Indikatoren und Trennung durch Filtration (LIEBERMAN und Mitarb. [25]). (*1* — Hochspannungskabel; *2* — GM-Röhren-Anschluß und -Fassung; *3* — Gummistopfen; *4* — GM-Röhre; *5* — Glasgefäß zur Auflösung; *6* — Gummischlauch; *7* — Glasfritte; *8* — Gummischlauch zur 100-ml-Spritze; *9* — Seitenrohr des Glasgefäßes)

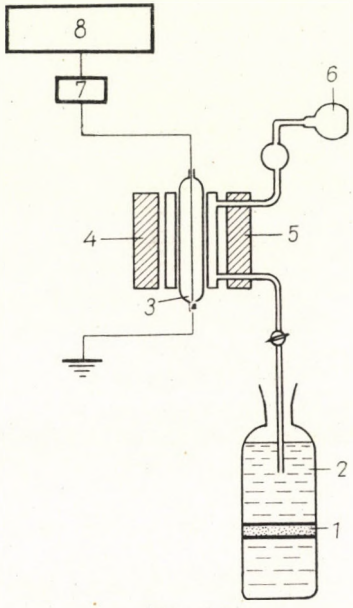


Abb. 4.26
Apparat zur Durchführung radiokomplexometrischer Titrationen unter Anwendung von festen Indikatoren und Trennung durch Flotation (BRAUN [1]). (*1* — Niederschlag; *2* — Titrationsgefäß; *3* — GM-Röhre; *4* und *5* — Bleimantel; *6* — Saugvor- richtung mit Gummiball; *7* — Vorverstärker; *8* — Zähler)

die Prüflösung getaucht. Die Membranen können in trockenem Zustand gelagert werden und verhalten sich beim Eintauchen in die Prüflösung, wie frisch gefällte Niederschläge. Entsprechend hergestellte Membranen können für eine große Zahl von Bestimmungen eingesetzt werden. Aus der Reihe der untersuchten Filterpapiere (Whatman Nr. 1, 3 und 4; Schleicher–Schüll 2043 b und Macherey–Nagel 62) erwiesen sich Whatman Nr. 1 und Schleicher–Schüll 2043 b am geeignetsten.

Für die Durchführung radiometrischer Titrationen unter Anwendung von Niederschlag-Membranen haben BRAUN und KŐRÖS [3] den in Abb. 4.27 gezeigten Titrierapparat konstruiert. Sein wesentlichstes Merkmal

stronger as a base than methylamine, and trimethylamine is weaker than methylamine. In the case of aromatic substituents the aryl radical attracts the electron pair of the nitrogen, so that its proton co-ordinating ability and so also its basicity decreases: thus base strength decreases in the order:

ammonia > aniline > diphenylamine > triphenylamine

According to Brown, the base strength of aliphatic amines is determined not only by the number and electron releasing character of the alkyl substituents but also by their steric requirement and electrostatic repelling effect. Thermal measurement data on complexes formed by trimethylborane and amines show that tertiary amine-trimethylborane complexes dissociate rapidly. Against Lewis acids of larger steric requirements the basicity order of these amines is as follows:

ammonia < methylamine < dimethylamine ⩾ trimethylamine:

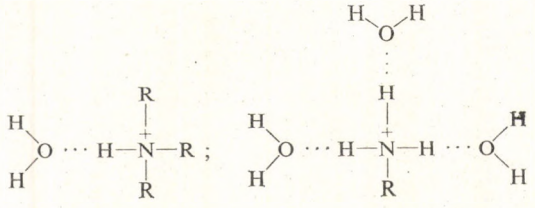
$$(CH_3)_3B + NH_3 = (CH_3)_3B \leftarrow NH_3$$

Steric hindrance becomes important when tri-t-butylborane, as a Lewis acid, and ethylamines, as bases, react:

ammonia < ethylamine ⩾ diethylamine > triethylamine

In Brown's hypothesis if the steric requirement of the groups bonded to the nitrogen atom is considerable, and additionally, if they are of decidedly polar character they exert a repulsive effect on each other as a consequence of which a so-called inner strain occurs in the amine molecule. The space-filling of the substituents limits the conversion of such amines into 'onium ions. With aliphatic amines the steric effect counteracts the electrostatic effect; with aromatic amines, base strength is decreased both by the steric hindrance effect of the substituent as well as by the electron-attracting mesomeric effect of the ring system. Thus, in the latter case the two effects are cumulative.

According to Bell and his co-workers the diminished base strength of tertiary amines in *aqueous media* may be attributed to lessened solvation of the conjugated acid ('onium ion) since in tertiary amines there are fewer hydrogen atoms available for H-bonding than e.g. in primary amines [46, 54, 55]:



The valence angle of water and alcohols is 109°, and it is not less in their conjugated acids, the oxonium ions, the latter being trigonal [394]. The valence angle at oxygen in diethyl ether is greater. For this reason it is far more difficult for the ether to co-ordinate a proton; it is a weaker base than water or alcohol. The intervalence angle of 1,4-dioxan at oxygen is fixed (approx. 109°); it is therefore a stronger base than di-n-butyl ether [505].

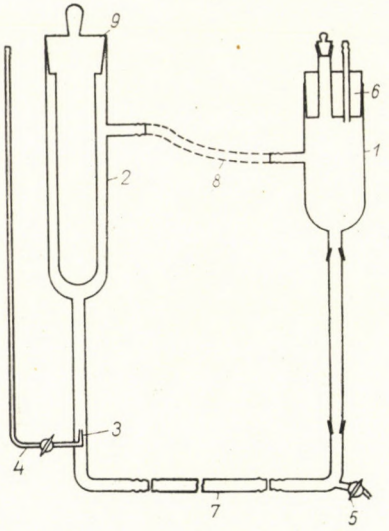


Abb. 4.27a
Zirkulationssystem des Titrierapparats für die Arbeit mit Niederschlagsmembranen (BRAUN und KŐRÖS [3]). (*1* — Gefäß für Zugabe und Entnahme; *2* — Gefäß für Membrane; *3* — Düse; *4* — Gaseinleitungsrohr; *5* — Ablaßhahn; *6* — Gummistopfen; *7* — Glasrohr unter dem Detektor; *8* — Verbindungsschlauch; *9* — Schliffrohr zur Befestigung der Membran)

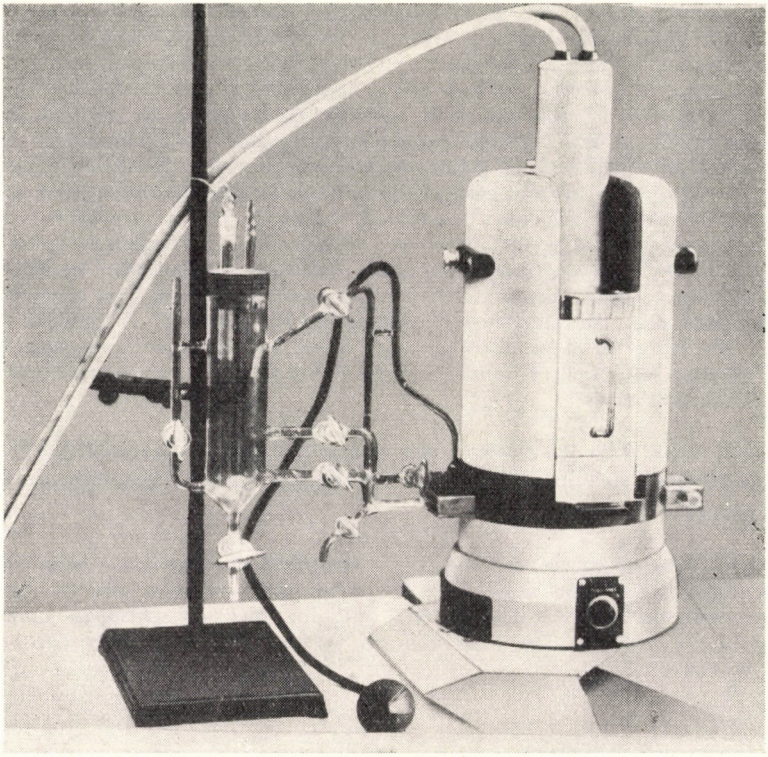
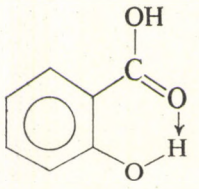
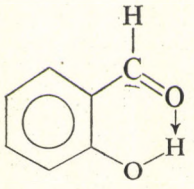


Abb. 4.27b
Fotografie des Titrierapparats

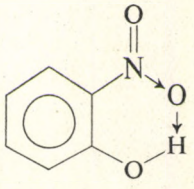
(c) *Ortho effect.* This effect is, from a theoretical aspect, not completely clarified and is therefore not fully applicable to all cases. When the *ortho* hydrogen atoms of a phenol are substituted by *iso*pentyl groups the solubility of the phenol in alkali is very slight; also, it does not show the ferric chloride colour reaction. This case emphasizes the steric type of *ortho* effect. The explanation for the *ortho* effect is, however, not the same when the *o*-substituent can form a hydrogen bond with the phenolic hydroxyl:



Salicylic acid pK_{acid} 2·97



Salicylaldehyde



o-Nitrophenol pK_{acid} 7·23

The above three compounds exhibit divergent properties when compared with their *meta* and *para* isomers: for example they can be sublimed and dissolve more readily in non-polar solvents. The strength of acids and bases is greatly influenced by *ortho* substitution. Almost all *ortho*-substituted benzoic acids are stronger than either benzoic acid itself or their *meta* or *para* isomers (Table 8).

The intramolecular H-bond in salicylic acid, as electron acceptor, decreases the electron density of the carbonyl group; salicylic acid is, therefore, a relatively strong acid.

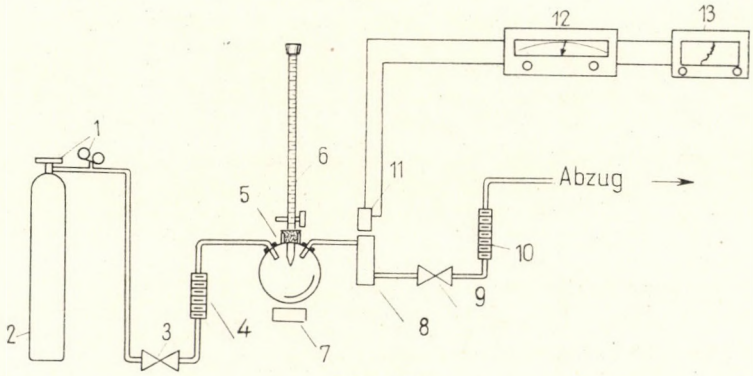


Abb. 4.28
Apparat zur Durchführung radiometrischer Titrationen unter Anwendung eines festen Kryptonats als Indikator (CHLECK [8]). (*1* — Ventil und Druckregler; *2* — Stickstoff-Flasche; *3* — Meßventil; *4* — Druckflußmesser; *5* — Reaktionsgefäß; *6* — Bürette; *7* — Magnetrührer; *8* — Zählkammer; *9* — Meßventil; *10* — Durchflußmesser; *11* — GM-Röhre; *12* — Ratemeter; *13* — Registriergerät)

besteht darin, daß die Messung der Radioaktivität der unter den Szintillationskristall geleiteten Lösung kontinuierlich erfolgt und die Niederschlag-Membran durch die zirkulierende Lösung kontinuierlich gespült wird.

Der Apparat besteht aus dem Detektor und die Zirkulationsvorrichtung. Die wichtigsten Bauelemente sind aus Abb. 4.27 ersichtlich. Es sind dies das Gefäß für die Membran *(2)* und das Zähl-Gefäß *(1)*. Sie stehen über dem unter dem Detektor hindurchgeführte Glasrohr *(7)* und den Gummischlauch *(8)* miteinander in Verbindung. Das Rohr *(9)* paßt mit einem Schliff in das Gefäß *(2)*. Es dient zur Befestigung der Membran, und zwar erfolgt diese mit Hilfe von zwei Gummiringen. In den unteren Teil des Gefäßes *(2)* ist die mit der Düse *(3)* versehene Glasröhre *(4)* geführt, durch die Luft in den Apparat geleitet werden kann. Sie hält die Lösung in dauernder Zirkulation und kann aus einem Gasbehälter oder mit Hilfe des Gummiballons *(6)* in den Apparat gedrückt werden. Besser ist es jedoch, unter Anwendung eines Vakuums zu arbeiten. Die Flüssigkeit wird dann durch Einleitung von Luft über die Röhre *(4)* in Zirkulation gehalten, deren Geschwindigkeit mit dem Vakuum zu regulieren ist, welches man über die durch den Gummistopfen des Gefäßes *(1)* geführte Röhre anlegt. Die Röhre in der anderen Bohrung dieses Stopfens dient zum Anschließen einer Bürette. Nach jeder Titration wird die Flüssigkeit aus dem Apparat über den Hahn *(5)* abgelassen.

Die in Abb. 4.28 skizzierte Vorrichtung stammt von CHLECK [8] für die Durchführung diskontinuierlicher Titrationen unter Anwendung fester Kryptonate.

Das Titriergefäß *(5)* ist der wichtigste Bestandteil des Apparats; es enthält die Prüflösung und auch das radioaktive Kryptonat. Zum Mischen wird ein Magnetrührer verwendet. Das freigesetzte ^{85}Kr wird mit Stickstoff-Schleppgas unter das GM-Zählrohr getragen. Die Radioaktivität wird nach Zugabe jeder Portion des Titriermittels gemessen.

Chapter 5

General Properties of Solvents

The solvent may influence the position of chemical equilibria either favourably or unfavourably. The success of determinations performed in non-aqueous media depends therefore on the choice of solvent. Selection of a suitable solvent is especially important when very weak bases or acids are titrated, since a number of neutral solvents, e.g. acetone, methyl ethyl ketone and methyl isobutyl ketone, are able to differentiate the weakly basic or acidic character of the compounds. Solvents of strongly acidic character such as acetic acid, or strongly basic character such as ethylenediamine, not only increase the strength of weak or moderately strength bases or acids but, at the same time, also bring them to the same level. This is termed a levelling effect. For this reason solvent mixtures are employed to an increasing extent.

29. Solvating Power

The solubility of organic compounds, because of their often complicated structures, is also influenced by intermolecular and intramolecular forces.

The solubility of organic compounds is determined by the following factors: (1) The presence of functional groups in the solute and the solvent molecules; their number, polarity, acidity, basicity and relative position in the molecule; (2) The dielectric constant of the solvent; (3) Intermolecular and intramolecular hydrogen bonds; (4) The number and position of carbon atoms within a homologous series; (5) The presence of double bonds and/or aromatic groups; (6) The presence or absence of steric hindrance. The choice of solvent determines which of these factors will decisively influence the solubility of a substance.

When ionic compounds are dissolved an important factor is the dielectric constant of the solvent, i.e. the extent to which electrostatic interaction between ions of opposite charge is decreased. Two ions of opposite charge in acetic acid possess only 1/6th of their interaction *in vacuo*, 1/16th of that in n-butanol, and one half

4.4 Endpunktbestimmung durch Trennung mit Ionenaustauschern

Ionenaustauscher zur Bestimmung des Endpunktes bei radiokomplexometrischen Titrationen verwendeten zuerst SCHUMACHER und FRIEDLI [29]. Ausgangspunkt war die Anwendbarkeit der papierchromatographischen Trennung (siehe Abschnitt 4.5). Sie konnten jedoch nachweisen, daß ihre theoretischen Ableitungen (vgl. Abschnitt 4.5) [30] auch für die Trennung durch Ionenaustausch gültig sind. Sie bestimmten Kobaltspuren durch Titration mit ÄDTE unter Anwendung des Anionenaustauschers Dowex 1 zur Trennung des Co^{2+} vom CoY^- (ÄDTE = H_4Y). STARÝ, RŮŽIČKA und ZEMAN [35] übertrugen die für die substöchiometrischen Isotopenverdünnungs-Analysen abgeleiteten theoretischen Ansätze auf die mit ÄDTE als Titriermittel durchgeführten radiometrischen Titrationen. Da bei den Titrationen mit ÄDTE negativ geladene bzw. ladungslose Chelate entstehen, können die Komponenten mit Ionenaustauschern gebunden werden. Der Endpunkt wird auf Grund der Aktivität der Eluate berechnet.

Man kann sowohl mit isotoper als auch mit nichtisotoper Markierung arbeiten. Im ersteren Fall wird zur Markierung eines der Isotopen des zu bestimmenden Elements verwendet. Im zweiten Fall verfolgt man die Titration mit Hilfe eines Elements, das mit der zugegebenen ÄDTE erst dann reagiert, wenn das zu bestimmende Element schon vollständig komplexiert ist, d. h. die Stabilität des ÄDTE-Komplexes des zur nichtisotopen Markierung verwendeten Elements muß wesentlich geringer als die des zu bestimmenden Elements sein.

Die zu den Bestimmungen benötigten optimalen Stabilitätsbedingungen und pH-Werte können berechnet werden.

Um zu gewährleisten, daß zur Bildung des Komplexes (MY) mehr als 99,9% der Chelatbildners (H_nY) verbraucht werden, muß die Bedingung erfüllt sein:

$$[MY] \geq 0{,}999\,[H_n Y]_0 \tag{4.35}$$

$[H_nY]_0$ = Konzentration des verwendeten Komplexbildners.

Die Gleichgewichts-Konzentration der Metallionen M ist:

$$[M] = [M]_0 - [MY] = [M]_0 - [H_nY]_0\,, \tag{4.36}$$

$[M]_0$ = Ausgangskonzentration der Metallionen.

Für die Gleichgewichts-Konzentration der Anionen Y gilt der Zusammenhang

$$\sum_{n=0} [H_nY] = [Y] \sum_{n=0} \frac{[H]^n}{k_0 \ldots k_n} \leq 0{,}001 [H_nY]_0, \tag{4.37}$$

worin

$$k_n = \frac{[H]\,[H_{n-1}Y]}{[H_nY]} \quad \text{und} \quad k_0 = 1\,. \tag{4.38}$$

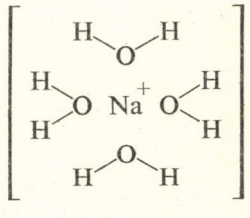
of that in cyclohexane. Therefore, the probability of the formation of ion-pairs is low in butanol, but is increased in acetic acid, and, to an even greater extent, in cyclohexane. It is difficult to distinguish between different types of association, and in solvents of poor solvating power many intermediate states are possible between dissociated ions, covalently bonded molecules and ion-aggregates.

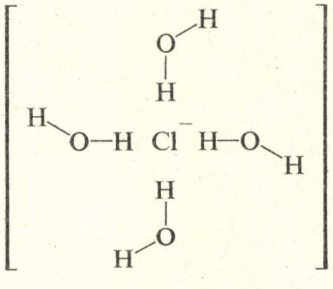
Well-established correlations exist between the dielectric constant of the solvent, the polarity of the solute and its solubility. In fact, although a high dielectric constant is necessary, it is not however a sufficient precondition for the solution of ionic compounds. The dielectric constant (ε) of liquid hydrogen cyanide is 116, yet it is a poor solvent for sodium chloride. In the case of organic compounds, the dielectric constant of the solvent is of secondary importance. The dielectric constant of propionic acid is ε 3·4; however, it dissolves polar organic compounds more easily than, for instance, chlorobenzene (ε = 5·6). However, the hydrogen bonding ability of the former solvent is of great importance, as owing to its lone pairs of electrons it should be able to establish co-ordinate bonds.

The majority of organic compounds contain both polar and non-polar groups, and the interaction of these with the solvent molecules influences the solubility differently. If the hydrocarbon part of the molecule is more dominant, its solubility in non-polar solvents increases, but if the molecule contains polar functional groups its solubility in a solvent 'similar to water' increases and decreases in a non-polar solvent. A typical example is the alkaloid tomatine, which is almost insoluble in carbon tetrachloride, but which is dissolved by adding the polar compound phenol to the solvent. (Chapter 24; Section 136.)

In general, increase in molecular weight leads to an increase in intermolecular forces in the solid compound. This results in a decrease in solubility (the molecular weight of tomatine is 1,034); examples of this are methyl acrylate and glucose which readily dissolve in water but whose polymers are insoluble.

Even more important than the dielectric constant is the specific interaction between the solute and the solvent. Ion-dipole interaction is an example of this type of interaction. When sodium chloride is dissolved, the oxygen atoms of the water dipoles are distributed in as close proximity to the Na^+ ion as is possible, as a result of the equilibrium between attraction and steric repulsion of the ion-dipole. The primary solvation shell surrounding the chloride ion is held by an interaction of H-bonding type. (Opinions on the exact number of water dipoles in the primary shell differ [73]):





(For an account of the solvation of alkali metal salts of carboxylic acids in glycol see: Chapter 22; Section 118.)

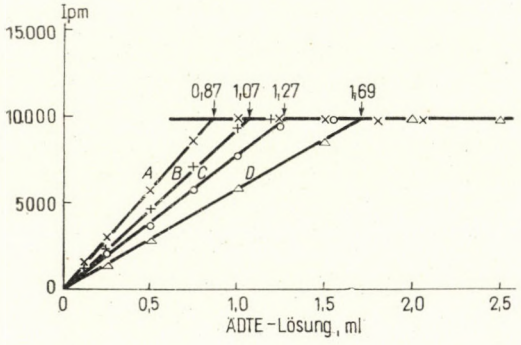


Abb. 4.29
Radiometrische Titration von In mit ÄDTE, untes Trennung durch Ionenaustausch (STARÝ, RŮŽIČKA und ZEMAN [35]. (*A* — 1 ml Standard ^{114m}In-Lösung; *B*, *C* und *D* — 1,00, 2,00 bzw. 4,00 ml inaktive In-Lösung, vermischt mit 1 ml Standard ^{114m}In- Lösung)

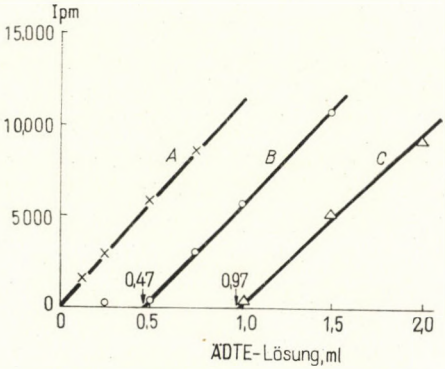


Abb. 4.30
Radiometrische Titration von Co mit ÄDTE, unter Trennung durch Ionenaustausch (in Gegenwart von ^{114m}In als nichtisotopen Indikator) (STARÝ, RŮŽIČKA und ZEMAN [35]). (*A* — 1,00 ml Standard ^{114m}In-Lösung; *B* und *C* — 1,00 bzw. 2,00 ml inaktiver Co-Lösung)

Setzt man nun (4.35–4.38) in den Ausdruck für die Stabilitätskonstante des Komplexes MY ein, so erhält man:

$$(4.39) \qquad K_{MY} = \frac{[MY]}{[M][Y]} = \frac{[H_nY]_0}{[M]_0 - [H_nY]_0} \cdot \frac{\sum_{n=0} \frac{[H]^n}{k_0 \ldots k_n}}{0{,}001\,[H_nY]_0} .$$

Wie aus (4.39) ersichtlich ist, wird der Wert der Stabilitätskonstante durch $\frac{[H_nY]_0}{[M]_0 - [H_nY]_0}$ nicht wesentlich beeinflußt. Bei höheren pH-Werten — bei denen der Komplexbildner vollständig dissoziiert ist — wird außerdem $\sum_{n=0} \frac{[H]^n}{k_0 \ldots k_n}$ gleich eins. Aus diesen Überlegungen folgt, daß für die Titration von Metallspuren nur solche Komplexe geeignet sind, bei denen $K_{MY} \geq 10^8$ ($[H_nY]_0 \leq 10^{-5}$ M). Dieser Forderung leisten fast alle Metallkomplexe der ÄDTE genüge.

Aus den obigen Ausführungen folgt weiter, daß die Metallionen, die mit der ÄDTE sehr stabile Komplexe bilden (z. B. Co^{3+}, Zr^{4+}, Fe^{3+}, In^{3+}, Th^{4+}), mit 10^{-6} bis 10^{-7} M ÄDTE-Lösungen selbst bei pH-Werten zwischen 2 und 3 titriert werden können. Zur Titration von weniger stabilen Komplexen muß bei höheren pH-Werten gearbeitet werden. Auf der Basis dieser theoretischen Überlegungen haben STARÝ, RŮŽIČKA und ZEMAN eine Methode zur Bestimmung von Spuren von Indium (isotoper Indikator

Specific interaction between the solute and the solvent becomes apparent, when for example an aqueous solution of organic base hydrochlorides containing functional groups of similar character is extracted, without the solution being made alkaline, by a solvent immiscible with water, and the extract of the free base formed in the course of hydrolysis is titrated. Similarly individual deviations may occur; this being another example of the differentiating effect of solvents. As an example: an aqueous solution of 0·1 M piperidinomethyltolylpropanone-HCl (PMTP), piperidinomethylcyclohexanone-HCl (PMCH) and piperidinomethyltetralone-HCl (PMT) was extracted with various solvents, and after addition of acetic acid to the non-aqueous phase, the base content was determined (with 0·01 N perchloric acid). The table below indicates, as percentages, the quantities of base dissolved in the organic solvent [313]:

Solvent	*PMTP*	*PMCH*	*PMT*
n-Hexane	2·6	1·0	2·3
Benzene	3·8	1·2	3·3
Ethyl ether	4·0	1·0	0·8
Chlorobenzene	5·2	1·2	1·2
Chloroform	11·6	1·0	6·7

The extent of the transfer of the above organic bases into the organic layer is influenced by the partition coefficient between water and the solvent immiscible with water, in other words, by the very divergent interaction between the two types of solvents and the organic molecule. Owing to specific interactions, very different results may be expected in the case of solvents possessing either the possibility of H-bonding (e.g. chloroform), or a dipole moment (for chlorobenzene $\mu = 1{\cdot}5$; benzene $\mu = 0$; n-hexane $\mu = 0{\cdot}08$), or a sharable electron pair (ether).

Solution is only one of the ways in which interaction between solvent and solute becomes apparent. Other interactions also take place, such as solvation, solvolysis, ionization, and association of molecules and ions.

30. Solvation

Solvation is closely connected with the process of solution. Generally speaking solvation includes all interactions between the solvent and the ions or molecules of the solute, since no distinction can be made between free solvent molecules and those bonded to ions or molecules (p. 26 in [294]). Ions or polar molecules become orientated in a polar solvent, and owing to the performance of electrostatic work, their energy content decreases and the system becomes more stable. The solvation energy is often of the same order as the covalent bond energy. When cations and Lewis acids become solvated nucleophilic solvent molecules are located in such a way that the former are overshadowed, while a covalent bond is formed; electron deficient solvent molecules not containing active hydrogen (e.g. liquid sulphur dioxide), interact with the electron-donor anion; in the case of solvents containing active or 'acidic' hydrogen, solvation of the anion can be related to the 'acidity' of the solvent. or its readiness to establish an H-bond (cf. Chapter 6; Section 38 (a)

^{114m}In) und Spuren von Kobalt (nichtisotoper Indikator ^{114m}In) durch Titration mit ÄDTE unter Anwendung einer Austauscher-Trennung ausgearbeitet.

Zur Titration von Indiumspuren wird eine Reihe von Prüflösungen mit gleichen Volumina hergestellt, die bekannte Mengen (1 μg/ml in 2,0 ml) Indium (markiert mit ^{114m}In) enthalten. Der pH der Lösungen wird auf einen Wert zwischen 2 und 3 eingestellt. Eventuell vorhandenes Eisen(III) wird durch Zugabe von 2 Tropfen 10%iger Ascorbinsäurelösung reduziert. Dann werden zunehmende Mengen 10^{-5} M ÄDTE-Lösung zu den Prüflösungen zugegeben. Nach genügend intensivem Rühren werden die Lösungen durch eine Serie von Kationenaustauschersäulen geschickt. Das Volumen der Eluate wird auf 10 ml aufgefüllt und je 4 ml werden zur Bestimmung der Aktivität entnommen. Die Ergebnisse werden graphisch dargestellt. Eine typische Titrationskurve dieser Art zeigt Abb. 4.29.

Da der Co^{3+}-Komplex der ÄDTE viel stabiler als ihr In^{3+}-Komplex ist, konnte ^{114m}In bei der Titration von Kobalt-Spuren angewandt werden. Die Kurve dieser Titration ist in Abb. 4.30 zu sehen.

4.5. Endpunktbestimmung durch papierchromatographische Trennung

SCHUMACHER und FRIEDLI [29] entwickelten eine vereinfachte Methode der radiokomplexometrischen Titration. Bei dieser wird die zur Endpunktbestimmung notwendige Trennung papierchromatographisch vorgenommen. Das Prinzip der Methode ist folgendes: Die zu bestimmenden Kationen M der Konzentration $[M]_t$ werden mit ihrem trägerfreien Isotop *M markiert. Dann gibt man so viel Komplexbildner hinzu, daß $[L]_t < [M]_t$ wird. Eine bestimmte Menge M wird als ML komplexiert, das unter bestimmten Bedingungen vom überschüssigen M getrennt werden kann. Ist $[L]_t$ und die Stöchiometrie der Komplexbildungsreaktion bekannt, so läßt sich $[M]_t$ mit Hilfe der nachstehenden Gleichungen berechnen.

Ist das Verhältnis (Q) der unter gleichen geometrischen Bedingungen gemessenen Radioaktivitäten

$$Q = \frac{[M]}{[ML]}, \tag{4.40}$$

ferner

$$[M]_t = [M] + [ML] \tag{4.41}$$

und nimmt man an, daß die gesamte Menge des zugegenen [L] bei der Bildung von ML verbraucht wird, d. h.

$$[ML] = [L]_t, \tag{4.42}$$

so kann der Wert von $[M]_t$ nach

$$[M]_t = [L]_t (1 + Q) \tag{4.43}$$

berechnet werden.

and p. 47 in [393]). The stabilities of the adducts so formed can be very dissimilar. Owing to the energy requirements for hydrogen bonding, H-bonds reduce the free energy of e.g. amines and acid amides; absence of H-bond formation increases basicity. Thus it is understandable that acid and base strengths measured in aqueous solvents are not always comparable with those found in non-aqueous solvents.

31. Solvolysis

Solvation may be closely followed by solvolysis when, owing to the electrostatic effect of anion or cation, the solvent dipoles leave the ion-dipole adduct as solvent anions or cations:

$$BH^+ClO_4^- + 2\,(AcOH)_2 \rightleftharpoons (B\text{H}.\ 2\ AcOH)^+ + (ClO_4.\ 2\ AcOH)^-;$$

$$(B\text{H}.\ 2\ AcOH)^+ \rightleftharpoons B.\ AcOH + AcOH_2^+$$

and

$$(ClO_4.\ 2\ AcOH)^- \rightleftharpoons ClO_4H.\ AcOH + AcO^-,$$

where BH^+ is the cationic acid formed by protonation of the nitrogen-containing base, $(AcOH)_2$ the acetic acid dimer, $AcOH_2^+$ the protonated solvent molecule (acetacidium ion) and AcO^- the acetate ion.

In solvents 'similar to water' [240], that is in those where the phenomenon of autoprotolysis has been demonstrated, the process of neutralization is interlinked with solvolysis:

$$BH^+AcO^- + AcOH_2^+ClO_4^- \rightleftharpoons BH^+ClO_4^- + (AcOH)_2$$

When strong or medium strength nitrogenous bases are dissolved in acetic acid a base acetate is formed so that it is the acetate ion which is titrated with perchloric acid. Because of the levelling effect, the base strengths are apparently the same (see: Chapter 3; Section 23).

Carboxylic acids also become solvated with the formation of a lyonium ion, e.g. in ethylenediamine:

$$R.\ COOH + C_2H_4(NH_2)_2 \rightleftharpoons R.\ COO^- + H_2N.\ C_2H_4.\ NH_3^+$$

Depending on the relative electrophilicity of the basic solvent used, the relative strengths of acids and acid analogues also change in such solvents [176]:

Acid	*In Water*	*In Dimethyl-formamide*	*In Ethylene-diamine*
Hydrochloric acid	Strong acid	Strong acid	Strong acid
Benzoic acid	Weak acid	Stronger acid	Strong acid
Phenol	Not titratable	Very weak acid	Weak acid

Die Bedingung: $[ML] = [L]_t$ ist nur dann erfüllt, wenn M und L einen 1 : 1-Komplex bilden, dessen Stabilität größer ist als die aus der Gleichung (4.44) ableitbare Größenordnung. Ist K_{ML} – die zur Befriedigung der Forderung (4.42) notwendige Stabilitätskonstante – nicht genügend groß, so resultiert der folgende systematische Fehler:

$$S_E = \frac{\alpha_H}{\alpha_H + [M]_t K_{ML}\left(\frac{Q}{1+Q}\right)}, \tag{4.44}$$

$$\alpha_H \equiv \sum_0^n [H]^i \prod_0^i K$$

$K_0 \equiv 1$ ist eine Protonierungsfunktion des Liganden L mit n Protonen, während K_i Protonierungskonstanten sind. S_E ist immer > 0.

Die zur Einzelmessung der Radioaktivität notwendige Trennung von M und ML verschiebt das Komplexbildungs-Gleichgewicht. Nimmt man an, daß der im Gleichgewicht vorhandene Überschuß des Komplexbildners gemeinsam mit dem Komplex vollständig entfernt wird, so ist

$$\beta = \frac{[M]_d}{[M]_t} = + \left(\frac{\alpha_H}{[M]_t K_{ML}(1+Q)}\right)^{\frac{1}{2}} \text{ bei } [M]_d \ll [M]_t. \tag{4.45}$$

$[M]_d = [M]$, gebildet aus der Dissoziation des Komplexes bei Unterschuß des Komplexbildners usw.

Verschiebt sich während der Trennung das Komplexbildungs-Gleichgewicht dauernd, so verursacht jede Trennung den folgenden systematischen Fehler:

$$S_E = \beta(1+Q) = + \left(\frac{\alpha_H (1+Q)}{[M]_t K_{ML}}\right)^{\frac{1}{2}}. \tag{4.46}$$

In dem zur Trennung verwendeten Medium muß die Halbwertszeit der Zersetzungsreaktion des Komplexes in der gleichen Größenordnung liegen wie die Gesamtdauer der Trennung.

Für solche Bestimmungen eignen sich mehrzähnige Komplexbildner, wie z. B. Aminopolycarbonsäuren als Titriermittel und die Papierchromatographie als Trennungsmethode am besten [17, 22, 23, 29]. Als praktisches Beispiel wird die Titration von Kobalt- und Terbiumspuren mit ÄDTE beschrieben.

Titration von Kobalt. Ein bekanntes Volumen von 10^{-5} M ÄDTE-Lösung wird zu einer auf pH = 8 eingestellten Lösung von Kobalt (III), markiert mit ^{60}Co, zugegeben. In diesem Medium wird $[CoY]^{2-}$ durch den Luftsauerstoff schnell zu $[CoY]^-$ oxydiert. Ein Volumen von 0,01–0,015 ml der Lösung wird nun auf chromatogra-

In inert solvents, e.g. hexane, benzene and carbon tetrachloride, interaction between the solute and the solvent is quite different, since no solvolysis occurs and the strengths of acids and bases are only slightly influenced by the solvent. However, the 'apparent' strengths of acids and bases may change with the strengths of the reference acids or bases, and as a result of association (see: Chapter 2; Sections 13, 14, and Chapter 3; Section 24).

Characteristic acid–base reactions such as, for instance, neutralization and colour change of the indicator in aprotic solvents are among those phenomena which considerably contributed to the evolution of acid–base theories which are more or less independent of the solvent. In inert solvents the formation of ion-pairs is possible, but dissociation and solvolysis do not occur, nor can a levelling effect be observed. Proton transfer takes place directly from the acid to the base in solution. In theory, inert solvents should simplify matters but, in practice, a number of experimental circumstances complicate titrations in such solvents. Their dielectric constant is low (on the average $\varepsilon = 2-6$); ion-pairs formed from the solutes in the course of interaction associate to a great extent, and carboxylic acids are present as dimers. Indicators also associate and as a consequence the Beer–Lambert law can no longer be applied. For this reason, data concerning acid–base reactions in aprotic or inert solvents apply only to the particular solvent used and are only a rough guide to results in other solvents.

32. Effect of Ionization and Dissociation

In the theory of titrations in non-aqueous media a distinction is drawn between ionization and dissociation. Ionization constants of acids and bases measured in solvents of low dielectric constants express the strength of acids and bases more accurately than does the dissociation constant [101]. If the ionization constants of e.g. *p*-dimethylaminoazobenzene, a strong base in acetic acid, is symbolized by (K_i), the dissociation constant of the ion pair by (K_d), and the 'over-all' dissociation constant by (K), then:

$$I + \mathrm{AcOH} \rightleftharpoons I\mathrm{H}^+\mathrm{AcO}^-, \quad K_i = 0{\cdot}10$$

Ionization

$$I\mathrm{H}^+\mathrm{AcO}^- \rightleftharpoons I\mathrm{H}^+ + \mathrm{AcO}^-, \quad K_d = 5{\cdot}0 \times 10^{-6}$$

Dissociation

and the over-all dissociation constant is:

$$K = \frac{K_i \times K_d}{(1 + K_i)} = 4{\cdot}6 \times 10^{-7}$$

where I = indicator,

$I\mathrm{H}^+$ = acidic form of the indicator.

In a solvent where H-bonding is possible (e.g. acetic acid) the first step in the process is the formation of a loose adduct, followed by the formation of an H-bond, and finally the ionization-dissociation state of equilibrium is reached. Thus, e.g. in nitrogenous bases the proton may be transferred to the nitrogen atom:

$$\mathrm{AcOH} + B \rightleftharpoons \mathrm{AcOH} \cdot B \rightleftharpoons \mathrm{AcO} \ldots \mathrm{H} \ldots B \rightleftharpoons \mathrm{AcO}^-\mathrm{H}B^+ \rightleftharpoons \mathrm{AcO}^- + B\mathrm{H}^+$$

Adduct formation — H-bond formation — Ionization-dissociation

(See also: Chapter 2; Section 11 (b).)

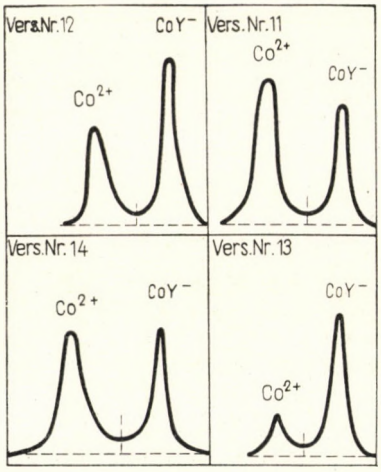


Abb. 4.31
Verteilung der Radioaktivität von Co^{2+} und $[CoY]^-$ (markiert mit ^{60}Co) auf Papierchromatogrammen (SCHUMACHER und FRIEDLI [29]). Die zugegebenen ÄDTE-Mengen nahmen in der Reihenfolge 11, 14, 12 und 13

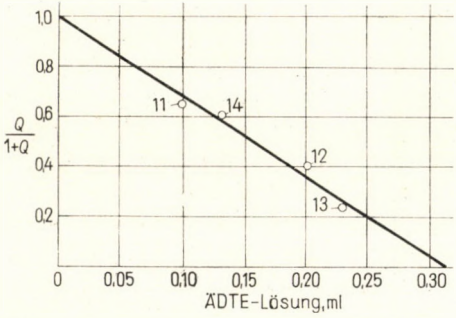


Abb. 4.32
Relative Aktivitäts-Verteilung der Flecke von Co^{2+} und $[CoY]^-$, markiert mit ^{60}Co und getrennt durch Papierchromatographie, als Funktion der zugegebenen Menge des Titriermittels ÄDTE (SCHUMACHER und FRIEDLI [29])

phisches Papier aufgebracht, und zwar so, daß der Durchmesser des Fleckes nicht mehr als 1,6–2,0 cm beträgt. Man läßt das Chromatogramm nun ca. 15 Stunden lang laufen (30–33 cm) und trocknet dann. Abschließend wird die Radioaktivität entlang des Streifens gemessen.

Die Verteilung der Radioaktivität bei vier verschiedenen Mengen der ÄDTE-Lösung zeigt Abb. 4.31. Die Kurven auf Abb. 4.31 wurden mit Hilfe eines Pantographen übertragen, die Fläche unter den Kurven wurde ausgeschnitten und ihre Größe gemessen. Die auf diese Weise integrierten Radioaktivitäts-Verhältnisse sind in Abb. 4.32 als Titrationskurve gezeigt. Die den Abb. 4.31 und 4.32 entsprechenden Werte sind in Tab. 4.2 zusammengefaßt.

Tabelle 4.2

Titration von 0,100 ml Kobalt-Lösung

Vers.-Nr.	10^{-5} M ÄDTE-Lsg. (ml)	Aktivitäten/mg Papier		Q	$\frac{Q}{1+Q}$	$[M]_f \times 10^{-5}$
		Co^{2+}	$[CoY]^-$			
11	0,100	151,0	79,3	1,90	0,655	2,90
12	0,200	87,5	127,0	0,690	0,408	3,32
13	0,230	23,8	79,3	0,300	0,230	3,38
14	0,130	67,5	43,5	1,55	0,607	2,99

In organic solvents capable of self-ionization, with a dielectric constant $\varepsilon < 40$, even a base perchlorate dissociates only partly; for the greater part it forms ion pairs (see also: Chapter 2; Sections 16 (a) and (b)).

33. Association

The survey is rendered more difficult by associations occurring in many organic solvents either between the solute molecules or between the solute and the solvent molecules respectively, and also because the degree of association changes not only from solvent to solvent but also as a function of the concentration. As a consequence, the equilibrium relations in an organic solvent are complicated and Ostwald's Law of Dilution is not valid even for dilute solutions. In solvents with small dielectric constants the activity of ions deviates greatly from unity; and this deviation can also be explained by the formation of ion-pairs and other associations [106, 260, 292, 389, 413, 447, 464, 559b]. The polarity of ion-pairs, their dissociation constants and degree of basicity depend upon the solvent, and in certain cases on the concentration. So e.g. charged complex ions are formed from molecules containing an amino group dissolved in acetic acid [561] as indicated below:

$$\left.\begin{matrix}(M_3Ac)^{2+} + 2Ac^- \\ (MAc_3)^{2-} + 2M^+\end{matrix}\right\} \rightleftharpoons (M_2Ac)^+ + (MAc_2)^- \rightleftharpoons (MAc)_3 \rightleftharpoons 3\ MAc \rightleftharpoons 3\ M^+ + 3\ Ac^-$$

$$1\ \text{N} \longleftarrow\!\!\!\!\!\!\longrightarrow 0{\cdot}1\ \text{N} \longleftarrow\!\!\!\!\!\!\longrightarrow 0{\cdot}01\ \text{N}$$

where M = cation, in general
Ac^- = acetate ion
Ac = acetate.

Owing to the secondary dissociation of complex ions, complexes formed from large cations dissociate in acetic acid to a greater extent than simple salts. In the very dilute solutions on the right of the above scheme, the usual dissociation of salts occurs. However, with increase in concentration the conductivity passes through a minimum since associations of the type $(MAc)_3$ occur. But with further increase in concentration (approx. 0·1 N) this triple complex gives rise to two complex ions, so that conductivity is again increased. Finally, on the left side of the scheme the process by which increasing association is accompanied by an increased dissociation is illustrated. The acidity or basicity of complex ions may change with concentration.

34. The Phenomenon of Amphoterism

Amphoteric substances may exhibit acidic or basic characteristics dependent upon the solvent. Two variants can be distinguished: (1) amphoterism arising in one functional group (e.g. in pyrrole), (2) amphoterism due to two different functional groups (e.g. sulphamic acid). A good example of this is potassium hydrogen phthalate (a standard compound) which can be titrated in water as an acid, but in acetic acid

4.6. Endpunktbestimmung durch fokussierenden Ionenaustausch

Die durch SCHUMACHER [27] eingeführte Trennung durch fokussierenden Ionenaustausch wurde zusammen mit STREIFF [30] zur Bestimmung des Endpunktes radiokomplexometrischer Titrationen angewandt.

Das Schema der angewandten Apparatur veranschaulicht Abb. 4.33. Sie besteht im Wesentlichen aus zwei Behältern, die durch einen Chromatographiepapier-Streifen verbunden sind. Ein Tropfen der verdünnten Lösung des untersuchte Kations M^{x+} wird in der Mitte auf diesen Streifen aufgebracht, der zur Kühlung durch ein CCl_4-Bad *(2)* geführt wird. Der Behälter mit der Kathode *(3)* enthält die Lösung eines Chelatbildners L^{y-}, der mit M^{x+} einen anionischen Komplex bildet (z. B. ein Acetat), der Behälter mit der Anode *(1)* eine Mineralsäure. Sobald diese Lösungen infolge der Kapillarität bis zum Fleck von M^{x+} gewandert sind, wird an die beiden Elektroden ein Potential von ca. 300–500 V angelegt. Die Protonen und die komplexierenden Anionen wandern einander entgegen und treten beim Zusammentreffen miteinander in Reaktion. Dies führt zu einem stationären Zustand, wobei entlang des Streifens ein pH-pL Gradient zustande kommt. In Abhängigkeit von der Konzentration des freien Liganden L^{y-} wird das Element M entweder als Kation M^{x+} (anodischer Teil) oder als Komplex-Anion (kathodischer Teil) vorliegen. Im elektrischen Kraftfeld wandern diese Ionen einander entgegen. Am Treffpunkt findet daher keine Wanderung statt. In diesem schmalen Streifen wird das Element M, gleichsam einem Fokus, angereichert (Fokus x_i). Abb. 4.34 veranschaulicht schematisch den Vorgang, der sich auf dem Papierstreifen abspielt. SCHUMACHER [28, 30] konnte nachweisen, daß dieser Fokus in erster Linie von der Stabilitätskonstante des Komplexes $[ML_n]^{-ny+x}$ abhängt. Für den exponentiellen Gradienten von L^{y-} gilt die Gleichung:

$$x_i = -\frac{1}{na} \ln K[L^{y-}]_a^n, \tag{4.47}$$

n = Zahl der Liganden im Komplex
a = positiver Gradient der Konzentration von L^{y-}, d. h. $d\ln [L^{y-}]/dx$
K = Stabilitätskonstante von $[ML_n]^{-ny+x}$
$[L^y]_a$ = Konzentration von L^{y-} im anodischen Teil der Trennungszone.

SCHUMACHER und STREIFF zeigten in einer späteren Arbeit [30], daß auf der stark sauren Seite des pH-Gradienten ein zweiter M^{x+}-Fokus erscheint, wenn die auf den Streifen aufgebrachte Lösung von M^{x+} auch eine bestimmte Menge ÄDTE enthält (d. h. wenn im System zwei Liganden vorhanden sind), oder wenn die ÄDTE-Lösung später auf den Streifen getropft wird. Die Intensität dieses Fokus ist der angewandten ÄDTE-Menge proportional. Die Bildung zweier fokussierter Zonen bei Gegenwart von zwei Liganden, die Komplexe unterschiedlicher Stabilitäten bilden, wurde

as a base. In the first case a solvent cation, H_3O^+, and in the second case a solvent anion, CH_3COO^-, is formed:

$$[C_6H_4(COOK)COO]H + H_2O \rightleftarrows C_6H_4(COOK)COO^- + H_3O^+$$

$$[C_6H_4(COOH)COO]K + CH_3COOH \rightleftarrows C_6H_4(COOH)_2 + CH_3COO^-K^+$$

Examples of amphoterism:

Compound	*Titratable as Acid by (Solvent, Titrant)*	*Titratable as Base by (Solvent, Titrant)*
Benzimidazole	DMF, CH_3OK	$EtCO_2H$, $HClO_4$
Isonicotinic acid hydrazide	Diethylamine, CH_3OK	$AcOH-CHCl_3$ $HClO_4$
Nitroguanidine and derivatives	DMF, CH_3OK	Trifluoroacetic acid, $HClO_4$
Pyrrole	Exceedingly weak base *and* acid, not titratable	
Sulphamic acid (standard compound)	DMF, $BuNH_2$, CH_3OK	AcOH, $HClO_4$
Theobromine	Py, CH_3OK	$AcOH-Ac_2O-C_6H_6$, $HClO_4$
Sulphonamides	DMF, Py, $BuNH_2$, acetone, CH_3OK	$AcOH-C_6H_6$, $HClO_4$
N-Benzoylbenzamidine	Py, TBAH	EG–IP, $HClO_4$

where AcOH = acetic acid
Ac_2O = acetic anhydride
$BuNH_2$ = n-butylamine
CH_3OK = alkali metal alkoxide in general
DMF = dimethylformamide
$HClO_4$ = perchloric acid titrant
$EtCO_2H$ = propionic acid
Py = pyridine
TBAH = tetrabutylammonium hydroxide
EG–IP = ethylene glycol–isopropanol solvent mixture (1 : 1).

The majority of acid amides are 'neutral' in acetic acid but in acetic anhydride they can be titrated potentiometrically; in liquid ammonia they behave as acids.

35. Summary

In solvents similar to water the interactions between solute and solvent are similar to the processes taking place in water, but qualitative and quantitative differences can be observed. These differences are caused by the smaller dielectric constants, by the formation of different ion pairs by further associations of varying types and by the change in the electrostatic field as a function of concentration (Table 11).

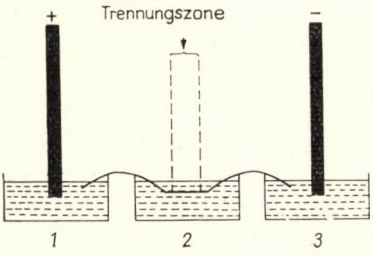


Abb. 4.33

Schema einer Vorrichtung zur Trennung durch fokussierenden Ionenaustausch (SCHUMACHER [27])

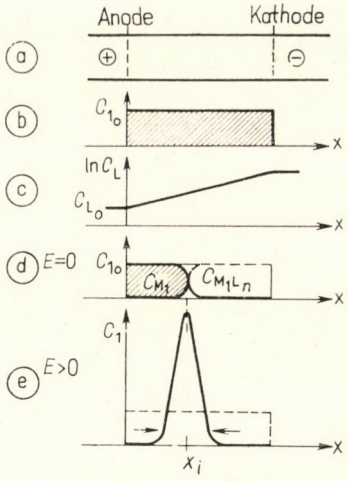


Abb. 4.34

Schematische Darstellung der Trennung durch fokussierenden Ionenaustausch (SCHUMACHER [27])

a — Anfangsbedingung; *b* — Herstellung eines C_L-Gefälles; *c* — ortsabhängige Komplexbildung; *d* — $C = C_{M_1} + C_{M_1L_n}$ vor Anlegen der Spannung; *e* — $C = C_{M_1} + C_{M_1L_n}$ nach Anlegen der Spannung

Doppelfokussierung genannt. In diesem Fall ist die Verteilung von M, d. h. das Verhältnis $[M]_{rechts}/[M]_{links}$ konstant und hängt nur von der Menge der vorhandenen ÄDTE ab.

Die Erscheinung kann bei allen Ionen beobachtet werden, die mit ÄDTE Komplexe bilden, deren Stabilität über einem bestimmten Wert liegt. Sie konnte daher bei mit ÄDTE durchgeführten radiometrischen Titrationen erfolgreich ausgenützt werden [28].

4.6.1. *Typen der Titration*

Auf der Basis der obigen Prinzipien haben SCHUMACHER und STREIFF [30] direkte und Verdrängungstitrationen ausgearbeitet.

Yttrium wurde mit ÄDTE unter Anwendung von trägerfreiem ^{90}Y zur Markierung titriert. Abb. 4.35 zeigt die Aktivitäten der fokussierten Zonen in verschiedenen Phasen der Titration. Die auf Grund dieser Werte aufgestellten Titrationskurven gibt Abb. 4.36 wieder. Mit ^{60}Co markierte Kobaltionen wurden sowohl mit 1,2-Diaminocyclohexan-N,N,N',N'-tetraessigsäure (DCTE) als auch mit ÄDTE titriert.

SCHUMACHER und STREIFF [30] gelangen auch Bestimmungen durch direkte Titration auf dem Papierstreifen. Sie können aber nur dann durch-

Table 11

EFFECT OF SOLVENTS ON THE SOLUTE

Inert Solvents	*Acidic or Basic Solvents*
A compound capable of ionization does not dissociate in inert solvents; the inherent acid or base strength remains, but there is no levelling effect; the strength of weak acids or bases is not increased.	In acidic or basic solvents the solute is ionized, and also (to a smaller extent) dissociated. It forms a complex with the solvent, as a consequence of which the inherent acid or base character is changed (mainly increased and levelled).
Solvent anions and cations are not formed; the solvent does not take part in the neutralization process. The product formed is of an additive or associative character.	The solvent promotes migration of the proton by giving rise to solvent anions or cations, i.e. the solvent takes part in the neutralization reaction. The reaction products are a salt and solvent molecule.
The nucleophilicity of the titrant base or base to be titrated must be greater than that of the base corresponding to the titrant acid or acid to be titrated.	The solvent must be a weaker acid or base than the acid or base to be titrated.
In some cases the use of special indicators is needed.	Many indicators and electrodes in current use are suitable for end-point indication.
Potentiometric titrations performed in non-polar solvents need the addition of electrolytic conductors. The titration itself requires special care.	

geführt werden, wenn ein entsprechendes radioaktives Isotop des zu bestimmenden Elements zur Verfügung steht.

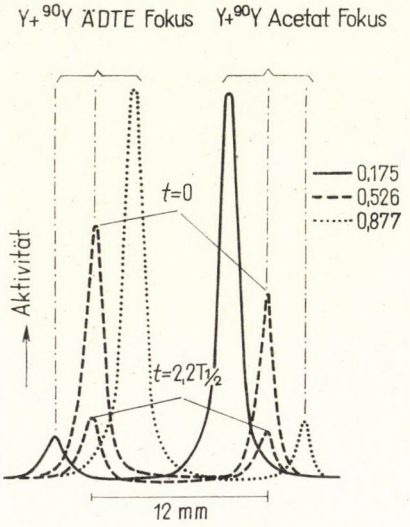


Abb. 4.35
Radiogramme der in den verschiedenen Phasen der Titration von Y erhaltenen Fokusse (SCHUMACHER und STREIFF [30])

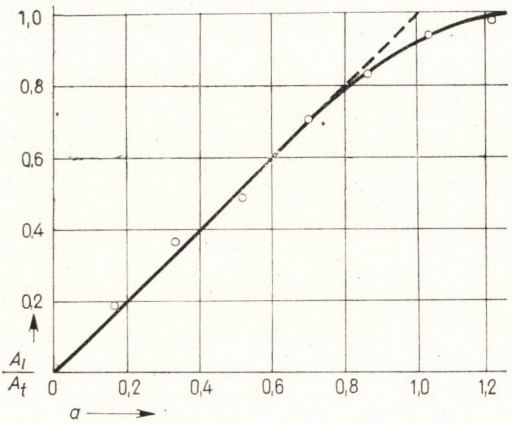


Abb. 4.36
Radiometrische Titration von Y mit ÄDTE, unter Trennung durch fokussierenden Ionenaustausch (SCHUMACHER und STREIF [30]). (a — Phase der Titration; A_l = Aktivität des linken Fokus; A_t = Gesamt-Aktivität; ÄDTE-Lösung = 0,0954 M)

Chapter 6

Solvents Used in Non-aqueous Titrimetry

A solvent only takes part in prototropic processes when its molecules contain a dissociable hydrogen atom or are able to bond with such an atom, e.g. acetic acid, pyridine, methanol. These are the more simple cases. There are, however, some though not many, solvents in whose neutralization reaction acetylium ions or chloride ions take part (Chapter 1; Section 5, and Chapter 2; Section 20 (e)). But solvents incapable of prototropic exchanges which possess only a low or zero dipole moment, and which do not form complexes, have scarcely any direct influence on the neutralization process, which depends all the more on the co-reactants. Such aprotic, inert solvents include n-hexane, cyclohexane, benzene, and carbon tetrachloride. In benzene, benzoic acid is a stronger acid towards diphenylguanidine than towards triethylamine (Chapter 2; Section 15 (e)). Some solvents are in a transitional category; these influence the neutralization reaction to a certain extent owing to their H-bonding abilities, dipole moments, complex-forming and nucleophilic or electrophilic properties. Examples are: chloroform, chlorobenzene, acetone, acetonitrile, nitromethane, methyl isobutyl ketone etc.

The dielectric constants of these solvents are lower than that of water; therefore the field of force effect of the solute ions and the electrostatic attraction increase:

$$p = (1/\varepsilon) \times (q_1 q_2 / r^2),$$

where ε = the dielectric constant (Table 12).

As a consequence, dissociation decreases and forces between ions increase, as does the tendency to associate. All these influence the colour change of the indicator and cause irregular inflexions at the potentiometric end-point.

The following five groups of solvent used in non-aqueous titrations are recognized: (1) aprotic, inert solvents, (2) differentiating solvents, (3) protogenic solvents, (4) protophilic solvents, (5) solvent mixtures.

Proton-releasing and proton-attracting solvents are equally capable of transferring or accepting hydrogen ions, that is, of proton exchange. Except when these solvents possess distinct acidic or basic properties they are called 'amphiprotic solvents'.

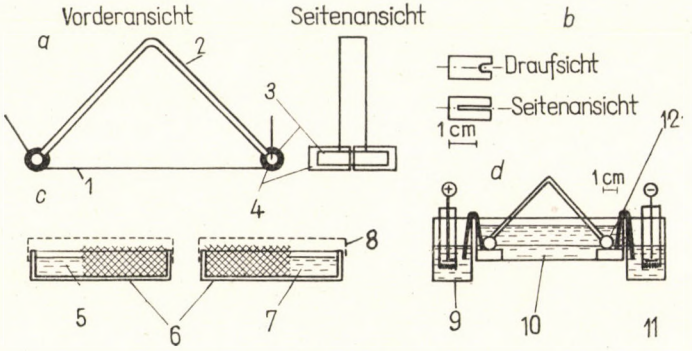


Abb. 4.37

Apparat zur Trennung durch fokussierenden Ionenaustausch (SCHUMACHER und STREIFF [30]). (*a* — Halterahmen für Papierstreifen; *b* — Teflonröhren; *c* — Schwämme zum Feuchthalten; *d* — Apparat) (*1* — Papierstreifen; *2* — Glasstab; *3* und *4* — Teflonröhren; *5* — Anodenraum; *6* — Küvetten; *7* — Kathodenraum; *8* — Deckel; *9* — Anode; *10* — CCl_4-Bad; *11* — Kathode; *12* — dickes Filtrierpapier)

Mit Hilfe der Verdrängungstitration ist es jedoch möglich, eine große Zahl von Elementen mit einem einzigen Titriermittel zu erfassen.

Elemente, deren Komplexe stabiler sind als der des Kobalt(II), stören bei der Doppelfokussierung von Kobalt mit ÄDTE oder DCTE. Auf diese Weise wird eine der zugegebenen Menge des zu bestimmenden Ions proportionale Menge Kobalt aus der linken Linie des durch ÄDTE oder DCTE fokussierten Kobalts verdrängt.

Bei Verdrängungstitrationen dieser Art werden 0,05–0,01 M Kobaltkomplex-Lösungen angewandt. Die genannten Autoren bestimmten Kupfer, Blei, Eisen(III), Kobalt(II) und Yttrium(III).

4.6.2. *Apparat und Methode der Titration*

Das Schema der verwendeten fokussierenden Vorrichtung [30] veranschaulicht Abb. 4.37.

Für Direkt-Titrationen wird wie folgt vorgegangen:

Bekannte Volumina des Titriermittels werden aus einer Bürette zu 2,00 ml betragenden aliquoten Teilen der Prüflösung zugegeben. Nach Zugabe jeder Portion werden mit einer Mikropipette Proben aus dem Reaktionsgemisch entnommen und auf einem Papierstreifen dem fokussierenden Ionenaustausch unterworfen. Darauffolgend wird die Aktivität entlang des Streifens gemessen. Die Aktivitäten der rechten und linken Maxima werden durch Integration der Aktivitäts-Verteilungskurve bestimmt. Auf Grund der erhaltenen Werte wird die Titrationskurve aufgestellt.

Ein ähnliches Verfahren wird auch bei den Verdrängungstitrationen angewandt.

Table 12

DIELECTRIC CONSTANTS OF SOLVENTS

ε (20°) [560, 866]

(Data are for guidance only, because the literature data often vary in the last decimal; sometimes even in the last but one)

Solvent	*Character (In practice)*	ε
n-Hexane, n-Heptane	Inert (apolar)	1·9
Cyclohexane	Inert	2·0
1,4-Dioxan	Inert	2·2
Carbon tetrachloride	Inert	2·2
Benzene	Inert	2·3
Propionic acid	Acidic	3·4 (40°)
Ethyl ether	Inert	4·3
Chloroform	Inert	4·8
n-Butylamine	Basic	5·3
Chlorobenzene	Inert	5·6
Acetic acid	Acidic	6·2
1,1,1-Trichloroethane	Inert	7·5
t-Butanol	Amphiprotic	10·9 (30°)
Pyridine	Basic	12·5
Methyl isobutyl ketone	Differentiating (inert)	13·0
Ethylenediamine	Basic	14·2
2-Methoxyethanol (glycol monomethyl ether, Cellosolve)	Amphiprotic	16·0
n-Butanol	Amphiprotic	17·1 (25°)
iso-Propanol	Amphiprotic	18·3 (25°)
Propionic anhydride	Acidic	18·3 (16°)
Methyl ethyl ketone	Differentiating (inert)	18·5
n-Propanol	Amphiprotic	20·1 (25°)
Acetic anhydride	Acidic (differentiating)	20·7
Acetone	Differentiating (inert)	21·0
Ethanol	Amphiprotic	24·3 (25°)
Propylene glycol-1,2	Amphiprotic	32·0
Methanol	Amphiprotic	32·6 (25°)
Nitrobenzene	Inert	34·8 (25°)
Nitromethane	Differentiating (inert)	36·0 (30°)
Acetonitrile	Differentiating (inert)	37·5
Dimethylformamide [503]	Basic (differentiating)	36·7*
Ethylene glycol	Amphiprotic	37·7 (25°)
Hydrazine	Basic	53
Formic acid	Acidic	58
Water	Amphiprotic	80·4
Formamide	Basic	109
Hydrogen cyanide	Acidic (inert)	115
N-Methylformamide [503]	Basic	190·5

* 26·6, Merck and Co. [595].

36. Aprotic, Inert Solvents

In inert solvents, such as hexane, benzene, carbon tetrachloride, chlorobenzene, the very variable strengths, inherent in acids and bases, are displayed (cf. Table 11).

4.7. Radiometrische Komplexbildungstitrationen

(Für alle Titrationen wurden Modell-Lösungen verwendet)

Bestimmte Komponente	Maßlösung	Zur Markierung in der Prüflösung verwendetes Radionuclid	Bemerkung	Literatur
Ag^+	Dithizon 34,0 μM	^{110m}Ag	pH = 1 (N H_2SO_4), Best. von 9–18 μg; Trennung durch Extraktion	[32]
	Dithizon 34,0 μM	^{65}Zn	Nichtisotope Markierung; pH = 5,3 (Acetatpuffer). Best. von 5–10 μg; Trennung durch Extraktion	[32]
$Ag^+ + Zn^{2+}$	Dithizon 34,6 μM	^{65}Zn	Nichtisotope Markierung; pH = 6,0; Best. von 32,4 μg Ag u. 11,0 μg Zn; Trennung durch Extraktion	[32]
$Hg^{2+} +$ $+ Ag^+ +$ $+ Zn^{2+}$	Dithizon 53,2 μM	$^{203}Hg +$ $+ {}^{65}Zn$	Nichtisotope Markierung; Hg + Ag pH = 1, Zn pH = 7; Best. von 2,0 μg Hg, 27,0 μg Ag, 6,2 μg Zn; Trennung durch Extraktion	[32]
$Ag^+ +$ $+ Cu^{2+} +$ $+ Cd^{2+}$	Dithizon	$^{110m}Ag +$ $+ {}^{115}Cd$	Best. von 78–101 μg Ag, 20–35 μg Cu, 26–32 μg Cd; Trennung durch Extraktion	[18]
Al^{3+}	$Ca(NO_3)_2 +$ + ÄDTE	^{110m}Ag als $AgIO_3$	Unter Anwendung von festem Indikator. Indirekte Best.: Rücktitration des ÄDTE-Überschusses mit $Ca(NO_3)_2$; Best. von 0,4–10 mg	[1]
Ca^{2+}	0,1 M ÄDTE	^{110m}Ag als $AgIO_3$	pH = 9–10 (NaOH); unter Anwendung von festem Indikator; Best. von 0,14–6,0 mg	[2, 5]
Cd^{2+}	Dithizon	^{115}In	Trennung durch Extraktion	[20]

Some of the inert solvents exert a differentiating effect on acids and bases and in these solvents a mixture of acids or bases can be titrated without the strength of the acids or bases being levelled. (See: Chapter 15; Section 95 and Chapter 25; Section 141.) However, compounds of very weak basicity or acidity cannot be titrated in every case because aprotic solvents lack the enhancing effect of strongly acidic or strongly basic solvents.

In the course of acid-base interaction, according to recent theories, it seems that the interaction never leads to total proton transfer without the influence of solvation. In non-polar solvents the hydrogen acid-acceptor base system can be considered to be a stable form, the stability of which is determined by a hydrogen bond established between proton donor and proton acceptor [766].

37. Differentiating Solvents

Walden and his collaborators [855, 856, 857] and later Fritz, Bruss and Wyld [105, 248] were concerned with the differentiating effect of acetone, acetonitrile, methyl ethyl ketone, methyl isobutyl ketone, nitromethane etc., on electrolytes. Ismaĭlov and co-workers [411, 414, 415] as well as Shkodin and co-workers [735, 736, 737a, 737b, 737c, 737d, 738, 739] were concerned with the differentiating effect of some solvents (formic acid, acetic acid, etc.) on acids, phenols, dicarboxylic acids and bases. Kreshkov and co-workers studied in detail the highly advantageous differentiating properties of methyl ethyl ketone, emphasizing the use of perchloric acid dissolved in methyl ethyl ketone as a titrant [474, 475, 479, 485].

The exponents of the dissociation constants of acids and bases in suitable differentiating solvents may differ considerably from one another, although the exponents measured in water are closer [411], e.g.:

Acid	p*K* *(Water)*	p*K* *(Acetone)*
Picric acid	0·8	3·17
Salicylic acid	2·97	9·53
Difference	2·17	6·36

The proton donor and proton acceptor abilities of differentiating solvents are generally hypothetical and ill-defined. The compound establishes a hydrogen bond or interacts with the solvent in some other little-known way and reacts with the standard solution as a solvated molecule or ion.

38. Origin of Differentiating and Levelling Effects

The differentiating effect can be ascribed partly to the specific interaction between solute and solvent and partly to the differing basicity or acidity of the solvent from that of water. Thus for example if the ionization constants of two acids, *A*H and *X*H, are 10^4 and 10^2, the hydrogen ion concentrations in their tenth-normal aqueous solution are 0·099999 N and 0·0999 N; i.e. the acid strengths are the same within the limits

Bestimmte Komponente	Maßlösung	Zur Markierung in der Prüflösung verwendetes Radionuclid	Bemerkung	Literatur
Co^{2+}	$3{,}62 \times 10^{-5}$ M Dithizon	^{60}Co	Trennung durch Extraktion; pH = 6,5–7,3 (Acetat-Puffer); Best. von 0,2–10,0 μg	[11]
	Dithizon, 21,6 und 34,2 μg	^{60}Co	Trennung durch Extraktion; pH = 7,0 (Acetat-Puffer); Best. von 8–10 μg	[32]
Co^{3+}	10^{-5} M ÄDTE	^{114m}In	Trennung durch Ionenaustausch; nichtisotope Markierung; pH = 6–8; Best. von 0,29–0,58 μg	[35]
	0,0960 M DCTE	^{60}Co	Trennung durch fokussierenden Ionenaustausch. Direkt-Titration; Best. von 5–10 μg	[30]
	0,0954 M ÄDTE	^{60}Co	Trennung durch fokussierenden Ionenaustausch. Direkt-Titration; Best. von 5–10 μg	[30]
	10^{-5} M ÄDTE	^{60}Co	Trennung durch Papierchromatographie. Best. von 5–10 μg	[29]
Co^{2+} + + Pb^{2+}	NH_4SCN	^{60}Co	Trennung durch Extraktion. In Ggw. von überschüssigem Pyridin	[15]
Co^{2+} + + Pb^{2+}	$3{,}92 \times 10^{-5}$ M Dithizon	^{60}Co	Trennung durch Extraktion; pH = 6,5; Best. von 10 μg Co, 15 μg Pb	[12]
Co^{2+} + + Ni^{2+}	Dithizon	^{60}Co	Trennung durch Extraktion; pH = 6,7; Best. von 2,0 μg Co, 15 μg Ni	[12]
Co^{2+} + + Zn^{2+}	$4{,}42 \times 10^{-5}$ M Dithizon	^{60}Co	Trennung durch Extraktion; pH = 5,7–6,9; Best. von 0,34–7,0 μg Zn, 2,0–10,0 μg Co	[11]

of experimental error. However, in a solvent the basicity of which is 10^6 times smaller than that of water, the ionization constants of the two acids are 10^{-2} and 10^{-4} respectively. Thus the hydrogen ion concentrations in their tenth-normal solution are 0·027 N (*A*H) and 0·0037 N (*X*H). So on this basis, their acid strength has become differentiated (p. 49 in [393], Fig. 28). Solvents may differ considerably from water not

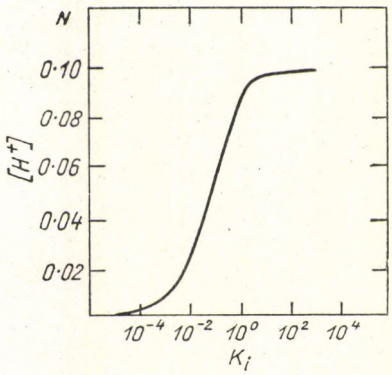


Fig. 28. Change of concentration of the hydrogen ion in a 0·1 N acid solution as a function of the ionization constant

only in basicity and acidity, but also in their specific interaction. The relative strengths of acids of identical charge type and similar character, e.g. HCl, HBr; and R. COOH, R. CH_2 COOH, however, vary only slightly with change of solvent.

Of the interactions between solvent and solute, that in which solvent anions or cations are formed produces a levelling effect, while interactions such as the establishment of a hydrogen-bond, bring about differentiating effects.

The occurrence of solvent anion or cation formation is, in itself, not sufficient to produce a levelling effect; the extent of ion formation is also very important. Weak or very weak bases only form acetate ions to a limited extent in acetic acid; but strong bases are converted almost entirely into acetates. In the former case the inherent differences in base strengths remain; in the latter the strengths become levelled. (See: Chapter 3; Section 23(a) and Chapter 2; Section 16(b)).

Inorganic acids (e.g., perchloric acid, *p*-toluenesulphonic acid, sulphuric acid, hydrochloric acid) remain strong in formic acid, but behave differently in acetic acid. This dissimilar behaviour is due to the great difference between the dielectric constants of the solvents [737c] (acetic acid 6·15, formic acid 58·5). The p*K* values of these acids increase as the dielectric constant of the diluent acid becomes lower. Thus solvents of low dielectric constants (e.g. acetic acid and trichloroacetic acid) differentiate the strength of $HClO_4$, H_2SO_4, $MeC_6H_4SO_3H$ and HCl, whereas in a solvent with high dielectric constant (e.g., formic acid or dichloroacetic acid) the strengths are levelled [737d].

The table below demonstrates the effect of formic acid, as a levelling solvent, on various bases [737b]:

Base	p*K* (H_2O)	p*K* (*H.COOH*)
Diethylamine	2·90	0·74
Codeine	6·05	0·81
Morphine	6·13	0·84
Urea	13·82	1·25

Bestimmte Komponente	Maßlösung	Zur Markierung in der Prüflösung verwendetes Radionuclid	Bemerkung	Literatur
Cu^{2+}	Dithizon	^{65}Zn	Trennung durch Extraktion; pH = 5,3; Best. von 5–10 μg	[32]
	Dithizon	^{115m}Cd	Trennung durch Extraktion; pH = 1,0 und 7,0; Best. von 10 μg Cu, 11 μg Zn	[20]
	0,1 M ÄDTE	^{110m}Ag als $AgIO_3$	Unter Anwendung von festem Indikator; pH = 2,0 und 9–10; Best. von 0,2–2,0 mg. Angewandt bei Bronze und Messing	[14]
	$[CoY]^{2-}$ (H_4Y = = ÄDTE)	^{60}Co	Trennung durch fokussierenden Ionenaustausch; Substitutions-Titration; Best. von 5–10 μg	[30]
Cu^{2+} + + Zn^{2+}	Dithizon	^{65}Zn	Trennung durch Extraktion; nichtisotope Markierung	[32]
Fe^{3+}	5×10^{-2} M ÄDTE	^{90}Y als $Y(C_2O_4)_3$	Unter Anwendung von festem Indikator; pH = 5,0 (Acetat-Puffer); Best. von 15–37 mg Fe_2O_3. Angewandt bei Portlandzement	[25]
	$[Co]Y^{2-}$	^{60}Co	Trennung durch fokussierenden Ionenaustausch; Substitutions-Titration; Best. von 5–10 μg	[30]
Hg^{2+}	$1{,}84\times10^{-5}$ M Dithizon	^{203}Hg	Trennung durch Extraktion; pH = 1,0 (0,1 N HNO_3); Best. von 4,0–40,00 μg	[11]
	62 μM Dithizon	^{203}Hg	Trennung durch Extraktion; pH = 0,5 (H_2SO_4); Best. von 110 μg	[32]

The hydrogen bond. It was observed long ago that compounds containing a hydroxyl group have a higher boiling point than their isomers which do not contain this group.

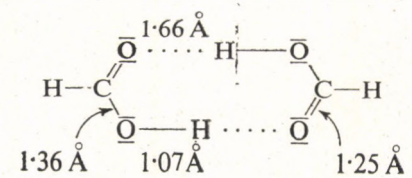
Ethanol	78·4°C	Dimethyl ether	—23·7°C
Propanol	97·2°C	Ethyl ether	7·6°C

The cause of this phenomenon is the interaction between the hydrogen atom of the OH group in one of the molecules and the oxygen atom of another molecule, resulting in a stronger bonding than the van der Waals forces, but having a smaller bond energy than the average covalent bond. This type of chemical bond, characteristic of the interaction between a hydrogen atom and an atom possessing a free electron pair was called a *hydrogen bond* or *hydrogen bridge* by Huggins, and also by Latimer and Rodebush [87, 500].

The formation of the H-bond and its strength depend on the acidity of the hydrogen donating molecule (its proton donor ability) and on the basicity of the *acceptor* atom containing the lone electron pair. In order that an H-bond can be formed the acceptor atom must normally be at least as basic as the nitrogen, oxygen and fluorine atoms in an uncharged molecule and the bonding hydrogen atoms must possess a stronger acidic character than that of the H atoms in saturated hydrocarbons, since otherwise the resultant very weak H-bond has very little importance. If, however, the H atom is too labile, i.e. if it actually is an 'acidic hydrogen', and the acceptor atom is too basic then the H atom is displaced in the field of force of the acceptor atom, and, in the course of proton transfer, a covalent bond comes into being:

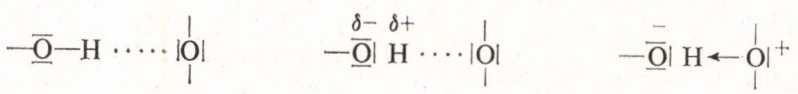
$$X \ldots H \ldots : Y \rightleftharpoons X^- \; H : Y^+$$

It is known that carboxylic acids are present in dimer form. Dimerization occurs through H-bonding:



In the above scheme the hydrogen atoms are not equally distant from the oxygen atoms (expressed in Ångström units) (cf. [399, 440, 327]). Mesomeric stabilization of the dimer does not, therefore, involve a resonance hybrid in which the H atoms would be equidistant from the oxygen atoms; dipole interaction may also play a part. Coulson [151] expressed the view that electrostatic interactions also come into play in hydrogen-bonding.

Summarizing it can be stated that in the formation of H-bonds *(a)* the relative nucleophilicity of the atoms taking part in hydrogen bonding, *(b)* the electrostatic dipole interactions and *(c)* to a certain extent, resonance effects, come into play (p. 260 in [605]).



a *b*

Bestimmte Komponente	Maßlösung	Zur Markierung in der Prüflösung verwendetes Radionuclid	Bemerkung	Literatur
Hg^{2+}	Dithizon	^{203}Hg	Trennung durch Extraktion; pH = 0,65 (Acetat-Puffer); Best. von 0,016–0,8 mg	[18]
Hg^{2+} + + Zn^{2+}	Dithizon	^{65}Zn	Trennung durch Extraktion; pH = 4,0; Best. von 0,1 mg Hg, 0,09 mg Zn	[32]
In^{3+}	10^{-5} M ÄDTE	^{114m}In	Trennung durch Ionenaustausch; pH = 2–3; Best. von 0,22–0,88 μg	[35]
	2×10^{-3} M Dithizon	^{115}In	Trennung durch Extraktion; pH = 5,2; Best. von 15–20 μg	[21]
	8-Oxychinolin	^{115}In	Trennung durch Extraktion; pH = 5,0; Best. von 70 μg	[21]
In^{3+} + + Cd^{2+}	2×10^{-3} N Dithizon	^{115}In	Trennung durch Extraktion; pH = 5,2; Best. von 20 μg In, 30 μg Cd	[21]
Mg^{2+}	0,1 M ÄDTE	^{110m}Ag als $AgIO_3$	Anwendung von festem Indikator; pH = 9–10; Best. von 0,1–5,0 μg	[2, 5]
Na^{+}	0,1 M ÄDTE	^{110m}Ag als $AgIO_3$	Indirekte Titration; Anwendung von festem Indikator; pH = 5 und 10; Na in Form von Natrium-Zink-Uranylacetat gefällt, Zn^{2+}-Gehalt des Niederschlages mit ÄDTE titriert. Best. von 0,35–6,0 mg	[1]
Ni^{2+}	CN^{-}, coulometrisch aus $K[Ag(CN)_2]$ hergestellt	^{110m}Ag als AgI	Anwendung von festem Indikator; radiocoulometrische Titration	[7, 36, 37]

Hydrogen bond formation and solvent-anion or -cation formation are interrelated processes:

$$(AH \ldots sH) \rightleftarrows (A^- sH_2^+); \quad (B \ldots sH) \rightleftarrows (BH^+ s^-)$$

where AH = the H-acid
sH = the amphiprotic solvent
A^- = the anion base
sH_2^+ and s^- = the solvent-cation and -anion
B = the base
BH^+ = the 'onium ion formed from the base by proton acceptance.

(See also: Chapter 2; Section 11 (b), and Chapter 5; Section 31.)

Some solvents have a differentiating and some a levelling effect; some solvents are between the two. The acidity and basicity of the solutes become differentiated when they form H-bonds with the solvent whereas considerable 'onium ion formation leads to levelling. The original acidic or basic character, however, changes in both cases.

The tendency of solvents to form H-bonds can also be determined by infrared analysis. When CH_3OD (deuteromethanol) is dissolved in a solvent the displacement ($\Delta\mu$) of the infrared absorbtion characteristic of the —O—D vibration from the value found in benzene solution is proportional to the hydrogen bonding tendency of the solvent [282]. The strength of the D-bond may be correlated with the basicity of the solvent and solubility of the proton donor solutes. However, no connection is found between the strength of the D-bond and the dipole moment of the solvent:

Solvent	$\Delta\mu$	*Solvent*	$\Delta\mu$
Benzene	0·00	Acetone	0·14
Chlorobenzene	0·02	1,4-Dioxan	0·14
Nitrobenzene	0·04	Diethyl ether	0·19
Acetonitrile	0·09	Aniline	0·27
Methyl ethyl ketone	0·11	Pyridine	0·27
Diethyl ketone	0·11	Ethylene glycol	0·31
Ethyl acetate	0·12	Piperidine	0·37

For further details of hydrogen-bonding theory, its experimental determination and importance see: [18, 19, 87, 90, 167, 282, 327, 341, 571, 771, 870].

39. Acidic Solvents

For the determination of water-insoluble weak bases, proton donating acidic solvents such as acetic acid and propionic acid are employed. Nitrogenous organic bases can be titrated as relatively strong bases by interaction with the solvent:

$$B + sH \rightleftarrows BH^+ + s^-$$

e.g. $C_6H_5NH_2 + CH_3COOH \rightleftarrows C_6H_5NH_3^+ + CH_3COO^-$

Base — Solvent — 'Onium ion — Solvent anion

Bestimmte Komponente	Maßlösung	Zur Markierung in der Prüflösung verwendetes Radionuclid	Bemerkung	Literatur
Pb^{2+}	$[CoY^2]^-$	^{60}Co	Trennung durch fokussierenden Ionenaustausch; Substitutions-Titration; Best. von 5–10 μg	[30]
	Dithizon	^{110m}Ag	Trennung durch Extraktion; Indirekte Titration; Best. von 14,0 μg	[32]
	NaI	^{109}Pd oder ^{131}I	Trennung durch Extraktion	[31]
	NH_4SCN	^{109}Pd	Trennung durch Extraktion	[31]
Sr^{2+}	0,1 M ÄDTE	^{110m}Ag als $AgIO_3$	Anwendung von festem Indikator; pH = 9–10; Best. von 0,1–5,0 mg	[2, 5]
Tb^{3+}	10^{-2} M ÄDTE	^{160}Tb	Trennung durch Papierchromatographie; Best. von 10 μg	[29]
WO_4^{2-}	0,1 M ÄDTE	^{110m}Ag als $AgIO_3$	Indirekte Titration; Anwendung von festem Indikator; pH = 10. Fällung von $CaWO_4$, Auflösung des Niederschlages und Titration des Ca^{2+} mit ÄDTE; Best. von 0,4–7,5 mg	[1]
Zn^{2+}	34,4 μM Dithizon	^{65}Zn	Trennung durch Extraktion; pH = 6,2–7,0 (Acetat-Puffer); Best. von 0,3–13,0 μg	[32]
	Dithizon	^{65}Zn	Trennung durch Extraktion; pH = 7,0–7,5 (NH_3); Best. von 22–40 μg in 1 g Substanz. Angewandt bei biologischen Stoffen	[33]

The base strength of amines is thus indirectly increased, and also levelled, and it is the acetate ion which is titrated:

$$CH_3COO^- + C_6H_5NH_3^+ + CH_3COOH_2^+ClO_4^- = C_6H_5NH_3^+ClO_4^- + 2CH_3COOH$$

Acetate ion 'Onium ion Acetacidium perchlorate Anilinium perchlorate Solvent

The reaction goes to completion if the base to be titrated is a stronger proton acceptor than the solvent and the conjugate base of the acid employed for titration. In the case of the above example:

$$C_6H_5NH_2 \gg CH_3COOH > ClO_4^-$$

Thus, the proton migrates from perchloric acid, through the intervention of acetic caid, to the aniline.

SOLVENTS SUITABLE FOR THE DETERMINATION OF BASES

Inert Solvents *(Listed in the order of increasing dielectric constants)*
n-Hexane, cyclohexane, dioxan, carbon tetrachloride, benzene, chloroform, chorobenzene, methyl isobutyl ketone, methyl ethyl ketone, acetone, acetonitrile.
Acidic or Amphiprotic Solvents *(Listed in the order of decreasing acidity)*
Formic acid, acetic acid, propionic acid, acetic anhydride, nitromethane, nitrobenzene, ethylene glycol, propylene glycol, 'Cellosolve', isopropanol.
Note: in the titration of bases 1,4-dioxan is considered as an inert solvent.

40. Basic Solvents

Proton acceptor basic solvents, such as for instance, ethylenediamine, pyridine n-butylamine and dimethylformamide, are used primarily for the solution of acids and acid-analogues (phenols, enols, imides, sulphonamides etc.), and in this case the conjugate base of the dissolved acid and the solvated proton are formed:

$$AH + s \rightleftarrows sH^+ + A^-$$

e.g. $[C_6H_5COO]H + C_5H_5N \rightleftarrows C_5H_5NH^+ + C_6H_5COO^-$

Acid Solvent 'Onium ion Conjugate base of the acid

Thus the acid strengths are increased and become levelled, and it is the 'onium ion which is titrated.

$$C_5H_5NH^+ + C_6H_5COO^- + CH_3ONa = C_6H_5COONa + C_5H_5N + CH_3OH$$

Pyridinium ion Benzoate anion Sodium methoxide Sodium benzoate Solvents

Bestimmte Komponente	Maßlösung	Zur Markierung in der Prüflösung verwendetes Radionuclid	Bemerkung	Literatur
Zn^{2+}	Dithizon	^{65}Zn	Trennung durch Extraktion; Best. von 2,0–59,0 μg Cu, 38,0 μg Zn. Angewandt bei Legierungen	[19]
Zn^{2+} + + Cu^{2+}	Dithizon	^{65}Zn	Trennung durch Extraktion; pH = 4,75 (Acetat-Puffer); Best. von 0,019–0,28 mg	[18]
Y^{3+}	0,0954 M ÄDTE	^{90}Y	Trennung durch fokussierenden Ionenaustausch; Direkt-Titration	[30]

4.8. Literatur

[1] Braun, T.: Acta Chim. Hung., *41*, 199 (1964)
[2] Braun, T.: Chim. analyt., *46*, 61 (1964)
[3] Braun, T. und Kőrös, E.: Proc. of the IAEA Symp. on Radiochemical Methods of Analysis, *11*, 213, IAEA, Wien (1965)
[4] Braun, T., Maxim, I. und Galateanu, I.: Nature, *182*, 936 (1958)
[5] Braun, T., Maxim, I. und Galateanu, I.: Shur. Analyt. Chim., *14*, 542 (1959)
[6] Braun, T. und Tölgyessy, J.: Talanta, *11*, 1543 (1964)
[7] Braun, T., Tölgyessy, J., Jesenák, V. und Hradil, M.: Acta Chim. Hung., *46*, 35 (1965)
[8] Chleck, D. J.: Proc. of the IAEA Symp. on Radiochemical Methods of Analysis, II, 273, IAEA, Wien (1965). Chem. Analyst, *54*, 83 (1965)
[9] Chleck, D. J., Maehl, R. und Cuchiara, O.: Report N. Y. — 0-2757-3, 1 Nov. (1963)
[10] Chleck, D. J., Maehl, R., Cuchiara, O. und Carnevale, E.: Internat. J. Appl. Radiation and Isotopes, *14*, 581 (1963)
[11] Duncan, J. F. und Thomas, F. G.: J. Inorg. Nucl. Chem., *4*, 376 (1957)
[12] Duncan, J. F. und Thomas, F. G.: Proc. Australian Atomic Energy Symp. Radioisotopes, Physical Sciences, 637 (1958)
[13] Flaschka, H.: EDTA Titrations, Pergamon Press, Oxford (1959)
[14] Galateanu, I., Maxim, I. und Braun, T.: Z. analyt. Chem., *172*, 274 (1960)
[15] Ionescu, S. und Grigorescu-Sabău, C.: Proc. Internat. Conf. on the Peaceful Uses of Atomic Energy, Genf *28*, 148 (1958)
[16] Iwantscheff, G.: Das Dithizon, Chemie Verlag, Weinheim (1958)
[17] Jager, H. und Schindler, O.: Helv. Chim. Acta, *40*, 1310 (1957)
[18] Korenman, I. M. und Schejanowa, F. R.: Trudy Kom. Analyt. Chim., *9*, 205 (1958)

A prerequisite for the determination is that the solvent molecule should be able to form an 'onium ion and, further, that the titrant should be more basic than the conjugate base of the solvent and the acid (or acid analogue) to be determined:

$$CH_3O^- \gg C_5H_5N \geq C_6H_5COO^-$$

The proton migrates through intervention of the solvent towards the methoxide anion base.

In order to obtain reliable titrimetric results (1) the solvent must have a low degree of self-ionization so that errors caused by solvolysis become insignificant and (2) the dielectric constant of the solvent must not be too small, otherwise detection of the end-point by potentiometric titration may be complicated.

SOLVENTS SUITABLE FOR THE DETERMINATION OF ACIDS (AND ACID ANALOGUES)

Inert Solvents *(Listed in the order of increasing dielectric constants)*
Benzene, toluene, chlorobenzene, methyl isobutyl ketone, methyl ethyl ketone, acetone, acetonitrile.
Basic or Amphiprotic Solvents *(Listed in the order of diminishing basicity)*
Ethylenediamine, n-butylamine, pyridine, dimethylformamide, 1,4-dioxan, ethyl ether, t-butanol, isopropanol, n-propanol, n-butanol, ethanol, methanol, Methyl Cellosolve, propylene glycol.

41. Solvent Mixtures

The advantages of solvent mixtures prepared from two or three components are as follows:

1. Not all compounds can be titrated in pure solvents, partly because of their poor solubility in the latter and partly also because of the separation of the neutraliza-

Table 13

SOLVENT MIXTURES SUITABLE FOR THE DETERMINATION OF ACIDS (AND ACID ANALOGUES)

Solvent Mixtures	*References*
Acetone-butanol	[692]
Acetone-pyridine	[307]
Benzene-isopropanol	[159, 530]
Benzene-methanol	[25, 153, 252, 665]
Benzene-pyridine	[307]
Chlorobenzene-ethyl ether	[753]
Chlorobenzene-methanol	(instead of benzene-methanol)
Chloroform-dimethylformamide	[153]
Chloroform-polyethyleneglycol-'400'	[788]
1,4-Dioxan-butanol	[692]
Ethylene glycol-acetone	[170]
Light petroleum-isopropanol	[530]
Toluene-isopropanol	[273]

[19] KORENMAN, I. M., SCHEJANOWA, F. R., MEZINA, H. M. und OSTASCHEWA, M. I.: Shur. Analyt. Chim., *12*, 48 (1957)
[20] KORENMAN, I. M., SCHEJANOWA, F. R., MITROCHINA, T. N. und TRAPESNIKOWA, T. N.: Trudy Chim. i Chim. Technol., *1*, 109 (1958)
[21] KORENMAN, I. M., SCHEJANOWA, F. R., MITROCHINA, T. N. und TRAPESNIKOWA, T. N.: Trudy Chim. i Chim. Technol. *2*, 414 (1959)
[22] KALLEN, J. und HEILBRONNER, E.: Helv. Chim. Acta, *43*, 489 (1960)
[23] KELLER, R. A. und GIDDINS, I. C.: J. Chromatog., *3*, 205 (1960)
[24] KUKULA, F. und KŘIVÁNEK, M.: Chem. Zvesti, *20*, 188 (1966)
[25] LIEBERMAN, R., TOWNLEY, CH. W., BROWN, CH. T., HOWES, JR. J. E., EWING, R. A. und SUNDERMAN, D. N.: BMI-Report-1508 (1961)
[26] RŮŽIČKA, J. und STARÝ, J.: Atomic Energy Review, *2*, 3 (1964)
[27] SCHUMACHER, E.: Helv. Chim. Acta, *40*, 228 (1957)
[28] SCHUMACHER, E.: Helv. Chim. Acta, *40*, 2322 (1957)
[29] SCHUMACHER, E. und FRIEDLI, W.: Helv. Chim. Acta, *43*, 1013 (1960)
[30] SCHUMACHER, E. und STREIFF, H. I.: Helv. Chim. Acta, *41*, 1771 (1958)
[31] SPACU, P. und VOICU, V.: Acad. Rep. Populare Romine, Studii Cercetari Chim., *10*, 305 (1962)
[32] SPITZY, H.: Microchim. Acta, 789 (1960)
[33] SPITZY, H. und DOSUDIL, I.: Microchim. Acta, 119 (1962)
[34] SPITZY, H. und DOSUDIL, I.: Proc. Internat. Symp. on Microchem. Techniques (Pennsylvania State Univ.), Wiley, New York (1962), S. 919
[35] STARÝ, J., RŮŽIČKA, J. und ZEMAN, A.: Talanta, *11*, 481 (1964)
[36] TÖLGYESSY, J., JESENÁK, V. und BRAUN, T.: Proc. of the IAEA Symp. on Radiochemical Methods of Analysis, *II*, 199, IAEA, Wien (1965)
[37] TÖLGYESSY, J., JESENÁK, V., BRAUN, T. und HRADIL, M.: Chem. Zvesti, *19*, 465 (1965)
[38] ILLASZEWICZ, A., MÜLLER, K. und SPITZY, H.: Microchem. J. *10*, 1 (1966)
[39] MÜLLER, K.: Anal. Chim. Acta *35*, 162 (1966)

tion product as a gelatinous precipitate as, for example, when benzoic acid is titrated with potassium methoxide in benzene. This can be avoided by adding methanol or isopropanol.

2. The ion solvating power of highly acidic or basic solvents may be combined with the desirable properties of inert or differentiating solvents. In such solvents the colour change of the indicator is sharp, and the potential jump often steeper than in acidic or basic solvents. Solvents of levelling character are mixed with inert solvents mostly in ratios from 1:1 to 1:20, e.g. acetic acid-carbon tetrachloride or pyridine-benzene etc. (For details of some solvent mixtures see: Tables 13 and 14.)

Table 14

SOLVENT MIXTURES SUITABLE FOR THE DETERMINATION OF BASES

Solvent Mixture	*References*
Acetic acid-acetic anhydride	[158, 288, 306, 310, 311, 314, 642, 707, 732, 854]
Acetic acid-acetone	[453]
Acetic acid-benzene	[575]
Acetic acid-carbon tetrachloride	[314, 658]
Acetic acid-chlorobenzene	[175, 317, 638]
Acetic acid-chloroform	[12, 28]
Acetic acid-cyclohexane	[860]
Acetic acid-dichloroethane	[130, 453]
Acetic acid-dioxan	[644]
Acetic acid-dioxan-acetic anhydride	[130]
Acetic acid-dioxan-nitromethane	[401]
Acetic acid-ethylene glycol	[635]
Acetic acid-nitromethane	[132]
Acetic anhydride-formic acid	[676]
Acetic anhydride-nitrobenzene	[865]
Acetic anhydride-nitromethane	[58, 249]
Acetone-phenol	[700]
Acetonitrile-chloroform-phenol	[123, 639]
Benzene-acetic acid	[496, 575]
Benzene-acetic anhydride	[703]
Benzene-chloroform	[158]
Benzene-chloroform-acetic anhydride	[158]
Benzene-nitrobenzene-acetic acid and benzene-nitrobenzene-trichloroacetic acid	[590]
Benzene-nitromethane	[586]
Carbon tetrachloride-phenol	[302, 323]
Chloroform-acetic acid	[28, 297, 587, 790]
Chloroform-isopropanol	[702]
Chloroform-isopropanol-phenol	[701, 702]
m-Cresol-acetonitrile	[787]
Ethyl acetoacetate-acetic acid	[453]
Ethylene glycol-phenol	[622]
Hexane-acetone	[586, 587]
Nitrobenzene-methanol	[579]
Nitrobenzene-xylene	[579]
Nitromethane-benzene-formic acid	[890]
Propionic acid-chlorobenzene-propionic anhydride	[311, 314]

5. Radiometrische Redox-Titrationen

5.1. Problem der Endpunktbestimmung

Das größte Problem bei den radiometrischen Redox-Titrationen ist – entsprechend wie bei den radiokomplexometrischen Verfahren – die Trennung der Komponenten. Sie ist nur unter Einschaltung eines zusätzlichen Trennungsprozesses möglich, und es ist in erster Linie auf die hieraus erwachsenden Schwierigkeiten zurückzuführen, daß auf diesem Gebiet wenig Fortschritte zu verzeichnen sind. Dennoch sind die wenigen – und meist nur vorläufigen – Ergebnisse, über die bisher berichtet wurde, von Interesse, da die zur Überwindung der Schwierigkeiten gemachten praktischen Vorschläge auf sehr beachtenswerte Möglichkeiten aufmerksam machen.

5.2. Endpunktbestimmung mit festen Indikatoren

Feste Indikatoren (siehe Abschnitt 4.3) können auch zur radiometrischen Endpunktbestimmung bei Redox-Titrationen angewandt werden [1, 2]. Titriert man oxydierende Ionen (Ox_2) mit reduzierenden Ionen (Red_1) in Gegenwart des festen Indikator-Niederschlages $*M_iB$, so ist die radiometrische Endpunktbestimmung unter gewissen Voraussetzungen möglich. Red_1 muß mit $*M_i$ Komplexe bilden, d. h. nach der Reduktion der Gesamtmenge von Ox_2 lösen weitere Mengen der Red_1-Ionen einen bestimmten Teil des $*M_i B$ auf gemäß:

$$*M_i B + Red_1 \rightleftharpoons *M_iRed_1 + B .$$

Die Vorbedingungen hierfür sind die folgenden:

(a) Die Normal-Redoxpotentiale der Systeme Ox_1/Ox_2 und Red_1/Red_2 sowie die Stabilitätskonstante des Komplexes $*M_iRed_1$ müssen so gewählt werden, daß Ox_2 durch Red_1 vollkommen reduziert wird, noch bevor Red_1 das $*M_i$ komplexiert.

(b) Die Stabilitätskonstante von $*M_iRed_1$ und das Löslichkeitsprodukt von $*M_iB$ müssen so aufeinander abge-

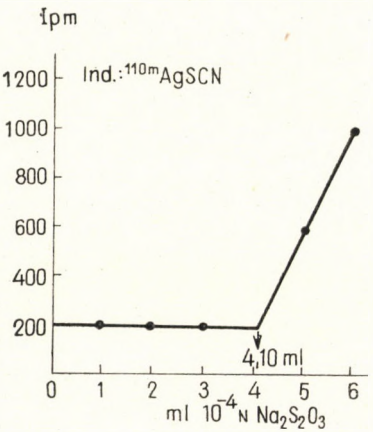


Abb. 5.1
Radiometrische Titration von I_2 mit $Na_2S_2O_3$ in Gegenwart von $^{110m}AgSCN$ als festem Indikator (BRAUN und KŐRÖS [27])

The proportion of acidic to inert solvent must be decided experimentally. Depending on solubility, the titration is improved if the amount of inert solvent, e.g. carbon tetrachloride, is about ten times that of the acidic solvent, e.g. acetic acid. In such cases the sharpness of colour change of the indicator is sufficient even for the titration of 0·001 N perchloric acid (Chapter 13; Section 72 [319]).

The so-called 'G–H' solvent mixtures [170, 489, 621], (that is, 'glycol-hydrocarbon') also belong to this group of solvent mixtures. The G component of this solvent mixture may be ethylene-, propylene- or diethylene-glycol, ethylene glycol ethyl- and methyl-ethers (Cellosolve, Methyl Cellosolve), while the H component may be chloroform, dioxan, isopropanol, butanol, pentanol, benzyl alcohol etc. The G component is suitable for dissolving compounds containing highly polar groups, while the H component decreases the viscosity of the glycols, and promotes the solution of aliphatic or aromatic compounds.

3. Precipitation of the neutralization product in crystalline form is brought about by inert solvents. This is often advantageous for the titration or the sharpness of colour change of the indicator [658], e.g. for the determination of sulphonamides. (See: Chapter 23; Section 131; [575]).

42. Choice of Solvents

Solvents should meet the following requirements: (1) They should not undergo undesirable side reactions either with the compound being titrated, or with the standard solution (this restriction does not include solvation and the formation of solvent anions or cations). (2) They must be able to dissolve the compound to at least such an extent that a 0·01 N solution can be prepared. (3) Solvents must allow the observation of the equivalence point either by use of an indicator or by potentiometric titration. (4) Finally, they should be easily purified.

For the choice of the solvent it is advisable, though not always necessary, to have full details of the solubility of the compound to be titrated, its sensitivity to light and the approximate acid or base constants (measured in water). (Tables: 1, 2, 3, 5, 6, 7, 8, 9, 28 and 29.) The most suitable indicator is generally chosen empirically. The exact colour change is checked by potentiometric titration (Chapter 12).

In the case of medium-strength or strong acids or bases, solvents of basic or acidic character are used. In the case of weak acids or bases, it is advisable to dilute the acidic or basic solvent with an inert solvent.

The data below furnish information on the 'strength' of acids and bases in non-aqueous media based on the pK values measured in water:

Acid	pK	*Base*	pK*	pK**
Strong	< 2	Strong	< 8	<10·5
Medium-strength	2– 8	Medium-strength	8–12	10·5–12
Weak	8–10	Weak	>12	>12
Very weak	>10			

* by titration with indicator

** potentiometric titration (cf. Figs 20 and 21).

stimmt sein, daß sich der Niederschlag während des Titrationsprozesses durch Komplexbildung auflöst.

Auf Grund dieser Überlegungen wurde 10^{-4} N Jodlösung unter Anwendung von ^{110m}AgSCN als festen Indikator titriert [2]. Die erhaltene Titrationskurve zeigt Abb. 5.1.

Die Wirkung des festen Indikators beruht auf der Reaktion:

$$m\,{}^{110m}\mathrm{AgSCN} + n\mathrm{S_2O_3^{2-}} \rightleftarrows [{}^{110m}\mathrm{Ag}_m(\mathrm{S_2O_3})_n]^{(2n-m)-} + m\mathrm{SCN^-}\,.$$

5.3. Endpunktbestimmung durch Lösungsmittelextraktion

Die Anwendung der Lösungsmittelextraktion zur Endpunktbestimmung bei den radiokomplexometrischen Titrationen ist bereits besprochen worden (vgl. Abschnitt 4.2). BRAUN und KŐRÖS [2] haben die Lösungsmittelextraktion auch zur Bestimmung des Endpunktes bei radiojodometrischen Titrationen angewandt. Aus der Reihe der Lösungsmittel ($CHCl_3$, CCl_4, o-Xylol) hat sich Tetrachlorkohlenstoff am besten bewährt.

Beim Schütteln einer sauren wäßrigen Lösung von 50 μg markiertem Jodid mit dem gleichen Volumen von Tetrachlorkohlenstoff geht 99,5% des Jods in das organische Lösungsmittel über. Enthält die Lösung dagegen nicht Jod sondern Jodid, so geht nur eine vernachlässigbare Aktivität in das organische Lösungsmittel über. Es wurde z. B. Thiosulfat mit Standard-Jodidlösung (markiert mit ^{131}I) titriert und die Radioaktivität während der Titration sowohl in der wäßrigen als auch in der organischen Phase gemessen. Solange noch Thiosulfat in der Lösung vorhanden war, konnte in der organischen Phase praktisch keine Radioaktivität nachgewiesen werden. Die Zugabe von überschüssiger Jodlösung bewirkte jedoch eine Zunahme der Radioaktivität in der organischen Phase. Eine typische Titrationskurve zeigt Abb. 5.2.

Auch umgekehrt konnte diese Titration erfolgreich durchgeführt werden. Die Kurve (Abb. 5.3) zeigt, daß die Radioaktivität (der organischen Phase) bis zum Endpunkt abnimmt.

5.4. Endpunktbestimmung mit Amalgamen

In gewissen Fällen können zur radiometrischen Endpunktbestimmung von Redoxreaktionen radioaktive Amalgame verwendet werden [1, 2].

Ein reduzierender Stoff (Red_1) reagiert mit einem oxydierenden Titriermittel (Ox_2) gemäß:

$$\mathrm{Red_1} + \mathrm{Ox_2} \rightleftharpoons \mathrm{Ox_1} + \mathrm{Red_2}\,.$$

Ist im titrierten System ein flüssiges Amalgam mit einem markierten Metallatom zugegen (dieses Amalgam muß zur Reduktion des oxydierenden Stoffes Ox_2 fähig sein), so reagiert nach Oxydation des gesamten Red_2 die Titriermittel mit dem Amalgam. Dadurch wird eine der Menge des überschüssigen Titriermittels proportionale Menge markierter $^*Me_i$-Ionen aus dem Amalgam in Freiheit gesetzt:

$$^*\mathrm{Me}_i\,(\mathrm{Hg}) + \mathrm{Ox_2} \rightleftharpoons \mathrm{Hg} + {}^*\mathrm{Me}_i + \mathrm{Red_2}\,.$$

In view of the specific interactions between solute and solvent, universally valid rules for the choice of the solvent cannot be given. An example for the titration of an organic base is as follows: an approx. 0·02 N solution is prepared in 20 ml acetic acid. Should the base be present as hydrochloride, it is dissolved in acetic acid containing 70–75 mg mercury(II) acetate per 20 ml (0·011–0·012 M). The stock solution is pipetted in portions of 1 ml into a 25–50 ml titrating flask or centrifuge tube and then diluted with each of the purified solvents listed below and titrated, in the presence of an indicator, from a microburette with 0·01 N perchloric acid in 1 : 1 acetic acid carbon tetrachloride. Mono-functional bases require approx. 2 ml standard solution. In this way information can be gained concerning the most suitable solvent mixture and indicator.

Solvent	*Indicator*
10 ml Carbon tetrachloride or $CHCl_3$	Crystal violet, α-naphtholbenzein
10 ml Propionic acid	Crystal violet, methanil yellow
10 ml Chlorobenzene	Crystal violet, methyl violet, bromophenol blue, α-naphtholbenzein, tropaeolin 00
10 ml Dioxan	Methyl violet, crystal violet
20 ml Dioxan	Methyl violet, methyl red
20 ml Acetonitrile	Methyl red
10 ml Acetonitrile	Methyl violet, α-naphtholbenzein, tropaeolin 00
10 ml Acetic acid-acetic anhydride 5:1	Crystal violet, cresol red
10 ml Nitromethane	Crystal violet, α-naphtholbenzein
10 ml Nitromethane-benzene 1:1	Quinaldine red
10 ml Methyl Cellosolve	Thymol blue, Congo red

When larger samples are titrated the colour change of the indicator in the most suitable solvent is separately checked by potentiometric titration in the presence of the compound and a standard such as diphenylguanidine. This procedure is of the utmost importance when methods for the determination of new compounds are being elaborated.

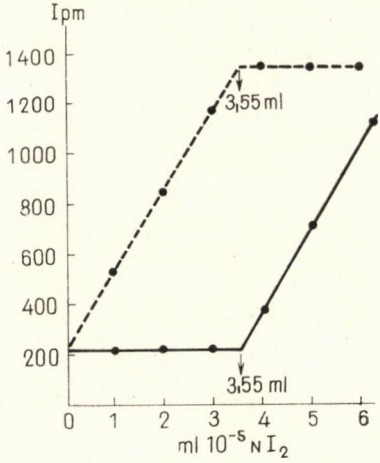


Abb. 5.2
Radiometrische Titration von $S_2O_3^{2-}$ mit I_2, unter Trennung durch Extraktion (BRAUN und KŐRÖS [2]) ---------- wäßrige Lösung; (——— organische Lösung)

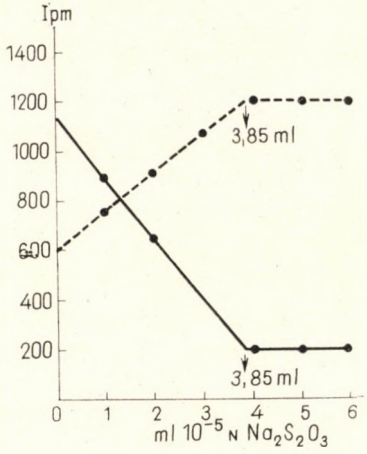


Abb. 5.3
Radiometrische Titration von I_2, mit $Na_2S_2O_3$ unter Trennung durch Extraktion (BRAUN und KŐRÖS [2]) (---------- wäßrige Lösung; ——— organische Lösung)

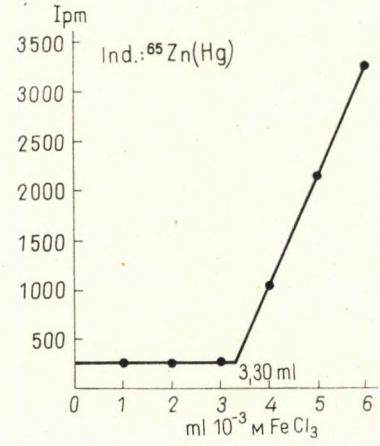


Abb. 5.4
Radiometrische Titration von Ascorbinsäure mit $FeCl_3$ in Gegenwart von ^{65}Zn-Amalgam (BRAUN und KŐRÖS [2])

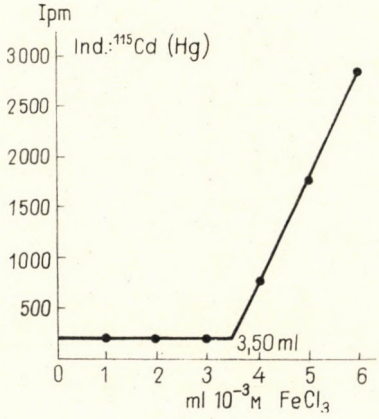


Abb. 5.5
Radiometrische Titration von Hydrochinon mit $FeCl_3$ in Gegenwart von ^{115}Cd-Amalgam (BRAUN und KŐRÖS [2])

Chapter 7

Chemical and Physico-chemical Characteristics of Solvents

43. Inert Solvents

n-Hexane, $CH_3(CH_2)_4CH_3$, *n-heptane*, $CH_3(CH_2)_5CH_3$ and *cyclohexane* (hexahydrobenzene), C_6H_{12}, are inert solvents and are used mixed with acetic acid, propionic acid and acetone [587, 860]. The water content of the latter, as well as that of the standard solution of perchloric acid must not exceed 0·05%, since otherwise the previously homogeneous solution separates in the course of titration, and aqueous acetic acid and indicator remain in the lower phase. For the preparation of absolutely water-free 0·03 N perchloric acid standard solution in dioxan, see: Chapter 9; Section 52 (b).

The solvents mentioned above are inflammable (Table 15).

Table 15

INERT SOLVENTS

Solvent	*Boiling Point* °C	*Specific Gravity* 20°C/4°C	*Refractive Index* $n_D^{20°}$
n-Hexane	68·7	0·659	1·3749
n-Heptane	98·4	0·684	1·3877
Cyclohexane	80·7	0·779	1·4262
Chloroform	61·2	1·489	1·4455
Carbon tetrachloride	76·8	1·594	1·4604
Benzene	80·1	0·879	1·5011
Chlorobenzene	131·7	1·106	1·5248
Acetone	56·2	0·791	1·3588
Methyl ethyl ketone	79·5	0·804	1·3785
Methyl isobutyl ketone	115·7	0·800	1·3958
Acetonitrile	81·6	0·783	1·3441

The solvating power of *chloroform*, $CHCl_3$, is greater than that of hexane. It is suitable for the extraction of milligram quantities of organic bases if concentration

Es bleibt also die Aktivität der wäßrigen Phase bis zum Endpunkt bei einem niedrigen Wert. Werden nun weitere Mengen des Titriermittels zugegeben, so reagiert dieses mit dem Amalgam und die Radioaktivität der Lösung steigt linear an.

In den bisher durchgeführten Versuchen wurde mit ^{65}Zn markiertes Zinkamalgam und mit ^{115}Cd markiertes Cadmiumamalgam verwendet. Abb. 5.4 zeigt die Kurve der Titration einer Lösung von Ascorbinsäure mit Eisen(III)chlorid in Gegenwart von mit ^{65}Zn markiertem Zinkamalgam, Abb. 5.5 die der Titration von Hydrochinon mit Eisen(III)chlorid in Gegenwart von mit ^{115}Cd markiertem Cadmiumamalgam.

5.5. Literatur

[1] Braun, T.: Chim. analyt., *46*, 61 (1964)
[2] Braun, T. und Kőrös, E.: Proc. of the IAEA Symp. on Radiochemical Methods of Analysis, *II*, 213, IAEA, Wien (1965)

of the extract is not needed (Chapter 8; Section 49 (j)). Because of its readiness to establish an H-bond its solvating power exceeds that of carbon tetrachloride (Chapter 3; Section 24 (b)).

The solvating power of *carbon tetrachloride*, CCl_4, is higher than that of hexane but lower than that of chloroform. It is suitable for the extraction of organic bases. The latter can be titrated in it with 0·01 N perchloric acid when acetic acid, propionic acid or acetic anhydride are added. If, however, solvents of the latter kind are not added, the titration can be performed with 0·005 N *p*-toluenesulphonic acid [299, 305]. Carbon tetrachloride is also employed mixed with phenol [302, 323].

For the preparation of 0·02 – 0·01 N perchloric acid standard solution, it is advisable to use as solvent a mixture of acetic acid (or propionic acid) and carbon tetrachloride in equal proportions, thus increasing the sharpness of colour change.

The most commonly used solvent for the non-aqueous titration of acids is *benzene*, C_6H_6, mixed with methanol, isopropanol or pyridine. For the determination of bases, it is mixed with acetic acid or acetic anhydride in an empirically established ratio. Owing to frequent emulsion formation it is less suitable for the extraction of organic bases than is carbon tetrachloride or chloroform. *Toluene* and *xylene* may be used in the same way as benzene.

Benzene forms additive complexes with electrophilic Lewis acids [243].

Of the chlorinated aromatic hydrocarbons *chlorobenzene*, C_6H_5Cl, mixed with acetic acid, propionic acid or acetic anhydride (1 : 1 – 10 : 1) is the most suitable solvent; with these mixtures, the sharpness of colour change of the indicator and that of the end-point in potentiometric titrations are improved. Its solvating power is higher than that of benzene, though far less than that of acetic acid. The higher solvating power of chlorobenzene in comparison with that of benzene can be accounted for partly by its dipole moment.

The observed dipole moment results from the mesomerism of chlorobenzene which opposes the inductive effect (-*I*) of the chlorine atom (p. 429 in [870]).



a *b* *c* *d*

The dipole moment of all chlorinated, saturated, aliphatic hydrocarbons is close to 2·0 D. The negative end of the dipole is in the direction of the chlorine atom. In the case of chlorobenzene the dipole is decreased by the canonical resonance forms *b*, *c* and *d*. As a result, its dipole moment (μ) is only 1·56 D.

The most suitable indicators in chlorobenzene are bromophenol blue, and, in the presence of acetic acid, triphenylmethane dyes. Depending on the strength of the dissolved base, the colour of bromophenol blue changes from purple to pink and finally to yellow (this is seen at, e.,g.: pK of atropine = 4·35; pK of strychnine = 6·0; pK of amidopyrine = 9·30). At the equivalence point the yellow changes to colourless (Chapter 23; Section 124 (b), [638]).

6. Addendum zur deutschen Ausgabe

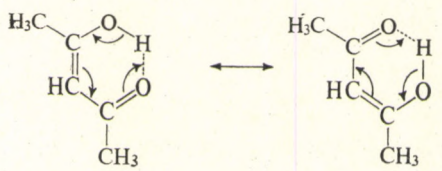
Tabellarische Zusammenfassung der seit dem Erscheinen der englischen Ausgabe veröffentlichten neueren Ergebnisse

Bestimmtes Element (Verbindung); untersuchtes (gelöstes) Problem	Maßlösung	Zur Markierung verwendetes Radiolnuclid	Bemerkung	Literatur
Theoretische Probleme der radiometrischen Fällungstitrationen			Der Zusammenhang einzelner Parameter der radiometrischen Fällungstitration eines markierten Ions mit inaktiver Maßlösung bei beliebiger Stöchiometrie der Fällungsreaktion wird untersucht. Die erhaltenen Zusammenhänge werden in dimensionslose Gleichungen umgeschrieben, für weite Grenzen der Veränderlichen ausgewertet und graphisch dargestellt, um den Einfluß der Versuchsbedingungen zu veranschaulichen. Eine Vereinfachung der Gleichung für niedrige Werte des Löslichkeitsproduktes erleichtert die Auswerung der Meßergebnisse. Für Serienanalysen wird eine graphische Auswertungsmethode vorgeschlagen	[10]
			Vorschlag zur Auswertung von Fällungstitrationen auf Grund des Anfangspunktes der Niederschlagsbildung. Sie wird für Maßanalysen von Lösungen, deren Konzentration mit der Löslichkeit des Niederschlages vergleichbar ist, empfohlen. Es wird eine beträchtliche Empfindlichkeit erwartet. Die Methode wurde experimentell nicht geprüft	[12]
			Ermittlung des Äquivalenzpunktes bei radiometrischen Fällungstitrationen durch Messung der Aktivität des Niederschlages. Eine praktische Anwendung dieser — experimentell nicht geprüften Methode — ist kaum zu erwarten	[11]

Chlorobenzene is not suitable for the determination of bases whose pK value, measured in water, is greater than 10. Chlorobenzene dissolves alkaloid salts only on the addition of acetic acid. For determinations of equivalent weights of picrates, a mixture of chlorobenzene-acetic acid-acetic anhydride or chlorobenzene-propionic acid-propionic anhydride (9 : 9 : 2) is suitable (Chapter 24; Section 135(c), [311, 314]).

For titration of weak acids and acid analogues (e.g. phenols) *acetone*, CH_3COCH_3, is a widely employed solvent and is also used mixed with pyridine in the ratio 4 : 1 [307]. According to Fritz and Yamamura, acids and acid analogues can be conveniently titrated in acetone with a standard solution of tetrabutylammonium hydroxide because the acidic and basic properties of the solvent scarcely interfere [258]. Under some circumstances acetone may form an anion, $(CH_3COCH_2)^-$, while because of its free electron pair, it is capable of forming a co-ordinate bond with a Lewis acid. Its dielectric constant is sufficiently large for potentiometric titrations to be performed. It is miscible in all proportions with water, methanol, acetic acid, benzene, carbon tetrachloride and pyridine. Acetone is inflammable.

Acetone is an exceedingly weak acid; its ionization constant is approx. 10^{-19} (cf. Table 10), although the formation constant of the carbanion (acetone anion) is $2{\cdot}8\times10^{-8}$. Acetone in a pure state contains only 0·00025% enol-form [729]. In acetylacetone the keto-enol equilibrium mixture contains 80% enol-form [145]. This phenomenon is attributable to the stabilizing effect of the intramolecular H-bonds. Since the ketoform, in water, also establishes H-bonds with the solvent, acetylacetone exists 15% in the enol form in water, but 92% in hexane or in the vapour-phase (see also Table 10):



Ethyl methyl ketone, $CH_3COC_2H_5$, and *isobutyl methyl ketone* (4-methyl-2-pentanone) are solvents with very good differentiating properties. The latter can be used successfully for differentiating titrations of acid analogues, as well as for those of aliphatic and aromatic amines [105, 479]. For potentiometric titrations of numerous substituted phenols in isobutyl methyl ketone the h.n.p. and pK values are roughly identical with those found in pyridine [595, 780].

Acetonitrile (methyl cyanide), CH_3CN, is practically an inert solvent, although towards picoline it behaves as an acid [829], and towards strong Lewis acids as a base [396, 501]. Acetonitrile being 'basic' is a good solvent for Lewis acids, e.g. $AlCl_3$. Aluminium chloride would be expected to exist in acetonitrile in complexed form with solvent molecules [396]. The self-ionization constant in the scheme:

$$2\,CH_3CN \rightleftharpoons CH_3\overset{+}{C}NH + CH_2CN^-$$

is $3{\cdot}16\times10^{-20}$ [689]. According to van der Heijde and Dahmen, the acidic range is even greater [371] and this is supported by more recent data according to which the self-ionization constant is 3×10^{-26} [140]. It is very difficult to determine the extent

Bestimmtes Element (Verbindung); untersuchtes (gelöstes) Problem	Maßlösung	Zur Markierung verwendetes Radionuclid	Bemerkung	Literatur
Theoretische Probleme der radiometrischen Fällungstitrationen			Es wird eine Methode der Äquivalenzpunktbestimmung bei Fällungstitrationen vorgeschlagen, die mit keinem durch die Löslichkeit des Niederschlages verursachten Fehler behaftet ist, so daß sie vor allem bei Titrationen stark verdünnter Lösungen Verwendung finden kann. Der Äquivalenzpunkt kann aus zwei Punkten der linearisierten Titrationskurve berechnet werden, außerdem können diese Daten zur Ermittlung des Löslichkeitsproduktes des Niederschlages herangezogen werden. Die Methode kann bei radiometrischen und ähnlichen Titrationen zur Anwendung gelangen, wenn die Reaktion nach der Gleichung $A + B = AB$ verläuft, und wenn das zu titrierende Ion aktiv ist	[14]
			In der Arbeit werden die bei der Titration durch die Löslichkeit des Niederschlages und Verdünnung der zu titrierenden Lösung mit dem Titriermittel verursachten systematischen Fehler radiometrischer und ähnlicher Fällungstitrationen untersucht. Es wurden die Gleichungen für die Fehler einiger laufend verwendeter Methoden zur Bestimmung des Titranden abgeleitet, wenn die Fällung nach der Gleichung vom Typ $A + B = AB$ verläuft, und das zu titrierende Ion aktiv ist. Es werden Tabellen der berechneten Fehler als Beispiele für die Anwendung der abgeleiteten Beziehungen angeführt	[15]
			Einige theoretische Probleme der linearen Fällungstitrationen. Untersuchung der Existenz von Extrema und ihrer Lage auf den Titrationskurven	[32]

of the self-ionization range because the strongest acid possible in acetonitrile ($CH_3\overset{+}{C}NH$) is not stable and on the other hand, the strongest base possible in acetonitrile (CH_2CN^-) self-condenses and the resultant product is a weak base [66]:

$$\begin{array}{l} CH_3-C=N^- \\ \quad\quad | \\ \quad CH_2-CN \end{array}$$

Therefore acetonitrile, although a polar solvent, may be classed with the inert solvents and is very suitable for differentiating titrations of acids, acid analogues and bases [155, 247].

Its basic nature is also connected with its polar character [828]:
acetonitrile behaving as a base [501]*:*

$$CH_3\overset{+}{C}=\overset{-}{N}: + BF_3 \longrightarrow CH_3CN{:}BF_3$$

acetonitrile behaving as an acid:

$$CH_3CN + B \longrightarrow \begin{array}{l} CH_3C = N^- \\ \quad | \\ \quad B^+ \end{array} \longrightarrow [B.\,CH_3]^+ + CN^- \qquad [829]$$

The relatively large dielectric constant of acetonitrile should favour dissociation of the $AlCl_3$-acetonitrile complex into ions [396]:

$$2\,CH_3CN.\,AlCl_3 \rightleftharpoons [CH_3CN.\,AlCl_2.\,NCCH_3]^+ + AlCl_4^-$$

Perchloric acid is a strong acid in acetonitrile [138]:

$$HClO_4 + CH_3CN \rightleftharpoons CH_3\overset{+}{C}NH + ClO_4^-$$

The reaction is not completed rapidly, solvation of the proton being a slow process (see: Chapter 2, Section 21(a)). Since the CH_3C^+NH ion is not stable, the strength of acids gradually diminishes in acetonitrile solution [468]. The cause of this is very probably either that the acid and solvent molecules react chemically or the acetonitrile decomposes [404, 424, 502].

Acid-base equilibria in acetonitrile have been also investigated by Kolthoff, Coetzee and co-workers [140, 465, 466, 603]. They found that, in acetonitrile, perchloric acid is completely dissociated. Sulphuric, nitric, hydrochloric and hydrobromic acids dissociate according to the equilibria:

$$2\,HA \rightleftharpoons H^+ + HA_2$$

The predominating equilibrium reaction of diphenylguanidine with acetonitrile is:

$$2\,B + CH_3CN \rightleftharpoons H\,B_2^+ + CH_2CN^-$$

(at concentrations of B greater than 5×10^{-2} M).

			Theoretische Überlegungen über die β-Rückstreuung bei Fällungstitrationen vom Standpunkt der Konzeption der β-Rückstreuung von R. H. Müller	[13]
Theoretische und praktische Probleme der radiometrischen Ionenaustausch-Titrationen			Anwendung fester, granulierter und flüssiger Ionenaustauscher bei radiochelatometrischen Titrationen. Isotope und nichtisotope Indikation. Genauigkeit und Empfindlichkeit der Methoden, Wahl der entsprechenden radioaktiven Indikatoren. Reaktionskinetische Probleme der Bestimmungen; Untersuchung ihrer optimalen Parameter	[17, 18, 19, 39, 40]
Neutronenabsorptions-Titrationen			Die wirksame Komponente der Maßlösung (oder der Prüflösung) muß ein Element mit großem Wirkungsquerschnitt für die thermischen Neutronen enthalten und die Möglichkeit der zweiphasigen Trennung der Produkte von den Ausgangskomponenten muß gegeben sein. Die Intensität der Neutronenstrahlung nach ihrem Durchgang durch die Prüflösung wird in den einzelnen Phasen der Titration gemessen. Z. B.: Fällungstitration: Bestimmung von Tl^+, Rb^+, Cs^+, K^+ mit $Na(C_6H_5)_4B$ als Maßlösung; Bestimmung von Alkaloiden mit HgI_4^{2-}-Maßlösung; Bestimmung von Sulfiden mit $CdNO_3$-Maßlösung usw. Extraktionstitrationen: Bestimmung von Cd^{2+} mit Dithizon-Maßlösung. Bei der Titration wird eine Pu—Be-Neutronen-Strahlenquelle und ein Neutronen-Szintillationszähler angewandt	[35, 45, 46]
Radiochelatometrische Titrationen unter Anwendung von radioaktiven Kryptonaten			Studium der Eigenschaften von radioaktiven Kryptonaten vom Gesichtspunkte ihrer Anwendung als Indikatoren bei radiochelatometrischen Titrationen. Theoretische Probleme der Maßanalyse	[36, 48]

The order of strength of some acids in acetonitrile is as follows:

acetic acid < acetyl chloride < picric acid < monochloroacetic acid < trichloroacetic acid [828]; perchloric acid > hydrobromic acid > 2,5-dichloroanilinium ion > hydrochloric acid > *p*-toluenesulphonic acid > sulphuric acid > diethylanilinium ion > fluorovalerianic acid > oxalic acid > phosphoric acid > benzoic acid > acetic acid [138].

The mixture, acetonitrile-chloroform-phenol (10 : 4 : 1) should be used as a solvent for the determination of alkaloid sulphates, because the majority of these compounds are only slightly soluble in acetic acid [123]. It is typical of the differentiating power of acetonitrile that it can be employed very satisfactorily for the potentiometric titration of e.g. dialkyl derivatives of *p*-phenylenediamine [521]:

Solvent	*Number of Inflections*	*Number of Protons Co-ordinated*
Acetic acid	1	2
Acetonitrile	2	2
Acetone	1	1

The same phenomenon becomes apparent when piperazine derivatives are determined (Chapter 23; Section 123) [132, 811]. For details of the ionization of acids in acetonitrile see: Chapter 2; Section 15 (a). Acetonitrile is miscible with water, ethanol, ethyl ether, benzene and acetic acid in all proportions.

44. Acidic Solvents

Formic acid, H. COOH, has a high dielectric constant $\varepsilon = 58{\cdot}5$ [812]. Amines and nitrogenous heterocyclic compounds have been titrated by Streuli in a mixture of nitromethane and formic acid [777].

The formic acid content of commercial formic acid is often only 90%. If the base or its hydrochloride salt does not dissolve in acetic acid or propionic acid but dissolves in 90% formic acid, then it should be dissolved in formic acid of known concentration and quality and mixed with an equal volume of acetic acid. Add to this solution an excess of a standard solution of perchloric acid together with sufficient acetic anhydride to react with the water content of the formic acid. *Cool while adding acetic anhydride, since the reaction of water with acetic anhydride is catalyzed by perchloric acid.* The excess of perchloric acid may be back-titrated with sodium acetate in acetic acid.

Bases insoluble in acetic anhydride should be dissolved first in 5 ml of 98% formic acid, then mixed with 50 ml acetic anhydride. This procedure is used, for example, with caffeine and theobromine (Chapter 23; Section 126, [676]). Quinine chlorohydrate can be titrated directly in acetic anhydride without the addition of mercury(II) acetate (Chapter 24; Section 136 (m), [676]).

Bestimmtes Element (Verbindung); untersuchtes (gelöstes) Problem	Maßlösung	Zur Markierung verwendetes Radionuclid	Bemerkung	Literatur
Automatische Einrichtungen für radiometrische Titrationen			Fällungstitrationen	[1, 2]
			Radiochelatometrische Titrationen unter Anwendung fester Indikatoren	[1, 2, 5, 34]
			Radiochelatometrische Titration unter Anwendung von Niederschlagsmembranen	[1, 2]
			Extraktionstitration	[27, 28]
			Radiometrische Titration unter Anwendung radioaktiver Kryptonate	[3, 7, 9, 31]
Ag^{+}	Diäthyldithiocarbamat	^{110m}Ag	Radiometrische Extraktions-Titration: 1,80 μg/ml	[29]
As^{3+}; Fe^{3+}	0,1 N $Ce(SO_4)_2$	^{110m}Ag als radioaktive Platte (0,5 g Ag; 600 μ Ci)	Kontinuierliche radiometrische Redox-Titration unter Anwendung eines radioaktiven Metall-Indikators. Medium: 2 N H_2SO_4; Katalysator: 2–10 Tropfen 0,001 M OsO_4	[5, 34]
Ca^{2+}	10^{-2} M ÄDTE	^{85}Kr als $AgIO_3$ [^{85}Kr]	Radiochelatometrische Titrationen. Nach Überschreiten des Äquivalenzpunktes reagiert der Überschuss der chelatbildenen Maßlösung mit dem radioaktiven Kryptonat unter Freisetzung von ^{85}Kr	[37]

Table 16

ACIDIC SOLVENTS

Solvent	*Boiling Point* °C	*Specific Gravity* 20°C/4°C	*Refractive Index* $n_D^{20°}$
Formic acid	100·7	1·220	1·3714
Acetic acid	117·7—118·1	1·049	1·3716
Propionic acid	140·8—141·4	0·993	1·3865
Acetic anhydride	140·0	1·049	1·3904
Propionic anhydride	167·0	1·011	1·4046
Nitromethane	101·3	1·13	1·3819
Nitrobenzene	210·8	1·203	1·5524
Methanol	64·7	0·791	1·3286
Ethanol	78·4	0·789	1·3614
n-Propanol	97·2	0·803	1·3855
iso-Propanol	82·4	0·785	1·3747 (25°C)
Ethylene glycol	197·9	1·113	1·4318
Propylene glycol-1,2	188 —189	1·136	1·4331
Glycol monomethyl ether (Methyl Cellosolve)	124·5	0·965	1·402
Glycol monoethyl ether (Cellosolve)	134·5	0·93	1·4076
Ethylene glycol dimethyl ether (dimethoxyethane)	85·2	0·869	
Polyethylene glycol-'400'		1·13	
t-Butanol	82·4—82·6 (m.p. = 25·6)	0·779*	

* at 26°C

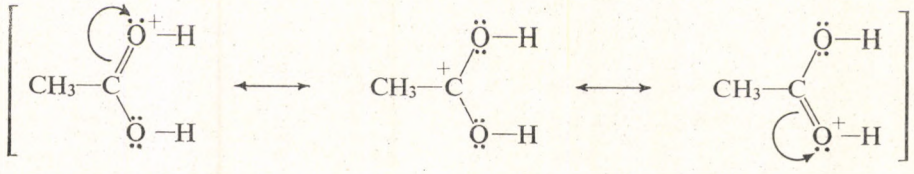
The most frequently used solvent for the determination of bases is *acetic acid*, CH_3COOH. Its properties will therefore be discussed in some detail.*

Acetic acid is an excellent solvent for many organic and inorganic compounds. Acids dissolved in acetic acid give rise to very variable concentrations of oxonium ions. In the case of methanedisulphonic, perchloric and chloromethanesulphonic acids, the concentration of oxonium ions is considerable; however, in the case of monochloroacetic acid it is insignificant and this compound dissolves largely in molecular form. The acetacidium ion is a stronger acid than the hydroxonium ion:

$$HClO_4 + CH_3COOH \rightleftharpoons CH_3COOH_2^+ + ClO_4^-;$$

$$HClO_4 + H_2O \rightleftharpoons H_3^+O + ClO_4^-$$

The acetacidium ion, $CH_3COOH_2^+$, is the conjugate acid of acetic acid as a weak 'base'. It is stabilized by mesomerism, which may be represented by the following resonance forms:



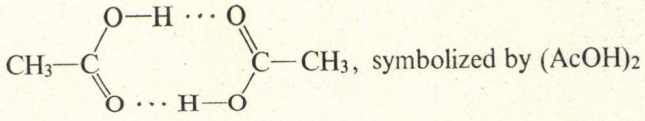
* See also: Heymann and Klaus: Chemie in wasserfreier Essigsäure, Chemistry of Lower Fatty Acids and Derivatives in: *Chemistry in Non-aqueous Ionizing Solvents*, Vol. IV. Edited by Jander, Spandau and Addison, Interscience, New York, 1963.

Cd^{2+}, Ca^{2+}	0,1 N NaF	^{85}Kr als Glaskryptonat	Fällungstitrationen unter Anwendung von Glaskryptonat	[42]
Co^{2+}	10^{-5} M ÄDTE	^{60}Co	Trennung durch Ionenaustausch (feste Ionenaustauscher u. Ionenaustausch-Membranen): 0,10–0,95 μg/ml	[1, 2, 21, 40]
Co^{2+}, Zn^{2+}	10^{-6} M ÄDTE	^{60}Co; ^{65}Zn	Trennung durch Ionenaustausch; isotope Indikation. Titration von 10^{-6} M Lösungen	[6]
Cu^{2+}	Diäthyldithiocarbamat	^{64}Cu	Radiometrische Extraktionstitration; 0,01 μg/ml	[29]
$Cu^{2+} + Ag^{+}$	Diäthyldithiocarbamat	^{64}Cu ^{110m}Ag	Radiometrische Extraktionstitration. Messung mit einem 200-Kanal-Impulsanalysator. Messung der Spitzen bei 0,51 MeV (^{64}Cu) und 0,68 MeV (^{110m}Ag)	[29]
Cu^{2+}, Mg^{2+}, Ni^{2+}, Zn^{2+}, Pb^{2+}	0,1 M ÄDTE	^{110m}Ag als $*AgIO_3$	Radiochelatometrische Titration unter Anwendung eines festen Indikators; Boratpuffer; automatischer Titrator	[5, 34]
Cu^{2+}, Ni^{2+}, Pb^{2+}, Zn^{2+}	0,1–0,01 M ÄDTE	^{110m}Ag als $*AgIO_3$	Radiochelatometrische Titration unter Anwendung eines festen Indikators; Boratpuffer (pH = 10,2); Untersuchung der Anwendbarkeit des festen $*AgIO_3$ als Indikator; Bestimmung von 1–100 μg	[33]
Fe^{3+}	Cupferron	$^{55,59}Fe$	Radiometrische Extraktion: 4,94 μg/ml	[29]
Fe^{3+}	5×10^{-3} M ÄDTE	$^{55,59}Fe$	Trennung durch Ionenaustausch; Bestimmung von 0,2% Fe im Arzneimittelpräparat Tinctura ferri aromatica	[24]
Fe^{3+}	10^{-2} M ÄDTE	^{85}Kr als $Y_2(C_2O_4)_3$ [^{85}Kr]	Radiochelatometrische Titrationen unter Anwendung von radioaktiven Kryptonaten	[47]
Hg^{+}	Dithizon	^{203}Hg	Radiometrische Extraktionstitration; 0,66 μg/ml	[29]

Acetic acid is a solvent 'similar to water' [240], and capable of self-ionization, forming a solvated proton and a base analogue, acetate ion (Chapter 1; Section 3). The ionic product of acetic acid is:

$$K = C_{AcOH_2^+} \cdot C_{AcO^-} = 3{\cdot}5 \times 10^{-15} \qquad [102]$$

Carboxylic acids in general, and so also acetic acid, are present in dimer form in the liquid phase (p. 261 in [605]). The formation of a molecular dimer can be explained in terms of hydrogen-bond formation: the functional group containing the active hydrogen enters into donor-acceptor interaction with the lone electron pair on an atom of another molecule [87]: $X-H \ldots Y$ (X = proton donor, Y = proton acceptor)



, symbolized by $(AcOH)_2$

(See also: Chapter 6; Section 38.)

Acetic acid itself is a poor conductor of electricity, but acetic acid solutions of compounds capable of ionization are good conductors. This provides evidence that these compounds are, at least partly, in a dissociated state, although the dielectric constant of acetic acid is small. This apparent contradiction may be resolved if the association of amines and also the increased dissociation of the complexes formed are taken into account (Chapter 5; Section 33, [561]).

Acetic acid is co-ordinatively unsaturated and forms complexes with some saturated compounds [561]. One of the most important of these is acetacidium perchlorate, first produced by B. Beér [354]. The perchlorate of acetic acid, a stable compound, forms an ionic lattice; the octet deficiency tending to arise in the course of polarization of the carboxyl group is compensated electromerically [205].

In the case of acetic acid also neutralization and solvolysis are opposed processes (Chapter 5; Section 31), and take place to some extent between dimerized or associated molecules and ions. In the course of neutralization the solvated proton is co-ordinated by the base analogue, acetate ion, and two solvent molecules are formed:

$$CH_3COO^- + CH_3COOH_2^+ = (CH_3COOH)_2$$

Weak bases in acetic acid only form 'onium acetates to a small extent. These bases, therefore, *directly* form bases in perchlorates when titrated with the standard solution[85]:

$$C_6H_5NH_2 \ldots CH_3COOH + CH_3COOH_2^+ \; ClO_4^- \rightleftharpoons C_6H_5NH_3^+ \; ClO_4^- + (CH_3COOH)_2$$

Strong and medium-strength bases are present as acetates mainly because of the levelling effect of acetic acid. There are limited data to indicate whether medium-strength bases are, totally or partly, converted into 'onium salts (Chapter 2; Section 16 (b)). However, depending on the equilibrium

$$B \ldots CH_3COOH \rightleftharpoons BH^+CH_3COO^-$$

acetic acid has a levelling effect on strong and medium-strength bases and a differen-

Bestimmtes Element (Verbindung); untersuchtes (gelöstes Problem	Maßlösung	Zur Markierung verwendetes Radionuclid	Bemerknng	Literatur
H_2SO_4, HCl HNO_3	0,1 N NaOH 0,5 N NaOH	^{85}Kr als Glaskryptonat	Neutralisationstitrationen unter Anwendung von Glaskryptonat	[44]
NaOH	HCl	^{85}Kr, als Mg- oder Zn-Kryptonat	Titration starker Base mit starker Säure. Nach Erreichung des Endpunktes reagiert der Säureüberschuß mit dem radioaktiven Kryptonat; ^{85}Kr wird in Freiheit gesetzt, dessen Aktivität mit einem GM-Zählrohr, Ratemeter und Registriervorrichtung verfolgt wurde	[3, 7, 31]
Ni^{2+}	0,1 M KCN	^{85}Kr als AgI [^{85}Kr]	Radiokomplexometrische Titrationen unter Anwendung von radioaktiven Kryptonaten	[38]
Pb^{2+}	10^{-3} M ÄDTE	^{65}Zn	Ionenaustausch-Titration, nichtisotope Indikation, 0,33–1,40 μg-Äqu. Pb	[23]
Th^{4+}	0,1 M NaF	^{85}Kr als Glaskryptonat	Titration in H_2SO_4 als Medium. Gemessen wird die Restaktivität des Glaskryptonats oder die Aktivität des freigesetzten ^{85}Kr. Nach Erreichung des Endpunktes greift das frei werdende HF die Glasoberfläche an und dies zieht die Freisetzung von ^{85}Kr bzw. die Abnahme der Aktivität des Glaskryptonats nach sich	[8, 9, 41, 43]
Y^{3+}	10^{-4} M ÄDTE	^{91}Y	Radiokomplexometrische Titration; Acetatpuffer (pH = 4,5); Trennung durch Papierelektrophorese (200 V/cm); 10^{-10} g/μl	[16]
Zn^{2+}	10^{-5} M DCYTE	^{65}Zn	Ionenaustausch-Titration; Membran-Trennung; bestimmte Menge: 0,02–0,01 μg Zn/ml	[25, 39, 40]

tiating one on weak and very weak bases (Chapter 6; Section 38). Figs. 20, 21 and 22 in Chapter 3 illustrate the levelling of strong and medium-strength bases and the differentiation of weak bases:

Base	p*K*	*Effect of Acetic Acid*
Guanidine	0·5	Levelling
Piperidine	2·8	Levelling
Pyridine	8·8	Levelling
p-Chloroaniline	10·1	Transition
m-Chloroaniline	10·5	Differentiating
m-Nitroaniline	11·4	Differentiating
o-Chloroaniline	11·4	Differentiating
p-Nitroaniline	13·0	Differentiating
Urea	13·5	Differentiating
o-Nitroaniline	14·2	Differentiating
Acetamide	14·5	Differentiating

Propionic acid, CH_3CH_2COOH, can be used in the same way as acetic acid in which the bases become levelled. The protonation constant of propionic acid is $-6{\cdot}8$ [202]. (The pK_{BH^+} value of acetic acid is $-6{\cdot}2$ [279].) The colour change of the indicator (crystal violet, methanil yellow) is often sharper. In potentiometric titrations the deflection in millivolts at the end-point is greater than with acetic acid [314, 374].

Piperidinomethyltolylpropanone picrate (20 mg) can be determined with 0·01 N perchloric acid in a mixture of chlorobenzene-acetic acid-acetic anhydride with an accuracy of $\pm 0{\cdot}7\%$ while in a mixture of chlorobenzene-propionic acid-propionic anhydride the accuracy is $\pm 0{\cdot}1\%$.

Propionic acid was used as a solvent in titrimetry as early as 1938 [801].

Acetic anhydride, $(CH_3CO)_2O$, a liquid with a caustic effect on the skin, is used as a solvent in non-aqueous titrations and also as a dehydrating and acetylating agent. Its solvating power is smaller than that of acetic acid, since the possibility of hydrogen bonding is less and there is no evidence of association [531]. Except with compounds containing acetylatable amino groups, neutralization reactions can be performed equally as well in acetic anhydride as in acetic acid.

In a pure state acetic anhydride dissociates according to the following scheme [531, 561, 722]:

$$(CH_3CO)_2O \rightleftharpoons \underset{\text{Acetyl cation}}{(CH_3CO)^+} + \underset{\text{Acetate ion}}{CH_3COO^-}$$

and the self-dissociation constant has been reported as 3×10^{-15} (at 20°C) [423]. The acetyl cation (acetylium ion) behaves in acetic anhydride like a proton in water, but it is not solvated [531].

In accord with the above dissociation scheme, compounds releasing acetyl cations are acid analogues (e.g. acetyl chloride) and those dissociating to give acetate ions are base analogues. Three sorts of ions behaving as acids can exist in acetic acid-acetic anhydride medium [110, 531]; a fourth, an ion of acid character, can exist only in pure acetic anhydride [831]:

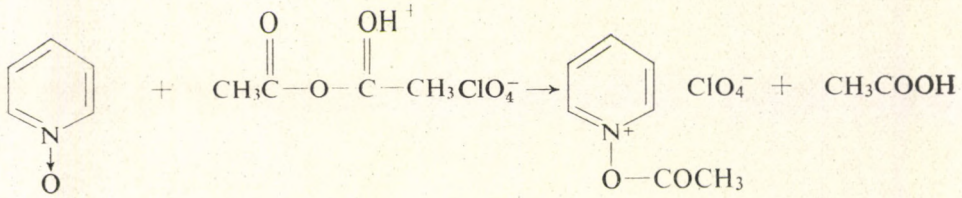
Zn^{2+}	0,1 M ÄDTE	^{60}Zn	Ionenaustausch-Titration; Membran-Trennung; bestimmte Menge: 654–0,706 μg Zn/ml	[30]
Vitamin B_{12}	10^{-5} M ÄDTE	^{60}Co	Das aus Vitamin B_{12} mit Ozon in Freiheit gesetzte Co^{3+} ist mit ^{60}Co markiert und wird durch einen Kationenaustauscher gebunden, dessen Aktivität gemessen wird. Der Kationenaustauscher wird dann mit einer substöchiometrischen Menge ÄDTE-Meßlösung in Reaktion gebracht, die mit einer bestimmten Menge des gebundenen Co reagiert und dieses vom Ionenaustauscher ablöst. Die Restaktivität des Ionenaustauschers wird gemessen. Aus dem Unterschied der Aktivitätswerte wird die Menge des Co und damit auch des Vitamin B_{12} mit Hilfe einer Kalibrationskurve festgestellt. Die Methode ist zur Bestimmung von Vitamin B_{12} in μg-Mengen geeignet	[20, 22, 26]

1. Acetacidium ion	$CH_3COOH_2^+$	Donor acid
2. Acetanhydridium ion	$(CH_3CO)_2OH^+$	Donor acid
3. Acetylium ion	$(CH_3CO)^+$	Acceptor acid
4. Acetyloxonium ion	$[(CH_3CO)_3O]^+$	Acceptor acid

Their order of strength is [878]:

$$CH_3COOH_2^+ < (CH_3CO)_2OH^+ < (CH_3CO)^+$$

The $(CH_3CO)_2OH^+$ reacts, e.g., with aromatic N-oxides in acetic anhydride as shown by the following equation:

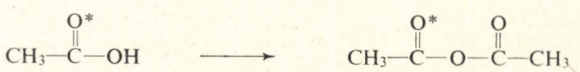


Titration of aromatic N-oxides with perchloric acid, see: [604, 880].

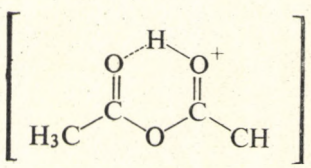
Usanovich provides detailed information on acid–base interactions in acetic anhydride [831]. In this amphoteric solvent acetyl chloride, benzoyl chloride and trichloroacetic acid behave as acids, and therefore can be titrated with sodium acetate [831]. In acetic anhydride numerous salts are solvolyzed. For example, aluminium chloride forms acetyl chloride and $AlCl(CH_3CO)_2$.

A possible explanation of the fact that acetic anhydride is 'more basic' than acetic acid, is as follows: although the localized electron density of the oxygen atom in the acetic acid molecule, (denoted by an asterisk), is decreased by the introduction of an acetoxy group and thus the 'basicity' of the molecule decreases, acetic anhydride is capable of co-ordinating protons, presumably by chelation, while acetic acid is present in dimer form [531]:

Theoretical decrease in 'basicity':



Practical increase in 'basicity':



Acetanhydridium ion (protonated acetic anhydride)

From a number of experiments the conclusion can be drawn that acetic anhydride can act either as proton donor or, as in the Perkin reaction, it may be a carbanion donor [429]. The self-ionization of acetic anhydride is in this case [676]:

6.1 Literatur

[1] BRAUN, T. und TÖLGYESSY, J.: The Pittsburgh Conference on Analytical Chemistry and Applied Spectroscopy, Pittsburgh, Febr. 20–25, 1966, Paper No. 160

[2] BRAUN, T., TÖLGYESSY, J. und KONEČNÝ, J.: Acta Chim. Hung., *49*, 131 (1966)

[3] CHLECK, D., MAEHL, R. und CUCCHIARA, O.: Development of Krypton 85 as a Universal Tracer, Continuation of Phase III., Areas of Application, Period Covered: Nov. 1, 1962–Oct. 31, 1963, USAEC Report NYO-2757-3, Parametrics, Inc., November 1963

[4] DILLINGER, P., TÖLGYESSY, J. und VARGA, Š.: Isotopenpraxis, *3*, 437 (1967)

[5] ILLASZEWICZ, A., MÜLLER, K. und SPITZY, H.: Microchemical Journal, *10*, Nr. 1–4, 1 (1966)

[6] ISHIBASHI, N., KOHARA, H. und FUKUDA, M.: Japan Analyst, *15*, 637 (1966)

[7] Isotope Technology Development, Isotopes Radiation Technol., *3* (3), 206–14 (1966)

[8] JESENÁK, V. und TÖLGYESSY, J.: Chem. listy, *60*, 577 (1966)

[9] JESENÁK, V., TÖLGYESSY, J., VARGA, S. und HRADIL, M.: Sbornik vedeckých prác chemickotechnologickej fakulty SVŠT (Sammelband d. wiss. Arb. d. Fakultät f. Chem. Technol. d. Slowakischen Technischen Hochschule), Bratislava, 1966, S. 117–136

[10] JESENÁK, V., VALTYNI, J. und TÖLGYESSY, J.: Atompraxis, *12*, 606 (1966)

[11] KLAS, J.: Chem. zvesti, *19*, 689 (1965)

[12] KLAS, J.: Chem. zvesti, *19*, 695 (1965)

[13] KLAS, J.: Chem. zvesti, *19*, 783 (1965)

[14] KLAS, J.: Collection Czechoslov. Chem. Commun., *31*, 3512 (1966)

[15] KLAS, J.: Collection Czechoslov. Chem. Commun., *31*, 3519 (1966)

[16] KNOBLOCH, V. und STARÝ, J.: Shur. Anal. Chim., *20*, 1160 (1965)

[17] KONEČNÝ, J.: Dissertation, FTJF ČVUT, Prag, 1966

[18] KONEČNÝ, J. und TÖLGYESSY, J.: Celoštátna konferencia »Problémy merania nizkých aktivit« (Konf. über »Probleme der Messung geringer Aktivitäten«), Stary Smokovec, 11. X.–14. X. 1965

[19] KONEČNÝ, J. und TÖLGYESSY, J.: Radioisotopy, *7*, Nr. 1, 87–103 (1966)

[20] KONEČNÝ, J. und TÖLGYESSY, J.: Radiochemical Conference, Bratislava, 6–10. September, 1966, S. 36

[21] KONEČNÝ, J. und TÖLGYESSY, J.: Vedecká konferencia chemických katedier Prirodovedeckej fakulty UK (Wiss. Konferenz d. naturwiss. Fakultäten), Smolenice 22–24. 9. 1965, Sammelband (unter Druck)

[22] KONEČNÝ, J. und TÖLGYESSY, J.: Chem. zvesti, *20*, 692 (1966)

[23] KONEČNÝ, J. und TÖLGYESSY, J.: Isotopenpraxis *3*, 479 (1967)

[24] KONEČNÝ, J., TÖLGYESSY, J. und BRAUN, T.: Acta Chim. Hung. *51*, 245 (1967)

[25] KONEČNÝ, J., TÖLGYESSY, J. und BRAUN, T.: Proceedings of the Analytical Chemical Conference, Budapest, Vol. *2*, 471–80 (1966)

[26] KONEČNÝ, J., TÖLGYESSY, J. und ŠARUŠUNOVÁ, M.: Z. anal. Chem. *232*, 343 (1967)

[27] KUKULA, F.: Tschechoslow. Patent. Č. PV-7201-65

[28] KUKULA, F.: Radiochemical Conference, Bratislava, 6–10. September 1966, S. 36

[29] KUKULA, F. und KŘIVÁNEK, M.: Chem. zvesti, *20*, 188 (1966)

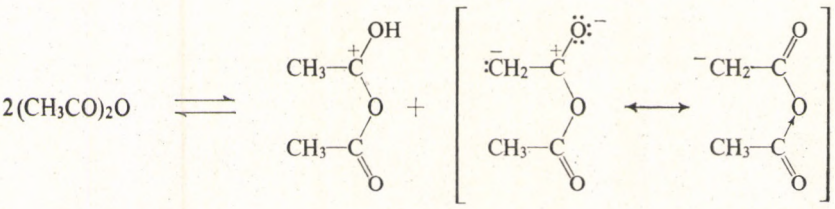
[30] LANDGREBE, A. R., MCSHARRY, W. O. und CEFOLA, M.: Inter. J. Appl. Radiation and Isotopes *19*, 23 (1968)

[31] MAEHL, R., CUCCHIARA, O. und CHLECK, D.: Chemist-Analyst, *54*, Nr. 3, 83 (1965)

[32] MARJANOW, B. M.: Shur. Anal. Chim., *21*, 905 (1966)

[33] MÜLLER, K.: Anal. Chim. Acta, *35*, 162 (1966)

[34] SPITZY, H.: 1965 International Symposium on Microchemical Techniques, 22–27 July 1965, Pennsylvania State University, University Park, Pennsylvania



(See: Chapter 24; Section 136 (m)).

In the potentiometric titration of bases, the addition of acetic anhydride increases the potential jump at the equivalence point. This can be ascribed to the increase in the ion activity of perchloric acid rather than to the dehydrating effect of the anhydride, i.e. formation of a stronger complex acid can be assumed [77]:

$$[ClO_4(CH_3-CO-O-OC-CH_3)_n]H$$

For details of 'acetyl perchlorates' with Lewis acid character see: Chapter 23; Section 130 (a).

Summarizing the above: acetic anhydride is a solvent 'similar to water', but in some respects it is simpler. For example, it does not associate and the acetylium ion is not solvated. Postulating the existence of a stable acetylium ion facilitates the understanding of many phenomena [531], e.g.:

Reaction of aliphatic acids with anhydrides:

$$2\,R'-COOH + (R''CO)_2O = 2\,R''-COOH + (R'CO)_2O$$

Disproportionation of mixed anhydrides:

$$2\,R'CO\,.\,O\,.\,OCR'' \rightleftharpoons (R'CO)_2O + (R''CO)_2O$$

Evidence for the existence of stable positive acyl ions is obtained from the ionization of 2,6-disubstituted benzoic acids in sulphuric acid; this can be followed by cryoscopic measurements [818]:

$$R\,.\,COOH + 2\,H_2SO_4 = RCO^+ + OH_3^+ + 2\,HSO_4^-$$

Propionic anhydride, $(CH_3CH_2CO)_2O$, is more suitable than acetic anhydride for the dehydration of propionic acid and can be used conveniently for the determination of base picrates [311] and hydroxyl numbers [640].

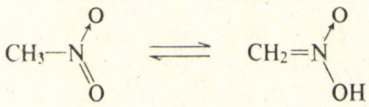
Nitromethane, CH_3NO_2, is a solvent of weak acidic character: $pK_{acid} = 10{\cdot}6$. It can be titrated with sodium methoxide in n-butylamine and with TBAH standard solution in pyridine [252, 780]. With strychnine, ephedrine and codeine it yields crystalline additive compounds [126, 507]. It is often used for differentiating titrations [132, 249].

In sulphuric acid nitromethane acts as a base [270].

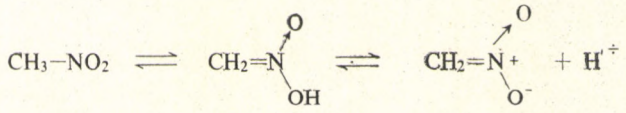
Of the few solvents containing a nitro group the rarely used *nitroethane* also exhibits a feeble acidic character, but its proton donor ability is small. According to Pearson and Dillon a distinction must be made between ionization and formation constant when carbanions are formed [630] (see: Chapter 2; Section 21).

[35] TÖLGYESSY, J.: Jad. energie, *12*, 81 (1966)
[36] TÖLGYESSY, J., BRAUN, T. und VARGA, Š.: Acta Chim. Hung. (unter Druck)
[37] TÖLGYESSY, J., JESENÁK, V., VARGA, Š. und HRONCOVÁ, D.: Chem. zvesti (unter Druck)
[38] TÖLGYESSY, J., JESENÁK V., VARGA Š. und SILEŠ B.: Isotopenpraxis *4*, 259 (1968)
[39] TÖLGYESSY, J., KONEČNÝ, J. und BRAUN, T.: First IMR International Symposium »Trace Characterization-Chemical and Physical« October 3–7, Gaithersburg, Maryland, U. S. A.; Preprints of Contributed Papers, S. 442–453
[40] TÖLGYESSY, J., KONEČNÝ, J. und BRAUN, T.: Nuclear Applications *3*, 383 (1967)
[41] TÖLGYESSY, J., KRIVÁŇ, V., JESENÁK, V. und VARGA, Š.: Arbeitstagung Angewandte Radioaktivität, 11. bis 14. Oktober 1966 in Leipzig, Zusammenfassungen der Vorträge, S. 67–68
[42] TÖLGYESSY, J., SÍLEŠ, B., JESENÁK, V. und VARGA, Š.: Isotopenpraxis (unter Druck)
[43] TÖLGYESSY, J., SÍLEŠ, B., JESENÁK, V. und VARGA, Š.: Isotopenpraxis (unter Druck)
[44] TÖLGYESSY, J., SÍLEŠ, B., VARGA, Š. und JESENÁK, V.: Isotopenpraxis (unter Druck)
[45] TÖLGYESSY, J., VARGA, Š. und DILLINGER, P.: Talanta *14*, 441 (1967)
[46] TÖLGYESSY, J., VARGA, Š. und DILLINGER, P.: Sbornik vedeckých prác Chemicko-technologickej fakulty SVŠT (Sammelband d. wiss. Arb. d. Fakultät f. Chem. Technol. d. Slowakischen Technischen Hochschule), Bratislava, 1967, S. 97—109
[47] TÖLGYESSY, J., VARGA, Š. und JESENÁK, V.: Isotopenpraxis *4*, 223 (1968)
[48] TÖLGYESSY, J., VARGA, Š., JESENÁK, V. und HRONCOVÁ, D.: Chem. zvesti *22*, 3. (1968)

It has not yet been settled whether the earlier view of Hantzsch on the formation of carbanions or the more recent one of Heijde [369, 370, 371] is to be regarded as valid. Aliphatic nitro compounds show nitro-isonitroso (nitronic acid) tautomerism:



In the course of salt formation, a slow and therefore measurable process, the above transformation can be followed using conductivity measurements. The following equilibrium is possible:



(I) (II)

Nitronic acid $\rightleftarrows A^- + H^+$

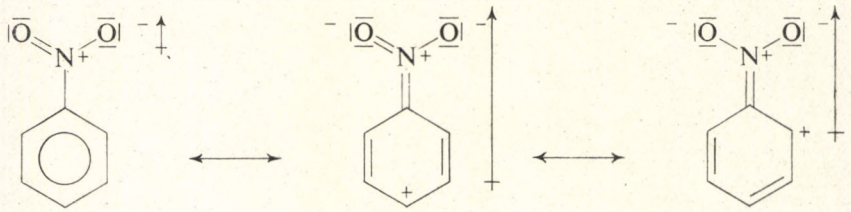
where A^- = the nitronate anion.

According to Hantzsch, the nitronic acid content of nitromethane in water is very small:

$$K = \frac{[II]}{[I]} = 1{\cdot}1 \times 10^{-7} \quad \text{and} \quad K_{acid} = \frac{[H^+]\,[A^-]}{[II]} = 5{\cdot}6 \times 10^{-4}$$

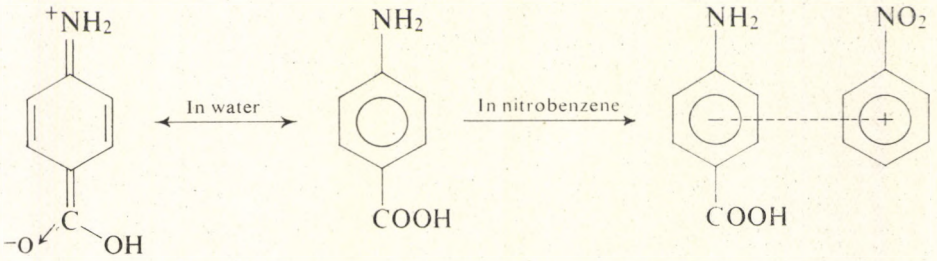
Nitrobenzene is a rarely used solvent, though in many cases it is more convenient than nitromethane. It is sometimes also employed mixed with acetic anhydride, benzene and heptane [579, 590, 865].

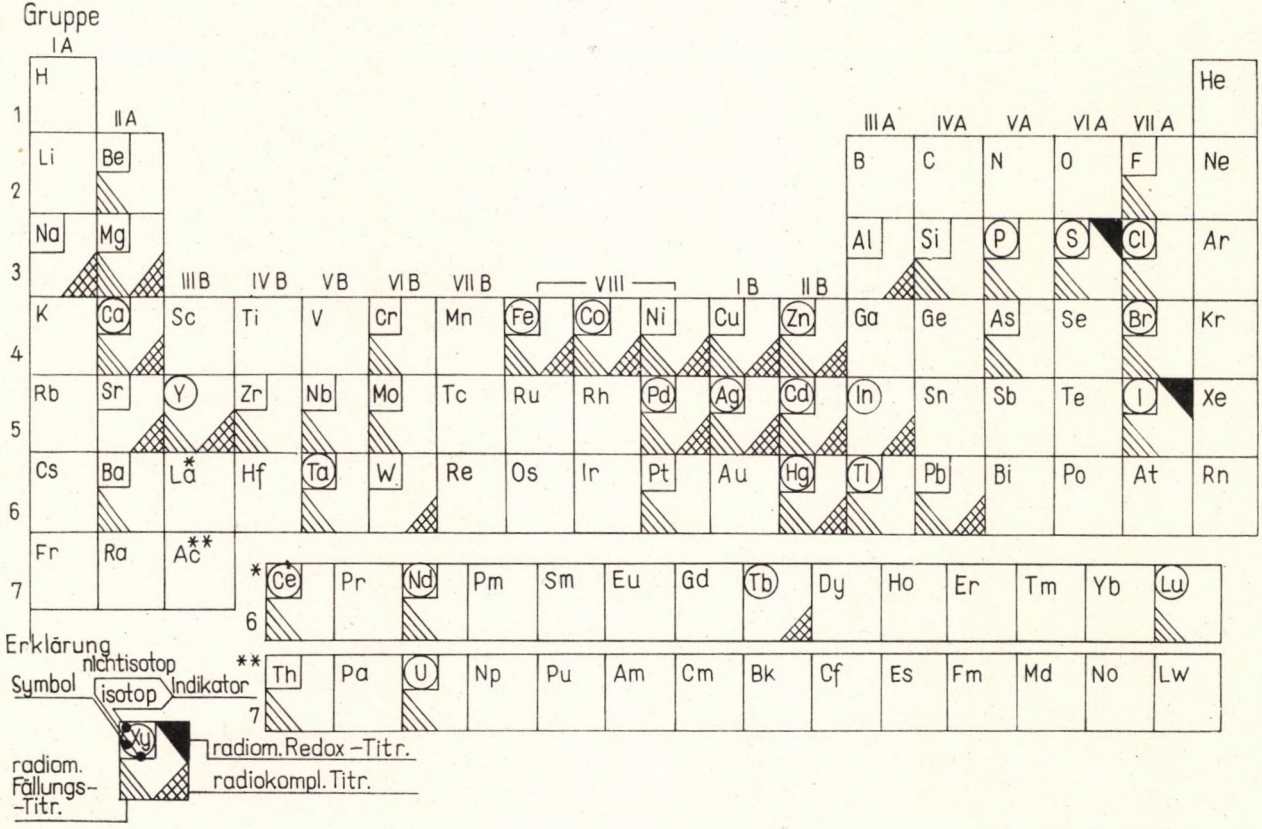
Its dipole moment (μ) is 3·97 D. The dipole moment of saturated aliphatic nitro compounds never exceeds 3·7 D. The amount by which the dipole moment of nitrobenzene exceeds that of the aliphatic compounds is due to the effect of mesomerism:



In accord with the Lewis acid-base theory, the weak acid character of nitrobenzene is explained by its π-complex forming ability with, for example, aromatic amines [585, 595]; a mixture of nitrobenzene and aniline becomes yellow (formation of a change-transfer complex).

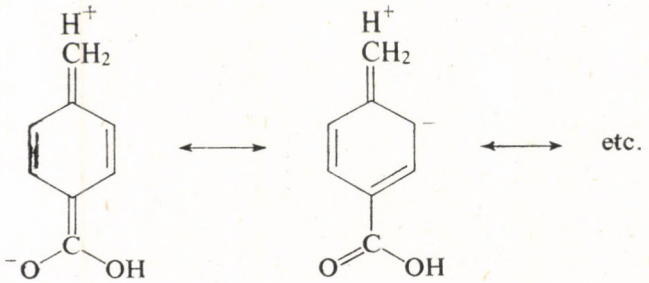
In nitrobenzene (and also in *o*-nitrotoluene), *p*-aminobenzoic acid is stronger than in water, because π-complex formation lowers the electron density of the ring:




Gruppe
IA
IIA
IIIB
IVB
VB
VIB
VIIB
VIII
IB
IIB
IIIA
IVA
VA
VIA
VIIA
H
He
Li
Be
B
C
N
O
F
Ne
Na
Mg
Al
Si
P
S
Cl
Ar
K
Ca
Sc
Ti
V
Cr
Mn
Fe
Co
Ni
Cu
Zn
Ga
Ge
As
Se
Br
Kr
Rb
Sr
Y
Zr
Nb
Mo
Tc
Ru
Rh
Pd
Ag
Cd
In
Sn
Sb
Te
I
Xe
Cs
Ba
La*
Hf
Ta
W
Re
Os
Ir
Pt
Au
Hg
Tl
Pb
Bi
Po
At
Rn
Fr
Ra
Ac**
1
2
3
4
5
6
7
* Ce Pr Nd Pm Sm Eu Gd Tb Dy Ho Er Tm Yb Lu
** Th Pa U Np Pu Am Cm Bk Cf Es Fm Md No Lw
Erklärung
Symbol
nichtisotop
isotop
Indikator
radiom. Redox-Titr.
radiokompl. Titr.
radiom. Fällungs-Titr.

In the resonance form on the left, the acid strength is lowered because of the greater electron density at the COOH group; the acid strength of the π-complex on the right of the scheme increases, because the nitrobenzene acts as an 'electron sink', thus lowering the electron density at the COOH group.

In a similar way, the effect of possible hyperconjugative resonance forms of *p*-toluic acid is also opposed by π-complex formation. Thus the development of such resonance forms, which diminish the acid character, is counteracted by the effect of charge-transfer-complex formation.



Alcohols are amphiprotic solvents. The order of their 'acidity' is as follows [394]:

isopropanol < n-propanol and n-butanol < ethanol < (water) < methoxypropanol < benzyl alcohol < methanol < 2-aminoethanol < methoxyethanol (Methyl Cellosolve) < ethoxyethanol (Cellosolve) < propylene glycol < ethylene glycol

For the titration of acids and acid analogues, alcohols are diluted with benzene (1 : 6–1 : 10) or with a mixture of pyridine and acetone (2 : 70 : 30). For the determination of ketones and aldehydes based on oxime formation a mixture of isopropanol and methanol (65 : 35) is used [314, 574]. This is one of the components of the G–H solvent systems [621, 750].

Glycols, such as ethylene glycol, propylene glycol etc. mixed with isopropanol, 1,4-dioxan or chloroform in a ratio of 1 : 1 may also be one of the components of G–H solvent mixtures. A very suitable solvent for the preparation of 0·1 N hydrochloric acid standard solution is a mixture of propylene glycol with chloroform (1 : 1). A mixture of glycol monomethyl ether and xylene (1 : 1) is an excellent solvent for the determination of saponification numbers of fats and waxes [330]. A mixture of polyethylene glycol '400' with chloroform has proved to be a useful solvent for the determination of barbituric acid derivatives [788]. For the preparation of a standard solution of lithium aluminium amide, glycol dimethyl ether is employed instead of tetrahydrofuran [761].

Amphoterism, a fundamental property of numerous solvents, frequently remains latent. Amphiprotic solvents represent a transition between acidic and basic solvents.

Because of its weak base strength the basic properties of water became known only relatively late. When a solution of hydrogen bromide in liquid ammonia is concentrated, solid ammonium bromide remains, since the equilibrium

$$NH_3 + HBr \rightleftharpoons NH_4^+Br^-,$$

Sachregister

Allobarbital, Bestimmung durch
Fällungstitration 66
Aluminium, Bestimmung von, unter
Anwendung fester Indikatoren 101, 102, 116
Amidopyrin, Bestimmung durch
Fällungstitration 66
Aminophyllin, Bestimmung durch
Fällungstitration 68
Apparat für radiometrische Titrationen von
Aylward u. Mitarb. 24
Braun 104
Braun u. Kőrös 104, 105
Chleck 106
Duncan u. Thomas 26, 95, 96
Langer 22
Lieberman u. Mitarb. 103, 104
Nuclear Chicago Corp. 25
Polewaja u. Mitarb. 22
Schumacher u. Streiff 115
Sirotina u. Alimarin 22
Spitzy 22, 23
Tölgyessy u. Mitarb. 42, 43, 47
Tölgyessy u. Šajter 26, 27, 28, 29
Arsen, Bestimmung durch
Fällungstitration 57
Redoxtitration 131
Automatisches radiocoulometrisches Titrimeter 47, 48
Automatische Titrationsvorrichtung 26–29, 130

Barbital, Bestimmung durch
Fällungstitration 66
Barium, Bestimmung durch
Fällungstitration 56
Beryllium, Bestimmung durch
Fällungstitration 57
Blei, Bestimmung durch
fokussierende Ionenaustausch-Trennung 120
Extraktionstitration
in Gegenwart von Kobalt 83, 88–90, 117
Fällungstitration 33, 61, 62, 131
in Gegenwart von Zink 33, 61, 62
Komplexometrische Titration 131, 132
Bleijodid, Bestimmung der Löslichkeit 53, 54
Brom, Bestimmung durch
Fällungstitration 36, 40, 57
in Gegenwart von Chlor und Jod 36
Bromadal, Bestimmung durch
Fällungstitration 66
Bromisoval, Bestimmung durch
Fällungstitration 66
Buttersäure, Bestimmung durch
Fällungstitration 40

Cadmium, Bestimmung durch
Fällungstitration 36, 57
in Gegenwart von Zink 36
Extraktionstitration 116
in Gegenwart von Indium 119
Kupfer 116
in Gegenwart von Silber und
Komplexometrische Titration mit Trennung durch Ionenaustausch 130
Caesium, Bestimmung des Löslichkeitsproduktes von $Cs_2(PtCl_6)$ 54
Calcium, Bestimmung durch
Fällungstitration 57
in Gegenwart von Blei 57
mit Anwendung von festen Indikatoren 99, 100, 116
komplexometrische Titration mit Trennung durch Ionenaustausch 130
Calciumbutyrat, Bestimmung durch
Fällungstitration 40
Capronsäure, Bestimmung durch
Fällungstitration 40
Carbonat, Bestimmung durch
Fällungstitration 59
Cerium, Bestimmung durch
Fällungstitration 57

at room temperature lies in the direction of the upper arrow. However, the equilibrium constant of the reaction

$$H_2O + HBr \rightleftarrows H_3O^+ + Br^-$$

is much smaller, i.e. at equilibrium, considerable quantities of water and hydrogen bromide are present. On evaporation, the volatile co-reactants are formed again owing to the shift of the equilibrium to the left.

For most solvents used in non-aqueous titrimetry, the ratio of the basic form to the conjugate acid form cannot be determined by measurements in the ultraviolet region, since the maximum is at a very short wavelength. Heston and Hall [382] determined the measurable proton activities

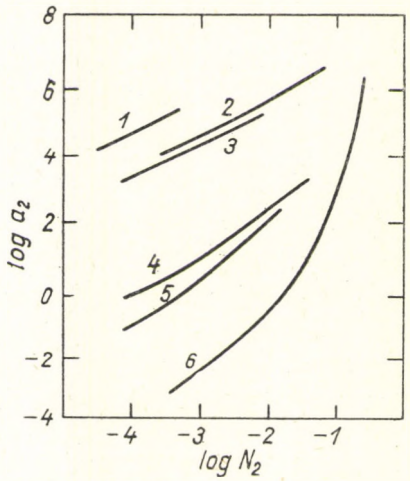


Fig. 29. Activities of hydrochloric acid in different solvents as a function of mole fraction according to Heston and Hall [382]. — *(1)* Benzene, *(2)* Nitrobenzene, *(3)* Acetic acid, *(4)* Ethanol, *(5)* Methanol, *(6)* Water

for proton donor acids electrometrically in solution and thus established the relative base strengths of some solvents (Fig. 29). In this figure the logarithm of the activity of hydrochloric acid (a_2) is plotted against the logarithm of the concentration of hydrochloric acid (N_2 = molar fraction of hydrochloric acid). This indicates that water is more 'basic' than methanol, that acetic acid is scarcely basic and that the 'basicity' of benzene is the smallest of all.

45. Basic Solvents

Ethylenediamine, $H_2N.CH_2CH_2.NH_2$, is used as a solvent for the titration of acid analogues (phenols, imides) since their acidic character is increased by ethylenediamine, while solvent cations are formed (Chapter 5; Section 31). It is a caustic, viscous liquid, fuming in air and absorbing atmospheric moisture and carbon dioxide. Colourless in the pure state, it becomes yellow on standing and a crystalline deposit of molecular formula $C_9H_{20}N_6$ is formed. It is advisable therefore to use ethylenediamine freshly distilled from metallic sodium in a nitrogen atmosphere.

n-Butylamine $CH_3(CH_2)_3NH_2$, is less basic than ethylenediamine, although still possessing distinct sensitivity to carbon dioxide. Both ethylenediamine and butylamine must be titrated in a closed system or an atmosphere of nitrogen. Before the titration, the solvent must be neutralized with the titrant (Chapter 10; Section 56). n-Butylamine is a suitable solvent for the titration of phenols and sulphonamide derivatives. It is a stronger base than dimethylformamide and therefore it is also suitable for the determination of those acid analogues which do not show an acidic character in dimethylformamide.

Chinin, Bestimmung durch
Fällungstitration 66
Chlor, Bestimmung durch
Fällungstitration 21, 36, 58
bei der Rückstreuung von e^--Strahlen 42
durch Absorption von e^--Strahlen 45, 58
in Gegenwart von Brom und Jod 36, 58
Chromat, Bestimmung durch
Fällungstitration 59
Citronensäure, Bestimmung durch
Fällungstitration 66
Cocain, Bestimmung durch
Fällungstitration 67
Codein, Bestimmung durch
Fällungstitration 67
Cyanid, Bestimmung durch
Fällungstitration 58

Doppelfokussierung 113
Dünnwand ß-Zähler-
Zentrifuge 30

Eisen, Bestimmung durch
fokussierenden Ionenaustausch 118
Extraktionstitration 80, 131
Fällungstitration 59
Komplexometrische Titration 131
mit Anwendung von festem Indikator 100, 118
Redoxtitration 131
Emetin-hydrochlorid, Bestimmung
durch Fällungstitration 66
Endpunktsbestimmung durch fokussierenden Ionenaustausch 112—115
durch papierchromatographische Trennung 109—111
durch Trennung mit Ionenaustauschern 107—109
mit festen Indikatoren 96—106
Prinzip der Methode 96—99
radioaktive Kryptonate 103
Typen der Titrationen 99—102
Ephedrin-hydrochlorid, Bestimmung
durch Fällungstitration 66
Essigsäure, Bestimmung durch
Fällungstitration 40
Extraktionstitration 73—96
direkte Titrationen 94—96
indirekte Titrationen 84—85
theoretische Grundlagen 85—92
Extrapolationsmethode 15—21

Fluor, Bestimmung durch
Fällungstitration 9, 59
Verwendung von radioaktiven Kryptonaten 102—104
Fokussierender Ionenaustausch 112—115

Halbautomatische Extraktionstitration 93—96
Hexacyanoferrat/II, Bestimmung durch
e^--Rückstreuung 43, 60
Fällungstitration 59
Hyoscyamin, Bestimmung durch
Fällungstitration 66

Indium, Bestimmung durch
Ionenaustausch 108, 119
Extraktionstitration 119
in Gegenwart von Cadmium 119

Jod, Bestimmung durch
Fällungstitration 10, 33, 60
in der Gegenwart von Chlor und Brom 36
in Gegenwart von Chromat 60
in Gegenwart von Sulfat 32—34
in Gegenwart von Sulfid 34
radiocoulometrische Titration 45—48, 60

Kobalt, Bestimmung durch komplexometrische Titration
mit Anwendung von fokussierender Ionenaustausch-Trennung 114, 115, 117
Extraktionstitration 79—90, 117
in Gegenwart von Blei 83, 88, 89, 117
in Gegenwart von Nickel 88, 117
in Gegenwart von Zink 82, 83, 117
Fällungstitration 32, 59
Ionenaustausch-Trennung 107, 108, 117
papierchromatographische Trennung 112, 113, 118
Komplexometrische Titration mit festem Indikator 130
mit radioaktivem Kryptonat 131
Kontinuierliche Titration 25—29, 93
Kupfer, Bestimmung durch komplexometrische Titration mit Anwendung von fokussierender Ionenaustausch-Trennung 118
von festen Indikatoren 99, 100, 118

Table 17

BASIC SOLVENTS

Solvent	*Boiling Point* °C	*Specific Gravity* 20°C/4°C	*Refractive Index* $n_D^{20C°}$
Ethylenediamine	116—117	0·898	1·4568
Piperidine	106·4	0·860	1·4530
n-Butylamine	76·2— 77·8	0·741	1·401
Pyridine	115·5	0·983	1·5100
Ethanolamine	171·1	1·022	1·4539
Dimethylformamide	153·0	0·945	1·4269
1,4-Dioxan	101·3	1·033	1·4224
Ethyl ether	34·6	0·708	1·3527
Tetrahydrofuran	64— 65	0·888	1·4076

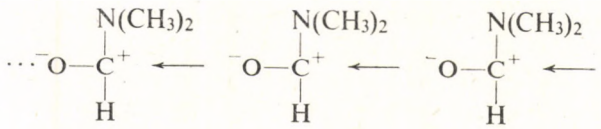
Despite its disagreeable odour, *pyridine*, C_5H_5N, usually mixed with benzene or acetone, is one of the most frequently employed solvents for the determination of acids and acid analogues. Ethylenediamine or butylamine and, in certain cases, dimethylformamide can generally be replaced by pyridine. Despite its low dielectric constant it is also a convenient solvent for ionic compounds. The use of a mixture of isomeric monomethylpyridines (picolines) (b.p. = 114–155°C) is more effective and cheaper than that of pure pyridine.

One of the advantages of pyridine is its limited differentiating ability. Thus for example, the relative acid strengths of many derivatives of benzoic acid and compounds containing the phenolic hydroxyl group can be estimated by potentiometric titration. A difference exceeding 500 mV in the half-neutralization potential values is obtained when phenols of acid strength pK_{acid} 10·6 and pK_{acid} 7·2 are titrated (cf. Table 3).

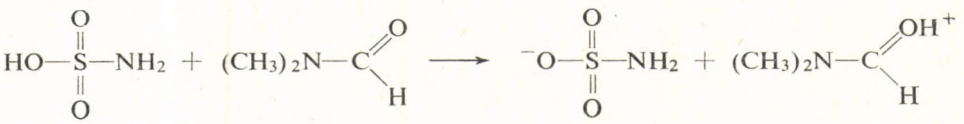
Ethanolamine, $H_2N.CH_2CH_2.OH$, generally used for the preparation of the standard solution of sodium aminoethoxide, is a highly basic solvent.

N,N-Dimethylformamide, $H.CON(CH_3)_2$, (DMF) is one of the most suitable solvents for the titration of acids and acid analogues. Colourless, odourless and less hygroscopic than ethylenediamine, its carbon dioxide sensitivity is so slight that it can be neglected. Thus, during titration, precautionary measures are unnecessary. The pH range of dimethylformamide, extending over 18 units, is also suitable for differentiating titrations [803].

Dimethylformamide molecules, owing to their highly polar character, probably form a 'polymeric' chain. Because of this, the positive charge of the nitrogen atom is decreased and, consequently, its proton-accepting ability is increased [768]:



DMF is a proton acceptor for sulphamic acid, which has an amphoteric character and is used as a standard reagent [118]:



Extraktionstitration 83, 118, 131
in Gegenwart von Silber und Cadmium 116
in Gegenwart von Zink 82, 83, 118
Fällungstitration 10, 59, 131
Substöchiometrische Extraktion 92

Lobelin, Bestimmung durch Fällungstitration 67
Löslichkeit, Löslichkeitsprodukte, Bestimmung durch 52—54
Lutetium, Bestimmung durch Fällungstitration 60

Magnesium, Bestimmung
durch Fällungstitration 61, 131
komplexometrische Titration mit Trennung durch Ionenaustausch 130
unter Anwendung eines festen Indikators 99, 119
Markierung,
isotopische 7, 74
nicht-isotope 8, 74—76, 79, 83, 109
Mitfällung 9
Untersuchung der 50, 51
Molybdän, Bestimmung durch Fällungstitration 61
Morphin, Bestimmung durch Fällungstitration 67

Natrium, Bestimmung
bei Anwendung von festem Indikator 100, 119
Natriumacetat, Bestimmung durch Fällungstitration 40
Natriumbenzoat, Bestimmung durch Fällungstitration 40
Natrium-p-aminosalicylat, Bestimmung durch Fällungstitration 67
Natriumhydroxyd
Neutralisationstitration 132
Neodym, Bestimmung durch Fällungstitration 61
Nickel, Bestimmung durch
Extraktionstitration 82, 131
in der Gegenwart von Kobalt 82, 88, 117
Fällungstitration 30, 32, 131
unter Anwendung eines festen Indikators, Radiocoulometrie 119
Komplexometrische Titration 131, 132
Niob, Bestimmung durch Fällungstitration 61

Oxalsäure, Bestimmung durch Fällungstitration 67
8-Oxychinolin, Bestimmung durch Fällungstitration 66

Palladium, Bestimmung durch
Extraktionstitration 81, 84, 120
Fällungstitration 62
Papaverin-hydrochlorid, Bestimmung durch Fällungstitration 67
Phasentrennung durch
Zentrifugieren 5, 29, 31, 41, 42, 45, 103
Filtration 5, 21—29, 30, 31, 41, 103
Flotation 30—32, 103
Phenobarbital, Bestimmung durch Fällungstitration 66
Phosphor, Bestimmung durch Fällungstitration 5, 62
Pilocarpin-hydrochlorid, Bestimmung durch Fällungstitration 67

Platin, Bestimmung durch Fällungstitration 63
Polywolframat-Ionen, Bestimmung ihrer Zusammensetzung 49
Fällungsmembrane 103, 104, 105
Procain-hydrochlorid, Bestimmung durch Fällungstitration 67

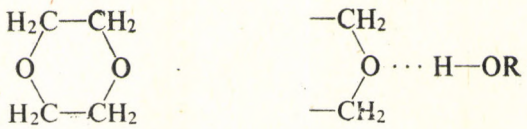
Quecksilber, Bestimmung durch
Extraktionstitration 76, 78, 80—82, 118, 131
in Gegenwart von Zink 80, 119
in Gegenwart von Zink und Silber 83—84, 116
Fällungstitration 60
Quecksilber-Hexacyanoferrat/II, Bestimmung über seine Zusammensetzung 50

Radioaktive Indikatoren
chemische Form 8
isomorphe 8
isotope 7, 11, 32
nicht-isomorphe 9, 10
nicht-isotope 5, 9, 11, 32, 83
radiochemische Reinheit 7
Wahl 7
Radioaktive Kryptonate 102
Radio-Argentometrie 5
Radiocoulometrische Titrationen 45—48
Radiokomplexometrie 5

In dimethylformamide anions appear to be unsolvated, while cations move with a solvation 'sheath' [662].

In dimethylformamide strong bases are converted into compounds with a base strength similar to that of sodium formate. Contaminants in dimethylformamide (formamide or methylformamide) presumably undergo hydrolysis by water and strong bases, to form ammonia, methylamine and formic acid. In compounds of the type $R_3NH^+ . HCOO^-$, formate is the anion base [176].

Owing to its stability and remarkable solvating power, *1,4-dioxan* is one of the most frequently used solvents. It is miscible with water, as well as with benzene. In non-aqueous titrations it is used as an inert solvent of feeble basic or differentiating properties. It is also used for the preparation of standard perchloric acid solutions. Its differentiating property is related to its H-bonding ability. Its solvating power for phenolic compounds, or for compounds containing an alcoholic hydroxyl group may be due to the formation of oxonium compounds by hydrogen bonding [242]:



Conductometric measurements prove that with formic acid for example it behaves as a base [565] (1,4-*DO* = dioxan):

$$1,4\text{-}DO + H.\,COOH \rightleftharpoons 1,4\text{-}DO.\,H.\,COOH \rightleftharpoons 1,4\text{-}DO.\,H^+ + HCOO^-$$

At the same time the basicity of dioxan is so low that heterocyclic and aliphatic amines can be titrated in it.

Diethyl ether, $C_2H_5.O.C_2H_5$, is rarely employed as a solvent. When organic bases in ether are to be titrated it is advisable to evaporate the solvent on a water bath in a gentle stream of air (see Fig. 103, p. 249). Titration is then performed with perchloric acid in a mixture of acetic acid and carbon tetrachloride.

Ethyl ether is a solvent 'similar to water':

$$C_2H_5.O.C_2H_5 \rightleftharpoons C_2H_5^+ + {}^-OC_2H_5$$

In the course of the reaction of ethyl bromide with lithium, lithium ethoxide is first formed and the solvent is subsequently regenerated:

$$C_2H_5Br + LiOC_2H_5 = C_2H_5.O.C_2H_5 + LiBr$$

Because of the self-ionization of the solvent a number of organic and inorganic compounds, when dissolved in ether, increase its conductivity (see above).

The order of dissociation of alkyl halides in ether is identical with that of halogen hydracids in water. Towards Lewis acids, ethyl ether is a base analogue [422]:

$$AlBr_3 + C_2H_5.OC_2H_5 \rightarrow C_2H_5^+ + [Br_3Al.OC_2H_5]^-$$

Radiometrische Endpunktsanzeige 3—5
Radiometrische Titration
Automatisierung der Titration 5, 25—29, 44
bei Komplexbildung 5, 73—121
beruhend auf der Absorption dere⁻-Strahlung 44—45
beruhend auf der Rückstreuung der e⁻-Strahlung 40—44
praktische Anwendungen 56—65, 116—121
bei Fällungsbildungen 3—72
kontinuierliche, automatische Titration 25—29, 44, 47
Bestimmung des Endpunktes 15—21
Bestimmung mehrerer Komponenten nebeneinander 32—37
bis zum Endpunkt 26—29
diskontinuierliche Titration 21—32
in nicht-wäßrigen Medien 10, 38—40
komplexometrische, unter Anwendung von radioaktiven Kryptonaten 129
kontinuierliche Titration 4, 25—29
Methoden der Abtrennung der Fällung 21—32
Neutronenabsorption 129
praktische Anwendung 56—68
spezielle Methoden 37—48
Technik der Titration 21—32
theoretische Grundlagen der Methode 11—15
theoretische Probleme der Fällungstitrationen 127—128
theoretische und praktische Probleme der Ionenaustauschtitrationen 129
Verschiedene Anwendungsmöglichkeiten 48—54
Rhodanid, Bestimmung durch Fällungstitration 63

Salpetersäure
Neutralisationstitration 132
Salzsäure
Neutralisationstitration 132
Sättigungsrückstreuung 132
Schwefelsäure,
Neutralisationstitration 132
Scopolamin-hydrochlorid, Bestimmung durch Fällungstitration 67
Separation durch Kollektoren 10
fokussierende Ionenaustauscher 112—115
Ionenaustauscher 10, 107—109
Lösungsextraktion 4, 73—96
Papierchromatographie 109—110
Silber
Extraktionstitration 73, 75, 76, 116, 130, 131
in der Gegenwart von Kupfer und Cadmium 116
in der Gegenwart von Quecksilber und Zink 83, 116
in der Gegenwart von Zink 82, 83, 116
Fällungstitration 56
bei Rückstreuung von e⁻-Strahlen 40, 41, 43
in Gegenwart von Blei 56
Silizium, Bestimmung durch Fällungstitration 63
Spezifische Aktivität,
Bestimmung von 54
Strichnin, Bestimmung durch Fällungstitration 68
Strontium, Bestimmung von,
bei Anwendung
von festen Indikatoren 99, 120
komplexometrische Titration mit Trennung durch Ionenaustausch 130
Substöchiometrische Isotopenverdünnungsanalysen 107
Sulfat, Bestimmung durch
Fällungstitration 33, 34, 63
in Gegenwart von Jodid 33, 34, 63
Sulfid, Bestimmung durch
Fällungstitration 34, 63
in Gegenwart von Jodid 34, 63

Tantal, Bestimmung durch Fällungstitration 64
Tebrium, Bestimmung durch
Trennung durch Papierchromatographie 120
Thallium, Bestimmung durch
Fällungstitration 17, 35, 36, 64
in Gegenwart von Indium 35, 64
in Gegenwart von Zink 35, 36, 64
Untersuchung der Mitfällung mit Silberjodid, Bleijodid, Bleisulfid und Silberchromat 50, 51
Theobromin, Bestimmung durch Fällungstitration 68
Theophyllin, Bestimmung durch Fällungstitration 68
Thiopental, Bestimmung durch Fällungstitration 68

The product formed can be titrated with alkali metal alkoxide [422]:

$$\xrightarrow{+CH_3ONa} [Br_3Al \cdot OC_2H_5]\,Na + C_2H_5 \cdot O \cdot CH_3$$

$$\downarrow \text{ Solvolysis}$$

$$NaBr + C_2H_5[Br_2Al\,(OC_2H_5)_2]$$

Photometric titration of ethyl ether with perchloric acid in 0·25 M acetic acid or in acetic anhy, dride in the presence of Sudan-III indicates very weak basicity [385].

The 'basicity' of solvents is relative. It is known that, in donor-acceptor complex formation, compounds containing an aromatic ring behave as 'bases' in aprotic solvents such as carbon tetrachloride towards proton donors. Infrared analysis, using pyrrole as the proton donor, produced the following 'basicity order' [435]:

chlorobenzene < bromobenzene < benzene < toluene < xylene

(cf. Chapter 7; Section 44. Regarding pyrrole see: Chapter 4; Sections 27 (e), (f). For complexometric determination of aromatic hydrocarbons see: Chapter 30; Section 167.)

Thiosulfat, Bestimmung durch Fällungstitration 63
Thorium, Bestimmung durch Fällungstitration 74, 132
Träger, Bestimmung durch Extraktionstitration 76, 78
Trennungs-Titrationen 3
Triphenylselenoniumjodobismuthit Bestimmung über die Zusammensetzung 49

Uran, Bestimmung
durch Fällungstitration 65
der spezifischen Aktivität des ^{237}U 55

Verdrängungstitration 115
Vitamin B_{18}
Komplexometrische Titration 133

Wismut, substöchiometrische Extraktion 92
Wolfram,
Bestimmung bei Anwendung von festem Indikator 100, 120

Yttrium, Bestimmung durch Fällungstitration 65
mit Anwendung von fokussierendem Ionenaustausch 113, 114, 121
Komplexometrische Titration 132

Zink, Bestimmung der spezifischen Aktivität von ^{65}Zn 54, 55
durch Extraktionstitration 80, 81, 87, 120, 121
in Gegenwart von Kobalt 82, 83, 117
in Gegenwart von Kupfer 84, 118, 121
in Gegenwart von Quecksilber 119
in Gegenwart von Quecksilber und Silber 84, 116
in Gegenwart von Silber 83, 84, 116
durch Fällungstitration 9, 10, 32, 33, 65, 131
in Gegenwart von Blei 33
in Gegenwart von Kadmium 36, 65
in Gegenwart von Kupfer 65
in Gegenwart von Thallium 35, 36
mit Anwendung eines festen Indikators 100, 101, 103
Komplexometrische Titration mit festem Indikator 130, 131
mit Ionenaustauschmembranen 132, 133
Zirkonium, Bestimmung durch Fällungstitration 10, 65
Zusammensetzung von Verbindungen, Bestimmung von 48—50

Chapter 8

Purification of Solvents

The solvent employed must be anhydrous, free from acid and base impurities and colourless. Acidic impurities can be formed during storage, e.g. hydrochloric acid in chloroform. Ethylenediamine and n-butylamine avidly absorb carbon dioxide from the air. Even traces of water in acetic acid must be considered as a basic contaminant, since it neutralizes perchloric acid (Chapter 3; Section 22 (a)). Occasionally alkali metal acetate also is a contaminant (as a result of interaction with the glass storage vessel, acetate ion being a base in acetic acid).

Purification of solvents involves three procedures: (1) removal of impurities, (2) drying and (3) fractional distillation. The first of these can be carried out by aqueous extraction, by extraction with concentrated sulphuric acid or with a concentrated solution of sodium hydroxide. Depending upon the chemical properties and degree of contamination the sequence and method of treatment may be changed. Apart from the above, special procedures must sometimes be applied, for example removing aldehydes from alcohols using 2,4-dinitrophenylhydrazine, removing acetic anhydride from acetic acid by using benzylamine, or freeing ethyl ether from peroxide, etc.

46. Purification Using Concentrated Sulphuric Acid and Sodium Hydroxide Solution

This process precedes dehydration and distillation, and can be employed only in the case of such solvents as are immiscible with water and do not react under normal conditions either with sulphuric acid or with sodium hydroxide; e.g. n-hexane, chloroform, carbon tetrachloride, benzene, toluene, xylene and chlorobenzene.

Used solvents can be collected and subsequently repurified. This also holds good for solvent mixtures, if one of the components can be extracted by water. However, it is not advisable to collect and repurify those solvent mixtures which contain two or three components and which cannot be separated by water, such as benzene-chloroform or acetone-pyridine. If the impure solvent contains emulsifying agents

Namenregister

Abramowa, W. F. 64, 69
Alimarin, I. P. 5, 10, 12, 16, 17, 22, 49, 50, 51, 57, 59, 64, 65, 69, 70, 71
Amano, H. 61, 64, 69
Aylward, G. H. 24, 59, 69

Basiński, A. 49, 69
Bebesel, P. 56, 58, 60, 66, 67, 68, 69, 71
Berry, D. S. 30, 63, 69
Blagojević, O. 56, 71
Bleschinskij, S. W. 64, 69
Bradhurst, D. H. 12, 49, 50, 69
Braun, T. 1, 3, 5, 10, 16, 19, 30, 32, 40, 41, 42, 45, 46, 47, 48, 59, 60, 61, 69, 71, 72, 75, 81, 82, 96, 97, 99, 100, 101, 103, 104, 105, 116, 118, 119, 120, 121, 122, 123, 124, 125, 126, 129, 130, 131, 132, 134, 135
Broda, E. 1
Brouchek, F. I. 59, 69
Brown, C. N. 101, 103, 104, 118, 122
Brown, W. G. 25, 72
Busew, A. I. 35, 36, 64, 65, 69
Býrko, V. M. 35, 36, 57, 64, 65, 69, 70

Carnevale, E. 102, 121
Casey, A. T. 63, 69
Charlot, G. 1
Cuchiara, O. 102, 121, 130, 132, 134
Cleck, D. I. 102, 103, 106, 121, 130, 132, 134
Coller, B. A. W. 12, 49, 50, 69
Csapó, Z. 58, 67, 71

Das, M. N. 38, 70, 71
Demina, E. A. 5, 6, 9, 10, 29, 65, 70
Dillinger, P. 40, 45, 58, 72, 129, 131, 134, 135
Dosudil, I. 81, 84, 120, 122
Driscoll, W. I. 30, 31, 71
Duncan, I. F. 5, 6, 11, 12, 25, 26, 49, 50, 52, 53, 54, 59, 73, 75, 80, 82, 83, 85, 88, 92, 95, 96, 117, 118, 121

Ellis, W. P. 9, 59, 71
Eristawi, D. I. 59, 69

Ewing, R. A. 101, 103, 104, 118, 122

Flaschka, J. 73, 121
Friedli, W. 107, 109, 110, 111, 117, 120, 122
Fritz, I. S. 38, 69

Galateanu, I. 5, 6, 30, 59, 61, 69, 71, 96, 99, 100, 101, 116, 118, 119, 120, 121
Golbraich, E. K. 64, 71
Garnett, I. L. 25, 59, 69
Giddins, I. C. 110, 122
Gibalo, I. M. 10, 12, 17, 49, 57, 64, 65, 69, 70
Goldman, J. A. 11, 70
Grigorescu-Sabau, C. 81, 117, 121

Hahn, O. 51, 70
Haissinsky, M. 1, 2
Hayes, I. W. 24, 59, 69
Hroncová, D. 131, 135
Heilbronner, E. 110, 122

Hradil, M. 119, 121, 130, 132, 134
Howes, I. E., jr. 101, 103, 104, 118, 122

Illaszewicz, A. 100, 122, 130, 134
Ionescu, S. 81, 117, 121
Ishibashi, N. 130, 134
Ismajlow, N. A. 10, 38, 39, 40, 69
Iwantscheff, G. 73, 121

Jager, H. 110, 121
Jasinski, T. 38, 70
Jatschimirskij, K. B. 40, 61, 62, 63, 72
Jesenák, V. 11, 13, 14, 15, 16, 17, 18, 19, 20, 40, 41, 42, 45, 46, 47, 48, 60, 66, 68, 70, 72, 119, 121, 127, 129, 130, 131, 132, 134, 135

Kallen, J. 110, 122
Kametani, F. 36, 54, 65, 70
Kaplan, L. 25, 72
Kataoka, A. 54, 65, 70
Keller, R. A. 110, 122

or contaminants which react with sulphuric acid with heat evolution and marked charring, it should be filtered through diatomaceous earth prior to extraction and fractionation.

Emulsifying agents include polyoxyethylene derivatives, higher molecular weight aliphatic cids and their salts, alkyl sulphonates, cholesterol, glucose, alkaloids etc. In addition to the mulsifying agents, phenols, glycols and their derivatives are also charred by concentrated ulphuric acid.

A *pretreatment*, consisting of extraction with a large volume of water, is used to separate acetic acid and pyridine from inert solvents such as carbon tetrachloride and benzene which are immiscible with water.

Transfer 1 litre of the solvent to a 2–3 l separating funnel and add 100–200 ml concentrated sulphuric acid. During the manipulation wear safety goggles. Initially, after each careful shake, open the stopper to equalize the pressure. When heat evolution no longer occurs, shake the organic solvent *vigorously* with the sulphuric acid for 2–3 min and then allow the mixture to stand.

After separation of the phases, the sulphuric acid is removed and the organic solvent is shaken with 500–1,000 ml water until the last wash water is neutral to Congo red. Generally 3–5 extractions are needed. Purification of the solvent is then continued by shaking with 100–200 ml 20–30% aqueous sodium hydroxide solution. The solvent is then freed from the caustic solution by washing in the separatory funnel until the last wash water is neutral to phenolphthalein.

When the sulphuric acid shows marked browning, shaking with the acid is repeated until no colour appears.

With careful work the loss of solvent is 5–10%.

47. Drying of Solvents

For this procedure, in principle one should always use the drying agent which reacts least with the solvent and is, at the same time, of the greatest efficiency in the given case. When metallic sodium or phosphorus pentoxide is used *preliminary drying* is essential. The comparative efficiency of some drying agents is as follows:

$$P_2O_5 \gg Al_2O_3 > CaSO_4 \text{ (Drierite)} > CaO > KOH > SiO_2 \text{ (Silica gel)} > NaOH > CaCl_2 > \\ > Na_2SO_4, \quad K_2CO_3$$

Depending on the experimental conditions the order of efficiency of drying agents may vary. The information given below *for the drying of gases* (abstract according to [821]) may offer a basis for conclusions also for the drying of solvents (the use of magnesium perchlorate is not advisable because of the risk of explosion).

Dehydration (preliminary drying) *with sodium sulphate or potassium carbonate* is carried out by adding 50 g of sodium sulphate or potassium carbonate (previously dried at 100–110°C and cooled in a desiccator) to 1 litre of the solvent. After shaking for 5–10 min, it is allowed to stand in the dark and the solvent is then filtered through a plug of cotton wool into a distillation flask. Before treatment with metallic sodium, preliminary drying is used for such solvents as dioxan and benzene.

Kimura, K. 36, 54, 65, 70
Klas, I. 11, 43, 70, 127, 128, 129, 134
Knobloch, V. 132, 134
Koch, H. 64, 70
Kohara, H. 130, 134
Korenmann, I. M. 5, 6, 9, 10, 29, 61, 64, 65, 70, 73, 74, 75, 76, 81, 83, 84, 93, 116, 118, 119, 121, 122
Kőrös, E. 75, 81, 82, 96, 97, 103, 104, 105, 121, 123, 124, 125, 126
Konečný, J. 129, 130, 131, 132, 133, 134, 135
Kreschkow, A. P. 38, 70
Krivanek, M. 76, 77, 81, 122, 130, 131, 134
Kriváň, V. 41, 70, 132, 135
Krygier, A. 49, 69
Kucharsky, J. 38, 70
Kukula, F. 76, 77, 81, 122, 130, 131, 134

Lacruche, B. 61, 71
Lambe, D. A. 1, 2
Langei, A. 1, 2, 5, 6, 11, 12, 16, 17, 22, 56r, 57, 58, 61, 62, 64, 65, 70
Law, S. W. 25, 59, 69
Leddicotte, G. W. 1, 2
Lieberman, R. 101, 103, 104, 118, 122

Maehl, R. 102, 121, 130, 132, 134
Majer, J. 33, 57, 58, 60, 63, 65, 66, 67, 68, 70, 71, 72
Majer, Vl. 11, 13, 71
Maranow, B. M. 57, 60, 61, 65, 71, 128, 134
Matsuo, J. 48, 49, 70, 71
Maxim, I. 5, 6, 30, 59, 61, 69, 71, 96, 99, 100, 101, 116, 118, 119, 120, 121
Meinke, W. W. 1, 2
Meites, L. 11, 70
Mevel, N. 61, 71
Mesina, H. M. 5, 6, 73, 75, 76, 83, 93, 121, 122
Mikheew, N. B. 1, 2, 61, 71
Mikheewa, L. 1, 2, 61, 71
Mirkina, S. L. 22, 61, 71
Mitrochina, T. N. 81, 84, 116, 118, 119, 122
Moeller, D. W. 12, 21, 58, 63, 64, 71
Moses, A. F. 1, 2
Müller, K. 100, 122, 130, 131, 134

Onstott, E. J. 9, 59, 71
Ostaschewa, M. I. 5, 6, 73, 75, 76, 83, 93, 121, 122

Palit, S. R. 38, 70, 71
Plotnikov, V. I. 56, 71
Polewaja, N. I. 22, 61, 71

Reynolds, S. A. 1, 2
Robb, W. 63, 69
Rosljakowa, E. N. 40, 61, 62, 72
Růžička, J. 90, 92, 107, 108, 117, 119, 122
Ryabchikov, D. I. 64, 71

Šafarik, L. 38, 70
Šajter, V. 5, 6, 25, 26, 27, 28, 29, 72
Saposchnikowa M. I. 5, 6, 9, 10, 65, 70
Šaršunova, M. 11, 13, 16, 33, 43, 57, 58, 60, 62, 63, 65, 66, 67, 68, 70, 71, 72, 73, 133, 134
Schiller, P. 56, 59, 62, 66, 70, 72
Schindler, O. 110, 121
Schönfeld, T. 1, 2
Schumacher, E. 107, 109, 110, 111, 112, 113, 114, 115, 117, 118, 120, 121, 122
Schweitzer, K. 64, 71
Scott, B. F. 30, 31, 63, 69, 71
Seal, M. S. 12, 21, 58, 63, 71
Serebrennikow, W. W. 57, 60, 61, 65, 71
Sejanowa, F. R. 5, 6, 9, 10, 29, 61, 64, 65, 70, 73, 75, 76, 81, 83, 84, 93, 116, 118, 119, 121, 122
Shinagawa, M. 48, 49, 71
Sirbu, I. 56, 58, 60, 66, 67, 68, 69, 71
Sirotina, I. A. 22, 50, 51, 57, 64, 65, 69, 70, 71
Sileś, B. 131, 132, 135
Somayayulu, G. R. 38, 70, 71
Sotnikow, W. S. 59, 69
Spacu, P. 62, 71, 81, 120, 122
Spitzy, H. 5, 6, 80, 81, 83, 84, 93, 94, 100, 116, 117, 118, 119, 120, 122, 130, 131, 134
Starý, J. 90, 92, 107, 108, 117, 119, 122, 132, 134
Stevančević, D. S. 56, 71
Stevenson, D. P. 11, 70
Straub, G. 58, 67, 71
Streiff, H. I. 107, 112, 113, 114, 115, 117, 118, 119, 120, 121, 122
Stürzer, U. 56, 61, 71
Sunderman, D. N. 101, 103, 104, 118, 122
Szymańsky, W. 49, 69

Terril, J. G. 12, 21, 58, 63, 71
Thomas, F. G. 5, 6, 11, 12, 25, 26, 52, 69, 73, 75, 80, 82, 83, 85, 88, 92, 95, 96, 117, 118, 121

Drying Agent	*Residual Water* $\mu g/l$
$Mg(ClO_4)_2 . 0{\cdot}12\ H_2O$	0·2
$Mg(ClO_4)_2 . 1{\cdot}48\ H_2O$ (Anhydrone)	1·5
BaO 96·2%	2·8
$Al_2O_3 . 0{\cdot}00\ H_2O$	2·9
P_2O_5	3·5—3·6
$CaCl_2 . 0{\cdot}18\ H_2O$	67
$CaSO_4 . 0{\cdot}02\ H_2O$ (Drierite)	67
Silica gel	70
$CaSO_4 . 0{\cdot}21\ H_2O$ (Anhydrocel)	206
$NaOH . 0{\cdot}03\ H_2O$	513
$CaO . 0{\cdot}00\ H_2O$	656
$KOH . 0{\cdot}52\ H_2O$	939

Sodium sulphate or potassium carbonate is used both for the preliminary as well as for the final drying if metallic sodium or phosphorus pentoxide is inapplicable e.g. with chloroform, carbon tetrachloride, acetone.

Potassium carbonate also neutralizes acidic impurities. It is used, primarily, for the drying of acetone, methyl ethyl ketone etc. For drying acetone with potassium carbonate see: [434].

Granular calcium chloride and calcium oxide are widely used drying agents which reduce the water content to approx. 0·05%. A disadvantage of calcium chloride is that it forms molecular compounds with some solvents. Calcium oxide again is active only when it does not contain any calcium carbonate.

Alumina, silicon dioxide, silica gel and anhydrous calcium sulphate (Drierite) are suitable desiccants where the water content must not exceed 0·05%. Calcium sulphate does not react with solvents, nor does it catalyze decomposition as is the case, for example, with aluminium oxide.

Magnesium perchlorate, though an excellent drying agent, often becomes dissolved, and in the course of distillation, dangerous explosions may occur.

Drying with *potassium hydroxide* is carried out by adding solid potassium hydroxide to pyridine, ethylenediamine and butylamine. After being shaken vigorously, the mixtures are allowed to settle for 2–3 days. In the case of pyridine and butylamine the brown or yellow coloured KOH is replaced if necessary. Finally after removal from the KOH, the solvents are fractionated. Strong alkali brings about hydrolysis of dimethylformamide.

Dehydration with metallic sodium can generally be used only for those solvents which do not react with it such as ethyl ether, dioxan, benzene.

The violence of the reaction can be lessened by cooling and the dehydrated solvent distilled from the reaction product, e.g. alcohols from metal alkoxide.

Treatment of chlorinated hydrocarbons with metallic sodium may cause explosion and should never be attempted.

The purified solvent, pre-dried with sodium sulphate or potassium hydroxide is filtered. 0·5–1·0 g of metallic sodium is added to one litre of an inert solvent and 2–3 g to one litre of methanol or isopropanol. Benzene or hexane can be distilled using metallic sodium residues but **peroxide must first be removed when distilling solvents**

Townley Ch. W. 101, 103, 104, 118, 122
Tölgyessy, J. 1, 5, 6, 10, 11, 13, 14, 15, 16, 17, 18, 19, 20, 22, 23, 24, 25, 26, 27, 28, 29, 30, 33, 34, 40, 41, 42, 43, 45, 46, 47, 48, 52, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 103, 119, 121, 133, 127, 129, 130, 131, 132, 134, 135
Trapesnikowa, T. N. 81, 84, 116, 118, 119, 122
Tschernij, V. S. 10, 38, 39, 40, 69
Tschernowa, N. N. 22, 61, 71
Tschitsiwadse, T. A. 59, 69
Tuler, W. 58, 60, 72
Varga, Š. 40, 41, 43, 56, 60, 72, 129, 130, 131, 132, 134, 135
Valtyni, J. 11, 19, 70, 127, 134
Voicu, V. 62, 71, 81, 120, 122

Wail, E. I. 10, 38, 39, 40, 69
Welwart, Y. 58, 60, 72
Wilzbach, K. E. 25, 72

Zapalowska, G. 49, 69
Zeman, A. 107, 108, 117, 119, 122

Yoffe, J. 58, 60, 72
Yoshida, M. 48, 49, 70, 71

Für Ausgabe und Herstellung verantwortlich: Gy. Bernát
Direktor des Verlages und der Druckerei der Ungarischen Akademie der Wissenschaften
Verantwortlicher Redakteur: E. Kállay · Technischer Redakteur: Á. Garamvölgyi
Einband und Schutzumschlag: J. Lózsy jun. · Satz.: New Times 10/11 p.
Gesamtherstellung: Akadémiai Nyomda, Budapest V. Gerlóczy u. 2.

in which it is liable to form, such as ethyl ether. After cooling, the unreacted metallic sodium in the distillation residue is decomposed by adding a small amount of alcohol.

The distillation residue is 5–20% depending on the boiling range.

For drying hydrocarbons and acetonitrile *phosphorus pentoxide* is used (see: acetonitrile). As with metallic sodium, drying is combined with distillation.

Lithium aluminium hydride is employed for the dehydration of tetrahydrofuran and ethylene glycol dimethyl ether ('glyme') [391, 761].

(a) *Dehydration of acetic acid*

1. The water content of acetic acid can be estimated in various ways. The melting point of anhydrous acetic acid is 16·65°C [381]. Between zero and 1% water content the melting point changes as follows [23]:

Water Content %	*M.p.* °C
0·0	16·65
0·2	16·28
0·4	15·84
0·6	15·47
0·8	15·12
1·0	14·80

The melting point of acetic acid is almost unaltered by perchloric acid, hence the water content of the standard solution can also be measured using a precision thermometer with 0·01° graduations.

An even simpler method is the estimation of the quantity of 0·1 N perchloric acid necessary for the colour change of crystal violet and also the relative sluggishness of the colour change. One drop of 0·1% crystal violet is added to 10 ml acetic acid. Depending on the water content of the acetic acid solution the colour changes are as follows [23]:

Water Content %	*Colour Change*
0·1	Sharp change: violet → green
0·2—0·3	Change: violet → blue → bluish green → green
Above 0·4	Sluggish change: as above

Very low water concentrations in acetic acid (0·009—1·7%) can be determined by spectrophotometric titration with an acetic anhydride titrant, in the presence of sulphuric acid as catalyst. The wavelength used is 256 mμ [100]. This method is, however, not convenient for routine determinations of the water content of acetic acid.

2. The *Karl Fischer titration* can be carried out most conveniently by the so-called 'dead stop' method [200, 610, 868].

15 ml Karl Fischer reagent (K. F. solution) are measured into a closed or semi-closed titration vessel of 30–40 ml capacity fitted with two blank platinum electrodes, and the electrodes are polarized by 30–40 mV voltage (Fig. 30). Because of the effect of the K.F. solution the

AUS DEN BESPRECHUNGEN ÜBER DIE ENGLISCHE AUSGABE

„. . . Die vielen Abbildungen und Literaturangaben erhöhen noch den Wert dieses, heute auf dem Büchermarkt praktisch konkurrenzlos dastehenden Werks."

CHEMISCHE RUNDSCHAU,
Solothurn, Schweiz

„. . . The authors have given a well-balanced, objective and critical evaluation of the subject . . ."

CHEMISTRY IN BRITAIN,
London

„. . . Das besprochene Buch ist ein wertvoller Beitrag zur Literatur der radioanalytischen Methoden. Es empfiehlt sich als ein nützliches Hilfsmittel in wissenschaftlichen Forschungsinstituten und Kontrollaboratorien. Auch als eine Aushilfe für Hochschulstudenten wird es brauchbar sein."

CHEMICKÉ ZVESTI,
Bratislava

„. . . The high standard of this book does credit to the authors; its careful editing and nice appearance praise the publishers."

ACTA CHIMICA, Budapest

„. . . Die klare und bündige Monographie von Braun und Tölgyessy gibt mit ihren zahlreichen praktischen Beispielen, mit der Behandlung der Theorie von Titrationen und mit der detaillierten Darlegung der technischen Ausführung eine gute Übersicht der radiometrischen Titrationen . . ."

MAGYAR KÉMIKUSOK LAPJA,
Budapest

electrode becomes depolarized and the needle of a galvanometer of 10^{-6} A sensitivity is displaced. A constant volume of the K.F. reagent is titrated with the solvent from a 0·01 ml graduated burette ('inverse titration'). At the end-point the galvanometer settles at zero. The K.F. solution is standardized against a methanolic solution of oxalic acid dihydrate [1·750 (0·175) g oxalic acid dihydrate, equivalent to 500 (50) mg water, are weighed and dissolved in 50 ml methanol distilled from metallic sodium]. One ml of this solution contains 10·0 (1·0) mg of water derived

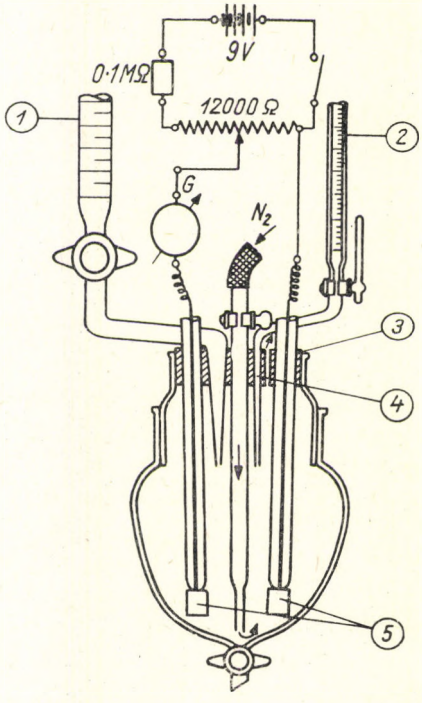


Fig. 30. Assembly for the Karl Fischer titration. — *(1)* Macroburette, *(2)* Microburette, *(3)* Cork stopper, *(4)* Hole, *(5)* Platinum electrodes

from the dihydrate. The water equivalent of the K.F. solution is then determined: this is the 'blank test'. Since the volume of the K.F. reagent is constant (let us say 15 ml) the volume of methanol required for the blank (A_2) contains just as much water as the volume of the solution of oxalic acid dihydrate in methanol (A_1). The latter contains not only the amount of water weighed in as dihydrate (B_{H_2O}), but also the small amount of water originally present in the methanol.

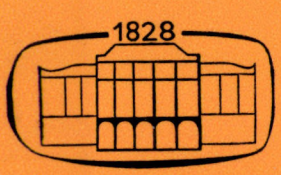
Calculations:

A_2–A_1 is proportional to the quantity of water ($A_1 \cdot B_{H_2O}$) and A_2 is proportional to x mg of water

where x = the water equivalent of the K. F. solution in mg
B_{H_2O} = the weight of hydrate water in mg/ml
($A_1 \cdot B_{H_2O}$) = the consumed 'hydrate water' in mg.

Example: the amount of K. F. reagent = 15 ml, oxalic acid dihydrate = 1·749 g/50 ml of methanol (i.e. 10 mg H_2O/ml). The mean value of three titrations shows that 9·33 ml of methanol distilled from metallic sodium, and 0·895 ml of methanol containing oxalic acid dihydrate, were required. Thus the water equivalent of the K.F. solution is:

$$\frac{9{\cdot}33 \times (0{\cdot}895 \times 10)}{9{\cdot}33 - 0{\cdot}895} = 9{\cdot}9 \text{ mg } H_2O$$


1828

and the water content of the methanol = 1·06 mg/ml. An advantage of the inverse titration is that the smaller the water content of the solution to be examined, the more of it is required for the constant volume of K.F. reagent.

The microburette is then rinsed with acetic acid and 15 ml of K.F. reagent are then titrated with the acetic acid to be investigated.

In addition to the dead-stop method the Karl Fischer titration can also be carried out by employing indicators such as methylene blue in pyridine or methanol.* In direct titration, the indicator mixture quinalizarin—naphthol green—methylene blue turns from ivy green to brown [581]. The Karl Fischer titration can also be performed photometrically (p. 55 in [200]).

3. *Acetic anhydride* is very suitable for the dehydration of acetic acid, while propionic anhydride is used for the dehydration of propionic acid. Dehydration may be accomplished in the presence of chromium trioxide as catalyst by boiling for 5–6 hours. When perchloric acid is the catalyst the acetic acid-acetic anhydride mixture is allowed to stand for 48 hours [657]. A prerequisite for obtaining good results is an accurate knowledge of the water content (Karl Fischer titration).

Transfer into a 3-l ground joint flask 2 l of acetic acid, adding a calculated quantity of acetic anhydride equivalent to its water content. As acetic anhydride is not always 100% pure, proportionately more may be needed. Add 1–2 g chromium trioxide and boil the acetic anhydride – acetic acid mixture for 5–6 hours under reflux using a drying tube filled with Silica gel to exclude moisture, then fractionate. As any excess of acetic anhydride interferes with the determination of primary or secondary amines, its presence should be checked by qualitative tests. See below (c), p. 142.

4. Acetic acid can also be dehydrated by passing it through a 4 ft long column of 1 in. diameter containing Linde 5A Molecular Sieve, followed by distillation. In this way the water content of acetic acid can be decreased to 0·007% [109].

(b) *Effect of water on perchloric acid titration.* In acetic acid a small amount of water takes up protons and is present as hydroxonium acetate:

$$H_2O + AcOH \rightleftharpoons H_3O^+AcO^- \qquad [644]$$

(See also: Chapter 3; Section 22 (a).)

In completely anhydrous acetic acid, the perchloric acid consumption by water can be detected electrometrically. In practice, however, if the perchloric acid is not weaker than 0·1 N up to

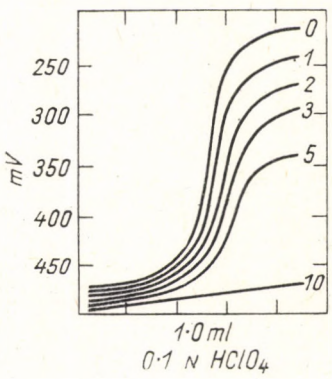


Fig. 31. Effect of water on the sharpness of potentiometric endpoint in perchloric acid titrations according to Pifer and Wollisch [644] (Numbers beside curves denote percentage water content)

* E. Fischer: *Angew. Chem.* **64,** 592 (1952).

about 1% of water does not interfere with the colour change of crystal violet or with the detection of the potentiometric end-point (Figs 31 and 32, [644] and [809]). Standard perchloric acid solution, when diluted with water, reacts in the following way [470, 763]:

$$CH_3COOH_2^+ClO_4^- + H_2O \rightleftarrows H_3O^+ClO_4^- + CH_3COOH$$

The acid products formed are too weak to interact with the indicator in an acetic acid medium.

(c) *Detection of acetic anhydride in acetic acid.* A number of partly qualitative, partly quantitative methods are known.

1. *Qualitative test* [57]: Dissolve 5% by volume of freshly distilled aniline in colourless pyridine (reagent I). Dissolve 1% v/v freshly distilled furfural in acetic

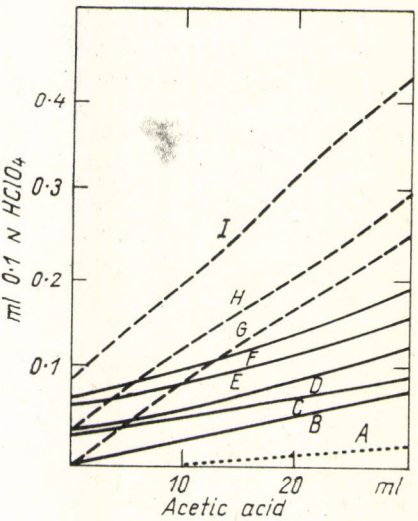


Fig. 32. Effect of water on perchloric acid consumption of acetic acid in presence of crystal violet according to Toennies and Callan [809]—*(A)* To blue colour change, no water present, *(B)* To green colour change, no water present, *(C)* To green colour change, 0·2% of water, *(D)* To green colour change, 0·4% of water, *(E)* To green colour change, 0·6% of water, *(F)* To green colour change, 1% of water, *(G)* To yellow colour change, no water present, *(H)* To yellow colour change, 0·2% of water, *(I)* To yellow colour change, 0·4 % of water

acid (reagent II). Mix one ml of reagent I with 10 ml of the sample and, before adding one ml of reagent II allow it to stand for one minute. In the presence of an acetic anhydride content over 0·5%, the solution is straw yellow, but below 0·5% it is vivid red.

2. *Qualitative test* [226]: In a small porcelain vessel 1 ml of the acetic acid to be investigated and two drops of the reagent are evaporated to dryness. In the presence of acetic anhydride, a violet colour appears. *Preparation of the reagent:* A 0.5% ferric chloride solution in ethanol is acidified with one drop of hydrochloric acid and saturated with hydroxylamine hydrochloride.

3. *Colorimetric control* [23]: Mix 1 ml of acetic acid with 5·00 ml of a 0·50% acetic acidic solution of 2,4-dichloroaniline (≡ 25 mg) and keep the mixture sealed for three hours at room temperature. Then dilute with 30 ml of dilute hydrochloric acid and add water to 100 ml. One ml of this solution with one ml of 0·25% sodium nitrite and one ml of dilute hydrochloric acid are allowed to stand for 5 minutes. After adding 1 ml of a 1% aqueous solution of the sodium salt of 8-ethoxynaphth-1-ol-3,6-disulphonic acid, make alkaline with 3 ml of a 15% solution of sodium hydroxide and dilute with water to the 100 ml mark. After twenty minutes measure the absorbance of the solution using a colour filter (type Pulfrich S 53) and calculate,

by employing a calibration curve, the quantity of undiazotized 2,4-dichloroaniline.

The percentage of acetic anhydride = $(25 - x) \times 0{\cdot}063$,

where x = the quantity of dichloroaniline in mg indicated by the absorbance curve.

4. *Titrimetric control* can also be accomplished by reaction with morpholine [431] (Chapter 16; Section 96 (a)).

(d) *Removal of acetic anhydride from acetic acid.* When easily acetylatable amines are titrated, even a minimum of acetic anhydride contamination can lead to erroneous results since the compound becomes partly or completely acetylated and as acid amide does not consume any, or scarcely any, perchloric acid. For example 2-naphthylamine, *p*-phenylenediamine, aniline, t-butylamine [612]; isonicotinic acid hydrazide [732]; isolysergic acid hydrazide [306] and *p*-anisidine [767] are easily acetylated. In these cases the acetic acid must be freed from acetic anhydride. The latter can also be formed at elevated temperatures even if the acetic acid originally did not contain any.

One litre of acetic acid, previously dehydrated by acetic anhydride, is mixed with 3 g of benzylamine and then fractionated. The acetic acid prepared in this way does not contain even trace quantities of acetic anhydride [767].

48. Fractional Distillation

Each of the anhydrous solvents is distilled and afterwards stored in batches of 1–5 l. Fractionation is performed in a distillation assembly with ground glass joints, fitted with a fractionating column (Fig. 33; [200]).

This column is efficient if the boiling point of the solvent being distilled does not exceed 120°C; an oil bath is employed. A solvent with a higher boiling point than this can be distilled only if the column is surrounded by a heating mantle. Distillation is carried out with the exclusion of atmospheric moisture.

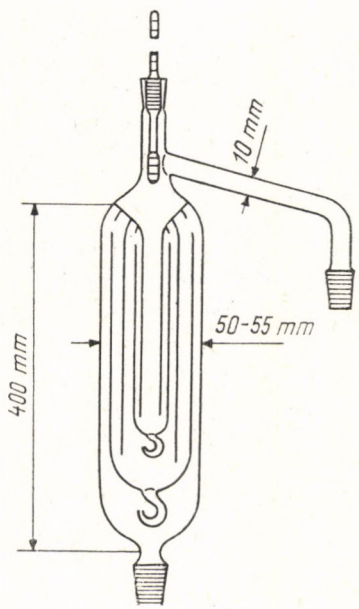


Fig. 33. Fractionating column for the purification of solvents [200]

When solvents of high melting point are distilled, particular attention must be paid that the cooling water is not too cold otherwise the solvent may solidify in the cooling coil. It is, therefore, advisable to use a long cooling coil with a slow water flow rate; sometimes the receiver flask is cooled separately by ice. **If these precautionary measures are not observed an explosion may occur.**

Solvent	*Solidification Point* °C
t-Butyl alcohol	25·6
Acetic acid	16·6
1,4-Dioxan	11·8
Ethylenediamine	8·6
Benzene	5·5

49. Special Purification Methods

(a) *Methanol and isopropanol*, when used for the determination of carbonyl groups based on oxime formation, are treated with 2,4-dinitrophenylhydrazine (1) or silver nitrate (2) in order to remove aldehydes and ketones.

1. Place 2 l of alcohol in a 3-l flask. Add 1–2 ml of concentrated hydrochloric acid and 1–2 g of dinitrophenylhydrazine and boil for 1 to 2 hours under reflux, then fractionate. Treat the distillate with 50 g of a mixture of potassium carbonate and activated charcoal in equal proportions (previously dried at 100–110°C), then filter and, after adding 2–3 g metallic sodium, fractionate.

2. Dissolve 5 g of silver nitrate in 1 litre of isopropanol and allow the solution to stand for 2 hours in direct sunlight. Boil for half an hour in a gentle stream of nitrogen under reflux, then fractionate.

(b) *Examination and purification of ethyl ether.*

1. *Testing for peroxide in ethyl ether.** **Distillation of ethyl ether, and also of tetrahydrofuran containing peroxide may lead to explosions causing grave accidents. Do not, therefore, distil peroxide-positive ethyl ether. In every case make sure beforehand that it is free from peroxide.**

Transfer 10 ml iron(II) thiocyanate solution into a 30 ml glass-stoppered bottle from which the air has been displaced by carbon dioxide. Fill to the brim with the ethyl ether to be investigated and insert the stopper in such a way that no space remains above the liquid level. Shake *vigorously* and allow it to stand for five minutes protected from the light. If the ethereal phase is pink, the peroxide content is above 0·00015%. *Preparation of the reagent:* mix 3 ml 2·5 M sulphuric acid with 35 ml of distilled water and boil to remove oxygen. Dissolve 1 g iron(II) sulphate in the boiling solution and after cooling, dissolve in it 0·5 g potassium thiocyanate. The red colour due to iron(III) thiocyanate is removed by adding small pieces of pure iron wire. Store in an oxygen-free atmosphere. The iron(III) thiocyanate contamination can also be removed by extraction with ethyl ether.

In ethyl ether, isopropyl ether, dioxan and tetrahydrofuran, traces of peroxide contamination can be detected by a reagent containing N,N-dimethyl-*p*-phenylene-

* *Analyst* **87**, 401 (1962).

diamine. As little as 10 μg/ml peroxide can be detected by the bluish-red tint (abs. maximum at 570 mμ). Detection of peroxides is made difficult by aliphatic aldehydes above a certain concentration (1,000 μg/ml). *Preparation of the reagent:* dissolve 300 mg of N,N-dimethyl-*p*-phenylenediamine sulphate in 10 ml water and dilute with 90 ml methanol. The assay is performed at room temperature, protected from the light: mix 2 ml of the solvent with 2 ml of the reagent and compare, after 5 minutes, with a mixture prepared in the same way but with a solvent distilled from metallic sodium. If ethyl ether is preserved with diethyl dithiocarbamate no colour reaction occurs [193].

2. For the *purification of ethyl ether containing peroxide*, shake 1 litre of ether with small portions of a solution prepared from 100 g crystalline iron(II) sulphate and 200–250 ml 10% sulphuric acid. If there is evolution of heat wait before further addition of the iron(II) sulphate solution. Continue shaking for 15 minutes, wash the separated ether carefully with water, then add it to a coarsely ground mixture of 20 g potassium permanganate and 30 g of potassium hydroxide. Shake a few times and allow it to stand overnight. The ether so purified can be distilled from metallic sodium.

3. Drying of ethyl ether with anhydrous magnesium sulphate see: [108].

For details of the freeing of Methyl Cellosolve from peroxide see: [417].

(c) Instead of purifying *chlorobenzene* with sulphuric acid and concentrated sodium hydroxide, take 1 litre of chlorobenzene and 20 g of granular calcium chloride, allow it to stand for 24 hours and then fractionate. Repeat this procedure.

(d) In order to purify *acetonitrile* pre-dry the commercial quality with sodium sulphate, add 25–30 g phosphorus pentoxide per litre, boil for 1–2 hours and finally fractionate. Repeated distillation from phosphorus pentoxide has a disadvantage in that it causes polymerization of the solvent. For recommended methods for purification, see: [139].

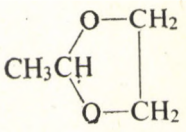
(e) Water is by far the most difficult contaminant to remove from *acetone*. This can be best accomplished by using potassium carbonate [434], since metallic sodium, phosphorus pentoxide and calcium chloride catalyze self-condensation, the products of which contaminate the solvent. Silicon dioxide (Silica gel) and alumina increase the water content of acetone, probably as a result of aldol condensations (p. 382 in [866]). The water content of ketones, esters and ethers can be determined photometrically with a reagent containing lithium chloride and cupric perchlorate in acetone [416].

Methanol contamination can be removed by use of potassium permanganate. Add 1–2 g of finely ground potassium permanganate to 1 litre of acetone and boil for 1–2 hours. After cooling, allow it to stand and if the solution remains pink fractionally distil, then dry with potassium carbonate and fractionally distil for a second time. After this treatment 0·1% of water remains in the acetone. With anhydrous calcium sulphate the water content can be reduced to 0·001%.

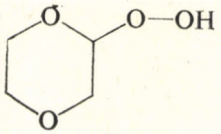
Purification of *methyl ethyl ketone* and *methyl isobutyl ketone* is carried out in a similar way. For information about purification of the former and of acetonitrile by passing through an activated alumina column, see: [105].

(f) *Investigation and purification of 1,4-dioxan.* Owing to the industrial preparative process, commercial dioxan contains various impurities and some also arise during

storage. Such impurities are for example glycol acetal, acetaldehyde, crotonaldehyde, ethylene glycol, ethylene oxide, water and dioxan peroxide [784]:



Glycol acetal



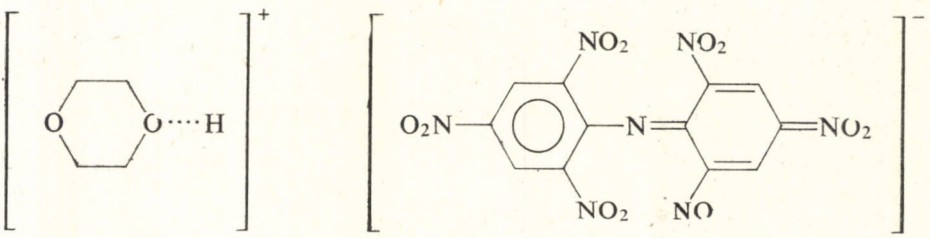
Dioxan peroxide

Dioxan, being an ether, is sensitive to atmospheric oxidation. On standing, peroxides are formed, which then give rise to aldehydes, acetic acid and other products. By distillation combined with metallic sodium treatment only part of the glycol acetal is removed (b. p., 82·5°C). The purification method to be used depends on the purpose for which the dioxan is required. For visual base titrations the simplest and quickest purification method suffices. For micro or semimicro potentiometric titrations, particularly if a differentiating titration is to be performed, it is advisable to use carefully purified dioxan.

1. *Testing the peroxide content of dioxan* [224]. Dissolve 9 g of iron(II) sulphate heptahydrate in 50 ml hydrochloric acid (1:1) and add 5 g of sodium thiocyanate and a small amount of granulated zinc. After decoloration dissolve a further 12 g of sodium thiocyanate in the solution and decant the unreacted zinc. One drop of the reagent mixed with two drops of dioxan yields a red colour in the presence of active oxygen, because the colourless iron(II) thiocyanate becomes oxidized to red iron(III) thiocyanate.

2. *Estimation of the peroxide content of dioxan.* Mix 20 ml dioxan with an aqueous solution of 5 ml saturated potassium iodide, 2 ml 2 N sulphuric acid and 2 ml starch solution and dilute with approx. 50 ml water until a blue colour appears. Titrate with 0·1 N thiosulphate solution. One ml standard solution is equal to 0·05 m.eq. of active oxygen.

3. *Detection of water in dioxan* [115, 225]. In anhydrous dioxan, dipicrylamine (hexanitrodiphenylamine) dissolves giving a pale yellow colour. On addition of a minute amount of water the solution becomes orange-yellow. Water dissociates into H^+ and OH^- ions as a consequence of which dioxan, being a weak proton acceptor, forms some cations, at the same time the dipicrylamine, owing to the effect of OH^- ion, is stabilized in a quinonoid anion form and with dioxan forms a soluble orange yellow salt:



4. *Purification of dioxan.* Shake the middle fraction of distilled dioxan for 24 hours with dry, carboxyl-type Amberlite IRC-50 cation exchange resin. After

filtration, boil for 1–2 hours with solid sodium hydroxide, then fractionate. The dioxan purified in this way is suitable for potentiometric titration [507].

5. *Purification of dioxan.* Dioxan is stored for some days over solid sodium hydroxide, the brown granules are replaced daily until they remain colourless and the solvent is then fractionated. After treatment with metallic sodium, it is fractionated once more [747].

6. For purification with asbestos wool, see: [741].

7. *Purification of dioxan for special purposes* [784]. Boil 1 litre of technical dioxan with 100 ml N hydrochloric acid for at least 10 hours under reflux. Glycol acetal undergoes hydrolysis under these conditions. During boiling direct a gentle stream of nitrogen through the system via a tube fitted in the condenser reaching about 1 cm above liquid level. Cool in a stream of nitrogen, then transfer to a 2 l separating funnel, add 50 g of sodium hydroxide and allow to stand for 1 day with frequent shaking. After this, remove the lower layer and repeat the sodium hydroxide treatment. Store the dioxan in dark bottles and, after adding metallic sodium, allow it to stand for 2 days.

After decanting the dioxan from the metallic sodium and adding a further 30 g of metallic sodium, boil for a day in a stream of nitrogen. Metallic sodium lacking a metallic lustre must be replaced.

The last phase of purification is fractional distillation. Transfer the dioxan to another flask and add a further 30 g of metallic sodium. This flask is then fitted with a fractionating column of high efficiency and at least 50 cm high.

Protect the contents of the receiver from moisture by fitting a drying tube filled with calcium chloride. Distillation is carried out in a nitrogen stream. The gas is introduced by two tubes: one, as already described, reaches above the liquid level, the other one terminates about 2 cm higher than the mercury bulb of the thermometer. By means of the second gas tube the nitrogen stream is made to flow in the direction of the evaporating dioxan. Prior to distillation the system is saturated with nitrogen through the lower nitrogen gas tube, but during distillation nitrogen is allowed to flow only through the upper tube. With this technique, the mercury column of the thermometer does not fluctuate. Distillation is performed very slowly and the first one-fifth of the distillate is rejected; up to one-tenth remains in the flask as residue.

Dioxan must be stored in brown, glass-stoppered bottles, filled to the neck. As with ethyl ether, storage over metallic sodium accelerates the formation of peroxide [784].

(g) *Purification of dimethylformamide.* In the presence of traces of water, dimethylformamide undergoes hydrolysis. The commercial grade of this product is often contaminated with water and formic acid. If distilled at normal atmospheric pressure, it is decomposed to a small extent, dimethylamine and carbon monoxide being formed. This decomposition is catalyzed at even lower temperatures by acidic contaminants [805]. When stored over potassium hydroxide dimethylamine is also formed. With water an addition compound is formed: DMF. 2 H_2O. When mixed with 20% water, the temperature of the dimethylformamide-water mixture rises by 20°. All this indicates that the dehydration of dimethylformamide is rather difficult.

1. *Purification with ion-exchange resin* [600]: 50 g of dry ion-exchange resin (Dowex 1 X10) converted to the hydroxyl form, is added to 500 ml of dimethylformamide and stirred for a few hours. After being decanted, the solvent is filtered.

2. *Purification with barium oxide* [660], see also [2]: After fractionation on a column filled with Raschig rings, the distillate is allowed to stand for 48 hours over barium oxide. After settling and being decanted the DMF is distil *in vacuo* in the presence of 1% boric acid. For purification for conductometric purposes, see: [805].

(h) *Purification of nitromethane* [135].

1. Mix 75 g ion-exchange resin Amberlite IR-120 (H^+ form) with anhydrous methanol, then let it settle and decant the methanol. Repeat this several times. Place the resin in a 2 × 25 cm chromatographic column and wash with 1 litre of methanol at a flow rate of 1–2 ml/min. Rewash the column with 300 ml nitromethane. This prepared resin bed is suitable for the purification of 15–25 litres of nitromethane at a flow rate of 2–5 ml/min.

2. Shake vigorously 1 litre of nitromethane with 3 × 300 ml water containing 2·5% sodium bicarbonate and 2·5% sodium bisulphite, and subsequently with 3 × 200 ml water followed by 100 ml 5% sulphuric acid and finally again with 3 × 200 ml water. Fractionate, after pre-drying with sodium sulphate.

3. For purification of nitromethane for special purposes, see: [520].

(i) *Purification of pyridine.*

1. *Aluminium oxide method* [30]: Shake 500 ml of pyridine with 20 g activated alumina (Merck, 71707) in a glass-stoppered bottle for 5 min., then filter through a 9 cm diameter glass filter covered by a layer of 5 g of diatomaceous earth (100 ml impure pyridine requires 0·2–0·4 ml of 0·1 N tetrabutylammonium hydroxide, whereas pyridine purified according to the above method requires only 0·05 ml).

The pH of a suspension prepared from 10 g active alumina and 90 ml distilled water is typically 10·0–10·2.

2. *Barium oxide method* [687]. Pyridine is boiled for 3 hours under reflux in the presence of powdered barium oxide. Atmospheric moisture and carbon dioxide must be excluded. After this, fractional distillation follows. The pyridine prepared in this way does not contain any carbon dioxide, which would influence the accuracy of titration with tetrabutylammonium hydroxide. Its water content is 0·02–0·04%.

3. *Drying can also be carried out by azeotropic distillation*, as follows: mix pyridine with 10% v/v benzene and fractionate (see Fig. 33). At 67°C a mixture of water, pyridine and benzene distils, then benzene and, finally at 116°C pyridine, with a water content of 0·05–0·08%, distils. However, pyridine can also be dried by the sodium hydroxide method, described for dioxan (Method (5)).

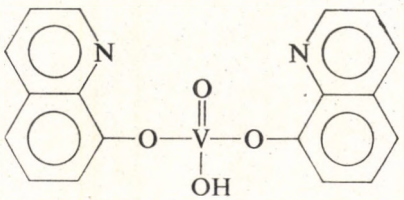
For the determination of barbituric acids by means of visual end-point detection *pyridine homologues* (boiling between 114 and 155°C) are also suitable solvents. For potentiometric titrations the fraction b. p. 134–140°C is preferable [370, 371, 372].

(j) *Reactive alkyl halide contaminants in chloroform; detection of ethanol in chloroform; preservation of chloroform.* Chloroform of commercial quality may contain aliphatic halide contaminants, such as methylene dichloride and chlorobromomethane [874, 875]. The latter, with trimethylamine, forms chloromethyltrimethylammonium bromide:

$$[ClCH_2 \,.\, N(CH_3)_3]^+Br^-.$$

Chloroform sometimes contains 0·25% chlorobromomethane.

Strong bases, such as for example, pyrrolidine, piperidine and ephedrine, interact with reactive alkyl halides and, probably, also with chloroform if the reaction is allowed to take place for any length of time at 60°C. For this reason, when alkaloids are extracted with chloroform, it is not advisable to concentrate the chloroform solution, because strychnine for example forms chloromethyl strychnine bromide. *Purification of chloroform from reactive alkyl halide contamination:* Boil 250 ml of chloroform with about 7 g pyrrolidine for 70 hours under reflux. Then fractionate and purify using concentrated sulphuric acid and sodium hydroxide; finally fractionate again. *Preservation of chloroform and carbon tetrachloride*, after purification, is achieved by adding 1 %v/v of light petroleum. The two solvents, when kept in closed bottles and protected from light, can be stored for 5–6 months without phosgene formation. Commercial chloroform is often preserved with ethanol. When microtitrations are performed with perchloric acid in acetic acid in the solvent mixture acetic acid-chloroform, the presence of ethanol is just as undesirable as that of water. Chloroform can be freed from ethanol by purification with concentrated sulphuric acid and subsequent washing with sodium hydroxide solution (see: Section 46). *Qualitative detection of ethanol contamination in chloroform.* For this purpose the solution of vanadium hydroxyquinolinate (oxinate) complex either in benzene or in *o*-dichlorobenzene is suitable (p. 172 in [224], [69, 112]):



In a micro-test tube 1–2 drops of chloroform are heated with 4–8 drops of reagent for 2–8 min on a water bath at 60°C. Simultaneously also 4–8 drops of reagent are heated as a blank. In the presence of ethanol the greyish-green reagent turns pink or red. *Preparation of the reagent:* 1 ml of an aqueous solution containing 1 mg vanadium in the form of ammonium vanadate is mixed with 1 ml aqueous solution of 2·5% 8-hydroxyquinoline containing 6% acetic acid. The aqueous solution is extracted with 30 ml benzene and the organic layer separated. The benzene solution of the reagent can be kept for 1 day; it contains the vanadium oxinate complex in solution. Using this method 20 μg ethanol can be detected.

(k) For *purification methods for rarely used solvents* see the literature. Aniline: p. 442 in [866], nitrobenzene: p. 432 in [866] and [469]; benzyl alcohol: [555]; trichloroethane: [38]; tetrahydrofuran: [391]; Cellosolve: [692]. For purification of solvents see also the detailed monograph of W. Bunge.*

50. Physiological Effects of Solvents

Every organic solvent suitable for dissolving fats and oils and possessing a high vapour pressure at room temperature is physiologically active. Poisoning can occur

* Houben-Weyl: *Methoden der organischen Chemie*, Band I, 2; *Allgemeine Laboratoriumspraxis*, Band II, p. 765, Stuttgart, Thieme Verlag 1959.

through the respiratory passages and to a smaller extent by absorption through the intact skin, sometimes also by destruction of the epithelial tissue. (If work is carried out carefully, poisoning through the intestinal tract is most unlikely.)

The most typical toxic effects of some solvents are as follows: of the saturated hydrocarbons, hexane has a narcotic, convulsive and skin irritating effect; benzene and toluene produce irritation, convulsions and on prolonged exposure, aplastic

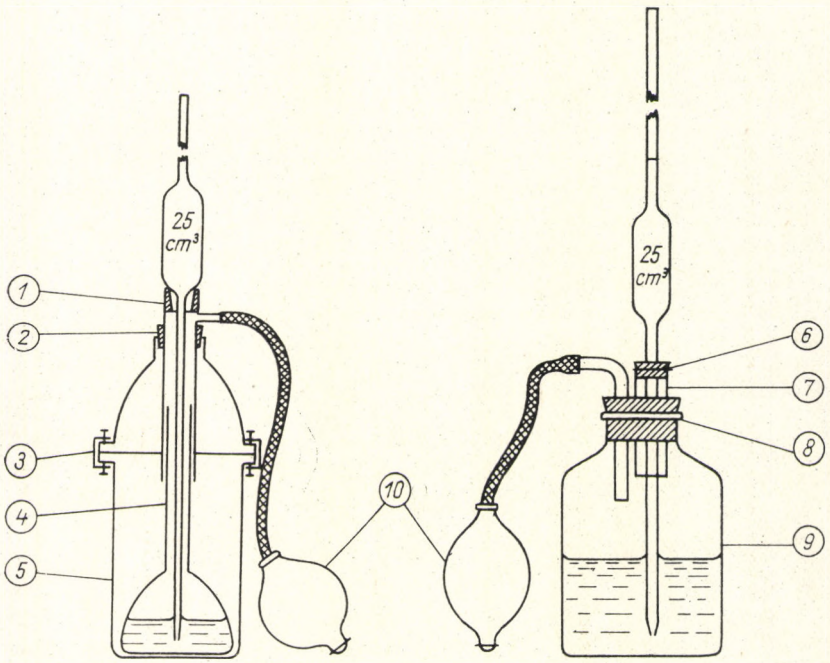


Fig. 34. Pipette-filling devices for toxic solvents. — *(1)* Rubber cone, *(2)* Rubber stopper, *(3)* Clamp, *(4)* Measuring flask, *(5)* Vacuum adapter, *(6)* Rubber bung, *(7)* Wide glass tube, *(8)* Rubber bung, *(9)* 250 ml wide mouth jar, *(10)* Rubber bulb

anaemia; the toxicity of chlorinated hydrocarbons is considerable and affects mainly liver metabolism. The intoxicating effect of alcohols is well known but it should be pointed out that the secondary alcohols are more dangerous. Methanol affects the optic nerves; glycols are kidney poisons. Ketones and ethers have narcotic effects; dioxan can cause grave liver and kidney damage. Acetic acid and propionic acid exert a caustic effect on the skin, and their anhydrides irritate the eyes. Pyridine is toxic and its vapours cause headache.

Numerous solvents cause obstinate dermatitis (eczema, irritation of the skin). *Toxicity of this type largely depends on individual sensitivity.*

From the point of view of laboratory safety measures, the above facts should be kept in mind. The equipment shown in Fig. 34 should be used for the pipetting of solvents (stock solutions) or an equivalent device (e.g. a pipette fitted with a bulb having a three-way valve).

For measuring out 5–50 ml of caustic solvents which have an objectionable odour in cases where a variation of 0·5–1 ml has no importance, e.g. acetic acid, acetic

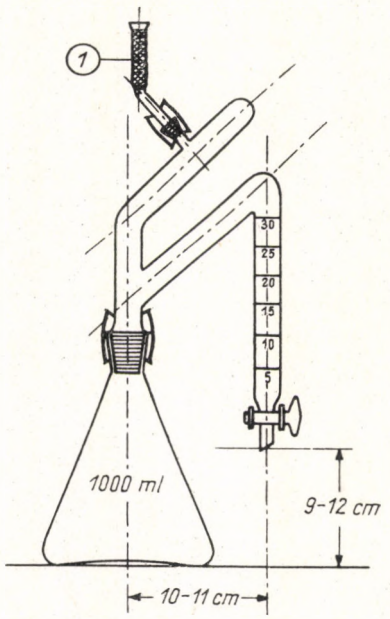


Fig. 35. Burette filling device due to Hädicke and Howorka [367]. *1* = Silica gel

anhydride, mercury(II) acetate in acetic acid solution, pyridine etc., the apparatus shown in Fig. 35 can be conveniently used [367]. By tilting the bottle, the calibrated feeder, fitted with a stop-cock, is filled with the solvent and the required quantity is allowed to flow out.

Chapter 9

Acidic Titrants

Organic nitrogenous bases can be accurately titrated by mineral acids dissolved in organic solvents [144, 146]. Conductometric investigations have proved that of these acids, perchloric acid is the strongest [470]; it dissolves in most organic solvents and the stability of its solutions in e.g. acetic acid or dioxan is satisfactory. In acetic acid, chloromethanedisulphonic acid, methanetrisulphonic acid [763] and fluoro-

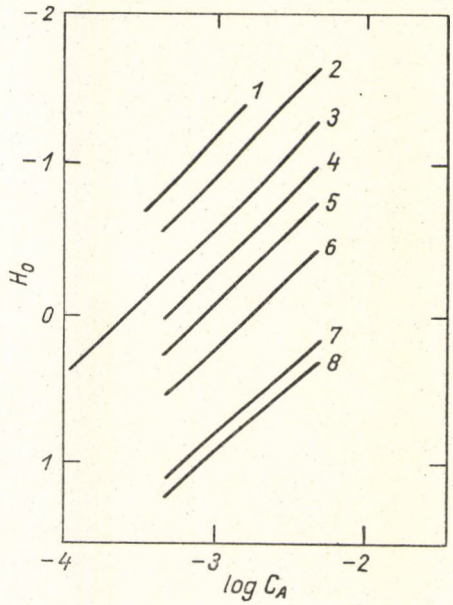


Fig. 36. H_0 values of some acids in acetic acid containing 0·12% of water according to Smith and Elliott [763]; see also: [625]. — *(1)* Methanetrisulphonic acid, *(2)* Chloromethanetrisulphonic acid, *(3)* Perchloric acid, *(4)* Chlorocarboxymethanesulphonic acid, *(5)* Chloromethanesulphonic acid, *(6)* Sulphuric acid, *(7)* Methanesulphonic acid, *(8)* Hydrochloric acid

sulphonic acid [627] are even stronger than perchloric acid but these, however, are not yet in general use. Fig. 36 shows H_0 values of strong acids in acetic acid medium [625, 763]; in this figure the Hammett acidity function is plotted as a function of the negative logarithm of acid concentration (C_A). It is apparent that in acetic acid,

perchloric acid is stronger than either sulphonic or hydrochloric acids (See: Chapter 2; Section 16.)

Moreover, with perchloric acid, highly dilute titrants (0·001 N) can be prepared and the sharpness of colour change, even in this case, does not fade to an undesirable extent. *p*-Toluenesulphonic acid or *p*-nitrotoluenesulphonic acid is also suitable for the preparation of 0·005 N – 0·001 N solutions [299, 318].

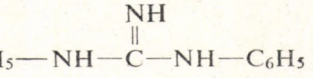
Of the standard acid solutions, those made from hydrochloric acid in G–H solvent mixtures, such as for example, 0·1 N hydrochloric acid in propylene glycol-chloroform, also work well in practice.

All titrants to be discussed are prepared using purified solvents.

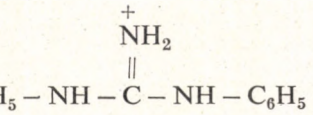
51. Hydrochloric Acid

(a) Preparation of 0·1 N *hydrochloric acid in propylene glycol-chloroform* [169, 621]: mix 10 ml of hydrochloric acid (sp. gr. 1·18) in a wide-mouthed conical flask first with 500 ml of 1,2-propane diol (sp. gr 1·43), then with 500 ml of chloroform and transfer to a burette with a container (an automatic burette; Fig. 37). This solution is standardized against a solution of *sym*-diphenylguanidine in the solvent mixture methanol-isopropanol (35 : 65).

Diphenylguanidine:



has a molecular weight of 211·3; $pK_b = 4{\cdot}00$ and owing to its high equivalent weight, it can be conveniently used as a standard substance. It is a monoacidic base, binding only one proton:



A solution of dimethyl yellow-methylene blue in methanol is a suitable indicator (see Table 24, p. 205). Three drops of indicator are needed for 20 ml of the titrant. The colour change is from green to amber. One ml of 0·1 N hydrochloric acid is equivalent to 21·13 mg diphenylguanidine.

Diphenylguanidine, if not pure, is first recrystallized from 95% ethanol, then from toluene and finally dried at 110°C [117]. It can also be dried, without decomposition, for 24 hours at 80°C or for 5 hours at 117°C [173]. Melting point, 149·4–149·9 °C. The product obtained in this way is not appreciably hygroscopic. It dissolves in acetic acid, dioxan, ethanol, chloroform, benzene, chlorobenzene, acetonitrile etc.

The hydrochloric acid titrant can also be standardized against mercury(II) oxide: weigh with 0·1 mg precision approximately 200 mg mercury(II) oxide and dissolve it in 5 ml of acetic acid with gentle heating, then evaporate nearly to dryness. Dissolve the residue in a mixture of 25 ml propylene glycol-chloroform (1 : 1) and neutralize in the presence of thymol blue as indicator. The mercuric acetate solution thus prepared is titrated with 0·1 N hydrochloric acid, one ml of which is equivalent to 10·83 mg of mercury(II) oxide.

Standardized in this manner, 0·1 N hydrochloric acid in propylene glycol-chloroform is suitable for the determination of the normality of, for example, the reagent mercury(II) acetate in methanol. (See: Chapter 27, Section 154; [804].)

(b) *Preparation of hydrochloric acid in methanol or glycol monomethyl ether solution.* For the preparation of 0·5 normal solutions, 50 ml of hydrochloric acid (sp. gr. 1·18) are mixed with 950 ml methanol cooled to 5–10°C, or glycol monomethyl ether at room temperature. Standardization: either by the method described above or against 0·1 N potassium hydroxide in isopropanol in the presence of thymolphthalein.

52. Perchloric Acid

When perchloric acid is dissolved in acetic acid, $CH_3COOH_2^+$ ion is formed. Compared with water, acetic acid is a considerably weaker proton acceptor, therefore, when a strong proton donor acid is dissolved, the equilibrium does not lie in the direction of the dissociation products, consequently, a strong proton donor acid is a weaker electrolyte in acetic acid than in water [420]. And yet an acetic acid solution of perchloric acid has a higher 'acidity' than an aqueous solution of perchloric acid because the acetacidium ion is a stronger proton donor than H_3O^+. The 'super acid' character of perchloric acid in acetic acid was first recorded by Conant and Hall [144].

Owing to the low dielectric constant of acetic acid only a small part of a dissolved salt is present in free ionic form, the greater part forms ion associations. The proton donating ability of proton donor acids does not necessarily lead to the formation of free ions [728]. Rather, a state of equilibrium must be postulated between ionization and dissociation [102, 464]:

$$CH_3COOH + HClO_4 \rightleftharpoons \underset{\text{Ionization}}{CH_3COOH_2^+ClO_4^-} \rightleftharpoons \underset{\text{Dissociation}}{CH_3COOH_2^+ + ClO_4^-}$$

Conductometric measurements throw light on dissociation [470], while the acidity of solutions is of greater importance for ionization. Cryoscopic measurements prove that, in acetic acid, perchloric acid is mainly present in a monomolecular form and not in a dissociated state [421].

(a) *Preparation of 0·1 N perchloric acid in acetic acid:* add to 975 ml anhydrous acetic acid free from acetic anhydride, 9 ml of 65–70% aqueous perchloric acid and 15–16 ml of acetic anhydride. The solution is mixed directly in the ground-glass-joint container of the automatic burette (see: Fig. 37). The standard solution can be used after being allowed to stand for one day because perchloric acid catalyzes the hydration of acetic anhydride. On mixing the solution, slight heat evolution may be noticed.

Standardization against diphenylguanidine [244, 450]: weigh with one-tenth mg accuracy 150–250 mg of diphenylguanidine and dissolve, with gentle heating, in 20–30 ml of neutralized solvent. If acetic acid is used, add 2–3 drops of 0·1% crystal violet and titrate from a burette graduated in 0·05–0·01 ml until a blue colour results (see: Chapter 13; Section 72). 21·13 mg of diphenylguanidine require one ml of 0·1 N perchloric acid.

Standardization against potassium hydrogen phthalate [175, 491, 730]: Potassium hydrogen phthalate behaves as a base in acetic acid (Chapter 5; Section 34). An ad-

vantage of this compound is that it is less hygroscopic than diphenylguanidine, but it has the disadvantage that it is insoluble in aprotic solvents, e.g. carbon tetrachloride, chlorobenzene etc. 20·41 mg of potassium hydrogen phthalate require one ml of 0·1 N perchloric acid.

Other standard substances. Sulphamic acid, $H_2N{\cdot}SO_3H$, an amphoteric compound, is equally as suitable for the standardization of perchloric acid, as for that of a standard

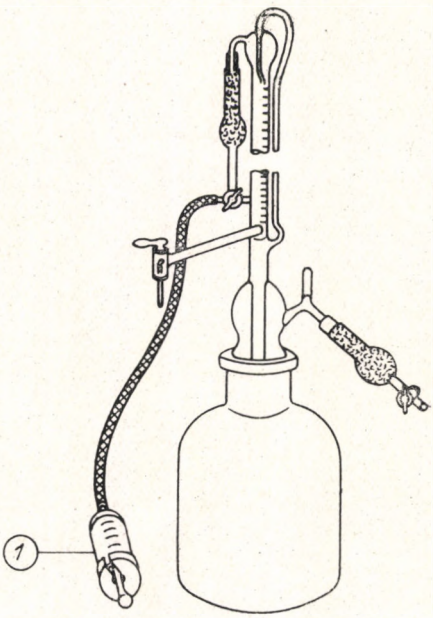


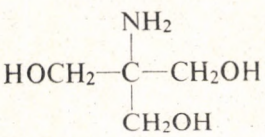
Fig. 37. Burette with reservoir for non-aqueous titrations. — *(1)* 50 or 100 ml syringe*

solution of alkali metal methoxide: 9·71 mg sulphamic acid require one ml of 0·1 N perchloric acid [118].

The acetic anhydride content of a standard solution of perchloric acid can be tested by standardizing its normality against piperazine adipate. Piperazine, in the presence of a small amount of acetic anhydride, is rapidly acetylated and the basicity of the nitrogen atoms becomes so low that they are no longer titratable with perchloric acid. The result, compared with values obtained from other standard substances, e.g. diphenylguanidine, shows whether the perchloric acid solution is contaminated with acetic anhydride [575]. For triphenylguanidine as a standard substance see: [390].

4-Aminopyridine ($K_{base} = 1{\cdot}3 \times 10^{-5}$) is also a suitable standard [335]; in acetic acid medium it also co-ordinates with one proton. 9·41 mg aminopyridine require 1 ml of 0·1 N perchloric acid.

Recently tris-(hydroxymethyl)-aminomethane has become more widely employed [238]; $K_{base} = 1{\cdot}2 \times 10^{-6}$:



* See also: W. J. Kirsten, 'Burette arrangement for some special titrations', *Analyt. Chem.* **29**, 461 (1957).

One ml of 0·1 N perchloric acid is equal to 12·11 mg of tris-(hydroxymethyl)-aminomethane. This compound is more soluble in acetic acid than either potassium hydrogen phthalate or diphenylguanidine. Its solubility is 1·7 mol/litre in acetic acid [877].

Other standard substances such as sodium carbonate and methyl nicotinate are nowadays only rarely used.

It is advisable to perform both the standardization and the titration in approximately the same volume. The solvent's and the indicator's over-all consumption of the standard solution may also be determined by a blank test. For this, however, 4–5 repeated experiments are needed and in this case previous neutralization of the solvent is unnecessary. When, using identical titration volumes and in the presence of an identical indicator, different standard substances are used, the 'correct' colour change may be different for each standard. For example, in the presence of crystal violet, potassium hydrogen phthalate must be titrated to blue, methyl nicotinate to bluish-green and diphenylguanidine to emerald green in order to obtain corresponding values [491, 730]. When standardizing perchloric acid, different values are obtained e.g. against aluminium oxinate and against potassium hydrogen phthalate [555].

Photometric standardization of 0·25 N perchloric acid in acetic acid [390]. (See also: Chapter 14.) Weigh approx. 0·97–1·0 g triphenylguanidine (mol. wt. 287·35) in a 100 ml volumetric flask and dissolve in about 50 ml acetic acid. Neutralize approx. 90% of the triphenylguanidine with perchloric acid, 100 ml of which contain 8 ml of a saturated acetic acid solution of quinaldine red, and dilute to the mark. Portions of 25 ml are titrated photometrically at 533 mμ by adding the standard solution in increments of 0·01 ml and continuing reading till the minimum approaches zero absorbance. A suitable device for photometric titrations is e.g. a circulating Erlenmeyer flask fitted to a colorimetric cuvette such as is used in the Bausch & Lomb Spectronic 20 (see: Chapter 14). The contents of the conical flask can be completely mixed in 20–25 sec. The absorption of the indicator in its basic form is measured in a similar concentration to that in which it is present in the solution being determined. The $I/I\mathrm{H}^+$ value is calculated on the basis

$$A/A_b - A$$

where A_b = the absorbance of the indicator acetate
A = the absorbance measured at different stages of the titration.

The quotient of the indicator is plotted as a function of the volume required in millilitres. The point of intersection of the curve with the axis indicates the equivalence point (Chapter 14; Sections 79 and 80). 71·84 mg of triphenylguanidine require 1 ml 0·25 N perchloric acid.

As lubricant and packing grease for ground-glass joints the following is recommended: 8 g of soluble starch are well mixed with 20–25 g glycerine placed on an asbestos pad and warmed to 140–160°C with constant stirring. The viscous fluid becomes transparent and faint brown. While still hot it is poured into a wide-mouthed bottle and preserved with 1–2 crystalline granules of phenol. Lubricant prepared in this manner is not at all, or only very slightly, dissolved by most organic solvents.

(b) *When perchloric acid in dioxan* is used and the base is dissolved in dioxan, its perchlorate is often precipitated as an insoluble salt. This enhances the sharpness of the colour change.

Preparation of perchloric acid in dioxan containing 0·2–0·3% water: 4·5 ml of 65–70% perchloric acid are mixed with 1,000 ml dioxan distilled from metallic sodium. One ml of 0·05 N solution prepared in this way is equivalent to 10·56 mg of diphenylguanidine dissolved in a solvent or solvent mixture similar to that employed for the titrant, preferably with methyl red as indicator.

Preparation of *anhydrous 0·03* N *perchloric acid in dioxan* [557]: transfer 8·5 ml of acetic anhydride to a 1 litre volumetric flask, cool the flask in crushed ice and add 2·85 ml of 65% perchloric acid carefully drop by drop to avoid a rapid rise in temperature. Dilute finally to 1 litre with dioxan freshly distilled from potassium hydroxide and passed through a Permutit C–50–D ion-exchange resin column.

(c) *The use of 0·01* N *perchloric acid in acetic acid-carbon tetrachloride* is practicable if the solvent mixture is not only the medium but is also used for the standard solution. The solubility of acetic acid and the inert character of carbon tetrachloride complement each other, thus a sharper colour change and a steeper potential jump are rendered possible. The use of propionic acid is even more favourable. The water content of the acetic acid should be below 0·05%. Mix 0·9 ml of 65–70% perchloric acid solution with 500 ml acetic acid and 5 ml acetic anhydride, let the well-stoppered solution stand overnight, then, after adding 500 ml of carbon tetrachloride, transfer to a burette with container. Standardization of solution: dissolve 90–110 mg of diphenylguanidine accurately weighed in a neutralized solvent and dilute in a volumetric flask to 100 ml. Titrate 10 ml portions of the stock solution: 2·113 mg of diphenylguanidine require one ml 0·01 N perchloric acid. The sample to be investigated is also dissolved in the neutralized solvent. The same pipette, rinsed with the solvent, should be used for standardization, as well as for the stock solution of the compound being determined since the pipettes are calibrated against water and the thickness of the solvent film adhering to the inner wall of the pipette differs from that of water. In this way, with 0·01 N solutions even 0·2–0·4% precision can be reached.

(d) A standard solution of 0·001 N *perchloric acid in acetic acid-carbon tetrachloride* is prepared from a 0·01 N solution by diluting ten-fold with a suitable solvent pair, e.g. acetic acid-carbon tetrachloride (1 : 1, 1 : 5, 1 : 10). (See also: Chapter 13; Section 72).

53. *p*-Toluenesulphonic Acid

Verländer [852] and later Dietzel and Paul suggested the use of H-acids in non-polar solvents. From the viewpoint of non-aqueous titrimetry the sulphonic acids are interesting since the presence of the sulphonic group implies strong acid properties.

Excellent precision is obtained in potentiometric titrations with methane- and ethane sulphonic acids in acetic acid solution (standard deviation of 0·2%). Unlike perchloric acid, they do not form precipitates in the titration of potassium acid phthalate [119].

p-Toluenesulphonic acid monohydrate dissolves easily in a mixture of carbon tetrachloride–phenol or chloroform–phenol (10 : 1). 0·001 N or 0·005 N standard solutions can be conveniently used for determinations routinely if – e.g. in the course of extractions – microtitration of some organic base in chloroform has to be performed [299, 301, 302, 305, 318]. Instead of a solution of *p*-toluenesulphonic acid in

chloroform, 0·002–0·005 N *p*-toluenesulphonic acid in ethylene glycol or in ethylene glycol-dioxan can be used for microdetermination of alkaloids [700, 701, 702].

Preparation of the solution: transfer 50 g of the middle fraction of previously distilled crystalline phenol to a 100 ml beaker and add to it 90 mg of *p*-toluenesulphonic acid monohydrate. The sulphonic acid, stirred with a glass rod, dissolves on heating. The phenolic solution is diluted with 200–300 ml chloroform, preserved by 1% v/v light petroleum and transferred to a 500 ml volumetric flask and then diluted to the mark. Allow to settle for 24 hours and then filter into a microburette with container [299]. The standard solution (0·005 N) is prepared from 450 mg of *p*-toluenesulphonic acid monohydrate.

Neutrality of the chloroform or carbon tetrachloride is confirmed as follows. Add 2–3 ml of freshly distilled water to 2–3 ml of the solvent, shake vigorously for half a minute and after separation of the phases, the addition of two drops of bromothymol blue should produce neither a yellow (acidic), nor a blue-green (basic) colour in the aqueous phase.

Standardization against atropine base: with one-tenth mg precision 3 × 20 mg of atropine base are dissolved in 3 × 100 ml of chloroform. For 5–10 ml of the solution one drop, for 15–20 ml two drops of a chloroform solution of dimethyl yellow indicator are used. A yellow to pink colour change occurs: 289·4 μg atropine base require one ml of 0·001 N *p*-toluenesulphonic acid. Diphenylguanidine is also suitable for standardization.

54. Use of Corrections

In non-aqueous titrimetry two sorts of corrections should be taken into account; one is for temperature, the other the solvent and indicator correction. Three methods are given for the determination of the latter:

1. Sample and standard substances are dissolved in an identical and previously neutralized solvent, in the presence of a given indicator;
2. The solvent's and the indicator's overall consumption of standard solution is determined by *separate titrations*, then subtracted from the volume consumed for the sample and the standard substance, respectively;
3. *Nearly equivalent* quantities of the compound to be determined and of the standard substance are dissolved in identical volumes of solvent (or solvent mixture) of identical composition and quality. Thus the factor of the standard solution also involves the blank correction. This method is convenient for potentiometric titrations.

Method 1 is the most simple; potentiometric titration also permits previous neutralization in the presence of a suitable indicator. Method 2 provides reliable results only when the mean value for at least three determinations is used as a correction. It is not advisable to proceed by taking ten times the amount of solvent plus indicator and then having divided by ten subtracting this from the volume consumed in the titration, since the sharpness of visual detection is also influenced by the layer thickness of the solution and its light refraction.

Anhydrous acetic acid and also the standard solution of perchloric acid have a relatively large coefficient of expansion. Hence, for standardization, the titrant

temperature is checked by a thermometer fitted to the burette and subsequently a correction of ± 0·0011 ml is applied per ml and per deg C [386, 730]:

$$N_1 = N_0 \ (1 \pm 0{\cdot}0011 \ \Delta)$$

where N_1 = normality at the temperature observed during titration
N_0 = normality at the temperature observed during standardization and
Δ = the measured difference of temperature between standardization and titration in deg C.

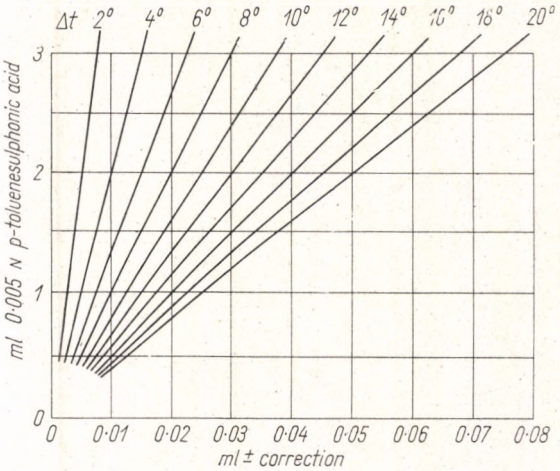


Fig. 38. Heat expansion nomogram of 0·005 N *p*-toluenesulphonic acid. 1° deviation from the temperature of standardization causes 1·25 ml of increase or decrease in volume of 1,000 ml standard solution. If temperature measured during titration is lower (+)-, if higher (—) correction must be applied

For a standard solution of *p*-toluenesulphonic acid in chloroform this value is 0·00125 (Fig. 38). During titration fluctuation of temperature should not exceed ± 0·5°C.

Chapter 10

Basic Titrants

55. Alkali Metal Hydroxide

(a) As regards the use of standard solutions of *potassium hydroxide* (or sodium hydroxide) *in methanol* (or in ethanol) it is well known that, in pure ethanol or in ethanol containing only *very little water*, the equilibrium

$$C_2H_5OH + HO^- \rightleftharpoons H_2O + C_2H_5O^-$$

favours the formation of ethoxide ions. Hence, a standard solution of alkali metal alkoxide can often be replaced by potassium hydroxide in alcohol, the preparation of which is simpler [153]:

Water Content of Alcohol	*OH^- Present in Total Base ($C_2H_5O^- + OH^-$)*		
	0·1 N	0·5 N	1·0 N
0%	0·8%	3·7%	6.9%
0·2%	1·5%	4·2%	7·5%
1·0%	4·1%	6·8%	9·6%

The above figures are confirmed by the decrease in the velocity of the hydrolysis of esters, which corresponds to the decrease in the water content of the potassium hydroxide in ethanol solution; at the same time, the infrared spectrum also shows a 75–100% uptake of the OH^- ions [116].

Preparation of 0·1 N standard solution: 6 g of solid potassium hydroxide (4 g of sodium hydroxide) are dissolved in 1,000 ml of absolute methanol (ethanol), with careful exclusion of atmospheric carbon dioxide and moisture. Standardization is carried out with 0·1 N hydrochloric acid, or with pure benzoic acid in methanol, or with palmitic acid or with potassium hydrogen phthalate, in the presence of thymolphthalein as indicator. 12·21 mg of benzoic acid, 25·64 mg of palmitic acid or 20·42 mg of potassium hydrogen phthalate require one ml of 0·1 N standard solution.

Solid hydroxides can also be dissolved directly in the container of the burette, by permitting a stream of nitrogen, washed by potassium hydroxide in concentrated alcohol and dried by silica gel, to pass into the bottle. This, at the same time, provides a means of stirring the solution.

(b) *Preparation of 0.1* N *potassium hydroxide in isopropanol:* dissolve 6 g of solid potassium hydroxide in 1,000 ml isopropanol, containing about 0·5–1% water. Boil for 10–15 min, excluding atmospheric carbon dioxide. This can be achieved either by closing the reflux condenser with a 'double absorption' tube containing silica gel and solid potassium hydroxide, or by directing a stream of washed and dried nitrogen into the boiling solution. Allow the cooled solution to stand for a few hours, while the insoluble potassium carbonate settles. Standardize against potassium hydrogen phthalate in the presence of 1-naphtholbenzeine or phenolphthalein [176, 530]. Potassium hydroxide in isopropanol or glycol monomethyl ether is used for the determination of the acid content of mineral oil and bitumen products [530, 692].

(c) Owing to its greater solvating power and higher boiling point (approx. 130°C) a standard solution of *potassium hydroxide in glycol monoethyl ether-xylene* is more suitable for the determination of saponification (ester) numbers than, for example, potassium hydroxide in n-propyl alcohol.

For the preparation of a 0·5 N solution, 30 g of potassium hydroxide are dissolved in 20 ml of water and made up to 1,000 ml with a mixture of glycol monoethyl ether (Cellosolve) and xylene (1 : 1 or 1 : 2). After two days the solution is decanted from potassium carbonate crystals which occasionally are precipitated on the wall of the flask [450]. The titrant is standardized against pure benzoic acid, palmitic acid or potassium hydrogen phthalate in the presence of thymolphthalein as indicator.

(d) *Preparation of sodium hydroxide in glycol monomethyl ether* see: Chapter 11; Section 60 (j).

56. Alkali Metal Alkoxide

Methanol, ethanol or isopropanol mixed with benzene in ratios 1:12–1:6 are the most suitable solvents for this group of titrants [252, 259, 372, 502, 694]. Monoethanolamine, ethylenediamine and pyridine are used more rarely [190, 432, 446, 601].

(a) Sodium methoxide in benzene–methanol is prepared using anhydrous benzene and methanol, freed from aldehyde and water. For the preparation of a 0·1 N solution, place one piece (2·2–2·5 g) of metallic sodium with clean surfaces in a mixture of 150 ml of methanol with 150 ml of benzene, cooled to 5–10°C (the metallic sodium should be previously dipped with the aid of pincers for 8–10 sec in ice-cold methanol). Connect the flask to a bulb condenser the opening of which is closed by an absorption tube filled with solid potassium hydroxide. The violence of gas evolution is diminished by cooling. After solution of the metallic sodium, the solution is diluted to one litre with benzene and poured immediately into a burette with container (Fig. 37). Should the sodium alkoxide solution separate or become turbid after the addition of benzene, 2–10 ml of methanol are added to the mixture until it becomes completely homogeneous. The smaller the amount of methanol used, the sharper the colour change of the indicator. For sodium methoxide at least 12–13% v/v, while for potassium methoxide 8% v/v of methanol are needed for the alkoxide to dissolve completely

in benzene. Potassium methoxide and lithium methoxide are prepared in the same way. An advantage of the latter is that, for example, when barbituric acid derivatives are titrated, no precipitate (which would lessen the sharpness of the end-point) is formed.

The titrant is standardized against benzoic acid or 2-phenylquinoline-4-carboxylic acid.

Standardization against benzoic acid: weigh, with 0·1 mg accuracy, 60–100 mg of benzoic acid and dissolve in 20–40 ml of a suitable solvent, the choice of the latter depending on the compound to be titrated (e.g. benzene-methanol, benzene-pyridine, pyridine-acetone, dimethylformamide). The solvent should be previously neutralized in the presence of thymol blue, azo-violet or another suitable indicator. Neutralization, solution and titration should preferably be carried out with exclusion of carbon dioxide (Figs 39, 40, 41 and 42). For the titration a burette graduated in 0·05 ml is used. Most of the indicators employed are sensitive to carbon dioxide; but n-butylamine and ethylenediamine combine with the latter. However, in pyridine

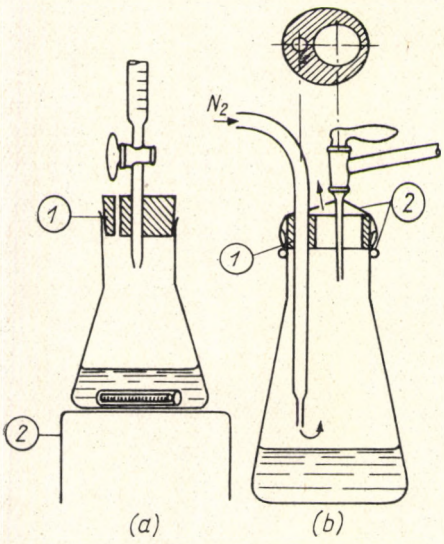


Fig. 39. Titration flasks and equipment for CO_2-sensitive indicator or solvent. — (a) Fixed flask, *(1)* Two-hole cork stopper, *(2)* Magnetic stirrer, (b) Movable flask using thin perforated rubber membrane, *(1)* Two-hole cork stopper, *(2)* Rubber membrane

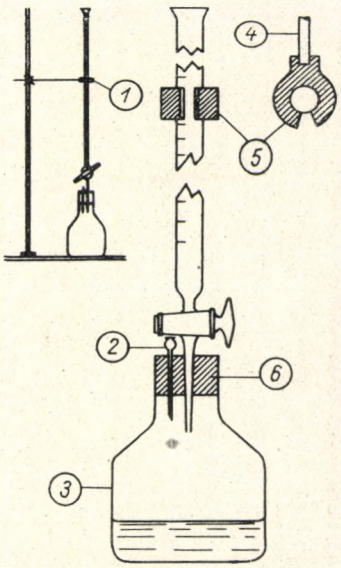


Fig. 40. Titration apparatus due to Kerny and Billon [453]. — *(1)* Elastic suspension, *(2)* Syringe, *(3)* Titrating flask, *(4)* Fixing rod, *(5)* Elastic supporting equipment of rubber, *(6)* Rubber stopper

and dimethylformamide, with practice, the titration can be carried out quickly, thus rendering precautionary measures unnecessary. In routine work, it is advisable to standardize every two days, but for occasional investigations, this should be done before every titration. The concentration of the indicator should be identical for both the standardization and the titration. One ml of 0·1 N solution is equivalent to 12·21 mg of benzoic acid.

Standardization against 2-phenylquinoline-4-carboxylic acid. A disadvantage of benzoic acid is that, during titration, alkali metal benzoate separates in the form

of a gelatinous precipitate. This can be prevented by adding 10% of methanol or isopropanol to the titrant. By so doing however, the sharpness of the end-point becomes obscure. The potassium salt of 2-phenylquinoline-4-carboxylic acid dissolves more easily and the acid is an excellent standard [307]. 24·925 mg of 2-phenylquinoline-4-carboxylic acid require 1 ml of 0·1 N solution.

Other suitable standard substances are: stearic acid (m.p. = 69·6–69·8°C) recrystallized from acetone and dried at 100°C *in vacuo* over sulphuric acid; palmitic acid (m.p. = 92·4–92·7°C) and myristic acid (m.p. = 54·4–54·8°C), particularly for stand-

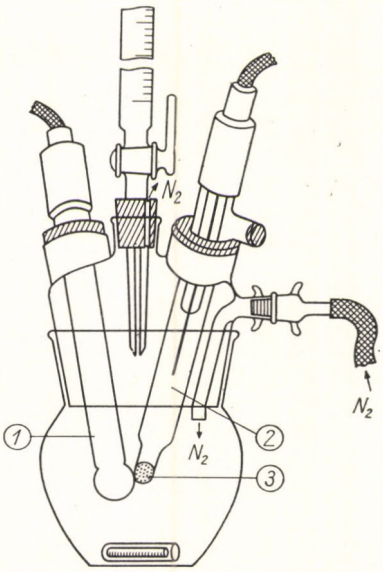


Fig. 41. Potentiometric titration flask. — *(1)* Glass electrode, *(2)* Ag/AgCl- or calomel electrode, *(3)* Porous glass or porcelain

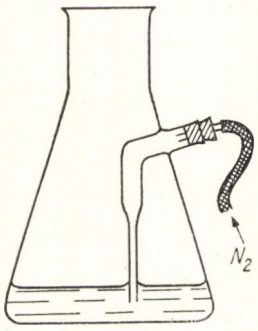


Fig. 42. Simple equipment for titration in a nis trogen atmosphere. Stream of inert gas allow- mixing but solution can also be stirred manually

ardization against 0·05 N *sodium ethoxide in ethanol* which is used for the determination of acid numbers.

(b) *0·02 N standard solution in benzene-methanol* is made by diluting 200 ml of sodium methoxide (0·1 N) with a mixture of benzene-methanol (9 : 1) to 1,000 ml. Nitrogen gas, washed by potassium hydroxide solution and dried with silica gel, should be allowed to bubble through the benzene-methanol solvent mixture. If the 0·02 N solution is to be stored for any length of time it should be kept in plastic or borosilicate bottles, under nitrogen. (See also: Chapter 21.)

57. Alkylammonium Hydroxide

Deal and Wyld were among the first to employ tetrabutylammonium hydroxide as a basic standard solution for the titration of weak acids [176]. Their isopropanol solution, however, contained 10% of water which may unfavourably affect the potentiometric titration of weak acids. Later they used tetrabutylammonium hydroxide (TBAH) in an anhydrous medium. TBAH is usually prepared from tetrabutylammonium iodide (mol. wt. of Bu_4NI = 369·4). The latter is either commercially available or can be prepared by boiling butyl iodide with tri-n-butylamine under reflux; the product obtained is then recrystallized from benzene [493].

The numerous methods for the preparation of the standard solution can be classified in three groups [159, 160, 164, 359, 361, 540].

Preparation of alkylammonium hydroxide from alkylammonium halides: (1) by means of basic anion exchange resin [395], (2) through interaction with silver oxide [159, 540] or by a combined silver oxide–anion exchange method [160, 164, 550] and finally (3) by the potassium hydroxide method [361].

For titration characteristics and factors affecting stability of quaternary ammonium hydroxide titrants see: [356, 357].

In methanol with silver oxide, a mixture of tetrabutylammonium methoxide and hydroxide is formed [136]:

$$2\,Bu_4N^+I^- + Ag_2O + CH_3OH \xrightarrow{\text{solvent}} 2\,AgI + Bu_4N^+OH^- + Bu_4N^+OCH_3^-$$

The preparation of the pure alkoxide form is difficult [359]. Even traces of water may give rise to a hydroxide. TBAH in an isopropanol medium is actually a mixture of TBAH and TBA-isopropoxide [358].

The preparation of a TBAH solution for visual titrations is simpler than that for potentiometric titrations which need greater care because occasional impurities may influence the potentiometric end-point. For example, a standard solution made by the silver oxide method must be passed through an Amberlite IRA-400 anion exchange resin column, when differentiating titrations of strong acids are to be performed [160]. Possible impurities in TBAH solution are [164, 550]: tributylamine, tributylammonium carbonate and a small amount of dissolved silver as an anionic complex. Potassium ions above a certain marginal concentration also have an undesirable effect on potentiometric titrations [355]. Carbonate contamination may originate from commercial silver oxide, although, TBAH being a powerful CO_2 abstractor, carbonate may also be formed during its preparation. All this shows that when the standard solution is prepared the possibility of contamination by atmospheric carbon dioxide must be avoided. Commercial Ag_2O may contain 0·08–0·2% CO_2. In general, the CO_2 content of a standard solution prepared by the silver oxide method is 0·5–1·0%, while that made by the anion exchange method is 0·3% [550].

(a) *Silver oxide* can be prepared with barium oxide (1) or with carbonate-free sodium hydroxide (2).

1. *Barium oxide method* [754]: Dissolve 34 g of silver nitrate in 200 ml of distilled water while a stream of nitrogen is allowed to bubble through the solution. Add to this solution a suspension prepared from 20 g *powdered* barium oxide with a small amount of carbon dioxide-free distilled water. After 30 min the deposited silver oxide is washed ten times with carbon dioxide-free water by decantation while nitrogen is continuously bubbled through the solution. It is also advisable to saturate the wash water with nitrogen gas. The washed silver oxide is finally dried with methanol.

2. *Preparation of silver oxide using carbonate-free sodium hydroxide* [164]: Dissolve 30 g of silver nitrate in 50 ml of carbon dioxide-free distilled water. Carbon dioxide can be removed either by boiling or by passing a stream of nitrogen through the water, possibly by both. After dissolution add 55 ml of 4 N carbonate-free sodium

hydroxide, shake the suspension vigorously, filter through a G/3 porosity glass funnel in a nitrogen atmosphere. Wash the silver oxide deposited on the filter surface with 750 ml of carbon dioxide-free distilled water, then with 300 ml of methanol. The 'methanol-moist' silver oxide is immediately used for the preparation of the standard solution. Experience shows that 'moist' silver oxide interacts with TBAI more efficiently than when dried [540].

(b) *Preparation of standard solutions containing tetrabutylammonium hydroxide.*

1. Preparation of 0·2 N TBAH in isopropanol with basic anion exchanger see: [359].

2. *Preparation of 0·1 N solution in benzene-methanol* with Ag_2O and Amberlite IRA-400 ion exchange resin [160]: Dissolve, in a well-fitting glass-stoppered bottle, 80 g of chemically pure TBAI in 180 ml of absolute methanol. Surround the bottle with crushed ice and when the temperature approaches 1–2°C, add 40 g of freshly prepared silver oxide, close the bottle hermetically and keep it at ice temperature for another hour with frequent and vigorous shaking. Filter through a fine porosity glass funnel directly into the storage vessel or burette with container. Wash the bottle and filter with 3 × 50 ml of cold benzene. Finally dilute the filtered solution to two litres with benzene distilled from metallic sodium. The level for two litres should be marked in advance on the vessel.

TBA-bromide in equimolar quantity can be used instead of TBAI, in which case shaking for 15 min is sufficient.

The TBAH solution must occasionally be purified. A 2·5 × 40 cm chromatographic tube is half-filled with Amberlite IRA-400 resin in hydroxyl form and washed with 2 N sodium hydroxide until a halide test on the wash water is negative. Washing with carbon dioxide-free distilled water is continued until the eluate is neutral. The column is dehydrated with 500 ml of absolute methanol, and finally 500 ml of a methanol-benzene solvent mixture is run in. The TBAH solution is then passed through this pre-treated column at a rate of 15–20 ml/min. It is collected directly in the burette container and protected from atmospheric carbon dioxide and moisture.

A standard solution so prepared is particularly suitable for the differentiating titration of a mixture of strong, medium-strength and weak acids in pyridine, since it does not contain impurities from the side reactions of TBAI and Ag_2O. For visual titrations TBAH standard solutions prepared in a simpler way are also convenient:

3. *Preparation of a 0·1 N TBAH standard solution* as described above but without purification on the anion exchange column; instead, a dry and *carbon dioxide-free* stream of nitrogen is passed through the standard solution for 5–10 min [159].

4. Preparation of tri-n-butylmethylammonium hydroxide in benzene-isopropanol (8 : 2) [540]. Suspend isopropanol H moist silver oxide, prepared from 40 g silver nitrate by the sodium hydroxide method, in a solution of 32·8 g $Bu_3MeN^+I^-$ in 90 ml of isopropanol. Shake for 15 min in a stoppered bottle, then filter the suspension through a glass filter directly into a dark storage vessel or the container of a semimicro burette. Wash the filter with 3 × 25 ml of isopropanol and dilute the filtrate with benzene to 1 litre. The standard solution can be stored for about a month without considerable loss of activity.

For the preparation of tetrabutylammonium hydroxide in benzene-isopropanol (8 : 2) from TBAH-monohydrate for potentiometric titrations in t-butanol see: [550].

5. For the preparation of tetramethylammonium and tri-n-butylmethylammonium hydroxide in pyridine see: [369, 370, 371].

6. *Preparation of 0·02* N *TBAH solution in benzene-methanol* [164]. Silver oxide needed for the conversion is made from carbonate-free NaOH (see above: (a)). Freshly precipitated methanol-moist silver oxide, produced from 30 g silver nitrate, is used for the preparation of 1 litre 0·1 N TBAH. Dissolve 40 g of pure TBAI in 95 ml of absolute methanol in a 1 litre stoppered bottle. Cool the solution in an ice-salt bath to −5 to −10°C. Add the silveroxide and saturate with dry carbon dioxide-free nitrogen. Seal the bottle and replace it in the cooling mixture. Allow it to stand for 1 hour with frequent and vigorous shaking. After adding 900 ml of benzene, saturate again with nitrogen gas and replace it for another 15 min in the cooling mixture. Filter the standard solution through a fine porosity glass funnel in a nitrogen atmosphere, directly into the container. Protect it from atmospheric carbon dioxide and moisture. When the solution reaches room temperature, dilute it to one litre with benzene distilled from metallic sodium. *The 0·02* N *standard solution is prepared from this stock solution:* 200 ml of the 0·1 N solution, after adding 30 ml of absolute methanol, is diluted to 1 litre with benzene.

In this way a carbonate-free standard solution can be prepared. In the cooled mixture the solubility of silver oxide decreases considerably but the low temperature inhibits the formation of amines during the reaction between alkylammonium halides and silver oxide.

In potentiometric titrations, a more reproducible potential deflection can be obtained when a 0·01 M solution of tetrabutylammonium bromide is used as electrolyte, in the usual calomel electrode. The electrolytic solution must be changed daily. For 0·02 N titrations it is advisable to free the solution to be determined from carbon dioxide by permitting a stream of washed nitrogen gas to pass through for 5–10 minutes before the titration. In this way the blank correction of the solution is diminished.

7. *Preparation of hexadecyltrimethylammonium hydroxide in isopropanol by substitution using potassium hydroxide* [361]. The reaction between potassium hydroxide and the halide salt of the quaternary base in isopropanol is indicated by

$$R_4NCl + KOH \xrightarrow{\text{Isopropanol}} R_4NOH + KCl \downarrow$$

The conversion factor is approx. 0·92. Separation of the potassium chloride promotes the reaction. Bromide or iodide salts are less suitable, since KBr or KI is more soluble in isopropanol than KCl.

Dry hexadecyltrimethylammonium chloride (70 g) is added to 1,000 ml of 0·22 N KOH in isopropanol and vigorously shaken for 15 min and allowed to settle. The clear liquid is transferred to the storage vessel.

By this method the alkylammonium hydroxide solution can be prepared in 1 hour; 2–3 hours are needed for the silver oxide, and 4–8 hours for the anion exchange methods. The solution is well suited to visual titrations, but its high potassium ion content (0·1–0·2% K^+) may cause disturbances in potentiometric titrations.

The presence of potassium ions in TBAH standard solution has a considerable disturbing effect when very weak acids are titrated potentiometrically in pyridine [355], and irreproducible potential jumps are also caused when potassium ions from the calomel electrode enter the solu-

tion being analyzed [358]. Hence, it seems advisable to charge the calomel electrode with an aqueous solution of 1 N tetrabutylammonium chloride instead of saturated potassium chloride. Fig. 43 indicates the disturbing effect of potassium ions on the shape of potentiometric curves.

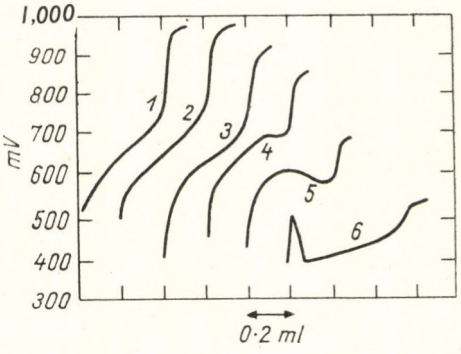


Fig. 43. Interference from potassium ions on glass electrodes. Potentiometric titration of phenol in pyridine with 0·25 N tetrabutylammonium hydroxide according to Harlow [355]. — *(1)* Potassium ion not present, *(2)* 0·0028 N, *(3)* 0·0046 N, *(4)* 0·0056 N, *(5)* 0·018 N, *(6)* 0·18 N K^+

8. For the determination of anhydrides, 0·1 N benzyltrimethylammonium hydroxide (Triton B) solution in pyridine is used [623]. For the preparation of triethyl-n-butylammonium hydroxide in benzene-methanol see: [258].

58. Titrants Containing Sodium Acetate

Basic compounds, which dissolve only slightly in acetic acid, may be dissolved by adding an excess of the standard solution of perchloric acid, occasionally also with heating. Then, for example when titrating disodium tartrate, the excess of perchloric acid is back-titrated with a solution of 0·1 N sodium acetate in acetic acid [70] (see also: Chapter 22; Section 117 (b)).

A standard solution of sodium acetate is suitable for the determination of sulphuric acid [288] or acetyl chloride [831], both in acetic anhydride medium.

Preparation of 0·1 N sodium acetate in acetic acid: (1) Weigh, with centigram accuracy, 8·2 g of anhydrous sodium acetate; powder finely, dry over phosphorus pentoxide and, after repeated grinding, dissolve in 1,000 ml of acetic acid. (2) Add 13·6 g of sodium acetate, containing three moles of water of crystallization, to 970 ml of acetic acid and 30 ml of acetic anhydride. The solution can be used after two to three days.

A standard solution of sodium acetate can also be prepared from sodium carbonate, since the latter undergoes solvolysis:

$$Na_2CO_3 + 2\,CH_3COOH = 2\,Na(CH_3COO) + H_2CO_3$$

Carbonic acid in this medium is just as unstable as in water and breaks down to carbon dioxide and water. 5·30 g of finely powdered sodium carbonate, previously dried at 270±10°C, are weighed with centigram accuracy and dissolved in 500 ml of acetic acid with gentle heat. 10–11 ml of acetic anhydride are added and the solution is diluted with acetic acid to 1,000 ml (cf. [208, 769]).

Chapter 11

Rarely Used Titrants

'Standard Solutions', the values (normality, factor, activity) of which are determined by blank tests during titration, will be discussed in detail when such determinations are dealt with.

59. Standard Solutions Prepared from Compounds Containing an Amino or Carboxyl Group

Various standard solutions are known derived from compounds containing an amino or carboxyl group. They are prepared by dissolving the amounts given in Table 18 of a solid, chemically pure compound (which is often, at the same time, also the standard substance) or of a freshly distilled base in organic solvents and diluting to 1,000 ml.

60. Other Titrants

(a) For the preparation of *perchloric acid in acetic acid-acetic anhydride* add 4·2–4·5 ml of 70–72% perchloric acid drop by drop to 500 ml of ice-cooled acetic acid and subsequently dilute with acetic anhydride to 1 litre with continuous stirring and *cooling*. A 0·05 N standard solution prepared in this way is suitable for the titration of nitrogenous bases, in acetic anhydride [778]: Chapter 3; Section 23 (c).

(b) For the preparation of a *standard solution of perchloric acid in nitromethane* 4·2–4·5 ml of 70–72% perchloric acid are diluted to 1 litre with purified nitromethane. The standard solution can be kept for about a month. It is standardized against potassium hydrogen phthalate. This standard solution is suitable for potentiometric titrations of organic bases containing nitrogen or phosphorus (phosphines) [779, 781]. (See: Chapter 3; Section 23 (d) and Chapter 31; Section 170.)

(c) *For the preparation of a standard solution of perchloric acid in propionic acid* add 35 g of propionic anhydride to 1 litre of pure propionic acid and mix, while

Table 18

STANDARD SOLUTIONS PREPARED FROM COMPOUNDS CONTAINING AMINO AND CARBOXYL GROUPS

Compound	*Normality*	*Equivalent weight*	*Sample*	*Solvent*	*Comment*
Benzoic acid	0·1	122·1	12·21 g	Benzene	*a*
Cyclohexylamine	1·0	99·17	115 ml	Methanol	*b*
Cyclohexylamine	0·5	99·17	57 ml	Tetrahydrofuran	*c*
Diphenylguanidine	0·01	211·3	2·113 g	Benzene Acetic acid Chlorobenzene Chloroform	*d*
Isoquinoline	0·5	129·15	59 ml	Benzene	*e*
N-Ethylpiperidine	0·1	113·2	14 ml	Acetone	*f*
Piperidine	0·1	85·15	9·9 ml	Isopropanol	*g*
Pyridine	0·1	79·1	8·1 ml	Acetic acid	*h*
Salicylic acid	1·0	138·1	138·1 g	Isopropanol-ethylene glycol 1 : 1	*i*
Triethylamine	2·0	101·2	—	Benzene	*j*
Tris-(hydroxymethyl)-aminomethane	0·1	121·5	12·15 g	Methanol	*k*
Tri-n-butylamine	0·1	185·3	24 ml	Dioxan	*l*
Tri-n-propylamine	0·1	143·3	19 ml	Chlorobenzene Acetone	*m* *f*

Legend:

a = For back-titration of the excess of alkaline standard solutions [121];
b = For differentiating titrations of nitrating or sulphonating acid mixtures [783];
c = For the determination of acid chlorides [519];
d = For back-titration of the excess of 0·01 N standard solution of perchloric acid;
e = For the determination of aluminium alkyl compounds [222];
f = For the determination of maleic and phthalic acids in the presence of their anhydrides [746];
g = For differentiating titrations of a mixture of sulphuric and other acids [170];
h = For differentiating titrations of hydrochloric and perchloric acids [736];
i = For back-titration of the excess of laurylamine when aldehydes are titrated, based on Schiff-base formation [751];
j = For the determination of acetic acid in the presence of acetic anhydride [564];
k = For the titration of perchloric acid, released from silver perchlorate, when acetylenic hydrogen is determined [32];
l = For the determination of acids in the presence of acid chlorides [623];
m = For the titration of hydrochloric acid in the presence of acid chlorides [753].

stirring, with 10 ml of perchloric acid (sp. gr. = 1·690). After 24 hours the solution can be used. Standardize against diphenylguanidine. In a propionic acid medium, the colour change of methanil yellow is particularly sharp, from pale yellow to purple [374, 375, 376, 377].

0·01 and 0·001 N perchloric acid standard solutions in propionic acid-carbon tetrachloride can be prepared in the same way as the analogous acetic acid standard solution. (See: Chapter 9; Section 52 (c) (d).)

(d) For the preparation of 0·1 N *perchloric acid in methyl ethyl ketone*, 8–9 m of 72% perchloric acid is mixed slowly, with stirring, with 1,000 ml of purified methy ethyl ketone. The solution is then saturated with dried nitrogen gas. The reagent is standardized against potassium hydrogen phthalate [479].

(e) *Preparation of perchloric acid in glycol monomethyl ether* (0·5 N): Add 40 ml of 70–72% perchloric acid carefully and dropwise, with stirring, into a 1 litre flask containing 500 ml of glycol monomethyl ether (Methyl Cellosolve). Finally dilute with glycol monomethyl ether to 1,000 ml. This standard solution is used in the determination of alcoholic hydroxyl groups by the phenyl isocyanate method, to titrate the dibutylamine which is used to combine with the excess of phenyl isocyanate [669]. It is standardized against tris(hydroxymethyl)-aminomethane in the presence of 0·1% bromocresol green in methanol. The colour change of the indicator is: blue → green → yellow. A more dilute standard solution (0·2 N) is used, in the determination of carbonyl groups by oxime formation, for the back-titration of the excess of hydroxylamine [259].

With 0·01 N perchloric acid in Methyl Cellosolve, small amounts of tertiary amines can be determined in the presence of large amounts of acid amides [690]. (See: Chapter 25; Section 146 (b).)

(f) When compounds containing carbonyl groups are determined with hydroxylamine formate, a 0·5 N solution of *nitric acid in glycol monomethyl ether* is used for the back-titration of the excess of reagent [691]. (See: Chapter 26; Section 152 (d)). 35 ml of concentrated, colourless nitric acid are dissolved in 500 ml Methyl Cellosolve. As stabilizing agents, 1 g of urea and 0·1 g of 1,4-diethoxybenzene are dissolved in the solution which is then diluted with the solvent to 1,000 ml. Standardization is performed against tris-(hydroxymethyl)-aminomethane. (See: Chapter 26; Section 152 (d).)

(g) Preparation of a standard solution of *hydrogen bromide* (0·1 N) *in acetic acid:* In a fume cupboard pass dry hydrogen bromide into 1 litre of acetic acid. From time to time check the normality of the solution. Weigh approx. 100 mg of anhydrous sodium carbonate, dried over phosphorus pentoxide and dissolve this in 5 ml of acetic acid. Titrate in the presence of crystal violet to bluish-green. This standard solution is employed for the determination of oxiran oxygen (α-epoxy group) [197, 198] (See: Chapter 27; Section 156.)

(h) For the preparation of a 0·2 N standard solution of *sodium aminoethoxide in ethylenediamine-ethanolamine* dissolve 4·5 g of metallic sodium with cooling in 200 ml of ethanolamine; then dilute with ethylenediamine to 1,000 ml. Potentiometric standardization can be performed against benzoic acid and phenolic compounds (*p*-hydroxybenzoic acid, 3,4-xylenol). It is used for the determination of peracids [554]. (See: Chapter 15, Section 93.)

(i) A standard solution of *sodium methoxide* (0·5 N) *in pyridine* is used for back-titration of the excess of acetylacetone or salicylaldehyde when primary amines are determined in presence of secondary and tertiary amines [157]. (See: Chapter 25; Section 144.)

A solution of 167 ml of methanolic sodium methoxide (approx. 3 N) and 40 ml of methanol is washed into a volumetric flask and made up to the mark with pyridine. Since it avidly absorbs carbon dioxide from the air it should be kept in a suitable burette (cf. Fig. 37). The solution is standardized against benzoic acid in pyridine in the presence of 1% thymolphthalein in pyridine as indicator.

For standard solutions of tetramethyl- or tributylmethyl-ammonium hydroxide in pyridine see: [369, 370, 371].

(j) For the preparation of 0·15 N or 0·55 N *sodium hydroxide in glycol monomethyl ether* proceed as follows: Mix 185 ml of carbonate-free, saturated aqueous sodium hydroxide first with 430 ml distilled water and then with 5,400 ml Methyl Cellosolve. The latter when exposed to the oxygen of the air, becomes yellow. The standard solution prepared in this way is about 0·55 N. Prepare the 0·15 N solution in a similar manner but mix only 55 ml of saturated, aqueous sodium hydroxide with 55 ml of water and 5,400 ml of Methyl Cellosolve. For applications of the standard solutions see: [257, 715, 716]. (See: Chapter 19; Section 112.)

(k) For direct titration of compounds containing alcoholic hydroxyl, a standard solution of *lithium aluminium di-n-butylamide in glycol dimethyl ether* is used instead of one in tetrahydrofuran [761]. Because of sensitivity to the moisture of the air, the preparation of the 0·25 N standard solution needs particular care and it must be kept in a nitrogen atmosphere. This method involves the possibility of sources of error and, therefore, study of the original literature is indispensable [383, 387, 391, 513, 514].

(l) For the preparation of a standard solution of *silver nitrate in isopropanol* weigh with 1 mg accuracy 1·699 g of silver nitrate and dissolve in 1,000 ml isopropanol, purified by silver nitrate. (See: Chapter 8; Section 49 (a).) The 0·01 N solution thus prepared is used for the determination of thiols [490]: Chapter 28; Section 160 (a).

(m) Standard solution of *potassium cyanide in isopropanol:* dissolve 3·25 g of potassium cyanide in 200 ml of distilled water and dilute with isopropanol in a volumetric flask, to 1 litre. The 0·05 M standard solution prepared in this way is suitable for the determination of elementary sulphur, e.g. in plant protectives [214]. (See: Chapter 28; Section 158.)

(n) *A standard solution of ammonium thiocyanate in acetone* is employed for the quantitative titration of methyl- and phenyl-chlorosilane [796, 797]. The 0·3 N solution is made as follows: Dissolve by heating 22·8 g of ammonium thiocyanate (recrystallized from methanol and dried in a vacuum desiccator) in 100 ml acetone, then make up to 1,000 ml. Standardize against silver nitrate standard solution in the presence of ferric salt. (See: Chapter 31.)

(o) The standard solution of 0·1 N *2-ethylhexanal in dioxan* is used for spectrophotometric titration of primary amines [518]. About 130 g of 2-ethylhexanal (mol. wt.: 128·4) freshly distilled and stored in a nitrogen atmosphere, are dissolved in dioxan, distilled from metallic sodium and passed through an active alumina column. The solution is diluted to 1 litre. Standardization is performed against n-butylamine solution. (See: Chapter 25; Section 147.)

(p) A standard solution of *aluminium chloride-isopropoxide in chloroform* is used for the determination of alkaloids. The formula of aluminium chloride-isopropoxide is

$$[(RO)_2AlCl].\ HCl,$$

where R = the isopropoxide group.

For the preparation and application of the standard solution see: [755, 756, 810].

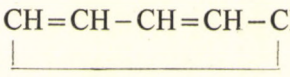
(q) *Acetic acid-bromine solution.* For a standard solution of 0·1 N and 0·05 N 2·5 ml and 1·25 ml, respectively of bromine are dissolved in 1,000 ml of acetic acid. The manipulation must be performed in a *well ventilated fume cupboard.* The solution should be kept cold, in dark glass-stoppered bottles. Its normality is determined either by using a solution of aqueous sodium arsenite or by the thiosulphate method (see: Chapter 29; Section 162 (a); [216]. The acetic acid-bromine solution is also used for potentiometric determinations of phenolic compounds based on bromine substitution, or for that of compounds containing double bonds (e.g. cholesterol) based on the addition of bromine [813, 199]. (See: Chapter 27; Section 155.)

(r) The standard solution of *copper(II) acetate* 0·05 M dissolved in *pyridine–ethanol mixture* is employed for the indirect determination of compounds containing a carbonyl group [107]. Dissolve 11 g of copper(II) acetate monohydrate in 1,000 ml of a solvent mixture of pyridine–ethanol (1 : 1) and filter after three days. (For standardization and applications see: Chapter 29; Section 163.)

(s) With a standard solution of *cerium(IV) ammonium nitrate in acetonitrile* alkyl xanthogenates (xanthates; dithiocarbonates) can be titrated, cerium(IV) being reduced to the valence (III) state [666a]. (See: Chapter 29; Section 164).

(t) The standard solutions: 0·05 M *cyclopentadiene in ethanol* and 0·1 M *tetracyanoethylene in methylene chloride* are used for the complexometric titration of dienes and aromatic hydrocarbons [618, 717].

For the preparation of a standard solution of cyclopentadiene, dimeric cyclopentadiene is 'cracked' at 160°C and the monomer thus produced is distilled once more. The fraction distilling over at 40°C is cooled with a mixture of ice and acetone; 0·8 g are dissolved in 250 ml absolute ethanol.



Cyclopentadiene
sp.gr. 0·805 (at 19°C)

The solution is standardized against tetracyanoethylene.

Preparation of a standard solution of tetracyanoethylene (TCNE): Dissolve, with gentle heating, 640 mg of TCNE in 40 ml of methylene chloride. Add 0·5 ml of dimethoxyethane to complete solution and dilute with methylene chloride to 50 ml. Because of a TCNE-dimethoxyethane complex, the solution has a pale yellow colour. It should be made freshly every day. The purity of TCNE may be checked by the Diels-Alder reaction with anthracene [618].

Chapter 12

Potentiometric End-point Detection

The equivalence point may be determined either by indicators or by physico-chemical methods: photometric end-point detection [86, 275, 276, 277, 675, 774a, 774b, 776], measurement of conductance [104, 470, 565, 577, 578, 579, 580], determination of the change of capacity of the solution and high-frequency titration [74, 177, 291, 395, 441, 495, 515, 664, 774a, 774b, 776, 892], thermometric titration [433, 451, 895],* by dielectrometric method based on the difference in the dielectric constants of acids, bases, and salts [410], or by potentiometric titration.

When the change of electromotive force read by a suitable potentiometer is plotted against the volume of the standard solution consumed, generally though not always, an S-shaped titration curve is obtained, its point of inflection indicating the equivalence point. In aqueous and non-aqueous media potentiometric measurements are performed in a similar way and with similar apparatus. There is a difference in the composition of the salt bridge established between the electrode and the solution being tested; and in titrations in inert solvents, there are differences in the shielding and earthing of the titration vessel. In acid–base titrations, the potential of the indicator electrode, immersed in the solution to be measured, is determined by the proton activity of the solution. Electromotive force is measured by a tube potentiometer of high internal resistance.

E.g. Titri pH Meter Type OP 401/1 (Radelkis, Budapest); 'Titriskop' Type E 166 or E 150 A (Metrohm, A. G.); Potentiograph E 336 (Metrohm); 'Titrator' TTT 1 (Radiometer, Copenhagen); Precision-Schell AC Dual Titrometer (Precision Scientific Co); Sargent-Malmstadt Automatic Spectro Electro Titrator (E. H. Sargent & Co); Recording Titrator (E. H. Sargent & Co); Quéré Titrator (H. Tinsley & Co. Ltd.); Precision-Dow Recordomatic Titrator. For titrations in inert solvents: Carey (Applied Physics Corp.) Model 31 vibrating reed electrometer.

* Thermometric titration is particulary useful for the determination of weak and very weak organic bases by titration with perchloric acid, e.g.: diphenylamine, urea, acetamide, acetanilide [451].

61. Area of Application

Potentiometric titrations can be applied over a wide area (Table 19). In addition to macro or semimicro routine analysis, use is made of potentiometric titrations in: (1) Differentiating titrations of acid or base mixtures; (2) Titrations of coloured solutions; (3) Determinations of exceedingly weak acids or bases in dilute solutions

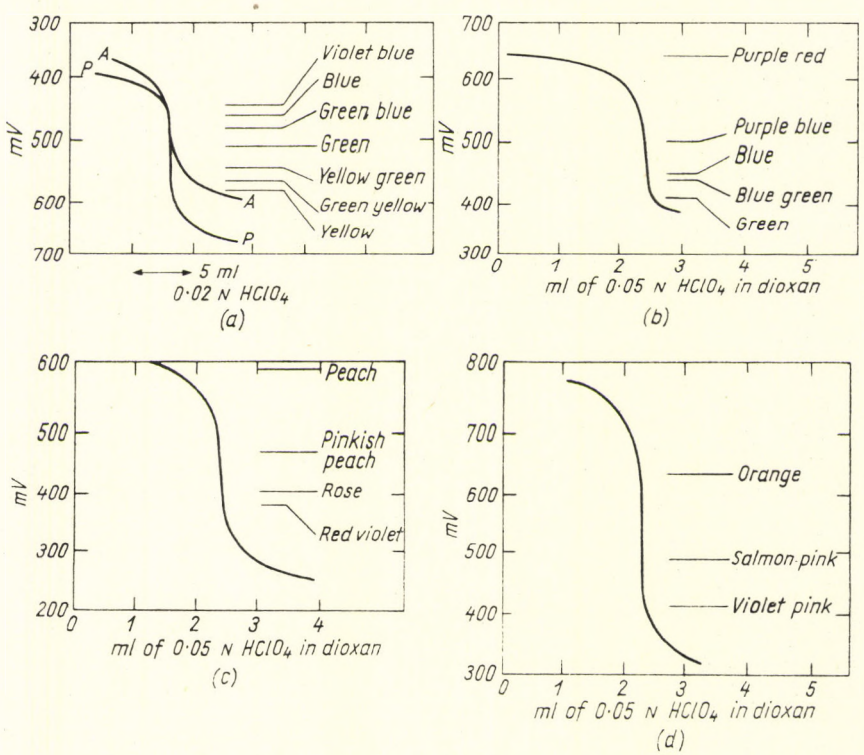


Fig. 44. Potentiometric titration and the colour change of indicators. — (a) Colour change of methyl violet in *(A)* acetic acid, in *(P)* propionic acid [375], (b) Colour change of methylene blue–quinaldine red in a mixture of nitromethane–benzene–formic acid (100 : 10 : 2) [890], (c) Colour change of methyl red in a mixture of aceto-nitrile–chloroform–phenol (100 : 20 : 10) [123], (d) Colour change of methyl red in a mixture of hexane–acetone (2 : 1) [587]

(below 0·01 N); (4) Determinations of relative acid or base strength; (5) Equivalent weight determinations; (6) Evaluation of the colour change of indicators (Fig. 44 a, b, c and d). The importance of this last use is evident since for example when sodium acetate in perchloric acid is titrated in an acetic acid medium, the correct colour change of methyl violet is to green-blue, while in propionic acid it is to green (Fig. 44a). For indicators, whose colour change passes through various shades, the correct tint must be checked near the equivalence point (within 5% before and after it), especially in the case of compounds not previously titrated. A number of these indicators is known in the methodology of non-aqueous titrations, e.g.: methyl violet, crystal violet, methyl red etc. (Fig. 44b). The composition of the solvent also influences the shade of methyl red (Fig. 44c and d).

Table 19

AREA OF APPLICATION OF POTENTIOMETRIC TITRATIONS. EXAMPLES:

	Solvent	*Standard Solution*	*References*
1. Differentiating titration of acid or base mixtures	Acetone	Et_3BuNOH	[258]
	Pyridine	Bu_4NOH	[160]
	Isobutyl methyl ketone	Bu_4NOH	[105]
	Ethylene glycol-acetone	Piperidine	[170]
	Isobutyl methyl ketone	$HClO_4$	[105]
	Acetonitrile	$HClO_4$	[247]
	AcOH—DI—NM	$HClO_4$	[401]
2. Titration of coloured solutions	Benzene-Ip	KOH	[530, 665]
	PE—Ip	KOH	[530, 665]
3. Microtitration of very weak acids	EDA, DMF	Bu_4NOH	[176, 359]
	Benzene-MeOH, DMF, Py	$NaOCH_3$	[562]
4. Measurement of relative acid or base strength	Acetonitrile, methyl ethyl ketone, Py	Bu_4NOH	[595, 780]
	Acetonitrile	$HClO_4$	[333]
	Nitromethane	$HClO_4$	[779]
	Acetic anhydride	$HClO_4$	[778]

Signs and abbrevations used: Et_3BuNOH = triethyl-n-butylammonium hydroxide; Bu_4NOH= tetrabutylammonium hydroxide; AcOH = acetic acid; DI = 1,4-dioxan; NM = nitromethane; Ip = isopropanol; PE = light petroleum; EDA = ethylenediamine; DMF = dimethylformamide; Py = pyridine; MeOH = methanol.

62. Conditions for Accuracy of Measurement

Accurate measurements require a potential difference of at least 200–300 mV/ml between the half-neutralization potential (the potential observed at the midpoint of the volume-consumed = h.n.p.) and the potential at the equivalence point. This varies with the strength of the acid or base to be determined, the solvent and the standard solution.

For example, in titrations of different acid analogues with 0·1 N lithium methoxide or tetrabutylammonium hydroxide (TBAH) in dimethylformamide medium the following very wide range of potential jumps near to the equivalence point has been measured (in mV) [7]:

Acid Analogues	*With $LiOCH_3$*	*With TBAH*
Resorcinol	10	75
Eugenol	15	100
Phenol	25	125
Propyl *p*-hydroxybenzoate	50	300
Picric acid	1,200	1,500

The above list also demonstrates that among acid analogues considerable differences of strength can be observed and also that even resorcinol, a very weak acid, can be measured with a suitable titrant. 75 mV/ml is the lowest acceptable limit in measure-

ments of potential jumps. When medium-strength bases are titrated with 0·01 N perchloric acid in propionic acid-carbon tetrachloride, changes of 500–1,000 mV/ml can be measured in the vicinity of the equivalence point [311, 314].

The *characteristic potential range of the solvent*, which sets a limit to the voltage change, from the beginning of the titration to its termination must be known; a constant temperature must be ensured during titration (±0·5°C); a suitable system of

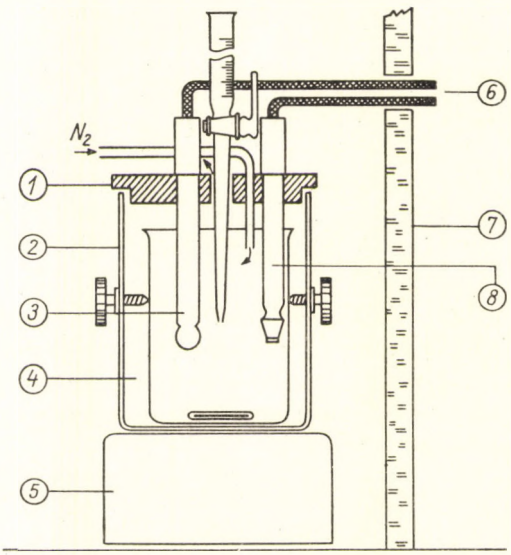


Fig. 45. Titration equipment for potentiometric determinations in inert solvents due to Harlow and Bruss [358]. — *(1)* Bakelite top, *(2)* Brass shield can, *(3)* Glass electrode, *(4)* 250 ml tallform beaker, *(5)* Magnetic stirrer, *(6)* Glass electrode adapter and vibrating reed electrometer, *(7)* Fume cupboard wall, *(8)* Calomel electrode

electrodes has to be found, in most cases empirically; fluctuations of the liquid junction potential as well as atmospheric moisture and the disturbing effect of carbon dioxide must be eliminated. With inert solvents, because of capacitative recharge and stray currents (Kriechströme), the titration vessel must be carefully earthed and screened and a special electrometer used [358]. (Fig. 45.) However, even if all these requirements are met, the accuracy of potentiometric titration does not always exceed that of visual titration.

63. Effect of the Solvent

The half-neutralization potential (h.n.p.) of acids and bases in different solvents is influenced by the following factors [333, 369, 370, 371, 778, 780, 782]:

(a) *Acidity or basicity of the solvent.* Measurements can be made only if the proton-donor ability of the solvent cation (sH_2^+) is less than that of the acid being determined and if the basicity of the solvent anion (s^-) remains below that of the base to be measured. H.n.p., above a certain acid or base strength, depends solely upon the strength of s^- and sH_2^+, respectively, (levelling effect) and the concentration of the dissolved compound. The more the solvent tends to accept protons from the dissolved acid the less it tends to release protons, for example, the electrode. Therefore, although the number of solvated protons is increased in a solution of a weak acid in a solvent of strong basicity, this favourable phenomenon is counteracted by the decreased

proton donor ability of the weak cation acid formed by strongly basic solvent molecules. For example:

$$[C_9H_6NO]H + H_2N(CH_2)_2NH_2 \rightleftharpoons H_2N(CH_2)_2NH_3^+ + C_9H_6NO^-$$

Hydroxyquinoline (Weak acid) | Ethylenediamine (Strong base) | Protonated ethylenediamine (Weak acid) | Hydroxyquinoline anion (Strong base)

$$H_2N(CH_2)_2NH_3^+ \rightleftharpoons H_2N(CH_2)_2NH_2 + H^+$$

and

$$[CH_3.C_6H_4.SO_3]H + CH_3COCH_3 \rightleftharpoons [CH_3COCH_3]H^+ + CH_3.C_6H_4.SO_3^-$$

p-Toluenesulphonic acid (Strong acid) | Acetone (Weak base) | Protonated acetone (Strong acid) | Toluenesulphonate anion (Weak base)

$$[CH_3COCH_3]H^+ \rightleftharpoons CH_3COCH_3 + H^+$$

(b) H.n.p. is primarily determined by *the intrinsic acidity or basicity of the acid or base* when a solvent of differentiating effect is used for the solution. For example, acetonitrile, acetone, methyl isobutyl ketone, pyridine, acetic anhydride, etc. When, however, the product of neutralization is a very stable salt (which does not dissolve or ionizes to a very limited extent), the h. n. p. is controlled either by the solubility product or the ionization constant.

(c) Acid and base strength, as well as h.n.p. are also influenced by the *dielectric constant of the solvent*, but the mechanism is still in doubt.

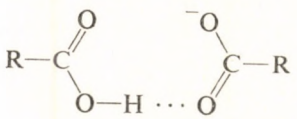
In general, the h.n.p. of cationic acids is independent of the dielectric constant of the solvent, while that of other acids, because of interaction with the solvent, does not show any regularity [186] (cf. Fig. 5).

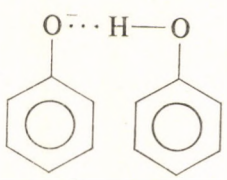
(d) *Associations causing irregular potentiometric curves.* In inert solvents, (e.g. toluene), acids and phenols are associated through hydrogen bonding.

In a weakly polar or a basic solvent this association either does not occur at all or only to a slight extent. In the course of titration, however, the conjugate base of the acid is formed i.e. the anion, whose proton affinity is considerably greater:

$$R.\,COO^- > R.\,COOH$$

Thus acid–acid anion complexes of greater stability than those of the carboxylic acid dimers are formed [35, 447, 559b]:





The formation of such complexes in inert media is substantiated very largely by conductometric [104, 559a], cryoscopic [447] and infrared spectrum investigations [33].

Phenols in pyridine [369] and toluene [358] behave similarly. During potentiometric titrations of monofunctional acids and phenols with 1·5 N tetrabutylammonium

hydroxide in isopropanol two inflections can sometimes be detected, indicating that two acids of different strength are being titrated. Since the first inflection appears at the midpoint of the titration, the formation of a 1 : 1 complex is indicated:

$$(C_6H_5O)^- \ldots HO-C_6H_5$$

The formation of a hydrogen-bonded phenol–phenoxide complex modifies the normal neutralization reaction of phenols (e.g. with methoxide or isopropoxide anion) in the following ways [358]:

1. *Titration of phenols with isopropoxide anion* [the standard solution Bu_4NOH in isopropanol actually contains a mixture of $(Bu_4N)^+OH^-$ and $(Bu_4N)^+(CH_3)_2CH-O^-$]:

$$C_6H_5OH + (CH_3)_2CH-O^- \rightleftarrows C_6H_5O^- + (CH_3)_2CHOH$$

2. *Formation of phenol-phenoxide anion complex:*

$$C_6H_5O^- + C_6H_5OH \rightleftarrows (C_6H_5O^- \ldots HO-C_6H_5)$$

3. *Titration of phenol-phenoxide anion complex:*

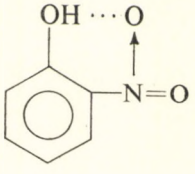
$$(C_6H_5O^- \ldots HO-C_6H_5) + (CH_3)_2CH-O^- \rightleftarrows 2C_6H_5O^- + (CH_3)_2CHOH$$

The phenol-phenoxide anion is much more stable than the phenol dimer and increases the apparent acid strength of the phenol. At the midpoint of the titration the amount of free phenol is small and the concentration of H^+ diminishes to a low level at which point titration of the hydrogen of the complex starts. By this time the acidic form is already stabilized by a complex formation whose acidic strength is lower than that of the free phenol. Though tetrabutylammonium cation does not figure in the above reaction scheme it is most probable that in an inert solvent it is mainly present as ion pairs [104], e.g.:

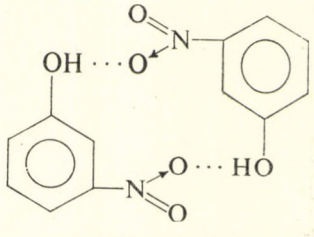
$$(C_6H_5OH \ldots OC_6H_5)^- (Bu_4N)^+ \text{ and } (C_6H_5O)^- (Bu_4N)^+$$

No hydrogen-bonded complex is formed in a solvent which itself establishes an H-bond with the solute. Therefore, when phenol is titrated in toluene, not with 1·5 N but with 0·1 N tetrabutylammonium hydroxide in isopropanol, approximately 1% of isopropanol, introduced by the more dilute standard solution, hinders the formation of a phenol-phenoxide anion complex.

Phenomena observed when *o*- and *m*-nitrophenol were determined, are evidence of the presence of H-bond complexes [358]. Thus, *ortho*-nitrophenol establishes *intra*-, while *meta*-nitrophenol sets up *inter*-molecular hydrogen bonds [628]:



o-Nitrophenol



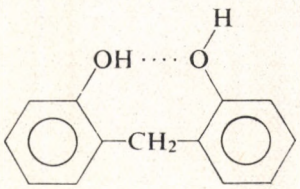
m-Nitrophenol

This also influences the formation of acid–acid anion complex. *o*-Nitrophenol shows one, while *m*-nitrophenol shows two inflections (the first one at the midpoint of titration).

Acid acid anion complexes of phenols with alkyl substituents located in the *ortho*-position are weaker, and the midpoint inflexion becomes gradually obscure as the shielding or steric hindering effect of the alkyl group increases. The order of stability of phenol-phenoxide anions is the following:

phenol > 4-methyl-2-t-butylphenol-> 6-methyl-2-t-butylphenol > 2,4,6-tri-t-butylphenol [358]

Bifunctional phenols behave in a similar way in toluene [770] and with favourable orientation one of the OH groups may have a more acidic character than the other, which may be so weak that it can no longer be titrated:



Shapes of irregular potentiometric curves may differ widely; four of these are represented below [369]:

1. Additional potential rise at half-neutralization point (Fig. 46a).
2. Asymmetric plateau ('Hump' [369], Fig. 46b).
3. Non-reproducibility of potentiometric curves, Fig. 46c).
4. Sudden potential drop at 25, 50 or 75% of neutralization (Fig. 46d).

In the course of titration the highly polar anions are not shielded sufficiently by the inert or only weakly basic solvent and acid–acid anion complexes or phenol-phenoxide anion complexes and dimer molecules are formed, causing the irregularities in curves *1* and *2* [369].

In inert solvents, polar molecules are orientated with respect to the surface of the electrode and they are also partly absorbed because of the poor solvating power of the solvent: thus the anomalous curves *3* and *4* result, though these may also appear because of the disturbing effect of K^+ ions [355]. The weaker the titrated acid, the more basic the solvent must be, so that acid molecules associate or become solvated with the solvent molecules and not with acid anions. Moderately strong carboxylic acids exhibit irregular titration curves in those solvents whose basicity is below that of pyridine. Owing to the excellent solvating abilities of amphiprotic solvents, 1% of methanol or isopropanol is sufficient to ensure that the tendency of the dissolved acid to form a complex with its own anion is inhibited.

Owing to steric hindrance, 4-methyl-2,6-dibutylphenol does not associate with its anion. Its titration curve is, therefore, normal, while 4-methyl-2-butylphenol shows a sudden rise at the half-neutralization point. Thiophenol also shows a normal S-shaped curve, since, as is well known, sulphur is less prone to hydrogen bonding than oxygen.

Experience shows that in potentiometric titration in solvents which themselves also establish H-bonds no associations causing irregular potentiometric curves are

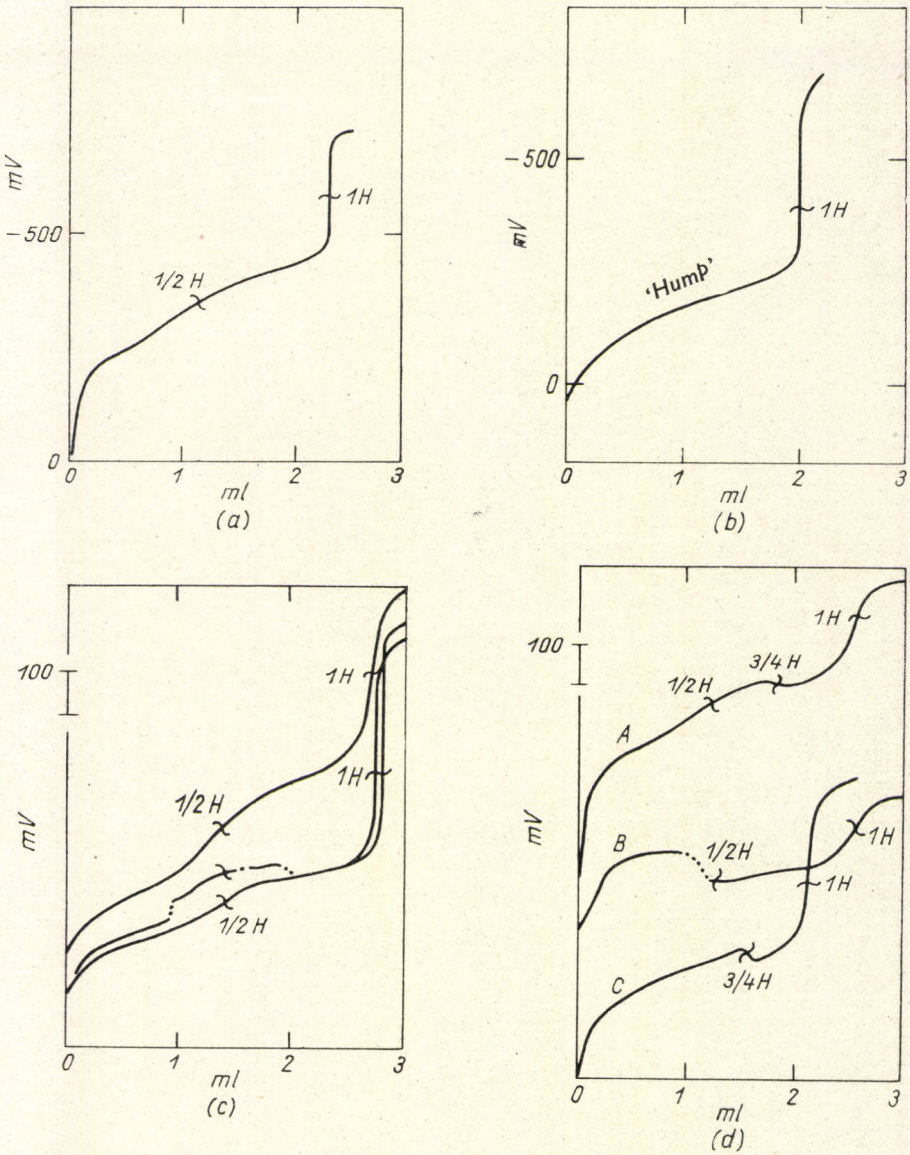


Fig. 46. Irregular potentiometric curves according to Heijde [369]. — (a) Titration of acetic acid in acetone with standard solution $MeBu_3NOH$ in pyridine; glass–calomel electrode system, (*b*) Titration of acetic acid in acetonitrile [as (a)], (c) Titration of formic acid in acetone with standard solution Me_4NOH in pyridine; glass–calomel system, (d) *(A)* Titration of phenol in pyridine and *(B)* Titration of cetylphenol in butylamine; glass–calomel electrode system, *(C)* Titration of benzoic acid in acetonitrile; Sb–calomel electrode system

formed. The lack of such intermolecular associations would render methanol and isopropanol suitable for differentiating titrations of weak acids, but the acidity of these solvents does not promote the titrations. t-Butanol (trimethylcarbinol, 2-methyl-2-propanol) is less acidic than the above simple alcohols (cf. Table 10) and is, therefore suitable for potentiometric titration of acids and phenols as well as for differen-

tiating determinations of a mixture of acids and phenols [253]. Of the strong acids perchloric acid remains dissolved in t-butanol for an unlimited period of time without showing any signs of decomposition, although the same does not hold good for either sulphuric or hydrochloric acid. Tetrabutylammonium hydroxide is stable for a short time, thus an excess of base, introduced with the standard solution in the

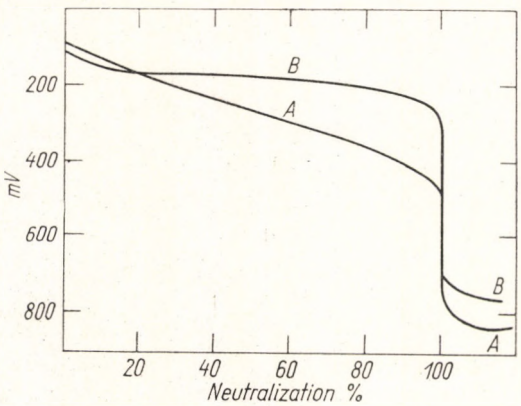


Fig. 47. Potentiometric titration of *p*-nitrophenol in acetone with 0·1 N triethylbutylammonium hydroxide, *(A)* and in t-butanol with 0·116 N tetrabutylammonium hydroxide in benzene-isopropanol *(B)* according to Fritz and Yamamura [258], and Fritz and Marple, resp. [253]

course of titration, produces stable potential values. t-Butanol, owing to this favourable effect, has an advantage in comparison with pyridine or acetone, where an excess of base often brings about fluctuating potential values. However, one of t-butanol's very characteristic properties makes it extremely convenient for differentiating titrations of phenols and nitrophenols: in potentiometric titrations of most carboxylic acids and phenols, the potentiometric curve in its 0–95% neutralization region has to cover an uncommonly great potential range. This is connected with the formation of acid–acid anion complexes [369] and because of this, potentiometric differentiating titrations may often fail. In the case of t-butanol, however, this potential range is smaller, hence the potential range, limited by this characteristic of the solvent, can hold more potential steps. Fig. 47 illustrates the titration curves of *p*-nitrophenol both in acetone and in t-butanol. In tertiary butanol, for example, a mixture of picric acid, 2,4-dinitrophenol, *o*-nitrophenol and phenol can be determined [253].

Because of the decomposition of tetrabutylammonium hydroxide in pyridine, in determinations of acid analogues even weaker than phenol, e.g. *o*-ethylphenol, the result of measurement is 102–104% of the theoretical value while in t-butanol it is 99·7% [253].

The irregularities of potentiometric titrations mentioned above are usually overlooked if measurements are not plotted graphically from beginning to end, but instead only a limited number of measurements are performed before and after the expected equivalence point; abnormal potentiometric curves do not mean that titrations cannot be carried out or that quantitative determinations are irreproducible.

(e) *Requirements for solvents and titrants:* The standard solution should be a compound of strong acidity or basicity. In a given solvent it should not form insoluble salts or stable complexes with the compound being determined and should not have a detrimental effect on the functioning of the electrodes. For the determination of bases, perchloric acid meets the above requirements. However, for the titration of

acids, alkali metal alkoxides are less suitable in solvents of low dielectric constant. The danger of forming precipitates is great and the highly mobile K^+, Na^+ and Li^+ ions affect the behaviour of the sensitive glass electrode (cf. Fig. 43).

For titrations of high accuracy it is advisable to dissolve both the standard compound and the compound to be determined in the same solvent, otherwise the dielectric, acidic or basic properties of the solvent may change during titration.

From these considerations the conclusion can be drawn that potentiometric determinations, and particularly microdeterminations, of acids present a far more difficult task than titration of bases.

64. Potential Range of Solvents

The meaning of 'acidity' or 'basicity' applied to solvents used for potentiometric determinations differs from the usual sense of these concepts. Values obtained from the mutual titration of strong acids and bases of 0·01 N concentration result in an

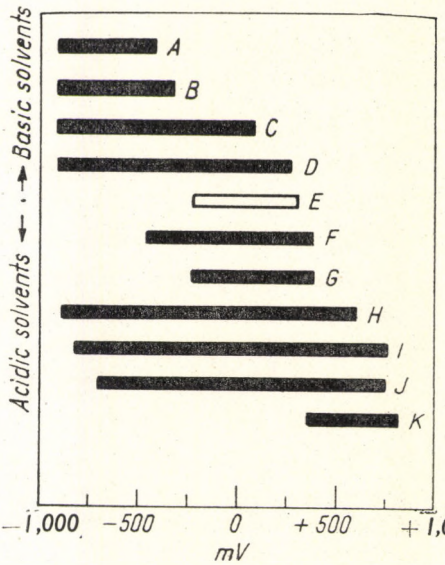


Fig. 48. Potential range of solvents according to Heijde [369, 370, 371]. — *(A)* Ethylenediamine, *(B)* n-Butylamine, *(C)* Pyridine, *(D)* Dimethylformamide, *(E)* Water, *(F)* Isopropanol, *(G)* Methanol, *(H)* Acetonitrile, *(I)* Acetone, *(J)* Chlorobenzene, *(K)* Acetic acid

empirical order, seen in Fig. 48 [369, 370, 371]: in $A-D$ the basicity of solvents decreases, in $F-K$ their acidity increases. Furthermore, it is apparent that large potential changes cannot be expected from solvents which are neither of great 'acidity' nor 'basicity', in contrast with inert or differentiating solvents. The h.n.p.'s of compounds can only be compared at a specified concentration. For example, the h.n.p. of a strong acid in pyridine varies from −1,100 to − 200 mV as the concentration of the acid changes from 0·005 N to 0·5 N.

65. Choice of Solvents

The h.n.p. of acids and bases reflects to a certain extent the intrinsic strengths of acids and bases. (See: Chapter 2; Section 16 (c) and Chapter 3; Section 23 (b) (c) (d)

and (e)). The measurement of the half-neutralization potential, however, is limited by the potential range of the solvent (Fig. 49).

Three possibilities are illustrated: (1) The lower limit of the potential range of the solvent is above the h.n.p. of the acid or base being determined: here acid strengths become enhanced and levelled while the bases cannot be titrated (Fig. 49, *B*).

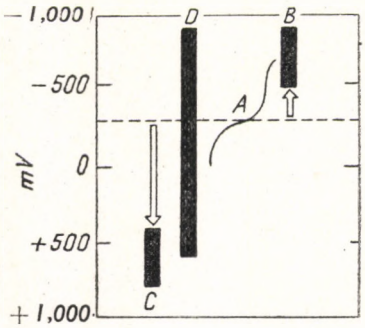


Fig. 49. Choice of solvents according to Heijde [369, 370, 371]. — *(A)* Section near to the half-neutralization point of the potentiometric titration curve, *(B)* Potential range of basic solvent, *(C)* Potential range of acidic solvent, *(D)* Potential range of aprotic solvent

(2) The upper limit of the potential range of the solvent is below the h.n.p. of the acid or base to be determined: here, base strengths are increased and levelled, while acids are not titratable (Fig. 49, *C*). (3) The potential range of the solvent coincides with the h.n.p. of the acid or base, thus their intrinsic strengths become apparent and titration can be performed (Fig. 49, *D*).

For uncharged H-acids and cationic acids of the type R_3NH^+, whose pK value measured in water is < 2, isopropanol, ketones and acetonitrile are suitable as solvents and sodium hydroxide or tetra-alkylammonium hydroxide in isopropanol as standard solutions.

For uncharged H-acids, as well as positively and negatively charged acids and also for Lewis acids with a pK value between 2 and 8 (measured in water) dimethylformamide, pyridine or one of the inert solvents or solvent mixtures may be used and as standard solutions, in addition to those mentioned in the above paragraph, tetrabutylammonium hydroxide in benzene-methanol is also suitable (Chapter 6; Sections 40 and 41 and Table 13). For acids with a pK value > 8 in water, a solvent mixture, n-butylamine or ethylenediamine may be used as a solvent, and tetra-alkylammonium hydroxide in benzene-methanol or pyridine is suitable as a standard solution. (See: Chapter 10; Section 57 (b).) In the case of Lewis acids the dissociation constant of the corresponding H-acid serves as a guide, e.g. $K_{SO_2} \sim K_{SO_3H_2}$.

For the potentiometric titration of strong or medium-strength bases (Chapter 6; Section 42) acetic or propionic acid and 0·1–0·001 N perchloric acid in acetic acid are used; in the case of weak bases, acetic or propionic acids are mixed with chlorobenzene or carbon tetrachloride, but with acetic anhydride for tertiary amines; 0·01 N perchloric acid in acetic acid–carbon tetrachloride is used as standard solution (Chapter 6; Sections 39 and 41, and Table 14).

66. Use of Supporting Electrolytes

To increase the conductivity of inert solvents of low dielectric constant a supporting electrolyte (or salt solution) is added. For this purpose e.g. Bu_3MeNI is suitable in a

concentration of $1{\cdot}5 \times 10^{-3}$ M and lithium chloride is also suitable 200 mg of this being dissolved by magnetic stirring in 50 ml of benzene–methanol (10 : 1) [153, 252, 665]; copper(II) acetate can also be used in an acetic acid medium. For base hydrochlorides mercury(II) acetate is used, partly to enhance conductivity and partly because it liberates the base from the hydrochloride [369, 370, 371, 207, 462, 644]. When the pK value of the acid to be titrated is > 2, tetra-alkylammonium iodide can be used as a supporting electrolyte. When, however, the pK value of the acid is < 2, first HI then iodine are formed during reaction in the inert solvent. In such cases base perchlorates or base *p*-toluenesulphonates must be used (e.g.: diethylanilinium perchlorate [192]). If the potentiometric measurement is performed only near the equivalence point, the neutralization product formed proves to be sufficient in an inert solvent as a supporting electrolyte, e.g. amine-perchlorate, provided it does not separate as an insoluble precipitate.

67. Electrodes

(a) *Indicator electrodes.* In the field of non-aqueous titration a *glass electrode* is usually employed as an *indicator electrode.* It can be used for the titration of bases and base halides in acetic acid medium [11, 60, 208, 244, 247, 248, 249, 450, 459, 548, 643, 644, 645, 732, 742, 769, 854], and in mixtures of acetic acid–carbon tetrachloride or acetic acid–chloroform and propionic acid–propionic anhydride-chlorobenzene [314], acetic acid–chlorobenzene [592], acetic acid–toluene [599], etc. Glass electrodes can also be used not only in acidic solvents but also in some of the differentiating and basic solvents such as acetone [124, 258, 746], acetonitrile [247, 248, 251, 155, 539], isobutyl methyl ketone [105, 359], pyridine [159, 161, 162, 780, 782], nitromethane [779], dimethylformamide [58, 176], methanol-benzene [58, 783], and G–H solvent mixtures [621, 788], etc.

In non-aqueous media, glass electrodes, even when of the same model may behave variably, particularly in inert solvents. The efficiency cannot always be regulated or improved by adding a supporting electrolyte. The behaviour of the electrode greatly depends on its 'pre-treatment'. However, the antecedents of every glass electrode cannot be given. In most cases, however, the electrode before being put to use is 'swollen' for 12–48 hours in the solvent in which it is going to be used [894]. This is also necessary for relative potential measurements. This renders the choice of a suitable solvent difficult and difficulties especially arise when the electrode must be exchanged in the course of titration because of a change of solvent prescribed by the technique. Thus it can happen that a glass electrode pre-treated in acetic anhydride does not work faultlessly in an acetic acid medium. In titrations with perchloric acid in acetic acid it has often proved sufficient to dip the glass electrode for one to two hours in a mixture of acetic anhydride-acetic acid (1 : 10). After use it is rinsed first with pure solvent, then with methanol and water, and stored in distilled water.

According to Zeidler [894] even a slight excess of perchloric acid has a harmful effect on the glass electrode, so much so, that in the subsequent determinations the potential jump either becomes flattened out or does not occur at all. On the other hand, it has been observed that the sensitivity of the glass electrode is increased when, prior to titration in perchloric acid, it is allowed to stand in a 10 : 1 mixture of acetic acid-acetic anhydride to which one or two drops of perchloric acid have been added

[314]. Such contradictions have necessitated the use of other types of indicator electrodes and new techniques. Nevertheless even now, glass indicator electrodes are usually used for potentiometric titrations because, when they are of good sensitivity, they work faultlessly and can sometimes be used for a number of years. In practice, no glass electrode can be produced whose membrane does not contain any water in the gel (even during production it comes in contact with water vapour, e.g. in the gas flame), therefore, it is probable that even in an anhydrous medium the water-containing gel membrane is the factor determining the potential (p. 79 in [725]).

Badoz–Lambling and co-workers [27] used glass electrodes filled with an organic solvent, e.g., acetonitrile for acid–base titrations in non-aqueous media. According to their comparative experiments, the constant potential is attained sooner when glass electrodes filled with acetonitrile are employed, and the reproducibility is ± 10 mV, whereas with 'aqueous' glass electrodes it is only ± 30 mV.

Retarded glass electrodes. A difficulty arising in non-aqueous titrations is that in diffusion processes irregular potentials are caused at the liquid junction of the reference electrode (e.g. a calomel electrode) between the saturated aqueous potassium chloride and the organic solvent. A number of electrode systems are suitable for the elimination of this difficulty. Among these, mention should be made of the retarded

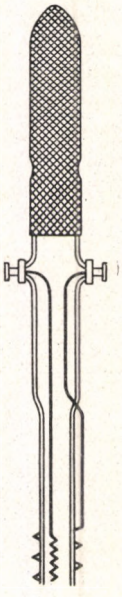


Fig. 50. Capillary electrode

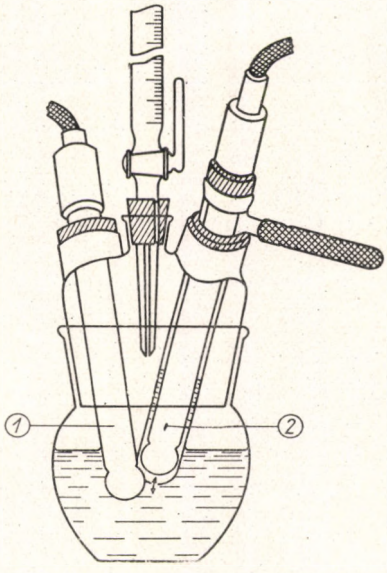


Fig. 51. Titration equipment with retarded glass electrode. — *(1)* Simple glass electrode, *(2)* Retarded glass electrode

glass electrode (a capillary type electrode) (Fig. 50 [420, 569]), the bimetallic electrode system and the calomel electrode prepared with potassium chloride, lithium chloride and tetrabutylammonium chloride and an organic solvent.

Retarded glass electrodes can be used for so-called direct differentiating titrations [444, 457], (not to be confused with titrations in solvents of differentiating properties!).

One of two identical glass electrodes is placed in a tube with a narrow opening. When the electrode is inserted in the tube it can hold approx. 1 ml of liquid. By using the retarded glass electrode as a reference electrode, fluctuation of the diffusion potential can be eliminated. However, a disadvantage of this method is that it operates more slowly than the usual potentiometric titration and the resistance of the electrode system is about 500 MΩ, so that the titration vessel and electrodes, after cleaning and drying, must be treated with silicone (e.g. Desicote [R], Beckman Instruments), and subsequently electrostatically shielded and earthed (Fig. 51).

After each 0·1–0·25 ml portion of the standard solution (ΔV) the difference of electromotive force is measured (ΔE). After each potential measurement the liquid in the tube is exchanged by use of a rubber bung and the titration continued till the highest ΔE is reached. The equivalence point can be calculated either by graphical plotting or by calculation. In both cases the end-point is reached either at the maximum $\Delta E/\Delta V$ value or when the value of $\Delta^2E/\Delta V^2$ becomes zero. For instance:

ml	mV	$\Delta E/\Delta V$	$\Delta^2E/\Delta V^2$	*Calculation*
5·00	250			
		13		
5·10	263		+15	$5{\cdot}20 + 0{\cdot}1\left(\frac{72}{72+45}\right) = 5{\cdot}262$ ml
		28		
5·20	291		+72	
		100		or
5·30	391		−45	
		55		
5·40	446		−33	$5{\cdot}20 + 0{\cdot}1\left(\frac{100-28}{100-28+100-55}\right)$
		22		
5·50	468		−12	
		10		$= 5{\cdot}262$ ml
5·60	478			

The above calculation can be also applied to normal potentiometric titrations and for any electrode system.

The solution around the retarded glass electrode causes negligible errors in measurement: approx. 0·03% [444].

For a critical discussion of various graphical methods and calculations, see the literature: [237, 517, 588].

In potentiometric titrations it is not necessary to add the standard solution in increments of 0·1 ml. After the first exploratory experiments, 3–4 readings should be sufficient before and after the equivalence point. Another method is always to add as much of the standard solution as is needed to observe about a 30 mV potential change. In this way the volume of the portions of the standard solution decreases gradually near to the equivalence point [258].

The potential of the indicator electrode *mercury-mercury(I) acetate* in acetic acid is determined by the concentration of $CH_3COOH_2^+$ and CH_3COO^- ions just as that of the glass electrode is determined by H^+ ion. Thus the two electrodes, though their design differs, serve the same purpose [713]. The $Hg/Hg_2(CH_3COO)_2$ electrode is basically a gold wire on one end of which an inner mercury film in the form of a droplet and an outer mercury(I) acetate layer are formed electrolytically. For its method of construction, see the literature: [713].

Some metal electrodes can also be classed as indicator electrodes:

(b) *Metal electrodes.* In many cases metal electrodes are suitable for the measurement of relative potential change. Usually the addition of quinhydrone or chloranil,

as a redox system, can be omitted. Platinum, gold, antimony, bismuth [894], molybdenum [56], platinum containing 10% rhodium [540], etc. are suitable indicator electrodes. According to Zeidler, a gold electrode of 1 cm^2 surface is the most suitable for the potentiometric titration of bases in methanol, ethanol, propanol, butanol, acetonitrile, acetic acid and acetic anhydride [894].

A platinum indicator electrode can also be used in ethylenediamine medium, for example, for the titration of phenols [285], when sodium aminoethoxide in ethylene-

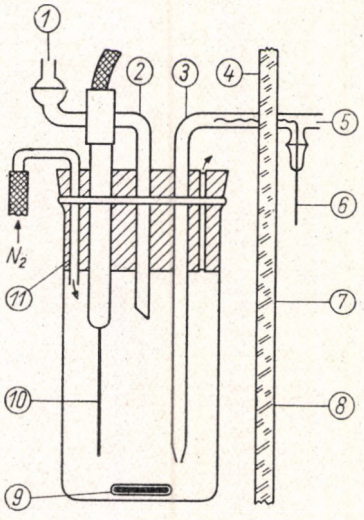


Fig. 52. Titration equipment with platinum–platinum electrode system according to Harlow, Noble and Wyld [359]. — *(1)* To solvent reservoir, *(2)* Solvent delivery tube, *(3)* Titrant delivery tube, *(4)* Inside of cupboard, *(5)* To titrator feed mechanism, *(6)* Platinum wire reference electrode, *(7)* Cupboard wall, *(8)* Outside of cupboard, *(9)* Magnetic stirrer, *(10)* Platinum indicating electrode, *(11)* Electrode holder (rubber)

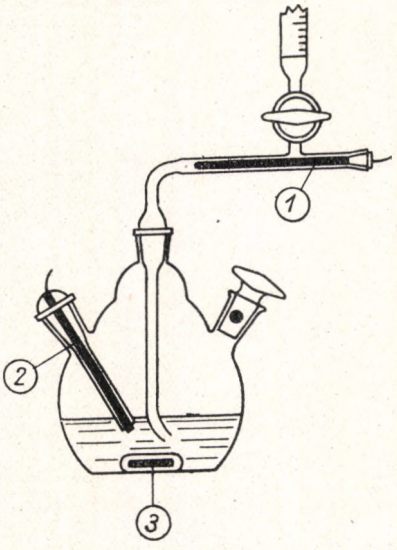


Fig. 53. Titration equipment with antimony–antimony electrode system, according to Moss, Elliott and Hall [601]. — *(1)* Reference electrode, *(2)* Indicator electrode, *(3)* Magnetic stirrer

diamine-ethanolamine is the standard solution [446]. For the titration of phenols in ethylenediamine, Harlow and co-workers recommend the use of a platinum electrode with anodic pre-polarization [359] as most suitable (Fig. 52). The functioning of the platinum indicator electrode depends on its surface and its pretreatment. Pretreatment seems to be desirable, but it must be repeated, prior to every determination. Despite pretreatment ageing of the electrode cannot be avoided. When this occurs the electrode must be kept for 3—4 hours in a 1 : 1 mixture of water-hydrochloric acid. Anodic polarization is performed for one minute in 1% sulphuric acid with a 3 V potential. Although its function is not yet quite clear it presumably acts as an oxygen electrode. About three times as great a potential jump can be measured at the equivalence point with an anodically pre-polarized platinum indicator electrode

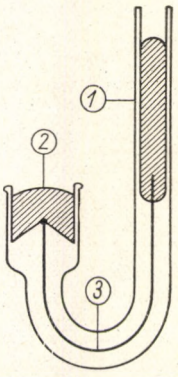


Fig. 54. 'J-shaped' mercury electrode according to Schmidt*. — *(1)* Hg-contact, *(2)* Hg-pool, *(3)* Pt-wire

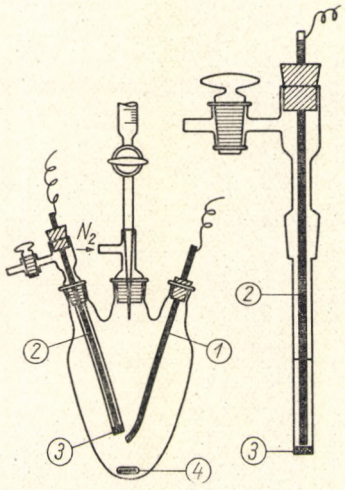


Fig. 55. Titration equipment with aluminium–aluminium electrode system according to Farina, Donati and Ragazzini [222]. — *(1)* Aluminium indicator electrode, *(2)* Aluminium reference electrode, *(3)* Porous glass plate, *(4)* Magnetic stirrer, *(2)* Electrode dipped in a 10% triethylaluminium solution in benzene

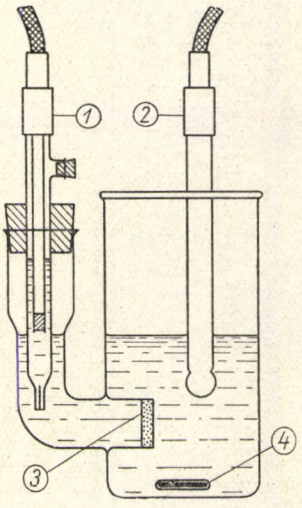


Fig. 56. Warner–Haskell type electrode vessel [860]. — *(1)* Calomel electrode, *(2)* Glass electrode, *(3)* Porous glass plate, *(4)* Magnetic stirrer

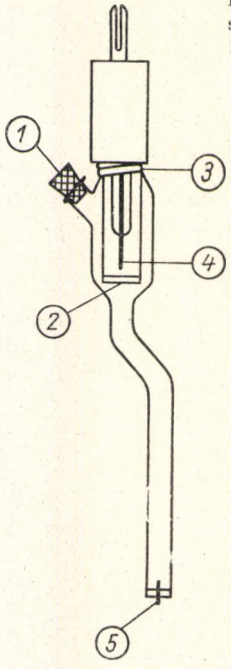


Fig. 57. Jena type calomel electrode (No. 9401). — *(1)* Opening for filling of the salt-bridge liquid, *(2)* Porous glass plate, *(3)* Screw thread, *(4)* Platinum wire, *(5)* Asbestos thread

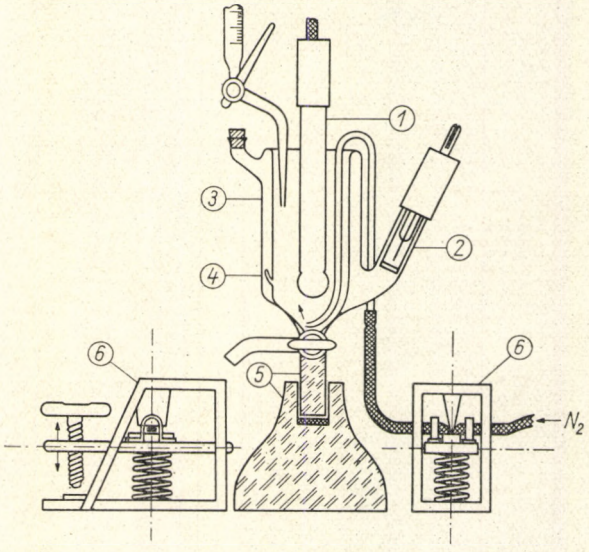


Fig. 58. Titration equipment for potentiometric semimicro-titrations. — *(1)* Glass electrode, *(2)* Side-arm with calomel electrode (Jena No. 9422), *(3)* Double walled titration vessel (Jena No. 9457), *(4)* Asbestos thread, *(5)* Support and socket (Jena No. 9454), *(6)* Key mechanism to cut off nitrogen for stirring

* *Chemist-Analyst* **51**, 56 (1962)

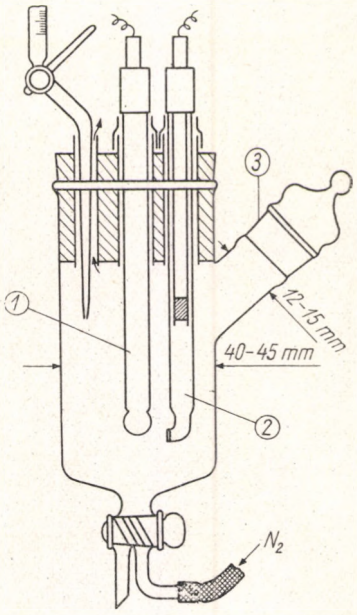


Fig. 59. Closed titration equipment for potentiometric, semimicrotitrations. Mixing by stream of nitrogen. — *(1)* Glass electrode, *(2)* Calomel- or Ag/AgCl electrode, *(3)* Side-arm for introduction of sample or inert gas

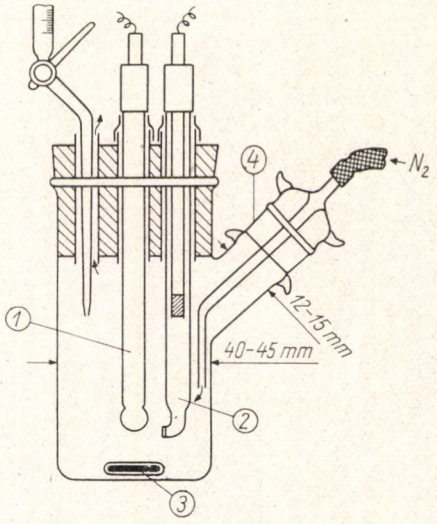


Fig. 60. Closed titration equipment for potentiometric semimicrotitrations. Mixing by magnetic stirrer. — *(1)* Glass electrode, *(2)* Calomel- or Ag/AgCl electrode, *(3)* Magnetic stirrer, *(4)* Side-arm for instruction of sample or inert gas

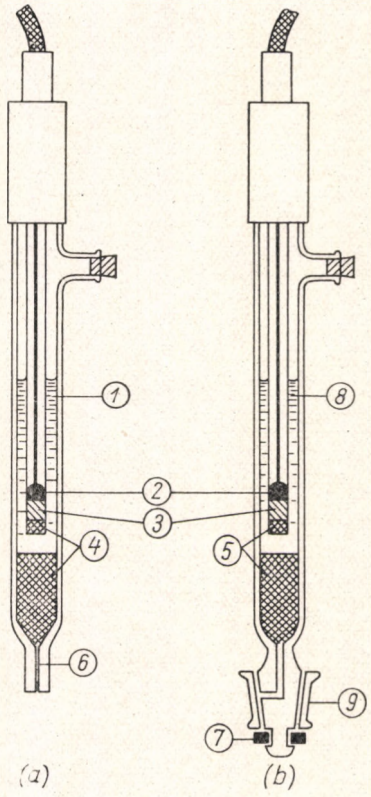


Fig. 61. Calomel electrodes (a) Fibre type, (b) Sleeve type. — *(1)* Saturated LiCl solution in acetic acid, *(2)* Mercury, *(3)* Calomel paste, *(4)* LiCl crystals, *(5)* KCl crystals, *(6)* Fine capillary blocked by thread, *(7)* Rubber washer, *(8)* Saturated KCl solution in methanol, *(9)* Ground glass sleeve

in ethylenediamine medium than with a glass electrode. In potentiometric titrations performed in ethylenediamine, the pre-polarized platinum electrode should be left for 2–3 min in the solution before addition of the standard solution.

A description of the use of various bimetallic electrode systems in methanol and acetic acid can be found in the literature, e.g.: [615]. Antimony electrodes can be

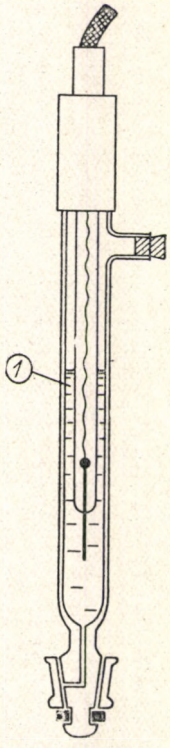


Fig. 62. Sleeve type silver–silver chloride electrode. — *(1)* Saturated KCl in AcOH or 10% LiCl in methanol

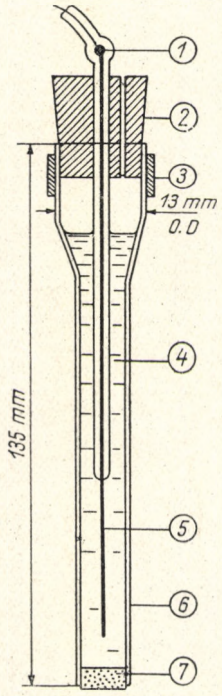


Fig. 63. Silver–silver chloride type electrode according to Glass and Moore [273]. — *(1)* Solder, *(2)* Neoprene stopper, *(3)* Tygon tubing, *(4)* 0·2 M tetramethylammonium-chloride in isopropanol, *(5)* No. 14 silver wire coated with Tygon paint to eliminate corrosion above the liquid level which leads to erratic potentials, *(6)* Borosilicate glass tube, *(7)* Porous porcelain plate

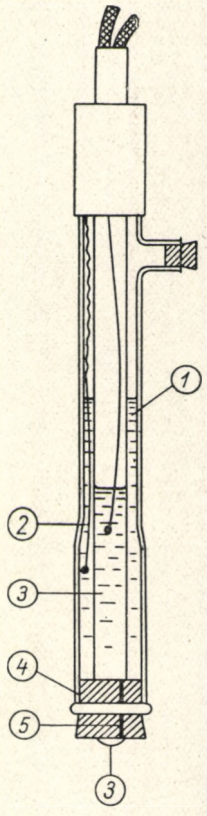


Fig. 64. Combined glass-Ag/AgCl electrodes according to Hefferen and Koehler [368]. — *(1)* KCl–AgCl electrolyte or KNO_3–AgCl electrolyte, *(2)* Silver wire with AgCl coated tips, *(3)* Glass electrode, *(4)* Stopper, *(5)* Linen fibre

employed as the indicator electrodes either in strongly basic solvents or in a mixture of benzene-methanol [252, 446, 601, 665]. For the methods of preparation and maintenance of antimony electrodes see the literature: [329, 860].

The functioning of an antimony indicator electrode is not always reliable [7, 285, 770], even if both the indicator and reference electrodes are of antimony (cf. [601]).

In principle, every electrode can be used as a reference electrode if the ionic activity of the solution in contact with the electrode is constant. This is made possible by an

ingenious device. The metal electrode (antimony, platinum), incorporated, for example, in the jet of the burette is held in the flowing titrant, Figs 52 and 53 (See also: Chapter 21 and [92, 105, 183, 359, 446, 601, 633, 770].)

(c) The J-shaped mercury electrode can be listed among the *special metal electrodes* and is employed for the titration of thiols in acetone: Fig. 54; [355, 674]. This type of electrode responds to standard solutions containing mercury(II) perchlorate (see: Chapter 28; Section 160 (d)). The electrode system aluminium–aluminium can be applied to the determination of alkyl aluminium compounds. The reference half-cell of the bimetallic electrode system is aluminium immersed in a solution of triethylaluminium in benzene (Fig. 55; [222] and Chapter 30; Section 166).

(d) In the special literature *reference electrodes* are widely discussed, the most commonly treated being one or other variant of the *calomel electrode*. In the new type of 'filled calomel electrode' the salt bridge is built in and communicates with the solution under test through a glass filter of fine porosity. Such are the *Warner–Haskell* type (Fig. 56) [372], and the Jena Types No. 9401 and No. 9422: Figs 57, 58, 59 and 60. The salt bridge of the last named may be a saturated solution of lithium chloride in acetic acid; the solution under test is stirred by a stream of nitrogen, the stirring being operated as shown in the figure. In a more simple variant the junction of the calomel electrode with the sample is through a thin asbestos thread sealed in the capillary (Fig. 61a, fibre type). American researchers favour the 'sleeve type' calomel electrode, in which the solution being titrated can be excluded from the salt bridge by a ground glass sleeve. This is diagrammatically represented in Fig. 61b.

Aqueous calomel electrodes have many disadvantages. For example, in acetic anhydride medium, heat evolution is noticed on the surface of the electrode. This influences diffusion processes anomalously. (See: Section 68.)

The *Ag|AgCl type electrode* can also be used as a reference electrode; it is, in fact, a silver wire coated with AgCl layer. In its simplest form it is directly immersed in the solution [244]. However, it is advisable to separate the reference electrode from the sample. In this case the arrangement of the Ag/AgCl electrode is identical with that shown in Fig. 57, while in Figs 62, 63 and 64 three other types can be seen [273], [368] and [592]. In order to stabilize the diffusion potential a salt bridge electrolyte prepared with an organic solvent must be used.

A glass electrode is also suitable as a reference electrode, e.g. in ethylenediamine, since the glass electrode does not respond to change in pH in the presence of Na^+ ions. In this case the indicator electrodes are antimony or platinum [10, 190 252, 372, 446].

68. Elimination of Liquid Junction-potential Fluctuation. Various Electrode Systems

Various types of electrodes are used to eliminate fluctuation of diffusion potential. In determinations in acetic anhydride medium, the aqueous potassium chloride solution in the calomel electrode interacts with the solvent and the potential changes, due to the evolution of heat. Mercury(II) acetate employed for the titration of amine hydrochlorides contaminates the electrode resulting in voltage fluctuations [643, 644]. Sources of error caused by liquid junction-potential are mostly eliminated if, in the mercury electrode, methanol saturated with KCl is used instead of saturated

aqueous potassium chloride. In the overwhelming majority of potentiometric titrations in non-aqueous media this type of calomel electrode is used and when the term 'calomel electrode' is used, one filled with a saturated solution of potassium chloride in methanol is to be understood. This type of electrode is suitable for titrations in acetone [258], acetonitrile, benzene-isopropanol, pyridine [159], acetic acid, benzene-chloroform acetic acid [158] (Fig. 61).

Instead of a solution of potassium chloride, a saturated solution of lithium chloride in acetic acid can be employed as a *salt bridge* in the calomel electrode if the determination is performed in acetic acid or acetic acid–acetic anhydride medium [144, 146, 314, 337, 730] (Figs 58, 59 and 60). For titrations in acetic anhydride, e.g. in the case of acid amides, the calomel electrode is filled with a solution of 0·1 N lithium per-

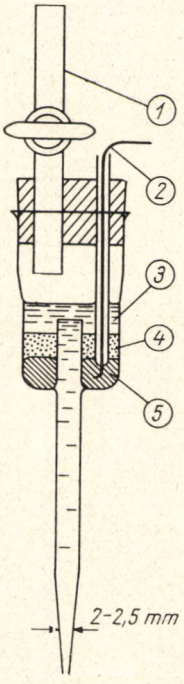


Fig. 65. Calomel electrodes with ethylenediamine due to Gran and Althin [285]. — *(1)* Suction stub for filling the electrode space by vacuum, *(2)* Pt wire soldered into thin glass pipe, *(3)* Ethylenediamine saturated with mercury(I) chloride and lithium chloride, *(4)* Calomel-mercury paste, *(5)* Mercury

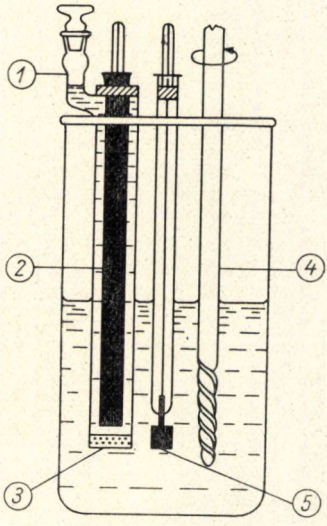


Fig. 66. Titration equipment with graphite–platinum electrode pair according to Zeidler [894]. — *(1)* Side-arm for suction of copper(II) acetate solution by vacuum (the inner space must be completely filled), *(2)* Graphite electrode, *(3)* Porous glass plate, *(4)* Stirrer, *(5)* Platinum-(or gold) electrode

chlorate in acetic anhydride (since lithium chloride dissolves poorly in acetic acid) [878]. Using a 'calomel electrode' filled with acetic acid saturated with mercury(I) chloride, sodium chloride and sodium perchlorate, potential measurements with a reproducibility of $\pm 0{\cdot}25$ mV are possible [102]. For titrations in benzene, toluene and light petroleum, a calomel electrode which contains 1 N tetrabutylam-

monium chloride instead of saturated potassium chloride is effective [358]. Owing to the decomposition of Hg_2Cl_2 no calomel electrode can be prepared with *saturated* solutions of Bu_4N^+ or Me_4N^+ salts [550]. For titrations in ethylenediamine, ethylenediamine saturated with lithium and mercury(I) chloride can be used as salt bridge [285] (Fig. 65).

In acetic acid an electrode system consisting of glass as indicator electrode and silver as reference electrode has found extensive use [244, 368]. In modern practice

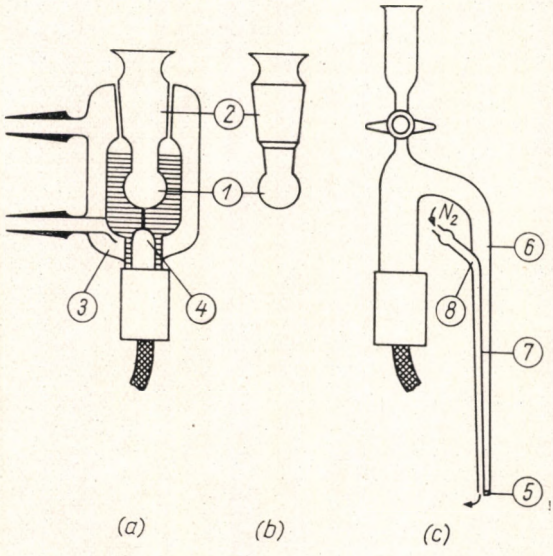


Fig. 67. Glass-calomel electrode system for potentiometric microtitrations due to Simon, Kováts, Chopard-dit-Jean and Heilbronner [754]. — (a) Cup-form glass electrode, (b) Titration vessel, and (c) Calomel reference electrode, *(1)* Glass electrode membrane of Corning glass 015, *(2)* Shortened ground glass joint No. 15. To avoid stray currents between sample and buffer solution above the ground surface the ground glass joints should be lubricated with silicone grease, *(3)* Water jacket, keeping the electrodes at constant temperature and, at the same time, shielding them against outer capacitive interference, *(4)* Electrode connection, *(5)* Ceramic diaphragm for contact between sample and saturated potassium chloride solution, *(6)* Neck of the reference electrode (c) separated by *(7)* partition into two separate channels, *(8)* Inflow of nitrogen stream (in order to mix sample and keep out CO_2). Prior to inflow of the nitrogen, it must be saturated with the solvent. Shaded lines (a) Aqueous buffer solution of pH ~ 6·8

the Ag/AgCl electrode is not immersed directly in the organic solvent but communicates with the sample through a salt bridge containing a supporting electrolyte: for titrations in acetic acid, this is a saturated solution of KCl in acetic acid [592], Fig. 62; for titrations with alkali metal methoxide, a solution of 10% LiCl in methanol [592], Fig. 62; in acetic anhydride, a bridge of acetic anhydride saturated with AgCl and LiCl are used [778]; for titrations with TBAH in toluene-isopropanol a suitable supporting electrolyte is 0·2 N Bu_4NCl in isopropanol [273] (Fig. 63). For *combined* glass-Ag/AgCl electrodes see: Fig. 64 and [368].

Instead of calomel and Ag/AgCl electrodes a graphite electrode is also suitable. This is shown diagrammatically in Fig. 66. In principle it is similar to a capillary electrode and can be prepared from the carbon rod of a flashlight dry cell. This is immersed in an acetic acid solution of copper(II) acetate and communicates with the solution being tested through a glass filter (*Zeidler graphite electrode* [894]). Sometimes copper(II) sulphate is used instead of copper(II) acetate [698]. The indicator electrode may be platinum or gold. For differentiating titrations in acetone, Malmstadt and Vassallo employed platinum containing 10% of rhodium as an indicator

electrode, while graphite (prepared from the lead of a 9 H pencil) served as reference electrode.

For microtitrations of acids, acid analogues and bases the modified 'Ingold' type glass electrode, kept at constant temperature, is suitable [407, 754]: 'Napf-Glasselektrode' Type 232-1 (W. Ingold, Frankfurt am Main). A diagrammatic representation of a microtitration assembly is shown in Fig. 67 [754].

Difficulties may arise if the 'most suitable' electrode is chosen according to data in the literature. Pellerin and Demay [633] have made detailed investigations with ten different electrode pairs. Their model experiments were carried out in acetic acid and dimethylformamide. In the first case potassium biphthalate was titrated with 0·1 N perchloric acid in acetic acid (a) while in the latter case benzoic acid was titrated with 0·1 N sodium methoxide in benzene-methanol (b). The table below summarizes the results obtained which – for easy comparison – are given uniformly as the Δ mV/Δ ml values.

Electrode System	*Maximum* $\frac{\Delta \text{ mV}}{\Delta \text{ ml}}$ (*a*)	*Value* (*b*)
Pt-polarized Pt (1)	12,500	6,500
Pt-polarized Pt (2)	4,900	3,100
Pt-Pt (3)	6,750	4,750
Polarized Pt-polarized Pt (3)	6,000	3,500
Pt-calomel (4)	4,350	5,000
Pt-calomel (5)	5,750	4,250
Glass-calomel (4)	5,600	750
Glass–calomel	5,150 (5)	700 (6)
Ag–glass	3,650	1,250
Combined glass–Ag/AgCl electrode	3,250	300

(1) The non-polarized electrode is placed in the flowing titrant; (2) the polarized electrode is placed in the flowing titrant; (3) one of the electrodes is placed in the flowing titrant. The electrolyte solution: (4) saturated aqueous KCl solution; (5) saturated LiCl solution in acetic acid; (6) saturated KCl solution in methanol.

From the table above it is obvious that the sharpest potential jump can be reached with a Pt–Pt electrode combination, particularly if the non-polarized electrode is placed in the titrant at constant ionic strength (in the exit tube of the burette).

Pellerin and Demay used for their experiments a 'soldered-in' platinum electrode of 1–3 cm length and 0·5–1·0 mm dia, pre-polarized for one minute in 1% sulphuric acid at 3–5 V.

Svoboda and Shain investigated the non-aqueous titration of weak acids and bases using the general techniques of constant current potentiometry [733, 787]*. Two platinum electrodes were polarized by a constant 1 μa current, and the potential between the two electrodes was measured. The electrodes were made by sealing platinum wire (0·016 in dia) into soft glass tubing so that about 1 cm of wire was exposed. Typical peak-shaped titration curves were obtained titrating several

* See also: Reilley, Cooke and Furman, *Anal. Chem.* **23**, 1223 (1951).

organic acids and bases. Bases were titrated in *m*-cresol–acetonitrile (1 : 1) using perchloric acid in *m*-cresol or acetonitrile.

Various types of reference electrodes, and electrode systems employed for the determination of weak acids (phenols) are tabulated in Tables 20 and 21. (See also: Chapters 18 and 21.)

69. Shape of Potentiometric Titration Curves

In non-aqueous media the shape of potentiometric curves depends upon the electrode used, the solvent, the standard solution and the acid or base strength of the compound to be determined. Further factors influencing the shape of the curves are K^+ or Na^+ contaminations, association between solvent and solute and also possible acid–acid anion complex formation. A number of potentiometric curves have already been presented (e.g. Figs 20, 23 and 25 are fairly normal).

Table 20

A SURVEY OF VARIOUS CALOMEL AND Ag/AgCl ELECTRODES.

Electrolyte Solution	*Type, Fig.*	*References*
CALOMEL ELECTRODES		
Methanol saturated with KCl	61b	[156, 158, 159, 160, 258, 540, 595, 780]
0·02 N LiCl in acetic acid		[389]
Acetic acid saturated with LiCl	58, 59, 60	[314]
Aqueous 1 N $Bu_4N^+Cl^-$	61b	[355]
0·01 N $Bu_4N^+Br^-$ in methanol	61a	[164]
Acetic acid saturated with Hg_2Cl_2, NaCl, $NaClO_4$		[102]
Isopropanol saturated with KCl		[579]
0·1 N $LiClO_4$ in acetic anhydride	61a	[878]
Ethylenediamine saturated with LiCl, and Hg_2Cl_2	65	[285]
KCl, in two-phase H_2O-t-butanol	68	[550]
Ag/AgCl ELECTRODES		
Acetic acid saturated with KCl	62	[592, 767]
10% LiCl in methanol	62	[592]
Acetic anhydride saturated with AgCl+ LiCl		[778]
$AgNO_3$ in acetonitrile		[648]
0·2 N $Bu_4N^+Cl^-$ in isopropanol	63	[273]

Figs 43 and 46 show irregular potentiometric curves, while in Fig. 44 the correlation between curve and colour change of the indicator can be seen.

In determinations using a glass indicator electrode and a silver reference electrode pair, a V-shaped maximum or minimum appears, while phenols exhibit the usual S-shaped curve [888]. A sudden potential change at the equivalence point can be attributed to the change of roles of the electrodes during titration (Fig. 69 *C*). From this phenomenon the conclusion may be drawn that at a certain phase of titration both types of electrodes function as indicator electrodes. Potential changes can be observed

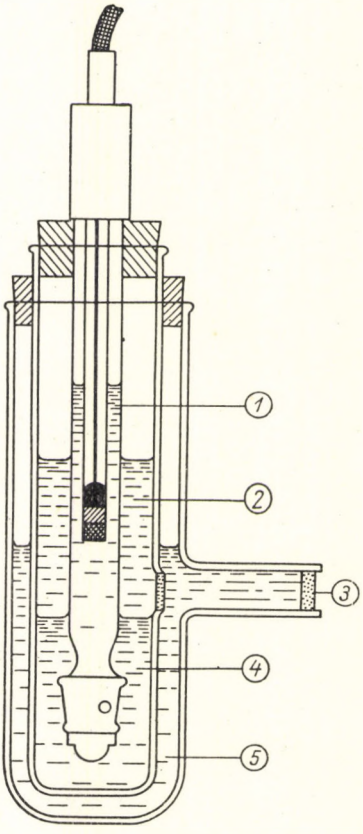


Fig. 68. 'Two-phase' calomel electrode according to Marple and Fritz [550]. — *(1)* Saturated aqueous KCl solution, *(2)* t-Butanol–water phase containing approx. 10% of water and approx. 0·056 M of KCl, *(3)* Ultra-fine porosity glass filter, *(4)* Water–butanol approx. 4·3 M of KCl, *(5)* t-Butanol saturated with tetrabutylammonium bromide

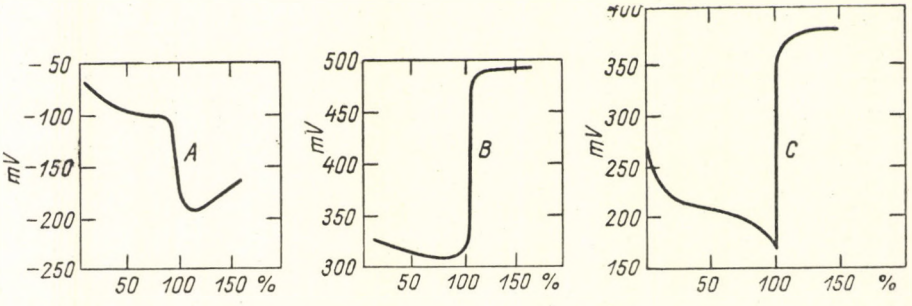


Fig. 69. Potentiometric determination of benzoic acid in pyridine with sodium methoxide according to Yakubik, Safranski and Mitchell [888]. — *(A)* Glass–calomel electrodes, *(B)* Silver–calomel electrodes, *(C)* Silver–glass electrodes

in the case of both electrodes. Up to the end-point, the glass electrode is probably the indicator electrode and the silver one the variable reference electrode. At the end-point, which in the case of sodium methoxide coincides with a colour change of thymol blue, the electrode potentials change to the opposite direction and the trend of electromotive force is reversed. Thus, the behaviour of the glass–silver electrode pair in pyridine in titrations with sodium methoxide is a function of both chemical and polarization effects [888].

Table 21

ELECTRODE SYSTEMS USED FOR THE DETERMINATION OF PHENOLS

Solvant	*Electrode System*	*Standard Solution*	*References*	*Fig.*
EDA	Antimony–antimony	Na-aminoeth-oxide	[601]	53
EDA	Platinum–calomel		[285]	54
EDA	Antimony–antimony	Na-aminoeth-oxide	[446]	53
EDA, Bz-MeOH	Platinum–platinum	Na-aminoeth-oxide	[92, 601]	
EDA, DMF	Glass–calomel	Bu_4NOH	[176]	61b
EDA, Py, MEK	Prepolarized platinum–platinum	Bu_4NOH	[359]	52
Py, DMF				
Acetonitrile	Glass–calomel	Bu_4NOH	[159]	61b
DMF	Antimony–calomel	$KOCH_3$	[113]	
Py	Platinum–calomel	KOH	[525]	
Py	Antimony–glass	$NaOCH_3$	[10]	
DMF	Glass–calomel	Bu_4NOH	[7]	61b
Py	Glass–calomel	Bu_4NOH and $KOCH_3$	[25, 355, 780]	
BM	Glass–platinum	Bu_4NOH	[105]	
Acetone	Glass–calomel	Et_3BuNOH	[258]	61a and b
Bz, To	Glass–calomel	Bu_4NOH	[358]	
t-Butanol	Glass–'two-phase' calomel	Bu_4NOH	[253, 550]	68

Abbreviations: Bz = benzene, DMF = dimethylformamide, EDA = ethylenediamine, MeOH = = methanol, MEK = methyl ethyl ketone, BM = isobutyl methyl ketone, Py = pyridine, To = toluene

With glass–silver electrode pairs the above phenomena can be observed in acetone, acetonitrile, a mixture of benzene–methanol, isopropanol, pyridine and dimethylformamide. Of these acetonitrile shows a maximum peak, the others a minimum peak in the mV deflection at the equivalence point. The same electrode pair produces S-shaped curves in aqueous media and in n-butylamine. An inflection is not apparent in benzylamine, ethylenediamine and piperidine.

A wire of 0·11 cm^2 surface can be used as a silver electrode; this must be polished from time to time or dipped in a concentrated solution of NH_4OH. The Beckman No. 4949-V6B silver electrode is also suitable [888]. (See also: Chapter 15; Section 95.)

Chapter 13

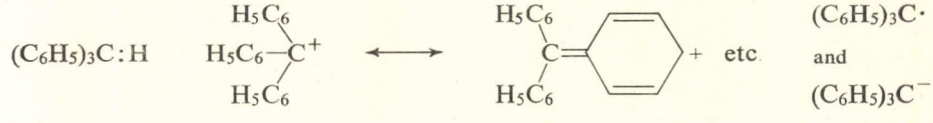
Indicators

Indicators have proved to be very suitable for the detection of the end-point especially if steep potential curves are observed in potentiometric titrations (cf. Fig. 44). In principle, indicators used in aqueous medium are also suitable for determinations in non-aqueous proton-containing or inert solvents. A practical difference is that the shade of colour change often differs from that observed in aqueous medium because, owing to the change of the solvent, the proton activity of the solution often varies and at the equivalence point the colour of the indicator is affected by the character and concentration of the ion [48, 207, 338].

70. Ionized Dyes, Indicators

The 'colour' of a compound is caused by the absorption of light quanta by its molecules from the visible wave range of the spectrum. The interaction between light and the compound raises the electronic system of the molecule from a lower to a higher level, i.e. it reaches an excited state. The absorption is shifted towards a longer wavelength (lower energy) in compounds which can be represented as hybrids of several resonance forms. This effect increases with increasing extent of conjugation (i.e. as the energy difference between the ground state and the excited state diminishes).

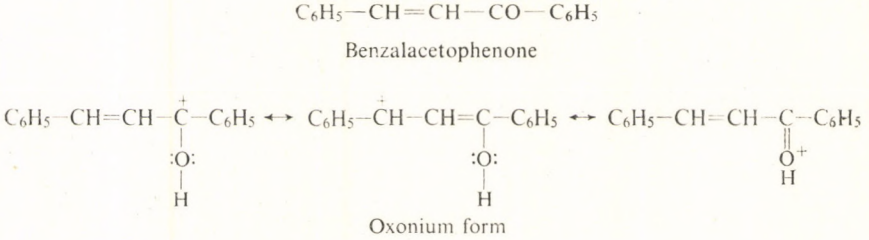
Triphenylmethane is 'colourless' but the triphenylmethyl radical and the triphenylmethyl carbenium ion or carbanion are coloured:



Resonance stabilization increases if the substituents OH, NH_2 and $N(CH_3)_3$ are attached to the aromatic ring in *ortho*- and *para*-positions. Such compounds

include crystal violet (hexamethyl-*p*-rosaniline hydrochloride), methyl violet (pentamethyl-*p*-rosaniline hydrochloride), malachite green (tetramethyl-di-*p*-diaminofuchsine hydrochloride) etc.

Many examples could be cited to show that the ionized form of compounds has a different or deeper colour compared with the non-ionized one (halochromism). Thus e.g. the conjugated oxonium form of benzalacetophenone is more strongly coloured than the base (benzalacetophenone is also a suitable indicator for very strong acids). When dissolved in sulphuric acid the freezing point depression of the latter indicates the formation of ions:



Benzalacetophenone

Oxonium form

Like the proton, Lewis acids also have a great affinity for the lone electron pair. Aluminium chloride forms a co-ordination complex with one molecule of benzalacetophenone, and in this case also a more strongly coloured product than the base is formed.

Indicators are weak bases or acids which change their colour during salt formation by changing their electronic configuration and thus their specific light absorption power. Base or acid strengths are relative and only approximately independent of the solvent. That is, in non-aqueous solvents the pK value of indicators of different charge type and structure may differ from that in an aqueous medium. Owing to the formation of associations, the dissociation constant and the degree of basicity depend on the solvent, and in certain cases also on the concentration of the compound. The effect of salt production influences the colour changes of indicators to different extents [292, 389, 464]. From all these facts it follows that for accurate determinations, the standard compound and the compound to be measured must have roughly identical ionic strength [611].

In aqueous media a correlation exists between the ratio of acidic to basic form of the indicator and the concentration of the hydrogen ion. Investigations by Kolthoff and Bruckenstein have proved that in titrations with perchloric acid in acetic acid, however, no simple correlation exists between the proportion of the acidic to basic form of the indicator and the pH value of the solution, which, in fact, depends upon the total concentration of perchloric acid and on the indicator perchlorate formation constant [101, 102, 464]. This concept marks a turning point in the field of acid–base investigations in acetic acid medium. Their method, fundamentally an indicator-spectrophotometric method, is suitable for the measurement of the dissociation constant of an acid, and the indicator perchlorate formation constant during interaction between a moderately weak acid and an indicator base.*

* See: detailed discussion in Kolthoff—Elving—Sandell: *Treatise on Analytical Chemistry*, Part I. Vol. 1, p. 475. Interscience, New York (1959).

In acetic acid, since its dielectric constant is low, even the strongest electrolytes are only slightly dissociated and are present mainly as ion pairs. The colour of the indicator base in pure acetic acid is determined by the equilibrium of the reaction:

$$I + \mathrm{AcH} \rightleftharpoons \underset{\text{Ionization}}{I\mathrm{H^+Ac^-}} \rightleftharpoons \underset{\text{Dissociation}}{I\mathrm{H^+} + \mathrm{Ac^-}}$$

where the acid forms of the indicator are $I\mathrm{H^+Ac^-}$ and $I\mathrm{H^+}$ and their spectra are identical. Neglecting dissociation, the ionization constant of the indicator is:

$$K_i^I = \frac{[I\mathrm{H^+Ac^-}]}{[I]} = \frac{[I_\mathrm{A}]}{[I_\mathrm{B}]},$$

where I_A = the acidic form of the indicator
I_B = the basic form of the indicator

with an indicator, where $K_i^I = 1$ in acetic acid, viz. $I\mathrm{H^+Ac^-} = 50\%$ and $I = 50\%$, the $I_\mathrm{A}/I_\mathrm{B}$ ratio cannot be decreased by adding base. This is a fundamental difference between water and acetic acid media. (Thus in water, the amount of ion pair $I\mathrm{H^+OH^-}$ is negligible and therefore does not determine the acid colour of the indicator. In acetic acid, however, the ion pair $I\mathrm{H^+Ac^-}$ is predominant. In acetic acid an indicator of very feeble basic character can be used whose K_i^I value is 0·01 or lower. In this case in pure acetic acid the acidic form of the indicator $I\mathrm{H^+Ac^-}$ is negligible.)

Dissociation of $I\mathrm{H^+ClO_4^-}$ is negligible in the course of interaction between indicator base and acid, since in the titration of bases, the concentration of perchlorate ion is so great that in the equilibrium

$$I + \mathrm{HClO_4} \rightleftharpoons \underset{\text{Ionization}}{I\mathrm{H^+ClO_4^-}} \rightleftharpoons \underset{\text{Dissociation}}{I\mathrm{H^+} + \mathrm{ClO_4^-}}$$

ionic dissociation is suppressed and the colour of the indicator depends on the ratio $\frac{[I\mathrm{H^+ClO_4^-}]}{[I].}$. In titrations with perchloric acid the indicator perchlorate formation constant is:

$$K_f^{I\mathrm{HClO_4}} = \frac{[I\mathrm{HClO_4}]}{[I] \cdot C_{\mathrm{HClO_4}}}$$

and the ratio of the acidic form of the indicator to its basic form, and hence the colour of the indicator, depends upon the total concentration of perchloric acid and the indicator perchlorate formation constant [101, 102, 464]:

$$\frac{[I_\mathrm{A}]}{[I_\mathrm{B}]} = \frac{[I\mathrm{HClO_4}]}{[I]} = K_f^{I\mathrm{HClO_4}} \times C_{\mathrm{HClO_4}}, \qquad (70.1)$$

where $I\mathrm{HClO_4}$ = the acidic form of the indicator
I = the basic form of the indicator
$K_f^{I\mathrm{HClO_4}}$ = the indicator perchlorate formation constant.

SOME INDICATOR PERCHLORATE FORMATION CONSTANTS IN ACETIC ACID
(cf. [388, 389, 390])

Indicator		*Formation Constant*	*Indicator*	*Formation Constant*
Ethyl red		4×10^9	Malachite green	2×10^5
Quinaldine red		1×10^7	*p*-Naphtholbenzeine	1×10^5
Crystal violet perchlorate	K_1	6×10^5	Nile blue A	4×10^4
	K_2	2×10^5	Sudan III	7×10^2

During titration the value of C_{HClO_4} is determined by the formation constant $K_f^{BHClO_4}$:

$$B + HClO_4 \rightleftarrows BHClO_4$$

where $$K_f^{BHClO_4} = \frac{C_{BHClO_4}}{C_{HClO_4} \cdot C_B} \qquad (70.2)$$

Combining Eqs (70.1) and (70.2)

$$\frac{[I_A]}{[I_B]} = \frac{K_f^{IHClO_4} \times C_{BHClO_4}}{K_f^{BHClO_4} \times C_B}$$

Other spectrophotometric investigations suggest [389] that the colour change of the indicator in acetic acid is dependent upon the relative concentration of the base present to that of its conjugate acid. In an aqueous solution containing a weak acid (e.g. benzoic acid) and its salt, with an indicator, the resultant state of equilibrium can be written as:

$$AH + I \rightleftarrows IH^+ + A^-$$

where I = the basic form of the indicator
IH^+ = the protonated form of the indicator.

The equilibrium constant of this process is:

$$K = \frac{(IH^+) \times (A^-)}{(AH) \times (I)} = \frac{K_{ind}}{K_{acid}}$$

The equilibrium constant is determined by the dissociation constants of the two processes and can be calculated from the ionization constants of the acid and the indicator.

Ions are very liable to form associates in acetic acid and indicators are no exceptions to this. Therefore, the behaviour of indicators, e.g. in acetic acid, can be schematically represented by the following general equation (cf. [389]):

$$SHA + IHAc \rightleftarrows IHA + SHAc$$

where S = the solvent or a base capable of proton acceptance
SHA = the association product of AH acid and S molecule
$IHAc$ = indicator-acetic acid association formed in acetic acid (viz. basic form of the indicator)
IHA = association product of indicator and strong acid.

In acetic acid very weak bases do not form 'onium acetates. Since indicators are generally very weak bases in acetic acid, the relative concentration of the indicator-acetic acid association controls the 'basic' colour of the solution. In this case the equilibrium constant is [389]:

$$K = \frac{(IHA)(SHAc)}{(SHA)(IHAc)}$$

Considerable difference exists between $IHAc$ and IHA, because the degree of proton transfer is different in the two associations. In the former case proton transfer extends at most to the H-bonding, while in the latter case, especially when titration is performed with perchloric acid, the nature of the proton transfer is shifted rather towards 'onium ion formation, as a consequence of which the spectral properties of $IHAc$ and IHA differ. The extent of proton transfer also varies depending upon whether S is a base molecule of considerable proton co-ordinating ability, or only a solvent molecule of slight basicity (e.g. acetic acid). In the latter case the overall reaction can also be written in a simpler way:

$$BH^+A^- + IHAc \rightleftarrows IHA + BH^+Ac^-$$

and

$$K = \frac{[IHA][BH^+Ac^-]}{[BH^+A^-][IHAc]}$$

where BH^+A^- = the ion pair formed from a strong acid (e.g. $HClO_4$) and base (e.g. diphenylguanidine)
BH^+Ac^- = the corresponding acetate.

The equilibrium constant in acetic acid medium involves the constants of four processes:

$$K = \frac{(K_{BH^+Ac^-})(K_{IHA})}{(K_{BH^+A^-})(K_{IHAc})}$$

1. The dissociation constant of the base acetate:

$$K_{BH^+Ac^-} = \frac{(BH^+)(Ac^-)}{(BH^+Ac^-)}$$

2. The dissociation constant of the base perchlorate:

$$K_{BH^+A^-} = \frac{(BH^+)(A^-)}{(BH^+A^-)}$$

3. The dissociation constant of the indicator acetate:

$$K_{IHAc} = \frac{(I\mathrm{H}^+)\,(Ac^-)}{(I\mathrm{H}Ac)}$$

4. The dissociation constant of the indicator perchlorate:

$$K_{IHA} = \frac{(I\mathrm{H}^+)\,(A^-)}{(I\mathrm{H}A)}$$

Each dissociation constant is influenced by the dielectric constant of the solvent and the presence of other ion pairs or foreign ions in the solution, hence the value of K can also change to a certain degree. Should the indicator acetate be a stronger base than the base acetate to be measured (which may happen when e.g. very weak bases are titrated) then the indicator will exhibit an acidic colour before the equivalence point, and so cannot be used for this determination. This is the case when, for example, ephedrine (*Eph*) is determined with perchloric acid in the presence of ethyl red indicator (ethyl red = *Er*):

$$\underset{\mathrm{K}\sim 10}{Eph\mathrm{H}^+ \ldots \mathrm{ClO}_4^- + Er.\ \mathrm{H}Ac \rightleftharpoons Er.\ \mathrm{HClO}_4 + Eph\mathrm{H}^+Ac^-}$$

When, however, the base acetate is a stronger base than the indicator acetate, then indicator perchlorate formation occurs after base perchlorate formation and the equivalence point of the titration can be detected by the indicator:

$$\underset{\mathrm{K}\sim 10^{-2}}{Eph\mathrm{H}^+ \ldots \mathrm{ClO}_4^- + Qr\mathrm{H}Ac \rightleftharpoons Qr \cdot \mathrm{HClO}_4 + Eph\mathrm{H}^+Ac^-},$$

where *Qr* = quinaldine red (colour change in titration with perchloric acid: red → colourless).

Thus, quinaldine red is suitable for the titration of alkaloids and other nitrogenous bases with a pK value of 4·7 or lower.

71. Choice of Indicators

The number of studies on the theoretical aspects of the choice of indicators is limited. On this question the publications of Higuchi and co-workers [389], Kolthoff and Bruckenstein [464] and Malmstadt [540] are of fundamental importance. Their fruitful ideas have had a favourable effect especially on the development of photometric end-point detection (see: Chapter 24). A detailed paper by Stock and Purdy deals with the application of indicators [775].

Tables 22 and 23 show the colour changes of indicators in the titrations of acids. From these it becomes apparent that, in acetone for example, azo-violet is suitable

Table 22

COLOUR CHANGE OF INDICATORS IN PSEUDO-BUFFER SOLUTIONS (pb) CONTAINING ACID AND Bu_3MeNOH IN ACETONE [540]

Compound (Solvent)	*Azo-Violet* *Acid Colour* ↓ *Alkaline Colour*	*Thymol-phthalein* *Acid Colour* ↓ *Alkaline Colour*	*Thymol Blue* *Acid Colour* ↓ *Alkaline Colour*	*Neutral Red* *Acid Colour* ↓ *Alkaline Colour*	mV *Deflection Measured by Glass–calomel Electrode System*
0·01 N					
$HClO_4$	Yellow	Colourless	Red	Red	+685
$HClO_4$ (pb)	Yellow	Colourless	Orange	Red	+580
HNO_3 (pb)	Yellow	Colourless	Yellow	Red	+200
Acetone	Yellow	Colourless	Yellow	Yellow	−150
Benzoic acid (pb)	Yellow	Colourless	Yellow	Yellow	−250
Anthranilic acid (pb)	Pink	Colourless	Yellow	Yellow	−350
o-Nitrophenol (pb)	Red	Colourless	Yellow	Yellow	−450
Phenol (pb)	Red	Blue	Blue	Yellow	−580
Bu_3MeNOH excess	Violet	Blue	Blue	Yellow	−750

for the titration of phenols; however, thymol blue is more suitable for the titration of substituted benzoic acids [540]. Tables 24, 25, 26 and 27 assist in the choice of some indicators, depending upon the solvent. The solvent itself, however, is determined by the strength of the acid or base to be tested.

The most commonly used indicators in non-aqueous titrimetry are *azo-violet* (4-(*p*-nitrophenylazo)-resorcinol), *thymol blue* (thymolsulphophthalein), belonging to the group of sulphophthaleins, and *crystal violet* (hexamethyl-*p*-rosaniline hydrochloride), belonging to the triphenylmethane dye class (usually mixed with some of the corresponding penta- and tetra-methyl compounds). In addition to these, the following indicators are used fairly often:

Group of Compounds	*Indicator*
Azo compounds	Alizarin yellow R, methanil yellow, dimethyl yellow, methyl orange, methyl red, tropaeolin 00, Congo red
Sulphophthaleins	Cresol red, bromophenol blue, bromothymol blue, bromocresol green
Phthalein compounds	Phenolphthalein, thymolphthalein
Nitro compounds	*o*-Nitroaniline
Triphenylmethane derivatives	Methyl violet, malachite green; and also: Quinaldine red, 1-naphtholbenzeine, Sudan III and Nile blue A

Table 23

CHOICE OF INDICATORS FOR PARTICULAR ACID STRENGTHS [540]

Acid or Acid Analogue	*1% Solution of Indicator in Methanol*	*Colour Change*	*Filter* mμ	*At the Equivalence Point Light Absorption is Increased (+) or Decreased (−)*
Very weak acids	Azo-violet	Red → blue	600	(+)
Substituted acetic acids	Thymolphthalein	Colourless → blue	575	(+)
Substituted benzoic acids	Thymol blue	Yellow → blue	575	(+)
Mineral acids	Neutral red	Red → yellow	550	(−)

Comment: The above acids can be titrated photometrically in acetone with tri-n-butylmethylammonium hydroxide in benzene-isopropanol (8:2) [540]

Table 24

CHOICE OF INDICATORS FOR USE IN INERT SOLVENTS*

Inert Solvent	*Indicator*	*Colour Change: (a) Alkaline → Acidic; (b) Acidic → Alkaline*
Acetone	1% Solution of azo-violet in methanol;	Red → blue (in the case of very weak acids) (*b*)
	0·3% Solution of thymol blue in methanol;	Yellow → red (*a*); yellow → blue (in the case of substituted benzoic acids) (*b*)
	0·2% Solution of phenolphthalein in methanol;	Colourless → red (*b*)
	0·2% Solution of thymolphthalein in methanol;	Colourless → blue (*b*)
	1% Solution of neutral red in methanol;	Red → yellow (in the case of mineral acids) (*b*)
Acetone, acetonitrile	0·2% Solution of *p*-hydroxyazobenzene in benzene;	Orange → yellow (*b*)
Acetone, acetonitrile, Ethyl methyl ketone, Isobutyl methyl ketone	Saturated solution of methyl red in acetonitrile;	Yellow → orange red → pink → → violet red (*a*)
	0·1% Solution of methyl violet in acetic acid;	Violet → deep blue → light blue (*a*)

* *Rarely used indicators are specified in the detailed discussion of the relevant methods.*

Continuation of Table 24

Inert Solvent	*Indicator*	*Colour Change: (a) Alkaline → Acidic; (b) Acidic → Alkaline*
Acetone, acetonitrile, Ethyl methyl ketone, Isobutyl methyl ketone	1% Solution of 1-naphtholbenzeine in isopropanol;	Yellow → pale green → grass green (*a*)
	0·5% Solution of tropaeolin 00 in acetic acid;	Yellow → cyclamen red → magenta (in the case of strong and medium-strength bases) (*a*)
Acetonitrile	Solution of 1% dimethyl yellow and 0·1% methylene blue in methanol;	Red brown → green (*b*)
	0·3% Solution of thymol blue in methanol;	In the case of weak acids: yellow → green → blue (*b*) In strong acids: red → yellow → → blue (*b*)
Benzene, chlorobenzene	0·1% Solution of dimethyl yellow in chloroform;	Yellow → pink (*a*)
	Saturated solution of phenolphthalein in benzene;	Colourless → red (*b*)
	Saturated solution of bromocresol purple in benzene;	Purple → yellow (*a*)
	Saturated solution of bromocresol green in benzene;	Blue → yellow (*a*)
Chlorobenzene	Saturated solution of bromophenol in chlorobenzene;	Dependent on the strength of the dissolved base: Purple, Pink, Intense yellow, Pale yellow → colourless
	0·1% Solution of methanil yellow in methanol	Yellow → violet (*a*)
Chloroform, carbon tetrachloride	0·1% Solution of dimethyl yellow in chloroform	Yellow → pink (*a*)
	1% Solution of cresolphthalein in methanol-chloroform (1 : 1)	Colourless → violet pink (*b*) (barbiturates)
Dichloromethane	0·1% Solution of dimethylamino azobenzene in chloroform	Yellow → pink (*a*)
Ethyl methyl ketone	Solution of 0·6% thymolphthalein and 0·4% tropaeolin 0, in dimethyl formamide	Yellow → green (*b*, barbiturates)

Table 25

Acidic Solvent	*Indicator*	*Colour Change:* (*a*) *Alkaline → Acidic;* (*b*) *Acidic → Alkaline*
Acetic acid, propionic acid	0·1–1·0% Solution of crystal violet in acetic acid;	Violet → deep blue → blue-green → → green-yellow (*a*)
	0·2% Solution of methyl violet in chlorobenzene;	Violet → blue → blue-green → → yellow (*a*)
	0·5% Solution of malachite green in acetic acid;	Blue-green → green → yellow (*a*)
	0·5% Solution of cresol red in acetic acid-chlorobenzene (1 : 1)	Yellow → pink → red (*a*)
	0·02% Solution of ethyl red in acetic acid;	Red → colourless (*a*)
	0·5% Solution of tropaeolin 00 in acetic acid;	In the case of strong or medium-strength bases: yellow-orange → → purple → magenta (*a*)
	0·02% Solution of Nile blue A in acetic acid;	Blue → colourless (*a*)
	0·02% Solution of Sudan III in acetic acid;	Yellow → red → blue (*a*)
	0·02% Solution of quinaldine red in acetic acid;	Deep red → colourless (*a*)
	Saturated solution of quinaldine red in acetic acid;	Deep red → yellow (*a*)
	0·02% Solution of 1-naphthol-benzeine in acetic acid;	Yellow → green (*a*)
	1% Solution of Celliton-echt-blau FR in acetic acid	Blue → reddish violet (*a*)
Acetic anhydride	0·1% Solution of crystal violet in acetic acid;	Blue → green-yellow → yellow (*a*)
Ethanol	0·5% Solution of thymolphthalein in methanol + 0·02% aqueous solution of methyl orange;	Yellow → green (*b*)
Isopropanol	0·1–1·0% Solution of 1-naphtholbenzeine in methanol or isopropanol;	Orange → brownish-green → → green (*b*)
Methanol	0·3% Solution of thymol blue in methanol; Solution of 0·1% thymol blue + 0·025% patent blue A in methanol;	Yellow → red (*a*) In the case of strong acids: purple → green (*b*)
Methyl Cellosolve	0·3% Solution of thymol blue in dimethylformamide;	Yellow → orange → red (*a*)
Propionic acid	0·2% Solution of methanil yellow in propionic acid-dioxan (1 : 1)	Pale yellow → purple (*a*)

Table 26

Alkaline Solvent	*Indicator*	*Colour Change: (a) Alkaline → Acidic; (b) Acidic → Alkaline*
n-Butylamine, pyridine, dimethylformamide	0·3% Solution of thymol blue in methanol or dimethylformamide;	Red → yellow → blue (dependent on acid strength) (*b*)
Ethylenediamine	0·15% Solution of nitroaniline in benzene;	Yellow → orange (*b*)
	0·05% Solution of *p*-nitro-*p'*-aminoazobenzene [798] in benzene	Red → (blue) → colourless (*b*)
Ethylenediamine, n-butylamine, pyridine, dimethylformamide	Saturated solution of azo-violet in benzene;	Acids: yellow → (orange) → → blue → violet (*b*); Phenols: orange → (red) → → blue → violet (*b*)
Dimethylformamide	0·2% Alizarin yellow in dimethylformamide;	Yellow → violet blue (*b*)
1,4-Dioxan	0·3% Solution of thymol blue in dioxan;	Red → yellow → blue (*b*)
	0·1% Solution of methyl red in dioxan	Yellow → orange → pink → deepens (*a*)

The above list is not complete, since in the methodology of non-aqueous titrations the number of indicators in use is rising rapidly. The large number of indicators listed in publications does not imply that all these are commonly employed in routine analysis. It must be realized that, nowadays, in addition to a host of solvent mixtures, already more than forty pure solvents are used as media, and the practical methodology also takes into account about 40 indicators [775]. It therefore becomes clear that the reader cannot be made familiar with the combinations of all these.

General prescriptions cannot be given for the concentration of indicator solutions: In practice it should suffice that 1–5 drops of a relatively dilute solution (0·1–1%) are added to a solution of 10–30 ml. In semimicro and microtitrations, especially when analysis in series are performed by using comparative solutions, it is advisable to employ more dilute (0·01%) indicator solutions and to pipette not just one or two drops but 1·0–5·0 ml accurately by means of e.g. an automatic pipette. It is important in microtitrations that the indicator solvent should be identical with, or at least similar to the sample solvent. For example: 10 ml of 0·002 M alkaloid base in chloroform–acetic acid (10 : 1) are titrated with 0·01 N perchloric acid in acetic acid –carbon tetrachloride (1 : 1). In this case, the *diluted* indicator solution should contain the acid and the inert solvent in such a proportion that the enhancing effect of the inert solvent should not be lessened. However, it may happen that in a solvent mixture identical in composition with the sample, the indicator is not stable or dissolves only poorly. In such a case *immediately* before the titration, an extremely dilute indicator solution is prepared in an appropriate volume and neutralized and from this solution the stock solution is prepared containing the substance to be tested.

Table 27

CHOICE OF INDICATOR FOR USE IN SOLVENT MIXTURES OF VARIOUS COMPOSITIONS

Solvent Mixture	*Indicator*	*Colour Change: (a) Alkaline → Acidic; (b) Acidic → Alkaline*
Acetone-acetic acid	0·25% Solution of methyl orange in acetone;	Yellow → orange (*a*)
Acetone-pyridine	0·3% Solution of thymol blue in methanol;	Yellow → blue (*b*)
	Saturated solution of azo-violet in benzene;	Yellow → orange → blue (*b*)
Acetone-acetic acid	Saturated solution of methyl red in acetonitrile;	Orange → salmon pink (*a*)
Acetone-acetic acid-acetic anhydride	Saturated solution of methyl orange in acetone;	Yellow → orange (*a*)
Acetonitrile—chloroform-phenol	Saturated solution of methyl red in acetonitrile;	Orange → pink → violet red (*a*)
Benzene-acetic acid	0·5% Solution of 1-naphtholbenzeine in acetic acid;	Back-titrated with sodium acetate: ivy green → grass green → yellow (*b*)
Benzene-isopropanol	0·1–1·0% Solution of 1-naphtholbenzeine in isopropanol or benzene-methanol;	Orange → brownish green (*b*)
Benzene-methanol	0·3% Solution of thymol blue in methanol;	Red → yellow → blue (*b*)
Benzene-nitromethane	1% Solution of tropaeolin 00 in methanol;	Yellow → magenta (*a*)
Benzene-pyridine	Similar to acetone-pyridine	
Dichloroethane-acetic acid-acetic anhydride	0·5% Solution of tropaeolin 00 in acetic acid;	Yellow → magenta (*a*)
Dioxan—acetic acid-acetic anhydride	0·2% Solution of crystal violet in acetic acid;	Violet → pale blue → green yellow (*a*)
Dioxan — chloroform	0·1% Solution of Congo red in methanol	Red → blue (*a*)
Acetic acid-benzene	0·5% Solution of tropaeolin in acetic acid;	Yellow → orange → purple → → magenta (*a*)

Continuation of Table 27

Solvent Mixture	*Indicator*	*Colour Change: (a) Alkaline → Acidic; (b) Acidic → Alkaline*
Acetic acid-dichloroethane and acetic acid-dioxan	0·1–1·0% Solution of methyl violet in acetic acid;	Blue → green-yellow (*a*)
Acetic acid-nitromethane	0·2% Solution of methyl violet on chlorobenzene;	Violet → blue → green (*a*)
Acetic acid—acetic anhydride	0·5% Solution of malachite green in acetic acid;	Back-titrated with sodium acetate: green-yellow → yellow-green (*b*)
	0·5% Solution of cresol red in 1 : 1 acetic acid–chlorobenzene;	Yellow → pink → red (*a*)
Acetic acid-chlorobenzene-acetic anhydride	0·2% Solution of methyl violet in chlorobenzene;	Violet → pale blue → yellow-green (*a*)
Acetic anhydride — benzene	similar to acetic acid–benzene;	
Acetic anhydride–nitromethane	0·5% Solution of 1-naphtholbenzeine in acetic acid;	Yellow → grass green → ivy green (*a*)
G—H solvent mixture	0·1% Solution of methyl orange in methanol, dioxan;	Yellow → orange (*a*)
	Aqueous solution of 0·15% methyl orange + 0·08% xylene cyanole FF	Green → orange (*a*)
	0·05–0·1% Methyl red in methanol;	Yellow → vivid pink (*a*)
Hexane–acetone	1% Solution of dimethyl yellow in chloroform;	Yellow → orange (*a*)
	0·1% Solution of methyl red in acetic acid;	Orange → vivid pink (*a*)
Ethyl methyl ketone–acetic anhydride	0·1% Solution of methyl violet in acetic acid;	Violet → green-blue (*a*)
Nitromethane–benzene	Solution of 0·1% methylene blue + 0·2% quinaldine red in methanol	Purple → blue → green (*a*)
Nitromethane–formic acid	As above	
Light petroleum–isopropanol	0·1–1·0% Solution of 1-naphtholbenzeine in isopropanol;	Orange → brownish green (*b*)
Propylene glycol–chloroform	0·2% Solution of thymol blue in methanol	Yellow → pink (*a*)

For this reason, it is difficult to evaluate precisely the effect of solvent mixtures discussed in the special literature because at the end of titration a solvent mixture is obtained which differs from that used at the outset. Therefore in photometric titrations, a standard solution is added from the microburette of such a concentration, e.g. 1·0–2·0 N, that the concentration of the indicator should be identical in both the standard solution and the sample.

Photometric titrations are far more accurate than the usual visual titrations. However, their great disadvantage is that usually a spectrophotometer is needed. When the sharpness of the end-point is obscure a simpler and expedient method is to check the absorption of the solution with, e.g., a Pulfrich Stufen Photometer using a dilute indicator solution; after overtitration the titrated solution is back-titrated by adding the stock solution of the compound to be tested, drop by drop, till the pre-determined absorption range is reached. Most indicators (crystal violet, methyl red, methanil yellow, alizarin yellow R etc.) used in non-aqueous titrations experience a considerable shift of absorption maximum around the equivalence point and in this way overtitration can be easily controlled. Thus, the volume of the standard solution consumed is equivalent to the standard volume of stock solution, e.g. 20 ml plus the amount of stock solution consumed for the back-titration, e.g. 0·15 ml, i.e. altogether: 20·15 ml.

72. Colour Change of Crystal Violet

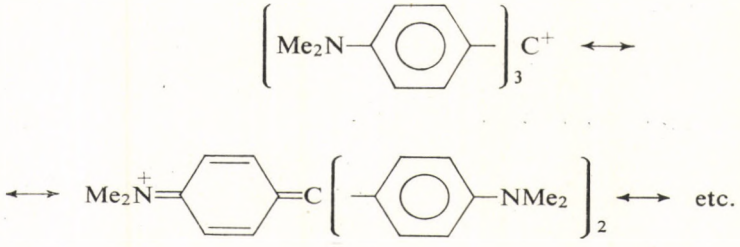
Crystal violet contains the *p*-dimethylamino-triphenylcarbenium ion, the central C-atom of which is co-ordinatively unsaturated and of ionic character; [187] and p. 285 in [597]:

$$(R_3C)^+Cl^- \text{ (or } OH^-)$$

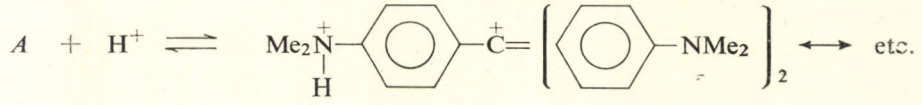
where R = the p-$(CH_3)_2NC_6H_4$ group.

The central C-atom owing to its electron deficiency, has electron attracting properties (*anti-auxochrome*); aromatic rings form the conjugated system between this C-atom and the electron-releasing dimethylamino group (an auxochrome). The auxochrome and anti-auxochrome are conjugated and resonance forms may be written. As a consequence of this resonance light absorption in the visible region results [726], [80, 881].

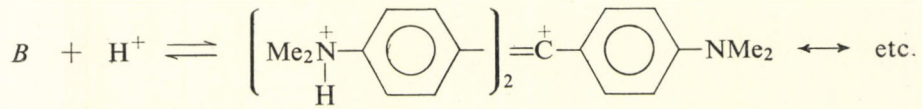
The nitrogen atoms of crystal violet are, however, also co-ordinatively unsaturated. For this reason the ionized dye can act as a polyacidic base by binding protons. In the course of proton acceptance, the interaction of the nucleophilic amino groups with the electrophilic central C-atom gradually decreases and as a consequence the colour of the indicator changes:



Violet *A*



Green blue *B*



Yellow *C*

The equilibria in the crystal violet–perchloric acid system proposed by Kolthoff and Bruckenstein are:

$$I^+ClO_4^- + HClO_4 \rightleftharpoons IH^{2+}(ClO_4^-)_2$$

$$IH^{2+}(ClO_4^-)_2 + HClO_4 \rightleftharpoons IH^{3+}(ClO_4^-)_3$$

$I^+ClO_4^-$ and $IH^{2+}(ClO_4^-)_2$ have absorption peaks at 590 and 630 mμ, respectively, and $IH^{3+}(ClO_4^-)_3$ has an absorption peak below 450 mμ.

Thus, the colour change of crystal violet is gradual and the sharpness of each transition decreases as successive protons are added, because the second and third proton approaches an already positively charged ionized dye. In acetic acid, however, the first transition is very sharp, since the proton affinity of base analogues is very much greater in acetic acid than in water, and the strength of cationic acids is considerably decreased. (Crystal violet is a base analogue until it binds a proton, but, at the same time, it is also a cationic acid because of its positive charge.) During titration the absorption maximum of crystal violet is 591 mμ, 1% before the equivalence point (violet), 595 mμ at the equivalence point (blue) and 627 mμ when 1% overtitrated (green blue). The danger of overtitration is thus practically eliminated because $\pm 1\%$ of the titrant is accompanied by a shift of 36 mμ of the absorption maximum [312].

Mention should be made of the fact that the sensitivity of the eye is very great. Thus, the difference between 'green' and 'light green' is clearly perceptible even though the separation of the maxima measured by the spectrophotometer is only 2 mμ. When base *p*-toluenesulphonates and ethanesulphonates are titrated with perchloric acid in dioxan at a concentration of 10^{-2} M, mistakes of visual detection, e.g. in differentiating between 'blue green' and 'green–light green' respectively, can cause errors of 1–2% in the case of medium-strength bases, and 2–5% with weak bases. The colour change of crystal violet is gradual in dioxan [321]:

Colour	*Absorption Maximum*, mμ	Δ mμ
Violet	594–598	
Blue	598–602	4
Green blue–blue green	622–626	24
Green ('Emerald green')	632–636	10
Light green	634–638	2
Yellow green	636–642	3

The titration of weak bases, e.g. aniline, in acetic acid does not produce a sharp colour change in crystal violet. In this and similar cases the correct shade is ultimately defined potentiometrically [15, 208] and the degree of light absorption determined at a given wavelength for the given indicator and base perchlorate concentration. By this means the end-point of the titration can be subsequently checked.

Pyridine-2-azo-*p*-dimethylaniline has been suggested as an indicator in the titration of amines in glacial acetic acid. The precision attainable is superior to that attainable with crystal violet [120].

Colour change of crystal violet in the determination of weak bases with 0·001 N *perchloric acid* [319]. As already mentioned, according to generally accepted usage, the correct colour change is electrometrically checked in the presence of a given compound and indicator, in an identical solvent. If necessary, the titration is performed to the identical shade of colour observed in the standardization of the titrant

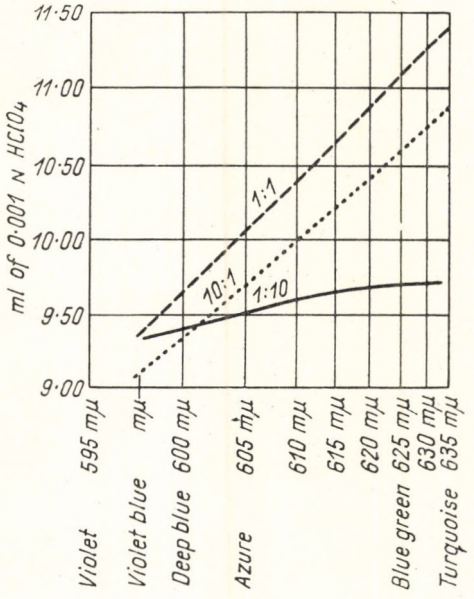


Fig. 70. Variation in colour change of crystal violet with change in composition of solvent mixture (AcOH-CCl_4), according to Gyenes. Titration of amidopyrine [319].

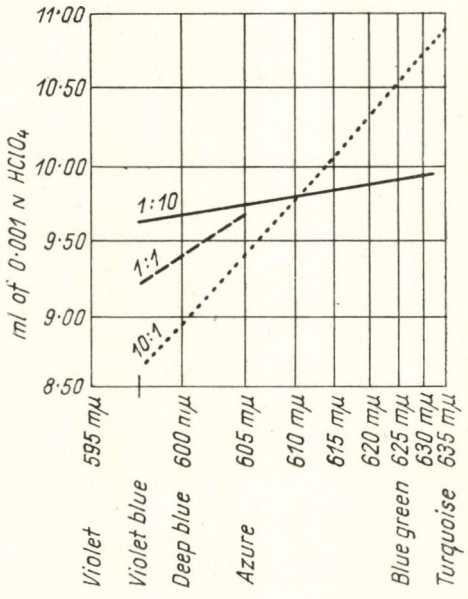


Fig. 71. Variation in colour change of crystal violet with change in composition of solvent mixture (AcOH-CCl_4), according to Gyenes. Titration of diphenylguanidine [319]

against diphenylguanidine or potassium biphthalate, etc. This procedure, however, may be a source of errors. If, for example, 1-phenyl-2,3-dimethyl-4-dimethylaminopyrazolone (pyramidone) is titrated in the presence of crystal violet with 0·001 N perchloric acid in the solvent mixtures acetic acid–carbon tetrachloride (10 : 1, 1 : 1, 1 : 10), and the titrant is standardized in a similar solvent mixture against diphenylguanidine of roughly identical molar concentration, a $100 \pm 0{\cdot}25\%$ value can be obtained only in the solvent mixture 1 : 1, where the shade of colour with the two bases of very different strengths is identical at the end-point. Diphenylguanidine is a strong base ($K = 6{\cdot}1 \times 10^{-5}$), pyramidone a weak one ($K = 6{\cdot}9 \times 10^{-10}$).

In the differentiating solvent mixture (1:10), the value found for pyramidone was 99·4–100·2% but only when the colour shades in the titration of the standard substance and of the base to be tested were *not the same*. In solvent mixtures with a levelling effect (10 : 1) the probable error in the determination was greater: ±0·8%. In the latter case, the results between the colour shades of blush violet and turquoise-blue changed between 80 and 120%, depending on the factor obtained for diphenylguanidine.

In the microtitration of weak bases it is therefore advisable to standardize the 0·001 N titrant against an identical compound of standard quality or against a base containing identical functional groups and of nearly identical strength with the base to be tested. In non-aqueous titrations, especially in those of 0·001 N concentration, it seems necessary to employ a series of standard substances with base strengths between $K_{base}\ 10^{-6}$ and 10^{-12}.

The enhancing effect of inert solvents on the colour change in microtitrations is shown in Figs 70 and 71.

73. Colour Change of Thymol Blue

In aqueous media, with increasing basicity thymol blue turns from red to yellow (pH 1·5) and from yellow to blue (pH 8·9). In non-aqueous media, this indicator behaves similarly and so it is suitable for the determination of mixtures of acids and acid analogues in methanol, dioxan, acetone, acetonitrile etc.

In acetone, for example, dependent on the acidity, the following colours can be seen:

With hydrochloric acid	Red
With acid chlorides	Pink
With nitric acid, carboxylic acids, anhydrides, phenols, amine hydrochlorides	Yellow
With alkali metal alkoxide or Bu_4NOH	Blue

If a weaker base, e.g. tri-n-butylamine is used as the titrant, only strong mineral acids can be titrated in the presence of thymol blue (cf. [623]). (See also: Table 22.)

74. Colour Change of Azo-violet

The behaviour of azo-violet (4-(*p*-nitrophenylazo)-resorcinol) is similar to that of thymol blue [307, 540, 798]. Thus, in a mixture e.g. of acetone-pyridine (4 : 1) the following colours are observed, dependent upon acid strength:

Phenylquinoline carboxylic acid	Lemon
Benzoic acid	Dark yellow
p-Hydroxypropiophenone	Orange yellow
Phenol	Red
8-Hydroxyquinoline	Violet

When titrating acids with potassium methoxide, the colour changes from yellow to red and from this, by adding a few more drops of the standard solution, to blue. With phenols the solution is originally orange or yellow-red and the end-point is

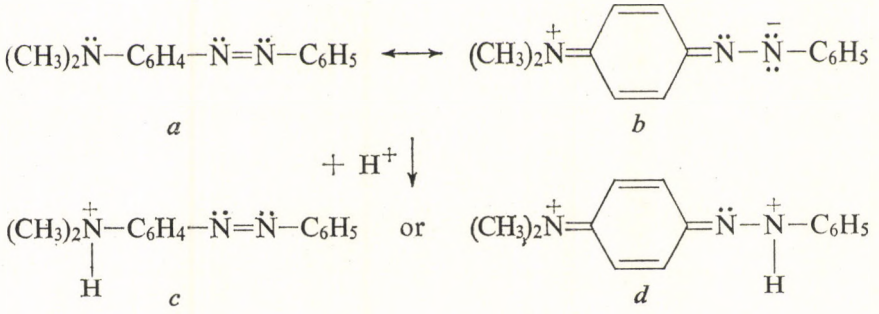
indicated by a clear blue which, however, depending on the solvent used may be of different shades (violet blue, cornflower blue, steel blue). In acetone azo-violet becomes yellow with perchloric acid, nitric acid or benzoic acid, pink with anthranilic acid, and blue with phenol or with an excess of Bu_4NOH. Takiura and Takino observed the following colours appearing at the end-point of titrations in pyridine (abridged) [798]:

o- and *m*-Nitrophenol	Dark red
p-Nitrophenol and *p*-hydroxyacetophenone	Green
p-Hydroxybenzoic esters	Blue
2,4-Dinitrophenol	Dark brown
2,4,6-Trinitrophenol	Dark red
2,4,6-Trihydroxybenzaldehyde	Light violet

These results show that in working out a new method – if azo-violet is used – a potentiometric check of the colour change of the indicator is practically indispensable, and, if necessary, a standard reagent identical with the compound to be tested but of standard purity, must be used.

75. Colour Change of Dimethyl Yellow

Dimethyl yellow (4-dimethylaminoazobenzene), was first used in titrations in benzene medium [852]. It is chiefly employed for microtitrations of bases in chloroform and carbon tetrachloride. Numerous alkaloid bases can be titrated accurately with a standard solution of *p*-toluenesulphonic acid of 0·005 N concentration in chloroform in the presence of dimethyl yellow which at the end-point turns from yellow to pink. Two hypotheses, an earlier and a more recent one, have been made regarding the structural change of 4-dimethylaminoazobenzene in the course of its protonation. Earlier spectroscopic investigations of Hantzsch and Hilscher [353] suggest a quinonoid rearrangement (*d*). On the other hand, in the presence of strong acids the ultraviolet spectrum points to a benzenoid structure: (*c*) [460, 568]. The greater base strength of the dimethylamino group as compared with the azo group supports the latter theory. However, after proton acceptance the quinonoid system of double bonds cannot include the nitrogen atom of the dimethylamino group, because the octet of the N-atom is complete:



76. Accuracy of Measurements. Calculations

In non-aqueous titrations, when 0·1 N–0·01 N perchloric acid is used, the probable margin of error is ±0·2 to ±0·4% in the case of bases the dissociation constant of which, measured in water, is not lower than 10^{-10}. If propionic acid is used instead of acetic acid the accuracy can be increased up to ±0·2% [313] (Fig. 72). In an inert solvent the accuracy of measurement with 0·005 N *p*-toluenesulphonic acid even on a

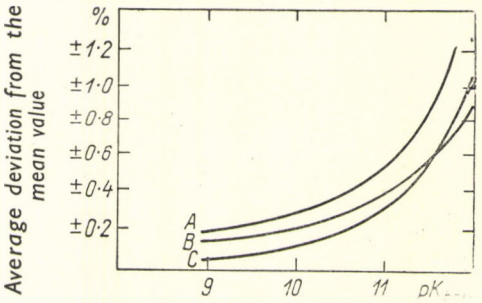


Fig. 72. Accuracy of determination of bases related to base strength measured in water, according to Gyenes [313]. — *(A)* In acetic acid, *(B)* In propionic acid, *(C)* In chlorobenzene

micro scale (e.g. 0·5–5 mg of alkaloids) is ±1%. Under convenient experimental circumstances weak bases ($pK > 12$) can be titrated with an accuracy of ±1%. *The precision of determinations is greatly increased by photometric end-point detection* even in the case of those bases which can be considered as being exceedingly weak, e.g. urea, thiourea etc.

The accuracy of measurements is adversely affected by a sluggish colour change at the end-point. Errors are progressively increased with the stepwise colour change of crystal violet or malachite green [463]:

Colour Change of Malachite Green	*Error of Determination*
Blue green → green	± 0·18
Green → yellow green	± 0·52
Yellow green → yellow	± 1·6

The accuracy of acid and acid analogue determinations greatly depends on the exclusion of atmospheric carbon dioxide. The less acidic the compound to be determined, the more basic must the solvent be. At the same time, however, the CO_2 abstracting power of the latter is also increased. The accuracy of titration of strong and moderately strong carboxylic acids or phenols is ±0·3 to ±0·8%, while that of very weak acid analogues is 1 to 2%.

In the discussion of the determinations, attention will be drawn to those cases where the accuracy of the titrations differs from the above values.

In non-aqueous titrations, the colour change of the indicator and the transitional shades do not depend solely on the quantity of the indicator used, the acid or base strength and the ionic concentration of the solution, but also on the change in the solvent during titration. In the solvent mixture pyridine–acetone, the colour change of azo-violet is sharp but the addition of methanol reduces this sharpness. Consis-

tent accuracy in determinations cannot be expected if in 20 ml of a 4 : 1 solution of acetone-pyridine, varying amounts of, e.g. *p*-hydroxypropiophenone are titrated with 0·1 N sodium methoxide in benzene-methanol, the methanol content of which is 10% v/v, when for the first titration 2 ml, for the second 10 ml and for the third 50 ml of standard solution are consumed. In the first case the methanol content of the titrated solution is 1%, in the second 3·3% and in the third case 7% v/v. When only two millilitres of the standard solution are consumed, the error of reading impairs the precision of determination, while in the case of 50 ml consumption the concentration of methanol diminishes the sharpness of colour change:

Mean Value of Consumed ml	*Number of Determinations*	*Probable Limits of Errors of Single Determination*
2·06	10	± 0·5%
10·25	5	± 0·3%
51·40	8	± 0·7%

Although the human eye is very sensitive to colour shades, *individual differences may occur, and sensitivity changes with time:*

Analyst	*Determination of Base Picrate on a Semimicro scale*
'A' (With great experience)	99·7 ± 0·2 (5 Determinations)
'B' (With little experience)	99·9 ± 0·55 (7 Determinations)
A year later:	
'A'	99·7 ± 0·6 (4 Determinations)
'B'	99·8 ± 0·25 (6 Determinations)

The consistency of these results does not necessarily mean that the determination is *accurate.* Thus two analysts in two neighbouring laboratories titrated, on a micro scale, alkaloids of standard purity under identical circumstances with the same standard solution. The result obtained by the first was 100·0 ± 0·8%, while that by the second 99·6 ± 0·3%. It should be noted that the methodological accuracy given in the literature depends also upon individual factors, e.g. individual colour sensitivity of the analyst.

Calculations. The calculations frequently employed in titrimetry will be outlined briefly: *Factor of the standard solution, f*:

$$f = \frac{\frac{a_{mg}}{E_g \times N}}{b}$$

where a_{mg} = the quantity of the standard substance (in mg)
E_g = gram equivalent weight of the standard substance
N = normality of the standard solution
b = the volume consumed (in ml).

Normality of the standard solution, N:

$$N = \frac{a \times 100}{c \times E}$$

where a = the weight of compound used as standard substance (in g)
E = one-tenth of the equivalent weight of the standard substance
c = the volume of standard solution consumed (in ml).

Equivalent weight of the compound being determined by E_g:

$$E_g = \frac{a \times 1{,}000}{c \times \mathrm{N}}$$

where a = weight of the compound to be tested (in g)
c = the volume consumed (in ml).

Percentage composition of the compound determined:

$$\% = \frac{c \times \mathrm{N} \times E}{a}$$

where E = one-tenth of the equivalent weight of the known compound.

Percentage content of a functional group, e.g. OH:

$$\mathrm{OH}\% = \frac{c \times \mathrm{N} \times 1{\cdot}7}{a}$$

where 1·7 = one-tenth of the equivalent weight of the hydroxyl group.

If the volume consumed for the blank test must also be taken into account, this is subtracted, if less than the volume consumed in the titration, but if more, then the volume obtained by titration is subtracted from the volume for the blank test:

% composition of the compound determined:

$$\% = \frac{(c - b) \times \mathrm{N} \times E}{a}$$

where c = the volume consumed in the titration
b = the blank for the solvent + indicator:

$$\% = \frac{(b - c) \times \mathrm{N} \times E}{a}$$

where b = the volume of the standard solution consumed for the blank test.

Such is the case when the reagent is e.g. hydroxylamine hydrochloride solution containing tributylamine. This is titrated with hydrochloric acid to obtain the blank volume and after oxime formation the hydrochloric acid produced reacts with the tributylamine so that the value obtained at the subsequent titration is smaller than the value for the blank test.

Chapter 14

Photometric End-point

Among the successful physico-chemical methods of determining the end-point in non-aqueous titrations the use of monochromatic (or nearly monochromatic) light absorption is one of the more recent, although preliminary investigations were carried out at the beginning of this century [806]. Müller and Patridge pioneered in this field [606]. Goddu and Hume [275, 276, 277], Mika (pp. 52–60 in [584]) and Osborn and collaborators expounded the basic principles of the method [617]. Later Higuchi and co-workers dealt in detail with titrations in acetic acid medium and published various types of graph and calculation [148, 390, 385, 670, 671]. Numerous authors have been concerned with photometric titrations using absorption in the ultraviolet [86, 675, 679]. Ellert and collaborators elaborated the photometric determinations of some drugs [209, 211]. Photometric titration of phenols is a somewhat more difficult task although in the specialist literature many practical examples can be found [405]. J. B. Headridge discusses photometric titration in his concise and didactic monograph.*

77. Fundamental Law of Photometry

In photometric titrations the standard solution is added to the sample in increments of 0·01–0·2 ml while the absorption of the light passing through the solution is measured. The Lambert–Beer law is the fundamental law of photometry:

$$\text{Absorbance, } A \text{ (or optical density, } E) = \log \frac{I^\circ}{I} = \varepsilon\ c\ d,$$

where I° = the intensity of the incident light
I = that of the transmitted light
ε = the extinction coefficient
c = the concentration of the absorbing solution

* *Photometric Titrations*, Pergamon Press, Oxford, 1961.

d = the layer thickness i.e. length of the light path traversing the absorbing medium in centimetres

$$T\,(\text{transmittance}) = \frac{I}{I^\circ} \quad \text{and} \quad -\log\frac{I}{I^\circ} = -\log T = \log\frac{I^\circ}{I}$$

78. Advantages and Limitations of Photometric Titration

The accuracy of photometric end-point detection is often greater than that of potentiometric measurements especially when logarithmic functions are used (cf. [774a, 774b]). Thus, for instance, if aluminium oxinate is titrated photometrically the accuracy is $\pm 0{\cdot}8\%$, while measured potentiometrically the error is $\pm 2{\cdot}3\%$ [659]. An advantage of photometric titrations compared with direct colorimetric determinations is that compounds which do not take part in the reaction but absorb at the same wavelength as the co-reactants do not interfere because only the *change of absorbance* at the equivalence point is important. Photometric titrations are extremely useful for differentiating titrations of multi-component systems. Thus, e.g. in a mixture of di-n-butylamine (pK 2·6), N,N-diethylaniline (pK 7·5), aniline (pK 9·4) and *o*-chloroaniline (pK 11·4) the concentrations of each can be determined with 0·5 N perchloric acid in acetonitrile [404]. Another advantage of photometric titration is that the end-point of the titration is not dependent upon measurements performed in the near vicinity of the stoichiometrical equivalence point. The two linear parts of the titration curve can be extrapolated and projection of the point of intersection on the x axis indicates the equivalence point.

On the other hand, it must be considered to be a limitation of photometric titrations that a spectrophotometer which often needs some modification is required, and moreover special cuvettes or titration vessels are needed. Because of the volume change of the sample, either a correction must be employed or a relatively concentrated standard solution used. In this case, however, a micro-burette graduated in 0·01 ml is needed.

79. Varieties of Photometric Titrations

A distinction is made between so-called *direct photometric titration* (self-indicator systems) and *indirect titration* (indicator added). In the former, the change of absorption of the *standard solution* or of the *compound to be tested*, or of the *reaction product* at the equivalence point is measured (e.g. in the ultraviolet region); in the second case the light absorption of the added indicator is measured. The light absorption of indicators employed in small amounts generally changes linearly, only in the vicinity of the equivalence point (cf. [390]).

80. Graphic Construction of Photometric Titration Curves. Shapes and Types of Titration Curves. Examples

The main conclusion to be drawn from the Lambert–Beer law is that the value of A measured by a suitable spectrophotometer is directly proportional to the concentration of the absorbing molecule. In titrations where the standard solution or the sub-

stance to be tested or the reaction product possesses light-absorbing properties at a given wavelength, the measured value of A is plotted against the volume of the standard solution consumed (V). If the reaction is complete, the point of intersection of the titration curve obtained indicates the end-point of the titration. In ideal conditions a plot of A against V yields a graph consisting of two straight lines extrapolated to intersect at the equivalence point.

The shape of titration curves depends on the standard solution, the light absorbing power of the compound to be measured or the indicator added to the system, the wavelength, the dissociation constant of the coloured compound and the solvent.

For photometric titrations the same technique and apparatus can be used in aqueous, as in non-aqueous media. However, it should be borne in mind that in non-aqueous solvents even strong electrolytes do not totally dissociate into their ions.

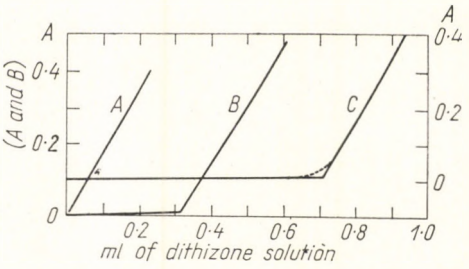


Fig. 73. Photometric titration of zinc with dithizone in benzene at 640 mμ, according to Marple, Matsuyama and Burdett [552]. — *(A)* Blank test, *(B)* Zinc standard, *(C)* Oil containing zinc

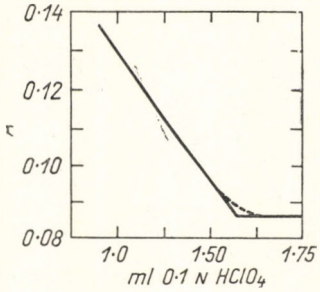


Fig. 74. Photometric titration of aluminium oxinate (226 mg) at 450 mμ, according to Powers, Day and Underwood [659]

For this reason, indicators behave in a different manner in non-aqueous solvents and no direct correlation exists between the I_A/I_B ratio of the indicator and pH value, as can be observed in aqueous medium (cf. Chapter 13). The precision of measurement, as well as the shape of the titration curve vary considerably depending on whether a *direct photometric titration* is performed or *addition of indicator* becomes neccessary. In the latter case the result of photometric titration is not always more accurate than that of the usual visual titration or electrometric end-point detection [583]; in certain cases, however, the accuracy of this method exceeds that of usual titrations (cf. [201, 385, 390, 670, 671]).

(a) *An example of change of absorption at the equivalence point because of excess of standard solution* is the determination of the zinc content of a benzene solution of lubricating oil containing zinc-dialkyl-dithiophosphate using a standard solution 0·05% dithizone in benzene [552] (Fig. 73).

(b) An example of the *change of light absorption by the compound to be measured* is the titration of aluminium oxinate and 8-chloroquinoline with perchloric acid in acetic acid [404, 659, 675]: (Figs 74 and 75).

(c) *For photometric titrations using indicators* Higuchi and co-workers, and also Ellert and collaborators have worked out detailed methods.

The shapes of the plots of A against V and of $1/T$ against V in many cases bear a resemblance to some electrometric titration curves. The point of inflection of the

curves of the functions A against V and $1/T$ against V is at that point where the first differential ratio reaches the maximum (cf. Figs 77 and 78). In order to determine the end-point of the titration more precisely, i.e. the point where the indicator suddenly changes its colour, the graph of

$$\frac{\Delta A}{\Delta V} \text{ against } V \text{ and } \frac{\Delta \frac{1}{T}}{\Delta V} \text{ against } V$$

can also be plotted.

For the indicator method, for example, a photocolorimeter with a 15 mm cuvette can be employed. Dissolve a weighed quantity of 0·5–1·0 m.eq. of the base in 20 ml of acetic acid and titrate with 0·1 N perchloric acid in acetic acid in the pres-

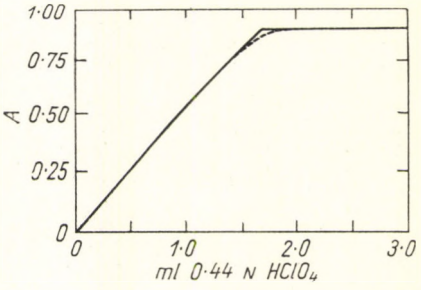


Fig. 75. Photometric titration of 8-chloroquinoline (130 mg) at 380 mμ, according to Hummelstedt and Hume [404]

ence of two drops of 0·5% methylene blue in acetic acid. Add the standard solution in increments of 0·05–0·2 ml and after each addition measure the light absorption. In this way numerous organic bases can be determined by using a colour filter of 550–580 mμ range [209]; Figs 76, 77 and 78: 1- and 2-naphthylamine, narceine, adrenaline, sulphathiazole, pyridine, quinine hydrochloride (the latter in the presence of mercury(II) acetate in nitromethane solution, the others in acetic acid).

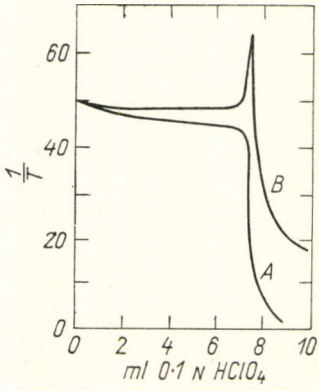


Fig. 76. Photometric titration of narceine in the presence of methylene blue indicator, according to Ellert, Jasinski and Marcinkowska [209]. — With filter *(A)* at 570–600 mμ and *(B)* at 550–580 mμ

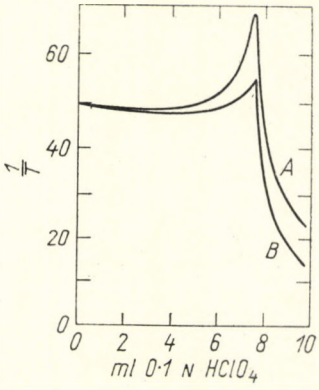


Fig. 77. Photometric titration of 1-naphthylamine *(A)*, and 2-naphthylamine *(B)*, in the presence of methylene blue indicator, according to Ellert, Jasinski and Marcinkowska [209]

In the case of caffeine, titration curves of different shape result depending on the indicator employed. Thus for example, a remarkable curve is obtained in the presence of safranin (a mixture of diamino derivatives of phenylphenazonium salts) in acetic anhydride medium: when the last few drops of 0·1 N perchloric acid are added the light absorption of the solution suddenly increases, followed by a marked decrease

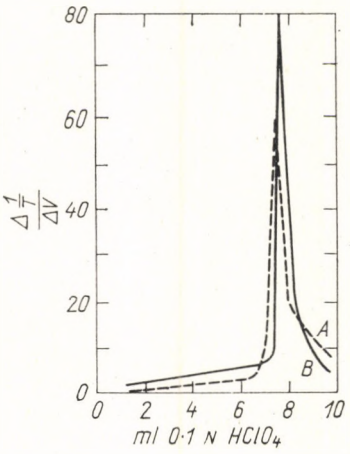


Fig. 78. Photometric titration of 1-naphthylamine *(A)*, and 2-naphthylamine *(B)*, in the presence of methylene blue indicator [209]

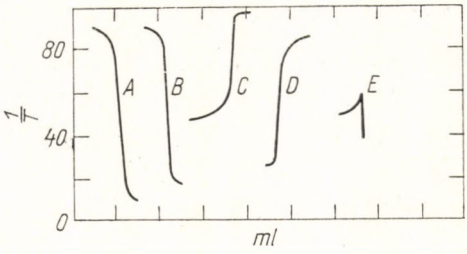


Fig. 79. Photometric titration curves of caffeine in acetic anhydride according to Ellert, Jasinski and Weclawska [211]. — In the presence of indicator, *(A)* Malachite green, *(B)* Nile blue, *(C)* Neutral red, *(D)* Sudan III, and *(E)* Safranine

(Fig. 79, curve *E)*. From the curve obtained in this way the end-point of the titration can be read directly [211].

In photometric titrations by the use of indicators, apart from those mentioned above plots of the following functions can be obtained:

$$\frac{I\mathrm{H}^+}{I} \text{ against } V, \quad \frac{I}{I\mathrm{H}^+} \text{ against } V \text{ and } \quad \frac{I\mathrm{H}^+}{I} \text{ against } \frac{1}{V}, \text{ etc.}$$

'*Type I' photometric curve* [390]. In normal visual titrations, when the indicator is present in only small amounts, the intensity of the colour change is only linear with respect to the quantity of the standard solution near the end-point. The equilibrium for the titration of a weak acid by a strong base in aqueous medium is the following:

$$A^- + I\mathrm{H}^+ \rightleftarrows A\mathrm{H} + I,$$

where $A\mathrm{H}$ and A^- = the weak acid and its conjugate base, respectively
$I\mathrm{H}^+$ and I = the protonated (acidic) and basic forms of the indicator.

The equilibrium constant K is therefore

$$K = \frac{[A\mathrm{H}]\,[I]}{[A^-]\,[I\mathrm{H}^+]} = \frac{K_I}{K_A}$$

Let the amount of acid to be measured in the titration system be equivalent to the volume S of the standard alkali solution, and let X be the volume of the standard solution added at any time during the titration. Then

$$K = \left[\frac{I}{I\mathrm{H}^+}\right]\frac{S - X}{X} \tag{80.1}$$

In systems where the value of K is smaller than 0·05, and where X approaches the value of S, the photometric curve is roughly linear near the equivalence point:

$$XK\left[\frac{I\mathrm{H}^+}{I}\right] = S - X \tag{80.2}$$

If the absorptiometrically determined value of $I\mathrm{H}^+/I$ is plotted against X a straight line is obtained which intersects the x axis and this corresponds to the equivalence point ($X = S$).

When weak acids are titrated by strong bases, the ratio $I\mathrm{H}^+/I$ decreases as titration proceeds. This kind of plot can be employed only if the value of K is small and that of $I\mathrm{H}^+/I$ becomes smaller than 1 only towards the end of titration (> 99%). This

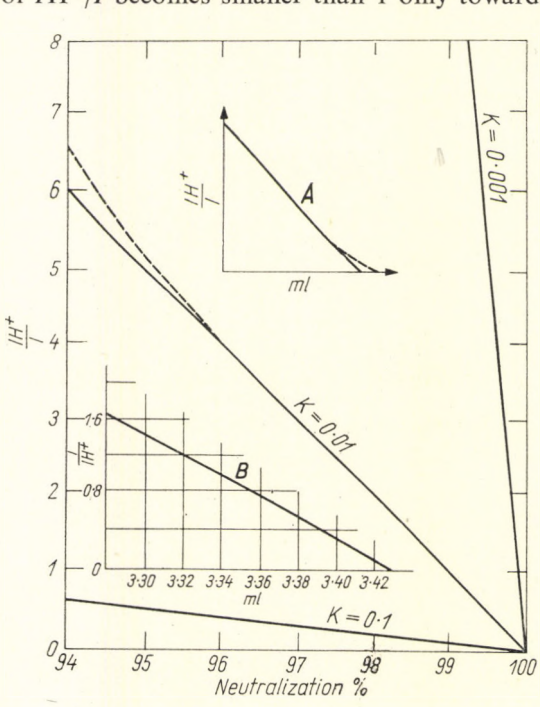


Fig. 80. 'Type I' photometric curves according to Higuchi, Rehm and Barnstein [390]. — Idealized curves: $K = 0{\cdot}1$, 0·01 and 0·001. *(A)* Idealized curve of acid titration, *(B)* Photometric titration of 242·6 mg triphenylguanidine with 0·25 N perchloric acid in presence of quinaldine red as indicator (533 mμ)

is shown in Fig. 80 which represents the ultimate stage of three idealized photometric curves where $K = 0{\cdot}1$, $K = 0{\cdot}01$ and $K = 0{\cdot}001$. This type of photometric titration curve in which the extrapolated straight line intersects the x axis and the plot for the titration of acids is $I\mathrm{H}^+/I$ against V, and that for the titration of bases is $I/I\mathrm{H}^+$ against V, is known as the 'Type I' curve [390] (Fig. 80, curves A and B).

Photometric curve 'Type II' [390]. Sometimes either it is impossible to employ indicators with a K value of 0·01 or less, or an indicator with a relatively large K

value, e.g., 0·05 *must* be used because a stronger acid has to be determined in the presence of a weaker one. In such cases another modification of Eq. (80.1) can be employed:

$$\frac{1}{X} = \frac{1}{S} + \frac{K}{S}\left[\frac{IH^+}{I}\right] \tag{80.3}$$

If the experimentally measured IH^+/I value is plotted as a function of the reciprocal of the volume of standard solution consumed then the intersection of the straight line with the x axis occurs when $1/X = 1/S$, i.e. the titration has reached the equiva-

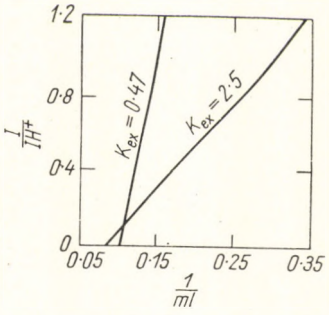


Fig. 81. Photometric titration curve 'Type II' according to Higuchi, Rehm and Barnstein [390]. Determination of urea with perchloric acid in presence of indicator Nile blue A ($K_{ex} = 0{\cdot}47$), or malachite green ($K_{ex} = 2{\cdot}5$)

lence point. The term 'Type II' is used for those photometric curves which, in the case of acids, are plots of IH^+/I against $1/V$, and in the case of bases of I/IH^+ against $1/V$ (Fig. 81).

Use of a 'modified Type II' titration curve in the case of small samples of very weak bases [148]. With exceedingly weak bases the plotting of a type II curve has sometimes led to inaccurate results. Since the base perchlorate formed undergoes solvolysis even in acetic acid it seems advisable to employ another kind of graph although in this case two complete titrations must be performed: one with a larger quantity of 20–30 mg, the other with a smaller amount of 5–7 mg. The reaction can be expressed:

$$BHA + I \overset{K_{ex}}{\rightleftharpoons} IHA + B, \tag{80.4}$$

where I may be e.g. Nile blue A, and B, e.g. urea.

The term used for the equilibrium constant of the above reaction scheme is the *exchange constant:*

$$K_{ex} = \frac{C_{IHA} \times C_B}{C_I \times C_{BHA}} = \frac{K_f^{IHA}}{K_f^{BHA}} \tag{80.5}$$

where K_f^{BHA} = the formation constant of BHA
K_f^{IHA} = the formation constant of the acidic form of the indicator, which is related to the position of the equilibrium $B + AH \rightleftharpoons BHA$.

Dissociation of the product formed is neglected in view of the low dielectric constant of acetic acid (cf. [101, 102, 464]).

The following equation represents the titration equilibrium of Eq. (80.4) [148]:

$$\frac{1}{X} = \left(\frac{K_{ex}}{S}\right) \times \left(\frac{I_B}{I_A}\right) + \frac{1}{S} \tag{80.6}$$

where S = the volume of the standard acid solution, equivalent to the weighed amount of base
X = the volume of the standard solution added at any time during the titration
I_B/I_A = the experimentally measured ratio of basic to acidic form of the indicator.

When the ratio of the basic and acidic forms of the indicator is plotted against $1/X$, a graph of 'Type II' is obtained.

When, in acetic acid, solvolysis is taken into account but dissociation neglected, the total concentration of perchloric acid during titration of the base before the end-point is X', and the total concentration of the base is S':

$$X' = C_{HClO_4} + C_{BHClO_4} \tag{80.7}$$

$$S' = C_B \quad + C_{BHClO_4} \tag{80.8}$$

The relation of the concentrations X' and S' to the volumes previously mentioned, X and S is as follows:

$$X' = \frac{X \times N}{V} \text{ and } S' = \frac{S \times N}{V}$$

where N = the normality of the standard solution
V = the total volume of the dissolved sample.

Let the volume of the standard acid solution at a given stage of the titration of the first solution (the smaller weight) be X_1, and for the second (greater weight) be X_2; let the acid concentrations, equivalent to the base be, analogously, S_1 and S_2. Given a constant I_B/I_A value, the titration can be expressed by the following equation:

$$\frac{1}{X_2 - X_1} = \left(\frac{K_{ex}}{S_2 - S_1}\right) \times \left(\frac{I_B}{I_A}\right) + \frac{1}{S_2 - S_1}$$

At a given I_B/I_A value the value of $1/(X_2 - X_1)$ can be calculated from the curves obtained by plotting the functions

$$\frac{I_B}{I_A} \text{ against } \frac{1}{X_1} \text{ and } \frac{I_B}{I_A} \text{ against } \frac{1}{X_2} \text{ (cf. Fig. 82)}$$

The intersection of the straight line of the 'modified Type II' titration with the x axis indicates the value of $S_2 - S_1$, i.e. the point of intersection is the corrected equivalence point for the difference between the first and second weights.

By this method in the presence of indicator Nile blue A, fairly exact results could be obtained when the following weak and extremely weak bases were titrated (first weight used: 5–7 mg; second weight: 25–35 mg. Standard solution = 0·1 N $HClO_4$ in acetic acid):

Base	*Probable % Error of Single Determinations*	K_{ex}
Acetamide	1·7	3·66
Urea	1·6	0·46
2,6-Dimethyl-γ-pyrone	0·3	0·28
Thiourea	0·5	0·25
Caffeine	0·9	0·16
Antipyrine	0·8	0·00
Triphenylguanidine	0·7	0·00

By plotting a 'modified Type II' titration curve, the end-point can be precisely determined if K_{ex} is very small. This method of calculation, however, is mainly employed for determination of the degree of basicity. In this case, however, it is advisable to apply a differentiating indicator whose exchange constant is greater than zero.

For the determination of photometric curves of 'modified Type II' titrations the *Bausch & Lomb Spectronic 20* colorimeter and the circulating Erlenmeyer colorimeter are suitable, as already mentioned (cf. Fig. 99).

A practical method of working is to mix the acetic acid solution of the indicator with a solution of perchloric acid in acetic acid in such a proportion that it contains a sufficiently high concentration of each. The normality of the perchloric acid-indicator solution is standardized against potassium hydrogen phthalate in the presence of 1-naphtholbenzeine. Small quantities of indicator (e.g. Nile blue A) do not affect the colour change of 1-naphtholbenzeine. Figure 82 shows a graph of two curves and the 'modified curve' plotted during such titration.

The 'modified Type II' calculation can be employed for the determination or estimation of the strength of such weak bases as chloroacetamide and diethyl ether [385].

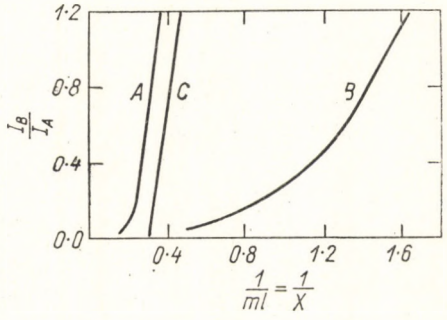


Fig. 82. 'Modified Type II' photometric titration curve according to Connors and Higuchi [148]. Photometric titration of urea with 0·098 N perchloric acid in presence of Nile blue A (632 mμ) *(A)* 24·2 mg, and *(B)* 4·84 mg of urea *(C)* Difference titration curve (19·36 mg)

In the case of extremely weak bases solvolysis is considerable even in acetic acid. Acid and base concentrations are represented by Eqs (80.7) and (80.8). The modified Eq. of (80.9) is

$$\frac{1}{X' - C_{HClO_4}} = \left(\frac{K_{ex}}{S'}\right) \times \left(\frac{I_B}{I_A}\right) + \frac{1}{S'} \qquad (80.9)$$

C_{HClO_4} must be determined separately by carrying out a blank test with acetic acid containing an indicator (e.g. Sudan III) in the same concentration as the solution to be tested (cf. Fig. 85, curve *B*). For the calculation, the value $1/X - C_{HClO_4}$ is plotted against I_B/I_A. Since in the blank test the indicator is the only base, the value of

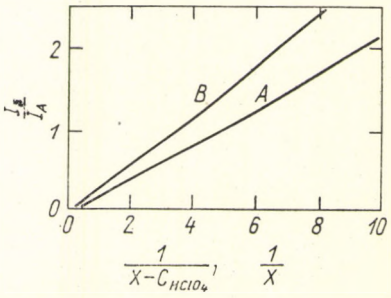


Fig. 83. Photometric titration of chloroacetamide with 0·5 N perchloric acid in presence of Sudan III indicator, according to Higuchi, Barnstein, Ghassemi and Perez [385]. — *(A)* 'Modified Type II' curve, *(B)* 'Type II' curve

C_{HClO_4} equals a given indicator ratio and can be calculated from the formation equilibrium of the indicator perchlorate: $I + HClO_4 \rightleftharpoons IHClO_4$,

$$K_f^{IHClO_4} = \frac{C_{IHClO_4}}{C_I \times C_{HClO_4}}$$

where

$$C_{HClO_4} = \left(\frac{1}{K_f^{IHClO_4}}\right) \times \left(\frac{I_A}{I_B}\right)$$

When the value of I_A/I_B is plotted as a function of C_{HClO_4} a straight line is obtained passing through the origin (Fig. 85, curve *B*). It is apparent that the amount of acid used for the formation of Sudan III-perchlorate for example is very small. The formation constant of Sudan III is about 700 [389].

In acetic acid, water is a base, and in order to eliminate its competitive influence, the acetic acid used as solvent contains 0·25 M of acetic anhydride.

Fig. 83 indicates that chloroacetamide, a very weak base, depending on the type of plot always gives a different tangent. The 'modified Type II' curve *(A)* gives the correct value of K_{ex}.

Basicity of some compounds in acetic acid compared with Sudan III:

Compound	K_{ex}	*Compound*	K_{ex}
1-Acetylpiperidine	0·014	2,4,6-Tribromoacetanilide	16
N,N-Dimethylformamide	0·14	Diethyl ether	1,400
Chloroacetamide	2·7	Phenobarbitone	not basic

The value of K_{ex} with a given indicator can be calculated in the following way:

$$K_{ex} = \frac{\frac{1}{X} - \frac{1}{S}}{\frac{I_B}{I_A}} \times S, \text{ or } \frac{\frac{1}{X - C_{HClO_4}} - \frac{1}{S}}{\frac{I_B}{I_A}} \times S$$

Fig. 84 represents the *idealized* tangents of value K_{ex} for bases of different strength (equimolar quantities of bases; $S = 3$ ml of standard solution).

'Type III' photometric curves [671]. In this case, essentially, the change of absorption *after the equivalence point* is plotted as a function of the volume consumed. The excess of standard solution equals $X - S$,

where X = the total added standard solution
S = the volume of the standard solution actually equivalent to the compound to be measured:

$$X - S = K\frac{I\mathrm{H}^+}{I}V,$$

where V = the total volume of the titrated system.

In the case of bases the function $I\mathrm{H}^+/I$ is plotted against X and intersection of the extrapolated straight line with the x axis gives the equivalence point. For this type of titration, those indicators are suitable whose colour change occurs

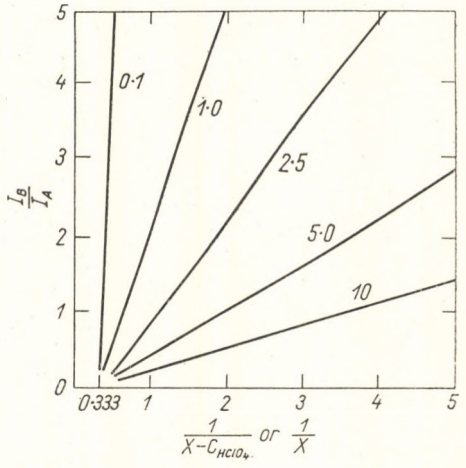


Fig. 84. Idealized tangents of K_{ex} 0·1, 1·0, 2·5 5·0 and 10

only with a great excess of perchloric acid. Colour change corresponds to the equilibrium:

$I + \mathrm{HClO_4} \rightleftharpoons I\mathrm{HClO_4}$, and the appropriate equilibrium constant is:

$$K = \frac{[I\mathrm{HClO_4}]}{[I]\,[\mathrm{HClO_4}]}$$

When the above equation is rearranged

$$\mathrm{HClO_4} = \frac{[I\mathrm{HClO_4}]}{[I]}K$$

and the value of $[I\mathrm{HClO_4}]/(I)$ is plotted as a function of the volume of perchloric acid, a straight line is obtained whose intersection with the x axis denotes the equi-

valence point (Fig. 85, curve *A*: titration of urea with perchloric acid in the presence of Sudan III, and curve *B*: blank test performed with acetic acid containing indicator).

The 'basic' colour of Sudan III ($C_6H_5-N=N-C_6H_4-N=N-C_{10}H_6OH$) is yellow and its 'acidic' colour blue. Its apparent basicity in acetic acid is so slight that in

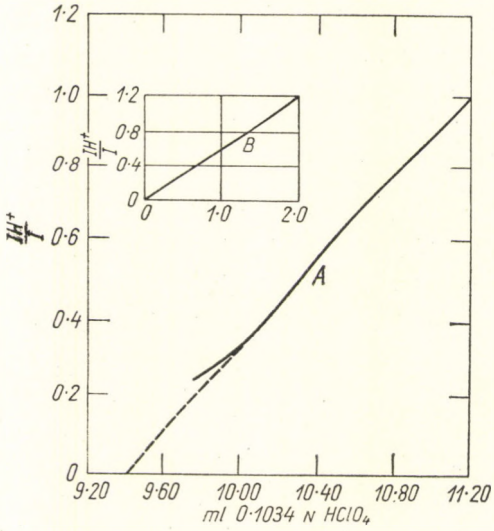


Fig. 85. Photometric titration curves 'Type III' according to Rehm and Higuchi [671]. — *(A)* Titration of 65·6 mg of urea in presence of Sudan III indicator (615 mμ), *(B)* Blank consumption of 25 ml acetic acid containing 0·2% of water and Sudan III

a solution of 0·05 M urea perchlorate in acetic acid, only 10% is converted to the acid form. Its maximum absorption is at 615 mμ.

Functions of 'Type III' are linear when the following equilibrium is shifted considerably to the left:

$$I + BH^+ClO_4^- \rightleftharpoons IH^+ClO_4^- + B$$

where B = the base to be titrated and $BH^+ClO_4^-$ the base perchlorate ion-pair.

The ratio of the acidic to the basic form of the indicator is determined absorptiometrically:

$$\frac{IH^+}{I} = \frac{A - A_b}{A_s - A}$$

where A_s = optical density of the the indicator perchlorate
A_b = optical density of the basic form of the indicator
A = optical density read during measurements.

The optical density of the acid form of the indicator is read *at the end of the titration after a large excess of perchloric acid has been added;* the value for the basic form of the indicator is read *prior to the beginning of titration.*

Concerning the use of Brilliant green, Rhodamine B and Victoria blue see: [463].

(d) *Photometric titration of bases using absorption in the ultraviolet.* Bricker and Sweetser were the first to employ this type of titration [86] which has many advantages, since numerous organic compounds possess a considerable light absorption

in the ultraviolet region but not in the visible. This method gives results in very good agreement with the Lambert–Beer law since because of its sensitivity highly dilute solutions can be used [675]; e.g. in the titration of *o*-chloroaniline (Fig. 86).

The most convenient wavelength for the measurement of *o*-chloroaniline base and *o*-chloroanilinium ion must be determined empirically; this wavelength, e.g. 312 mμ, is then used for the titration (Fig. 87). As titration proceeds, the absorbance decreases (Fig. 86). In the case of heterocyclic bases, such as quinoline or 8-chloroquinoline, the absorption maximum of the acid form ('onium ion) occurs at a somewhat higher wavelength than the one selected for the base. During titration therefore, the value of A increases (cf. Fig. 75) although the position of the absorption maximum scarcely changes.

Photometric titration of acetylatable aromatic amines can be performed with the standard solution 0·001 M acetic anhydride in pyridine [679].

For photometric titrations of weak bases, acetic acid and acetonitrile are suitable solvents [404]. The volume of the solution is 100–110 ml containing 0·5–2·5 m.e.q. of a monofunctional base. Since 0·5 N perchloric acid is employed as a standard solution, dilution can be neglected as a source of error and corrections are unnecessary. If the measured absorption increases during the titration the spectrophotometer is set at zero absorption before the standard solution is added. If the absorption decreases during the titration, a cuvette containing pure solvent is placed in the light path; the instrument is then re-zeroed and the solvent replaced

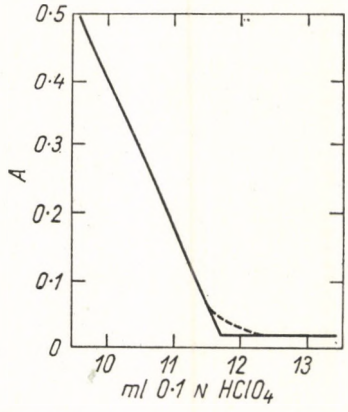


Fig. 86. Photometric titration of *o*-chloroaniline (312 mμ) according to Reilley and Schweizer [675]

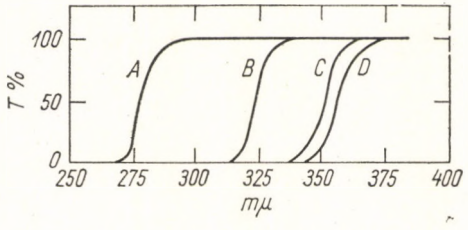


Fig. 87. Change of light transmittance according to Reilley and Schweizer [675]. — *(A)* *o*-Chloroanilinium ion, *(B)* *o*-Chloroaniline (5×10^{-4} N), *(C)* Quinoline (5×10^{-4}), *(D)* Quinolinium ion

by the compound to be tested. It is better if absorption decreases during titration, because errors due to dilution and extraneous light are smaller [277]. Most aromatic amines show a decreasing absorption if the wavelength chosen is on the long wavelength side of the absorption peak of the basic form. In the course of protonation the absorption is decreased and the maximum is shifted towards a shorter wavelength.

Bases whose aqueous pK values are less than 10, cannot be determined by photometric titration in acetic acid since they are totally or partially present in a proton-

Table 28

SUGGESTED WAVELENGTHS FOR THE PHOTOMETRIC TITRATION OF A SOLUTION OF BASES OF 10^{-2} M IN ACETONITRILE OR ACETIC ACID; LENGTH OF LIGHT PATH 5 CM AND STANDARD SOLUTION 0·5 N PERCHLORIC ACID [404]

Compound	p*K*	*In Acetonitrile* (mμ)	*In Acetic Acid* (mμ)
N,N-Diethylaniline	7·5	337	
N,N-Dimethylaniline	8·9	334	
Aniline	9·4	319	
p-Chloro-N,N-diethylaniline	9·5		342
p-Chloroaniline	10·0	333	327
m-Chloroaniline	10·5	325	
N,N-Dimethyl-*m*-nitroaniline	11·0		518
8-Chloroquinoline*	11·2		380
5-Nitro-1-naphthylamine	11·2	555	555
o-Chloroaniline	11·4	324	320
m-Nitroaniline	11·5		464
2-Methyl-5-nitroaniline	12·0		470
2,4-Dichloroaniline	12·2		335
N,N-Dimethyl-*p*-nitroaniline	12·5		470
2,5-Dichloroaniline	12·8		328
p-Nitroaniline	13·0		448
2-Chloropyridine*	13·3		294
4-Methyl-2-nitroaniline	13·5		520

* Absorbance increases in the course of measurement.

ated form. In this case they are dissolved in acetonitrile whose proton-donor readiness is slight. For the titration of extremely weak bases, e.g. *p*-nitroaniline (p*K* 13·0), 4-methyl-2-nitroaniline (p*K* 13·5) acetic acid is more suitable. Regarding *o*-nitroaniline (p*K* 14·3), see: [484].

(e) *Differentiating titration of bases.* Compounds of very similar base strength can also be titrated photometrically in a single mixture. A case in point is the mixture of 2-methyl-5-nitroaniline and 4-methyl-2-nitroaniline where the weaker base absorbs at the selected wavelength (522 mμ [404]) (Fig. 88). The reverse of this is observed

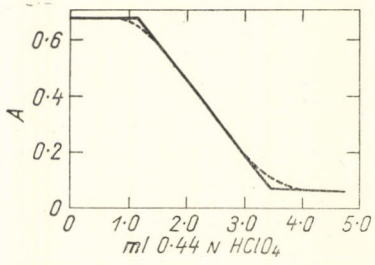


Fig. 88. Photometric titration of 0·5 m.eq. 2-methyl-5-nitroaniline and 1·0 m.eq. 4-methyl-2-nitroaniline in acetic acid at 522 mμ, according to Hummelstedt and Hume [404]

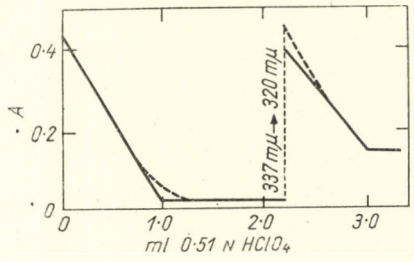


Fig. 89. Photometric titration of 0·512 m.eq. N,N-diethylaniline and 1·104 m.eq. aniline in acetonitrile, according to Hummelstedt and Hume [404]

in the solution of aniline (pK 9·42, 290 mμ) and N,N-diethylaniline (pK 7·48, 310 mμ) in acetonitrile. The stronger base absorbs at the longer wavelength but after protonation the absorption is shifted towards the shorter wavelength and after obtaining the first transition point (at a wavelength of 337 mμ) the apparatus is adjusted to record at a shorter wavelength and the titration continued (Fig. 89).

With more than three components and Δ pK < 1·5 differentiating titrations of bases cannot be performed in acetic acid. As acetonitrile has no levelling properties systems of four components can be dealt with.

(f) *Photometric titration of amine hydrochlorides.* In the titration of quinine hydrochloride, without the addition of mercury(II) acetate, one equivalent of perchloric acid is consumed in acetic acid medium, but in nitromethane, in the presence of mercury (II) acetate, quinine hydrochloride behaves as a bifunctional amine (cf. Chapter 24; Section 136). Quinine hydrogen perchlorate does not dissolve in acetic acid but is soluble in nitromethane [209]. A 0·5% solution of methylene blue in acetic acid is a suitable indicator and in the B. Lange colorimeter a filter with 550–580 mμ band width can be used. This example is of interest because the titration curve is irregular (Fig. 90).

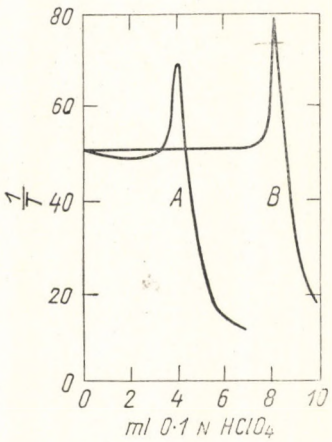


Fig. 90. Photometric titration of quinine hydrochloride according to Ellert, Jasinski and Marcinkowska [209]. — *(A)* As monofunctional base in acetic acid medium, *(B)* After adding mercury(II) acetate, as bifunctional base in nitromethane. In both cases in the presence of methylene blue (550–580 mμ)

(g) The *photometric titration of phenols* is a far more difficult task than that of bases and also less data are available in the literature. A suitable solvent is butylamine [570]. Solvents containing keto groups absorb strongly in the ultraviolet region and can, therefore, be employed only in the visible range. Of the solvents containing alcoholic functional groups, isopropanol proves to be useful. The Beckman Model DU spectrophotometer is a suitable device for titrations in the ultraviolet range [405]. The solution to be determined is protected from atmospheric carbon dioxide by a stream of nitrogen. As a standard solution, 0·4 N tetrabutylammonium hydroxide in isopropanol containing 10–15% methanol is suitable.

The composition of the standard solution and the formation of the phenol-phenoxide complex are the two factors which influence the result of measurement. The standard solution must not contain any contaminants of weak basicity such as carbonate. In isopropanol, phenol is strong enough to convert CO_3^{2-} to HCO_3^- but 2,4,6-trichlorophenol also reacts with HCO_3^-; reaction between pentachlorophenol and HCO_3^- ion is quantitative. It thus becomes apparent that the normality of the

standard solution is influenced both by carbonate contamination and by the acid strength of the standard substance. If a standard solution of Bu_4NOH is standardized against a weak acid and used for the titration of mixtures containing stronger acids, a lower result is obtained for the component of stronger acidity and a higher result is obtained for the component of weaker acidity though the total acid content may

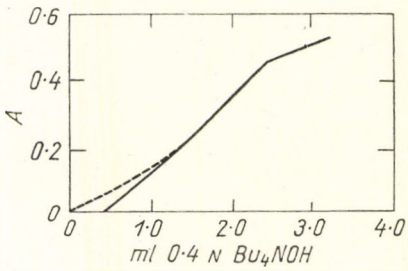


Fig. 91. Photometric titration of 1·012 m.eq. phenol (329 mμ) according to Hummelstedt and Hume [405]

be correct. Thus, when the standard solution of Bu_4NOH is employed for the titration of phenol it must first be run through an anion exchange column (Chapter 10; Section 57).

The absorption of the phenoxide ion is at a longer wavelength than that of the phenol. The wavelength selected should be near the slope of the longer wavelength of the phenoxide ion's absorption peak. Thus *theoretically* a photometric curve of linearly increasing absorption is obtained. However, in Fig. 91 it can be seen that

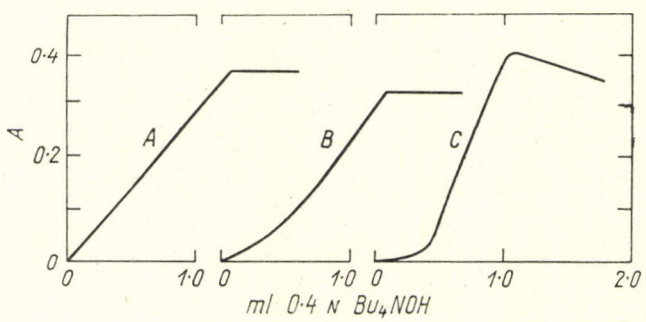


Fig. 92. Photometric titration curves of *m*-nitrophenol according to Hummelstedt and Hume [405]. — *(A)* 0·503 m.eq. In a mixture of isopropanol and ethanol (5 : 105) at 353 mμ, *(B)* 0·503 m.eq. In a mixture of isopropanol and benzene (5 : 105) at 560 mμ, *(C)* In benzene at 560 mμ

the titration curve is not linear and also it rises after the equivalence point; this can be attributed to the absorption by the titrant. Non-linear titration curves are characteristic of most phenolic compounds.

It is known that the phenoxide anion and phenol form a complex of H-bonded character (cf. Chapter 12; Section 63 (d)). In inert solvents the stability of the complex increases and the titration curve is less linear (Fig. 92). In the case of *o*-nitrophenol, complex formation does not occur because phenol-phenoxide complex formation is precluded by intramolecular hydrogen bonding (Fig. 93).

It is theoretically interesting that phenol-phenoxide complex formation is revealed much more clearly by photometric than by electrometric titration. In potentiometric titrations the inflection observed at the half-neutralization potential is influenced by the small difference between the acid strength of phenol and that the of phenol-phenoxide complex, and in conductometry by the dissociation constant of the two ion-pairs; in photometric titrations, however, the extent of absorption is directly correlated with complex formation. The intensity of ultraviolet absorption is influenced by hydrogen bonding without any change of wavelength [233, 234, 235].

The spectral characteristics of substituted phenols are not favourable for differentiating photometric titrations: stronger acids generally absorb at a longer wavelength than weaker ones. The absorption of a subsequent component is influenced by the earlier titration of the stronger phenol. This difficulty can be surmounted by chang-

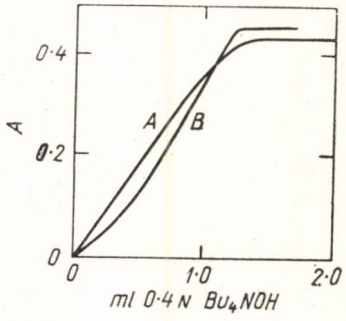


Fig. 93. Photometric titration curve of *o*- and *p*-nitrophenol according to Hummelstedt and Hume [405]. — *(A)* *o*-Nitrophenol in mixture of isopropanol and benzene (5:105) at 545 mμ, *(B)* *p*-Nitrophenol at 490 mμ

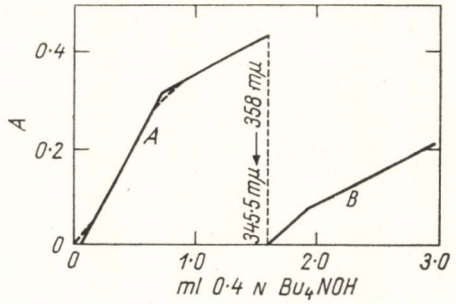


Fig. 94. Photometric titration of phenol mixtures according to Hummelstedt and Hume [405]. — *(A)* 0·291 m.eq. of 2,4,6-trichlorophenol (358 mμ), *(B)* 0·484 m.eq. of 2,4-dichlorophenol (345·5 mμ)

ing the selected wavelength of the spectrophotometer after the first inflection point and by enlarging the slit. A case in point is the titration of 2,4,6-trichlorophenol (p*K* 6·0, A) and 2,4-dichlorophenol (pK_a 7·7, *B*) (Fig. 94). The differentiating titration

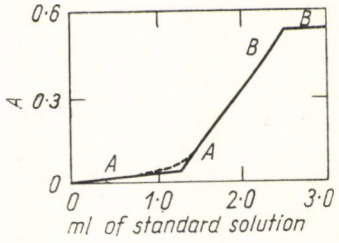


Fig. 95. Photometric titration of phenol mixtures according to Hummelstedt and Hume [405]. — (*A*) 0·509 m.eq. of *p*-nitrophenol and (*B*) 0·503 m.eq. of *m*-nitrophenol (555 mμ)

of *m*- and *p*-nitrophenol is more satisfactory: the anion of the stronger *p*-nitrophenol (p*K* 7·1) absorbs at a shorter wavelength than the *m*-nitrophenoxide anion (*m*-nitrophenol p*K* 8·3), therefore a change of wavelength during titration is not necessary (Fig. 95). Generally 0·3–0·55 m.eq. of phenolic compounds are titrated in 100 ml solvent (Table 29).

81. Suitable Apparatus for Photometric Titrations

The apparatus used for photometric titrations may be a spectrophotometer such as the Beckman Model B [277], or Coleman Model 14 [275], and for measurements in the ultraviolet the Beckman Model DU quartz spectrophotometer [86, 404, 675]. As regards photometers with colour filters (e.g. B. Lange colorimeter Model IV) see: [209]; or the Evelyn colorimeter [141].

The cell carrier as well as the cover and floor of a Beckman Model B (320–1,000 mμ) are removed and a magnetic stirrer and a titration beaker of about 150 ml inserted in their place [277]. The inside of the box inserted to replace the cell compartment should be painted with non-reflecting black paint. A 5 ml microburette is employed, so that its jet extends into the solution. The lower part of the microburette (between the cover and the graduation) should also be coated with black to avoid, as far as possible, the penetration of extraneous light. The titration beaker should be fixed as firmly as possible because the slightest movement may cause considerable changes in optical characteristics.

The standard 10 cm metal cover of the cuvette holder in the Beckman Model DU spectrophotometer must be replaced by a cover with a hole provided for the insertion of the burette and another one for a nitrogen stream. For measurements in the visible range, down to 240 mμ, 150 ml borosilicate beakers and those of Vycor glass (grade 7910, Corning Glass Works) can be used; the latter take the place of the cuvette holder. Drilled sponge rubber sheets serve for the exact positioning of the beakers and a magnetic stirrer is used for mixing the solution [404].

The Sargent–Malmstadt Automatic Spectro-Electro Titrator Model SE (E. H. Sargent & Co) is very suitable for photometric titrations, permitting the use of any

Table 29

SUGGESTED WAVELENGTHS FOR THE PHOTOMETRIC TITRATION OF A SOLUTION OF PHENOLS OF 10^{-2} M IN ISOPROPANOL. STANDARD SOLUTION: 0·4 N Bu_4NOH [405]

Compound	p*K*	mμ *(Cross-section of the Cuvette 5 cm)*
Pentachlorophenol	4·0	387
2,4-Dinitrophenol	4·0	507
2,4,6-Trichlorophenol	6·0	360
p-Nitrophenol	7·1	495
o-Nitrophenol	7·2	541
2,4-Dichlorophenol	7·7	351
2,4-Dibromophenol	7·7	359
m-Nitrophenol	8·3	570
o-Chlorophenol	8·4	337
o-Bromophenol	8·4	342
m-Chlorophenol	9·0	333
p-Bromophenol	9·3	342
p-Chlorophenol	9·4	341
1-Naphthol	9·5	408
2-Naphthol	9·7	408
Phenol	9·9	329

indicator by an automatic control and also allowing potentiometric end-point detection [537, 538, 540]. The six filters are of the interference type and cover the wavelength range 370 – 650 mμ. Beakers of 30 – 600 ml capacity are used as titration cells.

The Stone Automatic Titrator (E. Leitz Inc., New York) gives excellent results when there is a sharp colour change at the end-point.

The Quéré Titrator (H. Tinsley & Co. Ltd., London) may be adapted to record photometric titration curves and chromatograms.

The CENCO Titrator (Central Scientific Co., Chicago) is an automatic photometric titrator: the delivery of titrant is stopped when the transmission of the solution reaches a set value.

The Photometric Titration Assembly TTA 4 (Radiometer A/S, Copenhagen) uses polychromatic light and has a photoresistor of the CdS type as detector in a simple bridge system coupled to Radiometer Titrator Type TTT 1 or TTT 11 and Titrigraph Type SBR 1 or SBR 2.

Apparatus for simultaneous potentiometric and spectrophotometric titrations: [137]. A simplified apparatus for photometric titration is described by Agazzi and Bond [1]. The titration unit consists of a phototube and light source enclosed in glass tubes so that they can be immersed in a 250 ml beaker.

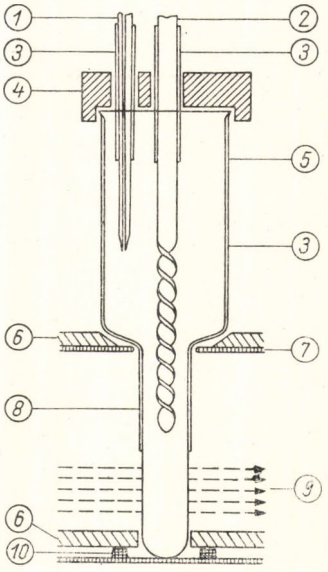


Fig. 96. Titration cell for photometric titration according to Goddu and Hume [275]. — *(1)* Microburette tip, *(2)* Stirrer, *(3)* Painted black, *(4)* Bakelite cover, *(5)* 150–200 ml beaker, *(6)* Wooden support, *(7)* Top of the instrument, *(8)* 15–24 mm tubing or a rectangular tube 18 × 30 mm [86], *(9)* Light path, *(10)* Guide bars

Various types of cuvettes can be employed: Fig. 96 [86, 141, 275, 552, 553, 659, 824]; Fig. 97 [789]; Fig. 98 [364]; the circulating Erlenmeyer and the Bausch & Lomb Spectronic 20 colorimeter are shown in Fig. 99 [670].

The sensitivity of the different methods is enhanced if an apparatus holding double photocells is used for measuring the absorption of the acidic as well as that of the basic indicator form [232].

Among the *factors influencing accuracy* mention should be made of the dilution of the initial solution during the addition of the standard solution. The change of indicator-concentration with volume change can be corrected by multiplying the measured absorption by $(V + v)/V$ where V is the volume of the initial solution and

v that of the standard solution. The correction, however, is often unnecessary as for example, if 2–3 ml of a standard solution of higher concentration are added to 100–150 ml volume. It goes without saying that when the equivalence point is plotted graphically, the volume of the standard solution represented on the x axis has to be multiplied by the factor of the titrant: $f(V)$.

During the titration, the *homogeneity* of the solution must be ensured by mechanical stirring (by means of a magnetic stirrer or by the bubbling through of inert gas) but without preventing radiation from passing through the solution. A cylindrical

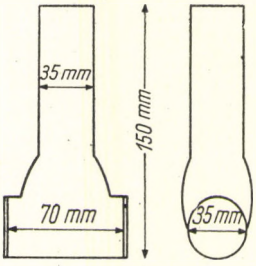


Fig. 97. Titration cell for photometric titration according to Sweetser and Bricker [789]

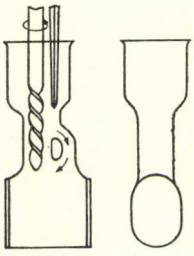


Fig. 98. Titration cell for photometric titration according to Havemann [364]

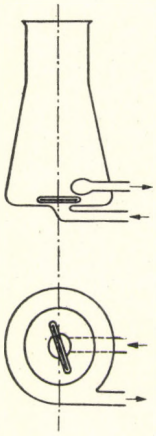


Fig. 99. Circulating Erlenmeyer flask for photometric titration according to Rehm, Bodin, Connors and Higuchi [670]

titration vessel should be placed in a cuvette of bigger size and with parallel walls containing a solvent of refractive index identical with that in the titration vessel [200].

A steady temperature should be maintained during titration.

Regarding the chosen wavelength, the following aspects must be taken into consideration: elimination of the disturbing effect of light-absorbing compounds that are not to be measured; the maximum light absorbance must remain within the measuring range of the apparatus, since high absorbance may be a serious source of errors. In the case of photometric titration curves where the point of intersection of the two straight lines is rounded off considerably, negative errors may arise on extrapolation.

An objective method of end-point calculation has been described by Grunwald [293].

Chapter 15

Determination of Acidic Substances

The determination of donor acids containing dissociable hydrogen atoms is discussed in this chapter. The dissociation constant (in water) of aromatic acids containing a carboxyl group is smaller than that of mineral acids and most of them have only a slight solubility in water. The strength of carboxylic acids containing a nitro-group in a *para*-position and that of sulphonic acids approaches the strength of mineral acids.

The functional group R. CO. OH is characteristic of carboxylic acids; equilibrium exists between its ionized and non-ionized form:

$$R-CO-OH \rightleftharpoons [R-COO]^- + H^+ \qquad (H = \text{ionizable hydrogen atom})$$

Their determination is based on the neutralization by alkali metal alkoxide, quaternary ammonium hydroxide (alkoxide) and compounds containing an amino group in inert or basic solvents or solvent mixtures. The end-point is determined either by indicators (visually or photometrically) or by electrometrical methods.

A titration in which the active *hydrogen atom* is a component of an *enol*, *imide*, *phenol* or some other proton donor group can also be regarded as a neutralization reaction. Compounds containing one of these groups are donor acids while those containing an acetyl cation or a partly polarized aromatic ring are acceptor acids. Examples of the latter are acetyl chloride and *m*-dinitrobenzene (Chapters 16 and 20). All these are called *acid analogues* and their determination is discussed in Chapters 16–21.

The choice of solvent depends on the solubility of the compound and its relative acid strength. When carboxylic acids are titrated, previous knowledge of the probable acid strength is advisable (Chapters 2 and 4); in a given solvent, the correct colour change of the indicator must be determined absolutely against a pure substance preferably by potentiometric control (Chapter 12).

Methanol, ethanol and isopropanol were formerly employed for the determination of organic acids in order that the solution should always remain as homogeneous

as possible, even if the titrant were aqueous alkali. Ethanol was used as a solvent for the determination of higher fatty acids 40 years ago [67].

The colour change of some indicators in ethanol is as follows (standard solution: sodium ethoxide in ethanol):

Indicator	*'Acidic Colour' → 'Alkaline Colour'*
Bromophenol blue, 0·1%	Yellow → green → blue
Methyl violet, 0·1%	Violet → colourless
Phenolphthalein, 1%	Colourless → red
Thymolphthalein, 1%	Colourless → blue

Sharpness of colour change can be enhanced by the indicator-mixture: thymolphthalein-methyl orange [709]: (cf. Table 25).

Later, alcohol was replaced by inert solvents and solvent mixtures such as acetone, chloroform, benzene, benzene-isopropanol, and instead of an aqueous standard solution, alcoholic alkali or alkali metal alkoxide were employed. Salts of weak acids undergo alcoholysis to a smaller extent than hydrolysis so that the colour change of the indicator is generally sharper.

In a further stage of development, the use of quaternary alkylammonium bases seemed preferable to that of alcoholic alkali or alkali metal alkoxide since the salts of the former with carboxylic acids, unlike those of alkali metals, dissolve in inert solvents.

For the determination of weak acids and acid analogues, basic solvents such as dimethylformamide, pyridine, n-butylamine and ethylenediamine have also proved to be suitable and for that of a mixture of acids, acetone, isobutyl methyl ketone, t-butanol etc.

Pyridine is one of those basic solvents which permit potentiometric or visual determinations of the relative strength of weak acids [780, 782] as well as differentiating titrations of acid mixtures [159]. It is characteristic of potentiometric titrations in pyridine that *m*- and *p*-hydroxybenzoic acids show two inflections while the *ortho* derivative has only one, demonstrating that in the latter only the $-COOH$ group is titratable (Fig. 100). For routine analysis of a great many samples potentiometric titration is time consuming and for this reason the use of indicators for end-point detection became general. Aliphatic carboxylic acids, benzoic acid, salicylic acid, nicotinic acid, *o*- and *p*-nitrophenol, 2,4-dinitrophenol, 2-mercaptobenzothiazole and a number of amino-acids can be titrated in pyridine, in the presence of *thymol blue* with a standard solution of Bu_4NOH. In the presence of *azo-violet* in pyridine, *p*-benzylphenol, 1- and 2-naphthol, 2,5-dimethylphenol, *p*-bromophenol, pyrogallol, phthalimide, salicylaldoxime, succinimide, acetylacetone, *p*-chlorothiophenol, benzylthiol and 5-amino-2-benzimidazolthiol can be determined as monofunctional acid analogues. In the presence of *azo-violet* two equivalents of standard solution are also consumed by *m*- and *p*-hydroxybenzoic, oxalic, malic, malonic, maleic, fumaric, succinic, phthalic and citric acids.

As regards the use of a standard solution containing piperidine or diethanolamine in pyridine see: [815].

Because of its numerous suitable properties *dimethylformamide* is one of the most widely used basic solvents. Many authors have dealt with titrations of acids and acid analogues in dimethylformamide [7, 113, 159, 176, 246, 448, 457, 562]. Most compounds containing phenolic hydroxyl can be titrated in dimethylformamide especially if they contain an electrophilic substituent enhancing the acidic character [176, 251]: e.g. $-CHO$, $-COR$, $-COOR$, $-CONH_2$ and $-NO_2$. The $-COOH$ group does not have the effect of increasing acid strength, characteristic of the above sub-

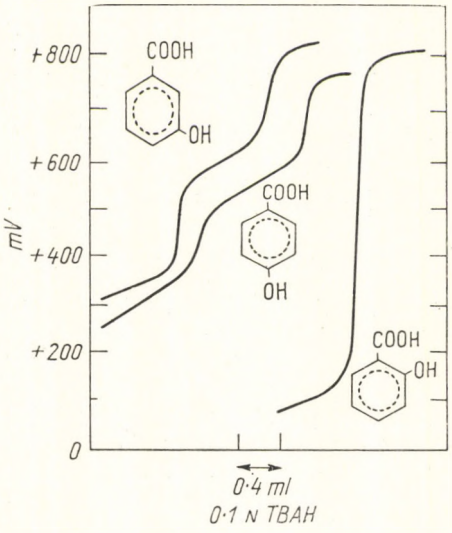


Fig. 100. Potentiometric titration curves of hydroxybenzoic acids according to Cundiff and Markunas [159]

stituents: e.g. the phenolic hydroxyl of salicylic acid contains a less active hydrogen. In certain cases dimethylformamide is also suitable for differentiating titrations. Thus by using platinum-calomel electrodes the titration of binary systems such as phthalic anhydride-monomethyl phthalate, oleic acid-monomethyl phthalate, oleic acid-phthalic anhydride can be achieved [457]. Regarding differentiating titration of acid mixtures see: Section 95 of this chapter. Concerning high-frequency titrations of acids and acid analogues in dimethylformamide see: [177, 441, 664].

Of the 'inert' solvents, *acetone* has proved to be suitable for routine analysis; in addition, it is easily available, cheap and can be readily purified [258]. As it has scarcely any acidic properties even very weak acids can be titrated in acetone and because of its slight basicity its levelling effect is insignificant. It is a widely used solvent in differentiating titrations [258] though in this respect ethyl methyl ketone [359] and isobutyl methyl ketone [105] are more suitable. The electrodes usually employed in potentiometric titration can also be used since a sufficiently great dielectric constant allows the observation of stable potentiometric inflections during titration. Strong acids and bases, however, react with acetone.

Carboxylic acids. Compounds containing enolic and phenolic hydroxyl, sulphonamide derivatives, acid analogues containing an imide group etc. can be titrated in acetone [258]. Tetrabutylammonium hydroxide or tri-n-butylmethylammonium hydroxide are suitable standard solutions. A solution of the latter in benzene-isopropanol (4 : 1) is very convenient for potentiometric titrations if platinum (containing 10% rhodium) is used as an indicator and graphite as the reference

electrode [540]. Extremely weak phenols can be titrated either by use of indicators or photometrically in an acetone medium in the presence of azo-violet. Other solvents can also be used, if, near the end-point, the solution contains at least 90% acetone. (See: Table 23.)

The differentiating properties of *acetonitrile* resemble those of acetone. In favourable cases, e.g. with a mixture of mandelic acid and 2-acetyl-1-naphthol, acid functions can be titrated with potassium methoxide.

The colour transition of the indicator *p*-hydroxyazobenzene from colourless to yellow makes the determination of acid carboxyls possible, and a subsequent titration in the presence of *azo-violet* that of phenolic hydroxyls. The colour change in the latter case is from orange → yellow → blue → green. The mixture can also be differentiated by potentiometric titration [251].

Glycol monomethyl and monoethyl ether (Methyl Cellosolve ®, Cellosolve ®) are frequently used solvents [330, 692], either alone or mixed with other solvents such as isopropanol, xylene, anisole, acetone, dioxan, n-butanol, etc. The compositions of the mixtures must be determined experimentally. This, however, also depends upon whether the acid is to be titrated potentiometrically or by use of an indicator. More rarely used solvents are benzyl alcohol and 1-phenylethanol. These are employed for the determination of acidic groups in polymers such as polyamides, polyethylene terephthalates, polyaminocaproic acids etc. [650, 714, 723, 858]. Titration is usually performed in hot solvents.

A basic principle to be observed is that the solvent should not contain any acidic or basic contaminants and that, before titration, atmospheric carbon dioxide should be neutralized by the standard solution. The substance to be tested is then dissolved in sufficient amount for 5–8 ml of the standard solution of 0·05–0·1 N concentration to be consumed. The solution of the substance for visual titrations should be in a volume of 20–30 ml while for potentiometric end-point detection the volume should be 25–50 ml. Hence the composition of the solvent changes only slightly. When changes of the dielectric and other properties are undesirable during titration, a smaller sample and a more concentrated standard solution in a micro-burette are used (cf. Chapter 14). The quantity of the sample should be so chosen that the standard solution consumed should not exceed 10% of the volume of the solvent.

It has proved difficult to find suitable solvent mixtures for the potentiometric determination of the acid content of highly coloured industrial and natural products. Lykken and co-workers found only two out of about 40 solvents and solvent mixtures suitable for the determination of the acid content of petroleum lubricants, vegetable and animal oils, waxes, fats, asphalt and bitumen derivatives, tar distillates and natural and synthetic resins. A mixture of benzene–isopropanol or petroleum–isopropanol (1 : 1) containing about 0·5% of water was found to be most suitable [530].

The choice of the solvent may be critical for the reproducibility of the determination. Thus for example when the acid number of vegetable and train oils is determined with potassium hydroxide in neutralized isopropanol in the presence of phenolphthalein, the accuracy of the titration is ±0·025 m.eq., but when measured potentiometrically it is ±0·043 m.eq. [9].

82. Aliphatic Acids

Weigh the fatty acids in such amount that a max. of 9–10 ml of 0·05 N standard solution should be consumed, and dissolve in 10–20 ml of absolute ethanol. Add 5 drops of thymolphthalein and 3 drops of methyl orange as indicator (Table 25), and after warming on a water bath to 65°C, titrate from a burette graduated in 0·05 ml with 0·05 N sodium ethoxide in ethanol till the first green colour appears (comparative solution: 20 ml of ethanol and 3 drops of methyl orange as indicator). The solvent's consumption of standard solution must be taken into account under identical circumstances. The standard solution is standardized against pure stearic acid [709]. (See: Chapter 10; Section 55.)

Fatty acids of higher carbon number can also be determined in benzene-methanol, n-butylamine and acetone as solvents with 0·1 N sodium methoxide in the presence of thymol blue [252]. *Oleic acid* can be determined in ethanol with potassium hydroxide in ethanol.

Determination of the basicity of commercial zinc stearate [527]. Weigh out 1 g of zinc stearate of commercial quality and dissolve in 50 ml of ethanol neutralized in the presence of phenolphthalein. Add25 ml of ethanolic oleic acid of 0·1 N concentration and boil for 30 min under reflux. After cooling the solution with ice, filter rapidly and wash the precipitate with neutralized ethanol. Titrate the oleic acid which was not consumed by basic zinc stearate, with 0·1 N potassium hydroxide in ethanol in the presence of phenolphthalein. A blank test is performed in a similar way.

It is advisable to determine the neutralization equivalent of fatty acids of higher molecular weight on a semimicro-scale by dissolving in a solution containing an excess of sodium methoxide of adequate normality e.g. 0·01 N and by back-titrating the excess of alkali with a standard solution containing oxalic acid [807]. Micro method: [808].

Weigh out about 10 mg of the fatty acids (a small Pyrex measuring vessel is usually used for the weighing). Transfer the sample together with the small measuring flask into a 150 ml conical titrating flask of heat-resistant glass with provision for the introduction of nitrogen gas. The fatty acid is dissolved in a mixture of 5 ml of methanol and 15 ml of benzene. In order to free the system from air it is swept out for two minutes by a stream of washed nitrogen; 4–5 drops of an indicator mixture (see below) and 10 ml of 0·01 N sodium methoxide in benzene-methanol are added. The latter is prepared similarly to the solution of 0·02 N concentration described in Chapter 10; Section 56 (b).

The excess alkali metal alkoxide is then back-titrated with a solution of 0·01 N oxalic acid in methanol-benzene to the transition from green-blue to yellow. A blank test is performed in a similar way. During titration the system must be protected from atmospheric moisture and carbon dioxide (for example, see apparatus in Figs 39, 40, 41 and 42).

The normality of the standard solution of potassium methoxide is standardized against oxalic acid. *Indicator mixture:* immediately prior to titration a 3 : 1 : 1 mixture is prepared from 0·4% solutions of phenol red, cresol red and bromothymol blue in methanol. *Preparation of* 0·01 N *oxalic acid in benzene-methanol:* 126 mg of oxalic acid dihydrate is dissolved in 10 ml of methanol and the volume made up to 100 ml with benzene.

This method is suitable for the determination of the neutralization equivalent of lauric, myristic, palmitic, stearic, oleic and linolenic acids.

83. Substituted Aliphatic Acids

Potentiometric indication is employed when the colour of the solution changes and darkens during titration, and especially when the transition at the end-point becomes sluggish or imperceptible. This may occur in the case of raw wool fat and also with substituted fatty acids such as 12-oxo-stearic, 9,10-dihydrostearic, 9,10-epoxystearic, aminostearic, 1-bromo- and mercapto-palmitic acids [665].

Weigh from the sample the amount needed to consume 6–8 ml of standard solution and dissolve this in a mixture of 50 ml benzene-methanol (3 : 1). Protect the system from atmospheric carbon dioxide. For this purpose the titration flask used by *Ogg* and co-workers for the determination of the carboxyl number of fatty acids is suitable. This is, in essence, a 250 ml ground-glass Erlenmeyer type flask in the side arms of which the antimony (indicator) and calomel (reference) electrodes are inserted [252, 616]. The electrodes are previously 'swollen' for 30 min in benzene-methanol: 0·2 g of lithium chloride are added to the solvent mixture as supporting electrolyte. After solution of the sample and the lithium chloride (that is after 10–15 min) the titration is performed with 0·1 N sodium methoxide using a magnetic stirrer. The standard solution is standardized under identical circumstances against pure palmitic, benzoic or phenylquinoline carboxylic acid. (Chapter 10; Section 56 and Chapter 15; Sections 86 and 88).

84. Saponification Numbers

Potassium hydroxide of 0·5 N concentration in glycol monoethyl ether-xylene is very suitable for the determination of the saponification (ester) numbers of fats and waxes, e.g. cotton seed, sesame, castor oil or coconut, hoof and fish oils [330]. Saponification can be accomplished in 10 min, on a steam bath in an open flask. For back-titration of the excess of potassium hydroxide, 0·5 N hydrochloric acid in methanol or glycol monoethyl ether is used with thymolphthalein as indicator.

85. Acid Number of Petroleum Products

In this case the solvent is a mixture of 500 ml of isopropanol to which 3–5 ml of water and subsequently 500 ml of benzene are added. 0·1 N potassium hydroxide in isopropanol is used as standard solution and 1-naphtholbenzeine as indicator (cf. Table 27).

Weigh in a 250 ml flask:

20	g	if the acid number to be expected is		0·0–3·0
2	g	if the acid number to be expected is		3·0–25·0
0·2	g	if the acid number to be expected is		25·0–250

Dissolve the sample in 100 ml of the solvent mixture (this may also be a mixture of light petroleum and isopropanol) and, after adding 3 ml of indicator, titrate at a temperature above 30°C, until the orange-yellow turns to brownish green.

For highly coloured solutions potentiometric titrations must be employed using a glass (indicator) and a calomel (reference) electrode pair [530].

In the case of mineral oils with an acid number below 0·05 no distinct potentiometric inflection point can be observed, hence visual end-point detection and the

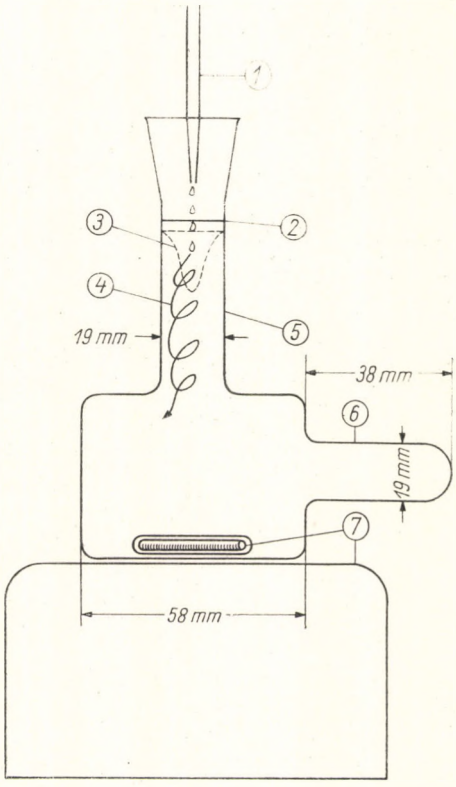


Fig. 101. Titration flask with side arms for the titration of coloured solutions due to Kukin [486]. — *(1)* 5 ml Koch microburette, *(2)* 120 ml calibration mark, *(3)* Vortex created by stirring, *(4)* Path of descending droplets of the titrant, *(5)* Elongated neck, *(6)* Side arm, *(7)* Magnetic stirrer and bar

use of a comparative solution are employed. A suitable apparatus is the titration flask with side-arms which is also a useful device for other titrations [486, 487] (Fig. 101).

When dark or coloured solutions are determined the apparatus shown in Fig. 102 helps observation of the transition [14]: the transmitted light passing through the solution can be observed on the screen as a clear-cut vivid patch of colour. Measurement must be performed in the shade. If necessary a colour filter can be inserted between the light source and the flask. [Determination of acid numbers of dark, colored oils by using lucigenin (dimethyldiacridylium nitrate), a chemoluminescent indicator, see: [889]. The titration is performed in methanol–benzene (2 : 1) medium, using 0·05 N sodium methoxide, ethoxide, butoxide, or sodium isopentyl oxide.]

Concerning burette stop-cocks for titrations in the dark see: p. 151 in [31].

In various sorts of tar and pitch products or in fractions of these obtained by rapid distillation, compounds containing phenolic hydroxyl can be titrated in

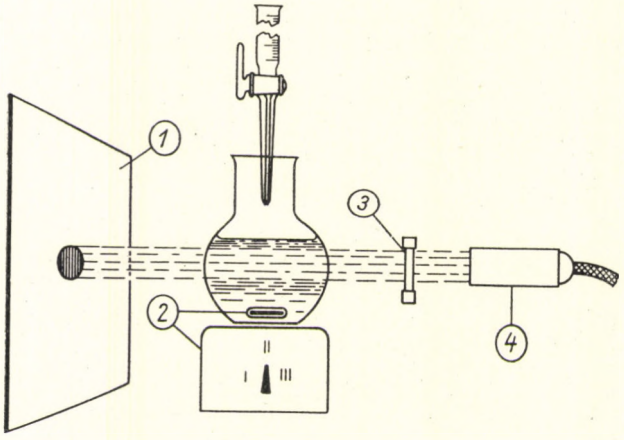


Fig. 102. Equipment for titrations performed in the dark due to Arbuzov, Kuznecov and Pavlov [14].—*(1)* White screen, *(2)* Magnetic stirrer, *(3)* Filter, *(4)* Light source

ethylenediamine, butylamine or pyridine solvent, with 0·05–0·1 N sodium methoxide or sodium aminoethoxide in benzene-methanol, using platinum (containing 10% rhodium)–antimony, antimony–Ag/AgCl, platinum–calomel or antimony–calomel electrodes [287, 486, 492, 530, 661]. In order to eliminate precipitate formation, 2,6-xylenol may be added to the solvent [287].

86. Benzoic Acid and Substituted Benzoic Acids

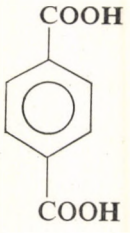
Usually benzene-methanol (10 : 1), pyridine, acetone or dimethylformamide are employed as solvents for the titration of aromatic acids. Conductometric measurements show that carboxylic acids dissolved in benzene are in an almost totally unionized state. However, the sharpness of the visual indication and the steepness of the potentional jump observed at the equivalence point often exceed those in aqueous or alcoholic media. It is a disadvantage of pure benzene that the alkali metal salts formed are precipitated or form a gelatinous mass affecting estimation of the endpoint. In some cases the same happens if acetone or butylamine is employed as solvent. Thymol blue is a suitable indicator in the solvent mixture benzene–methanol, while thymol blue, thymolphthalein, alizarin yellow or azo-violet are used in basic solvents (Tables 22, 23, 24, 26 and 27).

Glass-calomel and also antimony-calomel electrodes in basic solvents are convenient for potentiometric titrations in benzene–methanol (cf. Table 21). During titration the solution should be protected from atmospheric carbon dioxide because of the carbon dioxide sensitivity of the indicators which differs in the case of each solvent. In rapid titrations, errors caused by carbon dioxide are negligible, but in the case of potentiometric determinations, which take a longer time, this must be particularly taken into account and therefore, if possible, a closed system should be used: Figs 39, 40, 41, 42, 45, 52 and 53, and Chapter 21.

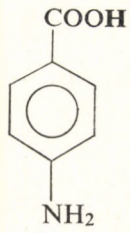
If atmospheric carbon dioxide is swept out and kept away by washed nitrogen, 1–2 mg of acid can be measured with $\pm 2\%$ accuracy by use of a standard solution of 0·02 N tetrabutylammonium hydroxide prepared from a 0·1 N solution by dilution with benzene. The compound to be measured and the standard substance are dissolved in a solvent of identical quality and volume, in nearly equivalent quantity. It is

essential that in every titration the concentration of the indicator should remain constant. This can be achieved by taking 1·0–3·0 ml of a highly dilute indicator solution. If possible, the solvent for the indicator and that for the compound to be tested should be identical.

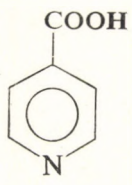
Benzoic acid, *o*-, *m*- and *p*-nitrobenzoic acid, hydroxybenzoic acid, aromatic dicarboxylic acids, aminocarboxylic acids, pyridine carboxylic acids etc. can be titrated in the solvent mixture benzene-methanol. Benzoic acid is suitable for the standardization of basic standard solutions (Chapter 10).



Aromatic dicarboxylic acid



Aminocarboxylic acid



Pyridine carboxylic acid

Undesirable gelatinous precipitates formed by alkali metal alkoxide can be avoided if a solution of TBAH in benzene–methanol or isopropanol is employed (Chapter 10; Section 57). Also, in potentiometric titrations, a more reproducible potential change can be attained with a *carbonate-free* standard solution of TBAH than with alkali metal alkoxide.

In potentiometric titrations in pyridine, with TBAH as standard solution, *m*- and *p*-hydroxybenzoic acid show two inflections, while *o*-hydroxybenzoic acid (salicylic acid) shows only one indicating the equivalence point of the carboxylic group [159]: (Fig. 100 and Chapter 2; Section 16 and Chapter 4). In pyridine, in the presence of azo-violet *p*- and *m*-hydroxybenzoic acid consume two equivalents of TBAH standard solution, while *o*-hydroxybenzoic acid in the presence of thymol blue consumes only one.

For the comparison of acid strength of benzoic acid derivatives see: Tables 1, 2 and 8.

Nicotinic acid and isonicotinic acid (pyridine-4-carboxylic acid), can be titrated with sodium methoxide in benzene and pyridine, respectively [832].

87. Testing of Pharmaceutical Preparations

The active acidic or basic therapeutic agents in tablets and powders can be directly titrated in non-aqueous media if other acidic or basic vehicles do not interfere with the determination (Table 30). The *finely powdered* tablet is suspended in a suitable solvent and titrated; in the case of acids and acid analogues, with alkali metal alkoxide or alkylammonium hydroxide; in the case of bases, with perchloric acid. The disturbing effect of, for example, stearic acid can be avoided if the finely ground powder is previously extracted with *light petroleum or n-hexane*. The majority of compounds containing polar functional groups, and salts of carboxylic acids, base hydrochlorides (sulphates etc.) do not dissolve in these solvents. Magnesium stearate dissolves in acetic acid as acetate. In such a case the powdered sample is suspended in purified acetic acid, occasionally with gentle heating, and titrated with perchloric acid. To this solution, a neutralized 3% solution of mercury(II) acetate in acetic acid is added and in this way a non-dissociable mercury(II)

halide and a free base (acetate) are formed from the base hydrochloride. The base is then titrated with perchloric acid. The perchloric acid titration of the therapeutic agent is affected to different degrees by the vehicles of the tablets. The extent of the disturbing influence depends upon the solvent used: being smaller in chloroform and greater in acetic acid [133]. (Table 30.) (Perchloric acid consumption of saturated solutions of the compounds in 50 ml of chloroform or acetic acid is listed in the table. Titrant consumptions of more than two millilitres are not shown.) The molar ratio of the base hydrochloride present in the tablet as active agent to magnesium stearate should, if possible, be not less than 40—50, since otherwise very variable and erroneous results may occur, especially in the solvent mixture chlorobenzene- acetic acid and when using a visual indicator, e.g. tropaeolin 00.

The active agent content of *injections* can be determined by solution and titration of the dry substance in non-aqueous solvents. This method, however, can only be employed if the active agent does not undergo decomposition under the influence of heat and water. Some buffer substances have a disturbing effect; thus sodium citrate can be titrated in acetic acid as a base and also, in a basic solvent, as an acid.

The active agent content of water-free ointments whose base is petroleum jelly or liquid paraffin can be determined without evaporation. The ointment is dissolved in a solvent mixture, depending upon the properties of the compound to be determined (the agent), e.g. in a mixture of polyethylene glycol '400'- chloroform or acetic acid–toluene.

Regarding assays of the active agent content of suppositories (morphine-HCl, papaverine-HCl, pyramidone) see: [367].

The active therapeutic agents of pharmaceutical preparations must often be extracted in the presence of accompanying disturbing substances in a glass-stoppered Erlenmeyer-type flask by rotatory movement for 30—180 min, or in a Napoli–Schmall separatory funnel [609], or, if the active agent is not heat-sensitive, in a Soxhlet apparatus. The Napoli–Schmall extractor

Table 30

PERCHLORIC ACID CONSUMPTION BY TABLET EXCIPIENTS IN ML OF 0·05 N $HClO_4$ [133]

Excipient	*In Chloroform*	*In Acetic Acid*
Beeswax	0	0
Calcium carbonate	0	0·13
Calcium phosphate, dibasic	0·04	> 2·00
Calcium phosphate, tribasic	0	0·58
Calcium stearate	0·06	> 2·00
Calcium sulphate	0	0·70
Carnauba wax	0	> 2·00
Cetyl alcohol	0·02	0
Gelatine	0	> 2·00
Lactose	0	0·02
Magnesium carbonate	0	> 2·00
Magnesium oxide	1·06	> 2·00
Magnesium stearate	0·14	> 2·00
Magnesium sulphate	0	0·08
Methyl cellulose	0	0·34
Polyethylene glycol 4000	> 2·00	0·06
Polyvinylpyrrolidone	> 2·00	> 2·00
Sodium alginate	0	0·98
Sodium carboxymethylcellulose	0·06	> 2·00
Sodium silicate	0	> 2·00
Sodium sulphate	0	1·18
Potato starch	0	0·06
Saccharose	0	0
Talcum	0·14	0·50
Tragacanth	0	0·38

is a cylindrical funnel with a sealed in G/3 or G/4 glass filter. After extraction the solution is filtered by vacuum in a suction flask. Extraction of the residue on the filter can then be continued with another suitable solvent.

Light petroleum, n-hexane and ligroin have been found to be the most suitable solvents for active compounds relatively insoluble in water; for compounds of higher water solubility, benzene, chloroform, carbon tetrachloride are the best solvents, and ethyl acetate is suitable for those comparatively soluble in water. It is advisable to distil off the ethyl acetate, then to dissolve the residue in a suitable solvent and to titrate with a non-aqueous standard solution. Concentration

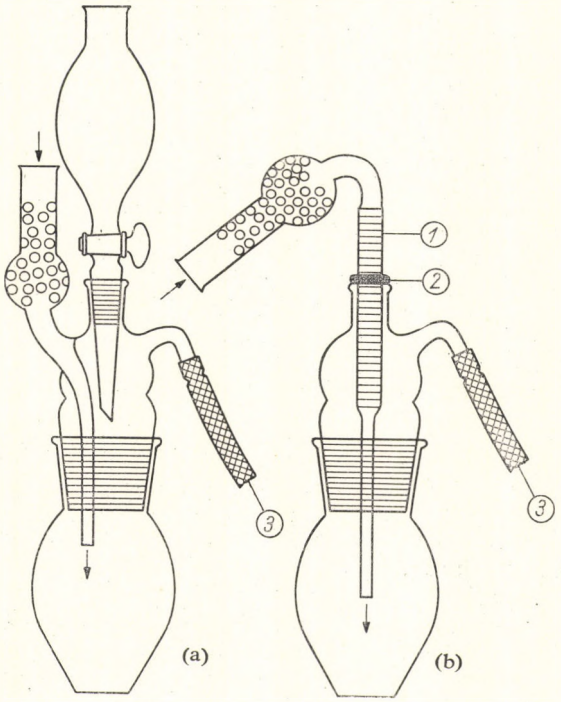


Fig. 103. Evaporating flasks.— *(1)* Cylindrical ground joint, *(2)* Fixing rubber bung, *(3)* Vacuum

is best performed in a conical ground flask in which evaporation of the solvent on a steam bath is promoted by allowing a stream of filtered and dried air to pass through (Fig. 103). In alternative (a) a continuous distillation by means of a charging funnel is shown, while the arrangement represented in alternative (b) allows lowering or lifting of the air-stream inlet tube according to the volume of the solution to be distilled.

The Jacobs–Singer type extractor is a convenient device for the extraction of aqueous solutions by solvents heavier or lighter than water [418]. Its advantage, in contrast to a separating funnel, is that it has no stop-cocks; thus the sample or its solution can be directly measured in the lower part (Fig. 104).

In every case the extract is dried with anhydrous sodium sulphate and in the case of light petroleum or benzene, diluted with carbon tetrachloride in equal proportion, the alkaline active agent is directly titrated with 0·005 N *p*-toluenesulphonic acid in the presence of dimethyl yellow. With benzene, chloroform or carbon tetrachloride extracts it is advisable to add 10–50% v/v of acetic acid (or acetic anhydride or propionic acid) and to titrate with 0·01 –0·001 N perchloric acid. In the case of acids and acid analogues the benzene extract is mixed with pyridine and titrated with a basic standard solution in the presence of thymol blue or azo-violet. Extracts with ethyl ether or ethyl acetate are evaporated on a steam bath by inserting a potassium hydroxide absorbing tube and blowing dry air through it (Fig. 103).

The aqueous solutions of base hydrochlorides (sulphates, ethanesulphonates, phosphates and nitrates) are, extracted in a separatory funnel after making alkaline, with solvents insoluble in water, and are titrated, as described above, with 0·005 N *p*-toluenesulphonic acid or 0·01 N perchloric acid. In the course of extraction, surface tension is increased by adding silicone

oil or octyl alcohol in the presence of emulsifying agents or solubilizing agents such as e.g. polyvinyl alcohol, polyvinylpyrrolidone, Tweens ^{R}, Spans ^{R} etc. Making the aqueous solutions alkaline should not lead to decomposition of the bases (alkaloids). The simplest method is to use saturated potassium bicarbonate instead of potassium carbonate or sodium hydroxide. Buffer solutions are useful because they fix the pH value and also have a salt effect. Selective extractions can also be performed with buffer solutions; thus the active agent can be extracted

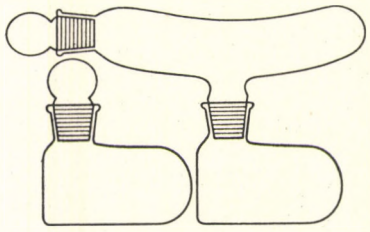


Fig. 104. Jacobs—Singer type extractor [418]. — Capacity of the upper part 100–150 ml; of the lower 25–50 ml. Ground joints are of identical size

at a lower pH, while the decomposition product, especially when it dissolves readily in water, is extracted only at a higher pH or by the joint effect of $KHCO_3 + KCl$ (salt effect).

The Schmall extractor [721, 883] is also an expedient device in the case of tedious extractions and is applicable to solvents heavier or lighter than water. However, it can be replaced by the simpler method using a separatory funnel.

When an emulsion is formed as a consequence of the separatory funnel method a centrifuging extraction is applied. The water-insoluble compound is separated from the aqueous solution containing the active agent as salt, by alkali or sulphuric acid. After extraction with a suitable solvent, it is transferred to a centrifuge and spun for 5–15 min at 3,000–4,000 rev/min. The organic solvent is filtered by suction with a syringe through a funnel containing sodium sulphate into a titrating flask. This procedure is repeated several times. The extract is titrated with perchloric acid or a basic standard solution according to circumstances.

For a summary of the titrations of therapeutic compounds with acid and acid analogue properties see: [24].

88. 2-Phenylquinoline-4-carboxylic Acid

2-Phenylquinoline-4-carboxylic acid can be used instead of benzoic acid for the standardization of alkaline titrants [307]. Suitable solvents are acetone-pyridine (4 : 1), benzene-methanol (9 : 1), benzene-pyridine (2 : 1), acetone-pyridine-methanol (70 : 30 : 2) and pyridine [832] in the presence of thymol blue or azo-violet. On titrating with a standard solution of potassium methoxide no precipitate is observed and the colour change of the indicator is sharper than in the case of benzoic acid: yellow → blue (thymol blue), yellow → red → blue (azo-violet).

Weigh 600–700 mg of phenylquinolinecarboxylic acid and dissolve in 100 ml of neutralized solvent in a measuring flask. 20 ml of the stock solution are titrated either with a standard solution of 0·1 N alkali metal alkoxide or alkylammonium hydroxide until a blue colour change occurs. 120–130 mg may be weighed directly; this consumes about 5 ml of standard solution. 24·93 mg phenylquinolinecarboxylic acid require 1 ml of 0·1 N alkaline solution.

89. *p*-Aminosalicylic Acid (PAS) [124]

Neutralize 50 ml of acetone in the presence of four drops of 0·3% thymol blue to blue, add 80–100 mg of finely powdered *p*-aminosalicylic acid, and after solution,

titrate with 0·1 N potassium hydroxide in alcohol, or potassium methoxide in benzene-methanol until a clear blue colour appears. Pyridine is also a suitable solvent [832]. One ml of a standard solution of 0·1 N concentration is equal to 15·31 mg of PAS.

Determination of PAS in tablets:

Weigh 15–20 finely ground tablets (= 80–100 mg of PAS) in a glass-stoppered Erlenmeyer flask. Add 40 ml of neutralized acetone and extract, either by using a swirling movement or by means of magnetic stirring. After allowing to stand for a few minutes filter by decantation and wash the flask and filter with 3 × 5 ml of neutralized acetone. The combined solutions are titrated as above. As regards disturbing effect of stearic acid see: Section 87.

90. Determination of Acetylsalicylic Acid in the Presence of Phenacetin and Caffeine [883]

The fine powder from tablets equivalent to about 500–600 mg of acetylsalicylic acid is freed from stearine in a glass-stoppered Erlenmeyer flask by extraction with 3 × 30 ml of light petroleum (boiling point = 30–60°C) then filtered through a 9 cm diameter filter paper. The dry powder together with the filter paper is replaced in the flask, and after adding 20 ml of 5% sulphuric acid, extracted with 5 × 40 ml of a mixture of chloroform-ethyl ether (1 : 3). The total extract is dried over sodium sulphate and evaporated nearly to dryness on a steam bath letting a stream of dry air pass through, by means of a suitable evaporating flask e.g. as shown in Fig. 103. The residue is then dissolved in 80 ml of dimethylformamide (neutralized in the presence of thymol blue), poured into a 100 ml measuring flask and diluted to the mark. 20 to 25 ml portions are then titrated with 0·1 N lithium methoxide [646] to blue. Lithium methoxide is less liable than potassium methoxide to form gelatinous precipitates with acids in organic solvents. 18·02 mg of acetylsalicylic acid require 1 ml of 0·1 N solution.

91. Cholic, Deoxy-, and Dehydro-cholic Acids [153]

Weigh a sample of 50–100 mg and dissolve either in 50 ml of a mixture of benzene-methanol (10 : 1) or by suspending in 2 ml of dimethylformamide while stirrring with a glass rod and adding 50 ml of chloroform. The compound is then titrated with 0·1 N potassium methoxide in benzene-methanol in the presence of two drops of thymol blue as indicator to blue, or in chloroform-dimethylformamide to purple-blue. 40·85 mg of cholic acid, 39·25 mg of deoxycholic acid and 40·25 mg of dehydrocholic acid require 1 ml of 0·1 N solution.

Cholic acid can also be titrated with 0·1 N sodium methoxide in the presence of hexamethylenetetramine in a pyridine medium [832].

92. Polybasic Acids [159, 160, 176, 252, 309, 324, 360, 480]

Because of the electrostatic effect of the anion formed during titration, dissociation of the second and third protons of polybasic acids takes place more slowly. (See: Chapter 4; Section 26.) In many cases, however, both acid functions of dibasic

acids can be titrated in suitable solvents. Thus malonic acid for example can be titrated only roughly with sodium methoxide in benzene-methanol in the presence of thymol blue, but in n-butylamine it can be titrated with precision as a dibasic acid.

In potentiometric titrations, a closed system containing a magnetic stirrer and a glass and calomel electrode pair are employed. Suitable apparatus can be seen in Figs 112, 113 and 114 in Chapter 21 (pp. 304–305). The curves may vary from acid to acid. With a standard solution of TBAH and in dimethylformamide the three isomers of phthalic acid have two inflection points; the first inflection is considerably sharper for phthalic acid, while the second is sharper for *m*- and *p*-phthalic acid (i.e. iso- and tere-phthalic acids). The most suitable solvents are pyridine or isopropanol since the extent of interaction of these dibasic acids with these solvents is less. The order of reactivity is

pyridine < isopropanol < acetone < isobutyl methyl ketone or acetonitrile < dimethylformamide.

Of the basic solvents, those possessing a greater potential range are more suitable for potentiometric titrations (Chapter 12).

It is characteristic of the levelling and enhancing effect of pyridine that the difference betwen the first and second inflection points of sulphuric or succinic acid is small measured in pyridine (for these acids it is 350 and 250 mV, respectively) although the dissociation constants of sulphuric acid in water are $K_1 = 10^{-1}$ and $K_2 = 1{\cdot}2 \times 10^{-2}$, but those of succinic acid are much smaller: $K_1 = 6{\cdot}9 \times 10^{-4}$ and $K_2 = 2{\cdot}5 \times 10^{-6}$ [159].

Weigh as much of the bi- or tri-functional acid as is necessary for 3–5 ml to be consumed for a potentiometric titration, and for visual end-point detection, 5–8 ml should be consumed. In the former case dissolve the acid in 50 ml of pyridine and in the latter use 25 ml of pyridine. Indicator solutions: 0·3 % thymol blue in isopropanol; for weak acids a saturated solution of azo-violet in benzene. The concentration of the standard solution of potassium methoxide or TBAH should, if possible, be below 0·1 N. For a given bifunctional acid it is advisable to check potentiometrically whether the equivalence point corresponds to the violet shade of blue of the colour change of azo-violet.

In the potentiometric titration of tri- and tetra-basic acids (citric acid, phosphoric acid, ethylenediaminetetra-acetic acid) in pyridine or dimethylformamide with a standard solution of TBAH in pyridine or dimethylformamide, three inflection points can be observed when measured potentiometrically [159]. When phosphoric acid is titrated with potassium methoxide in a solvent mixture of acetone-pyridine (4 : 1) to the first (red) transition of azo-violet, potassium dihydrogen phosphate is formed, thus 30–80 mg of phosphoric acid can be determined with a precision of $\pm 0{\cdot}8\,\%$ (also as the phosphoric acid salts of alkaloids [309]). (See also: Chapter 24; Section 140.) Tartaric acid, *o*-phthalic acid and maleic acid can be titrated as dibasic acids with 0·1 N potassium methoxide in pyridine medium with thymol blue as indicator. This method is also suitable for the determination of the acid component of ergot alkaloids [324]. Oxalic, malonic, maleic, fumaric, malic, succinic, *o*-phthalic and citric acids can be determined as dibasic acids with a standard solution of TBAH of 0·1 N concentration in a pyridine medium with azo-violet as indicator [159].

The importance of a precise determination of oxalic acid in non-aqueous media becomes obvious, primarily, in the case of 'indirect' methods. Two examples may be given here. The

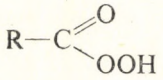
first is the determination of the neutralization equivalents of higher fatty acids on semimicro and micro scales [807 and 808]. When this method is applied, the excess of potassium methoxide is back-titrated by means of a standard solution containing oxalic acid and prepared with a solvent mixture of methanol-benzene (Chapter 15; Section 82). The second example relates to the determination of carbodi-imide derivatives; in this case the excess of oxalic acid left unchanged after the reaction with carbodi-imide is back-titrated with a standard solution of sodium methoxide prepared with benzene-methanol solvent mixture in the presence of thymol blue indicator [891].

Carbodi-imides of the general formula R—N=C=N—R′ react in dioxan with excess of oxalic acid to form a disubstituted urea, CO_2 and CO; R and R′ may be alkyl, aryl, or cyclohexyl:

$$R-N=C=N-R' + (COOH)_2 \rightarrow R-NHCONH-R' + CO_2 + CO$$

93. Peracids and Hydroperoxides

Among organic peroxides, the peroxy acids, hydroperoxides and peroxy derivatives of aldehydes (ketones) can be titrated as acids.



Peracid

The pK value of a peroxy acid is on the average 3·5 units greater than that of the corresponding organic acid; hydroperoxides and aldehyde peroxides are very weak acids with pK values of 11·6–12·8. Peroxy acids can be titrated potentiometrically in a single mixture and also in hydrogen peroxide, by employing an antimony-antimony electrode pair, with 0·2 N sodium aminoethoxide in ethylenediamine [554, 601]. Weigh into the closed titration flask system, shown in Fig. 53, 2–5 m. eq. of the peracid or hydroperoxide; dissolve in 50 ml of ethylenediamine and titrate with 0·2 N sodium aminoethoxide in ethylenediamine-ethanolamine. (For preparation of the standard solution see: Chapter 11.) One ml of a 0·2 N standard solution is equal to 15·21 mg of peracetic acid. The accuracy of measurement is ±2%.

94. Amino-acids

The basicity of amino groups is greatly decreased by basic solvents, while the acid strength of carboxyl groups is increased. Numerous amino-acids dissolve in pyridine containing 1–3% of water and can be titrated either potentiometrically or with a solution of TBAH of 0·1 N concentration in benzene-methanol in the presence of thymol blue. The sample is first dissolved in 0·5–1·5 ml of water, then 50 ml of neutralized pyridine are added. In this way alanine, leucine, threonine, asparagine, methionine, hydroxyproline, glutamine, glutamic acid and aspartic acid can be titrated [159].

When amino-acids are titrated in pyridine containing 1–3% of water the titrant can be standardized against benzoic acid or an *amino-acid of standard purity*. In both cases, however, the pyridine should contain the same amount of water and a nearly equimolar quantity of standard substance as of the compound to be measured in 50 ml of solvent. The concentration of the indicator should also be identical for the determination and for the standardization.

95. Determination of Acid Mixtures in Differentiating Solvents

Many studies are devoted to differentiating titrations of mineral and organic acids but no generally applicable procedure exists [105, 159, 160, 161, 170, 212, 258, 360, 414, 415, 480, 539, 550, 736, 783, 888].

Various acid mixtures, a common component of which is sulphuric acid, are employed in organic reactions such as sulphonation (sulphuric acid–sulphonic acid), nitration (sulphuric acid–nitric acid), esterification, etc. In many cases the analysis of these compounds can be performed in non-aqueous media.

The problem of differentiating titrations of binary mixtures of mono-, di- or tri-chloroacetic acid with hydrochloric acid in a solvent of ketonic character was solved by Izmaĭlov and co-workers [414, 415]. Acetic acid, being able to differentiate strong acids, was used by Shkodin and Izmaĭlov [736] for the determination of mixtures of perchloric acid-hydrochloric acid, perchloric acid–sulphuric acid and *p*-toluenesulphonic acid–nitric acid. Pyridine or dimethylaniline, dissolved in acetic acid, served as basic titrants. Lavine and Toennies [502] employed acetonitrile for the titration of perchloric acid–acetic acid mixtures; in the course of time this solvent became one of the most widely used solvents for the differentiating titration of acids and bases. Critchfield and Johnson solved the problem of sulphuric acid–hydrochloric acid and sulphuric acid–nitric acid mixtures by titration in acetonitrile with a standard solution containing morpholine [155]. Some research workers, however, use solvents of basic character, e.g. dimethylformamide or pyridine for the differentiating titration of acids [159, 176, 359], Fritz and Yamamura use acetone [258]. In practice acetone, acetonitrile, ethyl methyl ketone, isobutyl methyl ketone, ethylene glycol-isopropanol, methanol and pyridine have come into general use as solvents. t-Butanol is a promising solvent: [253, 550].

In differentiating titrations of mixtures of acids of different strength it is desirable that the solvent should interact with the dissolved compound as little as possible; in this way only the intrinsic strength of acids, determined by the molecular structure, manifests itself. From a theoretical aspect, inert solvents (carbon tetrachloride, benzene) ought to be the most suitable solvents, but because of their poor conductivity, potentiometric measurements may encounter difficulties and, moreover, the low dielectric constant of the solvent promotes the formation of disturbing associations (cf. Chapter 12; Section 63 (d)). For the determination of binary mixtures of mineral acids, solvents of the smallest possible basicity are suitable: the levelling effect counteracting the differentiating effect is, to a certain degree, correlated with the basicity of the solvent. (Pyridine is a fortunate exception since in spite of its basic properties it is suitable for differentiating titrations.)

In solvents of differentiating properties the titration of strong (mineral) acids in a single mixture is feasible. The measurement is performed with a standard solution of TBAH. Strong basic solvents (ethylenediamine, piperidine) can be employed for the titration of exceedingly weak acids; mineral and carboxylic acids are not differentiated. In dimethylformamide, pyridine and acetonitrile, a sharp inflection point can be located even in the case of very weak acids; strong and moderately strong carboxylic acids can be differentiated, while these solvents are not suitable for the differentiating titration of strong mineral acids. Mineral acids can be differentiated in methyl ethyl ketone but inflections of very weak acids (or acid analogues) are somewhat less distinct.

(a) *Titration in isobutyl methyl ketone.* The solvent 2-methyl-4-pentanone combines the favourable properties of acetonitrile and ethyl methyl ketone [105]. It is suitable for potentiometric titrations of bases and acids. With TBAH of 0·2 N concentration in isopropanol, strong and weak acids can be titrated in a single mixture even on a semimicro scale, e.g. perchloric acid, hydrochloric acid, salicylic acid, acetic acid

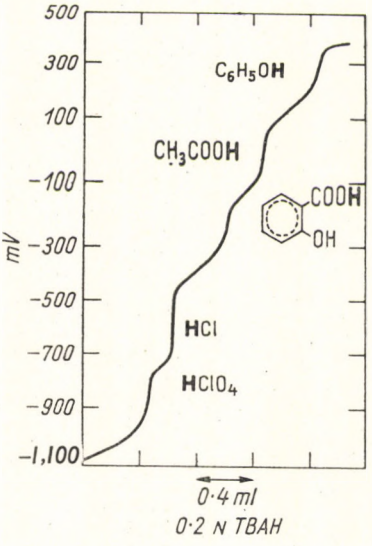


Fig. 105. Titration of a five-component system in methyl isobutyl ketone according to Bruss and Wyld [105]. — Glass–platinum electrode system

and phenol (Fig. 105, [105]). Owing to its wide potential range (about 1,400 mV) it is suitable both for the measurement of relative acid strength, and for the titration of a mixture of acids of various strengths if the difference between the inflection points of the individual components is 200–300 mV.

Since isobutyl methyl ketone of commercial quality may contain acidic contaminants it must be purified before use (Chapter 8; Section 49 (e)). Because of its slow CO_2 absorption, titration in a nitrogen atmosphere is unnecessary.

In the solvent isobutyl methyl ketone, a solution of TBAH in isopropanol (0·2 N) is a suitable titrant. Weigh in 20 ml of the solvent, approx. 0·2 m.eq. of acid mixture, and titrate with a standard solution of 0·2 N or 0·1 N TBAH in isopropanol from a burette graduated in 0·01 or 0·02 ml. Use a small titration vessel such as that suggested by Deal and Wyld, shown later in Fig. 114 (p. 305). Platinum inserted in the tip of the burette (cf. Fig. 52) or saturated calomel is suitable as a reference electrode (Chapters 12 and 21).

For the titration of acids in a single mixture, isobutyl methyl ketone is more suitable than ethyl methyl ketone, acetonitrile, pyridine, dimethylformamide or isopropanol (Figs 105 and 106). t-Butanol is also very suitable for the differentiating titration of acid analogues, as is ethyl methyl ketone (cf. Fig. 108 p. 258).

In non-aqueous solvents the order of the relative strength of acids is usually denoted by the half-neutralization point of these acids in relation to some reference acid. In potentiometric titrations of strong acids, the extent of inflection (i.e. the mV jump) in isobutyl methyl ketone is about five times that observed in ethylenediamine medium (in both cases with TBAH as standard solution). The relative position of the half-neutralization points of various acids is represented in Fig. 106.

When salicylic acid is titrated with TBAH in isobutyl methyl ketone, one inflection point can be seen indicating titration of the carboxyl group. However, when titrated in isobutyl methyl ketone medium, but with potassium hydroxide, two inflection points appear indicating neutralization of the COOH and phenol-OH groups. In ethylene glycol e.g. *p*, *p'*-dihydroxydiphenylmethane shows two inflections with TBAH in isopropanol but only one with potassium hydroxide in isopropanol [359].

Regarding the titration of acid mixtures in methyl ethyl ketone see: [114, 359, 477, 480, 485]. Thus, e.g., *o*-, *m*-, *p*-nitrobenzoic acid and nitrophenols can be titrated in the presence of nitric

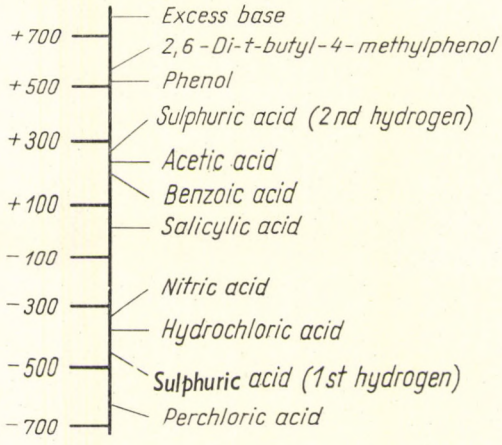


Fig. 106. Relative position of midpoint potentials of acids according to Bruss and Wyld [105]. — Solvent: methyl isobutyl ketone. Standard solution: 0·2 N tetrabutylammonium hydroxide in isopropanol. Electrodes: glass–calomel

acid in methyl ethyl ketone medium with a 0·1 N solution of tetraethylammonium hydroxide [478]: 30 ml of the solvent is neutralized to blue colour in the presence of thymol blue; 50–100 mg of the sample is dissolved in the neutralized solvent and potentiometrically titrated with a standard solution of Et_4NOH in benzene–methanol under a nitrogen atmosphere, using a glass–calomel electrode pair. In this case the acid mixture is resolved with a precision of $\pm 1\%$.

(b) *Determinations in acetone.* Anhydrous acetone is less suitable for differentiating titrations of strong mineral and carboxylic acids because during potentiometric titration, which takes rather a long time, it reacts with these acids [160, 258]. But it is suitable for the titration of a mixture of carboxylic acids. Thus dichloroacetic acid, for example, can be determined in the presence of acetic acid, and salicylic acid can be determined in the presence of methyl salicylate. However, in acetone containing a little water, mixtures of hydrochloric acid–sulphuric acid or nitric acid–sulphuric acid can be titrated with a standard solution containing tri-n-butylmethylammonium hydroxide either potentiometrically or visually in the presence of an indicator mixture of neutral red–thymolphthalein [539]. Weigh out 0·4–0·8 m. eq. of an acid mixture in 40 ml of neutralized acetone and titrate potentiometrically with 0·1 N TBAH using a glass and calomel electrode pair.

Gribova and Levin titrated potentiometrically the binary mixture of sulphuric acid with anthraquinone mono- or di-sulphonic acid, naphthalene monosulphonic acid or benzenesulphonic acid in acetone or acetonitrile media. Morpholine or diphenylguanidine dissolved in ethanol containing 10–15% glycerol served as standard solution. The precision of the determination was $\pm 2\%$ [289].

A mixture of maleic acid and phthalic acid may be analyzed by titration in acetone medium [543]. Weigh out a quantity of $< 0{\cdot}04$ m. eq. from the anhydrous sample and dissolve it in carefully dehydrated acetone (100 ml). Dilute 10 ml of the stock solution with 40 ml of acetone and titrate with 0·1 N potassium hydroxyde in ethanol using a glass–calomel electrode pair.

In the course of differentiating titrations, three inflections can be observed. The first inflection indicates the primary hydrogens of either of the two acids, the second that of the secondary hydrogen of phthalic acid, while the third shows the titration of the secondary hydrogen of maleic acid.

Critchfield and Johnson titrated sulphuric acid in the presence of other acids in an acetonitrile medium with a standard solution containing morpholine [155].

Pyridine is widely employed as a solvent for differentiating titrations of mineral and other acids [160, 161, 159, 162].

(c) *Determinations in pyridine.* Weigh a 0·7–0·8 m.eq. of the acid mixture and if necessary, dissolve it in 1·5 ml of water, then dilute with 50 ml of pyridine and titrate in a nitrogen atmosphere with a standard solution of TBAH in benzene-methanol, employing a glass and calomel electrode pair.

In a sulphuric-nitric acid mixture inflection point 1 shows the first equivalence of sulphuric acid and nitric acid, while inflection 2 indicates that of bisulphate. In the case of sulphuric and phosphoric acid three inflections can be observed: (1) first equivalence of sulphuric acid, (2) second equivalence of sulphuric and first of phosphoric acid, (3) second equivalence of phosphoric acid. The acid mixtures hydrochloric–sulphuric acid, sulphuric–perchloric acid, nitric–phosphoric acid, sulphuric–benzenesulphonyl chloride, sulphuric–benzenesulphonic acid, sulphuric–*p*-toluenesulphonic acid, sulphuric–methanesulphonic acid etc. can be titrated in a similar way [161, 162]. The accuracy of the determination of strong acids is ±0·3%, of weak acids ±0·5% and of very weak ones ±1%.

The determination of the alkoxyl group is an example of an ingenious method for performing a differentiating titration in pyridine, for in this case, making use of the two-step colour change indicator azo-violet, both hydrogen iodide (orange → red) and subsequently alkylpyridinium iodide $[C_5H_5NR]^+I^-$ (red → violet) can be titrated in one mixture, with a standard solution of TBAH of 0·02 N concentration. (See: Chapter 31; Section 168 [163].)

Titration of the mixtures hydrochloric acid-benzoic acid or benzoic acid-phenol is feasible potentiometrically in a pyridine medium with sodium methoxide in benzene-methanol by employing a glass and silver electrode pair. When the potential change

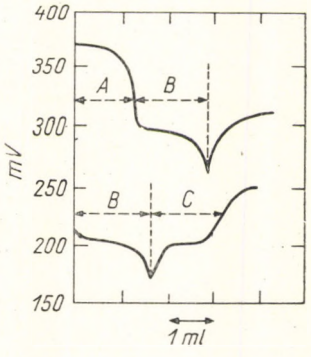


Fig. 107. Potentiometric titration curves of acid mixtures in pyridine according to Yakubik, Safranski and Mitchell [888]. — *(A)* Hydrochloric acid, *(B)* Benzoic acid, *(C)* Phenol. Standard solution: 0·1 N sodium methoxide in benzene–methanol. Electrodes: glass–Ag

is plotted against the volume consumed, hydrochloric acid and phenol show the usual *S*-shaped curve, while benzoic acid shows a minimum peak inflection curve (Fig. 107 [888]); (cf. Chapter 12; Section 69).

(d) *Titration in G–H solvent mixture* [170]. Sulphuric acid can be titrated potentiometrically in a glycol medium. A suitable standard solution is either NaOH in ethylene glycol-isopropanol or 0·1 N piperidine in isopropanol. Sodium hydroxide, however,

stored for more than a week is no longer suitable for differentiating titrations. By using a standard solution containing piperidine this disturbing effect is eliminated but a weak acid (e.g. acetic acid) cannot be titrated in a mixture with a mineral acid. The advantage of this standard solution is that when sulphuric acid is titrated the formation of sulphates is not accompanied by precipitation. A binary mixture of

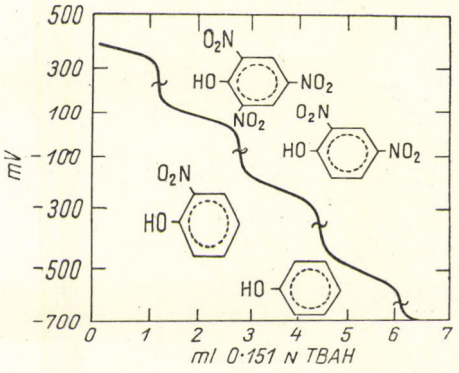


Fig. 108. Titration of a four component system in t-butanol according to Fritz and Marple [253]. — Standard solution: tetrabutylammonium hydroxide in benzene-isopropanol. Electrode see: Fig. 68

sulphuric and other acids can be titrated potentiometrically with a standard solution containing piperidine by using glass-saturated calomel electrodes. A 1:1 mixture of ethylene glycol-isopropanol is a suitable solvent. The accuracy of measurement is $\pm 1\%$. Determination of ternary mixtures by this method is less satisfactory.

The sulphuric or hydrochloric acid content of acetylating mixtures in diethylene glycol can be determined with triethanolamine in propanol of 0·05 N or 0·1 N concentration [213].

(e) *Methanol* is a suitable solvent for routine determinations of sulphonating and nitrating acid mixtures [783]. Cyclohexylamine in methanol is suitable as a titrant and is potentiometrically standardized against benzoic acid by means of a glass and calomel electrode system. Weigh a sample containing about 8 m.eq. of acid (S = weight of sample in mg) and dissolve in 50 ml of methanol. Titrate while stirring till the first potential jump *(a)*, then continue till the second jump *(b)*. Calculation in the case of binary systems of monobasic mineral acids with sulphuric acid:

$$\% \text{ of sulphuric acid} = \frac{(b-a) \times 98{\cdot}08 \times 100}{S}$$

$$\% \text{ of the other component of the acid mixture} = \frac{(2a-b)\ A \times 100}{S}$$

where A = the molecular weight of the acid (e.g. benzenesulphonic acid).

Titration of a mixture of 100–300 mg of Na_2SO_4–$C_6H_5SO_3Na \cdot H_2O$ can be achieved by the use of an ion exchange resin such as Wofatit KS in the following way: dissolve the salt mixture in 3 ml of water, let it run through a column of 30 × 2 cm diameter then elute with 150 ml of methanol and titrate as above [783].

(f) Regarding differentiating titrations in t-butanol see: [253, 550, 551]; Figs 68 and 108, and Chapter 12; Section 63 (a).

(g) Potentiometric differential titrations of a large number of acids and acid mixtures ranging in strength from mineral acids to phenols can be achieved using as solvent a commercially available mixture of N,N-dimethyl fatty amides consisting of approximately 95% N,N-dimethyl-lauramide, 3% N,N-dimethylmyristamide and 2% N,N-dimethylcapramide [678].

The titration procedure consists of dissolving the sample in 25 ml of the solvent and titrating under a nitrogen blanket, using as titrant tetra-n-butylammonium hydroxide in a benzene–isopropanol–water solvent. A reduced-scale titration cell can be used (Fig. 106). Potassium chloride is only slightly soluble in the solvent (Hallcomid M-12, C. P. Hall Co., Illinois), therefore the saturated calomel reference electrode contains saturated aqueous lithium chloride.

The glass–calomel electrode system in this solvent gave potential readings that were reproducible within 2 mV.

Chapter 16

Determination of Acid Anhydrides, Acyl Halides, Reactive Alkyl and Aralkyl Halides

Acyl chlorides and acid anhydrides are acceptor acids, the acetyl cation: CH_3CO^+ being the acidic species.

96. Acid Anhydrides

In an aqueous medium, and especially in the presence of pyridine as catalyst, acetic anhydride rapidly undergoes solvolysis and two molecules of acetic acid are formed, that is, it consumes two equivalents of aqueous alkali metal hydroxide. In the reaction between acetic anhydride and alkali metal methoxide in methanol, benzene-methanol or acetone, alkali metal acetate and methyl acetate are formed, i.e. one equivalent of standard solution is consumed [762]:

$$(CH_3CO)_2O + CH_3OK = CH_3COOK + CH_3COOCH_3$$

Acid anhydrides react in the same way with potassium hydroxide in ethanol, in an acetone medium [613]. Titrations performed in aqueous as well as in non-aqueous media, e.g. in the presence of thymol blue as indicator are suitable for the determination of a mixture of acetic anhydride and a carboxylic acid [762].

Phthalic anhydride can be titrated in a solvent mixture of benzene-methanol (3 : 1) with sodium methoxide in the presence of thymol blue [252], or potentiometrically with potassium hydroxide in dimethylformamide medium, using a platinum and a calomel electrode pair [457].

(a) *The morpholine method* [431]. In practice, the determination of small amounts of anhydride in the presence of large quantities of carboxylic acids and vice versa is more important. For the former determination the morpholine method is suitable, since with anhydrides, morpholine ($O(CH_2CH_2)_2NH$) forms equimolar amounts of the acid amide and of the carboxylic acid:

$$HN(CH_2CH_2)_2O + (CH_3CO)_2O \rightarrow CH_3CON(CH_2CH_2)_2O + CH_3COOH$$

Interaction with acetic anhydride for example is complete within 30 seconds. In methanol the excess of morpholine can be back-titrated with 0·1 N hydrochloric acid.

Transfer to a 250 ml glass-stoppered Erlenmeyer flask, 10 ml of acetic acid containing 0·01–0·5% acetic anhydride, add 50 ml of a 0·02 N solution of morpholine in methanol (1·74 ml of morpholine + 1,000 ml of methanol), mix, and allow the well-stoppered flask to stand for 5 min. Then titrate in the presence of 4–5 drops of an indicator mixture of dimethyl yellow-methylene blue (see: Table 24 and Chapter 9; Section 51(a)), with 0·1 N hydrochloric acid in methanol or propylene glycol-chloroform to amber. The titrant consumption of the morpholine solution is determined in the same way. The difference is proportional to the anhydride content: 10·21 mg of acetic anhydride require one ml of 0·1 N hydrochloric acid (~ 5 ml of 0·02 N morpholine solution). This method is employed for testing the anhydride content of anhydrous acetic and propionic acids: Chapter 8; Section 47 (c). For the determination of greater amounts of anhydride, solutions of 0·5 N concentration are used. The morpholine reagent must be protected from atmospheric carbon dioxide.

Propionic, butyric, glutaric, succinic and phthalic anhydrides can be determined by this method. One ml of 0·1 N hydrochloric acid is equivalent to: 13·01, 15·82, 17·02, 10·01 and 14·81 mg of the above anhydrides in that order. This method cannot be employed in the case of anhydrides whose corresponding acid has a greater ionization constant than 2×10^{-2} (e.g. maleic and citraconic anhydrides) since the carboxylic acid formed in methanol is slightly acidic for the indicator employed. The presence of other components such as ketenes, diketenes, acyl chlorides and mineral acids which react with morpholine and eliminate its basic character affect the titration undesirably.

(b) *The aniline method* [208]. Acetic anhydride reacts rapidly with aniline:

$$(CH_3CO)_2O + H_2N.C_6H_5 = CH_3CONH.C_6H_5 + CH_3COOH$$

The excess of aniline can be back-titrated with perchloric acid.

Weigh in a 100 ml measuring flask, with mg precision, 1 g of acetic anhydride and dilute to the mark with acetic acid *free from acetic anhydride* (Chapter 8, Section 47 (c) and (d)). After transferring 50 ml of a solution of 0·1 N aniline in acetic acid (9·1 ml aniline + 1,000 ml of acetic acid) into a 200 ml glass-stoppered Erlenmeyer flask, pipette into the latter a 20 ml portion of the stock solution. Allow the mixture to stand for 40 min at room temperature, then, after adding 0·1 ml of 0·1% crystal violet in acetic acid, titrate with 0·1 N perchloric acid in acetic acid to a clear *green* colour. It is advisable to use a comparative solution, since the acid amide formed is also, to a certain extent, basic in acetic acid. The perchloric acid consumption of 50 ml aniline solution is determined in a similar way. The difference between the two determinations is proportional to the acetic anhydride content.

Siggia and Hanna [748] employ an earlier, potentiometric variant of the aniline method where the medium both for the reaction as well as of the standard solution (0·2 N hydrochloric acid) is a mixture of ethylene glycol-isopropanol in the ratio 1 : 1 (cf. [621]). The adduct formed from aniline in excess with carboxylic acids can, in this case also, be titrated as a base.

97. Determination of Maleic Acid and Phthalic Acid in the Presence of their Anhydrides

Tri-n-propylamine and N-ethylpiperidine do not react with acid anhydrides, hence with a standard solution prepared from these in acetone or ethyl methyl ketone media (Table 18, *f*) carboxylic acids with dissociation constants not below 10^{-3} are titratable in the presence of their anhydrides [746, 56].

Weigh a sample containing about 0·2–2 mM of the acid to be tested and dissolve in 30–50 ml of acetone. Titrate potentiometrically in acetone with 0·1 N tri-n-propylamine using a glass-calomel electrode pair. This method is suitable for the determination of 0·2–75% maleic or phthalic acid in the presence of their anhydrides. For the determination of phthalic acid present as an impurity, the use of a molybdenum-calomel electrode pair is advantageous [56].

The normality of the standard solution is determined against pure maleic acid with regard to the fact that only one $-COOH$ group is titrated. 11·61 mg of maleic and 16·61 mg of phthalic acid require 1 ml of solution of 0·1 N concentration.

98. Determination of Acetic Acid Impurity in Acetic Anhydride

The acetic acid content of acetic anhydride is determined more accurately if the acetic acid is titrated directly [564], e.g. with a solution of 2 M triethylamine in benzene (Table 18, *j*):

For 0·6–3·5% acetic acid contamination, the precision of this method is ±0·07% (abs). Its disadvantage is that preparation of the standard solution is cumbersome.

Any possible acetylatable amine impurity in 500 ml triethylamine, previously dried by solid KOH, is reacted by boiling with 25 ml anhydride under reflux for 30 min. The excess anhydride is carefully reacted with 125 ml of 10 N NaOH by constant stirring and the triethylamine extracted with 500 ml of benzene. The benzene fraction is washed once more with 125 ml of alkali and subsequently fractionated; about 200 ml of fore-run are rejected and the receiver exchanged for a dry one, and the distillation is continued until the residue is approx. 100 ml. During distillation atmospheric moisture should be excluded. The second fraction is diluted with an equal amount of benzene (water < 0·05%). The titrant thus prepared is standardized against aqueous 0·5 N hydrochloric acid.

Measure 100 ml of acetic anhydride containing 5–50 m.eq. of acetic acid and titrate immediately in the presence of five drops of saturated methyl red in acetonitrile. Comparative solution: five drops of indicator + 100 ml of benzene. (3·13 moles of triethylamine require 1 mole of acetic acid.)

99. Acyl Chlorides

(a) Acetyl chloride can be titrated as an acid in acetic anhydride medium with sodium acetate in acetic acid [831]:

$$CH_3COCl + CH_3COO^-Na^+ \rightarrow NaCl + (CH_3CO)_2O,$$

or

$$CH_3COCl + (CH_3CO)_2O \rightarrow (CH_3CO)_3O^+ + Cl^-$$

and

$$CH_3(CO)_3O^+ + CH_3COO^- \rightarrow 2\,(CH_3CO)_2O$$

The following procedure is suggested: weigh 90–110 mg of acetyl chloride in a 25 ml measuring flask containing 5 ml of 100% acetic anhydride. Transfer to a 100 ml measuring flask, washing with acetic anhydride, and fill up to the mark. Pipette 20 ml portions of the stock solution into a 200 ml glass-stoppered Erlenmeyer flask (observing laboratory safety measures, Fig. 34), add 0·05–0·1 mg solid dimethylaminoazobenzene as indicator and titrate the red solution *very slowly* with 0·1 N sodium acetate in acetic acid to a yellow-pink colour (about 30 min). (Preparation of standard solution of sodium acetate: Chapter 10; Section 58.) The stoppered flask is allowed to stand for 30 min, titration is then continued *until the yellow colour persists.*

At the beginning of the titration, on adding 3–5 drops of sodium acetate, the solution becomes yellow, in the course of the titration, however, it regains its red colour and finally attains the slow transition from yellow to pink. After waiting for 30 min the change from orange to yellow is sharper.

The sodium acetate titrant is standardized against perchloric acid in the presence of dimethyl yellow indicator. 7·85 mg of acetyl chloride require 1 ml of 0·1 N sodium acetate. The accuracy is ±2%.

(b) Acid chlorides can also be determined by titrating (in acetone or dioxan) the hydrochloric acid formed in the course of esterification of the acyl chloride and an alcohol [623, 753]:

$$R.\,COCl + C_2H_5OH \rightarrow R.\,COOC_2H_5 + HCl$$

This titration can be performed with alkali metal alkoxide or tributylamine. In benzene, benzene-methanol or dioxan, acyl chlorides (and also acid anhydrides) can be determined as monofunctional acids with alkali metal alkoxide in the presence or thymol blue to a blue colour change [252, 623]:

$$R.\,COCl + NaOCH_3 = R.\,COOCH_3 + NaCl$$

For example, 3,5-dinitrobenzoyl chloride (in benzene) and benzoyl chloride (in benzene-methanol, 3 : 1) can be titrated in the presence of thymol blue [252]. In pyridine, however, against a standard solution of trimethylbenzylammonium hydroxide in pyridine (Triton B) they act as dibasic acids:

$$R'COCl + 2\,R_4NOH = [R'COO]NR_4 + R_4NCl + H_2O$$

(c) The hydrolysis of an acid chloride can also be performed in dioxan containing a small amount of water and pyridine [378]. The excess of water may be bound with acetic anhydride, and the pyridinium chloride formed titrated with perchloric acid standard solution in the presence of mercury(II) acetate. This determination can also be performed in presence of carboxylic acids and carboxylic anhydrides.

The weighed sample is transferred to a ground-glass flask, placed on a steam bath, and refluxed for 1 hour with 10 ml of the reagent containing pyridine. 10 ml of the reagent containing anhydride is added to the mixture, and heated for another hour. After cooling, 25 ml of acetic acid or propionic acid is added and titrated with 0·1 N perchloric acid in the presence of a few drops of 0·2% methanil yellow

indicator (in dioxan) until a pink colour is obtained. The titration, after adding 25 ml mercury(II) acetate reagent, is then continued to a pink colour. The standard solution consumed for the second titration is proportional to the quantity of acid chloride.

The reagent containing pyridine: A mixture of 20 g of pyridine and 1·8 g of distilled water is diluted to 500 ml with dioxan. *The reagent containing anhydride:* 11 g of 98% acetic anhydride is made up to 500 ml with dioxan. *Reagent containing mercury(II) acetate:* 22 g of mercury(II) oxide is dissolved in a mixture of 11 ml acetic anhydride and 1,000 ml acetic acid.

(d) The determination of halides of carboxylic acids and that of chlorides of sulphonic acids can also be performed in the presence of organic acids and alkyl halides. The acid chlorides are reacted with hexamethylene-imine (HMI) and the excess of the latter is titrated with 0·1 N hydrochloric acid in methanol [799].

$$R.\,CO.\,Hal + 2\,(CH_2)_6NH = R.CON(CH_2)_6 + (CH_2)_6NH.\,HHal$$

$$R.\,SO_2Cl + 2\,(CH_2)_6NH = R.SO_2N(CH_2)_6 + (CH_2)_6NH.HCl$$

Allow 30–70 mg of the sample to stand with 10 ml of the HMI solution for 5–10 min at room temperature. The excess of the HMI reagent is back-titrated in the presence of 5 drops of indicator mixture with 0·1 N hydrochloric acid in methanol. A blank test is run in the same way and the difference in the volumes is used in the calculation:

$$\% = \frac{(\text{blank test ml} - \text{titration ml}) \times \text{mol. wt.}}{\text{sample in g} \times 200}$$

Acetyl chloride, bromide, and iodide, the acid chlorides of monochloroacetic acid, propionic acid, oleic acid, isovalerianic acid, caproic acid and phenylacetic acid, in addition to benzenesulphonyl chloride, *p*-toluenesulphonyl chloride and 1,4-cyclohexanedisulphonyl chloride can also be titrated in this way.

Preparation of the HMI solution: an aqueous HMI solution of technical grade is saturated with sodium hydroxide, the supernatant liquid is decanted and dried over solid KOH. 20 g of the product collected between 137 and 138°C in the fractional distillation of the dried HMI is dissolved in 1,000 ml of methanol.

Indicator mixture: 10 mg of methylene blue and 40 mg of methyl red are dissolved in 100 ml of ethanol and diluted with 100 ml of distilled water. The colour change of the indicator is from green to violet. (Hydrochloric acid in methanol, see Chapter 9.)

(e) Acetyl chloride as a polar solvent; for titrations in acetyl chloride, see: [758].

100. Determination of a Mixture of Aroyl Chloride, Hydrochloric Acid and Carboxylic Acid

(a) *For the determination of a mixture of benzoyl chloride, hydrochloric acid and benzoic acid* proceed in the following way [623]: add 2 drops of thymol blue to a 2–5 ml portion of stock solution in dioxan, containing 0·2–1 mM aroyl chloride, in a 25 ml Erlenmeyer flask (cf. Chapter 13; Section 73 and Table 26). Titrate the free hydrochloric acid with a solution of 0·1 N tributylamine (Table 18 *l*) in dioxan

to a *yellow colour* (T_1). Magnetic stirring is advisable; the tip of the burette should be dipped below the liquid surface. After adding 5 ml of ethanol heat the mixture for 5–10 min to 80°C, to complete the liberation of hydrochloric acid from the acyl chloride. After renewed heating, titrate the hydrochloric acid with 0·1 N sodium methoxide in benzene-methanol to a *persistent yellow colour* (T_2). In the remaining portion of the stock solution carboxylic acid is titrated with sodium methoxide to a *blue thymol blue end-point* (T_3).

Calculation: m.eq. of hydrochloric acid $= T_1 \times N_1$

m.eq. of acid chloride $= T_2 \times N_2$

m.eq. of benzoic acid $= T_3 \times N_2 - (T_1N_1 + T_2N_2)$,

where T_1 = the volume consumed of the standard tributylamine solution (ml)

T_2 and T_3 = the consumption of methoxide (ml)

N_1 = the normality of the former

N_2 = the normality of the latter.

The behaviour of thymol blue in dioxan against single components and the titrating base, respectively, is as follows:

(1) *HCl + thymol blue:* faint red deepening on addition of alcohol. It is titratable with the same precision either with tributylamine (pale red → vivid yellow) or sodium methoxide in benzene-methanol (pale red → deep red → yellow, and with the smallest excess of $NaOCH_3$ to blue. The volume of standard solution consumed until a yellow–blue colour change is reached indicates the extent of contamination by weak acid).

(2) *Benzoic acid + thymol blue:* yellow, and on adding methoxide or alkylammonium hydroxide, blue at the equivalence point.

(3) *Benzoyl chloride + thymol blue:* faint pink, with one-two drops of tributylamine, vivid yellow; with an equivalent of sodium methoxide: blue.

(b) *Determination of hydrochloric acid in the presence of acid chloride* [753]. Weigh a sample containing at most 1 mM of hydrochloric acid, dissolve in a mixture of 50 ml ethyl ether-chlorobenzene (1 : 1) and titrate the free HCl potentiometrically with a standard solution of 0·1 N tripropylamine (see: Table 18, *m*). Standardize the latter against maleic acid in acetone. One ml of 0·1 N tripropylamine is equal to 3·6465 mg of hydrochloric acid or 11·61 mg of maleic acid (only one COOH group is titrated).

In dioxan the mineral acid can also be titrated with 0·1 N tributylamine in dioxan [623], in the presence of thymol blue, from red to yellow. The standard solution is standardized against 0·1 N hydrochloric acid in dioxan.

101. Determination of Acyl Chloride in the Presence of Easily Hydrolyzable Groups

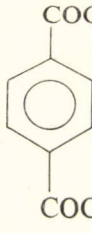
Acyl chlorides of aliphatic and aromatic carboxylic acids can be titrated in tetrahydrofuran directly with a standard solution of 0·5 N cyclohexylamine (CHA) in tetrahydrofuran (THF) (Table 18, *c*) potentiometrically standardized against hydrochloric acid, using glass-calomel electrodes. The reaction scheme is as follows [519]:

$$R.COCl + 2\,C_6H_{10}NH_2 \rightarrow R.CO.NH.C_6H_{10} + C_6H_{10}NH_2.HCl$$

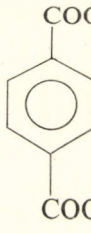
Carboxylic acid contaminants do not affect the titration but hydrochloric acid contamination does since cyclohexylamine reacts with the strong acid. The advantage of

THF is that the determination of acyl chlorides can be performed even in the presence of easily hydrolyzable groups, e.g. $-CH_2Cl$, $-CHCl_2$, $-CCl_3$.

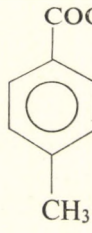
Weigh in a dry ground-glass measuring flask acyl chloride equivalent to 35–40 ml of standard solution. Transfer 10–15 ml of THF to a 150–200 ml beaker and pour in the weighed sample. Rinse the measuring flask with 30–40 ml of THF. After inserting the glass and calomel electrodes, titrate very slowly at a rate of at most 3 ml/min (regarding the course of titration and shape of curve see: [519]). Thus, for example, the following can be determined (in brackets mg equivalent to 1 ml 0·5 N standard solution): propionyl chloride (23·13) in the presence of butyric acid or acetic acid; lauryl chloride (54·69) in the presence of lauric acid, isophthaloyl dichloride (25·38) in the presence of isophthalic acid, *p*-trichloromethylbenzoyl chloride (67·49) in the presence of *p*-trichlorobenzoic acid and terephthaloyl dichloride (25·38) in the presence of seven contaminating components: terephthalic acid, *p*-toluic acid, phthalic anhydride, trichlorobenzene, benzotrichloride, benzyl chloride and benzal chloride.



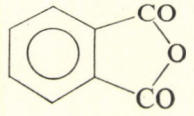
Terephthaloyl dichloride



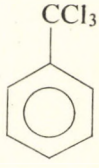
Terephthalic acid



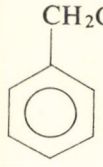
p-Toluic acid



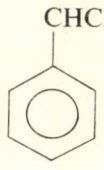
Phthalic anhydride



Benzotrichloride



Benzyl chloride



Benzal chloride

102. Reactive Alkyl Halides

Reactive alkyl and aralkyl halides react with aniline and the corresponding phenylalkylamine and anilinium halides are formed [623].

$$RCl + 2\,C_6H_5NH_2 \rightarrow C_6H_5NH_3^+Cl^- + C_6H_5NHR$$

The cationic acid formed can be titrated in aniline with sodium methoxide in the presence of thymol blue:

$$C_6H_5NH_3^+ + CH_3O^- \rightarrow C_6H_5NH_2 + CH_3OH$$

Weigh as much reactive alkyl halide as is needed to consume 2–5 ml of standard solution of 0·1 N. Dissolve the sample in 5 ml of *freshly distilled* aniline and boil

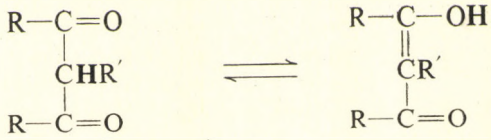
under reflux (depending upon its reactivity) for 20–30 min. After cooling, dilute with 10 ml of aniline and after adding 3 drops of thymol blue, titrate with 0·1 N sodium methoxide in benzene–methanol to green. The following compounds can be determined with an average ±0·7% precision:

Compound	*Boiling* (min)	mg *Equivalent*	*Compound*	*Boiling* (min)	mg *Equivalent*
Benzyl chloride	30	12·66	1-Bromodiethyl-acetylurea	20	23·71
Dibromoethylene	30	18·59	Cetyl bromide	30	30·53
n-Butyl iodide	20	18·40	1-Bromopentane	30	15·11
p-Bromoaceto-phenone	25	19·90	*p*-Nitrobenzyl chloride	25	17·16

Chapter 17

Determination of Compounds Containing Enolic Hydroxyl or Imide Group

Compounds containing an enolic hydroxyl group and exhibiting keto-enol tautomerism are weak acids (acid analogues):



Electrophilic groups increase acid strength (Chapter 4; Section 25 (c)). See also: pp. 230–236 in [605]. Compounds of the type, $R-CH_2-R'$ where R and R′ possess electron attracting properties, (e.g. $-COR$, $-COH$, $-COOH$, $-CONH_2$ $-CONHAr$ or CN) can be titrated as acids in dimethylformamide in the presence of azo-violet [246]. The electrophilicity of the amide group is not very great. Thus the colour change of the indicator in the case of malononitrile is sharp, with cyanoacetamide it is sluggish and malonamide does not show any acidic character. Compounds of the type $R-CO-CO-CH_2R'$ (e.g. diacetyl) exist only in the keto form and are not titratable as acids. With $-CONH_2$, $-CONHR$ and $-COONa$ groups the result of the titration is not predictable, particularly in the case of imides.

Keto-enol tautomerism does not depend only upon molecular structure but also on the solvent: the enol content of acetylacetone in water is 19%, in chloroform 79%, in benzene 85% and in hexane 92% (p. 226 in [605]).

103. Compounds Containing Enolic Hydroxyl

Suitable solvents are: benzene-methanol (3 : 1), acetone, pyridine, butylamine, ethylenediamine and dimethylformamide. This last can be used for enols whose pK value does not exceed 10 (in the presence of thymol blue or azo-violet) or 10·5–11

(for potentiometric titration). 0·1 N alkali metal methoxide or alkylammonium hydroxide is used as titrant [159, 246, 252, 258].

A sample of a monofunctional compound is dissolved in neutralized solvent to give a titration of approx. 5–8 ml. For visual end-point detection 20–30 ml of solvent is used and for potentiometric titrations 40–50 ml. For all potentiometric indications a glass–calomel electrode pair is used except for ethylenediamine for which antimony–antimony is used (Fig. 53). 2–4 drops of thymol blue or azo-violet and 3–5 drops of *o*-nitroaniline are used as indicators (Tables 23, 24, 26 and 27). In order of decreasing acid strength thymol blue, azo-violet and *o*-nitroaniline are used as indicators and dimethylformamide, pyridine, butylamine and ethylenediamine are employed as solvents (Table 31).

Table 31

DETERMINATION OF ENOLIC COMPOUNDS

Compound	*Solvent*	*Standard Solution*	*End-point*	*References*
Acetylacetone	Acetone	Bu_4NOH	Pot.	[258]
	Bu	$NaOCH_3$	Thymol blue	[252]
Acetylacetanilide	Acetone	Bu_4NOH	Pot.	[258]
	DMF	$NaOCH_3$	Azo-violet	[246]
Cyanoacetamide	EDA	$NaOCH_3$	*o*-Nitroaniline	[246]
	Acetone	Bu_4NOH	Pot.	[258]
Ethyl cyanoacetate	DMF	$NaOCH_3$	Azo-violet	[246]
	Acetone	Bu_4NOH	Pot.	[258]
Dibenzoylmethane	DMF	$NaOCH_3$	Thymol blue	[246]
	Acetone	Bu_4NOH		
		Bu_3MeOH	Pot.	[258, 540]
3,5-Dioxo-1,2-diphenyl-4-n-butyl-pyrazolidine	Benzene	$NaOCH_3$	Thymol blue	[303]
5,5-Dimethylcyclohexan-1,3-dione (dimedone)	DMF	$NaOCH_3$	Azo-violet	[246]
	Acetone	Bu_4NOH	Pot.	[258]
Ethyl malonate	DMF	$KOCH_3$	Azo-violet	[893]
Malononitrile	Acetone	Bu_4NOH	Pot.	[258]
	DMF	$NaOCH_3$	Azo-violet	[246]

Abbreviations: Bu = butylamine, DMF = dimethylformamide, EDA = ethylenediamine, Pot. = potentiometric end-point, Py = pyridine

(a) *Determination of malonic acid esters.* Diethyl malonate can also be titrated in a mixture with diethyl (1-methylbutyl)malonate in dimethylformamide in the presence of azo-violet (a) with 0·1 N potassium methoxide in benzene-methanol (sodium methoxide, in this case, produces lower values, and lithium methoxide is not suitable).

$$[(EtOOC)_2CR]\,H + KOCH_3 = [(EtOOC)_2CR]\,K + CH_3OH$$

Diethyl malonate

But diethyl (1-methylbutyl)malonate can be titrated with sufficient accuracy in a mixture with diethyl ethyl-(1-methylbutyl)malonate in ethylenediamine in the presence of *o*-nitroaniline (b) [893].

Substituted diethyl malonates, being weak acid analogues, may consume in method (a) a small amount of standard solution, i.e. as a % of the sample: diethyl (1-methylbutyl)malonate 2; s-butyl malonate 2·3; isopropyl malonate 4 and n-butyl malonate 13. As the size of the substituent increases, the weaker is the acidity of the substituted malonic acid ester.

(b) *Determination of diethyl malonate* (malonic acid diethyl ester) *in the presence of diethyl cyclohexylmalonate* (cyclohexylmalonic acid diethyl ester) [406]. Weigh and dissolve 250 mg of ester mixture in a measuring flask in a mixture of 100 ml of pyridine-benzene (5 : 1). Pipette a 20 ml portion of the stock solution into a 50 ml flask (cf. Figs 39, 40, 41 and 42), add 3 drops of saturated azo-violet indicator in benzene and saturate with nitrogen for 1–2 min. Titrate with 0·02 N potassium methoxide in benzene-methanol until an intensive blue colour is produced (Chapter 10; Section 56). Determine the standard solution consumption by the solvent in the same way and correct for the solvent. 3·20 mg of malonic acid diethyl ester require 1 ml of 0·02 N $KOCH_3$.

(c) *Determination of a mixture of diethyl malonate, diethyl cyclohexylmalonate and diethyl dicyclohexyl malonate* [406]. The total of diethyl malonate and mono-substituted components can be determined by titrating a 50–100 mg sample with 0·1 N potassium methoxide in ethylenediamine, in the presence of the indicator, *o*-nitroaniline. But when the titration is performed in pyridine-benzene (5 : 1), in the presence of azo-violet, only diethyl malonate can be determined with 0·02 N potassium methoxide. The disubstituted malonic acid ester without an active hydrogen cannot be titrated as an acid analogue.

104. Compounds Containing Imide or Amide Group

Though compounds containing $-CO-NH-CO-$, or $-NH-CO-NH$ groups are very weak acids, some types may be titrated precisely in suitable solvents (Table 32). The compounds of the type $R-NH-R'$ generally are weaker acids than those

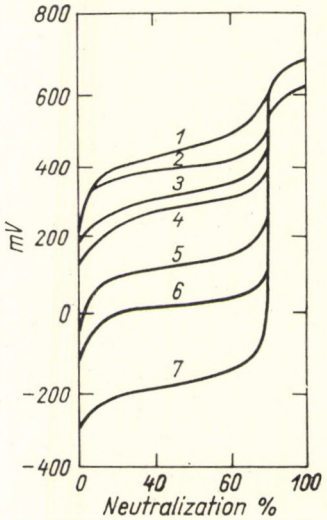


Fig. 109. Potentiometric titration curves of some acid analogues in pyridine according to Streuli [780]. — *(1)* Dicyandiamide, *(2)* Nitromethane, *(3)* Cyanamide, *(4)* Succinimide, *(5)* Phthalimide, *(6)* Cyanuric acid, *(7)* Barbituric acid

of the type $R-CH_2-R'$ [246], but if R or R′ are $-COR$, $-CHO$, $-COOR$ or $-CONHAr$ then they can be titrated either in the presence of an indicator or potentiometrically. In some cases the acid strength of imides is increased by the presence of an aromatic ring: acetylacetanilide ($CH_3COCH_2CONHC_6H_5$) can be titrated with sodium methoxide in dimethylformamide in the presence of azo-violet while acetylurea ($CH_3CONHCONH_2$) cannot. Acid strength is increased by replacing the carbonyl group by the thiocarbonyl group (>CS): *sym*-diphenylurea cannot be titrated, while *sym*-diphenylthiourea can be titrated in dimethylformamide in the presence of azo-violet [246].

Table 32

DETERMINATION OF COMPOUNDS CONTAINING IMIDE GROUP

Compound	*Solvent*	*Standard Solution*	*End-point*	*References*
1-Acetyl-2-thiohydantoin	Acetone	Bu_4NOH	Pot.	[258]
Barbituric acid	Py	Bu_4NOH	Pot.	[780]
Dicyclohexylcarbodi-imide	Dioxan	$NaOCH_3$	Thymol blue indirect method	[891]
sym-Diphenylthiourea	DMF	$NaOCH_3$	Azo-violet	[246]
5,5′-Diphenylhydantoin	Acetone	Bu_4NOH	Pot.	[258]
2,4-Dithiobiuret	DMF	$NaOCH_3$	Azo-violet	[246]
Dithio-oxamide	DMF	$NaOCH_3$	Azo-violet	[246]
1-Phenyl-3-cyclohexylthiourea	EDA	$NaOCH_3$	*o*-Nitroaniline	[246]
1-Phenyl-3-naphthyl- and 1-phenyl-3-(2-pyrimidyl)-thiourea	DMF	$NaOCH_3$	Azo-violet	[246]
Phthalimide	Acetone, Py	Bu_4NOH	Pot.	[258, 540, 780]
	DMF	$NaOCH_3$	Azo-violet	[246]
Hydantoin	DMF	$NaOCH_3$	Azo-violet	[246]
	Acetone	Bu_4NOH	Pot.	[258]
p-Nitrobenzenesulphonamide	Acetone	Bu_3MeNOH	Pot.	[540]
Succinimide	Py, acetone	Bu_4NOH	Pot.	[159, 258, 540, 780]
Theobromine	Py, $CHCl_3$	$NaOCH_3$	Azo-violet	[246]
Theophylline	DMF	$NaOCH_3$	Thymol blue	[566]
8-Chlorotheophylline	Py, $CHCl_3$	$NaOCH_3$	Thymol blue	[576]
2,4-Thiazolidindione	Acetone	Bu_4NOH	Pot.	[258]
Thiobarbituric acid	DMF	$NaOCH_3$	Thymol blue	[246]
Substituted phenylureas	Bu	Bu_4NOH	Pot., conductometric, spectrophotometric	[137]

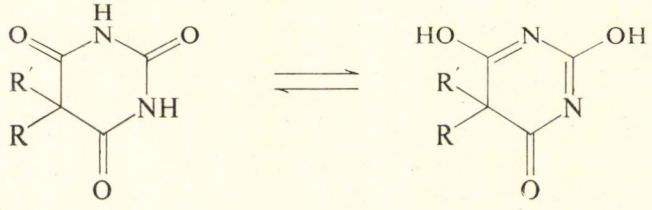
For abbreviations see: Table 31.

Many types of compounds, including many used extensively in chemotherapy, can be classed in this group, e.g.: barbituric acid, sulphonamide and purine derivatives. The two latter types also include compounds titratable as bases (Chapter 5; Section 34). The principles valid for the titration of enolic compounds also hold good in this

case. Among purine bases theophylline and aminophylline can be determined in dimethylformamide in the presence of thymol blue and theobromine in pyridine or ethylenediamine with azo-violet as indicator [49, 246, 566, 646]. Other compounds which possess an active H atom linked to a C or N atom, (when the molecule does not contain either phenolic, hydroxyl or carboxyl groups) can similarly be titrated in pyridine. For potentiometric titration a solution of alkylammonium hydroxide in benzene-methanol is a suitable standard: see: [780] and Fig. 109: barbituric acid (pK 4·0), phthalimide (pK 9·9), succinimide (pK 9·6), cyanamide (pK 9·4), dicyandiamide (pK 14·2), nitromethane (pK 10·6). (See also: Chapter 4; Section 25 (d).) Cyanamide and dicyandiamide can also be titrated in a mixture [780].

105. Barbituric Acid and Hydantoin Derivatives

Derivatives of barbituric acid and hydantoin can be titrated in inert or basic solvents (or solvent mixtures) with a standard solution containing alkali metal alkoxide or alkylammonium hydroxide in the presence of indicators such as thymol blue, phenolphthalein, thymolphthalein, *o*-cresolphthalein, azo-violet, alizarin yellow R, or potentiometrically using e.g. an antimony-glass electrode pair.



Main type of tautomerism in 5,5-disubstituted barbituric acids

The R and R′ substituents of barbituric acid or hydantoin cause variations in acid strength. Barbituric acid is about six times stronger than acetic acid (pK 3·98 and 4·76, resp.); 5-ethylbarbituric acid can be titrated with aqueous alkali in an aqueous medium in the presence of phenolphthalein (pK 4·42), but diethylbarbituric acid is a weak acid (7·91).

ACID STRENGTH OF SOME 5,5-DISUBSTITUTED BARBITURIC ACID DERIVATIVES

Barbituric Acid Derivatives	pK *Colorimetric*	pK *Potentiometric*
Phenylethylbarbituric acid	7·30	7·21
Cyclohex-1′-enylethylbarbituric acid	7·35	7·51
Isopropylbromoallylbarbituric acid	7·55	7·63
s-Butylbromoallylbarbituric acid	7·62	7·69
N-Methyl-phenylethylbarbituric acid	7·65	7·76
Diethylbarbituric acid	7·81	7·91
N-Methyl-cyclohex-1-enylmethylbarbituric acid	8·04	8·08

Poethke and Horn, *Arch. d. Pharm.* **287**, 487 (1954).

(a) *Titration in pyridine.* Pyridine or a mixture of pyridine homologues are suitable solvents for barbituric acid derivatives [372]. As a standard solution, 0·1 N sodium methoxide in benzene-methanol can be employed, while thymol blue, phenolphthalein or thymolphthalein are useful indicators. The colour change of the indicator may vary from one compound to another. Diethyl-, diallyl- and ethylbutyl-barbituric acids must be titrated until a blue shade of thymol blue appears, while ethylallylbarbituric acid must be titrated until a green colour change appears. It is advisable to use thymolphthalein for allylisopropyl derivatives and phenolphthalein for ethylphenylbarbituric acid. Cyclohexenylethylbarbituric acid does not yield good results either with indicators or potentiometrically but N-methyl derivatives can be determined potentiometrically.

The combined effect of the substituent, the indicator and the solvent is evident in the accuracy of measurements: N-methyl-phenylethylbarbituric acid gives with all three indicators the same low value (−2·5%), the N-methyl-ethylcyclohexenyl derivative is on the average 5% higher, while the values for phenylethylbarbituric acid increase gradually (thymol blue < phenolphthalein < thymolphthalein: [372]).

Phenylethylbarbituric acid, isopropylbromoallylbarbituric acid and some other barbiturates can be titrated in pyridine or a mixture of pyridine–benzene (5 : 1) with photometric end-point detection with an accuracy of ±1·2% [212]. Dissolve in 30 ml of pyridine containing 0·003% of thymol blue a weighed amount (0·5 m.eq.) of the barbituric acid derivative. Titrate with 0·1 N sodium methoxide in benzene-methanol containing the same amount of thymol blue as the compound to be tested. Measure the absorption after the addition of each portion of the standard solution and plot the results graphically. (See: Chapter 14.)

In pyridine, phenylethylbarbituric acid can be titrated in the presence of caffeine with thymol blue indicator and a standard solution of $NaOCH_3$ [832].

(b) *Titration in dimethylformamide.* Phenylethylbarbituric acid can be titrated with sodium methoxide in dimethylformamide in the presence of thymol blue as indicator, and butylethylbarbituric acid, being a weaker acid, in the presence of azo-violet [130]. A 0·2% solution of alizarin yellow R in dimethylformamide is also a suitable indicator (Table 26 [453]). Dissolve 150–200 mg of barbiturate in 50 ml of dimethylformamide previously neutralized in the presence of one drop of alizarin yellow R and titrate, excluding atmospheric carbon dioxide, with 0·1 N sodium methoxide in benzene-methanol to a blue violet colour change (Figs 39, 40, 41 and 42). Diethyl, phenylethyl, butylethyl, ethylpentyl, and N-methyl-phenylethylbarbituric acid can be titrated in this way [453].

Slow-release tablets containing barbituric acid derivatives and their sodium salts can be tested in an anhydrous medium [130]. One portion of the finely ground tablets is suspended in dimethylformamide, and another portion in acetic acid. The acetic acidic solution is prepared by gentle heating. After cooling, dioxan is added so that the ratio of acetic acid to dioxan should be 2 : 1. Dichloroethane can be used instead of dioxan. Free barbituric acid is titrated with the standard basic solution in the presence of alizarin yellow, while the sodium acetate formed in the acetic acid medium is titrated with 0·1 N perchloric acid in the presence of methyl violet to the transition from blue to green yellow.

When 10–20 ml of dimethylformamide are used as solvent and lithium methoxide as the standard solution, no gelatinous precipitate is observed and most barbituric acid derivatives can be measured precisely by titration to a deep blue colour with thymol blue as indicator [280, 452, 694, 846].

(c) *Titration in benzene-isopropanol.* For potentiometric measurements a 10 : 1 mixture of benzene-isopropanol can be used very conveniently. Even when mixed with 40% v/v of chloroform the end-point is not obscured (pure chloroform easily

polarizes electrodes). This is of importance when salts of barbituric acids, after acidification, are extracted with chloroform. In this solvent mixture, titrated with standard solution 0·1 N TBAH in the presence of thymol blue diethyl, phenylethyl, ethylisoamyl, allylisopropyl, diallyl and allylisobutyl-barbituric acids can be determined with $\pm 0{\cdot}1 - \pm 0{\cdot}2\%$ precision [504]. Weigh 0·5–0·8 m.eq. of barbituric acid derivative, previously dried for four hours at 80°C, dissolve in 20 ml of dimethylformamide or 50 ml of benzene-isopropanol neutralized in the presence of 5 drops of thymol blue and titrate from a burette graduated in 0·02–0·05 ml with 0·1 N lithium methoxide or a standard solution of TBAH to a deep blue colour. One ml of 0·1 N standard solution equals 0·1 m.eq. barbituric acid derivative.

(d) *Titration in chloroform* [794]. Dissolve 40 – 60 mg of the barbituric acid derivative in 20 ml of chloroform and, after adding 3–4 drops of 1% *o*-cresolphthalein (in $CH_3OH - CHCl_3$ 1 : 1), titrate with 0·1 N potassium methoxide in methanol or 0·1 N sodium methoxide in benzene-methanol. The indicator turns from colourless to a violet-pink colour. When the titration is carried out with sodium methoxide, 1 – 2 ml of methanol should be added previously to the solution.

(e) *Titration in methyl ethyl ketone* [684]. Dissolve 200 mg of barbituric acid derivative in 20 ml of methyl ethyl ketone, add 2 drops of indicator mixture (0·6 g thymolphthalein + 0·4 g tropaeolin 0 in 100 ml dimethylformamide) and titrate with 0·1 N tetrabutylammonium hydroxide till the colour changes from yellow to green.

(f) *Determination of salts of barbituric acid derivatives by extraction.* Dissolve an amount equal to 1·8–2·2 m.eq. of sodium salt in 10 ml of 0·1 N aqueous sodium hydroxide, acidify with 30–35 ml of 0·1 N sulphuric acid and extract with 6 × 20 ml of chloroform *(1)*, or 5 × 20 ml of ethyl ether *(2)*. The chloroform solution *(1)* dried with anhydrous sodium sulphate is evaporated to small volume, (see: evaporating flask in Fig. 103) and diluted to the mark in a 50 ml measuring flask with polyethylene glycol-400, or benzene-isopropanol: 20 ml of the stock solution are titrated potentiometrically with 0·1 N sodium methoxide [788] or with a standard solution of TBAH [504].

The solution in ethyl ether *(2)* is evaporated to dryness, the residue dissolved in dimethylformamide and titrated with 0·1 N lithium methoxide in the presence of thymol blue.

(g) *Determination of salts of barbituric acid derivatives with cation exchange resin* [844]. Dissolve 90–100 mg of the barbiturate in 20–25 ml of dimethylformamide. Transfer the solution to an Amberlite IRC-50 cation exchange column (H^+ form) and elute with dimethylformamide until the eluate volume is about 50 ml. Titrate with sodium methoxide in the presence of azo-violet to a permanent blue colour.

For solutions, dilute the amount equivalent to 100 mg of barbituric acid derivative to 25 ml with dimethylformamide and proceed as above.

For tablets, suspend the finely ground tablet in dimethylformamide and after vigorous shaking, filter into a measuring flask; wash the excipient of the tablet on the filter repeatedly with dimethylformamide. Titrate 50 ml of the eluate (~ 100 mg of barbiturate). The accuracy in the case of relatively pure samples is $\pm 1{\cdot}1\%$, in that of pharmaceutical preparations $\pm 1{\cdot}5\%$.

(h) Barbituric acid derivatives react with silver nitrate in pyridine and silver salts are formed, while the proton of the liberated nitric acid is bound by pyridine. The pyridinium ion thus formed can be titrated with a standard solution of NaOH in alcohol in the presence of thymol blue [266]. (Chapter 28; Section 160 (c).)

106. Sulphonamide Derivatives

Since the SO_2 group is strongly electrophilic, the hydrogen attached to the nitrogen atom in sulphonamides can be titrated as an acid in basic solvents [220, 250, 252, 452, 846], and in acetone [258]:

$$R-SO_2-NH-R' + KOCH_3 = R-SO_2-NK-R' + CH_3OH$$

The R′ substituent increases the acid strength in the following order:

phenyl > pyridyl > thiazoyl > hydrogen > naphthyl > benzyl > alkyl.

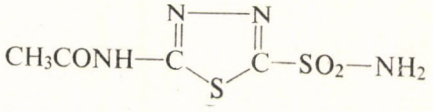
Sulphaguanidine has no acidic character. Most sulphonamide derivatives can be titrated in dimethylformamide and pyridine in the presence of thymol blue, while *p*-toluenesulphonamide and sulphanilamide can be titrated in butylamine in the presence of azo-violet.

For the determination of the above substances a finely powdered dry sample of 0·2–1·0 m. eq. (the quantity depends upon solubility) is weighed and dissolved in 10–50 ml of neutralized solvent, then titrated with 0·1 N alkali metal methoxide from a burette graduated in 0·02–0·05 ml.

In *dimethylformamide* the following compounds can be titrated with $NaOCH_3$ in benzene–methanol to a blue thymol-blue end-point: *p*-aminobenzenesulpha-methylpyrimidine, -dimethylpyrimidine, -pyrimidine, -pyridine, -thiazole, -methylthiazole. Alizarin yellow R (sodium salt of 4′-nitro-4-hydroxyazobenzene-3-carboxylic acid), is often used as indicator instead of thymol blue (Table 26, [453]). Aminobenzenesulphonamide can be determined in n-butylamine, in the presence of azo-violet, as can those compounds of the type RSO_2NHR' whose R or R′ substituent is the naphthyl-, anisyl-, benzyl-, tolyl- or *p*-bromophenyl group. Succinylsulphathiazole, *p*-aminobenzenesulphathiazole, -pyrimidine, -dimethylpyrimidine, and -methylpyrimidine can be titrated in pyridine, with sodium methoxide and in the presence of thymol blue [220].

Titration of sulphonamides is best performed in an apparatus affording the maximum protection from atmospheric carbon dioxide (Figs 39, 40, 41 and 42).

(a) *Determination of 2-acetylamino-1,3,4-thiadiazole-5-sulphonamide* (Acetazolamide).* Dissolve about 300 mg of sample in 30 ml of pyridine neutralized in the presence of azo-violet and titrate with sodium methoxide: or, dissolve 100 mg of the sample in 50 ml of dimethylformamide and titrate with sodium methoxide in the presence of 0·3 ml of alizarin yellow R to a grey-blue colour change.** In both cases 11·11 mg acetazolamide require 1 ml of 0·1 N alkaline standard solution:



(b) N-(4-Methylbenzenesulphonyl)-N′-butylurea *(Tolbutamide)* and N-(4-aminobenzenesulphonyl)-N′-butylurea *(Carbutamide)*, both antidiabetics, can be titrated

* *Drug. Stand.* **26**, 63 (1958).
** *Ann. pharm. franç.* **20**, 402 (1962).

with sodium methoxide in acetone or pyridine in the presence of phenolphthalein [471]. Since the molecule of *Carbutamide* contains an amino group it can be titrated in acetic acid with perchloric acid. One ml of 0·1 N sodium methoxide is equivalent to 27·04 mg of methylbenzenesulphonyl- or 23·13 mg of aminobenzenesulphonyl-butylurea.

107. Acid-analogue Condensed Heterocyclic Compounds

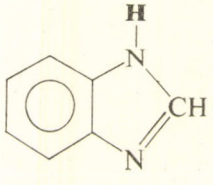
Benzimidazole, benzotriazole, 2-mercaptobenzothiazole and 5-amino-2-mercapto-benzimidazole can be titrated as acids with alkali metal alkoxide or alkylammonium hydroxide e.g.:

Compound	*Solvent*	*Standard Solution*	*End-point*	*References*
Benzimidazole	DMF	0·025 N $NaOCH_3$	Azo-violet	[562]
Benzotriazole	DMF	0·025 N $NaOCH_3$	Thymol blue	[562]
	Py	Bu_4NOH	Pot.	[780]
2-Mercaptobenzothiazole	Py	Bu_4NOH	Thymol blue	[159]
	Bu	$NaOCH_3$	Thymol blue	[252]
	Acetone	Bu_3MeNOH	Pot.	[540]
5-Amino-2-mercapto-benzimidazole	Py	Bu_4NOH	Azo-violet	[159]

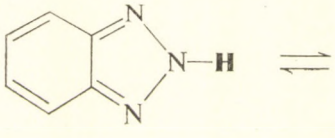
For abbreviations see: Table 31.

In propionic acid, benzimidazole can be titrated as a base with 0·1 N perchloric acid in propionic acid [377]; cf. [398] and Chapter 5; Section 34.

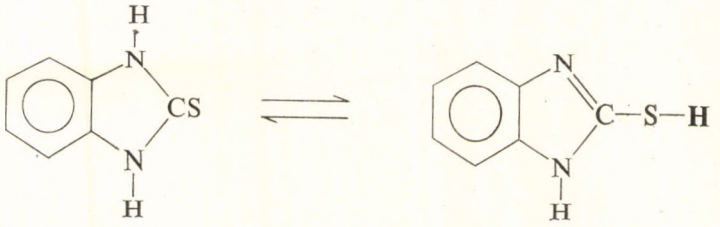
Substitution of the $-NH-CH=N-$ group by the $-S-C(-SH)=N$ group increases acid strength, and so 2-mercaptobenzothiazole is a strong acid analogue. The five-membered ring of benzotriazole is stabilized by its resonance with the benzene ring. These compounds also display tautomerism:



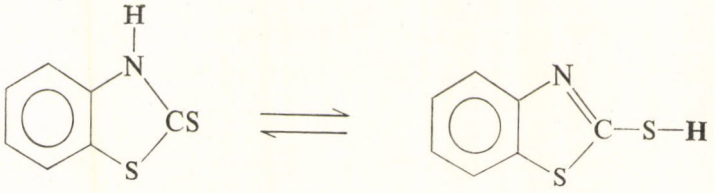
Benzimidazole



Benzotriazole

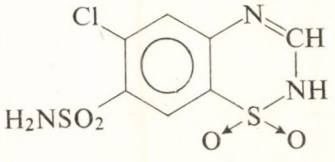


2-Mercaptobenzothiazole

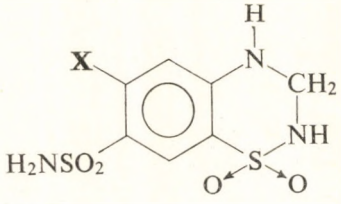


2-Mercaptobenzimidazole

(a) *Determination of 6-chloro-7-sulphamyl-1,2,4-benzothiadiazine-1,1-dioxide* (Chlorothiazide®).



Chlorothiazide® M.w. 295·7



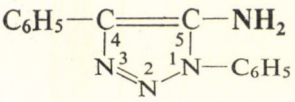
Dihydrochlorothiazide (X = Cl) and dihydrotrifluoromethylthiazide ($X = CF_3$)

Dissolve 100 – 150 mg of chlorothiazide in 50 ml of dimethylformamide, previously neutralized in the presence of 2 drops of alizarin yellow R, and titrate with 0·1 N sodium methoxide in benzene-methanol to a violet blue. During the titration, protect the solution from atmospheric carbon dioxide.* Azo-violet can also be used instead of alizarin yellow R [129]. 14·79 mg of chlorothiazide require one ml of 0·1 N alkaline standard solution. In dimethylformamide, in the presence of thymol blue chlorothiazide consumes only one equivalent of sodium methoxide [180]. Dihydrochlorothiazide and dihydrotrifluoromethylthiazide can be titrated in ethylenediamine, in the presence of azo-violet, as a bifunctional acid analogue:

Compound	*Solvent*	*Indicator*	*mg. Equiv. of One* ml 0·1 N *Standard Solution*
Chlorothiazide	DMF	Thymol blue	29·57
Dihydrochlorothiazide	EDA	Azo-violet	14·89
Dihydrotrifluoromethylthiazide	EDA	Azo-violet	16·55

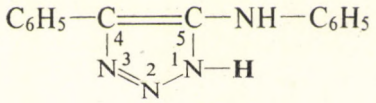
* *Ann. pharm. franc.* **20**, 295 (1962).

(b) Among *triazole derivatives*, the isomer (I) of diphenyl-5-amino-1,2,3-triazole in acetic acid can be titrated as a base with perchloric acid while the isomer (II) can be titrated as an acid in dimethylformamide in the presence of azo-violet. The position of the substituent thus determines the behaviour of the isomers [511]. Hence, the two isomers can also be determined in one mixture.



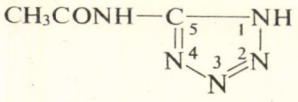
(I)

Basic isomer: 1,4-diphenyl-5-amino-1,2,3-triazole

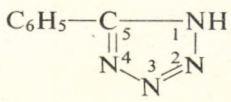


(II)

Acidic isomer: 4-phenyl-5-phenylamino-1,2,3-triazole



(III)



(IV)

(c) 5-*Acetylaminotetrazole* (III) can be titrated with sodium aminoethoxide as a bifunctional acid analogue and 5-phenyltetrazole (IV) as a monofunctional acid analogue in ethylenediamine, using antimony electrodes [534].

Chapter 18

Determination of Compounds Containing Phenolic Hydroxyl

108. Phenols

The acidic character of compounds containing phenolic hydroxyl is considerably influenced by the presence of a substituent. According to Fitz [258] acid strength is increased by the substituent R in the following order:

$$R = -NO_2 > -C(:O)H > -C(:O)R > -Cl, -Br > -C_6H_5$$

Alkyl substituents decrease the acid strength in the following order: methyl > ethyl > isopropyl.

The strength of acid analogues is influenced more by substitution in the *ortho* or *para* position than by substitution in the *meta* position. Hydrogen bonding may decrease acidity if an electrophilic group is in the *ortho* position. For example, all phenols having as *para* substituents: $-NO_2$, $-CHO$ and $-COCH_3$ are more acidic than the corresponding *ortho* compound.

(See also: Chapter 2, Table 3 and Chapter 4; Section 25 (c).)

Basic solvents are preferable for the determination of phenols (Table 33) while isobutyl methyl ketone, acetone, pyridine and t-butanol are suitable for potentiometric differentiating titration of phenols and stronger acids (acid analogues) in a single mixture [105, 159, 253, 258]: Figs 105, 107 and 108 and Chapter 12; Section 63 (d). It is best to choose the most suitable electrode system empirically. In pyridine medium, generally, Pt–calomel and Sb–calomel electrode pairs are preferable.

Of the basic solvents ethylenediamine has been employed by many investigators [176, 251, 285, 446, 601], but owing to its objectionable properties it has not come into general use. To a certain degree the same is true of piperidine. Dimethylformamide is a convenient solvent. It is odourless, only slightly hygroscopic, unreactive towards CO_2; it dissolves phenoxides well and can replace ethylenediamine in most cases [7]. In n-butylamine, and even more in ethylenediamine, precipitation may occur even with titrants of the TBAH type.

When phenols are titrated potentiometrically using glass and calomel electrodes potassium or sodium ions must be prevented from getting into the solution. These ions may cause irregular potentiometric curves [355]: Fig. 43 and Chapter 12; Section 63 (d). The potassium ions may

Table 33

DETERMINATION OF COMPOUNDS CONTAINING PHENOLIC HYDROXYL

Compound	*Solvent*	*Standard Solution*	*End-point Indication*	*References*
m-Acetamidophenol	EDA	$NaOCH_3$	*p*-Nitro-*p'*-aminoazobenzene	[798]
2-Acetyl-1-naphthol	DMF	$NaOCH_3$	Azo-violet	[251]
Benzyl mercaptan	Py	Bu_4NOH	Pot., Azo-violet	[159]
p-Benzylphenol	Py	Bu_4NOH	Pot.	[159]
o-, *m*-, *p*-Bromophenol	Acetone	Bu_4AOH	Pot.	[258]
p-Bromosalicylaldehyde	EDA	$NaOCH_3$	*p*-Nitro-*p'*-aminoazobenzene	[798]
o-, *m*-, *p*-Chlorophenol	Py	Bu_4NOH	Pot.	[780]
Cresols	Py	Bu_4NOH	Pot.	[780, 159]
Dienoestrol	DMF	Bu_4NOH	Pot.	[7]
Dihydroxydimethylresorcinol	Py	Bu_4NOH	Pot. Azo-violet	[159]
Ethyl vanillate	DMF	$KOCH_3$	Pot.	[113]
Eugenol	DMF	$KOCH_3$	Pot.	[113]
o-Hydroxyacetophenone	Acetone	Bu_4NOH	Pot.	[258]
p-Hydroxyacetophenone	Py	$KOCH_3$	Azo-violet	[798]
o-, *m*-, *p*-Hydroxybenzaldehyde	Acetone	Bu_4NOH	Pot.	[258]
p-Hydroxybenzoic esters	Py	$KOCH_3$	Azo-violet	[798]
n-Propyl *p*-hydroxybenzoate	DMF	Bu_4NOH	Pot.	[7]
Hydroquinone	DMF	Bu_4NOH	Pot.	[159]
p-Hydroxypropiophenone	DMF, acetone	Alkoxide	Azo-violet	[251, 307]
p-Hydroxypropiophenone	Py	KOH in ethanol	Pot. Thymolphthalein	[178]
o-Hydroxybenzyl alcohol	Py	Sodium aminoethoxide	Pot.	[287]
8-Hydroxy-5,7-di-iodoquinoline	DMF	$NaOCH_3$	Thymol blue	[448]

Continuation of Table 33

Compound	*Solvent*	*Standard Solution*	*End-point Indication*	*References*
4-Hydroxycoumarin derivatives	Py	KOH in ethanol	4-(*p*-Nitrophenylazo)-pyrocatechol	[419]
o-Hydroxybiphenyl	EDA	$KOCH_3$	*o*-Nitroaniline	[251]
8-Hydroxyquinoline	Acetone pyridine 4 : 1	$KOCH_3$	Azo-violet	[307]
Kojic acid = 5-hydroxy-2-(hydroxymethyl)-1,4-pyrone	Py	$NaOCH_3$	Azo-violet	[506]
Methyl salicylate	Acetone	Bu_4NOH	Pot.	[258]
1- and 2-Naphthol	Py	Bu_4NOH	Azo-violet Pot.	[159]
Nitrophenols	t-Butanol, acetone, pyridine	Bu_4NOH	Thymol blue	[159, 258, 780]
p-t-Pentylphenol	EDA	$KOCH_3$	*o*-Nitroaniline	[251]
Phenol	EDA, Py, DMF acetone	$KOCH_3$, Bu_4NOH	*o*-Nitroaniline, Azo-violet, Pot.	[7, 159, 251, 258, 780]
n-Propyl gallate	DMF	Bu_4NOH	Pot.	[7]
Phloroglucinol	EDA	$KOCH_3$	*o*-Nitroaniline	[258]
o-Phenylphenol	Py	Bu_4NOH	Azo-violet	[159]
Pyrocatechol	Py	Bu_4NOH	Pot.	[159]
Resorcinol	DMF	Bu_4NOH	Pot.	[7, 159]
Salicylamide	DMF	$NaOCH_3$	Azo-violet	[251]
Salicylaldehyde	Acetone	Bu_4NOH	Pot.	[258]
Salicylaldehyde thiosemicarbazone	EDA	$NaOCH_3$	*p'*-Nitro-*p'*-aminoazobenzene	[798]
Thymol	DMF	Bu_4NOH	Pot.	[7]
Trichlorophenol	DMF	$NaOCH_3$	Azo-violet	[251]
Vanillin	DMF	$NaOCH_3$	Azo-violet	[251]

(See also Table 21)

originate from the sample, the calomel electrode or from the standard solution of TBAH. K^+ contaminations due to the saturated potassium chloride solution of the calomel electrode can be avoided if the salt bridge electrolyte of the half cell is prepared from tetra-n-butylammonium chloride.

The use of TBAH standard solution for the titration of phenols in solvents of strong basicity provided an advance in the technique of potentiometric titration using a glass (indicator) electrode. In this case, standard solutions containing K^+ or Na^+ ions cannot be used. Not only do marked alkali metal contaminations of the standard solution have a disturbing effect but even the smallest contamination may influence the measurements, i.e. the potentiometric curve is shifted towards a more negative potential and inflections are smaller [355]. The effect of the K^+ ion is not related linearly to its concentration. The effect of the standard solution itself containing potassium ions as a contaminant becomes apparent in the form of an irregular curve as can be seen in Fig. 43. The 0·25 N TBAH standard solution also contains potassium ions in various concentrations; with 0·0055 N K^+ ion an inverse inflection appears directly before the normal inflection. The effect of Na^+ ions is similarly unfavourable. It is obvious that when the titration is performed (e.g. in pyridine) with a standard solution containing identical quantities of sodium ion contaminant the shape of the potentiometric curve becomes more irregular the greater the weight of the sample of phenolic compound, since more of the standard solution is consumed by the latter and thus the final concentration of the Na^+ ion is greater.

Small amounts of potassium or sodium ions do not change the result of titration if only a quantitative determination is required but if, for instance, the acid strength of weak acids is determined on the basis of half-neutralization potential, contamination by alkali metal ions must be carefully avoided when TBAH standard solution is prepared (Chapter 10; Section 57): the silver oxide and anion exchange resin must be washed with great care. Titration of phenols is best performed in an apparatus free from atmospheric carbon dioxide (Figs 39, 40, 41 and 42).

(a) *Titration in ethylenediamine* [251]. Using a graduated cylinder, transfer 25 ml of ethylenediamine to a 100–150 ml glass-stoppered Erlenmeyer flask and neutralize to red in the presence of two drops of 0·15% *o*-nitroaniline in benzene. Stopper the flask immediately. Weigh, from the compound to be tested, the amount needed for the consumption of 3–6 ml of 0·1 N standard solution. During the titration a stream of nitrogen is directed in the flask to the surface of the solution, and magnetic stirring is employed. In this way the disturbing effect of atmospheric carbon dioxide can be eliminated. Take the colour change from yellow to orange as the end-point. According to [392] the indicators benzopurpurin 4 B or tropaeolin 00 (Orange IV) are preferable to *o*-nitroaniline in ethylenediamine; the colour change of the former is red → blue, and the latter orange-yellow → blue. Takiura and Takino have recommended the use of *p*-nitro-*p'*-aminoazobenzene for titrations in ethylenediamine medium [798]. Colour change: red → (blue) → colourless.

(b) *Titration of p,p'-dihydroxydiphenylmethane* [359]. The favourable properties of TBAH solution in isopropanol compared with KOH in isopropanol are illustrated by titration of this bifunctional phenol in ethylenediamine. With TBAH *two* inflections are shown, while with KOH in isopropanol, *one* inflection indicates consumption of two equivalents of the standard solution. On neutralization of the first phenolic OH by TBAH a salt of low solubility is formed which, however, when neutralization is completed is redissolved. It is worth mentioning that this is one of the rare cases where a precipitate is formed with standard TBAH solution.

(c) *Titration in dimethylformamide* [251]. Add to 20 ml of DMF two drops of saturated azo-violet in benzene and neutralize with 0·1 N of $NaOCH_3$ or $KOCH_3$ in benzene–methanol to blue. Dissolve in this solution an amount of the compound to be tested equivalent to 3–8 ml of standard solution and continue titration to blue.

(d) *Potentiometric titration in DMF* [7]. For routine investigations ethylenediamine is less suitable than e.g. n-butylamine or dimethylformamide.

The latter is even less basic than n-butylamine but is especially suitable for the potentiometric titration of most phenolic compounds. Its advantage is that it has less affinity for atmospheric carbon dioxide and dissolves phenoxides more readily than butylamine or ethylenediamine. Even with standard TBAH solution precipitation may occur in the latter (b).

Weigh an amount of approx. 0·5 m.eq. of the compound containing the phenolic hydroxyl and dissolve in 25 ml of DMF neutralized in the presence of thymol blue or azo-violet, or occasionally alizarin yellow R.

Titrate in a 50–100 ml beaker closed by a cork stopper with four holes. Rubber plugs are attacked by DMF. During titration maintain magnetic stirring. Through the holes of the cork stopper the glass (indicator) and calomel (reference) electrodes, and the inlet tubes of the burette and the washed and dried nitrogen are introduced.

The inlet tube of the burette is inserted only loosely to allow nitrogen gas to escape. (See also: Figs 39, 40, 41 and 42.) For the titration, use a burette graduated in 0·05 ml and 0·1 N TBAH solution in benzene–methanol. The potential jump at the end-point is six times greater than that observed with e.g. lithium methoxide [7]. The mV inflection observed at the end-point reflects to a certain extent the relative acid strength of phenols: resorcinol (75 mV), oestradiol and ethynyloestradiol (100 mV), thymol (120 mV), dienoestrol (120 mV), hexoestrol and phenol (125 mV), stilboestrol (140 mV), oestrone (160 mV), n-propyl gallate (180 mV), vanillin (300 mV).

Butler and Czepiel performed titrations with 0·05 N potassium methoxide in benzene–methanol by using an antimony–calomel electrode system (Tables 21 and 33).

(e) *Titration of compounds containing a carboxyl group in the presence of compounds containing phenolic hydroxyl, in acetone or acetonitrile* [251]. Dissolve the sample in 30–40 ml of the solvent and titrate with 0·1 N potassium methoxide in the presence of two drops of 0·2% *p*-hydroxyazobenzene in benzene to a clear yellow colour: in this way the possible presence of a compound containing a carboxyl group is determined. Now, if another sample is titrated in ethylenediamine as above (a), then the difference between the titrations is in proportion to the amount of compound containing the phenolic hydroxyl.

(f) *Potentiometric titration in acetone* [258]. Weigh 0·4–0·8 m.eq. of the phenolic compound and dissolve it in 40 ml of purified acetone. Titrate using glass as indicator electrode and calomel as reference electrode. In the calomel electrode instead of aqueous KCl, a saturated solution of KCl in methanol is employed. Add as standard solution either 0·1 N Bu_4NOH or $BuEt_3NOH$ both in benzene-methanol from a burette graduated in 0·02 or 0·05 ml. Correct for the blank consumption of the solvent. If two or more inflections are observed use the difference in millilitres between two subsequent points of inflection to calculate the standard solution consumption. The titrant may be added in amounts such that the increase in deflection should be about 30 mV. Thus, on nearing the end-point of titration, the quantity of the standard solution added gradually decreases.

(g) *Potentiometric titration in isobutyl methyl ketone* [105]. Fig. 110 indicates the favourable properties of this solvent in the potentiometric titration of phenols. (See also: Chapter 15; Section 95.) In the potentiometric titration of phenolic compounds, a marked inflection can be observed when 0·2 N TBAH is employed as

standard solution. Platinum electrodes placed in a flowing titrant or a 'sleeve type' calomel electrode is suitable as a reference electrode (cf. Figs 41, 52, 61 and 114).

(h) *Titration in pyridine* [159]. Transfer 25 ml of pyridine, neutralized in the presence of 4 drops of thymol blue or azo-violet in benzene, to a 100–150 ml Erlenmeyer flask and dissolve in it as much of the sample as is needed for the consumption of

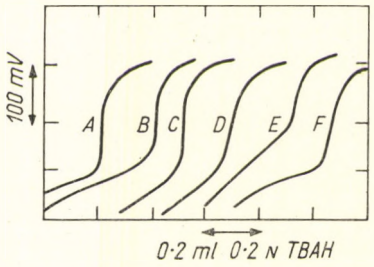


Fig. 110. Potentiometric titration of phenols according to Bruss and Wyld [105]. — *(A)* In piperidine, *(B)* In methyl isobutyl ketone, *(C)* In pyridine, *(D)* In acetonitrile, *(E)* In methyl ethyl ketone, *(F)* In ethylenediamine

6–8 ml standard solution of 0·1 N concentration. Titrate rapidly with 0·1 N TBAH in benzene-methanol (10 : 1) to a blue change of thymol blue or until azo-violet turns to violet, and, in some cases, to blue. Thymol blue is employed e.g. for the determination of nitrophenols, since these are stronger acid analogues.

(i) *Potentiometric titration in pyridine* [159, 780]. Weigh in a 100–200 ml vessel (a beaker or suitable titration flask as shown in Fig. 41, p. 163), an amount of the compound containing phenolic hydroxyl sufficient for the consumption of 2 – 10 ml of standard 0·1 N TBAH solution. Add 50 ml of pyridine and titrate from a semimicro burette using a glass–calomel electrode pair. In this case also it is advisable to direct a stream of nitrogen to the surface of the solution in order to exclude atmospheric carbon dioxide. Use magnetic stirring. Add the standard solution in increments of 0·1 ml, and, near to the equivalence point, 0·05 ml. Continue addition of the standard solution until the potential of the cell reaches the maximum, and on adding further standard solution remains relatively stable. If two points of inflection are observed calculate using the millilitre-difference of the two corresponding points of inflection.

In polyhydroxy compounds in pyridine medium, sometimes an intensive colour change can be noticed. Thus for example pyrogallol is deep blue, phloroglucinol vivid purple. This phenomenon can be ascribed to the oxidation of the ionized molecule, because in a nitrogen atmosphere a similar colouration does not develop [780].

(j) *p-Hydroxypropiophenone* can be determined with ±0·3% precision in a 4 : 1 mixture of acetone-pyridine [307]. It is also suitable for the standardization of standard solutions of potassium methoxide if the latter is used for the titration of phenolic compounds. The change of the indicator azo-violet colour from red to blue is sharp. Phenols substituted in the *para*-position are stronger than phenol itself. 16·42 mg of *p*-hydroxypropiophenone require 1 ml of 0·1 N potassium methoxide in benzene-methanol.

In pyridine, *m*- and *p*-hydroxybenzoic acids show two points of inflection, while *o*-hydroxybenzoic acid shows only one. TBAH as standard solution is used with glass–calomel electrodes (Fig. 100).

(k) *Titration in t-butanol* [253]. Transfer to a beaker with side-arms 50 ml of a solution containing the phenolic compound in an amount needed for the consumption

of 3–4 ml of 0·1 N TBAH in benzene–isopropanol (8 : 2). The beaker is connected to the half-cell as shown in Fig. 68. The glass electrode is immersed in the solution. Potentiometric titrations performed in t-butanol seem to be particularly convenient for the determination of nitrophenols [253] and for differentiating titrations of phenolic compounds in general [152]. (Figs 47 and 108.)

(l) The relatively strong base 1,1,3,3-tetramethylguanidine (containing 1 to 3% water), has also been proposed as a solvent for the titration of phenolic compounds [876].

109. Compounds Having an Oestrogenic Effect

(a) *Titration in dimethylformamide* [7]. Though synthetic compounds with oestrogenic effects are commonly bifunctional compounds, they can be titrated as monobasic acids in dimethylformamide [7]: see: Table below. Weigh 0·4–0·5 m.eq. of the compound and dissolve in 25 ml of DMF, previously neutralized in the presence of azo-violet, and titrate potentiometrically with 0·1 N TBAH using glass–calomel electrodes. Allow the glass electrode to stand previously in DMF for 24 hours:

Compound	mV *Jump at the Equivalence Point*	mg *Equivalent of One* ml 0·1 N *Standard Solution*
Diethylstilboestrol	140	26·83
Hexoestrol	125	27·04
Dienoestrol	120	26·63
Oestradiol	100	27·24
Oestrone	160	27·04
Ethynyloestradiol	100	31·64

(b) *Determination in pyridine* [25]. Dienoestrol, diethylstilboestrol and hexoestrol, when titrated in pyridine, consume one equivalent of 0·1 N TBAH or two equivalents of potassium methoxide; in both cases only one inflection point indicates the end of potentiometric titration (cf. Chapter 18; Section 108).

bis-Phenolic compounds, containing two *ortho* OH groups, consume only one equivalent of alkali because of H-bonding ([770] and Chapter 12; Section 63 (d)). In bis-phenolic oestrogens such as stilboestrol the distance between the phenolic functional groups is 8·55 Å, so that intramolecular H-bonding cannot be established.

Weigh about 0·5 m.eq. of the sample and dissolve in 80 ml of pyridine, neutralized in the presence of azo-violet. Titrate potentiometrically with potassium methoxide or TBAH. Use magnetic stirring and, during titration, let a stream of nitrogen pass over the solution (a suitable arrangement is shown in Fig. 38d). Dienoestrol can also be titrated visually in acetone in the presence of azo-violet.

(c) *Determination in a mixture of acetone–pyridine–methanol* (70 : 30 : 2) [309]. Dissolve 20–60 mg of diethylstilboestrol in 20 ml of the solvent mixture, neutralized in the presence of 0·2 ml of 0·1% azo-violet in chlorobenzene, and titrate with 0·1 N potassium methoxide in benzene–methanol to a steel blue. 13·42 mg of 4,4′-dihydroxy-α,α′-diethylstilbene require 1 ml of 0·1 N standard solution.

110. Phenolic Esters

Esters formed from carboxylic acid with phenols and/or substituted phenols, undergo *aminolysis* by methylamine or other strong bases such as ethylenediamine:

$$C_6H_5-O-C(:O)-R + H_2N(CH_2)_2NH_2 \rightarrow C_6H_5OH + H_2N(CH_2)_2NH-C(:O)-R \quad (110.1)$$

$$C_6H_5-O-C(:O)-Ar + H_2N(CH_2)_2NH_2 \rightarrow C_6H_5OH + H_2N(CH_2)_2-C(:O)-Ar \quad (110.2)$$

$$C_6H_5-O-C(:O)-Ar-OH + H_2N(CH_2)NH_2 \rightarrow C_6H_5OH + H_2N(CH_2)_2NH-C(:O)-Ar-OH \quad (110.3)$$

Thus, a phenol and an acid amide are formed. Weigh a sample of about 0·5 m.eq. into 20 ml of ethylenediamine neutralized in the presence of two drops of *o*-nitroaniline, and titrate with 0·1 N potassium methoxide to orange red. Phenyl acetate (110.1), propionate (110.1), benzoate (110.2), *o*- and *m*-tolyl acetate (110.1), 1-naphthyl acetate (110.1), diphenyl phthalate (110.2), phenyl salicylate (110.3) etc. can be determined with ± 1 to $\pm$ 2% precision [274].

Various phenol esters, dependent upon their substituents, show remarkable discrepancies when titrated in acetone with TBAH in benzene-methanol. Though the precision of measurement does not exceed that of the method of Glenn and Peake [274], it is suitable for the differentiating of various phenol esters [764]. Thus in the titration of phenyl acetate, transesterification takes place owing to the catalytic effect of the basic standard solution containing methanol:

$$R.COOC_6H_5 + CH_3OH \rightleftharpoons R.COOCH_3 + C_6H_5OH.$$

Thus, with phenol esters of aliphatic acids (e.g. phenyl acetate) one phenolic hydroxyl is liberated. When, however, an *ortho* or *para* OH or NH_2 substituent is located on the aromatic ring this prevents the trans-esterification e.g. in the case of *p*-aminophenyl acetate. In the case of acetylsalicylic acid, in contrast to the *m*- and *p*-isomers, the ester bond is not split.

Titration of p-nitrophenyl esters [872]. 'PNP-esters' behave as monobasic acids on titration with sodium methoxide, according to the reaction:

$$O_2N.C_6H_4.O.C(O)-R + NaOCH_3 \rightarrow CH_3.O.C(O)-R + O_2N.C_6H_4-ONa$$

On dissolving the PNP-esters in alcohol or alcohol-dioxan, adding thymol blue and titrating to the blue end-point, it was found that several carbobenzyloxyamino acid PNP esters can be determined with a precision of $\pm 2\%$. The thiophenyl esters react more slowly than the PNP esters.

Chapter 19

Determination of Compounds Containing Alcoholic Hydroxyl

In most cases acid analogues can be determined acidimetrically if a suitable solvent-standard solution and indicator or electrode system are employed. For example, trifluoroethanol can be titrated in butylamine with sodium aminoethoxide in ethanol-amine-ethylenediamine using antimony–glass electrodes [686].

Compounds containing an alcoholic hydroxyl group possess a very low acid strength. However, the conjugate acid of the base employed for the determination must be still weaker. Thus, for example, phenols can be measured with alkali metal methoxides, methanol being a weaker acid than phenol. Hence, it is to be expected that metal amides (e.g. lithium aluminium amide) are suitable for the titration of alcoholic hydroxyl. Acid strength and proton affinity, respectively, decrease in the following orders:

$$C_6H_5OH > CH_3OH > R_2NH; \quad R_2N^- > CH_3O^- > C_6H_5O^-$$

The 'neutralization' of alcohols by metal amides may be symbolized by the following reaction scheme:

$$R_2NM + HOR \rightarrow MOR + R_2NH$$

where M is the metal [387]. Lithium di-n-butylamide in tetrahydrofuran is a suitable standard solution for the determination of active hydrogen e.g. in the presence of *p*-phenylaminoazobenzene as indicator. Ethanol, n-butanol, 1-naphthol, n-pentanol, monoethanolamine, N-ethyl ethanolamine and many other compounds can be determined in this way. Accuracy of determination is $\pm 2{\cdot}5$ to $\pm 5\%$. This method has been employed in investigations of chemical structure, in order to determine the number of active hydrogen atoms originating from an alcoholic functional group. This technique, however, may be the source of many errors therefore a study of the original literature is indispensable [383, 387, 391, 513].

111. Determination by Esterification of Compounds Containing an Alcoholic Hydroxyl Group

The alcoholic hydroxyl group can be determined not only by 'acidimetry' but also by other methods as, for instance, by acylating with classical and well-known reagents all containing acceptor acids. Such are acetic anhydride, propionic anhydride, phthalic anhydride, acetyl chloride, benzoyl chloride, 3,5-dinitrobenzoyl chloride, stearyl chloride, etc. (acetylium ion, CH_3CO^+, is an acceptor acid).In most cases the addition of catalysts: perchloric acid, sulphuric acid, *p*-toluenesulphonic acid, boron trichloride or pyridine is necessary. Acetylation of t-alcohols is more diffcult.

The phenyl isocyanate method is also suitable for the determination of alcoholic functional groups in the course of which an N-phenylcarbamate, in tautomeric form, is produced.

Triethylenediamine, 1,4-diazabicyclo [2,2,2] octane, was found to have almost 100 times the catalytic activity of pyridine for the isocyanate–alcohol reaction.* Schenk, Wines and Mojzis found that triethylenediamine is superior to pyridine for base-catalyzed acetylation of organic hydroxyl groups [719].

(a) *Determination of the hydroxyl number with propionic anhydride.* Propionic anhydride with *p*-toluenesulphonic acid as catalyst is suitable for the determination of the hydroxyl content (propionyl number) e.g., of, glycols, polyoxyalkylene glycol derivatives or steroid alcohols [640, 772, 850].

During reaction between propionic anhydride and *p*-toluenesulphonic acid, protonated propionic anhydride is formed and this, like acetic anhydride, is converted into propionic acid and propionyl cation (cf. Chapter 7; Section 44).

$$(CH_3CH_2CO)_2O + H^+ \rightarrow (CH_3CH_2CO)_2OH^+ \rightarrow (CH_3CH_2CO)^+ + CH_3CH_2COOH$$

Propionyl cation is the acylating ion and in favourable cases even tertiary alcohols can be propionylated.

The acylating mixture is prepared by dissolving 1 g purified *p*-toluenesulphonic acid (free from sulphuric acid impurity) in 30 ml of acetic acid and adding 5 ml of propionic anhydride. The reagent must be used within 15 min of its preparation.

Weigh 0·5–1·5 m.eq. of a monofunctional compound *(a)* into a 5 ml conical ground glass acetylating flask, add 2·0 ml of acylating mixture and after dissolving, allow to stand for two hours at room temperature, or for 30 min at 100°C. After the acylated mixture is cooled (15 min), transfer the contents of the conical flask into a 500 ml thick-walled flask (bottle) into which 25 ml of 0·1 N aniline solution (0·9%) in benzene and 30 ml of acetic acid have been previously pipetted. Aniline reacts with propionic anhydride in excess to form the anilide and anilinium propionate. Allow the reaction to continue for 5–15 min, then titrate with 0·1 N perchloric acid in the presence of five drops of crystal violet to a green colour (*b* ml). The blank test is performed under identical conditions (*c* ml). The difference of the two measurements *(b–c)* is proportional to the propionic anhydride consumed.

$$(CH_3CH_2CO)_2O + ROH \rightarrow CH_3CH_2COOR + CH_3CH_2COOH;$$

$$(CH_3CH_2CO)_2O + 2\,C_6H_5NH_2 \rightarrow CH_3CH_2CONHC_6H_5 + CH_3CH_2COO^- \overset{+}{H_3}NC_6H_5$$

* J. Burkus, *J. Org. Chem.* **26**, 779 (1961).

Anilinium propionate is titrated with perchloric acid. The determination is obscured by acylatable amines.

The *hydroxyl number* is the amount of KOH (in mg) *equivalent* to the acid consumed in the acylation of one gram of a compound containing alcoholic (phenolic) hydroxyl group:

$$\text{Hydroxyl number} = \frac{(b - c) \times 56}{a}$$

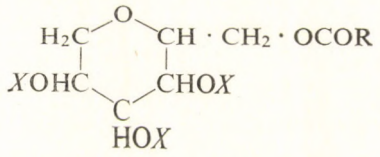
where a = weight (in g)
c = volume (in ml) of standard solution consumed for the blank
b = volume (in ml) consumed during titration.

The following data give an indication of the accuracy of measurements [640];

Compound	*Calculated OH Number*	*Measured OH Number*
Benzyl alcohol	518	512
Cyclohexanol	560	560
Deoxycholic acid	285	280
Deoxycorticosterone	169	168
Hydrocortisone	464	458
Methyl-*p*-hydroxybenzoate	368	369
Cortisone	311	319
n-Octanol	430	435
Isopropanol	933	933
Propylene glycol (acylated for 2 hours at 18°C)	1,473	1,473
Triphenylcarbinol	215	210

For the micro-propionylation method, see; [62].

(b) *Determination of hydroxyl numbers of surface active sorbiton adducts by p-toluenesulphonic acid-catalyzed acetylation* [772]. Sorbiton (monoanhydrosorbite): $C_6H_8O(OH)_4$; Span®; a high molecular weight surface active agent, is an ester of various fatty acids and sorbiton; Tween® is a polyoxyethylene derivative of sorbiton anhydride, partly esterified with fatty acids:



COR = e.g. oleoyl or lauryl; X = polyoxyethylene group

Weigh 5 to 6 m. moles of the compound containing the OH group into a 250 ml glass-stoppered Erlenmeyer flask, add precisely 5·00 ml of 2 M acetic anhydride in ethyl acetate, heat for five minutes on a 50 ± 1°C steam bath, swirl, and, after pressure equalization, heat the solution for another 10 min. After acetylation, hydrolyze the excess of acetic anhydride by adding first 2 ml of water and subsequently 10 ml of a 3 : 1 mixture of pyridine–water. After vigorous shaking wait 5 min, then titrate the acetic acid formed with 0·56 N potassium hydroxide in methanol (b ml). A blank is run in the same way (c ml); calculate by the difference between the two measurements. Use a solution of cresol red–thymol blue as indicator.

$$\text{Hydroxyl number of the compound} = \frac{\dfrac{100}{(c-b)\times f}}{a}$$

where a = the weight (in g)
c = the volume (in ml) found for the blank
b = the volume (in ml) found after acetylation (with 0·56 N standard solution)
f = factor of the standard solution.

Preparation of the reagents:

Anhydride reagent: dissolve 14·4 g of *p*-toluenesulphonic acid monohydrate in 360 ml of ethyl acetate. Agitate preferably with a magnetic stirrer, with protection from light. *Maintaining agitation:* add 120 ml of acetic anhydride in small quantities. The solution is pale yellow but the anhydride content remains unchanged for a few days.

0·56 N potassium hydroxide: dissolve 334 g of KOH in 2,000 ml of absolute methanol, allow to cool protected from moisture and atmospheric carbon dioxide, and filter off the precipitated carbonates if necessary. Finally make up to 9,000 ml with absolute methanol.

Indicator mixture: mix one part of neutralized 0·1% cresol red with three parts of neutralized 0·1% thymol blue (cf. [616]).

Since the catalyst perchloric acid also attacks the ester bonds, the values obtained are 20 to 30% higher than theoretical but with hydrochloric acid the values are about 15% lower.

(c) *Determination of alcoholic hydroxyl group by means of reaction with 3,5-dinitrobenzoyl chloride* [687]. 3,5-Dinitrobenzoyl chloride is a commonly used reagent for the esterification of compounds containing the hydroxyl group [516]. Its disadvantage is that it is hygroscopic; but its advantage, compared with acetic and phthalic anhydrides, is that even tertiary alcohols are esterified, and ketones and aldehydes, when present in concentrations less than 40%, do not interfere.

Alcohols react in pyridine according to the following scheme:

$$\text{R-OH} + 3,5\text{-}(NO_2)_2C_6H_3COCl + C_5H_5N \rightarrow$$

$$3,5\text{-}(NO_2)_2C_6H_3COOR + C_5H_5NH^+Cl^-$$

3,5-Dinitrobenzoyl chloride is hydrolyzed by water:

$$H-OH + 3,5\text{-}(NO_2)_2C_6H_3COCl + C_5H_5N \rightarrow$$

$$3,5\text{-}(NO_2)_2C_6H_3COOH + C_5H_5NH^+Cl^-$$

Of the reaction products, dinitrobenzoic acid and pyridinium chloride can be titrated simultaneously, potentiometrically as strong acids giving the first inflection. The equivalence point of the dinitrobenzoic acid ester, a weaker acid, is indicated by the second inflection in the curve. Dinitrobenzoyl chloride and dinitrobenzoic acid can be titrated as bifunctional compounds with standard TBAH solution in benzene–

methanol (cf. Chapter 20). The dinitrobenzoic acid ester formed is proportional to the OH content of the compound.

Determination is made easy because at the equivalence point of strong acids, the solution turns from yellow to red; a solution of dinitrobenzoic acid ester turns red with one drop of standard solution (the process producing the colour is not yet clarified). This colour change coincides with the first inflection point, thus denoting the amount of dinitrobenzoyl chloride used for esterification.

Visual titration: weigh 4·0 ml of dinitrobenzoyl chloride reagent and add exactly 1·0 ml of the stock solution of the compound to be measured into a 100–150 ml glass-stoppered Erlenmeyer flask. (Preparation of the stock solution: weigh about 4 m.eq. of the liquid into a previously weighed 10 ml measuring flask into which 3 ml of pyridine have been pipetted. After reweighing make up to the mark with pyridine.) Agitate and then allow the tightly stoppered solution to stand for 5–15 min. Hydrolyze the acid excess of chloride with 7–10 drops of water. Add 40 ml of pyridine to the hydrolyzed mixture, heat nearly to boiling, then cool, finally titrate with 0·2 N TBAH to the first vivid red colour. A semimicro-burette which enables the standard solution to be protected from moisture and carbon dioxide is most suitable. The tip of the burette should be under the surface of the solution to be tested. The latter should also be protected from atmospheric moisture. The blank is titrated in the same way. Solid alcohols are measured directly in the titrating flask using quantities of about 0·4 m.eq. To calculate the result use the difference between the millilitres consumed in the blank and titration. One m. mole of a monofunctional compound requires one ml of standard 0·2 N TBAH solution. For calculations see: Chapter 13; Section 76.

Preparation of reagents: 0·2 N TBAH in benzene–methanol (see: Chapter 10; Section 57) but with the modification that double the amount of alkylammonium iodide and silver oxide are required and 300 ml of methanol are needed instead of 180 ml. The solution passes through the anion exchange column at 7–10 ml/min.

Pyridine purified by the barium oxide method is a suitable solvent (Chapter 8; Section 49 (i)).

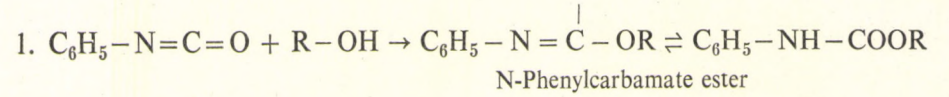
Prepare dinitrobenzoyl chloride reagent freshly by dissolving 1·15 g finely ground 3,5-dinitrobenzoyl chloride with gentle heating in 25 ml of pyridine. During solution, carefully exclude atmospheric moisture. Store the dry reagent over phosphorus pentoxide in a desiccator.

Primary aliphatic alcohols, such as cholesterol, propylene glycol, cyclohexanol, menthol, benzyl alcohol, cetyl alcohol, triethylene glycol, glycerol, dextrose, saccharose, pentaerythritol, mannose, stigmasterol, etc. can be determined by this method with an accuracy of about $\pm 0{\cdot}2$ to $\pm 0{\cdot}6\%$.

Of the five OH groups of (−) sorbose and fructose, four are esterified by acetylation for five minutes at room temperature, followed by immediate dilution with pyridine and titration. Tertiary alcohols, e.g. t-butanol or 2-methylbutan-2-ol must react for 24 or 48 hours. Triphenylmethanol is not affected even after reaction for 100 hours; 0·4 m. mol of ethanol can be measured with $\pm 2\%$ accuracy in the presence of 0·1–0·4 m. mol triphenylmethanol, tribenzylamine, acetone, cyclohexanone and benzaldehyde.

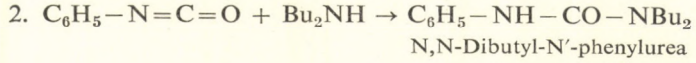
(d) *Determination of alcoholic hydroxyl groups by the phenyl isocyanate method* [669]. The method essentially consists in reacting the compound containing alcoholic OH with an excess of phenyl isocyanate, in the presence of tin(II) octanoate catalyst.

After the reaction has been completed, the unchanged phenyl isocyanate is bound with a known quantity of dibutylamine used in excess. The quantity of dibutylamine that has remained free is finally titrated with perchloric acid:



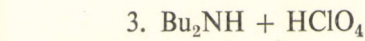
1. $C_6H_5-N=C=O + R-OH \rightarrow C_6H_5-N=C(OH)-OR \rightleftharpoons C_6H_5-NH-COOR$

N-Phenylcarbamate ester



2. $C_6H_5-N=C=O + Bu_2NH \rightarrow C_6H_5-NH-CO-NBu_2$

N,N-Dibutyl-N′-phenylurea



3. $Bu_2NH + HClO_4 = Bu_2NH_2^+ ClO_4^-$

Tin(II) octanoate, $Sn(C_8H_{15}O_2)_2$, is a relatively selective catalyst for the alcohol-isocyanate reaction. It is used in urethane foam formulations.

Two portions of the sample to be tested are weighed out, neither of them containing more than 11 m.eq. of OH groups, and placed in two 500 ml ground glass Erlenmeyer flasks. If the reaction is to be run at 98°C, heat and pressure resistant flasks should be used. The samples are dissolved in 25 ml of dimethylformamide each, and stirred until completely dissolved. Neither the DMF nor the toluene used (see below) should contain more than 0·01 % of water, since phenyl isocyanate is quantitatively decomposed by water. After dissolving, a reagent containing exactly 20 ml of phenyl isocyanate and 1·0 ml catalyst solution is added and the stoppered flasks are allowed to stand (see table on p. 293). At the same time, using identical pipettes and reagents, blank tests are made in two 500 ml Erlenmeyer flasks.

After the waiting time is over, precisely 20 ml of the reagent containing the dibutylamine is added to all four flasks and, after stirring, they are allowed to stand for 15 min. The solutions are finally diluted with 100 ml of Methyl Cellosolve each, and titrated with 0·5 N perchloric acid in Methyl Cellosolve. As indicator 0·1 % bromocresol green solution in methanol is used: the first characteristic yellow colour change indicates the end-point. One ml of 0·5 N perchloric acid is equivalent to 8·5 mg OH group. The volume consumed in the blank test must be taken into account and the calculation is made with the difference (see: Chapter 13; Section 76).

Solvents and reagents: carefully dried dimethylformamide and toluene ($H_2O < 0·01\%$). Phenyl isocyanate reagent 1 N: 109 ml (= 119 g) of phenyl isocyanate is dissolved in 500 ml of toluene and the solution made up to 1,000 ml. The reagent should be stored in a bottle closed with a cap lined with an aluminium foil. If a precipitate appears in the solution, fresh reagent must be prepared. Dibutylamine reagent, 2 N: 337 ml (= 256 g) of dibutylamine is diluted with toluene to 1,000 ml. Catalyst solution: 21 g of tin(II) octanoate is dissolved in 100 ml of toluene. Perchloric acid standard solution (in glycol monomethyl ether) (see: Chapter 11; Section 60 (e)).

By the method given above, the following compounds containing OH groups can be determined according to [669] (abridged):

Compound	*Reaction Time,* min	*Reaction Temperature,* °C	*Accuracy of the Determination*
n-Butanol	15	Room temp.	99·9 ± 0·34%
t-Butanol	15	98	
2,2-Dimethyl-1,3-butanediol	30	98	
2,2-Dimethyl-1,3-propanediol	60	Room temp.	
Sorbitol	60	,, ,,	
Propylene oxide adduct of sorbitol	30	,, ,,	110 ± 0·9 eq. wt.
Tripropylene glycol (2 ml of catalyst solution must be used)	30	,, ,,	

Water, primary and secondary amines interfere with the determination since they react quantitatively with phenyl isocyanate. Tertiary amines do not react; however, they consume perchloric acid. Aromatic OH compounds when present in quantities higher than 1% have a disturbing effect.

112. Application of Perchloric Acid Catalyst to Acetylations with Ethyl Acetate-acetic Anhydride or Pyridine-acetic Anhydride Reagent

Strong acids as e.g. perchloric and *p*-toluenesulphonic acid catalyze the acylation of compounds containing OH; the acetylation of primary and secondary alcohols then requires only 5 min with acetic anhydride in ethyl acetate [257].

The mechanism of the perchloric acid catalyzed acetylation in acetic acid [110], or ethyl acetate [257] is as follows:

$$Ac_2O + H^+ \rightarrow Ac_2OH^+; \quad Ac_2OH^+ \rightleftharpoons Ac^+ + AcOH$$

$$Ac^+ + R-OH \rightarrow R-OAc + H^+ \text{ (acetylation)}$$

In pyridine [257]:

$$C_5H_5NH^+ + Ac_2O \rightleftharpoons (C_5H_5NAc)^+ + AcOH$$

$$(C_5H_5NAc)^+ + R-OH \rightarrow R-OAc + C_5H_5NH^+ \text{ (acetylation)}$$

Ac_2O = acetic anhydride
Ac_2OH^+ = acetanhydrium ion
Ac^+ = acetylium ion, (cf. Chapter 7; Section 44).
For pyridine-acetylium ion see: [278].

Not only alcohols but also numerous other compounds can be acetylated (in the presence of catalytic amounts of perchloric acid) by acetic anhydride in ethyl acetate including phenols, polyphenols, hexoses, mercaptans, amines, ketoximes and *vic*-dioximes [715, 716]. The advantage of this method is that sterically hindered phenols can also be determined. When mixtures of compounds containing alcoholic and phenolic OH group must be analyzed, the total OH-content is determined by acetylation and that of the phenolic OH, acidimetrically. Nitroaniline derivatives are either weak bases, or extremely weak acids; their acid–base titration is difficult but their quantitative determination can be achieved by acetylation. 4-Methoxyphenol and

N-methylaniline can be determined with sufficient accuracy even in the presenec of a sterically hindered phenol of a less reactive aniline derivative, with 0·25 M acetic anhydride in pyridine.

For acetylation, anhydride reagents in ethyl acetate or pyridine are employed, dependent upon the problem to be solved. Acetic acid formed after the decomposition of excess acetic anhydride is titrated with 0·55 N or 0·15 N NaOH in Methyl Cellosolve. Thus, the last step of the procedure is the titration of acetic acid with a strong base. Information concerning the preparation of reagents is given below:

Reagent A

Solvent: Ethyl Acetate; Anhydride: 2 M; *Perchloric Acid: 0·15* M

Add 4 g (= 2·35 ml) of 72% perchloric acid to 150 ml of ethyl acetate (H_2O max.: 0·1%). While stirring continuously, mix with 8 ml of acetic anhydride and allow the stoppered solution to stand for 30 min at room temperature. Cool to 5°C, and, maintaining agitation, add 42 ml of acetic anhydride; keep for one hour at 5°C. The reagent thus prepared is usable for about two weaks.

Reagent B

Solvent: Ethyl Acetate; Annhydride: 0·25 M; *Perchloric Acid: 0·006* M

To 200 ml of ethyl acetate, add 0·10 ml of 72% perchloric acid and 6·5 ml of acetic anhydride drop by drop: use magnetic stirring for five minutes. Reagent can be used for about two weeks.

Reagent C

Solvent: Ethyl Acetate; Anhydride: 0·25 M; *Perchloric Acid: 0·003* M

Use only 0·05 ml of perchloric acid as catalyst, otherwise prepare as reagent B. Use after standing for one day.

Reagent D

Solvent: Pyridine; Anhydride: 2 M; *Perchloric Acid: 0·15* M

Add carefully, drop by drop and constantly stirring, 0·8 g (= 0·47 ml) of 72% perchloric acid to 30 ml of pyridine, and subsequently, maintaining agitation, 10 ml of acetic anhydride. Fresh reagent must be prepared daily.

Reagent E

Solvent: Pyridine; Anhydride: 0·25 M; *Perchloric Acid: 0·02* M

Add 0·12 ml of 72% perchloric acid to 80 ml of pyridine containing less than 0·1% of water, then mix with 2·5 ml of acetic anhydride and shake for five minutes. The reagent can be used for about one day.

Reagent F

Solvent: Pyridine; Anhydride: 0·35 M; *Perchloric Acid: 0·04* M

Apart from using 0·24 ml of perchloric acid and 3 ml of acetic anhydride prepare in the same way as reagent E.

Warning! Laboratory safety measures must be carefully observed when reagents containing perchloric acid are made up. Wear goggles and gloves and work in a fume cupboard. The prepared reagents should not be heated. The titrated solution, and also the blank, must be diluted immediately with tap water.

In addition to the above, 0·55 N and 0·15 N sodium hydroxide and indicator mixtures are needed: Chapter 11; Section 60 (j).

(For indicator mixture see: Section 111 (b).)

(a) *Determination of primary and secondary alcohols* [257]. Weigh 3–4 m. moles of a compound containing OH into a 100–150 ml glass-stoppered Erlenmeyer flask; add exactly 5·0 ml of reagent A, stir till dissolved and allow to stand for 5 min. Hydrolyze the excess of acetic anhydride with 1–2 ml of water and 10 ml of a 3 : 1 mixture of pyridine and water and allow to stand again for five minutes. After adding indicator mixture, titrate with 0·55 N sodium hydroxide and take the colour change from yellow to violet as the end-point (*c* ml); a blank test is run in the same way (*b* ml). Use the difference between the volumes consumed for the calculation. (Cf. Chapter 13; Section 76.)

Acetylating for five minutes enables aliphatic primary and secondary alcohols, benzhydrol, benzoin, cyclohexanol, glycerol, cellobiose (35 min), glucose (45 min), lactose, mannose, maltose etc. to be determined by this method; with an average accuracy of $\pm 0{\cdot}4\%$.

Reagent *D*, being a milder acetylating agent than reagent *A*, is used for the determination of primary alcohols in the presence of tertiary alcohols; (the reaction time is given in minutes in brackets): methanol (7–10), 2-ethylhexanol (10–15), cyclohexanol (18–20), 2-propanol (20–25).

(b) *Acetylation of phenols, thiols and amines* [716].

1. Weigh 3 to 4 m. moles of a compound containing OH, SH or NH_2 group into a 100–150 ml glass-stoppered Erlenmeyer flask; add exactly 5·0 ml of reagent *A*, mix till dissolved and allow to stand for five minutes. Hydrolysis of excess acetic anhydride as above (a). Titrate in the presence of the indicator mixture with 0·55 N sodium hydroxide in Methyl Cellosolve to a colour change from yellow to violet (*c* ml). A blank test is performed in the same way (*b* ml). To calculate the percentage use the difference $b-c$ (Chapter 13; Section 76).

2. If the sample is only 0·4–0·6 m. moles, the volume of the Erlenmeyer flask should be 50–100 ml and reagent *B* the acetylating agent. Otherwise proceed as described above in case (1), but add only 5 ml of pyridine-water (3 : 1) to hydrolyze the acetic anhydride. Standard solution: 0·15 N sodium hydroxide. The following can be determined with an accuracy of approx. $\pm 0{\cdot}4\%$ (minutes required for acetylation, and type of reagent in brackets): 2-t-butylphenol (5, *A*), 2,6-di-t-butyl-4-cresol (5, *A*), resorcinol (5, *A*), 2,6-di-isopropylphenol (5, *B*), 2,6-dimethylphenol (5, *B*), t-butylmercaptan (5, *A*), thiocresols (5, *A*), n-butylamine (15, *A*), N-methylaniline (10, *B*), 2-nitroaniline (60, *A*), 3-nitroaniline (20, *A*), 4-nitroaniline (75, *A*), *o*-phenylenediamine (5, *A*), diphenylamine (45, *A*).

Using reagent *E*, 4-methoxyphenol and N-methylaniline can be determined by the above method in the presence of sterically hindered phenols or aniline derivatives [716].

Sterically Hindered Phenols	mol% (*Reacted after* 20 min)
2,6-Di-t-butyl-*p*-cresol	5–10
2,6-Di-t-butylphenol	5–10
2-t-Butylphenol	5–10
2,6-Di-isopropylphenol	80
Methyl salicylate	80

Amines	mol% (*Reacted after* 15 min)
Diphenylamine	5–14
2-Nitroaniline	5–14
4-Nitroaniline	80

For the determination of 2-t-butylphenol in the presence of 2,6-di-t-butylphenol, reagent *C* and method (*b*, 2) are employed (25–66 mol% of butylphenol).

(c) *Determination of cyclohexanone oxime* [715]. Weigh a sample of 0·3–0·7 m. mole into a 50 ml glass-stoppered Erlenmeyer flask, add precisely 5·0 ml of reagent *F*, and, after dissolving, allow to stand for 5–10 min. Hydrolyze the excess of acetic anhydride with 0·10–0·15 ml of water, and, after waiting for another 10 min, dilute with 30 ml dimethylformamide neutralized in the presence of thymol blue. Finally titrate with 0·15 M sodium methoxide. A blank is run in the same way; to calculate use the difference between the two measurements. 16·97 mg of cyclohexanone oxime require 1 ml of 0·15 N standard solution. In this procedure the hydroxyl of the $-C=N-OH$ group is acetylated.

113. Determination of a Mixture of Compounds Containing Alcoholic Hydroxyl

Owing to the different size and structure of molecules, rates of reaction of a given reagent with the same functional groups in different organic compounds may vary considerably.

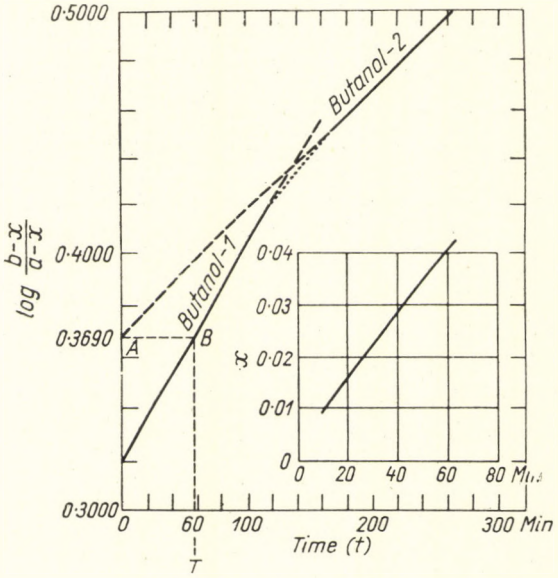


Fig. 111

A second-order reaction is one where the rate of reaction is proportional to the product of the molar concentrations of two co-reactants. Let us denote the co-reactants by *A* and *B*, their concentration by *a* and *b*, and the equivalent quantity of *A*

and B which has reacted at a certain time t by x. The rate of reaction is in this case:

$$dx/dt = k\,(b - x) \times (a - x)$$

On integration (taking $x = 0$, at $t = 0$; and $x = x$, at $t = t$) the rate constant of the reaction is:

$$k = \frac{2{\cdot}303}{t\,(b - a)} \log \frac{a\,(b - x)}{b\,(a - x)}$$

If the circumstances of the investigation and the concentration ratios are favourable mixtures of propan-1-ol and propan-2-ol, or butan-1-ol and butan-2-ol etc. can be determined [749]. To obtain a straight line in second-order reactions the value of $\log\,(b-x)/(a-x)$ must be plotted against t. When two second-order reactions take place in a single mixture a plot with two straight-line segments is obtained (Fig. 111). This holds good if the rates of reaction differ, e.g. butan-1-ol with acetic anhydride and butan-2-ol with acetic anhydride. For the determination, proceed as follows. By a known method, for example, acetylation, propionylation etc. the total butanol content of the binary system, e.g. butan-1-ol and butan-2-ol is determined. For this the stock solution is taken and the total butanol content expressed in molar concentration, a:

$$a = (D - C) \frac{N}{\text{aliquot of stock solution in ml}} \times \frac{E}{M}$$

where D = volume in ml consumed for the mixture pyridine–acetic anhydride–water (i.e. the blank test)
C = volume in ml consumed of the standard solution
N = normality of the standard solution
E = equivalent weight of the compound containing hydroxyl
M = molecular weight.

The sample, weighed into a 250 ml measuring flask, should not exceed 0·05 M of OH group. Add about 240 ml of pyridine, 10 ml of acetic anhydride and rapidly make up to the mark with pyridine. *Immediately note the time.* At intervals of 5–10 min pipette 10 ml aliquots into a glass-stoppered Erlenmeyer flask and add 5 ml of water to prevent further acetylation. *The time is noted again.* After 10 min titrate the acetic acid formed, with 0·1 N potassium hydroxide in the presence of the indicator mixture. For the preparation of the latter, mix two parts of a solution of 0·1% Nile blue in 50% ethanol with a solution of 1% phenolphthalein in 95% ethanol. The blank consumption of the reagent containing acetic anhydride is determined in the same way: in a 250 ml measuring flask, 10 ml of acetic anhydride is diluted with pyridine. 10 ml of this stock solution is mixed with 5 ml of water and, after 10 min, titrated as above. The molar concentration of the acetic anhydride solution (per litre):

$$b = \frac{D \times N}{\text{aliquot of stock solution in ml}} \times \frac{E}{M}$$

in this case E is the equivalent weight of acetic anhydride.

The decrease of molar concentration of the compound containing the hydroxyl group (x) is plotted as a function of time (minutes, t): Fig. 111. The value of log $(b-x)/(a-x)$ is also plotted against time.

The straight line representing the less reactive butan-2-ol is extrapolated to zero time. A line parallel to the abscissa connects the point of intersection A (log 0·369) with the straight line representing the more reactive butan-1-ol. The intercept B so obtained corresponds to a certain time T (e.g. $T = 59{\cdot}5$ min). By reading the graph of the function x against t, the decrease of molar concentration for time T can be found (e.g. $x = 0{\cdot}0398$). Thus the quantity of the more reactive component in the binary system expressed as a percentage is:

$$x/a \times 100$$

An alternative calculation is to take the reading of the value at point A, and to substitute this value as well as the known molar concentrations of the alcohol and the anhydride solutions into the following equation: decrease of molar concentration (at time T)

$$x = \frac{A' \times a - b}{A' - 1}$$

where a = the total molar concentration of the binary system containing the OH group
b = the molar concentration of acetic anhydride in pyridine
A' = the antilogarithm of the value for point A found by graphical extrapolation.

A simple example is given to illustrate the above [749]:

$a = 0{\cdot}2$ moles butanol/litre
$b = 0{\cdot}415$ moles acetic anhydride/litre
$A' =$ antilog $0{\cdot}3690 = 2{\cdot}339$.

On substituting:

$$x = \frac{2{\cdot}339 \times 0{\cdot}2 - 0{\cdot}415}{2{\cdot}339 - 1} = 0{\cdot}0395$$

Percentage of butan-1-ol in the binary system:

$$\frac{0{\cdot}0395}{0{\cdot}2} \times 100 = 19{\cdot}8\%$$

Calculation of the function x against t for the decrease of molar concentration: plot molar concentration of the total butanol content less molar concentration found after acetylation, at t time intervals.

Three advanced methods of calculation are proposed by Reilley and Papa by which slower reacting components can also be estimated [673].

It is advisable to use acetic anhydride in a molar ratio of 2 : 1 compared with the hydroxyl containing compound.

When co-reactants of higher reactivity exceed 70%, graphic calculation and assessment become more difficult. Too rapid a reaction rate may be another obstacle to resolving a binary system. The molar concentration of the reactants must not be identical because then $a = b$ and $\log (b - x)/(a - x) = 0$.

This method can also be applied to a mixture of aldehydes, ketones and primary amines [347, 749]. Its advantage is that isomeric or homologous binary (in some cases even ternary) mixtures containing identical functional groups can be determined. However, it is a time-consuming method needing considerable amounts of solvents (e.g. 500 ml of pyridine) and this must be considered a disadvantage.

Chapter 20

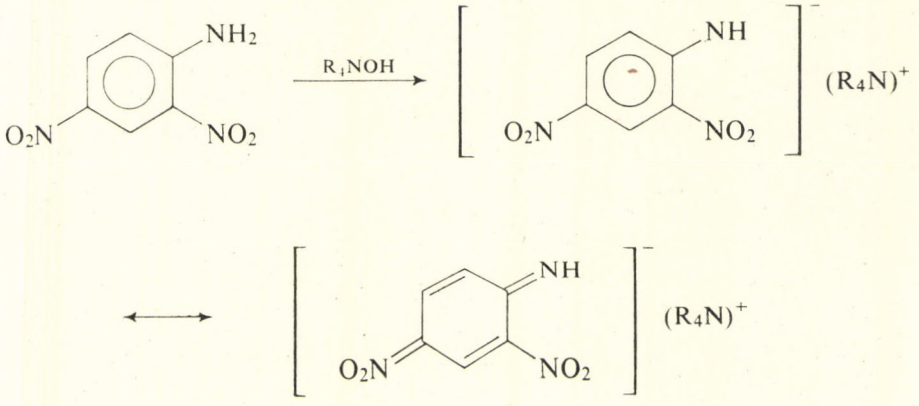
Determination of Nitro Compounds

114. Aromatic Nitro Compounds

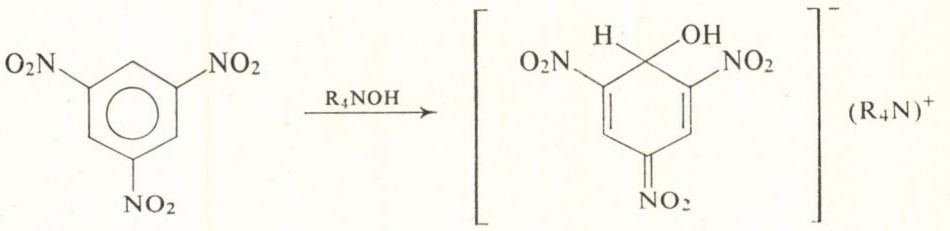
Nitro derivatives of benzene or phenol can be titrated as acids in pyridine or ethylenediamine [91, 93, 254, 731]. Phenolic hydroxyl and the carboxyl group are donor acids, in aromatic nitro compounds; while the partly polarized aromatic ring is an acceptor acid, and the reagent, possessing excess electrons, co-ordinates with the electron deficient carbon atom or that of diminished electron density.

When picric acid is potentiometrically titrated with sodium aminoethoxide in ethylenediamine one inflection can be observed but three equivalents are consumed. Thus besides the phenolic hydroxyl two carbon atoms of the ring also behave as acceptors. In the case of *m*-dinitrobenzene the consumption of two equivalents of standard solution is indicated by two inflections, implying co-ordination at two carbon atoms in the ring. Nitrobenzene cannot be titrated in ethylenediamine. In the sense of donor-base–acceptor-acid interaction, the reactivity of the polarized aromatic ring manifests itself not only towards alkoxide anions but, to a certain degree, also towards alcohols, dioxan and compounds containing an amino group.

In the case of nitroanilines and nitrodiphenylamines it can be assumed that one hydrogen of the amino group has an acidic character [254]:



In the case of trinitrobenzene the OH group of tetrabutylammonium hydroxide is added to the benzene ring, the negative change again being distributed on the oxygen of the nitro groups:



Numerous nitroaromatic compounds can be titrated potentiometrically in pyridine with 0·1 N triethylbutylammonium hydroxide in benzene-methanol [254]. Weigh in 0·4 to 0·8 m. eq. of the sample; dissolve in 40 ml pyridine neutralized in the pressnce of thymol blue or azo-violet, and, using glass–calomel electrodes, titrate with etandard solution containing $Et_3BuN^+OH^-$. The following give a sharp inflection:

Nitroaniline Derivatives	*Nitrodiphenylamine Derivatives*	*Polynitro Aromatic Compounds*
2,6-Dichloro-4-nitroaniline	4-Nitrodiphenylamine	2,4,6-Trinitrotoluene
2,4-Dinitroaniline	2,4-Dinitrodiphenylamine	1,3,5-Trinitrobenzene
2,4,6-Trinitroaniline (picramide)	Hexanitrodiphenylamine	2-Bromo-4,6-dinitrotoluene
		2,4-Dinitrotoluene

Determinations are less precise than for enols or phenols and the values obtained are somewhat high: 2- and 4-nitroaniline as well as 2-nitrodiphenylamine are not titratable.

Regarding the determination of 2-nitrodiphenylamine in the presence of 2,4-dinitrodiphenylamine, see [558]. N-Nitrosodiphenylamine can be titrated neither as an acid nor as a base. It is determined by an indirect method *via* the reaction with excess of 1-naphthylamine; (see: Chapter 23; Section 120 (e)).

Orchin and Woolfolk reported that 2,4,7-trinitrofluorenone enters into complex formation with polynuclear compounds, e.g.: perylene, fluoranthene, phenanthrene, chrysene, pyrene, anthracene.* These complexes are comparatively easy to prepare and have proved to be useful for the characterization of this group of aromatics. Cundiff and Marcunas [165] observed that the molecular complexes of trinitrofluorenone dissolved in pyridine can be titrated as acids: 2 to 20 mg of the trinitrofluorenone complex is dissolved in 50 ml of pyridine, and titrated potentiometrically, in a nitrogen atmosphere, with 0·01 N tetrabutylammonium hydroxide. See also: [159, 164]. The use of indicators in this determination is not satisfactory as all solutions become highly coloured in the course of the titration.

Besides the above compounds, 2,4-dinitrophenylhydrazine and also 2,4-dinitrophenylhydrazones, formed by reaction of aldehydes and ketones with the hydrazine, can be titrated as acids [731]. Dissolve 2–20 mg of the hydrazone in 50 ml of pyridine and titrate potentiometrically under a nitrogen blanket with standard 0·01 N or 0·02 N TBAH in benzene using a glass–calomel electrode system. This is a good method for the identification (by determination of equivalent weight) of compounds containing a carbonyl group; accuracy 2%, even with a sample of 1–2 mg. Regarding the titration of *p*-nitrophenylhydrazones, see [688].

* *J. Am. Chem. Soc.* **68**, 1727 (1946).

Trinitrotoluene, *dinitrotoluene* and *pentaerythritol tetranitrate* can be titrated in methyl isobutyl ketone with 0·1 N TBAH in benzene-methanol. The potentiometric titration is performed with a platinum (40% rhodium) indicator electrode and calomel reference electrode [710].

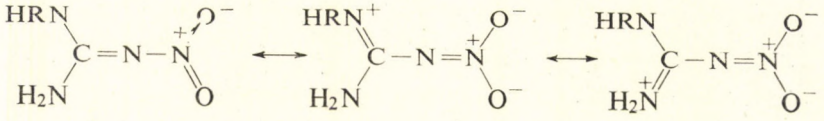
Trimethylenetrinitramine (Hexogen; hexahydro-1,3,5-trinitro-*s*-triazine, molecular weight 222.1) and octahydro-1,3,5,7-tetranitro-*s*-tetrazine (mol. wt. 296·2) may be titrated with TBAH titrant in the presence of azo-violet indicator in pyridine, piperidine, ethylenediamine, dimethylformamide, dioxan, tetrahydrofuran, acetone, methyl isobutyl ketone and acetonitrile. Trimethylenetrinitramine may also be titrated in dimethylformamide with sodium methoxide [223, 449, 710].

Determination of hexahydro-1,3,5,-trinitro-s-triazine (RDX) *in admixture with octahydro-1,3,5,7-tetranitro-s-tetrazine* (HMX), [759]. The method is based on the potentiometric titration in methyl isobutyl ketone—isopropanol mixture (4:1), with 0·1 N sodium methoxide in benzene—methanol as the titrant. The electrode system is a sleeve-type calomel electrode with potassium chloride in methanol and antimony–antimony oxide electrode.

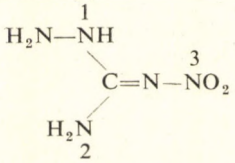
By incorporating 20% isopropanol in the methyl isobutyl ketone, the potentiometric titration curve of the mixture of RDX and HMX shows an inflexion which corresponds to that of the RDX. HMX even up to a concentration of about 80% does not interfere with the titration of RDX. In methyl isobutyl ketone RDX behaves relatively as a stronger acid than HMX. By lessening the basicity of the solvent, the difference in the acid strengths of RDX and HMX can be enhanced.

115. Nitroguanidine and Derivatives

The acidic character of nitroguanidine and derivatives becomes immediately apparent in dimethylformamide (cf. Chapter 2; Section 21). It can be assumed that the acidic hydrogen originates from the amino group bearing the electron attracting acid substituent [182, 183, 488]. Nitroguanidine is mesomeric:



1-Amino-3-nitroguanidine illustrates that the amino group can have the effect of increasing acid strength (cf. Chapter 4; Section 25 (e).



pK_a 10·60 [182]
10·47 [488]

Weigh nitroguanidine (pK_a 12·20) or its derivative in an amount which will give a titre of 3–9 ml of 0·1 N $NaOCH_3$ in benzene-methanol. Dissolve in 50 ml of dimethylformamide, neutralized in the presence of five drops of azo-violet, and titrate till a blue colour is produced; a nitrogen atmosphere improves titration. 1-Amino-, 1-phenyl-1-methyl-, 1-(2-pyridyl)-, 1-benzyl-, 1-benzoyl-, 1-(1- or 2-phenylethyl)-, 1-(*p*-dimethylaminophenyl)-, 1-(*p*-cyanophenyl)-nitroguanidine, nitroguanylmorpholine, etc. can be determined in this way. Of the listed compounds, 1-benzoyl-, and/or 1-(*p*-cyanophenyl)-nitroguanidine (pK_a 8·10 and /or 8·60) have the strongest acid character.

Nitroguanidine can also be titrated as a base with perchloric acid in trifluoroacetic acid [183].

Chapter 21

Semimicro and Micro Titration of Acids and Acid Analogues

Owing to the effect of atmospheric carbon dioxide, semimicro and micro titration of acids and acid analogues is far more difficult than microtitration of bases in acetic acid. The fact that when the normality of the titrant decreases, its efficiency also decreases, causes further difficulties. The normality of standard perchloric acid can be decreased even to 0·001 N without lessening the accuracy of measurement to an inconvenient degree. For titrations performed in basic solvents this cannot be applied directly since the blank value of the solvent and atmospheric CO_2 cause disturbances. If the titration volume is as small as possible, say 3 ml for a sample of 2–10 mg, this difficulty can be partly eliminated.

With such a small volume an adequate ratio between liquid surface and the volume of the liquid, and between the titration vessel's internal area and the titrated volume can be achieved only if the smallest possible titration vessel is used and complicated parts are omitted. For this reason, among others, the use of hydrogen electrodes is unsuitable [92, 176, 562, 601]. See Figs 112, 113 and 114.

The apparatus shown in Fig. 112 shows that an indicator electrode, inserted under the stopcock of the burette, can be employed as reference electrode as in this way it is immersed in a liquid of constant ion strength. The standard solution in the jet of the burette is the salt bridge and the upturned hook-like tip of the jet hinders convection. When the standard solution is fed in, the capillary is always filled with fresh solution, and hence diffusion errors are eliminated. A simple platinum electrode can be used as electrode [285]. With the technique described below and the apparatus shown in the figure good results can be achieved even if both the indicator electrode and the reference electrodes are of platinum. The solution should be agitated by a magnetic stirrer.

Because of the polarizability of the electrodes, potentiometric measurement should be, if possible, accomplished in such a way that the current passing through the system does not exceed 10^{-10} amp. Therefore, measurement by compensation cannot be employed even when a tube galvanometer is used.

Owing to the great resistance of the system, especially in a benzene-methanol solvent mixture, capacitive troubles arise and, therefore, it is advisable to place the

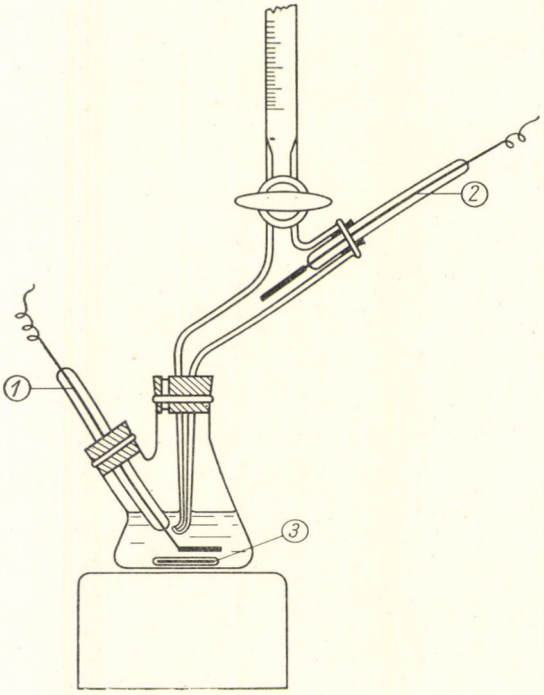


Fig. 112. Equipment for microtitrations due to Brockmann and Meyer [92]. — *(1)* Platinum indicator electrode, *(2)* Platinum reference electrode, *(3)* Magnetic stirrer

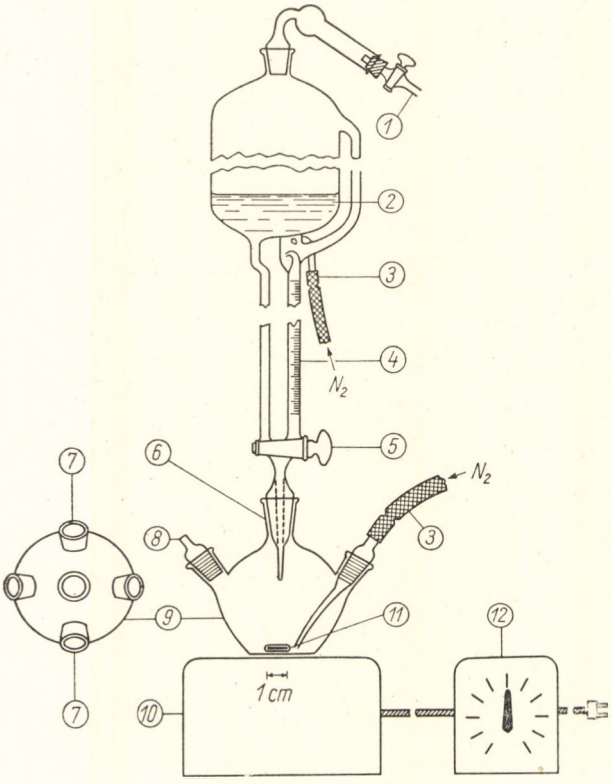


Fig. 113. Equipment for microtitrations due to Maurmeyer, Margosis and Ma [562]. — *(1)* Excess pressure outlet, *(2)* Titrant, *(3)* Nitrogen inlet, *(4)* Burette, *(5)* Two-way Teflon stopcock, *(6)* Ground glass joint, *(7)* Electrode inlets, *(8)* Nitrogen outlet, *(9)* Microtitration vessel of 50 ml capacity, *(10)* Magnetic stirrer, *(11)* Magnetic bar, *(12)* Rheostat

entire titration equipment in a Faraday cage. When ethylenediamine is used a film of the latter may mist over the burette and apparatus. Owing to the conductivity of the condensed vapour stray currents may arise; therefore the whole equipment must be kept clean and dry.

For micro titrations a 2 ml burette is used, and this as well as the vessel containing standard solution are protected from atmospheric moisture by a ground joint absorption tube. An Erlenmeyer flask of 5–10 ml volume is the titration flask, its side-arm

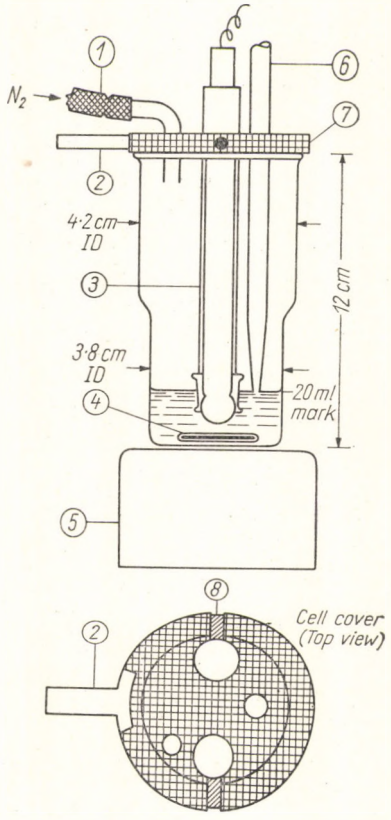


Fig. 114. Reduced-scale titration cell according to Deal and Wyld [176]. — *(1)* Nitrogen inlet, *(2)* Brass handle, *(3)* Glass and calomel electrodes, *(4)* Stirring bar, *(5)* Magnetic stirrer, *(6)* Microburette, *(7)* Bakelite cell cover, *(8)* Setscrew for electrodes

serving for introduction of the indicator electrode. The core of the magnetic stirrer is made of 8–10 mm wire incorporated and soldered in the capillary.

The platinum electrodes are 3 mm wide and 6 mm long laminae prolonged as platinum wires and soldered in a 7 cm long glass tube. Before use the electrodes are ignited in a non-luminous gas flame. Leads should be earthed.

Titration in ethylenediamine. Weigh 2–10 mg of the sample into a dry flask, insert the dry magnetic stirrer, make up the burette to the mark and clean the tip of the burette capillary, drawn out in a cone, with cotton-wool moistened with alcohol. Transfer 3 ml of ethylenediamine from an Ascarite-protected burette into a small flask and connect immediately with the burette (Fig. 112). Clean the flask carefully with cotton-wool moistened with alcohol, especially around the points of entry of the electrodes, then dry to avoid stray currents. When a constant potential is reached (1–5 min), titrate with 0·05 N sodium aminoethoxide in ethylenediamine.

Wash 120 mg of metallic sodium with ethanol and aminoethanol; dissolve (at 35C°) in 2 ml of aminoethanol in a 100 ml measuring flask previously flushed with nitrogen and finally dilute with ethylenediamine to the mark.

Agitate after addition of each portion of the standard solution, then switch off the magnetic stirrer and wait until a constant potential is established. The period for each potentiometric measurement is 20–40 min. The accuracy of measurement can be greatly increased if the following order is observed: blank–standardization–titration–standardization–blank.

The apparatus shown in Fig. 113 is suitable for semimicro titration of acids and acid analogues [562]. One of the five side-arms of the 50 ml titration flask is in line with the axis of the flask and serves for the introduction of the exit tube of the automatic burette. In two side-arms two electrodes are inserted: side-arms 4 and 5 serve for inlet and outlet of nitrogen. Magnetic stirring is employed. 0·02 N sodium methoxide is a suitable standard, with glass as the indicator electrode and calomel as the reference electrode. Standard solution is best stored in borosilicate bottles under nitrogen. During titration the electrodes should be 2 mm below the surface of the liquid and about 5 mm apart; 0·3% thymol blue in methanol or 0·5% azo-violet in benzene-methanol (1 : 2) should be used as indicator.

Acidic contamination of the solvent may cause large errors in the semimicro titration of acids, so that neutralization prior to titration is essential. In this respect pyridine and dimethylformamide are more suitable than methyl isobutyl ketone since 5 ml of the former two solvents may contain on an average 0·002 m.eq. of acidic impurities while methyl isobutyl ketone may contain 0·09 m.eq.

Prior to determination add 0·03 ml of thymol blue or 0·015 ml of azo-violet to the 5 ml solvent and regulate the nitrogen stream in such a way that bubbles can be counted, then neutralize with a solution of 0·02 N concentration to a blue colour. Weigh approx. 0·1 m.eq. of the sample into a small dry measuring vessel and admit through one of the side-arms into the apparatus. Reweigh the small vessel. Following dissolution of the compound, titrate under nitrogen to a clear blue colour. Determine the factor of the standard solution against benzoic acid similarly.

For potentiometric titrations neutralize 15 ml of the solvent, then proceed as above, but determine the end-point with electrodes.

Dimethylformamide, pyridine and methyl isobutyl ketone are suitable solvents. Numerous compounds containing phenolic and enolic hydroxyl or imino groups can be titrated accurately (Table 34).

For the potentiometric as well as visual determination of acids whose pK value does not exceed 10·5–11, dimethylformamide is a suitable solvent. Pyridine can be employed as solvent in cases where the potentiometric or visual detection of end-point in dimethylformamide fails (e.g. sulphanilamide, in presence of azo-violet). In some cases, however, barbiturates in the presence of thymol blue produce in pyridine an early colour change, and in the presence of azo-violet a sluggish change. The break in pyridine is sharper than in DMF, but estimation of potentiometric curves in the latter is better because in pyridine, after the potential has reached a maximum, a sudden drop can be noticed [562]. Methyl isobutyl ketone is suitable for the semimicro titration of acids with a pK value < 9.

The apparatus shown in Fig. 114 is suitable for semimicro titrations with standard KOH or TBAH in isopropanol [176]. It is well known that a glass electrode is insensitive in ethylenediamine if a standard solution containing Na^+ ions is used

Table 34

TITRATION OF ACID ANALOGUES WITH 0·02 N $NaOCH_3$ ACCORDING TO [562]

Compound	*In Dimethyl-formamide*	*In Pyridine*	*In Methyl Isobutyl Ketone*	mg *Equiv. of 1* ml *Standard Solution*
Acetoacetanilide	Azo-violet			3·544
p-Aminobenzenesulphonacetamide	Azo-violet (+)		Tb (−)	4·325
p-Aminobenzenesulphonamide		Azo-violet		3·444
2-(*p*-Aminobenzenesulphonamido)-pyrimidine	Tb (−)	Tb (+)		5·005
2-(*p*-Aminobenzenesulphonamido)-4-methylpyrimidine	Tb (+)			5·286
2-(*p*-Aminobenzenesulphonamido)-4,6-dimethylpyrimidine	Tb (−)		Tb (+)	5·566
2-(*p*-Aminobenzenesulphonamido)-thiazole	Tb			5·106
Benzimidazole	Azo-violet			2·363
Benzotriazole	Tb			2·382
Diethylbarbituric acid			Tb	3·684
Ethylbutylbarbituric acid	Tb			4·245
Ethylisopentylbarbituric acid	Tb			4·525
Ethylpentylbarbituric acid	Tb		Tb	4·525
Ethylphenylbarbituric acid	Tb		Tb	4·645
p-Hydroxybenzaldehyde	Tb			2·442
Phthalimide	Azo-violet			2·943
Resorcinol (by adding benzene)	Azo-violet			2·202
Succinimide	Azo-violet			1·982
Theophylline (anhydrous)	Tb			3·604
Thymol	Azo-violet			3·004

Abbrevations: Tb = thymol blue; (+) = slightly high; (−) = slightly low.

for titration [176]; in some cases therefore, they can be used as reference electrodes [446]. However, with standard solutions containing potassium or tetra-alkylammonium hydroxide in isopropanol, glass electrodes function satisfactorily as indicator electrodes. As a reference electrode the calomel electrode may be used (Fig. 61 (b). For the titration a 0·02 ml graduated 5 ml burette is employed. The standard solution of 0·1 N concentration is protected from atmospheric moisture and carbon dioxide by inserting a small tube containing Ascarite in the top of the burette. The magnetic stirrer is about 4 mm in diameter and 18 mm long. On the outer part of the small titration beaker a mark indicates 20 ml volume.

For potentiometric titrations a Precision Dual AC Titrometer with a millivolt range of +1,650 to −1,650 mV is suitable, or a Precision-Dow Recordomatic Titrator.

Weigh a sample which will consume 1–2 ml of 0·1 N KOH or TBAH in isopropanol. Dissolve in 20 ml solvent with magnetic stirring while a gentle stream of nitrogen is allowed to pass through the apparatus. Insert the electrodes without delay and close the apparatus so as not to expose it unnecessarily to atmospheric moisture and

CO_2. Add standard solution in increments of 0·02–0·05 ml and record the reading when the potential becomes constant. (Consider the cell potential constant if deflection of pH meter or millivolt meter is less than 2 mV within 30 sec.) Add the next portion of the titrant immediately. When the potential reaches its peak and subsequently begins to decrease record the maximum and add the next portion of the stand-

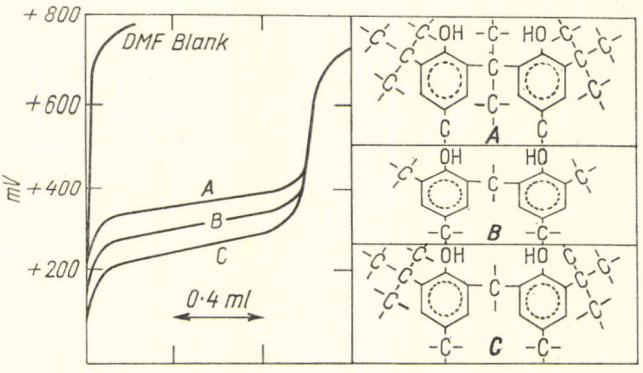


Fig. 115. Potentiometric curves of *o*-disubstituted phenols in dimethylformamide according to Deal and Wyld[176].— Standard solution: 0·1 N tetrabutylammonium hydroxide in isopropanol. Electrodes: glass–calomel (see: Fig. 114)

ard solution without delay. Continue titration till the potential reaches the mV value for the blank test of the solvent and remains constant or decreases steadily.

After titration, electrodes, titration beaker and other parts must be carefully cleaned.

Make a potentiometric blank test with 20 ml of solvent (e.g. ethylenediamine, dimethylformamide) in a similar way.

If the titrated compound shows two inflections in ethylenediamine, the difference between the first and second points of inflection is taken as the equivalent volume of the standard solution for calculation. In the case of only one inflection the large quantity of very weak acid may have obscured the end-point of the small quantity of strong acid. The inflection curve thus obtained corresponds to the potentiometric curve of the very weak acid only if the two curves or end-points are compared with a model test performed with phenol. To calculate results with weak acids use the difference between the titration of sample and the blank test.

For the titration of acid mixtures, e.g. hydrogen chloride-acetic acid-phenol, DMF is more convenient than EDA. (For differentiating titration of acid mixtures see Chapter 15.)

In the case of compounds containing two phenolic groups (e.g. catechol), even in DMF two inflections can be observed though the first is scarcely observable. With hydroquinone both end-points are faint; in this case TBAH must be used instead of KOH in isopropanol since following the neutralization of the first hydroxyl a precipitate is formed.

Polyfunctional phenols containing two OH groups in *ortho* positions show increased acid characteristics as compared with simple phenols. This may be attributed to the interaction of hydroxyl groups, as for example in the case of *o,o'*-di-

hydroxydiphenylmethane. Due to H-bonding only one phenolic hydroxyl is titrated [176, 770]; cf. Chapter 12; Section 63 (d). Potentiometric curves of the compounds shown in Fig. 115 provide information on their relative acid strength.

For titration of *p,p'*-dihydroxydiphenylmethane see: Chapter 18; Section 108 (b) and [176, 359]. For micro titration apparatus for visual and electrometric indication of end-point: see [62].

The apparatus is suitable for the determination of 10–25 μ.eq. of monofunctional compounds. Size of cuvettes for titration of solutions is 0·15–10 ml. Regarding the application of the Ingold-type 'Napf-Glaselektrode' see: [407, 754] and Fig. 67. Concerning the detailed methodology of volumetric micro titrations: see [584].

Chapter 22

Determination of Salts of Carboxylic Acids

In a suitable solvent and with a convenient standard, salts of organic compounds can be titrated either as acids or as bases. Salts of aromatic and aliphatic amines with strong mineral acids or sulphonic acids can be titrated as acids with alkali metal alkoxide or alkylammonium hydroxide as titrant in benzene-methanol or in a basic solvent. In acetic acid, salts of organic bases with halogen acids, on adding mercury(II) acetate, can be determined as bases with perchloric acid. The latter method will be dealt with in detail in Chapter 27.

Salts of carboxylic acids with alkali metals and alkaline earth metals, ammonia and organic bases can be titrated in suitable basic solvents as acids. However, much depends on solubility conditions. So, for instance, many salts of monofunctional car-

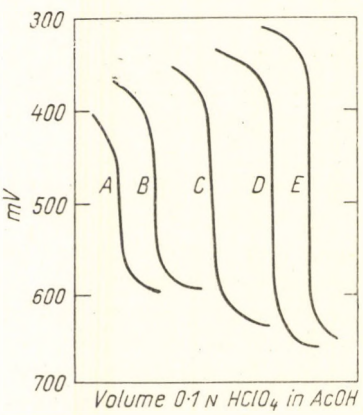


Fig. 116. Potentiometric titration curves of salts of carboxylic acids in acetic acid according to Markunas and Riddick [548]. — *(A)* Lithium benzoate, *(B)* Sodium acetate, *(C)* 2-Hydroxyethyltrimethylammonium dihydrogen citrate, *(D)* Ammonium acetate, *(E)* Potassium acetate

boxylic acids with ammonia or amino compounds dissolve in DMF and can be titrated with a basic standard solution in the presence of thymol blue; on the other hand, salts of polyfunctional carboxylic acids are mostly insoluble in DMF. In this case it is advisable to dissolve the sample in a small amount, say 0·1–1·0 ml, of water and

after adding 15 to 20 times that quantity of ethylenediamine to titrate the acid component of the compound in the presence of azo-violet.

Salts of carboxylic acids with alkali metals, alkaline earth metals and strong or medium-strength organic bases undergo solvolysis in acetic acid while equivalent acetate ions are formed. In this way such compounds can be titrated with perchloric acid as bases [15, 48, 374, 442, 470, 548, 862, 732, 769].

In acetic acid, depending upon cation and anion, salts show an acidic or basic character; the acidity or basicity of the solution is determined by the salt-forming anion and cation. Mercury(II) acetate, copper(II) acetate and cadmium(II) acetate are neutral in acetic acid. Alkali metal acetates and alkaline earth metal acetates are basic. Organic acids whose dissociation constant (in water) is 10^{-3} or less are generally neutral when dissolved in acetic acid. Salts of such acids e.g.: acetic, tartaric, citric, gluconic, malic, maleic, fumaric, benzoic, salicylic acid and barbituric acid derivatives etc. can be titrated with perchloric acid, like acetates.

Perchlorates, halides, bisulphates, persulphates, ferri- and ferro-cyanides are acidic, while phosphates, nitrates and the anions of most organic acids are basic in acetic acid [645]. (Cf. [470, 548].)

The acidity of cations increases when the size of the ion decreases or its charge increases [470, 645]:

$$Mg^{2+} > Ca^{2+} > Ba^{2+} > Li^{+} > Na^{+} > NH_4^{+}, K^{+}$$

This also influences the mV value of inflection obtained during potentiometric titration (Fig. 116). The acidity of potassium salts changes in the following order:

$$ClO_4^{-} > I^{-} > Br^{-} > Cl^{-} > NO_3^{-}$$

116. Titration in Basic Solvents

Weigh a sample amount giving a titration of 5–6 ml of 0·1 N sodium methoxide and dissolve in 15–20 ml of neutralized dimethylformamide, pyridine or ethylenediamine. If necessary heat gently. Use as indicator, dependent on acid strength, thymol blue or azo-violet [245]. For the technique of titration (e.g. use of nitrogen etc.) the directions outlined in Chapters 15–18 hold also in this case. (See also Figs 39, 40, 41 and 42.)

If a precipitate is formed, use a glass-stoppered Erlenmeyer flask and near the end-point, after adding the standard solution, shake vigorously, allow the solution to stand for 30–60 sec, then observe the colour of the indicator. If necessary continue titration till the colour of the indicator remains permanent for this time.

(a) *Determination of the citric acid content of caffeine citrate.* Weigh 80–100 mg. of caffeine citrate and dissolve in 15 ml DMF neutralized in the presence of two drops of azo-violet. Titrate with 0·1 N potassium methoxide in benzene-methanol till a blue colour is produced. 9·606 mg of citric acid require 1 ml of standard solution.

(b) *Determination of the benzoic acid content of ammonium benzoate.* Weigh a sample of 60–80 mg; dissolve first in 1 ml of distilled water, then add 20 ml of ethylenediamine neutralized in the presence of two drops of azo-violet. Titrate as in (a). 13·92 mg of ammonium benzoate require 1 ml of 0·1 N potassium methoxide. Standardize the titrant against benzoic acid in the same solvent mixture.

(c) *Measurement of the picric acid content of base picrates.* The picric acid content of base picrates can be estimated directly in dimethylformamide, while the base content of the picrate can be titrated in acetic acid with perchloric acid [58]. (Chapter 20; Section 114 and Chapter 24; Section 135.) Hence, base picrates can be estimated in two ways.

Weigh a sample of base picrate equivalent to 0·1–0·2 m.eq. of picric acid (the latter behaves as a monofunctional acid in DMF), dissolve in 15 ml of DMF previously neutralized in the presence of thymol blue and titrate from a burette graduated in 0·01 ml with sodium methoxide in benzene-methanol, to a blue-green end-point. 22·91 mg of picric acid requires 1 ml of 0·1 N solution.

(d) *Determination of the tartaric acid component of ergotamine tartrate* [324]. Weigh 200 to 250 mg of ergotamine tartrate (dried over phosphorus pentoxide) into a glass-stoppered flask and dissolve, protected from light, in 20–30 ml of pyridine, neutralized in the presence of 0·2 ml of 0·1% thymol blue. Titrate with 0·1 N potassium methoxide in benzene-methanol to a permanent blue colour. 7·504 mg of tartaric acid requires 1 ml of standard solution. Instead of thymol blue, one drop of 1% naphtholbenzeine in pyridine is also a convenient indicator. In this case the colour change is from yellow to green. Accuracy: ±1% [793].

Using this method the acid content of ergometrine maleate, ergotamine diphthalate and ergotoxine phosphate can also be determined [308, 324].

Calcium salts of acetylsalicylic acid, salicylic acid, diethylbarbituric acid and phenylquinoline carboxylic acid can be titrated with sodium methoxide in pyridine [832]. The acid component of atropine sulphate, codeine phosphate, hydrochlorides of cotarnine and hyoscine and some other salts of alkaloids can be determined by direct titration in pyridine with sodium methoxide in the presence of phenolphthalein [832].

(e) *Determination of the p-aminobenzoate of N,N-diethyl-leucinol methanesulphonate.* The acid component of salts of nitrogenous bases can also be determined with standard TBAH in benzene-methanol. So, e.g. when 100–200 mg of the sample are dissolved in 20 ml of dimethylformamide neutralized in the presence of thymol blue the methanesulphonate ion can be titrated with 0·05 N TBAH in benzene–methanol. 19·42 mg of the *p*-aminobenzoate of diethyl-leucinol methanesulphonate requires 1 ml of 0·05 N solution [322].

117. Titration in Acidic Solvents

Most salts formed from organic acids and alkali metals or amino compounds can be titrated with perchloric acid in acetic acid as acetates in the presence of crystal violet, or by potentiometric end-point detection [15, 48, 374, 442, 548, 682, 732, 769].

The indicator, containing the diphenylamine derivative Cellitonechtblau FR, yields a sharp colour change from blue to reddish violet; even the presence of 4% of water does not interfere with the sharpness of the colour change [473].

Dissolve about 3·5 m.eq. of the sample in 30 ml of acetic acid, if necessary with gentle heating, and titrate with 0·1 N perchloric acid in the presence of one drop of 1% crystal violet to a blue-green colour change. By this method e.g. the following can be determined (in brackets the mg.-equivalent of 1 ml solution of 0·1 N concentration): ammonium benzoate (13·92), ammonium salicylate (15·52), sodium ace-

tate (8·204), sodium salicylate (16·01), sodium benzoate (14·41), potassium acetate (9·815), guanidine acetate (11·91).

In some cases it is practical to dissolve the sample in excess of standard perchloric acid and then to back-titrate with 0·1 N sodium acetate in acetic acid [70]. In the case of tartrates, owing to their poor solubility a better result can often be achieved by using a dilute solution and 0·01 N standard solution [48]. The acetates of zinc, cobalt and manganese which give poor potentiometric end-points in acetic acid, give satisfactory end-points in methanol [667].

(a) *Determination of sodium salt of p-aminosalicylic acid.* Dissolve 40 to 50 mg of sodium PAS in 50 ml of methanol (neutralized in the presence of four drops of thymol blue) and titrate with 0·05 N perchloric acid in dioxan till the yellow colour becomes peach [124]. 10·56 mg of sodium PAS requires 1 ml of 0·05 N solution. Sodium PAS is easily dissolved in methanol and the amino group is titrated with perchloric acid.

In acetic acid, acetate ions are formed and when titrated potentiometrically with perchloric acid in acetic acid two inflections can be observed corresponding to the acetate ion and the amino group (equivalent weight, in this case, equals half the molecular weight). In acetic acid containing 10% of acetic anhydride one equivalent of perchloric acid is consumed because the primary amino group is acetylated [732].

(b) *Determination of disodium tartrate* [70]. Weigh 90–160 mg of the sample and dissolve in 30 ml of acetic acid, add exactly 25·00 ml of 0·1 N perchloric acid, and maintain agitation with a magnetic stirrer till dissolved (5–10 min). Then back-titrate the excess of perchloric acid potentiometrically with 0·1 N sodium acetate in acetic acid using as indicator a glass electrode and calomel as a reference electrode. The equivalence point is accurately located by plotting the function $\Delta E/\Delta V$ against V (see: Chapter 12):

$$\% = \frac{[(25\text{ ml} \times N_1) - (b \times N_2)] \times E}{a}$$

where a = weight of sample in grams
b = the standard sodium acetate consumed, (N_2 its normality)
N_1 = normality of standard perchloric acid
E = one-tenth of the gram-equivalent of the titrated compound

Disodium tartrate can also be determined by visual titration in the presence of two drops of 1% methyl violet to a colour change from green-blue to blue. Potassium sodium tartrate, potassium hydrogen tartrate, potassium acetate, lithium citrate, sodium benzoate and salicylate, and lithium benzoate can be titrated in the same way [70].

The advantage of the sodium acetate method is that excess of perchloric acid solubilizes the alkali metal salts which would otherwise dissolve only on heating; the colour change from green-blue to blue (crystal violet) is also sharper than when titration is performed directly with perchloric acid.

(c) *Trisodium citrate dihydrate* in acetic acid can be titrated either potentiometrically or in the presence of the indicator Oracet Blue [49, 680].

(d) *Determination of potassium sodium tartrate.* 0·6 g of $KNaC_4H_6O_6$, $4H_2O$ are dissolved in 50 ml of 0·1 N perchloric acid in acetic acid (potassium sodium tartrate

is almost insoluble in acetic acid owing to the formation of potassium hydrogen tartrate) and mix vigorously for 20 min with a magnetic stirrer. Finally back-titrate with 0·1 N potassium acetate in acetic acid.

Preparation of standard potassium acetate. Dissolve with gentle heating 6·91 g of potassium carbonate (previously dried at 150°C) in 200–300 ml of acetic acid. After cooling dilute to 1 litre.

(e) *Determination of sodium carboxymethyl cellulose* [743]. Weigh about 500 mg of sodium carboxymethyl cellulose and heat on a steam bath for 20 min with 80 ml of acetic acid, then cool to room temperature and titrate potentiometrically with 0·1 N perchloric acid in dioxan. 2·299 mg of the compound requires 1 ml of 0·1 N solution.

(f) *Determination of sodium benzoate.* Weigh approx. 150 mg of sodium benzoate in a 250 ml Erlenmeyer flask, dissolve with heating in 100 ml of acetic acid, and after cooling, add 10 ml of neutralized 3% mercury(II) acetate in order to stabilize the indicator. Indicator: 0·5% solution of Fettblau B (Ciba) in acetic acid. Titrate with 0·1 N perchloric acid in acetic acid until the indicator turns from blue first to violet then to pink. 14·41 mg of sodium benzoate requires 1 ml of standard solution. The result of model tests without mercury(II) acetate gave 99·45%; in the presence of mercury(II) acetate, 100·01%.

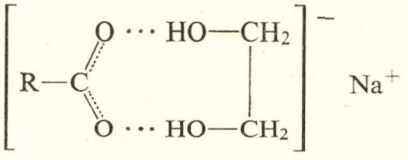
Diethyl-phenylethyl-barbituric acid, sodium *p*-aminosalicylate, sodium salicylate and soluble saccharin (sodium salt) can be titrated in a similar way but without mercury(II) acetate [682].

(g) *Determination of soluble saccharin* [326]. Weigh about 200 mg of finely powdered sample, dissolve in 30 ml of acetic acid and after adding one drop of 1% crystal violet titrate with 0·1 N perchloric acid to blue. One ml of standard solution is equivalent to 24·12 mg of sodium salt dihydrate or 18·32 mg of saccharin.

(h) Titrimetric determination of salts of nitro compounds, e.g. potassium cyclohexylnitronate, see [228].

118. Titration in G—H Solvent Systems

Glycols solvate the alkali metal salts of carboxylic acids by the formation of hydrogen bonds:



The change of the indicator colour is sharper if isopropanol, chloroform or benzyl alcohol is added to the glycol.

Weigh approx. 0·5 – 0·8 m.eq. of the alkali metal salt of a monofunctional carboxylic acid, dissolve in 5–10 ml of ethylene glycol or propylene glycol with shaking and gentle heating, then dilute with 5 to 10 ml of isopropanol, chloroform or benzyl alcohol. Add 3 – 5 drops of 0·05% methyl red as indicator and maintaining agitation, titrate slowly with 0·2 N hydrogen chloride or perchloric acid in propylene glycol-chloroform until the solution changes from yellow to pink: the change is very sharp. Among

others, sodium salts of caproic, lauric, oleic, stearic, butyric, cinnamic, mandelic and benzoic acid can be determined in a similar way [621]. The determination of salts of acids stronger than formic acid (pK 3·75) is inexact.

119. Titration in Differentiating Solvents

The limited solubility of some salts in acetic acid, pyridine, dimethylformamide etc. emphasized the necessity for other procedures. It is known that strong, medium-strength and weak acids can be titrated in a single mixture in pyridine [161]. When sulphuric acid is added to the concentrated aqueous solution of the metal salt of carboxylic acid, metal sulphate and free carboxylic acid are formed; the latter can be titrated in the presence of sulphuric acid with TBAH [162].

$$Cu(CH_3COO)_2 + H_2SO_4 \text{ (excess)} \rightarrow CuSO_4 + 2\,CH_3COOH$$

Weigh in a 100 ml measuring flask 0·5 m.eq. of the salt and dissolve in a mixture of 1 ml water and 2 ml N sulphuric acid. If necessary add another 3 ml of water, make up to the mark with pyridine (or acetone), shake vigorously and titrate 50 ml of the clear solution potentiometrically with 0·1 N TBAH. Determine the titrant consumption of the solvent and the 2 ml N sulphuric acid by a blank test. The liberated carboxylic acid or weak mineral acid brings about a subsequent additional inflection. Disodium hydrogen phosphate, sodium phosphite, copper(II)- and nickel(I)-acetate, potassium hydrogen phthalate, and sodium citrate can be titrated in acetone solution with 100 $\pm$ 0·4% accuracy. Determinations of sodium bromide, potassium bichromate and sodium hydrogen phosphate in pyridine are exact to 99 $\pm$ 0·3%. The components of sodium nitrate-sodium nitrite can be estimated in a mixture with an accuracy of 99·7 $\pm$ 1·3% or 99 $\pm$ 2%.

Kreshkov and co-workers have used methyl ethyl ketone, which has excellent differentiating properties, as a solvent for the titration of sodium or potassium salts of carboxylic acids, and for the analysis of salt mixtures [485], such as potassium salicylate–potassium benzoate, sodium acetate–potassium salicylate. Mixtures of the salts with the corresponding acids, for example, sodium oleate–oleic acid, sodium anthranilate–anthranilic acid, potassium benzoate–benzoic acid, etc., are titrated in a similar way. The carboxylic acid, however, is liberated not with sulphuric acid, but with standardized 0·1 N perchloric acid and the resulting mixture of acids is titrated potentiometrically with tetraethylammonium hydroxide standard solution, using a glass–calomel electrode pair.

Chapter 23

Determination of Nitrogenous Organic Bases

Of the titrations performed in non-aqueous media, determinations of strong and medium-strength organic bases containing nitrogen are those least liable to error. Determination of compounds of this type by non-aqueous methods is in line with the development of the pharmaceutical industry: the application of quality control and the need for analyses of mixtures of natural organic bases (alkaloids, glycoalkaloids, antibiotics) and therapeutic drugs containing different types of basic groups in synthetic compounds, became necessary. At present, it is possible to determine, e.g. the active-agent content of drugs containing alkaloids, trace the manufacturing process (extraction), and analyze the final pharmaceutical product by volumetric microanalysis.

Those monofunctional heterocyclic bases whose perchlorates dissolve poorly and whose dissociation constant (in water) is not below 10^{-12} can be titrated accurately with perchloric acid in acetic acid. Perchlorates of aliphatic and aralkyl amines are more easily dissolved and only those can be measured accurately whose dissociation constant in water is not less than 10^{-11}. This, however, is already a marginal value and in most cases potentiometric measurements must be used. In solutions of 0·01 N concentration, bases with a dissociation constant of 10^{-10} can be visually titrated in acetic acid with $\pm 0{\cdot}3\%$ accuracy if experimental conditions are favourable (cf. Fig. 72). For weaker bases the use of a solvent mixture is preferable, e.g. propionic acid–chlorobenzene, acetic anhydride–nitromethane, acetic anhydride–benzene, acetic acid–carbon tetrachloride, nitrobenzene–acetic anhydride (cf. Table 14).

For micro titrations 0·01–0·001 N perchloric acid, or 0·005 N *p*-toluenesulphonic acid is used. The former is best prepared in a 1 : 1 mixture of acetic or propionic acid and carbon tetrachloride. Titrate in a 15–25 ml centrifuge tube over a white ground; add two drops of 0·02% methyl violet in chlorobenzene to 3–5 ml of propionic acid, carbon tetrachloride or chlorobenzene solution containing 0·03–0·05 m.eq. of dissolved organic bases and titrate with 0·01 N perchloric acid till violet turns to blue.

The above account is designed to survey the feasibility of the determination of nitrogenous organic bases. A common feature of the compounds mentioned in this chapter is that their molecules contain one or more co-ordinatively unsaturated nitrogen atoms. Basicity is influenced by electron attracting or releasing subtituents and base strength may change from one solvent to another (see: Chapters 3 and 4).

Amino compounds, present in the form of salts, can be titrated in acetic acid as bases, depending upon the acid component. In the case of salts formed from organic acids, in contrast with those formed from halogen acids, it is unnecessary to add mercury(II) acetate in order to titrate the base component in acetic acid (e.g. ergometrine maleate). As a result of the presence of mercury(II) acetate, a non-dissociating mercury halide and free base are formed from halide salts (see: Chapter 25).

Bases soluble in acetic acid dissolve as acetates or as base–acetic acid adducts. The success of titration depends on whether the basicity of the compound containing the amino group remains relatively unchanged on solution, decreases, decreases to a great extent (e.g. in the course of acetylation) or vanishes (R_3NH^+). Depending upon the substituent, the solvent and the strength of acid anion, variants of these cases are possible.

The basicity of bases containing nitrogen is increased in acetic anhydride [249, 288, 732]. It is obvious that the latter cannot be employed with acetylatable amines, or only for the rare cases when titration can be performed rapidly at 0°C (e.g., diphenylamine [557]). Acetic anhydride or nitromethane-acetic anhydride are suitable media for the potentiometric titration of those weak bases whose dissociation constant (in water) is less than 10^{-12}: diphenylamine (pK, 13·15), quinoxaline (~13·2), theobromine (13·32), caffeine (13·40), urea (13·50), nicotinamide (13·60), thiourea (14·96), etc.

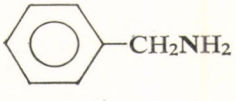
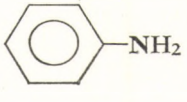
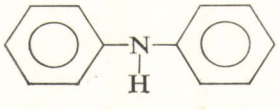
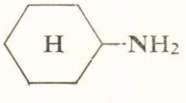
Most inorganic cations interfere with perchloric acid determinations (with the exception of Hg^{2+} and Cu^{2+}) since they form acetates by solvolysis.

Finally mention should also be made of those compounds which are not titratable with perchloric acid in acetic acid: pyrrole, N-alkylpyrroles, indole, carbazole, benzoxazole, pyrazine, benzotriazole, acetamide, phenothiazine, isatin, nitroanilines, etc.

The potentiometric differential titration of *o*-, *m*- and *p*-nitroanilines *as bases* is possible when the solvent used is 2 M nitrobenzene in benzene, modified with acetic acid or trichloroacetic acid in a concentration of 2·5 M [590]. *o*-Nitroaniline can be titrated spectrophotometrically at 505 mμ in a medium of acetic acid with perchloric acid [484].

120. Aliphatic, Aralkyl, Aromatic, and Hydroaromatic Nitrogenous Bases

(N = basic nitrogen atom, N = nitrogen atom of diminished basicity)

RNH_2	R_2NH	R_3N	$R-NH-NH_2$
Primary	Secondary	Tertiary amines	Hydrazine derivatives
			
Benzylamine	Aniline	Diphenylamine	Cyclohexylamine
pK 4·70	pK 9·42	pK 13·15	pK 3·21

Acetic acid containing 10–20% acetic anhydride is a suitable solvent for non-acetylatable amines. In the case of acetylatable amines, acetic anhydride is omitted and propionic acid, chlorobenzene, dioxan, acetonitrile and solvent mixtures are used, besides acetic acid (cf. Table 14 and Chapter 6; Section 39).

Weigh 0·3–0·8 m.eq. of monofunctional base, dissolve in 20–30 ml of neutralized solvent and titrate with 0·05–0·1 N perchloric acid in acetic acid or dioxan in the presence of a suitable indicator, depending upon the solvent. (Regarding choice of the indicators see: Chapter 13 and Tables 24, 25 and 27.)

For potentiometric titrations glass–calomel electrodes should be used. For potentiometric end-point detection it is advisable to neutralize the solvent after adding a suitable indicator. Concerning the correction for temperature effects see: Chapter 9.

In the case of volatile liquid bases it is advisable to prepare first a stock solution in benzene, toluene or (preferably) chlorobenzene, an adequate portion of which is mixed with acetic acid, propionic acid or acetic anhydride. Thus, rise of temperature caused by interaction between the amine and acidic solvent, accompanied by loss of the volatile base, can be lessened. With solutions of 0·01 N concentration similar precautions are unnecessary. Bases of poor solubility in chlorobenzene should be dissolved directly in solvent mixtures containing acetic acid.

In the case of bifunctional bases, following protonation of the first amino group, the proton-accepting ability of the second group decreases to a certain extent. It may also happen that in potentiometric measurements, e.g. with acetonitrile, two inflections are observed and the change of colour of crystal violet occurs occasionally after the addition of one or two equivalents of perchloric acid. In the potentiometric measurement of *o*-phenylenediamine two points of inflection, and in that of *m*- and *p*-phenylenediamine one point, correspond to two equivalents of perchloric acid [732].

In the case of N-aminopiperidine the $-NH_3^+$ group formed by protonation exerts a strong inductive effect ($-I$ effect) on the adjacent nitrogen atom, so that its electron density decreases and it is not able to accept a proton [732]. Therefore, potentiometrically only one inflection can be observed, indicating binding of one equivalent of perchloric acid. In acetic acid containing acetic anhydride only the nitrogen of the piperidine ring is titrated because the primary amino group becomes acetylated.

Piperidine is a strong base (pK 2·80) but N-substitution has a basicity-decreasing effect [333]: N-ethylpiperidine (pK 3·60), N-allylpiperidine (pK 4·32).

Numerous aliphatic, aromatic and other bases can be titrated in acetic acid with perchloric acid [72, 175, 244, 345, 374, 548, 599, 732, 802]. To enumerate all these would be impracticable, and only a few typical examples will be given.

(a) *Determination of aniline.* Weigh a 1–2 ml thin-walled, wide-mouthed injection ampoule, add drop by drop 0·4–0·5 ml of aniline and reweigh. Pour 80–85 ml of chlorobenzene into a 200 ml bottle of resistant glass and neutralize in the presence of five drops of 1% crystal violet with 0·1 N perchloric acid to green-blue. Insert the ampoule of aniline and smash it with a glass rod. Transfer the solution to a 100 ml measuring flask, through a funnel, flush the bottle with 5 × 2 ml of acetic acid and make up to the mark of the measuring flask. Titrate a 20 ml portion of the stock solu-

tion with 0·1 N perchloric acid in acetic acid, taking green-blue as the end-point. 9·312 mg of aniline requires 1 ml of standard solution.

Concerning rapid repeated titrations of substituted aniline derivatives (*p*-anisidine, *p*-toluidine, -chloroaniline, *p*-aminoacetophenone) see: [515].

(b) *Photometric titration of o-chloroaniline* [675]. Weigh sufficient *o*-chloroaniline (pK_b 11·4) to give 100 ml of a solution in acetic acid of approx. 0·1 N. Place it in the adapted cuvette of a Beckman DU type spectrophotometer and titrate at wavelength 312 mμ with 0·1 N perchloric acid. Plot the titre against absorbance (*A*). Correct each value of absorbance for volume. 12·76 mg of *o*-chloroaniline requires 1 ml of 0·1 N perchloric acid (Fig. 86, Chapter 14; cuvette, Fig. 96).

(c) *Determination of tribenzylamine.* Dissolve 140–160 mg of sample in a 100 ml measuring flask in a 10:1 mixture of acetic acid–acetic anhydride neutralized in the presence of crystal violet. Titrate 10 ml of the stock solution with 0·01 N perchloric acid until the violet turns to blue. 2·874 mg of tribenzylamine requires 1 ml of 0·01 N perchloric acid.

(d) *Determination of cyclohexylamine.* Dissolve 0·5–0·6 ml of cyclohexylamine, as described under (a), in 100 ml of propionic acid neutralized in the presence of 6–8 drops of metanil yellow and titrate a 20 ml portion with 0·1 N perchloric acid using glass–calomel electrodes, or visually to a colour change of metanil yellow to purple. 9·917 mg of cyclohexylamine requires 1 ml of 0·1 N solution.

(e) *Photometric end-point detection of 1-naphthylamine (pK 10·08) and 2-naphthylamine (pK 9·89)* is performed in the same way as the determination of narceine [209]; Fig. 77, Chapters 14 and 23; Section 121 (l).

The determination of N-nitrosodiphenylamine may be accomplished by an indirect method by titrating 1-naphthylamine [558]. A portion of the stock solution containing about 10 mg of N-nitrosodiphenylamine is dissolved in 10 ml of acetic acid and mixed with 75 mg of 1-naphthylamine in 15 ml of acetic acid. A further 75 ml of acetic acid is added and, protected from light, the solution is warmed for 30 min on a steam bath at 60°C. Cool in a dark place and titrate the excess 1-naphthylamine with 0·03 N perchloric acid in acetic acid. A blank test is run in the same way, without N-nitrosodiphenylamine. The titrations are performed potentiometrically using a glass-Ag/AgCl electrode system. The difference between the two titrations is used for the calculation. One ml of 0·03 N perchloric acid is equivalent to 5·946 mg of nitrosodiphenylamine and 4·296 mg of 1-naphthylamine.

(f) *Determination of amino-acids.* The preparation of a solution of 0·1 N amino-acid in acetic acid sometimes requires shaking for a few hours.The rate of solution can be increased by heating. For dissolving amino-acids the solvent-pair formic acid–acetic acid can be used (occasionally solubilizing with excess of perchloric acid); the excess of standard solution is back-titrated with a solution of glycine, sodium acetate, diphenylguanidine or guanidine acetate in acetic acid in the presence of crystal violet or 1-naphtholbenzeine. The method is limited in each case by the solubility of the amino-acids. The following can be titrated directly, potentiometrically, with 0·1 N perchloric acid in acetic acid (mg equivalent of 1 ml of 0·1 N solution in brackets): asparagine (13·21), anthranilic acid (13·71), *p*-aminobenzoic acid (13·71), glycine (7·507), *d*-valine (11·72), isoleucine (13·12), *l*-proline (11·51) *l*-tryptophan (20·42). Some of the amino-acids are first dissolved in 2 ml of formic acid, then diluted with 20 ml of acetic acid and titrated as above: *d*-glutamic acid (14·71), *l*-aspartic

acid (13·31), *l*-cystine (24·03), *dl*-valine (11·72) and *dl*-phenylalanine (16·52) are dissolved in 1 ml of formic acid. Another procedure in the case of aspartic and glutamic acids (14·71), cystine and alanine (8·909), *l*-serine (10·51), *l*-leucine (13·12) and *l*-tyrosine (18·12) is to dissolve about 0·8 m.eq. (with gentle heating) in 12·00 ml of 0·1 N perchloric acid and to back-titrate the excess of standard solution with 0·1 N guanidine in acetic acid. 1-Naphtholbenzeine is a suitable indicator [607, 732, 809].

Precipitation of insoluble perchlorate often affects visual indicators favourably. Precipitation can also be achieved by adding benzene or carbon tetrachloride to a solution of amino-acid in acetic acid [575]. In this way *p*-aminobenzoic acid and anthranilic acid can be titrated with 0·1 N perchloric acid in acetic acid in the presence of 1-naphtholbenzeine. In the former case, take 10 ml of acetic acid per mM of amino-acid and after adding the indicator dilute with 25 ml of benzene or carbon tetrachloride. In the case of anthranilic acid use 5 ml of acetic acid per mM of sample and dilute with 40 ml of benzene or carbon tetrachloride. An alternative method is to add a small excess of perchloric acid to the solution and after 30 min to back-titrate the excess of perchloric acid with a standard solution containing sodium acetate or diphenylguanidine.

(g) *Determination of N,N′-disubstituted* p-*phenylenediamine derivatives.* Nitrogen-substituted *p*-phenylenediamine derivatives, depending on the substituent, can be titrated by potentiometric measurement in acetic acid, acetonitrile or acetone.

When *dialkyl-p-phenylenediamine* derivatives are titrated in acetic acid one inflection points to the simultaneous protonation of both N-atoms; in acetonitrile two inflections indicate the differentiated titration of two N-atoms, and in acetone one potentiometric inflection shows protonation of only one N-atom. Thus in the latter solvent, the basicity of the molecule, following acceptance of the first proton, decreases to such an extent that it is not able to accept further protons [521].

In the above solvents *N-alkyl-N′-aryl*-p-*phenylenediamine* derivatives react with only one equivalent of perchloric acid.

The determination of N,N′-dialkyl- *(a)*, N-alkyl-N′-aryl- *(b)* and N,N′-diaryl-*p*-phenylenediamine derivatives *(c)* used as antioxidants in rubber products can be achieved by non-aqueous titrations. In the case of antioxidants of type *(a)* or *(b)* dissolve 20–100 mg in 50 ml of solvent and titrate potentiometrically with 0·1 N perchloric acid in acetic acid using glass as indicator- and Ag/AgCl as reference-electrode (Chapter 12, Figs 62, 63 and 64). For the titration of type *(c)* antioxidants: add about two equivalents of chloranil (tetrachloroquinone) to the sample in 50 ml acetic acid (a deep blue colour will appear) and then titrate. N,N′-Diaryl-*p*-phenylenediamine derivatives are very weak bases and on adding chloranil (tetrachloroquinone) they are oxidized to so-called Wurster salts and a strong base is formed. This is the acetate ion or tetrachlorohydroquinone anion:

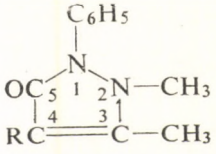
$$2\,RH-\ddot{N}-C_6H_4-\ddot{N}-HR + C_6Cl_4(:O)_2 + 2\,H^+ \xrightarrow{AcH}$$

$$2\,RH-\overset{+}{\underset{\cdot}{N}}-C_6H_4-\ddot{N}-HR + C_6Cl_4(OH)_2$$

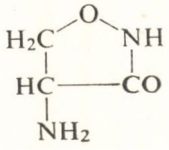
121. Heterocyclic Bases

Numerous natural or synthetic compounds of medicinal interest contain a heterocyclic nitrogen atom.

In many cases the nitrogen hetero-atom has no basic properties (e.g. phenothiazine) but if the molecule also contains simple primary, secondary or tertiary nitrogen the latter is titrated. In the case of such a compound containing heterocyclic nitrogen and also an amino substituent, using a visual indicator in acetic acid the amount of perchloric acid consumed in some cases is equivalent to the amino group only, the basicity of the hetero N-atom being slight, [e.g. amidopyrine (4- dimethylamino-2,3-dimethyl-1-phenyl-5-pyrazolone) 3-aminopyrazolone, dimethylaminoacetyl phenothiazine]; or the nitrogen hetero *n*-atom has no basic properties, e.g. cycloserine (*d*-4-amino-3-isoxazolidinone). In acetic acid containing 10% acetic anhydride, amidopyrine shows two inflections potentiometrically and two equivalents of perchloric acid are consumed [732] while under similar circumstances phenazone (2,3-dimethyl-1-phenyl-5-pyrazolone) takes up only one proton:

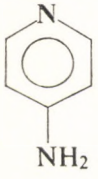


Phenazone: R = H
Amidopyrine: R = $(CH_3)_2N$

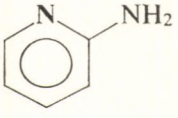


Cycloserine

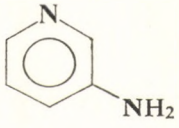
In other cases, however, the nitrogen hetero-atom is basic, e.g. 4-aminopyridine and 2-aminopyridine; in the case of 3-aminopyridine both N-atoms are basic [262]. (See also: Chapter 4; Section 27 (a).)



4-Aminopyridine

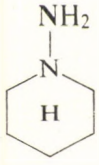


2-Aminopyridine

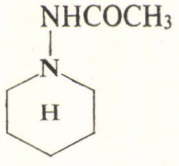


3-Aminopyridine

The amino-N-atom forms the basic group in N-aminopiperidine but the hetero N-atom does so in N-acetylaminopiperidine [732].

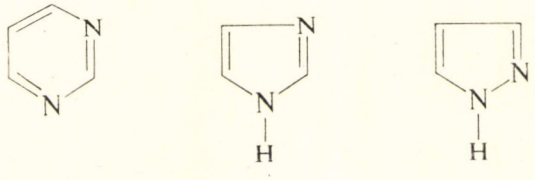


N-Aminopiperidine

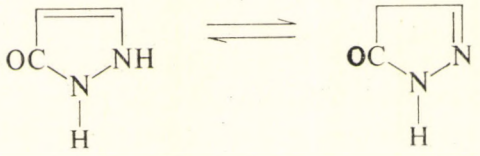


N-Acetylaminopiperidine

In general the basicity of the second N-atom decreases or vanishes in compounds containing two heterocyclic N-atoms, e.g. pyrimidine, imidazole, pyrazole (and also in hydrazines) owing to the inductive or mesomeric effect of the $[-\overset{|}{\underset{|}{N}}H]^+$ group formed on protonation. (See also: Chapter 4).



Pyrimidine Imidazole Pyrazole



Pyrazolone-5

(a) *Determination of pyridine and related compounds.* Depending on the compound to be estimated either the method described for aniline and N-aminopiperidine is employed or a solution is made by direct weighing without preparing a stock solution. A suitable solvent for pyridine, alkylpyridines, quinoline, isoquinoline and its alkyl derivatives as well as acridine is a neutralized mixture of chlorobenzene–acetic acid (1 : 1) [175]. End-point detection is carried out either potentiometrically or with crystal violet or 1-naphtholbenzeine.

Compound	mg *Equivalent of 1* ml *of 0·1* N $HClO_4$	p*K*
Pyridine	7·910	8·85 [497]
β-Picoline (3-methylpyridine)	9·312	7·96 [175]
2,6-Lutidine	10·72	6·58 [333]
γ-Collidine (2,4,6-trimethylpyridine)	12·12	6·68 [175]
Quinoline	12·92	9·20 [497]
Isoquinoline	12·92	8·70 [779]
Quinaldine (2-methylquinoline)	14·32	
Acridine	17·92	8·40 [2, 3]

(b) *Determination of pyridine carboxylic acid and derivatives and/or phenylquinoline carboxylic acid.* Many papers discuss potentiometric determinations of pyridine carboxylic acid, nicotinamide and phenylquinoline carboxylic acid [249, 437, 442, 732]. The following can be titrated potentiometrically in acetic acid containing 10% acetic anhydride [732] (in brackets, mg equivalent of 1 ml of 0·1 N perchloric acid): 2,3- and 4-pyridine carboxylic acid (12·31), nicotinamide (12·21), di-isonicotinyl-*p*-phenylenediamine (15·91), isonicotinazide (14·82), N-isonicotinylaminopiperidine (10·62), di-isonicotinylhydrazide (12·11); and isonicotinylhydrazones of pyruvic acid,

acetylamino-acetophenone, cyclohexanone and cycloheptanone. Nicotinamide can be titrated either potentiometrically or visually in the presence of triphenylmethanol indicator in a 4 : 1 mixture of nitromethane-acetic anhydride [249]. See: Section 125.

In a mixture of acetic acid – chlorobenzene (10 : 1) 5 drops of 0·05% methyl violet can be used as indicator. During titration crystalline perchlorate is sometimes precipitated; this increases the sharpness of the indicator colour change (nicotinamide; phenylquinoline carboxylic acid, 1 ml 0·1 N $HClO_4$ ~ 24·93 mg). Nicotinamide can also be photometrically titrated with 0·1 N perchloric acid in acetic acid with malachite green as indicator, at a wavelength of 620 mμ [65].

(c) *Determination of N-aminopiperidine.* Weigh 0·4 to 0·5 ml of sample according to the method described for aniline; since the compound is hygroscopic the ampoule is sealed (the drawn-out part remaining on the ampoule) in order not to absorb moisture during measurement. Transfer the ampoule to a glass-stoppered Erlenmeyer flask, then pour in a mixture of 10 ml of acetic anhydride and 20 ml of acetic acid and smash the ampoule with a glass rod. Moisten the stopper of the Erlenmeyer flask with acetic anhydride, and keep in a dark place for 30 min in order to acetylate the primary amino group. Now pour the solution into a 100 ml measuring flask; rewash the Erlenmeyer flask with acetic acid and dilute to the mark. Titrate the tertiary N-atom in 25 ml portions with 0·1 N perchloric acid using a glass–calomel electrode pair. Use cresol red as indicator for visual titration. 10·02 mg of N-aminopiperidine require 1 ml of 0·1 N perchloric acid.

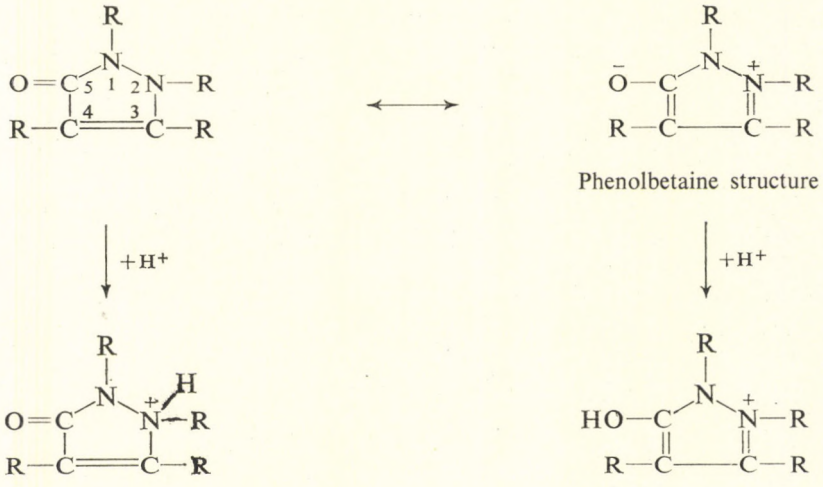
(d) *Determination of chloroquinoline derivatives; photometric determination of 8-chloroquinoline* [404]. Transfer 100–110 ml of a solution of acetic acid containing about 0·8 m.eq. of 8-chloroquinoline (pK 11·2) to a 150 ml titration cell (Wycor grade 7910, Corning Glass Works, Corning, N. Y.) and insert it in the cell-holder of the 10 cm cuvettes of Beckman DU type spectrophotometer. The preferred wavelength is 380 mμ (Chapter 14, Table 28). Since absorbance increases during titration, rezero the absorption of the instrument prior to addition of standard solution. Additions of perchloric acid of 0·5 N concentration are at the outset of titration 0·2 ml and near the vicinity of the end-point 0·05–0·1 ml. The photometric curve is plotted as the function A against V/f, where f = the factor of the standard solution. Projection of the intersecting straight lines on the x axis indicates the quantity consumed in ml, i.e. the equivalence point (cf. Fig. 75). 81·8 mg of 8-chloroquinoline require 1 ml of 0·5 N perchloric acid.

Determination of 5,7-dichloro-8-hydroxyquinaldine (Chlorquinaldol)*. Weigh approx. 300 mg of sample in a 200 ml wide-mouthed flask and dissolve in a mixture of 25·00 ml 0·1 N $HClO_4$, 25 ml acetic acid and 2 ml acetic anhydride, on a steam bath with gentle heating. Cover the flask with a small watch-glass and a large beaker. After cooling, titrate the excess of perchloric acid with 0·1 N potassium acetate in acetic acid using one drop of 0·5% malachite green as indicator. Colour change occurs from green-yellow to yellow-green. 22·81 mg of chlorquinaldol requires 1 ml of 0·1 N standard solution. 5,7-Dichloro-8-hydroxyquinoline is titratable in acetic anhydride [620].

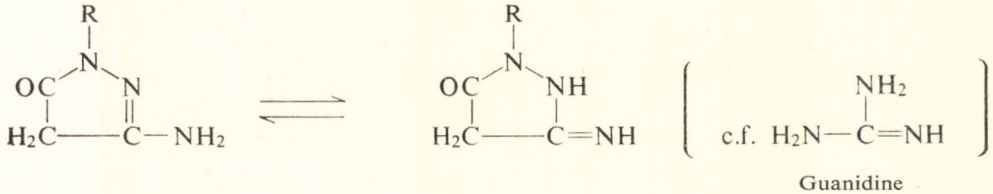
(e) *Determination of pyrazolone derivatives.* Veibel and co-workers investigated the effect of substituents at N_1, C_3 and C_4 of the pyrazolone ring [839, 840, 841],

* *Drug Std* **26,** 106 (1958).

and attribute the basicity of pyrazolones of phenazone type (antipyrine structure) to the contribution of the phenolbetaine resonance form:



Pyrazolone consumes one equivalent of perchloric acid but when an amino group is substituted in place of a hydrocarbon group on C_3, consumption of perchloric acid does not increase, probably owing to the guanidine-like structure of 3-amino-pyrazolone:



Potentiometric titration curves of phenyl pyrazolone derivatives show the following basicity order (in acetic acid) [445]:

4-aminoantipyrine > 1-phenyl-3-methylpyrazolone >
> antipyrine ⩾ amidopyrine

The non-aqueous determination of *amidopyrine* (4-dimethylamino-2,3-dimethyl--1-phenylpyrazol-5-one), pK 9·30, has been discussed (ref. [126]). The determination can be accomplished by a potentiometric method in acetic acid containing 10% acetic anhydride [732] and also in acetic acid in the presence of diethylbarbituric acid [13]. Amidopyrine can be determined in chloroform in the presence of diethyl-barbituric acid with 0·05 N *p*-toluenesulphonic acid in chloroform [649]. In chloro-benzene either potentiometric or visual titration can be performed, the latter with bromophenol blue as indicator [638], while in a mixture of benzene-acetic acid (3 : 1) it is either titratable potentiometrically or in the presence of the indicator tropaeolin 00 [496]. Neither acid analogues nor hydrochlorides of bases such as e.g. phenylethyl-

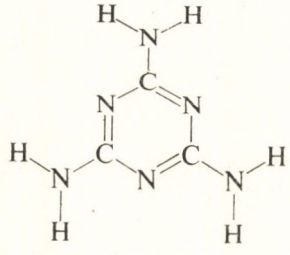
barbituric acid, bromoisovalerylurea, caffeine or ephedrine, interfere with the determination of amidopyrine in acetic acid [695].

Weigh 200–250 mg of amidopyrine and dissolve with gentle heating in 20 ml of benzene-acetic acid (3 : 1) neutralized in the presence of two drops of 1% tropaeolin 00 in acetic acid. Titrate with 0·1 N perchloric acid in acetic acid to a pink colour change. 23·13 mg of amidopyrine requires 1 ml of standard solution.

For the determination of amidopyrine, papaverine hydrochloride, phenylethylbarbituric acid and hydroxyquinolinesulphonic acid in pharmaceutical preparations, see: [835 and 837].

(f) *Determination of 2,4-diamino-5-(4'-chlorophenyl)-6-ethylpyrimidine* (Pyrimethamine).* Heat 200 mg of sample with 100 ml of acetone on a steam bath. Allow the solution to stand for one to two minutes, then cool and after adding 1 ml of methyl orange in acetone titrate with 0·1 N perchloric acid in dioxan till a pink colour is produced. 24·87 mg of Pyrimethamine require 1 ml of 0·1 N solution.

(g) *Determination of melamine in melamine resins* [461]. The melamine (2,4,6-triamino-1,3,5-triazine) content of melamine resins can be titrated directly with perchloric acid. Melamine behaves as a monofunctional base.



The nitrogen content of a variety of commercial resins was in good agreement when calculated from the results of titrations in non-aqueous media, compared with the values determined by Kjeldahl's method.

Weigh out precisely 0·5 g of a resin solution containing 50–70% dry material and dissolve it in 20 ml of an acetic acid-acetic anhydride (4 : 1) solvent mixture. Titrate with 0·1 N perchloric acid in acetic acid in the presence of crystal violet to the yellow colour change of the indicator.

Melamine content of the solid resin:

$$\% = \frac{c \times \text{N} \times 12{\cdot}6 \times 100}{a \times d}$$

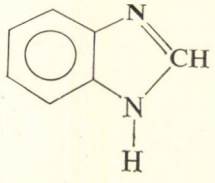
where a = weight of the resin solution (in g)
N = normality of the standard solution
c = consumed volume (in ml)
d = percentage dry material content of the resin solution.

(h) *Determination of 4-amino-3-isoxazolidinone* (Cycloserine) [698]. Weigh 50–60 mg of sample, dissolve in 25 ml of acetic acid neutralized in the presence of two drops of 0·2% crystal violet and titrate potentiometrically with 0·05 N perchloric acid in

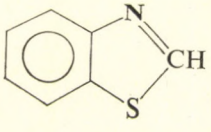
* *Ann. pharm. franç.* **20**, 86 (1962).

acetic acid using platinum as indicator electrode and graphite immersed in a saturated solution of copper(II) acetate as reference electrode (Zeidler graphite electrode: Chapter 12; Sections 67 and 68). 5·10 mg of Cycloserine require 1 ml of 0·05 N solution.

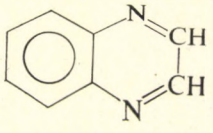
(i) *Benzimidazole* and its derivatives can be titrated in propionic acid with 0·1 N perchloric acid in propionic acid in the presence of the indicator methanil yellow [377], and *benzothiazole* and *quinoxaline* potentiometrically in a 4 : 1 mixture of nitromethane–acetic anhydride with standard perchloric acid in acetic acid. One ml of 0·1 N solution is equivalent to 11·81 mg of benzimidazole, 13·52 mg of benzothiazole and 13·01 mg of quinoxaline (see also: in this chapter: Section 125):



Benzimidazole



Benzothiazole



Quinoxaline

(j) *Acridine* can be titrated potentiometrically in acetic acid (see also: Section 121 (a)). Dissolve 30–180 mg of acridine in sufficient acetic acid to give a solution of about 0·1 M. Add 0·6 g of chloranil and 0·8 g of tetrachlorohydroquinone and titrate with 0·1 N perchloric acid using a platinum–calomel electrode system. The electrolyte of the calomel electrode is acetic acid saturated with lithium nitrate [608]. 17·92 mg of acridine requires 1 ml of 0·1 N solution.

(k) *Titration of alkaloids in the presence of malachite green as indicator* [822]. For titration with perchloric acid of codeine (pK 6·05), cryptopine, morphine (pK 6·17), thebaine (pK, 6·05) narcotine (pK 7·82) and papaverine (pK 8·10), malachite green is more suitable than crystal violet since its colour change comes closer to the potentiometric end-point than that of crystal violet.

Dissolve 250–350 mg of the alkaloid in 100 ml of acetic acid and after adding 1 ml of 0·001 M malachite green, titrate with 0·05 N perchloric acid in acetic acid. Near to the end-point add the titrant one drop at a time until the blue to blue-green colour becomes green. In order to determine the combined consumption of standard solution of the solvent and the indicator dissolve 100 mg of sodium perchlorate in 100 ml of acetic acid and titrate in the presence of 1 ml indicator solution to a green colour.

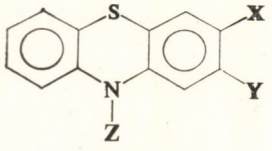
(l) *Determination of narceine with photometric end-point detection* [209]. Weigh 250–500 mg of narceine (pK 10·7) in 20 ml of acetic acid, add two drops of a solution of 0·5 % methylene blue in acetic acid and place it in the 15 mm cuvette of a photometer (e.g. Lange model IV). Titrate with 0·1 N perchloric acid in acetic acid at wavelengths 550–580 mμ, inserting an OG 2 type colour filter. Plot single portions of the standard solution as a function of $1/T$. The $1/T$ value shows a sudden rise at the equivalence point (cf. Fig. 76, curve *B*). 54·55 mg of narceine require 1 ml of 0·1 N standard solution. (2) By applying potentiometric end-point detection, a number of alkaloids, important pharmaceutically, can be titrated in propionic acid, e.g., brucine, codeine, narceine, narcotine, quinine, veratrine [663].

122. Phenothiazine Derivatives (Table 35)

For the determination of phenothiazine derivatives, solvents containing oxidizing agents such as peroxides must be avoided (e.g. dioxan). Suitable solvents are the mixtures: 1,2-dichloroethane-acetic acid, benzene-nitromethane or hexane-acetone, as well as acetone, acetonitrile and chlorobenzene.

(a) *Titration in a mixture of 1,2-dichloroethane–acetic acid* [130]: Weigh 150–200 mg of Chlorpromazine, Prochlorperazine or Promethazine base, dissolve in 30 ml of acetic acid containing 10 % acetic anhydride, dilute with 60 ml of dichloroethane and titrate with 0·1 N perchloric acid in acetic acid in the presence of indicator tropaeolin 00.

Table 35

Compound	*Phenothiazine Derivatives**  *Substituent*			*Molecular Weight*
	X	*Y*	*Z*	
1. Chlorpromazine	H	Cl	$-CH_2CH_2CH_2N(CH_3)_2$	318·9
—HCl				355·3
2. Promethazine	H	H	$-CH_2-CH(CH_3)-N(CH_3)_2$	284·4
—HCl				320·9
3. Prochlorperazine-2 HCl	H	Cl	$-CH_2CH_2-N\langle H \rangle N-CH_3$	373·9
				476·9
Prochlorperazine-dimaleate				606·1
4. Ahistan Ⓡ	H		$-CO-CH_2N(CH_3)_2$	284·4
5. Thiopropazate-2 HCl	H	Cl	$-(CH_2)_3-N\langle H \rangle N-CH_2CH_2OOC \cdot CH_3$	446·0
				518·9
6. Perphenazine-2 HCl	H	Cl	$-(CH_2)_3-N\langle H \rangle N-CH_2CH_2OH$	403·9
				476·9
7. Pecazine-HCl	H	H	$-CH_2-C_5H_9N-CH_3$ (N-methyl-piperidyl)	310·4
				346·9
8. Triflupromazine	H	$-CF_3$	$-CH_2CH_2CH_2N(CH_3)_2$	352·4
—HCl				388·9
9. Acepromazine	H	$-OCCH_3$	$-CH_2CH_2CH_2N(CH_3)_2$	326·5
—HCl				362·9
Acepromazine maleate				442·5

* pK values for phenothiazine derivatives, see: [125].

(b) *Titration in acetonitrile or chlorobenzene* [795]. Weigh 150–250 mg of N-(dimethylaminoacetyl)-phenothiazine (Ahistan ®), dissolve in 100 ml solvent neutralized in the presence of methyl violet or tropaeolin 00 and titrate 10 to 20 ml of the stock solution with 0·01 N perchloric acid. 2·844 mg of dimethylaminoacetylphenothiazine require 1 ml of 0·01 N perchloric acid.

(c) *Titration of bifunctional phenothiazine derivatives in benzene-nitromethane* [586]. Weigh 50 mg of Prochlorperazine, Thiopropazate or Perphenazine base, dissolve in 150 ml of benzene-nitromethane (2 : 1) and titrate in the presence of 3 drops of 1% tropaeolin 00 with 0·05 N perchloric acid in dioxan to a pink-violet colour change of the indicator. If the sample to be tested is the dimaleate or dihydrochloride of the base, saturate the aqueous solution with sodium sulphate to inhibit emulsification; basify with a minute amount of sodium hydroxide and extract with 6 × 15 ml of benzene. Add 40 to 50 ml nitromethane to the total extract and titrate as above. Concerning Prochlorperazine maleate, see also: Section 123 in this chapter.

The acidic component of the above tranquillizers can be determined in chloroform with KOH in methanol or standard $KOCH_3$ in dimethylformamide; in both cases thymol blue is a suitable indicator [586].

All three of the above mentioned phenothiazine derivatives contain a piperazine ring, hence they can be titrated as bifunctional bases. Pecazine-HCl, Triflupromazine-HCl and Acepromazine-maleate, since they contain only one titratable N-atom, behave as monofunctional bases.

(d) *Titration of monofunctional phenothiazine derivatives in acetone or a mixture of hexane-acetone* [586]. Weigh 70 mg of phenothiazine derivative and dissolve in 50 ml of acetone. In the case of hydrochlorides, the base is liberated with 0·5 ml of 6% mercury(II) acetate in acetic acid and titrated with 0·05 N perchloric acid in dioxan in the presence of two drops of 1% dimethyl yellow in chloroform till yellow turns to orange. Two drops of a 5% indicator are used for Acepromazine-maleate (colour change: orange-yellow to orange-red). From the aqueous solution of Pecazine-HCl the base can be extracted with 4 × 20 ml of hexane (see (c)); the total extract is diluted with 40 ml of acetone and titrated as above.

(e) *Determination of Chlorpromazine hydrochloride by extraction* [587]. Weigh about 50 mg of 10-(3-dimethylaminopropyl)-2-chlorophenothiazine hydrochloride into a separating funnel, dissolve in 20 ml of distilled water, basify with KOH and extract the base with 4 × 20 ml of hexane. Mix the total extract with 40 ml of acetone and titrate with 0·05 N perchloric acid in dioxan in the presence of 3 drops of 0·1% methyl red in acetic acid till the orange-yellow of the indicator turns to a pink shade. Of the two tertiary amino groups only that in the alkyl chain can be titrated. This determination can also be performed potentiometrically by using a glass–calomel electrode system (Fig. 44 d, Chapter 12).

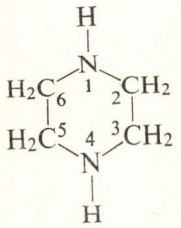
See also: Chapter 24; Section 136 (d).

123. Piperazine Derivatives

(a) *Basicity of piperazine and piperazine derivatives.* Consider the influence of methyl substitution on the base strength of piperazine and/or pyrazine (1,4-diazine) derivatives [454]:



Pyrazine (1,4-diazine)



Piperazine (hexahydro-1,4-diazine)

Methyl groups lower the basicity of piperazine, especially if substitution is on the nitrogen atom. Base strength is doubled by the introduction of a methyl group on the carbon atom of pyrazine in position 2, increased by ten times on the introduction of a second methyl group in position 5 or thirty times if it is in position 6. Methyl groups in all four possible positions increase the basicity of the compound by fifty times in comparison with pyrazine. In the course of titration with perchloric acid one N-atom is protonated [454].

Piperazine has pK_1 3·97 and pK_2 8·34; 2-methylpiperazine 4·10 and 8·54; 2,5-dimethylpiperazine: *cis*-, 4·02 and 8·77; *trans*-, 4·16 and 8·66; 2,3,5,6-tetramethylpyperazine 4·06 and 8·89; 1,2,4-trimethylpiperazine 5·64 and 10·06.

Pyrazine, p*K* 12·9; 2-methylpyrazine 12·5; 2,5-dimethylpyrazine 11·9; 2,3,5,6-tetramethylpyrazine 11·2.

The 1,4-disubstituted piperazine derivatives, when potentiometrically titrated, show one or two inflections in the curves, depending on the solvent and substituent. Thus, for instance, when 1-*p*-chlorobenzhydryl-4-*m*-methylbenzylpiperazine (Meclisine ®) is titrated potentiometrically with perchloric acid in acetic acid *one* inflection indicates two equivalents but in a solvent of differentiating properties, e.g. in acetonitrile or nitromethane, *two* inflections show protonation of the two tertiary N-atoms [132]. The end-point is sharpest when the final volume contains 22% acetic acid.

In the case of symmetrical substitution, e.g. 1,4-diphenylpiperazine in acetonitrile or nitromethane, one inflection can be observed and one equivalent of perchloric acid is consumed, showing that in these solvents the basicity of the second N-atom is too weak to co-ordinate the second proton; in acetic acid, however, two inflections indicate consumption of two equivalents of perchloric acid. In the case of piperazine in acetonitrile or acetic acid one inflection indicates reaction with two equivalents of perchloric acid.

The effect of substituents in *decreasing* base strength is as follows:
carbethoxy > phenyl > *p*-chlorobenzhydryl > benzyl > 2-(2′-hydroxyethoxy)ethyl > H.

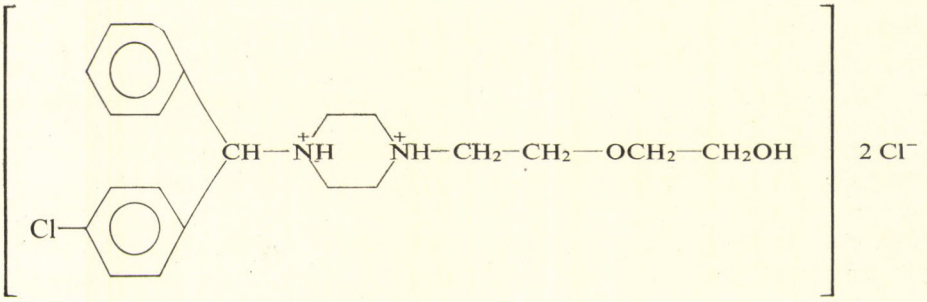
pK^{+}_{BH+} values of some piperazine derivatives [333]: 1-carbethoxypiperazine: 8·28; 1-benzoylpiperazine: 7·78; 1-tosylpiperazine: 7·44.

These examples indicate that in the titration of diacidic bases it must be decided separately for each case which kind of solvents are able to promote or hinder protonation (and therefore titration).

(b) *Determination of 1-(p-chlorobenzhydryl)-4-[2′(2″-hydroxyethoxy)-ethyl]-piperazine dihydrochloride* (Hydroxyzine).* Weigh 50 mg of Hydroxyzine in a 100 ml sepa-

* *Drug Stand.* **26**, 108 (1956).

rating funnel, dissolve in 10 ml of water, liberate the base with 20 ml of 0·1 N alkali and extract the base with 4 × 25 ml of chloroform. Dry the combined extracts with anhydrous Na_2SO_4, evaporate to about 15 ml (e.g. by means of the flask shown in Fig. 103 p. 249) and after adding 10 ml of acetic anhydride titrate with 0·02 N perchloric acid in acetic acid. 4·478 mg of hydroxyzine require 1 ml of 0·02 N solution:



An interesting compound is 3-chloro-10-[3′-(1″-methyl-4″-piperazinyl)-propyl]-phenothiazine (Prochlorperazine) which contains three tertiary N-atoms. Its salt formed with maleic acid can be titrated directly, without extraction, with 0·05 N perchloric acid in acetic acid in the presence of crystal violet [699]. The molecule combines with two equivalents of perchloric acid: thus, 9·35 mg of the base require 1 ml of 0·05 N perchloric acid (molecular weight 373·9).

For the determination of N-(β-3,4,5-trimethoxybenzoyl-hydroxyethyl)-N′-[γ-(3′-chloro-10′-phenothiazinyl)-propyl]-piperazine diethanesulphonate see: [321] (Chapter 24; Section 140).

(c) *Determination of piperazine and hydroxyethylpiperazine in one mixture* [811]. N-Hydroxyethylpiperazine in acetonitrile consumes two equivalents of perchloric acid. Piperazine as well as hydroxyethylpiperazine can be acetylated in acetonitrile-acetic anhydride or chloroform-acetic anhydride. N,N′-Diacetylpiperazine does not bind perchloric acid but N-acetyl-N′-hydroxyethylpiperazine binds one equivalent of perchloric acid. Thus, a mixture of piperazine and hydroxyethylpiperazine can be determined by titration with perchloric acid combined with acetylation.

A mixture of acetic acid and acetic anhydride (2 : 8) is suitable for this acetylation.

Weigh 50 to 70 mg of sample and dissolve in 25 ml of acetonitrile. Pipette 10 ml of this stock solution into a glass-stoppered flask, add 10 ml of acetylating mixture and allow to stand, well stoppered, for 90–100 min, then titrate with 0·05 N perchloric acid in acetic acid in the presence of crystal violet, taking a colour change from violet to blue as the end-point (*a* ml). Titrate another 10 ml of the stock solution without the acetylating mixture (*b* ml). To obtain the volume consumed by the piperazine subtract twice the amount of the volume consumed *after acetylation* (*a* ml) from the volume consumed in the titration without acetylation (*b* ml). One ml of 0·05 N perchloric acid is equivalent to 2·153 mg of piperazine or 6·51 mg of hydroxyethylpiperazine (the latter in acetylated form).

This method can be applied only if the reaction product is not contaminated by a third component e.g. bis(hydroxyethyl)piperazine. The latter is not acetylatable, so that misleading results are obtained. For measurements of ternary mixtures the above procedure must be modified.

Piperazine forms a compound, $C_4H_{10}N_2, CS_2$, with carbon disulphide, which is insoluble in chloroform.* In the case of piperazine conversion is 98·3 % and for hydroxyethylpiperazine (based on the formula $C_6H_{14}N_2O$, CS_2), 90–92 %. Bis(hydroxyethyl)piperazine does not form a precipitate and can be titrated with perchloric acid in acetic acid or in chloroform–carbon disulphide.

Weigh approx. 300 mg of ternary mixture (0–10 % piperazine, 80–90 % hydroxyethylpiperazine, 0–10 % bis(hydroxyethyl)piperazine) and dissolve in 50 ml of $CHCl_3$. Pipette from this stock solution 10 ml into a 50 ml flask, add 0·5 ml of CS_2 and boil for 40–80 min on a steam bath under reflux. After cooling, filter the solution through a G/4 porosity glass filter, wash the precipitate on the filter with 5 × 3 ml of $CHCl_3$ and titrate the bis(hydroxyethyl)piperazine in the total filtrate with 0·05 N perchloric acid. 4·536 mg of bis(hydroxyethyl)piperazine require 1 ml of 0·05 N standard solution.

Use two further 10 ml portions of the stock solution for titration with perchloric acid, once with acetylation and once without it. Subtract the volume found on titration of the filtrate from the volume following acetylation. Thus, the amount of standard solution consumed for hydroxyethylpiperazine, corrected for the amount of standard solution consumed for bis(hydroxyethyl)piperazine is obtained.

124. Titration of Bases in Chlorobenzene

(a) *Potentiometric determination* [638]. Dissolve 0·23–0·26 m.eq. of base in 25 ml of chlorobenzene and titrate with 0·05 N perchloric acid in acetic acid using a glass indicator electrode and calomel as reference electrode. Stop the magnetic stirrer employed for agitation during titration when readings of mV values are taken. In the case of bases insoluble in chlorobenzene dissolve 0·5 m.eq. in 50 ml of chlorobenzene containing 20 % acetic acid and titrate as above. A suitable ratio of standard solution versus test solution is 2 : 10. Accuracy of titrations of 0·1 m.eq. of atropine base is 100·5 ± 1·1 % and that of 0·2 m.eq. is 99·7 ± 0·55 %.

(b) *Visual end-point detection* [638]. Bromophenol blue is a suitable indicator. The initial colour of the solution depends on the strength of the dissolved base: purple (atropine, ephedrine), pink (strychnine), yellow (amidopyrine). Titration, in this case also, is performed with perchloric acid of 0·05 N concentration until the indicator becomes colourless. In the case of weak bases the formation of insoluble perchlorates increases accuracy. One ml of 0·05 N solution is equivalent to 14·47 mg of atropine (pK 4·35), 8·261 mg ephedrine (pK 4·68), 16·72 mg strychnine (pK 6·00) or 11·56 mg amidopyrine (pK 9·30).

125. Titration of Bases in Nitromethane

Compounds of weak basicity can be titrated potentiometrically in nitromethane or a mixture of nitromethane–acetic anhydride with 0·05 N perchloric acid in dioxan [126] or nitromethane [779].

* Castiglioni: *Z. f. anal. Chem.* **119**, 118 (1940).

(a) *Interaction of nitromethane with bases* [126]. Chatten and his collaborators investigated numerous alkaloids in nitromethane. Inflections of potentiometric curves suggest that bases whose pK value is below 11 interact with nitromethane, e.g. (pK value in brackets): atropine (4·35), ephedrine (4·68), cinchonine (5·85), strychnine (6·00), codeine (6·05) – (Fig. 117); solanine (6·66), narcotine (7·82), papaverine

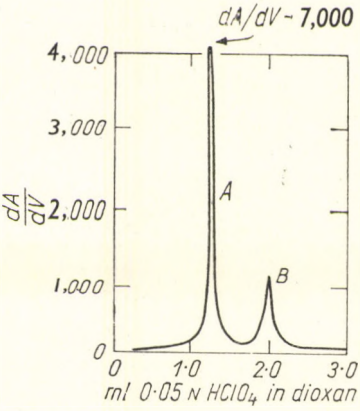


Fig. 117. Differential plot of codeine using nitromethane as solvent according to Chatten, Pernarowski and Levi [126]. — *(A)* The first maximum indicating neutralization of about 64% codeine base. *(B)* The second maximum (~ 100% titration) indicating titration of CH_2NO_2. **BH** typecompound, where **B** is the codeine base

(8·07), amidopyrine (9·30), narceine (10·7). Interaction may be attributed to the aci-form of nitromethane forming addition products with the alkaloids (Chapter 7; Section 44 and Chapter 2; Section 21).

(b) *Titration in nitromethane with 0·05* N *perchloric acid* [779]. A linear correlation exists between pK_{BH^+} value of bases and half-neutralization potential (h.n.p.) (Chapter 3. Section 23(d)). Titration is performed potentiometrically in nitromethane with glass-calomel electrodes. About 0·25 m.eq. of base are titrated in 100 ml of solvent (See Table 6 and Figs 24 and 25).

Preparation of the standard solution: dissolve 4·2 ml of 72% perchloric acid in 1,000 ml nitromethane. Standardize against potassium hydrogen phthalate. The standard solution remains stable for about a month.

(c) *Potentiometric titration in a mixture of nitromethane–acetic anhydride* (4 : 1) [249]. Weigh a sample of 0·3–0·8 m.eq. in 20 ml of solvent mixture. If the compound is of poor solubility dissolve previously in a small amount of acetic acid, if necessary with gentle heating. Titrate potentiometrically with 0·1 N perchloric acid in acetic acid with glass-calomel electrodes. By this method some heterocyclic bases can also be titrated besides t-aliphatic amines (in brackets mg equivalent to 1 ml of standard solution): benzothiazole (13·52), anhydrous caffeine (19·42), 5,7-dichloro-8-hydroxyquinoline (21·40); see also: Section 121(d), nicotinamide (12·21), 8-nitroquinoline (17·42), quinoxaline (13·01), theobromine (18·02), anhydrous theophylline (18·02).

It is noteworthy that triphenylmethanol can be titrated as a base and is, at the same time, a suitable indicator for the titration of benzothiazole, nicotinamide and quinoxaline; for caffeine, neutral red can be used as indicator.

126. Titration of Bases in Acetic Anhydride

The excellent properties of acetic anhydride as a solvent when bases of decreased basicity are to be determined have become generally recognized [58, 211, 249, 288, 676, 732, 778, 878].

Even those weak bases which cannot be determined visually or potentiometrically, either in acetic acid or in propionic acid, can be titrated in acetic anhydride. Examples are: caffeine, acid amides (pK 13·4), (see under this heading). Acetanilide in acetic anhydride is just on the limit of potentiometric titration (pK 13·39 [497]; pK_{BH^+}–0·9 [505]).

In some cases halides of bases can also be titrated without adding mercury(II) acetate to the solution (Chapter 24; Section 136 (m)).

Acetic anhydride affects the mucous membranes of the eyes, nose and mouth. Titration, therefore, should be performed under a well ventilated fume-hood. Only the non-acetylatable bases can be titrated in acetic anhydride or if the compound contains two basic N-atoms and one is a tertiary N-atom, acetylation of the primary or secondary amines contributes to the success of titration. The solvating power of acetic anhydride is not as high as that of acetic acid. The sample should be dissolved in 1 to 2 ml of formic acid and subsequently diluted with acetic anhydride. If crystal violet is the indicator the colour change occurs from blue or green-blue to yellow-green or yellow. The titrated solution must be destroyed with water.

(a) *Visual titration* [676]. Weigh a sample which will give a titration of 5–10 ml of 0·1 N perchloric acid in acetic acid. Add in a fume-hood 50 ml of acetic anhydride; cover the flask with a small beaker and maintain agitation with a magnetic stirrer until dissolved. Titrate in the presence of 5–6 drops of 0·1% crystal violet in acetic anhydride and correct for the blank of the solvent (in most cases this can be neglected). As examples antipyrine (18·82 mg) and nicotinamide (12·21) can be titrated in this way (in brackets mg equivalent of 1 ml of 0·1 N solution). In some cases the compound is only dissolved during titration: theophylline (18·02), 7-(2′-hydroxyethyl)-theophylline (22·42), nicotinic acid (12·31). Samples of caffeine and theobromine are first dissolved in 5 ml of 98% formic acid; 50 ml of anhydride is added and subsequently titrated as above. In the latter case the blank consumption of the solvent is greater. (See also Chapter 23; Section 129.)

Regarding determinations of 8-hydroxyquinoline, 3-methyl-8-hydroxyquinoline and 3-methyl-5,7-dichloro-8-hydroxyquinoline in acetic anhydride see: [620].

According to the recent literature organic bases containing nitrogen are protonated by the solvent while the acetic anhydride is converted to an anion; the latter reacts with the acetacidium ion [676]:

$$(CH_3CO)_2O + B \rightleftharpoons BH^+ + (CH_3 . CO. O. OC. CH_2)^- \qquad (126.1)$$

$$(CH_3. CO. O. OC. CH_2)^- + CH_3COOH_2^+ = (CH_3CO)_2O + CH_3COOH \qquad (126.2)$$

(b) *Potentiometric titration.* Potentiometric titrations in acetic anhydride medium show a linear correlation between pK_{BH^+} value of bases and half-neutralization potential [778] (Chapter 3; Section 23 (c), Table 5, Figs 23 and 24).

Titration is performed with 0·05 N perchloric acid in acetic acid-acetic anhydride (1:1): Chapter 11; Section 60 (a), or perchloric acid in acetic acid can also be used.

Weigh 1 m. eq. of the sample, dissolve in a measuring flask in 100 ml of acetic anhydride and pipette, by means of the device shown in Fig. 34, 25 ml into a 150–200 ml beaker. Add 75 ml of acetic anhydride and use a combination of glass-Ag/Ag Cl electrodes for the titration. The reference electrode is a spiral silver wire, the surface of which is electrolytically coated with AgCl and is immersed in a saturated solution of AgCl and LiCl in acetic anhydride (cf. Figs 62, 63 and 64). Other authors use a glass–calomel electrode system for the titration of acid amides. The electrolyte filling the electrode is, in this case, a 0·1 M solution of $LiClO_4$ in acetic anhydride [878].

(c) Determination of aromatic N-oxides with perchloric acid in acetic anhydride medium: see: [604, 880].

127. Semimicro, Micro, and Ultramicro Titration of Alkaloids and Other Bases

Therapeutically, most alkaloid bases are effective in a minute amount (e.g. Protoveratrine 0·1 mg) and the average alkaloid content of medicinal plants is also very low, 0·2–2 % (though cultivated species may possess a higher percentage). Hence for determinations micro methods, and in exceptional cases ultramicro titrations may prove necessary.

Semimicro analyses are intermediate in scale between macro and micro determinations. Taking an average equivalent weight as 200, the following weights are employed for non-aqueous titrations:

Macro method	100 –300 mg
Semimicro method	10 – 50 mg
Micro method	0·1– 5 mg
Ultramicro method	5 – 50 μg

(cf. [128] and [584]).

The conditions for macro or semimicro determinations (e.g. quantity of indicator, volume of solvent, etc.) cannot be adapted directly to micro or ultramicro determinations. For the titration of bases, 0·001 N perchloric acid can be used, but difficulties may arise if the strength of the base to be tested differs considerably from that of the base employed for standardization of the titrant, as already mentioned in Chapter 13; Section 72. Sometimes, especially for photometric titrations, it is advisable to use 0·5 N perchloric acid; in this case the so-called Gilmont-type microburette-pipette is a suitable device ([333] and p. 168 in [584]).

(a) *Titration with 0·005* N p-*toluenesulphonic acid* [299, 304, 696, 700]. The advantages of titration with 0·005 N *p*-toluenesulphonic acid may be summarized as follows [299]:

1. A 0·5–3·0 mg sample of the alkaloid base is sufficient for an analysis;
2. The most advantageous feature of the method is that after having extracted the alkaloid from its alkaline solution with chloroform and dried over anhydrous sodium sulphate, the chloroform solution may be titrated directly; thus it is not necessary to evaporate the solvent, to dissolve the base in 0·01 N standard hydrochloric acid, and to back-titrate with 0·01 N alkali. This means the elimination of three procedures and three sources of error;

3. The titration is much more accurate than it would be in aqueous medium. This is primarily owing to the very sharp colour change of dimethyl yellow indicator;

4. One drop of the standard chloroform titrant corresponds (for the microburette used, see: Figure in [299]) to 0·007 ml volume. In practice this means that when titrating dropwise near the end-point, even without the usual technique of adding fractions of a drop by touching the wall of the vessel with the tip of the burette, the probable error per one ml of titrant is only +0·7 %.

Other advantages are mentioned by Šafařic*: chloroform is an excellent solvent for organic bases; being a non-polar solvent, no salts are formed either with acids or bases, consequently it does not affect the equilibrium states of neutralization reactions.

A check of the optical rotation of optically active alkaloids should be carried out in the same solvent, as for non-aqueous titration. For the *determination of hyoscyamine base* weigh about 50 mg of sample and dissolve in 25 ml of chloroform. Measure the rotatory power of the solution (in a 2% solution in $CHCl_3$: $[\alpha]_D = -25{\cdot}2°$). From the rest of the stock solution, dilute 5 ml with chloroform to 100 ml and titrate after adding one to two drops of 0·1% dimethyl yellow in chloroform. Titrate a 5 ml portion from this second stock solution until the yellow colour turns to pink. 1·447 mg of hyoscyamine (atropine) base requires 1 ml of 0·005 N *p*-toluenesulphonic acid.

Rotatory power and percentage of e.g. ergotamine base are checked in the same way.

Bases whose dissociation constants (in water) are not smaller than 10^{-9} can be estimated similarly (*p*-toluenesulphonic acid is a weaker proton donor than acetacidium perchlorate) (in brackets mg equivalent of 1 ml 0·005 N solution): hyoscine (1·517), strychnine (1·672), chelidonine (1·766), codeine (1·497), jervine ($C_{26}H_{37}O_3N$, 2·057), vincamine (1·772), protoveratrine A + B (4·02), papaverine (1·695), tomatine (5·171), tomatidine (2·078), reserpine (3·044)** [41, 299, 301, 304, 305, 323, 701, 791, 792]. In the case of weaker bases ($pK_b \sim 11$) it is more advantageous to use, instead of chloroform, chlorobenzene or dichloromethane and 0·005 N *p*-toluenesulphonic acid in chloroform-ethanol (99 : 1) [696].

(b) *Determination of ergot alkaloids* [305]. Weigh 5–10 mg of ergot alkaloid on a semimicro balance and dissolve in 5–10 ml of purified chloroform preserved by 1% v/v of light petroleum. Titrate with 0·005 N *p*-toluenesulphonic acid in the presence of 1–3 drops of dimethyl yellow as indicator. Colour change is from yellow to light pink. 3·048 mg of ergocrystine require 1 ml of standard solution. Ergotamine-acetone compound, ergotamine-benzene compound and ergotoxine-benzene compound can be measured in the same way.

(c) *Determination of the hydrochloride of diethylaminoethyl benzilate* (Benactyzine hydrochloride) [757]. From the finely powdered tablets weigh an amount which will give a titration of 1–3 ml of 0·005 N *p*-toluenesulphonic acid into a 100 ml separating funnel.

Suspend the weighed sample in 10 ml of water, add 0·2 g of finely powdered $NaHCO_3$ and, after dissolving, extract the base with 2 × 40 ml and 2 × 30 ml of

* *Česk. Farm.* **11**, 387 (1962).

** p*K* 7·7. Krebs and Fütscher, *Arzneimittel-Forschung* **10**, 75 (1960).

chloroform. Dry the total extract with anhydrous Na_2SO_4 and concentrate to 5 ml. This can be done in the evaporating flask shown in Fig. 103. Add 4 drops of 0·1 % dimethyl yellow indicator in chloroform to the concentrated solution and titrate with 0·005 N *p*-toluenesulphonic acid to pink (1 ml ~ 1·8194 mg of Benactyzine-HCl).

(d) *Determination of reserpine in tablets.* The determination of a small quantity (0·1–0·25 mg) of alkaloid base of high molecular weight often meets with difficulties owing to the large amount of vehicle (tablet excipient) adsorbing the active agent of the tablet. If adsorption is reversible or the alkaloid does not undergo decomposition either during preparation of the tablet or during storage a quantitative test can be done in a non-aqueous medium [302].

Decomposition of alkaloid is often followed by chemisorption on the vehicle. In this case the undecomposed alkaloid is bound to a greater extent than the decomposition product (selective adsorption). This phenomenon, which can be explained by adsorption, can be observed most frequently with tablets prepared by aqueous granulation [300].

Extraction of the active agent is increased by adding 2–3 % of phenol to the extracting solvent ($CHCl_3$ or CCl_4) [323]. Phenol does not interfere with *p*-toluenesulphonic acid titrations.

Prepare a finely pulverized homogeneous powder from tablets of the sample, each tablet containing 0·1–0·25 mg of reserpine, and weigh the amount needed for consumption of 1–3 ml of 0·005 N *p*-toluenesulphonic acid in a 100 ml ground flask. Add 15 ml of carbon tetrachloride–phenol (100 : 2) neutralized in the presence of dimethyl yellow. Allow to stand for 30 min, assisting extraction of the reserpine base by rotating the flask, especially at first. After settling, filter in a carbon tetrachloride atmosphere [299] on 9 cm filter-paper such as Schleicher-Schüll 'Schwarzband' type. A carbon tetrachloride atmosphere is produced by placing on the bottom of a somewhat larger beaker than the funnel a layer of cotton wool and over it a harder filter-paper, both saturated with CCl_4. During filtration cover the filter with the beaker so fitted. Wash the vehicle left on the filter-paper with 3 × 3 ml of chloroform and titrate the total solution in the presence of dimethyl yellow: 3·044 mg of reserpine requires 1 ml of 0·005 N standard solution [41, 323]. The active agent of tablets containing protoveratrine A + B can be determined in a similar way [323].

Reserpine can also be extracted with chloroform, but without adding phenol if the technique used for the preparation of tablets precludes adsorption of the alkaloid base to the vehicle [792].

(e) *Determination of papaverine base with 0·005 N p-toluenesulphonic acid in ethylene glycol-isopropanol* [700]. Weigh 10–15 mg of papaverine base, dissolve in acetone, methyl isobutyl ketone or chloroform and titrate potentiometrically. If a small amount of phenol is added to the solution in acetone, titration can also be performed in the presence of methyl orange indicator. 1·695 mg papaverine base requires 1 ml of standard solution.

Morphine, codeine and thebaine can be titrated in a mixture of chloroform-isopropanol-phenol (10 : 1 : 1) with 0·002 N perchloric acid or *p*-toluenesulphonic acid in ethylene glycol-isopropanol (1 : 1) or ethylene glycol-dioxan (1 : 1) [702].

(f) *Titration with 0·001 N perchloric acid.* The standard solution can be prepared either with the solvent pair carbon tetrachloride–acetic acid or carbon tetrachloride-propionic acid: Chapter 9; Section 52 (d). Prepare from the alkaloid a stock

solution, each millilitre containing about 0·005 m.eq. of base (that is, 15 mg of an alkaloid of average molecular weight 300 are dissolved in 10 ml of neutralized solvent). Beware of placing the stock solution near to a heat source during parallel titrations. Allow the solvent or solvent mixture used for solution to stand in order to reach room temperature. By means of a precision pipette titrate 1 ml of stock solution in the presence of one drop of 0·1% of crystal violet or methyl violet in a conical centrifuge tube on a white ground, viewing from above. Use previously neutralized acetic or propionic acid as solvent if the weighed sample is a non-acetylatable base: or acetic anhydride or a mixture of these with an aprotic solvent in the ratio of 1 : 10 to 1 : 1. Standardize the solution in the same solvent with the same indicator concentration. If the base titrated has $pK < 10^{-9}$, the standardizing agent should be, if possible, either the same compound or one of nearly identical base strength to that of the base to be estimated, but of standard purity. For stronger bases diphenylguanidine can also be used as standardizing agent. In both cases, however, the compound to be tested and the standardizing agent should be of nearly identical molar concentration. Use the same pipette for both the compound to be tested as well as for the stock solution of the standardizing agent. Take care that the rate of titration is identical and avoid warming the pipette by the hand.

In a 1 : 3 mixture of acetic acid-chloroform, even bases with a base constant of 10^{-12}, and in acetic anhydride those of $10^{-13{\cdot}5}$ can be titrated in the presence of crystal violet [297]. 0·5 mg of aniline can be titrated potentiometrically in a mixture of cyclohexane–acetic acid (1 : 1) with 0·005 N perchloric acid in acetic acid using a Warner–Haskel type titration vessel [860]. (Fig. 56. See also: [450].)

(g) *Ultramicro titration of bases* requires especially great care [51, 584]. 50 μg of organic base are dissolved in 0·4 ml of acetic acid, dehydrated with particular care. A small test tube (30 mm × 11 mm) serves as titration vessel, closed by a cork stopper or rubber plug with polyethylene coating to prevent acetic acid absorbing water from the stopper. The basic dissociation constant of water is p*K* 12·53 (*Kolthoff* and *Bruckenstein*) its disturbing effect being smaller in potentiometric titrations but interfering to a greater extent in the case of visual titrations. Near the end-point the disturbing effect is increased, because water, as a weak base, disturbs the formation of indicator perchlorate (indicators are also weak bases).

In potentiometric ultramicro titrations the blank value of the solvent is increased only slightly by the small amount of water in 0·4 ml of acetic acid but with the gradual rise in the water content potentiometric curves become flattened out. In visual indications consumption of the standard solution increases considerably in the course of the blank test [51]:

Water Content in %	0·02	0·2	0·5	0·75	1·0	1·5
Volume consumed for potentiometric blank test (μl)	1·0	1·0	1·1	1·1	1·2	1·2
Volume consumed for visual blank test (μl)	1·2	1·4	1·9	2·3	3–3·5	4–5

Owing to the disturbing effect of water the small titration vessel and pipette must be rinsed with acetic acid containing crystal violet and a minimal amount of perchloric acid till the blue green colour of acetic acid persists. The titration tube is rinsed with acetic acid, dried in a nitrogen stream and sealed with a polyethylene-coated stopper.

The most suitable indicator is crystal violet [51]; for a complete break from violet to green 0·2–0·4 μl of 0·01 N perchloric acid are needed if 50 μg of base are titrated in 0·4 ml of acetic acid. In theory, for each base the correct colour change must be found individually; in many cases, however, two comparative solutions, a 'blue' *(a)* and a 'green-blue' *(b)* suffice:

(a) dissolve 0·6 g of urea in 78–80 ml of acetic acid, add 3·0 ml of 0·01 N perchloric acid and 3·3 ml of 0·01 % crystal violet and dilute with acetic acid to 100 ml;

(b) prepare as *(a)* but with 6·0 ml of perchloric acid.

It may happen that neutralization of 30 μg of bases yields a tint different from that for, say, 60 μg [146]. For example, when 50 μg of sodium acetate are titrated with 0·01 N perchloric acid in the presence of crystal violet a correct equivalence occurs with a blue colour while with 300 μg at a green colour, though the 'pH' values at the end-points are identical.

For ultramicro titrations sufficient of the sample is weighed so that the consumption of 0·01 N perchloric acid does not exceed 30–50 μl. If a large amount of solvent is used (1–2 ml) the blank consumption of the solvent may amount to 10 % v/v of the standard solution consumed for titration, but for 0·4 ml of solvent it is not more than 1 μl.

The result also depends on the time spent on titration. For visual indication it should not exceed 2–3 min while for potentiometric indication, 7–8 min is the maximum. From *Belcher*'s ultramicroburette [51] 4–5 μl of solution evaporate within 90 min.

Owing to volatility a number of bases cannot be stored in a desiccator following measurement: for example, 73 μg of *p*-anisidine lost 30 % of its weight within 3 hours. *p*-Toluidine is volatile to such an extent that it cannot even be weighed uncovered on a highly sensitive analytical balance.

For potentiometric ultramicro titrations a glass electrode of 3·5 mm spherical diameter and Ag/AgCl-electrode as reference electrode can be used. The electrolyte is a solution of 0·02 N sodium perchlorate monohydrate in acetic acid.

Precision of determination even in ultramicro amounts is ±1 %, but the acquisition of the necessary technique requires thorough study and practice [51].

The result of potentiometric micro titrations can be calculated graphically. See: pp. 17–25 in [584].

128. Active Agents in Medicinal Plants Containing Alkaloids

The estimation of the active agent content of dried and pulverized medicinal plants will be illustrated by four examples. Among the four different procedures the first three, with slight modification, are suitable for the determination of the active agent content of other plants containing alkaloids.

(a) *Determination of the total alkaloid content of the Little Periwinkle* (Vinca minor L.) [790]. Weigh with mg precision 3 g of the dried and finely pulverized above-ground parts of the plant and basify with 3 ml of 10 % ammonia solution. Extract the drug on a shaker with 1 × 20 and 2 × 10 ml of benzene and dilute the total filtered extract with benzene to 100 ml. Extract 20 ml of the stock solution with 3 × 10 ml of 2 % aqueous sulphuric acid, filter, then basify 20 ml of the acidic solution with a solution of NaOH to pH 8 and extract with 4 × 5 ml of chloroform. Dry the chloroform extract with anhydrous sodium sulphate, and evaporate 10 ml to dryness. Dissolve the remainder in a mixture of 10 ml of chloroform and 5 ml of acetic acid, and titrate

with 0·01 N perchloric acid in acetic acid-carbon tetrachloride (1 : 1) in the presence of one drop of crystal violet. 3·544 mg of vincamine base ($C_{21}H_{26}O_3N_2$) require 1 ml of standard solution. Of the two N-atoms in the molecule only one is titratable. In this way the alkaloid content of 0·20 g of the pulverized plant is determined.

(b) *Analysis of the belladonna root* (*Atropa belladonna L* [525, 526]). The procedure and apparatus described below are suitable for series-analysis. Extraction of the pulverized plant with organic solvent and transfer to an acidic (liquid) phase are carried out in a single working process.

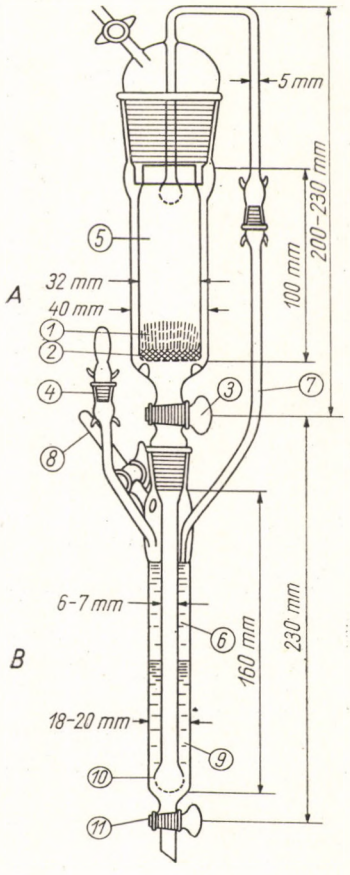


Fig. 118. Solid–liquid and liquid–liquid extractor for determination of the alkaloid content of medicinal plants, due to Lőrincz and Szász [525, 526]. — Signs and abbreviations below in text

Pulverize dry *Radix belladonna* finely and sift on a sieve of 0·30 mm mesh. Continue to grind and sieve the remaining coarse grist. Homogenize the yields from different siftings and dry over quicklime.

Two grams of the pulverized plant are ground in a mortar with 2 ml of 12% ammonia and spread on glass wool *(2)* placed in the muff of the extractor shown in Fig. 118. Open the cock *(3)* between solid–liquid extractor *(A)* and liquid–liquid extractor *(B)* and transfer 10 ml of 2% sulphuric acid through charging stub *(4)* into the cylinder of the liquid–liquid extractor. On the drug in the cylinder of the solid–liquid extractor *(5)* pour benzene in such an amount that benzene *(6)* reaches the circulating tube *(7)* in the lower part and covers the drug when the cock is closed.

After assembling, start the apparatus, by a continuous, gentle pressure through the pressure stub *(8)* so that the benzene above the sulphuric acid layer *(9)* is sprinkled onto the drug through the circulating tube, permeates through it and reaches the sulphuric acid layer through the perforated bulb *(10)*, accumulates on its surface and then sprays the drug through circulating tube *(7)*. By so doing circulation of the benzene phase is set in motion. While the benzene is permeating through the sulphuric acid solution, the alkaloid extracted from the drug by the benzene is

dissolved and transferred to the sulphuric acid phase. The greater part of the ballast-substance, dissolving in the benzene but not dissolving in suphuric acid, remains in the organic phase.

Continue the above *simultaneous solid–liquid and liquid–liquid extraction* for 1×2 and 3×1 hours. After each working process stop by discontinuing pressure, while cock *(3)* between the two parts is closed. After opening cock *(11)* on the lower part of the liquid–liquid extractor *(B)* discharge the acidic phase into a 50 ml measuring flask and pipette into the apparatus through the charging stub 10 ml of fresh 2% sulphuric acid. In this way about 40 ml of acid solution are obtained and made up to 50 ml with 2% sulphuric acid.

Basify 40 ml of the aqueous-acidic phase in the measuring flask with 10% sodium hydroxide to pH 8–9 and extract with 4×5 ml of chloroform. Dry the total chloroform solution with neutral anhydrous sodium sulphate and concentrate 10 ml on a steam bath to dryness. After cooling

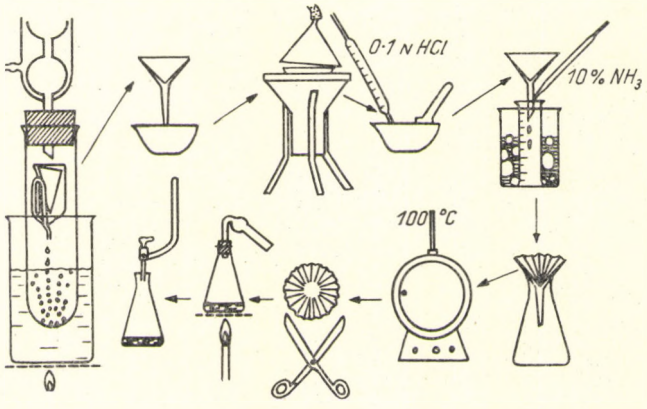


Fig. 119. Determination of tomatine. Diagram according to Gyenes [302]

dissolve the residue in 10 ml of chloroform, add 5 ml of acetic acid and titrate with 0·01 N perchloric acid in acetic acid in the presence of 0·1% crystal violet until a blue colour change occurs.

Apparatus shown in Fig. 110 can be connected in series by means of jointed air pressure pipes, thus the simultaneous functioning of 6–12 separate apparatuses is possible. The final solution in 15 ml chloroform–acetic acid contains the total alkaloids from 0·8 g of the pulverized plant. 2·894 mg of atropine requires 1 ml of 0·01 N solution.

(c) *Determination of the tomatine content of Lycopersicum esculentum var. ribesiforme and Licopersicum esculentum var. pruniforme* [302]. Sift 100 g of the pulverized dry plant (previously ground in a ball mill) on a 40 mesh sieve (0·42 mm mesh aperture) and subsequently on an 80 mesh sieve (0·177 mm mesh aperture). Measure with 0·1 g precision the unsifted part on the 40 mesh sieve, and the coarse powder passed through the 40 mesh sieve and the fine powder of the 80 mesh sieve and calculate the percentage composition of the grist.

Weigh 1·00 ± 0·01 g of the pulverized plant in a filter paper (9 cm) folded to funnel shape and extract with 30 ml of methanol for 40 min in a small Soxhlet apparatus. Add 1 ml of 25% ammonia through the condenser and continue extraction for another 20 min. Evaporate the extract in a porcelain dish, on a steam bath, to dryness, and after cooling pulverize carefully with 1 g of fine grained quartz sand and extract the base successively with 1×5 ml and 5×2 ml 0·1 N hydrochloric acid at 5–10°C. Filter the hydrochloric acid solution in an ice-cooled 25 ml precision glass test-jar and flush out the sand on the filter with 2–3 ml of distilled water. The greater part of the chlorophyll is retained with the quartz sand.

Basify the filtered solution with 1·5 ml of 10% ammonia to separate the tomatine base from the cooled mixture. Take the volume of the solution. After half an hour filter the precipitate on filter paper (9 cm) which has been washed with 200 ml of boiling distilled water and dried at 100°C. Spread the filter paper on a watch glass and dry for 20 min at 100°C, then cut the filter paper into pieces of 1 cm^2 and place these in a 100 ml glass-stoppered Erlenmeyer flask. Remove the dry glyco-alkaloids from the filter paper pieces with 15–20 ml of hot phenol–carbon tetrachloride (1 : 4), previously neutralized to pink with 0·005 N *p*-toluenesulphonic acid in the presence

of six drops of indicator dimethyl yellow. Titrate with *p*-toluenesulphonic acid till the solutio becomes permanently pink. During titration the solution must be repeatedly heated and chille after *vigorous shaking*. 5·171 mg of tomatine ($C_{50}H_{83}O_{21}N$, molecular weight 1,033) require 1 ml of 0·005 N solution. Correct the result obtained for the quantity of glyco-alkaloid remaining in the aqueous ammonia solution at 0°C; 0·17mg/ml. The above process is illustrated in Fig. 119.

The tomatine content of the three different sorts of grists is recalculated for the sample as a percentage ratio of grist distribution.

Solasonine is determined in the same manner [318].

(d) *Extraction of drugs containing alkaloids with acetic acid free from acetic anhydride* [23]. According to a commonly accepted method drugs are extracted with a lipophilic solvent while bases are liberated with aqueous alkali and ammonia from their salts. This results in a two-phase system which is not always desirable. The drug-containing alkaloids can be directly extracted with acetic acid but this method is a macro process and cannot be applied to all samples. A further disadvantage is that in the case of acetylatable alkaloids, the acetic acid must not contain even traces of acetic anhydride (Chapter 8; Section 47 (c)).

Determination of emetine content (p*K* 5·77). Heat two grams of pulverized drug to boiling under reflux with 20, 15 and 10 ml of acetic acid for 5 min. Filter each extract through a glass filter of G/3 porosity and mix in a 500 ml separating funnel. Rewash with approx. 50 ml of water and basify the acetic acid extract carefully (!) with a solution of ammonia (the separating funnel is continuously cooled under running water). Extract, avoiding vigorous shaking, with 1 × 100 ml and 2 × 50 ml of chloroform. Dry the extract with anhydrous sodium sulphate, evaporate on a steam bath under reduced pressure to dryness, dissolve the residue in 10 ml of acetic acid and titrate with 0·1 N perchloric acid in the presence of crystal violet. 24·03 mg of emetine requires 1 ml of standard solution (viz. total alkaloid is expressed as emetine).

For the determination of nicotine and nor-nicotine content of pulverized tobacco see: Chapter 25; Section 146 (a). For the determination of rubber in vegetable matter see: Chapter 29; Section 165.

129. Purine Bases

Owing to the 'acidic' imino group, some purine compounds can be titrated as acids [246, 566]. (Chapter 17; Section 104, Table 32.) However, acetic anhydride, when mixed with nitromethane, carbon tetrachloride or benzene, is able to increase the basicity of the nitrogen hetero atom to such a degree that some of these compounds can be titrated as bases. (See: Chapter 23; Section 125 (c); [249], Section 126 (a); [676].)

Caffeine and theobromine can also be titrated in benzene in the presence of the indicator Sudan III [681]. For the determination of theobromine the solvent mixture acetic anhydride–carbon tetrachloride is also suitable [658], and in the case of caffeine the solvent mixture acetic anhydride–chlorofom, indicator Sudan III [439].

In view of the therapeutic importance of some purine compounds (caffeine, theobromine, and theophylline) many other methods have been suggested. The relevant data were briefly summarized by Salvesen [703]; [11, 15, 636, 644, 681, 443].

For titration of purine bases potentiometric, photometric and visual end-points can be employed. Caffeine is determined by Salvesen in a mixture with sodium salicylate or sodium benzoate in the presence of tropaeolin 00 and methyl violet as indicators.

Several bases in one mixture can be determined in a solvent of differentiating properties, but two compounds of different base strength can also be titrated in one mixture by using two kinds of indicators provided that the ranges of the indicators' colour change differ widely and, at the same time, coincide with the equivalence points of the two bases.

(a) *Determination of caffeine sodium and salicylate (or benzoate)* [703]. Weigh a sample of approx. 400 mg and dissolve in 10 ml of acetic anhydride. After cooling add 20 ml

of benzene and 4 drops of 0·5% of tropaeolin 00 in acetic acid and titrate the sodium salicylate with 0·1 N perchloric acid till the yellow colour turns to orange yellow. 16·01 mg requires 1 ml of standard solution. Now add to the solution 4 drops of 0·1% methyl violet in acetic acid, continue titration and take the colour change of the indicator mixture from green to golden yellow as the end-point. This coincides with the equivalence point of caffeine. 19·42 mg anhydrous caffeine requires 1 ml of 0·1 N solution.

(b) *Determination of theobromine, dihydroxypropyltheophylline or theobromine and sodium salicylate* [704]. Weigh 300–400 mg of theobromine or dihydroxypropyltheophylline and dissolve with heating in 20 ml of a mixture of acetic acid–acetic anhydride (1 : 3) or 15 ml of acetic anhydride. Add 20–20 ml of benzene and five drops of 0·1% methyl violet in acetic acid and titrate with 0·1 N perchloric acid to a colour change from green to yellow. One ml of standard solution is equivalent to 18·03 mg of theobromine or 25·42 mg of dihydroxypropyltheophylline.

For the determination of theobromine and sodium salicylate dissolve about 350 mg of sample with heating in 25 ml of acetic acid–acetic anhydride (1 : 5) and after adding 20 ml of benzene, titrate as described for caffeine and sodium salicylate but instead of methyl violet use 7 drops of 0·1% crystal violet.

(c) *Titration of caffeine with photometric end-point detection* [211]. Weigh 0·5–1 m.eq. of caffeine and dissolve in 20 ml of acetic anhydride. Add 2 drops of 0·5% Safranine or Nile blue A as indicator and transfer to the 15 mm cuvette of a colorimeter, e.g. Lange model IV. Titrate with 0·1 N perchloric acid in acetic acid. For both indicators use a colour filter for 550–580 mμ light transmission (0 G 2). Calculate by plotting $1/T$ against V (see Fig. 79 and also Chapter 14). 19·42 mg of anhydrous caffeine requires 1 ml of 0·1 N perchloric acid.

Other purine derivatives e.g. adenine, guanine, hypoxanthine and adenosine, can be dissolved with gentle heating, in acetic acid, with excess of perchloric acid in acetic acid. Excess of standard solution can be back-titrated with 0·1 N sodium acetate in acetic acid in the presence of crystal violet. Precision of measurements is only 1–2% [188]. (See also [15].)

(d) *Determination of theophylline* [45, 654]. Weigh a sample of 100 mg, dissolve it in 2–3 ml of 0·1 N perchloric acid in acetic acid, add 30 ml of benzene-acetic anhydride solvent mixture (2 : 1) which has been previously neutralized in the presence of 6 drops of Sudan III indicator (in 0·5% acetic acid), and continue to titrate with 0·1 N perchloric acid. Prior to the end-point add 3–4 drops more of the indicator to the solution. 1 ml 0·1 N standard solution is equal to 18·03 mg of theophylline.

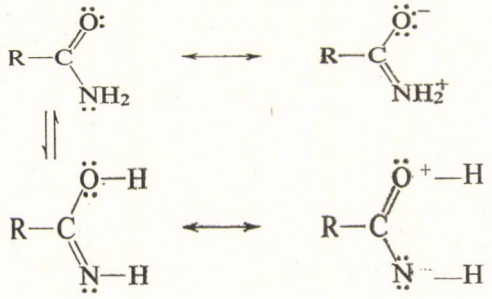
Addition of mercury(II) acetate enhances the base strength of theophylline; it is probable that the 'acidic' hydrogen of the imino group in the imidazole ring of the purine skeleton becomes substituted. In acetic anhydride and in the presence of mercury(II) acetate, theophylline can be titrated potentiometrically as a base.

(e) Simultaneous determination of theophylline and 7-hydroxyethyltheophylline: see: [512].

130. Acid Amides

Most acid amides are even weaker bases than water, but, at the same time, are also weak acids, being able to form metallic salts e.g. in liquid ammonia. Tautomerism

and resonance effects, and hydrogen bonding, contribute to the structure of acid amides (p. 90 in [380]):



Protonation of amides in acid solution occurs on oxygen, and not on nitrogen [403, 427, 438]:



Alkylation on the N-atom increases basicity of acid amides though to a smaller extent than in ammonia.

Concerning the effect of acylation and alkylation (methylation) on base strength see: [403, 556]. As regards the relative order of base strength of acid amides in photometric titrations with perchloric acid in the presence of Sudan III see: [385]. (See also: Chapter 14; Section 80 (c).)

Acid Amide	pK [403]	K_{ex} [385]
Formamide	−0·48	0.53
N-Methylformamide	−0·04	0·13
N,N-Dimethylformamide	−0·01	0·14
Acetamide	+0·11	0·10
N-Methylacetamide	+0·80	0·023

(a) *Determination of acid amides in acetic anhydride* [878]. On adding perchloric acid to acetic anhydride probably 'acetyl perchlorate', a Lewis-acid – $(CH_3CO)^+ClO_4^-$ – exists, forming a salt with an acid amide. Weigh 6–8 mM of sample and dissolve in 100 ml of acetic anhydride. Dilute a 10 ml portion with acetic anhydride to 100 ml and titrate potentiometrically with 0·1 N perchloric acid in acetic acid using a glass-calomel electrode system. The calomel electrode contains 0·1 M $LiClO_4$ dissolved in acetic anhydride as electrolyte. The glass electrode should be kept in acetic anhydride for 12 hours before use. The value of $\Delta e/\Delta v$ observed at the end-point (mV/ml) reflects to a certain degree the basicity of the acid amide (in brackets mg equivalent of 1 ml of 0·1 N solution and the *former* mV value): N,N-dimethylacetamide (8·712 mg; 300 mV), N,N-diethylacetamide (11·52 mg; 280 mV), thioacetamide (7·513 mg; 470 mV), N-formylpyrrolidine (9·913 mg; 300 mV), N-acetylpiperidine (12·72 mg; 470 mV).

In Wimer's study, apart from the above, the determination of 36 other compounds is described [878].

(b) *Determination of urea with photometric end-point detection* [390]. Weigh about 1·1–1·2 mM of urea in a 100 ml measuring flask; dissolve in 50 ml of acetic acid, add 10 ml of 0·01 % malachite green in acetic acid as indicator and make up to the mark with acetic acid. Titrate 20 ml of the stock solution with 0·1 N perchloric acid in acetic acid. Sample and titrant should contain malachite green in the same concentration. Titrate at 622 mμ and take readings at each 0·2 ml.

Calculate value of $I/I\mathrm{H}^+$ from the equation

$$\frac{I}{I\mathrm{H}^+} = \frac{A}{A_b - A}$$

where A_b = absorption of the basic form of the indicator
A = the single absorption values read during measurement.

The value $I/I\mathrm{H}^+$ is plotted as a function of the *reciprocal* of the volume in ml of perchloric acid and the intercept of the extrapolated straight line on the x axis indicates the equivalence point (see Chapter 14; Sections 79 and 80; [390]; Fig. 81).

Instead of malachite green, Nile blue can be employed as an indicator (at 632 mμ). When $I/I\mathrm{H}^+$ against 1/ml is plotted on an identical scale, with Nile blue A a steeper gradient is obtained: the K_{ex} value of malachite green-urea perchlorate is 2·5, while that of the Nile blue-urea perchlorate system is 0·47. (See Figs 81 and 84; Chapter 14.)

Titration can also be performed with Sudan III at wavelength 615 mμ. In this case, however, the photometric curve $I\mathrm{H}^+/I$ against ml is plotted because the less basic indicator changes colour after the equivalence point [671]; Fig. 85. (Photometric curve 'Type III'). Regarding photometric titration of small amounts of urea see Chapter 14, Modified curve 'Type II'

(c) *Determination of primary acid amides with dinitrobenzoyl chloride in dioxan* [596]. (Cf. Chapter 19; Section 11(c).)

Acid amides react with 3,5-dinitrobenzoyl chloride:

$$\mathrm{R.CONH_2} + 3,5\text{–}\mathrm{NO_2}\text{–}\mathrm{C_6H_3}\text{–}\mathrm{COCl} \rightarrow \mathrm{RCN} + 3,5\text{–}\mathrm{NO_2}\text{–}\mathrm{C_6H_3}\text{–}\mathrm{COOH} + \mathrm{HCl}$$

i.e., hydrogen chloride and dinitrobenzoic acid are formed; while with methanol hydrogen chloride and methyl dinitrobenzoate are formed.

Weigh 10 m.eq. of acid amide in a 250 ml measuring flask into which 15 ml of reagent and 5 ml of pyridine were pipetted previously. Place the flask on a steam bath at 60°C for 30–60 min, then chill the solution in crushed ice. Excess of acyl chloride is converted into methyl dinitrobenzoate, by carefully adding first 2 ml and after five minutes 25 ml of methanol. Titrate the solution obtained with 0·5 N sodium methoxide in the presence of phenolphthalein as indicator. A blank is run in the same way. The difference between the two measurements gives the acid amide content.

Preparation of the reagent: dissolve 461 g of 3,5-dinitrobenzoyl chloride in dioxan and dilute to 1 litre, shake with 3·4 g activated charcoal and, excluding atmosphere moisture, filter immediately into the container of the burette. (The solution is pale yellow.)

Acetamide (29·53 mg), propionamide (36·54 mg), salicylamide (68·56 mg), isobutyramide (43·56 mg), etc. can be determined with a precision of ±0·3% (in brackets mg equivalent of 1 ml of 0·5 N standard solution).

Formamide and derivatives can be hydrolyzed by boiling with potassium hydroxide in ethanol; the excess of alkali can be back-titrated with acetic acid in ethanol [408].

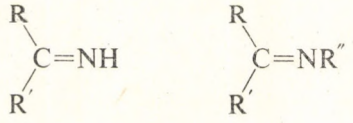
131. Sulphonamide Derivatives

Some sulphonamide derivatives can be titrated as acid analogues in a basic solvent (Chapter 17; Section 106) and also estimated in an acidic solvent as bases owing to an amino group or nitrogen hetero atom. In many cases, the formation of insoluble perchlorate may aid titration [264, 575]. Meulenhoff suggests the addition of benzene to the solvent with those sulphonamide derivatives where perchlorate does not separate during titration. To promote separation of mono- or di-perchlorates it seems advisable, after the addition of excess of perchloric acid, to dilute the solution with benzene and after a reasonable delay, to back-titrate the excess of standard solution with 0·1 N sodium acetate in acetic acid.

Suspend 0·8–0·9 m.eq. of *succinyl sulphathiazole* in 10 ml of acetic acid, add 10 ml of 0·1 N perchloric acid in acetic acid and dissolve the sample by heating while shaking vigorously (perchlorate may separate before solution of all the sample). After cooling dilute with 50 ml of benzene and back-titrate the excess of perchloric acid half an hour later, maintaining vigorous shaking, with a standard solution of sodium acetate in the presence of 1-naphtholbenzeine. 35·55 mg of succinyl sulphathiazole require 1 ml of 0·1 N perchloric acid.

With slight modifications sulphaguanidine, sulphapyridine and sulphathiazole can be titrated in essentially the same way [575]. In the case of sulphathiazole, chloroform is used instead of benzene to promote precipitation of sulphathiazole perchlorate. One ml of 0·1 N solution is equivalent to 11·62 mg of sulphaguanidine, 12·57 mg sulphapyridine and 25·53 mg sulphathiazole.

132. Ketimines. Benzamidine and Related Compounds. Compounds Containing Ethylene-imino Group



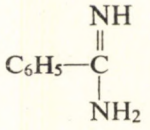
Ketimine Schiff base

(a) *Ketimines* can be titrated in acetic acid medium with 0·01 N perchloric acid in the presence of crystal violet.

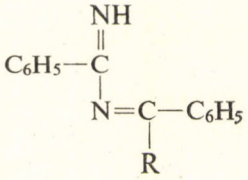
Weigh 0·05–0·10 m.eq. of ketimine derivative, dissolve in 10 ml of acetic acid and titrate with 0·01 N perchloric acid in the presence of crystal violet [642]. 1·811 mg of diphenylketimine requires 1 ml of standard solution.

(b) *Determination of benzamidine and related compounds* [50]. Benzamidine and some related compounds can be titrated potentiometrically as acids in pyridine

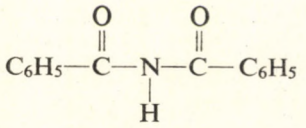
or dimethylformamide with standard TBAH in benzene-methanol, or as bases in a solvent mixture of ethylene glycol-isopropanol (1 : 1) with hydrochloric or perchloric acid.



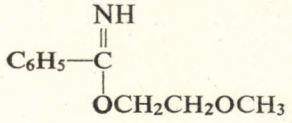
Benzamidine



N-Benzoylbenzamidine (R = OH); N-thiobenzoylbenzamidine (R = SH)



Dibenzamide



Methyl Cellosolve benzimidate

Compound	*Titrant*			*Comment*
	0·2 N *HCl*	0·1 N $HClO_4$	0·05 N *TBAH*	
Benzamidine	+	+	−	Titratable as base
Benzamidine benzoate	+	+	+	Amphoteric
N-Benzoylbenzamidine	+	+	+	Amphoteric
N-Thiobenzoylbenzamidine	−	−	+	Titratable as acid
Dibenzamide	−	−	+	Titratable as acid
Methyl Cellosolve benzimidate	+	+	−	Titratable as base

Inflections appearing in the curve of potentiometric titrations allow determination of mixtures, since these are formed in the order of strength of base analogues:

benzamidine > benzamidine benzoate > Methyl Cellosolve benzimidate > N-benzoylbenzamidine;

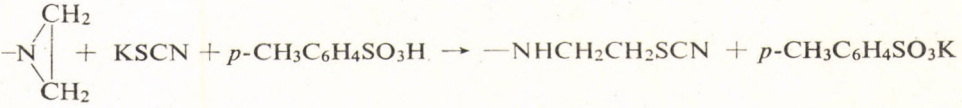
on the other hand, the order of acid analogues is:

dibenzamide > N-thiobenzoylbenzamidine > benzamidine benzoate > N-benzoyl benzamidine

Weigh an amount needed for the consumption of 2–5 ml of standard solution in a 30 ml titration beaker. For titrations in pyridine a nitrogen atmosphere is preferable. When the determination is performed in a 1 : 1 mixture of ethylene glycol-isopropanol the use of a closed titration system is unnecessary. In both cases use a glass–calomel electrode system, as alkaline titrant use the standard soluuion 0·05 N TBAH in benzene-methanol and as acidic titrant 0·2 N hydrogen chloride in G–H solvent, or 0·1 N $HClO_4$ in acetic acid. In the case of two or more inflections calculate with consecutive points of inflection.

When the titrant TBAH contains tetrabutylammonium carbonate as contaminant, in the case of benzoyl benzamidine (an exceedingly weak acid), high values are obtained if benzoic acid is the standardizing agent. Therefore it is advisable to standardize TBAH against pure benzoylbenzamidine.

(c) *Determination of compounds containing ethylene-imino group* [720]. Compounds containing ethylene-imino (aziridinyl) group react with thiocyanic acid with ring cleavage. According to Schlitt's method, thiocyanic acid is formed *in situ* from potassium thiocyanate and *p*-toluenesulphonic acid. The unchanged *p*-toluenesulphonic acid present after the reaction is back-titrated with potassium hydroxide in methanol, in the presence of a suitable indicator.



The above reaction goes quickly to completion.

Place a sample of 2·5 m.eq. in a 250 ml Erlenmeyer flask, and dissolve it in 50 ml of potassium thiocyanate reagent and precisely 10 ml of *p*-toluenesulphonic acid reagent by using a magnetic stirrer. The Erlenmeyer flask is fitted with a two-holed stopper; one of the holes serves for the introduction of nitrogen gas, while in the other the nozzle of a 50-ml burette is placed. Agitate the solution for a few minutes under nitrogen atmosphere, then add 6 drops of indicator and titrate the mixture with 0·1 N potassium hydroxide in methanol. For the determination of individual compounds, different indicators must be used, the colour changes of which must be checked previously by potentiometric detection.

A blank test must be performed in the same way in the absence of the sample.

It is advisable to use a freshly prepared solution of *p*-toluenesulphonic acid in methanol, because methyl *p*-toluenesulphonate is formed in the course of interaction between the methanol solvent and *p*-toluenesulphonic acid. The colour change of the indicator is less sharp if the indicator is not freshly prepared and, in that case, often two potentiometric inflections are observed.

Some *p*-toluenesulphonic acid preparations contain traces of iron(III) impurity. As a consequence, a red tint appears when the *p*-toluenesulphonic acid is added to the potassium thiocyanate solution. This colouring does not disturb the determination since the gradual fading of the colour of iron(III) thiocyanate indicates beforehand the approach of the end-point. In such a case, therefore, the chosen indicator should be added to the solution when the red tint begins to fade.

The required reagents are the following: potassium hydroxide of 0·1 N concentration in methanol, standardized against potassium hydrogen phthalate; potassium thiocyanate reagent prepared by dissolving 160 g of KSCN in 1,000 ml of methanol; *p*-toluenesulphonic acid reagent prepared by dissolving 73·2 g of *p*-toluenesulphonic acid monohydrate in 50 ml of distilled water and making up the solution with methanol to 1 l. Water is added in order to retard the formation of methyl sulphonate. Schlitt used for his investigations on aziridinyl compounds three different indicators, namely, 0·1 % bromothymol blue in methanol, the potassium salt of phenol red, also in 0·1 % concentration in methanol, and finally an indicator mixture prepared by mixing equal volumes of the two indicators mentioned above.

With the method described above the following compounds may be determined (the indicator used is shown in brackets): e.g. tris-1-(2-methyl)-aziridinylphosphine oxide [bromothymol blue], phenyl-bis-1-(2-methyl)-aziridinylphosphine oxide [indicator mixture], trimesoyl-1-(2-ethyl)aziridine [phenol red], tris(2-methyl)-aziridinyltriazine [bromothymol blue].

133. Hydrazine, Substituted Hydrazines, Hydrazides and Hydrazones

$H_2N-NH_2 \xrightarrow{+H^+} H_2N-NH_3^+$

Hydrazine — Hydrazinium ion

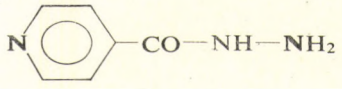
p*K* 5·52

$(CH_3)_2N-NH_2$

as-Substituted hydrazine [541]

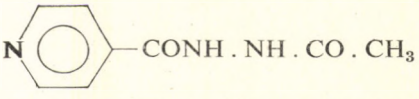
$p-H_2N-C_6H_4-CONH-NH_2$

p-Aminobenzoic acid hydrazide, potentiometrically titratable as a bifunctional base [732]



Isonicotinic acid hydrazide, potentiometrically titratable as bifunctional base [732]

Acetylated:



Titratable as heterocyclic monofunctional base [732]

$C_6H_5-NH-NH_2$

Phenylhydrazine

p*K* 8·80

2,4-Dinitrophenylhydrazine and 2,4-dinitrophenylhydrazones are scarcely basic and are titratable as acids: (Chapter 20; Section 114)

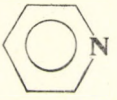
$R-CH=N-NH_2$; $R'RC=N-NH_2$

Hydrazones [541]

$RR'C=N-NH-COR''$

Non-basic hydrazone

$RR'C=N-NH-CO-R''$



Isonicotinyl hydrazone; due to substituent R″ bearing hetero N-atom titratable as base [732] (See: Chapter 23; Section 121 (b))

$R-CH=N-N=CH-R$

Aldazine, not basic [541]

(**N** = basic nitrogen atom; N = non-basic nitrogen atom or nitrogen of low basicity)

Hydrazine, substituted hydrazines, hydrazides and some of the hydrazones are monoacidic bases if the substituent R does not contain a second protonatable nitrogen-atom. Sensi and Gallo have discussed perchloric acid titration of these compounds in detail [732].

If the acetic acid used for solution contains traces of acetic anhydride, hydrazides become partly or totally acetylated and the results obtained are erroneous. Because of this, in the case of isonicotinic acid hydrazide and similar compounds, i.e. where besides acetylatable primary amino group a tertiary N-atom is also present, it is advisable to use acetic acid containing 10–20% of acetic anhydride for the solution of the sample and to titrate the monoacetylated product after 10–30 min with perchloric acid [732].

Hydrazides of the following acids can be titrated in totally anhydride-free acetic acid with glass–calomel electrodes (in brackets, mg equivalent of 1 ml of 0·1 N per-

chloric acid): benzoic acid (13·61), *p*-hydroxybenzoic acid (14·81), *p*-aminobenzoic acid (7·557), *p*-nitrobenzoic acid (18·11), phenylacetic acid (15·02), cyanoacetic acid (9·909).

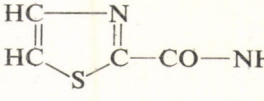
Should the molecule also contain a tertiary nitrogen atom it is advisable to acetylate the primary amino group.

(a) *Determination of isonicotinic acid hydrazide* (INH) [442] [732]. Weigh 100–120 mg of sample and dissolve in 20–30 ml of acetic acid containing 10% of acetic anhydride. Titrate potentiometrically with 0·1 N perchloric acid in acetic acid, using glass–calomel electrodes. 13·71 mg of acetylated product requires 1 ml of 0·1 N $HClO_4$.

In a mixture of acetic acid–chloroform (4 : 1) INH can be titrated as a base, but as acid in diethylamine with sodium methoxide [12].

(b) *Determination of isolysergic acid hydrazide* (ILH) [306]. Weigh 60–200 mg of sample and dissolve, protected from light, in 20 ml of acetic acid containing 15% acetic anhydride. Titrate after 10 min with 0·05 N perchloric acid in the presence of crystal violet. 14·12 mg of ILH requires 1 ml of standard solution.

Hydrazides of nicotinic and picolinic acid can be titrated similarly but the nitrogen hetero-atom of the hydrazide of 2-thiazolecarboxylic acid is of such weak basicity that the primary amino group must be titrated:



(Molecular weight: 143·16)

Hydrazones whose primary amino group is substituted by a group $-CO-R$ can only be titrated if the substituent R contains a basic N-atom. (See: Chapter 23; Section 121 (b).)

(c) *Determination of a mixture of hydrazine and 1,1-dimethylhydrazine** [541]. In acetic acid with salicylaldehyde, hydrazine forms the neutral salicylaldazine (133.1), while with 1,1-dimethylhydrazine a basic hydrazone is formed (133.2):

$$N_2H_4 + 2\,C_6H_4(CHO)OH \rightarrow HO-C_6H_4-CH=N-N=CH-C_6H_4-OH + 2\,H_2O \quad (133.1)$$

$$(CH_3)_2N-NH_2 + C_6H_4(CHO)OH \rightarrow HO-C_6H_4-CH=N-N(CH_3)_2 + H_2O \quad (133.2)$$

The base strength of salicylaldehyde 1,1-dimethylhydrazone is the same as that of 1,1-dimethylhydrazine and it can be titrated with perchloric acid in acetic acid.

Determine the weight of a 50 ml measuring flask containing 40 ml of acetic acid and add, *while cooling*, approx. 2 g of hydrazine mixture. Following cooling of the solution to room temperature reweigh the flask and make up to the mark with acetic acid. 1·0 ml of the stock solution is diluted with 20 ml of acetic acid, titrated with perchloric acid in the presence of methyl violet and the total base content determined *(A)*. Another 1·0 ml portion of the stock solution is mixed with 20 ml of acetic acid and 2 ml of salicylaldehyde and kept for 10 min at 50°C. The yellow salicylaldazine

* Hydrazine, monomethylhydrazine and 1,1-dimethylhydrazine are important as rocket fuels.

is precipitated. Add 6 drops of methyl violet and titrate with 0·01 N perchloric acid in dioxan till the brown-red (amber) solution turns to dark green *(B)*.

Calculation:

$$\text{Dimethylhydrazine } \% = \frac{(B - b_2) \times \text{N} \times 6{\cdot}01}{\text{wt of sample}};$$

$$\text{Hydrazine } \% = \frac{[(A - b_1) - (B - b_2)] \times \text{N} \times 3{\cdot}205}{\text{wt of sample}}$$

where A and B = volume of 0·1 N perchloric acid in dioxan consumed (ml)
b_1 = volume required for the solvent and the indicator (ml)
b_2 = volume of the blank test for salicylaldehyde (ml)
N = normality of the standard solution

6·01 = m.eq. × 100 of dimethylhydrazine
3·205 = m.eq. × 100 of hydrazine.

The use of potentiometric and photometric Type II end-point detection in the determination of hydrazine and 1,1-dimethylhydrazine mixtures by the salicylaldehyde method of Malone [541] was investigated by Burns and Lawler [109]. Using the two-step equilibria with crystal violet as indicator, the total alkali titration at 590 mμ, yields a sharper end-point directly than the titration curve monitored at 630 mμ. Since the use of crystal violet as indicator gives end-points which vary significantly between operators and depend on the nature of the light source, the method of Malone includes an 8 p.p.t. inherent error, which was reduced by the method proposed by Burns and Lawler to 6 p.p.t.

The photometric end-point techniques are somewhat cumbersome for routine use, therefore potentiometric detection is recommended [109], using a Beckman sleeve-type calomel electrode which contains glacial acetic acid saturated with lithium chloride.

(d) Acid–base method for the determination of mixtures of monomethylhydrazine and 1,1-dimethylhydrazine see: [542].

Chapter 24

Determination of Salts of Nitrogenous Bases

In the pharmaceutical industry many compounds containing basic nitrogen are prepared in the form of salts. Most of the salts formed with organic acids can be directly titrated with perchloric acid in acetic acid or in an acidic solvent mixture. In the case of salts formed with halogen acids, mercury(II) acetate is added to the solution; thus, non-dissociating mercury(II) halide and base acetate are formed [207, 462, 644].

$$2\ \text{B.HCl} + \text{Hg}(\text{CH}_3\text{COO})_2 = 2\ \text{B.CH}_3\text{COOH} + \text{HgCl}_2$$

95% of the sulphate ion of sulphates of bases combines with benzidine and the liberated base is titratable with perchloric acid [265]. Sulphates have poor solubility in acetic acid, but in a mixture of phenol, chloroform and acetonitrile (1 : 4 : 10) many alkaloid sulphates, phosphates, and some ethanesulphonates and *p*-toluenesulphonates (in dioxan) can be directly titrated with perchloric acid in dioxan [123, 321]. In the former solvent mixture, halides of bases cannot be titrated since owing to the mercury(II) acetate side reactions occur. In acetone medium or a mixture of acetonitrile–acetic anhydride–acetic acid (12 : 0·8 : 0·2) mercury(II) acetate can be used for the determination of hydrochlorides of bases [314, 587].

134. Salts Formed with Organic Acids by Alkaloids and Other Nitrogenous Bases

Organic acids whose dissociation constant (in water) is 10^{-3} or less are generally neutral when dissolved in acetic acid (Chapter 22). Thus, the basis of determination is titration of the base or base acetate liberated by acetic acid. However, the influence of the acid residue on the extent of inflection in potentiometric titration is not unimportant. This is best demonstrated by the differentiating titration of various diphenhydramine salts with a retarded glass electrode (Fig. 120).

Weigh a sample equivalent to 0·3–0·5 m.eq. of base, dissolve in 20 ml of acetic- or propionic acid or, in the case of non-acetylatable bases, in a mixture of acetic

acid–acetic anhydride (10 : 1), or in acetic acid–chlorobenzene (1 : 1), neutralized in the presence of crystal violet, and titrate with 0·05–0·1 N perchloric acid to a colour change from violet to blue. Ergot alkaloids should be dissolved protected from light. Ergotamine tartrate, bitartrate, biphthalate and ergometrine maleate can be titrated with ±0·5–1% accuracy [309, 324, 697]. One ml of 0·1 N perchloric acid is equivalent to 16·27 mg of ergometrine and 29·08 of ergotamine.

For the titration of physostigmine salicylate, morphine acetate and dihydrocodeinone tartrate [123] in the mixture phenol–chloroform–acetonitrile (1 : 4 : 10) an amount of the sample is weighed to give a titration of 2–3 ml of 0·05 N perchloric acid in

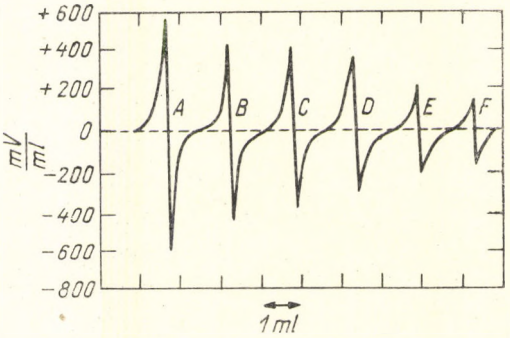


Fig. 120. Second derivative differential titration curves of acid salts of diphenhydramine (0·02 M) at 23 ± 1°C according to Kashima [444]. — *(A)* Succinate, *(B)* Fumarate, *(C)* Maleate, *(D)* Oxalate, *(E)* Nitrate, *(F)* Phosphate. — Solvent: acetic acid. Standard solution: 0·05 N perchloric acid in dioxan. Electrode system: glass–glass retarded electrodes (cf. Fig 51)

dioxan. Add 5 g crystalline phenol, 10–20 ml of chloroform and, after solution, 50 ml of acetonitrile and 1–2 drops of 0·25% methyl red in phenol–chloroform (1 : 50). Titration may also be followed potentiometrically (Fig. 44c).

1-(4′-Hydroxyphenyl)-2-methylaminoethanol tartrate (Sympatol ®) can be titrated in acetic acid with 0·05 N perchloric acid in dioxan in the presence of crystal violet [651].

Determination of 2-ethoxy-6,9-diaminoacridine (lactate) (ethacridine, Rivanol ®) [834]: dissolve 400 to 600 mg of ethacridine in 15 ml of methanol, add 2–3 drops of 0·5% thymol blue in methanol and titrate without delay with 0·1 N perchloric acid in dioxan to a colour change from yellow to orange. One ml of 0·1 N acid is equivalent to 25·33 mg of base, 34·34 mg of lactate and 36·14 mg of lactate-monohydrate. In the course of titration of the base or displacement titration of base lactate one equivalent of perchloric acid is consumed.

135. Base Picrates

A well-known method for the identification of bases is determination of the melting point of their picrates. A convenient method for determination of the equivalent weight of the base is determination of the base content of the picrate in a suitable solvent or solvent mixture by direct titration with perchloric acid [28, 58, 134, 311, 314, 366, 400, 425, 426] and estimation of the picric acid component with sodium methoxide in pyridine or dimethylformamide [58, 245]. (Cf. Chapter 20.)

A suitable solvent for determination of the base content of the picrate is acetic acid or the mixtures acetic anhydride–chlorobenzene, acetic anhydride–nitromethane or acetic acid–chloroform. In semimicro determinations of base picrates the ternary solvent mixtures acetic acid–acetic anhydride–chlorobenzene or propionic

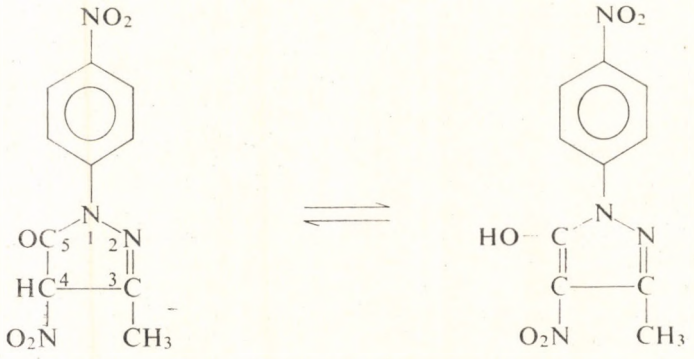
acid–propionic anhydride–chlorobenzene (9 : 2 : 9) have proved to be suitable. As titrant 0·05–0·1 N perchloric acid in acetic acid or 0·01 N perchloric acid in acetic acid–carbon tetrachloride (1 : 1), with crystal violet or methyl violet as indicator can be recommended.

$$C_5H_5N - - HOC_6H_2(NO_2)_3 \rightleftharpoons [C_5N_5NH]^+[(NO_2)_3C_6H_2O]^-$$

Pyridinium picrate

Picrate anion and the base are proton acceptors in acetic acid; pyridinium cation and picric acid behave as acids in dimethylformamide.

Like picric acid, picrolonic acid also forms insoluble salts with bases, and picrolonate can be titrated as a base in acetic acid, acetic anhydride or dioxan in the presence of methyl violet with 0·01 N perchloric acid in acetic acid. The anion of the picrolonate can be determined in pyridine with sodium methoxide in the presence of thymol blue [210].



Picrolonic acid, (4-nitro-3-methyl-1-*p*-nitrophenylpyrazolone-5) (mol. wt. 264·2)

(a) *Preparation of base picrate* [311, 314]. (1) Weigh 50 mg of the monofunctional hydrochloride of the base, dissolve in 10 ml of distilled water and heat to 60–70°C. Add 10 ml of a solution of 1·5% picric acid in methanol and heat until the picrate formed is dissolved, then allow to cool and keep for two days at 0°C. Filter the separated crystals on a G/3 porosity glass filter, wash subsequently five times with 2 ml of methanol–water (1 : 1) at 0°C, and finally dry *in vacuo* for 12 hours over KOH (5 mm/Hg).

(2) Alternatively, weigh 100–200 mg of the monofunctional hydrochloride of the base in a 100 ml beaker and dissolve in 2–4 ml of water with heating on a steam bath. Add 20–40 ml of an aqueous solution of boiling 1% picric acid and stir the solution, while heating for a few minutes, on a steam bath. After cooling, filter the crystals on G/3 porosity glass filter, wash with 5 × 5 ml distilled water at 0°C, and finally dry for 12 hours *in vacuo* over phosphorus pentoxide.

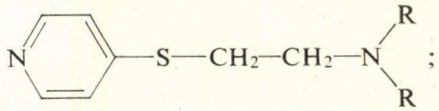
(b) *Titration of base picrate in acetic acid* [134]. Weigh 1–4 m.eq. of amine picrate and dissolve, if necessary with gentle heating, in 50 ml of acetic acid. Cool to room temperature and titrate with 0·1 N perchloric acid in acetic acid in the presence of six drops of 0·2% methyl violet in chlorobenzene. The colour of the indicator gradually changes from green to violet and finally with a sudden break to clear blue. Among others dimethylaniline, ethylenediamine, diethanolamine, aniline, 2-aminopyridine, 2,4,5-collidine and piperidine picrates can be titrated in this way.

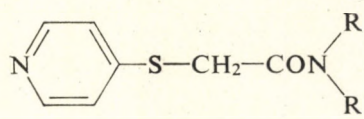
(c) *Titration of base picrate in a mixture of chlorobenzene–acetic acid–acetic anhydride or chlorobenzene–propionic acid–propionic anhydride* [311, 314]. Base picrates containing tertiary nitrogen can be titrated with accuracy either potentiometrically or in the presence of methyl violet with 0·01 N perchloric acid in one of the above-mentioned solvent mixtures in the ratio 9 : 9 : 2. The mV inflection observed at the end-point in a mixture containing propionic acid is twice that of a mixture containing acetic acid.

Weigh 20–40 mg of base picrate, dissolve in 10–20 ml of solvent mixture and titrate with 0·01 N perchloric acid either with a glass–calomel electrode pair or in the presence of methyl violet until the indicator turns azure. The electrolyte solution of the calomel electrode is acetic acid saturated with lithium chloride. The glass electrode, before use, should be kept for an hour in a mixture of acetic anhydride–acetic acid (1 : 9) containing a few drops of standard perchloric acid. In this way e.g. piperidinomethyltolylpropanone or piperidinomethylcyclohexanone picrates can be determined.

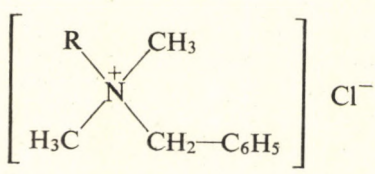
(d) *Identification of antihistamines by titration of the base picrate with perchloric acid* [28]. Dissolve about 40 mg of antihistamine picrate in 15 ml of acetic acid and add 15 ml of chloroform. Titrate either potentiometrically with a glass–calomel electrode system or visually with crystal violet with 0·02 N perchloric acid in acetic acid. In this manner identification (determination of equivalent weight) of twenty different antihistaminics (e.g. Diphenhydramine monopicrate, Piribenzamine dipicrate, Promethazine monopicrate, Cyclizin dipicrate, Chlorocyclizin dipicrate, etc.) is possible.

(e) *Titration of picrates of mercaptopyridine derivatives* [58]. Picrates of the dialkylamino derivatives of 4-mercaptopyridine can be titrated as bifunctional bases in acetic anhydride or nitromethane–acetic anhydride. The picrate of a 4-mercaptopyridine dialkylacetamide can be titrated as a monofunctional base. Picrates can also be titrated with sodium methoxide in dimethylformamide in the presence of thymol blue. In this case the picric acid content of the picrate is determined [58].





(f) *Determination of Zephirol*® [400]. In international nomenclature, compounds of the type below whose alkyl group R is of C_8H_{18} chain-length are designated as 'benzalconium' chlorides:



Weigh 80–100 mg of compound and dissolve in a small flask in 5 ml of water. Add 20 ml of saturated aqueous picric acid solution at room temperature and 1 ml of 10% hydrochloric acid. Heat for 1 hour on a boiling steam bath, then allow to stand for 1 hour at room temperature. Filter on paper. Wash flask and precipitate with 3 × 5 ml picric acid solution, but without carrying over the precipitate left in

the flask. Place funnel containing the filter paper on the flask, dissolve and transfer the precipitate with a small amount of acetone into the flask. Distil acetone (for precipitation as well as concentration the evaporation flask shown in Fig. 103 can be used), dissolve the residue in 20 ml of acetic acid and titrate with 0·1 N perchloric acid in acetic acid in the presence of 2–3 drops of 0·1 % crystal violet to a blue colour change. The benzalconium chloride content of Zephirol ® solution can be determined in a similar way. Weigh 1–1·5 g of the solution and after adding 20 ml of water manipulate with 20 ml of picric acid solution as above. Calculate assuming an average molecular weight of 390 [400].

See also: Section 137.

136. Halides of Nitrogenous Bases

The base component of hydrochloride salts of bases can be titrated in acetic acid' acetic acid–acetic anhydride, acetic acid–chlorobenzene, acetic acid–acetonitrile, acetic acid–dioxan media, etc. by first converting the halide acid with mercury(II)-acetate into mercury(II) chloride. (See: introduction to Chapter 24.) For this purpose 3 % mercury(II) acetate (of approx. 0·2 N) in acetic acid is used, by adding 10 ml of the latter to 10 ml of a solution of 0·1 N monofunctional hydrochlorides of bases; thus about 50 % of the mercury(II) acetate is converted to mercury(II) chloride. *Mercury(II) acetate has a solubilizing effect when the hydrochloride of the base does not dissolve in acetic acid* (e.g. in the case of some aromatic or aralkyl-amino alcohols). It is advisable to neutralize the solvent as well as the mercury(II) acetate reagent with perchloric acid in the presence of a suitable indicator, even if titration is performed potentiometrically (Chapter 9; Section 54).

For solutions of 0·05 N or lower concentration, a smaller amount of mercury acetate is used: 10–20 % excess is sufficient.

The hydrochlorides of many compounds of high pharmaceutical importance can be titrated in the presence of mercury(II) acetate either potentiometrically or by photometric end-point detection or visually in all three cases with 0·01–0·1 N perchloric acid. A full account of these would exceed the scope of this book; therefore only a few characteristic methods will be discussed below.

(a) *Determination of papaverine hydrochloride in chloroform medium* [836]. Weigh out precisely about 500 mg of papaverine hydrochloride, dissolve it in 50 ml of chloroform, add 5 ml of 6 % mercury(II) acetate solution in acetic acid, and two drops of 0·1 % metanil yellow indicator solution in methanol. Titrate with 0·1 N perchloric acid in dioxan until the yellow colour turns to violet. 37·58 mg of papaverine-HCl requires 1 ml of 0·1 N perchloric acid.

(b) *Photometric titration of quinine hydrochloride* [211]. Quinine hydrochloride can be titrated as a monofunctional base in acetic acid. Weigh 160–170 mg of sample, dissolve in 20 ml of acetic acid and add two drops of 0·5 % methylene blue in acetic acid as indicator. Titrate in a 15 mm cuvette of a colorimeter e.g. B. Lange model IV with 0·1 N perchloric acid (colour filter: OG 2; transmission range: 550–580 mμ). To calculate the result plot the photometric curve $1/T$ against V/f (see: Chapter 14, Fig. 90). Quinine hydrochloride can be titrated as a bifunctional base if the sample is dissolved in a mixture of 10 ml of nitromethane and 10 ml of 3 % mercury(II) acetate in acetic acid. One ml of 0·1 N perchloric acid is equivalent to 36·09 mg or 18·04 mg of anhydrous quinine-HCl.

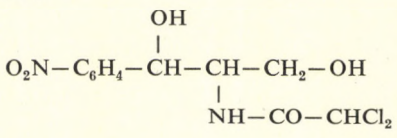
(c) *Determination of antibiotics.* There is no specific general method for determination of antibiotics either in aqueous or non-aqueous media either by gravimetry or titrimetry, since these compounds are of a variety of structural types.

Chlorotetracycline, *Tetracycline* and *Oxytetracycline* (base or hydrochloride) can be titrated potentiometrically with 0·05 N perchloric acid in dioxan. A suitable solvent is nitromethane containing formic acid. For end-point detection a glass–Ag/AgCl electrode system or the indicator mixture methylene blue-quinaldine red are equally suitable [890].

Weigh about 50 mg of the antibiotic in a 150 ml beaker and, maintaining magnetic stirring, dissolve in a mixture of formic acid–nitromethane (1 : 50). After solution add 5 ml of benzene and 1 ml of 6% mercury(II) acetate solution. Titrate with 0·05 N perchloric acid in dioxan in the presence of 0·1 ml indicator mixture to the appearance of the first green tint. One ml of titrant is equivalent to 25·77 mg Chlorotetracycline-, 24·85 mg Oxytetracycline- or 24·05 mg Tetracycline-hydrochloride.

For determination of antibiotics in ointments, suppositories and injections, see: [207, 742, 890]. Concerning Streptomycin and Dihydrostreptomycin sulphate see: [635]. For determination of Oxytetracycline base and hydrochloride in series titrations see: [524]. For determination of the equivalent weight of Nystatin, a fungicidal antibiotic, in a non-aqueous medium, see: [563].

Determination of Chloromycetin ® (Chloramphenicol, D-(−)threo-1-(*p*-nitrophenyl)-2-dichloroacetamidopropanediol-(1,3):



By hydrolyzing the amide bond with 25% hydrochloric acid, dichloroacetic acid and *d*-threo-1-(*p*-nitrophenyl)-2-aminopropandediol-1,3 are formed and the latter can be titrated with perchloric acid [705].

(d) *Determination of antihistamines* (see: Table 36). Antihistamines include compounds of highly varying structure; some contain one or two nitrogen hetero-atoms and in the aliphatic side-chain a tertiary N-atom. Often only the latter is titrated (cf. Chapter 23; Section 122 and Table 35).

Titration in acetone. Weigh about 50 mg of Promazin-HCl, dissolve in 40 ml of acetone, add 1 ml of a solution of 3% mercury(II) acetate in acetic acid and titrate with 0·05 N perchloric acid in dioxan in the presence of methyl red. 16·04 mg of Promazin-HCl requires 1 ml of standard solution [587].

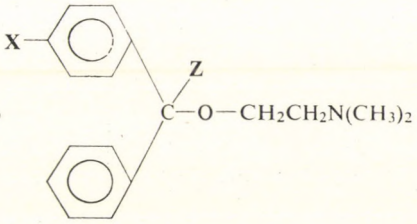
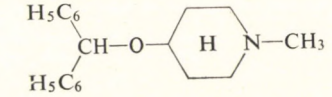
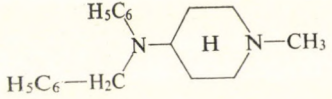
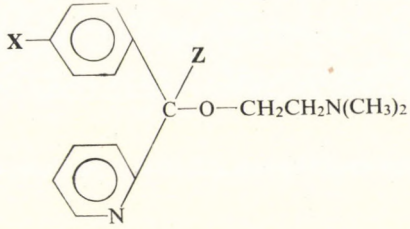
Weigh 280–300 mg of Chlorpromazin- or Promethazine-HCl and dissolve in a mixture of 5 ml 5% mercury(II) acetate and 100 ml of acetone. Add 1 ml of 0·25% methyl orange in acetone and titrate with 0·1 N perchloric acid. One ml of standard solution is equivalent to 35·53 mg Chlorpromazin-HCl or 32·09 mg of Promethazine-HCl [453].

In comparison with acetic acid, acetone has the advantage that when tablets are examined together with vehicles any magnesium stearate present does not consume perchloric acid.

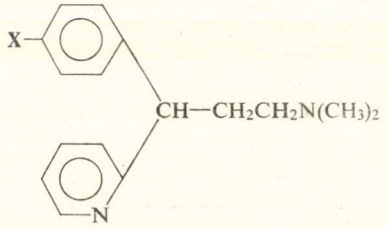
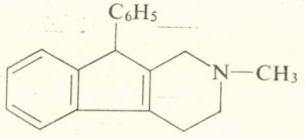
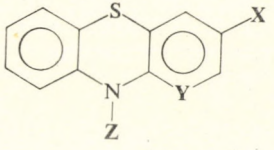
Titration in a mixture of benzene-acetic acid-acetic anhydride [683]. A systematic investigation of 25 antihistamines was performed by Rink and Riemhofer using potentiometric and visual indication. Suitable indicators are brilliant green, crystal violet and Fettblau B.

Table 36

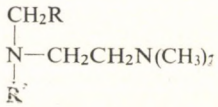
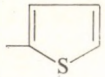
CONCISE TABLE OF ANTIHISTAMINES

	1. X and $Z = H$ Diphenhydramine, β-dimethylaminoethyl benzhydryl ether; 2. $X = Br$, $Z = H$ Bromodiphenhydramine, β-dimethylaminoethyl p-bromobenzhydryl ether; 3. $X = Cl$, $Z = CH_3$ Systral ®, β-dimethylaminoethyl -p-chloro-1-methylbenzhydryl ether; 4. Dimenhydrinate, β-dimethylaminoethyl benzhydryl ether 8-chlorotheophyllinate;
 	5. Piprinhydrinate, N-methylpiperidyl-(4)-benzhydryl ether 8-chlorotheophyllinate; 6. Soventol ®, N-phenyl-N-benzyl-4-amino-1-methyl-piperidine;
	7. $X = H$, $Z = CH_3$ Doxylamine, 2-[1-(2′-dimethylaminoethoxy)-1-methylbenzyl]-pyridine; 8. $X = Cl$, $Z = H$ Carbinoxamine, 2-[p-chloro-1-(dimethylamino-ethoxy)-benzyl]pyridine; 9. Pragman ®, 1-phenyl-1-p-tolyl-3-dimethylpropyl-amine;

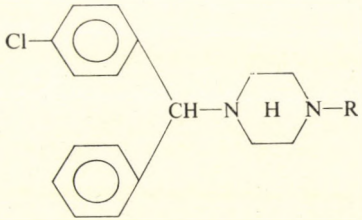
Continuation of Table 36

	10. X = Cl — Chlorphenamine, *d*-3-(*p*-chlorophenyl)-3-(2'-pyridyl)-N,N-dimethylpropylamine; 11. X = H — Pheniramine, 3-phenyl-3-[2'-(pyridyl)]-N,N-dimethylpropylamine; 12. X = Br — Brompheniramine, 3-(*p*-bromophenyl)-3-(2'-pyridyl)-N,N-dimethylpropylamine;
	13. Phenindamine, 2-methyl-9-phenyl-1,2,3,4-tetrahydropyridindene;
	14. X = H, Y = C, Z = 3-Dimethylaminopropyl — Promazin, N-(3-dimethylaminopropyl)-phenothiazine; 15. Promethazine, (see Table 35) 16. Chlorpromazine, (see Table 35) 17. X = H, Y = C, Z = $-CH_2-CH_2N$ (pyrrolidino) — Parathiazine, N-(*β*-pyrrolidinoethyl)-phenothiazine 18. X = H, Y = N, Z = 2-Dimethylaminopropyl — Isothipendyl, N-dimethylamino-isopropylthiophenylpyridylamine;

Continuation of Table 36

	19. R = Phenyl R' = 2-Pyridyl — Tripelennamine, N,N-dimethyl-N′-(2′-pyridyl)-N′-benzylethylenediamine
	20. R = *p*-Methoxyphenyl R′= 2-Pyridyl — Mepyramine,N,N-dimethyl-N′-(2′pyridyl)-N′-(*p*-methoxybenzyl)-ethylenediamine
	21. R =  R′ = 2-Pyridyl — Methapyriline, N,N-dimethyl-N′-[2′-pyridyl-]-N′-[2′-thiophenyl-(2)]-ethylenediamine
	22. R = *p*-Methoxyphenyl R'= 2-Pyrimidyl — Thonzylamine,N′-[2-pyrimidyl]-N′-[*p*-methoxybenzyl]-N,N-dimethylenediamine

Continuation of Table 36

	23. R = *p*-Chlorophenyl, R′= Pyridyl — Chloropyramine,N,N-dimethyl-N′-(2′-pyridyl)-N′-(*p*-chlorophenzyl)-ethylenediamine
	24. R = *p*-Bromophenyl, R′= Pyridyl — Hibernon®, N,N-dimethyl-N′-(2′-pyridyl)-N′-(*p*-bromobenzyl)-ethylenediamine
	25. R = Methyl — Chlorcyclizine, *dl*-1-(4′-chlorobenzhydryl)-4-methyl-piperazine
	26. R = CH_2–C_6H_4–$C(CH_3)_2$ — Buclizin, 1-(4′-chlorobenzhydryl)-4-(*p*-t-butyl-benzyl)-piperazine

Weigh sufficient of the compound to give a titration of about 10 ml of 0·1 N perchloric acid. Dissolve, if necessary with gentle heating, in 10 ml of mercury(II) acetate in acetic acid, cool to room temperature and add 25 ml of benzene and 5 ml of acetic anhydride to the solution. Titrate with perchloric acid in the presence of brilliant green. One ml of perchloric acid is equivalent to 14·59 mg of Tripelenamide-HCl, 15·84 mg of Soventol ® and 16·31 mg of Chloropyramine-HCl.

Titration in benzene-acetic acid [683] is performed as above but without acetic anhydride. One ml of 0·1 N perchloric acid is equivalent to 25·30 mg of Buclizin-HCl, 29·18 mg of Diphenhydramin-HCl, 34·03 mg of Systral® and 27·58 mg of Pragman®.

Titration in solvent mixture acetic acid–chloroform (a) or acetic acid–acetonitrile (b) [133]. Clair and Chatten investigated 18 different antihistamines. Weigh from the finely pulverized tablet an amount corresponding to 0·15–0·25 m.eq. of the compound. Add 15 ml of chloroform, stir for 15 min with a magnetic stirrer, filter through a glass filter, wash filter and precipitate with 2×5 ml of $CHCl_3$, and mix the filtrate with 25 ml of acetic acid *(a)* or acetonitrile *(b)*. Titrate with 0·05 N perchloric acid in dioxan in the presence of two drops of 0·5% crystal violet *(a)*, or two drops of 0·1% methyl red in methanol *(b)*.

In the case of hydrochloric salts of bases add 1 ml of 6% mercury(II) acetate to 50 ml of the mixture acetic acid–chloroform or to 50 ml of acetic acid–acetonitrile.

When tablets are tested, vehicles (excipients) must be taken into account. A survey of the disturbing effect of the latter is given in Table 30.

The following compounds can be titrated (Table 36); Nos 1, 2, 4 and 5 contain ether functions and one highly basic tertiary N-atom in the molecule (one equivalent of perchloric acid is consumed); in antihistamines Nos 7 and 8 (succinate and maleate) the benzene ring is substituted by a pyridyl group, and the ring nitrogen is less basic than alkylamine-N. In acetic acid–acetonitrile these two N-atoms can be titrated potentiometrically but for visual indication a solvent mixture acetic acid–chloroform is more suitable; in this case two equivalents of perchloric acid are consumed.

Nos 10, 11 and 12 (maleates) can be similarly titrated in a solvent mixture of acetic acid–chloroform. No. 13 (tartrate) is a four-ring system in which the N-atom of 2-methyltetrahydropyridindene in acetic acid–acetonitrile consumes one equivalent of perchloric acid. This compound dissolves poorly in chloroform but can be dissolved by adding phenol [123].

Nos 15, 17 and 18 contain a tertiary aliphatic N-atom besides a phenothiazine or thiophenylpyridylamine ring. In the case of Nos 15 and 17, in acetic acid–chloroform one equivalent of perchloric acid is consumed and one is consumed also in the case of No. 18 but acetic acid–acetonitrile must be employed as solvent (the nitrogen of the phenothiazine ring cannot be protonated).

Nos 19 (HCl), 20 (maleate), 21 (HCl) and 22 (HCl) can be regarded as substituted ethylenediamine derivatives and bind, in a mixture of acetic acid–chloroform, two equivalents of perchloric acid. Thonzylamine (No. 22) contains a pyrimidine ring, but the two nitrogen hetero atoms cannot be titrated (cf. Chapter 4; Section 27 (a)): in the mixture acetic acid–acetonitrile only one equivalent perchloric acid is consumed, but the colour change is sharp.

Compound No. 25 contains a piperazine ring: in acetic acid–acetonitrile one equivalent, and in acetic acid-chloroform two equivalents of perchloric acid are consumed (see also: [132] and Chapter 23; Section 123).

(Regarding diphenhydramine see also: [407] and [576], Fig. 120.)

(e) *Determination of anaesthetics. Determination after acetylation* [707]. Procaine (Novocaine) (*p*-aminobenzoate of 2-diethylaminoethanol) and Larocaine (*p*-aminobenzoate of 2,2-dimethyl-3-diethylaminopropanol) contain a primary amino group, while Tetracaine (*p*-butylaminobenzoate of *β*-dimethylaminoethanol) contains a secondary amino group directly on the aromatic ring. The compounds are employed therapeutically as the hydrochlorides. The primary or secondary and tertiary N-atom in these compounds can be titrated potentiometrically: two points of inflection can be observed. In the case of visual indication (with, e.g., crystal violet) colour change is not sharp; therefore, it is advisable to acetylate the primary or secondary amino group and then to titrate only the tertiary N-atom (see: Chapter 23; Section 133).

In acetic acid Procaine consumes one equivalent of perchloric acid to the colour change of quinaldine red, but two equivalents with 1-naphtholbenzeine [386].

Weigh about 200 mg of sample, dissolve in 20 ml of a mixture of acetic acid–acetic anhydride (5 : 1), heat till boiling, cool and mix with 20 ml of dioxan. The free base is liberated from the hydrochloride with 10 ml of mercury(II) acetate. Titrate in the presence of crystal violet. One ml of 0·1 N perchloric acid is equivalent to 27·27 mg of Procaine-HCl, 31·47 mg of Larocaine-HCl and 30·08 mg of Tetracaine-HCl.

Acetylation in acetone [453]. Tetracaine is rapidly acetylated in acetone-acetic anhydride, without heat. Weigh 250 mg of Tetracaine-HCl, dissolve in a mixture of 5 ml of 5% mercury(II) acetate and 5 ml of acetic anhydride, add 50 ml of acetone and titrate with 0·1 N perchloric acid in the presence of 1 ml of saturated methyl orange indicator in acetone. 400 mg of Chlorprocaine (2-chloro-4-aminobenzoate of 2-diethylaminoethanol hydrochloride) is acetylated in a mixture of 80 ml of acetic acid and 2 ml of acetic anhydride with heating on a steam bath; after cooling the base is liberated by adding 10 ml of 5% mercury(II) acetate and titrated with 0·1 N perchloric acid. 30·72 mg of Chlorprocaine requires 1 ml of 0·1 N standard solution.*

(f) *Determination of methyl 1-phenyl-1-piperidyl-(2)-acetate hydrochloride* (Centedrin ®) [317]. *Titration on semimicro scale*: Weigh 60–70 mg of sample and dissolve in 100 ml of a 1 : 10 mixture of acetic acid–chloroform neutralized in the presence of tropaeolin 00. Mix 10 ml of the stock solution with 0·2 ml of 3% mercury(II) acetate in acetic acid and titrate with 0·01 N perchloric acid in acetic acid–carbon tetrachloride (1 : 1) in the presence of 3 drops of 0·5% tropaeolin 00 in acetic acid till the indicator becomes magenta. 2·698 mg of Centedrin ® requires one ml of 0·01 N standard solution. *Titration in acetone:* methyl phenylpiperidylacetate hydrochloride does not dissolve in acetone but is soluble in a solution of mercury(II) acetate in acetic acid. Weigh 250–300 mg of sample and dissolve in 100 ml of acetone and 6% mercury(II) acetate in acetic acid solution (95 : 5) previously neutralized in the presence of methyl red. Dilute 20 ml of the stock solution with 20 ml of acetone and titrate with 0·05 N perchloric acid in dioxan until the orange yellow turns to a salmon colour. Use a saturated solution of methyl red in acetonitrile as indicator. 13·49 mg of Centedrin ® require 1 ml of 0·05 N standard solution.

The active agent content of tablets cannot be determined by direct titration in non-aqueous media, therefore the agent must be extracted in the form of base. Weigh 140–160 mg of the finely pulverized tablet in a 25 ml separating funnel, suspend in 1 ml of distilled water, add 5 ml of saturated potassium hydrogen carbonate solution and extract for 5 min with 1×10 and 3×5 ml chloroform. Dry the total extract

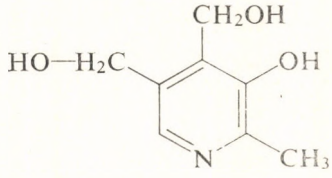
* *Drug. Stand.* **27**, 30 (1959).

with anhydrous sodium sulphate, mix with 2–3 ml acetic acid and titrate with 0·01 N perchloric acid. One ml of 0·01 N solution is equivalent to 2·698 mg hydrochloride salt or 2·333 mg of methyl phenylpiperidylacetate (free base).

For the determination of the hydrochloride of 1-phenyl-1-piperidylacetic acid 2-piperidylethyl ester in suppositories (Spasmonal ®) see: [367]).

(g) *Titration of ethyl 1-methyl-4-phenylpiperidine-4-carboxylate hydrochloride* (Pethidine ®) [453]. Weigh about 240 mg of sample, dissolve in 5 ml of 5% mercury(II) acetate in acetic acid, add 50 ml of acetone and titrate with 0·1 N perchloric acid in acetic acid. Indicator: 1 ml of 0·25% methyl orange in acetone. 28·38 mg of pethidine require 1 ml of 0·1 N solution. Pethidine-HCl can also be titrated in acetic acid in the presence of crystal violet [42].

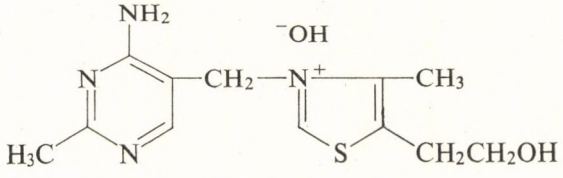
(l) *Determination of Pyridoxin-HCl* (vitamin B_6) [130, 453].



Pyridoxin (Vitamin B_6): 2-methyl-3-hydroxy-4,5-bis-(hydroxymethyl)pyridine

Weigh an amount of pyridoxin-HCl equivalent to 3–8 ml of 0·1 N perchloric acid, dissolve in 20 ml of acetic acid containing 10% of acetic anhydride, add 5 ml of 5% mercury(II) acetate and 10 ml of 1,2-dichloroethane and titrate in the presence of 4 drops of 0·2% 1-naphtholbenzeine in acetic acid. 20·56 mg pyridoxin-HCl requires 1 ml of 0·1 N perchloric acid. Solution can also be performed directly in 5 ml of 5% mercury(II) acetate, diluted with 25 ml of dichloroethane and then titrated as above.

(i) *Determination of Thiamin chloride* (vitamin B_1) [130, 453, 643]. *Semimicro titration* [643]. Weigh 50–60 mg of Thiamin chloride in a 200 ml Erlenmeyer flask. Dissolve with gentle heating in 5–10 ml of acetic acid. After cooling add 1 ml of 6% mercury(II) acetate and 70–80 ml of benzene. Titrate with 0·01 N perchloric acid in dioxan in the presence of 2–3 drops of 0·1% crystal violet. 1·686 mg of Thiamin chloride requires 1 ml of standard solution. *Determination of the active agent content of tablets containing vitamin B_1.* Weigh an amount of finely powdered tablet containing approx. 1 m.eq. of Thiamin chloride. Suspend in 10 ml of 5% mercury(II) acetate in acetic acid solution and agitate vigorously for a few minutes with a magnetic stirrer. Add 70–75 ml of ethyl acetoacetate. Even mild heating may cause errors in determination. Titrate with 0·1 N perchloric acid in acetic acid in the presence of 6 drops of 25% tropaeolin 00 (orange IV) in acetic acid. Ethyl acetoacetate dissolves Thiamin perchlorate. To avoid side reactions proceed as rapidly as possible. 16·86 mg of Thiamin chloride requires 1 ml of 0·1 N perchloric acid.



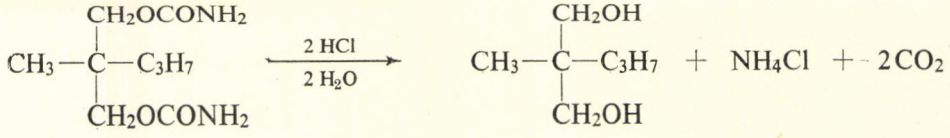
Thiamin base

(j) *Determination of sympathomimetic compounds* [651]. Dissolve 20–100 mg of hydrochloride in 15 ml of acetic acid neutralized in the presence of crystal violet. Mix with 5 ml of 5% mercury(II) acetate solution and titrate with 0·05 N perchloric acid in dioxan till the violet colour of the indicator turns blue. In this way ephedrine, norephedrine, 1-phenyl-2-methylaminopropane (Pervitin ®), 1-(3,4-dihydroxyphenyl)-2-aminopropane (Corbasil ®) and the hydrochloride salts of numerous other sympathomimetica can be determined.

Ephedrine-HCl can also be determined in acetone in the presence of mercury(II) acetate [453]. Regarding the determination of the alkaloid content of injections containing ephedrine-HCl, as well as ephedrine-phenacetin and ephedrine-phenylethylbarbituric acid mixtures see [651]. For determination of ephedrine in oils and inhalant preparations see: [637].

pK values for sympathomimetic amines see: [125].

(k) *Determination of 2-methyl-2-*n*-propyl-1,3-propanediol dicarbamate* (Meprobamate ®) [708]. By hydrolysis with hydrochloric acid, ammonium chloride, CO_2 and 2-methyl-2-n-propyl-1,3-propanediol are formed:



The equivalent amount of ammonium chloride formed is titrated in acetic acid with perchloric acid in the presence of mercury(II) acetate.

Weigh in a 250 ml wide-mouthed Erlenmeyer flask 60–110 mg of sample. Add 40 ml of pure concentrated hydrochloric acid. Cover with a watch glass and boil gently in a fume-cupboard for 45–60 min. Following hydrolysis, evaporate the hydrochloric acid solution nearly to dryness, add 10 ml of acetic acid and 10–15 ml solution of 5% mercury(II) acetate in acetic acid (neutralized in the presence of crystal violet) and dilute with 20 ml of dioxan after solution. Titrate with 0·1 N perchloric acid to a clear blue colour change. 10·91 mg of 2-methyl-2-*n*-propyl-1,3-propanediol dicarbamate requires 1 ml of standard solution.

In the meantime a blank is run to determine the possible ammonium chloride content of the hydrochloric acid. Evaporation of the hydrochloric acid hydrolysate to complete dryness is to be avoided, since NH_4Cl volatilizes at 100°C and crystalline ammonium chloride dissolves poorly in acetic acid.

(l) *Determination of mercurials via acetolysis* [149]. A procedure which utilizes a reversal of the Pifer–Wollish method [644] for the titration of amine hydrochlorides is useful for the determination of some mercurials.

The mercurials represented by the general formula R–Hg–R′ (in which one of the bonds may be a C–Hg bond) undergo acetolysis in acetic acid according to the following equations:

$$R-Hg-R' + AcOH \rightleftharpoons R-Hg-OAc + R'H$$

$$\text{and } R-Hg-OAc + AcOH \rightleftharpoons Hg(OAc)_2 + RH$$

If an excess of methylamine hydrochloride is added to the reaction mixture, an equivalent quantity of methylamine (as acetate) is formed which can be titrated with

perchloric acid:

$$R-Hg-OAc + CH_3NH_2.\,HCl \rightarrow R-Hg-Cl + CH_3NH_2.\,AcOH;$$

$$Hg(OAc)_2 + 2CH_3NH_2\,.\,HCl \rightarrow HgCl_2 + 2CH_3NH_2\,.\,AcOH$$

A sample corresponding to 0·5 to 0·8 m.eq. of mercurial is weighed into a flask and dissolved in acetic acid. Several drops of indicator are added (0·4% *p*-naphtholbenzeine in glacial acetic acid), and the solution is titrated with 0·1 N perchloric acid. The colour change is from yellow to green. A small excess of 0·1 N methylamine hydrochloride solution in glacial acetic acid is added, and the titration is continued to the end-point. The volume of perchloric acid solution consumed between the two end-points is equivalent to the mercurial in the sample, e.g.:

Mercurial	Equivalent wt	Bond type
Mercury(II) succinimide	198·4	2 Hg—N
Phenylmercury(II) acetate	336·8	Hg—O, Hg—C

Procedure for Thimerosal ® (equiv. wt. 202·4, bond type Hg−S, Hg−C). The sample is dissolved in acetic acid. Indicator and a small excess (1–2 ml) of methylamine hydrochloride solution are added, and the solution is titrated to the end-point with standard 0·1 N perchloric acid. The volume of perchloric acid consumed is equivalent to the mercurial plus any strongly basic component in the sample. The acetolysis of this compound gives sodium thiosalicylate and ethylmercury(II) acetate.

(m) *Titration of halides of bases in acetic anhydride medium.* In some cases, salts formed from bases containing nitrogen with halogen acids and quaternary halides can be titrated without the addition of mercury(II) acetate [619, 676, 778].

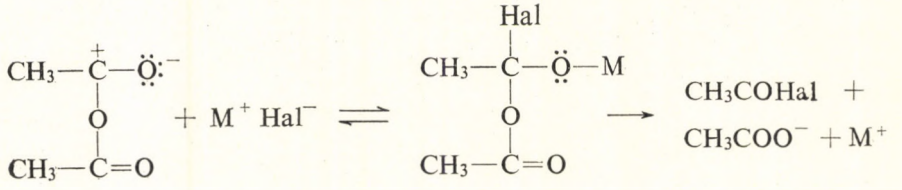
In the reaction between acetic anhydride and metal halide, acetyl halide and metal acetate can be detected [722]:

$$(CH_3CO)_2O \rightleftharpoons CH_3CO^+ + CH_3COO^- \qquad (136.1)$$

$$CH_3CO^+ + CH_3COO^- + M^+ + Hal^- \rightleftharpoons CH_3COHal + CH_3COOM \qquad (136.2)$$

where M^+ is the metal cation and Hal^- the halogen anion.

Presumably an additive reaction occurs between the metal ion of the halide and the carbonyl group of acetic anhydride followed by nucleophilic attack by the halide ion [676]:



Weigh a sample equivalent to 5–10 ml of 0·1 N perchloric acid and dissolve (in a fume cupboard) in 50 ml of anhydride. Titrate in the presence of crystal violet till blue or green-blue turns to yellow. (See: Chapter 13; Section 72.) In this way e.g. hydrochlorides of Lidocaine, quinine and narcotine and cetylpyridinium chloride can

be determined. Hyoscyamine and hyoscine hydrobromides are dissolved during titration. Hydrochlorides of thiamin, ephedrine, yohimbine and papaverine must be *first dissolved in 5 ml of 98% formic acid* and only then diluted with 50 ml of acetic anhydride. The titrant-consumption of the solvent mixture acetic anhydride–formic acid must be determined by a separate test and a suitable correction applied. (See also: Chapter 23; Section 126.)

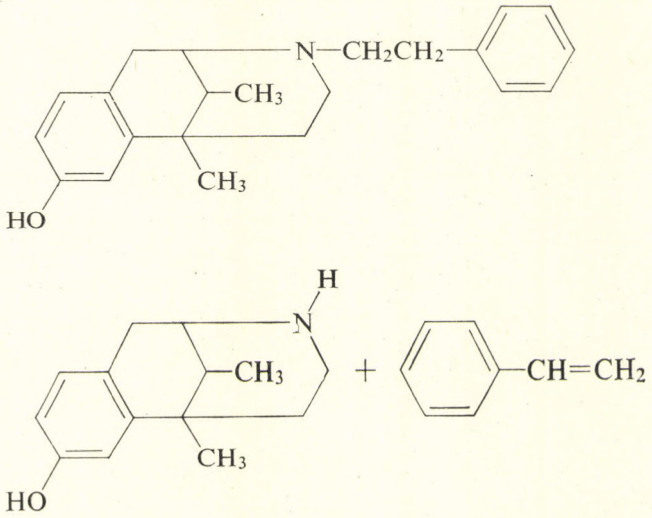
Regarding the titration of quinine hydrochloride in a solvent mixture of chloroform-acetic anhydride, using Sudan III as indicator, see: [655].

Regarding the titration of aniline hydrochloride see: [778].

As already mentioned, compounds containing a phenothiazine ring are sensitive to oxidation so they cannot be titrated in a solvent containing e.g. traces of peroxides (see: Chapter 23; Section 122). Neither can hydrochlorides of phenothiazine derivatives be titrated in acetic acid because the oxidizing effect of perchloric acid is presumably catalysed by mercury(II) acetate [619]. The red tint makes the colour change of crystal violet impossible to observe. In acetic anhydride the red tint is absent and hydrochlorides of Chlorpromazin, Promethazine and Diethazine can be titrated without the addition of mercury(II) acetate [619].

Weigh about 250 mg of the hydrochloride of the phenothazine derivative, dissolve in 10–15 ml of 95–100% acetic anhydride or a mixture of acetic anhydride–chloroform (1 : 1). Previously neutralize the solvent to yellow in the presence of three drops of crystal violet. Titrate with 0·1 N perchloric acid in acetic acid to a yellow colour change. One ml of 0·1 N perchloric acid is equivalent to the hydrochloride of 35·53 mg Chlorpromazin, 32·09 mg Promethazine and 33·48 mg Diethazine (the latter is N-(β-diethylaminoethyl)-phenothiazine hydrochloride).

(n) *Determination of halides of bases in the presence of a basic decomposition product soluble in hydrochloric acid (determination of Phenazocine)* [204]. Sometimes halides of bases are soluble in chloroform. This mainly occurs in the case of halide salts of alkaloid-like bases. Phenazocine hydrobromide is dissolved in chloroform even in a mixture with 0·1 N hydrochloric acid. It decomposes as follows:



Decomposition product

Weigh 100 mg of sample, dissolve in a separating funnel in 50 ml of 0·1 N hydrochloric acid, and extract phenazocine-HBr with 4 × 30 ml of chloroform. The decomposition product remains in the hydrochloric acid phase. Filter the chloroform into the titration flask through cotton-wool soaked in chloroform (the cotton-wool may be covered with some anhydrous sodium sulphate). Separating funnel and cotton-wool are flushed out with chloroform. Evaporate the solution to dryness on a steam bath. (The evaporating vessel shown in Fig. 103 can be used for this purpose and also for titration.) Dissolve the remainder by adding 25 ml of acetic acid and 10 ml of 6% mercury(II) acetate in acetic acid and titrate with perchloric acid in the presence of crystal violet. Observe the vanishing of the red tint through a yellow colour filter. 8·04 mg of phenazocine-HBr requires 1 ml of 0·02 N perchloric acid; accuracy is ±1%.

137. Quaternary Bases

The solvating power of solvent mixtures containing glycols is often better than that of acetic acid. Cationic soaps sometimes also dissolve well in a mixture of propylene glycol and isopropanol. Halide salts of quaternary bases can be titrated as bases with perchloric acid on adding mercury(II) acetate (hydrochloric acid would also titrate excess of mercury(II) acetate).

It has also been found possible to titrate the salts of heterocyclic quaternary ammonium bases — e.g. cotarnine chloride — with a standard solution of potassium cyanide in isopropyl alcohol [215]. (See also: Chapter 28.)

(a) *Titration in G–H solvent mixture.* Weigh 200–300 mg of sample and dissolve in 20–30 ml of G–H solvent mixture (Chapter 6; Section 41). Add a solution of mercury(II) acetate in about 20–50% excess and titrate with 0·1 N perchloric acid in isopropanol in the presence of bromophenol blue indicator (the result with potentiometric end-point detection is more precise). With this method e.g. lauryltrimethylammonium bromide and ethyltrimethylammonium chloride can be determined [489].

(b) *Titration in acetic acid. Titration of decamethylene-bis(trimethylammonium) bromide.* (Decamethonium bromide).* Dissolve about 400 mg of sample in 50 ml of acetic acid and after adding 2 ml of acetic anhydride heat on a steam bath till dissolved. After cooling, add 15 ml of 5% mercury(II) acetate to the solution and titrate with 0·1 N perchloric acid in acetic acid in the presence of two drops of indicator (1% crystal violet). 20·92 mg of decamethonium bromide requires 1 ml of 0·1 N solution:

$$[(CH_3)_3\overset{+}{N}-(CH_2)_{10}-\overset{+}{N}(CH_3)_3]\,2\ Br^-$$

(c) *Titration in propionic acid* [376]. Dissolve 300–400 mg of cetylpyridinium bromide or cetyltrimethylammonium bromide in 25 ml of 0·1 N mercury(II) propionate and titrate with 0·1 N perchloric acid in propionic acid in the presence of methanil from yellow to purple (Table 25). One ml of standard solution is equivalent to 38·44 mg of cetylpyridinium bromide or 36·44 mg of cetyltrimethylammonium bromide.

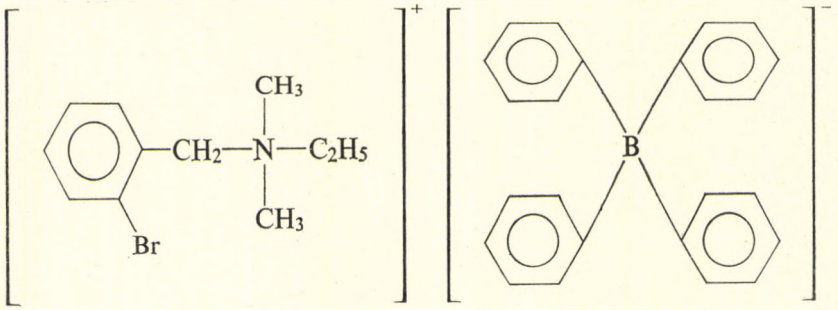
* *Drug Stand.* **26**, 136 (1958).

Preparation of mercury propionate: dissolve 22 g of mercury(II) oxide with gentle heating in 1,000 ml of propionic acid containing 14 g of propionic anhydride. *Preparation of 0·1 N perchloric acid in propionic acid:* mix, while cooling, 1,000 ml of propionic acid, 35 g of propionic anhydride and 10 ml of perchloric acid of density 1·690. (See also: Chapter 24; Section 135 (f).)

(d) *Titration in benzene-chloroform* [409]. Cetylpyridinium bromide can also be titrated in benzene-chloroform. A sample of about 300 mg that has been dried to constant weight at 40–50°C in vacuum is dissolved in a mixture of benzene-chloroform (30 : 2). After adding 3 ml of 6% mercury(II) acetate solution in acetic acid, titrate with 0·1 N perchloric acid in dioxan in the presence of metanil yellow.

138. Tetraphenylborates of Bases

It is known that many organic bases containing nitrogen (including quaternary bases) yield with sodium tetraphenylborate a precipitate of tetraphenylborate, insoluble in water (see also: Chapter 2; Section 19 (d)). Various solvents are suitable for dissolving tetraphenylborates, but the most convenient one must be decided on empirically. The tetraphenylborate anion is titrated as a base with perchloric acid [229, 267, 268, 316, 632]:



For the behaviour of tetraphenylboric acid in solution in anhydrous acetic acid, see: [632].

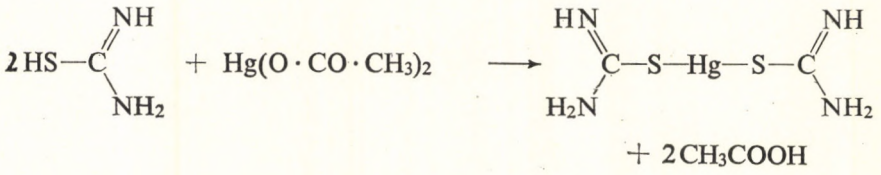
The tetraphenylborates of some anaesthetics can be titrated in a mixture of acetic acid-acetone [127]: dissolve 100 mg in 5 ml of acetone, add 45 ml of acetic acid and titrate with 0·05–0·1 N perchloric acid, for piperocaine to a blue colour, and for procaine or tetracaine to a green colour change.

For the solution of tetraphenylborates, acetone or dioxan is usually employed. N-*o*-Bromobenzyl-N-ethyl-N,N-dimethylammonium tetraphenylborate does not dissolve in dioxan but is soluble in acetone. The colour change in the latter, with titrant of 0·01 N concentration and methyl red, methyl violet or tropaeolin 00 as indicator, is sluggish. However, this compound can be readily titrated in a 1:1 mixture of methyl ethyl ketone-acetic anhydride to a green blue change of methyl violet [316]. Errors are miniminized if perchloric acid in excess is added to the sample till colour change occurs and the excess is back-titrated with 0·01 N sodium acetate in acetic acid. Weigh tetraphenylborate equivalent to 10–15 mg of bromobenzylethyl dimethylammonium ion; dissolve in a neutralized mixture of 10 ml methyl ethyl ketone-acetic anhydride (1 : 1), add 1 drop of 1% methyl violet and titrate slowly, maintaining constant stirring, to a green blue colour change. Continue addition of

0·01 N perchloric acid in acetic acid–carbon tetrachloride (1 : 1), (altogether e.g. 10·00–12·00 ml), finally back-titrate the yellow solution with 0·01 N sodium acetate to a green blue colour. This can be prepared from a 0·1 N solution (Chapter 10; Section 58). Standardize perchloric acid titrant against a fresh solution of diphenylguanidine in methyl ethyl ketone-acetic anhydride. In order to control normality of sodium acetate mix 10 ml of perchloric acid of known normality with 5 ml of methyl ethyl ketone and 5 ml of acetic anhydride and titrate with standard solution of sodium acetate in presence of methyl violet to a green-blue colour. 5·623 mg of bromobenzylethyldimethylammonium tetraphenylborate requires 1 ml of 0·01 N perchloric acid.

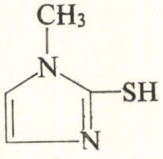
139. Bases in the Presence of either 'Acidic'—SH or =S Groups

The acidic SH or S group masks the basicity of amino compounds and disturbs titration with perchloric acid. By adding mercury(II) acetate the following can be titrated in acetic acid: 1-methyl-2-mercapto-imidazole, allylthiourea, Metothyrin®, thiourea, tetraethylthiuram disulphide (Antabuse ®), thiobarbituric acid derivatives (e.g. Intranarcon ® = potassium salt of 5-allyl-5-cyclohexenyl-2-thiobarbituric acid), etc.



Thiourea — Mercury dimercaptide

Weigh 50–70 mg of methylmercapto-imidazole, dissolve in 25 ml of 3% mercury(II) acetate solution, add 5 ml of acetic anhydride and titrate in the presence of 3–5 drops of 0·1% crystal violet. 11·42 mg of methylmercapto-imidazole require 1 ml of 0·1 N solution [42, 43, 44]:



If, on addition of mercury(II) acetate, turbidity develops, a solvent mixture of acetic anhydride–chloroform (1 : 1) is used and after adding 10 ml of 3% mercury(II) acetate the excess of standard perchloric acid solution is back-titrated with 0·1 N potassium acetate in acetic acid. 14·83 mg of tetraethylthiuram disulphide require 1 ml of 0·1 N $HClO_4$.

$(C_2H_5)_2N.CS.SS.CS.N(C_2H_5)_2$

Tetraethylthiuram disulphide

Micro determination of thiourea, see: [6].

140. Sulphates, Ethanesulphonates, *p*-Toluenesulphonates, Phosphates and Nitrates of Bases

Numerous methods are suitable for the determination of the above compounds.

Following basification using NaOH, $KHCO_3$, $NaHCO_3$, the aqueous solution of, for example, alkaloid salts is extracted with chloroform or carbon tetrachloride and the anhydrous extract, dried with sodium sulphate, is titrated with 0·005 *N*-*p*-toluenesulphonic acid or, after adding acetic acid, with 0·01 N perchloric acid (atropine sulphate, ergotoxine ethanesulphonate, strychnine sulphate, codeine phosphate) [299].

Vincaleukoblastine $C_{46}H_{58}O_9N_4$. can be titrated in a similar way with 0·005 N *p*-toluenesulphonic acid [436]*.

Determination of vincaleukoblastine sulphate (Velban ®, Vinblastine sulphate). VLB-sulphate contains water which can be removed by vacuum drying at about 50°C. The anhydrous material is very hygroscopic and absorbs about 2% moisture in 2 min when allowed to stand under room conditions. Equilibrium is reached in about 4 hours: therefore for accurate weighing allow the sample to stand for this time in the air. Weigh in a separating funnel with one-tenth mg accuracy a sample of about 25 mg; dissolve in a small amount of water; basify with sodium hydrogen carbonate and extract the liberated base with 1 × 10 ml and then with 3 × 5 ml of chloroform. Filter the chloroform extract through cotton wool covered with sodium sulphate into a 25 ml measuring flask, and dilute if necessary to the mark. Titrate 5 ml portions with 0·005 N *p*-toluenesulphonic acid in the presence of dimethyl yellow indicator. One ml of standard solution is equal to 2·026 mg of VLB-base or 2·317 mg Vincaleukoblastine sulphate monohydrate.

Measurement of moisture is carried out, at the same time as the above determination, by vacuum drying at 50°C for 16 hours.

When the so-called benzidine method is employed the approximate sulphate ion content of the sample must be known. 95% of the SO_4^{2-}-ion is bound in the form of benzidine sulphate, which is insoluble in acetic acid and the remaining small amount of free sulphuric acid, in most cases, does not essentially affect the colour change of the indicator [265].

Weigh an amount of 1 m.eq. base sulphate. Dissolve in 10 ml of acetic acid; add 0·05 N of benzidine base equivalent to 95% of the weighed sulphate ion and titrate, without filtration, with 0·1 N perchloric acid in the presence of 1 drop of 1% methyl violet. 19·58 mg of quinine sulphate dihydrate requires 1 ml of standard solution.

Regarding sulphates of streptomycin and dihydrostreptomycin see: [635].

Most alkaloid sulphates have only a low solubility in acetic acid; Chatten suggests [123] that in such a case titration should be performed in a mixture of acetonitrile-chloroform-phenol (10 : 4 : 1). Codeine phosphate can also be determined in this mixture in the presence of acetylsalicylic acid, phenacetin and caffeine [639].

(a) *Titration in a mixture of acetonitrile–chloroform-phenol* [123].

In the course of development of the methodology of non-aqueous titration, solvent mixtures are coming into more general use for the determination of mineral salts of bases also, since the millivolt inflection at the end-point is often greater and visual detection sharper.

* Neuss, Gorman, Svoboda, Maciak and Berr, *J. Amer. Chem. Soc.* **81**, 4754, (1959).

Using a 0·02 ml graduated semimicro burette weigh a sample which will give a titration of 2–3 ml of 0·05 N perchloric acid in dioxan. Dissolve the sample in 5 ml of freshly distilled phenol or a mixture of 5 g phenol and 10–20 ml chloroform and after adding 50 ml of acetonitrile, titrate either potentiometrically or in the presence of 1–2 drops of methyl red till a violet-red colour is produced. Nearing the end-point a transition through different shades of colour can be observed; the last colour change, however, is very sharp. (Fig. 44c.) With this method the following can be titrated potentiometrically as well as by visual end-point detection: *d*, *l*-1-phenyl-2-propylamine sulphate (Amphetamine ®, sulphates of ephedrine, morphine, codeine, strychnine and physostigmine, phosphates of codeine and Dimoxylin ® (the latter is: 6,7-dimethoxy-1-(4′-ethoxy-3′-methoxybenzyl)-3-methylisoquinoline phosphate). Sulphates of quinine, cinchonine and cinchonidine can be determined only by potentiometric titration.

(b) *Titration in dioxan. Determination of ethanesulphonates and p-toluenesulphonates of bases* [321]. When salts formed from organic bases containing nitrogen and strong acids (e.g. ethanesulphonic acid or *p*-toluenesulphonic acid) are titrated in non-aqueous media the following reactions may take place:

1. When dissolved in acetic acid, no acetate or very little is formed. The acetate ion is a strong base (acetic acid is a weak acid), while $CH_3C_6H_4SO_3^-$ ion and $C_2H_5SO_3^-$ ion are weak bases (the corresponding acids are strong acids). In titrations with perchloric acid in acetic acid, where $CH_3COOH_2^+$ ion is the protonated intermediate, a sharp colour change cannot be expected. In most cases the indicator shows an 'acidic' colour immediately after the addition at the first few drops of standard solution. In the case of a salt of a *weak base* and *p*-toluenesulphonic acid an adduct $B\ldots HSO_3 \cdot C_6H_4CH_3$ is present, and *p*-toluenesulphonic acid is of highly acidic character in acetic acid also; in the case of a salt formed from a *strong base* the ion in the ion-pair BH^+ $(CH_3C_6H_4 \cdot SO_3)^-$ is a strong cationic acid while the *p*-toluenesulphonate anion is a weak base.

The cationic acid character of the 'onium ion in the case of salts of quaternary bases (of general formula $R_4N^+X^-$) is not a result of proton co-ordination. If, in a salt of this type, X^- is a halide ion, owing to the effect of mercury(II) acetate in acetic acid medium, it is exchanged with an acetate ion and the latter can be titrated as a base. When, however, X^- is $(CH_3C_6H_4 \cdot SO_3)^-$ ion, formed from methyl *p*-toluenesulphonate, or methyl sulphate anion $CH_3SO_4^-$, formed from dimethyl sulphate, such quaternary salts do not form acetates, not even after adding mercury(II) acetate in acetic acid, and can, therefore, not be titrated.

2. In an aprotic or differentiating solvent perchloric acid itself neutralizes either the base or the ethanesulphonate or *p*-toluenesulphonate anion, without intervention of solvent cation (acetacidium ion):

$$R_3NH^+X^- + HClO_4 = (R_3NH^+ClO_4^- \rightleftarrows R_3N\ldots HClO_4) + HX;$$

$$R_4N^+X^- + HClO_4 = R_4N^+ClO_4^- + HX$$

Weigh about 0·5 m.eq. monofunctional or 0·25 m.eq. bifunctional base ethanesulphonate (or *p*-toluenesulphonate) and dissolve in 10–15 ml of neutralized dioxan. Titrate in the presence of crystal violet; with 0·05 N perchloric acid in dioxan piperidine, cyclohexylamine, morpholine, dimethylaminoacetylphenothiazine, vincamine, ethanesulphonate or *p*-toluenesulphonate to dull green; tribenzylamine-, piperidinomethyltolylpropanone and bromobenzyldimethylammonium *p*-toluenesulphonate to light emerald green, and ergotoxine ethanesulphonate and *p*-toluenesulphonate to light grass green. In the latter case, accuracy of determination is not better than ±2% while in the former, errors only reach about ±0·5%. N-[β-3,4,5-trimethoxybenzoxyethyl]-N′-[γ-(3′-chloro-10′-phenothiazinyl)-propyl]-piperazine

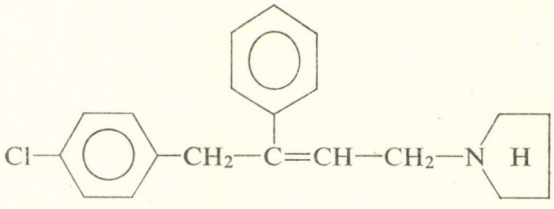
diethanesulphonate when titrated to emerald green can be determined with $\pm 1\%$ accuracy.

(Regarding the colour change of crystal violet see: Chapter 13.)

(c) *Determination of ergotoxine phosphate* [308]. Dissolve 100–150 mg of finely powdered ergotoxine phosphate, protected from light, in 20 ml of acetic acid. Titrate from a semimicro burette with 0·05 N perchloric acid in the presence of 1 or 2 drops of 0·1% crystal violet in acetic acid to a blue colour change. 34·37 mg of ergotoxine phosphate requires 1 ml of 0·05 N solution (the effective molecular weight of a mixture of 50% ergogrystine +25% ergoeryptine +25% ergocornine phosphate is 687·3).

(Concerning the determination of the phosphoric acid content of ergotoxine phosphate see: Chapter 22; Section 116 (d).)

(d) *Determination of Pyrrobutamine phosphate.** Weigh about 0·4 g of 1-[4-(*p*-chlorophenyl)-3-phenyl-2-butenyl]-pyrrolidine diphosphate, dissolve in 80 ml of acetic acid and titrate with 0·1 N perchloric acid in acetic acid in the presence of crystal violet. 50·79 mg of Pyrrobutamine requires 1 ml of 0·1 N perchloric acid.



(e) *Titration in acetic acid with 0·05 N perchloric acid in dioxan* [651]. In acetic acid some sympathomimetica can be titrated directly with perchloric acid in dioxan. Weigh 20–100 mg of sample, dissolve, if necessary with gentle heating, in 15 ml of acetic acid neutralized in the presence of crystal violet and titrate from a semimicro-burette to a blue colour change. One ml of 0·05 N solution is equivalent to the following: 18·43 mg Benzedrine® (1-phenyl-2-amino-propane sulphate), 21·43 mg Veritol® [1-(4-hydroxyphenyl) 2-methylaminopropane sulphate], 25·83 mg Butedrin® [1-(4--hydroxyphenyl) 2-n-butylaminoethanol sulphate] and 27·83 mg Aludrin® [1--3,4-dihydroxyphenyl) 2-isopropylaminoethanol sulphate dihydrate]. Benzedrine® and Butedrin® dissolve easily, Aludrin® on gentle heating, and Veritol® on prolonged heating.

(f) *Direct titration of base sulphates in acetic anhydride* or in a solvent mixture of acetic anhydride-chloroform: [655 and 706].

(g) *Determination of strychnine nitrate and atropine methonitrate* [656]. Owing to its reducing properties, ascorbic acid is suitable for reducing nitrate to nitrite in acetic acid; nitrite can be expelled by boiling and passing air through the system. Thus, base nitrate is converted into base acetate. (As regards the reducing properties of ascorbic acid see: Chapter 29; Section 162.) The ingenious method of Posgay and Bayer by means of which e.g. alkaloid nitrates can be directly titrated in acetic acid–acetic anhydride in the presence of crystal violet is based on this fact.

It is known that in the case of salts of quaternary bases used in pharmacology, e.g. atropine methonitrate, the base is not liberated on basification and cannot be

* *Drug Stand.* **27**, 58 (1959).

extracted by an organic solvent. The nitrate of pilocarpine can only be determined potentiometrically in a mixture of phenol–chloroform–acetonitirile [183].

Weigh 60–70 mg of strychnine nitrate and dissolve with heating in 10 ml of acetic acid. Dissolve 200 mg of finely powdered solid ascorbic acid in the hot solution and remove the nitrous vapours formed by an air current (for this purpose the apparatus shown in Figs 42 and 103 can be used). Continue careful boiling for 1 min, constantly maintaining a current of air. Add 20 ml of acetic anhydride to the cooled solution and titrate with 0·02 N perchloric acid in acetic acid–carbon tetrachloride (1 : 1) in the presence of 1–2 drops of 0·2% crystal violet in chlorobenzene to a green colour. Correct for the reagent blank. 7·948 mg of strychnine nitrate requires 1 ml of 0·02 N perchloric acid.

Atropine methonitrate can be determined in a similar way. Dissolve 150 mg of sample in 15 ml of acetic acid and reduce the nitrate with 1 g ascorbic acid to nitrite, and then proceed as above. 36·64 mg of atropine methonitrate requires 1 ml of 0·1 N perchloric acid.

Chapter 25

Determination of Mixtures of Nitrogenous Bases or Mixtures of Base Hydrochlorides

Though many methods are suitable for the determination of amine mixtures there is no generally applicable procedure. If in a differentiating solvent the strength of bases (Chapter 6) varies, binary and ternary amine mixtures can be resolved by potentiometric titration [247, 401, 404, 579]. By acetylation, in acetic acid, primary and secondary amines can be converted into acid amides which do not consume perchloric acid [158, 311, 312, 314, 612, 616, 750, 811, 854] and primary amines are converted with salicylaldehyde [156, 432, 750], acetylacetone [157] and 2-ethylhexaldehyde to imines, (in the latter case direct titration with 2-ethylhexaldehyde is possible: [518]). In pyridine, excess of salicylaldehyde can be back-titrated with sodium methoxide; secondary and tertiary amines not reacting with salicylaldehyde can be titrated in chloroform with standard acid [156, 432]. Primary aliphatic and aromatic amines can be converted with phthalic anhydride to phthalimides, neutural in acetic acid [262]. Finally there are distillation methods [166, 315], and others founded on varying changes of the indicator [156, 247, 703, 704] and some taking into account the differential rate of reaction of bases [347].

141. Amine Mixtures in Differentiating Solvents

Acetonitrile, acetone, methyl ethyl ketone, methyl isobutyl ketone, dioxan, nitromethane, nitrobenzene and various solvent mixtures such as, for instance, acetic acid–chloroform (1 : 10–2 : 100), nitrobenzene–heptane, acetic acid–dioxan–nitromethane, etc. are suitable solvents for the determination of amine mixtures (see: Chapter 2; Section 15; Chapter 6; Sections 37 and 38). The most suitable solvent or solvent mixture must be chosen for each case separately. When a new technique is being employed it is advisable to mix bases in different ratios and to decide the most favourable conditions for investigation during a model test.

It is characteristic of the varying effect of solvents that when e.g. a mixture of piperidine and pyridine is titrated potentiometrically in chlorobenzene with hydrogen-chloride in isopropanol only piperidine (pK 2·80) is measured and one inflection

can be seen. But in a mixture of acetic acid–chlorobenzene with perchloric acid in acetic acid the total base content is determined and here also only one inflection can be observed. In methyl isobutyl ketone with perchloric acid in dioxan two inflections indicate the end-points of the two components [105].

Differentiating potentiometric titration can also be carried out with 0·01 N perchloric acid in dioxan, e.g. in a mixture of acetic acid and chloroform (1:10). Potassium acetate (the acetate ion is a strong base), n-butylamine (pK 3·39), and pyridine

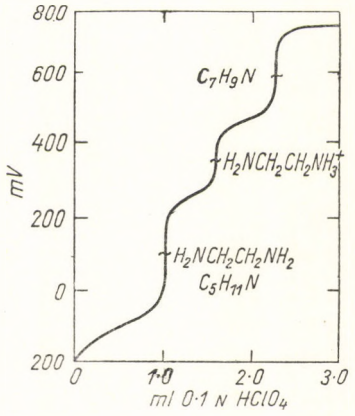


Fig. 121. Potentiometric titration of a mixture of piperidine, ethylenediamine and *p*-toluidine in nitrobenzene according to van Meurs and Dahmen [579]

(pK 8·85) each show one inflection [647]. In acetonitrile medium the binary mixtures of e.g. butylamine–pyridine, ethanolamine–aniline (pK 4·56 and 9·42), dibutylamine–butylamine salicylaldimine, aniline–*o*-chloroaniline (pK 9·42 and 11·4), β-phenylethylamine–aniline can be differentiated [247]. On the analogy of the above model mixtures this method can be applied to the analysis of some industrial intermediate products.

In the case of compounds containing a primary amino group the solvent containing a carbonyl group may lead to the formation of a *ketimine* giving lower values (ketimines are weak bases and can only be titrated in acetic acid: [642]). In such a case nitrobenzene or nitrobenzene–heptane should be used as a solvent and perchloric acid in dioxan as titrant [579]: piperidine, ethylenediamine and *p*-toluidine show three inflections (Fig. 121).

(a) *Titration in acetonitrile* [247] *can be performed either by potentiometric or visual indication.* Colour change of Eosin Y, a suitable indicator in this case, occurs at the end-point of the stronger, while that of methyl violet at that of the weaker base. Weigh 0·6–1·0 m.eq. of a mixture of butylamine–pyridine, dissolve in 20 ml of purified acetonitrile, add 6 drops of saturated Eosin Y in acetonitrile as indicator and titrate butylamine (B_1) with 0·1 N perchloric acid in dioxan to a faint yellow colour change of the indicator (m), then add to the solution 20 ml of acetic acid and 2 drops of 0·2% methyl violet in chlorobenzene and continue titration to a blue green colour (n). The second colour change indicates neutralization of pyridine (B_2).

Calculation: m.eq. $B_1 = (m - m_b)$N; m.eq. $B_2 = (n - n_b)$N

where B_1 = the stronger, and B_2 the weaker base

m = the standard solution consumed to the first equivalence point (in ml)

n = that from the fiirst to the second end-point (in ml)
m_b = standard solution consumed for the blank test to the first end-point
n_b = that consumed for the blank test from the first to the second end-point (in ml)
N = normality of perchloric acid.

In this and similar cases it is advisable to determine and apply the factor (normality) of the titrant for both solvents and both indicators.

In the case of physostigmine in the presence of tropaeolin 00 the equivalent weight is equivalent to the molecular weight of the alkaloid, while in the presence of crystal violet equiv. wt. = $\frac{\text{mol. wt}}{2}$, i.e. two equivalents of perchloric acid are consumed [264].

(b) *Titration in acetonitrile with photometric end-point detection. Determination of aniline and N,N-diethylaniline in one mixture* [404]. Weigh amine mixture (1·5–1·6 m.eq.) and dissolve in 100–110 ml of acetonitrile in a 150 ml titration cuvette (Fig. 96). A suitable proportion for the photometric titration of e.g. aniline: diethylaniline is 2 : 1 (Fig. 89) and a suitable measuring instrument e.g. Beckman Model B; 337 mμ is the chosen wavelength to the first equivalence point. In the course of protonation, the absorption of N,N-diethylaniline (pK 7·48) is shifted towards a shorter wavelength; thus, if the latter is modified to 320 mμ aniline can also be titrated continuously. 0·5 N perchloric acid solution in acetic acid in increments of 0·05–0·1 ml are added to the sample. The photometric curve (A against V) is plotted graphically. Intercepts of the straight lines extrapolated to the x axis indicate millilitres consumed at the end-point. One ml of 0·5 N $HClO_4$ is equivalent to 74·61 mg of diethylaniline or 46·56 mg of aniline.

(c) *Titration in acetic acid with photometric end-point detection. Determination of mixtures of 2-methyl-5-nitroaniline and 4-methyl-2-nitroaniline* [404]. Follow the procedure described above *(b)* except that acetic acid is used as solvent instead of acetonitrile. Wavelength employed is 552 mμ; a favourable ratio of bases in the case of 4-methyl- and 2-methyl-derivatives is 1 : 0·5 (Fig. 88). 76·07 mg of methyl nitroaniline require 1 ml of 0·5 N perchloric acid (Chapter 14).

(d) *Titration in methyl ethyl ketone* [474, 475, 479]. The use of methyl ethyl ketone is often advantageous in the potentiometric titration of bases as the common solvent for both the sample to be tested and for perchloric acid. With perchloric acid in methyl ethyl ketone in certain cases a greater potential jump can be observed than, e.g., with perchloric acid in dioxan. Kreshkov and co-workers resolved binary and ternary mixtures of bases in the following way: 30–50 mg of the sample was placed in a titrating beaker and dissolved in 20 ml of methyl ethyl ketone. Using a glass–calomel electrode pair, the titration was performed with 0·1 N perchloric acid in methyl ethyl ketone. To exclude carbon dioxide and moisture of the air, it is advisable to carry out the titration under a nitrogen atmosphere (it suffices to direct a stream of nitrogen gas to the surface of the solution). The titration of single bases can be carried out with 1–1·5% precision, while mixtures of bases can be resolved with an accuracy of 2·5–3·0%. Piperazine + methylbenzimidazole, piperazine + 2,2′-dimethyl-5,5′-dibenzimidazole, piperazine + 2,2′-dimethyl-5,5′-dibenzimidazole+diphenylmethane, piperidine + methylbenzimidazole + 3,5-dimethylpyrazole, piperazine + methylbenzimidazole + 3,5-dimethylpyrazole may be determined in the presence of one another in this way.

(e) *Determination of glucosides containing nitrogen in the presence of p-anisidine, p-phenetidine and p-toluidine* [767]. A suitable method for N-glucosides is potentiometric differentiating titration with 0·01 N perchloric acid in dioxan. A convenient electrode system is glass as indicator and Ag/AgCl as reference electrode with a liquid filling of acetic acid saturated with KCl. Various solvents may be employed depending on the composition of the mixture (see: table below). Accuracy of the determination of glucosides containing nitrogen is only ±1%. Depending on the strength of base the potential jump at the end-point is 25–220 mV. In the case of *p*-chloro- and *p*-bromo-aniline-N-glucosides a potential jump can no longer be observed. A 0·1 mM sample of compound is generally dissolved and titrated in 25 ml of solvent (methanol and glucose do not interfere).

Compound or Mixture (in Brackets p*K Value and* mg.*-Equivalent of 1* ml *0·01* N *Standard Solution)*	*Solvent, Number of Potentiometric Inflections (Roman Numerals), Equivalent Quantity of Titrant Consumed (Arabic Numerals)*			
	Acetic Acid	*Ethyl Acetate*	*Nitro-methane*	*Aceto-nitrile*
p-Anisidine (p*K* 8·71; 1·232 mg), *p*-phenetidine (p*K* 8·66; 1·372 mg), *p*-toluidine (p*K* 8·70; 1·072 mg)	I 1	I 1	I 1	I 1
N-Glucosides of above	I 1			
Amadori-products (strong bases)	I 1	I 1	I 1	I 1
p-Anisidine + *p*-anisidine-N-glucoside	I 2	II 2	I 1	I 1
p-Toluidine + *p*-toluidine-N-glucoside	I 2	I 1	I 1	I 1
p-Bromoaniline + *p*-bromoaniline-N-glucoside	I 1	I 1	I 1	I 1
p-Anisidine + *p*-anisidine-N-glucoside + Amadori product	I 3			
p-Anisidine-N-glucoside + Amadori product	I 2		II 2	
Amine + Amadori product	I 2	I 2	I 2	I 2

(f) *Titration in acetic anhydride. Successive determination of amines, sulphoxides and acid amides in the presence of one another* [64]. Aliphatic and aromatic (or heterocyclic) amines, sulphoxides and acid amides may be determined successively in the same sample. The sample to be tested should contain about 0·1–1 m. mole of each single component. It is dissolved in 50–75 ml of acetic anhydride and titrated potentiometrically with 0·05–0·1 N perchloric acid in dioxan, using a glass–calomel electrode system. The electrolyte solution of the calomel electrode is acetic acid saturated with lithium chloride. If the compounds to be tested are only slightly or not at all soluble in acetic anhydride, the sample should be previously dissolved in chlorobenzene, or dioxan, or nitromethane, and then diluted with acetic anhydride. The accuracy of the determination for samples of 2–20 mg is 1 to 2%.

142. Salicylaldehyde, Method I

In the potentiometric titration of amine mixtures salicylaldehyde was used by Wagner, Brown and Peters, for the binding of primary amines and the unreacted secondary + tertiary amines were estimated [854]. Johnson and Funk [432] measure the primary amine indirectly by back-titrating the non-reacted salicylaldehyde with sodium meth-

oxide in pyridine (Chapter 18). The salicylaldehyde must be free from salicylic acid. Pipette precisely 10 ml of 0·5 N salicylaldehyde solution in pyridine in a 250 ml Erlenmeyer flask, add a sample of amine mixture (which must not contain more than 3 m.eq. of primary amine), stopper and allow to stand for 15 min. After adding 1 ml of indicator (1% thymolphthalein or phenolphthalein in pyridine) titrate with 0·1 N sodium methoxide in pyridine (Chapter 11; Section 60 (h)). Run a blank to determine normality of reagent containing salicylaldehyde. Salts of ammonia and amino compounds, as well as piperidine, piperazine and morpholine have a disturbing effect. Ethanolamine cannot be determined in this way. The total base content in acetic acid can be determined by titration with perchloric acid. 0·1 m.eq. of aliphatic primary monofunctional amine requires 1 ml of 0·1 N sodium methoxide.

A characteristic example of the applicability of this method is that in a mixture of 2·4% ethylamine + 22·6% diethylamine + 2·3% trimethylamine + 0·9% ethanol + 71·8% water, 2·3% of ethylamine were found [432].

143. Salicylaldehyde, Method II

Another equally suitable method to determine aliphatic amines in a mixture is that in which the total of secondary and tertiary amines and subsequently salicylaldimine are titrated in a medium of differentiating properties using two different indicators [156].

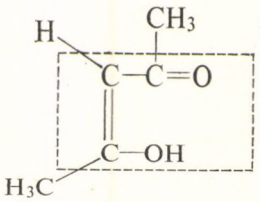
Weigh a mixture of amines containing max. 12·5 m.eq. primary and 12·5 m.eq. secondary and tertiary amines, in a 250 ml glass-stoppered Erlenmeyer flask: add 25 ml of chloroform and 5 ml of pure salicylaldehyde. If the solution becomes turbid dilute with a small amount of dioxan. Allow the stoppered flask to stand for 15 min, then titrate with 0·5 N perchloric acid in dioxan in the presence of 4–6 drops of 0·5% bromocresol green until the green colour disappears. The volume of standard solution consumed is equivalent to the amount of secondary and tertiary amines. The mixture is then diluted with 75 ml of dioxan and after adding 8–10 drops of 0·1% Congo red indicator in methanol, titration is continued until a clear green colour appears. The salicylaldimine formed from the primary amine is titrated in this way.

This method cannot be used for those compounds whose molecules contain primary and secondary or tertiary amino groups simultaneously. Ammonia, heterocyclic secondary amines (e.g. morpholine) and secondary amino-alcohols interfere. The following amines can be determined separately: butylamine, dibutylamine, diethylamine, di-(2-ethylhexyl)amine, dihexylamine, hexylamine, isopropylamine, methylamine, triethylamine, tripropylamine (chloroform 50 ml; salicylaldehyde 10 ml; dioxan 50 ml). The following have been determined in mixtures [156]: benzylamine–ethylcyclohexylamine, butylamine–dibutylamine, ethylamine–diethylamine, ethylamine–triethylamine, 2-ethylhexylamine–di(2-ethylhexyl)amine, ethylenediamine–tripropylamine, isopropylamine–di-isopropylamine and propylamine–tripropylamine.

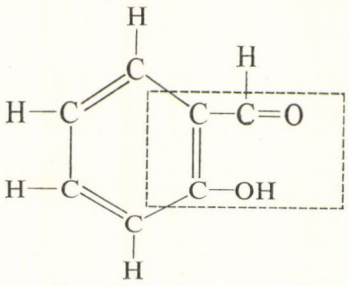
144. Acetylacetone Method

Acetylacetone (2,4-pentanedione) reacts with primary amines and an imine is formed. In essence, the enol form of acetylacetone reacts on the analogy of salicylaldehyde:

$$CH_3-CO-CH=C(OH)-CH_3 + RNH_2 \rightarrow CH_3-C(=N-R)-CH=C(OH)-CH_3 + H_2O$$



Acetylacetone



Salicylaldehyde

Salicylaldehyde imines are stabilized by resonance with the benzene ring and acetylacetone imines through resonance with an imine-ketamine form. Acetylacetone is a weak acid and can be titrated in pyridine medium with sodium methoxide in the presence of thymolphthalein (cf. Chapter 17 and Table 31). If excess of acetylacetone is added to a compound containing a primary amino group the excess of reagent can be back-titrated after imine formation [157].

Weigh precisely 10 ml of acetylacetone of 2·5 N concentration in two 250 ml pressure bottles. Transfer to one of the bottles a sample equivalent to 10 to 15 m. eq. of primary amine mixture and allow to stand for a given time at a given temperature (see: Table below). Prior to titration cool the bottles to room temperature, add 1 ml of 1% thymolphthalein in pyridine and titrate with 0·5 N sodium methoxide in pyridine till the indicator first turns to blue (Chapter 11; Section 60 (i)). Calculate using the difference in volume between blank and titration.

Preparation of acetylacetone reagent: dilute 260 ml of the middle fraction of freshly distilled acetylacetone to 1 litre with freshly distilled pyridine.

The acetylacetone method also enables determination of those amines which cannot be determined by the salicylaldehyde method: ethylene-amines, amino-alcohols, amino-acids and primary amines also containing heterocyclic nitrogen. By this method the following compounds can be determined with $\pm 0{\cdot}1-\pm 0{\cdot}3\%$ accuracy:

Compound	*Temperature* (°C)	*Time* (min)
Amino-ethanolamine, ethylenediamine	25	30– 60
N-Aminoethylpiperazine	0	30– 60
N-Aminopropylmorpholine, butylamine, ethanolamine, hexylamine, 1-amino-2-propanol	25	15– 60
Propylenediamine	25	60–120
Isopropylamine	98	15– 60
Benzylamine	25	15–120

This method is suitable for the determination of e.g. ethanolamine in the presence of diethanolamine or triethanolamine, as well as for the determination of

isopropylamine in the presence of di-isopropylamine and of ethylenediamine in the presence of piperazine.

145. Phthalic Anhydride Method

The Schiff base formed during reaction between a primary amine and salicylaldehyde in acetic acid consumes perchloric acid similarly to a primary amine. However, primary amines can be converted with phthalic anhydride to phthalimides, and these are neutral in acetic acid [262].

Weigh sufficient amine mixture for 1 g of phthalic anhydride (mol. wt. 148·1) to be in 2 to 3 times excess in relation to the primary amine. After adding 1 g of phthalic anhydride to 20–25 ml of stock solution containing acetic acid heat for 30–40 min on a steam bath and, after cooling, titrate the non-reacted secondary + tertiary amines potentiometrically with 0·1 N perchloric acid. Heat another portion of the stock solution with 10–15 ml of acetic anhydride as above and after cooling, titrate the tertiary amine with perchloric acid. As the acetylatable amines are converted to acid amides, they consume little or no perchloric acid.

146. Acetic Anhydride Method

(a) *Determination of nicotine, nornicotine and the total alkaloid content in tobacco powder* [158]. Weigh 2·5–3·5 g finely pulverized tobacco powder in a 250 ml glass-stoppered flask; add 1 g of granular barium hydroxide octahydrate and 15 ml of saturated aqueous barium hydroxide solution. Extract the thoroughly moistened tobacco powder in a vibrator for 15 min with a mixture of precisely 100 ml benzene–chloroform (**9** : 1). To facilitate filtration add about 2 g of diatomaceous earth (or Celit®), stir, and following deposition, filter the supernatant part through filter paper (Whatman No. 2) by decanting into another flask. Pipette 25×25 ml of the filtrate into two 100–150 ml Erlenmeyer flasks. Direct a stream of air for 5 min over the liquid surface in the first flask to remove any ammonia possibly present (a suitable device for this purpose is the evaporating flask shown in Fig. 103). Transfer 0·5 ml of acetic anhydride into the second flask. Titrate both solutions with 0·025 N perchloric acid in the presence of 1 drop of crystal violet.

Calculation:

$$\% \text{ of total alkaloids (as nicotine)} = \frac{V_1 \times N \times 32{\cdot}45}{\text{wt. of sample}}$$

$$\% \text{ of nicotine} = \frac{(2V_2 - V_1) \times N \times 32{\cdot}45}{\text{wt. of sample}}$$

$$\% \text{ of nornicotine} = \frac{(2V_1 - V_2) \times N \times 29{\cdot}64}{\text{wt. of sample}}$$

where V_1 = volume consumed to neutralize the non-acetylated solution (ml)
V_2 = volume consumed to neutralize the acetylated solution (ml)
N = normality of standard solution.

The reactivity of acetylatable amines towards acetic anhydride varies according to the substituent, possible steric hindrance etc. The relative order of possible acetylation of some amines in their 0·1 N solution in acetic acid with 1 M acetic anhydride, based on 90% conversion is as follows [612]: 2-naphthylamine, *p*-phenylenediamine, aniline, 2-t-butylamine (1 min); 2-methylaniline, 1-naphthylamine, N-methylaniline, 2,6-dimethylaniline (1–5 min); ethylenediamine, dibenzylamine, benzylamine (1–2 h); ethanolamine, piperidine, n-propylamine, n-butylamine, diethanolamine (2–6 h); isopropylamine (8–30 hours); di-n-butylamine, dimethylamine, di-n-propylamine (one week or even longer); di-isopropylamine.

The fact that ease of acetylation of individual bases extends over a wide range, given favourable circumstances, makes determination in a mixture practicable.

(b) *Determination of small amounts (0·01–0·02%) of tertiary amines in the presence of acetylatable amines* [690]. During acetylation with acetic anhydride, acid amides, formed with a majority of primary or secondary amines, though weak bases, still can prevent determination of a small amount of t-amine in acetic acid (or acetic acid–acetic anhydride): the colour change of the indicator becomes sluggish and the potentiometric curve is flattened.

Determination of a small amount of t-amine in the presence of a greater amount of acetylated amine can be performed with accuracy if the titration is carried out in Methyl Cellosolve as solvent with 0·01 N perchloric acid in Methyl Cellosolve instead of with acetic acid (acetic anhydride), which, to a certain degree, increases base strength of acid amides.

Methyl Cellosolve has proved to be more suitable than methanol, propan-2-ol, acetonitrile and glycols.

Depending on the strength of the base, 0·3% thymol blue in dimethylformamide or 0·1% Congo red in methanol can be used as indicator ($K = 10^{-4} - 10^{-7}$, or $10^{-8} - 10^{-10}$). In the presence of thymol blue: triethylamine ($K = 5{\cdot}7 \times 10^{-4}$), N,N-dimethylethanolamine ($1{\cdot}6 \times 10^{-5}$), N-ethylmorpholine ($3{\cdot}1 \times 10^{-7}$), and in the presence of Congo red: γ-picoline ($1{\cdot}1 \times 10^{-8}$) and dimethylaniline ($1{\cdot}6 \times 10^{-9}$) can be titrated.

Standard 0·01 N perchloric acid prepared with Methyl Cellosolve is decidedly more suitable than a solution prepared from the same solvent but containing hydrochloric acid. When the latter is used the potentiometric curve is levelled out and the change of thymol blue is more sluggish in proportion to the acyl amide present.

However, a disadvantage of this medium is that the basicity of some t-amines decreases: in the case of N-phenylpiperazine only the s-nitrogen atom is protonated ($K = 1 \times 10^{-6}$), and the t-N-atom cannot be titrated (1×10^{-12}). Thus, after acetylation the base character of N-phenylpiperazine vanishes in Methyl Cellosolve. Therefore, only those amines can be titrated whose base constant is not less than 10^{-10}.

Acetylation is an essential feature of Ruch and Critchfield's method. The reaction with a 10 : 2 mixture of Methyl Cellosolve–acetic anhydride is completed within 30 minutes. Acetylation in ethyl acetate, acetonitrile and chloroform requires only 15 minutes but for titration it must be diluted with some Methyl Cellosolve in a ratio of 1 : 3.

Accuracy of titration of t-amines is increased by acetic anhydride. Titration of pyridine, however, is less precise, because acetylpyridinium acetate is formed and this is a weaker base than pyridine itself.

The hydroxyl group of triethanolamine is acetylated within about 90 min: owing to the electron attracting property of acetoxy groups the basicity of the nitrogen atom decreases. This disturbing effect is smaller in the case of dimethylethanolamine because only one acetoxy group is formed. The method, however, is still suitable for determination of the triethanolamine content of impure monoethanolamine if acetylation lasts 30 min. A further field of application is the determination of the minimal triethylamine content of ethylamine or diethylamine, that of the tri-isopropylamine content of isopropylamine, the N-ethylmorpholine content of morpholine and the N,N-dimethylaniline content of aniline.

Weigh 5–7 g of sample to be tested (which, however, must not contain more than 0·5 m.eq. of t-amines), dissolve in 100 ml of Methyl Cellosolve and acetylate for 30 min by adding 20 ml of acetic anhydride. Titrate with 0·01 N perchloric acid in the presence of thymol blue or Congo red.

Relative error of determination of 0·01–0·2% t-amines is 80–100±5%.

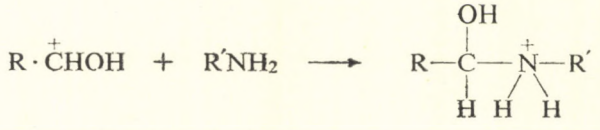
147. Photometric Titration of Primary Amines in the Presence of Secondary and Tertiary Amines

Primary aliphatic amines can be titrated with 0·1 M 2-ethylhexanaldehyde in dioxan even in the presence of s- and t-amines with acetic acid as catalyst [518]. Primary amines yield the corresponding imines. Optimum concentration of the catalyst is about 0·5 M (in dioxan solution). If less the reaction becomes slower, if higher than 0·5 M the amine becomes protonated and the following reactions are hindered [518]:

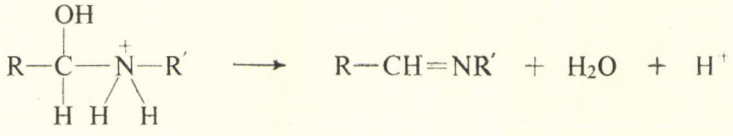
1. Addition of aldehyde proton:

$$R.CHO + H^+ \rightleftharpoons [R.CHOH]^+$$

2. Amine addition to the positive carbon of the protonated aldehyde:



3. Imine formation by dehydration:



Primary aliphatic amines cannot be determined in the presence of primary *aromatic* amines; though aromatic amines do not react with ethylhexanaldehyde to any considerable extent, the wavelength for the determination is 305 mμ and the intrinsic light absorption of the aromatic ring interferes. The addition of ethylhexanaldehyde after the end-point brings about considerable change in absorption at 305 mμ. The titrant is standardized against n-butylamine controlled by titration with perchloric acid. (For its preparation see Chapter 11; Section 60 (o).) Normality of a standard solutio n o

ethylhexanaldehyde is retained as long as it does not come in contact with atmospheric oxygen. It is advisable to fill the titrant-container with nitrogen. 50 ml quartz cuvettes are needed for the titration [570].

Dissolve the mixture, containing 0·15–0·45 M of aliphatic primary amines, in 100 ml of 0·5 M acetic acid in dioxan solution. Pipette precisely 1·00 ml of this stock solution into a quartz cuvette already containing 35 ml of a 0·5 M acetic acid solution in dioxan. Using monochromatic light of wavelength 305 mμ titrate with standard 0·1 N 2-ethylhexanaldehyde in dioxan. During measurement allow a stream of dry nitrogen to pass continuously through the solution; maximum absorption of 2-ethylhexanaldehyde is at 295 mμ. Here, however, residual absorption of the already-formed imine appears. The rate of formation of imine is not great but is increased by acetic acid. Acetates of n-butylamine, n-hexylamine, β-phenylethylamine, benzylamine and cyclohexylamine dissolve in dioxan. For the acetate of ethylenediamine, however, acetic acid in acetonitrile must be used instead of acetic acid in dioxan.

Accuracy by this method is ±0·6%.

148. Determination of Amine Mixtures by the Combined Method

(a) *Determination of aromatic amine mixtures* [750]. Tertiary amine is titrated after acetylation of primary and secondary amines (titration 1); total primary amine can be calculated by subtraction (titration 3 − titration 2); following reaction with salicylaldehyde only total of s- and t-amines are measured (second titration); s-amine can be calculated from the difference between the second and first titration. The third titration concerns the determination of the total base content.

Titration 1: weigh a 20 × 150 mm test tube containing a sample of about 0·02 M t-amines and embed in ice. Add 10 ml of acetic anhydride to the sample, carefully maintaining constant stirring and allow to stand for 15 min at room temperature. Transfer the contents of the tube by washing with 50 ml of ethylene glycol–isopropanol (1 : 1) into a titration beaker and titrate the tertiary amine potentiometrically with 1 N hydrochloric acid prepared with an identical solvent mixture.

$$\text{Moles of t-amine in 1 gram of sample:} \frac{\text{HCl ml} \times \text{N}}{\text{weighed grams} \times 1{,}000}$$

Titration 2: Dissolve a sample containing approx. 0·02 M of s- + t-amines in 50 ml of the above solvent mixture, add 5 ml of salicylaldehyde and allow to stand for 30 min, then titrate potentiometrically. Calculate secondary + tertiary amines in 1 g of sample as above.

Titration 3: Titrate a sample of about 0·02 M total amine content potentiometrically in 50 ml of solvent mixture. Calculate total amine content in one gram of sample as in Titration 1.

Calculation:

$$\text{M primary amine/g} = \frac{\text{M total amine}}{\text{g}} - \frac{\text{M secondary + M tertiary amine}}{\text{g}};$$

$$\text{M secondary amine/g} = \frac{\text{M secondary + M tertiary amine}}{\text{g}} - \frac{\text{M tertiary amine}}{\text{g}};$$

$$\text{M tertiary amine/g} = \text{see Titration 1.}$$

Gribova and Levin [290] have titrated aniline, hexylamine and dicyclohexylamine in the presence of one another. Resolving this mixture requires two titrations. When the titration is carried out in acetone solution with 0·1 N perchloric acid in dioxan using a glass–calomel electrode system, two potential jumps can be observed. The first indicates the common neutralization equivalent of cyclohexylamine and dicyclohexylamine, while the second is characteristic of the aniline. The second titration is preceded by a reaction with salicylaldehyde and now again two inflections appear, the first indicating dicyclohexylamine, and the second signal the common equivalence point of cyclohexylamine and aniline-salicylaldimine.

Bournique and Neuser [78] titrate the ternary mixture of butylamine–N-methylaniline–N,N-dimethylaniline in diethylene glycol–isopropanol. The first inflection indicates butylamine, while the second is the equivalence point of the two aromatic bases. After acetylation, only N,N-dimethylaniline is titrated.

(b) *Titration in ternary solvent mixture* [401].

Analysis of most amine mixtures can be dealt with by appropriately combining titration in a differentiating solvent, acetylation and Schiff-base formation. The pK difference between aliphatic and aromatic amines is on the average 5 units. Potentiometric differentiating titration can be performed in a slightly acidic, but at the same time, highly polar solvent, e.g. acetonitrile, nitromethane, or nitrobenzene. A suitable solvent mixture is acetic acid–dioxan–nitromethane (5 : 75 : 20) with 0·1 N perchloric acid in dioxan as titrant. Thus, e.g. a 6 component mixture can be determined with three titrations. By titrating part of a mixture of butylamine–dibutylamine–trimethylamine–aniline–methylaniline–pyridine in acetic acid with perchloric acid the total amine content is obtained (first titration). The second titration is carried out with acetic anhydride after acetylation, when only aliphatic and aromatic tertiary amines are titrated. The third titration is performed potentiometrically following reaction with salicylaldehyde. The first inflection indicates the end-point of s- + t-aliphatic amines, i.e. that of the stronger bases. At the second inflection s- + t-aromatic amines and Schiff-base of primary aliphatic amines are titrated. The third inflection indicates equivalence point for the weakest bases, .e. that of the Schiff-base of primary aromatic amines.

149. Distillation Methods

(a) *Separation of nitrogenous bases by superheated vapour distillation* [301, 315]. In a favourable case volatile bases can be separated from relatively less or non-volatile bases with superheated solvent vapour, e.g. that of benzene or chloroform.

The relative, empirical order of volatility of bases by distillation with a superheated stream of solvent, after evaporation of 5 ml of chloroform stock solution is as follows (in brackets, the quantity of benzene vapour necessary for distillation of 90% of the volatile base, expressed in ml of condensed benzene, and the boiling point of the base; [315] and unpublished data): propylamine (0·7; 49°C), butylamine (1·8; 77·8°C), dibutylamine (15; 159°C), tributylamine (73; 216·5°C), cyclohexylamine (6; 134°C), dicyclohexylamine (19; 247°C), piperidine (4·4; 106·4°C), N-(2-hydroxyethyl)-piperidine (7; 200–202°C), piperazine (10; 145–146°C), N-(2-hydroxyethyl)-piperazine (110; 242–244°C), pyridine (3; 115·5°C), 2-methylpyridine (4·4; 128·8°C), 2-aminopyridine (7·8; 204°C), aniline (6; 184·4°C), N-methylaniline (7·4; 196·3°C), *p*-toluidine (8·7; 200·6°C), benzylamine (6·0; 184–185C°), N-methylbenzylamine (6·5; 180–181°C), 4-methylbenzylamine (9·6; 194–196°C), morpholine (4·2; 129°C), N-(2-hydroxyethyl)-morpholine (12·4; 220–222°C), ethanolamine (2; 171°C), butanolamine (11; 206°C), diethanolamine (83; 272°C). Slightly volatile bases are e.g. N-piperidinomethyltolylpropanone [314], triethanolamine and bis-hydroxyethyl-piperazine (the quantity distilled changes linearly with the quantity of benzene distilled). In practice, atropine base, tribenzylamine and N-(2-pyridyl)-N-(*p*-chlorobenzyl)-N′,N′-dimethylethylenediamine are non-volatile.

Many bases with a boiling point between 100 and 280°C can be distilled with benzene vapour at about 95°C. Bases of a higher boiling point are less or non-volatile. For this determination the apparatus shown in Fig. 122 is suitable. With this method

tribenzylamine, for example, can be determined in the presence of benzylamine; piperidinomethyltolylpropanone after distillation of N-methylpiperidine, piperidine and N-hydroxyethylpiperidine impurities; 21-desoxy-21-N-(N′-methylpiperazinyl)-prednisolone, in the presence of N-methylpiperazine; and finally atropine base in a mixture of various volatile co-alkaloids.

Weigh a mixture equivalent to approx. 5×10^{-2} mM of monofunctional bases in a titration flask (Fig. 122) and dissolve in 3 to 5 ml of chloroform. In the case of a stock solution pipette 3–5 ml into the flask. Distil chloroform on steam bath

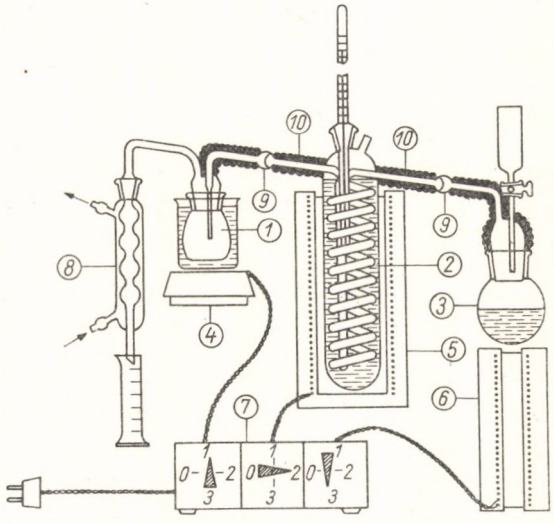


Fig. 122. Apparatus for distillation using superheated solvent vapour, due to Gyenes [315]. — *(1)* Titration flask in water bath, *(2)* Oil bath at 185 ± 2°C, *(3)* 200–250 ml flask with ground joints serving as solvent vapour developer, *(4)*, *(5)* and *(6)* Controllable electric heaters, *(7)* Electric mains, switching table, *(8)* Condenser, *(9)* Spherical ground joints, *(10)* Asbestos band insulation

while the temperature of the superheater is kept at 185±2°C. After concentration of the chloroform solution, bring the benzene, previously heated in the solvent vapour developer to boiling point, and allow its vapours to pass through the spiral of the superheater. Control with a graduated cylinder the quantity of solvent flowing through the apparatus; this is generally 100–120 ml. It is advisable to decide the convenient quantity by model tests previously. Following distillation by superheated solvent vapour remove the titration flask from the steam bath, chill, add 5 ml of neutralized acetic acid and titrate the non-volatilized base with 0·01 N perchloric acid. A 0·1 % solution of crystal violet serves as indicator. If the remainder is dissolved in chloroform or carbon tetrachloride, the remaining base (e.g. atropine) can be titrated also with 0·005 N *p*-toluenesulphonic acid, in the presence of dimethyl yellow, to a pink colour change.

Sometimes, a linear relation exists between the volatility of the less volatile base and the quantity of benzene vapour passed through (as condensate, expressed in ml). In this case a mixture of volatile and less volatile bases can be resolved if the quantity of less volatile base proportional to the distilled benzene is applied as a correction.

(b) *Determination of volatile bases in choline salts* [166]. The converse of the former method (a) can be employed for the determination of trimethylamine impurity in choline chloride, gluconate, dihydrogen citrate and hydrogen carbonate: the volatile base is driven out of the system with air, collected in acetic acid and titrated with perchloric acid. Suitable apparatus is shown in Fig. 123.

Weigh 50 ml of 40 to 70% aqueous choline salt solution and transfer to vessel (1). Add 50 ml of about 30% (w/v) of sodium hydroxide. Transfer 50 ml of acetic acid (neutralized in the presence of crystal violet) to an Erlenmeyer flask (2) and 10 ml in test tube (3). Let a stream of washed air pass through the apparatus for 75 min so that bubbles constantly arise in the basified choline salt solution. Now combine acet-

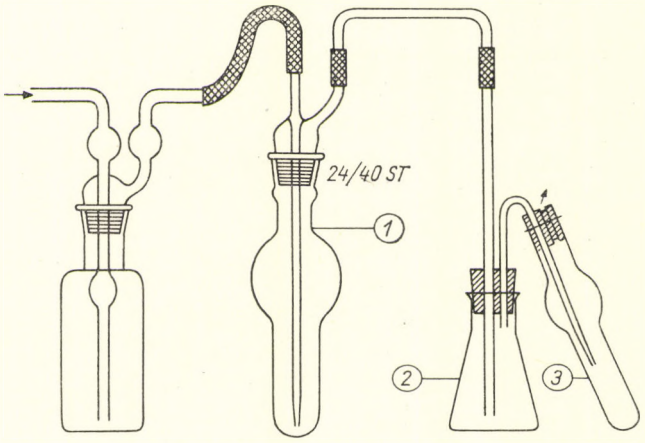


Fig. 123. Equipment for the determination of the trimethylamine content of choline salts according to Cundiff and Markunas [166]. — Signs and abbreviations in text

ic acid from vessels (2) and (3), add 15 ml of acetic anhydride, boil for 5 min in a fume cupboard and, after cooling, titrate with 0·1 N perchloric acid in acetic acid in the presence of crystal violet. 5·9 mg of trimethylamine require 1 ml of 0·1 N perchloric acid.

Regarding determination of choline salts of carboxylic acids see: [549].

For determination of piperazine, hydroxyethylpiperazine and bishydroxyethylpiperazine in one mixture see: Chapter 23; Section 123 (c).

For determination of hydrazine and *as*-dimethylhydrazine in one mixture see: Chapter 23; Section 133 (c).

For the determination of a mixture of compounds containing amino groups, based on differences in rate of reaction see: [347] (cf. Chapter 19; Section 113).

150. Determination of Hydrochlorides of Tertiary Amines in the Presence of Hydrochlorides of Acetylatable Amines [310, 312, 707]

It is known that tertiary amines can be titrated in the presence of acetylatable amines in acetic acid–acetic anhydride. It was stated before that hydrochlorides of primary, secondary and tertiary amines can be titrated separately if mercury(II) acetate is added to their solution in acetic acid. By combining these two procedures the hydrochlorides of tertiary amines can be titrated in a mixture with hydrochlorides of acetylatable amines. The acetylating agent is a mixture of acetic anhydride and a solution of mercury(II) acetate in acetic acid, viz. conversion of amine hydrochloride to base acetate takes place at the beginning of acetylation in the same reagent mixture.

Weigh from sample or stock solution an amount giving a titration of 6–8 ml perchloric acid of 0·05 N or 0·01 N concentration. Add, in an Erlenmeyer flask, sufficient acetylating agent to 5–10 ml of the sample or stock solution to give a total volume of 20–30 ml containing 40–80% acetic anhydride while the quantity of mercury(II) acetate, depending on the sample, should be 200–300 or 40–60 mg. Moisten the ground part of the flask with acetic anhydride. Acetylation is carried out at room temperature in 60–180 min. Subsequently titrate with 0·05 N or 0·01 N perchloric acid in the presence of 1 drop of 1% (or 2 drops of 0·2%) crystal violet till the violet colour of the indicator turns to blue. In every case correct for consumption of acetylating mixture.

Concerning anhydride content of the acetylating mixture and duration of acetylation, it is sufficient if the dissociation constant (in water) of the acetylatable amine is known, to acetylate as follows:

Dissociation Constant of the Base	*Anhydride Content of Acetylating Mixture*	*Time* min.
10^{-3}	40–80	180
10^{-4}	60	100
10^{-5}	40	80
10^{-6}	40	60

If the quantity of accompanying acetylatable amine exceeds 10% of the amine mixture then the latter, after acetylation, is diluted with acetic acid to 40% concentration and titrated with perchloric acid in the presence of 5 drops of 0·5% cresol red instead of crystal violet until change of indicator from yellow to red.

Accuracy of determination is influenced by the following: dissociation constant of acetylatable amine (measured in water), readiness of the acid amide formed to bind perchloric acid, ratio of molar concentration of tertiary and acetylatable amines, acetic anhydride content of the mixture and choice of indicator.

In a mixture of acetic acid–acetic anhydride at room temperature those amines whose dissociation constant measured in water are small can be acetylated with higher efficiency. The quantitative result of acetylation of amines of stronger basicity is lower (titrated in presence of cresol red): benzylamine 100%, ethylamine 97–98%, piperidine 97% and diethylamine 95%. This may be ascribed to the fact that amines are dissolved in acetic acid partly as 'onium salts, partly as amine-acetic acid solvates. The more basic the amine the more 'onium salt is formed (R_3NH^+) which, as donor acid, does not enter into interaction with the acetyl cation present in the acetylating mixture (CH_3CO^+ is acceptor acid) but readily with amine—acetic acid solvate ($R_3N\ldots CH_3COOH$) which is a donor base.

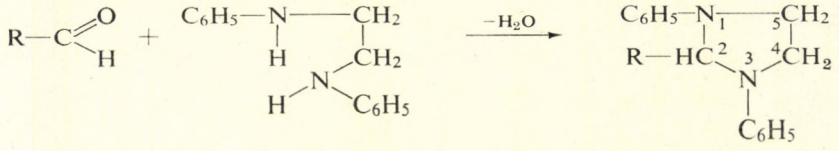
By this method the following can be determined: e.g. diethylaminoethyl chloride, hydrochloride in the presence of ethylamine or diethylamine hydrochloride, tribenzylamine hydrochloride in the presence of benzylamine hydrochloride, and piperidinomethylcyclohexanone hydrochloride in the presence of piperidine hydrochloride etc.

Chapter 26

Determination of Carbonyl Groups

151. Identification of Aldehydes and Ketones

(a) *Identification of aldehydes as imidazolidine derivatives* [842]. Compounds containing an aldehyde group form, with bis-phenylamino-1,2-ethane, 1,3-diphenyl-2-alkyl-(or aryl)-imidazolidine derivatives [859].

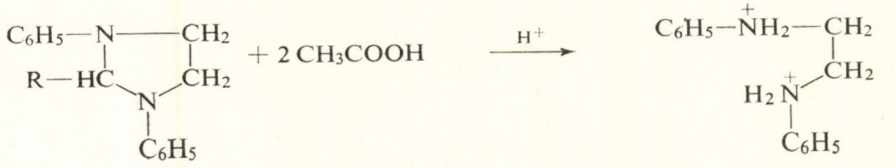


The imidazolidine derivatives can be titrated in acetic acid with 0·1 N perchloric acid either potentiometrically or by visual indicator; thus, it is possible to identify compounds containing an aldehyde group by determining the molecular weight of the condensation product formed. The molecular weight of the aldehyde can be calculated if 194·3 is subtracted from twice the equivalent weight found for the titrated imidazolidine, e.g.

2-methyl derivative, mol. wt. 238·3–194·3 = 44·0 (acetaldehyde)
2-ethyl derivative, mol. wt. 252·4–194·2 = 58·1 (propionaldehyde)
2-propyl derivative mol. wt. 266·4–194·2 = 72·1 (butyraldehyde) etc.

Weigh 200–300 mg of aldehyde, dissolve in 5 ml methanol, mix with 10 ml 5% bis-phenylamino-ethane in methanol solution and add aqueous 50% acetic acid drop by drop: the imidazolidine derivative generally separates in crystalline form. (If it does not, boil under reflux for five minutes.) Dissolve approximately 0·05 mM of the dried product in 20–25 ml of acetic acid and titrate either potentiometrically or with 0·1 N perchloric acid in acetic acid in the presence of crystal violet. Two equivalents of the titrant are consumed. According to studies by Veibel and Krogh Andersen, on adding perchloric acid, bis-phenylamino-1,2-ethane diperchlorate is formed; therefore, imidazolidine derivatives of some aldehydes (furfural, thiophen

aldehyde), cannot be titrated because coloured decomposition products are formed (this does not take place in the case of bis-(*p*-methoxybenzyl)-imidazolidine derivatives):



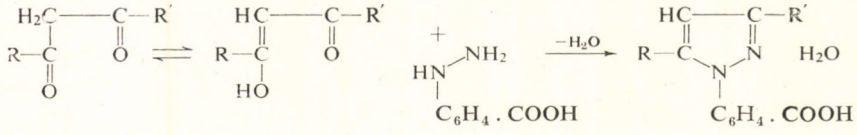
$+ RCH(OCOCH_3)_2$

Aldehyde diacetal

In the case of derivatives of imidazolidine from pyridyl aldehydes three equivalents of perchloric acid are consumed. The determination becomes less accurate the lower the molecular weight of the aldehyde.

Identification of aldehydes (and ketones) can be achieved also by reaction with 2,4-dinitrophenylhydrazine and subsequent titration of the hydrazone formed with standard TBAH in pyridine (Chapter 20).

(b) *Identification of β-diketones* [844]: β-diketones, when reacted with *p*-carboxyphenylhydrazine, form pyrazole derivatives, crystallizing with 1 mole of water, instead of hydrazones. The initial condensation product formed from benzoylacetone, dibenzoylmethane or acetylacetone, when recrystallized from aqueous ethanol yields the carboxyphenylhydrazone, which can be titrated as acid. But when dried in vacuum over phosphorus pentoxide, at 56°C, the pyrazole derivative is re-formed and thus the conclusion may be drawn that during drying ring closure takes place, and during recrystallization opening of the ring occurs. The pyrazole derivative can be estimated as a base with perchloric acid [838, 844]:



Aromatic α-diketones give rise to mono-*p*-carboxyphenylhydrazones and γ-diketones give dihydropyridazine derivatives. Both can be titrated as acids [838, 845].

152. Determination of Carbonyl Groups

A well-known method for the determination of compounds containing aldehyde or keto groups is founded on oxime formation with hydroxylamine, or on hydrazone formation by hydrazine derivatives. Colour change of the indicator is sharper in non-aqueous than in aqueous media. In the course of oxime formation in aqueous media hydrochloric acid and water are liberated:

$$R.CHO + NH_2OH.HCl \rightleftharpoons R.CH=NOH + H_2O + HCl$$

The reaction is carried out in the presence of base (e.g. pyridine, octadecenylamine, morpholine, n-tributylamine, etc.) since these bind hydrochloric acid.

Metcalfe and Schmitz apply octadecenylamine in methanol–isopropanol [574], Fritz and co-workers 2-dimethylaminoethanol in isopropanol [259] and Gyenes likewise tri-n-butylamine in methanol–isopropanol [314]. By using t-amine, the formation of Schiff base is eliminated. *Owing to the danger of acetal and ketal formation the correct order of mixing of reagents must be observed.* The scheme of reaction is as follows:

1. Formation of free hydroxylamine base:

$$(NH_3OH)^+Cl^- + B \rightarrow BH^+Cl^- + NH_2OH$$

where B is, e.g. tributylamine.

2. Oxime formation:

$$NH_2OH + \diagup C = O \rightleftharpoons \diagup C = NOH + H_2O$$

3. Titration of the hydroxylamine left in excess:

$$NH_2OH + H^+ \rightarrow (NH_3OH)^+$$

(a) *Determination of aldehydes with* as-*dimethylhydrazine* [752]. Aldehydes form hydrazones with *as*-dimethylhydrazine $(CH_3)_2N-NH_2$. Excess of reagent can be back-titrated potentiometrically with hydrochloric acid in methanol.

For the determination of aliphatic aldehydes weigh of the compound 0·002 M, and 0·01 M for aromatic aldehydes, and dissolve in 25·0 ml of dimethylhydrazine reagent. Depending on the reactivity of the aldehyde, allow the solution to stand for a time. Subsequently add 50 ml of methanol and, using glass-calomel electrodes, titrate potentiometrically in methanol with either 0·1 N or 0·5 N hydrochloric acid, depending on whether 0·2 M or 1·0 M dimethylhydrazine reagent was used.

DIMETHYLHYDRAZINE REAGENT (MOL WT. 60·10: SP. GR. AT 22°C 0·791)

Aldehyde	*Solvent*	*Molar Concentration*
Aliphatic	Ethylene glycol	0·2
Aromatic	Ethylene glycol	1·0
Disubstituted benzaldehyde	Methanol	1·0

$$\textit{Calculation: } \% \text{ of aldehyde} = \frac{(b - a) \times N \times E}{g}$$

where b = ml found for the blank test
a = ml consumed for titration
N = normality of standard solution
E = one tenth of equivalent weight of the compound
g = sample wt. in grams

The following compounds can be titrated with 0·3–0·8% accuracy (in brackets, reaction time in minutes): formaldehyde, acetaldehyde, propionaldehyde, butyraldehyde (15); cinnamaldehyde, crotonaldehyde, salicylaldehyde (30); anisaldehyde, benzaldehyde, *m*-nitrobenzaldehyde, 2,6-dichlorobenzaldehyde and 2,4-dimethoxybenzaldehyde (120).

Aromatic aldehydes can be determined in the presence of ketones but aliphatic aldehydes cannot.

(b) *Determination of aldehydes and ketones by the hydroxylamine method* [259] (Table 37). Weigh in a 150–200 ml glass-stoppered Erlenmeyer flask a sample of compound containing 1·5–2·5 mM of carbonyl group, add precisely 20·0 ml of 0·25 M 2-dimethylaminoethanol solution, and subsequently precisely 25·0 ml of 0·4 M hydroxylamine hydrochloride solution. Mix the contents and allow the stoppered flask to stand (see: table below). After the necessary waiting time add five drops of indicator mixture and titrate with perchloric acid from yellow to colourless or blue-grey. The calculation is the same as that given above.

Reagents:

Prepare *dimethylaminoethanol solution* by diluting 22·5 g of freshly distilled base with isopropanol to 1 litre;

Prepare *hydroxylamine hydrochloride solution* by dissolving 27·8 g of NH_2OH . HCl in 300 ml of purified methanol and diluting with purified isopropanol to 1 litre;

Prepare *indicator mixture* by dissolving 67 mg of Martius yellow (2,4-dinitro-1-naphthol) and 4 mg of methyl violet in 50 ml ethanol. For preparation of the standard solution see: Chapter 11; Section 60 (e).

The compounds which can be determined with 0·1–0·3% margin of error are listed in Table 37.

(c) *Determination of piperidinomethyltolylpropanone hydrochloride* [314]. The hydroxylamine method can be used for the determination of carbonyl group when

Table 37

DETERMINATION OF ALDEHYDES AND KETONES BY THE HYDROXYLAMINE METHOD [259]

Carbonyl Compound	*Reaction Time and Temperature*		Mol wt.
	min.	°C	
Acetophenone	45–60	70	120·14
Benzaldehyde	20	Room temp.	106·1
Benzoin	180	70	212·2
Butyraldehyde	20	Room temp.	216·3
Cyclohexanone	30	,, ,,	98·1
Dibenzyl ketone	30	,, ,,	210·3
Furfural	20	,, ,,	96·08
Methyl isobutyl ketone	30	,, ,,	100·2
p-Nitrobenzaldehyde	20	,, ,,	151·1
p-Hydroxybenzaldehyde	5–15	,, ,,	122·1
Salicylaldehyde	5–15	,, ,,	122·1
Vanillin	5–15	,, ,,	152·1

2 mM of aldehyde require 1 ml of 0-2 N perchloric acid

the compound contains a t-amino group, present as a salt. Weigh 130–150 or 260–300 mg of sample in a 200 ml glass-stoppered Erlenmeyer flask and dissolve in 10 or 20 ml approx. 0·1 M n-tributylamine. Add 10 or 20 ml of hydroxylamine hydrochloride solution of about 0·1 M. Prepare these reagents in methanol–isopropanol (35 : 65). Place a strip of filter paper between ground flask and stopper, then close the flask and put it for 5 to 10 min on a steam bath at 71–73°C. Decrease temperature to 69–70°C and after removing strip of filter paper seal the flask hermetically. Maintain this temperature for 50–55 min, then allow to cool to room temperature. Titrate the solution with 0·1 N hydrochloric acid in propylene glycol–chloroform (Chapter 9; Section 51 (a)). *Indicator:* a solution of 0·5 g dimethylaminoazobenzene and 0·05 g methylene blue in 60 ml methanol. Add 3 drops to 20 ml of the reaction mixture and 5 drops of indicator to 40 ml. For the blank test perform three simultaneous titrations with 10 or 20 ml of hydroxylamine reagent in tributylamine. Calculation is identical with that of above methods. 28·18 mg of hydrochloride salt of 1-piperidino-2-methyl-3-*p*-tolyl-propanone-3 require 1 ml of 0·1 N hydrochloric acid.

(d) *Macro and semimicro determination of aldehydes and ketones with hydroxylamine formate* [691]. For determination with hydroxylamine acetate see: [384].

An advantage of the hydroxylamine formate method in comparison with other similar methods is that 0·003–0·3% of aldehyde or ketone can be determined with ±5% accuracy. Results obtained are reliable even if organic acids, acetates, ketals and vinyl ethers are present (these are easily hydrolyzed in acetic acid). Formic acid in methanol is neutral to thymol blue and excess of hydroxylamine can be titrated with perchloric acid in dioxan [641]. It is probable that in the latter peroxides and compounds containing carboxyl groups are formed affecting the result of titration. Ruch, Johnson and Critchfield [691] use Methyl Cellosolve as solvent because methanol has a less differentiating effect. Instead of perchloric acid, these authors suggest a standard solution containing nitric acid prepared with Methyl Cellosolve because its solution is stable and does not hydrolyze acetals and ketals (for *preparation* see: Chapter 11; Section 60 (f)). *Standardization:* dissolve 1·5 g of tris(hydroxymethyl)aminomethane in 50 ml of boiling absolute methanol, dilute with 100 ml propylene glycol and titrate in the presence of 0·3% thymol blue in dimethylformamide from yellow to a distinct orange colour. 60·51 mg of tris(hydroxymethyl)aminomethane requires 1 ml of 0·5 N nitric acid in Methyl Cellosolve.

For determinations on a semimicro scale dilute the reagents used for the macro process with aldehyde-free methanol (Chapter 8; Section 49 (a)).

Preparation of 0·5 N hydroxylamine formate in Methyl Cellosolve: transfer 32 g of KOH to 350 ml of fresh Methyl Cellosolve; stimulate solution by adding 20 ml of 90% formic acid, neutralize in the presence of phenolphthalein, then basify again with 2–3 pea-sized grains of KOH and cool to 15°C. Dissolve 34 g of hydroxylamine hydrochloride in 650 ml of Methyl Cellosolve, cool to 15°C and mix with the former solution. Filter off the precipitated KCl. The solution is stable for two weeks.

Pipette precisely 5·0 ml of 0·1 N hydroxylamine formate into a 100–200 ml glass-stoppered Erlenmeyer flask and dissolve in it a sample containing max. 0·4 m.eq. of CO group. A blank is run in the same way. Allow the stoppered flask containing formaldehyde to stand at room temperature for 4 hours; that containing butyraldehyde and glyoxal for 30 min; waiting time for 2-ethylbutyraldehyde is 90 min, while for acetone 15 min are sufficient. After waiting, titrate with 0·02 N nitric acid in the presence of 3 drops of thymol blue till yellow turns to orange. It is advisable

to titrate the blank test first, and subsequently the compound to be estimated to the same tint. Calculate by the difference between the two measurements. Prepare standard solution 0·02 N nitric acid as well as reagent 0·1 N hydroxylamine formate from reagents of higher concentration with absolute methanol, free of aldehyde. Prior to determination, rinse flasks with pure solvent and dry them.

In the case of macro determinations (e.g. for titrations of individual compounds) the accuracy of the method is about $\pm 0{\cdot}2\%$. The margin of error is greater for semimicro titrations, but it is still adequate as, for example, 0·09% aldehyde impurity in vinyl ether could be measured with 98·5% accuracy (due to the volatility of vinyl organic ethers and acetaldehyde the reaction is performed at $-10°C$).

Acids whose ionisation constants are greater than 10^{-2}, as well as bases, salts of acids and anhydrides, have a disturbing effect.

It is advisable to determine the most suitable reaction time and concentration of reagents by model tests. If 0·02 N hydroxylamine formate is employed, isopropanol or benzene may occasionally prove to be more suitable solvents because they increase the speed of reaction.

For the macro method use 50 ml of 0·5 N hydroxylamine formate and dissolve in it a sample containing not more than 15 m.eq. of CO group. After reaction dilute with 125 ml of solvent mixture methanol–Methyl Cellosolve (50 : 75) and titrate with 0·5 N nitric acid in the presence of 5–6 drops of thymol blue.

For volatile compounds a part of the stock solution prepared with Methyl Cellosolve is weighed as sample.

DETERMINATION OF ALDEHYDES AND KETONES WITH HYDROXYLAMINE [691]

Carbonyl compound	mg *of Compound Equivalent to 1* ml *of Standard Solution*	
	0·02 N	0·5 N
Acetone	1·16	29·04
Formaldehyde	0·60	15.01
Glyoxal	1·16	29·04
Butyraldehyde	1·44	36·05
2-Ethylbutyraldehyde	2·00	50·08
Ethyl butyl ketone		57·09
Methyl ethyl ketone		36·05
Methyl isobutyl ketone		50·08

(e) *Determination of steroid ketones by means of the hydroxylammonium salicylate method* [284]. Steroid ketones can be classed with the less reactive ketones; their oximation, therefore, requires a longer time and higher temperature. Hence, it is recommended to employ for their determination hydroxylammonium salicylate which is more stable than either hydroxylammonium acetate or hydroxylammonium formate. A 0·1 N solution of hydroxylammonium salicylate in a solvent mixture of chloroform-methanol suffers, after boiling for three hours, only 0·7% decrease of activity. When stored at room temperature, the solution can be used for a month.

Weigh out into a 50-ml ground glass flask about 0·3 m.eq. of the sample; dissolve in 0·1 N hydroxylammonium salicylate reagent that has been prepared with precisely 10 ml chloroform-methanol (2 : 1) solvent mixture, and reflux for two hours on a steam bath. Let the mixture cool, then titrate with 0·05 N hydrochloric acid in propylene glycol-chloroform after adding one drop of dimethyl yellow-methylene blue indicator mixture. The colour of the solution changes from green to red while at the end-point a brown colour appears.

A blank is run in a similar way, in the absence of the steroid ketone. The difference between the two titrations is the measure of the ketosteroid content.

By this method, not too sterically hindered steroids containing isolated carbonyl groups as well as *cis*-enones can be determinated with $\pm 1{\cdot}5\%$ accuracy, such as oestrone, dehydro-*epi*-androsterone, pregnene-3β-ol-5,20-dione, triketocholanic acid.

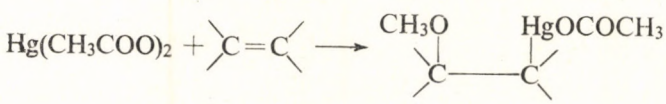
Preparation of hydroxylammonium salicylate: dissolve 40 g of sodium salicylate in 75 ml of water by gentle heating; add a solution of 17·4 g of hydroxylamine hydrochloride in 75 ml of water, and allow the mixture to stand overnight at 0°C. Filter the precipitate and wash with 20 ml of ice-cold distilled water. Dry for three hours *in vacuo* at 80°C.

Chapter 27

Determination of Multiple Bonds. Application of Mercury(II) Acetate Reagent. Application of Bromine in Acetic Acid or 0·1 N Hydrogen Bromide in Acetic Acid

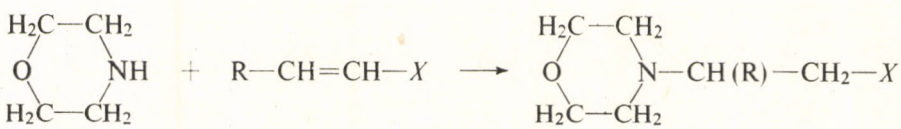
153. Internal Double Bond in Terminal or *cis*-Positions

Three methods will be described. One (a) is based on the addition of mercury(II) acetate in methanol [169, 885]; other (b) on the reaction of morpholine with α, β-unsaturated compounds, when t-amines are formed [154]. The third method (c) is similar to the morpholine process; however, instead of morpholine, hexamethylene-imine is allowed to react with the compound containing a double bond (e.g. methyl acrylate [800]).



$$Hg(CH_3COO)_2 + \rangle C{=}C\langle \longrightarrow \begin{matrix} CH_3O & & HgOCOCH_3 \\ \diagdown & & \diagup \\ & C\text{———}C & \end{matrix} + CH_3COOH \quad (153.1)$$

Reaction takes place rapidly in methanol, but slowly in water*. Mercury(II) acetate can be titrated precisely by Palit's method [621].



$$\begin{matrix} H_2C\text{—}CH_2 \\ O \quad\quad NH \\ H_2C\text{—}CH_2 \end{matrix} + R\text{—}CH{=}CH\text{—}X \longrightarrow \begin{matrix} H_2C\text{—}CH_2 \\ O \quad\quad N\text{—}CH(R)\text{—}CH_2\text{—}X \\ H_2C\text{—}CH_2 \end{matrix}$$

where X = a strong electron-attracting group. (153.2)

$$CH_2 = CH.\,COOCH_3 + HN(CH_2)_6 \rightarrow (CH_2)_6N.\,CH_2CH_2.\,COOCH_3 \quad (153.3)$$

* Wright, G. F., *J. Am. Chem. Soc.* **62**, 1993 (1935) and [885].

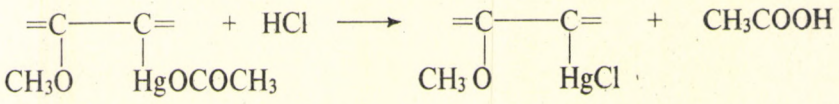
(a) Two variants of the *mercury(II) acetate method* are known. According to the first, the excess of mercury(II) acetate is back-titrated, while in the second the acetic acid formed is titrated.

1. Weigh about 2 mM of unsaturated compound in a glass-stoppered Erlenmeyer flask; add 20–25 ml of approx. 0·25 N mercury(II) acetate in methanol and allow the stoppered solution to stand for 10–30 min at 30°C. Prepare the reagent by dissolving 20 g of $Hg(CH_3COO)_2$ in a mixture of 500 ml of methanol and 1 ml of acetic acid and filter the solution before use.

After reaction is complete dilute the reaction mixture with 25 ml propylene glycol–chloroform (1:1) and using this solvent mixture for the preparation of 0·1 N hydrogen chloride; titrate with the latter in the presence of thymol blue. Colour change occurs from yellow to pink. A blank is run in the same way.

During titration mercury(II) acetate in excess consumes two equivalents of hydrogen chloride; furthermore the additive compound of mercury also consumes one equivalent [169 and 536]:

$$Hg(CH_3COO)_2 + 2\,HCl = HgCl_2 + 2\,CH_3COOH;$$



Thus, the difference between m.eq. of mercury(II) acetate employed and m.eq. of hydrogen chloride consumed expresses the quantity of unsaturated double bonds in mM.

$$\text{Unsaturated compound} \quad g = \frac{(b - a) \times N \times M}{1{,}000}$$

where b = 0·1 N hydrogen chloride consumed for the blank test (in ml)
N = normality of the standard solution
M = mol. wt. of sample, (in g)
a = standard solution consumed for titration.

Styrene, cyclohexene, allyl alcohol, allyl acetate, vinyl acetate etc. can be determined by this method [169]. For the determination of methyl and ethyl methacrylates a 0·1 M solution of mercury(II) acetate in methanol containing 0·01 M $HClO_4$ as catalyst is suitable [536]. Concerning the determination of 3-chloropropene see: [535].

2. Another variant of the mercury(II) acetate method is as follows [430]: pipette 50 ml of 0·12 M mercury(II) acetate in methanol into a 250 ml glass-stoppered flask and dissolve in it a sample containing 3–4 m.eq. of double bond. Allow the stoppered flask to stand; run a blank in the same way. After an interval (waiting time) add to the flask 2–4 g of NaBr and mix till dissolved. Mercury(II) acetate is converted to mercury(II) bromide, and after adding 1 ml of 1% phenolphthalein in methanol as indicator the liberated acetic acid is titrated with 0·1 N sodium hydroxide in methanol to a red colour. The difference of blank and titration in ml is proportional to the double bond content of the weighed sample. In the case of vinyl ethers chill the reaction mixture to −10°C. During titration the temperature should not rise above 15°C.

According to method 2, e.g. allyl alcohol (1), allyl acetate (60), cyclohexene (1), dichlorostyrene (120), N-vinylpyrrolidone (10), etc. can be determined (minutes of waiting time in brackets).

(b) *Morpholine method* [154]. Weigh a max. 20 m.eq. of unsaturated compound in a 250 ml glass-stoppered Erlenmeyer flask and add 10 ml of morpholine and 7 ml of aqueous 50% acetic acid with a graduated pipette. Allow the stoppered mixture to stand at room temperature (see: Table below), then add 50 ml of acetonitrile and 20 ml of acetic anhydride with constant stirring. When constant temperature is reached titrate with 0·5 N hydrochloric acid in methanol in the presence of 5–6 drops of methyl orange–xylene cyanol FF indicator solution to disappearance of the green colour. A blank test is carried out in the same way. *Preparation of the indicator:* dissolve 150 mg of methyl orange and 80 mg of xylene cyanol FF in 100 ml water.

During determination the t-amine, originating from morpholine and the compound containing double bond, is titrated, while morpholine in excess, owing to the effect of acetic anhydride, is converted to acid amide. The blank test consumes hardly any standard solution, because morpholine which does not give rise to t-amine is converted to N-acetylmorpholine. The basicity of the latter in acetic anhydride–acetonitrile is very low.

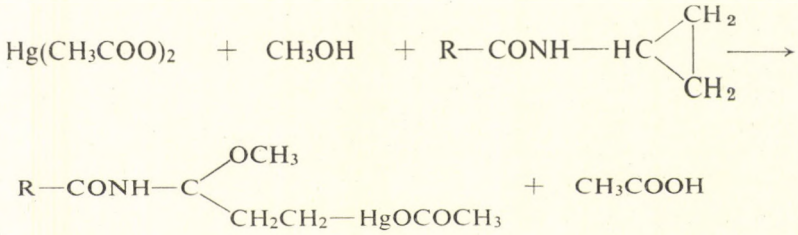
This method can be employed for acrylic derivatives:

Compound	*Time of Reaction in* min	*Temperature* °C	Mol. wt.	*Co-solvent*
Acrylamide	5–120	25	71·08	
Acrylic acid	15–120	98	72·06	+ 10 ml CH_3OH
Acrylonitrile	5– 60	25	53·06	
Methyl acrylate	5– 60	25	86·09	
Ethyl acrylate	5– 60	25	100·1	
Diethyl malonate	30– 90	25	160·2	40 ml Methanol + 2 ml 50% acetic acid

(c) *The hexamethylene-imine method* [800]. Prepare from the methyl acrylate sample a stock solution in methanol. A 5 ml portion of the stock solution is transferred with a pipette into a glass-stoppered flask. This sample must not contain more than 0·5 m. eq. of methyl acrylate. Now add 5 ml of a 1% hexamethylene-imine solution in dioxan and 0·2 ml acetic acid catalyst (1 : 1) and allow to stand, well stoppered, for a quarter of an hour. Thereafter add dropwise 5 ml of acetic anhydride to the solution, dilute with 5 ml of methanol, and titrate the formed methyl β,N-hexamethylene-imine propionate with 0·1 N hydrochloric acid in methanol, in the presence of 5 drops indicator mixture. 8·6 mg of methyl acrylate is equal to 1 ml of 0·1 N hydrochloric acid. Regarding the purification of hexamethylene-imine and the preparation of the indicator mixture see: Chapter 16; Section 99 [799].

154. Acyl Cyclopropylamines with Mercury(II) Acetate in Methanol [804]

The cyclopropyl ring of acyl cyclopropylamine reacts with mercury(II) acetate dissolved in methanol. The mechanism resembles that for other cyclopropane compounds [508]. Opening of the ring takes place between the substituted and non-substituted C-atom, and a methoxy group is added to the substituted C-atom:



When mercury(II) acetate is dissolved in methanol, methoxymercury(II) acetate is formed [169]:

$$Hg(CH_3COO)_2 + CH_3OH \rightarrow Hg(OCH_3)-O-COCH_3 + CH_3COOH$$

Acyl cyclopropylamines (sometimes exhibiting weak acidic characteristics) are such weak bases that they cannot be titrated in acetic anhydride (cf. [878]). As reagent 0·12 M mercury(II) acetate in methanol is used [430]: dissolve 40 g of mercury(II) acetate in 1 litre of methanol, add 3–8 drops of acetic acid and filter before use.

Weigh 1–4 m.eq. of sample in a glass-stoppered Erlenmeyer flask. Dissolve in 50 ml mercury(II) acetate reagent, and allow the stoppered solution to stand for 30 min. A blank test is carried out in the same way. Add to both flasks 2–4 g of finely powdered NaBr and stir with a magnetic stirrer till dissolved. After adding 1 ml of indicator (1% phenolphthalein in methanol) titrate the liberated acetic acid with 0·1 N NaOH in methanol. On the addition of sodium bromide, mercury(II) acetate is converted to mercury(II) bromide. Mercury(II) bromide and sodium acetate do not consume alkali in methanol.

The cyclopropyl derivative reacts very slowly at room temperature. It is, therefore, boiled with the reagent under reflux for 30 min. Atmospheric moisture and carbon dioxide must be carefully excluded by inserting an absorption tube filled with KOH.

The mercury(II) acetate reagent can be standardized against 0·1 N hydrogen chloride in propylene glycol–chloroform (1 : 1) in the presence of thymol blue. For the determination of methacrylate esters and 3-chloropropene by the mercury(II) acetate method see: [535, 536].

155. Double Bonds with 0·1 N Bromine Solution in Acetic Acid

A solution of bromine in acetic acid (Uhrig–Levin reagent) has long been used for the determination of olefinic unsaturation [823]. In anhydrous acetic acid bromine reacts as an oxidizing agent towards e.g. arsenic(III) but with saturated organic compounds substitution takes place while with unsaturated organic compounds addition occurs. The reaction is influenced by the presence of sodium acetate which, as proton acceptor, decreases the acidity of the medium [813].

(a) *Determination of cholesterol* [813]. Weigh 150–300 mg of cholesterol and dissolve in a mixture of 20 ml acetic acid, and 3 ml acetic acid saturated with sodium acetate. Heat to 60°C and titrate potentiometrically with 0·1 N bromine solution in acetic acid (Chapter 11; Section 60 (2)). As electrodes, a bright platinum spiral and saturated calomel are used. 19·33 mg of cholesterol requires 1 ml of standard solution.

(b) *Determination of 4-hydroxycoumarin and its derivatives* [199]. Dissolve in 20 ml of acetic acid a weighed amount (0·1–0·5 mM) of 4-hydroxycoumarin (boiling promotes solution) and, after cooling, titrate potentiometrically with 0·1 N bromine in acetic acid by means of platinum–calomel electrodes. Two equivalents of bromine require 1 mole of 4-hydroxycoumarin.

Dicoumarol, 3,3′-methylene-bis-(4-hydroxycoumarin), can be titrated to the appearance of a yellow tint caused by excess of bromine. Dissolve by heating 20–100 mg of dicoumarol in 20 ml of acetic acid. After cooling mix with 3 ml of saturated sodium acetate in acetic acid and titrate to the appearance of a permanent faint yellow colour. 16·81 mg of dicoumarol require 1 ml of bromine solution in acetic acid.

(c) *Bromometric determination of steroids containing a double bond in the Δ^5 position by combined application of mercury(II) chloride catalyst and sodium acetate* [283]. For the determination of compounds containing double bonds, bromine addition is sometimes a slow process even if direct titration is carried out with 0·1 N bromine in acetic acid solution at 60°C (e.g. cholesterol). However, bromometric titration of some steroids can be performed if mercury(II) chloride is employed as catalyst in addition to sodium acetate. It is advisable to use anhydrous acetic acid (distilled from chromium trioxide), containing 0·5 M sodium acetate and 0·08 M mercury(II) chloride, as solvent. With a solvent containing such a catalyst the additive reaction is accomplished within seconds, heating is unnecessary and the rate of disturbing substitution reactions causes only negligible errors even in diffuse sunlight.

In titrations of colourless solutions, the colour change of excess bromine indicates the end-point. This causes over-titration by about 0·5–1 %. When, however, the 0·1 N bromine solution in acetic acid is standardized under similar circumstances against arsenic trioxide this error can be eliminated. Coloured solutions are titrated potentiometrically by using platinum as the indicator and calomel as the reference electrode (the liquid filling of which is acetic acid saturated with lithium chloride). For the dead-stop method two smooth platinum electrodes can be employed.

Weigh approx. 0·5 mM of steroid and dissolve in 10 ml of acetic acid containing catalyst. Heat, if necessary. Titrate at room temperature with 0·1 N bromine in acetic acid. During titration shake the flask vigorously. Near to the end-point, add titrant rapidly but in single drops so they can be counted. The yellow colour of excess bromine should remain permanent for at least 15–20 sec.

Standardization of the titrant: dissolve about 50 mg of arsenic trioxide in 3 ml of 1 N NaOH and after adding 7 ml of 20 % hydrochloric acid, titrate with bromine in acetic acid to a faint yellow colour.

Preparation of catalyst in acetic acid: dissolve 68 g of sodium acetate trihydrate and 21·7 g of mercury(II) chloride in acetic acid (distilled from chromium trioxide) and make up to 1,000 ml. The solution can be kept in the dark for several months.

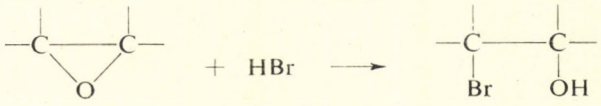
With this method e.g. diosgenine, solasodine, O,N-diacetylsolasodine, 3β-acetoxy-$\Delta^{5,16}$-pregnadiene-20-one Δ^5-pregnene-3β-ol-20-one, 16α,17α-epoxy-Δ^5-pregnene-3β-

ol-20-one, Δ^5-androstene-3β-ol-17-one, 3β-acetoxyΔ^5-androstene-17-one, 3β-formyloxy-17α,21-diacetoxy-Δ^5-pregnene-20-one, 17α-methyl-Δ^5-androstene-3β,17β-diol, can be determined.

In the case of steroids containing an isolated double bond the equivalent weight is half the molecular weight. Reproducibility of this method, depending upon the compound, is 98·2–101·0 ± 0·3%.

156. Oxiran Oxygen (α-Epoxide Group) [197, 198, 373]

Hydrogen bromide in acetic acid reacts with the α-epoxy group:

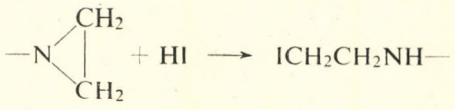


The epoxy-group can be directly titrated by end-point detection with an indicator.

Weigh 300–600 mg of sample containing epoxide group, dissolve in a small amount of benzene or chlorobenzene and titrate with 0·1 N hydrogen bromide in acetic acid in the presence of 5 drops of 0·1% crystal violet in acetic acid until indicator becomes blue-green. Use a magnetic stirrer and a closed apparatus. Also, take great care that the jet of the burette is directly above the surface of the liquid to be tested. Concerning preparation of the titrant and its standardization see: Chapter 11. Other Titrants (g). 1·6 mg oxiran oxygen requires 1 ml of hydrogen bromide solution. Accuracy of determination is ±1%.

The presence of carboxylic acid, aldehyde, ether, ester and peroxide does not interfere with titration. Hydroperoxides affect it to a certain degree but the presence of amines can be a source of major errors. In Durbetaki's newer method, oxiran oxygen can be titrated directly even in salts of epoxy-acids and in the presence of amines [198].

Durbetaki's method is rapid and capable of good results, but the reagent fumes in air and therefore requires special handling and frequent restandardization. In the procedure suggested by Jay [428], hydrogen bromide (or hydrogen iodide) is generated in situ by the addition of 0·1 N perchloric acid to Et_4NBr, or Bu_4NI reagent. HBr or HI rapidly opens the oxiran or aziridine ring:



HI is a more energetic ring-opening agent than HBr.

Into a 50 ml Erlenmeyer flask weigh a sample which contains 0·8 m.eq. of oxiran or aziridine compound. Dissolve in 10 ml of chloroform, acetone, benzene or chlorobenzene. Add 10 ml of quaternary bromide or iodide reagent and 2 to 3 drops of crystal violet indicator. Titrate with 0·1 N perchloric acid in acetic acid. Sharp endpoints are obtained especially for epoxides. The reagent blank is negligible.

Preparation of tetra-ethylammonium bromide reagent: Dissolve 100 g of Et_4NBr in 400 ml of anhydrous acetic acid. Add a few drops of indicator and neutralize with 0·1 N perchloric acid to a transitional colour.

Preparation of tetrabutylammonium iodide reagent: Dissolve 50 g of Bu_4NI in 500 ml of purified chloroform. This reagent can only be stored if it is not neutralized in advance with perchloric acid, and is kept in darkness.

157. Acetylenic Hydrogen

Monosubstituted derivatives of acetylene form compounds of type $R-C\equiv C-Ag$ with silver nitrate in aqueous ammonia medium while in alcohol those of type

$$R-C\equiv C-Ag\,.\,AgNO_3$$

are formed, if the excess of silver nitrate is not too great. When, however, the excess of silver nitrate is considerable, the latter compound becomes dissolved as

$$R-C\equiv C-Ag\cdot 6AgNO_3$$

(a) *Determination with silver nitrate in pyridine* [594]. Using silver nitrate dissolved in pyridine, equivalent nitric acid is liberated by the acetylene derivative. The former can be measured either potentiometrically or by indicator. Weigh 0·5 m.eq. of acetylene derivative and dissolve in 5·0 ml of N silver nitrate in pyridine previously neutralized in the presence of 5–10 drops of 1% thymol blue to a light blue colour: colour of indicator, due to solution, turns pale yellow or colourless. The liberated nitric acid is then titrated from a microburette with 0·1 N sodium hydroxide in methanol till a blue colour is produced. 3-Methylpent-1-yne-3-ol, ethinylcyclohexanol, 3-methylpent-1-yne-3-ol carbamate (see also: Chapter 31) and many other acetylene derivatives can be determined by this method.

(b) *Determination with silver perchlorate in methanol* [32]. Owing to the effect of silver perchlorate the acidic hydrogen of monosubstituted acetylene derivatives (cf. Table 10) can be exchanged for silver in methanol:

$$R-C\equiv C-H + 2\,AgClO_4 \rightarrow R-C\equiv C-Ag.\,AgClO_4 + HClO_4$$

The perchloric acid formed can be titrated with standard 0·1 N tris(hydroxymethyl)-aminomethane in the presence of the indicator mixture thymol blue–Patent blue A to a colour change from purple to green. Concerning the standard solution see Table 18: (k).

Dissolve a weighed amount of 1–3 m.eq. of acetylene derivative in 5–10 ml of neutralized methanol. Neutralize 10 ml of 1 M silver perchlorate solution in methanol in the presence of 3 drops of indicator to green. Mix the two solutions and after adding 5–10 drops of indicator titrate to a green colour change.

Preparation of silver perchlorate solution: dissolve 104 g of $AgClO_4$ in 500 ml of anhydrous methanol and store in a polyethylene bottle to avoid perchlorate explosion [32]. *Preparation of indicator mixture:* dissolve 100 mg of thymol blue and 25 mg of Patent blue A in 100 ml of methanol. This solution, owing to decomposition, must be remade weekly. But 1 g of thymol blue + 250 mg of Patent Blue A dissolved in 200 ml of dimethylformamide give a solution of higher stability, 2–3 drops of which are required for titration. (Barnes, private communication.)

If the sample contains strong acid as a consequence of which the indicator colours the solution purple, it is neutralized to green prior to mixing with silver perchlorate solution, with 0·1 N tris(hydroxymethyl)aminomethane. In the presence of weak acids

($K = 10^{-5}$ or below) neutralization is not necessary; if however, insoluble silver s als are precipitated the amount of methanol should be raised to 50 ml and 15–20 drops of indicator used.

In the presence of strong bases (alkali metal hydroxides) the solution develops a blue colour from the indicator. In this case it should be neutralized to purple with 0·1 N perchloric acid in methanol. If, in the presence of organic bases ($K = 10^{-3} - 10^{-6}$), the solution assumes a green tint from the indicator, the sample in methanol should be neutralized to purple.

Colour change of indicator mixture: with strong acids, purple; with organic bases and acids, green; with strong bases, blue.

2-Propyn-1-ol, 2-methyl-3-butyn-2-ol, 3-methyl-1-pentyn-3-ol, 3-methyl-1-hexyn-3-ol, 2-ethyl-1-heptyn-3-ol, 3-methyl-1-nonyn-3-ol and also solutions in acetone of acetylene, 1-pentyne and 1-hexyne can be titrated in this way. Regarding microdetermination of acetylenic hydrogen see: [298].

Chapter 28

Determination of Elementary Sulphur and Organic Compounds Containing Sulphur. Application of Silver Nitrate in Pyridine Reagent

158. Elementary Sulphur in Non-aqueous Media

Skoog and Bartlett have worked out a method for the volumetric determination of elementary sulphur by titrating its acetone solution with potassium cyanide in isopropanol [760]. Erdey and collaborators found that the solubility of sulphur in a mixture of benzene–acetone (4 : 1) is ten times that in acetone which by itself is able to dissolve only 0·32 mg/ml of sulphur. Moreover in this the accuracy of determination can also be improved [214, 215].

Determination of elementary sulphur in plant protectives. Extract in a vibrator with 80 ml of benzene for one hour about 300 mg of sample, previously dried in vacuum. Filter the solution into a 100 ml measuring flask and dilute to the mark with acetone. Mix 10–20 ml with 1 ml of water and 2–3 drops of bromothymol blue indicator and titrate with 0·05 M KCN solution in isopropanol e.g. in a constant-temperature titration vessel at 50–60°C until blue colour persists. Near to the end-point titrate slowly. The benzene must contain no more than 0·1 % of water since a higher water content would hinder extraction of sulphur.

For preparation of standard solution see: Chapter 11; Section 60 (m). Standardization: dilute 20 ml of a 0·05 N KCN solution with 50 ml of water, add 2 ml of 6 N NH_4OH solution and 0·6 g of NaI. Titrate with a solution of 0·05 N $AgNO_3$ till turbidity appears. Factor of standard solution

$$f_{KCN} = \frac{a \times f_{AgNO_3} \times 2}{b}$$

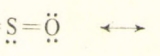
where a = ml of $AgNO_3$ solution consumed
b = amount in ml of KCN solution.

The sulphur content of therapeutical tablets containing elementary sulphur and activated charcoal can be determined analogously to the above method. In this case potentiometric titration with glass–calomel electrodes is preferable.

159. Organic Sulphoxides

Organic sulphoxides (e.g. dimethyl sulphoxide) can be titrated potentiometrically with standard perchloric acid solution in acetic anhydride [778, 879].

The sulphoxide group can be represented as a polarized resonance hybrid form, assuming that the outer electron shell of the sulphur atom can accommodate more than eight electrons ([863] p. 27).



Asymmetry of the molecule arises from the sulphur and the three atoms linked to it not being co-planar (p. 594 in [231]).

Weigh approx. 0·001 M of sulphoxide compound, dissolve in 75 ml of acetic anhydride and titrate potentiometrically with 0·1 N perchloric acid in dioxan using either a glass–calomel or glass–Ag–AgCl electrode pair (see: Section 130 (a)). Dimethyl, diphenyl, dibenzyl sulphoxides, etc. can be determined in this way. Sulphides and sulphones do not interfere with the determination.

It is noteworthy that phenothiazine-5-oxide can also be titrated in this way.

160. Alkane Thiols (Mercaptans). Applications of Silver Nitrate in Pyridine

A characteristic feature of thiols, which are very weak acids, is that with Ag^+ ion they form silver mercaptides, and mercury mercaptides with Hg^{++} ions.

(a) *Titration with silver nitrate in isopropanol* [490]. Transfer 20 ml of a mixture of isopropanol : 30% ammonia in the ratio of 10 : 1 into a flask, the stopper of which has two drilled holes (Figs 39, 40, 41 and 42). Add 1–2 ml of 0·01% dithizone solution in ammonia–isopropanol. Direct nitrogen over the solution, then weigh and dissolve 0·05–0·1 m.eq. of mercaptan derivative. Titrate in a nitrogen atmosphere with 0·01 N silver nitrate in isopropanol to colour change from orange yellow to deep red (as regards standard solution see: Chapter 11; Section 60 (l)). Among others, 5–20 mg of hexanethiol, butanethiol, dodecanethiol etc. can be titrated in this way. During the reaction nitric acid formed from silver nitrate is bound by ammonia and the vivid colour of the dithizone–silver co-ordination complex formed with excess of standard solution indicates the end-point.

Thiols also react with mercury salts, e.g. mercury(II) acetate, while a dimercaptide or acetoxy-mercury-mercaptide is formed. Excess of mercury(II) acetate in methanol solution is added to the mercaptan and, following reaction, back-titrated with 0·1 N hydrochloric acid in butanol in the presence of thymol blue indicator [489].

(b) *Application of silver nitrate in pyridine* [634]. Numerous organic compounds react with silver ions while protons are liberated:

$$R \,.\, C{\equiv}CH + Ag^+ \rightarrow R \,.\, C{\equiv}C \,.\, Ag^+ + H^+$$

$$BH_2 + 2Ag^+ \rightarrow BAg_2 + 2H^+$$

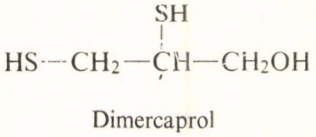
where BH_2 is e.g. a barbiturate molecule.

In pyridine, a similar process leads to the formation of pyridinium ion which, being a strong acid, can be titrated. This method can be employed for determination of acetylenic hydrogen (see: [594]) and that of barbiturates (see: [266]).

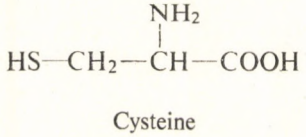
Weigh about 1 m.eq. of monofunctional compound, containing $-SH$ group, in a glass-stoppered Erlenmeyer flask. Dissolve in 15 ml of pyridine, add 5 ml of 0·5 M $AgNO_3$ solution in pyridine and allow to stand well-stoppered for 15 min. Titrate with 0·1 N NaOH in ethanol in the presence of 5 drops of thymolphthalein or thymol blue (a 1% or 0·1% solution in ethanol). (Chapter 10; Section 55 (a).)

Compounds insoluble in pyridine (e.g. cysteine) are first dissolved in 5 ml of water, ethanol or acetone. Subsequent procedure is as above.

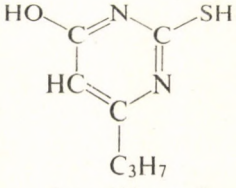
Each single $-SH$ functional group forms an equivalent pyridinium cation. Monofunctional compounds are e.g. thioglycerol, ethyl or butyl mercaptan; dimercaprol (i.e. BAL = British Anti-Lewisite, dithioglycerol), is a bifunctional compound. A way of proceeding for the titration of compounds containing another acidic functional group besides $-SH$ group is to titrate the carboxylic group in pyridine and then, after adding silver nitrate, to measure the $-SH$ group separately (thiosalicylic acid; cysteine). This technique is also suitable for the determination of thioglycolic acid, thiomalic acid, thiophenol, 1,2-dimercapto-benzothiazole (see also: Chapter 17. Acid-Analogue Condensed Heterocyclic Compounds), n-propylthiouracil etc. in addition to the above.



Dimercaprol



Cysteine



Propylthiouracil

This method is also suitable for the determination of the active agent content of tablets. Accuracy, $\pm 1\%$

(e) *Determination of barbituric acid derivatives with silver nitrate in pyridine* [266]. Compounds containing an imino group in addition to the $-SH$ group also liberate protons when they react with silver nitrate in pyridine:

$$BH_2 + 2Ag^+ + 2C_5H_4N \rightleftharpoons BAg_2 + 2C_5H_5NH^+$$

where BH_2 = the barbituric acid derivative.

Weigh 0·25–1 m. eq. of barbiturate in a conical titration vessel (for this purpose the evaporating flask shown in Fig. 103 is suitable). Dissolve in 5 ml of pyridine, add 10 ml of 0·5 M silver nitrate in pyridine solution and titrate with 0·1 N NaOH in ethanol in the presence of 4–5 drops of 1% thymol blue in ethanol. Diethyl-, butyl-ethyl-, ethylisopentyl-, ethylphenyl- and N-methylethylphenyl-barbituric acid can be determined with $\pm 1\%$ accuracy.

The active agent content of pharmaceutical products which contain a free barbituric acid derivative and, at the same time, its sodium salt must be determined by a combined method. First the acetate ion formed during reaction with the solvent is titrated with perchloric acid in acetic acid; a second portion of the sample is titrated according

to the above method [264]. To calculate, the fact that the sodium salt of barbituric acid consumes one equivalent of perchloric acid while in the reaction with silver nitrate two equivalents of sodium hydroxide are used has to be taken into account. Accuracy in the combined method is $\pm 2\%$.

(d) *Direct titration of mercaptans (thiols) with mercury(II) perchlorate* [255]. Thiols react with the Hg^{++} ion:

$$Hg^{++} + 2RSH \rightarrow (RS)_2Hg + 2H^+$$

Both visual and photometric end-points can be observed in the presence of freshly prepared 0·01% Michler's ketone in acetone (4,4-bis(dimethylamino)thiobenzophenone). For potentiometric titrations calomel is used as reference and mercury as indicator electrode; the latter is a 'J-type' Hg electrode (see: Fig. 54 [674] and footnote).*

This method is also suitable for the determination of traces of thiol; in this case photometric end-point detection is more convenient, with measurements taken at 580 mμ (for photometric titration a Beckman Model Band modified cuvette cell can be used: [256]).

Titration can be carried out in acetone, acetone–benzene or acetone–light petroleum (containing max. 40 v/v % of benzene or light petroleum). Weigh 0·3–1·0 mM of thiol derivative, dissolve in 100 ml of solvent, add 1 ml of pyridine and indicator sufficient for the solution to turn to vivid yellow green. Titrate with *aqueous* 0·05 M mercury(II) perchlorate to a blue colour change. Thus, the final volume of the solution contains 3–10% of water.

Preparation of the standard solution: dissolve 26 g of $Hg(ClO_4)_2 . 3 H_2O$ in 1 litre of aqueous 0·1 M perchloric acid. Standardize against 0·05 M ethylenediaminetetra-acetic acid (titrant) in the presence of pyridine as buffer (pH 6) and Michler's ketone.

For photometric titrations 0·006–0·5 mM of thiol is dissolved in 100 ml of solvent and titrated as above but the standard solution is accordingly more dilute: 0·0005–0·01 M.

(e) *Potentiometric titration of mercapto compounds by lead tetra-acetate* see: [785].

161. Titration with Perchloric Acid of Alkyl Xanthogenates, S-Alkyl- and S-Benzyl-Thiuronium Derivatives and Dialkyl-*p*-Bromophenacyl Sulphonium Compounds [59, 60, 724, 843]

(a) The formation of xanthogenates (xanthates, dithiocarbonates) is a reaction employed for identification of alcohols. Titration of the potassium alkyl xanthogenate with perchloric acid makes it possible to determine the equivalent or molecular weight of an alcohol:

$$ROCSS^- + CH_3COOH_2^+ = ROCSSH + CH_3COOH$$

In acetic acid xanthogenates are decomposed:

$$ROCSSK + CH_3COOH \rightarrow ROCSSH + CH_3COOK$$

$$\text{and } ROCSSH \rightarrow ROH + CS_2$$

* *Chemist-Analyst* **51**, 56 (1962).

The potassium acetate formed can be titrated as a base. Thus, xanthogenates whether decomposed or not, consume one equivalent of perchloric acid.

Weigh 200–300 mg of alkyl xanthogenate, dissolve in 15–20 ml of acetic acid and titrate with 0·1 N perchloric acid in the presence of crystal violet to a blue colour change.

(b) Salts of S-alkyl- or S-benzyl-thiuronium ion formed with picrate or carboxylate anion are suitable for the identification of -alcohols and carboxylic acids; these salts can be titrated as base with 0·1 N perchloric acid in the presence of crystal violet:

$$\left[\begin{array}{l} R-SC=NH_2 \\ \quad\quad | \\ \quad\quad NH_2 \end{array}\right]^+ X^- + CH_3COOH_2^+ \longrightarrow$$

$$\longrightarrow \left[\begin{array}{l} R-SC=NH_2 \\ \quad\quad | \\ \quad\quad NH_2 \end{array}\right]^+ + XH + CH_3COOH$$

where R = the alkyl or benzyl group

X^- = the picrate or carboxylate anion.

For titration of picrates see: Chapter 24; Section 135.

(c) *Identification of dialkyl sulphides (thioethers) as p-bromophenacyl sulphonium salts* [843]. Dialkyl sulphides form *p*-bromophenacyl sulphonium salts with *p*-bromophenacyl bromide:

$$R_2S + BrC_6H_4COCH_2Br \longrightarrow BrC_6H_4COCH_2-\overset{\overset{R}{|}}{\underset{\underset{R}{|}}{S^+}}Br^-$$

where Br^- is exchanged during picrate formation and the dialkylbromophenacyl sulphonium picrate formed can be titrated with perchloric acid in acetic acid in the presence of crystal violet to a green colour change.

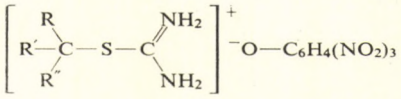
Preparation of alkyl xanthogenates (according to Whitmore and Lieber [59]). Dissolve with heating 0·5–0·6 g of KOH (about 0·01 M) in 1 g of the alcohol to be tested. After cooling add 1 ml of CS_2 (about 0·017 M) drop by drop. Should the temperature rise, the mixture must be chilled. Stir for a few minutes with a glass rod, then add 20 ml of ethyl ether and shake vigorously. Filter the separated potassium xanthogenate crystals and wash with a few ml of ethyl ether. Dissolve in a small amount of boiling acetone. After filtration and cooling add 20 ml of ethyl ether to precipitate the xanthogenate.

*Preparation of S-alkyl-thiuronium picrates of t-alcohols.** Shake one volume of t-alcohol with 5–6 volumes of conc. hydrochloric acid or 48% hydrobromic acid for a few minutes. The initially homogeneous mixture is separated into two parts, the upper being the alkyl halide.

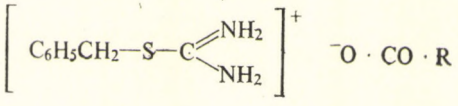
Boil under reflux 1 ml of alkyl halide with a solution prepared from 1 g of thiourea, 3 ml of water and 2 ml of ethanol until the alkyl halide has reacted (2–3 hours). The mixture is then poured

* S. Veibel: Identification des substances organiques, Masson et Cie, Paris, 1957, p. 69.

into 200 ml of aqueous 1% picric acid solution: S-alkyl thiuronium picrate is precipitated. After half an hour filter off and recrystallize from aqueous ethanol:



Preparation of S-benzyl-thiuronium salts of carboxylic acids (p. 145 in*): Mix 0·01 m.eq. of carboxylic acid with 8 ml of N NaOH, neutralize and dissolve in the presence of 2 drops of methyl red indicator with N alkali so that the solution should be as little alkaline as possible. Heat the solution to 90°C and add 2 g of S-benzyl thiuronium chloride dissolved in 5–10 ml of water. Embed the reaction mixture in ice without delay. Saturate the solution of the slowly crystallizing derivative with NaCl and promote the growth of crystals by chilling overnight.



The salts are easily hydrolyzed by hydroxyl ions, when benzyl mercaptans of objectionable odour are formed.

Preparation of dialkyl-p-bromophenacyl sulphonium picrates (cf. p. 264 in*). Dissolve 0·01 M dialkyl sulphide and 0·01 M *p*-bromophenacyl bromide in 10 ml of acetone containing 5% of water. Allow stoppered solution to stand for 24 hours. After decanting wash the crystals with ethyl ether. Dissolve in a small amount of water and transfer to a saturated aqueous picric acid solution. After filtration and drying, weigh and titrate with perchloric acid.

Diaryl sulphides and thioanisoles do not react with *p*-bromophenacyl bromide. Diallyl or dibenzyl sulphides, when boiled under reflux, yield bis-(*p*-bromophenacyl) sulphide [843].

* S. Veibel: Identification des substances organiques, Masson et Cie, Paris, 1957, p. 69.

Chapter 29

Redox Titration in Non-aqueous Media

The theory of redox titrations has not yet attained the level of development of acid–base titration theory. Research is in progress in Czechoslovakia, Great Britain, Hungary [217], India, Poland, USA and elsewhere.

Systematic investigation of chemical processes in non-aqueous media started as early as the beginning of this century [855]. The realization of the theoretical possibilities offered by non-aqueous solutions is reflected by the great variety of acid–base titrations in non-aqueous media. At the present time it cannot be foreseen whether redox titrations carried out in non-aqueous media will find as wide an application as acid–base titrations. However, it is to be expected that the appropriate choice of solvents and conditions will lead to the employment of redox titrations for some compounds which are not titratable in an aqueous medium.

According to Harned [362] normal potentials, in different solvents, change linearly with the reciprocal of the dielectric constant. In different solvents, however, dissociation relations and solvent effects in general exert their influence in different ways. Ions, for instance, may form larger aggregates (cf. Chapter 5; Section 33). Again, the electrode potential changes. Participation of the solvent in the reaction taking place between compounds dissolved in it may cause unexpected results.

The fundamental behaviour of electrodes in aqueous or in non-aqueous media is, in essence, the same. According to Conant and Chow [143] the redox potentials of some quinonoid compounds change in acetic acid according to the acidity of the solution. Investigations by Tomiček [217] prove that the redox potential of system chromium(VI)/chromium(III) changes according to the hydrogen potential of the acetic acid medium.

In the redox system ascorbic acid/dehydroascorbic acid in acetic acid medium the potential is changed by sodium acetate since the acetate ion, as a base, promotes dissociation of ascorbic acid by binding H^+ ions [217]. The redox potential of the bromide/bromine system in acetic acid depends upon the pH of the solution.* In the presence of hydrogen ions some bromide ions are converted to hydrogen

* Tomiček and Heyrovsky: *Coll. Czech* **15**, 997 (1950).

REDOX SYSTEM CHROMIUM(III)–CHROMIUM(VI) IN ACETIC ACID

Acidity ($HClO_4$)	*E (Pt-Calomel Electrodes)* mV
1 N	1,150
0·1 N	1,107
0·01 N	1,069
0·001 N	1,026
0·0001 N	980
acetic acid	(880) [217]

bromide since in an anhydrous medium no proton acceptor is present. Thus, the activity of bromide ions is decreased and the value of the ratio [Ox]/[Red] increased. On adding acetate the concentration of acetacidium ions is decreased, activity of bromide ions increased and redox potential diminished.

The data enumerated indicate clearly that in acetic acid medium the potential of a redox system depends on the ratio of the oxidized to reduced form and in many cases on the medium [217].

The number of redox titrations is relatively small. In this field Tomiček and collaborators performed pioneering work [816, 817]. Bromine in acetic acid [216, 897], potassium permanganate in acetic acid [131], chromium(II) acetate in dioxan [589, 591], copper(II) acetate in pyridine–ethanol solution [107], cerium(IV) ammonium

REDOX SYSTEM BROMINE–BROMIDE IN ACETIC ACID

Acidity	*E (Pt-Calomel Electrodes)* mV
1 N CH_3COONa	560
0·01 N CH_3COONa	640
0·001 N CH_3COONa	679
acetic acid	830
	(790) [217]
0·001 N $HClO_4$	930
0·01 N $HClO_4$	1,010
1 N $HClO_4$	1,050

nitrate solution in acetonitrile [666a, 666b, 666c, 666d], t-butyl hypochlorite in acetic acid [336], potassium bichromate solution in acetic acid [685], lead tetraacetate in acetic acid [785], etc. have been employed.

162. Determination of Ascorbic Acid in Non-aqueous Media [216, 666c]

(a) Ascorbic acid can be titrated with 0·05 N *bromine in acetic acid* in the presence of an indicator with redox properties. Such an indicator is e.g. the variamin blue derivative, N,N′-bis(*p*,*p*′-dimethoxydiphenylamine)thiourea, a 0·1% solution of

which in pyridine is used. (Though the solution eventually turns yellow or brown, it can be used for two weeks):

$$CH_3O.C_6H_4.NH.C_6H_4.NH.CS.NH.C_6H_4.NH.C_6H_4.OCH_3$$

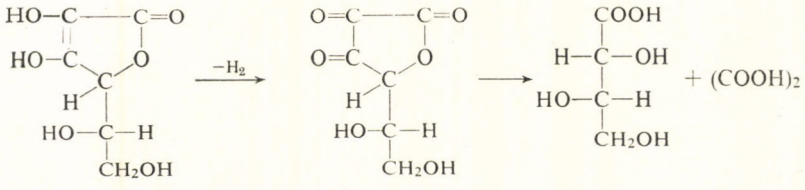
Salicylic acid cannot be titrated in anhydrous acetic acid but can be determined in a 1 : 1 mixture of acetic acid–water with bromine in acetic acid as standard solution [897]. Investigation showed that in acetic acid, sodium acetate takes over the role of water (as base) and most reactions can take place.

Weigh 30–60 mg of ascorbic acid, dissolve in 30 ml of acetic acid and add 10 ml of N sodium acetate in acetic acid and 4 drops of indicator. Titrate with 0·05 M bromine in acetic acid to violet (which should remain stable for 1 minute). Near to the end-point titrate slowly because the rate of reaction decreases. 4·4 mg of ascorbic acid requires 1 ml of 0·05 N bromine. Accuracy of measurement is 100·7 ± ±0·9%.

For preparation of bromine in acetic acid see Chapter 11; Section 60 (2). *Standardization:* mix 10 ml of titrant with 50 ml of freshly prepared 2% aqueous potassium iodide and titrate the iodine immediately with 0·05 N thiosulphate in the presence of 0·1% variamin blue indicator in pyridine.

(b) *Ascorbic acid* can also be titrated potentiometrically *in acetic acid–acetonitrile with standard cerium(IV)* ion [666c]. Titration, however, must be carried out in such a way that 2·0–5·0 ml of 0·05 N cerium(IV) ammonium nitrate in acetonitrile should be diluted to 10 ml with acetic acid and, by means of glass–platinum electrodes, the standard solution must be titrated with about 0·015 N ascorbic acid in acetic acid, prepared from the ascorbic acid to be tested (inverse titration). The use of a semimicro burette and magnetic stirrer is advisable. At the end-point a sudden potential drop of 100–120 mV can be observed. Oxidation of ascorbic acid continues to proceed through dehydroascorbic acid; the ratio of ascorbic acid and cerium(IV) is 1 : 4·005 [666c]. Thus, in an anhydrous medium with standard cerium(IV) oxidation is highly effective.

It is known that e.g. with alkaline hypoiodite or acidic permanganate solution, ascorbic acid finally becomes oxidized to threonic acid and oxalic acid:



163. Semimicro determination of Phenylhydrazine, Hydroxylamine and Compounds Containing Carbonyl Group with Copper(II) Acetate [107]

(a) Copper(II) ions oxidize phenylhydrazine or hydroxylamine while being reduced to copper(I) ions:

$$C_6H_5NH-NH_2 + 2Cu^{2+} + 2OH^- \rightleftharpoons C_6H_6 + 2Cu^+ + 2H_2O + N_2$$

$$2NH_2OH + 4Cu^{2+} + 4OH^- \rightleftharpoons N_2O + 4Cu^+ + 5H_2O$$

According to the above reaction 7–42 mg of phenylhydrazine and 3·5–17·5 mg of hydroxylamine can be determined by potentiometric titration [107]. 5 ml of pyridine are used as solvent with 0·05 M copper(II) acetate in pyridine–ethanol (1 : 1) solution as titrant (Chapter 11; Section 60 (r)). Standardization is best performed against pure phenylhydrazine hydrochloride. For titration platinum is used as indicator electrode, and calomel as reference electrode. Determination must be carried out in a nitrogen atmosphere in a small specially made apparatus (Fig. 124). Accuracy of determinations in the case of phenylhydrazine is $\pm 0{\cdot}1\%$ and for hydroxylamine $\pm 0{\cdot}5\%$. One ml of 0·05 M copper(II) acetate is equivalent to 3·615 mg of phenylhydrazine hydrochloride or 1·737 mg of hydroxylamine hydrochloride.

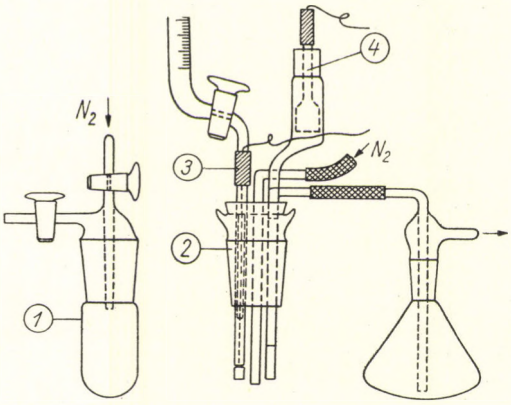


Fig. 124. Apparatus for potentiometric redox titrations with standard copper(II) acetate solution due to Budesinsky [107]. — *(1)* Reaction vessel, *(2)* Electrode assembly, *(3)* Platinum electrode, *(4)* Calomel electrode

(b) *Determination of compounds containing carbonyl group.* Weigh a sample of 0·15–0·2 m.eq. (*n* mg), dissolve in 5 ml of pyridine, add precisely 38–40 mg of phenylhydrazine hydrochloride (*A* mg). Saturate the solution for 5 min with a stream of nitrogen to exclude air, then heat for 15 min on a steam bath in a reaction vessel *(1)* (Fig. 124). After cooling to room temperature titrate potentiometrically under nitrogen (a = ml consumed). For titration insert electrode assembly *(2)* in the ground part of reaction vessel *(1)* (Fig. 124).

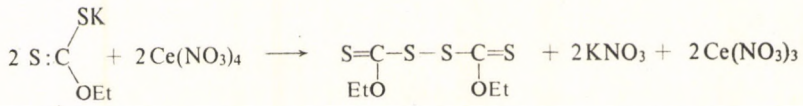
By this method the carbonyl group content of, e.g., acetone, benzaldehyde, isatin, methyl ethyl ketone, etc. can be determined.

$$\mathrm{CO}\% = \frac{19{\cdot}37}{n}\left(A - \frac{Ba}{b}\right)$$

where n = weight of sample (in mg)
A = weight of phenylhydrazine hydrochloride in mg
B = molecular weight of the former (144·6) in mg
b = equivalent ml of 0·05 M standard solution (40 ml).

164. Determination of Alkyl Xanthogenates (Xanthates) with Cerium(IV) Ammonium Nitrate [666a]

Potassium xanthate can be titrated in acetonitrile with 0·05–0·1 N cerium(IV) ammonium nitrate in acetonitrile. End-point of titration is indicated by yellow tint of excess of standard solution:

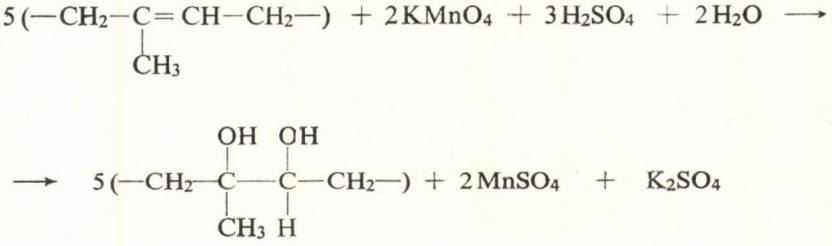


Weigh 5–25 mg of ethyl xanthate, dissolve in 10–15 ml of acetonitrile and titrate. The standard solution when added becomes colourless and white cerium(III) nitrate is precipitated.

Standardize the titrant against acidic potassium iodide solution: titrate the liberated iodine with thiosulphate.

165. Determination of Rubber in Vegetable Matter [131]

Rubber, having an unsaturated (polyisoprenoid) chain, can be titrated with 0·01 N permanganate in acetic acid in sulphuric acid-acetic acid-carbon tetrachloride. Two OH groups are added to the olefinic bond:



316·06 g of potassium permanganate are equivalent to 340 g of rubber.

Rubber is extracted from vegetable matter in a modified Soxhlet apparatus (Fig. 125). The solvent runs from the solvent container through distributor tube *(1)* and

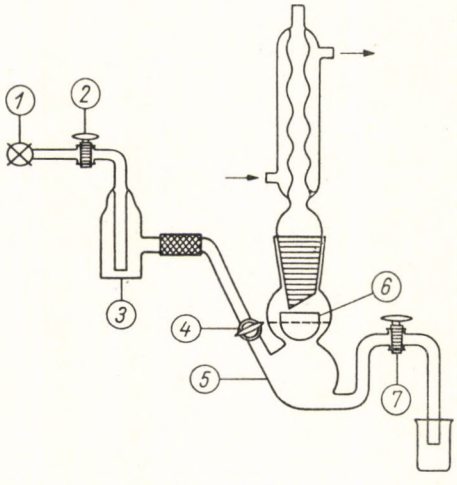


Fig. 125. Extractor for the determination of rubber in vegetable matter due to Chrastil [131]. – Signs and abbreviations: see below in text

cock *(2)* into compensating vessel *(3)* from where, through cock *(4)*, extraction flask *(5)* can be fed. Extraction muff *(6)* is placed above it. In the apparatus the solvent can be exchanged without discontinuing extraction and disassembling the apparatus by opening cocks *(2)*, *(4)* and *(7)*. For a series of determinations several extractors can be serially connected to distributor tube *(1)*. Hot extraction is employed and extraction

muff *(6)* is half-immersed in the liquid. Reflux of the solvent must be regulated so that the extracting solvent is warm. Flask *(5)* is heated on a steam or oil bath.

Weigh 1–5 g of finely pulverized vegetable powder and extract interfering material with 50 ml boiling acetone (10 hours). Extract rubber by three subsequent extractions with carbon tetrachloride (5 hours). Dilute the extract to 100–200 ml and after adding 1–5 drops of 96% sulphuric acid and acetic acid mixture (1 : 1) titrate, maintaining constant stirring, a 1 to 5 ml portion with 0·01 N $KMnO_4$ in acetic acid till red colour of the solution persists for 10 min. Prior to determination standardize the titrant against oxalic acid. Check permanganate consumption of the solvent by blank test.

Oxidation with periodic acid in non-aqueous media [668]. Vicinal glycols can be oxidized with triethylammonium periodate in ethanol–ethyl acetate solution. However, back-titration of periodic acid must be carried out in a medium diluted with water and with aqueous titrant.

Chapter 30

Titrations with Complex Formation in Non-aqueous Media

166. Alkylaluminium Compounds

The aluminium alkyl molecule is electron-deficient and can be considered a Lewis acid in complex formation with electron-donating reagents such as aromatic amines (e.g. isoquinoline), ethers and alcohols. Oxidation or hydrolysis of one of the Al–C bonds results in a reduction in electrophilicity of the molecule. Trialkylaluminium, dialkylaluminium hydride and dialkylaluminium halide are 'active' species, and form stable complexes with certain nitrogenous bases. Deactivated species such as dialkylaluminium alkoxides do not form stable complexes with bases.

Alkylaluminium compounds (AlR_3) and derivatives (e.g. mono- and di-halides ($AlRHal$ or $AlR(Hal)_2$) can be titrated potentiometrically with standard solutions containing isoquinoline [222]. Alkylaluminium compounds react with isoquinoline stoichiometrically to form stable complexes [75]. With compounds of type AlR_3 yellow-coloured (1 : 1) complexes are formed while AlR_2H-type compounds form red 2 : 1 complexes. (See also: Chapter 2; Section 20(f)) [833]. These complexes, dissolved in hydrocarbons, exhibit electrical conductivity, and so the reaction can be followed electrometrically. An aluminium rod is a suitable indicator electrode and as reference electrode an aluminium rod immersed in a solution of triethylaluminium in benzene can be used. The latter communicates through a porous surface (of 5–15 μ pore diameter) with the solution to be estimated (cf. Fig. 55). For trialkylaluminium compounds the reproducibility of measurements is 0·2–0·4%.

The water content of the solvent, benzene or n-heptane, and that of isoquinoline greatly influence titration. Decrease of alkylaluminium consumption is in linear correlation with the water content. From the aspect of purity of the alkylaluminium compound this must be taken into consideration and the moisture content must be known.

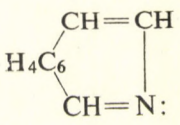
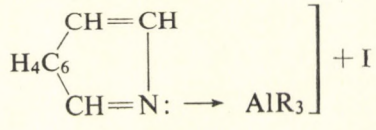
Aluminium mono-alkoxides, in the presence of trialkylaluminium compounds, do not react with isoquinoline. AlR_2Hal and $AlR(Hal)_2$-type compounds react in a similar way to those of type AlR_3 though coloured complexes are not formed. Titration gives the total of both types of compounds. If the ratio of $AlR_3/AlR(Hal)_2$ is $\leqq 1$ the characteristic yellow colouration of trialkylaluminium with isoquinoline

fails to occur. A mixture of trialkylaluminium and its etherate can be resolved potentiometrically. The first potential jump indicates the trialkyl compound and the second the etherate compound.

Direct a gentle stream of N_2 into the titration vessel (Fig. 55). The reference electrode contains 1–2 ml of a 10% triethylaluminium solution in benzene. Store the electrodes in a nitrogen atmosphere in diluted triethylaluminium solution. During titration the distance between electrodes should be 5–15 mm. Employ magnetic stirring. Titrate 5–10 mM of sample dissolved in 20–40 ml of completely anhydrous benzene. The standard solution containing isoquinoline (Table 18 (e)) dissolved in benzene or dibutyl ether can be 0·2 or 0·5 M. During titration carefully exclude atmospheric oxygen and ensure that the current of nitrogen is dry. Pure aluminium alkyl samples are extremely reactive to atmospheric moisture, and thus the precision and accuracy of the analysis depend to a large extent on the protection of the sample prior to and during the analysis. Take readings of the measuring instrument between a half and two minutes after adding a portion of the titrant. In the case of etherates wait for 10 minutes. See also: [740, 853].

A large number of methods have been suggested for various aluminium alkyl compounds, e.g. [328, 740, 853]. Hagen and Leslie have found that a large number of aluminium alkyls ranging from C_2 to C_{30} in chain length can be analysed by titration using triphenylmethane-type indicators, e.g. neutral violet, neutral red, methyl violet, basic fuchsin. These indicators form highly coloured reversible complexes with aluminium alkyls, and can be used as indicators for the volumetric determination of 'activity'. The intensity of the colour is greatly increased when two or more azomethine linkages are present in the indicator molecule. For the method and titration apparatus, see: [328]. Two reactions illustrate the basis of these titrations and are classified as (1) deactivation and (2) displacement reactions:

1. $[I{-}AlR_3] + R'OH \longrightarrow AlR_2OR' + RH + I$;

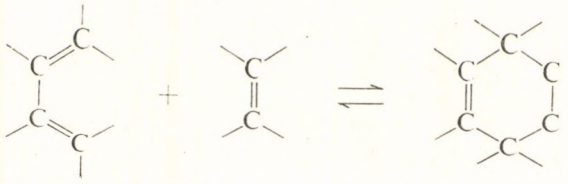
2. $[I{-}AlR_3] +$  $\longrightarrow$ 

A stronger base can be used to displace the indicator: pyridine, isoquinoline, hexyl alcohol (dissolved in xylene).

AlR_2H destroys the ability of these indicators to give sharp colour changes at the end-point, due to a reaction with the primary amino group or the formation of a covalent Al–N bond. The titration procedure utilizing visual indicators is applicable to trialkyl samples that contain little or no hydride [328].

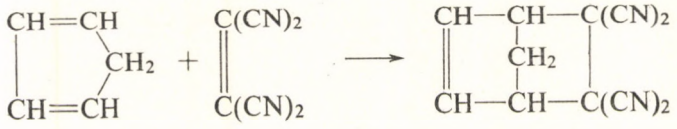
167. Diels–Alder-active Dienes and Aromatic Hydrocarbons

(a) *Determination of dienes* [618]. With dienophilic reagents, 1,3-dienes form adducts according to the following scheme ([870] p. 377):



Diene Dienophile Adduct

For determination of Diels–Alder-active 1,3-dienes, tetracyanoethylene (abbreviated to TCNE), $(NC)_2C=C(CN)_2$, is suitable. Mix excess of TCNE in known amount with compounds to be determined in methylene chloride medium. After Diels–Alder reaction has taken place at room temperature, back-titrate slowly the excess of TCNE with 0·05 M cyclopentadiene in ethanol when a colourless Diels–Alder adduct is formed:



To facilitate end-point detection use two indicators: (1) warning indicator, (2) end-point indicator:

1. Benzene containing 20% of phenanthrene:

$$C_5H_6 + TCNE[C_{14}H_{10}] \xrightarrow{\text{rapid}} C_5H_6{:}\ TCNE + C_{14}H_{10}$$

Red violet Colourless

2. Methylene chloride containing 1% of pentamethylbenzene

$$C_5H_6 + TCNE[C_6H(CH_3)_5] \xrightarrow{\text{slow}} C_5H_6{:}\ TCNE + C_6H(CH_3)_5$$

Red Colourless

Disappearance of the indicator red colour can also be traced photometrically at 525 mμ.

Regarding the preparation of standard solutions of TCNE and cyclopentadiene see: Chapter 11; Section 60 (t).

Weigh 320–390 mg of TCNE in a glass-stoppered Erlenmeyer flask. Add 50 ml of distilled methylene chloride and dissolve by heating. The volatility of methylene chloride can be decreased by adding chloroform. Add 1·25–1·5 mM of sample, close the flask and allow to stand for 10 min. Then titrate drop by drop with 0·05 M cyclopentadiene solution in the presence of 10 drops of warning indicator containing phenanthrene to disappearance of the red-violet colour. Add 5 drops of indicator containing pentamethylbenzene and titrate drop by drop until colourless. Anthracene, cyclopentadiene, cyclohexa-1,3-diene and 2,3-dimethylbutadiene etc. can be determined in this way.

The association constant for the π-complex, pentamethylbenzene-TCNE, is high ($K = 123$) and reaction of the complex with cyclopentadiene slow, therefore phenanthrene-TCNE π-complex of low stability ($K = 18$) is suitable as a warning indicator.

Accuracy of the determination is about 1%.

(b) *Determination of aromatic hydrocarbons* [717]. The π-electron system, the 'functional group' characteristic of the aromatic ring, has a relatively very weak basicity [435]. Some aromatic hydrocarbons form a more or less stable, coloured complex of non-ionic type with TCNE [573, 718].

According to Mulliken this sort of π-complex formation can be regarded as a Lewis acid–base interaction in which the complex bond is associated with transfer of π-electrons to the vacant orbital of the Lewis acid ('charge–transfer complex') [602].

Aromatic compounds are determined photometrically and change of absorption is plotted against ml consumed (Chapter 14). The molar ratio of complex formation is usually 1 : 1. Thus, e.g. light absorption of the complex 1,2,4,5-tetramethylbenzene-TCNE is identical whether mixed in a ratio of 5 : 1 or of 1 : 5.

According to Merrifield and Phillips the association constant (K) of some aromatic hydrocarbons may vary considerably [573]:

π-base	*Stability of TCNE-Complex (K)*	*λ Max* mμ [717]	*Precision* [717]
Hexamethylbenzene	263 [573]	545	99 ± 1%
Pentamethylbenzene	123	525	97 ± 2%
Fluoranthene	~90 [717]	540	100 ± 1%
Durene	54·2 [573]	480	99 ± 2%
Benzo[*a*]pyrene	~40 [717]	520	99 ± 2%
Naphthalene	11·7 [573]	550	90 ± 8%
Benzene	2 [573]	—	—
Chrysene	—	560	100 ± 1%
Perylene	—	460	101 ± 1%

$$K = \frac{(C)}{\{(TCNE) - (C)\}\{[B] - [C]\}}$$

where $(TCNE)$ = the initial molar concentration of tetracyanoethylene
(C) = molar concentration of the π-complex in a state of equilibrium
$[B]$ and $[C]$ = molar fraction of the aromatic π-base or the complex at equilibrium.

With photometric titrations, at the end-point obtained by extrapolation not every aromatic π-base forms a complex in ratio of 1 : 1 and on addition of further TCNE solution absorption is increased, which often renders calculation uncertain, especially with compounds of low K value.

Accuracy, however, can be increased if a spectrophotometric method is employed for detecting organic impurities ('trace analysis method' [672]), e. g. traces of naphthalene in phthalic anhydride.

Weigh about 0·3 mM ($K \sim 120$) or 0·6 mM ($K \sim 12$) of aromatic hydrocarbon in a 50–125 ml circulating Erlenmeyer flask (Fig. 99) and dissolve in 60 ml of chloroform. Connect with the 2·5 cm cuvette of a photometer (Bausch & Lomb Spectronic 20); set transmittance to 100% and titrate with a standard solution of 0·1 N TCNE employing magnetic stirring, at the chosen wavelength (see: Table above). For graphical plotting add the titrant in portions of 0·3 ml so that at least four points are measured before the half way point, and continue titration till the molar ratio of aromatic π-base and TCNE is about 1 : 2 to 1 : 3. Take readings of at least four points *after* the complex components have reached a ratio of 1 : 1·5.

Chapter 31

Determination of the Alkoxyl Group, Carbamic Acid Esters, Substituted Phosphines, Organosilicon Compounds

168. The Alkoxyl Group [163]

This method ingeniously simplifies the technique hitherto employed for the determination of the alkoxyl group. Alkyl iodide formed by reaction between the alkoxyl compound and hydriodic acid is absorbed in pyridine, together with the hydriodic acid distilling over:

$$R-I + C_5H_5N \rightarrow [C_5H_5NR]^+ I^-$$

Hydrogen iodide and alkylpyridinium iodide can be titrated in a mixture by means of a potentiometric differentiating titration in pyridine (Fig. 126). On the other hand titration can also be carried out with azo-violet indicator because the two-step colour change of the indicator enables in the first stage visual end-point detection of HI by orange turning to red, while the second equivalence point, indicated by change of the indicator from red to blue, corresponds to the alkylpyridinium iodide (Chapter 13; Section 74). As standard solution 0·02 N TBAH in benzene-methanol (see: Chapter 10; Section 57) and as indicator 0·5% azo-violet in pyridine are used. The standard solution consumed between the two inflections or colour changes is directly proportional to the alkoxyl content. Alkyl iodide and pyridine react stoichiometrically. Alkyl iodides are neutral in acetone, acetonitrile or methyl isobutyl ketone.

A suitable apparatus is shown in Fig. 127. Iodine and sulphides do not interfere with titration. For the determination of propoxy and butoxy groups, first boil for 2 hours.

Weigh 10–15 mg of sample in the reaction flask *(1)*. Weigh volatile compounds in gelatine capsules. Add 0·5 ml of xylene and dissolve, if necessary with heating. Add 5·0 ml of 55–58% hydriodic acid and a few boiling stones. In the receiving flask is 50 ml of neutralized pyridine distilled from barium hydroxide. The delivery tip should reach below the surface of the solvent (Fig. 127).

Allow a stream of nitrogen to pass through the apparatus at the rate of 1 bubble per second.

Heat the apparatus by applying a heating mantle so that the condensate is just above bulb *(2)*. Continue to pass N_2 through for 20 min and then increase the rate to 2–3 bubbles/second. Continue heating for 25 min for determination

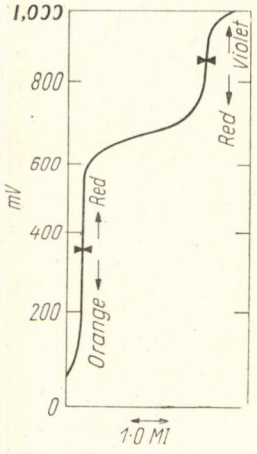


Fig. 126. Titration of a mixture of hydriodic acid-*n*-butyl iodide according to Cundiff and Markunas [163]. — Solvent: Pyridine. Standard solution: 0·02 N tetrabutylammonium hydroxide in benzene-methanol

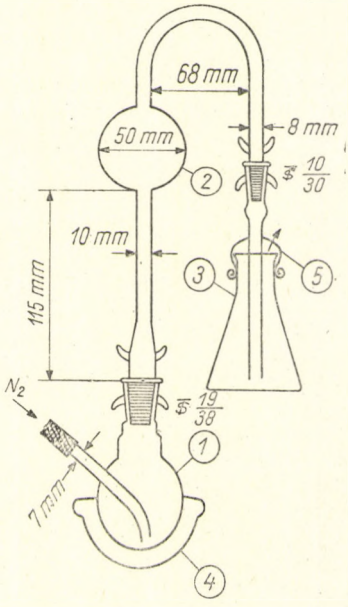


Fig. 127. Alkoxyl apparatus due to Cundiff and Markunas [163]. — *(1)* Reaction flask, *(2)* Bulb, *(3)* Receiver, *(4)* Heating mantle, *(5)* Thin, perforated rubber membrane

of methoxy group, for another 40 min for the ethoxy group. In the case of propoxy and butoxy group an additional 100 min is required and for the determination of S-methyl group another 160 min. A small amount of condensate may reach the receiving flask.

When heating is terminated rinse the exit tube with some neutralized pyridine. Gently boil the pyridine solution for two minutes in a nitrogen stream in a fume cupboard, then cool and titrate under nitrogen with standard 0·02 N TBAH. To calculate, take the blank consumption of the reagents into account. Standardization of the titrant can be performed against pure trimethoxybenzoic acid.

The high boiling points of alkyl iodides having more than four carbon atoms prevent their quantitative determination (isopentyl iodide, 1-iodoheptane, 1-iodohexadecane). If the alkyl iodide formed in a stoppered reaction tube is extracted with a known amount of benzene* and an aliquot of the benzene layer is treated with

* Kirsten and Ehrlich-Rogozinski, *Mikrochimica Acta* **4**, 786 (1955).

aniline [624], the hydriodic acid formed can be titrated with sodium methoxide using thymol blue as an indicator [203].

$$R-I + 2C_6H_5NH_2 \rightarrow C_6H_5NH_2 \cdot HI + C_6H_5NHR$$

$$HRNC_6H_5\,HI + NaOCH_3 \rightarrow HRNC_6H_5 + NaI + CH_3OH$$

169. Carbamic Acid Esters [121]

Numerous esters of carbamic acids are pharmaceutically and industrially important compounds:

$CO(NH_2)_2$ $CO(NH_2)OH$ $CO(NH_2)OR$ $\rightleftharpoons$ $C(OH)(OR)=NH$ Enolic form

Urea Carbamic acid Carbamic acid ester

The *carbamoyl group* ($-O-CO-NH_2$) is the common functional group of carbamic acid esters.

A carbamic acid ester, in its enolic form, reacts with alkali metal methoxide and splits into alkali cyanate and R–OH [121] aided by a basic medium:

$$R-O-C(OH)=NH + KOCH_3 \rightarrow R-O-C(OK)=NH + CH_3OH;$$

$$R-O-C(OK)=NH \rightarrow ROH + NCOK$$

This reaction does not take place with acid amides, urea, semicarbazide and biuret.

Weigh 1–2 m.eq. of carbamic acid ester in an *alkali-resistant flask*, dissolve in 10 ml of pyridine, add precisely 25 ml of 0·1 N alkali metal methoxide in benzene-methanol and boil under reflux for 1 hour. Exclude atmospheric moisture and carbon dioxide by means of an absorption tube filled with potassium hydroxide. Run a blank in the same way. After cooling, titrate with 0·1 N benzoic acid in benzene (Table 18*a*) in the presence of thymol blue till the blue of the indicator turns to yellow. To calculate

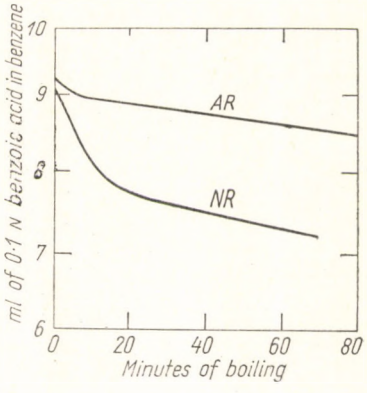


Fig. 128. Decrease of concentration of 10 ml 0·1 N KOH in xylene–Methyl Cellosolve in *(AR)* alkali resistant- and *(NR)* alkali non-resistant flasks

carbamoyl group use the difference between the two measurements. 0·1 m.eq. of carbamic acid ester requires 1 ml of 0·1 N solution (in brackets mg equivalent of 1 ml of 0·1 N solution) of ethylurethane (8·908), isobutyl carbamate (11·72), trimethylene dicarbamate (8·11), benzyl carbamate (15·11), phenyl carbamate (13·71), 2-methyl-2-n-propyl-1,3-propanediol dicarbamate (Meprobamate 10·91), phenyl ethynylcarbinol carbamate (Nirvotin ®, 17·52), carbaminoyl-β-methylcholine chloride, Urecholin chloride®, $H_2N-CO-O-CH(CH_3)-CH_2N^+(CH_3)_3Cl^-$, (19·67), 3-methylpentyne-1-ol-3 carbamate (Oblivon C ®, 14·12; see also: Chapter 27), 1-ethynylcyclohexyl carbamate (Ethinamate, 16·72).

Owing to the disturbing effect of accompanying substances the active agent of tablets must be previously extracted with benzene or methanol in a Soxhlet apparatus.

Fig. 128 indicates the decrease of efficiency between alkaline titrant boiled in an alkali-resistant flask and in a non-resistant one.

170. Substituted Phosphines [781]

Substituted phosphines are phosphorus analogues of amines: R_3P are the tertiary, R_2PH secondary, RPH_2 primary phosphines. Their relative base strengths when measuring half-neutralization potential potentiometrically are in close agreement with values obtained by other base-strength measurements. Phosphines can be titrated in nitromethane with 0·05 N perchloric acid in nitromethane with glass-calomel electrodes. (Chapter 11; Section 60 (b).)

Weigh 0·5–1 mM of compound and dissolve in 100 ml of nitromethane. Employ a magnetic stirrer. A large number of substituted phosphines can be titrated (in brackets pK_a values of bases): e.g. tricyclohexyl- (9·70), triethyl- (8·69), tri-n-propyl- (8·64), tris-(2-phenylethyl)- (6·60), tris-(*p*-methoxyphenyl)- (4·46), triphenyl- (2·73), dicyclohexyl- (4·55), bis-(2-phenylethyl-) phosphines (3·46). Tert-phosphines are the strongest bases. Base strength is decreased by aromatic and electronegative substituents. Thus the order of strength is as follows: tertiary > secondary > primary. The two latter groups include some phosphines which cannot be titrated satisfactorily.

171. Organosilicon Compounds

Chlorosilanes of general formula R_nSiCl_{4-n}, where R is a methyl, ethyl or phenyl group, react with potassium or ammonium rhodanide in ether, and potassium (ammonium) chloride is formed [796].

Weigh chlorosilane (about 1 ml) equivalent to approx. 100 mg of chlorine, dissolve in 10 ml of ethyl ether (of water content < 0·15%), add two drops of 0·5% iron(III) chloride solution in ether and titrate with 0·3 M rhodanide solution in acetone to a red colour change (Chapter 11; Section 60 (n)).

Accuracy of determination in the case of methylchlorosilanes is ±1% and in that of phenylchlorosilanes ±2%.

Visual or potentiometric determination of individual alkylchlorosilanes in methyl cyanide with organic bases, e.g., 0·05 N phenazone in methyl cyanide, or with a solution of amidopyrine in benzene see: [482]. The indicators used are crystal violet,

dimethylaminoazobenzene, bromocresol purple, bromophenol blue and methyl orange. Amperometric titration in methanol-benzene and acetic acid media see: [476].

The determination of binary- and ternary mixtures of methylchlorosilanes is based on the quantitative conversion of Me_3SiCl, Me_2SiCl_2, and $MeSiCl_3$ into the alkylthiocyanate derivatives by the action of ammonium thiocyanate. The differential conductometric titration is effected in methyl cyanide-ethyl ether (2 : 3) with 0·1 M amidopyrine in benzene [481].

Determination of the acetoxy group in various substituted acetoxysilanes in ethyl methyl ketone with methanolic sodium methoxide (0·1 N) in the presence of thymol blue indicator [191]:

$$R_nSi(OCOCH_3)_{4-n} + (4 - n)CH_3ONa \rightarrow R_nSi(OCH_3)_{4-n} + (4 - n)CH_3COONa$$

Potentiometric determination of nitrogen-containing organosilicon compounds, see: [483].

Determination of trace amounts of hydrochloric acid and chlorosilanes in siloxane materials: [533].

Determination of alkoxy groups in alkoxysilanes by acid-catalyzed acetylation: [532]. This method is essentially that developed by Fritz and Schenk [257] for the determination of organic hydroxyl groups (see Chapter 19). A wide variety of alkoxy and aryloxy silanes can be determined. The acetylation is quantitative in less than 2 min at room temperature with 0·06 M perchloric acid catalyst. The following scheme of reactions is suggested [532]:

$$Ac_2O + H^+ \rightleftharpoons Ac_2OH^+$$

$$Ac_2OH^+ \rightleftharpoons Ac^+ + AcOH$$

$$Ac^+ + \equiv SiOR \longrightarrow \equiv SiO^+R \quad (Ac)$$

$$\equiv SiO^+R \quad (Ac) + Ac_2O \longrightarrow \equiv SiOAc + AcOR + Ac^+$$

or

$$\equiv SiO^+R \quad (Ac) + AcOH \longrightarrow SiOAc + AcOR + H^+$$

Determination of mercaptosilanes by perchloric acid-catalyzed acetylation and with mercury(II) acetate: [61]. The assay of the Si–S–C linkage in mercaptosilanes can be effected by the perchloric acid-catalyzed acetylation method of Fritz and Schenk: [257]. The mechanism for the reaction of Ac_2O with the Si–S–C linkage may be the same as that suggested for this method employed for the determination of Si–O–C linkages: [532].

The hydrolysis of mercaptosilanes allows an indirect analysis of the mercapto group by reaction with excess of mercury(II) acetate. The excess is titrated with 0·2 N hydrochloric acid in butanol (see: [489] and Chapter 28).

Weigh a sample containing about 4 m.eq. of mercaptosilane into a 250 ml glass-stoppered Erlenmeyer flask. Dissolve the sample in 50 ml of toluene. Add precisely 50 ml of 0·2 N mercury(II) acetate reagent in methanol, and swirl the solution. Add three drops of 0·2% thymol blue indicator (in ethanol), and titrate slowly with 0·2 N hydrochloric acid in butanol to the red end-point. A blank is run in the same manner but without the sample. The mercaptosilane is calculated from the difference in volume between the sample and blank titrations.

References

A

[1] Agazzi and Bond, *Anal. Chem.* **33,** 972 (1961)
[2] Albert and Goldacre, *J. Chem. Soc.* **1943,** 454
[3] Albert and Goldacre, *J. Chem. Soc.* **1946,** 706
[4] Albert, Goldacre and Phillips, *J. Chem. Soc.* **1948,** 2240
[5] Albert and Phillips, *J. Chem. Soc.* **1956,** 1294
[6] Alicino, *Microchem. J.* **4,** 551 (1960)
[7] Allen and Geddes, *J. Pharm. Pharmacol.* **9,** 990 (1957)
[8] Altschuler, *J. Am. Chem. Soc.* **77,** 3480 (1955)
[9] Ames and Licata, *J. Am. Oil. Chem. Soc.* **25,** 203 (1948)
[10] Anastasi, Gallo and Mecarelli, *Mikrochim. Acta* **1956,** 252
[11] Anastasi, Gallo and Novacic, *J. Pharm. Pharmacol.* **7,** 263 (1955)
[12] Anastasi, Mecarelli and Novacic, *Mikrochim. Acta* **40,** 53 (1952)
[13] Anastasi, Mecarelli and Novacic, *Pharm. Acta Helv.* **30,** 55 (1955)
[14] Arbuzov, Kuznecov and Pavlov, *Zavod. Lab.* **27,** 225 (1961)
[15] van Arkel and Kroonenberg, *Pharm. Weekbl.* **87,** 137 (1952)
[16] Arndt, *Ber.* **63,** 2963 (1930)
[17] Arndt and Lorenz, *Ber.* **63,** 2124 (1930)
[18] Arshid, Giles and Jain, *J. Chem. Soc.* **1956,** 559
[19] Arshid, Giles, McLure, Ogilvie and Rose, *J. Chem. Soc.* **1955,** 67
[20] Ashworth, *Titrimetric Organic Analysis*, Part I. in Elving and Kolthoff: Chemical Analysis **XV.** Interscience, New York (1964)
[21] Audrieth, *Z. phys. Chem.* **165A,** 323 (1933)
[22] Audrieth and Kleinberg: *Non-Aqueous Solvents*, John Wiley & Sons, New York (1953)
[23] Auterhoff and Becker, *Arch. Pharm.* **293,** 1021 (1960)

B

[24] Backe-Hansen, *Norsk Farm. Selskap.* **17,** 1 (1955)
[25] Backe-Hansen and Wickstrom, *Norsk Farm. Selskap.* **19,** 193 (1957)
[26] Badger, *The Structures and Reactions of the Aromatic Compounds*, University Press, Cambridge (1954)
[27] Badoz-Lambling, Desbarres and Tacussel, *Bull. Soc. chim. France* **1962,** 53
[28] Baggesgaard-Rasmussen, Berger and Folting, *Dansk Tidsskr. Farm.* **32,** 29 (1958)
[29] Baker, *Nature* **137,** 236 (1936)
[30] Banick, *Anal. Chem.* **34,** 296 (1962)

[31] Bányai, *Kémiai Indikátorok*, Budapest, Műszaki Könyvkiadó (1961)
[32] Barnes, *Anal. Chem.* **31,** 405 (1959)
[33] Barrow, *J. Am. Chem. Soc.* **78,** 5802 (1956)
[34] Barrow, *J. Am. Chem. Soc.* **80,** 86 (1958)
[35] Barrow and Yerger, *J. Am. Chem. Soc.* **76,** 5211, 5247, 5248 (1954)
[36] Barrow and Yerger, *J. Am. Chem. Soc.* **77,** 4474 (1955)
[37] Barrow and Yerger, *J. Am. Chem. Soc.* **77,** 6206 (1955)
[38] Barton and Howlett, *J. Chem. Soc.* **1949,** 155
[39] Bates, *Anal. Chem.* **29,** 15A (1957)
[40] Bates and Schwarzenbach, *Helv. Chim. Acta* **38,** 699 (1955)
[41] Bayer, J., *Magyar Kém. Folyóirat* **62,** 355 (1956)
[42] Bayer and Posgay, *Pharm. Zhalle* **96,** 561 (1957)
[43] Bayer and Posgay, *Naturwissenschaften* **45,** 185 (1958)
[44] Bayer and Posgay, *Pharm. Zhalle* **100,** 65 (1961)
[45] Bayer, Posgay and Majlát, *Pharm. Zhalle* **101,** 476 (1962)
[46] Bayles and Chetwyn, *J. Chem. Soc.* **1958,** 2328
[47] Becker, *Ber.* **86,** 1150 (1953)
[48] Beckett, Camp and Martin, *J. Pharm. Pharmacol.* **4,** 399 (1952)
[49] Beckett and Tinley, *Titration in Non-aqueous Solvents*, British Drug Houses Ltd.
[50] Beggs and Spencer, *Anal. Chem.* **34,** 1590 (1962)
[51] Belcher, Berger and West, *J. Chem. Soc.* **1959,** 2877, 2882
[52] Bell, A. *Quart. Rev. London* **1,** 113 (1947)
[53] Bell, R. P., *Acids and Bases*, J. Wiley & Sons, New York (1956)
[54] Bell and Bayles, *J. Chem. Soc.* **1952,** 1518
[55] Bell and Trotman-Dickenson, *J. Chem. Soc.* **1949,** 1288
[56] Bellen, *Chem. Anal. (Warsaw)* **6,** 531 (1961)
[57] Benson and Kitschen, *Can. J. Research* Sect. F. 27 (1949)
[58] Bergamini and Mattei, *Sperimentale* **6,** 13 (1955)
[59] Berger, *Acta Chem. Scand.* **6,** 1564 (1952)
[60] Berger, *Acta Chem. Scand.* **8,** 427 (1954)
[61] Berger and Magnuson, *Anal. Chem.* **36,** 1156 (1964)
[62] Berrett, *Bull. Soc. chim. France* **1960,** 271
[63] Berthel and Sheppard, *J. Chem. Phys.* **21,** 1421 (1953)
[64] Bezinger, Gal'pern and Abdurachmanov, *Zh. Anal. Khim.* **16,** 91 (1961)
[65] Bianchi, *Il Farmaco* **16,** 476 (1961)
[66] Billon, *Bull. Soc. chim. France* **1962,** 863
[67] Bishop, Kittredge and Hildebrand, *J. Am. Chem. Soc.* **44,** 135 (1922)
[68] Bjerrum, *Chem. Rev.* **16,** 287 (1935)
[69] Blair and Pantouy, *Anal. Chim. Acta* **13,** 1 (1955)
[70] Blake, *J. Am. Pharm. Assoc. Sci. Ed.* **46,** 163 (1957)
[71] Blom and Edelhausen, *Anal. Chim. Acta* **13,** 120 (1955)
[72] Blumrich and Bandel, *Angew. Chem.* **54,** 374 (1941)
[73] Bockris, *Quart. Rev. London* **3,** 173 (1949)
[74] Bokina, Zarinsky and Shtifman, *Zh. Anal. Khim.* **19,** 635 (1964)
[75] Bonitz, *Ber.* **88,** 742 (1955)
[76] Bonner and Lockhart, *J. Chem. Soc.* **1957,** 364, 2840
[77] Boubli, *Boll. chim. pharm.* **94,** 186 (1955)
[78] Bournique and Neuser, *Chemist-Analyst* **53,** 41 (1964)
[79] Branch and Calvin, *The Theory of Organic Chemistry*, Prentice-Hall, Inc., New York (1941)
[80] Branch and Walba, *J. Am. Chem. Soc.* **76,** 1564 (1954)
[81] Branch and Yabroff, *J. Am. Chem. Soc.* **56,** 2568 (1934)
[82] Brand, Horning and Thornley, *J. Chem. Soc.* **1952,** 1374
[83] Braude and Nachod, *Determination of Organic Structures by Physical Methods*, Academic Press, New York (1955)
[84] Braude and Stern, *J. Chem. Soc.* **1948,** 1971, 1976, 1982
[85] Bennecke, *Die Titration schwacher Basen in Eisessiglösung*, F. Enke, Stuttgart (1951)
[86] Bricker and Sweetser, *Anal. Chem.* **24,** 409 (1952)

[87] Briegleb, *Z. Elektrochem.* **50,** 35 (1944)
[88] Briegleb, *Angew. Chem.* **62,** 262, 536 (1950)
(*b*) *Z. Elektrochem.* **53,** 350 (1949)
[89] Briegleb, Rüttiger and Jung, *Angew. Chem.* **75,** 671 (1963)
[90] Brill, *Z. Elektrochem.* **50,** 47 (1944)
[91] Brockmann and Meyer, *Naturwissenschaften* **40,** 242 (1953)
[92] Brockmann and Meyer, *Ber.* **86,** 1514 (1953)
[93] Brockmann and Meyer, *Ber.* **87,** 81 (1954)
[94] Brown, *Recent Chem. Progr.* **14,** 83 (1953)
[95] Brown and Barbaras, *J. Am. Chem. Soc.* **75,** 6 (1953)
[96] Brown, Bartholomay and Taylor, *J. Am. Chem. Soc.* **66,** 435 (1944)
[97] Brown and Johannesen, *J. Am. Chem. Soc.* **75,** 16 (1953)
[98] Brown and Kanner, *J. Am. Chem. Soc.* **75,** 3865 (1953)
[99] Brönsted, *Rec. Trav. chim.* **42,** 718 (1923)
[100] Bruckenstein, *Anal. Chem.* **31,** 1757 (1959)
[101] Bruckenstein and Kolthoff, *J. Am. Chem. Soc.* **78,** 10 (1956)
[102] Bruckenstein and Kolthoff, *J. Am. Chem. Soc.* **78,** 2974 (1956)
[103] Bruehlman and Verhoeck, *J. Am. Chem. Soc.* **70,** 1401 (1948)
[104] Bruss and Harlow, *Anal. Chem.* **30,** 1836 (1958)
[105] Bruss and Wyld, *Anal. Chem.* **29,** 232 (1957)
[106] Bryant and Wardrop, *J. Chem. Soc.* **1957,** 895
[107] Budesinsky, *Chem. listy* **52,** 2292 (1958)
[108] Burgstahler, Kulier and Worden, *J. Chem. Educat.* **39,** 578 (1962)
[109] Burns and Lawler, *Anal. Chem.* **35,** 802 (1963)
[110] Burton and Praill, *J. Chem. Soc.* **1950,** 1203
[111] Burwell and Langford, *J. Am. Chem. Soc.* **81,** 3799 (1959)
[112] Buscarons, Marin and Claver, *Anal. Chim. Acta* **3,** 310, 417 (1949)
[113] Butler and Czepiel, *Anal. Chem.* **28,** 1468 (1956)
[114] Bykova and Kazaryan, *Trudy Komiss. Anal. Khim., Akad. Nauk SSSR* **13,** 309 (1963)

C

[115] Caldas, *Chemist Analyst* **43,** 100 (1954)
[116] Caldin and Long, *J. Chem. Soc.* **1954,** 3737
[117] Carlton, *J. Am. Chem. Soc.* **44,** 1469 (1922)
[118] Caso and Cefola, *Anal. Chim. Acta* **21,** 205 (1959)
[119] Caso and Cefola, *Anal. Chim. Acta* **21,** 374 (1959)
[120] Caso and Cefola, *Anal. Chim. Acta* **29,** 127 (1963)
[121] Cerri, Spialtini and Gallo, *Pharm. Acta Helv.* **34,** 13 (1959)
[122] Chalandonand Susz, *Helv. Chim. Acta* **41,** 697 (1958)
[123] Chatten, *J. Pharm. Pharmacol.* **7,** 586 (1955)
[124] Chatten, *J. Amer. Pharm. Assoc., Sci. Ed.* **45,** 556 (1956)
[125] Chatten and Harris, *Anal. Chem.* **34,** 1495 (1962)
[126] Chatten, Pernarowski and Levi, *J. Am. Pharm. Assoc., Sci. Ed.* **44,** 332 (1955)
[127] Chatten, Pernarowski and Levi, *J. Am. Pharm. Assoc., Sci. Ed.* **48,** 276 (1959)
[128] Cheronis, *Micro and Semimicro Methods*, Interscience Publ. Inc., New York (1954)
[129] Chiang, *J. Pharm. Sci.* **50,** 885 (1961)
[130] Cholvy, *Ann. pharm. franç.* **18,** 138 (1960)
[131] Chrastil, *Chem. listy* **48,** 781 (1954)
[132] Ciaccio, Missan, McMullen and Grenfell, *Anal. Chem.* **29,** 1670 (1957)
[133] Clair and Chatten, *J. Pharm. Sci.* **50,** 848 (1961)
[134] Clark and Wang, *Anal. Chem.* **26,** 1230 (1954)
[135] Clarke and Sandler, *Chemist Analyst* **50,** 76 (1961)
[136] Cluett, *Anal. Chem.* **31,** 610 (1959)
[137] Cluett, *Anal. Chem.* **34,** 1491 (1962)
[138] Coetzee, *Diss. Abs.* **16,** 1071 (1956); Coetzee and Kolthoff, *J. Am. Chem. Soc.* **79,** 6110 (1957)

[139] Coetzee, Cunningham, McGuire and Padmanabhan, *Anal. Chem.* **34,** 1139 (1962)
[140] Coetzee and Padmanabhan, *J. Phys. Chem.* **66,** 1708 (1962)
[141] Cohen and Gordon, *Anal. Chem.* **28,** 1445 (1956)
[142] Cohn, McMeekin, Edsall and Blanchard, *J. Am. Chem. Soc.* **56,** 784 (1934)
[143] Conant and Chow, *J. Am. Chem. Soc.* **55,** 3745, 3752 (1933)
[144] Conant and Hall, *J. Am. Chem. Soc.* **49,** 3047, 3062 (1927)
[145] Conant and Thompson, *J. Am. Chem. Soc.* **54,** 4039 (1932)
[146] Conant and Werner, *J. Am. Chem. Soc.* **52,** 4436 (1930)
[147] Conant and Wheland, *J. Am. Chem. Soc.* **54,** 1212 (1932)
[148] Connors and Higuchi, *Anal. Chem.* **32,** 93 (1960)
[149] Connors and Swanson, *J. Pharm. Sci.* **53,** 432 (1964)
[150] Corwin and Ellingson, *J. Am. Chem. Soc.* **64,** 2098 (1942)
[151] Coulson, *Valence*, Oxford University Press, London (1952)
[152] Crabb and Critchfield, *Talanta* **10,** 271 (1963)
[153] Crisafio and Chatten, *J. Amer. Pharm. Assoc., Sci. Ed.* **44,** 529 (1955)
[154] Critchfield, Funk and Johnson, *Anal. Chem.* **28,** 76 (1956)
[155] Critchfield and Johnson, *Anal. Chem.* **26,** 1803 (1954)
[156] Critchfield and Johnson, *Anal. Chem.* **29,** 957 (1957)
[157] Critchfield and Johnson, *Anal. Chem.* **29,** 1174 (1957)
[158] Cundiff and Markunas, *Anal. Chem.* **27,** 1650 (1955)
[159] Cundiff and Markunas, *Anal. Chem.* **28,** 792 (1956)
[160] Cundiff and Markunas, *Anal. Chem.* **30,** 1447, 1450 (1958)
[161] Cundiff and Markunas, *Anal. Chim. Acta* **20,** 506 (1959)
[162] Cundiff and Markunas, *Anal. Chim. Acta* **21,** 68 (1959)
[163] Cundiff and Markunas, *Anal. Chem.* **33,** 1028 (1961)
[164] Cundiff and Markunas, *Anal. Chem.* **34,** 584 (1962)
[165] Cundiff and Markunas, *Anal. Chem.* **35,** 1323 (1963)
[166] Cundiff and Riddick, *Anal. Chem.* **24,** 910 (1952)
[167] Curran, *J. Am. Chem. Soc.* **67,** 1835 (1945)

D

[168] Dahmen, *Chim. anal.* **40,** 378, (1958)
[169] Das, *Anal. Chem.* **26,** 1086 (1954)
[170] Das and Mukherjee, *Anal. Chem.* **31,** 233 (1959)
[171] Davis and Hetzer, *J. Res. Nat. Bur. Stand.* **48,** 381 (1952)
[172] Davis and Hetzer, *J. Am. Chem. Soc.* **76,** 4247 (1954)
[173] Davis and Hetzer, *J. Res. Nat. Bur. Stand.* **60,** 569 (1958)
[174] Davis and Paabo, *J. Am. Chem. Soc.* **82,** 5081 (1960)
[175] Deal, Weiss and White, *Anal. Chem.* **25,** 426 (1953)
[176] Deal and Wyld, *Anal. Chem.* **27,** 47 (1955)
[177] Dean and Cain, *Anal. Chem.* **27,** 212 (1955)
[178] De Lorenzi and Credali, *Boll. chim. farm.* **95,** 325 (1956)
[179] Deno, *J. Am. Chem. Soc.* **74,** 2039 (1952)
[180] De Paulis and Dipietromaria, *Boll. chim. farm.* **99,** 15 (1960)
[181] Dermer, Wilson, Johnson and Dermer, *J. Am. Chem. Soc.* **63,** 2881 (1941)
[182] De Vries and Gantz, *J. Am. Chem. Soc.* **76,** 1008 (1954)
[183] De Vries, Schiff and Gantz, *Anal. Chem.* **27,** 1814 (1955)
[184] Dewar, *The Electronic Theory of Organic Chemistry*, Oxford (1954)
[185] Deyrup, *J. Am. Chem. Soc.* **56,** 60 (1934)
[186] Dilthey and Dinklage, *Ber.* **62,** 1834 (1929)
[187] Dilthey and Wizinger, *J. Prakt. Chem.* **2,** 118, 321 (1928)
[188] Dimroth and Meyer-Brunot, *Biochem. Z.* **323,** 338 (1952)
[189] Dippy, *Chem. Revs.* **25,** 151, 179 (1939)
[190] Doernberg, Hubacher and Lysyj, *J. Am. Pharm. Assoc., Sci. Ed.* **43,** 418 (1954)
[191] Drozdov and Vlasova, *Trudy Komiss. Anal. Khim., Akad. Nauk SSSR*, **13,** 187 (1963)
[192] Dubois and Lacaze, *Compt. rend.* **252,** 748 (1961)

[193] Dugan, *Anal. Chem.* **33,** 1930 (1961)
[194] Dulova and Kim, *Khim. Nauka i Prom.* **4,** 134 (1959)
[195] Dulova, Leont'ev and Kim, *Trudy Sredneziat. Gosudarst. Univ. im. V. I. Lenina, Khim.* **84,** 69 (1958)
[196] Dulova and Popova, *Trudy Sredneziat. Gosudarst. Univ. im. V. I. Lenina, Khim.* **84,** 63 (1958)
[197] Durbetaki, *Anal. Chem.* **28,** 2000 (1956)
[198] Durbetaki, *Anal. Chem.* **30,** 2024 (1958)
[199] Dušinský, G., *Chem. listy* **48,** 1868 (1954)

E

[200] Eberius, *Wasserbestimmung mit Karl-Fischer-Lösung*, Verlag Chemie, Weinheim/Bergstr. (1958)
[201] Ebert and Konopik, *Österr. Chem. Ztg.* **50,** 184 (1949)
[202] Edward and Wang, *Can. J. Chem.* **40,** 966 (1962)
[203] Ehrlich-Rogozinski and Patchornik, *Bull. Res. Counc. Israel,* **11A,** 190 (1962); *Anal. Chem.* **36,** 840 (1964)
[204] Eisdorfer, Rosen and Ellenbogen, *J. Pharm. Sci.* **50,** 612 (1961)
[205] Eistert, *Tautomerie und Mesomerie*, F. Enke, Stuttgart (1938)
[206] Eistert, *Chemismus und Konstitution*, F. Enke, Stuttgart (1948)
[207] Ekeblad, P., *J. Pharm. Pharmacol.* **4,** 636 (1952)
[208] Ellerington and Nicholls, *Analyst* **82,** 233 (1957)
[209] Ellert, Jasinski and Marcinkowska, *Acta Polon. Pharm.* **17,** 29 (1960)
[210] Ellert, Jasinski and Pavelczak, *Acta Polon. Pharm.* **19,** 69 (1962)
[211] Ellert, Jasinski and Weclawska, *Acta Polon. Pharm.* **17,** 145 (1960)
[212] Ellert, Jasinski and Weclawska, *Acta Polon. Pharm.* **19,** 75 (1962)
[213] Emelin and Svistunova, *Zadov. Lab.* **27,** 1458 (1961)
[214] Erdey, Gimesi and Rády, *Acta Chim. Hung.* **28,** 179 (1961)
[215] Erdey, Gimesi and Rády, *Talanta* **11,** 461 (1964)
[216] Erdey, Meisel and Rády, *Acta Chim. Hung.* **26,** 71 (1961)
[217] Erdey and Rády, *Acta chim. acad. sci. Hung.* **15,** 81 (1958)
[218] Everett, *Ind. chim. Belge.* **16,** 647 (1951)
[219] Everett and Wynne-Jones, *Proc. Roy. Soc.* **A 177,** 499 (1941)

F

[220] Faber, *J. Pharm. Pharmacol.* **6,** 187 (1954)
[221] Fajans, *Ber.* **21,** 709 (1919)
[222] Farina, Donati and Ragazzini, *Ann. chim. (Rome)* **48,** 501 (1958)
[223] Fauth, Frandsen and Havlik, *Anal. chem.* **36,** 380 (1964)
[224] Feigl, *Spot Tests in Organic Analysis*, Elsevier, Amsterdam (1956)
[225] Feigl, *Spot Tests in Inorganic Analysis*, Elsevier, Amsterdam (1958)
[226] Feigl, Anger and Frehden, *Mikrochemie* **15,** 19 (1934)
[227] Ferguson, *J. Chem. Educ.* **33,** 276 (1956)
[228] Feuer and Vincent, *Anal. Chem.* 35, 598 (1963)
[229] Flaschka and Barnard, jr., 'Tetraphenylboron as an Analytical Reagent' in Reilley: *Advances in Analytical Chemistry and Intsrumentation*, Vol. I., Interscience Inc., New York 1960
[230] Flexer, Hammett and Dingwall, *J. Am. Chem. Soc.* **57,** 2103 (1935)
[231] Fodor, *Szerves Kémia* I, II., Tankönyvkiadó, Budapest (1960)
[232] Fogg and Jellum, *Analyst* **87,** 302 (1962)
[233] Forbes and Knight, *Can. J. Chem.* **37,** 334 (1959)
[234] Forbes and Templeton, *Chem. & Ind. (London)* **1957** 77, 600
[235] Forbes and Templeton, *Can. J. Chem.* **36,** 180 (1958)
[236] Forman and Hume, *J. Phys. Chem.* **63,** 1949 (1959)
[237] Fortuin, *Anal. Chim. Acta* **24,** 175 (1961)

[238] Fossum, Markunas and Riddick, *Anal. Chem.* **23,** 491 (1951)
[239] Franklin, *J. Am. Chem. Soc.* **46,** 2137 (1924)
[240] Franklin, *The Nitrogen System of Compounds*, Reinhold Publishing Co., New York (1935)
[241] Freri, *Gazetta Chim. Ital.* **83,** 61 (1953)
[242] Freymann, *Compt. rend.* **204,** 41 (1937)
[243] Fripiat, Vankompernolle and Servais, *Bull. Soc. chim. France* **1960,** 250
[244] Fritz, *Anal. Chem.* **22,** 578, 1028 (1950)
[245] Fritz, *Anal. Chem.* **24,** 306 (1952)
[246] Fritz, *Anal. Chem.* **24,** 674 (1952)
[247] Fritz, *Anal. Chem.* **25,** 407 (1953)
[248] Fritz, *Anal. Chem.* **26,** 1701 (1954)
[249] Fritz and Fulda, *Anal. Chem.* **25,** 1837 (1953)
[250] Fritz and Keen, *Anal. Chem.* **24,** 308 (1952)
[251] Fritz and Keen, *Anal. Chem.* **25,** 179 (1953)
[252] Fritz and Lisicki, *Anal. Chem.* **23,** 589 (1951)
[253] Fritz and Marple, *Anal. Chem.* **34,** 921 (1962)
[254] Fritz, Moye and Richard, *Anal. Chem.* **29,** 1685 (1957)
[255] Fritz and Palmer, *Anal. Chem.* **33,** 98 (1961)
[256] Fritz and Pietrzyk, *Anal. Chem.* **31,** 1157 (1959)
[257] Fritz and Schenk, *Anal. Chem.* **31,** 1808 (1959)
[258] Fritz and Yamamura, *Anal. Chem.* **29,** 1079 (1957)
[259] Fritz, Yamamura and Bradford, *Anal. Chem.* **31,** 260 (1959)
[260] Fuoss and Krauss, *J. Am. Chem. Soc.* **55,** 2387 (1933)

G

[261] Gagnaux, Janjic and Susz. *Helv. Chim. Acta*, **41,** 1023, 1322 (1958)
[262] Galpern and Bezinger, *Zh. Anal. Khim.* **13,** 603 (1958)
[263] Gautier, *Bull. Soc. chim. France* **1960,** 1263
[264] Gautier and Pellerin, *Ann. pharm. franç.* **10,** 401 (1952)
[265] Gautier and Pellerin, *Ann. pharm. franç.* **12,** 505 (1954)
[266] Gautier, Pellerin and Pineau, *Ann. pharm. franç.* **16,** 625 (1958)
[267] Gautier, Renault and Pellerin, *Ann. pharm. franç.* **13,** 725 (1955)
[268] Gautier, Renault and Pellerin, *Ann. pharm. franç.* **14,** 337 (1956)
[269] Gehlen, *Z. phys. Chem.* **203,** 125 (1954)
[270] Gillespie, *J. Chem. Soc.* **1950,** 2542
[271] Gillespie, *J. Chem. Soc.* **1954,** 1851
[272] Gillespie, Hughes and Ingold, *J. Chem. Soc.* **1950,** 2473
[273] Glass and Moore, *Anal. Chem.* **33,** 494 (1961)
[274] Glenn and Peake, *Anal. Chem.* **27,** 205 (1955)
[275] Goddu and Hume, *Anal. Chem.* **22,** 1314 (1950)
[276] Goddu and Hume, *Anal. Chem.* **26,** 1679 (1954)
[277] Goddu and Hume, *Anal. Chem.* **26,** 1740 (1954)
[278] Gold and Jefferson, *J. Chem. Soc.* **1953,** 1409
[279] Goldfarb, Mele and Gutstein, *J. Am. Chem. Soc.* **77,** 6194 (1955)
[280] Goldstein and Dodgen, *Drug. Std.* **26,** 113 (1958)
[281] Goodhue and Hixon, *J. Am. Chem. Soc.* **56,** 1329 (1934); **57,** 1688 (1935)
[282] Gordy and Stanford, *J. Phys. Chem.* **8,** 170 (1940); **9,** 204 (1941)
[283] Görög, *Acta Chim. Hung.* **47,** 1 (1966)
[284] Görög and Tomcsányi, *Acta. Chim. Hung.* **47,** 121 (1966)
[285] Gran and Althin, *Acta Chem. Scand.* **4,** 967 (1950)
[286] Grant, Hunter and Massie, *Analyst* **88,** 134 (1963)
[287] Greenhow and Smith, *Analyst* **84,** 457 (1959)
[288] Gremillion, *Anal. Chem.* **27,** 133 (1955)
[289] Gribova and Levin, *Zavod. lab.* **24,** 1356 (1958)
[290] Gribova and Levin, *Zavod. Lab.* **25,** 38 (1959)
[291] Grove and Jeffery, *Talanta* **7,** 56 (1960)

[292] Grunwald, *Anal. Chem.* **26,** 1696 (1954)
[293] Grunwald, *Anal. Chem.* **28,** 1112 (1956)
[294] Gurney, *Ionic Processes in Solutions*, McGraw-Hill, New York (1953)
[295] Gutmann and Lindqvist, *Z. phys. Chem.* **203,** 251 (1954)
[296] Gutmann and Lindqvist, *Angew. Chem.* **66,** 330 (1954)
[297] Gutterson and Ma, *Mikrochim. Acta* **1960,** 1
[298] Gutterson and Ma, *Microchem. J.* **5,** 601 (1961)
[299] Gyenes, *Magyar Kém. Folyóirat* **56,** 383 (1950)
[300] Gyenes, *Magyar Kém. Folyóirat* **57,** 4 (1951)
[301] Gyenes, *Magyar Kém. Folyóirat* **59,** 12 (1953)
[302] Gyenes, *Magyar Kém. Folyóirat* **59,** 353 (1953)
[303] Gyenes, *Acta. Pharm. Hung.* **24,** 11 (1954)
[304] Gyenes, *Magyar Kém. Lapja* **10,** 12 (1955)
[305] Gyenes, *Magyar Kém. Folyóirat* **61,** 89 (1955)
[306] Gyenes, *Magyar Kém. Folyóirat* **62,** 26 (1956)
[307] Gyenes, *Magyar Kém. Folyóirat* **62,** 237 (1956)
[308] Gyenes, *Magyar Kém. Folyóirat* **62,** 239 (1956)
[309] Gyenes, *Magyar Kém. Folyóirat* **62,** 242 (1956)
[310] Gyenes, *Magyar Kém. Folyóirat* **63,** 94 (1957)
[311] Gyenes, *Magyar Kém. Folyóirat* **64,** 10 (1958)
[312] Gyenes, *Magyar Kém. Folyóirat* **65,** 264 (1959)
[313] Gyenes, *Acta Pharm. Hung.* **30,** 55 (1960)
[314] Gyenes, *Magyar Kém. Folyóirat* **66,** 55 (1960)
[315] Gyenes, *Acta Chim. Hung.* **26,** 403 (1961)
[316] Gyenes, *Magyar Kém. Folyóirat* **67,** 162 (1961)
[317] Gyenes, *Magyar Kém. Folyóirat* **67,** 371 (1961)
[318] Gyenes, 'Chemie u. Biochemie d. Solanum-Alkaloide', *Tagungsberichte* Nr. 27. Dtsch. Akad. d. Landwirtschaftswissenschaften z. Berlin, 177 (1961)
[319] Gyenes, *Acta Pharm. Hung.* **32,** 241 (1962)
[320] Gyenes, *Acta Pharm. Hung.* **34,** 99 (1964)
[321] Gyenes and László, *Magyar Kém. Folyóirat* **67,** 166 (1961)
[322] Gyenes and László, *Talanta* **10,** 567 (1963)
[323] Gyenes, Németh and Bayer, *Acta Pharm. Hung.* **27,** 23 (1957)
[324] Gyenes and Szász, *Magyar Kém. Folyóirat* **61,** 356 (1955)
[325] Gyenes and Szász, *Vest. Akad. Nauk Kaz.SSR.* **1,** 34 (1961)
[326] Gyenes and Váli, *Magyar Kém. Folyóirat* **61,** 90 (1955)

H

[327] Hadži and Thompson, *Hydrogen Bonding*, Pergamon Press, London (1959)
[328] Hagen and Leslie, *Anal. Chem.* **35,** 814 (1963)
[329] Haggard and Greenberg, *Science* **93,** 479 (1941)
[330] Hahn, *Anal. Chim. Acta* **4,** 577 (1950)
[331] Hahn, *Anal. Chim. Acta* **9,** 400 (1953)
[332] Hall, *J. Am. Chem. Soc.* **52,** 5115 (1930)
[333] Hall, jr., *J. Phys. Chem.* **60,** 63 (1956)
[334] Hall and Sprinkle, *J. Amer. Chem. Soc.* **54,** 3469 (1932)
[335] van Hall Stone, *Anal. Chem.* **27,** 1580 (1955)
[336] van Hall Stone, *Anal. Chem.* **30,** 1416 (1958)
[337] Hall Werner, *J. Am. Chem. Soc.* **50,** 2367 (1928)
[338] Hammett, *J. Am. Chem. Soc.* **50,** 2666 (1928)
[339] Hammett, *Chem. Revs.* **16,** 67 (1935)
[340] Hammett, *Physical Organic Chemistry*, McGraw-Hill Book Comp., New York (1940)
[341] Hammett, *J. Chem. Phys.* **8,** 644 (1940)
[342] Hammett and Deyrup, *J. Am. Chem. Soc.* **54,** 2721 (1932)
[343] Hammett and Deyrup, *J. Am. Chem. Soc.* **54,** 4239 (1932)
[344] Hammett and Deyrup, *J. Am. Chem. Soc.* **55,** 1900 (1933)

[345] Hammett and Paul, *J. Am. Chem. Soc.* **56,** 827 (1934)
[346] Hammond, *Steric Effects in Organic Chemistry*, Wiley & Sons, New York (1956)
[347] Hanna and Siggia, *Anal. Chem.* **34,** 547 (1962)
[348] Hansson, *Svensk Kem. Tidskr.* **67,** 256 (1955)
[349] Hantzsch, *Z. phys. Chem.* **61,** 257 (1907)
[350] Hantzsch, *Z. Elektrochem.* **29,** 221 (1923)
[351] Hantzsch, *Die Theorie der ionogenen Bindung als Grundlage der Ionentheorie*, Verlag Chemie, Leipzig (1924)
[352] Hantzsch, *Z. phys. Chem.* **63B,** 1782, 1789 (1930)
[353] Hantzsch and Hilscher, *Ber.* **41,** 1171 (1908)
[354] Hantzsch and Langbein, *Z. anorg. Chem.* **204,** 193 (1932)
[355] Harlow, *Anal. Chem.* **34,** 148 (1962)
[356] Harlow, *Anal. Chem.* **34,** 1482 (1962)
[357] Harlow, *Anal. Chem.* **34,** 1487 (1962)
[358] Harlow and Bruss, *Anal. Chem.* **30,** 1833 (1958)
[359] Harlow, Noble and Wyld, *Anal. Chem.* **28,** 787 (1956)
[360] Harlow and Wyld, *Anal. Chem.* **30,** 69 (1958)
[361] Harlow and Wyld, *Anal. Chem.* **34,** 172 (1962)
[362] Harned, *J. Am. Chem. Soc.* **60,** 336 (1938)
[363] Hart and Fish, *J. Am. Chem. Soc.* **82,** 5419 (1960)
[364] Havemann, *Biochem. Z.* **310,** 378 (1942)
[365] Hawke and Steigman, *Anal. Chem.* **26,** 1989 (1954)
[366] Hädicke and Howorka, *Pharm. Zhalle*, **99,** 312 (1960)
[367] Hädicke and Howorka, *Pharm. Zhalle*, **100,** 3 (1961)
[368] Hefferren and Koehler, *J. Pharm. Sci.* **50,** 582 (1961)
[369] van der Heijde, *Anal. Chim. Acta* **16,** 392 (1957)
[370] van der Heijde, *Anal. Chim. Acta* **17,** 512 (1957)
[371] van der Heijde and Dahmen, *Anal. Chim. Acta* **16,** 378 (1957)
[372] Heiz, *Dansk Tiddskr. Farm.* **20,** 69 (1952)
[373] Hennart and Merlin, *Chimie analytique* **39,** 269 (1957)
[374] Hennart and Merlin, *Chimie analytique* **39,** 385 (1957)
[375] Hennart and Merlin, *Chimie analytique* **40,** 20 (1958)
[376] Hennart and Merlin, *Chimie analytique* **40,** 167 (1958)
[377] Hennart and Merlin, *Chimie analytique* **40,** 264 (1958)
[378] Hennart and Vieillet, *Chimie analytique* **44,** 61 (1962)
[379] Henry, Hazel and McNabb, *Analyt. Chim. Acta* **15,** 187 (1956)
[380] Hermans, *Theoretical Organic Chemistry*, Elsevier, Amsterdam (1954)
[381] Hess and Haber, *Ber.* **70,** 2205 (1937)
[382] Heston and Hall, *J. Am. Chem. Soc.* **56,** 1462 (1934)
[383] Higuchi, 'Application of Lithium Aluminium Hydride to Organic Analyses' in Mitchell, Kolthoff, Proskauer and Weissberger: *Organic Analysis* II., 123 Interscience, New York (1954)
[384] Higuchi and Barnstein *Anal. Chem.* **28,** 1022 (1956)
[385] Higuchi, Barnstein, Ghassemi and Perez, *Anal. Chem.* **34,** 400 (1962)
[386] Higuchi and Concha, *J. Am. Pharm. Assoc., Sci. Ed.* **40,** 173 (1951)
[387] Higuchi, Concha and Kuramoto, *Anal. Chem.* **24,** 685 (1952)
[388] Higuchi and Connors, *J. phys. Chem.* **64,** 179 (1960)
[389] Higuchi, Feldman and Rehm, *Anal. Chem.* **28,** 1120 (1956)
[390] Higuchi, Rehm and Barnstein, *Anal. Chem.* **28,** 1506 (1956)
[391] Higuchi and Zuck. *J. Am. Chem. Soc.* **73,** 2676 (1951)
[392] Hillenbrand and Pentz, 'Determination of Amides and Related Compounds' in Mitchell, Kolthoff, Proskauer and Weissberger: *Organic Analysis*, III., Interscience, New York (1954)
[393] Hine, *Physical Organic Chemistry*, McGraw-Hill, New York (1956)
[394] Hine and Hine, *J. Am. Chem. Soc.* **74,** 5266 (1952)
[395] Hinswark and Stone, *Anal. Chem.*, **28,** 334 (1956)
[396] Hitchcock and Elving, *Anal. Chim. Acta* **27,** 501 (1962)
[397] Hixon and Johns, *J. Am. Chem. Soc.* **49,** 1786 (1927)

[398] Hofmann, *Chemistry of Heterocyclic Compounds* Vol. IV., Interscience, New York (1953)
[399] Hofstadter, *J. Chem. Phys.* **6,** 540 (1938)
[400] Howorka and Hädicke, *Pharm. Zhalle* **98,** 538 (1959)
[401] Huber, *Angew. Chem.* **72,** 865 (1960)
[402] Hughes and Ingold, *J. Chem. Soc.* **1935,** 244
[403] Huisgen and Brade, *Ber.* **90,** 1432 (1957)
[404] Hummelstedt and Hume, *Anal. Chem.* **32,** 576 (1960)
[405] Hummelstedt and Hume, *Anal. Chem.* **32,** 1792 (1960)

I

[406] Inczédy and Gimesi, *Acta Chim. Hung.* **31,** 347 (1962)
[407] Ingold, *Helv. Chim. Acta* **29,** 1929 (1946)
[408] Ioffe and Sergeeva, *Zh. Anal. Khim.* **12,** 540 (1957)
[409] Ionescu, Enache and Constantinescu, *Rev. chim. (Bucharest)* **14,** 534 (1963)
[410] Ishidate, Nishizava, Sano and Horikoshi, *J. Pharm. Soc. Japan.* **81,** 1303, 1307, 1310, 1313 (1961)
[411] Izmaĭlov, *Zh. anal. Khim.* **10,** 275 (1949)
[412] Izmaĭlov, *Zh. Fiz. Khim.* **24,** 321 (1950)
[413] Izmaĭlov, *Zh. Fiz. Khim.* **28,** 2047 (1954)
[414] Izmaĭlov and Belgova, *Zh. Obshchei Khim.* **9,** 453 (1939)
[415] Izmaĭlov, Shustova and Vodores, *Zh. Obshchei Khim.* **9,** 598 (1939)

J

[416] Jackwerth and Specker, *Z. anal. Chem.* **171,** 270 (1959)
[417] Jacobs, *Analyst* **85,** 257 (1960)
[418] Jacobs and Scheflan, *Chemical Analysis of Industrial Solvents*, Interscience, New York (1953)
[419] Jancik and Körbl, *Československ. Farm.* **5,** 408 (1956)
[420] Jander and Klaus, *Z. Elektrochem.* **58,** 237 (1954)
[421] Jander and Klaus, *J. Inorg. Nuclear Chem.* **1,** 228 (1955)
[422] Jander and Kraffczyk, *Z. anorg. allg. Chem.* **282,** 121 (1955)
[423] Jander and Surawski, *Z. Elektrochem.* **65,** 527 (1961)
[424] Janz and Danyluk, *J. Amer. Chem. Soc.* **81,** 3846, 3850 (1959)
[425] Jasinski, *Acta Polon. Pharm.* **14,** 45 (1957)
[426] Jasinksi and Misiak, *Chem. Anal. (Warsaw)* **9,** 113 (1964)
[427] Jaunin, Beretta-Piccoli and Charalambous, *Helv. Chim. Acta* **37,** 216 (1954)
[428] Jay, *Anal. chem.* **36,** 667 (1964)
[429] Johnson, Perkin reactions and related reactions, in *Organic Reactions* **1,** 210 (1947)
[430] Johnson and Fletcher, *Anal. Chem.* **31,** 1563 (1959)
[431] Johnson and Funk, *Anal. Chem.* **27,** 1464 (1955)
[432] Johnson and Funk, *Anal. Chem.* **28,** 1977 (1956)
[433] Jordan, *Chimia* **17,** 101 (1963)
[434] Jordan and Fischer, *Z. anal. Chem.* **168,** 182 (1959)
[435] Josien and Sourisseau, 'Contribution à l'étude des molecules aromatique considérés comme accepteurs de protons', in Hadži and Thompson: *Hydrogen Bonding*, Pergamon Press, London (1959)
[436] Jovánovics, Márk, Hörömpő and Szász, *Acta Pharm. Hung.* **34,** 36 (1964)

K

[437] Kahane, *Bull. Soc. chim. France* **1951,** 92
[438] Kahovec and Knollmüller, *Z. phys. Chem.* B**51,** 49 (1941)
[439] Kaleis, *Aptechnoe Delo* **7,** 63 (1958)
[440] Karle and Brockway, *J. Am. Chem. Soc.* **66,** 574 (1944)

[441] Karrman and Johansson, *Mikrochim. Acta* **11,** 1573 (1956)
[442] Kashima, *Bull. Nat. Hyg. Lab. (Tokyo)* **72,** 145, 151 (1954)
[443] Kashima, *J. Pharm. Soc. Japan* **74,** 1078 (1954)
[444] Kashima, *Chem. and Pharm. Bull.* **6,** 229 (1958)
[445] Kashima, Syoji and Tsuchiya, *Eisei shikenjo Hôkoku* **74,** 15 (1956)
[446] Katz and Glenn, *Anal. Chem.* **24,** 1157 (1952)
[447] Kaufman and Singleterry, *J. Phys. Chem.* **56,** 604 (1952)
[448] Kavarana, *Am. J. Pharm.* **131,** 184 (1959)
[449] Kaye, *Anal. Chem.* **27,** 292 (1955)
[450] Keen and Fritz, *Anal. Chem.* **24,** 564 (1952)
[451] Keily and Hume, *Anal. Chem.* **36,** 543 (1964)
[452] Keller and Weiss, *Pharmazie* **12,** 462 (1957)
[453] Kerny, Billon and Bigeard, *Ann. pharm. franç.* **17,** 284 (1959)
[454] Keyworth, *J. Org. Chem.* **24,** 1355 (1959)
[455] Kilpatrick and Kilpatrick, *Chem. Revs.* **13,** 131 (1933)
[456] Kilpi and Harjanne, *Suomen Kemistilehti* [B] **21,** 14 (1948)
[457] Kirrmann and Daune-Dubois, *Compt. rend.* **236,** 1361 (1953)
[458] Kirwood and Westheimer, *J. Chem. Phys.* **6,** 506, 513 (1938)
[459] Kleckner and Osol, *J. Am. Pharm. Ass., Sci. Ed.* **41,** 573 (1952)
[460] Klotz, Fiess, Ho and Mellody, *J. Am. Chem. Soc.* **76,** 5136 (1954)
[461] Knappe and Peteri, *Z. analyt. Chem.* **194,** 417 (1963)
[462] Kolling, *J. Am. Chem. Soc.* **79,** 2717 (1957)
[463] Kolling and Smith, *Anal. Chem.* **31,** 1876 (1959)
[464] Kolthoff and Bruckenstein, *J. Am. Chem. Soc.* **79,** 1 (1957); **78,** 1 (1956)
[465] Kolthoff, Bruckenstein and Chantooni, *J. Am. Chem. Soc.* **83,** 3927 (1961)
[466] Kolthoff and Chantooni, *J. Am. Chem. Soc.* **85,** 2196 (1963)
[467] Kolthoff and Coetzee, *J. Am. Chem. Soc.* **79,** 870, 1852, 6110 (1957)
[468] Kolthoff and Ikeda, *J. Phys. Chem.* **65,** 1020 (1961)
[469] Kolthoff, Stočesocá and Lee, *J. Am. Chem. Soc.* **75,** 1834 (1953)
[470] Kolthoff and Willmann, *J. Am. Chem. Soc.* **56,** 1007, 1014 (1934)
[471] Kráčmarová and Kráčmar, *Českoslov. Farm.* **7,** 566 (1958)
[472] Kraus, *The Properties of Electrically Conducting Systems*, Chemical Catalog Co. (1922)
[473] Krausz and Havas, *Magyar Kém. Folyóirat* **70,** 104 (1964)
[474] Kreshkov and Aldarova, *Trudy Komiss. Anal. Khim., Akad. Nauk SSSR* **13,** 315 (1963)
[475] Kreshkov and Aldarova, *Zh. Anal. Khim.* **19,** 537 (1964)
[476] Kreshkov, Bork and Aparsheva, *Zh. Anal. Khim.* **18,** 1149 (1963)
[477] Kreshkov, Bykova and Mhitaryan, *Zh. Anal. Khim.* **14,** 529 (1959)
[478] Kreshkov, Bykova, Rusakova and Kazaryan, *Zavod. Lab.* **28,** 11 (1962)
[479] Kreshkov, Bykova and Shemet, *Zh. Anal. Khim.* **16,** 331 (1961)
[480] Kreshkov, Bykova and Smolova, *Zh. Anal. Khim.*, **19,** 156 (1964)
[481] Kreshkov and Drozdov, *Dokl. Akad. Nauk. SSSR* **131** 1345 (1960)
[482] Kreshkov and Drozdov, *Izv. Vyssh. Ucheb. Zavedenii, Khim. i Khim. Technol.* **3,** 85 (1960)
[483] Kreshkov, Drozdov and Vlasova, *Zavod. Lab.* **26,** 108 (1960)
[484] Kreshkov and Vasil'ev, *Zh. Anal. Khim.* **17,** 908 (1962)
[485] Kreshkov, Yarovenko and Zel'manova, *Zh. Anal. Khim.* **17,** 780 (1962)
[486] Kukin, *Anal. Chem.* **29,** 461 (1957)
[487] Kukin, *Anal. Chem.* **30,** 1114 (1958)
[488] Kumler and Sah, *J. Org. Chem.* **18,** 669 (1953)
[489] Kundu and Das, *Anal. Chem.* **31,** 1358 (1959)
[490] Kunkel, Buckley and Gorin, *Anal. Chem.* **31,** 1098 (1959)
[491] Kühni, Grossglauser, Richard and Stump, *Pharm. Acta Helv.* **29,** 104 (1954)

L

[492] Lada, *Rocznicki Chem.* **29,** 950 (1955)
[493] Laitinen and Wawzonek, *J. Am. Chem. Soc.* **64,** 1765 (1942)
[494] Landee and Johns, *J. Am. Chem. Soc.* **63,** 2895 (1941)

[495] Lane, *Analyst* **80,** 675 (1955)
[496] Láng and Tavaszy, *Z. anal. Chem.* **158,** 339 (1957)
[497] Lange: *Handbook of Chemistry*, McGraw-Hill Book Company Inc., New York (1961)
[498] Langford and Burwell, *J. Am. Chem. Soc.* **82,** 1503 (1960)
[499] Lapidus, Lucas and Trémillon, *Bull. soc. chim. France* **1960,** 1849
[500] Latimer and Rodebush, *J. Am. Chem. Soc.* **42,** 1430 (1920)
[501] Laubengayer and Sears, *J. Am. Chem. Soc.* **67,** 164 (1945)
[502] Lavine and Toennies, *J. Biol. Chem.* **101,** 727, 732 (1933)
[503] Leader and Gormley, *J. Am. Chem. Soc.* **73,** 5731 (1951)
[504] Leavitt and Autian, *Drug Std.* **26,** 33 (1958)
[505] Lemaire and Lucas, *J. Am. Chem. Soc.* **73,** 5198 (1951)
[506] Leuts and Wagner, *Chemist Analyst* **50,** 43 (1961)
[507] Levi, Chatten and Pernarowski, *J. Am. Pharm. Ass., Sci. Ed.* **44,** 61 (1955)
[508] Levine and Kostin, *Zh. Obshchei Khim.* **23,** 1054 (1953)
[509] Lewis, *J. Franklin Inst.* **226,** 293 (1938)
[510] Lewis and Seaborg, *J. Am. Chem. Soc.* **61,** 1886 (1939)
[511] Lieber, Ramachandra Rao and Tai Siang Chao, *Anal. Chem.* **29,** 932 (1957)
[512] Linek and Peciar, *Chem. Zvesti* **16,** 692 (1962)
[513] Lintner, Schleif and Higuchi, *Anal. Chem.* **22,** 534 (1950)
[514] Lintner, Zuck and Higuchi, *J. Am. Pharm. Ass., Sci. Ed.* **39,** 418 (1950)
[515] Lippinkott and Timnick, *Anal. Chem.* **28,** 1690 (1956)
[516] Lipscomb and Baker, *J. Am. Chem. Soc.* **64,** 179 (1942)
[517] Liteanu and Cörmös, *Talanta* **7,** 32 (1960)
[518] Liu and Reynolds, *Anal. Chem.* **34,** 542 (1962)
[519] Lohr, *Anal. Chem.* **32,** 1166 (1960)
[520] van Looy and Hammett, *J. Am. Chem. Soc.* **81,** 3872 (1959)
[521] Lorenz and Parks, *Anal. Chem.* **34,** 394 (1962)
[522] Lowry, *Chem. & Ind.* **42,** 43 (1923)
[523] Lowry, *Chem. Revs.* **5,** 231 (1928)
[524] Löber and Hesse, *Pharmazie* **14,** 214 (1959)
[525] Lőrincz, *Magyar Kém. Folyóirat* **67,** 414 (1961)
[526] Lőrincz and Szász, *Acta Pharm. Hung.* **33,** 84 (1963)
[527] Lucchesi and Hirn, *Chemist Analyst* **50,** 109 (1961)
[528] Luder and Zuffanti, *The Electronic Theory of Acids and Bases*, Wiley & Sons, New York (1946)
[529] Lwowsky, *Angew. Chem.* **70,** 483 (1958)
[530] Lykken, Porter, Ruliffson and Tuemler, *Ind. Eng. Chem. Anal. Ed.* **16,** 219 (1944)

M

[531] Mackensie and Winter, *Trans. Faraday Soc.* **44,** 159, 171, 243 (1948)
[532] Magnuson, *Anal. chem.* **35,** 1487 (1963)
[533] Magnuson, *Chemist Analyst* **53,** 15 (1964)
[534] Maher and Yohe, *J. Org. Chem.* **23,** 1082 (1958)
[535] Mallik, *Anal. Chem.* **32,** 1369 (1960)
[536] Mallik and Das, *Chem. & Ind.* **1959,** 162
[537] Malmstadt and Roberts, *Anal. Chem.* **28,** 1408 (1956)
[538] Malmstadt and Vassallo, *Anal. Chim. Acta*, **16,** 455 (1957)
[539] Malmstadt and Vassallo, *Anal. Chem.* **31,** 206 (1959)
[540] Malmstadt and Vassallo, *Anal. Chem.* **31,** 862 (1959)
[541] Malone, *Anal. Chem.* **33,** 575 (1961)
[542] Malone and Biggers, *Anal. Chem.* **36,** 1037 (1964)
[543] Malyshev, *Zavod. Lab.* **28,** 927 (1962)
[544] Mandel, *Nature* **176,** 792 (1955)
[545] Mandel, *Anal. Chim. Acta* **15,** 301 (1956)
[546] Mandel, *Ind. chim. Belge* **23,** 722 (1958)
[547] Mansfield and Whiting, *J. Chem. Soc.* **1956,** 4761

[548] Markunas and Riddick, *Anal. Chem.* **23,** 337 (1951)
[549] Markunas and Riddick, *Anal. Chem.* **24,** 312 (1952)
[550] Marple and Fritz, *Anal. Chem.* **34,** 796 (1962)
[551] Marple and Fritz, *Anal. Chem.* **35,** 1223, 1305, 1431 (1963)
[552] Marple, Matsuyama and Burdett, *Anal. Chem.* **30,** 937 (1958)
[553] Marple, Przybylowicz and Hume, *Anal. Chem.* **28,** 1892 (1956)
[554] Martin, *Anal. Chem.* **29,** 79 (1957)
[555] Martin and George, *J. Chem. Soc.* **1933,** 1413
[556] Martin and Reece, *J. Chem. Soc.* **1960,** 4697
[557] Marvillet and Tranchant, *Chimie Analytique* **40,** 293 (1958)
[558] Marvillet and Tranchant, *Chimie Analytique* **43,** 169 (1961)
[559a] Maryott, *J. Res. Nat. Bur. Stand.* **38,** 527 (1947)
[559b] Maryott, *J. Res. Nat. Bur. Stand.* **41,** 1 (1948)
[560] Maryott and Smith, *Nat. Bur. Stand. Circ.* 514 (1951)
[561] Mass and Jander, *Fortschr. chem. Forsch.* **2,** 637 (1953)
[562] Mauermeyer, Margosis and Ma, *Mikrochim. Acta* **2,** 177 (1959)
[563] Mázor and Pápay, *Z. anal. Chem.* **184,** 272 (1961)
[564] McClure, Roder and Kinsey, *Anal. Chem.* **27,** 1599 (1955)
[565] McCurdy and Galt, *Anal. Chem.* **30,** 940 (1958)
[566] McEniry, *Ass. Agric. Chem.* **40,** 926 (1957)
[567] McEwen, *J. Am. Chem. Soc.* **58,** 1124 (1936)
[568] McGuire, Izzo and Zuffanti, *J. Org. Chem.* **21,** 632 (1956)
[569] McInnes and Jones, *J. Am. Chem. Soc.* **48,** 2831 (1926)
[570] McKinney and Reynolds, *Talanta* **1,** 46 (1958)
[571] Mecke, *Z. Elektrochem.* **50,** 57 (1944)
[572] Meerwein, Hinz, Hofmann, Kroning and Pfeil, *J. pract. Chem.* **147,** 257 (1937)
[573] Merrifield and Phillips, *J. Am. Chem. Soc.* **80,** 2778 (1958)
[574] Metcalfe and Schmitz, *Anal. Chem.* **27,** 138 (1955)
[575] Meulenhoff, *Pharm. Weekblad* **93,** 262 (1958)
[576] Meulenhoff and van Sonsbeek, *Pharm. Weekblad* **91,** 453 (1956)
[577] van Meurs and Dahmen, *Anal. Chim. Acta* **19,** 64 (1958)
[578] van Meurs and Dahmen, *Anal. Chim. Acta* **21,** 10 (1959)
[579] van Meurs and Dahmen, *Anal. Chim. Acta* **21,** 193 (1959)
[580] van Meurs and Dahmen, *Anal. Chim. Acta* **21,** 443 (1959)
[581] Michaelis, *Pharmazie* **13,** 740 (1958)
[582] Michaelis and Rona, *Biochem. Z.* **49,** 247 (1913)
[583] Mika, *Z. anal. Chem.* **128,** 159 (1948)
[584] Mika, *Die Methoden der Mikromassanalyse*, F. Enke, Stuttgart (1958)
[585] Miller and Wynne-Jones, *J. Chem. Soc.* **1959,** 2375.
[586] Milne, *J. Am. Pharm. Ass., Sci. Ed.* **48,** 117 (1959)
[587] Milne and Chatten, *J. Pharm. Pharmacol.* **9,** 686 (1957)
[588] Minczewski, *Chem. Anal. (Warsaw)* **3,** 453 (1958)
[589] Minczewski, *Zh. anal. Khim.* **15,** 151 (1960);
[590] Minczewski and Kiciak, *Chem. Anal. (Warsaw)* **8,** 239 (1963)
[591] Minczewski and Kolyga, *Chem. Anal. (Warsaw)* **3,** 463 (1958)
[592] Minczewski and Lada, *Roczniki Chem.* **29,** 919, 950 (1955)
[593] Minnick and Kilpatrick, *J. Phys. Chem.* **43,** 259 (1939)
[594] Miocque and Gautier, *Bull. Soc. chim. France* **1958,** 467
[595] Miron and Hercules, *Anal. Chem.* **33,** 1770 (1961)
[596] Mitchel and Ashby. *J. Am. Chem. Soc.* **67,** 161 (1945)
[597] Mohler, *Chemische Optic*, Sauerländer, Aarau (1951)
[598] Moore and Johns, *J. Am. Chem. Soc.* **63,** 3336 (1941)
[599] Moore, McCutchan and Young, *Anal. Chem.* **23,** 1633 (1951)
[600] Moskalyk, Chatten and Pernarowski, *J. pharm. Sci.* **50,** 179 (1961)
[601] Moss, Elliott and Hall, *Anal. Chem.* **20,** 784 (1948)
[602] Mulliken, *J. Am. Chem. Soc.* **74,** 811 (1952)
[603] Muney and Coetzee, *J. Phys. Chem.*, **66,** 89 (1962)
[604] Muth, Darlak, English and Hamner, *Anal. Chem.* **34,** 1163 (1962)

[605] Müller, *Neuere Anschauungen der organischen Chemie*, Springer, Berlin (1957)
[606[Müller and Patridge, *Ind. Eng. Chem.* **20**, 423 (1928)

N

[607] Nadeau and Branchen, *J. Am. Chem. Soc.* **57**, 1363 (1935)
[608] Naidu and Krishnan, *Anal. Chem.* **33**, 497 (1961)
[609] Napoli and Schmall, *Anal. Chem.* **23**, 1893 (1951)
[610] Nemitz, *Chem. Z.* **82**, 222 (1958)
[611] Newman, *J. Am. Chem. Soc.* **63**, 2431 (1941)
[612] Nicksic and Judd, *Anal. Chem.* **32**, 998 (1960)
[613] Nicolas and Burel, *Chimie analytique* **33**, 341 (1951)
[614] Nisonoff, Kuhn and Gurney, *J. Chem. Phys.* **20**, 985 (1952)
[615] Novák, *Chem. listy* **49**, 848, 934 (1955)

O

[616] Ogg, Porter and Willits, *Ind. Eng. Chem. Anal. Ed*, **17**, 394 (1945)
[617] Osborn, Elliott and Martin, *Ind. Eng. Chem. Anal. Ed.* **15**, 642 (1943)
[618] Ozolins and Schenk, *Anal. Chim.* **33**, 1035 (1961)
[619] Ömböly and Derzsi, *Z. anal. Chem.* **187**, 29 (1962)
[620] Ömböly and Derzsi, *Acta Pharm. Hung.* **32**, 246 (1962)

P

[621] Palit, *Ind. Eng. Chem. Anal. Ed.* **18**, 246 (1946)
]622] Palit and Singh, *J. Indian. Chem. Soc.* **33**, 507 (1956)
[623] Patchornik and Rogozinski, *Anal. Chem.* **31**, 985 (1959)
[624] Patchornik and Rogozinski, *Anal. Chem.* **33**, 803 (1961)
[625] Paul and Long, *Chem. Revs.* **57**, 1 (1957)
[626] Paul, Singh and Sandhu, *J. Chem. Soc.* **1959**, 315
[627] Paul, Vasisht, Malhotra and Pahil, *Anal. Chem.* **34**, 820 (1962)
[628] Pauling, *The Nature of the Chemical Bond*, Cornell University Press, New York (1948)
[629] Pearson, *J. Am. Chem. Soc.* **70**, 204 (1948)
[630] Pearson and Dillon, *J. Am. Chem. Soc.* **75**, 2439 (1953)
[631] Pearson and Vogelsong, *J. Am. Chem. Soc.* **80**, 1038 (1958)
[632] Pellerin, *Ann. pharm. franç.* **14**, 193 (1956)
[633] Pellerin and Demay, *Ann. pharm. franç.* **20**, 661 (1962)
[634] Pellerin and Gautier, *Ann. pharm. franç.* **19**, 81 (1961)
[635] Pénau, Saïas and Ferdet, *Ann. pharm. franç.* **11**, 740 (1953)
[636] Pernarowski, *Drug St.* **21**, 189 (1953)
[637] Pernarowski, *Drug St.* **22**, 1 (1954)
[638] Pernarowski and Blackburn, *J. Am. Pharm. Ass., Sci. Ed.* **47**, 585 (1958)
[639] Pernarowski, Chatten and Levi, *J. Am. Pharm. Ass., Sci. Ed.* **43**, 746 (1954)
[640] Pesez, *Bull. Soc. chim. France* **1954**, 1237
[641] Pesez, *Bull. Soc. chim. France* **1957**, 417
[642] Pickard and Iddings, *Anal. Chem.* **31**, 1229 (1959)
[643] Pifer and Wollish, *J. Am. Pharm. Ass., Sci. Ed.* **40**, 609 (1951)
[644] Pifer and Wollish, *Anal. Chem.* **24**, 300 (1952)
[645] Pifer and Wollish, *Anal. Chem.* **24**, 519 (1952)
[646] Pifer, Wollish and Schmall, *J. Am. Pharm. Ass., Sci. Ed.* **42**, 502 (1953)
[647] Pifer, Wollish and Schmall, *Anal. Chem.* **26**, 215 (1954)
[648] Pleskov, *J. Phys. Chem. (USSR)* **22**, 351 (1948)
[649] Poethke and Horn, *Pharm. Zhalle* **94**, 41 (1955)

[650] Pohl, *Anal. Chem.* **26,** 1614 (1954)
[651] Pohloudek-Fabini and König, *Pharmazie* **13,** 753 (1958)
[652] Pohloudek-Fabini and König, *Pharm. Zhalle* **98,** 176 (1959)
[653] Polgár and Jungnickel, 'Determination of Olefinic Unsaturation' in Mitchell, Kolthoff, Praskauer and Weissberger, *Organic Analysis*, Vol. III. Interscience, New York (1954)
[654] Posgay, *Pharm. Zhalle* **101,** 471 (1962)
[655] Posgay, *Pharm. Zhalle* **101,** 534 (1962)
[656] Posgay and Bayer, *Acta Pharm, Hung.* **33,** 9 (1963)
[657] Posgay and Hochmann, *Acta Pharm. Hung.* **27,** 263 (1957)
[658] Poulos, *Anal. Chem.* **24,** 1858 (1952)
[659] Powers, Day and Underwood, *Anal. Chem.* **30,** 254 (1958)
[660] Prey and Unger, *Österr. Chem. Ztg.* **61,** 10 (1960)
[661] Pringle, *Nature* **183,** 815 (1959)
[662] Prue and Sherrington, *Trans. Faraday Soc.* **57,** 1795 (1961)
[663] Przyszlakovski, *Acta Polon. Pharm.* **17,** 395 (1960)
[664] Purdy and Stock, *Drug St.* **26,** 177 (1958)

R

[665] Radell and Donahue, *Anal. Chem.* **26,** 590 (1954)
[666a] Rao and Murthy, *Z. analyt. Chem.* **177,** 86 (1960)
[666b] Rao and Murthy, *Z. analyt. Chem.* **180,** 169 (1961)
[666c] Rao and Murthy, *Z. analyt. Chem.* **187,** 97 (1962)
[666d] Rao and Murthy, *Z. analyt. Chem.* **195,** 406 (1963)
[667] Rashbrook, *Analyst* **87**, 826 (1962)
[668] Reddaway, *Analyst* **82,** 506 (1957)
[669] Read, Critchfield and Elder, *Anal. Chem.* **35,** 571 (1963)
[670] Rehm, Bodin, Connors and Higuchi, *Anal. Chem.* **31,** 483 (1959)
[671] Rehm and Higuchi, *Anal. Chem.* **29,** 367 (1957)
[672] Reilley and Crawford, *Anal. Chem.* **27,** 716 (1955)
[673] Reilley and Papa, *Anal. Chem.* **34,** 801 (1962)
[674] Reilley and Porterfield, *Anal. Chem.* **28,** 443 (1956)
[675] Reilley and Schweizer, *Anal. Chem.* **26,** 1124 (1954)
[676] Reiss, *Z. anal. Chem.* **167,** 16 (1959)
[677] Remick, *Electronic Interpretation of Organic Chemistry*, J. Wiley & Sons, New York (1949)
[678] Reynolds, Little and Pattengill, *Anal. Chem.* **35,** 973 (1963)
[679] Reynolds, Walker and Cochran, *Anal. Chem.* **32,** 983 (1960)
[680] Richardson, *Anal. Chim. Acta* **24,** 46 (1961)
[681] Rink and Lux, *Deut. Apoth. Ztg.* **99,** 1051 (1959)
[682] Rink, Lux and Franken, *Deutsch, Apoth. Zt.* **99,** 157 (1959)
[683] Rink and Riemhofer, in *Arch. Pharm.* **294** (1961), Mitteilungen d. deutsch. pharm. Ges. **31** [11] 197
[684] Rink and Riemhofer, *Deutsch, Apoth. Ztg.* 102, 1567 (1962)
[685] Riolo and Marcon, *Ann. Chim. (Rome)* **46,** 1121 (1956)
[686] Roberts, McBee and Hathaway, *J. Org. Chem.* **21,** 1369 (1956)
[687] Robinson, Cundiff and Markunas, *Anal. Chem.* **33,** 1030 (1961)
[688] Robinson, Sensabaugh and Markunas, *Anal. chem.* 35, 770 (1963)
[689] Romberg and Cruze, *Z. Elektrochem.* **63,** 404 (1959)
[690] Ruch and Critchfield, *Anal. Chem.* **33,** 1569 (1961)
[691] Ruch, Johnson and Critchfield, *Anal. Chem.* **33,** 1566 (1961)
[692] Ruehle, *Ind. Eng. Chem. Anal. Ed.* **10,** 130 (1938)
[693] Rumpf, *Chimie Analytique* **42,** 111 (1960)
[694] Ryan, Yanowski and Pifer, *J. Am. Pharm. Ass., Sci. Ed.* **43,** 656 (1954)

S

[695] Šafařik, *Československ. Farm.* **6,** 515 (1957)
[696] Šafařik, *Mikrochim. et Ichnoanalyt. Acta* **1963** (1), 26
[697] Šafařik and Bumba, *Pharm. Zhalle* **96,** 3 (1957)
[698] Šafařik and Špinková, *Československ. farm.* **7,** 76 (1958)
[699] Šafařik and Špinková, *Československ. farm.* **7,** 144 (1958)
[700] Sakurai, *J. Pharm. Soc. Japan.* **81,** 164 (1961)
[701] Sakurai and Awada, *J. Pharm. Soc. Japan* **76,** 1026 (1956)
[702] Sakurai, Yoneda and Nomura, *J. Pharm. Soc. Japan* **78,** 377 (1959)
[703] Salvesen, *Medd. Norsk Farm. Selskap.* **19,** 199 (1957)
[704] Salvesen, *Medd. Norsk Farm. Selskap.* **20,** 21 (1958)
[705] Salvesen, *Medd. Norsk Farm. Selskap.* **20,** 65 (1958)
[706] Salvesen, *Medd. Norsk Farm. Selskap.* **23,** 141 (1961)
[707] Salvesen, Kristoffersen and Aasbo, *Medd. Norsk Farm. Selskap.* **18,** 88 (1956)
[708] Salvesen and Solli, *Medd. Norsk Farm. Selskap.* **21,** 85 (1959)
[709] Sandin, Kulka and Woolley, *Ind. Eng. Chem. Anal. Ed.* **8,** 355 (1936)
[710] Sarson, *Anal. Chem.* **30,** 932 (1958)
[711] Satchell, *J. Chem. Soc.* **1958,** 3910
[712] Saunders, Stacey and Wilding, *Biochem. J.* **36,** 368 (1942)
[713] Scarano and Ceglie, *Anal. Chim. Acta* **12,** 292 (1955)
[714] Schaefgen and Flory, *J. Am. Chem. Soc.* **72,** 689 (1950)
[715] Schenk, *Anal. Chem.* **33,** 299 (1961)
[716] Schenk and Fritz, *Anal. Chem.* **32,** 987 (1960)
[717] Schenk and Ozolins, *Anal. Chem.* **33,** 1562 (1961)
[718] Schenk, Santiago and Wines, *Anal. Chem.* **35,** 167 (1963)
[719] Schenk, Wines and Mojzis, *Anal. Chem.* **36,** 914 (1964)
[720] Schlitt, *Anal. Chem.* **35,** 1063 (1963)
[721] Schmall, Pifer and Wollish, *Anal. Chem.* **24,** 1446 (1952)
[722] Schmidt, Blohm and Jander, *Angew. Chem.* **59,** 233 (1947)
[723] Schnell, *Makromol. Chem.* **2,** 172 (1948)
[724] Schotte and Veibel, *Acta Chem. Scand.* **7,** 1357 (1953)
[725] Schwabe, *Elektrometrische pH-Messung unter extremen Bedingungen*, Verlag Chemie, Weinheim/Bergstr. (1960)
[726] Schwarzenbach, Brandenberger, Ott and Hagger, *Helv. Chim. Acta* **20,** 490 (1937)
[727] Schwarzenbach and Egli, *Helv. Chim. Acta* **17,** 1176, 1183 (1934)
[728] Schwarzenbach and Stensby, *Helv. Chim. Acta* **42,** 2342 (1959)
[729] Schwarzenbach and Wittwer, *Helv. Chim. Acta* **30,** 656, 659, 663, 669 (1947)
[730] Seamann and Allen, *Anal. Chem.* **23,** 592 (1951)
[731] Sensabaugh, Cundiff and Markunas, *Anal. Chem.* **30,** 1445 (1958)
[732] Sensi and Gallo, *Ann. Chim. (Rome)* **43,** 453 (1953)
[733] Shain and Svodoba, *Anal. Chem.* **31,** 1857 (1959)
[734] Sheldon and Tyree, *J. Am. Chem. Soc.* **81,** 2290 (1959)
[735] Shkodin, *Zh. Obshchei Khim.* **10,** 1694 (1940)
[736] Shkodin and Izmaĭlov, *Zh. Obshchei Khim.* **20,** 38 (1950)
[737a] Shkodin, Izmaĭlov and Dzyuba, *Zh. Obshchei Khim.* **20,** 1999 (1950)
[737b] Shkodin, Izmaĭlov and Dzyuba, *Zh. Anal. Khim.* **6,** 273 (1951)
[737c] Shkodin, Izmaĭlov and Dzyuba, *Zh. Obshchei Khim.* **23,** 27 (1953)
[737d] Shkodin, Izmaĭlov and Dzyuba, *Ukrain. Khim. Zhur.* **20,** 595 (1954)
[738] Shkodin, Karkuzaki and Khimenko, *Zh. Obshchei Khim.* **27,** 29 (1957)
[739] Shkodin, Sadovnikaya and Panchenko, *Zh. Anal. Khim.* **17,** 540 (1962)
[740] Shtifman, Syaztsillo and Larikova, *Trudy komiss. Anal. Khim., akad. Nauk SSSR,* **13,** 325 (1963)
[741] Sideri and Osol, *J. Am. Pharm. Ass., Sci. Ed.* **42,** 586 (1953)
[742] Sideri and Osol, *J. Am. Pharm. Ass., Sci. Ed.* **42,** 688 (1953)
[743] Sideri and Osol, *J. Am. Pharm. Ass., Sci. Ed.* **44,** 759 (1955)
[744] Sidgwick, *J. Chem. Soc.* **127,** 907 (1925)
[745] Sidgwick, Taylor and Baker, *The Organic Chemistry of Nitrogen*, Second ed., Oxford University Press (1937)

[746] Siggia and Floramo, *Anal. Chem.* **25,** 797 (1953)
[747] Siggia and Hanna, *Ind. Eng. Chem. Anal. Ed.* **20,** 1084 (1948)
[748] Siggia and Hanna, *Anal. Chem.* **23,** 1717 (1951)
[749] Siggia and Hanna, *Anal. Chem.* **33,** 896 (1961)
[750] Siggia, Hanna and Kervenski, *Anal. Chem.* **22,** 1295 (1950)
[751] Siggia and Segal, *Anal. Chem.* **25,** 830 (1953)
[752] Siggia and Stahl, *Anal. Chem.* **27,** 1975 (1955)
[753] Siggia and Stahl, *Anal. Chem.* **28,** 1971 (1956)
[754] Simon, Kováts, Chopard-dit-Jean and Heilbronner, *Helv. Chim. Acta* **37,** 1872 (1954)
[755] Simonyi and Tokár, *Magyar Kém. Folyóirat* **64,** 151 (1958)
[756] Simonyi and Tokár, *Acta Chim. Hung.* **25,** 305 (1960)
[757] Simonyi, Tóth and Szabó, *Acta Pharm. Hung.* **30,** 129 (1960)
[758] Singh, Paul and Sandhu, *J. Chem. Soc.* **1959,** 845
[759] Sinha, Kulkarni and Rao, *Anal. Chem.* **36,** 894 (1964)
[760] Skoog and Bartlett, *Anal. Chem.* **27,** 369 (1955)
[761] Small, *Analyst* **84,** 117 (1959)
[762] Smith and Bryant, *J. Am. Chem. Soc.* **58,** 2452 (1936)
[763] Smith and Elliott, *J. Am. Chem. Soc.* **75,** 3566 (1953)
[764] Smith and Haglund, *Acta Chim. Scand.* **14,** 1349 (1960)
[765] Smith and Hammett, *J. Am. Chem. Soc.* **67,** 23 (1945)
[766] Sobczyk, 'Dielektrische Polarisation und die Wechselwirkung der Carbonsäure und Amine' in Hadži and Thompson, *Hydrogen Bonding*, Pergamon Press, 323 (1959)
[767] Sokolowski and Kolka, *Chem. Anal. (Warsaw)* **6,** 429 (1961)
[768] Soloway and Rosen, *Anal. Chem.* **29,** 1820 (1957)
[769] Spengler and Kaelin, *Pharm. Acta Helv.* **18,** 542 (1943)
[770] Sprengling, *J. Am. Chem. Soc.* **76,** 1190 (1954)
[771] Stanford and Gordy, *J. Am. Chem. Soc.* **63,** 1094 (1941)
[772] Stetzler and Smullin, *Anal. Chem.* **34,** 194 (1962)
[773] Stock and Purdy, *Chem. Revs.* **57,** 1159 (1957)
[774a] Stock and Purdy, *Lab. Pract.* **7,** 523 (1958)
[774b] Stock and Purdy, **11,** 116 (1962)
[775] Stock and Purdy, *Chemist Analyst* **48,** 22, 50, 55, (1959)
[776] Stock and Purdy, *Lab. Pract.* **11,** 21 (1962)
[777] Streuli, *Anal. Chem.* **27,** 1827 (1955)
[778] Streuli, *Anal. Chem.* **30,** 997 (1958)
[779] Streuli, *Anal. Chem.* **31,** 1652 (1959)
[780] Streuli, *Anal. Chem.* **32,** 407 (1960)
[781] Streuli, *Anal. Chem.* **32,** 985 (1960)
[782] Streuli and Miron, *Anal. Chem.* **30,** 1978 (1958)
[783] Stuck, *Z. anal. Chem.* **177,** 338 (1960)
[784] Stumpf, *Chemie und Anwendung des 1,4-Dioxans*, Verlag Chemie, Weinheim/Bergstr. (1956)
[785] Suchomelová and Zýka, *J. Electroanal. Chem.* **5,** 57 (1963)
[786] Susz and Lachavanne, *Helv. Chim. Acta* **41,** 634 (1958)
[787] Svoboda, *Anal. Chem.* 33, 1638 (1961)
[788] Swartz and Foss, *J. Am. Pharm. Ass., Sci. Ed.* **44,** 217 (1955)
[789] Sweetser and Bicker, *Anal. Chem.* **25,** 253 (1953)
[790] Szász, Kováts, Karácsony, Lőrincz and Bayer, *Planta Medica* **7,** 234 (1959)
[791] Szász, Szporny, Bittner, Gyenes, Hável and Magó, *Magyar Kém. Folyóirat*, **64,** 296 (1958)
[792] Szendey, *Arch. Pharm.* **291,** 215 (1958)
[793] Szendey, *J. Pharm. Sci.* **51,** 906 (1962)
[794] Szendey, *Arch. Pharm.* **296,** 126 (1963)

T

[795] Takácsi-Nagy and Lukáts, *III. Gyógyszerész Nagygyűlés*, Budapest (1959)
[796] Takiguchi, *Analyst* **83,** 482 (1958)
[797] Takiguchi and Hirata, *J. Chem. Soc. Japan. Ind. Chem. Sect.* **62,** 527 (1959)

[798] Takuira and Takino, *J. Pharm. Soc. Japan.* **74,** 971 (1954)
[799] Terent'ev, Obtemperanskaya, Buzlanova and Vlasova, *Zh. Anal. Khim.* **17,** 900 (1962)
[800] Terent'ev Obtemperanskaya, Volodzko and Buzlanova, *Zh. Anal. Khim.* **19,** 135 (1964)
[801] Terjesen and Sandved, *Kgl. Norske Videnskab. Selskabs Skrifter* **7,** 20 (1938)
[802] Terry, Eilar and Moe, *Anal. Chem.* **24,** 313 (1952)
[803] Tézé and Schaal, *Bull. Soc. chim. France* **1962,** 1372
[804] Theiwagt, *Anal. Chem.* **33,** 1391 (1961)
[805] Thomas and Rochow, *J. Am. Chem. Soc.* **79,** 1843 (1957)
[806] Tingle, *J. Am. Chem. Soc.* **40,** 873 (1918)
[807] Tiwari, Sristava and Sharma, *Z. anal. Chem.* **187,** 161 (1962)
[808] Tiwari and Sharma, *Z. anal. Chem.* **195,** 267 (1963)
[809] Toennies and Callan, *J. Biol. Chem.* **125,** 259 (1938)
[810] Tokár and Simonyi, *Magyar Kém. Folyóirat* **64,** 94, 379 (1958)
[811] Toldy, Csillag, Bobák and Gyenes, *Magyar Kém. Folyóirat* **67,** 180 (1960)
[812] Tomiček, *Sb. Celostátni Pracovni Konf. Anal. Chemiku* **1,** 246 (1952)
[813] Tomiček and Doležal, *Acta Pharm. Internat.* **1,** 31 (1950)
[814] Tomiček and Heyrovský, *Coll. Czech.* **15,** 997 (1950)
[815] Tomiček and Krepelka, *Chem. listy* **47,** 526 (1953)
[816] Tomiček, Stodolová and Herman, *Chem. listy* **47** 516 (1953)
[817] Tomiček and Valcha, *Coll. Czech.* **16,** 113 (1951)
[818] Treffers and Hammett, *J. Am. Chem. Soc.* **59,** 1708 (1937)
[819] Trémillon, *Bull. Soc. chim. France* **1960,** 1940
[820] Trotman-Dickenson, *J. Chem. Soc.* **1949,** 1293
[821] Trusell and Diehl, *Anal. Chem.* **35,** 674 (1963)
[822] Tuthill, Kolling and Roberts, *Anal. Chem.* **32,** 1678 (1960)

U

[823] Uhrig and Levin, *Ing. Eng. Chem. Anal. Ed.* **13,** 90, 194 (1941)
[824] Underwood, *Anal. Chem.* **26,** 1322 (1954)
[825] Usanovich, *Zh. Obshchei Khim.* **3,** 443 (1932)
[826] Usanovich, *Zh. Obshchei Khim.* **9,** 182 (1939)
[827] Usanovich, *Sto takoye kislotii i osnovaniya,* Alma-Ata (1953)
[828] Usanovich and Dulova, *Zh. Obshchei Khim.* **16,** 1978 (1946)
[829] Usanovich and Dulova, *Zh. Obshchei Khim.* **17,** 669 (1947)
[830] Usanovich and Kalabanovskaya, *Zh. Obshchei Khim.* **17,** 1235 (1947)
[831] Usanovich and Yatsimirskii, *Zh. Obshchei Khim.* **11,** 954, 957, 959 (1941)

V

[832] Vacek and Kračmár, *Československ. Farm.* **5,** 80 (1956)
[833] Vaillant, *Chimie Analytique* **39,** 413 (1957)
[834] Vasiliev, Mangu and Şişman, *Rev. Chim. (Bucharest)* **12,** 231 (1961)
[835] Vasiliev, Pazarina and Şişman, *Rev. Chim. (Bucharest)* **15,** 163 (1964)
[836] Vasiliev, Scîntee-Pazarina and Şişman, *Rev. Chim. (Bucharest)* **14,** 352 (1963)
[837] Vasiliev, Şişman and Scîntee-Pazarina, *Rev. Chim. (Bucharest)* **15,** 46 (1964)
[838] Veibel, *Chim. Anal. (Warsaw)* **36,** 145 (1954)
[839] Veibel, *Chem. Anal.* **3,** 207 (1958)
[840] Veibel, Eggersen and Linholt, *Acta Chem. Scand.* **6,** 1066 (1952)
[841] Veibel, Eggersen and Linholt, *Acta Chem. Scand.* **8,** 768 (1954)
[842] Veibel and Krogh-Andersen, *Anal. Chim. Acta* **15,** 15 (1956)
[843] Veibel and Nielsen, *Acta Chem. Scand.* **10,** 1488 (1956)
[844] Veibel, Nielsen and Refn, *Acta Chem. Scand.* **12,** 934 (1958)
[845] Veibel and Vrang, *Dansk Tiddskr. Farm.* **17,** 112 (1943)
[846] Vespe and Fritz, *J. Am. Pharm. Ass., Sci. Ed.* **41,** 197 (1952)
[847] Viberg, *Phys. Chem.* **A 171,** 1 (1934)

[848] Vincent and Blake, *J. Am. Pharm. Ass., Sci. Ed.* **48,** 359 (1949)
[849] Vogelsong, Univ. Microfilms, Ann Arbor, Mich. Publ. No. 19 605; ref.: Riddick, *Anal. Chem.* **30,** 793 (1958)
[850] Vogelzang and Stöver, *Pharm. Weekblad* **93,** 550 (1958)
[851] Volmer, *Annalen* **440,** 200 (1924)
[852] Vorländer, *Ber.* **36,** 1485 (1903)

W

[853] Wadelin, *Talanta* **10,** 97 (1963)
[854] Wagner, Brown and Peters, *J. Am. Chem. Soc.* **69,** 2609 (1947)
[855] Walden, *Elektrochemie nichtwässriger Lösungen*, Johann Ambrosius Barth, Leipzig (1924)
[856] Walden, Audrieth and Birr, *Z. Phys. Chem.* **160,** 337 (1932)
[857] Walden and Birr, *Z. Phys. Chem.* **144,** 269 (1929); **153,** 1 (1931)
[858] Waltz and Taylor, *Anal. Chem.* **19,** 448 (1947)
[859] Wanzlick and Löchel, *Ber.* **86,** 1463 (1953)
[860] Warner and Haskell, *Anal. Chem.* **26,** 770 (1954)
[861] Wassermann, *J. Chem. Soc.* **1959,** 986
[862] Wassermann, *Chem. Eng. News* **38,** H 51, 46 (1960)
[863] Waters, *Physical Aspects of Organic Chemistry*, Routledge and Kegan Paul, London (1953)
[864] Watt, Sowards and McBridge, *J. Am. Chem. Soc.* **77,** 5835 (1955)
[865] Wei-hwa, *Acta Pharm. Sin.* **4,** 217 (1956)
[866] Weissberger, Proskauer, Riddick and Toops: Organic Solvents, New York, Interscience Publishers (1955)
[867] Wepster, *Rec. trav. chim.* **71,** 1171 (1952)
[868] Werniment and Hopkinson, *Ind. Eng. Chem., Anal. Ed.* **15,** 272 (1943)
[869] Westheimer and Shookhoff, *J. Am. Chem. Soc.* **61,** 555 (1939)
[870] Wheland, *Resonance in Organic Chemistry*, Wiley and Sons, New York (1955)
[871] Wheland, Brownell and Mayo, *J. Am. Chem. Soc.* **70,** 2492 (1948)
[872] Wilchek and Patchornik, *Bull. Res. Council Israel*, 11A (1962)
[873] Willi, *Helv. Chim. Acta* **40,** 2032 (1957)
[874] Williams, *J. Pharm. Pharmacol.* **11,** 400 (1959)
[875] Williams, *Chem. & Ind.* **1960,** 900
[876] Williams and Custer, *Talanta* **9,** 175 (1962)
[877] Williams and Harley, *Chemist Analyst* **50,** 114 (1961)
[878] Wimer, *Anal. Chem.* **30,** 77 (1958)
[879] Wimer, *Anal. Chem.* **30,** 2060 (1958)
[880] Wimer, *Anal. Chem.* **34,** 873 (1962)
[881] Wizinger, *Organische Fasbstoffe*, F. Dümmler, Bonn, (1933)
[882] Wolf, *Anal. Chim. Acta* **1,** 90 (1947)
[883] Wollish, Colarusso, Pifer and Schmall, *Anal. Chem.* **26,** 1753 (1954)
[884] Wooding and Higginson, *J. Chem. Soc.* **1952,** 774
[885] Wright, *J. Am. Chem. Soc.* **57,** 1993 (1935)
[886] Wynne-Jones, *Proc. Roy. Soc.* **A 140,** 440 (1933)
[887] Wynne-Jones, *Proc. Roy. Soc.* **A 140,** 448 (1933)

Y

[888] Yakubik, Safranski and Mitchell, *Anal. Chem.* **30,** 1741 (1958)
[889] Yarovenko and Kosheleva, *Zavod. Lab.* **27,** 407 (1961)
[890] Yokoyama and Chatten, *J. Am. Pharm. Ass., Sci. Ed.* **47,** 548 (1958)

Z

[891] Zarembo and Watts, 'Determination of the Carbodiimide Function' *Microchemical Techniques*, Edited by N. D. Cheronis, Interscience, New York (1962)
[892] Zarinski and Couriev, *Zh. Anal. Khim.* **18,** 1306 (1963)
[893] Zaugg and Garven, *Anal. Chem.* **30,** 1444 (1948)
[894] Zeidler, *Z. anal. Chem.* **146,** 251 (1955)
[895] Zenchelski, *Anal. Chem.* **32,** 289 (1960)
[896] Ziegler and Dersch, *Ber.* **62,** 1833 (1929)
[897] Zýka, *Pharmazie* **9**, 812 (1954)
[898] Zýka and Berka: 'Use of Lead Tetraacetate as a Volumetric and Oxidimetric Reagent for Microanalytical Purposes'. *Microchemical Techniques*, Edited by N. D. Cheronic, Interscience, New York (1962)

Author Index

[The numbers in square brackets denote the reference numbers given in the text; the numbers following the names refer to the pages at which the respective reference numbers occur.]

A

[1] Agazzi, 237
[2] Albert, 85, 87, 148, 322
[3] Albert, 85, 87, 322
[4] Albert, 85
[5] Albert, 85
[6] Alicino, 369
[7] Allen, 175, 190, 197, 241, 279, 280, 281, 282, 283, 285
[8] Altschuler, 51
[9] Ames, 242
[10] Anastasi, 191, 197
[11] Anastasi, 184, 341
[12] Anastasi, 117, 349
[13] Anastasi, 324
[14] Arbuzov, 246
[15] van Arkel, 213, 311, 312, 341, 342
[16] Arndt, 81
[17] Arndt, 50
[18] Arshid, 114
[19] Arshid, 114
[20] Ashworth, 55
[21] Audrieth, 2
[22] Audrieth, 2, 48
[23] Auterhoff, 139, 142, 341

B

[24] Backe-Hansen, 250
[25] Backe-Hansen, 116, 197, 285
[26] Badger, 83
[27] Badoz-Lambling, 185
[28] Baggesgaard-Rasmussen, 117, 354, 382
[29] Baker, 93
[30] Banick, 148
[31] Bányai, 245
[32] Barnes, 169, 401
[33] Barrow, 30, 72, 177
[34] Barrow, 29
[35] Barrow, 68, 69, 70, 72, 177
[36] Barrow, 72
[37] Barrow, 72
[38] Barton, 149
[39] Bates, 31
[40] Bates, 31, 45
[41] Bayer, 335, 336
[42] Bayer, 363, 369
[43] Bayer, 369
[44] Bayer, 369
[45] Bayer, 342
[46] Bayles, 71, 99
[47] Becker, 67, 85
[48] Beckett, 198, 311, 312
[49] Beckett, 271, 313
[50] Beggs, 345
[51] Belcher, 337, 338
[52] Bell, 8
[53] Bell, 47, 48, 96
[54] Bell, 68, 72, 99
[55] Bell, 51, 99
[56] Bellen, 106, 187, 262
[57] Benson, 142
[58] Bergamini, 117, 184, 312, 333, 352, 354
[59] Berger, 406, 407
[60] Berger, 184, 406

[61] Berger, 423
[62] Berrett, 289, 309
[63] Berthel, 52
[64] Bezinger, 377
[65] Bianchi, 323
[66] Billon, 123
[67] Bishop, 240
[68] Bjerrum, 6
[69] Blair, 149
[70] Blake, 167, 313
[71] Blom, 58
[72] Blumrich, 318
[73] Bockris, 102
[74] Bokina, 173
[75] Bonitz, 415
[76] Bonner, 17
[77] Boubli, 129
[78] Bournique, 384
[79] Branch, 76, 91
[80] Branch, 211
[81] Branch, 93
[82] Brand, 44, 45
[83] Braude, 77
[84] Braude, 25, 45
[85] Bennecke, 126
[86] Bricker, 173, 219, 230, 236, 237
[87] Briegleb, 113, 114
[88] Briegleb, 22, 98
[89] Briegleb, 56
[90] Brill, 114
[91] Brockmann, 300
[92] Brockmann, 191, 197, 303, 304
[93] Brockmann, 300
[94] Brown, 98
[95] Brown, 98
[96] Brown, 71, 98
[97] Brown, 98
[98] Brown, 98
[99] Brönsted, 4
[100] Bruckenstein, 139
[101] Bruckenstein, 38, 105, 199, 200, 225
[102] Bruckenstein, 20, 37, 38, 39, 126, 154, 192, 195
[103] Bruehlman, 22
[104] Bruss, 173, 177, 178
[105] Bruss, 111, 122, 145, 175, 184, 191, 197, 241, 254, 255, 279, 375
[106] Bryant, 106
[107] Budesinsky, 172, 410, 411, 412
[108] Burgstahler, 145
[109] Burns, 350
[110] Burton, 127, 293
[111] Burwell, 48
[112] Buscarons, 149
[113] Butler, 197, 241, 280
[114] Bykova, 256

C

[115] Caldas, 146
[116] Caldin, 160
[117] Carlton, 153
[118] Caso, 133, 155
[119] Caso, 157
[120] Caso, 213
[121] Cerri, 169, 421
[122] Chalandonand, 54
[123] Chatten, 47, 117, 123, 174, 351, 361, 370
[124] Chatten, 184, 250, 313
[125] Chatten, 70, 327, 364
[126] Chatten, 129, 324, 331, 332
[127] Chatten, 368
[128] Cheronis, 334
[129] Chiang, 277
[130] Cholvy, 117, 273, 327, 363
[131] Chrastil, 410, 413
[132] Ciaccio, 117, 123, 129, 329, 361
[133] Clair, 248
[134] Clark, 352, 353
[135] Clarke, 148
[136] Cluett, 164
[137] Cluett, 237, 271
[138] Coetzee, 27, 123
[139] Coetzee, 145
[140] Coetzee, 122, 123
[141] Cohen, 236, 237
[142] Cohn, 34
[143] Conant, 409
[144] Conant, 152, 154, 192
[145] Conant, 122
[146] Conant, 64, 152, 192, 338
[147] Conant, 49, 50
[148] Connors, 52, 219, 225, 226, 227
[149] Connors, 364
[150] Corwin, 50
[151] Coulson, 113
[152] Crabb, 285
[153] Crisafio, 116, 160, 184, 251
[154] Critchfield, 395
[155] Critchfield, 123, 184, 254, 257
[156] Critchfield, 195, 374, 378
[157] Critchfield, 170, 374, 379
[158] Cundiff, 117, 192, 196, 374, 380
[159] Cundiff, 116, 164, 165, 184, 192, 195, 197, 240, 241, 247, 251, 252, 253, 254, 257, 269, 276, 279, 280, 281, 284, 301
[160] Cundiff, 164, 165, 175, 195, 251, 254, 256, 257
[161] Cundiff, 184, 254, 257, 315
[162] Cundiff, 184, 257, 315
[163] Cundiff, 257, 419, 420
[164] Cundiff, 164, 166, 195, 301
[165] Cundiff, 301

[166] Cundiff, 374, 385, 386
[167] Curran, 114

D

[168] Dahmen, 26, 27, 58
[169] Das, 153, 395, 396, 398
[170] Das, 116, 118, 169, 175, 254, 257
[171] Davis, 72
[172] Davis, 22, 32, 68, 69, 70
[173] Davis, 16, 32, 34, 47, 80, 91, 93, 153
[174] Davis, 30, 36
[175] Deal, 117, 154, 318, 322
[176] Deal, 48, 104, 134, 161, 163, 175, 184, 197, 241, 251, 254, 279, 303, 305, 306, 307, 308, 309
[177] Dean, 173, 241
[178] De Lorenzi, 280
[179] Deno, 17
[180] De Paulis, 277
[181] Dermer, 55
[182] De Vries, 302
[183] De Vries, 191, 302, 373
[184] Dewar, 14
[185] Deyrup, 25
[186] Dilthey, 50, 177
[187] Dilthey, 211
[188] Dimroth, 342
[189] Dippy, 77, 91
[190] Doernberg, 161, 191
[191] Drozdov, 423
[192] Dubois, 184
[193] Dugan, 145
[194] Dulova, 29
[195] Dulova, 29
[196] Dulova, 29
[197] Durbetaki, 170, 400
[198] Durbetaki, 170, 400
[199] Dušinský, 172, 399

E

[200] Eberius, 139, 141, 143, 238
[201] Ebert, 9, 221
[202] Edward, 127
[203] Ehrlich-Rogozinski, 421
[204] Eisdorfer, 366
[205] Eistert, 126
[206] Eistert, 75, 77, 78
[207] Ekeblad, 184, 198, 351, 356
[208] Ellerington, 167, 184, 213, 261
[209] Ellert, 219, 222, 223, 233, 236, 319, 326
[210] Ellert, 353
[211] Ellert, 219, 223, 333, 342, 355
[212] Ellert, 254
[213] Emelin, 258
[214] Erdey, 171, 403
[215] Erdey, 55, 367, 403
[216] Erdey, 172, 410
[217] Erdey, 409, 410
[218] Everett, 18, 26
[219] Everett, 71

F

[220] Faber, 275
[221] Fajans, 16
[222] Farina, 57, 169, 188, 191, 415
[223] Fauth, 302
[224] Feigl, 146, 149
[225] Feigl, 146
[226] Feigl, 142
[227] Ferguson, 93
[228] Feuer, 314
[229] Flaschka, 368
[230] Flexer, 43, 63
[231] Fodor, 8, 49, 50, 52, 55, 83, 404
[232] Fogg, 237
[233] Forbes, 235
[234] Forbes, 235
[235] Forbes, 235
[236] Forman, 73
[237] Fortuin, 186
[238] Fossum, 155
[239] Franklin, 2
[240] Franklin, 104, 126
[241] Freri, 52
[242] Freymann, 134
[243] Fripiat, 121
[244] Fritz, 154, 184, 191, 193, 318
[245] Fritz, 311, 352
[246] Fritz, 34, 241, 269, 271
[247] Fritz, 64, 68, 123, 175, 184, 374, 375
[248] Fritz, 111, 184
[249] Fritz, 66, 117, 129, 184, 317, 322, 323, 333, 341
[250] Fritz, 275
[251] Fritz, 184, 241, 242, 279, 280, 281, 282, 283
[252] Fritz, 116, 129, 161, 184, 190, 191, 243, 244, 251, 260, 269, 275, 276
[253] Fritz, 181, 197, 254, 258, 279, 284
[254] Fritz, 300, 301
[255] Fritz, 406
[256] Fritz, 406
[257] Fritz, 171, 293, 423
[258] Fritz, 68, 78, 122, 167, 175, 181, 184, 186, 192, 195, 197, 241, 254, 256, 269, 275, 279, 280, 281
[259] Fritz, 161, 170, 390, 391
[260] Fuoss, 106

G

[261] Gagnaux, 54
[262] Galpern, 89, 321, 374, 380
[263] Gautier, 16, 96
[264] Gautier, 345, 376, 406

[265] Gautier, 351, 370
[266] Gautier, 274, 405
[267] Gautier, 53, 368
[268] Gautier, 368
[269] Gehlen, 11
[270] Gillespie, 129
[271] Gillespie, 62
[272] Gillespie, 62
[273] Glass, 116, 190, 191, 193, 195
[274] Glenn, 286
[275] Goddu, 173, 219, 236, 237
[276] Goddu, 173, 219
[277] Goddu, 173, 219, 231, 236
[278] Gold, 293
[279] Goldfarm, 63, 127
[280] Goldstein, 273
[281] Goodhue, 28
[282] Gordy, 114
[283] Görög, 399
[284] Görög, 393
[285] Gran, 187, 190, 192, 193, 195, 197, 279, 303
[286] Grant, 58
[287] Greenhow, 246, 280
[288] Gremillion, 64, 117, 317, 333
[289] Gribova, 256
[290] Gribova, 384
[291] Grove, 173
[292] Grunwald, 106, 199
[293] Grunwald, 238
[294] Gurney, 10, 17, 18, 37, 103
[295] Gutman, 10, 11, 17, 22
[296] Gutmann, 10, 11, 17, 22
[297] Gutterson, 117, 337
[298] Gutterson, 402
[299] Gyenes, 121, 153, 158, 334, 335, 336, 370
[300] Gyenes, 336
[301] Gyenes, 335, 384
[302] Gyenes, 117, 121, 336, 340
[303] Gyenes, 269
[304] Gyenes, 334, 335
[305] Gyenes, 121, 335
[306] Gyenes, 117, 143, 349
[307] Gyenes, 116, 122, 163, 214, 250, 280, 281, 284
[308] Gyenes, 312, 372
[309] Gyenes, 251, 252, 285, 352
[310] Gyenes, 117, 386
[311] Gyenes, 117, 122, 129, 176, 352, 353, 354, 374
[312] Gyenes, 374, 386
[313] Gyenes, 103, 216
[314] Gyenes, 117, 122, 127, 131, 176, 184, 185, 192, 195, 351, 352, 353, 354, 374, 390, 391
[315] Gyenes, 374, 384, 385
[316] Gyenes, 15, 53, 368
[317] Gyenes, 117, 362
[318] Gyenes, 153, 341
[319] Gyenes, 118, 213
[320] Gyenes, 117
[321] Gyenes, 47, 212, 330, 351, 371
[322] Gyenes, 312
[323] Gyenes, 47, 121, 335, 336
[324] Gyenes, 251, 252, 312, 352
[325] Gyenes, 1, 11
[326] Gyenes, 314

H

[327] Hadži, 113, 114
[328] Hagen, 416
[329] Haggard, 190
[330] Hahn, 131, 242, 244
[331] Hahn, 57
[332] Hall, 52, 64, 65, 66, 67, 81
[333] Hall, 64, 67, 68, 69, 175, 176, 318, 322, 329, 334
[334] Hall, 65, 85
[335] van Hall Stone, 155
[336] van Hall Stone, 410
[337] Hall Werner, 64, 192
[338] Hammett, 198
[339] Hammett, 43
[340] Hammett, 43, 44, 46, 47
[341] Hammett, 114
[342] Hammett, 17, 21, 39, 43, 44, 45
[343] Hammett, 21, 39
[344] Hammett, 62
[345] Hammett, 318
[346] Hammond, 91
[347] Hanna, 299, 374, 386
[348] Hansson, 80
[349] Hantzsch, 62
[350] Hantzsch, 22
[351] Hantzsch, 31
[352] Hantzsch, 62
[353] Hantzsch, 215
[354] Hantzsch, 126
[355] Harlow, 164, 166, 167, 179, 191, 195, 197, 279, 282
[356] Harlow, 164
[357] Harlow, 164
[358] Harlow, 164, 167, 176, 177, 178, 179, 193, 197
[359] Harlow, 48, 164, 175, 184, 187, 191, 197, 241, 254, 256, 282, 309
[360] Harlow, 251, 254
[361] Harlow, 164, 166
[362] Harned, 409
[363] Hart, 50
[364] Havemann, 237, 238
[365] Hawke, 55
[366] Hädicke, 352
[367] Hädicke, 151, 248, 363

[368] Hefferren, 190, 191, 193
[369] van der Heijde, 166, 171, 176, 177, 179, 180, 181, 182, 183, 184
[370] van der Heijde, 148, 166, 171, 176, 182, 183, 184
[371] van der Heijde, 122, 148, 166, 171, 176, 182, 183, 184
[372] Heiz, 148, 161, 191, 273
[373] Hennart, 400
[374] Hennart, 127, 169, 311, 312, 318
[375] Hennart, 169, 174
[376] Hennart, 169, 367
[377] Hennart, 169, 276, 326
[378] Hennart, 263
[379] Henry, 56
[380] Hermans, 27, 81, 83, 94, 343
[381] Hess, 139
[382] Heston, 131
[383] Higuchi, 53, 171, 287
[384] Higuchi, 392
[385] Higuchi, 135, 219, 221, 227, 228, 343
[386] Higuchi, 159, 362
[387] Higuchi, 171, 287
[388] Higuchi, 38, 201
[389] Higuchi, 38, 106, 195, 199, 201, 202, 203, 228
[390] Higuchi, 38, 156, 201, 219, 220, 221, 223, 224, 225, 344
[391] Higuchi, 53, 139, 149, 287
[392] Hillenbrand, 282
[393] Hine, 25, 77, 78, 95, 104, 111
[394] Hine, 99, 131
[395] Hinswark, 164, 173
[396] Hitchcock, 122, 123
[397] Hixon, 28
[398] Hofmann, 276
[399] Hofstadter, 113
[400] Howorka, 352, 354, 355
[401] Huber, 117, 175, 374, 384
[402] Hughes, 25
[403] Huisgen, 343
[404] Hummelstedt, 123, 220, 221, 222, 231, 232, 236, 323, 374, 376
[405] Hummelstedt, 219, 233, 234, 235, 236

I

[406] Inczédy, 270
[407] Ingold, 194, 309, 361
[408] Ioffe, 345
[409] Ionescu, 368
[410] Ishidate, 173
[411] Izmaĭlov, 111
[412] Izmaĭlov, 36, 37, 47
[413] Izmaĭlov, 17, 106
[414] Izmaĭlov, 111, 254
[415] Izmaĭlov, 111, 254

J

[416] Jackwerth, 145
[417] Jacobs, 145
[418] Jacobs, 249, 250
[419] Jancik, 280
[420] Jander, 154, 185
[421] Jander, 154
[422] Jander, 134, 135
[423] Jander, 127
[424] Janz, 27, 123
[425] Jasinski, 352
[426] Jasinski, 352
[427] Jaunin, 343
[428] Jay, 400
[429] Johnson, 128
[430] Johnson, 396, 398
[431] Johnson, 260
[432] Johnson, 161, 374, 377
[433] Jordan, 173
[434] Jordan, 138, 145
[435] Josien, 135, 418
[436] Jovánovics, 370

K

[437] Kahane, 322
[438] Kahovec, 343
[439] Kaleis, 341
[440] Karle, 113
[441] Karrman, 173, 241
[442] Kashima, 311, 312, 322, 349
[443] Kashima, 341
[444] Kashima, 185, 186, 352
[445] Kashima, 324
[446] Katz, 161, 187, 190, 191, 197, 279, 307
[447] Kaufman, 106, 177
[448] Kavarana, 241, 280
[449] Kaye, 302
[450] Keen, 154, 161, 184, 337
[451] Keily, 173
[452] Keller, 273, 275
[453] Kerny, 117, 162, 273, 275, 356, 362, 363, 364
[454] Keyworth, 328, 329
[455] Kilpatrick, 68
[456] Kilpi, 34
[457] Kirrmann, 185, 241, 260
[458] Kirwood, 80
[459] Kleckner, 184
[460] Klotz, 215
[461] Knappe, 325
[462] Kolling, 84, 351
[463] Kolling, 38, 216
[464] Kolthoff, 106, 154, 199, 200, 203
[465] Kolthoff, 123
[466] Kolthoff, 28, 123

[467] Kolthoff, 27
[468] Kolthoff, 123
[469] Kolthoff, 68, 69, 70, 149
[470] Kolthoff, 142, 152, 154, 173, 311
[471] Kráčmarová, 276
[472] Kraus, 2
[473] Krausz, 312
[474] Kreshkov, 111, 376
[475] Kreshkov, 111, 376
[476] Kreshkov, 423
[477] Kreshkov, 256
[478] Kreshkov, 256
[479] Kreshkov, 111, 122, 170, 376
[480] Kreshkov, 251, 254, 256
[481] Kreshkov, 423
[482] Kreshkov, 422
[483] Kreshkov, 423
[484] Kreshkov, 232, 317
[485] Kreshkov, 111, 256, 315
[486] Kukin, 245, 246
[487] Kukin, 245
[488] Kumler, 302
[489] Kundu, 118, 404, 424
[490] Kunkel, 171, 404
[491] Kühni, 154, 156

L

[492] Lada, 246
[493] Laitinen, 163
[494] Landee, 28, 163
[495] Lane, 173
[496] Láng, 117, 324
[497] Lange, 66, 77, 78, 81, 82, 322
[498] Langford, 48
[499] Lapidus, 32, 38, 39
[500] Latimer, 113
[501] Laubengayer, 122, 123
[502] Lavine, 123, 161, 254
[503] Leader, 110
[504] Leavitt, 274
[505] Lemaire, 38, 45, 63, 66, 99, 333
[506] Leuts, 52, 281
[507] Levi, 129, 147
[508] Levine, 398
[509] Lewis, 6, 54
[510] Lewis, 8, 57, 58
[511] Lieber, 278
[512] Linek, 342
[513] Lintner, 171, 287
[514] Lintner, 171
[515] Lippinkott, 173
[516] Lipscomb, 290
[517] Liteanu, 186
[518] Liu, 171, 374, 382
[519] Lohr, 169, 265
[520] van Looy, 29, 148
[521] Lorenz, 123, 320
[522] Lowry, 4
[523] Lowry, 4
[524] Löber, 356
[525] Lőrincz, 197, 339
[526] Lőrincz, 339
[527] Lucchesi, 243
[528] Luder, 6, 9
[529] Lwowsky, 339
[530] Lykken, 116, 161, 175, 242, 245, 246

M

[531] Mackensie, 55, 127, 128, 129
[532] Magnuson, 423
[533] Magnuson, 423
[534] Maher, 278
[535] Mallik, 396, 398
[536] Mallik, 396, 398
[537] Malmstadt, 237
[538] Malmstadt, 237
[539] Malmstadt, 184, 254, 256
[540] Malmstadt, 164, 165, 187, 195, 203, 204, 205, 214, 237, 242, 271
[541] Malone, 348, 349, 350
[542] Malone, 350
[543] Malyshev, 256
[544] Mandel, 17
[545] Mandel, 9, 18, 47, 48
[546] Mandel, 18, 22
[547] Mansfield, 77
[548] Markunas, 184, 310, 311, 312, 318
[549] Markunas, 386
[550] Marple, 164, 165, 193, 195, 196, 197, 254, 258
[551] Marple, 258
[552] Marple, 221, 237
[553] Marple, 237
[554] Martin, 170
[555] Martin, 149, 156
[556] Martin, 343
[557] Marvillet, 157, 317
[558] Marvillet, 301, 319
[559a] Maryott, 177
[559b] Maryott, 68, 69, 106, 177
[560] Maryott, 110
[561] Mass, 126, 127
[562] Mauermeyer, 126, 127
[563] Mázor, 356
[564] McClure, 169, 262
[565] McCurdy, 134, 173
[566] McEniry, 341
[567] McEwen, 50, 96
[568] McGuire, 215
[569] McInnes, 185
[570] McKinney, 233, 383
[571] Mecke, 144

[572] Meerwein, 52, 80
[573] Merrifield, 418
[574] Metcalfe, 131, 390
[575] Meulenhoff, 117, 118, 155, 320, 345
[576] Meulenhoff, 361
[577] van Meurs, 173
[578] van Meurs, 173
[579] van Meurs, 117, 173, 195, 374, 375
[580] van Meurs, 173
[581] Michaelis, 141
[582] Michaelis, 16
[583] Mika, 221
[584] Mika, 219, 309, 334, 337, 338
[585] Miller, 130
[586] Milne, 117, 328
[587] Milne, 117, 120, 174, 328, 351, 356
[588] Minczewski, 186
[589] Minczewski, 410
[590] Minczewski, 117, 317
[591] Minczewski, 410
[592] Minczewski, 184, 191, 193, 195
[593] Minnick, 46, 47, 48
[594] Miocque, 405
[595] Miron, 34, 40, 110, 175, 195
[596] Mitchel, 344
[597] Mohler, 211
[598] Moore, 28
[599] Moore, 184, 318
[600] Moskalyk, 147
[601] Moss, 48, 161, 187, 190, 191, 197, 279, 303
[602] Mulliken, 418
[603] Muney, 123
[604] Muth, 128, 334
[605] Müller, 75, 83, 113, 126, 268
[606] Müller, 219

N

[607] Nadeau, 320
[608] Naidu, 326
[609] Napoli, 248
[610] Nemitz, 139
[611] Newmann, 62, 199
[612] Nicksic, 143, 381
[613] Nicolas, 260
[614] Nisonoff, 17
[615] Novák, 190

O

[616] Ogg, 244, 290, 374
[617] Osborn, 219
[618] Ozolins, 172, 416
[619] Ömböly, 365, 366
[620] Ömböly, 323, 333

P

[621] Palit, 118, 131, 153, 184, 261, 315, 395
[622] Palit, 117
[623] Patchornik, 167, 169, 214, 263, 264, 265
[624] Patchornik, 421
[625] Paul, 17, 43, 44, 45, 46, 63, 85, 152
[626] Paul, 55
[627] Paul, 152
[628] Pauling, 58, 75, 178
[629] Pearson, 51, 64 71
[630] Pearson, 129
[631] Pearson, 51, 64, 71
[632] Pellerin, 368
[633] Pellerin, 191, 194
[634] Pellerin, 404
[635] Pénau, 117, 370
[636] Pernarowski, 341
[637] Pernarowski, 364
[638] Pernarowski, 117, 121, 324, 331
[639] Pernarowski, 117, 370
[640] Pesez, 129, 288, 289
[641] Pesez, 392
[642] Pickard, 117, 345, 375
[643] Pifer, 184, 191, 363
[644] Pifer, 117, 141, 142, 184, 191, 225, 341, 351, 364
[645] Pifer, 184, 311
[646] Pifer, 272
[647] Pifer, 375
[648] Pleskov, 195
[649] Poethke, 324
[650] Pohl, 242
[651] Pohloudek-Fabini, 352, 364, 372
[652] Pohloudek-Fabini 44
[653] Polgár, 14
[654] Posgay, 342
[655] Posgay, 366, 372
[656] Posgay, 372
[657] Posgay, 141
[658] Poulos, 117, 118, 341
[659] Powers, 220, 221, 237
[660] Prey, 148
[661] Pringle, 246
[662] Prue, 134
[663] Przyszlakovski, 326
[664] Purdy, 173, 241

R

[665] Radell, 116, 175, 184, 190, 244
[666a] Rao, 172, 410, 412
[666b] Rao, 410
[666c] Rao, 410, 411
[666d] Rao, 410
[667] Rashbrook, 313

[668] Reddaway, 414
[669] Read, 170, 291, 292
[670] Rehm, 219, 221, 237, 238
[671] Rehm, 219, 221, 230, 344
[672] Reilley, 418
[673] Reilley, 298
[674] Reilley, 191, 406
[675] Reilley, 173, 219, 221, 231, 236, 819
[676] Reiss, 117, 123, 128, 333, 341, 365
[677] Remick, 20, 21, 48, 59
[678] Reynolds, 258
[679] Reynolds, 219, 231
[680] Richardson, 313
[681] Rink, 341
[682] Rink, 314
[683] Rink, 356, 361
[684] Rink, 274
[685] Riolo, 410
[686] Roberts, 287
[687] Robinson, 148, 290
[688] Robinson, 302
[689] Romberg, 21
[690] Ruch, 170, 381
[691] Ruch, 170, 392, 393
[692] Ruehle, 116, 149, 161, 242
[693] Rumpf, 77
[694] Ryan, 161, 273

S

[695] Šafařik, 325
[696] Šafařik, 334, 335
[697] Šafařik, 352
[698] Šafařik, 193, 325
[699] Šafařik, 330
[700] Sakurai, 117, 158, 334, 336
[701] Sakurai, 117, 158, 335
[702] Sakurai, 117, 158, 336
[703] Salvesen, 117, 341, 374
[704] Salvesen, 342, 374
[705] Salvesen, 356
[706] Salvesen, 372
[707] Salvesen, 117, 362, 386
[708] Salvesen, 364
[709] Sandin, 240, 243
[710] Sarson, 302
[711] Satchell, 57
[712] Saunders, 158
[713] Scarano, 186
[714] Schaefgen, 242
[715] Schenk, 171, 293, 296
[716] Schenk, 171, 293, 295
[717] Schenk, 172, 418
[718] Schenk, 418
[719] Schenk, 288
[720] Schlitt, 347
[721] Schmall, 250
[722 Schmidt, 127, 154, 365
[723] Schnell, 242
[724] Schotte, 406
[725] Schwabe, 185
[726] Schwarzenbach, 211
[727] Schwarzenbach, 47
[728] Schwarzenbach, 31
[729] Schwarzenbach, 94, 122
[730] Seamann, 154, 156, 159, 192
[731] Sensabaugh, 300, 301
[732] Sensi, 89, 117, 143, 184, 311, 312, 313, 317, 318, 320, 321, 322, 324, 333, 348, 349
[733] Shain, 194
[734] Sheldon, 55
[735] Shkodin, 111
[736] Shkodin, 111, 169, 254
[737a] Shkodin, 111
[737b] Shkodin, 111, 112
[737c] Shkodin, 111, 112
[737d] Shkodin, 111, 112
[738] Shkodin, 111
[739] Shkodin, 111
[740] Shtifman, 415, 416
[741] Sideri, 147
[742] Sideri, 184, 356
[743] Sideri, 314
[744] Sidgwick, 94
[745] Sidgwick, 94
[746] Siggia, 169, 184, 262
[747] Siggia, 147
[748] Siggia, 261
[749] Siggia, 297, 298, 299
[750] Siggia, 131, 374, 383
[751] Siggia, 169
[752] Siggia, 390
[753] Siggia, 116, 169, 263, 265
[754] Simon, 164, 193, 194, 309
[755] Simonyi, 171
[756] Simonyi, 171
[757] Simonyi, 335
[758] Singh, 264
[759] Sinha, 302
[760] Skoog, 403
[761] Small, 131, 139, 171
[762] Smith, 260
[763] Smith, 22, 38, 46, 142, 152
[764] Smith, 286
[765] Smith, 67, 68
[766] Sobczyk, 111
[767] Sokolowski, 143, 195, 377
[768] Soloway, 133
[769] Spengler, 167, 184, 311, 312
[770] Sprengling, 190, 179, 191, 285, 309
[771] Stanford, 114
[772] Stetzler, 288, 289
[773] Stock, 173

[774a] Stock, 173, 220
[774b] Stock, 173, 220
[775] Stock, 203, 208
[776] Sock, 173
[777] Streuli, 123
[778] Streuli, 64, 66, 67, 168, 175, 176, 195, 333, 365, 366, 404
[779] Streuli, 50, 64, 66, 67, 81, 168, 175, 184, 322, 331, 332
[780] Streuli, 40, 41, 42, 122, 129, 175, 176, 184, 195, 197, 240, 271, 276, 280, 281, 284
[781] Streuli, 67, 168, 422
[782] Streuli, 40, 41, 42, 68, 176, 184, 240
[783] Stuck, 134, 169, 254, 258
[784] Stumpf, 146, 147
[785] Suchomelová, 406, 410
[786] Susz Lachavanne, 54
[787] Svoboda, 117, 194
[788] Swartz, 116, 131, 184, 274
[789] Sweetser, 237, 238
[790] Szász, 117, 338
[791] Szász, 335
[2] Szendey, 335, 336
Szendey, 312
Szendey, 328

csi-Nagy, 328
uchi, 171, 422
chi, 171
214, 215, 280, 281, 282
264, 397
95, 397

0

374

98, 399

129
32, 36, 38, 39
ickenson, 51, 64, 71
37
26

U

[823] Uhrig, 398
[824] Underwood, 237
[825] Usanovich, 11
[826] Usanovich, 11
[827] Usanovich, 2, 11
[828] Usanovich, 59, 123
[829] Usanovich 123
[830] Usanovich, 57
[831] Usanovich, 64, 127, 128, 167, 262

V

[832] Vacek, 247, 250, 251, 312
[833] Vaillant, 8, 57
[834] Vasiliev, 352
[835] Vasiliev, 325
[836] Vasiliev, 355
[837] Vasiliev, 325
[838] Veibel, 64, 65, 389
[839] Veibel, 323
[840] Veibel, 323
[841] Veibel, 323
[842] Veibel, 388
[843] Veibel, 406, 407, 408
[844] Veibel, 274, 389
[845] Veibel, 389
[846] Vespe, 273, 275
[847] Viberg, 23
[848] Vincent, 129
[849] Vogelsong, 23, 70
[850] Vogelzang, 288
[851] Volmer, 52
[852] Vorländer, 157, 215

W

[853] Wadelin, 416
[854] Wagner, 117, 184, 374, 377
[855] Walden, 2, 111, 409
[856] Walden, 111
[857] Walden, 111
[858] Waltz, 242
[859] Wanzlick, 388
[860] Warner, 117, 120, 188, 190, 337
[861] Wassermann, 15
[862] Wassermann, 15, 311
[863] Waters, 79, 80, 83, 91, 404
[864] Watt, 23
[865] Wei-hwa, 117
[866] Weissberger, 110, 145, 149
[867] Wepster, 96
[868] Werniment, 139
[869] Westheimer, 80
[870] Wheland, 95, 114, 121, 416
[871] Wheland, 98

[872] Wilchek, 286
[873] Willi, 47
[874] Williams, 148
[875] Williams, 148
[876] Williams, 156, 285
[877] Williams, 156
[878] Wimer, 67, 128, 192, 195, 333, 334, 343, 398
[879] Wimer, 404
[880] Wimer, 128, 334
[881] Wizinger, 211
[882] Wolf, 27
[883] Wollish, 250, 251
[884] Wooding, 50, 96
[885] Wright, 395
[886] Wynne-Jones, 47
[887] Wynne-Jones, 18, 37

Y

[888] Yakubik, 195, 196, 197, 254, 257
[889] Yarovenko, 245
[890] Yokoyama, 117, 174, 356

Z

[891] Zarembo, 253
[892] Zarinski, 173
[893] Zaugg, 91, 269
[894] Zeidler, 184, 187, 192, 193
[895] Zenchelski, 173
[896] Ziegler, 139
[897] Zýka, 410, 411
[898] Zýka, 276

Subject Index

Acceptor acids, 9
Acceptor bases, 9
Accuracy, 216
Acetacidium ion, 125
Acetic acid, 125
dehydration, 139
differentiating effect, 127
merization, 126
rity in acetic anhydride, 262
lling effect, 126, 127
ionization, 126
ater in, 139
tic anhydride, 127
cetanhydridium ion, 128
cetate ion, 127
acetyl cation, 127, 128
cetyloxonium ion, 128
lehydrating agent, 141
etection in acetic acid, 142
oval from acetic acid, 143
nization, 127
ile, 122
tion in, 27
fication, 145
tion,
lic OH, 289, 293, 296
295
295
5
hydrogen, determination of, 401
des, determination of, 342
strength, 343
ation in acetic anhydride, 343
ea, with photometric end-point, 344
ith 2,4-dinitrobenzoyl chloride, 344
Acid anhydrides, determination of, 260
morpholine method, 260
aniline method, 261
Acid–base concepts, 1
Arrhenius–Ostwald, 2
early views, 1
Ebert–Konopik, 9
electronic theory, 4
ionotropy theory, 9
protonic theory, 4
solvent theory, 2
Usanovich, 11
Acid–base strength, relative order in acetic acid, 36
Acidic substances, determination of, 239 *et seg.*
acetylsalicylic acid, 251
aliphatic, 243, 244
amino acids, 253
benzoic, and substituted benzoic acids, 246
cholic acids, 251
mixtures in differentiating solvents, 254
peracids, 253
2-phenylquinoline-4-carboxylic acid, 250
polybasic acids,
solvent used, 240, 241, 242
Acidity and molecular structure, 74
Acidity function, Hammett's, 42
Acidity scale, 38, 39
Acid mixtures, determination of, 254
in acetone, 256
in t-butanol, 258
in methanol, 258
in G–H solvent mixture, 257
in isobutyl methyl ketone, 255
in N,N-dimethyl fatty amides, 259

in pyridine, 257
Acid number of petroleum products, 244
Acid strength, 14
comparison in various solvents, 45
determination, 30, 31
effect of *ortho* substitution, 100
influence of steric hindrance, 96
Acids, cationic, 50
Brönstedt H-acids, 16
determination of strength, 30, 31
effect of mesomerism 82
secondary, 57
weak, proton donor properties, 48
Acyl chlorides, determination of, 262
Alcoholic OH, determination of, 287
in mixture, 296
with acetic anhydride, 289, 293
with 2,4-dinitrobenzoyl chloride, 290
with metal amides, 287
with phenyl isocyanate, 291
with propionic anhydride, 288
Aldehydes, identification of, 388
Alkaloides, determination of, 326, 334
halide salts, 355
Alkoxyl group, determination of, 419
Alkylaluminium compounds, determination of, 415
Alkyl halides, determination of, 266
Amide group, determination of, 270
Amides as bases, determination of, 342
Amines (see also Bases), determination of, 316
mixtures, 374, 377, 378, 380, 383, 384
primary, in presence of sec. and tert. 382
tertiary (hydrochlorides) in presence of acetylable amines (hydrochlorides) 381, 386
Amino acids, determination of,
as acids, 253
as bases, 319
solvation, 29
Ammonium ions, solvation, 51
Amphoteric substances, 106
solvents, 131
Anaesthetics, determination of, 362
Anion transfer, 10
Antihistamines, determination of, 356
Aprotic solvents, 110, 120
Aromatic hydrocarbons, determination of, 418
Arrhenius–Ostwald theory, 2
Ascorbic acid,
redox titration, 410
with bromine in AcOH, 410
Association,
effect on base strength 70
effects in inert solvents, 72
equilibrium constants, 31
of benzoate anion, 30
Autoprotolysis constants, 21
Barbituric acid derivatives, 272
acid strength, 272
determination of salt, 274
tautomerism, 272
titration in benzene–sopropanol, 273
in chloroform, 274
in dimethylformamide, 273
in methyl ethyl ketone, 274
in pyridine, 273, 405
Base strength, 60
acetic acid, in, 64
effect of association 70
mesomerism, 82
resonance, 85
steric hindrance, 96
substituents, 80
half-neutralization potential in acetic acid, 63
in acetic anhydride, 65
in acetonitrile, 68
in nitromethane, 67
measurement of, 63
of weak bases in sulphuric acid, 62
Bases, determination of nitrogenous, 316 *et seq.*
acidamides, 342
aliphatic, 317
alkaloids, 326, 334, 336
amino acids, 319
aromatic, 317
benzamidine and related compounds,
ethylene-imino group, 345
heterocyclic, 321
hydrazides and hydrazones, 348
hydrazine and substituted hydrazines,
hydroaromatic, 317
ketimines, 345
in medicinal plants, 338, 339, 340, 341
micro, semimicro, and ultramicro, 334
mixtures in differentiating solvents, 374
with salicylaldehyde method, 377, 37
with acetic anhydride method, 380
with acetylacetone method, 378
with phthalic anhydride method
with distillation methods, 384
phenothiazine derivatives, 327
piperazine derivatives, 328
photometric end-point, by, 319, 326
purine bases, 341
salts of, 351
sulphonamides, 345
titration in acetic anhydride, 3
chlorobenzene, 331
nitromethane, 331
nitromethane–acetic anhydride
332
titration with 0·005 N *p*-toluenesulph
acid, 334

Basic solvents, 132
Basicity and molecular structure, 74
Basicity scale, 38
Benzoic acid, determination of, 246
Benzoic acids, substituted,
  correlation between pK and association constants, 34
  equilibrium constants 31
  substituent effect 32
Benzamidine and related compounds, determinations of, 345
Benzimidazole, determination of, 276
Benzotriazole, determination of, 276
p-Bromphenacylsulphonium compounds, determination of, 406
Brönsted–Lowry's protonic theory, 4

Carbamic acid esters, 421
Carbamoyl group, determination of, 421
Corrections, 158
  heat expansion nomogram, 159
Carbonyl group, determination of, 388
  with dimethylhydrazine, 390
    hydroxylamine, 391
    hydroxylamine formate, 392
    hydroxylammonium salicylate, 393
  formation of phenylhydrazones, 412
  semimicro method, 392
  steroid ketones, 393
Calculations, 217
Carboxylic acids, determination of
  salts of, 310
  titration in acidic solvents, 312
    basic solvents, 312
    differentiating solvents, 315
    G–H solvent system, 314
Complex formation titrations, 415
  alkylaluminium compounds, 415
  aromatic hydrocarbons, 418
  dienes, 416
Cyclohexanone oxime, determination of, 296
Cyclopropylamines, determination of, 398
Carbon dioxide as Lewis acid, 59
Carbonium ion, 50, 55
Carboxylic acid (see also: Acidic substances),
  substituent effect, 75
  talytic effect of H-acids, 4
  ion–anion theory, 9
  ion transfer, 10
  stants,
  acid–base dissociation, 19
  dielectric, of solvents, 110
  solvent, autoprotolysis, 21

  l sulphides, identification of, 407
  malonate, 270

Dienes, determination of, 416
ß-Diketones, identification of, 389
Double bond, determination of, 395
  hexamethylene-imine method, 397
  mercury(II) acetate method, 396
  morpholine method, 397
  steroid ketones, 399
  with bromine, 398
Dielectric constants, 110
  effect of, 26
Differentiating solvents, 27, 111
  origin, 111, 112
  H-bond, 113
Dimerization of carboxylic acids, 113
Dissociation constants, definition of, 19
Distillation,
  fractional, of solvents, 143
Donor acids, definition of, 9
Donor base, definition of, 9
Drying agents, 138
Drying of solvents, 137, 138

Electrodes, 184 *et. seq.*
  aluminium–aluminium, 188
  antimony–antimony, 187
  calomel, 188, 189, 191, 192
  combined, 190
  elimination of liquid junction potential, 191
  for determination of phenols, 197
  for micro titrations, 193
  glass, 184
  graphite–platinum, 192, 193
  indicator, 184
  J-shaped mercury, 188, 191
  mercury–mercury(I) acetate, 186
  metal, 186, 187
  platinum–platinum, 187, 194
  reference, 191
  retarded, 185
  silver–silver chloride, 189, 190
  two-phase, 196
Electrostatic field effect, 80
End-point detection,
  photometric, 219
  potentiometric, 173
  with indicators, 198
α-Epoxide group, determination of, 400
Ethylene-imino group, 347
Evaporating flask, 249
Extraction,
  solid–liquid and liquid–liquid for medicinal plants, 339
    of rubber, 413
Extractor
  Jacobs–Singer type 250
  solid–liquid and liquid–liquid, 339

G–H solvents mixture, 118
titration of acid in, 257
Gutmann–Lindqvist's ionotropy theory, 9

H-acids, 16
Half-neutralization potential, 40
Hammett's acidity function, 42
Hammett values of sulphonic acids, 152
Heteroconjugation, 28
Heterocyclic compounds,
determination of acid analogues, 276
determination of nitrogenous bases, 321
Homoconjugation, 28
Hydrazides and hydrazones, 348
Hydrazine and substituted hydrazines, 348
Hydrogen bond, 113
Hydroxyl number, 288, 289
Hydroxylamine, determination of,
with copper(II) ions, 411

Imidazolidine derivatives, 388
Imide group, determination of, 270, 271
Inert solvents, 110, 120
Indicators, 198 *et seq.*
choice, 203
colour change of crystal violet, 211
colour change of azo-violet, 214
colour change of dimethyl yellow, 215
colour change of thymol blue, 214
in acidic solvents, 207
in alkaline solvents, 208
in inert solvents, 205
in solvent mixtures, 209
theory of, 199
triphenylmethane dyes, 198
Inductive and other effects, 25
Ionization,
in acetonitrile, 27
in nitromethane, 29
of organic compounds, 14
and dissociation, 105
of weak bases in sulphuric acid, 62

Ketimines, determination of, 345
Keto-enol tautomerism, 93, 94
Ketones (see also carbonyl group),
resonance forms and acidity, 93

Levelling effect, 111
Lewis acids, 8, 53
catalytic effect, 8
reactions,
in acetyl chloride, 56
in nitrobenzene, 56, 57
Lewis' electronic theory, 6
Lubricant, 156
Lyate ions, 21
Lyonium ions, 21

Maleic acid, determination of,
in presence of their anhydride, 262
Malonic acid esters, determination of, 269
2-Mercaptobenzothiazole, determination of (as acid), 276
2-Mercaptobenzimidazole, determination of (as acid), 277
Mercaptans, determination of, 404
with silver nitrate,
in pyridine, 404
in isopropanol, 404
with mercury(II) perchlorate, 406
Mercurials, determination of,
via acetolysis, 364
Mesomeric and inductive effect, 82, 85 90,
Micro- and semimicro titrations of,
acids, 303, 305, 307
bases, 334
equipment, 304, 305, 309
Multiple bonds, determination of, 395
double bond, 295
acetylenic hydrogen, 401

Nitro compounds, determination of, 300
aromatic, 300
nitroguanidine and derivatives, 302
Nitroethane as secondary acid, 58
Nitromethane, 125, 129
ionization in, 29
purification of, 148
p-Nitrophenyl esters, determination of, as acids, 286

Oestrogenic effect, compounds having, 285
titration,
acetone–pyridine–methanol mixture, 285
dimethylformamide, 285
pyridine, 285
'Onium ions, 50
Organosilicon compounds, determination
422
Oxiran oxygen, determination of, 400
Oxonium ions, 52

Peracids, determination of, 253
Pharmaceutical preparations, 247
tablet excipients, 248
Phenolic hydroxyl group, determinati
279 *et seq.*

potentiometric titration, 282, 283, 284
substituent effect, 279
titration in acetone, 283
in t-butanol, 284, 285
in dimethylformamide, 282
in ethylenediamine, 282
in isobutyl methyl, ketone, 283
in pyridine, 284
Phenolic esters, determination of, 286
Phenylureas, determination of, 271
Phenylhydrazine, determination of,
with copper(II) ions, 411
Phosphines, determination of, 422
Photometric end-point, 219 *et seq.*
advantages, 220
apparatus, 236
cells, 237, 238
differentiating titration of bases, 232
fundamental law, 219
limitations, 220
titration curves, 221
type I, 223
type II, 224
type III, 229
titration in ultraviolet, 230
titration of phenols, 233
Phthalic acid, determination of, 262
Polybasic acids, determination of, 251
Potentiometric end-point, 173
accuracy, 175
area of application, 174, 175
calculation (end-point), 186
choice of solvent, 182
effect of the solvent, 176
electrodes, 184
equipment, 176, 187, 188, 189, 190
evaluation of the colour change of indicators, 174
irregular potentiometric curves, 177, 180
potential range of solvents, 182
shape of titration curves, 196, 180
supporting electrolytes, 183
Proton-donor, proton-acceptor, 5
Proton-transfer and proton-transfer energy,
definition of, 17
mechanism, 18
types of proton-transfer, 18
Purine bases, determination of,
as acids, 271, 272
as bases, 341

Quaternary bases, determination of, 367

Redox titrations, 409
Resonance,
effect on the strength of substituted benzoic acids, 91
and acidity of ketones, 93
Rubber in plant material, determination, of 413
Salts of carboxylic acids, determination of, 310
in acidic solvents, 312
in basic solvents, 311
in differentiating solvents, 315
in G–H solvent system, 314

Salts of nitrogenous bases, determination of, 351
formed, with organic acids, 351
with halogen acids, 352
with nitric acid, 370
with phosphoric acid, 370
with picric acid, 352
with sulphuric-, ethanesulphuric-, *p*-toluenesulphonic acids, 370
with tetraphenylboron, 368
Saponification number, 244
S-benzylthiuronium derivates,
determination of, 406
Solvation, 103
of amino acids, 29
of ammonium ions, 51
effect on base strength, 70
Solvent effect,
combined effect of solvent mixture, 24
of dielectric constant, 26
on the ionization and solvation of acids, 27
on the strength of acids, 22
solvating properties, 25
Solvent theory, 2
Solvents,
acetic acid, 125
acetic anhydride, 127
acetone, 122
acetonitrile, 122
acidic solvents, 114, 124
alcohols, 131
order of acidity, 131
amphiprotic solvents, 131
amphoterism, 106
aprotic (inert) solvents, 110, 120
association, 106
basic solvents, 115, 132
benzene, toluene, 121
n-butylamine, 132
carbon tetrachloride, 121
characteristics of,
acidic, 124, 125
basic, 132
inert, 120
chlorobenzene, 121
chloroform, 120
choice of, 118, 182

Solvents (continued)
dehydration of, 137
determination of water in, 139
diethyl ether, 134
differentiating, 27, 111
dimerization, 113
1,4-dioxan, 134
drying, 137
effect of ionization and dissociation, 105
effect of solvent on the solute, 108
ethanolamine, 133
ethyl methyl ketone, 122
ethylenediamine, 132
for determination of acids, 116
for determination of bases, 115
formic acid, 124
general properties, 101
glycols, 131
H-bond in solvents, 113
n-heptane, 120
n-hexane, 120
isobutyl methyl ketone, 122
isopropanol, 144
levelling effect, origin of, 111
mixtures for determination of acids, 116, bases 117
N,N-dimethylformamide, 133
nitrobenzene, 130
nitromethane, 129
physiological effect of, 149
potential range, of, 182
propionic acid, 127
propionic anhydride, 129
purification of, 136, 144
acetic acid, 139
acetonitrile, 145
benzene, 136
carbon tetrachloride, 136
chlorobenzene, 136, 145
chloroform 136, 148
dimethylformamide, 147
1,4-dioxan, 145, 146
ethyl ether, 144
isopropanol, 144
methanol, 144
nitromethane, 148
pyridine, 148
rarely used solvents, 149
pyridine, 133
solvating power, 101
solvation, 103
solvolysis, 104
Solvosystem,
cationotropic, 11
anionotropic, 11
Standardization,
of acidic titrants, 153, 154, 155, 156, 158
of basic titrants, 160, 162, 163
Steroids,
determination of double bond, 399
determination of ketogroup, 393
Strength of acids, determination of, 30, 31
Substituent effect,
in the aromatic ring, 77
on the acid strength, 32, 75
on the acidity of phenols and enols, 78
on the strength of bases, 80
Sulphonamide derivatives, 275, 345
Sulphonium ions, 52
Sulphur, elementary, determination of, in plant protectives, 403
Sulphoxides, determination of, 404
Sympathomimetics, determination of, 364

Tablet (excipients),
perchloric acid consumption, 248
Tetracyanoethylene, reagent, 417
1,1,3,3-Tetramethylguanidine as solvent, 285
Tetrazole derivatives, determination of, 278
Thioethers, determination of, 407
Thiols, determination of, 404
Titrants, acidic, 152 *et seq.*
hydrochloric acid, 153
perchloric acid, 154
p-toluenesulphonic acid, 157
standardization, 153, 154, 155, 156, 158
Titrants, basic, 160 *et. seq.*
alkali metal hydroxide, 160
alkali metal alkoxide, 161
alkylammonium hydroxide, 163
equipment, 162, 163
sodium acetate, 167
standardization, 160, 162, 163
Titrants, rarely used, 168 *et seq.*
aluminium isopropoxide, 171
amino-group, containing, 168
ammonium thiocyanate, 171
bromine in acetic acid, 172
carboxyl-group, containing, 168
cerium(V) ammonium nitrate, 172
copper(II) acetate, 172
cyclopentadiene, 172
2-ethylhexanal, 171
hydrogen bromide, 170
lithium aluminium di-n-butylamide, 171
nitric acid, 170
perchloric acid in various solvents, 168, 170
potassium cyanide, 171
silver nitrate, 171
sodium aminoethoxide, 170
sodium methoxide,
in Methyl Cellosolve, 171
in pyridine, 170

Titration,
coloured solutions, 245
in dark, 246
Triazole derivatives, determination of, 278
Trichloroacetic acid,
intercation with pyridine, 30
Triethylaluminium,
reaction with isoquinoline, 57

Water,
determination of, in solvents, 139
effect on titration, 141, 142
as base in acidic solvents, 60

Xanthogenates, determination of, 406, 412

Responsible for publication: Gy. Bernát
Director of the Publishing House
of the Hungarian
Academy of Sciences and of the Academy Press
Responsible editor: E.K. Kállay – Tóth. Technical editor: M. Meznerics
Jacket and cover by M. Koncz
Set in 10/11 point New Times Roman
Academy Press, Budapest

SCIENTIFIC PERIODICALS OF THE HUNGARIAN ACADEMY OF SCIENCES

ACTA CHIMICA publishes papers in the field of chemistry including inorganic and analytical chemistry, physical chemistry, organic chemistry, and chemical engineering. The treatises, published in English, German or Russian, with abstracts in a second language, are written by eminent scientists from Hungary and other countries. ACTA CHIMICA is published in 16 issues of some 100 to 110 pages each, making up four volumes a year. Size: 17×24 cm.

ACTA BIOCHIMICA ET BIOPHYSICA is a new scientific review of the Hungarian Academy of Sciences, devoted to new findings, methods and techniques in the field of fundamental biochemistry and biophysics. The treatises are mainly published in English. ACTA BIOCHIMICA ET BIOPYSICA is issued quarterly, making up a volume of some 400 to 500 pages a year. Size: 17×24 cm.

Distributors:

KULTURA, Budapest 62. P. O. B. 149

