The Determination of Ionization Constants

A Laboratory Manual

e-3

The Determination of Ionization Constants

A Laboratory Manual

THIRD EDITION

Adrien Albert
D.Sc. (Lond.), F.R.I.C.
Fellow of the Australian Academy of Science
Emeritus Professor, Department of Chemistry,
Australian National University
Research Professor,
Department of Pharmacological Sciences,
School of Medicine,
State University of New York,
Stony Brook

E.P. Serjeant
M.Sc. (N.S.W.)
Senior Lecturer in Chemistry,
Faculty of Military Studies,
University of New South Wales,
Duntroon, A.C.T

LONDON NEW YORK
CHAPMAN AND HALL

First published 1962 as
Ionization Constants of Acids and Bases
by Methuen & Co Ltd
Second edition published 1971
by Chapman and Hall Ltd
11 New Fetter Lane, London EC4P 4EE
Third edition 1984
Published in the USA
by Chapman and Hall
733 Third Avenue, New York NY10017

© 1984 Adrien Albert and E.P. Serjeant

Printed in Great Britain at the University Press,
Cambridge

ISBN 0 412 24290 7

All rights reserved. No part of this book may be reprinted, or reproduced or utilized in any form or by any electronic, mechanical or other means, now known or hereafter invented, including photocopying and recording, or in any information storage and retrieval system, without permission in writing from the Publisher.

British Library Cataloguing in Publication Data

Albert, Adrien
The determination of ionization constants.—
3rd ed.
1. Ionization 2. Acids 3. Bases
I. Title II. Serjeant, E. P.
546′24 QD561

ISBN 0–412–24290–7

Library of Congress Cataloging in Publication Data

Albert, Adrien, 1907—
The determination of ionization constants.

Bibliography: p.
Includes index.
1. Ionization constants—Measurement—Laboratory manuals. I. Serjeant, E. P. II. Title.
QD561.A366 1984 541.3′722′028 84–7497
ISBN 0–412–24290–7

The Determination of Ionization Constants

Preface

This practical manual is devised for organic chemists and biochemists who, in the course of their researches and without previous experience, need to determine an ionization constant. We are gratified that earlier editions were much used for this purpose and that they also proved adequate for the in-service training of technicians and technical officers to provide a Department with a p*K* service. The features of previous editions that gave this wide appeal have been retained, but the subject matter has been revised, extended, and brought up to date.

We present two new chapters, one of which describes the determination of the stability constants of the complexes which organic ligands form with metal cations. The other describes the use of more recently introduced techniques for the determination of ionization constants, such as Raman and nuclear magnetic resonance spectroscopy, thermometric titrations, and paper electrophoresis.

Chapter 1 gives enhanced help in choosing between alternative methods for determining ionization constants. The two chapters on potentiometric methods have been extensively revised in the light of newer understanding of electrode processes and of the present state of the art in instrumentation.

In the spectrometric methods chapter, the newer IUPAC symbols replace the old. Also the treatment of Hammett's acidity function has been brought up to date. This chapter concludes with help for the preparative organic chemist, namely a rapid spectrometric titration. This yields an approximate p*K*, knowledge of which will suggest conditions under which the new substance can be extracted and purified in higher yields.

The chapter on zwitterions and other ampholytes has been largely rewritten to give a clearer presentation, and much new information has been incorporated.

The tables of typical ionization constants, in Chapter 9, have been re-compiled from the most reliable of available values, and many additional substances will be found there. This chapter has a new section on substances which modify their ionization by equilibrating with pseudobases (e.g. acridinium and pyrylium salts, also triphenylmethane dyes). The chapter concludes with a new table of the ionization constants of 370 commonly prescribed drugs and other biologically active substances.

此为试读，需要完整PDF请访问：www.ertongbook.com

Help in the *interpretation* of ionization constants is provided. It is shown how these are related to solubility (Chapter 5), how the degree of ionization at any pH can be calculated (Appendix V), and how ionization constants can aid in deciphering an unknown structure (Chapter 1).

We advise a beginner, before he tackles any unknown substance, to 'enroll' in a *course* by repeating, in the order printed, each worked example in Chapters 2 and 4, both the practical work and the calculations (only easily procurable substances are needed). Much time can be saved in the calculations if the results are set out as shown in these worked examples.

The first examples require only a few, very simple calculations. We have taken care to define the parameters within which these simple methods suffice, and to state clearly when refinements of calculation are needed. We have introduced the more complicated calculations as gradually as possible, and with full explanatory detail. To lessen the tedium of the lengthier calculations, we have devised computer programs. These are presented in a form which clearly shows the pathways of their derivation, to help those who would like to use a desk (electronic) calculator instead of a computer.

Because this is a practical manual, we have touched only lightly on the theory of ionization (Chapter 1 and Appendices I and II). For theoretical study, E.J. King's book *Acid-Base Equilibria* (1965) and R.G. Bates' *Determination of pH, Theory and Practice* (1973) are recommended. Many useful data will also be found in *Electrolyte Solutions* by R.A. Robinson and R.H. Stokes (1959), and *Solution Equilibria* by F.R. Hartley, C. Burgess and R. Alcock (1980), the latter being particularly helpful with the experimental approach to finding stability constants of metal complexes.

We thank Dr D.D. Perrin for helpful discussions.

Contents

Preface

1 **Introduction** page 2
1.1 What is meant by 'ionization constants'? 2
1.2 Why do we determine ionization constants? 2
1.3 Brief summary of the chemistry of ionization 4
1.4 The nature of pK_a values 6
1.5 The shape of a titration curve 7
1.6 Methods commonly used for determining ionization constants 8
1.7 What degree of precision is required? 10
1.8 The effect of temperature on ionization constants 11
1.9 Molality and molarity 12

2 **Determination of Ionization Constants by Potentiometric Titration using a Glass Electrode** 14
2.1 Apparatus for general use 15
2.2 Preparation of solutions 22
2.3 Choice of concentration for the titration 24
2.4 Details of the titration method 25
2.5 Derivation and choice of equations for calculating pK_a 26
2.6 Some typical titrations (worked examples) 29
2.7 Precision and accuracy. Checking the precision obtained 31
2.8 Common sources of error, and their elimination 31
2.9 False constants 35
2.10 Partly aqueous solvents 35

3 **Refinements of Potentiometric Titration: Apparatus and Calculations** 40

A Apparatus

3.1 Semi-micro titrations 40
3.2 Micro titrations 43
3.3 The rapid-flow method 46
3.4 The hydrogen electrode 46

B Calculations

3.5 Monofunctional acids and bases 47

3.6 Method of calculation 51
3.7 Diacidic bases, dibasic acids and ampholytes 53
3.8 Overlapping ionization processes 56
3.9 Polyelectrolytes 61
3.10 Accuracy of the potentiometric method 62
3.11 Non-aqueous solvents 64

4 Determination of Ionization Constants by Spectrophotometry 70
4.1 Introduction 70
4.2 Apparatus 73
4.3 Buffers 73
4.4 Acidity functions 75
4.5 Preparation of the stock solution of the unknown 78
4.6 The search for the spectra of two pure ionic species 79
4.7 The choice of an *analytical wavelength* 79
4.8 Preliminary search for an approximate value of pK_a 80
4.9 Exact determination of pK_a 80
4.10 Worked examples 81
4.11 Activity corrections 84
4.12 Extensions of the spectrometric method 84
 (a) The pK_a of a very weak acid (graphical treatment) 84
 (b) Overlapping pK_a values 86
 (c) Computer program for overlapping values 89
4.13 Errors, precision and accuracy 93
4.14 Common sources of error 94
4.15 Spectrophotometric determination of the pK_a of a substance that lacks an absorption spectrum 94
4.16 A rapid method for the approximate measurement of pK_a 95

5 Relations between Ionization and Solubility. Determination of Ionization Constants by Phase Equilibria 102
5.1 Ionization constants in preparative work 102
5.2 Prediction of solubility from ionization constants 103
5.3 Determination of ionization constants from solubilities 105
5.4 Determination of ionization constants from vapour pressure, by partitioning between a pair of solvents, or by other phase equilibria 107

6 Determination of Ionization Constants by Conductimetry 110
6.1 Scope of the method 111
6.2 Apparatus 113
6.3 Procedure 115
6.4 Refinements of calculation 117

7 Some Other Methods for the Determination of Ionization Constants **120**
7.1 Raman spectrometry 120
7.2 Proton nuclear magnetic resonance 121
7.3 Nuclear magnetic resonance using other atoms 123
7.4 Thermometric methods 124

8 Zwitterions (Dipolar Ions) **126**
8.1 Zwitterions compared to ordinary amphoteric substances 126
8.2 How to distinguish zwitterions from ordinary ampholytes 128
8.3 Zwitterionic equilibria: macroscopic and microscopic constants 130

9 The Ionization Constants of Typical Acids and Bases **136**
A Organic Section
9.1 The oxygen acids (monobasic) 137
(a) Aliphatic carboxylic acids 137
(b) Aromatic carboxylic acids 140
(c) Aliphatic hydroxylic acids 142
(d) Aromatic hydroxylic acids (phenols) 144
(e) Other oxygen acids 144
9.2 The oxygen acids (dibasic) 147
9.3 Sulphur acids, nitrogen acids and carbon acids 150
(a) Mercaptans 150
(b) Nitrogen acids 150
(c) Carbon acids 150
9.4 The nitrogen bases (monoacidic) 150
(a) Aliphatic bases 150
(b) Aromatic and heteroaromatic bases 153
9.5 The nitrogen bases (diacidic) 156
9.6 Carbinolamine bases 157
9.7 Oxygen bases and carbon bases 160
9.8 Amphoteric substances 160
B Inorganic Section
9.9 Inorganic acids 162
9.10 Inorganic bases 164
C Biologically-Active Substances 166

10 Chelation and the Stability Constants of Metal Complexes **176**
10.1 The nature of chelation 178
10.2 Methods of calculation 179
10.3 Choice of ionic medium and the preparation of standard solutions 184
10.4 Measurement of pH and the calculation of pc_H 188
10.5 Common difficulties and how they can be overcome 190

11 Appendices **192**
I An outline of the Brønsted–Lowry Theory 192
II Comparison of classical and thermodynamic quantities 196
III Calculations of hydrogen ion activity and concentration: also of hydroxyl ion activity and concentration 197
IV Some effects of temperature on ionization constants 199
V How percentage ionized may be calculated, given pK_a and pH 203
VI An outline of the theory of pH 203

References **208**

Subject index **216**

The Determination of Ionization Constants

此为试读，需要完整PDF请访问： www.ertongbook.com

1 Introduction

1.1 *What is meant by 'ionization constants'?* page 2
1.2 *Why do we determine ionization constants?* 2
1.3 *Brief summary of the chemistry of ionization* 4
1.4 *The nature of* pK_a *values* 6
1.5 *The shape of a titration curve* 7
1.6 *Methods commonly used for determining ionization constants* 8
1.7 *What degree of precision is required?* 10
1.8 *The effect of temperature on ionization constants* 11
1.9 *Molality and molarity* 12

1.1 What is meant by 'ionization constants'?

In this book, the term 'ionization constant' means any constant which is used to measure the strength of acids and bases. Although sometimes referred to as 'dissociation constant', this term is vague because ionization forms only a corner of the vast field of dissociation phenomena. Thus substrates dissociate from enzymes, micelles dissociate into monomers, and iodine molecules dissociate into iodine atoms. Many other such equilibrium processes are known, but the majority of these dissociations are not ionizations. On the other hand zwitterions are ionized but they are not dissociated.

A minor objection to the term ionization constants is that the constant for a *base* represents an equilibrium in which one ion gives rise to another ion (see equation 1.3, p. 4). This difficulty disappears if we define ionization constants with reference to hydrogen and hydroxyl ions only.

This chapter *outlines* the concepts discussed later in the book. It is supplemented by a general revision of basic theory in Appendices I and II.

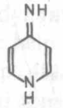
1.2 Why do we determine ionization constants?

Ionization constants reveal the proportions of the different ionic species into which a substance is divided at any chosen pH. Appendix V (p. 203) shows how to calculate the percentage of an acid or a base that is ionized at various values of pH and pK_a. It may be deduced from the equations of Appendix V, and also from Fig. 1.1 that a small change in pH can make a large change in the percentage ionized. This is particularly significant if the values of pH and pK lie close together, as they do near the point of half neutralization.

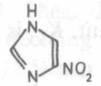
Information about ionization is useful in many ways. For example, different ionic species have different ultraviolet spectra, and significant spectrophotometry can be done only when the pH is so chosen that only *one* ionic species is present. The ionic species of a given substance differ in other physical properties, and in chemical and biological properties as well (Albert, 1979). Ionization constants, by defining the pH range in which a substance is least ionized, indicate the conditions under which it can be isolated in maximal yield (see Chapter 5) and this information has much value in preparative chemistry.

Ionization constants, too, can help to discover the structure of a newly isolated substance. The first question to ask is: Does the postulated structure predict the experimentally determined pK_a values, when calculated theoretically by the method of Perrin, Dempsey and Šerjeant (1981)? If so, a considerable verification of the proffered structure has been achieved. Several other ways in which ionization constants reveal structure will now be mentioned. For a fuller treatment of the subject, see Barlin and Perrin's review (1972).

When tautomerism is possible, the structure with the more weakly acidic proton is favoured because it must have the mobile hydrogen more firmly bonded. Ionization constants determinations first showed that 2- and 4-aminopyridine (pK_a 6·9 and 9·2) had the structures of primary amines in equilibrium with very little of the imine tautomers (e.g. (*1·1*)), because 1-methyl-2-imino- and 1-methyl-4-imino-pyridines had pK_as 12·2 and 12·5, respectively (Angyal and Angyal, 1952). Similar reasoning helped to assign structures to the products obtained by methylating the mono-aminopyrimidines, i.e. whether the exo- or the endo-nitrogen atom was alkylated (Brown, Hoerger and Mason, 1955). Again, the methylation of 4-nitroimidazole (*1·2*) gave 1- and 3-methyl derivatives, whose structures were easily assigned from the large and expected difference in pK_a (−0·53 and 2·13 units, respectively). (Grimison, Ridd and Smith, 1960).



(1.1)



(1.2)

The presence of *covalently* bound water can be detected in a heterocyclic amine by the anonomously high pK_a values that it engenders, by strengthening bases and weakening acids (Albert, 1976; Albert and Armarego, 1965).

To distinguish between a zwitterion and an ordinary ampholyte, in amphoteric substances, there is no better method than to compare the pK_a values as determined in water with those determined in dilute ethanol (see, further, Chapter 8).

Many pairs of geometrical isomers have had their members correctly assigned by comparison of ionization constants (Pascual and Simon, 1964). Axial carboxy groups are weaker than their equatorial analogues, and many conformational problems have been solved by this knowledge (Barlin and Perrin, 1972). Differences in pK_a values form the basis for separating many chemically similar substances, such as the various penicillins that arise side-by-side from a fermentation (see also Chapter 5, p. 103).

1.3 Brief summary of the chemistry of ionization

The Brønsted-Lowry theory (Brønsted, 1923) is the most useful and widely accepted description of the ionization of both acids and bases (see Appendix I). The underlying concept of this theory is the definition of an acid as any substance that can ionize to give a solvated hydrogen ion (i.e. a proton stabilized by interaction with either the solvent or a substance in solution). Conversely a base is a substance which can accept a hydrogen ion.

In this book we deal almost exclusively with the determination of ionization constants in aqueous solutions. Most salts are completely ionized in aqueous solution, but this is not the case with many acids and bases. Very strong acids and bases are definable as those completely ionized in the pH range 0–14. Less strong acids and bases are incompletely ionized in parts of this range as is calculable from their ionization constants by the equations given at the head of Appendix V. It should also be noted that, in parts of the above range, the ions of *salts formed from weak acids* (or *bases*) are partly hydrolysed in aqueous solution, i.e. those ions are in equilibrium with the corresponding neutral species. This behaviour is also taken care of in the equations of Appendix V.

Brønsted (1923) was the first to show the advantage of having the ionization of both acids and bases (i.e. conjugate acids) expressed on the same scale, just as pH is used for alkalinity as well as for acidity. For acids the ionization process is

$$HA \rightleftharpoons H^+ + A^- \tag{1.1}$$

and the ionization constant, K_a, is given by

$$K_a = \frac{\{H^+\}\{A^-\}}{\{HA\}} \tag{1.2}$$

where $\{\ \}$ represents the *activity* of each ionic species (in mol litre^{-1}).

For bases the ionization is

$$BH^+ \rightleftharpoons H^+ + B \tag{1.3}$$

and

$$K_a = \frac{\{H^+\}\{B\}}{\{BH^+\}}. \tag{1.4}$$

At a given temperature, the constants expressed by equations (1.2) and (1.4) are thermodynamic quantities also known as *thermodynamic ionization constants* which we shall refer to henceforth as K_a^T. These constants are independent of concentration, because all the terms involved are in terms of *activities* (see Appendix II). Another type of constant that we shall use is *the concentration ionization constant*, K_a^C, which is defined for acids as

$$K_a^C = \frac{[H^+][A^-]}{[HA]} \tag{1.5}$$

in which square brackets denote the *concentration* (as opposed to the activity) of each ionic species. To yield whole numbers (rather than negative powers of ten, which are hard to remember and clumsy to write), equation (1.5) is generally used in the following form, in which pK_a is the negative logarithm of the ionization constant:

$$pK_a = pH + \log[HA]/[A^-]. \tag{1.5a}$$

For bases, the corresponding expression is

$$K_a = \frac{[H^+][B]}{[BH^+]} \tag{1.6}$$

or

$$pK_a = pH + \log[BH^+]/[B]. \tag{1.6a}$$

The main difference between thermodynamic and concentration constants is that the *activities* of the ions have to be taken care of in calculating the former. These activities compensate for the attraction which ions can exert on one another (ion-pair effects) as well as the incomplete hydration of ions in solutions that are too concentrated. The lower the concentration, the less this interaction becomes until, at infinite dilution, the concentration constant becomes numerically equal to the thermodynamic constant. These differences are dealt with in Chapter 3 (p. 47) where help is given in deciding what allowance must be made for activity effects (p. 48). Equation (1.5) can be used for the sake of simplicity provided that: (a) constants are determined in solutions not stronger than 0·01 molar; and (b) only univalent ions are present.

For the present it need only be noted that the activity of a neutral species (molecule) does not differ appreciably from its concentration, at any dilution; and that pH, as commonly determined, is nearer to hydrogen ion activity than to hydrogen ion concentration, although at low ionic strength ($I = \leqslant 0{\cdot}01$) these terms do not differ greatly* between pH 2 and 10. Hence $\{A^-\}$ is the only unfamiliar quantity in equation (1.2), because $[HA]$ can be substituted for $\{HA\}$, and $\{H^+\}$ is read from the measuring instrument.

---

*See, further, Appendix III.

1.4 The nature of pK_a values

Ionization constants are small and inconvenient figures and hence it has become customary to use their negative logarithms (known as pK_a values) which are convenient both in speech and writing (see equation 1.5a). Thus the pK_a of acetic acid (4·76) corresponds to the ionization constant $1{\cdot}75 \times 10^{-5}$. Again, the p$K_a$ of ammonia is 9·26, which is more convenient to use than the ionization constant ($5{\cdot}5 \times 10^{-10}$). p$K_b$ values for bases (see Appendix I), found only in the older literature, (e.g. 4·74 for ammonia at 25°C) can be converted to pK_a values by subtraction from the negative logarithm of the ionic product of water (K_w) at the temperature of determination. The value of pK_w is 14·17 at 20°C, 14·00 at 25°C, and 13·62 at 37°C (see Appendix IV). Thus

$$\mathrm{p}K_a + \mathrm{p}K_b = 14{\cdot}00 \quad \text{at} \quad 25°\mathrm{C}. \tag{1.7}$$

It is evident that pK_a values are very convenient for comparing the strengths of acids (or of bases). The stronger an acid, the lower its pK_a; the stronger a base, the higher its pK_a.

Table 1.1 gives the approximate pK_a values of some common acids and bases. Acids and bases of equivalent strengths have been placed opposite one another. It will prove advantageous to commit this table to memory in order to have a number of reference points for assessing the significance of new pK_a values. Many more values are in Chapter 9. For help in rapid interconversion of K_a and pK_a see Table 11.1 on p. 195.

Table 1.1 Approximate strengths of some common acids and bases

Acids	pK_a	Bases	pK_a
Hydrochloric acid*	1	Sodium hydroxide*	13
Oxalic acid	2	Acetamidine	12
	3	Ethylamine	11
Benzoic acid	4		10
Acetic acid	5	Ammonia	9
Carbonic acid	6	Many alkaloids†	8
4-Nitrophenol	7		7
	8		6
Hydrocyanic acid, boric acid	9	Aniline, pyridine, quinoline	5
Phenol	10		4
	11		3
	12		2
Sucrose	13	4-Nitroaniline	1

*Completely ionized in the range pH 0–14.

†Also local anaesthetics and antipsychotics

1.5 The shape of a titration curve

When an acid is dissolved in water it ionizes in accordance with equation (1.1). The addition of hydroxyl ions (in the form of potassium hydroxide, for example) disturbs the equilibrium by combining with the hydrogen ions produced by ionization. This reaction greatly alters the ratio of ionized species to neutral species. For example, if exactly one mole equivalent of sodium hydroxide is added, the acid will be quantitatively converted to its anion (A^-), and hence the solution, if evaporated, will give the sodium salt. All the protons available from the acid will undergo the reaction with hydroxyl ions $H^+ + OH^- \rightarrow H_2O$. However, if only 0·1 mole equivalent of sodium hydroxide is added, then 10% of the amount of acid originally dissolved will be converted to the anion, leaving 90% of the original quantity as the neutral species of the acid (HA). Again, if 0·5 mole equivalent is added, the solution will contain equimolar amounts of (HA) and (A^-). Equation (1.5a) reveals that the pK_a value of the acid may be calculated if the pH is measured under conditions of partial neutralization, because the ratio $[HA]/[A^-]$ is known from the degree of neutralization. Thus when 0·1 mole equivalent has been added, the equation becomes $pK_a = pH + \log(90/10)$, or $pK_a = pH + 0{\cdot}95$; and for 0·5 mole equivalent $pK_a = pH + \log(50/50)$, i.e. at 50% neutralization the pK_a equals the pH. When plotted, as in Fig. 1.1, these results give a *titration curve*, which is

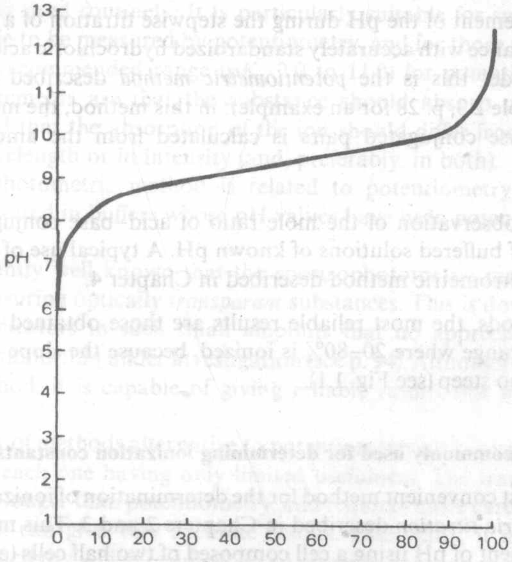


Figure 1.1 A typical titration curve.

此为试读，需要完整PDF请访问：www.ertongbook.com