

# $pK_a$

## PREDICTION FOR ORGANIC ACIDS AND BASES

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D. D. Perrin, Boyd Dempsey  
& E. P. Serjeant

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# Preface

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Many chemists and biochemists require to know the ionization constants of organic acids and bases. This is evident from the Science Citation Index which lists *The Determination of Ionization Constants* by A. Albert and E. P. Serjeant (1971) as one of the most widely quoted books in the chemical literature. Although, ultimately, there is no satisfactory alternative to experimental measurement, it is not always convenient or practicable to make the necessary measurements and calculations. Moreover, the massive  $pK_a$  compilations currently available provide values for only a small fraction of known or possible acids or bases. For example, the compilations listed in Section 1.3 give  $pK_a$  data for some 6 000–8 000 acids, whereas if the conservative estimate is made that there are one hundred different substituent groups available to substitute in the benzene ring of benzoic acid, approximately five million tri-substituted benzoic acids are theoretically possible.

Thus we have long felt that it is useful to consider methods by which a  $pK_a$  value might be predicted as an interim value to within several tenths of a pH unit using arguments based on linear free energy relationships, by analogy, by extrapolation, by interpolation from existing data, or in some other way. This degree of precision may be adequate for many purposes such as the recording of spectra of pure species (as anion, neutral molecule or cation), for selection of conditions favourable to solvent extraction, and for the interpretation of pH-profiles for organic reactions. Prediction is also valuable where the experimental  $pK_a$  determinations are difficult or impossible to perform, such as with weak acids and bases lacking adequate spectral differences in the acid and base forms, with substances that are unstable, or with substances that are insufficiently soluble.

The literature on  $pK_a$  prediction is scattered, but the bulk of it is comprised of two reviews dealing with organic bases (Clark and Perrin, 1964) and organic acids (Barlin and Perrin, 1966), a review of the use of  $pK_a$  values in structure elucidation (Barlin and Perrin,

1972), a paper on the prediction of the strengths of some organic bases (Perrin, 1965) and a recent lecture (Perrin, 1980). It seemed opportune to gather this material together, amplifying the methods of calculation, so as to provide a book that was a companion volume to *The Determination of Ionization Constants and Buffers for pH and Metal Ion Control* (Perrin and Dempsey, 1974). It is written with the same readers in mind, namely physical and organic chemists and biochemists.

The most useful methods of  $pK_a$  prediction are based on the assumption that within particular classes of acids and bases, substituents produce free energy changes which are linearly additive. This assumption has led to many published Hammett and Taft equations which are given in the Appendix together with extensive tables of substituent constants. A large number of worked examples using these equations, and other predictive methods occur throughout the text.

It is important to recognize situations where simple predictions may not be possible, perhaps because of steric or resonance interactions; some typical examples are discussed in Chapter 9. Many compounds, especially of biological origin, have complicated structures and may contain more than one acidic or basic centre. Such problems are considered, especially in Chapter 7. Throughout the book, practical rather than theoretical aspects of  $pK_a$  prediction are emphasized, but references to the literature are included which give further discussion of the theory on which the methods are based.

Canberra  
December, 1980

D. D. Perrin  
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E. P. Serjeant

# Contents

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<b>Preface</b>	<i>page ix</i>
<b>1 Introduction</b>	<b>1</b>
1.1 The concept of $pK_a$	1
1.2 The usefulness of $pK_a$ values	2
1.3 Compilations of $pK_a$ values	5
1.4 'Thermodynamic' and 'practical' ionization constants	5
1.5 Temperature effects	7
1.6 Solvent effects	9
1.7 Experimental determination of $pK_a$ values	9
<b>2 Molecular factors that modify <math>pK_a</math> values</b>	<b>12</b>
2.1 Inductive and electrostatic effects	12
2.2 Mesomeric effects	13
2.3 Steric effects	15
2.4 Statistical factors	16
2.5 Microscopic constants	17
2.6 Tautomerism	18
2.7 Structure and ionization	18
<b>3 Methods of <math>pK_a</math> prediction</b>	<b>21</b>
3.1 Linear free energy relationships	21
3.2 Prediction from class of compound	21
3.3 Prediction based on analogy	23
3.4 Extrapolation	24
3.5 Predictions based on theory	26
<b>4 Prediction of <math>pK_a</math> values of substituted aliphatic acids and bases</b>	<b>27</b>
4.1 $\Delta pK_a$ Values for aliphatic acids and amines	27
4.2 Examples of the use of $\Delta pK_a$ values	32

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4.3	The Taft equation	37
4.4	Examples of the use of Taft equations	40
<b>5</b>	<b>Prediction of <math>pK_a</math> values for phenols, aromatic carboxylic acids and aromatic amines</b>	<b>44</b>
5.1	The Hammett equation	44
5.2	Special $\sigma_{ortho}$ and $\sigma_{para}$ values for aromatic acids and bases	46
5.3	Examples of the use of Hammett equations	47
<b>6</b>	<b>Further applications of Hammett and Taft equations</b>	<b>53</b>
6.1	Prediction of $pK_a$ values of heteroaromatic acids and bases	53
6.2	Worked examples: heteroaromatic acids and bases	56
6.3	Prediction of $pK_a$ values of alcohols, aldehydes and other weak acids	60
6.4	Worked examples: alcohols, aldehydes and other weak acids.	61
6.5	Prediction of $pK_a$ values of weak bases	64
<b>7</b>	<b>Some more difficult cases</b>	<b>66</b>
7.1	Annelated rings as substituents	66
7.2	Polyaromatic acids and bases	70
7.3	Prediction when several acidic or basic centres are present	75
7.4	Prediction by considering fragments of molecules	78
<b>8</b>	<b>Extension of the Hammett and Taft equations</b>	<b>82</b>
8.1	An empirical extension to heterocycles	82
8.2	The prediction of $\rho$ values and generalized Hammett and Taft equations	87
8.3	Cation–pseudobase equilibria	89
8.4	Linear free energy relations for $pK_a$ values of organic phosphorus acids	91
<b>9</b>	<b>Examples where prediction presents difficulties</b>	<b>96</b>
9.1	<i>Cis</i> and <i>trans</i> isomers	96
9.2	Multiple $pK_a$ values in small molecules	96
9.3	Steric factors and strain	97
9.4	Covalent hydration	97

9.5	Protonation on carbon and bond migration	98
9.6	Keto–enol tautomerism	99
9.7	The principle of vinylogy (Fuson, 1935)	99
<b>10</b>	<b>Recapitulation of the main <math>pK_a</math> prediction methods</b>	<b>104</b>
10.1	Prediction using Hammett and Taft data	104
10.2	Constructing a Hammett or Taft equation	105
10.3	Where sigma values are not available	106
10.4	The $\Delta pK_a$ method	107
10.5	Analogy, modelling and fragmentation	108
10.6	Miscellaneous relationships	108
10.7	Polybasic acids	108
10.8	Ionic strength and temperature corrections	108
	<b>Appendix</b>	<b>109</b>
A.1	Substituent constants for the Hammett and Taft equations	109
A.2	Some Hammett and Taft equations for $pK_a$ values of organic acids at 25°	126
A.3	Some Hammett and Taft equations for $pK_a$ values of protonated bases at 25°	132
A.4	Special sigma constants for para substituents	136
A.5	Apparent $\sigma_{ortho}$ constants for use in Hammett equations	137
A.6	Sigma constants for heteroatoms in heterocyclic rings	139
	<b>References</b>	<b>140</b>
	<b>Index</b>	<b>143</b>



# Introduction

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Recent years have seen considerable effort put into quantitative explanation and prediction of the effect of substituents on physical properties such as ionization constants and on the reactivities of organic molecules. As a result it is now possible to predict to within several tenths of a pH unit many of the  $pK_a$  values which express the strengths of organic acids and bases. This book seeks to provide guidelines to enable such predictions to be made, illustrating the methods used and giving numerous worked examples.

## 1.1 The concept of $pK_a$

An acid is 'a species having a tendency to lose a proton' (Brönsted, 1923) while a base is 'a species having a tendency to add on a proton'. Hence for every acid, HA, there is a conjugate base,  $A^-$ :

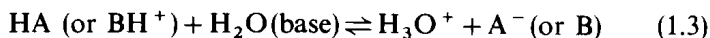


and for every base, B, there is a conjugate acid,  $BH^+$ :



Thus, acetic acid–acetate ion and ammonium ion–ammonia are examples of conjugate acid–base pairs. If HA (or  $BH^+$ ) has a great tendency to lose protons, it follows that its conjugate,  $A^-$  (or B), has only a small tendency to accept protons. In other words, if HA (or  $BH^+$ ) is a *strong* acid,  $A^-$  (or B) is a *weak* base, and vice versa.

Acids and bases so defined can only manifest their properties by reacting with bases and acids respectively. In aqueous solution, acids react with water acting as a base:



and bases react with water acting as an acid:



Quantitatively, the acid strength of HA, or  $BH^+$ , relative to the base

strength of water is given by the equilibrium constant expression for Equation (1.3):

$$K = \frac{(\text{H}_3\text{O}^+)(\text{A}^- \text{ or B})}{(\text{H}_2\text{O})(\text{HA or BH}^+)} = \frac{(\text{H}_3\text{O}^+)(\text{base species})}{(\text{H}_2\text{O})(\text{acid species})} \quad (1.5)$$

where parentheses denote activities.

As almost all measurements are made in dilute aqueous solution, the concentration of water remains essentially constant and its activity can be taken as unity. Letting  $\text{H}^+$  represent the solvated proton, we have  $K_a = (\text{H}^+)(\text{B})/(\text{A})$ , where  $K_a$  is the acidic dissociation (or ionization) constant, and B and A represent base and acid species, respectively. This equation can be written in the form

$$\text{p}K_a = \text{pH} + \log ((\text{A})/(\text{B})) \quad (1.6)$$

where  $\text{p}K_a$  is the negative logarithm of  $K_a$ , and is equal to the pH at which the activities of A and B are equal.

Equation (1.6) also expresses the strength of the conjugate acid of an organic base (commonly spoken of as 'the  $\text{p}K_a$  of the organic base', the 'basic  $\text{p}K_a$ ' or 'the  $\text{p}K$  for proton addition'). Thus  $\text{p}K_a = 9.25$  for the ammonium ion lies on the same scale as  $\text{p}K_a = 4.76$  for acetic acid and 10.00 for phenol. The greater the  $\text{p}K_a$  value, the weaker the substance as an acid, or, conversely, the stronger is its conjugate base. For any given solvent, the  $\text{p}K_a$  scale is convenient for expressing the strengths of both acids and bases. The earlier practice of defining the 'basic  $\text{p}K$ ',  $\text{p}K_b$ , from the relation

$$K_b = (\text{BH}^+)(\text{OH}^-)/(\text{B}) \quad (1.7)$$

is thus unnecessary. Note that  $\text{p}K_a$  and  $\text{p}K_b$  are related by the equation

$$\text{p}K_a + \text{p}K_b = -\log (\text{ionic product for water, } K_w) \approx 14 \quad (1.8)$$

Table 1.1 lists typical ranges of  $\text{p}K_a$  values for some of the more common types of acids and bases, while Table 1.2 gives specific examples.

## 1.2 The usefulness of $\text{p}K_a$ values

A large number of organic compounds, both natural and synthetic, contain acidic and/or basic groups which govern many of their chemical, physical and biological properties. For such compounds,

**Table 1.1** Typical ranges of  $pK_a$  values for organic acids, including conjugate acids of organic bases

Classes of compounds	Typical $pK_a$ ranges
Ethers (as bases)	-2 - -4
Pyrimidinium ions	1-2
Aliphatic dicarboxylic acids	1-4.5 (1st dissociation)
Anilinium ions	1-5†
$\alpha$ -Amino acids	2-3 (COOH)
Monocarboxylic acids	3-5‡
$RONH_3^+$	4-5
Pyridinium ions	4-6
Aliphatic dicarboxylic acids	5-7 (2nd dissociation)
Thiophenols	5-7
$\alpha$ , $\beta$ -Unsaturated aliphatic aminium ions	6-9
Imidazolium ions	7
Hydroxyheteroaromatics	7-11
Phenols	8-10§
Purines	8-10
$\alpha$ -Amino acids	9-10.5 ( $NH_3^+$ )
Saturated nitrogen heterocycles	9-11 ( $NH_3^+$ )
Aliphatic and alicyclic aminium ions	9-11
Thiols	9-11
Oximes	10-12
Guanidinium ions	11-14
Aldehydes	11-14
Azoles	13-16
Alcohols and sugars	13-16

But note: † 2-nitroanilinium ion,  $pK_a = -0.3$

‡ trifluoroacetic acid,  $pK_a = -0.26$ ; 2,4,6-trinitrobenzoic acid,  $pK_a = 0.65$

§ 2,4,6-trinitrophenol,  $pK_a = 0.22$

the proportions of the species (neutral molecule, anion, cation) that are present at a particular pH are determined by the  $pK_a$  value and can be calculated from Equation (1.6), conveniently rearranged in the form:

$$\frac{(\text{base})}{(\text{acid})} = 10^{pH - pK_a} \quad (1.9)$$

In spectrophotometry it is desirable to obtain the spectrum of a particular species free from its conjugate(s). For this requirement, it follows from Equation (1.9) that the pH of the medium should be outside the range,  $pK_a \pm 2$ . However, if the difference between pH and  $pK_a$  is less than 2, knowing the  $pK_a$  allows calculation of the necessary corrections.

In pharmacology, the  $pK_a$  controls many aspects of drug metabolism, including transport through membranes which are

**Table 1.2** Individual  $pK_a$  values of organic acids and bases in water at 20–25°

Bases	$pK_a$	Acids	$pK_a$
Pyrrole	– 3.8	Methane sulphonic acid	– 6.0
Indole	– 2.3	Aminoacetic acid	2.35
Tetrahydrofuran	– 2.1	2-Furoic acid	3.16
Urea	0.1	Formic acid	3.75
4-Pyrone	0.1	Benzoic acid	4.21
Diphenylamine	0.77	Succinic acid	4.22, 5.64
Oxazole	0.8	Acetic acid	4.76
Pyrimidine	1.23	Cyclohexanecarboxylic acid	4.90
Thiazole	2.44	Uric acid	5.83
Aniline	4.69	Thiophenol	6.52
Quinoline	4.92	<i>p</i> -Nitrophenol	7.15
Pyridine	5.23	Acetylacetone (enolic form)	8.13
Isoquinoline	5.42	Purine	8.93
Aminoacetic acid	9.78	Phenol	10.00
Triethylamine	10.78	Ethanethiol	10.54
Ethylamine	10.81	2-Pyridone	11.65
Diethylamine	11.09	Formaldehyde	13.29
Piperidine	11.28	Methanol	15.5
Acetamidine	~ 12.4	Pyrrole	~ 16.5

frequently permeable only to a particular species. In physiology, the effects of a substance of known  $pK_a$  can be considered in the light of the proportions of the various species existing under the appropriate pH conditions.

Considerations of theoretical aspects of proton addition and removal facilitate structural studies. In particular, the sites of successive proton addition and removal can be often assigned. In some cases, confirmation of structure can be made with the help of  $pK_a$  values. Likewise, the pH-profile in reaction kinetics depends closely on  $pK_a$  values.

In preparative chemistry,  $pK_a$  values can be used to select conditions for synthesis especially by considering the effects of pH on reaction products and on the properties of postulated intermediates not available for measurement. In the isolation of acids and bases from aqueous media by solvent extraction, the uncharged species is generally more soluble in the organic phase. The pH of the aqueous phase can be adjusted to its optimum value for extraction if the  $pK_a$  is known.

In analytical chemistry,  $pK_a$  values assist in the interpretation of pH titrations where multiple acidic or basic sites are present. Buffer

capacities can be calculated at known pH values and buffer concentrations, provided the  $pK_a$  of the buffer acid is known.  $pK_a$  values are also required in the estimation of micro-constants and in the calculation of tautomeric equilibria.

### 1.3 Compilations of $pK_a$ values

Extensive compilations of  $pK_a$  values are available. These include, in particular:

'Ionization constants (of heterocyclic substances)', Albert, A. (1963), in *Physical Methods in Heterocyclic Chemistry* (ed. Katritzky), Academic Press, New York, Vol. 1, p. 2.

*Dissociation Constants of Organic Acids in Aqueous Solution*, Kortum, G., Vogel, W. and Andrussov, K. (1961), Butterworths, London.

*Dissociation Constants of Organic Bases in Aqueous Solution*, Perrin, D. D. (1965), Butterworths, London.

*Dissociation Constants of Organic Bases in Aqueous Solution, Supplement 1972*, Perrin, D. D. (1972), Butterworths, London.

*Dissociation Constants of Inorganic Acids and Bases*, Perrin, D. D. (1969), Butterworths, London.

*Ionisation Constants of Organic Acids in Aqueous Solution*, Serjeant, E. P. and Dempsey, B. (1979), Pergamon, Oxford.

Among more limited collections there are:

'Heats of proton ionization and related thermodynamic quantities', Izatt, R. M. and Christensen, J. J. (1968), in *Handbook of Biochemistry* (ed. Sober, M. A.), J-49, Chemical Rubber Company, Cleveland, Ohio.

'Ionization constants of acids and bases', Jencks, W. P. and Regenstein, J. (1968), in *Handbook of Biochemistry* (ed. Sober, M. A.), J-150, Chemical Rubber Company, Cleveland, Ohio.

### 1.4 'Thermodynamic' and 'practical' ionization constants

Equation (1.6), where only activities are involved, gives the 'thermodynamic'  $pK_a$ . When concentrations of the acid and base species are used, a 'practical' or 'mixed' constant,  $pK'_a$ , is given:

$$pK'_a = (H_3O^+)[B]/[A] \quad (1.10)$$

where square brackets denote concentrations in moles  $l^{-1}$ .

A relation between  $pK_a$  and  $pK'_a$  can be derived beginning from

$$a_i = c_i f_i \quad (1.11)$$

where  $f_i$  is the activity coefficient (molar scale) of an ion of activity,  $a_i$ , and molar concentration,  $c_i$ . For an ion of charge,  $z_i$ , the activity coefficient is given for dilute solutions by the extended Debye-Hückel equation which is commonly written in the form (Davies 1938)

$$-\log f_i = Az_i^2 I^{1/2} / (1 + I^{1/2}) - 0.1 z_i^2 I \quad (1.12)$$

where the ionic strength

$$I = \frac{1}{2} \sum (c_i z_i^2) \quad (1.13)$$

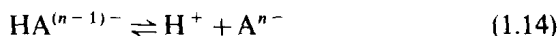
and  $A$  is a Debye-Hückel parameter, values of which are given in Table 1.3. Equation (1.12) is a good approximation at ionic strengths

**Table 1.3** *Values of the Debye-Hückel constant,  $A$ , for aqueous solutions*

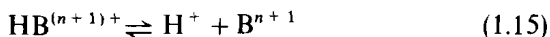
$t^\circ \text{C}$	$A$	$t^\circ \text{C}$	$A$	$t^\circ \text{C}$	$A$
0	0.4918	30	0.5161	70	0.5625
10	0.4989	40	0.5262	80	0.5767
20	0.5070	50	0.5373	90	0.5920
25	0.5115	60	0.5494	100	0.6086

below 0.1. Most of the reliable ionization constants that have been determined experimentally have been extrapolated to zero ionic strength giving 'thermodynamic' values.

Applying Equations (1.6), (1.10)–(1.13) to the systems



and



gives respectively the relations

$$pK'_a = pK_a - (2n-1)AI^{1/2}/(1+I^{1/2}) + 0.1(2n-1)I \quad (1.16)$$

and

$$pK'_a = pK_a + (2n+1)AI^{1/2}/(1+I^{1/2}) - 0.1(2n+1)I \quad (1.17)$$

$pK'$  values are useful in calculating buffer concentrations and in kinetic studies. These calculations are good approximations, at least

up to an ionic strength of 0.1, but diverge progressively at higher ionic strengths. As an example, the  $pK'_a$  of acetic acid is less than  $pK_a$  by 0.02, 0.05, 0.11 and 0.14, respectively, for ionic strengths of 0.001, 0.01, 0.1 and 0.2, while the  $pK'_a$  of ammonium ion is increased by the same amounts.

### 1.5 Temperature effects

From the definition of  $\Delta S^0 = -d(\Delta G^0)/dT$  and  $-\Delta G^0 = RT \ln K_a$ , where  $T$  is in degree Kelvin (K), it follows that for  $\Delta S^0$  in J deg<sup>-1</sup> mole<sup>-1</sup>

$$-d(pK_a)/dT = (pK_a + 0.052\Delta S^0)/T \quad (1.18)$$

If the approximation is made that the change in  $\Delta S^0$  with temperature is negligible it is possible to calculate  $pK_a$  values at temperatures other than 298 K.

For simple carboxylic acids,  $pK_a$  is around 4–5, and  $\Delta S^0$  is in the region  $-88 \pm 17$  J deg<sup>-1</sup> mole<sup>-1</sup> at 25° so the term in parentheses in Equation (1.18) is approximately zero. Examples are:

	$pK_a$	$\Delta S^0$	$-d(pK_a)/dT$
acetic acid	4.76	-73.6	0.0031
butanoic acid	4.82	-102	-0.0016
benzoic acid	4.20	-79.1	0.0003

Thus the  $pK_a$  values of common carboxylic acids vary only slightly with ambient temperature.

On the other hand, with phenols the greater  $pK_a$  values offset the effect of the entropy change ( $-100 \pm 17$  J deg<sup>-1</sup> mole<sup>-1</sup> at 25°) on  $d(pK_a)/dT$ , so the  $pK_a$  falls slightly with temperature rise. Typical examples are phenol and its 3-chloro-, 2-hydroxymethyl-, 4-nitro- and 2,5-dimethyl derivatives, for which  $d(pK_a)/dT = -0.013 \pm 0.002$ .

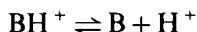
The entropy change for proton loss from heterocyclic compounds such as benzimidazole and purine is also around  $-105$  entropy units. Insertion of this value into Equation (1.18) leads to

$$-d(pK_a)/dT = (pK_a - 5.4)/T \quad (1.19)$$

Recently this equation was reported to give  $pK_a$  values extrapolated

from 25° to 85°C that agreed in general within 0.3 pK units with values obtained by isotope exchange measurements (Jones and Taylor, 1980).

The entropy change for the reaction



is less than for carboxylic acids and phenols because the number of ions and their charges do not change. For proton loss from monovalent organic cations,  $\Delta S^\circ$  lies in the range  $-17 \pm 25 \text{ J deg}^{-1} \text{ mole}^{-1}$  giving

$$-d(\text{pK}_a)/dT = \{(\text{pK}_a - 0.9)/T\} \pm 0.004 \quad (1.20)$$

so that over a wide range of pK<sub>a</sub> values the temperature coefficient varies linearly with pK<sub>a</sub>. Experimental values extend from  $-0.003$  for 2-nitroaniline (pK<sub>a</sub> =  $-0.26$ ) to  $0.035$  for pyrrolidine (pK<sub>a</sub> =  $11.31$ ). A table summarizing the observed and predicted effects of temperature on pK<sub>a</sub> values of 54 organic bases is given elsewhere (Perrin, 1964). The predicted decreases in pK<sub>a</sub> with rise in temperature for conjugate acids, BH<sup>+</sup>, are given in Table 1.4.

**Table 1.4** *Predicted effect of temperature change on pK<sub>a</sub> values of the conjugate acids, BH<sup>+</sup>*

pK <sub>a</sub>	$-d(\text{pK}_a)/dT$	pK <sub>a</sub>	$-d(\text{pK}_a)/dT$
1.0	0.000	8.0	0.024
2.0	0.004	9.0	0.027
3.0	0.007	10.0	0.031
4.0	0.010	11.0	0.034
5.0	0.014	12.0	0.037
6.0	0.017	13.0	0.041
7.0	0.020	14.0	0.044

Similarly, the relation

$$-d(\text{pK}_a)/dT = (\text{pK}_a)/T \quad (1.21)$$

gives a good approximation in the reaction



Values of  $-d(\text{pK}_a)/dT$  vary from  $0.021$  for 1,2-diaminocyclohexane (pK<sub>a</sub> =  $6.34$ ) to  $0.033$  for 1,6-diaminohexane (pK<sub>a</sub> =  $9.83$ ).

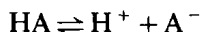
The basic pK<sub>a</sub> values (NH<sub>3</sub><sup>+</sup>) of amino acids and zwitterions have



temperature coefficients similar to those of aminium ions, ranging from  $-0.006$  for aniline-2-sulphonic acid ( $pK_a = 2.46$ ) to  $-0.025$  for proline ( $pK_a = 10.64$ ), and the same formula as for monovalent cations (Equation (1.20)) serves for their prediction.

## 1.6 Solvent effects

With acids ionizing according to



two ions are generated for each neutral molecule that dissociates. This equilibrium is very sensitive to the dielectric constant of the medium, so that the  $pK_a$  increases markedly (the acid becomes weaker) in solvents of low dielectric constant.

On the other hand, the ionization



involves no change in the number of ions, so that the effect of solvent is much less (a slight decrease in  $pK_a$  with decreasing dielectric constant). For this type of equilibrium, measurements made in mixed solvents can probably be extrapolated to give values in aqueous solution.

## 1.7 Experimental determination of $pK_a$ values

Notwithstanding the thousands of  $pK_a$  values available in the literature, this information is frequently lacking for particular acids and bases of interest. When time and materials permit, it is desirable to determine unknown constants experimentally.

The methods used for the determination of ionization constants in solution usually depend upon a quantitative assessment of the ratio of deprotonated/protonated forms for a compound under known conditions of acidity for the solvent medium. Although it is often possible to determine this ratio with high precision, the reliability of any of these methods depends ultimately upon the accuracy with which the appropriate acidity function can either be measured or assigned. The only acidity function of thermodynamic significance in aqueous solution is the quantity  $p(a_H \gamma_{Cl})$  which can be measured potentiometrically with the cell

$Pt; H_2 | H^+$  in aqueous solution,  $Cl^-$  (known molality)  $| AgCl; Ag$