PHYSICAL METHODS IN HETEROCYCLIC CHEMISTRY

A Comprehensive Treatise in Two Volumes

Edited by A. R. KATRITZKY

VOLUME 1

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Preface

Physical methods are perhaps the most important of all the influences which have contributed to the fundamental changes of the last 50 years in the theory and practice of organic chemistry. Effective chemical research can now hardly be carried out without the aid of a variety of physical measurements.

In the advance of physical techniques into organic chemistry, two main streams may be identified: physical chemists have commenced with the study of the simplest molecules and, using methods as rigorous as practicable, have proceeded stage by stage to structures of increasing complexity. Organic chemists have, by contrast, frequently made correlations of the (usually complex) structures with which they work: such correlations being, at least at first, purely empirical. Both streams are of vital importance to the overall development—they complement each other and chemists of each type need to be aware of the work in both streams.

The systematic application of physical methods to heterocyclic chemistry has been slower than that to the other two traditional divisions of organic chemistry. This is probably because the molecular complexity of the heterocyclic field has hindered the advance into it by the physical chemist. A result is that most reviews and expositions of a physical method, or of a group of physical methods, deal but cursorily with its application to compounds of the heterocyclic class. The present two volumes seek to fill this gap—each chapter gives but a brief outline of the general theoretical and experimental aspects of the subject, and then gets down to surveying the literature in which the method has been applied to heterocyclic problems. This literature is often voluminous and is nearly always scattered. It is hoped that the present collection of reviews will save individual research workers much time and effort in literature searching.

As Editor, I have been fortunate in being able to enlist an international team of authors who are among the leaders in their respective fields, and my thanks go to each of them for their cooperation. We have tried to cover the literature to the beginning of 1962.

A. R. KATRITZKY

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Ionization Constants

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I. INTRODUCTION

THE IONIZATION CONSTANTS of acids and bases are a measure of relative tendencies to lose or gain protons in solution. Hence, for example, they enable a series of acids to be arranged in order of ascending acidic strength.

In heterocyclic chemistry, this kind of information has many useful applications. For example, ionization constants can be used to investigate the position of equilibrium in tautomeric substances (see Section III, B, 4) and to help in diagnosing the structure of newly isolated substances.

By defining the pH range in which a substance is least ionized, ionization constants indicate the conditions for isolating the material in maximal yield. This indication follows from the fact that the percentage that is ionized depends on only two factors, the ionization constant and the pH. For example, if it is known that the ionization constant of acetic acid is 1.75×10^{-5}, then it can rapidly be calculated that at pH 5.55 about 86% is in the form of anion [*1*] and 14% in the form of neutral molecule [2].

$CH_3CO_2^-$ CH_3CO_2H
[*1*] [*2*]

Perhaps the most important use of ionization constants is in the determination of ultraviolet spectra. Different ionic species have different spectra, and little reliable or useful spectrophotometry can be carried out before ionization constants have been determined: thereafter, buffers can be chosen that are suitable for isolating each ionic species in a spectroscopically pure form (see Chapter 7, Section I).

A. Definition of Ionization Constant; Relationship to pK_a and to Percentage Ionized

In this chapter, the term *ionization constants* refers to those constants which are used to measure the strength of acids and bases. The term *dissociation constants* is avoided because it covers a much larger territory (e.g., the dissociation of oxygen molecules into oxygen atoms; the dissociation of substrates from enzymes) and it excludes consideration of zwitterions, which are ionized but not dissociated.

Unlike salts, most acids and bases are not completely ionized in aqueous solution. The degree of ionization depends on only two factors, (*a*) the ionization constant of the acid or base and (*b*) the chosen pH. Ionizations are equilibrium processes governed by the law of mass action. The attainment of equilibrium is practically instantaneous.

Equation (1) illustrates the kind of equilibria for which ionization constants are determined:

$$CH_3CO_2H \rightleftharpoons H^+ + CH_3CO_2^- \tag{1}$$

Thus, the ionization of acetic acid in solution gives hydrogen ions and acetate anions, and these form an equilibrium mixture. For a general introduction to the chemistry of ionization, see reference (60); for a more advanced treatise, see reference (268); for a practical manual with detailed instructions for determination of ionization constants and interpretation of the results, see reference (42).

The essential basis of ionization chemistry is the application of the law of mass action to ionic equilibria. Thus, the active mass of the *ions* derived from the ionization of acetic acid bears a fixed ratio to the active mass of the neutral *molecules*.[1] In other words, $(H^+)(CH_3CO_2^-)$ bears a fixed ratio to (CH_3CO_2H). This ratio is known as the acidic ionization constant K_a. Thus, for acetic acid,

$$K_a = \frac{(H^+)(CH_3CO_2^-)}{(CH_3CO_2H)} \tag{2}$$

This ratio has been found by experiment to be 1.75×10^{-5} moles per liter at 20° ("moles per liter" is usually omitted). In low concentrations (i.e. below 0.01 M), the activities of monovalent ions approach their concentrations. Under these conditions Eq. (2) can be used for any acid in the general form (3), where A^- is any anion.

$$K_a = \frac{[H^+][A^-]}{[HA]} \tag{3}$$

[1] Symbols (H^+) means active mass or activity of the hydrogen ion; $[H^+]$ means concentration of the hydrogen ion; pH is an abbreviation for $p(H^+)$ (143).

Taking logarithms gives the more useful Eq. (4a)

$$pK_a = pH + \log [HA] - \log [A^-] \tag{4a}$$

It will be realized that in aqueous solution the three components of the equilibrium are hydrated; thus, H^+ is used as an abbreviation for H_3O^+ (or H^+, H_2O).

In potentiometric titration, $[HA]$ and $[A^-]$ are not known and are replaced by the stoichiometric concentrations, i.e., those which would be present if the division into HA and A^- were proportional to that fraction of one equivalent of titrant that has been added. If the hydrogen ion, or hydroxyl ion concentration (whichever is larger) is included, as in Eq. (4b), full adjustment is made for this assumption.

$$pK_a = pH + \log ([AH]_{St} - [H^+] + [OH^-]) - \log ([A^-]_{St} + [H^+] - OH^-]) \tag{4b}$$

K_a is readily converted to pK_a by subtracting its logarithm from zero; for example, the K_a of acetic acid (1.75×10^{-5}) is converted to the logarithm $\bar{5}.243$, which when subtracted from 0 gives 4.757, which is the pK_a. Conversely, a pK_a value may be converted to an ionization constant by subtraction from zero and taking the antilogarithm of the figure so obtained.

In 1923, Brönsted extended the use of acidic ionization constants to include bases. There are many advantages in having the constants of both acids and bases expressed on the same scale, just as it is found convenient to use pH for alkalinity as well as acidity. Thus, for ammonia, the ionization constant is derived from Eq. (5),

$$K_a = \frac{[H^+][NH_3]}{[NH_4^+]} \tag{5}$$

This ratio has been found by experiment to be 5.5×10^{-10} at 25°. This equation can be used for other bases in the form

$$K_a = \frac{[H^+][B]}{[BH^+]} \tag{6a}$$[1]

where B is any neutral molecule capable of giving a cation BH^+. Earlier workers used a different constant, K_b, for the ionization of bases and wrote, for ammonia,

$$K_b = \frac{[OH^-][NH_4^+]}{[NH_4OH]} \tag{7}$$

[1] This equation is valid both for concentrations and activities because activity coefficients cancel out from the top and bottom lines. For potentiometric titration, the most useful form is:

$$pK_a = pH + \log ([BH^+]_{St} - [H^+] + [OH^-]) - \log ([B]_{St} + [H^+] - [OH^-]) \tag{6b}$$

from which K_b was found experimentally to be 1.8×10^{-5} at 25°. However, the use of K_b should be avoided because ionization constants are concerned primarily with hydrogen ions; thus, acids produce hydrogen ions and bases receive them. Moreover, the existence of hydrates, such as NH_4OH, has never been demonstrated and, in fact (because they would require pentacovalent nitrogen), they could not conceivably exist. Those workers who have used Eq. (7) have always substituted $[NH_3]$ for $[NH_4OH]$.

When taking the ionization constant of a base from the literature, it is important to note whether the authors have been using an equation of the type of Eq. (5) or of the type of Eq. (7).

The ionization constants of bases (K_a) are converted to pK_a values in the same way as was given above for acids. Thus, the K_a of ammonia (5.5×10^{-10}) becomes pK_a 9.26. When bases are expressed as K_b, it is

TABLE I
Calculation of the Percentage Ionized, Given pK_a and pH

pK_a - pH	If acid %	If base %
-4.0	99.990	0.010
-3.5	99.968	0.032
-3.0	99.90	0.10
-2.5	99.68	0.32
-2.0	99.01	0.99
-1.5	96.93	3.07
-1.0	90.91	9.09
-0.5	75.97	24.03
-0.3	66.61	33.39
-0.1	55.73	44.27
0	50.00	50.00
+0.1	44.27	55.73
+0.3	33.39	66.61
+0.5	24.03	75.97
+1.0	9.09	90.91
+1.5	3.07	96.93
+2.0	0.99	99.01
+2.5	0.32	99.68
+3.0	0.10	99.90
+3.5	0.032	99.968
+4.0	0.010	99.990

best to convert them first to pK_b by using the same procedure and then to subtract pK_b from the logarithm of the ionic product of water (K_w) at the temperature of determination; this operation gives pK_a. The value of pK_w at 20° is 14.17; at 25°, 14.00; at 37°, 13.62.

Table I shows what percentage of an acid (or base) is ionized at various values of pH and pK_a. These figures were calculated from Eq. (8) for acids and from Eq. (9) for bases.

$$\text{Per cent ionized (acid)} = \frac{100}{1 + \text{antilog } (pK_a - pH)} \tag{8}$$

$$\text{Per cent ionized (base)} = \frac{100}{1 + \text{antilog } (pH - pK_a)} \tag{9}$$

Table II gives the approximate pK_a values of some common acids and bases. It is evident that the higher the pK_a, the stronger the base,

TABLE II
Approximate Strengths of Some Common Acids and Bases[a]

Acids	pK_a	Bases	pK_a
Hydrochloric acid	-[b]	Sodium hydroxide	-[b]
	1		13
Oxalic acid	2	Acetamidine	12
	3	Piperidine, ethylamine	11
	4		10
Acetic acid	5	Ammonia	9
Carbonic acid	6	Many alkaloids	8
	7		7
	8		6
Boric acid	9	Pyridine, aniline	5
Phenol	10		4
	11		3
	12		2
Sucrose	13	3-Nitropyridine, pyrimidine	1

[a] Acids and bases of equivalent strength are placed opposite one another.
[b] Fully ionized, pK_a not easily measurable.

but the weaker the acid. If this table is committed to memory, a number of reference points will always be in mind for interpreting new pK_a values.

B. Methods Available for Determining Ionization Constants

Potentiometric titration is the most rapid and convenient method for determining ionization constants, and glass and calomel electrodes form the most serviceable pair. Carbonate-free potassium hydroxide is the best alkali to use as a titrant. The limits of pK_a determinable *accurately* with these electrodes are 1.25–11.0. The special glass electrodes supplied for highly alkaline regions do not appear to extend this range

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appreciably. Potentiometric titration with the hydrogen electrode is suited for pK values over 11. This electrode is a little more troublesome to use, and tests must be made to make sure that the substance is not reduced under the conditions used.

The use of *indicators* instead of electrodes to measure changes in pH during titration is a form of potentiometric titration seldom used. It can give reliable pK_a values in practiced hands, but is a tedious method.

Whereas potentiometric titration enables an ionization constant to be determined in 20 minutes, *ultraviolet spectrophotometry* usually requires a full working day. However, it is specially suitable for sparingly soluble substances and for work at very high and very low pH values which are beyond the range of the glass electrode. It cannot be used where both ionic species fail to absorb, or absorb at the same wavelengths. The use of Hammett's acidity function (H_0), usually in the form of strong solutions of sulfuric acid, has enabled the determination of pK_a values as low as —8.

Raman spectroscopy and *nuclear magnetic resonance* have proved useful for determining low pK_a values, viz., strong acids and weak bases.

The determination of ionization constants by *conductimetry* takes more time than for potentiometry, less than for spectrophotometry. It is an accurate but not very versatile method (e.g., it is unsuitable for measuring second or third constants on polyionic substances). It is most useful for very weak acids (i.e., those with a pK_a greater than 11).

Measuring the increase in *solubility* at various pH values can give approximate ionization constants in cases where neither potentiometry, spectrophotometry, nor conductimetry can be used, e.g., highly insoluble substances with no useful spectra. Determination of ionization constants by measuring the *rate of hydrolysis* of an ester, acetal, disaccharide, or glucoside has only historical interest; it has sometimes led to highly incorrect values.

Full practical details for determining ionization constants are available (42).

C. Interpretation of Ionization Constants

1. *Correlation of Structure with Properties*

The interpretation of the ionization constants of heterocyclic substances calls for some familiarity with the literature of the ionization constants of common aliphatic and aromatic substances, and their correlation with molecular structure. Convenient reviews of this subject are available (42, 99). The connections between structure and ionization

of heterocyclic substances are explained and illustrated in the present chapter, from Section II onwards.

2. Evaluation of the Reliability of Figures in the Literature

Sometimes the chemical literature provides two different pK_a values for the same ionization step of a given substance. Obviously, both values cannot be correct, and hence it becomes necessary to try to evaluate the reliability of each result. The best way to do this is to repeat the determination; but where this is not convenient, the following questions may be considered.

a. Was the determination performed in a single solvent, or in a mixture of water with an organic solvent? The majority of determinations are carried out in water, because this solvent gives the most generally useful information, with particular application to biological problems. However, a considerable body of work has been done on the titration of bases in anhydrous acetic acid, and it has been shown that the order of relative strengths of bases in this solvent roughly parallels their order in water (155). By adding 2.0 to the pK_a obtained, Hall hoped to obtain the results appropriate for water. In this way pK_a values of +0.06 and +0.4 were obtained for *o*-nitroaniline and pyrrole, respectively, but current values obtained more directly are −0.17 and −0.27, respectively.

These examples indicate the risk of extrapolating from titrations in pure solvents, but extrapolating from titrations in mixed solvents is still more dangerous. The interest in aqueous alcohol and acetone stems from the possibility of titrating, in such mixed solvents, substances that are sparingly soluble in water. It is often claimed that members of a series of chemically related substances preserve the same relative strength in a mixed solvent that they would show in water. This is not true if results of good precision are required. Thus, upon increasing the alcohol content of the solvent, the pK_a values of aniline and *N*-dimethylaniline behave differently, so that although aniline is the weaker base in 0–35% alcohol, it becomes the stronger base in 50%–100% alcohol (152). Acids also show this phenomenon. Thus, benzoic acid is four times as strong as acetic acid in water, but in 50% alcohol both acids have the same strength. Such irregularities occur most frequently when substances differ in their hydrophilic properties. The more lipophilic (hydrophobic) substance gathers to itself a higher proportion of the organic solvent than the solution on average possesses; this affects the pK_a, which is actually being determined in a solvent cage of low dielectric constant. Thus, the pK_a of pyridine in water is depressed by only 0.73 when redetermined in 50% alcohol, but that of the more hydrophobic acridine is

depressed by 1.49 (6). With increasing hydrophobic character, this effect passes through a maximum.

An attempt to defeat the bad effects of these diluted solvents has been made in recent years by titrating in a mixture of water and a slightly more hydrophilic solvent, such as a formamide or glycol derivative. Typical results are shown in Table III. Here the authors, who chose to titrate three isomeric pyrimidines in 66% aqueous formamide, undoubtedly placed the six constants in the same order which was found for them in water. But the results have no constant difference which could be related to the solvent change (the difference varies from −0.35 to +1.4 !). Perhaps the most revealing figure in this table is the basic pK_a for 4-amino-6-hydroxypyrimidine in 66% dimethylformamide, for which the authors were unable to record a finite value; yet other workers quite easily obtained a precise figure by simple titration in water.

TABLE III
Effect of Dimethylformamide
on Ionization of Three Isomeric Pyrimidines[a]

Pyrimidine	pK_a in water 20°		pK_a in 66% aqueous dimethylformamide[b] (294)	
	Basic	Acidic	Basic	Acidic
2-Amino-4-hydroxy	4.01 (193)	9.42 (193)	3.9	10.8
4-Amino-6-hydroxy	1.36 (84)	10.05 (84)	<2.5	11.3
4-Amino-2-hydroxy	4.45 (278)	12.2 (278)	4.8	>13

[a] Numbers in parentheses refer to references.
[b] Temperature not specified.

In view of the doubtful value of ionization constants obtained by titration in mixed solvents, very few will be used in this chapter. Such values will be quoted only when they shed light on a field hitherto unexplored and when the authors have attempted an extrapolation to corresponding values in water. Such values will be placed within parentheses.

Fortunately, the ready availability of ultraviolet spectrophotometers has facilitated the determination of pK_a values of the majority of sparingly soluble substances, so that titrations in mixed solvents are becoming rarer. Moreover, the advent of more delicate potentiometers, such as the "Vibron" vibrating-condenser electrometer, permits the potentiometric titration in water of many feebly soluble substances (42).

b. Was the determination performed on pure material? Purification for determining ionization constants should be at least as thorough as for elementary analysis. Because water is as misleading an impurity as

any other, the determination is best carried out on a portion of the specimen that has been submitted for analysis, and dried in the identical manner. Authors who make their determinations in sets are in a position further to check the purity of the substance during titration. It is commonly considered that 7–9 results (on one weighing of substance) make a useful set and that the spread, i.e., the extent to which the most extreme figures in the set deviate from the average, should not exceed ± 0.06 pK_a unit. Whereas in potentiometric titration and spectrophotometric determinations, the sets represent one portion of the substance measured at 7–9 stages of neutralization, in conductimetry the sets are made up of one portion measured at eight different dilutions or two portions at four dilutions.

This use of sets and spreads enables the reader to judge the precision of the work. The presence of water, carbon dioxide (in bases) and other impurities usually introduce such excessive spreads that the worker is led to reinvestigate his substance. If, at the other extreme of precision, the pK_a is derived from a single result, it can be given little credence. A statement that "The pK_a values were taken as equal to the pH at half-neutralization," reveals an approach full of pitfalls, and results obtained in this way are not included in the tables of this chapter.

c. Was the temperature sufficiently controlled? Conductivity measurements are very sensitive to small changes in temperature; also, the ionic product of water (which enters into some calculations) is temperature-sensitive. Again, many buffers and standard solutions (especially if alkaline) undergo significant changes of pH with temperature. Thus, 0.05 M borax has pH 9.398 at 0° and 8.887 at 60°; the pH of 0.01 N sodium hydroxide is 12.84 at 0° and 11.50 at 38°.

TABLE IV

Variation of the Degree of Ionization with Temperature[a] for 4-Aminopyridine[b]

Temperature °C	pK_a (in water)
0	9.873
20	9.252
25	9.114
35	8.845
50	8.477

[a] $\delta pK_a/\delta t = 0.028$.

[b] From reference (57).

The pK_a values of phenols and many other acids (but not carboxylic acids), and of all bases, change very much with temperature; such acids

become stronger, and bases weaker, as the solution becomes warmer. Table IV shows the effect of temperature on 4-aminopyridine which is used as a reference substance for the standardization of inorganic acids (57).

It is evident that for 4-aminopyridine (Table IV) the fall in pK_a per degree rise in temperature is 0.028. This may be viewed against the background of Hall and Sprinkle's investigation of the temperature coefficients of a variety of organic bases (156). They found that the coefficient increases with the strength of the base: those with pK_a 4, 5, 7, 9, and 11 had (averaged) coefficients of 0.013, 0.015, 0.017, 0.020 and 0.022, respectively. The coefficient of 4-aminopyridine is relatively high, as also is its dipole moment (about 4), and these properties may be connected. Knowledge of temperature coefficients is helpful in comparing results obtained at different temperatures.

d. Were thermodynamic corrections applied? If the solutions were no more concentrated than 0.01 M, the corrections would be small, and the author may choose to neglect them for his purposes. There are, however, circumstances in which they must not be neglected, and these will be reviewed below.

The need for thermodynamic corrections arises because ionization constants change with dilution, although there is seldom a detectable change below 0.001 M. The most accurate determinations are carried out at concentrations that produce significant readings on the chosen instrument, and these readings can be converted to thermodynamic ionization constants by the choice of an appropriate equation. An attempt will now be made to indicate which equations are appropriate in various circumstances.

(1) Thermodynamic corrections for potentiometric titrations. If the concentration is more than molar, no correction is possible. The corrections for diluter solutions involve the ionic strength, written as I (or μ) and defined thus:

$$I = 0.5\Sigma C_i z^2 \tag{10}$$

where C_i is the molar concentration of an ion, z is its valence, and the symbol Σ denotes summation. For the common case of a uni-univalent electrolyte, e.g. sodium benzoate, this expression is reduced to $I = C$.

The ionization constant yielded directly by potentiometric titration is appropriately denoted as K_a^M because it is a mixed constant, partly thermodynamic and yet partly concentration-dependent. This mixed character arises from the fact that a pH set is calibrated in terms of hydrogen ion activity [not hydrogen ion concentration (75)], whereas

the anion term in Eq. (11) is a concentration (not an activity). Thus,

$$K_a^M = \frac{(H^+)[A^-]}{[HA]} \tag{11}$$

and hence the thermodynamic constant K_a^T is calculated from

$$K_a^T = \frac{(H^+)[A^-]}{[HA]} \cdot f_{\pm}^{1:1} \tag{12}$$

where (H^+) is the hydrogen ion activity as measured; $[A^-]$ is the true concentration of anions (obtained from the stoichiometric concentration by hydrogen ion correction where necessary); and $f_{\pm}^{1:1}$ is the mean ionic activity coefficient for uni-univalent electrolytes. By substituting $f_{\pm}^{1:1}$, which it is laborious to measure directly, Eq. (12) becomes:

$$pK_a^T = pH + \log \frac{[HA]}{[A^-]} + \frac{0.505I^{1/2}}{1 + 1.6I^{1/2}} \tag{13}$$[3]

Thus, the mixed ionization constant obtained by potentiometric titration[4] may be converted to the thermodynamic ionization constant as follows:

$$pK_a^T = pK_a^M \pm \frac{0.5I^{1/2}}{1 + 1.6I^{1/2}} \qquad \begin{matrix}\text{(positive sign for acids;}\\ \text{negative sign for bases)}\end{matrix} \tag{14}$$[3]

Between $0.01\,M$ and $0.001\,M$ the following simplification of this equation may be used, although for many purposes no correction in this region may be significant:

$$pK_a^T = pK_a^M + 0.5I_m^{1/2} \qquad \text{(for acids; change + to − for bases)} \tag{15}$$

where I_m is the ionic strength at the midpoint of the titration (i.e., for a $0.01\,M$ titration, $I_m = 0.005$). In back titrations, the ionic strength is conveniently regarded as remaining steady at the concentration of salt taken (i.e., $I =$ the molarity).

Zwitterionic substances are exempt from the need for thermodynamic corrections.

It is now desirable to discuss cases where the above rules and relaxations are inapplicable. When authors add an extraneous salt "to achieve constant ionic strength," thermodynamic corrections must be based on the total electrolyte concentration, not simply on the concentration of substance being titrated. A more difficult case arises in titrating strong acids and weak bases in dilute solution. At the inevit-

[3] These equations are for 20°; for extension to other temperatures, see reference (42). Above $I = 0.1$, at least one extra term is required (268).

[4] i.e., K_a^M, which is sometimes, but quite inappropriately, called "the apparent ionisation constant."

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