The Determination of Acidity Constants

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I. Introduction

Acid-base properties and protonation-deprotonation equilibria are the most easily studied, and the most readily understood, chemical phenomena. Observations of the effects on acid-base equilibria of changing molecular structure have provided much of the theoretical foundation of modern organic chemistry. Attempts by research workers to relate their results to those of others have resulted in widespread use of the pK_a notation, particularly where it is felt there is some connection with the aqueous pH scale. In recent years a variety of new techniques have been developed, which reach out to compounds on the fringe of the popular notion of acid-base behavior. As the methods available for the determination of acidity constants have not previously been the subject of a comprehensive review, it is worthwhile examining the approaches possible over the whole acidity constant range and their contribution to a single, coherent pK_a scale.

The main aim of the present work is to bring together all the significant methods for the estimation of acidity constants. In particular, progress during the last 10 years is reviewed. As most work has been performed using aqueous pH values or acidity functions, these acidity scales are particularly emphasized. An objective of this review is to provide some indication of the utility of the pK_a concept and its limitations with present knowledge. The relationship of the conventional aqueous standard state for acidity constants to measurements using acidity functions, or determinations in mixed-aqueous and nonaqueous solvents, is discussed. The indirect methods needed to measure very high pK_a values are also considered. Various limited acidity scales result from these approaches and they require careful interpretation, particularly when they are compared with aqueous pK_a's.

In this review due emphasis is given to the two most important methods for acidity constant determination, involving potentiometry and ultraviolet spectroscopy. Rather than repeat the experimental details available in the laboratory manual of Albert and Serjeant,[1] more importance is placed on the interpretation and treatment of the data obtained by these methods. Other techniques are covered more superficially but with adequate references to ensure that the chosen method can be used correctly. Although certain standard texts[1-9] deal with particular aspects of acidity constant measurements, only the book by King[2] attempts a general treatment. Although Albert and Serjeant,[1] in their recently updated work, cover the major methods that can provide thermodynamic pK_a's in water, they neglect the extensive work that has been done to extend the acidity constant concept both into other media and far beyond the pH range. Nevertheless, this manual is essential for anyone considering the careful determination of acidity constants. The review by King[2] provides a more sophisticated insight into what is being measured.

II. Background

A. Theoretical

Although the more wide-ranging acid-base theory of Lewis has much to recommend it,[10] this review concentrates on the protonation-deprotonation equilibrium 1.

$$\text{acid} \rightleftharpoons \text{base} + \text{proton} \tag{1}$$

The utility of a wider interpretation of acidity and basicity involving hydrogen-bond formation has been discussed by Arnett.[11] Equation 1 depicts the Brønsted–Lowry concept of acids and bases, and is worthy of individual attention as it involves the simplest reversible organic reaction. Moreover the equilibrium has special significance in biological areas. The acid and base in such an equilibrium are described as a conjugate acid–base pair. As the equilibrium is almost invariably examined in a solvent (SH), all the species are solvated, a fact commonly ignored in simple treatments. The equilibrium may therefore be rewritten

$$\text{HX} + \text{SH} \rightleftharpoons \text{X} + \text{SH}_2 \tag{2}$$

where charges are neglected, to emphasize that acids and bases may be either neutral or charged.

The acidity constant K_a of the acid HX is defined as the equilibrium constant of eq 2 when studied in dilute solution. Under such conditions the acitivity of the solvent can be assumed constant and ignored. We then have

$$K_a = a_X a_{SH_2}/a_{HX} \tag{3}$$

where *a* represents the activities of the species involved. King[2] points out that equilibrium 2 is composed of two connected equilibria 4 and 5, involving ionization to form an ion pair and dissociation of this to give free ions (all species being solvated). This complication is particularly significant in solvents of low dielectric constant, where more work is required to separate ions.

$$\text{HX} + \text{SH} \overset{K_i}{\rightleftharpoons} \text{X}^-\text{SH}_2^+ \tag{4}$$

$$\text{X}^-\text{SH}_2^+ \overset{K_d}{\rightleftharpoons} \text{X}^- + \text{SH}_2^+ \tag{5}$$

The *acidity* constant K_a is related to the *ionization* constant K_i and the *dissociation* constant K_d by eq 6. This relationship, which is introduced incidentally by King, relies on a redefinition of K_a as an overall dissociation constant,[12] in which a_{HX} in eq 3 is replaced by $a_{HX} + a_{X^-SH_2^+}$. The ionization constant is largely influenced by

$$K_a = K_i K_d/(1 + K_i) \tag{6}$$

the structure of the compound under investigation, and K_d depends principally on the dielectric constant of the solvent. The two commonest types of acid are the neutral acid HA and the positively charged acid BH^+ (*i.e.*, the conjugate acid of a neutral base). The ionization of the former (eq 7) creates ions and is more sensitive to changes in dielectric constant, whereas the second type is relatively insensitive to this, as the ionization does not involve work in separating charges (eq 8).

$$\text{HA} + \text{SH} \rightleftharpoons \text{SH}_2^+ + \text{A}^- \tag{7}$$

$$\text{BH}^+ + \text{SH} \rightleftharpoons \text{SH}_2^+ + \text{B} \tag{8}$$

B. Acidity Scales

1. The pH Scale

The most useful solvent for the investigation of acidities is water, and use is made in that solvent of the pH scale,[3,4] effectively defined within ±0.02 unit as $-\log a_{H_3O^+}$ for the pH range 2–12. This allows the commonly met definition 9, sometimes called the Henderson–Hasselbalch equation. Unfortunately, the pH scale possesses certain limitations,[3,4] which mean that its usefulness is limited to the range $1 < \text{pH} < 13$. Beyond this range the pH scale is not precisely defined, and although useful comparisons may be made outside these limits, one must avoid attaching too much significance to the absolute values of pK_a's determined in very acidic or basic solutions. The theoretical and practical background to the pH scale is admirably covered by Bates[4] in a welcome new edition of his book on pH determination and requires no further comment here.

$$\text{p}K_a = -\log K_a = \text{pH} + \log a_{\text{acid}}/a_{\text{base}} = \text{pH} + \log a_{HX}/a_X \tag{9}$$

2. Acidity Functions

The pH scale has been extended at either end by the use of acidity functions,[3] which are derived from the pK_a's of compounds which ionize outside the pH range. Equation 3 can be rewritten as eq 10 in which [ ] refer to concentrations and γ is an activity coefficient. The acidity function H_x is then defined by eq 11. Comparison of this expression with eq 9 shows that the activity coefficient ratio γ_{HX}/γ_X has been neglected. For H_x to be a unique measure of acidity, h_x must be independent of the nature of the acid HX. In other words, γ_{HX}/γ_X must be constant. This requirement, known as Hammett's activity coefficient postulate, is now known not to hold generally, and a series of acidity functions (see section IV.C) have been generated, based on groups of indicators of similar structure, in which the activity coefficient ratio is constant only for the particular structural type.

$$K_a = \frac{[X]}{[HX]}\frac{\gamma_X}{\gamma_{HX}}a_{SH_2} = h_x\frac{[X]}{[HX]} \tag{10}$$

$$H_x = -\log h_x = \text{p}K_a - \log [HX]/[X] \tag{11}$$

The need for various expressions of acidity arises from the differing solvation requirements of conjugate acid–base pairs with dissimilar structures. No single acidity function can explain the protonation behavior of more than a limited range of compounds. For the protonation of a compound to be accurately described by H_x (where *x* refers to the charge type of the base), the activity coefficient behavior of the compound studied must be the same as that of the indicators used to establish the scale. Moreover, a plot of log *I* (=log [HX]/[X]) *vs.* H_x should be a straight line of slope −1.00. Many workers fail to substantiate the first condition; we shall consider the second in more detail in section II.D.

Hammett's H_0 scale (for the protonation of neutral bases) is well established in a variety of acids as the most useful single acidity function, and bases which follow H_0 are described as Hammett bases.[3,13,14] The scale, as modified by later workers, uses a series of primary nitroanilines as indicators. The confused area of non-Hammett bases is covered by Rochester,[3] whose review also updates earlier reviews on the application of acidity functions to basic media.[15] Boyd's review[14] concentrates on the validity and limitations of acidity functions and includes many tabulations of both acidity functions and indicator pK_a's which are merely referenced by Rochester. Bates[4] provides a list of acidity constants of Hammett indicators which is unfortunately out of date.

Whereas several of the minor variations in acidity functions are probably unnecessary, one of the most useful is the H_A function which is applicable to amides (including pyridones); pyridine *N*-oxides; sulfoxides; carbamates;

α,β-unsaturated aldehydes, ketones, and acids; and, most recently, phenyl-substituted ureas.[16] Unfortunately, there are problems, often ignored, in linking H_A to the standard state in water, and it has been suggested that H_A is too negative by about 0.3 unit.[17] This doubt is due to the dubious assumption that H_0 and H_A coincide up to 16% sulfuric acid.[18] Nevertheless, the correct anchoring of the H_A scale is supported by work on pyridine *N*-oxides,[19] which provide an acidity function identical with H_A as originally defined, and which is rigorously linked to the aqueous standard state.

Although pK_a determination using acidity functions has its drawbacks, it is the most commonly applied method for the study of weak bases and weak acids. The problems involved in the acidity function approach have been well reviewed.[11] Extrapolation from an acidity function to the pH scale is often of dubious worth,[20,21] and it has been claimed that thermodynamically meaningful pK_a's may only be precisely determined where pH can be used.[22] Outside this range the process is often inaccurate and arbitrary. It is important therefore to recognize the inherent limitations of a pK_a measured using one or another of the available acidity functions.[21,23] Nevertheless, the basis on which the H_0 scale was determined has now been independently validated.[24,25] So H_0 probably provides thermodynamically meaningful values for Hammett bases, even beyond the limit of 60% sulfuric acid suggested by Boyd.[14]

Even in a series of structurally related bases there are often appreciable differences in acidity function behavior. Arnett[11] discusses the importance of solvation effects on such behavior and makes the point that while strong bases may be studied in dilute aqueous solution, a relatively constant environment, weak bases must be studied in the continually changing medium of concentrated acid solutions. Although there are no solvation changes over the pH range (*i.e.*, pH 13–1), there are enormous differences in the solvation capability of 1 *M* sulfuric acid ($H_0 = -0.4$) and oleum ($H_0 \simeq -13$). The variation in hydration numbers for different cations, due to their differing hydrogen-bonding ability to water, is a principal cause of the multiplicity of acidity functions.

Work on acidity functions in alkaline solution has blossomed since the reviews by Bowden and Rochester.[15] The ionization of neutral acids to give singly charged anions is described by H_-. As in the acid region, the values of this acidity function depend on the series of indicators chosen. The range of alkalinity achievable by increasing the concentration of a strong base in purely aqueous solution is rather limited[3] (e.g., for 15 *M* potassium hydroxide, $H_- = 18.23$). Fortunately more wide-ranging acidity functions have been developed utilizing solutions containing a fixed amount of strong base and introducing a varying percentage of DMSO into the solvent. Aqueous mixtures give pK_a's firmly fixed to the aqueous pH scale and permit investigations down to $H_- = 26$. The various scales available are discussed in more detail in section IV.C.

3. Other Standard States

So far we have considered scales which are referred to the pure aqueous standard state. On occasion other standard states may be more relevant. Thus acidity constants referred to a standard state in DMSO are preferable to aqueous pK_a's when reaction kinetics and mechanisms in DMSO are under consideration. Many attempts have been made in the past to relate acidity constants determined in different solvents to an aqueous standard state, resulting in some success on an empirical basis. Thus the pK_a's determined by titration in glacial acetic acid for various weak bases parallel the aqueous values, and the two scales seem to be about 2 units apart.[4,11] The relationship is inexact, however, and possibly fortuitous as it was derived using values of H_0 at half-protonation (see section II.D), rather than the appropriate acidity function for individual compounds.

To compare acid strengths in different solvents, it is necessary to use the same standard state, and for convenience activity coefficients ${}_w\gamma_i$ relative to the pure aqueous standard state are generally chosen. For work in a different solvent the activity coefficients ${}_s\gamma_i$ referred to a standard state in that solvent are most relevant. Acidity scales in the two systems are then interrelated by the medium effect ${}_m\gamma_i = {}_w\gamma_i/{}_s\gamma_i$. Medium effects and their estimation have been thoroughly discussed by King[2] and by Bates.[4,26] If the medium effect for hydrogen ions, ${}_m\gamma_H$, was accessible, it would provide the basis for a universal scale of hydrogen ion activity, independent of solvent. Attempts to define this quantity have so far been unsuccessful. Therefore, we are obliged to accept, for the time being, the use of different acidity scales based on standard states in various solvents. Such a procedure involves smaller errors than those encountered in attempts at empirical linking with the aqueous standard state. Consequently, Bates and his coworkers[4,27] have, for example, defined an operational acidity scale in 50% methanol using standards in that solvent. Rochester[3] recommends maintaining a similar approach for acidity functions rather than using the present artificial bridge system.

C. Activity Corrections

The acidity constant as defined by eq 3 or 9 is thermodynamically significant, as it is related to the free energy of the ionization reaction, $\Delta G° = -RT \ln K_a$. Unfortunately, K_a cannot be measured directly, as most physical methods provide information on concentration rather than activity ratios. As the activity of the neutral species in eq 7 or 8 is approximately equal to its concentration, eq 12 and 13 may be used to calculate thermodynamic pK_a's

$$\mathrm{p}K_a = \mathrm{pH} - \log [\mathrm{A}^-]/[\mathrm{HA}] - \log \gamma_{\mathrm{A}^-} = \mathrm{p}K_a' - \log \gamma_{\mathrm{A}^-} \quad (12)$$

$$\mathrm{p}K_a = \mathrm{pH} - \log [\mathrm{B}]/[\mathrm{BH}^+] + \log \gamma_{\mathrm{BH}^+} = \mathrm{p}K_a' + \log \gamma_{\mathrm{BH}^+} \quad (13)$$

from the apparent acidity constants pK_a' measured using concentration ratios. Albert and Serjeant[1] summarize the situation and recommend when activity corrections should be applied. Frequently they can be neglected, particularly when other errors are more significant. If such corrections are ignored, then the error involved for a 0.01 *M* solution of a 1:1 electrolyte would be of the order of 0.05 p*K* unit.

Although an extended discussion of activity coefficients would be out of place, it is worth recording that the Debye–Hückel limiting law, eq 14, which assumes

$$-\log \gamma_i = A(z_i)^2\sqrt{\mu} \quad (14)$$

ions (of valency z_i) are point charges, can be used up to ionic strength $\mu = 0.01$. In this and related expressions the thermodynamically undefined activity coefficients of single ions are replaced by the mean activity coefficient γ_i. Above an ionic strength of 0.01, eq 15 should be used. This provides accurate results for univalent ions up to $\mu = 0.1$, which is the limiting ionic strength for accu-

$$-\log \gamma_i = \frac{A(z_i)^2\sqrt{\mu}}{1 + a_i B\sqrt{\mu}} \qquad (15)$$

rate work. Benet and Goyan[28] discuss the problem more thoroughly and indicate how the various constants A, B, and a_i may be chosen. King[2] deals with the simplified eq 16 proposed by Davies, which is much used in the most accurate work.[29,30]

$$-\log \gamma_i = \frac{A(z_i)^2\sqrt{\mu}}{1 + \sqrt{\mu}} - B(z_i)^2\mu \qquad (16)$$

Although activity corrections are straightforward when pH is used as an expression of acidity, the situation is more complex when acidity functions are used. If either the acid or base is neutral, then its activity coefficient may be ignored. Combination of eq 10 and 11 results in the expressions 17 and 18. Substitution of these equations into eq 19, which is the logarithmic form of the

$$H_0 = -\log h_0 = -\log[a_{H^+}(\gamma_B/\gamma_{BH^+})] = -\log a_{H^+} + \log \gamma_i \qquad (17)$$

$$H_- = -\log h_- = -\log[a_{H^+}(\gamma_{A^-}/\gamma_{HA})] = -\log a_{H^+} - \log \gamma_i \qquad (18)$$

$$\mathrm{p}K_a = -\log a_{H^+} + \log[HX]/[X] + \log \gamma_{HX}/\gamma_X \qquad (19)$$

acidity constant definition, results in expressions 20 and 21, which should be used for the determination of

$$\mathrm{p}K_a = H_0 + \log[BH^+]/[B] \qquad (20)$$

$$\mathrm{p}K_a = H_- + \log[HA]/[A^-] \qquad (21)$$

thermodynamic pK_a's with these particular acidity functions. As can be seen, the fortuitous cancellation of activity coefficients provides simple expressions for acidity functions, when they are used with acids of the corresponding charge type. There is no such cancellation if they are used with acids of inappropriate charge.

The situation is complicated when the accurately known acidity function p($a_H\gamma_{Cl}$) is used over the pH range.[29,31] This function, which may be used for neutral or charged acids, is defined by eq 22. Substitution of this

$$\mathrm{p}(a_H\gamma_{Cl}) = -\log a_{H^+} - \log \gamma_{Cl^-} \qquad (22)$$

expression into eq 19 produces different equations depending on the charge type of the acid. With this acidity function, cancellation simplifies the expressions for neutral acids but not those carrying a positive charge. Equations 23 and 24 are the relevant expressions for the determination of thermodynamic pK_a's under these conditions.

$$\mathrm{p}K_a = \mathrm{p}(a_H\gamma_{Cl}) + \log[HA]/[A^-] \qquad (23)$$

$$\mathrm{p}K_a = \mathrm{p}(a_H\gamma_{Cl}) + \log[BH^+]/[B] + 2\log \gamma_i \qquad (24)$$

To avoid errors in the activity corrections and reduce the effect of the liquid junction potential,[2,4] determinations may be performed at constant ionic strength using a swamping electrolyte such as potassium chloride or sodium chlorate. Measurements are performed at several ionic strengths, and the calculated pK_a's, corrected using eq 16, are extrapolated to zero ionic strength, to give an intercept equal to the thermodynamic pK_a. This method can result in very precise values being obtained in excellent agreement with other methods.[2,30]

D. pH and H_0 at Half-Neutralization

Many workers using expression 25 for the apparent acidity constant seem prepared to accept the pH at half-

$$\mathrm{p}K_a' = \mathrm{pH} - \log[A^-]/[AH] \qquad (25)$$

neutralization as a reasonable estimate of the pK_a. Then $[A^-] = [AH]$ and $\log[A^-]/[AH] = 0$. The errors likely to arise from this approach have been reviewed.[28] The increasing use of automatic titrators which conveniently provide a titration curve, complete with an inflection at the half-neutralization point, has encouraged this unfortunate tendency. Apart from the activity considerations neglected in eq 25, the approximation is only good when $K_a = \sqrt{K_w}$. The autoprotolysis constant or ionic product of water (pK_w) is conveniently 14.00 at 25°. This means that for pK_a's outside the range 7 ± 2.5 the approximation is rather poor, as corrections must be included for reaction with the solvent (hydrolysis). In most cases, therefore, it is better to use the titration data more effectively and ignore values of pK_a expressed as pH at half-neutralization.[1] The situation is even more complex in nonaqueous solvents where the approximation may no longer work at all.[32]

Although work in the pH region may well provide thermodynamically meaningful results, outside the pH range the situation is much more complex. If a thermodynamic acidity constant is to be obtained, the acidity function used must be applicable to the compound under study (see section IV.C). Thus the H_0 value at half-neutralization ($H_0^{1/2}$) is an adequate expression of the thermodynamic pK_a of a compound behaving as a Hammett base. Unfortunately the majority of compounds do not follow H_0 so that the apparent pK_a on that scale has no thermodynamic significance. It merely provides an indication of the strength of acid required for half-protonation. Such results are best referred to as values of H_0 at half-neutralization, rather than as acidity constants, apparent or otherwise. Nevertheless, these numbers do have some value as measures of basicity-solvation effects.[3,20,33] Many of the earlier results in the literature have been recalculated, as better and more relevant acidity functions are introduced. It has been sensibly recommended[3,16] that spectroscopic pK_a determinations using acidity functions should list the acid concentrations at half-protonation, to enable recalculation in the light of future discoveries.

Although $H_0^{1/2}$ may have no thermodynamic meaning, it does rank bases in an order applicable under conditions of appreciable protonation, and this is often the order of greatest practical significance.[20] This is seen in the useful correlations that are found between $H_0^{1/2}$ and other reactivity parameters.[20,22] Nevertheless, the values do suffer from not being on the pH scale. They are not directly referrable to dilute aqueous solution and the standard state free energy of ionization.

A recent paper[34] has underlined the problems associated with an imperfect knowledge of the relevant acidity function and the consequent necessity to deal in values of $H_0^{1/2}$. *N*-Acylthioureas have been shown to protonate initially on sulfur in 35–60% sulfuric acid and then on the amide oxygen in 65–96% acid. If this behavior was interpreted in terms of H_0, or any single acidity function, then it would seem that the sulfur atom was much more basic than the amide oxygen. However, as the initial protonation followed H_0''' and the second protonation followed H_A, the thermodynamic pK_a's of the two groups are almost identical. This arises because H_A increases with acid concentration much more slowly than H_0'''. The re-

TABLE I. Protonation of Benzoylthiourea

	Monocation	Dication
% H_2SO_4 for half-protonation	50.0	80.7
$H_0^{1/2}$	−3.38	−7.34
pK_a	−4.55 (H_0''')	−4.68 (H_A)

sults reported for benzoylthiourea are given in Table I, together with the corresponding values for $H_0^{1/2}$. It can be seen that, presumably because of differences in activity coefficient behavior, the oxygen and sulfur atoms have about equal basicities in spite of requiring different concentrations of sulfuric acid for protonation.

Plots of log I vs. $-H_0$ are often linear but with slopes considerably different from the 1.00 required for Hammett bases.[35] The slopes should be routinely listed,[11] as the divergence of a base from H_0 is a valuable piece of information. Groups of related compounds following the same acidity function (not H_0) will have similar values (m) for this slope. In fact when all the available acidity functions were plotted against H_0, each was found to give a straight line over a wide range,[36] *i.e.*, $H_x = mH_0 +$ constant. It now seems that this linearity may be fortuitous and apply only to solutions in sulfuric acid.[37]

Nevertheless, this linearity can be used to obtain better estimates of the pK_a by using eq 26 in calculations.[38,39]

$$pK_a = mH_0^{1/2} \tag{26}$$

$$\log I = m(H_0^{1/2} - H_0) \tag{27}$$

$$H_0 = pK_a - n \log I \tag{28}$$

The slope m is defined from the relationship 27, now usually employed rather than the earlier[19,40] equivalent formulation 28 using $n = 1/m$. A method using a weighted least-squares analysis for the calculation of n, assuming H_0 to be known exactly, has been described.[20] The authors suggest that for a series of related compounds with varying m values, the best estimate of thermodynamic pK_a's is obtained by calculating the average value of m and combining this with "smoothed" individual values for $H_0^{1/2}$, obtained from a correlation of measured $H_0^{1/2}$ values and σ constants.

These approaches are subject to quite large errors because it is rarely possible to determine m with a high degree of accuracy. In spectroscopic work a range of log I of ±1 is usually all that can be relied upon; outside this range, experimental errors rapidly increase.[41] Arnett and Anderson[42] point out that published slopes are seldom accurate to better than 0.1-0.2 unit, and as such slopes become better elucidated, many "thermodynamic" acidity constants may be drastically altered. Consequently, they suggest that it may be better to take $H_0^{1/2}$ as a real measure of basicity within a related series rather than attempt corrections for solvation using slopes not known with accuracy.

Even if the appropriate acidity function H_x for a group of compounds is known with some confidence, it is still worthwhile quoting the slopes of plots of log I vs. $-H_x$ along with the values of $H_x^{1/2}$. If the slopes are in the range 1.00 ± 0.05, the experimental $H_x^{1/2}$ value can be taken as a reasonable estimate of the thermodynamic acidity constant, provided the activity coefficient postulate (see section II.B) is satisfied. For this slope range there is no point in correcting the $H_x^{1/2}$ value by the equation corresponding to eq 26. The same remarks apply to slopes in the range 1.00 ± 0.10 but outside the range 0.95-1.05. These results can only be regarded as approximate and lose much of their thermodynamic significance. Outside this range, use of eq 26 or its equivalent is necessary to obtain even a crude estimate of the thermodynamic pK_a. In spite of assertions to the contrary,[43] values of slopes outside the range 0.9-1.1 must indicate the use of an inappropriate acidity function or else unacceptable experimental error. Either way the values obtained can have little thermodynamic meaning.

E. Methods Available

Various methods available for pK_a determination have been summarized during the last 10 years,[1,2,11,44,45] and King[2] provides a discussion of the relative merits of some of the methods and the degree of precision attainable with them. Albert and Serjeant's most excellent laboratory manual,[1] which has been revised, extended, and brought up to date gives detailed information on the two most useful methods. These are potentiometric titration and spectrophotometric determination, both of which can be applied with varying degrees of sophistication.

In general terms any physical property which varies with protonation may provide a suitable method for measurement of acidity constants. Many methods can provide only an indication of relative strengths rather than acidity constants.[46] Some of these are so insensitive that they are of little use. The most precise methods rely on pK_a's from conductance, optical, or precise emf measurements. These are capable of a precision of ±0.001 pK_a unit in careful hands. Methods involving nmr, pH measurements, etc., are generally less sensitive. As might be expected, over 90% of the pK_a's reported in the literature lie between 2 and 12, experimentally the most convenient range. However, as Arnett[23] points out, this pH range protonates only 5% of the groups that are common in organic chemistry, most of which are completely protonated in concentrated sulfuric acid.

The problems with acidity functions have already been mentioned, but they do provide a reasonable approach for many compounds. Arnett's basicity scale, using heats of ionization in fluorosulfuric acid,[23,47] is an exciting development which should provide good estimates of pK_a's in strong acids. The use of strongly basic solutions for weak acids has been briefly reviewed on several occasions.[45,48-51] A variety of methods have evolved, involving not only titrations[52] or spectral measurements[49,53,54] in nonaqueous systems but also the development of new concepts.

Studies on the stability of carbanions have resulted in an expansion of the notion of kinetic acidities.[5,48,50,51] Whereas thermodynamic acidities refer to the position of equilibrium between acids and their conjugate bases, kinetic acidities describe the rate at which acids donate protons to a reference base. The two approaches are related by the Brønsted equation, eq 29, and this empirical

$$\log k_1 = \alpha \log K_a + \text{constant} \tag{29}$$

correlation roughly holds over a wide pK_a range. This means that isotope exchange rates can be used to study "pK_a's" in the region 35-48. Other even more indirect methods have produced values greater than 50 on the "pK_a" scale.[50,55]

It is fundamental to the consideration of acidity constants that relative acidities are more easily and more accurately determined than absolute values. Therefore, it has become a common practice, particularly beyond the basic end of the pH scale, to determine acidity constants relative to a standard with an assumed pK_a value. Some of the problems consequent on this approach are discussed in section IV.D. Most such relationships outside the pH range can be considered to be accurate only over short ranges and for closely related compounds. Much more work is required before absolute values at either end of the pK_a scale can be quoted with confidence. In particular, new methods involving independent checks on pK_a values are needed. Several new methods applicable to very weak acids have been devised with considerable ingenuity. To suggest[45] that these methods are less rigorous than the classical approaches is to understate the case. The confusion in this area has resulted in big assumptions and bigger errors making a nonsense of quoting absolute values for such acidities. The pK_a label has been transmuted almost beyond recognition. Nevertheless, relative values do have some significance, although interpretation of them on an acidity scale seems to beg the question. The accurate construction of a pK_a scale would be quite remarkable if it could accommodate both protonated 2,4-dinitrofluorobenzene[56] ($pK_a = -14.5$) and triphenylcyclopropene[55] ($pK_a = 51$), a range of acidity constants greater than 10^{65}!

F. Effect of Temperature

Determination of acidity constants is usually performed at 25°, although in certain circumstances (e.g., using liquid ammonia as solvent[57,58]) other temperatures are used. The variation of pK_a with temperature is useful in obtaining thermodynamic information (see later), and cells are available[59] for pK_a determination up to 200°. King[2] discusses the variation of pK_a with temperature and considers the Harned–Robinson equation

$$pK_a = A/T - B + CT \qquad (30)$$

to be the best simple expression to use, as it fits most of the available data and is convenient to manipulate.[60,61] More recently,[38] an equation has been derived for anilinium ions which is based on thermodynamic reasoning[25] and seems capable of extrapolation over more than 100°. Unfortunately the equation as derived suffers from a confusion in the definition of T. Equation 31 presents the relationship in less ambiguous notation; all temperatures are on the absolute scale.

$$pK_T = pK_{298.15} - \frac{(T - 298.15)}{1.36T}(1.14\,pK_{298.15} + 2.28) \qquad (31)$$

Albert and Serjeant[1] review Perrin's work[62] on the temperature coefficients of organic bases. They recommend the simple eq 32 for nitrogenous bases in the range T = 288–308°K; outside this range the more complex expression 33 should be used. For the second ionization of dications eq 34 is sufficient. These equations

$$\frac{-d}{dT}(pK_a) = \frac{pK_a - 0.9}{T} \qquad (32)$$

$$\frac{-d}{dT}(pK_a) = \frac{pK_a + 0.218\Delta S°}{T} \qquad (33)$$

$$\frac{-d}{dT}(pK_a) = pK_a/T \qquad (34)$$

are quite reliable, but they are not applicable to the ionization of neutral acids, which increase the number of ions in solution on dissociation. Nevertheless, the equations are useful for comparing pK_a's in structurally related series, when some of the values from the literature refer to determinations at different temperatures.[63] Compounds vary somewhat in the sensitivity of their acidity constants to temperature changes. It is desirable, therefore, to provide a record of the temperature at which any particular determination is performed and also to keep the temperature constant during the experiment. For more accurate work direct measurement of the temperature of the solution is advised.[60]

III. Potentiometric Titration

A. Practical Considerations

King[2] provides a detailed treatment of titrations, and the many practical aspects of potentiometry are covered in a wide-ranging review.[64] A most useful book by Bates,[4] now available in a second edition, covers both practical and theoretical aspects of pH determination, and the text by Rossotti and Rossotti[7] on stability constants includes a discussion of cells and their use in the determination of acidities. Most titration situations are dealt with by Albert and Serjeant.[1] They describe what must now be regarded as the standard technique for pK_a determinations. Various improvements in their methods for handling data are described in sections III.C and IV.E. Both graphical and arithmetical techniques are available, and, for the well endowed, computerized iterative treatments are at hand.

Benet and Goyan[28] have reviewed the treatment of data from titrations, and a combination of Albert and Serjeant's technique with their approach should provide the experimenter with pK_a's to a precision of ±0.03, which is more than adequate for most purposes. The IUPAC compilations[65,66] list three classes of pK_a's depending on their precision. Values are regarded as reliable if their precision is ±0.005 or better, uncertain if $>\pm 0.04$, and approximate if their precision is between these limits. By far the majority of the values listed are in the uncertain category!

As mentioned in section II.E, titration experiments involving accurate emf measurements are capable of great precision.[2] Such determinations have been performed in cells without liquid junctions, using hydrogen and silver|silver chloride electrodes. Provided the temperature is controlled to within ±0.02°, a precision of ±0.001 pK_a unit is achievable, but only in the pK_a range 3–11. For these precise experiments in cells without liquid junctions, the use of pH is abandoned in favor of $p(a_H\gamma_{Cl})$, which is more accurately defined.[4,31] This quantity is a thermodynamically meaningful acidity function varying from 1.6 to 12.5, and its relationship to pH is adequately covered by King[2] and by Bates.[4] Routine determinations do not require this precision, and so the more convenient cells with liquid junctions are normally used, at a price of an uncertainty in the final value of about 0.03 pH unit. The commonest titration setup makes use of a pH meter with a glass and a calomel electrode, which are suitable for titrations in the pH range 2–11.

It is a well-established fact that the glass and calomel electrode arrangement can be used for reproducible titrations in mixed-aqueous and nonaqueous solvents. However, too little thought often goes into the significance of the pH-meter readings. As Bates has pointed out repeatedly, such pH values are almost totally devoid of quantitative significance.[4,26,67] The problems of cells with liquid junction have become all too serious when such systems are considered. All experimental efforts to prepare acidity scales suitable for different solvents have been thwarted by the indeterminate liquid junction potential.[4] Fortunately the determination of relative acidities seems reasonable, but reference to the standard state of pure water is not yet possible. The problem of the interpretation of the pH-meter reading is discussed further when we deal with mixed-aqueous solvents (section III.B).

In water, glass electrodes are limited to the determination of pK_a's in the region 1.25 to 11, although certain commercial electrodes are now available for higher pH's.[4] Outside this range hydrogen electrodes may be used. The special glass electrodes which are available for pH's >12 have a short lifetime and must not be exposed to acid. Compounds must be soluble enough to provide solutions of about 0.01 *M*. Albert and Serjeant[1] point out that glass electrodes are only accurate over a concentration range of 0.005–0.05 *M*. Crucial to the accuracy of a titration is the time lag between addition of titrant and equilibration of the electrodes. Addition of potassium chloride to the solution increases the speed at which equilibrium is attained for very dilute solutions and improves precision possibly by stabilizing the liquid junction potential.[4] Use of potassium chloride as a swamping electrolyte necessitates activity corrections but can provide good estimates of thermodynamic pK_a's. Slow equilibration is more noticeable in mixed-aqueous solvents, as the response frequently becomes more sluggish as the proportion of water in the solvent declines.

As Albert and Serjeant[1] deal thoroughly with the apparatus required for titrations on the macro, semimicro, and micro scales, it would be superfluous to discuss the details here. Results from automatic titrations can be more than adequate for routine determinations. Provided the titration is performed sufficiently slowly to allow time for equilibration, the results for known compounds agree well with literature values and are as precise as results from manual titrations. The convenience of the method and the provision of a permanent record are strong arguments in favor of adoption of automatic techniques, particularly in industrial laboratories handling large numbers of samples. In spite of Albert and Serjeant's assertion to the contrary, with care the results obtained are accurate enough for publication. The review by King[44] gives several references to the use of automatic apparatus, and Bates[4] discusses automatic titrators along with other apparatus for pH determination. Much of Simon's work in 80% methyl Cellosolve has been performed using an automatic titrator on samples of the order of 0.1 mg, dissolved in 1 ml of solvent.[68]

B. Mixed-Aqueous Solvents

1. Advantages and Disadvantages of Mixed Solvents

Water, with its particular relevance to biological systems, is the best solvent for the determination of acidity constants. It is unrealistic, however, of Albert[1,69] to condemn the results obtained in mixed-aqueous solvents as being of doubtful value. The solubility requirements for aqueous titrations are often too demanding, and many compounds are not suitable for spectrophotometric analysis. Fortunately glass electrodes show nearly the theoretical response in solvents containing up to 90% alcohol.[4] This renders possible the easy measurement of relative hydrogen ion activity in aqueous-alcoholic systems, particularly as the usual calomel electrode still provides a useful reference. These facts account for the popularity of mixed-aqueous systems, and Albert agrees that they have a use in comparing closely related compounds, provided results of high precision are not required. Many such systems are now in use or could be used. However, even if it is established that the titration setup responds satisfactorily in such a system, there is no guarantee that the "pH" values obtained have any quantitative significance.

Albert and Serjeant[1] mention several examples of anomalies arising from the use of mixed solvents, and they attribute these to variations in the lipid solubilities of different conjugate acid-base pairs. Benet and Goyan[28] consider that recent theory can explain much of the trouble, but conclude that at the moment there is no completely satisfactory method for converting results to the aqueous pK_a scale. Simon[68] prefers to abandon such attempts in favor of amassing a large amount of data in 80% methyl Cellosolve.[70] As this seems rather like an admission of defeat, this section considers in some detail the applicability of the aqueous standard state to pK_a's determined in mixed-aqueous solvents. It will be seen that in many cases quite reasonable estimates of aqueous acidity constants are available. Frequently the magnitude of the errors involved is less than that found with other methods.

There are two major complicating factors in the use of mixed-aqueous solvents. First of all, the different solvating power of the two components creates new complexities, and secondly the organic component contributes extra acidic and basic species to the solution. A more sophisticated, alternative interpretation of the problem has been proposed by Franks and Ives.[71] They consider the structure of alcohol–water solvents to be more relevant than the relative basicities of the components. The complex behavior of mixed-aqueous solutions has been the subject of two recent symposia,[72,73] both of which serve to emphasize the importance of solvent–structural considerations in hydrogen-bonded solvent mixtures.

2. Interpretation of Acidity

Although reproducible "pH" readings may be obtained in many mixed solvents, the pH meters are usually calibrated in aqueous buffers. Unfortunately, the asymmetry potential may shift on transfer of the glass electrode from such a buffer to a mixed solvent.[4] This means that absolute definitions of acidity in such systems may not be possible. Bates[4,26,67] regards "pH" values obtained under such conditions as totally devoid of quantitative significance. It is possible, however, to determine the stoichiometric significance of pH-meter readings by titration of hydrochloric acid with potassium hydroxide in the mixed solvent and comparison of the readings (B) with the calculated "pH." The difference between these values, log U_H, can be calculated from eq 35 and used

$$-\log [H^+] = B + \log U_H \qquad (35)$$

as a correction factor before attempts are made to compare results in solvents of varying compositions.[74] Values of log U_H, or the corresponding quantity after activity corrections, are available for mixtures of water and dioxane[74,75] and water and ethanol.[76,77] These corrections are by no means insignificant (0.2 to 0.4 pH unit in 35–65% aqueous alcohol); neither do they vary linearly with solvent composition. Consequently, they can have a marked effect on plots of apparent pK_a vs. composition of solvent. Unfortunately adoption of these, more "significant," pH values does not always improve attempted correlations with single physical properties of solvent mixtures.[75,76]

An alternative approach, employed by Bates and his coworkers,[4,78] involves determination of the difference between the apparent pK_a in a mixed solvent (pK_a') and the pK_a referred to the standard state in that solvent (p$_sK_a$). Titrations of both acetic acid and aniline in varying percentages of aqueous methanol gave a correction factor, which can be used to correct the pK_a' values from titration for other compounds, to give corresponding values for p$_sK_a$. Similarly "pH" readings can be corrected to give activities of hydrogen ions, relative to the standard state in that solvent. Thus it is possible to construct operational pH scales in mixed-aqueous solvents which have a definite significance in the study of chemical equilibria in the particular solvent used. Bates[4,26,67,79] has reviewed the problems involved in interpreting acid-base equilibria in terms of the acidity of the solution, both in mixed-aqueous solvents and more generally. As well as the empirical corrections mentioned above, Bates and his group have provided a useful practical pH scale in 50% methanol, which uses reference buffers in that solvent rather than the aqueous buffers used in the other approaches.[4,27]

3. Extrapolation Methods

Various graphical methods have been suggested as a means of extrapolating results obtained in mixed solvents to the value for pure water. Traditionally the logical approach of extrapolating values of pK_a' to aqueous values has been adopted. There is no theoretical basis which can be used to predict changes in pK_a' with solvent composition. Extrapolations are more suitably performed using p_sK_a values, when these are available, as the results are directly interpretable in terms of medium effects or free energies of transfer. The necessary theoretical background for this approach is established for methanol and ethanol,[4,79] and work is urgently needed for more "universal" solvent systems such as methyl Cellosolve-water.

Plots of pK_a' vs. per cent composition are rarely linear and are usually inadequate as a means of extrapolation. Extrapolated values may be highly suspect, unless results in 10 or 20% solvent are available.[1] As the dielectric constant of the medium plays an important part in the ionization equilibrium, it is not surprising that attempts have been made to correlate pK_a''s in mixed solvents of varying compositions with the dielectric constants of the appropriate mixtures.

The central importance of the dielectric constant (ϵ) of the solvent in the ionization equilibrium is expressed in the Born equation. This predicts that for neutral acids the change in pK_a from solvent to solvent should be proportional to the difference in $1/\epsilon$. The prediction is fairly well obeyed for pure solvents.[2,8,80] However, this simple electrostatic treatment has severe limitations, particularly when applied to mixed-aqueous solvents.[2,79] Over small ranges of ϵ the relationship is reasonably linear and can be used for short extrapolations to pure water. Accurate conductometric experiments in aqueous acetone[81] have produced linear plots of pK_a' vs. $1/\epsilon$ over modest ranges of ϵ (78.6 to 64.0). Even in this range, however, certain compounds deviated markedly from linearity. This is in line with other, more recent results[75,76] which showed marked deviations but over much greater dielectric constant ranges (78.5 to 32.8 in aqueous alcohol and 78.5 to *ca.* 9 in dioxane). Marked deviations at low values of ϵ are not unexpected as the equilibrium then involves ion pairs rather than solvated ions. Ionic association may be disregarded for solvent mixtures with dielectric constants greater than *ca.* 50 and is appreciable in solvents with dielectric constants less than 20. This means that for solvent mixtures in the intermediate range (*i.e.*, >80% ethylene glycol, >70% methanol, >50% ethanol, or 34-67% dioxane) the equilibrium measured becomes increasingly complicated by ion-pair effects.

Replacement of the traditional definition of acidity constant by one including the activity of the solvent results in some improvement in the linearity of plots of acidity constants vs. $1/\epsilon$. Thus plots of $p_sK_a + \log [H_2O]$ vs. $1/\epsilon$ are linear for $\epsilon > 50$ and can be extrapolated to provide reasonable aqueous pK_a's with an error of ±0.06 pH unit.[28] Bates[79] adopts a similar approach using the free energy of transfer $\Delta G_t°$ of the solute from water to the mixed solvent. He shows that plots of $\Delta G_t° + RT \ln a_w$ vs. $1/\epsilon$ are approximately linear for aqueous mixtures of dioxane or various alcohols. King also discusses this method of handling medium effects.[2]

Knowledge of $\Delta G_t°$ for the hydrogen ion would provide the basis for a universal scale of pH in various solvents. However, it is not directly determinable and various indirect approaches do not even agree on the sign of this quantity.[4,79] Wynne-Jones[80] suggested that many of the abnormalities in acid-base behavior in mixed solvents may be due to the peculiar behavior of the proton. To circumvent this he recommended comparing pairs of acids HX and HX′ and plotting $p_sK_r = p_sK_a(HX) - p_sK_a(HX')$ against $1/\epsilon$. Such lines are approximately linear.[8,79] Wynne-Jones also suggested that extrapolation of p_sK_r to $1/\epsilon = 0$ would give an "intrinsic" measure of acid strength relative to the chosen standard. At $\epsilon = \infty$, external electrostatic effects can be neglected. Unfortunately the solvent dielectric constant by itself does not determine acid-base behavior, and the important influence of solvation cannot be ignored. This fact, together with the length of extrapolation necessary, ensures that such "intrinsic" acidity constants are no more valuable than the usual aqueous pK_a reference scale.

4. Other Approaches

Other empirical approaches to the handling of pK_a's in mixed solvents have been developed by Glover[82] and by Grunwald and his school.[83] Glover's approach emphasizes the importance of solvation in equilibria in mixed solvents. He was able to explain the variations in apparent pK_a in aqueous dioxane by complex formation between dioxane and water and its effect on the solvation of the species in the ionization equilibrium. Although Glover's main work was in aqueous dioxane, he was able to show that his approach can be extended to other solvents, provided reasonable structures for the solvents are assumed. Glover effectively rewrote the ionization equation as eq 36, in which $n = x + y$ is the number of solvent molecules bringing about the ionization. This expression is related to conventional definitions of K_a by eq 37 in which it is understood that H^+ and A^- are solvated. In eq 37 and 38, the activity coefficient, rather than the activity of the solvent, is taken as one. By comparing results at different solvent compositions (*i.e.*, varying a_{SH}), values of n and pK'' can be obtained. It should be noted that n does not represent the complete solvation state as the solvation of HA is ignored.

$$HA + nSH \overset{K''}{\rightleftharpoons} H^+(SH)_x + A^-(SH)_y \qquad (36)$$

$$K_a = a_{H^+}a_{A^-}/a_{HA} = K''(a_{SH})^n \qquad (37)$$

$$i.e.,\ pK_a = pK'' - n \log a_{SH} \qquad (38)$$

For charged acids eq 36 should be rewritten as eq 39 in which the solvation of B is ignored. This allows the continued use of eq 38 where n now equals $x - z$. Glover prefers, for ease of calculation, an alternative formulation equivalent to eq 39 but involving the self-ionization of water. If the method is valid, it should provide constant values of pK'' over a wide range of solvent composition.

$$BH^+(SH)_z + nSH \rightleftharpoons H^+(SH)_x + B \qquad (39)$$

This indeed seems to be the case for several acids in 0–82% dioxane. However, as might be expected from Glover's circuitous treatment of charged acids, the method works better for the ionization of water or acetic acid than it does for ammonium or anilinium ions.

Grunwald and his coworkers,[83] by employing extrathermodynamic assumptions, attempted to set up an absolute acidity scale for mixed solvents. Their results for several carboxylic acids and ammonium ions in various ethanol-water mixtures, and for ammonium ions in mixtures of dioxane and water, are reasonably well correlated by their "activity postulate." Wynne-Jones, however, has pointed out that their approach is misconceived.[84] His work with substituted phenols demonstrates that Grunwald's basic assumption is not valid, and he dismisses the earlier work as being based on inaccurate data. Wynne-Jones' data was estimated as accurate to ±0.01 pK unit, whereas Grunwald's work is claimed to be accurate only to within ±0.05 pK unit.

5. Conclusions

It can be seen that there is an urgent requirement for work of the highest accuracy in this area. Moreover the classical electrostatic approaches, which ignore solvation, and assume freely rotating ions, are insufficiently sophisticated to account for the observed changes in pK_a as the composition of a mixed solvent varies. More work is required on the implications of structural alterations in the solvent. The redefinition of the ionization equilibrium by Glover, which allows study of solvation changes, could be a very productive approach.

Albert[69] has pointed out that irregularities in mixed-solvent pK_a's occur when substances of different hydrophilicity are being examined. The solvation sheath around the molecule results in the acidity constant being determined in a solvent cage of low dielectric constant, rather than in a homogeneous mixture of measureable dielectric constant ϵ. This preferential solvation is a competitive phenomenon akin to partitioning between water and such immiscible solvents as 1-octanol. It is surprising that no attempts have been made to rationalize the changes in acidity constant in varying solvent mixtures by using the partition coefficients of the compounds under study, along with the dielectric constants of the media employed. As the early work of Kolthoff and his coworkers demonstrated, it is possible to use partition coefficients alone, to predict the pK_a's in pure ethanol or methanol of several benzoic acids, given the corresponding values in water.[85] Their approach took no account of dielectric constant but seems reasonably successful, considering the experimental errors involved in their pK_a values.

Kolthoff[85] calculated partition coefficients by comparing solubility ratios in pure solvents. This approach is likely to give different results to those obtainable by the usual distribution method.[86] Nevertheless, it is the only way of obtaining the (most relevant) partition coefficients when the solvents are completely miscible. Obviously this approach could be extended directly to results in mixed-aqueous systems. As partition coefficients in related solvents can be interconverted by eq 40, it may be possible to use published[86] partition coefficients from, say, octanol-water to provide empirical correlations with results in aqueous alcohols.

$$\log P_2 = a \log P_1 + b \qquad (40)$$

Eventually such an empirical approach, or an advance in theory, will provide reasonable methods for transposing results from mixed solvents to a water-based scale. There is no need to wait until then before proceeding with determinations in such systems. However, a plea should be made for standardization before the number of mixed solvents in use increases even more. Although Benet and Goyan[28] recommend the use of methanol-water systems, Simon's group has done much to establish 80% methyl Cellosolve as the preferred mixed solvent.[68] We have found that 50% methyl Cellosolve has much to recommend it. The electrode response is faster than in the 80% solvent, increasing the reliability of automatic titrations. The solvent properties of the 50% mixture do not differ greatly from the more concentrated solvent, and a greater range of compounds can be studied as there is a much smaller effect on the pK_a in changing from water to the 50% mixture, rather than the 80% solvent. Finally the ionization in 80% methyl Cellosolve (ϵ = 32) may involve complications from ion-pair formation; these would be absent in the 50% solvent ($\epsilon \simeq 50$). Hence, it is more likely that results in the more dilute solvent can be transposed to an aqueous scale. Simon[68] demonstrates that there is only a rough parallel between aqueous pK_a's and his pK_{MCS} values. Of course this does not detract from his purpose of building up a large body of data in the 80% solvent as a reference system in its own right.

C. Treatment of Data

The pH at half-neutralization is not a sufficient indication of the pK_a, not only because of its neglect of activities, but also because it provides no indication of the precision of the estimate. The acidity constant should be calculated using 7–10 points on the titration curve preferably in the 10–90% ionization range (*i.e.*, pK_a ± 1 unit). Outside the pH range 4–10 for 0.01 *M* solutions, or the range 5–9 for 0.001 *M* solutions, corrections must be made for hydrolysis effects. Albert and Serjeant[1] deal adequately with this subject and also the need for activity corrections and how to perform them when necessary.

A major requirement of the method of Albert and Serjeant[1] is that the sample to be studied must be pure and dry. In other words, the initial concentration of the acid or base must be known exactly. Often this is not possible, particularly with hydrated compounds, and the resultant pK_a's can only be estimated approximately. However, Benet and Goyan[28] have developed a graphical method involving nonlogarithmic linear relationships, and this can be used for calculation with compounds containing neutral impurities (of which the commonest is water). They develop the general expression

$$[H^+] = K_a[(C_a + Z)/(C_b - Z)] \qquad (41)$$

where $Z = [X] - [M] - [H^+] + [OH^-]$, and $[X]$ = concentration of strong acid added, $[M]$ = concentration of strong base added, C_a = initial concentration of weak acid, and C_b = initial concentration of weak base.

For titration of a weak base with strong acid $C_a = 0$, hence

$$Z = C_b - K_aZ/[H^+] \qquad (42)$$

and a plot of Z against $Z/[H^+]$ will be a straight line with a slope equal to $-K_a$ and an intercept of C_b. Similarly, for titration of a weak acid with a strong base $C_b = 0$, therefore

$$Z = -C_a - Z[H^+]/K_a \qquad (43)$$

and a plot of Z vs. $Z[H^+]$ would give a straight line of slope $-1/K_a$ and an intercept of $-C_a$. In either case the pK_a is readily obtainable although no estimate of the precision is available. Because the expression for Z includes $[H^+]$ and $[OH^-]$, the method automatically corrects for hydrolysis effects and gives good results even in the pH ranges 1.5–5 and 9–11. Another advantage of the method is that erroneous points will lie off the straight line and can be ignored. The method has been shown to work well, and a modification of eq 41 has been introduced to allow for volume changes during the titration.[87] Precipitation during titration can also be handled.[88]

Another straight line method has been presented as an alternative to that just described.[89] By using suitable logarithmic scales it is possible to convert the normally sigmoid titration curve into a straight line. This method is useful when the substance precipitates during titration. An estimate of the pK_a can be had by extrapolation of the initial linear portion of the titration curve to obtain the pH at half-neutralization. An interesting paper has recently discussed more accurate methods for the calculation of acidity constants.[90] The authors discuss the source and magnitude of the systematic errors arising from the use of eq 9 in calculations. They present alternative equations requiring only a knowledge of the volume of titrant added and the resultant acidity. The method has some appeal but neglects to take account of the lack of accuracy implicit in the use of pH. This may render the results obtained less accurate than is claimed.

D. Overlapping Constants

The treatment of di- and triprotic acids is considered in section VIII.D. The situation is complicated when the acidity constants of the various groups are sufficiently close for their ionizations to overlap (*i.e.*, $\Delta pK_a < 2.7$). The normal equations are no longer applicable and recourse must be had to more sophisticated approaches. It is in this area, with its more involved theory, that computers have proved their worth. Not only can they deal with the routine, tedious calculations, they may also allow the use of iterative techniques, a powerful weapon in the more complex situations. By convention the various acidity constants pK_1 and pK_2 are assigned in order of increasing pK_a. Thus K_1 refers to the loss of the first proton from the polyprotic acid.

The oldest method for separating overlapping pK_a's of diprotic acids is due to Noyes. The method was modified by Britton,[91] and the extensive calculations required are the subject of an Algol program.[92] Albert and Serjeant[1] give a program in Fortran IV which is based on Speakman's equation (eq 44), in which $\bar{h}$ is the average number of protons removed from the polyprotic acid, and γ_2, γ_1, and γ_0 are the activity coefficients of the diprotic acid and its mono- and dideprotonated species. The derivation and use of eq 44 is covered by King but unfortunately misquoted in his book.[2] A plot of the two quantities in brackets has a slope of K_1 and an intercept of K_1K_2. King[2] also gives the general equation for n overlapping constants which can be treated on a computer if the measurements are precise enough for it to be worthwhile.

$$\left[\frac{\bar{h}}{2-\bar{h}}\;\frac{{a_H}^2\gamma_2}{\gamma_0}\right] = \left[\frac{1-\bar{h}}{2-\bar{h}}\;\frac{\gamma_2 a_H}{\gamma_1}\right]K_1 + K_1K_2 \quad (44)$$

Those without access to a computer or a desire for lengthy calculations can use a much simpler method recently published by Martin.[93] His method relies on measurement of hydrogen-ion concentration after the addition of 0.5, 1.0, and 1.5 equiv of titrant. He derives eq 45 and 46 for the calculation of K_1 and then K_2. The method assumes that hydrolysis corrections are unnecessary (which is somewhat limiting) and suffers from the same faults as does "pH at half-neutralization." The neglect of activity corrections becomes more serious when doubly charged ions are in solution; nevertheless, reasonable values were obtained in the pH range 6–10.

$$K_1 = [H^+]_{0.5} - 3[H^+]_{1.5} \quad (45)$$

$$K_2 = {[H^+]_{1.0}}^2/K_1 \quad (46)$$

An often-used approach involves removal of one of the ionizing groups by chemical reaction (*e.g.*, esterification) and assumes that the remaining group is unaffected by this change. Serious errors can creep into this approach but it is occasionally useful, particularly for the assignment of acidity constants to particular groups in complex molecules.[94] If by some such means as this pK_1 or pK_2 can be estimated, then the other constant is readily obtained by use of eq 47, which is, of course, the logarithmic form of eq 46. This equation forms the basis of another simple treatment of the titration curve of a dibasic acid.[95]

$$(pK_1 + pK_2)/2 = \text{pH(at 1 equiv)} \quad (47)$$

E. Nonaqueous Solvents

Acid–base behavior in inert organic solvents has been recently reviewed by Davis[9,96] and more briefly by Lagowski.[97] Both authors emphasize the importance of electrostatic and hydrogen-bonding effects in such solvents. Solvent–solute interactions can rarely be ignored, even in "inert" solvents.[97] Ritchie[98] has recently reviewed the influence of such interactions in dipolar aprotic solvents, with particular emphasis on acidities in acetonitrile, DMF, and DMSO. Davis[9] points out that there is no such thing as "pH" in say a benzene solution. Acid strengths may only be determined by comparisons of reactivity with a reference base. The various log K_{BHA} scales for acids and bases in any aprotic solvent cannot be merged into a single scale corresponding to the aqueous pK_a scale.

The main problems[2] with measuring acidity in nonaqueous solvents are that the electrodes used may not function reversibly, and the measured emf and the activity of the added strong acid may not confirm to the Nernst equation (eq 48). Moreover many solvents have high resistance, resulting in loss of sensitivity compared with water. There is also the problem for solvents of low dielectric constant that extensive ion association results in measurements being made on equilibrium 4, rather than the usually studied reaction 2. King points out that there is no single scale of acid strengths in solvents in which ion-pair formation occurs.[2] Nevertheless, crude empirical relations have been demonstrated between aqueous pK_a's and acidity constants measured in acetic acid using a chloranil electrode.[1,11] As some substances react with chloranil, glass electrodes are to be preferred. In acetic acid with a water content of 0–0.5% the glass electrode responds quantitatively over a wide acidity range[68] and has been used to study bases in the pK_a range +2.5 to −4 with some success.[11] Remarkably, acidity constants determined by a variety of methods in solvents of low dielectric constant ($\epsilon \simeq 5$) correlate with aqueous pK_a's almost as well as do those determined in alcohols, whose dielectric constants are much higher.[8]

$$E = E^0 - 2.303(RT/F)\log a_{H^+}a_{X^-} \quad (48)$$

A linear relationship has been demonstrated between pK_a's and the half-neutralization potential (HNP) for titrations in acetic anhydride, using perchloric acid and conventional glass and silver|silver chloride electrodes.[99] Heterocyclic compounds are the only large group for which this does not apply, a fact sometimes overlooked.[100] Solubility problems may be overcome by the addition of 1-2% water with apparently no effect on the results. The method, except for heterocyclic compounds, gives estimates of pK_a's within ±0.2 unit (the error for isoquinoline is 1.13 pK_a units). The use of HNP as a measure of relative base strengths has been examined in 11 different solvents.[101] Details of the titration procedure and the construction of improved salt bridges are available.[32,101]

Acidic solvents are useful for titrations of weak bases and strong acids; for weak acids, basic solvents are used. For example, *n*-butylamine can be used as a solvent to determine the relative order of acidities for amides[102] or ureas.[103] Much work has been done on titrations in pure alcoholic solvents,[8] but these only improve solubility properties rather than allow normally untitratable groups to be titrated. As in other systems careful standardization of procedure is required. Frequently this has not been done, so results in the literature are often not comparable.

An interesting recent development is the use by Ritchie and Uschold[52,104] of the glass electrode to determine the acidities of weak acids in DMSO. The specially modified electrode responds reversibly over 25 log units, and many of the pK_a's determined are identical with those from use of the acidity function H_-. Titrations are performed using dimsylcesium as the strong base, and the results are considered accurate to ±0.3 pK_a unit. The results are close to those reported by equilibration methods[104] and throw some light on the relative merits of acidity functions determined in mixtures of DMSO with water or alcohol. Further discussion is delayed until section IV.D.

IV. Ultraviolet Spectrophotometry

A. Introduction

If potentiometry is inappropriate, either because the compound is too weak as an acid or base or because it is not sufficiently soluble, then ultraviolet spectroscopic methods should be used. These are possible only if the site of protonation or deprotonation is conjugated with, or is an inherent part of, a chromophoric group in the compound. The sources of errors in spectrophotometric measurements have been discussed,[105] and the conditions necessary for the occurrence of isosbestic points have been considered.[106] As with titrations, Albert and Serjeant[1] thoroughly describe the basic method and some refinements of technique. There is therefore no need here to repeat the details of their method. This review concentrates on general points, with more detailed discussion of medium effects and their elimination and acidity functions and their selection. Various graphical methods for the treatment of data are also considered.

B. Medium Effects

The ultraviolet method relies on the isolation of spectral changes due entirely to protonation or deprotonation, so that the ratio of protonated to deprotonated forms can be calculated. This means that determinations must be performed over a range of 1.5 pH units or so, in order to detect decomposition or deviations from Beer's law. Such deviations are often negligible, even for highly charged ions at ionic strengths up to 0.1. Above this ionic strength the method can be unreliable.[3] Failure of the spectral curves to intersect at an isosbestic point generally indicates either medium effects on the spectra, or decomposition, or the presence of impurities, or more than one ionization process.[2] The appearance of an isosbestic point is necessary for meaningful measurements, and much energy has been put into finding methods for compensating for the absence of such a point when medium effects are distorting the spectra.

Several authors mention methods for the correction of medium effects,[3,18,107] but no extensive review is available. The effects are not so serious in basic media, and most work on their correction has been developed in acidic solvents. The effect is not directly related to acidity as such but depends on the compounds being studied and the acid in which they are dissolved. Simple substitution of perchloric acid for sulfuric acid sometimes improves the situation.[108] Often measurements in moderately concentrated acid are sufficient, as medium effects are then less serious than in more concentrated acid.[18,63]

The oldest method of treatment of medium effects involves lateral shifting of the spectra until they gave an isosbestic point. The method assumes that the medium effect alters only wavelengths and not intensities. It is widely used and results compare favorably with those from other methods. The selection of an isosbestic point is arbitrary, and different choices can give different results.[18] The most logical choice is the point of intersection of the two curves nearest the 50% ionization region.[3] However, if the effect is not constant over the whole spectrum, then improvement of one isosbestic point may not improve others in the same spectrum.[109]

Small medium effects can be treated by making use of fortuitous cancellation of opposing errors.[110] This can be done by appropriate selection of two wavelengths for the determination, such that the medium effects at each wavelength are in opposite directions. A more sophisticated variant of this method, due to Alder and his coworkers,[111] uses several wavelengths and a weighted least-squares approach. The method can be applied to quite large effects. Alternatively, the absorbance of the neutral or charged species can be regarded as an unknown together with the acidity constants. The least-squares approach again allows a satisfactory solution.[107]

One of the simplest and most convenient methods due to Katritzky and his coworkers[35] involves the assumption that medium effects are linear over short ranges. A graph is plotted of absorbance against acidity, and the two arms of the sigmoid curve are extended to cover the portion where the absorbance is changing rapidly. The optical density (D) at a particular acidity and the corresponding values for the protonated (D_∞) and unprotonated (D_0) species are then read directly from the graph. The method seems very reliable.[22]

A widely used method is based on Davis and Geissman's approach (see below) which weights the disappearance of one peak against the appearance of another.[33] The result is still a function of the wavelengths chosen[107] and is only good if they are well separated.[18] A modification of this approach[112] involves approximate determination of the pK_a by Davis and Geissman's method and then recalculation using values of D_0 and D_∞ based on the absorbance at 1.5 units either side of the crude pK_a. A second modification[113] is available, in which Davis and Geissman's method is combined with that of Katritzky and his coworkers, mentioned above.

Although medium effects are difficult to eliminate satisfactorily, detailed study of the nature of the effect allows adequate provision to be made.[107] The most accurate and involved approach involves analysis of the curves using characteristic vectors, which involve matrix manipulations on data from several wavelengths and various acidities.[109] Often the problem can be solved by graphical methods which allow estimation of D_∞ without measurements in concentrated acid. This approach assumes some knowledge of the protonation behavior of the base under study and is considered in more detail in section IV.E.

C. Selection of Acidity Functions

Having determined the ratio of protonated and unprotonated species, the next step is a meaningful calculation of the acidity constant using the most appropriate measure of acidity. The problems encountered outside the pH range have already been mentioned. Section II.B outlined the use of acidity functions as an extension of pH, and section II.D discussed their use in providing meaningful measures of acidity constants. It only remains to consider the methods for selecting the most appropriate acidity function.

The early hope that the relevant acidity function H_x could be selected solely on the basis of the charge x on the conjugate base has long since been abandoned. Nevertheless, this should be the first method to use in acidity function selection. There is little choice for doubly charged acids BH_2^{2+}, or neutral acids HA, the respective acidity functions being described as H_+ and H_-. For acids with a single positive charge, there is a wide choice available. In general, the most appropriate acidity function is one constructed using indicators closely related to the compound in question. Unfortunately, subjective similarity of structural type may not be a sufficient guide. Thus differing solvation requirements ensure that H_0 for primary anilines is substantially more positive than H_0''' for tertiary anilines.[3]

The wide range of alternatives to H_0 for describing the protonation of neutral bases is indicative of past interest in the area and its accessibility, rather than any peculiarities of this particular ionization equilibrium. Some of the available H_0's deviate markedly from the H_0 used to describe the protonation of primary anilines in sulfuric acid, which now has a central importance in the discussion of acidity functions. The various alternatives, together with the structural types to which they refer, are tabulated by Boyd[14] and discussed in more detail by Rochester.[3] They may be ranked in the following order of acidity: J_0 (triarylcarbinols) $>$ H_R' (diarylalkenes) $>$ H_0''' (tertiary amines) $\simeq$ H_I (indoles) $>$ H_0 (primary anilines) $>$ H_B (benzophenones) $>$ H_A (amides) $>$ log $[H_2SO_4]$. The symbol H_B is Rochester's more logical nomenclature for Bonner and Phillips "H_0" scale for benzophenones.[114] Boyd[14] recommends keeping the term H_0 for each scale, followed by an indication of the indicator type to which it refers. This seems confusing and Rochester's approach can be recommended, provided not too many more acidity functions are generated. Apart from the various acidity functions in sulfuric acid, a variety of acidity functions are available in other aqueous acids as well as different solvent systems.

The primary aniline H_0 scale in sulfuric acid has achieved its central importance both on historical grounds and because of the accuracy with which it is known. Since the classic review by Paul and Long,[115] parts of the scale have been redefined. The most accurate values now available are given in Table II. Below 10% (w/w) sulfuric acid, the values are those given by Bascombe and Bell,[116] and above 60% acid Jorgenson and Hartter's results[117] are listed. The values from 10 to 60% are from the review by Paul and Long. The reader is referred to Rochester's book or the original literature for intermediate values. More recently H_0 has been extended well into the superacid region[56] (*i.e.*, H_0 values down to -15). However, the indicators used were aromatic nitro compounds rather than primary anilines. This was necessary as no suitable anilines were available, but it does mean that the overlap with the established region is in doubt, as the nitro compounds may not be strictly Hammett bases.

TABLE II. The Most Reliable Values of the Hammett Acidity Function, H_0 (Primary Anilines as Indicators)

% (w/w) H_2SO_4	H_0	% (w/w) H_2SO_4	H_0	% (w/w) H_2SO_4	H_0
0.0049	3.03	10	−0.31	60	−4.46
0.0131	2.51	15	−0.66	64	−4.95
0.0590	1.99	20	−1.01	68	−5.50
0.248	1.43	25	−1.37	72	−6.10
0.612	1.06	30	−1.72	76	−6.71
2.26	0.48	35	−2.06	80	−7.34
5.10	0.09	40	−2.41	84	−7.97
8.3	−0.23	45	−2.85	88	−8.61
9.1	−0.27	50	−3.38	92	−9.29
		55	−3.91	96	−10.03

There has been little interest in setting up acidity functions for doubly charged acids, although it seems that there is no universal H_+ scale. For example, the second protonation of many compounds (e.g., aminopyridines, dimethylquinoxalines, and aminoacetophenones) follows H_0 but the second protonation of pyrazine and pyrimidine follows the H_A scale.[3] At the alkaline end of the pH region, the use of H_0 for the study of strong bases has not been explored, although H_- is available for strong neutral acids at the other end of the pH scale.

In recent years interest has increased in the study of acidity functions beyond pH 13, for use with weak uncharged acids. Rochester[3] lists values for acidity functions in this region, whereas Boyd[14] neglects them, quoting the review by Bowden[15] instead. The methods for achieving high alkalinity are less straightforward than the corresponding procedures in acid solution. Aqueous potassium hydroxide, for example, can only provide solutions of H_- up to ca. 19 (using indoles as indicators).[118] A common device for increasing the basicity of an aqueous solution of a strong base is to add an increasing quantity of DMSO to the solution. The concentration of strong base is held constant, and H_- values are available for aqueous solutions containing varying amounts of DMSO with either 0.011 or 0.0471 *M* tetramethylammonium hydroxide. The former scale[119] (maximum $H_- \simeq 26$) was established using anilines and diphenylamines as indicators, whereas the latter makes use of a series of substituted fluorenes[120] (see section IV.D). Although Bowden[15] points out that H_- should depend less on the type of indicator used than does H_0, there are nevertheless significant differences between scales generated using phenols, anilines, fluorenes, and other carbon acids. Thus the H_- scale based on fluorenes does not parallel the aniline acidity function and is not yet firmly anchored to aqueous pH; therefore, it lacks the rigor of the nitrogen acid scale.

Although the acidity functions in water seem quite well established, there is no single function available for nonaqueous and mixed-aqueous solvents. What little work has been done in this area is discussed by Rochester.[3] Attempts have been made to transpose a variety of acidi-

TABLE III. The MSAD Scale

Compound	pKa	Compound	pKa
Fluoradene	11	Triphenylmethane	32.5
Cyclopentadiene	15	Toluene (α position)	35
9-Phenylfluorene	18.5	Ethylene	36.5
Phenylacetylene	18.5	Benzene	37
Indene	18.5	Methane	40
Fluorene	22.9	Ethane	42
Acetylene	25	Cyclopentane	44
		Cyclohexane	45

ty functions in alcohols or alcohol-DMSO mixtures to the aqueous standard state by using suitable bridge compounds. Thus Bowden[7] transposed an acidity function H_M based on nitrogen acids in methanolic potassium methoxide to a corresponding H_- scale. Rochester[3] criticizes this treatment by pointing out anomalies that result in derived pK_a values. If acidity functions in mixed or nonaqueous solvents are adequately referred to the aqueous standard state, then the acidity constant determined for any particular indicator should be independent of the solvent system. Because of the errors involved in such empirical approaches, these attempts have little to recommend them, particularly as, for example, the methanolic standard state is most relevant to kinetic and mechanistic studies in methanol. In this connection it should be noted that an H_M scale has recently been constructed for this purpose, using hydrocarbon acids as indicators.[121]

D. Highly Basic Media

Although the discussion so far has emphasized work in acidic solutions, ultraviolet and visible spectroscopy provide powerful tools for examining compounds in highly basic media. The preparation and uses of such solutions have been briefly reviewed.[122] Recent reviews[5,45,48] amply cover the methods available for the determination of the acidities of carbon acids in highly basic solution. Because of the prime importance of carbanions in organic chemistry[5] and the need to quantify carbanion stability, much effort of late has been devoted to the exploration of these regions. Unfortunately, most solvent systems possess only a limited range of H_- and so the acidity function approach is only suitable for the comparatively strong carbon acids. Various ingenious methods have been devised to circumvent this difficulty. These approaches have resulted in a series of internally consistent acidity scales, none of which can be firmly linked to the aqueous pH scale. Nevertheless, as the study of H_- acidity functions continues, there is a real hope that eventually much of the relative data presently available will be given an absolute meaning. For the time being we must tolerate "pK" values quoted, as a matter of convenience, relative to some arbitrary standard.

The early work which established a pK_a scale from 15 to 30 using ethereal solutions has been confirmed to a large extent by the more refined work of Streitwieser and his colleagues,[49,123] using cyclohexylamine as a solvent. Cram,[5] in his wide-ranging review of carbanions, amalgamated the results of Streitwieser and various other workers to provide what he called the McEwen-Streitwieser-Applequist-Dessy (MSAD) scale, part of which is given in Table III. This internally consistent acidity scale is applicable to solvents of low dielectric constant (*i.e.*, $\epsilon < 20$), where extensive ion association occurs. The scale is arranged relative to an assumed pK_a for 9-phenylfluorene of 18.5. The pK_a of this compound is discussed in some detail later in this section.

Streitwieser and his coworkers have developed and refined the quantitative study of equilibrium acidities. A mixture of two acids in cyclohexylamine is treated with a strong base. The relative amount of free acid of each species at equilibrium provides a measure of their relative acidity. The strong base originally tried was the lithium salt of cyclohexylamine;[49] however, problems with ion-pair formation and the failure of the weaker acids to obey Beer's law resulted in the adoption of cesium cyclohexylamide as the base.[123] This gave a pK_a range up to 33.1 for diphenylmethane.

The "absolute" values were determined relative to 9-phenylfluorene, whose pK_a was available from acidity function studies. The value of 18.49 was selected as a good average of results in three different systems. Unfortunately two of the estimations were based on nitrogen-acid scales and the third on a disparate mixture of carbon acids. The situation is complicated by reports[54,104] that the acidity constant of 9-phenylfluorene could be seriously in error, and values of *ca.* 16.5 have been suggested. Ritchie[98] has reviewed this confused area quite recently and concludes that the best present value for this pK_a is 16.4. As there is much to recommend this view, it seems likely that the acidity constant of 9-phenylfluorene will be revised, resulting in the adjustment of most of the pK_a values at present quoted for weak hydrocarbon acids. Streitwieser accepts that even though his relative values should be reasonably accurate, the absolute magnitude of his results may be in doubt by 1-2 units.[124]

An unambiguous pK_a for 9-phenylfluorene will only be available when an acidity function using appropriate, closely related indicators has been constructed between the pH scale and ionization range of the compound in question. Attempts have been made by Cockerill and his coworkers[120] to construct, in aqueous DMSO mixtures, such a scale based entirely on substituted fluorenes. So far the scale spans the range of H_- from 14.7 to 24.5, relative to an assumed value of 18.59 for the pK_a of 9-phenylfluorene. When the gap between this scale and the pH range is bridged, it will allow work such as that of Streitwieser to be referred more accurately to the aqueous standard state.

If Streitwieser's results are recalculated using Ritchie's value for 9-phenylfluorene, then a series of acidity constants is obtained in cyclohexylamine which closely correspond with results from titrations in pure DMSO.[98] Moreover, there are similarities between results obtained in cyclohexylamine, which are crudely referred to water as a standard state, and various results from earlier acidity function studies. Rather than list absolute pK_a's which may be subject to change in the near future, Table IV contains values relative to 9-phenylfluorene, which has been included in at least five different acidity scales. Even if adequate reference to the aqueous standard state is possible for 9-phenylfluorene, many of Streitwieser's results could still not be regarded as closely linked to the aqueous pK_a scale. As Streitwieser and his coworkers point out, the results should be treated cautiously, as the conjugate bases of the hydrocarbon acids are ion pairs rather than pure carbanions. The absolute values obtained are of far less significance than the differences between them. The discrepanices between the lithium and the cesium based scales point to the dangers in assuming universally applicable pK_a scales for hydrocarbons.[123]

As the scope of Streitwieser's work increases, the impossibility of setting up such a universal pK_a scale becomes increasingly evident. Recent work[125] on acetyl-

TABLE IV. ΔpK Values Relative to 9-Phenylfluorene[a]

	A	B	C	D	E
Malononitrile	−5.4		−7.5		
9-Phenylfluorene	0	0	0	0	0
7*H*-Benzo[*c*]fluorene		1.0			1.03
Indene	2.1	1.4	0	1.6	
11*H*-Benzo[*a*]fluorene	1.5	1.5			
9-Methylfluorene	3.3	4.2			3.21
4*H*-Cyclopenta[*def*]-phenanthrene	3.6	4.1			3.20
Fluorene	4.1	4.2	4.4	3.9	3.51
9-Phenylxanthene	9.1	10.0		9.2	
Triphenylmethane	11.9	13.0	14.0	12.2	
Diphenylmethane	13.6	14.6		13.6	
Assumed pK_a for 9-phenylfluorene	16.4	18.5	18.5	16.6	18.59

[a] A: titration in DMSO (DMSO standard state).[52,104] B: cesium ion pairs in cyclohexylamine (approximately aqueous standard state).[123] C: MSAD scale (approximately aqueous standard state).[5] D: H_- based on nitrogen acids (aqueous standard state).[54] E: H_- based on fluorenes (aqueous standard state).[120]

enes shows a large pK_a difference between phenylacetylene (pK_a = 23.2) and 9-phenylfluorene (pK_a = 18.5), whereas on the MSAD scale they have the same pK_a. Thus it seems that acetylenic pK_a's cannot be referred to the aqueous scale by way of 9-phenylfluorene, probably because of different activity coefficient behavior of the two types of compound. As the anions of acetylenes do not have visible spectra, a modification of Streitwieser's normal technique was introduced.[125] The proportion of acetylenic acid in equilibrium with a suitable hydrocarbon indicator was determined from the reduction in absorbance when a known amount of acetylene was added to the indicator salt. Four different indicators gave results in close agreement. A similar approach[126] with fluorinated benzenes, followed by a correlation with rates of hydrogen-isotope exchange in methanolic sodium methoxide, allows the prediction of a pK_a for benzene of 43.0 ± 0.2. This is probably more accurate than the value of 37 quoted by Cram on the MSAD scale. Another extension of the technique allows direct determination of the acidities of relatively acidic hydrocarbons (*i.e.*, p$K_a \sim$ 13–14) in cyclohexylamine, referred to the solvent as standard state.[127]

Other workers have used liquid ammonia as a solvent, and this necessitates work at either low temperatures[57] or under pressure.[53] Equilibria are generated between two acids using sodium or potassium amide, and these can be studied by ultraviolet[57] or nmr techniques.[53] Shatenshtein[58] has reviewed much of his own work on hydrogen-isotope exchange rates in liquid ammonia, and Cram[5] discusses this work and its contribution to our knowledge of kinetic acidities (see section II.E).

E. Treatment of Data

Assuming that medium effects can be adequately handled (see section IV.B) and suitable values for the acidities of solutions are available (sections IV.C and IV.D), there may still be problems associated with analyzing the spectral data. Various methods for calculating pK_a's are considered in this section.

1. Estimation of D_0 and D_∞

A variety of methods have been developed for the treatment of data obtained from spectroscopic measurements. One of the most useful of these is due to Maroni and Calmon[128] and has been adopted in the revised version of Albert and Serjeant.[1] Rearrangement of the usual equation, eq 49, results in either eq 50 or 51, in which D is the optical density at the measured pH, and D_0 refers to the deprotonated and D_∞, to the protonated species.

$$\mathrm{p}K_a' = \mathrm{pH} + \log\,[(D - D_0)/[(D_\infty - D)] \tag{49}$$

$$D = D_0 - (1/K_a')(D - D_\infty)a_{\mathrm{H}^+} \tag{50}$$

$$D = D_\infty - K_a'(D - D_0)/a_{\mathrm{H}^+} \tag{51}$$

These equations may be used when, for reasons of decomposition or medium effects, either D_0 or D_∞ cannot be measured directly. Thus for weak acids D_0 may not be available in highly alkaline solutions, and for weak bases D_∞ may not be measurable in strong acids. For the former case, using eq 50, a plot of D against $(D - D_\infty)a_{\mathrm{H}^+}$, preferably using the method of least squares, gives a line of slope $-1/K_a'$ and intercept D_0. Use of eq 51 for weak bases results in a plot of D vs. $(D - D_0)/a_{\mathrm{H}^+}$ having a slope of $-K_a'$ and an intercept of D_∞. The merit of the method is not the graphical estimation of K_a' or $1/K_a'$ but the evaluation of D_0 or D_∞ which can then be used in eq 49 in the usual way. The acidity constants obtained are apparent pK_a's because the calculations use a mixture of activity and concentration terms. Corrections for activity coefficients may be applied, as described previously, to obtain thermodynamic values.

The method can be extended to the use of acidity functions by using h_x = antilog $(-H_x)$ in place of a_{H^+} in eq 50 and 51. This method then assumes the appropriateness of the chosen acidity function, and the value of D_∞ or D_0 obtained cannot then be used to verify this assumption.[63] Unfortunately, this problem has not always been appreciated.[129] Providing the acidity function used is appropriate for the compound studied, then the thermodynamic pK_a is obtained directly without the need for activity corrections.

2. Extrapolation Methods

An ingenious linear free energy method, which makes no assumptions about which acidity function a base follows, has been described by Bunnett and Olsen.[17] The ratio of protonated and unprotonated forms is obtained at various acid concentrations whose H_0 values are known. The procedure then involves plotting log [BH$^+$]/[B] + H_0 against H_0 + log [H$^+$]. The intercept when H_0 + log [H$^+$] = 0 equals the pK_a of BH$^+$. The method is based on eq 52, which the authors derive as the standard formulation

$$\log\,[\mathrm{BH}^+]/[\mathrm{B}] + H_0 = \phi(H_0 + \log\,[\mathrm{H}^+]) + \mathrm{p}K_a \tag{52}$$

of a linear free energy relationship. The method gives results in good agreement with those from the acidity function method and was, in fact, used to check the validity of several of the acidity functions.[17] The uncertainty in the determination was estimated to be ±0.2 pK_a unit, which justifies any approximation involved in their taking [H$^+$] = [H$_2$SO$_4$]. The method finds particular application for those compounds which do not have a suitable acidity function available. A recent application[130] of this approach to the protonation of methyl thioethers gave pK_a values in the range −6.7 to −6.9.

At infinite dilution, all activity coefficients equal 1, and eq 9 can be rewritten pK_a = log [HX]/[X] − log [H$^+$]. Thus extrapolation to infinite dilution, of a plot of the right-hand side of this equation against acid concentration, will provide a value for pK_a. Providing the acid concentration is kept below 2 *M*, the plots are linear for charged acids BH^+ and the extrapolation is reliable.[3] The linearity is due to the cancellation of the activity coefficient ratio log $\gamma_{BH^+}/\gamma_{H^+}$. An alternative extrapolation method involves plotting log [HX]/[X] against H_0 and extrapolating this to H_0 = 1, when $H_0 = [H^+]$, and the value of log [HX]/[X] gives the acidity constant.[20] Very weak bases, however, require long extrapolations from their protonation regions and then these methods are less satisfactory.

The extrapolations just described are not suitable for neutral acids HA as the activity coefficients γ for A^- and H^+ are multiplied and do not cancel. Consequently linear plots do not result. An alternative equivalent approach has been developed by More O'Ferrall and Ridd,[131] which relies on a knowledge of the self-ionization constant of the solvent. Their work was performed in methanol, but their method can easily be applied to water or any ionizing solvent. They considered eq 53 and determined the pK_b, where K_b is defined by eq 54. Extrapolation of eq 55 to infinite dilution provides a value for pK_b. As with the

$$HA + MeO^- \rightleftharpoons A^- + MeOH \qquad (53)$$

$$K_b = (a_{HA}a_{MeO^-})/(a_{A^-}a_{MeOH}) \qquad (54)$$

hence

$$pK_b = \log\frac{[A^-]}{[HA]} - \log[MeO^-] + \log\left(\frac{\gamma_{A^-}}{\gamma_{MeO^-}}\,\frac{a_{MeOH}}{\gamma_{HA}}\right) \qquad (55)$$

previous extrapolations, cancellation of the activity coefficient term log $\gamma_{A^-}/\gamma_{MeO^-}$ results in a straight line plot at low concentrations of methoxide ion. Thus an accurately determinable pK_b is obtainable for neutral acids, sufficiently strong to ionize at low concentrations of base. Problems could arise, however, when the pK_a is calculated by eq 56. Thus the pK_a values of More O'Ferrall and Ridd must now be increased by 0.22 unit as the value for pK_{MeOH} has been revised. The method can be applied with confidence in water because the values of pK_w are well known.[4] With very weak acids this method is inadequate as the long extrapolations required are not linear. Then, as with weak bases, resort must be had to the stepwise method of comparing pK_a's with known values of closely related compounds. This approach is essential for the establishment of acidity functions and is well covered by Rochester[3] and Boyd.[14]

$$pK_a = pK_{SH} - pK_b \qquad (56)$$

3. *Other Approaches*

Davis and Geissman developed a method which partially eliminates medium effects.[33] Two wavelengths are selected such that at one wavelength $D_0 \gg D_\infty$ and at the other $D_\infty \gg D_0$. At various acidities $\Delta D = D(\lambda_1) - D(\lambda_2)$ is measured and is plotted against H_0 (or some other appropriate acidity function). This procedure gives the usual sigmoid curve from which the acidity at half protonation can be ascertained. Katritzky and his coworkers[40] prefer the direct plotting of absorption at a suitable wavelength against H_0 as this gives smoother curves than Davis and Geissman's method.

As inflection points are often difficult to determine accurately, Stewart and Granger[112] have developed a modification of Davis and Geissman's method which can produce a straight line plot amenable to least-squares treatment. They let $\Delta D_B = D(\lambda_1) - D(\lambda_2)$ for the unprotonated species and $\Delta D_{BH^+} = D(\lambda_1) - D(\lambda_2)$ for the protonated compound. Then if ΔD is this quantity at an intermediate acidity H_x, a plot of log $(\Delta D_{BH^+} - \Delta D)/(\Delta D - \Delta D_B)$ vs. H_x should give a straight line of unit slope and an intercept of $H_x{}^{1/2}$. To make meaningful use of this method requires very careful selection of ΔD for B and BH^+, and medium effects may distort such an approach even though partial compensation is achieved (see section IV.B).

A refinement of Albert and Serjeant's spectroscopic method involves the use of the acidity function $p(a_H\gamma_{Cl})$ in place of pH. This function is much more accurately defined,[31] and its acidity may be corrected for the effect of addition of the compound (whose approximate pK_a must be known) by a computer procedure.[29,30] The pK_a can then be determined and corrected by addition of activity terms and the result of a series of such measurements at various ionic strengths, extrapolated to zero ionic strength. The resulting value is an accurate thermodynamic pK_a with a precision of the order of ±0.001. The method is useful at various temperatures between 0 and 95° for the calculation of thermodynamic quantities.

For the majority of weak bases, appropriate acidity functions are not known, and one must abandon attempts at precise experimental definitions of thermodynamic pK_a's and resort to obtaining reasonable estimates from a combination of methods. Greig and Johnson[22] recommend trying three approaches: (a) plot log [HX]/[X] against H_x, where H_x is such that m = 1; (b) assume that $H_x = mH_0$ and plot log [HX]/[X] vs. H_0; (c) use Bunnett and Olsen's linear free energy method. The first method assumes that a reasonably suitable acidity function is available, and the second and third methods are mutually contradictory, as plots of H_0 vs. log $[H^+]$ are not linear. Nevertheless, the results from the last two methods were not significantly different for carbonyl compounds.[22] Similarly, if these two methods are applied to the recent data on the protonation of methyl thioethers,[130] the resulting values for the pK_a's differ by less than 0.2 pH unit, which is well within the likely experimental error of the method. The likely errors in Bunnett and Olsen's method, particularly evident for compounds following H_A, have recently been discussed.[43]

Compounds which are transparent in the ultraviolet can be measured by observing the effect of the compound on the H_0 of a solution, as measured by an absorbing indicator also present in the test solution.[1,115]

F. Miscellaneous Applications

Ultraviolet spectrophotometers have been used to follow titration experiments on microgram quantities of material[132] and can be used to study rapid reactions with both continuous-flow and stopped-flow techniques.[133] When unstable species are being examined, rapid mixing techniques combined with back extrapolation are most useful.[134]

The problems with overlapping pK_a's are more complex in spectroscopic, as opposed to potentiometric, methods. The relevant theory has been summarized by King,[2] and Albert and Serjeant[1] give a general treatment which involves an iterative process. They provide a computer program in Fortran IV for the calculation of the results. A program has also been published recently by the same school which avoids the iteration and uses a computer library subroutine for solving sets of simultaneous equations.[135] If the absorption due to the monoprotonated species is very different from that from the unprotonated and diprotonated molecules, which in turn have similar absorptions, then a relatively simple treatment is available.[136]

V. *Other Spectroscopic Methods*

A. Nuclear Magnetic Resonance

The utility of ^1H nmr in equilibration studies has already been mentioned. It has an obvious use in deciding the site of protonation of a base. Studies[137,138] in superacid can easily be performed using this technique, particularly as low temperatures are readily attainable. Thus fluorosulfuric acid is liquid down to −89° (whereas sulfuric acid freezes at 10°) and the 1:1 mixture of fluorosulfuric acid and antimony pentafluoride ("magic acid") has been used[138] at −120°. Such low temperatures slow down proton-exchange rates sufficiently to allow a signal to be observed from the acidic hydrogen of the conjugate acid. At normal temperatures observations must be made on nonexchanging protons whose chemical shifts are affected by protonation. For success a significant difference is needed between the chemical shifts of the protonated and unprotonated forms, and this must be separable from the medium effects that can also influence chemical shifts.[139]

Early reports on the use of the technique were not promising,[13,139] and Arnett[11] suggested that for some groups of compounds the method was more suited to the study of medium effects rather than protonation. Application of nmr has met with mixed success in the determination of acidity constants. It seemed the method was useful for some groups of compounds, but others suffered from hydrogen bonding between the cation and the solvent. A recent paper points out that the procedure can, in fact, be employed successfully for a wide variety of functional groups.[140] The method is often suitable for weak acids and weak bases which are not amenable to spectrophotometric study. Unfortunately, quite high concentrations (*ca.* 0.1 *M*) are required, and this limits the technique somewhat, firstly because of solubility problems and secondly because activity corrections become difficult, particularly if an internal standard is also present. Performing measurements at higher frequencies, or using refinements such as computerized accumulation or Fourier transform techniques, should be helpful in reducing concentrations to more useful levels.

The simplest approach is to plot the changes in chemical shift against pH, or a suitable acidity function, and to take the pH at the inflection point as a measure of the pK_a value.[1,2] If the chemical shifts of protonated and unprotonated species are available, the normal calculations can be performed. Prolems arise, however, over the use of a suitable internal standard.

The common use of ammonium salts (*e.g.*, tetramethylammonium chloride) results in potential errors from hydrogen bonding with the solvent.[140] Although the effects are not important for protonated ketones, they appear significant for alcohols and ethers,[21] and this can explain the controversy over the pK_a's that have been obtained for various ethers.[140] A suitable device for minimizing these medium effects involves measuring the difference in chemical shifts between two protons in the same molecule. This difference is then plotted against pH or an acidity function to give the usual sigmoid curve.[140-142] The two protons chosen for this method should ideally be on adjacent atoms in the molecule, so that they are in approximately the same chemical environment. The advantages of this approach, avoiding internal standards and possible medium effects thereon, are partially offset by the smaller size of intramolecular shifts compared with absolute changes in chemical shift.[13]

The advantages and limitations of nmr in the study of the basicities of ketones have recently been discussed.[21] Bases too unstable for spectrophotometric work can easily be examined at the low temperatures achievable with certain superacids, and measurements are easily made over the whole of the Hammett scale (H_0 = 0 to −17.5). The method is rapid to perform and is not influenced to an appreciable extent by impurities. Thus some decomposition of the compound under study during the experiment will not invalidate the results. The presence of hydrogen fluoride as an impurity in some superacid media means that spectroscopic work is difficult. Nmr measurements can still be performed, however, by using a Teflon insert in the sample tube.[21] Unfortunately, the method is not very sensitive and results are probably only accurate to about ±0.3 pK_a unit, although greater accuracy may occasionally be achieved.[13,21]

The lack of precision in the method is illustrated by attempts to use the acidity function approach expressed in eq 57 for a series of related compounds.[141,143] The

$$\log [(\Delta\delta - \Delta\delta_0)/(\Delta\delta_\infty - \Delta\delta)] = mH_x + c \qquad (57)$$

values of *m* varied widely, resulting in some doubtful estimates of relative acidities. It was pointed out,[143] however, that the errors in *m* were partially compensated by errors in *c*, resulting in pK_a values which were "not too imprecise." Nevertheless, the claimed precision of ±0.05 unit gives a false impression of the accuracy of the method.

The use of nmr methods for determining microconstants and overlapping pK_a's has been reported,[144,145] and the methods of calculation have been discussed and refined.[145] Apart from the use of aqueous sulfuric acid, nonaqueous and mixed-aqueous solvents can be used.[145,146] Rochester[3] reviews acidity functions in deuterated acids. The use of paramagnetic shift reagents for the estimation of relative acidities has recently been mentioned.[147] The nmr spectra of lithium derivatives of weak carbon acids provide a crude method for estimating pK_a's on the MSAD scale.[148]

Nmr measurements of nuclei other than hydrogen have been used for pK_a determinations. Fluorine[11,146] and phosphorus,[149] in particular, have been mentioned, as has the potential of ^{13}C nuclear magnetic resonance.[138] Comparison of results from ^{31}P nmr and ^1H nmr for the basicities of some phosphine oxides demonstrates a medium effect on the phosphorus spectrum, which results in different values from the two methods.[149] The marked sensitivity of fluorine chemical shifts to nearby protonation makes fluorinated compounds particularly amenable to this method of pK_a determination.

B. Vibrational Spectra and Hydrogen Bonding

The phenomenon of hydrogen bonding, recently reviewed,[150] may be regarded as a step on the way to complete ionization. The Brønsted-Lowry theory of acids and bases takes no account of hydrogen bonds. Fortunately the more general acidity concept of Lewis does include such phenomena.[10] Arnett[11] discusses the wider interpretations of basicity and points out that there is no clear picture of the discontinuity between protonation and strong hydrogen bonding. Although great care is needed, hydrogen bonding and other types of complex formation may be useful for ranking weak bases or weak acids. For example, the hydrogen-bond strengths of various groups of compounds with either alcohols or phenols in carbon tetrachloride solution give similar pictures of relative base strengths.[150b]

Studies of the ability of compounds to form hydrogen bonds have provided new acidity scales as alternatives to the pK_a scale.[151,152] Although these scales have a variety of applications,[152] they are not in general related to the conventional pK_a scale.[153] Nevertheless, very approximate relationships are available between aqueous acidity constants and hydrogen-bond strengths for many compounds with entirely different functional groups. These allow pK_a estimations within ±2 units.[11] Much better correlations are available for compounds of similar structure.[154] In spite of its limitations, the technique is very useful for compounds which rapidly decompose on protonation or deprotonation. Thus aliphatic aldehydes undergo the aldol condensation in strong acid so rapidly that their basicities may only be measured by using hydrogen-bonded spectral shifts.[11]

Various methods exist for measuring the strength of hydrogen bonds, and of these the most useful technique involves infrared spectroscopy.[46,107,155] Commonly the strengths of hydrogen bonds are determined by the change in stretching frequency of suitable OH or NH bonds, although correlations of aqueous pK_a's with other frequencies have been reported. For example, infrared spectra in chloroform or carbon tetrachloride have been used to examine changes in the stretching frequencies of carbonyl[156] and nitro[157] groups, and these have been related to the basicities of the compounds studied. Equations have also been derived for primary and secondary nitrogenous bases which relate pK_a's and the slopes of "relative shift" plots.[158] These graphs plot the relative shifts of a compound's N-H bond in a variety of solvents, against the corresponding value for pyrrole. Relative shifts were calculated by eq 58, and the method provided reasonable estimates for the limited range of compounds studied.

$$\Delta = \frac{\nu_{\text{vapor}} - \nu_{\text{soln}}}{\nu_{\text{vapor}}} \tag{58}$$

In principle, Raman spectroscopy should provide a more direct approach to acidity constant determination than the methods mentioned using infrared studies. Until recently, however, the technique has been insufficiently sensitive to use with very dilute solutions. Consequently, it has found most application in the study of concentrated solutions of strong acids.[44] A detailed description of the quantitative Raman method has been published,[159] although the results of these workers have been reinterpreted.[160] It seems that Arnett's hope that Raman results would be unequivocal[11] is not borne out in practice. The method was used to study the protonation of the weak organic bases acetamide, methanol, acetone, and acetonitrile. The approach allows direct measurement of the ratio of protonated to unprotonated forms by comparison of the areas under the relevant absorption bands. This technique was found to be more reliable than simply comparing band heights.

A major drawback to the method is that only small molecules give spectra simple enough to be interpreted. Nevertheless, it can provide a useful check on estimates from other determinations. The recent introduction of laser sources for Raman spectroscopy[161] should result in the technique becoming more widely used, particularly when other spectral methods fail. As with nmr studies, care must be taken to ensure that hydrogen bonding does not distort attempts to measure protonation.

VI. Miscellaneous Methods

A. Calorimetry

The difficulties associated with the measurement of acidity constants outside the pH range are substantially due to there being no satisfactory definition of an acidity-basicity scale over the whole protonation-deprotonation range. Even the scales that are available cover only a limited span and are difficult to interrelate. Consequently, pK_a's determined until recently by, for example, the use of acidity functions have had scant justification. It is against this background of uncertainty that one welcomes Arnett's studies on the heat of protonation of organic bases in fluorosulfuric acid.[23,47] This work as well as demonstrating the validity of the acidity function approach has provided a basicity scale which covers more than 22 pK_a units.[24]

Originally Arnett and Burke demonstrated that heats of protonation in concentrated sulfuric acid were linearly related to the best estimates of aqueous pK_a's that were available.[24] However, the method gave different correlation lines for bases of different structures. More recently they have shown that a single line is obtained in fluorosulfuric acid and that this line can be used to estimate acidity constants with an accuracy better than ±0.7 pK_a unit. The equation of the line (eq 59) was derived for

$$-\Delta \bar{H} = 1.78\text{p}K_a + 28.1 \tag{59}$$

amines[23] and found to apply equally to most carbonyl compounds.[47] The apparently large error in the estimates using this equation seem to be as much a reflection of the inaccuracies in the literature pK_a's as of any error in the new method. Given such difficulties the correlation is remarkably good and should provide a new general basicity scale.

The overwhelming advantage of this method is that all measurements are made in the same medium (pure fluorosulfuric acid) and so medium effects cannot cloud the issue. A few anomalous results come from reaction with the solvent rather than protonation. The compounds can be checked for clean protonation by nmr. The heats of solution of the bases in the acid are corrected for the lattice energy of the pure solid or liquid by subtracting from the heat of solution in fluorosulfuric acid the heat of solution in carbon tetrachloride. On the rare occasions that compounds are insoluble in carbon tetrachloride, *sym*-tetrachlorethane is used instead. The value obtained is thus the heat of transfer of the base from a solution in the inert solvent to solution in fluorosulfuric acid. The calorimeter used is fully described,[162] together with some refinements in technique.[23] The measurements obtained are accurate and relatively easy to perform once the apparatus has been set up.

Fluorosulfuric acid possesses several advantages over sulfuric acid for these determinations. It is a better solvent and a stronger acid than sulfuric acid and provides a wider range of enthalpy values, which increases the sensitivity of the method. The pK_a range so far explored varies from 10.98 (diethylamine, ΔH = 47.7 kcal/mol, pK_a(calcd) = 11.01) to −12.4 (nitrobenzene, ΔH = −6.6 kcal/mol, pK_a(calcd) = −12.1). Exceptionally large discrepancies, particularly for saturated ketones, are unexplained, but the errors may be in the literature values. Measurements by a third independent technique are required to resolve the differences.

Other methods are available which also make use of thermodynamic measurements. In particular, the methods of differential enthalpy titration[2] and entropy titration[163] have been used. These thermometric titrations should have wide applicability in both aqueous and nonaqueous systems and could be especially useful when other methods prove difficult. Unfortunately Arnett and his coworkers[164] have recently shown that enthalpimetric titrations cannot be applied outside the pH range to weak bases (pK_a < 0) in aqueous sulfuric acid. Even though encouraging results were obtained in acetic acid–sulfuric acid mixtures, they considered the values obtained to be of dubious worth. These methods depend on deriving $\Delta H°$ for the ionization reaction and using this to calculate $\Delta G°$ and hence the pK_a. It was estimated that the entropy titration method gave acidity constants accurate to ±0.03 unit,[163] whereas Arnett's thermometric value for aniline[164] is quoted as 4.66 ± 0.09. If a suitable variation of this method could be developed for weak bases in strong aqueous acids, then the accuracy attainable would probably be worse than ±0.1 pH unit. An extended description is available of the apparatus and procedure necessary for the differential thermometric titration of, for example, amines with hydrochloric acid.[165]

B. Conductivity

The oldest methods for determination of acidity constants are based on measurements of conductivity. For many years the precision obtainable using the conductivity approach was unsurpassed. The uncertainties in conductivity measurements are very much less than those in the emf method.[2] However, the method is of limited applicability, and the calculations required are lengthy and tedious but fortunately amenable to computer treatment.[166] The theory of the approach is thoroughly discussed by King,[2] and details of the experimental approach are given by Albert and Serjeant.[1] Briefly, the simplest method relies on measurement of the equivalent conductance (Λ) and comparison of this with the measured or calculated limiting conductance (Λ_0). This gives the degree of ionization (α) from which the acidity constant may be calculated using the Ostwald dilution law for binary electrolytes (eq 60). The measurements are repeated at a variety of dilutions, thus giving various degrees of ionization without resort to titration. More complex equations allowing for interionic forces are available for work of the highest precision,[2] as deviations from the Ostwald dilution law are frequently encountered.[167]

$$K = \frac{\alpha^2 C}{1 - \alpha} = \frac{\Lambda^2 C}{\Lambda_0(\Lambda_0 - \Lambda)} \tag{60}$$

The method requires accurate temperature control because conductivity is sensitive to quite small temperature variations. The solvent and solute must be exceptionally pure, as small amounts of ionic impurities can render the results meaningless. The commonest impurity is dissolved carbon dioxide, whose complete exclusion is impractical. This means that the method is limited to moderately strong acids, whose ionization is not suppressed by the "carbonic acid" (pK_a = 6.5) present in solution. Accurate results are thus possible with carboxylic acids, whose pK_a's generally are less than 5, although the method is difficult to apply to the weaker second and third ionizations of polybasic acids. Variations of the technique are possible which allow its application to weak neutral acids[1] or weak bases,[13] although for these the method used is a form of conductometric titration, and the high ionic strengths involved necessitate activity corrections. Of particular interest is the use of conductivity measurements in sulfuric acid solutions, ably reviewed by Liler.[13]

C. Cryoscopic Measurements

For accurate application of the conductometric method in sulfuric acid, intimate knowledge is required of the self-ionization processes present in the solvent. The same knowledge is essential for the rarely used cryoscopic method of determination of acidity constants. Liler's review[13] covers the ground well, but freezing point depression is probably of more significance in studying complex modes of ionization than in the determination of acidity constants. The method is restricted to one temperature but has occasionally been used to confirm other measurements.[2]

D. Kinetic Methods

As many reactions involve specific catalysis by hydrogen ion or hydroxyl ion, it seems reasonable that a method should be available for acidity constant determination relating kinetic data to acidity. Such methods are available,[2,168] but the results should only be taken as an indication of the order of magnitude of the acidity constant.[11,46] Albert and Serjeant[1] go further and regard such results as being of historical interest only, as such catalytic methods have on occasion given highly erroneous results. These approaches suffer from indirectness and may be subject to large medium effects which would not be readily detected. A kinetic version of Bunnett and Olsen's linear free energy method is available[17] and gives results in agreement with those from their other method (see section IV.E) or the acidity function approach.

The correlation between kinetic and thermodynamic acidity has been mentioned in section II.E. The use of isotope exchange methods can give results that agree closely with values obtained using acidity functions. For example, base-catalyzed tritiation gives an estimate of ca. 33 for the pK_a of DMSO,[169] whereas the result from acidity function studies[54] is 32.9.

E. Distribution Methods

Solubility or distribution studies provide a variety of methods for the determination of acidity constants. The distributions measured may be between an aqueous phase and either a gas or a solid or an immiscible liquid.

The gaseous–aqueous equilibrium is applicable to volatile bases (B) and acids (HA) and is studied by measuring the vapor pressure (P) of solutions. The method assumes that Henry's law (eq 61) holds for the solute and

$$P = k[\mathrm{B}] \text{ or } k[\mathrm{HA}] \tag{61}$$

that the constant k does not change with acidity. The reasonable assumption that the ionized form BH^+ or A^- is involatile is also made. The ratio of protonated to unprotonated forms may then be determined by eq 62,

$$\frac{[\mathrm{HA}]}{[\mathrm{A^-}]} \text{ or } \frac{[\mathrm{B}]}{[\mathrm{BH^+}]} = \frac{P}{P_0 - P} \tag{62}$$

where P_0 is the vapor pressure of the solution containing no ionized solute. As with the other solubility methods, the results are not always accurate, although a reasonable value is obtained for hydrogen cyanide.[2] The method has been used to give approximate acidity constants for ammonia, boron trifluoride, and several volatile acids.[11,46] A more recent application[170] of this technique has given a value for the H_0 at half-protonation of diethyl ether of −3.53, agreeing closely with the value of −3.59 from partition measurements (see below).

A similar approach, with several refinements, can be applied to solubility studies of solids.[1,2,171] The method is laborious and inaccurate but may give results within ±0.1 unit in certain cases. The measurements must be performed in the presence of a swamping electrolyte, thus ensuring constant ionic strength and a reasonable precision. This means the values obtained bear no relation to thermodynamic values. Nevertheless, the method may be of use when other methods are inapplicable. The inaccuracies and invalid assumptions implicit in the method are discussed by Rochester.[3] King[2] gives details of a graphical method which may be applied to ampholytes ($H_2X^+ \rightleftharpoons HX \rightleftharpoons X^-$).

The problems implicit in distribution studies involving a pure solid or gaseous phase are increased when the second phase is an inert solvent. Nevertheless, the measurement of partition coefficients can give acceptable results.[2,11] The values obtained for various aliphatic ethers, although consistent with vapor pressure measurements, have been challenged by results from nonaqueous titrations and nmr studies,[138,140] and they disagree with estimates involving heats of protonation.[23] The partition coefficients are determined most conveniently by analysis of the organic layer using glc or ultraviolet spectrophotometry. It is desirable to choose a solvent which results in comparatively large, and hence easily measured, partition coefficients, although methods are available to deal with very small values.[172] The selection of solvents is complicated by the significant solubility of water in many "immiscible" solvents.[86] The method assumes that only the neutral form partitions into the organic solvent, and this assumption is invalid if there is significant miscibility between the two phases, possibly aided by the compound under study acting as a cosolvent. The pK_a may be calculated using eq 62 for the ionization ratio, where P is the measured partition coefficient and P_0 is the partition coefficient of the neutral species. Graphical methods are again available for amphoteric substances.[2]

F. Other Approaches

A variety of methods have been tried using various physical properties to determine acidity constants. These methods generally provide only crude estimates, rather than accurate pK_a's, but are useful when other methods fail. Studies of viscosity and dipole moments have been used,[46] as well as heats of mixing involving chloroform as a hydrogen-bond donor.[11] Properties such as refractive index[173] or polarographic half-wave potential[174] are amenable to treatment. The pK_a's of certain antibiotics have been estimated using the acidity dependence of R_f values from paper chromatography.[175] Acidity constants may also be obtained from the study of the effects of protonation on optical activity[2] and more recently circular dichroism.[176]

Proton affinities, measured in the gas phase, are linearly related to aqueous pK_a's in closely related groups of compounds;[177] although the absence of solvation effects can result in drastic changes in relative acidities. There is a strong case for claiming that, as solvation is complex and poorly understood, gas-phase acidities should be used as the basis for an absolute scale. The study of gas-phase acidity and basicity, still in its infancy, relies on ion cyclotron resonance spectroscopy, a technique whose applications have recently been reviewed.[178]

The variation with acidity of fluorescence and phosphorescence spectra may also be studied. The values obtained from these spectra refer to excited states rather than the usual ground state. The fluorescence spectrum provides information on the lowest excited singlet state, and phosphorescence refers to the lowest triplet state. The sites of protonation in excited states are not necessarily the same as in the ground state, which makes interpretation more difficult. Moreover, slow protonation in the excited state can introduce complications.[179] Experimental details are provided in a recent paper.[180] The theory involved has been discussed,[181] and the interpretation and significance of the results have been considered.[180,182]

Another high-energy system, which can be discussed in terms of acidity constants, is the activated transition state in various reactions. The pK_a's of such complexes are available from measurable reaction rates. The measurement and interpretation of these values have recently been reviewed.[183]

VII. Treatment and Interpretation of Acidity Constants

As the protonation equilibrium is the simplest chemical reaction that can be studied, it is not surprisingly amenable to treatment by the Hammett equation. The minimal steric requirements of the proton increase the applicability of the linear free energy treatment. Indeed Hammett used the ionization of benzoic acids in water to define his substituent constants, σ. Equation 63 relates the pK_a of a substituted compound to that of the unsubstituted parent (pK_0), and for benzoic acids in water at 25° the reaction constant $\rho = 1.00$ by definition.

$$pK_a = pK_0 - \rho\sigma \qquad (63)$$

Electron-donating groups have $\sigma < 0$ and electron acceptors have $\sigma > 0$. For protonation–deprotonation reactions $\rho > 0$, so in general an electron-withdrawing group should decrease the pK_a resulting in a stronger acid, whatever its charge type. A similar equation, the Taft equation, is available for aliphatic compounds and both equations have recently been reviewed.[184]

If a suitable series of compounds is being examined, it is well worthwhile attempting to correlate the pK_a's determined with the appropriate σ constants. The use of a minicomputer allows ready least-squares calculations of regression lines and easy estimation of the errors in the regression.[185] From the least-squares treatment the slope, $-\rho$, of the graph can be determined. The magnitude of ρ provides an index of the sensitivity of the reaction to substituent effects and can confirm conclusions on the site of protonation in the molecule.[63] Of course before such correlations can be attempted, corrections must be made to symmetrical polybasic acids or polyacid bases to allow for the effects of symmetry. If a neutral base has two equivalent basic sites, then symmetry will make the compound appear twice as strong as it should be on electronic considerations. A correction factor of log 2 subtracted from the pK_a will render the compound comparable with its unsymmetrical relatives.

The converse of the Hammett treatment also applies; thus given ρ for the group of compounds, individual pK_a's can be predicted from the acidity constant of the unsubstituted compound. The methods available for the prediction of pK_a's of organic acids[186] and bases[187] have been reviewed and used as an alternative to direct measurement on compounds whose acidity constants are normally difficult to determine.[188] The effects of structure on pK_a's have frequently been reviewed and require no further comment here.[44,69,189]

Swain and Lupton's treatment of σ constants, resulting in the identification of field and resonance components, provides a better prediction of substituent effects.[190] The separation of field, resonance, and steric effects using linear free energy relationships has been reviewed.[184b] As the number of attempted correlations of kinetic, thermodynamic, or spectral properties increases, more sets of substituent constants are developed. This unfortunate tendency is due to the simplicity of single-parameter correlations. Often the conclusions drawn are invalid,[191] and more meaningful correlations could be derived using an appropriate combination of two substituent parameters, as in eq 64.

$$\Delta pK_a = \rho_I\sigma_I + \rho_R\sigma_R \quad (64)$$

A recent paper[192] giving detailed consideration to the effect of nitrogen hybridization on basicity provides some interesting speculation on the excellent Hammett relationships found for aromatic amines. The authors suggest that the good $\sigma - pK_a$ correlations, found for both anilines and dialkylanilines, may be an accidental consequence of the approximate cancellation of equal and opposite hydrogen-bonding and hybridization effects.

Hydrogen bonding, which will vary from solvent to solvent, can have an important effect not only on the ionizing group in a molecule but also on substituent effects as well. Dippy and his coworkers[81] found significant variations in σ values from one mixed-aqueous medium to another and concluded that any compliance of results from mixed-aqueous solvents with the Hammett equation would be rare. Fortunately this is not the case.[63,68,193] Moreover, the equation has also been successfully applied to half-neutralization potentials determined in a variety of nonaqueous systems,[101] although variations in ρ values are not readily explained in these solvents. Acidity constants determined in 50% alcohol have been used to determine σ constants when the appropriate benzoic acids are too insoluble for titration in water.[194]

Occasionally, pK_a's are obtained which are considerably higher than those predicted by the linear free energy treatment. This occurs when an aromatic compound is susceptible to covalent hydration.[133,195] Hydration of a carbon–nitrogen double bond in a heteroaromatic system results in loss of aromaticity, a base-strengthening or acid-weakening effect. The result is that the measured acidity constant is an equilibrium value, intermediate between the pK_a's of the anhydrous and hydrated species. The presence of covalent hydration can be conveniently established using nmr, and a rapid reaction apparatus may be used to study the anhydrous species.[133] Of course, it is only legitimate to compare acidity constants of pure species by means of the Hammett equation.

VIII. Uses of Acidity Constants

The literature on pK_a's continues to grow, as for many compounds the acidity constant is the simplest and most easily measured parameter of chemical reactivity. Extensive compilations are available for the aqueous pK_a's of organic acids[65] and organic bases.[66] Values obtained in mixed solvents are not as well covered, although publications by Simon[70] deal adequately with acidity constants determined in 80% methyl Cellosolve. An extensive review by Brown, McDaniel, and Häfliger[189] deals systematically with the pK_a's of a large number of organic compounds, and reviews by Albert[69] concentrate on heterocyclic compounds. Albert and Serjeant[1] provide useful tables of about 400 typical acidity constants together with brief comments on some of the more interesting points. About 800 compounds have been arranged in order of their pK_a's, but without comment.[196]

Acidity constants may be measured for a variety of reasons, some of which have been briefly mentioned already. They provide for carbon acids an important contribution to the understanding of carbanion stability.[5] Similarly carbocation formation on protonation of unsaturated systems has attracted much attention.[138] Knowledge of pK_a's plays an important part in the discussion of catalytic phenomena. Their use in the development of acidity functions[3] has provided much information on activity coefficient behavior and solvation requirements. The study of acidity constants in different solvents generates a great deal of knowledge about solute–solvent interactions[6] and provides data of direct relevance to kinetic and mechanistic studies in that solvent. Most interest derives from the thermodynamic and structural implications of acidity constants. Before these are considered, a few words are necessary on the most obvious use of pK_a's, the calculation of the fraction of a compound ionized at a given pH.

A. Degree of Ionization

The pK_a of a compound once determined allows ready calculation of the percentage ionized at any given pH. The calculation is performed by rearrangement of eq 9 to give the general eq 65. For neutral bases, the fraction

$$\%\ \text{protonated} = 100/[1 + \text{antilog}\ (\text{pH} - pK_a)] \quad (65)$$

protonated is the same as the fraction ionized; for neutral acids, however, the fraction obtained is the proportion un-ionized. Albert and Serjeant[1] provide a list of results obtained by using such an equation over a pH range of pK_a ± 6 units. If an acidity function H_x is used instead of pH then a correction has to be applied to allow for the slope m of the plot of log I *vs.* $-H_x$ (see section II.D). Equation 65 must then be rewritten as eq 66. The fraction

$$\%\ \text{protonated} = 100/[1 + \text{antilog}\ (mH_x - pK_a)] \quad (66)$$

ionized once obtained is an important correction factor for many physical measurements, including ultraviolet spectra and partition coefficients. Knowledge of the strength of acid required to protonate a compound is of great importance in the investigation of the kinetics and mechanisms of organic reactions.[3,13] The fraction protonated is also of special significance in studies of the absorption, distribution, and eventual excretion of drugs.

Since most pharmacologically active substances contain acidic or basic functional groups, which are ionized to varying degrees at physiological pH's, acidity constants are of particular biological importance. Albert[197] has reviewed the influence of acidity constants on biological activity. It is not surprising, therefore, that many drugs have had their acidity constants measured.[197,198] The acidity constant of a drug can influence not only its activity directly but also its rate of absorption from, for example, the stomach with its high concentration of acid. The un-ionized form of a drug is generally more readily absorbed than its ionic form. Thus, in the stomach, drugs containing only neutral acidic groups are readily absorbed, whereas basic drugs are not appreciably absorbed until they reach the alkaline regions of the duodenum and the small intestine. Amino acids because of their zwitterionic character are ionized at all pH's so their absorption is erratic at all physiological acidities.

B. Thermodynamics of Ionization

As acidity constants are directly proportional to the free energy change of the ionization (eq 67), they can be

$$\Delta G^\circ = 2.303RTpK_a = \Delta H^\circ - T\Delta S^\circ \quad (67)$$

used as a means for thermodynamic investigation. The thermodynamics of ionization have been thoroughly and recently reviewed,[199] and there has been some discussion concerning the use of ΔG° rather than ΔH° for correlation with substituent effects.[2,199] Each thermodynamic quantity ΔX° can be broken down into internal and external (environmental) components by eq 68. In general,

$$\Delta X^\circ = \Delta X_{\text{int}} + \Delta X_{\text{env}} \quad (68)$$

ΔH_{int} is the most relevant quantity to use in correlations with substituent parameters. Fortunately, eq 69 holds sufficiently well to permit useful $pK_a - \sigma$ plots. A slightly more sophisticated version of eq 69 allows for variations in ρ values in different solvents.[199]

$$\Delta H_{\text{int}} \simeq \Delta G^\circ \tag{69}$$

Determination of pK_a's at several temperatures permits calculation of ΔG°, ΔH°, and ΔS° in good agreement with calorimetric values.[61] The difficulties have been discussed and computer methods have been given to overcome them.[200] Acidity constant determinations have been used to calculate resonance energies either directly[201] or with the help of tautomeric equilibria.[202] They have also been used to test theoretical treatments of σ constants.[203]

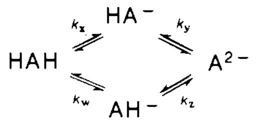
C. Structural Implications

Early interest in acidity constants was prompted by the help they gave in the determination of the structures of novel compounds by identification of the nature of any ionizing groups in the molecule. Modern spectroscopic techniques have reduced, but not eliminated, the application of this approach. Good reviews on this topic are available.[44,189] These reviews also discuss the applicability of the technique to the determination of the stereochemistry of an acidic or basic molecule. Acidity constants have been used in conformational analysis,[68,204] although results in this area should be treated with caution. Recently the pK_a's of "reporter groups" have been used in the investigation of active sites in enzymes.[205]

The nature of the site of protonation can be studied, not only by determination of the absolute magnitude of the acidity constant but also by examining the variation in pK_a with composition in mixed-aqueous solvents.[68] If the acid group is neutral, then the pK_a should increase on changing from water to a suitable mixed-aqueous system, as most of these have lower dielectric constants than water. Positively charged acids exhibit a decrease in acidity constant under the same conditions. For these the change in dielectric constant is less important and is overshadowed by the increased basicity of the solvent. Thus both neutral acids and bases are stronger in water than in aqueous-alcoholic systems. Changes in an unexpected direction could, for example, be due to zwitterion formation (see section VIII.D).

D. Microconstants

So far we have mainly considered the loss or gain of a single proton. King[2] provides an excellent treatment of diprotic and polyprotic species. Having obtained the measurable "macroscopic" pK_a's by the techniques discussed, these values, whether they overlap or not, can be used to study the microscopic ionization processes.[2,44] If we consider a dibasic acid HAH, this can lose either proton to give HA^- or AH^-, both of which may lose a proton to give A^{2-}.



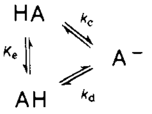
The acidity constants for each of these individual steps cannot be determined directly. The measured composite constants K_1 and K_2 (see section III.D) are related to the microscopic constants (k_w, k_x, k_y, k_z) by eq 70–72. These three equations are not sufficient to determine the four unknowns. We shall consider below how the necessary extra piece of information may be obtained. As the number of acidic protons increases, the number of microconstants rapidly expands. Thus for a triprotic acid there are in general 12 microscopic constants. Often, symmetry reduces this number to more manageable size, and citric acid, for example, has only seven such constants.

$$K_1 = k_w + k_x \tag{70}$$

$$1/K_2 = 1/k_y + 1/k_z \tag{71}$$

$$K_1K_2 = k_xk_y = k_wk_z \tag{72}$$

Similar cycles to that above may be set up for the protonation or deprotonation of tautomeric species, and again microscopic constants (k_c, k_d, K_e) are involved.



The definitions of the three constants and the measured pK_a this time provide eq 73 and 74. From these equations the useful relationship in eq 75 is readily derived for AH. This allows the correction of measured pK_a's for tautomerism, if the equilibrium constant K_e can be measured.[206] Conversely, if a good estimate of one of the microscopic acidity constants is available (*e.g.*, from the Hammett equation), then the measured pK_a can be used to determine K_e. This method is useful when $K_e > 30$ and conventional infrared and nmr techniques are not applicable.[207]

$$1/K_a = 1/k_c + 1/k_d \tag{73}$$

$$k_d = k_cK_e \tag{74}$$

$$pk_d = pK_a - \log(1 + K_e) \tag{75}$$

In general to determine microscopic constants an extra piece of information or a critical assumption is needed. The commonest approach is to remove one of the ionizing groups by, for example, esterification. The assumption is then made that the remaining ionizing group will be unchanged in its acidity constant. This approach based on the Ebert-Wegscheider hypothesis has obvious drawbacks but much early work is based on it. Refinements to the approach are possible.[208] It is sometimes feasible to measure one component of the equilibrium spectroscopically, and this simplifies matters greatly.[93] A calorimetric method is also worth mentioning.[209]

A recent paper describes two new graphical methods for the calculation of microconstants.[210] The first approach involves plotting eq 76 as a straight line of slope K_1K_2

$$([H_3O^+] + K_1) = k_w + K_1K_2(1 - \alpha)/[H_3O^+] \tag{76}$$

and intercept k_w. In this equation

$$\alpha = \frac{[AH^-] + [A^{2-}]}{[HAH] + [HA^-] + [AH^-] + [A^{2-}]}$$

The second method uses computer-based, nonlinear regression analysis, in which a theoretical curve is fitted to the titration curve. Another computer-based approach worth special mention uses the Hammett equation in one of several ways to obtain the best set of microconstants that fit the data available.[211]

The determination of microconstants allows calculation of the equilibrium constant between the two monoprotonated species[211] and is of particular application in the study of zwitterions. This phenomenon occurs when a molecule contains an acidic group strong enough to neutralize a basic group in the same molecule. The properties of zwitterions are discussed by Albert and Serjeant[1] who list the tests for zwitterionic character. Of particular benefit are studies in mixed-aqueous solvents, which reveal changes in the opposite direction to that expected, when the pK_a's are compared with those in water.

IX. Conclusions

This survey of the methods available for acidity constant determination has highlighted several features worthy of special emphasis. First of all, although there are many experimental methods available, most of these have either a limited range or a low level of accuracy. There is an urgent need for independent approaches to check, or more accurately, to arbitrate between the conflicting results that are available for compounds such as diethyl ether and acetone. New methods are also required to aid the rather doubtful extrapolations that have been made to very high pK_a values. To ensure that such methods are firmly anchored in the aqueous standard state, more careful work is required to establish the validity and applicability of acidity functions to compounds of differing structures.

On the theoretical side of the problem, a more detailed understanding is required of the nature of medium effects, not so much on spectral bands but on the ionization reaction itself. Such an understanding is essential if results referred to one standard state are ever to be other than empirically related to another standard state. Medium effects in mixed-aqueous solvents deserve special attention, as further work might well provide more refined extrapolation procedures from such solvents to aqueous pK_a values.

In the meantime we are left with a plethora of acidity scales, most of which are inadequately referred to the conventional aqueous standard state. Consequently, although relative values on such scales are meaningful in the conditions used, and may be capable of further refinement, the absolute values are almost completely without meaning and may be very misleading. The convenience of the pK_a notation will continue to ensure its survival even though it will have different meanings in different contexts. Progress toward a single comprehensive acidity constant scale will be slow, particularly as the most useful scale must be based on the aqueous standard state. It will be interesting to see how well gas-phase acidities and basicities can be moulded into an absolute scale, containing no complications due to solvation. Further work in this area is required, not so much to set up an absolute scale as to indicate more clearly the effects of solute-solvent interactions.

X. Addendum

Several important papers have appeared since the submission of this review. A convenient and rapid spectrophotometric titration method has been described, which can provide reliable results very simply although some accuracy is lost.[212] The technique is not suitable for very strong or very weak acids or bases, but should give reasonable results over most of the pH range. Values of H_A and H_0''' in aqueous perchloric acid are now available.[213] As with sulfuric acid, the various acidity functions in perchloric acid are linearly related to H_0 over a range of 8 units of H_0.

The most significant advance to be reported recently is the demonstration by Arnett and his coworkers that heats of deprotonation in DMSO correlate well with pK_a's referred to the aqueous standard state.[214] This new approach for acids directly complements their calorimetric method for bases in fluorosulfuric acid (see section VI.A). Moreover, the correlations obtained in the two methods have almost identical slopes. As the pK_a values used were derived from H_0 in acid solution, and H_- in basic solution, this correlation over nearly 50 pK_a units strongly supports the validity of the acidity function approach, as well as providing a much needed alternative approach to the determination of acidity constants.

Streitwieser and his colleagues,[215] using tritium exchange rates with lithium cyclohexylamide, have performed a short extrapolation of a Brønsted equation to give a new estimate for the pK_a of toluene. The new value of 40.9 is probably more reliable than the usually quoted figure of 35, given in the MSAD scale (see Table III). The work of Breslow and his coworkers has been reported more fully.[216] They used electrochemical reduction data to calculate "pK_a" values for compounds which are such weak acids that their ionization has not yet been detected! They suggest pK_a's for trialkylcyclopropenes which are greater than 60 (see section II.E).

The eight microscopic constants of glutathione have been directly determined by a ^{1}H nmr method.[217] The approach assumes that the changes in chemical shifts of specific protons attached to carbon are due only to the ionization of adjacent acidic groups. The method gave values in good agreement with those quoted in the literature.

XI. References and Notes

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