PHYSICAL METHODS IN HETEROCYCLIC CHEMISTRY

A Comprehensive Treatise in Five Volumes

Volume I—Nonspectroscopic Methods; Covering nonspectroscopic methods to 1962

Volume II—Spectroscopic Methods; Covering spectroscopic methods to 1962

Volumes III and IV—Covering methods other than X-ray structure analysis from 1963 to 1970

Volume V—Bond Lengths and Angles from X-Ray Crystallography; Covering X-ray structure analysis to 1970

(Volume V will include a general index to the work)

Physical Methods in

Heterocyclic Chemistry

Edited by

A. R. KATRITZKY

School of Chemical Sciences

University of East Anglia

Norwich, England

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Contributors to Volume III

Numbers in parentheses indicate the pages on which the authors' contributions begin.

ADRIEN ALBERT (1), *Department of Medical Chemistry, The John Curtin School of Medical Research, The Australian National University, Canberra, Australia*

P. ANDERSEN (27), *Chemistry Department, The University of Oslo, Oslo, Norway*

W. L. F. ARMAREGO (67), *The John Curtin School of Medical Research, Institute of Advanced Studies, The Australian National University, Canberra, Australia*

V. A. FERAPONTOV (297), *N. D. Zelinsky Institute of Organic Chemistry, U.S.S.R. Academy of Sciences, Moscow, U.S.S.R.*

YA. L. GOL'DFARB (297), *N. D. Zelinsky Institute of Organic Chemistry, U.S.S.R. Academy of Sciences, Moscow, U.S.S.R.*

O. HASSEL (27), *Chemistry Department, The University of Oslo, Oslo, Norway*

R. B. HOMER (397), *School of Chemical Sciences, University of East Anglia, Norwich, England*

G. SPITELLER (223), *Institute of Organic Chemistry, Göttingen, Germany*

F. M. STOYANOVICH (297), *N. D. Zelinsky Institute of Organic Chemistry, U.S.S.R. Academy of Sciences, Moscow, U.S.S.R.*

S. Z. TAITS (297), *N. D. Zelinsky Institute of Organic Chemistry, U.S.S.R. Academy of Sciences, Moscow, U.S.S.R.*

G. J. THOMAS, JR. (53), *Southeastern Massachusetts University, North Dartmouth, Massachusetts*

V. I. YAKERSON (297), *N. D. Zelinsky Institute of Organic Chemistry, U.S.S.R. Academy of Sciences, Moscow, U.S.S.R.*

Preface

Since the publication in 1963 of the first two volumes of this treatise, the application of physical methods to organic chemistry, and in particular to heterocyclic chemistry, has proceeded apace. The importance of physical methods to structure determination and to the understanding of inter- and intramolecular interactions has increased no less than the flood of new work. Heterocyclic chemists are thus faced with the necessity of having more to comprehend for the efficient execution of their own work.

The favorable reception given to Volumes I and II encouraged us to update the work. All the chapters comprising the first two volumes have (with two exceptions) been amended. In addition six new chapters are included covering methods which have achieved importance since 1963.

Volume III includes the chapters on ionization constants (A. Albert) and on ultraviolet spectra (W. L. F. Armarego), topics included in Volumes I and II, respectively. Volume III also covers the following new topics: gas electron diffraction (P. Andersen and O. Hassel), Raman spectroscopy (G. J. Thomas, Jr.), mass spectrometry (G. Spiteller), gas–liquid chromatography (Ya. L. Gol'dfarb *et al.*), and optical rotatory dispersion, circular dichroism, and magnetic dichroism (R. B. Homer).

Volume IV includes chapters on electric dipole moments (J. Kraft and S. Walker) and heteroaromatic reactivity (J. H. Ridd), which originally appeared in Volume I, and chapters on nuclear quadrupole resonance (E. A. C. Lucken), nuclear magnetic resonance (R. F. M. White and H. Williams), and infrared spectra (A. R. Katritzky and P. J. Taylor), which originally formed part of Volume II. Volume IV also includes one new topic: dielectric absorption (S. Walker).

Volume V is devoted to a single topic: bond lengths and angles from X-ray crystallography. This topic occupied a mere sixteen pages in Volume I; it is a measure of the immense advance that has been made in the subject that a tabulation of available molecular parameters for heterocycles fills a whole volume.

A work of this magnitude must of necessity contain many gaps and omissions. It is hoped, nevertheless, that the collection of the scattered literature references will be of considerable assistance in locating physical constants and other data.

I would like to thank the authors and Academic Press for their help and cooperation throughout the preparation of these volumes.

A. R. KATRITZKY

Preface to Volumes I and II

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

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

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

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

A. R. KATRITZKY

Contents of Other Volumes

· 1 ·

Ionization Constants

ADRIEN ALBERT

DEPARTMENT OF MEDICAL CHEMISTRY, THE JOHN CURTIN SCHOOL
OF MEDICAL RESEARCH, THE AUSTRALIAN NATIONAL UNIVERSITY,
CANBERRA, AUSTRALIA

I. INTRODUCTION, AND FURTHER OBSERVATIONS ON THE DETERMINATION OF IONIZATION CONSTANTS

A. Introduction

Since the appearance of the corresponding review[1] in Volume I, the ionization constants of a great many heterocyclic compounds have been published. It is proposed to discuss here the more unusual and interesting of these, including examples which open up a new or little explored field, also radical alterations to previous values (e.g., pyrrole). It has been thought unnecessary to list every new constant, many of which have been determined on substances differing only in some minor detail from an analog whose pK_a is well known. Many ionization constants not included here or in the previous review[1] can be located in the book "Dissociation Constants of Organic Bases in Aqueous Solution," published by the

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1. A. Albert, *in* "Physical Methods in Heterocyclic Chemistry" (A. R. Katritzky, ed.), Vol. I, p. 1. Academic Press, New York, 1963.

International Union of Pure and Applied Chemistry,[2] and in Barlin and Perrin's recent review on "Dissociation Constants in the Elucidation of Structure."[3] In *Chemical Abstracts*, the general section "Ionization, electrolytic" has been renamed "Ionization in liquids and electrolytes." A search under this general heading is often rewarding, and one can search again under particular headings such as "Acridines" and "Thiophens."

Apart from the determination of heterocyclic ionization constants, their prediction has become more reliable. The following are some uses for predicted values.

1. To decide if a substance is suitable for potentiometric titration, which is the most convenient method for determining a pK_a, but valid only if this lies between 1.25 and 11.0 (in fact the lower figure in this range cannot be less than the logarithm of the concentration, viz., 2.0 for a substance whose solubility in water is only 0.01 M).

2. As a warning to check the constitution, if the determined value differs greatly from the predicted value. The phenomenon of covalent hydration was discovered by such comparisons in the pteridine and quinazoline series.[1, p. 23]

3. To decide which new substances to synthesize when their usefulness will depend on their having certain ionization properties. Thus local anesthetics and antihistaminics are most effective if the pK_a values (basic) lie between 6 and 8.

Methods for the prediction of ionization constants are explained by Barlin and Perrin[3] and based on previous methods for bases[4] and acids.[5] Experience has shown that in uncomplicated cases it has usually been possible to predict a pK to within ± 0.2 of the value found experimentally later.[3] The foundation stone of prediction is the Hammett equation,[6]

$$\log (k/k_0) = \sigma\rho$$

where k_0 is the ionization constant for the nucleus, k the ionization constant for the substituted species, σ is the "substitutent constant" related to the substituent, and ρ is the "reaction constant" characteristic of a given series and related to the arbitrary value $\rho = 1$ for the ionization of benzoic acid and its derivatives.

The foundations of the use of this equation in heterocyclic chemistry

2. D. D. Perrin, "Dissociation Constants of Organic Bases in Aqueous Solution" (compiled for IUPAC). Butterworth, London and Washington, D. C., 1965.
3. G. B. Barlin and D. D. Perrin, *Tech. Org. Chem.* **11** (1971) (in press).
4. D. D. Perrin, *J. Chem. Soc.* p. 5590 (1965); J. Clark and D. D. Perrin, *Quart. Rev., Chem. Soc.* **18**, 295 (1964).
5. G. B. Barlin and D. D. Perrin, *Quart. Rev., Chem. Soc.* **20**, 75 (1966).
6. L. P. Hammett, "Physical Organic Chemistry." McGraw-Hill, New York, 1940.

were laid by Jaffé[7] who showed (1) that substituents in the 3- and 4-positions of pyridine have σ values approximating to those of *meta* and *para* substituents in aniline, and (2) that ring nitrogen atoms, also, behave as substituents with definite σ constants. For paraffinic heterocycles, the Taft equation is adapted similarly.

Where tautomerism occurs, values must be calculated for all the likely structures. How the α- (and γ-)hydroxyheterocycles (e.g., 4-pyridone) can be tackled is shown by Barlin and Perrin.[5]

B. The Determination of Ionization Constants

The two most used methods for the determination of pK_a values continue to be potentiometric titration and spectroscopy, detailed information on which is readily available.[8] Constants of substances for which these methods are unsuitable are now often determined by NMR spectroscopy[9] (see also Section III,C, below) or by Raman spectroscopy.[10] Comparison of τ values of a neutral species and its cations does not reliably disclose the site of protonation in a mesomeric base, if examined by proton resonance. However, ^{13}C—H satellite spectra of purine [1] showed that N-1 was the principal site of protonation, but that N-3 and N-7 also shared the first proton.[11]
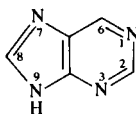
Purine

[1]

An almost bewildering variety of new apparatus is now available for measuring pH, but not all examples are suitable for determining a pK. The question remains: Can the set hold a standard buffer reading for 1 hr, to 0.01 pH unit? Certainly in this field, price is no guide to quality, except that vibrating condenser models, accurate to 0.002 pH, are bound to be expensive. Graph-drawing instruments are seldom precise enough for measurement of pK_a values. It is regrettable that some pK_a values are published without the relevant dilution being given, thus depriving the

7. H. H. Jaffé, *Chem. Rev.* **53**, 191 (1953).
8. A. Albert and E. P. Serjeant, "Ionization Constants of Acids and Bases. A Laboratory Manual." Methuen, London, 1962 (new edition in press).
9. G. C. Hood and C. A. Reilly, *J. Chem. Phys.* **32**, 127 (1960).
10. N. Deno and M. Wisotsky, *J. Amer. Chem. Soc.* **85**, 1735 (1963).
11. J. M. Read and J. H. Goldstein, *J. Amer. Chem. Soc.* **87**, 3440 (1965).

work of much of its value. Also regrettable is publication of potentiometrically determined values that transgress the limits given in (1) on p. 2 and, far from being merely inaccurate, are often the veriest nonsense. Ideally the referees should advise the authors while the paper is still in manuscript; but often the ionization constants occupy just a small proportion of an organic chemistry paper, and the referees are not always conversant with the principles of pK determination.

The advent of the computer has greatly simplified calculation of two overlapping pK_a values. In fact programs are shortly to be published for dealing with two, or more, overlapping values in a polyelectrolyte.[8] Computer programs can be applied to the results of either potentiometric or spectrometric methods.

It has become increasingly realized that the thermodynamic correction to be applied to the second ionization constant is quite large if the two constants have the same sign and are being measured potentiometrically. Lack of this correction (so easily inserted into a computer program) invalidates many a second constant in the literature.

pK_a Values below 0

Concerning the determination of the strength of very weak bases by spectrometry, the term "acidity function" of the solvent (usually moderately strong sulfuric acid) has become a wider concept than the simple (H_0) developed[12] by Hammett and Deyrup in 1932. These authors quite reasonably assumed that, in a given acidic solution, the degree of protonation would depend only on the ionization constant of the solute and its net electric charge. Contrary to these expectations, it has become clear that different structural classes of bases ionize to different degrees in any given *highly* acidic solution. Hence several different "acidity functions" exist side by side. One of the main differences in the behavior of solutes springs from the different degrees of hydrogen bonding of various cations to water, a solvent that becomes increasingly unavailable as the strength of acid is increased. Aniline-type cations form strong bonds to water in this way, whereas carbonium ions hardly do so.

For aniline-type cations, and most 6-membered heterocyclic ring cations, Hammett's H_0 is still considered valid. Carbonium ions, such as indole (see below, Section III,B), are perhaps best graded on the H_I scale[13] which gives more self-consistent results and reveals the indoles as weaker bases than they had appeared to be when the H_0 scale was used. This H_I function is similar in slope to the H_c function used for measuring the base

12. L. P. Hammett and A. J. Deyrup, *J. Amer. Chem. Soc.* **54**, 2721 (1932).
13. R. L. Hinman and J. Lang, *J. Amer. Chem. Soc.* **86**, 3796 (1964).

strength of aromatic hydrocarbons.[14] With these new acidity functions, as with the older H_0, the first aim is to find a solution of such acidity that the spectrophotometer records equal amounts of cation and neutral species for the solute. The difficulty has been only in assigning regularly graded logarithmic numbers to a series of less (and more) acidic solvents in such a way that their use constructs a sigmoid curve (as in a potentiometric titration) when plotted against the rise (and fall) in absorption of one of the species in an unchanging concentration of the solute.

Amides, also, require a special acidity function,[15] presumably because they protonate on the oxygen atom. The use of this H_A scale gives more self-consistent results and has shown amides to be weaker bases than the use of the H_0 scale had previously indicated. Not surprisingly, heterocycles which protonate on an oxygen atom require the use of the H_A function, namely, pyridine-1-oxides[16] and pyrid-2-ones.[17] Most pyrid-4-ones (unless carrying strongly electron-attracting substituents) are sufficiently strong bases to be measured by conventional methods, without recourse to acidity functions. But many α- and γ-oxoheterocycles are weaker bases than these, and have been measured on the H_0 scale. It is now evident that these published values are wrong, although not seriously so and are still exhibiting the correct ranking order.

Apart from these cases of C- and O-protonation, the H_0 acidity function continues to give satisfactory results. It has been necessary to revise[18, 19] the scale slightly, but only for values below -4 which will affect very few published heterocyclic constants.

A safeguard exists[18] for detecting "medium shifts," a frequent source of error in determinations of the strength of very weak bases by spectral means. Namely, the spectrum of the cation, as recorded at a H_0 value two units more negative than the supposed pK_a (i.e., where less than 1% of neutral species remains), should be compared with spectra found in stronger and yet stronger solutions of sulfuric acid. Ideally, these spectra should be identical, but this cannot be assumed until the test is made.

II. PARAFFINIC HETEROCYCLES

This area has not been very actively extended in the period under review. Dioxan, examined by Raman spectroscopy in aqueous solution was

14. M. T. Reagen, *J. Amer. Chem. Soc.* **91**, 5506 (1969).
15. K. Yates and J. B. Stevens, *Can. J. Chem.* **43**, 529 (1965).
16. C. D. Johnson, A. R. Katritzky, and N. Shakir, *J. Chem. Soc., B* p. 1235 (1967).
17. P. Bellingham, C. D. Johnson, and A. R. Katritzky, *J. Chem. Soc., B* p. 1226 (1967).
18. D. S. Noyce and M. J. Jorgenson, *J. Amer. Chem. Soc.* **84**, 4312 (1962).
19. C. D. Johnson, A. R. Katritzky, and S. A. Shapiro, *J. Amer. Chem. Soc.* **91**, 6654 (1969).

found[10] to have a pK_a of about -3.4, close to that of ethyl ether. A series of succinimides, most of them with an aryl group in the 3-position, have been shown[20] to be acids with pK values in the neighborhood of 8.

## III. THE HETEROAROMATICS

A. All Rings Six-Membered

The most investigated nuclei, under this heading, have been pyridine (because it is the simplest, and much else hinges on the results) and pyrimidine (because biochemists and molecular biologists are interested in the constants).

1. *Pyridines*

A representative selection of new pyridine results are set out in Table I, where they can be compared with the standard value for pyridine.[21] Perhaps the biggest change in pK_a value is that of 1-methylpyrid-4-onimine [2] (4-imino-1-methyl-1,4-dihydropyridine), which has gone up from 12.5 to ~15. The original value[22] was obtained by potentiometric titration which is now not regarded as reliable for pK_a values above 11. However, the spectrometric method was not used because the UV spectrum changes very little between pH 1 and 14, and in stronger alkali only a very small change takes place. However, an indicator method proved suitable.[23] 2,4-Dinitrodiphenylamine, which has[24] an acidic pK of 13.84, proved a suitable indicator (only the anion absorbed at 510 mμ). Addition of the pyridonimine to a mixture of the indicator and aqueous alkali *increased* the proportion of indicator anion. It was clear that the imine was a stronger base than the hydroxyl ion, and calculations pointed to 15 as an approximate pK_a. The published figures[22] for 1-methylpyrid-2-onimine (12.2) and 1-methylquinol-4-onimine (12.4), derived from potentiometric titrations, may need similar revision.
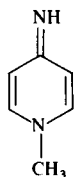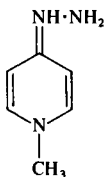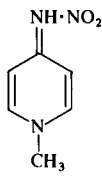
[2]   [3]   [4]

20. A. Foucard, H. Person, and M. Duclos, *Bull. Soc. Chim. Fr.* p. 2552 (1965).
21. E. Herington, *Discuss. Faraday Soc.* **9**, 26 (1950).
22. S. J. Angyal and C. L. Angyal, *J. Chem. Soc.* p. 1461 (1952).
23. B. D. Batts and E. Spinner, *Aust. J. Chem.* **22**, 2595 and 2611 (1969).
24. R. Stewart and J. P. O'Donnell, *J. Amer. Chem. Soc.* **84**, 493 (1962).

The studies of potential tautomerism in aminopyridines, reviewed by Albert,[1, pp. 31—36] have been extended to 4-hydrazino- and 4-nitroamino-pyridine.[23] Measured spectrometrically in water at 20°C, 4-hydrazino-pyridine gave pK_a values of 9.25 and 1.18 for the mono- and dication, respectively. The 1-methyl analog [3] (4-aminoimino-1-methyl-1,4-dihydro-pyridine) had a similar value for the dication (1.07) but the monocationic pK_a was much higher (~12.7) and the substance so unstable at pH 15 that the spectral readings had to be obtained in rapid-reaction apparatus. It was concluded that 4-hydrazinopyridine (in water) does not exist to any extent in an imino form analogous to [3].

4-Nitroaminopyridine, examined spectrometrically in water (20°C), gave an acidic pK_a at 6.87, and a basic value at 1.99. 4-Nitromethyl-aminopyridine, which naturally furnished no acidic group, turned out to be a much stronger base (pK_a 4.02). The 1-methyl analog [4] (1-methyl-4-nitroamino-1,4-dihydropyridine) had a basic value (1.85) very similar to that of 4-nitroaminopyridine. It was concluded that in water this latter substance existed largely in a nitrimine form analogous to [4]. This turned out to be true also for its solutions in ethanol, acetonitrile, and dimethyl-sulfoxide. In dioxan, however (aided by the low dielectric constant), it was about 94% in the nitroamino form.

Until recently, little was known of the base strength of nitropyridines. Before 1963, the pK_a of 3-nitropyridine (0.81) was the sole example, but it has now been joined by 4-nitropyridine (1.61) and mono-, di-, and tetra-alkyl derivatives of the latter.[25] Many 2- and 6-halogen derivatives of 3-nitropyridine have also been examined,[26] and display pK_a values in the −2 region (see Table I for examples of these and all other pyridines discussed here). A useful comparison of the values of 4-bromo-, 4-chloro-, and 4-iodopyridine has been made.[27] As is usual with ionization constants, varying the halogen makes only relatively small changes, iodine being the least base-weakening.

The three monovinylpyridines[28] all are weaker bases than the corresponding methylpyridines, but hardly differ from the phenylpyridines.[29]

4-Aminopyridines owe their ionic strength to extra resonance in the cation,[30] which requires that the amino group be coplanar with the ring. Substituents in the 3- and 5-positions do not depress the basic strength of 4-aminopyridine, indicating that there is no steric interference with flat-

25. J. M. Essery and K. Schofield, *J. Chem. Soc.* p. 2225 (1963).
26. J. D. Reinheimer, J. T. McFarland, R. A. Amos, J. M. Wood, M. Zahniser, and W. Bowman, *J. Org. Chem.* **34**, 2068 (1969).
27. E. Spinner, *J. Chem. Soc.* p. 3855 (1963).
28. G. Favini, *Gazz. Chim. Ital.* **93**, 635 (1963).
29. A. R. Katritzky and P. Simmons, *J. Chem. Soc.* p. 1511 (1960).
30. A. Albert, R. J. Goldacre, and J. N. Phillips, *J. Chem. Soc.* p. 2240 (1948).

ness. However, one methyl group, in the 3-position, is enough to weaken 4-dimethylaminopyridine tenfold, and increasing the steric hindrance (with two such methyl groups or an isopropyl group) decreases base strength still more.[31] Marked changes in UV spectra parallel these changes in pK_a. The ionization constants were determined at 5, 20, and 35°C, to calculate the thermodynamic quantities ΔG, ΔH, and $-T\Delta S$.[31]

Ionization constants of several aminonitro-, hydroxynitro, aminochloro-, and diaminopyridines have been determined and discussed.[32] These are substances much used in synthetic work, and it is proving useful to know their pK_a values, of which two are given in several cases (Table I).

Some selenopyridines have been compared with their sulfur and oxygen analogs; the favored tautomeric form of 2-selenopyridine has the $=Se$ form.[23]

Some pyridines with a basic side-chain nitrogen atom[34] (about pK_a 9), have been measured. They are interesting to pharmacologists because of the implied relationship to histamine (pK_a 9.80 and 5.94).

2. Some Other Families with 6-Membered (Nitrogen) Rings

Some values for quinoline and isoquinoline carboxylic acids, missing from Table IX in footnote 1, are available.[35]

An acidic pK_a for acridone (12.80) and a basic pK_a for 9-methylamino-acridine (10.43), determined[36] spectroscopically at 20°, fill significant gaps in the tables[37] of acridine ionization constants. They confirm that acridone is very much weaker as an acid than quinol-4-one (11.25), and that the weakness as a base of 9-dimethylaminoacridine (9.13) is due to prevention of coplanarity by hydrogen atoms in the 1- and 8-positions [5], somewhat similar to the case of 4-dimethylaminopyridine discussed above.
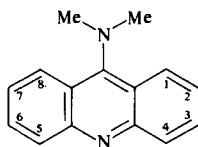
9-Dimethylaminoacridine

[5]

31. J. M. Essery and K. Schofield, *J. Chem. Soc.* p. 3939 (1961).
32. G. B. Barlin, *J. Chem. Soc.* p. 2150 (1964).
33. H. G. Mautner, S. Chu, and C. M. Lee, *J. Org. Chem.* **27**, 3671 (1962).
34. F. Holmes and F. Jones, *J. Chem. Soc.* p. 2398 (1960).
35. F. Holmes and W. Crimmin, *J. Chem. Soc.* p. 1175 (1955).
36. E. Kalatzis, *J. Chem. Soc., B* p. 96 (1969).
37. A. Albert, "The Acridines," 2nd ed. Arnold, London, 1966.

TABLE I
IONIZATION OF SUBSTITUTED PYRIDINES (IN WATER)

Pyridine	pK_a	Temp. (°C)	Method[a]	Reference
(Unsubstituted, for comparison)	5.158	25	ST	21
4-Nitro	1.61	20	ST	25
3-Nitro-2-bromo	−2.05	30	ST	26
3-Nitro-2-chloro	−2.44	30	ST	26
3-Nitro-6-bromo	−2.40	25	ST	26
3-Nitro-6-chloro	−2.85	30	ST	26
3-Nitro-6-iodo	−1.43	30	ST	26
4-Bromo	3.82	20	ST	27
4-Chloro	3.88	20	ST	27
4-Iodo	4.06	20	ST	27
2-Vinyl	(4.8)	25	S	28
3-Vinyl	(4.8)	25	S	28
4-Vinyl	(5.5)	25	S	28
2-Styryl	(5.1)	25	S	28
4-Amino	9.29	20	PT	31
4-Amino-3,5-dimethyl	9.53	20	PT	31
4-Methylamino	9.65	20	PT	31
4-Methylamino-3,5-dimethyl	9.96	20	PT	31
4-Dimethylamino	9.70	20	PT	31
4-Dimethylamino-3-methyl	8.69	20	PT	31
4-Dimethylamino-3,5-dimethyl	8.12	20	PT	31
4-Dimethylamino-3-isopropyl	8.26	20	PT	31
2-Amino-3-nitro	2.38	20	P	32
4-Amino-3-nitro	5.04	20	S	32
4-Methylamino-3-nitro	5.19	20	S	32
4-Ethoxy-3-nitro	2.67	20	S	32
2-Hydroxy-3-nitro	−4.0	20	S	32
	8.52[b]	20	S	32
4-Hydroxy-3-nitro	−0.70	20	S	32
	7.65[b]	20	S	32
5-Amino-2,4-dichloro	0.73	20	S	32
4,5-Diamino-2-chloro	4.79	20	S	32
	0.08[c]	20	S	32
2,3-Diamino-6-chloro	3.02	20	S	32
	−0.91[c]	20	S	32
2,3-Diamino	7.00	20	S	32
	−0.01[c]	20	S	32
3,4-Diamino	9.14	20	S	32
	0.49[c]	20	S	32
3-Amino-4-methylamino	9.57	20	S	32
	0.38[c]	20	S	32
4-Amino-3-methylamino	9.37	20	S	32
	0.12[c]	20	S	32

TABLE I (Continued)

Pyridine	pK_a	Temp. (°C)	Method[a]	Reference
2-Seleno	−1.00	?	S	33
	9.36[b]	?	S	33
2-Methylseleno	3.30			
2-Aminomethyl	8.62	25	P	34
	1.85[c]	20	S	34
2-β-Aminoethyl	9.52	25	P	34
	3.80[c]	25	P	34

[a] P, potentiometric; S, spectrometric; T, thermodynamic.
[b] Acidic ionization.
[c] The weaker of two basic groups.

Until 1963 there was confusion as to which cinnolines were methylated in the 1-, and which in the 2-position. Assignment of constitutions to the two methylation products of cinnolin-4-one,[38] enabled pK_a values to be determined[39] for authentic specimens of the N-1, N-2, and O-methyl derivatives of this substance and of cinnolin-4-thione.

Many ionization constants of pteridines have been published[40] since the previous list was compiled.[1] No attempt will be made to tabulate these here, because they must be interpreted in the light of the tendency of each compound to hydrate covalently, as has been done in most of the publica-

38. D. E. Ames and H. Z. Kucharska, J. Chem. Soc. p. 4924 (1963).
39. G. B. Barlin, J. Chem. Soc. p. 2260 (1965).
40. A. Albert, Y. Inoue, and D. D. Perrin, J. Chem. Soc. p. 5151 (1963); A. Albert and J. Clark, ibid. p. 1666 (1964); A. Albert and E. P. Serjeant, ibid. p. 3357; A. Albert and J. Clark, ibid. p. 27 (1965); D. J. Brown and N. Jacobsen, ibid. p. 1175; A. Albert and J. J. McCormack, ibid. p. 6930; N. Jacobsen, J. Chem. Soc., C p. 1065 (1966); A. Albert and J. J. McCormack, ibid. p. 1117; p. 63 (1968); A. Albert and H. Yamamoto, ibid. pp. 1181 and 2292; J. Clark and G. Neath, ibid. p. 1112 (1966); J. Clark, ibid. p. 1543 (1967); J. Clark and G. Neath, ibid. p. 919 (1968); J. Clark, P. N. Murdoch, and D. L. Roberts, ibid. p. 1408 (1969); J. Clark and W. Pendergast, ibid. p. 1751; J. Clark and P. N. Murdoch, ibid. p. 1882; W. Pfleiderer and R. Lohrmann, Chem. Ber. 95, 738 (1962); W. Pfleiderer, ibid. p. 749; W. Pfleiderer, E. Liedek, and M. Rukwied, ibid. pp. 755 and 1591; W. Pfleiderer and K. Deckert, ibid. p. 1597; G. Nübel and W. Pfleiderer, ibid. p. 1605; W. Pfleiderer, ibid. p. 2195; W. Pfleiderer and H. Fink, ibid. 96, pp. 2950 and 2964 (1963); D. Söll and W. Pfleiderer, ibid. p. 2977; W. Pfleiderer and F. Reisser, ibid. 99, 536 (1966); W. Pfleiderer and H. Zondler, ibid. p. 3008; W. Pfleiderer and E. Bühler, ibid. p. 3022; W. Pfleiderer, J. W. Bunting, D. D. Perrin, and G. Nübel, ibid. p. 3503; 101, 1072 (1968); D. J. Brown, B. T. England, and J. M. Lyall, J. Chem. Soc., C p. 226 (1966); D. J. Brown and N. W. Jacobsen, J. Chem. Soc. p. 3770 (1965).

tions cited. To begin with (unsubstituted) pteridine, NMR clearly showed that the cation, when freshly formed from the neutral species, instantly hydrates in the 3,4-position (kinetic equilibrium), but, after an hour had passed at room temperature, it was found to have gained two molecules of water in the 5,6- and 7,8-positions (thermodynamic equilibrium) with simultaneous loss of water from the 3,4-position.[41] Some closely related pteridines behave similarly, others quite differently; all these patterns of hydration are reflected in the ionization constants, because abolition of a double bond in a cation is a base-strengthening effect. Pteridine readily forms the anion [6] by loss of a hydrogen ion from its covalent hydrate. It has now been found that the monoanions of hydrated pteridin-2-one and pteridin-6-one can form dianions by a similar mechanism.[42]
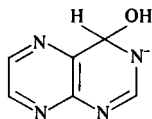
Anion of pteridine

[6]

For a review of covalent hydration, see Albert.[43] The effect is not confined to pteridines, quinazolines, and similar polyazanaphthalenes, but occurs also in 8-azapurines (see Section III,B, below), in pyrimidines carrying a potentially tautomeric and highly electron-attracting substituent (e.g., $-NO_2$, $-SO_2Me$) in the 5-position,[44] in tetrazolo[1,5-c]pyrimidine, and in nitrobenzofuroxans. In spite of these pyrimidine examples, it remains rare in single-ring substances, unless they are partly hydrogenated which is a disposing factor.

Rapid reaction apparatus (stopped flow) was used[45] to measure the ionization constants between the totally anhydrous species of the following heterocycles which have avidly hydrating cations: quinazoline, and several of its alkyl and methoxy derivatives, 1,3,5- (also 1,3,7-, 1,3,8-, and 1,4,6-) triazanaphthalene. The totally anhydrous value for quinazoline was 1.95, which may be compared with the totally hydrated value (7.77), and the intermediate (equilibrium) value obtained if rapid reaction apparatus is not used (3.51). It is revealing that those who "predict" the pK_a values of

41. A. Albert, T. J. Batterham, and J. J. McCormack, J. Chem. Soc., B p. 1105 (1966).
42. J. W. Bunting and D. D. Perrin, Aust. J. Chem. 19, 337 (1966).
43. A. Albert, Angew. Chem., Int. Ed. Engl. 6, 919 (1967).
44. D. J. Brown, P. W. Ford, and M. N. Paddon-Row, J. Chem. Soc., C p. 1452 (1968); M. E. C. Biffin, D. J. Brown, and T. C. Lee, ibid. p. 573 (1967).
45. J. W. Bunting and D. D. Perrin, J. Chem. Soc., B p. 436 (1966).

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Table II

Ionization of Substituted Pyrimidines (in Water)

</div>

Pyrimidine	pK_a	Temp. (°C)	Method[a]	Reference
(Unsubstituted, for comparison)	1.31	20	P	1, 30
	−6.3[c]	20	ST	45a
A. Pyrimidines without acidic or extra basic group				
5-Bromo-2-methoxy	−0.77	20	S	46
5-Bromo-4-methoxy	1.35	20	S	46
2-Chloro	<1	—	—	47
4,6-Dimethyl	(2.7)	—	P	47
4,6-Dimethoxy	1.49	20	S	48
2-Ethoxy	1.27	20	S	46
2-Methoxy	1.05	20	S	46
4-Methoxy	(2.5)	20	P	49
2-Methoxy-4-methyl	(2.1)	—	P	50
4-Methoxy-6-methyl	3.65	—	P	50
2-Methoxycarbonyl	−0.68	20	S	51
4-Methyl	1.98	20	P	30
5-Methylsulfinyl	0.42	20	S	53
5-Methylsulfonyl	0.97	20	S	53
2-Methylthio	0.59	20	S	52
4-Methylthio	2.48	20	P	52
B. Aminopyrimidines without acidic group				
4-Acetamido	2.76	20	S	54
2-Amino-5-bromo	1.95	20	S	55
4-Amino-5-bromo	3.97	20	S	36
4-Amino-2,6-dimethyl	6.98	20	—	56
2-Amino-4-dimethylamino	7.96	20	P	55
4-Amino-2-dimethylamino	7.64	20	P	57
4-Amino-5-formamido	4.45	20	S	54
2-Amino-4-methoxy	5.53	20	P	58
4-Amino-2-methyl	6.53	25	P	59
4-Amino-5-methylnitrosamino	3.69	20	P	60
2-Amino-4-methylthio	4.75	20	P	58
4-Amino-2-methylthio	4.91	20	P	58
4-Amino-6-methylthio	3.94	20	P	61
4-Amino-5-nitro	1.98	20	S	62
2-Benzylamino	3.56	20	P	63
5-Bromo-2-butylamino	2.21	20	S	46
5-Bromo-4·butylamino	4.49	20	S	46
5-Carbamoyl-2-methylamino	2.05	20	S	64
5-Chloro-2-methylamino	2.04	20	S	65
5-Cyano-2-methylamino	0.76	20	S	64