Stock solutions containing approximately 0.01 mole of indicator per liter of 41% ethanol–water were used to prepare a series of acidic and basic 41% ethanol–water and water solutions in which the indicator concentration was constant and approximately $1 \times 10^{-4} M$. The solvents used to prepare the indicator solutions were identical to those used in preparing the glucosylamine solutions. An additional indicator solution was prepared in which the concentration of hydrochloric acid was 1 M or greater. The indicator methyl yellow (pK_a 2.04)[9] was used in the 41% ethanol–water solutions while the indicators thymol blue (pK_a 1.52 ± 0.02), m-cresol purple (pK_a 1.59 ± .02), o-cresol red (pK_a 1.26 ± .02), or diphenylamine (pK_a 0.89 ± .02),[10] were used in the water solutions.

Acknowledgment.—The support of this work by a research grant no. E-3095 from the National Institute of Allergy and Infectious Diseases, Public Health Service, and a grant from the American Cancer Society, Minnesota Section, is gratefully acknowledged. We also wish to thank Professors Fred Smith and Maurice Kreevoy of the University of Minnesota for helpful suggestions regarding this work.

[9] From a large scale plot of values given by B. Gutbezahl and E. Grunwald, *J. Am. Chem. Soc.*, **75**, 559 (1953).

[10] These pK_a values were determined in our laboratories by the spectrophotometric method described by L. A. Fexser, L. P. Hammett, and A. Dingwall, *J. Am. Chem. Soc.*, **57**, 2103 (1935). Values previously reported are: thymol blue, pK_a 1.5 [W. C. Holmes and E. F. Snyder, *ibid.*, **47**, 221 (1925)]; m-cresol purple, pK_a 1.57 [B. Cohen, *Public Health Rept.* (U. S.), **32**, 3051 (1927)] and diphenylamine, pK_a 0.85 [N. F. Hall, *J. Am. Chem. Soc.*, **52**, 5124 (1930)].

Acid-Dissociations of 2-Hydroxypyridinium Ion

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Received February 4, 1963

During a discussion of Swain's evidence for polyfunctional catalysis, we became concerned about the difference in the order of acid-dissociation constants of 2-hydroxypyridine, implied by the presentation of the data,[1] and that inferred in an earlier paper[2] from data on pyridoxine (a 3-hydroxypyridine derivative).[3] A literature survey revealed that, in spite of extensive investigation by a number of authors, confusion about the correct assignments of pK_a' values for 2-hydroxypyridinium ion exists. The pK_b' values of 2-pyridone and its N-alkyl and O-alkyl derivatives are sometimes grouped together for comparison with no indication given that different functional groups are involved,[4] and some authors who seem to assign the lower pK_a' to O–H in one paper, or even in one section of a paper,[5] confuse the issue considerably by apparently attributing the higher pK_a' to O–H in a later paper or section.[6] Whereas controversy over the best structural representation for the neutral molecules is well resolved, the assignment of pK_a' values on the basis of quantitative data remains indefinite. Accordingly, we undertook a study of this system, confirming much of the published spectral data as well as obtaining some new data, and made a firm interpretation which is presented here.

Assignment of pK_a' Values.—The ultraviolet spectrum of 2-hydroxypyridine (2-pyridone),[7,8] like that of phenol, 3-hydroxypyridine,[2] and substituted 3-hydroxypyridines,[9,10] shows a single well resolved maximum in acid solution which is replaced by two maxima, one at a higher and the other at a lower wave length, in alkaline solution. The studies on 3-hydroxypyridine and its derivatives have established that the change in spectrum is almost entirely attributable to the phenol-to-phenolate transformation occurring as the pH is raised. The disappearance of the single "acid band" and the appearance of the two "alkaline bands" coincides with the change in the relative proportions of undissociated and dissociated groups as the pH approaches and passes the pK_a' for the phenolic hydroxyl. When neutral solutions of 2-hydroxypyridine, pyridoxine, and pyridoxine derivatives are made sufficiently basic to exceed the second pK_a' of the solute, the positions of the two bands shift slightly, but the spectra are essentially unchanged. Even benzene and cyclohexane solutions of 2-hydroxypyridine show similar spectra: one band in acidic solution, and two in neutral and basic solutions.[6,8,11,12]

The great similarity of these spectral data strongly suggests similar structural changes accompanying pH changes. There can be no doubt about the site of proton loss in phenol, and the assignment of the lower pK_a' to the O–H group in pyridoxine and its derivatives has not been disputed. The spectral changes for 2 hydroxypyridine solutions are essentially the same, and the situation (unlike that for 3-hydroxypyridine) is simplified by the absence of any detectible tautomeric equilibrium in neutral solution (99% amide form[13,14]).

The methiodides of both 2- and 3-hydroxypyridine exhibit a single pK_a' (<1.0 as estimated potentiometrically for N-methyl-2-hydroxypyridinium iodide[8] and 0.32 as measured spectrophotometrically for N-methyl-2-pyridone[5]; 4.96 for N-methyl-3-hydroxypyridinium iodide[14]). For the 3-hydroxy methiodide, a pK_a' of 4.96 establishes the enhanced acidic character of the phenolic O–H group when the ring can exist only in the

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[1] C. G. Swain and J. F. Brown, Jr., *J. Am. Chem. Soc.*, **74**, 2534 (1952). The apparent assignment of acid-dissociation constants does not affect the authors' main conclusions regarding the significant polyfunctional catalysis by 2-hydroxypyridine.

[2] S. A. Harris, T. J. Webb, and K. Folkers, *J. Am. Chem. Soc.*, **62**, 3198 (1940).

[3] Although no species properly described as 2-hydroxypyridine actually exists in any significant amount in solid or solution, the name is nonetheless a convenient one, especially when comparisons of several hydroxypyridines or -quinolines are being made. The name 2-pyridone (or α-pyridone) is probably better otherwise.

[4] M. I. Kabachnik, S. T. Ioffe, and Yu. N. Sheinker, *J. Gen. Chem. USSR*, **26**, 2257 (1956).

[5] A. Albert and J. N. Phillips, *J. Chem. Soc.*, 1294 (1956).

[6] A. Albert, *ibid.*, 1020 (1960).

[7] H. Specker and H. Gawrosch, *Ber.*, **75**, 1338 (1942).

[8] This research.

[9] V. R. Williams and J. B. Neilands, *Arch. Biochem. Biophys.*, **53**, 56 (1954).

[10] D. Metzler and E. E. Snell, *J. Am. Chem. Soc.*, **77**, 2341 (1955).

[11] S. F. Mason, *J. Chem. Soc.*, 5010 (1957).

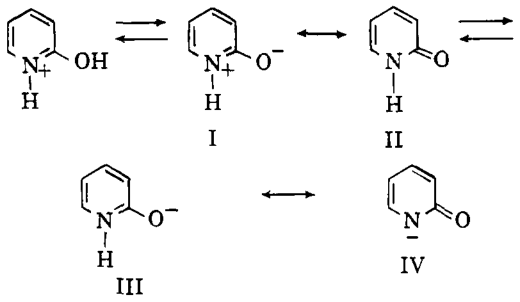
[12] Related data are obtained with 3-aminopyridine. In very strongly acidic solutions in which the solute exists as a dication, the single absorption maximum is near 260 mμ, and the spectrum is essentially that of pyridinium hydrochloride. The monocation, identified as 3-aminopyridinium ion, and the neutral molecule both display two maxima.[6]

[13] J. A. Berson, *J. Am. Chem. Soc.*, **75**, 3521 (1953).

[14] A. Albert, "Heterocyclic Chemistry," Essential Books, Fair Lawn, N. J., 1959, pp. 43–62.

pyridinium form. The same conclusion follows for the 2-hydroxy methiodide.[15]

The various species under discussion are shown in the following equations.



The anion existing high at pH is considered to be III[14] (with some contribution from IV). If one accepts the evidence that the neutral species must be a hybrid principally of I and II, and that the anion is III ⟷ IV, the assignment of the higher pK_a' to the N–H group follows inescapably.

It is our conviction that these data provide compelling evidence for a firm assignment: the lower pK_a' (0.75[5]) of 2-hydroxypyridine is for the dissociation of the O–H group, the higher pK_a' (11.6[5]) is for dissociation of the N–H group. Even though the compound, 2-hydroxypyridine, is a weaker acid than phenol and a weaker base than pyridine,[1] the O–H group in its conjugate acid is far more strongly acidic than is the O–H group in phenol, and the tertiary N is more strongly basic than that in pyridine.

Structure of the Neutral Molecule.—In spite of the ambiguity about the assignment of pK_a' values for 2-hydroxypyridinium ion, no authors have contended recently that the neutral species in water solution is the enol (lactim), 2-hydroxypyridine. Even though one early paper favored a zwitterion or betaine (I) formulation for the molecule on the basis of molar refractivity measurements,[16] the amide (lactam) formulation (II) has received major emphasis in recent years.[14,15b] These two formulas are canonical structures contributing to a resonance hybrid. The same data cited for pK_a' assignments strongly indicate that the contributions from the zwitterion structure are no less important than those from the amide. No lactam structure can be written for the neutral species 3-hydroxypyridine; only the zwitterion and the uncharged enol are reasonable formulations. Yet the ultraviolet spectral changes accompanying deprotonation of 3-hydroxypyridinium and 2-hydroxypyridinium ions are parallel. Even when the neutral uncharged species of 3-hydroxypyridine, which is spectrally distinguishable from its tautomeric zwitterion, is converted to the corresponding anion (an O–H to O$^-$ transformation), the single band at 277 mμ disappears and two alkaline bands remain. With pyridoxine, which, like 2-hydroxypyridine, does not give rise to significant amounts of hydroxy compound in neutral aqueous solution, only the zwitterion need be considered, and the assignment of pK_a' values with corresponding spectral changes is exactly analogous to the assignment we have made for 2-hydroxypyridine.

The infrared spectrum of aqueous solutions of 2-hydroxypyridine does show absorption bands near 1650–1600 cm.$^{-1}$, attributed to carbonyl absorption,[17,18] which are absent in the spectrum of 3-hydroxypyridine solutions[17]; both show absorption bands in the region attributed to amino acid zwitterions.[18] Infrared spectra of benzene solutions[8] of these compounds are very similar to those of aqueous solutions, just as the ultraviolet spectra are, and the nature of the solute in the two solvents is probably constant. X-ray crystallographic measurements on solid 2-hydroxypyridine have been interpreted as evidence that the isomeric zwitterionic structures make a major contribution (about 50%) to the actual structure of the compound.[19]

In view of these facts, the zwitterion formulation seems at least as adequate a structural representation of 2-hydroxypyridine as is the amide formulation. Some resonance stabilization must prevail with 2- and 4-hydroxypyridines,[15b] however, since the order of pK_a' values for the 2-, 3-, and 4- hydroxypyridines (as well as the hydroxyquinolines)[5] is not that of a simple inductive effect operating through different distances. However, assumptions involved in calculating the individual pK_a' values for both neutral species of 3-hydroxypyridine,[10] while entirely reasonable, may result in masking an actual inductive order.

Experimental

Ultraviolet spectra were obtained with a Beckman DK-1 spectrophotometer; in one case when benzene absorption interfered appreciably with spectral measurements on the solute, a Cary Model 14 spectrophotometer was used. Infrared spectra were obtained with a Perkin-Elmer Model 21 spectrophotometer. Melting points were determined in a Thomas–Hoover apparatus and are uncorrected. A Beckman pH meter and standard buffer solutions were used for pH measurements.

2-Hydroxypyridine was obtained as white crystals, m.p. 105.5–106.5°, by vacuum sublimation of a commercial sample (K and K Laboratories, Inc.). A benzene solution showed sharp, intense absorption bands at 1616, 1656, and 1678 cm.$^{-1}$, but none near 3400–3600 cm.$^{-1}$ (O–H absorption, phenol absorption usually strong).

N-Methyl-2-hydroxypyridinium iodide, m.p. 120.6–121.7°, was prepared by treatment of 2-hydroxypyridine with excess methyl iodide in benzene solution.[2]

Ultraviolet Absorption Data.—The λ_{max} in mμ (and $\epsilon \times 10^{-3}$) are given for aqueous solutions of 2-hydroxypyridine: in 1 *M* hydrochloric acid, 278 (6.58); at pH 6, 294 (5.90) and 224 (7.72); in 0.2 *M* sodium hydroxide solution, 294 (4.91) and 228 (9.91).

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(15) Protonation of 2-pyridone on N rather than on O was inferred from infrared and Raman data [(a) E. Spinner, *J. Chem. Soc.*, 1226 (1960)], but recent n.m.r. data have been interpreted to indicate only O-protonation of both 2- and 4-pyridone [(b) A. R. Katritzky, *Record Chem. Progr.* (Kresge-Hooker Sci. Lib.), **23**, 232 (1962)]. Ultraviolet data strongly disfavor an N-protonated structure. Ultraviolet spectra of 2-methoxypyridinium ion and 2-hydroxypyridinium ion in 1 *M* hydrochloric acid are nearly identical with one principal maximum at 278 mμ in both cases[8]; on the other hand, when the oxygen atom is clearly =O or —O$^-$, *e.g.*, 2-pyridone in ethanol or sodium ethoxide solution or *N*-methyl-2-pyridone in ethanol, the two alkaline bands (maxima at 297 and 227 mμ) are obtained.[7]

(16) F. Arndt, *Ber.*, **63**, 587, 2963 (1930).

(17) A. Albert and E. Spinner, *J. Chem. Soc.*, 1221 (1960).

(18) R. N. Jones and C. Sandorfy, "Technique of Organic Chemistry," Vol. 9, A. Weissberger, Ed., Interscience Publishers, Inc., New York, N. Y., 1956, pp. 520–523.

(19) B. R. Penfold, *Acta Cryst.*, **6**, 591 (1953).