Advances in Heterocyclic Chemistry

By A. R. KATRITZKY

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HETEROCYCLIC CHEMISTRY

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I. Introduction

The addition of water across carbon–carbon double bonds, a reaction thoroughly investigated by Lucas[1] and Taft,[2] requires strong activation and is catalyzed by hydrogen ions and hydroxyl ions. Addition of water across the C=O bond of aldehydes has also been studied kinetically.[3] Whereas chloral and formaldehyde are largely hydrated (at equilibrium in dilute aqueous solution), acetaldehyde and other

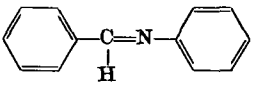
[1] H. J. Lucas, W. T. Stewart, and D. Pressman, *J. Am. Chem. Soc.* **66**, 1818 (1944).

[2] R. W. Taft, *J. Am. Chem. Soc.* **74**, 5372 (1952).

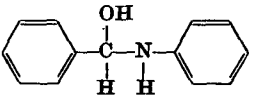
[3] R. P. Bell and B. deB. Darwent, *Trans. Faraday Soc.* **46**, 34 (1950).

saturated aliphatic aldehydes are only about 50% hydrated under these conditions. The hydration reaction, which gives 1,1-glycols, is catalyzed in both directions by hydrogen ions and hydroxyl ions [4] and requires little activation.

No comparable study of the hydration of the C=N bond has been made although its properties lie between those of the C=C and C=O bonds. The hydration of Schiff bases, such as benzylideneaniline (**1**), to cations of Dimroth bases, such as **2**, is well-known, but attempts to follow this reaction kinetically have been frustrated by the ready breakdown of the neutral species, e.g. **2**, to benzaldehyde and aniline. About ten years ago, workers in this Department were surprised to find the C=N bond in many pteridines is capable of hydration, analogous to the reaction **1** ⇌ **2**. The surprise stemmed principally



[1]



[2]

from the apparent loss of aromaticity upon hydration. What is still more surprising is that hydration of the C=N bond in nitrogen-containing heterocyclic compounds is not, as a rule, followed by fission of the C—N bond. These properties and their probable causes are discussed in this review.

The phenomenon of C=N hydration in pteridines was first observed in this Department in 1951,[5] although the correct interpretation was arrived at slowly.[6, 7] The first example was discovered as a result of the very curious behavior of 6-hydroxypteridine during titration.[5] With alkali, a curve is traced corresponding to a weak acid of pK_a 9.7. But, on back-titration with acid, this curve is not retraced; instead, a new curve appears corresponding to a much stronger acid of pK_a 6.7. It has been demonstrated [5, 8] that ring-opening does not take place and that the change is not tautomeric. In 1955, it was recognized that 6-hydroxypteridine is covalently hydrated in water, whereas its anion

[4] C. K. Ingold, "Structure and Mechanism in Organic Chemistry," p. 689. Bell, London 1953.

[5] A. Albert, D. J. Brown, and G. Cheeseman, *J. Chem. Soc.* 1620 (1952).

[6] A. Albert, *J. Chem. Soc.* 2690 (1955).

[7] D. J. Brown and S. F. Mason, *J. Chem. Soc.* 3443 (1956).

[8] A. Albert, *in* "The Chemistry and Biology of Pteridines" (G. E. W. Wolstenholme and M. P. Cameron, eds.), p. 204. Churchill, London, 1954.

is most stable in the anhydrous form.[6] The hydrated neutral species is a weaker acid than the anhydrous species, hence the hysteresis loop shown in Fig. 1.

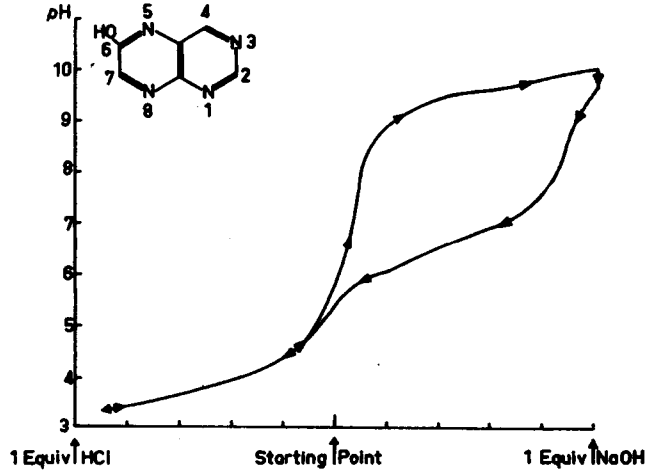
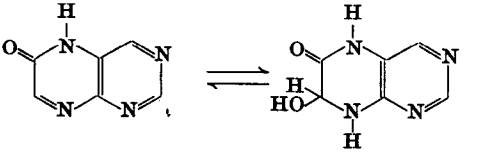


FIG. 1. Hysteresis loop produced when 6-hydroxypteridine is titrated with acid and alkali.

The water molecule was found to add across the 7,8-positions in 6-hydroxypteridine by Brown and Mason.[7] These authors showed that the neutral species of 6-hydroxypteridine exists mainly as 6,7-dihydroxy-7,8-dihydropteridine (**4**) in equilibrium with a little of **3**. The stable cation is largely derived from **4** and the stable anion largely from **3**.



[3] [4]

Following these discoveries, we have made an extensive experimental study of covalent hydration and find it is very common, not only in the pteridine series but also in several simpler families of polyazanaphthalenes.[9] The methods used to diagnose this phenomenon, its

[9] A. Albert, *in* "Pteridine Chemistry" (W. Pfleiderer and E. C. Taylor, eds.), p. 111. Pergamon Press, Oxford, 1964.

occurrence in the various heterocyclic families, factors in the stabilization of the covalent hydrates, ring-opening, and the chemical and biological implications are discussed in this review. Quantitative aspects are thoroughly covered by Dr. D. D. Perrin in the following review.[10] Where we have introduced a quantitative technique, it has been at Dr. Perrin's suggestion. Whenever the word "hydrate" is used in this review, it refers to water bound covalently as in **4**.

II. Diagnosis and Location of Covalent Hydration

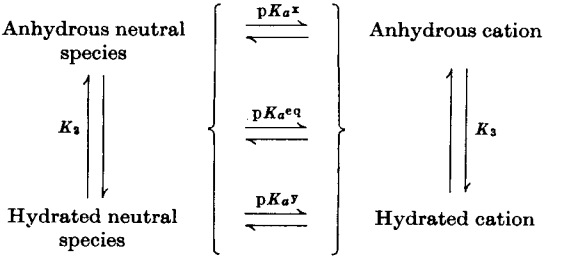
The choice of methods to diagnose covalent hydration in nitrogen-containing heteroaromatic compounds depends largely on the ratio of hydrated to anhydrous species at equilibrium in the cation, neutral species, or anion. This potentially complex situation is simplified in most cases because in one of two ionic species (e.g. cation and neutral species) the percentage of hydrate is usually comparatively small. Small as this percentage may be, it is never insignificant, because if marked hydration can be demonstrated in one ionic species, the equilibria involved (see equilibrium diagram in Section II, A) necessitate the presence of at least a trace of hydrate in the second ionic species. These minute percentages of hydrates influence the values of the equilibrium constants. For this reason the term "anhydrous" cannot be used in place of "predominantly anhydrous" when referring to a mixture containing $< 0.1\%$ of the hydrated species. The same argument pertains to the hydrated species, which must be in equilibrium with at least a very small amount of anhydrous species.

The following methods have been used to demonstrate a substantial degree of covalent hydration in the various ionic species. Usually, at least three of these methods have had to be applied before the phenomenon could be established beyond all doubt. Before enumerating these, it should be made clear that the presence or absence of strongly held water of crystallization is to be regarded as a competitive phenomenon which makes no contribution to a diagnosis of covalent hydration. Thus, 4,7-dihydroxy-6-methylpteridine, 2-hydroxypurine, and 4,5-diamino-2-hydroxypyrimidine all retain one molecule of water obstinately at 130° but give no indications of covalent hydration in any of the following tests. On the other hand, pteridine, which the tests show to be covalently hydrated to the extent of $\sim 22\%$ in solution, reveals no hydration upon elementary analysis after gentle drying at 20°.

[10] D. D. Perrin, following review, p. 43.

A. Anomalous Ionization Constants

It is a simple matter to determine an ionization constant and also to predict its magnitude.[11] When these values do not agree, and if ring-opening has been carefully excluded, the likelihood of covalent hydration must be considered. Equilibria encountered during the determination of the ionization constant of a hydrating heteroaromatic base are shown in the following diagram. Similar equilibria exist for



Equilibrium Diagram[11a]

hydrating bases which have an acid function, e.g. the hydroxypteridines. K_a^x and K_a^y are the *ionization* equilibrium constants for the anhydrous and the hydrated species, respectively, and should be experimentally realizable if measurements could be made much more rapidly than the time required to record significant hydration and dehydration. (Where more than one basic center is present, these experimentally determined pK values might, theoretically, be capable of further analysis into so-called "microscopic" pK values.) K_2 and K_3 are *hydration* equilibrium constants[10] which include the rates of hydration and dehydration of the neutral species and cation, respectively. If the equilibria K_2 and K_3 are set up rapidly (e.g. quinazoline) then the pK_a value obtained in a routine potentiometric or spectrometric determination is an overall value (denoted as pK_a^{eq}) which includes not only the hydration equilibria K_2 and K_3 but also the ionization constant of the anhydrous and hydrated species.

On the other hand, if the equilibria for K_2 and K_3 are attained slowly (see Fig. 1) and the optical density or pH readings are measured rapidly, either the pK_a^x or pK_a^y value can be obtained directly,

[11] A. Albert and E. P. Serjeant, "Ionization Constants of Acids and Bases." Methuen, London, 1962.

[11a] The ratios K_2 and K_3 are defined here so as to conform with the following review by Dr. D. D. Perrin.

depending on whether one starts from the predominantly anhydrous neutral species or the predominantly hydrated cation (or anion). However, if the solutions are allowed to come to equilibrium before each reading, only the pK_a^{eq} value can be obtained.

The pK_a^{eq} value always lies between the pK_a^x and pK_a^y values. Because aromatic or partly aromatic heterocyclic species, e.g. **3** (the concentrations of which are included in the pK_a^x expression), are weaker bases than the corresponding carbinolamines, e.g. **4** (the concentrations of which are involved in the pK_a^y expression), it follows that $pK_a^x < pK_a^y$. Because the anhydrous species is aromatic (or partly aromatic, if some of the conjugation may be in a —CO.NH— group) the basic pK_a^{eq} value is always higher than that which would be predicted for the aromatic system, and the substance behaves as if it were a stronger base than expected (e.g. quinazoline[12]: found, 3.51; expected, ~ 1.5). Hydration should always be suspected when potentiometric readings, made during determinations of pK values, show a drift. The hydration–dehydration process is acid and base catalyzed,[10] so if hydration is occurring, steady readings should be obtained progressively more rapidly as the hydrogen ion or hydroxyl ion concentration is increased. It must, however, be noted that reversible ring-opening after addition of water could show similar behavior, and other methods, described below, must be applied before hydration can be confirmed.

The constants pK_a^x, pK_a^{eq}, and pK_a^y are related in the following manner[10]:

$$K_2 = K_a^y(K_a^x - K_a^{eq})/K_a^x(K_a^{eq} - K_a^y),$$

$$K_3 = (K_a^x - K_a^{eq})/(K_a^{eq} - K_a^y),$$

where K_2 = (concentration of hydrated neutral species)/(concentration of anhydrous neutral species) and K_3 = [concentration of hydrated cation (or anion)]/[concentration of anhydrous cation (or anion)] at equilibrium. It is evident that K_2 and K_3 are independent of pH and dependent only on the three ionization constants. When base strengths are to be compared, only pK_a^x or pK_a^y values can be legitimately used, because only they are confined to pure species. If pK_a^{eq} values are compared, the results have no significance because K_2 and K_3 vary from one substance to another.

The above relationships can be used to calculate some of the con-

[12] A. Albert, W. L. F. Armarego, and E. Spinner, *J. Chem. Soc.* 2689 (1961).

stants which cannot be obtained by direct measurement, e.g. accurate values of K_2 or K_3.

It is presumptuous to report that a substance is not hydrated simply because there are no drifts in the readings obtained during potentiometric measurements or because the experimentally determined pK_a value is not very different from the predicted value. A small amount of hydration may cause only a small difference in the ionization constant and hence other tests should be applied. A number of heterocyclic compounds which have seemingly normal pK_a values may well be partially hydrated.

B. Electronic (Ultraviolet and Visible) Absorption Spectra

Addition of water across a C=N bond in a conjugated system breaks the conjugation and alters the electronic transitions. The ultraviolet and visible spectra of anhydrous and hydrated species are therefore usually dissimilar, and such differences have been used as the basis for much of the qualitative and quantitative work done on covalent hydration.

1. Spectra in Hydrocarbons and Dilute Aqueous Solutions

The spectra of an organic compound in various solvents differ only in small detail so long as no serious interaction takes place between solute and solvent. Thus the spectrum of a substance in an aprotic solvent (e.g. cyclohexane) should be almost the same as that in water. When addition of water occurs across a C=N bond, the spectrum of the hydrate in water can be vastly different from the spectrum of the anhydrous substance in cyclohexane, and this test has been used on several occasions[12–16] to determine whether or not a neutral species forms a hydrate in water. The test, however, is not valid if (*a*) the solute possesses the elements of water in the crystalline state, (*b*) the amount of hydrated species in aqueous solution is too small to cause any noticeable differences in the spectra,[13] or (*c*) the principal pathway of electronic transition in the molecule involves no affected bond.

Protonation of heteroaromatic compounds is known to produce only small shifts ($\pm$ 5 mμ) of the long-wave length band present in the case

[13] W. L. F. Armarego, *J. Chem. Soc.* 561 (1962).
[14] W. L. F. Armarego, *J. Chem. Soc.* 4094 (1962).
[15] W. L. F. Armarego, *J. Chem. Soc.* 4303 (1963).
[16] W. L. F. Armarego, *J. Chem. Soc.* 5030 (1962).

of the neutral species. On the other hand, if the cation is much more hydrated than the neutral species, these shifts (which may be hypsochromic or bathochromic) are normally larger than can be accounted

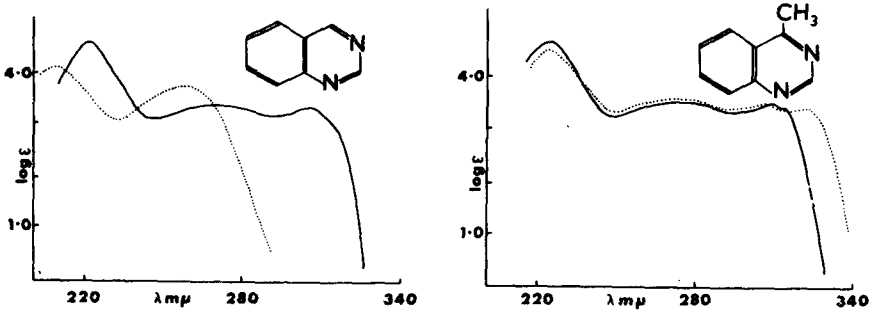


FIG. 2. (A) Ultraviolet spectra of quinazoline in water. Solid line, neutral species; dotted line, cation. (B) Ultraviolet spectra of 4-methylquinazoline in water. Solid line, neutral species; dotted line, cation.

for by protonation alone. Quinazoline, for example, shows a hypsochromic shift of 45 mμ [12] (see Fig. 2A), whereas 1,4,5,8-tetraazanaphthalene shows a bathochromic shift of 20 mμ (see Fig. 3).[15] For a few substances, e.g. pteridine and the *Bz*-nitroquinazolines, however,

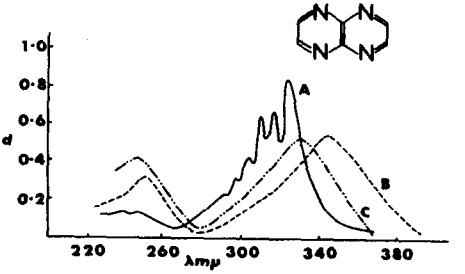


FIG. 3. Ultraviolet spectra of 1,4,5,8-tetraazanaphthalene in water. (A) Anhydrous neutral species, (B) hydrated cation, and (C) hydrated neutral species.

these spectral differences between the anhydrous and hydrated species are small. Similarly, for compounds with an acidic function and where the anions are predominantly anhydrous and the neutral molecules strongly hydrated, e.g. 2- and 6-hydroxypteridine,[7] large spectral differences between the anion and the neutral species are readily