

# Advances in Heterocyclic Chemistry

By A. R. KATRITZKY

Volume 4

Advances in  
HETEROCYCLIC  
CHEMISTRY

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## Preface

Four of the chapters in this the fourth volume of *Advances in Heterocyclic Chemistry* deal with topics which have never been reviewed before. The first simple isothiazole was studied by Dr. R. Slack in 1956, and he and Dr. K. R. H. Wooldridge review in their article the considerable progress which has been made since then. Similarly the discovery of the widespread occurrence of covalent hydration has been achieved by the Canberra School, and we now have authoritative reviews on the qualitative (Drs. A. Albert and W. L. F. Armarego) and quantitative (Dr. D. D. Perrin) aspects of covalent hydration. Following the realization of the importance of aryne intermediates in benzenoid chemistry, work has been done on hetarynes, and this field is now reviewed by Professor H. J. den Hertog and Dr. H. C. van der Plas who have themselves contributed much to this subject. The volume also includes a review of oxazolone chemistry by Dr. R. Filler and a survey of the reactions of azines with nucleophiles by Drs. R. G. Shepherd and J. L. Fedrick which complements the previous review by Professor Illuminati in Volume 3 of this series. The last chapter forms a very significant contribution to heterocyclic chemistry in correlating an enormous amount of data, scattered throughout the literature, on this important subject.

Suggestions for contributions to subsequent volumes of the series are welcomed; they should be submitted in the form of a short synopsis.

Thanks are due to the authors for their cooperation, the members of the Editorial Board, and the publishers. I am especially grateful to the assistant editors, Dr. A. J. Boulton and Dr. J. M. Lagowski, for all their help.

A. R. KATRITZKY

Norwich, England  
March, 1965

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# Covalent Hydration in Nitrogen-Containing Heteroaromatic Compounds: I. Qualitative Aspects

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## I. Introduction

The addition of water across carbon-carbon double bonds, a reaction thoroughly investigated by Lucas<sup>1</sup> and Taft,<sup>2</sup> 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.<sup>3</sup> Whereas chloral and formaldehyde are largely hydrated (at equilibrium in dilute aqueous solution), acetaldehyde and other

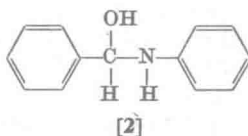
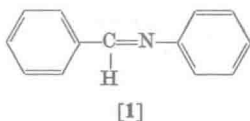
<sup>1</sup> H. J. Lucas, W. T. Stewart, and D. Pressman, *J. Am. Chem. Soc.* **66**, 1818 (1944).

<sup>2</sup> R. W. Taft, *J. Am. Chem. Soc.* **74**, 5372 (1952).

<sup>3</sup> 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<sup>4</sup> 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  $1 \rightleftharpoons 2$ . The surprise stemmed principally



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,<sup>5</sup> although the correct interpretation was arrived at slowly.<sup>6, 7</sup> The first example was discovered as a result of the very curious behavior of 6-hydroxypteridine during titration.<sup>5</sup> 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<sup>5, 8</sup> 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

<sup>4</sup> C. K. Ingold, "Structure and Mechanism in Organic Chemistry," p. 689. Bell, London 1953.

<sup>5</sup> A. Albert, D. J. Brown, and G. Cheeseman, *J. Chem. Soc.* 1620 (1952).

<sup>6</sup> A. Albert, *J. Chem. Soc.* 2690 (1955).

<sup>7</sup> D. J. Brown and S. F. Mason, *J. Chem. Soc.* 3443 (1956).

<sup>8</sup> 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.<sup>6</sup> The hydrated neutral species is a weaker acid than the anhydrous species, hence the hysteresis loop shown in Fig. 1.

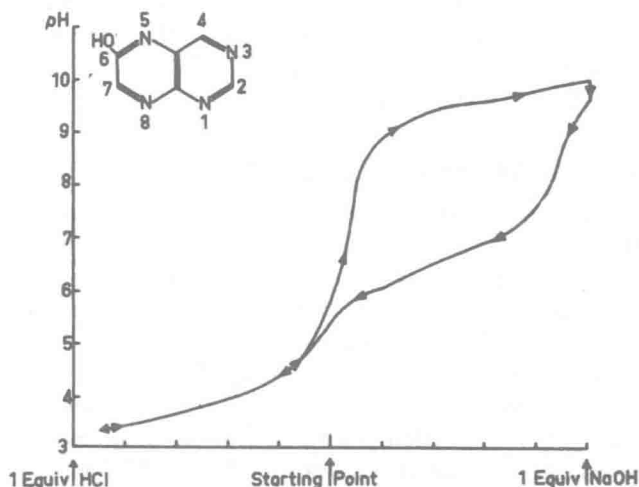
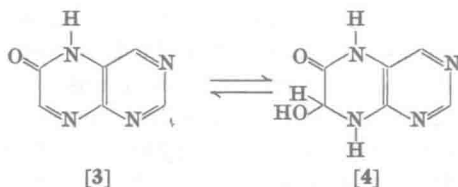


FIG. 1. Hysteresis loop produced when 6-hydroxypteridine is titrated with acid and alkali.

The water molecule was found to add across the 7,8-positions in 6-hydroxypteridine by Brown and Mason.<sup>7</sup> 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.



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 polyanaphthalenes.<sup>9</sup> The methods used to diagnose this phenomenon, its

<sup>9</sup> A. Albert, in "Pteridine Chemistry" (W. Pfeleiderer 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.<sup>10</sup> 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

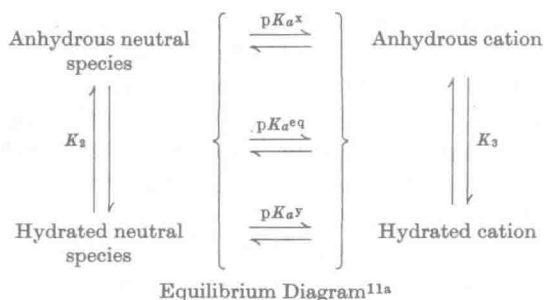
The choice of methods to diagnose covalent hydration in nitrogen-containing heteroaromatic compounds depends largely on the ratio of hydrated to anhydrous species at equilibrium in the cation, neutral species, or anion. This potentially complex situation is simplified in most cases because in one of 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 ~ 22% in solution, reveals no hydration upon elementary analysis after gentle drying at 20°.

<sup>10</sup> 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.<sup>11</sup> 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



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<sup>10</sup> 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,

<sup>11</sup> A. Albert and E. P. Serjeant, "Ionization Constants of Acids and Bases." Methuen, London, 1962.

<sup>11a</sup> 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  $-\text{CO}.\text{NH}-$  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<sup>12</sup>; found, 3.51; expected,  $\sim 1.5$ ). 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,<sup>10</sup> 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<sup>10</sup>:

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

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

where  $K_2 = (\text{concentration of hydrated neutral species}) / (\text{concentration of anhydrous neutral species})$  and  $K_3 = [\text{concentration of hydrated cation (or anion)}] / [\text{concentration of anhydrous cation (or anion)}]$  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-

<sup>12</sup> A. Albert, W. L. F. Armarego, and E. Spinner, *J. Chem. Soc.* 2689 (1961).