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INFLUENCE OF HYDRATION UPON TAUTOMERIC EQUILIBRIA

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It is now widely recognized that heteroaromatic tautomeric equilibria are sensitive to changes in solvent (1,2), and polarity is usually thought to be a determining factor (3). Although empirical solvent parameters like Kosower's Z-parameter (4) appear to be suitable in correlating experimental data (5,6), these do not provide a satisfactory interpretation of solvent effects. We now wish to report that for a set of α-hydroxy pyridines, the U.V. measured apparent tautomeric ratio, K_{ap}, is proportional to the activity of water (7), h, in water/polar aprotic solvent media (figure 1). The effect of water can therefore be interpreted as resulting from the preferential hydration of one tautomer by one water molecule

$$A, H_2O \underset{a_1}{\rightleftharpoons} A + H_2O\ , \qquad A \underset{K_T}{\rightleftharpoons} B$$

Since in polar aprotic solvents such as acetonitrile (D = 37.5), dimethyl sulfoxide (D = 46.7) and propylene carbonate (D = 64), the tautomeric equilibrium constants are usually very similar, but differ by several orders of magnitude from that in water (D = 80) (Table I),

TABLE I

Tautomeric Equilibrium Constants (lactam/lactim ratios) in Various Solvents.

Solvent	6-Chloro 2-pyridone	6-Methoxy 2-pyridone
Dimethylsulfoxide	0,031	0,081
Acetonitrile	0,065	0,23
Propylene Carbonate	0,06	0,21
Water	5,3 (ref.5)	50 (ref.8)

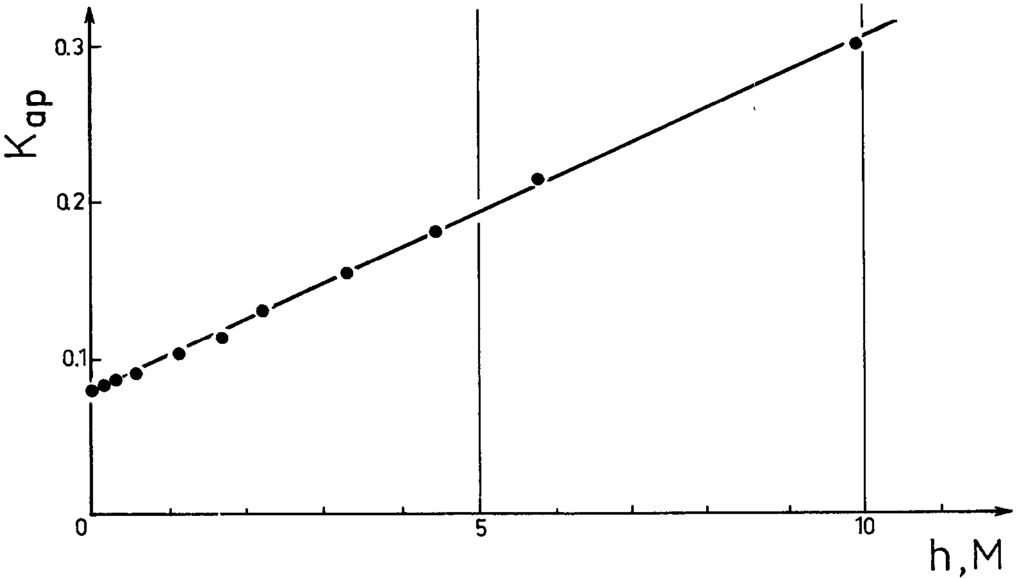


Figure 1.- Variations of K_{ap}, the tautomeric equilibrium constant measured by U.V. spectroscopy, as a function of the activity of water [7] for 6-chloro-2-pyridone.

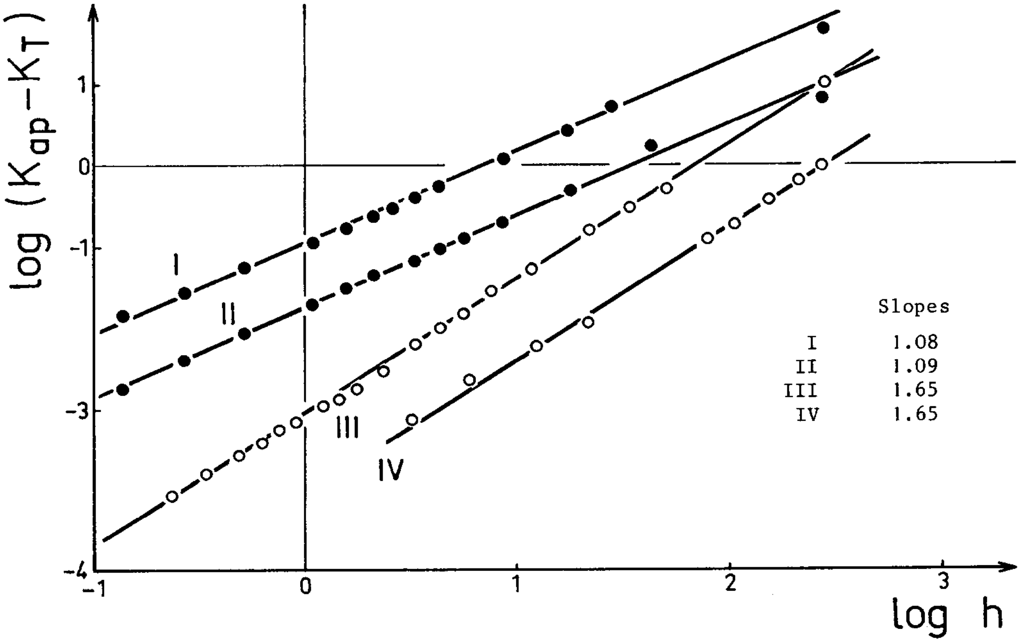


Figure 2.- Logarithmic plot of K_{ap} - K_T vs. the activity of water [7] in acetonitrile/water media Lactim-lactam tautomeric equilibria of 6-methoxy 2-pyridone (I) and 6-bromo 2-pyridone (II) . Zwitterion-neutral tautomeric equilibria of 3-hydroxy 2-methyl pyridine (III) and 3-hydroxy pyridine (IV)

it is assumed that in this latter medium, H-bonding solvation has the determining influence, and it might be useful to treat it like ordinary chemical equilibria which equilibrium constants (a_i, K_T) remain independent of the solvent composition. Since the U.V. spectra of heteroaromatic compounds in water/aprotic solvent media exhibit isosbestic points (6), the spectrum of tautomers A and B are assumed to remain unaffected by hydration and an apparent tautomeric ratio K_{ap} can be measured from these spectra:

$$K_{ap} = \frac{(A,H_2O) + (A)}{(B)} \qquad (1)$$

where (X) designs the concentration of the species X. For convenience in recording the UV spectra these are about 10^{-4}M and can therefore be identified with the activities.

$$\text{If } K_T = \frac{(A)}{(B)} \quad \text{and} \quad a_1 = \frac{(A,H_2O)}{(A)\ (h)}$$

we have : $K_{ap} = K_T + a_1.K_T\ (h)$ (2)

or $K_{ap}-K_T = a_1.K_T\ (h)$ (2')

These equations may be generalised to the case of the preferential hydration of tautomer A by x water molecules:

$$A,\ x\ H_2O \underset{a_x}{\rightleftharpoons} A + x\ H_2O$$

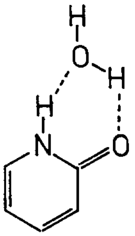
Then $K_{ap} = \dfrac{(A,\ x\ H_2O) + (A)}{(B)}$ with $a_x = \dfrac{(A,\ x\ H_2O)}{(A)\ \ (h)^x}$

which leads to:

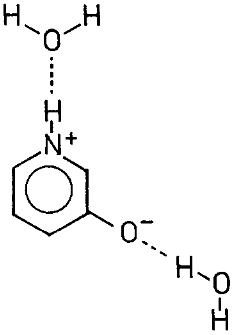
$$K_{ap}-K_T = a_x.K_T\ (h)^x \qquad (3)$$

Therefore the logarithmic plot of ($K_{ap}-K_T$) versus the activity of water (7), h, will give the value of x . In all examples studied this plot was linear over a wide range of concentrations, from 10^{-1}M to pure water (figure 2) and thereby justifies the hypothesis.

For the 2-hydroxy pyridines K_{ap} is defined as the lactam/lactim ratio. 2-Hydroxy pyridines are expected to form cyclic monohydrates (9) (V) which could contribute to the tautomeric interconversion mechanism (10). Indeed the lactam tautomer appears to be preferentially hydrated by one water molecule as x is practically equal to unity . It is also interesting to note that the association constant, a_x, does not seem to be much affected by the substitution on carbon 6 of the pyridine cycle .



V



VI

For both the 3-hydroxy pyridines studied, K_{ap}, is defined as the zwitterion to neutral tautomer ratio. This case appears more complicated than the previous one as the slopes of the logarithmic plot are far from integer values; however, it seems that we need to consider the hydration of the zwitterionic tautomer by two water molecules (VI) which would stabilize the electrical charges. Such situation also appears for the zwitterionic form of picolinic acid (11).

Though the hydration scheme is probably not as simple as suggested in this work, the variations of the tautomeric equilibrium constant in water/aprotic solvent media are directly related to the activity of water. Nonetheless, the slopes of the logarithmic plot of K_{ap} - K_T) are characteristic of the tautomeric system and such plots might be useful in determining by extrapolation the tautomeric equilibrium constant in either water or apolar aprotic solvent.

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