pH-Controlled Hydrogen-Bonding

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The pH-dependence of the degree of hydrogen-bonding between a base and its conjugate acid is considered. When only a small proportion of the total base is complexed, the amount complexed is proportional to $(1 + \cosh p)^{-1}$ where $p = 2.303 (pK_a - \text{pH})$, pK_a being the dissociation constant of the conjugate acid. This represents sharp pH-dependence. As the proportion complexed increases, the curve broadens, eventually becoming flat-topped, with more than half the base complexed over the range of pH values $pK_a \pm \log KC$, approximately. (K is the complex association constant and C is the formal base concentration, including all forms.) There are similarities to the extent of mono-protonation of a dibasic acid.

It is the purpose of this communication to draw attention to the sensitive pH-dependence of hydrogen-bonding in $(\text{AHA})^-$ or $(\text{BHB})^+$ systems, and its possible biochemical significance. Although equilibria involving complexing between acid and conjugate base

or base and conjugate acid

have been proposed in the interpretation of conductimetric and potentiometric studies (Muney & Coetzee, 1962; Bruckenstein & Mukherjee, 1962; Kolthoff & Chantooni, 1963; Coetzee *et al.*, 1964; Pawlak, 1973) necessarily implying the equations given here, no explicit discussion appears to have been made along the present lines.

Provided that the counter-ion does not interfere in hydrogen-bonding, in a solvent S

where $\text{B}(\text{S})$ represents the solvated base etc., K is the association constant of the complex, K_a the dissociation constant of $\text{BH}^+(\text{S})$, and eqns. (2) and (3) yield, taking all activity coefficients as unity,

$$[\text{BH}^+\text{B}] = \frac{KZ^2n}{(n+1)^2} \quad (4)$$

where Z is the total amount of uncomplexed base, i.e. $[\text{B}(\text{S})] + [\text{BH}^+(\text{S})]$, and $\log n = (pK_a - \text{pH})$, pK_a referring to equilibrium (2) in the solvent concerned, and pH also referring to this solvent. The function $n/(n+1)^2$ has a maximum value when $n = 1$, and

Fig. 1. pH-dependence of BH^+B -type hydrogen-bonding

When only a small fraction of the base is complexed, $[\text{BH}^+\text{B}]$ follows the curve shown. When this fraction increases a flat-topped curve, similar to that of Fig. 2, is followed.

$\text{pH} = pK_a$, and is strongly peaked, falling to less than 4% of this value when the pH differs by 2 units from pK_a (Fig. 1). Thus the occurrence of this hydrogen bond is sensitively dependent on the pH, in a reversible manner.

Numerous organic bases, including pyridine, quinoline, imidazole, methylimidazole, benzimidazole, thiazole and morpholine, form complexes of this type (Clements *et al.*, 1973a,b,c,d). In only a few cases have the association constants K been measured, and these appear to be very sensitive to the solvent, values ranging from 4.0 for the

pyridine complex (Coetzee *et al.*, 1964), in methyl cyanide, to about 3350 for the *n*-butylamine complex in nitrobenzene (Pawlak, 1973) (the units are not given, but probably are M^{-1}).

Returning to eqn. (4), we may consider the two extreme cases: (a) when K is small, the proportion of base complexed remains low at all pH values, i.e. Z is almost constant, so that $[BHB]^+$ will follow the curve of $Kn/(n+1)^2$ quite closely (Fig. 1); (b) when K is large, nearly all the base will be complexed over a range of pH on each side of pK_a , i.e. $[BHB]^+$ will follow a curve similar to the dashed line in Fig. 2. The range of pH allows calculation of K as follows:

Writing eqn. (4) as

$$\frac{[BHB]^+}{Z^2} = \frac{K}{2(1 + \cosh p)} \quad (5)$$

where $p = \ln n = 2.303(pK_a - \text{pH})$, then the values of p at which half the base is complexed, i.e. when $[BH^+B] = 0.25C$ and $Z = 0.5C$, where C is the total concentration of B in all forms, are given by

$$\frac{1}{C} = \frac{K}{2(1 + \cosh p)}$$

$$\text{i.e. } \cosh p = \frac{KC}{2} - 1 \quad (6)$$

This requires that $K > 4/C$ for the proportion of complex to reach half the total base concentration. If e^{-p} is small compared with e^{+p} , or vice versa, which will be the case for $K > \text{about } 6/C$, then the values of p for half-complexation are, approximately

$$p = \pm \ln(KC - 2) \simeq \ln KC$$

$$\text{or } \ln n = \pm \log KC$$

Hence if the pH range over which the base is half or more associated is measured, the spread is $\log KC$ units about pK_a . Thus measuring this spread provides a very simple means of determining association constants.

Turning to complexing when the bases differ, the pH-dependence is now quite altered. Fig. 2 shows the pH-dependence of the (BH^+) form of the bases. Combination with the equilibrium:

yields the curve shown for the extent of complexing. There is now a pH range, between the pK values of the two bases, in which complexing will be optimum, the extent being dependent on K , whereas outside this range the association will be quite sharply cut off.

A very wide range of complexes of this type, involving differing bases, have been shown to occur, mainly by spectroscopic means. To cite only one example (Dean & Wood, 1974), one expects the complex *N*-methylimidazole H^+ /thiazole to form in

Fig. 2. pH-dependence of ${}^1BH^+{}^2B$ -type hydrogen-bonding

pK_1 and pK_2 are the pK values of the two bases, which in the illustration differ by 6 units. The concentration of ${}^1BH^+{}^2B$ follows the exact shape shown only if the concentration of 1B and 2B are not appreciably diminished by complex-formation. The vertical scale is therefore expanded for this curve in comparison with those for 1B and 2B . —, Free 1B ; —, free 2B ; - · - · -, amount of $[{}^1BH^+{}^2B]^+$.

the pH range between 2.55 (pK_a of thiazole) and 6.95 (pK_a of *N*-methylimidazole). 'Proton-induced' hydrogen-bonding between many other biochemical species may be viewed in this way.

Finally, one may comprise in this scheme 'permanent' hydrogen-bonding between neutral molecules. Taking as an example complexing between methanol and pyridine, we can regard 1B as MeO^- , and 2B as pyridine. Over the wide pH range between the pK_a of pyridine (5.25) and the pK_a of MeO^- (15.5) (Ballinger & Long, 1960) hydrogen-bonding will be insensitive to pH control. A comparable situation is present in the hydrogen bonds formed between most neutral molecules.

It would seem likely that the sharp pH restriction of complexing when the systems have closely equal pK_a values and the limited range available when the pK_a values differ will be utilized advantageously in biochemical systems. The interaction of range and concentration implied by eqn. (6) also offers the possibility of biochemical exploitation.

The equations developed here are quite similar to those relating to the dissociation of a dibasic acid A (Dixon, 1973, 1974), the distinction being that in the present case $2[BH^+B] + [BH^+] + [B] = \text{constant}$, whereas with the acid $[AH_2^{2+}] + [AH^+] + [A] = \text{constant}$.

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