The Hydrogen Bond as a Key Factor in Efficient Intramolecular Proton Transfer Catalysis

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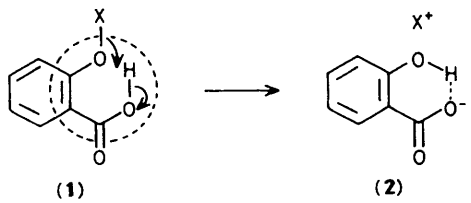
Efficient intramolecular catalysis by the Me_2NH^+ group of the naphthylammonium derivative (**6**) suggests that the thermodynamic stabilisation of the leaving group by intramolecular H-bonding plays a key kinetic role.

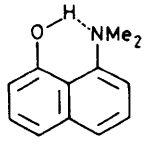
The measurement of effective molarities (EM)[1] for intramolecular reactions allows us to compare the efficiencies of the different classes of reactions thought to be involved in enzyme catalysis. Such comparisons reveal a striking dichotomy between intramolecular nucleophilic catalysis, which can be enormously efficient (EM often 10^8 M, rising to 10^{13} M in strained systems), and general acid–base catalysis (EM generally <10 M).[1,2] There are indications that general acid–base catalysis in enzyme reactions can be a great deal more efficient than this, and we would like to know why. Our best clue is that one system, *i.e.* salicylic acid derivatives (**1**), where X can be lost as a stable fragment X^+ (X = CHROR',[3] PO_3^{2-},[4] SO_3^-,[5]), shows exceptionally high (up to 10^5 M) EM for intramolecular catalysis by the CO_2H group [(**1**) → (**2**)]. Work on related systems[6,7] shows that the common structural feature associated with high efficiency is the *cis* coplanar arrangement [broken circle in (**1**)] of a carboxy group and a phenol (or enol[6]) oxygen. This suggests as possible key electronic factors either the conjugation between the CO_2H carbonyl group and the OX oxygen atom, obviously not relevant to enzyme systems, or the strong intramolecular hydrogen bond in the anion formed [*e.g.* salicylate, (**2**)]. So we have searched for alternative systems where a comparably strong H-bond exists between an OH group and a neighbouring general base.

One relevant system appears to be the aminonaphthol (**3**)[8] related to proton sponge (**4**).[9] There can be no conjugative interaction between the OH and NH^+ groups of the conjugate acid, but the strength of the hydrogen bond is shown by the high pK_a of the OH group of (**3**) (14.9,[8] higher than the second pK_a of salicylic acid). So we have prepared the methoxymethyl acetal (**5**) of (**3**), and now report its hydrolysis.

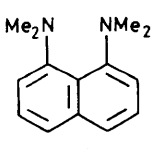
The pH–rate profile for the hydrolysis of (**5**) shows the usual



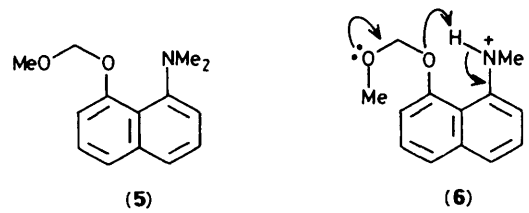
(**1**) (**2**)



(**3**)



(**4**)



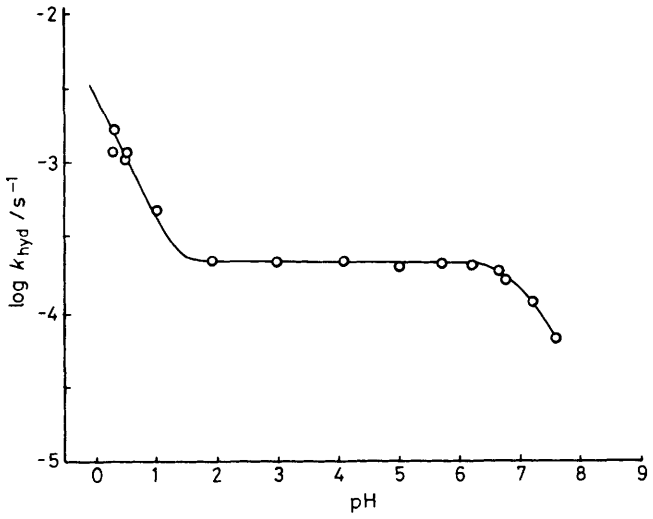


Figure 1. pH–rate profile for the hydrolysis of acetal (**5**), at 65 °C and ionic strength 1 M ($NaClO_4$) in water. The points are experimental, the curve calculated, using $k_{H^+} = 3 \times 10^{-3}$ dm^3 mol^{-1} s^{-1}, $k_0 = 2.0 \times 10^{-4}$ s^{-1} and $pK_a = 7.40$.

acid-catalysed reaction below pH 1, but is dominated by the reaction of the conjugate acid. (The apparent measured pK_a = 7.4: very high for an aniline because the NMe_2 group is rotated out of the plane of the aromatic ring.) This reaction is over 1000 times faster than expected[10] for the spontaneous hydrolysis of the methoxymethyl acetal of a naphthol of pK_a 9—10, consistent with catalysis of the reaction by the Me_2NH^+ group. (The factor is similar to that estimated[11] for the methoxymethyl acetal of salicylic acid.) The mechanism may be represented as shown in (**6**). Details of the proton transfer process are difficult to establish, since we have not been able to prepare ring-substituted derivatives of (**5**), but we note a solvent deuterium isotope effect, $k(H_2O)/k(D_2O) = 1.67$, similar to that (1.61, under the same conditions[3]) for the hydrolysis of the corresponding derivative of salicylic acid.

We conclude that the thermodynamic stabilisation of the leaving group derived from the strong intramolecular H-bonds of (**2**) and (**3**) is reflected in the transition state for acetal cleavage. The three-dimensional structures of proteins provide ideal conditions for the formation of strong H-bonds between substrate leaving groups and active site catalytic groups. Our evidence suggests that significant kinetic advantages may result.

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