General Acid Catalysis and Kinetic Isotope Effects for Intramolecular Addition–Elimination between Amino and Amide Groups in 1-Amino-8-trifluoroacetylaminonaphthalene; Observation of a Biphasic Brønsted Plot

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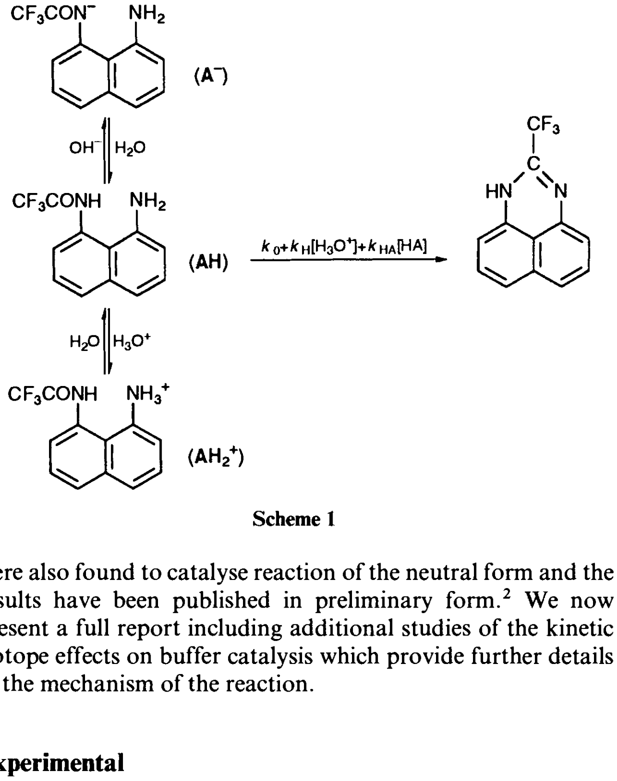
The intramolecular addition–elimination of 1-amino-8-trifluoroacetylaminonaphthalene to 2-trifluoromethylperimidine in 70% (v/v) $Me_2SO–H_2O$ is catalysed by general acids, and catalytic coefficients (k_{HA}) for 11 buffer acids and hydronium ion have been measured. A Brønsted plot of $\log k_{HA}$ against pK_a gives a slope close to zero for catalysis by acids with pK_a < *ca.* 8.5 and a slope close to unity for acids with pK_a > *ca.* 8.5. The results are explained by a mechanism involving intramolecular addition of the amino group to the amide carbonyl to give a zwitterionic intermediate present in low concentration followed by rate-limiting protonation of the intermediate by hydronium ion and by buffer acids. The break point in the plot of $\log k_{HA}$ against pK_a which occurs at pK_a 8.5 corresponds to the pK value of the hydroxy group of the zwitterionic intermediate. Kinetic solvent isotope effects on the values of k_{HA} have been measured and an average value k_{HA}/k_{DA} 1.52 ± 0.2 is found. The absence of a maximum in the value of k_{HA}/k_{DA} with pK_a confirms that the rate-limiting protonation is controlled by diffusion steps. The proposed mechanism is preferred to one in which the biphasic Brønsted plot is explained by a change in rate-limiting step from acid-catalysed intramolecular addition in the presence of strong acids to acid-catalysed elimination from the addition intermediate in the presence of weak buffer acids.

The form of the rate–pH profile[1] for the intramolecular addition–elimination of 1-amino-8-trifluoroacetylaminonaphthalene in 70% (v/v) $Me_2SO–H_2O$ to give 2-trifluoromethylperimidine shows that 1-amino-8-trifluoroacetylaminonaphthalene reacts in the neutral form (AH) by spontaneous and hydronium ion-catalysed pathways and species in which the amino group is protonated (AH_2^+) or in which the amide group is ionised (A^-) are unreactive, Scheme 1. Buffer acids were also found to catalyse reaction of the neutral form and the results have been published in preliminary form.[2] We now present a full report including additional studies of the kinetic isotope effects on buffer catalysis which provide further details of the mechanism of the reaction.



Scheme 1

Experimental

Materials.—A solution of 1-amino-8-trifluoroacetylaminonaphthalene in 70% (v/v) $Me_2SO–H_2O$ or $Me_2SO–D_2O$ was prepared by hydrolysis[3] of 1,8-bis(trifluoroacetylamino)naphthalene at a concentration of *ca.* 2×10^{-4} mol dm^{-3} in 70% (v/v) $Me_2SO–H_2O$ or $Me_2SO–D_2O$ in the presence of potassium hydroxide (0.01 or 0.002 mol dm^{-3}). The solution was usually left overnight and the base concentration was checked by titration on completion of the hydrolysis. This solution was used for kinetic studies of the reaction of 1-amino-8-trifluoroacetylaminonaphthalene to 2-trifluoromethylperimidine in the presence of buffers. The identity of the reaction has been established previously.[1] Substituted phenol, carboxylic acid and benzimidazole buffers were made by partial neutralisation of the buffer acid with potassium hydroxide solution and the ionic strength was adjusted to 0.25 mol dm^{-3} for all measurements by addition of potassium chloride. The solvent was prepared by volume from Me_2SO (Fluka, *puriss* grade) and doubly distilled water or deuterium oxide (Aldrich 99.9 atom% D). For reactions in 70% (v/v) $Me_2SO–D_2O$ the making up of solutions introduced less than *ca.* 1% H into the solvent.

Kinetic Measurements.—Kinetic measurements were made at 25.0 °C in 70% (v/v) $Me_2SO–H_2O$ and 70% (v/v) $Me_2SO–D_2O$ in the presence of buffers. The reactions were begun by mixing equal volumes of a solution of 1-amino-8-trifluoroacetylaminonaphthalene in 70% (v/v) $Me_2SO–H_2O$ or 70% (v/v) $Me_2SO–D_2O$ with a solution of buffer in the same solvent. After mixing, the initial concentration of 1-amino-8-trifluoroacetylaminonaphthalene was *ca.* 1×10^{-4} mol dm^{-3} and formation of 2-trifluoromethylperimidine was followed by measuring the increase in absorbance at *ca.* 350 nm. Buffer concentrations were limited to the range 0.01–0.1 mol dm^{-3} since at higher concentrations, association of phenol buffers occurs in this solvent.[4,5] In most cases reactions took place with half-lives of less than 5 s and measurements were made using the stopped-flow technique (Hi-Tech SF51). For measurements in 4-chlorophenol, phenol and benzimidazole buffers, the reactions occurred more slowly and the change in absorbance was followed using a conventional spectrophotometer (Perkin Elmer λ5). Reactions were first-order with respect to 1-amino-8-trifluoroacetylaminonaphthalene and were followed for at least two half-lives.

Absorbance data from the stopped-flow instrument were

Table 1 Acid catalytic coefficients[a]

Acid	pK_a[b]	k_{HA}/dm^3 mol^{-1} s^{-1}	k_{DA}/dm^3 mol^{-1} s^{-1}	k_{HA}/k_{DA}
H_3O^+	−1.23	367.0 ± 90		
Cl_2CHCO_2H	2.92	71.9 ± 6		
$ClCH_2CO_2H$	4.70	72.6 ± 6	59.5 ± 5	1.22 ± 0.2
$MeOCH_2CO_2H$	5.72	58.1 ± 6		
$ClCH_2CH_2CO_2H$	6.22	46.9 ± 5	36.5 ± 5	1.32 ± 0.4
CH_3CO_2H	6.90	48.4 ± 5	29.5 ± 3	1.64 ± 0.4
2,4,6-$Cl_3C_6H_2OH$	8.30	20.6 ± 6	12.6 ± 1	1.63 ± 0.6
4-CNC_6H_4OH	9.38	3.65 ± 0.6		
2-BrC_6H_4OH	10.72	0.98 ± 0.2	0.55 ± 0.05	1.78 ± 0.6
4-ClC_6H_4OH	11.68	0.045 4 ± 0.001		
C_6H_5OH	12.62	0.007 89 ± 0.001 7		
Benzimidazole	13.15	0.001 78 ± 0.000 19		

[a] The values for k_{HA} and k_{DA} refer to 70% (v/v) $Me_2SO–H_2O$ and 70% (v/v) $Me_2SO–D_2O$ respectively at ionic strength 0.25 mol dm^{-3} and 25.0 °C. [b] Values of pK_a refer to 70% (v/v) $Me_2SO–H_2O$ at ionic strength 0.25 mol dm^{-3} and 25.0 °C.

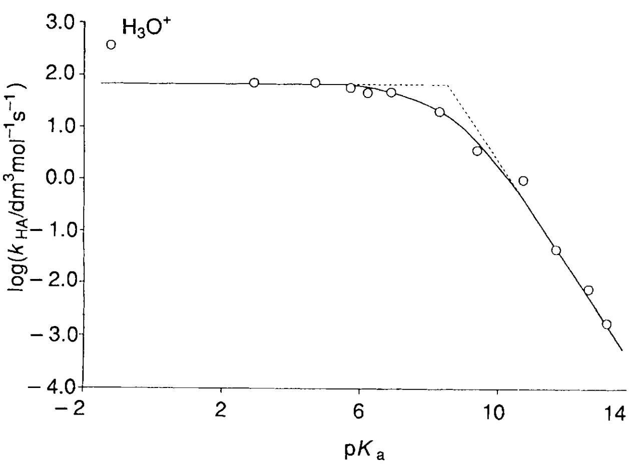


Fig. 1 Brønsted plot of acid catalytic coefficients (logk_{HA}) against pK_a; (○), experimental values; the solid line is a plot of eqn. (3) assuming normal proton transfer behaviour to and from an intermediate of pK_a 8.5

taken directly into an Apple IIGS microcomputer and first-order rate coefficients (k_{obs}) were calculated by linear regression analysis of the usual logarithmic plot. Rate coefficients for reactions followed by conventional spectrophotometry were obtained by fitting data of absorbance against time with an exponential function using a program run on a VAX 8000. For all buffers the dependence of the first-order rate coefficient on buffer concentration was linear with an intercept at zero buffer concentration. The contribution by buffer to the observed rate was small especially for the more weakly acidic buffers, *e.g.* in a 0.1 mol dm^{-3} phenol buffer at a buffer ratio of unity, the buffer makes a *ca.* 50% contribution to the observed rate coefficient.

The present measurements make use of carboxylic acid, phenol and benzimidazole buffers in 70% (v/v) $Me_2SO–H_2O$ at 25.0 °C and ionic strength 0.25 mol dm^{-3}. The pK_a values of the carboxylic acids have been measured[6] at 20.0 °C and ionic strength 0.25 mol dm^{-3} in 70% (v/v) $Me_2SO–H_2O$ and these results were used in the present work without correcting for the difference in temperature. The pK_a values of the phenols and benzimidazole have been measured[4] at 20.0 °C and ionic strength 0.50 mol dm^{-3} in 70% (v/v) $Me_2SO–H_2O$. For the present work these values were corrected to ionic strength 0.25 mol dm^{-3} using the Debye–Hückel approximation.[1]

Results and Discussion

Buffer Catalytic Coefficients.—By studying the linear dependence of the observed first-order rate coefficient (k_{obs}) on buffer concentration at different buffer ratios, it was established that catalysis was due to the buffer acid, eqn. (1). The intercept

$$k_{obs} = k + k_{HA}[HA] \qquad (1)$$

(k) of the plots of k_{obs} against [HA] corresponds to reaction with participation by solvent (H_2O, H_3O^+ and OH^-). Measurements were made for 11 buffers at different buffer ratios and k_{HA} was obtained as the average value of the gradients of plots of k_{obs} against [HA] at the different buffer ratios. The results have been published in preliminary form.[2] In the case of catalysis by chloroacetic, 3-chloropropionic and acetic acids, and for 2,4,6-trichlorophenol and 2-bromophenol, the kinetic data have now been extended to include measurements in 70% (v/v) $Me_2SO–D_2O$. To provide reliable values for the solvent isotope effects on the catalytic coefficients, measurements in 70% (v/v) $Me_2SO–H_2O$ for these buffers were repeated and carried out at the same time as the measurements in 70% (v/v) $Me_2SO–D_2O$. The combined results in 70% (v/v) $Me_2SO–H_2O$ and the new values in 70% (v/v) $Me_2SO–D_2O$ are given in Table 1. The results in 70% (v/v) $Me_2SO–H_2O$ are shown in the form of a Brønsted plot in Fig. 1 of logk_{HA} against pK_a for the buffer catalyst.

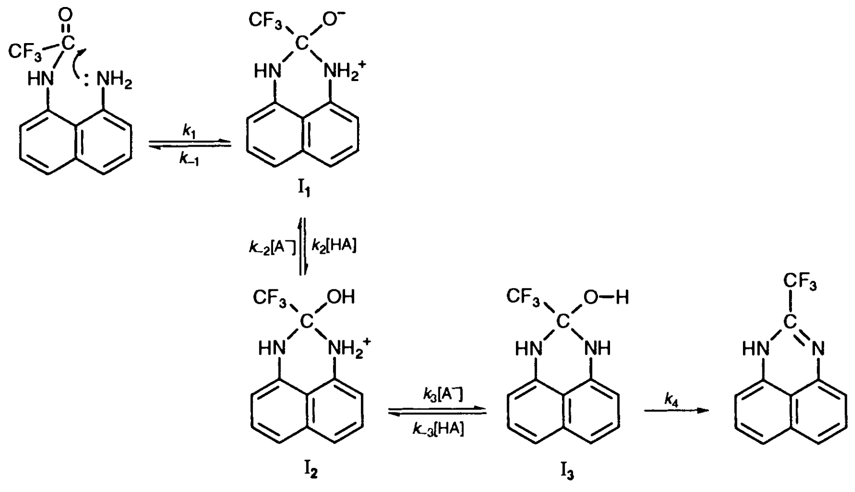
The observed biphasic dependence of the logarithm of the rate coefficient for acid catalysis (k_{HA}) on the pK_a of the catalyst is explained by Scheme 2. For this mechanism, the measured second-order rate coefficient for catalysis by buffer acid is given by eqn. (2) on the assumption that the intermediates are present

$$k_{HA} = k_1k_2k_3/k_{-1}(k_3 + k_{-2}) \qquad (2)$$

in low concentration and that $k_{-1} > k_2$ [HA] and $k_4 > k_{-3}$ [HA]. On condition that $k_3 > k_{-2}$, eqn. (2) further reduces to eqn. (3) in which $K_1 = k_1/k_{-1}$ is the equilibrium constant for

$$k_{HA} = k_2K_1 \qquad (3)$$

intramolecular addition of the amino group to the amide carbonyl. Proton transfer to the zwitterionic intermediate from buffer acids is a normal proton transfer reaction involving oxygen acids and bases and is expected to occur at the diffusion-limited rate in the thermodynamically favourable direction. The break point in the plot of logk_{HA} against pK_a corresponds to the pK value of the ionised hydroxy group in I_1. For reaction in the presence of acids with pK_a < 8.5 the rate coefficient for proton transfer (k_2) to the zwitterionic intermediate is expected to be that for the diffusion-controlled encounter of the reactants, and the overall catalytic coefficient should be independent of the pK_a value of the acid. Hence in this region of the plot in Fig. 1 the fit to the data is drawn with zero slope. For weaker acids with pK_a > 8.5 the rate coefficient for proton transfer in the

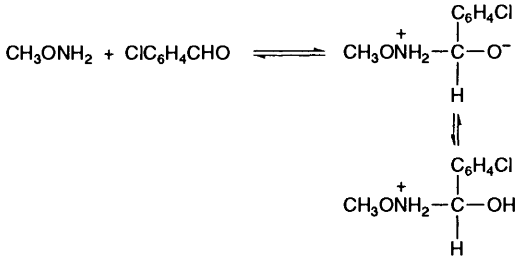


Scheme 2

forward direction (k_2) is the product of the unfavourable equilibrium constant for the proton transfer reaction and the rate coefficient for the diffusion-controlled encounter of the products. The rate coefficient k_2 is then directly proportional to the equilibrium constant for the proton transfer and decreases linearly as the acid dissociation constant (K_a) of the buffer decreases. Since the buffer catalytic coefficient (k_{HA}) is given by eqn. (3), the predicted variation of logk_{HA} with pK_a is linear with slope -1.0. The two lines in Fig. 1 are extrapolated to a break point at pK_a *ca.* 8.5.

The point at logk_{HA} 2.56 and pK_a -1.23 in Fig. 1 is the result for catalysis by hydronium ion for which a second-order rate coefficient of k_H 367 dm^3 mol^{-1} s^{-1} was found.[1] This is *ca.* fivefold greater than the average value of k_{HA} for catalysis by the three strongest acids for which the proton transfer step occurs with a diffusion-limited rate coefficient in the forward direction. The higher rate for hydronium ion is compatible with the enhanced diffusion rate of hydronium ion and this therefore accounts for the positive deviation of H_3O^+ from the Brønsted plot.

The break point in the Brønsted plot (Fig. 1) leads to the value pK_a 8.5 for acid dissociation of the hydroxy group in the intermediate I$_2$ to give the ionised form I$_1$ and is similar to the values that have been estimated[7] for tetrahedral intermediates formed by intermolecular addition to carbonyl groups. For example, the intermolecular addition of methoxylamine to 4-chlorobenzaldehyde, Scheme 3, gives an intermediate with a



$$CH_3ONH_2 + ClC_6H_4CHO \rightleftharpoons CH_3\overset{+}{O}NH_2{-}\underset{H}{\overset{C_6H_4Cl}{C}}{-}O^- \rightleftharpoons CH_3\overset{+}{O}NH_2{-}\underset{H}{\overset{C_6H_4Cl}{C}}{-}OH$$

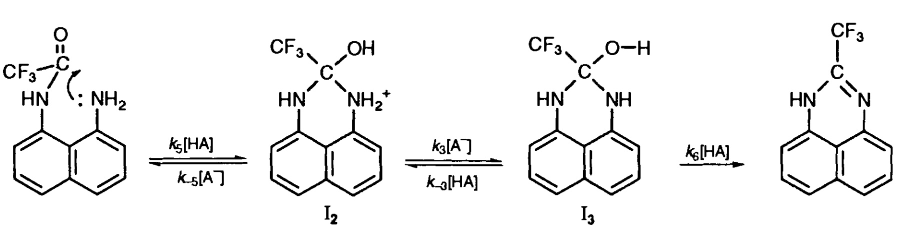
Scheme 3

hydroxy group for which pK_a *ca.* 8.6 in aqueous solution has been calculated from a similar break point in a Brønsted plot.[8] The pK_a value of the hydroxy group in I$_2$ can be estimated from a $\sigma^*\rho$ plot measured for alcohol dissociation[9] and given by p$K_a = 15.74 - 1.32\sigma^*$. Using σ^* values[10] of 2.61 and 4.37 for CF_3 and $PhNH_2^+$ respectively, and the value σ^* 0.62 for NH_2 (since that for PhNH is not available) gives pK_a 5.7 for I$_2$ in aqueous solution. The present results refer to 70% (v/v) Me_2SO–H_2O as solvent and using the difference in the measured[4] pK_a values of phenol in H_2O (9.57) and 70% (v/v) Me_2SO–H_2O (12.48) at ionic strength 0.5 mol dm^{-3}, the value pK_a *ca.* 8.6 is predicted for dissociation of the hydroxy group of I$_2$ under the experimental conditions. This value is in good agreement with the result pK_a *ca.* 8.5 calculated from the break point in the Brønsted plot.

The intramolecular addition of the amino group to the amide carbonyl in 1-amino-8-trifluoroacetylaminonaphthalene illustrates the advantage of an intramolecular reaction over its intermolecular counterpart. The intermolecular reaction of an aromatic amine with an amide carbonyl would not occur to any detectable extent. The equilibrium constant K_1 for formation of the zwitterionic intermediate can be calculated from the values of the buffer catalytic coefficients (k_{HA}) and a lower limit can be estimated for the rate coefficient (k_1) for this addition. The average value of k_{HA} for catalysis by the three strongest carboxylic acids for which the proton transfer step is diffusion controlled (k_2 1×10^{10} dm^3 mol^{-1} s^{-1}) has the value k_{HA} *ca.* 68 dm^3 mol^{-1} s^{-1} and using eqn. (3) gives K_1 *ca.* 7×10^{-9}. The assumption $k_{-1} > k_2[HA]$ is made in deducing eqns. (2) and (3), and using the values k_2 1×10^{10} dm^3 mol^{-1} s^{-1} and [HA] 0.1 mol dm^{-3} leads to the result $k_{-1} > 1 \times 10^9$ s^{-1}. This can be combined with the value K_1 *ca.* 7×10^{-9} to give $k_1 > 7$ s^{-1}

The value K_1 *ca.* 7×10^{-9} is to be compared with the result 4.0×10^{-6} dm^3 mol^{-1} estimated as the value of the equilibrium constant for the intermolecular addition in Scheme 3. The intermolecular reaction involves a nucleophile and a carbonyl group with much higher intrinsic reactivity towards intermolecular reaction than the amino and amide groups of 1-amino-8-trifluoroacetylaminonaphthalene. Despite this, the intramolecular addition occurs with an equilibrium constant which does not differ greatly from that for the reaction in Scheme 3. The intramolecular addition with $k_1 \gg 7$ s^{-1} is remarkably facile in comparison with similar intermolecular reactions at carbonyl groups. For example, the reaction of hydroxide ion with 1-acetoxynaphthalene occurs[11] with a second-order rate coefficient of 1.4 dm^3 mol^{-1} s^{-1}. An ester carbonyl is considered to be many orders of magnitude more susceptible to nucleophilic attack than an amide carbonyl and hydroxide ion is a much stronger nucleophile than an aromatic amine. Despite the lower intrinsic reactivities of the reactant groups in the intramolecular reaction, this occurs with a larger rate coefficient.

A possible alternative explanation for the biphasic Brønsted plot in Fig. 1 is provided by the mechanism in Scheme 4 which involves the same intermediates I$_2$ and I$_3$ as in Scheme 2. If it is assumed that the addition and elimination steps are general-



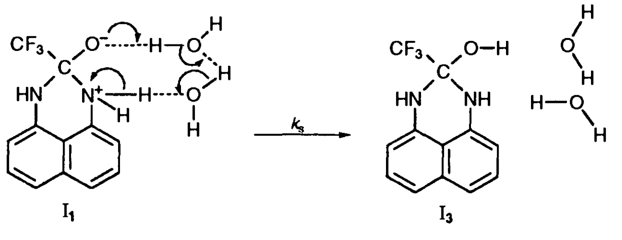
Scheme 4

acid catalysed and the low concentration intermediates I_2 and I_3 are interconverted rapidly, the expression in eqn. (4) is obtained for the rate coefficient for catalysis by buffer acids. In eqn. (4) $K_3 = k_3/k_{-3}$ is the value of the equilibrium constant for

$$k_{HA} = k_5k_6/(k_{-5}/K_3 + k_6) \qquad (4)$$

proton transfer between I_2 and I_3 and the buffer components. In terms of this mechanism the break point in the Brønsted plot is explained by a change from rate-limiting intramolecular addition in the presence of strongly acidic/weakly basic buffers to rate-limiting elimination in weakly acidic/strongly basic buffers. If, for reaction in the presence of a strongly acidic buffer with $pK_a < 8.5$ the assumption $k_{-5}/K_3 \ll k_6$ is made, eqn. (4) leads to $k_{HA} = k_5$ corresponding to rate-limiting intramolecular addition catalysed by buffer acid. For a weakly acidic/strongly basic buffer, k_{-5} and K_3 will be increased and k_6 will be decreased. If the condition $k_{-5}/K_3 \gg k_6$ is assumed to apply for reaction with a weakly acidic buffer, eqn. (4) is reduced to $k_{HA} = (k_5/K_3k_{-5})k_6$ in which $(k_5/k_{-5}K_3)$ is the equilibrium constant for the equilibrium between 1-amino-8-trifluoroacetylaminonaphthalene and I_3. Reaction then involves intramolecular addition to give I_3 in a rapid pre-equilibrium followed by rate-limiting elimination catalysed by general acid with rate coefficient k_6. The values of the rate coefficients (k_5 and k_6) of the rate-limiting steps under the two different conditions are both expected to decrease as the pK_a value of the acid catalyst increases. If different values of the Brønsted exponent apply for acid-catalysed addition and elimination, a biphasic Brønsted plot will be observed with two limbs of different slope.

The slopes of the Brønsted plot in Fig. 1 at low and high pK_a are sufficiently close to zero and unity to provide evidence for Scheme 2 in preference to Scheme 4. Linear regression analysis of the data for the five most acidic buffer acids gives a slope $\alpha = 0.05$, and for the five weakest acids $\alpha = 0.91$ is obtained. In addition, the mechanism in Scheme 2 can be used to provide a satisfactory explanation for the high value of the spontaneous rate of reaction (k_0 *ca.* 1.4 s^{-1}) calculated from the pH dependence of the rate coefficient extrapolated to zero buffer concentration.[1] In terms of Scheme 2, the spontaneous reaction can be explained by a solvent mediated proton switch[12] which brings about the conversion of I_1 to I_3 by a concerted proton transfer from the protonated amino group to the ionised hydroxy group in a single step through one or two intervening water molecules, Scheme 5. Similar routes have been suggested in related reactions to account for substantial spontaneous rates.[12] Assuming that the rate coefficient (k_s) of the proton switch is low in comparison with the rate coefficients k_{-1} and k_4 in Scheme 2, then this leads to the expression $k_0 = K_1k_s$ for the spontaneous reaction. Use of K_1 *ca.* 7 × 10^{-9} and k_0 *ca.* 1.4 s^{-1} gives the result k_s *ca.* 2 × 10^8 s^{-1} which is close to the values found previously[12] for similar proton switches in aqueous solution. It is not possible to include a simple proton switch into the mechanism in Scheme 4. In terms of this Scheme, if H_2O is participating as a weakly acidic catalyst [pK_a *ca.* 19 in 70% (v/v) Me_2SO–H_2O[4]] in assisting elimination from I_3, the value of k_0 is many orders of magnitude greater than would be predicted on the basis of the Brønsted plot for buffer acids. For these reasons the mechanism in Scheme 2 is preferred over that in Scheme 4.



Scheme 5

Kinetic Isotope Effects on Buffer Catalysis.—In the preferred mechanism Scheme 2, protonation of the intermediate I_1 by buffer acids is identified as the rate-limiting step. This is a normal proton transfer between oxygen acids and bases and kinetic solvent isotope effects on the buffer catalytic coefficients were measured to provide further mechanistic details about the process. Previously[13,14] it has been found that isotope effects on some normal proton transfers in aqueous solution exhibit a sharp maximum value as the p*K* difference (Δp*K*) between the acid-base partners in the reaction is varied. The maximum occurs at the point where the p*K* values are matched (Δp*K* = 0). The isotope effect is thought[14] to vary because, as Δp*K* is varied from a negative through zero to a positive value, the rate-limiting step in the overall proton transfer changes from a reactant encounter step to partially rate-limiting proton transfer, and then again to a product encounter step. The values of the isotope effect even at the maximum are usually quite low k_H/k_D *ca.* 2.5 to 3.5 and the maximum occurs within a range of Δp*K* *ca.* ±3. In the present work isotope effects have been measured for catalysis by five carboxylic acids for which the p*K* difference between the buffer acid and the zwitterionic intermediate varies from −4 to +2, Table 1. The isotope effect has a low average value of k_{HA}/k_{DA} 1.52 ± 0.2 and no apparent maximum. This result is interpreted to mean that for protonation of the ionised hydroxy group in the intermediate I_1 by carboxylic acids, the extent to which the actual proton transfer step contributes is low and the reaction is essentially controlled by diffusion steps.

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