Cyclic Imine Formation by Intramolecular Nucleophilic Addition and Elimination between an Amino Group and Amide Carbonyl; Rate–pH Profile for the Reaction of 1-Amino-8-trifluoroacetylaminonaphthalene to 2-Trifluoromethylperimidine

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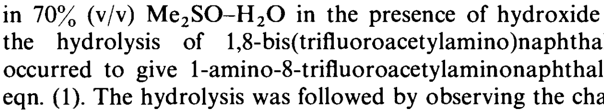
The kinetics of the cyclisation of 1-amino-8-trifluoroacetylaminonaphthalene to 2-trifluoromethylperimidine have been studied in the range pH 0.6–13 in 70% (v/v) Me_2SO–H_2O in the presence of buffers and in solutions of hydrochloric acid. The first-order rate coefficient (k) obtained in the presence of hydrochloric acid or determined by extrapolation of the observed rate coefficient in buffers to zero buffer concentration gives a pH dependence with two plateau regions. The results are explained by assuming that reaction of 1-amino-8-trifluoroacetylaminonaphthalene occurs by spontaneous and hydronium-ion catalysed pathways and that forms of the amide in which the amide group is ionised or the amino group is protonated are unreactive. The rate–pH profile is fitted by the expression $k = K_1(k_0 + k_H[H_3O^+])[H_3O^+]/(K_1K_2 + K_1[H_3O^+] + [H_3O^+]^2)$ in which K_1 is the acid dissociation constant of the protonated amino group in protonated 1-amino-8-trifluoroacetylaminonaphthalene and K_2 is the acid dissociation constant of the amide group in 1-amino-8-trifluoroacetylaminonaphthalene. The rate coefficients k_0 and k_H refer, respectively, to spontaneous and hydronium-ion catalysed cyclisation pathways. Catalysis by buffer acids is also observed. The mechanism of the reaction involves intramolecular addition of the amino group in 1-amino-8-trifluoroacetylaminonaphthalene to the amide carbonyl followed by elimination of water.

Previous studies[1] have shown that the hydrolysis of 1,8-bis(trifluoroacetylamino)naphthalene in 70% (v/v) Me_2SO–H_2O containing tetramethylammonium hydroxide occurs as in eqn. (1) to give 1-amino-8-trifluoroacetylaminonaphthalene which under the reaction conditions is present as the amide anion and does not react further. In isolating the product of reaction it was found that addition of acid to the solution of 1-amino-8-trifluoroacetylaminonaphthalene monoanion resulted in the rapid formation of 2-trifluoromethylperimidine, eqn. (2), and we now report kinetic studies of this reaction.

(1)



(2)

Experimental

Products of Reaction.—In previous work[1] it was shown that in 70% (v/v) Me_2SO–H_2O in the presence of hydroxide ion the hydrolysis of 1,8-bis(trifluoroacetylamino)naphthalene occurred to give 1-amino-8-trifluoroacetylaminonaphthalene, eqn. (1). The hydrolysis was followed by observing the change in the UV–VIS spectrum and also by ^{19}F NMR spectroscopy. When the solution after hydrolysis was acidified by addition of hydrochloric acid a rapid reaction took place and the UV–VIS spectrum of the resulting solution was found to be identical with the spectrum of a solution of 2-trifluoromethylperimidine under the same conditions. On a preparative scale 2-trifluoromethylperimidine was isolated in 99% yield. In the present work the kinetics of the reaction of 1-amino-8-trifluoroacetylaminonaphthalene to 2-trifluoromethylperimidine have been investigated in 70% (v/v) Me_2SO–H_2O.

Materials.—A solution of 1-amino-8-trifluoroacetylaminonaphthalene in 70% (v/v) Me_2SO–H_2O was prepared by allowing 1,8-bis(trifluoroacetylamino)naphthalene at a concentration of *ca.* 2×10^{-4} mol dm^{-3} to hydrolyse in the presence of 0.01 mol dm^{-3} potassium hydroxide. The solution also contained 0.24 mol dm^{-3} potassium chloride to give a total ionic strength of 0.25 mol dm^{-3}. This solution was used for kinetic runs.

Buffer solutions in 70% (v/v) Me_2SO–H_2O were made up by partial neutralisation of the buffer acid with standard potassium hydroxide. The solvent mixture was made up by volume from double distilled water and dimethyl sulfoxide.

Kinetic Procedures.—The kinetics of the reaction in eqn. (2) were studied at 25 °C in 70% (v/v) Me_2SO–H_2O at ionic strength 0.25 mol dm^{-3}. The reaction was begun by mixing a solution of buffer or hydrochloric acid with a solution of 1-amino-8-trifluoroacetylaminonaphthalene (2×10^{-4} mol dm^{-3}) prepared as above. Both solutions contained the necessary quantity of potassium chloride to maintain a total ionic strength of 0.25 mol dm^{-3}. The increase in absorbance at *ca.* 350 nm accompanying the formation of 2-trifluoromethylperimidine was followed with time. The reactant was in deficit compared with hydrochloric acid or buffer and the reactions were accurately first order in 1-amino-8-trifluoroacetylaminonaphthalene. For reactions at pH >10 in buffers of benzimidazole, phenol and 4-chlorophenol, the change in absorbance was observed by means of a conventional spectrophotometer (Perkin-Elmer λ5). At pH <10 in buffers of 4-cyanophenol, 2,4,6-trichlorophenol, acetic acid, 3-chloropropionic acid, chloroacetic acid, dichloroacetic acid and in hydrochloric acid solutions, the reaction occurs with $t_{\frac{1}{2}} < 3$ s and the stopped-flow technique was used to follow the change in absorbance. Values of the first-order rate coefficients were obtained as the

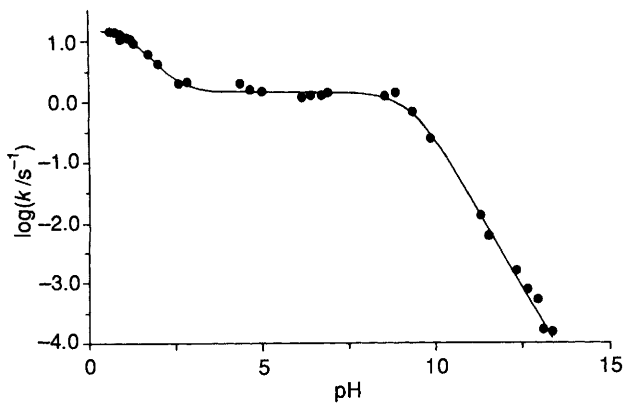


Fig. 1 Rate–pH profile for the cyclisation of 1-amino-8-trifluoroacetylaminonaphthalene to 2-trifluoromethylperimidine; solid points are experimental values of log (k/s^{-1}) and the line is a best-fit plot of eqn. (5)

gradients of plots of $\ln(A_\infty - A)$ *vs.* time where A_∞ is the absorbance after complete reaction and A is the absorbance during the reaction. For the reactions followed using a conventional spectrophotometer the rate coefficients were reproducible to $\pm 2\%$. Using the stopped-flow method the absorbance readings were taken directly from the stopped-flow instrument (Hi-Tech SF51) through an A–D converter (Daisi A1-13) into an Apple IIGS microcomputer for calculation. First-order rate coefficients were obtained as the average of at least five stopped-flow determinations for each solution and were usually reproducible to within $\pm 2\%$.

In each buffer solution, the reaction was followed at a series of buffer concentrations (0.01–0.1 mol dm^{-3}) at fixed buffer ratio. For the weakly acidic buffers (benzimidazole, phenols) catalysis was almost undetectable but in the presence of more strongly acidic carboxylic acid buffers, catalysis was easily demonstrated. The reaction was found to be first order in buffer and the observed rate coefficients were extrapolated to zero buffer concentration to give values of the rate coefficient (k) for reaction involving species derived from the solvent.

Measurement of p*K values in* 70% (v/v) $Me_2SO–H_2O$.—Analysis of the kinetic results gives rise to a pK value for protonation of the amino group in 1-amino-8-trifluoroacetylaminonaphthalene in 70% (v/v) $Me_2SO–H_2O$ (see Discussion). For comparison, the pK value of 3-nitroaniline was measured directly in aqueous solution and in 70% (v/v) $Me_2SO–H_2O$ at 25.0 °C and ionic strength 0.25 mol dm^{-3}. Spectrophotometric measurements[2] were made in solutions containing 3-nitroaniline at a total concentration of *ca.* 1×10^{-4} mol dm^{-3} in the presence of varying concentrations of hydrochloric acid and with potassium chloride added to maintain constant ionic strength. Absorbance readings were taken at *ca.* 370 nm. Values of the acid dissociation constant (K) of protonated 3-nitroaniline were obtained from the expression $K = (A - A_{BH^+})[H_3O^+]/(A_B - A)$ in which A_{BH^+} is the absorbance in the presence of *ca.* 2 mol dm^{-3} HCl in which the amine is almost fully protonated, A_B is the absorbance with the amine entirely in the base form and A is the absorbance for solutions containing protonated and unprotonated forms of the amine at a particular concentration of HCl. For the data in 70% (v/v) $Me_2SO–H_2O$ a small correction was applied to the value of A_{BH^+} because the amine is not fully protonated in the presence of 2.0 mol dm^{-3} HCl. The results in aqueous solution gave an average value of $K = 3.6 \pm 0.6 \times 10^{-3}$ mol dm^{-3} corresponding to pK 2.44 $\pm$ 0.08 at ionic strength 0.25 mol dm^{-3} and 25 °C in good agreement with the literature[3] value 2.46 at 25 °C and infinite dilution. In 70% (v/v) $Me_2SO–H_2O$ an average value of K 0.135 $\pm$ 0.02 mol dm^{-3} (pK 0.87 $\pm$ 0.07) was obtained at ionic strength 0.25 mol dm^{-3} and 25 °C.

Calculation of Buffer pH *Values.*—The pK values of the buffers used in the present work are based on experimental data[4,5] determined in 70% (v/v) $Me_2SO–H_2O$. For acetic, 3-chloropropionic, chloroacetic, and dichloroacetic acid the published pK values[4] refer to 20.0 °C and an ionic strength of 0.25 mol dm^{-3} in comparison with the present conditions of 25.0 °C and ionic strength 0.25 mol dm^{-3}. No correction was applied for the difference in temperature. For benzimidazole, phenol, 4-chlorophenol and cyanophenol, the published values[5] refer to 20.0 °C and ionic strength 0.5 mol dm^{-3}. These were corrected to the ionic strength used in the present studies (0.25 mol dm^{-3}) using the Debye–Huckel equation[6] according to which p$K_{0.25}$ at ionic strength 0.25 mol dm^{-3} (I_1) is related to p$K_{0.5}$ at 0.5 mol dm^{-3} (I_2) by eqns. (3) and (4). In eqn. (3) the

$$pK_{0.25} - pK_{0.5} = 2A[(\sqrt{I_2})/(1 + \sqrt{I_2}) - (\sqrt{I_1})/(1 + \sqrt{I_1})] \quad (3)$$

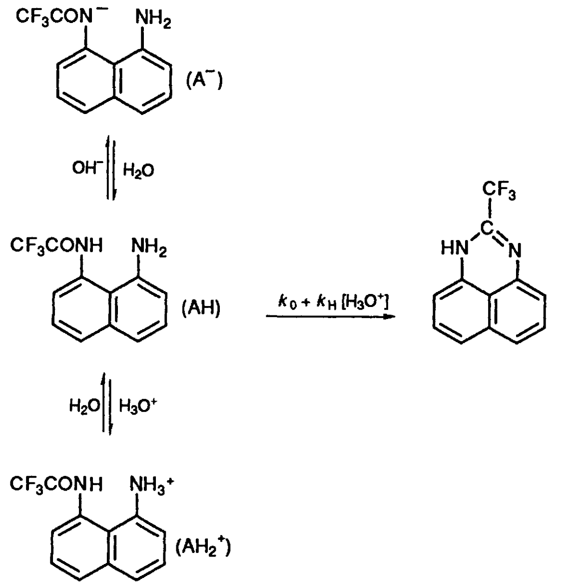
$$pK_{0.25} - pK_{0.5} = 0.138 \quad (4)$$

value $A = 0.86$ was used for 70% (v/v) $Me_2SO–H_2O$. This was calculated[6] from the value $A = 0.51$ for aqueous solution using the estimated relative permittivity ε 55.5 for 70% (v/v) $Me_2SO–H_2O$. Kinetic measurements were also carried out in buffers of 2,4,6-trichlorophenol for which a pK in 70% (v/v) $Me_2SO–H_2O$ has not been measured. An approximate pK was estimated from the value in aqueous solution using the results for four other phenols and five carboxylic acids known in aqueous solution[7] and in 70% (v/v) $Me_2SO–H_2O$.[4,5] A plot of the pK for each acid in aqueous solution *vs.* the pK in 70% (v/v) $Me_2SO–H_2O$ was approximately linear (correlation coefficient 0.99). From the value pK 6.23 for 2,4,6-trichlorophenol[7] in aqueous solution the result pK 8.30 was estimated for 70% (v/v) $Me_2SO–H_2O$. For solutions of hydrochloric acid and for buffer solutions, respectively, the expressions pH $= -\log$[HCl] and pH = pK + log r where r is the buffer ratio (r = [buffer anion]/[buffer acid] were used.

Results and Discussion

The values of k determined as the observed first-order rate coefficient for reaction in hydrochloric acid solutions or obtained as the intercept at zero buffer concentration from plots of the observed first-order rate coefficient *vs.* buffer concentration are shown as the solid points in Fig. 1. The rate–pH profile is explained by the reactions given in Scheme 1 according to which 1-amino-8-trifluoroacetylaminonaphthalene reacts by a spontaneous and a hydronium-ion catalysed pathway and forms of the amide in which the amide proton is dissociated or the amino group is protonated are relatively unreactive compared with the neutral form. For Scheme 1 the rate expression in eqn. (5) was derived assuming that the proton transfers occur rapidly compared with the cyclisation. In eqn. (5), the equilibrium constant (K_1) for dissociation of the NH_3^+ group in the protonated form of 1-amino-8-trifluoroacetylaminonaphthalene (AH_2^+) is defined by $K_1 = [AH][H_3O^+]/[AH_2^+]$ and the equilibrium constant for dissociation of the neutral amide (AH) to the monoanion (A^-) is given by $K_2 = [A^-][H_3O^+]/[AH]$. The rate coefficients k_0 and k_H refer, respectively, to the spontaneous and hydronium-ion catalysed cyclisation of the neutral form of 1-amino-8-trifluoroacetylaminonaphthalene.

Eqn. (5) was initially fitted to the experimental results in three separate pH ranges. Over the range pH 4.7–8.9, k is constant within experimental error. In this region the spontaneous reaction of the neutral form of 1-amino-8-trifluoroacetylaminonaphthalene is predominant and the average of eight values of k at different pH values in this range gave k_0 =



$$k = K_1(k_0 + k_H[H_3O^+])[H_3O^+]/(K_1K_2 + K_1[H_3O^+] + [H_3O^+]^2) \quad (5)$$

Scheme 1

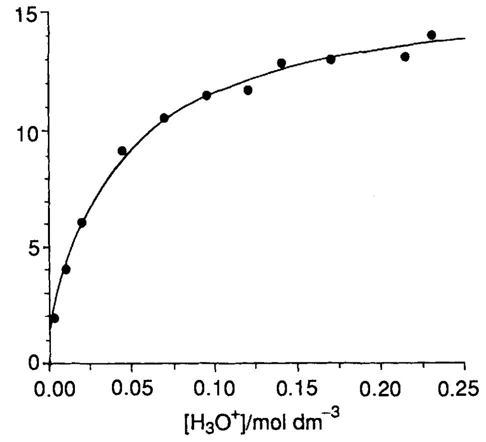


Fig. 2 Plot of first-order rate coefficient (k/s^{-1}) for cyclisation of 1-amino-8-trifluoroacetylaminonaphthaleneto2-trifluoromethylperimidine in hydrochloric acid solutions; solid points are experimental values and the curve is a best-fit of eqn. (6)

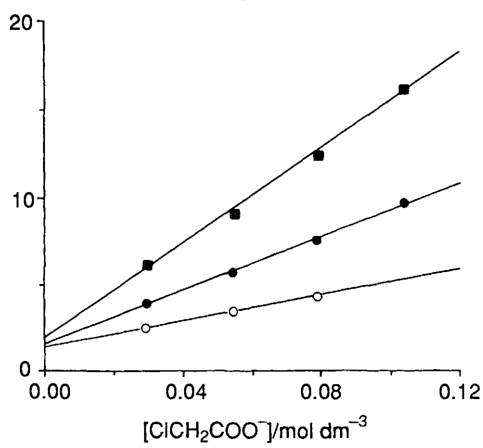


Fig. 3 Observed first-order rate coefficient (k_{obs}/s^{-1}) for the cyclisation of 1-amino-8-trifluoroacetylaminonaphthalene to 2-trifluoromethylperimidine in chloroacetic acid buffers at buffer ratios (r = [buffer anion]/[buffer acid]) of r 0.5 (■), r 1.0 (●) and r 2.0 (○)

1.36 ± 0.08 s^{-1}. Eqn. (5) is compatible with a value of k which is independent of pH under conditions where $k_0 \gg k_H[H_3O^+]$ and $K_1[H_3O^+] \gg K_1K_2 + [H_3O^+]^2$ and eqn. (5) is then reduced to $k = k_0$.

The data obtained in the presence of hydrochloric acid concentrations in the range 0.002 63–0.2307 mol dm^{-3} (pH 2.58–0.638) are shown in Fig. 2 in which the points are the experimental results. The data are accurately fitted by the expression in eqn. (6) which is obtained from eqn. (5) by making the approximation $K_1K_2 \ll K_1[H_3O^+] + [H_3O^+]^2$. In this pH range the concentration of the amide monoanion (A$^-$) is negligible. Eqn. (6) can be rearranged to give eqn. (7) and a plot

$$k = K_1(k_0 + k_H[H_3O^+])/(K_1 + [H_3O^+]) \quad (6)$$

$$(k - k_0)/[H_3O^+] = -k/K_1 + k_H \quad (7)$$

of the experimental results as $(k - k_0)/[H_3O^+]$ *vs.* k using $k_0 = 1.36$ s^{-1} deduced from data in the pH range 4.7–8.9 was linear with correlation coefficient 0.98. The results K_1 0.0438 mol dm^{-3} and k_H 366.5 dm^3 mol^{-1} s^{-1} were obtained from the values of the gradient and intercept. These values together with $k_0 = 1.36$ s^{-1} were used in eqn. (6) to calculate the curve in Fig. 2.

For data at pH values above 11, the approximations $k_0 > k_H[H_3O^+]$ and $K_1K_2 > K_1[H_3O^+] + [H_3O^+]^2$ apply and eqn. (5) reduces to eqn. (8). Hence the values of k at pH

$$k = (k_0/K_2)[H_3O^+] \quad (8)$$

values in the range 11.3 to 13.3 were plotted against the calculated hydronium ion concentration. The best line from linear regression analysis (correlation coefficient 0.999) gave an intercept, 4.4 × 10^{-6} s^{-1}, which is negligible in comparison with the lowest value of k, and a gradient 2.88 × 10^9 dm^3 mol^{-1} s^{-1}. Using k_0 1.36 the value of the gradient leads to $K_2 = 4.7 \times 10^{-10}$ mol dm^{-3}.

The best-fit results for k_0 1.36 s^{-1}, k_H 366.5 dm^3 mol^{-1} s^{-1}, K_1 0.0438 mol dm^{-3} and K_2 4.7 × 10^{-10} mol dm^{-3} obtained by separately fitting the kinetic data in three pH ranges were used in eqn. (5) to provide a fit over the complete pH range and this is shown as the line in Fig. 1.

For the reactions in buffer solutions values of k were obtained as the intercepts (at zero buffer concentration) of linear plots of the observed rate coefficient (k_{obs}) *vs.* buffer concentration. In the more weakly acidic buffers the effect of buffer concentration on the first-order rate coefficient was small. For example, in a 1:1 phenol buffer (pK 12.62) at buffer concentrations of 0.029 47, 0.054 07, 0.078 67 and 0.1033 mol dm^{-3} the following values of 10^3 k_{obs} were obtained: 0.867, 1.149, 1.255 and 1.33 s^{-1}. In a 1:1 cyanophenol buffer (pK 9.38) at buffer concentrations of 0.0270, 0.0520, 0.0760 and 0.101, the values of k_{obs} were 0.764, 0.832, 1.025 and 1.0647 s^{-1}. In the more strongly acidic buffers, *e.g.* chloroacetic acid (pK 4.70), the buffer component has a larger effect and values of k_{obs} *vs.* the concentration of the basic buffer component at three buffer ratios are shown in Fig. 3. The plots were fitted using eqn. (9) in which r is the buffer ratio (r =

$$k_{obs} = k + k_{HA}[ClCH_2CO_2^-]/r \quad (9)$$

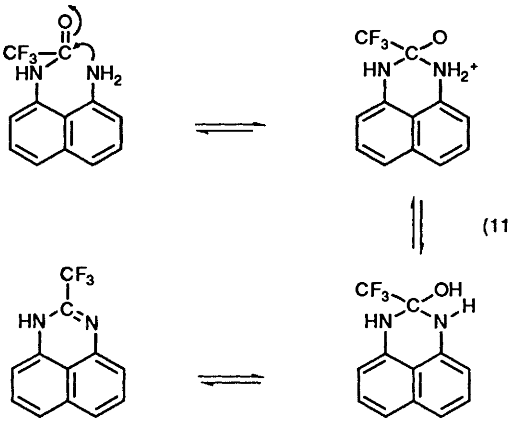
$[ClCH_2CO_2^-]/[ClCH_2CO_2H]$) and k_{HA} is the rate coefficient for catalysis by the acid component of the buffer. The values of k_{HA} calculated from the results at buffer ratios r = 0.5, 1.0 and 2.0 by linear regression analysis (correlation coefficients 0.999, 1.000 and 1.000) were, respectively, 68.3, 77.8 and 74.7 dm^3 mol^{-1} s^{-1}, giving an average value k_{HA} 73.6 ± 4 dm^3 mol^{-1} s^{-1}. The value k = 1.6 ± 0.2 s^{-1} was obtained as the average of the intercepts of the plots at each buffer ratio; k (s^{-1}) 1.91 (r = 0.5), 1.57 (r = 1.0) and 1.41 (r = 2.0). The data show that chloroacetic acid catalyses the reaction and are incompatible with catalysis by chloroacetate ion. A similar conclusion is reached if the data are plotted in the form of eqn. (10). A linear plot of

$$k_{obs} = k + k_{HA}[ClCH_2CO_2H] \qquad (10)$$

k_{obs} *vs.* $[ClCH_2CO_2H]$ at the three buffer ratios was treated by linear regression analysis and gave $k = 1.41\ s^{-1}$ and k_{HA} 74.7 $dm^3\ mol^{-1}\ s^{-1}$ with correlation coefficient 1.000.

The values of the equilibrium constants K_1 and K_2 obtained by fitting eqn. (5) to the pH dependence of k (Fig. 1) correspond to pK_1 *ca.* 1.4 for dissociation of the protonated amino group in protonated 1-amino-8-trifluoroacetylaminonaphthalene and pK_2 *ca.* 9.3 for dissociation of the amide proton of 1-amino-8-trifluoroacetylaminonaphthalene in 70% (v/v) Me_2SO-H_2O at 25 °C and ionic strength 0.25 mol dm^{-3}. The result pK_2 is similar to the value pK 9.5 found[8] for dissociation of 1-trifluoroacetanilide in aqueous solution to give the anilide anion. The result, pK_1 *ca.* 1.4, for acid dissociation of the protonated amino group in protonated 1-amino-8-trifluoroacetylaminonaphthalene is to be compared with the value[3] pK 3.9 for 1-aminonaphthalene in aqueous solution at 298.15 K and infinite dilution. The electron-withdrawing effect of the trifluoroacetylamino substituent would be expected to lower the pK of 1-amino-8-trifluoroacetylaminonaphthalene relative to that of 1-aminonaphthalene. The lowering can be roughly estimated from the relationship $pK = 3.85-2.81\ \Sigma\sigma$ found[9] for the effect of 2-, 3- and 4-substituents on the aqueous pK value of 1-aminonaphthalene. Taking 8-substitution as similar to 4-substitution leads to the prediction that the 8-trifluoroacetylamino substituent (σ_m 0.30) would bring about a lowering in pK of *ca.* 0.84 units giving an estimated aqueous pK value of 3.1 for 1-amino-8-trifluoroacetylaminonaphthalene. For 3-nitroaniline we have found that the change in solvent from aqueous solution to 70% (v/v) Me_2SO-H_2O results in a decrease in the measured pK value from 2.44 to 0.87. Therefore it would be predicted for 1-amino-8-trifluoroacetylaminonaphthalene that an aqueous pK value of 3.1 would be reduced to 1.5 for 70% (v/v) Me_2SO-H_2O which is similar to the value calculated from the kinetic results.

The cyclisation of 1-amino-8-trifluoroacetylaminonaphthalene to 2-trifluoromethylperimidine is likely to occur by the addition/elimination mechanism in eqn. (11). The reversible intermolecular addition of amines and ketones to give imines is known to occur by a similar mechanism[10] and depending on the structure of the reactants any of the steps may be rate limiting. The term $k_H[H_3O^+]$ in eqn. (5) arises from catalysis by hydronium ion and this catalysis and that by buffer acids, eqn. (10), could operate on any of the steps. The term k_0 in eqn. (5) refers to uncatalysed cyclisation. If this reaction involves rate-limiting addition, k_0 is identified as the rate coefficient for intramolecular nucleophilic attack by the amino group on the amide carbonyl in 1-amino-8-trifluoroacetylaminonaphthalene. The value k_0 1.36 s^{-1} is high in comparison with the value of the rate coefficient 0.0106 $dm^3\ mol^{-1}\ s^{-1}$ found[1] for intermolecular reaction of hydroxide ion with the neutral amide carbonyl in the monoanion of 1,8-bis(trifluoroacetylamino)naphthalene, especially in view of the difference in basicity* of *ca.* 17.6 pK units between the amino group in 1-amino-8-trifluoroacetylaminonaphthalene and hydroxide ion under the present conditions. High effective molarities have been found previously for intramolecular nucleophilic addition[11] and a similar explanation may apply in this case. However a detailed explanation must await studies which will provide further mechanistic evidence.



(11)

Acknowledgements

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* The ionic product of water in 70% (v/v) Me_2SO-H_2O at 283.15 K and ionic strength 0.25 mol dm^{-3} has a value K_s 1.62 × 10^{-18} $mol^2\ dm^{-6}$ (reference 5) from which pK 19.0 is calculated for the acid dissociation of water. The value pK 1.5 was deduced for the amino group in 1-amino-8-trifluoroacetylaminonaphthalene from the kinetic data so that the hydroxide ion is 17.6 pK units more basic than the amino group in this solvent.

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