Kinetic Solvent Isotope Effects and Activation Parameters for the Intramolecular Addition–Elimination between Amino and Amide Groups in 1-Amino-8-trifluoroacetylnaphthalene under Acidic Conditions

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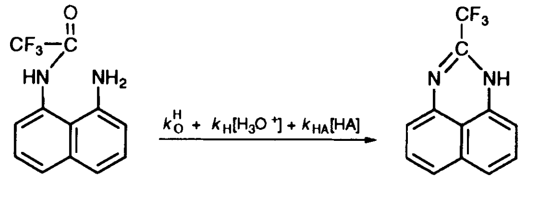
Rates of the reaction of 1-amino-8-trifluoroacetylaminonaphthalene to 2-trifluoromethylperimidine in the presence of acid have been measured in 70% (v/v) $Me_2SO–H_2O$ over a range of temperatures and in 70% (v/v) $Me_2SO–D_2O$. The dependence of the first-order rate coefficient on hydronium ion concentration has been fitted to the expression $k = (k_0^H + k_H[H_3O^+])/(1 + K^H[H_3O^+])$ in which the terms k_0^H and k_H correspond respectively to spontaneous and hydronium ion catalysed reactions of the neutral form of 1-amino-8-trifluoroacetylaminonaphthalene and K^H is the equilibrium constant between 1-amino-8-trifluoroacetylaminonaphthalene and its protonated form which is unreactive. Solvent isotope effects and thermodynamic parameters for the individual terms in the rate expression are explained by a mechanism in which 1-amino-8-trifluoroacetylaminonaphthalene reacts by intramolecular addition of the amino group to the amide carbonyl to give a zwitterionic tetrahedral intermediate which undergoes rate-limiting protonation by hydronium ion at the diffusion-limited rate and undergoes a rate-limiting proton switch with participation by water. In particular the kinetic solvent isotope effect on the hydronium ion catalysed reaction is low (k_H/k_D 1.41) as expected for a diffusion-controlled reaction. The standard entropy change for the intramolecular addition is unfavourable ($\Delta S^\circ - 81$ J K^{-1} mol^{-1}) and the entropy of activation for the solvent-mediated proton switch is also large and negative ($\Delta S^\ddagger - 61$ J K^{-1} mol^{-1}).

The rate–pH profile for the addition–elimination of 1-amino-8-trifluoroacetylaminonaphthalene to 2-trifluoromethylperimidine in 70% (v/v) $Me_2SO–H_2O$, eqn. (1), has been explained[1] by a scheme involving spontaneous and hydronium ion catalysed reactions (rate coefficients, k_0^H and k_H, respectively). Forms of 1-amino-8-trifluoroacetylaminonaphthalene in which the amino group is protonated or the amide group is ionised are unreactive. Reaction of the neutral species was also found to be catalysed by buffer acids.[2] In the present work we report studies of solvent isotope effects and activation parameters of the reaction in order to provide further information about the reaction mechanism.



(1)

Experimental

It was established in previous work[1] that when 1-amino-8-trifluoroacetylaminonaphthalene is introduced into acidic 70% (v/v) $Me_2SO–H_2O$, elimination of water to give 2-trifluoromethylperimidine occurs, eqn. (1). In the present work the kinetics of the reaction have been studied over a range of hydrochloric acid concentrations at temperatures of 15.8, 25.3, 35.0 and 43.4 °C in 70% (v/v) $Me_2SO–H_2O$ and at 25.0 °C in 70% (v/v) $Me_2SO–D_2O$. The ionic strength was maintained at 0.25 mol dm^{-3} by addition of potassium chloride. The reaction occurs with half lives of less than 0.5 s and the stopped-flow method (Hi Tech SF 51) was used to study the kinetics. The reactant was prepared[1] as a solution of 1-amino-8-trifluoroacetylaminonaphthalene in 70% (v/v) $Me_2SO–H_2O$ or in 70% (v/v) $Me_2SO–D_2O$ in the presence of 0.001 mol dm^{-3} potassium hydroxide under which conditions the amide proton is ionised and 1-amino-8-trifluoroacetylaminonaphthalene is then stable. The reaction was begun by mixing this solution in the mixing chamber of the stopped-flow instrument with an equal volume of a solution of hydrochloric acid (0.005 to 0.50 mol dm^{-3}) in 70% (v/v) $Me_2SO–H_2O$ or in 70% (v/v) $Me_2SO–D_2O$ containing sufficient potassium chloride to give a total ionic strength of 0.50 mol dm^{-3}. Reaction solutions were thermostatted before mixing. The increase in absorbance at 350 nm was followed with time and the data were transferred through an A/D convertor to an Apple IIGS microcomputer for calculations. Values of first-order rate coefficients (k) were calculated by linear regression analysis of plots of $\ln(A_\infty - A_t)$ against time, where A_t is the absorbance at time t and A_∞ is the absorbance after complete reaction. The values of k were reproducible to within ± 2% and the average of values from at least five determinations was taken.

Results and discussion

Solvent Isotope Effects.—The variations of k with hydronium ion concentration ($L_3O^+ = H_3O^+$ or D_3O^+) in 70% (v/v) $Me_2SO–H_2O$ and 70% (v/v) $Me_2SO–D_2O$ at 25.3 and 25.0 °C, respectively are given in Fig. 1. This dependence is explained by a scheme involving reaction of the neutral form of 1-amino-8-trifluoroacetylaminonaphthalene by spontaneous and hydronium ion catalysed pathways for which the rate coefficients are k_0^H and k_H, respectively in 70% (v/v) $Me_2SO–H_2O$ and k_0^D and k_D in 70% (v/v) $Me_2SO–D_2O$. The reactive neutral species is in rapid equilibrium with the protonated form which is unreactive. For this scheme the dependence of k against $[H_3O^+]$ is given by eqn. (2) in which the equilibrium constant for protonation of the amino group is $K^H = [RH^+]/[R][H_3O^+]$. A first-order dependence on hydronium ion is observed at low acidities because reaction of the neutral form of 1-amino-8-trifluoroacetylaminonaphthalene is acid catalysed. At high acidities, however, the amino group is protonated and

Table 1 Analysis according to eqn. (2) of the dependence of the first-order rate coefficient for addition–elimination of 1-trifluoroacetylaminonaphthalene

Solvent	T/°C	k_H or k_D/dm^3 mol^{-1} s^{-1}	$k_0{}^H$ or $k_0{}^D$/s^{-1}	K^H or K^D/dm^3 mol^{-1}
$Me_2SO–H_2O$[a]	15.8	255	0.869	29.2
$Me_2SO–H_2O$[a]	25.3	380	1.30	22.4
$Me_2SO–H_2O$[a]	35.0	577	1.90	19.6
$Me_2SO–H_2O$[a]	43.4	856	2.87	18.6
$Me_2SO–D_2O$[a]	25.0	270	0.700	59.5

[a] 70% (v/v).

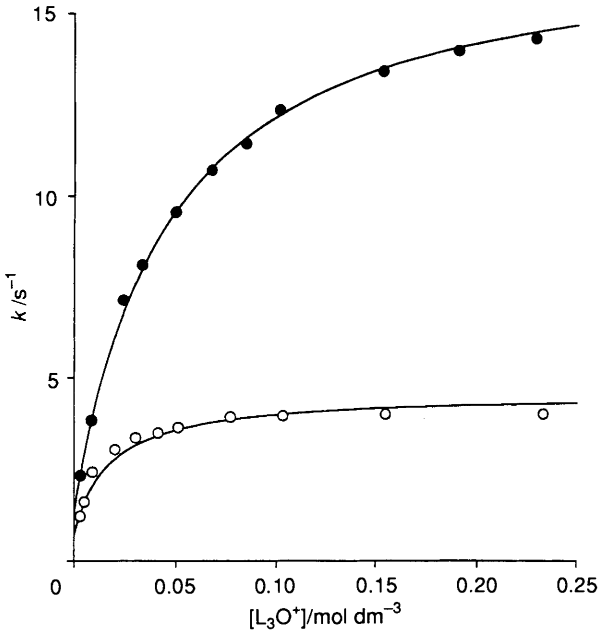


Fig. 1 Dependence of the first-order rate coefficient for the reaction in eqn. (1) on hydronium ion concentration (L = H or D) in 70% (v/v) $Me_2SO–H_2O$ (●) and 70% (v/v) $Me_2SO–D_2O$ (○)

since the concentration of the neutral form is then inversely proportional to hydronium ion concentration the overall reaction becomes zero-order in hydronium ion. Fits of eqn. (2)

$$k = (k_0{}^H + k_H[H_3O^+])/(1 + K^H[H_3O^+]) \quad (2)$$

$$(k - k_0{}^H)/[H_3O^+] = -kK^H + k_H \quad (3)$$

to the kinetic data were obtained by plotting the results in the form of eqn. (3) according to which the function $(k - k_0{}^H)/[H_3O^+]$ varies linearly with k. To plot the data in this way, values of $k_0{}^H$ in 70% (v/v) $Me_2SO–H_2O$ and $k_0{}^D$ in 70% (v/v) $Me_2SO–D_2O$ were calculated by extrapolation of the plots of k against $[L_3O^+]$ in Fig. 1 to zero lyonium ion concentration. The values of $k_0{}^H$ and k_H in 70% (v/v) $Me_2SO–H_2O$ and $k_0{}^D$ and k_D in 70% (v/v) $Me_2SO–D_2O$ which give the best fits to the data are shown in Table 1 and the solid lines through the experimental values of k in Fig. 1 were constructed using these results. The values of k calculated from eqn. (2) using the constants in Table 1 differ from the experimental values (11 data points) with average deviations of 1.5% and 3.8%, respectively in 70% (v/v) $Me_2SO–H_2O$ and 70% (v/v) $Me_2SO–D_2O$.

Activation Parameters.—Experimental values of k at different hydronium ion concentrations in 70% (v/v) $Me_2SO–H_2O$ at 15.8, 25.3, 35.0 and 43.4 °C are plotted in Fig. 2. Fits of eqn. (2) to the experimental results using the values of $k_0{}^H$, k_H and K^H given in Table 1 are shown as the solid lines. The best-fit values of k differ from the experimental values (11 data points) with average deviations of 2.0, 1.5, 2.2 and 2.3% at 15.8, 25.3, 35.0 and 43.4 °C, respectively.

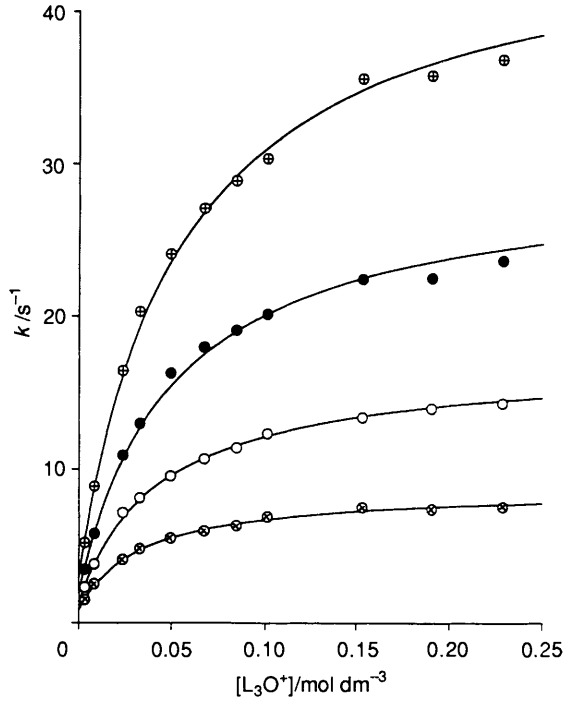
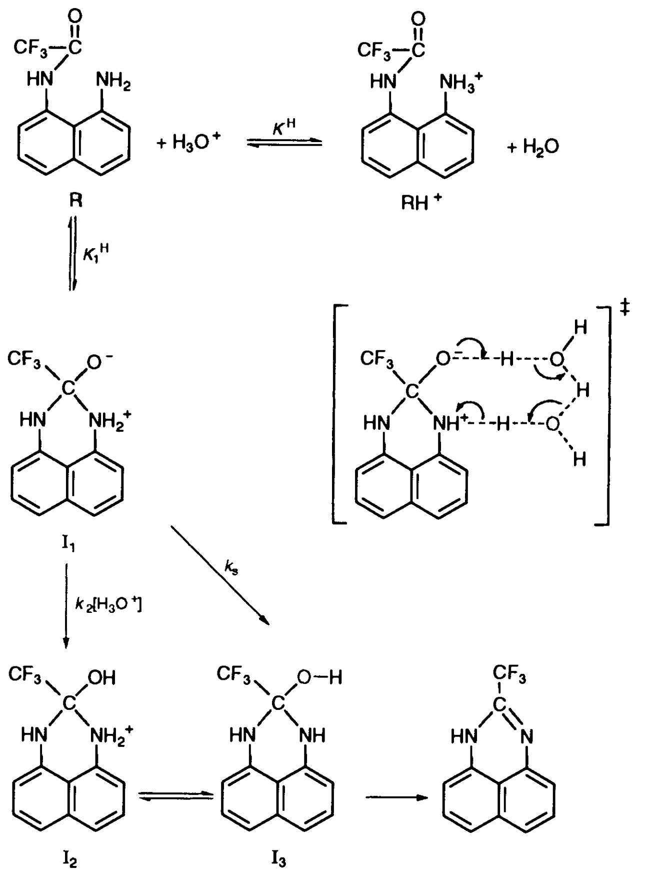


Fig. 2 Dependence of the first-order rate coefficient for the reaction in eqn. (1) on hydronium ion concentration (L = H or D) in 70% (v/v) $Me_2SO–H_2O$ at different temperatures (°C) (15.8, ⊗; 25.3, ○; 35.0, ●; 43.4, ⊕)

Activation parameters for the terms in the rate law corresponding to the spontaneous and the acid catalysed reactions were calculated from linear regression plots of $\ln(k_0{}^H/T)$ and $\ln(k_H/T)$ respectively against $1/T$. For the spontaneous reaction the results $\Delta H^\ddagger$ 30.0 kJ mol^{-1} and $\Delta S^\ddagger$ -142.1 J K^{-1} mol^{-1} were obtained and for acid catalysis the values $\Delta H^\ddagger$ 30.7 kJ mol^{-1} and $\Delta S^\ddagger$ -92.3 J K^{-1} mol^{-1} were calculated. The values of K^H at different temperatures were plotted in the form $\ln(K^H)$ against $1/T$ to give the values $\Delta H°$ -12.4 kJ mol^{-1} and $\Delta S°$ -15.7 J K^{-1} mol^{-1} for the standard enthalpy and entropy of protonation of the amino group in 1-trifluoroacetylaminonaphthalene.

Mechanism of Addition–Elimination.—For the addition–elimination of 1-amino-8-trifluoroacetylaminonaphthalene to give 2-trifluoromethylperimidine, eqn. (1), rate coefficients for catalysis by buffer acids gave a biphasic Brønsted plot of $\log k_{HA}$ against pK_a with slopes of zero and unity.[2] A mechanism was proposed involving formation of a zwitterionic intermediate in low concentration by intramolecular addition of the amino group to the amide carbonyl. This is followed by rate-limiting protonation of the intermediate by buffer acids in a diffusion-controlled reaction. The same mechanism is given in Scheme 1



Scheme 1

for catalysis by hydronium ion. A possible route to explain the large spontaneous term (k_0^H) in the rate law is also shown in Scheme 1 and involves interconversion of intermediates I_1 and I_3 by a solvent-mediated proton switch.[4] The value of the rate coefficient for the spontaneous reaction k_0^H 1.30 s^{-1}, when converted to a second-order rate coefficient of *ca.* 0.07 dm^3 mol^{-1} s^{-1}, is similar in magnitude to the catalytic coefficient for a buffer acid[2] of pK_a *ca.* 11. Therefore, since the value pK_a *ca.* 19 has been found[3] for water in 70% (v/v) $Me_2SO–H_2O$ the spontaneous reaction cannot be understood in terms of water behaving as a Brønsted acid catalyst. Proton switch mechanisms have been suggested previously to explain the high magnitude of spontaneous terms in acyl transfer reactions.[4]

For the mechanism in Scheme 1 the expression in eqn. (4) is

$$k = K_1^H(k_s^H + k_2^H[H_3O^+])/(1 + K^H[H_3O^+]) \quad (4)$$

$$k_0^H = K_1^H k_s^H \text{ and } k_H = K_1^H k_2^H \quad (5)$$

obtained for the first-order rate coefficient for formation of the perimidine on the assumption that the tetrahedral intermediates are present in low concentration. It is also necessary to assume that the rate of protonation of the zwitterionic intermediate (I_1) by hydronium ion and the rate of the conversion of I_1 to I_3 by the proton switch are lower than the rates of the subsequent reaction steps and lower than the rate at which I_1 reverts to 1-amino-8-trifluoroacetylaminonaphthalene. In eqn. (4), K_1^H is the equilibrium constant for the intramolecular addition to give I_1. In terms of this mechanism the rate coefficients in eqn. (2) are given by the expressions in eqn. (5).

The value of K^H deduced from the dependence of k on hydronium ion concentration in 70% (v/v) $Me_2SO–H_2O$ corresponds to pK_a 1.4 for dissociation of protonated 1-amino-8-trifluoroacetylaminonaphthalene under these conditions. Assuming that the protonation of I_1 by hydronium ion is diffusion limited (k_2^H 3 × 10^{10} dm^3 mol^{-1} s^{-1}) the values of k_0^H and k_H at 25.3 °C obtained from the kinetic analysis lead to K_1^H 1.3 × 10^{-8} and k_s^H 1.0 × 10^8 s^{-1}. The latter result is similar to previous estimates of the value of the rate coefficient for proton switch reactions.[4]

The equilibrium isotope effect K^H/K^D 0.38 calculated from the results in Table 1 is consistent with the value expected for the solvent isotope effect on protonation of an amino group. The result corresponds to a solvent isotope effect on the ratio of acid dissociation constants of the protonated amine in 70% (v/v) $Me_2SO–H_2O$ and 70% (v/v) $Me_2SO–D_2O$ of 2.7 which is within the range of values commonly found for solvent isotope effects on the dissociation of acids, including protonated amines, in aqueous solution.[5] The low values of the kinetic solvent isotope effect on the rate coefficient for hydronium ion catalysis k_H/k_D 1.4 is compatible with the mechanism in Scheme 1. According to this mechanism the catalytic coefficient is given by the product of the equilibrium constant for intramolecular addition of the amino group to the amide carbonyl to form I_1 and the rate coefficient for protonation of I_1 by hydronium ion to give I_2 in a diffusion-controlled reaction, $k_H = K_1^H k_2^H$ as in eqn. (5). The overall solvent isotope effect k_H/k_D is small because the isotope effect K_1^H/K_1^D consists of a small medium effect and a small secondary isotope effect and since the proton transfer step involving hydronium ion is a diffusion-controlled process, the isotope effect k_2^H/k_2^D will also have a value close to unity. The kinetic solvent isotope effect on the spontaneous reaction k_0^H/k_0^D 1.9 is composed of a solvent isotope effect on the equilibrium constant for the intramolecular addition and a kinetic solvent isotope effect on the proton switch, $k_0^H/k_0^D = (K_1^H/K_1^D) \times (k_s^H/k_s^D)$. If as expected the isotope effect on the intramolecular addition has a value close to unity (K_1^H/K_1^D *ca.* 1.0) it follows that k_s^H/k_s^D *ca.* 1.9. A solvent isotope effect of this magnitude is expected for a proton switch mechanism.[6]

The standard thermodynamic quantities for dissociation of the protonated amine calculated from the values of K^H in Table 1 are $\Delta H°$ + 12.4 kJ mol^{-1} and $\Delta S°$ + 15.7 J K^{-1} mol^{-1}. In aqueous solution the enthalpy of ionisation of protonated amines shows[7] a roughly linear correlation with pK_a value so that strongly acidic protonated amines have low positive values of $\Delta H°$; the value $\Delta H°$ + 12.4 kJ mol^{-1} fits in with this correlation. The calculated values of the enthalpy and entropy of activation for the hydronium ion catalysed reaction, $\Delta H^‡$ 30.7 kJ mol^{-1} and $\Delta S^‡$ − 92.3 J K^{-1} mol^{-1}, permit values to be estimated for the standard enthalpy and entropy changes for the intramolecular addition of the amino group to the amide carbonyl as the first step in the mechanism shown in Scheme 1. For the diffusion-limited protonation it is assumed that the enthalpy and entropy of activation respectively have values of $\Delta H^‡$ 10 kJ mol^{-1} and $\Delta S^‡$ − 11 J K^{-1} mol^{-1} which correspond to a rate coefficient of k_2^H 3 × 10^{10} dm^3 mol^{-1} s^{-1}. When combined with the measured activation parameters deduced from the temperature dependence of k_H these estimates lead to values for the standard enthalpy and entropy changes for the intramolecular addition to form I_1 of $\Delta H°$ 21 kJ mol^{-1} and $\Delta S°$ − 81 J K^{-1} mol^{-1}. The large and negative value of the entropy change associated with this reaction is to be expected for a process involving formation of a cyclic intermediate by an intramolecular addition. Rotational freedom is lost in the cyclisation and also the formation of a zwitterionic species is likely to involve solvation changes which contribute to the decrease in entropy. The enthalpy and entropy of activation for the spontaneous reaction, $\Delta H^‡$ 30.0 kJ mol^{-1} and $\Delta S^‡$ − 142.1 J K^{-1} mol^{-1}, are each comprised of two terms: the standard enthalpy and entropy of the intramolecular addition to give I_1 and the enthalpy and entropy of activation of the proton switch.

The proton switch involves proton transfer from the NH^+ site to the O^- site in I_1 through two water molecules to give I_3 as shown in Scheme 1. If the standard enthalpy and entropy changes calculated for the equilibrium formation of I_1 (ΔH° 21 kJ mol^{-1} and ΔS° − 81 J K^{-1} mol^{-1}) are combined with the values of $\Delta H^\ddagger$ and $\Delta S^\ddagger$ for the spontaneous reaction, activation parameters for the solvent-mediated proton switch of $\Delta H^\ddagger$ 9 kJ mol^{-1} and $\Delta S^\ddagger$ − 61 J K^{-1} mol^{-1} are calculated. For a reaction with a transition state involving proton transfer through two water molecules, a large and negative entropy of activation is expected.

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