Mechanism of an Intramolecular Addition–Elimination between Amino and Amide Groups; a Biphasic Brønsted Plot for Acid Catalysis as Evidence for Rate-limiting Proton Transfer to the Addition Intermediate

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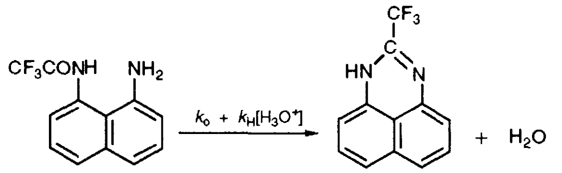
Formation of 2-trifluoromethylperimidine from 1-amino-8-trifluoroacetylaminonaphthalene involves intramolecular nucleophilic addition of the amino group to the amide carbonyl followed by elimination to form the cyclic imine; a biphasic Brønsted plot with slopes α *ca.* 0 and 1.0 respectively for catalysis by acids (HA) with pK_{HA} values below and above a break point at pK_{HA} 8.5 is compatible with rate-limiting protonation of the zwitterionic addition intermediate by general acids and with a proton switch mechanism for reaction with water.

Nucleophilic addition of an amine to a carbonyl group followed by elimination of water to give an imine is an important reaction with numerous applications in organic chemistry[1] and biochemistry.[2] The reaction can occur by a variety of mechanisms depending on the structure of the reactants. We now report details of the mechanism of an intramolecular example in which addition–elimination between an amine and an amide carbonyl occurs.

The rate–pH profile[3] for formation of the cyclic imine 2-trifluoromethylperimidine from 1-amino-8-trifluoroacetyl-



(1)

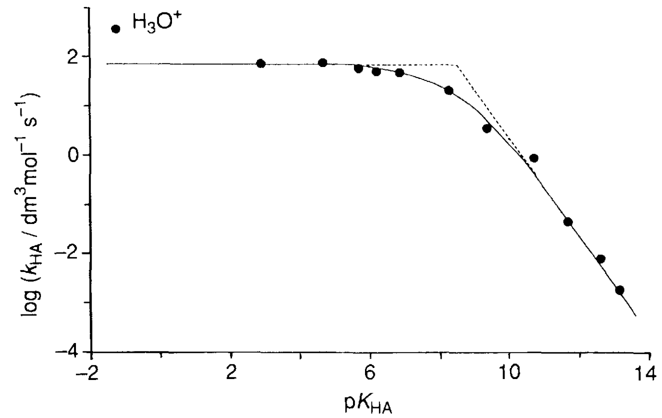


Fig. 1 Brønsted plot for acid catalysis in the cyclisation of 1-amino-8-trifluoroacetylaminonaphthalene to 2-trifluoromethylperimidine; the filled circles are experimental values and the curve is constructed for normal proton transfer to and from an intermediate of pK 8.5

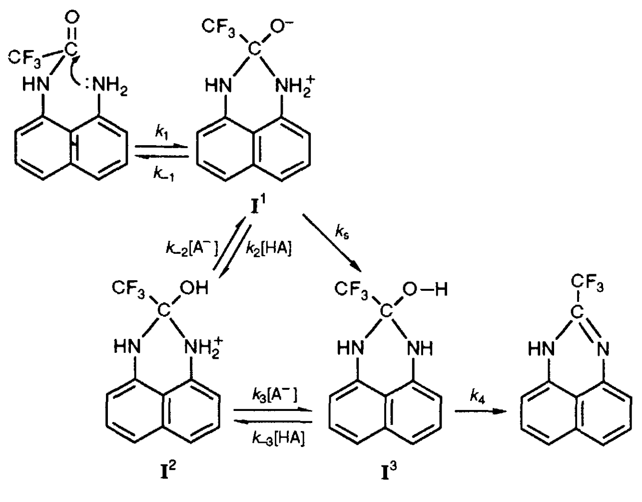
aminonaphthalene in 70% (v/v) $Me_2SO–H_2O$, eqn. (1), shows that reaction occurs by spontaneous (k_0 1.36 s^{-1}) and hydronium ion (k_H 366.5 $dm^3\ mol^{-1}\ s^{-1}$) catalysed pathways and that forms of 1-amino-8--trifluoroacetylaminonaphthalene in which the amino group is protonated (pK 1.4) or the amido group is ionised (pK 9.3) are unreactive.

We now report detailed studies of the reaction in eqn. (1) in the presence of buffers in 70% (v/v) $Me_2SO–H_2O$ at 298.15 K and ionic strength 0.25 mol dm^{-3}. The buffers used were carboxylic acids, phenols and benzimidazole for which pK values have been measured in this solvent.[3,4] The concentration of 1-amino-8-trifluoroacetylaminonaphthalene was in deficit compared with the buffer, and for each buffer, first-order rate coefficients for reaction (1) were determined at buffer concentrations in the range *ca.* 0.01 to 0.1 mol dm^{-3} for three buffer ratios r = [buffer anion]/[buffer acid] = 0.5, 1.0 and 2.0. The first-order rate coefficients (k_{obs}) obtained by the stopped-flow technique were reproducible to within ±2% and the dependence on buffer concentration was linear, eqn. (2). For each buffer, the value of k_{HA} was obtained from the gradient of plots of k_{obs} against $[A^-]$ and the average of values at each buffer ratio was taken. In eqn. (2), k is the rate coefficient for reaction involving species derived from water.[3] The values of k_{HA} for the eleven buffers together with the rate coefficient for catalysis by hydronium ion[3] are shown in Fig. 1 in which $\log k_{HA}$ is plotted against pK_{HA}. If Brønsted plots are drawn for the three most strongly acidic and the three most weakly acidic buffers, values of the Brønsted exponent α of 0.03 and 0.94, respectively, are obtained. Statistical corrections for the different numbers of basic sites in the carboxylate and phenolate ions have not been applied.

$$k_{obs} = k + k_{HA}[A^-]/r \qquad (2)$$

A mechanism consistent with the biphasic Brønsted plot is shown in Scheme 1 in which it is assumed that the intermediates are present in low concentration. For the pathway involving buffer the assumptions $k_{-1} \gg k_2[HA]$ and $k_4 \gg k_{-3}[HA]$ lead to eqn. (3) for the rate coefficient for buffer

$$k_{HA} = k_1k_2k_3/k_{-1}(k_3 + k_{-2}) \qquad (3)$$



Scheme 1

catalysis. The reversible interconversions of I^1 to I^2 and I^2 to I^3 occur by normal proton transfer steps and it will be assumed that the rate coefficients have diffusion-limited values in the thermodynamically favourable directions.[5] If it is assumed that the diffusion-limited value of k_3 exceeds that of k_{-2} because of the different charge type, eqn. (3) is reduced to $k_{HA} = k_2K_1$, in which K_1 is the equilibrium constant for intramolecular nucleophilic addition to form the zwitterionic intermediate I^1. The variation of k_{HA} with the pK_{HA} value of the buffer is then determined by the variation of k_2. The value of k_2 is assumed to be diffusion-limited (k_2 1×10^{10} $dm^3\ mol^{-1}\ s^{-1}$) and independent of K_{HA} for proton transfer from acids (HA) which have lower pK_{HA} values than the pK value, p$K(I^2)$, of the hydroxy group in I^2, and k_2 is assumed to vary directly with K_{HA} for the reaction of acids for which pK_{HA} exceeds p$K(I^2)$. For acids with pK_{HA} within ±3 units of p$K(I^2)$, k_2 is assumed to show a curved dependence with pK_{HA}.[5] Making these assumptions the data in Fig. 1 are fitted (solid line) using the value p$K(I^2)$ 8.5 which is similar to previous estimates[6] for tetrahedral intermediates like I^2. The value of p$K(I^2)$ can be estimated by extrapolation of a σ*ρ plot[7] of the aqueous pK values of alcohols and the result when corrected[3] to 70% (v/v) $Me_2SO–H_2O$ is p$K(I^2)$ 7.8 which is compatible with the value calculated from the kinetic data. The limiting rate (k_{HA} *ca.* 67.6 $dm^3\ mol^{-1}\ s^{-1}$) of proton transfer from acids with p$K_{HA} < 8.5$ when combined with k_2 1×10^{10} $dm^3\ mol^{-1}\ s^{-1}$ and the expression $k_{HA} = k_2K_1$ gives the value K_1 6.8×10^{-9} for the equilibrium constant for intramolecular nucleophilic addition of the amino group to the amide carbonyl.

The data point for hydronium ion, k_H 366.5 $dm^3\ mol^{-1}\ s^{-1}$, is *ca.* 5.4-fold above the line defined for proton transfer from carboxylic acids in Fig. 1. This is expected in view of the higher diffusion-limited rate for hydronium ion.

A mechanism involving general acid catalysis of the addition and elimination steps would also explain a biphasic Brønsted plot if different values of the Brønsted exponent applied for each step and if a change in rate-limiting step occurred at the break point. This could arise if for the reaction in weakly acidic–strongly basic buffers the reverse of the carbonyl addition step was strongly catalysed by buffer base in which case elimination would be rate-limiting. For strongly acidic–weakly basic buffers, elimination would be faster than the reverse of the carbonyl addition and acid-catalysed addition would be rate-limiting. Although a change in slope of the Brønsted plot could be explained in this way as the buffer pK_{HA} is increased, the mechanism is not compatible with the limiting values of α close to zero and unity which are observed for the two phases of the Brønsted plot.

The high value of the rate coefficient k_0 1.36 s^{-1} for the spontaneous reaction can be understood in terms of Scheme 1 by assuming that the zwitterionic intermediate $\mathbf{I}^1$ is converted directly to $\mathbf{I}^3$ by a water-mediated proton switch.[6] If it is assumed that $k_{-1} \gg k_s$ the rate coefficient for spontaneous cyclisation is given by $k_0 = K_1 k_s$. Using the result $K_1 = 6.8 \times 10^{-9}$ it follows that $k_s = 2.0 \times 10^8\ s^{-1}$ which is close to the values that have previously been found[6] for water-catalysed proton switch reactions and therefore confirms the validity of the proposed mechanism.

The rate-limiting step in the cyclisation of 1-amino-8-trifluoroacetylaminonaphthalene is a proton transfer which is diffusion-limited for reaction in the presence of buffers with $pK_{HA} < 8.5$. Even though the rate-limiting step is a diffusion-controlled process, cyclisation occurs relatively slowly because addition of the amino group to the amide carbonyl in 1-amino-8-trifluoracetylaminonaphthalene is strongly unfavourable with K_1 6.8×10^{-9}. Although the intramolecular addition of the aromatic amino group to the amide carbonyl in 1-amino-8-trifluoroacetylaminonaphthalene is unfavourable it is much more favourable than the corresponding intermolecular reaction.[8]

Equipment grants from the SERC and the University of London Central Research Fund and studentships from the SERC (to A. S. B.) and the Government of Pakistan (to M. A. M.) are gratefully acknowledged.

Received, 19th May 1992; Com. 2/02616C

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