Catalysis in Ester Aminolysis in Aprotic Solvents. The Amine-catalysed Reaction of Imidazole with 4-Nitrophenyl Trifluoroacetate in Aqueous Acetonitrile

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The imidazolysis of 4-nitrophenyl trifluoroacetate has been investigated in aqueous acetonitrile containing 0.56 mol dm^{-3} of water. The reaction is found to be general base-catalysed by pyridines and 1-methylimidazole. The catalytic abilities of sterically unhindered pyridines correlate with their aqueous pK_a values with a Brønsted β value of 0.79. The high value of β is thought to reflect the electrophilicity of the substrate and the polarity of the medium.

Studies on acyl-transfer reactions are of importance when attempting to understand the mechanism of enzyme actions.[1] Further, it has been suggested that the microenvironment of the active sites of enzymes are better mimicked by aprotic solvents than by aqueous media because of the hydrophobic properties of the enzyme active sites.[2–4]

The mechanism of ester aminolysis in aqueous media is fairly well understood.[1b,5] Although quite a large amount of information also exists about the kinetics and mechanism of ester aminolysis in aprotic media, relatively little is known about the general base-catalysed aminolysis under these conditions, and despite the biological importance of imidazole, only few reports concern its reactions.[2a,3,6–10]

The kinetics governing the reaction between imidazole and 4-nitrophenyl trifluoroacetate in aqueous acetonitrile (0.56M-H_2O) has been determined previously.[11] This reaction obeys the rate law (1) where [ImH] is the imidazole concentration, k_0

$$k_{obs.} = k_0 + k_1[\text{ImH}] + k_2[\text{ImH}]^2 \qquad (1)$$

is the rate coefficient for the neutral hydrolysis, k_1 is the rate coefficient for the general base-catalysed hydrolysis by imidazole, and k_2 is the rate coefficient for the imidazole-catalysed nucleophilic attack of imidazole. In 0.56M-water in acetonitrile, the second-order rate coefficients for the general base-catalysed hydrolysis of 4-nitrophenyl trifluoroacetate by sterically unhindered pyridine bases correlate with the aqueous pK_a values of the bases with a Brønsted β value of 0.59.[11] In this context, it was of interest to study the amine-catalysed reaction of imidazole with 4-nitrophenyl trifluoroacetate in the same reaction media.

Experimental

Materials.—4-Nitrophenyl trifluoroacetate was prepared according to Sakakibara and Inukai[12] and was recrystallized from hexane, m.p. 37—38 °C (lit.,[12] 36—38 °C). Amines were purified as previously described.[11] Acetonitrile (Merck; maximum water content 0.03%) used in the preparation of the kinetic solutions and for the stock solutions of the substrate was spectrophotometric grade and was used as received. Freshly prepared amine solutions were always used.

Kinetics.—Reaction rates were determined by following the formation of 4-nitrophenol using a Perkin-Elmer 550 spectrophotometer at 310 nm. The reactions were started by injection of a solution of the substrate in acetonitrile (1—3 mm^3) into the reaction solution which had been preheated in the optical cell (3 cm^3) in the thermostatted cell compartment of the spectrophotometer. The initial substrate concentration was $(4 \pm 1) \times 10^{-5}$ mol dm^{-3}. The temperature during the run was measured with a calibrated NTC-thermistor and was accurate to 0.1 °C. The first-order rate coefficients $k_{obs.}$ were calculated using equation (2), where A_∞, A_t, and A_0 are the

$$k_t = \frac{1}{t}\ln\frac{A_\infty - A_0}{A_\infty - A_t} \qquad (2)$$

absorbance values at the end of the reaction, at time t, and at the beginning of the reaction, respectively. The standard deviations of the mean value of $\bar{k}_t$, the mean value of k_t for a run, were 0.5—1%. Each run was at least duplicated, in most cases three determinations were performed. The rate coefficients were reproducible to within ±2%.

Results

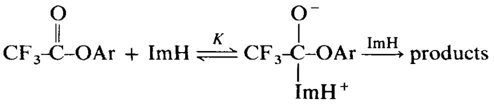
The reaction between imidazole and 4-nitrophenyl trifluoroacetate was studied in the presence of several tertiary amines. The experimental conditions of the reactions and the values of $k_{obs.}$ are shown in Table 1. The kinetic data fit equation (3),

$$k_{obs.} = k_0 + k_1[\text{ImH}] + k_2[\text{ImH}]^2 + k'_1[\text{B}] + k_{cat.}[\text{ImH}][\text{B}] \qquad (3)$$

where B is the added amine. The reaction associated with the k'_1 term is the general base-catalysed hydrolysis of the ester by the amine B.[11] With a constant concentration of imidazole, a plot of $k_{obs.}$ *vs.* [B] yielded in each case a straight line with intercept $k_0 + k_1[\text{ImH}] + k_2[\text{ImH}]^2$ and slope $k'_1 + k_{cat.}[\text{ImH}]$. The values of $k_{cat.}$ for each amine B were calculated from the slopes of the plots with the aid of k'_1 values determined previously.[11] The $k_{cat.}$ values are given in Table 2. The relative constancy of the intercept ($k_0 + k_1[\text{ImH}] + k_2[\text{ImH}]^2$) around its calculated value 2.93×10^{-2} s^{-1} [k_0, k_1, and k_2 from ref. (11)] could be observed (Table 1). The $k_{cat.}$ value for 1-methylimidazole (8 970 dm^6 mol^{-2} s^{-1}) is comparable with the k_2 value for imidazole (7 800 dm^6 mol^{-2} s^{-1}).[11] These amines show equal aqueous basicity.[13]

Discussion

For the imidazole-catalysed reaction of imidazole with 4-nitrophenyl trifluoroacetate a reaction sequence such as that shown in the Scheme, consisting of a reversible formation of a



$$\mathrm{CF_3\overset{\overset{\displaystyle O}{\|}}{C}{-}OAr} + \mathrm{ImH} \underset{}{\overset{K}{\rightleftharpoons}} \mathrm{CF_3\overset{\overset{\displaystyle O^-}{|}}{\underset{\underset{\displaystyle ImH^+}{|}}{C}}{-}OAr} \xrightarrow{\text{ImH}} \text{products}$$

Scheme.

Table 1. Experimental conditions and first-order rate coefficients ($k_{obs.}$) for the amine-catalysed reaction of imidazole with 4-nitrophenyl trifluoroacetate in 0.56M-water in acetonitrile at 298.2 K[a]

Amine	Range of [amine]/ mol dm^{-3}	$k_{obs.}/10^{-2}$ s^{-1}	Number of runs	Intercept[b]/10^{-2} s^{-1}
Pyridine	0.005—0.025	2.86—3.69	15	(2.96 ± 0.04)
3-Methylpyridine	0.005—0.025	3.08—4.71	15	(2.69 ± 0.01)
3,4-Dimethylpyridine	0.002—0.010	3.32—5.45	15	(2.80 ± 0.06)
2,4-Dimethylpyridine	0.002—0.010	3.37—5.42	15	(2.87 ± 0.03)
1-Methylimidazole	0.0005—0.0025	3.81—8.26	13	(2.91 ± 0.07)

[a] The imidazole concentration was 1.5×10^{-3} mol dm^{-3}. Five different concentrations were used for each amine. [b] The value for $k_0 + k_1[\text{ImH}] + k_2[\text{ImH}]^2$ in equation (3); the calculated value is 2.93×10^{-2} s^{-1}.[11]

Table 2. Rate coefficients $k_{cat.}$ for the amine-catalysed reaction of imidazole with 4-nitrophenyl trifluoroacetate in 0.56M-water in acetonitrile at 298.2 K

Amine	pK_a[a]	pK_{HB}[b]	$k_{cat.}$/dm^6 mol^{-2} s^{-1}
Pyridine	5.22	1.88	65 ± 20
3-Methylpyridine	5.63	1.97	129 ± 11
3,4-Dimethylpyridine	6.46		620 ± 80
2,4-Dimethylpyridine	6.63	2.17	640 ± 40
1-Methylimidazole	6.95	2.50	8 970 ± 370

[a] The aqueous pK_a values [ref. (13)]. [b] The logarithms of the formation constants for the 4-fluorophenol hydrogen-bonded complex in carbon tetrachloride (L. Joris, J. Mitsky, and R. W. Taft, *J. Am. Chem. Soc.*, 1972, **94**, 3438; R. W. Taft, D. Gurka, L. Joris, P. von Schleyer, and J. W. Rakshys, *J. Am. Chem. Soc.*, 1969, **91**, 4801).

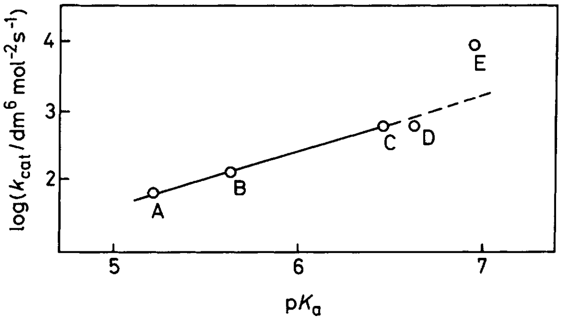


Figure 1. Dependence on aqueous amine basicity of the third-order rate coefficients for the amine-catalysed reaction of imidazole with 4-nitrophenyl trifluoroacetate in 0.56M-water in acetonitrile at 298.2 K. A, pyridine; B, 3-methylpyridine; C, 3,4-dimethylpyridine; D, 2,4-dimethylpyridine; E, 1-methylimidazole

zwitterionic tetrahedral intermediate, had been previously assigned.[11] The breakdown of the intermediate was concluded to be rate-limiting. If the primary reaction product, 1-trifluoroacetylimidazole, is rapidly hydrolysed,[11] the reaction is, in fact, a general base-catalysed nucleophilic catalysis of ester hydrolysis. The substantial negative activation enthalpy, −18.9 kJ mol^{-1}, observed for this reaction[11] is consistent with a reaction process involving an exothermic equilibrium prior to the product-forming step. Such a mechanism was originally proposed by Menger and co-workers for ester aminolysis in aprotic solvents,[3b,6] and thereafter it has been accepted for several reactions with varying combinations of amines, esters, and solvents.[7,8,9b,14] Recently, Nagy *et al.*[15] suggested a mechanism for ester aminolysis in aprotic solvents in which the attacking nucleophile forms an *n*–π type molecular complex with the substrate. The complex is converted in the subsequent step into the tetrahedral intermediate. The rate-limiting breakdown of the intermediate to products was thought to be spontaneous or catalysed by an amine monomer or by an amine dimer.

Catalysis by bases other than the attacking amine has been observed in several studies concerning ester aminolysis in aprotic solvents, *e.g.*, 1,4-diazabicyclo[2.2.0]octane (DABCO) catalyses the reaction of butylamine with phenyl acetate in chlorobenzene,[16a] the reaction of butylamine with 4-nitrophenyl acetate in diethyl ether,[16b] and the reaction of pyrrolidine with 4-nitrophenyl acetate in acetonitrile.[6] Benzoate ion catalyses the reaction of imidazole with 4-nitrophenyl acetate in 1M-water in acetonitrile[2a,9d] and in toluene,[3b] and the reaction of piperidine with 4-nitrophenyl acetate in toluene.[3b]

The first systematic study with respect to the effect of the structure of the catalysing base was performed by Su and Watson.[7] In the butylaminolysis of 4-nitrophenyl acetate in chlorobenzene, the catalytic abilities of different types of catalysts correlated with the abilities of the catalysts to form hydrogen-bonded complexes rather than with their aqueous basicities.[7] The catalytic coefficients correlated by the equation $\log k_{cat.} = 1.2H - 3.3$, where H is the logarithm of the formation constant of the hydrogen-bonded complex with 4-fluorophenol in chlorobenzene. It was deduced that the catalysts facilitate the expulsion of the phenolate anion from the addition intermediate by accepting the ammonium proton in the transition state to an extent equivalent to that of hydrogen-bonded complex formation with 4-fluorophenol.[7] With a single class of catalysts and in the absence of severe steric hindrance, the catalytic ability followed aqueous basicity; *e.g.* for pyridines $\Delta \log k_{cat.}/\Delta pK_a \approx 0.3$.

Tertiary amine catalysis has been observed in the butylaminolysis of 4-nitrophenyl 3,5-dinitrobenzoate in benzene.[15] The catalysis was provided both by the tertiary amine alone and by butylamine–tertiary amine complex. In both cases, the catalytic ability did not correlate with the aqueous basicity but with the hydrogen-bond forming ability of the catalysts. The authors did not consider the effects of solvent on the relative basicity of the catalysts, although they used different types of amines.

The logarithms of the rate coefficients $k_{cat.}$ determined in the present study (Table 2) are plotted against the aqueous pK_a values in Figure 1. For the three unhindered pyridine bases a linear Brønsted line with a β value of 0.79 ± 0.02 is obtained. This β value is meaningful taking the assumption that the pK_a shift from water to 0.56M-water in acetonitrile is constant for all pyridine bases. The steric hindrance by the 2-methyl substituent accounts for the small deviation of 2,4-dimethylpyridine from the line in Figure 1.[8,11,17] A notable positive deviation is observed for 1-methylimidazole. Similar deviation of imidazoles from the Brønsted plot was previously observed for the amine-catalysed hydrolysis of 4-nitrophenyl trifluoroacetate in 0.56M-water in acetonitrile.[11] The apparent enhanced reactivity of imidazoles as compared with pyridines can be tentatively attributed to a somewhat higher ΔpK_a for the conjugate acids of imidazoles than for those of pyridines for the solvent change

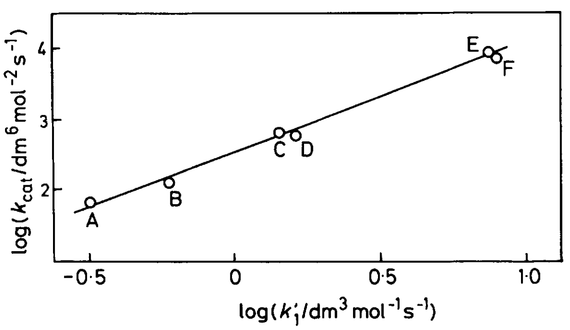


Figure 2. A double-logarithmic plot correlating the third-order rate coefficients for the amine-catalysed reaction of imidazole with 4-nitrophenyl trifluoroacetate against the second-order rate coefficients for the amine-catalysed hydrolysis of 4-nitrophenyl trifluoroacetate in 0.56M-water in acetonitrile at 298.2 K. The point for imidazole [ref. (11)] is included. A, pyridine; B, 3-methylpyridine; C, 3,4-dimethylpyridine; D, 2,4-dimethylpyridine; E, 1-methylimidazole; F, imidazole

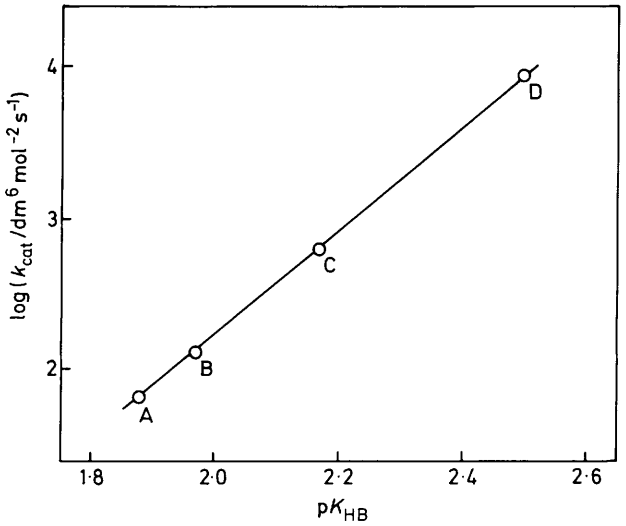


Figure 3. Plot of the logarithms of the third-order rate coefficients for the amine-catalysed reaction of imidazole with 4-nitrophenyl trifluoroacetate in 0.56M-water in acetonitrile at 298.2 K *vs.* the hydrogen-bond forming ability of the amines with 4-fluorophenol in carbon tetrachloride. A, pyridine; B, 3-methylpyridine; C, 2,4-dimethylpyridine; D, 1-methylimidazole

from water to the water–acetonitrile mixture employed. The average ΔpK_a for the transfer of substituted ammonium ions from water to acetonitrile is 7.3 but it varies somewhat for different types of compounds.[18]

When the $k_{cat.}$ values (Table 2) are plotted logarithmically against the k'_1 values, the rate coefficients for the amine-catalysed hydrolysis of 4-nitrophenyl trifluoroacetate in 0.56M-water in acetonitrile,[11] a fairly good correlation is observed (Figure 2; the k_1 and k_2 values for imidazole are included in the Figure[11]). This implies similar relative reactivity differences between imidazoles and pyridines in these two reactions. The value of the slope of the plot, 1.6, indicates a more advanced proton transfer in the transition state of the catalysed imidazolysis as compared with the general base-catalysed hydrolysis. A plot of log $k_{cat.}$ *vs.* the pK_{HB} values (*cf.* Table 2) was found to be linear and of slope 3.5 (Figure 3). In that case 1-methylimidazole fits the same line as pyridines.

The first step in any proton transfer is the formation of a hydrogen bond between the proton donor and the proton acceptor.[19] Singh and Taft[8] suggested for the general base-catalysed reactions in aprotic solvents a multi-parameter equation such as (4) to analyse the contribution of proton-

$$\log k = a\,pK_{HB} + b\,pK_a + c \qquad (4)$$

transfer and hydrogen-bonded complex energetics in the transition states. In the base-catalysed butylaminolysis of 4-nitrophenyl trifluoroacetate in chlorobenzene and 1,2-dichloroethane, the correlation with the hydrogen-bond forming ability (pK_{HB}) is dominant, whereas the proton-transfer energetics dominate in the base-catalysed methanolysis of the same ester in the same solvents (0.495M-MeOH).[8] In 1,2-dichloroethane, the more polar of the two solvents, the catalytic coefficients of methanolysis correlate with pK_a values only. Singh and Taft[8] have proposed that in the general base-catalysed reactions in aprotic solvents the increased polarity of the solvent, the increased Lewis acidity of the substrate, and the decreased basicity of the attacking nucleophile lead to transition states with increased contributions of proton-transfer energetics relative to the hydrogen-bonded complex energetics. Weak bases but strong hydrogen-bond acceptors, such as dimethylformamide and dimethyl sulphoxide, are very effective catalysts in the butylaminolysis of 2-hydroxy-5-nitro-α-toluenesulphonic acid sultone in toluene, the catalytic constants being well correlated by the hydrogen-bonding parameter pK_{HB}. However, the same catalysts are ineffective in the more polar acetonitrile.[4b]

In the amine-catalysed reaction of imidazole with 4-nitrophenyl trifluoroacetate, the catalysing amine presumably accepts the ammonium proton from the tetrahedral intermediate and thereby impairs the back-reaction of the intermediate to reactants.[6,11] The observed β value, 0.79, implies that the reaction occurs with considerable proton transfer to the catalysing base in the transition state. Further, a more advanced proton transfer in the catalysed imidazolysis than in the general base-catalysed hydrolysis of 4-nitrophenyl trifluoroacetate is obvious (Figure 2, slope = 1.6). In the latter reaction the catalyst is assumed to assist the attack of water on the carbonyl carbon in the formation of an addition intermediate.[11,20] The value of 0.79 falls in fact near the range of β usually observed for nucleophilic catalysis in aqueous solutions.[5a,21] However, the value of β obviously also reflects the acidity of the nucleophile and the present work deals with a molecule other than water as the proton donor.

The high value of β observed in the present work is consistent with the suggestion[8] that the increased polarity of the solvent and the increased Lewis acidity of the substrate lead to an increased degree of proton transfer in the transition state in the general base-catalysed reactions in aprotic solvents. The dielectric constant of acetonitrile is high,[22] the strong Lewis-acid character of 4-nitrophenyl trifluoroacetate is evident,[8] and imidazole is a much weaker base than butylamine.[13,18] The value of β (0.79) is 2.6 times as high as that determined for the general base-catalysed butylaminolysis of 4-nitrophenyl acetate by pyridines in chlorobenzene.[7] When the logarithms of the third-order rate coefficients for the three pyridine bases used by Singh and Taft[8] in the base-catalysed butylaminolysis of 4-nitrophenyl trifluoroacetate in 1,2-dichloroethane are plotted against aqueous pK_a values, they fit a single line of slope 0.56. In spite of the good correlation shown in Figure 3, it appears likely that the proton-transfer energetics are dominant relative to hydrogen-bond forming energetics in the transition state of the present reaction. The amines used in the present work are, however, structurally as alike to each other as possible in order to avoid relative pK_a shifts of the conjugate acids of the amines from water to the aqueous acetonitrile. Therefore, the results are insufficient to finally justify whether the correlation of the catalytic ability is with the proton basicity or with the hydrogen-bond-forming ability of the amines.

Additional studies with other types of catalysts, substrates, and solvents are required in order to determine more exactly the catalytic efficiency of weakly basic groups in general base-catalysed ester aminolysis in aprotic solvents. When justifying whether the catalytic coefficients correlate with the basicity of the catalysts, one must be careful with the use of aqueous pK_a values because of varying solvent effects on the basicities of different types of compounds.

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