Kinetics and Mechanisms of Reactions of Pyridines and Imidazoles with Phenyl Acetates and Trifluoroacetates in Aqueous Acetonitrile with Low Content of Water: Nucleophilic and General Base Catalysis in Ester Hydrolysis

Helmi Neuvonen
Department of Chemistry and Biochemistry, University of Turku, SF-20500 Turku, Finland

Reactions of pyridines and imidazoles with substituted phenyl acetates and trifluoroacetates have been studied in acetonitrile and in water–acetonitrile containing 0.56 mol dm^{-3} of water. The water isotope effects, steric effects, the effect of water in the reaction medium, and the derived Brønsted β and Hammett ρ values have been used as mechanistic criteria. Pyridines and imidazoles catalyse the hydrolysis of phenyl trifluoroacetates by general base catalysis while imidazole acts as nucleophile toward 4-nitrophenyl and 2,4-dinitrophenyl acetates. As indicated by the second-order dependence on amine concentration beside the first-order term in amine, the reaction of imidazole exhibits general base catalysis in the case of both phenyl acetates and phenyl trifluoroacetates. This reaction obviously is general base-catalysed nucleophilic reaction of imidazole. The activation parameters $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ derived for the reactions of pyridine and imidazole with 4-nitrophenyl trifluoroacetate and for the reaction of imidazole with 4-nitrophenyl acetate are consistent with the proposed reaction mechanisms.

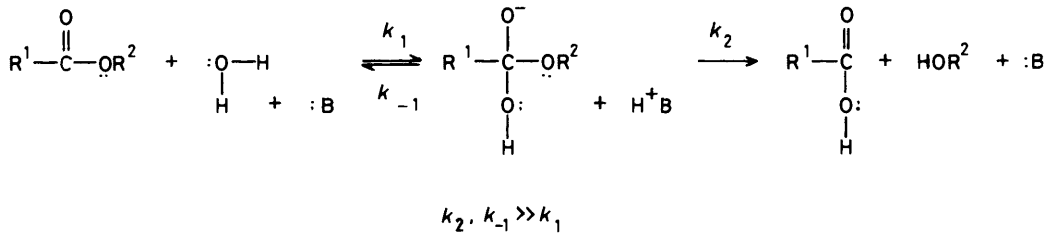
A wide variety of weak bases, like amines and oxygen anions, can catalyse the hydrolysis of carboxylic acid esters.[1] Since the first discovery of the two types of mechanisms, general base catalysis[2] (Scheme 1) and nucleophilic catalysis[3] (Scheme 2) in the base-catalysed ester hydrolysis, there have been numerous investigations which have shown that the mode of the catalysis depends both on the structure of the ester and on that of the base.[1,2,4,5] In general base catalysis the base :B assists the attack of water on the carbonyl carbon, whereas in nucleophilic catalysis the base attacks the ester directly giving an unstable intermediate (**2**) (Scheme 2) which is rapidly hydrolysed. The notations $B_{AC}3$ and $B_{AC}N$ were suggested for general base catalysis and nucleophilic catalysis, respectively.[6]

It appears that esters activated by electron-withdrawing substituents in the acyl moiety, such as ethyl dichloroacetate and difluoroacetate, are subject to general base catalysis while esters activated in the leaving alcohol moiety, such as phenyl-substituted phenyl acetates, are subject to nucleophilic catalysis.[2] However, there also are exceptions to this rule.[4,6,7] It has also been demonstrated that the two mechanisms may occur concurrently.[8]

If the alcoholic group departs much faster than the nucleophile from the tetrahedral addition intermediate (**1**) (Scheme 2), the formation of the intermediate is the rate-limiting step of the nucleophilic reaction, while if the expulsion of the nucleophile proceeds much faster than that of the leaving group, the breakdown of the intermediate is rate limiting. The partitioning of the intermediate in the direction of products or reactants depends on the relative leaving ability and thus on the relative basicity of :B and R^2O^-. The decreasing leaving ability of the leaving alcoholic group of the ester can also cause a change in the mode of the catalysis:[2,4b,5] a transition from nucleophilic (Scheme 2) to general base catalysis (Scheme 1) with increasing basicity of the leaving group has been observed, for example, in the acetate-catalysed hydrolysis of aryl acetates[5] and in the imidazole-catalysed hydrolysis of alkyl and aryl acetates.[4b]

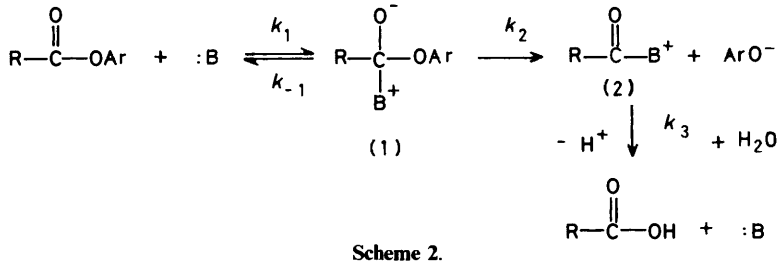
The study of the base-catalysed hydrolysis of carboxylic acid esters has been of great importance in attempts to understand the mechanism of enzyme action. In view of the significance of the elucidation of the factors governing the mode of this kind of catalysis, the effect of the structure of the leaving group of the ester and that of the catalysing base have been widely studied, but the effect of the acyl group has received much less attention. The aim of the study[9] reported here was to investigate whether strongly electronegative substituents in the acyl group could overcome the effect of a good leaving group of an ester and cause a change from nucleophilic to general base catalysis in the base-catalysed ester hydrolysis. As mentioned above, the partitioning of the intermediate (**1**) (Scheme 2) and thus the rate-limiting step of a nucleophilic reaction depends on the relative leaving ability of the nucleophile and the leaving group of the ester. In addition to the pK_a value of the conjugate acid of the nucleophile and the pK_a value of the alcohol, several other factors contribute to the relative leaving ability of the nucleophile and the leaving group.[10–14] For a given basicity toward a proton, amines are usually better leaving groups than alkyl or aryl oxide anions from a tetrahedral addition intermediate formed by nucleophilic amine attack on ester carbonyl.[10,13–15] It has been shown that electron-withdrawing acyl substituents of the ester favour the expulsion of amine from the addition intermediate relative to the expulsion of the alcoholic group of the ester.[13,14c,d] Gresser and Jencks[13b] proposed that electronegative acyl substituents increase the value of ΔpK_a, the pK_a difference between the pK_a of the conjugate acid of the amine and that of the alcohol group of the ester, at which there occurs a change in the rate-limiting step of ester aminolysis by affecting unfavourably the leaving ability of the anionic alcohol group. Therefore, it was of interest to study whether this kind of effect could cause a change from nucleophilic to general base catalysis in base-catalysed ester hydrolysis analogously with the change observed[4b,5] with increasing basicity of the leaving group.

4-Nitrophenyl acetate and trifluoroacetate were chosen as the parent model compounds. The substitution at the phenyl group, however, was also varied to demonstrate the effect of the structure of the leaving group. Pyridines and imidazoles were used as the catalysing bases. To reduce the contribution of the neutral hydrolysis of the esters of trifluoroacetic acid, the reactions were studied in aqueous acetonitrile with low content of water.



$k_2, k_{-1} \gg k_1$

Scheme 1.



Scheme 2.

Experimental

Materials.—4-Nitrophenyl and 2,4-dinitrophenyl acetates were prepared from the corresponding phenols and acetic anhydride.[14b,16] The former ester was recrystallized from hexane, m.p. 79.5—80 °C (lit.,[17] 79.5—80 °C) and the latter first from a mixture of benzene and light petroleum (b.p. 50—70 °C) and then from hexane, m.p. 71.5—72 °C (lit.,[18] 71—71.5 °C). The preparation and purification of the phenyl esters of trifluoroacetic acid have been described previously.[19] The pyridine bases and 1-methylimidazole were purified by distillation: pyridine (E. Merck AG; reinst) b.p. 114.5—115.5 °C at 1 atm, 3-chloropyridine (E. Merck AG; zur Synthese) b.p. 55 °C at 31 mmHg, 3-methylpyridine (Fluka AG; purum) b.p. 45 °C at 30 mmHg, 4-methylpyridine (Fluka AG; pract.) b.p. 49 °C at 31 mmHg, 3,4-dimethylpyridine (Merck-Schuchardt; zur Synthese) b.p. 72.5 °C at 24 mmHg, 2,4-dimethylpyridine (L. Light) b.p. 49—51 °C at 29 mmHg, 2,6-dimethylpyridine (B.D.H.; 99%) b.p. 141—142 °C at 1 atm, and 1-methylimidazole (Fluka AG; purum) b.p. 107 °C at 47 mmHg. Imidazole (Schuchardt) and 2-methylimidazole (Fluka AG; purum) were recrystallized twice from benzene. [*N*-^{2}H]Imidazole was prepared by the method of Garfinkel and Edsall[20] from imidazole by dissolving twice in deuterium oxide and evaporating to dryness.

Acetonitrile (Merck; max. H_2O 0.03%) was used as received. Mixtures of acetonitrile and water were prepared from distilled water or from heavy water (Norsk hydroelektrisk Kvaelstofaktieselskab; 99.8% D_2O).

For the amines a stock solution was prepared in the particular solvent or solvent mixture and the solutions required for the kinetic measurements were diluted from this. Freshly prepared solutions were always used.

Kinetics.—Reaction rates were determined by following the increase in absorption owing to the formation of the phenolic product (phenol at 270 nm; 4-chlorophenol at 282 or 290 nm; 3-chlorophenol at 282 nm; 3-nitrophenol at 333 nm; 4-nitrophenol at 310 or 345 nm; 2,4-dinitrophenol at 328 nm), except the reaction of imidazole with 3-nitrophenol trifluoroacetate for which the ester decay was followed (at 250 nm). A Perkin-Elmer 46 or 550 spectrophotometer with a thermostatted cell compartment was used with 1 cm silica cells. The temperatures of the reaction solutions were measured in the optical cell with a calibrated NTC-thermistor. The temperature was accurate to 0.05—0.1 K below 308 K and to 0.1—0.3 K above that temperature. The absorbance changes were recorded with a printer–timer system. The reactions were followed continuously for *ca.* six half-lives and the final value was observed after ten half-lives. The concentrations used were in the range *ca.* 2×10^{-5}—5×10^{-4} mol dm^{-3} for the esters and those given in Tables for the amines.

Some reactions were followed by scanning the u.v. spectrum repetitively using the Perkin-Elmer 550 spectrophotometer provided with a recorder.

The reactions were studied in unbuffered solutions. With the exception of the few cases stated below, the amine was in great excess over the ester and the first-order rate coefficients k_{obs} were calculated by Guggenheim's method.[21] The standard deviation of the rate coefficient was in general 0.2—0.3% but could be somewhat higher, up to 0.7%. The rate coefficients were reproducible to within ±1—2%. It was checked, for every different type of reaction, that the linear plots of ln $(A_\infty - A_t)$ *versus* time gave essentially the same values as Guggenheim's method. In the reactions of imidazole and 2-methylimidazole with 4-nitrophenyl trifluoroacetate and in the reaction of imidazole with 3-nitrophenyl or 3-chlorophenyl trifluoroacetate, the ratio [amine]/[ester] was in the range *ca.* 20—40 for the lowest amine concentrations employed. In these cases, the decrease in the amine concentration during the reaction caused a slight time-dependence of the first-order rate coefficient. For these reactions, equation (1) was used to calculated the observed

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

rate coefficient. The standard deviation of the mean of $\bar{k}_t$, the mean value of k_t for a run, was *ca.* 1%. The rate coefficients were reproducible to within ±1—2%. The values of c_t, the time-average concentrations of the phenolic product corresponding to each particular value of k_t, could be calculated with the aid of the molar absorptivity of the product phenol in the experimental conditions using the trapezoidal rule (2).[22] The mean value of c_t for a run is denoted by $\bar{c}_t$.

$$c_t = \frac{1}{t} \int_0^t x\,dt \approx \frac{1}{2t} \sum_{n=1}^{i} (x_n + x_{n-1})(t_n - t_{n-1}) \qquad (2)$$

x = concentration of the phenolic product = A/ε,
A = absorbance, ε = molar absorptivity of the phenolic product

Table 1. Experimental conditions and first-order rate coefficients (k_{obs}) for the reactions of amines with 4-nitrophenyl and 2,4-dinitrophenyl acetates[a]

Ester	Amine	Range of [amine] / mol dm^{-3}	10^3 k_{obs}/s^{-1}	Number of runs
4-Nitrophenyl acetate	Imidazole[b]	0.05—0.25	0.1270—1.3527	5
	Imidazole[c]	0.1—0.5	0.2008—2.543	10
	Imidazole	0.1—0.5	0.2924—3.520	10
	Imidazole[d]	0.1—0.5	0.4948—5.755	10
	Imidazole[e]	0.1—0.5	0.8106—8.860	10
	[N-^2H]Imidazole[f]	0.1—0.5	0.2509—2.847	13
	2-Methylimidazole	0.08—0.40	0.1273—1.317	12
2,4-Dinitrophenyl acetate	Imidazole	0.01—0.05	7.445—40.71	5

[a] In 0.56M-water in acetonitrile and at 298.2 K, unless otherwise stated. [b] In acetonitrile. [c] At 291.7 K. [d] At 307.9 K. [e] At 317.3 K. [f] In 0.56M-deuterium oxide in acetonitrile.

Table 2. Experimental conditions and first-order rate coefficients (k_{obs}) for the reactions of amines with substituted phenyl trifluoroacetates[a]

Phenyl substituent	Amine	Range of [amine] / mmol dm^{-3}	10^3 k_{obs}/s^{-1}	Number of runs
4-Nitro	3-Chloropyridine	40—200	0.530—2.564	10
	Pyridine[b]	4—20	0.974—4.820	5
	Pyridine	4—20	1.300—6.388	5
	Pyridine[c]	4—20	1.689—8.183	5
	Pyridine[d]	4—20	2.140—10.310	5
	Pyridine[e]	4—20	0.545—2.552	5
	3-Methylpyridine	4—20	2.372—11.85	10
	4-Methylpyridine	4—20	3.418—17.36	15
	3,4-Dimethylpyridine	4—20	6.07—32.97	14
	2,4-Dimethylpyridine	4—20	5.59—29.62	15
	2,6-Dimethylpyridine	2.5—12.5	1.142—5.473	15
	1-Methylimidazole	1—5	7.28—37.82	12
	Imidazole[b]	0.8—2	10.69—49.53	14
	Imidazole	0.8—2	10.42—45.57	14
	Imidazole[c]	0.8—2	10.98—42.68	14
	Imidazole[d]	0.8—2	11.43—40.87	14
	[N-^{2}H]Imidazole[e]	0.8—2	6.83—33.8	14
	Imidazole[f]	0.5—2.5	1.07—22.1	9
	2-Methylimidazole	0.8—2	24.0—70.9	21
3-Nitro	3,4-Dimethylpyridine	5—25	5.19—26.53	15
	Imidazole	1—5	5.23—50.7	15
3-Chloro	3,4-Dimethylpyridine	5—25	1.151—5.842	15
	Imidazole	5—25	5.56—61.1	15
4-Chloro	3,4-Dimethylpyridine	5—25	0.612—3.337	15
	Imidazole	5—25	2.983—24.78	15
None	3,4-Dimethylpyridine	20—100	0.647—3.749	12
	Imidazole	25—125	4.35—59.56	10

[a] In 0.56M-water in acetonitrile and at 298.2 K, unless otherwise stated. [b] At 288.2 K. [c] At 308.2 K. [d] At 318.2 K. [e] In 0.56M-deuterium oxide in acetonitrile. [f] In acetonitrile.

Results

In the experimental conditions used, spontaneous hydrolyses of the esters were negligibly slow, except the reaction of 4-nitrophenyl trifluoroacetate. The rate coefficients for the neutral hydrolysis of this ester have been determined previously[19] and these values have been used for the calculations in this study.

For esters of acetic acid, only the reactions of imidazole bases carrying a transferable proton, *i.e.* imidazole and 2-methylimidazole but not 1-methylimidazole or pyridines, were reactive enough for rate measurements and showed first-order kinetics when the amine was in excess over the ester.

Tables 1 and 2 summarize the experimental conditions and the range of the first-order rate coefficients for the reactions investigated. For the reactions of pyridines and 1-methylimidazole with the esters, k_{obs} was found to be related to the concentration of amine according to equation (3), in which k_0

$$k_{obs} = k_0 + k_1[B] \quad (3)$$

denotes the rate coefficient of the neutral hydrolysis. The reactions of imidazole and 2-methylimidazole showed both first- and second-order dependences on amine concentration [equation (4)], except the reaction of imidazole with phenyl

$$k_{obs} = k_0 + k_1[B] + k_2[B]^2 \quad (4)$$

trifluoroacetate. In the latter case, first-, second-, and third-order terms in imidazole were detected. Because the neutral hydrolysis did not produce any detectable effect on the reaction rate, k_1, k_2, and k_3 could be determined by equation (5).

$$k_{obs} = k_1[B] + k_2[B]^2 + k_3[B]^3 \quad (5)$$

It is assumed that the concentration of the phenolic product, $\bar{c}_t$ [equation (2)], at the same time gives the concentration of the acid component formed during the hydrolysis of esters of trifluoroacetic acid. In acetonitrile trifluoroacetic acid is a 10^3—

Table 3. Second- and third-order rate coefficients for the reactions of amines with 4-nitrophenyl and 2,4-dinitrophenyl acetates[a,b]

Ester	Amine	$10^3 k_1$/dm^3 mol^{-1} s^{-1}	$10^2 k_2$/dm^6 mol^{-2} s^{-1}
4-Nitrophenyl acetate	Imidazole[c]	1.85 ± 0.07	1.43 ± 0.04
	Imidazole[d]	1.28 ± 0.03	0.75 ± 0.01
	Imidazole	1.97 ± 0.03	1.01 ± 0.01
	Imidazole[e]	3.36 ± 0.07	1.61 ± 0.02
	Imidazole[f]	5.75 ± 0.05	2.39 ± 0.01
	[N-^{2}H]Imidazole[g]	1.92 ± 0.09	0.75 ± 0.03
	2-Methylimidazole	1.23 ± 0.05	0.52 ± 0.02
2,4-Dinitrophenyl acetate	Imidazole	726 ± 4	181 ± 1

[a] In 0.56M-water in acetonitrile and at 298.2 K, unless otherwise stated. [b] Errors shown are standard deviations. [c] In acetonitrile. [d] At 291.7 K. [e] At 307.9 K. [f] At 317.3 K. [g] In 0.56M-deuterium oxide in acetonitrile.

Table 4. Second-, third-, and fourth-order rate coefficients for the reactions of amines with substituted phenyl trifluoroacetates[a,b]

Phenyl substituent	Amine	pK_a^c	k_1/dm^3 mol^{-1} s^{-1}	k_2/dm^6 mol^{-2} s^{-1}
4-Nitro	3-Chloropyridine	2.84	0.0125 ± 0.0001	
	Pyridine[d]	5.22	0.243 ± 0.003	
	Pyridine		0.320 ± 0.003	
	Pyridine[e]		0.407 ± 0.002	
	Pyridine[f]		0.513 ± 0.005	
	Pyridine[g]		0.125 ± 0.002	
	3-Methylpyridine	5.63	0.596 ± 0.005	
	4-Methylpyridine	5.98	0.863 ± 0.004	
	3,4-Dimethylpyridine	6.46	1.65 ± 0.02	
	2,4-Dimethylpyridine	6.63	1.46 ± 0.01	
	2,6-Dimethylpyridine	6.72	0.429 ± 0.002	
	1-Methylimidazole	6.95	7.54 ± 0.06	
	Imidazole[d]	6.95	6.39 ± 0.34	9 650 ± 240
	Imidazole		7.83 ± 0.23	7 800 ± 160
	Imidazole[e]		9.10 ± 0.26	6 270 ± 180
	Imidazole[f]		10.8 ± 0.3	5 070 ± 180
	[N-^{2}H]Imidazole[g]		4.1 ± 0.2	6 900 ± 160
	Imidazole[h]		0.63 ± 0.12	3 360 ± 70
	2-Methylimidazole	7.85	27.9 ± 0.4	4 240 ± 310
3-Nitro	3,4-Dimethylpyridine	6.46	1.065 ± 0.005	
3-Chloro			0.230 ± 0.002	
4-Chloro			0.136 ± 0.001	
None			0.0392 ± 0.0007	
3-Nitro	Imidazole	6.95	4.20 ± 0.12	1 120 ± 40
3-Chloro			0.778 ± 0.020	6.46 ± 1.2
4-Chloro			0.493 ± 0.013	18.2 ± 0.8
None[i]			0.128 ± 0.002	1.56 ± 0.05

[a] In 0.56M-water in acetonitrile and at 298.2 K, unless otherwise stated. [b] Errors shown are standard deviations. [c] Aqueous pK_a values of the amines. [d] At 288.2 K. [e] At 308.2 K. [f] At 318.2 K. [g] In 0.56M-deuterium oxide in acetonitrile. [h] In acetonitrile. [i] For this reaction $k_3 = (9.87 \pm 0.33)$ dm^9 mol^{-3} s^{-1} was detected.

10^7 times stronger acid than the conjugate acids of the amines employed.[2,3] Thus it is evident that in the experimental conditions used trifluoroacetic acid will be dissociated and a respective amount of the amine will be protonated. Therefore, for the reactions of imidazole or 2-methylimidazole with 4-nitrophenyl trifluoroacetate, the term [B] − $\bar{c}_t$ was employed instead of [B] in equation (4) because in these reactions the [B]/$\bar{c}_t$ ratio could be as small as 20. The $\bar{c}_t$ values varied from 2.0×10^{-5} to 5.3×10^{-5} mol dm^{-3}, being in general, however, in the range $(2.5—3.5) \times 10^{-5}$ mol dm^{-3}. In other reactions, this kind of correction was unnecessary. Tables 3 and 4 give the second-, third-, and fourth-order rate coefficients for the reactions investigated.

The u.v. spectral scans carried out for the reaction of imidazole with 4-nitrophenyl acetate ([Im] 0.3 mol dm^{-3}) or 4-nitrophenyl trifluoroacetate ([Im] 1.0×10^{-3} mol dm^{-3}) in 0.56M-water in acetonitrile did not show any marks of an unstable intermediate, 1-acylimidazole, but two isosbestic points could be observed in both cases. This means that there is no intermediate, or if it exists, it is hydrolysed rapidly. The third possible explanation is that 1-acylimidazole is formed but it is stable to the reaction conditions.

Discussion

Reactions of 4-Nitrophenyl and 2,4-Dinitrophenyl Acetate.— In this study, the rate law (6) was observed for the reaction of

$$k_{obs} = k_1[\text{Imidazole}] + k_2[\text{Imidazole}]^2 \quad (6)$$

imidazole with 4-nitrophenyl and 2,4-dinitrophenyl acetate. In aqueous solution, the nucleophilic mechanism is observed for the imidazole-catalysed hydrolysis of 4-nitrophenyl acetate, and the reaction shows only first-order dependence on amine concentration.[3] However, in 1M-water in acetonitrile, the reaction of imidazole with 4-nitrophenyl acetate also follows the

rate law (6).[24] Hogg *et al.*[24b] proposed the nucleophilic role of imidazole for the reactions associated with the k_1 and k_2 terms. The present values of k_1 and k_2 for the reaction of 4-nitrophenyl acetate (Table 3) are in accord with the values obtained previously in 1M-water.[24] The failure to observe any unstable intermediate also agrees with the discovery of 1-acetylimidazole and 4-nitrophenol as the sole reaction products in 1M-water in acetonitrile.[24b] Thus the reaction in the present case is obviously imidazolysis and not imidazole-catalysed hydrolysis of the ester. The reaction of imidazole with 4-nitrophenyl acetate was, however, studied in greater detail, mainly to get data in the present experimental conditions for comparison with the unknown reaction of amines with 4-nitrophenyl trifluoroacetate.

The first-order term in imidazole shows a water isotope effect (Table 5) which is too small to suggest any proton transfer in the rate-limiting step but is consistent with a mechanism like that given in Scheme 3.[1c,e,f,24b,25] The second-order term in imidazole suggests that the nucleophilic reaction of imidazole is subject to general base catalysis involving a second molecule of amine as catalyst. The general base catalysis is very common in ester aminolysis both in aqueous solutions[4b,26,27] and in aprotic solvents.[28,29] The water isotope effect observed for the k_2 term (Table 5) is in accord with a mechanism like that given in Scheme 4.[24b,26b,27] The arrows in Schemes 3 and 4 do not concern the timing of proton transfers and bond-making and -breaking processes but they show the attacking and leaving groups.

The steric effects observed in the case of 4-nitrophenyl acetate (Table 5) are smaller than those found for nucleophilic reactions in solutions rich in water but the decrease in both k_1 and k_2 due to the 2-methyl substitition of imidazole is obvious and consistent with the reaction pathways given in Schemes 3 and 4.[30]

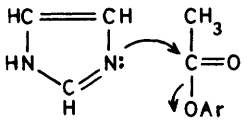
The absence of water from the reaction medium affects only slightly the rate coefficients (*cf.* Table 3), supporting the assumption that water does not participate in the reaction of imidazole with 4-nitrophenyl acetate.

The existence of a tetrahedral addition intermediate is quite well established in several ester aminolyses[13,14a,b,31] although its occurrence has been questioned in some cases.[32] For ester aminolysis in aprotic solvents Menger and his co-workers[28] proposed a reaction mechanism (Scheme 5) where a zwitterionic tetrahedral intermediate is formed in a reversible step and its breakdown to products is the rate-limiting step of the reaction. The collapse of the intermediate may be un-catalysed or it may be general base-catalysed by a second molecule of the amine or also by other bases. This mechanism has been established for several reactions of amines with esters in aprotic solvents[28,29,33] and it also is likely for the reaction of imidazole with 4-nitrophenyl and 2,4-dinitrophenyl acetate in the present case. The reactivity of 2,4-dinitrophenyl acetate compared with that of 4-nitrophenyl acetate is *ca.* 400-fold in the k_1 reaction and *ca.* 200-fold in the k_2 reaction (Table 3). This is in accord with a rate-limiting breakdown of the addition intermediate.[4b,28b,34] In aqueous solution, the attack of imidazole is rate limiting in the nucleophilic reaction toward 4-nitrophenyl acetate.[4b] Thus the change of the reaction medium from aqueous solution to aqueous acetonitrile with low content of water seems to result in a change in the rate-limiting step, from formation to breakdown of a tetrahedral addition intermediate. This change can be explained by the effect of the reaction medium on the relative basicity of the nucleophile and the leaving group of the ester. Although the basicities of the 4-nitrophenoxide ion and imidazole are nearly equal in water,[35] in acetonitrile the pK_a value of 4-nitrophenol is 21 and a value of *ca.* 14 can be evaluated for the imidazolium ion.[23a,35b,36] If the preferential hydration of ionic species[37] does not significantly change the relative basicities of amines and phenoxide ions, the 4-nitrophenoxide ion is several powers of ten more basic than imidazole in acetonitrile containing a small amount of water. Therefore, it is understandable that in the present reaction conditions the expulsion of imidazole takes place considerably easier than the expulsion of the 4-nitrophenoxide ion from the intermediate (**3**). This explains the rate-limiting breakdown of the intermediate.[4b,10,11,13b]

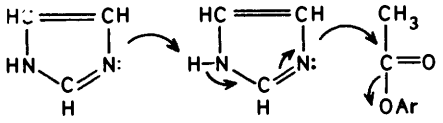
Table 5. Water isotope effects and steric effects for the reactions of amines with esters $RCOOC_6H_4$-4-NO_2 in 0.56M-water in acetonitrile at 298.2 K[a]

R	Amine	Rate coefficient	$k(H_2O)/k(D_2O)$	$k(Im)^b/k(2\text{-MeIm})^c$
CH_3	Imidazole	k_1	1.03 ± 0.06	1.6 ± 0.1
		k_2	1.35 ± 0.07	1.9 ± 0.1
CF_3	Imidazole	k_1	1.9 ± 0.2	0.28 ± 0.01
		k_2	1.1 ± 0.05	1.8 ± 0.2
CF_3	Pyridine	k_1	2.6 ± 0.06	

[a] The error estimates are calculated with the aid of standard deviations of the rate coefficients. [b] Rate coefficients for the reaction of imidazole. [c] Rate coefficients for the reaction of 2-methylimidazole.

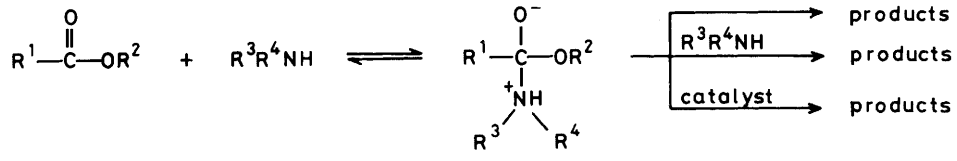


Scheme 3.

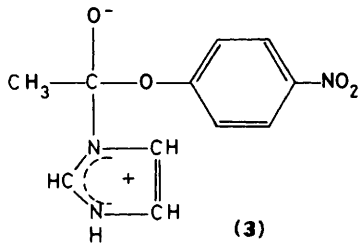


Scheme 4.

Reactions of Substituted Phenyl Trifluoroacetates.—The high values of the water isotope effects for the k_1 reactions of pyridine and imidazole with 4-nitrophenyl trifluoroacetate (Table 5) indicate a rate-limiting proton transfer and suggest general base-catalysed hydrolysis rather than nucleophilic reaction of amine for these reactions.[1c,e,f,25] A considerably smaller value is observed for the nucleophilic reaction (k_1) of imidazole with 4-nitrophenyl acetate in the same reaction conditions. For the



Scheme 5.



(3)

second-order term in imidazole, the water isotope effect is quite small in the reaction of 4-nitrophenyl trifluoroacetate. It is, however, consistent with imidazole-catalysed nucleophilic reaction of imidazole.[26b,27] The lack of the second-order term in 1-methylimidazole also suggests this mechanism.

The second-order rate coefficients for the reactions of 3,4-dimethylpyridine and imidazole as well as the third-order rate coefficients for the reaction of imidazole with substituted phenyl trifluoroacetates are reasonably well correlated by the σ^0 substituent constants (Figure 1). The σ^0 constants are used instead of the σ constants due to the somewhat better correlation obtained with them. The derived values of ρ are 2.2 ± 0.02 and 4.4 ± 0.2 for the k_1 and k_2 reactions of imidazole, respectively, and 2.0 ± 0.04 for the reaction of 3,4-dimethylpyridine.

For the k_1 and k_2 reactions of imidazole with phenyl trifluoroacetates a reverse order of the ρ values is observed compared with that observed for the uncatalysed and general base-catalysed nucleophilic reactions of amines with phenyl esters in aqueous solutions[26c,27b,38,39] or in acetonitrile.[28a] However, for the k_1 and k_2 reactions of imidazole with nitrophenyl acetates the 'normal' order of the sensitivities to the structure of the leaving group is observed; a second nitro group at the phenyl moiety accelerates the k_1 reaction twice as much as the k_2 reaction (Table 3). Therefore, it is evident for phenyl trifluoroacetates that if the second-order reaction in imidazole represents the general base-catalysed nucleophilic reaction of amine, the first-order reaction in amine is not a nucleophilic reaction but the general base-catalysed hydrolysis. Consistent with this conclusion is the fact that the ρ values, 2.2 and 2.0, respectively, observed for the k_1 reactions of imidazole and 3,4-dimethylpyridine are close to the ρ value 2.4 observed for the neutral hydrolysis of substituted phenyl trifluoroacetates in 3.89M-water in acetonitrile.[19] This reaction is thought to involve a general base-catalysed attack of water, another molecule of water functioning as the catalyst.[19] On the other hand, the high value of ρ, 4.4, observed for the second-order reaction in imidazole, is comparable to those found for the uncatalysed and general base-catalysed reactions of pyrrolidine with phenyl acetates in acetonitrile, 6.2 and 5.3, respectively.[28a]

The ρ values determined for the displacement reactions of phenyl esters in nonaqueous solvents or in water–organic solvent mixtures with low content of water cannot be directly compared with the reaction constants derived in aqueous solutions.[32a,40] If the pK_a values of some phenols in acetonitrile[23a] are plotted against the aqueous pK_a values,[35a] a linear correlation with the slope of 1.68 ± 0.09 is obtained. With the aid of this value the 'corrected' values of ρ, 1.3 and 1.2, respectively, are obtained for the k_1 reactions of imidazole and 3,4-dimethylpyridine. These values are close to the ρ value of 1.5 found for the general base-catalysed hydrolysis of phenyl quinoline-6-carboxylates in 20% acetonitrile–water.[38] Furthermore, they are considerably smaller than the ρ values observed for nucleophilic reactions of amines with esters in aqueous solutions[3b,27b,38,41] and are consistent with a mechanism where the C–OAr bond cleavage has not proceeded far.

The correction of the present ρ for the second-order reaction

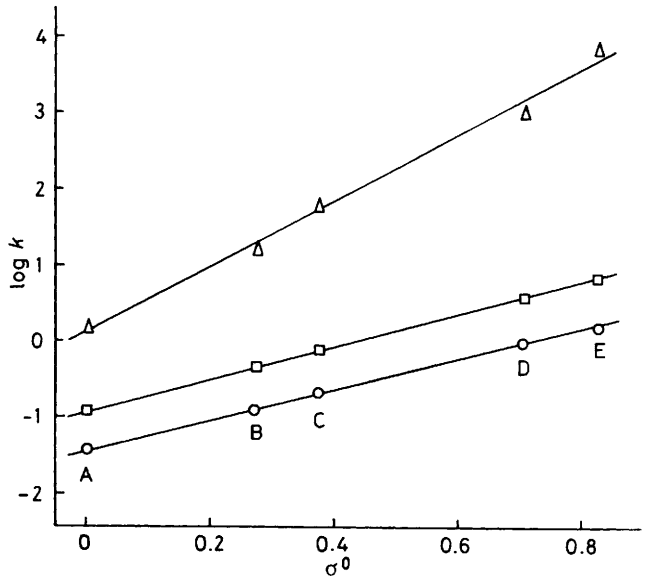


Figure 1. Plots of log k *versus* σ^0 for the reactions of 3,4-dimethylpyridine and imidazole with substituted phenyl trifluoroacetates in 0.56M-water in acetonitrile at 298.2 K. The rate coefficients k are in $dm^3\ mol^{-1}\ s^{-1}$ for the reactions first-order in 3,4-dimethylpyridine (○) or imidazole (□) and in $dm^6\ mol^{-2}\ s^{-1}$ for the reaction second-order in imidazole (△). A, phenyl; B, 4-chlorophenyl; C, 3-chlorophenyl; D, 3-nitrophenyl; E, 4-nitrophenyl

in imidazole by the factor 1.68 gives the value 2.6. Such a high value suggests a more advanced C–OAr bond-breaking in the transition state for the present case as compared with the aqueous reactions[26c,27b,39] and is indicative of the mechanism proposed by Menger and his co-workers[28] for the general base-catalysed ester aminolysis in aprotic solvents (*cf.* Scheme 5).

Extensive C–OAr bond-breaking in the transition state should allow an effective resonance interaction between the phenolic oxygen and the substituents in the leaving group. Thus the requirement to use the σ^- substituent constant, 1.24, for the 4-nitro group is to be expected, but such a high value is not needed (*cf.* Figure 1). However, this is not unusual for nucleophilic displacement reactions of phenyl esters by amines[27b,39,41,42] although the rate-limiting breakdown of the addition intermediate has been established for this kind of reaction.[13–15,31,38]

The second-order rate coefficients for the reactions of amines with 4-nitrophenyl trifluoroacetate are plotted logarithmically as a function of the basicity of the amine in Figure 2. Aqueous pK_a values are used because the values in the present experimental conditions are not available, neither are the values in acetonitrile known for all the amines. However, for a series of pyridine bases it can be assumed that the change in pK_a for the solvent change from water to the reaction solution employed is the same for all the amines.[23d] Thus obviously the Bronsted β value obtained is comparable with those determined in aqueous solutions. The rate coefficients for the sterically unhindered pyridines (A—E in Figure 2) are well correlated by a single line with slope 0.59 ± 0.01. In aqueous solutions, the β values observed for general base-catalysed hydrolyses of esters are usually *ca.* 0.4—0.7,[2,6,38,43] while those ascertained for nucleophilic reactions of amines with esters are *ca.* 0.8—0.9.[15,31,42,44,45] Because ester aminolyses in aprotic solvents obviously proceed through the rate-limiting breakdown of an addition intermediate,[28] β values close to one are expected for these reactions.[15,31,42,44,45] Thus the value of β observed in this study, 0.59, is indicative of general base-catalysed hydrolysis rather than nucleophilic attack by pyridines. However, there are some reports giving β values of *ca.* 0.5 for nucleophilic reactions

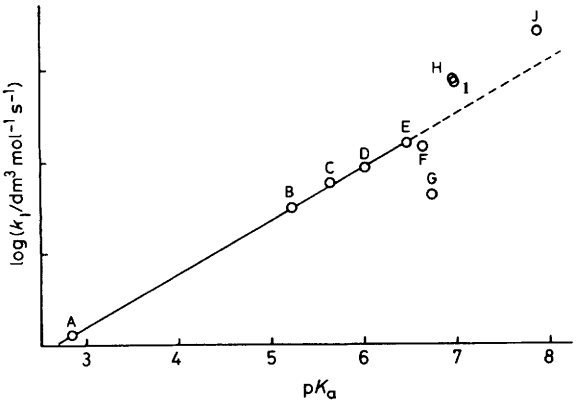


Figure 2. A Brønsted plot of log k_1 for the reactions of amines with 4-nitrophenyl trifluoroacetate in 0.56 M-water in acetonitrile at 298.2 K *versus* the aqueous pK_a values.[35b] A, 3-chloropyridine; B, pyridine; C, 3-methylpyridine; D, 4-methylpyridine; E, 3,4-dimethylpyridine; F, 2,4-dimethylpyridine; G, 2,6-dimethylpyridine; H, imidazole; I, 1-methylimidazole; J, 2-methylimidazole

of amines with esters in acetonitrile.[36,46] Thus the assignment of the reaction mechanism exclusively on the basis of the value of β is uncertain. More unambiguous information is obtained when inspecting the steric effects. It is seen that 2,6- and 2,4-dimethylpyridines are slightly less reactive than could be supposed on the basis of the Brønsted line shown in Figure 2. In nucleophilic reactions the steric effects are usually large. 2-Methylpyridine is $< 10^{-2}$ times as reactive as pyridine in its nucleophilic reaction toward acetic anhydride[47] and 2,4-dinitrophenyl acetate.[8] On the other hand, in general base-catalysed reactions the methyl groups on the carbons next to the attacking nitrogen only slightly affect the reactivity.[33a,48] Thus the steric effects observed in this study are more consistent with the general base-catalysed than with the nucleophilic mechanism.

The points for imidazole, 1-methylimidazole, and 2-methylimidazole fall above the line defined by pyridines in Figure 2. For general base-catalysed reactions in aqueous solution, imidazole usually fits the same Brønsted line with different oxygen and nitrogen bases.[1c,2,43b,48c,49] On the other hand, it is typical for nucleophilic reactions that different types of amines fit parallel but separate lines.[15,45] In the present case, however, 2-methylimidazole is 3.6 times as reactive as imidazole in reaction first-order in amine, and this is not consistent with a nucleophilic pathway.[30] In the reaction of 4-nitrophenyl acetate, 2-methyl substitution of imidazole retards both the k_1 and k_2 terms. A steric effect is also found in the case of 4-nitrophenyl trifluoroacetate for the reaction second-order in amine (Table 5). If the general base-catalysed mechanism is assumed for the reactions first-order in amine, the apparent enhanced reactivity of imidazoles as compared with pyridines (Figure 2) can be related to a somewhat higher change in pK_a of the conjugate acids for imidazoles than for pyridines for the solvent change from water to the water–acetonitrile mixture employed.

In the reaction of imidazole with 4-nitrophenyl trifluoroacetate, the sensitivity of the k_1 term to the presence of water in the reaction medium (Table 4) is quite different from that observed for 4-nitrophenyl acetate (Table 2) and gives additional evidence for general base-catalysed hydrolysis. The rate coefficient found in acetonitrile, 0.63 dm^3 mol^{-1} s^{-1}, can reveal some moisture of the solvent which allows the general base-catalysed hydrolysis to occur, or it can represent a small nucleophilic portion of the reaction.

The above considerations clearly rule out the nucleophilic attack by pyridines or imidazoles on phenyl trifluoroacetates in the reaction first-order in amine, and the mechanism involving a general base-catalysed attack of water is evident for this reaction. All the results for the reaction second-order in amine may be accounted for by the general base-catalysed nucleophilic reaction of amine. The reaction probably involves rate-limiting breakdown of a tetrahedral addition intermediate. The mechanism of the third-order reaction in imidazole, which was observed for phenyl trifluoroacetate, was not investigated in detail. Previously, a third-order term in imidazole has been detected at least in the imidazolysis of benzoyl fluoride in acetonitrile[50] and in the imidazolysis of 4-nitrophenyl propionate in benzene.[29b]

The general base-catalysed nucleophilic reaction of imidazole with phenyl trifluoroacetates can represent imidazolysis or hydrolysis, *i.e.*, 1-trifluoroacetylimidazole can be stable or unstable in the experimental conditions. The u.v. spectral scans did not show any temporary intermediate during the reaction of imidazole with 4-nitrophenyl trifluoroacetate. Taking into account the high reactivity of esters of trifluoroacetic acid toward water, this presumably is due to a too rapid hydrolysis of 1-trifluoroacetylimidazole to allow its detection.

Table 6. Activation parameters at 298.15 K for the reactions of imidazole or pyridine with esters $RCOOC_6H_4$-4-NO_2 in 0.56M-water in acetonitrile.

R	Amine	Rate coefficient	$\Delta H^{\ddagger}$/kJ mol^{-1}	$\Delta S^{\ddagger}$/J mol^{-1} K^{-1}
CH_3	Imidazole	k_1	42.3 ± 0.8 [a]	−155 ± 2[a]
		k_2	32.7 ± 0.4	−173 ± 1
CF_3	Imidazole	k_1	10.7 ± 0.4	−192 ± 1
		k_2	−18.9 ± 0.3	−234 ± 1
CF_3	Pyridine	k_1	16.5 ± 0.2	−199 ± 1

[a] Errors shown are standard deviations.

On the Activation Parameters.—In the present case, the thermodynamic activation parameters $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ are not very useful as mechanistic criteria. However, the values given in Table 6 can be discussed in the light of the conclusions drawn above. For reactions of amines with esters, the general base-catalysed nucleophilic reaction has typically lower enthalpies of activation than the uncatalysed nucleophilic reaction but the increase of the reaction order is usually accompanied by a decrease of the entropy of activation.[27b,c] Thus the values of $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ observed for the k_1 and k_2 terms in the reaction of imidazole with 4-nitrophenyl acetate are consistent with the reaction pathways given in Schemes 3 and 4, respectively. For the k_1 reaction of imidazole or pyridine with 4-nitrophenyl trifluoroacetate, $\Delta H^{\ddagger}$ is of the same extent but $\Delta S^{\ddagger}$ is less negative than the corresponding activation parameter observed for the second-order rate coefficient ($k_0/[H_2O]$) of the neutral hydrolysis of 4-nitrophenyl trifluoroacetate in 0.56M-water in acetonitrile; $\Delta H^{\ddagger}$ 13.1 kJ mol^{-1} and $\Delta S^{\ddagger}$ −282 J mol^{-1} K^{-1}.[19] A negative value of the enthalpy of activation observed for the reaction second-order in imidazole indicates an exothermic equilibrium before the product-forming step and is consistent with the mechanism discussed above; a two-step process involving the formation of an addition intermediate by the attack of imidazole in the fast step and the imidazole-catalysed breakdown of the addition intermediate in the rate-limiting step.[33,50] The exothermicity of the addition step presumably is due to the activating effect of the trifluoromethyl group.[33,51]

The Effect of the Acyl Group.—The present work establishes that in the reaction of imidazole with 4-nitrophenyl esters there occurs a change in the reaction mechanism from nucleophilic

reaction of amine to general base-catalysed hydrolysis when the acyl moiety is changed from acetyl to trifluoroacetyl group. This change in mechanism can be attributed to the increased electrophilicity of the carbonyl carbon as in accord with the results which show that the electron withdrawal from the central carbon favours amine expulsion relative to aryl oxide expulsion from the tetrahedral addition intermediate formed in ester aminolysis.[13a,14c,d] The increased electrophilicity of the central atom destabilizes the transition state for the negatively charged oxyanion expulsion relative to neutral amine expulsion.[13a] The general base-catalysed addition of the hydroxy group of water can be regarded as being rate limiting in the general base-catalysed hydrolysis of phenyl trifluoroacetates[19] and the electronegative acyl substituents favour the addition step. Thus, while the trifluoro substitution of the acyl group of 4-nitrophenyl acetate facilitates the general base-catalysed hydrolysis, it evidently changes the relative leaving ability of the phenolic group and the nucleophile, and decreases the contribution of the nucleophilic reaction of amine by affecting unfavourably the partitioning ratio of the tetrahedral intermediate [(1) in Scheme 2].

Beside the general base-catalysed hydrolysis of phenyl trifluoroacetates there occurs the imidazole-catalysed nucleophilic reaction of imidazole. The latter reaction evidently involves proton transfer from the nitrogen of the tetrahedral intermediate. The relative leaving ability of the phenolic group increases because imidazole anion is a poorer leaving group than the neutral imidazole.[23a,35b] This makes the nucleophilic reaction possible regardless of the unfavourable effect of the acyl group.

The present results do not give any rule to predict the effect of the acyl group on the mechanism of the ester hydrolysis catalysed by weak bases but they clearly show the significance of the acyl substitution in this respect.

Acknowledgements

I thank Professor E. K. Euranto for helpful discussions. The research was supported by the Emil Aaltonen Foundation.

References

1 (*a*) M. L. Bender, *Chem. Rev.*, 1960, **60**, 53; (*b*) T. C. Bruice and S. J. Benkovic, 'Bioorganic Mechanisms,' Benjamin, New York, 1966, vol. 1, p. 1; (*c*) S. L. Johnson, *Adv. Phys. Org. Chem.*, 1967, **5**, 237; (*d*) W. P. Jencks, 'Catalysis in Chemistry and Enzymology,' McGraw-Hill, New York, 1969; (*e*) E. K. Euranto, in 'The Chemistry of Carboxylic Acids and Esters,' ed. S. Patai, Interscience, London, 1969, p. 505; (*f*) A. J. Kirby, in 'Comprehensive Chemical Kinetics,' eds. C. H. Bamford and C. F. H. Tipper, Elsevier, Amsterdam, 1972, vol. 10, p. 57.
2 W. P. Jencks and J. Carriuolo, *J. Am. Chem. Soc.*, 1961, **83**, 1743.
3 (*a*) M. L. Bender and B. W. Turnquest, *J. Am. Chem. Soc.*, 1957, **79**, 1652; (*b*) T. C. Bruice and G. L. Schmir, *ibid.*, p. 1663.
4 (*a*) J. F. Kirsch and W. P. Jencks, *J. Am. Chem. Soc.*, 1964, **86**, 833; (*b*) *ibid.*, p. 837.
5 V. Gold, D. G. Oakenful, and T. Riley, *J. Chem. Soc. B*, 1968, 515.
6 E. K. Euranto, *Ann. Acad. Sci. Fennicae, Ser. A. II*, 1970, No. 152.
7 B. M. Anderson, E. H. Cordes, and W. P. Jencks, *J. Biol. Chem.*, 1961, **236**, 455; T. C. Bruice, T. H. Fife, J. J. Bruno, and P. Benkovic, *J. Am. Chem. Soc.*, 1962, **84**, 3012.
8 A. R. Butler and I. H. Robertson, *J. Chem. Soc., Perkin Trans. 2*, 1975, 660.
9 H. Neuvonen, Ph.D. Thesis, University of Turku, 1985.
10 N. Gravitz and W. P. Jencks, *J. Am. Chem. Soc.*, 1974, **96**, 499.
11 C. D. Ritchie, *J. Am. Chem. Soc.*, 1975, **97**, 1170.
12 P. Campbell and B. A. Lapinskas, *J. Am. Chem. Soc.*, 1977, **99**, 5378.
13 (*a*) M. J. Gresser and W. P. Jencks, *J. Am. Chem. Soc.*, 1977, **99**, 6963; (*b*) *ibid.*, p. 6970.
14 (*a*) E. A. Castro and F. J. Gil, *J. Am. Chem. Soc.*, 1977, **99**, 7611; (*b*) E. A. Castro and M. Freudenberg, *J. Org. Chem.*, 1980, **45**, 906; (*c*) E. A. Castro and G. B. Steinfort, *J. Chem. Soc., Perkin Trans. 2*, 1983, 453; (*d*) E. A. Castro and C. L. Santander, *J. Org. Chem.*, 1985, **50**, 3595.
15 W. P. Jencks and M. Gilchrist, *J. Am. Chem. Soc.*, 1968, **90**, 2622.
16 F. D. Chattaway, *J. Chem. Soc.*, 1931, 2495.
17 B. S. Hartley and B. A. Kilby, *Biochem. J.*, 1954, **56**, 288.
18 M. L. Bender and B. W. Turnquest, *J. Am. Chem. Soc.*, 1957, **79**, 1656.
19 H. Neuvonen, *J. Chem. Soc., Perkin Trans. 2*, 1986, 1141.
20 D. Garfinkel and J. T. Edsall, *J. Am. Chem. Soc.*, 1958, **80**, 3807.
21 A. A. Frost and R. G. Pearson, 'Kinetics and Mechanism,' Wiley, New York, 1969, p. 473.
22 P. Salomaa, *Ann. Univ. Turku., Ser. A XIV*, 1953, No. 1.
23 (*a*) J. F. Coetzee, *Prog. Phys. Org. Chem.*, 1967, **4**, 45; (*b*) C. D. Ritchie, in 'Solute–Solvent Interactions,' eds. J. F. Coetzee and C. D. Ritchie, Marcel Dekker, New York, 1969, p. 227; (*c*) G. A. Forcier and J. W. Olver, *Electrochim. Acta*, 1970, **15**, 1609; (*d*) R. P. Bell, 'The Proton in Chemistry,' Chapman and Hall, London, 1973, 2nd edn., p. 64.
24 (*a*) G. Wallerberg, J. Boger, and P. Haake, *J. Am. Chem. Soc.*, 1971, **93**, 4938; (*b*) J. L. Hogg, R. Morris, III, and N. A. Durrant, *ibid.*, 1978, **100**, 1590.
25 R. E. Robertson and P. M. Laughton, in 'Solute–Solvent Interactions,' eds. J. F. Coetzee and C. D. Ritchie, Marcel Dekker, New York, 1969, p. 473.
26 (*a*) J. F. Bunnett and G. T. Davis, *J. Am. Chem. Soc.*, 1960, **82**, 665; (*b*) W. P. Jencks and J. Carriuolo, *ibid.*, p. 675; (*c*) T. C. Bruice and M. F. Mayahi, *ibid.*, p. 3067.
27 (*a*) M. Caplow and W. P. Jencks, *Biochemistry*, 1962, **1**, 883; (*b*) T. C. Bruice and S. J. Benkovic, *J. Am. Chem. Soc.*, 1964, **86**, 418; (*c*) W. P. Jencks and M. Gilchrist, *ibid.*, 1966, **88**, 104; (*d*) J. F. Kirsch and A. Kline, *ibid.*, 1969, **91**, 1841.
28 (*a*) F. M. Menger and J. H. Smith, *J. Am. Chem. Soc.*, 1972, **94**, 3824; (*b*) F. M. Menger and A. C. Vitale, *ibid.*, 1973, **95**, 4931.
29 (*a*) C.-W. Su and J. W. Watson, *J. Am. Chem. Soc.*, 1974, **96**, 1854; (*b*) F. Rivetti and U. Tonellato, *J. Chem. Soc., Perkin Trans. 2*, 1977, 1176.
30 T. C. Bruice and G. L. Schmir, *J. Am. Chem. Soc.*, 1958, **80**, 148; M. Akiyama, Y. Hara, and M. Tanabe, *J. Chem. Soc., Perkin Trans. 2*, 1978, 288.
31 A. C. Satterthwait and W. P. Jencks, *J. Am. Chem. Soc.*, 1974, **96**, 7018, 7031.
32 (*a*) C. D. Ritchie, J. E. VanVerth, and P. O. I. Virtanen, *J. Am. Chem. Soc.*, 1982, **104**, 3491; (*b*) D. F. DeTar, *ibid.*, p. 7205.
33 (*a*) T. D. Singh, Ph. D. Thesis, University of California, 1974; T. D. Singh and R. W. Taft, *J. Am. Chem. Soc.*, 1975, **97**, 3867.
33 (*b*) T. Laasik, A. Uri, and A. Tuulmets, *Org. React. (Tartu)*, 1978, **15**, 571.
34 Y. Pocker and D. L. Ellsworth, *J. Am. Chem. Soc.*, 1977, **99**, 2284.
35 (*a*) G. Kortüm, W. Vogel, and K. Andrussow, 'Dissociation Constants of Organic Acids in Aqueous Solution,' Butterworths, London, 1961; (*b*) D. D. Perrin, 'Dissociation Constants of Organic Bases in Aqueous Solution,' Butterworths, London, 1965.
36 M. J. Gregory and T. C. Bruice, *J. Am. Chem. Soc.*, 1967, **89**, 4400.
37 B. G. Cox, *J. Chem. Soc., Perkin Trans. 2*, 1973, **607**; B. G. Cox, R. Natarajan, and W. E. Waghorne, *J. Chem. Soc., Faraday Trans. 1*, 1979, **75**, 86.
38 P. Y. Bruice and T. C. Bruice, *J. Am. Chem. Soc.*, 1974, **96**, 5523.
39 L. doAmaral, K. Koehler, D. Bartenbach, T. Pletcher, and E. H. Cordes, *J. Am. Chem. Soc.*, 1967, **89**, 3537.
40 T. C. Bruice and A. Turner, *J. Am. Chem. Soc.*, 1970, **92**, 3422; R. Goitein and T. C. Bruice, *J. Phys. Chem.*, 1972, **76**, 432.
41 L. A. Cohen and S. Takahashi, *J. Am. Chem. Soc.*, 1973, **95**, 443.
42 T. C. Bruice, A. Donzel, R. W. Huffman, and A. R. Butler, *J. Am. Chem. Soc.*, 1967, **89**, 2106.
43 (*a*) A. R. Fersht and A. J. Kirby, *J. Am. Chem. Soc.*, 1967, **89**, 4853, 4857; (*b*) M. Komiyama and M. L. Bender, *Bioorg. Chem.*, 1977, **6**, 13.
44. W. P. Jencks and J. Carriuolo, *J. Am. Chem. Soc.*, 1960, **82**, 1778; A. R. Fersht and W. P. Jencks, *ibid.*, 1970, **92**, 5442.
45 T. C. Bruice and R. Lapinski, *J. Am. Chem. Soc.*, 1958, **80**, 2265.
46 F. Dutka, T. Kőmives, and A. F. Márton, *Magy. Kem. Foly.*, 1976, **82**, 237.
47 A. R. Butler and V. Gold, *J. Chem. Soc.*, 1961, 4362.
48 (*a*) F. Covitz and F. H. Westheimer, *J. Am. Chem. Soc.*, 1963, **85**,

1773; (*b*) S. L. Johnson, *ibid.*, 1964, **86**, 3819; (*c*) T. H. Fife and D. M. McMahon, *J. Org. Chem.*, 1970, **35**, 3699; (*d*) M. Akiyama, M. Ihjima, and Y. Hara, *J. Chem. Soc., Perkin Trans. 2*, 1979, 1512.
49 T. H. Fife, R. J. Bambery, and B. R. DeMark, *J. Am. Chem. Soc.*, 1978, **100**, 5500,
50 O. Rogne, *J. Chem. Soc., Chem. Commun.*, 1975, 25.
51 M. L. M. Schilling, H. D. Roth, and W. C. Herndon, *J. Am. Chem. Soc.*, 1980, **102**, 4271.

Received 3*rd March* 1986; *Paper* 6/424