

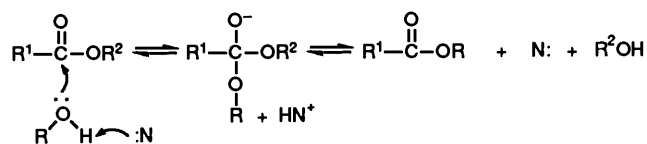
## General Base Catalysis in the Methanolysis of 4-Nitrophenyl Acetates

Helmi Neuvonen\*

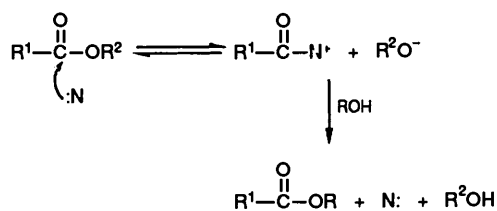
Department of Chemistry and Biochemistry, University of Turku, SF-20500 Turku, Finland

The rates of the methanolysis of 4-nitrophenyl acetate, chloroacetate, and dichloroacetate have been measured in the presence of pyridines and imidazoles. Methyl substitution at the 2- and 6-positions in pyridine causes only a slight reduction in reactivity. A Brønsted  $\beta$  value of 0.48 has been evaluated for the catalysed methanolysis of 4-nitrophenyl chloroacetate by pyridines. The entropy of activation for the pyridine-catalysed methanolysis of 4-nitrophenyl dichloroacetate exhibits a substantial, negative value,  $-164 \text{ J mol}^{-1} \text{ K}^{-1}$ . These results indicate that pyridine bases act as general base catalysts and not as nucleophiles in the methanolysis of 4-nitrophenyl acetates. Nucleophilic catalysis possibly occurs in the imidazole-catalysed methanolysis of 4-nitrophenyl acetate and chloroacetate. This suggestion is based on the steric effect caused by 2-methyl substitution of imidazole. The higher reactivity of imidazole as expected from the reactivity of pyridines confirms this conclusion.

The alcoholysis of carboxylic acid esters is usually not catalysed by bases other than alkoxide ions. However, when the esters contain strongly electron-withdrawing substituents in either the acyl or alkoxy group, catalysis by other bases has also been observed. Both general base catalysis, where attack of an alcohol molecule on the carbonyl group of the ester is assisted by partial bond formation to the base (Scheme 1), and nucleophilic catalysis, where the base attacks the ester carbonyl to give an intermediate which is subsequently alcoholysed (Scheme 2), have been detected.<sup>1-5</sup>



Scheme 1.



Scheme 2.

The base catalysed alcoholysis of esters has received attention not only from the standpoint of physical organic chemistry, but also because several hydrolytic enzymes, such as  $\alpha$ -chymotrypsin appear to cleave esters by acyl transfer to an alcoholic function, the hydroxy group of serine, followed by the hydrolysis of the acyl enzyme. The acylation of serine, as well as the subsequent deacylation step, is presumably assisted by general base catalysis by the imidazole group of a histidine residue of the enzyme.<sup>6,7</sup> A direct nucleophilic attack by an imidazole nitrogen of the histidine of  $\alpha$ -chymotrypsin yielding a transient acylimidazole which rapidly collapses to serine-acylated enzyme has also been proposed for some non-specific substrates.<sup>8</sup>

While the kinetics of weakly base catalysed hydrolysis of esters have been thoroughly investigated, much less information is available upon which to base mechanistic conclusions con-

cerning ester alcoholysis. In the acetate-ion-catalysed reaction of 4-nitrophenyl acetate, nucleophilic catalysis of acyl transfer from 4-nitrophenol to methanol seems to be preferred over general base catalysis, when compared with acyl transfer to water.<sup>4a</sup> Imidazole, pyridine, and methyl substituted pyridines catalyse, as nucleophiles, the hydrolysis of 4-nitrophenyl and 2,4-dinitrophenyl acetates.<sup>9</sup> The nucleophilic mechanism has also been suggested for the pyridine-catalysed methanolysis of some nitrophenyl acetates.<sup>3c-f</sup> There is no reason to suspect that the proposed mechanism for the reactions of 2,4-dinitrophenyl and 2,4,6-trinitrophenyl acetates is incorrect,<sup>3c,d</sup> but the arguments regarding the mechanism of the reactions of 2-nitrophenyl<sup>3f</sup> and 4-nitrophenyl acetates<sup>3e</sup> are not quite convincing. In the catalysed methanolysis of the two last mentioned esters both 2-methylpyridine and 2,6-dimethylpyridine are less reactive than might be expected on the basis of their  $pK_a$  values, however, they are more effective than pyridine. Without considering other possibilities, the authors suggest the nucleophilic mechanism for these reactions.<sup>3e,f</sup> However, the steric effects observed are characteristic, rather, of a general base catalysed, than of a nucleophilic mechanism.<sup>10-12</sup> Therefore, it is of interest to consider further these and related reactions. The pyridine-catalysed methanolyses of acetic acid esters are inconveniently slow. We have therefore studied only the imidazole-catalysed methanolysis of 4-nitrophenyl acetate, while both pyridines and imidazoles are used as the catalyst for 4-nitrophenyl chloroacetate and dichloroacetate.

### Experimental

**Materials.**—4-Nitrophenyl acetate was prepared from 4-nitrophenol and acetic anhydride, m.p.  $79.5-80^\circ \text{C}$  (from hexane) (lit.,<sup>13</sup>  $79.5-80^\circ \text{C}$ ). 4-Nitrophenyl chloroacetate and dichloroacetate were prepared from 4-nitrophenol and the corresponding acid chlorides, m.p.  $96-97^\circ \text{C}$  (from hexane) (lit.,<sup>14</sup>  $95-97^\circ \text{C}$ ) and  $30-30.5^\circ \text{C}$  (from hexane) (lit.,<sup>15</sup>  $30.6^\circ \text{C}$ ), respectively.

Imidazole (Schuchardt) and 2-methylimidazole (Fluka AG, *purum*) were recrystallized from benzene. Pyridine (E. Merck AG, *reinst*), 3-methylpyridine (Fluka AG, *purum*), 4-methylpyridine (Fluka AG, *pract.*), and 2,6-dimethylpyridine (BDH, 99%) were purified by fractional distillation from potassium hydroxide pellets.

Methanol (E. Merck AG, *getrocknet, pro analysi*, maximum

**Table 1.** Experimental conditions and first-order rate coefficients ( $k_{\text{obs}}$ ) for the amine-catalysed methanolysis of esters  $\text{RCO}_2\text{-C}_6\text{H}_4\text{-4-NO}_2$  in methanol with buffer ratio  $([\text{AmH}^+]:[\text{Am}])$  1:1, at constant ionic strength  $\mu = 0.25 \text{ mol dm}^{-3}$ , and at 298.2 K, unless otherwise stated.<sup>a</sup>

R	Amine	Range of [amine]/mmol dm <sup>-3</sup>	$k_{\text{obs}}/10^{-4} \text{ s}^{-1}$	Number of runs
CH <sub>3</sub>	Imidazole <sup>b,c</sup>	50–250	1.672–9.944	17
	Imidazole <sup>b,d</sup>	50–250	1.668–9.594	11
	2-Methylimidazole <sup>e</sup>	50–250	0.6768–3.069	14
CH <sub>2</sub> Cl	Pyridine	50–250	0.7335–3.455	16
	3-Methylpyridine	50–250	1.049–5.173	17
	4-Methylpyridine	50–250	1.802–8.411	20
	2,6-Dimethylpyridine	50–250	0.8225–3.066	15
	Imidazole	5–25	13.51–63.66	15
	Imidazole <sup>d</sup>	5–25	19.60–69.11	16
	2-Methylimidazole	5–25	24.03–60.52	15
CHCl <sub>2</sub>	Pyridine <sup>e</sup>	5–25	5.349–19.49	15
	Pyridine	5–25	6.461–23.74	15
	Pyridine <sup>f</sup>	5–25	8.508–30.50	15
	Pyridine <sup>g</sup>	5–25	11.30–37.85	14
	2,6-Dimethylpyridine	5–25	7.581–20.53	15

<sup>a</sup> Five different concentrations were used for each amine. <sup>b</sup>  $\mu = 0.125 \text{ mol dm}^{-3}$ . <sup>c</sup>  $[\text{AmH}^+]:[\text{Am}] = 1:2$ . <sup>d</sup>  $[\text{AmH}^+]:[\text{Am}] = 1:4$ . <sup>e</sup> At 293.2 K. <sup>f</sup> At 303.2 K. <sup>g</sup> At 308.2 K.

water content 0.01%) was used as received. Hydrogen chloride, made by dropping concentrated sulphuric acid into sodium chloride, was dried with sulphuric acid, and dissolved in methanol. The solution was titrated with aqueous sodium hydroxide and diluted as required. Owing to its instability a fresh solution was prepared immediately prior to each set of measurements.

Amine buffers were prepared by partial neutralization of weighed samples of the amine with a standardized hydrogen chloride solution of methanol. Ionic strength was held constant with lithium chloride (E. Merck AG). The methoxide ion concentrations of the buffers can be calculated from the  $\text{p}K_{\text{a}}$  values of the amines and from the methanol autoprotolysis constant (17.20),<sup>16</sup> if the  $\text{p}K_{\text{a}}$  value of the amine in methanol is known.

**Kinetics.**—Reaction rates were determined by observing the increase in absorption at 310 nm owing to the formation of 4-nitrophenol. A Gilford 2600 microprocessor-controlled spectrophotometer equipped with a Gilford Thermostat Temperature Controller was used. The temperatures of the reaction solutions were measured in the optical cell with a calibrated NTC-thermistor. The temperature was accurate to  $\pm 0.05 \text{ }^\circ\text{C}$ . The absorbance changes were recorded with a printer. The reactions were studied in methanol in buffered solutions of the amines and their conjugate acids under pseudo-first-order conditions, with the amine catalyst in excess, at an ionic strength of  $0.25 \text{ mol dm}^{-3}$  (maintained with lithium chloride), except the imidazole-catalysed reaction of 4-nitrophenyl acetate for which the ionic strength was  $0.125 \text{ mol dm}^{-3}$ . For the imidazole-catalysed reaction of 4-nitrophenyl acetate the buffer ratios  $([\text{AmH}^+]:[\text{Am}])$  1:2 and 1:4 were used and for the 2-methylimidazole-catalysed reaction of the same ester the buffer ratio was 1:2. The rates of the imidazole-catalysed methanolysis of 4-nitrophenyl chloroacetate were measured with the buffer ratios 1:1 and 1:4. In other cases  $[\text{AmH}^+]:[\text{Am}]$  was 1:1. Substrate concentrations were in the range  $(6\text{--}10) \times 10^{-5} \text{ mol dm}^{-3}$ .

The first-order rate coefficients ( $k_{\text{obs}}$ ) were calculated by Guggenheim's method.<sup>17</sup> Each run was at least duplicated, in most cases three or four determinations were performed. The rate coefficients were reproducible to within  $\pm 3\%$ . The standard deviations of the rate coefficients were 0.2–0.5%. It was checked that the linear plots of  $\ln(A_{\infty}-A_t)$  versus time gave essentially the same values as Guggenheim's method.

## Results

Table 1 summarizes the experimental conditions and the range of the first-order rate coefficients for the reactions investigated. The lyate-catalysed or uncatalysed methanolysis was negligibly slow for 4-nitrophenyl acetate while a definite intercept value was observed for 4-nitrophenyl chloroacetate and dichloroacetate when the observed rate coefficients were plotted against the catalyst concentration. The intercept values are shown in Table 2. The intercept rises with an increase in the methoxide ion concentration or with an increase in temperature.

The second-order rate coefficients ( $k_1$ ) were obtained from the slopes of the plots of the first-order rate coefficients against the free amine concentrations except for the imidazole-catalysed reaction of 4-nitrophenyl acetate. For the latter case the plot of  $k_{\text{obs}}$  versus imidazole concentration showed upward curvature indicating that the reaction displays both first-order and second-order dependence on the catalyst concentration. Because the solvolysis reaction did not affect the rate, the second-order rate coefficient ( $k_1$ ) was obtained as the intercept and the third-order rate coefficient ( $k_2$ ) as the slope of the plot of  $k_{\text{obs}}/[\text{Im}]$  versus  $[\text{Im}]$  according to equation (1) where  $[\text{Im}]$  is the free amine concentration of imidazole.

$$k_{\text{obs}} = k_1[\text{Im}] + k_2[\text{Im}]^2 \quad (1)$$

The second- and third-order rate coefficients determined are shown in Table 2.

The  $k_1$  and  $k_2$  values obtained for the imidazole-catalysed reaction of 4-nitrophenyl acetate for 1:2 imidazole buffer were in accord with the values for 1:4 buffer to within experimental error. Similarly the  $k_1$  value for the imidazole-catalysed methanolysis of 4-nitrophenyl chloroacetate for 1:1 imidazole buffer agreed well with the value for 1:4 buffer. There was no manifestation of general acid or methoxide ion catalysis. Therefore, it was assumed that the free amine was the active species in all cases.

## Discussion

**Steric Effects.**—For the methanolysis of both 4-nitrophenyl chloroacetate and dichloroacetate, pyridine is a more powerful catalyst than 2,6-dimethylpyridine, but the reactivity difference is small, pyridine being, respectively, 1.2 and 1.3 times as reactive as 2,6-dimethylpyridine (Table 2). The  $\text{p}K_{\text{a}}$  values of

**Table 2.** Second- and third-order rate coefficients ( $k_1$  and  $k_2$ , respectively) for the amine-catalysed methanolysis of esters  $\text{RCO}_2\text{-C}_6\text{H}_4\text{-4-NO}_2$  in methanol with buffer ratio ( $[\text{AmH}^+]:[\text{Am}]$ ) 1:1, at constant ionic strength  $\mu = 0.25 \text{ mol dm}^{-3}$  and at 298.2 K, unless otherwise stated.

R	Amine	$\text{p}K_a$ in water <sup>a</sup>	$\text{p}K_a$ in methanol <sup>b</sup>	$k_1/10^{-3} \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$	$k_2^{\text{intercept}}/10^{-6} \text{ s}^{-1}$	$[\text{MeO}^-]/10^{-12} \text{ mol dm}^{-3}$
CH <sub>3</sub>	Imidazole <sup>d,e,f</sup>	6.95		3.24 ± 0.06		
	Imidazole <sup>d,g,h</sup>			3.22 ± 0.03		
	2-Methylimidazole <sup>e</sup>			1.20 ± 0.01		
CH <sub>2</sub> Cl	Pyridine	5.22	5.37	1.37 ± 0.01	5.0 ± 1.2	1.5
	3-Methylpyridine	5.63	5.82	2.04 ± 0.03	8.4 ± 4.2	4.2
	4-Methylpyridine	5.98	6.16	3.30 ± 0.02	17 ± 3	9.1
	2,6-Dimethylpyridine	6.72	6.86	1.13 ± 0.02	27 ± 4	46
	Imidazole	6.95		252 ± 4	39 ± 59	
	Imidazole <sup>g</sup>			247 ± 4	680 ± 60	
	2-Methylimidazole	7.85		183 ± 1	1 480 ± 30	
CHCl <sub>2</sub>	Pyridine <sup>i</sup>	5.22	5.37	69 ± 3	200 ± 50	1.5
	Pyridine			86 ± 2	240 ± 30	
	Pyridine <sup>j</sup>			107 ± 3	340 ± 60	
	Pyridine <sup>k</sup>			131 ± 3	530 ± 60	
	2,6-Dimethylpyridine			6.72	6.86	

<sup>a</sup> Ref. 23. <sup>b</sup> Ref. 18. <sup>c</sup> The value for intercept when plotting the  $k_{\text{obs}}$  values (Table 1) against the free amine concentration. <sup>d</sup>  $\mu = 0.125 \text{ mol dm}^{-3}$ . <sup>e</sup>  $[\text{AmH}^+]:[\text{Am}] = 1:2$ . <sup>f</sup> For this reaction  $k_2 = (2.9 \pm 0.3) \times 10^{-3} \text{ dm}^6 \text{ mol}^{-2} \text{ s}^{-1}$  was detected. <sup>g</sup>  $[\text{AmH}^+]:[\text{Am}] = 1:4$ . <sup>h</sup> For this reaction  $k_2 = (2.5 \pm 0.2) \times 10^{-3} \text{ dm}^6 \text{ mol}^{-2} \text{ s}^{-1}$  was detected. <sup>i</sup> At 293.2 K. <sup>j</sup> At 303.2 K. <sup>k</sup> At 308.2 K.

pyridines in methanol are close to the values in aqueous solution.<sup>18</sup> 2,6-Dimethylpyridine in methanol is 30 times more basic than pyridine.<sup>18</sup> Typically for nucleophilic reactions methyl substituents adjacent to the attacking nitrogen reduce the reactivity of pyridine significantly. Pyridine-catalysed methanolysis of benzenesulphonyl chloride takes place by a nucleophilic mechanism.<sup>19</sup> For that case, the reactivity of 2-methylpyridine is less than 1% of that expected based on its  $\text{p}K_a$ . In the nucleophile-catalysed methanolysis of 2,4-dinitrophenyl acetate<sup>3d</sup> and of 2,4,6-trinitrophenyl acetate,<sup>3c</sup> pyridine is 27 and 77 times as effective as 2,6-dimethylpyridine, respectively. For hydrolysis reactions there also are several examples of the blocking effect of pyridine methyl substituents in the nucleophilic catalysis.<sup>10b,12,20</sup>

The steric effects are also observed in general base catalysed reactions but they are slight or of moderate size.<sup>2,3a,10a,d,21</sup> In the general base catalysed hydrolysis of methyl ethylene phosphate, pyridine is 2.8 times as reactive as 2,6-dimethylpyridine<sup>10a</sup> and in the general base catalysed methanolysis of 5-phenyltetrahydrofuran-2,4-dione enol benzoate, 2,6-dimethylpyridine is 1.8 times as effective as pyridine.<sup>3a</sup>

The steric effects observed in the present study for the methanolyses of 4-nitrophenyl chloroacetate and dichloroacetate catalysed by pyridine bases are much smaller than those usually found for nucleophilic reactions<sup>3c,d,10b,12,19,20</sup> but they are of the same size as those generally observed for general base catalysed reactions, thus suggesting the latter mechanism for the reactions under consideration.<sup>2,3a,10a,d,21</sup>

In the second-order reaction ( $k_1$ ), imidazole is, respectively, 2.7 and 1.4 times as reactive as 2-methylimidazole towards 4-nitrophenyl acetate and chloroacetate (Table 2). The steric effects of the 2-methyl substitution are somewhat smaller than those observed for nucleophilic reactions in aqueous solution<sup>11a,22</sup> but they are of the same size as those found in acetonitrile with a small amount of water.<sup>21</sup> In aqueous solution 2-methylimidazole is *ca.* ten times as basic as imidazole<sup>23</sup> and it can be assumed that this relative difference in their basicity is valid both in acetonitrile with low content of water and in methanol.<sup>18,24</sup> The lower reactivity of 2-methylimidazole as compared with imidazole seems to exclude the general base catalysed reaction.<sup>11b,21</sup>

The third-order reaction ( $k_2$ ) is found only for the imidazole-catalysed methanolysis of 4-nitrophenyl acetate (Table 2). Within experimental error the value for  $k_2$  is the same for 1:2

and 1:4 imidazole buffers, and the reaction obviously represents imidazole-catalysed nucleophilic reaction of imidazole.<sup>10a,21,25</sup> The absence of a detectable  $k_2$  term in the 2-methylimidazole-catalysed reaction is evident. It was evaluated that a  $k_2$  value larger than  $5 \times 10^{-4} \text{ dm}^3 \text{ mol}^{-1} \text{ s}^{-1}$  could have been clearly detected. Thus, the ratio  $k_2(\text{imidazole})/k_2(2\text{-methylimidazole})$  is greater than *ca.* 6. In a  $0.56 \text{ mol dm}^{-3}$  solution of water in acetonitrile, imidazole is approximately twice as reactive as 2-methylimidazole in the amine-catalysed nucleophilic reaction of amine for the reactions of both 4-nitrophenyl acetate and trifluoroacetate.<sup>21</sup>

**Catalyst Basicity.**—One feature of kinetic behaviour which distinguishes between nucleophilic and general base reactions is the higher sensitivity to the catalyst basicity of the former reaction compared with the latter. The Brønsted  $\beta$  values are *ca.* 0.8–0.9 for nucleophilic reactions<sup>9c,26</sup> while those ascertained for general base catalysed reactions are *ca.* 0.5.<sup>21,27,28</sup> We have determined the catalytic coefficient for three unhindered pyridines (Table 2) in the catalysed methanolysis of 4-nitrophenyl chloroacetate. The calculation of the Brønsted  $\beta$  value with the aid of these three points using methanolic  $\text{p}K_a$ s gives a value of  $(0.48 \pm 0.07)$ . Despite the inaccuracy of a  $\beta$  value determined using three points only, this value implies general base rather than nucleophilic catalysis. If a Brønsted line is drawn through the points for pyridines, it is seen that the point for imidazole falls considerably above this line. This indicates a change in mechanism from a general base reaction of pyridines to a nucleophilic reaction of imidazole, which is in accordance with the steric effects observed for the imidazole-catalysed methanolysis of 4-nitrophenyl chloroacetate.

**UV Scans.**—Qualitative evidence for the formation and decomposition of a transient reaction product was obtained from the UV spectral scans of the imidazole-catalysed methanolysis of 4-nitrophenyl acetate. This was indicated by a moving isosbestic point of *ca.* 240–242 nm during the scanning drives. The similarity to the  $\lambda_{\text{max}}$  value of 1-acetylimidazole (245 nm in water)<sup>29</sup> supports the idea of nucleophilic attack of imidazole on the acyl carbon. A stable isosbestic point occurs at 289 nm. The UV scans carried out for the imidazole-catalysed methanolysis of 4-nitrophenyl chloroacetate did not show an unstable intermediate but two stable isosbestic points (239 and

286 nm) were observed. If 1-chloroacetylimidazole is formed, as expected, it is rapidly methanolysed.

**The Activation Parameters.**—The activation parameters  $\Delta H^\ddagger = 29.7 \pm 0.2 \text{ kJ mol}^{-1}$  and  $\Delta S^\ddagger = -164 \pm 1 \text{ J mol}^{-1} \text{ K}^{-1}$  were determined for the pyridine-catalysed methanolysis of 4-nitrophenyl dichloroacetate. The enthalpy of activation is not very informative in the present case because in the light of the literature data there is no distinct difference in the magnitude of  $\Delta H^\ddagger$  when the general base catalysed and nucleophilic reactions are compared.<sup>10c,11,30,31</sup> Instead of that, the entropy of activation is expected to be more negative for the general base catalysed, than for the nucleophilic reaction, *i.e.* the increase in reaction order lowers the entropy of activation.<sup>10c,11,30,31</sup> In aqueous solution  $\Delta S^\ddagger$  values from  $-120$  to  $-150 \text{ J mol}^{-1} \text{ K}^{-1}$  are most typical for nucleophilic reactions of amines with esters<sup>10c,11a,30,31</sup> while values of  $-170$  to  $-180 \text{ J mol}^{-1} \text{ K}^{-1}$  have been observed for general base catalysed hydrolysis.<sup>11b</sup>

We have calculated on the basis of the literature data<sup>3d</sup> the  $\Delta S^\ddagger$  values for the methanolysis of 2,4-dinitrophenyl acetate catalysed by pyridine bases. For the pyridine-catalysed nucleophilic reaction a value of  $-102 \text{ J mol}^{-1} \text{ K}^{-1}$  is obtained. For the sterically hindered bases (2-methylpyridine, 2,6-dimethylpyridine, and 2,4,6-trimethylpyridine) the  $\Delta S^\ddagger$  values are *ca.*  $-160$  to  $-170 \text{ J mol}^{-1} \text{ K}^{-1}$ . The decrease in  $\Delta S^\ddagger$  as the steric crowding increases is in accordance with the assumption that a change in mechanism from nucleophilic to general base catalysis occurs. For the neutral methanolysis of chloromethyl trichloroacetate a  $\Delta S^\ddagger$  value of  $-202 \text{ J mol}^{-1} \text{ K}^{-1}$  is found.<sup>32</sup> A general base catalysed  $B_{AC}3$  mechanism involving at least two methanol molecules in the transition state of the rate-determining step has been proposed for this reaction. Pyridine bases catalyse as nucleophiles the methanolysis of benzene sulphonyl chloride.<sup>19</sup> For different substituted pyridines the  $\Delta S^\ddagger$  value is between  $-117$  and  $-130 \text{ J mol}^{-1} \text{ K}^{-1}$ . Schowen and Behn<sup>4a</sup> have given a  $\Delta^\ddagger S$  value of  $-163 \text{ J mol}^{-1} \text{ K}^{-1}$  for the acetate-catalysed methanolysis of 4-nitrophenyl acetate, but the value is based on rate determinations at two temperatures only. This reaction is proposed to take place by a nucleophilic mechanism.

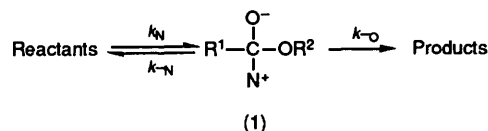
Taking into account the available literature data it can be said that the  $\Delta S^\ddagger$  observed in the present study for the pyridine-catalysed methanolysis of 4-nitrophenyl dichloroacetate shows such a negative value,  $-164 \text{ J mol}^{-1} \text{ K}^{-1}$ , that it confirms the earlier conception of the general base catalysed methanolysis in the case of pyridine-catalysed reactions.

## Conclusions

The present work gives strong evidence that the methanolysis of 4-nitrophenyl chloroacetate or dichloroacetate catalysed by pyridine bases takes place by general base catalysis rather than by nucleophilic catalysis. The previous investigations concerning pyridine-catalysed methanolysis of 4-nitrophenyl and 2-nitrophenyl acetates showed steric effects less than or equal to those observed in this study.<sup>3e,f</sup> Therefore, it is also probable that these reactions take place as general base reactions, although the Brønsted  $\beta$  values, 0.67 and 0.73, respectively, observed for 4-nitrophenyl and 2-nitrophenyl esters are somewhat high. As mentioned earlier, sterically unhindered pyridines function as nucleophilic catalysts in the hydrolysis of 4-nitrophenyl acetate. The same mechanism is assumed for the pyridine-catalysed hydrolysis of 4-nitrophenyl chloroacetate and it is also obvious for 4-nitrophenyl dichloroacetate.<sup>14</sup> Accordingly, a change in mechanism seems to occur in the pyridine-catalysed reaction when compared with the hydrolysis

and methanolysis reactions of the 4-nitrophenyl esters. Thus, the previous conclusion<sup>4</sup> concerning ester reactions which states that nucleophilic catalysis of acyl transfer to alcoholic function is preferred over general base catalysis, when compared with acyl transfer to water, is much too generalized.

On the nucleophilic pathway the reaction obviously passes through a tetrahedral intermediate (1) (Scheme 3).<sup>26e,33,34</sup> The



Scheme 3.

partitioning of the intermediate in the direction of reactants or products (*i.e.*  $k_{-N}/k_{-O}$ ) depends on the relative leaving ability of the nucleophile and the leaving group of the ester.<sup>33b</sup> In addition to the  $pK_a$  value of the conjugate acid of the nucleophile and that of the alcohol, other factors also contribute to their relative leaving ability.<sup>33-35</sup> If a change in the reaction medium, in the structure of the esters, or in that of the catalysing base is accompanied by a sufficiently unfavourable change in the partitioning of the intermediate in the direction of products, then a change in the reaction mechanism from nucleophilic to general base catalysed reaction can take place. Such a change in mechanism with increasing basicity of the leaving group has been observed, for example, in the acetate-catalysed hydrolysis of aryl acetates<sup>36</sup> and in the imidazole-catalysed hydrolysis of alkyl and aryl acetates.<sup>37</sup>

For the acetate-catalysed solvolysis of 4-nitrophenyl acetate, by changing the solution from water to methanol, a change occurs in the relative leaving ability of the acetate ion and the 4-nitrophenoxide ion in the direction favouring nucleophilic catalysis.<sup>4a</sup> In the case of pyridine-catalysed solvolysis of 4-nitrophenyl acetates the change in the relative leaving ability is in the opposite direction. The  $\Delta pK_a$ s of the conjugate acid of pyridine are 5.2 in water<sup>23</sup> and 5.4 in methanol<sup>18</sup> while those of 4-nitrophenol are 7.2 in water and 11.2 in methanol.<sup>38</sup> Accordingly, the  $\Delta pK_a$  [ $= pK_a(\text{leaving alcohol}) - pK_a(\text{conjugate acid of the catalyst})$ ] is 2.0 in water but 5.8 in methanol. There is a remarkable solvent-induced change in the relative leaving ability of the catalysing base and the ester leaving group from a tetrahedral intermediate assumed to occur on the route of the nucleophilic reaction. The change favours the partitioning of the intermediate in the direction of reactants and makes the nucleophilic pathway more difficult and the general base catalysis more efficient. This effect explains the change observed in the reaction mechanism from nucleophilic to general base catalysis in the pyridine-catalysed acyl transfers from 4-nitrophenol to methanol when compared to acyl transfers to water.

There is some evidence indicating a change in mechanism with increased basicity of the catalyst in the amine-catalysed methanolysis of the 4-nitrophenyl esters investigated. Although pyridines obviously function as general bases, imidazole seems to act as a nucleophile in the reaction of both 4-nitrophenyl acetate and chloroacetate. If the  $pK_a$  for the conjugate acid of imidazole is changed as little as those of pyridines by the solvent change from water to methanol,<sup>18,23</sup> its  $pK_a$  in methanol is around 7 and  $\Delta pK_a$  for  $pK_a(4\text{-nitrophenol}) - pK_a(\text{conjugate acid of imidazole})$  is *ca.* 4. Imidazole is known to be a poorer leaving group from tetrahedral intermediates than other amines of similar basicity.<sup>35a,b,37</sup> In aqueous solution, imidazole-catalysed hydrolysis of phenyl acetate ( $\Delta pK_a$  3.0) is entirely accounted for by a nucleophilic pathway<sup>39</sup> while the reaction of 2,2,2-trifluoroethylacetate ( $\Delta pK_a$  5.4) represents general base catalysed hydrolysis.<sup>25b,37</sup>

It is obvious that one decisive point affecting the reaction mechanism of enzyme-catalysed acyl transfer reactions must be the microenvironmental medium effect of the active site of the enzyme on the reacting groups, *i.e.* on the relative leaving ability of the attacking and leaving groups.

## References

- 1 J. Koskikallio, in 'The Chemistry of Carboxylic Acids and Esters,' ed. S. Patai, Interscience, London, 1969, p. 103.
- 2 S. L. Johnson, *J. Am. Chem. Soc.*, 1964, **86**, 3819.
- 3 (a) A. Kirkién-Konasiewicz and A. Maccoll, *J. Chem. Soc.*, 1961, 5421; (b) A. Kirkién-Konasiewicz, *ibid.*, p. 5430; (c) A. Kirkién-Konasiewicz and A. Maccoll, *ibid.*, 1964, 1267; (d) W. R. Ali, A. Kirkién-Konasiewicz, and A. Maccoll, *ibid.*, 1965, 6409; (e) A. Kirkién-Konasiewicz, A. M. Gude, M. McGraw, M. Knight, and A. Maccoll, *Chem. Ind. (London)*, 1967, 1527; (f) A. Kirkién-Konasiewicz, R. J. Simkin, and R. Murphy, *ibid.*, 1968, 1842.
- 4 (a) R. L. Schowen and C. G. Behn, *J. Am. Chem. Soc.*, 1968, **90**, 5839; (b) A. E. Williams, J. K. Lee, and R. L. Schowen, *J. Org. Chem.*, 1973, **38**, 4053.
- 5 T. D. Singh and R. W. Taft, *J. Am. Chem. Soc.*, 1975, **97**, 3867.
- 6 F. H. Westheimer, *Adv. Phys. Org. Chem.*, 1985, **21**, 1.
- 7 T. H. Fife, *Adv. Phys. Org. Chem.*, 1975, **11**, 1.
- 8 C. D. Hubbard and J. F. Kirsch, *Biochemistry*, 1972, **11**, 2483; C. D. Hubbard and T. S. Shoupe, *J. Biol. Chem.*, 1977, **252**, 1633.
- 9 (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; (c) W. P. Jencks and M. Gilchrist, *ibid.*, 1968, **90**, 2622.
- 10 (a) S. L. Johnson, *Adv. Phys. Org. Chem.*, 1967, **5**, 237; (b) A. R. Butler and V. Gold, *J. Chem. Soc.*, 1961, 4362; (c) A. R. Butler and I. H. Robertson, *J. Chem. Soc., Perkin Trans. 2*, 1975, 660; (d) F. Covitz and F. H. Westheimer, *J. Am. Chem. Soc.*, 1963, **85**, 1773.
- 11 (a) M. Akiyama, Y. Hara, and M. Tanabe, *J. Chem. Soc., Perkin Trans. 2*, 1978, 288; (b) M. Akiyama, M. Ihjima, and Y. Hara, *ibid.*, 1979, 1512.
- 12 L. W. Deady and W. L. Finlayson, *Aust. J. Chem.*, 1983, **36**, 1951.
- 13 B. S. Hartley and B. A. Kilby, *Biochem. J.*, 1954, **56**, 288.
- 14 K. Koehler, R. Skora, and E. H. Cordes, *J. Am. Chem. Soc.*, 1966, **88**, 3577.
- 15 R. Buyle, *Helv. Chim. Acta*, 1964, **47**, 2449.
- 16 C. Reichardt, 'Solvent Effects in Organic Chemistry,' Verlag Chemie, Weinheim, 1979, p. 283.
- 17 A. A. Frost and R. G. Pearson, 'Kinetics and Mechanisms,' Wiley, New York, 1969, p. 473.
- 18 C. H. Rochester, *J. Chem. Soc., B*, 1967, 33.
- 19 O. Rogne, *J. Chem. Soc., B*, 1971, 1334.
- 20 J. M. Briody and D. P. N. Satchell, *J. Chem. Soc.*, 1965, 3778.
- 21 H. Neuvonen, *J. Chem. Soc., Perkin Trans. 2*, 1987, 159.
- 22 T. C. Bruice and G. L. Schmir, *J. Am. Chem. Soc.*, 1958, **80**, 148.
- 23 D. D. Perrin, 'Dissociation Constants of Organic Bases in Aqueous Solution,' Butterworths, London, 1965.
- 24 (a) R. P. Bell, 'The Proton in Chemistry,' Chapman and Hall, London, 1973, 2nd edn., ch. 4, p. 44; (b) C. D. Ritchie, R. J. Minasz, A. A. Kamego, and M. Sawada, *J. Am. Chem. Soc.*, 1977, **99**, 3747; (c) C. D. Ritchie and P. D. Heffley, *ibid.*, 1965, **87**, 5402.
- 25 (a) M. Caplow and W. P. Jencks, *Biochemistry*, 1962, **1**, 883; (b) J. F. Kirsch and W. P. Jencks, *J. Am. Chem. Soc.*, 1964, **86**, 833.
- 26 (a) T. C. Bruice and R. Lapinski, *J. Am. Chem. Soc.*, 1958, **80**, 2265; (b) W. P. Jencks and J. Carriuolo, *ibid.*, 1960, **82**, 1778; (c) T. C. Bruice, A. Donzel, R. W. Huffman, and A. R. Butler, *ibid.*, 1967, **89**, 2106; (d) A. R. Fersht and W. P. Jencks, *ibid.*, 1970, **92**, 5442; (e) A. C. Satterthwait and W. P. Jencks, *ibid.*, 1974, **96**, 7018, 7031.
- 27 W. P. Jencks and J. Carriuolo, *J. Am. Chem. Soc.*, 1961, **83**, 1743.
- 28 A. R. Fersht and A. J. Kirby, *J. Am. Chem. Soc.*, 1967, **89**, 4853, 4857; E. K. Euranto, *Ann. Acad. Sci. Fenn., Ser. A2*, 1970, **152**; P. Y. Bruice and T. C. Bruice, *J. Am. Chem. Soc.*, 1974, **96**, 5523.
- 29 M. J. Gregory and T. C. Bruice, *J. Am. Chem. Soc.*, 1967, **89**, 2121.
- 30 T. C. Bruice and S. J. Benkovic, *J. Am. Chem. Soc.*, 1964, **96**, 418.
- 31 W. P. Jencks and M. Gilchrist, *J. Am. Chem. Soc.*, 1966, **88**, 104.
- 32 L. T. Kanerva, *J. Chem. Soc., Perkin Trans. 2*, 1986, 1433.
- 33 (a) M. J. Gresser and W. P. Jencks, *J. Am. Chem. Soc.*, 1977, **99**, 6963; (b) *ibid.*, 6970.
- 34 E. A. Castro and F. J. Gil, *J. Am. Chem. Soc.*, 1977, **99**, 7611; E. A. Castro and M. Freudenberg, *J. Org. Chem.*, 1980, **45**, 906.
- 35 (a) N. Gravitz and W. P. Jencks, *J. Am. Chem. Soc.*, 1974, **96**, 499; (b) C. D. Ritchie, *ibid.*, 1975, **97**, 1170; (c) P. Campbell and B. A. Lapinskas, *ibid.*, 1977, **99**, 5378.
- 36 V. Gold, D. G. Oakenful, and T. Riley, *J. Chem. Soc., B*, 1968, 515.
- 37 J. F. Kirsch and W. P. Jencks, *J. Am. Chem. Soc.*, 1964, **86**, 837.
- 38 G. Kortüm, W. Vogel, and K. Andrussov, 'Dissociation Constants of Organic Acids in Aqueous Solution,' Butterworths, London, 1961; B. W. Clare, D. Cook, E. C. F. Ko, Y. C. Mac, and A. J. Parker, *J. Am. Chem. Soc.*, 1966, **88**, 1911.
- 39 D. G. Oakenfull, *J. Chem. Soc., B*, 1970, 197.

Paper 9/02413A

Received 7th June 1989

Accepted 12th December 1989