Intramolecular General Base Catalysis in the Hydrolysis of 3-Dimethylaminopropionates†

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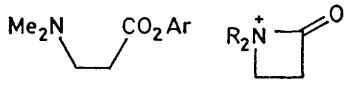
The hydrolysis of *p*-nitrophenyl 2-dimethylaminobenzoate, and of a series of substituted-phenyl 3-dialkylaminopropionates, is subject to intramolecular catalysis by the dialkylamino group. A general base catalysis mechanism is indicated. General base catalysis of hydrolysis by tertiary nitrogen is characterised by solvent deuterium isotope effects which fall with increasing basicity of the general base, to as low as $k_H/k_D = 1.4$. These low values are associated with a significant increase in the sensitivity of the reaction to the basicity of the leaving group, compared with similar reactions catalysed by oxyanions.

As part of our investigations [1,2] of the dependence on structure of the efficiency of intramolecular catalysis, we sought a system susceptible to a substantial range of structural variation, which would show intramolecular general base catalysis. A likely candidate appeared to be the β-dialkylamino-ester system (1), in which nucleophilic catalysis is inhibited by ring-strain in the required



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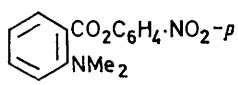


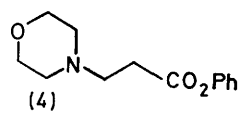
(3)

intermediate (2). A test of the mechanism, using the rigid *p*-nitrophenyl 2-dimethylaminobenzoate (3), showed the behaviour expected for an ester undergoing hydrolysis with catalysis by an internal general base.‡ Our next step was to examine a series of six substituted-phenyl 3-dimethylaminopropionates, to establish the kinetic behaviour of the system in detail before going on to study the effects of varying structure.

EXPERIMENTAL

Materials and methods are described only where they differ from those described elsewhere.[2]

Substituted-phenyl 3-Dimethylaminopropionates (1) *and* (4).—These were prepared from the phenol and the parent acid by a one-pot procedure, as follows. The dimethylamino-acid hydrochloride and thionyl chloride (1.1 equiv.) were heated together in an oil-bath, in a long tube, sealed with a drying tube and fitted with a magnetic stirrer. After 1 h at 55—60 °C the phenol (2 equiv.) was added to the reddish liquid and stirring was continued until a homogeneous solution was obtained. The oil-bath temperature was then raised to 100 °C and stirring continued for a further 20 min. The mixture was then allowed to cool, and the oil poured into ether; slow crystallisation occurred, to give an off-white solid containing some unchanged acid. For the *m*-chloro- and *m*- and *p*-nitro-phenyl esters, the thionyl chloride–phenol treatment was repeated once. The crude *esters* were recrystallised many times from chloroform–ether [dimethylformamide–ether for the *m*-nitrophenyl ester, and the morpholino ester (4)] to give satisfactory analyses



(4)

(Table 1). I.r. and n.m.r. spectra confirmed the expected structures in each case. p-*Nitrophenyl 2-dimethylaminobenzoate* (3) was prepared similarly, but in the cold from *NN*-dimethylanthranilic acid (3.30 g) and *p*-nitrophenol (2.78 g) in pyridine (10 ml). The solution was stirred and cooled in

† No reprints available.

‡ Recently Bruice and Bruice [3] have demonstrated intramolecular general base catalysis by the quinoline nitrogen of the hydrolysis of a series of substituted-phenyl quinoline-8-carboxylates, another rigid system with the nitrogen *ortho* to the ester group.

[1] A. J. Kirby and P. W. Lancaster, *J.C.S. Perkin II*, 1972, 1206.

[2] A. J. Kirby and G. J. Lloyd, following paper.

[3] P. Y. Bruice and T. C. Bruice, *J. Amer. Chem. Soc.*, 1974, **96**, 5523.

ice while thionyl chloride (2.38 g) was added over 20 min. The mixture was kept at 4 °C for 16 h and filtered, and the pyridine was evaporated from the filtrate to leave an orange solid. This was dissolved in 2M-HCl and extracted with ether several times. On neutralising the aqueous phase ($NaHCO_3$) a yellow solid precipitated. This was taken up in chloroform and the solution dried ($MgSO_4$) and evaporated.

Kinetic Measurements.—These were made mostly at 20.6 °C, after a preliminary examination of the phenyl ester (1e) at 39.6 °C. The slower hydrolyses of (3) and (4) were also followed at 39.6 °C. Reactions were started by adding a stock solution of ester in dimethyl sulphoxide (40 μl) to the aqueous buffer constituents (2 ml), preincubated in the cuvette of the spectrophotometer. For the anthranilate the solvent contained ethanol (20% v/v) for solubility reasons. Changing the volume of added stock solution by a factor of four did not affect the observed rate of hydrolysis. Reactions were generally followed for more than three half-lives, but for some slower (low pH) reactions with (1e) and (4) the initial rate method was used.

Attempted Trapping Experiment.—An obligatory intermediate in the intramolecular nucleophilic catalysis mechanism for hydrolysis of an aryl 3-dialkylaminopropionate is the four-membered cyclic acyltrialkylammonium compound (2). This should be a reactive acylating agent, and might be trapped by a suitable nucleophile. We therefore carried out the hydrolysis of the *p*-nitrophenyl ester (1a) in the presence of aniline, using conditions which proved successful (at lower pH) in trapping the reactive acylating agent formed during the hydrolysis of *p*-nitrophenyl malonate.[4] 0.4M-Carbonate buffer (75% free base; pH 10.33; 1 ml) containing aniline (0.05M) was added to each of two tubes containing the *p*-nitrophenyl ester (1a) (12.5 mg). This solution, containing equal concentrations of aniline and ester, was incubated at 39 °C. After 10 min 0.5M-phosphate buffer (4 ml; 25% free base; pH 6.04) was added, and each solution extracted with ether to remove *p*-nitrophenol. The ether layers showed u.v. absorption corresponding to the presence of aniline and *p*-nitrophenol, but the aqueous phase was transparent between 225 and 450 nm. Under these conditions the anilide, $Me_2{}^+NH{\cdot}CH_2{\cdot}CH_2{\cdot}CO{\cdot}NHPh$, should have remained in the aqueous phase. Since the sensitive u.v. test shows no trace of anilide, we conclude that none is formed.

RESULTS

The time-dependent u.v. spectra of several esters showed only changes associated with the disappearance of the ester and the appearance of the substituted phenolate, with no evidence for the formation of an intermediate. The hydrolysis of the phenyl ester (1e) was followed by n.m.r. in carbonate buffer in D_2O, and the products were shown to give signals identical with those of phenol and 3-dimethylaminopropionate under the same conditions.

The hydrolysis reactions were catalysed by the free base form of most of the buffers used to maintain pH, and the data given refer to linear extrapolations to zero buffer concentration based on 4—5 points each. Catalysis by carbonate was not significant, however, even for the most reactive ester (1a). Full pH–rate profiles for three representative esters at 39.6 °C are shown in Figure 1. In each case the ascending limb at high pH shows a break close to the expected pK_a of the dimethylamino group, and levels out to a more or less well-defined plateau, before the OH^- reaction sets in and the curve resumes its upward course.

TABLE 1

Properties of aryl 3-dialkylamino-ester hydrochlorides used

			Found (%)				Required (%)			
Comp.	Ar	M.p. (°C)	C	H	N	Cl	C	H	N	Cl
(1a)	*p*-$NO_2{\cdot}C_6H_4$	154—155	48.1	5.7	10.45	12.75	48.1	5.45	10.2	12.95
(1b)	*m*-$NO_2{\cdot}C_6H_4$	157—160	48.1	5.7	10.2	13.1	48.1	5.45	10.2	12.95
(1c)	*m*-ClC_6H_4	149—151	50.1	5.75	4.75	13.2	50.0	5.7	5.3	13.4
(1d)	*p*-ClC_6H_4	142—145	49.7	5.75	5.1	13.4	50.0	5.7	5.3	13.4
(1e)	Ph	135—137	57.0	7.0	6.4	15.65	57.5	6.95	6.10	15.45
(1f)	*p*-MeC_6H_4	153—156	59.2	7.3	5.65	14.8	59.1	7.4	5.75	14.6
(3)		95—97	62.6	10.1	5.0		62.9	9.8	4.9	
(4)		176—180	56.4	6.85	5.15	12.95	57.45	6.65	5.15	13.05

The data for each ester fit the rate law (i), where k_H is the

$$k_{obs} = (k_o + k_H a_H)a_H/(a_H + K_a) + (k_n + k_{OH}[OH^-])K_a/(a_H + K_a) \quad (i)$$

second-order rate constant for the acid-catalysed hydrolysis of the protonated ester, and k_0 the rate constant for its spontaneous hydrolysis; k_{OH} is the rate constant for alkaline hydrolysis of the unprotonated ester, and k_n the corresponding rate constant for spontaneous hydrolysis; K_a is the dissociation constant of the protonated amino-group of the ester. Above pH 7 the first term can be neglected [apart

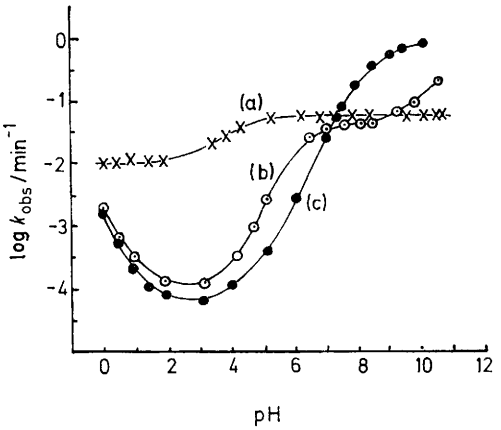


FIGURE 1 pH–Rate profiles for the hydrolysis of (a) *p*-nitrophenyl 2-dimethylaminobenzoate (3), (b) phenyl 3-morpholinopropionate (4), and (c) phenyl 3-dimethylaminopropionate (1e) at 39.6 °C

[4] A. J. Kirby and G. J. Lloyd, *J.C.S. Perkin II*, 1976, 1762.

from a small contribution from k_o for the *p*-nitrophenyl ester (1a)], and data collected for the six substituted aryl 3-dimethylaminopropionate esters (1a—f) at 20.6 °C between pH 6.5 and 11 were analysed on the basis of equation (ii),

$$k_{obs} = k_o + k_{OH} K_W/a_H + k_{obs} a_H/K_a \qquad \text{(ii)}$$

using a Hewlett–Packard 9100B calculator and a standard three-variable least squares linear regression program. The constants obtained in this way are given in Table 2. (Note

TABLE 2

Rate constants for the hydrolysis of substituted-phenyl 3-dialkylaminopropionates and related esters in water at ionic strength 1.0

Ester	(1a)	(1b)	(1c)	(1d)	(1e)	(1f)	(3) [a]	(4)
				Data at 39.6 °C				
pK_a					8.47		4.01	6.37
k_H/dm³ mol⁻¹ min⁻¹					1.64×10^{-3}		*b*	1.86×10^{-3}
k_o/min⁻¹					6.5×10^{-5}		1.07×10^{-2}	1.17×10^{-4}
k_n/min⁻¹					0.64		5.29×10^{-2}	4.05×10^{-2}
k_{OH}/dm³ mol⁻¹ min⁻¹					196		4.75	147
				Data at 20.6 °C				
pK_a	8.86	8.74	9.08	8.80	8.87	8.93		
k_{OH}	1 800	490	83	80	26	28		
k_n	1.94	1.22	0.64	0.31	0.165	0.123		
$k_n(D_2O)$	1.42				0.109			
k_H/k_D	1.4				1.5		2.3	2.1
$\Delta H^‡$/kcal mol⁻¹					13.3		13.5	
$\Delta S^‡$/cal K⁻¹ mol⁻¹					−25		−29	

[a] In 20 : 80 v/v ethanol–water, ionic strength 0.8. [b] Acid catalysis not detectable down to pH 0.1.

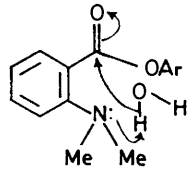
that measurements were not continued into strong alkali, and values of k_{OH} are not of high accuracy.)

DISCUSSION

The eight β-dialkylamino-esters examined in this work show pH–rate profiles of the expected form (Figure 1). At low pH these represent the spontaneous and acid-catalysed hydrolysis of the protonated ester, while the significant reactions above pH 7 are the spontaneous and alkaline hydrolysis of the unprotonated compound. The carbonyl group of the protonated ester would be expected to be slightly more electrophilic, yet in every case the spontaneous hydrolysis reaction is faster for the species with a free amino-group. The absolute rates of the pH-independent hydrolysis reactions are higher than expected on simple electronic grounds even for the protonated esters: k_o for the phenyl ester (1e), for example, is about 10 times larger than the rate constant for spontaneous hydrolysis of phenyl acetate,[5] and for *p*-nitrophenyl *o*-dimethylammoniobenzoate k_o is over 200 times greater than for *p*-nitrophenyl *p*-nitrophenylbenzoate.[6] Those factors suggest that there may be significant catalysis by the neighbouring $Me_2{}^+NH$ groups. If this is true such catalysis is generally much less efficient than catalysis by the free Me_2N group: for example k_n for phenyl 3-dimethylaminopropionate is *ca.* 10 000 times larger than k_o at 39.6 °C (Table 2). In this paper we limit discussion to the pH-independent hydrolysis of the unprotonated amino-esters.

There is sufficient evidence from the pH–rate profiles that these reactions involve intramolecular catalysis by the dimethylamino group. The reactions depend on the basic form of a group ionising just below pH 9, as expected for the dimethylamino group of these compounds; and the large rate enhancements, of up to 10^5-fold for the pH-independent hydrolysis of (1e) relative to phenyl acetate, rule out external catalysis, or simple electronic effects of the NMe_2 group.

The problem of mechanism is most straightforward for the anthranilate derivative (3). All the kinetic parameters are consistent with intramolecular general base catalysis (5), and since this is also the expected mechanism we will not rehearse various alternatives. We note in particular the solvent deuterium isotope effect, $k_H/k_D = 2.28$, and the substantial negative entropy of activation,



(5)

−29.3 cal K⁻¹ mol⁻¹, characteristic [2] of a transition state involving the cleavage of an O–H bond, and requiring two molecules to come together in solution.

In the series of substituted-phenyl 3-dialkylamino propionates an additional problem is the possibility that the mechanism may change from general base to nucleophilic catalysis, since the latter mechanism is generally more sensitive to the basicity of the leaving group. So we used esters with a range of leaving groups, from *p*-tolyl

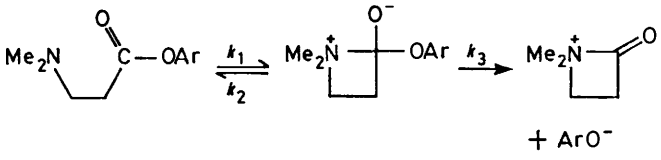
[5] W. P. Jencks and M. Gilchrist, *J. Amer. Chem. Soc.*, 1968, **90**, 2622.

[6] J. F. Kirsch, W. E. Clewell, and A. Simon, *J. Org. Chem.*, 1964, **33**, 127.

to *p*-nitrophenyl, and looked in more detail at one ester at each end of the reactivity scale.

The phenyl ester (1e) shows a moderately large negative entropy of activation of -24.9 cal K^{-1} mol^{-1}, in the region expected for a reaction involving intramolecular general base catalysis; but the solvent deuterium isotope effect is substantially smaller than is normally found for this mechanism ($k_H/k_D = 1.5$). This might be an indication that the hydrolysis of the phenyl ester involves concurrent nucleophilic and general base catalysed reactions: in which case one would expect the *p*-nitrophenyl ester (1a) to show a higher proportion of nucleophilic catalysis. But k_H/k_D (=1.4) for this ester is not significantly smaller than for the phenyl ester. If a mixture of mechanisms is involved, it would appear that the mixture does not change substantially with changing leaving group. This would require nucleophilic catalysis in our system to be considerably less sensitive to the basicity of the leaving group than with compounds showing less strain in the transition state. The following argument suggests that the strained system should, if anything, be more sensitive.

The nucleophilic reaction has been well-characterized by Bruice and Benkovic.[7] Both external catalysis by trimethylamine and intramolecular catalysis by the dimethylamino group of the hydrolysis of substituted-phenyl esters show high sensitivity to the pK_a of the substituted phenol [measured by $\beta_{LG} = 1.03$ and 1.2 (ρ = 2.2 and 2.5) respectively] in unstrained systems. This is consistent with a transition state in which bond breaking is well advanced, and thus a mechanism in which the breakdown of the tetrahedral addition intermediate is



SCHEME

rate-determining. If we consider this mechanism for the 3-dimethylaminopropionate system (Scheme), it is apparent that strain will affect both steps of the reaction. Clearly k_2 will be increased, relative to an unstrained system, because this step relieves strain directly; k_3, on the other hand, will be decreased, because the generation of a trigonal carbon in a small ring leads to a further increase of strain.[8] We do not therefore need to know anything about the sizes of these effects to be reasonably certain that, compared with an unstrained system, k_2/k_3 will be increased, and thus k_3 even more securely rate-determining in the reaction of the Scheme. The transition state should thus be later, corresponding to an increased sensitivity to the basicity of the leaving group.

[7] T. C. Bruice and S. J. Benkovic, *J. Amer. Chem. Soc.*, 1963, **85**, 1.

The observed sensitivity to the leaving group (Figure 2; $\beta_{LG} = 0.54$, $\rho = 1.2$) is less than half that expected for nucleophilic catalysis. We conclude, therefore, that the dimethylamino group in our system acts as a general

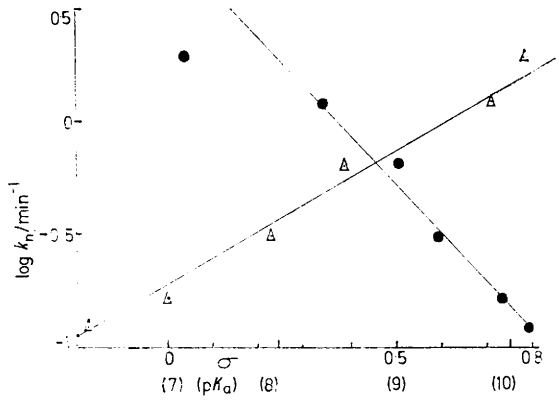
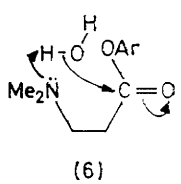


FIGURE 2 Linear free energy relationships between the rate constants (k_n; Table 2) for intramolecular catalysis by the Me_2N group, and the pK_a of the leaving group (●), and Hammett's σ (△), for the substituted-phenyl 3-dimethylaminopropionates (1a—f), at 20.6 °C and ionic strength 1.0

base to catalyse the hydrolysis of the neighbouring ester group (6). The linear free energy relationships shown in Figure 2 suggest that this is true for all six substituted-phenyl 3-dimethylaminopropionates (1a—f). A changeover to nucleophilic catalysis would result in a positive deviation for the *p*-nitrophenyl compound, in contrast to the negative deviation actually observed (Figure 2). The Bruices[3] found such behaviour for catalysis by trimethylamine of the hydrolysis of a series of aryl quinoline-6- and -8-carboxylates: in their systems positive deviations are seen for the 2,4-dinitrophenyl esters, and a changeover to nucleophilic catalysis is confirmed by the fall in the solvent deuterium isotope effect ($k_H/k_D < 1$) for these compounds. They too found $\rho = 1.2$, and k_H/k_D in the region of 1.5, for catalysis by trimethylamine of the hydrolysis of the remaining substituted phenyl quinoline-6- and -8-carboxylates, and assigned a general base catalysis mechanism for this reaction.



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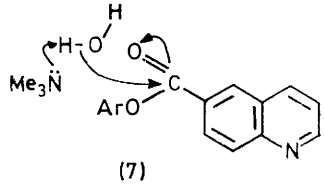
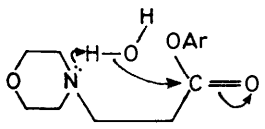


(7)

The evidence from these very different systems [(6) and (7)] suggests that the solvent deuterium isotope effect for general base catalysis is genuinely smaller for catalysis by strongly basic amines than for familiar re-

[8] G. H. Whitham, 'Alicyclic Chemistry,' Oldbourne Press, London, 1963. p. 36.

actions catalysed by carboxylate * or imidazole † groups. Since we found a ' normal ' value of $k_H/k_D = 2.3$ for the similar reaction (5) of our anthranilate derivative (3), the isotope effect appears to be dependent on the basicity of the general base. We therefore measured k_H/k_D for the morpholinopropionate ester (4), which should give a reaction (8) with transition state geometry almost identical with that of (6), but has a substantially less basic aliphatic amino group (pK_a 6.37 at 39.6 °C). The observed k_H/k_D value for (8) is 2.1, consistent with the suggested dependence of k_H/k_D on the pK_a of the general base.‡ The lower isotope effects found for general base catalysis by trimethylamine are associated with small but significant increases in the sensitivity of these reactions to the basicity of the leaving group. For carboxylate-[2,9] and water catalysed-[12] hydrolysis of substituted phenyl ester, β_{LG} is −0.43 and −0.38, respectively, and is −0.38 also for alkaline hydrolysis.[13] For the general base-catalysed hydrolysis of the substituted-phenyl quinolinecarboxylates described above,[3] β_{LG} is −0.51, similar to that (−0.54) found for the 3-dimethylaminopropionates described in this work.



(8)

These results enable us to characterize the general base catalysis mechanism with reasonable confidence, given sufficient data. But the distinction from nucleophilic catalysis is not sufficiently clear-cut to allow an assignment of mechanism on the basis of a single criterion, or even on the basis of results with a single compound. Since we had hoped to go on to examine the dependence on structure of the efficiency of intramolecular general base catalysis in the dialkylaminopropionate system, where a changeover to nucleophilic catalysis is likely, the availability of a simple test of mechanism was important. Such a test is evidently not feasible, and we have not extended this study to *C*-substituted propionate derivatives. We describe a study with a more suitable system in the following paper.[2]

The efficiency of catalysis in the reactions described here can be estimated in terms of the effective concentration[14] of the dimethylamino group. Compared with external catalysis[7] by trimethylamine of the hydrolysis of substituted-phenyl acetates at 20 °C, this ranges from about 20M for phenyl 3-dimethylaminopropionate (1e) to less than 0.5M for the *p*-nitrophenyl ester (1a). These are minimum values, because the observed reaction of phenyl acetate with trimethylamine[7] involves nucleophilic catalysis: and the difference from the true value increases as the basicity of the leaving group falls, because of the higher sensitivity of the nucleophilic mechanism to this factor. A direct comparison with external general base catalysis by trimethylamine is only possible for the anthranilate derivative (3): using the Bruices ' data[3] for *p*-nitrophenyl quinoline-6- and -8-carboxylates for the comparison, the effective concentration of the dimethylamino group of (3) is only 0.25M.

We thank the Salters' Company, for a Scholarship (to G. J. L.).

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* The k_H/k_D value is 2.2 for the intramolecular and acetate-catalysed hydrolysis of aspirin,[9] and for the hydrolysis of monophenyl malonate anion.[2]

† The k_H/k_D value is 3.23 for the hydrolysis of 2-(imidazol-4-yl)-phenyl acetate.[10]

‡ Variation of k_H/k_D with the pK_a of the general base is well known in simple systems involving proton transfer from carbon.[11]

[9] A. R. Fersht and A. J. Kirby, *J. Amer. Chem. Soc.*, 1967, **89**, 4857.

[10] S. M. Felton and T. C. Bruice, *J. Amer. Chem. Soc.*, 1969, **91**, 6721.

[11] R. P. Bell, ' The Proton in Chemistry,' Chapman and Hall, London, 2nd edn., 1973, p. 262.

[12] A. J. Kirby in ' Comprehensive Chemical Kinetics,' eds. C. H. Bamford and C. F. H. Tipper, Elsevier, Amsterdam, 1972, vol. 10, p. 154.

[13] T. C. Bruice and M. F. Mayahi, *J. Amer. Chem. Soc.*, 1960, **82**, 3067.

[14] W. P. Jencks, ' Catalysis in Chemistry and Enzymology,' McGraw-Hill, New York, 1969, p. 10.