Nucleophilic and General Base Catalysis by Pyridine and Methylpyridines in the Hydrolysis of Aryl Acetates

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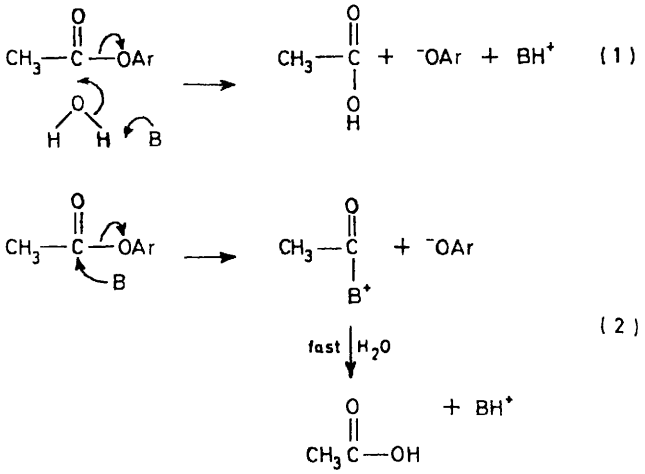
Pyridine bases catalyse the hydrolysis of aryl acetates and activation parameters for several of these reactions have been determined. The size of the kinetic isotope effect indicates nucleophilic catalysis. Substitution at the 2-position in pyridine prevents nucleophilic catalysis, but a much slower general base catalysed pathway was detected and it is argued that this occurs even when nucleophilic catalysis appears to be the mechanism. Anion desolvation may be important in the reaction with hydroxide ion with aryl esters.

Two mechanisms have been proposed [1] for the base-catalysed hydrolysis of aryl acetates: (1) general base catalysis, where attack of a water molecule on the carbonyl group of the aryl ester is assisted by partial bond formation to the base (B) and, (2) nucleophilic



catalysis where the base attacks the ester directly to give an intermediate which is rapidly hydrolysed. The mechanism of hydrolysis of aryl acetates has been examined in great detail because they are substrates for various esterases but, in spite of this, it is still not possible to predict with certainty if any particular base will act as a general base or a nucleophilic catalyst. Gold and his co-workers [2,3] have demonstrated that, in certain instances, the two mechanisms may occur concurrently. This was shown by trapping the intermediate produced in the nucleophilic pathway and comparing the amount of intermediate formed with the amount of reactant consumed. Their general conclusion [3] was that the better the leaving group (*i.e.* the lower the pK_a of the phenol) the greater the tendency for nucleophilic catalysis to occur. For example, the acetate-catalysed hydrolysis of 2,3-dinitrophenyl acetate is 100% nucleophilic, while for 4-methylphenyl acetate the reaction is 100% general base catalysed. For phenols of intermediate leaving tendency both pathways may occur and acetate-catalysed hydrolysis of 4-nitrophenyl acetate is 70% nucleophilic and 30% general base. It is not difficult to understand the onset of nucleophilic catalysis as the leaving tendency improves but there is no obvious reason why general base catalysis should cease. Implicit in the analysis of Gold and his co-workers is the notion that general base catalysis occurs with all esters but, once nucleophilic catalysis becomes possible, it is the predominant pathway. Indeed, in an excellent review of this topic, Johnson [4] quotes Brønsted β values of *ca.* 0·5 and *ca.* 0·8 for general base and nucleophilic catalysis and it is clear that, except in a few special borderline cases, it would be difficult to detect the general base catalysed reaction when nucleophilic catalysis occurs. However, in this paper we report a method of demonstrating the persistence of a general base catalysed reaction even when the reaction appears to be completely nucleophilic.

Pyridine is an effective catalysis in the hydrolysis of acetic anhydride [5] but its activity is completely removed by substitution of a methyl group at the 2-position.[6] This is due to steric hindrance to nucleophilic attack as the same effect is observed if substitution occurs in the anhydride, *e.g.* pyridine is not a catalyst for the hydrolysis of 2,2-dimethylpropionic anhydride.[7] Pyridine is also a catalyst for the hydrolysis of aryl acetates [8] and if the mechanism is the same, then the ability of pyridine to act as a nucleophile in this reaction also can be removed by substitution at the 2-position. Any general base catalysed reaction which occurs concurrently will then be the only reaction and, under these circumstances, it will be possible to observe and characterise this reaction pathway. As the nucleophilic pathway is likely to be much more effective than the general base catalysed reaction (to judge from the Brønsted β factors) those reactions involving both pathways must be very fast if the latter pathway is to be detected. Therefore, this study has necessitated the use of stopped-flow spectrophotometry.

[1] See T. C. Bruice and S. J. Benkovic, 'Bioorganic Mechanisms,' Benjamin, New York, 1966, vol. 1, p. 1.
[2] D. G. Oakenfull, T. Riley, and V. Gold, *Chem. Comm.*, 1966, 385.
[3] V. Gold, D. G. Oakenfull, and T. Riley, *J. Chem. Soc.* (*B*), 1968, 515.
[4] S. L. Johnson, *Adv. Phys. Org. Chem.*, 1967, **5**, 237.
[5] S. L. Bafna and V. Gold, *J. Chem. Soc.*, 1953, 1406.
[6] V. Gold and E. G. Jefferson, *J. Chem. Soc.*, 1953, 1409; A. R. Butler and V. Gold, *ibid.*, 1961, 4362.
[7] A. R. Butler and V. Gold, *J. Chem. Soc.*, 1962, 976.
[8] W. P. Jencks and J. Carriuolo, *J. Amer. Chem. Soc.*, 1960, **82**, 1778.

RESULTS AND DISCUSSION

The hydrolysis of 4-nitrophenyl acetate in a series of buffers made from pyridine and 3-methylpyridine was examined at three temperatures and the results are given in Table 1. A plot of k_{obs} against concentration of free (*i.e.* unprotonated) pyridine and 3-methylpyridine is linear in all cases with no intercept. The catalytic coefficients are given at the foot of each column and were used to calculate activation parameters for the two reactions (Table 5).

One of the criteria for nucleophilic catalysis is that, as a water molecule is not involved in the rate-determining step, the $k(H_2O)/k(D_2O)$ value should be about unity.[1] Although this criterion must be used with caution, it has fairly wide validity. The rate of the pyridine-catalysed hydrolysis of 4-nitrophenyl acetate in D_2O at 25° was measured and the results are given in Table 2. The catalytic coefficient is $1{\cdot}86 \times 10^{-3}$ l mol^{-1} s^{-1} and so $k(H_2O)/k(D_2O)$ for this reaction is 1·0. We have good grounds, therefore, for believing that the reaction exhibits nucleophilic catalysis.

TABLE 1

Hydrolysis of 4-nitrophenyl acetate in buffered solution

	10^4k_{obs}/s^{-1}		
t/°C	25·5	35·5	45·0
$[C_5H_5N]_t$/M			
0·080	1·96	4·56	8·42
0·16	3·68	7·70	
0·24	5·26	10·2	20·3
0·32	6·88	12·8	
0·40	8·32	15·8	30·6
10^3k/l mol^{-1} s^{-1}	1·88	3·42	6·80
$[CH_3C_5H_4N]_t$/M			
0·080	6·50	8·70	16·0
0·16	8·70	17·7	34·6
0·24	12·0	24·5	46·3
0·32	14·7	30·1	51·4
0·40	19·6	36·5	66·7
10^3k/l mol^{-1} s^{-1}	4·46	8·12	14·9

TABLE 2

Hydrolysis of 4-nitrophenyl acetate catalysed by D_2O at 25°

$[C_5H_5N]_t$/M	0·11	0·26	0·36	0·46
10^4k_{obs}/s^{-1}	2·02	4·90	6·80	8·20

Gold *et al.*[2] suggested another criterion for nucleophilic catalysis: they found that in the acetate-catalysed hydrolysis of aryl acetates nucleophilic catalysis is associated with a small negative entropy of activation (−10 cal mol^{-1} K^{-1}) while for general base catalysed reactions the value is much more negative (−30 cal mol^{-1} K^{-1}). The absolute values of $\Delta S^{\ddagger}$ observed in the present reactions are not the same as those found for the acetate-catalysed reactions, and so this criterion does not confirm the mechanism as nucleophilic catalysis, but a change in the value of $\Delta S^{\ddagger}$ will be used later to indicate a change of mechanism. There can be little doubt, in view of the size of the kinetic isotope effect and the previous study[5] of the role of pyridine in the hydrolysis of acetic anhydride, that the present reactions exhibit nucleophilic catalysis.

As described previously, substitution of a methyl group at the 2-position of pyridine prevents nucleophilic catalysis for steric reasons, and so, if 2-methylpyridine accelerates the hydrolysis of 4-nitrophenyl acetate the mechanism cannot be nucleophilic catalysis. When the experiment was tried no reaction, other than spontaneous hydrolysis, could be detected. However, the pyridine-catalysed hydrolysis of 4-nitrophenyl acetate is not a particularly rapid reaction and, if the general base-catalysed pathway is only a small fraction of the total reaction, then that reaction may be too slow to detect. The obvious next step is to use a more reactive ester and this was done. However, this study with 4-nitrophenyl acetate has established that pyridine-catalysed ester hydrolysis is nucleophilic. With the more reactive ester this would not have been possible as the quantities required to measure the kinetic isotope effect in a stopped-flow apparatus are too great.

The ester chosen for further study was 2,4-dinitrophenyl acetate. Its rate of hydrolysis in the presence of pyridine, 3-methylpyridine, and 4-methylpyridine was examined by use of a stopped-flow spectrophotometer and a typical set of results, those for 4-methyl pyridine, is given in Table 3. The catalytic coefficient for these three bases are collected in Table 4 and the activation parameters for the hydrolysis of both 4-nitrophenyl acetate and 2,4-dinitrophenyl acetate are given in Table 5. It is reasonable to deduce from the constant values of $\Delta S^{\ddagger}$ for

TABLE 3

Hydrolysis of 2,4-dinitrophenyl acetate catalysed by 4-methylpyridine

	k_{obs}/s^{-1}		
t/°C	25·2	34·8	44·5
$[4\text{-}CH_3C_5H_4N]_t$/M			
0·036	0·34	0·50	0·78
0·040	0·48	0·71	1·08
0·054	0·51	0·85	1·26
0·072	0·63	0·94	1·43
0·20	1·94	3·22	4·96
0·40	3·38		

TABLE 4

Catalytic coefficients for the base-catalysed hydrolysis of 2,4-dinitrophenyl acetate

	k/l mol^{-1} s^{-1}		
t/°C	25·2	34·8	44·5
Pyridine	1·60	2·70	4·20
3-Methylpyridine	6·50	9·90	15·1
4-Methylpyridine	8·02	12·9	20·0

the two esters that the mechanism of hydrolysis is the same, *i.e.* nucleophilic. The increased susceptibility of 2,4-dinitrophenyl acetate to attack resides in change in the value of $\Delta H^{\ddagger}$.

With 2,4-dinitrophenyl acetate as substrate it was found that 2-methylpyridine does act as a catalyst although the rate of reaction is much slower than with

the other bases. The catalytic coefficients for this reaction at 25·3, 34·9, and 45·3° are $2·80 \times 10^{-3}$, $4·93 \times 10^{-3}$, and $8·05 \times 10^{-3}$ l mol^{-1} s^{-1}, and the activation parameters are reported in Table 5. The change in

TABLE 5

Activation parameters for the base-catalysed hydrolyses of aryl acetates at 25°

Substrate	Base	$\Delta H^{\ddagger}$/ kcal mol^{-1}	$\Delta S^{\ddagger}$/ cal mol^{-1} K^{-1}
4-Nitrophenyl acetate	Pyridine	11·6	−32 (±1)
4-Nitrophenyl acetate	4-Methylpyridine	10·6	−34 (±1)
2,4-Dinitrophenyl acetate	Pyridine	8·7	−30 (±1)
2,4-Dinitrophenyl acetate	3-Methylpyridine	7·4	−31 (±1)
2,4-Dinitrophenyl acetate	4-Methylpyridine	7·7	−29 (±1)
2,4-Dinitrophenyl acetate	2-Methylpyridine	9·2	−40 (±1)

both $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ clearly indicates a different mechanism and a more negative value for $\Delta S^{\ddagger}$ is what Gold *et al.*[2] observed in going from nucleophilic to general base catalysis. The reaction with 2-methylpyridine is slow enough to permit the use of normal spectrophotometric methods and so the solvent isotope effect was measured. The molar rate constant for reaction in D_2O is $7·50 \times 10^{-4}$ l mol^{-1} s^{-1} and so the value of $k(H_2O)/k(D_2O)$ is 3·7, a value consistent with general base catalysis where, as a water molecule is involved in the rate-determining step, there is a substantial change in going from H_2O to D_2O. It is clear, then, that 2-methylpyridine catalyses the reaction by general base catalysis, although the only detectable reaction with the closely related, but sterically unhindered, bases is nucleophilic catalysis. It seems reasonable to conclude that general base catalysis occurs with all the pyridine bases and that, with these bases at least, general base and nucleophilic catalysis are concurrent pathways and one is not replaced by the other as the leaving tendency of the departing phenoxide changes.

Rather surprisingly a plot of pyridine pK_a for the three pyridines used against log k is not linear, as it is for 4-nitrophenyl acetate.[1] However, the pK_a of 2-methylpyridine is very similar to that of 4-methylpyridine (6·02 and 5·97 respectively) and so if 2-methylpyridine could act as a nucleophile the value of k_n would be *ca.* 8·0 l mol^{-1} s^{-1} at 25°. Thus, the value of k_n/k_{gb} is *ca.* 3500 for these bases. When nucleophilic catalysis can occur the general base-catalysed pathway is, therefore, insignificant.

There is one part of the work of Gold *et al.*[2,3] which argues against our interpretation. They found a linear relationship between log k_{OAc} and the pK_a of the displaced phenoxide, although the reaction changes from 100% general base to 100% nucleophilic catalysis. If nucleophilic catalysis occurs in addition to the general base-catalysed reaction, then this linearity should be discontinuous. The work of Gold *et al.* was analysed in terms of two intersecting straight lines in a preliminary account [2] and we feel that this must be the correct analysis, although their results are not, by themselves, convincing on this point.

The hydrolysis of 4-nitrophenyl acetate and 2,4-dinitrophenyl acetate in alkaline solution has also been examined (Table 6). For the two reactions at 25°

TABLE 6

Hydrolysis of aryl esters in alkaline solution

		k_{obs}/s^{-1}		
	t/°C	25·5	35·5	45·0
	[KOH]/M			
4-Nitrophenyl acetate	0·050	0·31	0·86	
	0·10	0·78		2·90
	0·20	1·24	3·22	5·59
	0·30	2·16		8·25
	0·40	3·02	6·00	
	0·50	3·98	7·94	
k/l mol^{-1} s^{-1}		7·46	14·1	27·0
2,4-Dinitrophenyl acetate	0·050	3·28	6·20	10·6
	0·15	9·15	17·5	32·4
	0·25	15·7	29·5	53·2
k/l mol^{-1} s^{-1}		62·0	117	212

$\Delta H^{\ddagger}$ is essentially the same (11·5 and 12·0 kcal mol^{-1}), while there is a small change in $\Delta S^{\ddagger}$. This change is too small to discuss further but desolvation of the nucleophile may play a part on determining the rate of reaction.[9]

EXPERIMENTAL

Materials.—4-Nitrophenyl acetate was recrystallised from ethanol. 2,4-Dinitrophenyl acetate was prepared by the method of Blacksma.[10] The main experimental difficulty in this study was purification of the pyridine bases. Normal laboratory samples are often very impure and the validity of these experiments necessitates that, in particular, 2-methylpyridine contains no base unsubstituted at the 2-position as an impurity. We were fortunate to obtain from Midland-Yorkshire Tar Distillers Ltd. samples of 2-, 3-, and 4-methylpyridine which were 99·9% pure with respect to total base content. 3- and 4-Methylpyridine were dried over KOH and carefully fractionally distilled before use. 2-Methylpyridine was refluxed with boron trifluoride, which reacts with any unsubstituted material, and distilled.[11] A second treatment with boron trifluoride was found to have no effect on the efficiacy of 2-methylpyridine as a catalyst in the hydrolysis of 2,6-dinitrophenyl acetate. We assumed, therefore, that it was sufficiently pure. Had its small catalytic effect been due to other pyridine bases present as impurities then there would not have been a change in $\Delta S^{\ddagger}$ and the kinetic isotope effect for this reaction. The buffered solutions were prepared by half neutralisation of the pyridine base with HCl. On dilution, the ionic strength was kept constant (0·50M) by addition of KCl.

[9] C. D. Ritchie, *Accounts Chem. Res.*, 1972, **5**, 348.
[10] J. J. Blacksma, *Chem. Weekblad.*, 1909, **38**, 717.
[11] H. C. Brown, S. Johnson, and H. Podall, *J. Amer. Chem. Soc.*, 1954, **76**, 5556.

Kinetic Method.—For the slow reactions, one drop of a solution of the ester in acetonitrile was added to the buffer in a cuvette in the thermostatted cell holder of a Unicam SP 500 spectrophotometer. The increase in absorption at 400 (4-nitrophenyl acetate) or 406 nm (2,4-dinitrophenyl acetate) was monitored. First-order rate constants were calculated by the method of Swinbourne [12] and the reaction was first order over three half-lives.

For the fast reaction a Canterbury stopped-flow spectrophotometer was used. A solution of ester in water (made 0·001M in HCl to suppress hydrolysis) was placed in one reservoir and the buffer in the other. The change in absorption after mixing was displayed on a cathode ray oscilloscope and photographed. The reaction was found to obey good first-order kinetics. The values of k_{obs} given in the Tables are the mean of two or three runs.

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[12] E. S. Swinbourne, *J. Chem. Soc.*, 1960, 2371.