Reactions of Carbonyl Compounds in Basic Solutions. Part III.[1] The Mechanism of the Alkaline Hydrolysis of Methyl 2-Aroyl- and 2-Acyl-benzoates and Related Esters

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Rate coefficients have been measured for the alkaline hydrolysis of a comprehensive series of methyl 2-acyl- and 2-aroyl-benzoates and closely related esters in 70% (v/v) dioxan–water at several temperatures. The entropies and enthalpies of activation have been evaluated. The effect of substitution in the 2-acyl system has been correlated with the steric substituent parameter, E_s. The relative rates of hydrolysis, activation parameters, substituent effects, solvent isotope, and solvent effects have been used to delineate the importance and extent of neighbouring-group participation by the keto- or formyl-carbonyl groups in the alkaline hydrolysis of the esters under study.

SEVERAL studies [1-6] have indicated participation by suitably orientated keto- or formyl-carbonyl groups in ester hydrolysis. Bender and his co-workers [2] observed the extremely rapid alkaline hydrolysis of methyl 2-formylbenzoate and postulated a mechanism involving intramolecular catalysis. In addition to the exceptional rapidity of hydrolysis, they cited the closely analogous morpholine-catalysed hydrolysis of this ester. Just before, a similar mechanism had been suggested by Newman and Hishida [3] for the alkaline hydrolysis of methyl 2-benzoyl-6-methylbenzoate. The latter reaction was faster than that for the unsubstituted 2-benzoyl ester. Later these observations were extended to the 6-methyl- and 6-chloro-substituted methyl 2-benzoyl and 2-acetylbenzoates.[4] As the 6-substituted all hydrolysed faster than the unsubstituted esters, it was concluded that this was due to steric facilitation and that the rate-determining step was the intramolecular nucleophilic step when participation occurred. However we [1] had studied the alkaline hydrolysis of a series of 3′- and 4′-substituted methyl 2-benzoylbenzoates and found that all this series reacted by an intramolecular path. Recently two studies of closely related systems have been made. An investigation of the hydrolysis of 2-acetylphenyl benzoate and mesitoate detected intramolecular participation from both rate and product studies.[5] Further, intramolecular catalysis by γ-keto-groups in the alkaline hydrolysis of aliphatic esters has been indicated by their abnormally low enthalpies of activation.[6]

It is our intention to make a comprehensive survey of the occurrence of intramolecular catalysis in the alkaline hydrolysis of 2-aroyl- and 2-acyl-benzoates and closely related esters. The kinetics of the alkaline hydrolysis of a series of 2-keto- and 2-formyl-benzoates have been studied. The relative rates of hydrolysis, the activation parameters, the results of variation of the alkoxyl group, substituent, and solvent, and solvent isotope effects are discussed to delineate the mechanisms of hydrolysis.

EXPERIMENTAL

2-Formylbenzoic acid, 2-acetylbenzoic acid, and 2-benzoylbenzoic acid were commercially available. 2-Propionylbenzoic acid, 2-isobutyrylbenzoic acid, and 2-pivaloylbenzoic acid were prepared from the corresponding dialkylcadmium and phthalic anhydride.[7] 2-Phenylacetylbenzoic acid was prepared by the hydrolysis of benzylidenephthalide.[8,9] 9-Oxofluoren-1-carboxylic acid was prepared by the oxidation of fluoranthen.[10]

Methyl 2-benzoylbenzoate and methyl 9-oxofluoren-1-carboxylate were prepared by Fischer–Speier esterification of the acid in methanol.[11] Methyl 2-formylbenzoate and methyl 2-acetylbenzoate were prepared from the acid and methyl iodide in acetone.[12] Methyl 2-propionylbenzoate was prepared from the acid and diazomethane. An ice-cold solution of diazomethane in ether [13] was added to the acid until in excess. The solution was stirred for ½ h until the reaction was complete and no more nitrogen was evolved. Sufficient dilute acetic acid in ether was then added to react with excess of diazomethane. The solution was filtered and the solvent removed under reduced pressure without heating. The last traces of solvent were removed by keeping the solution under reduced pressure (about 1 mmHg) for 24 h to give the ester as a colourless oil. It was not possible to purify the ester by distillation under reduced pressure since it appears to rearrange thermally to give the cyclic or pseudo-ester. Methyl 2-isobutyrylbenzoate and methyl 2-pivaloylbenzoate, prepared analogously, behave similarly. However, the purity of these esters was assessed to be greater than 99% from their ^{1}H n.m.r. spectra and from g.l.c.

Isopropyl 2-benzoylbenzoate was prepared by Fischer–Speier esterification of the acid in isopropyl alcohol. The crude ester was recrystallised from methanol to give the *ester* as colourless prisms, m.p. 62 °C (Found: C, 76·1; H, 6·0; O, 17·9. $C_{17}H_{16}O_3$ requires C, 76·1; H, 6·0; O, 17·9%).

Diphenylmethyl 2-benzoylbenzoate was prepared from

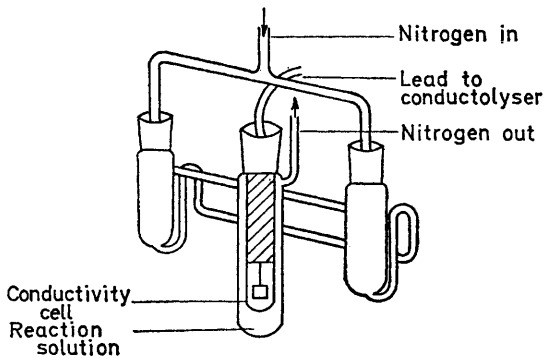
[1] Part II, K. Bowden and G. R. Taylor, preceeding paper. See also *Chem. Comm.*, 1967, 1112.
[2] M. L. Bender and M. S. Silver, *J. Amer. Chem. Soc.*, 1962, **84**, 4589; M. L. Bender, J. A. Reinstein, M. S. Silver, and R. Mikulak, *ibid.*, 1965, **87**, 4545.
[3] M. S. Newman and S. Hishida, *J. Amer. Chem. Soc.*, 1962, **84**, 3582.
[4] M. S. Newman and A. L. Leegwater, *J. Amer. Chem. Soc.*, 1968, **90**, 4410.
[5] H. D. Burrows and R. M. Topping, *Chem. Comm.*, 1969, 904.
[6] K. C. Kemp and M. L. Mieth, *Chem. Comm.*, 1969, 1260.
[7] P. L. De Benneville, *J. Org. Chem.*, 1941, **6**, 462.
[8] C. L. Arcus and R. E. Marks, *J. Chem. Soc.*, 1956, 1627.
[9] R. Weiss, *Org. Synth.*, 1943, Coll. Vol. II, p. 61.
[10] N. Campbell and K. F. Reid, *J. Chem. Soc.*, 1958, 4743.
[11] E. Fischer and A. Speier, *Ber.*, 1895, **28**, 3252.
[12] M. S. Newman and K. Naiki, *J. Org. Chem.*, 1962, **27**, 863.
[13] T. J. De Boer and H. J. Backer, *Rev. Trav. chim.*, 1954, **73**, 229.

the acid and diazophenylmethane. A solution of diazodiphenylmethane [14] in light petroleum (b.p. 40—60 °C) was added dropwise to a solution of the acid in a 1 : 1 mixture of ether–light petroleum until in excess. After *ca.* 1 h a precipitate had formed which dissolved on the addition of benzene. The solution was stirred for 12 h and then extracted with chloroform. The chloroform layer was washed with saturated sodium carbonate solution and finally dried ($MgSO_4$). After evaporation of the solvent, the crude ester was recrystallised from ethanol to give the *ester* as colourless needles, m.p. 132—133 °C (Found: C, 82·5; H, 5·1; O, 12·4. $C_{27}H_{21}O_3$ requires C, 82·5; H, 5·1; O, 12·3%).

Isopropyl benzoate was prepared by Fischer–Speier esterification of the acid in isopropyl alcohol. A sample of diphenylmethyl benzoate was kindly supplied by Dr. M. J. Price. After recrystallisation or distillation, and drying in a vacuum desiccator (P_2O_5), all the above compounds, except where indicated, had m.p.s. or b.p.s in good agreement with literature values.

Solvents were purified as described in Part II.[1]

Kinetic Procedure.—Two kinetic procedures were used; one for a ' slow ' hydrolysis and one for a ' fast ' hydrolysis. A ' slow ' reaction is defined arbitrarily as one where the time to reach the conductance at completion is greater than 2 h and a ' fast ' reaction where the time to reach conductance at completion is less than 2 h. The kinetic procedure for a ' slow ' reaction has been described.[1,15] The modified apparatus for the ' fast ' hydrolyses, shown



Conductivity apparatus for ' fast ' hydrolysis reactions

in the Figure, was designed by Dr. K. Bromley. The conductivity cell was placed in the centre tube. Then, 10 ml of the ester solution (2×10^{-2}M) was pipetted into one of the outer tubes and 10 ml of the base solution (2×10^{-2}M) was pipetted into the other tube. The apparatus was then placed in a thermostatted water-bath maintained at 30 ± 0·03 °C to attain the temperature of the bath. The conductivity cell was connected to an L.K.B. conductolyser (type 5300B). The output of the conductolyser was connected to a Toa Electronics Ltd. recorder (model EPR-2TB). At the start of the kinetic run, the ester and base solutions were simultaneously blown into the tube containing the conductivity cell with dry nitrogen. The apparatus was designed to allow rapid and uniform mixing of the two solutions as they enter the centre tube. The conductance of the solution was then continuously monitored by the conductolyser and the recorder indicated the fall in conductance with increase in time.

The rate coefficients were usually calculated from the conductivities by the method of Daniels *et al.*[16] as in Part I.[15] When both measurements of the initial conductance and that at completion were unreliable, Tobey's method [17] was used. The latter was necessary for the hydrolysis of diphenylmethyl benzoate, diphenylmethyl 2-benzoylbenzoate, and methyl 2-phenylacetylbenzoate.

The products of hydrolysis were analysed and found to be the anion of the benzoic acid in quantitative yield. However, an immediate pale brown colour appeared in the solution of methyl 2-phenylacetylbenzoate on mixing with base. This appeared to be due to formation of the anion of 2-phenylindane-1,3-dione arising from either a very small impurity in the ester or a side-reaction resulting from base-catalysed cyclisation of the ester. The latter reaction occurs as a major path in related systems.[18]

Solubility Measurements.—The solubilities were measured in dioxan–water by the ' cloud-point ' method.

Oxygen-18 Exchange Studies.—The alkaline hydrolyses were studied by use of ^{18}O-enriched water (1·63 atoms %, Yeda R and D Co.). Hydrolyses under normal kinetic conditions (equal ester and base concentrations) occasionally gave acid products containing *traces* of ester (mass spectrometry cannot be used to estimate the enrichment when the acid contains traces of the more volatile ester). The reactions were carried out in excess of base (0·02M-ester, 0·12M-base) for approximately ten ' half-lives ' of the ester. After neutralisation and removal of the solvent, the acid was isolated and purified. The mass spectrum of each sample and control (using both ester with ordinary water and acid with enriched water) was recorded on an A.E.I. MS9 spectrometer. Repeated scans of the spectra were made.

RESULTS AND DISCUSSION

The alkaline hydrolysis of all the esters studied is of the first order both in ester and hydroxide anion. A number of criteria for the occurrence of neighbouring-group participation in the alkaline hydrolysis of 2-aroyl- or -acyl-benzoates and related esters have been suggested.[1-6] Certain of these and other mechanistic probes have been tested for a comprehensive series of these esters. Rate coefficients for the methyl esters in 70% (v/v) dioxan–water at several temperatures, all including 20·0 °C, are shown in Table 1.

Relative Rates.—Significant rate enhancement, above that expected if normal unassisted ester hydrolysis occurred, is excellent evidence for participation by intramolecular nucleophilic catalysis.[19] Estimates of ' expected ' rate ratios, relative to that of methyl benzoate, are in Table 2, together with the observed rate ratios at 20 °C. These ' expected ' values are estimated from the known steric and polar effects of *ortho*-substituents on

[14] W. Schroeder and L. Katz, *J. Org. Chem.*, 1954, **19**, 718.
[15] K. Bowden, M. J. Hanson, and G. R. Taylor, *J. Chem. Soc.* (*B*), 1968, 174.
[16] F. Daniels, J. W. Williams, P. Bender, R. A. Alberty, and C. D. Cornwall, ' Experimental Physical Chemistry,' McGraw-Hill, New York, 1962, p. 135.
[17] S. W. Tobey, *J. Chem. Educ.*, 1962, **39**, 473.
[18] K. Bowden and A. M. Last, *Chem. Comm.*, 1970, 1315, and unpublished studies.
[19] B. Capon, *Quart. Rev.*, 1964, **18**, 45.

the alkaline hydrolysis of methyl and ethyl benzoates,[20-22] together with the *para*-σ values for these aroyl and acyl groups.[23-25] The significant enhancements, *i.e.*, $k/k_0 > 40$, observed for the 2-formyl, -acetyl, -propionyl, -isobutyryl, and -phenylacetyl esters clearly indicate hydrolysis by intramolecular catalysis. The 2-pivaloyl

TABLE 1

Rate coefficients for the alkaline hydrolysis of methyl 2-aroyl- and 2-acyl-benzoates in 70% (v/v) dioxan–water *

Acyl or aroyl substnt.	10^3k_2/l mol^{-1} s^{-1} 1·0 °C	10·0 °C	20·0 °C	30·0 °C
1 H	144,000	207,000 †	271,000	
2 Me	2230	3890	6450	
3 CH_2Me	742	1160	2050	
4 $CHMe_2$	260	439	761	
5 CMe_3	7·80	12·1	21·6	
6 CH_2Ph	102	205	531	
7 Ph		21·0	48·0	112
8 Fl ‡		29·9	52·3	90·7
9 Benzoate §		3·50	8·50	17·4

* Rate coefficients were reproducible to within ±3%. Ester and base were at 0·01M concentration, except for ester (1), where ester and base were at 0·0025M concentration. † At 12·0 °C. ‡ Methyl 9-oxofluoren-1-carboxylate. § Methyl benzoate.

TABLE 2

Relative rate ratios for the alkaline hydrolysis of methyl 2-aroyl- and 2-acyl-benzoates in 70% (v/v) dioxan–water at 20 °C

Acyl or aroyl substnt.	k/k_0 Observed	'Expected' *	Enhancement
H	31,900	5·0	6400
Me	759	1·0	760
CH_2Me	241	1·0	240
$CHMe_2$	89·5	1·0	90
CMe_3	2·54	0·5	5·1
CH_2Ph	62·5	1·5	42
Ph	5·65	1·0	5·6
Fl ‡	6·15	— †	—
Benzoate §	1·00	1·0	—

* Ratios are the maximum that could reasonably be expected. † There appears to be no reliable method of estimating this ratio. ‡ See Table 1. § See Table 1.

and 2-benzoyl esters have much smaller rate enhancements, *i.e.*, $5 < k/k_0 < 10$, albeit that these are based on the maximum reasonably estimated for the 'expected' ratios. On this evidence *alone*, it is only possible to state that the latter two esters are very probably hydrolysing with intramolecular catalysis.

Substituent Effects at the Neighbouring Carbonyl Group.—Taft [26] has suggested the relations (1), (2), and (3), employing the polar and steric substituent parameters [26,27] σ_I and E_s respectively. The parameters used are those for R in 2-R·COC_6H_4·CO_2Me. The only

$$\log (k/k_0) = \rho_I\sigma_I + \delta E_s \quad (1)$$

$$\log (k/k_0) = \rho_I\sigma_I \quad (2)$$

$$\log (k/k_0) = \delta E_s \quad (3)$$

statistically significant correlation obtained was that shown in Table 3 from equation (3) with a range of

TABLE 3

Taft steric reaction constant for the alkaline hydrolysis of the methyl esters in 70% (v/v) dioxan–water at 20 °C

δ	log k_0	r	s	t	n
1·494	0·553	0·991	0·201	15·0	6

r is the correlation coefficient, s the standard deviation, t Student's 't' statistic, and n the number of substituents.

substituents (1—6, Table 1).* However these substituents do not, in any case, have large polar effects. It must be emphasised that the E_s parameters for R are those obtained from the system, RCO_2R'. Steric effects are not normally additive and, in the system under study, a 'bulky' buttressing system occurs. However this correlation clearly demonstrates the strongly inhibiting effects of bulky groups *at* the neighbouring carbonyl group by severely destabilising the crowded transition state. Bell [28] has reported an analogous correlation (4) for the equilibrium hydration

$$\log K = -2{\cdot}6\sigma^* - 1{\cdot}3E_s + 2{\cdot}70 \quad (4)$$

of carbonyl compounds. This clearly demonstrates the inhibition of formation of the tetrahedral hydrate attributed to steric crowding. Our correlation has a very similar steric reaction constant, δ, of 1·5. This confirms attack at the neighbouring carbonyl group and, thus, intramolecular catalysis.

Activation Parameters.—The activation parameters for the alkaline hydrolysis of the esters in 70% aqueous dioxan are shown in Table 4. The enthalpies of activation of the 2-formyl, -acetyl, -propionyl, -isobutyryl, and -pivaloyl, as well as the 9-oxofluoren, esters are exceptionally small ($\Delta H^‡$ between 4·7 and 8·9 kcal mol^{-1}). These effects parallel those observed for the hydrolysis of γ-keto-esters.[6] They clearly indicate an energetically *highly* favourable reaction path with very small enthalpy requirements. What is less obvious is that these small enthalpies of activation are associated with rather large negative entropies of activation ($\Delta S^‡$ between −26 and −39 cal mol^{-1} K^{-1}). The 2-benzoyl and -phenylacetyl have considerably larger enthalpies and smaller negative

* Parameters for the phenyl group (7, Table 1) which exist [26,27] were not successful here. This appears to arise from the resonance interactions present in the benzoyl system.

[20] N. B. Chapman, J. Shorter, and J. H. P. Utley, *J. Chem. Soc.*, 1963, 1291.
[21] D. P. Evans, J. J. Gordon, and H. B. Watson, *J. Chem. Soc.*, 1937, 1430.
[22] Y. Iskander, R. Tewfik, and S. Wasif, *J. Chem. Soc.* (*B*), 1966, 424.
[23] A. A. Humffray, J. J. Ryan, J. P. Warren, and Y. H. Yung, *Chem. Comm.*, 1965, 610.
[24] W. N. White, R. Schlitt, and D. Gwyn, *J. Org. Chem.*, 1961, **26**, 3613.
[25] K. Bowden and M. J. Shaw, *J. Chem. Soc.* (*B*), 1971, 161.
[26] R. W. Taft, in 'Steric Effects in Organic Chemistry,' ed. M. S. Newman, John Wiley and Sons, Inc., New York, 1956, ch. 13.
[27] M. Charton, *J. Org. Chem.*, 1964, **29**, 1222.
[28] R. P. Bell, *Adv. Phys. Org. Chem.*, 1966, **4**, 1.

entropies of activation than the other 2-keto-esters. No linear relation appears to exist between changes in entropy and enthalpy, but the alkyl substituents (2—5, Table 4) appear to be isoenthalpic. The entropy parameter for the alkaline hydrolysis of methyl benzoate

TABLE 4

Activation parameters for alkaline hydrolysis of methyl 2-aroyl- and 2-acyl-benzoates at 20·0 °C *

Acyl or aroyl substituent	$\Delta H^{\ddagger}$/cal mol^{-1}	$\Delta S^{\ddagger}$/cal mol^{-1} K^{-1}
1 H	4700	−31
2 Me	8400	−26
3 CH_2Me	7900	−30
4 $CHMe_2$	8400	−30
5 CMe_3	8000	−39
6 CH_2Ph	13,300	−15
7 Ph	13,700	−18
8 Fl ‡	8900	−34
9 Benzoate §	13,100	−23

* Values of $\Delta H^{\ddagger}$ are accurate to within ±500 cal mol^{-1}, and of $\Delta S^{\ddagger}$ to within ±2 cal mol^{-1} K^{-1}, with exception of the 2-phenylacetyl ester whose accuracy limits are twice that of the other esters. ‡ See Table 1. § See Table 1.

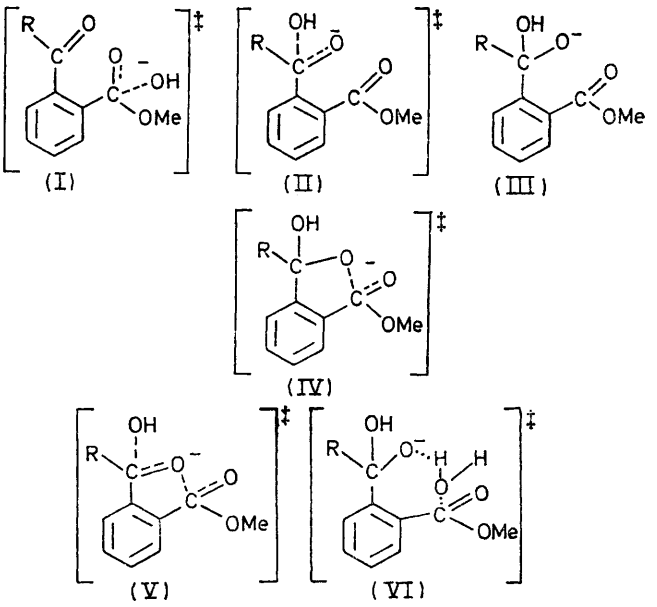
bridges these two groups, whereas its enthalpy of activation compares closely with those of the second group.

At this stage it is useful to consider the details of the hydrolytic mechanisms of both the normal and intramolecular catalytic routes. The intramolecular route has been outlined in Part II.[1] Several mechanistic divisions can be suggested, *i.e.*, (*a*) normal direct ester hydrolysis with rate-determining attack at the ester carbonyl-carbon [transition state (I), carbonyl-hydroxide anion bond highly formed]; (*b*) hydrolysis by intramolecular catalysis with rate-determining attack at the acyl or aroyl carbonyl-carbon [transition state (II), carbonyl-hydroxide anion bond highly formed]; (*c*) hydrolysis by intramolecular catalysis with rate-determining attack at the ester carbonyl-carbon, preceded by formation of the intermediate (III) [transition state (IV)]; (*d*) a concerted process with the rate-determining attack at the acyl or aroyl carbonyl-carbon synchronised with intramolecular attack at the ester carbonyl-carbon [transition state (V)]; and (*e*) hydrolysis by intramolecular general-base catalysis in which the alkoxide anion of the intermediate (III) removes a proton from an attacking water molecule,[2] preceded by formation of this intermediate [transition state (VI)]. Similarly, general-acid catalysis by the conjugate acid of the intermediate (III) of the hydroxide anion hydrolysis of the ester [2] could occur. The last pathway seems very unlikely as it is not important in ester hydrolysis for other neighbouring groups which are stronger 'general' acids and possible examples of participation by alcoholic hydroxyl groups do not produce the dramatic rate enhancements noted in this study.[19,29]

[29] T. C. Bruice and S. J. Benkovic, 'Bioorganic Mechanisms,' vol. 1, W. A. Benjamin, Inc., New York, 1966.

[30] E. Gaetjens and H. Morawetz, *J. Amer. Chem. Soc.*, 1960, **82**, 5328; T. C. Bruice and S. J. Benkovic, *ibid.*, 1963, **85**, 1; 1964, **86**, 418.

If hydration of the acyl or aroyl group is rapid and energetically favourable, it is likely that the intramolecular attack on the ester will be rate-determining [case (*c*) or (*e*)]. If hydration becomes much less rapid and favourable, the latter process can become more difficult than the intramolecular attack [case (*b*)]. The concerted process (*d*) will occur when the conditions for (*c*) are evident and when formation of the 'internal' nucleophile promotes intramolecular attack. If hydration is very slow and highly unfavourable, the normal route of ester hydrolysis could supercede [case (*a*)].



The results of the study of activation parameters encourages us tentatively to assign detailed mechanistic paths. Comparisons available between intramolecular and intermolecular catalysis of the hydrolysis of esters indicate that the rate enhancement arises, mainly, from a more favourable entropy of activation for the hydrolysis having intramolecular catalysis.[30,31] The entropy factor responsible ($\Delta\Delta S^{\ddagger}$ *ca.* 10—20 cal mol^{-1} K^{-1}) is conserved by requiring one less molecule to form the transition state.[32] However, the particular hydrolysis under study here requires both the ester and hydroxide anion in the transition state and, therefore, is *not* analogous to these previous studies. The observed entropies of activation here are similar or even more negative than those normally found for bimolecular ester hydrolyses.[33] The large group of esters having very small enthalpies of activation and large negative entropies of activation (1—5, 8; Table 4) could fit the requirements of case (*c*), (*d*), or (*e*). Thus a very high degree of orientation and ordering are required for transition states (IV)—(VI).

[31] J. W. Thanassi and T. C. Bruice, *J. Amer. Chem. Soc.*, 1966, **88**, 747.

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

[33] J. F. Corbett, A. Feinstein, P. H. Gore, G. L. Reed, and E. C. Vignes, *J. Chem. Soc.* (*B*), 1969, 974.

The hydration of the acylbenzoates (1—6; Table 4) would be expected to be energetically favoured in comparison with that of the aroylbenzoates (7, 8; Table 4).[28] The extra-resonance interactions of the second ' phenyl ' group in the benzophenone or fluorenone would be expected to be unfavourable; whereas the relief of ring strain in the fluorenone will be favourable. However, the appearance of the planar fluorenone in the first group confirms the importance of steric effects already noted. These must be very severe for the already non-planar benzophenone on forming a tetrahedral configuration at the keto-carbonyl carbon.

The size of the entropies of activation for these substrates could be consistent with intramolecular general-base catalysis [transition state (VI)] in which a water molecule is involved. The evidence from the hydration of aldehydes or ketones and acid-catalysed reactions involving a water molecule in the transition state,[34,35] *i.e.*, *A*-2, indicate loss of translational and rotational freedom of water resulting in a considerable decrease in entropy. This amounts to about −18 cal mol^{-1} K^{-1} or even less. However, the solvent isotope effects indicate that this possibility is unlikely (see below). The direct observation of the intermediate resulting from intramolecular nucleophilic attack in the very closely related morpholine-catalysed hydrolysis of methyl 2-formylbenzoate,[2] together with the similarity of the entropies of activation for the piperazine-catalysed ($\Delta S^{\ddagger}$ −48 cal mol^{-1} K^{-1}) and the hydroxide anion hydrolyses ($\Delta S^{\ddagger}$ equal to −36 cal mol^{-1} K^{-1}) of the latter ester in water,[36] strongly suggest direct nucleophilic participation as in case (*c*) or (*d*). Further, the leaving group in these methyl esters is only 2—3 pK_a units more basic than the catalyst.[37] The importance of a small difference in preferring the nucleophilic to the general-base or other pathway has been noted by others.[31,38]

The second group of esters (6, 7; Table 4) have considerably larger enthalpies of activation and smaller negative entropies of activation. There is good evidence both from our consideration of relative rates and from our previous study [1] of 3′- and 4′-substituent effects in the 2-benzoyl ester that these esters hydrolyse with intramolecular catalysis. It seems possible that these two esters hydrolyse as described in case (*b*). The circumstances of this case are analogous with normal ester hydrolysis but having reaction occurring at the keto-carbonyl carbon in the rate-determining step.

Alkoxy Group Effects.—Variation of the alkoxyl group was examined as shown in Table 5. As the effects of the isopropoxy- and diphenylmethoxy-groups are almost identical, they can be discussed simultaneously. The effect of these groups on the hydrolysis of the unsubstituted benzoate is to reduce the rate by a factor of *ca.* 16. This is undoubtedly mainly due to the ' bulk ' steric effects of these groups. However their effect on the hydrolysis of the 2-benzoylbenzoates is to reduce the rate by a factor of only *ca.* 5. Thus the enhancements of these two 2-benzoyl esters, relative to their respective benzoates, are about 20, compared with *ca.* 6 for the methyl esters. This provides further evidence for

TABLE 5

Rate coefficients for the alkaline hydrolysis of certain esters in 70% (v/v) dioxan–water at 30·0 °C *

Ester	$10^3 k_2$/l mol^{-1} s^{-1}
Diphenylmethyl 2-benzoylbenzoate	23·8
Diphenylmethyl benzoate	1·05
Isopropyl 2-benzoylbenzoate	21·4
Isopropyl benzoate	1·17

* See Table 1.

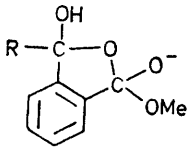
occurrence of intramolecular catalysis for the 2-benzoyl esters. If *normal* ester hydrolysis had occurred, the factor would have been expected to rise, not fall, because of buttressing in the crowded *ortho*-substituted ester. The small reduction observed for the substitution of the bulky alkoxyl group in the 2-benzoylbenzoate system seems to agree better with direct nucleophilic attack [case (*b*)], than with the intramolecular attack (*c*) or (*d*). In the latter more severe crowding, analogous to the benzoate system, would be expected.

Effects of 6-Substituents.—Newman's group [3,4] have studied the effect of 6-methyl and 6-chloro-substituents on the rates of alkaline hydrolysis of methyl 2-benzoyl * and 2-acetylbenzoates. The 6-substituted esters hydrolyse faster than the corresponding unsubstituted esters. Newman [3] has interpreted this as a steric effect by the 6-substituent twisting the ester group out of the plane of the aromatic ring. It was considered that this would facilitate the intramolecular step by giving rise to preferred geometry for intramolecular attack. They were unable to explain why this effect was much greater for the 2-benzoyl than for the 2-acetyl system.[4] Our previous evidence [1] and present discussion indicate that these systems, including *both* parent esters, hydrolyse with intramolecular catalysis. It seems very likely that the formation of the intermediate (VII) would have similar substituent effects from the 6-position to those observed for *ortho*-substitution in the alkaline hydrolysis of methyl benzoates.[20,21] A likely explanation of these accelerations appears to be that the 6-substituents reduce the effective ' bulk ' of the ester group as an ' *ortho* '-substituent to the keto-carbonyl group in the formation of the intermediate (III) by twisting the ester group away from the seat of the primary attack. As the

* After we had personally communicated our results for hydrolysis in 70% dioxan–water to Professor Newman, he informed us that his reported [3] rate coefficient for methyl 2-benzoylbenzoate was in error. Our rate coefficient [1] has been confirmed by titrimetric, absorption spectroscopic, and conductivity methods. This considerably reduces the acceleration previously noted [3] and, as suggested by Newman, our comments here refer to his later study.[4]

[34] L. L. Schaleger and F. A. Long, *Adv. Phys. Org. Chem.*, 1963, **1**, 1.
[35] Y. Pocker and D. G. Dickerson, *J. Phys. Chem.*, 1969, **73**, 4005.
[36] G. Dahlgren and D. M. Schell, *J. Org. Chem.*, 1967, **32**, 3200.
[37] G. B. Barlin and D. D. Perrin, *Quart. Rev.*, 1966, **20**, 75.
[38] A. R. Fersht and A. J. Kirby, *J. Amer. Chem. Soc.*, 1968, **90**, 5818.

transition state becomes more advanced towards the formation of intermediate (VII), this acceleration will be



(VII)

progressively reduced. Assuming that substituents in the benzoate ring give rise to the same substituent polar effects as those in the benzoyl ring for attack at the keto-carbonyl group and allowing for the medium change from 70% to 30% (v/v) dioxan–water,[39] we can correct the 'steric' enhancements observed by Newman [4] for the polar effect of the 6-substituents, as shown in Table 6.

TABLE 6

Effects of 6-substituents [4] k/k_0 *

6-Substituent	2-Benzoyl esters Found	2-Benzoyl esters Corrected	2-Acetyl esters Found	2-Acetyl esters Corrected	Unsubstituted esters [20,21] Found
Me	4·3	6	1·4	2	~0·1$_5$
Cl	32	6	7·4	1·$_5$	~2·0

* Rate relative to unsubstituted 2-benzoyl- or 2-acetyl-benzoates or benzoate.

This explanation would then agree with our tentative interpretation of the activation parameters of the parent esters. The 2-benzoyl esters have a rate enhancement of *ca.* 6 caused by either 6-substituent arising from the secondary steric effect described acting in a transition state similar to (II). The 2-acetyl esters have a rate enhancement of *ca.* 2 arising from a similar cause, but more in keeping with an advanced transition state similar to (IV) or (V).

Solvent Isotope Effects.—The solvent isotope effects were examined for the alkaline hydrolysis of the 2-acetyl, 2-benzoyl, and unsubstituted esters in 70% aqueous dioxan at 20·0 °C as shown in Table 7. In all

TABLE 7

Solvent isotope effects on the alkaline hydrolysis of certain esters at 20·0 °C *

Acyl or aroyl substituent	10^3k_2/l mol^{-1} s^{-1} In 70% (v/v) dioxan–water	In 70% (v/v) dioxan–deuterium oxide	k_{H_2O}/k_{D_2O}
Me	6450	9450	0·68
Ph	48·0	54·8	0·88
Benzoate §	8·50	9·74	0·87

* See Table 1. § See Table 1.

cases, rate enhancements in the deuterium oxide solvent system were observed and are similar to values found for related hydrolyses.[15,40] This can be attributed to the greater nucleophilicity of the deuteroxide than the hydroxide anion. It is important to point out that this evidence very probably excludes the two further mechanistic possibilities offered by Bender *et al.*,[2] *i.e.*, intramolecular general-base catalysis by the intermediate anion (III) removing a proton from an attacking water molecule or intramolecular general acid-hydroxide anion catalysis in which the conjugate acid of (III) facilitates hydroxide anion hydrolysis. Both the latter mechanisms would very probably involve isotope effects resulting in k_{H_2O}/k_{D_2O} being equal to or greater than unity.[29,41,42] Thus, the pre-equilibrium formation of the intermediate (III) would be favoured in D_2O and this would result in estimates of about 0·8—0·5 for K_{H_2O}/K_{D_2O}; whereas the general-base catalysis step would be expected to be favoured in H_2O and related reactions have k_{H_2O}/k_{D_2O} *ca.* 2.[29,32,41] However, it is also obvious that the observed solvent isotope effects cannot be used as a criteria for the occurrence of this type of intramolecular catalysis. Calculations (estimates of the pK_a values required were made from Barlin and Perrin's review [37]) based on the method of Bunton and Shiner [42] for water as solvent indicate the same effects for electrostatic and covalent binding in the transition state (II) (k_H/k_D at 20 °C = 0·78 and 0·82 respectively) for intramolecular catalysis as those for transition state (I) for normal ester hydrolysis. Similar calculations for the transition state (IV) for intramolecular catalysis with electrostatic and covalent binding (k_{H_2O}/k_{D_2O} at 20 °C = 0·68 and 0·82 respectively) were made. Both these calculations assumed two acceptor sites for unbound, anionic transition-state oxygen atoms. Although our measurements were made in aqueous dioxan rather than water, they could indicate greater development for the transition state of the 2-acetyl ester as tentatively suggested. The small decrease in k_{H_2O}/k_{D_2O} would then be attributed to decreased protic solvation required by the latter transition state.

Solvent Effects.—The effect of varied aqueous dioxan mixtures on the alkaline hydrolysis of the 2-acetyl, 2-benzoyl, and unsubstituted esters at 20·0 °C was

TABLE 8

Variation of dioxan–water composition on the alkaline hydrolysis of certain esters at 20·0 °C *

Acyl or aroyl substituent	10^3k_2/l mol^{-1} s^{-1} in % (v/v) dioxan–water 40	50	60	70
Me	7310	6640	6530	6450
Ph	82·4	59·8	45·7	48·0
Benzoate §	16·2	12·8	9·38	8·50

* See Table 1. § See Table 1.

examined as shown in Table 8. Solubility problems with the ester or base prevented study of a wider range of compositions. All the esters show a small decrease in rate of hydrolysis with increasing dioxan content.

[39] K. Bowden and G. R. Taylor, unpublished studies.
[40] K. B. Wiberg, *Chem. Rev.*, 1955, **55**, 713.
[41] M. L. Bender, E. J. Pollock, and M. C. Neveu, *J. Amer. Chem. Soc.*, 1962, **84**, 595.
[42] C. A. Bunton and V. J. Shiner, *J. Amer. Chem. Soc.*, 1961, **83**, 3207, 3214.

This solvent effect does not appear to be a useful criterion for distinguishing between normal and intramolecular-catalysed hydrolysis. It is probable that only a complex theory can relate these changes in rate to the composition of aqueous dioxan mixtures.[43] It was tempting to attribute the somewhat greater fall in rate with increasing dioxan content for the 2-benzoyl and unsubstituted benzoates to greater demand for protic solvation in the latter transition states relative to that of the 2-acetyl ester, as this would have agreed with the tentative interpretation of the variation in the solvent isotope effects. Solubility studies were attempted by use of the techniques illustrated by Parker and his co-workers.[44] Unfortunately the limited solvent range made the separation of single-ion activities impractical. However, using the relative solubilities of the esters (see Table 9) as a measure of initial state stabilisation [45] for

TABLE 9

Solubilities of certain esters in various dioxan–water mixtures at 20 °C

	Solubility/M * in % (v/v) dioxan–water			
Methyl ester	40	50	60	70
2-Acetylbenzoate	0·374	0·531	0·781	1·29
2-Benzoylbenzoate	0·0380	0·0880	0·219	0·523
Benzoate	0·143	0·257	0·502	0·971

* Solubilities were reproducible to within ±2%.

the esters together with the rates of hydrolysis, we can separate out the effect of the solvent on the hydroxide anion-transition state stabilities, $\Delta\Delta G^{\ddagger}_{OH}$, relative to those in 70% dioxan–water (see Table 10). As the

TABLE 10

Relative stabilities in dioxan–water mixtures at 20 °C

	$\Delta\Delta G^{\ddagger}_{OH}/2{\cdot}303RT$ * in % (v/v) dioxan–water			
Methyl ester	40	50	60	70
2-Acetylbenzoate	0·49	0·37	0·22	0·0
2-Benzoylbenzoate	0·80	0·68	0·40	0·0
Benzoate	0·55	0·40	0·24	0·0

* Values are considered accurate to within ±0·05 unit.

effects on the hydroxide anion are common to all the series, the solvent effects on the transition states can be directly compared. This treatment indicates similarities between the 2-acetyl and the unsubstituted benzoate, while the 2-benzoyl ester appears to have a transition state less affected by decreasing availability of protic solvation. This could be caused by steric inhibition of solvation in the transition state of the ' bulky ' 2-benzoyl system; but these effects could just as well be caused by the same structural features which gave rise to different variations in the initial state stabilities.

Oxygen-18 Exchange.—The results of the ^{18}O-enriched water hydrolyses are shown in Table 11. The hydrolysis

TABLE 11

^{18}O-Enriched water hydrolyses

	Enrichment/atom % *	
Methyl ester or control acid	$M + 2/M$	$(M - CO_2H) + 2/(M - CO_2H)$
2-Benzoylbenzoate at 50 °C	1·9	1·5
Benzoate at 30 °C	1·5	0·0
2-Benzoylbenzoic at 50 °C	1·5	1·5
Benzoic at 30 °C	0·0	0·0

* Solvent enrichment $1{\cdot}6_3$ atoms %. The mass spectral measurements are considered to be accurate to ±0·1 atom %.

of the 2-formyl and 2-acetylbenzoates could not be studied by this mass spectrometric method. The former gives a product containing traces of 2-hydroxymethylbenzoic acid, while the acid derived from the latter has a spectral breakdown with coincident peak areas due to $(M - CO_2H)$ and $(M - MeCO)$. A consideration of the possible courses of enrichment in the alkaline hydrolysis of 2-aroyl- and 2-acylbenzoates relative to the possible mechanisms can be made. Normal, direct ester hydrolysis [case (*a*)] will result in enrichment at the ester carboxyl, *i.e.*, equivalent to single enrichment at the $M + 2$ peak; but, if exchange at the keto-group occurs *sufficiently* rapidly, also enrichment at keto-carbonyl, *i.e.*, equivalent to double enrichment at the $M + 2$ peak. The intramolecular hydrolysis paths [cases (*b*), (*c*), or (*d*)] will result in enrichment at the keto-carbonyl; but, if exchange at the keto-group occurs *much* more rapidly than hydrolysis, also enrichment at the ester carboxyl. The other path (*e*) will result in enrichment at both groups. It is known [46] that exchange with the carboxylate anion is extremely slow, while exchange with the keto-carbonyl group is fairly rapid, in aqueous dioxan containing base. These have been confirmed by demonstrating no enrichment into the benzoate anion and single enrichment into the 2-benzoylbenzoate anion, under the conditions of our study (see Table 11). Enrichment in the hydrolysis of methyl benzoate in aqueous dioxan does not show significant concurrent oxygen carbonyl exchange,[47,48] as noted by the more recent study.[48] The result for the hydrolysis of 2-benzoylbenzoate shows only slightly over single enrichment. Moreover, the mass spectral breakdown indicates * that the enrichment is mainly at the keto-carbonyl and is equal to a single enrichment. This can only be caused by hydroxide attack at the keto-carbonyl group, followed

* Scrambling of the oxygens could possibly occur in the ion; but, in this case, the result for the exchange of the acid itself appears to deny this possibility.

[43] E. Tommila, *Ann. Acad. Sci. Fennicae, Series A*, 1967, **139**, 1.

[44] R. Alexander, E. C. F. Ko, Y. C. Mac, and A. J. Parker, *J. Amer. Chem. Soc.*, 1967, **89**, 3703; A. J. Parker and R. Alexander, *ibid.*, 1968, **90**, 3313; R. Alexander, E. C. F. Ko, A. J. Parker, and T. J. Broxton, *ibid.*, p. 5049; E. C. F. Ko and A. J. Parker, *ibid.*, p. 6447.

[45] *Cf.* C. A. Bunton and L. Robinson, *J. Amer. Chem. Soc.*, 1968, **90**, 5965.

[46] D. Samuel and B. L. Silver, *Adv. Phys. Org. Chem.*, 1965, **3**, 123.

[47] M. L. Bender and R. J. Thomas, *J. Amer. Chem. Soc.*, 1961, **83**, 4189.

[48] S. A. Shain and J. F. Kirsch, *J. Amer. Chem. Soc.*, 1968, **90**, 5848.

immediately by intramolecular attack, and this must be more rapid than keto-carbonyl exchange. The small exchange at the carboxyl group could arise from either direct hydrolysis or keto-carbonyl exchange, followed by intramolecular transfer. This result agrees with and confirms our interpretation of an intramolecular hydrolysis for this ester.

Our conclusions are that, of the criteria tested, the relative rate ratio is very useful as long as it is based on realistic estimates of the 'expected' rate, while the activation parameters provide excellent evidence if the catalysis is very marked. Analysis of substituent effects is highly indicative particularly when it is able unambiguously to detect the seat of primary reaction. Other probes studied gave limited or no real evidence in differentiating the mechanisms.

We thank the S.R.C. for a research studentship (to G. R. T.).

[0/592 *Received, April* 16*th*, 1970]