Intramolecular Catalysis. Part 2.[1] Mechanism of Hydrolysis of Alkyl 8-Hydroxy-1-naphthoates

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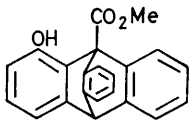
The hydrolysis of alkyl 8-hydroxy-1-naphthoates in alkaline 30% (v/v) dioxan–water has been investigated. The pH'–rate profiles, activation parameters, comparison with the rates of hydrolysis of model compounds and 8-hydroxy-1-naphthoic acid lactone, and kinetic solvent isotope and other effects indicate a mechanism involving intramolecular catalysis, either by general base or by general acid specific base. The significance of the results is discussed in relation to the factors governing such mechanistic pathways.

SEVERAL workers [2-4] have discussed potential sources of the special catalytic power of enzymes. Important roles for proximity,[2,3] orientation,[4] and steric strain [3] have been suggested. The orientational concept of 'orbital steering' [4,5] has been both criticised [6,7] and offered in a modified form.[8] These factors must first be clearly defined in model systems employing intramolecular catalysis.

Several esters and amides with proximate phenolic hydroxy-groups are hydrolysed with enhanced rates. An early example was methyl 1-hydroxy-9-triptoate (1).[9] Hydrolysis of this ester has been considered to involve



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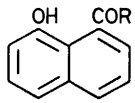

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intramolecular nucleophilic participation *via* the lactone.[2,10] Following a study of the hydrolysis of *p*-nitrophenyl 5-nitrosalicylate,[11] Capon and Ghosh [12] studied the hydrolysis of substituted phenyl salicylates. Both studies indicated intramolecular catalysis by the phenolate anion *via* a general base pathway, rather than reaction involving nucleophilic catalysis by phenolate anion or general acid catalysis of phenolic ester with hydroxide anion. Similar results have been obtained for both methyl and phenyl salicylates.[13,14] Catechol esters also are hydrolysed with intramolecular catalysis.[12] Nucleophilic catalysis is impossible here because of the symmetry, and hydrolysis by a general base pathway *via* the phenolate anion was indicated. Hydrolysis *via* lactone intermediates occurs for aryl 2-hydroxyphenylacetates and 3-(2-hydroxyphenyl)propionates, resulting from nucleophilic catalysis by, presumably, the phenolate anion.[15]

The hydrolysis of salicylamides has been studied at 100 °C and was considered to proceed by either general base catalysis by the phenolate anion or by general acid catalysis with hydroxide anion.[16] Menger and Brock [17] investigated the hydrolysis of *N*-butyl-8-hydroxy-1-naphthamide (2; R = $NHBu^n$) to test suggested mechanistic pathways for the hydrolysis of enzyme-bound amide substrates for α-chymotrypsin. The stability of the conjugate anion *under mild conditions* caused them to conclude that intramolecular catalysis is not favoured in this system.

We now describe a detailed investigation of the hydrolysis of alkyl 8-hydroxy-1-naphthoates (2; R = OMe, OEt, or OBu^t) and related substrates. The favourable proximity and orientation of substituent and reaction site here enable an evaluation of these factors.

EXPERIMENTAL

Materials.—Methyl and ethyl 1-naphthoate were prepared by Fischer–Speier esterification of the acid in the corresponding alcohol.[18] Reaction of 1-naphthoyl chloride with phenol in benzene gave phenyl 1-naphthoate.[19] The lactone of 8-hydroxy-1-naphthoic acid was synthesised by diazotisation of the lactam of 8-amino-1-naphthoic acid.[20] 8-Hydroxy-1-naphthoic acid lactone was treated with the corresponding sodium alkoxide in the alcohol to give methyl and ethyl 8-hydroxy-1-naphthoate, and with potassium t-butoxide in dimethyl sulphoxide (DMSO) to give t-butyl 8-hydroxy-1-naphthoate.[20,21] 8-Hydroxy-1-naphthoic acid was prepared by hydrolysis of the lactone with aqueous sodium hydroxide, followed by careful neutralisation with ice-cold hydrochloric acid.[22] Methylation of methyl 8-hydroxy-1-naphthoate by methyl iodide in acetone in the

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[18] J. F. Corbett, A. Feinstein, P. H. Gore, G. L. Reed, and E. C. Vignes, *J. Chem. Soc.* (*B*), 1969, 974.
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[20] A. J. Birch, M. Salahud-Din, and D. C. C. Smith, *J. Chem. Soc.* (*C*), 1966, 523.
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[22] A. G. Ekstrand, *J. prakt. Chem.*, 1888, **38**, 278.

presence of potassium carbonate gave methyl 8-methoxy-1-naphthoate in a similar manner to the methylation procedure of Birch *et al.*[20] (*cf.* ref. 23). The crude product of the latter reaction was hydrolysed with aqueous sodium hydroxide to give 8-methoxy-1-naphthoic acid.[20,23] 1-Carboxy-5,8-naphthoquinone was prepared by the oxidation of 5-amino-1-naphthoic acid.[24] 1-Naphthoic acid and 1-naphthol were obtained commercially. The lactone was purified by chromatography on neutral alumina in benzene. After repeated recrystallisation to constant m.p. and drying in a vacuum desiccator (P_2O_5) or fractionally distilling at reduced pressure, the esters and related compounds had m.p.s or b.p.s in good agreement with literature values. The physical constants of these compounds are listed in Table 1, together with the recrystallisation solvents. Solvents were purified as previously described.[25] Inorganic salts were of analytical grade and were used without further purification.

TABLE 1

Physical constants of esters and related compounds

	M.p. (°C)	Lit. m.p. (°C)	Ref.	λ/nm *
Methyl-1-naphthoate	(B.p. 114° at 0.9 mmHg)	(B.p. 126—128° at 2 mmHg)	18	310
Ethyl 1-naphthoate	(B.p. 142° at 3.5 mmHg)	(B.p. 133—136° at 2.3 mmHg)	18	308
Phenyl 1-naphthoate	97—98 [a]	98—99	19	315
Methyl 8-hydroxy-1-naphthoate	95—96 [a]	91—93, 93—95	20, 21	225—364
Methyl 8-methoxy-1-naphthoate	51 [a]	51—52	23	294
Ethyl 8-hydroxy-1-naphthoate	47—48 [b]	49—50	21	254—257
t-Butyl 8-hydroxy-1-naphthoate	117—118 [b]	112—113	21	257
8-Hydroxy-1-naphthoic acid lactone	103—104 [c]	99—101	20	343
8-Hydroxy-1-naphthoic acid	169.5—170 [a]	169	22	
8-Methoxy-1-naphthoic acid	162—163 [a]	161—162	20	
5-Carboxy-1,4-naphthoquinone	168 †,[c]	164 †	24	

* Used in kinetic measurements (*not* λ_{max} values for the esters). † Darkening point; turns black at 180 °C.

[a] From benzene. [b] From benzene–hexane. [c] From benzene–ethanol.

TABLE 2

Hydrolysis of alkyl 8-hydroxy-1-naphthoates at 40.0 °C in 30% (v/v) dioxan–water (μ = 1.0) *

Alkyl group									
Me	pH′	8.18	9.09	9.56_5	9.60	10.04	10.23	10.30	10.58
	$10^5k_1/s^{-1}$	0.584	4.03	12.1	11.2	21.3	26.1	29.5_5	40.3
		10.82	11.02	11.31	11.43	11.46	11.70	12.47 †	13.27 †
		41.8	37.2	36.2	30.8	29.4	26.5	26.3_5	32.3
	pD′ ‡	9.16	9.54	10.19	10.60	11.19	11.43	12.87 †	
	$10^5k_1/s^{-1}$	1.41	3.39	14.2	21.6	24.8	25.3	19.9	
Et	pH′	9.01	9.64	10.07	11.87	12.47 †			
	$10^5k_1/s^{-1}$	1.10	4.01	15.0	13.1	13.3			

* Rate coefficients were reproducible to within ±5%. † See Experimental section. ‡ See Experimental section and ref. 27.

Kinetic Measurements and Results.—Solutions in dioxan–water (30% v/v) were prepared by adding the aqueous buffer solution to the correct volume of dioxan in a volumetric flask. Reactions were studied spectrophotometrically by use of a Unicam SP 800 spectrophotometer and the cell temperature was controlled to within ±0.05 °C by means of a Churchill thermocirculator. The solution was pipetted into two 1 cm spectrophotometer cells and the cells were closed with silicone rubber serum caps. The solutions could be purged by passing ' oxygen-free ' nitrogen for 1 min using hypodermic needles for inlet and exhaust. After the cells had been in the thermostatted cell holder to enable thermal equilibration, the hypodermic needles were removed and *ca.* 5 μl of a solution of the substrate under investigation in dioxan (or, in suitable instances, DMSO) was added from a Hamilton microsyringe, such that the final substrate concentration in the cell was *ca.* 5×10^{-5} M. The complete u.v. spectrum in the range 200—450 nm was recorded continuously or at predetermined intervals using the Unicam SP 825 program recorder. This enabled the substrate and product spectra to be recorded, as well as intermediate states including isosbestic points if present. A comparison of the spectra of the products of the hydrolysis of the alkyl 8-hydroxy-1-naphthoates, with those of 8-hydroxy-1-naphthoic acid lactone and 8-hydroxy-1-naphthoic acid under identical conditions, indicated the last-named to be the initial product. From the lactone, the acid can be prepared quantitatively from the hydrolysis. However, in solutions of pH′ 10.5 and above and at temperatures of above 30 °C, a ' secondary ' product was slowly formed. The latter was found to be 1-carboxy-5,8-naphthoquinone by comparison of the u.v. spectrum of the reaction product with that of the authentic compound, under identical conditions. The formation of the ' secondary ' product was much faster in the presence of air but could not be completely suppressed under all circumstances by conducting the reaction under nitrogen as described above.

The rate measurements were made using the procedure described above but by monitoring at selected fixed wavelengths based either on the maximum change in absorption between the substrate and product or on the isosbestic point between the initial and ' secondary ' product, under the particular pH′ conditions studied. The optical density was displayed on a Beckman 1005 chart recorder as a function of time. The final optical density was normally assumed to be that measured after ten ' half-lives ' had elapsed, although for very slow reactions Guggenheim's [26] method

[23] E. Bretscher, H. G. Rule, and J. Spence, *J. Chem. Soc.*, 1928, 1493.

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[25] K. Bowden and F. A. El-Kaissi, *J.C.S. Perkin II*, 1977, 526 and references therein.

[26] E. A. Guggenheim, *Phil. Mag.*, 1926, **2**, 538.

was used. The wavelengths employed are shown in Table 1. For methyl, ethyl, t-butyl, and phenyl 1-naphthoate, as for methyl 8-methoxy-1-naphthoate, the alkaline hydrolyses gave the expected products. Reactions of all the latter esters and the lactone were first-order in both substrate and hydroxide anion. Tables 2—5 show the rate coefficients for the hydrolyses under the conditions stated. Catalysis by buffer constituents was found to be negligible for all substrates. The hydrolyses of the esters and the lactone were studied at a constant ionic strength of 1.0 (sodium chloride).

TABLE 3

Hydrolysis of esters in 30% (v/v) dioxan–water (μ = 1.0) *

	10^4k_1/s^{-1}
t-Butyl 8-hydroxy-1-naphthoate (pH′ 12.47 at 40.0 °C) †	0.700 (60.5 °C)
8-Hydroxy-1-naphthoic acid lactone (pH′ or pD′ in the range 6—7)	0.098 3 (20 °C) [0.089 8 (20 °C)] ‡
	10^4k_2/l mol^{-1} s^{-1}
Ethyl 1-naphthoate	0.870_5 (40.2_5 °C)
Methyl 8-methoxy-1-naphthoate	0.530 (60.5 °C)

* See Table 2. † See Experimental. ‡ In 30% (v/v) dioxan-deuterium oxide.

TABLE 4

Hydrolysis of esters and lactone at several temperatures in 30% (v/v) dioxan–water (μ = 1.0) *

	10^4k_1/s^{-1}
Methyl 8-hydroxy-1-naphthoate (pH′ 12.47 at 40.0 °C) ‡	2.64 (40.2_5 °C), 8.60 (50.8 °C), 24.3 (60.5 °C), 54.0 (69.4 °C) [2.00 (40.2_5 °C)] †
	10^2k_2/l mol^{-1} s^{-1}
Methyl 1-naphthoate	0.474 (19.9_5 °C), 1.00 (30.2 °C), 1.94 (40.2_5 °C), 3.73 (50.2_5 °C) [0.580 (19.9_5 °C)] †
8-Hydroxy-1-naphthoic acid lactone	10 100 (21.6 °C), 14 700 (29.9 °C), 24 000 (38.5_5 °C), 37 200 (48.3 °C)
Phenyl 1-naphthoate	0.246 (20.4_5 °C), 0.465 (29.4_5 °C), 0.912 (38.8 °C), 1.62 (48.5 °C)

* See Table 2, except for the lactone and phenyl 1-naphthoate which were ±3%. † In 30% (v/v) dioxan–deuterium oxide. ‡ See Experimental section.

TABLE 5

Hydrolysis of methyl 8-hydroxy-1-naphthoate at 40.0 °C in solvents of various compositions * †

	10^4k_1/s^{-1} in x% (v/v) dioxan–water					
x	10%	15%	20%	30%	40%	50%
	5.33_5	4.58	4.01_5	2.63_5	2.65	2.62_5
	in x% (v/v) DMSO–water					
x	10%	15%	30%	50%		
	5.02	4.67_5	3.31_5	1.21_5		

* See Table 2. † Solutions (μ = 1.0) 0.1M in NaOH.

pH′ and pK_a′ Measurements.—The pH′ values of the reactant solutions were measured at the temperature of the kinetic experiment using a Pye–Ingold high alkali $401E_07$ combined glass and reference electrode and a Pye 290 direct reading pH meter. The glass electrode was standardised using borate and potassium hydrogen phthalate solutions. Measurements made before and after kinetic experiments indicated no significant changes. The pH′ values for the 30% (v/v) dioxan–water 0.01M-HCl and -NaOH at ionic strength 1.0 are shown in Table 6. The effective pH′ values of 0.158M- and 1.0M-NaOH in 30% v/v dioxan–water (μ = 1.0) were those calculated by extrapolation from the measured pH′ values at 40.0 °C shown in Table 6, *i.e.* 12.47

TABLE 6

pK_a Values of naphthols at 40.0 °C and pH′ measurements in 30% (v/v) dioxan–water (μ = 1.0)

	pK_a	λ/nm *
1-Naphthol	9.96 (±0.03)	332
Methyl 8-hydroxy-1-naphthoate	10.02 (±0.06)	342
Ethyl 8-hydroxy-1-naphthoate	10.17 (±0.06)	342
t-Butyl 8-hydroxy-1-naphthoate	10.5 (±0.1)	344
8-Hydroxy-1-naphthoic acid (pK_a^2)	11.5 (±0.1)	340

		pH′	
T/°C	pK_w	0.01M-HCl	0.01M-NaOH
20.0	14.02	1.99_5	12.01
30.0	13.60_5	1.99_5	11.60
40.0	13.29 †	1.98	11.27
50.0	13.05	1.98	11.03
60.0	12.81	1.98	10.79

* Used in pK_a determinations (*not* λ_{max} values). † pK_{D_2O} found to be 14.09; *cf.* ref. 27.

and 13.27, respectively. The pD′ values were obtained by adding 0.40 to the pH meter readings.[27] The latter correction was confirmed by measurements of pH′ of NaOH and NaOD in aqueous dioxan solutions.

Under the conditions of the kinetic study the alkyl 8-hydroxy-1-naphthoates ionise to give the monoanion; 8-hydroxy-1-naphthoic acid gives the dianion. The pK_a′ values of the phenols were therefore measured in 30% (v/v) dioxan–water at 1.0 ionic strength and 40.0 °C using the spectrophotometric equipment and pH meter described above and using Albert and Serjeant's method.[28] The pK_a′ values and wavelengths used are shown in Table 6.

I.r. Spectral Measurements.—A Perkin-Elmer 225 double-beam grating spectrophotometer was used. The ester and acids were studied in a 1 cm quartz cell at room temperature at 0.005M and 0.01M concentrations in spectroscopic grade AnalaR carbon tetrachloride, except for 8-hydroxy-1-naphthoic acid for which a saturated solution was used. Those measurements associated with the monomeric ν_{OH} are reported in Table 7 and were considered to be accurate to within ±2 cm^{-1}.

TABLE 7

I.r. stretching frequencies of esters and acids in carbon tetrachloride

	ν_{OH}/cm^{-1} *
Methyl 8-hydroxy-1-naphthoate	3 180 (w)
Ethyl 8-hydroxy-1-naphthoate	3 173 (w)
t-Butyl 8-hydroxy-1-naphthoate	3 175 (w)
8-Hydroxy-1-naphthoic acid	3 517 (34), 3 160 (w)
8-Methoxy-1-naphthoic acid	3 527 (28) †
1-Naphthol	3 608 (22)
1-Naphthoic acid	3 539 (35) †

* Half-intensity bandwidths (cm^{-1}) in parentheses; w indicates 'wide,' *i.e.* >100 cm^{-1}. These latter values were very difficult to estimate owing to overlap of ν_{OH} with ν_{CH} bands, *e.g.* methyl 8-methoxy-1-naphthoate has ν_{CH} 2 835, 2 900, 2 942, 2 996, and 3 054 cm^{-1}. † Lit. values [29,30] are, for 8-methoxy-1-naphthoic acid 3 529 (24) cm^{-1}, and for 1-naphthoic acid 3 538 (34) cm^{-1}.

[27] L. Pentz and E. R. Thornton, *J. Amer. Chem. Soc.*, 1967, **89**, 6931; P. K. Glasoe and F. A. Long, *J. Phys. Chem.*, 1960, **64**, 188; B. Zerner and M. L. Bender, *J. Amer. Chem. Soc.*, 1961, **83**, 2267.
[28] A. Albert and E. P. Serjeant, 'Ionization Constants of Acids and Bases,' Methuen, London, 1962.
[29] H. A. Lloyd, K. S. Warren, and H. M. Fales, *J. Amer. Chem. Soc.*, 1966, **88**, 5544.
[30] K. Bowden, M. J. Price, and G. R. Taylor, *J. Chem. Soc.* (*B*), 1970, 1022.

DISCUSSION

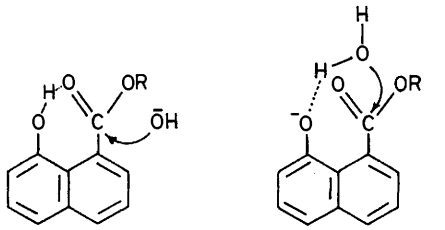
The pH′–rate profile for the hydrolysis of both methyl and ethyl 8-hydroxy-1-naphthoate in 30% (v/v) dioxan–water at 40.0 °C (Figure), exhibited a plateau at high pH′. This behaviour corresponds to a rate law for two kinetically equivalent paths, *i.e.* hydroxide anion-catalysed hydrolysis of the un-ionised ester or hydrolysis of the ionised ester. The latter path (general base or nucleophilic catalysis) is described by equation (i) for, for example, general base catalysis. The former path (general acid and no catalysis) can be described by the

$$k_1 = k_{gb}K_a'/(K_a' + a_{H^+}') \qquad (i)$$

relation (ii) for, for example, general acid catalysis (*cf.* ref. 14). Plots of either $1/k_1$ against a_{H^+}' or k_1 against $k_1a_{H^+}'$ yield linear relations [3] as shown in Table 8. The pK_a' values so obtained are identical within experimental error with those obtained directly (see Table 6).

$$k_1 = k_{ga}K_a'/K_w' \qquad (ii)$$

There are four possible pathways for the alkaline hydrolysis of the alkyl 8-hydroxy-1-naphthoates: (*a*) normal unassisted hydroxide-anion hydrolysis of the un-ionised ester; (*b*) intramolecular general-acid catalysed reaction of the un-ionised ester with hydroxide anion (3); (*c*) intramolecular general base catalysed reaction



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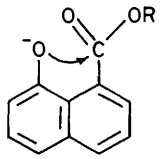

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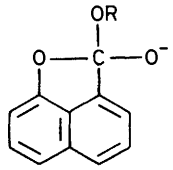

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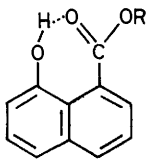
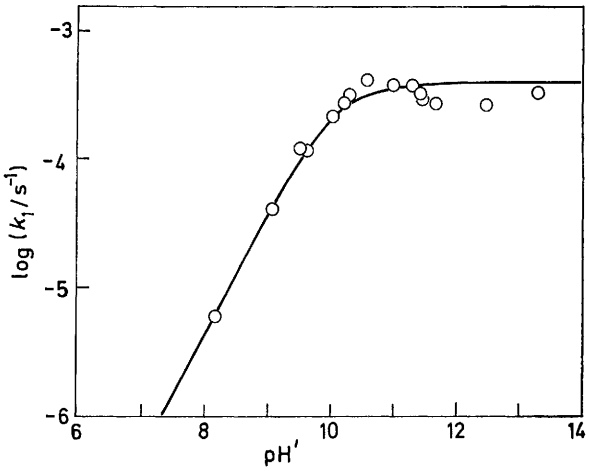


(7)

of the ionised ester with water (4); (*d*) intramolecular nucleophile catalysed reaction, followed by rapid hydrolysis of the lactone (5). (The latter step has been found to be fast, as compared with the hydrolysis of the alkyl ester, and has been studied separately as described below.)



pH′-rate profile for the hydrolysis of methyl 8-hydroxy-1-naphthoate in 30% (v/v) dioxan–water at 40.0 °C; circles are experimental points and the line follows equation (a), Table 8

The pathways involving neighbouring group participation [(*b*)—(*d*)] all imply rate increase in relation to that expected for the normal unassisted hydrolytic pathway (*a*). The latter can be estimated from that for an alkyl 1-naphthoate, together with the expected polar and steric effects of the 8-hydroxy-substituent. Our previous study [31] of 8-substituent effects on the alkaline hydrolysis of methyl 1-naphthoate in 70% (v/v) dioxan–water and the present study of methyl 8-methoxy-1-naphthoate in 30% (v/v) dioxan–water all indicate severe retardation arising from the dominant steric ' bulk ' effect of the *peri*-substituent. An ' expected ' rate for the unassisted hydrolysis of methyl 8-hydroxy-1-naphthoate can be estimated as $<5 \times 10^{-4}$ l mol^{-1} s^{-1} at 40 °C (*cf.* Tables 3 and 4, and ref. 31). The relevant second-order rate coefficient calculated for methyl 8-hydroxynaphthoate is *ca.* 0.77 l mol^{-1} s^{-1} at 40 °C (Table 8) and this clearly indicates the occurrence of neighbouring group participation. The three possible pathways (*b*)—(*d*) can now be considered in relation to the available evidence.

Substituent Effects.—Whether the first- or second-order rate coefficients are considered, the effect of variation of the alkyl group causes rate decreases with increasing chain branching in the alkyl group, *i.e.* rate order: Me > Et ⩾ Bu^t (Tables 2 and 3). This is consistent with the mainly steric ' bulk ' effects on a bimolecular transition state as in (*b*) or (*c*) [or even for (*a*); *cf.* ref. 32]. However, a nucleophilic pathway as (*d*) would be expected to relieve steric ' bulk ' interactions in forming the transition state and, as such, can be excluded.

Kinetic Solvent Isotope Effects.—In general, specific base and general base catalysis appear to have k_{H_2O}/k_{D_2O} values of <1 and >2, respectively,[2] whereas nucleophilic catalysis *usually* has values in the range 0.8—1.9.

[31] K. Bowden and A. M. Last, *J.C.S. Perkin II*, 1973, 345.
[32] See ref. 17 and references therein.

Methyl 1-naphthoate, studied here, and related esters [25] have values in the range 0.8—0.9 for their hydroxide anion-catalysed hydrolysis. The hydrolyses of phenyl salicylate, catechol benzoate, and aspirin have values in the range 1.7—2.2 and all apparently are hydrolysed *via* general base catalysis.[10,12] The values found in this study for methyl 8-hydroxy-1-naphthoate are in the range 1.1—1.4 (for example k_{gb}) and 0.5—0.6 (for example k_{ga}). These results do not allow an unambiguous assignment of the mechanism. Calculations by Bunton and Shiner's method [34] indicate that all paths discussed are possible.

Solvent effects on the rates of reaction have been studied using aqueous dioxan and DMSO (Table 5). Under conditions of 'complete' ionisation, the rates decrease both with increasing dioxan and with increasing DMSO content. Changes in pK_w', pK_a', and the 'activities' of the species involved with the solvent composition all occur. However, the increased basicity and nucleophilicity of phenolate and hydroxide anions would be expected to be the dominant feature as the DMSO content is increased.[34] Only path (*d*) would not be expected to show significant decreases in rate in *both* solvent mixtures, as is observed, under the conditions of pH′ used.

Activation Parameters.—Table 9 shows the activation parameters for the hydrolysis of methyl 8-hydroxy-1-naphthoate under conditions of 'complete' ionisation. The enthalpy and entropy of activation are calculated on the basis of kinetic behaviour as described by equation (i). The $\Delta S^{\ddagger}$ value could match both paths (*c*) and (*d*); but appears to be large for a bimolecular reaction (general base catalysis) and small for a unimolecular reaction (nucleophilic catalysis). In the absence of the pK_a' values of the substrate at all temperatures, such considerations for path (*c*) cannot be made.

TABLE 8

Regression analyses for pH′–rate correlations in the hydrolysis of alkyl 8-hydroxy-1-naphthoates in 30% (v/v) dioxan–water at 40.0 °C (μ = 1.0) *

Methyl ester	$10^4 k_{gb}/s^{-1}$ †	pK_a'	n	r
(a) $1/k_1$ *vs.* a_{H^+}'	3.70 (±0.28)	9.97_5 (±0.03)	16	1.000
(b) k_1 *vs.* $k_1 a_{H^+}'$	3.55 (±0.24)	9.89_5 (±0.07_5)	16	0.852
(c) $1/k_1$ *vs.* a_{D^+}'	3.48 (±0.28)	10.53 (±0.05)	7	0.998
(d) k_1 *vs.* $k_1 a_{D^+}'$	2.59 (±0.35)	10.28_5 (±0.12)	7	0.852
Methyl ester				
(e) $1/k_1$ *vs.* a_{H^+}'	2.19 (±0.71)	10.28_5 (±0.23)	5	0.996
(f) k_1 *vs.* $k_1 a_{H^+}'$	1.24 (±0.50)	10.64_5 (±0.37)	5	0.400

* n = Number of points, r = correlation coefficient. † From equation (i); alternative relation (ii) gives, for example, k_{ga} as 0.765 [relation (a) for methyl ester], 1.26 [relation (c) for methyl ester], and 0.222 [relation (e) for ethyl ester] l mol^{-1} s^{-1}.

TABLE 9

Activation parameters for the hydrolysis of esters and lactone in 30% (v/v) dioxan–water at 30.0 °C (μ = 1.0)

	$\Delta H^{\ddagger}$/cal mol^{-1}	$\Delta S^{\ddagger}$/cal mol^{-1} K^{-1}
Methyl 8-hydroxy-1-naphthoate	21 600 (±400)	−7 (±1)
Methyl 1-naphthoate	12 200 (±100)	−28 (±1)
8-Hydroxy-1-naphthoic lactone	8 800 (±300)	−24 (±1)
Phenyl 1-naphthoate	12 100 (±200)	−29 (±1)

Hydrolysis of 8-Hydroxy-1-naphthoic Acid Lactone.—The alkaline hydrolysis of the lactone is first-order in both the substrate and hydroxide ion. The hydrolysis of the lactone (Table 4) is very rapid and, at 40 °C, *ca.* 2 600 times faster than that of phenyl 1-naphthoate. Contrary to Menger and Brock,[17] we believe that the larger reactivity ratio *observed here* arises from *both* the '*cis*' conformation and ring strain; the latter being decreased in the rate-determining formation of the tetrahedral intermediate (6; R = H); *cf.* ref. 25. However, ring strain will *mainly* affect the collapse of (6; R = H), making the ring fission step to products even more favourable than the comparable step for phenyl 1-naphthoate. Thus, *if* the lactone were to be formed in the hydrolysis of esters of the type (2; R = alkoxy), tetrahedral intermediates of the type (6; R = alkyl) would preferentially collapse back to the initial state, the monoanion. Nucleophilic catalysis can only occur in these systems if the esters have a *better* leaving group than the internal aryloxy-group.

The activation parameters for the hydrolysis of the lactone and phenyl 1-naphthoate shown in Table 9 demonstrate that the increased reactivity of the lactone comes mainly from the enthalpy term. This arises, as stated above, from the '*cis*' conformation and ring strain and amounts to *ca.* 3.3 kcal mol^{-1}.

The neutral or uncatalysed hydrolysis of the lactone (Table 3) was found to be very slow, as would be expected. The rate ratio of the hydroxide to water reaction (*ca.* 6 × 10^6 : 1) and k_{H_2O}/k_{D_2O} (*ca.* 1.1) at 20 °C are similar to the corresponding values for related esters and lactones.[33]

pK_a' *Values of 8-Hydroxy-1-naphthoates.*—Table 6 shows the pK_a' values of the 8-hydroxy-1-naphthoates in 30% (v/v) dioxan–water at 40 °C. While the *peri*-alkoxycarbonyl group is only slightly acid-weakening, the carboxylate anion group is strongly so. The same type of behaviour has been found in the salicyclate system.[35] Thus intramolecular hydrogen bonding in water is very important in stabilising the monoanions of both 8-hydroxy-1-naphthoic and salicylic acids, but appears unimportant for the corresponding esters.

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I.r. Stretching Frequencies of Esters and Acids.—Table 7 shows the hydroxy-stretching frequencies of the esters and acids in carbon tetrachloride. The 8-hydroxyl-1-naphthoic acid and its three alkyl esters all show absorptions clearly in the region for phenolic hydroxy-groups intramolecularly hydrogen-bonded to ester carbonyl oxygen (previously shown [29,36,37] to occur between 3 050 and 3 290 cm^{-1} with ' wide ' half-intensity bandwidths, *i.e. ca.* 100 cm^{-1}, without any absorptions for unbonded phenolic hydroxy-groups at *ca.* 3 600 cm^{-1}, with ' narrow ' half-intensity bandwidths,[29] *i.e. ca.* 20 cm^{-1}). Conversely, the absorption for the carboxylic acid hydroxy-group of 8-hydroxy-1-naphthoic acid is clearly in the unbonded region,[29,30] as is that of 8-methoxy-1-naphthoic acid. The intramolecularly hydrogen-bonded structure (7), having a seven-membered ring, is related to those of methyl salicylates and hydroxynaphthoates (2-OH,1-CO_2H; 1-OH,2-CO_2H; and 3-OH,2-CO_2H)[38] with six-membered rings. It appears that ring size and steric effects are less important for hydroxy-esters and acids than for other intramolecularly hydrogen-bonded systems; *cf.* ref. 39.

Proposed Mechanism and Implications.—The hydrolysis of alkyl 8-hydroxy-1-naphthoates proceeds with neighbouring group participation. As for the hydrolysis of methyl salicylates,[13,14] the general base and the general acid specific base paths, (*b*) and (*c*), respectively, seem equally likely.

The anions of the 8-hydroxy-1-naphthoate esters have almost ideal initial state geometry for the nucleophilic path (*d*); *cf.* ref. 17. The present and related results [12-15] emphasise the crucial roles of the leaving group and the structure of the intermediate. A favourable nucleophilic path requires, in addition to proximity and orientation factors, a ' good ' leaving group, *e.g.* in the present cases, an aryloxy-group, and an intermediate without excessive ring strain. Both these factors are not present for all salicylates studied,[12-14] and are apparently present for aryl 2-hydroxyphenylacetates and 3-(2-hydroxyphenyl)propionates.[15] In this study, the factors have not been found to be present for the alkyl 8-hydroxy-1-naphthoates. However they *could* still be for phenyl esters of the same system.

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