Additivity of Substituent Effects in the Alkaline Hydrolysis of Alkyl Benzoates

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The kinetics of hydrolysis of some methyl, ethyl, isopropyl, and t-butyl esters of substituted benzoic acids were studied in 70% v/v dioxan–water. The substituent effects and their additivity were examined. The hydrolysis of the methyl benzoates follows the sequence of relative rates (at 40°) 4-nitro 71, 2-methyl-4-nitro 11, parent 1.0, 3-methyl 0.71, 4-methyl 0.51, 2-methyl 0.14, 2,5-dimethyl 0.090, 2,3-dimethyl 0.065, 2,4-dimethyl 0.055, 2-ethyl 0.046.

THE factors, steric and electronic, which govern the rates of alkaline hydrolysis of carboxylic esters are now well understood.[1,2] This is a good system, therefore, for studying the cumulative effect of substituents. The present work describes our results on the effect of methyl substitution on the hydrolysis of methyl, ethyl, isopropyl, and t-butyl esters of benzoic and *p*-nitrobenzoic acids.

The Ester Alkyl Group.—For each of the ten acids given in Table 1 the kinetics of alkaline hydrolysis were obtained for at least two esters (Me and Et). Comparison of the data for different alkyl esters proved instructive. As for the corresponding benzoic acid esters [2] the rate sequence was Me > Et > $\mathrm{Pr^i}$ > $\mathrm{Bu^t}$, as anticipated from the general electron release by alkyl groups. Each step in this sequence corresponds to larger increases in $\Delta G^{\ddagger}$: the first substitution (Me $\longrightarrow$ Et) involves an increase (standard deviation in parentheses) of 2.7 ($\pm$0.47), the second (Et $\longrightarrow$ $\mathrm{Pr^i}$) of 5.4 ($\pm$0.9), and the third ($\mathrm{Pr^i}$ $\longrightarrow$ $\mathrm{Bu^t}$) of 8.0 ($\pm$0.06) kJ $\mathrm{mol^{-1}}$. In most cases this lowering of rate constant is due more to increases in $\Delta H^{\ddagger}$ rather than to decreases in $\Delta S^{\ddagger}$.[1a]

The Taft linear free energy relationship $\log(k/k_0) = fA$, to which hydrolytic reactions have been shown to conform,[3] can be applied using the reaction constant $f = 0.953$,[2] together with known values [3] of A, *viz.* Me 0.00, Et −0.49, $\mathrm{Pr^i}$ −1.29, and $\mathrm{Bu^t}$ −2.83. This gives us predicted values of relative rate constants, whatever the nature of the acid, for the esters: Me 100, Et 34.1, $\mathrm{Pr^i}$ 5.90, and $\mathrm{Bu^t}$ 0.201. For the rate data, computed for 40 °C, given in Table 1 we observe regular decreases in relative rate constants (M $\longrightarrow$ Et $\longrightarrow$ $\mathrm{Pr^i}$ $\longrightarrow$ $\mathrm{Bu^t}$), in good agreement with those predicted. Mean values found for the present data and some data published previously,[2] with standard deviations, were Me 100, Et 36.7 ($\pm$7.9), $\mathrm{Pr^i}$ 5.1 ($\pm$1.8), and $\mathrm{Bu^t}$ 0.27 ($\pm$0.05). This shows that even for acids for which one might expect anomalies due to steric interactions the progressive behaviour of alkyl esters is near normal; certainly, no regular pattern could be recognised for departures from the mean.

Esters of the Toluic Acids and o-*Ethylbenzoic Acid.*—Esters of the monosubstituted acids undergo saponification with rates which follow the sequence benzoic > *m*-toluic > *p*-toluic > *o*-toluic > *o*-ethylbenzoic. This represents the sequence of electron release by alkyl groups from the appropriate nuclear positions arising from a general increase in the enthalpies of activation $\Delta H^{\ddagger}$, with additional steric hindrance in the case of *o*-alkyl substitution. The decrease in rate constants (increase in $\Delta H^{\ddagger}$) of *o*-methyl or -ethyl esters, relative to the corresponding benzoates, may be due in part to a 'primary steric effect',[1a] in which *ortho*-substituents cause an increase in non-bonded interactions in the tetrahedral transition state.[4] A bulky *ortho*-substituent may also hinder the orientation of solvent molecules at the reaction site more in the transition state than in the initial state.[1a,2] This 'steric inhibition of solvation' would result in an increase in $\Delta H^{\ddagger}$ as well as an increase in the entropy of activation $\Delta S^{\ddagger}$.[1a] This effect has been observed for a series of methyl esters of *o*-alkyl benzoates [1a] and for α-type esters of the naphthalene, anthracene, and phenanthrene series.[2] It would appear also to be important for several esters in Tables 1 and 2, in particular ethyl *o*-toluate and methyl *o*-ethylbenzoate, which exhibit substantial increases in the entropy of activation ($\Delta\Delta S^{\ddagger}$ +34 and +30 J $\mathrm{K^{-1}\,mol^{-1}}$, respectively).

This analysis of our results clearly recognises the presence of steric effects; Charton [5] has, however, concluded that 'in general the alkaline hydrolysis of *o*-substituted benzoate esters is subject only to electrical substituent effects and is independent of steric effects'.

Additive Effect of Two Methyl Substituents.—From the known effect on the rate constants of *o*-, *m*-, and *p*-methyl substituents one can predict those for the dimethyl derivatives (Table 3). Alternatively one can employ the Hammett equation,[6] by assuming that ρ values for benzoates apply equally well to *o*-toluates. The predicted values for rate constants of ester hydrolysis are invariably too high, the rates for methyl 2,4- and 2,5-dimethylbenzoates being predicted with some success. Not surprisingly for methyl 2,6-dimethylbenzoate, an ester where a second methyl substituent produces a major change in geometry, a rate is predicted *ca.* 600

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TABLE 1

Rate constants of the alkaline hydrolysis of esters of substituted benzoic acids in 70% v/v dioxan–water

No.	$ArCO_2R$		10^3k_2/dm^3 mol^{-1} s^{-1} (t/°C)	10^3k_2 (313.2 K computed)/ dm^3 mol^{-1} s^{-1}
	Ar	R		
1	Ph	Me [a]		27.9
2		Et [a]		10.2
3		Pr^i [a]		1.77
4		Bu^t [a]		0.080
5	2-MeC_6H_4	Me	1.87 (30), 2.73 (35), 4.00 (40), 5.48 (45), 8.02 (50)	3.90
6		Et	0.70 (30), 1.32 (35), 1.70 (40), 2.92 (45,) 4.32 (50)	1.85
7		Pr^i	0.16 (45), 0.26 (50), 0.37 (55), 0.50 (60)	0.112
8	3-MeC_6H_4	Me	3.92 (20), 6.00 (25), 8.38 (30), 13.2 (35), 19.9 (40), 29.3 (45)	19.7
9		Et	2.4 (30), 3.8 (35), 5.8 (40), 8.2 (45)	5.65
10		Pr^i	0.98 (45), 2.5 (55), 4.4 (60)	0.566
11	4-MeC_6H_4	Me	4.17 (25), 6.23 (30), 9.53 (35), 14.3 (40)	14.2
12		Et	2.67 (35), 4.23 (40), 6.3 (45), 9.1 (50)	4.14
13		Pr^i	0.81 (45), 1.23 (50), 2.05 (55), 2.90 (60)	0.51
14	2-EtC_6H_4	Me	1.98 (45), 2.88 (50), 4.58 (55), 6.63 (60)	1.27
15		Et	0.58 (45), 0.875 (50), 1.28 (55)	0.39
16	2,3-$Me_2C_6H_3$	Me	0.638 (25), 0.818 (30), 1.26 (35), 1.92 (40), 2.56 (45), 3.59 (50)	1.82
17		Et	0.280 (30), 0.408 (35), 0.673 (40), 0.887 (45), 1.46 (50)	0.64
18	2,4-$Me_2C_6H_3$	Me	1.00 (35), 1.52 (40), 2.36 (45), 3.35 (50)	1.53
19		Et	0.68 (45), 0.95 (52), 1.30 (55), 1.77 (60)	0.46
20	2,5-$Me_2C_6H_3$	Me	1.24 (30), 1.78 (35), 2.39 (40), 3.66 (45), 4.82 (50)	2.50
21		Et	0.320 (30), 0.488 (35), 0.742 (40), 1.10 (45), 1.55 (50)	0.732
22	4-$O_2NC_6H_4$	Me	109 (0), 131 (2), 147 (4), 178 (6), 211 (8), 230 (10), 289 (12)	1 990
23		Et	41.1 (0), 65.0 (5), 102 (10), 155 (15), 236 (20)	1 080
24		Pr^i	22.8 (15), 35.6 (20), 50.0 (25), 75.7 (30), 104 (35), 148 (40)	149
25		Bu^t	2.1 (25), 2.9 (30), 4.2 (35), 5.6 (40), 9.0 (45), 13.3 (50)	6.17
26	2-Me-4-$O_2NC_6H_3$	Me	33.1 (10), 49.7 (15), 71.6 (20), 107 (25), 156 (30)	311
27		Et	10.6 (10), 17.0 (15), 26.2 (20), 37.3 (25), 54.1 (30)	114
28		Pr^i	4.92 (25), 7.08 (30), 10.5 (35), 16.1 (40), 21.8 (45)	15.5
29		Bu^t	0.18 (25), 0.31 (30), 0.39 (35), 0.63 (40), 1.07 (45), 1.42 (50)	0.65

[a] Data from ref. 2.

TABLE 2

Derived data for the alkaline hydrolysis of esters of substituted benzoic acids in 70% v/v dioxan–water

No.	$\Delta H^‡$/kJ mol^{-1} (298.2 K)	$\Delta S^‡$/J K^{-1} mol^{-1} (298.2 K)	$\Delta G^‡$/kJ mol^{-1} (298.2 K)
1	51.9	−109	84.5
2	54.4	−109	87.0
3	57.7	−113	91.6
4	65.7	−113	99.6
5	56.9	−109	89.4
6	69.7	−75	92.0
7	64.2	−115	98.6
8	57.9	−93	85.6
9	63.0	−87	88.8
10	82.2	−45	95.6
11	61.5	−84	86.5
12	65.1	−83	89.7
13	75.2	−68	95.5
14	69.5	−79	93.0
15	65.6	−101	95.7
16	54.6	−123	91.2
17	63.9	−102	94.3
18	64.9	−91	92.2
19	54.9	−133	94.6
20	53.3	−124	90.3
21	62.2	−106	93.8
22	49.2	−82	73.7
23	55.7	−67	75.5
24	53.2	−91	80.3
25	57.7	−103	88.3
26	52.8	−86	78.4
27	55.2	−87	81.0
28	57.2	−97	86.1
29	64.2	−100	94.2

times faster than the experimental. Similarly, the rate for methyl 2,4,6-trimethylbenzoate is predicted too high by a factor of *ca.* 300.

The method using the Hammett equation gives smaller errors for the methyl esters, whilst both methods give equally poor predictions for the ethyl esters. The data in Table 3 suggest that a second methyl substituent exerts a stronger than expected deactivating effect on ester hydrolysis. The greatest departures occur with the esters of 2,3-dimethylbenzoic acid. A similar departure from additivity was observed for the hydrolysis of ethyl 2,3-dichlorobenzoate in an aqueous ethanol solvent.[7] Our data is in line with the observation that 2,3-dimethylbenzoic acid is an appreciably stronger acid than predicted.[8] It is apparent that the 'buttressing effect'[9] of contiguous methyl groups exerts an additional rate-lowering effect on the ester hydrolysis. The methyl substituents will promote rotation of the ester side chain away from a coplanar conformation, and hinder access of hydroxy-ions from either side of the ester group. For more highly hindered esters, as for methyl 2,4,6-trimethylbenzoate,[10] methyl *o*-t-butylbenzoate,[1a] or methyl 9-anthroate,[2] a marked increase in steric inhibition of solvation (affecting mainly the transition state) is expec-

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ted.[1a] A sharp increase in $\Delta S^{\ddagger}$ [1a] and, usually, an increase in $\Delta H^{\ddagger}$,[1a,2] are then observed. For the esters of 2,3-dimethylbenzoic acid, however, increases in $\Delta S^{\ddagger}$ were not observed: the diminution of rate evidently results from an increase in $\Delta H^{\ddagger}$.

Tests for additivity (*cf.* ref. 11) for the hydrolysis of methyl-substituted benzoates were performed using, separately, differences in $\Delta H^{\ddagger}$ (*cf.* analysis of activation energy differences [7]) or differences in $\Delta S^{\ddagger}$. In every case the experimental data were very poorly predicted; in part, the reason may be insufficient accuracy of the parameters used. However, using differences in the free energies of activation (Table 4) reasonable predictions could be obtained.

TABLE 3

Experimental and predicted rate constants of alkaline hydrolysis of alkyl dimethylbenzoates in 70% v/v dioxan–water

ArCO$_2$R Methyl substituents in Ar	R	Rate constants					
		10^3k_2/dm^3 mol^{-1} s^{-1} (40 °C)			10^3k_2/dm^3 mol^{-1} s^{-1} (30 °C)		
		Exp.	Predicted, method A [a]	Prediction error (%) [b]	Exp.[c]	Predicted, method B [d]	Prediction error (%) [b]
2,3	Me	1.82	2.75	+34	0.885	1.29	+31
2,4	Me	1.53	1.99	+23	0.711	0.775	+8
2,5	Me	2.50	2.75	+9	1.24	1.29	+4
2,6	Me	8.9×10^{-4} [e]	0.55	+99.8			
2,4,6	Me	8.6×10^{-4} [e]	0.28	+99.7	10^3k_2/dm^3 mol^{-1} s^{-1} (25 °C)		
2,3	Et	0.64	1.02	+37	0.182	0.314	+42
2,4	Et	0.46	0.75	+39	0.143	0.172	+17
2,5	Et	0.732	1.02	+28	0.212	0.314	+32

[a] Calculated from rates of *o*-toluate, on appropriate substitution by a second methyl group; for Me esters: *o*-Me 0.140, *m*-Me 0.706, *p*-Me 0.509; for Et esters: *m*-Me 0.554, *p*-Me 0.406. [b] (Predicted − experimental)/predicted. [c] Extrapolated. [d] Calculated from rates of *o*-toluate using the Hammett equation, and ρ 2.20 for hydrolysis of methyl benzoates at 30° [K. Bowden and G. R. Taylor, *J. Chem. Soc.* (*B*), 1971, 145], or ρ 2.58 for hydrolysis of ethyl benzoates at 25°, calculated (method of least squares) from available rate data (C. C. Price and R. H. Michel, *J. Amer. Chem. Soc.*, 1952, **74**, 3652, ref. 2, and Table 1). σ values used were −0.069 (*m*-Me) and −0.170 (*p*-Me) (D. H. McDaniel and H. C. Brown, *J. Amer. Chem. Soc.*, 1958, **23**, 420). [e] Rate constants extrapolated to 40° (method of least squares) from rate data in the temperature range 100—150 °C, obtained for 60% v/v dioxan–water;[10] the solvent correction is based on rate constants (10^3k_2) for hydrolysis of methyl benzoate at 20° in 70% v/v dioxan–water = 8.50 dm^3 mol^{-1} s^{-1}, and in 60% v/v dioxan–water = 9.38 dm^3 mol^{-1} s^{-1} [K. Bowden and G. R. Taylor, *J. Chem. Soc.* (*B*), 1971, 145] giving a ratio of 0.906.

TABLE 4

Experimental and predicted free energy differences ($\Delta\Delta G^{\ddagger}$) for alkyl dimethylbenzoates

ArCO$_2$R Methyl substituents in Ar	R	$\Delta\Delta G^{\ddagger}$ (observed)/ kJ mol^{-1}	$\Delta\Delta G^{\ddagger}$ (predicted) [a]/ kJ mol^{-1}	Error (%) [b]
2,3	Me	+6.7	+6.0	−12
	Et	+7.3	+6.8	−7
2,4	Me	+7.7	+6.9	−12
	Et	+7.6	+7.7	+1
2,5	Me	+5.8	+6.0	+3
	Et	+6.8	+6.8	0

[a] Increments are: *o*-Me +4.9 (or +5.0), *m*-Me +1.1 (or +1.8), *p*-Me +2.0 (or 2.7), for methyl (or ethyl), respectively. [b] (Predicted − experimental)/predicted.

TABLE 5

Effect of *o*-methyl and *p*-nitro-substitution on the rate constants of hydrolysis of alkyl esters of benzoic acids

	Rate ratio (at 40 °C)			
	Effect of *o*-Me substitution		Effect of *p*-NO$_2$ substitution	
Ester	Benzoate	*p*-Nitrobenzoate	Benzoate	*o*-Toluate
Me	7.2	6.4	71	80
Et	5.5	9.5	106	62
Pr$^{\text{i}}$	16	9.6	84	140
Bu$^{\text{t}}$		9.5	77	

Nitro-substituted Esters.—We wished to study a series of alkyl esters (Me, Et, Pr$^{\text{i}}$, and Bu$^{\text{t}}$) for a benzoic acid substituted in the *ortho*-position. The data for the esters of *o*-toluic acid itself were not appropriate, since our experimental method does not give sufficiently precise rate constants for slow reactions, *viz.* where $k_2 < 2 \times 10^{-4}$ dm^3 mol^{-1} s^{-1} (estimated for t-butyl *o*-toluate, k_2 *ca.* 1×10^{-5} dm^3 mol^{-1} s^{-1}). Since a *p*-nitro-group is known strongly to activate the alkaline hydrolysis of alkyl benzoates,[12] we examined instead the hydrolysis of alkyl 2-methyl-4-nitrobenzoates (Tables 1 and 2). The most sterically hindered ester, t-butyl 2-methyl-4-nitrobenzoate, underwent hydrolysis at a rate relative to the methyl ester (*ca.* 0.2%) not significantly lower than for the *p*-nitrobenzoates (ratio *ca.* 0.3%) which undergo reaction much more rapidly. This suggests that for the series of esters Me, Et, Pr$^{\text{i}}$, and Bu$^{\text{t}}$ there is no sudden change of mechanism, as, for example, from $B_{\text{Ac}}2$ to $B_{\text{Al}}2$. In contrast, the acid hydrolysis of t-butyl benzoate follows an alkyl–oxygen fission mode, $A_{\text{Al}}1$.[13] For the series of esters of 2-methyl-4-nitrobenzoic acid there is a progressive and regular increase in $\Delta H^{\ddagger}$ (by steps of 2.4, 3.0, and 7.0 kJ mol^{-1}, respectively), and a small decrease in $\Delta S^{\ddagger}$ (from −86 to −100 J K^{-1} mol^{-1}), whereas in the series of *p*-nitrobenzoates the ethyl ester appears to be anomalous, and whereas the hydrolyses of the esters of the benzoate series are essentially isoentropic. The sharp increase in $\Delta S^{\ddagger}$ usually obtained for very

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bulky *ortho*-substituents,[1a,10] seems not to take place with our t-butyl esters.

Table 5 summarises the effect on rate constants of hydrolysis on *o*-methyl and *p*-nitro-substitution in alkyl benzoates. Again, the ethyl esters appear to be out of step with the other alkyl esters.

EXPERIMENTAL

Esters.—Methyl, ethyl, and isopropyl esters were prepared by the Fischer–Speier procedure, t-butyl esters by a modification of the method of Brewster and Ciotti.[14] The esters were carefully purified and had physical constants very close to those in the literature. New compounds were *ethyl 2,3-dimethylbenzoate*, an oil, b.p. 84—87° at 0.8 mmHg, n_D^{25} 1.512 9 (Found: C, 74.0; H, 7.8. $C_{11}H_{14}O_2$ requires C, 74.1; H, 7.9%); *ethyl 2-methyl-4-nitrobenzoate*, crystals, m.p. 69° (Found: C, 57.7; H, 5.2; N, 6.8. $C_{10}H_{11}NO_4$ requires C, 57.4; H, 5.3; N, 6.7%); *isopropyl 2-methyl-4-nitrobenzoate*, crystals, m.p. 25° (Found: C, 59.5; H, 6.0; N, 6.4. $C_{11}H_{13}NO_4$ requires C, 59.2; H, 5.9; N, 6.3%); and *t-butyl 2-methyl-4-nitrobenzoate*, crystals, m.p. 50.5° (Found: C, 70.0; H, 6.4; N, 6.0. $C_{12}H_{15}NO_4$ requires C, 60.8; H, 6.4; N, 5.9%).

Kinetic Procedure.—The kinetic procedure used has been described in detail in an earlier paper.[15] The coefficient of cubical expansion of 70% v/v dioxan–water used was calculated as 8.56×10^{-4} K^{-1} from published data of densities of dioxan and of water at various temperatures.

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