The Alkaline Hydrolysis of Substituted Ethyl Benzoates. The Additive Effects of Substituents.

By BRYNMOR JONES and JOHN ROBINSON.

[Reprint Order No. 6201.]

A kinetic study is reported of the alkaline hydrolysis of 34 substituted ethyl benzoates. Of these, twenty were disubstituted and one trisubstituted; the remainder were monosubstituted esters whose rate constants were required for an analysis of the cumulative effects of groups on reactivity.

It has been shown that the resultant effect of two substituents, in those esters where the possibility of group interaction is at a minimum, is very close to the sum of their separate effects. In the remainder, the additive relationship is less exact.

THE discovery of a number of organic reactions in which the influence of polar substituents on the rates of reactions may be accounted for almost solely by changes in the energy of activation—the entropy of activation remaining virtually unchanged—led to a number of investigations of the cumulative effects of substituents. Until recently, almost all systematic studies covering a wide range of substituents were restricted to the determination of the influence of single substituents. Only for the nuclear chlorination of aromatic ethers of the types *p*-RO·C_6H_4X and RO·$C_6H_3X_2$, where some two hundred ethers have been examined, had a comprehensive study been made of the influence of two or more substituents. Here the important conclusions were reached, not only that differences in rate resulting from the presence of substituents could be accounted for satisfactorily by changes in the energy of activation, but also that the resultant effect of two substituents is very closely the algebraic sum of their individual effects (*J.*, 1928, 1006; 1935, 1831; 1942, 418, 676; 1954, 1775).

In 1949 further evidence for the additive effect of substituents was revealed. Stubbs and Hinshelwood (*J.*, 1949, S 71) found that in the benzoylation of anilines a polar substituent at a given position in the aniline alters the free energy of activation ($-\boldsymbol{R}T \ln k$) by an amount which is characteristic of the substituent and is independent of the presence of a second substituent, while Shorter and Stubbs (*J.*, 1949, 1180) showed from an analysis of the available dissociation constants of a wide range of benzoic acids that the change in the free energy of ionisation ($-\boldsymbol{R}T \ln K$) produced by two or more substituents is in many instances nearly the sum of the effect of these groups when present separately; the most notable exceptions are certain 2 : 6- and 2 : 3-disubstituted acids.

About the same time, evidence of a similar additivity was found for the alkaline hydrolysis of some disubstituted ethyl benzoates (Brynmor Jones and Robinson, *Nature*, 1950, **165**, 453), and more recently for the bromination of aromatic ethers by hypobromous acid in aqueous acetic acid (Branch and Brynmor Jones, *Research*, 1952, **5**, No. 7; *J.*, 1954, 2317; 1955, 2921).

The earlier studies of the alkaline hydrolysis of ethyl benzoates (cf. Ingold and Nathan, *J.*, 1936, 222; Evans, Gordon, and Watson, *J.*, 1937, 1430; Tommila and Hinshelwood, *J.*, 1938, 1801; Tommila, *Ann. Acad. Sci. Fennicae*, Ser. No. *A*. 57, No. 133, 1941 *et seq.*) had established that for a wide range of monosubstituted esters *meta*- and *para*-substituents markedly affect the energy of activation without appreciably altering the entropy factor. On the other hand, *ortho*-substituents, with the single exception of fluorine, affect both the energy and the entropy term.

The present investigation extends these studies to include some twenty disubstituted esters. In view of the known effect of *ortho*-substituents on the entropy of activation, the esters selected had the two substituents in either the 3 : 4- or the 3 : 5-positions. For the present analysis of additive effects comparable values were required also of the effects of a number of individual groups. The rates for thirteen monosubstituted ethyl benzoates have therefore been determined. These are given in Table 3. Where the rates had been determined by earlier workers, good agreement was found with the values in the present study. This is clear from the data in Table 1 where the rates of the substituted and the unsubstituted ethyl benzoates found by various workers are expressed as ratios (k_s/k_u). In four of the five investigations the solvent was aqueous ethyl alcohol. The values in column 5 were obtained by Tommila with aqueous acetone as medium, and the differences between the ratios in columns 5 and 6 may arise from the fact that the group dipole moments are not the same in the two solvents.

TABLE 1. *Comparison of the rates of hydrolysis of substituted and unsubstituted ethyl benzoates* (*given as velocity ratios,* k_s/k_u). (For references see text.)

Substituent	Ingold & Nathan	Evans, Gordon, and Watson	Kindler	Tommila	This paper
4-OMe	0·208	—	0·214	—	0·219
4-Me	0·456	—	0·480	0·396	0·458
4-Cl	4·31	—	4·33	4·04	4·34
3-Me	—	0·697	0·706	0·502	0·708
3-Cl	—	7·68	7·41	6·29	7·62
3-NO_2	—	69·08	63·48	47·21	68·3
4-NH_2	0·0231	—	0·0233	0·030	0·0244
3-OMe	—	—	1·20	1·355	1·33
3-Br	—	—	8·06	6·17	8·10
4-OEt	—	—	0·22	0·207	0·199
4-OPr^i	—	—	0·212	—	0·194
3-Me, 4-Me	—	—	0·333	—	0·320
3-Cl, 4-Cl	—	—	—	17·47	24·1
3-Br, 5-Br	—	—	—	31·20	65·2
3-Me, 5-Me	—	—	—	0·338	0·498

The velocities of reaction of four typical esters were determined at 25° and 35°, and the energies of activation and the entropy factors evaluated. These are given in Table 2.

TABLE 2.

Ester	10^3k_{25}	10^3k_{35}	$\log_{10} PZ$	E (cal.)
Et benzoate	0·607	1·61	9·8	17,730
Et 3 : 5-dimethylbenzoate	0·302	0·825	9·9	18,330
Et 4-methoxy-3-nitrobenzoate	6·36	15·90	9·8	16,330
Et 3 : 5-dibromobenzoate	39·6	60·95 (at 30°)	9·8	15,300

Complete lists of rate constants and of energies of activation are summarised in Tables 2—5. To facilitate comparison of these results with those for the benzoylation of anilines, the data are arranged in a similar manner (cf. Stubbs and Hinshelwood, *loc. cit.*).

TABLE 3. *Velocity constants and activation energies* (E') *for monosubstituted ethyl benzoates.*

Subst.	10^3k_{25}	E' (cal.) *	Subst.	10^3k_{25}	E' (cal.) *	Subst.	10^3k_{25}	E' (cal.) *
(H)	0·607	17,730 †	*p*-Cl	2·64	16,860	*p*-OEt	0·121	18,690
p-Me	0·278	18,190	*m*-Cl	4·63	16,530	*p*-OPr^i	0·118	18,700
m-Me	0·430	17,930	*m*-NO_2	41·5	15,230	*p*-O·CH_2·CH:CH_2	0·144	18,580
p-OMe ...	0·133	18,630	*m*-Br	4·92	16,490	*p*-O·CH_2Ph	0·140	18,600
m-OMe ...	0·805	17,560	*p*-NH_2 ...	0·00148	—			

* Calc. as $E' = 2{\cdot}303\boldsymbol{R}T[\log_{10}(PZ)_{\mathrm{H}} - \log_{10}k_{25}]$.
† Calc. from log k_{25} with non-exponential term equal to that for ethyl benzoate.

TABLE 4. *Increments in activation energy due to single substituents.*

Subst.	$\Delta E'$	Subst.	$\Delta E'$	Subst.	$\Delta E'$	Subst.	$\Delta E'$
(H)	0	*m*-OMe	−170	*m*-NO_2	−2500	*p*-OPr^i	+970
p-Me	+460	*p*-Cl	−870	*m*-Br	−1240	*p*-O·CH_2·CH:CH_2	+850
m-Me	+200	*m*-Cl	−1200	*p*-OEt	+960	*p*-O·CH_2Ph	+870
p-OMe	+900						

TABLE 5. *Disubstituted ethyl benzoates.*

Substituents	10^3k_{25}	E'	E' (predicted)	$\Delta E'$	$\Delta E'$ (predicted)	[$\Delta E' - \Delta E'$ (predicted)]
H	0·607	17,730	—	—	—	—
3-Me, 4-Me	0·194	18,410	18,390	+680	+660	+20
3-Me, 5-Me	0·302	18,140	18,130	+410	+400	+10
3-Cl, 4-Me	1·97	17,030	16,990	−700	−740	+40
3-NO_2, 4-Me	16·8	15,760	15,690	−1970	−2040	+70
3-OMe, 4-OMe	0·214	18,350	18,460	+620	+730	−110
3-Cl, 4-OMe	0·709	17,640	17,430	−90	−300	+210
3-Br, 4-OMe	0·728	17,620	17,390	−110	−340	+230
3-NO_2, 4-OMe	6·36	16,340	16,130	−1390	−1600	+210
3-OMe, 5-OMe	1·04	17,410	17,390	−320	−340	+20
3-Cl, 4-OEt	0·649	17,690	17,490	−40	−240	+200
3-Br, 4-OEt	0·663	17,680	17,450	−50	−280	+230
3-Cl, 4-OPr^i	0·701	17,650	17,500	−80	−230	+150
3-Br, 4-OPr^i	0·699	17,650	17,460	−80	−270	+190
3-NO_2, 4-OPr^i	5·05	16,480	16,200	−1250	−1530	+280
3-Cl, 4-O·CH_2·CH:CH_2 ...	0·763	17,590	17,380	−140	−350	+210
3-Cl, 4-O·CH_2Ph	0·748	17,600	17,400	−120	−330	+210
3-Cl, 4-Cl	14·6	15,850	15,660	−1880	−2070	+190
3-Cl, 5-Cl	39·7	15,250	15,330	−2480	−2400	−80
3-Br, 5-Br	39·6	15,260	15,250	−2470	−2480	+10
3-Br, 5-Me	3·45	16,700	16,690	−1030	−1040	+10
3-OMe, 4-OMe, 5-OMe ...	0·927	17,480	18,290	−250	+560	−810

DISCUSSION

Constancy of the Entropy Factor.—The present data show that for three disubstituted ethyl benzoates with divergent rates of hydrolysis the value of the entropy factor is virtually the same as for ethyl benzoate. When values of $\log_{10} k_{25}$ are plotted against E the points fall on, or near to, a line of slope $-2{\cdot}303\boldsymbol{R}T$.

Cumulative Effect of Substituents.—The rates of hydrolysis of the substituted ethyl *p*-alkoxybenzoates, except those containing an *iso*propoxy-group, give velocity ratios, $k_{\mathrm{X}}^{\mathrm{OR}}/k_{\mathrm{X}}^{\mathrm{OMe}}$, which are constant to within 4%. These results (Table 6), which are directly analogous to those for the nuclear chlorination of ethers, where the constancy of the entropy factor has been determined experimentally (*J.*, 1942, 418), show that in ester hydrolysis the alkoxy-groups and the polar substituent contribute almost additively to the energy of

TABLE 6. *Relative rates of hydrolysis of* 3-X-*substituted* 4-*alkoxybenzoic esters. Values of* $100k_{\mathrm{X}}^{\mathrm{OR}}/k_{\mathrm{X}}^{\mathrm{OMe}}$.

Subst. X	R = Me	Et	Pr^i	CH_2Ph	CH_2·CH:CH_2
H	100	91	89	105	108
Cl	100	92	99	106	108
Br	100	92	96	—	—
NO_2	100	—	79	—	—

activation. The overall differences in the rates of hydrolysis, however, are much smaller than for halogenation and, on this evidence alone, the constancy of the entropy factor for a wider range of esters cannot be regarded as established. In the 3-substituted 4-alkoxybenzoic esters only one of the two variable substituents, the 3-substituent, is directly attached to the benzene nucleus, for the R group functions by modifying the directive power of the OR group, and esters in which the two substituents are directly attached to the nucleus were therefore examined.

If the entropy factor is assumed to be constant, the change in the energy of activation produced by single substituents may be calculated by means of the relation $\Delta E' = -2{\cdot}303\boldsymbol{R}T \log_{10} k_s/k_u$; and, if moreover substituent effects are additive, the observed increment in activation energy due to two substituents will be the sum of the increments due to each substituent alone, *i.e.*, $\Delta E'_{XY} = \Delta E'_X + \Delta E'_Y$. For instance, in ethyl 4-methyl-3-nitrobenzoate the individual group increments are $E'_{3\text{-}NO_2}$ —2500 cal. and $E'_{4\text{-Me}}$ + 460 cal. The predicted additive increment should, therefore, be —2040 cal. The observed value is —1970 cal. The difference of 70 cal. is well within the probable deviation (estimated at 100 cal.) which could occur without infringement of the additive relationship. Analysed in this way, the results for the 3-substituted 4-alkoxybenzoic esters show that the average difference between the observed and the calculated increments is of the order of 200 cal.

Of the remaining ten esters, eight give results in very close agreement with the predicted values. Of these, five have the substituents in the 3 : 5-positions, where group interaction would be at a minimum, and three are derivatives of ethyl *p*-toluate. The other two esters, ethyl 3 : 4-dichlorobenzoate and ethyl 3 : 4-dimethoxybenzoate, give differences between observed and calculated values of E' of +190 and —110 cal. respectively (cf. Table 5).

It is not possible to compare the present data closely with those for the benzoylation of disubstituted anilines since, unfortunately, there are only four cases where the nature and the position of the substituents are the same in the two series. The differences between the observed and the calculated energy increments for these are given in Table 7. In three of the four cases there is excellent agreement. The difference of 190 cal. found in the benzoylation of 3 : 5-dibromoaniline must arise from experimental error. For the only other amine of like orientation, 3 : 5-dimethylaniline, the divergence is 40 cal.

TABLE 7. *Divergences between observed and calculated increments in activation energy.*

Subst.	Benzoyln. of anilines	Hydrol. of esters
3 : 4-Me$_2$	+40	+20
3 : 5-Me$_2$	+40	+10
3 : 5-Br$_2$	+190	+10
3-Cl, 4-Me	+60	+40

It is difficult to estimate with certainty the divergences which may be allowed between observed and predicted changes in energy while maintaining the concept of additivity. For the benzoylation, Stubbs and Hinshelwood estimate the permissible divergence to be about ±75 cal., and they conclude that " the resultant effect of two substituents is very closely the sum of their individual effects," although for eight of the 21 disubstituted anilines the differences between the observed and predicted values of $\Delta E'$ are in the range 100—240 cal.

The present study shows that while the resultant effect of two substituents on the rates of hydrolysis of a wide range of ethyl benzoates may not be strictly additive in all cases it approximates closely to the sum of the individual effects in many cases. When the two substituents are in the 3 : 5-positions, the combined effect is the algebraic sum of their separate effects.

EXPERIMENTAL

Kinetic Measurements.—The method of Evans, Gordon, and Watson (*loc. cit.*) was adopted, but a minor modification was made to ensure a more precise definition of zero time. The ester and alkali solutions were mixed at 25° in equimolecular proportions (M/20) and, within a few seconds of mixing, 10 ml. of the mixture were withdrawn and the hydroxyl-ion concentration was determined. This value was used as the initial concentration (a) in equation, $k = x/[ta(a - x)]$, where x is the change in concentration of hydroxyl ion in time t. In all instances the reaction was bimolecular and strictly quantitative. The precision of the experimental method was satisfactory, but unfortunately the most divergent rate constants in the series of disubstituted esters covered only a 200-fold range. Typical results are given below, with the rate constants expressed as l. mole^{-1} sec.$^{-1}$.

Rate of alkaline hydrolysis of ethyl 4-methyl-3-nitrobenzoate in 84·6% aqueous ethyl alcohol at 25°.

t (min.)	$a - x$	10^3k	t (min.)	$a - x$	10^3k
0	(a = 0·939)	—	0	(a = 0·950)	—
4	0·789	16·87	4	0·798	16·70
8	0·678	17·07	8	0·688	16·70
15	0·546	17·03	15	0·562	16·57
25	0·432	16·66	25	0·430	16·97
40	0·328	16·49	40	0·320	17·67
60	0·248	16·49	60	0·248	16·55
90	0·177	16·97	90	0·179	16·80
120	0·142	16·60	120	0·135	17·25
	Mean	16·77		Mean	16·90

Mean of two determinations 16·8.

Purification of the Alcohol.—The reaction medium was aqueous ethyl alcohol (84·6% w/w) prepared by diluting purified alcohol with freshly boiled, distilled water. Absolute alcohol was purified first by being refluxed with quicklime for 2 hr., and then allowed to remain in contact with the quicklime for 24 hr. Anhydrous silver oxide was added, and the alcohol shaken at intervals during 24 hr. The dry alcohol was distilled in an all-glass apparatus, with rigorous precautions to exclude moisture. The diluted alcohol had d_4^{20} 0·8319, corresponding to 84·6% w/w alcohol.

Mono- and Di-substituted Benzoic Acids and Esters.—Some of the esters were purchased. Liquids were fractionated thrice under reduced pressure, considerable head and tail fractions being rejected at each distillation, and the middle fractions only used for subsequent distillation. The b. p.s of the purified esters were: ethyl benzoate, 97°/20 mm.; ethyl *p*-anisate, 139°/25 mm.; ethyl cinnamate, 139·5°/17 mm. Ethyl *p*-aminobenzoate, crystallised from absolute alcohol, had m. p. 92°. Other esters, prepared from acids which were commercially available and had been crystallised to constant m. p. from acetic acid, were treated similarly. The physical constants of these acids and of their esters, which, when solid, were crystallised from absolute alcohol, were as follows:

Substituted benzoic acids		Et esters
m-Cl,	m. p. 158°	b. p. 120°/25 mm.
m-Br,	,, 155	,, 129°/11 mm.
m-NO_2,	,, 142	m. p. 42°
p-Cl,	,, 235	b. p. 115°/15 mm.
3 : 4-Cl_2,	,, 202	m. p. 37°

The remaining acids and esters were prepared by standard methods. *m*-Toluic acid, m. p. 110°, was obtained from *m*-toluidine *via* the nitrile. Its ester had b. p. 85°/2 mm. The alkoxybenzoic acids were obtained from the appropriate hydroxy-acids (cf. *J.*, 1929, 2660; 1935, 1874).

Alkoxybenzoic acids		Et esters
m-OMe,	m. p. 106°	b. p. 134·5°/20 mm.
p-OEt,	,, 194	,, 127°/3 mm.
p-OPr^i,	,, 163	,, 119°/2 mm.
p-O·CH_2Ph,	—	,, m. p. 46°

The *p*-alkoxybenzoic acids were chlorinated and brominated, in glacial acetic acid at room temperature, by dichloramine-T or bromine. Nitration of these acids and of *p*-toluic acid was carried out in the same solvent at 70° with fuming nitric acid. 3-Chloro-4-methoxybenzoic acid, m. p. 214°, gave an ethyl ester, m. p. 76°; 3-bromo-, m. p. 218°, and 3-nitro-4-methoxybenzoic acid, m. p. 192°, gave esters melting at 74° and 101° respectively.

For the preparation of 3 : 5-dichloro-, m. p. 184°, and 3 : 5-dibromo-benzoic acid, m. p. 230°, anthranilic acid was halogenated in acetic acid, deamination of the purified products giving the

3 : 5-dihalogenobenozic acids in high yield. Ethyl 3 : 5-dichloro- and 3 : 5-dibromo-benzoate had m. p. 37° and 58° respectively after crystallisations from ethyl alcohol.

3-Chloro-4-methylbenzoic acid, m. p. 198° (ethyl ester, b. p. 135°/14 mm.), was prepared by the Sandmeyer reaction from the amino-acid obtained by the reduction of 4-methyl-3-nitrobenzoic acid.

Methylation of orcinol, and oxidation of the 3 : 5-dimethoxytoluene with permanganate, gave 3 : 5-dimethoxybenzoic acid, m. p. 182° (ethyl ester, m. p. 27°). 3 : 4-Dimethylbenzoic acid, m. p. 166° (ethyl ester, b. p. 120°/12 mm.), was synthesised from 3 : 4-dimethylaniline and the intermediate dimethylbenzonitrile; the isomeric 3 : 5-dimethyl acid, m. p. 165°, was prepared by oxidation of mesitylene with hot dilute nitric acid (its ethyl ester distilled at 120°/10 mm.).

The physical constants and the analyses of a number of other *acids* and *esters* are given below, X being halogen or nitrogen.

Disubstituted benzoic acids.

		Found (%)				Required (%)		
	M. p.	C	H	X	Formula	C	H	X
3-Chloro-4-ethoxy …………	208°	54·3	4·7	17·7	$C_9H_9O_3Cl$	53·9	4·5	17·7
3-Bromo-4-ethoxy …………	210	45·1	3·7	32·7	$C_9H_9O_3Br$	44·1	3·7	33·0
3-Chloro-4-*iso*propoxy ……	127	56·0	5·2	17·1	$C_{10}H_{11}O_3Cl$	56·0	5·2	16·6
3-Bromo-4-*iso*propoxy ……	129	46·9	4·5	30·5	$C_{10}H_{11}O_3Br$	46·3	4·3	30·9
3-Nitro-4-*iso*propoxy ………	158	53·2	4·9	6·0	$C_{10}H_{11}O_5N$	53·3	4·9	6·2

Ethyl esters.

		Found (%)				Required (%)		
	M. p.	C	H	X	Formula	C	H	X
3-Chloro-4-ethoxy …………	51°	58·4	5·9	15·8	$C_{11}H_{13}O_3Cl$	57·8	5·7	15·5
3-Bromo-4-ethoxy …………	59	48·4	4·7	29·3	$C_{11}H_{13}O_3Br$	48·4	4·8	29·3
3-Chloro-4-*iso*propoxy ……	48	59·2	6·1	14·9	$C_{12}H_{15}O_3Cl$	59·4	6·2	14·6
3-Bromo-4-*iso*propoxy ……	50	50·2	5·1	27·9	$C_{12}H_{15}O_3Br$	50·2	5·2	27·9
3-Nitro-4-*iso*propoxy ………	52	57·2	6·0	5·8	$C_{12}H_{15}O_5N$	56·9	5·9	5·5
4-Allyloxy-3-chloro …………	63	59·8	5·8	15·0	$C_{12}H_{13}O_3Cl$	59·9	6·1	14·8
4-Benzyloxy-3-chloro ………	66	65·7	5·2	12·3	$C_{16}H_{15}O_3Cl$	66·1	5·2	12·2
3-Bromo-5-methyl …………	27	48·9	4·5	32·8	$C_{10}H_{11}O_2Br$	49·3	4·5	32·9

3 : 4 : 5-Trimethoxybenzoic acid, m. p. 168° (cf. *Org. Synth.*, Coll. Vol. I, 1st edn., 537), gave an ethyl ester, m. p. 56°.

3-*Bromo*-5-*methylbenzoic acid.* Two routes to this acid were investigated : one from 4-bromo-2-methylacetanilide, the other, which gave a better overall yield, from 4-methyl-2-nitroaniline. The aniline was brominated in acetic acid to give 2-bromo-4-methyl-6-nitroaniline, m. p. 66°, in 96% yield; diazotisation and deamination gave 3-bromo-5-nitrotoluene, m. p. 82°; reduction with freshly etched iron powder and concentrated hydrochloric acid in 50% aqueous alcohol then gave 3-bromo-5-methylaniline as the hydrochloride in 100% yield. A suspension of this hydrochloride (15 g.) in a mixture of concentrated hydrochloric acid (15 ml.) and water (100 ml.) at 0° was diazotised (5 g. of sodium nitrite in 20 ml. of water) and then neutralised carefully with sodium carbonate; this solution was added slowly with vigorous stirring to an ice-cold solution of potassium cuprocyanide [from cuprous cyanide (8 g.) in a solution of potassium cyanide (18 g. in 60 ml. of water)] covered with a layer of benzene (100 ml.). The solution was stirred for 30 min. at 0—5°, then for 2 hr. at room temperature, and warmed to 55°. The preparation was completed by steam-distillation, and the *nitrile*, after two crystallisations from carbon tetrachloride, was obtained as pale yellow prisms, m. p. 62° (Found : C, 49·5; H, 2·9; N, 7·2; Br, 40·5. C_8H_6NBr requires C, 50·0; H, 2·9; N, 7·1; Br, 40·8%). Hydrolysis of the nitrile with 60% sulphuric acid (90 min.) gave a theoretical yield of 3-bromo-5-methylbenzoic acid, which crystallised from alcohol as colourless prisms, m. p. 177°. Ethyl 3-bromo-5-methylbenzoate was obtained from alcohol as small colourless prisms, m. p. 27°.

Grants to the Department from The Distillers Company Limited and from Imperial Chemical Industries Limited are gratefully acknowledged. One of the authors (J. R.) is indebted to the University College of Hull for a Research Studentship.

THE UNIVERSITY OF HULL.

[*Received, March 7th*, 1955.]