24. *The Cumulative Effects of Substituents on the Alkaline Hydrolysis of Benzoic Esters.*

By J. F. J. DIPPY, B. D. HAWKINS, and B. V. SMITH.

The rates of alkaline hydrolysis of 2-methoxyethyl esters of the mononitro- and dinitro-benzoic acids in 9 : 1 w/w 2-methoxyethanol–water have been determined for the purpose of testing additivity relationships. The steric and the mesomeric interactions of the groups in the esters and corresponding acids are discussed and compared with group interactions in dichloro- and dimethoxy-benzoic systems previously studied. Regularities in cumulative effects are few, and only partial support for the additivity principle is forthcoming from systems in which it might be expected to apply.

HAMMETT'S equation, as originally proposed,[1] was applicable only to *meta*- and *para*-substituted aromatic compounds. Steric effects in *ortho*-substituted compounds are held to be mainly responsible for the failure of the simple relation here, and departures from additivity in disubstituted compounds will be determined partly by such steric effects. Jaffé,[2] in reviewing the relatively scanty data available for disubstituted systems, concludes that the equation $\log (k/k_0) = \rho\Sigma\sigma$ is generally a valid expression provided that serious steric interaction is absent, and to gain a better understanding of the behaviour of disubstituted compounds in this context the present work was undertaken.

One of the earliest and most satisfactory correlations attempted by Hammett was that between the rates of hydrolysis of benzoic esters and the acid strengths of the corresponding acids. The substituent constant, σ, is actually defined as $\log K/K_u$ when K and K_u represent respectively the dissociation constants of the substituted acid and parent benzoic acid in water at 25°. However, the more the system under consideration departs from the benzoic acid pattern, the greater is the likelihood of disturbance in following the original Hammett relation. Thus for phenols and amines it was recognised that σ-values derived from benzoic acid might be inappropriate, and " exalted " values of σ were needed for certain groups, these new values taking account of the different mesomeric interaction; this view, originally due to Hammett, has been re-stated by Jaffé [2] and Taft.[3] The view of van Bekkum, Verkade, and Wepster,[4] however, is that a range of values for σ is to be expected, owing to widely variable mesomeric interactions. In disubstituted compounds these reservations might apply in still greater measure because of the possibility of modified mesomeric interactions between the substituents themselves, apart from any multiplication of steric interactions. In such systems, therefore, Jaffé's equation will be valid provided only that these additional interactions are absent or insignificant (notably in the 3,5-disubstituted compounds).

It is noteworthy that Shorter and Stubbs [5] concluded that the deviations from additivity in the strengths of 3,5-disubstituted benzoic acids were negligible, whereas Dippy and Hughes [6] using their more accurate results for acid strengths have since provided evidence both for and against this generalisation. Steric interactions affect the remaining disubstituted benzoic acids, and are of two kinds, namely, where the substituents are adjacent (i) to the reacting group, and (ii) to each other but remote from the functional group, *i.e.*, 3,4-disubstitution. Examination of the acid strengths mentioned above shows that both types of steric effect produce deviations from additivity.

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[1] Hammett, *J. Amer. Chem. Soc.*, 1937, **59**, 96; *Trans. Faraday Soc.*, 1938, **34**, 156; " Physical Organic Chemistry," McGraw-Hill Co., New York, 1940, pp. 184 ff.

[2] Jaffé, *Chem. Rev.*, 1953, **53**, 191.

[3] Taft in " Steric Effects in Organic Chemistry," ed. M. S. Newman, Wiley and Sons, New York, 1956, p. 576 ff., and references there cited.

[4] van Bekkum, Verkade, and Wepster, *Rec. Trav. chim.*, 1959, **78**, 815.

[5] Shorter and Stubbs, *J.*, 1949, 1181.

[6] Dippy and Hughes, *Tetrahedron*, 1963, **19**, 1527.

The cumulative effect of substituents on rate processes has been examined for relatively few cases. One of the first examinations was performed by Blakey, McCombie, and Scarborough[7a] and concerned the saponification of ethyl esters of disubstituted benzoic acids; an analysis of their results shows that additivity is obtained in few cases. Jones *et al.*[7b] later claimed that additivity is observed in the chlorination of disubstituted phenolic ethers, and found[7c] that the rates of hydrolysis of ethyl 3,4- and 3,5-disubstituted benzoates showed additivity in many cases. More recently, in an examination of the cumulative effect of two chloro-substituents on various processes, Mather and Shorter[8a] concluded that for the hydrolysis of ethyl dichlorobenzoates additivity was obtained, provided that the substituents were not adjacent to each other or to the functional group. More recently, Buckley, Chapman, and Shorter[8b] examined the reaction of dichlorobenzoic acids with diphenyldiazomethane, and observed some small departures.

In order to examine more closely the cumulative effect of nitro-substituents on reactivity, the saponification rates of 2-methoxyethyl dinitrobenzoates have now been studied and selected monosubstituted benzoates have been included for comparison. The 2-methoxyethyl esters were chosen because of their solubilities, and the hydrolysing medium was 9 : 1 w/w 2-methoxyethanol–water.

The saponification rates have been correlated with acid strength data for water[9] and for 4 : 1 w/w 2-methoxyethanol–water.[10] Strengths of dichloro- and dimethoxy-benzoic acid in the latter medium are also reported here, enabling the hydrolysis-rates of Jones *et al.* to be incorporated in the present review.

EXPERIMENTAL

Acids.—2,3-Dinitrobenzoic acid was prepared by adding 6-nitro-*o*-toluidine (15 g.) to a mixture of glacial acetic acid (400 ml.) and 30% aqueous hydrogen peroxide (72 ml.) with shaking and stirring.[11] After 2 days the amine had all reacted and yellow crystals of 2-nitroso-3-nitrotoluene, m. p. 126—126·5° (lit.,[12] 127°), were deposited. A further crop was obtained from the filtrate by adding hydrogen peroxide and storage. The combined materials (yield 80—90%) were oxidised in one step to 2,3-dinitrobenzoic acid (70% yield), m. p. 206—207·5° (lit.,[13] 203°) by the method described by Langley[14a] for 2,5-dinitrobenzoic acid. The final purification of this (and the other dinitrobenzoic acids) was by crystallisation from aqueous alcohol.

Oxidation of 2,4-dinitrotoluene either with 1 : 1 fuming nitric acid–glacial acetic acid or with potassium dichromate–concentrated sulphuric acid gave 2,4-dinitrobenzoic acid (yields *ca.* 25% and *ca.* 65%, respectively). This method was also used for preparing 2-6-dinitrobenzoic acid (m. p. 202—203°) from 2,6-dinitrotoluene (yield *ca.* 50%). The use of nitric acid or potassium permanganate as oxidant gave poor yields of discoloured acid.

Attempted oxidation of 4-nitro-*o*-toluidine and 2-nitro-*p*-toluidine by the peracetic acid method gave yellow solids (m. p. 192—194° and 232—234°, respectively). Repeated recrystallisation of the latter compound from benzene afforded orange-yellow rhombs m. p. 236—238°, formulated as *4,4′-dimethyl-2,2′-dinitroazoxybenzene* (Found: C, 52·9; H, 3·6; N, 17·5. $C_{14}H_{12}N_4O_5$ requires C, 53·1; H, 3·8; N, 17·7%). The former compound is almost certainly that obtained by Meisenheimer and Hesse[12] on alkaline reduction of 2,5-dinitrotoluene. The amines were satisfactorily oxidised by Langley's persulphate method[14] (with improved yields), very efficient stirring being an important requirement. The intermediate 4-nitroso-3-nitrotoluene (75% yield) gave in the second step a *ca.* 85% yield of 3,4-dinitrobenzoic acid, m. p. 165—166·5° (lit.,[15] 165°). 2,5-Dinitrobenzoic acid, prepared in this way, had m. p. 177—179° (lit.,[14b] 177°).

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[7] (*a*) Blakey, McCombie, and Scarborough, *J.*, 1926, 2867; (*b*) Jones *et al.*, references cited in 7 (*c*); (*c*) Jones and Robinson, *J.*, 1955, 3845.

[8] (*a*) Mather and Shorter, *J.*, 1961, 4744; (*b*) Buckley, Chapman, and Shorter, *J.*, 1963, 178.

[9] Dippy, Hughes, and Laxton, *J.*, 1956, 2995.

[10] Simon, Lyssy, Mörikofer, and Heilbronner, " Zusammenstellung von Scheinbaren Dissoziationkonstanten in Lösungsmittelnsystem Methylcellosolve–Wasser," Juris-Verlag, Zürich, 1959.

[11] Cf. Holmes and Bayer, *J. Amer. Chem. Soc.*, 1960, **82**, 3454.

[12] Meisenheimer and Hesse, *Ber.*, 1919, **52**, 1173.

[13] Sirks, *Rec. Trav. chim.*, 1908, **27**, 221.

[14] Langley, (*a*) *Org. Synth.*, 1942, **22**, 45; (*b*) *J. Amer. Chem. Soc.*, 1948, **70**, 1633.

[15] Laxton, Thesis, London, 1954.

Esters.—The 2-methoxyethyl esters were prepared by heating the benzoic acid with a large excess of Methylcellosolve and a catalytic amount of either concentrated sulphuric acid or boron trifluoride–ether complex. In some cases an excess of benzene was also added, and water formed in the reaction was removed as the water–benzene azeotrope or as the Methylcellosolve–water azeotrope.[16] The residue was added to water and extracted three times with ethyl acetate, and the extracts were washed with aqueous sodium carbonate and then water. The product, after removal of the solvent *in vacuo* from the dried extract, was recovered by distillation or crystallisation. Yields were usually 50—85%, and further purification was effected with the aid of Spence's grade O alumina. The ester of 2,6-dinitrobenzoic acid, however, was prepared only with difficulty, and the successful method was to treat 2,6-dinitrobenzoyl chloride, in dry benzene, with a large excess of cooled Methylcellosolve, followed by storage. The ester was recovered in the normal manner and crystallised from benzene–light petroleum (b. p. 40—60°) in plates or needles.

The m. p. or b. p., yields of purified materials, and analyses of the 2-methoxyethyl esters are summarised in Table 1.

Solvents.—Methylcellosolve (2-methoxyethanol) (B.D.H.) was heated under reflux for 4 hr. with " AnalaR " anhydrous potassium carbonate. The carbonate was then removed, sodium (3 g./l.) added, and the whole heated for a further 2 hr. The Methylcellosolve was then distilled through a lagged Vigreux column and the fraction of b. p. 124·0°/760 mm.[16] was set aside for storage under nitrogen, out of contact with air. This fraction was used for the preparation of 9 : 1 w/w 2-methoxyethanol–water, which was made up in large batches. Ethanol was purified by the phthalate method and was stored under nitrogen; the density of the product was determined, and the calculated amount of water added to produce the correct solvent composition.

TABLE 1.

Substituted 2-methoxyethyl benzoates.

Substituent	B. p./mm. and/or m. p.	Yield (%)	Calc. (%)			Formula	Found (%)		
			C	H	N		C	H	N
H	67°/0·10 *	85	66·65	6·7	—	$C_{10}H_{12}O_3$	66·35	7·1	—
3-CH_3	76°/0·10	83	68·0	7·3	—	$C_{11}H_{14}O_3$	68·2	7·7	—
4-CH_3	110°/0·12	85	68·0	7·3	—	,,	67·7	7·4	—
4-OCH_3	101°/0·15	85	62·8	6·7	—	$C_{11}H_{14}O_4$	62·8	7·1	—
4-Br	99°/0·26	92	46·3	4·25	—	$C_{10}H_{11}BrO_3$	46·7	4·46	—
2-NO_2	140°/0·70,† m. p. 27°	35 ‡	53·3	4·9	6·2	$C_{10}H_{11}NO_5$	53·3	4·9	6·3
3-NO_2	118°/0·15	69	53·3	4·9	6·2	,,	53·4	5·0	6·6
4-NO_2	m. p. 51—52° §	56	53·3	4·9	6·2	,,	53·5	4·6	6·1
2,3-$(NO_2)_2$	92·5—93·5	69	44·5	3·7	10·4	$C_{10}H_{10}N_2O_7$	44·9	4·1	10·3
2,4-$(NO_2)_2$	57—58	50	44·5	3·7	10·4	,,	44·7	3·8	10·9
2,5-$(NO_2)_2$	105—106	67	44·5	3·7	10·4	,,	44·4	3·2	10·9
2,6-$(NO_2)_2$	105·5—106	—	44·5	3·7	10·4	,,	44·7	3·9	10·5
3,4-$(NO_2)_2$	42·5—43·5	66	44·5	3·7	10·4	,,	44·6	3·8	10·4
3,5-$(NO_2)_2$	51—52	82	44·5	3·7	10·4	,,	44·7	3·5	10·5

* Prep. described by Murakami, *Chem. High Polymers* (*Japan*), 1951, **8**, 85, without physical constants. † Lowe, *J. Amer. Chem. Soc.*, 1952, **74**, 841, gives b. p. 118—119°/0·07 mm., but no m. p. ‡ Low yield owing to losses in crystallisation. § Dermer and Durr, *J. Amer. Chem. Soc.*, 1954, **76**, 912, give m. p. 49°.

Kinetic Measurements.—Preliminary work on the hydrolysis of selected ethyl esters in 17 : 3 w/w ethanol–water indicated a second-order reaction and showed agreement with previous work. The ethyl esters of dinitro-acids, however, were too sparingly soluble in this ethanolic medium at 0° (the estimated temperature for convenient reaction rate); moreover, strong colour reactions were given by these solutions with alkali, and similar colours were obtained with aqueous acetone.

2-Methoxyethanol showed none of these disadvantages and it was established that over the period of time and under the standard reaction conditions used for kinetic runs this solvent suffered no significant constitutional change. It was also advantageous that a solvent of similar composition was chosen by Simon, *et al.*[10] for the pK_a measurements of a wide range of organic acids. It was found that the hydrolysis rate of ethyl esters in 2-methoxyethanol–water were

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[16] Weissberger, " Techniques of Organic Chemistry," Interscience Publ., Inc., New York, Vol. VII, p. 249.

vitiated by *trans*-esterification and consequently the 2-methoxyethyl esters were chosen for use in this solvent, whereupon no drift in k_2 was observed. Runs were followed acidimetrically, essentially by the procedure of Evans, Gordon, and Watson [17] with Bromothymol Blue as indicator, although end-points were improved by performing titrations in an atmosphere of nitrogen. On quenching the reaction sample in acid, the two esters that displayed noticeable nucleophilic loss of a nitro-group gave rise to traces of nitrous acid which interfered with the titration. However, this interference was overcome by means of an initial prolonged bubbling of nitrogen through the solution before the titration.

Thermostat-baths were maintained constant to ±0·1°. Solutions of alkali in Methylcellosolve were best made up by mixing aqueous alkali with Methylcellosolve to give the correct composition, followed by storage in the dark.

The rate constants (l. mole^{-1} sec.$^{-1}$), calculated from standard formulæ, are shown in the Tables and represent the mean of at least three determinations. Specimen runs are shown in Table 2. Additional results for the alkaline hydrolysis of certain ethyl dichloro- and dimethoxy-benzoates in 84·6% w/w ethanol–water are listed in Table 3.

TABLE 2.

(*a*) Hydrolysis of 2-methoxyethyl 3-nitrobenzoate at 25·0° in 9 : 1 w/w 2-methoxyethanol–water.

Initial [ester] = 0·0447M. Initial [alkali] = *ca.* 0·05M.

Titres are expressed in ml. of 0·0335N-NaOH; T_t = excess of alkali in reaction solution, in the same units.

Time (min.)	Titre	T_t	T_t-T_∞	10^3k_2 (l. mole^{-1} sec.$^{-1}$)
0	12·89	16·39	12·43	—
1	14·11	15·17	11·21	32·7
2	15·19	14·09	10·13	33·6
4	16·71	12·57	8·61	31·3
7	18·48	10·80	6·84	32·3
10	19·74	9·54	5·58	32·7
15·5	21·30	7·98	4·02	33·2
30	23·19	6·09	2·13	32·4
∞	25·32	3·96	—	—
			Average	32·7

(*b*) Hydrolysis of 2-methoxyethyl 2,4-dinitrobenzoate at 0·0° in 9 : 1 w/w 2-methoxyethanol–water.

Initial [ester] = 0·0418M. Initial [alkali] = *ca.* 0·05M.

Titres are expressed in ml. of 0·0335N-NaOH; T_t = excess of alkali in the reaction solution, in the same units.

Time (min.)	Titre	T_t	T_t-T_∞	10^3k_2 (l. mole^{-1} sec.$^{-1}$)
0	12·00	16·98	10·95	—
2	13·60	15·38	9·35	24·1
4	14·80	14·17	8·14	23·7
7	16·31	12·67	6·64	24·2
11	17·67	11·31	5·28	24·0
16	18·92	10·06	4·03	24·4
22	19·99	8·99	2·96	25·0
30	20·78	8·20	2·17	24·3
∞	22·95	6·03	—	—
			Average	24·2

TABLE 3.

Hydrolysis of selected disubstituted ethyl benzoates in 84·6% w/w ethanol–water at 25° (k_2 in l. mole^{-1} sec.$^{-1}$).

Subst.	H	2,3-(OMe)$_2$	3,5-(OMe)$_2$	2,4-Cl$_2$	2,4-Cl$_2$
10^3k_2: this work ...	0·720	1·07	1·11	7·91	16·97
lit.	0·607; [7c] 0·646 [8a]	—	1·04 [7c]	7·29 [8a]	14·6; [7c] 15·7 [8a]

Determination of Acid Strengths.—The strengths of selected mono- and di-substituted benzoic acids were measured in 4 : 1 2-methoxyethanol–water by Simon's micro-pH titration method.[10] A water-jacketed constant-temperature cell was used, details of which are available elsewhere.[18] The calomel–glass electrode system was used in conjunction with an E.I.L. pH meter, model 23A. Regular standardisation of the electrode system was carried out, with 0·05M-potassium hydrogen phthalate as standard (pH_{25} = 4·005).

The acid (*ca.* 10^{-3}M) was titrated with alkali in a nitrogen atmosphere. Both the acid and alkali were made up in 4 : 1 w/w Methylcellosolve/conductivity-water. The pK_a values were calculated from the theoretical half-neutralisation point, or from the Henderson equation by averaging the values obtained from the linear portion of the pH-titration curve. Results are collected in Table 4; each pK_a value is the mean of at least three determinations.

[17] Evans, Gordon, and Watson, *J.*, 1937, 1430.

[18] Smith, Thesis, London, 1959.

TABLE 4.

pK_a values of benzoic acids in 4 : 1 w/w 2-methoxyethanol–water at 25°.

Subst.	10^3[acid] (M)	pK_a	pK_a (ref. 10)	Subst.	10^3[acid] (M)	pK_a
H	3·784	6·64	6·63	2,3-$(OMe)_2$	4·105	6·52
2,4-Cl_2 ...	4·108	5·24		3,4-$(OMe)_2$	3·896	6·92
2,5-Cl_2 ...	4·154	5·07		3,5-$(OMe)_2$	4·082	6·53
3,4-Cl_2 ...	3·891	5·57	5·56			

Nucleophilic Aromatic Substitutions in 2-Methoxyethyl Dinitrobenzoates.—The infinity titres of the saponification reactions of certain esters used in this investigation were vitiated by nucleophilic replacement of the nitro-group. This was demonstrated by the isolation of the appropriate products, and identification of the nitrite ion. The rate varied with the orientation of substitution of the two nitro-groups, but was never such as to affect the saponification rates significantly if suitable temperatures were chosen. Substitution occurred with greatest ease for 2,5- and 3,4-dinitro-esters, replacement at the strongly activated 2- or 4-position taking place.

2-Methoxyethyl 3,4-dinitrobenzoate with aqueous sodium hydroxide, sodium ethoxide, and sodium 2-methoxyethoxide gave respectively 4-hydroxy- (m. p. 180°; lit.,[19] 182—183°), 4-ethoxy-, (m. p. 199—201°; lit.,[20] 201°), and 4-2′*methoxyethoxy*-3-*nitrobenzoic acid*, cream-coloured needles (from aqueous ethanol), m. p. 135—136° (Found: C, 50·3; H, 4·6; N, 5·8. $C_{10}H_{11}NO_6$ requires C, 49·8; H, 4·6; N, 5·8%). The *ethyl ester* of the last acid crystallised from ethanol in rods m. p. 76—78° (Found: C, 53·8; H, 5·4; N, 5·1. $C_{12}H_{15}NO_6$ requires C, 53·5; H, 5·6; N, 5·2%). A ready nucleophilic displacement of the 4-nitro-group in 3,4-dinitrobenzoic acid has been found,[19] and a similar loss of halogen in 4-halogeno-3-nitrobenzoic acids [21a] and esters [21b] is well established.

With the ester of 2,5-dinitrobenzoic acid, similar replacements occurred, though less readily, giving 2-hydroxy-, m. p. (and mixed m. p.) 226—227° (lit.,[22] 228°), and 2-ethoxy-5-nitrobenzoic acid, m. p. 159—161° (lit.,[23] 163°), with sodium hydroxide and sodium ethoxide, respectively. Our observations do not support those of Langley [14b] who claimed nucleophilic replacement of both nitro-groups in 2,5-dinitrobenzoic acid by aqueous alkali, but do accord with the nucleophilic displacement of the 2-halogen in 2-halogeno-5-nitrobenzoic acid [24a] and ester.[24b] Much slower formation of nitrite ion was observed with the esters of 2,3-dinitrobenzoic and 2,6-dinitrobenzoic acid in hot alkaline media. The former ester, with aqueous alkali at 100°, gave 2-hydroxy-3-nitrobenzoic acid monohydrate (m. p. 127°; lit.,[25] 127°). The anhydrous acid had m. p. 145° (lit.,[25] 146°). Replacement of a 2-nitro-group in a range of 2,3-dinitrobenzene derivatives is well known.[26]

DISCUSSION

(*a*) *Nitro- and Dinitro-esters.*—The reaction velocity data (Table 5) when examined in the light of the appropriate σ-constants based on acid strengths, establish with certainty that no rigid additivity rule can be applied. Nevertheless, it is noteworthy that the departures from additivity are nearer to being the same as those reflected in the dissociation constants of corresponding acids where no substituent occupies the 2(or 6)-position. This becomes apparent on inspection of Figs. 1(a) and (b) (see also Tables 6 and 7).

In Fig. 1(a) the pK_a values for nitrobenzoic acids in aqueous solution (Table 6) are plotted against log k_2, for a single temperature, and, for comparison, points representing the 3- and 4-methyl, 4-methoxy-, and 4-bromo-compound are included. Fig. 1(b) makes use of acid strengths in 4 : 1 w/w 2-methoxyethanol–water.

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[19] Goldstein and Voegeli, *Helv. Chim. Acta*, 1943, **26**, 475.

[20] Kliegl and Holle, *Ber.*, 1926, **59**, 907.

[21] (*a*) Davies and Wood, *J.*, 1928, 1129; (*b*) Borsche, *Ber.*, 1921, **54**, 661.

[22] Barany and Pianka, *J.*, 1946, 965.

[23] Chattaway, *J.*, 1926, 2225.

[24] (*a*) Slothouwer, *Rec. Trav. chim.*, 1914, **33**, 334; (*b*) Turner and Le Fèvre, *J.*, 1927, 1117.

[25] Hirve and Meldrum, *J. Indian Chem. Soc.*, 1928, **5**, 95.

[26] Holleman and Ter Weel, *Rec. Trav. chim.*, 1916, **35**, 46; Holleman and van Haeften, *ibid.*, 1921, **40**, 94; Borsche, *Ber.*, 1923, **56**, 1501; Kenner and Parkin, *J.*, 1920, 856; Blanksma, *Chem. Weekblad*, 1908, **5**, 789 (*Chem. Zentr.*, 1908, II, 1826).

TABLE 5.

Rate constants (k_2 in l. mole^{-1} sec.$^{-1}$) for alkaline hydrolysis of 2-methoxyethyl substituted benzoates in 9 : 1 w/w 2-methoxyethanol–water.

Subst.	0·0°	15°	25°	40°	50°	$10^3K_{\mathrm{H_2O}}$
H			0·471	2·41	5·75	0·063
2-NO$_2$			4·60	20·0	44·8	6·71
3-NO$_2$	2·37	12·78	32·4			0·321
4-NO$_2$	4·02	21·1	52·5			0·376
2,3-(NO$_2$)$_2$	41·1	189	448			14·1
2,4-(NO$_2$)$_2$	25·6	113; 121·1 *	271			37·6
2,5-(NO$_2$)$_2$			375			23·9
2,6-(NO$_2$)$_2$			0·371			72·5
3,4-(NO$_2$)$_2$	154	681	*ca.* 1550			1·52
3,5-(NO$_2$)$_2$	145	678	*ca.* 1500			1·50
3-Me			0·338			0·054
4-Me			0·211			0·042
4-OMe			0·111			0·034
4-Br			2·74			0·107

* This value was found for 15·7°.

TABLE 6.

Deviations from additivity in the acid strengths of dinitrobenzoic acids in water at 25°.

Substituent	2-NO$_2$	3-NO$_2$	4-NO$_2$	2,3-(NO$_2$)$_2$	2,4-(NO$_2$)$_2$	2,5-(NO$_2$)$_2$	2,6-(NO$_2$)$_2$	3,4-(NO$_2$)$_2$	3,5-(NO$_2$)$_2$
pK_a	2·173	3·495	3·425	1·851	1·425	1·622	1·139	2·818	2·824
p$K_{\mathrm{calc.}}$	—	—	—	1·465	1·395	1·465	0·143	2·717	2·787
Deviation (%)	—	—	—	−14·1	−1·1	−5·8	−24·5	−6·7	−2·8

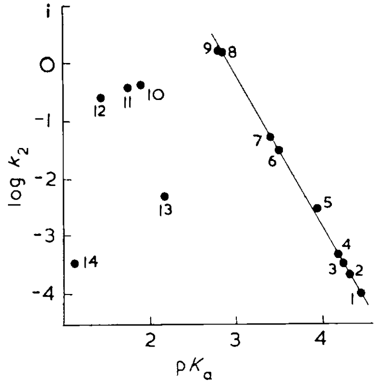

FIG. 1(a).

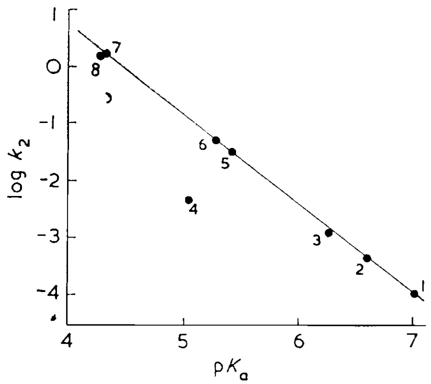

FIG. 1(b).

FIG. 1(a). Plot of the logarithm of the second-order rate constant (k_2 in l. mole^{-1} sec.$^{-1}$) for the alkaline hydrolysis of 2-methoxyethyl benzoates against the logarithm of the acid dissociation constant, in water.

(1) 4-OMe; (2) 4-Me; (3) 3-Me; (4) H; (5) 4-Br; (6) 3-NO$_2$; (7) 4-NO$_2$; (8) 3,5-(NO$_2$)$_2$; (9) 3,4-(NO$_2$)$_2$; (10) 2,3-(NO$_2$)$_2$; (11) 2,5-(NO$_2$)$_2$; (12) 2,4(NO$_2$)$_2$; (13) 2-NO$_2$; (14) 2,6-(NO$_2$)$_2$.

FIG. 1(b). Plot of the logarithm of the second-order rate-constant (k_2 in l. mole^{-1} sec.$^{-1}$) for the alkaline hydrolysis of 2-methoxyethyl benzoates against the logarithm of the acid dissociation constant in 9 : 1 w/w 2-methoxyethanol–water.

(1) 4-Me; (2) H; (3) 4-Br; (4) 2-NO$_2$; (5) 3-NO$_2$; (6) 4-NO$_2$; (7) 3,4-(NO$_2$)$_2$; (8) 3,5-(NO$_2$)$_2$.

The deviations from additivity in the acid strengths of the dinitrobenzoic acids derived by Dippy and Hughes [6] are collected in Table 6. The deviations in the ester-hydrolysis rates, expressed as 100 $(\sigma_{obs} - \sigma_{calc})/\sigma_{calc}$ are set out in Table 7. By using the values of σ derived from acid strengths, ρ was obtained from $\log k_2 - \log k_2{}^\circ = \rho\sigma$, where k_2 and $k_2{}^\circ$ are the second-order rate constants for hydrolysis of substituted and unsubstituted esters, respectively. Esters with a 2-nitro-group give widely scattered values of ρ; the remainder showed less variability and the value for the 3-nitro-group (ρ 2·59) was selected as a standard, by means of which new values of σ_{obs} were derived. The last two columns in Table 7 show σ_{calc}-values for the disubstituted esters, and the percentage deviation from additivity, respectively.

It is possible to discern three types of behaviour in Tables 6 and 7 and Figs. 1(a) and (b).

TABLE 7.

Substituent constants and deviations from additivity in the saponification of 2-methoxyethyl benzoates.

Subst.	$\log k_2$ (25°)	σ from acid strength	$\sigma_{obs.}$ (ρ 2·59)	$\sigma_{calc.}$	Deviation (%)
H	−3·327	—			
2-NO$_2$	−2·337	2·030	0·382	—	
3-NO$_2$	−1·489	0·710	0·710	—	
4-NO$_2$	−1·280	0·778	0·790	—	
2,3-(NO$_2$)$_2$	−0·349	2·352	1·150	1·092	5·0
2,4-(NO$_2$)$_2$	−0·567	2·778	1·066	1·172	−9·0
2,5-(NO$_2$)$_2$	−0·426	2·581	1·120	1·092	2·5
2,6-(NO$_2$)$_2$	−3·431	3·063	−0·040	0·764	−105·2
3,4-(NO$_2$)$_2$	0·190	1·385	1·358	1·500	−9·5
3,5-(NO$_2$)$_2$	0·179	1·379	1·354	1·420	−4·9
3-Me	−3·471	−0·069	−0·056	—	
4-Me	−3·676	−0·170	−0·134	—	
4-OMe	−3·955	−0·268	−0·243	—	
4-Br	−2·562	0·232	0·295	—	

(1) The 3- and 4-nitro- and 3,5-dinitro-acids and esters give linear plots in Figs. 1(a) and (b). Moreover, the deviation calculated for the dinitro-acid is negligible (if deviations of ±5% are considered insignificant). 3,5-Disubstituted systems conform to this pattern in many examples.

(2) The 3,4-dinitro-acid and ester exhibit deviations of −6·7% and −10·5%, respectively. This similarity of behaviour implies a reproducibility of the steric interaction between groups when they are remote from the reaction centre.

(3) The remaining four esters all have a 2-nitro-group. The largest deviation is shown by the 2,6-dinitro-ester, and is undoubtedly associated with the primary steric effect of the two *ortho*-substituents, so inhibiting the attack of a nucleophile on the carbonyl-carbon atom. The deviation from additivity for the acid is much smaller and is consistent with the smaller steric requirement of proton transfer. The other three dinitro-esters exhibit much smaller departures from additivity, although not consistently with those shown by the corresponding acids.

From hydrolyses conducted at three temperatures, the activation energies given in Table 8 were determined, and from the plot of these values against $\log k_{25}$ (Fig. 2) the reasonable linearity of the points representing the 3,4- and the 3,5-disubstituted compounds is noted. For the other two disubstituted esters small departures from linearity are observed. The value of $\log PZ$ for these hydrolyses shows a smaller variation than in analogous reactions, and the influence of the substituent is exhibited mainly in the energy term.

(*b*) *Methoxy- and Dimethoxy-esters.*—For comparison with earlier work selected ethyl dimethoxybenzoates in 84·6% w/w ethanol–water were hydrolysed and the strengths of the corresponding acids were obtained by potentiometric titration in 4 : 1 w/w 2-methoxyethanol–water (values for monomethoxybenzoic acids in this solvent were available [10]).

The results (Table 9) show the deviations from additivity in the acid strengths and the corresponding deviations in the rates of ester hydrolysis, including values calculated from the results of Jones and Robinson.[7c]

The deviations shown by the 2,3-dimethoxy-acid and ester are both large but of opposite sign, pointing to some mutual interaction between the 2- and the 3-methoxyl group which affects both the proton-transfer and saponification processes. The ultraviolet absorption spectrum of 2,3-dimethoxybenzoic acid is very similar to that of 2-methoxybenzoic acid;[27] no appreciable further twisting of the carboxyl group in the disubstituted compound is indicated.

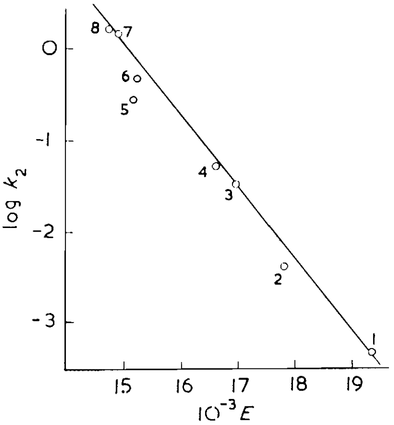

FIG. 2. Plot of the logarithm of the second-order rate constant (k_2 in l. mole^{-1} sec.$^{-1}$) for the alkaline hydrolysis of 2-methoxyethyl benzoates against the energy of activation (E in kcal. mole^{-1}).

(1) H; (2) 2-NO_2; (3) 3-NO_2; (4) 4-NO_2; (5) 2,4-$(NO_2)_2$; (6) 2,3-$(NO_2)_2$; (7) 3,5-$(NO_2)_2$; (8) 3,4-$(NO_2)_2$.

The 3,4-dimethoxy-acid shows exact additivity, although the ester hydrolysis gives a deviation of —15·6%, calculated from the results of Jones and Robinson. The strength of 3,5-dimethoxybenzoic acid, on the other hand, gives a deviation of —28·1%, which recalls the deviation of —32% exhibited by 3,5-dihydroxybenzoic acid (in water) for which no ready explanation was offered.[28] The deviation in rate of ester hydrolysis is less than for the acid, but in the same direction; it is greater than that calculated from the earlier results.

TABLE 8.

Energies of activation (cal. mole^{-1}) for alkaline hydrolysis of 2-methoxyethyl benzoates.

Subst.	H	2-NO_2	3-NO_2	4-NO_2	2,3-$(NO_2)_2$	2,4-$(NO_2)_2$	3,4-$(NO_2)_2$	3,5$(NO_2)_2$
E	19,310	17,740	16,930	16,550	15,260	15,130	14,810	14,920

TABLE 9.

Acid strengths and saponification rates of dimethoxybenzoic acids and esters.

	Acid strengths		Saponification rates	
Substituent	pK_a	Deviation (%)	10^3k_2	Deviation (%)
H	6·63	—	0·713	—
2-OMe	6·76	—	0·647	—
3-OMe	6·55	—	0·805	—
4-OMe	7·00	—	0·133	—
2,3-$(OMe)_2$	6·52	—340	1·083	125
3,4-$(OMe)_2$	6·92	0	0·214	—15·6[7c];
3,5-$(OMe)_2$	6·52$_5$	—28·1	1·115	—4·9[7c]; —20·3

It must be pointed out that whereas the order of strengths of methoxybenzoic acids in water is $m > o > H > p$, the order in 4 : 1 w/w 2-methoxyethanol–water is $m > H >$

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[27] Ungnade, Pickett, Rubin, and Youse, *J. Org. Chem.*, 1951, **16**, 1318.
[28] Dippy, Hughes, and Bray, *J.*, 1959, 1717.

$o > p$.[10] Thus it seems that the heavily solvated carboxyl group of the acid, in water, is twisted out of the plane of the ring to a greater degree than in 2-methoxyethanol–water (cf. Davis and Hetzer [29]).

(*c*) *Chloro- and Dichloro-esters.*—The additivity relations in the dichlorobenzoic acids and esters were recently examined by Mather and Shorter [8a] and by Buckley, Chapman, and Shorter.[8b] In contrast to the dinitro-acids and -esters, deviations from additivity are here usually smaller, a trend confirmed in the present supplementary work which comprises measurements of acid strengths in aqueous Methylcellosolve and saponification rates in aqueous ethanol (see Table 10, which includes results from previous measurements).

TABLE 10.

Deviations from additivity in the acid strengths and saponification rates of dichlorobenzoic acids and esters.

	Deviation (%) in the acid			Deviation (%) in the ester hydrolysis	
Subst.	Ref. 8*a*	Ref. 28	This work	Ref. 8*a*	This work
	(H_2O)	(H_2O)	(80% MCS *)		
2,3-Cl_2	−1·2			−16	
2,4-Cl_2	2·7	2·65	−2·79	3·0	6·43
2,5-Cl_2	0·6	6·38	−0·64	3·0	
2,6-Cl_2	0·8	3·57		—	
3,4-Cl_2	−6·5		−6·14	−9·0	−8·63
3,5-Cl_2	2·6			1·0	

* 4 : 1 Methylcellosolve–water.

With the dichloro-esters the most appreciable deviations occur when the chlorine substituents are adjacent to each other; thus 3,4-dichlorobenzoic acid and ester show deviations that are of comparable magnitude and of the same sign. As suggested by Mather and Shorter the interference of the adjacent chlorine substituents can be minimised only if they adopt a staggered conformation. By contrast no reproducibility is evident in the 2,3-dichlorobenzoic acid and ester series.

(*d*) *Other Substituents.*—The σ-values derived from the hydrolyses of the *para*-substituted benzoic esters included for testing linearity are given in Table 11. It is of interest to compare with these the values for the 4-methoxy, 4-methyl, and 4-bromo-substituents derived from analogous saponifications.[4] Our values for these substituents lie within the range of σ-values, which are derived from variable mesomeric interaction with the functional group, and it appears also that the solvent dependence of σ is appreciable.

TABLE 11.

Values of σ for the alkaline hydrolysis of benzoic esters.

		Substituent		
		4-OMe	4-Me	4-Br
Reaction and solvent	Temp.	σ	σ	σ
$Ar{\cdot}CO_2Me + OH^-$: 56% Me_2CO	25°	−0·213	−0·114	—
$Ar{\cdot}CO_2Et + OH^-$: (*a*) 84·6% EtOH	(i) 25	−0·255	−0·128	—
	(ii) 25	−0·257	−0·127	0·279
(*b*) 87·8% EtOH	30	−0·252	−0·119	0·281
(*c*) 56% Me_2CO	25	−0·188	−0·128	0·312
$Ar{\cdot}CO_2{\cdot}C_{10}H_{19} + OH^-$: MeOH	30	−0·267	−0·157	0·268
$Ar{\cdot}CO_2{\cdot}C_3H_7O + OH^-$: 90% $Me{\cdot}O{\cdot}CH_2{\cdot}CH_2{\cdot}OH$	25	−0·243	−0·134	0·295
$Ar{\cdot}CO_2H + H_2O$	25	−0·268	−0·170	0·232
σ^n (ref. 4)		*	−0·129	0·265

* If all σ values of ref. 4 are used, $\sigma^n = -0{\cdot}175$; if anilines are excluded, $\sigma^n = -0{\cdot}111$.

(*e*) In conclusion it may be said that the kinetic results for alkaline hydrolyses of dinitro-, dimethoxy-, and dichloro-substituted benzoic esters, taken separately, do not lead

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[29] Davis and Hetzer, *J. Res. Nat. Bur. Stand.*, 1958, **60**, 569; *J. Phys. Chem.*, 1957, **61**, 123.

to identical conclusions. Whereas the 3,5-disubstituted compounds show good additivity in the dinitro- and dichloro-series, the dimethoxy-compounds reveal a large deviation. Again, the reproducibility of the steric interaction in 3,4-disubstituted systems is not a feature of the dimethoxy-compound.

These and other irregularities apparent in this review suggest that there is no real basis for a comprehensive relationship governing the influence of two or more substituents on the hydrolysis of benzoic esters.

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