The Effects of Structure and of Ring-size upon Some Properties of Monoand Di-alkoxybenzoic Acids

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The pK_a values of methylenedioxy-, ethylenedioxy-, and trimethylenedioxy-benzoic acid (II; n = 1, 2, and 3; $R = CO_{9}H$) and the rates of alkaline hydrolysis of the corresponding ethyl esters have been determined. Dissociation of the acids (II) varies in the order, n = 1 < n = 2 < n = 3, whereas the order of reactivity for ester hydrolysis is n = 2 < n = 1 < n = 3. The effect of variation in n upon the reactivity of the esters provides further evidence for the operation of an inductive interaction between the oxygen atoms, which is relayed through the methylene chain which links them. For the corresponding carboxylic acids, this inductive interaction appears to have little significance. No additivity in the cumulative effects of the oxygen atoms has been observed.

For aromatic ethers of the type (I), it has already been shown 1 that their properties are influenced by the magnitude of the dihedral angle between the plane of the aromatic ring and that of the oxygen atom's bonds. Furthermore, extension of this study to ethers of the types (II) and (III) provided results which were interpreted ^{2,3} as demonstrating the operation of two superposed effects: (i) the steric inhibition of conjugation between the 4-oxygen atom and the aromatic ring, and (ii) the relaying through the methylene chain of an (electron-attractive) inductive effect due to the 3-oxygen atom.

The reactions whose rates were thus correlated with the structures of (I), (II), and (III) were nuclear bromination of the ethers (R = H) and unimolecular solvolysis



of the chloromethyl derivatives $(R = CH_2Cl)$, respectively. Both of these reactions involve the formation of positively charged transition states which are more strongly stabilised by resonance interactions than are the ground states of the corresponding molecules. It was of interest to ascertain whether the effects which influence the rates of nuclear bromination and of unimolecular solvolvsis are also operative in determining the dissociation of the aromatic carboxylic acids (II; $R = CO_{2}H$) and the rates of alkaline hydrolysis of their ethyl esters. The results could also have some bearing upon the problem of the cumulative effect of substituents upon the rates of reactions.

TABLE 1

Velocity coefficients and Arrhenius parameters for alkaline hydrolysis of the esters in 70% (w/w) ethanol, and pK_a values for the corresponding acids in water containing 5%(v/v) ethanol

Ethyl benzoates										
10 ⁴ k,										
		(l. mole-	¹ sec. ⁻¹)	Ε		Benzoic acids				
	Substituents	25°	35°	(kcal.)	$\log A$	$\mathrm{p}K_{\mathrm{a}}$	σ			
1.	Nil	12.1	26.8	14.5	7.7	4.23^{+}	0.00			
2.	3-MeO	13.6 *	33.7	16.6	9.3	4·09 †	+0.14			
3.	4-MeO	2.76 *	6.67	16.1	$8 \cdot 2$	4·55 †	-0.32			
ŧ.	3,4-(MeO) ₂	4.00	9.53	15.9	$8 \cdot 2$	4.43	-0.20			
5.	3,4-O•CH ₂ O	4.81	12.4	17.3	9.4	4.50	-0.27			
3.	3,4-0·[CH ₂] ₂ ·O	3.50	9.14	17.5	9.4	4.35	-0.15			
7.	3,4-O•[CH ₂] ₃ •O	6.89	$17 \cdot 2$	16.7	9.1	4.23	0.00			
* Velocity ratios (ksubst./kunsubst.): 3-MeO, 1.12; 4-MeO,										
	0.228. Jones an	nd Robi	nson 4	give: 3	B-MeO,	1.33;	4-MeO,			
0.219. † pK _a values in water (Jones and Speakman ⁵): nil,										
	4.93 3-MeO 4.11 4-MeO 4.59									

TABLE 2

Hammett substituent constants, and deviations from additivity in the alkaline hydrolysis of the esters, and the dissociation of the acids

	Ethyl benzoates			Benzoic acids				
Substituents	$\sigma_{obs.}$		% dov	n K	pK_a	% dov		
Nil	(p = 2.01)	Ucalc.	uev.	PA:02	(carc.)	uev.		
3-MeO	+0.025			4.09				
4-MeO	0.32			4.55				
3,4-(MeO) ₂	-0.24	-0.295	-19	4.43	4.41	+11		
3,4-O·CH ₂ ·O	-0.20	-0.295	-32	4.50	4.41	+50		
3,4-O•[CH ₂] ₂ •O	-0.522	-0.295	9	4.35	4.41	-33		
3,4-O·[CH ₂] ₃ ·O	-0.15	-0.292	-59	4.23	4.41	-100		
	% deviation =			% deviation =				
	$100(\sigma_{ m obs.}-\sigma_{ m calc.})$) $100(pK_{calc.} - pK_{obs.})$				
	$\sigma_{\rm calc.}$			$pK_{benzoic} - pK_{calc.})$				
	$\sigma_{ m calc.} = \Sigma \sigma_{ m obs.}$			$pK_{calc.} = pK_{a}(3-MeO) +$				
$pK_a(4-MeO) - pK_a(benz$					penzoic).			

Tables 1 and 2 contain the results. The plots in the Figure are of $\log k_2$ for the saponification of the esters at 25° versus the σ -values derived from the dissociation constants of the acids. Line A (r = 0.97) correlates satisfactorily the data for compounds 1-4 in Table 1;

- ³ G. Baddeley and M. A. Vickars, J. Chem. Soc., 1963, 765.
- ⁴ B. Jones and J. Robinson, J. Chem. Soc., 1955, 3845.
 ⁵ B. Jones and J. C. Speakman, J. Chem. Soc., 1944, 19.

¹ G. Baddeley, N. H. P. Smith, and M. A. Vickars, J. Chem. Soc., 1956, 2455.
 ² G. Baddeley and N. H. P. Smith, J. Chem. Soc., 1961, 2516.

line B correlates the results of Dippy, Hawkins, and Smith,⁶ the σ -values here being appropriate to the solvent 4:1 (w/w) 2-methoxyethanol-water. Allowing for the difference in solvent compositions, and their relative effects on K_a values, there is fair agreement between lines A and B. The results for the heterocyclic compounds (nos. 5—7) show significant divergence from the line A.



Plot of log k_2 for saponification of the esters at 25° against the σ values derived from the dissociation constants of the acids

O Results of Dippy, Hawkins, and Smith (ref. 6)

• Present results; the numbers correspond to those of the compounds in Table 1

The values of pK_a and of $k_{\text{subst.}}/k_{\text{unsubst.}}$ for the substituents H, 3-, and 4-MeO are in reasonable agreement with those obtained by other workers.^{4,5}

Using the values of σ obtained from the dissociation constants of the acids, the value of ρ was calculated for the alkaline hydrolysis of each of the corresponding esters. Of these values, that for 4-MeO ($\rho = 2.01$) was chosen as a standard (since it was close to the value reported by van Bekkum, Verkade, and Wepster⁷), and using it, a new set of $\sigma_{obs.}$ was calculated (cf. Dippy, Hawkins, and Smith⁶). The deviations from additivity of the effects of the substituents in the esters were derived using the expression, $100(\sigma_{obs.} - \sigma_{calc.})/\sigma_{calc.}$; also, the deviations for the corresponding acids were obtained by Dippy and Hughes's method.⁸

These data are in Table 2. Of the disubstituted esters recorded in this Table, only the 3,4-dimethoxy-case has been reported previously; in agreement with Dippy,⁶ the deviation in the rate of ester hydrolysis is in the same direction and of the same magnitude, but in contrast to Dippy, the dissociation of the acid shows a deviation of

⁷ H. van Bekkum, P. E. Verkade, and B. M. Wepster, *Rec. Trav. chim.*, 1959, **78**, 815.

+11% . The heterocyclic compounds all show significant deviations from additivity.

The data in Table 1 show the following. (i) The introduction of a 3-MeO group produces a greater change in the dissociation of the acid than it does upon the rate of ester hydrolysis. (ii) A 3-MeO group increases the dissociation of 4-methoxybenzoic acid to a slightly lesser extent than it does benzoic acid, whereas in hydrolysis it increases the reactivity of ethyl 4-methoxybenzoate to a greater extent than that of ethyl benzoate. (iiii) Incorporation of the two oxygen atoms in a five-membered ring decreases the dissociation of the acid (II; n = 1; $R = CO_2H$) and increases the rate of hydrolysis of the ester (II; n = 1; $R = CO_2Et$), relative to the 3,4dimethoxy-analogues (IV; $R = CO_2H$ and CO_2Et , respectively). (iv) Variation in the size of the heterocyclic ring produces divergent effects: the acid strength increases in the order n = 1 < n = 2 < n = 3; the order for the increase in the rate of ester hydrolysis is n = 2 < n = 1 < n = 3.

It is clear that changes in structure do not bring about exactly parallel changes in the properties of the acids and of their esters, even though the same modes of electronic interaction operate in the molecules of each of these types of compound. The effect of variation of ring-size upon the rate of ester hydrolysis provides additional evidence for the operation of an inductive interaction between the oxygen atoms through the chain of methylene groups (cf. refs. 2 and 3). Because the curtailment of conjugation of the 4-oxygen atom with the benzene ring will decrease the stabilisation of the ground state of the ester more than that of the transition state (V) for hydrolysis, the variation in size of ring alone upon the rate should provide the sequence, n = 1 < n =2 < n = 3. In isolation, the inductive electron-withdrawal by the 3-oxygen atom, which opposes the electromeric release of electrons by the 4-oxygen atom (thereby stabilising the ester relative to the transition state), and which decreases rapidly as n varies 1 to 2 to 3, should give the reactivity sequence, $n = 1 \gg n = 2 > n = 3$. The superposition of these two effects gives the observed sequence for the ester hydrolysis [see (*iv*) above].

The observed variations in the dissociation of the acids (II; n = 1, 2, and 3; $R = CO_2H$) with ring-size may be explained solely in terms of the conformational effects of the heterocyclic rings.

If the inductive interaction through the methylene groups were to have any significance in determining the dissociation of the acids, then its operation should make compound 5 a stronger acid than compound 4. As this is not observed for the acids, yet for the corresponding esters, the reactivities towards alkaline hydrolysis are in the sequence compound 5 > compound 4, it would appear that the transmission of the electron-attraction of the 3-oxygen atom through the chain of methylene groups has the nature of a time-dependent (inductomeric) effect.

⁸ J. F. J. Dippy and S. C. R. Hughes, *Tetrahedron*, 1963, 19, 1527.

⁶ J. F. J. Dippy, B. D. Hawkins, and B. V. Smith, J. Chem. Soc., 1964, 154.

The enhanced effect upon the rate of hydrolysis produced by the 3-MeO group in ethyl 3,4-dimethoxybenzoate (IV; $R = CO_2Et$), relative to its effect in ethyl 3-methoxybenzoate, may be attributed to steric congestion between the methoxy-groups in (IV). Such congestion may be relieved by rotation of the O-Me groups about the Carom.-O bond so as to adopt conformations in which there is minimal interpenetration of the van der Waals radii of one oxygen atom and the methyl group attached to the other. Should the 4methoxy-group be thus rotated from coplanarity with the benzene ring, the stabilisation of the ester (relative to the corresponding transition state) will be diminished and the hydrolysis reaction accelerated. Molecular models, the dimensions of which include the van der Waals radii of non-bonded atoms, indicate that such steric interaction in the conformation depicted in (VI) (the two O-Me bonds lying in the plane of the benzene ring) cannot be discounted.

The effect previously described 2 as 'built-in solvation', which was invoked to explain the rate-enhancing effect of the 3-methoxy-group upon the unimolecular lysis of the corresponding pure ethyl esters, followed by recrystallisation.

Benzoic acid and 4-methoxybenzoic acid were commercial specimens, and were recrystallised to constant m.p.

3-Methoxybenzoic acid (needles from aqueous ethanol, m.p. $105-106^{\circ}$) was obtained ⁹ by the methylation of 3-hydroxybenzoic acid using dimethyl sulphate in the presence of aqueous sodium hydroxide.

3,4-Dimethoxybenzoic acid. Vanillin was methylated using the method of Barger and Silberschmidt,¹⁰ and the resulting 3,4-dimethoxybenzaldehyde was oxidised with aqueous potassium permanganate ¹¹ to 3,4-dimethoxybenzoic acid. The acid separated from aqueous acetic acid in needles, m.p. 182–182.5° (Found: C, 59.6; H, 5.5. Calc. for $C_9H_{10}O_4$, C, 59.4; H, 5.5%).

3,4-Methylenedioxybenzoic acid, m.p. 229—230°, was obtained as previously described.¹¹

3,4-Ethylenedioxybenzoic acid. 1,4-Dioxatetralin ¹² (23·7 g.) was dissolved in ethylene dichloride (30 ml.) and was treated with a solution in ethylene dichloride (20 ml.) of the complex formed from acetyl chloride (14 g.) and anhydrous aluminium chloride (27 g.). After 5 hr. at room temperature, the mixture was decomposed and the product, 3,4-ethylenedioxyacetophenone, b.p. $158^{\circ}/3.5$ mm. (15·3 g.,

	Ethy	l substituted	benzoates				
			Found (%)			Required (%)	
Substituents	B.p./mm.	$n_{\rm D}(^{\circ}{\rm C})$	С	H	Formula	С	н
Nil	$95 - 97^{\circ}/16$	$1.5077/19^{d}$					
3-MeO	132 - 134/12	1 5146/17 °					
4-MeO	131133/9	1·5266/19 °					
3,4-(MeO),	160/10	1.5364/19					
3,4-Ò·CH,•O	103 - 104 / 0.5		61.8	$5 \cdot 1$	$C_{10}H_{10}O_{4}$	61.9	$5 \cdot 1$
3,4-O·[CH,],O	132/0.6		63.6	5.6	$C_{11}H_{12}O_4$	63.5	$5 \cdot 8$
3,4-O·[CH ₂] ₃ ·O	128 - 129 / 0.2	1.5398/21	64.7	6.5	$C_{12}H_{14}O_4$	64.8	$6 \cdot 3$
	^a 1.5068 (ref. 14).	^b 1.491 (ref.	15). ° 1·5	245 (ref. 1	6).		

solvolysis of 3,4-dimethoxybenzyl chloride (IV; $R = CH_2Cl$), does not appear to be operative in the hydrolysis of ethyl 3,4-dimethoxybenzoate. (If it were, it would have contributed more to the stabilisation of the ground state and would have therefore *diminished* the rate of hydrolysis.)

The failure of the **3,4**-disubstituted compounds presently studied to exhibit additivity in the effects of the oxygen atoms is doubtless due to the steric, conformational, and electronic factors which have been shown to operate, and to vary with structure. For this reason, these results limit further the concept of additivity of substituents' effects as applied to substituted benzoic acids and their derivatives.

EXPERIMENTAL

Acids.—With the exception of benzoic acid and 4methoxybenzoic acid, the specimens of the acids used for the pK_a determinations were obtained by the alkaline hydro-

⁹ J. B. Cohen and H. W. Dudley, *J. Chem. Soc.*, 1910, 97, 1740.

¹⁰ G. Barger and R. Silberschmidt, J. Chem. Soc., 1928, 2924.
 ¹¹ R. L. Shriner and E. C. Kleiderer, Org. Synth., Coll. Vol. II, p. 538.

¹² L. Gattermann, Annalen, 1907, **357**, 373.

49%), was isolated. It solidified in the receiver; upon recrystallisation from benzene-light petroleum (b.p. 60— $80^\circ)$, needles, m.p. $84-85^\circ$, were obtained (Found: C, 67·3; H, 5·7. C₁₀H₁₀O₃ requires C, 67·4; H, 5·6%). [The semicarbazone separated from ethanol in needles, m.p. 203·5-204·5° (Found: 56·2; H, 5·7; N, 17·9. C₁₁H₁₃N₃O₃ requires C, 56·2; H, 5·5; N, 17·9%).]

3,4-Ethylenedioxyacetophenone (6.6 g.) was oxidised with alkaline sodium hypochlorite solution and gave 3,4-ethylenedioxybenzoic acid (5.3 g., 80%), needles (from water), m.p. 138—139° (Found: C, 59.9; H, 4.4. Calc. for $C_9H_8O_4$, C, 60.0; H, 4.4%).

3,4-Trimethylenedioxybenzoic acid. 3,7-Dioxa-1,2-benzocycloheptene ¹³ (30 g.) was acetylated under the Friedel-Crafts conditions above, and afforded 3,4-trimethylenedioxyacetophenone (21.8 g., 57%), b.p. 131-133°/0.6 mm. (Found: C, 68.8; H, 6.0. $C_{11}H_{12}O_3$ requires C, 68.8; H, 6.3%). Its semicarbazone formed needles (from ethanol), m.p. 197-197.5° (Found: C, 58.0; H, 6.0; N, 17.1. $C_{12}H_{15}N_3O_3$ requires C, 57.8; H, 6.0; N, 16.8%). On

¹⁵ T. G. H. Jones and F. B. Smith, J. Chem. Soc., 1928, 68.

¹⁶ Beilstein, ' Handbuch der Organischen Chemie,' vol. 9, 2nd suppl., p. 96.

TABLE 3

¹³ K. Ziegler, A. Lüttringhaus, and K. Wohlgemuth, Annalen, 1937, 528, 162.

¹⁴ Beilstein, 'Handbuch der Organischen Chemie,' vol. 9, 2nd suppl., 1949, p. 88.

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oxidation with alkaline sodium hypochlorite, the above ketone (20 g.) gave 3,4-trimethylenedioxybenzoic acid (17.7 g., 88%), needles (from water), m.p. 148—149° (Found: C, 61.9; H, 4.9%; Equiv., 192. $C_{10}H_{10}O_4$ requires C, 61.7; H, 5.1%; Equiv., 194).

Esters.—With the exception of ethyl benzoate, which was purchased and purified by fractional distillation, all the esters were prepared by reaction of the acid with absolute ethanol in the presence of a small quantity of concentrated sulphuric acid. Their b.p.s, refractive indices, and analytical data are in Table 3.

Determination of the Strengths of Substituted Benzoic Acids by Potentiometric Titration.—Titrations were followed using a Cambridge pH-meter, using glass and calomel electrodes; the meter was standardised at pH 4 and 9 with phthalate and borate buffer solutions. The acids were kept over concentrated sulphuric acid under a vacuum at room temperature. 50-ml. aliquots of solutions (*ca.* 0.003M) of the acids, prepared under nitrogen in deionised water containing 5% (v/v) ethanol, were titrated with carbonatefree potassium hydroxide solution (0.05N). The pH of the solution was recorded after each addition of 0.5 ml. of titrant until near the equivalence point, when readings were taken at 0.05-ml. intervals. Throughout the titration a steady stream of nitrogen gas was passed through the solution, and the titration vessel was suspended in a thermo-

¹⁷ R. P. Linstead, J. A. Elvidge, and M. Whalley, 'A Course in Modern Techniques of Organic Chemistry,' Butterworths, London, 1955, p. 157. stat maintained at $25 \pm 0.5^{\circ}$. The pK_a value was obtained by the graphical determination of the pH at the halfequivalence point.¹⁷ The values of pK_a quoted in Table 1 represent the means of at least five determinations for each acid.

Determination of the Rates of Alkaline Hydrolysis of the Esters.—The method of Evans, Gordon, and Watson 18 was used, with minor modifications. The reaction medium was prepared by mixing absolute ethanol with deionised water to give 70% (w/w) ethanol; the value of d_4^{20} was 0.8676. For the determinations of rate, $[OH^-] = 2[Ester]$, and the second-order velocity coefficients were calculated using the standard formula. The reaction was timed from the point of half-delivery of the first aliquot removed for analysis. Aliquots of the mixture were run into standard hydrochloric acid, and the excess of acid was titrated with standard sodium hydroxide solution, using Bromothymol Blue as indicator in conjunction with an external colour standard. At 35°, the reactions were performed in sealed tubes. In the calculation of the velocity coefficients at this temperature, allowance has been made for the expansion of the solvent. At each temperature, at least three determinations of rate were made, and the individual values of k_{2} for each ester agree to $\pm 2\%$. The thermostat temperatures were accurate to $\pm 0.2^{\circ}$.

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¹⁸ D. P. Evans, J. J. Gordon, and H. B. Watson, J. Chem. Soc., 1937, 1430.