

**1037.** *The Effects of ortho-Substituents on Reactivity. Part I. The Alkaline Hydrolysis of Substituted Ethyl Phenylacetates.*

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Rates of hydrolysis of ethyl phenylacetate and 24 nuclear-substituted derivatives have been measured at 24.8° in aqueous ethanol (85.4% w/w of ethanol). All the *ortho*-substituents examined retard hydrolysis, even the nitro-group which from the *para*-position greatly accelerates it. Measurements at other temperatures show that the low rates are associated with high activation energies, and that the pre-exponential factor of the Arrhenius equation does not vary with substituents beyond the limits of experimental error.

Comparison of the results with those obtained with aqueous acetone (56% w/w) of acetone and with aqueous ethanol of different compositions as solvents reveals that the effects of substituents, and in particular of *ortho*-substituents, are affected by the solvent. It is therefore suggested that an important factor in the retarding influence of *ortho*-substituents in the alkaline hydrolysis of ethyl phenylacetates is steric interference with solvation of the transition state.

THE effects of *meta*- and *para*-substituents on reactions occurring in aromatic side chains have been extensively studied, and the data have been correlated by means of the Hammett and related equations.<sup>1</sup> The success of such equations implies that the effect of each substituent can be represented by a parameter with a characteristic value which holds good for a variety of reactions and equilibria. For only a relatively small number of reactions and equilibria have the effects of an appreciable number of *ortho*-substituents been accurately measured, and although attempts have been made to correlate the data available<sup>2</sup> there is still no method which is generally accepted. Steric and other effects arising from the proximity of the substituents to the reaction centre vary with the reaction as well as with the substituent and so make it impossible to represent the effects of *ortho*-substituents as simply as those of *meta*- and *para*-substituents. Effects peculiar to *ortho*-substituents have often been referred to as "*ortho*-effects," and this term will be used here without implication as to the causes.

The work now reported forms part of a programme aimed at obtaining additional quantitative values for the effects of *ortho*-substituents, and the correlation of the effects with the structure of the reactants and the reaction conditions. We base our work on alkaline ester hydrolysis because its mechanism is well understood and because results for some types of ester were already available.

The alkaline hydrolysis of substituted ethyl benzoates has been widely studied; the effects of *ortho*-substituents were examined by Kindler<sup>3</sup> for hydrolysis in 87.83% w/w ethanol-water at 30°, by Evans, Gordon, and Watson<sup>4</sup> for hydrolysis in 84.8% ethanol-water at 25°, and by Tommila and Hinshelwood<sup>5</sup> for hydrolysis in 56% acetone-water at 25°. The last two groups made further rate measurements at other temperatures, and showed that while *meta*- and *para*-substituents affect the activation energy they cause little or no change in the Arrhenius pre-exponential factor; hydrolyses

<sup>1</sup> Hammett, "Physical Organic Chemistry," McGraw-Hill, New York, 1940, p. 184; Jaffé, *Chem. Rev.*, 1953, **53**, 191; van Bekkum, Verkade, and Wepster, *Rec. Trav. chim.*, 1959, **78**, 815.

<sup>2</sup> (a) Taft, in "Steric Effects in Organic Chemistry," ed. Newman, Wiley, New York, 1956, p. 556; (b) Farthing and Nam, in "Steric Effects in Conjugated Systems," ed. Gray, Butterworths, London, 1958, p. 131.

<sup>3</sup> Kindler, *Annalen*, 1926, **450**, 1; 1927, **452**, 90; 1928, **464**, 278; *Ber.*, 1936, **69**, 2792.

<sup>4</sup> Evans, Gordon, and Watson, *J.*, 1937, 1430.

<sup>5</sup> Tommila and Hinshelwood, *J.*, 1938, 1801; Tommila, *Ann. Acad. Sci. Fennicae*, 1941, **A57**, No. 13; 1942, **A59**, No. 3; *Suomen Kemistilehti*, 1942, **15B**, 10; Tommila, Brehmer, and Elo, *Ann. Acad. Sci. Fennicae*, 1945, AII Chem., No. 16.

of the *ortho*-substituted esters (except *o*-fluoro) were markedly slower than those of the *para*-isomers, and the low rates were associated with low values of the pre-exponential factor, the activation energies for *ortho*- and *para*-isomers being similar. Chapman, Shorter, and Utley<sup>6</sup> recently reported results for the alkaline hydrolysis of methyl *o*-halogenobenzoates in 80% v/v methanol-water, and methyl *o*-alkylbenzoates in this solvent and in 60% v/v dioxan-water. The pre-exponential factor is again low for the *o*-halogeno-esters (except *o*-fluoro), but along the series of alkyl-substituted esters, methyl, ethyl, isopropyl, *t*-butyl, it varies in a complex manner, most remarkably having for the *o*-*t*-butyl-substituted ester in 80% v/v ethanol-water a value within the experimental error the same as for the unsubstituted ester, and in 60% dioxan-water a value considerably higher than that which applies for the unsubstituted ester.

The rates of alkaline hydrolysis of *ortho*-substituted ethyl *trans*-cinnamates in 85.4% ethanol-water<sup>7</sup> are similar to those of the *para*-isomers, and the pre-exponential factor has the same value for *ortho*-substituted as for the unsubstituted and *meta*- and *para*-substituted esters. This simple situation presumably arises from the ethoxycarbonyl group's being held at a considerable distance from any *ortho*-substituent.

In view of the difference between the benzoates and cinnamates in the effects of *ortho*-substituents the effects of substituents on the alkaline hydrolysis of ethyl phenylacetate have been studied. The only previous work on this reaction<sup>3,8</sup> did not include *ortho*-substituted esters. To facilitate comparison with other series of esters, the solvent for the first set of measurements was aqueous ethanol containing 85.4% w/w ethanol, which is the same as was used for ethyl cinnamates and similar to that used by Evans, Gordon, and Watson for ethyl benzoates. While this work was in progress, Dr. R. O. C. Norman kindly made available to us results for hydrolysis of *meta*- and *para*-substituted ethyl phenylacetates in 56% acetone-water,<sup>8,9</sup> and we have measured the rates of hydrolysis of *ortho*-substituted esters in this solvent. We have also made measurements for some esters in 80%, 70%, and 60% ethanol-water.

## RESULTS

The results are recorded in Tables 1—4. The velocity coefficients, *k*, are second-order coefficients in l. mole<sup>-1</sup> sec<sup>-1</sup>.

TABLE 1.

Velocity coefficients (l. mole<sup>-1</sup> sec.<sup>-1</sup>) for the alkaline hydrolysis of ethyl phenylacetates in 85.4% w/w ethanol-water at 24.8°.

Subst.	H	<i>o</i> -F	<i>p</i> -F	<i>o</i> -Cl	<i>m</i> -Cl	<i>p</i> -Cl	<i>o</i> -Br	<i>p</i> -Br	<i>o</i> -I	<i>m</i> -I	<i>p</i> -I	<i>o</i> -NO <sub>2</sub>	<i>m</i> -NO <sub>2</sub>
10 <sup>3</sup> <i>k</i>	9.20	8.20	17.0	4.52	25.0	22.2	4.14	23.9	3.85	24.0	23.2	7.19	70.6
Subst.	<i>p</i> -NO <sub>2</sub>	<i>o</i> -Me	<i>p</i> -Me	<i>o</i> -Bu <sup>t</sup>	<i>p</i> -Bu <sup>t</sup>	<i>o</i> -MeO	<i>m</i> -MeO	<i>p</i> -MeO	<i>p</i> -NH <sub>2</sub>	<i>p</i> -NMe <sub>3</sub> <sup>+</sup>	2,6-Cl <sub>2</sub>	3,4-(MeO) <sub>2</sub>	
10 <sup>3</sup> <i>k</i>	71.5	3.00	7.48	0.489	8.12	1.44	10.3	8.10	4.59	69.5	0.372	10.6	

TABLE 2.

The pre-exponential factor.

Subst.	H	<i>o</i> -Cl	<i>p</i> -Cl	<i>o</i> -I	<i>o</i> -NO <sub>2</sub>	2,6-Cl <sub>2</sub>
10 <sup>3</sup> <i>k</i> (0.0°) .....	0.954		2.51			
10 <sup>3</sup> <i>k</i> (15.0°) .....	4.08					
10 <sup>3</sup> <i>k</i> (24.8°) .....	9.20	4.52	22.2	3.85	7.19	0.372
10 <sup>3</sup> <i>k</i> (35.2°) .....	20.9	10.5		13.5*	17.0	1.56*
log <sub>10</sub> <i>A</i> .....	8.7	8.6	8.8	8.7	8.9	9.2

\* At 40.2°.

<sup>6</sup> Chapman, Shorter, and Utley, *J.*, 1963, 1291.

<sup>7</sup> Brynmor Jones and Watkinson, *J.*, 1958, 4064.

<sup>8</sup> Norman, Radda, Brimacombe, Ralph, and Smith, *J.*, 1961, 3247.

<sup>9</sup> Norman and Ralph, preceding paper.

TABLE 3.

Velocity coefficients (l. mole<sup>-1</sup> sec.<sup>-1</sup>) for the alkaline hydrolysis of ethyl phenylacetates in 56% w/w acetone-water at 25.0°.

Subst.	H	<i>o</i> -F	<i>o</i> -Cl	<i>o</i> -Br	<i>o</i> -I	<i>m</i> -I	<i>o</i> -Me	<i>o</i> -Bu <sup>t</sup>	2,6-Cl <sub>2</sub>
10 <sup>3</sup> <i>k</i> .....	4.39 *	3.23	1.49	1.33	1.16	7.20	1.13	0.150	0.138

\* Norman *et al.*<sup>8,9</sup> give 4.40, 4.48.

TABLE 4.

Velocity coefficients (l. mole<sup>-1</sup> sec.<sup>-1</sup>) for the alkaline hydrolysis of ethyl phenylacetates in 80%, 70%, and 60% w/w ethanol-water at 24.8°.

Subst.	10 <sup>3</sup> <i>k</i>			Subst.	10 <sup>3</sup> <i>k</i>		
	80%	70%	60% EtOH		80%	70%	60% EtOH
H .....	12.2	16.9	21.6	<i>o</i> -NO <sub>2</sub> .....			13.0
<i>o</i> -Cl .....			8.33	<i>m</i> -NO <sub>2</sub> .....			128
<i>p</i> -Cl .....			49.3	<i>p</i> -NO <sub>2</sub> .....	92.0	126	160
<i>o</i> -Br .....			7.63	<i>o</i> -Me .....	3.75	4.86	6.03
<i>o</i> -I .....	4.70	5.74	6.57	<i>p</i> -Me .....	9.95	13.5	17.5
<i>p</i> -I .....	30.0	39.1	47.6	<i>p</i> -Bu <sup>t</sup> .....			17.0

## DISCUSSION

The most striking feature of the results in Table 1 is that all the *ortho*-substituents examined exert a retarding influence on the hydrolysis. This is true even for substituents such as the nitro-group which from the *meta*- and *para*-position strongly accelerate the reaction. Di-*ortho*-substitution has a particularly severe effect; thus, while a single *o*-chloro-substituent reduces the rate by a factor of slightly over 2, a second such substituent causes a further reduction by a factor of more than 12. It has been suggested<sup>10</sup> that the effects of *ortho*- and *para*-substituents transmitted *via* the bonds of the molecule should not differ greatly, so the *ortho*-effects may be roughly assessed by comparison of the hydrolysis rates of isomeric *ortho*- and *para*-substituted esters. Such a comparison is made in Table 5. Certain correlations between the retarding effects of the

TABLE 5.

Ratios ( $k_{ortho}/k_{para}$ ) of velocity coefficients for the alkaline hydrolysis of *ortho*- and *para*-substituted ethyl phenylacetates and ethyl benzoates.

Series	F	Cl	Br	I	NO <sub>2</sub>	Me	Bu <sup>t</sup>	MeO	EtO
Et phenylacetates (85.4% ethanol, 24.8°) .....	0.482	0.204	0.173	0.166	0.101	0.401	0.060	0.178	—
Et phenylacetates (56% acetone, 25°) <sup>8,9*</sup> .....	0.465	0.153	0.132	0.166	0.099	0.357	0.069	—	—
Et benzoates (84.8% ethanol, 25°) <sup>4</sup> .....	1.84	0.520	—	—	0.075	0.274	—	—	—
Et benzoates (56% acetone, 25°) <sup>5</sup> .....	2.07	0.377	0.215	0.134	0.069	0.296	—	—	1.94

\* Also present work.

*ortho*-substituents and their sizes are evident. The  $k_{ortho}/k_{para}$  values for the halogens decrease as the size of the halogen increases. Similarly, the *o*-t-butyl group exerts a much more powerful retarding effect than the *o*-methyl group, and this is particularly significant because the polar effects of the alkyl groups must be relatively small. We therefore ascribe the *ortho*-effects to steric factors.

Table 5 also includes  $k_{ortho}/k_{para}$  for the alkaline hydrolysis of ethyl benzoates. The *ortho*-effects in the two series appear to be of the same order of magnitude, which is

<sup>10</sup> Ref. 2a, p. 649.

surprising since a methylene group separates the ring and the ethoxycarbonyl group in the ethyl phenylacetates. By contrast, while the strengths of isomeric *ortho*- and *para*-substituted benzoic acids<sup>11</sup> differ greatly, those of the corresponding phenylacetic acids<sup>11</sup> are so similar as to indicate that *ortho*-effects are small or absent.

There are, however, differences between the *ortho*-effects which operate in benzoic and phenylacetic ester hydrolyses. First, the *o*-fluoro-substituent in the benzoate series accelerates the hydrolysis, relatively to both the unsubstituted ester (by a factor  $\sim 5$ ), and the *para*-isomer, while in the phenylacetate series *o*-fluoro is a retarding substituent, and the *o*-fluoro-ester is hydrolysed less than half as fast as the *para*-isomer. Also, in the benzoate series the ethoxy-group exerts a weaker retarding effect from the *ortho*- than from the *para*-position, which is the reverse of the behaviour shown by the methoxy-group in the phenylacetate series. A particularly important difference is that whereas most *ortho*-substituents in the benzoate series appreciably reduce the Arrhenius pre-exponential factor from the substantially constant value which applies for the hydrolysis of the unsubstituted and *meta*- and *para*-substituted esters,<sup>4,5</sup> in the phenylacetate series the pre-exponential factor has, within the experimental error, the same value for the *ortho*-substituted esters as for the others. It was expected that the pre-exponential factor would be unaffected by the introduction of *meta*- and *para*-substituents, as in the alkaline hydrolysis of ethyl benzoates<sup>4,5</sup> and cinnamates.<sup>7</sup> Norman and his co-workers<sup>8</sup> have shown that *m*- and *p*-nitro-substituents in ethyl phenylacetate do not significantly affect the factor for hydrolysis in 56% acetone, and Table 2 shows its constancy for hydrolysis in 85.4% ethanol of six esters including three with a single *ortho*-substituent and one with substituents in both *ortho*-positions. Thus, whereas the slow hydrolysis of *ortho*-substituted ethyl benzoates is usually associated with a low pre-exponential factor, the energies of activation for *ortho*- and *para*-isomers being in most cases similar, the slow hydrolysis of *ortho*-substituted ethyl phenylacetates is associated with a high energy of activation. The predominant causes of the *ortho*-effects in the two series may therefore be different.

In general, substituents close to a reaction centre may exert, in addition to polar effects transmitted through the intervening bonds, primary and secondary steric effects and direct field effects; they may also interfere with solvation. Primary steric effects would arise in these hydrolyses if the *ortho*-substituents produced crowding in the transition state, where the hydroxide ion is becoming attached to the carbonyl-carbon atom. Such interaction seems likely in the hydrolysis of benzoates but is probably of less importance in that of phenylacetates, the ester group being further from the ring. Secondary steric effects resulting from interference by *ortho*-substituents with the coplanarity of the ring and the ethoxycarbonyl group almost certainly operate in the ethyl benzoate series. The relatively high acidities of the *ortho*-substituted benzoic acids have been ascribed to such effects.<sup>12</sup> However, these cannot be dominant in the hydrolysis since they should lead to acceleration, and retardation is observed. Secondary steric effects of this type cannot arise in the phenylacetate series since the ethoxycarbonyl group is not conjugated with the ring. Another possibility is that the  $\text{CH}_2\cdot\text{CO}_2\text{Et}$  group may interfere with the conjugation of *ortho*-substituents with the ring. The electron-attracting mesomeric effect, and hence the accelerating influence, of the nitro-group might be reduced in this way, but since the nitro-group also exerts an electron-attracting inductive effect, a secondary steric effect of this kind could hardly reduce the hydrolysis rate to less than that of the unsubstituted ester. Nor is it possible to interpret the retarding effects of the other *ortho*-substituents on this basis. Direct field effects cannot be of major importance in the phenylacetate series, for both electron-attracting (*e.g.*, halogen) and electron-releasing (*e.g.*, alkyl) substituents in the *ortho*-position cause retardation. They may,

<sup>11</sup> Dippy, *Chem. Rev.*, 1939, **25**, 151.

<sup>12</sup> Ingold, "Structure and Mechanism in Organic Chemistry," Bell, London, 1953, p. 743; Dippy, Hughes, and Laxton, *J.*, 1954, 1470.

however, be important in the benzoate series; the accelerating effect of the *o*-fluoro-substituent and the weaker retarding effect of the *o*-ethoxy- than of the *p*-ethoxy-group could arise either from direct field effects or from more effective internal transmission of inductive effects from the *ortho*- than from the *para*-position.<sup>13</sup>

Thus, while it is possible to account for the *ortho*-effects in the alkaline hydrolysis of the benzoic esters in terms of dominating primary steric effects, perhaps with direct field effects also contributing, none of the proximity effects so far considered seems adequate to explain the *ortho*-effects observed in the alkaline hydrolysis of ethyl phenylacetates, though primary steric effects may be partly responsible. Evidence pointing to the importance of steric inhibition of solvation has been obtained by comparison of substituent effects on the hydrolysis in different solvents.

*The Influence of Solvent.*—Linear relations are commonly observed when  $\log k$  values for a reaction of one series of *meta*- and *para*-substituted derivatives are plotted against those for another. This is the basis of the Hammett equation. A good correlation would be expected between two sets of data for the same reaction conducted under different conditions. Accordingly,  $\log k/k_0$  values for hydrolysis of the ethyl phenylacetates in 56% acetone–water have been plotted against those for hydrolysis in 85.4% ethanol–water in Fig. 1 ( $k_0$  is the velocity coefficient for hydrolysis of the unsubstituted ester; values of  $k$  and  $k_0$  for the aqueous acetone medium are from references 8 and 9 and Table 3). Even the points relating to *meta*- and *para*-substituted esters show a scatter which is much too great to be attributed to experimental error. Evidently the effects of substituents are not equally affected by the change of solvent. The line shown takes into account the *meta*- and *para*-substituent points (except *p*-Bu<sup>t</sup>, *p*-NH<sub>2</sub>, and *p*-NMe<sub>3</sub><sup>+</sup>, concerning which see the discussion by Norman and Ralph<sup>9</sup>). The points relating to *ortho*-substituents all deviate considerably from it, and within the groups of halogen and alkyl substituents the deviations increase with substituent size.

Having thus observed that the effects of *ortho*-substituents are sensitive to a change in solvent, we measured hydrolysis rates in aqueous ethanol media of different compositions. The results are shown in Table 4 and Fig. 2, where  $\log k/k_0$  values for hydrolysis in 80, 70, and 60% ethanol–water are plotted against values for 85.4% ethanol–water. The points representing the unsubstituted, and *p*-nitro- and *p*-methyl-substituted esters are collinear in each case, and the slopes of the lines are close to 1, indicating that change of solvent from 85.4% to 60% ethanol–water has little effect on the Hammett constant  $\rho$ . However, there are significant deviations from these lines, and they increase as the water content of the solvent increases. The disposition of the points in the plot of the 60% ethanol results against the 85.4% ethanol result resembles that in Fig. 1 (see, for instance, the points representing the *m*-nitro, *p*-iodo, *p*-*t*-butyl, and all the *ortho*-substituted esters), and it is evident from both Figures that changes in the effects of substituents relative to each other have occurred with change of solvent.

Norman and Ralph<sup>9</sup> discuss the influence of solvent on the effects of *para*-substituents. Appreciable deviations occur also with some *meta*-substituents. Correlations between the deviations observed with *ortho*-substituents and their sizes have been mentioned already. The halogens show deviations increasing F < Cl < Br < I; *o*-methyl shows a deviation similar to that of the chloro- or bromo-substituents which are of similar size, while *o*-*t*-butyl shows a much larger one; the *o*-nitro-point deviates to about the same extent as the *o*-bromo-point in Fig. 2, though somewhat less in Fig. 1.

All the *ortho*-substituted esters are hydrolysed more slowly in the solvents of higher water content than would be expected from the rates of hydrolysis of the remaining esters; in other words, the *ortho*-effects increase with the water content of the solvent. This suggests that the *ortho*-substituents interfere with solvation of the transition state, for if as the water content of the solvent increases this solvation becomes increasingly important,

<sup>13</sup> Chapman, Shorter, and Utley, *J.*, 1962, 1824.

any interference with it will become increasingly significant. Although the results in Table 4 show that an increase in water content of the aqueous-ethanol solvent leads to faster hydrolysis, this could be due to increase in the hydroxide-ion concentration resulting from displacement of the equilibrium  $\text{HO}^- + \text{EtOH} \rightleftharpoons \text{EtO}^- + \text{H}_2\text{O}$ , and therefore does not necessarily indicate increased solvation-stabilisation of the transition state. However, Tommila and his co-workers<sup>14</sup> have shown for the alkaline hydrolysis of ethyl benzoates that increase in the water content of aqueous-acetone solvent

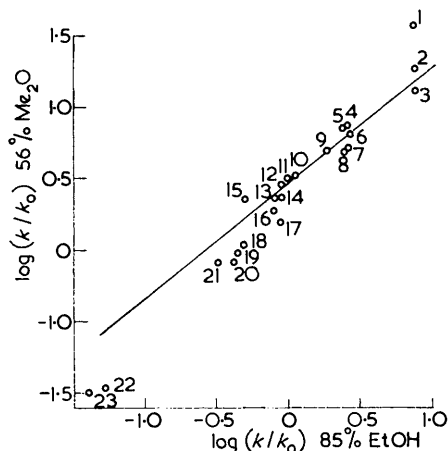


FIG. 1. Plot of  $\log k/k_0$  for hydrolysis of ethyl phenylacetates in 56% acetone-water against  $\log k/k_0$  for hydrolysis in 85.4% ethanol-water. Substituents: 1, *p*- $\text{NMe}_3^+$ . 2, *p*- $\text{NO}_2$ . 3, *m*- $\text{NO}_2$ . 4, *p*-Br. 5, *p*-Cl. 6, *m*-Cl. 7, *m*-I. 8, *p*-I. 9, *p*-F. 10, *m*-MeO. 11, H. 12, *p*-MeO. 13, *p*-Me. 14, *o*-F. 15, *p*- $\text{NH}_2$ . 16, *o*- $\text{NO}_2$ . 17, *p*-*t*-Bu. 18, *o*-Cl. 19, *o*-Br. 20, *o*-I. 21, *o*-Me. 22, *o*-*t*-Bu. 23, 2,6- $\text{Cl}_2$ .

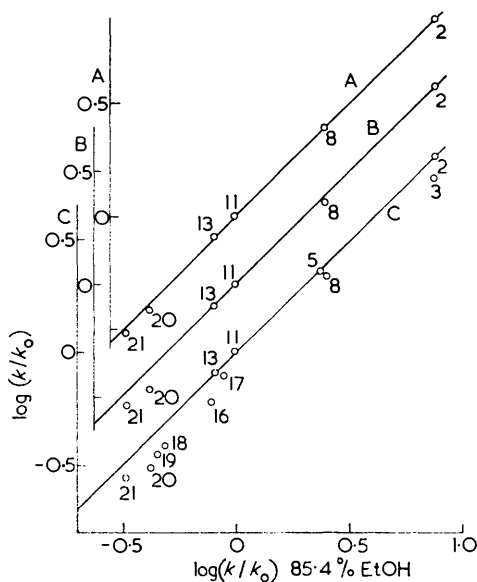


FIG. 2. Plot of  $\log k/k_0$  for hydrolysis of ethyl phenylacetates in (A) 80%, (B) 70%, and (C) 60% ethanol-water against  $\log k/k_0$  in 85.4% ethanol-water. Substituents designated as in Fig. 1.

accelerates hydrolysis and lowers the activation energy, and therefore it seems safe to suppose that an increase in water content does increase the solvation-stabilisation of the transition state.

We therefore consider that steric interference with solvation of the transition state is, at least in part, responsible for the *ortho*-effects observed in the alkaline hydrolysis of ethyl phenylacetates. It is not possible on the basis of our results to say whether other factors also contribute; we have pointed out that primary steric effects may do so. Interference with solvation would be expected to raise the activation energy, which is the result obtained. It could, in principle, also affect the entropy of activation,<sup>6</sup> but the constancy of the Arrhenius pre-exponential factor indicates that it does not. The absence of *ortho*-effects on the acid strengths of phenylacetic acids does not conflict with this interpretation since, while the difference in solvation between the acid and the anion must make an important contribution to the position of equilibrium, the steric requirements for solvation of these species may well not be so great as in the transition state of the hydrolysis, where the carbonyl carbon atom is covalently attached, or partially attached, to four other atoms instead of to three.

Velocity coefficients being available for the alkaline hydrolysis of a considerable

<sup>14</sup> Tommila, Nurro, Murén, Merenheimo, and Vuorinen, *Suomen Kemistilehti*, 1959, **B32**, 115.

number of substituted ethyl benzoates in 85 and 87.8% ethanol-water, and in 56% acetone-water, we have constructed logarithmic plots corresponding to that for ethyl phenylacetates in Fig. 1. The scatter of points is considerably less. The point relating to ethyl *o*-nitrobenzoate shows no significant deviation; the *o*-halogens and *o*-methyl deviate in the same direction as in Fig. 1, though somewhat less. A plot of  $\log k/k_0$  in aqueous acetone containing 600 ml. water per l.<sup>14</sup> against  $\log k/k_0$  in a similar solvent with 400 ml. water per l. (56% w/w)<sup>5</sup> has also been constructed. The only *ortho*-substituents for which data are available are *o*-fluoro, *o*-chloro, and *o*-methyl, and none of these shows significant deviation. Substituent effects on the alkaline hydrolysis of ethyl benzoates are evidently considerably less sensitive to change in solvent than are those on the hydrolysis of ethyl phenylacetates. While steric interference with solvation of the transition state may contribute to the *ortho*-effects in the benzoate hydrolysis, it would seem not to be the main cause. Here the *ortho*-substituents are much closer to the reaction centre, and it is probable that the dominant factor is steric interaction in the transition state between the *ortho*-substituent and the groups attached to the carbonyl-carbon atom. This would restrict the conformational freedom of the transition state, which would explain why in the ethyl benzoate series the *ortho*-effects are associated with reductions in the pre-exponential factor of the Arrhenius equation rather than with increased activation energies.

*Transmission of Substituent Effects.*—The velocity coefficients in Table 1 show clearly the effect of the methylene group of the phenylacetic esters in blocking resonance interaction between substituents and the ethoxycarbonyl group. This is particularly marked in the case of mesomeric electron-release from *para*-substituents. Thus, the *p*-methoxy-group exerts a weaker retarding effect on the hydrolysis than the *p*-methyl group; its retarding effect is also weaker than the accelerating effect of the *m*-methoxy-group, so that 3,4-dimethoxy-substitution leads to acceleration in contrast with the strong retardation which is observed in the hydrolysis of benzoic<sup>15</sup> and cinnamic esters.<sup>7</sup> Electron release from the *p*-amino-group is similarly much attenuated. Nevertheless, with 85.4% ethanol as solvent, the effects of the *p*-alkyl groups lie in the Baker-Nathan order (*p*-methyl retards more strongly than *p*-*t*-butyl) as in hydrolysis of the benzoates<sup>16</sup> and cinnamates<sup>7</sup> in similar solvents. That this should be so even where mesomeric electron-release from *para*-substituents is, relative to other substituent effects, severely attenuated in transmission to the reaction centre is evidence against C-H hyperconjugation as the cause of the Baker-Nathan order of *p*-alkyl-substituent effects in these hydrolyses. The observed sensitivity of the order to the solvent used<sup>9,16</sup> suggests that the determining factor may be the influence of the alkyl groups on solvation.

## EXPERIMENTAL

*Ethyl Phenylacetates.*—Ethyl phenylacetate was purchased. We thank Dr. R. O. C. Norman for *p*-fluorophenylacetic acid and the methiodide of ethyl *p*-dimethylaminophenylacetate. Other substituted phenylacetic acids were prepared by methods in the literature (in most cases, either through the benzyl halide and cyanide, or by the Willgerdt reaction of the appropriate acetophenone). *o*-*t*-Butylphenylacetic acid was prepared from *o*-*t*-butylbenzoic acid.<sup>17</sup> The acids, often after distillation under reduced pressure, were crystallised at least twice, usually from benzene, light petroleum, or mixtures thereof, and were esterified by the method used for cinnamic acids.<sup>7</sup> The esters were fractionated or crystallised several times before their hydrolysis rates were determined. Physical properties and analyses of new compounds are given in Table 6.

*Solvents.*—The aqueous-ethanol solvents were prepared by dilution of absolute ethanol ("clinical") with freshly boiled, distilled water to give mixtures containing 85.4%, 80.0%,

<sup>15</sup> Brynmor Jones and Robinson, *J.*, 1955, 3845.

<sup>16</sup> Berliner, Beckett, Blommers, and Newman, *J. Amer. Chem. Soc.*, 1952, **74**, 4940.

<sup>17</sup> Zanten and Nanta, *Rec. Trav. chim.*, 1960, **79**, 1211.

TABLE 6.

## Phenylacetic acids and ethyl phenylacetates.

Subst.	Acid,		Et ester,		Subst.	Acid,		Et ester,	
	m. p.	b. p./mm.	m. p.	b. p./mm.		m. p.	b. p./mm.	m. p.	b. p./mm.
<i>o</i> -F .....	59°	—	—	65°/0.5	<i>p</i> -NO <sub>2</sub> .....	153°	63.5°	—	—
<i>p</i> -F .....	84.5	—	35°	—	<i>o</i> -Me .....	88.5	—	82°/0.5 ‡	—
<i>o</i> -Cl .....	94.5	—	—	126°/13	<i>p</i> -Me .....	92.5	—	88°/0.8	—
<i>m</i> -Cl .....	78	—	—	130°/12 *	<i>o</i> -Bu <sup>t</sup> .....	84	—	90°/0.5	—
<i>p</i> -Cl .....	105	—	—	130°/13	<i>p</i> -Bu <sup>t</sup> .....	81	—	102°/0.4	—
<i>o</i> -Br .....	107.5	—	37	—	<i>o</i> -MeO .....	123	—	137°/12	—
<i>p</i> -Br .....	117	—	31.5	—	<i>m</i> -MeO .....	70	—	152°/19 §	—
<i>o</i> -I .....	113	—	44	—	<i>p</i> -MeO .....	86	—	144°/10	—
<i>m</i> -I .....	129	—	—	166°/10 †	<i>p</i> -NH <sub>2</sub> .....	200	51	—	—
<i>p</i> -I .....	140	—	28	—	2,6-Cl <sub>2</sub> .....	158	33 ¶	—	—
<i>o</i> -NO <sub>2</sub> .....	140	—	64	—	3,4-(MeO) <sub>2</sub> ...	98	—	—	172°/14
<i>m</i> -NO <sub>2</sub> .....	121	—	—	125°/0.5					

\* Found: C, 60.4; H, 5.6; Cl, 17.9. C<sub>10</sub>H<sub>11</sub>ClO<sub>2</sub> requires C, 60.5; H, 5.6; Cl, 17.9%. † Found: C, 41.2; H, 3.6. C<sub>10</sub>H<sub>11</sub>IO<sub>2</sub> requires C, 41.4; H, 3.8%. ‡ Found: C, 74.0; H, 8.0. C<sub>11</sub>H<sub>14</sub>O<sub>2</sub> requires C, 74.1; H, 7.9%. § Found: C, 68.0; H, 7.2. C<sub>11</sub>H<sub>14</sub>O<sub>3</sub> requires C, 68.0; H, 7.3%. ¶ Found: C, 51.5; H, 4.4. C<sub>10</sub>H<sub>10</sub>Cl<sub>2</sub>O<sub>2</sub> requires C, 51.5; H, 4.3%.

70.0%, and 60.0% w/w ethanol (determined by specific gravity). The 56% w/w acetone was prepared by addition to 400 ml. water of sufficient "AnalaR" acetone to bring the total volume to 1 l. at 25°.

*Velocity Measurements.*—For measurements in the aqueous-ethanol solvents the method was that used for ethyl cinnamates; <sup>7</sup> hydrolysis rates in aqueous acetone were determined by a method similar to that used by Tommila and Hinshelwood <sup>5</sup> except that the solutions of both the ester and the sodium hydroxide were prepared in aqueous acetone. All runs showed strictly second-order kinetics throughout.

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