

817. *The Alkaline Hydrolysis of Nuclear-substituted Ethyl Cinnamates. The Cumulative Effects of Substituents.*

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Rates of hydrolysis of ethyl cinnamate and 28 nuclear-substituted derivatives with one, two, or three substituents have been measured at 24.8° in aqueous ethanol (85.4% of ethanol w/w). Additional measurements at other temperatures show that with the introduction of substituents, even into the *ortho*-position, the non-exponential factor of the Arrhenius equation does not vary beyond the limits of experimental error.

The cumulative effects of substituents indicate that when two substituents occupy the 2- and 4- or 3- and 5-positions their combined effect on the energy of activation is normally close to the sum of their individual effects. For other orientations, while the effects are sometimes approximately additive, there are often significant, and sometimes large, deviations from additivity.

In a previous paper¹ the cumulative effects of substituents on the alkaline hydrolysis of ethyl benzoate were studied because earlier results^{2,3} had led to the belief that substituents in a benzene nucleus could contribute independent and additive increments to the energy of activation of reactions of the molecule in which they occur. There was also evidence of an analogous additivity of substituent effects on equilibria.⁴ Agreement between the observed increments in energy of activation due to the substituents and values predicted on an additive basis was usually found¹ for 3 : 5-disubstitution; for 3 : 4-disubstitution substituent effects were approximately additive in some cases, but not in others. In the one case of trisubstitution (3 : 4 : 5-trimethoxy) investigated, the substituent effects were far from additive.

Other orientations of substituents were not examined because Ingold and Nathan,⁵ Evans, Gordon, and Watson,⁶ and Tommila and Hinshelwood⁷ had shown that *ortho*-substituents in ethyl benzoate influence the non-exponential (entropy) factor of the Arrhenius equation as well as the energy of activation. *meta*- and *para*-Substituents have no detectable effect on the non-exponential factor, and with this taken as constant it was possible to calculate the contributions made by the substituents to the energy of activation from rate measurements at a single temperature. If the non-exponential factor varies, as it does when *ortho*-substituents are introduced, such contributions can be

¹ Brynmor Jones and Robinson, *J.*, 1955, 3845.

² Bradfield and Brynmor Jones, *J.*, 1928, 1006; Brynmor Jones, *J.*, 1935, 1831; 1942, 418, 676; Brynmor Jones and Sleight, *J.*, 1954, 1775.

³ Stubbs and Hinshelwood, *J.*, 1949, S71.

⁴ Shorter and Stubbs, *J.*, 1949, 1180.

⁵ Ingold and Nathan, *J.*, 1936, 222.

⁶ Evans, Gordon, and Watson, *J.*, 1937, 1430.

⁷ Tommila and Hinshelwood, *J.*, 1938, 1801; Tommila, *Ann. Acad. Sci. Fennicae*, 1941, A, 57, No. 13 and succeeding papers.

obtained only from the energies of activation corresponding to the substituted and unsubstituted compounds, and values thus obtained are not sufficiently accurate for examination of the validity of the additivity principle.

The effects peculiar to *ortho*-substitution are presumably steric, and therefore should be less likely to arise in the hydrolysis of esters having the ester group at some distance from the benzene ring, as in the ethyl *trans*-cinnamates, where the double bond makes the side chain rigid, and so ensures that the ester group cannot lie close to *ortho*-substituents. Furthermore, as the ethoxycarbonyl group remains conjugated with the ring, the polar effects of nuclear substituents should be qualitatively similar to those operating in the hydrolysis of benzoates, and large enough to cause rate differences measurable with sufficient accuracy.

These predictions are supported; Kindler⁸ determined rates of alkaline hydrolysis for substituted ethyl cinnamates in aqueous ethanol (87.83% of ethanol w/w) and found not only that substituent effects were quite large, but also that the rates of hydrolysis of six *ortho*-substituted esters were not greatly different from those of the *para*-isomers. However, as he worked at 30° only, his data do not yield conclusions about the constancy of the non-exponential factor; nevertheless, the velocities show a marked contrast with those for the corresponding ethyl benzoates, where the fall in the non-exponential factor due to *ortho*-substitution is reflected in rate coefficients which are very much lower for *ortho*- than for the *para*-substituted esters. It is also significant that the strengths of isomeric *ortho*- and *para*-substituted cinnamic acids are of the same order, whereas the strengths of *ortho*- are very different from those of the *para*-substituted benzoic acids.⁹

RESULTS

In order to facilitate correlation of the results with earlier ones^{1,6} for ethyl benzoates similar conditions were used. Aqueous ethanol contained 85.4% of ethanol (w/w). The velocity coefficients at 24.8° are summarised in Table 1, and Table 2 gives results for those esters whose rates of hydrolysis were measured at more than one temperature. Second-order rate constants, *k*, are in l. mole⁻¹ sec.⁻¹.

TABLE 1. Velocity coefficients for the alkaline hydrolysis of ethyl cinnamates at 24.8°.

Subst.	10 ³ <i>k</i>	Subst.	10 ³ <i>k</i>	Substs.	10 ³ <i>k</i>	Substs.	10 ³ <i>k</i>
H	1.39	<i>p</i> -Pr ¹	0.881	2-MeO, 3-MeO	1.15	3-NO ₂ , 4-MeO	3.69
<i>o</i> -Cl	3.48	<i>o</i> -MeO	0.517	2-Cl, 4-Cl	6.87	3-Me, 4-MeO	0.415
<i>m</i> -Cl	3.97	<i>m</i> -MeO	1.56	2-MeO, 4-MeO	0.189	3-MeO, 4-MeO	0.677
<i>p</i> -Cl	2.65	<i>p</i> -MeO	0.528	2-MeO, 5-Cl	1.54	3-MeO, 4-EtO	0.646
<i>o</i> -NO ₂	10.1	<i>m</i> -EtO	1.51	3-Cl, 4-Cl	6.65	3-EtO, 4-EtO	0.632
<i>m</i> -NO ₂	10.4	<i>p</i> -EtO	0.504	3-NO ₂ , 4-Me	6.74	3-Cl, 5-Cl	12.1
<i>m</i> -Me	1.16			3-NO ₂ , 4-Pr ¹	6.69	2-MeO, 3-MeO,	0.526
<i>p</i> -Me	0.870			3-Cl, 4-MeO	1.40	4-MeO	

TABLE 2. The non-exponential factor.

Subst.	H	<i>o</i> -Cl	<i>p</i> -Pr ¹	<i>p</i> -MeO	2-MeO, 3-MeO	3-Cl, 4-Cl	3-Cl, 4-MeO
10 ³ <i>k</i> (24.8°) ...	1.39	3.48	0.881	0.528	1.15	6.65	1.40
10 ³ <i>k</i> (35.3°) ...	3.68	9.11 †	2.38 †	1.48	3.13	17.05	3.70 †
log ₁₀ <i>A</i>	10.0 *	10.0	9.9	9.9	9.9	9.9	9.8

* Derived from a linear plot of *k* against 1/*T* [with additional values for 10³*k* at 15.05° (0.496) and 45.1° (8.83)], which also gives the energy of activation *E* as 17,300 cal./mole.

† Temperature, 35.1°.

DISCUSSION

Correlations with Existing Data.—Nine esters in Table 1 were used by Kindler.⁸ For these, a plot of logarithms of our velocity coefficients (*k_c*) against logarithms of the corresponding values from Kindler's data (*k_c'*) shows that a linear relation log₁₀ *k_c* = 1.02 log₁₀ *k_c'* - 0.07 is followed sufficiently closely to indicate satisfactory agreement.

⁸ Kindler, *Annalen*, 1926, **450**, 1; 1927, **452**, 90; 1928, **464**, 278; *Ber.*, 1936, **69**, 2792.

⁹ Dippy, *Chem. Reviews*, 1939, **25**, 151.

A plot of $\log_{10} k_c$ against values ($\log_{10} k_b$) for sixteen similarly-substituted ethyl benzoates¹ was also linear, individual points showing only small, random deviations from the line for the equation $\log_{10} k_c = 0.52 \log_{10} k_b - 1.23$. The existence of such a relation had been demonstrated.¹⁰ It applies for substituents in the *meta*- and *para*-positions only and, if the non-exponential factors for both ester series are independent of substitution in these positions, it means that the changes in energy of activation produced by a given substitution in the two series are related by the equation $\Delta E_c = 0.52 \Delta E_b$. This implies that substituent effects in the cinnamic are only about half as great as in the benzoic series even though conjugation remains.

Constancy of the Non-exponential Factor.—Velocity coefficients in Tables 1 and 2 are accurate to $\pm 2\%$, and temperatures to $\pm 0.03^\circ$. Consequently, errors in values of $\log_{10} A$ calculated from velocity coefficients at two temperatures 10° apart are *ca.* $\pm 5\%$. That for ethyl cinnamate, based on four results ranging over 30° , is more accurate. The data in Table 2 therefore indicate that the non-exponential factor A does not vary beyond the limits of experimental error; this is true for *ortho*- as well as for *meta*- and *para*-substitutions.

Effects of Substituents on the Energy of Activation.—Increments $\Delta E'$ in the free energy of activation associated with the various substituents can be calculated from the velocity coefficients in Table 1 by means of the equation

$$\Delta E' = E' - E'_0 = 2.303 RT \log_{10} k/k_0$$

in which k_0 and E'_0 refer to unsubstituted ethyl cinnamate, and k and E' to the substituted ester. Values of $\Delta E'$ for monosubstitution are listed in Table 3, and for polysubstitution in Table 4 ($\Delta E'_{\text{obs.}}$).

TABLE 3. Effects of single substituents on the free energy of activation.

Subst.	$\Delta E'$ (cal./mole)					
	Cl	NO ₂	Me	Pr ¹	MeO	EtO
<i>ortho</i>	-540	-1170	—	—	+590	—
<i>meta</i>	-620	-1190	+110	—	-70	-50
<i>para</i>	-380	—	+280	+270	+570	+600

TABLE 4. Cumulative effects of substituents.

Subst.	$\Delta E'_{\text{obs.}}$	$\Delta E'_{\text{calc.}}$	$10^3 k_{\text{calc.}}$	$\frac{100k_{\text{calc.}}}{k_{\text{obs.}}}$	Subst.	$\Delta E'_{\text{obs.}}$	$\Delta E'_{\text{calc.}}$	$10^3 k_{\text{calc.}}$	$\frac{100k_{\text{calc.}}}{k_{\text{obs.}}}$
2-MeO, 3-MeO ‡	+110	+520	0.580	50	3-NO ₂ , 4-MeO *	-580	-620	3.93	106
2-Cl, 4-Cl	-950	-920	6.63	97	3-Me, 4-MeO	+720	+680	0.441	106
2-MeO, 4-MeO	+1180	+1160	0.196	104	3-MeO, 4-MeO †	+430	+500	0.593	88
2-MeO, 5-Cl	-60	-30	1.48	96	3-MeO, 4-EtO †	+450	+530	0.566	88
3-Cl, 4-Cl †	-930	-1000	7.57	114	3-EtO, 4-EtO †	+470	+550	0.548	87
3-NO ₂ , 4-Me	-940	-910	6.47	96	3-Cl, 5-Cl	-1280	-1240	11.3	94
3-NO ₂ , 4-Pr ¹	-930	-920	6.55	98	2-MeO, 3-MeO,	+580	+1090	0.306	58
3-Cl, 4-MeO *	0	-50	1.51	108	4-MeO ‡				

Values of $\Delta E'$ become equal to increments in the energy of activation, ΔE , if A is constant. Although this condition appears to be fulfilled, the degree of accuracy of the values of A is insufficient to justify our assuming $\Delta E' = \Delta E$. Accordingly, we first examine the cumulative effects of substituents on the free energy of activation, and then the relation between these and the corresponding effects on the energy of activation.

Cumulative Effects of Substituents.—Table 4 also contains values of $\Delta E'_{\text{calc.}}$ calculated by summation of the appropriate values from Table 3. The additivity can be judged by comparison with $\Delta E'_{\text{obs.}}$. Alternatively, observed and calculated velocity coefficients can be compared, for if the velocity coefficients for the reaction of the parent compound and two monosubstituted derivatives are, respectively, k_0 , k_X , and k_Y , and if in the reaction of the corresponding disubstituted compound, velocity coefficient k_{XY} , the substituents contribute additively to the free energy of activation, then $k_{XY} = k_X k_Y / k_0$. In Table 4

¹⁰ Hammett, *J. Amer. Chem. Soc.*, 1937, **59**, 96.

velocity coefficients thus calculated ($k_{\text{calc.}}$) are listed, and compared with the observed velocity coefficients ($k_{\text{obs.}}$) from Table 1.

The estimated limits of accuracy being taken into account, $100 k_{\text{calc.}}/k_{\text{obs.}}$ will lie between 93 and 108 if the substituents contribute additively to the free energy of activation. Substituent effects can thus be described as additive or approximately additive in the hydrolysis of nine of the fifteen polysubstituted esters considered (those italicised in Table 4). This class includes all those in which the substituents are *meta* to each other and also, amongst several instances of 3:4-disubstitution, two (*) which deviated considerably from additivity of substituent effects in the alkaline hydrolysis of ethyl benzoate.

In four cases of 3:4-disubstitution (†) there are fairly small, but significant, deviations from additivity, and in two cases (‡) the deviations are large. A moderate deviation, in the same direction as that reported here, was found with ethyl 3:4-dichlorobenzoate. That the deviations recorded for 3:4-dialkoxy-substitution are real is apparent from their consistency: $100k_{\text{calc.}}/k_{\text{obs.}}$ for ethyl 3:4-dimethoxy-, 4-ethoxy-3-methoxy-, and 3:4-diethoxy-cinnamates, respectively, is 88, 88, and 87, and, further, 3:4-dimethoxy-substitution in ethyl benzoate,¹ ethyl phenylacetate,¹¹ and ethyl β -phenylpropionate¹¹ respectively it is 82, 86, and 88.

Stubbs and Hinshelwood have shown that additivity of increments in free energy of activation probably reflects a corresponding additivity in the energy of activation. We conclude that this is true for our nine cases.

The situation is less straightforward where deviations from additivity as judged on a free-energy basis are found. Such deviations might reflect deviations from additivity in the energy of activation, and/or they might be due to small (and, by our technique, undetectable) variations in A . Now, changes in A due to nuclear substitution have been measured in the alkaline hydrolysis of aromatic esters only when the substituents are close to the ester group.^{6,12} In ethyl *trans*-cinnamates, however, nuclear substituents cannot be in the vicinity of the reacting group, so deviations from additivity in the free energy of activation seem less likely to result from variations in A than from deviations from additivity in the energy of activation.

Failure of substituents to contribute additively to the energy of activation may be attributed to interaction between them. Two substituents in the same molecule will polarise each other as well as the reaction centre, and this mutual interaction may modify the effect which each exerts at the reaction centre. Such polar interaction will be most pronounced when substituents capable of exerting strong conjugative effects are *ortho* or *para* to each other, and will be least with substituents *meta* to each other. Thus, it is significant that in most cases of 2:4- and 3:5-disubstitution good agreement with the concept of additivity has been found.

With substituents *ortho* to each other, steric as well as polar interactions are likely to arise. Results from 3:4-dialkoxy-esters suggest that there is an approximately constant interaction between the adjacent alkoxy groups, but the data do not indicate whether this is polar or steric. The observed rates of hydrolysis may be higher than the predicted rates through the operation of a steric effect such that a 3- prevents a 4-alkoxy-group from lying in the plane of the ring, so that its electron-releasing mesomeric effect is weakened (the influence of a 3-methyl group in considerably diminishing the retarding effect of a 4-dimethylamino-group on the alkaline hydrolysis of ethyl benzoate has thus been interpreted¹³), but this is a doubtful explanation for 3:4-dialkoxy-substitution in view of other results in Table 4 for esters with a 4-alkoxy group and a bulky 3-substituent (*e.g.*, methyl or nitro) which do not indicate interference with the mesomeric effect of the 4-alkoxy group.

¹¹ Brynmor Jones and Watkinson, unpublished results.

¹² Fisher, Murdoch, Packer, Topsom, and Vaughan, *J.*, 1957, 4358.

¹³ Price and Lincoln, *J. Amer. Chem. Soc.*, 1951, 73, 5838.

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The large discrepancies between the observed and calculated rates of hydrolysis of the 2:3-dimethoxy- and 2:3:4-trimethoxy-esters can be attributed with more confidence to steric interference with mesomeric electron-release from the 2-methoxy-group which is here flanked by bulky substituents in both the 1- and the 3-position. The 4-methoxy-group in ethyl 3:4:5-trimethoxybenzoate is in an analogous situation, and the results obtained ¹ with this ester ($100k_{\text{calc.}}/k_{\text{obs.}} = 25$) can be similarly explained.

EXPERIMENTAL

Materials.—Ethyl cinnamate and nitrocinnamic acids were purchased. Other cinnamic acids were prepared from the corresponding benzaldehydes.

We thank Dr. J. Robinson for 3-chloro-4-methoxybenzaldehyde.

*Cinnamic acids.*¹⁴ Benzaldehydes (0.1 mole) were heated with malonic acid (0.12—0.2 mole) and piperidine (1 ml.) in pyridine (40—50 ml., b. p. 114—116° *) at 100° until 30 min. after visible evolution of carbon dioxide had ceased (*i.e.*, usually, for 1.5—2 hr.), and the solution was then boiled for 15 min., cooled, and poured into concentrated hydrochloric acid and ice. The cinnamic acid precipitated (yield, $\geq 80\%$) was crystallised at least twice (thrice or more if its ethyl ester was liquid) from ethanol, slightly aqueous acetic acid, or, occasionally, benzene.

Ethyl cinnamates. Cinnamic acids (0.1 mole) were boiled with absolute ethanol (1 mole) containing 3—5% of concentrated sulphuric acid for 5 hr. and the esters were isolated by treatment of the cooled reaction mixture with saturated aqueous sodium hydrogen carbonate.

TABLE 5. *Cinnamic acids and ethyl cinnamates.*

Subst.	Acid M. p.	Ethyl ester			Subst.	Acid M. p.	Ethyl ester	
		M. p.	B. p. °/mm.	$n_D^{20}/^{\circ}\text{C}$			M. p.	B. p. °/mm.
H	—	—	138/14	1.5592/20.5	2:4-Cl ₂	233.5	53.5	162/5 ^c
<i>o</i> -Cl	208°	—	159/14	1.5670/20.3	3:4-Cl ₂	218	56	156/2 ^d
<i>m</i> -Cl	162.5	31°	132/2	—	3:5-Cl ₂	173.5	74	178/12
<i>p</i> -Cl	247.5	16	160/11	1.5768/20.4	4-Me-3-NO ₂	174	95.5	191/12
<i>o</i> -NO ₂	242.5	42	166/4	—	3-NO ₂ , 4-Pr ¹	138	58	189/2
<i>m</i> -NO ₂	—	75	193/10	—	5-Cl, 2-MeO	200	37.5	166/4
<i>p</i> -NO ₂	288	137	—	—	3-Cl, 4-MeO	244 ^f	61	170/4 ^g
<i>m</i> -Me	118	—	146/10 ^a	1.5562/20.4	4-MeO, 3-NO ₂	248	100	230/8
<i>p</i> -Me	197	—	151/4	—	4-MeO, 3-Me	201 ^h	36.5	184/11
<i>o</i> -Pr ¹	158	—	169/14	1.5509/20.5	2:3-(MeO) ₂	180	44	166/5
<i>o</i> -MeO	183.5	35	162/9	—	2:4-(MeO) ₂	187.5	60	208/11
<i>m</i> -MeO	117.5	—	170/10	1.5646/20.3	3:4-(MeO) ₂	180	55.5	161/2
<i>p</i> -MeO	171.5, 187.5 *	50	156/4	—	4-EtO, 3-MeO	200 (dec.)	109.5	—
<i>m</i> -EtO	131.5	—	175/11	—	3:4-(EtO) ₂	159.5	59	—
<i>p</i> -EtO	192.5, 196 *	38.5	154/2	—	2:3:4-(MeO) ₃	170.5	50	207/14 ^k

* Clearing point of mesomorphic acid.

New compounds.—^a Found: C, 76.1; H, 7.6. C₁₂H₁₄O₂ requires C, 75.8; H, 7.4. ^b Found: C, 69.9; H, 6.8. C₁₂H₁₄O₃ requires C, 69.9; H, 6.8. ^c Found: C, 54.1; H, 4.2; Cl, 28.9. C₁₁H₁₀O₂Cl₂ requires C, 53.9; H, 4.1; Cl, 28.9. ^d Found: C, 53.9; H, 4.2; Cl, 29.0. Found: C, 53.9; H, 4.0; Cl, 28.7. ^e Found: C, 56.2; H, 4.0; Cl, 17.3. C₁₀H₉O₃Cl requires C, 56.5; H, 4.3; Cl, 16.7. ^f Found: C, 60.0; H, 5.5; Cl, 14.7. C₁₂H₁₃O₃Cl requires C, 59.9; H, 5.4; Cl, 14.7. ^g Found: C, 68.4; H, 6.3. C₁₁H₁₂O₃ requires C, 68.7; H, 6.3. ^h Found: C, 71.2; H, 7.5. C₁₃H₁₆O₃ requires C, 70.9; H, 7.3. ⁱ Found: C, 67.2; H, 7.4. C₁₄H₁₈O₄ requires C, 67.2; H, 7.3. ^k Found: C, 63.1; H, 6.8. C₁₄H₁₆O₅ requires C, 63.1; H, 6.8%.

Liquid esters were fractionated repeatedly under reduced pressure: solid esters were crystallised to constant m. p. from ethanol, light petroleum (b. p. of various ranges), or light petroleum-benzene, usually after being first distilled under reduced pressure. Yields were almost quantitative except from 2:4-dimethoxycinnamic acid. This gave mainly a substance which was apparently polymeric (a viscous liquid which slowly solidified, and was insoluble in

* This was the main fraction obtained when "redistilled" pyridine was dried over sodium hydroxide and distilled. A sample obtained in the same way from "technical" pyridine gave products which were coloured, and comparatively difficult to purify.

ether, soluble in acetone, and decomposed on attempted vacuum-distillation). Esterification at room temperature with hydrogen chloride as catalyst again gave mainly the polymer. A 40–50% yield of the ester was obtained when the acid was boiled for 2.5 hr. with ethanol containing 5% of toluene-*p*-sulphonic acid.

Physical data and analyses of new compounds are in Table 5.

Solvent.—"Absolute" ethanol was purified by Smith's method¹⁵ and diluted with freshly boiled distilled water to give a mixture containing 85.4% (w/w) of ethanol (determined by specific gravity).

Velocity Measurements.—The method used was essentially that described by Evans, Gordon, and Watson.⁶ Atmospheric carbon dioxide was excluded from sodium hydroxide solutions, and all solutions were standardised before or during each run. The initial concentrations of alkali and ester were equal (*ca.* 0.05M) and velocity coefficients were calculated from $k = x/at(a - x)$. All kinetics were strictly of the second order. The following details of a run with 0.0500M-ethyl *m*-methylcinnamate and 0.0500M-alkali at 24.8° are typical, zero and infinity titres being calculated from concentrations. The mean value of 10^3k is 1.16 l. mole⁻¹ sec.⁻¹:

<i>t</i> (min.)	0	90	150	190	230	270	310	350	390	430	∞
Titre (ml.) ...	3.02	5.33	6.33	6.88	7.31	7.67	8.00	8.32	8.54	8.80	9.62
10^3k	—	1.17	1.16	1.17	1.17	1.15	1.15	1.17	1.15	1.17	—

Duplicate runs were carried out for all esters at 24.8° at different times (often the ester was redistilled or recrystallised between runs) and gave mean velocity coefficients agreeing to within ±1%.

Grateful acknowledgment is made to the Distillers Co. Ltd. and to Imperial Chemical Industries Limited for grants. The authors are also indebted to the Department of Scientific and Industrial Research for a maintenance grant (to J. G. W.).

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[*Received, April 29th, 1958.*]

¹⁵ Smith, quoted by Vogel, "A Textbook of Practical Organic Chemistry," Longmans, Green & Co., London, 2nd edn., 1951, p. 166.