The *E*1cb Route for Ester Hydrolysis; Volumes of Activation as an Additional Criterion of Mechanism

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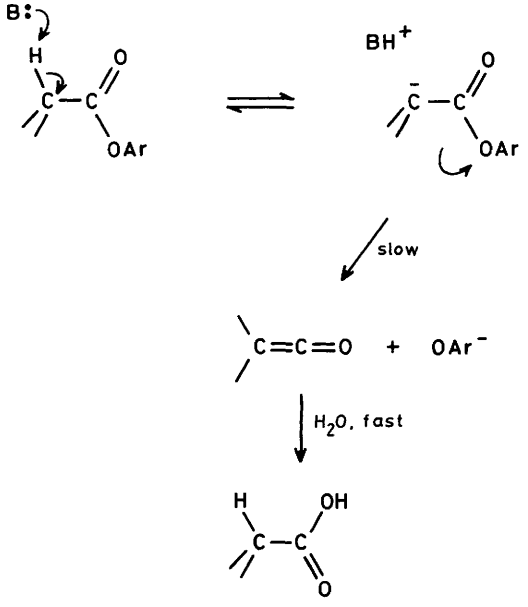
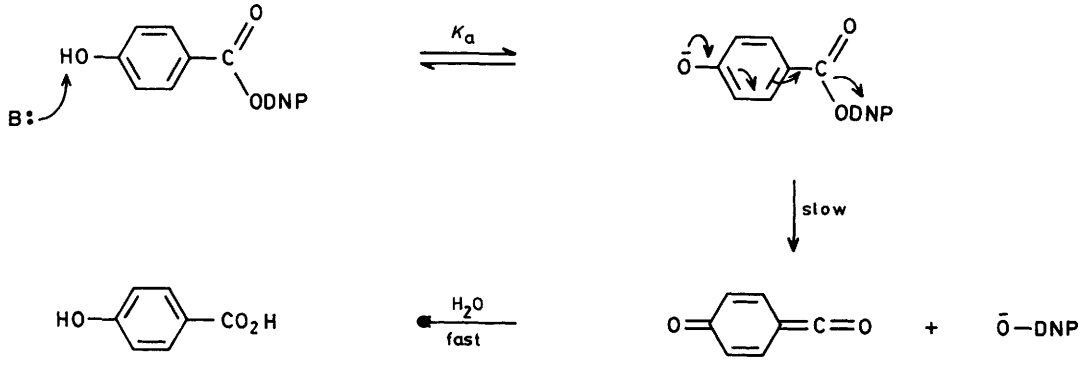
Hydrolyses of esters which possess an acidic proton at the α or vinylogous position can, in principle, hydrolyse by the *E*1cb route *via* a ketenoid intermediate. To the kinetic evidence for such a mechanism in the hydrolyses of 4-hydroxybenzoates, malonates, acetoacetates and fluorenecarboxylates is now added the further criterion of volumes of activation. Values of $\Delta V^{\ddagger}$ for reactions proceeding by the *E*1cb route are positive and contrast with the negative values associated with hydrolyses by the more usual $B_{Ac}2$ mechanism.

The *E*1cb mechanism of ester hydrolysis (Scheme 1) was first identified by Holmquist and Bruice [1,2] in 1969 from the study of



Scheme 1.

the pH-dependence of the rates of hydrolysis of phenyl malonates and, since that date, many other esters have been inferred to hydrolyse in an analogous fashion. The structural requirements for this pathway to be followed in preference to the more usual addition–elimination mechanism ($B_{Ac}2$) are the availability of a stabilised carbanion α to the carboxy group (or some suitable vinylogous structure) with $pK_A < pK_w$ and also a leaving anion of high nucleofugacity; a nitrophenolate typifies the latter. In addition to the obvious candidates for *E*1cb hydrolysis, malonates, acetoacetates and cyanoacetates, and β-oxoesters (together with their thio analogues),[3–5] Williams, Thea, and co-workers have supplied information that hydrolyses of 4-hydroxybenzoates and 4-hydroxybenzenesulphonates also proceed by this route (Scheme 2). The principle evidence for these mechanistic assignments has been the observation of anomalous pH–rate profiles. Typically, rates of hydrolysis in buffered solution were found to be abnormally high in the region of dissociation of the acidic hydrogen and to exhibit a plateau indicative of rate-determining proton removal by general base catalysis and a sharp discontinuity indicative of mechanistic change. The *E*1cb mechanism is inferred to take place within the plateau region in which saturation kinetics apply and the rate-determining step, fission of the conjugate base, is now independent of the base. At a pH below this region where rates are proportional to $[OH^-]$, hydrolysis occurs by the $B_{Ac}2$ route. At high pH beyond the plateau rates also return to dependence on OH^- (or H_-) but now attack must take place on the conjugate base of the ester. Deviations from linear free energy relationships have been observed attributable to a change in mechanism. Rates of hydrolysis of (X-)phenyl malonates show deviations for X = NO_2 which react 10^2—10^3 times faster than predicted for the $B_{Ac}2$ pathway from rates of less acidic members of this series. These mechanistic criteria are indirect and at times difficult to interpret. Plateaux in the pH–rate curves become inflexions for esters with less acidic hydrogens than malonates and mixed mechanisms may be occurring, the proportions of each com-



Scheme 2.

Table 1. Properties of esters studied

Ester	M.p.	Lit.
2,4-Dinitrophenyl 4-hydroxybenzoate	162	164[a]
2,4-Dinitrophenyl 3-hydroxybenzoate	180	
4-Nitrophenyl benzoate	144	145[b]
2,4-Dinitrophenyl 4-acetamidobenzoate	154	156
Ethyl 4-nitrophenyl malonate	61	61[c]
Ethyl 2-nitrophenyl methylmalonate	Oil	
Ethyl 2,4-dinitrophenyl dimethylmalonate	Oil	
2,4-Dinitrophenyl acetate	70	70[d]
2,4-Dinitrophenyl 4-nitrophenylacetate	135	
4-Nitrophenyl diphenylacetate	89	89[e]
2-Nitrophenyl 4-nitrophenylacetate	91	
3-Nitrophenyl acetoacetate	74	74[f]
2-Nitrophenyl cyanoacetate	71	71[g]
3-Nitrophenyl cyanoacetate	111	
4-Nitrophenyl cyanoacetate	99	
4-Methoxyphenyl fluorene-9-carboxylate	92	91[h]
3-Nitrophenyl fluorene-9-carboxylate	111	112[h]
4-Chlorophenyl fluorene-9-carboxylate	115	114[h]
2,2,2-Trifluoroethyl fluorene-9-carboxylate	86	85[h]
3-Nitrophenyl 9-methylfluorene-9-carboxylate	125	
2,4-Dinitrophenyl 4-hydroxycinnamate	141	

[a] G. Cevasco, G. Guanti, A. R. Hopkins, S. Thea, and A. Williams, *J. Org. Chem.*, 1985, **50**, 479; [b] G. Cilento, *J. Am. Chem. Soc.*, 1953, **75**, 374; [c] B. Holmquist and T. C. Bruice, *J. Am. Chem. Soc.*, 1969, **91**, 2993; [d] J. F. Kirsch and W. P. Jencks, *J. Am. Chem. Soc.*, 1964, **86**, 837; [e] J. Walinsky, D. Buza, E. Czerwinska-Fejgin, and W. Zamlynsky, *Chem. Anal.* (*Warsaw*), 1959, 4989; [f] R. N. Lacy, *J. Chem. Soc.*, 1954, 854; [g] ref. 2; [h] ref. 11.

ponent varying with pH. It is of importance to establish other criteria and volumes of activation are now shown to be a reliable guide to distinguishing between the *E*1cb and $B_{Ac}2$ mechanisms. A few examples have been recorded of the pressure-dependence of rates of elimination by the *E*1cb route and volumes of activation shown to be positive.[6,7] This is to be expected for a reaction in which the slow step is fragmentation and, if also the case for *E*1cb ester hydrolysis, would provide an unambiguous distinction from a reaction by the addition–elimination route for which $\Delta V^{\ddagger}$ is negative. It would be expected that rates of *E*1cb reactions would decrease with pressure while those of $B_{Ac}2$ reactions would increase. This assumption has been borne out as the following data shows.

Experimental

Nitrophenyl esters of aromatic carboxylic acids were prepared by the following general method:[8] carboxylic acid (100 mmol) and nitrophenol (100 mmol) were dissolved in dry ether or tetrahydrofuran (*ca.* 50 ml) and dicyclohexylcarbodi-imide (110 mmol) was added. The mixture was stirred at room temperature for periods varying from several hours to two days, completion of the reaction being judged by complete precipitation of dicyclohexylurea. After filtration, the solvent was removed under reduced pressure and the solid ester purified by recrystallisation to constant m.p. Ethyl hydrogen malonate was the acid used for the preparation of ethyl nitrophenylmalonates by this method.

Nitrophenyl acetoacetates were prepared by passing ketene (generated by the pyrolysis of acetone) into a solution of the nitrophenol in dichloromethane. M.p.s of the esters studies are given in Table 1.

Kinetic measurements were carried out in water or in aqueous acetone or methanol buffered at a pH between 7—12, the concentrations of the esters being *ca.* 10^{-4}M. The choice of conditions was determined by the reactivities of the substrates

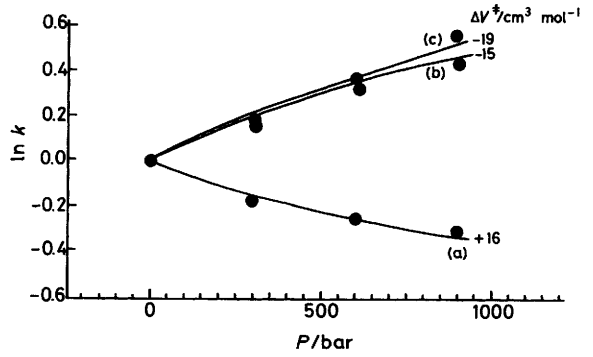


Figure 1. Plots of ln *k* against pressure for hydrolyses of some substituted benzoate esters; substituents; (a) 2,4-dinitrophenyl 4-hydroxybenzoate, (b) 2,4-dinitrophenyl 3-hydroxybenzoate, (c) 2,4-dinitrophenyl 4-methoxybenzoate

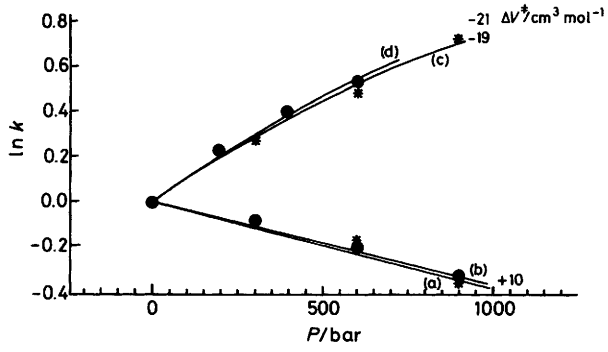


Figure 2. Plots of ln *k* against pressure for hydrolyses of some malonate esters; (a) ethyl 4-nitrophenyl malonate, (b) ethyl 2-nitrophenyl methylmalonate, (c) ethyl 2-nitrophenyl dimethylmalonate, (d) ethyl 2,4-dinitrophenyl dimethylmalonate

and their acidities but rate measurements were, in general, made within the plateau region of their rate–pH profiles while in some cases measurements were made throughout the pH range. Rates of reaction were obtained by following the appearance of the dinitrophenol (DNP) product by spectrophotometry, monitoring the reaction solutions at a wavelength around 400 nm. Some hydrolytic studies were carried out over a range of temperature enabling the activation parameters to be determined. Rate measurements under pressure were carried out in the same way using the high-pressure optical cell assembly previously described.[9] Temperatures were maintained to ± 0.5 °C and pressures to ± 10 bar. All reactions were conducted in duplicate and the pair of results (differing by less than 5%) averaged. The reactions observed were of pseudo-first-order and rate constants were evaluated using the Guggenheim method with a linear least-squares fit. Standard deviations in the rate constants were of the order 2% of their value. Volumes of activation were determined using equation (1); the constants A, B, and C were obtained by a computed fit of a plot between ln *k* and pressure.

$$RT\,\mathrm{d}\ln k/\mathrm{d}p = -\Delta V^{\ddagger} = RT(\mathrm{A} + \mathrm{B}p + \mathrm{C}p^2) \quad (1)$$

$$\mathrm{B} = -\Delta V^{\ddagger}/RT \quad (2)$$

Partial molar volumes of reagents and products were measured by means of a Paar high precision densitometer, values being obtained at concentrations 0.05 and 0.1M. Volumes of reaction were then calculated and volume profiles drawn for the reactions studied. Rate constants, volumes of activation and

Table 2. Rates and conditions of hydrolyses of esters as a function of pressure

Entry	Ester	Solvent and conditions	p/bar	$10^4\ k/s^{-1}$
1(a)	2,4-Dinitrophenyl 4-hydroxybenzoate	Water; pH 8.00 (borax); 29.8 °C	1	8.70
			300	7.38
			600	6.70
			900	6.25
1(b)		Water–methanol (70:30 v/v); pH 8.20 (borax); 29.0 °C	1	5.78
			300	4.99
			600	3.71
			900	3.29
1(c)		Water–acetone (55.6:44.4 v/v); pH 8.20 (borax); 28.0 °C	1	7.00
			300	6.20
			600	5.18
			900	4.38
1(d)		Water–acetone (55.6:44.4 v/v); pH 10.1 (hydrogen carbonate); 28.0 °C	1	9.30
			300	8.77
			600	7.96
			900	7.24
1(e)		Water–acetone (57.2:42.8 v/v); pH 12.5 (KCl–NaOH); 25.0 °C	1	18.9
			300	22.8
			600	25.9
			900	29.1
2	Ethyl 4-nitrophenyl malonate	Water; pH 5.05 (acetate); 30.6 °C	1	8.38
			300	7.86
			600	7.08
			900	6.15
3	3-Nitrophenyl acetoacetate	Water–acetone (85.7:14.3 v/v); pH 4.6 (acetate); 30.0 °C	1	5.67
			300	7.39
			500	7.87
			700	9.46
4	2,4-Dinitrophenyl 4-methoxybenzoate	Water–acetone (55.6:44.4 v/v); pH 10.1 (hydrogen carbonate); 28.8 °C	1	8.38
			300	10.1
			600	12.0
			900	13.2
5	4-Nitrophenyl benzoate	Water–acetone (55.6:44.4 v/v); pH 10.1	1	5.85
			300	7.46
			600	8.71
			900	9.98
6	2,4-Dinitrophenyl 3-hydroxybenzoate	Water–acetone (55.6:44.4 v/v); pH 10.7 (hydrogen carbonate); 29.0 °C	1	6.82
			300	8.47
			600	9.84
			900	11.9
7	2,4-Dinitrophenyl 4-acetamidobenzoate	Water–acetone (55.6:44.4 v/v); pH 8.0 (hydrogen carbonate); 27.0 °C	1	6.16
			300	7.33
			500	8.36
			700	8.96
8	Ethyl 2-nitrophenyl methylmalonate	Water; pH 8.00 (borax); 23.0 °C	1	19.10
			300	17.05
			600	15.10
			900	13.45
9	Ethyl 2-nitrophenyl dimethylmalonate	Water–acetone (57.2:42.8 v/v); pH 11.3 (carbonate); 28.7 °C	1	6.43
			300	8.50
			600	10.5
			900	13.0
10	Ethyl 2,4-dinitrophenyl dimethylmalonate	Water–acetone (57.2:42.8 v/v); pH 9.9; 23.0 °C	1	12.8
			200	15.9
			400	18.7
			600	21.7
11	2-Nitrophenyl 4-nitrophenylacetate	Water–acetone (57.2:42.8 v/v); (a) pH 7.5 (TRIS buffer); 24.0 °C	1	5.49
			300	6.71
			500	7.40
			700	7.68
		(b) pH 6.9 (imidazole); 24.5 °C	1	11.7
			300	14.9
			500	17.5
			700	21.1
12	2,4-Dinitrophenyl 4-nitrophenylacetate	Water–acetone (57.2:42.8 v/v); pH 7.0 (TRIS buffer); 23.0 °C	1	23.0
			300	25.4
			500	27.2
			700	29.9

Table 2 (*continued*)

Entry	Ester	Solvent and conditions	p/bar	10^4 k/s^{-1}
13	4-Nitrophenyl diphenylacetate	Water–acetone (57.2:42.8 v/v); pH 9.6 (hydrogen carbonate); 24.0 °C	1	3.29
			300	4.55
			500	5.17
			700	5.93
14	Ethyl acetoacetate	Water; pH 11.2 (carbonate); 34.0 °C	1	5.67
			300	7.39
			400	7.87
			600	9.46
15	2,4-Dinitrophenyl acetate	(a) Water; pH 4.75 (acetate); 28.0 °C	1	2.05
			300	3.08
			600	3.51
			900	4.3
		(b) Methanol; pH 4.75 (acetate); 28.0 °C	1	5.60
			300	6.62
			600	8.31
			900	10.2
		(c) Ethanol; pH 4.75 (acetate); 28.0 °C	1	4.62
			300	6.64
			600	7.73
			900	9.36
16	3-Nitrophenyl cyanoacetate	Water; pH 7.4 (TRIS buffer); 31.0 °C	1	16.8
			300	21.8
			600	28.3
			800	33.3
17	4-Nitrophenyl cyanoacetate	Water; pH 7.0; 28.7 °C	1	6.54
			300	8.98
			600	10.8
			900	14.0
18	2-Nitrophenyl cyanoacetate	(a) Water; pH 4.75 (acetate); 30.2 °C	1	9.30
			300	11.3
			600	13.5
			900	16.2
		(b) Water; pH 5.05 (acetate); 31.0 °C	1	12.5
			300	14.9
			600	17.3
			900	20.2
19	2,4-Dinitrophenyl 4-hydroxycinnamate	Water–acetone (60:40 v/v); pH 8.44 (TRIS buffer); 29.0 °C	1	27.5
			150	31.1
			250	33.6
20	4-Chlorophenyl fluorene-9-carboxylate	(a) Water–ethanol (60:40 v/v); pH 10.0 (hydrogen carbonate); 33.5 °C	1	19.7
			200	23.1
			400	26.8
			600	30.4
		(b) Water–ethanol (60:40 v/v); pH 11.35 (carbonate); 27.8 °C	1	16.8
			300	18.1
			600	19.3
			900	21.5
		(c) Water–ethanol (60:40 v/v); pH 12.5 (NaON + KCl); 29.2 °C	1	10.6
			300	12.5
			600	13.4
			900	14.7
21	4-Methoxyphenyl fluorene-9-carboxylate	(a) Water–ethanol (60:40 v/v); pH 11.37 (carbonate); 31.0 °C	1	15.9
			300	24.7
			600	33.3
			900	42.0
		(b) Water–ethanol (60:40 v/v); pH 12.5 (NaOH + KCl); 33.0 °C	1	18.6
			200	25.0
			400	31.1
			600	37.1
22	2,2,2-Trifluoroethyl fluorene-9-carboxylate	Water–ethanol (60:40 v/v); pH 11.45 (carbonate); 33.0 °C	1	7.93
			200	10.3
			400	13.4
			600	16.7
23	3-Nitrophenyl fluorene-9-carboxylate	Water–acetone (60:40 v/v); pH 11.1; 30.8 °C	1	4.92
			300	5.92
			600	7.32
			900	9.48

Table 3. Activation parameters for hydrolyses of esters

Entry	Ester	pH[a]	$\Delta V^{\ddagger}$/cm^3 mol^{-1} [c]	E_A/kJ mol^{-1} [c]	$\Delta S^{\ddagger}$/J K^{-1} mol^{-1} [c]
1	2,4-Dinitrophenyl 4-hydroxybenzoate	8.0	+16.5		
		8.2 M	+16.6	114	+65
		8.2 A	+13.5 (−21[b])		
		10.1 A	+7.1		
		12.5 A	−18		
2	Ethyl 4-nitrophenyl malonate	5.05	+10.0 (−2)	115	+79
3	3-Nitrophenyl acetoacetate	4.6 A	+8.0	94	+9
4	2,4-Dinitrophenyl 4-methoxybenzoate	10.3 A	−19.2 (−5)	82	−35
5	4-Nitrophenyl benzoate	10.1 A	−21.4		
6	2,4-Dinitrophenyl 3-hydroxybenzoate	10.7 A	−14.8 (−21)		
7	2,4-Dinitrophenyl 4-acetamidobenzoate	9.8 A	−17.2		
8	Ethyl 2-nitrophenyl methylmalonate	8.00	+10.0 (−17)		
9	Ethyl 2-nitrophenyl dimethylmalonate	11.3 A	−19.6 (−23)		
10	Ethyl 2,4-dinitrophenyl dimethylmalonate	9.9 A	−21.4	86	−26
11	2-Nitrophenyl 4-nitrophenylacetate	6.9 A	−20.6		
		7.5 A	−20.7		
12	2,4-Dinitrophenyl 4-nitrophenylacetate	7.0 A	−9.1		
13	4-Nitrophenyl diphenylacetate	9.6 A	−29.6		
14	Ethyl acetoacetate	11.2	−21.6		
15	2,4-Dinitrophenyl acetate	4.74	−19.7		
		4.75 M	−16.9	63	−106
		4.74 E	−18.9		
16	3-Nitrophenyl cyanoacetate	7.0	−23		
		7.4	−20.5		
17	4-Nitrophenyl cyanoacetate	7.0	−20.6	55	−130
		4.75	−17.4	64	−102
18	2-Nitrophenyl cyanoacetate	4.40		89	−20
		4.70	−15.5	64	−96
		5.05	−13.5		
19	2,4-Dinitrophenyl 4-hydroxycinnamate	8.44	−20.3		
20	4-Chlorophenyl fluorene-9-carboxylate	10.0 E	−21.8 (−10)	63	−100
		11.3 E	−10.0	85	−30
		12.5 E	−13.0		
21	4-Methoxyphenyl fluorene-9-carboxylate	11.4 E	−40		
		12.5 E	−40	45	−160
22	2,2,2-Trifluoroethyl fluorene-9-carboxylate	11.5 E	−36 (−14)	30	−207
23	3-Nitrophenyl 9-methylfluorene-9-carboxylate	11.1 A	−18.4		
24	3-Nitrophenyl fluorene-9-carboxylate	9.17 A		56	−100

[a] The organic component of the aqueous–organic solvent is indicated thus: A = acetone, E = ethanol, M = methanol. [b] Numbers in parentheses refer to volumes of reaction calculated from partial molar volumes in the pure organic solvent indicated. [c] The limits of uncertainty in $\Delta V^{\ddagger}$, $\Delta S^{\ddagger}$, and E_A have a standard deviation of about 5%.

of reaction, and partial molar volumes are summarised in Tables 2—3. A glass electrode was set up for use at pressures up to 500 bar. It was ascertained that the pH of the buffers used changed negligibly under the pressures used for kinetic studies.

Discussion

All measured rates obeyed first-order kinetics and plots of ln k against pressure changed smoothly, in many cases almost linearly over the range studied though in some there was discernible curvature indicative of a measurable compressibility of activation. No attempt was made to evaluate this quantity since there was no apparent correlation between the curvature of the plot and the inferred mechanism of the reaction. Temperature variation was made over the range 20—60 °C and energies and entropies of activation determined from the rates.

Volumes of activation for the nitrophenyl esters listed in Table 2 fall into two distinct categories, positive and negative. It is notable that all those esters which exhibit positive values are capable of reaction by the $E1cb$ route and possess a suitable acidic proton. The hydrolysis of 4-hydroxybenzoate (Entry 1) has been studied over a range of pH values wherein it may be seen that the volumes of activation are large and positive within the plateau region in which the $E1cb$ mechanism is deemed to operate. There is a fall-off in value at higher pH actually becoming negative above pH 12 in the region associated with $B_{Ac}2$ displacement on the conjugate base of the ester. In agreement with this interpretation, the parent compound, 4-nitrophenyl benzoate (Entry 5), 4-nitrophenyl diphenylacetate (Entry 13), and the 4-methoxy and 3-hydroxy analogues (Entries 4 and 6) which are unable to eliminate phenolate ion and form a ketonoid intermediate, show negative volumes of activation, the latter compound even in the pH region around 10 at which the phenolic group is ionised, Figure 1. These observations clearly reveal mechanistic differences, a positive volume of activation being in accordance with expectations for a dissociative slow step and a negative value well authenticated for $B_{Ac}2$ ester hydrolysis,[10] an associative process. The nitrogen analogue, 4-acetamidobenzoate (Entry 7), by this criterion does not hydrolyse by the $E1cb$ route and presumably this can be accounted for by the much lower acidity of the amino proton compared with a phenolic proton. Similarly, neither the cyanoacetates (Entries 16, 17) nor the 2- or 4-nitrophenylacetates (No. 12) exhibit $E1cb$ mechanisms since they are not sufficiently acidic to ionise at pH 7 at which hydrolytic rates are quite fast, presumably by attack of water.

It is perhaps surprising that 4-hydroxycinnamate (Entry 19), the vinylogue of 4-hydroxybenzoate, hydrolyses with a large and negative volume of activation evidently by the $B_{Ac}2$ route. While an intermediate of the type 2 seems quite feasible, a

possible reason for the preference for the addition–elimination pathway might lie in the cinnamate group existing in an unfavourable conformation with the aryl ring orthogonal to the ethylenic double bond.

In the acetoacetate and malonate series (Table 2, Entries 3 and 14, and 2 and 7—10, respectively) the contrast is again observed between volumes of activation for esters which possess an acidic α-proton, which are positive and those for esters which do not (the dialkylmalonate esters) and which are negative, an observation which reinforces confidence in this mechanistic criterion, Figure 2. The interpretation of volumes of activation for hydrolysis of the esters of fluorene-9-carboxylic acid is less straightforward. The mechanism by which hydrolysis occurs has been shown to be dependent upon the nucleofugacity of the phenol,[11] resulting in a Brønsted plot with a sharp discontinuity. According to this, phenyl esters bearing $-M$ substituents (–NO_2, –CN, –CO·R) lie within the range for which the *E*1cb mechanism operates ($\beta_{LG} = -1$) while hydrolysis of esters with relatively poor leaving groups including alkyl appears to be by the $B_{Ac}2$ route ($\beta_{LG} = +0.11$). 4-Methoxyphenyl, phenyl, and 4-chlorophenyl lie in the borderline region in which it might be supposed that a mixed mechanism is likely. The pK_a values of all these esters are around 10 so that essentially complete dissociation must have occurred by pH 12. This, however, has been shown not to be a reliable indication that the most favourable pathway is *E*1cb. Volumes of activation are substantially negative for all the examples of fluorene-9-carboxylate esters studied which are all from the second group of the Brønsted plot and for which the $B_{Ac}2$ or a mixed mechanism would be expected. It was not possible to include examples at present from the first group since their rates of hydrolysis were too high to be followed by our method. These, however, will be examined at a later date. The value of $\Delta V^{\ddagger}$ for hydrolyses of 4-methoxyphenyl and trifluoroethyl fluorene-9-carboxylates are highly negative, much more so than is found for other $B_{Ac}2$ reactions, while the value for the 4-chlorophenyl ester is much less negative consistent with a mixed mechanism. These observations parallel the entropies of activation. Presumably the former react by attack of water on the conjugate base accompanied by a considerable increase in solvation. The 9-methyl analogue which is unable to ionise but must hydrolyse by attack of OH^- on the neutral substrate has $\Delta V^{\ddagger}$ in the normal range, -20 cm^3 mol^{-1}.

Note added in proof: The hydrolysis of *p*-nitrophenyl phenylcarbamate appears also to occur by the *E*1cb route; $\Delta v^{\ddagger}$ $+13$ cm^3 mol^{-1}. We thank Miss T. Metz for this measurement.

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