Effect of an Aromatic Ester Conjugate Base on *E*1cB Ester Hydrolysis. Alkaline Hydrolysis of Fluorene-9-carboxylate Esters

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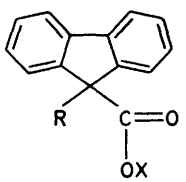
A series of alkyl and substituted-aryl esters of fluorene-9-carboxylic acid have been synthesised and their alkaline hydrolyses studied. The pH profiles for hydrolysis indicated substrate ionisation at higher pH values (confirmed by spectral studies) and kinetic pK values for a number of these esters were obtained at 25 °C. At high pH ($\gg$pK_a) the rate of hydrolysis became independent of pH with the observed rate constant in this high pH plateau region being called k'. A plot of the logarithm (to base 10) of k' *versus* the pK_a of the conjugate acid of the appropriate leaving group consisted of two limbs, A and B, flanking a minimum. The slopes of the plots described above for regions A and B were -1.01 ± 0.05 and $+0.11 \pm 0.01$, respectively. Region A, of high negative slope, was shown to correspond to an *E*1cB reaction of the title esters on the basis of linear free energy relationship arguments, the solvent deuterium kinetic isotope effect, activation parameters, and comparison with the 9-methyl-blocked analogues, as well as by the observation of saturation kinetics in aniline buffers at low pH. Region B was shown to correspond to a rate-determining step of attack of hydroxide ion on the limiting amount of ester in its neutral form. The low eliminative reactivity of fluorene ester anions was discussed along with factors considered in the literature for explaining elimination rates of ester anions.

WHILST a great deal is known about alkene-forming elimination reaction mechanisms and about addition–elimination (AE) routes of acyl transfer, only recently has emphasis been laid on the participation of elimination mechanisms as a class in the field of acyl transfer. Current interest in this area is aimed at delineating the features responsible for the dictation of mechanism for substrates which are, at least potentially, elimination–addition (EA) active. Two central problems are the natures of the driving forces for the *E*1cB (and *E*2) modes of acyl transfer and the definition of which structural and energetic features control the points at which mechanisms change from *E*2 to *E*1cB, from *E*1cB to $B_{AC}2$, *etc.*

A variety of driving forces [1] have been probed for *E*1cB reactions and it appears that the degree of activation of the leaving group is dominant. However, it has also been hinted in a few cases that the pK_a of the α-site [2] and the nature of the (hetero)-α-atom [3] exert an influence. However, little systematic work is yet available on this aspect. For this reason the fluorene-9-carboxylic esters (1a—m) were selected for study as the conjugate base of these would be aromatic [4] [with 14 π-electrons, $n = 3$ in the Hückel $(4n + 2)$ rule]. Consequently, the electron-pair required for the *E*1 step would be extensively delocalised relative to other *E*1cB substrate anions.



(1) (R = H) a; X = *p*-$NO_2C_6H_4$
b; X = *m*-$NO_2C_6H_4$
c; X = *p*-ClC_6H_4
d; X = *m*-ClC_6H_4
e; X = *p*-CNC_6H_4
f; X = *p*-$CH_3COC_6H_4$
g; X = *p*-$CH_3OC_6H_4$
h; X = *p*-$CH_3C_6H_4$
i; X = C_6H_5
j; X = $HC{\equiv}C{\cdot}CH_2$
k; X = CF_3CH_2
l; X = C_2H_5
m; X = CH_3

(2) (R = CH_3) a; X = *p*-$NO_2C_6H_4$
b; X = 2,4-$(NO_2)_2C_6H_3$

A wide range of leaving groups was chosen because of mechanistic changeovers common in EA/AE borderline systems. These changeovers arise chiefly from the very high leaving group sensitivity of the *E*1cB route. When the leaving group becomes poor, the elimination step can no longer compete with the corresponding bimolecular reactions and a mechanistic change is enforced. For example, for methylaminosulphonates, poorer leaving groups are believed to require a nucleophilic push from solvent in an essentially *E*1 transition-state, whereas the more active esters in this series follow a clean *E*1cB mechanism.[5] Acetoacetate esters change mechanism from *E*1cB for aryl esters to a $B_{AC}2$ attack of hydroxide ion on neutral ester for alkyl leaving groups:[6] similar behaviour has been seen for thiolacetoacetates [7] and has been reported also for *N*-acetylcarbamates.[8] A change from *E*1cB to *E*2 has been recognised [3] for aryl methanesulphonates as the leaving group becomes more active. In this case mechanistic changeover is enforced by the lifetimes of the predicted conjugate bases of very activated sulphonyl derivatives (with p$K_{L.G.}$ <6) becoming too short ($\lesssim 10^{-13}$ s) for them to exist as discrete intermediates, *i.e.* their predicted rates of breakdown in the *E*1 step would exceed the ' vibration limit ' approximately set by the vibration time of an S–OAr bond. With the esters of fluorene-9-carboxylic acid the ' super-stabilised ' aromatic conjugate base was anticipated to decrease absolute *E*1cB reactivity and a consequent mechanistic change appeared likely. In fact, we have reported in a preliminary communication [9] that such a change in mechanism occurred for weaker leaving groups in system (1) and indeed a Brönsted leaving group plot with a positive slope in alkaline media was observed (see Figure 1). We now report mechanistic details of this system. There have been some recent comparative

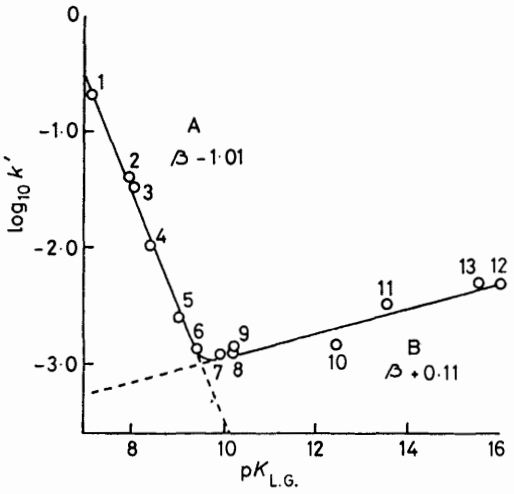


FIGURE 1 Brönsted leaving group plot of the dependence of $\log_{10} k'$ (for the pH-independent rate at pH $\gg$ pK_a) *versus* p$K_{L.G.}$ (the pK_a values of the conjugate acids of the leaving groups) for fluorene-9-carboxylate esters (1). The descending limb (region A) follows the equation $\log_{10} k' = -1.01$ p$K_{L.G.}$ (± 0.05) + 6.53 (± 0.45). The ascending limb (region B) follows the equation $\log_{10} k' = +0.11$ p$K_{L.G.}$ (± 0.02) − 4.01 (± 0.21). The points are experimental: the solid line follows the above equations in regions A and B, and a smooth curve through the data in the intermediate region. The leaving groups' identities (given by the nature of R) are indicated by the numbers as follows: (1) *p*-nitrophenyl; (2) *p*-cyanophenyl; (3) *p*-acetylphenyl; (4) *m*-nitrophenyl; (5) *m*-chlorophenyl; (6) *p*-chlorophenyl; (7) phenyl; (8) *p*-cresyl; (9) *p*-methoxyphenyl; (10) 2,2,2-trifluoroethyl; (11) propargyl; (12) ethyl; (13) methyl

reports of alkaline solvolyses of related esters in dipolar aprotic and aqueous media.[10]

EXPERIMENTAL

Materials.—Fluorene-9-carboxylic acid, phenols, and alcohols for synthesis were obtained from the Aldrich Chemical Co. or Fluka.

Synthesis of Esters of Fluorene-9-carboxylic Acid.—These were prepared *via* fluorene-9-carbonyl chloride,[11] m.p. 75—77 °C (lit.,[12] 77 °C) by the following general method (except for the methyl and ethyl esters), described in detail for the *p*-nitrophenyl ester.

To a stirred solution of fluorene-9-carbonyl chloride (0.914 g, 4 mmol) in dry methylene dichloride (40 ml) at room temperature a solution of *p*-nitrophenol (0.56 g, 4 mmol) and triethylamine (0.6 ml as catalyst) in methylene dichloride (50 ml) was added dropwise over 40 min. After stirring for 20 min, the solvent was removed and a slightly yellow solid was obtained. The solid was washed with 10 ml of cooled diethyl ether (while the container was immersed in ice–water) and then washed with cooled water (10 ml). The ether phase was separated from the solid. Recrystallisation from acetone–water gave *p*-nitrophenyl fluorene-9-carboxylate as needles, yield 0.9 g (68%), m.p. 156—158 °C. Analytical data for the esters thus prepared are listed in Table 1.

The methyl and ethyl esters were prepared by literature procedures [13] with m.p. 65—67 °C (lit.,[13] 63—66 °C) and 43—45 °C (lit.,[13] 42—45 °C), respectively.

Synthesis of Esters of 9-Methylfluorene-9-carboxylic Acid.—These were prepared from 9-methylfluorene-9-carbonyl chloride, prepared from the corresponding acid and phosphorus pentachloride in a manner similar to that for fluorene-9-carbonyl chloride;[11] their analytical data are collected in Table 2. 9-Methylfluorene-9-carbonyl chloride was recrystallised from dry, light petroleum (b.p. 60—80 °C) as needles, m.p. 95—96 °C, in 90% yield. 9-Methylfluorene-9-carboxylic acid,[14] m.p. 170—171 °C (lit.,[14] 170—171 °C) was prepared by saponification of its methyl ester, m.p. 108—109 °C (lit.,[14] 108—109 °C), which was isolated by reaction of fluorene-9-carboxylic acid methyl ester with methyl iodide as described.[14]

Purification of Reagents.—Phosphate, carbonate, and borate buffers were prepared from analytical reagent grade material and ionic strengths were held at 0.1M with KCl or NaCl. Acetonitrile was dried over molecular sieves (Type 4A), was fractionally distilled from phosphorus pentaoxide under dry and carbon dioxide-free nitrogen, refluxed over calcium hydride (5 h), and finally fractionally distilled under nitrogen (very slowly), b.p. 81 °C at 760 mmHg, (lit.,[15] 81.6 °C). Morpholine was purified by distillation after refluxing (24 h) over sodium metal under dry nitrogen, b.p. 125—126 °C at 740 mmHg (lit.,[16] b.p. 128.3 °C).

Methods.—Rate measurements were performed using the SF-3A stopped-flow spectrometer MK IV or Pye-Unicam SP8-100 u.v.–visible spectrophotometer. The SF-3A Canterbury apparatus, employed for following the progress of the fast reactions, consisted of a flow-unit and a control-unit fitted with an oscilloscope, Datalab transient recorder (DL 910) and a J.J. Instruments CR 650 chart recorder. Equal volumes of reagents were mixed such that the final

TABLE 1

Analytical data for esters (1) of fluorene-9-carboxylic acid

Ester	M.p. [a] (°C)	Expected (%) C	H	N	F or Cl	Molecular formula	Found (%) [b] C	H	N	F or Cl
(1k)	83—85	65.8	3.8		19.5(F)	$C_{16}H_{11}F_3O_2$	65.6	3.8		19.2(F)
(1j)	58—60	82.3	4.8			$C_{17}H_{12}O_2$	82.1	4.8		
(1i)	90—92	83.9	4.9			$C_{20}H_{14}O_2$	83.6	4.9		
(1a)	156—158	72.5	3.9	4.25		$C_{20}H_{13}NO_4$	72.4	3.9	4.0	
(1b)	110—112	72.5	3.9	4.25		$C_{20}H_{13}NO_4$	72.2	3.9	3.9	
(1c)	112—114	74.9	4.1		11.1(Cl)	$C_{20}H_{13}ClO_2$	74.4	4.1		11.2(Cl)
(1d)	86—88	74.9	4.1		11.1(Cl)	$C_{20}H_{13}ClO_2$	74.3	4.1		11.0(Cl)
(1e)	130—132	81.0	4.2	4.5		$C_{21}H_{13}NO_3$	80.7	4.2	4.3	
(1f)	157—158	80.5	4.9			$C_{22}H_{16}O_3$	80.1	4.8		
(1g)	89—91	79.8	5.1			$C_{21}H_{16}O_3$	79.6	5.0		
(1h)	115—117	84.0	5.3			$C_{21}H_{16}O_2$	83.8	5.3		

[a] Melting points measured using a Reichert Koflerblock instrument. [b] Analysed by Microanalytical Laboratory, Department of Chemistry, University of Manchester.

TABLE 2

Analytical data for esters (2) of 9-methylfluorene-9-carboxylic acid

Ester	M.p. (°C)	Expected (%) C	H	N	S	Molecular formula	Found (%) C	H	N	S
(2b)	118—120	64.6	3.2	7.2		$C_{21}H_{14}N_2O_6$	64.3	3.6	7.0	
(2a)	101—103	73.0	4.3	4.1		$C_{21}H_{15}NO_4$	72.8	4.4	3.8	

absorbance change was ≤ 0.1 for stopped-flow work. Ester syringe solutions were 0.27% v/v in acetonitrile before mixing. Average rate constants from a minimum of four stopped-flow runs were taken. A Churchill thermocirculator was used to control the temperature of the four-cell holder of the SP8-100 spectrophotometer to ± 0.1 °C, and correct temperature equilibration was ascertained by immersion of a thermocouple in the cell. For conventional kinetic studies stock solutions of esters were prepared by weighing ester (*ca.* 2 mg) into a 2 ml volumetric flask and making up to the mark with acetonitrile. U.v.–visible spectrophotometry was carried out using 10 mm path-length cells containing appropriate media (3 ml), which were left in cell holders for 10 min to attain the reaction temperature. The required amount of substrate (10—50 μl stock solution) was injected into the sample cell with a Hamilton syringe, stirred rapidly with a Teflon stirring rod and recording started. A suitable wavelength (Table 3) for following the reaction was determined from repetitive spectral scanning of a reacting mixture. Rates of hydrolysis of 4-nitrophenyl and 2,4-dinitrophenyl 9-methylfluorene-9-carboxylate were followed at 400 and 269 nm, respectively.

TABLE 3

Alkaline plateau rate constants (k') and apparent acid dissociation constants for esters of fluorene-9-carboxylic acid at 25 °C and ionic strength 0.1M. Also given are the wavelengths used for kinetic study (λ_{kin})

Ester	$10^3k'/s^{-1}$ [a]	pK_{ester}^{app}	$pK_{L.G.}$ [e]	λ_{kin}/nm
(1a)	200 ± 2	9.9 [b]	7.14	400
(1e)	39.9 ± 0.2	9.84 [b]	7.95	328
(1f)	32.8 ± 0.6	9.8 [b]	8.05	376
(1b)	10.1 ± 0.2	10.2 [b]	8.39	326
(1j)	3.15 ± 0.01	11.3 [b]	10.35 [f]	326
(1m)	5.12 ± 0.1	11.8 [c]	15.5 [f]	324
(1l)	4.86 ± 0.02	11.7 [c]	16.0 [g]	324
(1d)	2.22 ± 0.02	10.24 [d]	9.02	328
(1c)	1.46 ± 0.02	10.32 [d]	9.38	328
(1i)	1.09 ± 0.01	10.42 [d]	9.92	328
(1h)	1.10 ± 0.03	10.50 [d]	10.19 [h]	328
(1g)	1.40 ± 0.04	10.52 [d]	10.27	326
(1k)	1.46 ± 0.05	10.99 [d]	12.43 [f]	322

[a] Means with deviations of at least three different hydroxide ion concentrations from 0.025—0.10M except for the *p*-nitrophenyl ester for which the range was 0.01—0.25M-NaOH. [b] Values indicated thus are from $\log_{10}k_{obs}$ *versus* pH plots, corrected where necessary for slight buffer concentration effects as described in the text. [c] Values from K_w/K_a determined from k_{obs} *versus* $[HO^-]$ saturation plots. [d] Values calculated from $pK_{ester}^{app} = 8.26 + 0.22pK_{L.G.}$, the linear free energy relationship which is obtained for the *p*-NO_2, *p*-CN, *p*-Ac, *m*-NO_2, propargyl, methyl, and ethyl esters. [e] Ionization constants obtained, except where indicated, from W. P. Jencks and J. Regenstein in 'Handbook of Biochemistry,' ed. H. A. Sober, Chemical Rubber Publishing Co., Cleveland, Ohio, 1970, 2nd. edn., Section J-187; G. Kortum, W. Vogel, and K. Andrusson, 'Dissociation Constants of Organic Acids in Aqueous Solution,' Butterworths, London, 1961. [f] P. Ballinger and F. A. Long, *J. Am. Chem. Soc.*, 1959, **81**, 1050; 1960, **82**, 795. [g] W. K. McEwen, *J. Am. Chem. Soc.*, 1936, **58**, 1124. [h] M. M. Fickling, A. Fischer, B. R. Mann, J. Packer, and J. Vaughan, *J. Am. Chem. Soc.*, 1959, **81**, 4226.

RESULTS

Hydrolysis of some of the esters, depending on the conditions, showed either a single step or a fast step with a much slower one. Hydrolysis of *p*-nitrophenyl, *m*-nitrophenyl, *p*-acetylphenyl, and *p*-cyanophenyl esters of fluorene-9-carboxylic acid in various buffered solutions showed two steps, but only the second, slower step was studied. For example, the observed reaction progress curve for the hydrolysis of *p*-cyanophenyl fluorene-9-carboxylate in borate buffer was as represented in Figure 2a. The extraction of the rate constant for the slower process was readily achieved in these studies by plotting $\log_{10}(A_t - A_\infty)$ *versus* t which, after initial curvature, became linear in the region corres-

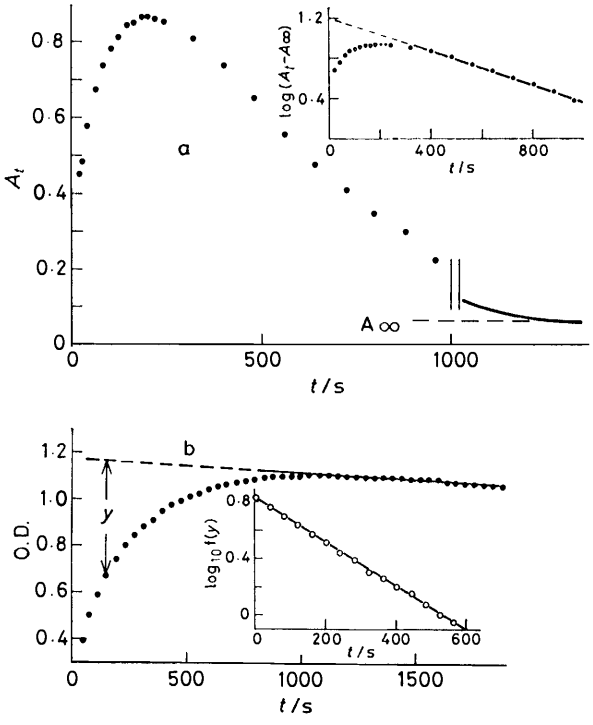


FIGURE 2 a, Hydrolysis at 25 °C of *p*-cyanophenyl fluorene-9-carboxylate in 1.25mM-borate buffer (pH 8.68, μ 0.1M) followed by plotting absorbance at 328 nm *versus* time. The inset shows the logarithmic replot used to determine k_2 for the latter, slower phase (points shown are experimental, line is derived by linear least-squares regression analysis of the data in the latter stages of reaction only). b, Time course of the reaction of *p*-nitrophenyl fluorene-9-carboxylate with aniline buffer followed at 400 nm. The inset shows the logarithmic replot used to determine k (points for this are experimental, line is derived by linear least-squares regression analysis of the data). The reaction was conducted at ionic strength 0.1M, 25 °C, 10% v/v acetonitrile with $[PhNH_2]$ 0.045M, 90% free base

ponding to the slower process (see inset to Figure 2a; k_{obs} was $-2.303 \times$ slope of final linear section).

For buffered solutions with pH values $\gtrsim 7$, the slower process was usually followed for two-step reactions and in a few cases such rate constants decreased (very slightly) as the buffer concentration was reduced, although usually such rate constants were independent of buffer concentration. pH Profiles were constructed by plotting $\log_{10}k_{obs}$ for the slow process *versus* pH; in a few cases, as discussed above, values of k_{obs} had to be extrapolated to zero buffer concentration (k_{spon}) before use in pH profiles (see Figure 3, for

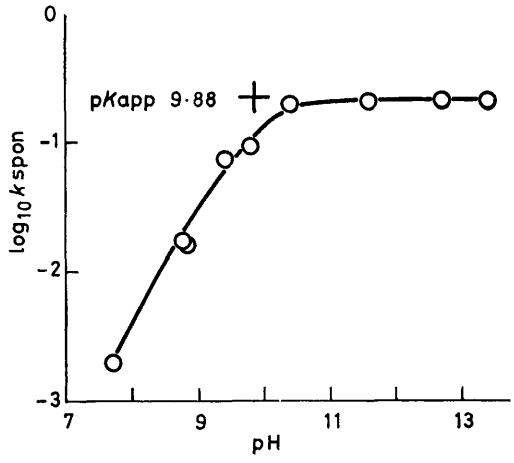


FIGURE 3 pH–Rate profile at 25 °C and $\mu = 0.1$M for the hydrolysis of *p*-nitrophenyl fluorene-9-carboxylate. The rate constants refer to the slow step, where biphasic kinetics occurred, and were extrapolated to zero buffer concentration where necessary. The points are experimental, line is theoretical for an acid of pK_{app} 9.88 and a limiting value of $\log_{10} k_{spon}$ at high pH of -0.68

example). A referee has pointed out that the slight concentration dependence of rate constant for the slower step may arise not only from a $B_{AC}2$ contribution but also from the kinetic procedure used to extract the rate constant. These small effects (<10% change in rate constant) were observed only for the *p*-nitrophenyl ester. They were not detected with the *p*-acetylphenyl ester or for the *p*-cyanophenyl ester.

Some esters gave pH profiles similar to that shown in Figure 3 for the *p*-nitrophenyl ester, *i.e.* *m*-nitrophenyl, *p*-acetylphenyl, and *p*-cyanophenyl. Thus, at high pH the slow process rate constant becomes pH-independent and is called k'. For alkyl esters, the pK_{app} value, the inflexion in the pH profile, fell in the pH region corresponding to sodium hydroxide media. For such esters, rate constants showed saturation kinetics, levelling at higher hydroxide ion concentration (Figure 4) and obeyed the equation $k_{obs} = k'/(1 + K_w/K_a[HO^-])$ from which k' and K_w/K_a were obtained by a linear plot of $1/k_{obs}$ *versus* $1/[HO^-]$. The pK_{app} values for some esters of fluorene-9-carboxylic acid which were obtained from the inflexions of $\log_{10}k_{obs}$ *versus* pH plots are collected in Table 3 along with pK_a values for some other esters calculated from K_w/K_a values and a value of 10^{-14} for K_w.

Alkaline hydrolysis of all esters of fluorene-9-carboxylic acid showed single-step kinetics with good pseudo-first-order rate constants independent of hydroxide ion concentration (*i.e.* $= k'$) in the range 0.02—0.10M-NaOH. Values of k' were determined, therefore, in such strongly basic solutions at 25 °C for esters of varying leaving group (Table 3). For the aryl esters there is poor correlation of $\log_{10}k'$ with Hammett σ constants. However, if Hammett σ^- values are used and the *p*-OCH_3, *p*-CH_3 and H compounds excluded (leaving six points) a good relationship is obtained [equation (1)].

$$\log_{10}k' = (2.1 \pm 0.1)\,\sigma^- - 3.4\,(\pm 0.1) \qquad (1)$$

The deviation of the poorer leaving groups is accentuated when a Brönsted plot for leaving group variation is plotted to include data for alkyl esters also (see Figure 1). In this case the Brönsted plot of $\log_{10}k'$ *versus* $pK_{L.G.}$ (the pK_a of the conjugate acid of the appropriate leaving group) consists of two separate lines, A and B, of equations (2) and (3) respectively, flanking a minimum. Such an observation of

$$\text{A}\quad \log_{10}k' = (-1.01 \pm 0.05)pK_a + (6.60 \pm 0.45) \qquad (2)$$

$$\text{B}\quad \log_{10}k' = (0.11 \pm 0.01)pK_a + (-4.08 \pm 0.17) \qquad (3)$$

a positive value of $\beta_{L.G.}$ (region B) for basic ester hydrolysis has not been reported previously [9] to our knowledge.

The k' term for the hydrolysis of *m*-chlorophenyl ester was studied in sodium deuterioxide–D_2O media at 25 °C (μ 0.1M held with KCl). The value of k'_D was $1.69 \pm 0.02 \times 10^{-3}$ s^{-1}. Comparison with k'_H ($= 2.22 \pm 0.02 \times 10^{-3}$ s^{-1}) gives $k'_H/k'_D = 1.3$. Values of k'_H and k'_D are means of four and three determinations of k_{obs} at different $[HO^-]$, respectively.

As the dependence of k_{obs} on $[HO^-]$ for the alkyl esters was hyperbolic, complete $[HO^-]$–k_{obs} profiles were determined for the methyl and ethyl esters at a series of temperatures. Data are plotted in Figure 4 for the methyl ester.

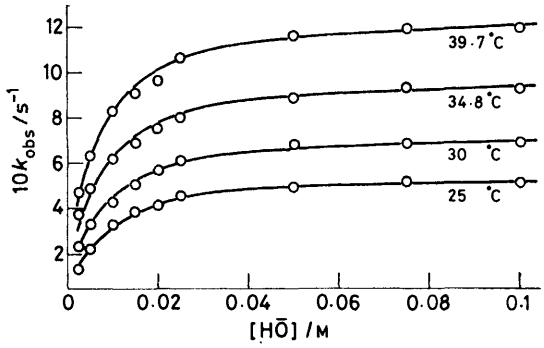


FIGURE 4 Plot of k_{obs} *versus* hydroxide ion concentration for the alkaline hydrolysis of methyl fluorene-9-carboxylate, measured at μ 0.1M and the temperatures indicated. Lines are theoretical using the equation $k_{obs} = k'/(1 + K_w/K_a[HO^-])$ with k' and K_w/K_a values as described in the text

For each temperature extracted values of k' and K_w/K_a are summarised in Table 4, along with activation parameters for the derived kinetic terms [K_a, k', k_{HO^-}(calc.)] at 25 °C. Also included are the activation parameters for the k' term for the *m*-chlorophenyl and propargyl esters. Plots of $\log_{10}$ (parameter) *versus* $1/T$ were linear; activation parameters were calculated using a computer program written by the late Professor J. N. Bradley.

Hydrolysis of the *p*-nitrophenyl ester in aniline buffers showed two steps. A fast primary step is followed by a very much slower reaction. The slower reaction corresponds to those studied above and data are collected in Table 5 and plotted in Figure 5. The faster reaction could easily be

TABLE 4

Microscopic kinetic parameters and derived activation parameters (calculated at 25 °C) for alkaline hydrolyses of aryl and alkyl fluorene-9-carboxylates at ionic strength 0.1M

	Term (ester)							
	$10^3\ k'/s^{-1}$				$K_a.K_w^{-1}$/l mol^{-1} [a]		k_{HO^-}(calc.)/l mol^{-1} s^{-1} [b]	
T/°C	*m*-ClC$_6$H$_4$O	OEt	OMe	Propargyloxy	OEt	OMe	OEt	OMe
25.0	2.27	5.16	5.62	3.21	191.7 ± 32	141.8 ± 7.1	0.99 ± 0.14	0.797 ± 0.04
29.7		6.54			217.3 ± 22		1.42 ± 0.14	
30.0	3.80		7.39	6.85		164.9 ± 1.3		1.22 ± 0.09
34.2		7.93			251.7 ± 41		1.99 ± 0.33	
34.8			9.84	9.14		182.4 ± 14		1.79 ± 0.14
35.0	6.13							
39.0		9.33			281.3 ± 44		2.62 ± 0.41	
39.7			12.60	11.81		194.6 ± 14		2.45 ± 0.18
					K_a			
E_a/ kJ mol^{-1}	78.1 ± 1.4	35.5 ± 0.7	44.3 ± 0.2	40.2 ± 2.0	79.6 ± 0.4	72.7 ± 2.0	53.6 ± 1.4	59.6 ± 2.1
$\Delta H^{\ddagger}$/ kJ mol^{-1}	75.3 ± 1.4	31.0 ± 0.7	41.7 ± 0.8	37.7 ± 2.0	77.1 ± 0.4	70.2 ± 2.0	51.1 ± 1.4	57.3 ± 2.1
$\Delta S^{\ddagger}$/ J K^{-1} mol^{-1}	−40.5 ± 0.5	−184.8 ± 2.3	−148.2 ± 2.6	−165.9 ± 6.5	−209.9 ± 1.5	−253.3 ± 7.0	−73.0 ± 4.5	−54.8 ± 6.8

[a] The values of $K_a.K_w^{-1}$ quoted were derived by linearisation and least-squares regression analysis of the observed data. The activation parameters in this column refer to the extracted values of K_a for the calculation of which values of K_w at 25, 30, 35, and 40 °C used were 1.008×10^{-14}, 1.469×10^{-14}, 2.089×10^{-14}, and 2.919×10^{-14}, respectively (taken from R. G. Bates, 'Determination of pH,' Wiley, New York, 1965). Values of pK_a for the methyl ester at 25, 30, 34.8, and 39.7 °C thus obtained were 11.85, 11.62, 11.42, and 11.25, respectively. For the ethyl ester pK_a values were 11.71, 11.49, 11.27, and 11.08 at 25, 29.6, 34.2 and 39.0 °C, respectively. [b] k_{HO^-}(calc.) = $k'K_a/K_w$.

TABLE 5

Rate constants for alkaline hydrolysis and acid dissociation constants of various esters

Ester	pK(ester) [a]	k'/s^{-1}	Reference
MeCOCH$_2$CO·OC$_6$H$_4$NO$_2$-*p* (3)	8.5	185	6
NCCH$_2$CO·OC$_6$H$_4$NO$_2$-*p* (4)	(8.57)$_{app}$	1.74	23*b*
Me$_2$S$^+$CH$_2$CO·OC$_6$H$_4$NO$_2$-*o* (5)	(9.08)$_{app}$	1.20	23*b*
EtOCO·CH$_2$CO·OC$_6$H$_4$NO$_2$-*p* (6)	10.4	220	6
EtOCOCH$_2$CO·OC$_6$H$_4$NO$_2$-*o* (7)	9.4	100	6
p-Nitrophenyl fluorene-9-carboxylate (8) [= (1a)]	(9.88)$_{app}$	0.2	This work
MeCONHCO·OC$_6$H$_4$NO$_2$-*p* (9)	10.10 [b]	12.7 [b]	
O$^-$·CO·OC$_6$H$_4$NO$_2$-*p* (10)	1.03 [c]	2.5×10^6 [d]	
p-O$_2$NC$_6$H$_4$NHCO·OC$_6$H$_4$NO$_2$-*p* (11)	11.07 [e]	8.04×10^3 [e]	

[a] Values marked app are taken from kinetic inflections in pH profiles and, therefore, probably reflect composite rate constants in some cases. Other values are by titration. [b] Calculated from the data of ref. 8. [c] The value was calculated using pK_a 3.7 for HOCO·OCH$_3$ (C. Faurhold, *Z. Phys. Chem.*, 1927, **126**, 211) and assuming β_{pK_a} for such monocarbonate esters was 0.2 [in line with β_{K_a} values reported for acetoacetates [7] and fluorene esters (this work)]. [d] Calculated from the data of C. K. Sauers, W. P. Jencks, and S. Groh, *J. Am. Chem. Soc.*, 1975, **97**, 5546. [e] Calculated from the data of A. F. Hegarty and L. N. Frost, *J. Chem. Soc., Perkin Trans. 2*, 1973, 1719.

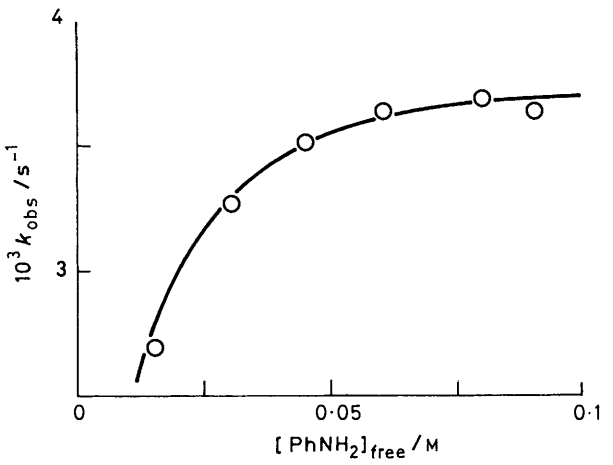


FIGURE 5 Plot of k_{obs} (fast step) *versus* [PhNH$_2$]$_{free}$ for the hydrolysis of *p*-nitrophenyl fluorene-9-carboxylate at 25 °C and μ = 0.1M in 90% free base aniline buffer and 10% v/v acetonitrile. Points are experimental; line is calculated using the equation $k_{obs} = k_{max.}\ [PhNH_2]_{free}/([PhNH_2]_{free} + K)$ with $k_{max.} = 3.96 \times 10^{-3}$ s^{-1} and $K = 6.34 \times 10^{-3}$ mol l^{-1}

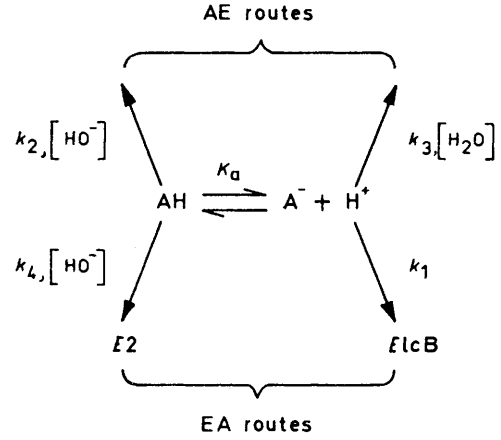
isolated from the slower reaction under these conditions. In cases where the rate coefficients for fast followed by slow processes differ considerably, the progress curve is as seen in Figure 2b. The effect of the slow step is to introduce a linear drift in the 'infinity value' of the faster process. The rate constant is obtained by plotting $\log_{10}Y$ *versus* time where Y is the difference in reading at a given time between the observed time course and the linear portion of the trace extrapolated back through the early stages of reaction (see Figure 2b). The rate constant for the fast process is $-2.303 \times$ slope of $\log_{10}Y$ *versus* t. For reaction in aniline buffers, the maximum value of the rate coefficient for the faster process thus estimated was *ca.* 4×10^{-3} s^{-1}. The rate constant for the corresponding slower process was obtained as 6.7×10^{-5} s^{-1}, two orders of magnitude less. It is this difference which allows this simple kinetic analysis procedure. For *p*-nitrophenyl fluorene-9-carboxylate, saturation was observed at higher aniline concentrations for the fast step (see Figure 5).

Both 4-nitrophenyl and 2,4-dinitrophenyl 9-methylfluorene-9-carboxylate showed first-order dependences on hydroxide ion concentration when hydrolysed at 1.0M ionic strength and 25 °C in the presence of 20% (v/v) acetonitrile,

the respective second-order rate constants for hydroxide ion attack (k_{HO^-}) being 2.11 and 11.1 l mol^{-1} s^{-1}.

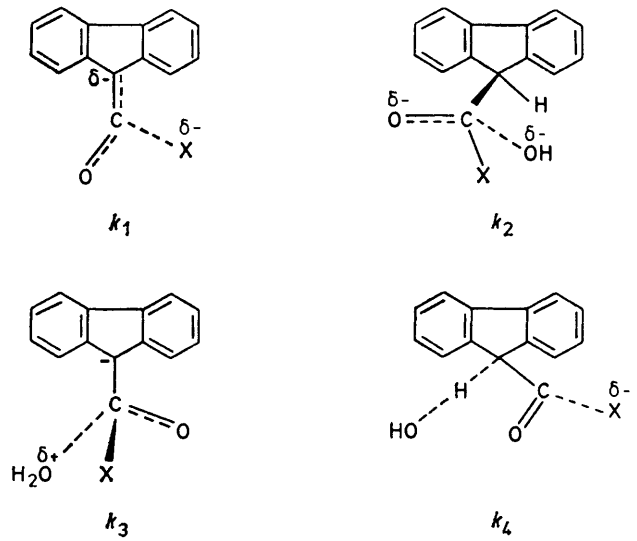
DISCUSSION

A *pH Profiles*.—The reason for the saturation behaviour in the pH profiles may be described mechanistically as follows. There are four possible mechanisms (Scheme 1) for base-catalysed hydrolysis of an ester with a labile proton on the atom α to the acyl function.



SCHEME 1

The k_1 process refers to unimolecular collapse of the ester conjugate base, the k_2 process to bimolecular attack of HO^- on the neutral form, and the k_3 process to bimolecular attack of a water molecule on the anion of the ester. The k_4 process represents $E2$ attack of hydroxide ion on neutral ester. The transition states corresponding to processes k_1—k_4 are given in Scheme 2.



SCHEME 2

Equilibrium analysis of this kinetic scheme yields equation (4) under pseudo-first-order conditions, where

$$\frac{\text{Rate}}{[\text{ester}]} = k_{obs} = \frac{k'}{(1 + K_w/K_a[HO^-])} \quad (4)$$

k' is a composite of the rate constants for four mechanisms [$k' = k_1 + k_3 + K_w(k_2 + k_4)/K_a$]. When [$H^+$] $\ll K_a$, $k_{obs} = k'$ (k' will be referred to as the alkaline plateau rate constant). The existence of a ' saturation ' pH profile is consistent thus with both EA and AE mechanisms. The k_2 and k_4 processes possess saturation kinetics because although there is extensive formation of S^-, reaction is *via* the SH form.

It is commonly assumed that an $E2$ mechanism can be distinguished from an $E1$cB mechanism if saturation kinetics (with respect to base concentration) are observed. This assumption requires that the elimination of the anion (k_1) with full proton removal and a lone-pair with a net negative charge in the α-position is faster than for the $E2$ analogue where proton removal from the α-position is only partly advanced in the transition state. This assumption, reasonable for most systems, is only fully justified if the $E1$ and $E2$ *elimination* steps have identical stereoelectronic requirements. This may not always be so in view of suggestions [17,18] that a *cis*-elimination mode may be preferred by the $E1$cB reaction, in contrast to the well established *trans*-route for the $E2$ process.[18] Consequently, it is wise to consider the k_4 process even if saturation kinetics are observed.*

The inflexions in the pH profiles for the 4-nitrophenyl and other esters provide indirect evidence that the ester anions are formed under these conditions. Additional support lies in the spectra (Figure 6) of 4-chlorophenyl

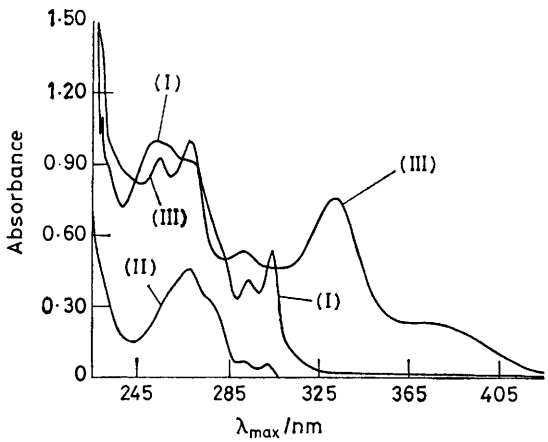


FIGURE 6 Spectra of: (I) *p*-chlorophenyl 9-methylfluorene-9-carboxylate in 0.6M-sodium hydroxide; (II) *p*-chlorophenyl fluorene-9-carboxylate in phosphate buffer (pH_{app} 6.0); (III) *p*-chlorophenyl fluorene-9-carboxylate in 0.06M-sodium hydroxide. All media were 40% (v/v) ethanol–water

fluorene-9-carboxylate in phosphate buffer (pH_{app} 6; 40% EtOH–H_2O) and sodium hydroxide (0.06M; 40% EtOH–H_2O) media. In the latter, new bands [$\lambda_{max.}$ 320

* A referee has pointed out that the stereoelectronic argument justifying the inclusion of k_4 as an alternative mechanism requires that the rate of racemisation at the α-position is slower than hydrolysis. He also pointed out that the observation of saturation kinetics for aniline catalysis shows otherwise, excluding the $E2$ route in this case. Also arguing against the $E2$ route in region A are the high, negative value of $\beta_{L.G.}$ and the entropy of activation.

nm ($\log_{10}\varepsilon$ *ca.* 4.1), $\lambda_{max.}$ 375 nm ($\log_{10}\varepsilon$ *ca.* 3.5)] appeared at longer wavelengths and decayed with time. Such longer wavelength bands would be expected for an aromatic anion. There was no similar $\lambda_{max.}$ shift for 4-chlorophenyl 9-methylfluorene-9-carboxylate in sodium hydroxide (0.06M; 40% EtOH–H_2O) solution and the spectrum of this ester in base resembled closely that of the 9H analogue in neutral acidic media.

B *Linear Free Energy Relationships.*—The high value of ρ^- (= 2.1) and its dependence on Hammett σ^- is consistent with rate-determining C–OAr cleavage with rapid, prior ionisation of the C–H group, followed by expulsion of the aryl oxide anion.[1] Moreover, there must be considerable negative charge on the phenoxide moiety of the transition state (σ^- fit) as expected for k_1 being rate limiting. The deviation of the poorer leaving group is accentuated on the Brönsted plot for leaving group variation (Figure 1), which includes alkyl esters, and consists of two regions which are analysed separately below.

(a) *Region A of Brönsted plot.* For the descending limb (region A) of the $\beta_{L.G.}$ plot the mechanism of hydrolysis is most likely *E*1cB in view of the highly negative $\beta_{L.G.}$ (also the high ρ^- value and σ^- fit). It has been reported that $\beta_{L.G.}$ values of *ca.* −1.2 are typical of *E*1cB routes,[1] whereas for the corresponding bimolecular process, the range is $\beta_{L.G.} = -0.05$ to −0.4, *e.g.* the value of $\beta_{L.G.}$ is −1.29 for *E*1cB hydrolysis of aryl acetoacetate esters compared with −0.05 for the $B_{AC}2$ hydrolysis of alkyl acetoacetates.[6] The apparent second-order rate constants for attack by hydroxide ion ($k^{app}_{HO^-}$) can be derived from equation (4). At low values of [HO^-] (*i.e.* when little substrate ionisation has occurred), equation (4) gives (5) or $k^{app}_{HO^-} = k'K_a/K_w$.

$$k_{obs} = k'K_a\,[HO^-]/K_w \qquad (5)$$

In addition, from this, equation (6) is obtained. Using β

$$\log_{10} k^{app}_{HO^-} = \log_{10} k' + \log_{10} K_a + pK_w \qquad (6)$$

to denote the scope of a plot of a given kinetic parameter *versus* the pK_a of appropriate leaving group conjugate acid yields [equation (7)]. The term β_{pK_a} is the slope of

$$\beta_{k^{app}_{HO^-}} = \beta_{k'} - \beta_{pK_a} \qquad (7)$$

a plot of the pK of the substrate (denoted pK^{app}_{ester} in Table 3), *versus* the pK_a of the leaving group conjugate acid. For this system such a plot has the equation $pK^{app}_{ester} = 0.22\ pK_{L.G.} + 8.26$ (r 0.945) for eight esters. Thus, $\beta k^{app}_{HO^-}$ is *ca.* (−1.01 − 0.22) or −1.23. This value is considerably more negative than the value of β_{HO^-} for leaving group variation in esters undergoing bimolecular nucleophilic attack by hydroxide ion (for example $\beta_{k_{HO^-}}$ for $CH_3CO{\cdot}OR$ [19] or $CH_3CO{\cdot}SR$ [20] is *ca.* −0.3). However, it is close to the value reported (*ca.* −1.38) for alkaline hydrolysis of acetothiolacetates following an *E*1cB route.[7] Such leaving group sensitivities have proven to be amongst the most dependable criteria of mechanism in this area.

The value of $k^{app}_{HO^-}$ for *p*-nitrophenyl fluorene-9-carboxylate, calculated using $k^{app}_{HO^-} = k'K_a/K_w$ (2.6×10^3 l mol^{-1} s^{-1}) is *ca.* 10^3-fold greater than that of the 9-methyl analogue (2.1 l mol^{-1} s^{-1}) for which the ionisation process has been blocked, confirming a disparity in mechanism for the two esters. This difference in rate constant is not as great as the 10^8-fold reported [5] for the alkaline hydrolysis of 4-nitrophenyl *N*-methylaminosulphonate and its corresponding disubstituted ester or the 10^6-fold difference [21] found for aryl *N*-alkyl- and *NN*-dialkylcarbamates. However, it is unlikely that the steric hindrance from methyl groups in the 9-position could cause such a lower rate (see below).

The entropy of activation for the k' term of 3-chlorophenyl fluorene-9-carboxylate ($\Delta S^{\ddagger}$ −9.7 cal mol^{-1} K^{-1}) * is consistent with a unimolecular transition state but some solvent interaction may be involved making it more negative than the value expected [22] for simple unimolecular ester hydrolysis.

The deuterium oxide kinetic solvent isotope effect on k' for *m*-chlorophenyl fluorene-9-carboxylate is $k_H'/k_D' = 1.3$. There should be no primary solvent isotope effects for the *E*1 step [21] but non-unity kinetic solvent isotope effects have been observed for *E*1cB hydrolyses *e.g.* *p*-nitrophenyl *N*-methylaminosulphonate [5] (k_H'/k_D' 1.35). In this case it was suggested that there was a large solvation change on going from ground- to transition-state in the *E*1 process (as could be expected from the highly charged ground-state which disperses its charge in the transition-state). The non-unity effect for the fluorene ester might also reflect such solvation effects and/or some nucleophilic assistance by solvent of leaving group expulsion. The saturation dependence (Figure 5) on aniline concentration seen for 4-nitrophenyl fluorene-9-carboxylate is in agreement with the *E*1cB route proposed for this ester. Such saturation plots are common for *E*1cB processes [6,23] and indicate a change in rate-determining step from base-catalysed proton removal at low buffer levels to rate-determining collapse of the ester conjugate base at higher buffer concentrations. The scheme followed is (8) where relationship (9) holds.

$$SH \underset{k_{BH^+}[BH^+]}{\overset{k_B[B]}{\rightleftharpoons}} S^- \xrightarrow{k_{elim}} \text{keten} \xrightarrow[\text{fast}]{H_2O,B} \text{products} \qquad (8)$$

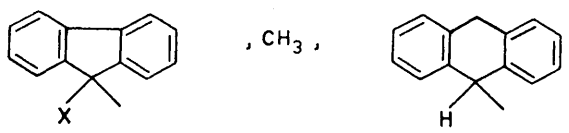
$$k_{obs} = k_{elim}k_B[B]/(k_{elim} + k_{BH^+}[BH^+]) \qquad (9)$$

(b) *Region B of Brönsted plot.* For the ascending limb (region B) of Figure 1, if the k' term refers to attack of HO^- on the small amount of substrate present in its un-ionized form, $k' = k_2K_w/K_a$ and $\beta_{k'} = \beta_{k_2} - \beta_{K_a}$ where $\beta_{k'} = 0.11$ and $\beta_{K_a} = -0.22$ and β_{k_2} is the calculated $\beta_{L.G.}$ value for the k_2 term. Thus, β_{k_2} (= +0.11 − 0.22) = −0.12 is low compared with $\beta_{L.G.}$ values for bimolecular nucleophilic attack of hydroxide ion on carbonyl esters, *e.g.* for $CH_3CO{\cdot}OR$ [19] $\beta_{L.G.} = -0.32$ and for

* 1 cal = 4.184 J.

$B_{AC}2$ hydrolysis of alkyl acetoacetates $\beta_{k_{HO^-}}^{app}$ is 0.3.* However, it is in accord with a bimolecular route with an unusually low leaving group sensitivity. If the k' term referred to k_3 (nucleophilic attack of H_2O on the anion) $\beta_{k'}$ would presumably be negative. As discussed for region A, $\beta_{k'}$ for an $E1cB$ process is very large and negative, thus removing the $E1cB$ process as a possibility for region B. A value of $\beta_{k_{HO^-}}$ (*ca.* −0.24) was calculated for the bimolecular alkaline hydrolysis of 9-methylfluorene esters using the observed second-order hydroxide ion rate cofficients and $\beta_{k_{HO^-}} = \Delta \log_{10} k_{HO^-}/\Delta pK_{L.G.}$. Although the data are limited to two esters, the sensitivity to change in leaving group is lower than for acetate esters ($\beta_{L.G.} = -0.32$).[19] This lower sensitivity might be caused by the highly electron-withdrawing ($\sigma^* = 0.32$) [24] nature of the 9-methylfluorene moiety and is also apparently reflected in the value of $\beta_{k_{HO^-}}$ for 9-H fluorene esters (region B).

It has been shown previously [25] that the alkaline hydrolysis of fluorene-9-carboxylic and 9-methylfluorene-9-carboxylic methyl esters fit a modified Taft equation which also applies to the data for a range of methyl esters, *viz.* RCO·OCH$_3$ where R is given in Scheme 3.



X = H, Me, Et, Pr^i, Ph

SCHEME 3

Consequently, it is most likely that these esters hydrolyse in base by the same $B_{AC}2$ mechanism, as both the $E1cB$ and $E2$ pathways are excluded by the absence of ionisable α-hydrogen sites on several of the esters. Acetate esters [19,20] have been shown not to hydrolyse by an elimination pathway. Also arguing against the $E2$ pathway for this region is the lack of chemical precedent for a mechanistic change from $E1cB$ to $E2$ as the leaving group becomes less active (*i.e.* as one goes from the aryl esters of region A to the alkyl esters of region B). For aryl phenylmethanesulphonate hydrolysis where an $E1cB$–$E2$ mechanistic transition has been detected, the more active leaving groups enforce the operation of the $E2$ route, esters with weaker leaving groups following an $E1cB$ pathway.

The $\Delta S^{\ddagger}$ values for $k_{HO^-}^{app}$ for methyl fluorene-9-carboxylate are consistent with a bimolecular mechanism (Table 4) although considerably less negative than comparable entropies of activation for non-ionisable esters [1,26] (*e.g.* for alkaline hydrolysis of PhNMe·CO·OEt, $\Delta S^{\ddagger}$ is −164.3 J mol^{-1} K^{-1} and for Ph$_2$N·CO·OC$_6$H$_4$NO$_2$-*p* $\Delta S^{\ddagger}$ is −112 J mol^{-1} K^{-1}). This difference presumably reflects the composite nature of the $k_{HO^-}^{app}$ parameter for the fluorene-9-carboxylates (*i.e.* the non-productive ionisation process for these esters is reflected in the value for $\Delta S^{\ddagger}$).

C *Ease of Elimination from Ester Anions.*—In Table 5 are collected some elimination data for carboxy esters following the $E1cB$ pathway. If one compares the rates of elimination of esters (3) and (6) with that of (8), the fluorene derivative, it is clear that although the pK_a of ester (8) is intermediate between those of (3) and (6), nonetheless, it cleaves at *ca.* 1/1 000 the rate of (3) and (6). It will be shown below that ester pK_a is not a useful guide to elimination rates in general, but the low elimination reactivity of (6) needs explanation.

For *N*-substituted carbamate phenyl esters a rough correlation between ester pK_a and k_{elim} has been reported;[2] the higher the pK_a, the faster the elimination as might be anticipated on a first analysis. However, carbon acidic esters do not follow this correlation. For example, while the pK_{app} of the fluorene ester (8) is greater than that of the acetoacetate ester (3), it eliminates at 1/1 000 the rate. Also, the pK of the acetoacetate (3) is less than that of the malonate (6) but they eliminate at similar rates.

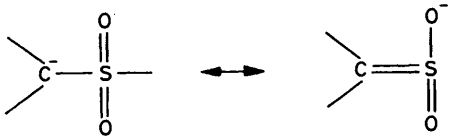
Another correlation, reported for sulphonyl derivatives [3] (HXSO$_2$·OC$_6$H$_4$NO$_2$-*p*), is that the rate of elimination varies with the elemental nature of X (*i.e.* PhCH$^-$ 10^7 > MeN$^-$ 10^7 > O). This order of internal nucleophilicities is a reasonable reflection of the relative, normal nucleophilicities of C-anions *versus* N-anions *versus* O-anions. It also follows the order of ester pK_a values. However, if we consider the carbonyl analogues (HXCO·OC$_6$H$_4$NO$_2$-*p*) the order of elimination rates is O$^-$ (2.5×10^6) ≫ CH$_3$COC$^-$H (185) > CH$_3$CON$^-$ (10). It makes little difference which C-ester is considered; O$^-$-CO·OC$_6$H$_4$NO$_2$-*p* elimination is very much faster than either RC$^-$H-CO·OC$_6$H$_4$NO$_2$-*p* or RN$^-$CO·OC$_6$H$_4$-NO$_2$-*p*. The order (O ≫ C ≳ N) is *not* the order of relative pK values of the ester (as was the case for HXSO$_2$·OC$_6$H$_4$NO$_2$-*p*) nor is it in the order of nucleophilicities of external anions towards a carbonyl centre. The HXCO·OC$_6$H$_4$NO$_2$-*p* system also differs from HXSO$_2$·OC$_6$H$_4$NO$_2$-*p* when C- and N-internal nucleophiles are compared. For the sulphonyl group the C-anion was 10^7-fold faster in elimination than the N-anion, while for the HXCO·OC$_6$H$_4$NO$_2$-*p* system the difference is less than an order of magnitude. Thus there are both qualitative and quantitative differences in the features controlling elimination for the −CO·OC$_6$H$_4$NO$_2$-*p* and −SO$_2$·OC$_6$H$_4$NO$_2$-*p* systems.

SCHEME 4

One difference between the CO and SO$_2$ systems, certainly as far as α-carbanion effects are concerned, is the mechanism of anion stabilisation. In the CH$^-$·CO system the carbanion is stabilised not only by the induc-

* This was calculated by taking $\beta_{k'} = -0.05$ for basic hydrolysis of alkyl acetoacetates [6] and $\beta_{K_a} = -0.25$ for alkaline hydrolysis of alkyl acetoacetates and thiolacetoacetates.[7]

tive effect of the carbonyl group but also by delocalisation from $2p$–$2p$ overlap as in Scheme 4. The α-



SCHEME 5

sulphonyl carbanions are stabilised, in contrast, mainly by electron-withdrawing effects,[27] *i.e.* there is little resonance of the type shown in Scheme 5.

We are grateful to the SERC for funds to purchase the stopped-flow instrumentation.

[1/867 *Received*, 28*th May*, 1981]

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