An *E*1cB Mechanism for the Alkaline Hydrolysis of Thiolesters of Fluorene-9-carboxylic Acid: Effect of Ester Conjugate Base Structure on Differential Eliminative Reactivity of Oxygen and Sulphur Nucleofuges

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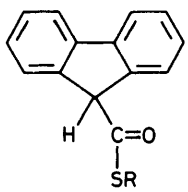
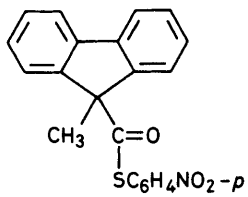
The alkaline hydrolysis of a series of thiolesters of fluorene-9-carboxylic acid has been studied and pseudo-first-order rate constants, k_{obs} (hydroxide ion in excess), showed saturation with respect to hydroxide ion concentration for any given ester. The kinetic expression describing such behaviour was found to be $k_{obs} = k'/(1 + K_w/K_a[HO^-])$ where k' is the limiting rate constant at high base concentrations and K_a is the acid dissociation constant of the acidic ester. Values of $\log_{10}k'$ followed a Brønsted correlation (with the pK_a of the conjugate acid of the appropriate leaving group) with equation $\log_{10}k' = 6.10 - 1.14\ pK_{l.g.}$ (r 0.9700). There was no significant steric effect on k' as the 2'-methoxythiophenyl ester obeyed the above relationship. Esters with poorer leaving groups (*S*-benzyl, *S*-n-propyl) deviated positively from the correlation. For active thiolesters of fluorene-9-carboxylic acid the highly negative value of $\beta_{l.g.}$ for the k' term (slope of the Brønsted plot), along with the saturation kinetics and a positive/zero value (+4.6 ± 6.1 J K^{-1} mol^{-1}) for the entropy of activation for the *S*-phenyl ester was evidence of an *E*1cB alkaline hydrolytic mechanism. In support of this were the low solvent deuterium kinetic solvent isotope effect on k' (k_H/k_D = 1.37) and the rate inhibition on 9-methylation. Comparison of fluorene-9-esters with acetoacetic esters showed that there was less difference in reactivity between oxygen and sulphur esters for the former, an effect explained as lying in the highly delocalised nature of the fluorene ester conjugate bases.

In spite of a large physical organic literature for the elimination–addition mechanism of acyl transfer,[1] little [2] quantitative data are available for thiolesters. Recently, however, thiolacetoacetate esters (CH_3COCH_2COSR) including *S*-acetoacetyl coenzyme A were shown to hydolyse *via* a keten mechanism,[3] while the thiolacetates, including *S*-acetyl-coenzyme A followed a normal associative $B_{AC}2$ route.[4] The route followed by the acetates appears to be dictated by their high pK_a values (*ca.* 26) which prevent a kinetically sensible degree of ionisation in aqueous media. However, the acetate esters must lie close to a mechanistic borderline as *S*-malonylcoenzyme A analogues ($\bar{O}_2CCH_2COSR$) are aminolysed *via* an elimination–addition pathway.[5] In order to investigate further such mechanistic features for thiolesters, we have studied a number of thiolesters of fluorene-9-carboxylic acid (1): the oxy-esters of these follow an *E*1cB hydrolysis mechanism for leaving groups stronger than OPh but a $B_{AC}2$ route (HO^- on neutral ester) for poorer leaving groups.[6]



(1)



(2)

a; R = C_6H_5
b; R = $C_6H_4NO_2$-*p*
c; R = C_6H_4Cl-*p*
d; R = $C_6H_4CH_3$-*p*
e; R = Pr^n
f; R = $CH_2C_6H_5$
g; R = $C_6H_4OCH_3$-*o*
h; R = $C_6H_4OCH_3$-*p*
i; R = $C_6H_4NO_2$-*m*
j; R = C_6H_4F-*p*
k; R = C_6H_4Br-*p*
p; R = $C_6H_4NHCOCH_3$-*p*

Experimental

Fluorene-9-carboxylic acid and thiols were obtained from Aldrich or Fluka. *p*-Nitrothiophenol was purified as described.[7] *m*-Nitrothiophenol was prepared as follows. Glucose (10.5 g, 0.05 mol) was mixed with 3,3'-dinitrodiphenyl disulphide (15.4 g, 0.05 mol) and left to stand overnight in ethanol (150 ml). The mixture was then heated at 60—70 °C with 20 ml of 10% sodium hydroxide solution. The reaction mixture was poured into cold water (250 ml), quickly filtered, and the filtrate added dropwise to concentrated H_2SO_4 (40 ml) in crushed ice (300 g). A red-coloured liquid formed (under the aqueous layer) and was removed and distilled under reduced pressure. *m*-Nitrothiophenol was obtained as a yellow liquid, b.p. 125 °C at 0.5 mmHg (lit.,[8] 125—126 °C at 0.5 mmHg).

Thiolesters of fluorene-9-carboxylic acid and 9-methylfluorene-9-carboxylic acid were prepared as described for their oxygen analogues,[6] analytical data being reported in Table 1.

p-Nitrothiophenyl 9-methylfluorene-9-carboxylate, prepared from 9-methylfluorene-9-carbonyl chloride [6] had m.p. 133—135 °C (Found: C, 69.7; H, 4.1; N, 3.7; S, 8.9. $C_{21}H_{15}NO_3S$ requires C, 69.8; H, 4.2; N, 3.9; S, 8.9%).

Methods.—Instrumentation and techniques have been previously described.[6] In thiolester hydrolyses all water used for buffer preparation *etc.* was degassed prior to use. Kinetics were studied in the presence of 10^{-4}M-edta to minimise oxidation problems. Kinetics were studied under pseudo-first-order conditions in strongly alkaline media, *i.e.* with hydroxide ion in considerable excess over ester. Good semi-logarithmic plots were obtained usually to >90% of reaction. Rate constants were usually calculated by non-linear regression analysis using the first-order rate equation and estimates of the final absorbance value (by visual inspec-

Table 1. Analytical data for thiolesters of fluorene-9-carboxylic acid

Ester	M.p. (°C)	Calc. (%) C	H	S	N or Cl	Molecular formula	Found (%) C	H	S	N or Cl
(1a)	110—112	79.5	4.6	10.6		$C_{20}H_{14}O$	79.2	4.6	10.3	
(1b)	132—134	69.2	3.8	9.2	4.0 (N)	$C_{20}H_{13}NO_3S$	68.9	3.7	9.1	3.8 (N)
(1c)	135—137	71.3	3.9	9.5	10.6 (Cl)	$C_{20}H_{13}ClOS$	71.1	3.8	9.4	10.6 (Cl)
(1d)	118—120	79.8	5.1	10.1		$C_{21}H_{16}OS$	79.6	5.0	10.0	
(1e)	54—56	76.1	6.0	11.9		$C_{17}H_{16}OS$	75.8	6.0	12.0	
(1f)	107—109	79.8	5.1	10.1		$C_{21}H_{16}OS$	79.8	5.0	9.9	
(1g)	134—135	75.9	4.9			$C_{21}H_{16}O_2S$	76.1	4.8		
(1h)	116—117	75.9	4.9			$C_{21}H_{16}O_2S$	75.7	4.7		
(1i)	146—148	69.2	3.8	9.2	4.0 (N)	$C_{20}H_{13}NO_3S$	69.1	3.7	9.4	3.6 (N)
(1j)	114—115	75.0	4.1			$C_{20}H_{13}FOS$	75.1	4.0		
(1k)	138	63.0	3.4			$C_{20}H_{13}BrOS$	62.8	3.3		
(1l)	202—205	73.5	4.7		3.9 (N)	$C_{22}H_{17}NO_2S$	73.2	4.7		3.5

tion) and of k_{obs} by computerised semilogarithmic plotting of $\log_{10}(A_t - A_\infty)$ *versus* time. For low hydroxide ion concentrations there were two steps detected for the *S*-phenyl ester (≤ 0.005M), the *S*-*p*-cresyl ester ([HO$^-$] ≤ 0.015M), and for the *S*-*p*-chlorophenyl ester ([HO$^-$] ≤ 0.01M). In these cases only the slow step is reported. Faster reactions, necessitating stopped-flow measurements, were studied using techniques previously described [6] using nitrogen-scrubbed media and a Canterbury SF-3A stopped-flow spectrometer, which was interfaced to an Exidy Sorcerer microcomputer for data processing.

The pK_a of 4-fluorothiophenol (redistilled and stored under nitrogen) was measured at 25 °C, ionic strength 0.1M spectroscopically at 258 nm in buffers at four pH values spanning the pK_a.

Results

The esters (1) showed similar general kinetic properties to their oxy-analogues, whose properties have been reported previously.[6] For example, for esters (1a, c, d, and k), complete k_{obs} *versus* [HO$^-$] profiles were measured and exhibited saturation with respect to hydroxide ion concentration. For these esters the rate data followed the kinetic expression (1)

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

from which k' and K_w/K_a terms could be readily extracted by a linear transformation of (1) and a replot (see Figure 1). The k' term, called the [HO$^-$]-independent alkaline plateau rate constant, could be readily measured for a variety of thiolesters by using high hydroxide ion concentrations. Values of k' were therefore determined as the average rate constants for at least four different hydroxide ion concentrations, differing widely enough to ensure that the k_{obs} values were pH independent in that region (usually hydroxide ion concentrations of 0.025, 0.05, 0.075, and 0.10M were used with the ionic strength maintained at 0.10M with KCl where necessary). Values of k', $K/_wK_a$ *etc.* are recorded in Table 2.

The value of k' was measured at a number of temperatures for the thiophenyl ester using this procedure. Rate constants, k', were as follows (temperatures in parentheses): 0.0299 ± 0.0010 s^{-1} (20.5 °C); 0.0515 ± 0.0009 s^{-1} (24.7 °C); 0.0914 ± 0.0010 s^{-1} (29.8 °C); 0.133 ± 0.001 s^{-1} (33.8 °C). Activation parameters derived for k' from these data were E_a 84.1 ± 1.7 kJ mol^{-1}; $\Delta H^\ddagger$ 81.6 ± 1.7 kJ mol^{-1} and $\Delta S^\ddagger$ 4.6 ± 6.1 J K^{-1} mol^{-1}.

Rates of hydrolysis (k') for (1a) were compared in sodium deuterioxide–D_2O with sodium hydroxide–H_2O media (25 °C, ionic strength 0.1M). The value of k_D' (k' in D_2O) was 0.0422 ± 0.0006 s^{-1}, compared with k'_H = 0.0580 ± 0.0010 s^{-1} giving a solvent deuterium kinetic isotope effect of k_H'/k_D' = 1.37.

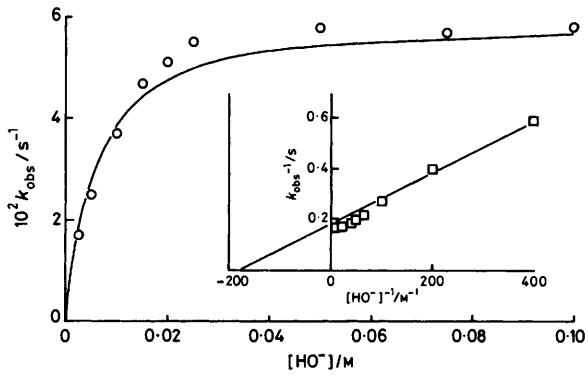


Figure 1. Plot of k_{obs} *versus* hydroxide ion concentration at 25 °C, ionic strength 0.1M for thiophenyl fluorene-9-carboxylate. Points are experimental; line is theoretical using equation (1) with values of k' = 0.06 s^{-1} and K_a/K_w = 185 mol l^{-1} (Table 2). The inset shows the experimental data plotted in double reciprocal form; the line was derived by linear least squares regression analysis and yields the above values for k' and K_a/K_w

In sodium hydroxide media (at 409 nm) *p*-nitrothiophenyl 9-methylfluorene-9-carboxylate (2) followed first-order kinetics with respect to hydroxide ion concentration giving k_{HO^-}, the second-order rate constant for hydroxide ion attack, as 0.191 l mol^{-1} s^{-1} (six points) at 25 °C, ionic strength 0.1M (held with KCl) and 33% v/v acetonitrile.

Values of $\log_{10}k'$ followed a Hammett relationship for the *m*- and *p*-substituted aryl leaving groups. Using Hammett σ values the equation describing the correlation was $\log_{10}k' = 2.37\sigma - 1.27$ (r 0.986). The equation when the σ^- value was used for the *p*-nitro derivative was $\log_{10}k' = 1.76\sigma^- - 1.26$ (r 0.977).

The Brønsted plot (see Figure 2) of $\log_{10}k'$ *versus* p$K_{l.g.}$ (the pK_a of the conjugate acid of the appropriate leaving group) indicated more complex behaviour when a wider range of ester reactivity was considered. It appears that the n-propyl, and possibly the benzyl, esters deviate from the Brønsted relationship which holds closely for the other esters. If all eleven esters were included the Brønsted correlation was $\log_{10}k' = 3.76 - 0.75\ pK_{l.g.}$ (r 0.9612). Omitting the n-propyl ester yielded $\log_{10}k' = 4.72 - 0.91pK_{l.g.}$ (r 0.9699) and omitting both n-propyl and benzyl esters yielded the equation $\log_{10}k' = 6.10 - 1.14\ pK_{l.g.}$ (r 0.9700). The 2-methoxy-

Table 2. Kinetic data for thiolesters of fluorene-9-carboxylic acid in aqueous solution at 25 °C and ionic strength 0.1M (held with KCl)

Ester	pK_{RSH} [a]	$10^2k'$ (± standard deviation)/ s^{-1}	K_a/K_w/ 1 mol^{-1}	λ_{kin}/nm
(1a)	6.52	6.00 (±0.01) [b]	185 ± 28	328
(1b)	4.71	573 (±1) [c]		409
(1c)	6.13	13.0 (±0.1) [b]	118 ± 39	348
(1d)	6.82	3.00 (±0.02) [b]	179 ± 61	348
(1e)	10.65	0.0201 (±0.0002)		344
(1f)	9.43	0.0315 (±0.0002)		350
(1g)	6.89 [e]	3.42 (±0.07)		340
(1h)	6.77	1.58 (±0.01) [d]		340
(1i)	5.24	245 (±13)		340
(1j)	6.62 [f]	4.21 (±0.03)		340
(1k)	6.02	16.6 (±0.06) [b]	61.5 ± 4.9	340
(1l)	6.08 [g]	5.84 (±0.06)		340

[a] pK_a of the conjugate acid of the thiolate nucleofuge taken unless otherwise noted from W. P. Jencks and J. Regenstein, 'Handbook of Biochemistry and Molecular Biology,' Chemical Rubber Co., Cleveland, 1976, 3rd edn., vol. I, p. 346. [b] k' values marked thus were obtained by double reciprocal plotting of $k_{ob.}/[HO^-]$ data. Others were obtained as the means of at least three different hydroxide ion concentrations. [c] In the presence of 10% acetonitrile (v/v) for solubility reasons. [d] The value of k' in the presence of 30% acetonitrile (v/v) was 1.77 ± 0.06 × 10^{-2} s^{-1}. [e] From P. DeMaria, A. Fini, and F. M. Hall, *J. Chem. Soc., Perkin Trans. 2*, 1974, 1443. [f] Determined spectrophotometrically in this study, μ = 0.1M at 258 nm; value has a standard deviation of ±0.13. [g] At ionic strength 1.0M from D. Hupe and W. P. Jencks, *J. Am. Chem. Soc.*, 1977, **99**, 451.

thiophenyl ester fits the last two correlations well indicating that no significant steric effect operates from the nucleofuge.

Discussion

The dependences of k_{obs} on hydroxide ion concentration observed for the hydrolysis of thiolesters of fluorene-9-carboxylic acid are similar to those observed for the oxyester analogues [6] and are typical of processes complicated by or involving substrate ionisation. Whilst saturation kinetics are consistent with a process involving unimolecular elimination of thiolate ion from the ester conjugate base (*E*1cB) they are also consistent with a non-obligatory conjugate base route, *i.e.* the ester anion is formed as a dead-end branch and is not on the productive pathway.

The dependence of the alkaline plateau rate constant (k') on leaving group pK_a is high ($\beta_{l.g.}$ is either −0.91 or −1.14 depending on whether correlation B or A of Figure 2 is used). Such high values of $\beta_{l.g.}$ for the k' term are typical of *E*1 processes of ester anions. There is not much data available for thiolester eliminations but $\beta_{l.g.}$ for the k' term for thiol-acetoacetate esters ($CH_3CO\cdot\bar{C}HCOSR$) is −1.1. Typically for *E*1cB reactions $\beta_{l.g.}$ values of k' terms of oxyesters are of the order of −1 whereas the values of $\beta_{l.g.}$ for k' terms of

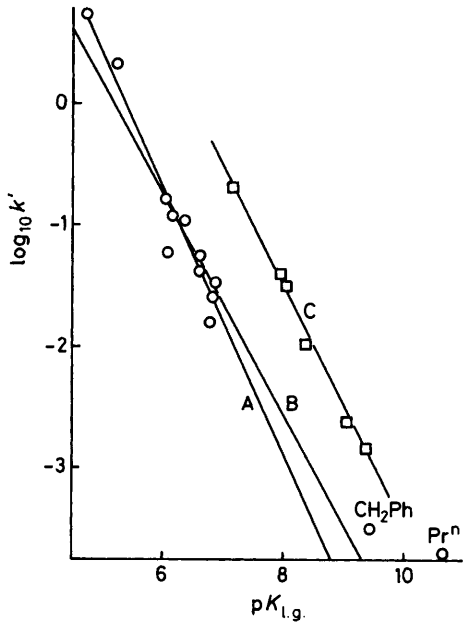


Figure 2. Brønsted plot for leaving group dependence of k' term. Points are experimental. The lines are theoretical for the equations $\log_{10}k' = 6.10—1.14\ pK_{l.g.}$ (line A, omitting both n-propyl and benzyl esters for the correlation) and $\log_{10}k' = 4.72—0.91\ pK_{l.g.}$ (line B, omitting only the n-propyl ester). Line C is data for the *E*1cB reaction (k' term) of oxygen esters of fluorene-9-carboxylic acid taken from ref. 6

ionisable esters following bimolecular mechanisms are in the region of zero (or indeed slightly positive for the oxygen alkyl esters of fluorene-9-carboxylic acid [6]). For poor leaving groups the elimination step becomes prohibitively slow for many systems and a change to a bimolecular mechanism is enforced.[1-3,6] Such a mechanistic change presumably accounts for the positive deviation of the n-propyl (and probably the benzyl) ester from the Brønsted leaving group correlation (Figure 2). Mechanistic changeover occurs for the thiolesters at $pK_{l.g.}$ *ca.* 9 for fluorene-9-carboxylates similarly to the oxy-analogues for which mechanistic changeover is at $pK_{l.g.}$ *ca.* 9.5. For any given leaving group pK_a the oxy-analogues eliminate approximately an order of magnitude faster than the thiolesters. The value of $\beta_{l.g.}$ for the k' term of the fluorene-9-carboxylate *O*-esters [6] was −1.01.

In further support of an *E*1 process for the k' term of activated thiolesters of fluorene-9-carboxylic acid is the observed value of $\Delta S^{\ddagger}$ of +4.6 J mol^{-1} K^{-1} for the *S*-phenyl ester. For unimolecular reactions $\Delta S^{\ddagger}$ values are near zero or slightly positive, although in aqueous media, especially with ionised substrates, more negative values are sometimes found.[1] The value of the kinetic deuterium solvent isotope effect on k' for this ester (k_H/k_D 1.37) is also in line with an *E*1cB transition state.

One can estimate a k_{HO^-} value (the apparent second-order rate constant for hydroxide ion attack) for 4-bromothiophenyl fluorene-9-carboxylate using $k_{HO^-} = k'K_a/K_w$. Using data from Table 2, we find that $k_{HO^-} = 0.166 \times 61.5 \simeq 10$ l mol^{-1} s^{-1}. The second-order rate constant for 4-nitrothiophenyl 9-methylfluorene-9-carboxylate was measured (although in a somewhat different medium for solubility) as 0.191 l mol^{-1} s^{-1}, which is *ca.* 52 fold smaller. The 4-bromothiophenyl 9-methylfluorene-9-carboxylate would be expected to be somewhat less base-labile than the 4-nitrothiophenyl so that the actual ratio of k_{HO^-} for 9-H/9CH_3 is $\geqslant 52$ (one

can estimate a value of *ca.* 100 fold if one uses a value of $\beta_{l.g.}$ of 0.24 for the Brønsted leaving group selectivity for k_{HO^-} for 9-methylfluorene esters [6] and considers the difference in pK_a between 4-nitro- and 4-bromo-thiophenol). Although not enormous this two orders of magnitude rate decrease on 9-methylation is too large to be a simple steric effect and is in line with a mechanistic difference, with a $\beta_{AC}2$ route for the 9-methyl and *E*1cB for the 9-hydrogen active esters.

Comparison of O- *and* S-*Esters of Fluorene*-9-*carboxylic Acid.*—The results for the eliminations of the activated thiolesters (A, B) and oxyesters (C) of fluorene-9-carboxylic acid are summarised in Figure 2. For any given pK_a (leaving group) the oxy-esters eliminate approximately one order of magnitude more rapidly than the thiolesters. For acetoacetate esters ($CH_3COC\bar{C}HCOXR$; X = S, O) undergoing a (similar) elimination process, the oxyesters eliminate *ca.* 2—3 orders of magnitude more rapidly. It is possible that the conjugate base stabilisation afforded by aromaticity for the fluorene esters not only makes them inherently less reactive towards elimination than the acetoacetates * but also alters the balance of features which control and/or dominate the elimination step. For the more stabilised fluorene esters there is significantly less dispersion between *O*- and *S*-esters (*ca.* 1 order of magnitude) than for the less stabilised acetoacetates. It presumably matters little to the fluorene anion with its charge largely located in the aromatic rings (and *not* on the C_9 α to the C=O group) whether the activated leaving group is sulphur- or oxygen-derived.† The elimination is more controlled by the lack of charge availability for the elimination step. For the acetoacetates elimination was dominated by the leaving group whereas for the extra-delocalised anions of fluorene-9-carboxylates this additional feature is less marked, although presumably also present for the delocalised enolate ions of the acetoacetates.

Comparing the SPh and OPh fluorene esters the thiolester anion eliminates PhS^- ion 181-fold faster than PhO^-. For acetoacetates the elimination rate ratio (PhS^-/PhO^-) was only 18, whereas for $PhSO_2\bar{C}HCH_2XPh$ the ratio was close to 1 (in ethanolic sodium ethoxide [9]). Elimination rates have been shown to be dependent not only on the nature of the leaving group (nucleofuge) but also on the portion of the molecule from which the nucleofuge departs. We call this 'remaining' moiety the *residuum.*

Acknowledgement

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* One way of comparing inherent reactivities of these systems is to used the Brønsted leaving group correlations which are of the form $\log_{10}k' = C - \beta pK_{l.g.}$ The parameter *C*, the hypothetical rate of elimination for an arbitrary leaving group pK_a (here zero), gives a measure of such eliminative reactivity. Values of *C* for acetoacetates are +11.50 (oxy) and +7.60 (sulphur) whereas for fluorene-9-carboxylates they are +6.60 (oxy), +4.7 to +6.1 (sulphur).

† A referee has pointed out that the similarities in $\beta_{l.g.}$ for the *O*- and *S*-esters argues against such arguments. He correctedly asserted that there appears to be a charge imbalance. However, in view of the rather limited data yet available for the ester ionisation processes of these esters (O and S) the use of Leffler ($\beta^{k'}/\beta_{overall}$) parameters *etc.* to assess charge distributions is premature.