A Mechanistic Change in the Alkaline Hydrolysis of Esters of Fluorene-9-carboxylic Acid

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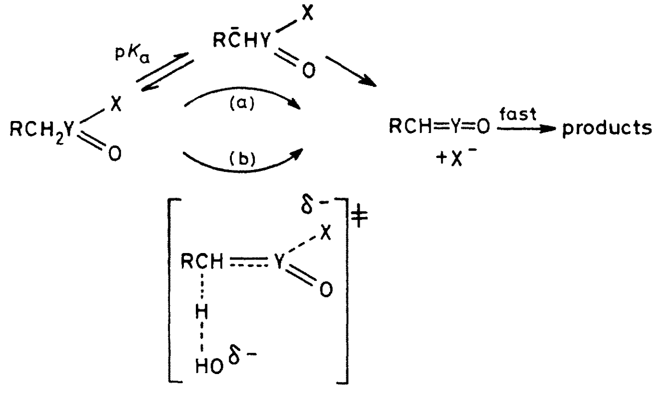
Summary. The Brønsted leaving group (β_{lg}) plot for the alkaline hydrolysis of fluorene-9-carboxylate esters in the pH region corresponding to the existence of the ester anion shows a minimum flanked by a region of high negative β_{lg} $(-1{\cdot}01)$, corresponding to an *E*1*cb* pathway and, for esters of $pK_{lg} > 9{\cdot}5$, a region of positive β_{lg} $(+0{\cdot}11)$.

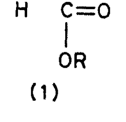
RECENTLY emphasis has been placed on the factors controlling the points of mechanistic changeover for acidic substrates, which can undergo acyl transfer not only by the familiar bimolecular, associative route, but also *via* elimination–addition pathways [commonly the $(E1cb)_{\mathrm{R}}$ mechanism, Scheme 1(a), *via* the substrate anion, *e.g.* *N*-phenylcarbamates[1] and acetoacetates[2]]. For aryl phenylmethanesulphonates ($\mathrm{p}K_{\mathrm{lg}} <$ *ca.* 6), which have strongly activated leaving groups, the required rate constant for the elimination of the aryloxy-group (X^-) from the conjugate base would have to be greater than the vibration rate of the SO_2–X bond.[3] Consequently, the proton transfer and SO_2–X cleavage steps become concerted in an *E*2 process [Scheme 1(b)].[3] On the other hand, as the leaving group becomes poorer, there comes a point at which the rate of elimination from the anion is so slow that a competing mechanism can take over. This change is manifested in a break in the Brønsted leaving group (β_{lg}) plot. For acetoacetate esters the β_{lg} value for the alkaline pH region (with a pH-independent rate constant, k'), in which the ester is fully ionized, changes from $-1{\cdot}29$ for the aryl esters [$(E1cb)_{\mathrm{R}}$ route] to $-0{\cdot}05$ for the alkyl esters, corresponding to $\beta_{\mathrm{lg}} = -\ 0{\cdot}35$ for the $k(\mathrm{HO}^-)$ term for the alkyl esters.[2]



SCHEME 1

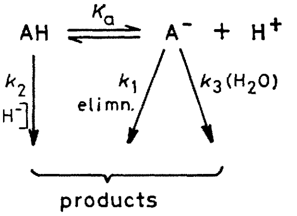
A break in β_{lg} for *N*-acetylcarbamates[4] has been recorded and a similar explanation of a change from an $(E1cb)_{\mathrm{R}}$ to a $B_{\mathrm{Ac}}2$ rate (HO^- attacking a neutral ester) for less active esters has been given.

We have been studying the reactivity of esters of fluorene-9-carboxylic acid (**1**) with aromatic conjugate bases (*cf.* ethyl indole-2-carboxylate for which an *E*1*cb* mechanism has been proposed[5]). For the esters (**1**) we have found that the β_{lg} plot for the k' term ($\mathrm{pH} \gg \mathrm{p}K_{\mathrm{a}}$ of ester) possesses a well defined minimum at $\mathrm{p}K_{\mathrm{lg}}$ *ca.* 9·5 (see the Figure). The rates of basic hydrolysis of the anions with $\mathrm{p}K_{\mathrm{lg}} >$ *ca.* 9·5 actually *increase* with $\mathrm{p}K_{\mathrm{lg}}$. To our knowledge there is no previous report of a *positive* β_{lg} value in alkaline hydrolysis.



(1)

The esters (**1**) were synthesised *via* the acid chloride[6] and their hydrolysis rates studied in aqueous solution at ionic strength 0·1 M and 25 °C. Pseudo-first-order rate constants (k') were independent of hydroxide ion concentration in the range 0·01—0·10 M for all the esters studied. At lower pH values, as the ester $\mathrm{p}K_{\mathrm{a}}$ was traversed, rate constants decreased in line with the Henderson–Hasselbach equation. Such kinetic behaviour is typical of ionizable substrates following the kinetic Scheme 2.[1–4] In some cases, kinetic $\mathrm{p}K_{\mathrm{a}}$'s were obtained from these pH profiles.



SCHEME 2

For the descending limb (region A) of the β_{lg} plot the mechanism of hydrolysis is most likely $(E1cb)_{\mathrm{R}}$ in view of the highly negative β_{lg} ($-1{\cdot}01 \pm 0{\cdot}05$), a $\Delta S^{\ddagger}$ value of $-9{\cdot}7$ cal K^{-1} mol^{-1} for the *m*-chlorophenyl ester (some solvent interaction may be involved), and the correlation, necessitated by the good β_{lg} plot, of the rate constants in this

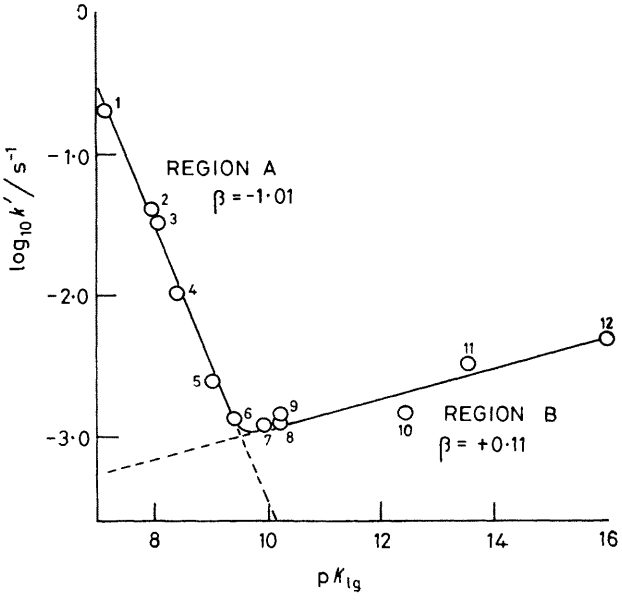


FIGURE. Brønsted leaving group plot of the dependence of $\log_{10}k'$ (for the pH independent rate at $\mathrm{pH} \gg \mathrm{p}K_{\mathrm{a}}$) *versus* $\mathrm{p}K_{\mathrm{lg}}$ (the $\mathrm{p}K_{\mathrm{a}}$'s of the conjugate acids of the leaving groups) for the fluorene-9-carboxylate esters (**1**). The descending limb (region A) follows the equation $\log_{10}k' = -\ 1{\cdot}01\mathrm{p}K_{\mathrm{lg}}(\pm 0{\cdot}05) + 6{\cdot}53\ (\pm\ 0{\cdot}45)$. The ascending limb (region B) follows the equation $\log_{10}k' = +\ 0{\cdot}11\ '\mathrm{p}K_{\mathrm{lg}}(\pm 0{\cdot}02) - 4{\cdot}01\ (\pm 0{\cdot}21)$. 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, prop-2-ynyl; and 12, ethyl.

region with Hammett σ^- values (ρ^- 2·11 ± 0·12)[1,2] For the ascending limb (region B), $\beta_{lg} = +0{\cdot}11 \pm 0{\cdot}02$, the situation is not yet clear However, a mechanistic change is indicated by the abruptness of the change in slope as well as the change in sign of β_{lg} If the rate constant in region B (k') refers to attack of HO^- on the small amount of substrate in its unionized form, $k' = k_2K_w/K_a$ and $\beta(k') = \beta(k_2) + \beta(pK_a)$ A plot of pK_a for the fluorene esters *versus* pK_{lg} gives a slope $[\beta(pK_a)] = ca\ \ +0{\cdot}2$ implying $\beta(k_2) = ca\ \ -0{\cdot}1$, a low value compared with k_2 terms for $MeCO_2R$[7] ($\beta - 0{\cdot}3$) and $MeCOCH_2CO_2$–alkyl[2] ($\beta - 0{\cdot}35$) If the k' term referred to k_3 (nucleophilic attack of H_2O on the anion) $\beta(k')$ would presumably be negative As pointed out by a referee, the low β values for the 'ascending limb' region make detailed quantitative assessments difficult

If one uses the extrapolation of line B of the Figure to calculate the hypothetical rate constant for the 'competing' reaction for the *p*-nitrophenyl ester the *E*1*cb* rate enhancement is found to be only 331 Frequently, *E*1*cb* processes for *p*-nitrophenyl esters are very much faster than the competing reactions (*e g* × 10^6 for the *N*-methylcarbamate, *NN*-dimethylcarbamate pair)[8] Such a low value reflects the mechanistic change at pK_{lg} *ca* 9·5 and may be caused by an inherently low eliminative reactivity of the aromatic anions of (**1**) Comparing *p*-nitrophenyl esters of fluorene-9-carboxylic acid (pK_{ester} 9 9) and acetoacetic acid[2] (pK_{ester} 8 5), the rate constants for elimination of the *p*-nitrophenolate ion are 2 s^{-1} and 193 s^{-1}, respectively Further investigation of this aspect and the low (presumed) β_{lg} for k_2 in the alkyl ester region is required

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