The Influence of Electron Delocalization on the Rate Constants for Competing $B_{Ac}2$ and *Elcb* Ester Hydrolyses

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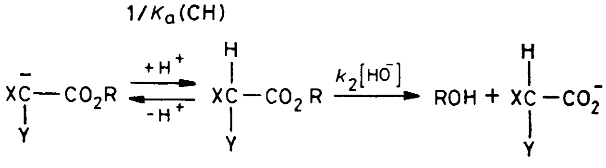
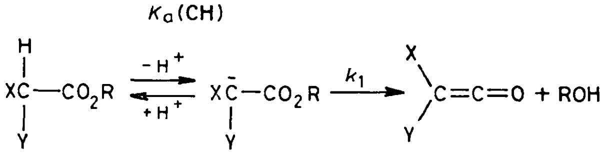
Summary The influence of electron-pair delocalization and leaving-group basicity upon the $(E1cb)_{anion}$ and $(B_{Ac}2)_{anion}$ mechanisms of ester hydrolysis are discussed.

Two mechanisms account for the pH-independent rate constant (k_{pl}), observed at pH $>$ pK_a(CH) for hydrolysis of esters possessing an α-ionizable proton. For the $(B_{Ac}2)_{anion}$ mechanism (equation 1) $k_{pl} = k_2K_w/K_a(CH)$, while for the $(E1cb)_{anion}$ mechanism (equation 2) $k_{pl} = k_1$. Which mechanism prevails is determined by the basicity of the RO$^-$ leaving group.[1-3] The change in mechanism from *E*1*cb* to $B_{Ac}2$ is quite evident in the abrupt change to smaller slope when log k_{pl} for a series of esters is plotted *vs.* the pK_a of the conjugate acid (HOR) of the leaving group [pK_a(LG)].[1]

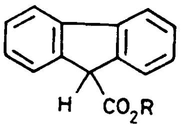


$$\overset{1/K_a(CH)}{\mathrm{X\bar{C}(Y)\!-\!CO_2R} \underset{-H^+}{\overset{+H^+}{\rightleftharpoons}} \mathrm{XC(H)(Y)\!-\!CO_2R}} \xrightarrow{k_2[H\bar{O}]} \mathrm{ROH + XC(H)(Y)\!-\!CO_2^-} \quad (1)$$



$$\overset{K_a(CH)}{\mathrm{XC(H)(Y)\!-\!CO_2R} \underset{+H^+}{\overset{-H^+}{\rightleftharpoons}} \mathrm{X\bar{C}(Y)\!-\!CO_2R}} \xrightarrow{k_1} \mathrm{(X)(Y)C{=}C{=}O + ROH} \quad (2)$$

Alborz and Douglas, in a recent communication,[3] provided a plot of log k_{pl} *vs.* pK_a(LG) for the hydrolysis of esters (**1**) of fluorene-9-carboxylic acid in which the slope corresponding to k_{pl} for the $B_{Ac}2$ mechanism is positive. We are led to divulge our observation of a similar phenomenon in the hydrolysis of the cyanoacetates (**2**), which in conjunction with the previous results with the acetoacetates (**3**)[2] and esters (**1**), allows a description of the importance of electron-pair delocalization in the *E*1*cb* and $(B_{Ac}2)_{anion}$ mechanisms to be made.



(**1**)

$NCCH_2CO_2R$ (**2**)

$MeCOCH_2CO_2R$ (**3**)

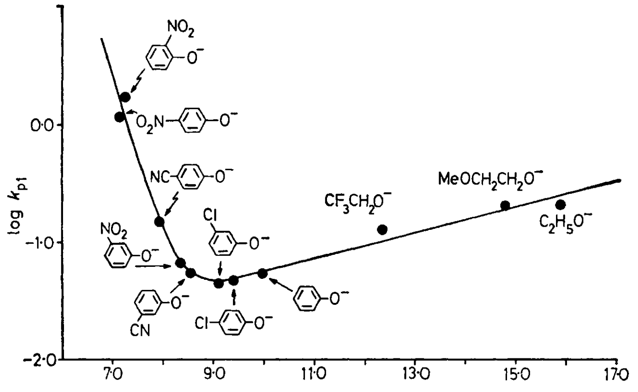


FIGURE. Plot of log k_{pl} (k_{pl} in s^{-1}) *vs.* pK_a of the conjugate acid of the leaving group [pK_a(LG)] for the cyanoacetates (**2**). The points are experimental and the line is theoretical, having been derived from the following empirical equation:

$$k_{pl} = 10 \exp[-1{\cdot}42\, pK_a(LG) + 10{\cdot}38] + 10 \exp[0{\cdot}11\, pK_a(LG) - 2{\cdot}36].$$

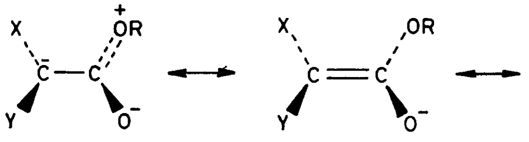
The esters (**2**) were prepared from cyanoacetic acid and the appropriate alcohols [with $(CF_3CO)_2O$] or phenols (with $POCl_3$). Ester hydrolysis in water–acetonitrile 99:1 v/v at 30 °C (μ = 1·0 by addition of KCl) was followed by monitoring the disappearance of the carbanion at *ca.* 243 nm. A plot of log k_{pl} *vs.* pK_a(LG) for the esters (**2**) is shown in the Figure. The slope of the plot is large and negative (−1·42) for good leaving groups and small and positive (+ 0·11) for esters with more strongly basic leaving groups. Values of k_{pl} falling on the portion of the plot with positive slope pertain to $(B_{Ac}2)_{anion}$ hydrolysis (equation 1).† The slope of the plot is defined as β_{pl} [$= d\{\log k_{pl}\}/d\{pK_a(LG)\}$]. The pK_a(CH) value should also be sensitive to pK_a(LG) [$\beta_{CH} = d\{pK_a(CH)\}/d\{pK_a(LG)\}$] as should the second-order rate constant (k_2) for HO^- attack upon the ester moiety of the undissociated carbon acid ester [$\beta_2 = d\{\log k_2\}/d\{pK_a(LG)\}$]. It then follows that $\beta_{pl} = \beta_2 + \beta_{CH}$. A plot of kinetically determined pK_a(CH) values *vs.* pK_a(LG) yields $\beta_{CH} = +0{\cdot}36$, implying $\beta_2 = -0{\cdot}25$. The negative value of β_2 establishes that k_2 (equation 1) decreases in the normal fashion with increase in the proton basicity of RO^-. A similar treatment was applied to the results of the hydrolyses of the esters (**3**) and the determined β values for esters (**1**), (**2**), and (**3**) are provided in the Table.

TABLE. Comparison of β values.

	*E*1*cb*	$B_{Ac}2$		
Ester	β_{pl}	β_{pl}	β_2	β_{CH}
(**1**)[a]	−1·01	+0·11	−0·1	+0·2
(**2**)[b]	−1·42	+0·11	−0·25	+0·36
(**3**)[c]	−1·29	−0·05	−0·35	+0·3
$MeCO_2R$[d]			−0·26	

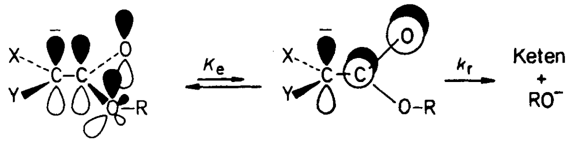
[a] Ref. **3**. [b] This study. [c] Ref. 1; β_{CH} calculated from data in ref. 1. [d] T. C. Bruice, T. H. Fife, J. J. Bruno, and N. E. Brandon, *Biochemistry*, 1962, **1**, 7.

The positive values of β_{CH} show that pK_a(CH) increases with increase in pK_a(LG). This destabilization of the carbanion by electron donation to the ester carbonyl by the OR group is attributable to cross-conjugation [*i.e.* canonical form (I) *vs.* (II)].[4] The extent of carbanion destabilization appears to decrease with an increase in electron delocalization from carbon to the X and Y groups, as would be expected from a diminution of the cross-conjugation effect.‡



(I) (II)

In discussing the influence of pK_a(LG) upon the rate constant β_{pl} for the $(E1cb)_{anion}$ reaction it is necessary to consider the equilibrium between the preferred conformation (III) and the conformation (IV) required to enter the transition state. In (IV) the carbanion is destabilized with increase in electron density in the bonding orbital of the OR moiety through vertical overlap (*i.e.* Hoffmann hyperconjugation[5]). Therefore, the greater the electron density on the ether oxygen, the higher the free energy content of (IV) and the smaller the overall rate constant $K_e k_r$. This expected effect was indeed seen to decrease with increase in carbanion electron-pair delocalization into X and Y.



(III) (IV)

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† The term k_{pl} might relate to nucleophilic attack of water on the ester moiety of the substrate carbanion (k_3), as discussed by Williams and Douglas (A. Williams and K. T. Douglas, *Chem. Rev.*, 1975, **75**, 62). However, to our knowledge, k_{pl} is always larger than the rate constant $k(H_2O)$ for nucleophilic attack of H_2O on the un-ionized ester which (as originally noted by A. Williams, *J. Chem. Soc., Perkin Trans. 2*, 1972, 808), in turn, should be much greater than k_3 owing to the strong electron-donating effects of the carbanion lone pair. The possibility that $k_{pl} = k_3$ is ruled out.

‡ The β_{CH} difference between (**1**) and (**2**) has significance because the data cover a wide range of pK_a(LG) values (7·16—15·99). On the other hand, the difference in β_{pl} between (**1**) and (**2**) is large but there still remains some ambiguity because the data cover a relatively small range of pK_a(LG) values [7·16—9·99 for (**1**) and 7·16—8·0 for (**2**)].

We have previously shown that the rate constants for HO$^-$-catalysed (k_2) and water-catalysed [$k(H_2O)$] hydrolysis of *o*-nitrophenyl esters of substituted acetic acids are related by equation (3).[2] From equation (3) and a knowledge of $k(H_2O)$ ($1{\cdot}21 \times 10^{-5}$ dm^3 mol^{-1} s^{-1}) for *o*-nitrophenyl cyanoacetate k_2 was calculated. Extrapolation of the positive slope line of the Figure provides a hypothetical k_{pl} value

$$\log k_2 = 0{\cdot}84 \log k(H_2O) + 8{\cdot}0 \qquad (3)$$

of $2{\cdot}7 \times 10^{-2}$ s^{-1} from which k_2 may also be calculated. The hypothetical values of k_2 so calculated ($7{\cdot}4 \times 10^3$ *vs.* $6{\cdot}6 \times 10^3$ dm^3 mol^{-1} s^{-1}) are in reasonable agreement so that the kinetic advantage of the *E*1*cb* over the $B_{Ac}2$ mechanism [$k_1K_a(CH)/k_2K_w$] may be determined. From the above data, taken together with literature values, we arrive at the following ratios of $k_1K_a(CH)/k_2K_w$: NCCH$_2$CO$_2$R (2×10^2), EtO$_2$CCH(Me)CO$_2$R (2×10^2), fluoren-9-yl-CO$_2$R′ (3×10^2), EtO$_2$CCH$_2$CO$_2$R′ (8×10^3), MeCOCH$_2$CO$_2$R (10^5), and MeNHCO$_2$R (10^5) where R = *o*-nitrophenyl and R′ = *p*-nitrophenyl.

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