Control of the Dissociative Mechanism in the Hydrolysis of Aryl 4-Hydroxybenzoates

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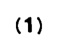
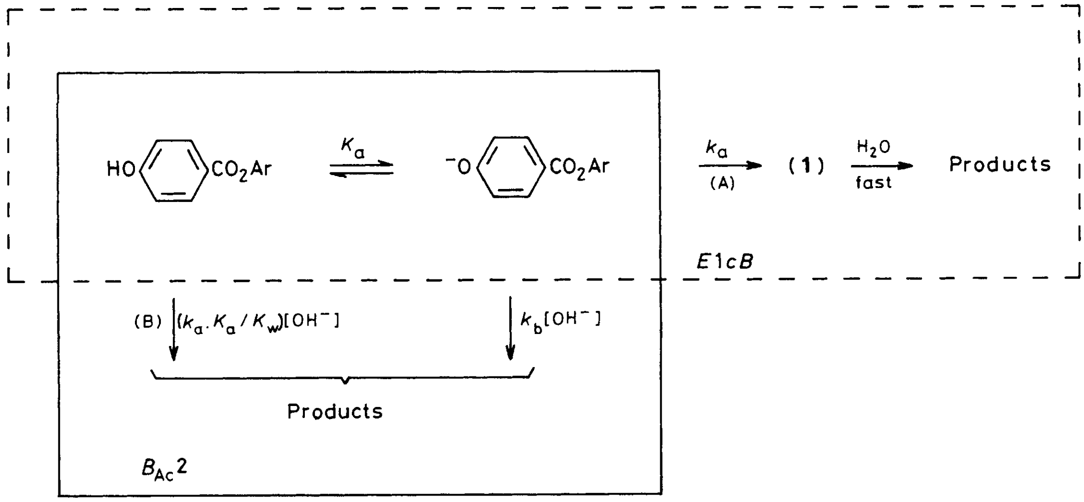
The title esters hydrolyse in mildly alkaline aqueous solution *via* either a *E*1*cB* or $B_{Ac}2$ mechanism, depending on the basicity of the leaving phenolate ion; at high pH's a bimolecular anion–anion reaction carries the reaction flux.

Recent work[1] from these laboratories on the alkaline hydrolysis of 2′,4′-dinitrophenyl 4-hydroxybenzoate has furnished convincing evidence that an *E*1*cB* mechanism occurs which proceeds *via* the *para*-oxoketene intermediate (**1**). This finding has been further substantiated by subsequent studies[2] on the highly hindered 2′,4′-dinitrophenyl 2,6-dimethyl-4-hydroxybenzoate, which proved to be, *inter alia*, more reactive than the parent ester towards HO^-, again consistent with the *E*1*cB* mechanism. However, it was previously reported[3] that 4′-nitrophenyl 4-hydroxybenzoate hydrolyses in mildly alkaline buffers *via* the ordinary $B_{Ac}2$ mechanism.



(**1**)



Scheme 1

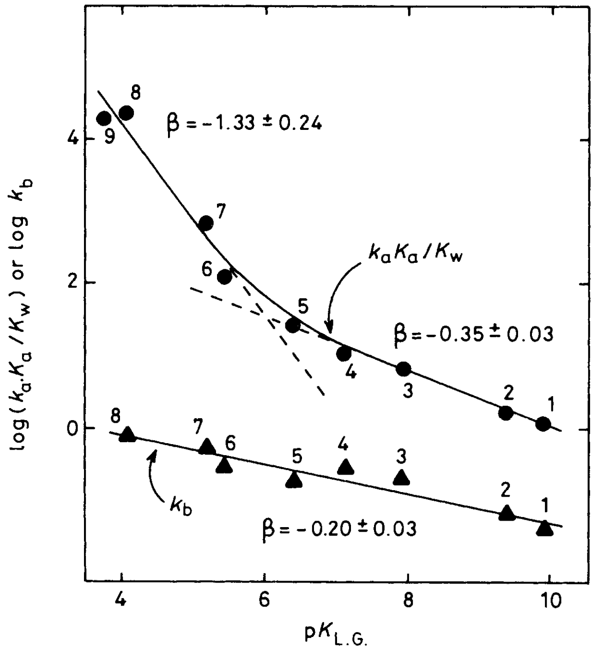


Figure 1. Plot of log $(k_a.K_a/K_w)$ and log k_b (aqueous solution, 60 °C, ionic strength made up to 0.1 M with potassium chloride) for the hydrolysis of substituted aryl 4-hydroxybenzoates *vs.* the pK_a of the conjugate acid of the leaving group ($pK_{L.G.}$). The points represent the following 4-hydroxybenzoates: (1) phenyl; (2) 4′-chlorophenyl; (3) 4′-cyanophenyl; (4) 4′-nitrophenyl; (5) 2′-nitro-4′-chlorophenyl; (6) 2′-chloro-4′-nitrophenyl; (7) 2′,5′-dinitrophenyl; (8) 2′,4′-dinitrophenyl; (9) 2′,6′-dinitrophenyl.

These apparently conflicting results may be easily reconciled if one assumes that a change in mechanism takes place as the pK_a of the leaving phenol is varied.

Aryl substituted 4-hydroxybenzoate esters hydrolyse in alkaline buffers according to the rate law (1) which can be derived from Scheme 1. Standard treatment of data according to equation (1) gave values of K_a, k_a, and k_b for each substrate. The values of K_a obtained kinetically are identical (within the experimental error) to those measured spectrophotometrically for the ionization of the phenolic group of the same hydroxy esters. Second-order rate constants k_b refer to reaction of hydroxide ion with the conjugate base of the hydroxy ester and give rise to a linear Brønsted-type relationship (Figure 1). The small slope is consistent with that calculated from the ρ observed for hydroxide attack on substituted aryl benzoates,[4] which is known to proceed *via* a $B_{Ac}2$ mechanism.

$$k_{obs} = \{k_a + k_b[HO^-]\}/(1 + a_H/K_a) \qquad (1)$$

The first-order rate constant k_a refers to paths (A) or (B) which are kinetically indistinguishable. The plot against $pK_{L.G.}$ of the logarithm of the second-order rate constant for reaction between hydroxide ion and neutral ester $(k_a.K_a/K_w)$ exhibits a break in linearity at $pK_{L.G.}$ *ca.* 6 and upward curvature. This is consistent with a sharp change in the electronic nature of the transition state reflecting a change in mechanism[5] (Figure 1) which we believe is from *E1cB* [path (A)] for weakly basic leaving groups to $B_{Ac}2$ [path (B)] for strongly basic ones. The 4-oxyanion is not able to expel a strongly basic leaving group in this system, and the addition of a hydroxide ion to the ester is necessary to provide the driving force for this to be accomplished. The very large leaving group effect on $(k_a.K_a/K_w)$ ($\beta = -1.3$) compared with that for the overall equilibrium hydrolysis of esters[6] and that for alkaline hydrolysis of aryl carbamates[5] is further strong support for the *E1cB* type of mechanism for the hydrolysis of aryl 4-hydroxybenzoates possessing active leaving groups.

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