Steric and Electronic Control of the Dissociative Hydrolysis of 4-Hydroxybenzoate Esters

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The introduction of two *ortho* methyl substituents changes the propensity of 4-hydroxybenzoates to react *via* the oxo-ketene pathway by nearly one million-fold; the increased reactivity of the hindered conjugate base over that of the parent is assigned to enhanced internal nucleophilicity of the 4-oxyanion.

Recently we demonstrated that 2,4-dinitrophenyl 4-hydroxybenzoate was hydrolysed in mild alkali *via* an elimination–addition mechanism involving a *para*-oxo-ketene intermediate.[1] We considered the possibility of favouring the dissociative pathway by utilising a 'B-strain' effect[2] whereby compression energy due to steric crowding in the ground-state trigonal carbon ester is relieved in the transition-state as the central carbon becomes di-co-ordinate. Such crowding could also depress the associative mechanism involving bimolecular attack of the hydroxide ion on the ester. We therefore studied the hydrolysis of 2,4-dinitrophenyl 4-hydroxy-2,6-dimethylbenzoate† and of its corresponding 4-methoxy derivative over a range of pH.

The hydrolysis reactions of the esters were pseudo first order and the rate constants obeyed the kinetic rate laws, equation (1) and equation (2), for the 4-hydroxy and 4-methoxy esters,

$$k_{\text{obs}}^{4\text{-OH}} = k_{\text{a}}/(1 + a_{\text{H}}/K) \qquad (1)$$

$$k_{\text{obs}}^{4\text{-OMe}} = k_{\text{OH}}[\text{OH}^-] \qquad (2)$$

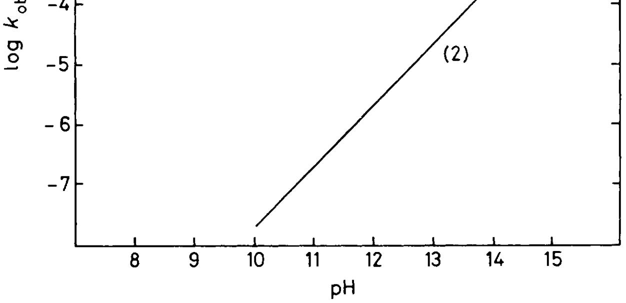

Figure 1. Dependence on pH of the hydrolysis of 2,4-dinitrophenyl 4-hydroxy-2,6-dimethylbenzoate (1) and 2,4-dinitrophenyl 4-methoxy-2,6-dimethylbenzoate (2) at 25 °C, 40% (v/v) dioxane–water, and 1.0 M ionic strength maintained with KCl. The lines are calculated from equations (1) and (2) and the parameters are given in the text. The value of pK_w for this system is 15.25.

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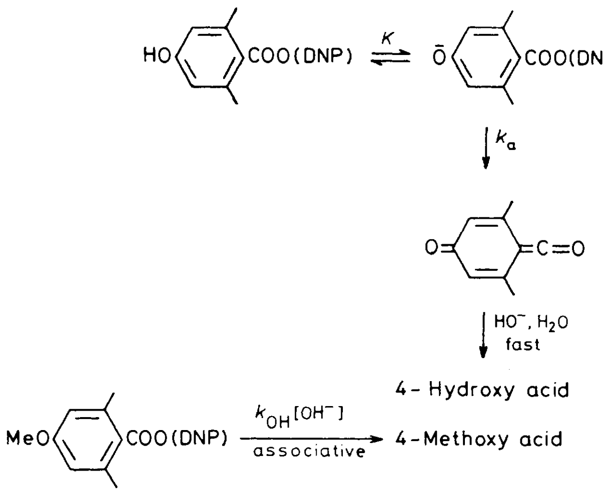
† This compound was prepared from 4-hydroxy-2,6-dimethylbenzoic acid and 2,4-dinitrophenol using dicyclohexylcarbodiimide; the starting acid was obtained from the 4-benzyloxy-1-bromo-2,6-dimethylbenzene by a Grignard reaction with carbon dioxide. The 4-methoxy-2,6-dimethylbenzoate was obtained from its corresponding acid by a similar process. All the compounds had satisfactory elemental and spectroscopic analyses.



Scheme 1. DNP = 2,4-dinitrophenyl.

respectively, as depicted in Figure 1. No buffer catalysis was observed and the rate constants were measured using 0.01 M tris(hydroxymethylamino)methane and 0.01 M carbonate buffers. Values of k_a, pK, and k_{OH}, obtained from fitting the data to equations (1) and (2), are 0.33 s^{-1}, 9.64, and 3.9 × 10^{-3} dm^3 mol^{-1} s^{-1}, respectively. No titration pK was measured with the 4-hydroxy-2,6-dimethylbenzoate as this compound decomposed too rapidly at the higher pH's. Arrhenius parameters at 25 °C were determined at two pH's: $\Delta H^{\ddagger} = 6.1$ kcal/mol and $\Delta S^{\ddagger} = -8.0$ cal/K/mol (for pH 7.98, $k_{obs} = k_a K/a_H$); $\Delta H^{\ddagger} = 9.13$ kcal/mol and $\Delta S^{\ddagger} = 5.5$ cal/K/mol (for pH 11.05, $k_{obs} = k_a$) (1 cal = 4.184 J).

The parent system[1] was shown to involve a dissociative route for the spontaneous hydrolysis of the anion. Added nucleophile does not enhance the rate constant and the formation of significant quantities of trapped product indicates the participation of an intermediate.[1] Comparison of the reactivity with the 4-methoxy ester and studies of the temperature dependence of the reaction also indicate a dissociative path as the major route for the parent. The rate enhancement (3.5 × 10^7) for the apparent second order rate constants (4-OH over 4-OMe) for the 2,6-dimethyl esters is evidence that the hindered ester also takes a dissociative path (Scheme 1). This conclusion is reinforced by the Arrhenius parameters.

The value of k_a for the 2,6-dimethyl ester is some 1000-fold larger than that[1] of the parent. The ratio of the reaction flux through dissociative and associative mechanisms is a dramatic 3.5 × 10^7-fold compared with 250-fold[1] for the parent ester. We derive the flux through the associative pathway from k_{OH} for the 4-methoxy derivative assuming that the substitution of methyl for hydrogen has little effect on the bimolecular attack at a remote site.

Study of precision space-filling models (CPK, from the Ealing Corporation) indicates that although the ester group in the 2,6-dimethyl species cannot easily take up a 'planar' conformation with respect to the aromatic ring the 'perpendicular' conformation should have no steric strain. Simple force field studies using Derisson and Smit's equations and parameters[3] indicate that the 'perpendicular' conformations of both parent and 2,6-dimethyl species have no steric strain. The planar conformation of the parent, while strained, is more stable than that of the 2,6-dimethyl ester. The greater reactivity of the 2,6-dimethyl oxyanion compared with the parent towards dissociation cannot be due to 'B-strain' as might have been expected because the ground-states of both anions are unstrained.

We ascribe the enhanced value of k_a to the greater propensity of the 4-oxyanion to donate its electrons to expel the 2,4-dinitrophenolate as measured by the pK of the phenol (9.64) compared with that of the parent (7.68).[1] The difference in pK values and hence in 'internal nucleophilicity'[4] is due to the inductive effect of the two methyl substituents *meta* to the hydroxy group. The 2,6-dimethyl groups also sterically hinder the ester from becoming planar with the aromatic ring and hence prevent mesomeric stabilisation of the 4-oxyanion.

The very much enhanced ratio of reaction flux (3.5 × 10^7) *via* the *para*-oxo-ketene to the bimolecular path compared with that (250)[1] for the parent system is due to both increased reactivity of the 2,6-dimethyl oxyanion and decreased reactivity of bimolecular attack of hydroxide ion owing to steric hindrance by the adjacent 2,6-dimethyl groups.

The data presented here strengthen the evidence for a *para*-oxo-ketene intermediate and extend our understanding of control of the mechanism.

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References

1 S. Thea, G. Guanti, G. Petrillo, A. Hopkins, and A. Williams, *J. Chem. Soc., Chem. Commun.*, 1982, 577.

2 H. C. Brown and R. S. Fletcher, *J. Am. Chem. Soc.*, 1949, **71**, 1845.

3 J. L. Derisson and P. H. Smit, *Acta Crystallogr., Sect. A*, 1978, **34**, 842.

4 M. B. Davy, K. T. Douglas, J. S. Loran, A. Steltner, and A. Williams, *J. Am. Chem. Soc.*, 1977, **99**, 1196.