There is no Evidence for Electrostatic Catalysis of Vinyl Ether Hydrolysis in Water

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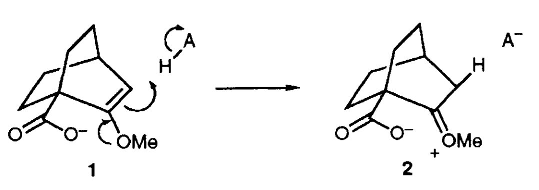
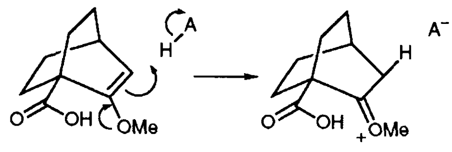
The apparent catalysis by the neighbouring carboxylate group in the acid-catalysed hydrolysis of 2-methoxybicyclo[2.2.2]octene-1-carboxylate **1** is accounted for by the change in inductive effect on ionisation of the CO_2H group.

Electrostatic catalysis remains one of the least well understood factors involved in enzyme mechanisms. Calculations for systems in the gas phase show that enormous effects are possible, but experimental evidence has proved difficult to obtain, and there is no unambiguous demonstration of a strong positive electrostatic effect on catalysis in a simple system in water. Thus, a report by Bergman and Halvarsson[1] that the acid-catalysed hydrolysis of the vinyl ether **1** is 32 times faster for the anion than for the undissociated form **3** is of particular interest. Since the neighbouring carboxy group cannot participate directly, for simple reasons of geometry, either as a nucleophile or as a general acid, the effect was interpreted in terms of electrostatic stabilisation of the



1 **2**



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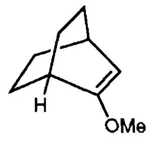

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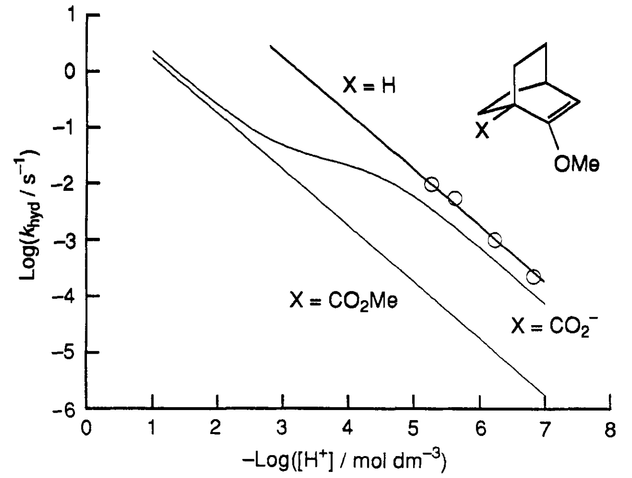

Fig. 1 pH-rate profile (25 °C, ionic strength 0.1 mol dm^{-3}) for the hydrolysis of **5** (heavy line), compared with that for the carboxylic acid **3** and its methyl ester.[1] The points are experimental, the lines calculated, using k_H = 17.7 and 23.0 dm^3 mol^{-1} s^{-1} for X = CO$_2$Me and CO$_2$H, 740 and 1790 dm^3 mol^{-1} s^{-1} for X = CO$_2^-$ and H, respectively, and pK_a = 4.45 for the CO$_2$H group of **3**.

developing oxocarbocation **2** by the adjacent carboxylate anion.

An alternative explanation is that the anion **1** is hydrolysed more rapidly not because CO$_2^-$ stabilises the developing oxocarbocation, but because the neutral CO$_2$H group of the acid form **4** destabilises it by inductive electron-withdrawal. Acetal hydrolysis, which also goes by way of intermediate oxocarbocations, is well known to be sensitive to the electronic effects of α-substituents. A simple calculation based on a ρ*-value of 3.6[2] and σ-values[3] of 0.45 and zero for CO$_2$H and CO$_2^-$, respectively, suggests that a difference of 40-fold in reactivity might reasonably be expected. This is comparable with the reported rate ratio of 32.3.

As a simple test of this proposition we have prepared† and measured the rate of hydrolysis of the unsubstituted system **5**.‡ The through-bond effects of CO$_2^-$ and H are identical (σ-values are zero, or close to zero for both), so any significant electrostatic effect of CO$_2^-$ would be apparent as a faster rate of acid-catalysed hydrolysis for **1**. In fact the unsubstituted compound is actually hydrolysed more rapidly than **1** (Fig. 1). We conclude that there is still no unambiguous demonstration of a strong positive electrostatic effect on catalysis in a simple system in water.

We thank the SERC for a Studentship, to N. H. W. This work was presented at the Third European Symposium on Organic Reactivity (ESOR III) in Gothenberg, July 1991.

Received, 9th August 1991; Com. 1/04176B

References

1 T. Halvarsson and N.-Å. Bergman, *J. Org. Chem.*, 1991, **56**, 251; *J. Chem. Soc., Chem. Commun.*, 1989, 1219.
2 M. M. Kreevoy and R. W. Taft, *J. Am. Chem. Soc.*, 1975, **77**, 5590.
3 Good values of σ* or σ$_I$ are not available, but various substituent constants for CO$_2$H and CO$_2^-$ differ by 0.4–0.5 on the σ-scale. See, for example, C. D. Ritchie and W. F. Sager, *Prog. Phys. Org. Chem.*, 1964, **2**, 323; C. Hansch, A. Leo and R. W. Taft, *Chem. Rev.*, 1991, **91**, 165.

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† Bicyclo[2.2.2]octanone was converted (potassium hydride in dimethylformamide) to the potassium enolate, which was methylated on oxygen with dimethylsulphate. Purification was by column chromatography [eluent 97:3 light petroleum (b.p. 30–40 °C):triethylamine]; the fractions were washed with sodium hydrogen carbonate solution and water, dried over sodium sulphate and potassium carbonate and concentrated to give the pure vinyl ether.

‡ The hydrolysis of **5** was followed under pseudo-first-order conditions at 25 °C in aqueous acetate and phosphate buffers, with the ionic strength maintained at 0.1 mol dm^{-3} with KCl. The decrease in UV absorption at 215 nm was followed on a Cary 3 spectrophotometer, and obeyed the first-order rate equation accurately. Rate constants were calculated over the first 4 half lives, and the rate profile obtained by extrapolating to zero buffer concentration.