# Intramolecular Catalysis in Acetal Hydrolysis

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RECENTLY intramolecular catalysis was observed in the hydrolysis of 2-carboxyphenyl $\beta$-D-glucoside but since possible reaction intermediates were not available there was some uncertainty as to the nature of this catalysis.[1] We have now investigated the hydrolysis of an analogous acetal, 2-methoxymethoxybenzoic acid (I), and observed similar intramolecular catalysis and since possible intermediates could be synthesised the mechanism has been more firmly established. This is the first reported example of intramolecular catalysis in the hydrolysis of a simple acetal. The hydrolysis of (I) in the pH range 3·1—5·5 follows a rate law: rate = $k$[unionised form], and at pH 4·11 the rate is 650 times greater than that for methyl 2-methoxymethoxybenzoate (II) and at pH 4·08 it is 300 times greater than for 4-methoxymethoxybenzoic acid (III). Possible mechanisms which would account for this enhanced rate involve intramolecular general acid catalysis (mechanism 1) and a combination of intramolecular nucleophilic catalysis and specific hydronium ion catalysis (mechanisms 2 and 3) which are all kinetically equivalent. Mechanism 2 can be eliminated since it was found that the postulated intermediate (IV) is stable under conditions in which (I) is hydrolysed

rapidly. The hydrolysis of methoxymethyl salicylate (V), the postulated intermediate of mechanism 3, however proceeded more rapidly than that of the acetal (I) and at pH 4·08 and 45·0° this reaction had a rate constant 1·16 × 10⁻³ sec.⁻¹ compared to that for the hydrolysis of the acetal (I), 6·13 × 10⁻⁴ sec.⁻¹, and mechanism 3 must therefore be considered seriously. It was found however that when the hydrolysis of (I) was followed spectro-



(I)      (II)      (III)
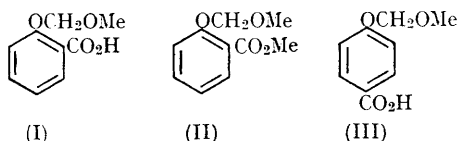
photometrically at 41,430 cm.⁻¹, the isobestic wavenumber ($\epsilon$ = 4000) of (I) and the product, salicylic acid, the absorbance remained constant throughout the reaction although at this wavenumber the value of $\epsilon$ for methoxymethyl salicylate is 9770. Computer simulation of the hydrolysis (University of London Atlas) assuming mechanism 3 and using the known value of $k_2$ and a wide range of values of $k_1$ showed that a constant value of the

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[1] B. Capon, *Tetrahedron Letters*, 1963, 911; for other relevant discussion see M. L. Bender and M. S. Silver, *J. Amer. Chem. Soc.*, 1963, **85**, 3006 and T. H. Fife, *ibid.*, 1965, **87**, 271.

absorbance would only be obtained at this wavenumber throughout the reaction if the value of $k_1$ was less than $5 \times 10^{-5}$ sec.$^{-1}$ However since the

followed and that the high rate of hydrolysis of (I) is due to intramolecular general acid catalysis. The solvent deuterium isotope effect, measured in
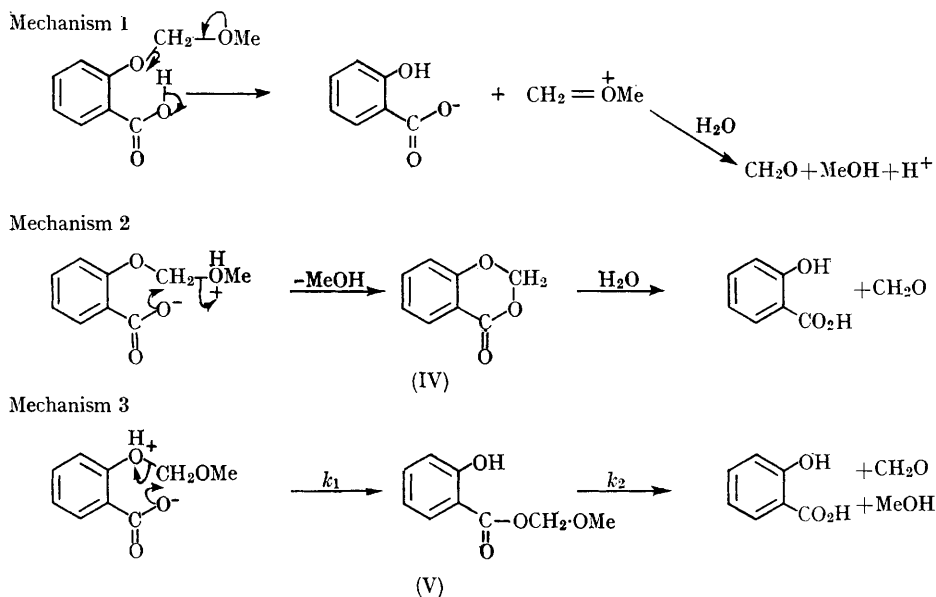


rate constant for the hydrolysis of (I) was determined from measurements at another wavenumber (33,700 cm.$^{-1}$) to be much greater than this *i.e.* $6 \cdot 13 \times 10^{-4}$ sec.$^{-1}$, mechanism 3 is excluded. It is therefore concluded that mechanism 1 is being

$4 \times 10^{-3}$M-hydrochloric acid at $45 \cdot 0°$, $k_{obs}$ ($H_2O$) — $k_{obs}$ ($D_2O$) $= 1 \cdot 43$, is also consistent with this interpretation.