Intermolecular General Acid Catalysis in Acetal Hydrolysis

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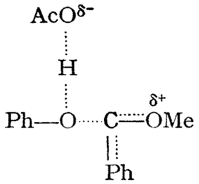
ALTHOUGH acetals and orthoesters are closely related structurally, their hydrolyses differ, as the former normally react with specific acid catalysis and the latter with general acid catalysis.[1] It is difficult to accept that this is more than a quantitative difference and it was thought that, by selecting an acetal of suitable structure, general acid-catalysis might be found. Benzaldehyde methyl phenyl acetal is such an acetal.† In acetate buffers of constant ionic strength and pH, the plot of k_{obs} for its hydrolysis against acetic acid concentration is a straight line (see Table). This is the result of kinetic general acid catalysis since the slope is independent of pH. Kinetic general acid catalysis could arise from mechanistic general acid catalysis or from a mechanism involving nucleophilic and specific acid catalysis. The latter is excluded, however, since it would be expected to be more important in the hydrolysis of formaldehyde methyl phenyl acetal for which no general acid catalysis could be detected. True general acid catalysis is, therefore, taking place.

The acetic acid-catalysed hydrolysis of benzaldehyde methyl phenyl acetal in acetic acid–sodium acetate buffers of pH 4·68 *in which the ioni strength is maintained constant by the addition of potassium chloride* ([$CH_3\cdot CO_2Na$] = [$CH_3\cdot CO_2H$])

[$CH_3\cdot CO_2H$]	0·200	0·400	0·500	0·600	0·800	1·000
$10^3 k_{obs}$(sec.$^{-1}$)	2·98, 3·06	4·65	5·27, 5·27	5·85, 6·05	6·71, 7·00	8·03 ,7·91
$10^3 k_{calc}$(sec.$^{-1}$)	3·37	4·57	5·17	5·77	6·96	8·16

Slope = $5{\cdot}98 \times 10^{-3}$ l.mole^{-1}sec.$^{-1}$, s.d. $2{\cdot}6 \times 10^{-4}$; intercept = $2{\cdot}18 \times 10^{-3}$ sec.$^{-1}$, s.d. $1{\cdot}8 \times 10^{-4}$.

The solvent isotope effects are $k(HOAc)/k(DOAc) = 2{\cdot}14 \pm 0{\cdot}03$ and $k(H_3O^+)/k(D_3O^+) = 1{\cdot}01 \pm 0{\cdot}03$, and the Brønsted α-coefficient calculated from the catalytic constants for catalysis by acetic, formic, and chloroacetic acid is 0·58. These figures indicate that proton transfer is much less complete in the transition state than in that for the general acid-catalysed hydrolysis of orthoesters for which $k(H_3O^+)/k(D_3O^+)$ is *ca.* 0·5 and α is *ca.* 0·8. This suggests that the oxygen to which proton transfer is occurring is much more basic in the transition state with the acetal than with the orthoester. This can only be accomplished if carbon–oxygen bond breaking is well developed in the transition state for the acetal and the mechanism is a concerted electrophilic substitution on oxygen with a transition state as (I). The effect of substituents in the phenoxy-group also support this transition state, as $\rho = +0{\cdot}8$ for the acetic acid-catalysed reaction, suggesting that C–O bond breaking has run ahead of O–H bond forming. This value is quite different from the value of $-0{\cdot}66$ found for the specific acid-catalysed hydrolysis of aryl β-D-glucosides of $-0{\cdot}92$ for the hydronium ion-catalysed



(I)

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† The reasons for selecting this acetal will be outlined in the full paper.

hydrolysis of 2-aryloxytetrahydropyrans in 50% aqueous dioxan.[2] Significantly, however, it is very similar to the values of +1 to +1·5 found for the enzymically catalysed hydrolysis of glycosides.[3] It would also be expected, on the basis of this mechanism, that substitution in the aldehyde phenyl group would yield a negative ρ-value and we are currently investigating this point.

Recently, Fife and Jao have reported that the hydrolyses of 2-*p*-nitrophenoxy- and 2-*p*-chlorophenoxy-tetrahydropyran (but not that of *p*-methoxyphenoxytetrahydropyran) show general acid catalysis in formate buffers.[3] The effects were smaller than observed in this work, even though the solvent was 50% aqueous dioxan. Emphasis was placed on the importance of oxygen basicity in facilitating general acid catalysis. Although we agree that this is an important factor, in our view the stability of the intermediate carbonium ion is equally or more important, and this is supported by the much greater sensitivity of the hydrolysis of benzaldehyde methyl phenylacetal to buffer concentration. Fife and Jao did not report the α-coefficient, nor the solvent isotope effect and ρ-value for the formic acid-catalysed hydrolysis of the aryloxytetrahydropyrans. The value of $k(H_3O^+)/k(D_3O^+)$ for the *p*-nitrophenoxy-compound, 0·75, and the ρ-value for the H_3O^+-catalysed reactions, −0·92, are significantly different from the values found in this work and suggest a mechanism in which there is a much greater degree of proton transfer in the transition state.

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[1] E. H. Cordes, *Progr. Phys. Org. Chem.*, 1967, **4**, 1.

[2] T. H. Fife and L. K. Jao, *J. Amer. Chem. Soc.*, 1968, **90**, 4081.

[3] For a review, see B. Capon, *Chem. Rev.*, in the press.