Efficient intramolecular general acid catalysis of the hydrolysis of a dialkyl acetal

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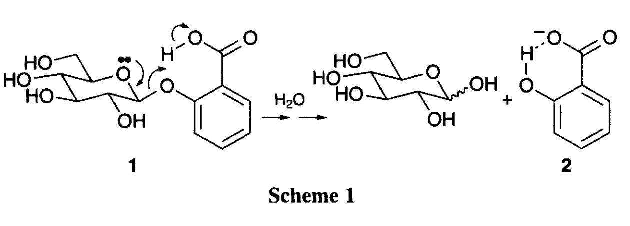
The hydrolysis of benzaldehyde acetal 3, catalysed by the neighbouring carboxy group, is some 10^5 times faster than that of a comparable system 6, which does not form a strong intramolecular hydrogen bond in the transition state for the reaction.

General acid catalysis is an essential part of the mechanism of action of glycosyl transfer enzymes.[1] Typical glycoside substrates are extremely unreactive near pH 7, so this catalysis is evidently highly efficient. An unsolved question is whether general acid catalysis alone, together with the special micro-environment of an active site, can account for this efficiency; so far chemical models fall conspicuously short. Thus the classical model for this part of the mechanism, the hydrolysis of salicyl β-D-glucopyranoside **1**, was studied conveniently at 91.3 °C,[2] despite the good phenolic leaving group, and even though it takes advantage of the formation of a strong intramolecular hydrogen-bond in the salicylate anion **2** produced (Scheme 1).[3]

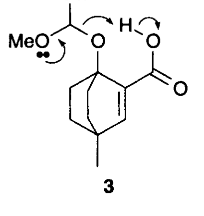
We have identified the development of such a strong intramolecular hydrogen bond as the key to efficient intramolecular general acid catalysis[4] and have suggested that it is a likely feature of general acid–base catalysis in enzyme reactions. In a glycosyl transfer reaction this would involve the formation of a strong hydrogen bond from CO_2H to a developing alkoxide anion. We report results with a model system which confirm that such an interaction can lead to efficient catalysis.

Strong intramolecular hydrogen bonds are not common in water, so the design of our test system is based on the well-established salicylic acid structure. The rates of reactions like that depicted in Scheme 1 are known to be sensitive to the basicity of the leaving group,[5] so one certain result of making the group an alkoxide will be a sharp decrease in reactivity. To compensate—and so be confident of seeing a measurable reaction—we use a reactive benzaldehyde acetal. The resulting system **3**† is so reactive that below pH 6.5 (at 20 °C) its hydrolysis (monitored by the release of benzaldehyde) must be followed by stopped-flow.



1 **2**

Scheme 1



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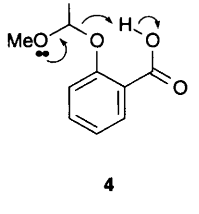

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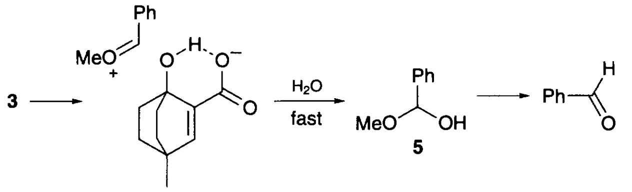
Under acidic conditions (pH < 6.5) marked deviations from first-order kinetics are observed. These can be quantitatively accounted for in terms of two consecutive reactions, of which one is buffer-catalysed. This was identified by its kinetic behaviour as the breakdown of the known[7] hemiacetal **5** (Scheme 2).

Separating the data for hemiacetal hydrolysis reveals the pH–rate profile for the initial acetal cleavage reaction (Fig. 1, solid symbols), which is fast enough below pH 6.5 for the hemiacetal to accumulate. The profile has the expected form[3] with the region above pH 2.5 representing the cleavage of the acetal acid **3** (k_0). Below pH 2.5 the reaction is specific acid catalysed (k_{H^+}). The apparent pK_a (4.7 ± 0.1) is consistent with the ionisation of an acrylic acid.

Compound **3** is the first dialkyl acetal of benzaldehyde to show detectable intramolecular general acid catalysis. Fife and Przystas[8] found no significant catalysis by the neighbouring



Scheme 2

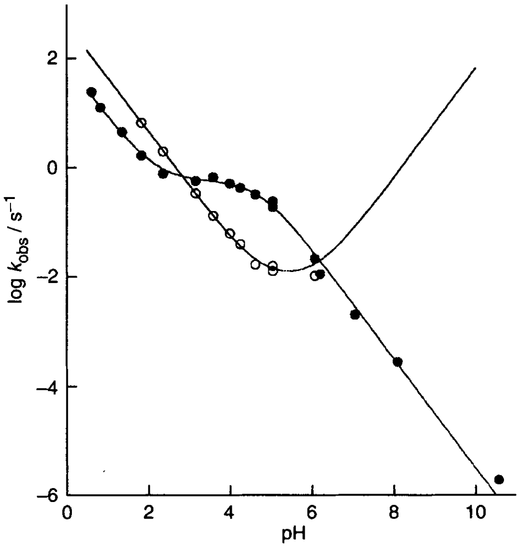
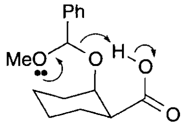


Fig. 1 pH–Rate profiles for the two consecutive reactions observed in hydrolysis of acetal **3**; (●) disappearance of **3**; (○) hydrolysis of hemiacetal **5**. The curves are calculated, using for the reaction of **3**, k_{H^+} 84 $dm^3\ mol^{-1}\ s^{-1}$, k_0 0.59 s^{-1} and pK_a = 4.7, and for hydrolysis of **5**, k_{H^+} 460 $dm^3\ mol^{-1}\ s^{-1}$, k_0 0.008 s^{-1} and k_{OH} 1.2 × 10^6 $dm^3\ mol^{-1}\ s^{-1}$; hydroxide-catalysed hydrolysis of **5** is not observed (it is too fast for hemiacetal to accumulate in our reaction); k_{OH} is assumed to be 1.73 times faster than the value measured at 15 °C by Capon *et al.*,[7] as are both k_{H^+} and k_0.

CO_2H group of the acetal **6**‡ and estimated an upper limit for the rate constant for the reaction shown of 2.3×10^{-5} s^{-1} (at 50 °C in 50% aqueous dioxane). Our measured rate constant for the reaction of **3** is 0.59 ± 0.09 s^{-1} which is 26 000 times faster at 20 °C and thus of the order of 10^5 times faster if the difference in temperature is allowed for. Catalysis is clearly exceptionally efficient in the reaction of **3**.



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It is not possible to measure an accurate effective molarity (EM) for the catalytic CO_2H group of **3** because the corresponding intermolecular reaction is not detectable. (Nor could it be measured for the methyl ester of **3**, which gave complex kinetics under the relevant conditions.) Our best estimate is based on k_{H+} as a measure of intrinsic reactivity and a Brønsted α-value of 0.87, derived by Jensen *et al.*,[9] who established the dependence of α on the leaving group for different benzaldehyde acetals. (The point for catalysis by H_3O^+ falls on the Brønsted line for these correlations.) This gives a second-order rate constant for catalysis by a general acid with $pK_a = 4.7$ of 2.1×10^{-4} and thus an EM of 2800 for the CO_2H group of **3**. An important objective of future work is to determine how EM in these efficient systems depends on structure, particularly intrinsic reactivity and the geometry of the hydrogen bond in the transition state.

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Footnotes

† Compound **3** was generated from its stable methyl ester by reaction with sodium trimethylsilanolate(Me_3SiONa) in diethyl ether[6] and characterised directly by NMR spectroscopy.

‡ Catalysis was observed in two acetals **6** (Ph = Ar) derived from benzaldehydes with electron-withdrawing substituents.

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