Intramolecular Proton Transfer Catalysis of Ether Hydrolysis

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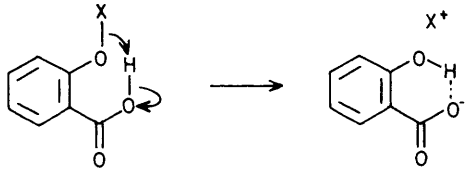
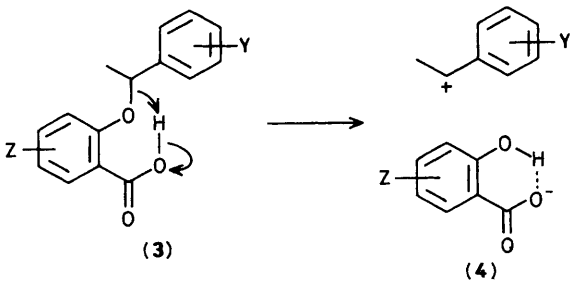
Efficient intramolecular catalysis by the CO_2H group results in rapid hydrolysis of 1-arylethyl ethers of salicylic acid.

We are interested in mechanisms for general acid–base catalysis because these are the mechanisms most commonly used by enzymes.[1] The most efficient,[2] and thus some of the most interesting, reactions of this sort are the intramolecular general acid catalysed hydrolyses of derivatives (**1**) of salicylic acid.[3] The systems studied so far, *i.e.* acetals (X = CHROR'[4]) and phosphate and sulphate monoesters (X = PO_3^{2-},[5] SO_3^-,[6]), have in common a group which can lose the salicylate monoanion to generate a relatively stable species X^+ (**2**).

They also share a common mechanism, which can be represented as shown in (**1**) → (**2**). But this representation conceals an apparent anomaly: classical general acid catalysis would involve proton transfer to the leaving group oxygen concerted with O–X cleavage yet the evidence from structure–reactivity correlations (Brönsted $\alpha \simeq 0$)[4–7] is that no significant proton transfer has occurred in the transition state



(**1**) (**2**)



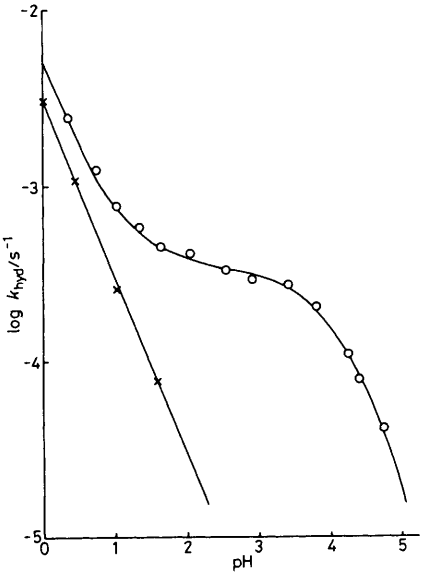


Figure 1. pH–rate profiles for the hydrolysis of (**3**) (Y=Z=H) and its methyl ester (×) at 39 °C and ionic strength 1M (KCl) in water. The points are experimental, the curves calculated using k_{H^+} = 3.01 × 10^{-3} and 4.56 × 10^{-3} dm^3 mol^{-1} s^{-1} for the ester and acid, respectively, and k_0 = 3.44 × 10^{-4} s^{-1}, pK_a = 3.95 for the acid form.

for O–X cleavage. We report results with a new system designed to undergo the same type of reaction (**1**) → (**2**), and to allow a detailed study of the mechanism.

It seemed likely that simple carbocations might be generated from ethers (**1**) (X = alkyl) of salicylic acid, if X^+ is sufficiently stable. We chose to work with 1-arylethyl ethers (**3**): substitution reactions of 1-arylethyl derivatives have been studied in extensive detail in recent years,[8] from various points of view,[8,9] and are moderately well understood. We should therefore be able to compare salicylate monoanion with other, simpler, leaving groups, and also probe the developing carbocation, by varying substituents in the two aromatic rings.

All the compounds (**3**) we have examined so far are hydrolysed more rapidly than expected for simple aryl 1-arylethyl ethers. Figure 1 shows pH–rate profiles for the hydrolysis of (**3**) Y = Z = H and (straight line) of its methyl ester. At pH values above the pK_a the hydrolysis of (**3**) (Y = Z = H) is 900 times faster than that of its methyl ester, which should be subject to similar electronic effects. This is classical evidence for catalysis by the neighbouring CO_2H group, and we have no reason to doubt that the mechanism is once again the one we are interested in, see (**1**). The reaction is very sensitive to substitution in the benzylic ring ($\rho^+ = -4.9 \pm 0.5$ for Z = H, Y = 4-Me, H, 3-Br), as expected for a reaction generating a carbocation. And preliminary results show a substantial effect of substituents (Z) in the salicylic acid leaving group. For five compounds (**3**), Y = H (Z = 4-MeO, 5-Me, H, 5-Cl, and 5-NO_2), the plateau rate is correlated by σ, with ρ 1.25 ± 0.08. The more complete Jaffé treatment (as used in ref. 4), which allows the separation of the effects of substituents into ρ (phenol) and ρ (CO_2H), gives values of 0.96 ± 0.10 and 0.23 ± 0.14, respectively. Once again, the acid strength of the CO_2H group has little, if any, effect on the rate of the reaction it is catalysing so effectively. Evidently we have another example of this intriguing mechanism, and are now in a position to look at it over a range of carbocation lifetimes.

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