Efficient Intramolecular General Acid Catalysis of Vinyl Ether Hydrolysis by the Neighbouring Carboxylic Acid Group

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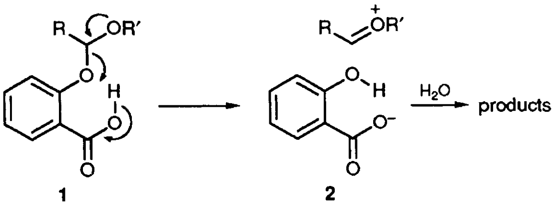
Intramolecular catalysis by the CO_2H group of the hydrolysis of *E*-1-methoxy-2-(2-carboxyphenyl)ethylene **5**, shows an effective molarity of almost 300 M, the highest measured for intramolecular proton transfer to carbon.

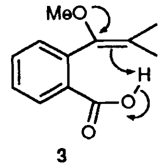
Intramolecular general acid–base catalysis is an intrinsically inefficient process, with measured effective molarities (EM) rarely exceeding 10 M.[1] A striking exception is intramolecular general acid catalysis of the hydrolysis of salicylic acid derivatives such as acetals **1**, where EM values > 10^4 M have been measured.[1,2] Our recent work[3] suggests that the key to this high efficiency lies in the strong intramolecular hydrogen bond in the salicylate monoanion **2** produced, which has already developed far enough to stabilise the transition state for its formation.



1 **2**

The hydrolysis of vinyl ethers in water is general acid catalysed. The mechanism is well established, and involves rate determining proton transfer to carbon. Intramolecular proton transfer to carbon appears to be particularly inefficient, with EM for the intramolecular general acid catalysed hydrolysis of vinyl ethers typically around 1 M. Kresge,[4] for example, measured an EM of only 1.1 M for intramolecular general acid catalysis of the hydrolysis of **3**, a process expected to be efficient because the reverse reaction, the enolisation of **4**, shows one of the highest EM (56 M) measured for intramolecular general base catalysis.[1,5]

Remarkably, the hydrolysis of the 'carbon analogue' **5** of the salicylic acid acetal **1** has not been studied. We have



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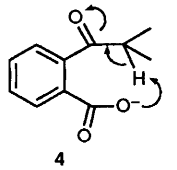

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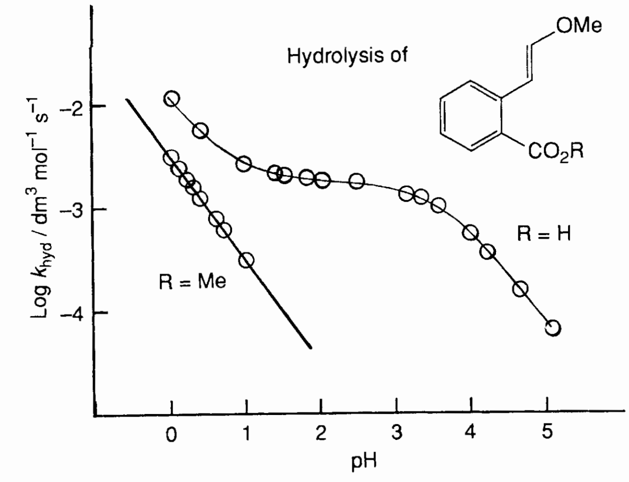
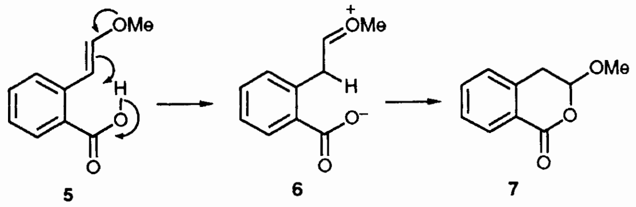


Fig. 1 pH-Rate profiles (39°, ionic strength 1.0 mol dm^{-3}) for the hydrolysis of **5** and its methyl ester in water. The points are experimental, the lines calculated, using k_H = 3.38 × 10^{-3} for the ester; 1.04 × 10^{-2} and 7.97 dm^3 mol^{-1} s^{-1} for the acid and its anion, respectively; and a pK_a of 3.66 for the acid.

prepared **5**,† and find that it is hydrolysed with intramolecular general acid catalysis, with the highest EM yet measured for proton transfer to carbon.‡



The pH-rate profile for the hydrolysis§ of **5** is compared in Fig. 1 with that for its methyl ester. Catalysis by buffer acids could not be detected for the hydrolysis of **5** but was measured for the reaction of the ester. The measured EM‡ for intramolecular general acid catalysis by the CO_2H group of **5** is 290 M. At first sight this result may seem to rule out strong intramolecular H-bonding as the source of high efficiency, since a strong hydrogen bond to C–H would be unusual. However, the C–H bond next to the oxocarbocation centre of **6** is expected to be a very strong acid,¶ and work continues on this question.

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† 1-Methoxyindene (T. W. Doyle, *Can. J. Chem.*, 1970, **48**, 1629, was ozonolysed in dichloromethane at −78 °C and worked up with dimethylsulphide to give (2-methylcarboxyphenyl)acetaldehyde. The potassium enolate was formed in tetrahydrofuran using potassium hydride, and methylated on oxygen with dimethylsulphate to give the methyl ester of **5**. The ester was stirred in aqueous sodium hydroxide (2 mol dm^{-3}) overnight; this solution was acidified and rapidly extracted with diethyl ether to give **5** which was finally purified by column chromatography (eluant 19 : 1 dichloromethane : methanol).

‡ The hydrolysis of **5** was followed at 39 °C under pseudo-first-order conditions in aqueous HCl and in formate and acetate buffers [ionic strength 1 mol dm^{-3} (KCl)]. Runs were started by adding a stock solution of **5** (10 μl) in dioxan to buffer (290 μl), and monitoring the decrease in UV absorption at 265 nm. Buffer catalysis by formic and cyanoacetic acids was measured under the same conditions for the hydrolysis of the methyl ester: the very short extrapolation of the two-point Brønsted plot to pK_a = 3.66 gave an estimated second-order rate constant of 6.1 × 10^{-6} dm^3 mol^{-1} s^{-1} for catalysis by an external acid with the same pK_a as **5**. The plateau rate for **5** is 1.75 × 10^{-3} s^{-1}.

§ The reaction is not formally a hydrolysis, because the product is the cyclic acylal **7**, rather than the aldehyde; indicating that the cyclisation of the oxocarbocation **6** is faster than its hydration. (And also that **6** is a full intermediate, with a lifetime long enough to allow the conformational change necessary for cyclisation.)

¶ The conjugate acid ($PhCH_2CH{=}OH^+$) of phenylacetaldehyde is a convenient model. The pK_a of the C–H bond (pK^{CH}) can be calculated from pK^{OH}, for the protonated aldehyde group, and the known pK^E (−3)[6] for enolisation. pK^{OH} for a protonated aldehyde is likely to be less than −8,[7] so pK^{CH} (= pK^{OH} + pK^E) is expected to be less than −5.