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AN INTRAMOLECULAR BIFUNCTIONAL INTERACTION IN THE HYDROLYSIS OF METHYL 2,6-DIHYDROXYBENZOATE

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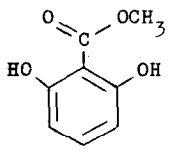
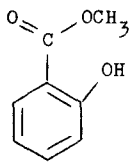
We wish to report the first example of an intramolecular bifunctional general acid-base interaction (non-nucleophilic) by two hydroxyl groups in the hydrolysis of a simple carboxylic ester. Previous examples of bifunctional interactions in the hydrolysis of carboxylic acid derivatives have included examples of a nucleophilic-general acid catalysis by carboxyl groups in an ester and an amide (1). Evidence for these bifunctional interactions included a bell-shaped pH - rate profile with the maximum rate occurring at the pH corresponding to the maximum concentration of the singly ionized species determined by spectrophotometry, and a rate enhancement of 40 - 66-fold for the hydrolysis of this species relative to corresponding derivatives with only one of the catalytic species present (1). We have investigated the kinetics of the hydrolysis of methyl 2,6-dihydroxybenzoate (I) in aqueous acetonitrile solution at 60°C and have found a bell-shaped pH - rate profile, as shown in Fig. 1. The pH - rate profile for the mono-substituted ester, methyl salicylate (II), is also shown in Fig. 1.

The rate profile for the hydrolysis of methyl salicylate is sigmoidal, indicating a concentration dependence on the anionic form of the ester. This type of concentration dependence has been observed previously for other derivatives



I



II

of salicylic acid (2,3), and for the p-nitrophenyl ester the mechanism has been shown to be an intramolecular general base catalysis (2). For II, depending on the actual mechanism, the rate constant can be calculated as $k_1^{II} = 2.48 \times 10^{-3}$ sec^{-1} for the solvolysis of the ionized ester (general base catalysis), or $k_2^{II} = 14.9$ $M^{-1}sec^{-1}$ for the second-order hydroxide ion-catalyzed hydrolysis of the un-ionized ester (general acid catalysis). The kinetic $pK_a^{II} = 9.22$ agrees with the pK_a of 9.26 determined by a spectrophotometric method.

The bell-shaped rate profile for the hydrolysis of methyl 2,6-dihydroxybenzoate was analyzed by the method of Alberty and Massey (4). Rate constants calculated by this method are $k_1^I = 1.59 \times 10^{-3}$ sec^{-1} for the solvolysis of the mono-ionized ester (see mechanism III below), or $k_2^I = 80.0$ $M^{-1}sec^{-1}$ for the second-order hydroxide ion-catalyzed hydrolysis of the un-ionized ester (mechanism IV). The pK_a's calculated by this method are $pK_1^I = 8.30$ and $pK_2^I = 10.50$, in agreement with the values of 8.22 and 10.42 determined spectrophotometrically.

It is well established that 2,6-disubstituted derivatives of benzoic acid hydrolyze extremely slowly with respect to the unsubstituted or 2-monosubstituted derivative (5,6). Using rate constants obtained by Newman for the hydrolysis of methyl 2,6-dimethylbenzoate at 125°C as well as activation energies for that process (6), the rate of hydrolysis of the dimethyl derivative at 60°C can be estimated to be of the order of 10^{-9} sec^{-1} at pH of 9. The rate enhancement for the dihydroxy compound is thus of the order of $10^5 - 10^6$ over similarly 2,6-disubstituted derivatives.

Two kinetically indistinguishable mechanisms can be suggested for the hydrolysis which include both hydroxyl groups in the transition state. Mechanism III is a concerted general acid-general base catalyzed solvolysis of the mono-ionized ester, similar to the general base catalyzed hydrolysis of salicylic

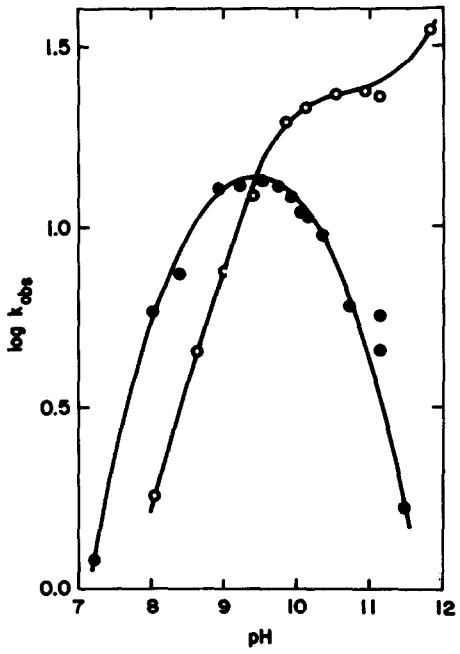
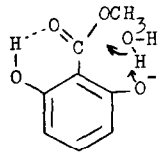
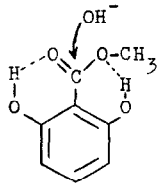


Fig. 1. pH - rate profile for the kinetics of hydrolysis of methyl 2,6-dihydroxybenzoate (I, ●) and methyl salicylate (II, ○) in 1.15% acetonitrile-water at 60°C.

acid derivatives (2). Mechanism IV is a hydroxide ion-catalyzed hydrolysis of the un-ionized ester aided by a bifunctional general acid catalysis by the two adjacent hydroxyl groups. Either of these mechanisms seems equally likely for the reaction (7).



III



IV

If the rate constants for mechanisms III and IV are compared to the corresponding salicylate mechanism, a rate enhancement of 5.4-fold is calculated for mechanism IV over the general acid catalyzed hydrolysis of methyl salicylate,

whereas mechanism III would occur 1.6 times slower than the general base catalyzed solvolysis of methyl salicylate.

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7. These mechanisms are in contrast to the hydrolysis of catechol mono-5-nitrosalicylate, an ester which also has two ortho-hydroxyl groups, but which shows no evidence of a bifunctional interaction (8).
8. M. L. Bender and F. L. Killian, unpublished results.