

The Hydrolysis of Methyl Hydrogen Orthophthalate in Water

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The hydrolysis of methyl hydrogen orthophthalate in water has been studied over a pH range of -0.05 to 6.97 at 90°C . The pH was adjusted with hydrochloric acid or a citrate-phosphate buffer solution. In the acid range two reactions take place concurrently, one (intermolecular catalysis) at a rate proportional to the concentration of added hydronium ion and the other (intramolecular catalysis) at a rate independent of this concentration. The reaction mechanisms are discussed.

In a study of the hydrolysis of ethyl hydrogen maleate and ethyl hydrogen citraconate in the acidic range,¹ it was found that the rates of the reactions in water are independent of the concentration of added hydronium ion, at least when this is low (intramolecular catalysis). The rates were found to be proportional to the concentration of the undissociated ester. When acetone was added to the solution, the contribution of intramolecular catalysis decreased rapidly and the influence of the strong acid added (intermolecular catalysis) became clearly evident. The study was later extended to the hydrolysis of acid esters of *o*-phthalic and maleic acids in the acidic range in water and water-dioxane and water-acetone mixtures.² The hydrolysis of the mono-methyl, monoethyl, and monopropyl esters of orthophthalic acid in water was found to be subject to strong intramolecular catalysis, the rate being proportional to the concentration of the undissociated ester acid. Organic solvents such as acetone and dioxane strongly suppress intramolecular catalysis, and with a high proportion of an organic component in the solvent intermolecular catalysis became clearly evident. Ethanol was not found to exert any specific effect. A discussion of the mechanism of the intramolecularly catalysed reaction led to the conclusion that two or three molecules of water take part in the rate-determining stage of the reaction. The reaction was considered to take place by normal acyl-oxygen fission with the undissociated carboxyl group acting as the intramolecular catalyst.

The formation of an anhydride as an intermediate is suggested by the acceleration of the reaction on introduction of a methyl group into maleic ester acid to give citraconic ester acid. However, other observations, such as the rate of formation of the anhydride from the ester acid, the usual solvent

effect of ethanol on the hydrolysis of ethyl hydrogen maleate, and inability to detect the anhydride with aniline, did not support the view that the anhydride is formed as an intermediate in the hydrolysis of monoalkyl esters. The mechanisms of the two hydrolytic reactions were concluded to be otherwise similar except that the hydrogen ion is transferred to the ester group from the solvent in the intermolecularly catalysed reaction, but from the adjacent carboxyl group in the intramolecularly catalysed reaction.

Bender and his co-workers³ studied the hydrolysis of monomethyl orthophthalate at pH values from 0.8 to 2.3 adjusted with hydrochloric acid and from 2.6 to 7.0 adjusted with citrate-phosphate buffer solutions. However, their results deviate from those presented above and the mechanism proposed differs accordingly. The data of these workers suggest that the carboxylate ion functions as a nucleophilic catalyst and that phthalic anhydride is formed as an intermediate. The data in question have been discussed by Ågren *et al.*,⁴ Ebersson,⁵ and Thanassi and Bruice.⁶ It has been suggested that the components of the citrate-phosphate buffers may exert specific effects on the hydrolysis of monomethyl orthophthalate. Thanassi and Bruice in a study of monomethyl orthophthalate and Ebersson in a study of monomethyl 3,6-dimethylphthalate concluded that the rate of hydrolysis is proportional to the concentration of the undissociated ester acid, thus confirming earlier results.^{1,2} In the mechanism proposed by Ebersson, the formation of the anhydride is the rate-determining stage. Thanassi and Bruice did not propose any detailed mechanism but only several possible models. The mechanism has been discussed recently by Killian,⁷ Hurst and Bender,⁸ and Capon,⁹ who all consider that anhydride formation is a possible intermediate in the reaction. The data of Ågren *et al.*⁴ suggest that the hydrolysis of monoethyl orthophthalate in water is also catalysed intermolecularly at high mineral acid concentrations (at very low pH values).

The aim of the work described below was to clarify the mechanism of hydrolysis of monomethyl orthophthalate in the acid range. The first problem was to determine whether the components of citrate-phosphate buffer exert specific effects on the hydrolysis. The rate of the intermolecularly catalysed acid hydrolysis of methyl hydrogen orthophthalate in water was then measured and compared with the previously reported rates of the same reaction in mixtures of water and organic solvents.²

EXPERIMENTAL

Procedure. The kinetic experiments were run in water solution, the pH of which was varied from -0.05 to 1.20 with hydrochloric acid and from 2.83 to 6.97 by adding citrate-phosphate buffer solutions composed of 0.2 M citric acid and 0.4 M dipotassium hydrogen phosphate in various ratios. The initial concentration of the ester in the experiments was about 3×10^{-3} M and the temperature 90.0°C. The ester solution containing hydrochloric acid or buffer solution was transferred with a pipette in 5 or 10 ml amounts to Pyrex ampoules, which were sealed by fusion before immersion in a water bath at 90°C. After a suitable interval, an ampoule was removed from the water bath and cooled in an ice bath. The reaction mixture was then diluted with 1 M potassium phosphate solution of pH about 7. The absorbance of the resulting solution at 279 nm was measured with a Beckman DU spectrophotometer. The rate constants were calculated from the equation

$$k = \frac{2.303}{t} \log \frac{A_0 - A_\infty}{A_t - A_\infty}$$

where A_0 is the initial absorbance, A_∞ the final absorbance, and A_t the absorbance at time t .

Chemicals. Monomethyl orthophthalate was prepared by the method of Eliel and Burgstahler.¹⁰ The melting point of this ester was 83°C. The other chemicals were guaranteed reagents from E. Merck. The water used had been distilled twice.

Results. The results are presented in Table 1.

Table 1. The rates of hydrolysis of monomethyl orthophthalate in aqueous solutions of various pH values at 90°C.

pH	-0.05	0.31	0.66	0.66 ^a	0.66 ^b	0.92	0.92 ^c	1.20	2.83	3.17	4.74	6.97
$k \times 10^4$ min ⁻¹	138	105	91.2	92.4	93.7	83.6	83.9	82.4	81.2	66.5	7.44	2.56

^a 0.32 M KCl. ^b 0.96 M KCl. ^c 0.16 M KCl.

DISCUSSION

The rate constant of the hydrolysis of monomethyl orthophthalate in 0.02 M hydrochloric acid at 90°C was earlier² found to be $12\,000 \times 10^{-8} \text{ s}^{-1}$ or $72 \times 10^{-4} \text{ min}^{-1}$. This value is about 15 % smaller than the value obtained in the present study. The rate constant of the reaction in an acetate buffer solution of pH 2.83, found in the present study, is likewise 15 % lower than the rate constant of the reaction in a citrate-phosphate buffer of the same pH (Table 1). Thanassi and Bruce⁶ obtained the value $85 \times 10^{-4} \text{ min}^{-1}$ for the rate constant in a potassium phosphate buffer of pH 2.00 at 91.3°C. This is in good agreement with the values obtained in the present study. The buffer, as Thanassi and Bruce had also noted, has a certain effect on the rate of hydrolysis of monomethyl phthalate. In the light of the results of the present study, however, it is seen that the citrate-phosphate buffer does not essentially alter the course of the hydrolysis.

The data in Table 1 further show that hydrochloric acid has a significantly greater effect than potassium chloride on the rate of hydrolysis of monomethyl orthophthalate. Hence in water monomethyl phthalate also undergoes a normal intermolecularly catalysed acid hydrolysis with a rate constant of $8 \times 10^{-5} \text{ M}^{-1} \text{ s}^{-1}$. This is about twice the value $4.2 \times 10^{-5} \text{ M}^{-1} \text{ s}^{-1}$, which is the rate constant of the acid-catalysed hydrolysis in a 90 % acetone-water mixture at the same temperature.² The changes in the rate constants of the hydrolysis of monoethyl succinate and monoethyl fumarate when the solvent is changed from water to a 90 % acetone-water mixture are of the same order as in the case of monomethyl orthophthalate, although the rate constant of the hydrolysis of the last mentioned ester is significantly lower in value than those of the first two.¹ In addition it may be mentioned that the rate constants

for the hydrochloric acid-catalysed hydrolysis of ethyl hydrogen *p*-phthalate and ethyl hydrogen *m*-phthalate in a 50 % acetone-water mixture at 95°C are 91×10^{-6} and $69 \times 10^{-6} \text{ M}^{-1} \text{ s}^{-1}$, respectively.² The corresponding rate constant for ethyl hydrogen *o*-phthalate in the same conditions was found to be $60 \times 10^{-6} \text{ M}^{-1} \text{ s}^{-1}$. According to the results presented above, it seems unlikely that the mechanism of the intermolecularly catalysed hydrolysis of methyl hydrogen orthophthalate differs from the $A_{AC}2$ mechanism, as Hurst and Bender have claimed.⁸

The rate of the intramolecularly catalysed hydrolysis of monomethyl orthophthalate falls steeply, as the proportion of organic solvent in the reaction medium is increased.² In this respect monomethyl phthalate behaves differently from monophenyl orthophthalate, for instance, the hydrolysis of which in dioxan-water mixtures accelerates slightly with increasing dioxan content.¹¹ In the case of the phenyl ester the mechanism of the reaction has been shown to be nucleophilic intramolecular catalysis by the ionized carboxyl group, with the anhydride as an intermediate.⁶ The observation that intramolecular catalysis of methyl orthophthalate occurs only after hydration makes an anhydride intermediate less probable. The higher rate of the intramolecularly catalysed hydrolysis of ethyl hydrogen citraconate as compared with ethyl hydrogen maleate¹ can be explained by assuming that the methyl substituent facilitates the transfer of hydrogen ion from the carboxyl group to the ester group. One would expect that the hydration of the carboxyl group would make it possible for the carboxyl group to function as an intramolecular catalyst, *i.e.* to promote the transfer of the proton to the ester group. The intermolecularly and intramolecularly catalysed reactions can both be considered to be acid catalyses. The water is probably added to the protonated ester group in both cases.

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