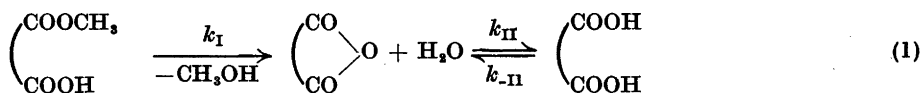# Intramolecular Carboxyl Group Catalysis in the Hydrolysis of Methyl Hydrogen 3,6-Dimethylphthalate

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The hydrolysis of methyl hydrogen 3,6-dimethylphthalate has been investigated. The pH-rate profile indicates that the half ester in the undissociated form undergoes cyclization in a slow step with the formation of the corresponding anhydride, which is hydrolyzed in a subsequent fast step. The anhydride exists in equilibrium with the acid in aqueous solution, as can be shown by preparative and spectrophotometric methods. The equilibrium constant c_{anh}/c_{acid} is about 0.8.

In a previous communication[1] it was qualitatively shown for methyl hydrogen 2,3-di-(t-butyl)-succinate that the unionized ester was capable of cyclization in aqueous solution with the formation of the anhydride, which was extremely resistant towards hydrolysis and could be isolated as such. The ionized form was completely inert under the reaction conditions employed. The results pointed towards the possibility that intramolecular carboxyl group catalysis might play a role in facilitating the hydrolysis of monomethyl esters of certain dicarboxylic acids (eqn. 1) in the same way as intramolecular carboxylate ion catalysis has been shown to operate in the hydrolysis of monoaryl esters of dicarboxylic acids.[2-4]

$$\begin{pmatrix} COOCH_3 \\ COOH \end{pmatrix} \xrightarrow[-CH_3OH]{k_I} \begin{pmatrix} CO \\ CO \end{pmatrix} O + H_2O \underset{k_{-II}}{\overset{k_{II}}{\rightleftharpoons}} \begin{pmatrix} COOH \\ COOH \end{pmatrix} \tag{1}$$

Methyl hydrogen 2,3-di-(t-butyl)-succinate would then correspond to an extreme case with $k_{II} \ll k_I$, making possible the isolation of the anhydride.

In this paper results from preparative and kinetic experiments on the hydrolysis of methyl hydrogen 3,6-dimethylphthalate are described. This compound constitutes a clean-cut case of intramolecular carboxyl group catalysis as judged from its pH-rate profile and the ratio between k_I and k_{II}.

RESULTS

Previous reports indicate that the question about the existence of free 3,6-dimethylphthalic acid is subject to controversy. Contrary to Freund and Fleischer,[5] Newman and Lord [6] could not prepare the acid by acidification of a solution of its salt at 0°, but instead obtained the anhydride. Other investigators have reported the isolation of an acid-anhydride mixture by this procedure.[7,8]

It turned out, however, that the free acid actually could be isolated by careful acidification of a solution of its salt at 0°. After washing with water and air drying the solid had an elemental analysis and equivalent weight corresponding to that of the free acid and showed a titration curve with a weakly developed break for the first ionization step and a sharp break for the second one. In the solid state the infra-red spectrum had the characteristic broad carboxyl group absorption band in the $3200-2500$ cm^{-1} region and a carbonyl band at 1680 cm^{-1} with no bands from the anhydride detectable. The anhydride has its carbonyl bands at 1754 and 1837 cm^{-1} (lit.[9] values 1760 and 1840 cm^{-1}), distinctly separated from that of the acid. The acid was stable in the solid state over a period of more than a year, while a saturated solution in water began to deposit crystals of the anhydride after 5 min standing. This shows that the acid is in equilibrium with the anhydride in aqueous solution and since the anhydride is much less soluble it is continuously removed by precipitation until the solution is saturated with respect to the anhydride.

3,6-Dimethylphthalic acid melted with decomposition at $145-150°$ as determined with the aid of a melting point microscope; on the Kofler "Heizbank" the m.p. rose to about 170° with decomposition.

Methyl hydrogen 3,6-dimethylphthalate was prepared by treating the anhydride with a solution of sodium methoxide in methanol. The ester was stable at room temperature in the solid state and could be recrystallized from benzene, if the solution was not heated above 50°. Its infra-red spectrum had a broad carboxyl group absorption band in the $3200-2500$ cm^{-1} region and carbonyl bands at 1731 and 1670 cm^{-1}. When examined in the melting point microscope it melted completely with decomposition at $100-106°$ and upon further heating crystals began to appear at about 115°. At 125° the sample had solidified completely and then melted again at $140-141°$. The remaining material was identified as the anhydride by its infra-red spectrum.

Heating a saturated aqueous solution of the methyl ester at 60° for 2 h effected a complete conversion into the anhydride and methanol, the presence of which was established by v.p.c. analysis.

Taken together, these facts qualitatively show that the reaction scheme (1) might be applicable to methyl hydrogen 3,6-dimethylphthalate, with the complication that the hydrolysis product is an equilibrium mixture of anhydride and acid. Kinetic experiments at different hydrogen ion concentrations confirm this hypothesis. Table 1 gives the observed rate constants at 61.7° in aqueous solution for the hydrolysis of methyl hydrogen 3,6-dimethylphthalate at different hydrogen ion concentrations and in Fig. 1 the pH-rate profile has been plotted. The pH-rate profile is of the shape that is predictable

Table 1. Observed first-order rate constants for the hydrolysis of methyl hydrogen 3,6-dimethylphthalate in aqueous solution at different hydrogen ion concentrations at 61.7°.

pH	k_{exp} in min^{-1}
2.00	0.043
2.70	0.045
3.12	0.021
3.40	0.019
3.60	0.015
3.75	0.010
4.00	0.0057
4.15	0.0038
4.50	0.0022
5.08	0.00076

from eqn. (1), with a sigmoid shape around the pH corresponding to the pK of the ester and k_{exp} decreasing rapidly as the pH increases through this region. By rearrangement of the relationship $k_{exp} = k_I/(1 + K/[H^+])$ one obtains $1/k_{exp} = 1/k_I + K/k_I[H^+]$, where K is the ionization constant of the half ester (Fig. 2). The linearity of this plot quantitatively confirms the kinetic dependence on undissociated half ester in this region. From this relation the best values of k_I and K fitting with the experimental values were calculated by the method of least squares, giving $k_I = 0.040$ min^{-1} and p$K = 3.3$. This pK value was in reasonable agreement with that determined by potentiometric titration of the ester, 3.5.

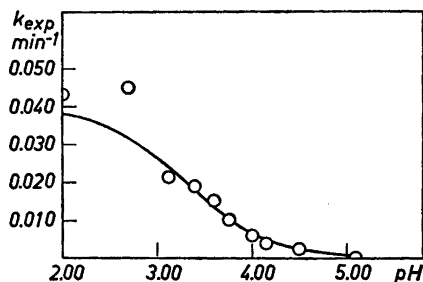*Fig. 1.* Circles correspond to experimental values and the curve is the theoretically calculated one from $k_{exp} = 0.040$ min^{-1} and p$K = 3.3$.
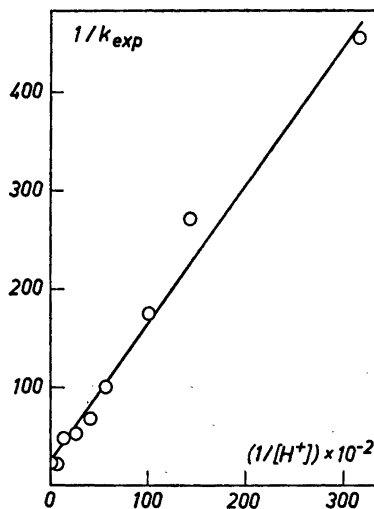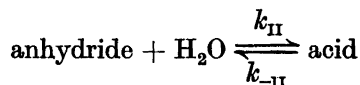
Fig. 2. Plot of $1/k_{exp}$ against $1/[H^+]$. From the line the values $k_I = 0.040$ min^{-1} and p$K = 3.3$ were calculated.

However, in order to demonstrate that hydrolysis actually occurs it is necessary to show that the acid is formed in measurable amounts, *i.e.* that the equilibrium

$$\text{anhydride} + \text{H}_2\text{O} \underset{k_{-\text{II}}}{\overset{k_{\text{II}}}{\rightleftharpoons}} \text{acid}$$

is not completely on the anhydride side.

The sum of the rate constants $k_{\text{II}} + k_{-\text{II}}$ was obtained by measuring the change in optical density in freshly prepared solution of anhydride or acid at 322 mμ, where the anhydride has the maximum of a moderately strong absorption band but not the acid (as estimated by extrapolating the optical density to zero mixing time of the reactants). Measurements were carried out in 0.01 M hydrochloric acid where the ionization of the acid was almost totally suppressed (as estimated from the titration curve) and consequently the observed rate constant will be the sum of those for the forward and reverse reactions. At $61.5 \pm 0.5°$ this value was 1.12 and 1.13 min^{-1}, as measured by approaching the equilibrium from the side of the anhydride and acid, respectively.

Furthermore, it was possible to obtain a value of the extinction coefficient at 322 mμ of the anhydride by extrapolating the optical density to zero mixing time of the reactants. This gave $\varepsilon = 7000$, from which it could be calculated that the equilibrium mixture contained 32 % anhydride, corresponding to an equilibrium constant $c_{\text{anh}}/c_{\text{acid}} = 0.5$. From this value and $k_{\text{II}} + k_{-\text{II}} = 1.12$, k_{II} and $k_{-\text{II}}$ were calculated to be 0.75 and 0.37 min^{-1}. Because of the uncertainty in estimating $\varepsilon_{\max}$ for the anhydride these values are subject to considerable error.

By measuring the solvolysis rate by the pH-stat method at pH 5.30, where the contribution from the reverse reaction is very small, a more accurate value of k_{II} could be obtained, 0.66 min^{-1}, in fair agreement with the above value. Using this value $c_{\text{anh}}/c_{\text{acid}}$ is about 0.8.

Solutions of the half ester, anhydride, and acid of the same concentrations showed the same UV-spectra within the experimental errors after the equilibrium had been established in 0.01 M HCl (for the half ester about 3 h, for the acid and anhydride about 10 min).

DISCUSSION

Many well-established cases of intramolecular carboxylate ion catalysis in the hydrolysis of aryl hydrogen esters of dicarboxylic acids are known,[2-4] and in these cases evidence for the existence of an anhydride intermediate has been obtained by indirect methods. For *n*-alkyl esters only a few cases with results of importance for this problem have been investigated, namely methyl and ethyl hydrogen phthalate and ethyl hydrogen maleate and citraconate. For methyl hydrogen phthalate, Bender *et al.*[10] obtained a pH-rate profile at 109° consistent with a mechanism involving carboxylate ion attack on the carbomethoxy group to form phthalic anhydride as an intermediate, which is subsequently hydrolyzed by water in a fast step. However, for the ethyl

ester at 110°, Ågren et al.[11] found a pH-rate profile of a wholly different shape, with a constant plateau between pH 1 and 3 and then a sharply decreasing observed first-order rate constant between 3 and 7 and then a sharp rise above pH 7. This behavior points towards a mechanism according to (1) but since pH measurements were carried out at 25° and kinetic ones at 110° the data do not allow any conclusions of quantitative nature to be drawn. The discrepancy between the two sets of data is not easy to explain; it seems highly improbable that there should be such a mechanistic difference between the hydrolyses of a methyl and an ethyl ester of the same acid. It may be that the buffers used have exerted some catalytic influence in the methyl ester case, as suggested by Ågren et al. The work on ethyl maleate and citraconate[12] indicated that the rate of hydrolysis was proportional to the concentration of undissociated ester acid and at least approximately independent of the hydrogen concentration in the range where ionization was totally suppressed. For the amide acid, phthalamic acid, Bender, Chow, and Chloupek[13] showed that the hydrolysis of the amide group was facilitated by the unionized carboxyl group, which has also been shown for succinanilic acid, investigated by Higuchi et al.[14] In these cases the existence of anhydride intermediates could be demonstrated indirectly.

Evidently, the hydrolysis of methyl hydrogen 3,6-dimethylphthalate is a more clear-cut example of intramolecular carboxyl group catalysis than the cases hitherto investigated due to the buttressing effect of the methyl groups. The anhydride is formed from the ester upon melting, boiling it in organic solvents, or merely heating it in aqueous solution at 60° for a few hours. Once formed, the anhydride is rapidly hydrolyzed to the acid (the ratio between k_{II} and k_I is about 17), an equilibrium containing anhydride to the extent of 30—40 % being eventually established. Upon increasing pH in a region around the pK value of the acid, the observed first-order rate constants decrease as the concentration of unionized ester acid decreases. It might be argued that hydrolysis actually is not complete at, say, pH 3.0, since the acid is in equilibrium with the corresponding anhydride. This is, however, only a quantitative difference from other dicarboxylic acids and no mechanistic difference is implied by this fact, since even in the case of succinic acid the anhydride has been shown to exist in equilibrium with the acid in aqueous solution,[14] let be that c_{anh}/c_{acid} at 25° is of the order 10^{-7}. It seems probable that the existence of an acid-anhydride equilibrium in aqueous solutions of 1,2-dicarboxylic acids is a general phenomenon, provided the steric arrangement of the carboxyl groups is such as to allow the formation of an anhydride. The effectiveness of this type of catalysis is shown by comparison with the rate constant for the acid catalyzed hydrolysis of methyl benzoate at pH 2.78, which can be estimated to be of the order of 10^{-7} min^{-1} at 60° from Bolin's values at 80°,[15] i.e. a rate enhancement by at least five orders of magnitude from the intermolecular to the intramolecular case. This is about the same ratio as between the rate constants of the intramolecularly catalyzed hydrolysis of phthalamic acid and the [H$^+$]-catalyzed hydrolysis of benzamide at a comparable [H$^+$].[13]

It may be noted that the cyclization of methyl hydrogen 3,6-dimethylphthalate in aqueous solution has much in common with the cyclization of

dicarboxylic acids in aqueous solution. Also here the undissociated species, the free diacid, is kinetically active as has been shown for succinic acid [14] and dimethyl-, methylethyl-, and diethylmaleic acid.[16] It is probable that the cyclization of the half ester is also an equilibrium reaction, although it is effectively irreversible under the reaction conditions employed in this investigation.

EXPERIMENTAL

3,6-Dimethylphthalic anhydride. This compound was prepared according to the directions given by Newman and Lord.[6] Final purification was achieved by two recrystallizations from ethyl acetate-benzene and subsequent sublimation, m.p. 142—143°, reported 142—143°.

3,6-Dimethylphthalic acid. The anhydride was dissolved in boiling 10 % aqueous potassium hydroxide, the solution cooled to 0° and acidified by 10 % hydrochloric acid with rapid stirring. The precipitate was filtered, washed several times by water and air-dried at room temperature, m.p. as determined by the melting point microscope 145—150° (decomp.), about 170° (decomp.) as determined on the Kofler "Heizbank", reported [5] 145° (decomp.). (Found: C 62.1; H 5.3; equiv. weight 97. Calc. for $C_{10}H_{10}O_4$: C 61.9; H 5.2; equiv. wt. 97.1). In contrast to the anhydride, the acid dissolved momentarily in aqueous sodium carbonate solution with carbon dioxide evolution.

Methyl hydrogen 3,6-dimethylphthalate. 3,6-Dimethylphthalic anhydride (0.05 mole) was dissolved in methanol (60 ml). A solution of sodium (0.05 mole) in methanol (30 ml) was then added and the solution was evaporated to dryness at 45—50°. The residue was dissolved in water, the solution filtered and acidified by 10 % hydrochloric acid at 0°. The solid was filtered off, air-dried and recrystallized twice from benzene. It is essential to use short heating periods and not to exceed 50° during recrystallization. The crystals melted at 100—106° (decomp.), new crystals appeared at 115° and at 125° the sample had solidified completely. The final m.p. was 140—141°; the infra-red spectrum of the remaining material showed it to be the anhydride. (Found: C 63.3; H 5.4; equiv. wt. 209. Calc. for $C_{11}H_{12}O_4$: C 63.5; H 5.8; equiv. wt. 208.)

Conversion of the acid into the anhydride in aqueous solution. 3,6-Dimethylphthalic acid (0.20 g) was dissolved in water (20 ml) at 25—30°. The solution was filtered and allowed to stand. After a few minutes crystals began to deposite and after one hour they were collected by filtration (0.11 g). According to its m.p. and infra-red spectrum it was the anhydride.

Conversion of the methyl ester into the anhydride in aqueous solution. Methyl hydrogen 3,6-dimethylphthalate (0.15 g) was dissolved in water (40 ml) at 40—50°, the solution was filtered and allowed to stand at 60° in a closed vessel for 2 h. After cooling, the precipitate was filtered (0.08 g) and identified as the anhydride by its m.p. and infra-red spectrum. In the filtrate the presence of methanol could be shown by v.p.c. analysis on a column with tetraethyleneglycol dimethyl ether as the stationary phase.

Kinetic experiments. In order to avoid the use of buffers the kinetics of the hydrolysis of the half ester were determined by the pH-stat method at pH values above 3. Below pH 3, constant hydrogen concentrations were maintained by hydrochloric acid solutions and the kinetics were followed spectrophotometrically at 322 mμ.

A typical pH-stat run was carried out in the following way: The closed titration vessel was charged with 20.0 ml of carbon dioxide free water and a known amount of standard base. After thermal equilibration had been established a stock solution of the methyl ester in dioxane (usually about 0.1 ml) was added by means of a syringe, until the desired pH value was obtained. The kinetics were then followed in the usual way by recording against time the amount of standard base necessary to keep the pH constant. The pH value was read directly on the pH meter and a mean value from 10—15 readings during the run was used as the final pH value.

The spectrophotometric determinations were made by a Beckman DK-2 spectrophotometer equipped with a time-drive attachment. A stock solution of the methyl ester was added directly into the pre-thermostated cell, containing 3.00 ml of hydrochloric acid

and the kinetics were followed by recording against time the increase in optical density at 322 mμ. After each run the spectrum of the solution was taken in order to confirm the presence of the anhydride. All rate constants were evaluated by the Guggenheim method. Rate constants for the solvolysis of the anhydride and cyclization of the acid were determined as described previously.[16,17]

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