

Studies on Succinic Acids

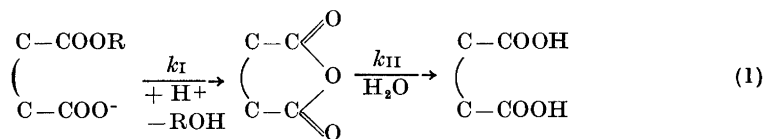
VI*. On the Hydrolysis of Monomethyl Esters of Tetraethyl- and *Rac.*-2,3-Di-(*tert.*-butyl)-Succinic Acid

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The possibility of intramolecular *carboxyl* group catalysis in the hydrolysis of monomethyl esters of dicarboxylic acids exhibiting anomalously high K_1/K_2 -ratios is discussed on the basis of the behaviour of monomethyl tetraethyl- and *rac.*-2,3-di-(*tert.*-butyl)-succinate upon attempted hydrolysis at different hydrogen ion concentrations.

It is well established that intramolecular carboxylate ion catalysis plays an important role in the hydrolysis of monoaryl esters of substituted succinic and glutaric acids¹⁻³. By detailed kinetic analysis and tracer experiments it has been shown that these rapid hydrolyses proceed through a cyclic anhydride intermediate formed by the attack of a neighbouring carboxylate ion on the ester moiety, followed by solvolysis of the anhydride (1).



Originally it was thought that the group displaced from the ester group had to consist of a stabilized ion of some sort, *e.g.*, a phenoxide ion, but later on evidence was presented that the *n*-alkyl ester, methyl hydrogen phthalate, is also hydrolyzed according to the mechanism (1)⁴. Only in the case of *p*-methoxyphenyl 3,6-endoxo- Δ^4 -tetrahydrophthalate could the anhydride be directly observed by determining the rate of base addition necessary to maintain a constant pH during the solvolysis of the intermediate¹. This rate was identical at pH 5.5 and pH 6.5 with that observed in the solvolysis of authentic *exo*-3,6-endoxo- Δ^4 -tetrahydrophthalic anhydride.

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In the hydrolysis of alkyl-substituted monoaryl succinates and glutarates the rate of ester hydrolysis increased with increasing degree of alkyl substitution in the carbon chain as would be predicted by consideration of the "geminal dimethyl effect" normally operating in ring closure reactions¹. It was concluded that the increase in rate accompanying alkyl substitution was due to a decrease in the probability of unprofitable rotamer distributions in which the reacting groups were directed away from each other. When the carbophenoxy and carbonyl groups were rigidly held in an eclipsed conformation, as in the monoesters of maleic and 3,6-endoxo- Δ^4 -tetrahydrophthalic acids, a pronounced rate enhancement on anhydride formation was observed.

These data strongly support the conclusion that the distribution of conformations in the monoesters of dicarboxylic acids is influenced by alkyl substitution in much the same way as in the corresponding diacids. An anomalously high K_1/K_2 -ratio of a dicarboxylic acid implies that the favoured conformation has the carboxyl groups close to each other making strong electrostatic interaction and intramolecular hydrogen bonding possible^{5,6}. In Fig. 1 it is shown that there is a rough linear correlation between the logarithm of the relative rate of monoester solvolysis and the ΔpK of the corresponding diacid.

The kinetic data were taken from the work of Bruce and Pandit¹ and the ΔpK values were obtained from various sources⁷⁻⁹. If the data obtained by Gaetjens and Morawetz³ for the hydrolysis of mono-*p*-acetamidophenyl esters of the diastereoisomers of 2,3-dimethyl- and 2,3-diisopropylsuccinic acid are treated in the same way, it is found that the meso-diisopropyl compound falls completely out of the scheme. However, since the stereochemical homogeneity of this compound was not rigorously proved, it is possible that partial epimerization had occurred during the preparation of the intermediate anhydride. This has been observed under similar conditions in a number of cases¹⁰⁻¹².

Thus, it may be safely concluded that a high K_1/K_2 -ratio of a diacid is accompanied by a high rate of intramolecular carboxylate ion attack in its monoester and that this effect is mainly steric in origin. From this point of view studies on the hydrolysis of monomethyl tetraethyl- and *rac.* 2,3-di-(*tert.*-butyl)-succinate⁵ have been initiated, as the corresponding acids exhibit very high K_1/K_2 -ratios in water (ΔpK 4.58 and 8.0, respectively)¹³ and in 50 % by weight ethanol (ΔpK 6.6 and 9.5, respectively)⁵. The methyl esters were chosen since only one case of intramolecular catalysis in *n*-alkyl esters has been studied previously⁴ and it could also be expected that the rate constants for the hydrolysis of the aryl esters would be too high to be measurable³. This paper is a report of the preparative part of the study, which allows some preliminary conclusions to be drawn regarding the hydrolysis mechanism.

RESULTS AND DISCUSSION

When monomethyl *rac.*-2,3-di-(*tert.*-butyl)-succinate (I) was refluxed for 15 h in 5 % aqueous sodium carbonate solution, where it exists only in its ionized form, no hydrolysis took place and the ester was almost quantitatively recovered. Under the same conditions, *rac.*-2,3-di-(*tert.*-butyl)-succinic anhydride (II) was completely hydrolyzed within 4 h. Boiling I at pH 7 in 50 % by volume dioxane-water, where about 50 % of the ester exists in the ionized

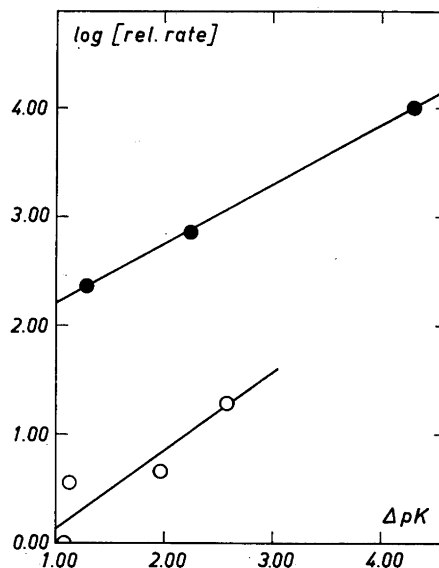
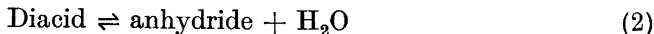


Fig. 1. Plots of $\log (k_I/k_{I \text{ glutarate}})^1$ versus ΔpK^{7-9} ● Monoesters of diacids with 1,2-carboxyl groups (succinic ⁷, 2,2-dimethylsuccinic ⁹, maleic acid ⁷). ○ Monoesters of diacids with 1,3-carboxyl groups (glutaric ⁷, 2,2-dimethylglutaric ⁸, 3-methylglutaric ⁷, 3,3-dimethylglutaric acid ⁷).

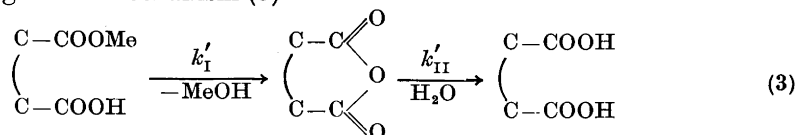
state, gave the anhydride in almost quantitative yield. Under the same conditions II was not affected. Finally, boiling I in 50 % dioxane-water at pH 1.5 for 15 h gave the anhydride, and likewise II alone was not affected by this treatment.

These results differ from those obtained previously for monoaryl esters ¹⁻³ in the following ways: Firstly, under the conditions most favourable for intramolecular carboxylate ion attack, no hydrolysis took place although any anhydride formed would have been hydrolyzed. Secondly, at a hydrogen ion concentration (pH 7) where the unionized form exists in appreciable quantity, the anhydride was formed but not hydrolyzed, presumably due to steric hindrance to the approach of lyate species to the anhydride carbonyl group ¹. Thirdly, at pH 1.5, where only the unionized form can exist, the anhydride was formed but not hydrolyzed. This is a special case, since at this pH the equilibrium (2) is completely on the side of the anhydride under the reaction conditions employed.



Only at pH values where the diacid is appreciably neutralized is (2) displaced to the left.

Evidently we cannot consider this reaction as an example of intramolecularly catalyzed hydrolysis, as actually no hydrolysis occurs. However, if we picture the reaction as an example of intramolecular carboxyl group catalysis according to the mechanism (3)



we may consider I as an extreme case with $k'_I \gg k'_{II}$. Intramolecular carboxyl group catalysis has been observed in the hydrolysis of the amide acid, phthalamic acid¹⁴, and cannot be excluded in the case of methyl hydrogen phthalate, for which intramolecular carboxylate ion catalysis has been postulated⁴. A weakly active carboxyl group catalysis might be masked by intramolecular hydrogen ion catalysis and would not be easily detected. Pekkarinen's¹⁵ work on the hydrolysis of monoethyl maleate and citraconate is also worth mentioning in this connection. In aqueous solution the hydrolysis rate of these esters was found to be proportional to the concentration of the undissociated ester acid and at least approximately independent of the hydrogen ion concentration in the range where ionization was totally suppressed. This effect was attributed to internal hydrogen bond formation in the ester acid.

Monomethyl tetraethylsuccinate (III) turned out to be a less extreme case than I. When III was boiled in 50 % dioxane-water at pH 7, where about 50 % of the ester acid exists in the carboxylate ion form, tetraethylsuccinic anhydride (IV) and tetraethylsuccinic acid could be isolated in approximately equimolecular amounts from the reaction mixture. The same treatment at pH 1.5 yielded the anhydride exclusively, whereas boiling for 15 h in 5 % aqueous sodium carbonate solution produced an almost quantitative yield of the diacid. Under the same conditions, IV was recovered unchanged at pH 1.5, solvolyzed to an extent of 60 % at pH 7, and completely hydrolyzed in sodium carbonate solution.

These results clearly indicate that mechanism (3) is feasible also for III and in such case the rate constants for anhydride formation and hydrolysis at pH 7 (k'_I and k'_{II}) are of the same order of magnitude. At pH 1.5 equilibrium (2) is on the side of the anhydride and no hydrolysis will occur. In sodium bicarbonate solution complete hydrolysis occurred, which may be due to intramolecular carboxylate group catalysis or intermolecular hydroxide ion catalysis. Evidently mechanism (1) cannot be excluded in this case.

Summarizing, the monoesters I and III differ from previously studied compounds of this type in the following respects:

1. Due to steric hindrance to hydrolysis the intermediate anhydrides can be isolated and identified.

2. At hydrogen ion concentrations where the corresponding diacid exists in the unionized form the anhydride (II or IV) is the thermodynamically stable form even in aqueous solvents¹⁶. This behaviour is well known from the series of alkyl-substituted maleic acids^{17,18} and there is also kinetic evidence that "normal" dicarboxylic acids, *e.g.*, succinic acid¹⁹, can exist in equilibrium with its anhydride in water at elevated temperatures, although the concentration of anhydride at equilibrium is very low. Tetramethylsuccinic acid appears to be an intermediate case between these two extremes, the equilibrium in aqueous solution at room temperature being essentially on the side of the acid and at 70° displaced about 25 % towards the side of the anhydride¹⁶.

3. Mechanism (1) is of no or very little importance in the hydrolysis of I but is possible for III. Mechanism (3) involving intramolecular carboxyl group catalysis is possible in the hydrolysis of III.

As evidence or mechanism (3) the cases described in this work must be considered as extreme ($k'_I \geq k'_{II}$). More suitable cases would involve mono-methyl esters of diacids with high K_1/K_2 -ratios, where the hydrolysis of the corresponding anhydrides is not subjected to steric hindrance from bulky alkyl groups in the carbon chain. Such acids include maleic and alkyl-substituted maleic acids^{1,15,17,20}, tri- and tetramethylsuccinic acid^{1,21}, *cis*-diacids in the bicycloheptane series, and *cis*-caronic acid. Kinetic studies on the hydrolysis of methyl esters of some of these acids as well as I and III are under way.

EXPERIMENTAL

Materials. The monoesters I and III were prepared as described previously⁵.

Hydrolysis experiments. 1 A. *Monoester I in 5 % aqueous sodium carbonate (pH 11).* I (1.0 g) was boiled for 15 h with 30 ml of 5 % aqueous sodium bicarbonate (pH about 11). Cooling and acidification precipitated the unchanged monoester in almost quantitative yield.

1 B. *Monoester I in 50 % dioxane-water of pH 7.* I (1.0 g) was dissolved in 30 ml of 50 % by volume dioxane-water and the pH was adjusted to 7.0 (as measured by the glass electrode) by addition of 10 % aqueous sodium hydroxide. The solution was refluxed for 15 h and then cooled in an ice-bath. Ice-cold 1 % aqueous sodium carbonate (70 ml) was added in order to precipitate the anhydride and to keep any unreacted ester in solution. After half an hour the solid (0.80 g, 87 %) was filtered, m.p. 112–115°*, mixed m.p. with authentic anhydride (II) 113–115°. Minute amounts of the monoester were obtained from the mother liquor upon acidification.

1 C. *Monoester I in 50 % dioxane-water of pH 1.5.* I (1.0 g) was dissolved in 30 ml of 50 % aqueous dioxane-water and the pH was adjusted to 1.5 by the addition of 10 % aqueous hydrochloric acid. The solution was refluxed for 15 h, cooled in an ice-bath and diluted with 70 ml of ice-cold 1 % aqueous sodium carbonate. Filtration gave the anhydride (II) in 90 % yield. Minute amounts of the monoester were recovered from the mother liquor upon acidification.

2. *Anhydride II.* When II was treated as under 1 A, B, and C, complete hydrolysis occurred at pH 11. (In a separate experiment it was found that hydrolysis was complete after 4 h). At pH 1.5 and pH 7 the anhydride was recovered unchanged (pH 7 was maintained by means of a phosphate buffer).

3 A. *Monoester III in 5 % aqueous sodium carbonate.* III (1.0 g) was boiled under reflux for 15 h with 30 ml of 5 % aqueous sodium carbonate. Cooling and acidification gave a 90 % yield of tetraethylsuccinic acid, m.p. 135–143° (decomp.), mixed m.p. with the authentic acid, 137–45° (decomp.).

3 B. *Monoester III in 50 % dioxane-water of pH 7.* III (1.0 g) was treated as under 1 B, yielding 45 % of the anhydride IV, m.p. 81–83°, mixed m.p. with authentic tetraethylsuccinic anhydride 80–83°. Acidification of the mother liquor gave 40 % of the diacid, m.p. 130–44° (decomp.).

3 C. *Monoester III in 50 % dioxane-water of pH 1.5.* III (1.0 g) was treated as under 1 C, which gave anhydride IV in 85 % yield, m.p. 80–82°.

4. *Anhydride IV.* Treating IV under the conditions given under 1 A, B, and C resulted in complete hydrolysis at pH 11, 60 % hydrolysis at pH 7 (phosphate buffer), and no hydrolysis at pH 1.5.

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