

The Kinetics and Mechanisms of the Uncatalyzed and Acid-Catalyzed Hydrolysis of 1,3-Dioxolone-(4) and Its Methyl Derivatives. Part I. Dioxolones Derived from Formaldehyde

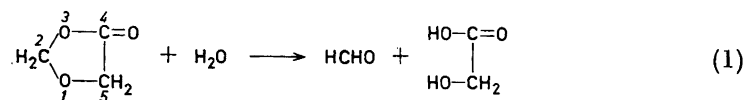
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1,3-Dioxolone-(4) and its 5-methyl and 5,5-dimethyl derivatives have been synthesized from formaldehyde and α -hydroxy-acids and the kinetics of their hydrolysis in water and dilute hydrochloric acid solutions have been studied. Two reactions, one an uncatalyzed reaction and the other catalyzed by hydrogen ion, were found to take place concurrently. In about 0.1 M hydrochloric acid, the contribution of the catalyzed reaction is 80–90 % of the over-all reaction. At constant hydrogen ion concentration the over-all reaction is kinetically of the first order. The reaction in an initially neutral solution is autocatalytic owing to the release of hydrogen ions by the α -hydroxy-acid formed.

From the effects of structure on the values of the rate coefficients and the thermodynamic functions of activation derived from the latter, it is concluded that the acid-catalyzed reaction is of the type of normal ester hydrolysis involving a bimolecular acyl-oxygen fission. The mechanism of the uncatalyzed reaction is also concluded to be mainly, if not solely, a bimolecular acyl-oxygen fission, although there is some indication that a unimolecular alkyl-oxygen fission mechanism might have a minor contribution to this reaction.

The neutral and acid-catalyzed hydrolysis reactions of 1,3-dioxolone-(4) and its derivatives represent interesting problems for kinetic study.



Like alkoxymethyl esters^{1,2}, these compounds are both acetals and esters and therefore they may react simultaneously by different mechanisms. Also their close structural similarity to the 5-membered cyclic acetals, 1,3-dioxolane and its derivatives^{3,4}, suggests that similar constitutional effects might become evident in the kinetics of both groups of compounds.

The rates of the uncatalyzed and acid-catalyzed hydrolysis reactions of a number of derivatives of 1,3-dioxolone-(4) were studied previously by Palo-

maa, Salmi and Wallin ⁵, but several reasons gave cause to undertake a more extensive study of these reactions. Firstly, the parent compound of the group, 1,3-dioxolone-(4), has not apparently been synthesized previously or studied kinetically, and the same applies to other simple members of the group that can be derived from glycolic acid. Secondly, the possibility that the derivatives with no substituent in position 2, *i.e.* those derived from formaldehyde, undergo uncatalyzed hydrolysis has not been examined. Thirdly, the influence of the geometric isomerism of certain disubstituted derivatives has not been taken into account. Fourthly, the influence of structural factors on various possible mechanisms has not been elucidated.

The first part of this investigation relates only to dioxolones derived from formaldehyde because these were found to differ clearly in both their formal kinetics and mechanism of hydrolysis from those dioxolones with one or two methyl substituents on carbon 2.

EXPERIMENTAL

Materials. The parent member of the group, 1,3-dioxolone-(4), proved to be the most difficult to synthesize since both the compounds formaldehyde and glycolic acid required for its synthesis are very sparingly soluble in those non-hydroxylic solvents which could be employed and furthermore possess a tendency to form high-molecular by-products. Although the yields were low (1–2 % of theory), it was possible to prepare enough 1,3-dioxolone-(4) for the kinetic studies by boiling glycolic acid with an excess of formaldehyde in the presence of acid catalyst in a large volume of benzene. The details of one typical synthesis are the following. Glycolic acid (0.3 mole; from Fluka A. G.) was refluxed with 2 moles of formaldehyde (as paraformaldehyde) and 8 g of *p*-toluenesulfonic acid in 500 ml of benzene for a period of 20 h. The benzene layer was then separated from a thick tarlike mass of polymeric matter that separated to the bottom of the vessel and neutralized and dried with anhydrous potassium carbonate. The fraction remaining after the benzene was distilled off was distilled at reduced pressure in a Todd precision fractionation assembly. The main part boiled at 65°C/16 mm Hg and had the following physical constants: $n_D^{25} = 1.4182$, $d_4^{25} = 1.2936$; $[R]_{\text{obs.}} = 17.14$ ($[R]_{\text{calc.}} = 17.10$). Values given by Vogel ⁶ for atom and group refractivities were used to calculate the mole refraction of the compound.

5-Methyl-1,3-dioxolone-(4) was prepared by refluxing 6 moles of lactic acid (90 %, E. Merck A. G.) in 300 ml of benzene in an azeotropic distillation assembly. When about 80 % of the water introduced with the lactic acid had been removed, 18 moles of formaldehyde (as paraformaldehyde) and 8 g of *p*-toluenesulfonic acid were added and the mixture refluxed in the same apparatus for several hours, during which time all the remaining water and that formed in the reaction was removed from the reaction mixture. The total yield of 5-methyl-1,3-dioxolone-(4) was about 80 % as calculated from the amount of lactic acid used, but only the purest distillate (about 40 % of theory) was employed in the kinetic experiments. This distillate had the following physical properties: b.p. 79.5°C/27 mm Hg, $n_D^{20} = 1.4176$, $d_4^{20} = 1.1826$; $[R]_{\text{obs.}} = 21.74$ ($[R]_{\text{calc.}} = 21.73$). The same compound was synthesized by Palomaa, Salmi and Wallin ⁵ by heating lactic acid, paraformaldehyde and *p*-toluenesulfonic acid with anhydrous sodium sulfate in a sealed tube at 160°C.

5,5-Dimethyl-1,3-dioxolone-(4) was prepared by boiling under reflux a mixture containing 5 moles of formaldehyde (as paraformaldehyde), 0.67 mole of *a*-hydroxyisobutyric acid (Heidenheimer Chemisches Laboratorium A.G.), 16 g of *p*-toluenesulfonic acid and 1000 ml of benzene. The reaction product was isolated and purified as in the case of 5-methyl-1,3-dioxolone-(4). The distillate fraction employed in the kinetic experiments had the following physical constants: b.p. 71.5°C/49 mm Hg, $n_D^{20} = 1.4114$, $d_4^{20} = 1.1108$; $[R]_{\text{obs.}} = 25.98$ ($[R]_{\text{calc.}} = 26.35$).

The water used in the kinetic experiments was distilled water that had been boiled to remove carbon dioxide. The reaction media containing hydrogen chloride were prepared by diluting reagent grade hydrochloric acid with water; their concentrations were determined by titration with standard sodium hydroxide solutions.

Kinetic measurements. The hydrolysis reactions were followed by adding samples withdrawn from the reaction mixture to ice-water mixtures and titrating them with an approximately 0.04 standard M diethylamine solution using a mixture of bromothymol blue and neutral red ($pK = 7.51$) as indicator. Eight to ten samples were taken during the course of a reaction and several samples after the reaction had proceeded to completion. The initial dioxolone concentration was about 0.1 M. In the experiments between 15 and 35°C, samples were taken from the reaction mixtures with a 5-ml semiautomatic pipet, whereas in the experiments at higher temperatures the reaction mixture was prepared at room temperature and 5-ml aliquots were transferred to glass ampoules about 6 ml in capacity, which were then sealed and placed in a thermostat. After the ampoules had come to the thermostat temperature, the first ampoule was removed for analysis similarly as in an earlier study of the acid-catalyzed hydrolysis of formic esters⁹ and successive ampoules at suitable intervals.

Rate equations and calculations. It was found experimentally that the hydrolysis of the dioxolones that can be derived from formaldehyde proceeded in accordance with the following formal rate law:

$$\frac{dx}{dt} = (k_o + k_a[H^+])(a-x) \quad (2)$$

where a denotes the initial dioxolone concentration, x the concentration of dioxolone that had reacted by time t , k_o the rate coefficient of the neutral reaction and k_a the rate coefficient of the acid-catalyzed reaction. The variation of the experimentally determined over-all rate coefficient, $k_o + k_a[H^+]$, for 5-methyl-1,3-dioxolone-(4) as a function of the hydrogen ion concentration is shown in Fig. 1.

When the reaction medium contains initially a sufficiently high mineral acid concentration, the hydrogen ion concentration does not change to any significant extent during the reaction owing to the formation of α -hydroxy-acid from the dioxolone. Hence the over-all first-order rate coefficient, $k_o + k_a[H^+]$, remains constant during the reaction and its value can be calculated from the ordinary first-order rate equation as shown by the data for a typical experiment in Table 1. When the reaction medium was initially neutral, however, the relative magnitudes of the rate coefficients k_o and k_a were such that the reaction became autocatalytic owing to the gradual increase in the concentration of hydrogen ion released by the formed α -hydroxy-acid. The rate coefficient calculated from the first-order rate equation increased with time and the following method had to be employed to evaluate the rate coefficient k_o .

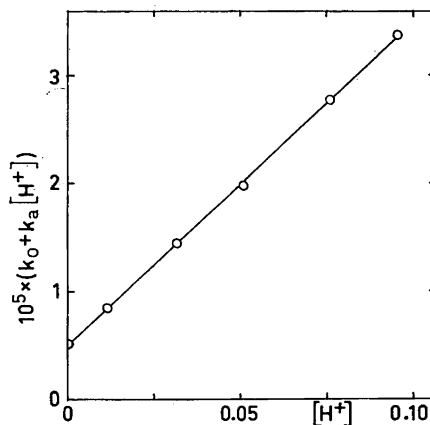


Fig. 1. The hydrolysis of 5-methyl-1,3-dioxolone-(4) in water and dilute hydrochloric acid solutions at 35°C. The dependence of the over-all first-order rate coefficient on the acidity of the reaction medium.

Table 1. Hydrolysis of 5-methyl-1,3-dioxolone-(4) in 0.0510 M hydrochloric acid at 15°C.

| t , min | 0 | 632 | 1472 | 2087 | 2881 | 4434 | 7209 | 10098 |
|---|-------|-------|------|------|------|------|------|-------|
| $10^2(a-x)$, moles/l | 12.20 | 10.69 | 9.00 | 7.88 | 6.74 | 4.86 | 2.75 | 1.55 |
| $10^6(k_0 + k_a[\text{H}^+])$, s ⁻¹ | — | 3.50 | 3.44 | 3.48 | 3.43 | 3.46 | 3.44 | 3.40 |

Mean $k_0 + k_a[\text{H}^+] = 3.45 \times 10^{-6}$ s⁻¹.

When the reaction mixture contains no added strong acid, the hydrogen ion concentration of the mixture at time t is given with sufficient accuracy by $[\text{H}^+] = \sqrt{Kx}$, where x is the concentration of the formed α -hydroxy-acid, *i.e.* the concentration of dioxolone that has reacted at time t , and K the dissociation constant of the acid. Eqn. (2) then takes the form

$$\frac{dx}{dt} = (k_0 + k_a\sqrt{K}\sqrt{x})(a-x) \quad (3)$$

Of course, eqn. (3) can be completely integrated but the following partially integrated form is more suitable for the present calculations:

$$\frac{1}{t} \ln \frac{a}{a-x} = k_0 + k_a\sqrt{K} \frac{1}{t} \int_0^t \sqrt{x} dt = k_t \quad (4)$$

The rate coefficient k_t that is computed from the first-order rate equation varies with time since it is equal to the sum of the constant term k_0 and the integral term, which increases with time. When the value of the latter term is determined at each time t and subtracted from the corresponding computed over-all rate coefficient k_t , the value of the rate coefficient k_0 of the uncatalyzed reaction is obtained.

The integral in eqn. (4) was evaluated from successive values of x relating to different times t by the trapezoidal rule:

$$\int_0^{t_i} \sqrt{x} dt = \frac{1}{2} \sum_{\nu=1}^i (\sqrt{x_\nu} + \sqrt{x_{\nu-1}})(t_\nu - t_{\nu-1}) \quad (5)$$

$i = 1, 2, 3, \dots$

where the value of $x_{\nu-1}$ when $\nu = 1$ is the value of x obtained for the first sample taken from the reaction mixture. The value of k_a required in the calculation was evaluated

Table 2. Hydrolysis of 5,5-dimethyl-1,3-dioxolone-(4) in water at 35°C.
 $k_a = 1.04 \times 10^{-4}$ l mole⁻¹ s⁻¹. $K = 1.28 \times 10^{-4}$ mole/l.

| t , min | 0 | 3036 | 4293 | 4297 | 7561 | 10070 | 11532 | 13142 | 14480 | ∞ |
|---|------|------|------|------|------|-------|-------|-------|-------|----------|
| $10^2 \cdot x$, moles/l | 0.03 | 0.41 | 1.95 | 1.96 | 3.09 | 3.83 | 4.21 | 4.56 | 4.73 | 6.17 |
| $10^6 \cdot k_t$, s ⁻¹ | — | 1.40 | 1.46 | 1.46 | 1.52 | 1.60 | 1.65 | 1.69 | 1.67 | — |
| $10^6 k_a\sqrt{K} \frac{1}{t} \int_0^t \sqrt{x} dt$, s ⁻¹ | — | 0.08 | 0.10 | 0.10 | 0.14 | 0.16 | 0.17 | 0.18 | 0.18 | — |
| $10^6 \cdot k_0$, s ⁻¹ | — | 1.32 | 1.36 | 1.36 | 1.38 | 1.44 | 1.43 | 1.41 | 1.39 | — |

Mean $k_0 = 1.39 \times 10^{-6}$ s⁻¹.

Table 3. Hydrolysis of 1,3-dioxolone-(4) and its 5-substituted methyl derivatives at different temperatures in water and in dilute hydrochloric acid solutions. The over-all first-order rate coefficients and the rate coefficients of the neutral and acid-catalyzed reactions.

| | °C | [H ⁺] moles/l | $10^6(k_o + k_a[H^+])$ s ⁻¹ | $10^6 \cdot k_o$ s ⁻¹ | $10^6 \cdot k_a$ l mole ⁻¹ s ⁻¹ |
|--------------------------------|-------|---------------------------|--|----------------------------------|---|
| 1,3-Dioxolone-(4) | 15 | — | 1.217 | | |
| — » — | 15 | 0.0510 | 3.64 | 1.217 | 47.2 |
| — » — | 15 | 0.0993 | 5.89 | | |
| — » — | 25 | — | 2.96 | | |
| — » — | 25 | 0.0991 | 15.5 | 2.96 | 126.5 |
| — » — | 35 | — | 7.18 | | |
| — » — | 35 | 0.0508 | 23.3 | 7.18 | 311 |
| — » — | 35 | 0.0988 | 37.6 | | |
| 5-Methyl-1,3-dioxolone-(4) | 15 | — | 0.965 | | |
| — » — | 15 | 0.0510 | 3.45 | 0.965 | 48.4 |
| — » — | 15 | 0.0961 | 5.60 | | |
| — » — | 25 | — | 2.13 | | |
| — » — | 25 | 0.0111 | 3.54 | 2.13 | 135 |
| — » — | 25 | 0.0509 | 8.74 | | |
| — » — | 25 | 0.0959 | 15.4 | | |
| — » — | 35 | — | 5.07 | | |
| — » — | 35 | 0.0111 | 8.39 | | |
| — » — | 35 | 0.0375 | 14.4 | 5.07 | 297 |
| — » — | 35 | 0.0508 | 19.7 | | |
| — » — | 35 | 0.0761 | 27.7 | | |
| — » — | 35 | 0.0956 | 33.6 | | |
| — » — | 35 | 0.0956 | 33.8 | | |
| 5,5-Dimethyl-1,3-dioxolone-(4) | 35 | — | 1.39 | | |
| — » — | 35 | 0.0986 | 11.65 | 1.39 | 104.1 |
| — » — | 47.68 | — | 3.87 | | |
| — » — | 47.68 | 0.0972 | 33.6 | 3.87 | 306 |
| — » — | 61.50 | — | 13.6 | | |
| — » — | 61.50 | 0.0966 | 97.2 | 13.6 | 865 |

Table 4. Values of the parameters of the Arrhenius equation, entropies of activation, and rate coefficients at 25°C of the neutral and acid-catalyzed hydrolysis reactions of 1,3-dioxolone-(4) and its 5-substituted methyl derivatives.

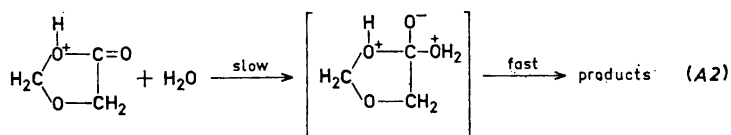
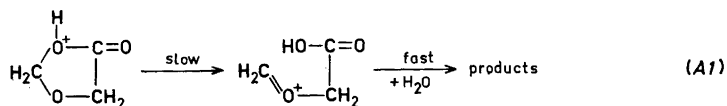
| | | <i>E</i> kcal/mole | log <i>A</i> | ΔS^\ddagger E.U. | $10^6 \cdot k^{25^\circ\text{C}}$ or l mole ⁻¹ s ⁻¹ |
|--------------------------------|---------------------------|-----------------------|--------------|--------------------------|--|
| 1,3-Dioxolone-(4) | Acid-catalyzed hydrolysis | 17.0 | 8.56 | -21.4 | 125 |
| 5-Methyl-1,3-dioxolone-(4) | » » » | 16.4 | 8.13 | -23.3 | 128 |
| 5,5-Dimethyl-1,3-dioxolone-(4) | » » » | 16.4 | 7.64 | -25.6 | 42.8 |
| 1,3-Dioxolone-(4) | Uncatalyzed hydrolysis | 16.0 | 6.22 | -32.0 | 3.02 |
| 5-Methyl-1,3-dioxolone-(4) | » » | 15.0 | 5.33 | -36.1 | 2.23 |
| 5,5-Dimethyl-1,3-dioxolone-(4) | » » | 17.6 | 6.63 | -30.1 | 0.507 |

from the plot of the over-all rate coefficient versus hydrogen ion concentration for the same reaction in media containing mineral acid. The values of the dissociation constants K of glycolic and lactic acid at different temperatures were taken from the data reported by Harned and Owen⁸, but corresponding values were not available for α -hydroxyisobutyric acid. As the dissociation constants of glycolic and lactic acids do not differ significantly from each other and the contribution of the term in eqn. (4) representing the acid-catalyzed reaction to the over-all rate coefficient k_t is relatively small, it was possible to employ the values of the dissociation constant of lactic acid for α -hydroxyisobutyric acid. Table 2 shows data from typical experiments for the evaluation of the rate coefficient k_o of the uncatalyzed reaction.

RESULTS AND DISCUSSION

The over-all rate coefficients of the hydrolysis reactions of dioxolones derived from formaldehyde and the values of the rate coefficients of the neutral (k_o) and acid-catalyzed (k_a) reactions under different conditions are given in Table 3. The values of the rate coefficient of the neutral reaction were computed directly from eqn. (4) as described above, and the values of the rate coefficient of the acid-catalyzed reaction were obtained from the plot of the over-all rate coefficient *versus* hydrogen ion concentration. Values of the parameters of the Arrhenius equation and the activation entropies calculated for both reactions by the method of least squares are given in Table 4.

When it is taken into account that the studied compounds are both acetals and esters, the following mechanisms *A 1* and *A 2* may be proposed for their acid-catalyzed hydrolysis:

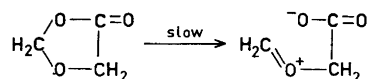


The preliminary uptake of a proton and the resonating structures of the reaction intermediates are not indicated in these reaction equations. Despite the close structural similarity of 1,3-dioxolones and 1,3-dioxolans, which latter react by the *A 1* mechanisms of hydrolysis⁴, the present data suggest that the hydrolysis of dioxolones derived from formaldehyde takes place by the latter mechanism.

The values of the quantities in Table 4 for the catalyzed reactions are similar to those generally observed for reactions proceeding by the normal type of ester hydrolysis mechanism which involves an attack of water on the carbonyl group. The activation entropies have relatively large negative values which are much lower than the activation entropies for reactions of type *A 1* such as those of the 1,3-dioxolans⁴. The influence of methyl substituents at position 5 on the rate is relatively slight as expected by the bimolecular mecha-

nism of ester hydrolysis, where the substituent effect of the alkyl component is usually mainly of the steric type. When it is noted that the water molecule may approach the carbonyl group from either side of the ring in the *A 2* reactions of dioxolones, it is reasonable to assume that the reaction will be significantly retarded by substituents sterically only when such substituents are located on both sides of the ring in the close vicinity of the reaction center. This is supported by the observation that 5,5-dimethyl-1,3-dioxolone-(4) undergoes acid-catalyzed hydrolysis at a rate that is only about one third of the rate of hydrolysis of 1,3-dioxolone-(4) and its 5-monomethyl derivative.

Of the three types of uncatalyzed mechanism by which esters have been observed to react⁹, *viz.* bimolecular and unimolecular alkyl-oxygen fission and the bimolecular acyl-oxygen fission, only the latter two mechanisms can be considered to apply to the studied esters from the point of view of structural effects. The occurrence of the unimolecular alkyl-oxygen fission mechanism with the rate-determining stage would be promoted by the possibility of reso-



nance in the fission product. On the other hand, the fact that the compounds undergo neutral hydrolysis at a readily measured rate which is some four powers of ten higher than that of, for instance, ethyl acetate¹⁰, is also compatible with the bimolecular mechanism, since negative substituents, especially when they are in the acyl component, should greatly increase the rate of hydrolysis. Also factors associated with cyclic structure of the molecules, such as the release of the bond-angle strain in the rate-determining stage, may promote the neutral hydrolysis of the dioxolones. A bimolecular mechanism of neutral hydrolysis similar in principle to the mechanism of normal alkaline hydrolysis is supported further by the observation that the dioxolones decompose almost instantaneously in alkaline media.

The large negative values of the activation entropies (Table 4) are of the magnitude generally observed in bimolecular neutral ester hydrolysis¹¹. The activation energies are a few kilocalories per mole higher than those of the reactions of open-chain esters that have been found to proceed by this mechanism. When the large differences in the polarities of the parent acids and the factors associated with cyclic structure of the dioxolones are noted, the values of the activation energies cannot be considered comparable, however. In a subsequent paper it will be shown that when one or two methyl groups are introduced into dioxolones at position 2, the activation energy and entropy of activation of the neutral hydrolysis increase greatly, which suggests that the mechanism changes into one involving a unimolecular alkyl-oxygen fission. Hence it is quite possible that the rates of hydrolysis of the dioxolones considered above may include a minor contribution arising from the latter mechanism.

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