

The Kinetics of the Uncatalyzed and Acid-Catalyzed Hydrolysis of 1,3-Dioxolone-(4) and Its Derivatives

Part III. Experiments in Moderately Concentrated Acids and in Deuterated Solvents

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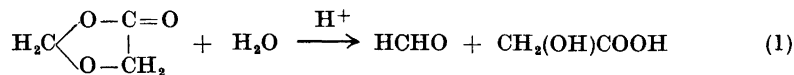
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The rates of hydrolysis of 1,3-dioxolones containing no, one, or two methyl substituents on the carbon atom between the two ether oxygen atoms have been studied in moderately concentrated hydrochloric acid solutions and in mixtures of light and heavy water. The results indicate that the dioxolones which have no substituents on the carbon atom 2 hydrolyze by the normal type of acid-catalyzed ester hydrolysis, whereas 2-methyl-substituted dioxolones display features that cannot be directly reconciled with either a normal type or an A-1 type of ester hydrolysis. The empirical criterion of Bunnett suggests that a water molecule is also involved in the formation of the critical complex.

The presence of a covalent attached water molecule in the critical complex derived from 2-methyldioxolones is also supported by experiments in light and heavy water and in their mixtures. The gross deuterium solvent isotope effect ($k_D/k_H = 1.68$) is comparable to that found in the normal type of ester hydrolysis, being thus lower than in well-established A-1 reactions of acetals and acetal-esters. Moreover, the behavior in H_2O-D_2O mixtures of different compositions conforms to an equation which is based on three exchangeable hydrogen atoms in the critical complex, whereas that for but one exchangeable hydrogen does not.

The hydrolysis mechanism of 2-methyl-substituted dioxolones is discussed in terms of the conformation of the dioxolone ring. Stereochemical differences between the hydrolysis reactions of dioxolones and dioxolanes are considered.

The kinetics of the acid-catalyzed hydrolysis reactions of aliphatic and cyclic acetal-esters have been discussed in a number of earlier papers.¹⁻⁵ The experimental data obtained for aliphatic acetal-esters¹⁻³ were consistent with an A-1 type of hydrolysis mechanism, excepting some particular instances in which an ester hydrolysis mechanism of the normal $A_{AC}2$ type became



commensurate with the former mechanism, whereas the acid-catalyzed hydrolysis of 1,3-dioxolone-(4) and its methyl-substituted derivatives^{4,5} showed certain anomalies.

The most difficult problem was in the acid-catalyzed hydrolysis of 2-methyl-substituted dioxolones. All the data for dioxolones with an unsubstituted carbon atom 2 were consistent with the $A_{AC}2$ mechanism of ester hydrolysis, but an introduction of one or two methyl groups at this carbon atom greatly increased the hydrolysis rate and altered the values of the activation parameters, thus indicating a change in the mechanism of hydrolysis. The present study was undertaken to obtain more extensive experimental information concerning the kinetic behavior of dioxolones in their acid-catalyzed hydrolysis reaction and the possible hydrolysis mechanisms involved.

EXPERIMENTAL

Materials. The 1,3-dioxolones used were prepared and purified as described in the previous papers of this series.^{4,5} The derivatives of 1,3-dioxolane, which were employed in comparative kinetic studies, were synthesized as described below.

4,4-Dimethyl-1,3-dioxolane was prepared by distilling an equimolar mixture of formaldehyde di-amylacetal and isobutylene glycol with *p*-toluenesulphonic acid as the catalyst. The crude dioxolane, which was first distilled off, was subsequently purified by careful fractional distillations in a Todd precision fractionation assembly. The following physical constants were recorded for the purified product: b.p. 93.4–93.5°C/749 torr, d_4^{20} 0.9446, n_D^{20} 1.3988, $[R]_D$ 26.14 (calc. 26.22).

2,4,4-Trimethyl-1,3-dioxolane was synthesized in a similar way starting from acetaldehyde di-amylacetal and isobutylene glycol. B.p. 100.0–100.2°C/756 torr, d_4^{25} 0.8920, n_D^{25} 1.3913, $[R]_D$ 30.96 (calc. 30.84).

2,2,4,4-Tetramethyl-1,3-dioxolane was prepared from isobutylene glycol and acetone by a method similar to that used by Leutner⁶ to synthesize some other dioxolane derivatives. B.p. 110.3–110.7°C/760 torr, d_4^{20} 0.8769, n_D^{20} 1.3940, $[R]_D$ 35.79 (calc. 35.47).

Deuterium oxide was from Norsk Hydro-Elektrisk Kvaestofaktieselskab, Norway. Its deuterium content was determined by precision density measurements.⁷ As the electrolytic enrichment of deuterium in the production of this water also involves a considerable enrichment of ¹⁸O, the samples of the standard waters employed were first normalized to the same isotopic oxygen content, using the sulfur dioxide equilibration procedure described by Kirshenbaum.⁸

Kinetic measurements. The experimental kinetic procedures used at low acidities and the methods of calculating the rate coefficients were those described in the previous papers.^{4,5} In moderately concentrated hydrochloric acid solutions, the reactions of the dioxolones derived from formaldehyde or acetaldehyde were followed by analyzing the aldehyde liberated as described in connection with studies of aliphatic acetal-esters.¹ Unfortunately, this method could not be employed when the rates of dioxolones derived from acetone were measured because the method of analysis fails with acetone. The latter reactions were therefore followed by determining the concentration of unconverted dioxolone at suitable time intervals; this same method was previously employed to the hydrolysis rates of carboxylic esters in solutions of moderately high acidity.⁹

Table 1 gives first-order rate coefficients *k* for the acid-catalyzed hydrolysis of dioxolones containing no, one, or two methyl substituents on the carbon atom 2. The directly measured overall rate coefficients *k'* include a minor contribution from the uncatalyzed hydrolysis,^{4,5} which has been subtracted to obtain the values of *k*. This contribution is a few per cent at the lowest acidities used and becomes insignificant at relatively high acid concentrations.

Table 1. Hydrolysis of some methyl derivatives of 1,3-dioxolone-(4) and 1,3-dioxolane in moderately concentrated aqueous hydrochloric acid solutions at 25°C. k' = overall first-order rate coefficient; k = first-order rate coefficient of the acid-catalyzed reaction.

Substrate	Acid concn. mole/l	$10^4 \times k' \text{ s}^{-1}$	$10^4 \times k \text{ s}^{-1}$
5-Methyldioxolone	0.971	1.55	1.53
»	1.94	3.44	3.42
»	2.92	5.85	5.83
»	3.89	8.89	8.87
2,5,5-Trimethyldioxolone	0.793	4.08	3.53
»	0.971	5.28	4.73
»	1.94	14.3	13.7
»	2.92	30.7	30.2
»	3.89	58.0	57.5
2,2,5,5-Tetramethyldioxolone	0.971	3.88	3.74
»	1.94	11.1	11.0
»	2.92	23.7	23.6
»	3.89	48.4	48.3
4-Methyldioxolane	1.02	0.0603	0.0603
»	2.06	0.223	0.223
»	3.06	0.644	0.644
»	4.07	1.76	1.76

Table 2. Deuterium solvent isotope effect on the hydrolysis of 2,5,5-trimethyldioxolone-(4) in $\text{H}_2\text{O}-\text{D}_2\text{O}$ mixtures at 25°C. k_0 = rate coefficient of the uncatalyzed reaction; k_a = rate coefficient of the acid-catalyzed reaction.

Deuterium atom fraction	$10^4 \times k_0 \text{ s}^{-1}$	$10^4 \times k_a$	$l \text{ mole}^{-1} \text{ s}^{-1}$
0.000	0.541	3.84	
0.129	0.530	4.02	
0.258	0.509	4.20	
0.387	0.505	4.56	
0.517	0.500	4.82	
0.646	0.479	5.24	
0.775	0.485	5.53	
0.905	0.449	5.91	
0.993	0.437	6.42	
1.000	0.436 ^a	6.45 ^a	

$k_D/k_H = 1.68$ (catalyzed reaction), 0.82 (uncatalyzed reaction)

^a extrapolated values

Table 2 shows the results for the hydrolysis of 2,5,5-trimethyldioxolone in $\text{H}_2\text{O}-\text{D}_2\text{O}$ mixtures. The rate coefficients k_0 and k_a relating to the uncatalyzed and acid-catalyzed hydrolysis reactions, respectively, were determined as the intercept and slope of the plot of the directly measured overall first-order rate coefficient against the lyonium concentration of the reaction solution.⁵ The acid concentrations (hydrochloric acid was used in

Table 3. Rate coefficients k_a for the acid-catalyzed hydrolysis of some methyl-substituted 1,3-dioxolanes in dilute aqueous hydrochloric acid solutions at different temperatures.

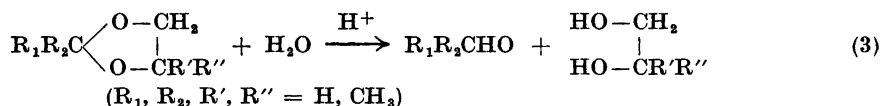
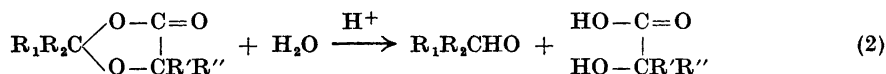
	$10^4 \times k_a \text{ l mole}^{-1} \text{ s}^{-1}$					
	25°C	35°C	45°C	52.06°C	63.81°C	77.48°C
4,4-Dimethyldioxolane	0.0129	0.0537		0.513	1.86	8.82
2,4,4-Trimethyldioxolane	50.8	159	508			
2,2,4,4-Tetramethyldioxolane	250	859	2540			

these experiments) varied from an initially neutral solution up to about 0.15 M acid, and the plots were linear in all cases.

Table 3 gives the rate coefficients measured for the acid-catalyzed hydrolysis of a number of methyl-substituted 1,3-dioxolanes at low acid concentrations (0.005 to 0.05 M). The technique of these measurements was the same as that of earlier dioxolane studies.¹⁰

DISCUSSION

Kinetic parameters of the acid-catalyzed hydrolyses of 1,3-dioxolones and 1,3-dioxolanes. Although the acid-catalyzed hydrolysis reactions of 1,3-dioxolones (eqn. 2) and 1,3-dioxolanes (eqn. 3) take place formally in a similar way, their

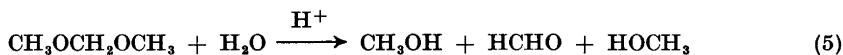
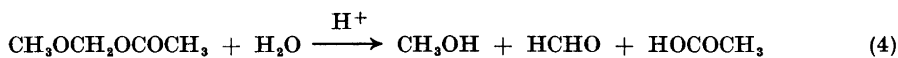


kinetic values show clearly detectable differences. This is seen from Table 4, in which some of the data of previous investigations^{4,9,10} are contrasted with those of the present study. The values given for the rate coefficients k_a at 25°C are those calculated from the parameters of the Arrhenius equation, which were obtained by the method of least squares from the plot of $\log k_a$ against $1/T$.

Table 4 reveals that the reactions under comparison may be roughly divided into three distinct classes, although some borderline cases may well exist. The first class, dioxolanes, represents acetal hydrolysis and all the observed kinetic values are easily understood by the A-1 mechanism of hydrolysis, if the stereochemical factors involved are taken into account.¹⁰ For instance, the activation entropies are positive or but slightly negative. Dioxolones, on the other hand, are both esters and acetals and hence one could expect various reaction mechanisms to be possible. In fact, in the second group, in the dioxolones that have an unsubstituted carbon atom 2, the rate of the normal ester hydrolysis

of the $A_{AC}2$ type is faster than that of any other plausible reaction path. The values of the activation entropy, which range from -21 to -26 E.U., as well as the actual magnitudes of the rate coefficients conform well to this mechanism.⁴ The third group, the dioxolones that possess one or two methyl groups at the carbon atom 2, is the most problematic. The activation entropies, *viz.* -4 to -9 E.U., seem to fall into an intermediate range. It might be suggested that this behavior were a result of concurrent $A_{AC}2$ and A-1 reactions, but this explanation is unsatisfactory.⁵

An interesting observation is that in the 2-methyl-substituted dioxolones the rate coefficients vary with the structure of the rest of the molecule very similar to that in the corresponding dioxolanes. This indicates that the stereochemical factors involved in the both ring disruption reactions must be similar and the reaction mechanisms closely related. However, the fact that 2-substituted dioxolones hydrolyze in most cases much slower than the corresponding dioxolanes is less readily understood by an A-1 mechanism. Thus, *e.g.*, methoxy-methyl acetate (eqn. 4) is hydrolyzed by this mechanism approximately 100 times faster than dimethyl formal¹¹ (eqn. 5), the reason being that the acetyl-



oxy group is a much better leaving group for this mechanism than the methoxy group.

Studies in moderately concentrated acid solutions. From Table 1, which contains kinetic data at moderately concentrated hydrochloric acid solutions for some examples of the three classes of compounds discussed above, it is seen that the susceptibility of the rate coefficients to the acidity of the reaction medium increases in the following sequence: dioxolones with an unsubstituted 2-carbon, 2-methyl-substituted dioxolones, and dioxolanes. Thus the

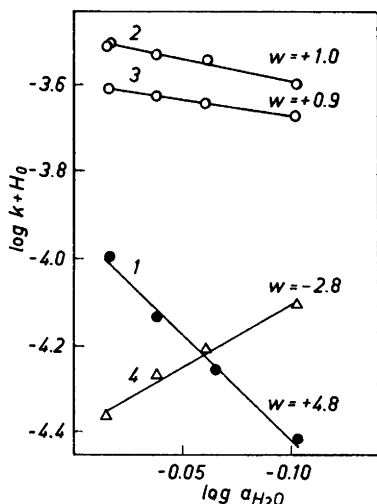


Fig. 1. The Bunnett w -values for the acid-catalyzed hydrolyses of dioxolones and dioxolanes in moderately concentrated hydrochloric acid solutions at 25°C . 1. 5-Methyldioxolone. 2. 2,5,5-Trimethyldioxolone. 3. 2,2,5,5-Tetramethyldioxolone. 4. 4-Methyldioxolane (log $k + 1$).

behavior of 2-methyldioxolones is of an intermediate character also in this respect, in addition to that discussed above. This is seen more definitely from Fig. 1, in which the values of $(\log k + H_0)$ have been plotted against the logarithm of the activity of water, according to the method of Bunnett.¹² The water activities used were interpolated from the values given by Bunnett, and the values of the H_0 acidity function were those of Long and Paul.¹³

Although the general utility of studies in moderately concentrated acids as a mechanistic tool can be questioned,^{12,14} they should give valuable information in case of a group of structurally similar basic substrates like those of the present study. Thus the fact that the slopes w of the plots for 2-substituted dioxolones are distinctly between those of the two other plots emphasizes the different character of the reactions involved.

The Bunnett w -value, +4.8, determined for 5-methyldioxolone is of a magnitude generally observed in ester hydrolysis of the $A_{AC}2$ type,¹² viz. +4 to +5, and thus confirms the above conclusions. The value -2.8, derived for 4-methyldioxolane, is typically that expected for an A-1 hydrolysis of acetals in hydrochloric acid solutions.¹² The values for the 2-dioxolones, which are about +1, fall into an intermediate region. According to the empirical criterion of Bunnett, these values should indicate that a water molecule acts as a nucleophile and therefore, differing from the A-1 mechanism, a water molecule is covalently attached to the critical complex.

Deuterium solvent isotope effects. When discussing a generalized form of the theory of solvent isotope effects in mixtures of light and heavy water Salomaa, Schaleger and Long¹⁵ showed that under certain circumstances these isotope effects could be used to make a distinction between different accessible transition state structures. The acid-catalyzed hydrolysis of 2-methyl-substituted dioxolones is a typical example of reactions in which such a distinction should be possible.

If it is assumed that the transition state has but one exchangeable hydrogen atom, as is the case with the A-1 mechanism, eqn. (6) can be derived for the kinetic behavior in mixed H_2O - D_2O solvents. Here k_H , k_n and k_D are the rate coefficients in light water, in mixed water of deuterium atom fraction n , and in heavy water, respectively, and l is the isotopic fractionation factor for hydronium ion, having a value of 0.67 at 25°C. A small uncertainty in the value of the latter quantity does not affect the results.¹⁵

$$\frac{k_n}{k_H} = \frac{1 - n + nl^3k_D/k_H}{(1 - n + nl)^3} \quad (6)$$

Alternatively, one might suggest that a water molecule is also involved in the formation of the transition state. In this case the transition state has three exchangeable hydrogens, which gives

$$\frac{k_n}{k_H} = \frac{(1 - n + nl(k_D/k_H)^{1/3})^3}{(1 - n + nl)^3} \quad (7)$$

Here it has been assumed that the three exchangeable hydrogens are equivalent with respect to their isotopic exchange reactions, *i.e.* that the isotopic fractionation factor is the same for each of these hydrogens. Actually, the magni-

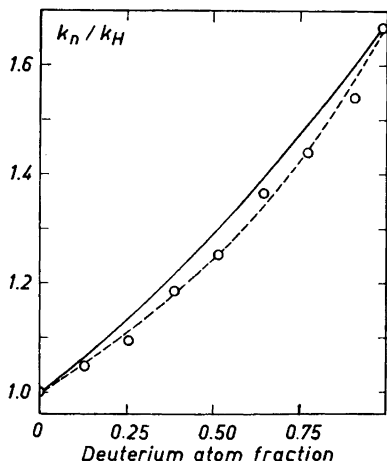


Fig. 2. Observed and calculated values for the relative rate coefficients (k_n/k_H) of the acid-catalyzed hydrolysis of 2,5,5-trimethyldioxolone in light water-heavy water mixtures at 25°C. *Solid line*, calc. from eqn. (6) (one exchangeable hydrogen in the transition state); *broken line*, calc. from eqn. (7) (three exchangeable hydrogens in the transition state).

tudes of the latter quantities may slightly differ, but this is of no significance for the practical applications, because an equation of type (7) is not sensitive enough to detect such differences.¹⁵

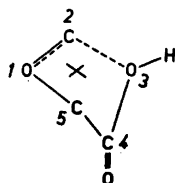
In Fig. 2 the experimental kinetic values measured for a 2-methyl-substituted dioxolone in H_2O - D_2O mixtures are compared with those predicted by eqns. (6) and (7). It is seen that eqn. (7) gives a good fit to the data, whereas eqn. (6) does not. This indicates that a water molecule is also incorporated in the transition state, the same conclusion as was drawn from measurements at relatively high acidities (see above). It must be noted, however, that with more than three exchangeable hydrogens, say five, equations of type (7) become relatively insensitive for the detection of the number of these hydrogens and, therefore, they can be fitted to the data almost as well as eqn. (7). Hence the only statement that can be made is that the data are well predicted by theory, if one assumes the presence of *at least* three exchangeable hydrogen atoms in the transition state.

The actual magnitude of the gross deuterium solvent isotope effect ($k_D/k_H = 1.68$) is also consistent with more than one exchangeable hydrogen in the transition state, if the reaction involves a pre-equilibrium protonation.¹⁵ Fortunately, a direct comparison can be made to hydrolyses of similar compounds which, by independent kinetic evidence, can be assumed to hydrolyze by the A-1 mechanism. For instance, the hydrolysis of an open-chain acetal-ester, methoxymethyl acetate,³ shows a k_D/k_H value of 2.23, and that of a 5-membered cyclic acetal, γ -ethoxy- γ -butyrolactone,¹⁶ a similar value of 2.37. The value observed in the present study, 1.68, is lower and, accidentally, the same as that measured for the $A_{AC}2$ hydrolysis of methyl acetate.¹⁵

Hydrolysis mechanism of 2-methyl-substituted dioxolones. It was pointed out above that aliphatic acetal-esters hydrolyze by the A-1 mechanism much more readily than the corresponding acetals (see eqns. 4 and 5). The intriguing question is, why do not the 2-dioxolones utilize a similar A-1 path as dioxolanes and, correspondingly, hydrolyze much faster than the latter, as this should

be the easiest route for the reaction to occur. As the polar factors for an A-1 reaction are much more favorable in case of dioxolones, but, contradictorily, they hydrolyze in most cases even much slower (Table 4), it follows that the A-1 reaction of dioxolones is retarded by the stereochemical factors involved.

The conformation of a substituted dioxolone ring is probably like that of cyclopentanone and methylenecyclopentane,^{71,81} viz. a "half-chair" form with the doubly bonded carbon atom located on the average plane of the ring. The transition state of the A-1 hydrolysis, in which the bond between the ring atoms 1 and 2 has a partial double-bond character, must assume either a planar form or, preferentially, an "envelope" form (III). It may be inferred from these



(III)

models and from experimental observations discussed below that there is considerable angle strain in these transition states in comparison to the corresponding forms derived from dioxolanes, in which the carbon atom 4 possesses sp^3 -hybridized bonds.

The ring structure of the transition state under discussion resembles closely that of 3-cyclopenten-1-one. Benington and Morin¹⁹ made several unsuccessful attempts to prepare this compound by different ring closure reactions. Alder and Flock²⁰ were the first to report a synthesis by pyrolysis, though in poor yield, using, however, a starting material in which the 5-membered ring structure was already present. These observations indicate that this type of a substituted ring is considerably more strained than the cyclopentene ring itself. The comparative calculations of Bartlett and Rice²¹ are also very interesting in this respect. They estimated that the angle strain in the planar form of the Δ^3 -cyclopentenyl cation exceeds that of cyclopentane by 5 kcal per mole, and in the bent forms the differences are even greater. This originates from the geometry at the carbon atom 4: in the cyclopentenyl cation like in the transition state of dioxolone hydrolysis, the ring bonds from this carbon are sp^2 -bonds, whereas in the transition state derived from dioxolanes they are sp^3 -hybridized. In addition to the angle strain, bond oppositions may have an effect in the same direction.

The steric factors discussed above rationalize the observation that a normal A-1 mechanism is retarded in dioxolones as compared to dioxolanes. Hence a change of hybridization to sp^3 at the carbon atom 4 of the transition state should accelerate the hydrolysis of dioxolones. In water solution this is most easily achieved by a nucleophilic action of a water molecule. In addition to the proton uptake equilibrium, the hydrolysis thus presumably involves also a water-carbonyl addition equilibrium followed by a rate-determining unimolecular decomposition of the intermediate formed or, alternatively, the rate-determining stage is that between the carbonyl carbon atom of the pro-

tonated substrate and a water molecule. Both of these alternatives are in good agreement with the experimental observations discussed in the preceding sections.

Finally, it must be noted that in such 5-membered cyclic acetal-esters in which the partial double bond of the transition state of A-1 hydrolysis is not between the ring atoms, the stereochemical factors are naturally quite different from those discussed above. Thus Fife,¹⁶ who investigated the hydrolysis of γ -ethoxy- γ -butyrolactone, demonstrated that this reaction proceeds *via* a normal A-1 mechanism.

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