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The Hydrolysis of 1,3-Dioxolan and Its Alkyl-Substituted Derivatives. Part I. The Structural Factors Influencing the Rates of Hydrolysis of a Series of Methyl-Substituted Dioxolans

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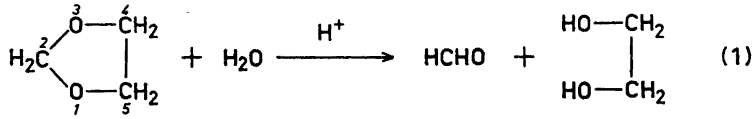
The acid-catalysed hydrolysis reactions of 1,3-dioxolan and its 2-methyl, 4-methyl, 2,2-dimethyl, 2,4-dimethyl (*cis* and *trans* forms), 2,2,4-trimethyl, 4,4,5,5-tetramethyl and 2,4,4,5,5-pentamethyl derivatives have been studied kinetically at different temperatures using dilatometric and titrimetric methods. The results are discussed in the light of the mechanism of acetal hydrolysis and it is shown that the rates of hydrolysis of the compounds are mainly influenced by structural factors of two types, polar factors that are similar to those observed in acyclic acetals, and steric strain due to the methyl substituents that enters the picture when the transition state is approached.

By considering the possible influence of the above factors on the rates of hydrolysis of the two isomeric 2,4-dimethyl-1,3-dioxolans, it is concluded that the low-boiling isomer, which hydrolyses about four times as fast as the high-boiling isomer, is the *cis* form. This conclusion is in agreement with that based on a comparison of the properties of the isomers with those of the known 1,3-dimethyl*cyclo*pentane isomers.

1,3-Dioxolan and its derivatives are acetals which undergo hydrolysis in acid media.



(1)

The hydrolysis reactions of these compounds have been studied kinetically to only a limited extent. Leutner [1,2] measured the rates of hydrolysis of dioxolan and several of its methyl derivatives, but only at one temperature; one of the compounds he studied was 2,4-dimethyldioxolan, but he did not take into

consideration that *cis* and *trans* forms of this compound exist. Laurent *et al.*[3] recently measured the rates of hydrolysis of unsubstituted 1,3-dioxolan at several temperatures. More extensive studies of the rates of hydrolysis of dioxolan derivatives containing aryl substituents in position 2 have been carried out by Ceder [4].

The purpose of the present investigation was to obtain a more detailed picture of the influence of structural factors, in particular the stereochemical configurations of the molecules, on the kinetics of hydrolysis of alkyl-substituted 1,3-dioxolans. A further aim was to find out whether kinetic data can be used to decide the configurations of geometric isomers that cannot readily be determined by other methods.

EXPERIMENTAL

Chemicals. 1,3-Dioxolan was synthesised from ethylene glycol and paraformaldehyde by the method of Delepine [5] in which concentrated sulphuric acid is employed as the catalyst. The layer containing the acetal was dried with potassium carbonate before it was distilled by fractionation to isolate the desired dioxolan from other higher-boiling formals present. The dioxolan was then treated with sodium bisulphite to remove any formaldehyde present and distilled once again from metallic sodium. The final product boiled at 74.2–74.7°C/756 torr and had the following physical properties: $d_4^{20} = 1.0624$, $n_D^{20} = 1.3992$, $[R]_D = 16.87$ (*calc.* 16.97).

2-Methyl-1,3-dioxolan was prepared by the same method from ethylene glycol and paraldehyde. B.p. 81.3–81.8 °C/767 torr, $d_4^{20} = 0.9814$, $n_D^{20} = 1.3972$, $[R]_D = 21.63$ (*calc.* 21.59). The compound has been synthesised by the same method by Hibbert and Timm [6].

4-Methyl-1,3-dioxolan was prepared from propylene glycol and paraformaldehyde as described by Clarke [7]. B.p. 83.7–84.2°C/756 torr, $d_4^{20} = 0.9906$, $n_D^{20} = 1.3989$, $[R]_D = 21.51$ (*calc.* 21.59).

2,2-Dimethyl-1,3-dioxolan was prepared according to Leutner [1] from ethylene glycol and acetone. B.p. 91.1–91.5°C/762 torr, $d_4^{20} = 0.9443$, $n_D^{20} = 1.3980$, $[R]_D = 26.10$ (*calc.* 26.22).

The *cis* and *trans* forms of 2,4-dimethyl-1,3-dioxolan were prepared by heating an acidified mixture of acetaldehyde di-*n*-amyl acetal and propylene glycol and distilling the two isomers from the reaction mixture. The method was the same as that employed by Lucas and Guthrie [8] except that the mixture of isomers obtained was heated under reflux in the presence of *p*-toluenesulphonic acid before the two components were separated by fractionation under alkaline conditions (a Todd precise fractionation assembly was employed). This was done because the method of preparing the two isomers by distilling an acidified mixture of the di-*n*-amyl acetal and propylene glycol undoubtedly favours the formation of the low-boiling isomer. The following physical constants were obtained for the two isomers:

Isomer I, b.p. 90.3–90.5°C/757 torr, $d_4^{20} = 0.9280$, $n_D^{20} = 1.3940$, $[R]_D = 26.33$ (*calc.* 26.22).

Isomer II, b.p. 93.2–93.3°C/759 torr, $d_4^{20} = 0.9322$, $n_D^{20} = 1.3956$, $[R]_D = 26.31$ (*calc.* 26.22).

2,2,4-Trimethyl-1,3-dioxolan was prepared by the same method as 2,2-dimethyl-1,3-dioxolan from acetone and propylene glycol. B.p. 99.6–100.0°C/761 torr, $d_4^{20} = 0.9011$, $n_D^{20} = 1.3946$, $[R]_D = 30.88$ (*calc.* 30.84). This compound has been previously described by Böeseken and Hermans [9].

4,4,5,5-Tetramethyl-1,3-dioxolan was prepared from pinacol and paraformaldehyde as described by Leutner [2]. B.p. 123.8–124.2°C/755 torr, $d_4^{20} = 0.9146$, $n_D^{20} = 1.4120$, $[R]_D = 35.42$ (*calc.* 35.47).

2,4,4,5,5-Pentamethyl-1,3-dioxolan was prepared by the same method from pinacol and paraldehyde. B.p. 133.2–134.0°C/760 torr, $d_4^{20} = 0.8957$, $n_D^{20} = 1.4110$, $[R]_D = 39.98$ (*calc.* 40.09).

Table 1. Dilatometrically determined mean rate coefficients (and their standard deviations) for various derivatives of 1,3-dioxolan at different temperatures.

	10^3k l mole^{-1} s^{-1}		
	10°C	20°C	30°C
2-Methyl-1,3-dioxolan	1.87 ± 0.012	7.13 ± 0.04	25.4 ± 0.1
2,2-Dimethyl-1,3-dioxolan	21.1 ± 0.05	75.5 ± 0.4	264 ± 3
2,4-Dimethyl-1,3-dioxolan (the low-boiling form)	3.02 ± 0.01	11.1 ± 0.1	34.0 ± 0.1
2,4-Dimethyl-1,3-dioxolan (the high-boiling form)	0.793 ± 0.010	2.68 ± 0.02	9.26 ± 0.02
2,2,4-Trimethyl-1,3-dioxolan	22.3 [a] ± 0.3	86.4 ± 0.5	255 [b] ± 1
2,4,4,5,5-Pentamethyl-1,3-dioxolan	0.295 ± 0.003	1.08 ± 0.009	3.36 [b] ± 0.02

[a] temperature 10.06°C [b] temperature 30.13 °C

Kinetic measurements. The rates of the reactions were followed by two procedures. A dilatometric method was employed when following the rates of dioxolan derivatives with one or two methyl groups at position 2 (*i.e.* acetals derived from acetaldehyde and ketals derived from acetone) and a titrimetric method based on the analysis of formaldehyde when following the reactions of dioxolan and its derivatives that did not have substituents at position 2 (*i.e.* acetals derived from formaldehyde).

A) Dilatometric method. The thermostats employed were heated by electricity and cooled with water and equipped with sensitive mercury-toluene regulators that maintained the temperature constant within ± 0.002°C during the experiments. The dilatometers, about 15 ml in capacity, had two capillary tubes of equal diameter (inside diameter about 0.2 mm) and were of the type *C* of Benford and Ingold [10]. After the reaction mixture had been introduced into the dilatometer, one of the capillary tubes was closed with a mercury lock because it was found that the liquid in the two capillary arms did not remain exactly at the same level during the experiments. The reaction mixture was prepared by mixing equal volumes of an aqueous hydrochloric acid solution and an aqueous solution of the dioxolan under study. The mixture was then immediately transferred to the dilatometer by suction. The first reading was taken when temperature gradients had disappeared, about 10 min after the solutions had been mixed. About ten readings were taken during the course of the reaction, generally from 15 to 80 % change, and several readings of the final level. The rate coefficients were computed from the first-order rate equation, which the data for the reactions satisfied fairly well. In some cases the method of Guggenheim [11] for the evaluation of rate coefficients was also applied, in which cases the number of readings taken during the course of the reaction was much larger. Both methods of calculation yielded identical values for the rate coefficients of the compounds examined.

The distilled water employed in preparing the solutions for the dilatometric rate measurements was boiled with potassium permanganate and sulphuric acid to remove

Table 2. The influence of the initial acetal concentration on the dilatometrically measured rate of hydrolysis of 2-methyl-1,3-dioxolan.

°C	20.00	20.00	19.88	19.88	20.00
Initial concn. mole/l	0.069	0.136	0.136	0.265	0.507
10^3k l mole^{-1} s^{-1}	6.83	7.13	6.93	7.25	7.51

Table 3. Mean rate coefficients (and their standard deviations) derived from data obtained by the titrimetric method for the hydrolysis of 1,3-dioxolan and its 4- and 5-substituted methyl derivatives.

	°C	10^4k l mole^{-1} s^{-1}
1,3-Dioxolan	51.34	0.850 ± 0.005
—»—	66.84	5.54 ± 0.04
—»—	82.80	27.9 ± 0.3
4-Methyl-1,3-dioxolan	51.34	1.14 ± 0.008
—»—	66.79	7.26 ± 0.05
—»—	82.82	33.6 ± 0.3
4,4,5,5-Tetramethyl-1,3-dioxolan	67.44	1.49 ± 0.01
—»—	82.80	8.69 ± 0.05
—»—	98.21	37.8 ± 0.3

any organic impurities and distilled after being made alkaline. The hydrogen chloride concentrations of the reaction mixtures varied between 0.002 – 0.05 M depending on the rate of the reaction in question. The initial acetal concentrations were approximately 0.13 M except in the experiments that were carried out to determine the effect of the initial acetal concentration on the rate. Mean values obtained for the rate coefficients of the reactions that were followed dilatometrically at different temperatures are given together with their standard deviations in Table 1. Table 2 shows the results of the study of the effect of the initial acetal concentration on the rate of its hydrolysis. The rate coefficients are seen to have increased with the acetal concentration. As, however, the majority of the experiments was carried out employing relatively low initial acetal concentrations which in addition were approximately equal, this variation with concentration could not appreciably influence the conclusions drawn in a comparison of the rates of reaction of the different acetals.

B) Titrimetric method. This method was based on the titration of the aldehyde liberated in the reaction as in a study of the aliphatic acetals of formaldehyde [12]. In the experiments carried out at temperatures above 50°C, samples of the reaction mixture were sealed in small ampoules employing the same technique as in an earlier study of the hydrolysis of alkyl formates at high temperatures [13]. The mean rate coefficients computed from the titrimetric data are presented in Table 3. Table 4 shows data for three reactions obtained by both the dilatometric and titrimetric methods.

DISCUSSION

Values of the Arrhenius parameters computed by the method of least squares for the hydrolysis of the dioxolan derivatives and the values of the activation entropy at 25°C computed from these are given together with the rate coefficients at 25°C in Table 5. The dioxolan derivatives are grouped according to the parent aldehyde or ketone.

Table 4. Dilatometrically and titrimetrically measured rate coefficients for various derivatives of 1,3-dioxolan. 25°C.

	10^2k l mole^{-1} s^{-1} dilat.	titrim.
2-Methyl-1,3-dioxolan	1.36	1.41
2,4-Dimethyl-1,3-dioxolan (low-boil. form)	1.95	2.08
2,4-Dimethyl-1,3-dioxolan (high-boil. form)	0.507	0.497

Table 5. Values of the parameters of the Arrhenius equation, activation entropies at 25°C and rate coefficients at 25°C for the hydrolysis of 1,3-dioxolan and its methyl-substituted derivatives.

	E kcal/mole	log A	ΔS^* E.U.	$10^4 k$ l mole^{-1}s^{-1}
(*I*) 1,3-Dioxolan	25.48	13.10	− 0.57	0.0265
(*II*) 4-Methyl-1,3-dioxolan	24.68	12.69	− 2.43	0.0402
(*III*) 4,4,5,5-Tetramethyl-1,3-dioxolan	26.43	13.14	− 0.38	0.00592
(*IV*) 2-Methyl-1,3-dioxolan	22.25	14.44	+ 5.57	136
(*V*) 2,4-Dimethyl-1,3-dioxolan (*a*)	20.66	13.43	+ 0.96	195
(*VI*) 2,4-Dimethyl-1,3-dioxolan (*b*)	20.95	13.06	− 0.74	50.7
(*VII*) 2,4,4,5,5-Pentamethyl-1,3-dioxolan	20.63	12.40	− 3.77	18.9
(*VIII*) 2,2-Dimethyl-1,3-dioxolan	21.54	14.95	+ 7.88	1440
(*IX*) 2,2,4-Trimethyl-1,3-dioxolan	20.74	14.37	+ 5.24	1460

[a]) The low-boiling isomer [b]) The high-boiling isomer

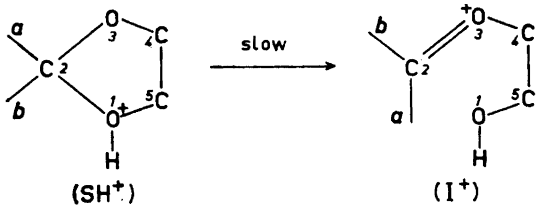
If the rate coefficients at 25°C given in Table 5 for the dioxolans studied by Leutner [1,2] are compared with the rate coefficients reported by the latter author, it is found that the values for the compounds *IV* and *VIII* are in good agreement, but the values for the compounds *I* and *III* differ by 10—15 %. The rate coefficients for the compounds *V*, *VI* and *VII* show very poor agreement. An obvious reason for the dicrepancy in the case of the compounds *V* and *VI* is that Leutner considered these isomers to be a single compound; actually, his rate coefficients decreased some 80 % in value toward the end of the reaction, evidently owing to the different rates of hydrolysis of the two component isomers present.

The activation entropies given in Table 5 are nearly of the magnitude generally found for unimolecular *A-1* reactions [14]. It is thus highly probable that the dioxolans hydrolyse by essentially the same mechanism as acyclic acetals [15]. More reliably this is seen from the observed structural effects although in some respects the latter deviate from those found for the acyclic acetals (*vide infra*).

From the values of Table 5 it is seen that the introduction of a methyl substituent at the carbon 2 of the 1,3-dioxolan ring effects a great increase in the rate of hydrolysis, the rate coefficients of the 2-methyl-substituted dioxolans being from 1 200 to 5 000 times the rate coefficients of the dioxolans with no substituent on carbon 2. The higher rates of hydrolysis of the the 2-methyl dioxolans are primarily due to low activation energies. This parallels the increase in rate by a factor of about $10^{3.5}$ when a methyl substituent is introduced into an aliphatic formal to give the corresponding acetal of acetaldehyde [15]. A rate increase of the same order is observed when a second methyl substituent is added to the same carbon atom as shown by the rates of hydrolysis of the acyclic acetals of acetaldehyde and the ketals of acetone. However, as seen from Table 5, the introduction of a second methyl group into 2-methyl-substituted dioxolans at position 2 leads to an increase in the rate that is of the order of one power of ten. The rates of hydrolysis of 2,2-dimethyldioxolans

are thus exceptionally low; also the activation energies do not decrease in a uniform manner as in the case of the dioxolans derived from formaldehyde and acetaldehyde. Furthermore, it is seen from Table 5 that the introduction of one or more methyl groups at the carbons 4 and 5 in the dioxolan ring has an even more complex effect on the rate of hydrolysis, for in some cases the rate increases slightly, while in other cases, when there are several methyl substituents in the molecule, the rate decreases clearly. A possible explanation for these observations which is based on the stereochemistry of the reaction is presented below.

According to the widely accepted mechanism of acetal hydrolysis [15], the slow, rate-determining stage that follows the proton uptake in the hydrolysis of dioxolans may be written as follows:



(2)

The reaction intermediate I^+ that is formed from the conjugate acid SH^+ of the substrate has a mesomeric structure resonating between the carbonium and oxonium ion structures. As a consequence the 2,3-bond in this intermediate has a partial double-bond character.

As to polar factors, electron-releasing substituents such as alkyl groups should greatly increase the rate when they are located at the reaction centre, the carbon atom 2. Alkyl groups on the carbon atoms 4 and 5 should also increase the rate, although to a much lesser extent. The polar influence of these groups should facilitate the reaction when they are on either side of the bond that is broken in reaction (2) as indicated by the observation that alkyl groups promote the hydrolysis of dialkyl formals both when they are substituents in the stem of the molecule and when they are a part of the leaving group [16]. There is, however, an essential difference between the structural factors that have an influence on the key stage of the hydrolysis in the case of acyclic acetals and the 1,3-dioxolan derivatives. Owing to the partial double-bond character of the 2,3-bond in the ion I^+, the nuclei that are joined by the 2,3-, 3,4-, *a*- and *b*-bonds tend to be in the same plane. From this it follows that in the attainment of the transition state of reaction (2) the bonds *a* and *b* must be bent to a certain extent toward the plane of the dioxolan ring. This cannot be achieved without a certain amount of steric strain whose magnitude depends upon the substituents attached to the ring.

This steric strain readily explains the anomalies observed in the reactions of the 2-methyl-substituted derivatives of 1,3-dioxolan. When a methyl group is introduced into dioxolan at position 2, the increase in the rate of hydrolysis is almost as great as the difference in the rates of an acyclic acetal of formaldehyde and the corresponding acetal of acetaldehyde. In the case of 2-methyldioxolan, it is obviously the bond joining the hydrogen atom to carbon

atom 2 that is bent toward the centre of the dioxolan ring in reaction (2) because this produces much less strain than the bending in this direction of the bond joining the methyl group to the carbon atom 2. The steric strain is thus of the same magnitude as in the reaction of unsubstituted dioxolan and a "normal" rate of hydrolysis is observed. In the case of 2,2-dimethyl-1,3-dioxolan, however, one of the bonds joining a methyl group and carbon atom 2 must be bent toward the dioxolan ring and owing to the size of the methyl group this leads to a much greater steric strain than in the case of a hydrogen atom. Consequently 2,2-dimethyl-1,3-dioxolan hydrolyses at a much lower rate than if only polar effects were decisive as in the case of the corresponding acyclic compounds.

The steric strain effect of methyl substitution at positions 4 and 5 in 1,3-dioxolan may be expected to be quite small compared to the effect of the substitution at position 2 owing to the greater distance from the reaction centre, but even this effect can be distinguished in the data of Table 5. For example, 4,4,5,5-tetramethyl-1,3-dioxolan hydrolyses more slowly than unsubstituted 1,3-dioxolan and 2,4,4,5,5,-pentamethyl-1,3-dioxolan hydrolyses at a lower rate than 2-methyl-1,3-dioxolan. Thus the steric strain effects of the methyl groups overweigh their polar rate-increasing effects that are based on their electron-releasing character. The steric effect of the methyl group does not become evident in the case of 4-methyl-1,3-dioxolan because the reaction may primarily take place by the less demanding of two alternative routes: that of the bonds *a* and *b* which is on the side opposite the 4-methyl group bends toward the ring and this bending does not produce any more strain than that produced in unsubstituted 1,3-dioxolan. As a result the rate is slightly higher than that of 1,3-dioxolan in accordance with the polar character of the methyl group.

The rates of hydrolysis of the geometric isomers of 2,4-dimethyl-1,3-dioxolan provide an interesting illustration of the structural effects just discussed. As the steric strain is more pronounced when substituents are located at carbon atom 2 than when they are in other positions, it is the carbon to hydrogen bond in the above isomers (and in general, in the dioxolans derived from acetaldehyde) that is bent toward the middle of the dioxolan ring in reaction (2). If, now, the 4-methyl group is on the same side of the ring as this bond (*i.e.* in the *trans* form of 2,4-dimethyl-1,3-dioxolan) the 4-methyl group should retard the reaction by its steric influence; in the opposite case (the *cis* form of 2,4-dimethyl-1,3-dioxolan), the steric conditions are similar to those prevailing in the absence of the 4-methyl substituent (*i.e.* in 2-methyl-1,3-dioxolan). As the polar effects may be expected to be similar in both cases, it follows that the *cis* form of 2,4-dimethyl-1,3-dioxolan should hydrolyse faster than the *trans* form. The values of the rate coefficients for the isomers in Table 5 thus lead to the same conclusion about the configurations of these isomers as Barker, Bourne, Pinkard, Stacey and Whiffen [17] arrived at when they compared the properties of these compounds with those of the isomeric dimethyl*cyclo*pentanes whose configurations had been established by another method. The assignment of the *cis* structure to the low-boiling isomer of 2,4-dimethyl-1,3-dioxolan is also in agreement with the results of a study of the *cis-trans* isomerization reactions of these compounds [18].

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