The Acid-Catalyzed Hydrolysis of 2-Phenyl-2,4,4,5,5-pentamethyl-1,3-dioxolane and Tetramethylethylene Glycol Acetals of Aromatic and Aliphatic Aldehydes

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The rates of hydrolysis of several *para*-substituted benzaldehyde acetals of ethanol, ethylene glycol, and tetramethylethylene glycol have been measured in H_2O at 30°. The tetramethylethylene glycol acetals all hydrolyze very slowly in comparison with the other types of acetals. For example, 2-(*p*-methoxyphenyl-4,4,5,5-tetramethyl-1,3-dioxolane has a second-order rate constant 40,000 times less than that for *p*-methoxybenzaldehyde diethyl acetal. The rates of hydrolysis of 2-alkyl-4,4,5,5-tetramethyl-1,3-dioxolanes are also much slower in 50% dioxane–H_2O than those of the corresponding diethyl acetals or 1,3-dioxolanes, and the sensitivity of the rate to inductive effects is less ($\rho^* = -2.2$). The ΔS^* for hydrolysis of 2-(*p*-nitrophenyl)-4,4,5,5-tetramethyl-1,3-dioxolane in aqueous HCl is −15.8 eu. Substitution of a methyl group at the reaction center slows the hydrolysis of tetramethylethylene glycol acetals greatly; 2-phenyl-2,4,4,5,5-pentamethyl-1,3-dioxolane hydrolyzes 540 times more slowly than the corresponding benzaldehyde derivative. Thus, this data in conjunction with data previously reported points strongly to the participation of water in the hydrolysis of the 4,4,5,5-tetramethyl-1,3-dioxolanes with the most likely possibility involving an A2 mechanism.

There is little doubt that the acid-catalyzed hydrolysis of acetals generally involves preequilibrium protonation of the substrate followed by a unimolecular rate-determining decomposition to an alcohol and a resonance-stabilized carbonium ion.[1] It has recently been found in this laboratory, however, that the hydrolysis of certain 2-(*para*-substituted phenyl)-4,4,5,5-tetramethyl-1,3-dioxolanes in water proceeds in a manner markedly different from that of normal acetals.[2] The application of various mechanistic criteria gave evidence which pointed consistently to a mechanism involving solvent participation in the rate-determining step. If water is actively involved in the transition state then possible mechanisms would involve either partially rate-determining protonation by hydronium ion or nucleophilic assistance by water in an A2-type reaction. The A2 mechanism was preferred[2] in view of the extreme slowness of the reactions in comparison with those of analogous diethyl and ethylene glycol acetals of substituted benzaldehydes previously studied in 50% dioxane–H_2O;[3,4] the D_2O solvent isotope effect ($k_{D_2O}/k_{H_2O} = 2.4$) indicated that proton transfer was essentially complete, and the magnitude of the slope of a plot of log $k_{obsd} + H_0$ *vs.* log a_{H_2O} was 1.9. Capon and Thacker[5] recently presented similar data for the hydrolysis of methyl furanosides which can be interpreted in terms of an A2 mechanism, although other possibilities were also considered.

It would be expected that replacement of the hydrogen at the acetal carbon by an alkyl group would markedly reduce the rate if attack by solvent was occurring at that position. The rate of hydrolysis of 2-phenyl-2,4,4,5,5-pentamethyl-1,3-dioxolane has accordingly been measured and has been found to be extremely slow in comparison with that for the corresponding benzaldehyde derivative.

It would appear likely that the differences in behavior between tetramethylethylene glycol acetals and ethylene glycol or diethyl acetals are produced by steric inhibition of the normal A1 reaction by the presence of methyl groups at the 4 and 5 positions of the 1,3-dioxolane ring, thus allowing other mechanisms to become observable. It was therefore of importance to assess the influence of the 2 substituent on these reactions. Accordingly the rates of hydrolysis have been measured for a series of acetals where the 2 substituent is alkyl rather than aryl.

Experimental Section

Materials.—The acetals of substituted benzaldehydes were those previously reported.[2,3] Acetals of aliphatic aldehydes were prepared by the same methods. 2-Propyl-4,4,5,5-tetramethyl-1,3-dioxolane boiled at 77–78° at 28.7 mm, $n^{22}D$ 1.4235. *Anal.* Calcd for $C_{10}H_{20}O_2$: C, 69.72; H, 11.70. Found: C, 69.54; H, 11.82. 2-(β-Chloroethyl)-4,4,5,5-tetramethyl-1,3-dioxolane boiled at 74–75° at 4.8 mm, $n^{25.5}D$ 1.4370. *Anal.* Calcd for $C_9H_{17}ClO_2$: C, 56.10; H, 8.89; Cl, 18.40. Found: C, 56.17; H, 8.95; Cl, 18.22. 2-(β-Phenylethyl)-4,4,5,5-tetramethyl-1,3-dioxolane boiled at 113° at 3.5 mm, $n^{24}D$ 1.4925. *Anal.* Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 76.85; H, 9.34. The sodium salt of 2-(β-carboxyethyl)-4,4,5,5-tetramethyl-1,3-dioxolane was prepared from the corresponding methyl ester (bp 81–84° at 1.9 mm, $n^{25}D$ 1.4380) by a procedure previously described.[6] The salt was recrystallized from an ethanol–ether mixture. *Anal.* Calcd for $C_{10}H_{17}O_4Na$: C, 53.56; H, 7.64. Found: C, 53.65; H, 7.41. 2-Propyl-1,3-dioxolane boiled at 134–140°, $n^{23}D$ 1.4498 (lit.[7] bp 130–135°). Butyraldehyde diethyl acetal had bp 59–60° at 33 mm, $n^{24}D$ 1.3975 (lit.[8] bp 143–144°).

2-Phenyl-2,4,4,5,5-pentamethyl-1,3-dioxolane was prepared by a ketal interchange method. Equivalent amounts of acetophenone, ethyl orthoformate, and tetramethylethylene glycol were allowed to stand for 12 hr in the presence of a trace of *p*-toluenesulfonic acid. Ethanol was then slowly distilled from the reaction mixture. When all of the ethanol had been removed the residue was taken up in benzene and washed with 0.1 *M* NaOH solution. The benzene extract was dried over sodium sulfate. The benzene was then evaporated, and the liquid residue was distilled. The product boiled at 77–78° at 1.2 mm, $n^{24}D$ 1.4890. *Anal.* Calcd for $C_{14}H_{20}O_2$: C, 76.32; H, 9.15. Found: C, 76.41; H, 9.27.

Dioxane was purified by the method of Fieser.[9] Acetonitrile

(1) For the evidence which has led to this mechanism and the pertinent references, see E. H. Cordes in "Progress in Physical Organic Chemistry," Vol. 4, A. Streitwieser, Jr., and R. W. Taft, Ed., John Wiley & Sons, Inc., New York, N. Y., 1967, p 1.

(2) T. H. Fife, *J. Amer. Chem. Soc.*, **89**, 3228 (1967).

(3) T. H. Fife and L. K. Jao, *J. Org. Chem.*, **30**, 1492 (1965).

(4) T. H. Fife and Lily Hagopian, *ibid.*, **31**, 1772 (1966).

(5) B. Capon and D. Thacker, *J. Chem. Soc., B.*, 185 (1967).

(6) T. H. Fife, *J. Amer. Chem. Soc.*, **87**, 271 (1965).

(7) M. J. Astle, J. A. Zaslowesky, and P. G. Lafytis, *Ind. Eng. Chem.*, **46**, 787 (1954).

(8) S. M. McElvain, R. L. Clarke, and G. D. Jones, *J. Amer. Chem. Soc.*, **64**, 1966 (1942).

(9) L. F. Fieser, "Experiments in Organic Chemistry," 3rd ed, D. C. Heath and Co., Boston, Mass., 1955, p 284.

was Eastman Kodak Spectrograde and was further purified by twice distilling it from P_2O_5 and once from K_2CO_3.

Kinetic Measurements.—The equipment and procedures were the same as previously employed.[2,3] The rates were measured spectrophotometrically on a Zeiss PMQ11 spectrophotometer by following the appearance of the aldehyde or ketone product. The acetals were dissolved in dioxane, and the rates were initiated by adding 1 drop of this solution to 3.5 ml of acidic solution in the cuvette with a calibrated dropping pipet and vigorous stirring. The cuvette was then stoppered tightly with a Teflon stopper. At the conclusion of each reaction the ultraviolet spectrum of the solution was found to be identical with that of the appropriate aldehyde. For rate measurements in the presence of various salts the acetals were dissolved in acetonitrile, and 1 drop was added to the solution in the cuvette.

Results

The rates of hydrolysis of several *para*-substituted benzaldehyde acetals of ethanol, ethylene glycol, and tetramethylethylene glycol have been measured in aqueous solutions at 30°. The data are reported in Table I. It can be seen that the tetramethylethylene glycol acetals hydrolyze in each case much more slowly than the corresponding ethylene glycol or diethyl acetal. Replacing the hydrogen at the acetal carbon by a methyl group in the case of 2-phenyl-2,4,4,5,5-pentamethyl-1,3-dioxolane further reduces the rate by a factor of 540 compared with 2-phenyl-4,4,5,5-tetramethyl-1,3-dioxolane.

TABLE I

RATES OF HYDROLYSIS OF SUBSTITUTED BENZALDEHYDE ACETALS OF ETHANOL, ETHYLENE GLYCOL, AND TETRAMETHYLETHYLENE GLYCOL IN H_2O AT 30°

Acetal	pH	k_{obsd}, min^{-1}	k_H,[a] l. mol^{-1} min^{-1}	k_{rel}[b]
(a) 2-(*p*-Methoxyphenyl)-4,4,5,5-tetramethyl-1,3-dioxolane[c]	1.0[d]	0.400	4.00	1.0
(b) 2-(*p*-Methoxyphenyl)-1,3-dioxolane	3.07[e]	3.50	4,113	1,030
(c) *p*-Methoxybenzaldehyde diethyl acetal	5.25[f]	0.901	160,000	40,000
(d) 2-Phenyl-4,4,5,5-tetramethyl-1,3-dioxolane[c]	1.0[d]	0.0739	0.739	1.0
(e) 2-Phenyl-2,4,4,5,5-pentamethyl-1,3-dioxolane	0[g]	0.00137	0.00137	0.00185
(f) 2-Phenyl-1,3-dioxolane	3.07[e]	0.215	252.6	342
(g) Benzaldehyde diethyl acetal	3.55[h]	3.81	13,510	18,280

[a] k_{obsd}/a_H. [b] Relative rate ratios within each series where the *para* substituent is the same for all compounds. [c] Data from ref 2. [d] 0.1 *M* HCl. [e] HCl solution, $\mu = 0.1$ *M* with KCl. [f] Acetate buffer; buffer catalysis was not observed; $\mu = 0.1$. [g] 1.0 *M* HCl. [h] Formate buffer; buffer catalysis was not observed; $\mu = 0.1$.

A series of 2-alkyl-4,4,5,5-tetramethyl-1,3-dioxolanes was studied in 50% dioxane–H_2O. The rates of hydrolysis are presented in Table II. The 2-propyl derivative hydrolyzes much more slowly than the ethylene glycol or diethyl acetal, but the effect of methyl group substitution in the 1,3-dioxolane ring is less marked than when the substituent at the 2 position is substituted phenyl. The four tetramethylethylene glycol acetals studied gave a linear plot of log k_{obsd} at one acid concentration *vs.* σ^*, the Taft substituent constant,[10] shown in Figure 1 with a slope, ρ^*, of -2.2.

The smaller relative rate differences for the 2-alkyl compared with the 2-aryl derivatives are at least partly due to the change in solvent from H_2O to 50% dioxane–H_2O. In Table III are given rate constants and relative rate ratios for hydrolysis of the various benzaldehyde acetals in 50% dioxane–H_2O. It can be seen that the differences in rate are less pronounced in 50% dioxane–H_2O than in H_2O. This is due to the organic solvent mixture having a smaller rate-retarding effect on the hydrolysis of the tetramethylethylene glycol acetal.

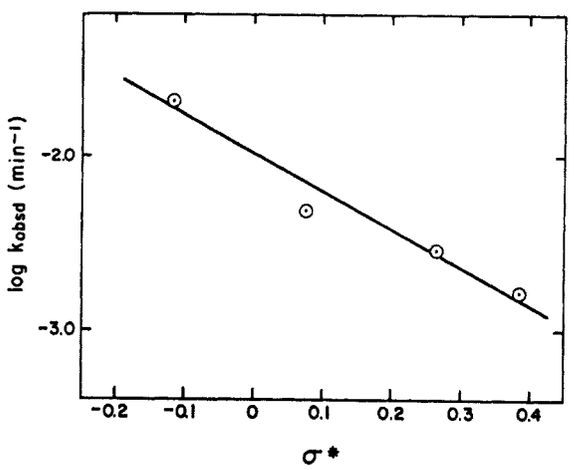


Figure 1.—Plot of log k_{obsd} *vs.* σ^* for hydrolysis of 2-alkyl-4,4,5,5-tetramethyl-1,3-dioxolanes in 50% dioxane–H_2O at 30° and pH 0.30.

TABLE II

RATES OF HYDROLYSIS OF ACETALS OF ALIPHATIC ALDEHYDES IN 50% DIOXANE–H_2O AT 30°

Acetal	σ^*[a]	pH	k_{obsd}, min^{-1}	k_H,[b] l. mol^{-1} min^{-1}	k_{rel}
(a) Butyraldehyde diethyl acetal		2.37	0.122	28.5	695.1
(b) 2-Propyl-1,3-dioxolane		0.30[c]	0.289	0.578	14.1
(c) 2-Propyl-4,4,5,5-tetramethyl-1,3-dioxolane	−0.115	0.30[c]	0.0207	0.041	1.0
(d) 2-(β-Phenylethyl)-4,4,5,5-tetramethyl-1,3-dioxolane	0.08	0.30[c]	0.00483	0.0097	
(e) 2-(β-Carboxyethyl)-4,4,5,5-tetramethyl-1,3-dioxolane	0.265[d]	0.30[c]	0.0026	0.0052	
(f) 2-(β-Chloroethyl)-4,4,5,5-tetramethyl-1,3-dioxolane	0.385	0.30[c]	0.00166	0.0033	

[a] Reference 10. [b] k_{obsd}/a_H. [c] 1.0 *M* HCl–dioxane (v/v). [d] A σ^* of +2.94 was reported for the undissociated carboxyl group,[10] but T. C. Bruice and D. Piszkiewicz [*J. Amer. Chem. Soc.*, 89, 3568 (1967)] found that a value of +2.08 gave a better fit to their data. Therefore, the value of σ^* employed in the present study was $2.08/(2.8)^2$ since Taft[10] recommended 2.8 as the factor for attenuation of the inductive effect per methylene group interposed between the substituent and the reaction center.

TABLE III

RATE CONSTANTS FOR HYDROLYSIS OF ACETALS IN 50% DIOXANE–H_2O (v/v) AT 30°

Compound	pH	k_{obsd}, min^{-1}	k_H, l. mol^{-1} min^{-1}	k_{rel}
Benzaldehyde diethyl acetal[a]	4.12	0.0549	723.3	4465
2-Phenyl-1,3-dioxolane[a]	2.36	0.111	25.4	157
2-Phenyl-4,4,5,5-tetramethyl-1,3-dioxolane	0.30[b]	0.0812	0.162	1.0
2-Phenyl-2,4,4,5,5-pentamethyl-1,3-dioxolane	*c*	0.00124	0.0005	0.003

[a] Reference 3. [b] 1.0 *M* HCl–dioxane (v/v). [c] 4.80 *M* HCl–dioxane (v/v).

(10) R. W. Taft, Jr., in "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley & Sons, Inc., New York, N. Y., 1956, p 556.

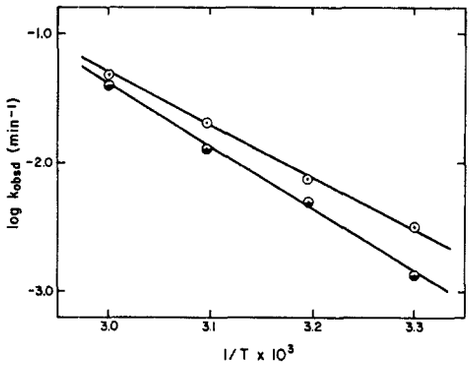


Figure 2.—Plot of log k_{obsd} *vs.* $^1/_T$° *K* for hydrolysis of 2-(*p*-nitrophenyl)-4,4,5,5-tetramethyl-1,3-dioxolane in 0.1 *M* HCl, ⊙, and 2-phenyl-2,4,4,5,5-pentamethyl-1,3-dioxolane in 1.0 *M* HCl, ◒.

The hydrolysis of 2-(*p*-nitrophenyl)-4,4,5,5-tetramethyl-1,3-dioxolane in 0.1 *M* HCl and the hydrolysis of 2-phenyl-2,4,4,5,5-pentamethyl-1,3-dioxolane in 1.0 *M* HCl was studied as a function of temperature. Rates were determined at 30, 40, 50, and 60° (±0.1). Rates were measured in triplicate at each temperature with an average deviation of less than 2% in each case. The rate constants are given in Table IV, and plots of

TABLE IV

RATE CONSTANTS (k_{obsd}, min^{-1}) FOR HYDROLYSIS OF 2-(*p*-NITROPHENYL)-4,4,5,5-TETRAMETHYL-1,3-DIOXOLANE IN 0.1 *M* HCl AND 2-PHENYL-2,4,4,5,5-PENTAMETHYL-1,3-DIOXOLANE IN 1.0 *M* HCl AT VARIOUS TEMPERATURES

Compound	Temp, °C	k_{obsd}, min^{-1}
2-(*p*-Nitrophenyl)-4,4,5,5-tetramethyl-1,3-dioxolane	30	0.0032
	40	0.0076
	50	0.0207
	60	0.0490
2-Phenyl-2,4,4,5,5-pentamethyl-1,3-dioxolane	30	0.00137
	40	0.00505
	50	0.0132
	60	0.0394

log k_{obsd} *vs.* $^1/_T$ are shown in Figure 2. Activation parameters were determined and are reported in Table V. The errors reported in ΔH^* and ΔS^* were calculated from the standard error of the plot of ln k_{obsd} *vs.* $^1/_T$. A highly negative value of ΔS^* (−15.8 eu) was found for the *p*-nitro derivative.

TABLE V

ACTIVATION PARAMETERS FOR HYDROLYSIS OF TETRAMETHYLETHYLENE GLYCOL ACETALS IN H_2O

Compound	ΔH^*, kcal/mol	ΔS^*, eu[a]
2-Phenyl-4,4,5,5-tetramethyl-1,3-dioxolane[b]	16.1 ± 0.5	−14.2 ± 1.7
2-(*p*-Nitrophenyl)-4,4,5,5-tetramethyl-1,3-dioxolane	17.5 ± 0.3	−15.8 ± 0.9
2-Phenyl-2,4,4,5,5-pentamethyl-1,3-dioxolane	21.6 ± 0.4	−8.6 ± 1.2

[a] Calculated at 30° with the rate constant having the units of l. mol^{-1} sec^{-1}. [b] Reference 2.

In Table VI rate constants are given for hydrolysis of the acetals in aqueous HCl with various salts added. High concentrations of iodide ion in 0.01 *M* HCl increase the rate of hydrolysis of 2-(*p*-methoxyphenyl)-4,4,5,5-tetramethyl-1,3-dioxolane to a greater extent than equal concentrations of the less nucleophilic chloride or perchlorate ion, but the magnitude of the effect is fairly small. From the similarity of the rate constants with added chloride, bromide, or perchlorate ion it would appear that these ions are influencing the reaction primarily by an ionic strength effect.

Discussion

The tetramethylethylene glycol acetal of *p*-methoxybenzaldehyde hydrolyzes in water approximately 1030 times more slowly than the corresponding ethylene glycol derivative and 40,000 times more slowly than the corresponding diethyl acetal. The relative rate ratios are less for the unsubstituted compound, but it can be seen in Table I that introduction of methyl groups into the 4 and 5 positions of the 1,3-dioxolane ring has still resulted in an extremely large rate retardation. These rate differences are also found when the substituent at the 2 position is alkyl rather than aryl, although the effects are less pronounced. From the data in Table II it can be seen that 2-propyl-4,4,5,5-tetramethyl-1,3-dioxolane hydrolyzes 695 times more slowly than the corresponding diethyl acetal in 50% dioxane–H_2O. The large rate differences observed with the *p*-methoxyphenyl derivatives are due in part to the fact that the *p*-methoxy group enhances the rate of hydrolysis of the diethyl acetal by resonance interaction with the incipient carbonium ion in the transition state,[3] whereas such a facilitating effect is absent in the case of the tetramethylethylene glycol acetal.[2] Still, other factors must also be of great importance as evidenced by the relatively slow rates of hydrolysis of the 2-alkyl-4,4,5,5-tetramethyl-1,3-dioxolanes.

A plot of the logarithms of the rate constants for hydrolysis of the 2-(substituted phenyl)-4,4,5,5-tetramethyl-1,3-dioxolanes *vs.* σ, the Hammett substituent constant,[11] was found to be linear[2] with a ρ of −2.0 in contrast to the marked upward curvature found for *para*-substituted benzaldehyde diethyl acetals and ethylene glycol acetals;[3] by employing *meta* substituents ρ was found to be −3.35 for hydrolysis of those compounds.[3] The linearity of the relationship with σ in the case of the tetramethylethylene glycol acetals and the less negative value of ρ compared with that for diethyl acetals indicated that the transition state had much less carbonium ion character. Nucleophilic attack by solvent at the reaction center would also result in a more positive value of ρ.

When the substituent at the 2 position is alkyl, the sensitivity of the reaction to polar effects is also considerably smaller with the tetramethylethylene glycol acetals. The ρ^* of −2.2 is much less negative than the value of −3.60 found for hydrolysis of diethyl acetals in 50% dioxane–H_2O.[12] The smaller sensitivity to inductive effects with the 2-alkyl-4,4,5,5-tetramethyl-1,3-dioxolanes is similar to that found in the substituted benzaldehyde series and also indicates that the transition state for hydrolysis of these tetramethylethylene glycol acetals of aliphatic aldehydes has less carbonium

(11) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, Chapter VII; H. H. Jaffé, *Chem. Rev.*, **53**, 191 (1953).

(12) M. M. Kreevoy and R. W. Taft, Jr., *J. Amer. Chem. Soc.*, **77**, 5590 (1955).

TABLE VI

RATE CONSTANTS (min^{-1}) FOR HYDROLYSIS OF ACETALS IN HCl SOLUTIONS CONTAINING VARIOUS SALTS AT 0.2 *M*

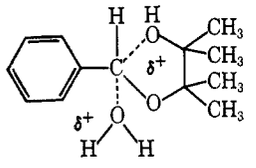
Acetal	HCl	$NaClO_4$	NaCl	NaBr	NaSCN	NaI
2-(*p*-Methoxyphenyl)-4,4,5,5-tetramethyl-1,3-dioxolane[a]	0.1 *M*					
	0.400[b]	0.469	0.451	0.469	0.497	0.490
	0.01 *M*					
	0.0419					0.0475[c]
		0.0469	0.0460			0.0530
		0.0539[d]	0.0499[d]			0.0649[d]
	0.1 *M*					
2-(*p*-Nitrophenyl)-4,4,5,5-tetramethyl-1,3-dioxolane[e]	0.0207	0.0214	0.0216	0.0224	0.0241	

[a] Data obtained at 30°. [b] Data from ref 2. [c] 0.01 *M* HCl, 0.1 *M* NaI. [d] 0.01 *M* HCl, 0.4 *M* salt. [e] Data obtained at 50°.

ion character than in the cases of the corresponding diethyl acetals. The 2-propyl derivative, however, does hydrolyze four times more slowly than 2-phenyl in 50% dioxane–H_2O. This result can best be explained on the basis of resonance effects by the phenyl substituent,[12] and shows that the acetal carbon must still have at least some positive charge in the transition state. However, the small rate difference of 4 can be contrasted with the factors of 25 and 44 for hydrolysis of the butyraldehyde and benzaldehyde diethyl and ethylene glycol acetals.

Other pronounced differences in hydrolytic behavior were also found between the various types of substituted benzaldehyde acetals,[2] and general acid catalysis was observed in the hydrolysis of 2-(*p*-methoxyphenyl)-4,4,5,5-tetramethyl-1,3-dioxolane in formic acid buffers. These differences pointed strongly to a change in mechanism due to methyl substitution in the 1,3-dioxolane ring with the most likely possibility being an A2 reaction involving attack of water on the protonated acetal.

The large rate decrease (540 times) produced by replacing the hydrogen at the acetal carbon by a methyl group in 2-phenyl-2,4,4,5,5-pentamethyl-1,3-dioxolane strongly suggests that attack by solvent is taking place at that position during hydrolysis of the acetals as in mechanism 1. Acetophenone diethyl ketal hy-



(1)

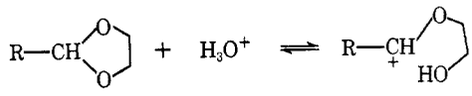
drolyzes faster than benzaldehyde diethyl acetal, the reaction proceeding by an A1 mechanism.[4] 2-Phenyl-2-methyl-1,3-dioxolane does hydrolyze more slowly than 2-phenyl-1,3-dioxolane but only by a factor of 5.[4] Thus, in terms of an A1 mechanism it would be expected that methyl group substitution at the reaction center would accelerate the reaction since polar effects of the methyl group would stabilize an intermediate carbonium ion or, perhaps since a 1,3-dioxolane ring is opening, the rate would be only slightly reduced. It might also reasonably be expected that the methyl group would facilitate the rate if partially rate-determining proton transfer to oxygen from hydronium ion was occurring as in the hydrolysis of ortho esters.[13] Since the reaction center probably does bear some positive charge in the transition state it is likely that bond breaking is proceeding to a greater extent than bond making with solvent, in mechanism 1.

(13) C. A. Bunton and R. H. DeWolfe, *J. Org. Chem.*, **30**, 1371 (1965).

The ΔS^* of −15.8 eu found in this study for the hydrolysis of 2-(*p*-nitrophenyl)-4,4,5,5-tetramethyl-1,3-dioxolane is further evidence for the involvement of solvent in the rate-determining step. Positive entropies of activation have been observed in numerous instances for reactions involving unimolecular decomposition of a protonated intermediate, while reactions in which solvent participates should have ΔS^* values that are highly negative.[14,15] A value of −15.8 eu is clearly more in accord with solvent involvement than with a unimolecular rate-determining step. It is of interest that ΔS^* becomes more negative as electron withdrawal by the *para* substituent becomes greater.

The ΔS^* of −8.6 eu for hydrolysis of 2-phenyl-2,4,4,5,5-pentamethyl-1,3-dioxolane is similar to that observed for ethylene glycol acetals and ketals.[3,4] The transition state for hydrolysis of that compound may therefore have considerably more unimolecular character than is the case with the other tetramethylethylene glycol acetals. This would be reasonable since the presence of the methyl group would strongly inhibit nucleophilic attack. If this is indeed the case then a semiquantitative assessment of the ability of the tetramethyl-1,3-dioxolane ring system to inhibit A1 hydrolysis with aromatic derivatives is possible since the second-order rate constant for hydrolysis of the tetramethylethylene glycol derivative of acetophenone is 10^7 times less than that of benzaldehyde diethyl acetal. Acetophenone diethyl ketal was not sufficiently soluble in H_2O for accurate measurement of its rate of hydrolysis in that solvent, but in 50% dioxane–H_2O it was found to hydrolyze 33 times faster than benzaldehyde diethyl acetal.[4] Therefore, if the reasonable assumption is made that the ratio of the rate constants would be approximately the same in H_2O, then 2-phenyl-2,4,4,5,5-pentamethyl-1,3-dioxolane is 3×10^8 times less reactive than acetophenone diethyl ketal.

Capon and Thacker[5] suggested that the slightly negative ΔS^* values for hydrolysis of 2-substituted 1,3-dioxolanes[3] and furanosides[5] might result from reversibility of an initial ring-opening step so that $k_{obsd} = k_2K$, where K is the equilibrium constant for ring



(2)

opening and k_2 is the rate constant for reaction of water with the oxocarbonium ion intermediate.

A similar argument can be advanced for incursion of attack by solvent on the protonated acetal with the

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tetramethylethylene glycol acetals. Geminal methyl group substitution at the 4 and 5 positions of the 1,3-dioxolane ring would greatly favor reclosure of the ring, if unimolecular C–O bond breaking was occurring, by restricting unfavorable rotation of the alcohol group away from the carbonium ion center. Since the alcohol group is held in close proximity to the carbonium ion, reaction of the carbonium ion with water might not be able to compete with ring closure. If ring closure to form starting material from a carbonium ion intermediate is extremely facile, then the reaction might only proceed readily to products if bond making with a water molecule can occur before the leaving group is completely free, *i.e.*, without formation of a carbonium ion as a discrete intermediate in the ring-opening reaction (1). Thus an A2-type reaction would allow products to be formed but at a very slow rate which, of course, is observed.

The lack of large anion effects is in accord with this explanation. The anions studied differ greatly in their ability to act as nucleophiles,[16] but the α-halo ethers that would be formed by nucleophilic attack of a halide anion on the protonated acetal would ionize rapidly to carbonium ion[17] which then could undergo a fast ring closure to regenerate the starting material. Thus, anion effects should be small and might only be observable with very powerful nucleophiles such as iodide ion.

The lack of large anion effects in these reactions is also in accord with a mechanism involving partially rate-determining protonation of the acetal by hydronium ion. Such a mechanism very likely occurs with acetals in which there is strong electron withdrawal in the leaving group so that basicity is greatly reduced while C–O bond breaking is facilitated.[18] Thus it has recently been found that for hydrolysis of 2-(*p*-nitrophenoxy)tetrahydropyran the D_2O solvent isotope effect is close to unity and a pronounced general acid catalysis by formic acid can be observed, while with 2-(*p*-methoxyphenoxy)tetrahydropyran the ratio k_D/k_H is 2.48 and general acid catalysis can not be detected.[18] In the case of the tetramethylethylene glycol acetals, however, where strong electron withdrawal in the leaving group is not present, there is no reason to suspect that basicity has been significantly reduced.[19] Also the magnitude of the D_2O solvent isotope effect[2] and the large rate retardation produced by methyl group substitution at the reaction center provide strong arguments against the occurrence of rate-determining protonation in these reactions. Therefore, while slow protonation cannot be conclusively ruled out at this time for the tetramethylethylene glycol acetals, the bulk of the evidence points to the A2 mechanism 1.

The evidence in accord with an A2 mechanism lends support to the possibility that the weak general acid catalysis by formate buffer observed with 2-(*p*-methoxyphenyl)-4,4,5,5-tetramethyl-1,3-dioxolane involves nucleophilic attack by formate ion on the protonated acetal. Favorable pathways not involving a carbonium ion are, of course, available for decomposition of an acylal intermediate to aldehyde in acidic solution.[20]

Registry No.—Table I (b), 2403-50-1; Table I (c), 2403-58-9; Table I (e), 17414-56-1; Table I (f), 936-51-6; Table I (g), 774-48-1; Table II (a), 3658-95-5; Table II (b), 3390-13-4; Table II (c), 17396-24-6; Table II (d), 17396-25-7; Table II (e), 17396-26-8; Table II (f), 7451-02-7; 2-phenyl-4,4,5,5-tetramethyl-1,3-dioxolane, 1831-57-8; 2-(*p*-nitrophenyl)-4,4,5,5-tetramethyl-1,3-dioxolane, 16837-06-2; 2-(*p*-methoxyphenyl)-4,4,5,5-tetramethyl-1,3-dioxolane, 16825-51-7.

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(19) Steric hindrance to solvation of the conjugate acids might result in some reduction in basicity, but if hindrance to solvation was an important factor in these reactions more positive ΔS^* values would result in comparison with those found for normal acetals rather than the much more negative values actually observed.

(20) P. Salomaa, *Acta Chem. Scand.*, **11**, 239 (1957).