duplicate the remarkable specific biological hydroxylations of which there are abundant examples.[11-13]

Experimental Section

Analyses by Gas Chromatography. All gas chromatograms (gc) were obtained on a Barber-Colman Series 5000 instrument equipped with a flame ionization detector. The fuel gas was a mixture of hydrogen and air, and the carrier gas was nitrogen. The glass U columns were 0.25 in. × 6 ft.

For the cyclohexane and cyclohexyl trifluoroacetate analyses, 3% SE 30 on 45–60 Gas Chrom W was used at 90° with 3-hexyl trifluoroacetate (bp 128–129°) as an internal standard. For the detection of cyclohexanone, an EGSS-X column was used as well as the SE-30 column. For the decyl trifluoroacetates and the bistrifluoroacetates of 1,*x*-octanediols, 20% SE 30 on 80–100 Gas Chrom W was used at 150°. Flow rates were 23 ml min^{-1}.

Gc Standards for Bistrifluoroacetates of 1,*x*-Octanediols. Mixtures of chloro-1-octanols were available from a previous study.[1] These were converted into a mixture of octanediols by refluxing with 10% aqueous KOH for 3 days. The octanediols were converted into diacetates by treatment with acetic anhydride at 100°. The diacetates had retention times on SE-30 in the same order as the chloro-1-octyl acetates[1] and with the same relative band areas. This shows that the mixture retained the same proportions during hydrolysis. Part of the octanediol mixture was converted into the bistrifluoroacetates, and their relative retention times are summarized in Table II. Identification rested on identity of gc retention times, separately and in mixtures.

Heptyl Trifluoroacetate Gc Standards. 1-Heptanol was commercially available and was converted into the trifluoroacetate by mixing with CF_3COOH. The three heptanones (2, 3, and 4) were commercially available. They were reduced to the alcohols with $NaBH_4$ in ethanol and the alcohols converted into the trifluoroacetates. Relative retention times are listed in Table III. Identification rested on identity of gc retention times, separately and in mixture. No trace of heptanones could be detected by gc in the heptyl trifluoroacetate products.

Decyl Trifluoroacetate Gc Standards. All five decanols were commercially available and were converted into the trifluoroacetates by mixing with CF_3COOH. Relative retention times are listed in Table III. Identification rested on identity of gc retention times, separately and in mixtures.

Triethylamine Oxide. This was prepared by a procedure similar to that reported.[14,15] To a solution of 20 g (0.20 mol) of Et_3N in 20 ml of methanol, 45 ml (0.40 mol) of cold 30% H_2O_2 was slowly added. An ice bath was used to keep the temperature below 25°. After standing for 24 hr, excess H_2O_2 was destroyed by adding MnO_2 and stirring until O_2 evolution ceased. The solution was filtered to remove MnO_2, extracted with diethyl ether to remove Et_3N, and concentrated to a syrup under vacuum. The nmr spectrum of Et_3NO consists of a quartet at δ 3.18 and a triplet at 1.17. Also present was a singlet at δ 4.90 due to H_2O. This decreased with pumping. The reagent used for the oxidations had the composition $Et_3NO \cdot 1.1H_2O$.

Oxidation of Cyclohexane. A heterogeneous mixture of 10 mmol of cyclohexane, 10 mmol of Et_2NOH (or Et_3NO), 10 mmol of $FeSO_4 \cdot 7H_2O$, and 40 ml of CF_3COOH was stirred and heated at 65–72° for 24 hr. The product was isolated by addition of the reaction mixture to water, ether extraction, washing the extract with water and 10% aqueous Na_2CO_3, and distillation. Several such runs were combined to give a 25% yield of distilled cyclohexyl trifluoroacetate. This was identified by boiling point (identical with the 148–149° reported),[16] gc retention time, and nmr spectrum which was identical in every detail [broad band δ 4.97 (α-H); complex multiplet 0.7–1.3 (10 H)] with that of a sample prepared from cyclohexanol and CF_3COOH.

Oxidations of 1-Octyl Trifluoroacetate, Heptane, and Decane. These were conducted in a manner identical with that used with cyclohexane except that 25 mmol of Et_2NOH or Et_3NO was used. It was important to conduct the isolation rapidly and cold to avoid hydrolysis. Any alcohols arising from hydrolysis could be converted back into trifluoroacetates by addition of a little trifluoroacetic anhydride.

Acknowledgment. This work was supported by a grant from the National Science Foundation.

(11) C. W. Bird and P. M. Molton, "Topics in Lipid Chemistry," Vol. 3, F. D. Gunstone, Ed., Elek Science, London, 1972, p 125.
(12) D. F. Jones and R. Howe, *J. Chem. Soc.*, 2801 (1968).
(13) G. S. Fonken and R. A. Johnson, "Chemical Oxidations with Microorganisms," Marcel Dekker, New York, N. Y., 1972.
(14) J. P. Ferris, R. D. Gerwe, and G. R. Gapski, *J. Org. Chem.*, **33**, 3493 (1968).
(15) S. N. Lewis, "Oxidation," Vol. I, R. L. Augustine, Ed., Marcel Dekker, New York, N. Y., 1969, p 248.
(16) H. A. Staab and G. Walther, *Angew. Chem.*, **72**, 35 (1960).

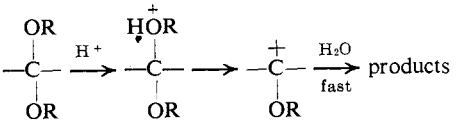
Substituent Effects in Acetal Hydrolysis

Victor P. Vitullo,* Ralph M. Pollack,* William C. Faith, and Mark L. Keiser

Contribution from the Department of Chemistry, University of Maryland, Baltimore County, Baltimore, Maryland 21228. *Received April 22, 1974*

Abstract: The rates of acid-catalyzed hydrolysis of five para-substituted 2-phenyl-2-methyl-1,3-dioxolanes have been measured in aqueous HCl solution at 25°. The rate constants correlate well with the Yukawa–Tsuno equation, giving $\rho = -2.9$ and $r = 0.3$. On the basis of these values, an explanation is advanced to account for the fact that an anomalously small rate increase is observed for 2-phenyl-2-methyl-1,3-dioxolane hydrolysis over 2-methyl-1,3-dioxolane hydrolysis.

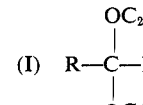
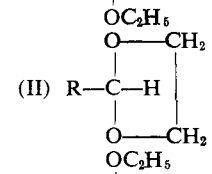
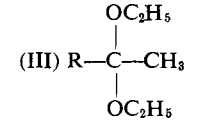
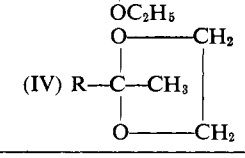
The mechanism of the acid-catalyzed hydrolysis of acetals and ketals has been the subject of numerous investigations as this process is an excellent model for the action of lysozyme and other glycosidases. In spite of the fact that the main features of the overall mechanism are well understood,[1] there are many aspects which have not as yet been satisfactorily explained.



A particularly perplexing set of observations is the effect of phenyl substitution at the pro-acyl carbon.[2]

(1) E. H. Cordes, *Progr. Phys. Org. Chem.*, **4**, 1 (1967).
(2) The term pro-acyl carbon has been proposed by Kresge[3] to refer to the carbon atom which becomes the acyl carbon after hydrolysis.
(3) Y. Chiang, A. J. Kresge, P. Salomaa, and C. I. Young, *J. Amer. Chem. Soc.*, **96**, 4494 (1974).

Table I. Effects of Methyl and Phenyl Substituents on the Rate of Acid-Catalyzed Hydrolysis of Acetals and Ketals

Compd	$k_{R=CH_3}/k_{R=H}$	$k_{R=C_6H_5}/k_{R=H}$	$k_{R=C_6H_5}/k_{R=CH_3}$	$\rho_{R=C_6H_4X}$	r
(I) 	6×10^3 [a]	1.7×10^6 [a]	3×10^1	-3.35 [b]	0.5 [b]
(II) 	5×10^3 [c]	2.7×10^5 [d]	5.4×10^1	-3.25 [b]	0.5 [b]
(III) 	3×10^3 [a]	9×10^2 [a,e]	0.3	-2.29 [f]	0.13 [f]
(IV) 	1×10^1 [c]	4×10^1 [g]	4	-2.9 [g]	0.3 [g]

[a] 49.6% aqueous dioxane at 25°: M. M. Kreevoy and R. W. Taft, Jr., *J. Amer. Chem. Soc.*, **77**, 5590 (1955). [b] 50% aqueous dioxane at 30°: T. H. Fife and L. K. Jao, *J. Org. Chem.*, **30**, 1492 (1965), and ref 1. [c] Water at 30°: ref 5. [d] Water at 30°: O. Cedar, *Ark. Kemi*, **6**, 523 (1954). [e] 50% aqueous dioxane at 30°: ref 4. [f] Dimethyl ketals in 5% dioxane at 30°: G. M. Loudon and C. Berke, *J. Amer. Chem. Soc.*, **96**, 4508 (1974). [g] Water at 25°: this work and ref 5.

Table I gives values for the replacement of hydrogen by phenyl in a series of acetals and ketals. For replacement of hydrogen by phenyl in formaldehyde acetals (series I and II), the rate increase is quite large (>10^5-fold) as expected for a process leading to a carbonium ion. For diethyl acetals of acetaldehyde (III), the effect of phenyl substitution is substantially reduced (*ca.* 10^3-fold). Finally, and most striking, phenyl substitution in the acetal from ethylene glycol and acetaldehyde (IV) gives a rate increase of only 40-fold.

Fife and Hagopian[4] have suggested that the substituent effects in IV might be due to steric inhibition of resonance, but they were unable to rule out specific steric interactions between the methyl group at the proacyl carbon and the dioxolane ring in the transition state.[5] In order to differentiate between these two possibilities, we prepared a series of ring-substituted 2-phenyl-2-methyl-1,3-dioxolanes and hydrolyzed them in acid solutions.

Results and Discussion

The rates of hydrolysis of the ethylene ketals of acetophenone and four para-substituted acetophenones were measured at 25.0 ± 0.2° in HCl solutions at an ionic strength of 1.0 *M* (NaCl). Pseudo-first-order rate constants were measured spectrally at two acid concentrations differing by at least a factor of 5. The second-order rate constants are given in Table II. Attempts at correlating these rates with either σ or σ^+ values[6,7] resulted in distinct curvature in the plots of log k *vs.* the substituent constant. Use of the Yukawa–Tsuno equation[8] (eq 1) gave a linear relationship with $\rho = -2.9$ and $r = 0.3$. These results, along with other relevant data, are given in Table I.

$$\log k = \rho[\sigma + r(\sigma^+ - \sigma)] \quad (1)$$

Table II. Rates of Acid-Catalyzed Hydrolysis of Para Substituted 2-Phenyl-2-methyl-1,3-dioxolanes in Water at 25° (μ = 1.0)

Substituent	k_{H^+}, l. mol^{-1} sec^{-1} [a]	k_{rel}
CH_3O	8.68 ± 0.14	16.5
CH_3	1.95 ± 0.17	3.71
H	$5.25 \pm 0.14 \times 10^{-1}$	1.00
Cl	$2.08 \pm 0.07 \times 10^{-1}$	0.391
NO_2	$2.93 \pm 0.08 \times 10^{-3}$	0.0056

[a] Rate constants were measured by following the formation of ketone spectrophotometrically at at least two acid concentrations. Rate constants are the average of four or more runs in all cases.

In order to determine the cause of the drastically reduced phenyl to hydrogen rate ratio in IV ($k_{R=Ph}/k_{R=H}$ = 40), we note first that the ρ value of −2.9 is only slightly less negative than the ρ values for I and II, which have phenyl to hydrogen ratios of greater than 10^5-fold. If steric hindrance to coplanarity of the phenyl ring were the cause of the small effect of phenyl substitution in IV, as previously suggested,[4] then the ρ value for IV should be substantially less negative than for I or II. The very modest differences between ρ values for series I, II, and IV support a structure for IV in which the phenyl ring is able to conjugate effectively with the incipient positive charge, *i.e.*, that steric inhibition to resonance is minimal. Since the phenyl ring in III transmits electronic effects only slightly less effectively than the phenyl group in I or II, it must be concluded that conjugative interaction of the phenyl ring in III with the incipient carbonium ion center is substantial.

Further evidence that steric hindrance to conjugation does not adequately explain these results can be obtained by noting that there is no correlation between the observed ρ values and the susceptibility of the rate to replacement of hydrogen by phenyl. For example, series IV with the lowest phenyl to hydrogen ratio is *not* the least sensitive to substitution in the phenyl ring.

(4) T. H. Fife and L. Hagopian, *J. Org. Chem.*, 31, 1772 (1966).
(5) P. Salomaa and A. Kankaanperä, *Acta Chem. Scand.*, **15**, 871 (1961).
(6) L. P. Hammett, "Physical Organic Chemistry," 2nd ed, McGraw-Hill, New York, N. Y., 1971, Chapter 11.
(7) H. C. Brown and Y. Okamoto, *J. Amer. Chem. Soc.*, **79**, 1913 (1957); **80**, 4979 (1958).
(8) Y. Yukawa and Y. Tsuno, *Bull. Chem. Soc. Jap.*, **32**, 965, 971 (1959).

Of particular importance is the fact that series III with a phenyl to hydrogen ratio of almost 10^3 has a ρ value substantially less negative than series IV, which has a much lower phenyl to hydrogen ratio. If we take the value of ρ as a qualitative measure of the ability of the phenyl group to conjugate with the incipient positive charge, then we would expect the phenyl to hydrogen ratio to parallel the ρ values in the absence of other factors. The fact that it does not suggests other factors are important.

An alternative explanation for the small effect of phenyl substitution for IV is the one proposed by Salomaa and Kankaanperä[5] to explain the low effect of methyl substitution in this same series. They suggested that in the transition state for the hydrolysis of dioxolanes there is a significant steric interaction between *one* of the substituents in the 2 position and the ring. Since either substituent can be bent toward the ring in the transition state, the magnitude of this steric strain will be determined by the smaller of the two substituents. In the case of 1,3-dioxolane itself (series II), substitution of a methyl group at position 2 causes a rate increase similar to that observed in the acyclic analogs since the carbon–hydrogen bond will be bent toward the ring for both 1,3-dioxolane and 2-methyl-1,3-dioxolane, and the steric strain produced by this hydrogen will be minimal. For 2,2-dimethyl-1,3-dioxolane, on the other hand, a carbon–carbon bond at position 2 must be bent toward the ring leading to much greater steric strain and a rate lower than expected on the basis of electronic effects.

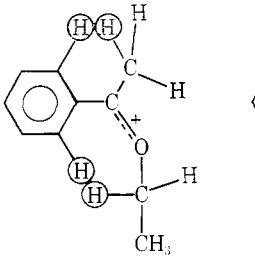
A similar explanation may be invoked to explain the diminished effect of a phenyl substituent in series IV. In 2-methyl-2-phenyl-1,3-dioxolane, there is steric strain due to the methyl group. This interaction is not present in 2-methyl-1,3-dioxolane since for this compound the carbon–hydrogen bond at position 2 can be bent toward the ring in the transition state. Consequently, the phenyl to hydrogen ratio is lower than expected.

We are now in a position to evaluate the relative importance of the two possible causes of the low phenyl to hydrogen ratio in series IV. By comparing phenyl to methyl ratios in each series (Table I), it is possible to keep steric interactions with the dioxolane ring in II and IV constant. These ratios then represent a measure of electronic effects and should correlate with the ρ values. A look at Table I shows that this expectation is in fact fulfilled. Series III, with the lowest sensitivity to substituent effects, for example, has the lowest phenyl to methyl ratio.

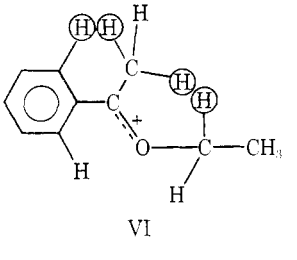
This analysis suggests that the extent of conjugative interaction of the phenyl group varies and that it is this factor which is responsible for the variable phenyl to methyl ratios. Support for this interpretation comes from a consideration of the r values which are a measure of the relative importance of inductive and resonance effects.[8] Those compounds which show a large phenyl to methyl ratio (I and II) give substantially larger r values than the ones with smaller phenyl to methyl ratios (III and IV).[9]

Turning now to the 2-methyl-1,3-dioxolanes (IV), we see that the phenyl to methyl ratio suggests that the rate constant for 2-methyl-2-phenyl-1,3-dioxolane is about tenfold smaller than would be predicted on the basis of a steric interaction of the 2-methyl substituent with the dioxolane ring. This effect might reasonably be ascribed to steric hindrance to conjugation. Therefore, it appears that the reduction of 10^4 in the phenyl to hydrogen ratio for IV may be divided into a tenfold effect due to steric hindrance to conjugation and a 10^3-fold effect due to steric interaction of the 2-methyl group with the dioxolane ring.

For series III, both the low value of the phenyl to methyl ratio and the low sensitivity to ring substituent effects may be explained by steric hindrance to resonance of the phenyl ring by the 2-methyl substituent in a manner similar to that suggested by Kresge[3] to explain phenyl effects on ortho ester hydrolysis. In the cation formed during hydrolysis of acetophenone diethyl acetal, there are two possible conformations, assuming conjugative interaction from both the oxygen and the phenyl ring (V and VI). In both V and VI, there are



V



VI

significant interactions between the ortho hydrogens of the benzene ring, the methyl hydrogens, and the α hydrogens of the ethoxy group. These interactions can be minimized by twisting the phenyl ring out of the plane in a conformation like V, thus causing reduced resonance interaction and a less negative ρ value as seen in III. These steric interactions are, of course, absent in series I and II, where there is no methyl group on the pro-acyl carbon.

If steric considerations do, in fact, explain the low phenyl to methyl ratio for III, then the magnitude of the steric effect in V and/or VI should be about 3 kcal (*ca.* 200-fold rate difference). The relevant interactions in V are approximately those of the methyl and phenyl groups in *cis*-1-phenylpropene and 2-phenylpropene. Since *cis*-1-phenylpropene and 2-phenylpropene are each 1 kcal/mol less stable than *trans*-1-phenylpropene,[11] we estimate the steric strain in V to be in the neighborhood of 2 kcal/mol. A similar analysis of VI using *cis*-2-butene and 2-phenylpropene as models again gives an estimate for the strain of 2 kcal/mol.[11] These estimates for the steric interactions are quite close to the *ca.* 3 kcal/mol required.

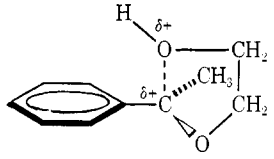
Steric hindrance to resonance in the transition state from 2-methyl-2-phenyl-1,3-dioxolane is not appreciable since there is no longer any interaction possible between the α hydrogens of the alkoxy group and the ortho

(9) It should be noted that a relationship between ρ and r in closely related reactions has recently been shown by Loudon[10] so that the arguments based on ρ and r are not necessarily independent.

(10) G. M. Loudon and C. Berke, *J. Amer. Chem. Soc.*, **96**, 4508 (1974).

(11) D. R. Stuv, E. F. Westrum, Jr., and G. C. Sinke, "The Chemical Thermodynamics of Organic Compounds," Wiley, New York, N. Y., 1969.

hydrogens of the phenyl ring. This is due to the requirement that the carbon–oxygen bond of the alkoxy group must now be in a plane perpendicular to the phenyl ring at the transition state (VII). Steric inter-



VII

action of the ortho hydrogens is now restricted solely to the methyl hydrogens. The phenyl ring then is expected to be twisted less than in the corresponding acyclic case, as is apparently the case.

Experimental Section

All melting points are uncorrected. Nmr spectra were recorded at 60 MHz on a Perkin Elmer R-20A spectrometer.

Materials. Distilled water and reagent grade sodium chloride were used in all kinetic experiments.

The ring-substituted 2-phenyl-2-methyl-1,3-dioxolanes were prepared by the following general method: 0.05 mol of the corresponding acetophenone, 0.05 mol of ethylene glycol, 1.0 g of Amberlite 120 ion-exchange resin (acid), and 150 ml of benzene were refluxed from 12 to 72 hr. The water which formed was collected by use of a Dean-Stark trap. The ion-exchange resin was filtered off and the solvent removed on a rotary evaporator. The *p*-nitro derivative and the parent compound were purified by recrystallization from hexane. The *p*-Cl, *p*-CH_3O, and *p*-CH_3 derivatives could not be crystallized and were purified by gas chromatography on a 5 ft × 0.25 in. 20% SE-30 column at 175°. In all cases, two major peaks were obtained, the first due to residual ketone and the second due to the ketal. The gc showed about 50–70% conversion to ketal after 1 day reflux for all compounds. No attempt was made to maximize yields.

2-Phenyl-2-methyl-1,3-dioxolane was obtained in 66% yield after refluxing overnight: mp 57–58° (lit.[4] 57–58°); nmr (CCl_4) δ 1.50 (s, 3 H), 3.65 (m, 4 H), 7.05 (m, 5 H).

2-*p*-Nitrophenyl-2-methyl-1,3-dioxolane was obtained in 58% yield after 72 hr reflux: mp 72.0–73.5°; nmr (CCl_4) δ 1.52 (s, 3 H), 3.75 (m, 4 H), 7.34 (d, 2 H, J = 14 Hz), 7.84 (d, 2 H, J = 14 Hz). *Anal.* Calcd for $C_{10}H_{11}NO_4$: C, 57.41; H, 5.30. Found: C, 57.38; H, 5.40.

2-*p*-Methoxyphenyl-2-methyl-1,3-dioxolane was collected by glc as a low-melting solid after 12 hr reflux: nmr ($CDCl_3$) δ 1.51 (s, 3 H), 3.72 (s, 3 H), 3.8 (m, 4 H), 6.70 (d, 2 H, J = 14 Hz), 7.26 (d, 2 H, J = 14 Hz). *Anal.* Calcd for $C_{11}H_{14}O_3$: C, 68.02; H, 7.10. Found: C, 68.04; H, 7.11.

2-*p*-Chlorophenyl-2-methyl-1,3-dioxolane was collected by glc as a liquid after 48 hr reflux: nmr ($CDCl_3$) δ 1.49 (s, 3 H), 3.75 (m, 4 H), 7.24 (m, 4 H). *Anal.* Calcd for $C_{10}H_{11}O_2Cl$: C, 60.46; H, 5.58. Found: C, 60.33; H, 5.62.

2-*p*-Methylphenyl-2-methyl-1,3-dioxolane was collected by glc as a liquid after 72 hr reflux: nmr ($CDCl_3$) δ 1.52 (s, 3 H), 3.80 (m, 4 H), 7.12 (d, 2 H, J = 15 Hz), 7.29 (d, 2 H, J = 15 Hz). *Anal.* Calcd for $C_{11}H_{14}O_2$: C, 74.13; H, 7.92. Found: C, 73.95; H, 7.80.

Kinetics. The rates of hydrolysis of the ketals were monitored spectrophotometrically at the λ_{max} of the corresponding acetophenone product at 25.0 ± 0.2° and ionic strength 1.0 (NaCl) using a Cary 16K spectrophotometer. An acetonitrile solution of the ketal was injected into a standardized HCl solution which had been preequilibrated for 15 min at 25.0°. The final concentration of acetonitrile was about 0.5% in all cases. All reactions were followed to greater than 90% completion and gave excellent first-order kinetics. Pseudo-first-order rate constants were obtained by nonlinear, least-squares regression analysis.

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, and to the National Science Foundation for support of this research. We also wish to thank Professors A. J. Kresge and G. M. Loudon for communication of results in their laboratories and for helpful comments.