Employing the uniformly charged-sheet model[23] as described elsewhere,[3] the qualitative features of the pH–rate profile for aspirin decomposition in PEI solutions are correctly reproduced and the maximum k for the aspirin–PEI reaction is predicted to occur at pH 8.1. However, the model predicts a very flat maximum in discrepancy with the sharp maximum observed experimentally (Figure 1); the rate is predicted to be reduced by a factor 10 at pH 3.5 compared to the value at the maximum, instead of the observed value of 1000. A similar result was obtained from preliminary calculations employing the more realistic cylindrical model for PEI.[24] On the other hand, the cylindrical model for PVBA-Cl solutions predicts satisfactorily the magnitude of the increase of rate constant observed in alkaline solution for the bimolecular reaction between aspirin anion and OH^-.

Acknowledgment. The authors are grateful to Jorge Larocca for performing a few experimental measurements and to D. Turyn for helpful discussions. They also thank the Universidad de Buenos Aires and the Consejo Nacional de Investigaciones Científicas y Técnicas (Argentina) for financial support.

(24) A. Katchalsky, *Pure Appl. Chem.*, **26**, 327 (1971).

Effect of Phenyl Substitution on Ortho Ester Hydrolysis[1]

Y. Chiang, A. J. Kresge,* P. Salomaa, and C. I. Young

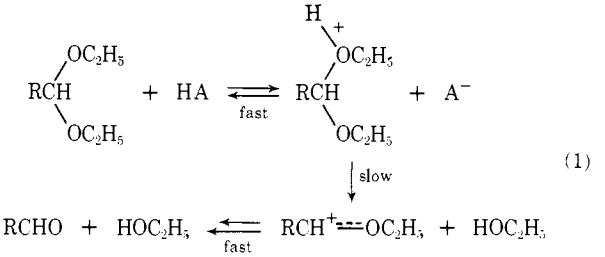
Contribution from the Department of Chemistry, Illinois Institute of Technology, Chicago, Illinois 60616. *Received December 12, 1973*

Abstract: Phenyl substitution at the pro-acyl carbon atom of the cyclic ortho ester 2-methoxy-1,3-dioxolane increases its rate of hydrolysis by a factor of 40. This stands in marked contrast to the retardation normally found for corresponding phenyl substitution in the hydrolysis of acyclic ortho esters and offers strong support for steric inhibition of resonance in the acyclic case. The hydrolysis of these cyclic substrates shows general acid catalysis, which, coupled with the fact that phenyl does accelerate, requires either (1) a concerted mechanism with proton transfer and C–O bond breaking in the same transition state, (2) a stepwise mechanism with proton transfer and C–O bond breaking in separate steps occurring at comparable rates, or (3) spectator catalysis.

The hydrolysis of acetals, ketals, and ortho esters has figured prominently in studies into the nature of acid–base catalysis, and these reactions have also received considerable attention in connection with investigations of the mechanism of lysozyme action. As a result of this large body of work, the broad features of these hydrolyses are now well understood.[2] Certain disturbing details, however, still remain, one of which is the effect of phenyl substitution at the pro-acyl carbon atom.[3]

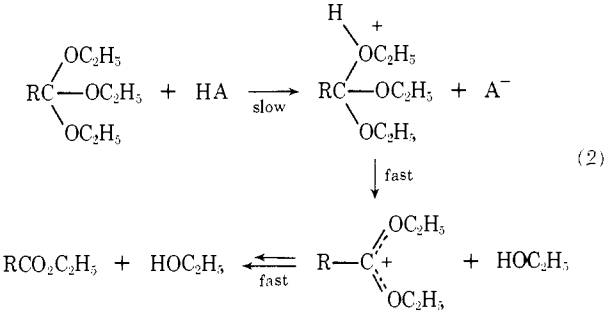
Introduction of a phenyl group at the pro-acyl carbon atom of an acetal greatly facilitates reaction, as it should for a process whose rate-determining step puts positive charge at this position (eq 1); for example, $C_6H_5CH(OC_2H_5)_2$ is 2×10^5 times more reactive than $HCH(OC_2H_5)_2$.[4] Similar substitution in ortho esters, on the other hand, has no accelerating effect, and $C_6H_5C(OC_2H_5)_3$ is actually 40% *less* reactive toward hydrolysis than $HC(OC_2H_5)_3$.[5]

This striking difference in behavior may be attributed



(1)

to a shift in rate-determining step. Conversion of an acetal into an ortho ester through introduction of another alkoxyl group lowers the oxygen basicity of the substrate, which slows the initial protonation step of the hydrolysis reaction. The additional alkoxyl group also raises the stability of the alkoxy carbonium ion intermediate, and that speeds up the C–O bond-breaking step. These changes combine to make protonation slower than C–O bond breaking, and proton transfer becomes the rate-determining step in the hydrolysis of simple orthobenzoate esters (eq 2, R = C_6H_5).



(2)

(1) This work was supported by a research grant from the National Science Foundation to I. I. T. (No. GP 23578) and a travel grant from the Finnish Academy to P. S.

(2) For reviews, see E. H. Cordes and H. G. Bull, *Chem. Rev.*, in press; T. H. Fife, *Accounts Chem. Res.*, **5**, 264 (1972); R. H. DeWolfe, "Carboxylic Ortho Acid Derivatives," Academic Press, New York, N. Y., 1970, p 134 ff; E. H. Cordes, *Progr. Phys. Org. Chem.*, **4**, 1 (1967).

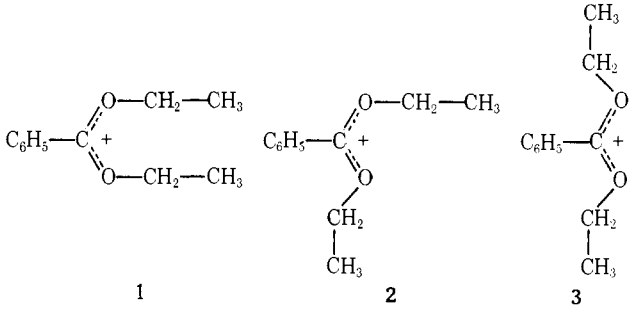
(3) The carbon atom of acetals, ketals, and ortho esters which bears the multiple ether groups is sometimes called the "acyl carbon." However, it becomes an acyl carbon atom only after hydrolysis, and we therefore propose the more accurate term "pro-acyl carbon."

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

(5) R. H. DeWolfe and J. L. Jensen, *J. Amer. Chem. Soc.*, **85**, 3264 (1963).

This explanation is consistent with the fact that the hydrolysis of most simple acetals is catalyzed only by hydronium ions, whereas the hydrolysis of many ortho esters shows general acid catalysis. For orthobenzoates themselves, however, general acid catalysis has been reported only in the case of hydrolysis in aqueous methanol;[6] it appears to be absent for the reaction in wholly aqueous solution.[5,7] This fact is in apparent contradiction to the mechanism of eq 2.

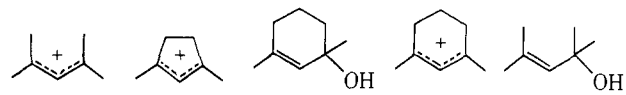
The difference in phenyl group effect on acetal and ortho ester hydrolysis may also be explained by postulating that steric effects interfere with resonance stabilization of the phenyldialkoxy cation formed in orthobenzoate hydrolysis. Such an ion can, in principle, exist in three conformations, with the alkyl groups in either a cis, cis (**1**), a cis, trans (**2**), or a trans, trans (**3**)



1 **2** **3**

arrangement. In the cis, cis conformation, however, the α-carbon atoms of the alkoxyl groups are only 2.2–2.4 Å apart; such close approach would produce serious crowding between the atoms directly attached to these carbons, *e.g.*, between the methylene hydrogens of the diethoxy cation **1**, which makes this conformation an unfavorable one. In either of the other two conformations, on the other hand, a trans α-carbon atom comes to within *ca.* 1.7 Å of an ortho hydrogen of a phenyl substituent situated at the pro-acyl carbon, provided that this benzene ring is coplanar with the O–C–O cationic system. This rather severe interference can of course be removed by twisting the phenyl group out of the O–C–O plane, but that destroys, or at least reduces, conjugative stabilization by the phenyl group. These strains can also be relieved by sacrificing conjugation between an alkoxyl group and the positive carbon; this, however, in view of the generally greater stabilizing effect of alkoxyl groups on cationic centers, seems less likely, and its result will at any rate be the same: substitution of inductive destabilization for conjugative energy lowering.

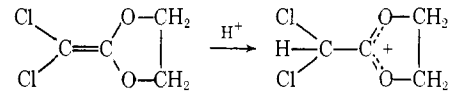
Steric effects in three-center cationic systems such as these are thought to be responsible for the comparative instability of the 1,1,3,3-tetramethylallyl cation, **4**; the equilibrium constant for the acid dissociation of this species to the corresponding diene is greater by more than four orders of magnitude than the acidity constant of its cyclic analog, the 1,3-dimethyl-2-cyclopentenyl cation, **5**.[8] A similar explanation may be advanced to account for the fact that the acid-catalyzed dehydration of 1,3-dimethyl-2-cyclohexenol (**6**), which occurs *via* the allylic cation **7**, is 100 times more rapid than the same reaction of 2,4-dimethyl-3-penten-2-ol (**8**).[9] The effect can also be seen in the hydrolysis of the dichloroketene



4 **5** **6** **7** **8**

$pK_a = -6.3$ $pK_a = -1.9$

acetals **9**[10] and **10**,[11] which takes place through rate-determining formation of dialkoxy cations, eq 3 and 4;



(3)

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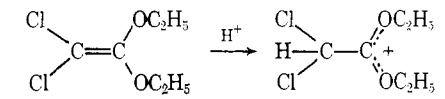


(4)

10

the cyclic substrate **9** is 30 times more reactive than its acyclic analog **10**.

In each of these three examples, steric interference with resonance in the cis,cis conformation of the cation could be relieved by forming the interfering groups into a small ring. This suggests that joining the α-carbon atoms of an ortho ester into a 1,3-dioxolane ring, as in **11**, should relieve the strain here as well, and that would

11 **12**

allow a phenyl group at the pro-acyl carbon atom to exert its expected stabilizing effect. This idea is supported by directly measured heats of formation of 4,4-dimethyl-1,3-dioxolenium ions, **12**, from unsaturated ester precursors which show that phenyl substitution at the 2 position makes these reactions more exothermic.[12]

These considerations lead to the prediction that phenyl substitution at the pro-acyl carbon atom of 2-methoxy-1,3-dioxolanes will accelerate their hydrolysis, provided that the unexpected phenyl group effect observed in acyclic ortho ester hydrolysis is the result of steric inhibition of resonance. If, on the other hand, the effect is produced by a shift in rate-determining step, phenyl substitution will retard hydrolysis of cyclic and acyclic ortho esters alike. In order to determine which of these alternatives is correct, we have examined the behavior of the relevant cyclic substances.[13]

Experimental Section

Materials. 2-Methoxy-1,3-dioxolane and 2-methoxy-2-phenyl-1,3-dioxolane were prepared by transesterification from the corresponding trimethyl ortho esters (Aldrich Chemical Co.) and ethylene glycol.[15] The substances so obtained had physical properties which

(6) H. Kwart and M. B. Price, *J. Amer. Chem. Soc.*, **82**, 5123 (1960).

(7) H. G. Bull, K. Koehler, T. C. Pletcher, J. J. Ortiz, and E. H. Cordes, *J. Amer. Chem. Soc.*, **93**, 3002 (1971).

(8) N. C. Deno and P. C. Scholl, *J. Amer. Chem. Soc.*, **93**, 2702 (1971); N. C. Deno, R. C. Haddon, and E. Nowak, *J. Amer. Chem. Soc.*, **92**, 6691 (1970).

(9) A. J. Kresge and Y. Chiang, unpublished work.

(10) V. Gold and D. C. A. Waterman, *J. Chem. Soc. B*, 849 (1968).

(11) T. S. Straub, Ph.D. Thesis, Illinois Institute of Technology, 1970.

(12) J. W. Larsen, S. Ewing, and M. Wynn, *Tetrahedron Lett.*, 539 (1970).

(13) Phenyl substitution at the pro-acyl carbon atom of 2-alkyl-1,3-dioxolanes is also known to slow the hydrolysis of these ketals, and the effect has been assigned to steric inhibition of resonance.[14] The retardation here, however, seems to require the presence of another sizable group at the 2 position and is therefore different from the effect proposed in the present study.

(14) T. H. Fife and L. Hagopian, *J. Org. Chem.*, 31, 1772 (1966).

(15) A. Kamkaanpera, *Suom. Kemistilehti B*, **43**, 133 (1970).

agreed with literature values[15,16] and nmr spectra which were consistent with their structures.

Buffer solutions were prepared from reagent grade acids and bases and deionized water which had been purified further by distillation from alkaline permanganate in glass apparatus.

Kinetics. Reactions were monitored spectroscopically by following the increase in carboxylic acid ester absorbance (at 220 nm for the formate ester and at 230 nm for the benzoate ester). Buffer solutions contained in silica cuvettes were first allowed to come to temperature equilibrium with the cell compartment of the spectrometer (Cary Model 15), which was thermostated by circulating water from a constant-temperature bath operating at 25.0 ± 0.02°. Neat ortho ester was then added in amount sufficient to give a final absorbance reading of the order of 1.0, the cuvette was shaken to effect solution, and continuous recording of absorbance as a function of time was begun. The record was continued for 3–4 half-lives, and infinite-time readings were taken after 10–12 half-lives. First-order rate constants were evaluated visually as slopes of plots of $\ln (A_\infty - A)$ *vs.* time.

Product Analysis. Several drops of 2-methoxy-1,3-dioxolane were added to 1 ml of acidified D_2O. Shaking quickly produced a clear solution whose nmr spectrum indicated that the major reaction products were methanol and 2-hydroxyethyl formate, and that only minor amounts of ethylene glycol and methyl formate were produced. Comparison of integrated signal intensities gave 20:1 as the molar ratio of the two sets of products.

A similar experiment could not be performed with 2-phenyl-2-methoxy-1,3-dioxolane because the reaction products here were not sufficiently soluble in water to give good nmr signals. A spot test for ethylene glycol based upon periodic acid oxidation and precipitation of the resulting iodate with silver ion[17] was therefore used instead. No positive test could be obtained with 2-methoxy-2-phenyl-1,3-dioxolane hydrolysis reaction mixtures, although control experiments showed that an amount of ethylene glycol corresponding to 0.1% of the molar amount of ortho ester could be detected. 2-Methoxy-1,3-dioxolane hydrolysis reaction mixtures, on the other hand, did give strongly positive tests.

Results

Both of the cyclic ortho esters investigated proved to have convenient rates of hydrolysis at acidities of the order of pH 4–6, and kinetic measurements were therefore made in buffer solutions. Formic and acetic acid as well as biphosphate ion buffers were used for the unsubstituted substrate, 2-methoxy-1,3-dioxolane, and acetic acid and biphosphate ion buffers were used for its 2-phenyl analog. The results of these experiments are summarized in Table I.

Although the measurements in formic acid solution were done at three different buffer ratios and the buffer acid concentration was varied by a factor of 7, no consistent change in rate constant with buffer acid concentration could be detected. It was therefore assumed that hydrogen ion was the only effective catalyst in these solutions, and catalytic coefficients were evaluated by simply dividing observed first-order rate constants by hydrogen ion concentrations. The latter were obtained by calculation from the stoichiometric compositions of the solutions; 3.751 was used as the pK_a of formic acid,[18] and activity coefficients were estimated using the extended Debye–Hückel equation with an ion-size parameter of 6.0 Å. This treatment gave a nicely consistent set of bimolecular rate constants whose standard deviation is only 2.2% of the mean value.[19]

(16) H. Baganz and L. Domaschke, *Chem. Ber.*, **91**, 650 (1958); A. Rieche, E. Schmitz, and E. Beyer, *ibid.*, **91**, 1942 (1958).

(17) F. Fiegel, "Spot Tests in Organic Analysis," Elsevier, New York, N. Y., 1956, p 127.

(18) H. S. Harned and N. D. Embree, *J. Amer. Chem. Soc.*, **56**, 1042 (1934).

(19) This is the standard deviation of the sample consisting of 18 measurements; the error limits listed in Tables I and II are standard deviations of mean values; *i.e.*, standard deviations of the samples divided by the square root of the number of measurements in each sample.

Table I. Rates of Ortho Ester Hydrolysis in Wholly Aqueous Buffer Solutions at 25°

10^2[HA], M	10^3k, sec^{-1}
2-Methoxy-1,3-dioxolane	
HA = HCO_2H; [HA]/[NaA] = 0.31; ionic strength maintained at 0.040 M with NaCl	
0.63	13.1, 13.2, 13.3
1.26	13.1, 13.3, 13.3
HA = HCO_2H; [HA]/[NaA] = 0.55; ionic strength maintained at 0.040 M with NaCl	
0.89	23.5
1.34	23.2, 23.4, 23.4
1.87	22.8, 23.4, 23.4
HA = HCO_2H; [HA]/[NaA] = 1.02; ionic strength maintained at 0.040 M with NaCl	
2.05	4.36, 4.45, 4.45
4.10	4.51, 4.54
$k_{H^+} = (1.738 \pm 0.009) \times 10^2\ M^{-1}\ sec^{-1}$	
HA = CH_3CO_2H; [HA]/[NaA] = 1.0; ionic strength maintained at 0.040 M with NaCl	
0.81	4.25, 4.30
0.84	4.20, 4.25
1.60	4.28, 4.30
2.30	4.35, 4.36
3.01	4.42
4.03	4.45, 4.45, 4.48
$10^3\ k_{obsd}\ (sec^{-1}) = (4.19 \pm 0.02) + (6.74 \pm 0.61)$[HA]; $r = 0.962$	
$k_{H^+} = (1.696 \pm 0.008) \times 10^2\ M^{-1}\ sec^{-1}$	
HA = $H_2PO_4^-$; [HA]/[NaA] = 7.0; ionic strength maintained at 0.10 M with NaCl	
1.41	0.236, 0.237
3.03	0.242, 0.243
5.26	0.249, 0.249
6.96	0.254, 0.256
$10^4\ k_{obsd}\ (sec^{-1}) = (2.32 \pm 0.01) + (3.27 \pm 0.13)$[HA]; $r = 0.995$	
$k_{H^+} = (1.808 \pm 0.008) \times 10^2\ M^{-1}\ sec^{-1}$	
2-Phenyl-2-methoxy-1,3-dioxolane	
HA = CH_3CO_2H; [HA]/[NaA] = 0.261; ionic strength maintained at 0.040 M with NaCl	
0.211	45.4, 45.7
0.473	46.2, 46.4
0.840	47.0, 47.3
1.04	47.6, 47.8, 47.9
$10^2\ k_{obsd}\ (sec^{-1}) = (4.50 \pm 0.01) + (26.3 \pm 1.6)$[HA]; $r = 0.987$	
$k_{H^+} = (7.05 \pm 0.02) \times 10^3\ M^{-1}\ sec^{-1}$	
HA = CH_3CO_2H; [HA]/[NaA] = 0.246; ionic strength maintained at 0.040 M with $NaClO_4$	
0.154	44.4, 44.5
0.304	44.8, 45.0
0.539	44.7, 45.1, 45.5
0.982	46.0, 46.2, 46.4
$10^2\ k_{obsd}\ (sec^{-1}) = (4.41 \pm 0.02) + (20.5 \pm 2.6)$[HA]; $r = 0.942$	
$k_{H^+} = (7.32 \pm 0.03) \times 10^3\ M^{-1}\ sec^{-1}$	
HA = $H_2PO_4^-$; [HA]/[NaA] = 2.0; ionic strength maintained at 0.10 M with NaCl	
0.67	2.90, 2.94
1.60	3.06, 3.06
2.22	3.13, 3.14
2.98	3.28, 3.31
3.97	3.41, 3.41
$10^2\ k_{obsd}\ (sec^{-1}) = (0.282 \pm 0.002) + (1.52 \pm 0.06)$[HA]; $r = 0.994$	
$k_{H^+} = (7.73 \pm 0.04) \times 10^3\ M^{-1}\ sec^{-1}$	
Trimethyl Orthoformate	
HA = HCO_2H; [HA]/[NaA] = 0.55; ionic strength maintained at 0.040 M with NaCl	
2.21	35.5, 35.6, 35.6
$k_{H^+} = (2.63 \pm 0.01) \times 10^2\ M^{-1}\ sec^{-1}$	
Trimethyl Orthobenzoate	
HA = HCO_2H; [HA]/[NaA] = 0.55; ionic strength maintained at 0.040 M with NaCl	
1.32	9.35, 9.35
2.21	9.45, 9.46, 9.46
$k_{H^+} = (6.97 \pm 0.02) \times 10\ M^{-1}\ sec^{-1}$	

In acetic acid and especially in biphosphate buffers, on the other hand, observed rate constants for the

hydrolysis of both cyclic ortho esters showed a clear if weak tendency to increase with increasing buffer acid concentration. A linear relationship between these two variables was therefore assumed, and the data were subjected to least-squares analysis. The results confirm that statistically valid relationships between observed rate constants and undissociated acid concentration do exist in all cases; correlation coefficients relating the two variables, for example, lie in the range 0.942–0.995 (r, Table I).

Although thus undoubtedly real, the observed variations in rate constant with buffer acid concentration were nevertheless in all cases rather small; in only one instance, the hydrolysis of 2-phenyl-2-methoxy-1,3-dioxolane in biphosphate buffers, did the specific rate increase by as much as 17% over the concentration range studied; in all other cases the changes ranged from only 4 to 8%. It seems appropriate, therefore, to inquire whether the observed relationships could be due not to general acid catalysis but rather to changes in specific salt effect produced as buffer components are replaced by inert electrolyte. It has in fact been demonstrated recently that general acid catalysis can easily be simulated in this way in an aqueous dioxane solvent.[20] Differences in salt effect will of course be considerably smaller in a wholly aqueous medium such as that employed here, but nevertheless the general magnitude of specific ion interaction coefficients[21] suggests that effects of the order of a few per cent at the concentrations used here are easily possible.

The work in aqueous dioxane suggests a method of testing for the presence of such an artifact. It was found there that NaCl and $NaClO_4$ give qualitatively different behavior when used as inert electrolytes in carboxylic acid buffer solutions; NaCl simulates general acid catalysis whereas $NaClO_4$ gives an *inverse* relationship between observed rate constant and undissociated acid concentration. A series of experiments was therefore performed here, using 2-phenyl-2-methoxy-1,3-dioxolane in acetic acid buffers, in which $NaClO_4$ was substituted for the NaCl normally employed as the inert electrolyte. The results (Table I) show that $NaClO_4$ does in fact reduce the dependence of observed rate constant upon buffer acid concentration; with NaCl, a fivefold increase in acetic acid concentration raised the specific rate of hydrolysis by 4.8%, whereas, with $NaClO_4$, a sixfold change in concentration produced only a 3.8% increase in rate constant. The relationship between rate constant and buffer acid concentration, however, remained direct: it did not become inverse. This indicates that, even though differences in specific salt effect are operative, general acid catalysis is unmistakably present.

It is significant that the small difference between the NaCl and $NaClO_4$ solutions observed here is in quantitative agreement with specific salt effect on ortho ester hydrolysis determined in a recent study of this phenomenon at much greater ionic strengths.[22] That study, moreover, showed that specific salt effects on this reaction increase in magnitude with increasing delocalization of charge in the anion of the salt. This suggests that the specific salt effects of carboxylate ions will be intermediate between those of chloride and perchlorate ions; and that reinforces the idea that replacing the acetate ion in acetic acid buffers with chloride ion on one hand and with perchlorate ion on the other, as was done in the experiments discussed above, should change the specific salt effect in different directions. This corroborates the conclusion that the present reactions are in fact experiencing general acid catalysis.

These considerations imply that general acid catalytic coefficients based upon data obtained from buffer solutions in which NaCl is the inert electrolyte will be somewhat greater than true values. The results for NaCl and $NaClO_4$ solutions in Table I suggest, however, that the error from this source in the present study is likely to be only *ca.* 10%, which is little more than the uncertainty in the rate constants themselves. The effect on hydronium ion catalytic coefficients, moreover, is less than the variation introduced by changing the buffer acid.

Hydronium ion catalytic coefficients for buffer solutions showing general acid catalysis were obtained by dividing the intercepts of least-squares relationships between observed rate constants and undissociated acid concentrations by hydrogen ion concentrations of the buffer solutions. Hydrogen ion concentrations were again obtained by calculation from stoichiometric buffer compositions, thermodynamic dissociation constants, and estimated activity coefficients. The pK_a of acetic acid was taken to be 4.756[23] and activity coefficients in its buffers were calculated as for formic acid solutions. For biphosphate ion, $pK_a = 7.200$[24] was used, and activity coefficients were estimated using the formula $\log f = -ZAI^{1/2}/(1 + BaI^{1/2}) + \beta I$ with values of the parameters recommended by Grybowski.[24] The good agreement among values obtained in different buffer solutions attests to the essential validity of this treatment.

A few measurements were also made of the rates of hydrolysis of the acyclic analogs of the two cyclic ortho esters studied here, trimethyl orthoformate and trimethyl orthobenzoate. These experiments were done in formic acid buffer solutions, and the data, summarized in Table I, were treated assuming no catalysis by undissociated acid molecules. The resulting hydronium ion catalytic coefficient for trimethyl orthobenzoate, $k_{H^+} = 69.7 \pm 0.2\ M^{-1}\ sec^{-1}$, is in good agreement with the published value, 74 M^{-1} sec^{-1}, which is based upon more extensive measurements made over a wide pH range.[7] The result obtained here for trimethyl orthoformate, on the other hand, $k_{H^+} = 263 \pm 1\ M^{-1}$ sec^{-1}, is significantly greater than the literature value, 202 M^{-1} sec^{-1};[25] the latter, however, was measured in unbuffered solutions of $[H^+] \simeq 10^{-4}\ M$, and a value of 308 M^{-1} sec^{-1} may in fact be calculated from subsequent data for biphosphate buffers published from the same laboratory.[26]

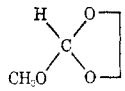
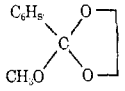
Comparison of the present results with literature values may be made at one other point; k_{H^+} for the

(20) P. Salomaa, A. Kankaanpera, and M. Lahti, *J. Amer. Chem. Soc.*, **93**, 2084 (1971).
(21) E. A. Guggenheim and J. C. Turgeon, *Trans. Faraday Soc.*, **51**, 747 (1955).
(22) C. A. Bunton and J. D. Reinheimer, *J. Phys. Chem.*, **74**, 4457 (1970).
(23) H. S. Harned and R. W. Ehlers, *J. Amer. Chem. Soc.*, **55**, 652 (1933).
(24) A. K. Grybowski, *J. Phys. Chem.*, **62**, 555 (1958).
(25) A. Kankaanpera and M. Lahti, *Suom. Kemistilehti B*, **43**, 75, 101 (1970).
(26) A. Kankaanpera and M. Lahti, *Suom. Kemistilehti B*, **43**, 105 (1970).

hydrolysis of 2-methoxy-1,3-dioxolane has been reported[15] as 95.7 M^{-1} sec^{-1}, whereas the value obtained here is 175 ± 3 M^{-1} sec^{-1}. Exact details of the conditions under which the previous measurements were made are unfortunately not given; it may be, however, that very dilute unbuffered acid solutions were again used, in which case the discrepancy between present and previous values becomes understandable.

These and all other rate constants measured here are summarized in Table II.

Table II. Summary of Rate Constants

Substrate	Catalyst	k, M^{-1} sec^{-1} [a]
	H^+	$(1.75 \pm 0.03) \times 10^2$
	CH_3CO_2H	$(6.74 \pm 0.61) \times 10^{-3}$
	$H_2PO_4^-$	$(3.27 \pm 0.13) \times 10^{-4}$
	H^+	$(7.37 \pm 0.20) \times 10^3$
	CH_3CO_2H	$(2.34 \pm 0.29) \times 10^{-1}$
	$H_2PO_4^-$	$(1.52 \pm 0.06) \times 10^{-2}$
$HC(OCH_3)_3$	H^+	$(2.63 \pm 0.01) \times 10^2$
$C_6H_5C(OCH_3)_3$	H^+	$(6.97 \pm 0.02) \times 10$

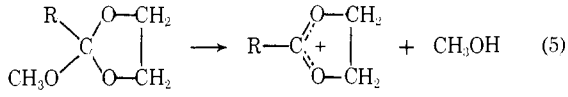
Relative Reactivities

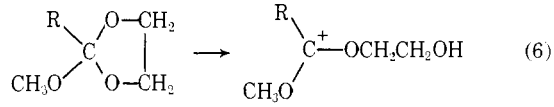
Dioxolane series			
Catalyst	H^+	CH_3CO_2H	$H_2PO_4^-$
$k(C_6H_5)/k(H)$	42.2 ± 1.1	34.8 ± 5.3	46.3 ± 2.6
Acyclic series			
Catalyst	H^+		
$k(C_6H_5)/k(H)$	0.265 ± 0.001		

[a] 25°.

Discussion

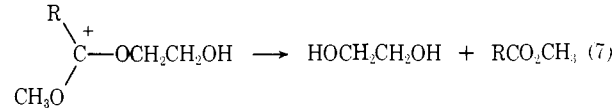
Position of Initial C–O Bond Cleavage. The hydrolysis of 2-methoxy-1,3-dioxolanes can in principle occur either through initial loss of the exocyclic methoxyl group (eq 5) or by initial cleavage of a ring C–O bond

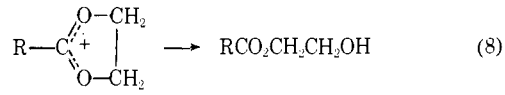

(5)


(6)

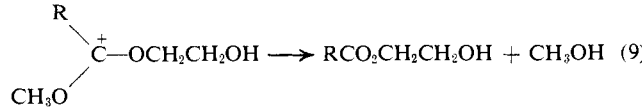
(eq 6). Since the latter reaction does not give a 1,3-dioxolenium ion, it is of no value in testing the hypothesis that steric inhibition of resonance prevents a phenyl substituent at the pro-acyl carbon atom from accelerating the rate of hydrolysis of an acyclic ortho ester. It is important, therefore, that initial ring C–O bond cleavage may be ruled out as an important reaction pathway on the basis of the product studies performed here.

This conclusion is based upon the fact that these hydrolyses stop at the alcohol and carboxylic acid ester stage; under the conditions employed, further hydrolysis of the carboxylic acid esters does not take place. That follows from the known slow rates of hydrolysis of ordinary carboxylic acid esters at the pH's employed, and it is furthermore required by the fact that the kinetic runs, which were followed by measuring ester carbonyl group uv absorption, all had stable end points. In this circumstance, ethylene glycol can appear as a reaction product only through hydrolysis *via* the acyclic intermediate (eq 7), *i.e.*, through initial ring C–O bond

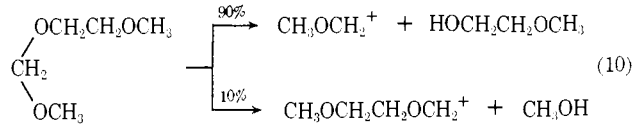

(7)


(8)

cleavage, for further reaction of a 1,3-dioxolenium ion must give an ethylene glycol ester (eq 8). The fact that ethylene glycol is produced only to the extent of 5 mol % in the hydrolysis of 2-methoxy-1,3-dioxolane and not at all (<0.1 mol %) in the hydrolysis of 2-phenyl-2-methoxy-1,3-dioxolane therefore suggests that little or no acyclic intermediate is formed. The latter need not, of course, react to produce ethylene glycol, for it too may give an ethylene glycol ester (eq 9). β-Oxyethoxyl


(9)

groups, however, cleave much more readily than methoxyl groups in reactions such as these; β-methoxyethyl methyl formal, for example, hydrolyzes with predominant β-methoxyethoxyl group loss (eq 10).[27]


(10)

Thus, only a minor portion of the acyclic intermediate can be expected to react according to eq 9, and the absence of ethylene glycol can be taken as evidence for the nonoccurrence of initial C–O bond cleavage. This conclusion is consistent with the known preference for exocyclic group cleavage in the hydrolysis of 2-alkoxytetrahydrofurans and 2-alkoxytetrahydropyrans.[28]

Phenyl Group Effect and the Reaction Mechanism. The fact that the amount of ethylene glycol produced drops from 5 mol % in the hydrolysis of 2-methoxy-1,3-dioxolane to less than 0.1 mol % in the hydrolysis of its 2-phenyl analog suggests, according to the arguments of the previous section, that phenyl substitution strengthens the preference for exocyclic group cleavage and dioxolenium ion formation. This in turn implies that the phenyl group stabilizes the dioxolenium ion and the transition state leading to it, and it implies further that this transition state is rate determining, *i.e.*, that the phenyl group is in this case exerting its expected rate-accelerating effect.

These implications are supported by directly measured rates of reaction. The data summarized in Table II show that phenyl substitution at the 2 position of 2-methoxy-1,3-dioxolane raises its rate of hydrolysis by a factor of approximately 40, both for catalysis by the hydronium ion and for catalysis by general acids. Corresponding phenyl substitution in acyclic ortho esters, on the other hand, is rate retarding; the present results give a fourfold decrease for the trimethyl series, in keeping with the retardation observed in the triethyl series.[5]

(27) P. Salomaa, *Ann. Acad. Sci. Fenn., Ser. A2*, No. 103, 1 (1961).
(28) A. Kankaanpera and K. Miikii, *Suom. Kemistilehti B*, 41, 42 (1968); 42, 430 (1969).

It is difficult to account for the accelerative effect of phenyl observed here without using a conjugative interaction between the benzene ring and the positive charge of the dioxolenium ion hydrolysis reaction intermediate. As was detailed above, there is reason to expect such conjugation to be sterically impeded in acyclic dialkoxy carbonium ions, and phenyl substitution there should retard the reaction by inductive electron withdrawal, as is observed. The present results thus provide strong support for the hypothesis that steric inhibition of resonance prevents a phenyl group at the pro-acyl carbon atom of acyclic ortho esters from exerting an accelerative effect on their hydrolysis.

These results also have certain implications on the mechanism of these reactions. The fact that phenyl accelerates requires positive charge to be developing at the pro-acyl carbon atom in the rate-determining transition state of these hydrolyses; this in turn implies that C–O bond breaking is occurring in the rate-determining step. The reaction of the cyclic substrates also shows general acid catalysis, which requires that the conjugate base of the catalyzing acid be part of the rate-determining activated complex; this in turn implies, but does not absolutely require, that proton transfer be taking place in the rate-determining step.

These requirements are met by a concerted mechanism in which proton transfer and C–O bond breaking occur in the same rate-determining transition state. The bond-making and bond-breaking processes need not, of course, be exactly synchronous. Indeed, the very weak general acid catalysis actually observed implies that proton transfer would have to be nearly complete at such a transition state, and the fact that the 40-fold phenyl group acceleration actually found is so much less than the factor of 10^5 observed in acetal hydrolysis suggests that C–O bond breaking would have just begun.

The requirement that both proton transfer and C–O bond breaking occur in the rate-determining step is not compatible, on the other hand, with stepwise mechanisms, such as those shown in eq 1 and 2, where one of the steps is slow and the other is fast. It can, however, be accommodated by a stepwise scheme with two transition states of comparable free energy. Neither step would then be very much faster than the other, and each would be partly rate determining; this would allow observed rate constants to reflect the characteristics of both steps, *i.e.*, to show both general acid catalysis and a phenyl group acceleration.

Such a stepwise mechanism also provides an explanation for the absence of general acid catalysis in the hydrolysis of acyclic orthobenzoates. The C–O bond-breaking step here does not, for steric reasons, benefit from phenyl group resonance, and it is therefore more difficult than in the cyclic case; the protonation step for acyclic ortho esters, on the other hand, should have much the same velocity as in the cyclic case. These circumstances raise the free energy of the second transition state without affecting very much that of the first; and that renders proton transfer fast and reversible and C–O bond breaking slow, which leads to specific hydrogen ion catalysis. These arguments may be extended to orthoformates, whose hydrolysis also does not benefit from phenyl group resonance, and whose oxygen basicity, moreover, is not reduced by the phenyl group inductive effect. These circumstances make for an even greater disparity in the rates of the two steps, again in the direction giving specific hydrogen ion catalysis. The hydrolysis of orthoformates, however, is unmistakably general acid catalyzed.

There is still a third mechanism which is compatible with simultaneous general acid catalysis and phenyl group acceleration. In this scheme, recently dubbed "spectator catalysis," [29] proton transfer is rapid and reversible and C–O bond breaking is slow. The latter, however, is more rapid than diffusion apart of the protonated substrate and the conjugate base of the catalyst, which are held together by hydrogen bonding and Coulomb attraction, and the conjugate base is therefore part of the rate-determining activated complex. Since in this mechanism proton transfer is complete at the rate-determining transition state, general acid catalysis would be weak and difficult to observe; the probable strong exothermicity of the second step would also require C–O bond breaking to be not very far advanced at its transition state, and that would lead to only a small phenyl group acceleration.

It is difficult to decide among these possibilities on the basis of currently available information, but we hope that work now underway will permit a choice.

(29) L. D. Kershner and R. L. Schowen, *J. Amer. Chem. Soc.*, **93**, 2104 (1971).