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Ortho Ester Hydrolysis: Direct Evidence for a Three-Stage Reaction Mechanism

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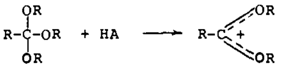
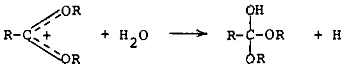
Received October 18, 1978

Abstract: Direct evidence is supplied for the existence of 1,3-dioxolenium ion and hydrogen ortho ester intermediates in the acid-catalyzed hydrolysis of a series of 2-aryl- (and 2-cyclopropyl-) 2-alkoxy-1,3-dioxolanes. These two intermediates require a three-stage reaction path: (1) loss of the exocyclic alkoxy group from the substrate to generate the dioxolenium ion, (2) reaction of this ion with water to form hydrogen ortho ester, and (3) breakdown of the hydrogen ortho ester to carboxylic acid products. Rate constants for all three stages and equilibrium constants for stage 2 were measured in some cases and were estimated in others. Differential substituent effects of phenyl and cyclopropyl on stages 1 and 3 are shown to be responsible for the changes in rate-determining step which these systems undergo between low (stage 3 rate determining) and high (stage 1 rate determining) pH. The purely aliphatic ortho esters 2-methoxy-1,3-dioxolane and 2-methyl-2-methoxy-1,3-dioxolane were found not to give this change in rate-determining step.

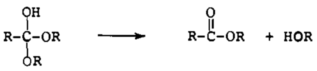
It is now generally accepted that the acid-catalyzed hydrolysis of ortho esters consists of three separate reaction stages: (1) generation of a dialkoxy carbonium ion, (2) hydration of this ion to a hydrogen ortho ester, and (3) breakdown of the latter to alcohol and carboxylic acid ester products (eq 1-3).[1] This reaction mechanism, though quite reasonable, is based upon kinetic information, which, until very recently, was obtained under conditions where the first stage is rate determining; there was therefore no direct kinetic evidence for the rest of the reaction scheme. In a preliminary account of the present study,[2] we reported that we discovered conditions under which, with certain substrates, the third stage of this three-stage sequence is rate determining. This enabled us to detect the dialkoxycarbonium ion intermediates in these reactions, to estimate rate and equilibrium constants for their decay to hydrogen ortho esters, and to measure rate constants for the conversion of the latter to ultimate reaction products. We thus provided direct kinetic evidence for the full reaction scheme. We now describe that work in full.



$$\mathrm{R{-}C(OR)_3 + HA \longrightarrow R{-}C^{+}(OR)_2 + HOR + A^-} \quad (1)$$

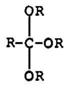


$$\mathrm{R{-}C^{+}(OR)_2 + H_2O \longrightarrow R{-}C(OH)(OR)_2 + H^+} \quad (2)$$



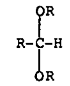
$$\mathrm{R{-}C(OH)(OR)_2 \longrightarrow R{-}C({=}O){-}OR + HOR} \quad (3)$$

Ortho esters (**1**) are trigeminal ethers, and their chemistry is quite similar in many respects to that of their geminal ether analogues, acetals (**2**) and ketals (**3**). The latter two, like ortho esters, undergo facile acid-catalyzed hydrolysis, and this is also a three-stage process involving two reaction intermediates quite similar to those of eq 1-3: monoalkoxycarbonium ions are formed as the counterparts of the dialkoxycarbonium ions generated in eq 1, and these are hydrated to hemiacetals or hemiketals as the analogues of the hydrogen ortho esters formed in eq 2.[1] Much new insight into the nature of these hydrolyses has been gained through the recent detection of these two kinds of intermediates as transient species formed in certain examples of these reactions. Thus, hemiacetals have been detected in the hydrolysis of strained acetals in which one of the alkoxy groups is part of a three-membered[3] or four-membered[4] ring, or in which both alkoxy groups are unusually bulky;[5] very recently, hemiacetals were even discovered in the hydrolysis of simple aromatic acetals such as benzaldehyde diethyl acetal.[6] Hemiacetals have also been found in the hydrolysis of acylals,[7] and hydrogen ortho esters have been found in the hydrolysis of acyloxy ortho esters.[8] Oxocarbonium ions have also been detected in some ortho ester and ketal hydrolyses: dialkoxycarbonium ions in the case of aromatic ortho esters[9] and alkoxytropylium and alkoxydiphenylcyclopro-



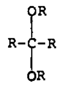
$$\mathrm{R{-}C(OR)_3}$$

1



$$\mathrm{R{-}CH(OR)_2}$$

2



$$\mathrm{R{-}CR(OR)_2}$$

3

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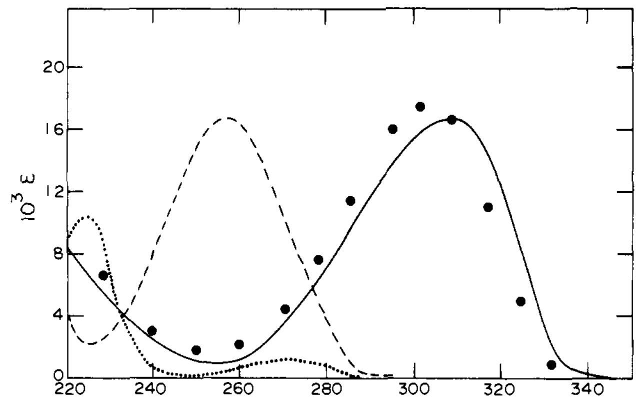
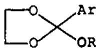


Figure 1. Ultraviolet spectra of 2-(*p*-methoxyphenyl)-2-methoxy-1,3-dioxolane in 0.001 M NaOH (···), 2-hydroxyethyl *p*-methoxybenzoate in H_2O (- - -), and 2-(*p*-methoxyphenyl)-1,3-dioxolenium fluoroborate in 85% H_2SO_4 (——). The points (●) are the extinction coefficients of the transient species observed during the hydrolysis of 2-(*p*-methoxyphenyl)-2-methoxy-1,3-dioxolane in 0.5 M $HClO_4$.

penium ions in the hydrolysis of the corresponding ketals.[9,10] In no case, however, before the study we describe here,[2] were both kinds of intermediate detected together in the same reacting system. Our examples, therefore, offer unique opportunities for obtaining information on all three hydrolysis reaction stages for a single substrate.

The substrates we used in this work were for the most part 2-aryl-2-alkoxy-1,3-dioxolanes (**4**), but we did occasionally employ the corresponding amide acetals (**5**). The hydrolysis of such amide acetals is complex, and it forms the subject of a separate study.[11] For the present purposes it is sufficient to know that these substances give dialkoxycarbonium ion intermediates very rapidly in acid solution, much faster than the corresponding ortho esters, and they therefore provide a convenient entry into the later stages of ortho ester hydrolysis.



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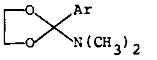


5

Experimental Section

Materials. The ortho esters and amide acetals used as substrates were samples whose synthesis is described elsewhere.[11,12] 2-Aryl-1,3-dioxolenium ions were prepared as their fluoroborate salts from silver fluoroborate and the appropriate β-bromoethyl benzoate ester.[12a,b]

2-Phenyl-2-(2,2-dichloroethoxy)-1,3-dioxolane labeled with tritium in the dichloroethoxy group was prepared by transesterification[12c] from 2-phenyl-2-methoxy-1,3-dioxolane and 2,2-dichloroethanol-*2-t*. The latter was obtained by lithium aluminum hydride reduction[13] of methyl dichloroacetate-*t*, which in turn was prepared by hydrogen exchange between unlabeled methyl dichloroacetate and tritiated water. The exchange was effected at room temperature in a methanol-dioxane solvent using sodium methoxide as the catalyst; a similar experiment using methanol-*O-d* followed by NMR analysis showed that exchange did in fact take place at the desired position.

All other materials were best available commercial grades; water was redistilled in an all-glass apparatus.

Kinetics. Kinetic measurements were made spectroscopically and also by a radiochemical labeling technique. Two spectrometers were used: a Cary Model 118C instrument, equipped with jacketed multiple sample cell block (operating at 25.0 ± 0.01 °C) and automatic sample changing and recording facility, and a Durrum-Gibson stopped-flow machine (operating at 25.0 ± 0.1 °C). Measurements with the Cary spectrometer were initiated by adding 5 μL of an alcoholic solution of substrate to 3 mL of an aqueous solution of acid or buffer of the appropriate concentration; final substrate concentrations in the reaction mixtures were of the order of 5×10^{-5} M. Stopped-flow measurements were carried out by mixing a solution of substrate (5×10^{-5} M) in very dilute aqueous NaOH (5×10^{-4} M) with an equal volume of the appropriate aqueous acid. Changes in optical density were recorded on a storage oscilloscope, and data were subsequently read from a photograph of this trace. Stopped-flow experiments using dioxolenium salts as substrates were performed by mixing a rigorously dried acetonitrile solution of the salt with an equal volume of aqueous acid. In these experiments no correction was made to account for the mixing artifacts associated with mixing CH_3CN and aqueous solutions in a stopped-flow apparatus. Control experiments demonstrated that the amplitudes of the mixing relaxations ($\Delta OD \approx 0.05$) were considerably smaller than the amplitudes associated with the chemical change ($\Delta OD \approx 0.7$-1.0).

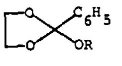
The kinetic data obtained in the various experiments in general conformed to the first-order rate law within experimental accuracy. Observed first-order rate constants were calculated by linear least-squares fitting of the data to an appropriate expression. Deviations from first-order kinetics (to be discussed below) were observed in runs starting with ortho ester carried out in weakly acidic solutions (pH 2-4, dependent on ortho ester).

The radiochemical technique measured the rate of loss of 2,2-chloroethanol-*2-t* from 2-phenyl-2-(2,2-chloroethoxy-*2-t*)-1,3-dioxolane by separating the alcohol product from unreacted starting material and subjecting the latter to radioassay by liquid scintillation counting. This was accomplished by extracting quenched samples of reaction mixtures with toluene, washing the toluene extracts three times with dilute aqueous alkali (control experiments showed that this removed >99% of the dichloroethanol), and then subjecting aliquots of the dried toluene solutions to liquid scintillation counting. Infinite-time readings were taken after 10 half-lives, and rate constants were calculated as slopes of plots of log $[(CPM)_t - (CMP)_\infty]$ vs. time. The data conformed to the first-order rate law exactly.

Results

UV Spectra. A typical set of UV spectra is given in Figure 1. It may be seen that cyclic aromatic ortho esters, such as 2-(*p*-methoxyphenyl)-2-methoxy-1,3-dioxolane, absorb only weakly, if at all, over most of the UV region and have moderately strong absorption maxima only below 230 nm. The ultimate benzoate ester hydrolysis products, on the other hand, absorb strongly in the region 230-260 nm, and the hydrolysis reaction can therefore be monitored easily by following the appearance of product. The intermediate dioxolenium ions have absorption maxima in yet another region of the spectrum, near 300 nm, and again the absorption is strong; the appearance and disappearance of these intermediates can therefore be readily observed. The other kinds of reaction intermediate, the hydrogen ortho esters, have not been isolated and their spectra are not known. There is no reason to believe, however, that these would be significantly different from the spectra of the corresponding ortho esters, for the two types of compound differ only by substitution of a hydroxy group for an alkoxy function.

Kinetics. Rates of hydrolysis of a series of 2-phenyl-2-alkoxy-1,3-dioxolanes (**6**) were determined in dilute HCl solution by measuring the rate of appearance of benzoate ester product. For each substrate replicate determinations (two to four) were made at each of six to eight acid concentrations in the range 0.002-0.1 M at an ionic strength of 0.10 M (maintained with NaCl). Average values of first-order rate constants obtained in this way are listed in Table S1.[14] These observed first-order rate constants, k_{obsd}, were accurately related to acid concentration in the manner of eq 4 and best values of the uncatalyzed components, k_0, and the hydrogen ion catalytic coefficients, k_{H^+}, were obtained by linear least-squares analysis. The results are summarized in columns three and four of Table I, where these rate constants are given the superscript "3" because, as



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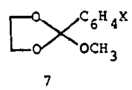

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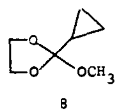

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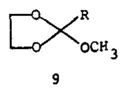


9

Table I. Rate Constants for the Hydrolysis of a Series of 2-Substituted 2-Phenyl-1,3-dioxolanes at 25 °C ($\mu = 0.10$ M)

substituent in 2 position	$10^2 k_{H^+}{}^1$, $M^{-1}\,s^{-1}$ [a]		$10^2 k_{H^+}{}^3$, $M^{-1}\,s^{-1}$ [b]	$k_0{}^3$, s^{-1} [b]
OCH_2CH_3	81.8 ± 0.8		3.09 ± 0.01	1.40 ± 0.03
OCH_3	54.0 ± 0.7		3.18 ± 0.03	1.45 ± 0.06
$OCH_2CH_2OCH_3$	26.2 ± 0.3		2.93 ± 0.10	1.15 ± 0.29
OCH_2CH_2Cl	18.4 ± 0.2		2.85 ± 0.04	1.38 ± 0.11
$OCH_2{\equiv}CH$	16.6 ± 0.5		2.91 ± 0.03	1.30 ± 0.10
OCH_2CHCl_2	12.4 ± 0.2		3.05 ± 0.02	1.36 ± 0.07
		av	3.00 ± 0.13	1.34 ± 0.11

[a] Measured in phosphonate anion buffers (pH 5-8).[12a] [b] Measured in dilute HCl solutions (pH 1-3).

will become evident later, they pertain to the third stage of the three-stage reaction sequence (eq 1-3).

$$k_{obsd} = k_0 + k_{H^+}[H^+] \tag{4}$$

Similar kinetic measurements in dilute HCl solution were also made for a series of 2-(substituted phenyl)-2-methoxy-1,3-dioxolanes (**7**), 2-cyclopropyl-2-methoxy-1,3-dioxolane (**8**), 2-methyl-2-methoxy-1,3-dioxolane (**9**, with R = CH_3), 2-methoxy-1,3-dioxolane (**9** with R = H), and the amide acetals, 2-phenyl-2-(*N,N*-dimethylamino)-1,3-dioxolane (**5** with Ar = C_6H_5) and 2-(4-methoxyphenyl)-2-(*N,N*-dimethylamino)-1,3-dioxolane (**5** with Ar = *p*-$CH_3OC_6H_4$). The first-order rate constants obtained are listed in Table S1.[14] For most of these substrates, observed first-order rate constants again conformed accurately to eq 4, and best values of k_0 and k_{H^+} were also obtained by linear least-squares analysis. The results are listed in columns five and six of Table II, again as $k_0{}^3$ and $k_{H^+}{}^3$. The substrates with cyclopropyl or 4-methoxyphenyl substituents at the 2 position, however, gave observed first-order rate constants which, though linearly related to acid concentration at low acidities, began to show a saturation in their dependence upon acidity when acid concentrations were raised above a few hundreths molar. The data were therefore fitted (by successive approximations) to a more complex expression which will be developed later (eq 9) and values of k_0 and k_{H^+} were obtained in this way. These are also listed in Table II. For many of these substrates, rate measurements were also made in $HClO_4$ solutions at an ionic strength of 1.0 M. This allowed high acid concentrations to be reached and the deviations from nonlinear dependence of k_{obsd} upon $[H^+]$ to become more apparent. These data are also listed in Table S1.[14]

For a few substrates hydrolysis rates were also determined by monitoring the decrease in concentration of the dioxolenium ion intermediate. In all cases these observed first-order rate constants were identical within experimental error with those measured by following the appearance of carboxylic acid ester product. These rate constants are also listed in Table S1.[14]

Some rates of hydrolysis were measured in wholly aqueous buffer solutions as well: for 2-methyl-2-methoxy-1,3-dioxolane ($H_2PO_4^-$ buffers) by monitoring the increase in product ester absorbance, and for 2-phenyl-2-(2,2-dichloroethoxy)-1,3-dioxolane ($H_2PO_4^-$, $CHCl_2PO_3H^-$, and $CH_3PO_3H^-$ buffers) by the radiochemical tracer technique; these data are summarized in Tables S2 and S3, respectively.[14] Observed first-order rate constants in these solutions were accurately proportional to buffer acid concentration, and general acid, k_{HA}, as well as hydronium ion, k_{H^+}, catalytic coefficients were obtained from the data in the usual way.[12]

Rates of benzoate ester product formation from 2-phenyl-1,3-dioxolenium fluoroborate were also measured by the stopped-flow method by mixing a solution of the salt in rigorously dried acetonitrile with wholly aqueous hydrochloric acid or formic or acetic acid buffer solutions (Table S4).[14] These experiments were performed for the purpose of constructing a rate profile for this reaction in 50% aqueous acetonitrile. Observed rate constants were therefore not dissected into buffer component catalytic coefficients, but the data were simply extrapolated to zero buffer concentrations by linear least-squares analysis. Hydrogen ion concentrations in the buffer solutions were estimated from pH meter readings using the reference point $pH_{measd} = 2.15$ for a 0.010 M HCl solution in this solvent ($\mu = 0.10$ M).

Discussion

Change in Rate-Determining Step. All of the available evidence indicates that generation of the dialkoxycarbonium ion intermediate is the slow step in the acid-catalyzed hydrolysis of simple ortho esters at high pH, i.e. that stage 1 of the three-stage mechanism given in eq 1-3 is rate limiting.[1] That this applies as well to the cyclic ortho esters studied here is attested to by the fact that the dialkoxycarbonium formed from these substrates can be trapped by hydroxylamine, and the reaction diverted to *N*-hydroxybenzimidate ester products, without affecting the rate of reaction.[15] Additional support comes from the experiments performed here using a radiochemical tracer (tritium) in the exocyclic alkoxy group of 2-(2,2-dichloroethoxy)-2-phenyl-1,3-dioxolane. It is known that 1,3-dioxolenium ions are formed in the hydrolysis of substrates such as these by preferential loss of the exocyclic group,[12c] and, as Figure 2 shows, this exocyclic group is lost in $H_2PO_4^-$ buffers of pH ≃7 at the same rate as carboxylic acid ester product is formed. Similar results were obtained in $CH_2ClPO_3H^-$ and $CH_3PO_3H^-$ buffers in the pH range 6-8 (Table S3).[14]

Table II. Rate and Equilibrium Constants for the Hydrolysis of 2-Substituted 2-Methoxy-1,3-dioxolanes at 25 °C in Aqueous Solution[a]

	$\mu = 0.1$ (NaCl-HCl)						$\mu = 1.0$ ($NaClO_4$-$HClO_4$)	
substituent	$k_{H^+}{}^1$, $M^{-1}\,s^{-1}$ [b]	$k_0{}^2$, s^{-1}	$k_{H^+}{}^{-2}$, $M^{-1}\,s^{-1}$	$k_{H^+}{}^3$, $M^{-1}\,s^{-1}$	$k_0{}^3$, s^{-1}	pK_R	$k_{H^+}{}^3$, $M^{-1}\,s^{-1}$	pK_R
cyclopropyl	5.0×10^4	(3.1×10^3)[c]	(4.0×10^4)[d]	1.1×10^3	1.0	1.1		
p-methoxyphenyl	1.9×10^4	1.2×10^3	1.5×10^4	7.5×10^2	1.4	1.1	1.3×10^3	1.8
p-tolyl	1.3×10^4	(1.0×10^4)[c]	(1.0×10^4)[d]	5.6×10^2	1.4	(0.0)[e]	1.0×10^3	0.7
phenyl	5.4×10^3	(1.7×10^4)[c]	(4.3×10^3)[d]	3.0×10^2	1.5	(−0.6)[e]	6.1×10^2	0.1
p-fluorophenyl	5.0×10^3	(1.3×10^4)[c]	(4.0×10^3)[d]	2.4×10^2	1.6	(−0.5)[e]	4.3×10^2	0.2
p-chlorophenyl	3.3×10^3			1.7×10^2	1.7	(−0.9)[f]	2.5×10^2	
p-bromophenyl	3.0×10^3			1.6×10^2	1.9	(−1.0)[f]		
m-chlorophenyl				1.1×10^2	2.3	(−1.5)[f]		
p-nitrophenyl	3.9×10^2			3.7×10^1	2.4	(−2.4)[f]		

[a] Values in parentheses are estimated; others are directly measured. Superscripts 1, 2, or 3 designate the step of the three-stage reaction scheme (eq 1-3) to which a given parameter refers. [b] From ref 12b; see also ref 12a for revised value of $k_{H^+}{}^1$ for phenyl substituent. [c] Estimated from $k_{H^+}{}^{-2}$ and K_R. [d] Estimated as $0.8k_{H^+}{}^1$. [e] Estimated as pK_R ($\mu = 1.0$) = 0.7. [f] Estimated from σ–ρ relationship.

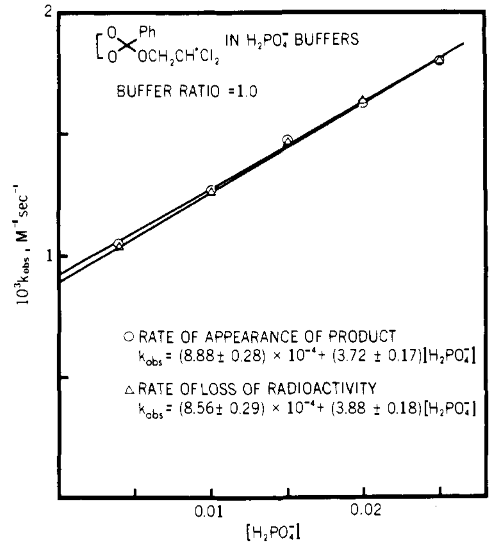


Figure 2. Comparison of rates of hydrolysis of 2-phenyl-2-(2,2-dichloroethyl)-1,3-dioxolane as measured by appearance of benzoate ester product and disappearance of radioactively labeled exocyclic alkoxy group.

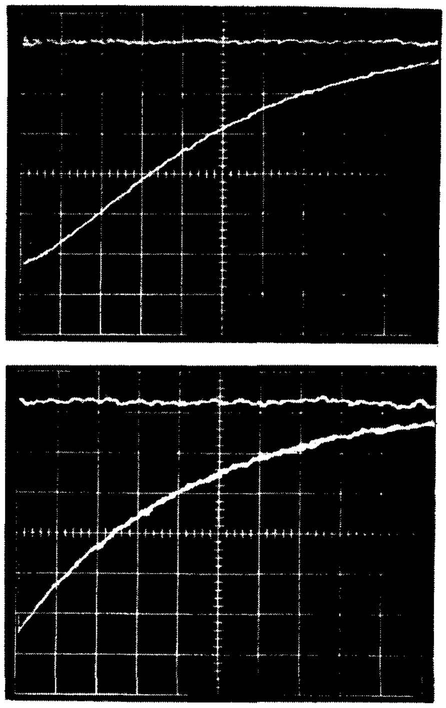


Figure 3. Stopped-flow traces for the hydrolysis of 2-(p-methoxyphenyl)-2-methoxy-1,3-dioxolane as measured by the appearance of benzoate ester product at λ 258 nm; upper trace, [HCl] = 5×10^{-4} M, 100 ms/division; lower trace, [HCl] = 5×10^{-3} M, 50 ms/division; μ = 0.04 M for both runs.

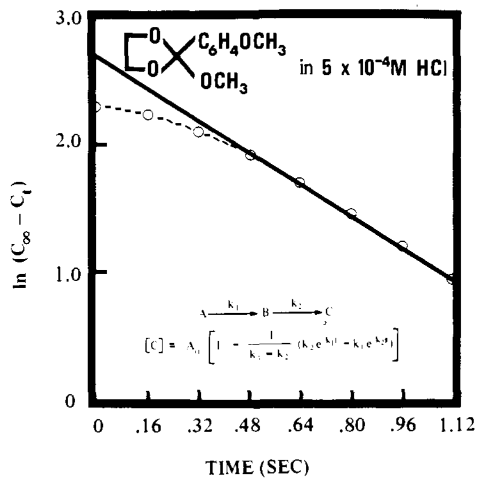


Figure 4. Rate data of Figure 3, upper trace, plotted as two consecutive first-order reactions; the solid line shows the limiting behavior when step 1 is virtually complete and step 2 is rate limiting.

This assignment of rate-determining step is consistent with the fact that rate constants measured under these conditions are characteristic of the exocyclic groups. As column 2 of Table I shows, values of k_{H^+} determined in phosphonate anion buffers of pH 5-8,[12a] labeled $k_{H^+}{}^1$ because they pertain to the first reaction stage, for a series of 2-alkoxy-2-phenyl-1,3-dioxolanes vary by a factor of 7 from 82 to 12 $M^{-1}\,s^{-1}$ as the group is changed systematically from OCH_2CH_3 to OCH_2CHCl_2. Hydronium ion catalytic coefficients measured at lower pH, in HCl solutions, however, are independent of the nature of the exocyclic group. This is illustrated by the data of column 3 of Table I: the same group of substrates which gave the sevenfold variation in $k_{H^+}{}^1$ now produces a constant specific rate: the values of $k_{H^+}{}^3$ listed here show an extreme variation of only 9% and have a standard deviation which is only 4% of the average; these differences are within the uncertainty of the experimental method. This constancy of specific rate extends also to the uncatalyzed components of these hydrolysis reactions measured at low pH: values of $k_0{}^3$ obtained by fitting the data to eq 4 show differences which are also experimentally insignificant.

The new hydronium ion catalytic coefficient measured at low pH ($k_{H^+}{}^3$), moreover, is considerably smaller, by factors ranging from 4 to 30, than any of the hydronium ion catalytic coefficients determined at high pH ($k_{H^+}{}^1$). Similar behavior for other substrates may be seen by comparing the $k_{H^+}{}^1$ and $k_{H^+}{}^3$ values of Table II; in all cases, the former is substantially greater than the latter.

The same quantity is obviously not being measured at high as at low pH, and this suggests that different steps of the overall process are being observed under the two sets of reaction conditions. This hypothesis is supported by the behavior of the systems at intermediate acidities: the appearance of product shows an induction period, as illustrated in Figure 3, upper trace, which is absent from the reaction at other acidities (Figure 3, lower trace). Data gathered in this intermediate region, moreover, conform accurately to the standard rate expression for two consecutive reactions[16] when rate constants measured at high and at low acidities are used as the specific rate parameters in this expression (see Figure 4).

This shows that, whereas dialkoxycarbonium ion formation is rate determining at high pH, some other step in the reaction process becomes rate limiting at low pH. This new slow step must involve further reaction of some intermediate which is common to the entire group of 2-alkoxy-2-phenyl-1,3-dioxolanes of Table I, inasmuch as all of the substances in this group give the same hydronium ion catalytic coefficient at low pH ($k_{H^+}{}^3$). Since it is the exocyclic alkoxy group which differentiates the members of this group, this new slow step must occur after this exocyclic group is lost. There are two steps in the general mechanism for ortho ester hydrolysis which meet this requirement: hydration of the 2-phenyl-1,3-dioxolenium ion (eq 6) formed from a 2-alkoxy-2-phenyl-1,3-dioxolane (eq 5), and decomposition of the hydrogen ortho ester hydration product (eq 7); the new slow step may therefore be either one of these two reactions.

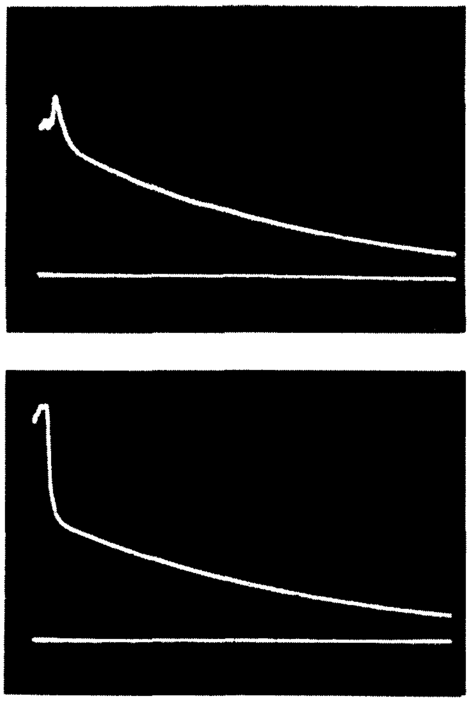
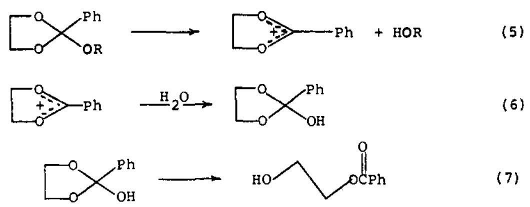


Figure 5. Stopped-flow traces illustrating the biphasic decay of the 2-(*p*-methoxyphenyl)-1,3-dioxolenium ion in 0.02 M $HClO_4$: upper trace, ion generated from ortho ester; lower trace, ion generated from amide acetal; 5 ms/division in both cases.



Detection of Dialkoxycarbonium Ion Intermediates. Dialkoxycarbonium ions can be prepared as moisture-sensitive but otherwise relatively stable salts by standard methods;[17] they are also generated by dissolving the corresponding ortho esters in concentrated sulfuric acid.[18] These ions have characteristic UV spectra with absorption maxima near 300 nm (Figure 1, solid line), and, by making observations with a stopped-flow spectrometer, we were able to detect transients which absorb in this region during the hydrolysis of some cyclic ortho esters under certain reaction conditions. Figure 1 shows that the absorption spectrum of the transient species of 2-methoxy-2-(*p*-methoxyphenyl)-1,3-dioxolane in 0.5 M $HClO_4$, constructed by combining points from individual measurements made at different wavelengths, is quite similar to that of an authentic sample of the fluoroborate salt of this ion dissolved in 85% H_2SO_4; the slight difference in the position of λ_{max} can be attributed to a not unexpected solvent effect.[19]

In relatively strongly acidic solutions, such as those used to construct the spectrum shown in Figure 1, the absorbance of the transient dioxolenium ion decays in a simple exponential fashion; the data obey the first-order rate law and give specific rate constants identical with those measured for the hydrolysis of the ortho ester under the same conditions by monitoring the appearance of carboxylic acid ester product. In more dilute acids, but still in the low pH region, the decay of the transient dioxolenium ion shows an initial faster phase in addition to the slower decrease described above. Figure 5 illustrates this biphasic decay behavior for the 2-(*p*-methoxyphenyl)-1,3-dioxolenium ion generated from 2-methoxy-2-(*p*-methoxyphenyl)-1,3-dioxolane in 0.02 M $HClO_4$ and also from the corresponding amide acetal, 2-(*N*,*N*-dimethylamino)-2-(*p*-methoxyphenyl)-1,3-dioxolane; the initial phase is particularly prominent in the latter case because the very rapid generation of the dioxolenium ion from the amide acetal allows clean separation of the decay process from the generation reaction.

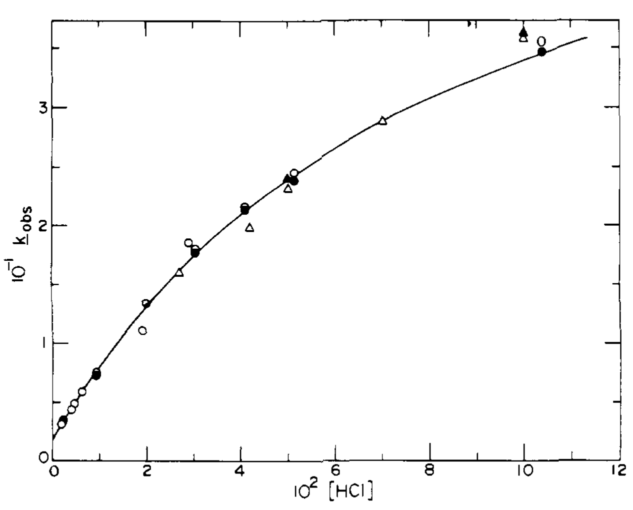
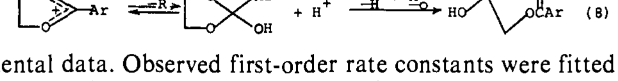


Figure 6. Relationship between acid concentration and observed first-order rate constants for the hydrolysis of 2-(*p*-methoxyphenyl)-2-methoxy-1,3-dioxolene (circles) and the corresponding amide acetal, 2-(*p*-methoxyphenyl)-2-(*N*,*N*-dimethylamino)-1,3-dioxolane (triangles). Open symbols denote rate of formation of benzoate ester product and filled symbols denote rate of disappearance of dioxolenium ion.

Although this initial decay is very rapid, data can be obtained which give a reasonable fit to the first-order rate law. Rate constants derived in this way are independent of acidity, in the range 0.002–0.01 M HCl, and their average value, $k_O{}^2 = (1.0 \pm 0.2) \times 10^3\ s^{-1}$, is of the magnitude expected for reaction of the 2-(*p*-methoxyphenyl)-1,3-dioxolenium ion with water.[18b]

Considerably more accurate first-order rate constants can be obtained from the second, slower (but still quite fast) portion of the biphasic dioxolenium ion decay. These rate constants are identical within experimental error with rate constants measured by monitoring the appearance of carboxylic acid ester product, and they are the same when the dioxolenium ion is generated from the amide acetal as when it is generated from the ortho ester (Figure 6). This part of the decay reaction is acid catalyzed, but, as Figure 6 shows, the relationship between observed rate constant and acid concentration is not linear. The impending saturation of the catalytic effect shown at higher acid concentrations suggests that the decay reaction is coupled to a proton-transfer equilibrium, and a scheme in which the dioxolenium ion is in equilibrium with a proton plus hydrogen ortho ester, while the latter undergoes rate-determining decomposition to product, eq 8, is consistent with the experimental data.



Observed first-order rate constants were fitted to the rate law for this process, eq 9, and best values of the three parameters, $k_O{}^3$, $k_{H^+}{}^3$, and K_R were obtained. These are listed in Table II; they were also used to draw the line through the experimental points shown in Figure 6.

$$k_{obsd} = \frac{k_O{}^3 + k_{H^+}{}^3[H^+]}{1 + [H^+]/K_R} \tag{9}$$

This interpretation of the slow portion of the biphasic dioxolenium ion decay leaves the initial fast phase to represent the fast reaction of dioxolenium ion with water which occurs

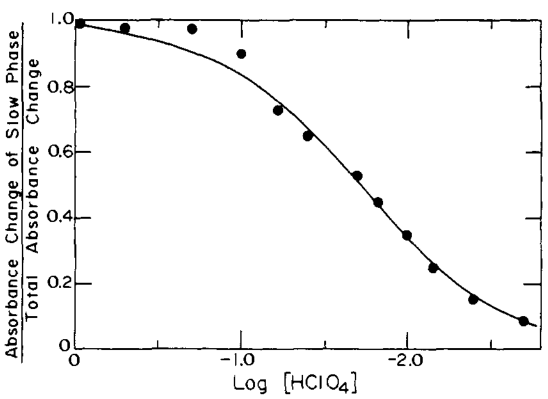


Figure 7. Sigmoid titration curve obtained from the absorbance changes in the biphasic decay of the 2-(*p*-methoxyphenyl)-1,3-dioxolenium ion in $HClO_4$ solutions at an ionic strength of 1.0 M. The ordinate is the ratio of (absorbance change given by slow phase)/(total absorbance change of both phases).

until equilibrium concentrations of the ion and hydrogen ortho ester are reached. If this view of the situation is correct, then the absorbance change realized in the fast phase of the decay should be proportional to the concentration of hydrogen ortho ester present at equilibrium, and the absorbance change given by the slow phase should be proportional to the concentration of dioxolenium ion at equilibrium. The relative magnitude of the two absorbance changes does vary with hydrogen ion concentration as expected on the basis of this explanation and the chemistry of the equilibrium reaction of eq 8; in particular, at sufficiently high acidities (0.5 M for the 2-(*p*-methoxyphenyl)-1,3-dioxolenium ion) where this equilibrium should be completely to the left, the fast phase disappears entirely. It is possible, in fact, to use these absorbance changes to construct the sigmoid titration curve shown in Figure 7, and, from its inflection point, to obtain an estimate of the equilibrium constant for this reaction; the result, $pK_R = 1.7$, is in very good agreement with the value obtained from a kinetic analysis using eq 9, $pK_R = 1.8$. (Both of these pK_R values refer to an ionic strength of 1.0 M.)

Additional support for the essential validity of this interpretation of the experimental observations comes from the value of the rate constant for the reverse reaction in the equilibrium step of eq 8, $k_{H^+}{}^{-2}$, which may be calculated from K_R and the specific rate of the forward reaction, $k_O{}^2$: $K_R = k_O{}^2/k_{H^+}{}^{-2}$.[20] This reverse reaction, loss of -OH from the hydrogen ortho ester, under catalysis by H^+, is very similar to the loss of $-OCH_3$ from the ortho ester itself, and the two processes should therefore have similar rates. This is, in fact, the case: for the hydrolysis of 2-methoxy-2-(*p*-methoxyphenyl)-1,3-dioxolane the calculated value of $k_{H^+}{}^{-2}$ is 1.5×10^4 M^{-1} s^{-1} whereas the measured rate constant for $-OCH_3$ loss, $k_{H^+}{}^1$, is 1.9×10^4 M^{-1} s^{-1}.

Stopped-flow spectrometric methods also revealed a dioxolenium ion intermediate during the hydrolysis of 2-methoxy-2-cyclopropyl-1,3-dioxolane. Here, however, unlike in the 2-(*p*-methoxyphenyl) system, the first phase of the dioxolenium ion decay was too fast to be seen and only the second phase was observed, although the existence of the first phase could be inferred from the acidity dependence of the variation of the absorbance change of the phase observed. First-order specific rates of decay of this ion were identical with first-order rate constants for the appearance of carboxylic acid product, and, from the curved relationship between these and hydronium ion concentration, values of K_R, $k_{H^+}{}^3$, and $k_O{}^3$ were obtained; these are listed in Table II. Because the first phase of dioxolenium ion decay was not observed here, the rate constant for reaction of this ion with water, $k_O{}^2$, could not be determined and $k_{H^+}{}^{-2}$ could not in turn be calculated via the relationship $K_R = k_O{}^2/k_{H^+}{}^{-2}$. A value of $k_{H^+}{}^{-2}$ could nevertheless be estimated by using the similarity of the $k_{H^+}{}^{-2}$ and $k_{H^+}{}^1$ processes noted above for the 2-(*p*-methoxyphenyl) system. In that case $k_{H^+}{}^{-2}/k_{H^+}{}^1$ was found to be 0.8, and, assuming a similar value of this ratio holds for the cyclopropyl system, $k_{H^+}{}^{-2} = 0.8\ k_{H^+}{}^1 = (0.8)(5.0 \times 10^4) = 4.0 \times 10^4$ M^{-1} s^{-1}. This estimate leads, via $K_R = k_O{}^2/k_{H^+}{}^{-2}$, to $k_O{}^2 = 3.2 \times 10^3$ s^{-1}, which is just beyond the capability of the stopped-flow method and thus rationalizes our inability to detect the first phase of dioxolenium ion decay in this system.

These experiments with cyclopropyl and *p*-methoxyphenyl substituted 1,3-dioxolanes were performed in solutions of 0.10 M ionic strength and were therefore limited to acidities no greater than $[H^+] = 0.10$ M. Under these conditions, dioxolanes with less strongly electron-donating substituents gave dioxolenium ion intermediates only in low concentration, but in more acidic solutions, which required higher ionic strengths ($\mu = 1.0$ M), strong dioxolenium ion absorbance was found during the hydrolysis of 2-(*p*-tolyl)-, 2-phenyl-, and 2(-*p*-fluorophenyl)-1,3-dioxolane. Here, just as in the cyclopropyl system, only the second, slower, phase of the dioxolenium ion decay could be seen, and estimates of rate constants for the reaction of these ions with water ($k_O{}^2$), made as described above for the cyclopropyl system, once again showed that the initial fast phase occurred during the mixing time of the stopped-flow instrument. First-order rate constants calculated from the slower second phases were again identical with specific rates of appearance of carboxylic acid ester product, and values of K_R and $k_{H^+}{}^3$ were obtained from the curved relationship between these rate constants and $[H^+]$, via eq 9; at the high acidities employed, uncatalyzed contributions to the rates were very small, and reliable estimates of $k_O{}^3$ could not be made. The results obtained are summarized in Table II.

Observations at this higher ionic strength were also made with 2-(*p*-methoxyphenyl)-2-methoxy-1,3-dioxolane, and comparison of these with measurements made at $\mu = 0.10$ M showed appreciable salt effects on K_R and $k_{H^+}{}^3$: $pK_R = 1.1$ at $\mu = 0.10$ M and 1.8 at $\mu = 1.0$ M, and $k_{H^+}{}^3 = 7.5 \times 10^2$ M^{-1} s^{-1} at $\mu = 0.10$ M and 13×10^2 M^{-1} s^{-1} at $\mu = 1.0$ M. Similar salt effects on carbonium ion–carbinol equilibria in acid solutions have been observed before and have been found to arise from an increase in the rate of reaction of carbinol with H^+, augmented somewhat by a decrease in the rate of reaction of the carbonium ion with H_2O.[21] This suggests that the increase in pK_R in the present case is produced by a rise in the rate of reaction of hydrogen ortho ester with H^+ to form dioxolenium ion ($k_{H^+}{}^{-2}$), coupled with a decrease in the rate of reaction of the ion with water ($k_O{}^2$). The latter may be attributed to a decrease in the activity of water in the more concentrated salt solutions,[9] and the former to an increase in hydrogen ion activity with increasing ionic strength; such an increase in hydrogen ion activity would raise $k_{H^+}{}^3$ as well.

It is likely that the change of 0.7 in pK_R on going from solutions of $\mu = 0.10$ M to solutions of $\mu = 1.0$ M found for the 2-(*p*-methoxyphenyl)-1,3-dioxolenium ion applies to other members of the series as well,[22] and this difference was therefore used to estimate pK_R values at $\mu = 0.10$ M for dioxolenium ions for which reliable measurements could only be made at $\mu = 1.0$ M. These, together with values of $k_{H^+}{}^{-2}$ calculated by the relationship used before for the cyclopropyl system, $k_{H^+}{}^{-2}/k_{H^+}{}^1 = 0.8$, and the values of $k_O{}^2$ derived therefrom, are listed in Table II.

In the hydrolysis of other dioxolanes with 2-phenyl substituents containing electron-withdrawing groups, only weak transient dioxolenium ion absorbances could be detected, even in these more strongly acidic solutions. No quantitative measurements of pK_R could therefore be made with these compounds. Using the four pK_R values which could be measured,

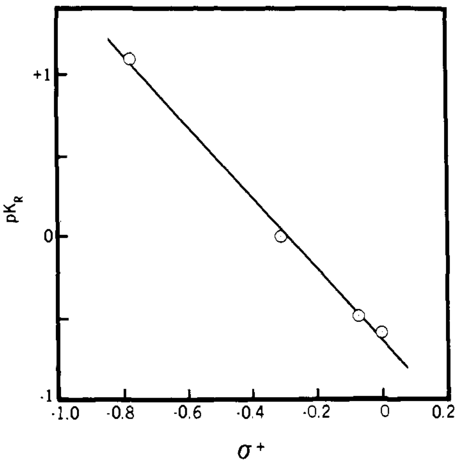


Figure 8. Correlation with σ^+ of pK_R values for the reaction of 2-aryl-1,3-dioxolenium ions with water.

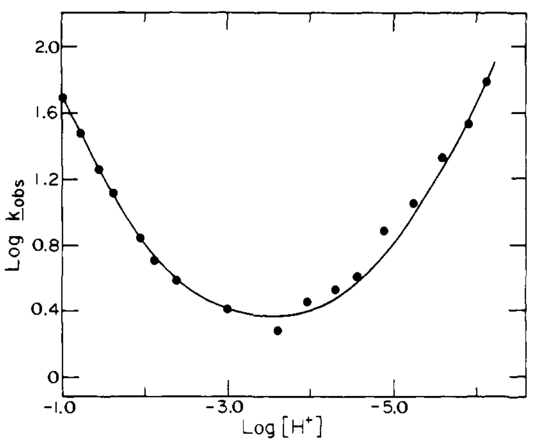


Figure 9. Rate profile for the decomposition of 2-hydroxy-2-phenyl-1,3-dioxolane generated from 2-phenyl-1,3-dioxolenium fluoroborate in 50% aqueous acetonitrile.

a reasonable correlation with σ^+ is found (Figure 8). The pK_R values listed in Table II for the substrates with electron-withdrawing groups have been estimated by extrapolation using this correlation.

Decomposition of Hydrogen Ortho Ester Intermediates. The evidence presented above shows that, at low pH, decomposition of the hydrogen ortho ester intermediate is the slow step in the hydrolysis of the aromatic and cyclopropyl cyclic ortho esters studied here. At high pH, on the other hand, the first stage of the three-stage mechanism of eq 1-3, formation of a dioxolenium ion, is rate determining. This change in rate-determining step is the result of an efficient base catalysis of the hydrogen ortho ester decomposition reaction, which begins to operate at a fairly low pH. As the pH is increased, this base catalysis speeds up hydrogen ortho ester decomposition, and, since dioxolenium ion formation is not base catalyzed at all, hydrogen ortho ester decomposition soon becomes much faster than dioxolenium ion formation and the latter becomes the rate-determining step.

We were able to demonstrate this base catalysis for the decomposition of the hydrogen ortho esters which occurs in the presently studied reactions by generating them in solutions containing bases and measuring their rates of reaction there. This required entry into the ortho ester hydrolysis reaction system after its rate-determining step, which we accomplished by using preformed dioxolenium ions as the kinetic substrates. Since the reactions are fast, stopped-flow techniques were required, and, since dioxolenium ion salts are unstable in water, one of the solutions mixed had to be nonaqueous. We chose acetonitrile for this purpose because experiments showed that the artifacts which usually attend the mixing of two dissimilar solutions are minimal for the acetonitrile-water combination.

The instrument with which we performed these measurements can only mix two solutions in equal amounts, and the reaction rates which we determined therefore refer to 50% aqueous acetonitrile (v/v). The behavior in this medium may be quantitatively different from that in wholly aqueous solution, but there is no reason to believe that it is not a good qualitative indication of the situation there.

When an acetonitrile solution of 2-phenyl-1,3-dioxolenium fluoroborate was mixed in the stopped-flow apparatus with either dilute aqueous HCl or dilute aqueous formic or acetic acid buffer solutions, no absorbance attributable to dioxolenium ion could be detected, even immediately after mixing. This is consistent with the fast rate of reaction of this ion with water in wholly aqueous solution and the large value of K_R for this system (Table II). The formation of carboxylic acid ester product, on the other hand, occurred more slowly and could be followed easily by the stopped-flow technique. The data obtained adhered to the first-order rate law exactly; first-order rate constants are summarized in Table S4.[14] In buffer solutions this process showed both general acid and general base catalysis, conforming to the rate law shown in eq 10. Values of k_0 gave the rate profile shown in Figure 9; it may be seen that catalysis by H^+ gives way to a brief "uncatalyzed" region at $[H^+] = 10^{-3}$-10^{-4} M and that catalysis by HO^- becomes important rather early at H^+ concentrations as great as 10^{-4} M.

$$k_{obsd} = k_0 + k_{HA}[HA] + k_B[B] \qquad (10)$$

Additional evidence confirming this pattern of reactivity may be adduced from the behavior of amide acetals.[11] These substances generate dioxolenium ions very rapidly in acidic and neutral solution, but they are moderately stable in aqueous alkali. They can therefore be used to produce hydrogen ortho esters in wholly aqueous solution and to study the decomposition of these substances in that medium. The picture which results is very similar to that shown in Figure 9. In particular, there is a very early emergence of a hydroxide ion catalyzed reaction, at an acidity as great as pH 4, with a very large specific rate constant: $k_{HO^-}{}^3 = 6 \times 10^{10}$ M^{-1} s^{-1} for the 2-phenyl system.[23]

With this information, it is possible to construct the rate profile for ortho ester hydrolysis shown in Figure 10. The solid lines in this diagram refer to the first and third stages in the hydrolysis of 2-methoxy-2-phenyl-1,3-dioxolane. Stage 1 is subject to acid catalysis only, and its rate simply decreases with decreasing acidity in the linear fashion shown. Since the specific rate of this step, $k_{H^+}{}^1 = 5400$ M^{-1} s^{-1}, is greater than that of stage 3, $k_{H^+}{}^3 = 300$ M^{-1} s^{-1}, stage 3, i.e., hydrogen ortho ester decomposition, is rate-determining at low pH. Near pH 2, however, the uncatalyzed component of stage 3, $k_0{}^3 = 1.5$ s^{-1}, begins to add to the rate of this step, and at pH 3-4 hydroxide ion catalysis starts to contribute as well. As a result, the rate of stage 3 levels off and then begins to rise while the rate of stage 1 continues to fall. The two rates eventually cross, and stage 1, the initial reaction of ortho ester to give dioxolenium ion, becomes rate-determining.

The broken lines in this figure illustrate these rate relationships for the 2-methoxy-2-(*p*-nitrophenyl)-1,3-dioxolane system. The rates of both stages 1 and 3 are slowed by the introduction of the *p*-nitro substituent, the former somewhat more than the latter. The uncatalyzed component of stage 3, on the other hand, is accelerated slightly. The net result of this

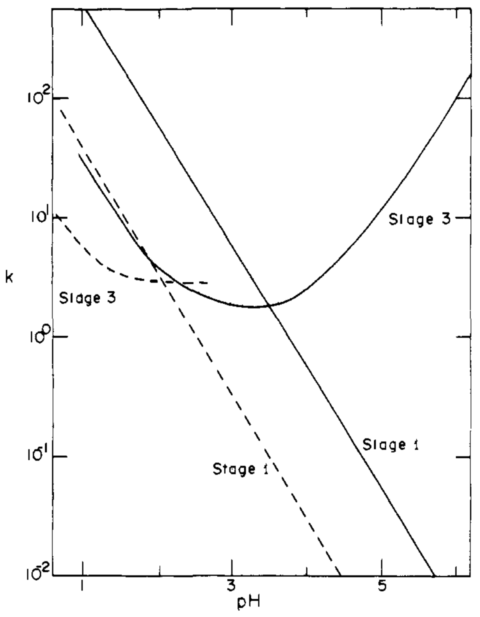
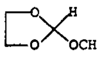


Figure 10. Rate profiles for the first and third stages in the hydrolysis of 2-phenyl-2-methoxy-1,3-dioxolane (——) and 2-(p-nitrophenyl)-2-methoxy-1,3-dioxolane (---) in wholly aqueous solution at 25 °C.

is an earlier crossover point and a smaller region in which stage 3 is rate determining.

These rate relationships also lead to the expectation that the dioxolenium ion–hydrogen ortho ester equilibrium of stage 2 will be a rapidly attained preequilibrium whenever stage 3, hydrogen ortho ester decomposition, is rate determining. For this to be the case, hydrogen ortho ester must revert to dioxolenium ion faster than it goes on to carboxylic acid ester product, i.e., $k_{H^+}{}^{-2}$ must be greater than $k_{H^+}{}^3$. It was pointed out above that the reverse of stage 2 is very similar to stage 1 in the forward direction—one reaction involves the loss of HO while the other involves the loss of CH_3O from a 2-substituted 1,3-dioxolane moiety—and, as a result, $k_{H^+}{}^{-2} \approx k_{H^+}{}^1$. When stage 3 is rate determining, $k_{H^+}{}^1 > k_{H^+}{}^3$, and, if $k_{H^+}{}^{-2} \approx k_{H^+}{}^1$, then $k_{H^+}{}^{-2}$ must be greater than $k_{H^+}{}^3$ as well.

Origin of the Change in Rate-Determining Step. We were unable to detect dioxolenium ion intermediates during the hydrolysis of the aliphatic ortho esters 2-methoxy-1,3-dioxolane (**10**) and 2-methyl-2-methoxy-1,3-dioxolane (**11**). These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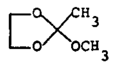
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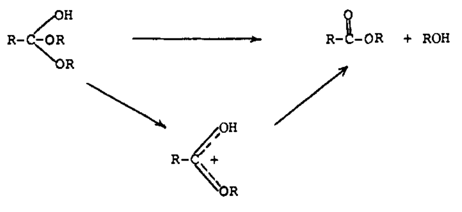
substrates, moreover, give hydronium ion catalytic coefficients in dilute HCl solution, $k_{H^+} = (1.83 \pm 0.1) \times 10^2\ M^{-1}\ s^{-1}$ (**10**) and $(1.40 \pm 0.03) \times 10^3\ M^{-1}\ s^{-1}$ (**11**), which are not significantly different from values obtained in biphosphate buffers at pH $\simeq$ 7: $k_{H^+} = (1.75 \pm 0.03) \times 10^2\ M^{-1}\ s^{-1}$ (**10**)[12c] and $(1.50 \pm 0.03) \times 10^3\ M^{-1}\ s^{-1}$ (**11**). Aliphatic dioxolanes such as this, therefore, do not undergo a change in rate-determining step between low and high pH, and the first stage of the three-stage reaction mechanism remains rate limiting throughout.

It can be argued that this is the normal situation, and that the aromatic and cyclopropyl derivatives which we found to undergo a change in rate-determining step are showing unusual behavior. This follows from the fact that the first and third stages of ortho ester hydrolysis consist of chemical reactions which must occur by rather similar paths in acid solution, and which should therefore have specific rates which are, to a first approximation, not grossly dissimilar. Stage 3, however, has open to it a mechanism (eq 11) which avoids an unstable cationic intermediate, **12**, not unlike that generated in stage 1 (eq 1), and it might therefore be expected to be the somewhat slightly faster process. Thus, stage 3 should normally be faster than stage 1, even in acid solution, and no change in rate-determining step should occur upon going to less acidic media.



(11)

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It follows then, that a change in rate-determining step must be brought about by a perturbation which makes stage 1 faster than stage 3 in acid solution and thereby permits a switch to occur when base catalysis of stage 3 takes over. The perturbation which serves this purpose in the case of the aromatic dioxolanes studied here appears to be the phenyl group effect.[12c] Phenyl substitution at the *pro*-acyl carbon atom of ortho esters which give acyclic dialkoxycarbonium ions is known to lower the rate of hydrolysis of these substances, because a steric effect operates in stage 1 to inhibit the normal cation-stabilizing ability of the benzene ring. In cyclic species, such as the 2-phenyl-1,3-dioxolenium ion, this steric inhibition is relieved, and phenyl substitution in ortho esters which give such ions accelerates the rate of reaction of stage 1 in the hydrolysis of these substances. For example, phenyl substitution at the *pro*-acyl carbon atom of 2-methoxy-1,3-dioxolane gives the stage 1 rate acceleration of $k_{H^+}{}^1(Ph)/k_{H^+}{}^1(H) = 5400/175 = 31$.[24] The effect on stage 3 is more difficult to estimate, inasmuch as a change in rate-determining step was not observed for the reference compound, 2-methoxy-1,3-dioxolane, and a value of $k_{H^+}{}^3(H)$ could therefore not be determined. However, a lower limit can be placed upon $k_{H^+}{}^3(H)$, for, if stage 1 is to be rate limiting throughout, $k_{H^+}{}^3(H)$ must be greater than $k_{H^+}{}^1(H)$. Calculations using the standard expression for two consecutive first-order reactions[16] and various ratios of the two rate constants showed that, if the second reaction is not at least five times as fast as the first, the rate of formation of product will show a clearly discernible induction period such as that visible in the upper trace of Figure 4. Since no such induction period was seen during the hydrolysis of 2-methoxy-1,3-dioxolane, $k_{H^+}{}^3$ for this substance can be taken to be at least five times $k_{H^+}{}^1$, or $k_{H^+}{}^3 > 5 \times 175 \simeq 900\ M^{-1}\ s^{-1}$. This gives a phenyl group effect on stage 3 in the hydrolysis of 2-methoxy-1,3-dioxolane of $k_{H^+}{}^3(Ph)/k_{H^+}{}^3(H) < 300/900 < 0.3$. The differential phenyl group effect on stage 1 vs. stage 3 in this system is therefore equal to or greater than $31/0.3 \simeq 100$; i.e. phenyl substitution at the *pro*-acyl carbon atom raises the rate of stage 1 relative to that stage 3 by a factor of at least 100; this is enough to make stage 1 faster than stage 3 in acid solutions and allow a change in rate-determining step to occur in less acidic media.

A similar differential phenyl group effect operates in the hydrolysis of the substituted phenyl dioxolanes examined here, although it diminishes with the introduction of electron-withdrawing groups and for p-nitrophenyl has dropped to half its unsubstituted, phenyl group value. In the cyclopropyl system, the perturbation which makes stage 1 faster than stage 3 in acid solutions is a large accelerative effect of the cyclopropyl group upon $k_{H^+}{}^1$, 50 000/175 = 286. The changes in rate-determining step observed in other systems may also be traced to an increase in the rate of stage 1: in the case of acyloxy ortho esters[8] and acylals,[7] through introduction of a better leaving group, and in the case of cyclic[3,4] or *tert*-butyl[5] acetals, through the release of ring strain or steric crowding.

Lifetime of Tetrahedral Intermediates. In a recently advanced theory of stereoelectronic control of the hydrolysis of carboxylic acid esters and amides, it is proposed that the nature of the products obtained is governed by the conformation of the tetrahedral intermediate formed during the course of these reactions.[25] This theory requires tetrahedral intermediates to be relatively short lived; specifically in its application to cyclic, e.g., six-membered ring, systems it implies that these intermediates react before chair-chair interconversions can take place.[26] Since these tetrahedral intermediates in the case of ester hydrolysis are in fact the same as the hydrogen ortho esters detected in the present study, the measurements of their lifetimes made here have a direct bearing upon this assumption of the stereoelectronic theory. In particular, the data of Table II show that, under certain conditions, tetrahedral intermediates are relatively stable, with lifetimes approaching one second. Since chair-chair interconversions generally occur in times much shorter than this, this assumption of the stereoelectronic theory cannot be universally correct.

Acknowledgment. We are grateful to the Natural Sciences and Engineering Research Council Canada (formerly National Research Council of Canada), the National Science Foundation of the United States, and the donors of the Petroleum Research Fund, administered by the American Chemical Society, for their financial support of this work.

Supplementary Material Available: Tables S1-S4 of rate constants (7 pages). Ordering information is given on any current masthead page.

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The Substituent Effect on the Thermal Decomposition of Acetal Hydrotrioxides. Polar and Radical Decomposition Paths

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Abstract: Low-temperature ozonation of aliphatic and aromatic acetals leads to oxygen-rich intermediates, acetal hydrotrioxides **1-3**, the NMR spectra of which show two absorptions at δ 13 ppm downfield from Me_4Si. Decomposition of these compounds, which affords among other products singlet oxygen and peroxides, involves nonradical and radical processes. The kinetics of decomposition has been studied by NMR spectroscopy and activation parameters have been determined. Electron-withdrawing substituents in **3** accelerate decomposition in diethyl ether while electron-donating groups retard it (Hammett ρ value 1.2 ± 0.2). Considerable charge separation in the transition state for the decomposition has been proposed.

Introduction

The chemistry of organic polyoxides of the type RO_nR (R = alkyl; n = 3, 4) has been a matter of considerable interest during the past 2 decades.[1] Spectroscopic[1k,n] and theoretical[2] evidence has been given in recent years for their existence. Much less is known about alkyl hydropolyoxides, RO_nH. Alkyl hydrotrioxides have been proposed as unstable intermediates in ozonation of various organic compounds, i.e., ethers,[3] silanes,[4] amines,[5] alcohols,[6] ketones,[6a,8] and aldehydes.[6b,9] It was only recently that Murray et al. reported the first spectroscopic evidence for their existence.[9b]

0002-7863/79/1501-2677$01.00/0