Ortho Ester Hydrolysis: Concerted Nature of the Dialkoxycarbonium Ion Forming Stage
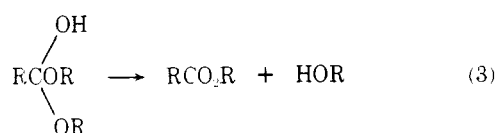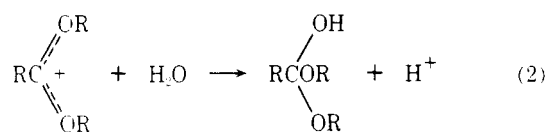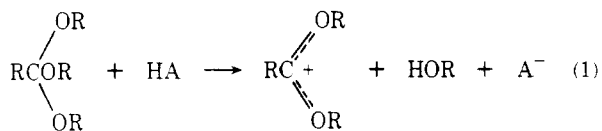
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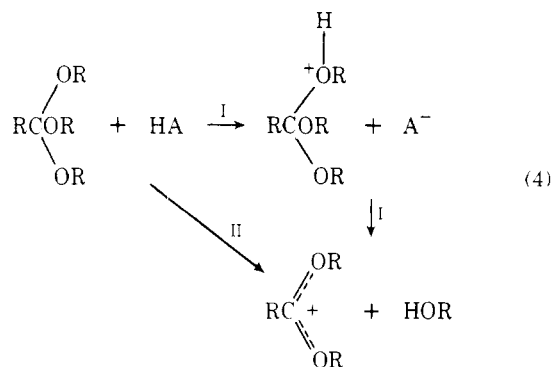
Rates of hydrolysis of a group of 2-alkoxy-2-phenyl-1,3-dioxolanes catalyzed by a series of monohydrogenphosphonate anions, RPO_3H^-, in aqueous solution were measured under conditions where loss of the exocyclic group is rate determining. These data give Brønsted relations whose exponents decrease with decreasing basicity of the exocyclic oxygen atom [R(exocyclic alkoxy group) = OCH_3, 0.90; $OCH_2CH_2OCH_3$, 0.85; OCH_2CH_2Cl, 0.80; $OCH_2C\equiv CH$, 0.70; OCH_2CHCl_2, 0.69], which, according to an argument based upon "tilting" potential energy surfaces, requires the proton transfer and C–O bond breaking that occur in this reaction stage to be concerted rather than stepwise.

In preceding papers,[1] we showed that under certain conditions the acid-catalyzed hydrolysis of carboxylic acid ortho esters undergoes a change in rate-determining step and that dialkoxycarbonium ions may be detected as reaction intermediates. This provided the first direct support of the commonly accepted three-stage mechanism for this reaction: (1) generation of a dialkoxycarbonium 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).

$$RC \underset{OR}{\overset{OR}{\big(}} OR + HA \longrightarrow RC^+ \underset{OR}{\overset{OR}{\big(}} + HOR + A^- \quad (1)$$

$$RC^+ \underset{OR}{\overset{OR}{\big(}} + H_2O \longrightarrow RC \underset{OR}{\overset{OH}{\big(}} OR + H^+ \quad (2)$$

$$RC \underset{OR}{\overset{OH}{\big(}} OR \longrightarrow RCO_2R + HOR \quad (3)$$

In the first of these three reaction stages, two bonding changes occur: (1) a proton is transferred from the catalyst to an ether oxygen atom of the substrate, and (2) the C–O bond joining this oxygen to the pro-acyl carbon atom is cleaved. These bonding changes can, in principle, occur either separately or together, and the mechanism of this reaction stage may therefore be either stepwise (eq 4, route I) or concerted (eq 4, route II).

$$RC \underset{OR}{\overset{OR}{\big(}} OR + HA \overset{I}{\longrightarrow} RC \underset{OR}{\overset{+OR-H}{\big(}} OR + A^- \quad (4)$$

(route II diagonal) $RC^+ \underset{OR}{\overset{OR}{\big(}} + HOR$

It is possible to distinguish between these two alternatives through the use of three-dimensional reaction coordinate contour diagrams or "tilting" potential energy surfaces. This method of viewing complex reactions was first introduced by Albery in connection with solvent isotope effects,[2] but it is now better known for its application to olefin-forming elimination reactions by More O'Ferrall[3] and to carbonyl group additions by Jencks.[4]

A schematic representation of such a surface for the first stage of ortho ester hydrolysis is shown in Figure 1. The starting materials, ortho ester (SOR) and acid (HA), are in the depression A, at the upper right of this diagram, and the products, dialkoxycarbonium ion (S^+), alcohol (HOR), and conjugate base of the catalyst (A^-), are at C in the lower left; the horizontal coordinate represents proton transfer, and the vertical coordinate denotes C–O bond cleavage. The stepwise reaction path then follows the edges of this diagram, from A through transition state 1 ($\ddagger_1$) to B and then down to C, whereas the concerted route lies along the diagonal from A to C and involves passage through transition state 2 ($\ddagger_2$).

Using this diagram, different predictions of the effect upon the system of structural changes in R may be made for the two reactions paths. If, e.g., an electron-withdrawing group is introduced into R, the oxygen atom of SOR will become less basic, and the energy difference between SOR and its conjugate acid will increase. This will raise the upper left-hand corner of the surface, consequently moving $\ddagger_1$ toward this corner and producing a greater extent of proton transfer in $\ddagger_1$ (Hammond postulate,[5] parallel effect); this would be evident as an increase in the Brønsted exponent α for this reaction step.[6] On the other hand, the same change in R will have the opposite effect on the concerted reaction path, inasmuch as an increase in the height of B will tilt the potential energy surface and cause $\ddagger_2$ to slide down away from this corner (Thornton rule;[7] perpendicular effect); this displacement has a component along the proton transfer coordinate which is in the direction of *less* proton transfer, and that would produce a decrease rather than an increase in the Brønsted exponent.

The experiment which this analysis suggests requires a rather special kind of ortho ester, for only one corner of the potential energy surface can be altered, i.e., the nature of R must be changed without affecting the energy of the dialkoxycarbonium ion S^+. This means that structural variations must be confined to only one of the alkoxy groups of $RC(OR)_3$, and this varied group, moreover, must always be the one which leaves in the dialkoxycarbonium ion forming stage of this reaction. These conditions are not easily met with ordinary acyclic ortho esters, but they can be realized in the cyclic 2-aryl-2-alkoxy-1,3-dioxolane series, where the exocyclic group is known to be lost in preference to ring cleavage (eq 5).[1,8] We accordingly prepared a series of such cyclic ortho esters, with appropriate structural variations in R, and measured their
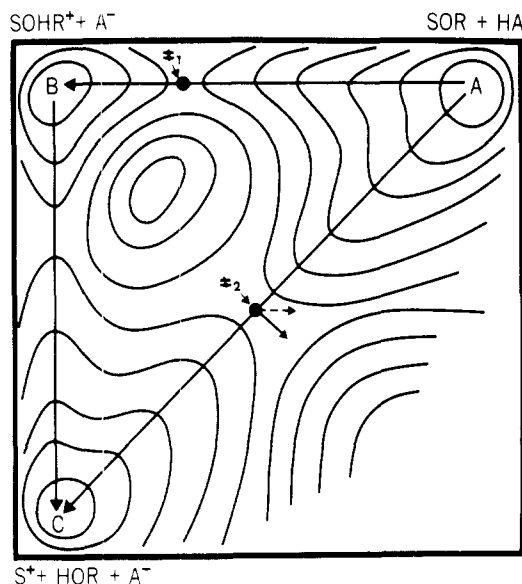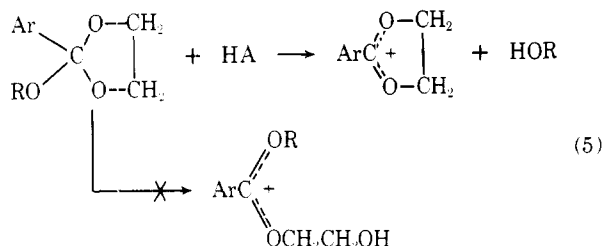
Figure 1. Schematic representation of potential energy surface for the first stage of ortho ester hydrolyis.

Figure 2. Relationship between observed first-order rate constants and biphosphate ion concentration in the hydrolysis of 2-(2-methoxyethoxy)-2-phenyl-1,3-dioxolane in biphosphate–monohydrogenphosphate buffer solutions at 25 °C. Upper line, buffer ratio = 7; lower line, buffer ratio = 2.

$$Ar \underset{RO}{\overset{O-CH_2}{\underset{O-CH_2}{C}}} + \; HA \; \longrightarrow \; ArC\overset{O-CH_2}{\underset{O-CH_2}{+}} + \; HOR \quad (5)$$

rates of acid-catalyzed hydrolysis, using a series of monohydrogenphosphonate ion catalysts. These measurements were made in the pH range 5–8, where dialkoxycarbonium ion formation is known to be the rate-determining stage in the hydrolysis of these ortho esters.[1]

Experimental Section

Materials. The cyclic ortho esters were prepared from trimethyl orthobenzoate by acid-catalyzed transesterification. Trimethyl orthobenzoate (Aldrich Chemical Co.) was first converted into 2-methoxy-2-phenyl-1,3-dioxolane by treatment with ethylene glycol and Dowex 50W-X4 acid resin, and other 2-alkoxy-2-phenyl-1,3-dioxolanes were then obtained by treating the 2-methoxy derivative with the appropriate alcohol and catalyst (either Dowex resin or *p*-toluenesulfonic acid). The NMR and IR spectra of all of these ortho esters were consistent with their proposed structures, and all new substances gave satisfactory elemental analyses.[9] Samples for kinetic measurements were purified by gas chromatography.

Phosphonic acids were prepared as described;[10] all other materials were best available commercial grades. Buffer solutions were prepared using water redistilled in an all-glass apparatus.

Kinetics. Rates of ortho ester hydrolysis were determined spectrophotometrically by following the increase in benzoate ester absorbance at 231 nm ($\epsilon \simeq 12\,000$). Measurements were made using a Cary Model 118 spectrometer equipped with a jacketed multiple sample cell block through which water was circulated from a constant temperature bath operating at 25.0 ± 0.01 °C. Before a kinetic run, 3-mL aliquots of buffer solution were placed in 1-cm quartz cells, and these were then allowed to reach temperature equilibrium with the cell block. Reactions were initiated by adding 5 μL of an ethanol solution of ortho ester to the quartz cell, shaking the cell vigorously for a few seconds, and then replacing the cell into the cell block. Reactions were followed to completion (10–12 half-lives), and pseudo-first-order rate constants were calculated by least-squares analysis as gradients of ln $(A_\infty - A)$ upon time. Runs with correlation coefficients less than 0.9999 were rejected.

Reactions in trichloromethyl phosphonic acid solutions were too rapid to be measured by this technique, and a Durrum-Gibson stopped-flow spectrometer was therefore used instead. A solution of
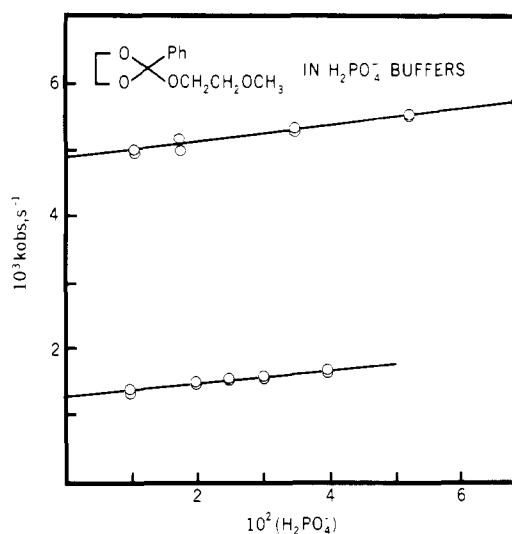
ortho ester, typically 5×10^{-5} M, dissolved in $\sim 2 \times 10^{-5}$ M NaOH was placed in one drive syringe of the apparatus, and the buffer solution was placed in the other. The solutions were then mixed (~ 2 ms) and the subsequent reaction was followed and recorded on a storage oscilloscope. The display was then photographed, and data were read from the photograph and treated as described above for the slower runs. Three or four runs were typically made with the same solutions and the results were averaged.

Results

Rates of hydrolysis of five different 2-alkoxy-2-phenyl-1,3-dioxolanes were measured in aqueous buffer solutions of biphosphate ion and five alkyl monohydrogenphosphonate anions. For each substrate–buffer combination, first-order rate constants were determined (generally in duplicate and sometimes in triplicate) in a series of solutions of varying buffer concentration but constant buffer ratio. Buffer acid concentrations were changed several fold in the range 0.0025 to 0.070 M, and ionic strength was maintained constant at 0.10 M by the addition of sodium chloride. Sodium ion was also the counterion used in conjunction with the anionic buffer species. These data are summarized in Table S1[11] (see Supplementary Material paragraph).

General acid catalysis was not as pronounced in these reactions as we found previously for other examples of proton transfer from monohydrogenphosphonate anions to neutral substrates.[12] Nevertheless, observed first-order rate constants, k_{obsd}, did depend significantly upon undissociated buffer acid concentration, [HA] (Figure 2 gives some typical examples,), and second-order general acid catalytic coefficients could be obtained as gradients of k_{obsd} upon [HA]. Least-squares analysis gave the results listed in Table I.

The examples of Figure 2 show also that catalytic coefficients obtained in this way were independent of buffer ratio: the uppermost set of data in this figure, obtained at [HA]/[NaA] = 7, gave $k_{HA} = (1.13 \pm 0.07) \times 10^{-2}$ M^{-1} s^{-1}, whereas the lower set, obtained at [HA]/[NaA] = 2, gave $k_{HA} = (0.96 \pm 0.08) \times 10^{-2}$ M^{-1} s^{-1}. This indicates that there is no catalysis by basic buffer species, as is to be expected for this reaction.

The complete rate law for ortho ester hydrolysis, eq 6, shows that intercepts of plots such as those of Figure 2, where [H$^+$] is constant, consist of contributions to catalysis by H$^+$ and also by H$_2$O.

Table I. Summary of Catalytic Coefficients for the Hydrolysis of 2-Alkoxy-2-phenyl-1,3-dioxolanes in Aqueous Solution at 25 °C[a]

catalyst	pK_a	k_{HA}, M^{-1} s^{-1}, for R =[b]				
		OCH$_2$CH$_2$Cl$_2$[e]	OCH$_2$C≡CH[f]	OCH$_2$CHCl[g]	OCH$_2$CH$_2$OCH$_3$[h]	OCH$_3$[i]
CCl$_3$PO$_3$H$^-$	4.93[c]		1.12 ± 0.05	0.844 ± 0.077	0.706 ± 0.087	1.78 ± 0.17
CHCl$_2$PO$_3$H$^-$	5.60[c]	0.318 ± 0.011	0.266 ± 0.007	0.150 ± 0.014	0.103 ± 0.011	0.280 ± 0.031
CH$_2$ClPO$_3$H$^-$	6.59[c]	0.0809 ± 0.0017	0.0714 ± 0.0009	0.0261 ± 0.0009	0.0129 ± 0.0014	0.0374 ± 0.0026
CH$_2$OHPO$_3$H$^-$	7.36[c]	0.0168 ± 0.0003	0.0159 ± 0.0004	0.00640 ± 0.00060	0.00330 ± 0.00044	0.00877 ± 0.00089
CH$_3$PO$_3$H$^-$	8.00[e]	0.00688 ± 0.00070	0.00795 ± 0.00027	0.00224 ± 0.00021	0.00132 ± 0.00009	0.00241 ± 0.00011
H$_2$PO$_4^-$	7.20[d]	0.0372 ± 0.0017	0.0290 ± 0.0011	0.0179 ± 0.0005	0.0104 ± 0.0005	0.0157 ± 0.0008
H$_3$O$^+$	−1.74	1237 ± 16	1655 ± 45	1844 ± 15	2618 ± 30	5395 ± 69
H$_2$O	15.74	(1.09 ± 0.08) × 10^{-5}	(8.2 ± 1.9) × 10^{-6}	(1.1 ± 0.4) × 10^{-5}	(1.9 ± 0.7) × 10^{-5}	(3.4 ± 1.8) × 10^{-5}

[a] Ionic strength = 0.10 M. [b] R = alkoxy group in the 2 position of 2-alkoxy-2-phenyl-1,3-dioxolane. [c] Reference 10. [d] A. K. Grybowski, *J. Phys. Chem.*, **62**, 555 (1958). [e] Registry no. 64020-50-4. [f] Registry no. 64020-47-9. [g] Registry no. 64020-48-0. [h] Registry no. 64020-49-1. [i] Registry no. 19798-73-3.

$$k_{obsd} = k_{H^+}[H^+] + k_{H_2O}[H_2O] + k_{HA}[HA] \qquad (6)$$

Values of the catalytic coefficients k_{H^+} and k_{H_2O} were therefore obtained by least-squares analysis of the relationship between the intercepts, $(k_{H^+}[H^+] + k_{H_2O}[H_2O])$, and [H$^+$]; the latter were calculated from the known buffer ratios and published pK_a's[10] using activity coefficients recommended by Bates[13] or calculated by the formula $\log f = -0.5 Z^2 I^{1/2}/(1 + I^{1/2}) + BI$ with $B = 0.1$ for univalent ions and $B = 0.4$ for divalent species.

The results of this treatment are listed in Table I. In two cases, k_{H_2O} was also measured directly in 0.1 M NaOH solutions, and the values obtained were consistent with those deduced from the behavior in buffers: for 2-(2,2-dichloroethoxy)-2-phenyl-1,3-dioxolane, $k_{H_2O} = (1.02 ± 0.01) × 10^{-5}$ M^{-1} s^{-1} (direct measurement) and $(1.09 ± 0.08) × 10^{-5}$ M^{-1} s^{-1} (buffer solutions), and for 2-(2-propynoxy)-2-phenyl-1,3-dioxlane, $k_{H_2O} = (4.93 ± 0.07) × 10^{-6}$ M^{-1} s^{-1} (direct measurement) and $(8.2 ± 1.9) × 10^{-6}$ M^{-1} s^{-1} (buffer solutions). The large uncertainties in the value of k_{H_2O} listed in Table I are a consequence of the small contribution to the overall rate made by the term $k_{H_2O}[H_2O]$ under most of the conditions employed here.

Two of the rate constants measured here have been determined before:[8] k_{HA} for hydrolysis of 2-methoxy-2-phenyl-1,3-dioxolane catalyzed by H$_2$PO$_4^-$ is reported to be (1.52 ± 0.06) × 10^{-2} M^{-1} s^{-1}, in good agreement with $k_{HA} = (1.57 ± 0.08) × 10^{-2}$ M^{-1} s^{-1} obtained here; but for the same substrate k_{H^+} is reported as $(7.37 ± 0.20) × 10^3$ M^{-1} s^{-1}, which is considerably greater than $k_{H^+} = (5.40 ± 0.07) × 10^3$ M^{-1} s^{-1} found here. In the previous study, however, the catalytic effect of water was not taken into account when obtaining k_{H^+}, and, when this omission is rectified, k_{H^+} drops to $5.44 × 10^3$ M^{-1} s^{-1}, in good agreement with the present value.

Discussion

Brønsted Plots. The present data make available five sets of phosphonate acid ion catalytic coefficients for the hydrolysis of five cyclic ortho esters, and each of these sets gives a good Brønsted plot, such as the example shown in Figure 3. These Brønsted plots all appear to be linear, but they are undoubtedly only linear segments of more extensive curved relationships (Brønsted plots often have only gentle curvature which cannot be detected over a limited range of catalytst pK_a such as that used here).[14]

In each of these five cases, the catalytic coefficient for biphosphate ion fits the Brønsted relationship quite well. This has been noted before in the hydrolysis of methyl α-cyclopropylvinyl ether,[12b] and it indicates that this catalyst forms a homogeneous set with alkylphosphonate anions, RPO$_3$H$^-$, in keeping with its hydroxyphosphonate ion structure, HOPO$_3$H$^-$.
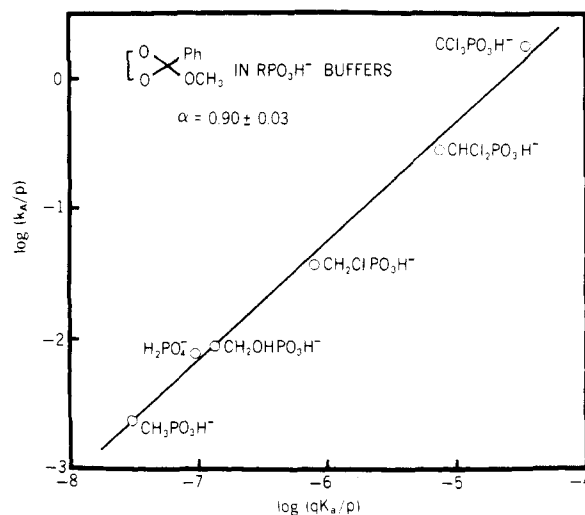

Figure 3. Brønsted plot for the hydrolysis of 2-methoxy-2-phenyl-1,3-dioxolante catalyzed by monohydrogenphosphonate anions.

The other catalytic coefficients determined here, those for H$_2$O and H$_3$O$^+$, fit these linear Brønsted relations less well. The points for H$_2$O show especially marked deviations: these all lie above the Brønsted line, and the factors by which they deviate range from $3 × 10^2$ to $4 × 10^5$. The H$_3$O$^+$ points, on the other hand, all deviate in the negative direction, and the factors here are much more modest, ranging from 20 to 120.

It is noteworthy that these H$_3$O$^+$ deviations are as small as they are (an order of magnitude less than the H$_3$O$^+$ deviations found in previous applications of monohydrogen phosphonate anions in general acid catalysts[12]), inasmuch as that accounts for the relative weakness of the general acid catalysis found here (see above). In these previous studies, phosphonate anions were found to be superior general acid catalysts, giving large general acid and small hydronium ion contributions to observed rates. This effect was ascribed to electrostatic interaction between the negative charge of the phosphonate ion and the positive charge developing on the substrate in the transition state,[15] which stabilized the latter and made the phosphonate ion catalytic coefficient greater than it would be otherwise. This electrostatic effect appears to operate in the present reactions as well, inasmuch as phosphonate anions are better catalysts than neutral acids of the same pK_a,[16] and the source of the difference between the present reaction and the previously studied systems must therefore lie in enhanced hydronium ion catalytic coefficients in the present case. It is significant in this connection that the previous reactions were all examples of vinyl ether hydrolysis in which the proton transfer is to carbon, whereas in the present reaction proton transfer is to an ether oxygen atom. In aqueous solution,
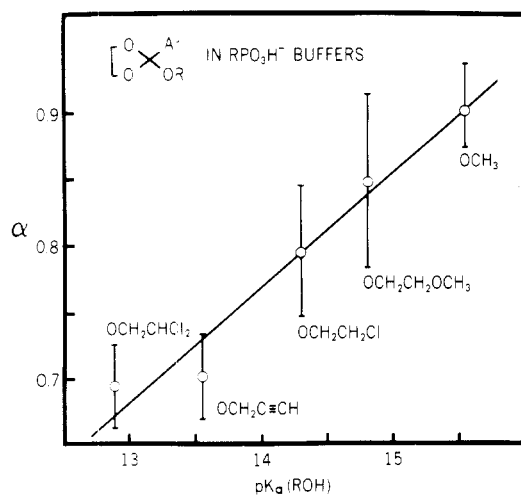
Figure 4. Relationship between acidity of leaving alcohol (and basicity of corresponding ether) and Brønsted exponent for the acid-catalyzed hydrolysis of 2-alkoxy-2-phenyl-1,3-dioxolanes.

Table II. Brønsted Exponents for the Hydrolysis of 2-Alkoxy-2-phenyl-1,3-dioxolanes

alkoxy group	pK_a of the corresponding alcohol[a]	α
OCH_3	15.7	0.90 ± 0.03
$OCH_2CH_2OCH_3$	14.82	0.85 ± 0.07
OCH_2CH_2Cl	14.31	0.80 ± 0.05
$OCH_2C\equiv CH$	13.55	0.70 ± 0.03
OCH_2CHCl_2	12.89	0.69 ± 0.03

[a] Reference 18.

oxygen bases such as this are hydrogen bonded to the solvent through their localized electron pairs, and they are therefore particularly easily protonated by the hydronium ion, via a Grotthuss chain mechanism, inasmuch as the hydronium ion itself fits into the hydrogen-bonded network of the solvent especially well.[14] Carbon bases with delocalized electron pairs, such as vinyl ethers, do not, of course, hydrogen bond with the solvent, and they therefore cannot benefit from a similar effect.

Reaction Mechanism. The criterion for distinguishing stepwise from concerted mechanisms for ortho ester hydrolysis advanced at the beginning of this paper requires knowledge of the basic strength of the oxygen atom which receives the proton in the first stage of this reaction. This information is unfortunately not available for the present substrates, nor would it seem to be readily obtainable. The high reactivity of these substances precludes direct measurement of the protonation equilibrium in acidic solutions, and indirect determination by the infrared frequency shift method, a technique which has been used successfully for symmetrical acyclic ortho esters,[17] would give information about only the most basic oxygen in the present substrates, which would not necessarily be the oxygen of interest.

It would seem reasonable to assume, however, that the basic strengths of these ether oxygen atoms are inversely proportional to the acidities of the corresponding alcohols, and the pK_a's of the requisite alcohols are well known.[18] These are listed in Table II along with the presently determined Brønsted exponents. It may be seen that, although the combined uncertainties of adjacent pairs of exponents often exceed their difference, there is an unmistakable trend for the exponents to decrease with increasing alcohol acidity and therefore also with decreasing ether oxygen basicity (Figure 4). Since this is the result predicted for the concerted mechanism and the opposite of that anticipated for the stepwise reaction path, it may be concluded that the first stage of ortho ester hydrolysis is in fact a concerted one-step reaction, just as written in eq 1.

This conclusion, strictly speaking, applies only to the hydrolysis of the somewhat special cyclic ortho esters investi-

gated here. There is no reason to believe, however, that other ortho esters should behave differently. This generalization is supported by the fact that concerted mechanisms have recently been established for the closely related general acid catalyzed hydrolysis of benzaldehyde aryl methyl acetals,[19] and also for the general acid catalyzed expulsion of alcohol from N-acyl ester aminals to form the phthalimidium cation.[20]

Registry No.—Trimethyl orthobenzoate, 707-07-3; ethylene glycol, 107-21-1; 2,2-dichloroethanol, 598-38-9; 2-propyn-1-ol, 107-19-7; 2-chloroethanol, 107-07-3; 2-methoxyethanol, 109-86-4.

Supplementary Material Available: Table S1 of rates of hydrolysis (11 pages). Ordering information is given on any current masthead page.

References and Notes

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