pH–Product and pH–Rate Profiles for the Hydrolysis of Methyl Ethylene Phosphate. Rate-Limiting Pseudorotation

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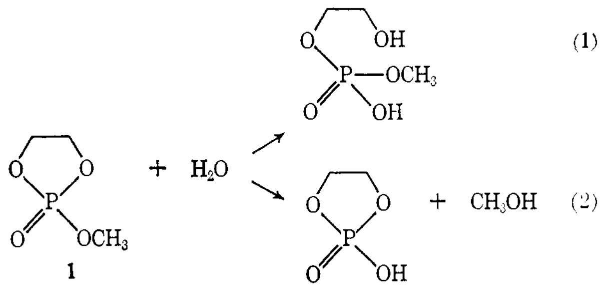
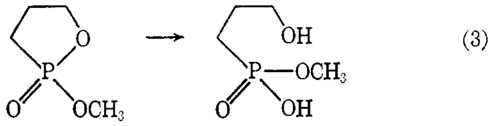
Abstract: The hydrolysis of methyl ethylene phosphate in dilute acid solution has previously been shown to occur both with ring opening and with cleavage of the exocyclic methyl group, whereas the methyl ester of propylphostonic acid reacts under these conditions only with ring opening. These facts had been correlated with the theory that hydrolysis of the exocyclic methoxyl group takes place only after pseudorotation about the central phosphorus atom. The complete pH–product profile for the hydrolysis of methyl ethylene phosphate is shown in Figure 3 and explained in the text. The drop in the percentage of exocyclic cleavage in strongly acid solution may be correlated with rate-limiting pseudorotation; the rise in the percentage of exocyclic cleavage in strong alkali may be correlated with the ionization of both the hydroxyl groups in the pentacovalent intermediate so as to produce two O$^-$ groups; according to theory, these should occupy equatorial positions, and so the ionization could force a pseudorotation that promotes exocyclic cleavage. The kinetic equations for the over-all process exhibit unusual features that are discussed.

Methyl ethylene phosphate, **1**, undergoes hydrolysis 10^6 times as rapidly as does trimethyl phosphate. In dilute acid solution, the products are both those of ring opening and of exocyclic cleavage.[1–4]



By contrast, under these experimental conditions, the methyl ester of propylphostonic acid hydrolyzes exclusively with ring opening.



These facts have been explained on the assumption that hydrolysis occurs by a mechanism of symmetrical type, by way of a trigonal-bipyramidal intermediate formed under specified constraints.[3,4] These constraints are that the five-membered ring shall occupy one apical and one equatorial position, so as to minimize ring strain,[5–7] and that an alkyl group (when present) shall preferentially occupy an equatorial position in the trigonal bipyramid.[8–12]

The exocyclic cleavage of the methoxyl group can occur, consistent with these constraints, if but only if the molecule undergoes pseudorotation about the central phosphorus atom.[4,8–13] Recently, we have offered evidence that, in some cases, pseudorotation can become the rate-limiting process in hydrolysis.[14] The two competing reactions shown in eq 1 and 2 may depend differently on the acidity of the solution. The rate for ring opening should increase linearly with acidity, at least until the solution is so concentrated that ionic strength effects become large,[15] whereas the rate for exocyclic cleavage may reach a plateau with increasing acidity if pseudorotation becomes rate limiting. If these conditions are valid, then the ratio of products obtained in the hydrolysis of methyl ethlyene phosphate should vary with acidity in a predictable way: the fraction of exocyclic cleavage should diminish with increase in acidity. These predictions have led to a detailed examination of the pH–product profiles for the hydrolysis of methyl ethylene phosphate. This profile is complicated, but is consistent throughout with pseudorotation theory.

Experimental Section

Materials. Methyl ethylene phosphate was prepared by appropriate modifications of the procedure of Boisdon, *et al.*,[16] for ethyl

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[1] F. Covitz and F. H. Westheimer, *J. Amer. Chem. Soc.*, **85**, 1773 (1963).

[2] E. A. Dennis and F. H. Westheimer, *ibid.*, **88**, 3432 (1966).

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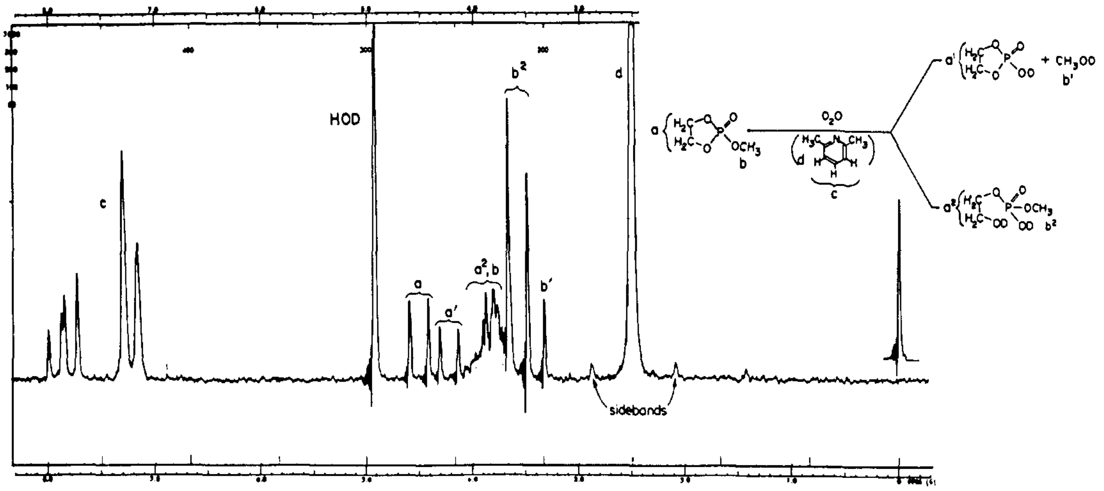

Figure 1. Nmr spectrum for the hydrolysis of methyl ethylene phosphate in lutidine buffer. The various nmr signals are identified in the equations.

ethylene phosphate. Methyl dichlorophosphate[17] was prepared by mixing equimolar quantities of dry methanol and phosphorus oxychloride at 0°, while dry nitrogen was passed through the solution. The remaining hydrogen chloride was removed under vacuum at room temperature, and the product distilled through a 5-in. Vigreux column at 47° (10 mm) (lit.[17] 62–64° (15 mm)) in 80% yield. The nmr spectrum showed the expected doublet for the methoxyl group at δ 4.0, and a small doublet (impurity; possibly a disproportionation product) at δ 3.85. A 0.5-mole sample of this product was added at room temperature over 1.5 hr to a solution of 0.5 mole of ethylene glycol and 1 mole of 2,6-lutidine in 250 ml of dry benzene. The mixture was stirred for 6 hr and filtered, and the filter cake washed with ether. After the solvent had been removed, the residue from the filtrate and washings was distilled under vacuum, and then redistilled at 85° (0.1 mm). The product (15% yield) showed ir and nmr spectra identical with those of material prepared by an alternative method.[1,2]

Products. Nmr Method. The products of hydrolysis of methyl ethylene phosphate were determined by nmr spectroscopy. In neat liquid, the spectrum of methyl ethylene phosphate shows a strong doublet (the methoxyl group) at δ 3.8 ($J_{\text{P-H}} = 14$ Hz) and a second doublet (the methylene groups) at δ 4.4 ($J_{\text{P-H}} = 10$ Hz). The hydrolysis of methyl ethylene phosphate in water at concentrations useful for nmr spectroscopy is so rapid that a clean spectrum of the starting material has not been obtained, but the spectrum of a solution of methyl ethylene phosphate in D_2O and lutidine, taken immediately after mixing, is shown in Figure 1. Here the signal for the methylene groups of the ester appears as a doublet at δ 4.5, those for the methylene group of hydrogen ethylene phosphate at δ 4.2, and those for the methoxyl group of hydrogen methyl hydroxyethyl phosphate as a doublet at δ 3.6; the singlet for methanol itself is cleanly separate at δ 3.4. (The peaks that arise from the lutidine buffer are well removed from the region of interest.) Each product has been identified by a comparison of its nmr peaks in the reaction mixture with those of an authentic sample of pure material.[18–20] The appearance of methanol was confirmed by adding more of it to the reaction mixture, and again determining the nmr spectrum. The peaks assigned to the spectrum of methyl ethylene phosphate in D_2O are reasonable ones when compared with those of the neat liquid; they are further identified on the basis of their rapid disappearance as the reaction proceeds. (In dilute solutions in most solvents, the signals from the methylene groups are complicated, as might be expected since the protons are diastereotopic.)

Quantitative estimates of products were made after the reaction had proceeded long enough (seconds to hours) so that all of the methyl ethylene phosphate had reacted to produce ethylene phosphate, methanol, and methyl hydroxyethyl phosphate. In strong acid or strong base, however, further reaction takes place, although at a lower rate. In acid, the presence of the cyclic ester as an intermediate is inferred from the appearance of dihydrogen hydroxyethyl phosphate; since methyl hydroxyethyl phosphate is hydrolyzed only slowly even under strongly acidic conditions, dihydrogen hydroxyethyl phosphate could not have arisen from this source. In strong base, the anion of ethylene phosphate undergoes hydrolysis at a known rate.[18] The hydrolysis of the anion of ethylene phosphate will account for the formation of the dianion of hydroxyethyl phosphate, whereas the hydrolysis of methyl hydroxyethyl phosphate in alkali is too slow to account for its formation.

Hydrolyses were conducted by dissolving methyl ethylene phosphate with rapid stirring in various acid or basic solutions. The solutions for assay of products in the range of pH 2–12 were maintained at the appropriate pH by the addition of base through an Aminco automatic buret, controlling the pH with a Radiometer TTT1b titrator equipped with a scale expander. The ester was added through a Hamilton syringe, at appropriate rates so that the titrator could follow.

Nmr measurements were carried out with a Varian A-60 spectrometer.

Product Analysis. Vpc Method. The product analysis for solutions prepared under the same experimental conditions as for kinetic experiments (*i.e.*, dilute solutions of methyl ethylene phosphate) were carried out by the vpc method developed by F. Mirer and previously described,[14,21] using a Hewlett-Packard 5754A gas chromatograph and a flame ionization detector. The reaction mixtures were quenched with acid after a brief exposure (*e.g.*, 1 min) to strong alkali, so as to minimize hydrolysis of the methyl hydroxyethyl phosphate first formed.

Kinetics. The rates of reactions were measured by the nmr and pH-stat methods previously[14] described.

Results

Kinetics. The rates of hydrolysis of methyl ethylene phosphate at various pH values are presented in Table I. These rate constants were determined with concentrations of methyl ethylene phosphate in the range of 0.004–0.008 *M*, where the rate constants obtained are substantially independent of the concentration of the ester. In more concentrated solutions, however, in the region around pH 5 (where the rate is low), the apparent first-order rate constant is a function of the ester concentration. For example, at an ester concentration of 0.2 *M*, the first-order "constant" drifted

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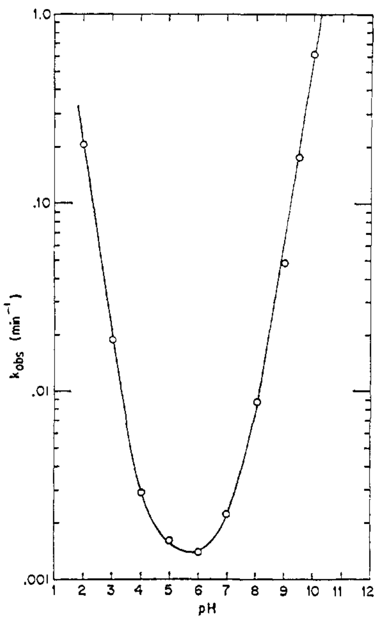

Figure 2. Rates of hydrolysis of methyl ethylene phosphate at 25°.

downward, during an individual experiment, from 33 to 12 × 10^{-5} sec^{-1}; even the latter value is three times that obtained in dilute solutions. At still higher concentrations (around 0.5 *M*) the hydrolysis is second order.[22] However, since the second-order process might result in the formation of more or less methanol (*i.e.*, more or less exocyclic cleavage) than the first-order reaction, the product studies here reported have been restricted to those in dilute solutions. For this reason, the results of product analysis by the vpc method are preferred over those determined (more conveniently) by nmr.

Table I. Hydrolysis of Methyl Ethylene Phosphate in H_2O at 25° [a,b]

pH obsd	k_{obsd}, min^{-1}
2.01	0.21[c]
3.01	0.019
4.00	0.0028
5.00	0.0016
6.00	0.0014
7.00	0.0023
8.00	0.0089
8.00	0.0090
8.50	0.021
9.00	0.049
9.00	0.050
9.00	0.051
9.50	0.18
10.00	0.61

[a] Concentration about 0.006 *M*. [b] Data taken from ref 23. [c] New data; the value given in ref 23 is in error.

The pH-rate profile for the hydrolysis of methyl ethylene phosphate is shown in Figure 2. The observed rate constant at 25° can be expressed as

$$k_{obsd} = k_{H^+}(H^+) + k_w + k_{OH^-}(OH^-) \qquad (4)$$

where $k_{H^+} = 0.35\ M^{-1}\ sec^{-1}$, $k_w = 2.3 \times 10^{-5}\ sec^{-1}$, and $k_{OH^-} = 64\ M^{-1}\ sec^{-1}$. The solid line in Figure 2 has been drawn according to eq 4.

The kinetics for the hydrolysis of methyl ethylene phosphate were previously determined (somewhat less precisely but in greater detail) by Covitz.[23]

Products. The amounts of exocyclic cleavage for methyl ethylene phosphate are presented in Tables II and III. The data obtained by the vpc method in H_2O are at least in qualitative agreement with those obtained by the nmr method in D_2O. However, the nmr method gives consistently higher values, by a few per cent, in the region of strong alkali. Although the vpc data are moderately reproducible (see Table II), the absolute amounts are uncertain, to perhaps 10% of these amounts, because of difficulties in standardizing the analyses where minute amounts of methanol are analyzed in the presence of an almost overwhelming excess of water.

Table II. Per Cent Exocyclic Cleavage[a] for Methyl Ethylene Phosphate in H_2O

pH	%	$HClO_4$, *M*	%
2	55		
2	42[b]	5.0	5
3	42	2.5	10
4	37	0.95	22
5	23	0.50	31
5	31	0.10	45
6	22	0.05	54
6	29	0.05	55
7	17	0.02	55
8	5		
8	6		
9	4		
10	2		
10	2		
11	1		
13	1		
14	4		
c	9		

[a] Vpc method. [b] Value in question. [c] 5 *M* NaOH.

Table III. Per Cent Exocyclic Cleavage[a] for Methyl Ethylene Phosphate in D_2O

$DClO_4$, *M*	%	NaOD, *M*	%
7.4	4	10	14
6.1	5	5.0	11
5.3	5	2.3	8
3.8	10	0.2	1
2.5	10		
1.2	19		
0.1	53		

[a] Nmr method.

Discussion

Methyl Ethylene Phosphate. The complicated pH-product profile for the hydrolysis of methyl ethylene phosphate, shown in Figure 3, can be accounted for on the basis of the pH-rate profile (Figure 2) and the theory of pseudorotation. The argument will be presented in several parts, corresponding to the different regions of the roller coaster in Figure 3.

Acid Region. The dependence of the per cent of exocyclic cleavage on acidity in the region from pH 4

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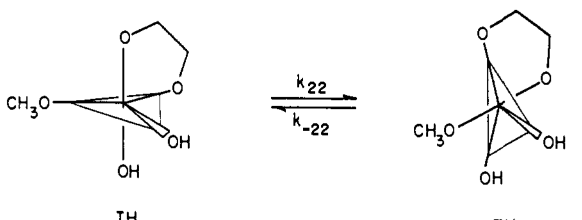
[22] The polymerization of ethyl ethylene phosphate has been described by J. P. Vives, A. Munoz, J. Navech, and F. Mathis, *Bull. Soc. Chim. Fr.*, 2544 (1965).

[23] F. Covitz, Ph.D. Thesis, Harvard University, 1965; *Dissertation Abstr.*, 27, 2291B (1967).

to strong acid can be understood on the basis of the assumption that, for exocyclic cleavage in strong acid, the pseudorotation process itself becomes rate limiting. The assumptions are these: the rate of reaction of methyl ethylene phosphate with water, to form the intermediate IH_3^+, is acid catalyzed, but pseudorotation, which takes place by the interconversion of the unprotonated intermediates IH_2 to JH_2, occurs at a rate that is independent of acidity. (See eq 5 for the structures of IH_2 and JH_2.) Products are formed by way of the intermediates IH_3^+ and JH_3^+ from the reaction of the ester with water and acid. With these assumptions, then, the rate of ring cleavage (endocyclic cleavage) *via* the first intermediate, IH_3^+, will increase with increasing acidity, since this does not require pseudorotation. However, the rate of exocyclic cleavage is controlled by the slower of the two processes: hydration of the phosphorus atom or the pseudorotation represented by eq 5.



(5)

IH_2 JH_2

Therefore, as the acidity is increased, a point may be reached where the rate of pseudorotation and hence of exocyclic cleavage fails to keep pace with the rate of ring opening, so that the yield of exocyclic products falls toward zero. This is the behavior that is observed. Furthermore, the shape of the pH-product profile is as predicted from the theory suggested. The chemical equations for the mechanism described above are shown in eq 6; the corresponding equation for the fraction, *f*, of exocyclic cleavage is given by eq 7. The derivation of this equation is presented in the Appendix. Here

$$\begin{aligned}
&\text{MEP} + H_2O + H^+ \underset{k_{-31}}{\overset{k_{31}}{\rightleftharpoons}} IH_3^+ \\
&IH_3^+ \overset{K_3}{\rightleftharpoons} IH_2 + H^+ \\
&IH_2 \underset{k_{-22}}{\overset{k_{22}}{\rightleftharpoons}} JH_2 \\
&JH_3^+ \overset{K_3'}{\rightleftharpoons} JH_2 + H^+ \qquad (6) \\
&IH_3^+ \xrightarrow{k_{33}} \text{MHEP} + H^+ \\
&JH_3^+ \xrightarrow{k_{34}} \text{MHEP} + H^+ \\
&JH_3^+ \xrightarrow{k_{35}} \text{EP} + H^+
\end{aligned}$$

MEP stands for methyl ethylene phosphate, MHEP for methyl hydroxyethyl phosphate, and EP for ethylene phosphate; MHEP and EP may be present either as the anions (at low acidity) or as the un-ionized acids (at high acidity).

$$f = \frac{\alpha}{1 + \beta(H^+)} \qquad (7)$$

Equation 7 requires that the fraction of exocyclic cleavage decreases with increasing acidity, and predicts the shape of the curve for *f* plotted against (H^+). The solid line in Figure 3, from pH 2 to strong acid, is drawn according to eq 7 where $\alpha = 0.50$ and $\beta = 1.5$.

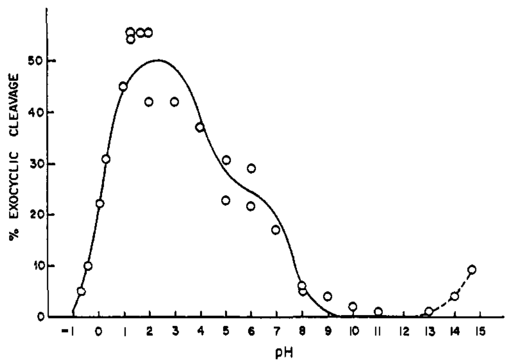


Figure 3. pH-product profile for the hydrolysis of methyl ethylene phosphate in water at 25°.

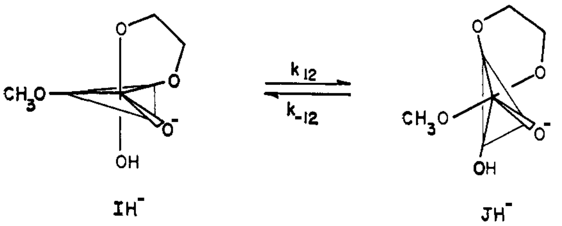
The idea of rate-limiting pseudorotation in acidic solutions has already been suggested by a consideration of the pH-rate profile for the hydrolysis of the ethyl esters of highly strained phosphinic acids.[14] The notion that pseudorotation takes place by way of electrically neutral unprotonated intermediates, such as IH_2 and JH_2, rather than by way of their conjugate acids IH_3^+ and JH_3^+, has also been explained.[14] In essence, the rule[8] that electron-withdrawing substituents should preferentially be placed in apical positions requires that IH_2 or JH_2 be protonated preferentially in the apical position, and so mitigates against the pseudorotation of IH_3^+, since such pseudorotation would place a protonated (and hence electron withdrawing) oxygen atom in an equatorial position.

pH-Rate and pH-Product Profiles. In the pH region from pH 4 to 11, the fraction of product formed with exocyclic cleavage decreases from about 50% to near zero. The complicated curve in the region from pH 4 to 11 can be expressed quantitatively in terms of the fractions of reaction that occur by way of acid catalysis, by water catalysis, and by hydroxide ion catalysis, with the quantitative assumptions that the acid-catalyzed reaction gives 50% exocyclic cleavage, the water reaction gives 25% exocyclic cleavage, and the hydroxide ion reaction gives ~0% exocyclic cleavage. The solid line in Figure 3 has been drawn between pH 4 and 11 according to eq 8, where the term in $k_3(^-OH)$ has been

$$f = \frac{0.50k_{H^+}(H^+) + 0.25k_w}{k_{H^+}(H^+) + k_w + k_{OH^-}(OH^-)} \qquad (8)$$

omitted from the numerator because its coefficient (the per cent exocyclic cleavage by the basic mechanism) is negligible.

The Region from pH 4 to 11. Although one may formally correlate the pH-rate profile and the pH-product profile, questions remain as to the interpretation of these data. The reaction with dilute alkali presumably takes place through the monoanions, IH^-



(9)

IH^- JH^-

and JH^-. The anionic oxygen atom is more electron donating than the electrically neutral oxygen atom of an OH or OCH_3 group, and will therefore be expected to assume an equatorial position in IH^-, rather than an apical position; this expectation has previously been established in an entirely independent example by Frank and Usher.[24] The ion, IH^-, has been formulated in accord with these principles.

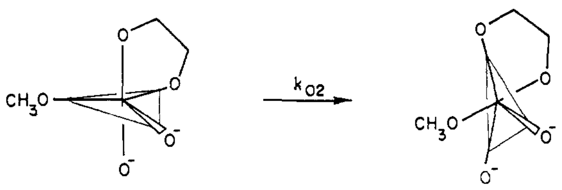
Since IH_2 is an unstable intermediate, its ionization constants cannot be measured. However, an order-of-magnitude estimate of the first ionization constant may be made from the empirical equation of Branch and Calvin;[25] this suggests that the p*K* for IH_2 is about 9. The value is consistent with the assumption of a change in rate-limiting step near neutrality.

Since the fraction of exocyclic cleavage is near zero in the pH region 8–11, where the anions IH^- and JH^- are important species, one must assume that the rate of cleavage of IH^- greatly exceeds the rate at which IH^- pseudorotates to JH^-. This assumption is a reasonable one. In dilute acid solution, the major species present in solution are the electrically uncharged molecules IH_2 and JH_2. These intermediates can undergo pseudorotation, but must be protonated for acid-catalyzed formation of products. In other words, the electrically neutral intermediate for pseudorotation is present in solution at a much higher concentration than the protonated intermediate needed for rapid reaction. (The cleavages of IH_2 and JH_2 themselves correspond to the water-catalyzed reactions, and are slow). By contrast, the intermediates IH^- or JH^- may undergo pseudorotation or may cleave directly. Since IH^- is in the correct protonation state for reaction and since it can cleave only by opening the ring, ring opening will be favored in basic, relative to dilute acid, solution.

The fraction of exocyclic cleavage that has been obtained in the water-catalyzed reaction is reasonable, but cannot be derived from present theory. The water reaction requires the direct decomposition of IH_2 or JH_2 to products, or kinetically equivalent processes, such as the acid-catalyzed decomposition of IH^- and JH^-. There is no reason to assume that the relative rates of ring opening and exocyclic cleavage will be the same in neutral solution as in acid (see Appendix for equations). Hydrolysis of cyclic phosphate esters in neutral solution, with complete retention of the ring structure, have previously been recorded both in an aprotic solvent[26] and in water.[27] Detailed explanation of these examples is not available.

Strong Alkali. In strong alkali, the fraction of exocyclic cleavage rises linearly with the hydroxide ion concentration, to a value of about 15% exocyclic cleavage in 10 *M* alkali. This finding is consistent with the theory of pseudorotation.[28]

In I^{2-}, one of the negative charges is apical, and one equatorial. Consistent with our prior discussion, this intermediate should be unstable relative to J^{2-}, where



$I^=$ $\qquad$ $J^=$ $\qquad$ (10)

both negative charges are equatorial. Therefore the second ionization of the intermediates should *force* pseudorotation of I^{2-}, and lead to J^{2-}. Further, the large negative charge on J^{2-} should ensure that decomposition occurs promptly, and therefore probably with little discrimination, so that exocyclic cleavage should compete with ring opening, as it does.

The second p*K* for IH_2 can be estimated by the method of Branch and Calvin[25] as somewhere near 13. This estimate does not, of course, take into account the difference between apical and equatorial positions. The statement that negatively charged oxygen atoms preferentially assume equatorial positions implies that the p*K* of an apical hydroxyl group will be greater, and may be much greater, than that of an equatorial hydroxyl group. Nor can one easily deduce the p*K* from the pH–rate profile since the kinetics are complicated (see Appendix). Nevertheless, the rise in the fraction of exocyclic cleavage in the region around pH 14 is at least consistent with the expected ionization in this region of the intermediate IH^-.

The intervention of dianions in exocyclic cleavage is also implied by the increase of the fraction, *f*, of such cleavage with the concentration of alkali. The rate of reaction in strong alkali is too fast to measure by conventional techniques. If, however, one assumes that the rate for ring opening is proportional to the concentration of alkali, and then notes that the fraction of exocyclic cleavage is also proportional to alkali, it follows that the rate for exocyclic cleavage is increasing with the square of the alkali concentration, or in direct proportion to the concentration of the dianion, J^{2-}.

Kinetics. The kinetic equations for the hydrolysis of methyl ethylene phosphate are presented in the appendix. The rate equation for reaction in acid solution is

$$v = k_{H^+}(\mathrm{MEP})(H^+) = k_{\mathrm{obsd}}(\mathrm{MEP}) \qquad (11)$$

where

$$k_{H^+} = \frac{\alpha + \delta(H^+)}{1 + \epsilon(H^+)} \qquad (12)$$

where α, δ, and ϵ are functions of the *K*'s and *k*'s shown in eq 6. This equation implies that, in acid solution, the rate need not be strictly proportional to the acidity; the rate "constant," k_{H^+}, is independent of the acid concentration when that concentration is either high or low, but somewhat dependent on acid concentration at intermediate acidities. Until and unless the various rate and ionization constants are known, however, it is not possible to state what is meant by "high" or "low" acidity, or how large the deviations from a constant value for k_{H^+} will be. Similarly, the equations in dilute alkali lead to the expression

$$v = k_{OH^-}(\mathrm{MEP})(OH^-) = k_{\mathrm{obsd}}(\mathrm{MEP}) \qquad (13)$$

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[24] D. S. Frank and D. A. Usher, *J. Amer. Chem. Soc.*, **89**, 6360 (1967).

[25] G. E. Branch and M. Calvin, "The Theory of Organic Chemistry," Prentice-Hall, Inc., New York, N. Y., 1941, p 204.

[26] F. Ramirez, O. P. Maden, N. B. Desai, S. Meyerson, and E. M. Banas, *J. Amer. Chem. Soc.*, **85**, 2681 (1963).

[27] M. G. Newton, J. R. Cos, Jr., and J. A. Bertrand, *ibid.*, **88**, 1503 (1966).

[28] An alternative explanation for the results in strong alkali, invoking a hexacoordinated phosphorus intermediate, is probably possible but without support.

where

$$k_{\mathrm{OH^-}} = \frac{\tau}{1 + \eta(\mathrm{OH^-})} \qquad (14)$$

Again, the rate "constant" is a function of acidity, although the variation with pH need not be large, and the "constant" will approach definite values in either moderately strong or very weak base. Further, the possible variations of $k_{\mathrm{H^+}}$ and $k_{\mathrm{OH^-}}$ with pH may be obscured if the variations occur in the region where the water reaction is dominant. The pseudorotation mechanism, therefore, is not necessarily inconsistent with a "respectable" pH-rate profile, such as that shown in Figure 2 and represented by eq 4; the mechanism does not, however, demand that the profile be so neat. Perhaps more precise data than those so far obtained will be required to test the validity of eq 12 and 14. Quantitative equations are given in the Appendix.

Methyl Propylphostonate. Previous research[2] had indicated that methyl propylphostonate undergoes hydrolysis in acid exclusively with ring opening. The entire pH-product profile is now under investigation.[29] Although the purification of the compound presents some difficulties, current research shows that the pH-product profile here is in accord with prediction; in particular, exocyclic cleavage occurs in strong base.

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Appendix

General Solution. The complete set of chemical equations for the hydrolysis of methyl ethylene phosphate (MEP) to yield a mixture of methyl hydroxyethyl phosphate (MHEP) and ethylene phosphate (EP) are given below.

$$\left.\begin{array}{ccccc}
\mathrm{MEP} + \mathrm{H_3O^+} & \underset{k_{-31}}{\overset{k_{31}}{\rightleftharpoons}} & \mathrm{IH_3^+} & \underset{k_{-32}}{\overset{k_{32}}{\rightleftharpoons}} & \mathrm{JH_3^+} \\
 & & {\scriptstyle K_3}\upharpoonleft\downharpoonright & & \upharpoonleft\downharpoonright{\scriptstyle K_3'} \\
\mathrm{MEP} + \mathrm{H_2O} & \underset{k_{-21}}{\overset{k_{21}}{\rightleftharpoons}} & \mathrm{IH_2} & \underset{k_{-22}}{\overset{k_{22}}{\rightleftharpoons}} & \mathrm{JH_2} \\
 & & {\scriptstyle K_2}\upharpoonleft\downharpoonright & & \upharpoonleft\downharpoonright{\scriptstyle K_2'} \\
\mathrm{MEP} + {}^-\mathrm{OH} & \underset{k_{-11}}{\overset{k_{11}}{\rightleftharpoons}} & \mathrm{IH^-} & \underset{k_{-12}}{\overset{k_{12}}{\rightleftharpoons}} & \mathrm{JH^-} \\
 & & {\scriptstyle K_1}\upharpoonleft\downharpoonright & & \upharpoonleft\downharpoonright{\scriptstyle K_1'} \\
\mathrm{MEP} + 2{}^-\mathrm{OH} & \underset{k_{-01}}{\overset{k_{01}}{\rightleftharpoons}} & \mathrm{I^{2-}} & \underset{k_{-02}}{\overset{k_{02}}{\rightleftharpoons}} & \mathrm{J^{2-}}
\end{array}\right\} \qquad (15)$$

$$\left.\begin{array}{l}
\mathrm{IH}_n \xrightarrow{k_{n3}} \mathrm{MHEP} \\
\mathrm{JH}_n \xrightarrow{k_{n4}} \mathrm{MHEP} \\
\mathrm{JH}_n \xrightarrow{k_{n5}} \mathrm{EP}
\end{array}\right\}$$

The following definitions facilitate handling the kinetic equations

$$v_i = \sum_{n=0}^{3} k_{ni}(\mathrm{IH}_n)/(\mathrm{IH_3^+}) \text{ or } \sum_{n=0}^{3} k_{ni}(\mathrm{JH}_n)/(\mathrm{JH_3^+}) \qquad (16)$$

Since $(\mathrm{H^+})(\mathrm{IH}_{n-1})/(\mathrm{IH}_n) = K_n$, and $(\mathrm{H^+})(\mathrm{JH}_{n-1})/(\mathrm{JH}_n) = K_n'$

$$v_i = k_{0i}\frac{K_1K_2K_3}{(\mathrm{H^+})^3} + k_{1i}\frac{K_2K_3}{(\mathrm{H^+})^2} + k_{2i}\frac{K_3}{(\mathrm{H^+})} + k_{3i} \qquad (17)$$

where $i = -1, 2,$ or 3, and

$$v_j = k_{0j}\frac{K_1'K_2'K_3'}{(\mathrm{H^+})^3} + k_{1j}\frac{K_2'K_3'}{(\mathrm{H^+})^2} + k_{2j}\frac{K_3'}{(\mathrm{H^+})} + k_{3j} \qquad (18)$$

where $j = -2, 4,$ or 5.

The steady-state kinetic equations corresponding to the set of chemical equations (eq 15) are then

$$\frac{\mathrm{d}}{\mathrm{d}t}\sum_{n=0}^{3}(\mathrm{IH}_n) = 0 \text{ and } \frac{\mathrm{d}}{\mathrm{d}t}\sum_{n=0}^{3}(\mathrm{JH}_n) = 0 \qquad (19)$$

or

$$V(\mathrm{MEP}) - (v_1 + v_2 + v_3)(\mathrm{IH_3^+}) + v_{-2}(\mathrm{JH_3^+}) = 0$$

$$v_2(\mathrm{IH_3^+}) - (v_{-2} + v_4 + v_5)(\mathrm{JH_3^+}) = 0$$

where

$$V = k_{31}(\mathrm{H^+}) + k_{21} + k_{11}(\mathrm{OH^-}) + k_{01}(\mathrm{OH^-})^2 \qquad (20)$$

Equations 19 can be solved for $(\mathrm{IH_3^+})$ and $(\mathrm{JH_3^+})$. When each individual rate determination is carried out at a constant pH, so that $-\mathrm{d}(\mathrm{MEP})/\mathrm{d}t = k_{\mathrm{obsd}}(\mathrm{MEP}) = v_3(\mathrm{IH_3^+}) + (v_4 + v_5)(\mathrm{JH_3^+})$

$$k_{\mathrm{obsd}} = \frac{v_2v_4 + v_2v_5 + v_{-2}v_3 + v_3v_4 + v_3v_5}{(v_{-1} + v_3)(v_{-2} + v_4 + v_5) + v_2(v_4 + v_5)}V \qquad (21)$$

Furthermore, the fraction of exocyclic cleavage is

$$f = \frac{v_2v_5}{v_2v_4 + v_2v_5 + v_{-2}v_3 + v_3v_4 + v_3v_5} \qquad (22)$$

The general eq 21 and 22 can be simplified to deal with the separate pH regions by ignoring the rate constants that are not relevant (*e.g.*, the hydroxide ion rate in the strong acid region). The equations are not significantly simplified by making the approximate assumption that the ionization constants for IH_n and JH_n only differ because of statistical factors, and similarly that k_{i1}, k_{i3}, k_{i4} and k_{i5} only differ by statistical factors for any given value of i.

Acid Region. For the acid region, $v_1 = k_{31}$, $v_{-1} = k_{-31}$, $v_2 = k_{22}K_3/(\mathrm{H^+})$, $v_{-2} = k_{-22}K_3'/(\mathrm{H^+})$, $v_3 = k_{33}$, $v_4 = k_{34}$, $v_5 = k_{35}$, and $V = k_{31}(\mathrm{H^+})$. Then $k_{\mathrm{obsd}} = k_{\mathrm{H^+}}(\mathrm{H^+})$, where

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(29) F. Mirer, unpublished results.

$$k_{\mathrm{H}^+} = k_{31}\frac{k_{22}k_{34}K_3 + k_{32}k_{35}K_3 + k_{-22}k_{33}K_3' + (k_{33}k_{34} + k_{33}k_{35})(\mathrm{H}^+)}{k_{-22}k_{-31}K_3' + k_{-22}k_{33}K_3' + k_{22}k_{34}K_3 + k_{22}k_{35}K_3 + (k_{-31}k_{34} + k_{-31}k_{35} + k_{33}k_{34} + k_{33}k_{35})(\mathrm{H}^+)} \qquad (23)$$

and

$$f = \frac{k_{22}k_{35}K_3}{k_{22}k_{34}K_3 + k_{22}k_{35}K_3 + k_{-22}k_{33}K_3' + (k_{33}k_{34} + k_{33}k_{35})(\mathrm{H}^+)} \qquad (24)$$

These equations are of the form already given as eq 12 and 7.

Neutral Region. The kinetic equations and the equation for the fraction of exocyclic cleavage in the region from pH 4 to 11 are complicated and cannot easily be reduced to a simple form. The rate can be expressed by the equation

$$k_{\mathrm{obsd}} = Q[k_{31}(\mathrm{H}^+) + k_{21} + k_{11}(\mathrm{OH}^-)] \qquad (25)$$

where

$$Q = \frac{\vartheta + \kappa(\mathrm{H}^+) + \lambda(\mathrm{H}^+)^2}{1 + \mu(\mathrm{H}^+) + \nu(\mathrm{H}^+)^2} \qquad (26)$$

and the fraction of exocyclic cleavage by the equation

$$= \frac{\xi(\mathrm{H}^+) + \pi(\mathrm{H}^+)^2}{1 + \varphi(\mathrm{H}^+) + \chi(\mathrm{H}^+)^2} \qquad (27)$$

Here ϑ, κ, λ, μ, ν, ξ, π, φ, and χ are functions of the various constants of eq 15. The way in which Q depends on pH is obscure, but it could easily be relatively insensitive to the concentration of hydrogen ion, so that the dependence of the rate on acidity would be controlled by the expression in square brackets in eq 25. Even if Q varied somewhat with acidity, this variation might not be easy to detect in a complicated pH-rate profile such as that represented by eq 4. The fraction, f, of exocyclic cleavage, as shown in eq 27, decreases to zero in regions of low acidity.

Strong Alkali. In strong alkali eq 22 reduces to an equation of the form of eq 14. Then f can be proportional to the hydroxide ion concentration, or, in very strong alkali, be independent of the hydroxide ion concentration. The data so far obtained correspond only to the region where f is proportional to (OH^-).

The Mechanism and Micellar Catalysis of the Acid Cleavage of α-Phenylvinyl Diethyl Phosphate[1]

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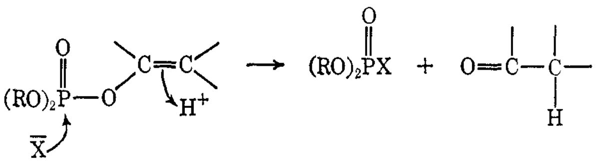
Abstract: The acid cleavage of α-phenylvinyl diethyl phosphate follows an A-S$_E$2 mechanism. Plots of log k_ψ against $-H_0'$ are linear with slopes 1.07–1.4 for hydrochloric, perchloric, and sulfuric acids, with $-\phi = 0.2$–0.6. In moderately concentrated acid the Arrhenius parameters depend on both acidity and temperature, but in dilute acid $\Delta S^* = -8.8$ eu, $k_{\mathrm{H_2O}}/k_{\mathrm{D_2O}} = 2.5$, and the positive salt effect of $\mathrm{LiClO_4}$ is greater than that of LiCl, although $\mathrm{LiClO_4}$ "salts in" and LiCl "salts out" the substrate. At concentrations above the cmc, sodium lauryl sulfate is an effective catalyst of the acid cleavage and $k_{\mathrm{H_2O}}/k_{\mathrm{D_2O}} \approx 2.2$. The catalysis is inhibited by cations with the rate sequence no salt > Li^+ > Na^+ > $(\mathrm{CH_3})_4\mathrm{N}^+$.

The acid-catalyzed cleavage of enol phosphates has been considered as a model reaction for biological phosphorylations by phosphoenolpyruvic acid, and a general discussion of these reactions has been given by Bruice and Benkovic.[2] The postulated mechanism for acid-catalyzed phosphorylation by an enol phosphate involves attack of the proton and the nucleophile as shown in I.[2,3]

Enol phosphates are more reactive than the corresponding trialkyl phosphates, whose hydrolysis is not strongly dependent upon acidity and involves carbon- rather than phosphorus–oxygen fission.[4]



I

The various bond-making and -breaking steps may be stepwise, rather than concerted, and the addition of the proton could be fast and be followed by a rate-limiting attack of water and breaking of the phosphorus–oxygen bond. The available evidence suggests, however, that the transition state has little carbonium ion character, because the rate sequence with substituents, R, in the 1 position is $\mathrm{CH_3} > \mathrm{C_6H_5} > \mathrm{CO_2C_2H_5} > \mathrm{H}$.[2]

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