mL of dry DMF, and 4.8 g (34.5 mmol) of K_2CO_3 were stirred under argon at 25 °C for 24 h. The solvent was evaporated in vacuo, and the residue was partitioned between CH_2Cl_2 and water. The CH_2Cl_2 phase was concentrated and filtered through a pad of silica gel. The product was recrystallized from hot acetone to give 1.03 g (32%) of **16**: MS (FABS, NOBA) *m/e* 1404 (M^+, 100). ^1H NMR (360 MHz, 22 °C, $CDCl_3$) δ 0.83 (t, 12 H, alkyl-CH_3), 1.22 (m, 24 H, $-CH_2CH_2CH_2-$), 1.95 (m, 14 H, $ArCH_3$ and CH_2, α to methine), 2.58 (s, 6 H, $ArCH_3^b$), 3.65 (m, 4 H, H^a), 6.04 (s, 2 H, H^c), 6.96 (s, 2 H, H^c); dimer (360 MHz, −18 °C, $CDCl_3$) δ 1.69 (s, 6 H, $ArCH_3^b$), 1.92 (m, 8 H, CH_2, α to methine), 2.62 (s, 6 H, $ArCH_3^b$), 3.60 (m, 4 H, H^a), 6.02 (s, 2 H, H^c), 6.93 (s, 2 H, H^c); monomer (360 MHz, −18 °C, $CDCl_3$) δ 2.01 (m, 8 H, CH_2, α to methine), 2.19 (s, 6 H, $ArCH_3^b$), 2.48 (s, 6 H, $ArCH_3^b$), 3.70 (m, 4 H, H^a), 6.05 (s, 2 H, H^c), 7.03 (s, 2 H, H^c). $-CH_2CH_2CH_2-$ resonances of monomer and dimer overlap. Anal. Calcd (dried at 150 °C (10^{-5} Torr), 12 h) for $C_{68}H_{64}Cl_8N_8O_8$: C, 58.13; H, 4.59. Found: C, 57.86; H, 4.71.

9,17-Methano-11*H*,13*H*,15*H*-bisbenzo[5′,6′]quinoxalino-[2″,3″:2′,3′][1,4]benzodioxonino[10′,9′:5,6:9″,10″:8,9][1,4]dioxonino[2,3-*b*]quinoxaline-8,18-diol, 11,13,15,40-Tetramethyl-, Stereoisomer (31). To a dry solution (stirred under argon) of octol **18**[4] (0.544 g, 1 mmol) and quinoxaline **27** (0.597 g, 3 mmol) in dry DMSO (30 mL) was added $CsHCO_3$ (1.166 g, 6 mmol). After 2 days of stirring at 25 °C, all the quinoxaline was consumed to produce a mixture of **31** and **1**. The precipitate that formed was filtered, and the filtrate was evaporated in vacuo to give a dark solid. Cavitand **1** was present only in the precipitate, whereas **31** was present in both phases, which were combined and chromatographed on silica gel with CH_2Cl_2/EtOAc (9:1, v/v) as the mobile phase to give 0.367 g (40%) of **31**: mp > 360 °C; MS (FAB, NOBA), 923 ($M^+ + 1$, 100). ^1H NMR (500 MHz $CDCl_3$) δ 1.74 (d, 3 H, $H^{d''}$), 1.80 (d, 6 H, H^d), 1.84 (d, 3 H, $H^{d'}$), 4.53 (q, 1 H, H_a''), 5.53 (m, 4 H, $H^c + H^{b'}$), 7.06 (s, 2 H, $H^{c'}$), 7.21 (s, 2 H, H^a), 7.35 (s, 2 H, $H^{b'}$), 7.37 (b s, 2 H, OH), 7.52 (m, 4 H, AA′BB′ m + t, $H^h + H^i$ or H^f), 7.59 (t or d, 2 H, H^i, or H^j), 7.74 (d of d, 2 H, H^f, or H^e), 7.84 (m center of AA′BB′, 2 H, H^g), 7.94 (d of d, 2 H, H^e or H^f), 8.11 (s, 2 H, H^b); (500 MHz, $(CD_3)_2SO$ δ 1.75 (d, 3 H, $H^{d''}$), 1.86 (d, 6 H, H^d), 1.94 (d, 3 H, $H^{d'}$), 4.46 (q, H, $H^{a''}$), 5.54 (q, 2 H, H^a), 5.68 (q, H, $H^{a'}$), 6.88 (s, 2 H, $H^{a''}$), 7.59 (t, 2 H, H^i or H^j), 7.69 (m, 6 H, H^e or $H^f + H^i$ or Hj + H^c), 7.75 (m center of AA′BB′ 2 H, H^b), 7.97 (d, 2 H, H^e or H^f), 7.98 (s, 2 H, $H^{b'}$), 8.04 (m center of AA′BB′, 2 H, H^g), 8.08 (s, 2 H, H^b), 9.86 (b s, 2 H, OH). Anal. Calcd for $C_{56}H_{38}N_6O_8 \cdot 2H_2O$: C, 70.14; H, 4.41. Found: C, 69.87; H, 4.68.

Crystal Structure Data on 3·2CH_2Cl_2. Compound 3·2CH_2Cl_2 crystallizes from CH_2Cl_2 as colorless, multifaceted crystals in the tetragonal system $P4_12_12$. Unit cell dimensions are as follows: a = 13.009 (2) Å, c = 47.221 (7) Å, V = 7991 Å^3, Z = 4 (the monomer has a 2-fold axis). The crystal was examined on a modified Syntex $P\bar{1}$ diffractometer, CuK_α radiation, at 295 K. The structure was determined by direct methods. Refinement of 238 parameters (2433 reflections with $I > 3_\sigma(I)$) has an agreement value, r, currently at 0.13. One solvent molecule is in the upper cavity and one is in the lower cavity. A possible third (unlocated) solvent is interstitial.

NMR Experiments. Analytical NMR samples were prepared in volumetric glassware. The purity of the NMR solvents were as follows: $CDCl_3$ minimum isotopic purity 99.96%; $C_6D_5CD_3$ minimum isotopic purity 99.96%; CD_2Cl_2 minimum isotopic purity 99.96%; $(CD_3)_2CO$ minimum isotopic purity 99.96%; CD_3OD minimum isotopic purity 99.96%; CD_3NO_2 99.1 atom%; THF-d_8 99.5 atom %; 1,1,2,2-$C_2D_4Cl_4$ 99.6 atom %. The temperature of the probe was calibrated using the difference in chemical shifts between the two peaks of MeOH as a standard. For spectra obtained at other than ambient temperature, the sample was equilibrated for at least 10 min at the temperature of the experiment before data were acquired. Typical relaxation delays were 1 s. NMR samples were immersed in an ice bath at the temperature of the experiment for 30 min prior to any data collection to ensure no precipitation occurred.

Supplementary Material Available: References 15a–i in the text apply to supplementary materials. Figures 1–9, which are plots of temperature against proton chemical shifts in the 500-MHz ^1H NMR spectra of compounds **13** (in $C_6D_5CD_3$), **14** (in $C_6D_5CD_3$), **5** (in $CDCl_3/CS_2$, 1/1 v/v), **6** (in $CDCl_3$), **8** (in $CD_3C_6D_5$), **8** (in $CDCl_3$), **9** (in $CDCl_3$), **17** (in $CDCl_2CDCl_2$), and **16** (in $C_6D_5CD_3$), respectively (9 pages). Ordering information is given on any current masthead page.

Endocyclic Cleavage in the Alkaline Hydrolysis of the Cyclic Phosphonate Methyl Propylphostonate: Dianionic Intermediates and Barriers to Pseudorotation

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Abstract: The hydrolysis of methyl propylphostonate in basic solutions leads exclusively to products resulting from cleavage of the internal ester linkage. On the basis of the mechanism of reaction deduced from the study of cyclic phosphate triesters, it is expected that the addition of hydroxide generates a five-coordinate phosphorus intermediate that reacts with a second hydroxide to give a dianion. Stereoelectronic properties of this dianionic intermediate prevent pseudorotation and lead to the exclusive formation of the endocyclic cleavage product, methyl (γ-hydroxypropyl)phosphonate. These results are consistent with a semiempirical formulation developed by Holmes. Ab initio calculations on related gas-phase systems, aimed at explaining the complex catalytic pathway of ribonuclease, do not suggest the consistent patterns observed in the present study and related experimental observations. Thus, the effects of solvation on reactivity patterns of cyclic phosphate esters are very significant.

The mechanisms of nucleophilic substitution reactions of phosphate esters and related derivatives have been developed in terms of early empirical and theoretical generalizations of Westheimer,[1] Muetterties,[2,3] and Berry.[4] The reactivity patterns of cyclic phosphates have been rationalized in terms of these generalizations,[5] and this information has been used to understand the mechanisms of reactions of complex systems, including the hydrolysis of ribonucleic acids.[6] Holmes extended the basis for

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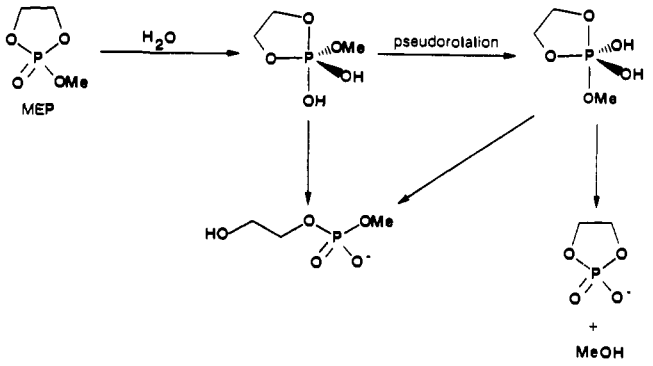
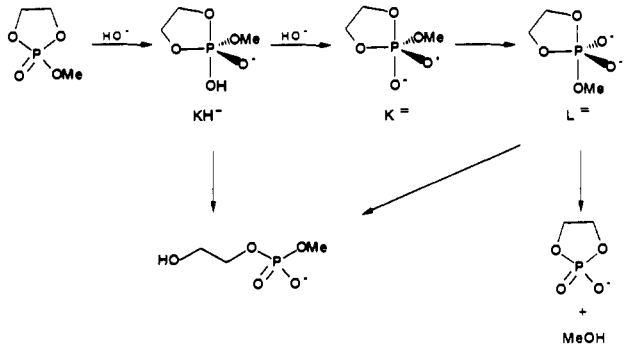
Scheme I



Scheme II

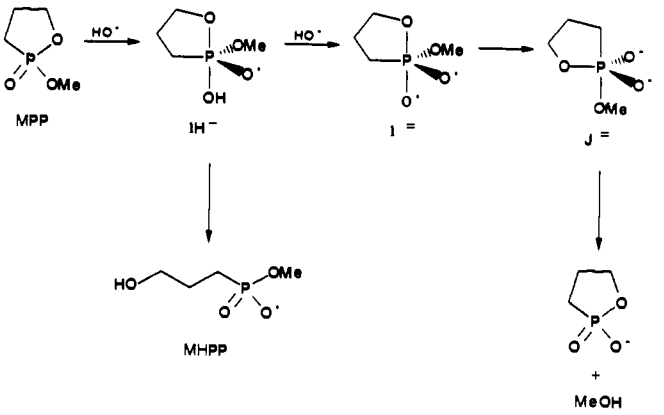


understanding these reactions with a set of semiquantitative procedures based on observations of stable analogues of reaction intermediates and molecular orbital calculations.[7] Further theoretical work[8-10] has suggested additional guidelines that may apply in consideration of the reactivity patterns of these species.

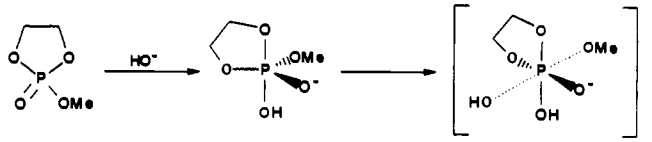
In the hydrolysis of methyl ethylene phosphate (MEP), a mechanistic distinction can be made between reactions that exclusively cleave the internal ester bonds and those that also cleave the P–O bond to the external ester.[11] The route that leads to cleavage of the methoxy group requires pseudorotation of the initially formed intermediate (Scheme I).[1,11] Thus, if decomposition routes for the intermediates are available that are much faster than pseudorotation, products that can result only from the pseudorotated intermediate will not be observed.

The hydroxide-catalyzed reaction of MEP leads exclusively to ring opening.[11] However, it is observed that there is an increasing amount of initial exocyclic cleavage above pH 12. This requires a second-order dependence on hydroxide concentration for the exocyclic cleavage process.[11,12] This kinetic result led to the proposal that the initially formed intermediate, KH^-, undergoes a second ionization to form intermediate K^{2-} (Scheme II). The second ionization forces pseudorotation of K^{2-} to intermediate L^{2-} in order to overcome the unfavorable stereoelectronic consequences arising from placing a negatively charged oxygen ligand in an apical position.[11,12] In L^{2-} the methoxy group is in an appropriate position for departure and rapid exocyclic cleavage competes with ring opening. Rapid reaction occurs because the reactant is highly strained while the transition state is expected to be similar to the strain-free five-coordinate intermediates.[1,13]

Scheme III



Scheme IV



Methyl propylphostonate (MPP) is a phosphonate analogue of MEP in which a methylene group replaces one of the oxygen atoms contained in the five-membered ring.[14] If the reaction of MPP in highly alkaline solution occurs by a mechanism parallel to that of MEP, (Scheme III) then a strain-free intermediate, I^{2-}, with an anionic oxygen ligand generated in an apical position will result. Pseudorotation of I^{2-} to J^{2-} places the methylene group adjacent to phosphorus in a stereoelectronically undesirable position according to Muetterties' preference rules and Holmes' calculations. However, this is compensated to some degree by the movement of the oxyanion from the apical to the equatorial position. Holmes' analysis leads to the conclusion that the energetic barrier to placing a methylene group in an apical position is higher than that for having an oxyanion in the same position. In that case, Holmes' method leads to the prediction that *in basic solutions, pentacoordinate phosphorus intermediates derived from MPP will not undergo pseudorotation, and therefore exocyclic cleavage will not be observed.* On the other hand, intermediates derived from MEP will undergo pseudorotation that permits exocyclic cleavage as shown in Scheme II.

Karplus and Lim proposed that dianionic pentacoordinated intermediates derived from ethylene phosphate cannot exist.[10] The dianionic *intermediate* derived from addition of hydroxide to MEP (followed by ionization, Scheme II) differs from that that would be derived from addition of hydroxide to ethylene phosphate only by exchange of a methyl group for a proton. If the Karplus–Lim gas-phase calculation on ethylene phosphate could be generalized (to related molecules and to the solution phase) then we would conclude that the dianionic intermediate from MEP should not exist.

If dianionic intermediates cannot form, then the exocyclic cleavage reaction must come from another path that involves 2 equiv of hydroxide reacting with MEP. If ionization cannot occur, then addition of a second hydroxide ion in the transition state of the rate-determining step would lead to such an observation. This would lead to reaction via a hexacoordinated phosphorus transition state (hexacoordinate *intermediates* have been ruled out by labeling studies but transition states are possible, Scheme IV).[15,16] Such a mechanism should apply equally well to MEP and MPP and therefore we would expect parallel behavior of the two systems with respect to exocyclic cleavage. On the other hand, if solvation

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and specific energetics of intermediates are critical, then we can draw no general conclusion from those results.[17]

A report of preliminary studies that find exocylic cleavage of MPP in strongly basic solutions[19,11] would require reversal of the relative apicophilicity of a ring methylene and oxyanion according to Holmes' analysis.[7] Thus, we have reinvestigated the hydrolysis of MPP in strongly basic solutions. We find that the results conform to the predictions provided by Holmes' method and confirm the existence of dianionic intermediates.

Experimental Section

Materials and Methods. Chemicals for syntheses were purchased from the Aldrich Chemical Co. and distilled prior to use. Solvents were purchased from Caledon Laboratories Ltd. and BDH Chemicals. Deuterium oxide (99.97%) was from Ontario Hydro (Toronto, Canada). Concentrated sodium deuteroxide, deuterium chloride solutions, and ^{18}O-enriched water were obtained from Aldrich. Chromatographic media were purchased from the Sigma Chemical Co. and Bio-Rad Laboratories.

Dilute solutions of sodium deuteroxide were titrated with standardized hydrochloric acid. The reported isotopic content of stock solutions is that provided by the supplier. ^{13}C (proton decoupled) and ^1H NMR spectra were obtained with a Varian Gemini-200 spectrometer. Chemical shifts for proton NMR spectra in chloroform-*d* solutions are relative to internal tetramethylsilane. For deuterium oxide solutions, ^1H chemical shifts are relative to the residual HDO peak set at δ 4.68 and ^{13}C chemical shifts are relative to dioxane at δ 67.4 (internal standard). Proton-decoupled ^{31}P NMR spectra were recorded on a Varian XL-200 spectrometer, and chemical shifts are relative to external 85% phosphoric acid. pH measurements were conducted with a Radiometer pH meter 27 (GK-202B combination electrode).

Dimethyl (γ-Acetoxypropyl)phosphonate. This material was prepared by the method of Finke and Kleiner.[20] Allyl acetate (22.7 g, 0.227 mol) containing 3 mol% *tert*-butyl peroxide was added dropwise to dimethyl phosphite (25 g, 0.227 mol) contained in a three-necked flask equipped with a reflux condenser and immersed in an oil bath at 150 °C. The temperature of the reaction solution was slowly raised to 170 °C during addition. The mixture was maintained at 170 °C for 3 h then distilled under reduced pressure through a vacuum-jacketed Vigreux column (bp 100 °C (0.120 Torr): yield 78%; ^{31}P NMR (chloroform-*d*) δ 35.7.

Dimethyl (γ-Hydroxypropyl)phosphonate. Dimethyl (γ-acetoxypropyl)phosphonate (8.8 g, 0.042 mol) was dissolved in 35 mL of dry methanol. To this was added 1 mL of a saturated solution of anhydrous hydrogen chloride in methanol. The mixture was heated for 4 h with the resulting methyl acetate removed by distillation. The remaining solvent was removed by rotary evaporation, and the residual oil was stirred at room temperature (0.05 Torr) for 3 h then distilled as reported:[21] ^1H NMR (D_2O) δ 3.64–6.69 (d, 6 H), 3.49–3.56 (t, 2 H), 1.58–1.94 (m, 4 H); ^{31}P NMR (D_2O) δ 37.5; ^{13}C NMR (D_2O) δ 61.81–62.18 (d, J_{P-C} = 18.8 Hz), 53.72–53.80 (d, J_{P-C} = 3.8), 24.82–24.91 (d, J_{P-C} = 4.8 Hz), 18.55–21.33 (d, J_{P-C} = 140.2 Hz).

Methyl propylphostonate (MPP) was prepared by two methods. We adapted the procedure developed by Eberhard and Westheimer for the synthesis of ethyl propylphostonate.[22] Thus, dimethyl(3-bromopropyl)phosphonate (35 g, 0.14 mol, prepared by the method of Helferich and Curtius[23]) was heated at 160–170 °C under nitrogen for 2 h. Product was obtained by multiple vacuum distillations of the resulting liquid through a vacuum-jacketed Vigreux column (bp 50–53 °C (0.03–0.04 Torr)): yield 50%; ^1H NMR (chloroform-*d*) δ 1.55–2.70 (m, 4 H), 3.68–3.93 (d, 3 H), 4.00–4.70 (m, 2 H); ^{31}P NMR δ 51.2. This procedure produced material that contained an impurity that was removed only after many distillations. MPP was preferably prepared by heating dimethyl γ-hydroxypropyl phosphonate at 100 °C under nitrogen for 1 h. This reaction was more efficient than the literature procedure (70% yield), and pure product was obtained after two vacuum distillations through a jacketed Vigreux column. Materials from both studies were used for kinetic and product studies and gave indistinguishable results.

Sodium Propylphostonate. Sodium iodide (2.50 g, 0.0167 mol) was dissolved in 80 mL of dry butanone. MPP (2.0 g, 0.0147 mol) was added, and the mixture was refluxed for 8 h and then kept in an ice bath for 1 h. The resulting precipitate was filtered off and washed thoroughly with cold butanone. The precipitate was then dissolved in an acetone/methanol (2:8) mixture and applied to a silica gel column. The column was washed with acetone/methanol (2:8) and the product eluted with methanol. Removal of methanol, first by rotary evaporation and then by heating the resulting white powder at 80 °C under vacuum for 24 h, yielded pure sodium propylphostonate in 76% yield: ^1H NMR (D_2O) δ 3.84–3.97 (m, 2 H), 1.93–2.16 (m, 2 H), 1.44–1.58 (m, 2 H); ^{31}P NMR (D_2O) δ 47.05; ^{13}C NMR (D_2O) δ 67.03–67.23 (d, J_{P-C} = 10.1 Hz), 24.92–24.96 (d, J_{P-C} = 1.7 Hz), 18.82–21.21 (d, J_{P-C} = 120 Hz).

Lithium Methyl (γ-Hydroxypropyl)phosphonate. Methyl propylphostonate (1 g, 0.015 mol) was hydrolyzed to sodium methyl(γ-hydroxypropyl)phosphonate by addition of methyl propylphostonate to a solution of deuterium oxide maintained at pD 9.0–9.5 by addition of a 1 M NaOD solution with a Hamilton syringe. After hydrolysis, the reaction mixture was lyophilized, yielding a white powder that rapidly absorbed water when exposed to air to produce a colorless syrup. The syrup was diluted to about 2 mL with water and then applied to a Dowex 50W-X8 column, lithium form, and eluted slowly with water. Lyophilization yielded pure product in 90% yield (white powder): ^1H NMR (D_2O) δ 3.36–3.50 (m, 5 H), 1.38–1.65 (m, 4 H); ^{31}P NMR (D_2O) δ 29.6; ^{13}C NMR (D_2O) δ 62.83–63 (d, J_{P-C} = 18.4 Hz), 51.86–51.93 (d, J_{P-C} = 3.6 Hz), 26.27–26.36 (d, J_{P-C} = 4.5 Hz), 21.16–23.87 (d, J_{P-C} = 136.3 Hz).

Reaction and Quench Procedures. Freshly distilled MPP was added with a Hamilton syringe to 300 μL of NaOD solution that was vigorously magnetically stirred. The vial was immediately stoppered and the contents frozen by submersion of the vial in a carbon dioxide/acetone bath (quenching by neutralization would generate excessive heat). The vial was then removed from the bath and left to thaw on the surface of a magnetic stirring motor. When the stirring bar began to move, concentrated DCl was added so that pH paper gave a reading between 7 and 9. The mixture was then cooled in an ice bath and transferred to a 5-mm NMR tube, and ^1H NMR and ^{31}P NMR spectra were immediately recorded. For reactions performed in solutions of pD 10.0, the procedure was as follows: 20 μL of MPP was added to 5.0 mL of NaOD in deuterium oxide at pD 10.0. The measured pD of the solution was maintained constant by the addition of a 1.0 M NaOD from a Radiometer Autoburette 13 in conjunction with a Radioimeter TTT80 titrator and pH meter 27 (GK-202B combination electrode). After the reaction was complete, 1.0 mL of the solution was transferred to a 5-mm NMR tube. ^1H and ^{31}P NMR spectra were recorded.

Solutions of high base concentration are also high in ionic strength, and this will prevent dissolution of the added reactant through a salting-out effect. Therefore, MPP was dissolved in 100 μL of deuterium oxide and then added to 300 or 400 μL of concentrated sodium deuteroxide. In separate experiments, the sodium deuteroxide solution was added to the MPP dissolved in deuterium oxide. The mixtures were immediately quenched as described previously and NMR spectra recorded.

Product Analysis. The ^1H NMR signal for the methyl group of methanol from the reaction of MPP in a concentrated sodium deuteroxide solution appears at δ 3.5 (after acid quench). The signal for the γ-methylene protons of methyl (γ-hydroxypropyl)phosphonate (MHPP, see Scheme III) appears as a triplet at δ 3.7–3.8. This is coincident with the downfield half of the doublet for the methoxyl group from MHPP. Methanol and MHPP were identified by a comparison of NMR peaks with those of authentic samples of pure material. The amount of methanol produced in the reaction was determined from the ratio of the integration of the methanol methyl peak to that of the sum of the integrations of the methanol methyl signal and twice that of the upfield half of the doublet due to the methoxyl group of MHPP.

The proton-decoupled ^{31}P NMR spectrum for the reaction of MPP in a concentrated sodium deuteroxide solution after acid quench shows a singlet for MHPP at δ 30.4. In addition to the MHPP signal, two signals of equal intensity appear at δ 29.0 and 30.0, which are due to a dimeric species, consistent with expectations from earlier on reactions of cyclic phosphate triesters in basic solutions.[12,24] The amount of dimer produced in the reaction was determined by measuring the ratio of the average

(17) Professor Lim informed us (after submission of our original manuscript) that calculations on intermediates derived from methyl ethylene phosphate, using the same basis set as used for ethylene phosphate, show the existence of metastable dianionic pentacoordinate intermediates. Professors Lim and Karplus have further informed us that ab initio calculations on these highly charged and unstable five-coordinate phosphate dianions will have to take into account effects of solvation in order to explain the basis of empirical rules for reactivity patterns of phosphates. Earlier calculations on MEP using a more limited basis set[18] are not suitable for comparison as noted in the discussion by Karplus and Lim on the subject of ethylene phosphate derived intermediates.

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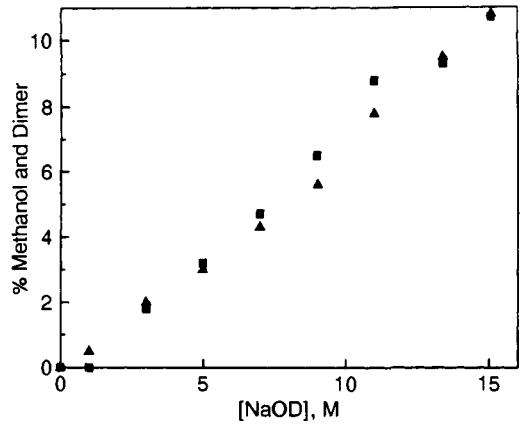


Figure 1. Effect of base concentration on percentage of methanol (▲) and dimer (■) formed. Reactions in deuteroxide solutions of 1.0 M or greater were performed at room temperature by adding 21.4 μL of MPP to 300 μL of NaOD solution and freeze quenching as described in the Experimental Section. The "0 M" deuteroxide point was carried out in a pD stat at pD 10.0 with 20 μL of MPP in 5.0 mL of D_2O (see Experimental Section). Percent methanol was determined using ^1H NMR with an estimated error of ±1% based on an average of three measurements. Percent dimer was determined using ^{31}P NMR with an estimated error of ±1.5% based on an average of three measurements.

Table I. Effects of the Amount of MPP Added on Percentage of Methanol Formed for the Reaction of MPP in Sodium Deuteroxide Solutions[a]

[NaOD] (M)	% methanol (μL of MPP)				
	21.4	10.7	5.4	2.1	1.1
7.0	4.3	4.4	3.4	3.3	3.3
9.0	5.6	5.0	4.8	4.9	4.9
11.0	7.8	7.5	7.5	7.0	6.9
13.4	9.5	9.2	9.2	9.0	9.1

[a] All reactions were performed by adding the appropriate amount of MPP to 300 μL of NaOD solution and freeze quenching as described in the Experimental Section. See Figure 1 for estimated error.

intensity of the two dimer signals in the ^{31}P NMR to that of the combined intensities of the signal due to MHPP and the average of the two dimer signals.

Quantitative analysis using ^{31}P NMR is complicated by possible variations in nuclear Overhauser effect (NOE) and relaxation time between products.[25,26] In order to use ^{31}P NMR for quantitative analysis, we employed a relaxation delay (25 s) that was at least twice the relaxation time (T_1) of the phosphate products to prevent partial saturation of the signals. Although it is possible that the NOE for MHPP differs from that of the dimer, methanol production determined by ^1H NMR approximately parallels dimer production as determined by ^{31}P NMR (see Figure 1), which suggests that the NOE in the two phosphate products is approximately the same.

Isotopic Labeling. Reactions conducted in basic ^{18}O-enriched deuterium oxide were performed using the quench procedure described previously. The ^{18}O content in the phosphate products was analyzed using isotopically shifted peaks in ^{31}P NMR spectra.[27] The hydrolysis reaction measurement was repeated twice, and identical results were obtained.

Results

Proton NMR Analysis of Products. The addition of MPP to sodium deuteroxide solutions (1 M or less) produces only MHPP. At sodium deuteroxide concentrations greater than 1 M, a signal due to the methoxyl protons of methanol was apparent at δ 3.5 if MPP was added without being first dissolved in deuterium oxide. In that case, the relative amount of methanol produced increases with deuteroxide concentration and is independent of the amount of MPP added (Figure 1 and Table I). These observations are consistent with earlier reports of this product being formed.[19]

(25) Pregosoin, S.; Kuntz, R. W. *31-P and 13-C NMR of Transition Metal Phosphine Complexes*, Springer: Berlin, 1979; pp 14–15.
(26) Shoolery, J. N. *Prog. Nucl. Magn. Res. Spectrosc.* **1977**, *11*, 79.
(27) Cohn, M.; Hu, A. *Proc. Natl. Acad. Sci. U.S.A.* **1978**, *200*, 1975.

Table II. Effect of Predissolving MPP[a] in Deuterium Oxide on Percentage of Methanol and Dimer Formed for the Reaction of MPP in Concentrated Sodium Deuteroxide Solutions

μL of MPP	μL of D_2O[b]	[NaOD][c] (M)	% MeOH	% dimer
10.7	100	10.0	0	0
2.1	100	10.0	0	0
10.7	0	10.0	6.5	6.2
2.1	0	10.0	6.5	7.5
10.7	100	12.1	0	0
10.7	0	12.1	8.0	9.0
10.7	100[d]	not added	no reaction	no reaction

[a] All reactions were performed using the freeze quench method as described in the Experimental Section with the exception of the control expt. [b] Amount of D_2O added to MPP before addition to base solution. [c] Final concentration of NaOD. [d] Control experiment: MPP was dissolved in 100 μL of D_2O, frozen in dry ice/acetone bath, and thawed, and 500 μL of D_2O was added and a spectrum recorded.

Table III. Effects of the Amount of MPP Added on Percentage of Dimer Formed for the Reaction of MPP in Sodium Deuteroxide Solutions[a]

[NaOD] (M)	% dimer (μL of MPP)				
	21.7	10.7	5.4	2.1	1.1
7.0	4.7	4.6	4.7		
9.0	6.5	6.5	6.3	5.5	6.3
11.0	8.8	8.5	8.8	7.9	8.0
13.4	9.3	9.3	9.5	9.1	9.0

[a] All reactions were performed by adding the appropriate amount of MPP to 300 μL of NaOD solution and freeze quenching as described in the Experimental Section. See Figure 1 for estimated error.

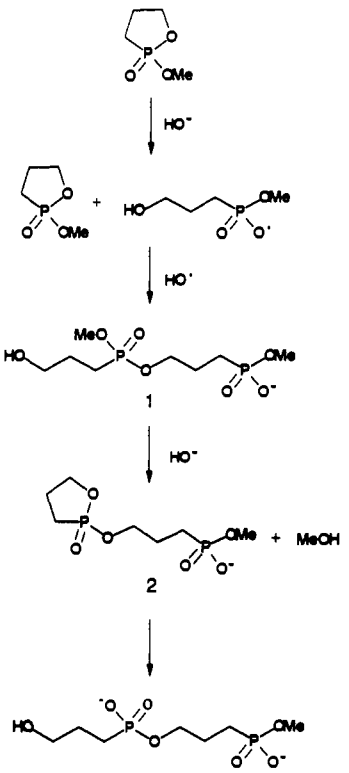
When MPP was dissolved in deuterium oxide prior to reaction in base (no reaction occurs in the neutral solution during the time of the experiment in control samples), MHPP was the only product observed above trace levels (Table II). The results were the same whether the solution of MPP was added to the sodium deuteroxide solution or the sodium deuteroxide solution was added to the aqueous solution of MPP.

Phosphorus NMR Analysis of Products. When MPP was added directly to sodium deuteroxide solutions at base concentrations less than 1 M, a single peak due to MHPP appeared at δ 30.4. At deuteroxide concentrations greater than 1 M, in addition to the MHPP signal, two phosphorus signals of equal intensity from an additional product appear. The latter peaks are assigned to a dimeric species. The relative yield of the dimer increases with deuteroxide concentration (Figure 1). The absolute concentration of reacting MPP did not affect the ratio of dimeric to monomeric products, indicating that the dimer formation process is occuring prior to dissolution (Table III). Signals due to products that would result from direct exocyclic cleavage of MPP, propylphostonate, and (γ-hydroxypropyl)phosphonate were not observed. When MPP was dissolved in deuterium oxide prior to reaction in base MHPP was the only product observed (Table II).

Isotope Labeling Experiments. MPP was hydrolyzed in concentrated sodium deuteroxide in $H_2{}^{18}O$ and quenched as in the unlabeled solutions. The products were analyzed for isotope incorporation by ^{31}P NMR as described in the Experimental Section. In all cases, 1 equiv of label from solvent was incorporated into the phosphate products. This indicates that P–O rather than C–O cleavage occurs in the hydrolysis of MPP and that hexacoordinate intermediates do not form. For a full discussion of a similar analysis on MEP, see the earlier paper by Kluger and Thatcher.[15]

Dimer Formation and Methanol Production. Since methanol production parallels dimer formation (see Figure 1), methanol production is a result of dimer formation or vice versa. Since the absolute concentration of reacting MPP did not affect the ratio of dimeric to monomeric products (see Table III), the dimer formation process probably occurs at the interface of undispersed MPP droplets. A mechanism and structure consistent with these results is shown in Scheme V.[28]

Scheme V



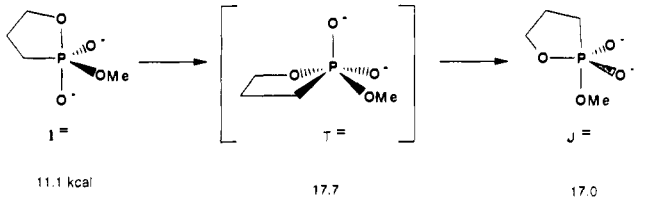
A reaction between hydroxide and MPP at the droplet interface produces MHPP. The MHPP can either be dispersed into solution or react with the local high concentration of MPP to form the triester dimer **1**, which may then undergo a cyclization reaction to produce methanol and cyclic triester dimer **2**. This reacts with hydroxide to form the observed dimer product. Thus, dimer formation and methanol production are a result of a reaction between undispersed MPP and MHPP. Cyclization of triester dimer **1** should be rapid enough to produce methanol under the conditions employed in these studies. This was confirmed by reacting dimethyl (γ-hydroxypropyl)phosphonate in a concentrated NaOD solution followed by rapid quenching of the sample. ^{1}H NMR analysis revealed that all of the dimethyl (γ-hydroxypropyl)phosphonate had reacted to form methanol and MHPP.

Our results show that the reaction of dissolved MPP with deuteroxide leads exclusively to the formation of endocyclic cleavage product, MHPP. MPP does not undergo exocyclic cleavage in strong base. Methanol production is a result of a reaction between undissolved MPP and the endocyclic cleavage product, MHPP.

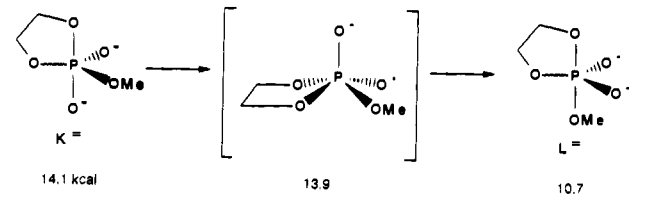
Discussion

Relative Apicophilicities Using the Holmes Formulation. The mechanism proposed for the reaction of MEP in strong base can be extended to the reaction of MPP. In the case of MEP, ionization of the apical hydroxyl group in the first intermediate (Scheme II) generates intermediate K^{2-} in which an oxyanion occupies an apical position. This ionization promotes pseudorotation to the isomeric species, L^{2-}, in which the ligands attached to phosphorus in the five-membered ring exchange positions along with the oxyanion and methoxyl groups. This moves the methoxyl group to an apical position from which it can depart in competition with ring opening. The analogous mechanism for MPP is shown in Scheme III. The two possible five coordinate dianionic intermediates, I^{2-} and J^{2-}, lead to different products. Thus, if pseudorotation occurs, only exocyclic cleavage results. Application of the Holmes model to intermediates I^{2-} and J^{2-} gives an estimate of the quantitative energy difference between the two intermediates (Scheme VI). The transition state for the pseudorotation between I^{2-} and J^{2-} is approximated by the square planar isomer T^{2-}. Since T^{2-} and J^{2-} are about 6 kcal greater in energy than I^{2-}, ionization of the apical hydroxyl group of IH^- to form I^{2-} should not force a pseudorotation to J^{2-} and MPP should not undergo exocyclic cleavage even in strong base. This is in contrast to the conformational energies reported for analogous intermediates formed during the hydrolysis of MEP (Scheme VII).[7] In this case the isomer L^{2-} is lower in energy than K^{2-} and is formed without any intervening barrier. Thus, this semiempirical approach for estimating the conformational energies of pentacoordinated intermediates is consistent with our experimental results.

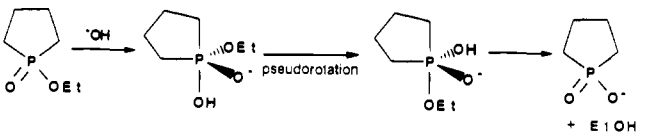
Scheme VI



Scheme VII



Scheme VIII



Related Reactions of Phosphinates. Unlike the five-membered cyclic phosphonate and phosphates, the five-membered ring phosphinate, ethyl butylphosphinate, hydrolyzes in base less than 100 times faster than does its acyclic analogue, ethyl diethylphosphinate.[30,14] In the cyclic phosphinate, the intermediate must necessarily have a methylene group in an apical position. This is due to initial formation of a high-energy intermediate in which the ring methylene must be placed in an apical position (Scheme VIII). Pseudorotation of this intermediate so that the ethoxyl group is apical still results in the formation of a species in which a methylene group (of the ring) is in an apical position. This is comparable to the situation required for exocyclic cleavage in MPP. Since ethyl butylphosphinate hydrolyzes approximately 10^5 slower than ethyl propylphostonate, it is reasonable to expect that endocyclic cleavage of MPP is favored over exocyclic cleavage by a factor of about 10^5. This is consistent with our finding exclusive endocyclic cleavage with MPP even in very strong base.

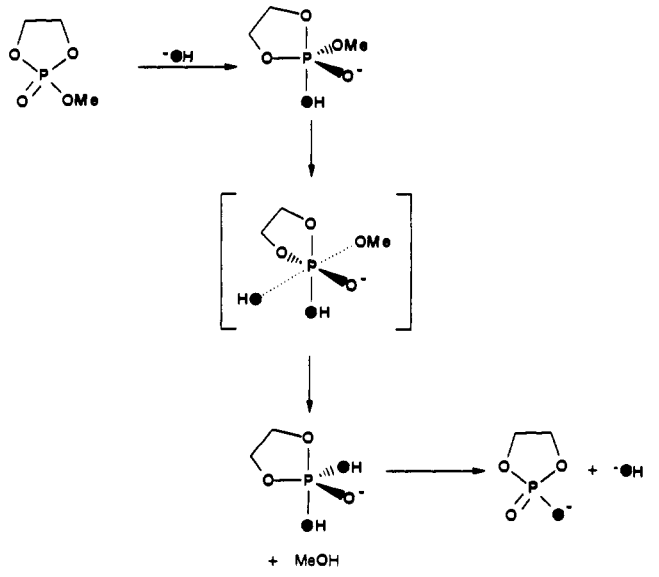
Dianionic Intermediates. Karplus and Lim reported ab initio calculations for the addition of hydroxide to ethylene phosphate.[10] When a split-valence 3-21G* basis set that included the polarization functions (3d orbitals) on the phosphorus atom as well as a 3-21+G* basis set was employed, no stable dianionic pentacovalent intermediate was found along the reaction coordinate. On the basis of these results, they suggested that dianionic pentacovalent phosphoranes are too unstable to exist in this reaction manifold. As we have explained in the introduction, extension

(28) A similar mechanism was proposed by Gorenstein[29] to account for some of the methanol and dimer produced when methyl ethylene phosphate is hydrolyzed in concentrated deuteroxide. However, Kluger and Thatcher[12] have shown that dimer formed during the hydrolysis of methyl ethylene phosphate may be due to a reaction between exocyclic cleavage product, ethylene phosphate, and endocyclic cleavage product, methyl hydroxyethyl phosphate. Attempts to synthesize the dimer that is formed during MPP hydrolysis by a similar route proved unsuccessful.

(29) Gorenstein, D. G.; Yang, J. *Tetrahedron* **1987**, *43*, 479.

(30) Asknes, G.; Bergesen, K. *Acta. Chem. Scand.* **1966**, *30*, 2508.

Scheme IX



of these conclusions to MEP would lead to the prediction that the cleavage in strong base that is second order in hydroxide involves a mechanism that does not proceed through a dianionic intermediate.

Thatcher and Kluger have shown by ^{18}O labeling that 1 equiv of oxygen from solvent water is incorporated into ethylene phosphate, the phosphate product that results from exocyclic ester cleavage in the hydrolysis of MEP.[15] Since hexacoordinated phosphorus will be octahedrally situated, symmetry requires that more than 1 equiv of ^{18}O would be incorporated into ethylene phosphate. Therefore, hexacoordinate intermediates can be ruled out. Furthermore, mechanisms involving C–O cleavage of the exocyclic ester can be ruled out since this would give no ^{18}O incorporation. Thus, the only remaining possibility for a mechanism that is second order in hydroxide but that does not involve a dianionic pentacoordinated intermediate involves a hexacoordinate transition state resulting from the addition of hydroxide to the monoanionic species (Scheme IX). In this case, the first ^{18}O adds to form the pentacoordinate intermediate and specifically occupies an apical position. Exocyclic displacement by a constrained equatorial S_N2 mechanism leads to ^{18}O incorporation in an equatorial position. Expulsion of the apical hydroxide–^{18}O ligand therefore leads to the incorporation of the single ^{18}O that is in the equatorial position into ethylene phosphate. The mechanism does not involve pseudorotations of intermediates, and therefore, MPP should be equally susceptible to exocyclic cleavage. Since MPP does not undergo exocyclic cleavage, we may rule out the hexacoordinate transition-state mechanism that had remained as a possibility from earlier studies. This shows that dianionic five-coordinate phosphorus species do exist as intermediates in at least some reactions.

Conclusions

The hydrolysis of methyl propylphostonate in basic solutions occurs via a five-coordinate phosphorus intermediate that is a monoanion or dianion. In either case, pseudorotation does not occur, and the exclusive products are those that result from cleavage of the ester within the ring. The results are consistent with the empirical model that has been developed by Holmes.

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