propane, a Syntex-Nicolet P3f diffractometer equipped with a graphite monochromated Mo $K_\alpha$ radiation source. The structures were solved by direct methods using the MULTAN80[29] package and refined by full matrix least-squares refinement. The final cycles of the least-squares refinement[30] assumed the non-hydrogen atoms to vibrate anisotropically and the hydrogen atoms to vibrate isotropically. Final electron density difference maps showed no significant features. All calculations were done on a Digital Equipment VAX 11/750.

**1,1-Diphenyl-2,2-diisopropyl-3-(2,2-diphenylvinyl)cyclopropane.**[28] Crystals were orthorhombic, space group P(BCA), with $a$ = 10.782 (2) Å, $b$ = 16.599 (2) Å, $c$ = 29.947 (4) Å, and $d_{calcd}$ = 1.132 g cm$^{-3}$ for $Z$ = 8. The size of the crystal used for data collection was 0.9 × 0.8 × 0.35 m. A total of 6728 independent reflections were measured for 3.5° < 2$\theta$ < 56.8°, of which 4095 were considered to be observed [$F_o > 3\sigma(F_o)$]. The final discrepancy indices are $R$ = 0.042 and $R_w$ = 0.057.

**1,1-Diphenyl-2,2-dimethyl-3-(2,2-dimesitylvinyl)cyclopropane.**[28] Crystals were monoclinic, space group $P2_1/C$, with $a$ = 10.627 (3) Å, $b$ = 25.527 (6) Å, $c$ = 11.662 (2) Å, $\beta$ = 114.69(2)°, and $d_{calcd}$ = 1.124 g cm$^{-1}$ for $Z$ = 4. The size of the crystal used for data collection was 0.15 × 0.20 × 0.25 mm. A total of 3931 independent reflections were measured for 3.5° < 2$\theta$ < 45.77°, of which 2002 were considered to be observed [$I > 3\sigma(I)$]. The final discrepancy indices are $R$ = 0.051 and $R_w$ = 0.056.

***trans*-1,1-Diphenyl-2-isopropyl-2-methyl-3-(2,2-diphenylvinyl)cyclopropane.**[28] Crystals were triclinic, space group $P\bar{1}$, with $a$ = 10.801 (3) Å, $b$ = 13.141 (2) Å, $c$ = 10.774 (2) Å, $\alpha$ = 114.01(2)°, $\beta$ = 105.16(2)°, $\gamma$ = 66.98(2)°, and $d_{calcd}$ = 1.115 g cm$^{-3}$ for $Z$ = 2. The size of the crystal used for data collection was 0.28 × 0.35 × 0.40 mm. A total of 5254 independent reflections were measured for 3.5° < 2$\theta$ < 52.87°, of which 2860 were considered to be observed [$F_o > 3\sigma(F_o)$]. The final discrepancy indices are $R$ = 0.052 and $R_w$ = 0.058.

***cis*-1,1-Diphenyl-2-isopropyl-2-methyl-3-(2,2-diphenylvinyl)cyclopropane.**[28] Crystals were triclinic, space group $P\bar{1}$, with $a$ = 10.062 (13) Å, $b$ = 10.787 (10) Å, $c$ = 13.221 (25) Å, $\alpha$ = 104.50 (11)°, $\beta$ = 104.58 (12)°, $\gamma$ = 105.13 (9)°, and $d_{calcd}$ = 1.115 g cm$^{-3}$ for $Z$ = 2. The size of the crystal used for data collection was 0.15 × 0.23 × 0.50 mm. A total of 3425 independent reflections were measured for 3.5° < 2$\theta$ < 45.0°, of which 2224 were considered to be observed [$F_o > 3\sigma(F_o)$]. The final discrepancy indices are $R$ = 0.074 and $R_w$ = 0.083.

**Molecular Mechanics Calculations.** Calculations were carried out using the MMPI and MM2 programs of Allinger.[14c,e] All calculations were done on a Digital Equipment VAX 11/750. Geometries were input using the MENU[14a] program in Tribble.[14b] The extended (*W*) conformation of the dienes was found to be of lowest energy. The twist angle around one of the diphenylvinyl double bonds in each diene was then fixed at different values. The steric energy was minimized with this fixed twist angle, and all other variables were free. The twisting results from MMPI are listed in Table IV. The initial geometries of the cyclopropyldicarbinyl diradicals were generated by bonding C-2 and C-4 in the minimum energy conformations of the dienes and placing the residual diarylmethyl radical centers in a transoid relationship using the DISPLAY[14a] program in Tribble.[14b] The results for the diradicals are listed in Table V.

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**Registry No.** 1, 99342-80-0; 2, 99342-99-1; 3, 99342-82-2; 4, 99342-94-6; 5, 4160-97-8; 6, 4160-99-0; 7, 99342-76-4; 8, 99342-95-7; 9, 19184-67-9; 10, 99342-77-5; 11, 99342-96-8; 12, 99342-81-1; 13, 99342-78-6; 14, 99342-97-9; 15, 99342-82-2; 16 (isomer 1), 99342-84-4; 16 (isomer 2), 99342-85-5; 17, 99342-86-6; 18, 99342-87-7; 19, 99342-88-8; 20, 99342-89-9; 21, 99342-90-2; 22, 99342-91-3; 23, 99342-92-4; 24, 99343-00-7; 25a, 99343-02-9; 25b, 99343-03-0; 26, 99343-01-8; $Ph_2C{=}CHC(i\text{-}Pr)_2CH_2C(OH)Ph_2$, 99342-79-7; $Ph_2C{=}C(CH_3)C(CH_3)_2CH(CH_3)C(OH)Ph_2$, 99342-93-5; $Ph_2C{=}CHC(CH_3)(i\text{-}Pr)CH_2C(OH)Ph_2$, 99342-98-0; 5,5-dimesityl-1,1-diphenyl-3,3-dimethyl-4-pentenol, 99342-83-3.

**Supplementary Material Available:** Tables consisting of crystal data, intensity collections parameters, fractional coordinates, interatomic distances, and figures (25 pages). Ordering information is given on any current masthead page.

(29) Germain, G.; Main, P.; Woolfson, M. M. *Acta. Crystallogr. Sect. A: Cryst. Phys., Diffr., Theor. Gen. Crystallogr.* **1971**, *27*, 368-376.

(30) (a) Atomic form factors were from Cromer, D. T.; Mann, J. B. "International Tables for X-ray Crystallography"; Kynock Press: Birmingham, England, 1974; Vol. 4, pp 99-101, Table 2.2B. (b) The atomic form factor for hydrogen was from Stewart, R. F.; Davidson, E. R.; Simpson, W. T. *J. Chem. Phys.* **1965**, *42*, 3175-3187.

# Exocyclic Cleavage in the Alkaline Hydrolysis of Methyl Ethylene Phosphate: Pseudorotation of a Pentavalent Intermediate or Reaction via a Hexavalent Intermediate?

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The observation of increasing exocyclic cleavage of methyl ethylene phosphate in alkaline solution was the first evidence for hydrolysis of a phosphate ester by reaction with 2 equiv of hydroxide. Kinetically equivalent mechanisms provide a role for a second hydroxide after the first hydroxide adds to form a pentavalent intermediate. These are (1) proton abstraction, pseudorotation, and exocyclic cleavage and (2) addition to form a hexavalent phosphorus intermediate followed by exocyclic cleavage. The mechanisms can be distinguished by patterns of isotope incorporation from solvent into the product of exocyclic cleavage. The hydrolysis of methyl ethylene phosphate was carried out in $D_2O$ containing $D_2{}^{18}O$, and the pattern of isotopically shifted phosphorus NMR peaks of ethylene phosphate (and its hydrolysis product hydroxyethyl phosphate) rules out the involvement of hexavalent phosphorus intermediates. The formation of ethylene phosphate via anionic pentavalent intermediates contradicts predictions of a stereoelectronic theory that places great energetic advantage in cleaving the endocyclic ester bond.

Our understanding of the mechanisms of hydrolysis of phosphate esters depends largely upon the work of Westheimer in which rules describing the behavior of pentavalent phosphorus intermediates were developed.[1,2]

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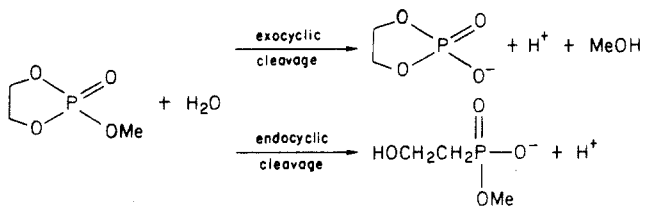
**Scheme I**




An important aspect of this work was the demonstration that pseudorotation of the intermediate is often a necessary step in the reaction process. In particular, exocyclic cleavage of a cyclic ester requires pseudorotation of an intermediate.[1-6] Elegant stereochemical studies by Knowles' group have given strong support for the mechanism since pseudorotation leads to substitution with retention of relative configuration of phosphorus.[7] The hydrolysis of methyl ethylene phosphate is of particular interest since it is subject to competing reaction pathways that can establish general reaction patterns for phosphate esters (Scheme I).[4-6]

The observation of an increasing proportion of exocyclic cleavage in increasingly alkaline solutions has been interpreted in terms of a mechanism in which pseudorotation of an intermediate is promoted by hydroxide.[4] A monoanionic intermediate is formed by addition of hydroxide, and this intermediate undergoes nearly exclusive *endocyclic* cleavage. Since the formation of the intermediate is first order in hydroxide and this gives endocyclic cleavage, an increase in the proportion of exocyclic cleavage with increasing hydroxide requires that the exocyclic cleavage process involves 2 equiv of hydroxide.[4-6]

It was proposed that the second equivalent of hydroxide functions as a Brønsted base, removing a proton from the apical hydroxyl group of the monoanionic intermediate.[4-6] The resulting dianion rapidly pseudorotates via a square-pyramidal transition state to place the anionic ligands in equatorial positions.[4,5] It was noted that a kinetically equivalent but less likely role for the second equivalent of hydroxide is formation of a hexavalent intermediate from the pentavalent intermediate that then undergoes exocyclic cleavage.[4] The mechanistic ambiguity has received recent notice,[8,9] and the hexavalent route has received vigorous support.[10]

Gorenstein and co-workers have used isotope incorporation data to try to choose between the mechanisms.[8,9,11] The involvement of hexavalent intermediates requires that 2 equiv of hydroxide adds to the substrate. Pentavalent intermediates require the addition of only 1 equiv of hydroxide. These workers report that when the hydrolysis of methyl ethylene phosphate is conducted in solvent containing $D_2{}^{18}O$ and 5 M sodium deuteroxide, 1 equiv of $^{18}O$ is incorporated into the product of *endocyclic* cleavage, methyl hydroxyethyl phosphate. They also report that they do not observe peaks corresponding to the products that would result from exocyclic cleavage. Exclusive endocyclic cleavage is consistent with the requirements of their stereoelectronic theory.[9,11]

Although the principle used for the analysis by Gorenstein and co-workers is correct, the compound analyzed does not provide the necessary test. The increase in exocyclic cleavage of methyl ethylene phosphate with increasing hydroxide concentration is the only evidence for a process that is second order in hydroxide.[4,6,10] If products of exocyclic cleavage are not observed, then one cannot know to what extent endocyclic cleavage arises from a two-hydroxide route (or indeed that there is such a route). Therefore, ethylene phosphate (or its hydrolysis product, hydroxyethyl phosphate) must be detected and analyzed in order to test conclusively for the involvement of hexavalent intermediates in the exocyclic cleavage process.

We have recently demonstrated that initial exocyclic cleavage of methyl ethylene phosphate with increasing base concentration does occur in this system,[6] contrary to other reports.[9,11] Thus, we have examined incorporation of isotopically labeled water into the product of exocyclic cleavage to settle the question of the involvement of pentavalent vs. hexavalent phosphorus intermediates in the two-hydroxide reaction.

## Experimental Section

**Instruments.** Fourier transform phosphorus spectra were obtained with a Varian XL-200 pulsed spectrometer at 80.57 MHz with inverse-gated broad-band proton decoupling (30° pulse angle, 6-μs pulse width, 4-s delay). Chemical shifts downfield of the reference are indicated as positive. Full-scale signal-to-noise ratio is >200:1. The lowest signal-to-noise ratio (for the smallest peaks analyzed) is 20:1, based on measurement of mean peak-to-peak base-line noise levels. Proton NMR analysis was done with the same instrument configured at 200 MHz without decoupling. All solutions volumes were measured with Eppendorf digital pipets (manufacturer's reported accuracy ±1.5%)

**Materials.** Deuterium oxide (99.9%) and concentrated NaOD were obtained from Merck Sharp & Dohme and deuterium oxide-$^{18}O$ (82% $^{18}O$, 95% deuterated) was obtained from Miles Laboratories. Diluted solutions of sodium deuteroxide were prepared and titrated with Fisher Reagent hydrochloric acid. The reported isotopic content of stock solutions is based on the manufacturer's assay of the reagent solvent. Methyl ethylene phosphate and sodium ethylene phosphate were freshly prepared and purified as described previously.[6,12]

**Reactions. Phosphorus NMR Analysis.** Methyl ethylene phosphate (20 μL) was added to the inner surface of a 5-mm-diameter NMR tube containing sodium deuteroxide (240 μL, 5 M) in $D_2O/D_2{}^{18}O$. The tube was capped and shaken. The reaction was stopped by cooling the tube in a solution of dry ice in acetone and adding 300 μL of DCl solution (made from 95 μL of concentrated HCl and 200 μL of $D_2O$) to bring the solution to pD 11. Further hydrolysis of sodium ethylene phosphate, which is base catalyzed, is self-quenched by the product, monosodium hydroxyethyl phosphoric acid, an acid of pK 6. Ethylene phosphate is produced initially to an extent of about 8% of the total products under these conditions.[4,10] The major (92%) product of the initial hydrolysis of methyl ethylene phosphate, sodium methyl hydroxyethyl phosphate, hydrolyzes via formation of ethylene phosphate to produce hydroxyethyl phosphate at less than $^1/_{1000}$ the rate of the initial reaction.[6] This is not sufficient to interfere and is reduced further since the solution is brought to pD 11. The peak assignment for ethylene phosphate was confirmed by addition of a genuine sample of unlabeled material. The hydrolysis experiment was repeated three times, and identical results (within reported experimental error) were obtained. The reaction was repeated in 5 M NaOD, $D_2{}^{16}O$, with substrate concentration reduced by a factor of 10.

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(5) Holmes, R. R. "Pentacoordinated Phosphorus"; American Chemical Society: Washington, DC, 1980; Vol. 2, pp 100–109.
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(9) Taira, K.; Fanni, T.; Gorenstein, D. G. *J. Org. Chem.* **1984**, *49*, 4531.
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(11) Taira, K.; Fanni, T.; Gorenstein, D. G. *J. Am. Chem. Soc.* **1984**, *106*, 1521.
(12) Kluger, R.; Wasserstein, P. *Tetrahedron Lett.* **1974**, 3451.

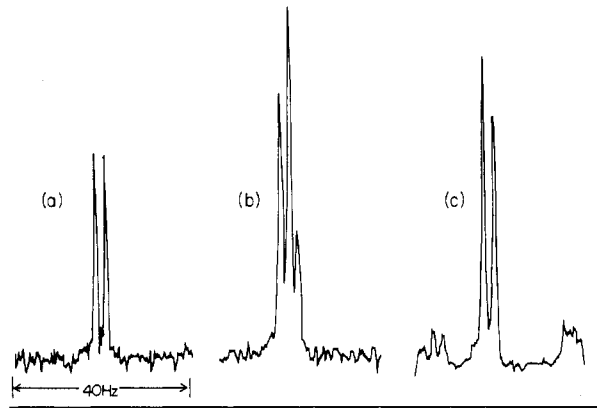
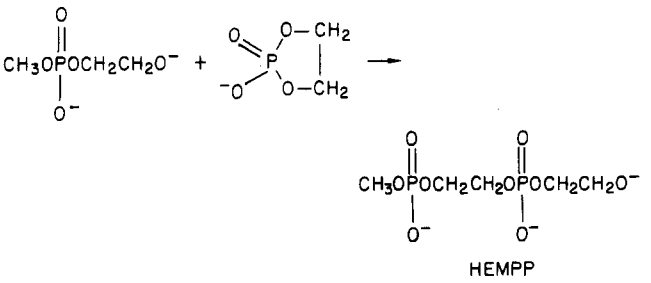



**Figure 1.** Separate 0.5 ppm sections of the 80.57-MHz phosphorus NMR spectrum after reaction of methyl ethylene phosphate in 5 M NaOD containing 48% $^{18}O$ followed by partial neutralization with DCl. Peaks corresponding to products that are the result of exocyclic cleavage of methyl ethylene phosphate are shown. In addition, there is a large peak due to the product of endocyclic cleavage, methyl hydroxyethyl phosphate, at −1.0 ppm. Chemical shifts are downfield from trimethyl phosphate in deuterium oxide (a) ethylene phosphate (15.9 ppm), (b) hydroxyethyl phosphate (1.4 ppm) (c) HEMPP (One set of peaks is shown at −1.3 ppm; there is another set at −2.3 ppm. Peaks due to higher oligomers can be seen as well). The lowest field peak in each set corresponds to material with no $^{18}O$.

**Scheme II**




**Reactions. Proton NMR Analysis.** Methyl ethylene phosphate (3 μL) was added to 1.8 mL of 4 M NaOD solution, giving a concentration of 0.017 M substrate. This solution was immediately cooled in a dry ice slurry and then brought to pD 11 with DCl in $D_2O$. The FT NMR spectrum was obtained, and the intensity of the integral of the signal for the methyl group of methanol compared to that for the methyl group of remaining phosphate methyl esters. The reaction was repeated at a substrate concentration of 0.10 M.

## Results

**Product Patterns.** Isotope incorporation from 5 M $NaO^{18}D$ in deuterium oxide (oxygen isotopes containing 48% $^{18}O$) into the products of hydrolysis of methyl ethylene phosphate was measured by observing the products' phosphorus NMR spectra after solutions were cooled and brought to pD 11. The addition of acid dilutes the $^{18}O$ content of the solvent to 22%. The phosphorus NMR spectrum was recorded immediately and after 3 h. The spectra were indistinguishable. Sections of the spectrum are presented in Figure 1. We see peaks corresponding to ethylene phosphate (15.9 ppm), hydroxyethyl phosphate (1.62 ppm), and methyl hydroxyethyl phosphate (−1.0 ppm) as well as those due to the product of reaction between ethylene phosphate and methyl hydroxyethyl phosphate (−1.1, −2.3 ppm; see Scheme II).[6,13]

Since the reaction solvent contains $^{18}O$, the products incorporate the label and, as a result, isotopically shifted

(13) Vives, J. P.; Munoz, A.; Navech, J.; Mathis, F. *Bull. Soc. Chim. Fr.* **1965**, 2544.

**Table I. Predicted and Observed Peaks in the Phosphorus NMR Spectrum for Reaction of Methyl Ethylene Phosphate[a]**

| matl | NMR peaks, $^{18}O$ per mol | rel intens | fractnl integ signal for compd | | |
|---|---|---|---|---|---|
| | | | obsd | calcd pentavalent | calcd hexavalent |
| | | Primary Products | | | |
| EP[b] | 0 | 52 | 0.52 | 0.52 | 0.44 |
| | 1 | 45 | 0.48 | 0.48 | 0.49 |
| | 2 | 0 | 0.00 | 0.00 | 0.08 |
| MHEP[c] | 0 | 1000 | 0.52 | 0.52 | 0.51 |
| | 1 | 900 | 0.48 | 0.48 | 0.48 |
| | 6 | 0 | 0.00 | 0.00 | 0.01 |
| | | Secondary Product | | | |
| HEP[d] | 0 | 29 | 0.34 | 0.27[e] (0.37[f]) | |
| | 1 | 34 | 0.49 | 0.50[e] (0.51[f]) | |
| | 2 | 12 | 0.17 | 0.23[e] (0.11[f]) | |
| | 3 | 0 | 0.00 | 0.00[e] (0.00[f]) | |

[a] In 5 M NaOD containing 48% $^{18}O$ followed by addition of $D_2O$ containing DCl to give a final $^{18}O$ content of 22%. Integrals were obtained from expanded spectra and reported fractional values are set so that the total signal for a compound totals 1.0 (deviations are due to rounding of fractions). Intensities are readings from the condensed spectrum with the entire field swept. Abbreviations: ethylene phosphate, EP; hydroxyethyl phosphate, HEP; methyl hydroxyethyl phosphate, MHEP. The basis of the entries is explained in the text. [b] Estimated error of integrated peaks for this compound is ±0.03 (minimum detectable signal is 0.02 above base-line noise). [c] Estimated error of integrated peaks for this compound is ±0.005. [d] Estimated error of integrated peaks for this compound is ±0.05. [e] If hydrolysis of EP occurs before addition of acid. [f] If hydrolysis of EP occurs after addition of acid.

peaks[14] appear. The signals for ethylene phosphate correspond to material with no label and material with one mol of $^{18}O$/mol in proportion to the isotopic distribution of the solvent (Table I). No signal for ethylene phosphate incorporating 2 equiv of $^{18}O$ is seen (upfield of the peak of the unlabeled material by twice the shift of the monolabeled material). The spectrum has a sufficient signal-to-noise ratio to detect species present at low concentrations. The noise level near the peak for unlabeled ethylene phosphate is such that a signal corresponding to 4% of that peak can be readily detected (Figure 1). Thus, a peak corresponding to 2% of the total of ethylene phosphate present could be detected. The signal for methyl hydroxyethyl phosphate also consists of two peaks, reflecting the solvent isotope distribution corresponding to incorporation of no $^{18}O$ and 1 equiv of $^{18}O$.

**Secondary Product due to Hydrolysis.** Hydroxyethyl phosphate is produced by hydrolysis of ethylene phosphate in a moderately fast reaction.[6,15] The phosphorus NMR signal consists of three peaks, corresponding to material with no $^{18}O$ incorporation, material incorporating 1 equiv of $^{18}O$, and material with 2 equiv of $^{18}O$ (Table I). The absence of an upfield signal (for material incorporating 3 equiv of $^{18}O$) is consistent only with a mechanism involving pentavalent intermediates. The integrated peaks of hydroxyethyl phosphate indicate that it contains a lower relative concentration of $^{18}O$ than does ethylene phosphate. Since the partially neutralized solution has a lower $^{18}O$ content than the initial reaction solution (since $D_2{}^{16}O$ is used to make the DCl solution), the results indicate that ethylene phosphate has undergone further hydrolysis after acid has been added (eventually the reaction is self-quenching since the product is acidic). Errors in the in-

(14) (a) Lowe, G.; Sproat, B. S. *J. Chem. Soc., Chem. Commun.* **1978**, 565. (b) Cohn, M.; Hu, A. *Proc. Natl. Acad. Sci. U.S.A.* **1978**, *751*, 200.
(15) Kumamoto, J.; Cox, J. R., Jr.; Westheimer, F. H. *J. Am. Chem. Soc.* **1956**, *78*, 4858.

tegrated signal are sufficiently large that the secondary hydrolysis cannot be scrutinized. The calculated isotope distribution of hydroxyethyl phosphate that would arise from a hexavalent intermediate mechanism (in the initial hydrolysis of methyl ethylene phosphate) will also agree with the data for the major peaks, within the range of error. However, the route involving hexavalent phosphorus can be ruled out by the more accurate data available for the precursor of hydroxyethyl phosphate, ethylene phosphate, and is supported by the absence of a triply shifted peak for hydroxyethyl phosphate.

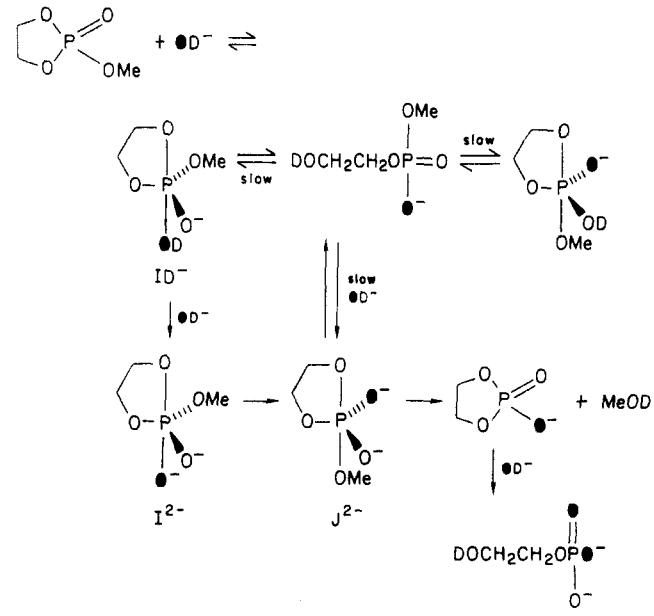
**Secondary Products due to Reactions between Products.** We have previously shown that methyl hydroxyethyl phosphate adds to ethylene phosphate under basic conditions (Scheme II).[6] The product, which we designate hydroxyethyl (methyl hydroxyethyl phosphate) phosphate, HEMPP, was originally reported for the reaction of the corresponding ethyl ester with limited water.[13] The reaction that forms HEMPP competes with the reaction in which hydroxide adds to ethylene phosphate to give hydroxyethyl phosphate.[6] At the high substrate concentrations used for our phosphorus NMR studies, a significant amount of HEMPP forms by this process, which is second order in substrate.

The peaks corresponding to HEMPP (Figure 1) indicate the presence of 1 equiv of $^{18}O$ bonded to each phosphorus. The mechanism in Scheme II is consistent with this observation but so are at least two other routes. Vives et al. also proposed that compounds of this type could be produced by the dimerization of the endocyclic cleavage product followed by hydrolysis of the ester or by the reaction of the endocyclic cleavage product with triester followed by hydrolysis.[13] The alternative proposals can be tested by observing the dependence of methanol production on substrate concentration since the latter two require that the relative amount of methanol (compared to methyl hydroxyethyl phosphate and HEMPP) will increase with substrate concentration. It has been shown that relative production of methanol is the same at substrate concentrations of 0.3 and 0.6 M,[6] and GC analysis of more dilute solutions gave similar results.[4] As a further test, we determined the yield of methanol from methyl ethylene phosphate at two different but low substrate concentrations (0.017, 0.10 M) in 4 M NaOD by FT proton NMR. The measured fraction of methoxy groups present as methanol in both samples was 6%, based on integration, and is within the range that has previously been reported.[4,6] Thus, we confirm the mechanism in Scheme II that requires that dimerization is a consequence rather than a cause of exocyclic cleavage. Phosphorus NMR analysis conducted at lower substrate concentrations as expected shows decreased amounts of the dimeric material relative to ethylene phosphate.[16]

## Discussion

Our results clarify the stoichiometry and mechanism of the reaction of methyl ethylene phosphate with deuteroxide to produce ethylene phosphate. First, since deuteroxide is incorporated into ethylene phosphate, as evidence by $^{18}O$ incorporation from the solvent, the expulsion of methoxide involves P–O rather than C–O cleavage. This shows that deuteroxide adds to phosphorus rather than to carbon. Second, the incorporation of 1 rather than 2 equiv of deuteroxide into ethylene phosphate establishes that the exocyclic cleavage results from a process that involves addition of only 1 equiv of deuteroxide at phosphorus. This rules out intermediates that would form by addition of 2 equiv of deuteroxide.

**Scheme III**




**Pseudorotation Route.** A mechanism for exocyclic cleavage of methyl ethylene phosphate via a dianionic pentavalent intermediate[4] is shown in Scheme III. This has been modified to incorporate our results with deuterium labeling shown and $^{18}O$ indicated as ●.

The intermediate formed by addition of deuteroxide to methyl ethylene phosphate incorporates 1 equiv of $^{18}O$ to form intermediate $ID^-$. The added ligand must occupy an apical position and the ring must occupy the remaining apical position, according to the reaction patterns that were elucidated by Westheimer.[2] Groups must leave from apical positions exclusively, the reverse of the addition process. Intermediate $ID^-$ either ring opens directly to produce methyl hydroxyethyl phosphate or reacts with the second equivalent of deuteroxide to form the conjugate base, $I^{2-}$. Since the methoxy group is in an equatorial position, it cannot leave directly. A negatively charged oxygen ligand is strongly electron donating, and such electropositive ligands preferentially occupy equatorial positions. One of the $O^-$ ligands is in an apical position, making the intermediate high in energy relative to pseudorotamers (stereoisomers that are interconvertible by pseudorotation) in which both of these ligands occupy equatorial positions.

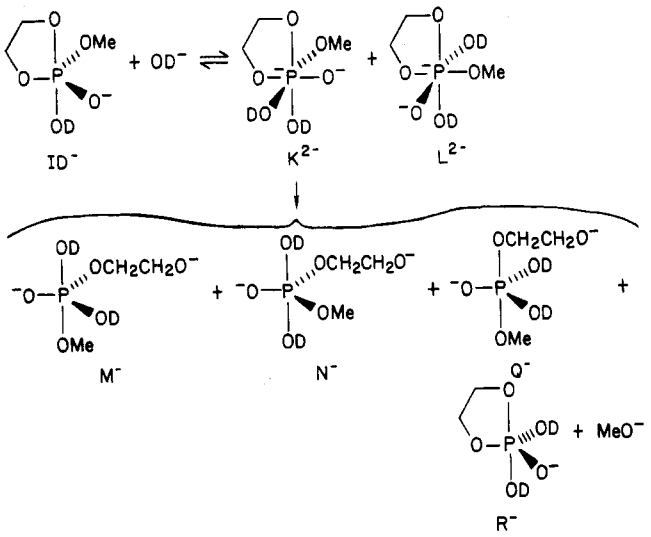
Pseudorotation of $I^{2-}$ thus is a rapid process, resulting in the lower energy isomer $J^{2-}$ with the strongly electropositive $O^-$ ligands both in equatorial positions.[5] This pseudorotation places the methoxy group in an apical position from which it can depart as methoxide, leaving ethylene phosphate. Alternatively, the ring of $J^{2-}$ can open to produce methyl hydroxyethyl phosphate.

**Hexavalent Phosphorus Route.** We observe production of ethylene phosphate and methyl hydroxyethyl phosphate containing $^{18}O$ according to the distribution expected if the reaction involves pentavalent intermediates. Do these results also rule out the possibility of intermediates in which phosphorus is hexacoordinate?

Scheme IV summarizes key features of a mechanism for hydrolysis of methyl ethylene phosphate with both exocyclic and endocyclic cleavage occurring from a hexavalent phosphorus intermediate. The initially formed pentavalent intermediate, $ID^-$, reacts with deuteroxide to form a hexavalent intermediate. In Scheme IV, two stereochemically distinct hexavalent intermediates are shown with deu-

(16) Thatcher, G. R. J. Ph.D. Thesis, University of Toronto, 1985.

**Scheme IV**



terons placed arbitrarily on two of the oxy ligands. In strongly basic solutions, prototopic shifts should be fast so that protonation state does not distinguish the ligands. Methoxide, deuteroxide, or one of the ring ligands is expelled from this intermediate to produce some or all of the distinct pentavalent intermediates, $M^-$, $N^-$, $Q^-$, and $R^-$. The pentavalent intermediates then break down to form methyl hydroxyethyl phosphate and ethylene phosphate. The latter would result exclusively from $R^-$. Since we observe that hydroxyethyl phosphate is not an initial product (with rapid quenching, we see ethylene phosphate but not hydroxyethyl phosphate in the phosphorus NMR spectrum), for this mechanism to be viable, deuteroxide must be expelled in preference to alkoxide from the pentavalent intermediate and $Q^-$ must be excluded.

The calculations for incorporation of $^{18}O$ in the hexavalent mechanism in Table I assume that the oxy ligands are isotopically equilibrated. That is, in going from pentavalent coordination to hexavalent and back to pentavalent, the oxygens become indistinguishable. Expulsion of methoxide or expulsion of one of the ring ligands from the hexavalent intermediate produces pentavalent intermediates with a probability of one-third that the $^{16}O$ ligand will reside in an apical position. When deuteroxide is expelled from the intermediate with $^{16}O$ in the apical position, a phosphate ester containing 2 equiv of $^{18}O$ (ethylene phosphate or methyl hydroxyethyl phosphate) will result. If $^{16}O$ occupies an equatorial position, then $^{18}O$ deuteroxide will be expelled from an apical position. The results in Table I disagree with these predictions and therefore isotopically equilibrated hexavalent intermediates can be ruled out. At first sight this appears to establish that the reaction must occur by the exclusively pentavalent mechanism, but is there a more specific mechanism that will still permit reaction via a hexavalent intermediate?

Unlike reactions involving pentavalent intermediates, mechanistic rules for reactions proceeding via hexavalent intermediates have yet to be established. Can restrictive assumptions be made that will still account for our experimental observations while allowing the possibility of reaction via hexavalent intermediates?

In the reaction in which alkoxide is expelled from a hexavalent intermediate, 2 equiv of $^{18}O$ derived from deuteroxide are present. In order for $^{18}O$ to be expelled, this intermediate must produce a pentavalent intermediate with $^{16}O$ necessarily in an equatorial position and $^{18}O$ in an apical position, because expulsion occurs from apical positions of pentavalent intermediates. Pseudorotation cannot be considered since this would permit the $O^{16}$ to attain an axial postion. The addition of deuteroxide ($^{18}O$) to methyl ethylene phosphate ($^{16}O$) specifically places $^{16}O$ in the equatorial position of the originally formed and $^{18}O$ in the axial position of the initial pentavalent intermediate. This set of circumstances then requires that there be a way in which that originally equatorial ligand can specifically return to an equatorial position upon return from hexavalency. If we can show that specificity is not achieved, we can cite our experimental results as absolutely ruling out hexavlent intermediates.

All possible hexavalent intermediates in this reaction can be divided into two types exemplified by $K^{2-}$ and $L^{2-}$ in Scheme IV; $K^{-1}$ has the methoxyl cis to both ring ligands and $L^{2-}$ has the methoxyl trans to one of the ring ligands. In type $K^{2-}$ intermediates, each alkoxy ligand (methoxyl and ring) is trans to an oxygen ligand and cis to the other oxygen ligands. Since we observe both exocyclic and endocyclic cleavage, and oxygens cannot have unique properties, this intermediate cannot provide the necessary correlation with the ligand locations in the pentavalent intermediates. Even if we require that the leaving group be specifically cis or trans with respect to an $O^-$, any group can leave and therefore no unique rule can apply.

Intermediates of type $L^{2-}$ require expulsion of a ligand cis to an oxygen since both endocyclic and exocyclic cleavage occur and a trans rule would permit only ring cleavage. This makes the oxygens equivalent for the collapse process and prevents correlation of the original equatorial oxygen with the same position in the final intermediate. Other sets of restrictions appear to be reducible to these cases. For example, one reasonable possibility is that the deuteroxide attacks the pentavalent intermediate in the equatorial plane trans to the $O^-$ group to minimize steric and electrostatic interactions. This generates a type $L^{2-}$ intermediate with the oxygen that had been equatorial in the unique position trans to the ring ligand. Since the position is unique, in a restricted mechanism, alkoxide could not be expelled without violating microscopic reversibility. If a less strict rule applies, then any cis expulsion is possible and correlation with the original equatorial position is lost.

This reasoning accounts for all reactions which would proceed via a hexavalent intermediate and give singly labeled product. Thus, since we see no doubly labeled ethylene phosphate or methyl hydroxyethyl phosphate and we do see the label distribution expected for exclusively pentavalent intermediates, our data rule out hexavalent intermediates which could be proposed for even more specific mechanisms.

**Stereoelectronic Influences.** Gorenstein and coworkers have proposed a stereoelectronic theory to account for reaction patterns of phosphate esters. They have noted that the theory requires intermediate $J^{2-}$ (Scheme III) to react exclusively to give endocyclic cleavage.[9,11] Our recent report of significant exocyclic cleavage in the alkaline hydrolysis of methyl ethylene phosphate is in direct conflict with the requirements of the theory if the reaction proceeds via a pentavalent intermediate.[6] Our determination that exocyclic phosphorus–oxygen bond cleavage does result from reaction of a pentavalent intermediate establishes that the proposed orbital interactions[9,11] must be overwhelmed by the other enthalpic and entropic effects that control the reactivity of cyclic phosphates.[5]

## Conclusion

The possible reaction patterns of phosphate esters have not been elucidated to the same extent as have those for

carboxylate esters. The discovery of a reaction pathway involving 2 equiv of base was followed by speculation about implications for general reactivity patterns.[4-6,9-11] Our work establishes product patterns that define the structure and general reactivity of intermediates in this pathway. Product and reactivity patterns in related cases of phosphate ester hydrolysis involving other catalysts such as Brønsted bases[17] and metal ions[18-21] remain to be elucidated. Since these pathways are likely to be important components of enzymatic catalysis of the reactions of phosphate esters, nucleotides, and nucleic acids, their elucidation will be of continuing importance.

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**Registry No.** Methyl ethylene phosphate, 2196-04-5.

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# Mechanism of Cyclopentene-1-carboxaldehyde Formation by Ring Contraction of 2,3-Epoxycyclohexanols. Improved Synthetic Procedures

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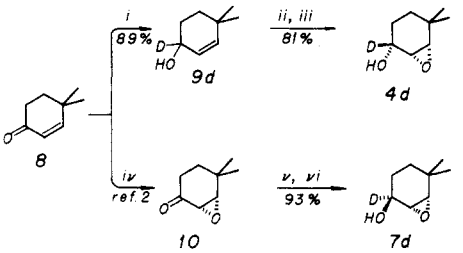
Complete analysis of the reaction mixtures from lithium bromide induced skeletal rearrangement of *cis*- and *trans*-1-deuterio-4,4-dimethyl-2,3-epoxycyclohexanol (**4d** and **7d**) showed that the formation of specifically deuterated 5,5- and 3,3-dimethylcyclopentene-1-carboxaldehydes (**1d**, **2d**, and **2**) occurred by a route that requires the participation of practically all possible configurational and conformational halohydrin intermediates. Small amounts of cyclohexenones were formed by intramolecular hydride (or deuteride) shifts in the lithium alcoholates of the epoxy alcohols and halohydrins. Nondeuterated trans epoxy alcohols were found to produce one aldehyde (**1** or **2**) almost exclusively whereas cis epoxy alcohols gave mixtures of **1** and **2**. Both *cis*- and *trans*-5,5-dimethyl-2,3-epoxycyclohexanol (**6** and **15**) gave isomer-free 4,4-dimethylcyclopentene-1-carboxaldehyde (**3**).

Although many examples of epoxide rearrangements are known,[1] skeletal rearrangements of epoxy alcohols seem to be rather neglected. We reported[2] a synthesis of the cyclopentene-1-carboxaldehydes **1-3** by lithium bromide mediated rearrangement of the *cis*-2,3-epoxycyclohexanols **4-6**. The last one gave access to *isomer-free* 4,4-dimethylcyclopentene-1-carboxaldehyde (**3**; Table I). This aldehyde (and the isomer **1**) has since then been utilized as a starting material in several natural product syntheses.[3] We have now improved the preparation of these aldehydes and obtained experimental evidence that suggests a rather intricate mechanism for the rearrangement of both *cis*- and *trans*-2,3-epoxycyclohexanols (Schemes 2 and 3).

The ring-opening, formation, and rearrangement reactions of epoxides[1] under basic or neutral conditions are governed by a few empirical "rules": (i) the ring opening reaction is $S_N2$ (or borderline $S_N2$) in character; (ii) Lewis acids catalyze these reactions (e.g., $Li^+$, $Mg^{2+}$, $H^+$, $BF_3$); (iii) in cyclohexane epoxides, the ring-opening is trans-1,2-diaxial in character (Fürst-Plattner rule); (iv) epoxide-ring formation from halohydrin salts requires a 1,2-trans-diaxial arrangement of the participating groups (microscopic reversibility of the Fürst-Plattner rule[1]); (v) in the rearrangement of cyclohexane derivatives, the migrating group and the leaving group must have an antiperiplanar relationship.

Scheme I[a]




[a] (i) $LiAlD_4$; (ii) *m*-CPBA; (iii) preparative gas chromatography; (iv) $H_2O_2$; (v) $NaBD_4/CeCl_3$; (vi) preparative liquid chromatography.

It is known from our earlier work[2] that the isomeric *cis*-2,3-epoxycyclohexanols **4** and **5**, on treatment with lithium bromide/hexamethylphosphoric triamide (HMPA), rearrange to give the aldehydes **1** and **2** in the approximate ratio 4:1 and 1:4, respectively. However, the **1**/**2** ratios per se do not give any clues to the detailed mechanism of the reaction. We now report a highly probable route to the cyclopentene-1-carboxaldehydes **1** and **2** (and **3**) based on rearrangement of the specifically deuterated cis and trans epoxy alcohols **4d** and **7d**, followed

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