7 mm i.d. quartz tube. Either type of sample was placed in a water-jacketed quartz condenser and irradiated under a continuous fine stream of nitrogen using six 8-W low-pressure Hg lamps arranged in a circular array of diameter 1.5 in. around the condenser.

Samples were monitored by NMR analyses at ambient temperature. The chemical shifts (δ) are reported in ppm downfield from Me_4Si with methylene chloride (δ 5.30) as a secondary standard.

The irradiated mixtures were neutralized by dropwise addition to a rapidly stirred aqueous suspension of aqueous sodium bicarbonate and extracted with ether. GC analyses were carried out on the concentrated ether extracts by using the 10 ft × $^1/_8$ in. o.d. column described earlier. Preparative collections were accomplished by using the 6 ft × $^1/_4$ in. o.d. column.

2,6-Dimethyl-4-hydroxypyrylium Cation ($1H^+$). GC analysis at 140 °C of the neutralized ether extract exhibited three products. Retentions of 4,6-dimethyl-2-pyrone (**7**), 5,6-dimethyl-2-pyrone (**3**), and 4,5-dimethyl-2-pyrone (**2**) relative to 2,6-dimethyl-4-pyrone (**1**) are 0.76, 0.80, and 1.29, respectively.

2,3-Dimethyl-4-hydroxypyrylium Cation ($8H^+$). GC analysis at 140 °C of the neutralized ether extract exhibited five products. Retentions of 5-methyl-2-acetylfuran (**12**), 3,6-dimethyl-2-pyrone (**11**), 3,4-dimethyl-2-pyrone (**9**), 5,6-dimethyl-2-pyrone (**3**), and 4,5-dimethyl-2-pyrone (**2**) relative to 2,3-dimethyl-4-pyrone (**8**) are 0.23, 0.64, 0.94, 1.27, and 2.01, respectively.

2-Methyl-3-ethyl-4-hydroxypyrylium Cation ($13H^+$). GC analysis at 140 °C of the neutralized ether extract exhibited four products. Retentions of 5-methyl-2-propionylfuran (**17**), 4-methyl-3-ethyl-2-pyrone (**14**), 5-methyl-6-ethyl-2-pyrone (**15**), and 6-methyl-5-ethyl-2-pyrone (**16**) relative to 2-methyl-3-ethyl-4-pyrone (**13**) are 0.35, 1.08, 1.38, and 1.61, respectively.

2,3,6-Trimethyl-4-hydroxypyrylium Cation ($18H^+$). GC analysis at 170 °C of the neutralized ether extract exhibited one product. The retention of 4,5,6-trimethyl-2-pyrone (**19**) relative to 2,3,6-trimethyl-4-pyrone (**18**) is 2.1.

2,3,5,6-Tetramethyl-4-hydroxypyrylium Cation ($22H^+$). GC analysis at 170 °C of the neutralized ether extract exhibited one product. The retention of 3,4,5,6-tetramethyl-2-pyrone (**23**) relative to 2,3,5,6-tetramethyl-4-pyrone (**22**) is 2.4.

Registry No. **1**, 1004-36-0; $\mathbf{1H^+}$, 41463-78-9; **3**, 4209-44-3; **8**, 73761-48-5; $\mathbf{8H^+}$, 62968-76-7; **11**, 53034-20-1; **12**, 1193-79-9; **13**, 92490-73-8; $\mathbf{13H^+}$, 62968-77-8; **15**, 62968-85-8; **16**, 72185-13-8; **17**, 10599-69-6; **18**, 13519-43-2; **18**-d_6, 92490-77-2; $\mathbf{18H^+}$, 73761-43-0; **19**, 14818-31-6; **22**, 14901-87-2; **22**-d_6, 92490-78-3; $\mathbf{22H^+}$, 51595-74-5; **23**, 51595-76-7; $CH_3C(O)CH(CH_3)C(O)CH_3$, 815-57-6; $HO(CH_2)_2OH$, 107-21-1; $CH_3C(O)CH(Et)C(O)CH_3$, 1540-34-7; $CH_3C(O)CH(CH_3)(CH_2)CO_2H$, 6818-07-1; $CH_2{=}CHC(O)CH_3$, 78-94-4; $(EtOC(O))_2C(CH_3)(CH_2)_2C(O)CH_3$, 10433-88-2; $CH_3CH_2C(O)CH_2CH_3$, 1629-58-9; $CH_3CH_2C(O)CH(CH_3)(CH_2)_2C{\equiv}N$, 33739-94-5; $CH_3CH_2C(O)CH(CH_3)(CH_2)_2CO_2H$, 59627-89-3; $CH_3(CH_2)_2C(O)CH_3$, 107-87-9; $CH_3C(O)CH(Et)(CH_2)_2C{\equiv}N$, 10413-02-2; $CH_3C(O)CH(Et)(CH_2)_2CO_2H$, 39517-97-0; $CH_3CH{=}C(CH_3)C(O)CH_3$, 565-62-8; $(EtOC(O))_2CHCH(CH_3)CH(CH_3)C(O)CH_3$, 16728-78-2; $CH_3C(O)CH(CH_3)CH(CH_3)CH_2CO_2H$, 90113-51-2; $(EtOC(O))_2C(CH_3)CH(CH_3)CH(CH_3)C(O)CH_3$, 92490-80-7; $CH_3C(O)CH(CH_3)CH(CH_3)CH(CH_3)CO_2H$, 92490-81-8; 3-methyl-4,4-(ethylenedioxy)pentan-2-one, 6050-54-0; ethyl 2,4-dioxo-5-methyl-6,6-(ethylenedioxy)heptanoate, 92490-74-9; 2,3-dimethyl-4-pyrone-6-carboxylic acid, 92490-75-0; 2-methyl-3-ethyl-4-pyrone-6-carboxylic acid, 92490-76-1; 5,6-dimethyl-3,4-dihydro-2-pyrone, 4054-96-0; diethyl methylmalonate, 609-08-5; 3,6-dimethyl-3,4-dihydro-2-pyrone, 20155-55-9; acrylonitrile, 107-13-1; 3,4-dihydro-5-methyl-6-ethyl-2-pyrone, 59627-90-6; 3,4-dihydro-6-methyl-5-ethyl-2-pyrone, 4054-97-1; diethyl malonate, 105-53-3; 3,4-dihydro-4,5,6-trimethyl-2-pyrone, 92490-79-4; 3,4-dihydro-3,4,5,6-tetramethyl-2-pyrone, 92490-82-9.

Stereoelectronic Effects in the Hydrolysis of Ethyl and Methyl Ethylene Phosphates

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Ethyl and methyl ethylene phosphates **1** are shown to hydrolyze with complete endocyclic cleavage between pH 8 and 15 to yield ethyl and methyl 2-hydroxyethyl phosphates **3**, respectively. A much slower reaction involving recyclization of the methyl hydroxyethyl phosphate **3** to form ethylene phosphate **4**, which undergoes rapid further hydrolysis to 2-hydroxyethyl phosphate **5**, is conveniently monitored by ^{31}P NMR. The strained cyclic five-membered ring phosphate triester **1** reacts 10^8- to 10^{12}-fold faster than its strain-free initial diester product **3** via a common phosphorane intermediate/transition state **2**. When **1** is hydrolyzed in $H_2{}^{18}O$, only mono-^{18}O-labeled ester **3** is formed but no doubly ^{18}O-labeled **3** is detected. All reactions proceed with complete P–O cleavage as monitored by ^{18}O isotope shifts on the ^{31}P signals of the products. These results are consistent with the stereoelectronic effect, and a mechanism involving a hexacoordinate phosphorus intermediate can be ruled out.

The rate of hydrolysis of five-membered-ring cyclic phosphates such as methyl ethylene phosphate and ethylene phosphate is 10^6 to 10^8 times that of their acyclic analogues, trimethyl phosphate and dimethyl phosphate, respectively.[1] Westheimer and co-workers[1] proposed that this rate acceleration was due to relief of ring strain in the five-membered rings. However, as they later pointed out,[2] the energy released in a strained cyclic ester in going to a "strain-free" cyclic phosphorane transition state is insufficient to explain the total lowering of activation energy. We proposed,[3] based on molecular orbital calculations, that a significant fraction of this difference comes from orbital stereoelectronic effects in the tirgonal-bipyramid transition states. In this article we provide experimental support for the stereoelectronic effect in the hydrolysis of cyclic five-membered-ring phosphate esters. Preliminary communication of a portion of these studies has been made.[4]

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(3) Gorenstein, D. G.; Luxon, B. A.; Findlay, J. B.; Momii, R. *J. Am. Chem. Soc.* **1977**, *99*, 4170.
(4) (a) Taira, K.; Gorenstein D. G. *J. Am. Chem. Soc.* **1982**, *104*, 6130. (b) Taira, K.; Fanni, T.; Gorenstein, D. G. *Ibid.* **1984**, *106*, 1521.

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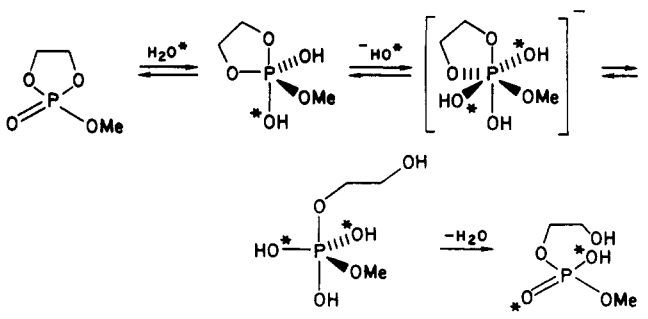
Scheme I



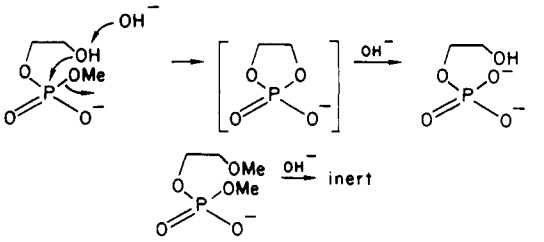
Furthermore, the role of the hexacoordinate phosphorus intermediate in the reactions of phosphate esters has been the subject of much speculation but little experiment. Kluger et al.[5] observed that the fraction of exocyclic cleavage for methyl ethylene phosphate increases linearly with hydroxide ion concentration from ~0% at pH 11–13 to about 15% cleavage in 10 M alkali. They suggest this result is consistent with the required pseudorotation of a dianionic pentaoxyphosphorane intermediate. They further indicate that an explanation involving a hexacoordinate phosphorus intermediate, although unsupported, cannot be eliminated.

Ramirez[6a] and Gillespie et al.[6b] indicate that the hydrolysis of methyl ethylene phosphate is second order in hydroxide (as suggested by Kluger et al.'s observation of an increase in exocyclic cleavage with strong base[5]) and argue for formation of a hexacoordinate intermediate in strong alkali as shown in Scheme I.

This hypothesis has gained wide-spread recognition and has even been presented in a text[7] as a quite reasonable mechanistic possibility. The more recent preparation[8,9] of stable hexacoordinated phosphorus anions $(PhO)_6P^-$ and $(CH_3O)_6P^-$ and the kinetic data[10] supporting a hexacoordinate intermediate in the hydrolysis of $(ArO)_5P$ suggest that the earlier hypothesis for the involvement of a hexacovalent intermediate in the strong alkali hydrolysis of methyl ethylene phosphate is certainly quite reasonable. However, we now present ^{18}O-labeling results which argue against the formation of such a species in the hydrolysis of both ethyl and methyl ethylene phosphates.

Neutral phosphate triesters readily undergo acid- or base-catalyzed hydrolysis with alkyl (C–O cleavage) and/or phosphoryl (P–O) scission.[11,12] For example, trimethyl and triethyl phosphate undergo hydrolysis in neutral water via an S_N2 mechanism with alkyl (C–O) scission. Acid-catalyzed hydrolysis also proceeds with alkyl scission.

On the other hand, the base-catalyzed hydrolysis of trimethyl phosphate proceeds by P–O bond scission to produce dimethyl phosphate which does *not* readily hydrolyze further to monomethyl phosphate. The half-life for hydrolysis of this dimethyl phosphate is 16 days at 100 °C, and the mechanism involves alkyl scission.[11] On the other hand, some diesters such as 2-hydroxyethyl methyl phosphate undergo base hydrolysis much faster than dimethyl phosphate. This is accounted for by anchimeric assistance by the vicinal hydroxyl group via the formation of a five-membered cyclic phosphate.[11,13,14]



In order to understand more clearly the several processes involved in RNA hydrolysis,[15,16] Westheimer's group[5,17–22] and Brown's group[23–25] examined the properties of simpler model systems. We have continued the study of the mechanism of hydrolysis of the simpler cyclic esters such as ethyl ethylene phosphate and methyl ethylene phosphate,[4] hopefully resolving a number of mechanistic questions left unanswered by the extensive earlier studies.

Experimental Section

^1H and ^{31}P NMR spectra were recorded on a Bruker WP-80 spectrometer at 80 and 32.4 MHz, respectively, or ^1H NMR on a 60-MHz Varian T-60 spectrometer. High-field NMR was done at the Purdue Biological NMR Facility. Chemical shifts in parts per million for ^{31}P spectra are referenced to external 85% H_3PO_4.

Chemicals were generally of highest purity. All solvents were distilled before use and stored over 4-Å molecular sieves (Grace Chemical Co.).

Synthesis. Both ethyl and methyl ethylene phosphate were prepared by the general method of Kluger et al.[5] with some modification since simultaneous addition of ethylene glycol and corresponding alkyl dichlorophosphate to a solvent, with vigorous stirring, resulted in improved yields.

Ethyl Ethylene Phosphate (EEP). Ethyl dichlorophosphate (0.64 mol, prepared from ethanol and phosphoryl chloride and purified by distillation at 53 °C (6.5 mm)) diluted to 250 mL with benzene (dried with NaH and distilled) and ethylene glycol (0.64 mol, distilled at 194–195 °C) with 2,6-lutidine (1.28 mol, distilled at 135 °C) also diluted to 250 mL with dry benzene were added simultaneously into 200 mL of dry benzene, with stirring at room temperature, under argon atmosphere over a period of 2 h. The stirring was continued at room temperature for 8 h. After removal of salts and solvent, ethyl ethylene phosphate was vacuum distilled first at 90–95 °C (0.15–0.2 mm) and then at 90–93 °C (0.1 mm) (There were no detectable impurities from the ^1H and ^{31}P NMR spectra even after the first distillation.): yield after the second distillation, 62%; ^1H NMR ($CDCl_3$) δ 4.42 (apparent d J_{HP} = 11

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Chart I

pH	5.0	6.0	7.1	7.3	7.5	8.0	9.5	5 M NaOH
^{31}P chem shift	1.3	2.0	3.7	3.9	4.1	4.2	4.2	4.9

Table I. pH vs. Percent Exocyclic Product

	NaOH, M					
pH	4.7	6	7	8	9	5
% exo prodt of MEP	27 (27)[a]	11 (56)	7 (9)	0 (23)	0 (36)	0 (56)
% exo prodt of EEP	27 (20)		8 (64)	0 (36)	0 (40)	0 (68)

[a] The numbers in parentheses indicate S/N ratios for the ^{31}P spectra.

Hz, ethylene, 4 H), 4.17 (m, J_{PCH_2} = 10 Hz, $J_{CH_2CH_3}$ = 7 Hz, methylene, 2 H), 1.37 (t, J = 7 Hz, methyl, 3 H); ^{31}P NMR ($CDCl_3$) 17.5 ppm.

Methyl ethylene phosphate (MEP) was prepared by the method described for EEP except smaller quantitites (e.g., methyl dichlorophosphate (0.10 mol, purchased from Aldrich) diluted to 70 mL with dry benzene and 0.10 mol of ethylene glycol diluted in 23.5 mL of 2,6 lutidine and 50 mL of dry benzene were added simultaneously to 50 mL of dry benzene). Methyl ethylene phosphate distilled at 80 °C (0.09 mm) (lit.[5] bp 85 °C (0.1 mm): yield, 43%; ^{1}H NMR ($DCDl_3$) δ 4.44 (apparent d, J = 10 Hz, 4 H), 3.80 (d, J = 12 Hz, 3 H); ^{31}P NMR ($CDCl_3$) 18.5 ppm.

Hydrolysis in $H_2{}^{18}O$. EEP. A 50-μL sample of 0.155 M ethyl ethylene phosphate in dry dioxane was added to 0.49 mL of 5.0 M NaOH (72% $H_2{}^{18}O$/22% D_2O) at room temperature, and the solution was quickly frozen in an acetone/dry ice bath. To the almost frozen solution, was carefully added 66.6 μL of 36 N H_2SO_4. The pH of the solution was adjusted to about 9 with a Tris buffer solution. Up to this point everything was carried out within a minute. Some inorganic precipitate was filtered through a nitric acid and EDTA solution treated disposable pipet plugged with EDTA-treated cotton and Chelex-100 (Bio-Rad) ion exchange resin.

MEP. For the ^{18}O-labeling experiment the identical quenching method described for EEP was used except that 20 μL of neat methyl ethylene phosphate were added to 1.0 mL of 5.0 M NaOH (53% $H_2{}^{18}O$/47% D_2O), of which 0.5 mL of solution was quickly freeze-quenched and the rest of the solution was kept at room temperature in order to analyze the secondary reaction product. When a 50-μL sample of 0.090 M MEP was used, the identical result (no detectable exocyclic product at t = 0) was obtained.

Product Identification. Acid hydrolysis of MEP produced both 2-hydroxyethyl methyl phosphate **3** and 2-hydroxyethyl phosphate **4**[5] of which only the monoester **4** was titrable as shown in Chart I. Therefore, **3** could always be distinguishable from **4** at any pH.

pH–Product Profile. A 50-μL sample of 0.090 M EEP or MEP in dry dioxane was mixed with 0.5 mL of corresponding 0.1 M buffer solution (pH 4.7 and 6, acetate buffers; pH 7, 8, and, 9, Tris buffers) and product ratios were analyzed by ^{31}P NMR. Results are shown in Table I and Figure 1.

Results and Discussion

Hexacoordinate Intermediate. The ^{31}P NMR spectrum of the 5 M NaOH (72% $H_2{}^{18}O$/28% D_2O) hydrolysis product of ethyl ethylene phosphate, quenched as quickly as possible, shows peaks assigned to the endocyclic product **3** (R = Et). The two signals represent the mono-^{18}O-labeled ester **3** (1.33 ppm) and the unlabeled (^{16}O) ester **3** (1.36 ppm). The magnitude of the upfield shift for the ^{18}O-labeled ester is consistent with the expected ^{18}O isotope shift on the ^{31}P chemical shift for a singly ^{18}O-labeled compound.[26-28] The intensity of the upfield signal at 1.33

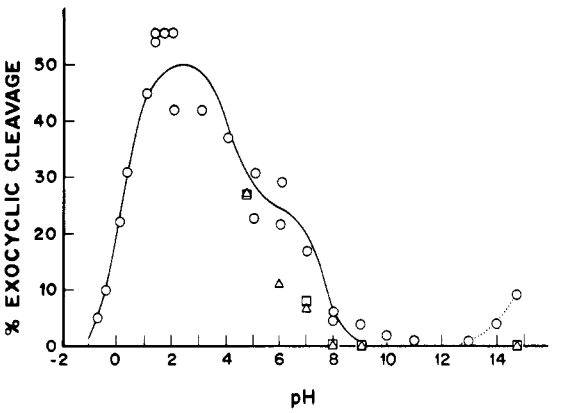

Figure 1. Percentage exocyclic cleavage of methyl ethylene phosphates (○, △) and ethyl ethylene phosphate (□) vs. pH. Data from Kluger et al.[5] (○) and our own work (△, MEP; □, EEP).

ppm relative to the downfield signal (71:30) is also in agreement with the incorporation of 1 equiv of solvent oxygen (72% ^{18}O) into the endocyclic product **3**. If two ^{18}O atoms had been incorporated into the product as would be required[29] for a mechanism involving a hexacoordinate intermediate, then another ^{18}O-labeled signal would have been observed upfield of the singly ^{18}O-labeled signal. Within the S/N (±5%) of the spectrum we can rule out any hexacoordinate intermediate.[29]

Similar labeling results were obtained in dilute acid (pH 2–7) where both exocyclic cleavage product, 2-hydroxyethyl phosphate (**5**) (25% at pH ~5) and endocyclic cleavage product, ethyl 2-hydroxethyl phosphate **3**, were observed by ^{31}P NMR. Again, for the endocyclic product **3** (R = Et), only unlabeled (0.59 ppm) and singly ^{18}O-labeled (0.62 ppm) ^{31}P signals in the ratio of 1:1 were observed when ^{18}O enrichment of the water was 50%. For the exocyclic product, 2-hydroxyethyl phosphate (**5**), three ^{31}P signals are observed in the expected ratio of 1:2:1 for incorporation from solvent of no ^{18}O (0.80 ppm), one ^{18}O (0.78 ppm), and two ^{18}O (0.76 ppm) atoms. The first formed exocyclic product is ethylene phosphate (**4**) (mono-^{18}O-labeled from one water molecule), which under our conditions rapidly further hydrolyzes to 2-hydroxyethyl phosphate (**5**) (incorporating a second water molecule giving some di-^{18}O-labeled product).

The ^{31}P NMR spectra of 5 M NaOH (53% $H_2{}^{18}O$/47% D_2O) hydrolysis products of methyl ethylene phosphate quenched as quickly as possible as described in our previous paper[4a] or stopped 23 h after the reaction had started differ significantly. As observed for ethyl ethylene phosphate, only the endocyclic cleavage product methyl 2-hydroxyethyl phosphate **3** was found when the reaction was immediately quenched. The two signals, in a ratio of approximately 1:1, represent the mono-^{18}O-labeled ester **3** (2.489 ppm) and the unlabeled (^{16}O) ester **3** (2.518 ppm)

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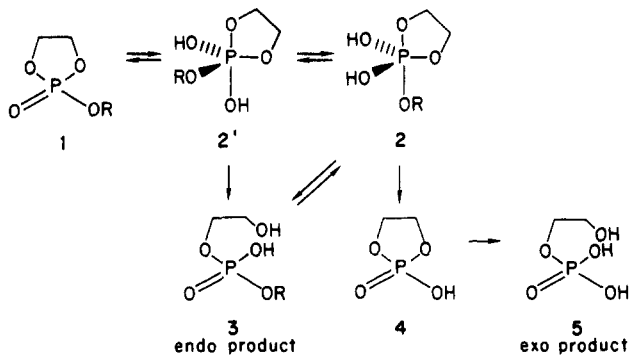
(29) It is possible to envision a mechanism involving a hexacoordinate intermediate that does not isotopically equilibrate the original phosphoryl oxygen and the water oxygens so that loss of two oxygens from this intermediate does not yield a doubly ^{18}O-labeled **5**. However, this would require a violation of the principle of microscopic reversibility, assuming an octahedral intermediate (i.e., the three HO(P) groups should be equivalent in the hexacoordinate intermediate of Scheme I and loss of labeled or unlabeled oxygen should be energetically equivalent, ignoring a small ^{18}O isotope effect). If the phosphoryl oxygen could always be chemically distinguished from hydroxide oxygen in the pentacovalent and hexacoorinate intermediates, then it is conceivable that our observed labeling results could not rule out a hexacoordinate intermediate. This would be possible, for example, if the phosphoryl oxygen was always anionic while the labeled solvent oxygen molecules were always neutral hydroxyl groups in the intermediates. However, it is highly unlikely that tautomerization ($^-$OPOH ⇄ HOPO$^-$) is going to be slower than hydroxide attack on a pentacoordinate intermediate.

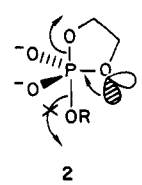
Scheme II



with the ^{18}O separation of 0.916 Hz (0.029 ppm). Again, identical ^{18}O-labeling evidence argues against a hexacoordinate intermediate in the alkaline hydrolysis of *methyl ethylene phosphate*. If two ^{18}O atoms had been incorporated into the product **3** (R = Me) as would be required for a mechanism involving a hexacoordinate intermediate, then another ^{18}O-labeled signal would have been observed upfield of the singly ^{18}O-labeled signal (2.489 ppm). Within the detection limit (±3%) of the spectrum we can again rule out any hexacoordinate intermediate. If the reaction in 5 M NaOH (50% $H_2{}^{18}O$) is not quenched by neutralization, the initially formed methyl 2-hydroxyethyl phosphate **3** undergoes a slow further reaction to yield 2-hydroxyethyl phosphate (**5**). Thus, after 23 h in 5 M NaOH, the only ^{31}P signals observed are for the monoester **5** (ca. 60%) and diester **3** (ca. 40%). The diester **3** still appears as a doublet, assigned to unlabeled and mono-^{18}O-labeled diester. The monoester **5** appears as a triplet with the expected ^{31}P peaks for unlabeled ester at 4.869 ppm, mono-^{18}O-labeled at 4.847 ppm, and di-^{18}O-labeled at 4.820 ppm in the ratio of 1:2:1, respectively. The significance of these results will be discussed in the Anchimeric Assistance Section below.

Percent Exocyclic Cleavage. When these cyclic esters were subjected to hydrolysis, we obtained the pH–product profile shown in Figure 1 and Table I, which is very similar to that described by Kluger et al. except in 5 M NaOH.[5] The hydrolysis of these cyclic triesters is known to follow Scheme II.[1] The initially formed exocyclic cleavage product **4** undergoes rapid hydrolysis to produce monoester **5** which can easily be identified by ^{31}P NMR as this is the only pH-dependent signal.[4]

In the dianionic form of **2**, which forms via the dianion **2'** after rapid pseudorotation[5] in 5 M NaOH, the two lone pairs on the basal ring oxygen (assumed sp^3 hydridized)[30] are oriented partially antiperiplanar (app) to the axial ring ester bond leaving group. The molecular orbital calcu-

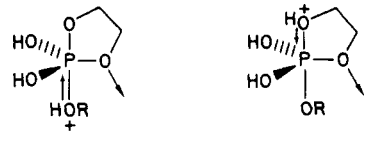


2

lations suggest that this app lone pair orientation could significantly facilitate P–O ester bond cleavage and that proper orbital overlap (the stereoelectronic effect) could be responsible for as much as 11 kcal/mol lowering of transition-state energies.[3,31,32] Indeed as we argued earlier, in the five-membered-ring cyclic esters the ring constrained the lone pairs in a stereoelectronically favorable orientation while in the acyclic transition state, proper app lone pair overlap would require "freezing" of one or more rotational degrees of freedom about the ester bonds.[32] It is thus significant that a considerable portion of the rate difference between cyclic and acyclic reactions is entropically driven.[32,33]

However, a major difficulty with the stereoelectronic effect explanation for the proposed[3] 10^3–10^5 stereoelectronic effect rate acceleration (4–6 kcal/mol difference in activation energies) was the observation of significant exocyclic cleavage in the reaction.[1,5] In dilute acid and, in particular, in strong alkali methyl ethylene phosphate has previously been shown to hydrolyze to yield not only the expected endocyclic product, methyl 2-hydroxyethyl phosphate **3** but also as much as 1–50% of the exocyclic product, 2-hydroxyethyl phosphate (**5**).[5] While the exocyclic cleavage in acid could be reconciled with the stereoelectronic effect (see below), the 9% and 15% (±5%)[5] exocyclic cleavage in 5 and 10 M alkali, respectively, was at odds with the stereoelectronic effect: note the basal oxygen lone pairs of the ring-constrained pentacovalent transition state are app *only to the apical endocyclic ester bond and not to the exocyclic bond.*

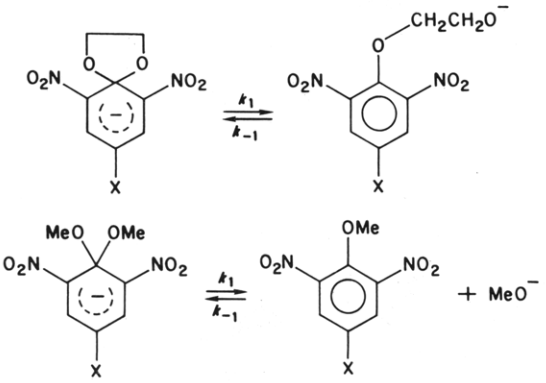
We now, however, find no exocyclic cleavage (0 ± 3%) for both ethyl and methyl ethylene phosphate between pH 8 and 15, consistent with the stereoelectronic effect. Even in 5 M NaOH, a rapid freeze/acid quench (after less than 2 s of reaction)[4] leads to 100% endocyclic cleavage product in both methyl and ethyl ethylene phosphate. Although the exocyclic cleavage could still be assisted by the lone electron pairs on the equatorial anionic oxygens in 5 M NaOH, the endocyclic cleavage is still favored because it is assisted by *all* three equatorial oxygen lone pairs, especially those on the equatorial ring-oxygen. This is why we do *not* observe any exocyclic cleavage product in alkaline conditions. Analysis in the acidic region is more complicated because of a "reverse anomeric effect".[30] Although, to date, the origin of the reverse anomeric effect is not well understood, dipole moment arguments[30] suggests that protonation on the exocyclic ester oxygen is favored over the endocyclic oxygen in acidic media. This would thus favor exocyclic cleavage.



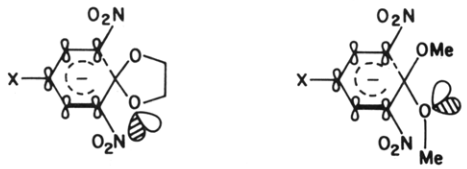
Related Systems. Bernasconi and Howard[34] thoroughly investigated the breakdown of spiro cyclic and acyclic Meisenheimer complexes derived from 1-(2-hydroxyethoxy)-2,6-dinitro-4-X-benzenes and 2,6-dinitro-4-X-anisoles, respectively, where X was Cl, CF_3, NO_2, or SO_2CF_3.

They conclude that the difference in intrinsic reactivity between the two families is quite large ($\Delta\Delta G^{\ddagger}$ = [$\Delta G^{\ddagger}$ (k_1)acyc] – [$\Delta G^{\ddagger}$(k_1)cyc] = 3.80 – 5.34 kcal/mol), and this difference increases as the X substituent becomes more electron withdrawing. The most likely explanation for the difference in reactivity is attributable to a stereoelectronic effect. Just as is the case of endocyclic cleavage of **2**, in the spiro cyclic complexes, the orientation of the lone-pair

(30) Kirby, A. J. "The Anomeric Effect and Related Stereoelectronic Effects at Oxygen"; Springer-Verlag: Berlin, 1983.
(31) Gorenstein, D. G.; Findlay, J. B.; Luxon, B. A.; Kar, D. *J. Am. Chem. Soc.* **1977**, *99*, 3473.
(32) Gorenstein, D. G.; Luxon, B. A.; Findlay, J. B. *J. Am. Chem. Soc.* **1979**, *101*, 5869.
(33) Aksnes, G.; Bergesen, *Acta. Chem. Scand.* **1966**, *20*, 2508.
(34) Bernasconi, C. F.; Howard, K. A. *J. Am. Chem. Soc.* **1983**, *105*, 4690–4697, and reference therein.

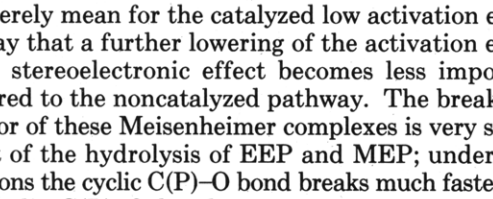


orbitals on oxygen stereoelectronically favors ring cleavage. On the other hand, in the acyclic (1,1-dimethoxy) complexes the lone-pair orbitals are not constrained to the proper orientation unless the complex first undergoes an unfavorable conformational change.



The fact that $\Delta\Delta G^{\ddagger}$ increases with the electron-withdrawing strength of the X substituent supports this interpretation because transfer of nonbonding electron density (n orbital) from the nonreacting oxygen into the antibonding orbital (σ^*) of the scissile bond becomes more important when a transfer of charge density from the benzene ring (p–σ^* type interaction) is less available because of an electron-withdrawing X group. Since the stereoelectronic effect presumably arises from the n↔σ^* mixing,[3,30] the rate difference dependence on substitutent is most reasonable.

More importantly, the study of Bernasconi and Howard[34] further indicates that the difference in intrinsic reactivity is smaller for the acid-catalyzed compared to the noncatalyzed pathway, and this difference diminishes with increasing acidity of the catalyst. For the specific acid-catalyzed pathway, the reactivity difference between the two families nearly disappears ($\Delta\Delta G^{\ddagger}$ spans a range ~0.09 to ~0.2 kcal/mol). This means that in acidic media one does not observe much of a stereoelectronic effect. This may merely mean for the catalyzed low activation energy pathway that a further lowering of the activation energy by the stereoelectronic effect becomes less important, compared to the noncatalyzed pathway. The breakdown behavior of these Meisenheimer complexes is very similar to that of the hydrolysis of EEP and MEP; under basic conditions the cyclic C(P)–O bond breaks much faster than the acyclic C(P)–O bond. However, the acyclic bond cleavage k_1(acyc) starts to compete with the cyclic bond cleavage k_1(cyc) upon an increase in acidity of the medium.



If we use the same dipole moment analysis,[30] in the case of protonation of the Meisenheimer complexes, then protonation will be favored for the acyclic complexes. This interpretation is at least consistent with Bernasconi and Howard's observation[34] of less negative ρ values and smaller Bronsted α values in the cyclic families, indicating

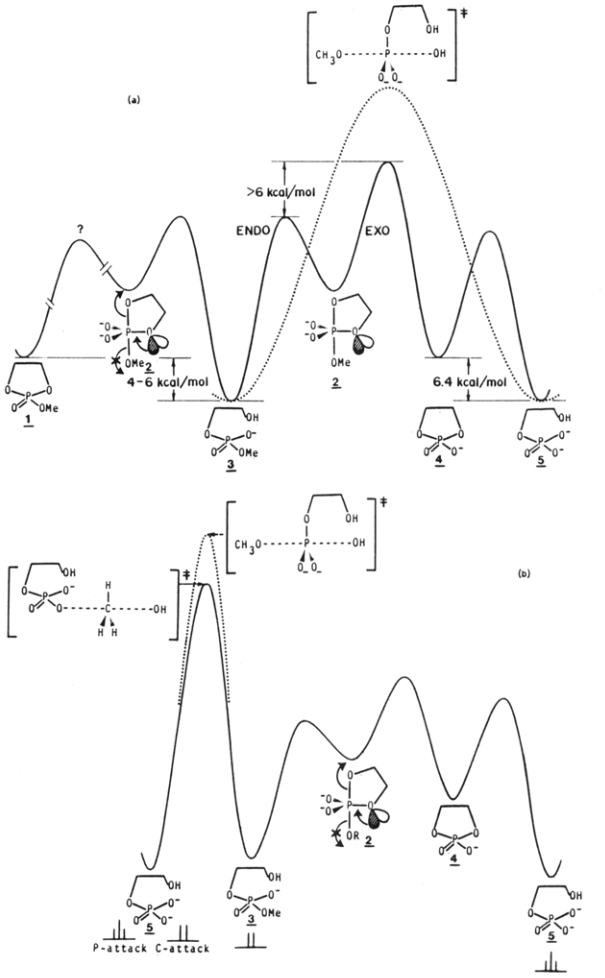


Figure 2. Reaction profiles for base-catalyzed hydrolysis of methyl ethylene phosphate **1** and methyl 1-hydroxyethyl phosphate **3** with relative energies (a) and expected ^{31}P NMR signals (b).

that less positive charge (H^+) has been transferred to the cyclic system from the catalyst in the transition state.

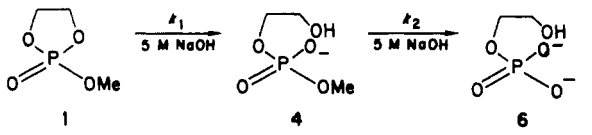
Anchimeric Assistance. The diester **3** undergoes further slow hydrolysis to produce 2-hydroxyethyl phosphate (**5**) if the reaction is not stopped by neutralization. The secondary reaction (k_2) of the methyl hydroxyethyl phosphate **3**, although quite slow compared to the MEP **1**, is much faster than the hydrolysis of a simple diester such as dimethyl phosphate[1,5] ($k \simeq 2 \times 10^{-9}$ min^{-1} mol^{-1}).[35] This certainly is attributable to recyclization to reform the pentacovalent intermediate **2**. This anchimeric assistance mechanism can be clearly proven by our ^{18}O labeling experiment (bottom of Figure 2b, expected ^{18}O incorporation in 50% $H_2{}^{18}O$ hydrolysis which corresponds to the observed results). Thus, the initial product **3** derived exclusively from a P–O cleavage reaction consists of 50% of singly ^{18}O-labeled and another 50% ^{18}O-unlabeled diesters, of which according to the anchimeric assistance mechanism of Figure **2b**, *mono-^{18}O-labeled* (*50%*) diester produces 25% di-^{18}O-labeled monoester **5** and 25% mono-^{18}O-labeled **5**, then the *^{18}O-unlabeled* diester (50%) produces 25% mono-^{18}-labeled **5** and 25% ^{18}O-unlabeled **5**. As a result, the monoester **5** is expected to show three signals corresponding to di-, mono-, and nil-^{18}O-labeling in the ratio of 1:2:1, respectively. This is exactly what we observe (^{31}P signals, 4.820, 4.847, and 4.869 ppm in the ratio of

(35) Kumamoto, J.; Cox J. R., Jr.; Westheimer, F. H. *J. Am. Chem. Soc.* **1956**, *78*, 4858.

1:2:1), supporting the anchimeric assistance mechanism and exclusive P–O cleavage for both primary and the secondary hydrolysis *without* any detectable oxygen exchange from solvent during the course of the entire reaction.

The identical ^{18}O-labeling results could have been obtained if the diester **3** underwent complete P-attack hydrolysis without cyclization (see Figure 2b). However, this mechanism is impossible because C-attack is known to be the lower energy pathway for hydrolysis of diesters in basic media.[11,13] When C-attack is almost impossible as in the case of the base-catalyzed hydrolysis of diphenyl phosphate, only P–O cleavage can occur. However, this proceeds very slowly (the half-life for the hydrolysis of diphenyl phosphate in neutral water at 100 °C has been estimated at 180 years), enhanced only by the better leaving ability of phenoxide, relative to alkoxide.[11] In addition to this, if direct P-attack by OH^- replacing alkoxide were the mechanism, we could have obtained some methyl phosphate together with 2-hydroxyethyl phosphate.

Estimation of the Magnitude of the Stereoelectronic Effect. From the labeling studies, as we discussed above, we can conclude that the pathway for the formation of **5** from **3** is **3** → **2** → **4** → **5** as schematically shown in Figure 2b. (The expected ^{18}O incorporation in each product in 50% $H_2{}^{18}O$ is also shown.) During the formation of **5** from **3**, the 2-hydroxyl group should intramolecularly attack phosphorus from the backside with respect to the methoxy group, leading to the formation of the pentacoordinate intermediate **2**, since the methoxy group has the highest apicophilicity compared to the other two anionic oxygens. The observed rate constant[36] (k_2) for the formation of **5** via **2** from **3** in 5 M NaOH is ca. 5×10^{-4} min^{-1}. A simple extrapolation from Kluger et al.'s pH vs. rate profile[5] suggests that the rate constant for the formation of **3** from **1** via **2′** and **2** (Scheme II) is about 10^5–10^9 min^{-1} in 5 M NaOH.[37] Therefore, the strained cyclic five-membered-ring phosphate triester **1** reacts 10^8- to 10^{12}-fold faster than its strain-free initial diester product **3** via the common intermediate **2**.



$(k_1/k_2 = 10^8$–$10^{12})$

Since both endocyclic and exocyclic products must be formed through the same transition state/intermediate **2** and since **3** is 4–6 kcal/mol lower in energy than MEP, **1**, only 10^3–10^4 of the observed 10^8–10^{12} rate acceleration is due to ring strain effects. Similarly only 4–6 kcal/mol of the difference between the recyclization reaction activation energy for **3** → **2** → **4** and the endocyclic reaction activation energy (**1** → **2** → **3**) is attributable to ground-state destabilization of **1**. Thus the rate of partitioning of **2** must favor the endocyclic path by a factor of 10^5–10^8 over the exocyclic path, although a portion of this difference is also attributable to an *increase* in ring strain in forming the strained ethylene phosphate **4** in the exocyclic cleavage path.[38] This factor of 10^5–10^8, corresponding to a 7–11 kcal/mol difference in activation free energies, as we suggested,[3,31,32] arises at least in part from the stereoelectronic effect.

Conclusions

These results confirm that *no* oxygen exchange from solvent occurs with intermediates during the course of the entire reaction, or with starting material or products, and that 100% P–O cleavage occurs for MEP, EEP, and their initial products derived by anchimeric assistance, without formation of any hexacoordinate intermediate. In addition, most significantly, the reactivity difference between strained cyclic five-membered-ring esters and their acyclic counterparts can be accounted for by the combination of ring strain relief and stereoelectronic effects in the transition state/intermediate.

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Registry No. **1** (R = Me), 823-31-4; **1** (R = Et), 823-31-4; **3** (R = Me), 67846-69-9; **3** (R = Et), 5178-07-4; **4**, 6711-47-3; **5**, 1892-26-8.

Supplementary Material Available: ^{31}P NMR spectra with ^{18}O-labeling of ethyl 2-hydroxyethyl phosphate (Figure 1S), 2-hydroxyethyl phosphate and ethyl 2-hydroxyethyl phosphate generated from the pH 5, 50% $H_2{}^{18}O$ hydrolysis of ethyl ethylene phosphate (Figure 2S), methyl 2-hydroxyethyl phosphate (Figure 3S), and 2-hydroxyethyl phosphate and methyl 2-hydroxyethyl phosphate, generated from the 5 M NaOH, 53% $H_2{}^{18}O$ hydrolysis of methyl ethylene phosphate (Figure 4S) (4 pages). Ordering information is given on any current masthead page.

(36) Measured by ^{31}P NMR by following the appearance of 2-hydroxyethyl phosphate from methyl 2-hydroxyethyl phosphate.

(37) MEP rate data was extrapolated from Kluger et al.[5] to 5 M NaOH and assumed either first-order (10^5 min^{-1}) or second-order hydroxide[5] (10^9 min^{-1}) catalyzed hydrolysis of MEP.

(38) The transition state, however, will be closer in structure to the high energy trigonal bipyramidal pentacovalent intermediate **2**, which is expected to have little bond angle strain.[1,5]