erization to other retinol isomers at least during the first 5 h and also apparently to near 20 h.

Thermolysis of 11-*cis*,13-*cis*- (9b) and 9-*cis*,11-*cis*,13-*cis*-Retinal (11b). The retinal (10–15 mg) was dissolved in $CDCl_3$ in an NMR tube and placed in the NMR probe heated to 40 °C (±3 °C). The reaction progress was followed by measuring the peak heights of the starting and product retinal aldehyde signal (near δ 10). On the basis of inspection of the NMR spectra, the 9-cis,11-cis,13-cis isomer **11b** isomerizes cleanly to the 9-*cis*,13-*cis*-retinal, and the 11-cis,13-cis isomer **9b** to 13-*cis*-retinal. First-order rate plots of the data obtained reveal straight lines with half-lives for both reactions of ~2.3 h.

Acknowledgment. The U.S. Public Health Service (NIH Grants EY-02452 and EY-02202 and, in part, NCI Contract N01-CP-05715), the University of California Cancer Research Coordinating Committee (Grant 79R4), and the Intramural Research Fund, University of California, Riverside, provided financial support for this project. Authentic specimens or precursors to authentic specimens of various retinoids used for spectral and/or chromatographic comparisons were made available by Dr. Gary Olson and Dr. David Coffen of the Hoffmann-LaRoche Co. (Nutley, NJ). Chemicals were also provided by Badische-Anilin Und Soda-Fabrik, A.G. (Ludwigshafen). Spectral data for 9-*cis*,11-*cis*-retinal was kindly provided to us prior to publication by Professor Robert S.H. Liu.

Registry No. 5a, 74792-67-9; **5b**, 74722-99-9; **8a**, 22737-96-8; **8b**, 564-87-4; **9a**, 17706-49-9; **9b**, 564-88-5; **11a**, 74743-94-5; **11b**, 67737-36-4; **13a**, 17974-59-3; **13b**, 74723-00-5; **15a**, 74723-01-6; **15b**, 84303-93-5; **15d**, 74915-94-9; **16a**, 74723-02-7; **16b**, 84303-94-6; **16d**, 74915-94-9; **17** (R_t = *tert*-butyl), 84303-95-7; **22**, 84303-96-8; β-ionone, 79-77-6; isopentenyl alcohol, 763-32-6; 3,4-dibromo-3-methylbutanol, 10518-50-0; 2-methoxy-2-methylbut-3-yne, 13994-57-5; 13-*cis*-retinal, 472-86-6; CuMMB, 66769-63-9.

Supplementary Material Available: Spectral and analytical data (10 pages). Ordering information is given on any current masthead page.

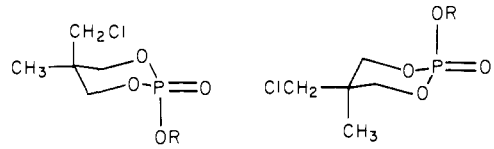
A Cyclic Phosphate: Base and Metal Acetate Catalyzed Ring Opening

William G. Wadsworth and William S. Wadsworth, Jr.*

Contribution from the Department of Chemistry, South Dakota State University, Brookings, South Dakota 57007. *Received August 13, 1982*

Abstract: Six-membered ring phosphates in which a good leaving group is absent undergo methanolysis to give acyclic products that can reclose to the original cyclic system. Under basic conditions the sequence is not stereospecific, which is explained by assuming an indiscriminant attack by alkoxide ion at more than one face of the tetrahedral phosphate. A ring opening–closing–opening sequence is described. Lead(II) acetate, as its hydrate, is unique in its ability to catalyze ring opening and closure. The sequence, unlike base catalysis, is stereospecific and yields only that isomer expected if attack occurs axially to give an oxyphosphorane intermediate in which the ring spans axial–equatorial positions.

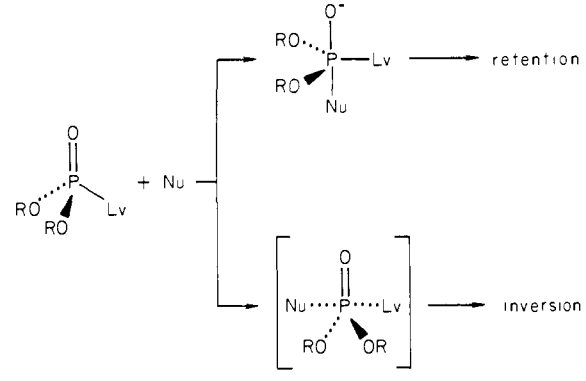
The 2-substituted-5-(chloromethyl)-5-methyl-2-oxo-1,3,2-dioxaphosphorinane system



has proven to be most valuable in allowing us to determine the stereochemistry of substitution reactions. Cis and trans isomers can easily be distinquished one from the other by simple NMR measurements. The rings are conformationally immobile with the result that the methyl hydrogens have different chemical shifts as do those of the chloromethyl group. With this tool the course of substitutions at the phosphorus atom has been determined with ease.[1,2]

In a series of papers we have attempted to outline those factors which give rise to either retention or inversion at the phosphorus atom.[3–5] In summary, we find that back-bonding between attacking nucleophile and the phosphorus atom is of prime importance. Efficient back-bonding which leads to retention is enhanced by factors which increase the positive character at the phosphorus atom such as electron-withdrawing ligands or by Lewis acids which bond to the basic phosphoryl oxygen. In contrast, inversion is favored by nucleophiles which are poor back-bonders and by leaving groups weakly bonded to phosphorus.

Retention is commonly pictured as proceeding via a trigonal-bipyramidal intermediate or transition state whereas inversion is depicted as a direct S_N2 displacement.



More recently, we have concentrated upon alcoholysis of esters and have found, in accordance with the above, that alkoxide ions substitute in all cases by complete retention; a high degree of back-bonding between nucleophile and phosphorus atom exists

(1) Wadsworth, W. S., Jr., Larsen, S.; Horten, H. L. *J. Org. Chem.* **1973**, *38*, 256.
(2) Wadsworth, W. S., Jr. *J. Org. Chem.* **1973**, *38*, 2921.
(3) Wadsorth, W. S., Jr.; Wilde, R. L. *J. Org. Chem.* **1976**, *41*, 1264.
(4) Bauman, M.; Wadsworth, W. S., Jr. *J. Am. Chem. Soc.* **1978**, *100*, 6388.
(5) Gehrke, S. H.; Wadsworth, W. S., Jr. *J. Org. Chem.* **1980**, *45*, 3921.

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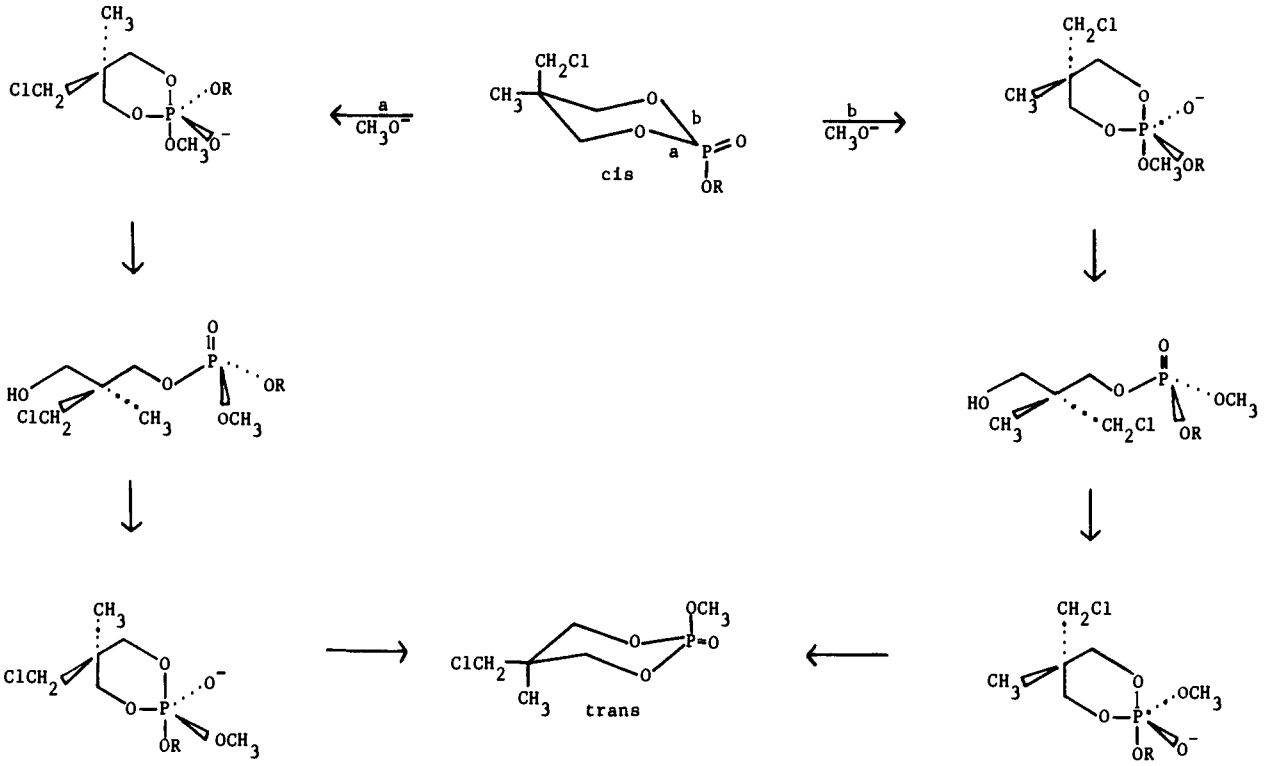
Scheme I

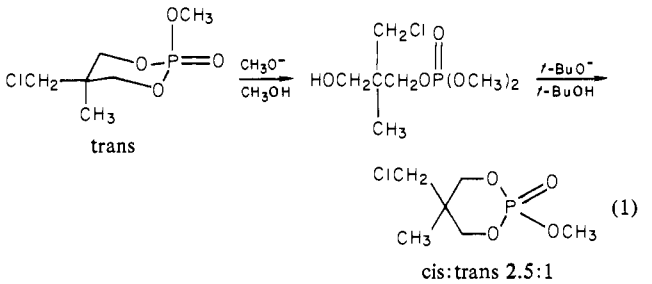


in the transition state leading to the trigonal bipyramid.[6] Base-catalyzed methanolysis gives a satisfactory Hammett plot with esters in which the leaving groups, the 2-substituents, are substituted phenoxide ions. This, combined with steric effects, leads to the conclusion that under basic conditions, the first step, formation of a trigonal bipyramid, is rate determining.

To this point, the phosphorinane system has been employed only to study the displacement of the 2-substituent. We now report our findings with systems in which the 2-substituent is a poor leaving group and ring opening is competitive. Ring opening and subsequent migrations have been investigated in detail by others.[7] Our results, however, are quite different from those previously reported. With our simpler system, we can observe the opening and previously unreported ring re-formation directly without recourse to degradative procedures. Also, in contrast to previous systems, ring opening can occur with equal probability at either of the two possible sites, thereby eliminating complications due to steric effects. The reactions reported here might be of importance for, among others, cyclic AMP, which acts as an enzyme regulator, contains the 1,3,2-dioxaphosphorinane ring system.

Results and Discussion

Base Catalysis. Base-catalyzed ring opening was carried out by adding alcoholic solutions containing 0.1 M *t*-BuOK to the esters such that reactant and catalyst were present in equivalent amounts. The trans 2-methyl ester opened to give an easily identifiable product, eq 1. The opening is irreversible for the anion



trans

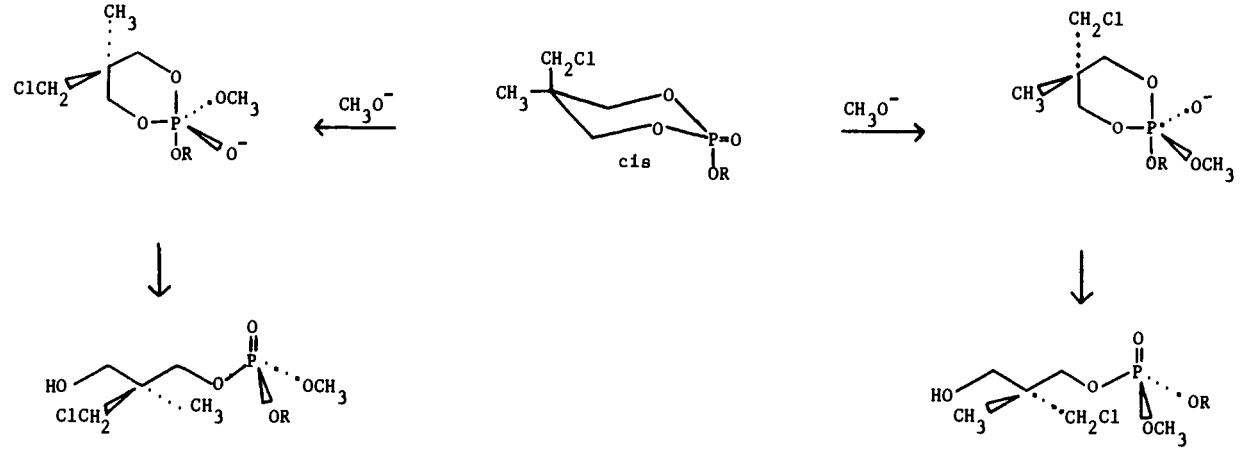
cis:trans 2.5:1 (1)

first formed upon ring opening is rapidly protonated and methoxide ion is not a strong enough base to reconvert the substituted neopentyl alcohol function to its anion. By means of a stronger base, ring closure can occur to give a thermodynamically controlled mixture of isomers in which the original trans is the minor component. A similar ratio is obtained from the cis 2-methyl ester. Due to steric effects, tertiary butoxide ion does not attack the phosphorus atom. The results indicate that the cyclic form must be of lower energy than the acyclic and that ring opening is successful only because of protonation of the newly formed anion, the product of kinetic control. Because of the lack of concurrent isomerization of starting material, which if it did occur could be easily detected by NMR spectroscopy, protonation must be much faster than ring reclosure. Ring opening and closing can be conveniently accounted for by evoking those rules commonly associated with the structure and mode of formation of a trigonal bipyramid[8] (Scheme I). Attack occurs from an axial position requiring the ring to span axial–equatorial positions. Ring opening produces a pair of enantiomers. The opposite isomer, the trans, would also produce a pair of enantiomers, diastereomers of the first.

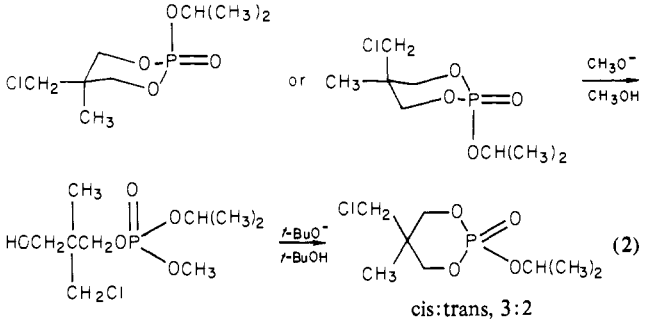
The product of ring closure is dependent upon whether the methoxide ion or original 2-substituent departs. If the former occurs, ring opening and closing are merely reversible processes and reactant is recovered.[9] Loss of the 2-substituent would give the trans 2-methyl ester from an initial cis isomer and the cis 2-methyl ester from an intial trans isomer. In the case of the individual isomeric 2-methyl esters, formation of a thermodynamically controlled product mixture from each upon methanolysis and closure is expected in light of the proposed scheme. By means of our system, we have a simple test for some of the assumptions commonly made with regards to the structure of trigonal-bipyramidal intermediates or transition states formed during the course of substitutions at phosphorus.

(6) Wadsworth, W. S., Jr. *ACS Symp. Ser.* **1981**, *No. 171*, 547.
(7) Hall, C. R.; Inch, T. D. *Tetrahedron* **1980**, *36*, 3059.
(8) Westheimer, F. H. *Acc. Chem. Res.* **1968**, *1*, 70. For a recent review, see: Holmes, R. R. *ACS Monogr.* **1980**, *No. 176*.
(9) It is possible that intermediates are formed which might undergo pseudorotation. Such a course is unlikely for pseudorotation would place the negative oxygen in an axial position, a violation of the preference rules.[8] The ring would span equatorial positions and the sequences under no circumstances could be stereospecific. Such is clearly not the case.

Scheme II



To test the scheme, the isopropyl esters were selected which upon treatment with methoxide ion ring open to give acyclic product (eq 2). No evidence for direct displacement of the



cis:trans, 3:2 (2)

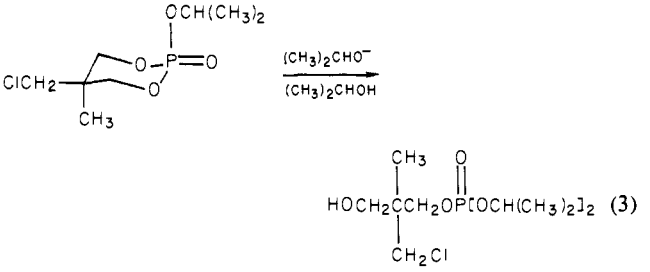
isopropoxide ion by the less basic methoxide ion was observed for no cyclic methyl ester was detected during the course of the reactions. Also, no concurrent isomerization of starting materials took place. The less thermodynamically stable trans isomer ring opens faster than the more stable cis, $k = 0.154$ h^{-1} vs. $k = 0.055$ h^{-1}. Regardless of the starting isomer, ring closure in which only the less basic methoxide ion is lost gives an identical mixture of cyclic isomers, a 3:2 ratio of cis and trans.

The lack of stereospecificity under basic conditions is unexpected. An explanation must take into account the stereospecificity observed in those cases where the 2-substituent is a good leaving group. Without going through an acyclic intermediate, the retention product is formed exclusively.

The results can be accommodated if we assume that attack by methoxide ion is indiscriminate and can approach from three of the possible four faces of the tetrahedral phosphate. Approach from the face opposite the 2-substituent, in the case of a good leaving group, would lead to inversion which is not observed. Steric arguments can be advanced; the 5-substituent blocks access to the face. Space-filled models clearly demonstrate the possibility. Inversion requires either an excellent leaving group or an electrophilic catalyst in which case the ring may be distorted.[10]

Attack at either face opposite a ring oxygen would lead to the enantiomers as depicted in Scheme I. Attack opposite the phosphoryl oxygen, perhaps from an equatorial position or an axial position followed by pseudorotation, would lead to a set of enantiomers which are diastereomers of the first (Scheme II). Similar schemes can be drawn for the trans isomer. Thus, ring opening is nonstereospecific. Likewise, ring closure with loss of methoxide ion would occur starting with all four stereoisomers, and attack could be at any face of an acyclic phosphate. A thermodynamically controlled product ratio under these circumstances is not unlikely. In all cases, direct collapse of the original adducts or transition states by loss of 2-substituent preceding ring opening would lead to the product of retention which conforms to experimental results.

Our proposed mechanism, indiscriminant attack by alkoxide ion and, in the case of a good leaving group, direct collapse of an initially formed adduct or transition state, would gain credence if both it and a stereospecific ring opening and closure could be demonstrated on an identical system. Before relating such a possibility, it is interesting to note that the isopropyl esters also ring open in the presence of isopropoxide ion, eq 3. The less stable



(3)

trans ester, $k = 0.185$ h^{-1}, again opens faster than the cis, $k = 0.086$ h^{-1}. Due probably to steric effects, ring opening of trans methyl ester by methoxide ion, $k = 0.924$ h^{-1}, is faster than ring opening of trans isopropyl ester by either methoxide, $k = 0.154$ h^{-1}, or isopropoxide ion, $k = 0.185$ h^{-1}. Perhaps due to its greater basicity, isopropoxide ion is slightly more effective than methoxide ion in opening the trans isopropyl ester.

When trans methyl ester is treated with isopropoxide ion, ring opening is followed by closure and final opening, all in a sequential manner (Scheme III). Starting material was not isomerized as reaction proceeded. The cyclic isopropyl esters are produced in the thermodynamic ratio and, therefore, not by direct attack on the methyl ester. The final result is identical if isolated acyclic methyl isopropyl ester is treated with isopropoxide ion. The latter ion is a strong enough base to effect ring closure which must be faster than direct substitution of methoxide ion. The driving force for the sequence is the replacement of weaker bases by stronger bases and the greater thermodynamic stability of the cyclic system over the acyclic.

These reactions can be easily followed by NMR spectroscopy. Among other things, chemical shifts of the original 5-methyl hydrogens, as determined for each pure compound, are different for each species. Peaks assigned to each compound rise and fall as expected as the reactions progress. The doublets due to splitting of methyl hydrogens by phosphorus and the upfield doublet due to methyl hydrogens of isopropyl groups are also useful.

Metal Acetate Catalysis. We recently reported upon the metal ion catalyzed methanolysis of phosphate esters.[11] With good

(10) That acyclic phosphates in which backside attack is not hindered are more prone to undergo substitution by inversion than 2-oxo-1,3,2-dioxaphosphorinanes has been demonstrated. Hall, C. R.; Inch, T. D.; Pottage, C. *Phosphorus Sulfur* **1981**, *10*, 229.

Scheme III

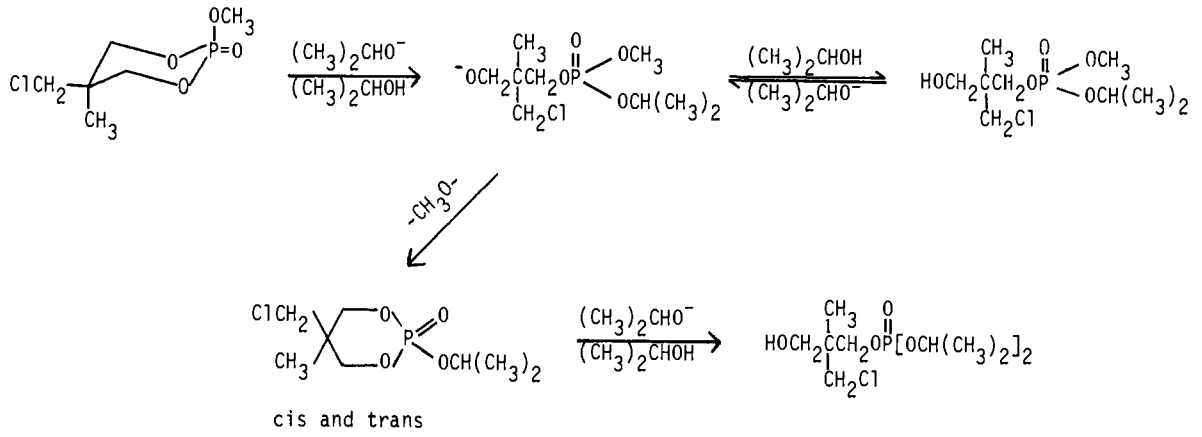


Table I. Methanolysis of 2-Phenylthio Esters Catalyzed by Silver Nitrate[a]

ester	$AgNO_3$, mol/L	products trans, %	products cis, %
trans	0.1	62	38
trans	0.2	40	60
trans	0.4	25	75
cis	0.1	25	75
cis	0.2	61	39
cis	0.4	81	19

[a] Solutions 0.1 M in ester. Reactions carried out at either reflux or room temperature.

leaving groups, either zinc acetate or chloride catalyzed both the inversion and retention process. The inversion route increased in importance as the catalyst was better able to complex with the leaving group. Clearly, electrophilic catalysis in which the metal complexes with the leaving group lowers the energy of activation of the direct displacement mechanism. In a second example, addition of silver nitrate to methanolic solutions of *trans*-2-chloro-5-(chloromethyl)-5-methyl-2-oxo-1,3,2-dioxaphosphorinane allowed methanolysis to be complete instantaneously. Only the product of inversion, the cis methyl ester, was obtained. Without silver ion, reaction requires days for completion. The trans 2-thiophenyl ester is similarly catalyzed by silver nitrate with the amount of inversion increasing with catalyst concentration (Table I). In these cases no concurrent ring opening is noted.

In the absence of a good leaving group, we would expect reduced catalytic activity. In preliminary work such appeared to be the case. Magnesium acetate, which like zinc and lead acetates does catalyze the methanolysis of 2-*p*-nitrophenyl esters, does not catalyze the methanolysis of the cyclic 2-methylphosphorinanes. Zinc acetate does, but at a very slow rate. Surprisingly, lead acetate is most effective (Figure 1) and ring opening, as in base catalysis, is the result. The success could, in the case of lead acetate, be attributed to the formation of a relatively stable oxyphosphorane intermediate in which the phosphoryl oxygen is bonded to the metal atom.

In contrast to base-catalyzed methanolysis where the least stable trans isomer is the more reactive, both cis and trans 2-methyl esters undergo lead acetate catalyzed methanolysis at approximately equal rates, Figure 1. Rates were compared by following the ring opening of each cyclic methyl ester separately under identical conditions or by employing a mixture of isomers and measuring the isomer ratio of unreacted esters as reaction proceeded. The latter process was carried out in deuterated methanol and followed directly by NMR spectroscopy. Isomer ratios remained constant over the first 80% of the reaction. A fourfold increase in catalyst concentration produced a doubling of the rate. Rates are essentially independent of methanol concentration, for the rate of ring opening was only slightly reduced in going from 100% methanol to a 20% methanol–80% dimethyl sulfoxide solvent mixture.

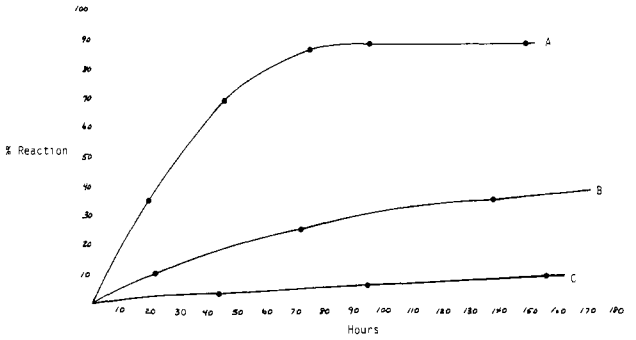


Figure 1. Lead acetate catalyzed methanolysis of 2-substituted phosphorinane esters: A, cis and trans methyl; B, cis and trans isopropyl; C, cis and trans methyl catalyzed by zinc ion. Solutions 0.1 M in ester and catalyst. Reactions carried out at room temperature.

Our evidence supports the formation of an intermediate followed by a slow rate-determining step. The intermediate, which is in equilibrium with reactant, is most likely a lead acetate stabilized oxyphosphorane which, on the basis of rate data, is composed of 1 mol of catalyst to 2 mol of methyl ester and, although evidence is lacking, 2 mol of alcohol.

Lead acetate catalyzed ring opening does not go to completion, Figure 1. The acyclic dimethyl ester is in equilibrium with the cyclic methyl esters present in a thermodynamically controlled ratio. The catalyzed equilibrium greatly favors the acyclic dimethyl ester which constitutes 89% of the final mixture. The cyclic isopropyl esters undergo ring opening by methanolysis at a slower rate than the methyl esters, probably due to steric effects. It is important to mention that like the methyl esters, lead acetate catalyzed methanolysis of trans isopropyl esters also gives an equilibrium mixture. Significantly, however, the acyclic product is in equilibrium only with the trans ester, not with a thermodynamically controlled mixture of cyclic esters. Likewise, at equlibrium, the acyclic ester obtained by methanolysis of cis isopropyl ester is in equilibrium only with starting cyclic cis ester.

The apparent ability of lead acetate to bond to phosphoryl oxygen, whereas zinc and magnesium acetates have very little or no such ability, would indicate that methanolic solutions of lead acetate are more acidic than their zinc or magnesium counterparts. None of the acetates appear to ionize appreciably; upon solvent removal under reduced pressure they are recovered with essentially none of the acetate ion displaced. The difference in catalytic activity appears to be simply a function of the hydration energy which is greater for the smaller ions (Zn^{2+}, Mg^{2+}) than for the larger (Pb^{2+}). Indeed, water of hydration can be easily removed from lead acetate by placing the hydrate under vacuum at moderately elevated temperatures whereas the hydrates of zinc and magnesium acetate require more stringent conditions. It is perhaps tightly bound solvent which prevents zinc and magnesium

(11) Wadsworth, W. S., Jr. *J. Org. Chem.* **1981**, *46*, 4080.

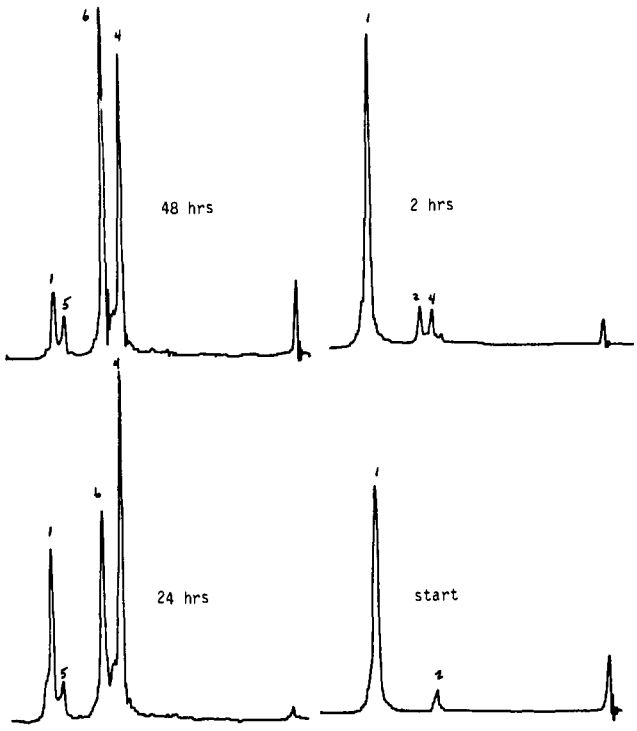
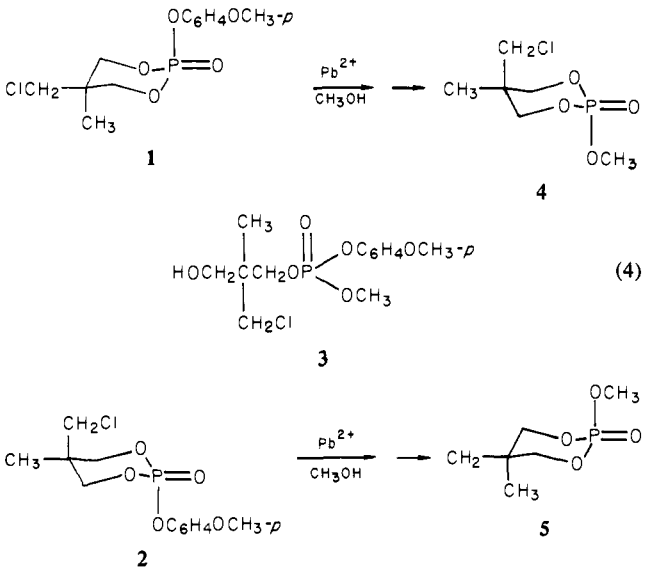


Figure 2. Lead acetate catalyzed methanolysis of trans 2-*p*-methoxyphenyl ester, **1**. Shown are the 5-methyl hydrogens. Reactions, 0.1 M in ester and catalyst, were run at room temperature for the times shown.

acetates from forming a complex with phosphoryl oxygen and being effective catalysts. In all the work reported the normal hydrated acetates were employed.

If the hypothesis that lead acetate catalyzes methanolysis by promoting the formation of a trigonal-bipyramidal intermediate is correct, reactions may be stereospecific. A lead acetate catalyzed sequence of ring opening and closing should lead to a methyl ester with a configuration opposite that of the starting material (Scheme I). In order to test this hypothesis, we resorted to a system with a leaving group which would be better than methoxide ion but not one which would be expected to promote direct collapse of an oxyphosphorane intermediate. Methanolysis of trans 2-*p*-methoxyphenyl ester led to ring opening followed by closure to give predominantly the cis 2-methyl ester (eq 4). The cis starting



(4)

material gave the trans 2-methyl ester. Fortunately, ring closure of **3** is faster than the ring opening of the cyclic methyl esters to acyclic dimethyl ester **6** [$HOCH_2C(CH_3)(CH_2Cl)CH_2OP(O)(OCH_3)_2$], the final product. Again, reactions were followed by

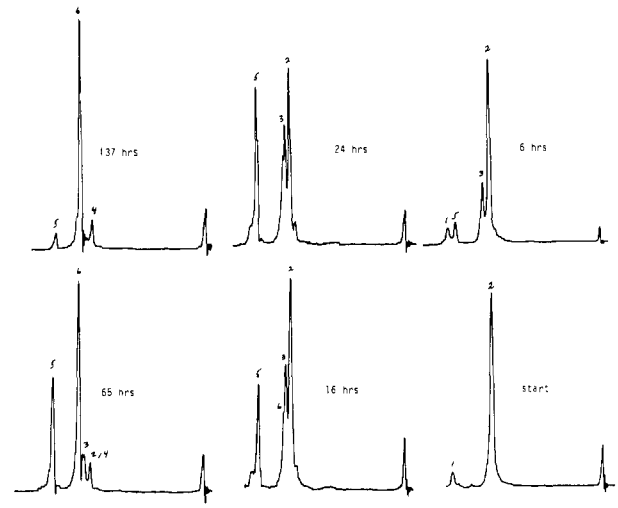
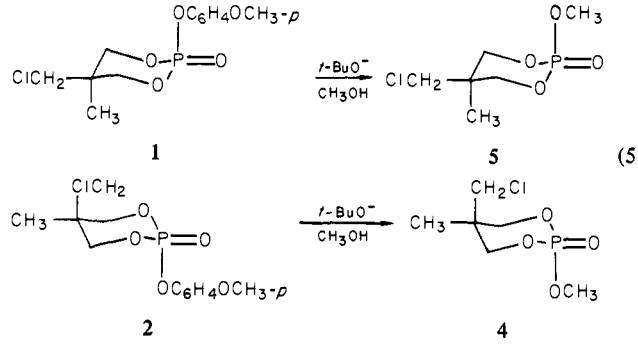


Figure 3. Lead acetate catalyzed methanolysis of cis 2-*p*-methoxyphenyl ester, **2**. Shown are the 5-methyl hydrogens. Reactions, 0.1 M in ester and catalyst, were run at room temperature for the times shown.

observing the changes in intensity of absorption due to the hydrogens of the 5-methyl group or, in the acyclic case, of hydrogens of the methyl group that originated as a 5-methyl group (Figures 2 and 3). The chemical shifts of the methyl hydrogens were determined from the pure compounds. Other spectral changes confirmed our assignments. As with the 2-methyl esters, sodium acetate did not catalyze methanolysis except at a very slow noncompetitive rate. In the case of the trans ester **1**, the acyclic product **3** does not appear except as a small hump which is in contrast to the cis isomer where the concentration of **3** becomes quite pronounced. Ring closure of the acyclic diastereomer produced from **1** gives **4**, the more stable cis methyl ester. Thus, it is perhaps not surprising that its closure would be faster than that of its diastereomer which yields **5**.

The catalysis by lead acetate is in contrast to simple base catalysis where both the cis and trans 2-*p*-methoxyphenyl esters give products of retained configuration, eq 5. There is no in-



(5)

dication of acylic intermediate **3** with either isomer (Figure 4). Direct collapse of an oxyphosphorane anion is indicated.

In the lead acetate catalyzed methanolysis there is some indication of the opposite isomer being formed. This may be due to the slight lack of purity of staring material. Also, in case of lead acetate catalysis, the equilibrium which exists between the final product, the acyclic dimethyl ester **6**, and cyclic methyl ester gives rise in the final stages to a small amount of the opposite methyl ester isomer.

With the 2-*p*-methoxyphenyl esters it is evident that lead acetate catalyzed ring opening is faster than displacement of the aromatic ligand. Since it is, as shown, a simple matter to determine the substitution route, it was of interest to look at other 2-substituted phosphorinane systems, especially those with a more efficient leaving group.

trans-2-(*p*-Nitrophenyl)phosphorinane undergoes lead acetate catalyzed methanolysis by displacement of the *p*-nitrophenoxide group without ring opening. The methyl isomer ratio indicated

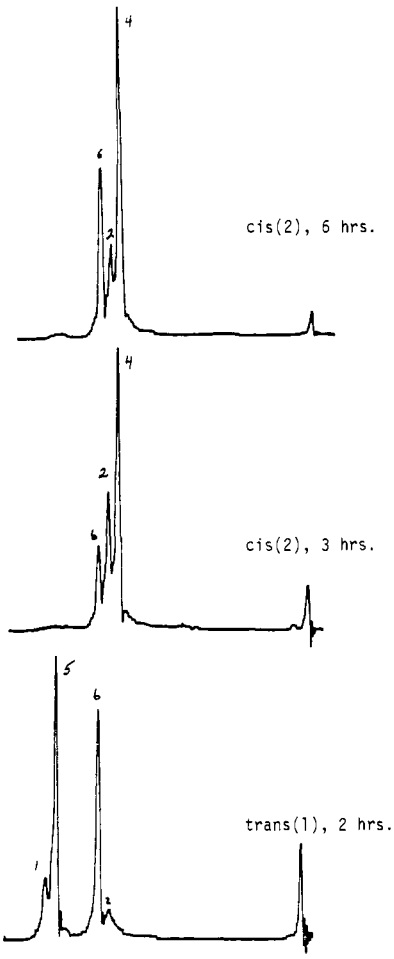


Figure 4. Base-catalyzed methanolysis of 2-*p*-methoxyphenyl esters. Shown are the 5-methyl hydrogens. Reactions, 0.1 M in ester and *t*-BuO^-, run at room temperature for the times shown.

that approximately 85% went by inversion. Since the isomer ratio remained constant during the course of the reaction and no acyclic intermediate is detected, inversion, in this case of an excellent leaving group made even better by the presence of lead acetate, is probably the result of direct S_N2 displacement. The small amount of retention is perhaps due to direct collapse of an oxyphosphorane intermediate. In contrast to trans 2-*p*-methoxyphenyl ester, lead acetate catalyzed methanolysis of trans 2-*p*-nitrophenyl ester is complete in 4 h, a significantly faster rate.

Methanolysis of *trans*-2-(phenylthio)phosphorinane is complicated for apparently all possible mechanisms are operative. The percent of acyclic intermediate rose and fell as reaction proceeded with the percent inversion increasing from 19% at 43% reaction to 57% at 100% reaction. The product of inversion must also arise from direct displacement for isomer ratios are effected by lead acetate concentration. A fourfold increase in lead acetate concentration caused an increase of from 19% to 31% inversion after 0.5 h at room temperature. In contrast to methanolysis, 2-propanolysis gave the 2-isopropyl isomer whose ratio did not vary during the course of the reaction. An acyclic intermediate was not observed. The inversion product, 47%, must arise only from direct displacement while collapse of an intermediate oxyphosphorane prior to ring opening may account for retention. In both these cases, as reaction proceeds lead bis(phenyl sulfide) precipitates and thus the metal acetate is a reactant.

Summary

We have shown that substitution at phosphorus in a six-membered ring phosphate can take place by three possible routes: direct displacement, particularly in cases where the attacking nucleophile cannot efficiently back-bond to phosphorus and the bond between the leaving group and phosphorus is weak; base or, in the case of a good leaving group, metal acetate catalyzed nucleophilic attack whereupon an oxyphosphorane transition state or intermediate undergoes direct collapse with a leaving group departing from either an axial or equatorial position; and finally, ring opening and closing via a lead acetate stabilized oxyphosphorane intermediate. The first and third processes lead to products of inversion while the second leads to retention.

Experimental Section

^1H NMR spectra were recorded on a Perkin-Elmer R-12B spectrophotometer and chemical shifts, reported in parts per million, measured relative to an internal tetramethylsilane standard with $CDCl_3$ as solvent. Isomer and product ratios were obtained by integration of peaks due to 5-methyl hydrogens or in the case of the acyclic products by integration of peaks due to 2-methyl hydrogens. ^{13}C NMR spectra were recorded on a JEOL FX-100 spectrometer and the ^{31}P NMR spectra on a NT-150 spectrometer. The preparation and properties of *cis*-2-chloro-5-(chloromethyl)-5-methyl-2-oxo-1,3,2-dioxaphosphorinane (phosphorochloridate) have been previously published.[12]

***cis*-2-Methoxy-5-(chloromethyl)-5-methyl-2-oxo-1,3,2-dioxaphosphorinane.** The phosphorochloridate (4.36 g, 0.02 mol) was added to methanol (25 mL) in which was dissolved potassium *tert*-butoxide (2.24 g, 0.02 mol). The mixture was stirred for 10 min and the solvent removed under reduced pressure. The residue was dissolved in methylene chloride and the solution washed with distilled water and dried over $MgSO_4$. Solvent removal gave a white crystalline residue which was recrystallized from toluene; 3.7 g (85%), mp 112–113 °C; ^1H NMR 0.90 (5-methyl hydrogens). Anal. Calcd for $C_6H_{12}ClO_4P$: C, 33.64; H, 5.60; Cl, 16.35. Found: C, 33.97; H, 5.95; Cl, 16.41.

The preparation of the trans 2-methyl ester was reported previously.[1] A methanolic solution of the phosphorochloridate without added base was allowed to stand at room temperature for one week and the product isolated as outlined above. ^1H NMR 1.22 (5-methyl hydrogens).

Base-Catalyzed Methanolysis of *cis*- or *trans*-2-Methoxy-5-(chloromethyl)-5-methyl-2-oxo-1,3,2-dioxaphosphorinane. *cis*- or *trans*-2-methoxy-5-(chloromethyl)-5-methyl-2-oxo-1,3,2-dioxaphosphorinane (1.07 g, 0.005 mol) was added to 50 mL of a methanolic solution of potassium *tert*-butoxide, 0.1 M. The mixture was allowed to stand for 48 h and then added to 150 mL of water. The solution was extracted with two 20-mL portions of methylene chloride and the combined extracts dried over $MgSO_4$. After filtration, solvent was removed under reduced pressure and residue distilled, bp 130 °C (1.0 mm), to give 0.95 g (77.2%) of dimethyl 2-(chloromethyl)-2-methyl-3-hydroxypropyl phosphate. Anal. Calcd for $C_7H_6ClO_5P$: C, 34.15; H, 6.50; Cl, 14.23. Found: C, 34.32; H, 6.60; Cl, 14.17. The 2-methyl hydrogens and carbon absorbed as follows: ^1H NMR 1.03 (3 H); ^{13}C NMR 16.99. ^{31}P NMR (85% H_3PO_4 external standard) 2.23. All other peaks in the spectra were easily assigned to the proposed structure. The rate of ring opening was determined by an identical procedure except that reaction time were varied. Rate constants were determined from half-lives.

Ring Closure of Dimethyl 2-(Chloromethyl)-2-methyl-3-hydroxypropyl Phosphate. The acyclic phosphate obtained as in the previous procedure, but based on 0.001 mol of reactants and without final distillation, was treated with 10 mL of a *tert*-butyl alcohol solution which was 0.1 M in potassium *tert*-butoxide. The solution was allowed to stand at room temperature for 1 h before the addition of 30 mL of water. The solution was extracted with two 20-mL portions of methylene chloride and the combined extracts dried over $MgSO_4$. After filtration, solvent was removed under reduced pressure to give a mixture of the cyclic 2-methyl esters. The ^1H NMR spectrum of the mixture was identical with that of a two to one mixture of cis to trans methyl esters. An identicial mixture was obtained regardless from which cyclic 2-methyl ester the acyclic dimethyl ester was prepared.

***cis*-2-Isopropyloxy-5-(chloromethyl)-5-methyl-2-oxo-1,3,2-dioxaphosphorinane.** Phosphorochloridate (10 g, 0.046 mol) was added with stirring to 100 mL of 2-propanol which contained sodium isopropoxide (0.046 mol); the latter prepared by slowly adding sodium (1.06 g, 0.046 mol) to 2-propanol. The solution was stirred at room temperature for 1 h and filtered, and the solvent was removed under reduced pressure. The residue which remained crystallized on standing and was recrystallized twice from heptane (5.2 g, 46.7%), mp 71–72 °C. In order to prevent ring opening by isopropoxide ion, excess base must be avoided. Anal. Calcd for $C_8H_{16}ClO_4P$: C, 39.67; H, 6.61; Cl, 14.46. Found: C, 39.52; H, 6.67; Cl, 14.38. ^1H NMR 0.91 (5-methyl hydrogens). At elevated temperatures the product decomposes by elimination of propylene.

***trans*-2-Isopropyloxy-5-(chloromethyl)-5-methyl-2-oxo-1,3,2-dioxa-**

(12) Wadsworth, W. S., Jr. *J. Chem. Soc., Perkin Trans. 2* **1972**, 1686.

phosphorinane. Phosphorochloridate (10 g, 0.046 mol) was dissolved in 100 mL of 2-propanol and the solution allowed to stand for 20 days. Solvent was removed at reduced pressure to give a residue which crystallized on standing. The product was recrystallized from heptane to give the pure trans isomer (7.2 g, 64.7%): mp 70 °C. Anal. Calcd for $C_8H_{16}ClO_4P$: C, 39.67; H, 6.61; P, 12.81. Found: C, 39.49; H, 6.86; P, 12.88. ^1H NMR 1.20 (5-methyl hydrogens).

Base-Catalyzed Methanolysis of *cis*- or *trans*-2-Isopropyloxy-5-(chloromethyl)-5-methyl-2-oxo-1,3,2-dioxaphosphorinane. 2-Isopropyloxy-5-(chloromethyl)-5-methyl-2-oxo-1,3,2-dioxaphosphorinane (0.97 g, 0.004 mol) was added to 40 mL of a methanolic solution of potassium *tert*-butoxide, 0.1 M. The solution was allowed to stand for 48 h. Excess alcohol was removed at reduced pressure, 30 mL of water added to the residue, and the water solution extracted with two 20-mL portions of methylene chloride. The combined extracts were dried over $MgSO_4$ and solvent removed under reduced pressure. The viscous residue was distilled (138 °C (0.5 mm)) to give methyl isopropyl 2-(chloromethyl)-2-methyl-3-hydroxypropyl phosphate (0.90 g, 83%). Anal. Calcd for $C_9H_{20}ClO_5P$: C, 39.42; H, 7.30; Cl, 12.77. Found: C, 39.33; H, 7.24; Cl, 12.93. The 2-methyl hydrogens and carbon absorbed as follows: ^1H NMR 1.03 (3 H); ^{13}C NMR 16.93. All other peaks in the spectra were easily assigned to the proposed structure. Rates of ring opening were, as before, determined by varying reaction times.

Ring Closure of Methyl Isopropyl 2-(Chloromethyl)-2-methyl-3-hydroxypropyl Phosphate. The acyclic phosphate obtained in the previous procedure but based on 0.001 mol of reactants and without the final distillation was treated in an identical manner as reported for the ring closure of the acyclic dimethyl ester. Regardless as to whether the *cis*- or *trans*-2-isopropyloxy-5-(chloromethyl)-5-methyl-2-oxo-1,3,2-dioxaphosphorinane was used as the starting material, the ring closure gave an identical mixture of cyclic 2-isopropyl esters; a 3:2 mixture of cis to trans.

2-Propanolysis of *cis*- or *trans*-2-Isopropyloxy-5-(chloromethyl)-5-methyl-2-oxo-1,3,2-dioxaphosphorinane. The 2-isopropyl ester (0.24 g, 0.001 mol) was treated with 10 mL of 2-propanol, 0.1 M in potassium *tert*-butoxide. For completion, the solution was allowed to stand at room temperature for 3 days. To the solution was added 30 mL of water, and the product was extracted with two 20-mL portions of methylene chloride. The combined extracts were dried over $MgSO_4$ and solvent removed under reduced pressure. A viscous liquid residue remained whose ^1H NMR and ^{13}C NMR spectra conformed to that expected of diisopropyl 2-(chloromethyl)-2-methyl-3-hydroxypropyl phosphate. The product was not purified further. Anal. Calcd for $C_{11}H_{24}ClO_5P$: C, 43.70; H, 7.95; Cl, 11.59. Found: C, 43.59; H, 8.01; Cl, 11.47. ^1H NMR 1.01 (2-methyl hydrogens). With either isomer ring opening occurred without noticeable concurrent isomerization of starting material.

Methanolysis of *cis*- and *trans*-2-(Phenylthio)-5-(chloromethyl)-5-methyl-2-oxo-1,3,2-dioxaphosphorinane. Methanolic silver nitrate solutions of either the cis or trans 2-thiophenyl ester were prepared by adding 10 mL of the methanolic solutions containing variable concentrations of silver nitrate to the ester (0.29 g, 0.001 mol). Solutions were stirred at room temperature for 10 h and filtered. To the filtrate was added 30 mL of distilled water, and the solution was extracted with two 20-mL portions of methylene chloride. The combined extracts were dried over $MgSO_4$ and solvent removed under reduced pressure to give a viscous liquid residue which crystallized on standing. The ratio of cis to trans cyclic 2-methyl esters was obtained by integration of peaks assigned to the 5-methyl hydrogens, Table I.

Methanolysis Catalyzed by Lead Acetate. A standard procedure was used in all cases. To the starting cyclic ester (0.001 mol) was added 10 mL of a methanolic solution of $Pb(OCOCH_3)_2 \cdot 3H_2O$, 0.1 M. The rate of ring opening by methanolysis was followed by allowing solutions to stand at room temperature for different lengths of time. Distilled water, 30 mL, was added to the mixtures and product isolated by extraction with methylene chloride in a procedure identical with those given above. The percent reaction, Figure I, was determined from the ^1H NMR spectra of the product which contained the starting material and acyclic ring-opened product only. Ratios were obtained by integration and comparison of peaks due to 5-methyl hydrogens and 2-methyl hydrogens, respectively.

***cis*- and *trans*-2-[(*p*-Methoxyphenyl)oxy]-5-(chloromethyl)-5-methyl-2-oxo-1,3,2-dioxaphosphorinane.** In a variation of a procedure reported previously,[1] an equivalent of phosphorochloridate was added to dry acetonitrile containing 1 equiv of *p*-methoxyphenol, triethylamine, and lithium perchlorate. Lithium ion directs substitution to retention.[4] The solution was stirred at room temperature for 2 h and swamped with water. The crystalline solid was removed by suction filtration, washed with dilute KOH, dried, and recrystallized from CCl_4. The product is 96% cis. ^1H NMR 0.92 (5-methyl hydrogens).

A repeat of the procedure but without the lithium perchlorate gave a 10:1 trans to cis ratio of isomers. The trans isomer in over 96% purity could be obtained by repeated fractional recrystallization from 2-propanol. Anal. Calcd for $C_{12}H_{16}ClO_5P$: C, 47.06; H, 5.23; Cl, 11.44. Found: C, 46.89; H, 5.12; Cl, 11.61. ^1H NMR 1.25 (5-methyl hydrogens).

Methanolysis of *cis*- and *trans*-2-[(*p*-Methoxyphenyl)oxy]-5-(chloromethyl)-5-methyl-2-oxo-1,3,2-dioxaphosphorinane. Base-catalyzed methanolysis and lead acetate catalyzed methanolysis of these isomers were carried out by procedures identical with those described above. Product ratios were determined by integration of ^1H NMR spectra and from the known chemical shifts of 5-methyl and 2-methyl hydrogens as determined from pure compounds.

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