Chemistry of Phosphate Esters: Stereochemical Evidence for a Dissociative Mechanism

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CHEMISTRY OF PHOSPHATE ESTERS: STEREOCHEMICAL EVIDENCE FOR A DISSOCIATIVE MECHANISM

By

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In memory of
my departed father
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INTRODUCTION

Phosphorus plays an important role in the chemistry of life and phosphate esters and diesters are the principal modes in which it performs its essential functions.¹

Phosphate esters have a general structure which consists of a phosphorus atom doubly bonded to an oxygen and to three other ligands through oxygen, as in ATP or in DNA, fig. 1. The latter is a polymeric diester of phosphoric acid.

The organophosphates play a role in polypeptide or protein synthesis.¹² The organophosphates are considered to be the storehouse as well as carrier of energy for biological functions.² ATP supplies the necessary energy for many metabolic processes through hydrolysis. The fig. 2 represents such a process. The symbol signifies that associated with the change of one molecule of A to B, a molecule of ATP loses its terminal phosphate group and is converted into ADP. The hydrolysis of ATP to ADP releases energy which is used in the conversion of A to B. The mechanism by which ATP hydrolyses to ADP is not known with certainty.

Besides the vital role played by phosphate esters in life, some organophosphorus compounds are found to be poisonous.¹ Their poisoning effect is due to the inhibition
of essential enzyme activities by masking active sites of the enzymes. The general structure of organophosphorus poisons can be represented by a structure, fig. 3. Where $M_1$ and $M_2$ are groups difficult to displace from a phosphorus atom, eg, alkoxy, dialkyl amino or alkyl and $X$ is a fairly good leaving group. Slight modifications in structure dramatically change the efficiency of poisons.
which are utilized in the synthesis of a wide variety of chemical weapons.

Some organophosphorus compounds have been found to be very effective pesticides. Examples are Parathion, Paraoxon, Malathion, etc., fig. 4. Although, the effectiveness of various pesticides are known, the mechanisms by which they act are not fully understood.

Some organophosphorus compounds have fire and flame retardant properties and are used as components of building materials.
Many attempts have been made to elucidate the various mechanisms by which phosphates act in biological and other systems. There are many suggestions regarding mechanisms all of which fit into one of two broad categories.

1. Associative.
2. Dissociative.
Of these two, the associative type displacement has been of interest to most investigators and this pathway has been established with certainty. On the other hand, less work has been done and there has been much controversy surrounding the dissociative mechanism.

The dissociative mechanism is believed to be important because it has been thought that it represents the actual biological processes by which life utilizes phosphophosphate esters. The schemes in fig. 5, represent the two types of displacement at the phosphorus atom. There has been a number of proposals which suggest a dissociative mechanism in displacements at phosphorus. This type of mechanism warrants an intermediate with a reduced coordination number. In the phosphate esters this intermediate would be a phosphacylium ion analogous to a carboacylium ion generated from an acyl halide, fig. 6. Among several structural possibilities, a phosphacylium ion could retain the geometry of the starting material. This pathway then would produce a stereospecific product where the leaving group is replaced by the nucleophile while retaining the absolute configuration around the phosphorus atom, fig. 7. For the second possibility, the intermediate phosphacylium ion could attain planarity. If this is the case then nucleophilic substitution should give upon substitution a mixture of isomers. The phosphorus atom would
be prone to be attacked by nucleophile from both sides, perpendicular to the plane of the ion, fig. 8. The ratio of isomers of the product may be equal or different depending on thermodynamic and kinetic parameters.

ASSOCIATIVE MECHANISM

\[
\begin{align*}
\text{RO}_2P\text{L}v & \quad + \quad \text{Nu} \\
\rightarrow & \\
\text{RO} & \quad \text{Nu} \\
\text{P} & \quad \text{Nu} \\
\text{OR} & \quad \text{L}v \\
\rightarrow & \\
\text{Nu} & \quad \text{OR} \\
\text{P} & \quad \text{OR} \\
\text{L}v & \quad + \\
\end{align*}
\]

DISOCIATIVE MECHANISM

\[
\begin{align*}
\text{RO}_2P\text{L}v & \quad \rightarrow \\
\rightarrow & \\
(\text{RO})_2P & \quad \rightarrow \\
\text{Nu} & \quad (\text{RO})_2P\text{Nu}
\end{align*}
\]

Figure : 5

The third and final possibility involves equilibration of the intermediate. The nucleophile attacks from either side resulting in a non stereospecific product, the ratio dependent on the direction of the equilibrium, fig. 9.
Both a molecular orbital and valence bond model can be used to describe the bonding in tetracoordinated phosphorus. The molecular orbital approach does not necessarily require the use of phosphorus 3d orbitals and the inclusion of such orbitals remains controversial, whereas the valence bond approach requires the inclusion of 3d orbitals.
A simplified valence bond model has a tetrahedral arrangement about phosphorus which utilizes sp³ hybrid orbitals of phosphorus and ligand orbitals. The fifth valence electron of the phosphorus is forced to occupy a 3d
orbital. In the phosphorus-oxygen bond the oxygen is sp$^2$ hybridized with two lobes accommodating non bonding electron pairs and the other electron in the p-orbital. Overlap between phosphorus and oxygen then forms a sigma and a pi bond. Direct sp’d hybridization in phosphorus is not likely because of the high energy necessary to promote an electron to an empty 3d orbital.

In the thiophosphoryl system(P=S), sulfur with its d-orbitals should be more capable of forming effective backbonding to phosphorus. We would expect that in the thiophosphate systems, a phosphacylium ion, if it does form, would be more stable than its oxo-counterpart.

Therefore, our first objective was to find a suitable phosphate system which would generate a phosphacylium ion intermediate of sufficient stability for detection.
HISTORICAL

Studies have been done to elucidate the mechanism by which phosphates undergo substitution reactions and much controversy exist over the results.\textsuperscript{5-13} Mechanisms have been postulated on the basis of kinetics and stereochemical results and both associative and dissociative type pathways have been proposed. Although there are many examples of displacements at phosphorus proceeding by an associative mechanism, few authentic examples exist for a dissociative mechanism.\textsuperscript{5-9} Our interest is in the dissociative mechanism which should produce a phosphacylium ion as an intermediate.

It has been known for some time that certain organic reactions involve a positively charged intermediate known as an acylium ion.\textsuperscript{10} The species has a resonance structure, fig. 10. Tretters, Hammett et al\textsuperscript{11} have shown that the acylium ion is produced when an orthosubstituted benzoic acid is dissolve in sulfuric acid, fig. 11.

In the Friedel-Craft acylation, the acylium ion is generated as an intermediate from the reaction of Aluminum chloride and an acyl halide.\textsuperscript{10} This ion in turn takes part in electrophilic substitutions, fig. 12. Carboxylic acid esters also undergo nucleophilic substitution via a dissociative mechanism involving an intermediate acylium
The analogous "phosphacylium cation" is the subject of this thesis, fig. 13.

\[ R-C=\overset{\ominus}{\underset{\ominus}{\circ}} \leftrightarrow R-C=\overset{+}{\underset{+}{\circ}} \]

Figure: 10

\[
\begin{align*}
H_3C-\begin{array}{c}
\text{CH}_3 \\
\text{CH}_2O
\end{array} & \text{C-OH} + 2H_2SO_4 \rightarrow H_3C-\begin{array}{c}
\text{CH}_3 \\
\text{CH}_3
\end{array} \text{C=O} + H_3O^+ + HS0_4^-
\end{align*}
\]

Figure: 11

\[
R-\overset{\ominus}{\underset{\ominus}{\circ}} + \overset{\circ}{\text{C}} + \text{AlCl}_4^- \rightarrow \overset{\circ}{\text{C}} R + \text{AlCl}_3 + \text{HCl}
\]

Figure: 12

The development of the mechanistic aspects of organophosphorus chemistry has been largely based on analogy.
to hydrocarbon mechanisms. This is particularly noted in the case of carboxylic acid esters and phosphoric acid esters.

Several attempts to prove the dissociative mechanism which might involve the intermediate phosphacylium ion have been reported. These mainly have involved phosphate derivatives. For example, phosphoramidates, where the substituents might participate in the stabilization of the intermediate with reduced coordination number.

On the basis of an oxygen kinetic isotope effect study, Reimschussel and Paneth have suggested a dissociative pathway in the thermal isomerization of bis(5,5-dimethyl-2-oxo-1,3,2-dioxaphosphorinyl)sulfide, fig. 14.

The first attempt from the stereochemical approach to prove the existence of a phosphacylium ion intermediate was made by polish workers, Michaelski et al. They studied
the synthesis and stereochemistry of mixed phosphorus-sulfonic anhydrides which are suitable for this investigation from the point of leaving group characteristics, electronic and stearic effects, fig. 15. These effects should promote the involvement of a dissociative mechanism during nucleophilic displacement at the tetracoordinated phosphorus center. They found, under conditions favorable for formation of a stable thiophosphacylium ion that during displacement the S-O bond breaks leaving P-O bond intact. This was proved by 19O scrambling. They also found that hydrolysis of optically active mixed phosphorus-sulfonic anhydrides produce 100% inversion of the original configuration, fig. 16. From their observations they concluded that the phosphacylium ion was certainly not an intermediate; the hydrolysis involves a concerted mechanism.
The possibility of the existence of a dissociative process has been enhanced by the work of Westheimer and his collaborators. Their studies were mainly directed towards the synthesis and identification of a monomeric
metaphosphate ion formed through a dissociative mechanism. In particular, their objective was to identify the metaphosphate ion, CH₃PO₃, resulting from the fragmentation of erythro-1-phenyl-1,2-dibromo-propyl phosphonate in the presence of 2,2,6,6-tetramethyl piperidine, fig. 17. The fragmentation pattern was discovered by Conant and his collaborators in the 1920's and rediscovered by Maynard and Swan in 1963.¹⁶ The fragmentation pattern known as the Conant-Swan fragmentation is stereospecific. The erythro isomer forms the trans while the threo isomer yields the cis alkene,¹⁶ fig. 18. Westheimer has succeeded in proving the existence of methyl metaphosphate which results from the above fragmentation process by trapping the reaction species in different ways, fig. 19.

Ramirez et al¹⁷ reported the existence of metaphosphate in the decomposition of substituted phosphates; 2,4-dinitrophenyl phosphate and erythro-1-phenyl-1,2-dibromo-propyl phosphonic acid in the presence of a hindered base, B, diisopropyl ethylamine, fig. 20. In order to trap the reactive metaphosphate, an equimolar mixture of methanol and t-Butanol was employed. The product mixture contained more methyl phosphate than t-butyl phosphate and the result attributed to stearic differences between the nucleophiles. The processes involved in the
\[ \text{C}_6\text{H}_5\text{BrCHBrCH}_3 + a\text{BH}^+ \rightarrow \text{C}_6\text{H}_5\text{CBr=CHCH}_3 + [\text{CH}_3\text{PO}_2]^- + \text{Br}^- + \text{BH}^+ \]

\( a \rightarrow \text{BASE} \)

Figure: 17

![Chemical diagram showing transformation between Erythro and Trans forms](image)

![Chemical diagram showing transformation between Threo and Cin forms](image)

Figure: 18

Westheimer and Ramirez studies are parallel in a formal
sense to the enzymatic transformation of phosphenol pyruvate from pyruvate and ATP.\textsuperscript{18,19}

Lowe and Sproat\textsuperscript{20} have found that pyruvate kinase acts on ATP in the absence of pyruvate or phosphenol
pyruvate to scramble the oxygen atom about the beta phosphorus atom, fig. 21. They proposed that the enzyme splits off monomeric metaphosphate which then rejoins the beta phosphorus atom following its rotation. From their evidence for the formation of a metaphosphate via a dissociative mechanism, the possibility for the existence of a phosphacylium ion as an intermediate is greatly enhanced.

A certain class of ATP-dependent amido transferases can convert a carbonyl group into a C=N group with stoichiometric cleavage of ATP to ADP and \( \text{PO}_4^{2-} \), fig. 22. Labelling experiments have shown the transfer of
the carbonyl oxygen into inorganic phosphate. These processes formally resemble the preparation of ketimine and benzimidate as promoted by monomeric methyl metaphosphate. In one of the two possible enzyme catalyzed pathways, ATP attacks the carbonyl group to activate it for nucleophilic attack, whereas in the other a tetrahedral intermediate is formed which is subsequently trapped by ATP. The concentration of the tetrahedral intermediate on the enzyme may well be substantial, and the proximity to ATP could favor a bimolecular reaction. Several other biochemical processes resemble the previously discussed systems. Perhaps
ATP functions in this way, as well as others, to activate a carbonyl group via the transfer of monomeric metaphosphate. Even if the attack of monomeric metaphosphate on the carbonyl oxygen provides the first step in the reaction, one must consider whether ATP phosphorylates the carbonyl by direct attack or by prior dissociation to the monomeric metaphosphate.

Figure: 22

Proof of the existence of a dialkyl phosphacylium cation, as an intermediate should have great implications
with respect to the probability of monomeric metaphosphate formation.

There has been much interest among investigators whether a phosphacylium type cation does exist as an intermediate during the hydrolysis of phosphate esters and their analogues. Some investigators argue strongly in favor of its existence and some are against it.

Dostrovsky and Halman have concluded from their studies of the hydrolysis of dialkyl phosphorochloridate, \((\text{RO})_2\text{POCl}\), that this chloridate is prone to react by an SN² mechanism even in a solvent of high ionizing power. Hall extended the above chloridate system to N,N,N',N'-tetramethyl phosphorodiamidic chloride, \([(\text{CH}_3)_2\text{N}]_2\text{POCl}\), and found that the kinetics of hydrolysis favored an SN¹ type mechanism, fig. 23.

Hudson and Keay reported evidence that the P-Cl bond of a phosphorochloridate,
undergoes fission in formic acid to give a phosphacylum cation.

\[
\left[ \text{CH}_3\text{N}_2 \right]_2 \text{POCl} \rightarrow \left[ \text{CH}_3\text{N}_2 \right]_2^+ \overset{\text{H}_2\text{O}}{\rightarrow} \left[ \text{CH}_3\text{N}_2 \right]_2^0 \overset{\text{P-OH}}{\rightarrow} 
\]

Figure : 23

Haake and Ossip\(^6\) suggested a dissociative mode of solvolysis of phosphinyl chloride in aqueous acetone when the chloridate is stearically hindered, for example, t-butyl phosphinyl chloride. The large t-butyl group suppresses the more preferable associative mechanism. Their evidence supportive for the existence of a phosphacylium ion has been enhanced by the observation of phosphacylium ions, \(\text{RR}'\text{P}^+=\text{O}\), as an important fragment in the mass spectra of a phosphinyl chloride.\(^{25}\)

From the cryoscopic measurements in 100% sulfuric acid Haake and Ossip concluded that a phosphinamidate can hydrolyze by a sequences whereby phosphinylium ion exists as an intermediate,\(^6\) fig. 24. There has been considerable interest in compound which have the P-N moiety.\(^1\),\(^2\)
Phosphinamidates has been used as phosphorylation reagents for the synthesis of phosphate derivatives. By means of chemical dynamics it has been demonstrated that the P-N bond of \( HO_3P-NHR \) is unstable and either generates the reactive metaphosphate ion, \( PO_3^- \), in a unimolecular dissociative decomposition or undergoes rapid bimolecular transfer of the \( PO_3^- \) moiety to generate a new phosphate derivative.\(^{25,27}\)

\[
(\text{HO})_2\text{SO}_2 + (\text{C}_6\text{H}_5)_2\text{PN} \left(\text{CH}_3\right)_2 \rightleftharpoons (\text{C}_6\text{H}_5)_2\text{PN} \left(\text{CH}_3\right)_2^+ + \text{HOSO}_3^- \\
(\text{HO})_2\text{SO}_2 + (\text{C}_6\text{H}_5)_2\text{PNH} \left(\text{CH}_3\right)_2 \rightleftharpoons (\text{C}_6\text{H}_5)_2\text{P}^+\text{OSO}_3^- + \text{H}_2\text{N} \left(\text{CH}_3\right)_2 \\
(\text{HO})_2\text{SO}_2 + (\text{C}_6\text{H}_5)_2\text{P}^+\text{OSO}_3^- \rightleftharpoons (\text{C}_6\text{H}_5)_2\text{P}^+\text{OSO}_3 ^- + \text{HOSO}_3^- \\

\text{Figure: 24}

A definitive study of nucleophilic substitution at phosphorus in trialkyl phosphates which are thought to be representative of high energy phosphates found in biological systems, for example, ATP, is hindered due to the lack of a suitable substrate. Our research group has discovered that
2-substituted-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxa-phosphorinans, fig. 25, are suitable substrates for the study of the mechanism of substitution at phosphorus. From the dependency of isomerization of the phosphorinan on the 2-substituent and on solvent polarity, it was suggested that isomerization might proceed through ionization and could be detected.

![Diagram of compound](image)

Figure : 25

The treatment of cis-chloridate, which is the only product from an Arbuzov type reaction between methyl bicyclic phosphite and sulfuryl chloride, fig. 26, with nucleophiles yields both cis and trans products fig. 27. The ratio of the isomers obtained as product is found to be dependent on several factors; the nature of the solvent, added salts present and the basicity of the nucleophile. effects of lithium ion and other ions, solvent polarity, acidity etc. on the stereochemistry of the product have been discussed. As a result, in a series of papers our research group has proposed mechanisms by which the
stereochemistry of substitutions of 2-substituted 5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxa-phosphorinans is controlled. 

\[
\begin{align*}
\text{CIS} & \quad \text{Figu…}
\end{align*}
\]

Figure : 26

\[
\begin{align*}
\text{Nu} & \quad \text{CIS} \quad \text{TRANS}
\end{align*}
\]

Figure : 27

We have also found that backbonding between the phosphorus atom and the attacking nucleophile is of prime importance. Efficient backbonding which leads to retention of configuration is enhanced by factors which increase the
positive character at the phosphorus atom, i.e., electron withdrawing ligands or lewis acids which bond to the basic phosphoryl oxygen. In contrast inversion is favored in the case of poor backbonding between nucleophile and substrate and by leaving groups weakly bonded to phosphorus. As the phosphorus-leaving group bond is weakened the chances of a dissociative mechanism increase and at the extreme the bond will break to generate a phosphacylium cation. In this latter case the reactions should lose their stereospecificity.

Addition of an electrophilic catalyst which can complex with the leaving group and subsequently weaken the phosphorus-leaving group bond might promote the dissociative mechanism.

Metal ions have been found to have significant effects on the methanolysis of phosphate esters. They also catalyze the methanolysis reaction. Metal ions complexing with the leaving group enhances the positive character at phosphorus making it more prone to be attacked by nucleophiles.

In catalyzing certain methanolysis reactions it has been found that the efficiency of lead acetate is large, much more efficient than sodium acetate. Marked difference in the stereochemistry of the product has also been reported. Lead acetate leads to products of inversion
whereas sodium acetate produces a product which results from 100% retention. The anomaly in the results is due to the ability of lead acetate in methanolic solution to complex with the leaving group and thereby help to break the phosphorus-ligand bond.

Attempts to prove the existence of a phosphacylium ion have involved only the trans phosphorinan. For a definitive proof of the existence of a phosphacylium ion we should carry out the methanolysis reactions under identical conditions with the cis-phosphorinan system. An identical product isomer ratio from both the starting cis and trans phosphorinans would indicate that a phosphacylium ion could exist as an intermediate. If a phosphacylium ion does exist as an intermediate we should get the same product isomer ratio irrespective of the starting isomer, fig. 28,
Figure: 28
DISCUSSION

There is no direct method available to detect the existence of phosphacylum cations in a chemical reaction. However, studies have been carried out which detect their existence indirectly. The studies analyze the products of substitution which use as reactants possible precursors of phosphacylum ions. The 2-substituted-5-chloromethyl-5-methyl-2-oxo-1,3,2-phosphorinan systems were found suitable to study the possible existence of the phosphacylum ions. The geometry of such system can be determined and investigated by the simple proton nmr chemical shift values of the 5-methyl or 5-chloromethyl group protons. If both cis and trans isomers of a phosphorinan system give identical product isomer ratios, a common intermediate is highly probable, fig. 28. In summary, the special qualities (conformational immobilities, easy of isomer identification etc.) have made the 2-chloro-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan system an invaluable tool in the possible detection of a phosphacylum cation intermediate. The chloridate, the precursor, prepared by treating methyl bicyclic phosphite with Sulfuryl chloride, fig. 30. The reaction produced the cis-isomer only, both the 5-chloromethyl and the phosphoryl oxygen are on the same side of the ring. The trans isomer would have the groups on opposite side of the phosphorinan ring, fig. 31.
Methanolysis or substitution by methyl alcohol was the first reaction performed on the chloridate. Under neutral condition, methanolysis proceeds with 100% inversion of configuration while under basic condition 100% retention is observed, nmr # 1 and nmr # 2, fig. 29.

The first effort at forming a precursor of phosphacylium cation involved the preparation of 2-amino-
phosphorinan followed by its diazotization in methanol, fig. 32. Diazotization was attempted for it is widely assumed that diazonium salts decompose to give carbocations, especially in the case of primary amines, although to our knowledge, the diazotizations of phosphoramidates has not been reported. If successful the counterpart to a carbocation, the phosphacylium ion would be an expected intermediate. The product was obtained in high yield with a 2.5 to 1.0 cis to trans ratio. The esters are stable under the reaction conditions; they do not equilibrate. The possibility of the existence of a phosphacylium cation, the intermediate shown above, would have been enhanced if we could treat the isomeric cis-2-amino-phosphorinan under
identical conditions and obtain the same product ratio. Unfortunately, at the time we were unable to prepare the desired cis-2-aminophosphorinan, although attempts were made, fig. 33. t-Butyl hypochlorite reacted with ammonia and p-toluene sulfonamide to give chloroamine and p-toluene sulfonamidochloride respectively but none of them reacted with the bicyclo phosphite to give phosphoramidate. On the other hand chloridate reacted with sodamide under and without N₂ atmosphere to give a phosphorimidate and phosphoranic acid respectively but no amide was formed, nmr # 3. The cis amide has now been prepared by other means (by another member of our group) and this was supplied for our diazotization studies. As with the trans isomer, the product of inversion, although a different isomer predominates. The fact that an equal product isomer ratio is not obtained from both isomeric starting materials indicates that a common intermediate, a phosphacylium ion, is not involved. The fact that both starting isomers give a mixture of methyl esters and not only the product of inversion, certainly could reinforce the hypothesis that diazotization proceeds through a transition state in which bond breaking, the loss of nitrogen, is far advanced before bond making becomes significant, fig. 35. Indeed, there may in the transition state be much positive characters at phosphorus. fig. 34.
In order to prove or disprove the dissociative mechanism, we have run identical reactions under identical conditions using pairs of isomers.

Isomeric mixtures of a 2-thiophenyl ester has been prepared by treating phosphorochloridate solution in acetonitrile with sodium thiophenoxyde, fig. 36. Treatment of methyl bicyclic phosphite with benzenesulfinyl chloride gave the cis isomer, fig. 37. Both the isomers of
\[
t\text{-BuOCl} + \text{NH}_3 \xrightarrow{\text{CCl}_4} \text{NH}_2\text{Cl} + t\text{-BuOH}
\]
\[
\text{NO REACTION}
\]

\[
P\text{-H}_3\text{C}_6\text{H}_4\text{SO}_2\text{NH}_2 + t\text{-BuOCl} \xrightarrow{\text{CH}_3\text{CN}} \text{H}_3\text{C}_6\text{H}_4\text{SO}_2\text{NCl} + t\text{-BuOH}
\]
\[
\text{NO REACTION}
\]

\[
\text{cis} + \text{NaNH}_2 \xrightarrow{\text{CH}_3\text{CN}} \text{Cl}_2\text{H}_2\text{C}
\]

\[
\text{Figure : 33}
\]

2-thiophenyl ester undergoes methanolysis slowly in the absence of a catalyst to give retention products only,
The result is in contrast to the uncatalyzed methanolysis of 2-chlorophosphorin an where only inversion is observed. The reason for the anomaly is not known but possibly has to do with the enhanced backbonding between sulfur and phosphorus. As a result of backbonding, the phosphorus-sulfur bond may be stronger than the phosphorus-chlorine bond and therefore an $\text{SN}_2$ reaction prohibited by a
relatively high energy of activation. Addition of silver nitrate diverts the reaction to inversion with the amount of inversion increasing with catalyst concentration, fig. 39, table 1. Both starting isomers give isomeric product mixtures but in each case the ratios are not identical and indeed are nearly opposite. It is, therefore, apparent that a common intermediate, phosphacylumin cation, is not likely.

![Chemical reaction diagram](image)

Figure: 36

Pyrophosphate are of general interest due to the common occurrence of the moiety in biological systems. The p-o-p bond is highly reactive and evidence for a dissociative mechanism to yield reactive metaphosphate ion has been described by a number of investigators. It was of interest to investigate and determine the stereochemistry of the products of
methanolysis of a pyrophosphate. Treatment of an acid with a chloridate gave a mixture of three isomers of a bis-phosphorinan, fig. 40. The trans-trans isomer was present in only minor quantities. No attempt was made to isolate the
three separate components. The configuration ratio was varied by simply varying the conditions under which the pyrophosphate was prepared. Without added catalyst, other than base, the product configuration consisted of 60% cis and 40% trans. Advantage was taken of the ability of silver ion to direct displacement of chloride ion by inversion to give a product mixture consisting of 36% cis and 64% trans. Methanolysis of the two product mixtures were carried out using various catalysts, table 2. From the table it is clear that product ratio varies with reactant ratios which again indicates the lack of a common intermediate and
formation of an \textit{phosphacylium} ion. Our results are in contrast with the usual mechanism, dissociative, credited to cleavage of pyrophosphate.

![Chemical structures](image)

\textbf{Figure: 40}

The better the leaving group, the weaker the bond between the phosphorus and the leaving group and more the possibility of nucleophilic substitution through a phosphacylium cation. In order to take advantage of an outstanding leaving group, we studied the 2,4-dinitrophenoxy phosphorinan system. The two nitro groups which can efficiently complex with an electrophillic catalyst, lead acetate, confer outstanding leaving group activity to the dinitro phenoxy substituent. The cis and trans isomers of
2,4-dinitrophenoxyl phosphorinian were prepared by adding sodium-2,4-dinitrophenoxide to the chloridate, fig. 41. The weakly basic nucleophile produced initially the trans isomer, the inversion product. By allowing the reaction mixture to stand in the presence of the phenoxide ion, an equilibrium mixture is obtained in which the cis isomer predominates over the trans. In this manner and by fractional recrystallization mixtures enriched in either the trans or cis isomers were obtained. Because of the difficulties in separating the isomers completely by fractional recrystallization, enriched mixtures were employed, Table 3. Since different isomer mixtures gave different product ratios, again it is unlikely that a common intermediate is produced from each starting material.

\[
\begin{align*}
\text{CIS} & \quad \text{CH}_3 - \quad \text{O} - \quad \text{P} - \quad \text{O} - \quad \text{Cl} \\
\text{CH}_2 \text{Cl} & \\
\text{CIS} & + \quad \text{NO}_2 - \quad \text{O} - \quad \text{P} - \quad \text{O} - \quad \text{Na} \quad \text{NO}_2 \\
& \quad \text{CHCN} \quad \text{Cl} - \quad \text{H}_2 \text{C} - \quad \text{O} - \quad \text{P} - \quad \text{O} - \quad \text{H}_3 \text{C} - \quad \text{NO}_2 \\
& \quad \text{H}_3 \text{C} - \quad \text{CH}_2 \text{Cl} \\
& \quad \text{CIS AND TRANS}
\end{align*}
\]

Figure: 41

Nucleophilic displacement at phosphorus has been studied under different conditions. Methanolysis of cis
chloridate in the presence of Ag\(^+\) gives 100% inversion. When isopropyl alcohol was used, again only the product of inversion was obtained. Methanolysis in the presence of a base proceeds by 100% retention, fig. 42. If phosphacylium ion is an intermediate, alcoholysis would be expected to produce an isomeric mixture of products.

\[
\begin{align*}
\text{CH}_3\text{OH} + \text{Ag}^+ & \rightarrow \text{CH}_3\text{C} - \text{c} \text{H}_3 \text{P=O} \\
\text{cis} & \rightarrow \text{CH}_3\text{OH, OH}^- \\
\text{H}_3\text{C} - \text{C} \text{H}_2\text{Cl} & \rightarrow \text{H}_3\text{C} - \text{C} \text{H}_2\text{Cl} \text{OCH}_3 \\
\end{align*}
\]

Figure : 42

A phosphacylium ion formed from a 2-thio-phosphorinan system, would be expected to have enhanced stability, longer life time and perhaps be simpler to detect. Sulfur in contrast to oxygen would be expected to better backbond to phosphorus and in turn stabilize a
cationic intermediate. Therefore, a number of attempts were made to elucidate the mechanism of displacement at phosphorus in thiophosphate systems.

The first 2-thio-phosphorinan system that was studied was 2-chloro-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan. The isomeric mixture of the chloridate was prepared by treating thiophosphoryl chloride with 2-chloromethyl-2-methyl-propane-1,3-diol in the presence of pyridine, fig. 43, nmr # 4. Trans chloridate was isolated by fractional crystallization from a hexane-chloroform mixture (10:1), nmr # 5. The pure cis isomer could not be isolated. The trans chloridate did not react with methanol in the presence of silver nitrate which is in contrast to its oxo counterpart which readily undergoes methanolysis under identical conditions with 100% inversion, fig. 44. We are not certain as to why the P-Cl bond is more readily broken in the P-O case than in the P=S system. It might be due to more efficient backbonding to phosphorus in the sulfur case, that the positive character of phosphorus is lessened and thus its electrophilicity and susceptibility toward a nucleophile greatly reduced. The result also indicates the nonexistence of a phosphacylium ion as an intermediate for if the substitution does go through a cation intermediate we would expect a much more efficient reaction in the thio-phosphoryl case for sulfur should
stabilize the cation through its d-orbitals and backbonding to phosphorus.

\[
\begin{align*}
\text{CIS} & \quad \text{TRANS} \\
\text{H}_3\text{C} & \quad \text{Cl} \\
\text{CH}_2\text{C} & \quad \text{CH}_2\text{OH} \\
\text{ClH}_2\text{C} & \quad \text{CH}_2\text{OH}
\end{align*}
\]

Figure 43

The inconclusive results obtained upon the diazotization of the phosphoramidates prompted the synthesis and diazotization of the 2-amino-2-thio-phosphorinans. Because of the enhanced stability of thiophosphorinans, already mentioned, we hoped to be able to readily prepare both isomers of the 2-thiophosphoramidate. Also as mentioned previously, it was hoped that a thiophosphacylium ion would be more stable than its oxygen analogue and greater evidence of a cationic intermediate would be obtained. An isomeric mixture of 2-amino-2-thio-phosphorinan was prepared by passing ammonia gas through a warm acetonitrile solution of the trans thio-chloridate, Fig. 45, nmr # 6. Cis-isomer was isolated from the isomeric mixture by recrystallization.
from boiling water, nmr # 7. The isomeric trans amide could not be isolated. It is of interest that while the oxygen analogue upon aminolysis gave a single amide strictly by inversion, the thiophosphoryl chloridate gave a mixture of isomers. the results again may reflect the fact that direct displacement may take place in the oxygen case but an addition-elimination mechanism may prevail in the thiophosphoryl system.

Several attempts to prepare the isomeric trans-hydrazide failed, fig. 46.
The 2-thiophosphoramidate was subjected to acid catalyzed methanolysis with hydrochloric, sulfuric and p-toluene sulfuric acids as catalysts. The acid catalyzed methanolysis produced complicated mixtures of esters, by substitution of the amido group. In addition to the expected ester formation it was found that the acids catalyze formation of thiomethyl esters with the methyl group at sulfur, fig. 47. It was also found that the stronger acids catalyze methanolysis at sulfur most efficiently, nmr # 8, nmr # 9, and nmr # 10.
Figure 46

To learn more about the above process and for comparisons of physical properties, we wished to prepare the above thiol ester by an independent method. Fortunately, after several attempts we succeeded by treating cis-phosphorinan esters with methyl iodide, fig. 48, nmr # 11, a reported reaction. 34

To elucidate the mechanism of this interesting reaction, we treated a series of methanolic solutions of the thio esters with the methyl group at oxygen with concentrated sulfuric acid. Under the same reaction
conditions we find that a transfer process does not take place, fig. 49. From our observations, we conclude that the methyl-sulfur bond must be formed from the amide and not from a previously formed thio phosphoryl ester, fig. 50. A thermodynamic ratio of isomers is obtained due to pseudorotational permutations of the intermediate.

The diazotization of the cis-thiophosphoramidate in the presence of methanol was performed, fig. 51. The nmr of the product mixture did not show any clear cut identifiable product rather the product mixture looked very complex, nmr # 12. This is in contrast to its oxo counterpart.
Our attempts to prove the existence of a phosphacylium ion as an intermediate in solvolysis reaction has taken on a new life with the discovery that a 2-hydrizinophosphorinan gives upon acid catalyzed methanolysis a mixture of isomers irrespective of the geometry of starting material, fig. 52. Without a strong acid catalyst methanolysis does not take place. The results are in marked contrast to the acid catalyzed methanolysis of a simple phosphoramidate where inversion is the only route observed, fig. 53.
In the case of hydrazides, it seems obvious that protonation of the hydrazino moiety would convert it into a very reactive leaving group. The fact that both isomers of
the reactant give a nearly identical product ratio certainly points to the possibility that a phosphacylium ion or phosphacylium ion like intermediate is formed, fig. 54. From the results, we conclude that the cation is most likely is planar at the phosphorus atom and that the phosphorinan ring maintains its original conformation.

With this background it was worthwhile us to look at other systems which could generate a very reactive
upon acidification. A phosphorylated imidazole is a likely candidate for upon protonation a neutral leaving group would be formed. Also, the system is akin to biological system for imidazole is not unlike the pyrimidine bases in its structure and reactivity. The early attempts to prepare an
prepare an imidazole were unsuccessful for the product once formed rapidly hydrolyzed to salt, insoluble in benzene, the solvent in which the reaction was conducted, fig. 55. The desired 2-imidazolyl phosphorinan could be isolated if solvents were freshly distilled and glassware scrupulously dried. Under such conditions product recrystallizable from toluene could be obtained in fairly high yield. NMR data can be readily employed to distinguish between the desired phosphoramidate and phosphate salt. For the salt, proton absorption in the aromatic region has a different pattern and chemical shift separation than that found in the product.
It is not surprising that due to the high reactivity of the product that CDCl₃ solutions show via nmr slow isomerization to a mixture of geometrical isomer, fig. 56. The isomer ratio is considerably different from that found with aromatic esters (2:1) which may be a consequence of the P-N versus P-O bond found in the latter. The isomerization may be catalyzed by a small amount of free base found in the recrystallized product, formed upon unavoidable hydrolysis. From chemical shift differences, particularly of the 5-methyl hydrogens, the isomer appears to have the indicated structure, phosphoryl oxygen axial in both isomers, as is found in similar N-alkyl substituted phosphoramidates.
Figure: 56

Uncatalyzed methanolysis of the trans phosphorylated imidazole gave cis methyl esters almost exclusively. The small amount of the opposite isomer can be attributed to partial isomerization of starting material. This result is not unfamiliar to the methanolysis of the 2-chlorophosphorinanan where also a good leaving group is displaced by complete inversion. In contrast, acid catalysis (p-toluene sulfonylic or tetrafluoroacetic acid) produced almost exclusively the methyl esters of opposite configuration, the trans, fig. 57. The almost complete retention observed is just the opposite of the acid catalyzed methanolysis of N-alkyl phosphoramidates (inversion only) and is not dissimilar to the result obtained earlier with the hydrazides. As in the latter case, we invoke a phosphacylium like intermediate, fig. 57. Just how free the ion is of the leaving group prior to solvent attack is unknown but the fact that almost complete retention is observed it may be
more free than in the case of acid catalyzed methanolysis of the hydrazides. Again, results would indicate that the ion retains its original conformation and that planarity is not attained at the phosphorus atom.

Figure: 57

The nearly complete change in stoichiometry upon addition of acid must mean that in the imidazole case as well as with the hydrazides that a complete change in
mechanism of solvolysis must occur in the presence of acid. Certainly, protonation and conversion to a better leaving group is mandated. This along with the greatly enhanced reactivity of the reactants, especially striking in the case of the hydrazides, would argue for a dissociative mechanism or at least a pathway in which bond breaking is far advanced prior to bond formation. Structural results, which to our knowledge are the first evidence for the first order heterolysis of a phosphorus nitrogen bond, gives strong evidence that a phosphacylium ion is not planar. Results are dramatically similar to the phosphoryl free radical in which the orbital containing the lone electron is confined to that position it occupies prior to homolysis. Our results indicate that hybridization about phosphorus is similar for the radical and cation.
RESULTS AND SUMMARY

Methanolysis of 2-chloro-phosphorinan under neutral conditions or in the presence of an electrophilic catalyst, e.g., Ag\(^+\), proceed by 100% inversion while under basic conditions the reaction proceeds with 100% retention. The high stereospecificity in each case is indicative of an associative and not a dissociative process. In contrast to the chloridate system the thio counterpart does not undergoes solvolysis even in the presence of Ag\(^+\) ion. The thio phosphates are chemically unreactive compared to the phosphates.

Both cis and trans isomers of 2-thiophenyl ester undergo solvolysis to give retention products only. Again the stereospecific nature of the reaction does not favor a dissociative mechanism. Even in the presence of an electrophilic catalyst a common intermediate is not indicated. Equal product isomer ratios are not obtained from each isomeric starting material.

The different product isomer ratios, obtained from the methanolysis of two samples of phosphate enriched in two different reactant isomers, also does not proceed by a dissociative mechanism. If the reaction did follow a dissociative pathway, identical product isomer ratios should be obtained from both starting isomers, which is not the case.
Diazotization of both cis and trans isomers of a phosphoramide in the presence of methanol produce mixture of isomers of esters with different ratios. The ratio is dependent upon the starting isomer. The product of inversion was found to be predominant irrespective of the starting isomer. The fact that an equal product isomer is not obtained from isomeric starting material indicates the lack of a common intermediate, the phosphacylium ion. The fact that both starting isomers give a mixture of methyl esters and not only the product of inversion, is in contrast to the acid catalyzed methanolysis of simple phosphoramidates which produce inversion products only. The results reinforce the hypothesis that diazotization proceeds through a transition state in which bond breaking, the loss of nitrogen, is far more advanced than the bond making and that the phosphorus atom in the transition state has considerable positive character.

The thio counterpart of the phosphoramide system gives a complex product mixture upon diazotization. We had expected a more resonance stabilized phosphacylium ion intermediate with the thio phosphate system.

Solvolysis of a phosphorylated imidazole has given us our first evidence for the formation of a phosphacylium ion intermediate based on a stereochemical approach. Uncatalyzed methanolysis of the trans-phosphorylated
imidazole produces exclusively the cis-methyl ester whereas in the presence of a strong acid the trans-methyl ester is the exclusive product. This result is in contrast to the acid catalyzed methanolysis of N-alkyl phosphoramidate which proceeds by inversion only. Our observation of this very reactive system argue in favor of a phosphacylium cation like intermediate formed during solvolysis. The retention product can be accounted for by assuming the existence of an intermediate cation which is essentially free from the leaving group. The ion retains its original configuration and planarity is not obtained at the phosphorus atom. The nearly complete change in stereochemistry upon addition of acid means that a change in mechanism of solvolysis must occur in the presence of the acid. Upon protonation, the imidazole group becomes an excellent leaving group.

Thus, we have the first evidence based on stereochemical evidence for a phosphacylium ion intermediate.

From our observations, we conclude that for the formation of a phosphacylium cation intermediate a P-N bond rather than either a P-O or P-S bond must break. This requirement can be rationalized by the fact that nitrogen has only one pair of unused sp³ electrons whereas oxygen or sulfur has two pairs of non bonding electrons. As a result, the backbonding between phosphorus and nitrogen will be much
less than between phosphorus and either oxygen or sulfur. The reduced backbonding enables the phosphorus and nitrogen bond to be broken which leads to the generation of the phosphacylium ion intermediate.
EXPERIMENTAL

$^1$H NMR spectra were reported on a Perkin-Elmer R-12B spectrophotometer and chemical shifts, reported in parts per million, measured relative to an internal standard, tetramethyl silane, with CDCl$_3$ as solvent. Isomer and product ratios were obtained by intrigueation of peaks due to 5-methyl hydrogens.

The elemental analysis were done by Galbraith Laboratories Inc., Knoxville, Tennessee.

Melting points were taken by a Thomas Hoover capillary melting point apparatus and are uncorrected.

Preparation of t-butyl hypochlorite

T-Butyl alcohol, 74 g (1 mole) was added to a cooled (15-16°C) solution of sodium hydroxide, 80 g (2 mole), dissolved in 500 mL of water. Enough water is added to make a homogeneous mixture. Chlorine gas was passed through the mixture for 30 minutes at a rate of approximately 1 liter per minute and then for an additional 30 minutes at a slower rate with continuous stirring. The upper oily layer was separated and washed with 10% sodium carbonate solution until the washings were no longer acidic to congo red. The liquid product was washed four times with equal volumes of water and dried over anhydrous calcium chloride. The mixture was filtered to remove the calcium chloride and the liquid product purified by distillation.
The yield is 104 g (96%), boiling point 77-78°C

**Preparation of methyl bicycrophosphite**

An equimolar (0.5 mole) mixture of 1,1,1-triiodhydroxy methylethane and trimethyl phosphite in 100 mL toluene was distilled slowly for 24 hours until methanol formation was completed. The temperature was maintained at around 120°C. The toluene was then stripped off under reduced pressure maintaining the rotary evaporator's bath temperature at around 90°C. The white crystalline product was distilled under high vacuum (10^-1 torr, 120°C) and collected over an ice bath, nmr # 16

The yield is 33% (reported 40%), melting point 97-98°C

**Preparation of 2-chloromethyl-2-methylpropane-diol**

Thionyl chloride, 119g (1 mole), was added dropwise to 1,1,1-triiodhydroxy methylethane, 120g (1 mole), and pyridine, 80g (1mol), and the mixture finally heated at 140-160°C (bath) for 20 hours. The cooled mixture was diluted with water (1 volume) and extracted with ethyl acetate(total 500 mL). The extract was washed with 2N hydrochloric acid, then with water and dried over anhydrous magnesium sulfate. Distillation of the solution gave the diol (40g, 30% yield) b.p 100-103°/0.3 mm (reported); 140-142°/1 torr (observed) m.p 81-82°C
Preparation of 2-chloro-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan

Thio phosphoryl chloride, 37g (0.22 mole), was added dropwise with stirring and cooling to 1-chloromethyl-1,1-dihydroxy methyl ethane, 30.14g (0.22 mole), ether (150 mL), and pyridine, 34.7g (0.44 mole). The solution was stirred for 1 hour and filtered. The filtrate was washed with 5% HCl and water, and dried over anhydrous magnesium sulfate. The solvent was removed to give a white solid (36g, 70% yield) which consisted of cis and trans isomer in a 7 to 8.5 ratio, nmr # 4. The nmr peak at 0.9 and 1.2 ppm were assigned to the 5-methyl protons of cis and trans isomer respectively. The isomeric mixture was recrystallized 4 times from a hexane-chloroform (10:1) mixture to isolate pure trans isomer, nmr # 5. Calculated for C₅H₉ClO₂PS; C, 25.53; H,3.83; Cl, 30.21, S, 13.77, m.p 64-65°C

Methanolysis of trans-2-chloro-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan in the presence of silver nitrate

A silver nitrate solution, 25 mL (0.001M) in methanol was added to the chloridate 0.216g (0.001 mole), all at once. The mixture was refluxed for 3 hours after which time solvent was stripped off under reduced pressure.
The residue was taken up in methylene chloride and filtered. The methylene chloride was stripped off from the filtrate under reduced pressure to give a solid precipitate. The nmr spectra of this solid was found to be exactly the same as that of the starting material, nmr # 17. The reaction did not take place.

**Preparation of 2-thiophenoxy-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan.**

Phosphorochloridate, 8.72g (0.04 mole), and sodium thiophenoxide, 5.28g (0.04 mole), were added to 40 mL of freshly distilled acetonitrile. The mixture was stirred at room temperature for 3 hours and stripped off under reduced pressure. The residue was washed with water and recrystallized from carbon tetrachloride to give 9.4g (80.3% yield) of product, m.p 88-89°C. From the nmr spectrum of the product the material proved to be a mixture of cis and trans isomers. Recrystallization did not change the isomer ratio of the crude product. Calculated for C_{11}H_{14}ClO_{3}PS; C, 45.24; H, 4.79; Cl, 11.98. Found C, 45; H, 4.72; Cl, 12.07.

**Methanolysis of cis or trans 2-thiophenyl-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan.**

Methanolic silver nitrate solution of either the cis or trans-2-thiophenyl ester were prepared by adding 10 mL
of the methanolic solution containing variable concentration of silver nitrate to the ester (0.29g, 0.001 mole). Solutions were stirred at room temperature for 10 hours and filtered. To the filtrate was added 30 mL of distilled water and the solution extracted with two 20 mL portions of methylene chloride. The combined extracts were dried over anhydrous magnesium sulfate 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 integrating the peaks assigned to the 5-methyl hydrogens, table # 1.

Preparation of 2-(2,4-Dinitrophenoxy)-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan.

To 30 mL of acetonitrile was added 2-chloro-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan, 4.36g (0.02 mole), and sodium 2,4-dinitro phenoxide, 4.12g (0.02 mole). The mixture was stirred for an half hour at room temperature and diluted with 200mL water. After standing overnight the solution was suction filtered, the precipitate washed with water and dried over acetone under reduced pressure. The product was dissolved in 25 mL of methylene chloride and the organic layer washed with aqueous 0.1M KOH. The organic layer was dried over anhydrous magnesium sulfate and solvent removed under reduced
pressure. The solid residue was recrystallized from carbon tetrachloride. As determined from nmr spectrum, the product contained 96% of the trans isomer and 4% of the cis. No attempt was made to maximize the yield which increased as the reaction time was increased. Thermodynamic control became more influencial with reaction time such that after two days the product contained only 6% of the trans isomer and 94% of the more stable cis.

The methanolysis of 2-(2,4-dinitrophenoxy)-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan catalyzed by lead acetate.

To 10 mL of a methanolic solution of lead acetate, 0.1M Pb(C₂H₃O₂)₂·3H₂O, was added 93% trans, 7% cis-2-(2,4-dinitrophenoxy)-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan, 0.336g (0.001 mole). The solution was stirred at room temperature for two hours during which time a heavy yellow precipitate was formed. The mixture was filtered and the precipitate washed with methylene chloride, 20 mL. The combined filtrates were washed with water followed by 0.1M aqueous KOH. The organic layer was dried over magnesium sulfate and solvent removed under reduced pressure, 50°C at 30 mm. The nmr of the residue, indicated the reaction to be 92% complete and methyl esters present as a mixture of isomers, 66% trans and 34% cis.
What is most important, the isomer ratio did not vary except within a few percent regardless of the configuration of the starting material. Precipitation of the 2,4-dinitrophenoxide ion as its lead salt, prevented concurrent isomerization of starting material by the ion.

Preparation of 2-amino-5-chloromethyl-5-methyl-2-thio-1,3,2- dioxaphosphorinan

Through a warm acetonitrile solution of the isomeric mixture of the chloridate, ammonia gas was passed until precipitate formation was completed. The reaction mixture was filtered and the solvent removed from the filtrate under reduced pressure to give a crystalline semisolid. This semisolid consisted of both cis and trans isomers of the 2-aminophosphorinan, nmr # 6, from which the cis isomer was isolated by crystallization twice from hot water, nmr # 7. NMR peak at 0.9 ppm was assigned to the 5-methyl group protons of the cis amide. m.p 125-126°C. Calculated for C₅H₁₁O₂NClSP; C, 27.85; H, 5.142; N, 6.495; S, 14.867; Cl, 16.441 found: C, 27.93; H, 5.33; N, 6.25; S, 15.04; Cl, 16.61.
Methanolysis of cis-2-amino-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan in the presence of hydrochloric acid.

To pure cis-phosphoramidate, 0.216g (0.001mole), dissolved in 25 mL of methanol was added 1 mL of concentrated hydrochloric acid. The solution was allowed to stand for four days. Solvent was removed under reduced pressure, and the residue taken up in methylene chloride, washed with 4% aqueous KOH followed by water and dried over anhydrous magnesium sulfate. Magnesium sulfate was removed by filtration under reduced pressure to give a white precipitate. The nmr spectrum of the product indicated the existence of a small amount of the isomeric mixture of the methyl ester along with some ring opened product, nmr # 8.

Methanolysis of cis 2-amino-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan in the presence of p-toluene sulfonic acid.

The same procedure was followed as for the methanolysis of the phosphoramidate in the presence of hydrochloric acid except instead of using hydrochloric acid, p-toluene sulfonic acid was used. The yield was small and the nmr of the product was complexed and difficult to interpret, nmr # 9.
Methanolysis of cis-2-amino-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan in the presence of conc. sulfuric acid.

To the amide solution, 0.216g (0.001 mole), in methanol was added 2 mL of conc. sulfuric acid and the reaction mixture was allowed to stand for 5 days. Solvent was stripped off under reduced pressure, the residue taken up in methylene chloride, washed with 4% Aquous KOH solution followed by water and dried over anhydrous magnesium sulfate. The reaction mixture was filtered and methylene chloride was stripped off under reduced pressure to give a crystalline precipitate. The nmr spectrum of the final product gave evidence for the presence of an isomeric mixture of the desired methyl ester along with some methyl thioester, nmr # 10. Two peaks at 2.1 and 2.2 ppm were assigned to the protons of the thiomethyl group and peaks at 0.9 and 1.2 ppm were to the 5-methyl protons of the cis and trans ester respectively.

Diazotization of cis-2-amino-5-chloromethyl-5-methyl-2-thio-1,3,2- dioxaphosphorinan in the presence of methanol.

To the methanolic solution of the cis amide, 0.216g (0.001 mole), in 25 mL of methanol, sodium nitrite, 1.38g (0.02 mole), was added and through the mixture hydrogen chloride gas was passed for one hour with the reaction
vessel in an ice bath. The mixture was allowed to stand for two hours, filtered, washed with water and solvent removed under reduced pressure to give a sticky liquid. The liquid was extracted with methylene chloride and washed with 4% aqueous KOH. The organic layer was separated, dried over anhydrous magnesium sulfate, filtered and the methylene chloride removed under reduced pressure to give a solid product. The nmr spectrum of the product was complicated and difficult to interpret, nmr # 12.

**Preparation of 2-imidazolyl-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan.**

The procedure must be conducted under absolutely anhydrous conditions. Imidazole, 1.36g (0.02 mole), was dissolved in 50 mL of freshly distilled benzene. The solution was refluxed with with a Dean-Starke side arm in order to remove the last traces of moisture. To the solution held at 60-65°C (needed to keep imidazole in solution) was added 2-chloro-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan, 2.18g (0.01 mole), dissolved in 50 mL of freshly distilled benzene. The addition was carried out dropwise with stirring at such a rate as to maintain the temperature at 60-65°C. Maximum yields were obtained by conducting the addition under an inert atmosphere, dry nitrogen. The upper liquid was decanted from the viscous
precipitate and solvent removed under reduced pressure, 30 mm (warm water bath). On standing while tightly stoppered, the liquid residue slowly crystallized. By use of carefully dried glassware the residue was recrystallized from freshly distilled toluene. If the procedure is carried out carefully, very little, if any, toluene insoluble material is formed. The final product was dried under high vacuum, 0.1 mm (70°C), 1.45g (58% yield), mp 93-95°C. Anal: Calculated for C₈H₁₂ClN₂O₃P: C, 38.40; H, 4.80; N, 11.20; Found; C, 38.56; H, 4.91; N, 10.97. ¹H nmr : 1.02 ppm (CH₃), 3.78 ppm(CH₂Cl) Upon recrystallization from moist toluene a precipitate, insoluble in hot toluene, was formed, m.p 143-144°C. ¹H nmr ; 0.98 ppm (CH₃), 3.75 ppm (CH₂Cl). A CDCl₃ solution of the imidazole derivative slowly isomerized to give a new set of peaks, 1.21 ppm (CH₃), 3.65 ppm(CH₂Cl)

*Methanolysis of trans-2-imidazolylphosphorinan;*

The imidazole derivative obtained from the above procedure was placed in 10 mL of distilled methanol. The solution was allowed to stand at room temperature for an half hour, then solvent removed under reduced pressure (30 mm, 50°C). The viscous residue was taken up in 25 mL of water and the aqueous solution was extracted twice with 25 mL
portions of methylene chloride. The combined extracts were
dried over anhydrous magnesium sulfate and stripped at
reduced pressure. A white crystalline residue remained (85% yield) whose proton nmr spectrum was identical to that of
authentic cis methyl ester. $^1$H nmr; 0.93 ppm (CH$_3$), 3.80
ppm (CH$_2$Cl), 3.81 ppm (OCH$_3$).

Acid catalyzed methanolysis of trans-2-imidazolyl phosphorinan.

Procedure was repeated exactly as above with the exception that 10 mL of a 0.2M solution of p-toluene sulfonyl acid (0.002 mole) was added to 0.35g (0.0014 mole) of the phosphorylated imidazole. The residue obtained after the final stripping gave an $^1$H nmr spectrum identical to that of authentic trans methylester. $^1$H nmr; 1.25 ppm (CH$_3$), 3.51 ppm (CH$_2$Cl), 3.80 ppm (OCH$_3$),
($^3$POCH$_3$ 0.18 ppm.)

Preparation of methyl ester from the 2-chloro-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan

To the isomeric mixture of the chloridate, 2.67g (0.01 mole), was added methanol, 25 mL, and the solution refluxed for five days. The mixture was cooled and hydrogen chloride gas was passed through the solution for five hours. The reaction mixture was cooled in an ice bath. From this isomeric mixture of the ester, cis isomer, 1.0g (40% yield), was isolated by recrystallization from methanol, nmr # 18.
Reaction between cis 2-methoxy-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan and nitrous acid.

To a solution of the cis methyl ester, 0.250 g (0.001 mole), dissolved in 25 mL of methanol sodium nitrite, 0.69 g (0.01 mole), was added and through the mixture dry hydrogen chloride gas passed for two hours. The mixture was filtered, the solvent removed under reduced pressure and the solid residue taken in methylene chloride. The mixture was dried over anhydrous magnesium sulfate. The reaction mixture was filtered and methylene chloride was removed under reduced pressure to give a white precipitate. The nmr spectrum of the product confirmed it to be the same as that of the starting material, nmr #19. Therefore, it has been concluded from the result that the nitrous acid does not have any effect on the ester.

Reaction between 2-methoxy-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan and methyl iodide.

To methyl iodide, in a nmr tube, solid cis methyl ester was dissolved and the solution was allowed to stand for two weeks. The solvent was removed under reduced pressure to give a solid product. The nmr spectrum of the product gave evidence for the existence of methyl thioester in the reaction product, nmr #11. Two small peaks at 2.2 and 2.4 ppm were assigned to the protons of the thiomethyl group.
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<table>
<thead>
<tr>
<th>Isomer</th>
<th>AgNO₃ (moles/l)</th>
<th>Trans, %</th>
<th>Cis, %</th>
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</thead>
<tbody>
<tr>
<td>trans</td>
<td>0.1</td>
<td>62</td>
<td>38</td>
</tr>
<tr>
<td>trans</td>
<td>0.2</td>
<td>40</td>
<td>60</td>
</tr>
<tr>
<td>trans</td>
<td>0.4</td>
<td>25</td>
<td>75</td>
</tr>
<tr>
<td>cis</td>
<td>0.1</td>
<td>25</td>
<td>75</td>
</tr>
<tr>
<td>cis</td>
<td>0.2</td>
<td>61</td>
<td>39</td>
</tr>
<tr>
<td>cis</td>
<td>0.4</td>
<td>81</td>
<td>19</td>
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Solutions 0.1M in ester. Reactions carried out at both reflux and room temperature without a change in isomer ratios.
Table II. Methanolysis of Pyrophosphate Mixtures.

<table>
<thead>
<tr>
<th>Pyrophosphate</th>
<th>Catalyst</th>
<th>Trans, %</th>
<th>Cis, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>36% cis, 64% trans</td>
<td>Hg(OAc)$_2$</td>
<td>78</td>
<td>22</td>
</tr>
<tr>
<td>36% cis, 64% trans</td>
<td>Pb(OAc)$_2$·3H$_2$O</td>
<td>72</td>
<td>28</td>
</tr>
<tr>
<td>60% cis, 40% trans</td>
<td>Pb(OAc)$_2$·3H$_2$O</td>
<td>52</td>
<td>48</td>
</tr>
<tr>
<td>60% cis, 40% trans</td>
<td>Hg(OAc)$_2$</td>
<td>60</td>
<td>40</td>
</tr>
<tr>
<td>60% cis, 40% trans</td>
<td>Zn(OAc)$_2$·2H$_2$O</td>
<td>46</td>
<td>54</td>
</tr>
<tr>
<td>60% cis, 40% trans</td>
<td>t-BuOK</td>
<td>39</td>
<td>61</td>
</tr>
</tbody>
</table>

*aReactions 0.1M in pyrophosphate and catalyst. Reactions run at room temperature.*
Table III. Ratio of cis and trans 2,4-dinitrophenoxy phosphorinan obtained at different reaction times

<table>
<thead>
<tr>
<th>time (^a) (hr.)</th>
<th>trans (inv.),%</th>
<th>cis (ret.),%</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>96</td>
<td>4</td>
</tr>
<tr>
<td>1.5</td>
<td>93</td>
<td>7</td>
</tr>
<tr>
<td>2.5</td>
<td>73</td>
<td>27</td>
</tr>
<tr>
<td>72.0</td>
<td>6</td>
<td>94</td>
</tr>
</tbody>
</table>

\(^a\) Run in CH\(_3\)CN at room temperature.
Spectrum 1. NMR spectrum of cis-2-methoxy-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan in chloroform-d with TMS as internal standard.
Spectrum 2. NMR spectra of trans-2-methoxy-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan in chloroform-d with TMS as internal standard.
Spectrum 3. NMR spectrum of phosphorimide in chloroform-d with TMS as internal reference.
Spectrum 4. NMR spectrum of 7:8,5,cis:trans-2-chloro-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan in chloroform-d with TMS as internal reference.
Spectrum 5. NMR spectrum of trans-2-chloro-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan in chloroform-d with TMS as internal reference.
Spectrum 7. NMR spectrum of cis-2-amino-5-chloromethyl-5-methyl-2-thio-1,3,2-
dioxaphosphorinan in chloroform-d with TMS as internal reference.
Spectrum 8. NMR spectrum of methanolysis of cis-2-amino-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan in the presence of conc. HCl in chloroform-d with TMS as internal reference.
Spectrum 9. NMR spectrum of methanolysis of cis-2-amino-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan in the presence of para toluenesulfonic acid in chloroform-d with TMS as internal reference.
Spectrum 11. NMR spectrum of 2-thiomethyl-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan in chloroform-d with TMS as internal reference.
Spectrum 12. NMR spectrum of methanolysis of cis-2-amino-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan through diazotization in chloroform-d with TMS as internal reference.
Spectrum 13. NMR spectrum of phosphorinic acid in chloroform-d with TMS as internal reference.
Spectrum 14. NMR spectrum of cis-2-chloro-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan in chloroform-d with TMS as internal standard.
Spectrum 15. NMR spectrum of trans-2-amino-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan in chloroform-d with TMS as internal standard.
Spectrum 16. NMR spectrum of bicycrophosphite in chloroform-d with TMS as internal reference.
Spectrum 17. NMR spectrum of silver nitrate catalyzed methanolysis of trans-2-chloro-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan in chloroform-d with TMS as internal reference.
Spectrum 18. NMR spectrum of methanolysis of trans-2-chloro-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan by reflux method in chloroform-d with TMS as internal reference.
Spectrum 19. NMR spectrum of 2-methoxy-5-chloromethyl-5-methyl-2-thio-1,3,2-dioxaphosphorinan treated with nitrous acid in chloroform-d with TMS as internal reference.
Spectrum 20. NMR spectrum of phosphorylated imidazole in chloroform-d with TMS as internal reference.
Spectrum 21. NMR spectrum of methanolysis of phosphorylated imidazole in chloroform-d with TMS as internal reference.
Spectrum 22. NMR spectrum of acid catalyzed methanolysis of phosphorylated imidazole in chloroform-d with TMS as internal reference.