Stereochemistry of Reactive Intermediates in Organophosphorous Chemistry

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STEREOCHEMISTRY OF REACTIVE INTERMEDIATES IN ORGANOPHOSPHOROUS CHEMISTRY

BY

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A thesis submitted in partial fulfillment of the requirements for the degree of Master of Science
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STEREOCHEMISTRY OF REACTIVE INTERMEDIATES
IN ORGANOPHOSPHOROUS CHEMISTRY

This thesis is approved as a creditable and independent investigation by a candidate for the degree, Master of Science, and is acceptable for meeting the thesis requirements for this degree. Acceptance of this thesis does not imply that the conclusions reached by the candidate are necessarily the conclusions of the major department.

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To my wife, Usha
and son, Arun.
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STEREOCHEMISTRY OF REACTIVE
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Abstract
ALAGAPPAN THENAPPAN

A new synthetic route to produce a phosphonyl radical in the ground state has been devised. The radical is capable of maintaining its structural integrity and geometry. In polar aprotic solvents the radical can equilibrate depending upon reaction conditions. Our results are significant for they show that the homolytic cleavage of a phosphorous oxygen bond could by changing the configuration at phosphohrous, influence the biological properties of naturally occurring compounds.

The stereochemistry of 2-substituted-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinans can be established by proton NMR spectroscopy. Methanolysis of 2-hydrizinophosphorinans has been investigated. Cis and trans 2-hydrizinophosphorinans undergo acid catalyzed methanolysis to give products of both retention and inversion. The product ratio is dependent upon the strength of the acid used. Under strong acid conditions, the product ratio is nearly identical for both the cis and trans isomers. Stereochemical evidence for the participation of a phosphacylium ion-like intermediate is presented.
INTRODUCTION

Phosphorus plays a vital role in all life forms, and phosphate esters are the principal mode in which it performs its essential functions.¹

Phosphate esters are classified according to the number of alkoxide ligands present, Figure 1. Triesters are entirely covalent compounds which do not occur naturally. Mono- and di-esters contain ionizable hydrogen atoms which can be replaced by metallic or non-metallic cations, Figure 2.²

Phosphate esters find numerous applications as plasticisers, flame retardants, reagents in the preparation of organophosphorus polymers and in solvent extraction of heavy metal cations.

In biological systems, phosphate esters play important roles ranging from mobile energy sources such as pyrophosphates to purely structural functions as in the hereditary material deoxyribonucleic acid (DNA). Major energy storage and transfer mechanisms in all living systems involve the synthesis and breakdown of phosphate ester linkages such as those present in adenosine diphosphate, ADP,
Figure 2

and adenosine triphosphate, ATP, Figure 3.

ADP, n=1 and ATP, n=2

Structures of Un-ionized forms of ADP & ATP

Figure 3
While many phosphate esters play a central role in sustaining living systems, some are vehicles of death. Sarin is one of the deadliest of the so-called nerve gases, Figure 4. The lethal dose of this material for man may be less than 1 mg. These nerve agents are cholinesterase inhibitors; they chemically inhibit the transmission of nerve impulses.

Organophosphates (or organophosphonates) are recognized as active pesticides. Certain organophosphorus compounds have the ability to mimic naturally occurring carboxylic esters and hence inhibit essential enzymes (e.g. acetylcholinesterase). Organophosphorus insecticides are generally rapid acting, highly effective in small concentrations and have a low persistence. They are easily broken down to non-toxic materials. It is because of the importance to life and its functions, we chose to learn more about phosphorous compounds and their reactions.

A complete understanding of the chemistry of any class of compounds requires an understanding of the mechanisms by which
compounds react and in turn a description and chemistry of intermediates which form and disappear during the course of a reaction. Thus the main objective of this thesis is to find an acceptable system in which we can observe stereochemical evidence for the existence of reactive intermediates in organophosphorous chemistry. 

**Reactive Intermediates**

a) Phosphonyl Radicals:

Phosphorus radicals are frequently proposed as transient intermediates in many reactions. There are two main types of phosphorous radicals. The first type has seven electrons (one unpaired) in the valence shell of the phosphorous atom and is exemplified by either the phosphino radical, R$_2$P•, the phosphonyl radical, (RO)$_2$P=O or the phosphinium radical cation, R$_3$P$.^*$. The second type has nine electrons (one unpaired) around the phosphorous atom and is illustrated by the phosphoranyl radical, R$_4$P• (or (RO)$_4$P•) and by the phosphinium radical anion, R$_3$P$.^*$. It is the phosphonyl radical in which we are interested. It is characterised by a phosphorous atom doubly bonded to one oxygen and singly bonded to two oxygen atoms, Figure 5.

![Figure 5](image)
The radical can or cannot retain its configuration. An answer will be sought regarding the structure and geometry of the phosphonyl radicals in Part I of this thesis.

b) Phosphacylium Ion:

The phosphorous counterpart to a carbocation, "the phosphacylium ion" is another possible intermediate. It is characterized by a tetravalent structure, Figure 6.

![Figure 6](image)

Figure 6

Nucleophilic substitution at phosphorous has received considerable attention in recent years. It is generalized by Equation 1,

\[
\begin{align*}
\text{RO} & \quad \text{P} \quad \text{O} \\
\text{OR} & \quad \text{P} \quad \text{X} \\
& \quad \text{Y}^- \\
\text{Y} & \quad \text{P} \quad \text{OR} + \text{X}^- \\
\end{align*}
\]

where \( \text{Y}^- \) is the nucleophile and \( \text{X} \) is the leaving group. Mechanisms have been postulated on the basis of kinetic and stereochemical results. Depending on the conditions such as catalyst, attacking nucleophile and the nature of the leaving group four mechanisms of substitution at phosphorous are possible. They take one of two
directions, a stepwise bimolecular associative or a unimolecular
dissociative pathway. In the associative pathway three mechanisms
have been postulated. They are with inversion of configuration,
with retention of configuration and indiscriminate attack by the
nucleophile.

Associative type mechanisms at phosphorous have been studied
extensively in this laboratory and a series of papers have been
published outlining those factors which give rise to either
retention or inversion at phosphorous.\(^5\)

The unimolecular dissociative mechanism which might produce
a phosphacylium cation has been the subject of controversy. It
is directly analogous to the \(S_N1\) mechanism of carbon chemistry with
a carbocation as the intermediate. It is because these dissociative
mechanisms may closely exemplify those of biological systems that
they are under constant scrutiny. An acceptable system in which we
can observe substitution via a dissociative mechanism with a phos-
phacylium ion intermediate will be discussed in the second part of
this thesis.

In both the case of radicals and ions, the 2-substituted-5-
(chloromethyl)-5-methyl-2-oxo-1,3,2-dioxaphosphorinan system has
proved to be a most valuable system. The special qualities such
as conformational immobility, ease of isomer identification, ease
of establishing isomer ratios and ease of handling has made this
system an invaluable tool.
PART - 1

Phosphonyl Radicals
INTRODUCTION

Phosphonyl radicals have seven electrons (one unpaired) in the valence shell of the phosphorous atom. They are characterized by a phosphorous atom doubly bonded to one oxygen and singly bonded to two oxygen atoms, Figure 7. They should be represented as a resonance hybrid of three canonical forms, e.g. (a,b,c) but are more conveniently represented by structure b, Figure 8. Phosphonyl radicals have long been recognized as intermediates in some reactions of dialkylphosphites.  

Free radicals are believed to be responsible for the induction of certain types of cancer. Since cancer is in essence the mutation of a normal cell, any interaction of radicals with DNA or RNA could, in principle, initiate mutations. Since the backbone
of the nucleic acids is composed of phosphate ester moieties, one can immediately recognize the reason for a study of phosphorous radical chemistry. X-rays and γ-rays are used increasingly for sterilization and preservation of foods. Thus, it is important to understand the effect of such radiation on phosphorous compounds which occur naturally or artificially. It is conceivable that in certain cases radiation breaks a phosphorous-oxygen bond to generate a radical closely akin to a phosphonyl radical.

It appears that the configuration at phosphorous plays a vital role in membrane activity and any influences which change the configuration at phosphorous must have a pronounced effect on cell activity. Model studies by Tsai, et al., suggest that phospholipid membranes could be chiral at phosphorous and the configuration at phosphorous could be important in the structure and properties of membranes. Indeed there is increasing evidence for the involvement of the phosphate head group in protein-lipid interactions. Orientation and flexibility of head groups of phospholipids have been studied.

One possible means of altering the configuration is homolytic cleavage of a phosphorous oxygen bond either by radiation or by chemical means. Although possible, it is by no means certain that a cleavage of this type would lead to a configurational change. Thus the main question which this thesis will attempt to answer is whether a phosphonyl radical, generated in the ground state, does or does not retain its configuration. For our studies we generate the
phosphonyl radicals, \((RO)\_2^\cdot P=O\), in solution, and draw conclusions by examining product ratios.
Phosphonyl radicals in all cases have been generated photolytically and studied in terms of their EPR spectra.\textsuperscript{10-13}

In a related study, it was reported that the free radical addition of menthyl methylphosphinate to alkenes proceeds with inversion of configuration at phosphorus.\textsuperscript{14} Later K. Mislow and his coworkers have corrected the earlier work by reporting that the dibenzoylperoxide catalyzed addition of menthyl phenylphosphinate to cyclohexene occurs with retention of configuration.\textsuperscript{15} It is evident that phosphinate free radicals under the conditions employed appear to retain the geometry of their precursor.

Unlike phosphonyl radicals, phosphinate free radicals are characterized by a phosphorous atom doubly bonded to one oxygen and singly bonded to two different ligands, only one of which is an alkoxy group, Figure 9.

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{diagram.png}
\caption{Figure 9}
\end{figure}

Homolytic addition of dialkoxyphosphonyl radicals to benzene were detected by EPR and optical modulation spectroscopy.\textsuperscript{16} The rate constants for the addition was also studied. Also, phosphonyl radicals have been trapped by radical scavengers such as
t-nitrosobutane and the resultant relatively stable nitroso radicals, Figure 10, studied by EPR.17 Nothing is known about the geometry or structural integrity of phosphonyl radicals in chemical reactions. Our phosphorinan ring system, owing to its special qualities, lends itself to a study of the geometry and structure of phosphonyl radicals. By generating the radical in the ground state, under exothermic conditions from both cis and trans isomers, final product ratios will be an indication of the geometry of the intermediate radical.
Prior to this work, phosphonyl radicals were generated by photolysis of, or radical abstraction from either dialkyl (or aryl) phosphine oxides, Equation 2, O-alkyl alkylphosphinates, Equation 3, or dialkylphosphonates,\(^1\) Equation 4.

\[
\begin{align*}
\text{R}_2\text{PH} &\quad \xrightarrow{\text{hr}} \quad \text{R}_2\text{P}^* & (O)\text{II} \\
\text{RO} &\quad \xrightarrow{\text{hr}} \quad \text{RO}^* & (O)\text{II} \\
(\text{RO})_2\text{PH} &\quad \xrightarrow{\text{hr}} \quad (\text{RO})_2^* & (O)\text{II}
\end{align*}
\]

The problem encountered in attempting to study the geometry and structural integrity of phosphonyl radicals is the lack of a suitable system in which the configuration about the central phosphorous atom can be determined.

We are fortunate enough to have at our disposal a system
which lends itself to a study of the configuration about the central phosphorous atom. The system employed is the 2-substituted-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan system. It can exist as one of two possible geometrical isomers. The two isomers are distinguishable from one another by simple NMR measurements. Due to the lack of conformational mobility of the ring, the 5-methyl-hydrogens and 5-chloromethylhydrogens of cis and trans isomers have significantly different chemical shifts.

If a reaction is carried out on a known isomer and the product configuration is determined, the relative stereospecificity or non-stereospecificity can be studied. If a net stereospecificity of the reaction can be ascertained, we can make a judgment regarding the intermediates of the reaction. The radical can be generated from either of the two isomers and the geometry of the products arising from the radicals can be studied. The product ratio is an indication of the geometry of the intermediate radical.

In our first attempt to prepare a radical, it was decided to follow the work of Dr. A.G. Davies, et al.\textsuperscript{10} and generate the radical from 5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan, a cyclic hydrogen phosphite, Figure 11. The reactant needed for the preparation of the cyclic hydrogen phosphite is 2-chloro-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan, the chloridate. It is prepared by treating methyl bicyclic phosphite with sulfuryl chloride in the normal Arbuzov manner,\textsuperscript{18} Equation 5. Arbuzov reactions entail the reaction of trialkylphosphites with an alkylhalide to give
dialkylphosphonate, Equation 6. The reaction of methylbicyclic phosphate with sulfuryl chloride gives only one isomer, the cis-chloridate due to the mode of displacement. Its geometry is a consequence of the mechanism of the Arbuzov reaction. The 5-chloromethyl group and the phosphoryl oxygen are on the same side of the ring in
the case of the cis-configuration, whereas in the trans isomer the
two groups are on the opposite sides of the phosphorinan ring system,
Figure 12.

Since lithium aluminum hydride is known to convert dialkyl-
phosphinyl chloride, \([R_2P(O)Cl]\), to dialkyl phosphineoxide,
\([R_2P(O)H]\), an attempt was made to reduce the cis-chloridate
using the same reagent in ether solution. The expected cyclic hydro-
gen phosphite did not form. Instead ring opening occurs to give
2-chloromethyl-2-methylpropane-1,3-diol, Equation 7, in very low
yield. The product obtained was isolated and purified. The NMR
spectrum and the melting point were identical to an authentic com-
 pound prepared previously. In a second attempt, the reducing
agent was poisoned using three equivalents of tertiary butyl alcohol.
Reduction of the chloridate was carried out under similar conditions
with the new poisoned reducing agent. Again the formation of 2-
chloromethyl-2-methylpropane-1,3-diol as the only isolable product
indicates that the phosphorinan ring system is not stable to reducing conditions.

In a more direct approach to the cyclic hydrogen phosphite, 2-chloromethyl-2-methylpropane-1,3-diol was treated with diethyl hydrogen phosphite, Equation 8. The reaction was carried out at an elevated temperature with toluene as solvent. The reaction did not proceed to give the desired cyclic product even under reflux conditions. Recovery of the reactants after the removal of solvent
confirms that reaction did not take place. Having realized that the phosphorinan ring system is susceptible to reducing agents, a different approach was selected to prepare the phosphonyl radical. The approach selected was an oxidative pathway. Prior work suggests that hydrazine derivatives constitute a very useful group of radical initiators. The formation of a molecule of nitrogen provides a strong driving force for dissociation. An attempt was made to prepare phosphonyl radicals in the ground state by oxidizing a hydrazine derivative of the phosphorinan ring system.

**Preparation of trans-2-Hydrazino-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan, the trans-Hydrazide.**

The trans-hydrazide prepared from cis-chloridate is required as a precursor. Treatment of two equivalents of hydrazine with cis-chloridate gives the trans-hydrazide, Equation 9. The reaction proceeds by inversion to give only one isomer, the trans-hydrazide which is typical for all non-charged amines. Inversion can be explained on the basis of a lack of backbonding between the nucleophile and phosphorus. The chemical shift values of the 5-methyl
hydrogens is proof that the chloromethyl group is equatorial which places the new ligand also equatorial. This structural assignment is entirely in agreement with simple amides prepared from the cis-chloridate and primary or secondary amines. The conformations of the latter have been determined by X-ray crystallography.\textsuperscript{23}

Elemental analysis conforms to the expected empirical formula of the product. Derivatives of the trans-hydrazide prepared from both acetone and benzaldehyde conclusively confirms the structure, Scheme I. The different chemical shifts of the methyl groups a and b (Scheme I) in the acetone derivative indicates that the groups are in a different environment. This suggests that the derivatives could have a spirophosphorane ring structure. In a model compound such as 2-N,N-dimethyl-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan, Figure 13, only one peak is observed for the N-methyl hydrogens. Absence of a peak at 1689-1471 cm\textsuperscript{-1} due to C=N stretching in the IR spectrum strongly suggests the possibility of the spirophosphorane ring structure for the derivatives. The ring structure was also suggested by the NMR spectrum of the acetone derivative at elevated temperatures. The two methyl peaks failed to coalesce to give a simple broad peak even upon reflux of a deuterated dimethylsulfoxide solution of the derivative. Appearance of a weak peak at about 150 ppm in the completely decoupled \textsuperscript{13}C NMR spectrum is evidence of a non-protonated carbon atom.\textsuperscript{24} Such a carbon atom appears in both the straight chained and cyclic structure.

In order to oxidize the trans-hydrazide, tertiary butyl-
Scheme I
hypochlorite was selected as the oxidizing agent. Tertiary butyl-hypochlorite is known to convert amines to N-chloroamines. It is soluble in many organic solvents and the bulky hydrocarbon moiety, for steric reasons, does not combine with the phosphorinan ring system. In fact, we have never been able to isolate the 2-tertiary-butoxy ester, Figure 14, under any conditions.
Oxidation of trans-Hydrazide in Tertiary butylalcohol.

Treatment of trans-hydrazide with two equivalents of tertiary butylhypochlorite at an elevated temperature (~50°C) gives a new product, trans-chloridate, in high yield, Scheme II. Tert. butyl-

Scheme II

alcohol, water and tert. butylchloride were isolated as byproducts. A quantitative evolution of nitrogen gas was measured. Trans-chloridate was the only isomer formed; the other isomer was not detected. The chemical shifts of hydrogens on the 5-methyl group are, as expected, downfield from those of the corresponding cis isomer. The
structure of the new product, the trans chloridate, was confirmed by conversion with primary and secondary amines to known amides, Scheme III. Attempted recrystallization of the new product from hot water produced a stable pyrophosphate, Equation 10.

In the solvent t-butyl alcohol, the ratio of hydroxyl groups to hydrocarbon moiety is relatively low. The tertiary butoxy radical, if formed, does not recombine with the phosphonyl radical
due to steric reasons. The phosphonyl radical produced combined with the chlorine radical to give the phosphorochloridate with retained stereochemistry. This is true even though the isomer formed is thermodynamically the least stable. The lifetime of the phosphonyl radical must have been very short and recombination with the chlorine radical may have taken place within the solvent cage. The fact that the least stable chloridate is exclusively formed, suggests that the phosphonyl radical retains its original geometry. The phosphorous atom, unlike the carbon radical, does not rehybridize nor does the radical approach planarity. The nature of the byproducts and the fact that t-butylhypochlorite readily converts amines to N-chloroamines suggests that our proposed mechanism is correct; chloridate is formed via a phosphonyl radical. Cyclic hydrogen phosphite cannot be an intermediate in chloridate formation; t-butylhypochlorite under identical conditions does not oxidize diethylhydrogen phosphite to give phosphorochloridate, Equation 11.
Oxidation of trans-Hydrazide in Benzene.

Treatment of trans-hydrazide with two equivalents of tertiary butyl hypochlorite in benzene at an elevated temperature gives a dark viscous liquid. Several attempts to purify the viscous liquid have failed.

Oxidation of trans-Hydrazide in Acetonitrile.

In the solvent acetonitrile, treatment of trans-hydrazide with two equivalents of tertiary butylhypochlorite gives a mixture of isomeric chloridates with the retention product as the predominating isomer. Again, the products were identified not only via NMR spectroscopy but also by conversion to a known amide. It appears that the lifetime of the radical is increased in acetonitrile, and this increased lifetime could have led to the isomeric mixture. A second possibility could be due to the polar nature of the radical transition state. This could be especially true where the counter radical involved is highly electronegative, Figure 15. In the second part of this thesis ample evidence will be given to show that the phosphorous cation, unlike the radical, does not retain its geometry. At this stage, it is conceivable that the solvent has an important role in deciding the geometry and structure of the phos-
Phosphonyl radical. Polar solvents with a high dielectric constant enable a radical transition state with some ionic character to form. The polarized radical may not completely retain its geometry.

The results obtained in tetrahydrofuran are the same as those found in acetonitrile, Table I. These results confirm that the phosphonyl radical produced in the ground state may equilibrate slowly in polar solvents.

**Oxidation of trans-Hydrazide in Isopropylalcohol.**

Upon oxidation of the trans-hydrazide with two equivalents of tertiary butylhypochlorite in isopropylalcohol, the solvent is preferentially oxidized to acetone. The reaction is exothermic. Under the reaction conditions acetone is removed leaving behind the substrate unreacted.

**Oxidation of trans-Hydrazide in Methanol.**

In the solvent, methanol, the results obtained are quite different. Oxidation of hydrazide with two equivalents of tertiary
Table I. Oxidation of trans-Hydrazide with two Equivalents of Tertiary Butylhypochlorite in Different Solvents.

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Chloridate Ratios</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% cis (Inversion)</td>
<td>% trans (Retention)</td>
</tr>
<tr>
<td>tert. BuOH</td>
<td>-</td>
<td>100</td>
</tr>
<tr>
<td>CH$_3$-C≡N</td>
<td>37</td>
<td>63</td>
</tr>
<tr>
<td>T.H.F.</td>
<td>37</td>
<td>63</td>
</tr>
</tbody>
</table>
butylhypochlorite gives a mixture of methyl ester isomers, in the thermodynamic ratio\textsuperscript{22} with the cis predominating. An initial interpretation of the result suggests that chlorine radical prefers to abstract a hydrogen radical from the solvent. The resulting methoxy radical could have combined with the phosphonyl radical to give a high yield of methyl esters. Actually the phosphonyl radical does not form in methanol. Hydrochloric acid generated in the reaction catalyzes the methanolysis of the 2-hydrazoneadduct perhaps via a phosphacylium ion (Part II).

**Trapping Attempts**

K.U. Ingold, et al. have successfully trapped simple phosphonyl radicals with 2,4,4-trimethylpent-2-ene.\textsuperscript{13} The resulting adduct radical is studied in terms of its EPR spectra. In a similar attempt to trap our phosphonyl radicals generated by oxidation of trans-hydrazone, preferential oxidation of the substituted pentene is observed. Reactants are recovered after the removal of the solvent.

**Preparation of cis-2-Hydrazone-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan, the cis-Hydrazone.**

Treatment of trans-chloridate prepared from trans-hydrazone, Scheme II, with two equivalents of hydrazine gives the cis-hydrazone, Equation 12. Since hydrazides are prone to acid hydrolysis, this reaction must be carried out under completely dry conditions. Surprisingly, the cis-hydrazone does not have its 2-substituent group in the equatorial position. The NMR data indicates that the
hydrazine moiety in the cis-isomer is axial, which is different from the simple phosphoramidates, Table II. The same anomaly is true in the case of the cis-amide analogue prepared by treatment of trans-chloridate with gaseous ammonia, Equation 13. It appears that in these two exceptional cases, that the desire of the ring to attain a stable conformation overcomes the stabilization due to an anomeric effect, an effect exclusively felt by amido groups when they are in the equatorial position. Interaction, 1,3-dipolar and relief of steric strain could have also contributed to the conformational irregularity. X-ray crystallography studies have shown that 3,cis-2-oxo-2-(dimethylamino)-5-tert. butyl-1,3,2-oxaazaphosphorinan, Figure 16, adopts a chair conformation with the 2-substituent in the axial position. Steric effects of the t-butyl group at the 5-position
Table II. Chemical Shifts of 5,5-disubstituted-2-amino-1,3,2-dioxaphosphorinans.\textsuperscript{a}

\[
\begin{align*}
\text{trans} & & \text{cis} \\
\begin{array}{|c|c|c|c|c|}
\hline
R & \text{CH}_3 & \text{CH}_2\text{Cl} & \text{CH}_3 & \text{CH}_2\text{Cl} \\
\hline
\text{NC}_5\text{H}_{11} & 0.98 & 3.83 & 1.28 & 3.60 \\
\text{NHC}(\text{CH}_3)_3 & 0.95 & 3.70 & - & - \\
\text{NHC}_6\text{H}_5 & 0.99 & 3.51 & - & - \\
p-\text{NHC}_6\text{H}_4\text{OCH}_3 & 0.90 & 3.68 & - & - \\
\text{NHCH}_2\text{C}_6\text{H}_5 & 0.90 & 3.62 & 1.11 & 3.45 \\
\hline
\end{array}
\end{align*}
\]

\textsuperscript{a}Measured with a Varian A-60A instrument. In parts per million downfield from external TMS in CDC\textsubscript{13}.
Figure 16

is greater than that of dimethylamino group at the 2-position. This larger steric effect of the t-buty1 group forces the dimethylamino group to be axial rather than equatorial.

**Oxidation of cis-Hydrazide in Tertiarybutanol.**

Treatment of cis-hydrazide with two equivalents of tert. butylhypochlorite in tert. butanol gives a mixture of isomers of the chloridate with the retention product as the predominating isomer. Again, the products were identified not only via their NMR spectra but also by conversion to known amides. No tert. butyl ester is formed. The reason for the partial isomerization of the radical can be rationalized on the basis that the radical tends to attain a most stable ring conformation. Interaction, 1,3-dipolar, could have led the less stable radical to leak to the more stable one, Equation 14. Solvents such as methylene chloride used in the process of purification of the chloridate, do not cause isomerization. Upon standing at room temperature for 24 hours, a sample of trans-
chloride dissolved in methylene chloride showed no evidence of isomerization.

The factors which influence the lifetime of the phosphonyl radical were investigated. The nature of the solvent has a role to play in varying the lifetime of the phosphonyl radical as evident from Table I. In addition, the lifetime of the counter radical could influence the conformational stability of the phosphonyl radical. In order to acquire more knowledge in this area, several approaches were taken to increase the lifetime of the counter radical involved in the oxidation of the hydrazides. Attempts were made to prepare a trans-2-alkyl(aryl)hydrazino adduct by reacting trans-hydrazide either with methyl iodide, acetic anhydride or benzyl chloride. The attempts were not successful due to the fact that the amino group of the 2-substituent position is not basic enough to be alkylated or acylated. In a more direct approach, treatment of cis-chloridate with two equivalents of phenyl hydrazine gave the trans-phenyl hydrazinoadduct in high yield, Equation 15. Due to lack of backbonding between the incoming group and phosphorous, inversion takes place exclusively. As in the case of simple
hydrazides, only one isomer, the trans isomer is formed. The structural assignment is based on NMR chemical shift values.

In an attempt to oxidize the trans-phenylhydrazide in tertiarybutanol using two equivalents of tertiarybutylhypochlorite, the phosphorinan ring, as evidenced from the spectrum of the product, opens to give unknown products. Though the reason is not exactly known, one possibility could be that the oxidizing agent used was too strong.

Previous studies indicate that yellow mercuric oxide can be effectively used as an oxidizing agent to produce azo compounds from substituted phenylhydrazides. Accordingly, oxidation of trans-phenyl hydrazide in benzene with yellow mercury oxide gives the azo intermediate, Equation 16. Isolation of an equivalent of water and mercury as the byproducts confirms that oxidation takes place. A dimethyl formamide solution of the presumed azo compound was heated at an elevated temperature. Although nitrogen was evolved, the
phosphorinan ring system apparently was not retained. The NMR spectrum of the product closely resembled the spectrum of biphenyl.
SUMMARY

A new synthetic route to produce a phosphonyl radical in the ground state has been devised. The radical is capable of maintaining its structural integrity and geometry. In polar aprotic solvents the radical can equilibrate depending upon reaction conditions. Our results are significant for they show that the homolytic cleavage of a phosphorous oxygen bond could by changing the configuration at phosphorous, influence the biological properties of naturally occurring phosphorous compounds.
PART - II

Phosphacylium Ion
INTRODUCTION

The recognition of monoesters of phosphoric acid as important intermediate metabolites and diesters of phosphoric acid as important components of nucleic acids has led to extensive investigations into all aspects of the chemistry and biological action of phosphate esters. Energy transducers in bio-chemical systems such as phosphoric anhydrides (ATP), phosphoramides (phosphocreatine) or enol phosphates (phosphoenolpyruvate) involve the synthesis and breakdown of phosphate ester linkages. An understanding of the mechanisms of phosphorylation and dephosphorylation are paramount to an understanding of the role of many important phosphorous compounds in life.

The mechanisms by which phosphate esters undergo chemical transformations are not well understood. Mechanisms in organophosphorous chemistry have always been interpreted based on analogy to classical carbon chemistry mechanisms. This is especially true in the comparison of carboxylic acid esters with phosphoric acid esters. Many reactions of phosphate esters have been postulated to take place by way of two major mechanisms. One major mechanism of phosphorylation is analogous to the $S_{N2}$ reaction of carbon chemistry whereas the other involves pentacoordinated intermediates. Beside these two associative mechanisms, a dissociative pathway which involves either monomeric metaphosphate or a phosphacylium ion as an intermediate is possible. The latter is in rough analogy to the $S_{N1}$ reaction found in carbon chemistry. Although there are many examples of displacement at phosphorous proceeding by associative pathways, there are only a
few authentic examples of the dissociative route.\textsuperscript{29,30}

**Dissociative mechanism**

Carboxylic acid esters can undergo displacements via a dissociative route, a mechanism which involves an acylium ion intermediate. Acylium ions have been recognized as intermediates in certain organic reactions for many years. They exist as a positively charged species. According to valence terminology, the charge is distributed between carbon and oxygen, Figure 17. Due to the high electronegative nature of oxygen, the charge is assumed to exist primarily on carbon. Since every atom of the acylium ion has an octet of electrons, they are more stable than carbocations. They have been detected by cryoscopic methods. Early studies have shown that acylium ions are generated when an orthosubstituted benzoic acid is dissolved in sulfuric acid,\textsuperscript{31} Equation 17. They can also be produced by

$$R^+ - C = O$$

\text{(Figure 17)}

$$R^+ - C = O$$

Electron transfer reactions
Friedel-Crafts acylation reactions. Addition of a Lewis acid such as aluminum chloride to certain alkyl halides produces the acylium ion, Equation 18. Acylium ions generated in this manner can act as electrophiles, Equation 19. Acylium ions do not undergo the rearrangements which are so common with carbocations.

By analogy, the phosphorous counterpart, the phosphacylium ion, Figure 18, might be an intermediate in the dissociative displacement reactions of phosphoric acid esters. Our objective in this
section is to find a suitable system which will give us direct stereochemical evidence for the participation of a phosphacylium ion. The system we used is again the 2-substituted phosphorinan ring system. It is ideally suited for the detection of a phosphacylium ion as an intermediate in a displacement reaction at phosphorous. Elaborate studies in the past have shown that the possible geometrical isomers (cis and trans) are conformationally immobile.\(^{22,18,5}\) Both cis and trans isomers of reactants and products are distinguishable by simple NMR measurements. If both the cis and trans isomers of the reactant give identical product ratios, a common intermediate is highly probable.

Prior to this work there was no strong stereochemical evidence to support either the existence of a phosphacylium ion as an intermediate or a dissociative displacement. This thesis will present the first stereochemical evidence for the participation and existence of a phosphacylium ion.
HISTORICAL

Substitution at phosphorous in phosphate systems has traditionally been postulated as proceeding through associative pathways. The intermediate or transition state has a pentacoordinated phosphorous atom, Equation 20. Many lines of evidence, based on kinetic and stereochemical results,\textsuperscript{32} have been developed to support this mechanism. Isotope labelling has also been used to establish the type of P-X bond cleavage.\textsuperscript{33} As required by any bimolecular transition state, the entropy of activation for most of the reactions following the associative pathway is moderately large and negative. Displacement reactions at a tetrahedral phosphorous proceeding by a dissociative pathway are few and largely confined to phosphate derivatives. Dissociative mechanisms have been promoted by a number of laboratories to explain the reactivity of ATP and p-nitrophenylphosphate esters under certain conditions.\textsuperscript{34-40} It is now generally accepted that substitution with certain simple ionic phosphate esters take place not by direct attack on the phosphorous atom, but by a unimolecular elimination mechanism. Most involve a hypothetical
metaphosphate intermediate. The possibility of a unimolecular mechanism by way of a monomeric metaphosphate ion has been studied extensively by Westheimer and his coworkers.

**The Monomeric Metaphosphate Mechanism**

Monomeric metaphosphate ion, $\text{PO}_3^-$, is thermally stable. It has been detected in the gaseous phase in a negative ion mass spectrometer. It readily reacts with nucleophiles or polymerizes to various phosphates. Monomeric sodium metaphosphate has been prepared at high temperatures (1600°C), trapped in a liquid argon matrix and identified by infra-red spectroscopy. Monomeric methyl metaphosphate can be generated by the decomposition of a beta-halophosphonate, Equation 21. The reaction is stereospecific and involves a trans-elimination. The erythro isomer yields the E-olefin, whereas the threo isomer yields the Z-olefin. The metaphosphates generated in these reactions are strong electrophiles and will attack the activated aromatic rings of substituted anilines at -80°C, Equation 22. Although most of the product isolated in this reaction consisted of polymeric methyl metaphosphate, electrophilic substitution took place to give a low yield of aromatic phosphonic acids. Only a powerful electrophile can give rise to substitution products under these experimental conditions. The extent of aromatic substitution is
dependent upon the solvent employed. Nucleophilic solvents, such as acetonitrile and dioxane, almost quench the substitution reaction. The metaphosphate acting as an electrophile adds to the unshared electron pairs of acetonitrile and dioxane to produce a less active and more selective phosphorylating agent. The new agent produced can attack the nucleophilic nitrogen of methylaniline, but not the ring. Methylmetaphosphate has been trapped successfully by a number of reagents, i.e., acetophenone. Here the metaphosphate attacks the carbonyl group of the ketone to produce a ketophosphate, Equation 23. The initial product, the ketophosphate, tautomerizes to the more stable enol form. The preparation of enolphosphates can also be
achieved with a monomeric metaphosphate ion in place of methyl metaphosphate. In addition to the reaction of metaphosphates with ketones to yield enol phosphates, they can be used to promote the formation of Schiff bases, Equation 24. F. Ramirez, et al., has found two

additional methods to generate the metaphosphate ion in solution. Either reaction of 2,4-dinitrophenylphosphate(1) or erythro-1-phenyl-1,2-dibromopropylphosphonic acid(2) with base at 25°C readily gives the metaphosphate ion, Scheme IV. As in previous studies, the
metaphosphate ion was trapped with a nucleophile. The nucleophile used in this case was an equimolar mixture of methanol and t-butanol. Reaction of metaphosphate ion towards nucleophiles is selective. The ion showed preference for methanol over tertiary butanol presumably for steric reasons.

I. Oney, et al., have reported that the solvolysis of dimethylphosphoramidate, [(CH₃O)₂P(O)NH₂], proceeds via a metaphosphate intermediate. It undergoes phosphorous-oxygen bond cleavage in dilute alkali. A special mechanism proposed by P.S. Traylor and his associates for the alkaline hydrolysis of N,N'-dipropylphosphorodiamidic chloride involves the formation of an anion of the phosphorodiamidate as an intermediate, Equation 25. Based on kinetic
results, considerable support for the formation of a monomeric metaphosphate intermediate is advanced.

The possible participation of a phosphacylium cation formed during nucleophilic substitution has been investigated in only a few laboratories.\textsuperscript{47-50} The possibility for formation of such an intermediate through a dissociative mechanism has usually been regarded to be very low. Haake and his coworkers have found evidence for its participation in the hydrolysis of sterically hindered chlorophosphinates\textsuperscript{47} and phosphinamides.\textsuperscript{48} Rearrangement of bis(5,5-dimethyl-2-oxo-1,3,2-dioxaphosphorinanyl) sulfoxide may involve a dissociative mechanism,\textsuperscript{51} Equation 26. Isotope labelling experiments and kinetic studies have clarified the positions of attack by water on the tripolyphosphate chain of ATP and on the diphosphate chain of ADP at
pH values ranging from 0 to 8.3. At very low pH values, the non-
enzymatic hydrolysis proceeds by addition-elimination pathway where-
as at pH 8.3, the hydrolysis occurs by elimination-addition. Over
the entire pH range studied, no oxygen exchange was detected between
water, ATP, ADP and inorganic phosphate. J. Michalski and his co-
workers looked for stereochemical evidence for the existence of a
phosphacylium cation during nucleophilic displacement at a tetra-
coordinate phosphorous ester. They used a mixed phosphorous-
sulfonic anhydride, chiral at phosphorous, to study the stereo-
chemistry, Figure 19. The system they selected is ideally suited

![Figure 19](image)

for the study; the leaving group has favorable electronic characteris-
tics for a unimolecular dissociation. Evidence that the transition
state in the alkaline hydrolysis of the optically active mixed an-
hydride is relatively polar was found. That a phosphacylium ion
acts as an intermediate in the hydrolysis is still uncertain,
Equation 27. Since the hydrolysis was stereospecific, proceed-
ed by complete inversion, there is no likelihood for cation
formation. In analogy with carbon chemistry, formation of the ion
would be expected to lead to racemization. It would appear that the intermediate in the hydrolysis contains a pentacoordinated phosphorous atom with a leaving group and attacking nucleophile attached concurrently.

That pentavalent, tetracoordinate phosphorous is reluctant to react by a dissociative mechanism was explained on the basis of changes in bond energies.\(^{47}\) The reluctance of tetracoordinate pentavalent phosphorous to reduce its coordination number was summarized: "The energy of solvation of the dissociated species plus the increase in bond energy in the remaining bonds is less than the bond energy of the bond which breaks in the dissociation," Equation 28. Phosphinic acids, \(R_2PO_2H\), and their derivatives have been studied by NMR and by cryoscopic methods. Freezing point depression studies
have disproved the existence of a phosphacylium ion.

Further, a number of additional studies on biological systems should be mentioned. G. Lowe and his associates have reported that phosphoryl transfer in adenosine triphosphate occurs by a dissociative mechanism.\textsuperscript{54} This transfer is catalyzed by rabbit muscle pyruvate kinase. Conversion of uridine triphosphate (UTP) to cytidine triphosphate (CTP) by the enzyme CTP-synthetase was shown to occur via a tetrahedral intermediate.\textsuperscript{55} Rose and his coworkers have proposed enolpyruvate as a transient intermediate in the enzymatic reaction of phosphoenolpyruvate (PEP) with phosphatase,\textsuperscript{56} Equation 29.
For the reaction of inosinic acid with L-aspartate to yield adenylosuccinate, evidence was presented by Libermann for the transfer of carbonyl oxygen to inorganic phosphate,⁵⁷ Scheme V. Though the

\[
\begin{align*}
\text{HO}_2\text{C} & \text{CH} \text{CH}_2 \text{CO}_2\text{H} \\
\text{N} & \text{H} \\
\text{O} & \text{H}
\end{align*}
\]

\[
\begin{align*}
\text{OH} & \text{N} \\
\text{O} & \text{H}
\end{align*}
\]

r ibose-5'-phosphate

+ GTP

\[
\begin{align*}
\text{ribose-5'}-\text{phosphate} & \text{GDP} + \text{Pi}
\end{align*}
\]

Adenylosuccinate $\rightarrow$ A5P + (fumarate)

A5P $\rightarrow$ adenosine-5'-phosphate

GTP $\rightarrow$ Guanosine triphosphate

Scheme V

mechanisms of these bio-chemical reactions are not known in detail, they are at least in a formal sense, parallel to the one studied by Westheimer and Ramirez; a metaphosphate ion involved as an intermediate in dissociative displacement reactions. These studies enhance the possible existence of a dissociative displacement reaction. Dissociative displacements might occur either via a monomeric metaphosphate or by a dialkoxyphosphorous cation (phosphacylium ion). Proof for the existence of a cation should have great biological implications. The fact that a cationic intermediate has not prior to
this time been detected or described makes our study timely.
SYNTHESIS, RESULTS AND DISCUSSION

Although the $S_N^2(P)$ mechanism is familiar in phosphorous chemistry, evidence for a $S_N^1(P)$ mechanism has been slow to appear. The most convincing evidence for the existence of a dissociative mechanism has been presented by Westheimer, Ramirez and their co-workers. Their proposal involves a monomeric methyl metaphosphate as an intermediate. Authentic stereochemical evidence for a dissociative displacement, however, has not been presented.

The 2-substituted-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan system has proven to be a most valuable system in determining the stereochemistry of substitution reactions. In the presence of a good leaving group at the 2-substituent position, the phosphorinan ring system undergoes solvolysis both by retention and inversion. Factors which give rise to either retention or inversion at the phosphorous atom have been studied extensively in this laboratory. One deciding factor is the extent of backbonding between attacking nucleophile and the phosphorous atom. Efficient backbonding leads to retention whereas inversion is favoured by nucleophiles which are poor backbonders. An increase in the positive character at the phosphorous atom can increase the efficiency of backbonding. Either electron withdrawing ligands attached to the phosphorous atom or Lewis acids bonded to the basic phosphoryl oxygen can increase the positive character of the phosphorous atom.

In the earlier part of this thesis, we mentioned that the oxidation of trans-2-hydrazino-5-chloromethyl-5-methyl-2-oxo-1,3,2-
dioxaphosphorinan, the trans hydrazide, in methanol with tert. butyl-hypochlorite gave a mixture of isomeric methyl esters. The formation of the esters could have occurred by heterolysis, acid catalyzed solvolysis. This led us to investigate the acid catalyzed solvolysis of the 2-hydrazino adduct. It is important to note that in the absence of an acid catalyst substitution does not occur.

**Methanolysis of Hydrazides using Hydrogen Chloride as Catalyst**

Passing hydrogen chloride gas through a solution of the trans-hydrazide in methanol gives a mixture of isomeric methyl esters with the inversion product as the major isomer (81%), Scheme VI. The cis-hydrazide, in contrast, under identical conditions gives 67% of its inversion product. These room temperature reactions are much faster than the corresponding methanolysis of 2-N,N-dimethylamido-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan which proceeds very slowly by 100% inversion. Other phosphoramidates have also been reported to undergo acid catalyzed solvolysis by 100% inversion.\(^{58}\) Since the hydrazides give both inversion and retention and at a faster rate, they must solvolyze by a mechanism which is different from that of the phosphoramidates.

In the case of the hydrazides, the high percentage of inversion is a consequence of monoprotonation of the leaving group by the relatively weak acid, hydrogen chloride. As a result of monoprotonation and the resulting negative inductive effect, the bond to the leaving group is stretched. Bond stretching increased the positive character at the phosphorous atom with the positive reactive site attacked by
Scheme VI
the nucleophile predominantly from the backside in an $S_N2$ fashion. The fact that retention is also observed must mean that bond breaking is farther along in the transition state than in the case with simple amides where 100% inversion is observed. The greater retention in the cis-case, Scheme VI, can be explained by assuming that bond breaking in the transition state is even more advanced than is the case in the methanolysis of the trans-hydrazide. Dipolar interactions would be expected to be greater in the cis starting material ($\text{NH}_2\cdot\text{NH}$-axial) than the trans and steric effects would accelerate the departure of the leaving group. In the case of the trans-isomer, attack of the nucleophile occurs before complete departure of the leaving group to give a transition state with considerable positive character at phosphorous. In the case of the cis-isomer, tendency towards planarity may take place and attack of the nucleophile occurs from both sides of the plane to give more of the retention product, Scheme VII.

**Attempts to Stabilize the Positively Charged Intermediate: - Solvent Effects**

Solvents with high dielectric constant are known to stabilize ionic species. In an attempt to stabilize the possible phosphacylium ion-like intermediate, methanolysis was carried out in an equal volume of acetonitrile and methanol. Treatment of trans-hydrazide with gaseous hydrogen chloride in the solvent mixture gives a very low yield of methyl esters and a large quantity of crystalline product. Single crystal neutron diffraction studies indicate that acetonitrile reacts
Planar transition State

Scheme VII
with hydrogen halides to give crystalline imminohydrohalide, Figure 20.

\[
\begin{array}{c}
\text{H}_3\text{C} \\
\text{C} \equiv \text{N} \\
\text{Cl} \\
\text{H} \\
\end{array}
\quad [\text{Cl}]^-
\]

Figure 20

Treatment of cis-hydrazone with gaseous hydrogen chloride in an equal volume of methanol and acetonitrile gives exclusively imminohydrochloride as the only product. In another attempt, trans-hydrazone, dissolved in an equal volume of methanol and dimethylformamide, which had not been previously distilled, was treated with gaseous hydrogen chloride. The only product isolated was 2-hydroxy-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan, Figure 21.

\[
\begin{array}{c}
\text{ClH}_2\text{C} \\
\text{O} \\
\text{P=O} \\
\text{H}_3\text{C} \\
\text{O} \\
\text{O} \\
\end{array}
\]

Figure 21

It appears that the trans-hydrazone in the presence of even a very low concentration of water and acid, undergoes instantaneous hydrolysis
to give the stable 2-hydroxy phosphorinan. It is evident from this experiment that hydrazides are prone to acid hydrolysis and water must be excluded completely in their reactions.

**Methanolysis of Hydrazides using Different Acid Catalysts**

Treatment of the trans-hydrazide in methanol with 50% (by volume) of trifluoroacetic acid (TFA) gives a mixture of isomeric methyl esters. In contrast to catalysis by HCl, the major product in this room temperature solvolysis is the trans-isomer, the retention product, Scheme VIII. Most interestingly, treatment of cis-hydrazide, under identical conditions gives almost the same product ratio. The results are best explained by assuming a change in mechanism from a predominate associative route in the HCl catalyzed solvolysis to a predominate dissociative pathway under strongly acidic conditions. The change in mechanism with strength of the acid may be accounted for by diprotonation and formation of a superior leaving group, Figure 22. Though our proposed mechanism is contrary to the fact that two positively charged atoms cannot be adjacent to each other, there is a likelihood of a second proton approaching only after the phosphorous-nitrogen bond has undergone considerable stretching and the second nitrogen has acquired negative character. When a methanolic solution of trans-hydrazide was treated with paratoluene sulfonic acid, PTSA, a mixture of isomeric methyl esters, similar to that obtained with TFA was formed, Equation 30. Again the major product was the trans-isomer, the retention product. We believe that this result which strengthens our assumption that nucleophilic substitution
at phosphoryl centre occurs by different mechanisms, one by mono-
protonation and another by diprotonation of the leaving group. The
fact that a nearly identical product ratio is formed from both isomers
of the hydrazide (Scheme VIII) indicates that a common intermediate
is highly probable. A slight difference in the product ratio in
the case of the cis isomer can be explained by the assumption that in
the transition state the phosphacylium ion intermediate is not completely
free. It is evident from the product ratio that the intermediate is tending towards planarity and attack of the nucleophile occurs from both sides of the plane before the departure of the leaving group. It appears that the ratio of products formed in the acid catalyzed solvolysis of the hydrazides depends, in part, upon the structure of
their precursor.

The trans-2-methoxy-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxa-
phosphorinan, which is thermodynamically less stable than the cis
isomer, does not isomerize under any conditions to give a mixture of
cis and trans isomers. Thus, the isomer ratios formed in the solvolysis
reflect the mode of substitution and are not a result of the isomeriza-
tion of the product following its formation.

**Attempted Electrophilic Substitution**

Treatment of the trans-hydrazide with TFA in benzene gives a dark
viscous liquid. Absence of an aromatic peak in the NMR spectrum indi-
cates that electrophilic substitution has not taken place. The phos-
phacylium ion-like intermediate, if formed, must have a very short
lifetime or be a poor electrophile. Before it gets trapped by benzene,
it might have undergone rearrangement. Though there is no direct
structural evidence, appearance of an additional doublet peak at 2 ppm
in the NMR spectrum strongly suggests the presence of a new material.
A possibility could be opening of the phosphorinan ring system to give
a relatively stable metaphosphate ion, Equation 31. Monomeric

\[
\begin{align*}
\text{C}_1\text{H}_2\text{C} & \quad \text{CH}_2 \quad \text{O} \\
\text{H}_3\text{C} & \quad \text{CH}_2 \quad \text{O} \\
\end{align*}
\]

\[
\rightarrow
\begin{align*}
\text{C}_1\text{H}_2\text{C} & \quad \text{CH}_2 \quad \text{O} \\
\text{H}_3\text{C} & \quad \text{CH}_2 \quad \text{O} \\
\end{align*}
\]

31 (monomeric metaphosphate ion)
metaphosphate ion is known to polymerize readily to give phosphates. ²⁸

No attempt was made to isolate the new product.

Our above experiments indicate that the stereochemical outcome of methanolysis of the hydrazides is dependent upon the strength of the catalyst used. We assume that the phosphacylium ion, although not completely free, approaches a planar configuration in which the chloromethyl group, as is the case with esters, prefers an axial position. If such is the case, preferred attack from the least hindered side very nicely explains our product ratios, Figure 23.

![Figure 23](image)
SUMMARY

The stereochemistry of 2-substituted-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinans can be established by proton NMR spectroscopy. Methanalysis of 2-hydrazinophosphorinans has been investigated. Cis and trans-2-hydrazinophosphorinans undergo acid catalyzed methanalysis to give products of both retention and inversion. The product ratio is dependent upon the strength of the acid used. Under strong acid conditions, the product ratio is nearly identical for both the cis and trans isomers. Stereochemical evidence for the participation of a phosphacylium ion-like intermediate is presented.
EXPERIMENTAL

$^1$H NMR spectra were recorded on a Perkin-Elmer R-12B spectrophotometer at 60 MHz. Tetramethyl silane (TMS) was used as an internal standard. Isomer ratios were obtained by integration of peaks due to 5-methyl hydrogens. $^{13}$C NMR spectrum was recorded on a JEOL FX-100 spectrophotometer and the IR spectra on a Perkin-Elmer 700 spectrometer. All melting points were in degrees centigrade and are uncorrected. Values were determined on a MeL-Temp melting point apparatus. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tennessee, 37921.

**Methyl bicyclic phosphite**

A mixture of 1,1,1-tris hydroxy methyl ethane, 60.0g (0.50 mol), and trimethylphosphite, 62.0g (0.05 mol), in 100 ml of toluene was distilled for 24 hours until methanol formation was complete. The temperature of the reaction was maintained between 110-120°. Toluene was removed under reduced pressure. The resulting white crystalline solid was distilled under 1 mm of pressure and collected over an ice bath.

**cis-2-Chloro-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan, (cis-chloridate)**

A solution of methyl bicyclic phosphite, 37.0g (0.23 mol), in 200 ml of carbon tetrachloride was added dropwise with constant ice-bath cooling and stirring to a solution of sulfuryl chloride, 33.75g (0.24 mol), in 200 ml of carbon tetrachloride. After the exothermic addition, the solution was stirred for 1 hour and
stripped under reduced pressure. The liquid residue which crystallized on standing was recrystallized from carbon tetrachloride to give 85% yield of white crystalline product, mp. 69-71°.

**Reduction of cis-chloridate using Lithium Aluminium Hydride**

The cis chloridate, 2.96g (0.0135 mol), dissolved in 25 ml of dry ether was added dropwise during one hour to a well stirred suspension of 1.70g (0.045 mol) of LiAlH₄ in 50 ml of dry ether. The reaction was carried out in a nitrogen atmosphere and the temperature was maintained @ -2°C during the addition and for an additional reaction period of one hour. Decomposition of excess LiAlH₄ was accomplished at 10° by the cautious addition of excess water followed by 125 ml of 15% aqueous sulfuric acid. The ether layer was separated and thoroughly washed with 6% potassium carbonate solution and then with water. The organic layer was separated and dried using anhydrous magnesium sulfate. The solvent was removed under reduced pressure. The NMR spectrum of the crude material using CDC₁₃ showed the presence of 2-chloromethyl-2-methylpropane-1,3-diol. The yield obtained was low.

Lithium tri-t-butoxyaluminium hydride, LiAlH[OC(CH₃)₃]₃

Dropwise addition of 74g (1 mol) of t-butanol at room temperature to a stirred solution of 12g (0.31 mol) of LiAlH₄ in 100 ml of ether produces a white precipitate of lithium tri-t-butoxyaluminium hydride in quantitative yield. The new reagent proved to be a milder reducing agent than LiAlH₄.
Reduction of cis-Chloridate using Lithium tri-t-butoxyaluminium hydride

The cis-chloridate, 2.19g (0.01 mol), dissolved in 25 ml of dry ether was added dropwise during one hour to a well stirred suspension of 7.62g (0.03 mol) of LiAlH\[OC(CH_3)\_3\]_3 in 50 ml of dry ether. The reaction was carried out in a nitrogen atmosphere with the temperature maintained at -2°C during the addition and an additional reaction period of one hour. Excess LiAlH\[OC(CH_3)\_3\]_3 was decomposed by the cautious addition of water at 10° followed by 15% aqueous sulfuric acid. The ether layer was separated, thoroughly washed with 6% potassium carbonate solution and then with water. The organic layer was dried over anhydrous MgSO₄. The NMR spectrum of the crude material, after the removal of solvent, indicated the presence of 2-chloromethyl-2-methyl-propane-1,3-diol. The reaction was repeated by adding the reducing agent to cis-chloridate. Again the product isolated was 2-chloromethyl-2-methylpropane-1,3-diol.

cis-2-Chloromethyl-2-methylpropane-1,3-diol

Thionylchloride, 59.5g (0.5 mol), was added dropwise to 1,1,1-trishydroxymethylethane, 60g (0.5 mol), and pyridine, 40g (0.05 mol), and the mixture heated at 140-160° for 20 hours. The cooled mixture was diluted with an equal volume of water and extracted with ethyl acetate (total 250 ml). The extract was washed with 2N-hydrochloric acid, then with water and dried. Distillation of the solution gave 20g of diol (30% yield), mp 80-82°.
Reaction of cis-2-Chloromethyl-2-methylpropane-1,3-diol with diethyl hydrogen phosphite

A mixture of diol, 3.5g (0.0125 mol), and diethyl hydrogen phosphite, 3.5g (0.0125 mol), in 50 ml of toluene was heated gently for one hour with constant stirring. No product such as ethanol was collected. The solvent was removed under reduced pressure and the crude material on distillation (1 mm of Hg) gave a white solid product, mp. 75-76°. The NMR spectrum of the product in CDCl₃ showed that the diol had not reacted with diethylhydrogen phosphite.

trans-2-Hydrazino-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan, trans-Hydrazide

The cis-chloride, 2.18g (0.01 mol), was dissolved in 50 ml of acetonitrile and the solution added dropwise to 0.64g (0.02 mol), of 95% Hydrazine. The reaction was carried out with constant stirring and ice-bath cooling during the addition and an additional reaction period of one hour. The product obtained was filtered at an elevated temperature to remove the insoluble hydrazine hydrochloride. Solvent was removed from the filtrate under reduced pressure. The resulting solid was recrystallized from acetonitrile to give 1.30g (60% yield) of white crystalline solid, mp. 156°.

Anal. calcd. for C₅H₁₂O₃PN₂Cl: C, 27.99; H, 5.64; N, 13.05; Cl, 16.52.

Found: C, 28.23; H, 5.79; N, 13.23; Cl, 16.66.
trans-5-Chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinanoyl-2-
benzaliminoylhydrazone

Recrystallized trans-hydrazone, 1.07g (0.005 mol), and benzaldehyde, 0.53g (0.005 mol), were mixed together in 100 ml of methanol and the mixture stirred for thirty minutes with cold water bath cooling. The solvent was removed under reduced pressure and the resulting yellow solid recrystallized twice from carbon tetrachloride to give 0.7g (46% yield) of white crystalline product, mp. 173-174°.

Anal. calcd. for C_{12}H_{16}O_{3}N_{2}PCl: C, 47.62; H, 5.33; N, 9.25; Cl, 11.71. Found: C, 47.68; H, 5.40; N, 9.27; Cl, 11.79.

trans-5-Chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinanoyl-2-
propanoiminoylhydrazone

A solution of trans-hydrazone, 1.07g (0.005 mol) in 25 ml of acetone was stirred for thirty minutes with cold water bath cooling. The solvent was removed under reduced pressure and the resulting solid was recrystallized from carbon tetrachloride. Yield of the white crystalline product was 0.85g (67%), mp. 155-156°.

Anal. calcd. for C_{8}H_{16}O_{3}N_{2}PCl: C, 37.73; H, 6.33; Cl, 13.92; N, 11.00. Found: C, 37.46; H, 6.16; Cl, 14.18; N, 10.62.

The NMR spectrum using CD_{3}OD showed the presence of only one isomer, the trans.
trans-2-N,N-Dimethyl-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan

Dimethylamine (25% H₂O) was heated and the gas evolved passed into 2-chlorophosphorinan, 4.36g (0.02 mol), dissolved in 40 ml of acetonitrile. The gas was passed through a cold condenser to remove the moisture prior to its addition to the chloridate solution. The solution was cooled in an ice bath and stirred while the amine was bubbled in. After white precipitate ceased forming, the solution was suction filtered and the filtrate stripped under reduced pressure. The crystalline residue was recrystallized from hot water, 3.8g (84.4%), mp. 148-150°.

Anal. calcd. for C₁₇H₁₅ClN₀₃P: C, 37.00; H, 6.60; N, 6.17. Found: C, 36.91; H, 6.59; N, 6.31.

The NMR spectrum of the product is as expected for the assigned structure.

tertiary Butylhypochlorite

A solution of 80g (2 mol) of NaOH in about 500 ml of water was prepared in a 3-neck flask equipped with a mechanical stirrer, a gas inlet tube reaching nearly to the bottom of the flask and a gas outlet tube. To a cooled solution (15-20°) of NaOH, 74g (1 mol), of tert. butylalcohol was added with enough water to form a homogenous solution. With constant stirring, chlorine gas was passed through the mixture for 30 minutes at a rate of approximately 1  l. per minute and then for an additional 30 minutes at a rate of 0.5-0.6  l. per minute. The upper oily layer was separated and washed
with 50 ml portions of 10% sodium carbonate solution until the washings were no longer acidic to congored. The product was finally washed with water (4 x 200 ml) and dried over calcium chloride. The yield obtained was 80g (73%). The product was stored in a ground glass stoppered flask and kept in the dark in a refrigerator.

**Oxidation of trans-Hydrazide with tert. butylhypochlorite in tertiary butanol**

Tert. butylhypochlorite, 1.08g (0.01 mol), was dissolved in 50 ml of tert. butanol and the solution added dropwise during fifteen minutes to a solution of 1.07g (0.005 mol), of trans-hydrazide in 50 ml of tert. butanol. The addition was carried out at an elevated temperature (\( \sim 50^\circ \)) with constant stirring. Identical conditions were maintained for an additional period of fifteen minutes and the solvent removed under reduced pressure. The resulting yellow liquid product was dissolved in 100 ml of methylenechloride, washed with 2% aqueous sodium bicarbonate followed by water. The organic layer was dried over anhydrous MgSO\(_4\). Removal of the solvent under reduced pressure gave a yellow liquid product. The NMR spectrum showed the presence of only one isomer, the trans-chloridate. Recrystallization of the product from hot water gave a white crystalline solid whose spectrum was identical to that of pyrophosphate.

The nitrogen gas released during the reaction was collected by displacement of water in a gas burette. The uncorrected volume of the gas was measured. The volume of pure nitrogen was calculated at standard temperature and pressure. From the volume, the number
of moles of nitrogen gas evolved was determined.

The identification of other reaction products, tertiary butylchloride, hydrogenchloride, was achieved using a Porapak-Q packed column in a Fisher gas chromatograph series 2400. The product obtained on oxidation of trans-hydrazide with tert. butylhypochlorite in tert. butanol was confirmed by converting it to known amide.

cis-2-Piperidino-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan

A solution of piperidine, 1.35g (0.015 mol), in 50 ml of acetonitrile was added dropwise to a solution of freshly prepared, crude trans-chloridate, 0.5g (0.0025 mol), dissolved in 50 ml of acetonitrile. The addition was carried out with constant stirring and ice bath cooling. After the initial exotherm had subsided, the solution was stripped under reduced pressure and the crystalline residue washed well with water. The insoluble material was dried, 0.4g (30% yield), mp. 181-182°. The NMR spectrum showed the presence of a single isomer with the chloromethyl group equatorial.

cis-2-Benzylamido-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan

A solution of benzylamine, 1.6g (0.015 mol), in 100 ml of acetonitrile was added dropwise with constant stirring and ice bath cooling to an acetonitrile solution of freshly prepared, crude trans-chloridate, 0.5g (0.0025 mol). After the initial exotherm had subsided, the solvent was removed under reduced pressure. The crystalline residue was recrystallized from CCl₄ to give the product, 0.21g (30% yield), mp. 88-89°. The NMR spectrum showed the presence of
a single isomer with the chloromethyl group equatorial.

**cis-2-Amido-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan**

The crude trans-chloridate, 0.5g (0.0025 mol), was dissolved in 100 ml of acetonitrile. The solution was stirred in an ice bath and dry ammonia gas was bubbled through for twenty minutes. The amide precipitated out as a white solid. Upon completion of the precipitation, the solvent was removed under reduced pressure and the crude solid was recrystallized from acetonitrile to give a white crystalline solid.

**Oxidation of diethylhydrogen phosphite with tert. butyl hypochlorite in tert. butanol**

Tert. butylhypochlorite, 1.08g (0.01 mol), was dissolved in 50 ml of tert. butanol and the solution added dropwise to a solution of diethyl hydrogenphosphite, 1.38g (0.01 mol), in 50 ml of tert. butanol. The reaction mixture was stirred in an ice bath for fifteen minutes and stripped under reduced pressure. The NMR spectrum of the crude material showed the presence of diethylhydrogenphosphite.

**Oxidation of trans-Hydrazide using tert. butylhypochlorite in benzene**

A solution of tert. butylhypochlorite, 1.08g (0.01 mol), in 50 ml of benzene was added dropwise to trans-hydrazide, 1.07g (0.005 mol), dissolved in 50 ml of benzene. The reaction was carried out at an elevated temperature (≈50°) with stirring and with the addition carried out over a period of 30 minutes. The solvent was removed under reduced pressure. The resulting yellow viscous liquid did
not crystallize on standing. Attempts to recrystallize the viscous liquid failed.

**Oxidation of trans-Hydrazide with tert. butylhypochlorite in acetonitrile**

trans-Hydrazide, 1.07g (0.005 mol), and tert. butylhypochlorite, 1.08g (0.01 mol), were dissolved in 100 ml of acetonitrile. The mixture was stirred for half an hour with ice bath cooling, filtered and the filtrate stripped of solvent under reduced pressure. The resulting yellow liquid residue was dissolved in acetonitrile, to which a slight excess of piperidine, 1.35g (0.015 mol), was added. After the initial exotherm had subsided, the solvent was removed under reduced pressure to give a brown crystalline solid. The solid was recrystallized from n-heptane to give a very low yield of a mixture of isomeric 2-piperidinophosphorinans with the cis-isomer (chloromethyl group equatorial) predominating.

**Oxidation of trans-Hydrazide with tert. butylhypochlorite in tetrahydrofuran (THF)**

Two equivalents of tert. butylhypochlorite and an equivalent of trans-hydrazide were dissolved in 100 ml of THF. The mixture was stirred for half an hour with ice bath cooling. The rest of the experiment was followed as above (using acetonitrile). Though attempts to recrystallize the crude residue failed, the NMR spectrum showed the presence of an isomeric mixture of 2-piperidinophosphorinans with the same ratio as that of acetonitrile experiment.
Oxidation of trans-Hydrazide with tert. butylhypochlorite in
Isopropylalcohol

Addition of tert. butylhypochlorite, 0.87 g (0.008 mol), to
isopropyl alcohol was exothermic. The solution was cooled and added
dropwise to trans-Hydrazide, 0.86 g (0.004 mol), with stirring and
ice bath cooling. The resulting solution was filtered and from the
filtrate solvent was removed under reduced pressure. The NMR
spectrum of the crude material showed the presence of starting
material. Due to prior oxidation of the alcohol solvent, oxidation
of the hydrazide did not take place.

Oxidation of trans-Hydrazide with tert. butylhypochlorite in methanol

Tert. butylhypochlorite, 0.87 g (0.008 mol), and trans-Hydra­
zide, 0.86 g (0.004 mol), were dissolved in 100 ml of methanol. The
mixture was stirred for half an hour with ice bath cooling. A
quantitative evolution of nitrogen gas was observed. The solution
was filtered. The removal of the solvent from the filtrate gave
a yellow liquid residue. The crude residue was dissolved in
methylene chloride, washed with 2% potassium hydroxide solution,
followed by dilute hydrochloric acid and water. The organic layer
was separated and dried over magnesium sulfate. Removal of the sol­
vent under reduced pressure gave a mixture of isomeric methyl esters,
50% yield. The NMR spectrum showed the ratio of isomers as 3 to 1
with the cis predominating.
Oxidation of trans-Hydrazone with tert. butylhypochlorite in 2,4,4-trimethyl-2-pentene

Addition of tert. butylhypochlorite, 0.54g (0.005 mol), to 25 ml of substituted pentene was exothermic. The solution was cooled and added dropwise to trans-hydrazone, 0.54g (0.0025 mol). The mixture was stirred for half an hour in an ice bath and the solution stripped under reduced pressure to give a liquid residue. The NMR spectrum of the liquid residue matches the authentic spectra of 2,4,4-trimethyl-2-pentene, which indicates that oxidation did not take place.

cis-2-Hydrazino-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan, cis-Hydrazone

The trans-chloridate obtained as in the previous procedure, but based on 0.02 mol of reactants was dissolved in 100 ml of methylene chloride, the solution washed with 2% aqueous NaHCO₃, followed by water and dried over MgSO₄. Solvent removal gave a gummy liquid residue which was dissolved in 100 ml of acetonitrile. To the solution was added dropwise 95% Hydrazine, 1.36g (0.04 mol). The mixture was stirred for half an hour with ice bath cooling, filtered and solvent stripped under reduced pressure from the filtrate to give a white solid. Recrystallization of the crude solid from acetonitrile gave cis-hydrazone, mp. 177-178°.

Anal. calcd. for C₅H₁₂O₃PN₂Cl: C, 27.99; H, 5.64; N, 13.05; C1, 16.52.

Found: C, 27.61; H, 5.68; N, 12.43; C1, 15.67.
The NMR spectrum showed the presence of a single isomer with the hydrazine substituent at the axial position.

**Oxidation of cis-Hydrazide with tert. butylhypochlorite in tertiary butanol**

Tertiary butylhypochlorite, 1.08g (0.01 mol), and cis-Hydrazide, 1.07g (0.005 mol), were dissolved in 100 ml of tert. butanol. The mixture was stirred for half an hour at 50°. The resulting solution was filtered and removal of solvent from the filtrate gave a liquid residue. To the residue dissolved in 100 ml of acetonitrile, excess piperidine, 0.02 mol, was added with stirring and ice bath cooling. After the initial exotherm had subsided, the solution was stripped under reduced pressure to give a crude crystalline residue. The residue was dissolved in methylenechloride, washed with water and dried over MgSO₄. Removal of the solvent gave a yellow solid product which was recrystallized from heptane. The yield was very low. The NMR spectrum of the recrystallized product showed the presence of a mixture of isomeric 2-piperidinophosphorinanans with the trans-isomer (chloromethyl group axial) predominating.

**Isomerization of trans-chloridate in dichloromethane**

The unstable trans-chloridate obtained as in the previous procedure, but based on 0.005 mol of reactants, was dissolved in 100 ml of dichloromethane, washed with 2% aqueous NaHCO₃, followed by water and dried over anhydrous MgSO₄. Removal of the solvent under reduced pressure gave a crude liquid residue which was
dissolved in 100 ml of acetonitrile. Excess piperidine, 0.015 mol, was added to the acetonitrile solution of chloridate with stirring and ice bath cooling. The solution was stripped under reduced pressure and the crystalline residue was washed well with water. The insoluble material was recrystallized from heptane to give 30% yield of the product, mp. 180-181°. The NMR spectrum of the product showed the presence of cis-2-piperidinophosphorinan as the only one isomer which indicates that the trans-chloridate did not isomerize in dichloromethane.

trans-2-Phenylhydrazino-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan, trans-Phenylhydrazide

A benzene solution of cis-phosphorochloridate, 4.38g (0.02 mol), was added dropwise to a mixture of phenylhydrazine, 2.08g (0.02 mol), and triethylamine, 2.04g (0.02 mol) dissolved in 100 ml of benzene. The addition was done with stirring and ice bath cooling and identical conditions were maintained for an additional thirty minutes. Formation of white precipitate of triethylamine hydrochloride was observed. The mixture was allowed to stand for 24 hours. The precipitate was filtered and benzene was removed from the filtrate under reduced pressure. The crude solid was recrystallized from toluene to give 3.46g (60%) yield, mp. 140-142°.
Oxidation of trans-2-phenylhydrazino-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan using yellow mercury oxide

The phenyl hydrazide, 10.1g (0.035 mol), and mercury oxide, 7.6g (0.035 mol), were added to 200 ml of benzene. The mixture was refluxed for four hours with stirring. Quantitative formation of water was observed using Dean and Starke apparatus. The solution was filtered and the filtrate was stripped of solvent to give a dark viscous residue which do not crystallize on standing. Attempts to recrystallize the residue failed.

Methanolysis of trans-2-hydrazino-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan using gaseous hydrogen chloride as catalyst

To a methanolic solution of trans-hydrazide, 0.54g (0.0025 mol), hydrogen chloride gas was passed through for fifteen minutes. The reaction was stirred with cold water bath cooling. A white precipitate was slowly formed on bubbling the gas. The precipitate was filtered and removal of the solvent from the filtrate gave a white solid. It was dissolved in methylenechloride, washed with 2% aqueous NaHCO₃, followed by water and dried over MgSO₄. The solution stripped under reduced pressure to give a mixture of isomeric methyl esters. The percentage of cis (chloromethyl group axial) to trans (chloromethyl group equatorial) was 81 to 19.

Methanolysis of cis-2-hydrazino-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan using gaseous hydrogen chloride as catalyst

As in the previous experiment, hydrogen chloride gas was bubbled through a methanolic solution of cis-hydrazide, 0.54g
(0.0025 mol), for fifteen minutes. The crude product obtained was dissolved in methylene chloride and purified as above. Removal of the solvent gave a mixture of isomeric methyl esters with the trans isomer predominating (67%).

Methanolysis of trans-hydrazide in the presence of acetonitrile using hydrogen chloride gas as catalyst

Hydrogen chloride gas was passed through a mixture of trans-hydrazide, 0.54g (0.0025 mol), dissolved in an equal volume of acetonitrile and methanol for fifteen minutes. The mixture was stirred with cold water bath cooling. A large quantity of white crystalline product precipitated out. The precipitate was filtered and the filtrate stripped of solvent under reduced pressure. The resulting crude white solid dissolved in methylene chloride, washed with 2% aqueous NaHCO₃, followed by water and dried over MgSO₄. Removal of the solvent gave a very low yield of methyl esters. The ratio of cis to trans was 1 to 2. The white crystalline solid obtained on large yield was identified as Imminohydrochloride. ⁵⁹

Methanolysis of trans-hydrazide in the presence of dimethylformamide (DMF) using hydrogen chloride gas as catalyst

To a mixture of trans-hydrazide, 0.54g (0.0025 mol), dissolved in an equal volume of methanol and dimethylformamide, hydrogen chloride gas was bubbled through for fifteen minutes. The mixture was cooled and stirred as above. Methanol was removed under reduced pressure. DMF removal was effected by dissolving
the solution in methylene chloride and washing the solution with water (5 x 100 ml). Methylene chloride layer was removed and dried over anhydrous MgSO₄. Removal of the solvent under reduced pressure gave a low yield of 2-hydroxy-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan as the only product. Methyl esters were not isolated.

**Methanolysis of cis-hydrazone in the presence of acetonitrile using hydrogen chloride as catalyst**

Methanolysis of cis-hydrazone, 0.54g (0.0025 mol), in the presence of acetonitrile was carried out as in the previous experiment. The only isolated product was imminohydrochloride.

**Methanolysis of trans-hydrazone with trifluoroacetic acid (TFA) as catalyst**

A solution of trans-hydrazone, 0.54g (0.0025 ml), dissolved in an equal volume of methanol and TFA (25 ml of each) was stirred for fifteen minutes in a cold water bath. The solution was stripped under reduced pressure and the resulting residue was dissolved in methylene chloride, washed with 2% aqueous NaHCO₃, followed by water and dried over MgSO₄. NMR spectrum of the crude material obtained, after the removal of the solvent, showed the presence of isomeric methyl esters. The percentage of cis to trans was 33 to 67.

**Methanolysis of cis-hydrazone with TFA as catalyst**

As in the previous experiment, methanolysis was carried out with cis-hydrazone, 0.54g (0.0025 mol), dissolved in an equal volume of methanol and TFA. The methyl esters formed were isolated as
above. The percentage of cis to trans was 43 to 57.

**Methanolysis of trans-hydrazone with paratoluene sulfonic acid as catalyst**

A mixture of trans-hydrazone, 0.43g (0.002 mol), and 0.1M of PTSA were dissolved in 50 ml of methanol and the mixture was stirred for fifteen minutes using cold water bath. The solution was stripped under reduced pressure and the resulting residue was dissolved in methylene chloride, washed with 2% aqueous NaHCO₃, followed by water and dried over MgSO₄. Removal of the solvent gave crude methyl esters. The percentage of cis to trans was 33 to 67.

**Methanolysis of trans-2-N,N-dimethylamidophosphorinan with TFA as catalyst**

trans-Dimethylamidophosphorinan, 0.5g (0.0022 mol), was dissolved in a mixture of 80 ml of methanol and 20 ml TFA. The mixture was stirred for fifteen minutes with cold water bath cooling and allowed to stand at room temperature for seven days. The solution stripped under reduced pressure gave a liquid residue. It was dissolved in methylene chloride, washed with 2% aqueous NaHCO₃, followed by water and dried over MgSO₄. Removal of the solvent gave the reactant, which showed that trans-2-N,N-dimethylamidophosphorinan did not undergo methanolysis under these conditions.

**Attempted electrophilic substitution of a phosphacylum ion-like intermediate with benzene**

trans-Hydrazone, 0.54g (0.0025 mol), was dissolved in an equal volume of benzene and trifluoroacetic acid (50 ml of each) and
the mixture was stirred for fifteen minutes using cold water bath cooling. The solution was stripped under reduced pressure and the crude material obtained was dissolved in methylene chloride, washed with water and dried over MgSO₄. Removal of the solvent gave a dark viscous liquid. Attempts to recrystallize the crude product have failed. NMR spectrum of the dark viscous liquid shows the absence of an aromatic peak.
1. NMR spectrum of cis-2-chloro-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan in chloroform-d with TMS as internal standard.
2. NMR spectrum of trans-2-hydrazone-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan in methanol-d with TMS as internal standard.
4. NMR spectrum of trans-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinanyl-2-benzaliminoylhydrazone in chloroform-d with TMS as internal standard.
3. NMR spectrum of trans-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinanyl-2-propanoiminoylhydrazine in chloroform-d with TMS as internal standard.
5. NMR spectrum of trans-N,N-dimethylamido-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan in chloroform-d with TMS as internal standard.
6. NMR spectrum of crude trans-2-chloro-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan in chloroform-d with TMS as internal standard.
7. NMR spectrum of cis-2-piperidino-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan in chloroform-d with TMS as internal standard.
8. NMR spectrum of cis-2-benzylamido-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan in chloroform-d with TMS as internal standard.
9. NMR spectrum of cis-2-amido-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan in methanol-d with TMS as internal standard.
11. NMR spectrum of cis-2-hydrazino-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan in methanol-d with TMS as internal standard.
12. NMR spectrum of trans-2-phenylhydrazino-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan in methanol-d with TMS as internal standard.
13. NMR spectrum of yellow mercury oxide oxidized product of trans-2-phenylhydrazino-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan in methanol-d with TMS as internal standard.
15. NMR spectrum of gaseous hydrogen chloride catalyzed methanolysis of trans-2-hydrazino-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan in chloroform-d with TMS as internal standard.
17. NMR spectrum of gaseous hydrogen chloride catalyzed methanolysis of trans-2-hydrazino-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan in the presence of acetonitrile, in chloroform-d with TMS as internal standard.
18. NMR spectrum of trifluoroacetic acid catalyzed methanolysis of trans-2-hydrazino-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan in chloroform-d with TMS as internal standard.
19. NMR spectrum of trifluoroacetic acid catalyzed methanolysis of cis-2-hydrazino-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan in chloroform-d with TMS as internal standard.
20. NMR spectrum of paratoluene sulfonic acid catalyzed methanolysis of trans-2-hydrazino-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan in chloroform-d with TMS as internal standard.
21. IR spectrum of trans-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinanyl-2-propano-iminoyl hydrazine as KBr pellet.
22. IR spectrum of trans-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinanyl-2-
benzaliminoyl-hydrazine with nujol as mulling agent.
23. $^{13}$C NMR spectrum of trans-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinanyl-2-propanoiminoyl-hydrazine in chloroform-d with off resonance decoupled protons.
24. $^{31}$P NMR spectrum of trans-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinanyl-2-propanoiminoyl-hydrazine with phosphoric acid as internal standard.
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