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Nucleophilic Substitution at Phosphorus: Phosphate Thioesters

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NUCLEOPHILIC SUBSTITUTION AT PHOSPHORUS: PHOSPHATE THIOESTERS

BY

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NUCLEOPHILIC SUBSTITUTION AT

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This thesis is approved as a creditable and independent investigation by the candidate for the degree, Master of Science, and is acceptable as meeting the thesis requirements for this degree, but without implying that the conclusions reached by the candidate are necessarily the conclusions of the major department.

Thesis Adviser Date

Head, Chemistry Department Date

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TO MY PARENTS, MR. AND MRS. LEVI WILDE

AND MY WIFE, MIKI.

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INTRODUCTION

Hybridization of carbon has been determined to take three possible forms, each having a different geometry about the atom. The amount of pi (π) bonding dictates the hybridization. Carbon atoms which are bonded by two π and two sigma (σ) bonds are sp hybridized. Those with one π and three σ bonds have sp^2 hybridization and trigonal configuration while sp^3 hybridization demands a tetrahedron.

Nucleophilic substitution at carbon occurs readily, especially at sp^3 hybridized carbons. The ease of substitution at carbon with sp^3 hybridization is dependent upon steric factors, basicity of the nucleophile, basicity of the leaving group, possible salt effects, solvent polarity, and the mechanism by which substitution takes place.

There are two modes of substitution at carbon which are limiting, Snl and Sn2. The first occurs by a two-step mechanism in which the leaving group leaves the carbon prior to attack by the nucleophile. This process demands the formation of an intermediate which is, in most cases, a carbonium ion. The carbonium ion exists in a trigonal configuration and is planar. The carbonium ion is open to attack from either side by the nucleophile which can result in products with opposite configurations.

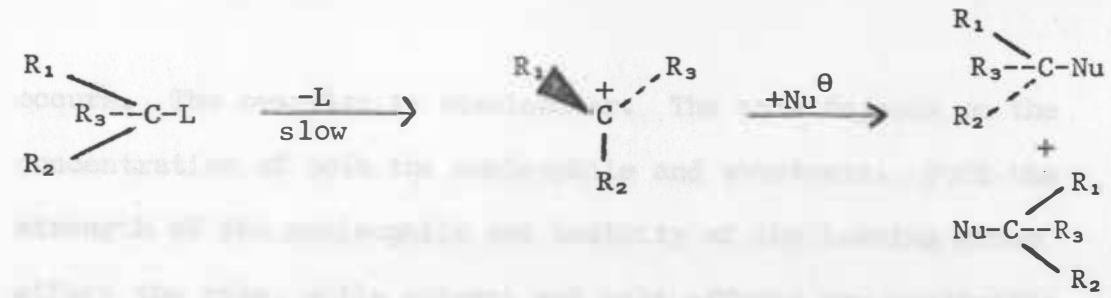


Figure 1

The formation of the intermediate is the rate-determining step. Therefore, the rate of reaction depends only upon the initial concentration of the starting material, not on the strength or concentration of the nucleophile. A carbonium ion that is stabilized by electronic effects undergoes substitution at a faster rate than one in which the energy of activation for carbonium ion formation is not lowered by such effects.

The Sn2 mechanism requires attack at carbon by the nucleophile with a simultaneous discharge of the leaving group. The nucleophile attacks from the opposite side of carbon forming a transition state in which the nucleophile and the leaving group are both semi-attached to the carbon and at a maximum distance apart (Figure 2). An inversion of configuration

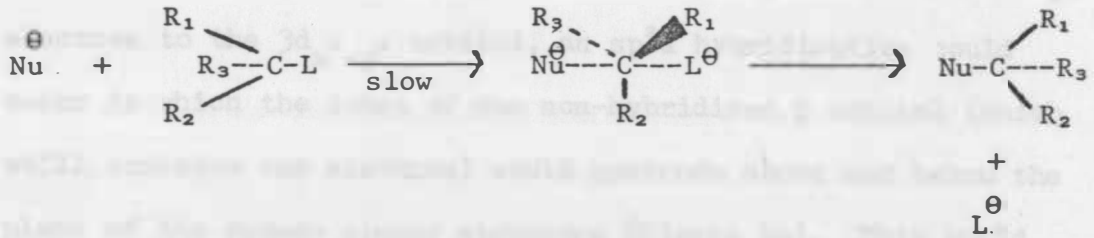
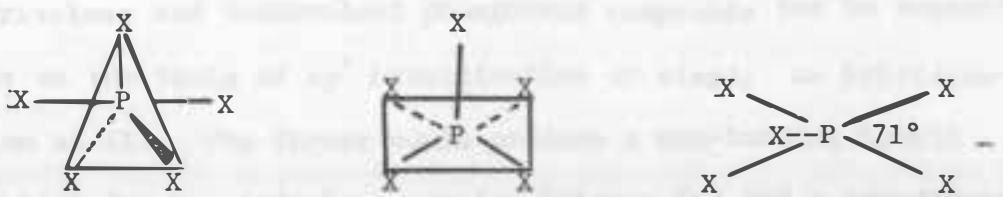


Figure 2

occurs. The reaction is bimolecular. The rate depends on the concentration of both the nucleophile and substrate. Both the strength of the nucleophile and basicity of the leaving group affect the rate, while solvent and salt effects are negligible.

Phosphorus, with a [Ne] $3s^2 3p^3$ electronic configuration and vacant d orbitals, may hybridize in a number of ways, sp^3d, $spd\text{-}sp^3$, sp^2d or sp^3. The first results in a trigonal bipyramidal structure when one 3s electron is promoted to the $3d_{z^2}$ orbital (Figure 3a) or a square pyramid when the electron enters the

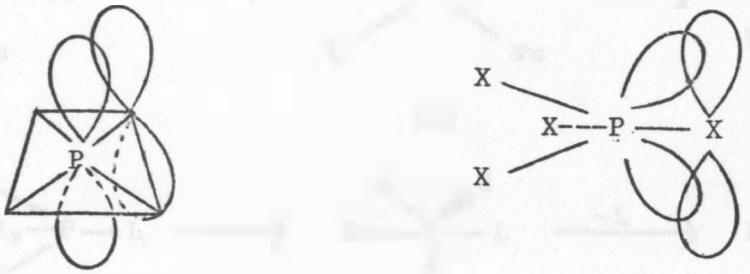


(a) (b) (c)

Figure 3

$3d_{x^2-y^2}$ orbital (Figure 3b). The second combines one of the sp^3 orbitals with a d_{xy} orbital to give a structure in which two spd bonds are 71° apart (Figure 3c).[1] These structures are all formed with phosphorus-ligand σ bonds. Upon promotion of one 3s electron to the $3d_{x^2-y^2}$ orbital, an sp^2d hybridization could occur in which the lobes of the non-hybridized p orbital (which still contains one electron) would protrude above and below the plane of the square planar structure (Figure 4a). This would allow a $p\pi\text{-}p\pi$ bond to form between phosphorus and its ligand.

Under similar conditions sp^3 hybridization could also occur in which the unhybridized d orbital with one electron could form a $d\pi$-$p\pi$ bond between phosphorus and its ligand (Figure 4b).



(a) (b)

Figure 4

Trivalent and tetravalent phosphorus compounds can be accounted for on the basis of sp^3 hybridization or simply no hybridization at all. The former would produce a non-bonding hybrid orbital for the trivalent species (Figure 5a) and a coordinate covalent bond for the tetravalent compound. This would result in the formation of a phosphonium ion (Figure 5b).

(a) (b)

Figure 5

As with carbon, phosphorus can undergo substitution reactions. The possibility of different mechanisms, which lead to either retention or inversion of configuration or both, exist. Retention is believed to go through a square pyramidal transition

state[2,3] (Figure 6a) and inversion through the trigonal bipyramidal geometry[3] (Figure 6b).

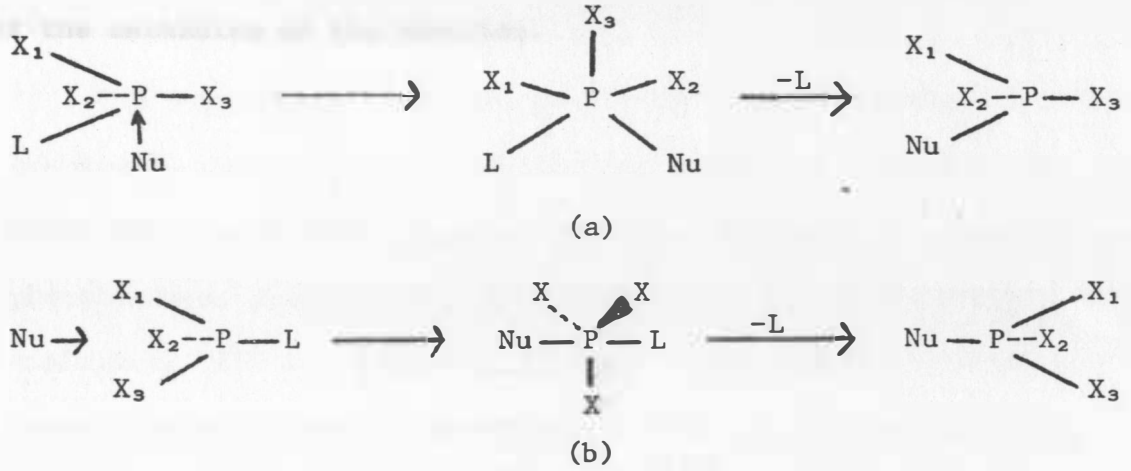


Figure 6

The stereochemistry of nucleophilic substitution at phosphorus has been the subject of increasingly important research since the discovery of the importance of phosphorus in biological systems as well as some synthetic procedures. Nucleotide triphosphates have long been known to supply energy for biological reactions. Monophosphate diesters form long chains known as polynucleotides, which when biologically synthesized, become deoxyribonucleic acids (DNA) or ribonucleic acids (RNA). These contain the biological code for protein synthesis and are the means by which characteristics are passed on to offspring. Therefore, without these phosphates, life as we know it would not exist. Phosphorus compounds have also been found to inhibit biological functions - e.g. inhibition of acetylcholine esterase - and have therefore become important as pesticides and in chemical warfare.

Some of these reactions are simple nucleophilic attacks on phosphorus. As yet, very little is known about the stereochemistry or the mechanism of the reaction.

HISTORICAL

Carbonyl vs. Phosphoryl

The organophosphorus compounds which are of greatest concern to us, are those which contain the phosphoryl (P=O) or thionophosphoryl (P=S) functional group. Included are phosphates, phosphonates, phosphonites, phosphine oxides and their sulfur analogues. All are generally believed to go through similar transition states upon substitution. However, due to dissimilar substituents on the phosphorus and the subtle difference between the phosphoryl and thionophosphoryl bond, variations in transition states are possible.

Although a parallel can be drawn between phosphoryl and carbonyl compounds, similarities are the exception rather than the rule. Carbonyl compounds undergo nucleophilic substitution with the formation of stable intermediates. The carbon atom of the intermediates are sp^3 hybridized. The nucleophile initially attacks the carbonyl carbon atom through the carbon's p orbital (Figure 7). In contrast, when a nucleophile attacks the

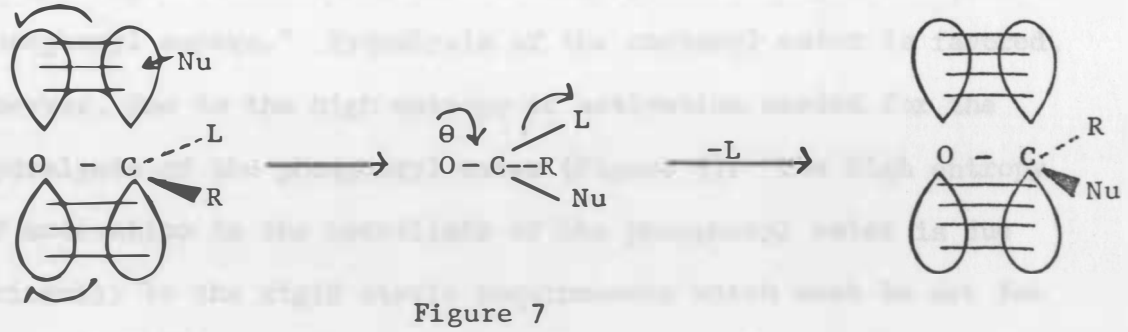


Figure 7

phosphorus in phosphoryls a stable intermediate is not formed. A bond is formed in the transition state between the attacking group and phosphorus through a phosphorus d orbital. The transition state is pentacovalent and may have the form of either a trigonal bipyramid (if the d_{z^2} orbital is used) or a square pyramid (if the orbital used is a $d_{x^2-y^2}$).[2,3,4,5,6]

Hydrolysis of carbonyl esters with ^{18}O labeled water gives, in part, a product which contains two labeled oxygen atoms.[7] Similar hydrolysis of phosphoryl compounds produces a compound with only one labeled oxygen (Figure 8).[4,8,9] Similar energies

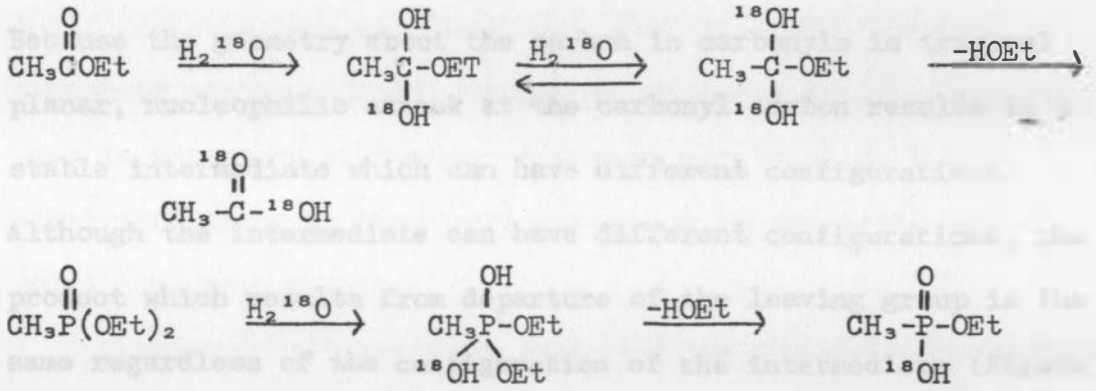


Figure 8

of activation have been found for the hydrolysis of carbonyl and phosphoryl esters.[4] Hydrolysis of the carbonyl ester is favored, however, due to the high entropy of activation needed for the hydrolysis of the phosphoryl ester (Figure 9). The high entropy of activation in the hydrolysis of the phosphoryl ester is due primarily to the rigid steric requirements which must be met for the nucleophile to attack the phosphorus atom.[4]

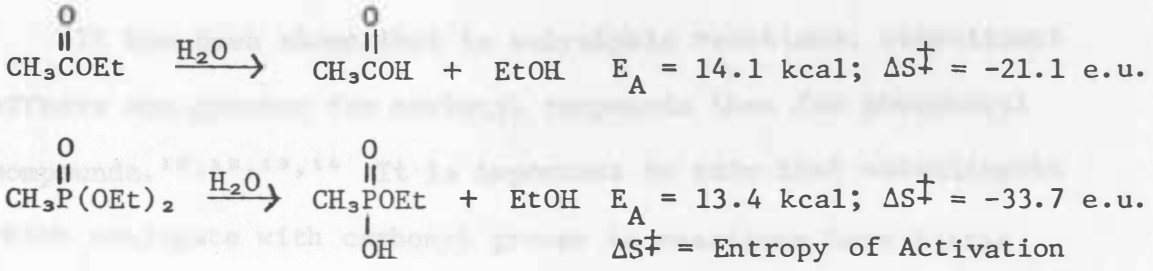


Figure 9

Dissimilarities in stereochemical pathways which result from nucleophilic substitution have also been found between carbonyl and phosphoryl compounds. Direct nucleophilic substitution at phosphorus in phosphoryls and thionophosphoryls has been found to proceed with complete inversion of configuration (Figure 6b).[11,12] Because the geometry about the carbon in carbonyls is trigonal planar, nucleophilic attack at the carbonyl carbon results in a stable intermediate which can have different configurations. Although the intermediate can have different configurations, the product which results from departure of the leaving group is the same regardless of the configuration of the intermediate (Figure 10).

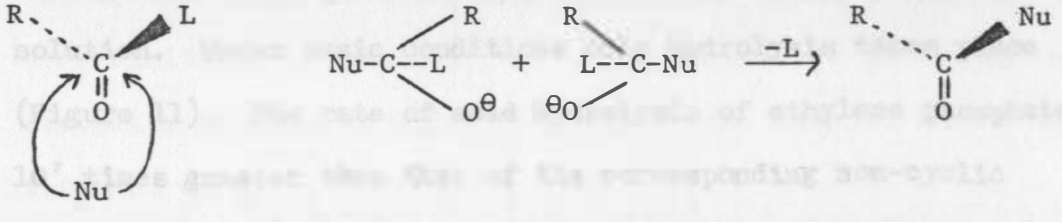


Figure 10

It has been shown that in solvolysis reactions, substituent effects are greater for carbonyl compounds than for phosphoryl compounds.[10,12,13,14] It is important to note that substituents which conjugate with carbonyl groups in reactions have little or no effect on phosphoryl bonds under identical conditions.[12]

Phosphates: Preparation and Reaction

Studies of nucleophilic substitution at phosphorus in phosphates and their sulfur analogues have been limited. Optical activity has been the basis for most studies of nucleophilic substitution at phosphorus. However, preparation of phosphate compounds which contain an optically active phosphorus atom is extremely difficult. A good system by which the electrophilicity of phosphoryl groups can be measured, has until now, been absent.

Westheimer[5,16] has shown that ethylene phosphate is extremely reactive and undergoes hydrolysis and ^{18}O exchange in acid solution. Under basic conditions only hydrolysis takes place (Figure 11). The rate of acid hydrolysis of ethylene phosphate is 10^7 times greater than that of its corresponding non-cyclic analogue.[2,15,17] The high reactivity has been explained in terms of relief of strain in the molecule upon formation of a transition state.[5,16,18]

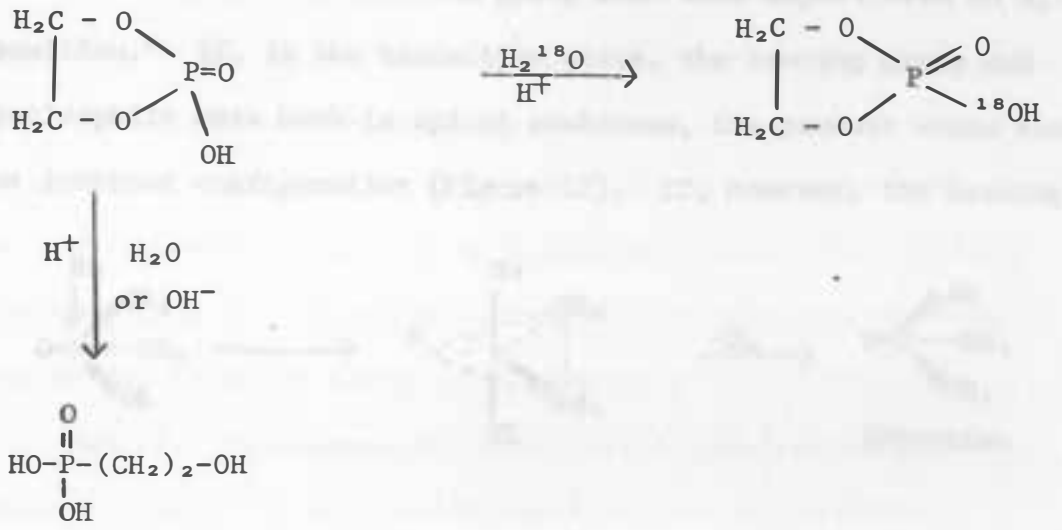


Figure 11

These reactions led to the conclusion that, as in other phosphoryl compounds, the transition states are of two possible geometries - trigonal bipyramid or square pyramid.[2] It is thought that the above reactions proceed via direct nucleophilic substitution without the formation of a stable intermediate.[2,19]

Westheimer's work, as well as the work of most others in the field, was conducted in aqueous solutions. This, in itself, is very limiting, as solubility of the substrate and nucleophiles becomes a problem. However, some important theories have come from the work.

Westheimer explained the rapid hydrolysis of cyclic phosphate esters as being due to the position of nucleophilic attack. He assumed that the nucleophile must attack from an apical position due to a minimum of steric hindrance at that position.

He theorized that the leaving group must also depart from an apical position.[5] If, in the transition state, the leaving group and nucleophile were both in apical positions, the product would have an inverted configuration (Figure 12). If, however, the leaving

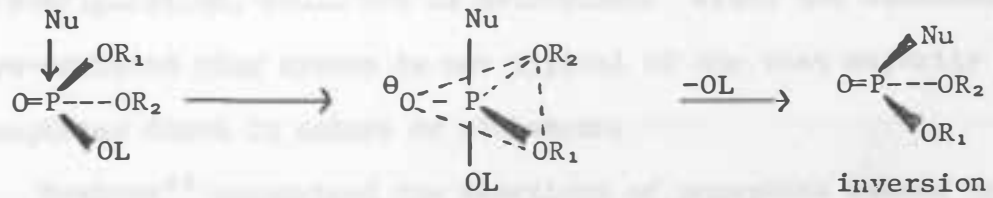


Figure 12

group is in the equatorial position in the transition state, the molecule must undergo pseudo-rotation to place it in the required apical position.[5,6,20,21,22] The result is retention of configuration (Figure 13).

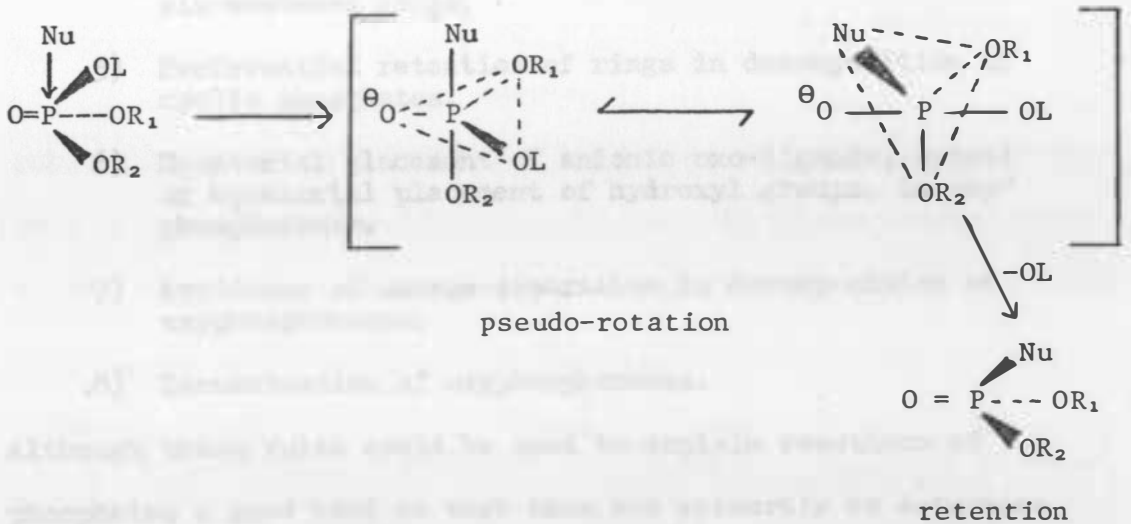


Figure 13

The theory explained kinetic data but interpretation of results was limited by reaction conditions, water as a solvent. Although substrates were used in which the end product could be identified, the mechanism of attack, i.e. inversion or retention of configuration, could not be determined. Also, the strained five-membered ring system is not typical of the vast majority of phosphates found in nature or elsewhere.

Ramirez[23] summarized the reactions of phosphate esters by sketching eight rules by which reactions can be explained.

1) Intermediacy of oxyphosphoranes.

2) Apical entry-departure.

3) Polarity rule (d orbital effects and ligand-ligand interactions taken into account).

4) Equatorial-apical placement of four and five-membered rings in contrast to diequatorial for six-membered rings.

5) Preferential retention of rings in decomposition of cyclic phosphates.

6) Equatorial placement of anionic oxo-ligands, apical or equatorial placement of hydroxyl groups, in oxyphosphoranes.

7) Avoidance of charge-separation in decomposition of oxyphosphoranes.

8) Isomerization of oxyphosphoranes.

Although these rules could be used to explain reactions of phosphates a good tool to test them and primarily to determine whether inversion or retention of configuration takes place upon substitution at phosphorus was lacking.

A system was devised in our laboratory by which substitution at phosphorus in phosphates (and phosphonates) could be followed as well as other stereochemical consequences.[24,25] Inversion and retention of configuration is determined by simple NMR spectra.[26] The system employs 2-substituted-5-halomethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinans both isomers of which can be prepared.

Preparation of cis-2-chloro-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan (chloridate (1)) is accomplished by treatment of methyl bicyclic phosphite with either chlorine or sulfuryl chloride (Figure 14).[26] Using the chloridate (1) as a

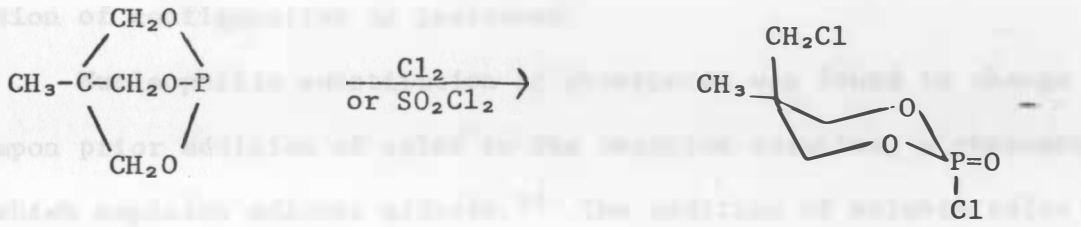


Figure 14

substrate, numerous substituted phosphates were prepared. Treatment of the chloridate (1) with nucleophiles causes substitution at the phosphorus and results in a phosphate triester (Figure 15).

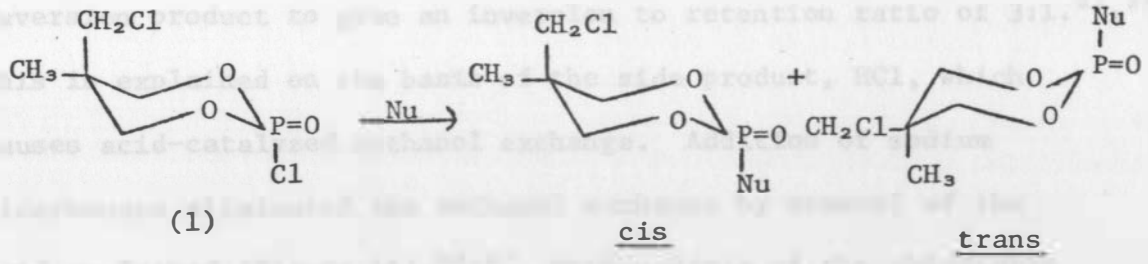


Figure 15

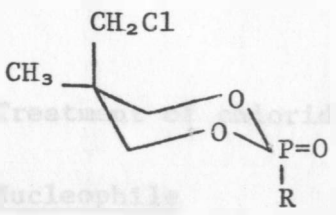
Substitution at phosphorus was found to be a kinetically controlled reaction which gives, in most instances, both isomers of the product. The ratio of geometrical isomers varies with the basicity of the nucleophile (Table 1).[26] The polarity of the solvent also affects the amount of each isomer produced (Table 2).[26] Inversion of configuration upon nucleophilic substitution at phosphorus in the chloridate (1) is predominant with weakly basic nucleophiles. Inversion is also predominant when the chloridate (1) is treated with charged nucleophiles in polar solvents. When non-polar solvents are used (ones in which salts have little solubility) retention of configuration is increased.

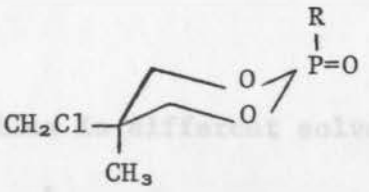
Nucleophilic substitution at phosphorus was found to change upon prior addition of salts to the reaction solution, a phenomenon which explains solvent effects.[27] The addition of soluble salts to the reaction mixture enhanced the inversion pathway (Table 3).[27]

Methanolysis of chloridate (1) gave a product which contained both isomers of the phosphate methyl ester. The ratio of inversion (trans) to retention product was found to be 3:2.[26,27] Prior addition of sodium bicarbonate to the solvent increased the inversion product to give an inversion to retention ratio of 3:1.[26,27] This is explained on the basis of the side product, HCl, which causes acid-catalyzed methanol exchange. Addition of sodium bicarbonate eliminated the methanol exchange by removal of the acid as formed (Figure 16).[26,27] Methanolysis of the chloridate (1) with silver nitrate or tetramethylammonium chloride led to

Table 1

Phenyl esters obtained from chloridate (1) and R-phenoxide ion.[a]





% retention	R	% inversion
7	SC_6H_5	93
57	$OC_6H_4OCH_3$	43
50	$OC_6H_4CH_3$	50
48	OC_6H_5	52
36	OC_6H_4Br	64
6	$OC_6H_4NO_2$	94

[a]% obtained by integrated peak areas in $CDCl_3$. Reactions were carried out in dried CH_3CN.

Table 2

Treatment of chloridate (1) with nucleophiles in different solvents.

Nucleophile	Products in CH_3CN		Products in C_6H_6	
	% cis	% trans	% cis	% trans
$NaOC_6H_5$	48	52	85	15
$NaOC_6H_4OCH_3$	57	43	88	12
$NaOC_6H_4NO_2$	6	94	40	60

Table 3

Effect of added salts on inversion-retention ratio in addition of sodium p-methylphenoxide to chloridate (1).

solvent	% trans (inversion)	% cis (retention)
CH_3CN	55.8	44.2
CH_3CN + sat. NaCl	65.8	34.2
CH_3CN + 1 eq. $(CH_3)_4\overset{+}{N}Cl^-$	88.8	11.2
CH_3CN + 1 eq. $LiClO_4$	12.2	87.8
$HCN(CH_3)_2$	80.2	19.8
$HCN(CH_3)_2$ + 1 eq. $(CH_3)_4N^+Cl^-$	95.2	4.8
$HCN(CH_3)_2$ + 1 eq. $LiClO_4$	47.4	52.6

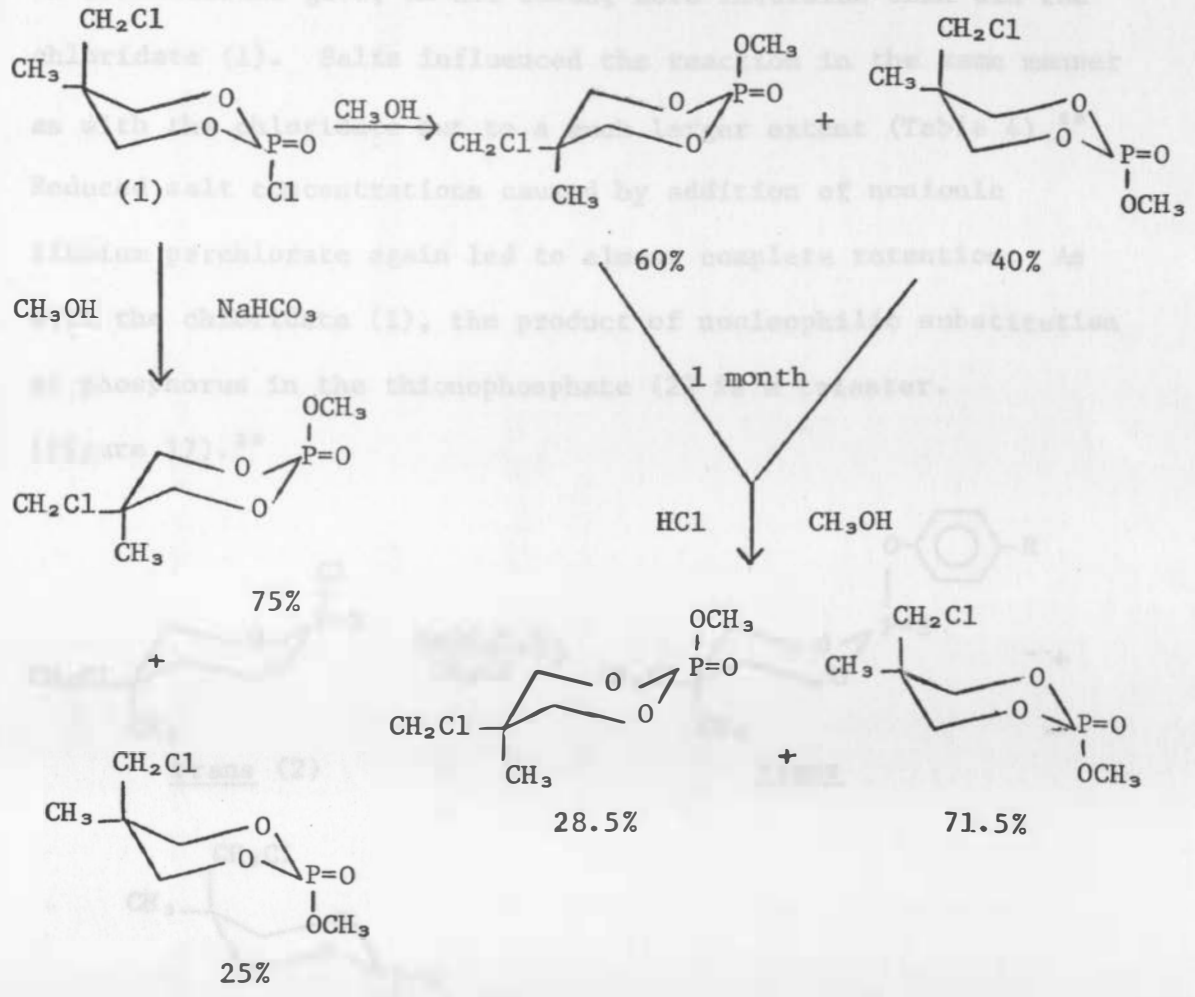


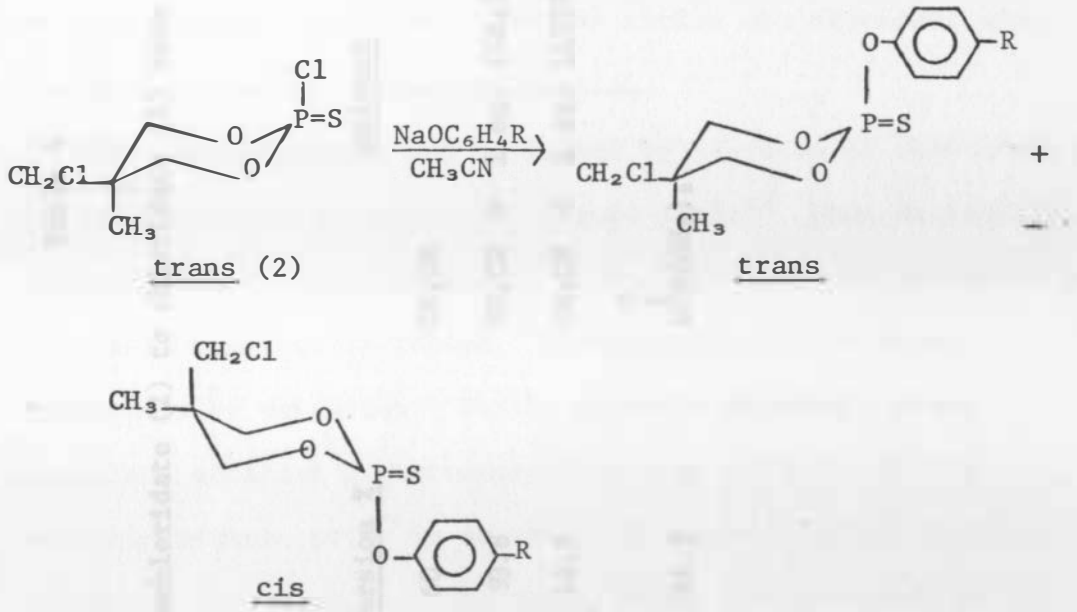
Figure 16

complete inversion due to the salt effects.[26,27]

The stereochemistry of substitution in the preparation of phosphate triesters can therefore be controlled by a change in reaction conditions. Addition of salts leads to substitution with an increase in inversion of configuration.

A trans-2-thiono-analogue of the chloridate was also prepared and reactions proved to be very similar to those of the chloridate (1). Treatment of the thionochloridate (2) with charged nucleophiles

in acetonitrile gave, in all cases, more inversion than did the chloridate (1). Salts influenced the reaction in the same manner as with the chloridate but to a much larger extent (Table 4).[28] Reduced salt concentrations caused by addition of nonionic lithium perchlorate again led to almost complete retention. As with the chloridate (1), the product of nucleophilic substitution at phosphorus in the thionophosphate (2) is a triester. (Figure 17).[28]



trans (2) trans

cis

Figure 17

The phosphate triesters react in much the same way as the chloridate. Treatment of trans-2-p-nitrophenoxy-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan with sodium p-methyl-phenoxide in acetonitrile gave a product which contained both isomers. The trans isomer (retention product) was 55.5% of the product. Addition of salt, $(CH_3)_4N^+Cl^-$, increased the inversion

Table 4

Comparison of thionochloridate (2) to chloridate (1) upon nucleophilic substitution at phosphorus.

retention %	inversion %	solvent	inversion %	retention %
40	60	CH_3CN	46.5	53.5
6.2	93.8	CH_3CN + 1 eq. $(CH_3)_4N^+Cl^-$	88.8	11.2
87.5	12.5	CH_3CN + 1 eq. $LiClO_4$	12.2	87.8
5.7	94.3	$HCN(CH_3)_2$	80.2	19.8

product to 86%. Use of N,N-dimethylformamide (DMF) as a solvent, without salt, also increased the inversion product (75%).[27] As with the chloridates (1 and 2) use of a system with reduced salt concentration increased the amounts of retention to almost the total exclusion of inversion.[27]

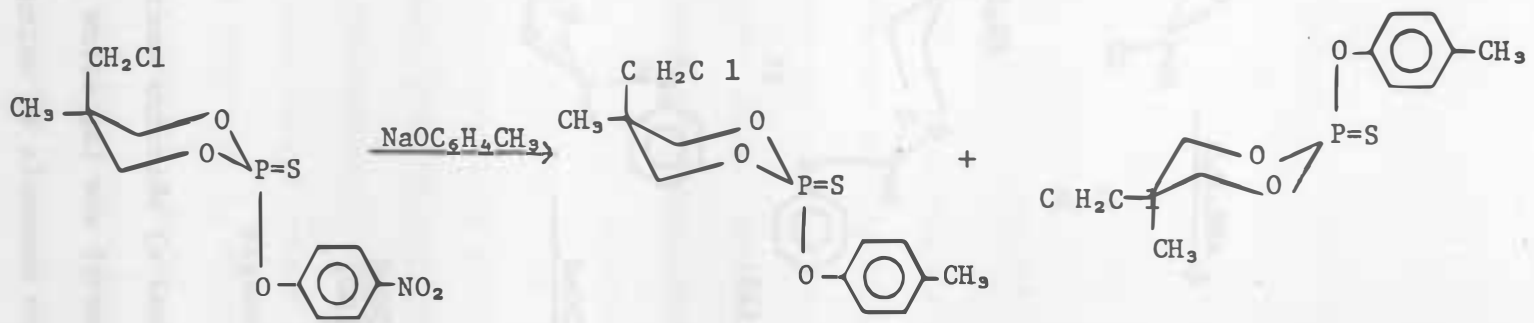
Substitutions with thionophosphate triesters are influenced in the same manner as the phosphate triesters. Salts and solvents also influence the stereochemistry of nucleophilic substitution (Table 5),[28] but not to the extent of the chloridates (1 and 2) or the phosphate triesters. Isomer ratios are dependent upon the geometry of the starting material.

Monothiophosphates can be formed by reaction of chloridate (1) with sodium thiophenoxide (Figure 18a).[26] Upon nucleophilic substitution of the thio groups with sodium p-methylphenoxide a phosphate triester is formed. Surprisingly, it is formed completely by retention. Unlike previous phosphate ester examples, addition of tetramethylammonium chloride to the reaction mixture prior to addition of the nucleophile did not influence the reaction. The reaction was not diverted to the inversion pathway (Figure 18b).[27] The phosphate triester is the only phosphate studied which is not influenced by the presence of added salt and, unlike other phosphates, undergoes nucleophilic substitution by complete retention.

Some light was thrown on the possible mechanism of nucleophilic substitution at phosphorus when it was found that a complex formed

Table 5

Nucleophilic substitution at phosphorus in thionophosphates under different solvent conditions.



Solvent	% cis	% trans
CH_3CN	95.2	4.8
CH_3CN + 1 eq. $(CH_3)_4\overset{+}{N}Cl^-$	80	20
$HCN(CH_3)_2$	87.1	12.9
$HCN(CH_3)_2$ + 1 eq. $(CH_3)_4\overset{+}{N}Cl^-$	76.2	23.8

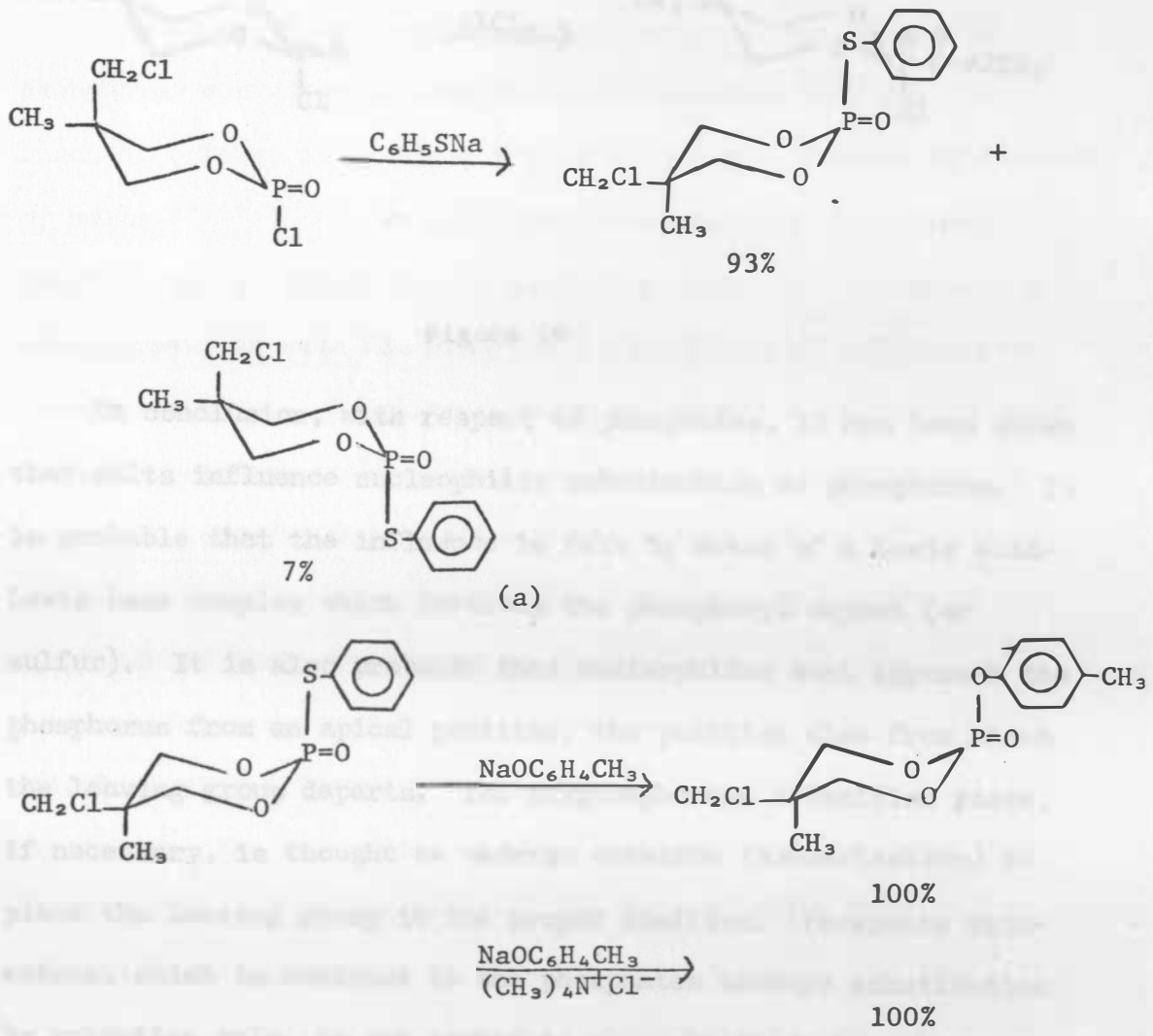


Figure 18

between aluminum chloride (a Lewis acid) and chloridate (1).[27] An insoluble white gel was formed upon addition of the chloridate (1) to a solution of aluminum chloride in anhydrous diethyl ether. The complex was shown to form through the oxygen and not through the chlorine (Figure 19).[27]

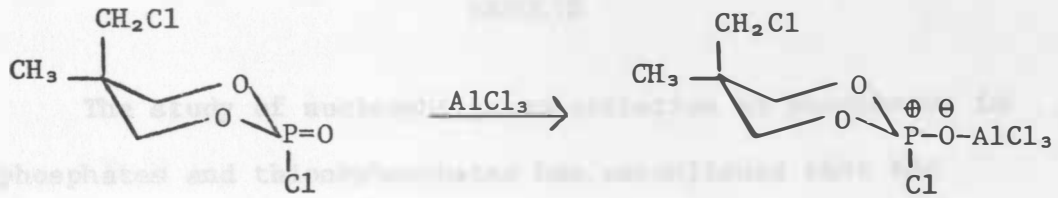


Figure 19

In conclusion, with respect to phosphates, it has been shown that salts influence nucleophilic substitution at phosphorus. It is probable that the influence is felt by means of a Lewis acid-Lewis base complex which involves the phosphoryl oxygen (or sulfur). It is also probable that nucleophiles must approach the phosphorus from an apical position, the position also from which the leaving group departs. The oxyphosphorane transition state, if necessary, is thought to undergo rotation (isomerization) to place the leaving group in the proper position. Phosphate thioesters, which in contrast to the phosphates undergo substitution by retention only, do not appear to abide by these theories.

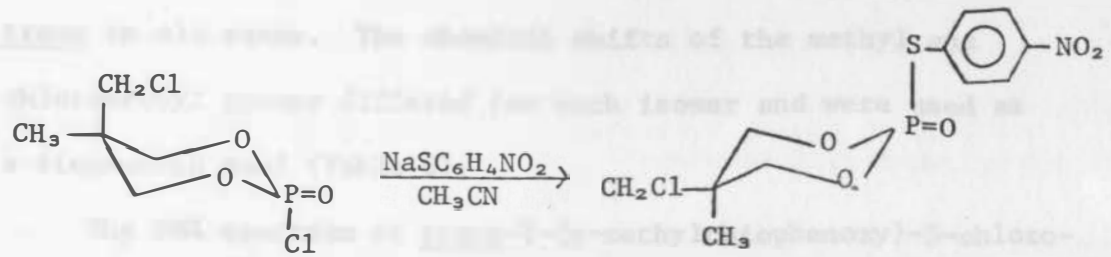
It was my objective to try to determine the mechanism of nucleophilic substitution at phosphorus in monothiophosphate triesters and to apply what I learn to the other phosphate systems. I also tried to obtain more data to show that the Lewis acid-base type complex through the phosphoryl oxygen is existent and does influence the reaction.

RESULTS

The study of nucleophilic substitution at phosphorus in phosphates and thionophosphates has established that the reaction pathway is markedly influenced by the presence or absence of salts.[25,26,27,28] We have expanded the study of nucleophilic substitution at phosphorus by employing phosphate thioesters as substrates. As with the study of nucleophilic substitution at phosphorus in the phosphates and thionophates, a system was used by which reaction pathways and products could be determined by simple NMR spectra observations. The configuration of isomers was determined by comparison of NMR spectra with spectra of compounds of known configuration.[25,26,27,28,29,30] The substrates synthesized for these studies were 2-(p-substituted-thiophenoxy)-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinans. The two groups on the fifth position were used for determination of isomer ratios. The isomer ratios were determined by comparison of peak integrations.

Trans-2-(p-nitrothiophenoxy)-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan was prepared by treatment of cis-2-chloro-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan (chloridate (1)) with freshly synthesized sodium p-nitrothiophenoxide[31,32,33] (Figure 20). The phosphate thioester was isolated in very low yield (2%). The NMR spectra showed a one hundred percent trans configuration. Other 2-(p-substituted-

thiophenoxy)-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinans



cis (1) trans 100%

Figure 20

(p-methyl, p-methoxy, p-fluoro, and p-bromo) were prepared by treatment of chloridate (1) with triethylamine and p-substituted-thiophenol (Figure 21).

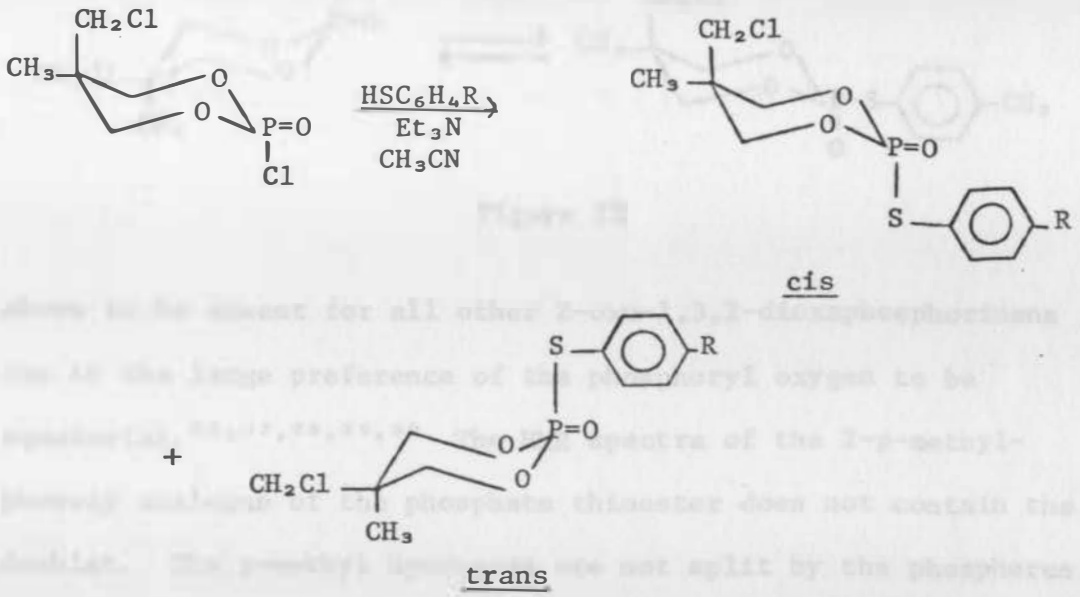


Figure 21

Yields varied, possibly in relation to the pKa value of the thiol. The products were determined by NMR to be 80-90% trans in all cases. The chemical shifts of the methyl and chloromethyl groups differed for each isomer and were used as a diagnostic tool (Table 6).

The NMR spectrum of trans-2-(p-methylthiophenoxy)-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan showed a splitting of the p-methyl hydrogens by the phosphorus atom. It is not likely that the doublet is due to conformational mobility in the phosphorinan ring (Figure 22). Conformational mobility has been

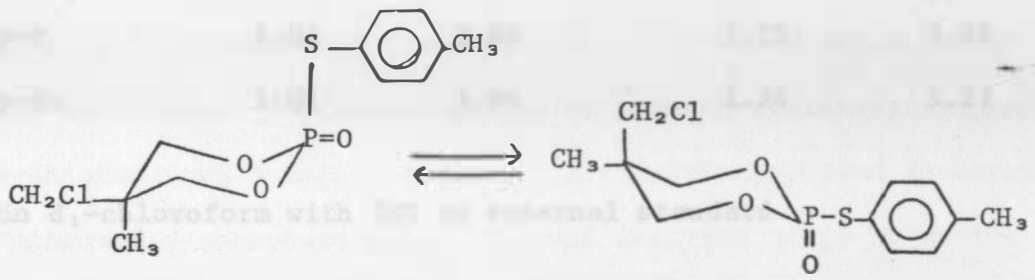


Figure 22

shown to be absent for all other 2-oxo-1,3,2-dioxaphosphorinans due to the large preference of the phosphoryl oxygen to be equatorial.[26,27,28,29,30] The NMR spectra of the 2-p-methylphenoxy analogue of the phosphate thioester does not contain the doublet. The p-methyl hydrogens are not split by the phosphorus atom. The oxygen evidently hinders the splitting of the p-methyl hydrogens by the phosphorus atom, an effect which is not

Table 6

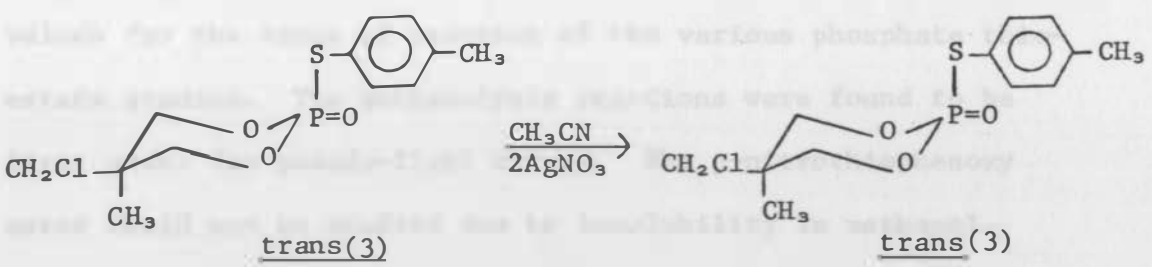
Chemical shifts* of methyl and chloromethyl groups on position five in 2-(p-substitutedthiophenoxy)-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan in ppm(δ).

	cis		trans	
Compound	CH_3	CH_2Cl	CH_3	CH_2Cl
p-NO_2	-	-	1.34	3.38
p-CH_3	0.98	3.83	1.18	3.18
p-OCH_3	1.02	3.94	1.22	3.18
p-F	1.01	3.88	1.22	3.26
p-Br	1.01	3.96	1.24	3.27

*in d_1-chloroform with TMS as external standard

observed in the phosphate thioester. The methyl hydrogens in p-methoxythiophenoxy phosphate ester also are not split by the phosphorus atom. Again, an oxygen atom hinders the effect. Futhermore, changes of solvent (chloroform, methanol, acetonitrile) did not influence the coupling constant (distance between the peaks of the doublet).

Methanolysis studies of the phosphate thioesters were undertaken to determine the kinetic order and effect of the leaving group, if any, on the rate of substitution at phosphorus in phosphate thioesters. Prior to this, a study of the stability of the phosphate thioesters and the methanolysis product (2-methoxy-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan) was undertaken. No isomerization of trans-2-(p-methylthiophenoxy)-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan (p-methyl-thiophenoxy phosphate ester (3)) was observed after an acetonitrile solution had stood for four days. Treatment of an acetonitrile solution of the p-methyl thiophenoxy phosphate esters with two equivalents of silver nitrate for four days also produced no isomerization of the phosphate thioester (Figure 23). The



trans(3) trans(3)

Figure 23

methanolysis product, methyl ester, also showed no isomerization when dissolved in methanol, even after treatment of a methanolic solution with silver nitrate (Figure 24).

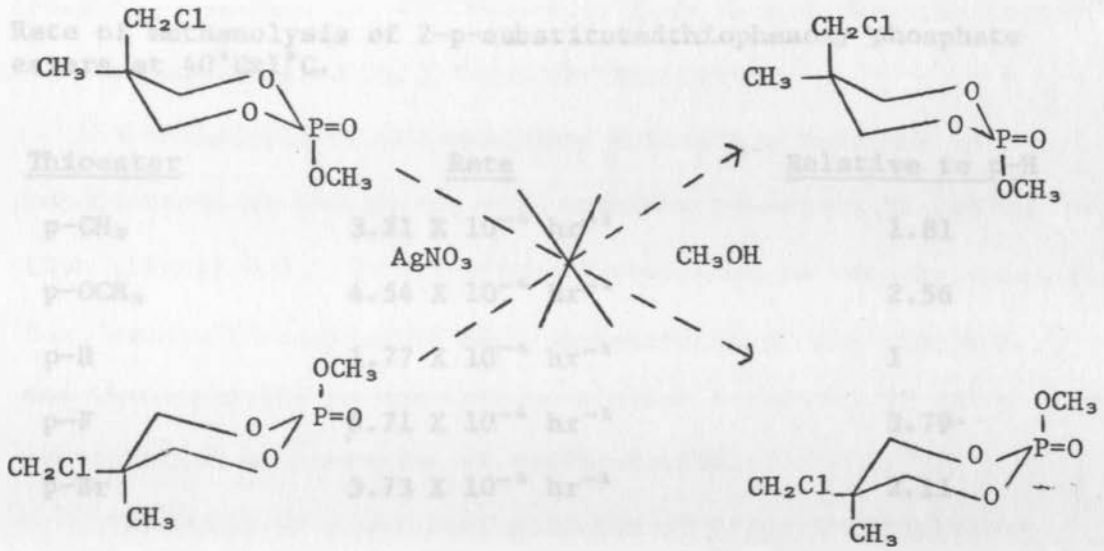


Figure 24

Methanolysis of phosphate thioesters was carried out in d_4-methanol at 40°C±1°C. The reaction was followed via NMR and the rate determined by plotting the natural logarithm of the concentration of the phosphate thioester against time. The slope was determined by the least squares method. Table 7 gives the values for the rates of reaction of the various phosphate thioesters studied. The methanolysis reactions were found to be first order (or pseudo-first order). The p-nitrothiophenoxy ester could not be studied due to insolubility in methanol. Methanolysis of the phosphate thioesters took from three to six

Table 7

Rate of methanolysis of 2-p-substitutedthiophenoxy phosphate esters at 40°C±1°C.

Thioester	Rate	Relative to p-H
p-CH_3	3.21 X 10^{-4} hr^{-1}	1.81
p-OCH_3	4.54 X 10^{-4} hr^{-1}	2.56
p-H	1.77 X 10^{-4} hr^{-1}	1
p-F	6.71 X 10^{-4} hr^{-1}	3.79
p-Br	3.73 X 10^{-4} hr^{-1}	2.11

months to go to completion.

The NMR spectra of the methoxy phosphate ester showed splitting of the methoxy methyl by the phosphorus as in the case of the p-methylthiophenoxy phosphate ester.[26] However, the coupling constant for the former is much larger than the latter - ∿18 cps as compared to 2.3 cps for the latter.

Methanolysis of the phosphate thioesters resulted in substitution at phosphorus with complete retention of configuration (Figure 25). Substitution by retention is totally unexpected, for, even with negligible salt concentrations, the phosphates and thionophosphates gave products which resulted, in part, from substitution by inversion of configuration.

Treatment of a methanol solution of trans-p-methylthiophenoxy phosphate ester (3) with one equivalent of silver nitrate for one week resulted in both isomers of the methyl ester being formed. The retention isomer (trans) was 53% of the product. In contrast to the methanolysis of the phosphate thioesters in the absence of silver nitrate, which took months, the methanolysis of the phosphate thioesters with one equivalent of silver nitrate present was 70% complete in seven days (Figure 25). A seven day methanolysis of trans-p-methylthiophenoxy phosphate with two equivalents of silver nitrate present increased the inversion product to 65%. Again the reaction was more complete in the seven day period than methanolysis without added silver

nitrate. Only 12% of the recovered product was found to be starting material (Figure 25).

Salts were found to influence the pathway of nucleophilic substitution at phosphorus in phosphate thioesters only if the salt was a strong Lewis acid. In the case of trans-2-thiophenoxy-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan, nucleophilic substitution at phosphorus with one equivalent of tetramethylammonium chloride present did not divert the substitution pathway from complete retention.[27]

Previously, aluminum chloride was found to complex with the phosphoryl oxygen in the chloridate (1).[27] Due to the effect of a strong Lewis acid on the methanolysis of phosphate thioesters, we conducted studies to further investigate complex formation.

Infrared spectra of chloroform solutions of phosphate esters and phosphate thioesters were obtained. A solvent blank was used in the standard beam to offset most of the solvent absorption. Introduction of aluminum chloride to the sample solution broadened phosphoryl bond absorption (Spectra 8-13). Trans-2-(p-methylphenoxy)-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan was used as the phosphate ester and trans-2-(p-fluorothiophenoxy)-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan was used as the phosphate thioester.

The infrared spectrum of the aluminum chloride-chloridate (1) complex was also obtained and compared to that of the

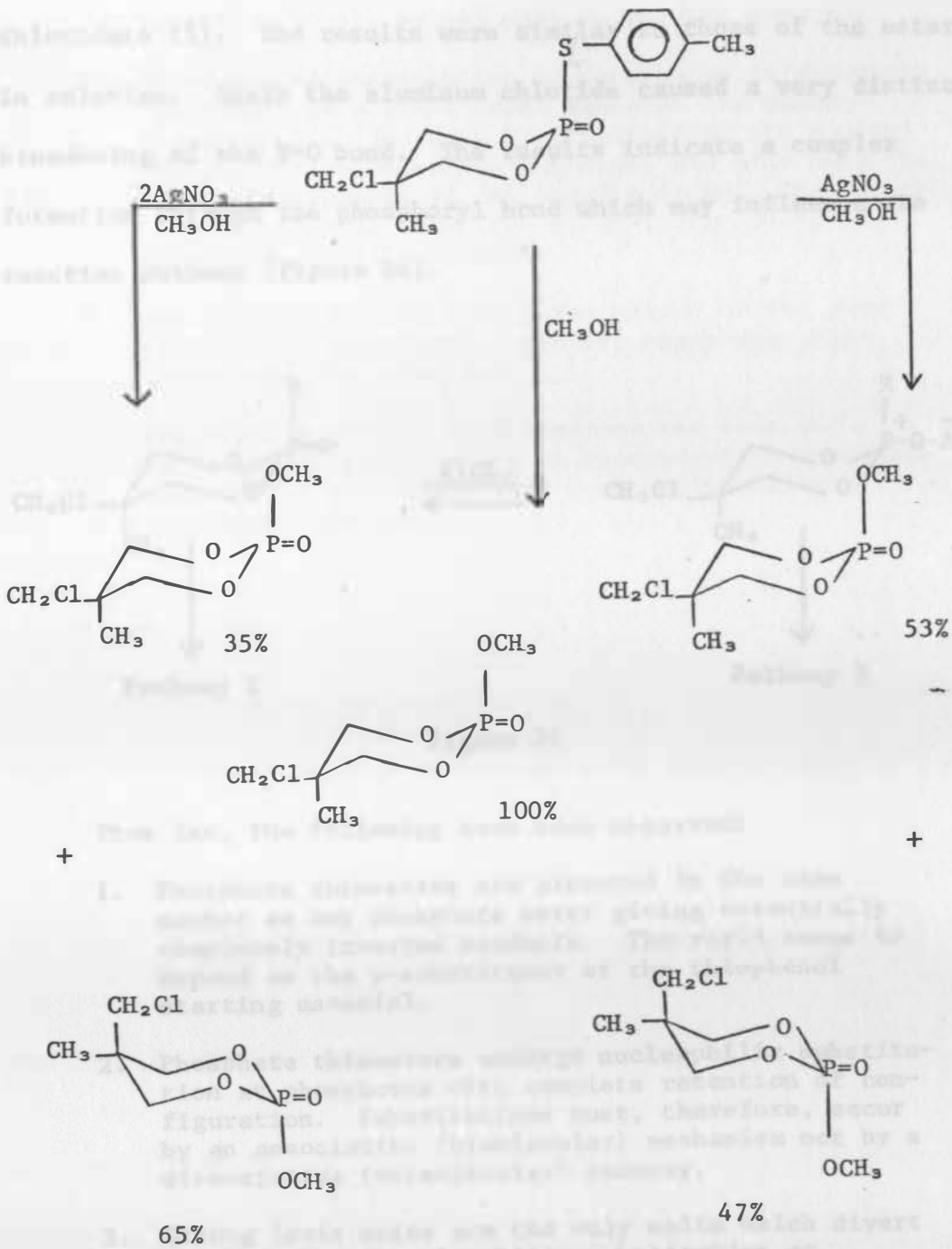

S
CH3
P=O
O
O
CH2Cl
CH3
2AgNO3
CH3OH
AgNO3
CH3OH
CH3OH
OCH3
P=O
CH2Cl
CH3
35%
53%
100%
+
+
CH2Cl
CH3
OCH3
65%
47%

Figure 25

chloridate (1). The results were similar to those of the esters in solution. Again the aluminum chloride caused a very distinct broadening of the P=O bond. The results indicate a complex formation through the phosphoryl bond which may influence the reaction pathway (Figure 26).

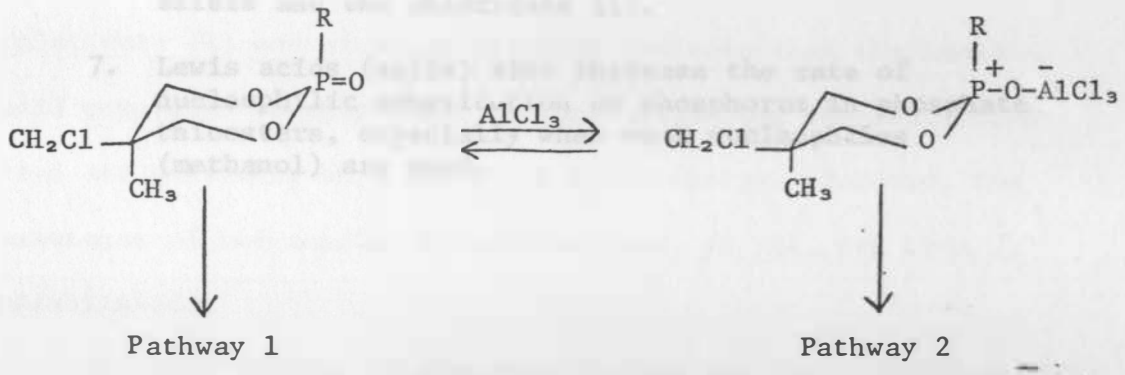


Figure 26

Thus far, the following have been observed:

1. Phosphate thioesters are prepared in the same manner as any phosphate ester giving essentially completely inverted products. The yield seems to depend on the p-substituent of the thiophenol starting material.

2. Phosphate thioesters undergo nucleophilic substitution at phosphorus with complete retention of configuration. Substitutions must, therefore, occur by an associative (bimolecular) mechanism not by a dissociative (unimolecular) pathway.

3. Strong Lewis acids are the only salts which divert the pathway of nucleophilic substitution at phosphorus in phosphate thioesters to inversion. The reaction rate is increased as well.

4. The phosphorus interacts with the methyl substituent in the p-methylthiophenoxy phosphate ester causing a

splitting of the methyl peak in the NMR spectra.

5. Nucleophilic substitution at phosphorus in phosphate thioesters is a first order reaction (or pseudo-first order). The rate is dependent on the concentration of the phosphate thioester and also upon the electronic demands of the leaving group. The possible rate determining formation of an intermediate is, therefore, highly unlikely.

6. Lewis acids (salts) affect the nature of the phosphoryl bond in phosphate esters, phosphate thioesters and the chloridate (1).

7. Lewis acids (salts) also increase the rate of nucleophilic substitution at phosphorus in phosphate thioesters, especially when weak nucleophiles (methanol) are used.

DISCUSSION

Part I

Discovery of a Lewis acid complex in which the Lewis acid complexes with a phosphoryl oxygen has led us to study the effect of complexing on the phosphoryl bond stretching frequency.

Infrared absorption studies of the isolated complex of chloridate (1) and aluminum chloride indicate that the Lewis acid complexes to phosphoryl oxygen, broadening the absorption band and generally shifting it to lower energy. However, the existence of the complex in solution had, as yet, not been established.

Solution studies of phosphate esters and phosphate thioesters in the presence of added aluminum chloride leads us to conclude that the presence of Lewis acids weakens the phosphoryl bond. The infrared spectrum of a solution with aluminum chloride present shows a lowering of the phosphorus-oxygen bond energy. The spectra of many phosphates indicates that the complex is in equilibrium with the uncomplexed phosphate ester.(Figure 27). It is the complex that is thought to be responsible for a shift in reaction pathway to a pathway favoring inversion of configuration.

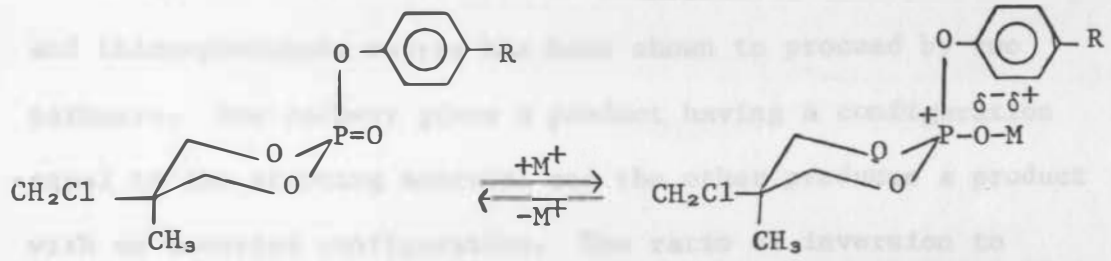
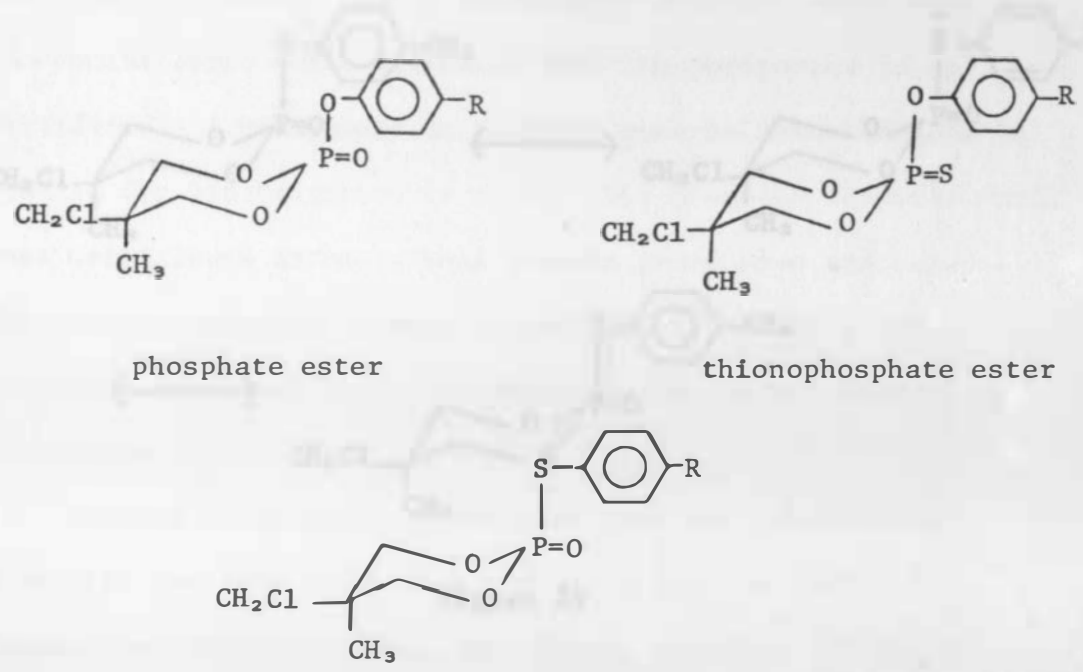


Figure 27

Part II

Nucleophilic substitution at phosphorus in phosphate esters and thionophosphate esters has been shown to proceed by two pathways. One pathway gives a product having a configuration equal to the starting material and the other produces a product with an inverted configuration. The ratio of inversion to retention depends on the configuration of reactant as well as the type of phosphate ester used. The greatest factor governing the pathway is the absence or presence of salt in a reaction mixture.[26,27,28] Phosphate esters and thionophosphate esters undergo nucleophilic substitution at phosphorus in much the same manner. In both, nucleophilic substitution at phosphorus proceeds primarily with retention of configuration in the absence of salts and almost completely with inversion when salts are present.[26,27,28] In contrast, phosphate thioesters undergo nucleophilic substitution at phosphorus with complete retention of configuration. Only the presence of very strong Lewis acids changes the reaction pathway to inversion.

In comparing the three types of phosphate esters, the main distinguishing feature is the sulfur atom, its presence and position (Figure 28). The substitution of sulfur for oxygen in the phosphoryl position does not drastically influence the result of nucleophilic substitution at phosphorus. However, the replacement of thiophenoxide for phenoxide as the leaving



phosphate ester

thionophosphate ester

phosphate thioester

Figure 28

group, makes nucleophilic substitution at phosphorus with retention absolute. No inversion of configuration is observed. How does sulfur in thiophenoxy phosphate esters influence the reaction?

Phosphorus is shown to couple with the methyl hydrogens in 2-p-methylthiophenoxy phosphate ester. The coupling indicates that splitting by phosphorus is transmitted through the aromatic ring. It is unlikely that coupling over such a distance (seven bonds) could occur through sigma bonds, therefore a conjugated π system is required (Figure 29).[34] Since the thiophenoxy group

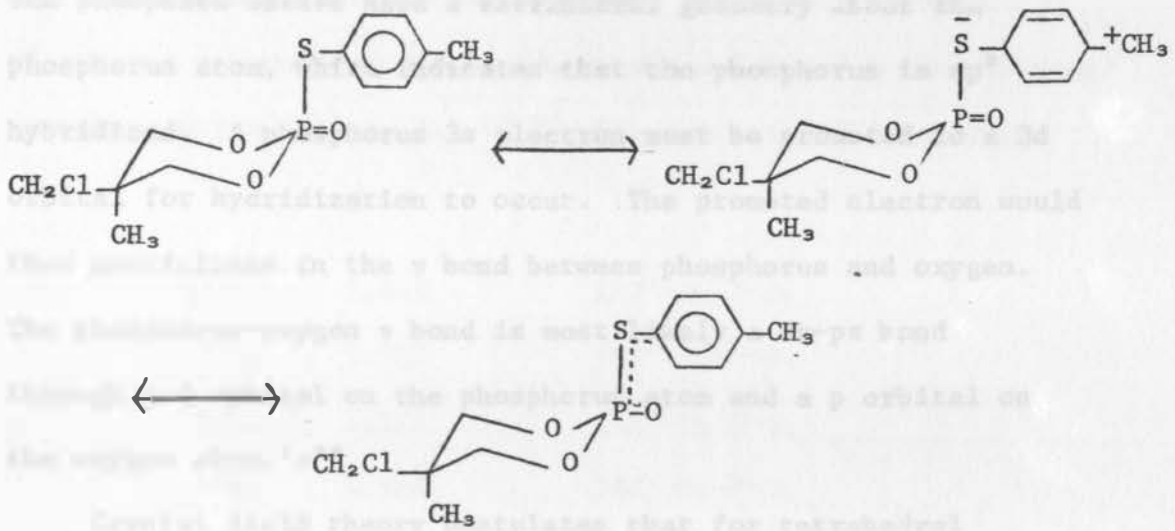


Figure 29

is conjugated with the phosphorus atom, various p-substituted thiophenoxy leaving groups would be expected to influence the reaction rate in a predictable manner if the departure of the leaving group takes place in the rate-determining step.[35] Such is the case.

The big difference between a bonded oxygen atom and a bonded sulfur atom is the presence of d orbitals on the sulfur which are lacking on the oxygen atom. Sulfur, which has vacant 3d orbitals, could very readily conjugate to the phosphorus by means of a $d\pi$-$d\pi$ system. The sulfur, through its d orbitals, could also conjugate to the π system of the aromatic ring.

The phosphorus atom is π bonded to the phosphoryl oxygen.

The phosphate esters have a tetrahedral geometry about the phosphorus atom, which indicates that the phosphorus is sp^3 hybridized. A phosphorus 3s electron must be promoted to a 3d orbital for hydridization to occur. The promoted electron would then participate in the π bond between phosphorus and oxygen. The phosphorus-oxygen π bond is most likely a $d\pi$-$p\pi$ bond through a d orbital on the phosphorus atom and a p orbital on the oxygen atom.[1,36]

Crystal field theory postulates that for tetrahedral geometry, the five d orbitals are split into two sets of degenerate orbitals, the e_g and the t_{2g} orbitals (Figure 30).[1]

Figure 30

The two e_g orbitals, because of direction away from the four ligands of the tetrahedron, become orbitals of low energy. The three t_{2g} orbitals have higher energy because they are directed at the four ligands.[1] Hence repulsion increases their energy.[37] However, because of the π bond it is unlikely that the system about the phosphorus is that of a true tetrahedron. Rather, a strained tetrahedron is expected. Indeed an irregular tetrahedron

has been shown by X-ray studies to best represent the structure of related compounds - phenoxy phosphate ester and p-bromophenoxy phosphate ester (Figure 31).[29,30] The two sets of degenerate

$P-O_3$	1.44Å	$107°-O_1-P-O_2$
$P-O_1$	1.55Å	$115°-O_2-P-O_3$
$P-O_2$	1.57Å	$114°-O_3-P-O_4$
$P-O_4$	1.59Å	$106°-O_4-P-O_1$
		$101°-O_2-P-O_4$
		$112°-O_1-P-O_3$

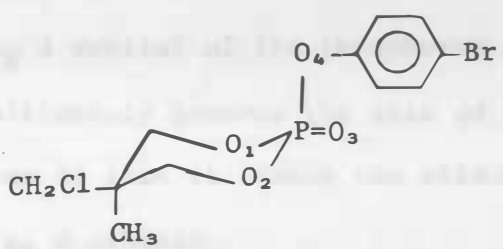


Figure 31

orbitals in the tetrahedral structure are, more than likely, not degenerate. The loss of degeneracy lowers the energy of one of the e_g orbitals (Figure 32). The phosphorus d orbital of lowest energy would then be the orbital which accepts the promoted 3s electron.

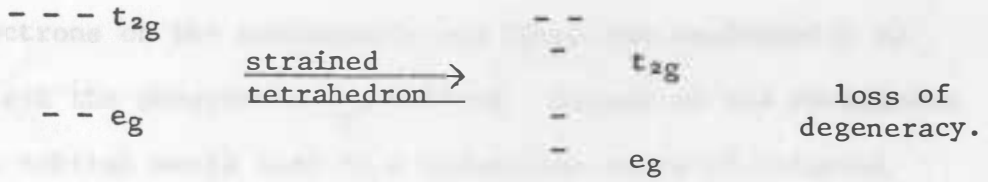


Figure 32

The promoted 3s electron of phosphorus has entered the lowest energy e_g orbital and has formed a π bond to the phosphoryl oxygen. The presence of π electrons in the lowest energy e_g orbital would cause an electron-electron repulsion between these π electrons and the electrons of an attacking nucleophile. Therefore, any nucleophilic attack at a d orbital must occur at the other e_g d orbital of the phosphorus atom. The π bonding d orbital ultimately governs the site of attack by a nucleophile at phosphorus in that it limits the attack to the non-bonding phosphorus e_g d orbital.

A $d\pi$-$p\pi$ phosphoryl or thionophosphoryl bond may employ the phosphorus $d_{x^2-y^2}$ orbital. The π bond which results would be polar because the point of overlap of the phosphorus $d_{x^2-y^2}$ orbital with the phosphoryl oxygen p orbital would be closest to the oxygen atom. The electron density of the π bond would exist mainly on the phosphoryl oxygen atom and result in a slight separation of charges between the phosphoryl oxygen and the phosphorus. The π electrons in the $d_{x^2-y^2}$ orbital would repel

electrons on the nucleophile and force the nucleophile to attack the phosphorus d_{z^2} orbital. Attack on the phosphorus d_{z^2} orbital would lead to a transition state of trigonal bipyramidal geometry and ultimately result in inversion of configuration (Figure 33).

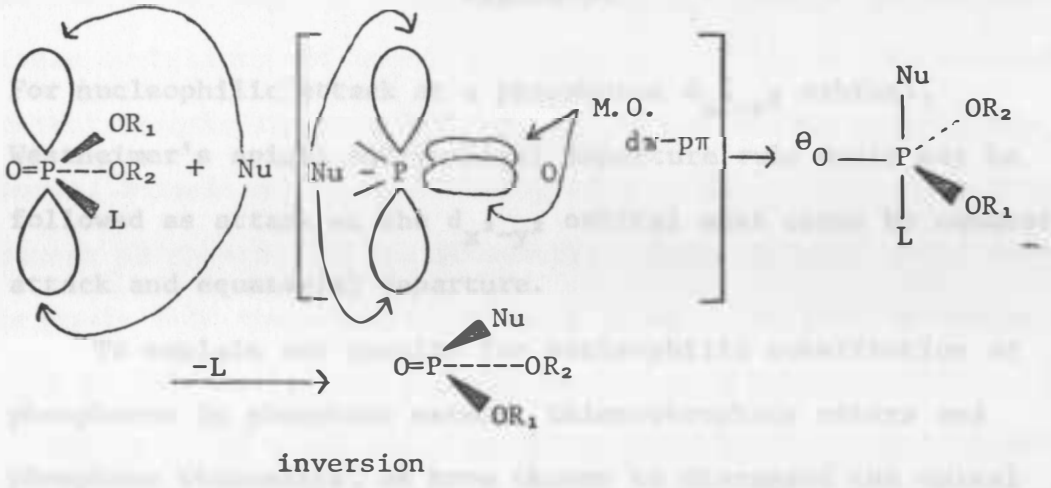


Figure 33

A filled phosphorus-oxygen (sulfur) dπ-pπ bond which employs a phosphorus d_{z^2} orbital would force due to electron repulsion, nucleophilic attack at the $d_{x^2-y^2}$ orbital of the phosphorus, an orbital with low electron density. The transition state which results is square pyramidal and would lead to complete retention of configuration in the product (Figure 34).

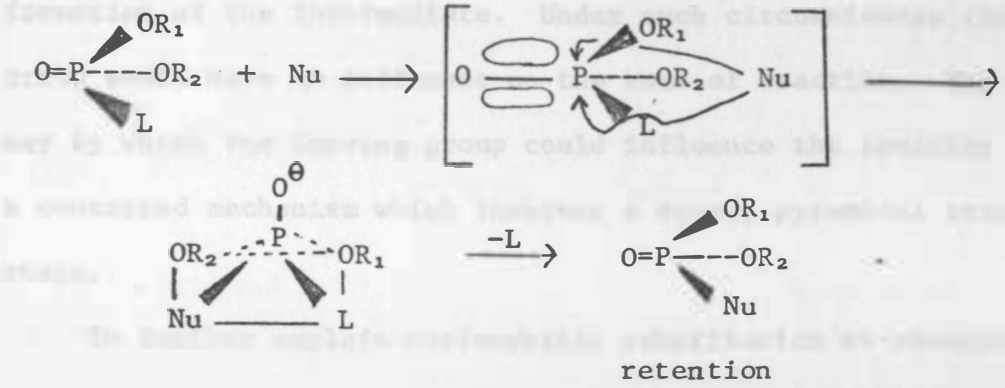


Figure 34

For nucleophilic attack at a phosphorus $d_{x^2-y^2}$ orbital, Westheimer's apical entry-apical departure rule would not be followed as attack at the $d_{x^2-y^2}$ orbital must occur by equatorial attack and equatorial departure.

To explain our results for nucleophilic substitution at phosphorus in phosphate esters, thionophosphate esters and phosphate thioesters, we have chosen to disregard the apical entry-apical departure rule. Our results show a distinct preference for nucleophilic substitution at phosphorus in the absence of any other influences to proceed via a pathway by which retention of configuration is favored, a pathway which requires equatorial attack and departure.

Our results also indicate that the leaving group influences the reaction rate. For a pathway in which a stable intermediate intervenes, the rate-determining step should, as in the

case of substitution at carbonyl carbon in carbon esters, be the formation of the intermediate. Under such circumstances the leaving group would have no influence on the rate of reaction. The only pathway by which the leaving group could influence the reaction rate is by a concerted mechanism which involves a square pyramidal transition state.

To further explain nucleophilic substitution at phosphorus in phosphate, and thionophosphate esters, we assume a phosphorus-oxygen (sulfur) dπ-pπ bond to exist through the d_{z^2} orbital on the phosphorus. Linear combination of atomic orbitals (LCOA)[38] gives the molecular orbital description as $1/2(P_{x_1}-P_{x_2}-P_{x_3}+P_{x_4})$.[39] The description, of course, depends on the coordinates used in the system. The dπ-pπ bond between phosphorus and the phosphoryl oxygen (sulfur) could not conjugate with the adjoining phenoxy group. The phenoxy oxygen atom which is attached to the phosphorus, has no d orbitals and has filled p orbitals. The π electrons in the phosphoryl bond would therefore, remain localized between the phosphorus and the phosphoryl oxygen atoms.

Also, there would be significant backbonding through the vacant phosphorus $d_{x^2-y^2}$ orbital to a filled p orbital of the phosphoryl oxygen. The phosphorus $d_{x^2-y^2}$ orbital would then contain backbonding electrons. The backbond, as in the case of the $d_{x^2-y^2}\pi$-pπ bond would be polar as the electron density would exist mainly on the phosphoryl oxygen. However, this would further stabilize the $d_{z^2}\pi$-pπ bond. The actual structure could be a resonance hybrid between three existing limiting forms (Figure 35).

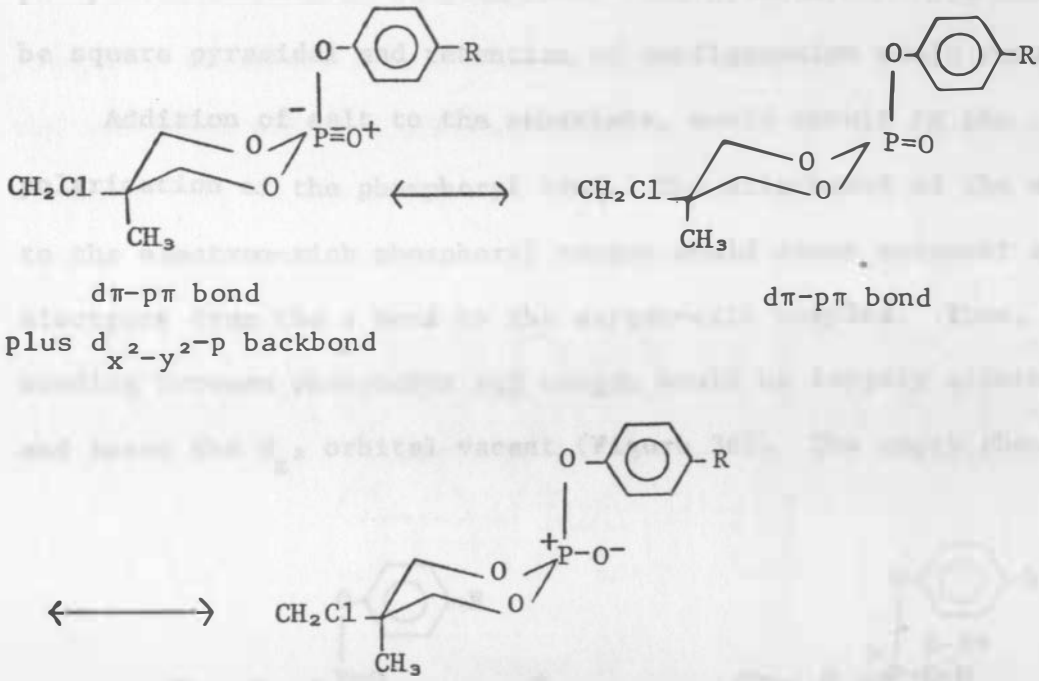


Figure 35

A nucleophilic attack on the d_{z^2} phosphorus orbital would result in inversion of configuration while nucleophilic attack on the phosphorus $d_{x^2-y^2}$ orbital would give a product with retention of configuration. However, the π electrons in the d_{z^2} phosphorus orbital would repel the electrons of the nucleophile thus forcing the nucleophile to attack the phosphorus $d_{x^2-y^2}$ orbital. Although the $d_{x^2-y^2}$ orbital contains backbonding electrons (both donated by the phosphoryl oxygen), electron density in the backbond is located mostly at the phosphoryl oxygen. Hence repulsion of the attacking nucleophile by the electron deficient $d_{x^2-y^2}$

phosphorus-orbital is at a minimum. The transition state would be square pyramidal and retention of configuration would result.

Addition of salt to the substrate, would result in the polarization of the phosphoryl bond. The attachment of the salt to the electron-rich phosphoryl oxygen would cause movement of electrons from the π bond to the oxygen-salt complex. Thus, π bonding between phosphorus and oxygen would be largely eliminated and leave the d_{z^2} orbital vacant.(Figure 36). The empty phosphorus d_{z^2}

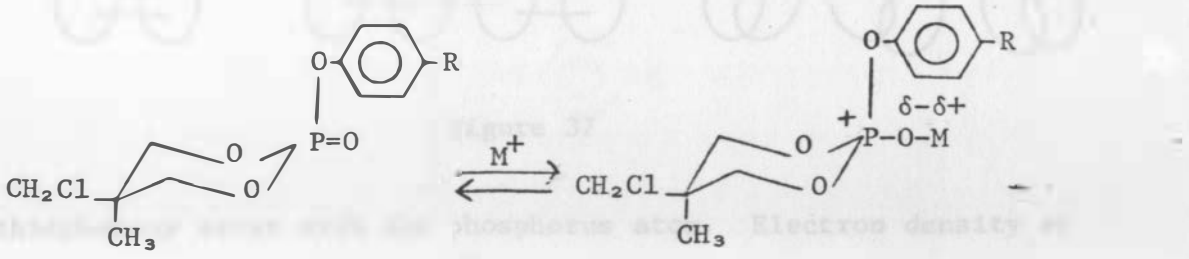


Figure 36

orbital (lowest energy d orbital on the phosphorus) would be open to attack by the nucleophile. Attack by the nucleophile at the phosphorus d_{z^2} orbital would give a trigonal bipyramidal transition state and result in inversion of configuration. The d_{z^2} orbital would be more available for attack by the nucleophile than the $d_{x^2-y^2}$ orbital because of its low energy. Therefore, nucleophilic substitution at phosphorus in the presence of salts should result in a large increase in the inversion product. The predicted results agree with our observations.

In contrast to the phosphate and thionophosphate esters, the phosphate thioester presents a different π orbital picture due to the available sulfur d orbitals (Figure 37). Conjugation from the aromatic ring to the phosphoryl oxygen could exist and would account for the coupling of the hydrogens on the p-methyl of the

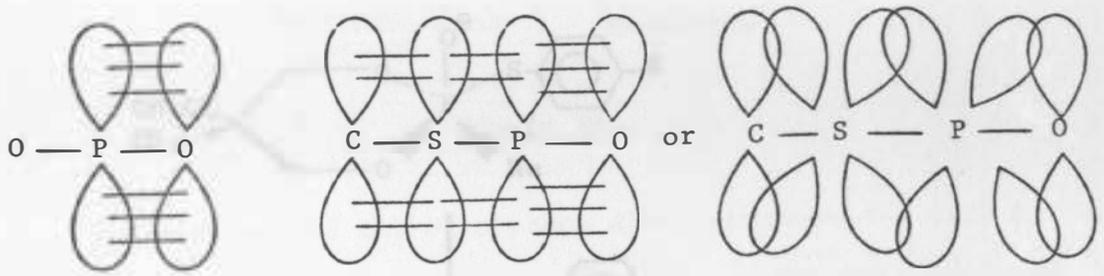


Figure 37

thiophenoxy ester with the phosphorus atom. Electron density at phosphorus via its d_{z^2} orbitals could remain high with or without the influence of an added cation. Nucleophilic attack on the phosphorus, could only be accomplished through the attack of the nucleophile on the phosphorus $d_{x^2-y^2}$ orbital. The result would be complete retention of configuration in the product (Figure 38).

Addition of weak Lewis acids would not be expected to influence the reaction pathway. The polarization of the phosphoryl oxygen bond in the phosphate thioester would require a very strong Lewis acid to lower the electron density about phosphorus. Addition of tetramethylammonium chloride does not

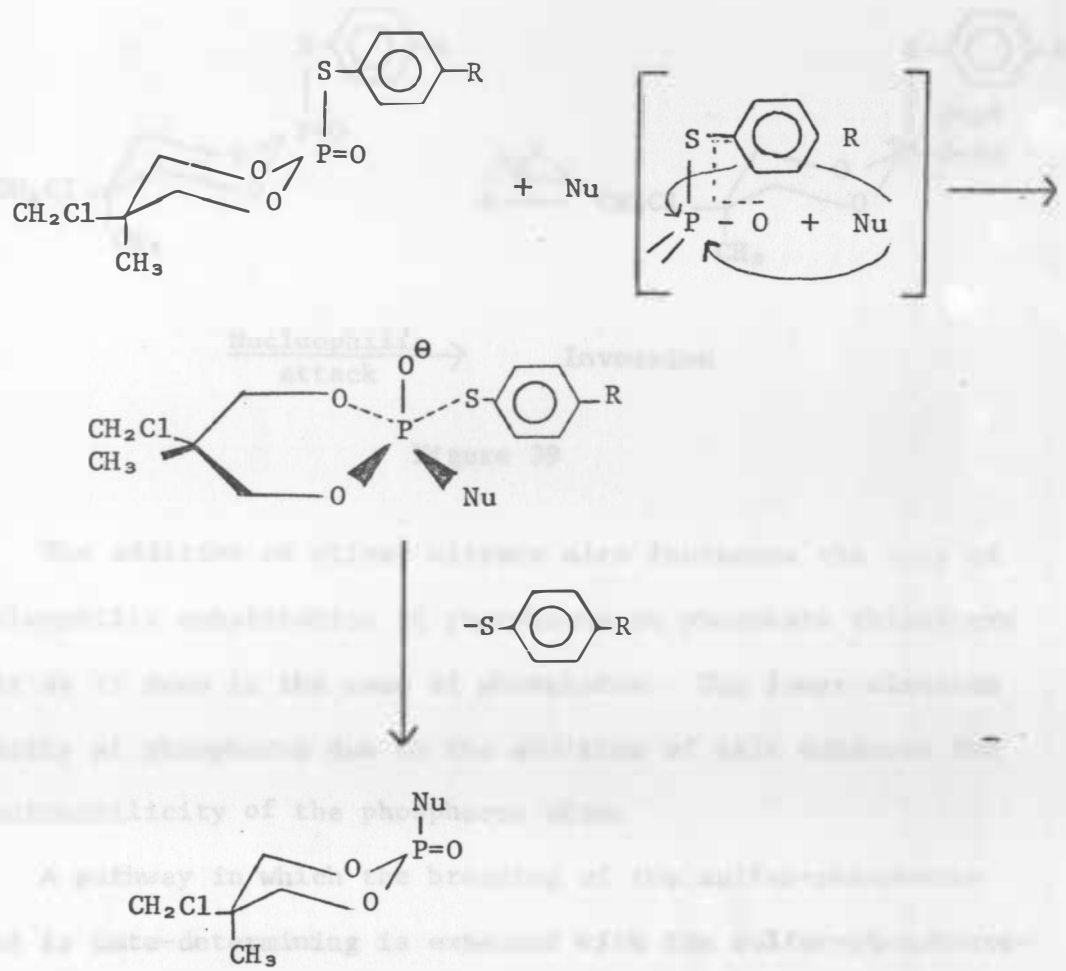


Figure 38

divert the reaction from complete retention.[27] The use of silver nitrate, however, did divert the reaction to increased inversion of configuration. Silver ion, a strong Lewis acid, by complexing with phosphoryl oxygen depletes the d_{z^2} orbital at phosphorus of electrons and allows nucleophilic attack at the orbital thereby increasing the amount of inversion (Figure 39).

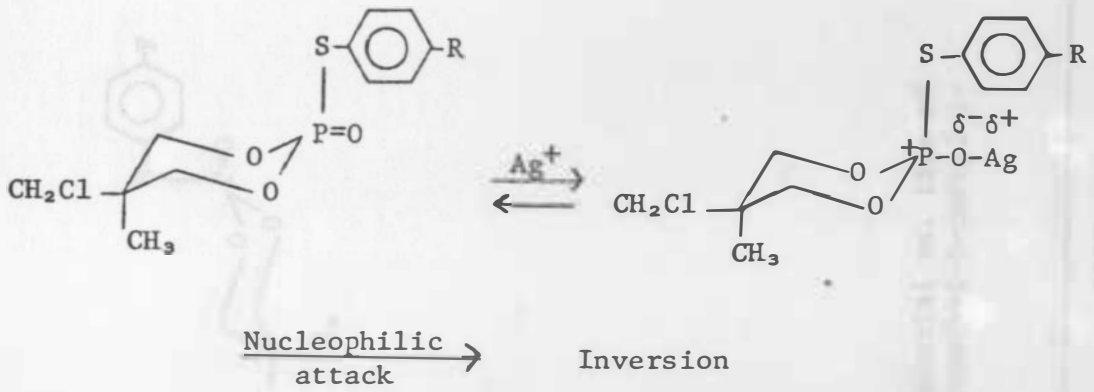


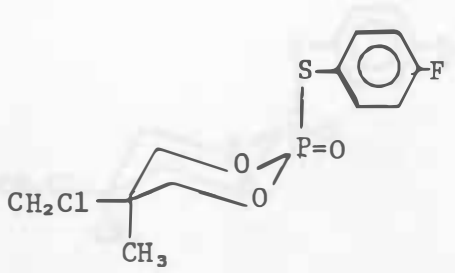
Figure 39

The addition of silver nitrate also increases the rate of nucleophilic substitution at phosphorus in phosphate thioesters just as it does in the case of phosphates. The lower electron density at phosphorus due to the addition of salt enhances the electrophilicity of the phosphorus atom.

A pathway in which the breaking of the sulfur-phosphorus bond is rate-determining is expected with the sulfur-phosphorus-oxygen dπ system. Indeed, we have found that the nature of the p-substituent on the thiophenoxy group influences the rate of nucleophilic substitution at phosphorus in phosphate thioesters.

A donating group in the para position makes the thiophenoxy group a stronger base. The sulfur-phosphorus σ bond and the dπ bond system is strengthened in relation to the unsubstituted thiophenoxy ester. An electron withdrawing group would have an opposite effect. These expectations are realized in a gross sense but a simple free energy relationship between rate and

Figure 40

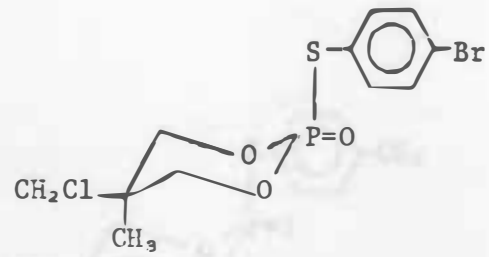


slope = $-k = -6.71 \times 10^{-4}\ hr^{-1}$

$k = 6.71 \times 10^{-4}\ hr^{-1}$

Plot of natural logarithm of percent starting material vs. time of methanolysis of 2-(p-fluorothiophenoxy)-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan at 40°C±1°C.

Figure 41

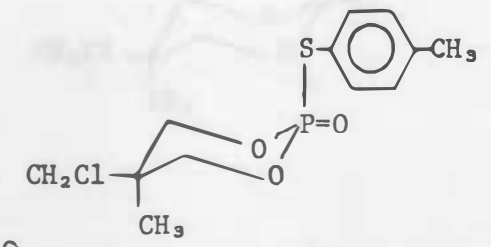


slope = $-k = -3.73 \times 10^{-4}\ hr^{-1}$

$k = 3.73 \times 10^{-4}\ hr^{-1}$

Plot of natural logarithm of percent starting material vs. time of methanolysis of 2-(p-bromothiophenoxy)-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan at 40°C±1°C.

Figure 42

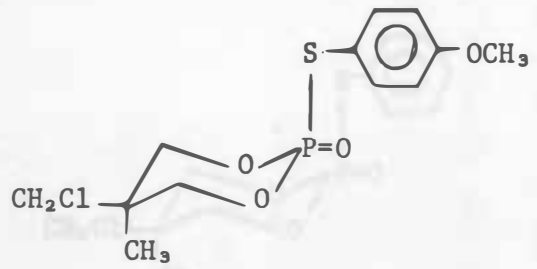


slope = $-k = -3.21 \times 10^{-4}\ hr^{-1}$

$k = 3.21 \times 10^{-4}$

Plot of natural logarithm of percent starting material vs. time of methanolysis of 2-(p-methylthiophenoxy)-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan at 40°C±1°C.

Figure 43

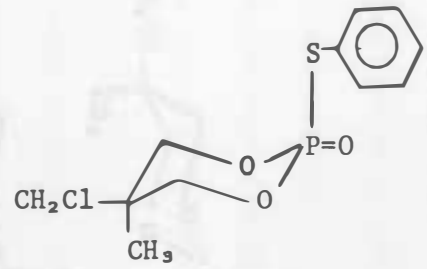


slope = $-k = -4.54 \times 10^{-4}\ hr^{-1}$

$k = 4.5 \times 10^{-4}\ hr^{-1}$

Plot of natural logarithm of percent starting material vs. time of methanolysis of 2-(p-methoxythiophenoxy)-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan at 40°C±1°C.

Figure 44



slope = $-k = -1.77 \times 10^{-4}\ hr^{-1}$

$k = 1.77 \times 10^{-4}\ hr^{-1}$

Plot of natural logarithm of percent starting material vs. time of methanolysis of 2-(p-thiophenoxy)-5-chloromethyl-5-methyl-2-oxo-1, 3,2-dioxaphosphorinan at 40°C±1°C.

substituent is not attained (Figure 40-44). The lack of such a relationship may very well indicate that the reaction is auto-

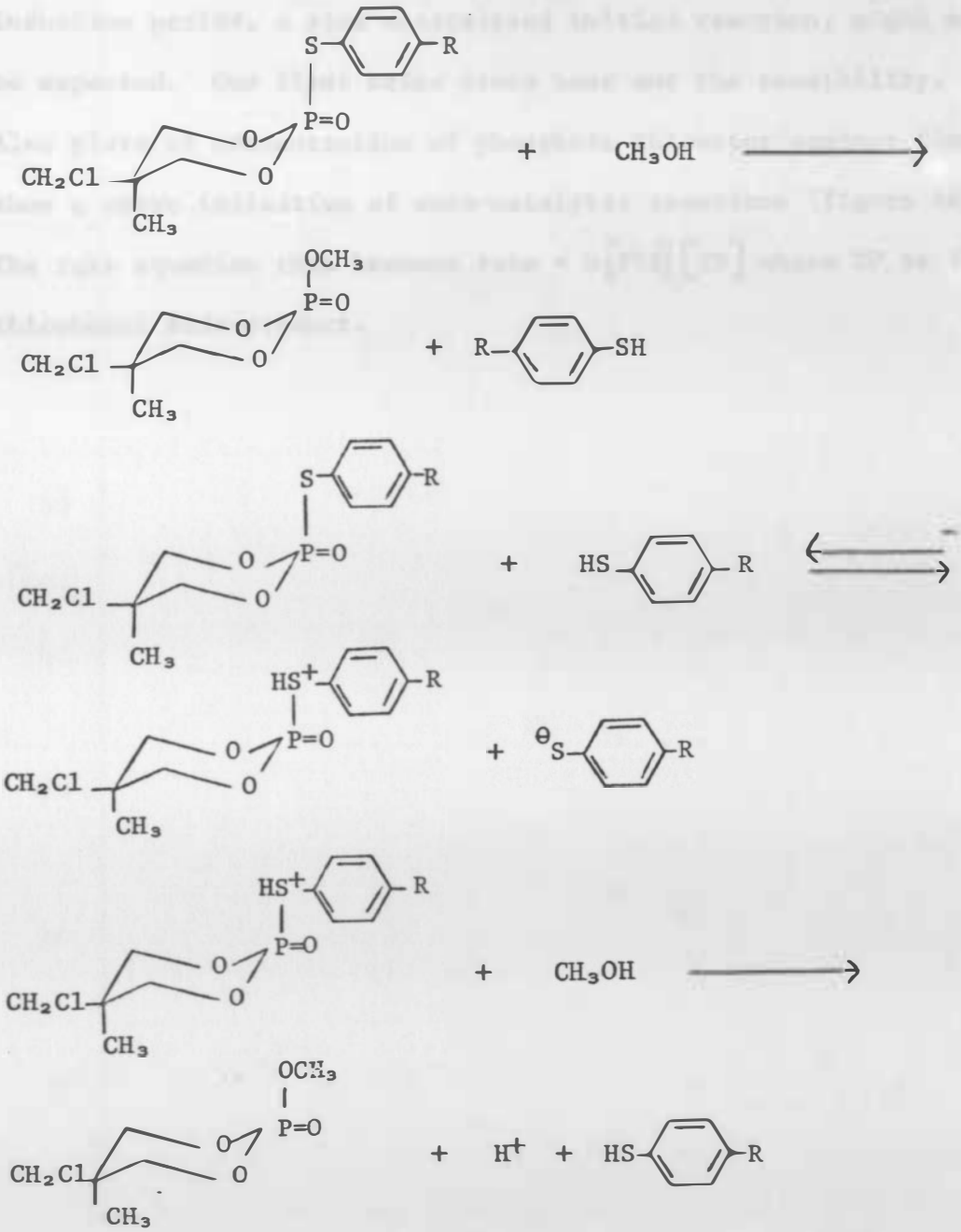
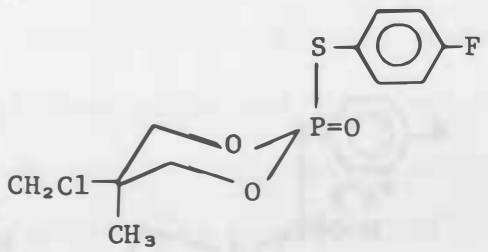


Figure 45

catalytic. If such is the case the expected first order rate relationship would not hold. The rate would increase as the concentration of catalyst ($R-C_6H_4-SH$) built up (Figure 45). An induction period, a slow uncatalyzed initial reaction, might also be expected. Our first order plots bear out the possibility. Also plots of concentration of phosphate thioester against time show a curve indicative of auto-catalytic reactions (Figure 46).[40] The rate equation thus becomes rate = $k[PTE][TP]$ where TP is the thiophenol side-product.

Figure 46

Plot of percent starting material vs. time of methanolysis of 2-(p-fluorothiophenoxy)-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan at 40°C±1°C.



CONCLUSION

In summary, the mechanism of nucleophilic substitution at phosphorus includes two separate pathways, one favored by the presence of salts and one favored in the absence of salts (Figure 47).

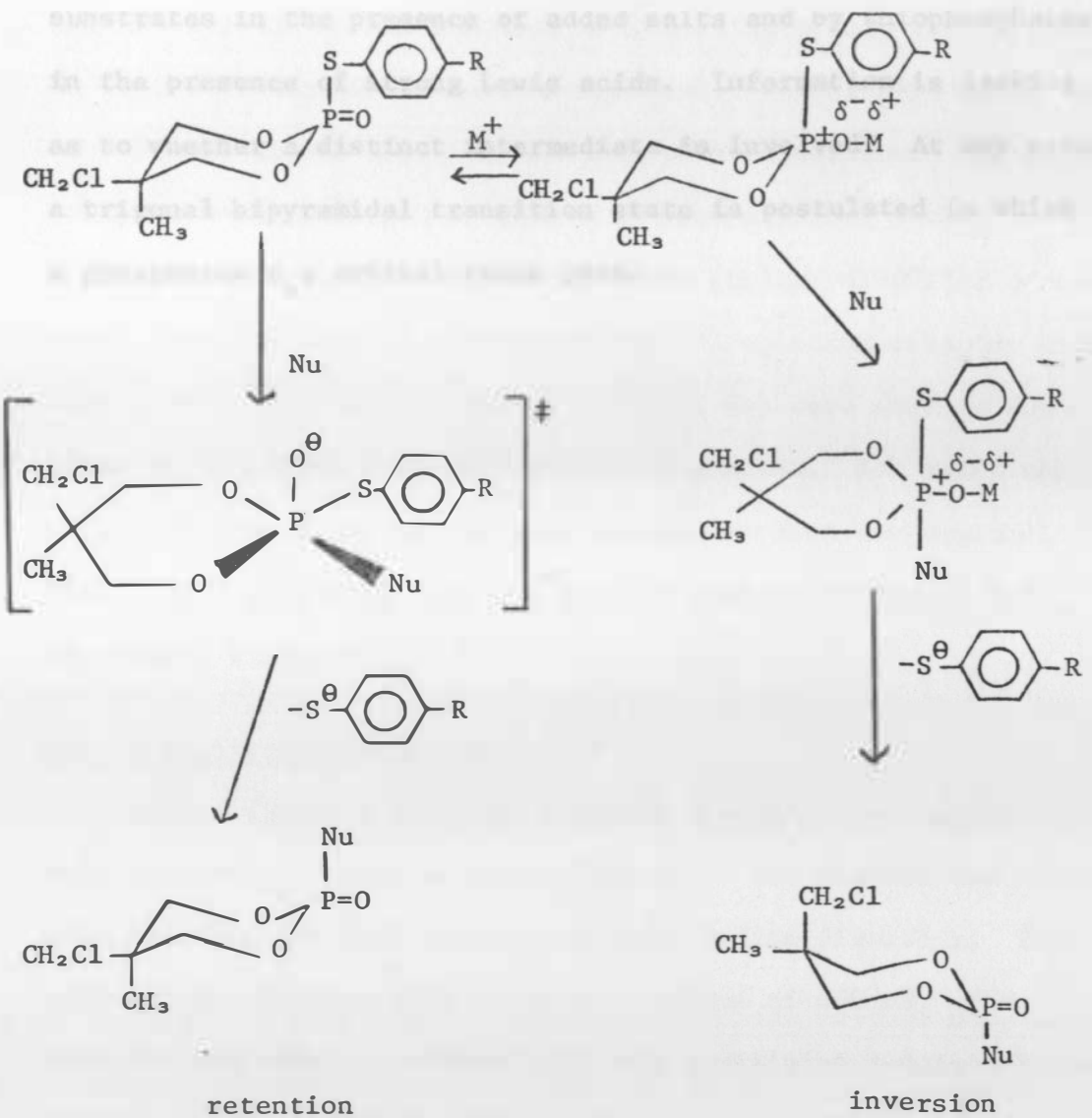


Figure 47

The first may be acid catalyzed and does not require an intermediate. It is favored by thiophosphate substrates and by phosphate and thionophosphate substrates in the absence of added salts. A square pyramidal transition state is postulated in which phosphorus $d_{x^2-y^2}$ orbitals are involved.

The second is favored by phosphate and thionophosphate substrates in the presence of added salts and by thiophosphates in the presence of strong Lewis acids. Information is lacking as to whether a distinct intermediate is involved. At any rate, a trigonal bipyramidal transition state is postulated in which a phosphorus d_{z^2} orbital takes part.

EXPERIMENTAL

Proton Nuclear Magnetic Resonance (H-NMR) spectra were obtained on a Varian A-60A spectrophotometer at 60 MHz. Tetramethyl silane (TMS) in deuterated chloroform was used as an external standard. Cis and trans ratios were determined by peak integration in the NMR spectra. All melting points were reported in degree centigrade and are uncorrected. Values were determined on a Thomas Hoover capillary melting point apparatus. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tennessee. Infrared spectra (unless specified otherwise) were obtained on a Perkin-Elmer 521 spectrophotometer with CsBr 1 mm cavity cells. Cavity cells (1 mm) were used in both beams to eliminate most of the solvent spectra. All reactions, unless otherwise indicated, were studied at room temperature. Thiols were purchased from the Aldrich Chemical Company, Inc., Milwaukee, Wisconsin.

Sodium p-nitrothiophenoxide[32,33,34]

Sulfur (32 g, 1 mol) was added to a solution of sodium sulfide (240 g, 3 mol) in water (290 ml). The mixture was heated with stirring for four hours to prepare sodium disulfide. The solution was diluted with water to a volume of 600 ml. The solution was added to ethanol (150 ml) containing p-nitrochlorobenzene (157 g, 1 mole). After stirring for two hours, water

(300 ml) was added. The solution was poured into saturated aqueous sodium hydroxide (1 l.). The precipitate, red plates, was filtered and by heating, redissolved in water (1.1) containing sodium sulfide (15 g, 0.2 mole). The solution was filtered into saturated aqueous sodium hydroxide (500 ml). Filtration isolated red plates (50 g, 30% yield).

Trans-2-(p-nitrothiophenoxy)-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan

Sodium p-nitrothiophenoxide (1.77 g, 0.01 mol) was dissolved in acetonitrile (50 ml) and cis-2-chloro-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan (2.19 g, 0.01 mol) was added. The solution was stirred for five days then poured into water (1.1) to precipitate the product. The cream-colored precipitate was washed thoroughly with water and dried under reduced pressure. Recrystallization in toluene gave pale yellow needles (.52 g, 2% yield) m.p. 115-117° (spectrum 1).

Analysis: Calculated for $C_{11}H_{13}ClNO_5PS$: C, 39.11; H, 3.85; S, 9.48. Found: C, 39.20; H, 3.97; S, 9.60.

Cis- and Trans-2-(p-methylthiophenoxy)-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan

Cis-2-chloro-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan (2.18 g, 0.01 mol) was dissolved in acetonitrile (15 ml). A solution of triethyl amine (3 ml) and p-methylthiophenol (2.5 g, 0.02 mol) in acetonitrile (15 ml) was added and the mixture stirred for five days. The final solution was filtered into cold

water (300 ml) to precipitate the product. The gray solid obtained by filtration was washed thoroughly with water and dried under reduced pressure (gray solid turned white). After recrystallization in carbon tetrachloride, a white product (2.19 g, 71% yield) was obtained, m.p. 129-130°, 87% trans (spectrum 2).

Analysis: Calculated for $C_{12}H_{16}ClO_3PS$: C, 46.98; H, 5.22; S, 10.44. Found: C, 47.11; H, 5.32; S, 10.36.

Cis- and Trans-2-(p-bromothiophenoxy)-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphosphorinan

p-Bromothiophenol (3.78 g, 0.02 mol) and triethyl amine (3 ml) were dissolved in acetonitrile (15 ml). The solution was added to acetonitrile (15 ml) in which cis-2-chloro-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan (2.19 g, 0.01 mol) was dissolved and was stirred for three days. The solution was filtered into water (500 ml) to precipitate the product. The precipitate was washed thoroughly with water and hexane, air dried, and recrystallized from carbon tetrachloride. White beads (3.4 g, 92% yield) were obtained m.p. 127-130°, 93% trans (spectrum 3).

Analysis: Calculated for $C_{11}H_{13}ClBrO_3PS$: C, 35.53; H, 3.50; S, 8.61. Found: C, 35.67; H, 3.44; S, 8.42.

Cis- and Trans-2-(p-fluorothiophenoxy)-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan

p-Fluorothiophenol (2.5 g, 0.02 mol) and triethyl amine (3 ml) were dissolved in acetonitrile (15 ml). The solution was

added to acetonitrile (15 ml) in which cis-2-chloro-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan (2.18 g, 0.01 mol) was dissolved. The final solution was stirred for three days then filtered into cold water (500 ml) to precipitate the product. The precipitate was washed thoroughly with water and air dried (yield 1.75 g). The white beads were recrystallized three times from carbon tetrachloride (.18 g, 26% yield) m.p. 82-84 , 90% trans (spectrum 4).

Analysis: Calculated for $C_{11}H_{13}ClFO_3PS$: C, 42.51; H, 4.19; S, 10.31. Found: C, 42.47;, H, 4.16; S, 10.42.

Cis- and Trans-2-(p-methoxythiophenoxy)-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan

p-Methoxythiophenol (2.8 g, 0.02 mol) and triethyl amine (3 ml) were dissolved in acetonitrile (15 ml). A solution of cis-2-chloro-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan (2.19 g, 0.01 mol) in acetonitrile (15 ml) was added. The final solution was stirred for three days and then filtered into cold water (500 ml) to precipitate the product. The precipitate was washed thoroughly with water and air dried. The white solid was recrystallized twice from carbon tetrachloride to give a white powder (2.65 g, 82% yield) m.p. 107-109, 88% trans (spectrum 5).

Analysis: Calculated for $C_{12}H_{16}ClO_4PS$: C, 44.65; H, 4.96; S, 9.92. Found: C, 44.41; H, 4.79; S, 9.83.

Attempted preparation of Cis- and Trans-2-P-acetamidothiophenoxy-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan

p-Acetamidothiophenol (3.3 g, 0.02 mole) and triethyl amine (3 ml) were dissolved in acetonitrile (15 ml). A solution of cis-2-chloro-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan (2.18 g, 0.01 mol) in acetonitrile (15 ml) was added. The final solution stirred for three days and filtered into cold water (500 ml) to precipitate the product. The precipitate was washed thoroughly with water and air dried. The product was recrystallized from carbon tetrachloride. An NMR spectrum indicated no product in the solid material.

Methanolysis of trans-2-(p-methylthiophenoxy)-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan in the presence of one equivalent of silver nitrate

Trans-2-(p-methylthiopenoxy)-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan (87% trans, .76 g, 3.34×10^{-3} mol) was added to methanol (30 ml) in which silver nitrate (.6 g, 3.5×10^{-3} mol) had been dissolved. The solution was stirred for one week and filtered. The methanol was evaporated slowly leaving a white solid. The solid was dissolved in carbon tetrachloride and filtered to remove the inorganic by-products. The carbon tetrachloride was removed under reduced pressure leaving a white gel. The NMR spectrum revealed 30% starting material, 37% trans-2-methoxy-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan and 33% cis-2-methoxy-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan (spectrum 6).

Methanolysis of trans-2-(p-methylthiophenoxy)-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan in the presence of two equivalents of silver nitrate

Trans-2-(p-methylthiophenoxy)-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan (87% trans, .76 g, 3.4 X 10^{-3} mol) was added to methanol (40 ml) in which silver nitrate (1.2 g, 7.0 X 10^{-3} mol) had been dissolved. The solution was stirred for one week and filtered. The methanol was slowly evaporated leaving a white solid. The solid was dissolved in carbon tetrachloride and filtered to remove the inorganic by-products. The carbon tetrachloride was removed under reduced pressure giving a white gel. The NMR spectrum revealed 12% starting material, 31% trans-2-methoxy-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan and 57% cis-2-methoxy-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan (spectrum 7).

Isomerization of trans-2-thiophenoxy-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan in acetonitrile in the presence of two equivalents of silver nitrate

Trans-2-thiophenoxy-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan (.76 g, 3.5 X 10^{-3} mol) was added to acetonitrile (30 ml) in which silver nitrate (1.2 g, 7.0 X 10^{-3} mol) had been added. The mixture was stirred for three hrs. and poured into water (500 ml) to precipitate the product. The precipitate was washed thoroughly with water and air dried (.63 g, 83% recovery). The NMR spectrum showed no isomerization of the starting material.

Isomerization of trans-2-(p-methoxythiophenoxy)-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan in acetonitrile in the presence of two equivalents of silver nitrate

Trans-2-(p-methoxythiophenoxy)-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan (88% trans, .76 g, 3.4×10^{-3} mol) was added to acetonitrile (30 ml) to which silver nitrate (1.2 g, 7.0×10^{-3} mol) had been added. The mixture was stirred for four days and poured into water (500 ml) to precipitate the product. The precipitate was washed thoroughly with water and air dried (.68 g, 89% recovery). The NMR spectrum showed that no isomerization had taken place.

Isomerization of 2-methoxy-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan in methanol

Trans-2-methoxy-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan was added to methanol. After three months the NMR spectrum of recovered reactant showed no change from the original.

Isomerization of 2-methoxy-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan in methanol with silver nitrate

Cis-2-chloro-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan was added to methanol in which silver nitrate had been dissolved. After one week, the methanol was allowed to evaporate slowly. The white solid was partially dissolved in carbon tetrachloride. The carbon tetrachloride solution was evaporated leaving a liquid. The NMR spectrum of the liquid was obtained. Pure trans-2-methoxy-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan was shown to be present thereby eliminating

the possibility of isomer interconversion.

Methanolysis of trans-2-(p-fluorothiophenoxy)-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan

Trans-2-(p-fluorothiophenoxy)-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan (87% trans, 0.051 g, 1.6 X 10^{-4} mol: was placed in an NMR tube and d_4-methanol (0.67 g, 0.73 ml at 25°C) was added. The tube was sealed and the reaction solution kept at 40°C ±1°C in an oil bath and the reaction followed via NMR.

Methanolysis of trans-2-(p-bromothiophenoxy)-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan

Trans-2-(p-bromothiophenoxy)-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan (93% trans, 0.055 g, 1.5 X 10^{-4} mol) was placed in an NMR tube and d_4-methanol (0.812 g, .91 ml at 25°C) was added. The tube was sealed and the reaction solution kept at 40°C±1°C in an oil bath and the reaction followed via NMR.

Methanolysis of trans-2-(p-methylthiophenoxy)-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan

Trans-2-(p-methylthiophenoxy)-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan (87% trans, 0.043 g, 1.4 X 10^{-4} mol) was placed in an NMR tube and d_4-methanol (0.802 g, .91 ml at 25°C) was added. The tube was sealed and the reaction solution kept at 40°C±1°C in an oil bath, and the reaction followed via NMR.

Solvolysis of trans-2-(p-methoxythiophenoxy)-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan

Trans-2-(p-methoxythiophenoxy)-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan (88% trans, 0.031 g, 9.6×10^{-5} mol) was placed in an NMR tube and d_4-methanol (0.724 g, 0.81 ml at 25°C) was added. The tube was sealed, and the reaction solution kept at 40°C±1°C in an oil bath, and the reaction followed via NMR.

Solvolysis of trans-2-thiophenoxy-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan

Trans-2-thiophenoxy-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan (100% trans, 0.037 g, 1.3×10^{-4} mol) was placed in an NMR tube and d_4-methanol (0.649 g, 0.73 ml at 25°C) added. The tube was sealed, and the reaction solution kept at 40°C±1°C in an oil bath, and the reaction followed via NMR.

Effects of Lewis acid on P=O absorption in 2-(p-methylphenoxy)-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan

2-(p-Methylphenoxy)-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan (5.0 mg, 1.6×10^{-5} mol) was dissolved in chloroform (0.5 ml). An infrared spectrum of the solutions was obtained. Half of the solution was removed from the cavity cell, a saturated solution of anhydrous aluminum chloride in chloroform added to fill the cavity cell and the spectrum again obtained (spectra 8 and 9).

Effect of Lewis acid on P=O absorption in 2-(p-fluorothiophenoxy)-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan

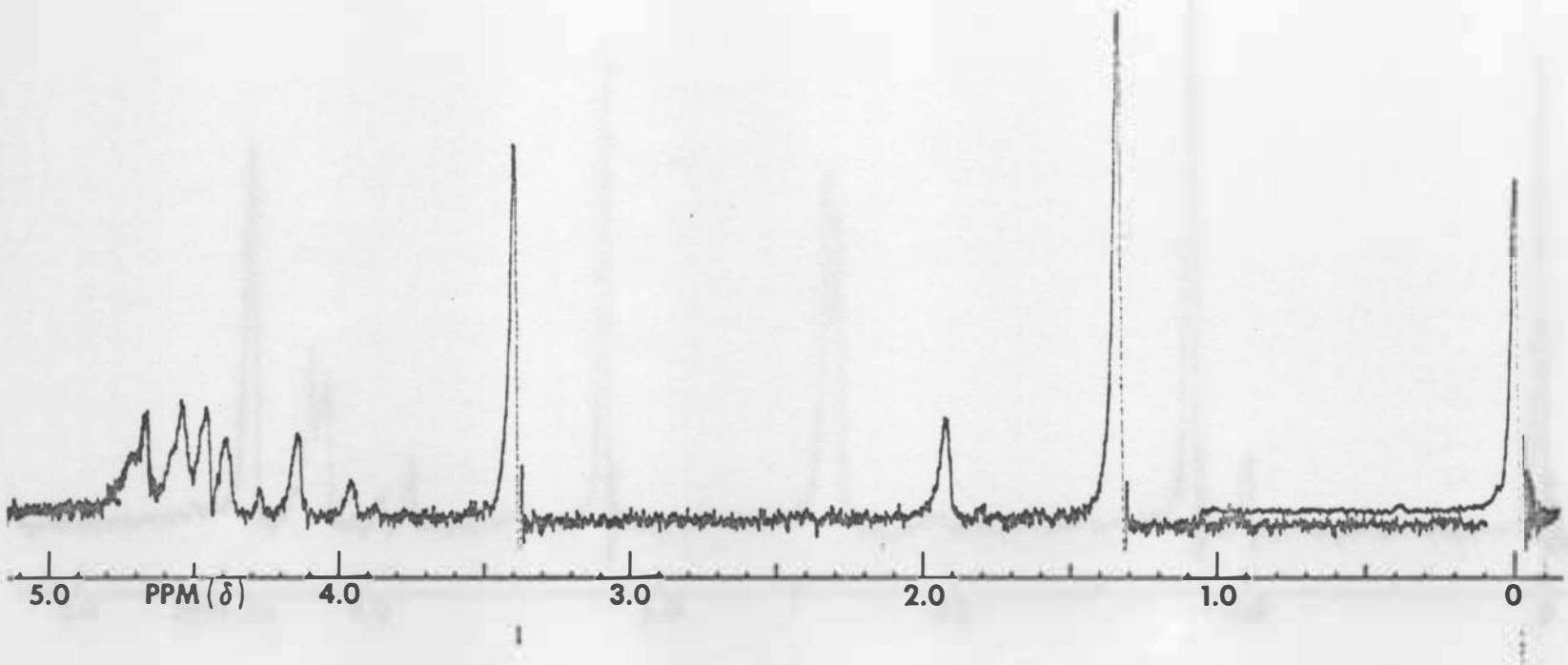
2-(p-Fluorothiophenoxy)-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan (5.0 mg, 1.6×10^{-5} mol) was dissolved in chloroform (0.15 ml). An infrared spectrum of the solution was obtained. Half the solution was removed from the cavity cell, a saturated solution of anhydrous aluminum chloride in chloroform added to fill the cell and the infrared spectrum again obtained (spectra 10 and 11).

Effects of Lewis acid on P=O absorption in 2-chloro-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan

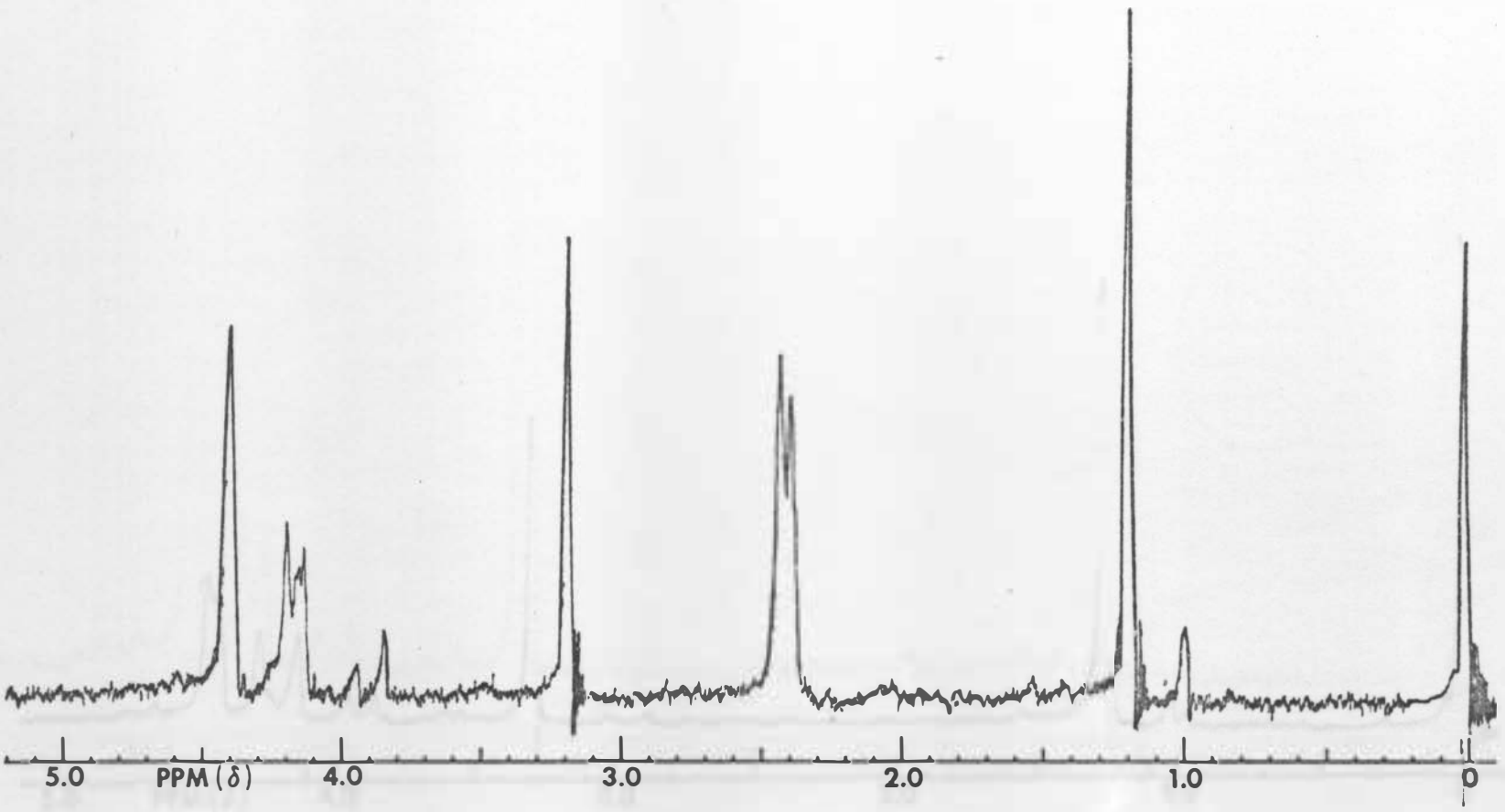
An infrared spectrum of 2-chloro-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan in nujol was obtained on cesium bromide plates. The aluminum chloride-2-chloro-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan complex was prepared.

The infrared absorption of the complex was obtained unmixed on cesium bromide plates (spectra 12 and 13).

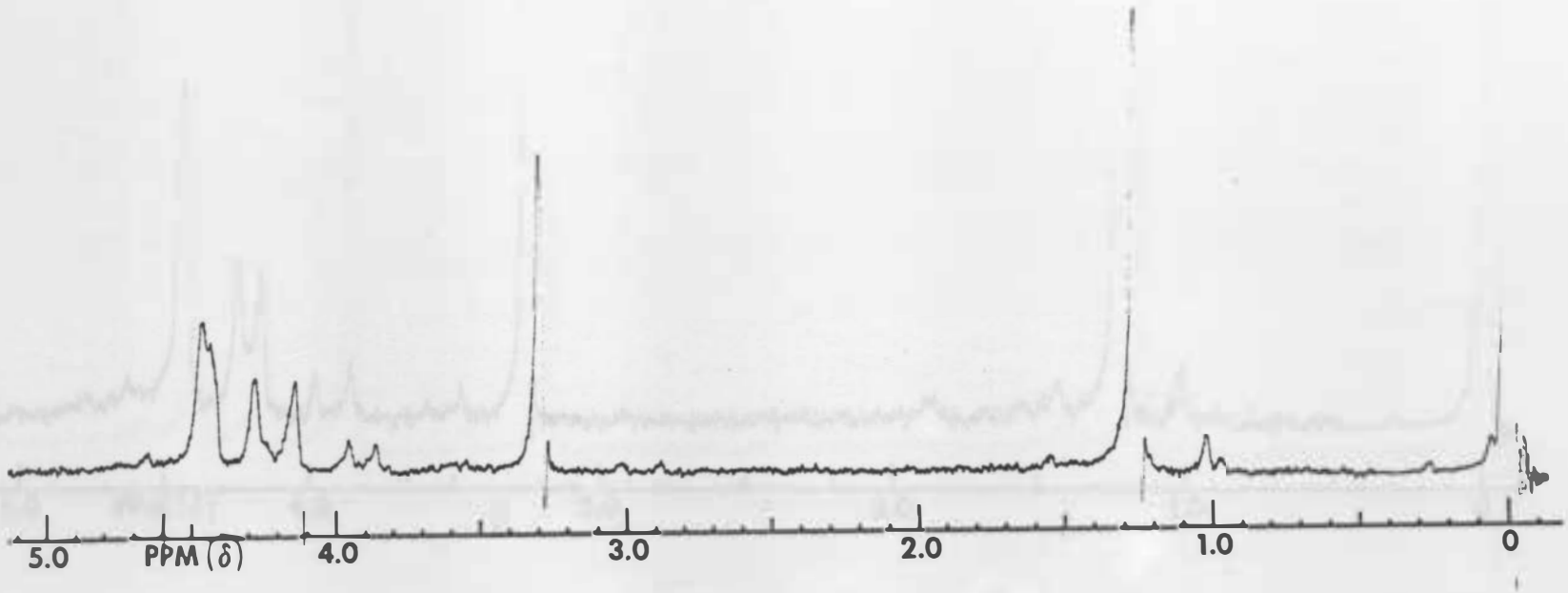
APPENDIX



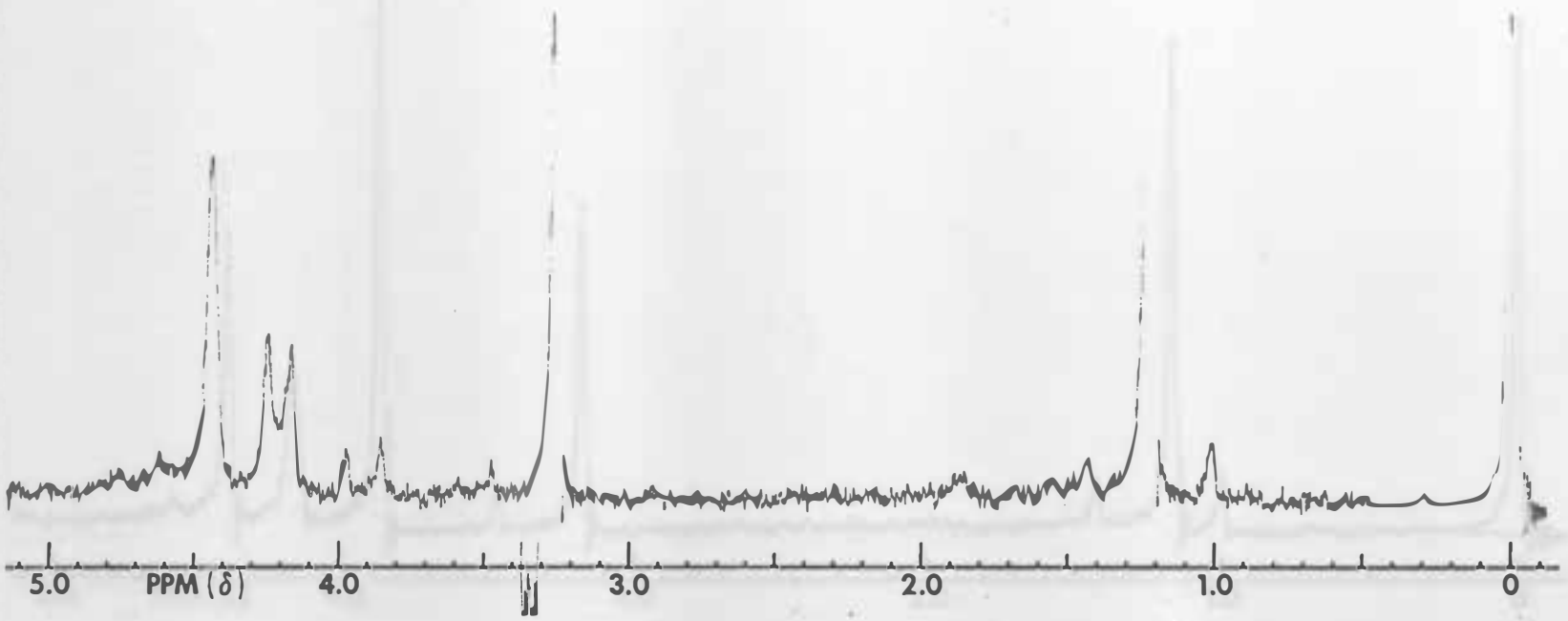
Spectrum 1: NMR spectrum of trans-2-(p-nitrothiophenoxy)-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan in chloroform-d_1 with TMS as external standard.



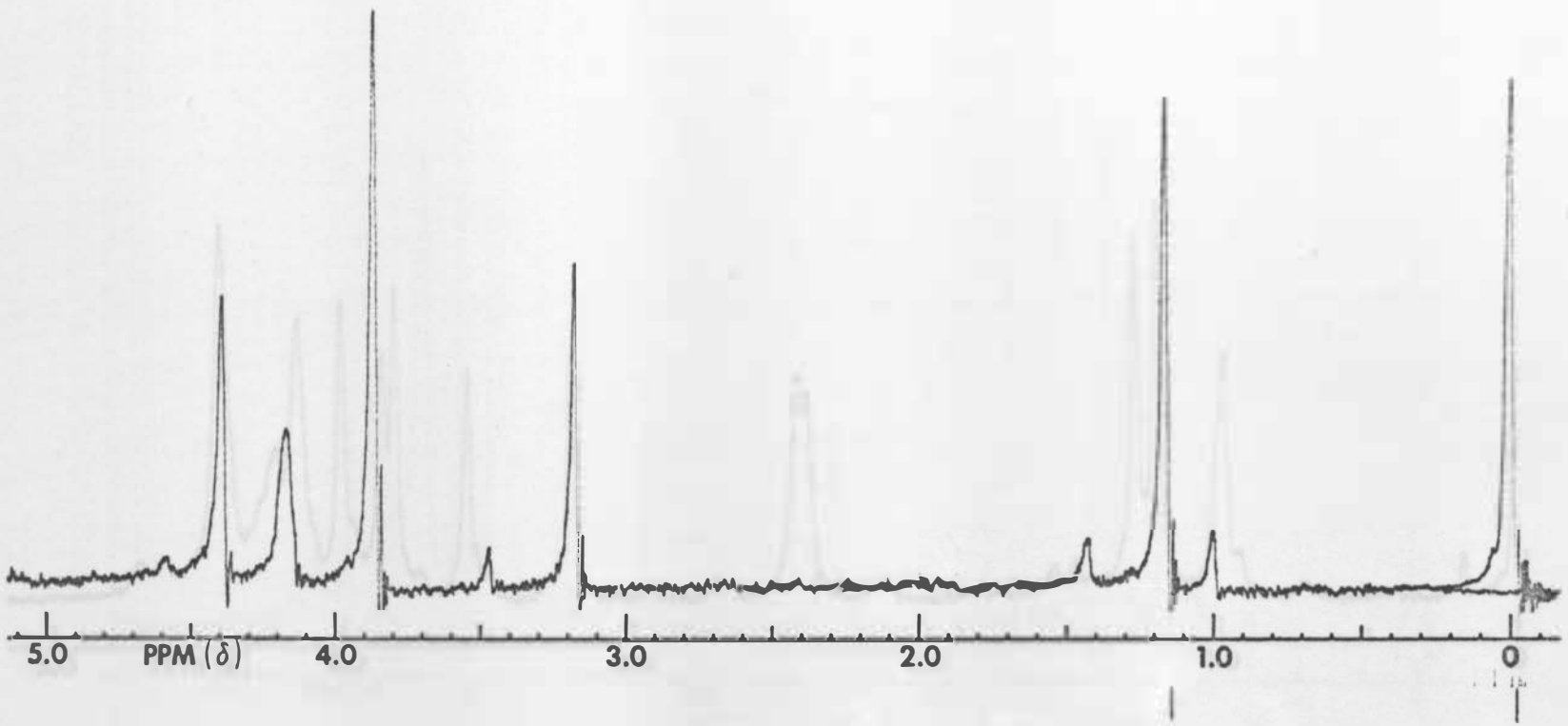
Spectrum 2: NMR spectrum of trans-2-(p-methylthiophenoxy)-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan in chloroform-d_1 with TMS as external standard.



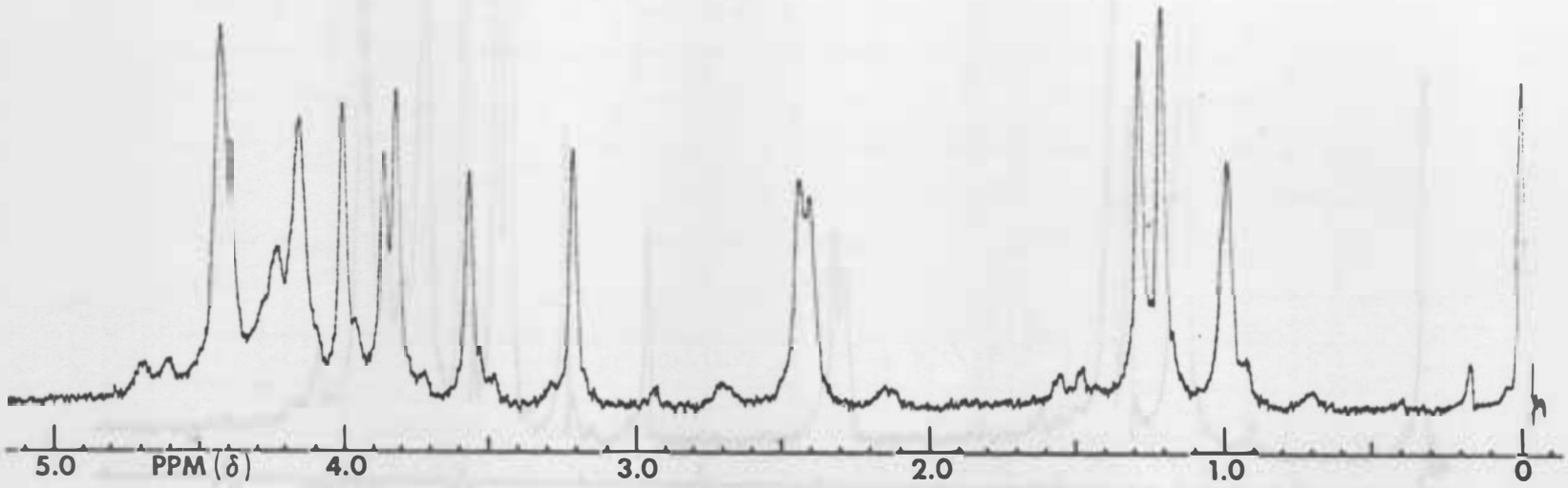
Spectrum 3: NMR spectrum of trans-2-(p-bromothiophenoxy)-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan in chloroform-d_1 with TMS as external standard.



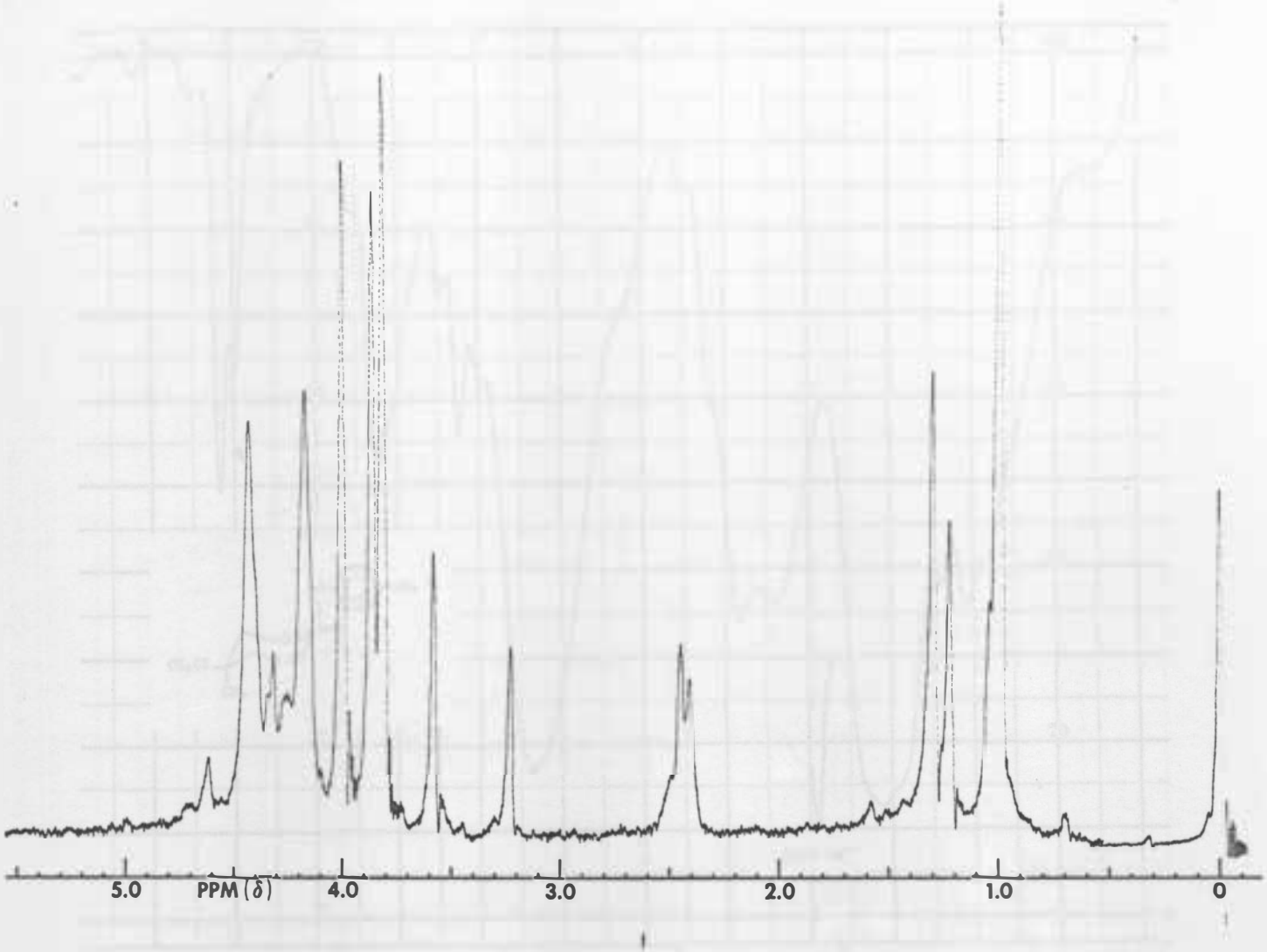
Spectrum 4: NMR spectrum of trans-2-(p-fluorothiophenoxy)-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan in chloroform-d_1 with TMS as external standard.



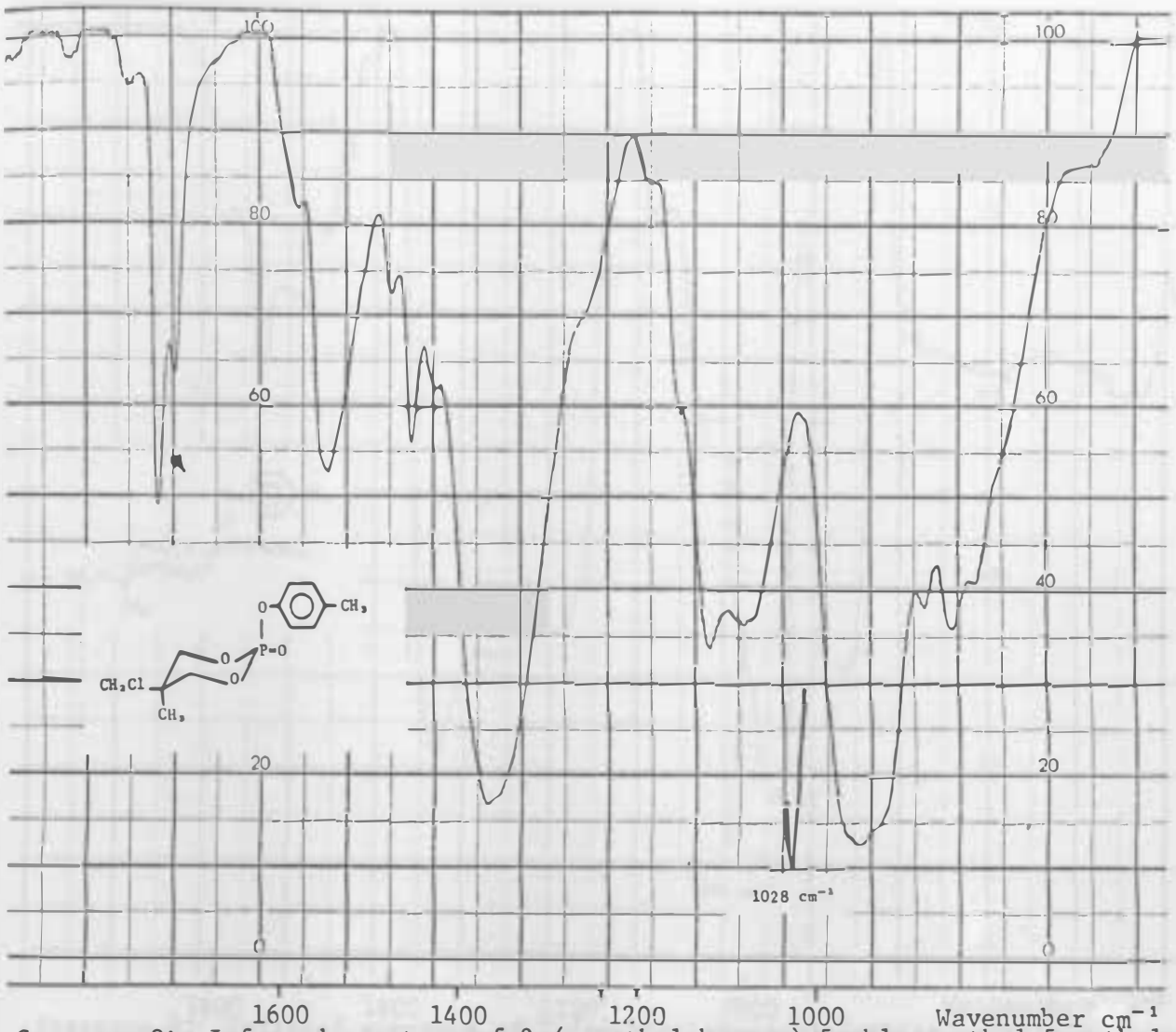
Spectrum 5: NMR spectrum of trans-2-(p-methoxythiophenoxy)-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan in chloroform-d_1 with TMS as external standard.



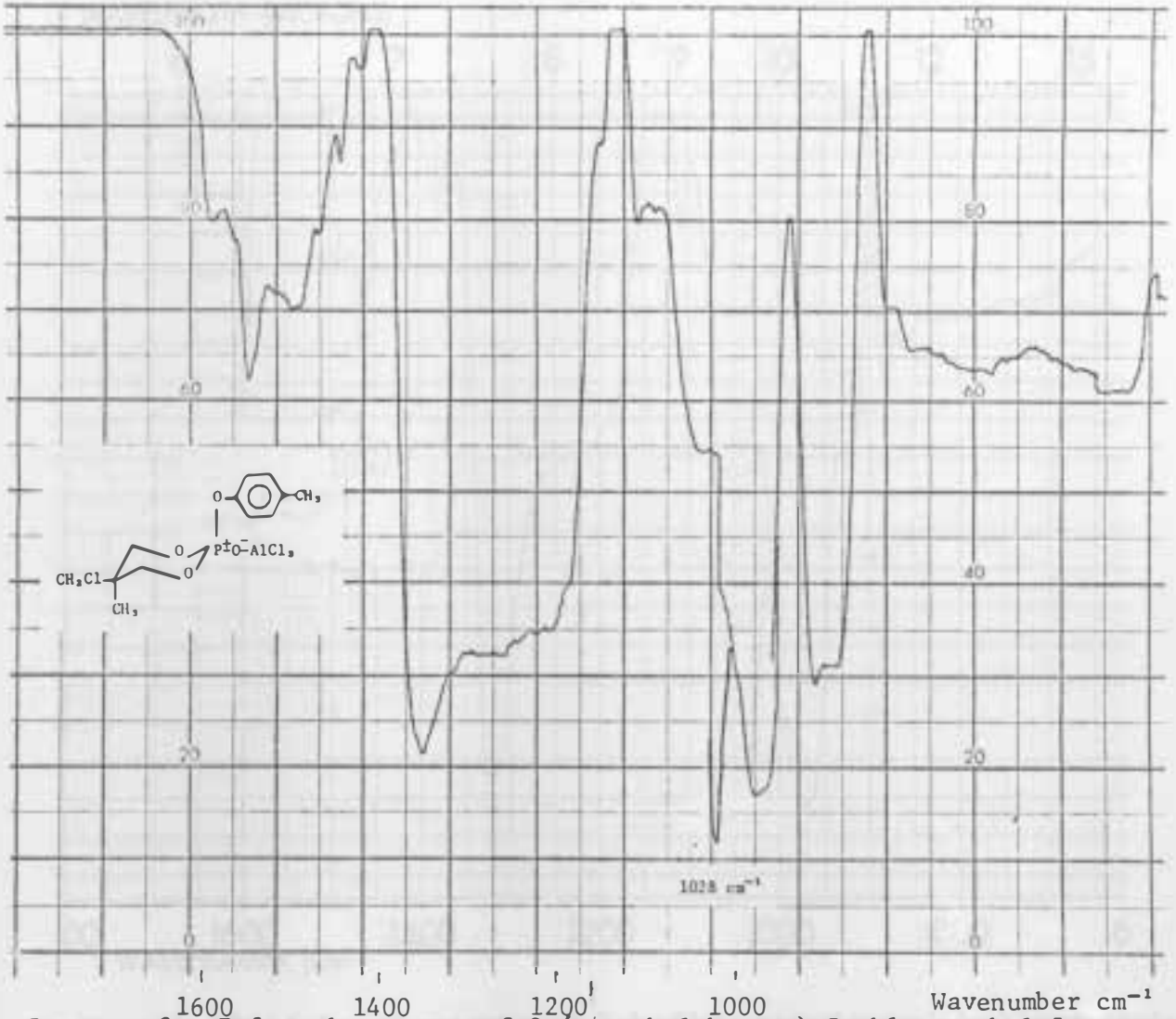
Spectrum 6: NMR spectrum of methanolysis product of trans-2-(p-methylthiophenoxy)-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan with one equivalent of silver nitrate present, in chloroform-d_1 with TMS as external standard.



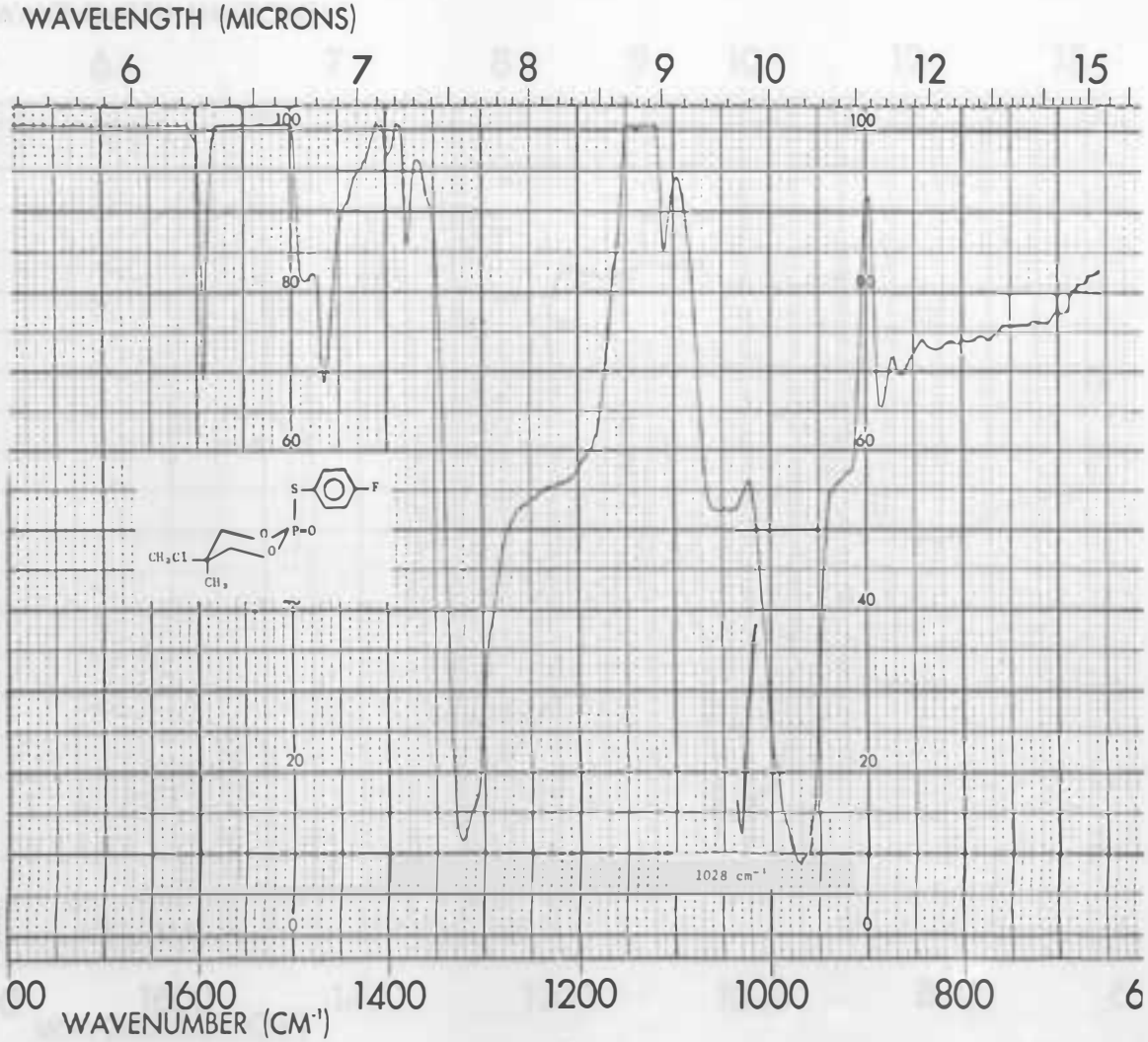
Spectrum 7: NMR spectrum of methanolysis product of trans-2-(p-methylthiophenoxy)-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan with two equivalents of silver nitrate present, in chloroform-d_1 with TMS as external standard.



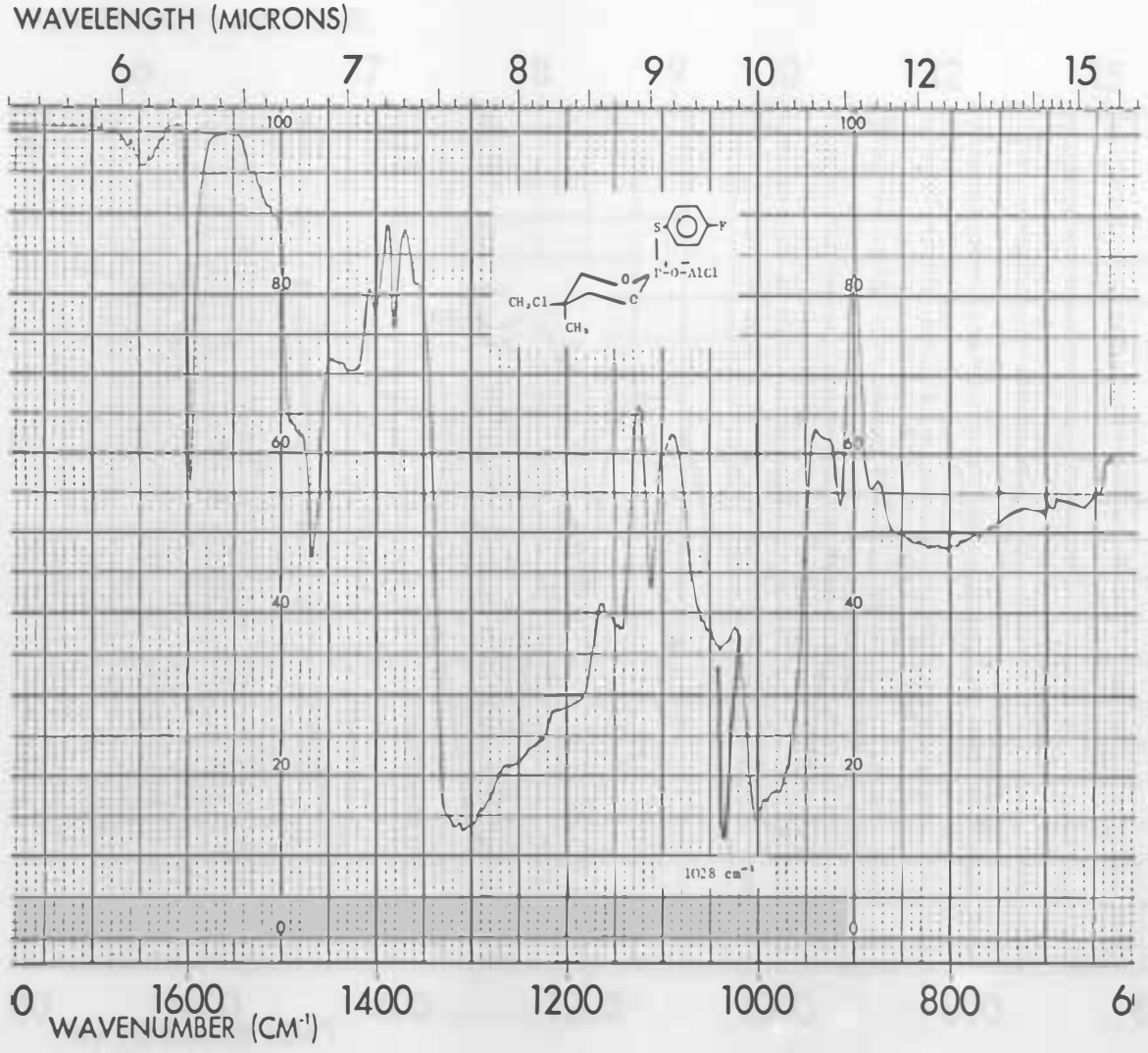
Spectrum 8: Infrared spectrum of 2-(p-methylphenoxy)-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan in chloroform solution shows strong P=O absorption at 1370 cm^{-1}.



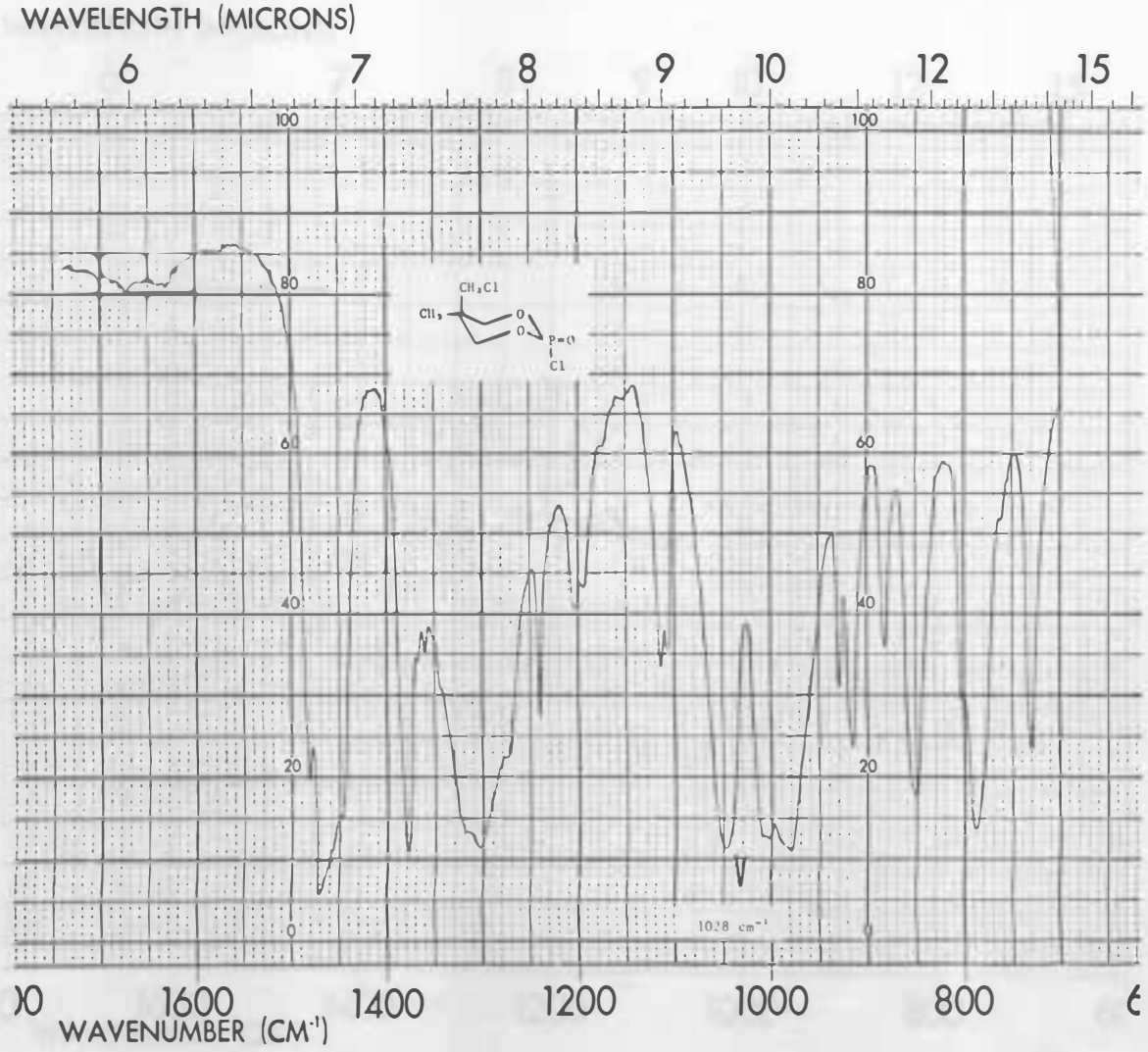
Spectrum 9: Infrared spectrum of 2-(p-methylphenoxy)-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan in chloroform solution with aluminum chloride present shows broadening of P=O absorption at 1370 cm^{-1}.



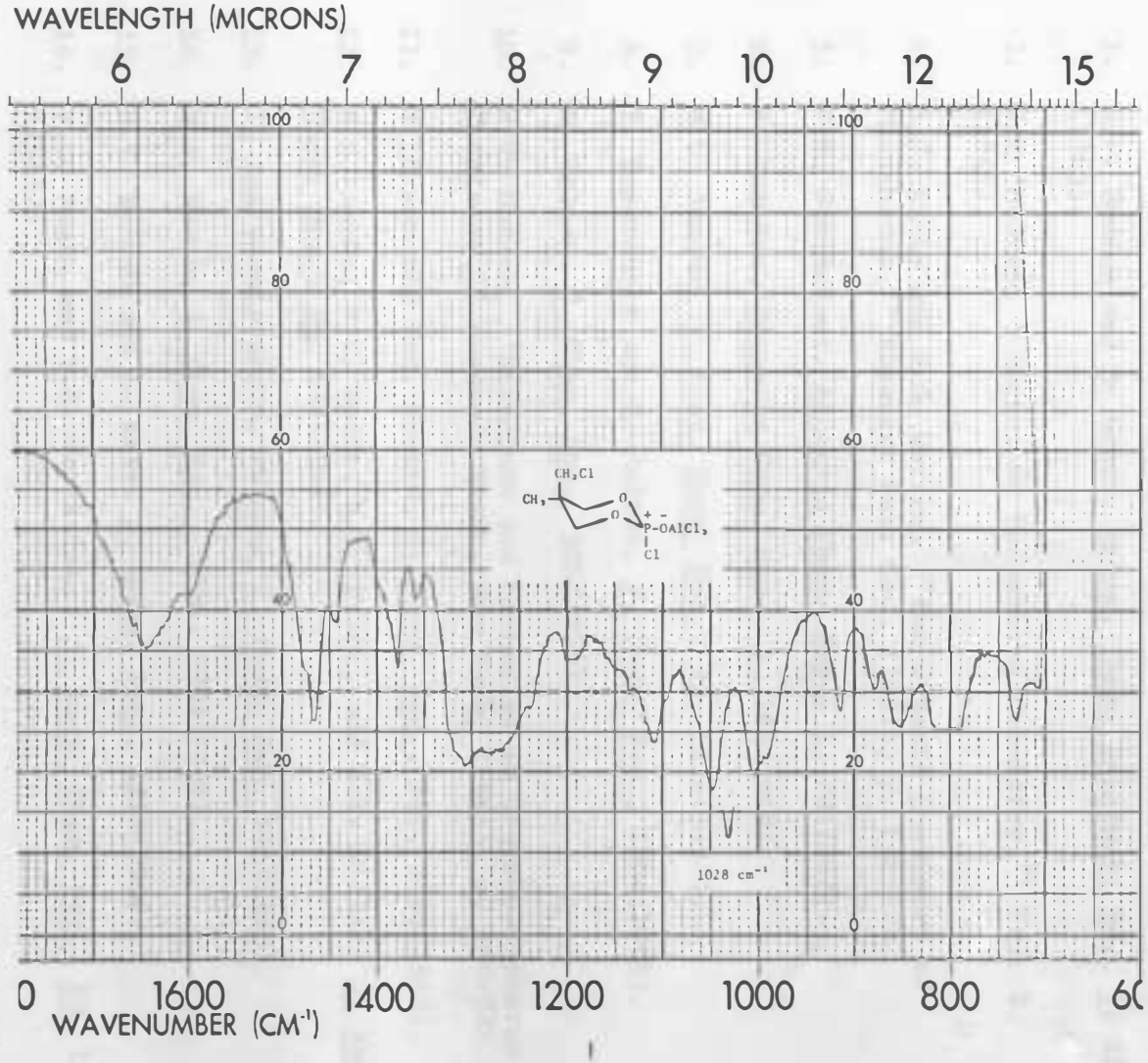
Spectrum 10: Infrared spectrum of 2-(p-fluorothiophenoxy)-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan in chloroform solution shows strong P=O absorption at 1320 cm^{-1}.



Spectrum 11: Infrared spectrum of 2-(p-fluorothiophenoxy)-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan in chloroform solution with aluminum chloride present shows broadening of P=O absorption at 1320 cm^{-1}.



Spectrum 12: Infrared spectrum of 2-chloro-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan shows strong P=O absorption at 1300 cm^{-1}.



Spectrum 13: Infrared spectrum of 2-chloro-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan-aluminum chloride complex in nujol shows broadening of P=O absorption at 1300 cm^{-1}.

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