# HYDROXYALKYL- AND HYDROXYARYL-DIPHENYLPHOSPHINATES: SYNTHESIS AND CHEMICAL EXCHANGE STUDIES

by

EDWARD PAUL SEGSTRO

A thesis
presented to the University of Manitoba
in partial fulfillment of the
requirements for the degree of
MASTER OF SCIENCE
in
CHEMISTRY

Winnipeg, Manitoba, 1983

# HYDROXYALKYL- AND HYDROXYARYL-DIPHENYLPHOSPHINATES: SYNTHESIS AND CHEMICAL EXCHANGE STUDIES

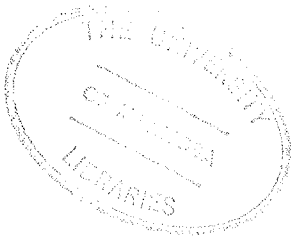
BY

EDWARD PAUL SEGSTRO

A thesis submitted to the Faculty of Graduate Studies of the University of Manitoba in partial fulfillment of the requirements of the degree of

MASTER OF SCIENCE





I hereby declare that I am the sole author of this thesis.

I authorize the University of Manitoba to lend this thesis to other institutions or individuals for the purpose of scholarly research.

EDWARD PAUL SEGSTRO

I further authorize the University of Manitoba to reproduce this thesis by photocopying or by other means, in total or in part, at the request of other institutions or individuals for the purpose of scholarly research.

EDWARD PAUL SEGSTRO

The University of Manitoba requires the signatures of all persons using or photocopying this thesis. Please sign below, and give address and date.

## ABSTRACT

The synthesis of four new diphenylphosphinates is described, together with the characterization of two of them by elemental analysis, mass spectrometry, and by NMR spectroscopy.

The behavior in solution, in the presence of base, of diphenylphosphinates containing a hydroxyl group adjacent to the phosphoryl function was investigated. The presence of the hydroxyl group permits the formation of a cyclic five-membered ring and pentacovalent phosphorus. Equilibration in the NMR spectra may or may not take place at ambient temperatures. Equilibrium constants for the interaction of the various bases with the phosphinate ($Ph_2P(O)OC_6H_4OH$), 29, are given.

## ACKNOWLEDGMENTS

I wish, here, to express my gratitude to Dr A. F. Janzen for his continual advice and patience.

There are many other members of the Chemistry Department to whom thanks are due but special mention should be made here of Dr N. R. Hunter and Dr T. Schaefer for helpful discussions, Dr J. L. Charlton for the use of computer programs and for helpful discussions, Mr R. K. Marat and Dr A. E. Lemire for running the NMR spectra on the Bruker WH-90, and Mr W. D. Buchannon for obtaining the mass spectra.

I wish also to acknowledge the timely assistance of Mr M. Segstro in preparing many of the diagrams included.

Finally, I wish to thank my wife, Elaine, for her steadfast support and for help in typing the manuscript.

"One's ideas must be as broad as nature
if they are to interpret nature."

Sherlock Holmes,
A Study in Scarlet.

LIST OF TABLES


| Table | | page |
|---|---|---|
| 1. | $^{13}C$ NMR of Glycerol Phosphates. . . . . | 78 |
| 2. | $^{31}P$ NMR Data for $Ph_2P(O)OC_6H_4OH$ (29). . . . . | 89 |
| 3. | $^{13}C$ NMR Data for $Ph_2P(O)OC_6H_4OH$ (29) in CD2C12. . . | 90 |
| 4. | $^{1}H$ NMR Data for $Ph_2P(O)OC_6H_4OH$ (29) in CD2C12. . . . | 91 |
| 5. | $^{31}P$ NMR Chemical Shifts of $Ph_2P(O)OC_6H_4OH$ (29) (in $CH_2Cl_2$): Pyridine as Added Base. . . . . | 92 |
| 6. | $^{31}P$ NMR Chemical Shifts of $Ph_2P(O)OC_6H_4OH$ (29) (in $CH_2Cl_2$): Triethylamine as Added Base. . . . . | 93 |
| 7. | $^{31}P$ NMR Chemical Shifts of $Ph_2P(O)OC_6H_4OH$ (29) (in $CH_2Cl_2$): Dimethylsulphoxide as Added Base. . . . | 93 |
| 8. | $^{31}P$ NMR Chemical Shifts of $Ph_2P(O)OC_6H_4OH$ (29) (in $CH_2Cl_2$): Imidazole as Added Base. . . . . | 93 |
| 9. | $^{31}P$ NMR Chemical Shifts of $Ph_2P(O)OC_6H_4OH$ (29) (in $CH_2Cl_2$): Dioxane as Added Base. . . . . | 94 |
| 10. | $^{31}P$ NMR Data for $(MeO)_3PO$ in $CH_2Cl_2$: Pyridine as Added Base. . . . . | 100 |
| 11. | Comparison of $^{31}P$ Chemical Shifts for Compounds 29 and 32: Pyridine as Added Base. . . . . | 100 |
| 12. | $^{31}P$ NMR Chemical Shifts of $Ph_2P(O)OC_6H_4OH$ (29) (in $CH_2Cl_2$): Trifluoroacetic Acid Added. . . . . | 105 |
| 13. | Results of NLIN Analysis of the $^{31}P$ Chemical Shift Data: One-Step Mechanism. . . . . | 109 |

14. $^{1}H$ NMR Chemical Shifts of $Ph_2P(O)OC_6H_4OH$ (29) (in $CD_2Cl_2$): Pyridine as Added Base. . . . . 118

## LIST OF SCHEMES AND FIGURES


| Scheme | | page |
|---|---|---|
| 1. | Enzymatic Hydrolysis of RNA | 2 |
| 2. | Berry Pseudorotation | 10 |
| 3. | Turnstile Rotation | 12 |
| 4. | Hydrolysis of Methyl Ethylene Phosphate: Westheimer's Hypothesis | 17 |
| 5. | Isomerization of Diphenylphosphinates 52 and 53 in Solution | 21 |
| 6. | Possible Pathways to $^{19}F$ NMR Equilibration of Phosphinates 43 and 44 | 80 |
| 7. | Deprotonation and Nucleophilic Ring-Closure of $Ph_2P(O)OC(CF_3)_2C(CF_3)_2OH$ (26) | 83 |
| 8. | Pseudorotational Processes of Compounds 48, 49, 50, and 51 | 87 |
| 9. | Deprotonation and Nucleophilic Ring-Closure of $Ph_2P(O)OC_6H_4OH$ (29) | 101 |
| 10. | Mechanistic Possibilities for Interaction of $Ph_2P(O)OC_6H_4OH$ with $CF_3COOH$ | 104 |
| 11. | Synthesis of $(C_6H_4O_2)_2PPh$, 39, from $PhPCl_2$ | 123 |

| Figure | | page |
|---|---|---|
| 1. | $^{1}H$ NMR Spectrum of cis-Tetrahydro-3,4-furandiol . . | 33 |
| 2. | $^{19}F$ NMR Spectrum of Phosphinate 26 . . . . . | 40 |
| 3. | $^{19}F$ NMR Spectrum of Phosphinate 26 in the Presence of Pyridine . . . . . | 40 |
| 4. | $[^{19}F]$-$^{13}C$ NMR Spectrum of Phosphinate 26 in the Presence of Pyridine . . . . . | 41 |
| 5. | $^{1}H$ NMR Spectrum of $Ph_2P(O)OC_6H_4OH$ (29) . . . . . | 49 |
| 6. | $[^{31}P]$-$^{1}H$ NMR Spectrum of $Ph_2P(O)OC_6H_4OH$ (29) . . . . | 50 |
| 7. | $[^{1}H]$-$^{13}C$ NMR Spectrum of $Ph_2P(O)OC_6H_4OH$ (29) . . . . | 56 |
| 8. | $[^{1}H]$-$^{13}C$ NMR Spectrum of Glycerol-1-phosphate . . . | 61 |
| 9. | $[^{1}H]$-$^{13}C$ NMR Spectrum of Glycerol-2-phosphate . . . | 62 |
| 10. | Calculated $^{1}H$ NMR Spectrum of $Ph_2P(O)OC_6H_4OH$ (29) | 114 |
| 11. | Calculated $[^{31}P]$-$^{1}H$ NMR Spectrum of $Ph_2P(O)OC_6H_4OH$ (29) . . . . . | 115 |

CONTENTS

ABSTRACT . . . . . iv

ACKNOWLEDGMENTS . . . . . v

LIST OF TABLES . . . . . vii

LIST OF SCHEMES AND FIGURES . . . . . ix

page

INTRODUCTION . . . . . 1

GENERAL PROCEDURES, SOLVENTS, AND INSTRUMENTAL . . . . . 27

EXPERIMENTAL . . . . . 31

RESULTS AND DISCUSSION . . . . . 77

Appendix page

A. . . . . 125

B. . . . . 127

C. . . . . 129

D. . . . . 130

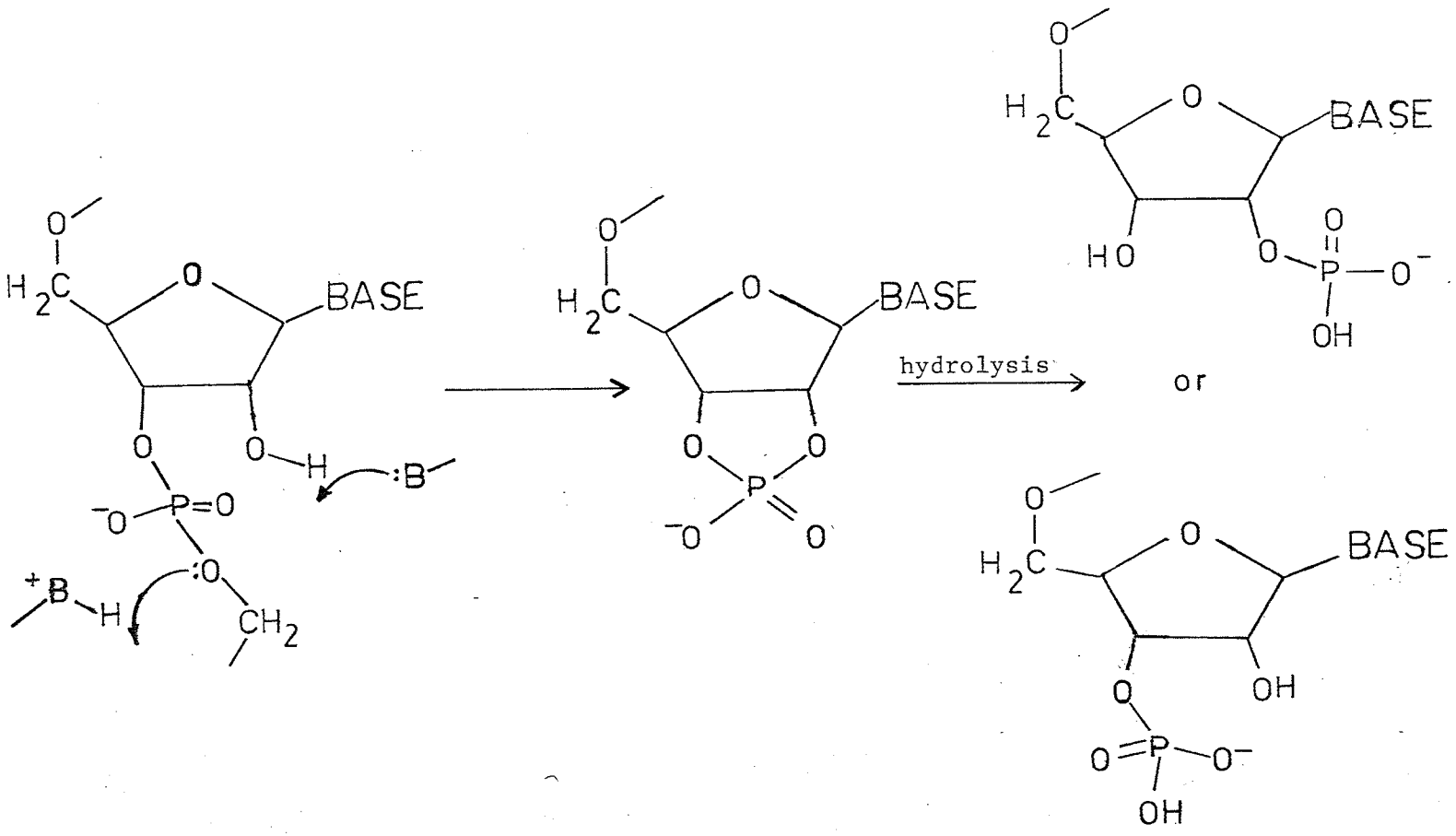
REFERENCES . . . . . 131

# INTRODUCTION

## Biological Background.

Both RNA and DNA can be hydrolyzed under enzymatic or under non-enzymatic conditions. Except for recombination and for excision repair, however, DNA is not generally broken down in living cells, but RNA breakdown does occur (1). As well, dilute alkali will hydrolyze RNA, while DNA is unaffected (2,3). These differences in behaviour of RNA and DNA originate in the presence of a 2'-hydroxyl group on the sugar residue in RNA and its absence in DNA (4a).

One of the proposed mechanisms of action of the enzyme Ribonuclease-A (3,5), which hydrolyzes RNA, involves general acid and general base catalysis by histidine residues in the active site of the enzyme which contain an imidazole-type function. As shown in Scheme 1, a 2',3'-cyclic phosphate is initially formed which is then rapidly hydrolyzed to either a nucleoside 2'- or 3'-monophosphate. DNA, which lacks the 2'-hydroxyl group, cannot form such cyclic intermediates.



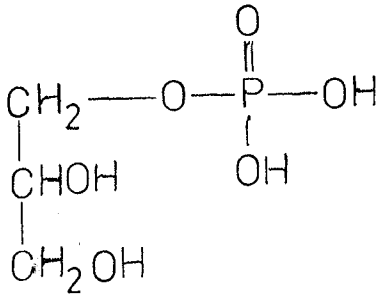

Scheme 1. Enzymatic Hydrolysis of RNA

Phosphate Ester Hydrolysis: Early Investigations.

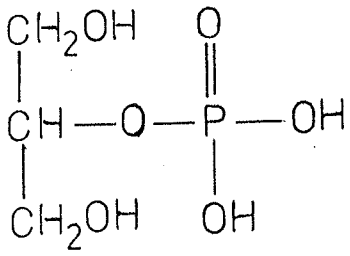
The discovery (6) that 2-dihydrogenphosphate-1,2,3-propanetriol (glycerol-2-phosphate), 2, could be converted into the isomeric 1-dihydrogenphosphate (glycerol-1-phosphate), 1, in strongly acidic solution led Verkade et al. (7) to propose a cyclic intermediate for the interconversion. When the isomerization was carried out in the presence of $^{32}P$-labelled inorganic phosphate, Chargaff (8) found no radioactivity in the glycerol phosphates, demonstrating the intramolecular nature of the reaction, and supporting the involvement of a cyclic intermediate.

In 1959, Brown et al. (9) carried out alkaline hydrolyses of the glyceryl esters of myoinositol-1-phosphate, 3, and myoinositol-2-phosphate, 4. In each case, the products comprised a mixture of myoinositol-1-phosphate, myoinositol-2-phosphate, glycerol-1-phosphate, and glycerol-2-phosphate. However, the relative amounts of the isomeric 1- and 2-phosphates formed were consistent with the isomer ratios found for the alkaline hydrolysis of the cyclic myoinositol-1,2-phosphate and of cyclic glycerol-1,2-phosphate. It was thus clearly shown that five-membered-ring intermediates were involved in the hydrolysis of phosphate esters.

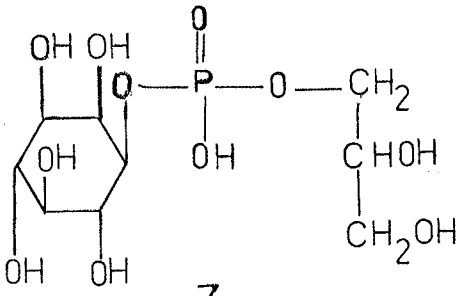
In 1956, Westheimer et al. (10a) noted that although the five-membered cyclic phosphates, which are intermediates in RNA hydrolysis, are rapidly hydrolyzed to monophosphates



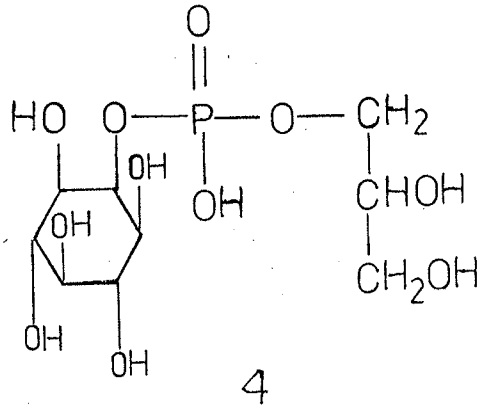
1



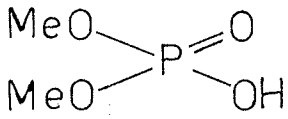
2



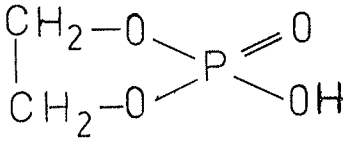
3



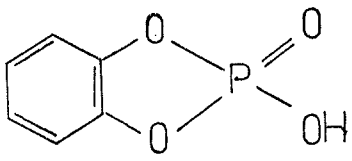
4



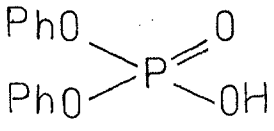
5



6



7



8

in alkaline solution, most diesters of phosphoric acid were known to be relatively resistant to such hydrolysis. In a comparison of the rates of hydrolysis of dimethylhydrogenphosphate, 5, potassium salt, and 2-hydroxy-2-oxide-1,3,2-dioxaphosphole, 6, potassium salt, these authors found the rate of hydrolysis for 6 exceeded that for 5 by a factor of $5 \times 10^6$.

Khorana (11) confirmed that five-membered cyclic phosphates were highly labile to acidic and to alkaline hydrolysis. Six-membered cyclic phosphates, however, were found to be very stable under these conditions and seven-membered rings even more so.

The hydrolysis of aromatic esters of phosphoric acid was also investigated (12). In a comparison of the rates of alkaline hydrolysis of 2-hydroxy-2-oxide-1,3,2-benzodioxaphosphole, 7, and diphenylhydrogenphosphate, 8, it was found that the cyclic ester 7 was hydrolyzed $6 \times 10^6$ times faster than was 8.

It was suggested (10b,13) that strain in the ring of five-membered cyclic phosphates might account for the greatly increased rate of hydrolysis of these compounds in comparison to acyclic dialkyl and six- or seven-membered cyclic phosphates.

To demonstrate that strain existed in five-membered cyclic phosphates, Westheimer showed (13) that the enthalpy of hydrolysis with ring opening of compound 9 was greater

than the enthalpy of hydrolysis of the acyclic analogues, 10 and 11, by about 29-38 kJ/mole, subsequently corrected to 21-25 kJ/mole (4b). He further suggested that if ring strain was relieved during formation of the transition state in hydrolysis, it could probably explain the high rate of reaction of the five-membered cyclic phosphates.

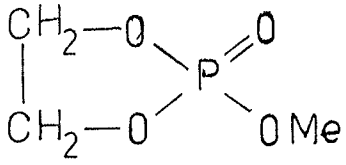
In 1967, Kugel and Halmann (14) re-emphasized a fact reported previously (13,15,16) that although dialkyl phosphates are, in general, very stable to alkaline hydrolysis, those substituted dialkyl phosphates which contain a hydroxyl substituent adjacent to the phosphoryl group, such as in compound 13, do undergo very rapid hydrolysis in alkaline solution. Yet these compounds, being acyclic, would not encounter ring strain.

Other inconsistencies in the idea that ring strain was responsible for the rapid rate of hydrolysis of cyclic phosphates were apparent. The rate of hydrolysis of 2-hydroxy-4-hydroxymethyl-2-oxide-1,3,2-dioxaphosphole, 12, was measured as a function of pH and was found to be rapid only below pH 3 and above pH 12 (14); this observation was reported qualitatively by Ukita et al. (17). Ring strain would be expected to result in rapid hydrolysis at all pH values, not merely at the extremes of the pH scale. Furthermore, Kugel and Halmann (14) suggested that, in alkaline hydrolysis, the transition state in the bimolecular mechanism occurred during the bond-forming phase, while the ring

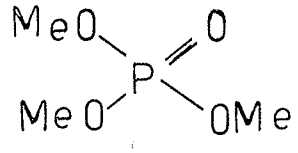
was still largely intact, rather than in the latter, bond-breaking phase.

The hydrolysis of 2-hydroxy-2-oxide-1,3,2-dioxaphosphole, 6, in $^{18}O$-labelled water, resulted (18,19a) in rapid $^{18}O$-exchange into unreacted 6 at a rate which was 20% of that of hydrolysis. Similarly, the rapid hydrolysis of the methyl ester, 9, produced 70% of the ring-opened product, 13, and 30% of 6 by exocyclic cleavage (18,19a). That $^{18}O$-exchange and exocyclic cleavage occurred at rates comparable to that of ring-opening, about $10^6$ to $10^8$ times faster than for acyclic analogues (4b,18,20a), also argued against the release of ring strain upon ring-opening as being the accelerating factor.

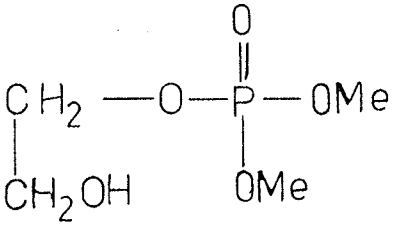
In order to account for the experimental facts, Westheimer proposed that hydrolysis of cyclic phosphates involved five-coordinate transition states (21), subsequently determined to be reaction intermediates (22), which were under favourable conditions able to undergo pseudorotation (23). The idea of five-coordinate intermediates in hydrolyses was not, however, a new one having been investigated since the 1950s (24) and Berry had already presented the concept of pseudorotation in trigonal bipyramidal structures in 1960 (25). As well, Hamer independently postulated the pseudorotation of trigonal bipyramidal intermediates to explain his stereochemical results (26).



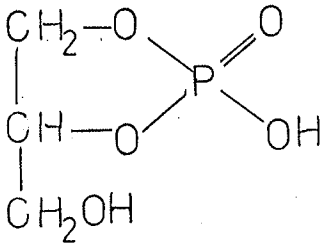
9



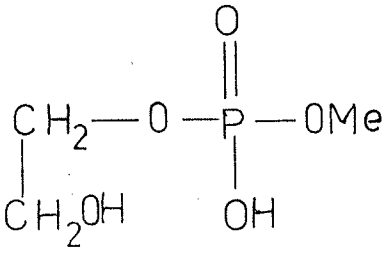
10



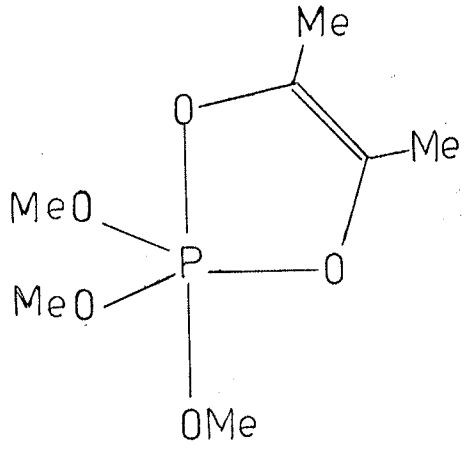
11



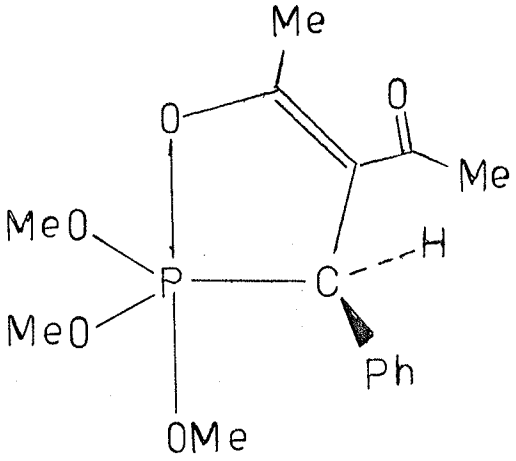
12



13



14



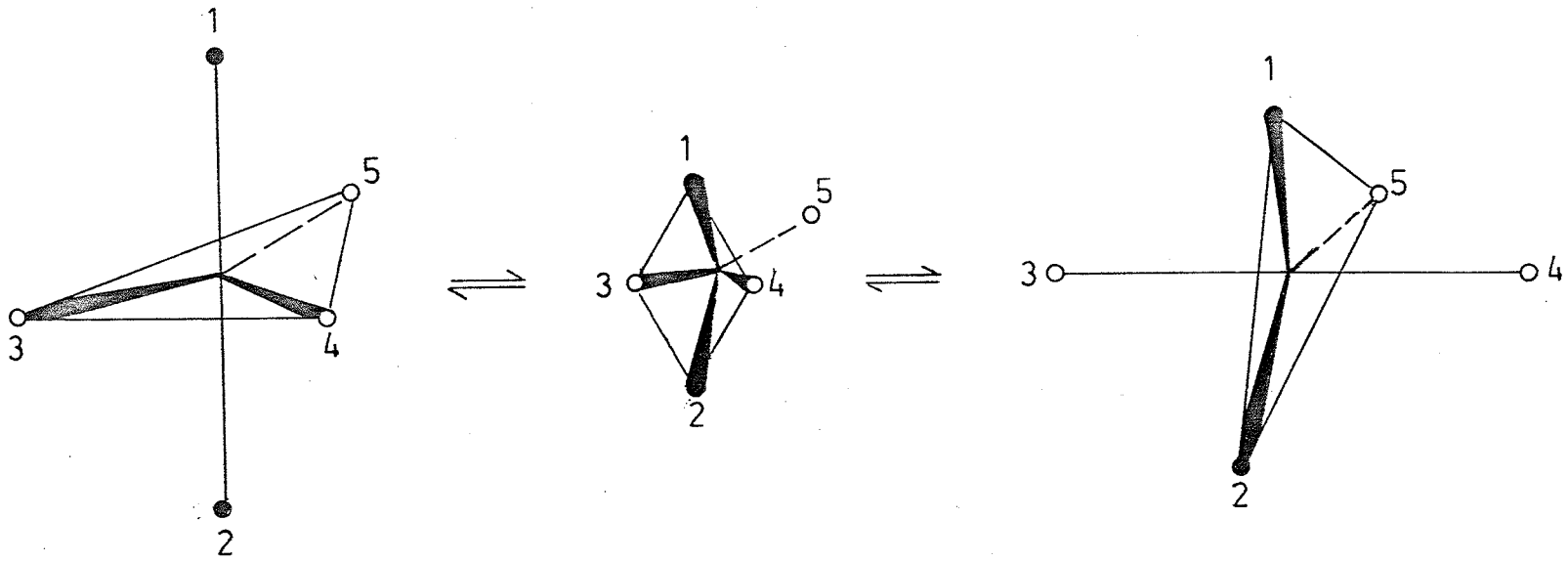
15

Trigonal Bipyramidal Molecules and Pseudorotation.

Pseudorotation can be defined as an intramolecular process which permutes the positions of groups about a central atom (27a). Specifically, Berry pseudorotation (BPR) is a mechanism whereby two equatorial groups of a trigonal bipyramid are interchanged with the two axial groups while the third equatorial group, known as the pivot ligand, retains its equatorial position (27b). This process is illustrated in Scheme 2.

The isomerization is postulated to take place through a square pyramidal transition state or intermediate (18,19b,28,29) in which the central atom lies above the basal plane. In this tetragonal pyramid, the internal angle, at the central atom, between two diagonally-opposed ligands is ideally 150° (19c,29). When the isomerization is complete, the newly formed TBP is oriented as if a 90° rotation about the pivotal bond had occurred. In fact, neither rotation of the molecule nor relative, internal rotations are a part of the Berry process.

Of the alternative mechanisms of intramolecular exchange (19b), the major one will be briefly described here: turnstile rotation (19d,29,30,31). In turnstile rotation (TR), as in BPR, the two axial ligands become equatorial and two of the three equatorial ligands become axial groups. However turnstile rotation, unlike Berry pseudorotation, is envisioned as an actual internal rotation

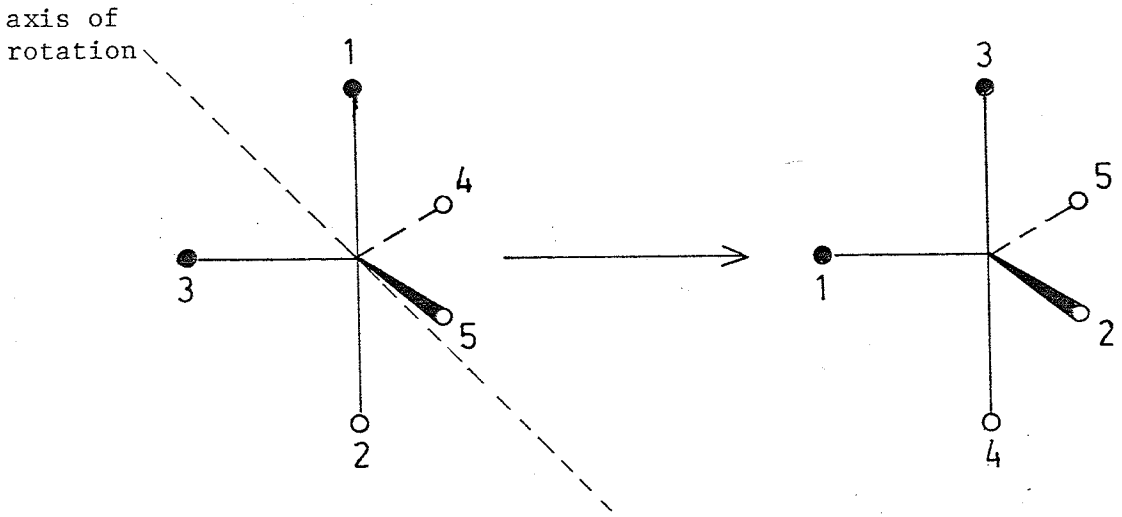



Scheme 2. Berry Pseudorotation

process (30), with the two parts of the molecule rotating relative to each other. The five ligands are divided into an axial-equatorial pair and a trio. The pair ligands undergo a 180° rotation and, simultaneously, the ligands of the trio rotate in the opposite direction by 120° (see Scheme 3); in this, the movement of the trio is like that of a turnstile.

Although the TR process has the same steric result as BPR, and can account for intramolecular exchange in some cases where Berry pseudorotation must be ruled out on the basis of severe ring constraints (19d,29,30,31), BPR is energetically favoured (32b) and its simplicity, and its applicability to the studies described herein, justify its use, exclusively, throughout the rest of this thesis.

Both of the structures in the Berry mechanism, the trigonal bipyramid (TBP) and the tetragonal pyramid, are calculated to be of comparable thermodynamic stability. With all ligands identical, the tetragonal pyramid would be expected to be only about 6 kJ/mole higher in energy than the TBP (19e). However, in the vast majority of cases, five-coordinate phosphorus compounds are found experimentally to exhibit trigonal bipyramidal geometry in the ground state (18,19f,28-30); for exceptions to this generalization, however, see for example, Mootz et al. (33) or Holmes et al. (34). The positions occupied by the five ligands are determined by the following factors:




Scheme 3. Turnstile Rotation

1. the steric interaction between the ligands,
2. the electronegativity of the ligands,
3. the participation of the phosphorus 3d-orbitals in bonding.

The result of these three factors is referred to by Ugi and Ramirez (29) as the "generalized polarity rule". As a result of the hybridization of atomic orbitals required to satisfy the TBP geometry, the axial bonds are longer than comparable equatorial bonds (19g,22,29,31) and, the more electronegative ligands tend to occupy the axial positions while less electronegative groups prefer the equatorial positions (18,19g,22,31,35). In addition, in trigonal bipyramids containing four- or five-membered rings, the placement of the ring is generally axial-equatorial (18,22). However, there are cases where a five-membered ring is found in a diequatorial position; see, for example, Schmutzler et al. (36).

The $^{19}F$ NMR spectrum of $CH_3PF_4$ shows only one fluorine signal (18,30) indicating magnetic equivalence of all four fluorine atoms. Since the structure is known to be TBP, the equivalence can best be explained by a pseudorotation process which employs an equatorial methyl group as the pivot ligand. In this way, the less electronegative methyl group can consistently occupy the more favourable equatorial position while pseudorotation exchanges the axial and equatorial fluorines.

Consideration of the polarity rule, above, and of the axial-equatorial placement of four- and five-membered rings provides a rationalization for why molecules like $CH_3PF_4$ and compound 14 (in which either of the two equatorial methoxy groups can serve as the pivot ligand) readily undergo pseudorotation, whereas $(CH_3)_2PF_3$ and compound 15 do not (18). While the $^1H$ NMR spectrum of 15 shows only one methoxy signal at room temperature (rapid intramolecular exchange), the low temperature spectrum shows two separate methoxy signals in a 2:1 ratio. However, the $^1H$ NMR spectrum of 14 exhibits only one methoxy signal even at -100°C. Pseudorotation about one of the two equatorial methyl groups of $(CH_3)_2PF_3$ would place the second methyl group in an unfavourable axial position. In the case of compound 15, pseudorotation about one of the equatorial methoxy substituents would again result in an alkyl group occupying an unfavourable axial position, while pseudorotation about the alkyl substituent would place the ring in a more strained diequatorial position.

It should be noted at this point that six-coordinate phosphorus compounds are also well known (32a) and are currently postulated to be intermediates in the hydrolysis of phosphate esters (22,37,38).

Phosphate Ester Hydrolysis: Westheimer's Hypothesis (18,23).

Although it had been shown that five-membered cyclic phosphates hydrolyze many times more rapidly than their acyclic analogs (10a,12), and further, that such cyclic phosphates encounter ring strain (13), other studies (14,39,40) were not consistent with the suggestion that the release of ring strain upon ring-opening provided the driving force for the rapid hydrolyses. Thus, Westheimer's proposal (21) that hydrolysis of cyclic phosphates proceeded by way of a trigonal bipyramidal intermediate was subsequently broadened (18) so as to include the following conditions:

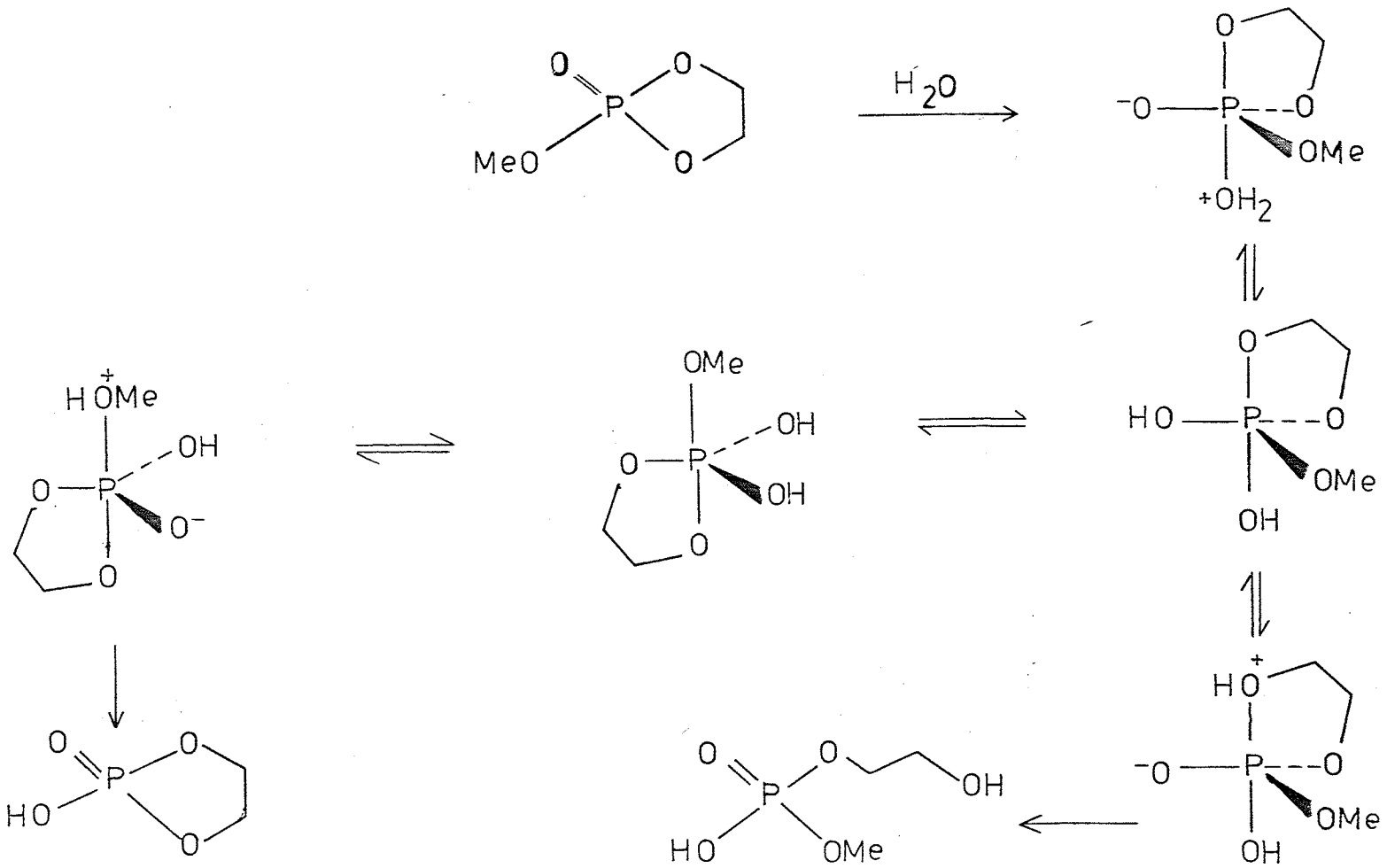
1. the five-membered ring occupies an axial-equatorial position,
2. alkyl groups preferentially occupy equatorial positions, while ligands bonding to phosphorus through an oxygen atom tend to occupy the axial (or apical) positions,
3. hydrolysis may involve pseudorotation of the trigonal bipyramidal intermediate,
4. the attacking group enters at an apical position, while the leaving group departs from an apical position.

Ring strain was still presumed to cause the rapid rates of hydrolysis, not through release of strain on ring fission, but through relief of strain achieved on forming the tri-

gonal bipyramidal intermediate in which axial-equatorial placement of the ring provides for a favourable ring angle at phosphorus of about 90°.

Hydrolysis of the cyclic phosphate, 9, in weakly acidic solution, was found to produce both the ring-opened product, 13, and the cyclic diester, 6. A detailed discussion of the effect of pH on this reaction is given by Luckenbach (19h). The mechanism for the reaction, embodying Westheimer's hypothesis, is shown in Scheme 4. A water molecule adds to the phosphate and occupies an apical position. The phosphoryl oxygen takes up an equatorial position as a hydroxyl group after proton transfer. The five-coordinate structure can then be protonated; the apical oxygen atoms are the favoured sites due to the higher electron densities at the apical positions. Consequently, pseudorotation of the protonated species is unlikely since this would force the protonated group into an unfavourable equatorial position. If the alkoxy group is protonated, cleavage of the P-O bond, followed by loss of a proton from the equatorial hydroxyl, leads to the ring-opened 13; if the hydroxyl group is protonated, the breaking of its P-O bond is a degenerate process resulting in the reformation of compound 9.

The trigonal bipyramid can undergo Berry pseudorotation before protonation, with the equatorial hydroxyl as the pivot, thus placing the methoxy group in an apical



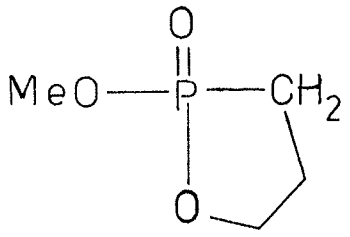
Scheme 4.
Hydrolysis of Methyl Ethylene Phosphate: Westheimer's Hypothesis

position. Protonation on the methoxy oxygen, followed by P-O bond fission and deprotonation of the equatorial hydroxyl yields methanol and the cyclic phosphate, 6. Thus, the relief of ring strain accompanying the formation of the five-coordinate intermediate can account for both rapid ring-opening and rapid exocyclic cleavage. Several workers, including Westheimer (18) himself, have pointed out that the reduction in ring strain on forming the five-coordinate intermediate only accounts for a part of the difference in activation energy for the cyclic and acyclic reactions; for a possible explanation see Gorenstein et al. (41,42).

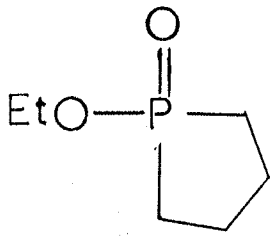
Westheimer's hypothesis, then, also accounts for the hydrolysis of compound 16, which proceeds at an accelerated rate but almost exclusively with ring fission, and of compound 17, whose rate of reaction is not enhanced relative to the rate for 18 (39). For these two cyclic molecules, pseudorotation of the intermediate would be expected to be energetically unfavourable, although not forbidden.

Hydroxyphosphoranes.

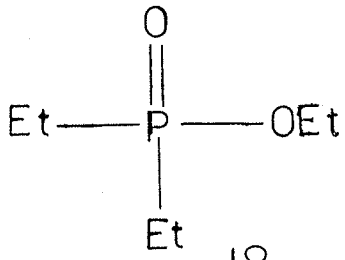
Those phosphorus esters which possess a hydroxyl substituent adjacent to the phosphoryl group are known to undergo rapid hydrolysis in both acidic and alkaline solution (14-16). Catalysts for the hydrolysis assist in the ring-closure to the cyclic five-coordinate intermediate: acids by protonation of the phosphoryl oxygen (43), ren-



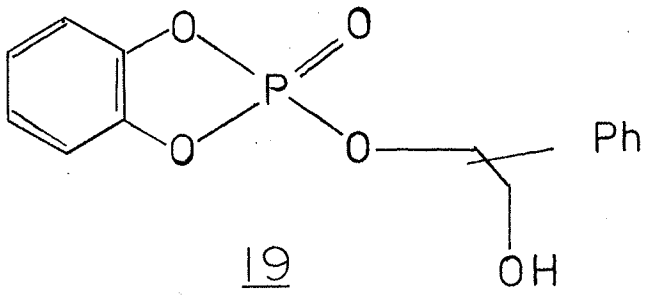
16



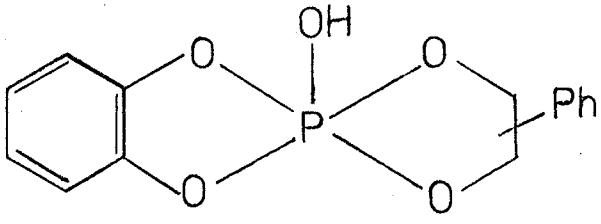
17



18



19

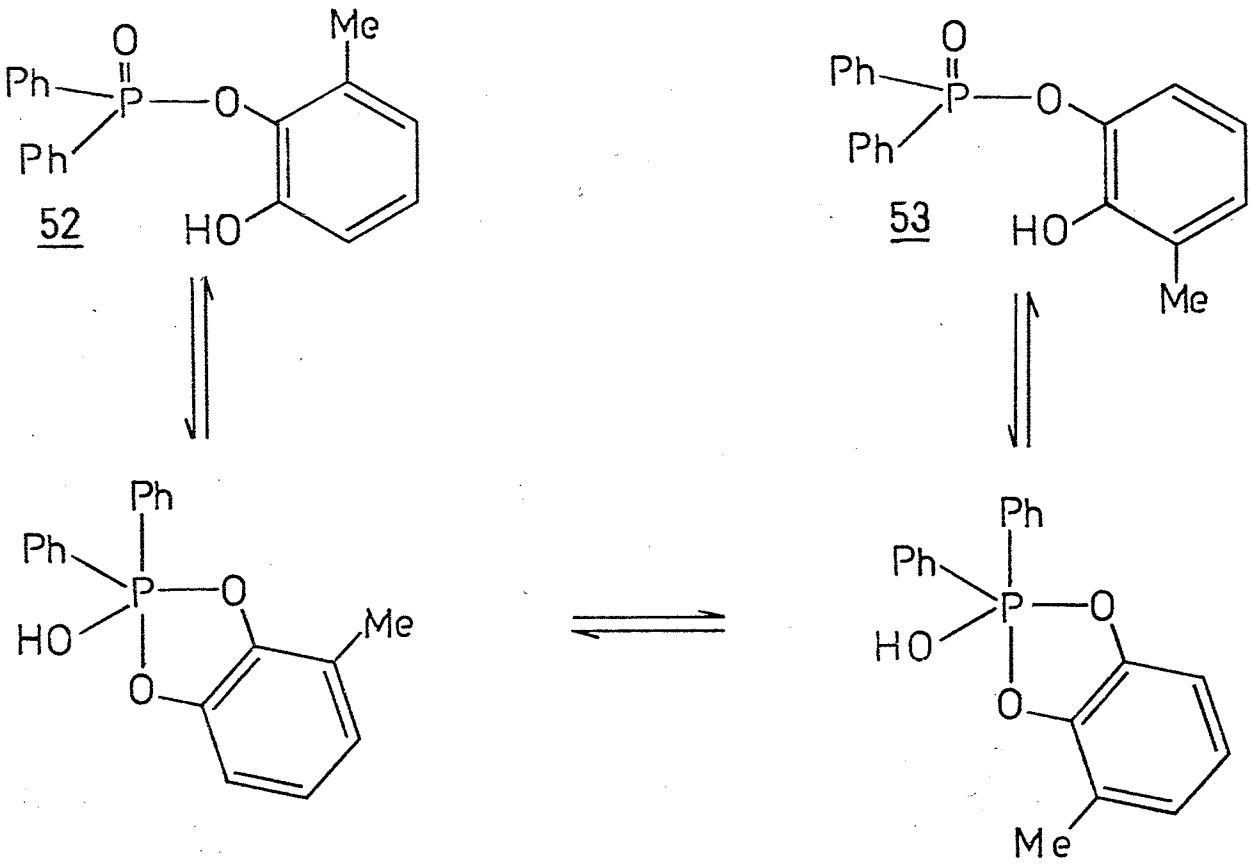


20

dering the phosphorus atom more susceptible to nucleophilic attack, and bases by deprotonation of the hydroxyl group (5,44) producing the more nucleophilic oxy-anion. The mode of action of metal ion catalysts is not as well understood (3,4c,20b,22).

The five-coordinate intermediates are either hydroxyphosphoranes or their conjugate bases, phosphoran-oxide anions (45,46). Although stable hydroxyphosphoranes were reported at least as far back as 1963 (32c,46), they are ill-defined and it was not until the mid- and late-1970s that well-documented evidence of their existence was forthcoming. In 1974, Koizumi et al. (47) provided indirect evidence of a hydroxyphosphorane intermediate in a nucleophilic displacement reaction at phosphorus. In 1976, Munoz et al. (48) made the same interpretation in order to explain their own results. As well, in that same year, an NMR study of the isomerization of phosphinic esters furnished further evidence of the existence of hydroxyphosphoranes (49). As illustrated in Scheme 5, the isomerization involves the pseudorotation of the intermediate hydroxyphosphorane. Its existence was demonstrated by chemical trapping with diazomethane, producing the corresponding methoxyphosphorane along with the expected 2-methoxyphenyl phosphinates.

Direct observation of hydroxyphosphoranes was subsequently reported by several laboratories (43,46,50). Munoz (50) observed the upfield displacement of the $^{31}P$




Scheme 5. Isomerization of Diphenylphosphinates 52 and 53 in Solution

chemical shift of 19 as successive quantities of triethylamine were added. Furthermore, the process was reversible with addition of trifluoroacetic acid, indicative of an equilibrium. In addition, it was found that lowering the temperature of an equimolar mixture of 19 and triethylamine to -60°C shifted the equilibrium entirely to the triethylamine salt of the hydroxyphosphorane 20; this, too, was reversible. Although Munoz described the species as a triethylammonium salt, his results (51) for a similar compound were re-examined by Granoth and Martin (45) in light of their own studies on the acidities of hydroxyphosphoranes. They concluded that the results were more compatible with a triethylamine complex than with a salt. It is notable that the $^{31}P$ NMR spectrum showed only one signal (for each isomer), representing the weighted average of the chemical shifts of 19 and 20, over the entire temperature range indicating that the equilibrium is rapid on the NMR time-scale.

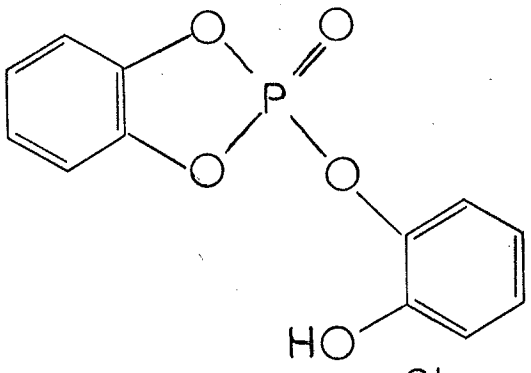
Ramirez (43), on the other hand, reported a slower equilibrium between 21 and 22. (It was uncertain whether the crystalline compound isolated was 21 or 22.) At -48°C two separate, sharp signals were observed in the $^{31}P$ NMR spectrum. These were seen to broaden and coalesce as the temperature was increased. As well, the hydroxyphosphorane could be trapped with diazomethane and with acetylchloride. Interestingly, while Ramirez obtained the hydroxyphosphorane

22 on treatment of the corresponding trimethylsiloxyphosphorane with HCl, Schmutzler et al. (52) were unable to synthesize the hydroxyphosphorane 23 from its corresponding trimethylsiloxyphosphorane by treatment with HCl, but obtained instead the acyclic isomer, 2-hydroxy-1,1,2,2-tetrakis(trifluoromethyl)ethyldimethylphosphinate.

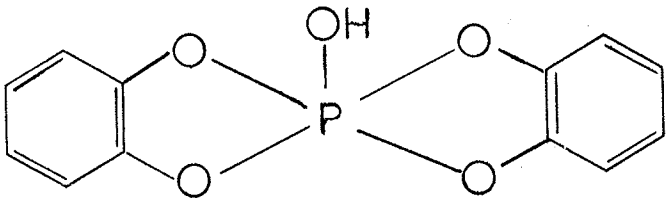
Since 1978, several complexes and salts of hydroxyphosphoranes and phosphoranoxides have been isolated as crystalline solids (45,51,53,54). As well, their reactivities and their physico-chemical properties have begun to be studied (45,55). These recent studies have important implications for the work described in the main body of this thesis.

Intent of this Study.

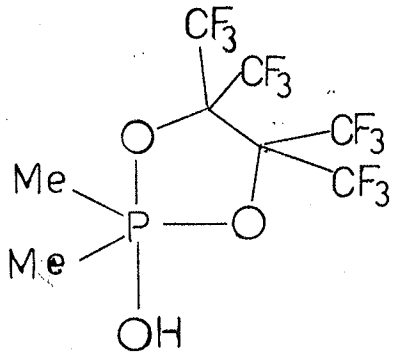
The base-catalyzed hydrolysis of ribonucleic acid (and of similar compounds) has been shown to comprise two separate reactions (Scheme 1). The first is a transesterification resulting in the formation of a cyclic diester; Markham and Smith first isolated and identified these intermediates (56,57). Subsequently, the cyclic product can be hydrolyzed to produce (usually) a mixture of two possible products (3). Studies on the model compound 24 by Usher et al. (44) showed that the hydrolysis of the cyclic product was about 1000 times slower than the original ring-closure reaction.



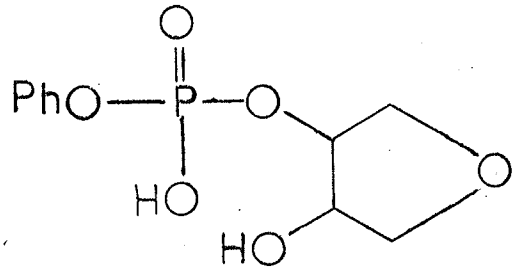
21



22



23



24

It has been suggested (44) that the transesterification is a multi-step process involving a pre-equilibrium deprotonation followed by ring-closure (possibly to a trigonal bipyramidal intermediate) and expulsion of the exocyclic alkoxy group. Since these authors found no evidence for a five-coordinate intermediate, they chose to favour an "in-line" S(N)2 displacement, remarking however that a trigonal bipyramidal intermediate could not be ruled out. Apparently the alternative transesterification - migration of the phosphate group to the 2'-position - does not occur (58a) and the cyclic structure is preserved (4d).

In order to gain further insight into the pre-equilibrium deprotonation and the ring-closure, it was decided that NMR spectra of phosphates such as glycerol-1-phosphate should, under certain conditions (eg. pH, temperature), be able to provide for mechanistic interpretations. Subsequently, it became apparent that the phosphinate structure, with only one ester group, should provide a better model. Presumably such a structure should allow both for the deprotonation and for nucleophilic ring-closure, but an S(N)2 displacement is not possible here due to the lack of a readily displaceable group; thus any further reaction of the ring-closed species can only involve ring-opening.

The major considerations in the choice of ester group were:

1. the presence of a plane of symmetry in the corresponding diol, and
2. that the corresponding diol be readily available, or easily synthesized.

Satisfying the first requirement ensures greater simplification of the NMR spectrum than would otherwise be the case. The second requirement obviously simplifies the synthesis of the phosphinate. Therefore, the alcohols chosen were 1,2-dihydroxybenzene (catechol), cis-tetrahydro-3,4-furandiol, and 1,2-dihydroxy-1,1,2,2-tetrakis(trifluoromethyl)ethane (perfluoropinacol).

The intent of this study, then, was to synthesize appropriate model compounds and to obtain $^{1}H$, $^{13}C$, and $^{31}P$ NMR spectra of these compounds in order to attempt to define the mechanistic process(es) taking place when bases, of varying base strengths, are added to the phosphinates in solution.

## GENERAL PROCEDURES, SOLVENTS, AND INSTRUMENTAL

General.

Most reactions were carried out either in a glass vacuum line, by conventional techniques, or in a nitrogen-atmosphere dry box due to the moisture- and/or air-sensitive nature of many of the compounds used. No systematic attempts were made to optimize the reaction conditions so as to obtain maximum yields of product. Most sample preparations, for NMR spectra, were also done in the dry box.

Melting points were taken in capillary tubes and are uncorrected. Elemental analyses were carried out by Micro-Tech Laboratories, Skokie, Illinois, and by Galbraith Laboratories, Knoxville, Tennessee.

Computer analyses were performed on an Amdahl 470-V7 computer.

Due to restrictions on the availability of certain non-standard characters on the print train used to reproduce this thesis, the following changes to conventional notation have been made:

1. ($^{31}$P) will represent the $^{31}$P chemical shift (in ppm); similar notation for other nuclei.

2. $[^{1}H]$-$^{31}P$ will represent proton-decoupled $^{31}P$ NMR; similar notation for other nuclei.
3. S(N)2 will represent substitution nucleophilic bimolecular.
4. SQRT will represent the square root operator.

Solvents.

With the exception of $D_2O$ and pyridine-d5, all deuterated solvents, once opened, were stored over 3A Davison molecular sieve (Fisher). $D_2O$ and pyridine-d5 were obtained from Merck Sharp and Dohme Isotopes, the others from Aldrich Chemical Co. and/or Stohler Isotope Chemicals.

Methanol (Fisher) and benzene (Fisher) were stored over molecular sieve. n-Hexane (Fisher) was stirred over anhydrous magnesium sulphate (Fisher) for twelve hours, then filtered in a dry nitrogen atmosphere and stored over molecular sieve in the dry box. Anhydrous diethyl ether (Fisher), once opened, was stored under nitrogen in the dry box.

Dichloromethane (Fisher) was fractionated from anhydrous calcium chloride (Fisher) and collected over molecular sieve, then stored in the dry box.

Purified and dried pyridine was kindly provided by Mr W. J. P. Blonski, while dried p-dioxane was obtained courtesy of Dr A. Queen. Both were stored in the dry box.

Triethylamine (Eastman) was purified (59) by heating under reflux with 20-25% (molar basis) phthalic anhydride (Fisher), followed by distillation, and was then stored in the dry box. Diethylamine (Fisher) was allowed to stand over KOH (Fisher) overnight. It was heated under reflux with KOH for 30 minutes and then distilled under nitrogen. Phosphorus trichloride (BDH Chemicals) was distilled under nitrogen and stored away from light.

Dimethylsulphoxide (Baker) was stirred over calcium hydride (Fisher) for twenty-five hours, then distilled under vacuum from a fresh portion of $CaH_2$ onto molecular sieve (60-62a). Storage was under nitrogen in the dry box.

Instrumental.

Nuclear magnetic resonance spectra were recorded on a Varian A-56/60A NMR spectrometer at 56.4 and 60 MHz for $^{19}F$ and $^{1}H$, respectively, for routine proton and fluorine spectra; probe temperatures were measured either with a mercury thermometer or with a copper-constantan thermocouple. $^{31}P$, $^{13}C$, and non-routine $^{1}H$ spectra were recorded on a Bruker WH-90 NMR spectrometer using 36.443, 22.63, and 90 MHz for these nuclei, respectively.

Unless otherwise stated, all NMR chemical shifts reported are positive to low field and negative to high field of external reference compounds: $CFCl_3$ for $^{19}F$, 85% $H_3PO_4$ for $^{31}P$, and tetramethylsilane (TMS) for $^{1}H$ and $^{13}C$

spectra. Among those compounds used as internal, secondary standards in some of the NMR spectra are the following:

1. $CD_2Cl_2$, ($^{13}C$) = 53.78 ppm
2. $CDCl_3$, ($^{13}C$) = 77.2 ppm
3. $C_6D_6$, ($^{13}C$) = 128.0 ppm
4. 1,4-dioxane, ($^{13}C$) = 67.86 ppm
5. acetone ($CH_3$), ($^{13}C$) = 31.58 ppm
6. $CHDCl_2$, ($^{1}H$) = 5.32 ppm
7. acetonitrile, ($^{1}H$) = 1.96 ppm
8. perfluoropinacol, ($^{19}F$) = -70.0 ppm
9. hexafluorobenzene, ($^{19}F$) = -162.9 ppm

All mass spectra were recorded on a Finnigan 1015 mass spectrometer at 60 eV. Measurements of pH (and/or pD) were made using a Radiometer PHM 28 pH meter.

# EXPERIMENTAL

## 2-Chloro-2,2-dihydro-2,2-diphenyl-4,4,5,5-tetrakis(trifluoromethyl)-1,3,2-dioxaphospholane(25).

Following the procedure of Pollitt (63), compound 25 was prepared as outlined below.

In a typical reaction, hexafluoroacetone (21.4 mmol) (Matheson) was condensed into a thick-walled glass reaction tube containing diphenylphosphinous chloride (2.26 g, 10.2 mmol) (Aldrich) at -196°C. The tube was then flame-sealed under vacuum and the contents were allowed to react upon warming to room temperature. Two separate layers were visible. However, after one week, only one layer was observed and the reaction was judged to be complete. The product was not isolated but was identified via the products of its reaction with other compounds (see below).

## 2-Hydroxy-1,1,2,2-tetrakis(trifluoromethyl)ethyldiphenylphosphinate(26).

Compound 26, first prepared by Pollitt (63) and subsequently characterized by NMR (64), was required for $^{13}C$ NMR exchange studies. A sealed reaction tube containing approximately 10 mmol of compound 25 (prepared as in the

previous section) and some excess hexafluoroacetone was frozen in liquid nitrogen, transferred immediately to a nitrogen-atmosphere dry box, and broken open. Upon warming, the hexafluoroacetone escaped.

The contents of the tube were allowed to drain into a 50 mL round-bottomed flask and were then dissolved in 7 mL of acetonitrile (Aldrich); the solution had a pastel green colour. Water was added, in excess, with stirring. An oil separated, which then precipitated as a white solid.

After filtration, the crude product was dissolved in 10 mL of dichloromethane. A 1-2 mL portion of petroleum ether (37.8-56.9° fraction) (Fisher) was added and the mixture of solvents was removed on a rotary evaporator (Buchler Instruments) until the product just began to precipitate. The mixture was cooled on ice until the remainder of the product crystallized. The solvents were decanted and more petroleum ether was added. The crystals were filtered and then washed with petroleum ether. Removal of all traces of solvent gave $(C_6H_5)_2P(O)OC(CF_3)_2C(CF_3)_2OH*xH_2O$, m.p. 121-124° (63), in <25% yield (based on diphenylphosphinous chloride used). The evidence for $H_2O$ in the crystals was obtained through NMR experiments which will be described later. A further recrystallization, from acetonitrile, gave the phosphinate 26, m.p. 125-127°, $^{19}F$ NMR: septets at -67.2 and -69.4 ppm, $^5J(FF)$ = 10 Hz. These results compare very well with those of Janzen et al. (64).

Figure 1.
$^{1}H$ NMR Spectrum of
cis-Tetrahydro-3,4-furandiol.

cis-Tetrahydro-3,4-furandiol(27).

Using the procedure of Otey and Mehltretter (65), three successive portions (10.3, 10.1 and 10.1 g) of meso-erythritol (Aldrich) were heated under vacuum with 1 g of Dowex 50W-X8 (Baker) cation exchange resin; the same sample of resin was used each time. The product distilled out of the flask at temperatures which varied between 112 and 125°C for the three samples but averaged about 117°C. The amount of 27 obtained was 23.9 g (92% of theoretical yield); recovery of 27 from the distilling flask, column and condenser would have further increased the yield.

NMR analysis of the product confirmed that it was the diol 27 and was of high purity. The $[^{1}H]$-$^{13}C$ spectrum, in $D_2O$, showed two peaks: 72.14 ppm (methine $^{13}C$) and 72.68 ppm (methylene $^{13}C$); these are tentative assignments. The $^{1}H$ spectrum (Fig.1), also in $D_2O$, was virtually identical to that obtained by Mazurek and Perlin (66).

Oxidation of Diphenylphosphinous Chloride to Diphenylphosphinic Chloride(28).

In a typical oxidation, diphenylphosphinous chloride (7.7 g, 35 mmol)(Alfa) was added to 50 mL of benzene in a two-necked round-bottomed flask placed on ice and fitted with a condenser. Oxygen was bubbled into the solution at a fairly slow rate, passing first through an empty trap to prevent contact of organic materials with $O_2$ at the cylinder

in the event of the development of negative pressure in the system. The stream of oxygen passed from the condenser and bubbled through a second trap, containing vacuum pump oil, whereby the oxygen flow rate as well as the build-up of negative pressure, could be monitored. The entire operation was carried out behind safety glass, in a fume hood.

Heat was evolved during the reaction and thus, when evolution of heat ceased, the reaction was judged to be complete; this generally occurred after 15-20 minutes.

On one occasion, in order to obtain a $^{31}P$ NMR spectrum of the reaction mixture, the oxidation was terminated before completion. The spectrum (in $C_6D_6$) showed three signals: The major peak at 41.77 ppm was assigned to $Ph_2P(O)Cl$ (67a), a secondary signal at 81.98 ppm was assigned to $Ph_2PCl$ (67b), while the minor peak at 26.60 ppm was due to the acid, $Ph_2P(O)OH$ (68,69).

Chemical Exchange in the $^{19}F$ and $^{13}C$ NMR Spectra of 2-Hydroxy-1,1,2,2-tetrakis(trifluoromethyl)ethyl-diphenylphosphinate(26).

In the first of several attempts to observe chemical exchange in the $[^{19}F]$-$^{13}C$ NMR spectrum of the phosphinate 26, 0.228 g of the compound and 0.15 mL of pyridine (Baker) from a previously opened bottle of undetermined age were added to 3 g of $CD_2Cl_2$ in an NMR tube. The spectrum showed only (ignoring phenyl and pyridine carbons) the $^{13}C$ signals

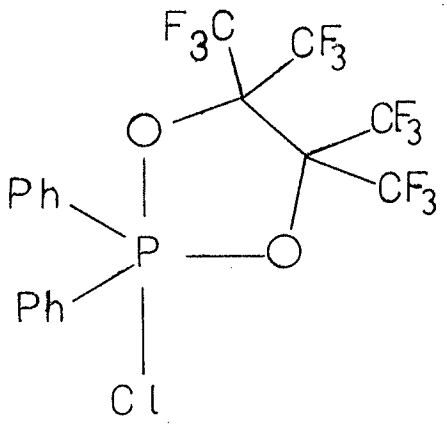
of free perfluoropinacol: $^{13}CF_3$ at 122.8 ppm and $^{13}C$-OH at 82.5 ppm.

In order to dry the pyridine, it was allowed to stand over KOH pellets (Fisher) for 65 hours, and then distilled under vacuum, from a fresh portion of KOH, directly onto molecular sieve.

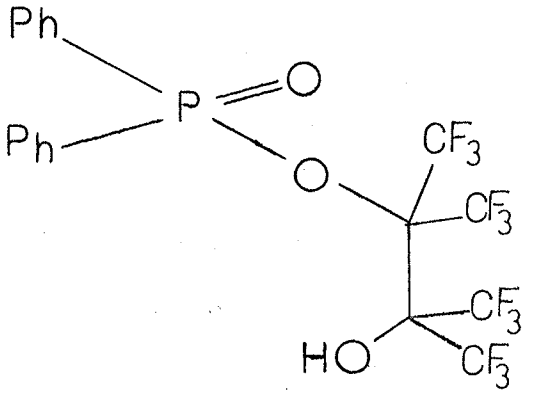
Another sample was prepared, consisting of 0.277 g of the phosphinate 26, and 0.2 mL of dried pyridine in 2 mL of $CD_2Cl_2$ solution. The $[^{19}F]$-$^{13}C$ FT-NMR data from only 114 transients were recorded due to a loss of field stabilization at that point. However, these few scans were enough to show that there were again only 2 peaks (again ignoring phenyl and pyridine carbons) but this time at the expected positions: a broad signal at 85.0 and a slightly broadened signal at 121.7 ppm. Janzen et al. (64) found the corresponding $^{13}C$ signals for 26, in the absence of base, to be at 81.9 and 88.0 ppm, and at 120.7 and 121.7 ppm.

The $^{19}F$ spectrum (in $CD_2Cl_2$), obtained some 90 hours after the $[^{19}F]$-$^{13}C$ spectrum was run, showed: perfluoropinacol, s, -70.0 ppm; a broad peak at -68.1 ppm; an unidentified doublet at -74.2 ppm, $^3J(FH)$ = 6 Hz; and a very minor unidentified signal at -75.5 ppm. The $^{19}F$ signals were identified by comparison with the results of Janzen et al. (64).

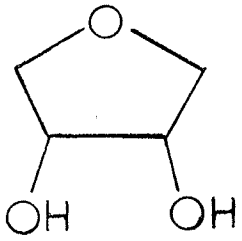
In order to obtain a $[^{19}F]$-$^{13}C$ spectrum with an increased S/N ratio, compound 26 (0.195 g), along with dried



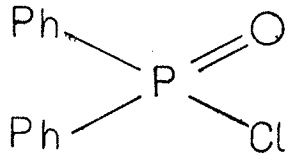

25



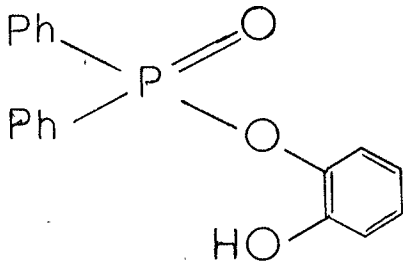

26



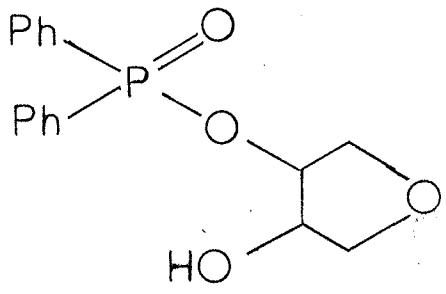

27




28




29




30

pyridine (0.1 mL), were dissolved in $CD_2Cl_2$ (2 mL). Only the hydrolysis product, perfluoropinacol, was observed (once more the phenyl and pyridine carbon signals are ignored) with singlets at 82.6 ppm ($^{13}C$-OH) and 122.9 ppm ($^{13}CF_3$).

A sample of pyridine was then obtained from Mr W. J. P. Blonski. Pyridine from this source is dried and purified by an involved procedure (70): 1.5 L of pyridine is allowed to stand over chlorosulphonic acid (8-12 mL) for 1 hour. The mixture is heated under reflux for a minimum of 2 hours, followed by distillation, using a Vigreux column, directly onto calcium hydride, taking care to exclude moisture. The mixture is heated under reflux again and is then distilled directly onto Linde molecular sieve. Pyridine from this source was used in all subsequent experiments.

The phosphinate 26 (0.194 g) was dissolved in $CH_2Cl_2$ (2 mL). After 16 hours the $^{19}F$ NMR spectrum showed two septets at -67.2 and -69.4 ppm, $^5J(FF)$ = 10 Hz and a minor, sharp singlet at -70.0 ppm, assigned to perfluoropinacol. Upon addition of the dried pyridine (0.1 mL), the $^{19}F$ spectrum immediately showed only the -70.0 ppm singlet of the hydrolysis product, perfluoropinacol.

It was apparent that, since this pyridine was indeed well-dried and since, with pyridine less rigorously dried (over KOH), the 114-scan $[^{19}F]$-$^{13}C$ spectrum did not show immediate hydrolysis, the only remaining factor was the source of the sample: compound 26 was available from the

synthesis described previously, having been recrystallized once from petroleum ether, as well as from a sample kindly provided by Dr A. E. Lemire.

Having used the former sample for the previous experiment, it was now repeated using that provided by Dr Lemire. Before pyridine was added, the $^{19}F$ spectrum (Fig.2) showed only the phosphinate 26 (septets, -67.2 and -69.4 ppm) and no perfluoropinacol. Upon addition of pyridine, a broad peak at -68.0 ppm replaced the original septets; a perfluoropinacol peak was also observed (s, -70.0 ppm) (Fig.3).

The spectrum was obtained again after 1.5, 9, and 21 hours. The broad peak continued to be the major signal, but decomposition did give rise to a doublet at -74.2 ppm ($^{3}J(FH)$ = 6 Hz), and a singlet at -75.5 ppm; these were not identified.

Finally, after a second recrystallization, the purified and dried phosphinate 26 (0.144 g) and pyridine (0.1 mL) were dissolved in $CD_2Cl_2$ (1.5 mL). The $[^{19}F]$-$^{13}C$ spectrum (Fig.4) exhibited both the sharp signals at 82.7 and 122.9 ppm due to free perfluoropinacol, and the expected broad peaks: a slightly broadened $^{13}CF_3$ signal at 121.7 and a broad $^{13}C(CF_3)_2$ signal at 85.0 ppm.

Figure 2.
$^{19}F$ NMR Spectrum of Phosphinate 26.

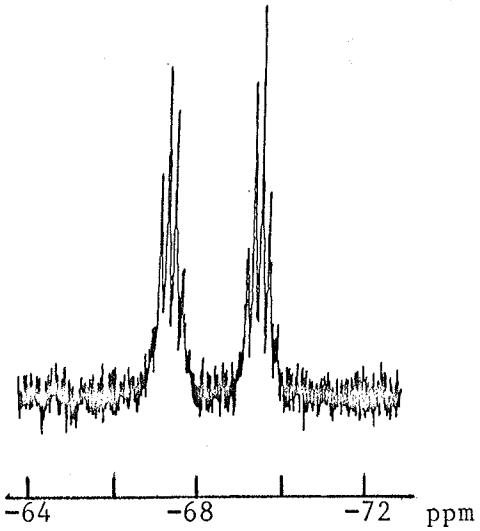



Figure 3.
$^{19}F$ NMR Spectrum of Phosphinate 26 in the Presence of Pyridine.

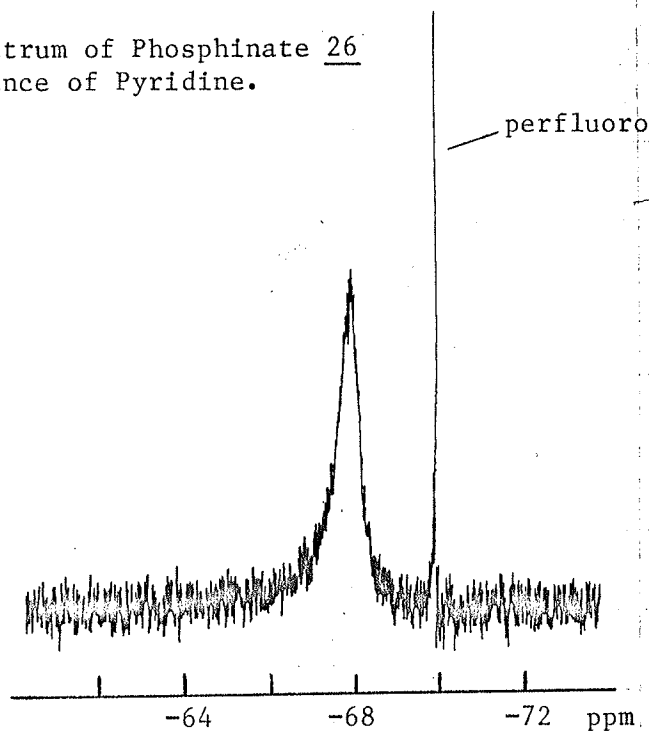
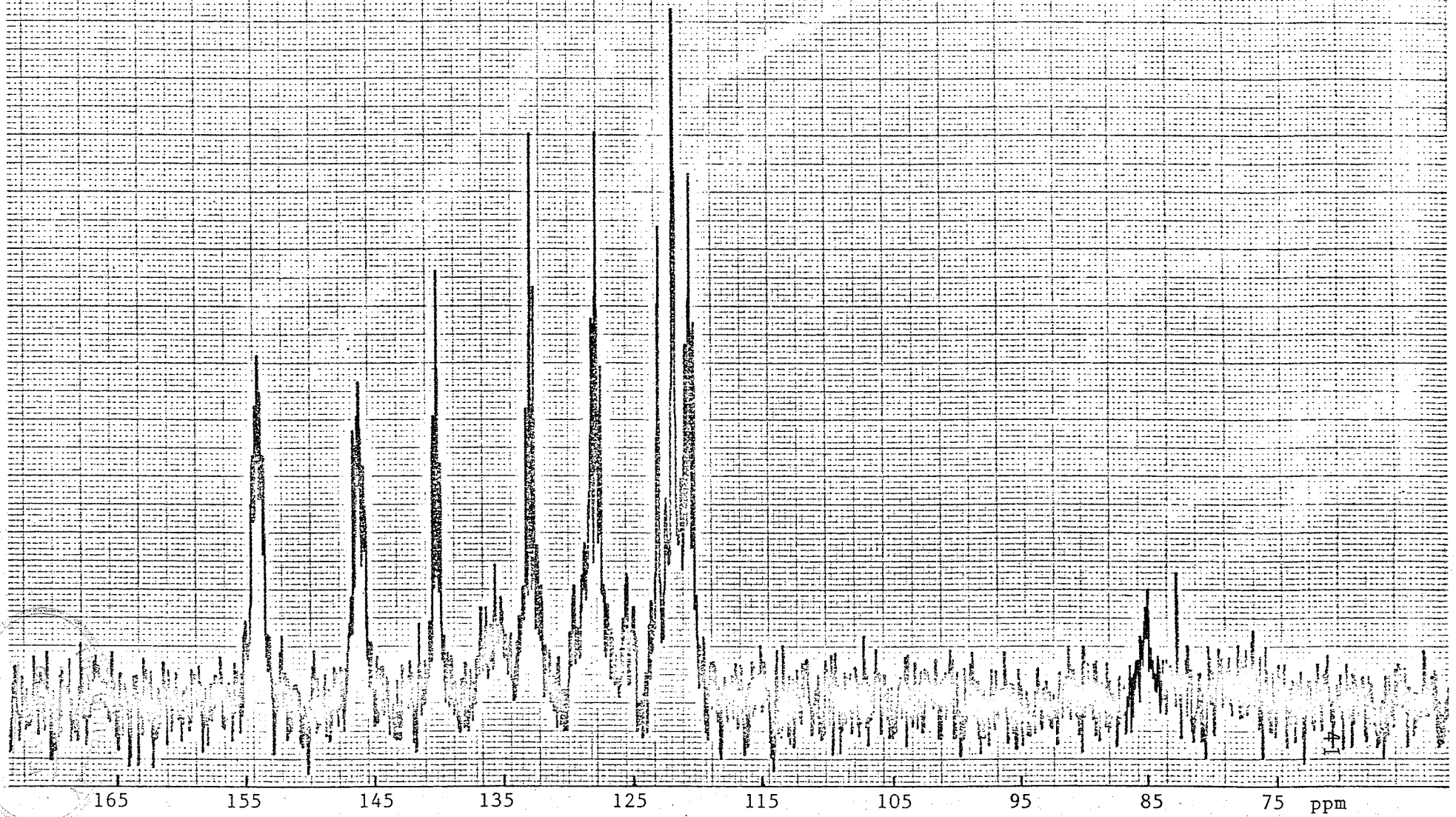


Figure 4.
$[^{19}F]$–$^{13}C$ NMR Spectrum of Phosphinate 26 in the Presence of Pyridine.



2-Hydroxyphenyldiphenylphosphinate(29).

To 40 mL dry benzene was added diphenylphosphinous chloride (12.3 g, 56 mmol). This was oxidized to diphenylphosphinic chloride, 28, as described above. The solution was then transferred to the dry box and placed in a clean, dry separatory funnel.

To a 250 mL round-bottomed flask, containing 30 mL dry benzene, 1,2-dihydroxybenzene (catechol) (6.39 g, 58 mmol) (BDH Chemicals) and dry pyridine (4.4 g, 56 mmol) were added. With continuous swirling and mixing, the solution of the phosphinic chloride, 28, was added, dropwise, over 30-40 minutes, to the benzene solution of catechol and pyridine. Heat was evolved and after about 25% of the chloride had been added, white vapours were seen to be given off. When the addition was complete, two layers were observed: a pale yellow upper layer with suspended white crystals and a viscous, brown layer below.

The solids were filtered off and were washed twice with dichloromethane. Mass spectral analysis showed $M^+$ at m/e 310, but also pyridine and pyridinium ions at m/e 79 and 80. The solid was then washed several times with water and was dried at room temperature on the vacuum line. Vacuum sublimation was attempted in order to obtain the pure compound, but resulted only in decomposition. Purification by the method of Magdeev et al. (71) for a similar compound was also unsuccessful. However, recrystallization from 1:1

benzene-methanol (Goda et al. (72) recrystallized 4-hydroxyphenyldiphenylphosphinate from benzene-methanol) gave large rhomboid crystals; traces of solvent were removed on the vacuum line; m.p.: decomposed at 172°; there appeared to be a change in the morphology of the crystals at about 134°C.

The dichloromethane washes (above) were combined with the filtrate and about 30% of the solvent mixture was removed on a rotary evaporator; the remainder was left to stand overnight. In the morning, there were two layers, as before, with a precipitate suspended in the upper layer. The solids were again filtered off and were purified as mentioned above. The two layers of the filtrate were separated. The brown, lower layer was found by $^{1}H$ NMR (in $CD_3CN$) to contain catechol, pyridine hydrochloride, and other, unidentified compounds. The solvents were removed from the upper layer and the remaining solid was again treated as above. The total yield of crude product was >39% of theoretical.

Compound 29 was thus obtained pure; elemental analysis: calculated (for $C_{18}H_{15}O_3P$) C, 69.68; H, 4.87%; found C, 69.51; H, 4.87%; $^{31}P$ NMR: 38.04 ppm in $CDCl_3$, 37.80 in $CD_2Cl_2$.

The synthesis of 29, from catechol and diphenylphosphinic chloride, 28, in the absence of pyridine or other base used to remove the HCl produced, was attempted but no

evidence for the formation of $Ph_2P(O)OC_6H_4OH$, 29 was found. Henglein and Kramer (73) report that $Me_3SiCl$ will react with only one of the hydroxyl groups of catechol, but that in the presence of base (pyridine/formamide) both hydroxyl groups are silylated.

cis-3-Diphenylphosphinatotetrahydro-3,4-furandiol(30).

Diphenylphosphinous chloride (7.7 g, 35 mmol) was oxidized in benzene as described above. To this solution, pyridine (2.82 g, 36 mmol) was added. A solution of cis-tetrahydro-3,4-furandiol, 27, (3.70 g, 36 mmol) in about 30 mL dichloromethane was also prepared.

In a dry nitrogen atmosphere, the diphenylphosphinic chloride, 28, was added dropwise, with stirring, to the solution of the diol, 27, over 20-30 minutes. No heat was evolved nor were there any vapours seen to be given off; only an emulsion formed.

The next day, having stirred the mixture again, long, broad, clear, plate-like crystals were visible at the benzene-dichloromethane interface. After several more days, a second solid had begun to precipitate. n-Hexane (5 mL) was added and resulted in an immediate precipitation of solid material.

During the next several hours, another 12 mL of hexane were added, in small portions, each time causing further precipitation, and then the mixture was filtered.

The solid material was washed with hexane; the wash was then combined with the hexane-benzene filtrate with a resultant minor clouding. This was subsequently also filtered.

Separation by partitioning between water and benzene appeared to be unsuccessful. Mass spectral analysis showed a large amount of pyridine present, as well as some unreacted 27 but no pyridinium compound. Vacuum sublimation was found to cause decomposition.

The material remaining in the original reaction flask, including the plate-like crystals, was washed several times with small portions of water to remove pyridine hydrochloride. Mass spectral analysis showed very little pyridine present and essentially no pyridinium ion. However, $^{31}P$ NMR (in $CDCl_3$) showed that there were two phosphoryl compounds present: 35.04 and 31.85 ppm, while $^{1}H$ NMR and mass spectral analysis indicated the presence of unreacted 27.

The yield of crude product was 3.96 g (37% of theoretical). Recrystallization from 1:1 benzene-methanol gave white crystals; traces of solvent were removed on the vacuum line; the mass spectrum clearly revealed the parent ion peak at m/e 304; m.p.: decomposed at 177° (there appears to be a change in the morphology of the crystals at about 108°C); $^{31}P$ NMR (in $CDCl_3$): 32.33 ppm. However, the elemental analysis was found to be high in carbon: calculated (for $C_{16}H_{17}O_4P$) C, 63.16; H, 5.63%; found C, 66.11; H, 4.86%.

Another recrystallization from 1:1 benzene-methanol gave white, needle-shaped crystals. Elemental analysis showed the crystals of compound 30 to be essentially pure: calculated (for $C_{16}H_{17}O_4P$) C, 63.16; H, 5.63%; found C, 63.35; H, 5.47%.

Diphenylphosphinic Acid(31).

Diphenylphosphinous chloride (3.0 mL, 17 mmol) was oxidized by the method reported above. Water (0.31 mL, 17 mmol) was added and the mixture was stirred vigorously for 30 minutes. A white solid precipitated and the benzene was removed on a rotary evaporator. Diethyl ether was added three times, and removed each time on the rotary evaporator, as a means of removing more of the remaining benzene.

Another portion of ether was added, the solid was filtered off and traces of solvent were removed on the vacuum line. The yield of crude product was 2.0 g (55% of theoretical). The $^{31}P$ NMR (in ethanol) showed two signals: compound 31 at 25.7 ppm; this compares well with the results of Moedritzer (68,69), and a very minor signal at 21.6 ppm, assigned to $Ph_2P(O)H$ (69,74).

$^1H$ NMR Studies on 2-Hydroxyphenyldiphenylphosphinate(29).

A sample of 29 in dichloromethane-d2 (55 mg/mL) was prepared. At 34°C, the $^1H$ spectrum exhibited some

broadening of the OH peak at 8.5 ppm. This broadening was found to increase as the temperature was lowered to -11 and to -32°C with the peak position remaining relatively constant.

A second sample (31 mg/mL), containing a bead of 3A molecular sieve, was also prepared and was allowed to spin, to effect mixing, in the probe of the spectrometer for 1 hour. $^1H$ spectra were then obtained at -31, -25, and -19°C over a 2-hour period: the signal was still quite broad. However, after standing for 1-2 days over the sieve the OH signal was found to be sharp (9.0 ppm) at both -43° and +40°C.

The solution was decanted from the molecular sieve into a clean, dry NMR tube. The spectrum, at +40°, still exhibited a sharp hydroxyl peak. A minute amount of water was added, but the signal had broadened only very slightly after 15 hours. The addition of more water resulted in the return of a broad signal at +40°C.

$^1H$ NMR spectra of $Ph_2P(O)OC_6H_4OH$, 29, with pyridine-d5 added, in $CD_2Cl_2$ solution were obtained. The crystals were weighed out, 5 mg on average, and deposited in an NMR tube and a small amount of $CD_2Cl_2$ was added. Syringes (Hamilton) of various capacities were used to add the required amounts of base to the NMR tubes. Then $CD_2Cl_2$ was added to bring the volumes up to 0.5 mL. The entire operation was carried out so as to minimize exposure to air

and moisture. In the absence of pyridine, the hydroxyl proton gave rise to a broad signal at 9.01 ppm. The amount of broadening increased with increasing amounts of pyridine added, while the peak position shifted in a regular fashion to lower field. The catechyl region of the spectrum showed significant changes while the phenyl region did not.

High resolution $^{1}H$ NMR spectra, at 90 MHz, of 29 in $CD_2Cl_2$ were also obtained. The sample was degassed by five freeze-pump-thaw cycles and was then flame-sealed under vacuum. Both $^{31}P$-coupled and $^{31}P$-decoupled spectra were obtained at 27°C (Figs. 5 and 6).

A second sample of 29 was prepared, this time with 0.19 M pyridine-d5, and was degassed and sealed as above. Once again, relatively large changes were observed in the catechyl region of the spectrum, while the phenyl region again did not appear to change.

In the hope that spectra obtained at higher temperatures would provide evidence for exchange, a sealed, degassed sample of $Ph_2P(O)OC_6H_4OH$, 29, in $C_6D_6$ (10 mg/mL), with added pyridine-d5 (37 mg/mL), was prepared. Although the catechyl region did, once more, show significant changes over the temperature range of 32° to 67°C, a large part of this region was obscured by overlap with a part of the phenyl region as a result of aromatic solvent-induced shifts.

Figure 5.

$^{1}H$ NMR Spectrum of $Ph_2P(O)OC_6H_4OH$ (29)

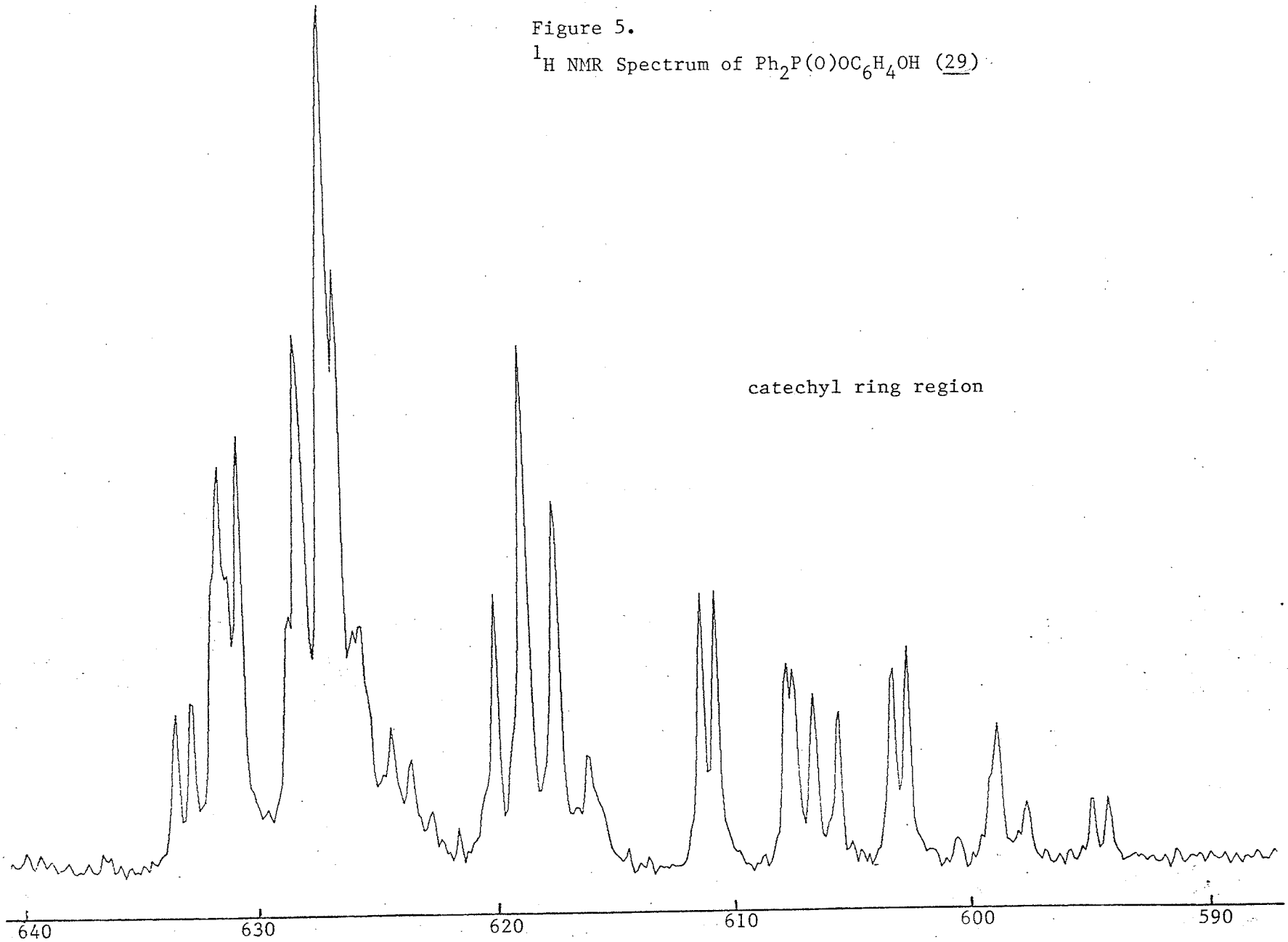
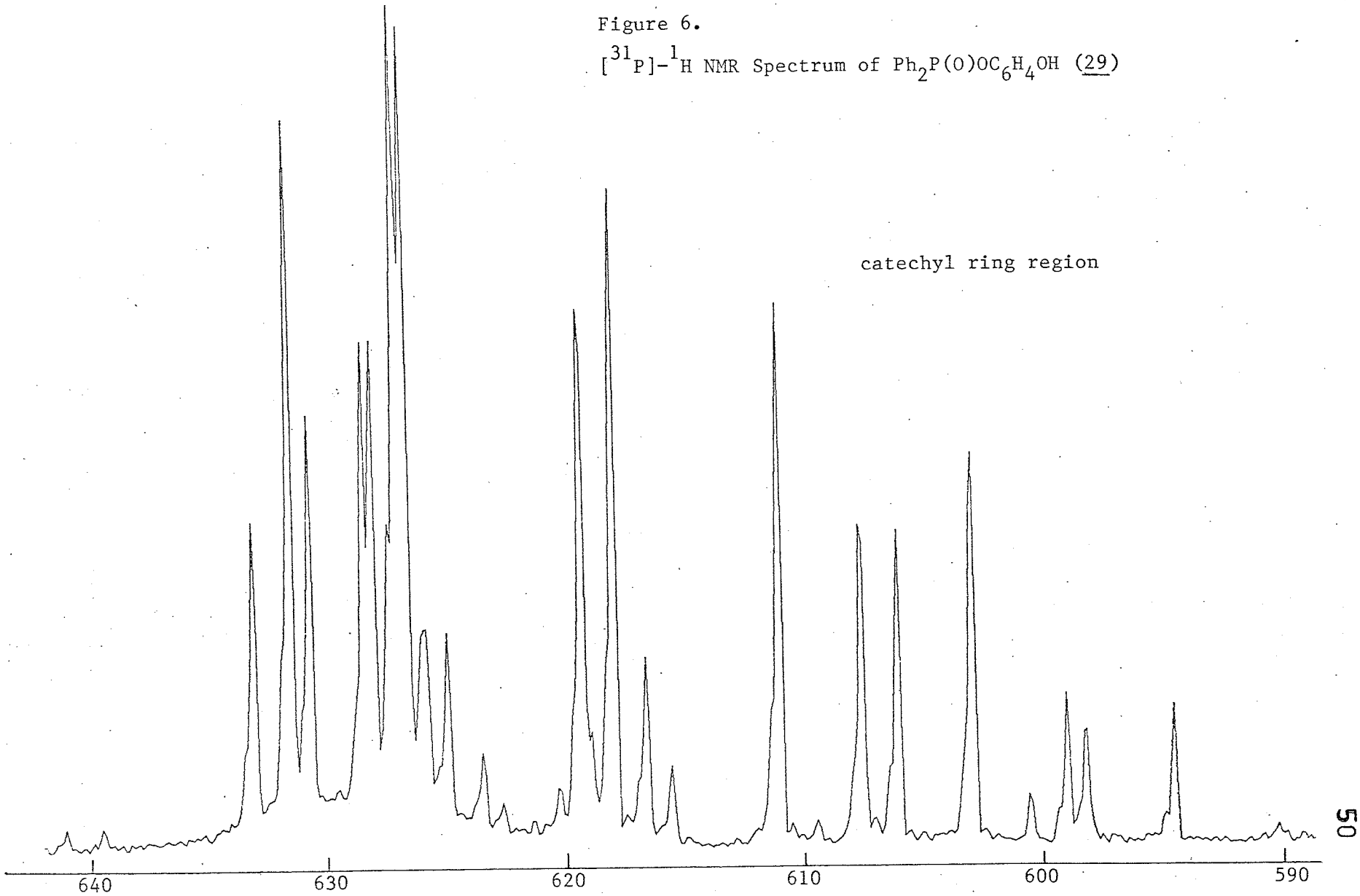


Figure 6.

$[^{31}P]-^{1}H$ NMR Spectrum of $Ph_2P(O)OC_6H_4OH$ (29)



A sealed, degassed sample of 29 in dimethylsulphoxide-d6 (9.8 mg/mL) was then prepared. However, as the temperature was increased, the sample began to decompose, as evidenced by the fact that a second ambient temperature spectrum run afterward was not the same as before increasing the temperature, and by the appearance of additional peaks in the $^{31}P$ NMR spectrum.

In $CDCl_3$ (10 mg/mL), compound 29, with added pyridine-d5 (36 mg/mL), gave high resolution $^{1}H$ NMR spectra which again followed the pattern of previous samples. Between 32° and 62°C, it was the catechyl region of the spectrum which again showed changes, although in this case (due mainly to the smaller temperature range available, since chloroform has a b.p. of 62°C) the changes were not as pronounced as in the other spectra.

## $^{31}P$ NMR Studies on 2-Hydroxyphenyldiphenylphosphinate(29).

A large series of $^{31}P$ NMR spectra were obtained for 29 in $CH_2Cl_2$ solution at 27°C with varying amounts of added base; the bases used were pyridine, triethylamine, dimethylsulphoxide (DMSO), imidazole and 1,4-dioxane. The amount of 29 used was kept relatively constant at 10 mg/mL. The samples were prepared as described for $^{1}H$ NMR, again taking care to minimize exposure to air and moisture. Syringes were used to add base to the NMR tubes - imidazole was, of course, measured out by weight. Dichloromethane was added

to bring the volumes up to 2.00 mL. A capillary tube containing $D_2O$ was inserted to provide a deuterium lock for the spectrometer.

In the absence of base, the $^{31}P$ chemical shift was found to be ($^{31}P$) = 37.80 ppm (in $CH_2Cl_2$). The chemical shift moved to higher field as more base was added: 29.85 ppm in pyridine, 29.07 ppm in DMSO, and 33.75 ppm in 1,4-dioxane.

Compound 29 was found to be insoluble in triethylamine and in $CH_2Cl_2$ solutions of triethylamine where the amine concentration was greater than about 4 M. In addition, the triethylamine-containing solutions offered visible evidence of decomposition, changing from colourless through yellow to brown over a period of 2-3 days, whereas such discolouration was not apparent with the other bases. The $^{31}P$ NMR spectrum of one discoloured sample exhibited two signals, 35.17 and 15.35 ppm, with no signal at the original 36.05 ppm position.

In addition to determining the effect of adding bases to solutions of 29, trifluoroacetic acid was also added. The change in $^{31}P$ chemical shift was to lower field of its position in $CH_2Cl_2$: 43.16 ppm in $CF_3COOH$.

Finally, the effect of temperature on the $^{31}P$ chemical shift of $Ph_2P(O)OC_6H_4OH$, 29, was studied. A sample consisting of 29 (19.3 mg) and pyridine (1.50 mL), made up to 2.00 mL with dichloromethane, was prepared. Using an ex-

ternal acetone-d6 lock, the spectra were recorded at +27, -53, and -63°C, giving rise to $^{31}P$ signals at 31.07, 29.66, and 29.62 ppm, respectively. The chemical shift was thus observed to move slowly upfield as the temperature was decreased but no appreciable line broadening was observed.

Assessment of the Solvent Effect on $^{31}P$ Chemical Shifts: Trimethylphosphate.

In an attempt to assess the solvent effect on the chemical shift of the phosphinate, 29, solutions of trimethylphosphate, $(MeO)_3PO$, in $CH_2Cl_2$, with various amounts of added pyridine, were prepared, using syringes to measure out both the trimethylphosphate and the pyridine. The $^{31}P$ chemical shift (external $D_2O$ lock) was found to move upfield only slightly as more pyridine was added: 1.39 ppm in $CH_2Cl_2$; 1.10 ppm in pyridine; Jones and Katritzky (75) report the $^{31}P$ chemical shift of $(MeO)_3PO$ in various solvents.

Assessment of the Solvent Effect on $^{31}P$ Chemical Shifts: Synthesis of 2-Trimethylsiloxyphenyldiphenylphosphinate(32).

In a dry, nitrogen atmosphere, compound 29 (72.5 mg, 0.234 mmol) was, with patient coaxing, finally dissolved in 1.7 mL of dichloromethane; chlorotrimethylsilane (29.6 µL, 0.233 mmol) was added and mixed. Subsequently, triethyl-

amine (32.5 μL, 0.233 mmol) was added. Within one minute, powdery white flakes of triethylamine hydrochloride had formed on the lip of the reaction tube as well as in the surrounding atmosphere.

In order to bring about complete precipitation of the triethylamine hydrochloride, cyclohexane was added, dropwise. Cloudiness developed in the upper, cyclohexane layer and the reaction tube was refrigerated for several hours. The cloudiness had become a large, white, fluffy band, positioned at the bottom of the cyclohexane layer. Extending downward from the interface were several needle-like crystals.

After overnight refrigeration, the two layers were separated and a $^{1}H$ NMR spectrum of each was obtained. Since both layers showed phenyl, catechyl, and trimethylsilyl proton signals, they were combined again and the solvents were removed on the vacuum line. The residue was twice washed with water to remove triethylamine hydrochloride and was then dried under vacuum for 2.5 hours.

The solid was dissolved in 3 mL of dichloromethane and aliquots were removed for NMR samples; varying amounts of pyridine were added and the $^{31}P$ chemical shifts were determined. An external capillary tube containing $C_6D_6$ was used as the deuterium lock. There were two signals in each spectrum: one due to unreacted $Ph_2P(O)OC_6H_4OH$, 29, and the other due to the silylated derivative, 32. The signals both

moved upfield with increasing pyridine concentration but the $^{31}P$ chemical shift of 32 changed only slightly: from 29.83 ppm in the absence of pyridine to 29.04 ppm in a 9.3 M solution of pyridine in dichloromethane; that of unreacted 29 changed from 38.62 to 31.33 ppm, respectively.

Further identification of the solids giving rise to these two $^{31}P$ signals came from the mass spectrum which showed parent ion peaks for both compound 29, at m/e 310, and compound 32, at m/e 382, as well as $(M-CH_3)^+$, $(M-2CH_3)^+$, and $(M-3CH_3)^+$ peaks for compound 32.

## $^{13}C$ NMR Studies on 2-Hydroxyphenyldiphenylphosphinate(29).

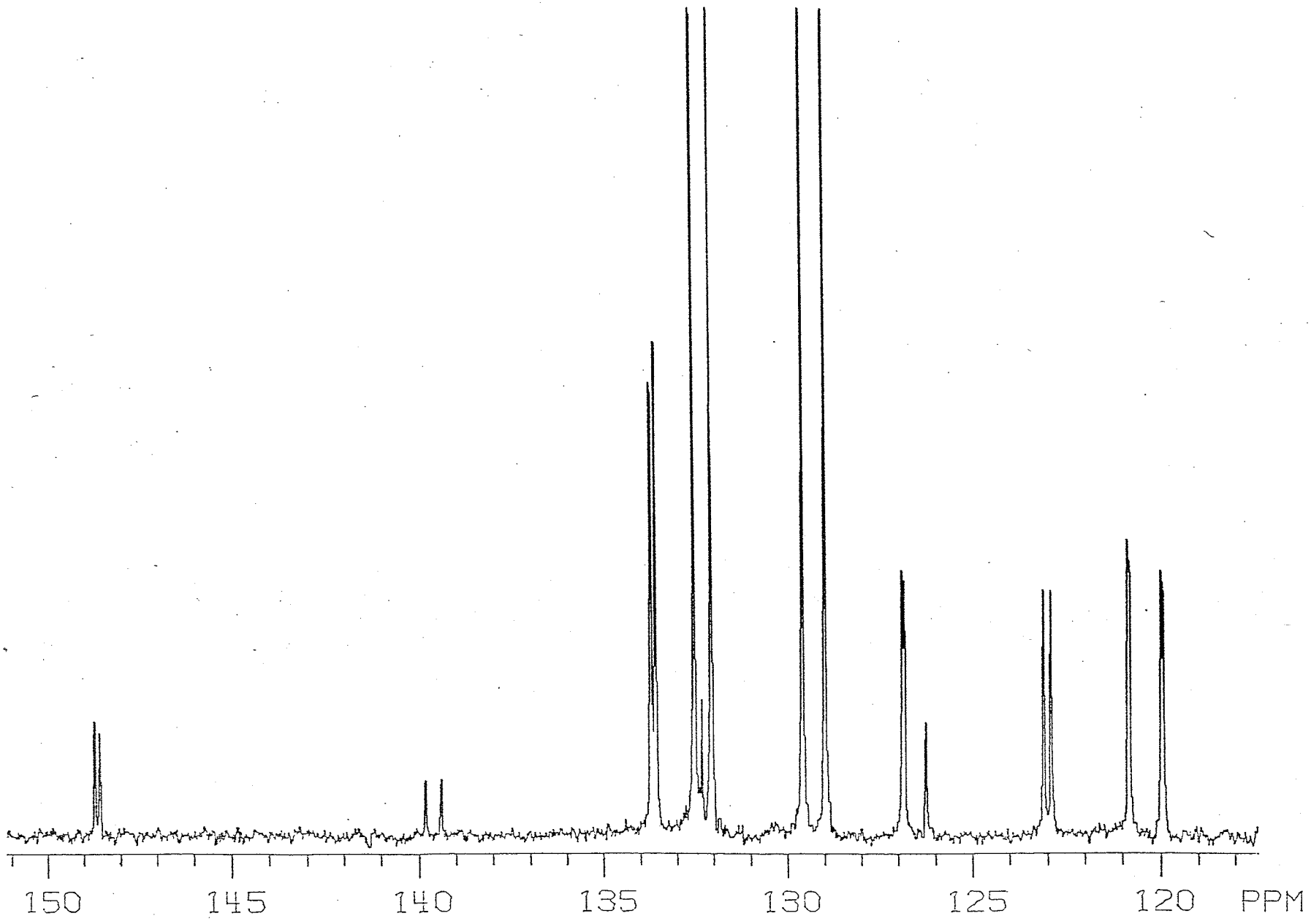
A sample of 29 in $CD_2Cl_2$ (20 mg/mL) was prepared and the $[^1H]$-$^{13}C$ NMR spectrum was obtained (Fig.7).

A sample of 29 (75.9 mg, 0.244 mmol) in $CDCl_3$ (1.5 mL) was prepared and triethylamine (10 µL, 0.072 mmol) was added. The $[^1H]$-$^{13}C$ NMR spectrum was very similar in appearance to that in Figure 7; however, this will be discussed later, under Results and Discussion.

## Diethylphosphoramidous Dichloride(33).

Phosphorus trichloride (20.0 mL, 0.229 mol) was placed in a 500 mL, 2-necked flask fitted with a condenser and drying tube, along with 175 mL petroleum ether (37-58° fraction; Fisher). Diethylamine (47.5 mL, 0.459 mol) and

Figure 7.
$[^{1}H]-^{13}C$ NMR Spectrum of $Ph_2P(O)OC_6H_4OH$.



125 mL petroleum ether were placed in a dropping funnel. The flask was placed in a dry ice-acetone bath.

With constant stirring, the diethylamine was added dropwise over a period of five hours with the formation of large amounts of white precipitate. During this time, two 25 mL portions of petroleum ether were added to the mixture to facilitate stirring. When the addition was complete the flask was slowly warmed to room temperature and was left to stir overnight.

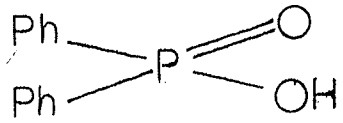
The diethylamine hydrochloride was removed by filtration under nitrogen. Most of the petroleum ether was then removed using a rotary evaporator. The mixture was distilled under nitrogen and three fractions were obtained. $^{31}P$ NMR showed the following signals: in the first fraction, 219.18 ppm assigned to phosphorus trichloride (67c) and -3.05 ppm assigned to phosphorus oxychloride (67d); the second fraction contained $PCl_3$ (219.33 ppm); the $^{31}P$ NMR spectrum of the third fraction showed a signal at 162.03 ppm assigned to diethylphosphoramidous dichloride (67e) and only a very minor peak at 219.28 ppm due to $PCl_3$.

The $^{1}H$ NMR spectrum of 33 compared very well with that of van Linthoudt et al. (76).

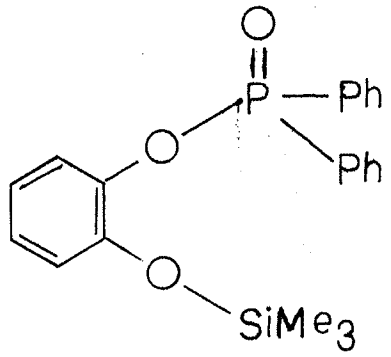
Attempts to Observe Rapid Exchange in 1- and 2-(Dihydrogenphosphate)-1,2,3-propanetriols, disodium salts, by NMR.

Solutions of the 1- and 2-dihydrogenphosphate-1,2,3-propanetriols (glycerol-1-phosphate, 1, and glycerol-2-phosphate, 2, respectively), disodium salts (Sigma), were prepared in $D_2O$, 1 N DCl, and 3 N DCl with concentrations of 0.45 M (glycerol-1-phosphate only; glycerol-2-phosphate concentration was 0.46 M), 0.75, and 0.72 M, respectively, taking into account the water of hydration in the samples. The $^1H$ NMR spectra were monitored over a 47-hour period. No rapid exchange was observed, but after about 20 hours, some degree of isomerization in the acidic samples of the glycerol phosphates was noted. After 47 hours, the spectra of the glycerol-1-phosphate samples were no longer changing, but the glycerol-2-phosphate samples had not yet attained equilibrium.

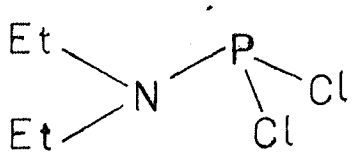
The $^1H$ NMR spectrum of glycerol-1-phosphate in $D_2O$ was also monitored as a function of pH. The concentration of 1 was fairly constant over all the samples, ranging from 0.37 to 0.41 M. The pH was adjusted with $HClO_4$ (71%, Fisher) and covered the range 4.6 to 0.1, but no rapid, intramolecular exchange was observed. Three of the samples (pH 4.6, 3.3, and 0.5) were each run at three higher temperatures: 55, 65, and 80°C, but again no rapid exchange was observed.



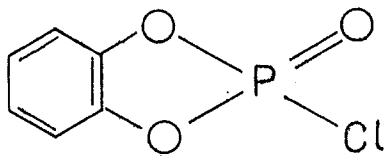

31



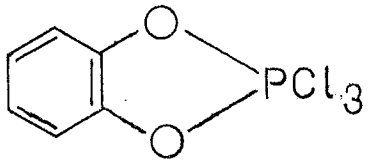

32



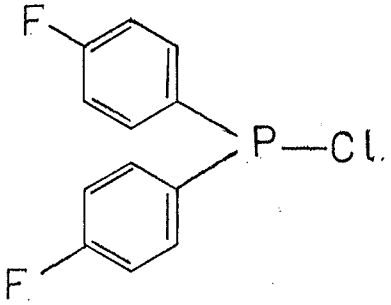

33




34




35




36

In a final attempt to promote rapid exchange in glycerol-1-phosphate, $Ba^{2+}$ ion, as $BaCl_2$ (Baker), was added to the three samples used in the temperature study, above, in concentrations of about 0.04 M. The $^1H$ spectra were obtained at ambient temperature and once more no rapid exchange was found.

The $^{13}C$ NMR spectra of the glycerol phosphates in $D_2O$ were also obtained (Figs. 8 and 9). The chemical shifts and coupling constants will be presented later, under Results and Discussion.

Reaction of Compound 25 with Alcohols.

A sealed reaction tube containing 10 mmol of compound 25 was opened by the procedure given in the previous section. The contents of the tube were allowed to drain, in three approximately equal amounts (3.3 mmol), into small vials.

1) Reaction with 1,2,3-Propanetriol.

To one of the vials, 1,2,3-propanetriol (glycerol) (0.30 g, 3.2 mmol) (Chem Service) was added. An immediate reaction was observed as evidenced by the evolution of gas. Triethylamine (0.65 g, 6.5 mmol) was added. Subsequently, 2-3 mL of N,N-dimethylformamide (DMF) (Fisher) was added as solvent.

Figure 8.
$[^{1}H]$-$^{13}C$ NMR Spectrum of Glycerol-1-phosphate.

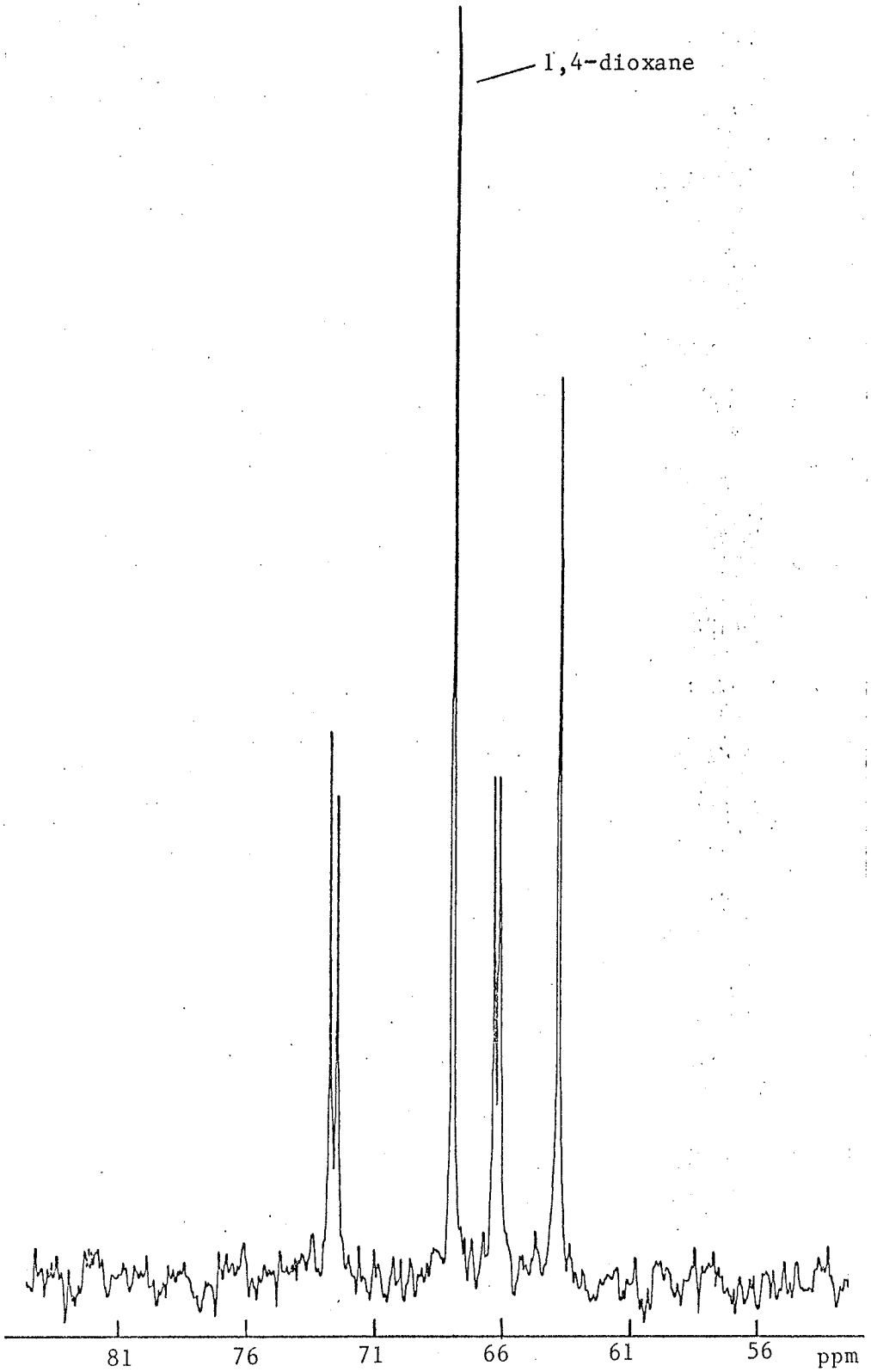
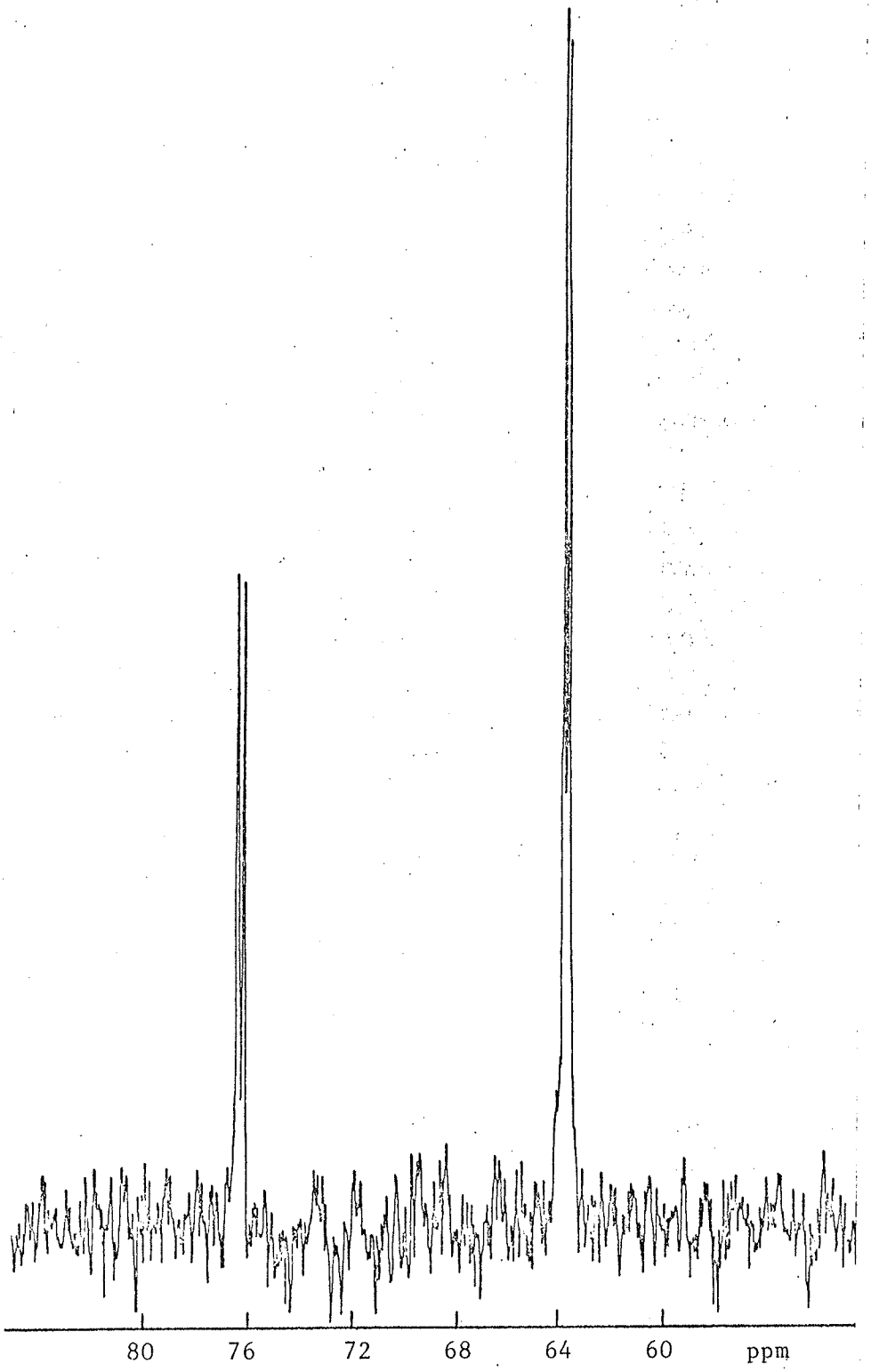


Figure 9.

$[^{1}H]$-$^{13}C$ NMR Spectrum of Glycerol-2-phosphate.



The mixture separated relatively quickly into three layers: a pale yellow solution above, a somewhat darker yellow solution below, and a layer of white, suspended solid between. $^{1}H$ NMR (in $D_2O$), in comparison with the Sadtler spectra for triethylamine hydrochloride (77a), and for triethylamine (77b), showed the solid to be the hydrochloride: t, 1.24 ppm, q, 3.16 ppm, $^{3}J(HH)$ = 7.2 Hz; traces of DMF were visible; no signals were observed in the $^{19}F$ NMR spectrum.

The upper DMF layer was found to consist of perfluoropinacol ($^{19}F$: s, -70.3 ppm) (70), triethylamine ($^{1}H$: t, 0.70 ppm; q, 2.5 ppm, largely obscured by solvent peaks; $^{3}J(HH)$ = 7.2 Hz), glyceryl $^{1}H$ signals centered on 3.2 ppm, and an "acidic" proton peak at 6.10 ppm.

$^{1}H$ and $^{19}F$ NMR spectra of the lower DMF layer presented the following: aromatic (phenyl) multiplet(s) ($^{1}H$: 7.0 - 7.4 ppm), triethylamine ($^{1}H$: t, 0.70 ppm; q, 2.5 ppm, largely obscured by solvent peaks, $^{3}J(HH)$ = 7.2 Hz), glycerol and/or glyceryl $^{1}H$ signals centered on 3.2 ppm, an "acidic" proton peak at 6.25 ppm, perfluoropinacol ($^{19}F$: s, -70.3 ppm), 1,1,1,3,3,3-hexafluoropropan-2-ol ($^{19}F$: -75.6 ppm, $^{3}J(FH)$ = 6 Hz), a signal due to a hexafluoroisopropoxy group on 5-coordinate phosphorus ($^{19}F$: d, -72.3 ppm, $^{3}J(FH)$ = 6 Hz), a somewhat obscure group of signals probably due to bidentate perfluoropinacolyl groups on 5-coordinate phosphorus ($^{19}F$: -67 ppm), a signal assigned to hexafluoro-

acetone hydrate ($^{19}F$: s, -78.2 ppm), and unidentified multiplet(s) between -79.8 and - 80.6 ppm; the $^{19}F$ signals were assigned by comparison with the results of Janzen et al. (64); as well, in a separate experiment, the $^{19}F$ chemical shift of 1,1,1,3,3,3-hexafluoropropan-2-ol (50% v/v in $C_6F_6$) was measured as -74.9 ppm, d, $^3J(FH)$ = 5.8 Hz.

2) Reaction with 1,1,1,3,3,3-Hexafluoropropan-2-ol.

1,1,1,3,3,3-Hexafluoropropan-2-ol, sodium salt (0.64 g, 3.4 mmol), obtained courtesy of Dr A. E. Lemire, was added to another of the vials containing compound 25. Subsequently, 2-3 mL of benzene-d6 was added as solvent.

The mixture separated into a white precipitate, presumed to be NaCl, and a clear solution. The $^1H$ and $^{19}F$ NMR spectra of the benzene-d6 solution showed, by comparison with the results of Janzen et al. (64): more than one hexafluoroisopropoxy group ($^1H$: septets, 4.7 ppm, $^3J(HF)$ = 5.5 Hz), aromatic (phenyl) multiplet(s) ($^1H$: 6.4 - 6.6 and 6.9 - 7.7 ppm), 1,1,1,3,3,3-hexafluoropropan-2-ol ($^{19}F$: d, -74.9 ppm), 2-(1',1',1',3',3',3'-hexafluoropropoxy)-2,2-dihydro-2,2-diphenyl-4,4,5,5-tetrakis-(trifluoromethyl)-1,3,2-dioxaphospholane ($^{19}F$: d, -66.9 ppm, $^4J(FP)$ = 2.5 Hz; d, -71.9 ppm, $^3J(FH)$ = 6 Hz), hexafluoroisopropoxy groups on 4-coordinate phosphoryl phosphorus ($^{19}F$: d, -73.1 ppm), and a signal assigned to hexafluoroacetone hydrate ($^{19}F$: s, -77.7 ppm).

3) Reaction with 1,2-Dihydroxybenzene.

1,2-Dihydroxybenzene (catechol) (0.36 g, 3.3 mmol) was added to the third vial. Evolution of gas provided visible evidence of reaction. Triethylamine (0.65 g, 6.5 mmol) was added, followed by 2-3 mL of DMF (Fisher) as solvent. The mixture remained murky for several days, eventually separating into a light brown sediment and a dark brown solution. $^{1}H$ NMR revealed that the reaction mixture consisted of triethylamine hydrochloride (t, 0.92 ppm; q, 2.85 ppm; $^{3}J(HH)$ = 7.3 Hz), compounds containing phenyl groups (7.1 - 7.7 ppm), compounds containing the catechyl ring system (6.3 - 6.7 ppm), and hexafluoroisopropoxy-containing compounds (multiplets, 4.7 ppm). There was an "acidic" proton signal at 8.90 ppm as well as an unidentified broad peak at 6.0 - 6.1 ppm and three unidentified signals between 2.0 and 2.2 ppm.

The $^{19}F$ NMR spectrum revealed: perfluoropinacol (s, -69.6 ppm), 1,1,1,3,3,3-hexafluoropropan-2-ol (d, -75.3 ppm, $^{3}J(FH)$ = 6 Hz), a hexafluoroisopropoxy group on 4-coordinate phosphoryl phosphorus (d, -73.3 ppm), and three unidentified peaks at -66.7, -66.8, and -67.3 ppm, one or more of which may have been due to a bidentate perfluoropinacolyl group on 5-coordinate phosphorus.

The $[^{1}H]$-$^{31}P$ NMR spectrum, obtained after several days, revealed no less than eighteen signals, seven in the region to low field of $H_3PO_4$ representing phosphoryl

compounds, eight in the phosphorane region to high field, and three to very high field in the six-coordinate phosphorus region (Munoz et al. (48) reported the presence of six-coordinate phosphorus compounds containing the catechyl ring moiety in DMSO and DMF solutions of compound 21); all remain unidentified.

Attempted Synthesis of 3-Dihydrogenphosphate-tetrahydro-3,4-furandiol.

The procedure of Usher et al. (44) was used, with a slight modification (the disodium salt of phenylphosphate (Sigma) was used in place of phenyldihydrogenphosphate), in order to synthesize 3-dihydrogenphosphatetetrahydro-3,4-furandiol. However, both the NMR and mass spectra were unable to provide any evidence for the desired product.

Grignard Reactions.

In an attempt to determine the feasibility of synthesizing diphenylphosphinic-d10 chloride from bromobenzene-d5 via a Grignard reaction, the initial trials were carried out with less costly starting materials: bromobenzene and 4-bromofluorobenzene.

1) Attempted Synthesis of Diphenylphosphinous Chloride(28).

In a typical reaction, bromobenzene (34.8 g, 0.222 mol) (Fisher) was placed in a dropping funnel and 10 mL of anhydrous diethyl ether (Fisher) were added. Magnesium metal turnings (5.39 g, 0.222 mol) (Fisher) were placed in a 250 mL round-bottomed flask, fitted with a reflux condenser and a drying tube, together with 40 mL of anhydrous ether. A few tiny crystals of iodine were also added.

The iodine dissolved to give a blood red solution, but very soon the colour disappeared. The bromobenzene solution was added dropwise with stirring. Local ebulition was observed in the vicinity of the magnesium turnings. As more bromobenzene was added, the ether began to boil and a pale yellow colour gradually returned. After the addition was complete, the boiling continued for some 10 - 15 minutes after which the mixture was heated under reflux for an additional two hours.

The flask was then cooled and placed in an ice bath. Diethylphosphoramidous dichloride (17 g, 0.1 mol) was placed in a dropping funnel. This was added very slowly, over a period of two hours, with constant stirring. The reaction was immediate and very vigourous with the formation of lumps of yellow solid (presumed to be magnesium halide salts).

When the addition of 33 was complete, the mixture was allowed to warm slowly to reflux temperature. Heating, under reflux, was maintained for several hours.

Subsequently, the mixture was cooled and placed in a dry ice-acetone bath. Anhydrous HCl was bubbled slowly through the solution, with constant stirring, and resulted in an immediate precipitation of a white solid. The process was periodically interrupted to allow the solid to settle. When further passage of HCl no longer produced visible precipitate, the flask was warmed slowly to room temperature. Anhydrous HCl was again introduced into the mixture for several minutes. No further solid formation was noted.

Benzene was added in order to precipitate any salts still dissolved in the ether; further precipitation of solid material was observed. Mass spectral analysis of the solid indicated the presence of triphenylphosphine ($M^+$ at m/e 262) as well as one or more oxides ($Ph_2PO^+$ at m/e 201). The $^{31}P$ NMR spectrum of the supernatant showed only two signals, at 10.63 and 7.16 ppm, which remain unidentified. However, the mass spectrum of the solid remaining after evaporation of solvents from the supernatant showed it to be biphenyl ($M^+$ at m/e 154).

2) Attempted Synthesis of bis(4-Fluorophenyl)phosphinous Chloride(36).

Following the same procedure as above, but with 4-bromofluorobenzene instead of bromobenzene, the Grignard reaction was carried out. After the addition of anhydrous HCl, the solids were filtered off and the distillation of

the presumed product, 36, was begun. However, this was unsuccessful both at atmospheric and at reduced pressures. Only the ether was removed and the viscous mass remaining would not distil out.

3) Attempted Synthesis of N,N-Diethyl-P,P-bis(4-fluorophenyl)phosphinic Amide(37).

4-Fluorophenyl magnesium bromide was prepared from magnesium turnings (0.67 g, 28 mmol) and 4-bromofluorobenzene (3.0 mL, 27 mmol) (Aldrich), and was allowed to react with diethylphosphoramidous dichloride (2.38 g, 13.7 mmol), as in 1) above. When the reaction was complete, the flask was warmed to room temperature. Benzene (25 mL) was then added and the ether was removed using a rotary evaporator.

The mixture was then filtered, the solids washed with benzene, and the washings combined with the filtrate. Following the procedure outlined earlier, oxygen gas was bubbled through the solution in order to oxidize the phosphine(s).

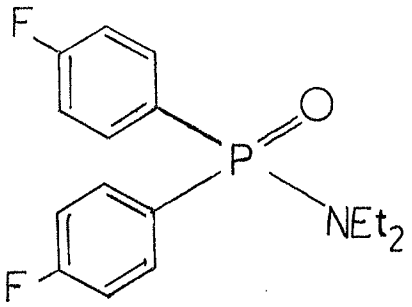
$^{31}P$ NMR revealed three signals in the phosphine region, and more than 14 signals in the phosphoryl region; the major peaks occurred at 33.6 and 33.1 ppm; all remain unidentified.

Attempted Synthesis of bis(3,5-Dichlorophenyl)-N,N-diethylaminophosphine(38).

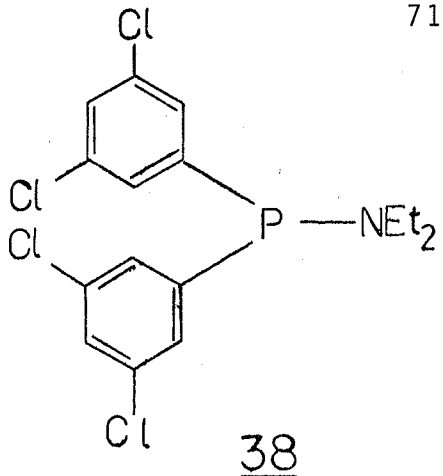
3,5-Dichlorophenyl magnesium iodide was prepared from magnesium turnings (0.56 g, 23 mmol) and 1,3-dichloro-5-iodobenzene (6.21 g, 22.8 mmol), obtained courtesy of Mr T. Thompson, as in the previous section. Diethylphosphoramidous dichloride (2.02 g, 11.6 mmol) was weighed out into a small vial. Upon addition of anhydrous diethyl ether (Fisher) from a newly opened can, and subsequent transfer to a dropping funnel, a small amount of white solid was seen to have formed.

Because the amount of precipitate was very small, it was decided to continue with the synthesis and to expect a slightly reduced yield. The flask containing the Grignard reagent was cooled in a dry ice-carbon tetrachloride bath. The solution of 33 in ether was added dropwise with stirring. A very slow reaction, as evidenced by the formation of some solid material, took place. The solids were separated by filtration. Subsequent distillation of the filtrate, under nitrogen, removed only the ether; vacuum distillation resulted only in the formation of a very hard, dark, brittle, glass-like solid.

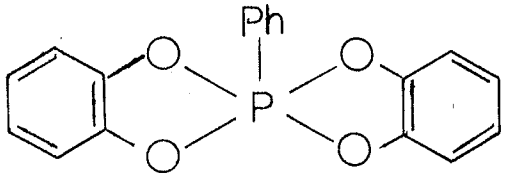
Mass spectral analysis of the white solid which had precipitated out of solution when 33 was added to anhydrous diethyl ether (above) showed the solid to be diethylammonium chloride: m/e 36/38 and m/e 73.



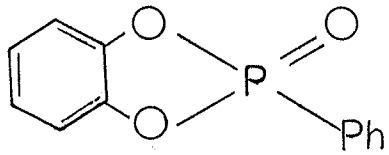

37



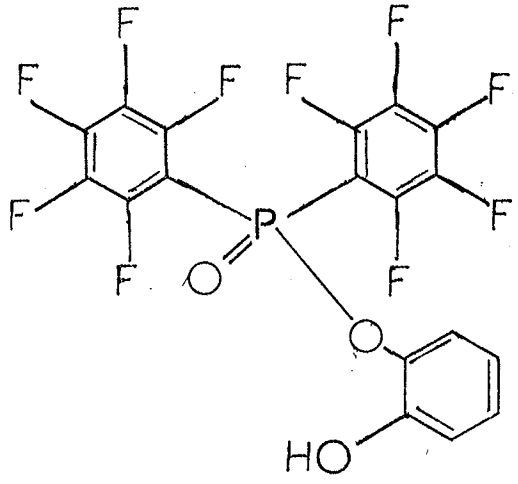

38



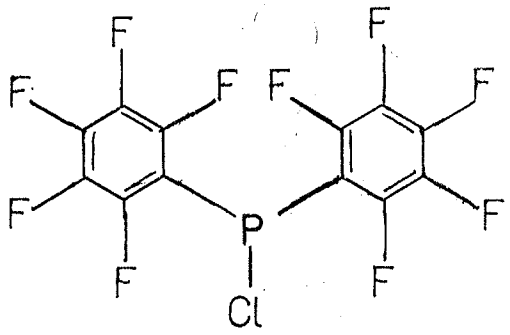

39




40




41




42

In subsequent repeated attempts, great care was taken to ensure that the ether was dry: anhydrous diethyl ether (Fisher) from a newly opened can was stored over sodium metal (which invariably retained its clean, shiny surfaces) and was handled only in a dry nitrogen atmosphere (the drying agents used were $P_2O_5$ and $CaSO_4$); glassware was oven dried overnight at over 150°C and, while hot, was transferred to the dry box. However, on the occasions that the formation of the Grignard reagent appeared to be successful, addition of 33 to the ether resulted in the formation of relatively large amounts of diethylammonium chloride (as confirmed by mass spectrometry) and the synthesis of 38 was consequently unsuccessful. However, addition of $PCl_3$ to the ether did not result in the formation of any precipitate. On other occasions, even formation of the Grignard reagent did not occur as evidenced by the significant amounts of unreacted magnesium metal present.

Synthesis of Diphenylphosphinic Chloride(28).

In an attempt to determine the feasibility of synthesizing diphenylphosphinic-d10 chloride from $PCl_3$ and benzene-d6, the initial trials were carried out with the less costly starting material: benzene.

Following the procedure of Legin (81), benzene (13.2 g, 0.169 mol), $PCl_3$ (7.72 g, 0.0562 mol), and $AlCl_3$

(7.50 g, 0.0562 mol) (BDH) were heated under reflux for 20 hours. Some more benzene was added (two layers were formed: a clear upper layer and a dark, greenish lower one; they were immiscible.) and oxygen gas was then bubbled through the solution for 1.5 hours (effecting thorough mixing). Subsequently a very small portion of the upper layer was allowed to stand in contact with the atmosphere until the solvent had evaporated. The solid remaining behind was tentatively identified as diphenylphosphinic acid, 31, by mass spectrometry (base peak: $Ph_2PO^+$ at m/e 201), confirming the presence of two phenyl groups attached to phosphorus.

Distillation of the lower layer, under reduced pressure ($10^{-3}$ Torr), resulted only in the removal of solvent, while the other materials formed such an extremely viscous mass in the flask that stirring and distillation were not possible. In the earlier stages of the distillation, before the viscosity had become too great, yellow-orange solids were deposited throughout the lower portions of the Vigreux column; the solids did not yield a mass spectrum, even at 70 eV. Although the identity and properties of these orange-yellow solids remain unknown, Senear et al. (82) have warned that the waxy yellow solid collected at the end of the distillation of diphenylphosphinous chloride, while hot, will ignite on contact with air. Neither use of a shorter column, nor elimination of the column altogether, yielded any better result.

Removing solvent from the clear, upper layer yielded a colourless, somewhat viscous liquid: ($^{31}P$) = 43.0 ppm, assigned to $Ph_2P(O)Cl$ (67a); the yield was estimated at <10%.

Now, Buchner and Lockhart (83) state that treatment with $POCl_3$ will effect the removal of $AlCl_3$ as an insoluble complex. In the event that this could increase the yield of 28, the reaction was tried again. After 24 hours of heating under reflux, $POCl_3$ was added and the mixture heated to reflux temperature once more. However, no precipitate had formed after 2.5 hours, distillation was again unsuccessful, and the attempt was abandoned.

Attempted Synthesis of 2-Hydroxyphenyldiphenylphosphinate(29).

In the hope that the 3-hour procedure for synthesis of $PhPCl_2$ (62b) would be of use in the synthesis of 28, benzene (20.0 g, 0.256 mol), $PCl_3$ (11.6 g, 0.0848 mol), and $AlCl_3$ (11.3 g, 0.0847 mol) were gently heated under reflux for two hours; the mixture was then heated vigourously, again under reflux, for another hour. While the mixture was still hot, $POCl_3$ (13.0 g, 0.0848 mol) was added dropwise to complex the $AlCl_3$ (83). Very little precipitate formed; the mixture was then filtered. Oxygen gas was then bubbled through the solution by the technique mentioned previously.

Catechol (9.33 g, 0.0848 mol) and pyridine (6.68 g, 0.0844 mol) were added to 15 mL of benzene in a round-bottomed flask. To this was added, dropwise with stirring, the solution of the phosphorus compound(s). Some heat was evolved, two layers were formed, and a white precipitate slowly began to form at the glass wall of the flask. Mass spectral analysis showed the crystals to be pyridine hydrochloride.

The solids were filtered off and the two layers, a viscous brown lower layer and a clear upper layer, were separated by means of a separatory funnel. The lower layer was twice extracted with benzene. These washes were combined with the upper layer and the solvent was then removed by means of a rotary evaporator. The solid material left behind was analyzed by mass spectrometry, which revealed the presence of 2-phenyl-2,2'-spirobi(1,3,2-benzodioxaphosphole), 39 ($M^+$ at m/e 324), catechol (m/e 110), 2-phenyl-2-oxide-1,3,2-benzodioxaphosphole, 40 (m/e 232), and $C_6H_4O_2P^+$ (m/e 139). However, ions with two phenyl groups attached to phosphorus gave rise only to very minor peaks: $Ph_2P(O)OC_6H_4OH$, 29, (m/e 310) and $Ph_2PO^+$ (m/e 201).

Synthesis of 2-Hydroxyphenyl-bis(pentafluorophenyl)-phosphinate(41).

Bis(pentafluorophenyl)phosphinous chloride, 42 (2.00 g, 4.99 mmol) (Strem) was dissolved in 50 mL of benzene and was oxidized with $O_2$ by the technique mentioned previously; the solution was then transferred to a dropping funnel.

Catechol (0.55 g, 5.0 mmol) and pyridine (0.40 g, 5.1 mmol) were placed in a round-bottomed flask containing 5 mL of benzene. Over a period of 20 minutes the phosphinic chloride solution was added dropwise with constant stirring. Vapours were seen to be given off, the mixture became milky white and, later, crystals appeared on the walls of the flask. When the addition was complete, the mixing was continued for several minutes. The contents were allowed to stand for several days with intermittent mixing.

Mass spectrometry showed the white precipitate to be pyridine hydrochloride. The clear supernatant was decanted from the crystals adhering to the walls and from the viscous brown residues on the bottom of the flask. Removal of benzene from the supernatant by means of a rotary evaporator left a slightly yellow "slush" which was found (mass spectrometry) to consist of the phosphinate, 41 ($M^+$ at m/e 490) and unreacted starting material, the phosphinous chloride, 42 (m/e 400/402). However the isolation and characterization of the product was not pursued.

## RESULTS AND DISCUSSION

### Glycerol Phosphates.

Bailly's discovery (6) that glycerol-1-phosphate, 1, and glycerol-2-phosphate, 2, were interconvertible led to proposals (7) that a cyclic intermediate was involved. Since then, the proposals have been gradually refined until now the evidence points to the involvement of cyclic, 5-coordinate intermediates in the exchange process (84), as well as 5- and even 6-coordinate species in the hydrolysis of phosphate esters (20c,21-24,37,38,47).

Because of the intention to study the isomerization of these and other compounds, it was determined that the $^{1}H$ and/or $^{13}C$ NMR spectra of these glycerol phosphates should be obtained under conditions of rapid interconversion. Since no isomerization occurs in neutral or alkaline solution (15,55b,85), 1 and 2 were dissolved in 1 N DCl and in 3 N DCl. However, the isomerization was exceedingly slow and thus no exchange broadening, nor collapse of peaks, was observed in the $^{1}H$ NMR spectra.

Various combinations of pH (0.1 - 4.6) and temperature (35°,55°,65°,80°C) were utilized to attempt to increase the rate of interconversion to a point where some

evidence of the exchange process would be visible in the $^{1}H$ NMR spectra. However, this did not occur.

Since metal ions are known to catalyze the hydrolysis of phosphate esters (3,4c,10,22), an attempt was made to increase the rate of exchange in the glycerol phosphate system by the addition of $Ba^{2+}$ ion. Once again, however, no rapid exchange was observed. The pH of the samples used was in the range of 0.5 to 4.6 before addition of $BaCl_2$. As previously mentioned, no isomerization takes place in neutral or alkaline solution. However, metal ions which catalyze hydrolyses of phosphate mono-esters are presumed to be most effective in the pH region where the phosphate exists as the dianion (4c), in the case of glycerol-1-phosphate at pH values above 6.5, since the $pK_2$ of glycerol-1-phosphate is 6.44 (17). This may explain why $Ba^{2+}$ ion failed to promote rapid exchange.

TABLE 1

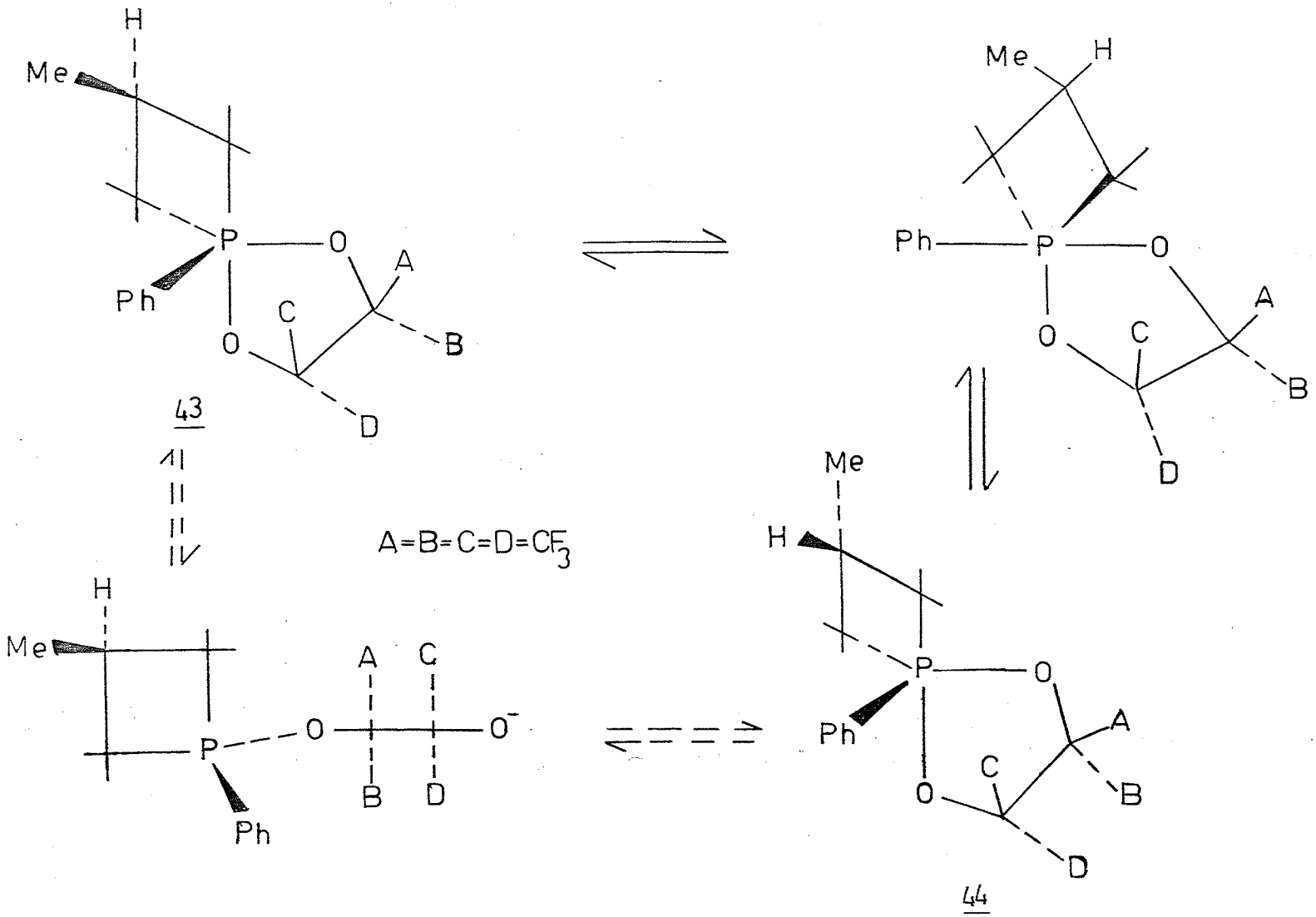
$^{13}C$ NMR of Glycerol Phosphates.

| Cmpd | Nucleus | ($^{13}C$) (ppm ) | Coupling (Hz) |
|---|---|---|---|
| 1 | C1 | 72.59 | $^{2}J(POC) = 6.47$ |
| | C2 | 66.10 | $^{3}J(POCC) = 4.82$ |
| | C3 | 63.64 | -- |
| 2 | C1/C3 | 63.67 | $^{2}J(POC) = 5.00$ |
| | C2 | 76.16 | $^{3}J(POCC) = 4.07$ |

Although no rapid exchange was observed in the glycerol phosphate system, two very good $[^1H]$-$^{13}C$ NMR spectra, in $D_2O$, were obtained (Figs. 8 and 9). Table 1 summarizes the chemical shifts and coupling constants.

2-Hydroxy-1,1,2,2-tetrakis(trifluoromethyl)ethyldiphenylphosphinate(26).

In recent years, several NMR studies (29,31,35-38,52,86,87) of phosphoranes, and phosphorus esters, containing the perfluoropinacolyl moiety, $-OC(CF_3)_2C(CF_3)_2O-$, have been reported. Trippett (35) observed the equilibration of certain groups in compound 43. From -60 to +160°C, the $^1H$ NMR spectrum did not show any changes, the twelve 2- and 4-methyl protons giving rise to a pair of doublets; there was no equilibration of the cis (43) and trans (44) isomers. However, at room temperature, in the $^{19}F$ NMR spectrum of 43, A and C are equivalent, as are B and D, both signals having fine structure. Coalescence of the two signals occurs at 140°C, making A equivalent to B and C to D. Such equilibration could be brought about by either of the two pathways in Scheme 6; however, the coalescence temperature was found to be independent of the nature of the solvent, thus arguing against a dissociative mechanism and favouring the pseudorotation pathway. The activation energy for this equilibration process was found to be 82.0 kJ/mole.

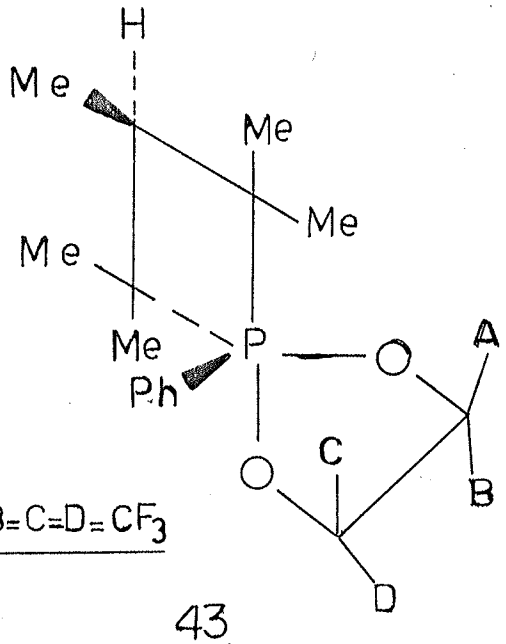



Scheme 6.
Possible Pathways to $^{19}F$ NMR Equilibration of Phosphinates 43 and 44

As expected (32d), the reaction of two moles of hexafluoroacetone with one of trimethylsilyldimethylphosphinite gave compound 45 (52), whose reaction with $H_2O$ or HCl was found to produce the ring-opened dimethylphosphinate 46 (36,52). In an analogous condensation and hydrolysis in this work, the diphenylphosphinate 26 was obtained from diphenylphosphinous chloride via 25.

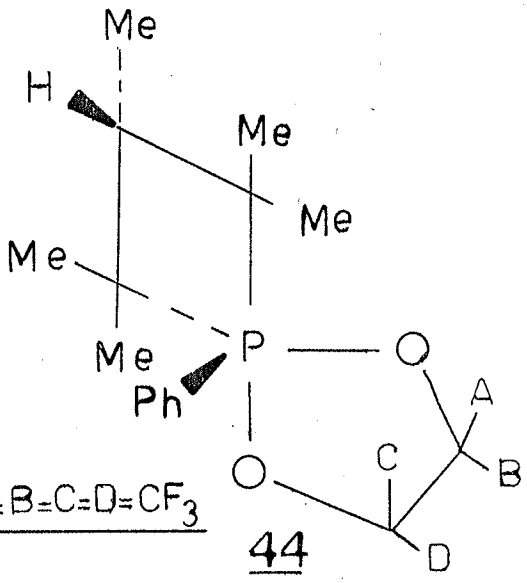
In $CD_2Cl_2$ solution, compound 26 gave rise to two septets at -67.2 and -69.4 ppm in the $^{19}F$ NMR spectrum (Fig.2). Since the molecule contains a free hydroxyl group adjacent to the phosphoryl function, it ought to be possible for a nucleophilic ring closure, as described in the Introduction, to take place. Pyridine was added to promote the ring closure by abstraction of the proton of the hydroxyl group. The $^{19}F$ NMR spectrum then exhibited a broadened peak at -68.0 ppm, intermediate between, and having replaced, the original septets (Fig.3). Thus, the molecule was undergoing a rapid exchange process equilibrating the $CF_3$ groups.

In order for the $CF_3$ groups in compound 26 to become equivalent, either the perfluoropinacolyl moiety must be lost by a dissociative process, which can be ruled out by the fact that a separate, and sharp, signal for free perfluoropinacol is also visible in the spectrum (Fig.3), or a nucleophilic ring closure (see Scheme 7) to structure 47 (or its conjugate base), followed by a subsequent ring opening, must occur.



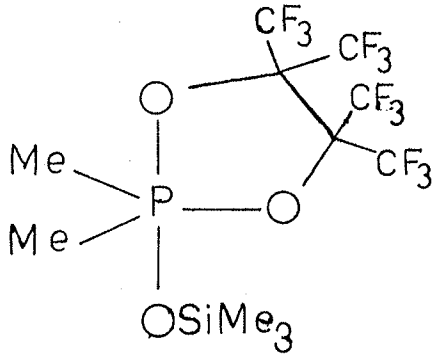

A=B=C=D=$CF_3$

43

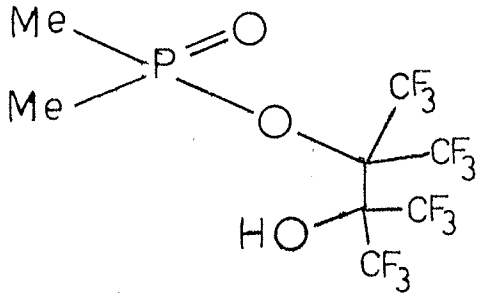



A=B=C=D=$CF_3$

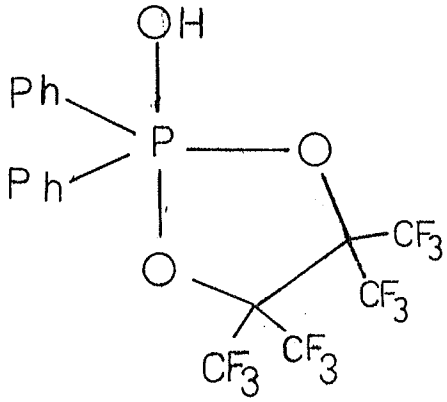
44



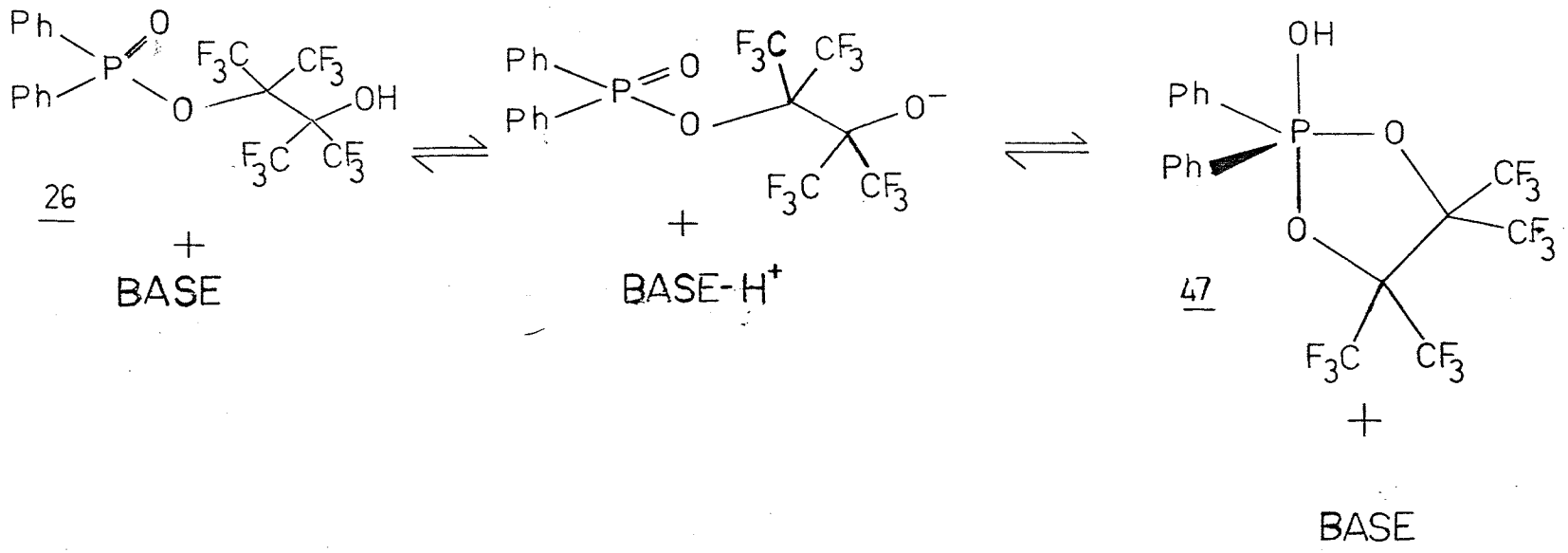

45




46




47




Scheme 7.
Deprotonation and Nucleophilic Ring-Closure of $Ph_2P(O)OC(CF_3)_2C(CF_3)_2OH$ (26)

The [$^{19}$F]-$^{13}$C NMR spectra agree fully with the $^{19}$F spectra here obtained. Addition of pyridine results (Fig.4) in broad exchange peaks at the intermediate 85.0 and 121.7 ppm positions, as compared with the non-exchanging signals at 81.9 and 88.0, and at 120.7 and 121.7 ppm (64). Again, the presence of separate, sharp signals for free perfluoropinacol rule out any dissociative process of equilibration.

Now ..hether the exchange takes place via a stepwise mechanism, as depicted in Scheme 7 where first, deprotonation of the hydroxyl group occurs, followed by ring-closure, or whether these steps are concerted, is not known. However, the exchange process (that is, the sum total of these steps) is rapid enough to exhibit equilibration in the NMR spectra, and thus none of the individual steps are slow.

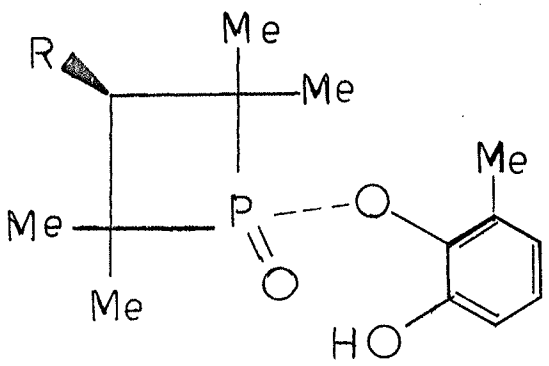
2-Hydroxyphenyldiphenylphosphinate(29).

Phosphorus compounds containing the catechyl moiety, -$OC_6H_4O$-, have been the object of much study by NMR (43,46,48,50,78-80,86,88) and by other techniques: see, for example, Mootz (33), Holmes (34), Boer (89), and Allcock (90). Kemp and Trippett (46,49) compared the interconversion of 48 and 49 (R=H,Me) with that of 52 and 53 by monitoring the positions of the aromatic methyl protons in the $^1$H NMR spectrum. Although 48 and 49 equilibrated rapidly above 70° (R=H) or 80°C (R=Me), even after increasing the

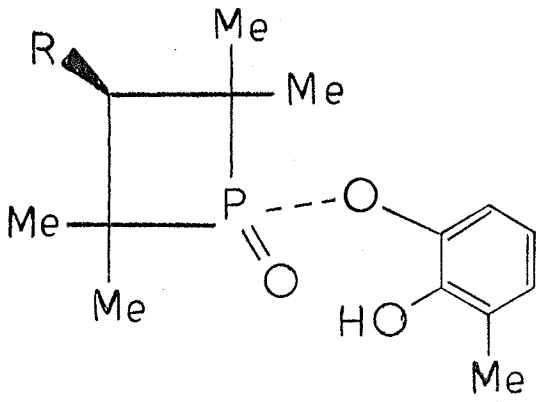
temperature to 180°C no evidence was found in the NMR spectra for the presence of the cis isomers (50 and 51). Scheme 8 outlines the pseudorotational processes consistent with the data (46).

Reaction of a mixture of 48 and 49 with diazomethane (46,49) produced about 5% (R=H; 12% when R=Me) of the methoxyphosphorane, 54, thus providing strong evidence for the existence of hydroxyphosphoranes in solution and thus as intermediates in the isomerization. In the case of compounds 52 and 53 however, no evidence for the formation of a methoxyphosphorane was found upon treatment of a mixture of the isomers with diazomethane. Therefore, either the concentrations of the hydroxyphosphoranes postulated (46,49) to be intermediates in the isomerization of 52 and 53 are very low, or the rates of methylation of the hydroxyphosphoranes are much slower than that of the acyclic phosphinates; of course, both factors could be operative simultaneously.

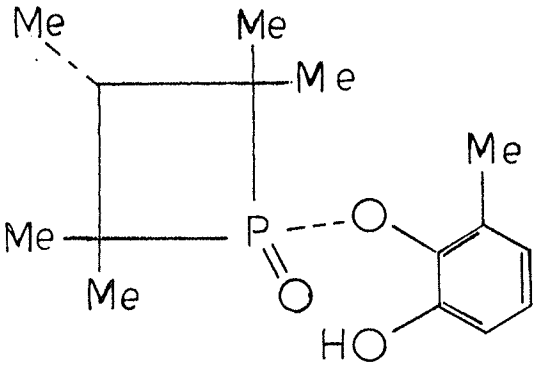
One other alternative is that the isomerization does not proceed via hydroxyphosphoranes at all, but by some other mechanism. A dissociative mechanism of some sort would appear to be highly unlikely, having been ruled out in the isomerization of compound 26, as noted in the previous section. As well, the fact that there is no cis-trans equilibration in the esters 48 and 49 (R=Me) also argues against a dissociative mechanism.



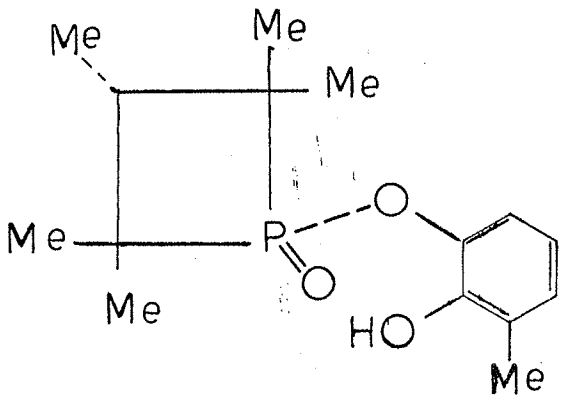

48



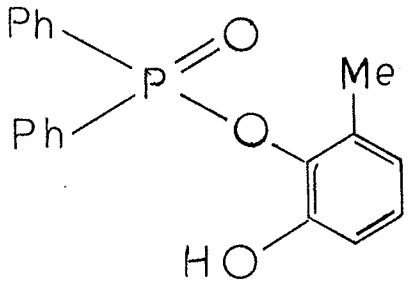

49



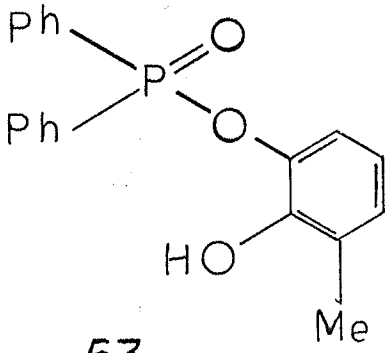

50



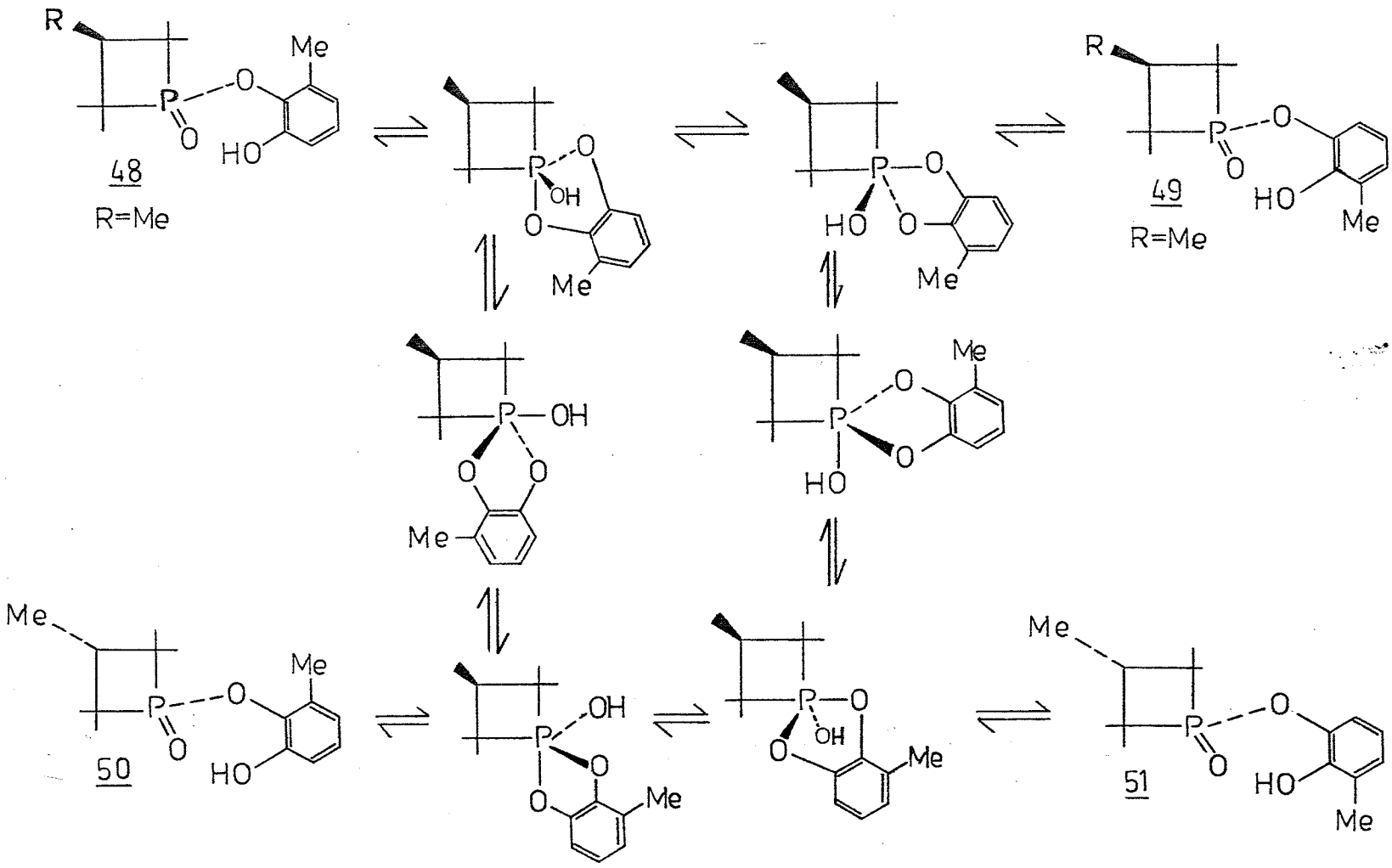

51




52



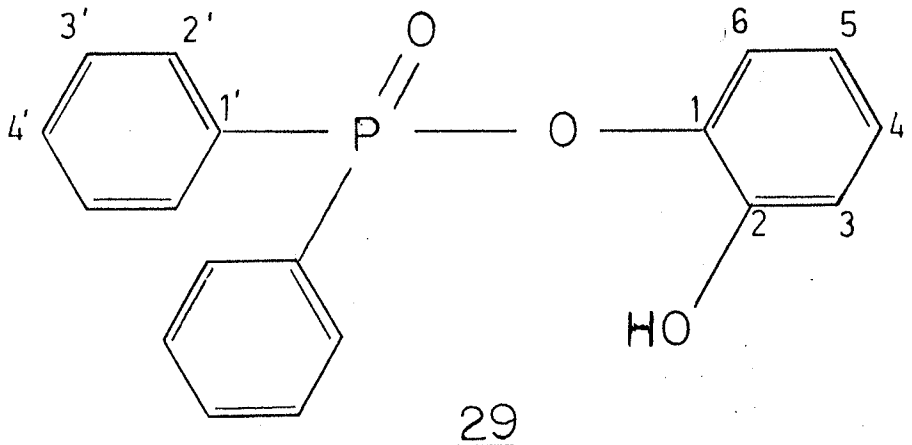

53




Scheme 8.
Pseudorotational Processes of Compounds 48, 49, 50, and 51.

The synthesis of $Ph_2P(O)OC_6H_4OH$, 29, for this work was straightforward. The method employed was similar to that used by Trippett (46) for the synthsis of 52 and 53 (similar yields also were obtained), and to that of others (91,92). As mentioned in the Experimental section, purification by sublimation was attempted, but it was unsuccessful. One possible reason for this is that phosphinic acids, when heated by themselves, are known to undergo a characteristic redox disproportionation at about 150° (93). This may also explain the morphology changes, and the decomposition, of the crystals when a determination of the melting point of the compound was attempted. However, recrystallization from 1:1 benzene-methanol was successful and the subsequent elemental analysis showed the compound to be pure.

The NMR spectra of compound 29 were obtained and the relevant data are presented in Tables 2, 3, and 4: in Table 3, the assignments are based on comparisons with published and unpublished spectra of catechol (94,96), phenol (95,96), triphenylphosphate (96), triphenylphosphine (96), diethylphenylphosphonate (97), 2-hydroxy-1-trimethylsiloxybenzene, and 1,2-bis(trimethylsiloxy)benzene; in Table 4, the assignments are based on comparison with the spectrum of 2-hydroxy-1-methoxybenzene (98) (see also Lambert (99) and Castellano (100) for chemical shifts and coupling constants of catechol); the positions are numbered as indicated below.




29

TABLE 2

$^{31}P$ NMR Data for $Ph_2P(O)OC_6H_4OH$ (29).

| Solvent | ($^{31}P$) (ppm) |
|---|---|
| $CH_2Cl_2$ | 37.80 |
| $CDCl_3$ | 38.04 |
| $C_5H_5N$ | 29.85 |
| $(CH_3)_2SO$ | 29.07 |
| $CF_3COOH$ | 43.16 |
| 1,4-dioxane | 33.75 |

TABLE 3

$^{13}C$ NMR Data for $Ph_2P(O)OC_6H_4OH$ (29) in $CD_2Cl_2$.

| Nucleus | ($^{13}C$) (ppm) | Coupling (Hz) |
|---|---|---|
| C1 | 139.6 | $^2J(POC) = 9.50$ |
| C2 | 148.6 | $^3J(POCC) = 3.15$ |
| C3 | 119.9 | $^4J(POCCC) = 1.23$ |
| C4 | 126.8 | $^5J(POCCCC) = 1.27$ |
| C5 | 120.8 | $^4J(POCCC) = 0.68$ |
| C6 | 122.9 | $^3J(POCC) = 4.56$ |
| C1' | 129.2 | $^1J(PC) = 137.1$ |
| C2' | 132.2 | $^2J(PCC) = 10.62$ |
| C3' | 129.2 | $^3J(PCCC) = 13.58$ |
| C4' | 133.6 | $^4J(PCCCC) = 2.89$ |

1) $^{31}P$ NMR Studies: Spectra.

If compound 29 behaved similarly to compound 26 upon addition of pyridine or another base, then its NMR spectra, too, should show evidence of chemical exchange. If ring-closure to a five-coordinate species did occur, the $^{31}P$ signal would be shifted to higher field if the rate of ring-closure was rapid; if the rate was slow, a second signal would appear to higher field of the original signal.

TABLE 4

$^1$H NMR Data for $Ph_2P(O)OC_6H_4OH$ (29) in $CD_2Cl_2$.

| Nucleus | ($\delta^1$H) (ppm) | Coupling (Hz) |
|---|---|---|
| H3 | 6.981 | $^5J$(POCCCH) = -0.31 |
| | | $^3J$(H4,H3) = 8.12 |
| | | $^4J$(H5,H3) = 1.59 |
| | | $^5J$(H6,H3) = 0.31 |
| H4 | 7.000 | $^6J$(POCCCCH) = 1.04 |
| | | $^3J$(H3,H4) = 8.12 |
| | | $^3J$(H5,H4) = 7.41 |
| | | $^4J$(H6,H4) = 1.59 |
| H5 | 6.709 | $^5J$(POCCCH) = -0.83 |
| | | $^3J$(H4,H5) = 7.41 |
| | | $^3J$(H6,H5) = 8.08 |
| | | $^4J$(H3,H5) = 1.59 |
| H6 | 6.902 | $^4J$(POCCH) = 1.34 |
| | | $^3J$(H5,H6) = 8.08 |
| | | $^4J$(H4,H6) = 1.59 |
| | | $^5J$(H3,H6) = 0.31 |

Therefore, the $^{31}P$ chemical shift was monitored as a function of the concentration of added base; the concentration of 29 was kept fairly constant. The results of these experiments are given in Tables 5, 6, 7, 8, and 9. The reduced concentration variable, R, is defined as

$$R = [\text{base}]/[\text{Cmpd 29}]$$

TABLE 5

$^{31}P$ NMR Chemical Shifts of $Ph_2P(O)OC_6H_4OH$ (29) (in $CH_2Cl_2$): Pyridine as Added Base.

| Cmpd (mol/L) | Base (mol/L) | R | ($^{31}P$) |
|---|---|---|---|
| 0.0632 | 0.00 | 0.00 | 37.80 |
| 0.0322 | 0.0031 | 0.096 | 37.79 |
| 0.0313 | 0.0062 | 0.198 | 37.77 |
| 0.0322 | 0.0171 | 0.531 | 37.73 |
| 0.0311 | 0.0323 | 1.04 | 37.68 |
| 0.0322 | 0.0645 | 2.00 | 37.53 |
| 0.0317 | 0.118 | 3.72 | 37.35 |
| 0.0324 | 0.145 | 4.48 | 37.28 |
| 0.0324 | 0.189 | 5.83 | 37.13 |
| 0.0327 | 0.286 | 8.75 | 36.88 |
| 0.0322 | 0.416 | 12.9 | 36.51 |
| 0.0322 | 0.497 | 15.4 | 36.30 |
| 0.0313 | 1.99 | 63.6 | 33.59 |
| 0.0314 | 3.98 | 126.8 | 31.94 |
| 0.0316 | 9.12 | 288.6 | 30.29 |
| 0.0322 | 12.4 | 385.1 | 29.85 |

TABLE 6

$^{31}P$ NMR Chemical Shifts of $Ph_2P(O)OC_6H_4OH$ (29) (in $CH_2Cl_2$): Triethylamine as Added Base.

| Cmpd (mol/L) | Base (mol/L) | R | ($^{31}P$) |
|---|---|---|---|
| 0.0632 | 0.00 | 0.00 | 37.80 |
| 0.0314 | 0.0496 | 1.58 | 37.42 |
| 0.0323 | 0.0989 | 3.06 | 37.05 |
| 0.0326 | 0.252 | 7.73 | 36.05 |
| 0.0324 | 0.503 | 15.5 | 34.49 |
| 0.0317 | 1.51 | 47.6 | 32.40 |
| 0.0326 | 3.95 | 121.2 | 30.11 |

TABLE 7

$^{31}P$ NMR Chemical Shifts of $Ph_2P(O)OC_6H_4OH$ (29) (in $CH_2Cl_2$): Dimethylsulphoxide as Added Base.

| Cmpd (mol/L) | Base (mol/L) | R | ($^{31}P$) |
|---|---|---|---|
| 0.0632 | 0.00 | 0.00 | 37.80 |
| 0.0319 | 0.500 | 15.7 | 35.92 |
| 0.0316 | 1.69 | 53.5 | 32.98 |
| 0.0321 | 4.02 | 125.2 | 30.90 |
| 0.0321 | 7.75 | 241.4 | 29.67 |
| 0.0317 | 14.1 | 445. | 29.07 |

TABLE 8

$^{31}P$ NMR Chemical Shifts of $Ph_2P(O)OC_6H_4OH$ (29) (in $CH_2Cl_2$): Imidazole as Added Base.

| Cmpd (mol/L) | Base (mol/L) | R | ($^{31}P$) |
|---|---|---|---|
| 0.0632 | 0.00 | 0.00 | 37.80 |
| 0.0321 | 0.503 | 15.7 | 34.24 |
| 0.0321 | 1.00 | 31.2 | 33.31 |
| 0.0322 | 2.06 | 64.0 | 32.63 |
| 0.0322 | 3.00 | 93.2 | 32.37 |

TABLE 9

$^{31}P$ NMR Chemical Shifts of $Ph_2P(O)OC_6H_4OH$ (29) (in $CH_2Cl_2$): Dioxane as Added Base.

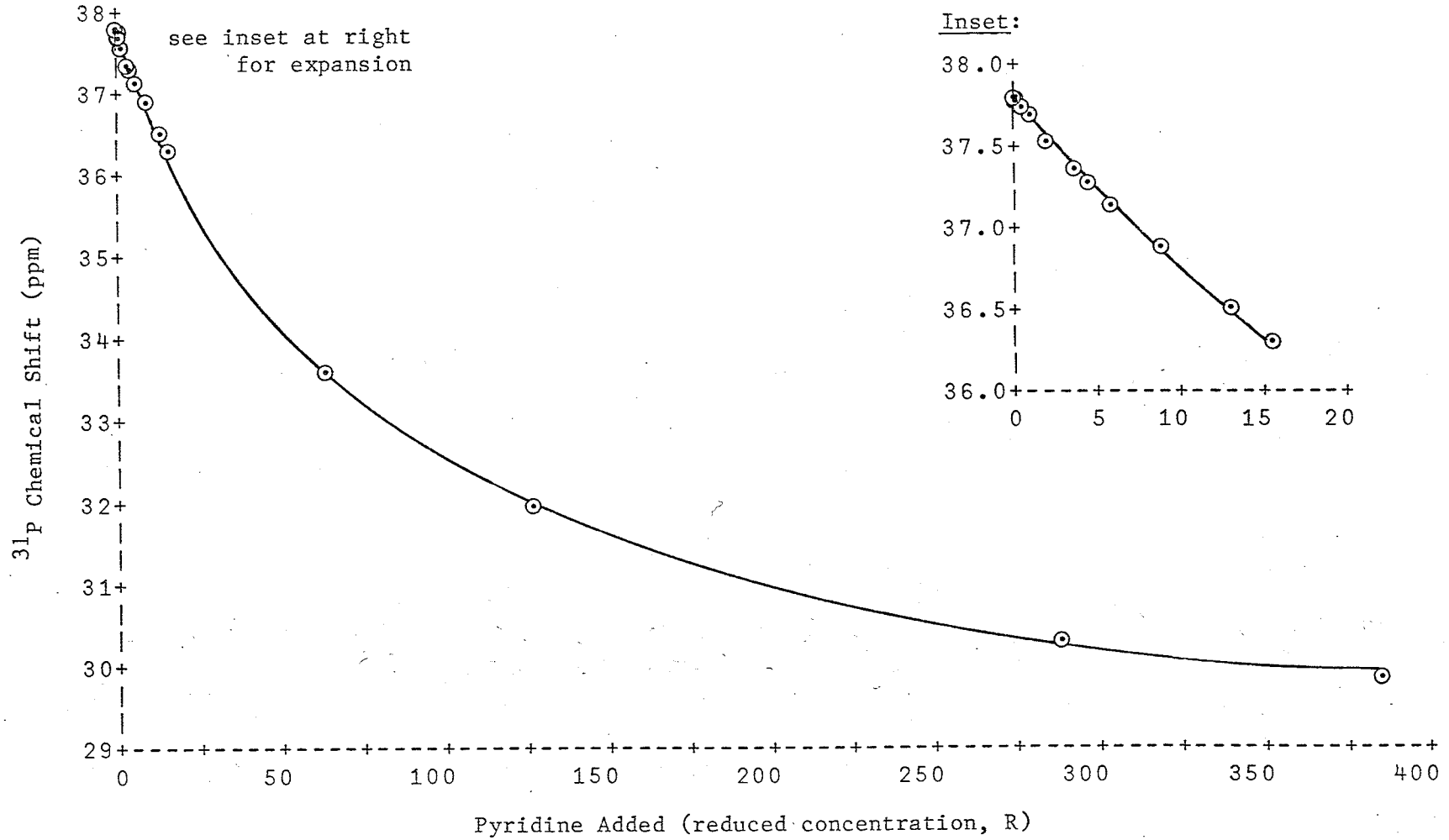
| Cmpd (mol/L) | Base (mol/L) | R | ($\delta^{31}P$) |
|---|---|---|---|
| 0.0632 | 0.00 | 0.00 | 37.80 |
| 0.0322 | 0.587 | 18.2 | 37.42 |
| 0.0322 | 1.64 | 50.9 | 36.91 |
| 0.0317 | 3.99 | 126. | 35.81 |
| 0.0321 | 7.62 | 237. | 34.67 |

In each case, only one $^{31}P$ signal was observed in the spectrum. As can be seen from Graphs 1 through 5, where the above data are plotted, the chemical shift of 29 moves regularly upfield as more base is added.

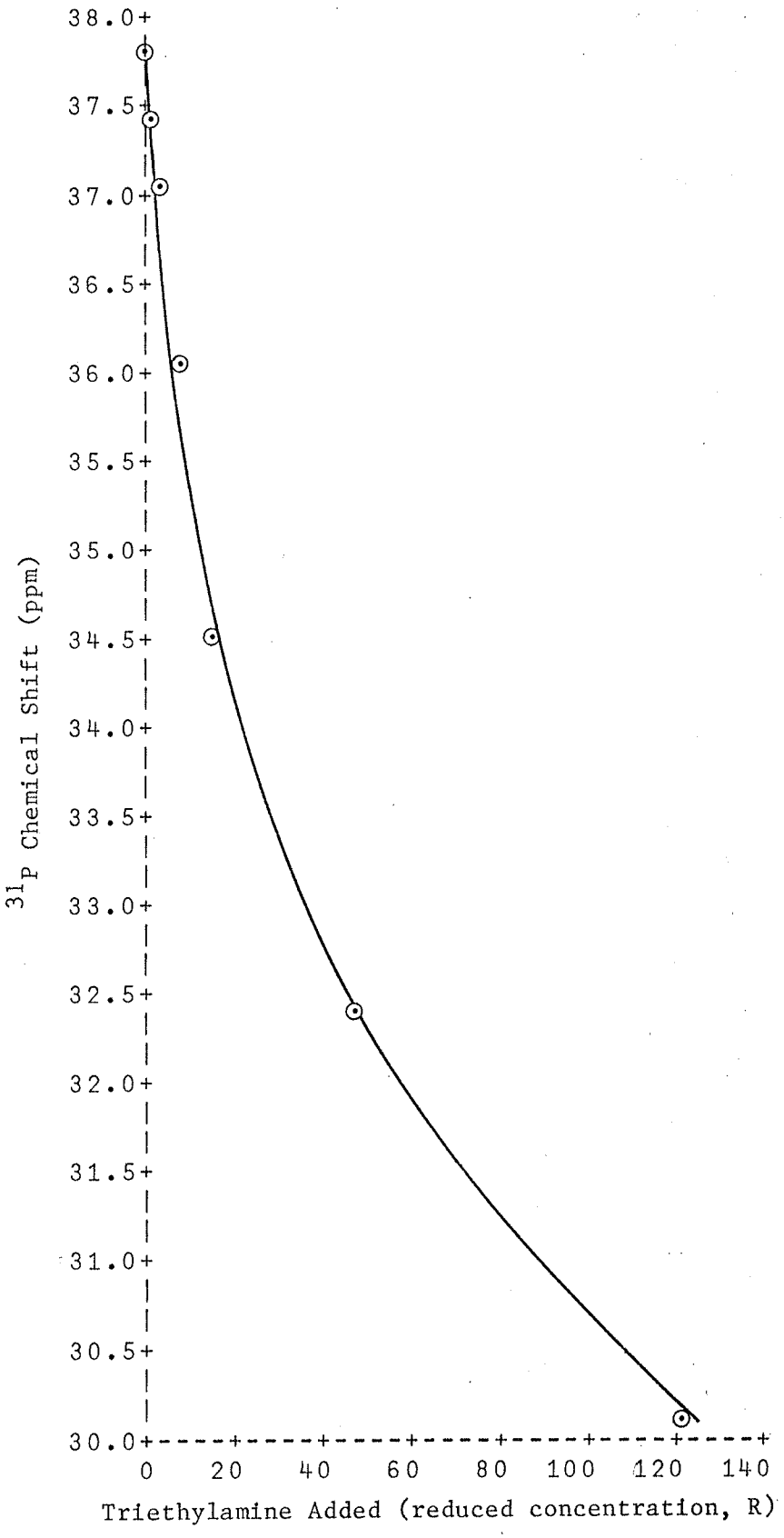
In order to determine that what was being observed was not merely a solvent effect, the $^{31}P$ chemical shift of trimethylphosphate (0.071 M in $CH_2Cl_2$ solution) was monitored as a function of pyridine concentration. The data are given in Table 10. Since this molecule does not possess a free hydroxyl group, no nucleophilic ring-closure can take place. Thus the change in chemical shift can be attributed to a solvent effect. As can be seen from the data in Table 10, this effect is quite small for trimethylphosphate.

As well, the change in $^{31}P$ chemical shift of 2-trimethylsiloxyphenyldiphenylphosphinate, 32, was observed as a function of pyridine concentration. Both 32 and 29 were present in the sample. The data are presented in Table 11.

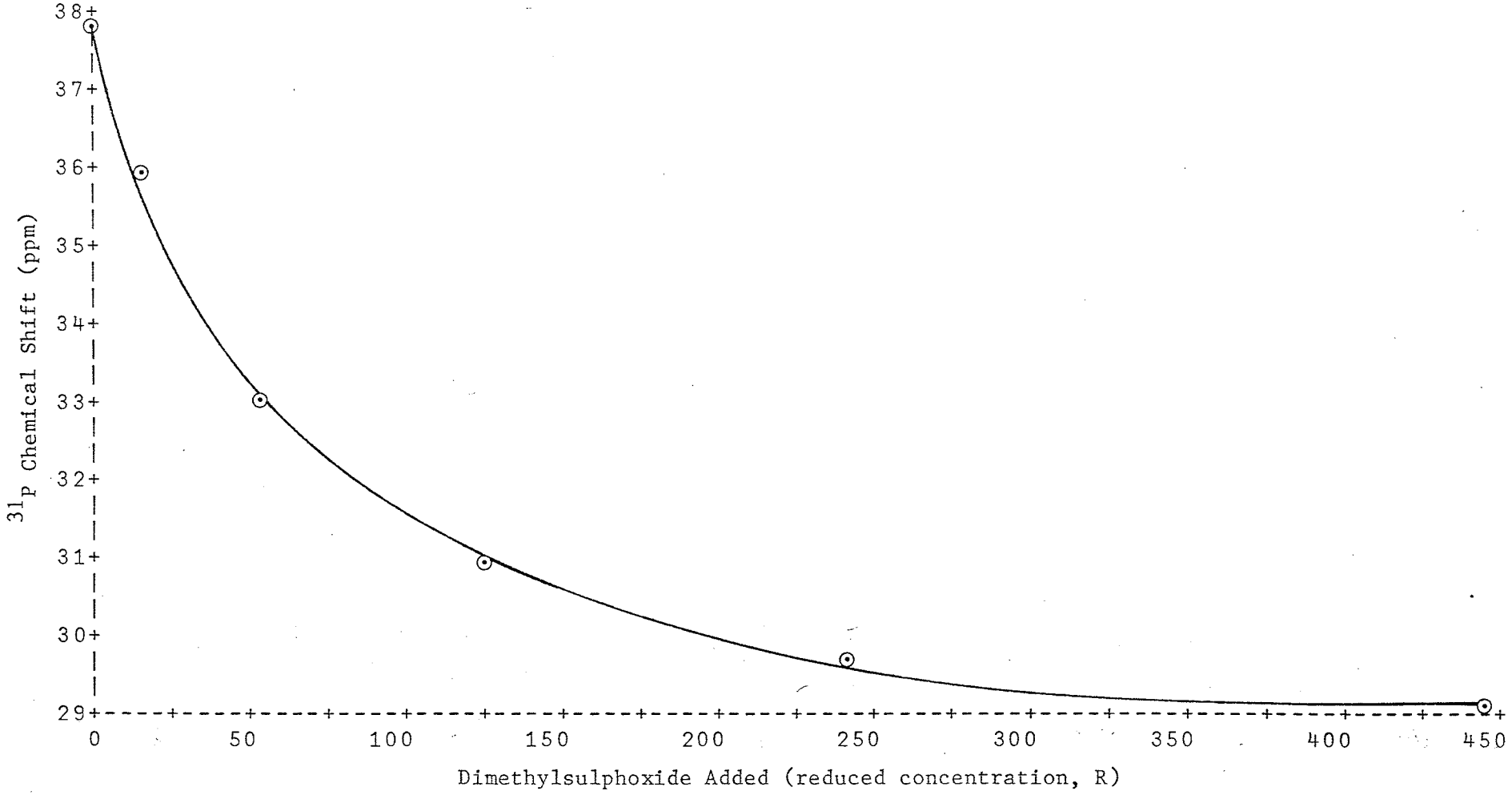
Graph 1. Effect of Added Pyridine on $^{31}P$ Chemical Shift of Compound 29.



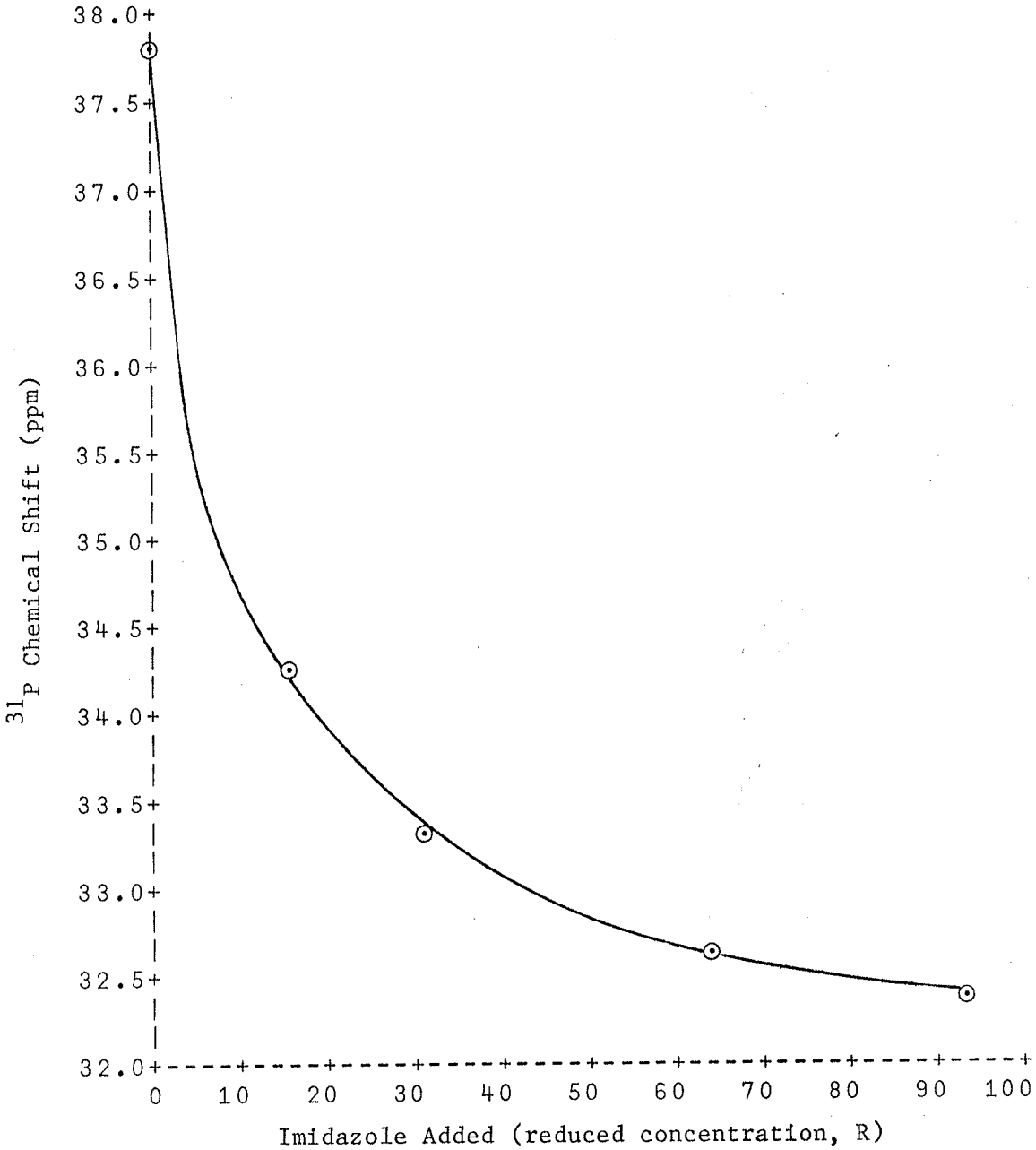
Graph 2. Effect of Added Triethylamine on $^{31}P$ Chemical Shift of Compound 29.



Graph 3. Effect of Added DMSO on $^{31}P$ Chemical Shift of Compound 29.



Graph 4. Effect of Added Imidazole on $^{31}P$ Chemical Shift of Compound 29.



Graph 5. Effect of Added 1,4-Dioxane on $^{31}P$ Chemical Shift of Compound 29.

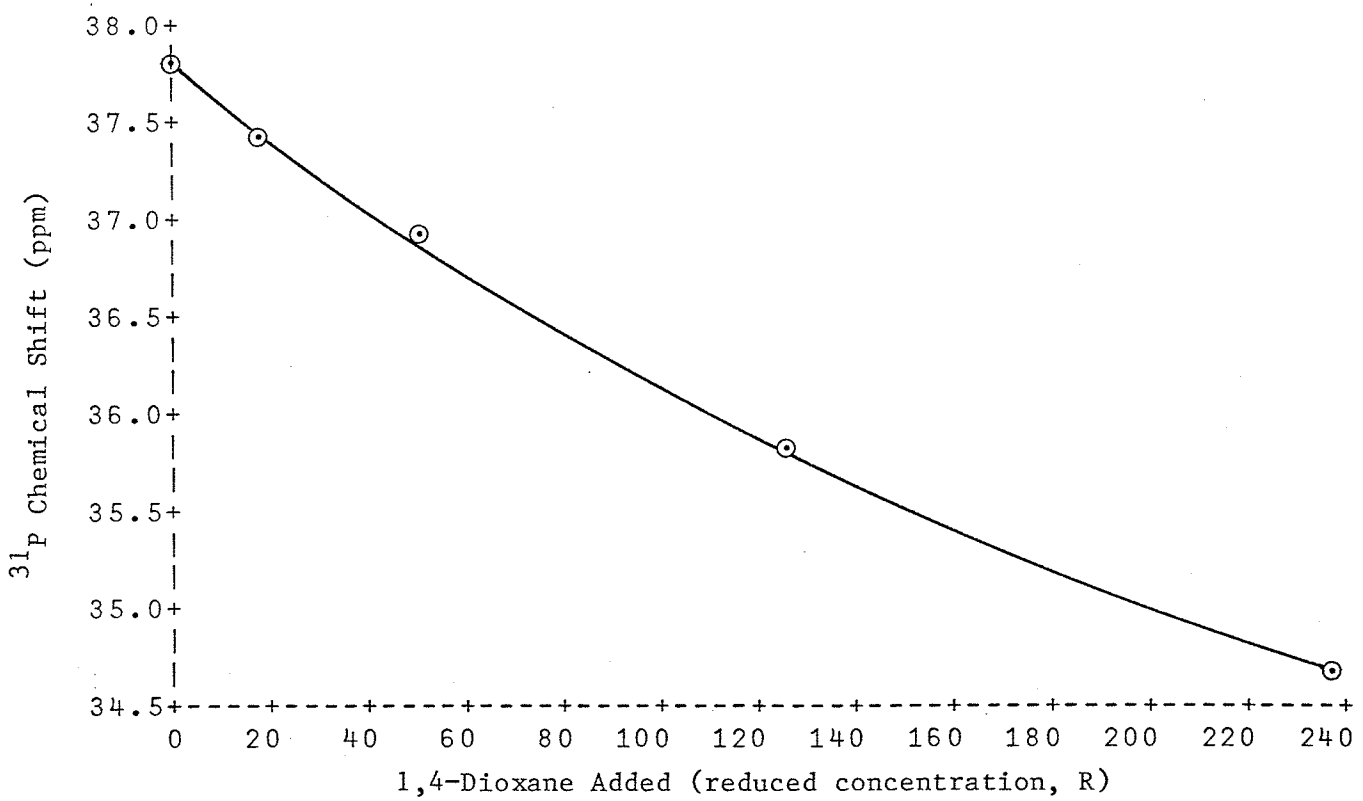


TABLE 10

$^{31}P$ NMR Data for $(MeO)_3PO$ in $CH_2Cl_2$: Pyridine as Added Base.

| Cmpd (mol/L) | Base (mol/L) | ($^{31}P$) |
|---|---|---|
| 0.0705 | 0.00 | 1.39 |
| | 2.98 | 1.28 |
| | 5.77 | 1.21 |
| | 12.4 | 1.10 |

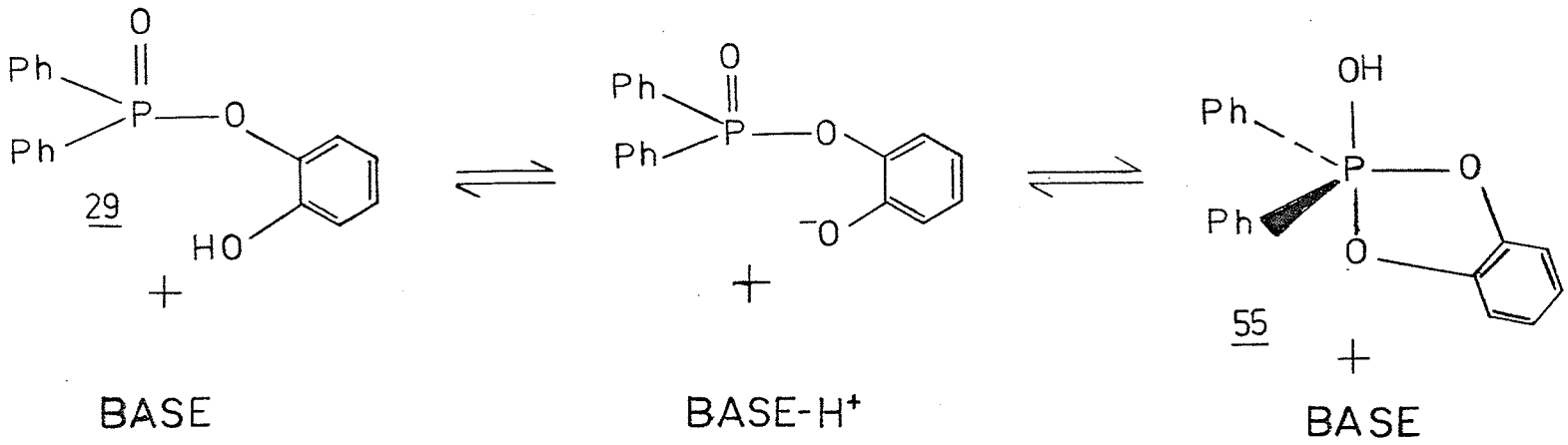
TABLE 11

Comparison of $^{31}P$ Chemical Shifts for Compounds 29 and 32: Pyridine as Added Base.

| Base (mol/L) | $^{31}P$ Chemical Shift Cmpd 29 | Cmpd 32 |
|---|---|---|
| 0.0 | 38.62 | 29.83 |
| 3.1 | 33.87 | 29.62 |
| 6.2 | 32.19 | 29.37 |
| 9.3 | 31.33 | 29.04 |

In the case of compound 32, the 2-hydroxy group is blocked, preventing nucleophilic ring-closure, whereas pyridine can deprotonate 29 and thus promote ring-closure. Again, it can be seen (Table 11) that the solvent effect is small and that large changes in the $^{31}P$ chemical shift values for 29 are not due to such solvent effects. Rather, the movement of the $^{31}P$ chemical shift of 29 can be attributed to a base effect; the magnitude of the solvent effect was not determined for any of the other bases.

The $^{31}P$ chemical shift of a sample containing 0.031 mol/L 29 and 9.31 mol/L pyridine, in $CH_2Cl_2$ solution,




Scheme 9.
Deprotonation and Nucleophilic Ring-Closure of $Ph_2P(O)OC_6H_4OH$

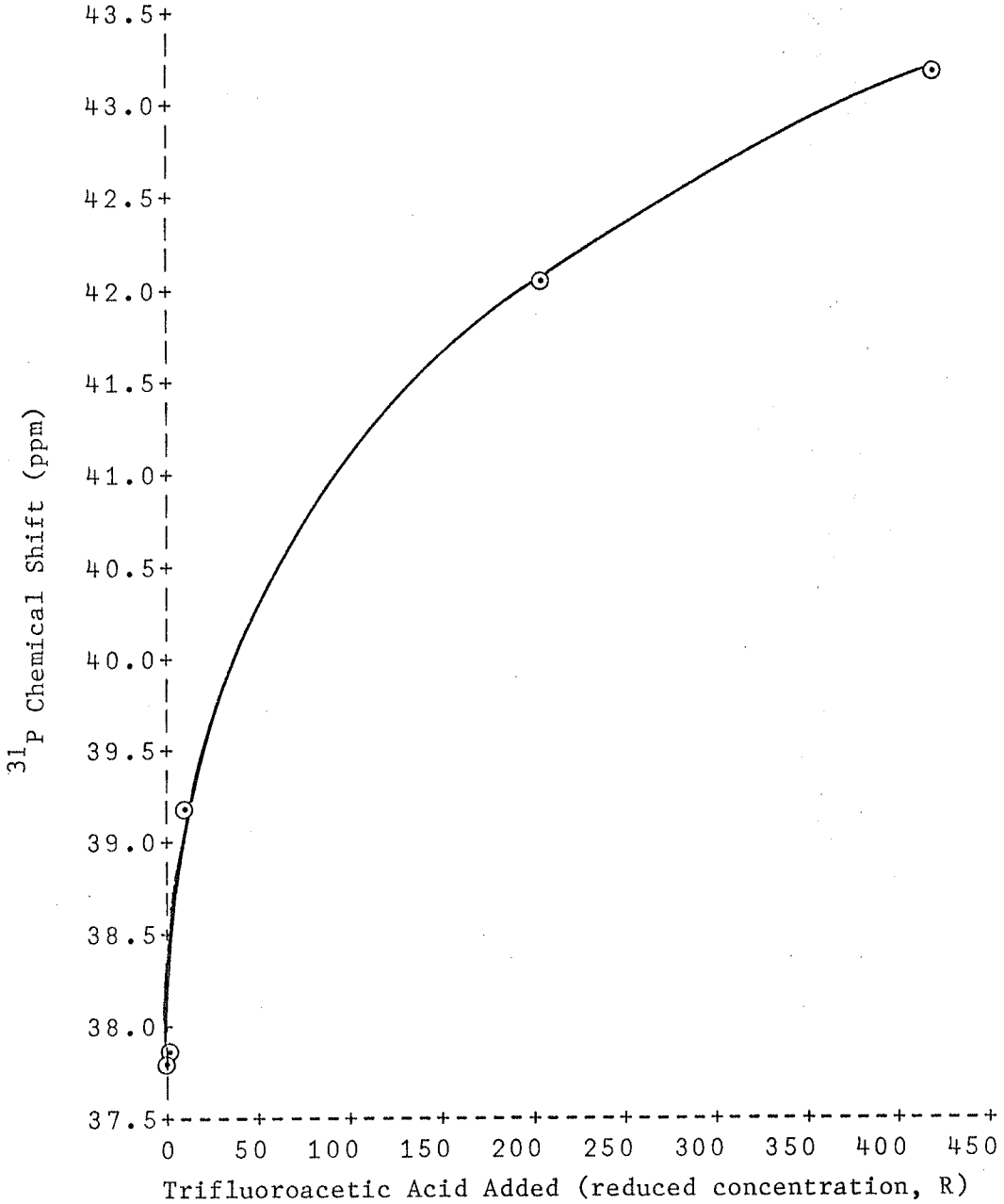
was observed to move very slowly to higher field as the temperature was lowered: 31.07, 29.66, and 29.62 ppm at +27, -53, and -63°C, respectively. However, no appreciable line broadening was observed.

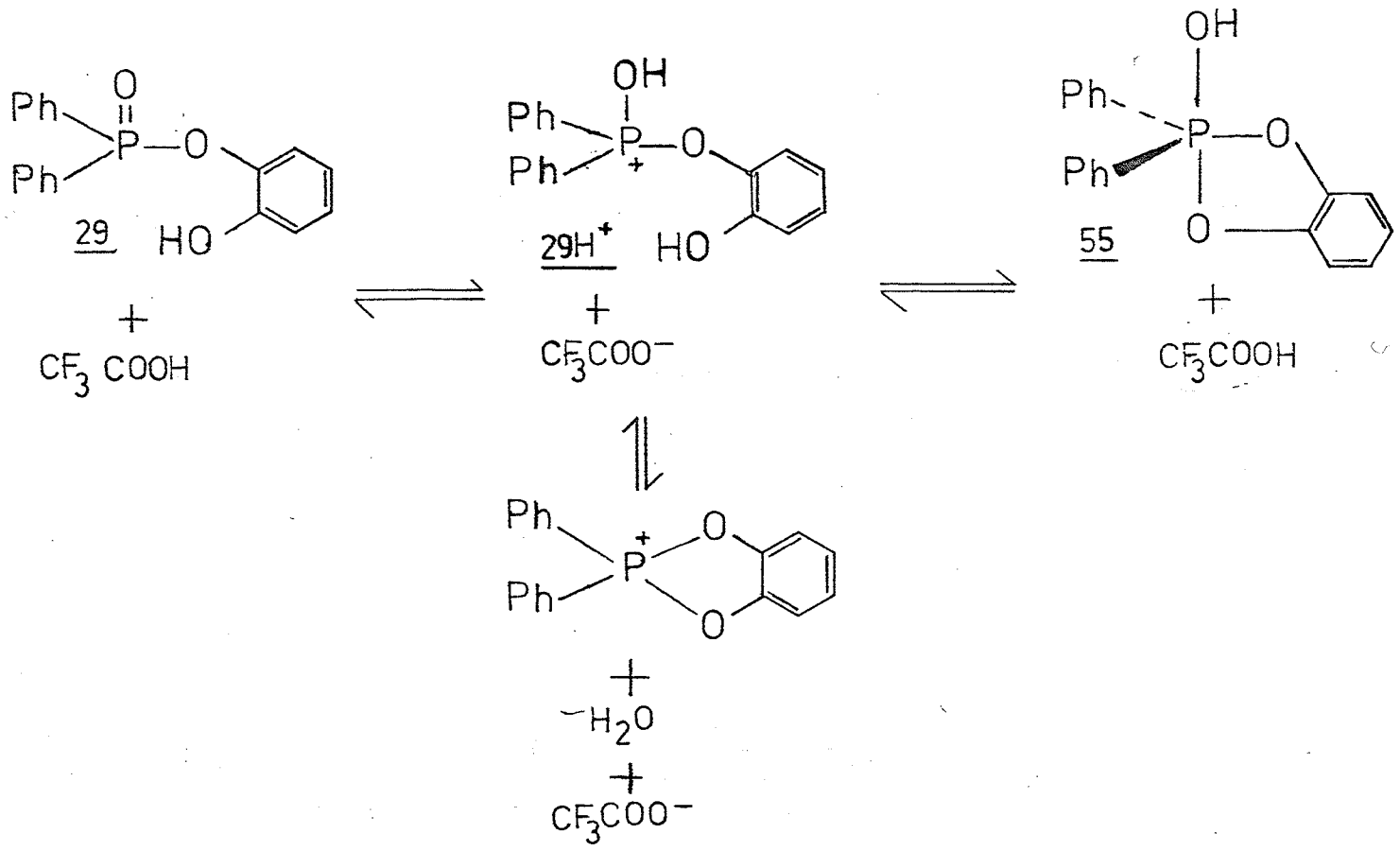
The $^{31}P$ NMR data suggest that, in the presence of base, a rapid equilibrium exists between 4- and 5-coordinate species. This, then, is consistent with other studies (43,46,48-50) and with the investigation of compound 26 carried out in this work and elsewhere (64). A mechanism analogous to that proposed for 26 is illustrated in Scheme 9; the same limitation also applies, namely that it is uncertain whether the ring-closure is a two-step process, with deprotonation as the first step, or whether a concerted mechanism is operative. This question will be addressed again later.

It has been mentioned previously (see Introduction) that acids, as well as bases, can promote nucleophilic ring-closure (23,43,84) in compounds with a hydroxyl substituent adjacent to a phosphoryl function such as is the case in $Ph_2P(O)OC_6H_4OH$, 29. Therefore, it was decided to obtain several $^{31}P$ NMR spectra of 29 with added trifluoroacetic acid (TFA). The data are given in Table 12 and are plotted on Graph 6.

Scheme 10 illustrates several mechanistic possibilities which could account for the behavior of 29 in TFA. The first is that 29 is merely protonated, the first step in

Graph 6. Effect of Added Trifluoroacetic Acid on $^{31}P$ Chemical Shift of Compound 29.






Scheme 10.
Mechanistic Possibilities for Interaction of $Ph_2P(O)OC_6H_4OH$ with $CF_3COOH$

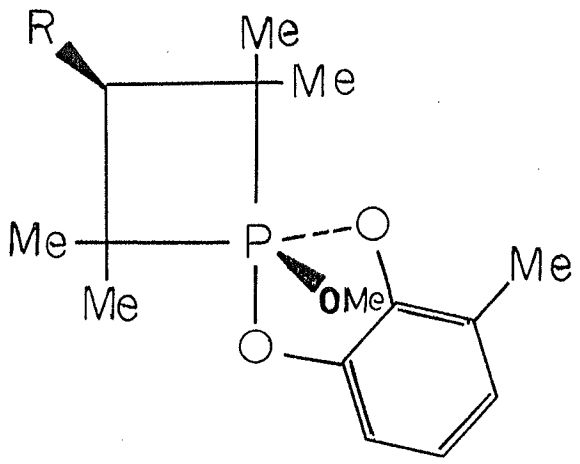
TABLE 12

$^{31}P$ NMR Chemical Shifts of $Ph_2P(O)OC_6H_4OH$ (29) (in $CH_2Cl_2$): Trifluoroacetic Acid Added.

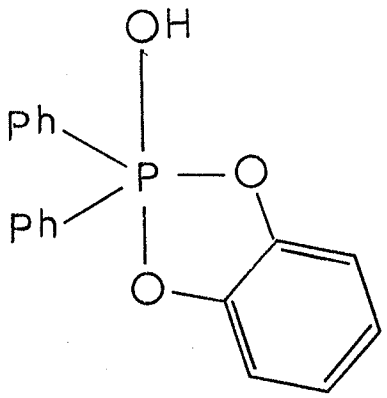
| Cmpd (mol/L) | Acid (mol/L) | R | ($^{31}P$) |
|---|---|---|---|
| 0.0632 | 0.00 | 0.00 | 37.80 |
| 0.0321 | 0.0121 | 0.377 | 37.80 |
| 0.0321 | 0.0303 | 0.94 | 37.85 |
| 0.0322 | 0.337 | 10.5 | 39.16 |
| 0.0327 | 6.73 | 206. | 42.05 |
| 0.0322 | 13.5 | 419. | 43.16 |

Scheme 10 (46; see also Appendix D). The ($^{31}P$) value of 43.16 ppm could possibly be attributed to a phosphonium ion. However, many similar phosphonium ions have chemical shifts in the range of 50 to 60 ppm: $Ph_2P(OMe)_2SbCl_6$, ($^{31}P$) = 61.2 ppm (101), ($^{31}P$) = 61.3 ppm (102a); $Ph_2P(OH)_2HSO_4$, ($^{31}P$) = 53.0 ppm (102b); $Ph_2P(OH)NMe_2HSO_4$, ($^{31}P$) = 50.0 ppm (102c); $Ph_2P(OMe)NMe_2SbCl_6$, ($^{31}P$) = 57.5 ppm (102d). It can be speculated, then, that the observed chemical shift is, as appears to be the case when bases are added, a weighted average of the limiting chemical shifts of two or more species, either 29 and $29H^+$, or 29, $29H^+$, and 55 (see Scheme 10). However, it has not been possible, in this work, to determine which of these two possibilities, if either, is correct.

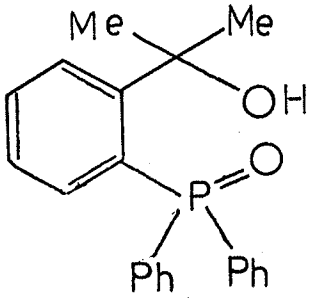
One other alternative remains. Granoth (103) has stated that the low field $^{31}P$ chemical shift (73.6 ppm) observed when compound 56 is dissolved in TFA, is due to the dehydrated product, 57. It is conceivable that



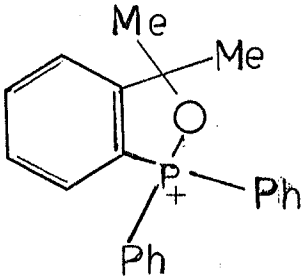

54




55




56




57

$Ph_2P(O)OC_6H_4OH$, 29, similarly dehydrates in TFA to yield a phosphonium ion (see Scheme 10). Once again, however, it has not been possible, in this work, to determine the contribution of such a species to the observed $^{31}P$ chemical shift. Nevertheless, Graph 6 shows a definite trend for which further studies should be able to provide an explanation.

2) $^{31}P$ NMR Studies: Calculations.

The shapes of the chemical shift vs reduced base concentration curves reflect the differing base strengths of the bases added. For example, triethylamine is generally considered to be a stronger base than is pyridine and Graph 2 is indeed a steeper curve than is Graph 1, indicating, for triethylamine, a larger change in chemical shift per unit amount of base added. This will be discussed in greater detail, later.

Referring to Scheme 9, and proceeding on the assumption that the deprotonation and the ring-closure are concerted, a mathematical model for the $^{31}P$ chemical shift can be derived; the full derivation is given in Appendix B. The model requires three parameters:

1. ($^{31}P$) for 29, DA, which is fixed at DA = 37.80 ppm in the regression analysis; the linearity of Graph 1 is high for R values between 0 and 0.53, allowing for an accurate extrapolation to R=0,

2. ($^{31}P$) for 55, or its conjugate base 55-$H^+$, DF,

3. the equilibrium constant, K.

Using the non-linear regression procedure NLIN (104), the data in Tables 5 through 9 were analyzed statistically to provide the best-fit values of the parameters. The technique employed is a modification of that suggested by Shapiro (105). The chemical shift, DA, is a constant. A reasonable value is chosen for DF and the residual sum of squares (RSS) is minimized iteratively with respect to K. By choosing various DF values, the best fit of the model to the data can readily be obtained.

The starting value chosen for DF, the ($^{31}P$) of 55, was DF = -16.3 ppm (32e). Now, whether the contributing species is 55 or 55-$H^+$ is not critical because, in a solvent such as $CH_2Cl_2$, the anion would be expected to have a counterion of some kind in close proximity. As well, it would appear that as long as the basic framework of the phosphorane (ie. the number of oxygen, carbon, or other substituents, the number and size of rings, and so on) remains unchanged, specific alkyl, aryl, silyl, or other substituents exert only a small effect on the $^{31}P$ chemical shift; many illustrations of this fact have been reported: see, for example, the $^{31}P$ chemical shifts reported for an oxy-anion (triethylammonium salt) vs a hydroxyl group (55); see also, Granoth (45,54), Trippett (46), Munoz (50,51), Ramirez (43), and Schmutzler (52).

The eventual "best" value for DF was based on the best fit of the pyridine data (Table 5) to the model. Since there are more data for pyridine than for any other base (Tables 6 - 9), this determination of DF could be expected to be more reliable than if it had been based on the fewer data for another base. In subsequent calculations therefore, the chemical shift used was DF = -8.0 ppm.

TABLE 13

Results of NLIN Analysis of the $^{31}P$ Chemical Shift Data: One-Step Mechanism.

| Base | K x$10^4$ | RSS (*) | SEE (**) | I (+) |
|---|---|---|---|---|
| $Et_3N$ | (2.88 +/- 0.26) | 1.054 | 0.46 ppm | 0.99 |
| imidazole | (2.31 +/- 0.38) | 2.048 | 0.83 ppm | 0.91 |
| DMSO | (1.42 +/- 0.21) | 4.641 | 1.08 ppm | 0.94 |
| pyridine | (1.066 +/- 0.075) | 2.748 | 0.44 ppm | 0.99 |
| 1,4-dioxane | (0.165 +/- 0.031) | 0.464 | 0.39 ppm | 0.94 |

(*)RSS = residual sum of squares (see text)
(**)SEE = standard error of estimate (see text)
(+)I = index of multiple correlation (see text)

The equilibrium constants, as determined by NLIN, for the one-step, concerted mechanism are given in Table 13, along with the minimized RSS, the standard error of estimate (SEE), and the index of multiple correlation (I); reported uncertainties in K are the asymptotic standard errors as

calculated by NLIN. The RSS is the sum of the squared differences between observed and calculated values of the dependent variable and thus measures the variability of the observed values about the regression line. The SEE is another measure of the size of the residuals and indicates the accuracy with which values of the dependent variable can be estimated from the observed values of the independent variable(s) (106a). Although, strictly speaking, there are two independent variables, the amount of 29 added to each sample tube varied only by about 1.5 %, or less, and thus remained fairly constant. The standard error of estimate can therefore be approximated by

$$SEE = SQRT(RSS/(n - 2))$$

where n is the number of observations. The I value is a measure of the degree of relationship, or correlation, between the dependent and the independent variables and is given by (106b)

$$I^2 = 1 - (SEE^2/s^2)$$

where $s^2$ is the variance (107) of the observed values of the dependent variable.

As can be seen from Table 13, triethylamine appears to be the strongest base, having the largest equilibrium constant for the equilibrium illustrated in Scheme 9; as might have been expected, 1,4-dioxane would appear to be the

weakest base. However, it must be borne in mind that the relative strengths of bases in an organic solvent such as $CH_2Cl_2$ do not necessarily parallel their relative strengths in aqueous solution (108).

The degree of fit of the data to the model, as expressed by the standard error of estimate and by the index of multiple correlation, is fairly good for the pyridine and triethylamine data. However, the dimethylsulphoxide, 1,4-dioxane, and imidazole data do not fit the model nearly as well. There could be several reasons for this. The small number of observations increases the uncertainties associated with the parameters and results in a poorer degree of fit. As well, it may be that although the solvent effect for the nitrogen base, pyridine, was small this may not have been the case for the oxygen bases, DMSO and dioxane. Thus, for these bases, a solvent effect may be superimposed on the base effect. If this is the case, since the model does not account for solvent effects, the degree of fit might be expected to be worse. For imidazole, the effect of the saturated ring nitrogen on the equilibrium in question is also not known. It remains a possibility too, of course, that the model is simply not correct in the cases of DMSO, or dioxane, or imidazole.

Returning now to the mechanism of Scheme 9, the $^{31}P$ NMR data can also be analyzed in terms of a two-step mechanism, where the deprotonation and the ring-closure are

not concerted. The full derivation of this model is given in Appendix A; five parameters are now required:

1. ($^{31}$P) for 29, DA, which remains fixed as before at 37.80 ppm,
2. ($^{31}$P) for 55, or 55-$H^+$, DF, which was determined previously to be -8.0 ppm,
3. ($^{31}$P) for the conjugate base of 29, DC,
4. the equilibrium constant for the deprotonation, K1,
5. the equilibrium constant, K2, for the ring-closure.

The only estimates of K1 (for the pyridine data, which has the largest number of observations) available are based on pKa values of 5.25 (109a) or 6.28 (110) for pyridine, and pKa = 9.85 (109b) for catechol. These result in K1 values of $2.51 \times 10^{-5}$ and $2.67 \times 10^{-4}$, respectively. In addition, no estimate of DC is available: for 29, ($^{31}$P) = 38.62 ppm ($C_6D_6$ lock); for 32, ($^{31}$P) = 29.83 ppm; for 52 and 53, ($^{31}$P) = 37.6 ppm (46), nor is there an estimate for K2.

With five parameters and only sixteen data points at most (Table 5), the parameters are very highly correlated and simultaneous iterations on more than one parameter give erroneous results (such as K1 < 0) with very large associated uncertainties. As well, it might also mean that considering the two steps of Scheme 9 and Appendix A as distinct and separate is incorrect and that the deprotonation and ring-closure are, in fact, concerted.

3) $^{1}$H NMR Studies.

The $^{1}$H chemical shifts, and the coupling constants, given in Table 4 were obtained through DAVINS (111,112) least squares analysis of the high resolution $^{1}$H and [$^{31}$P]-$^{1}$H NMR spectra of $Ph_2P(O)OC_6H_4OH$, 29, in $CD_2Cl_2$ at 27°C. The experimental spectra are shown in Figures 5 and 6, while the calculated spectra are presented in Figures 10 and 11.

As outlined in the Experimental section, various efforts were made, through variable temperature NMR and by addition of pyridine-d5 or DMSO-d6, to effect a rapid exchange such that equilibration of the catechyl ring protons would be visible in the $^{1}$H NMR spectrum. However, although the appearance of the catechyl region of the spectrum changed significantly with temperature and with addition of base, while the corresponding phenyl region remained essentially unchanged, no equilibration, ie. no symmetrical spectrum (catechyl portion), was observed.

Evidence provided by $^{31}$P NMR suggests that the rate of ring-closure, and the subsequent ring-opening, is rapid. However, no equilibration was observed in the $^{1}$H NMR spectra. This implies that ring-closure and ring-opening both involve the same P-O bond, while the original ester P-O bond remains intact.

If the temperature is increased enough, rapid equilibration is observed in the NMR spectra of compounds 48 and

Figure 10.

Calculated $^{1}H$ NMR Spectrum of $Ph_2P(O)OC_6H_4OH$ (29)

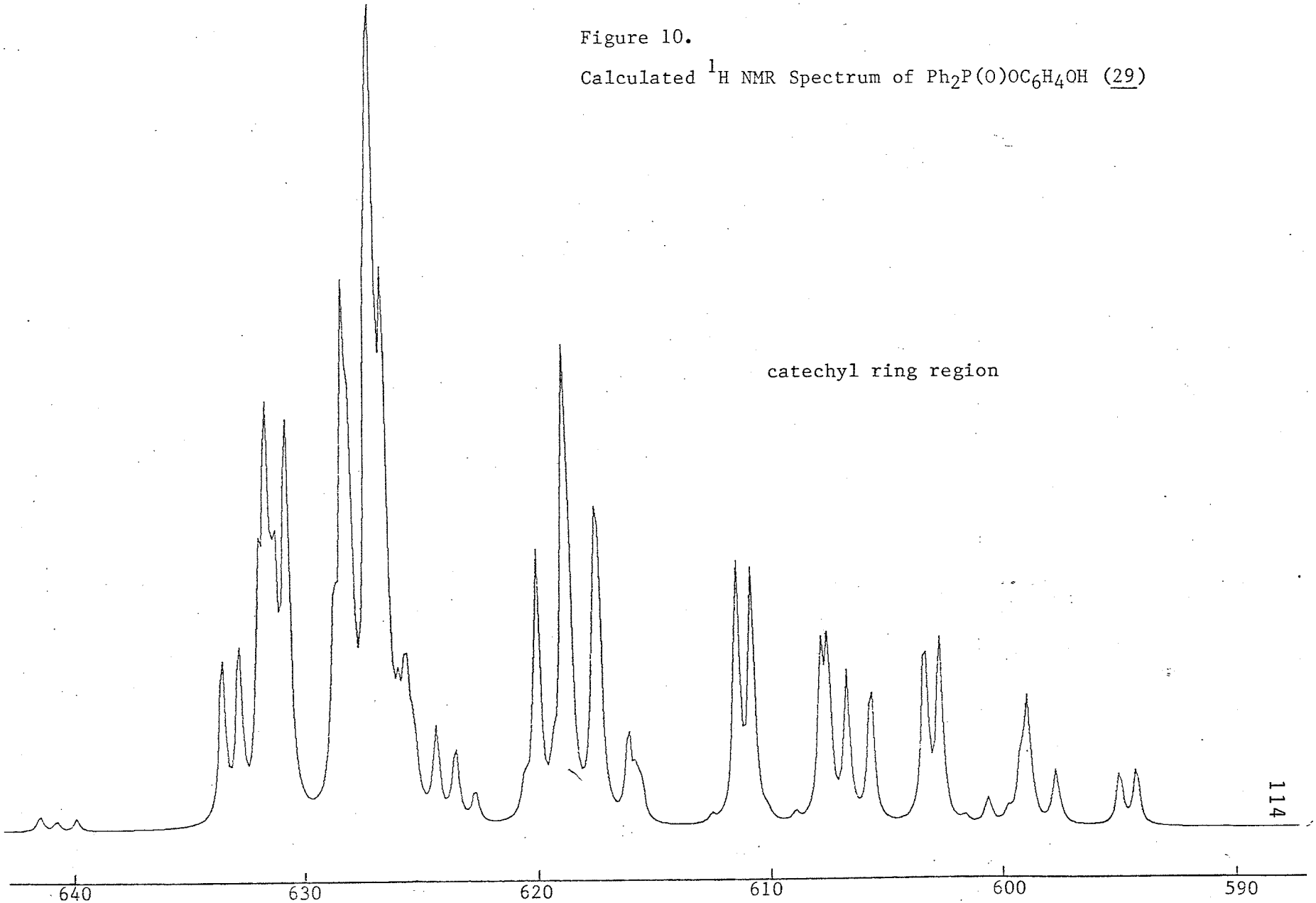
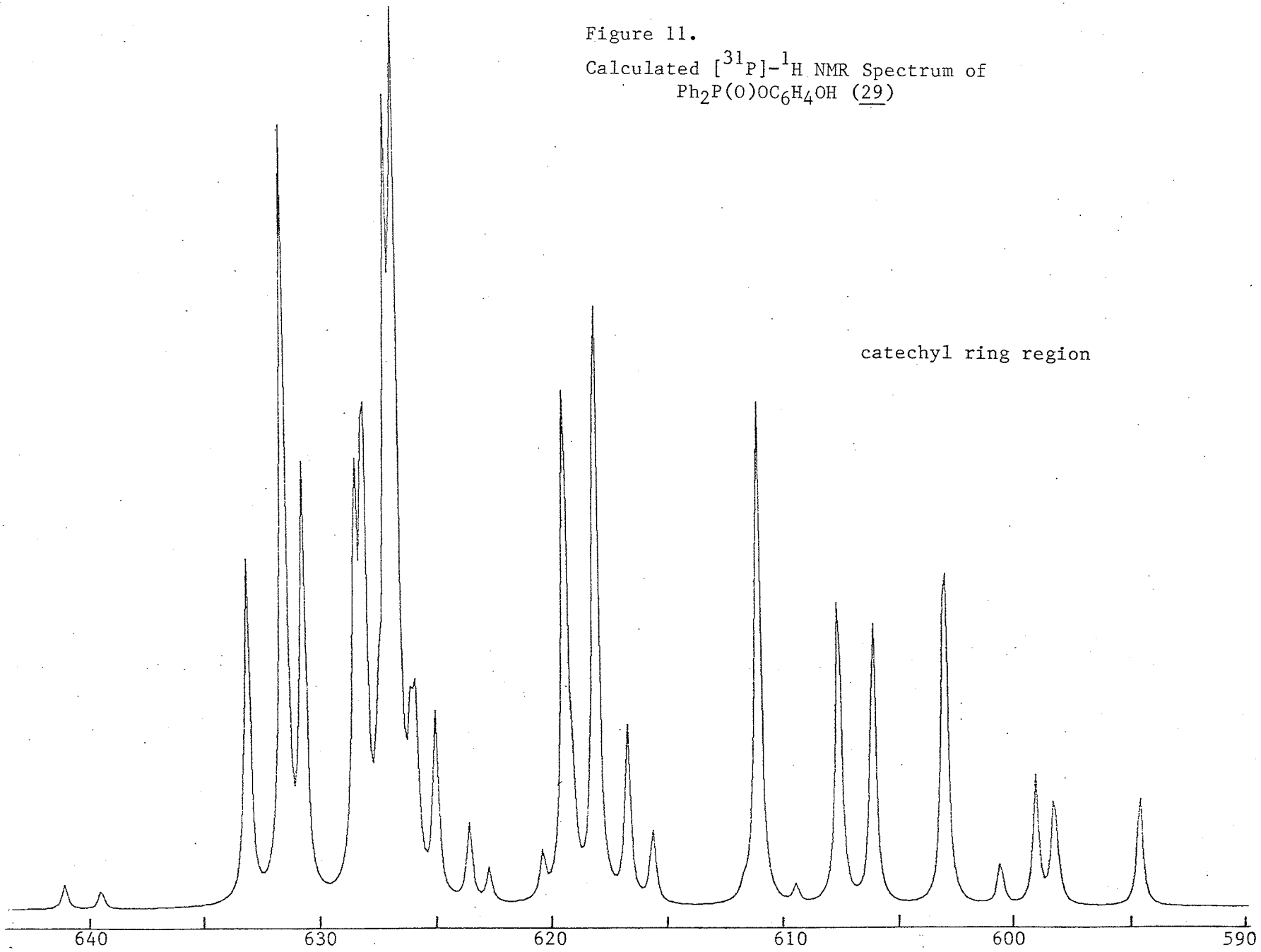


Figure 11.

Calculated $[^{31}P]-^{1}H$ NMR Spectrum of $Ph_2P(O)OC_6H_4OH$ (29)



49 (46,49). When dimethylsulphoxide-d6 was used as solvent and the temperature was increased, the sample began to decompose; Munoz (113), too, noted the decomposition of phosphates at elevated temperatures in DMSO. The use of benzene-d6 as solvent posed a different problem. Due to aromatic solvent induced shifts, there was now an overlap of the phenyl and catechyl regions. The relatively low boiling point of $CDCl_3$ limited the increase in the temperature when it was employed as a solvent for 29. In each of these cases, therefore, it was not possible to observe coalescence of the separate signals to yield a symmetrical spectrum.

Several $^1H$ NMR spectra of compound 29, with various amounts of pyridine-d5 added, were obtained. Appendix C provides a derivation of a model, which is consistent with Scheme 9, for the deprotonation of the hydroxyl group of 29 and the relevant data are provided in Table 14; these data are also illustrated on Graph 7.

The $^1H$ chemical shift of the hydroxyl group is seen to move regularly to low field in the direction of the expected chemical shift of the protonated pyridine, about 17 ppm (extrapolation of the data of Schaefer et al. (114), yields a value of 16.9 ppm for the chemical shift of the $N\text{-}H^+$ proton of pyridine hydrochloride in $CH_2Cl_2$, in the absence of moisture; as well, Brzezinski and Zundel (115) report that the $N\text{-}H^+$ proton chemical shifts of the dipyridyl compounds studied ranged from 15.8 to 17.9 ppm). The signal

Graph 7. Effect of Added Pyridine on Hydroxyl Proton Shift for Compound 29.

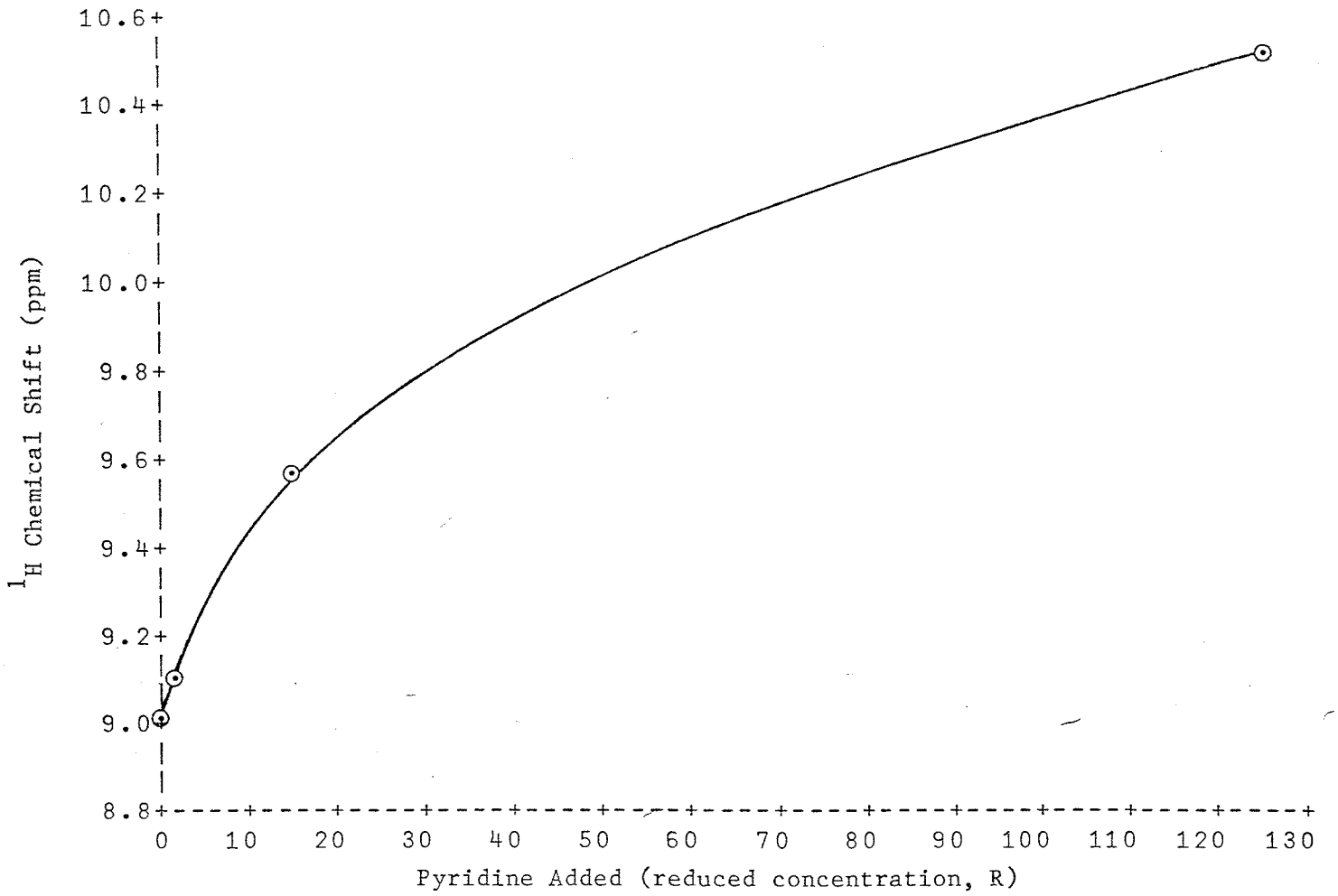


TABLE 14

$^{1}H$ NMR Chemical Shifts of $Ph_2P(O)OC_6H_4OH$ (29) (in $CD_2Cl_2$): Pyridine as Added Base.

| Cmpd (mol/L) | Base (mol/L) | R | ($\frac{1}{2}$H) |
|---|---|---|---|
| 0.0296 | 0.00 | 0.00 | 9.01 |
| 0.0355 | 0.065 | 1.82 | 9.10 |
| 0.0355 | 0.529 | 14.9 | 9.57 |
| 0.0228 | 2.86 | 125. | 10.52 |

is also seen to broaden significantly as more pyridine is added. However, with only four data points, no statistical analysis is possible and the observations are included only as qualitative evidence to support the conclusions drawn from the $^{31}P$ NMR data.

4) $^{13}C$ NMR Studies.

The $[^{1}H]$-$^{13}C$ NMR spectrum of $Ph_2P(O)OC_6H_4OH$, 29, in $CD_2Cl_2$ was obtained and is shown in Figure 7; the relevant data are given in Table 3. In addition, the $[^{1}H]$-$^{13}C$ NMR spectrum of a sample of 29 in $CDCl_3$, with added triethylamine, was obtained. However, as was the case with the $^{1}H$ spectra, there was no evidence of equilibration. The evidence from $^{13}C$ NMR, then, also seems to indicate that if the ring-closure and ring-opening is fast (as evidenced by $^{31}P$ NMR), then in each case the same P-O bond is involved, while the original ester P-O bond remains intact.

Other Compounds, Reactions, and NMR Studies.

1) cis-3-Diphenylphosphinatotetrahydro-3,4-furandiol(30).

The synthesis of compound 30, from 27, was analogous to the synthesis of 29. This compound, like 29, underwent an irreversible change on melting which, here too, may be explained as a redox disproportionation (93). The initial elemental analysis was found to be high in carbon: calculated (for $C_{16}H_{17}O_4P$) C, 63.16; H, 5.63%; found C, 66.11; H, 4.86%. Since the calculated C/H percentages for the hydrolysis product of 30, diphenylphosphinic acid ($C_{12}H_{11}O_2P$), 31, are C, 66.06 and H, 5.08%, and corresponded more closely with the values found in the analysis than did the calculated values for 30, it was decided to synthesize an authentic sample of the diphenylphosphinic acid, 31, for comparison by NMR. The $^{31}P$ NMR spectrum of 30 was obtained: only one signal was visible, ($^{31}P$) = 32.33 ppm in $CDCl_3$ and it was significantly different from that of 31: ($^{31}P$) = 25.7 ppm (in ethanol). The results of a subsequent elemental analysis were good: calculated (for $C_{16}H_{17}O_4P$) C, 63.16; H, 5.63%; found C, 63.35; H, 5.47%.

2) Grignard Reactions: Diphenylphosphinous Chloride and Compounds 36, 37, and 38.

The attempts to synthesize compounds 36, 37, 38, and diphenylphosphinous chloride, where the first stage in the synthesis was a Grignard reaction, all met with failure. On some occasions the in situ formation of the Grignard reagent was successful, as evidenced by the gradual disappearance of, and local ebulition in the vicinity of, the magnesium metal, and the next stage of the synthesis was begun. However, on other occasions, the magnesium remained unreacted. The reaction conditions appeared to be the same on each occasion. The surfaces of the magnesium were clean, a tiny amount of $I_2$ had been added (116a,117), and the mixture was heated very gently under reflux. Great care was taken to avoid moisture: the diethyl ether was stored over Na metal and the glassware was dried at 150°C (see Experimental section). However, the results were not reproducible; inconsistent results with Grignard reagents and Grignard reactions were experienced generally in this laboratory around this time. However, other than a cursory examination of certain factors, an in-depth investigation into the possible causes, which was beyond the scope of this thesis, was not carried out.

On those occasions when the formation of the Grignard reagent proceeded well, other problems occurred. In general it was not possible to isolate the final

products: either attempted distillations, at atmospheric and at reduced pressures, resulted in decomposition, or a large number of products were formed, making separation and identification difficult.

One other major problem was encountered, again only on some occasions. This was the apparent hydrolysis of diethylphosphoramidous dichloride, 33, in diethyl ether. This occurred despite the precautions taken against moisture. In fact, $PCl_3$ did not hydrolyze under the identical conditions, using ether from the same source. A potassium iodide test for peroxides (116b) was negative. No explanation for any of these occurrences has yet been found.

3) Friedel-Crafts Reactions.

When $PCl_3$, $AlCl_3$, and benzene were heated under reflux in order to obtain $Ph_2P(O)Cl$, via $Ph_2PCl$, there was some evidence of the substitution of two phenyl groups for two of the chlorine atoms of $PCl_3$: some $Ph_2P(O)OH$ was isolated after contact of part of the mixture with the atmosphere. However, attempted distillation of the desired product resulted only in the formation of a viscous mass which could not be distilled.

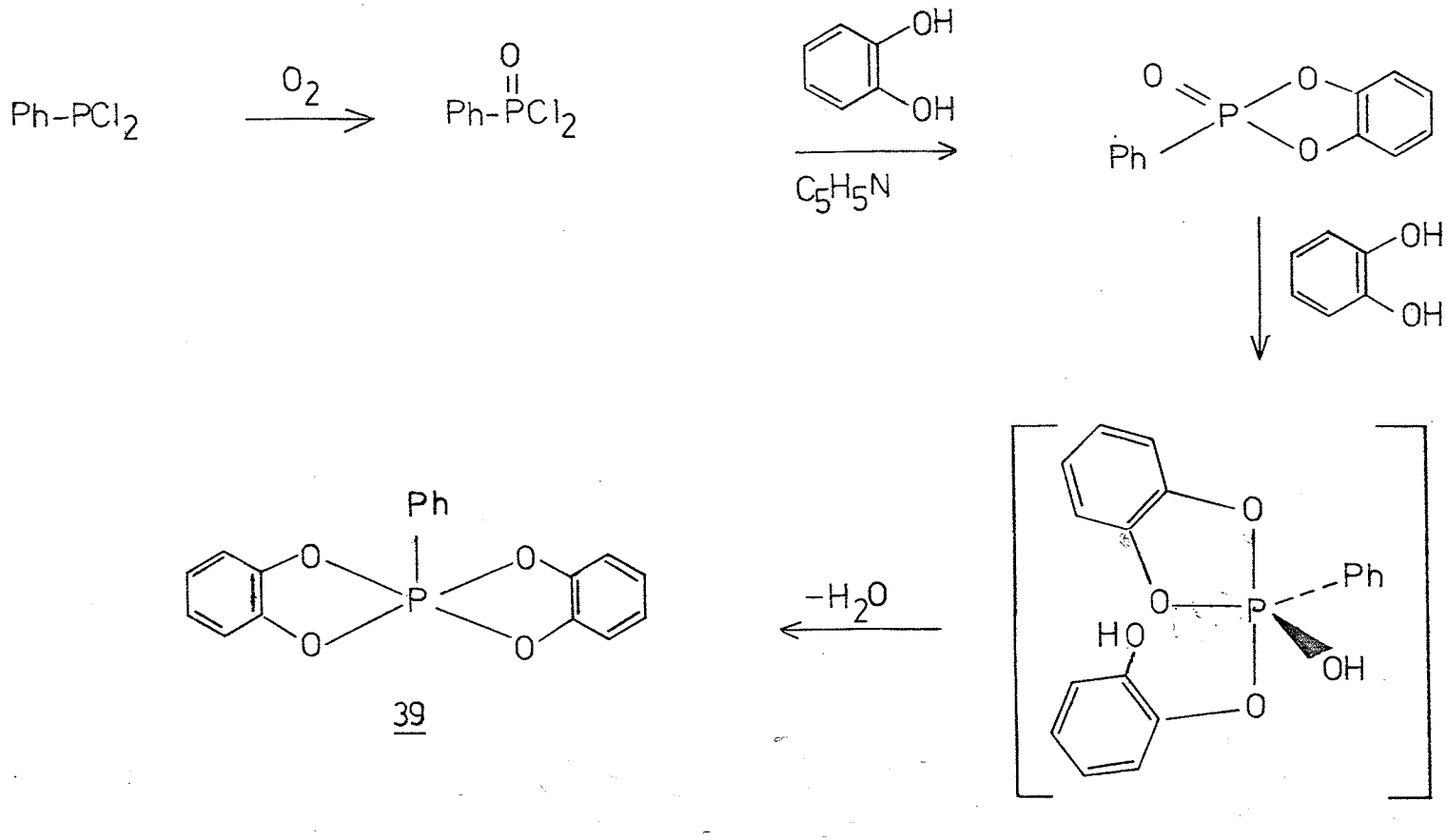
The attempted utilization of $Ph_2P(O)Cl$ in situ to produce $Ph_2P(O)OC_6H_4OH$, 29, gave an interesting result. The major initial product was, in fact, the monosubstituted $PhPCl_2$ as evidenced by the product of the subsequent

reactions with catechol in the presence of pyridine. The reactions are shown in Scheme 11 and bear some resemblance to the reaction scheme outlined by Koizumi (47).

## Summary and Conclusions.

In this thesis, the synthesis of two new compounds, 2-hydroxyphenyldiphenylphosphinate, 29, and cis-3-diphenylphosphinatotetrahydro-3,4-furandiol, 30, was carried out and was confirmed by elemental, NMR, and mass spectral analyses. As well, detailed NMR studies on these and other compounds, notably 2-hydroxy-1,1,2,2-tetrakis(trifluoromethyl)ethyldiphenylphosphinate, 26, and the glycerol phosphates, 1 and 2, were carried out. Two other new compounds were also synthesized, but were not fully characterized: 2-trimethylsiloxyphenyldiphenylphosphinate, 32, and 2-hydroxyphenyl-bis(pentafluorophenyl)phosphinate, 41.

It was the intent of this study to obtain evidence, by NMR, for rapid chemical exchange in these molecules. Schemes 7, 9, and 10 outline the processes by which such exchange is postulated to take place. In fact, no exchange was observed in the NMR spectra of the glycerol phosphates. For compound 26, rapid chemical exchange was observed in both the $^{19}F$ and $[^{19}F]$-$^{13}C$ NMR spectra, at ambient temperature. Pyridine had been added to the sample to promote the nucleophilic ring-closure by abstraction of the hydroxyl proton, and no exchange was observed in the absence of pyridine.




Scheme 11. Synthesis of $(C_6H_4O_2)_2PPh$ (39) from $PhPCl_2$

In the case of compound 29, addition of various bases to the sample was observed ($^{31}P$ NMR) to promote rapid ring-closure, but no equilibration of $^{1}H$ or $^{13}C$ NMR signals was observed. If an appropriate solvent can be found, then further NMR studies of 29, with or without added base, may also reveal rapid equilibration at elevated temperatures. The addition of trifluoroacetic acid to a sample of 29, resulting in a low-field shift of the $^{31}P$ signal, would also appear to be worthy of closer examination. At the present time it is not possible to choose between the three possible processes of Scheme 10.

The difference in behavior of 26, where equilibration was rapid, and 29 probably lies in the highly electronegative $CF_3$ groups of the former. It is known, for example, that cyclic 5- and 6-coordinate structures with highly electronegative groups tend to be more stable, relative to their 4- and 5-coordinate (respectively) ring-opened isomers, than are those with less electronegative groups (38,118).

## Appendix A

$^{31}$P NMR: Two-Step Mechanism.

Following is the derivation of the equation representing the 'two-step' mechanism. The mechanism is

$$A + B \rightleftharpoons C + D \quad (1)$$

$$C \rightleftharpoons F \quad (2)$$

where A represents compound 29 and C is its conjugate base,

B represents the organic base added and D is its conjugate acid,

and F represents the ring-closed phosphorane oxide anion, 55-H$^+$.

The equilibrium constants, K1 and K2, are defined as

$$K1 = (C)(D)/(A)(B) \quad (3)$$

$$K2 = (F)/(C) \quad (4)$$

where A, B, C, D, and F now represent molar concentrations.

Equation (4) can be modified to give

$$(K2+1) = (F/C) + (C/C) = (F+C)/(C) \quad (5)$$

while eq.(3) can be rearranged to

$$D = K1(A)(B)/(C) \quad (6)$$

The 'charge-balance' equation is

$$D = F + C \quad (7)$$

and thus

$$C = D/(K2+1) \quad (8)$$

The total concentrations of A and B are given by $A_0$ and $B_0$, respectively. Therefore,

$$A = A_0 - C - F = A_0 - D \quad (9)$$

$$B = B_0 - D \quad (10)$$

and eq.(6) becomes

$$D = (K1)(A_0-D)(B_0-D)/(D/(K2+1)) \quad (11)$$

Rearrangement of eq.(11) into the standard quadratic form

$$D^2(J-1) - D(J)(M) + J(A_0)(B_0) = 0 \quad (12)$$

where $J = K1(K2+1)$

and $M = A_0 + B_0$

and then solving for D by the quadratic formula gives

$$D = ((J*M) +/- SQRT(J^2M^2-4J(J-1)A_0B_0))/(2J-2) \quad (13)$$

Only the negative root in eq.(13) has any physical significance.

Now, the observable in the system is the $^{31}P$ NMR chemical shift (CS) which is the weighted mean of the limiting shifts of the three species A, C, and F.

$$CS = (A*DA + C*DC + F*DF)/A_0 \quad (14)$$

where DA, DC, and DF are the limiting shifts of A, C, and F, respectively.

Substituting eqs.(4) and (9) into (14) gives

$$CS = (DA(A_0-C-K2(C)) + DC(C) + K2(C)DF)/A_0 \quad (15)$$

Substitution of eq.(8) and subsequent simplification leads to the model

$$CS = DA - D(DA(K2+1) - DC - (K2)DF)/(A_0(K2+1)) \quad (16)$$

## Appendix B

### $^{31}$P NMR: One-Step Mechanism.

The 'one-step' mechanism is given in equation (1) below.

$$A + B \rightleftharpoons D + F \qquad (1)$$

where A represents compound 29,

B represents the organic base added and D is its conjugate acid,

and F represents the phosphorane oxide anion, 55-$H^+$.

The equilibrium constant is defined as

$$K = (D)(F)/(A)(B) \qquad (2)$$

where A, B, D, and F now represent molar concentrations.

The 'charge-balance' equation is

$$D = F \qquad (3)$$

and the total concentrations of A and B are represented by $A_0$ and $B_0$, respectively. Therefore,

$$K = F^2/((A_0-F)(B_0-F)) \qquad (4)$$

and

$$F^2 = K(F^2 - F(A_0+B_0) + A_0B_0) \qquad (5)$$

By the quadratic formula

$$F = (K*M +/- SQRT(K^2M^2-4K(K-1)A_0B_0))/(2(K-1)) \qquad (6)$$

where $M = A_0 + B_0$. Only the negative root in eq.(6) has physical significance.

The observable is the $^{31}P$ NMR chemical shift (CS) which is the weighted mean of the limiting shifts, DA and DF, of A and F, respectively.

$$CS = (A*DA + F*DF)/A_0 \quad (7)$$

Since $A = A_0 - F$

$$CS = (DA(A_0-F) + (F)DF)/A_0 \quad (8)$$

Upon simplification, the model is given as

$$CS = DA + F(DF-DA)/A_0 \quad (9)$$

## Appendix C

$^1$H NMR: A Model Representing Proton Transfer.

The equilibrium for the proton transfer is

$$A + B \rightleftharpoons C + G \qquad (1)$$

where A is compound 29 and G is its conjugate base, whether open-chain or ring-closed,

and B is the organic base added and C is its conjugate acid.

The equilibrium constant is defined as

$$K = (C)(G)/(A)(B) \qquad (2)$$

Following an analysis similar to that outlined in Appendix B, one obtains the model

$$CS = DA + C(DC-DA)/A_0 \qquad (3)$$

where CS is the observed $^1$H chemical shift of the proton undergoing transfer and is the weighted mean of the limiting shifts, DA and DC, of A and C, respectively, and where $A_0$ is the total concentration of A.

## Appendix D

$^{31}$P NMR: A Model for Protonation of the Phosphoryl Group.

The equilibrium can be represented as

$$A + B \rightleftharpoons C + D \qquad (1)$$

where A is compound 29 and C is its conjugate acid, and B is the organic acid added and D is its conjugate base.

The equilibrium constant is defined as

$$K = (C)(D)/(A)(B) \qquad (2)$$

Following an analysis similar to that outlined in Appendix B, one obtains the model

$$CS = DA + C(DC-DA)/A_0 \qquad (3)$$

where CS is the observed $^{31}$P chemical shift and is the weighted mean of the limiting shifts, DA and DC, of A and C, respectively, and where $A_0$ is the total concentration of A.

## REFERENCES


1. B. D. Davis, R. Dulbecco, H. N. Eisen, H. S. Ginsberg, and W. B. Wood, Jr, Microbiology, 2nd ed., Harper & Row, Hagerstown, MD (1973), pp.343-4, 238, 242

2. A. L. Lehninger, Biochemistry, 2nd ed., Worth Publishers, New York (1975), p.322

3. J. R. Cox, Jr, and O. B. Ramsay, Chem. Rev. 64 317 (1964), and references therein.

4. T. C. Bruice and S. J. Benkovic, Bioorganic Mechanisms, Vol. II, W. A. Benjamin, New York (1966). (a) p.42-3, and references therein; (b) p.18, and references therein; (c) p.61; (d) pp.37,41

5. D. G. Oakenfull, D. I. Richardson, Jr, and D. A. Usher, J. Am. Chem. Soc. 89 5491 (1967)

6. M. C. Bailly, Compt. Rend. 206 1902 (1938)

7. P. E. Verkade, J. C. Stoppelenburg, and W. D. Cohen, Rec. trav. chim. Pays-Bas 59 886 (1940)

8. E. Chargaff, J. Biol. Chem. 143 455 (1942)

9. D. M. Brown, G. E. Hall, and R. Letters, J. Chem. Soc. 3547 (1959)

10. J. Kumamoto, J. R. Cox, Jr, and F. H. Westheimer, J. Am. Chem. Soc. 78 4858 (1956); (b) see note 11), p.4860

11. H. G. Khorana, G. M. Tener, R. S. Wright, and J. G. Moffat, J. Am. Chem. Soc. 79 430 (1957)

12. E. T. Kaiser and K. Kudo, J. Am. Chem. Soc. 89 6725 (1967)

13. J. R. Cox, Jr, R. E. Wall, and F. H. Westheimer, Chem. Ind. 929 (1959)

14. L. Kugel and M. Halmann, J. Am. Chem. Soc. 89 4125 (1967)

15. D. M. Brown, "Phosphorylation" in Advances in Organic Chemistry, Vol. 3, R. A. Raphael, E. C. Taylor, and H. Wynberg (eds), Wiley-Interscience, New York (1963), p.81-2, and references therein.

16. D. M. Brown and D. A. Usher, Proc. Chem. Soc. 309 (1963)

17. T. Ukita, N. A. Bates, and H. E. Carter, J. Biol. Chem. 216 867 (1955)

18. F. H. Westheimer, Acc. Chem. Res. 1 70 (1968), and references therein.

19. R. Luckenbach, Dynamic Stereochemistry of Pentaco-ordinated Phosphorus and Related Elements, Georg Thieme Publishers, Stuttgart (1973). (a) p.96-7; (b) p.221-3, and references therein; (c) p.3-5; (d) p.223-7; (e) p.2; (f) p.9; (g) p.9-10; (h) p.101-4

20. J. Emsley and D. Hall, The Chemistry of Phosphorus, Harper & Row, London (1976). (a) p.329-30; (b) p.327-8; (c) p.336-8, and references therein.

21. P. C. Haake and F. H. Westheimer, J. Am. Chem. Soc. 83 1102 (1961)

22. P. Gillespie, F. Ramirez, I. Ugi, and D. Marquarding, Angew. Chem. Int. Ed. Engl. 12 91 (1973), and references therein.

23. E. A. Dennis and F. H. Westheimer, J. Am. Chem. Soc. 88 3432 (1966)

24. D. Samuel and B. L. Silver, "Oxygen Isotope Exchange Reactions of Organic Compounds" in Advances in Physical Organic Chemistry, Vol. 3, V. Gold (ed.), Academic Press, London (1965), p.177

25. R. S. Berry, J. Chem. Phys. 32 933 (1960)

26. N. K. Hamer, J. Chem. Soc., C, 404 (1966)

27. K. F. Purcell and J. C. Kotz, Inorganic Chemistry, Saunders, Philadelphia (1977). (a) p.403; (b) p.404

28. R. R. Holmes, Acc. Chem. Res. 5 296 (1972)

29. I. Ugi and F. Ramirez, Chem. Brit. 8 198 (1972)

30. I. Ugi, D. Marquarding, H. Klusacek, and P. Gillespie, Acc. Chem. Res. 4 288 (1971)

31. F. Ramirez and I. Ugi, Bull, Soc. Chim. France 453 (1974)

32. D. Hellwinkel, "Penta- and Hexaorganophosphorus Compounds" in Organic Phosphorus Compounds, Vol. 3, G. M. Kosolapoff and L. Maier (eds), Wiley-Interscience, New York (1972). (b) p.234; (c) pp.266,284,288,289; (d) p.193-4, and references therein; (e) p.289

33. H. Wunderlich, D. Mootz, R. Schmutzler, and M. Wieber, Z. Naturforsch. 29b 32 (1974)

34. T. E. Clark, R. O. Day, and R. R. Holmes, Inorg. Chem. 18 1668 (1979)

35. R. K. Oram and S. Trippett, J. Chem. Soc. (Perkin I) 1300 (1973), and references therein.

36. D. Schomburg, O. Stelzer, N. Weferling, R. Schmutzler, and W. S. Sheldrick, Chem. Ber. 113 1566 (1980)

37. A. Queen, A. E. Lemire, and A. F. Janzen, Int. J. Chem. Kinetics 13 411 (1981)

38. F. Ramirez, G. V. Loewengart, E. A. Tsolis, and K. Tasaka, J. Am. Chem. Soc. 94 3531 (1972)

39. E. A. Dennis and F. H. Westheimer, J. Am. Chem. Soc. 88 3431 (1966)

40. F. Covitz and F. H. Westheimer, J. Am. Chem. Soc. 85 1773 (1963)

41. D. G. Gorenstein, B. A. Luxon, J. B. Findlay, and R. Momii, J. Am. Chem. Soc. 99 4170 (1977)

42. D. G. Gorenstein, B. A. Luxon, and J. B. Findlay, J. Am. Chem. Soc. 101 5869 (1979)

43. F. Ramirez, M. Nowakowski, and J. F. Marecek, J. Am. Chem. Soc. 99 4515 (1977)

44. D. A. Usher, D. I. Richardson, Jr, and D. G. Oakenfull, J. Am. Chem. Soc. 92 4699 (1970)

45. I. Granoth and J. C. Martin, J. Am. Chem. Soc. 101 4618 (1979), and references therein.

46. G. Kemp and S. Trippett, J. Chem. Soc. (Perkin I) 879 (1979), and references therein.

47. T. Koizumi, Y. Watanabe, Y. Yoshida, and E. Yoshii, Tetrahedron Lett. 1075 (1974)

48. A. Munoz, M. Gallagher, A. Klaebe, and R. Wolf, Tetrahedron Lett. 673 (1976)

49. G. Kemp and S. Trippett, Tetrahedron Lett. 4381 (1976)

50. C. Bui Cong, A. Munoz, M. Sanchez, and A. Klaebe, Tetrahedron Lett. 1587 (1977)

51. A. Munoz, B. Garrigues, and M. Koenig, J. Chem. Soc. (Chem. Comm.) 219 (1978)

52. M. Volkholz, O. Stelzer, and R. Schmutzler, Chem. Ber. 111 890 (1978)

53. Y. Segall and I. Granoth, J. Am. Chem. Soc. 100 5130 (1978)

54. I. Granoth and J. C. Martin, J. Am. Chem. Soc. 100 5229 (1978)

55. Y. Segall and I. Granoth, J. Am. Chem. Soc. 101 3687 (1979)

56. R. Markham and J. D. Smith, Nature 168 406 (1951)

57. R. Markham and J. D. Smith, (a) Biochem. J. 52 552 (1952); (b) Biochem. J. 52 558 (1952)

58. A. J. Kirby and A. R. Fersht, "Intramolecular Catalysis" in Progress in Bioorganic Chemistry, Vol. 1, E. T. Kaiser and F. J. Kezdy (eds), Wiley-Interscience, New York (1971). (a) p.75, and references therein; (b) p.72

59. L. F. Fieser and M. Fieser, Reagents for Organic Synthesis, Vol. 2, Wiley, New York (1969), p.427

60. Y. Mehmet and J. B. Hyne, Phosphorus Sulfur 1 47 (1976)

61. D. Martin, A. Weise, and H.-J. Niclas, Angew. Chem. Int. Ed. Engl. 6 318 (1967)

62. Weygand/Hilgetag Preparative Organic Chemistry, G. Hilgetag and A. Martini (eds), Wiley, New York (1972). (a) p.1102; (b) p.711

63. R. Pollitt, M.Sc. Thesis, University of Manitoba, 1969

64. A. F. Janzen, A. E. Lemire, R. K. Marat, and A. Queen, in print.

65. F. H. Otey and C. L. Mehltretter, J. Org. Chem. 26 1673 (1961)

66. M. Mazurek and A. S. Perlin, Can. J. Chem. 41 2403 (1963)

67. M. M. Crutchfield, C. H. Dungan, J. H. Letcher, V. Mark, and J. R. Van Wazer, Topics in Phosphorus Chemistry, Vol. 5: P-31 Nuclear Magnetic Resonance, Wiley-Interscience, New York (1970). (a) p.282 and references therein; (b) p.242 and references therein; (c) p.238 and references therein; (d) p.280 and references therein; (e) p.275 and references therein; (f) p.444 and references therein; (g) p.289 and references therein;

68. K. Moedritzer, J. Am. Chem. Soc. 83 4381 (1961)

69. K. Moedritzer, L. Maier, and L. C. D. Groenweghe, J. Chem. Eng. Data 7 307 (1962).

70. W. J. P. Blonski, private communication.

71. I. M. Magdeev, Ya. A. Levin, and B. E. Ivanov, Zh. Obshch. Khim. 42 2415 (1972)

72. K. Goda, H. Gomi, M. Yoshifuji, and N. Inamoto, Bull. Chem. Soc. Japan 47 2453 (1974)

73. F. A. Henglein and J. Kramer, Chem. Ber. 92 2585 (1959)

74. L. Maier, Helv. Chim. Acta 51 1608 (1968)

75. R. A. Y. Jones and A. R. Katritzky, Angew. Chem. 74 60 (1962)

76. J. P. van Linthoudt, E. V. van den Berghe, and G. P. van der Kelen, Spectrochimica Acta 36A 315 (1980)

77. The Sadtler Standard Spectra, Sadtler Research Laboratories, Philadelphia (1966- ). (a) no. 9397; (b) no. 29

78. F. Ramirez, A. J. Bigler, and C. P. Smith, Tetrahedron 24 5041 (1968)

79. A. Skowronska, J. Mikolajczak, and J. Michalski, J. Chem. Soc. (Chem. Comm.) 791 (1975)

80. F. Ramirez, M. Nowakowski, and J. F. Maracek, J. Am. Chem. Soc. 98 4330 (1976)

81. G. Ya. Legin, Zh. Obshch. Khim. 46 545 (1976)

82. A. E. Senear, W. Valient, and J. Wirth, J. Org. Chem. 25 2001 (1960)

83. B. Buchner and L. B. Lockhart, J. Am. Chem. Soc. 73 755 (1951)

84. S. L. Buchwald, D. H. Pliura, and J. R. Knowles, J. Am. Chem. Soc. 104 845 (1982)

85. B. Serdarevich, J. Am. Oil Chem. 4 381 (1967)

86. G.-V. Roeschenthaler, K. Sauerbrey, and R. Schmutzler, Israel J. Chem. 17 141 (1978), and references therein.

87. J. A. Gibson, G.-V. Roeschenthaler, and R. Schmutzler, J. Chem. Soc. (Dalton) 918 (1975), and references therein.

88. D. Hellwinkel and H.-J. Wilfinger, Chem. Ber. 103 1056 (1970)

89. F. P. Boer, Acta Crystallogr. B28 1201 (1972)

90. H. R. Allcock and E. C. Bissell, J. Chem. Soc. (Chem. Comm.) 676 (1972)

91. P. Haake and C. E. Diebert, J. Am. Chem. Soc. 93 6931 (1971)

92. K. Goda, R. Okazaki, K. Akiba, and N. Inamoto, Bull. Chem. Soc. Japan 51 260 (1978)

93. W. A. Frank, "Phosphonous Acids (Thio-, Seleno-Analogs) and Derivatives" in Organic Phosphorus Compounds, Vol. 4, G. M. Kosolapoff and L. Maier (eds), Wiley-Interscience, New York (1972), p.310ff

94. W. B. Smith and T. W. Proulx, Org. Magn. Reson. 8 205 (1976)

95. K. N. Scott, J. Am. Chem. Soc. 94 8564 (1972)

96. L. F. Johnson and W. C. Jankowski, Carbon-13 NMR Spectra: A Collection of Assigned, Coded, and Indexed Spectra, Wiley-Interscience, New York (1972)

97. T. A. Modro, Can. J. Chem. 55 3681 (1977)

98. T. Schaefer and T. A. Wildman, Can. J. Chem. 57 450 (1979)

99. F. Lambert, M. Ellenberger, L. Merlin, and Y. Cohen, Org. Magn. Reson. 7 266 (1975)

100. S. Castellano and R. Kostelnik, Tetrahedron Lett. 5211 (1967)

101. A. Schmidpeter and H. Brecht, Z. Naturforsch. 24B 179 (1969)

102. Annual Reports on NMR Spectroscopy, Vol. 5B, E. F. Mooney (ed.), Academic Press, London (1973). (a) p.203 and references therein; (b) p.187 and references therein; (c) p.204 and references therein; (d) p.210 and references therein;

103. I. Granoth, R. Alkabets, and E. Shirin, J. Chem. Soc. (Chem. Comm.) 981 (1981)

104. SAS User's Guide: Statistics, 1982 Edition, A. A. Ray (ed.), SAS Institute Inc., Cary, NC, p.15ff

105. B. L. Shapiro and M. D. Johnston, Jr, J. Am. Chem. Soc. 94 8185 (1972)

106. M. Ezekiel and K. A. Fox, Methods of Correlation and Regression Analysis, 3rd ed., Wiley, New York (1959). (a) p.126-7; (b) pp.128,191,251

107. R. J. Senter, Analysis of Data, Scott, Foresman and Company, Glenview, IL (1969), p.241

108. A. Albert, "Ionization Constants" in Physical Methods in Heterocyclic Chemistry, Vol. 1, A. R. Katritzky (ed.), Academic Press, New York (1963), p.8-9

109. CRC Handbook of Chemistry and Physics, 56th ed., R. C. Weast (ed.), CRC Press, Cleveland (1975). (a) p. D-148; (b) p. D-151

110. C. A. Streuli, Anal. Chem. 30 997 (1958)

111. Quantum Chemistry Program Exchange 13 378 (1979)

112. D. S. Stephenson and G. Binsch, (a) J. Magn. Reson. 37 395 (1980); (b) J. Magn. Reson. 37 409 (1980)

113. A. Munoz, B. Garrigues, and M. Koenig, Tetrahedron 36 2467 (1980)

114. G. Kotowycz, T. Schaefer, and E. Bock, Can. J. Chem. 42 2541 (1964).

115. B. Brzezinski and G. Zundel, Chem. Phys. Letters 70 55 (1980).

116. A. I. Vogel, B. S. Furniss, A. J. Hannaford, V. Rogers, P. W. G. Smith, and A. R. Tatchell, Vogel's Textbook of Practical Organic Chemistry including Qualitative Organic Analysis, 4th ed., Longman, London (1978). (a) p.363; (b) p.270

117. L. F. Fieser, Organic Experiments, Heath, Boston (1964), p.91

118. K.-P. John, R. Schmutzler, and W. S. Sheldrick, J. Chem. Soc. (Dalton) 1841 (1974)