CONFORMATIONAL ANALYSIS OF SOME NOVEL ISOMERIC PHOSPHATE
ESTERS BY PHOSPHORUS NUCLEAR MAGNETIC RESONANCE SPECTROSCOPY

by

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B.Sc., University of British Columbia, 1966

A THESIS SUBMITTED IN PARTIAL FULFILMENT OF
THE REQUIREMENTS FOR THE DEGREE OF

MASTER OF SCIENCE
in the Department of
CHEMISTRY

We accept this thesis as conforming to the required standard

THE UNIVERSITY OF BRITISH COLUMBIA
April, 1969
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Date May 2, 1969
ABSTRACT

A series of isomeric, six-membered, cyclic phenyl phosphate esters has been obtained by column chromatography of the mixtures of isomers obtained by reaction of phenyl phosphorodichloridate with appropriate 1,3-diols. The conformational analysis of the isomers was undertaken using both $^1$H and $^{31}$P n.m.r. The basic conformation of the 2-oxo-2-phenoxy-1,3,2-dioxaphosphorinane ring system is that of a "flattened-chair". The thermodynamic free energy difference between "chair" conformations is sufficiently large for the basic ring to exist essentially in one favoured conformation, rationalized to have an axial phenoxy substituent.

The stereospecific nature of $^{31}$P-CH has been confirmed by using $^1$H n.m.r. to determine conformations.

Long-range, $^4$J, $^{31}$P-$^1$H coupling constants have been found to be stereospecific in nature and useful in facilitating assignment of conformations for methyl-substituted-2-oxo-2-phenoxy-1,3,2-dioxaphosphorinanes.

Similar ring systems having different substituents at phosphorus have been studied and the conformations of these derivatives are seen to differ depending on the nature of the phosphorus substituent. The conformation of a cyclic nucleotide has been determined from its $^{31}$P n.m.r. spectrum.

The use of computer programming techniques and hetero-
nuclear double resonance techniques, greatly facilitated the analysis of the n.m.r. spectra discussed.

An interesting deceptively-simple type of ABX n.m.r. spectrum has been found for many of these cyclic phosphate derivatives and the explicit analysis of this system is presented.
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ACKNOWLEDGEMENT

I wish to express my sincere appreciation to Dr. L.D. Hall for his patient guidance throughout this study and acknowledge valuable discussion with other members of this laboratory and Dr. C.A. Fyfe. I thank my wife and son for their infinite patience.
INTRODUCTION
Knowledge that the phosphorus atom plays a vital role in the chemistry of the life process has existed since the early years of this century. The original discovery that the presence of inorganic phosphate ions was essential to the process of alcoholic fermentation was followed by the discovery that many organic phosphate esters were intermediates in biosynthetic reactions. More recently, it has also been found that phosphorylation reactions effect the transfer and storage of energy in cells. Other phosphate esters form important structural components of cells and constitute the "molecular backbone" of the vitally important nucleic acids.

The study of the chemical synthesis and reactions, especially hydrolysis, of phosphate esters is now well developed (1). The synthesis of most of the naturally-occurring phosphate esters has been well described in the literature and it has been possible to totally synthesize polynucleotides. Such processes as the mechanism and relative rates of hydrolysis of differing phosphate esters and the relative ease of formation of cyclic phosphates from acyclic phosphates, have also been studied.

The development of the organophosphorus field as a whole has been extensive from a synthetic viewpoint, the different possible valence states of the phosphorus atom leading to a wide range of classes of compounds. Throughout the organophosphorus field and, in particular, concerning organophosphate esters, stereoisomeric and conformational properties of molecules have not,
in general, been investigated. The gross geometry of DNA is known to be helical but little of the detailed conformation in solution has been determined. The conformational analysis of mononucleotides by proton magnetic resonance, p.m.r., spectroscopy has been undertaken with some success but little is known about the conformation of the phosphate group in such systems. The conformational properties of the relatively more simple cyclic phosphates are similarly undetermined as are those of most organophosphorus heterocyclic compounds in general. The lack of a generally applicable technique for studying these properties is evident.

P.M.R. spectroscopy has been successfully developed as a technique for the study of the conformational properties of organic molecules in general. In particular, this technique has the distinct advantage when considering bio-organic molecules that it examines molecules in solution, potentially approaching the "in vivo" state.

Of the two fundamental experimental observables associated with p.m.r. spectroscopy, the chemical shift (δ), and the coupling constant (J), it is the coupling constant which has provided the greatest information with respect to molecular geometry. The dependence of the magnitude of the coupling constant between vicinal hydrogens (J_{HCH}) on the dihedral angle (ϕ) between the projected C-11 bonds is well known (2). This familiar $J = \cos^2 \phi$ function has been the subject of considerable modification (3)
in attempts to include the further apparent coupling constant dependencies on such things as deviations of the system from tetrahedral carbon, electronegativity of neighbouring substituents, and configurational effects of these latter. Basically, however, it is usually possible to derive an experimental plot of $J$ versus $\phi$ for a particular family of molecules if a few model compounds of known geometry are available. In this manner, dependencies of the coupling constant on factors other than the dihedral angle are kept to a minimum.

Using such an approach, conformational studies have recently involved similar dependencies of couplings of nuclei other than hydrogen. Considerable use has been made of known $J_{\text{HCCF}}$ dependencies on $\phi$ (4) and $^{13}\text{C}$ and $^{31}\text{P}$ dependencies are being developed (5).

A previous study by the author had established the partial angular dependence of vicinal POCH coupling constants (6). The analysis of the $^{31}\text{P}$ n.m.r. spectrum of 5,5-dimethyl-2-oxo-2-phenoxy-1,3,2-dioxaphosphorinane (I) showed that $J_{\text{trans}} >> J_{\text{gauche}}$. 

\begin{align*}
\text{I} & \quad J_{\text{POCH}_\text{e}} = 21.3 \\
& \quad J_{\text{POCH}_\text{a}} = 2.8
\end{align*}
It was suggested that POCH coupling constants might provide useful information concerning the conformations of phosphate esters in a similar way that p.m.r. couplings had previously facilitated studies of other organic systems. It further seemed likely that phosphorus-proton couplings should be more sensitive to changes in stereochemical environment than proton-proton couplings*

The initial purpose of the present study is concerned in part with the development of the above suggestion, namely, that $^{31}$P n.m.r. constitutes an effective and generally applicable technique for studying conformations of phosphate esters. Our approach has involved a study of a wide range of cyclic phosphate derivatives.

During the synthesis of the required derivatives, a novel type of isomerism at phosphorus has been discovered. Furthermore, a number of other interesting stereospecific dependencies of $^{31}$P n.m.r. parameters have been elucidated.

Methyl substituted six-membered cyclic phosphates appeared to be ideal model systems for the study. A wide variety of compounds were available via straightforward synthetic

* Reliable values for $J_{\text{HCCH}}$ average about 10 Hz. for $J_{\text{trans}}$ and about 2 Hz. for $J_{\text{gauche}}$. 
procedures. The phenyl esters* were chosen for a number of reasons: they are soluble in a variety of organic solvents, they are not expected to have pH and ionic dependent n.m.r. spectra, and phenyl p.m.r. resonances do not mask important ring proton resonances.

We were further attracted to derivatives of the 1,3,2-dioxaphosphorinane system because many of these are, in fact, important materials. Thus, the 2-hydroxy-2-oxo-dioxaphosphorinane ring system occurs in nature. Furthermore, certain derivatives have commercial importance as pesticides, lubricants, plasticizers, and nerve gases, among others. The results obtained were thus anticipated to have some general implications.

The main theme of this thesis then, is concerned with the synthesis and separation of cyclic phenyl phosphates and with a study of their n.m.r. spectra and conformations. The potential application of some of the results obtained during this work to biochemically important molecules is illustrated at the end of this thesis.

* 2-oxo-2-phenoxy-1,3,2-dioxaphosphorinanes
RESULTS AND DISCUSSION
This part of the present thesis has been divided into four main sections. The first two sections deal with the synthesis, separation and conformational analysis of several methyl-substituted, six-membered cyclic phenyl phosphates. Established n.m.r. parameter dependencies on structure are used to determine the conformational properties of the cyclic esters. The third section describes the stereospecific nature of n.m.r. parameters associated with the $^{31}$P nucleus as established and confirmed by the results of the first two sections. The final section is intended to bring the results of the present study into the perspective of their potential application to studies of phosphate derivative conformations in general, especially those concerning naturally occurring materials.

The isomeric 4,6-dimethyl-2-oxo-2-phenoxy-1,3,2-dioxaphosphorinanes

The most simple synthetic route to the 2-oxo-2-phenoxy-1,3,2-dioxaphosphorinane ring system involves reaction of an appropriate 1,3-diol with phenyl phosphorodichloridate (A). This reagent has been widely used under a variety of conditions to synthesize cyclic phenyl phosphate esters in good yield (7,8). In a previous study (6) by the author, reaction of A with 2,2-dimethylpropan-1,3-diol afforded a single crystalline product (I).
The n.m.r. spin system of I is formally of the type "AA'BB'MN3X"* for which explicit analysis of the observed n.m.r. transition frequencies and intensities, in terms of the n.m.r. parameters, is not possible. Fortunately, since many of the long-range coupling constants are very small, the observed spectrum was considerably more simple than that possible and a so-called "first-order analysis"** of the spectrum was immediately obtained.

* Using the notation of reference 9.

** The term "first-order analysis" is used to describe the assignment of coupling constants and chemical shifts to spectral splittings and multiplet centres respectively, as they appear experimentally. For "weakly coupled" (coupling constants small relative to chemical shift differences) spin systems, the errors involved are usually negligible. For more highly coupled systems, the first order analysis can be misleading and subject to considerable error.
It was from the first order analysis of the $^{31}$P spectrum that the stereospecific dependence of $J_{\text{POCH}}$ was first determined as $J_{\text{trans}} = 21.3\text{Hz}$. $J_{\text{gauche}} = 2.8\text{Hz}$. The explicit analysis of the complete n.m.r. spectrum of I has since been reconsidered in the light of heteronuclear double resonance experiments and with the aid of computer-simulated spectra. Pertinent aspects of the explicit analysis of the n.m.r. spectrum of I are presented in Appendix A and the data summarized in Table 1. The refined values for $J_{\text{POCH}}$ thus lead to a reformulation of the dependence, thus $J_{\text{trans}} = 22.5\text{ Hz}$. $J_{\text{gauche}} = 1.7\text{ Hz}$.

Throughout the present study, use has been made of both heteronuclear and homonuclear double resonance techniques and a modified LAOCOON III computer program to aid in spectral assignment and obtain accurate n.m.r. data where necessary. Use of these techniques is summarized in Appendix B.

In an attempt to explore the further generality of the above angular dependence, the synthesis of several other methyl-substituted 2-oxo-2-phenoxy-1,3,2-dioxaphosphorinanes was undertaken.

Whereas reaction of A with 2,2-dimethylpropan-1,3-diol afforded a single, crystalline product, a similar reaction

* Although a general explicit solution does not exist for many n.m.r. spin systems, computer methods enable numerical approximations, well within experimental error, to be made of the desired parameters, providing sufficient experimental data are available.
with a commercial sample of pentan-2,4-diol afforded a syrupy material (II), shown by TLC to have three components. The $^{31}p$ n.m.r. spectrum of the mixture (figure 1) showed three separate resonances, one of these having a large, $\approx 17$ Hz., splitting. Column chromatography (silica gel / ethyl acetate) of the syrupy mixture, monitored by TLC, provided an efficient means of separating the three components, labelled II(a), II(b), II(c), in order of decreasing Rf value. The resulting, crystalline component II(a) had m.p. 94°C. and $^{31}p$ chemical shift +125.8 p.p.m. (relative intensity =1) while the syrupy components II(b) and II(c) had $\delta^{31}p$ +125.9 p.p.m. (rel. int. =1) and +123.6 p.p.m. (rel. int. =1), respectively. These phosphorus chemical shifts are consistent with those of phosphate triesters in general. The elemental analyses of all three components are identical and consistent with that expected for structure II.

The 100 M.Hz. p.m.r. spectra (figure 2) of all three components are very similar and the general features of these spectra are consistent with attributing the three components to the
## Table 1

N.M.R. Parameters for 5,5-dimethyl-2-oxo-2-phenoxy-1,3,2-
dioxaphosphorinane

<table>
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<th>A</th>
<th>B</th>
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<td></td>
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<tr>
<td>$\tau \ H_{4a}$</td>
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<td></td>
</tr>
<tr>
<td>$\tau \ H_{4e}$</td>
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<td></td>
</tr>
<tr>
<td>$\tau \ Me_a$</td>
<td>8.74</td>
<td>9.16</td>
</tr>
<tr>
<td>$\tau \ Me_e$</td>
<td>9.16</td>
<td>9.32</td>
</tr>
<tr>
<td>$\delta^{31}P$</td>
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<td></td>
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<td><strong>Coupling Constants</strong></td>
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<td>4e,4a</td>
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<td>11.0</td>
</tr>
<tr>
<td>4e,6e</td>
<td>3.0</td>
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<td>4e,6a</td>
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</tr>
<tr>
<td>4e,P</td>
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<td>23.3</td>
</tr>
<tr>
<td>4a,6a</td>
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<td></td>
</tr>
<tr>
<td>4a,P</td>
<td>1.7</td>
<td></td>
</tr>
</tbody>
</table>

A. Room temperature CDC1\textsubscript{3}

B. -80\textdegree C. in CH\textsubscript{2}Cl\textsubscript{2}
$^{31}$P n.m.r. spectra of the 4,6-dimethyl-1,3,2-dioxaphosphorinanes

A: Spectrum of the unseparated mixture of isomers.  
B: Isomer II(a).  
C: Isomer II(b).  
D: Isomer II(c).
Figure 2a

$^1$H n.m.r. spectrum of 4,6-dimethyl-1,3,2-dioxaphosphorinane. Isomer II(a).

A: Normal spectrum. B: Spectrum obtained while irradiating $^{31}$P.
* Spinning sidebands of the methyl resonance.
\[ ^1H \text{n.m.r. spectrum of } 4,6\text{-dimethyl-1,3,2-dioxaphosphorinane. Isomer II(b).} \]
$^1H$ n.m.r. spectrum of 4,6-dimethyl-1,3,2-dioxaphosphorinane. Isomer II(c).

A: Normal spectrum. B: Spectrum obtained while irradiating $^{31}P$. 
three possible geometrical isomers of 4,6-dimethyl-2-oxo-2-phenoxy-1,3,2-dioxaphosphorinane depicted below.

\[
\begin{align*}
\text{H} & \quad \text{Me} & \quad \text{O} & \quad \text{PO} & \quad \text{O} & \quad \text{OPh} \\
\text{H} & \quad \text{Me} & \quad \text{O} & \quad \text{PO} & \quad \text{O} & \quad \text{OPh} \\
\text{H} & \quad \text{Me} & \quad \text{O} & \quad \text{PO} & \quad \text{O} & \quad \text{OPh}
\end{align*}
\]

Thus the spectra show a complex multiplet centered in the \( \tau 5.2 - 5.4 \) range, of relative intensity 2, due to protons on carbon atoms 4 and 6 being coupled to virtually every other nuclear species present. A further complex multiplet centred in the range \( \tau 8.0 - 8.2 \), of relative intensity 2, due to the methylene ring protons, is followed by methyl proton resonances of relative intensity 6 centered in the range \( \tau 8.5 - 8.7 \). The phenyl resonances at ca.\( \tau 2.8 \) of relative intensity 5, have not been illustrated.

The complete assignment of these p.m.r. spectra was facilitated by heteronuclear decoupling and the spectra obtained while irradiating the phosphorus resonances demonstrate, in comparison with the normal spectra, removal of extensive long-range, \( ^4J \) coupling of this nucleus into the methyl and methylene protons. Detailed spectral data for each of the isomers has been obtained.
in part, by a first order analysis and in part with the aid of computer-simulated spectra. This data is presented in table 2.

The appearance of a large, \(=17\text{Hz.}\) splitting in the \(^{31}\text{P}\) n.m.r. resonance of isomer II(b) implies a \textit{trans} POCH coupling in accord with the result from I. This enables assignment of the structure II(b), the cyclic phenyl phosphate ester of d,l-pentan-2,4-diol, as depicted, to this product. The presence of two, non-equivalent methyl resonances in the p.m.r. spectrum confirms this assignment.

![Diagram of IIb]

The absence of any large splittings in the \(^{31}\text{P}\) resonances of components II(a) and II(c) suggests \textit{gauche} POCH coupling relationships for these isomers. The p.m.r. spectra of these two isomers are virtually identical and the single methyl resonance is consistent with the structures II(a) and II(c).

![Diagrams of IIa and IIc]
Table 2

N.m.r. data for the isomeric 4,6-dimethyl-1,3,2-dioxaphosphorinanes

<table>
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<tr>
<th>CHEMICAL SHIFTS</th>
<th>τ 4e</th>
<th>τ 4a</th>
<th>τ 6e</th>
<th>τ 6a</th>
<th>τ 5e</th>
<th>τ 5a</th>
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<th>τ Me&lt;sub&gt;a&lt;/sub&gt;</th>
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<td></td>
<td>533.1</td>
<td></td>
<td>533.1</td>
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<tr>
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<td>520.0</td>
<td>816.1</td>
<td>793.5</td>
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<tr>
<td>II(c)</td>
<td></td>
<td>525.9</td>
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<td>525.9</td>
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<th>4e5e</th>
<th>4a6a</th>
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<tr>
<td>II(b)</td>
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<td>3.2&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>3.1</td>
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<td>0.7</td>
<td>2.3</td>
<td></td>
<td></td>
<td>6.4</td>
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</tbody>
</table>

<sup>a</sup> Unequivocal assignment has not been possible. Interchange of these values has been assumed for the discussion of this molecule in the text.
By using the observed steric dependence of $J_{P\text{CH}}$, it has been possible to assign structures and basic, approximate chair conformations to the three geometrical isomers of II.

Assignment of absolute configuration at the phosphorus atom, however, is based on a rationalization of certain circumstantial data. A discussion of the data available concerning configurational assignment at phosphorus is presented in Appendix C. A proposed rationale of the factors governing conformational preference in these compounds is also presented as the basis of the configurational assignments of this thesis. It is felt, however, that sufficient data is not yet available to confirm these assignments, and the configurations depicted, though internally consistent, are thus tentative.

More detailed conformational information about the "chair" structures of isomers II is available from the p.m.r. data for these compounds. As mentioned in the introduction, use of $^{3}J_{\text{HCCH}}$ coupling constants to determine dihedral angles between vicinal hydrogen atoms in organic systems has been widespread and a good deal is known of the quantitative limits of the method. In order to minimize many of the inherent inaccuracies of this type of application, the n.m.r. data of 2-oxo-2-phenoxy-1,3,2-dioxaphosphorinane (III) for which an X-ray structure determination is available, will be used as a standard.
Thus, gross effects of changes in total electronegativity of the system, in relative symmetry about the various carbon atoms, and in so-called "orientational effects" of the vicinal protons, are expected to be negligible* and comparisons of p.m.r. data of compounds II with this standard should provide insight to subtle conformational changes.

The n.m.r. spectrum of III has been previously studied by the author (6) and an interesting long-range, $^4J_{^3P-^1H}$, coupling constant dependence resulted from a first-order analysis of the C₅ methylene proton resonances. With the subsequent publication (11) of an X-ray determination of the structure of this molecule, the complete analysis of this n.m.r. system has been undertaken. Due to the very highly-coupled nature of this seven spin system, an approximate, first-order analysis of the n.m.r. spectrum was impossible.

* For a summary of the significance of these effects in general applications of the Karplus equation see reference 10.
Extensive use of a suitably modified version of the LAOCOON III computer program * provided the results presented in table 3, for a theoretical spectrum which corresponds closely to that observed experimentally for III. These results should provide an ideal model for relating p.m.r. data of other, similar, compounds to conformational properties, provided the preferred conformation of III is well determined.

The crystal structure of III, determined by X-ray diffraction techniques, has recently become available (11) and it is intended to assume the pertinent structural parameters of this result. There are two fundamental assumptions to be made in this regard. The first, that the shape of the ring in solution is either the same as, or very similar to that of the crystalline form, is a basic assumption which cannot easily be circumvented but must nonetheless be made in order to place the results of the present study in an absolute perspective. The final discussion of this thesis will deal more with this point. The second assumption to be made at this time is that the molecule in solution exists exclusively in one conformation. This assumption can be either confirmed or overcome by comparing the n.m.r. spectrum of the compound at room temperature with that obtained at very low temperatures**

* See Appendix B.

** For a discussion of low temperature n.m.r. experiments see page 53.
Table 3  

N.M.R. Parameters for 2-oxo-2-phenoxy-1,3,2-dioxaphosphorinane

<table>
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<tr>
<th>CHEMICAL SHIFTS</th>
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<th>τ5e</th>
<th>τ5a</th>
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<th>4a,5a</th>
<th>4a,6e</th>
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<th>4e,P</th>
<th>5e,5a</th>
<th>5e,P</th>
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<td>11.4ₐ</td>
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<td>0.0</td>
<td>2.9ᵈ</td>
<td>2.7</td>
<td>5.2ᵇ</td>
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<td>21.9</td>
<td>15.3</td>
<td>2.7</td>
<td>&lt;0.9</td>
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<td>5e,P</td>
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</tbody>
</table>

ₐ First order numbers.
ᵇ "probable error" 0.8 Hz.
ᶜ homonuclear spin-decoupling result
ᵈ Successive computer runs vary this value seriously since these transitions cannot be assigned directly, ± 1 Hz.
Unfortunately, we have not yet been able to satisfactorily perform this experiment due mainly to instrumental difficulties *.

At this time, on the basis of some preliminary low temperature n.m.r. results for I and X**, we feel that III exists in a single conformation to an extent of greater than 95%.

In terms of the above two assumptions we accept the conformation of III as depicted in figure 3. Essentially the structure is a cyclohexane-type chair which has been flattened and widened at the phosphorus end of the ring. The structural data around the ring fragment C₄-C₅-C₆, is identical to that for cyclohexane within experimental error, the flattening being exclusively found in the phosphorus end. From the data of table 3, it is seen that a $J_{POCH}$ trans value of 21.9 Hz corresponds to a dihedral angle of 173° and that a $J_{POCH}$ gauche value of 2.9 Hz corresponds to a dihedral angle of 67°.

The above values for $J_{POCH}$ trans and gauche are similar to those obtained for I and on this basis, the conformation of I is taken to be that of III. Having thus justified the preliminary conformational assignments of the isomers II using $J_{POCH}$, it is appropriate to now discuss their p.m.r. spectra.

---

* The low-temperature capability of the Varian HA-100 spectrometer (ca. -80°) is not sufficiently low to be sure that the possible equilibrium process would be slow enough. Also, the very high resolution of peaks required to properly analyze this 7-spin system is lost due to viscosity broadening at these temperatures.

** See Appendix A and p. 53 respectively.
Isomers II(a) and II(c) have very similar n.m.r. spectra and the data of table 2 is similar for each isomer. The differences which do exist for $J_{4a,5e}$ and $J_{4a,5a}$ are not sufficiently significant, beyond experimental error, to attribute to any difference in the conformations of the two molecules. In comparison with the data for III, it is seen that only the geminal, $5e$, $5a$, coupling constant does not agree within experimental error. Since the $4a$, $5e$ and $4a$, $5a$ coupling constants of II(a) and II(b) agree well with those of III, the conformation of the $C_4$-$C_5$-$C_6$ parts of these molecules is taken to be the same. The similarity of the $J_{P,4a}$ gauche couplings ($P,4a$) is taken to mean that the $P$-$O$-$C$-$H$ dihedral angles are similar. Thus, isomers II(a) and II(c) exist in the flattened-chair conformation typical of III. A satisfactory measure of the accuracy of this statement, based on other similar applications would be a ±5% limit on possible changes in dihedral angle for the relevant bonds.

The p.m.r. data for isomer II(b) is perhaps more interesting, since there are more comparisons possible due to asymmetry of the molecule. The trans-diaxial $4e,5a$ coupling constant for II(b) is smaller than for III by ca. 2.5Hz., $J_{4e,5e}$ is larger (by ca. 1.6Hz.) as is, perhaps, $J_{6a,5e}$ (by ca. 0.5Hz.). The $J_{P,4a}$ trans coupling of 17.0Hz. is somewhat smaller than for III and I by (ca. 3Hz.) Such data can usually be explained in one of three ways.
Either the molecule is undergoing rapid conformational inversion as in B, or it exists in a distorted conformation, or both.

For B, in which the molecule exists in two now "typical", flattened chair conformations which differ only in the configuration at the phosphorus atom, the room temperature n.m.r. data is expected to be the weighted average of that for each conformation. The observed n.m.r. coupling constants for II(b) are consistent with conformational "time-averaging" between the two "typical" conformations as in B. The 4a, 5a coupling constant (8.6 Hz.) would be expected to be somewhere between the values of 4e,5e (2.7 Hz.) and 4a,5a (11.4 Hz.) for III, depending on the relative populations of the two conformers. Similarly, the value for 4e,5e is somewhere between that of 4e,5e and 4a,5a for III.

The experimental values for $J_{4e,5a}$ and $J_{4a,5e}$ as well as those for $J_{P-O-C-H}$ and $J_{P-O-C-C-H}$ also agree well with the suggestion of a conformationally inverting system.
Figure 3

Structural Parameters of 2-oxo-2-phenoxy-1,3,2-dioxaphosphorinane*. 

<table>
<thead>
<tr>
<th>Central Bond</th>
<th>Dihedral Angle</th>
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</thead>
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<tr>
<td>P_2-O_1</td>
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</tr>
<tr>
<td>O_1-C_6</td>
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<tr>
<td>C_6-C_5</td>
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<tr>
<td>C_5-C_4</td>
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<td>C_4-O_3</td>
<td>52°</td>
</tr>
<tr>
<td>O_3-P</td>
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</tr>
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</table>

* From reference 11.
By assuming that the configuration at the phosphorus atom does not affect seriously the magnitudes of the individual couplings *, the relative populations at room temperature of the two conformations of II(b) may be calculated.

The expression $J_{\text{average}} = \alpha J_{B1} + (1-\alpha) J_{B2}$, where $\alpha$ is the fraction of the population in conformation B1, $J_{B1}$ is the value of the coupling constant for B1, and $J_{B2}$ is the value of the coupling constant for conformation B2, can be used. For the conformational equilibrium between B1 and B2, the value for $\alpha$ can be calculated using five different sets of coupling constants. The results, using III as the standard are as follows:

- $J_{\text{POCH}}$  \[ \alpha = 0.74 \]
- $J_{\text{P,CH}_3}$  ** \[ \alpha = 0.78 \]
- $J_{\text{P,H}_5}$  ** \[ \alpha = 0.62 \]
- $J_{5a,6a}$ \[ \alpha = 0.68 \]
- $J_{4e,5a}$ \[ \alpha = 0.92 \]

It is felt that the variation of these values is due to the variation in the accuracies of the proton-proton coupling constants as determined for III and II(b). That the values calculated from the two phosphorus couplings agree well, can be taken as a measure of the sensitivity with which these depend

---

* A good approximation in view of the similarity of the couplings for II(a) and II(c).
** Using the stereospecific dependence of these couplings discussed on pp.44-50 and using II(a) as the model.
on dihedral angles. Fortunately, the phosphorus-hydrogen coupling constants can often be accurately determined in systems for which the remaining p.m.r. analysis is difficult.

The low temperature n.m.r. spectrum (-80°C.) of II(b) was not entirely satisfactory* and values for $J_{4e,5e}$ and $J_{6a,5e}$ were not significantly different.

At this time it is not possible to firmly decide that II(b) is conformationally time averaging though the above observations tend to suggest this. The isomer B1, having the same configuration at phosphorus as I, II(a) and III, is expected to be the preferred one**.

The considerable number of $^4J$, long-range coupling constants determined for these isomers will be discussed later.

* See footnote bottom of p.22.
** See also Appendix C.
Further isomeric pairs of cyclic phenyl phosphates

In an attempt to explore the generality of the isomerisation at phosphorus as described in the previous section, several other "asymmetric" diols were reacted with phenyl phosphorodichloridate. The conformational analysis of some of the resulting isomeric phenyl phosphates was undertaken by p.m.r. and $^{31}$P.m.r. spectroscopy both in order to establish the generality of the "flattened chair" characteristics of the ring system and also to provide more data in support of the interesting long-range $^{31}P$-$^1H$ coupling observations for the system II.

In a now typical reaction, 2-methyl-pentan-2,4-diol was reacted with phenyl phosphorochloridate to give a semi-crystalline mixture of products IV.

The product mixture showed two components by TLC and had two resonances of about equal intensity in the $^{31}$P n.m.r. spectrum. Column chromatography of the mixture provided separation of a crystalline, faster-running (on TLC and column) component [IV(a)]
from a syrupy component [IV(b)]. The p.m.r. spectra of both isomers were virtually identical and consistent with the structures depicted below for the two expected isomers of 4,4,6-trimethyl-2-oxo-2-phenoxy-1,3,2-dioxaphosphorinane.

Assignment of the n.m.r. spectra of both isomers was effected by standard first order methods and subsequently confirmed by computer techniques. Due to the very highly-coupled nature of the C5 protons in both isomers, an unequivocal assignment of the n.m.r. spectra was impossible. As a result, some of the n.m.r. parameters have not been determined. Such data as are available are presented in table 4. In a manner analogous to that used to assign structures and conformations to isomers II, the n.m.r. data suggests that isomers IV(a) and IV(b) have identical, flattened-chair conformations, similar to that for III. Thus a small J_P-OCH implies an axial hydrogen at C6. A large vicinal 5a,6a coupling constant defines a trans diaxial relationship and the 5e,6a coupling constants compare favorably with that from III. Basically the same long-range 31P-1H
coupling constant dependencies are noted as before.

Similar results have been obtained from 4-methyl-2-oxo-2-phenoxy-1,3,2-dioxaphosphorinane (V). Reaction of phenylphosphorodichloridate with butan-1,3-diol provided a mixture of the isomeric phosphates. This mixture was readily separated into a crystalline isomer [V(a)] and a syrupy isomer [V(b)] by column chromatography.

The n.m.r. spectra of these compounds have been obtained and analyzed as completely as possible using techniques available. The n.m.r. parameters are listed in table 5. The data for V(a) suggest that the conformation of this molecule is identical to that for the model III. In particular, the large, 23 Hz., \( \text{trans} \) \( \text{POCH} \) coupling constant agrees well with that of III and I. The large \( 5a,6a \) \( \text{trans} \) diaxial coupling constant and the small \( 5e,6a \) \( \text{gauche} \) coupling constant are consistent with those for III. The conformation of V(a), depicted above, shows assignment of the presumably stable, equatorial phosphoryl oxygen configuration.
There has been insufficient data obtained from the highly complex n.m.r. spectrum of isomer V(b) to adequately describe the conformation of this molecule. The somewhat low values obtained for $J_{\text{POCH trans}}$ (=10 Hz.) and $J_{\text{POCCH}_3}$ (1.9 Hz.) tend to suggest that this molecule is undergoing rapid conformational inversion at room temperature and that there is an equilibrium mixture of significant populations of both conformations.
Table 4

N.M.R. Parameters for 4,4,6-trimethyl-2-oxo-2-phenoxy-1,3,2-dioxaphosphorinane

<table>
<thead>
<tr>
<th>CHEMICAL SHIFTS</th>
<th>( \tau_{\text{Me}_{4a}} )</th>
<th>( \tau_{\text{Me}_{4e}} )</th>
<th>( \tau_{\text{Me}_{6e}} )</th>
<th>( \tau_{6a} )</th>
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<th>( \tau_{5a} )</th>
<th>( \delta_{31P} )</th>
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<td>8.66</td>
<td>8.69</td>
<td>5.24*</td>
<td>8.20*</td>
<td>8.11*</td>
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<thead>
<tr>
<th>COUPLING CONSTANTS</th>
<th>( P_{\text{Me}_{4a}} )</th>
<th>( P_{\text{Me}_{4e}} )</th>
<th>( P_{\text{Me}_{6e}} )</th>
<th>( P_{6a} )</th>
<th>( H_{6,\text{Me}_{6}} )</th>
<th>( P_{5e} )</th>
<th>( P_{5a} )</th>
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<th>( 5e,6a )</th>
<th>( 5a,6a )</th>
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<tbody>
<tr>
<td>IV(a)</td>
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<td>2.85</td>
<td>2.65</td>
<td>1.3</td>
<td>6.30</td>
<td>2.3</td>
<td>1.0</td>
<td>14.7</td>
<td>3.5*</td>
<td>10.5*</td>
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<tr>
<td>IV(b)</td>
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<td>2.1</td>
<td>( \sim 2* )</td>
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* First order numbers only.
Table 5

N.M.R. data for 4-methyl-2-oxo-2-phenoxy-1,3,2-dioxaphosphorinane

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<th>τ6a</th>
<th>τ6e</th>
<th>δ³¹P</th>
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<table>
<thead>
<tr>
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<th>CH₃,P</th>
<th>6e,P</th>
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<tbody>
<tr>
<td>V(a)</td>
<td>6.5</td>
<td>2.8</td>
<td>22.7</td>
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<td>V(b)</td>
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<td>1.9</td>
<td>10ᵃ</td>
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</tr>
</tbody>
</table>

ᵃ ±5Hz.
As further support for the generality of formation of isomeric pairs of cyclic phenyl phosphates in reactions of unsymmetrical diols with phenyl phosphorodichloridate, several other compounds were made. In each case, the isomeric pairs of compounds could be separated readily by column chromatography. Thus both geometrical isomers of 5-methyl-5-nitro-2-oxo-2-phenoxy-1,3,2-dioxaphosphorinanone (VI), 5-methyl-2-oxo-2-phenoxy-1,3,2-dioxaphosphorinanone (VII), and 5,5-dimethyl-4-isopropyl-2-oxo-2-phenoxy-1,3,2-dioxaphosphorinanone (VIII) have been synthesized.

To this point in the discussion, we have been primarily concerned with delineation of a somewhat novel type of isomerization around the phosphorus atom in a series of cyclic phosphate esters. Since a considerable amount of synthetic work involving these ring systems exists in the literature (12) it is perhaps surprising that existence of this type of isomerization has not been previously noted. In particular, compounds IV and V have previously been reported by a different method (13), involving displacement of halogen on phosphorus by phenoxide.
ion, but the possibility of isomers was not discussed. It is hoped that the characterization of isomeric pairs of compounds by n.m.r. presented herein will enable the course of such displacement reactions on phosphorus to be more clearly recognized. The cyclic phenyl phosphates, synthesized using phenyl phosphorodichloridate, which have been reported in the literature (14) are expected to, in fact, consist of a 1:1 mixture of the two possible geometrical isomers at the phosphorus atom.

Prior to the publication of some of the preliminary results of the present study (15), a mixture of isomeric methyl phosphates as hydrolysis products of five-membered cyclic oxyphosphoranes, had been reported by Ramirez (16). The n.m.r. data for these five-membered cyclic methyl phosphates are included in the discussion of a Karplus-type relationship for $J_{POCH}$ to follow. Denney and Denney had also reported (17) the presence of isomeric six-membered cyclic methyl phosphates as oxidation products of certain cyclic methyl phosphites and reported separation of the methyl phosphate analogs of V by distillation and glpc. Recently, confirmation of the physical properties of IV, V and VIII has been published (18).

The use of $^{31}$P n.m.r. parameters has so far been restricted to application of the experimental observation from compounds III and I that $J_{POCH}$ trans is much greater than $J_{POCH}$ gauche. The conformations in solution of the seven
compounds of II, IV and V, have been considered in terms of this dependence and also from detailed study of the p.m.r. data. In a sense, detailed consideration of the p.m.r. data over-determines the system in question since the general shape of the ring system is implied from the phosphorus n.m.r. spectrum. The p.m.r. data, however, has been obtained in order both to confirm the generality of the $J_{\text{POCH}}$ dependence and also to give insight into interesting dependencies of long-range, $^4J$ phosphorus-hydrogen coupling constants, to be discussed.

The conformation of the parent, 2-oxo-2-phenoxy-1,3,2-dioxaphosphorinane ring system has been taken to be that of the flattened-chair described in the X-ray result. The activation energy required for the conformational inversion process which could take place, is assumed* to be accessible at room temperature. Thus the assumption made is that an equilibrium mixture of the two basic conformations possible exists and that the thermodynamic free energy difference between these is such that, at room temperature, one conformation predominates to the extent of greater than 95%. The conformation in which the phenoxy substituent is axial is taken to be the most stable. The structure of I is by analogy and isomers II(a), II(c), IV(a), IV(b) and V(a) are all taken to be similarly conformationally pure; isomers II(c) and IV(b) having the

* By analogy with this observation for other single six-membered ring systems.
opposite configuration at phosphorus. The free energy differences between the conformations of II(a), IV(a), and V(a) would be expected to be even greater than that for I and II in that classical non-bonded interactions of axial methyl groups in the inverted conformers, would be expected to further de-stabilize these structures. Presumably, the free energy differences attributed to these steric interactions of axial methyl groups are sufficiently large, compared with those of the axial-equatorial substituents at phosphorus, to populate the depicted conformations of II(c) and IV(b) (inverted configurations at phosphorus) by greater than 95%.

It is thus possible to estimate the thermodynamic free-energy difference of conformational preference at phosphorus as being much less than that of the conformational preference of two cis 1,3-methyl substituents. The suggestion that significant populations of both conformers of II(b) and V(b) exist at room temperature is consistent, in that the free-energy difference of substituents at phosphorus is now no longer greatly different than that for a single axial-methyl substituent.
Stereospecific dependencies of $^{31}$P n.m.r. parameters

Having now established the conformations of several sets of isomeric phosphates it is appropriate to more closely examine the nature of the $J_{POCH}$ dependence used. Although the terms $J_{\text{trans}}$ and $J_{\text{gauche}}$ have been used freely, it is evident from the X-ray data for III that $\text{trans}$ for this system has been used to imply a dihedral angle of 173° and $\text{gauche}$, similarly, 67°. Thus $J_{\text{trans}}$ and $J_{\text{gauche}}$ as used in the conformational analysis so far do not correspond to coupling constants for P-O-C-H dihedral angles of 180° and 60°. This distinction is an important one in considering applications of the results outside the basic 1,3,2-dioxaphosphorinane ring system. Two aspects of this are significant. One, the establishment of an experimental curve of $J_{P-O-C-H}$ vs. dihedral angle, requires a number of accurate coupling constants corresponding to a range of known dihedral angles. This curve would be of considerable value in considering conformations of different sized ring systems, as well as of some theoretical interest. The other important aspect of these coupling constant dependencies is their application to conformationally mobile systems (i.e. acyclic phosphate esters) which requires reliable values of $J_{POCH}$ for dihedral angles 180° and 60°. All of these more quantitative considerations require knowledge of the relative signs of the $J_{POCH}$ couplings.

It is not felt at this time that sufficient data exist
either in the literature or as a result of the present study to attempt to define a complete experimental plot of $J_{POCH}$ vs. dihedral angle but such data as are available has been plotted in figure 4. The superimposed curve is a typical Karplus-type curve* as theoretically formulated (19) for H-C-C-H fragments and has been included for comparison only.

Somewhat more successful at this time is a consideration of conformationally mobile, acyclic systems. The observed N.M.R. coupling of phosphorus into the hydrogen nuclei of a freely-rotating methyl group in a compound such as trimethyl phosphate (D) should be the weighted average of the rotamer coupling constants as in E, F and G. Thus, $J_{av.} = (J_{180} + 2J_{60})/3$ assuming the idealized rotamer condition that the energy minima occur at 120° intervals of rotation around the O-C bond. Using the values of $J_{trans}$ and $J_{gauche}$ for compound I, $J_{av.} = 8.7$ Hz..

\[ \text{CH}_3\overset{\text{O}}{\text{C}} \]
\[ \text{CH}_3\overset{\text{O}}{\text{P}} - \text{O} \]
\[ \text{OCH}_3 \]

D

* The $J_{HCCH}$ axis of this curve has been expanded to provide comparison with the somewhat larger $J_{POCH}$ data.
The experimental value for trimethyl phosphate is 11.2 Hz.

Presumably, the use of values not corresponding to exact 180° and 60° dihedral angles accounts for the largest part of this deviation, and, assuming the general characteristics of the Karplus curve (figure 4) to hold for $J_{PCH}$ vs. $\phi$, $J_{180}^o$ is expected to be larger than $J_{\text{trans}}$ and $J_{60}^o$ larger than $J_{\text{gauche}}$. At this time an estimate* of $J_{180}^o$ and $J_{60}^o$ is 25 Hz. and 3 Hz. respectively. These numbers now give a $J_{\text{av}}$ value of 10.3 Hz., in good agreement with the experimental number. Once reliable values for $J_{180}^o$ and $J_{60}^o$ have been established, the "reverse" process can be used to estimate the populations of different rotamers in any given system, using the observed value for $J_{PCH}$. An example of this

* These numbers are arrived at by extrapolating an assumed Karplus curve for $J_{PCH}$. The expected error in these numbers due to experimental error and the above assumption is ±2 Hz.
Figure 4

Plot* of $J_{POCH}$ vs. Dihedral Angle

- Reference 16, This molecule may be significantly time averaging.
- Reference 23, The original discovery that $J_{POCH}$ trans is greater than $J_{gauche}$, determined for tricyclic molecules.

* The curve is that of the Karplus equation(2) as derived for $J_{HCCH}$ couplings in ethane fragments.
kind of application using the above estimated values of $J_{180}$ and $J_{60}$, is presented in Appendix D. The probable accuracy of the resulting rotamer populations is likely to be ±5-10%. One very useful result from calculations such as these, however, is confirmation of the relative signs of the two coupling constants. The absolute sign of the averaged POCH coupling constant is known to be positive (20).

Although analysis of the n.m.r. spectrum of I, aided by computer techniques, results in assignment of similar signs for $J_{\text{trans}}$ and $J_{\text{gauche}}$, this could not be confirmed unambiguously by double resonance techniques due to the overall complexity of the n.m.r. spin system. However, since $J_{\text{av}}$ is positive, then $J_{\text{gauche}}$ and $J_{\text{trans}}$ must also be positive since the previously calculated $J_{\text{av}}$ (+8.7 Hz.) agrees more closely with experiment. Calculated values for $J_{\text{av}}$ of +6.4 Hz. and -6.4 Hz. would result from opposite signs of $J_{\text{gauche}}$ and $J_{\text{trans}}$. With the recent finding (21) that certain $^2J$ phosphorus hydrogen coupling constants have different signs for different relative molecular geometries, it was felt that a further, independent determination of $J_{\text{POCH}}$ relative signs would be appropriate. The six-membered cyclic phenyl phosphate derived from o-hydroxybenzyl alcohol (IX) was chosen, the expected "ABX" n.m.r. spin system being amenable to unequivocal relative sign determination by double resonance techniques.
A crystalline product IX was obtained upon reaction of phenyl phosphorodichloridate with o-hydroxybenzyl alcohol. Elemental analysis and n.m.r. data for the compound are entirely consistent with the structure depicted for the cyclic phenyl phosphate. The conformation of this molecule in solution is expected to be the "half-chair" (H) for which the dihedral angles of the P-O-C-H bonds are thought to be close* to those for the typical "flattened-chair" conformations discussed previously. The p.m.r. spectrum of this molecule is presented in figure 5.

* From studies of a molecular model, the differences are expected to be less than 10°.
This spectrum is quite unlike that expected for the "AB" part of a typical "ABX" spin system. This observed, so-called "deceptively-simple" spectrum has been previously reported in the literature (22) and was thought to be unsuitable for analysis. To the best of the author's knowledge, no explanation or analysis of this type of deceptively-simple spectrum has been reported in the literature.

Since a fortuitous equivalence of several n.m.r. parameters of an "ABX" spin system causes the observed phenomenon, the transition frequencies for this deceptively-simple spectrum can quite simply be related to those expected for a "typical" ABX spectrum. The deceptively-simple spectrum can thus be explicitly analyzed as is to give the n.m.r. parameters and the relative signs of the AX and BX coupling constants. This treatment is discussed in E* and has been confirmed by a computer-simulated spectrum for compound IX. A double resonance, "spin-tickling" experiment has also been done on this spin system and confirms that $J_{POCH_A} = 6.84$ Hz. and $J_{POCH_B} = 19.64$ Hz. have the same relative sign. Details of this experiment are also included in the appendix. Complete n.m.r. spectral data for compound IX are presented in table 6.

In summary of the currently available results on stereospecific dependencies of $^{31}$P-O-C-$^1$H coupling constants in phosphate triester systems the following observations are presented.

* Appendix E.
The POCM coupling constant is very sensitive to changes in relative geometry of the phosphate system, in particular, of the dihedral angle between the P-O and C-H bonds in the POCM fragment. This observation and the results of similar studies (23-30) on other classes of phosphorus derivatives are in general agreement with the suggestion that $^1H-^1H$ and $^{31}P-^1H$ couplings have similar stereospecificities, although magnitudes of the individual couplings differ.

The sign of $J_{POCM}$ does not change in going from a gauche to a trans arrangement of the coupling nuclei. The conformational analysis of further cyclic phosphate derivatives and quantitative estimates of rotamer populations for acyclic phosphate systems should be possible using the results of the present study.

The detailed study of the n.m.r. spectra and conformations of compounds II, III, IV and V gives considerable insight to the stereospecific behaviour of long-range, $^4J_{POCCH}$ coupling constants.

The magnitude of the $^4J$ phosphorus coupling through oxygen into a methyl group is dependent on the dihedral angle between the P-O and C-CH$_3$ bonds. A trans coupling ($J$) of 2.3 - 2.8 Hz. is observed in compounds II(a), (c), and IV(a)
from phosphorus into an **equatorial** methyl group while a **gauche** coupling (K) of less than 0.8 Hz. * is observed in compound IV(a) from phosphorus into an **axial** methyl group.

The P-O-C-CH\textsubscript{3} coupling constant of 2.80 Hz. observed for compound V(a) would suggest that this isomer in fact has similar geometry to that of the model conformation (III). The intermediate coupling constant values for V(b) (1.90 Hz.) suggests that this isomer has a significant population of the inverted conformation. The value for II(b) (2.30 Hz.) may not be inconsistent with the previous determination that this isomer exists to a significant extent in the inverted conformation if the apparently low **trans** value (2.30 Hz.) for II(c) is attributed to the effect of the orientation of the phenoxy substituent**.

The value of 2.10 Hz. for IV(b) would thus be consistent with

---

* Estimated from the line width of the resonance.

** An effect which might be due to different effective electronegativities of the phosphoryl oxygen and phenoxy groups.
a typical, single conformation. Thus, $J_{\text{POCCH}_3}^{\text{trans}} = 2.80$ Hz. for an axial phenoxy substituent and $J_{\text{POCCH}_3}^{\text{trans}} = 2.30$ Hz. for an equatorial substituent, would better formulate this stereospecificity.

Long-range, $^4 J$, POCCH coupling has also been assigned from phosphorus into the $C_5$ hydrogen atoms of compounds II(a), (b), (c), III, and V(a). Thus coupling into an equatorial $H_5$ nucleus ranges from 2.4 Hz. to 2.8 Hz. (L) while coupling into an axial $H_5$ (M) is in the range 0.7 Hz. to 1.0 Hz. The couplings for II(b), as expected, are intermediate between these ranges.

Confirmation that these changes in magnitude of the long-range coupling constant are due to changes in molecular geometry and that all of these couplings have the same sign comes from consideration of the averaged coupling constant observed for freely rotating systems *. Consider a typical isomer N, having

* The sign of the long-range coupling constant in triethyl phosphate is known to be the same as that of the $^3 J$ coupling, positive (31).
1H N.M.R. Spectrum of o-hydroxybenzyl alcohol cyclic phenyl phosphate

A Deceptively-Simple ABX Spectrum
Table 6

N.M.R. Parameters for o-hydroxybenzyl alcohol cyclic phenyl phosphate

![Chemical Structure](image)

<table>
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<td>$\tau_A$</td>
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<tr>
<td>$\tau_B$</td>
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<td>$\delta P_{31}$</td>
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<table>
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<th>Coupling Constants</th>
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</tr>
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<tr>
<td>$J_{P,H_A}$</td>
<td>6.84 Hz.</td>
</tr>
<tr>
<td>$J_{P,H_B}$</td>
<td>19.64 Hz.</td>
</tr>
<tr>
<td>$J_{H_A,H_B}$</td>
<td>14.40 Hz.</td>
</tr>
</tbody>
</table>
an axial methyl substituent at C₄. The dihedral angles between

the P-O bond and the C₄-C₅ bond and the P-O bond and the

C₄-CH₃ bond, all relative to the C-O bond, are approximately

the same (gauche). From C₄, H₅e is now trans to the C-O

bond while the CH₃ hydrogen atoms are freely rotating. As a

test that all the ⁴J, ³¹P-¹H coupling constants previously

described are indeed stereospecific and that their signs are

all the same, one should be able to predict the magnitude of

the coupling into axial methyl groups using the couplings into the

C₅ protons. Thus J_{axial} = (J_{5e} + 2J_{5a}) / 3. The coupling constants
to be used for J_{5e} and J_{5a}, however, should be one-half of the

observed coupling constants, since coupling into the methyl
group proceeds by only one bonding pathway and coupling into

the C₅ protons proceeds by two essentially identical bonding

pathways. The result predicted for an axial methyl group is

0.63 - 0.72 Hz. (from II(a), II(c), and III) which agrees

well with experimental data for IV(a) and IV(b). The 0.8 Hz.

value for II(b) is slightly higher due to the significant
conformational "exchange" of the axial methyl group to an equatorial position in the other conformer.
Other 2-oxo-1,3,2-dioxaphosphorinane systems

The first three sections of this discussion have involved the study of a series of isomeric pairs of cyclic phenyl phosphates. From this study, several dependencies of $^{31}\text{P}-^1\text{H}$ coupling constants have been established and the conformational analysis of these phosphorus-containing heterocycles, in terms of these dependencies has been considered. These cyclic phenyl esters have been considered as suitable model systems for a more general study of the conformational analysis of phosphate esters and their derivatives.

It is the purpose of this section to probe some aspects of the application of the established results. In particular, the effect of changing the substituent on the phosphorus atom in six-membered rings, will be considered.

The synthesis of a large number of six-membered cyclic phosphate derivatives (P) has been reported in the literature (32).

\[
\begin{array}{c}
\text{Me} \\
\text{O} \\
\text{Me} \\
\text{O} \\
\text{P} \\
\text{X}
\end{array}
\]

\[X = R, OR, NR_2, H, Cl, SH\]

The n.m.r. spectra of many of these derivatives have recently been reported (22). The analysis of some of the n.m.r. spectra
was undertaken, but for several compounds the spectra were of the deceptively-simple type, discussed previously for IX and not analyzed. N.m.r. data for the three compounds (Q) was interpreted in a similar sense to that of this thesis in that

\[ \begin{align*}
X = & \alpha \text{CH}_3 \\
\beta \text{CH}_2\text{Ph} \\
\gamma \text{NHCMe}_3
\end{align*} \]

\[ \text{Q} \]

\[ J_{\text{POCH}} \text{ axial was given as } 7.8 - 10 \text{ Hz. and } J_{\text{POCH}} \text{ equatorial as } 13.8 - 16.3 \text{ Hz.}. \] Although these \( J_{\text{gauche}} \) values are less than the \( J_{\text{trans}} \) values, the magnitude of the couplings clearly do not agree with those of the present study (1.7 and 22.5 Hz.). Other workers (33) report equal \( J_{\text{gauche}} \) and \( J_{\text{trans}} \) (11 Hz.) coupling constants for a system similar to Q(b).

Since the authors of the above results appear not to have considered the possibilities of rapid conformational exchange in the above systems, the temperature dependence of the n.m.r. spectrum of 5,5-dimethyl-2-oxo-2-phenyl-1,3,2-dioxaphosphorinane(X) has been investigated.
This molecule, a cyclic phenyl phosphonate, is the analog of I, lacking one oxygen atom. The room temperature p.m.r. spectrum of this compound contrasts sharply with that of I as shown in figure 6. The two methyl resonances of X are apparently equivalent and analysis of the spectrum provides values, \( J_{4e,4a} = 11.1 \text{ Hz.} \), \( J_{\text{POCH}} \) "axial" = 11.1 Hz., and \( J_{\text{POCH}} \) "equatorial" = 11.1 Hz.. The p.m.r. spectrum of X was subsequently obtained at ca. -80° C. and analysis provided values \( J_{\text{gauche}} = 7.8 \text{ Hz.} \), \( J_{\text{trans}} = 15.9 \text{ Hz.} \). At this temperature, the methyl resonances were well chemically shifted. These results are interpreted, at least in part, to suggest that X exists in an equilibrium mixture of both conformations at room temperature, and that the populations of these are about the same. The observed room temperature coupling constants are thus the average of those for each conformation and as the temperature is lowered, the position of equilibrium shifts sufficiently to show significantly different values for the averaged couplings. Unfortunately, with the low-temperature
capability of the instrumentation currently available limited to \(-80^\circ\text{C.}\), a sufficiently low temperature was not obtained in order to reach a "coalescence temperature" for this equilibrium*. This experiment, if successful, would confirm the existence of two conformational species.

It is nevertheless felt, however, that the results of the literature discussed are due to equilibrium mixtures of both possible "flattened-chair" conformations existing in significant amounts such that the observed room temperature n.m.r. data is simply the weighted average of that for each conformation.

It thus seems likely that the conformational preference for a phenoxy substituent at phosphorus, which provides a preferred conformation for compound I, is not shared by a phenyl substituent as in X. Thus the conformational preference of a phosphoryl oxygen and a phenyl substituent seem to be about the same, whereas, as depicted throughout this thesis the conformational preference of a phenoxy substituent seems to be distinctly axial.

The 2-chloro-2-oxo-1,3,2-dioxaphosphorinane ring system is an important intermediate in the synthesis of cyclic phosphate derivatives in general. The n.m.r. spectrum of 5,5-dimethyl-2-

* The coalescence temperature is that below which two separate n.m.r. resonances are observed, one for each conformation.
$^1$H N.M.R. Spectra of Substituted 5,5-dimethyl-2-oxo-1,3,2-dioxaphosphorinanes

* decomposition impurities
chloro-2-oxo-1,3,2-dioxaphosphorinane (XI) (figure 6) has been analyzed in the same manner as for I. The n.m.r. data are presented in table 7. This compound has a deceptively-simple spectrum of the type illustrated in figure 5 when run at 60 M.Hz., and has been previously reported as unsuitable for ABX analysis (22). The deceptively-simple spectrum is, however, completely analyzable by analogy with that described for IX in Appendix E. The results are the same as for the analysis of the more normal appearing spectrum at 100 M.Hz. (figure 6).

The $J_{\text{POCH}}$ trans value of 28.6 Hz. and the $J_{\text{POCH}}$ gauche value of 2.9 Hz. are considerably larger than the corresponding coupling constants for the phenoxy analog I. There are several possible explanations for this discrepancy. The conformation of XI could be such that the observed values for $J_{\text{POCH}}$ correspond to dihedral angles of very close to 180° and 60°. This could be due to a very strong preference for the chloro-substituent to be axial.
Alternatively, the conformation of XI could be that of the basic ring structure and the conformational standard III as well as I could be equilibrium mixtures of conformations having significant populations of phenoxy-equatorial at room temperature. Thirdly, the conformation of XI could be the same as that for I and III and the increased values of the coupling constants could be attributed to effects of the chloro-substituent, electronegativity or otherwise.

At this time, in the absence of adequate low-temperature measurements and without firm knowledge of the configuration at the phosphorus atom in XI, it is not possible to unequivocally distinguish between these three rationales. The second rationale would tend to suggest that compound V(a) should exist more in the preferred, phenoxy-axial, conformation than I or III due to steric interactions of an axial methyl group which are absent for I and III. $J_{\text{POCH}}^{\text{trans}}$ for V(a) would thus be larger than that for I and III and this is not the case. That the electronegativity of OPh is larger than that of Cl is consistent with rationale three. At this time we are only able to suggest that it is either the first or the third case.

It is interesting to consider whether dipolar interactions of the substituent on the phosphorus atom with the oxygen "lone-pairs" play a vital role in determining the conformations of these systems. This so-called "anomeric effect" (34) tends to
influence substituents vicinal to the oxygen lone-pairs such that the most dipolar substituent tends to cancel the net dipole through the oxygen lone-pairs. Thus the preferred conformation of trimethylene sulphite(R) has the dipolar S=O bond axial, tending to cancel the effective dipoles of the oxygen lone-pairs (35).

The preferred conformational behaviour of the electronegative OPh substituent of I as opposed to the less electronegative CH$_2$Ph substituent for Q(b) of presumably conformational inhomogeneity, is in agreement with such an idea as is the proposed result for XI.

Application of the results for the stereospecificity of J$_{POCH}$ to phosphate systems of naturally-occurring materials is simplified by the inherent equilibration at phosphorus, 5,5-dimethyl- due to proton exchange. The p.m.r. spectrum of 2-hydroxy-2-oxo-1,3,2-dioxaphosphorinane XII is presented in figure 6.
As would be expected for a symmetrical molecule of this type, the n.m.r. spectrum shows the averaged parameters for the two conformations. The $J_{POCH}$ value of 12.0 Hz. is in good agreement with that predicted for the average of the two couplings (12.1 Hz., from I). Thus the change from OPh to OH at phosphorus does not change the magnitudes of the POCH couplings.

The $\text{^{31}P}$ n.m.r. spectrum of adenosine 3',5'-cyclic phosphate (XIII) was obtained at room temperature, in $\text{H}_2\text{O}$ solution.

The resonance at +114.3 p.p.m. had a large splitting of 20.7 Hz. due to POCH coupling to the H$_{5'}$ proton. In accordance with the stereospecificity of $J_{POCH}$ determined earlier, the
conformation of this molecule is defined to be that of the flattened-chair depicted.

The essential assumption that has been made at the beginning of this discussion concerning the absolute structure of 2-oxo-2-phenoxy-1,3,2-dioxaphosphorinane, has not been further dealt with. It is felt that the assumption of the X-ray result has been justified in the sense of application of the developed results by the internal consistency with which these results have been able to both rationalize and predict the spectroscopic parameters of a number of molecular conformations. However, until a very good independent method for determining the conformations of organic molecules in solution is developed, accepting the philosophical dilemma of extrapolating from the solid state will remain an inherent part of applied spectroscopic techniques in conformational analysis.
Table 7

N.M.R. Parameters for 5,5-dimethyl-2-chloro-2-oxo-1,3,2-dioxaphosphorinane

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<td>(\tau_{4e})</td>
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<td>(4e,P)</td>
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<tr>
<td>(4e,6e)</td>
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</tr>
<tr>
<td>(4a,4e)</td>
<td>11.1</td>
</tr>
<tr>
<td>(4e,6a)</td>
<td>0.0</td>
</tr>
<tr>
<td>(4a,6a)</td>
<td>0.0</td>
</tr>
</tbody>
</table>
General Methods

(a) Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected.

(b) Micro-analyses were carried out by Mr. P. Borda of this department.

(c) All $^1$H n.m.r. spectra were measured with a Varian HA-100 spectrometer operating in the frequency sweep mode using tetramethylsilane (T.M.S.) as internal reference. Proton chemical shifts are all reported in the $\tau$ scale.

(d) $^{31}$P n.m.r. spectra were measured at 40.477 M.Hz. using a Varian HA-100 spectrometer with a sealed capillary of $P_4O_6$ as internal reference. The spectrometer was used in either the HR-mode or in the locked field sweep mode. Chemical shifts are reported in p.p.m. relative to $P_4O_6$. 
Cyclic Phenyl Phosphates

Cyclic phenyl phosphates were prepared by the following general method adapted from Meston (37). Phenyl phosphoro-dichloridate (1.1 mole equivalents)* was added dropwise with stirring to a solution of ca. 0.03 moles of diol dissolved in ca. 40 ml. of anhydrous pyridine cooled in an ice bath. The reaction mixture was left to stand in the refrigerator (ca. 3°C.) overnight. A small quantity (ca. 10 ml.) of water was added to the reaction mixture to dissolve precipitated pyridinium hydrochloride and the entire solution was added to ca. 100 ml. of water in a separatory funnel. The resulting solution was extracted five times with chloroform. The combined chloroform extracts were dried over anhydrous Na₂SO₄ for several hours and then evaporated to give the product.

For reactions of unsymmetrical diols, the product obtained as above was, in fact, the expected mixture of all possible geometric isomers. Using EtOAc as eluant, TLC and ³¹P n.m.r. showed these mixtures to contain the cis and trans isomers in approximately equal amounts.

Thin layer chromatography using silica gel** with ethyl acetate as eluant was used routinely to identify mixtures

* This reagent was a commercial product obtained from the Aldrich Chemical Co., Milwaukee, Wisconsin.
** Fischer S-662 or B.D.H. 15049.
of isomers and monitor the contents of column chromatography fractions.

Column chromatography was used to separate mixtures of isomers and a standard technique was used throughout. A 45 cm., 16 mm. dia. silica gel column was prepared and ca. 0.5 gm. of compound mixture dissolved in ca. 5 ml. of ethyl acetate introduced. The column was eluted with ethyl acetate or, for slightly better separation in certain cases, 50/50, v/v, ethyl acetate/benzene, and ca. 2 ml. fractions were collected. These fractions were conveniently monitored using TLC and appropriate series of fractions were combined and evaporated to give the pure isomers.

2-oxo-2-phenoxy-1,3,2-dioxaphosphorinane (I):

5,5-dimethyl-2-oxo-2-phenoxy-1,3,2-dioxaphosphorinane (III):

The synthesis of these compounds has been previously described by the author (6) and in the literature (37,38).

4,6-dimethyl-2-oxo-2-phenoxy-1,3,2-dioxaphosphorinane (II):

The mixture of the three isomers of this compound was prepared by the general method using the commercially available* mixture of meso- and dl- pentan-2,4-diol. The mixture gave three spots on TLC corresponding to three isomers II(a), II(b), and II(c).  

* Frinton Laboratories, South Vineland, N.J.
II(b), II(c), in order of decreasing Rf value. The syrupy mixture was separated by column chromatography, as in the general method, into the three pure (by TLC and $^1$H and $^{31}$P n.m.r.) isomers. Isomer II(a) crystallized spontaneously and had m.p. 93.0 - 95.5° C. Isomers II(b) and II(c) were syrupy liquids. The $^{31}$P chemical shifts of these compounds were, respectively, 125.8 p.p.m., 126.0 p.p.m., and 123.6 p.p.m.

Analysis calculated for C$_{11}$H$_{15}$O$_4$P: C, 54.6; H, 6.2.
Found: II(a): C, 54.3; H, 6.4. II(b): C, 54.3; H, 6.3. II(c): C, 54.4; H, 6.3.

4-methyl-2-oxo-2-phenoxy-1,3,2-dioxaphosphorinane (V):-
The mixture of isomers of this compound derived from butan-1,3-diol were separated as above to give the faster running (on TLC) isomer II(a) and the other isomer II(b) in approximately equal amounts by TLC. Crystalline isomer II(a) had m.p. 91-92° C. and $^{31}$P chemical shift 125.7 p.p.m. The syrupy isomer II(b) had $^{31}$P chemical shift 125.2 p.p.m. Analysis calculated for C$_{10}$H$_{13}$O$_4$P: C, 52.6; H, 5.7. Found: II(a): C, 52.6; H, 5.8. II(b): C, 52.6; H, 5.6.

4,4,6-trimethyl-2-oxo-2-phenoxy-1,3,2-dioxaphosphorinane (IV):-
The reaction of phenyl phosphorodichloridate with 2-methylpentan-2,4-diol afforded a mixture of two isomers. These isomers were readily separated using column chromatography as before.
The crystalline, faster running isomer on TLC, IV(a), had m.p. 104 - 106°C and $^{31}\text{P}$ chemical shift 127.0 p.p.m. The slower running isomer II(b) had $^{31}\text{P}$ chemical shift 126.0 p.p.m. Analysis calculated for $C_{12}H_{17}O_4$: C, 56.3; H, 6.7. Found: II(a): C, 56.4; H, 6.6; II(b): C, 56.1; H, 6.5.

5-methyl-5-nitro-2-oxo-2-phenoxy-1,3,2-dioxaphosphorinane (VI):-
5-methyl-2-oxo-2-phenoxy-1,3,2-dioxaphosphorinane (VII):-
5,5-dimethyl-4-isopropyl-2-oxo-2-phenoxy-1,3,2-dioxaphosphorinane (VIII):-

Synthesis and separation of isomers for each of these compounds was entirely by the general method. Only the two isomers of VII were non-crystalline products. Isomer VI(a), faster running on TLC, had m.p. 156.5 - 157.5°C. Isomer VI(b) had m.p. 118.0 - 119.5°C. Analysis calculated for $C_{10}H_{12}NO_6P$: C, 44.0; H, 4.4; N, 5.1. Found: VI(a): C, 44.1; H, 4.6 N, 5.2. VI(b): C, 43.9; H, 4.6; N, 5.1.

Isomers VIII were as reported in the literature (18).

$\alpha$-hydroxybenzyl alcohol cyclic phenyl phosphate (IX):-
The crystalline product from the reaction of $\alpha$-hydroxybenzyl alcohol and phenyl phosphorodichloridate had m.p. 79.5 - 81.0°C and $^{31}\text{P}$ chemical shift 147.5 p.p.m.
Miscellaneous Dioxaphosphorinanes

5,5-dimethyl-2-oxo-2-phenyl-1,3,2-dioxaphosphorinane (X):-
This compound was prepared by the method of McConnell and Coover (39) and had m.p. 106 - 108°C.; lit.m.p. 103 - 105°C.
$^{31}$P resonance at 98.0 p.p.m. was an apparent quintet $J=11$ Hz.

2-chloro-5,5-dimethyl-2-oxo-1,3,2-dioxaphosphorinane (XI):-
5,5-dimethyl-2-hydroxy-2-oxo-1,3,2-dioxaphosphorinane (XII):-
These compounds were prepared by the method of Edmundson (40) and had identical melting points.

Adenosine-2'-phosphate (XIV):-
Adenosine-3',5'-cyclic phosphate (XIII):-
The compounds were the generous gift of Dr. M. Smith.
Analysis of Spectra

\(^{31}\text{P}\) chemical shifts are accurate to 0.1 p.p.m. unless otherwise specified.

All spectra were run in CDCl\(_3\) solution at concentrations of 20 - 30% wt./vol. unless otherwise specified.

Assignment of methyl resonances is on a first order basis.

\(^1\text{H}\) chemical shifts are accurate to within 0.02\(\text{T}\) and coupling constants to within 0.2 Hz. unless otherwise specified.

The spectra for I are discussed in Appendix A.

The spectra for compounds II were iterated using the LAOCOON III computer program to best fit. The only parameters that could not be iterated were the \(\text{P,4e}\) and \(\text{P,4a}\) coupling constants. These couplings as estimated from the phosphorus spectra and the bandwidths of the 4,6 protons, and are thought to be accurate to ±0.5 Hz. for II(a) and II(c) and ±1.0 Hz. for II(b). The assignment of 4e5e and 4a5e for II(b) is not unambiguous. These numbers could be reversed. Unfortunately, homonuclear double resonance experiments in which the methyl resonances are irradiated, have not been successful due to the proximity of the methylene protons. The removal of the methyl coupling into the \(\text{C}_4,\text{C}_6\) protons would have permitted assignment of these couplings. The remaining coupling constants for II(b) and II(c) are thought to be well within the stated
limits above. For II(a) the coupling constants from the computer program are slightly less accurate but should be within 0.2 Hz. for the smaller couplings. $J_{4a,5a}$ and $J_{5e,5a}$ are probably within 0.5 Hz., having "probable errors" of 0.34 and 0.53 Hz. respectively. The chemical shift assignment for 4e and 6a of II(b) may also be reversed.

The analysis of the n.m.r. spectra for III is described in some detail in Appendix B.

Complete analysis of the spectra for compounds IV proved to be impossible due to their highly-coupled nature in the deceptively-simple $C_5$ proton region. The deceptively-simple spectra were again of the type discussed in Appendix E. Although explicit analysis was not possible, a nearly complete assignment of transitions was possible and is consistent with the data of table 4. Several of the numbers are first-order approximations and are expected to be within 10% of their true values.

The p.m.r. spectrum of V(b) has not yet been fully assigned. The $C_5$ proton resonances are, in part, taken to be of a deceptively-simple form. The splitting in the $^{31}P$ resonance spectrum is much less than 20 Hz., in contrast to the 22.7 Hz. splitting in the $^{31}P$ resonance of V(a).

The p.m.r. spectrum of V(a) has been assigned on a first-order basis with the aid of computer-simulated spectra. A sufficiently good assignment of the transition frequencies
was not obtained to permit an iterative, best-fit calculation to be made. With the exception of the data regarding the methyl resonance, which is within experimental accuracy, the accuracy of the parameters is expected to be within 10%.

The n.m.r. analysis of IX is given in Appendix E.

The n.m.r. analyses of X and XII are precise and expected to be well within computer analyses.

The analysis for XI is similar to that for I and the computer iterated parameters have "probable errors" within experimental accuracy.

The $^{31}$P n.m.r. spectra of XIII and XIV were obtained by summing repeated scans (22 scans and 31 scans, respectively) of their spectra obtained at saturation concentration conditions in H$_2$O. A Varian C-1024 computer for time-averaging was used.
APPENDIX A

The n.m.r. spectrum of 5,5-dimethyl-2-oxo-2-phenoxy-1,3,2-dioxaphosphorinane

The n.m.r. spectrum of 5,5-dimethyl-2-oxo-2-phenoxy-1,3,2-dioxaphosphorinane (figure 6) is of the type AA'BB'M3N3X. Since the M3N3 (methyl resonance) region of the spectrum is first-order with respect to the AA'BB' region, this spin system has been analyzed as an AA'BB'X system. The 31P spectrum was basically a tripled-triplet due to a large coupling with the upfield set of chemically equivalent protons and a small coupling with the downfield set of protons. A homonuclear spin-decoupling experiment was performed in order to assign these protons. Irradiation of the low-field methyl resonance produced visible sharpening of the low-field set of methylene resonances while leaving the upfield set unaffected. In accordance with the established steric dependence of long-range proton-proton coupling constants of methyl groups (41), the low-field methylene protons, having the small coupling with phosphorus, were designated axial. It was not possible to directly calculate the true n.m.r. parameters of this system since explicit transition frequencies and energies cannot be formulated (42).

The LAOCOON III computer program was thus used to reproduce the theoretical n.m.r. spectrum associated with the
chemical shifts and coupling constants which were approximated from the above interpretation of the experimental spectrum. The cross-ring, axial-axial, long-range coupling constant was entered as zero and the calculated spectrum best resembled the experimental when the similar axial-equatorial, $^4J$, coupling was set to zero. The experimental transition frequencies were then entered as data and, after two iterations of the n.m.r. parameters, the root mean square error of the matched transition frequencies was reduced from 2.718 to 0.275 Hz.

The largest probable error of the parameters, as calculated by the program, was 0.16 Hz. for $J_{p-H_{axial}}$, for which experimental transition frequencies were expected to be slightly inaccurate due to broadening of resonances by the axial methyl coupling mentioned above. That the relative signs of the two phosphorus coupling constants are the same was confirmed by comparisons of the transition intensities of the two possible assignments.

The p.m.r. spectrum of this compound was also obtained at $-80^\circ$C. in CH$_2$Cl$_2$ solution. Although the value for $J_{P-OCH}$ trans was found to be slightly larger than the room temperature result, the accuracy with which the transition energies were assigned was low due to broadening of the resonances. The reliability (+1Hz.) of this determination thus does not permit any significance to be attached to the difference.
APPENDIX B

Homonuclear and Heteronuclear Double Resonance Techniques and Computer Program

The use of $^1$H homonuclear decoupling experiments was limited throughout this study. With the exception of that used to assign the spectrum of I, these experiments were not of general use in aiding spectral assignment due to the very wide bandwidth of many of the proton resonances. In general, the large amount of power required to decouple protons having large splittings was such that neighbouring resonances of other protons were perturbed, leading to ambiguous results.

Heteronuclear decoupling was, however, extremely useful in analysis of spectra. Experiments in which the proton resonances were observed while irradiating strongly at the phosphorus resonance frequency, were particularly useful in assigning the spectra of isomers II (see figure 2). All of the long-range phosphorus hydrogen coupling constants reported were confirmed by collapsing the splittings due to these by irradiating the $^{31}$P resonance. The heteronuclear decoupler used in this study was built by Mr. R. Burton of this department (43). The equipment consists of a double-tuned probe adapter for observing $^1$H at 100 M.Hz. while irradiating $^{31}$P. The decoupling frequency is produced by a Hewlett Packard Frequency Synthesizer which is coupled to a Hewlett Packard Power Amplifier
The use of double resonance experiments has been well reviewed in the literature (44,45).

Throughout the analysis of spectra, considerable use was made of a LAOCOON III computer program. The original program was kindly provided by Aksel Bothner-By*. The program has been suitably modified for the IBM 360/67 system currently in use at this university. Part of this program has been modified to include a histogram plot sub-program adapted from the LAME n.m.r. program kindly provided by Dr. John Martin**. Further modification of the program has extended the number of individual transitions calculated from 300 to 500. This is particularly useful for 7-spin systems. Thus the program used has the additional options of a histogram plot of the n.m.r. spectrum and a calculation of up to 500 transition frequencies.

Two kinds of applications of this program are useful and are illustrated in the analysis of the p.m.r. spectrum of II. The observed spectrum, at first sight, is depressing. Only the high-field resonance is assignable and this is seen to be of the H₅e proton, a sextet due to 5 equal coupling constants to the H₄,6 protons and phosphorus. This is confirmed by irradiating phosphorus, causing collapse of this resonance to

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* Mellon Institute, Pittsburgh, Pa..
** University of Alberta, Edmonton, Alberta.
a quintet. Close examination of the low-field $H_{4,6}$ resonance reveals four very intense transitions. These are immediately suspected of being deceptively-simple in the sense of Appendix E. The coupling due to $H_{5e}$ is seen and the other coupling of this quartet must, by definition of the condition for seeing this deceptively-simple spectrum, be the average of the $4e,5a$ and $4a,5a$ couplings. The outer transitions of the other $AA'BB'$ sub-spectrum can be determined and the large splitting in the $^{31}P$ resonance gives a first-order $J_{PCH_e}$ value. Using first-order, guessed chemical shifts, all data is entered into the LAOCOON III program and a set of calculated transition frequencies is obtained. These frequencies are matched with the experimental frequencies in a subsequent computer run and a least-squares iterative fit is obtained. The output n.m.r. parameters are given in table 3. It is felt that the accuracy of these parameters is considerably higher than that quoted since better fitted spectra have been obtained using series of "AB MN" (4-spin) approximations, which are not entirely valid. Until more transitions can be definitely experimentally assigned (perhaps at 200 M.Hz.) however, it is not possible to reduce the random error in assigning frequencies to a small number of transitions.
Throughout this study, the configuration at the phosphorus atom has been tentatively assigned. No direct results have been reported in the literature regarding this question. Edmundson (46) has discussed the possibility of using the I.R. stretching frequency of a P=O bond to distinguish between axial and equatorial phosphoryl oxygen and discounts this on the basis of similar observed frequencies for compounds assumed to have different configurations at phosphorus. In fact, the n.m.r. data available for these compounds (33) suggest that neither molecule exists in a single conformation*. It is felt that the usefulness of I.R. for determining configuration at phosphorus should remain an open one until definite configurational isomers have been studied. Other workers have rationalized configuration at phosphorus in other systems by considering the consequences of steric interactions of the expected configurations (47), on the basis of $^1$H chemical shifts (16), and dipole moment measurements (50).

We have assumed the phenoxy-axial configuration on the basis of the X-ray result for III. Compound I has also been assigned this structure, assuming it to be the more

* By analogy with compound X of this thesis.
thermodynamically stable one. Interestingly, for the isomeric pairs of compounds studied, the faster-running isomer on TLC is crystalline whereas the other isomer is often a syrup. The $^{31}\text{P}$ chemical shifts for the pairs of isomers are separated by \textit{ca.} 1 p.p.m., the crystalline one being to higher field. Since these, higher-field, chemical shifts more closely correspond to those of I and III, these isomers have been assigned the same configuration at phosphorus.
APPENDIX D

Calculation of the Rotamer Populations of Adenosine-2'-Phosphate

The observed $^3$P n.m.r. spectrum of adenosine-2'-phosphate contains a 7.4 Hz. splitting due to coupling of the phosphorus with the 2' proton.

The population of each of the three favoured rotamers can be calculated using the $J_{POCH}$ values for $180^\circ$ (25 Hz.) and $60^\circ$ (3 Hz.) determined previously. For two of these rotamers, the dihedral angle of the PO-CH bond is $60^\circ$ and for the other it is $180^\circ$. Let the fraction of the trans ($180^\circ$) rotamer be $\alpha$, then the following equation gives $J_{av.}$ in terms of the fractional populations and coupling constants for the individual rotamers.

$$J_{av.} = \alpha J_{180} + (1-\alpha)J_{60}$$

The result is $\alpha = 0.20$, or, the trans rotamer is only populated to the extent of 20% while the two gauche rotamers are populated 40% each.
Similar calculations have recently been published (48) using $J_{\text{POCH}}$ values similar to those above but derived in a somewhat less satisfactory manner, in that the trans value was not obtained directly by experiment.
Deceptively-Simple ABX Spectra

Deceptively-simple n.m.r. spectra have been treated in the literature (49) and, for the ABX system, may occur when $\delta_{AB}$, (the chemical shift difference between the AB protons) is equal to or nearly equal to zero. The resulting 11 line spectrum compares with the 12 lines usually expected (ignoring combination lines). When $L^*$ is also zero a five line spectrum is obtained corresponding to an $A_2X$ spin system. For both cases of these deceptively-simple spectra, the observed AB resonances are completely symmetrical about $v_{AB}$ (the average resonance frequency of A and B) and the X region collapses from a four-line resonance to a triplet or a doublet.

The n.m.r. spectrum of IX is a deceptively-simple ABX having an unsymmetrical 5 line AB region and a normal 4 line X resonance. The analysis of this type of spectrum has not previously been brought to the general attention of the literature presumably because the conditions for this deceptively-simple appearance of an ABX system do not often occur in all proton "ABX" cases. This kind of spectrum has, however, been found for compounds III, V(b), IX, and XI of this thesis. Since deceptively-simple spectra result from fortuitously degenerate transitions, complete analysis of

* $L^* = \frac{1}{2} \left( J_{AX} - J_{RX} \right)$
spectra is not usually possible and it is desirable to try to destroy the simple appearance by changing solvents and/or resonance frequencies.*

For the nine-line case of IX this attitude is not warranted and, in fact, quite the opposite is true.

The transition energies and intensities for a normal ABX spectrum are presented in table 8.

The condition for observing this deceptively simple spectrum is that $\delta_{AB} = \delta L$; thus the chemical shift difference between A and B is equal to one-half the difference of the AX and BX coupling constants. Inserting this condition into the expressions for the transition frequencies of the normal case results in the transition frequencies and intensities of table 9, the deceptively-simple case. The spectra are completely and simply analyzed.

The separation of the single, intense peak of intensity 4, and the centre of the AB sub-quartet gives $N$, one-half the sum of the two X-couplings. This can be checked in the X-resonance. The separation of transitions 2 and 6 or 4 and 8 results in a value for $D$. $J_{AB}$ can be determined directly, and thus $L$ can be obtained from the equation in table 9. $L$ and $N$ define $J_{AX}$ and $J_{BX}$.

A spin-tickling experiment, irradiation of a single

* Thus changing chemical shift differences of the A and B resonances such that the deceptively-simple conditions no longer hold.
transition, confirmed the similarity of signs of $J_{AX}$ and $J_{BX}$. Computer techniques also confirmed the assignment.

Thus deceptively-simple spectra of this type are of considerable advantage, particularly as sub-spectral parts of more complex spectra where identification of the intense transition is comparatively greatly facilitated by the presence of this type of deceptively-simple spectrum.
### Table 8

**Normal ABX Energies**

<table>
<thead>
<tr>
<th>ABX</th>
<th>Energy</th>
<th>Rel. Intensity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>( \nu_{AB} - \frac{1}{2} J_{AB} - \frac{1}{2} N - D - )</td>
<td>(1 - \sin 2\phi^-)</td>
</tr>
<tr>
<td>2</td>
<td>( \nu_{AB} - \frac{1}{2} J_{AB} + \frac{1}{2} N - D + )</td>
<td>(1 - \sin 2\phi^+)</td>
</tr>
<tr>
<td>3</td>
<td>( \nu_{AB} + \frac{1}{2} J_{AB} - \frac{1}{2} N - D - )</td>
<td>(1 + \sin 2\phi^-)</td>
</tr>
<tr>
<td>4</td>
<td>( \nu_{AB} + \frac{1}{2} J_{AB} + \frac{1}{2} N - D + )</td>
<td>(1 + \sin 2\phi^+)</td>
</tr>
<tr>
<td>5</td>
<td>( \nu_{AB} - \frac{1}{2} J_{AB} - \frac{1}{2} N + D - )</td>
<td>(1 + \sin 2\phi^-)</td>
</tr>
<tr>
<td>6</td>
<td>( \nu_{AB} - \frac{1}{2} J_{AB} + \frac{1}{2} N + D + )</td>
<td>(1 + \sin 2\phi^+)</td>
</tr>
<tr>
<td>7</td>
<td>( \nu_{AB} + \frac{1}{2} J_{AB} - \frac{1}{2} N + D - )</td>
<td>(1 - \sin 2\phi^-)</td>
</tr>
<tr>
<td>8</td>
<td>( \nu_{AB} + \frac{1}{2} J_{AB} + \frac{1}{2} N + D + )</td>
<td>(1 - \sin 2\phi^+)</td>
</tr>
<tr>
<td>9</td>
<td>( \nu_X - N )</td>
<td>1</td>
</tr>
<tr>
<td>10</td>
<td>( \nu_X + D_+ - D_- )</td>
<td>(\cos^2 (\phi_+ - \phi_-))</td>
</tr>
<tr>
<td>11</td>
<td>( \nu_X - D_+ + D_- )</td>
<td>(\cos^2 (\phi_+ - \phi_-))</td>
</tr>
<tr>
<td>12</td>
<td>( \nu_X + N )</td>
<td>1</td>
</tr>
<tr>
<td>13</td>
<td>( 2\nu_{AB} - \nu_X )</td>
<td>0</td>
</tr>
<tr>
<td>14</td>
<td>( \nu_X - D_+ - D_- )</td>
<td>(\sin^2 (\phi_+ - \phi_-))</td>
</tr>
<tr>
<td>15</td>
<td>( \nu_X + D_+ + D_- )</td>
<td>(\sin^2 (\phi_+ - \phi_-))</td>
</tr>
</tbody>
</table>

\[ L = \frac{1}{2} J_{AX} - \frac{1}{2} J_{BX} \]
\[ N = \frac{1}{2} J_{AX} + \frac{1}{2} J_{BX} \]
\[ D^\pm = \frac{1}{2} \left[ (\delta_{AB} \pm L)^2 + J_{AB}^2 \right]^{1/2} \]
\[ D^\pm \sin 2\phi^\pm = \frac{1}{2} \delta_{AB} \pm 1/2L \]
\[ D^\pm \cos 2\phi^\pm = \frac{1}{2} \delta_{AB} \pm 1/2L \]
Table 9

Deceptively Simple ABX

δAB = L

<table>
<thead>
<tr>
<th>#</th>
<th>Energy</th>
<th>Rel. Intensity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>νAB-J_{AB} -1/2N</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>νAB-1/2J_{AB} +1/2N-D+</td>
<td>1-sin 2ϕ+</td>
</tr>
<tr>
<td>3</td>
<td>νAB - 1/2N</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>νAB+1/2J_{AB} +1/2N-D+</td>
<td>1+sin 2ϕ+</td>
</tr>
<tr>
<td>5</td>
<td>νAB-1/2N</td>
<td>2</td>
</tr>
<tr>
<td>6</td>
<td>νAB-1/2J_{AB} +1/2N+D+</td>
<td>1+sin 2ϕ+</td>
</tr>
<tr>
<td>7</td>
<td>νAB+J_{AB} -1/2N</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>νAB+1/2J_{AB} +1/2N+D+</td>
<td>1-sin 2ϕ+</td>
</tr>
<tr>
<td>9</td>
<td>νX-N</td>
<td>1</td>
</tr>
<tr>
<td>10</td>
<td>νX+D -1/2J_{AB}</td>
<td>cos² (ϕ+ -45°)</td>
</tr>
<tr>
<td>11</td>
<td>νX-D +1/2J_{AB}</td>
<td>cos² (ϕ+ -45°)</td>
</tr>
<tr>
<td>12</td>
<td>νX + N</td>
<td>1</td>
</tr>
<tr>
<td>13</td>
<td>2νAB-νX</td>
<td>0</td>
</tr>
<tr>
<td>14</td>
<td>νX-D -1/2J_{AB}</td>
<td>sin² (ϕ+ -45°)</td>
</tr>
<tr>
<td>15</td>
<td>νX+D +1/2J_{AB}</td>
<td>sin²(ϕ+ -45°)</td>
</tr>
</tbody>
</table>

\[
\begin{align*}
D^+ & = \frac{1}{2}(4L^2 + J_{AB}^2)^{-1/2} \\
D^- & = \frac{1}{2}J_{AB} \\
\sin 2ϕ_+ & = \frac{J_{AB}}{2D^+} \\
ϕ_+ & = 45^°
\end{align*}
\]


10. see references 3 and 4.


14. see reference 8 and reference 1, p. 46.

19. see reference 2.
43. R. Burton and L.D. Hall, to be published.
46. Reference 7.
47. Reference 5 (b).