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Untrastructural Morphology of Bovine Herpesvirus Infected Cells

Carol Ann Larson

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THE STEREOCHEMISTRY OF 5-CHLOROMETHYL-5-METHYL-2-OXO-2-PHENOXY-1,3,2-DIOXAPHOSPHORINAN
and
THE REACTION OF PHENOXIDE ION WITH 2-CHLORO-5-CHLOROMETHYL-5-METHYL-2-OXO-1,3,2-DIOXAPHOSPHORINAN

BY

SAMUEL DEAN LARSEN

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

Thesis Advisor / Date

Head, Chemistry Department Date

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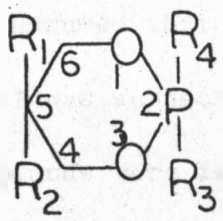
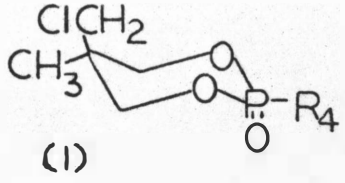
I. THE STEREOCHEMISTRY OF 5-CHLOROMETHYL-5-METHYL-2-OXO-2-PHENOXY-1,3,2-DIOXAPHOSPHORINAN

INTRODUCTION

The primary objective of the research outlined in Part One is to assign the stereochemistry of some phosphorus containing heterocycles. In order to avoid confusion over nomenclature, most of the compounds described in this thesis will be named as derivitives of the 1,3,2-dioxaphosphorinan ring.



For compounds described in the Experimental section, the designation of <u>cis</u> and <u>trans</u> will be assigned according to the arrangement of the phosphoryl oxygen at position 2 in relation to the chloromethyl group at C-5. Axial (ax) and equatorial (eq) designations will also refer to the chloromethyl group at 5, unless otherwise stated. Thus, the axial chair conformer of <u>trans</u>-5-chloromethyl-5-methyl-2-oxo-2-(R_4)-1,3,2-dioxaphosphorinan refers to (1).



(1)

Most of the compounds described in the Experimental section will be referred to by Roman numerals as outlined in Table (1). The stereochemistry has been established for compounds (III), (IV), (VI), and (VII). However, the stereochemistry of compounds (VIII)-(XVII) and (V) is not known and therefore, the relationship of substituents at C-5 to P-2 as outlined in

Table (1) is arbitrary.

The reaction of (IV) with sodium phenoxide yielded a mixture of compounds which were found to be isomers of 5-chloromethyl-5-methyl-2-oxo-2-phenoxy-1,3,2-dioxaphosphorinan. NMR signals at 0.96 δ and 1.28 δ were assigned to methyl groups. Chloromethyl groups were assigned to signals at 3.34 δ and 3.77 δ. It is assumed that the product is a mixture of two isomers. When this material was subjected to chromatographic analysis (see Experimental) two compounds were isolated; isomer A (mp 105) and isomer B (mp 136). The nmr spectrum of A included signals at 0.96 δ and 3.77 δ. Likewise, the spectrum of B indicated signals at 1.28 δ and 3.34 δ. Recombination of A and B gave a spectrum similar to the one obtained from the original mixture.

The purpose of Part One is to define the stereochemistry of isomer A and isomer B. It should be noted, A is synonymous with (VIII) and B is synonymous with (IX).

TABLE 1

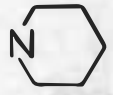
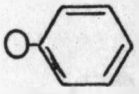
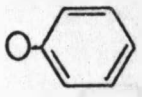
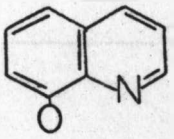
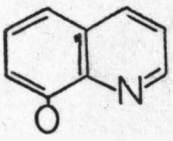
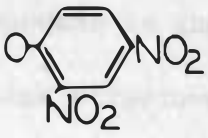
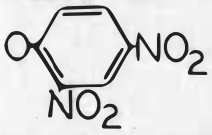
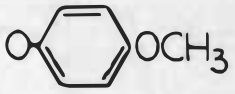
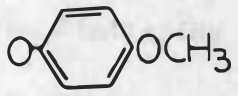
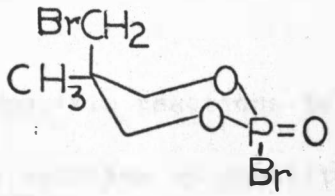
Compound	R_1	R_2	R_3	R_4
(III)	CH_2Br	CH_3	Br	O
(IV)	CH_2Cl	CH_3	Cl	O
(V)	CH_2Cl	CH_3	OH	O
(VI)	CH_2Cl	CH_3	O	
(VII)	CH_3	CH_2Cl	O	
(VIII) or A	CH_2Cl	CH_3	O	
(IX) or B	CH_3	CH_2Cl	O	
(X)	CH_2Cl	CH_3	O	
(XI)	CH_3	CH_2Cl	O	

TABLE 1 cont.

Compound	R_1	R_2	R_3	R_4
(XII)	CH_2Cl	CH_3	O	
(XIII)	CH_3	CH_2Cl	O	
(XIV)	CH_2Cl	CH_3	O	
(XV)	CH_3	CH_2Cl	O	
(XVI)	CH_2Cl	CH_3	O	
(XVII)	CH_3	CH_2Cl	O	

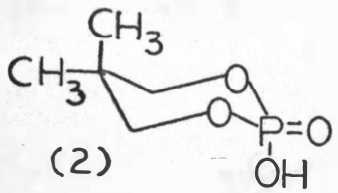
HISTORICAL

Perhaps the most detailed and accurate stereochemical information of phosphorus containing heterocycles, as well as other compounds in the solid state, comes from X-ray diffraction data. The molecular structure of cis-2-bromo-5-bromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan has been reported by Beineke.[1]

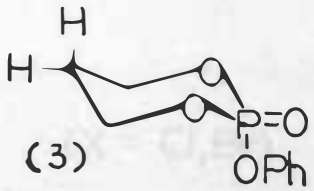


(III)

The conformation of (III) is a slightly distorted chair with the bromo and bromomethyl groups in axial positions. Interestingly, the flattening of the phosphate end of the ring in (III) causes reduction of steric interactions between bromine at P-2 and the axial hydrogens at C-4 and C-6.[2] The crystal structures of two compounds closely related to (V) and (VIII), respectively, have also been reported.[3,4]

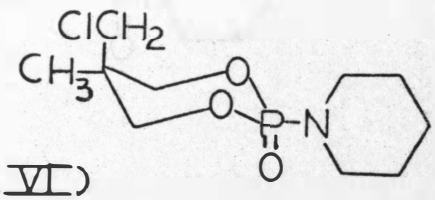


(2)



(3)

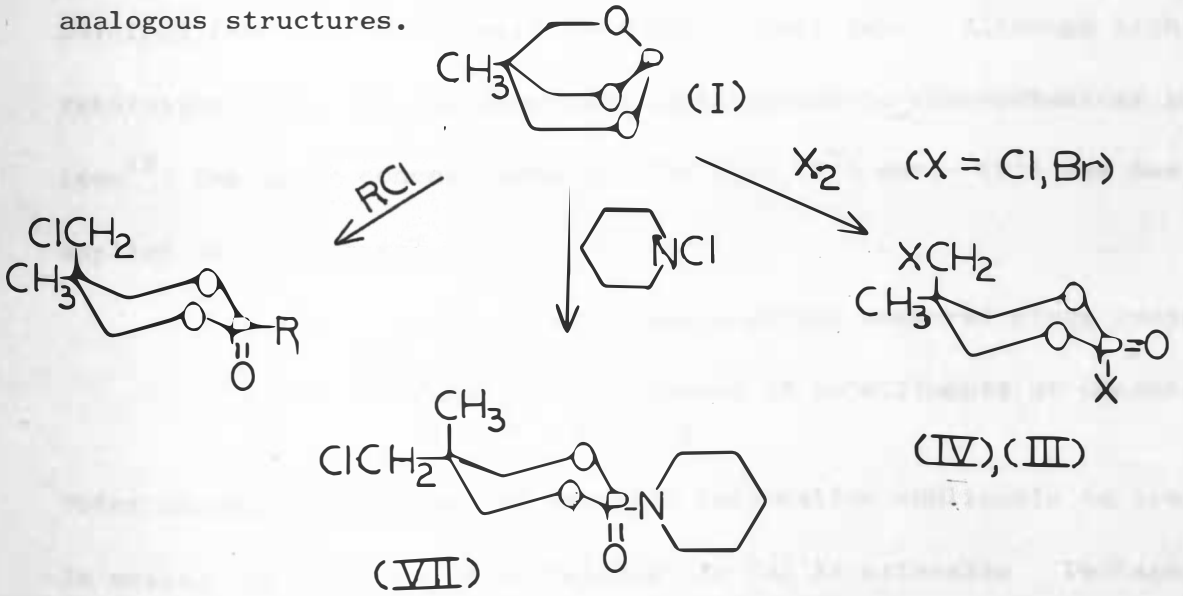
It should be noted that both compounds have chair conformations and both P=O bonds are equatorial. In contrast to this, recent work with trans-5-chloromethyl-5-methyl-2-oxo-2-piperidino-1,3,2-dioxaphosphorinan indicates that P=O is axial.[5]



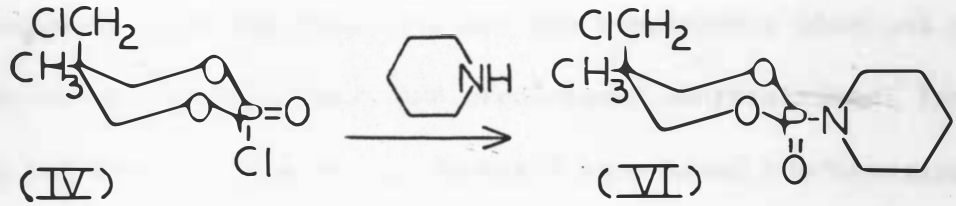
(VI)

Like the conformation of (III), the phosphate end of the amidate (VI) is flattened. Although the conformation of (III) and (VI) is known in the solid state, X-ray data is not applicable to determining conformational forms in solution. Providing that no bonds are broken, however, the configuration at phosphorus remains fixed in relation to substituents at C-5 for (III) and (VI).

The utilization of stereospecific reactions is one method of fixing the configuration at phosphorus relative to substituents at C-5. Wadsworth and Emmons used 1-alkyl-4-phospha-3,5,8-trioxabicyclo(2.2.2)octanes and alkyl halides to obtain phosphonates which have a single configuration.[6] Later, cis-5-chlormethyl-5-methyl-2-oxo-2-piperidino-1,3,2-dioxaphosphorinan (VII) was obtained using N-chloropiperidine and methyl bicyclic phosphite (I).[7] Cis-2-chloro-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan (IV) and (III) were also obtained, confirming their analogous structures.



Recently, Edmundson has prepared a series of cis-aralkyl-phosphonates using (I) and the appropriate aralkyl chloride. He has used these compounds as models for comparison with analogous cis and trans isomers prepared from non-stereospecific reactions.[8] In a similar manner, Wadsworth and Horten[9] utilized (VI) in comparison with the trans isomer isolated from the reaction of piperidine with (IV).



(IV) (VI)

Other interesting but less applicable stereospecific reactions of phosphorus containing compounds are discussed by Gallagher and Jenkins.[10]

Although some attempts have been made to relate infrared[11,33] and dipole moment data[12] to conformational properties of phosphorus containing heterocycles, the majority of stereochemical information has been obtained from nuclear magnetic resonance (nmr) data. Although high resolution (P^{31}) nmr has important applications to stereochemical problems[13], the major concern here will be with (H^1) nmr. (H^1) nmr has been applied in two general areas,

(A) conformational aspects of six-membered rings containing phosphorus
(B) configurational aspects of substituents at phosphorus in six-membered rings.

Unfortunately, the amount of detailed information applicable to area (B) is small. In contrast, data relevant to (A) is extensive. Perhaps the reason for this is that spectral properties of phosphorus containing

heterocycles exhibit features which are common with non-phosphorus containing rings. It is noteworthy that work with other six-membered heterocycles provides conformational models for analogous phosphorus compounds.[14]

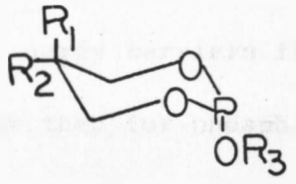
A great deal of research has been devoted to 1,3-dioxanes and related compounds in the past decade. Ramey and Messick[15] have used long-range proton coupling to suggest specific molecular forms. Jones and Ladd[16] employed coupling constants and low temperature chemical shifts to deduce molecular structure, and predominant conformational isomers. In a similar manner, Abraham and Thomas[17] have based conformational assignments on low temperature nmr for 1,3-dioxanes based on nmr spectra. Anteuis, Swaelens, and Gelan[20] have used the geminal coupling constants of methylene protons in 1,3-dioxanes as a tool for conformational description. Anderson and Brand[21] have derived thermodynamic parameters for the chair to chair interconversion of 1,3-dioxanes based on nmr spectra. Low temperature nmr was employed by Eliel and Martin[22] for the derivation of thermodynamic parameters of similar substituted 1,3-dioxanes. The same techniques employed for determining conformational forms of 1,3-dioxanes have been used for 1,3,2-dioxaphosphorinans and related phosphorus containing compounds. For example, thermodynamic parameters were determined from low temperature nmr spectra of cyclic thiophosphates by Katritzky, et al.[23] The techniques used were analogous to the ones outlined in the above references.

There are certain spectral features of phosphorus containing hetero-

cycles which make them unique. One unique feature is the ability of phosphorus to couple with hydrogen through four or more bonds.[10] Several authors[24] have suggested that there is a dihedral relationship[25] for phosphorus-hydrogen coupling and this may be utilized in the description of conformational forms. The idea of a dihedral relationship for phosphorus-hydrogen coupling has received strong support in the past few years, although no theoretical treatment has been made available.[36] Kainosho and Makamura[26] reported work on a conformationally immobile cyclic phosphite from which an empirically derived table of coupling constants and dihedral angles was obtained. This data crudely demonstrates that a dihedral dependency does exist. A number of other references supporting this idea appeared in a paper by Bentrude and Hargis.[27]

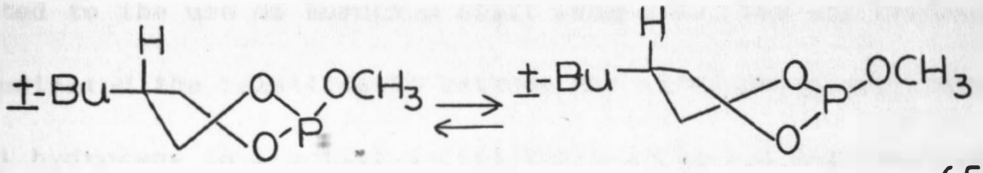
The ability of phosphorus to couple with hydrogen in six-membered heterocycles often results in making complex (H^1) spectra more complex or, in certain cases, deceptively simple.[28] As an aid to analyzing these spectra, computer iterative techniques have been applied by several authors.[29,30] Bentrude and Hargis[27] have analyzed the proton spectra of 5-t-butyl-2-methoxy-1,3,2-dioxaphosphorinan using the LAOCN3 iterative computer program.[31] White, McEwen, Bertrand, and Verkade[32] likewise have analyzed the spectra of several 5,5-disubstituted 1,3,2-dioxaphosphorinans. The chemical shifts and coupling constants derived from the detailed analysis of these spectra has aided in making conformational assignments and in certain cases configurational assignments.

The results of these analyses show that the 1,3,2-dioxaphosphorinan ring has some interesting properities. Verkade, et al.[32] have found for various substituted phosphites that the 1,3,2-dioxaphosphorinan ring is relatively mobile. In most cases, however, a single conformer predominates with the electron pair at phosphorus, preferring the equatorial position.



(4)

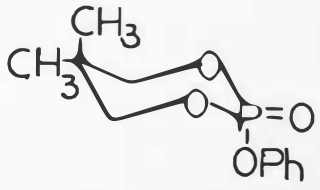
The authors suggest that other conformers may also be present in equilibrium with (4). Bentrude[27] supports this idea and suggests that rapidly equilibrating twist boat forms may be present.



(5)

Verkade suggests that in the case of phosphates, the phosphoryl oxygen is the controlling factor in determining the stereochemistry in solution. He argues that in the case of 5,5-dimethyl-2-oxo-2-phenoxy-1,3,2-dioxaphosphorinan, the predominant molecular form in solution is the chair form with the P=O bond preferring an equatorial position.[33]

(6)



He bases his argument on the fact that the 2-phenoxy group for 2-oxo-2-phenoxy-1,3,2-dioxophosphorinan has been found to be axial in the solid

state.[4] Campbell and Hall have employed similar reasoning for other dioxaphosphorinans.[38]

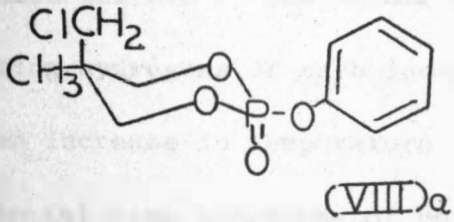
Edmundson[34] has also found conformational mobility in 2-alkyl-2-oxo-1,3,2-dioxaphosphorinans with dominant chair forms when the alkyl substiuents are bulky.[35] Katritzky, et al.,[23] support Edmundson's conclusions and found that the energy barriers for ring inversion of thiophosphates is generally higher than for phosphonates.[36] In contrast to Verkade's results, Edmundson has shown that bulky alkyl substituents prefer equatorial positions.[35]

Although nmr data applicable to determining the configuration of the substituents at phosphorus is quite limited, one noteworthy example is related to the use of Europium shift reagents. Yee and Bentrude[37] have demonstrated the relationship between the axial phosphoryl oxygen and axial hydrogens in 2-methyl-5-tert-butyl-2-oxo-1,3,2-dioxaphosphorinan using $Eu(dpm)_3$.

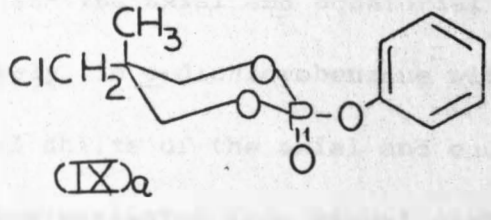
VARIABLE TEMPERATURE NMR STUDIES

Relationship of Stereochemistry of A and B

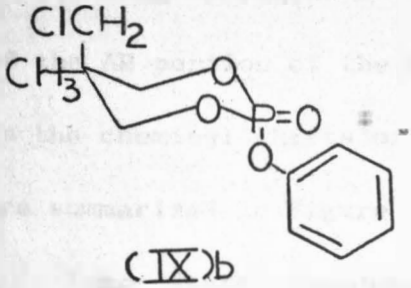
Since mixtures of A and B were separated at room temperature it may seem obvious that A and B are geometrical isomers and not conformers. The establishment of this fact is necessary to avoid confusion over the relationship of the stereochemistry of the two isomers. If only the chair forms are considered, four isomers of 5-chloromethyl-5-methyl-2-oxo-2-phenoxy-1,3,2-dioxaphosphorinan can exist.



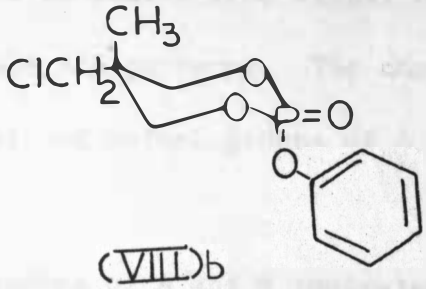
(VIII)a



(IX)a



(IX)b



(VIII)b

VIIIa and IXa are trans and cis geometrical isomers respectively, as are VIIIb and IXb. If A and B are to be considered as conformational isomers then the activation energy barriers must be sufficiently high to prevent interconversion at room temperature.

All attempts to convert A into B at higher temperatures (and vice versa) failed. Heating either isomer at 185°C for four days in sealed evacuated tubes resulted in no change. Evidence for this was provided

by the fact that no new signals appeared in the nmr spectrum of either heated material. Failure to convert A into B by heating is not conclusive proof that A and B cannot be conformers. It may only mean that both isomers are conformationally immobile at higher temperatures. This is, however, extremely unlikely since analogous dioxaphosphorinan compounds have been found to be mobile over wide temperature ranges.[23]

The nmr spectra of isomers A and B show pronounced changes with temperature increase. Figures (1) and (2) show the change in the absorption pattern of the chloromethyl groups and the axial and equatorial ring hydrogens of each isomer, respectively, in o-dichlorobenzene with an increase in temperature. The chemical shifts of the axial and equatorial ring hydrogens of both isomers were estimated from visual analysis of the AB portion of the deceptively simple ABX patterns. The changes in the chemical shifts of the chloromethyl and methyl groups of A and B are summarized in Figure (3).

Temperature dependency of the nmr spectra of A and B indicates that both isomers are conformationally mobile.[7] Evidence for ring inversion is provided by the fact that the difference in the chemical shifts of the axial and equatorial ring hydrogens decrease with increasing temperature.[32] The movement of the methyl and chloromethyl signals with change in temperature is also evidence of conformational mobility.[23] Thus, if A and B were mobile conformers, the methyl signals (or chloromethyl signals) arising from each isomer would move together and co-

alesce at higher temperatures.[32] This was not observed (see Figure 3) since all signals moved downfield and remained separate. In spite of the fact that the chloromethyl and methyl signals associated with each isomer move, both isomers may nonetheless be distinguished from each other in the temperature range studied. Since A and B are non-interconvertable and conformationally mobile, A and B must be geometrical isomers. If both A and B are in chair forms then: if A = VIIIa, B ≠ VIIIb; or if A = IXa then B ≠ IXb.

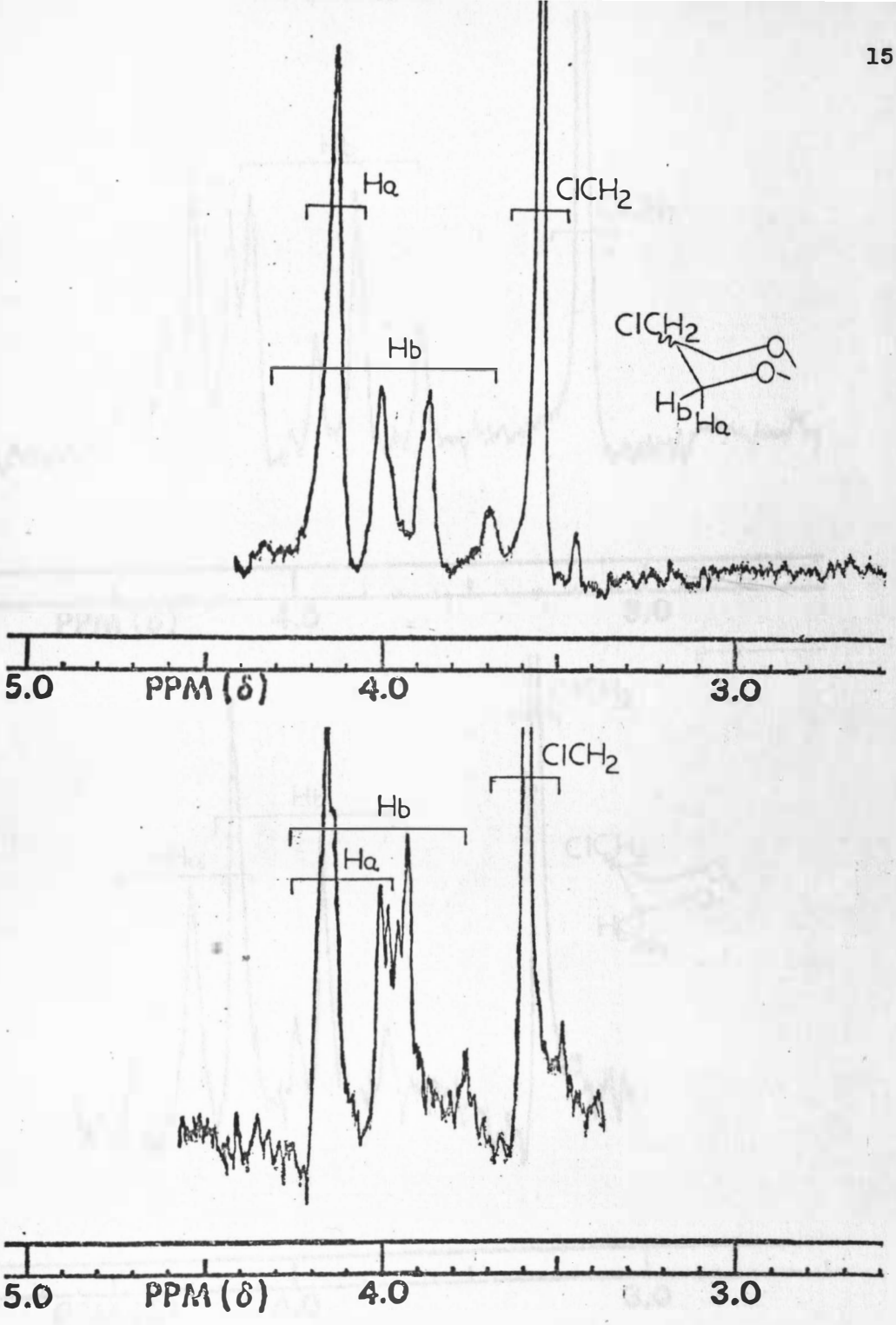


Figure (1)
Methylene Spectra of compound A in o-dichlorobenzene
Top 66° C. Bottom 166° C.

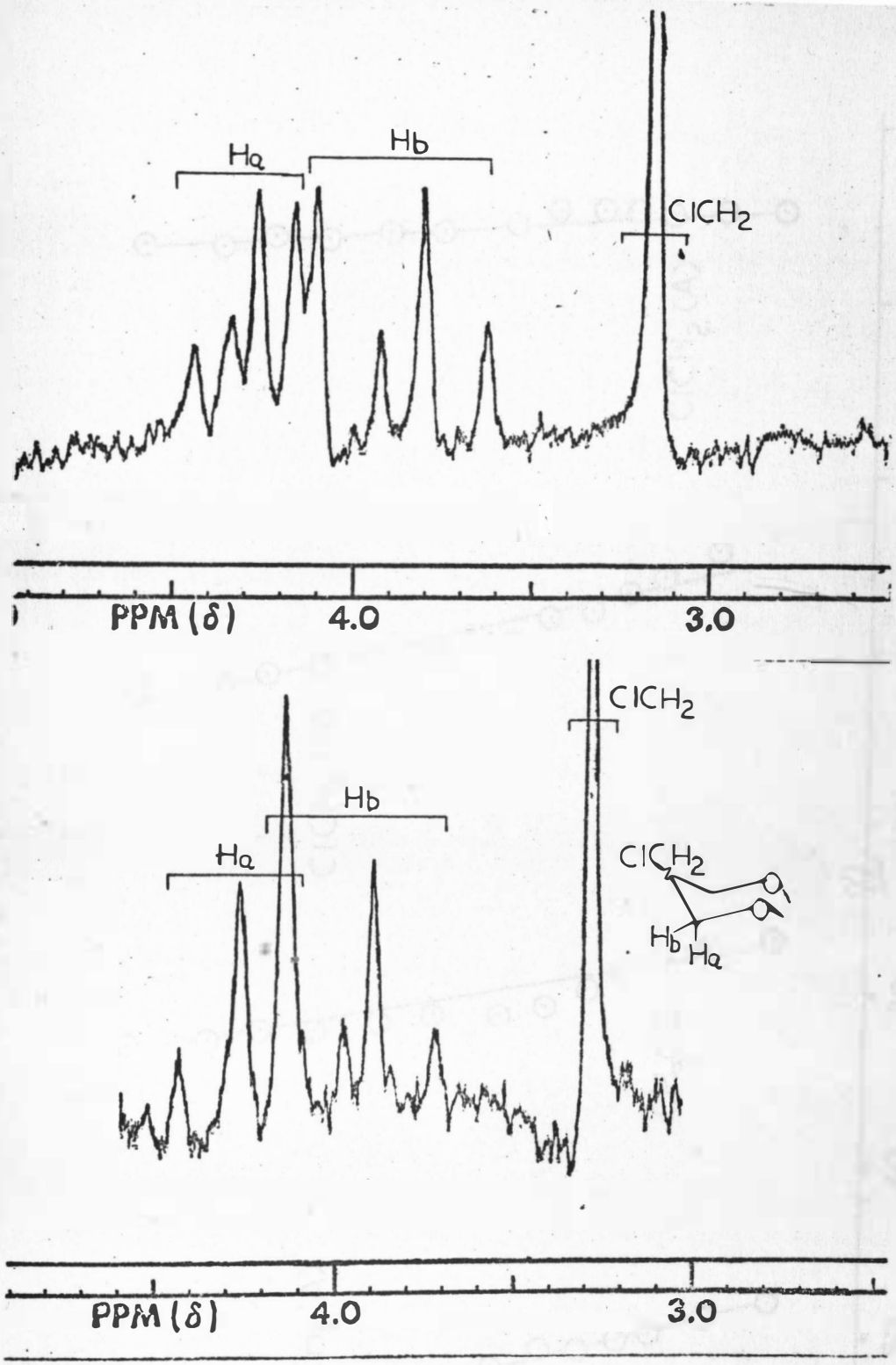
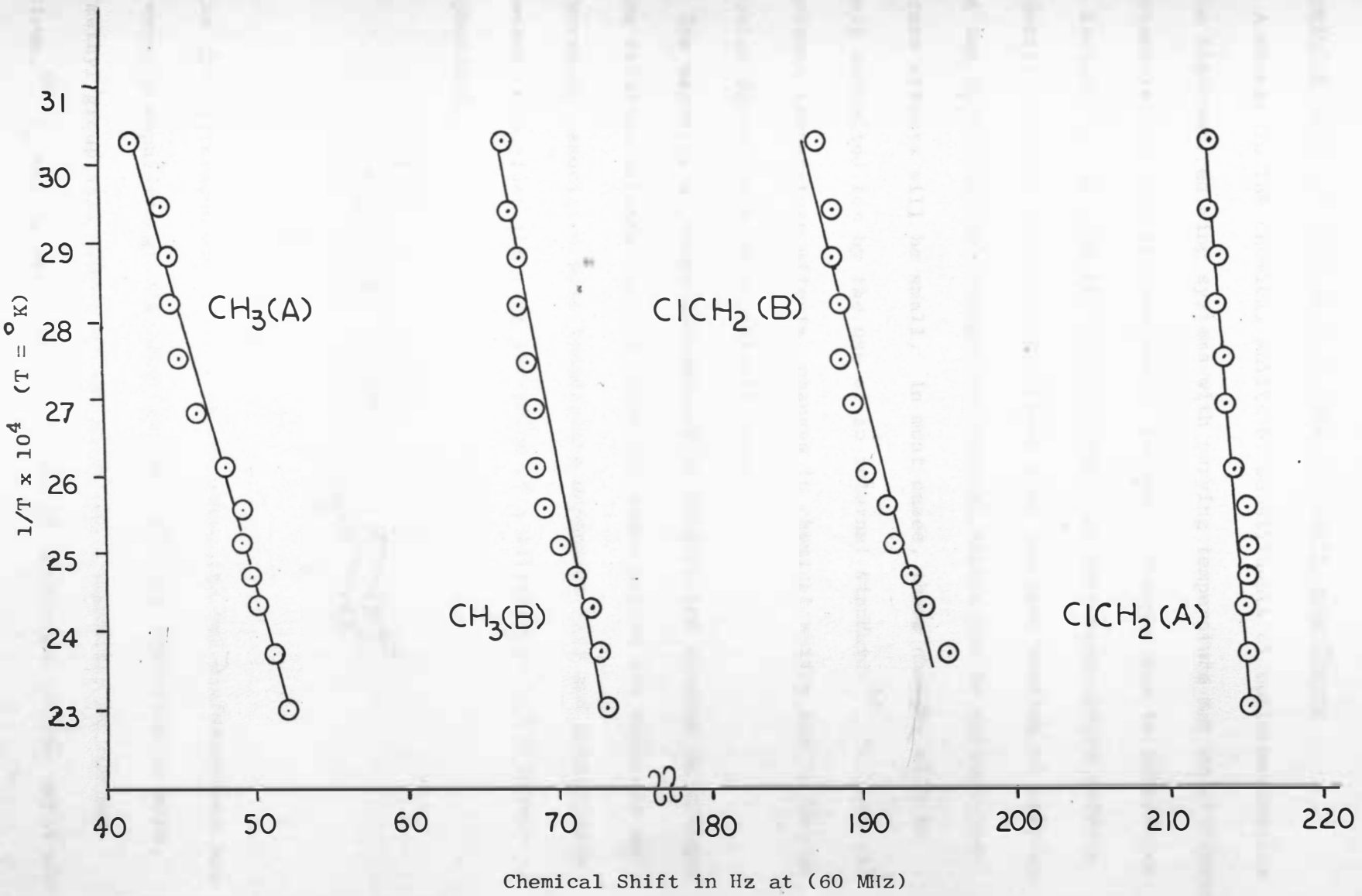


Figure (2)
Methylene Spectra of compound B in o-dichlorobenzene
Top 66° C. Bottom 166° C.

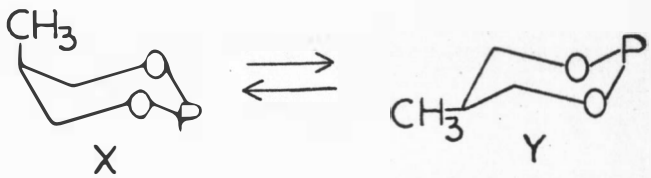
Figure (3)
Chloromethyl and Methyl Chemical shifts of A and B.



Determining Conformer Ratios from Chemical Shift Data-Theory

A change in the chemical shifts of substituents of conformationally mobile six-membered ring systems with varying temperature may be attributed to intermolecular and intramolecular factors. Changes due to intermolecular factors can be classified into various solvent-temperature effects. If specific solvent-solute interactions like hydrogen bonding or complexation can be eliminated, changes in chemical shifts due to solvent temperature effects will be small. In most cases, these changes will be largely corrected for by the use of an internal standard.[39] In contrast to solvent-temperature effects, changes in chemical shifts due to intramolecular factors may be relatively large.

The majority of these intramolecular factors are related to changes in the relative orientations of bonds and atoms within the molecule and are normally associated with temperature dependent rate and equilibrium processes. Consider the ring inversion of a substituted 1,3,2-dioxaphosphorinan.



If the ΔG difference for x and y is not zero, the two conformations are not equally populated at all temperatures. If ring inversion is slow, the methyl group will absorb at two different frequencies in the nmr spectrum.[40] V_o and V_1 are the frequencies of absorption in the axial and

equatorial position. If ring inversion is rapid, however, the methyl group will absorb at one frequency (δ) in the nmr spectrum. The relationship of (δ) to V_o and V_1 depends on the relative populations of x and y and is given by eq (1).[41,42]

$$K = \frac{V_o - \delta}{\delta - V_1} \qquad \text{eq (1)}$$

Since the equilibrium constant (K) is dependent upon temperature by eq (2), a redistribution of the population of x and y caused by variation in temperature will result in a change in the chemical shift of the methyl group (δ).[41,42]

$$K = e^{-\Delta G/RT} \qquad \text{eq (2)}$$

R = 1.987 kcal/mole-degree; T = temperature (degrees Kelvin); and ΔG is the free energy difference of conformers x and y in kcal/mole. Rearrangement of eq (1) and eq (2) clearly shows that δ is a function of T,

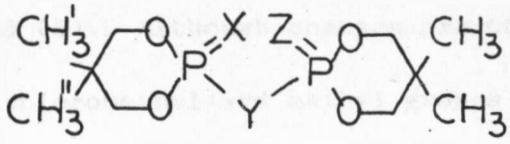
$$\delta = \frac{V_o + V_1 e^{Q}}{1 + e^{Q}} \qquad \text{eq (3)}$$

where $Q = -\Delta G/RT$.

It should be noted that in actual practice, δ is rarely a function of temperature alone as outlined in eq (3). The total change in the chemical shift δ in a given temperature range is usually influenced by solvent-temperature effects. If the solvent-temperature effects in δ

are relatively large, eq (3) will not give an accurate estimate of δ. Conversely, if V_o and V_1 are known for a pair of rapidly interconverting conformers of unequal energy, the calculation of ΔG with experimentally observed values of δ and T from eq (1) and eq (2) may lead to errors. Results and criticisms of this method are given by Eliel and Martin.[43,44]

Katritzky, et al.[23], have employed chemical shift data to calculate conformer ratio in some cyclic thiophosphates.



Variable temperature studies revealed that in certain cases the change in the chemical shift of CH_3' and CH_3'' was in some cases pronounced and in others slight. For example, Katritzky found for X = Z = O and Y = S, the chemical shift varied only 1.2 cps for CH_3' and CH_3'' in a temperature range of -76° C to +127° C. In contrast to this, the chemical shift of CH_3' and CH_3'' varied 12.1 cps and 6.6 cps, respectively, over the same temperature range for X = Z = Se, Y = S-S. Furthermore, the difference in the chemical shifts of CH_3' and CH_3'' remained approximately constant for X = Z = O, Y = S but varied 18.7 cps for X = Z - Se, Y = S-S. Katritzky interpreted the results of these temperature studies in terms of the change or lack of change in the difference of the chemical shift of CH_3' and CH_3''. It is assumed that the solvent-temperature effect contribution to the change in chemical shifts in any given compound could be canceled by taking the difference in the change in the chemical

shifts of CH_3' and CH_3''. Thus, lack of change in this difference implies that the compound is essentially conformationally immobile. A change in the difference implies conformational mobility and is used in the calculation of the ratio of conformers.

Calculation of Conformer Ratios for A, B, and Related Compounds

The experimental data derived from a variable temperature study of A and B and related compounds is given in Tables (2) and (3) and in Figures (4) and (5). Although changes are observed in the chemical shifts of the chloromethyl and methyl groups in all compounds studied, it is impossible to determine from chemical shift data alone whether these changes are due to conformational mobility and solvent-temperature effects or solvent-temperature effects alone. Application of the latter case to any given compound implies complete conformational immobility. Each compound demonstrated changes in the nmr spectrum which were indicative of perturbations in rate processes. For example, the lowering of temperature resulted in the broadening of chloromethyl and methyl signals, although complete separation of signals was not observed. In all cases, changes in the absorption pattern of the ring hydrogens were observed. It is assumed, therefore, that changes in the chemical shifts of these compounds is a result of conformational mobility and not solvent-temperature effects alone.

The calculation of conformer ratios for compounds (IV)-(VI), A, B, (XII), and (XIII) is based on a method similar to the one outlined by

Katritzky.[23] V_o and V_1 can be expressed in linear form by rearrangement of eq (3).

$$\delta(1 + e^{Q}) = V_o + V_1 e^{Q} \qquad \text{eq (4)}$$

is the observed chemical shift of any functional group and $Q = -\Delta G/RT$. V_o is the limiting chemical shift of any functional group in a given magnetic environment and is usually associated with the major conformer. V_1 is the limiting chemical shift of the same functional group in a different magnetic environment or environments and is associated with the minor conformational form or forms. The advantage of defining V_o and V_1 in general terms is that assumptions concerning the stereochemistry of the molecule containing the functional group may be avoided. The implicit assumption is that there exist only two conformationally mobile forms in which the functional group is allowed to exist in different magnetic environments. If one conformational form dominates, the ΔG difference of the two (or more) conformers cannot be zero. If V_o and V_1 are known, the ratio of major conformers to minor conformers may be calculated from eq (1) and δ. However, the prior knowledge of V_o and V_1 is not absolutely necessary in all cases. The reason for this is that if the appropriate value of ΔG is substituted in eq (4), a plot of $\delta(1 + e^{Q})$ versus e^{Q} will be linear with V_o and V_1 as intercept and slope, respectively. The appropriate value of ΔG is chosen from a series of trial values. The trial value which results in the smallest deviation from linearity, as evaluated by a least squares regression analysis[45], is assumed to be the correct value. The ratio of conformers may be calculated from this ΔG

TABLE 2

METHYL CHEMICAL SHIFTS* FROM (TMS) AT DIFFERENT TEMPERATURES

Temperature °C	(IV)	(V)	(VI)	A	B	(XII)	(XIII)
- 58@	65.5#	56.5	57.5	62.5	85.0	66.0	91.5
- 48	64.0	57.0	57.0	62.5	84.0	65.0	91.0
- 36	63.5	58.0	57.0	62.0	83.0	64.0	90.0
- 23	63.0	58.5	56.5	61.5	82.5	63.0	89.0
+ 7	62.5	58.5	56.5	60.5	81.5	62.0	87.0
+ 22	62.0	59.0	56.5	60.5	81.0	61.5	86.0
+ 40	61.5	59.0	56.0	60.5	80.5	61.0	85.0
+ 52	61.5	59.0	56.0	60.0	80.0	61.0	84.5
Solvent:	$CDCl_3$	CD_3OD	CD_3COCD_3	CD_3COCD_3	CD_3COCD_3	CD_3COCD_3	CD_3COCD_3

*In cps at 60 MHz.

@All errors estimated at $\pm$ 1 C

#All errors estimated at $\pm$ 1 cps

TABLE 3

CHLOROMETHYL CHEMICAL SHIFTS* FROM (TMS) AT DIFFERENT TEMPERATURES

Temperature °C	(IV)	(V)	(VI)	A	B	(XII)	(XIII)
- 58@	240.5#	228.0	235.0	241.5	228.5	233.0	211.5
- 48	230.0	227.5	233.5	239.0	226.0	231.5	210.5
- 36	237.0	226.0	232.0	238.5	223.0	230.5	208.5
- 23	235.0	225.0	229.5	236.0	220.5	229.0	205.5
+ 7	232.0	223.0	227.0	233.0	217.5	227.5	202.5
+ 22	231.5	222.0	226.5	232.5	217.0	226.5	201.5
+ 40	230.5	220.3	225.0	231.0	215.0	224.5	201.0
+ 52	229.5	220.0	224.5	230.5	213.5	223.5	200.5
Solvent:	$CDCl_3$	CD_3OD	CD_3COCD_3	CD_3COCD_3	CD_3COCD_3	CD_3COCD_3	CD_3COCD_3

*In cps at 60 MHz
@All errors estimated at ± 1 C
#All errors estimated at ± 1 cps

Figure (4)
Methyl chemical shift vs $1/T \times 10^4$

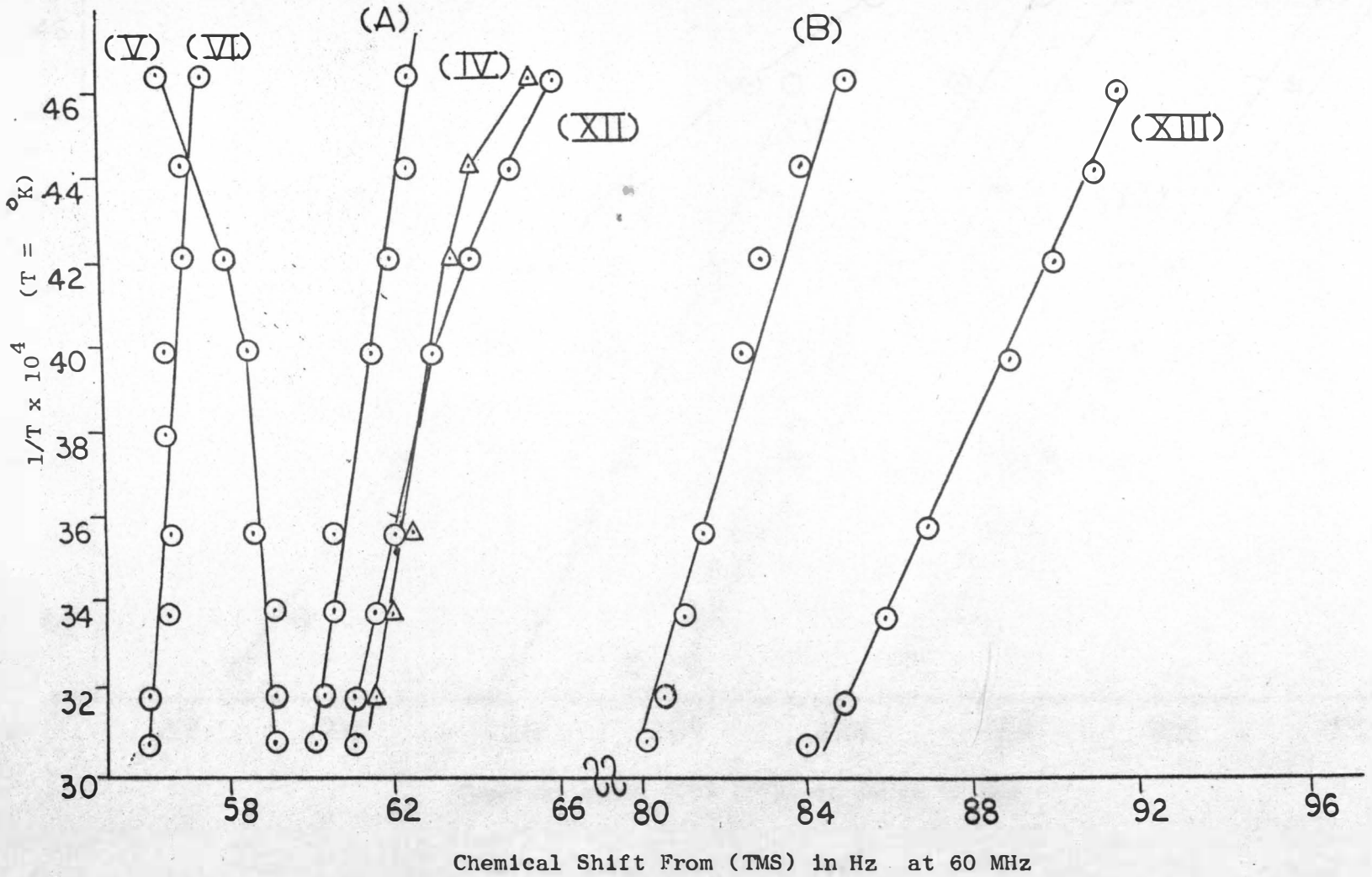
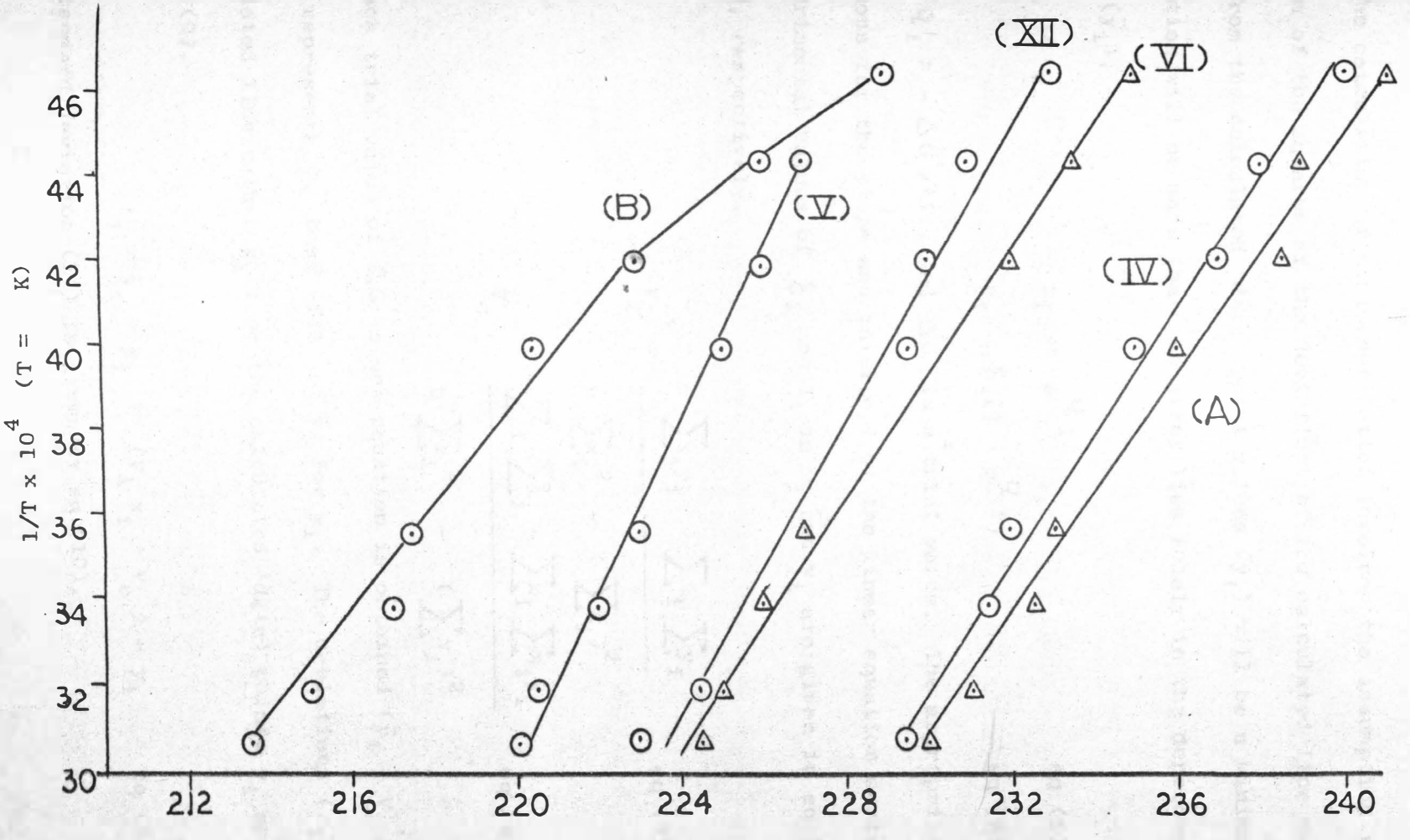


Figure (5)
Chloromethyl chemical shift vs $1/T \times 10^4$



value in eq (2).

The calculation of conformer ratios involves the assumption that the sum of the squares of the deviations of the calculated line values ($\bar{y}_i$) from the calculated 'data' point values (y_i) will be a minimum. The assumption will be made that the error lies solely in the dependent variable ($\bar{y}_i$),

$$x_i = e^{Q_i} \qquad \text{eq (5)}$$

$$y_i = \delta_i(1 + e^{Q_i}) \qquad \text{eq (6)}$$

where $Q_i = -\Delta G'/RT_i$, and $\Delta G'$ is a trial value. The appropriate expressions for the slope and intercept of the linear equation derived from n experimental values of δ_i and T_i in x_i and y_i are given in eq (7) and eq (8), respectively.

$$V_1' = \frac{n\sum x_i y_i - \sum x_i \sum y_i}{n\sum x_i^2 - (\sum x_i)^2} \qquad \text{eq (7)}$$

$$V_o' = \frac{\sum y_i \sum x_i - \sum x_i \sum x_i y_i}{n\sum x_i^2 - (\sum x_i)^2} \qquad \text{eq (8)}$$

For each trial value of $\Delta G'$ a new equation is obtained ($\bar{y}_i = V_1' x_i + V_o'$) which represents the best 'fit' of $\bar{y}_i$ for y_i. The deviations (r_i) of the calculated line values $\bar{y}_i$ from the calculated 'data' points y_i are given by eq (9).

$$r_i = \bar{y}_i - y_i = (V_1' x_i + V_o') - y_i \qquad \text{eq (9)}$$

The standard deviation (E') is given by eq (10).

$$E' = \sqrt{\frac{\sum (r_i)^2}{n - 1}} \qquad \text{eq (10)}$$

For each $\Delta G'$ value there is an associated E' value. The $\Delta G'$ value which yields the smallest E' value is assumed to be the correct one since E is a measure of the total deviation from linearity.

Obtaining values of E' for each trial $\Delta G'$ value is an extremely tedious process. For this reason, a computer program was written (OLSVAG) for the evaluation of E' utilizing equations (2) and (4)-(10). A listing of OLSVAG is provided in the Appendix. The program utilizes n values of T_i and δ_i and calculates n values of x_i and y_i. The best value of $\Delta G'$, substituted in increments of 0.01 kcal/mole, is chosen with the smallest E' value. It is assumed that the procedure of 'guessing' ΔG plays an active role in the minimization of E'. The validity of this assumption is established in Figure (6). The results of this analysis appear in Tables (4) and (5). Errors in the ΔG values given in the Tables were calculated from errors in the observed chemical shift values δ, and are intended to be only rough estimates.

The results as outlined in Tables (4) and (5) are derived from the change in the chemical shift of the methyl and chloromethyl groups, respectively, of compounds (IV), (V), (VI), A, B, (XII), and (XIII). It should be noted, with the exception of (V), B, and (XIII), the results obtained from both functional groups on the same compound do not agree. The individual values derived from the methyl and chloromethyl shifts of

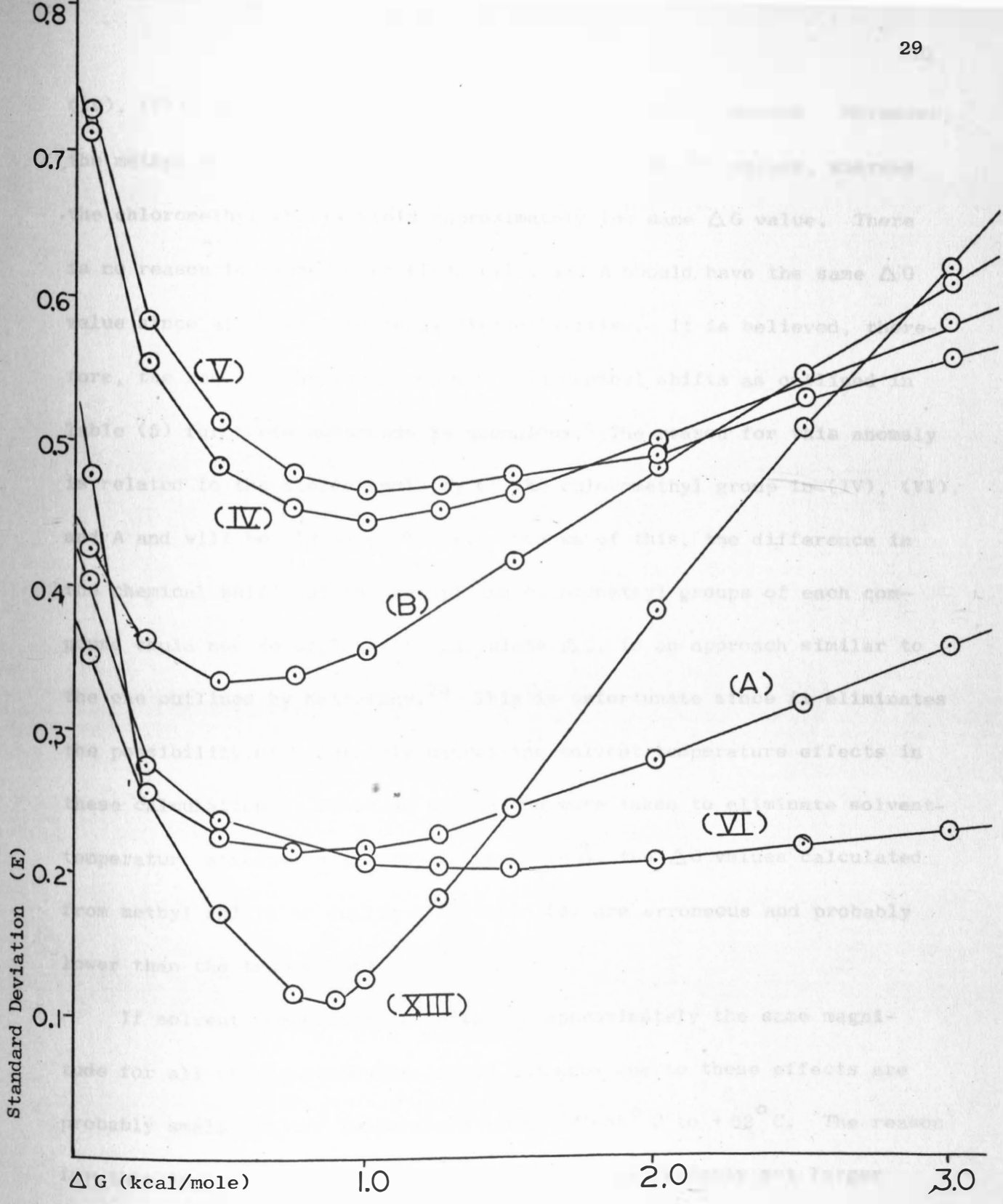


Figure 6

Free Energy versus Standard Deviation (E).

(IV), (VI), and A do not yield the same ΔG for each compound. Moreover, the methyl shifts yield unique and slightly higher ΔG values, whereas the chloromethyl shifts yield approximately the same ΔG value. There is no reason to expect that (IV), (VI), and A should have the same ΔG value since all have structural dissimilarities. It is believed, therefore, the results obtained from the chloromethyl shifts as outlined in Table (5) for these compounds is anomalous. The reason for this anomaly is related to the stereochemistry of the chloromethyl group in (IV), (VI), and A and will be discussed later. Because of this, the difference in the chemical shifts of the methyl and chloromethyl groups of each compound could not be employed to calculate ΔG, in an approach similar to the one outlined by Katritzky.[23] This is unfortunate since it eliminates the possibility of accurately cancelling solvent-temperature effects in these calculations. Since no provisions were taken to eliminate solvent-temperature effects on the total change in δ, the ΔG values calculated from methyl shifts as outlined in Table (4) are erroneous and probably lower than the true values.

If solvent-temperature effects are approximately the same magnitude for all of the compounds tested, changes due to these effects are probably small, in the temperature range of -58° C to $+52^{\circ}$ C. The reason for this is that solvent-temperature effects are probably not larger than the smallest change observed in this temperature range, namely 1.5 Hz for the methyl chemical shift of compound (VI). In other words, if

TABLE 4

CALCULATED CONFORMER POPULATIONS FROM METHYL CHEMICAL SHIFTS

Compound	V_o (Hz)	V_1 (Hz)	$-\Delta G$ (kcal/mole)	% Dominant Conformer[@]
(IV)	68.4	26.6	0.99 ± 0.3	81
(V)	55.1	81.5	1.07 ± 0.3	84
(VI)	57.9	39.1	1.39 ± 0.3	91
A	66.2	37.0	0.83 ± 0.3	75
B	95.2	41.9	0.59 ± 0.3	63
(XII)	76.3	20.0	0.61 ± 0.3	64
(XIII)	101.4	22.1	0.84 ± 0.3	76

@ At 25° C

TABLE 5

CALCULATED CONFORMER POPULATIONS FROM CHLOROMETHYL CHEMICAL SHIFTS

Compound	V_o (Hz)	V_1 (Hz)	$-\Delta G$ (kcal/mole)	% Dominant Conformer@
(IV)	269.1	140.2	0.52 ± 0.3	58
(V)	238.0	148.3	0.89 ± 0.3	88
(VI)	265.1	133.8	0.51 ± 0.3	58
A	267.3	140.1	0.57 ± 0.3	62
B	257.4	98.3	0.62 ± 0.3	65
(XII)	238.5	122.7	1.24 ± 0.3	88
(XIII)	230.6	104.7	0.72 ± 0.3	70

@ At 25 °C

(VI) is conformationally immobile then 1.5 Hz represents a change due to solvent-temperature effects alone. ΔG values were calculated for (IV), A, B, (XII), and (XIII) from the difference in the change in the respective methyl chemical shifts and the methyl chemical shift in (VI). ΔG values calculated in this manner represent an attempt to compensate for the solvent-temperature effects in these compounds and thus obtain values which are more representative of the true value. The results of these calculations appear in Table (6).

The variable temperature studies as stated earlier in this section have shown that the assumption of the existence of more than one conformational form for A and B is a valid one. These studies have also shown that A cannot be a conformer of B. In spite of conformational mobility and although the range of ΔG values given in Table (6) are only crude approximations of the true values, the assumption that A and B exist primarily in one conformational form is not inconsistent with these results. The knowledge that A and B exist in dominant conformational forms is helpful in the detailed analysis of the nmr spectra of these materials.

TABLE 6

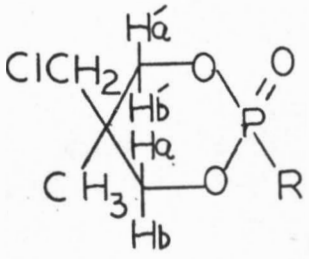
CALCULATED RANGE OF CONFORMER POPULATIONS FROM DIFFERENCE IN METHYL CHEMICAL SHIFTS

Compound	Range of $-\Delta G$ (kcal/mole)	% Range of Dominant Conformer
(IV)	0.99 - 1.32	81 - 90
A	0.83 - 1.29	75 - 89
B	0.59 - 0.78	63 - 73
(XII)	0.61 - 0.76	64 - 72
(XIII)	0.86 - 1.00	76 - 82

SPIN-SPIN COUPLING ANALYSIS

The Use of LAOCN3 in Analyzing Spectra

The nmr spectra of methylene protons of 2-substituted, 5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinans may be formally described as an $AA'BB'$ portion of an $AA'BB'K_2Q_3X$ system, where X = P, $Q_3 = CH_3$, and $K_2 = CH_2Cl$.[26]



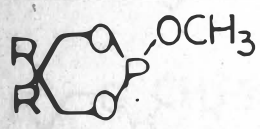
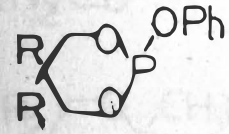
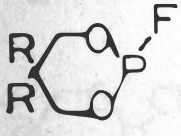
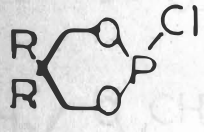
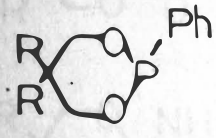
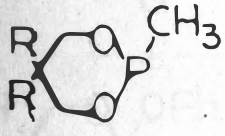
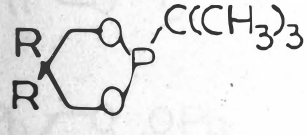
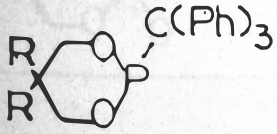
Since long range coupling with CH_3 and CH_2Cl is small, the system is often described as an $AA'BB'X$ system or more simply as an ABX system.[30,23]

ABX analysis of several dioxaphosphorinans has yielded one important feature of the methylene spectra of these compounds. In most cases where stereochemical assignments have been made, phosphorus hydrogen coupling is greater for H_b protons than for H_a protons. (See Table 7) This information and the utilization of the computer program LAOCN3 were useful in the analysis of spectra described in this section.

A complete description of LAOCN3 may be found in several sources.[46-9] Sample input and output data is provided in the Appendix. This program has two capabilities: 1) from an arbitrary set of chemical shift and coupling constant data for a system of two to seven $\frac{1}{2}$ spin nuclei, it can generate a table of frequencies and intensities of the lines expected in the nmr spectrum; 2) if calculated spectrum is similar to the observed spectrum, the program can perform iterative calculations in which the

TABLE 7

METHYLENE CHEMICAL SHIFTS AND COUPLING CONSTANTS OF SOME SUBSTITUTED DIOXAPHOSPHORINANS

Structure	H_a	H_b *	$J(POCH_a)$	$J(POCH_b)$ #	Ref.
	4.05	3.20	2.8	10.8	50
	4.25	3.35	2.8	10.8	50
	4.10	3.35	2.8	10.8	50
	4.30	3.45	6.0	10.8	50
	3.45	3.20	3.0	10.2	50
	4.18	3.82	9.9	14.0	28
	4.35	3.70	2.0	19.0	28
	4.27	3.48	6.6	14.7	28

* ppm
\# Hz
R = CH_3

TABLE 7 cont.

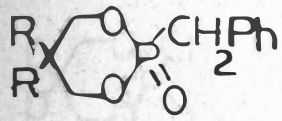
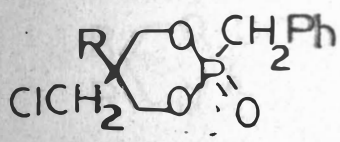
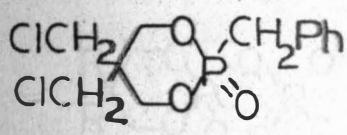
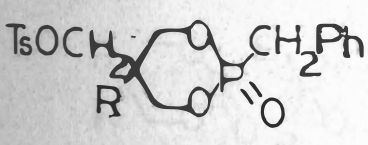
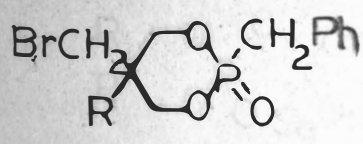
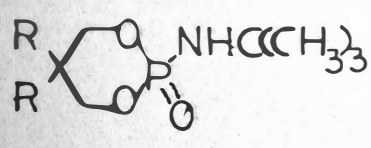
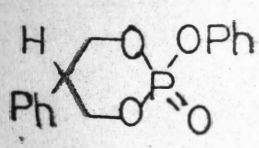
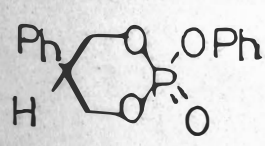
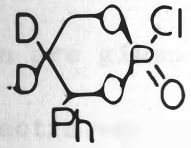
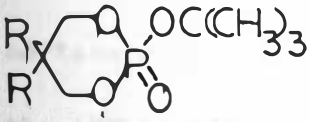
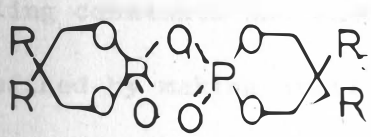
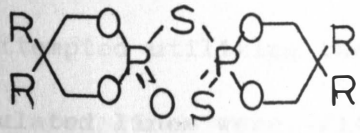
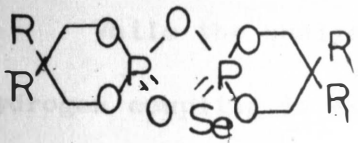
Structure	H_a	H_b	$J(POCH_a)$	$J(POCH_b)$	Ref.
	4.17	3.70	7.8	14.9	28
	4.32	3.78	12.0	11.0	28
	4.02	3.04	-	-	8
	4.18	3.71	13.0	10.4	8
	3.98	3.48	3.85	18.7	8
	4.22	3.85	7.8	16.3	28
	-	-	1.4	22.9	38
	-	-	3.9	20.2	38

TABLE 7 cont.

Structure	H_a	H_b	$J(POCH_a)$	$J(POCH_b)$	Ref.
	4.98	4.68	5.4	29.2	36
	4.04	3.85		21.0	30
	4.38	3.85	3.9	24.6	23
	4.46	3.97	1.4	24.6	23
	4.25	4.01	4.6	23.0	23

calculated lines are brought as close as possible to the observed lines.

A series of ABX spectra were calculated using LAOCN3 by which the chemical shifts and coupling constants were varied. Some of these spectra are given in Figure (7). General features of these calculated ABX spectra were observed in the actual spectra of compounds (IV), A, and B. In certain cases, a characteristic eight line pattern of the AB portion of the ABX spectra could be identified and approximate values for coupling constants and chemical shifts were assigned. These parameters were refined by making small changes in their values and noting the resultant changes in the calculated spectra. Finally, iterative calculations were attempted utilizing the more complex AA'BB'X approximation in which calculated lines were 'fit' to observed lines.

While the analysis of (IV) and B is simplified because phosphorus-hydrogen coupling is evident in both the AA' and BB' portions of the AA'BB'X spectra, the analysis of compound A is complicated by the fact that the AA' portion is collapsed into a single peak. (See Figure 9) Although the exact value of $J(POCH_a)$ cannot be determined from these types of spectra[30], the calculated ratic of H_a to the most intense peak in H_b varies with $J(POCH_a)$. This suggests a method of obtaining an approximate value of $J(POCH_a)$. The calculated intensity ratio increases from 4.7:1 for $J(POCH_a)$ = 0 Hz to 8:1 for $J(POCH_a)$ = 2.0 Hz. Compound A has an observed intensity ratio of 5:1 implying that the value of $J(POCH_a)$ is close to zero. Alternatively, it has been suggested that

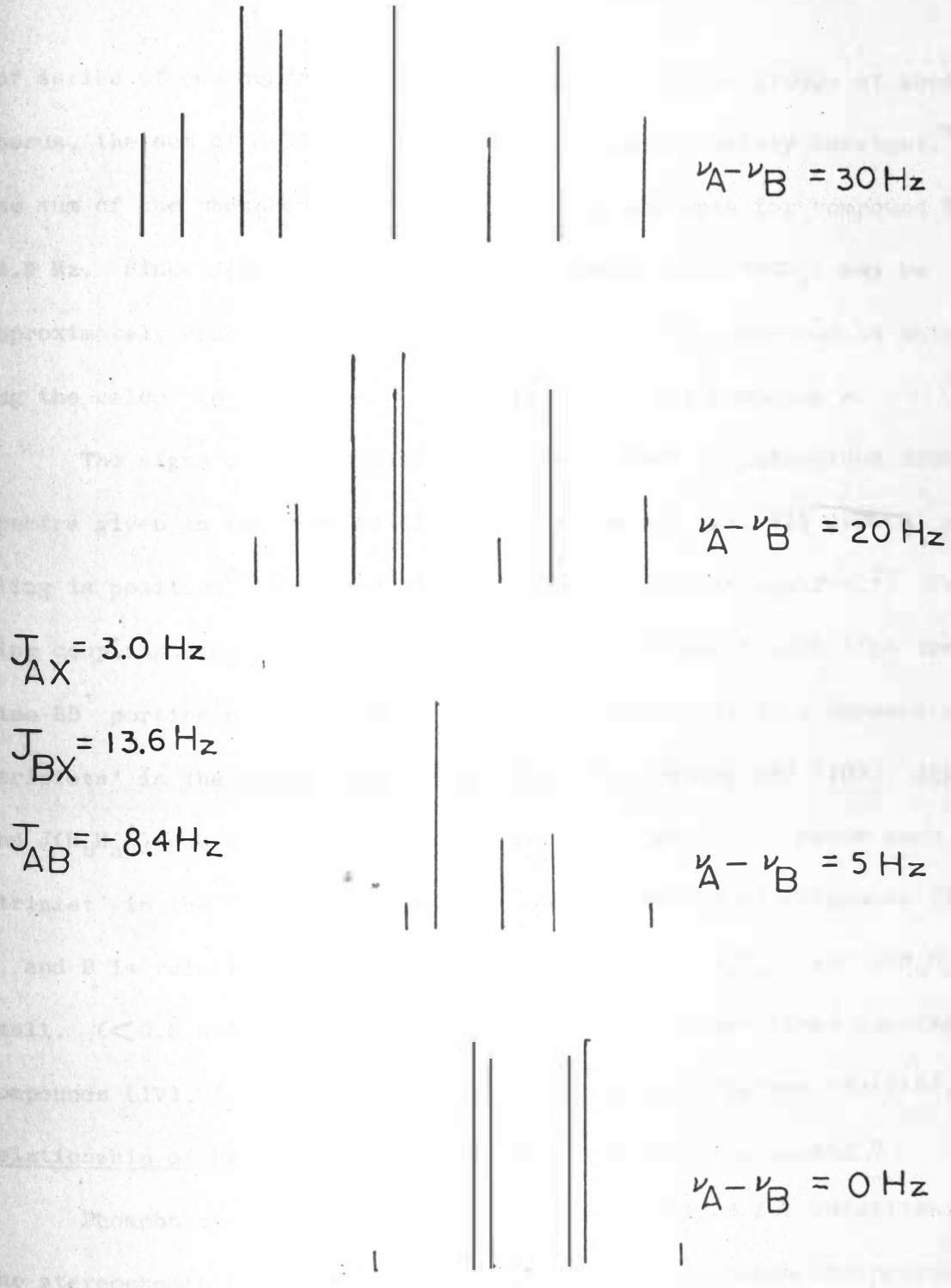


Figure 7

Calculated NMR Spectra for a 3 Spin System

for series of compounds which have similar functional groups at phosphorus, the sum of $J(POCH_a)$ and $J(POCH_b)$ is approximately constant.[8,23] The sum of the phosphorus-hydrogen coupling constants for compound B is 24.8 Hz. Since $J(POCH_b)$ = 21.4 Hz for compound A, $J(POCH_a)$ may be approximately equal to 3.4 Hz. The value of 3.4 Hz was used in obtaining the calculated spectra shown in Figure (9) for compound A.

The signs of the coupling constants cannot be determined from the spectra given in Figures (8)-(10). It is assumed that all J(POCH) coupling is positive[51] and that all geminal coupling is negative.[25] Cross ring coupling $J(H_bH_b')$ or $J(H_aH_a')$ causes splitting in each line the four line BB' portion of the AA'BB'X spectra.[30] This splitting appears as 'triplets' in the calculated spectra given in Figures (8)-(10). $J(H_aH_b')$ and $J(H_bH_a')$ cause further splitting in each 'triplet'. Since each 'triplet' in the BB' portion of the observed spectra of compounds (IV), A, and B is relatively unsplit, the magnitude of $J(H_aH_b')$ and $J(H_bH_a')$ is small. ($<$0.5 Hz) The results of the analysis of methylene spectra of compounds (IV), A, and B is shown in Table (8) and Figures (8)-(10).

Relationship of Ring Conformation to Coupling in (IV), A, and B

Phosphorus-hydrogen coupling has been utilized for establishing the stereochemistry of many dioxaphosphorinans. Although phosphorus-hydrogen coupling is dependent on hybridization of phosphorus and the nature of substituents attached to phosphorus, stereochemical information is based on evidence that J(POCH) coupling is a function of the

TABLE 8

RESULTS OF SPECTRAL ANALYSIS OF THREE DIOXAPHOSPHORINANS

Compound	Solvent	Chemical Shifts (Hz)* H_a' / H_a	Chemical Shifts (Hz)* H_b' / H_b	Coupling Constants $^{\#}J(H_bH_b')$	Coupling Constants $^{**}J(H_aH_b)$	Coupling Constants $^{@}J(POCH_a')$ / $J(POCH_a)$	Coupling Constants $^{@}J(POCH_b')$ / $J(POCH_b)$
IV	CCl_4	254.2	256.2	3.3	-11.5	2.7	28.3
A	CD_3COCD_3	262.0	252.8	3.4	-11.2	(3.4)	21.4
B	CD_3COCD_3	270.1	247.2	2.9	-10.7	4.7	20.1

* At 60 MHz

\# $J(H_aH_a')$, $J(H_aH_b')$, and $J(H_bH_a') < 0.5$ see Ref. 30

** Assumed to be negative, see Ref. 25

@ Assumed to be positive, see Ref. 51

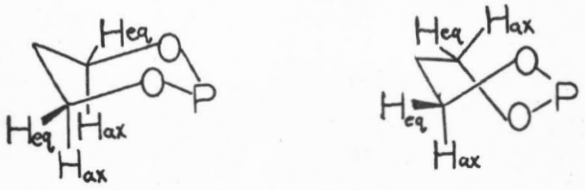
TABLE 8 cont.

RESULTS OF SPECTRAL ANALYSIS OF THREE DIOXAPHOSPHORINANS

Compound	Temperature (^{o}C)	Peaks obsd	Transitions calcd	RMS error (Hz)	Max error (Hz)
IV	40	12	48	0.241	0.294
A	40	13	36	0.299	0.433
B	40	13	48	0.177	0.390

dihedral angle between H-C and P-O bonds.[24] This is analogous to vicinal H-H coupling described by the Karplus equation.[25] Although some attempts have been made to extablish exact values for J(POCH) and dihedral angles in various phosphorus containing systems, conflicting results have appeared. (See Table 9) In spite of this, several dioxaphosphorinan compounds have been assigned chair conformations based on values of $J(POCH_{eq})$ = 20-30 Hz and $J(POCH_{ax})$ = 0-5 Hz implying dihedral angles of 180 and 60, respectively.[8,33,23]

Although the J(POCH) values given in Table (8) compare favorably with values suggesting dihedral angles of 180 and 60, (assuming $H_a = H_{ax}$ and $H_b = H_{eq}$) chair conformations cannot be assigned based on J(POCH) data alone. The reason for this is that of the three major conformational forms of six-membered ring systems, (chair, twist-boat, boat) both chair and twist-boat forms have the same dihedral angle relationships for H_{ax} and H_{eq}.[33]



The dihedral angles for H_{ax} and H_{eq} in boat conformers are equivalent, implying that $J(POCH_{ax}) = J(POCH_{eq})$. The nmr spectrum of compound (II) confirms this since $J(POCH_{ax}) = J(POCH_{eq})$ = 6.0 Hz and all dihedral angles are approximately 120.

TABLE 9

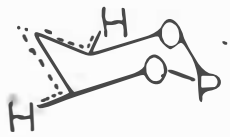
ANGULAR DEPENDENCE OF P-H COUPLING

Type	Approximate angle, degrees	J (Hz)	Ref.
P(III)*-O-C-H	30	2.8	52
P(III)-O-C-H	60	2.5	26
P(III)-O-C-H	113	1.7	26
P(III)-O-C-H	128	4.4	26
P(III)-O-C-H	163	9.6	26
P(III)-O-C-H	180	10.8	52
P(IV)-O-C-H	60	6.0	28
P(IV)-O-C-H	60	1.9	53
P(IV)-O-C-H	180	22.4	28
P(IV)-O-C-H	180	21.6	53
P(IV)-C-C-H	30	7.0	54
P(IV)-C-C-H	60	12.0	54
P(IV)-C-C-H	90	0	54
P(IV)-C-C-H	180	35.0	54

* Roman numerals refer to valency of phosphorus

(II)

For this reason, it is possible to eliminate the boat conformer as the major conformational for (IV), A, and B. The question of whether (IV), A, and B are in chair or twist-boat forms is related to the cross ring coupling in these compounds. The $J(H_bH_b')$ values for (IV), A, and B are 3.3, 3.4, and 2.9, respectively. $J(H_bH_b')$ coupling represents long range coupling through four σ bonds. Effective coupling ($>$ 1.0 Hz) through four single bonds is usually confined to a planar 'W' or zig-zag configuration of atoms.[55,32]



This configuration eliminates the possibility of effective cross ring coupling for the twist-boat conformation. For this reason, (IV), A, and B have been assigned chair conformations. Accordingly, H_a and H_a' are axial protons and H_b and H_b' are equatorial protons.

The Relationship of Phosphorus-Hydrogen Coupling to Conformer Ratios

The variation of spectral parameters with change in temperature, as outlined earlier, was interpreted as a consequence of the changing ratio of rapidly interconverting conformers. Consider conformational equilibria involving predominantly two chair forms.

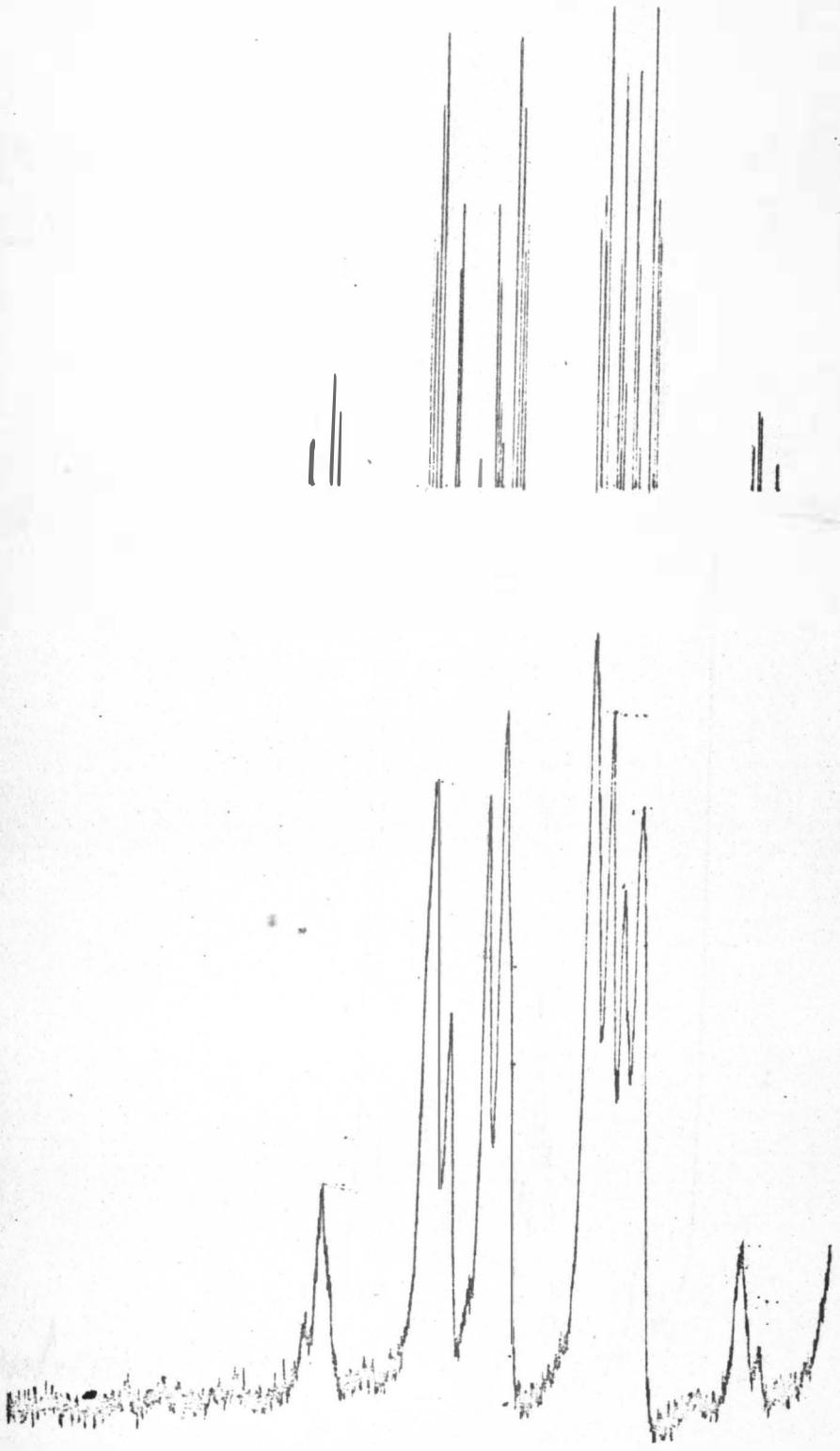


Figure 8

Top: Calculated methylene nmr spectrum
Bottom: Observed spectrum for compound (IV)

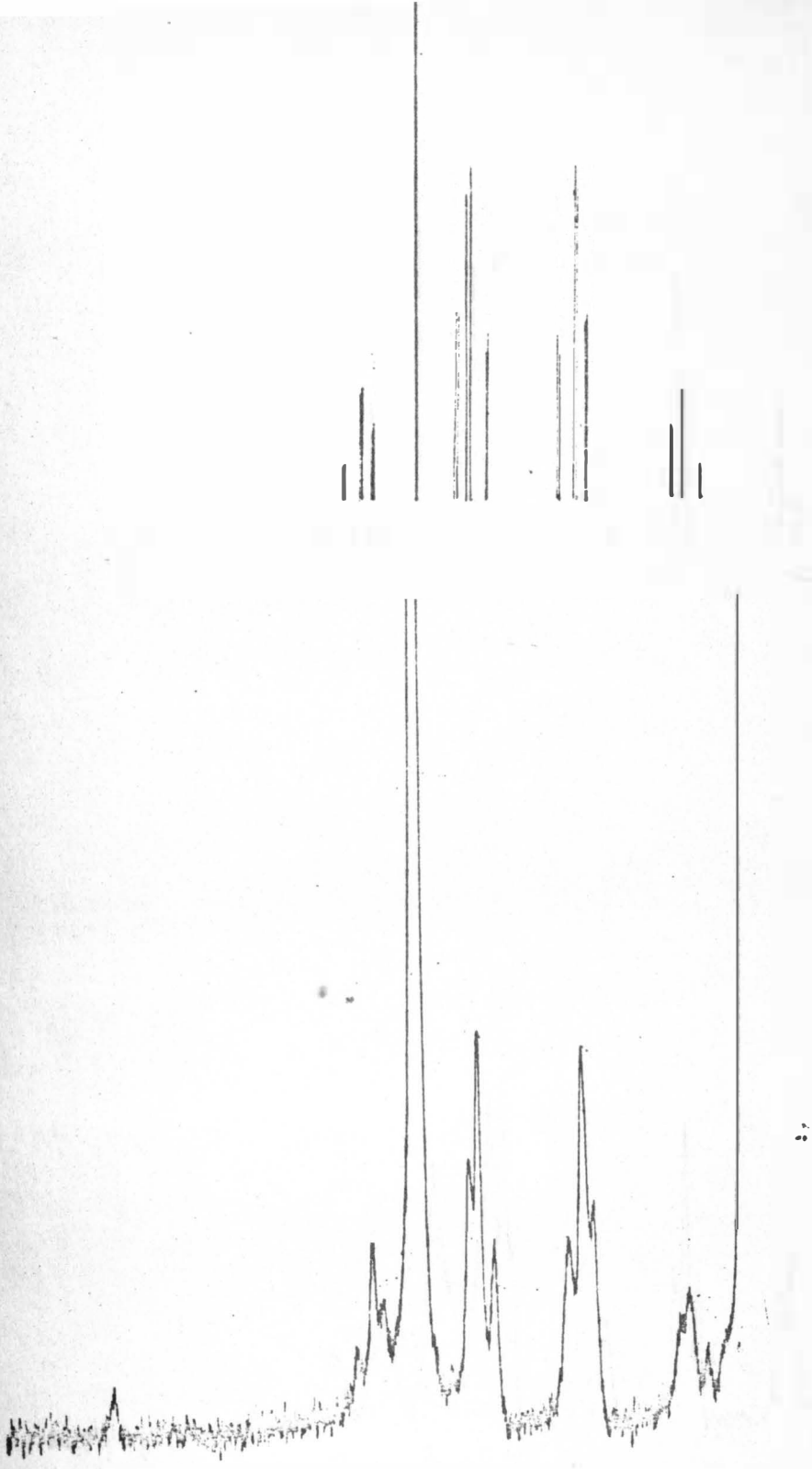


Figure 9

Top: Calculated methylene nmr spectrum

Bottom: Observed spectrum for compound A

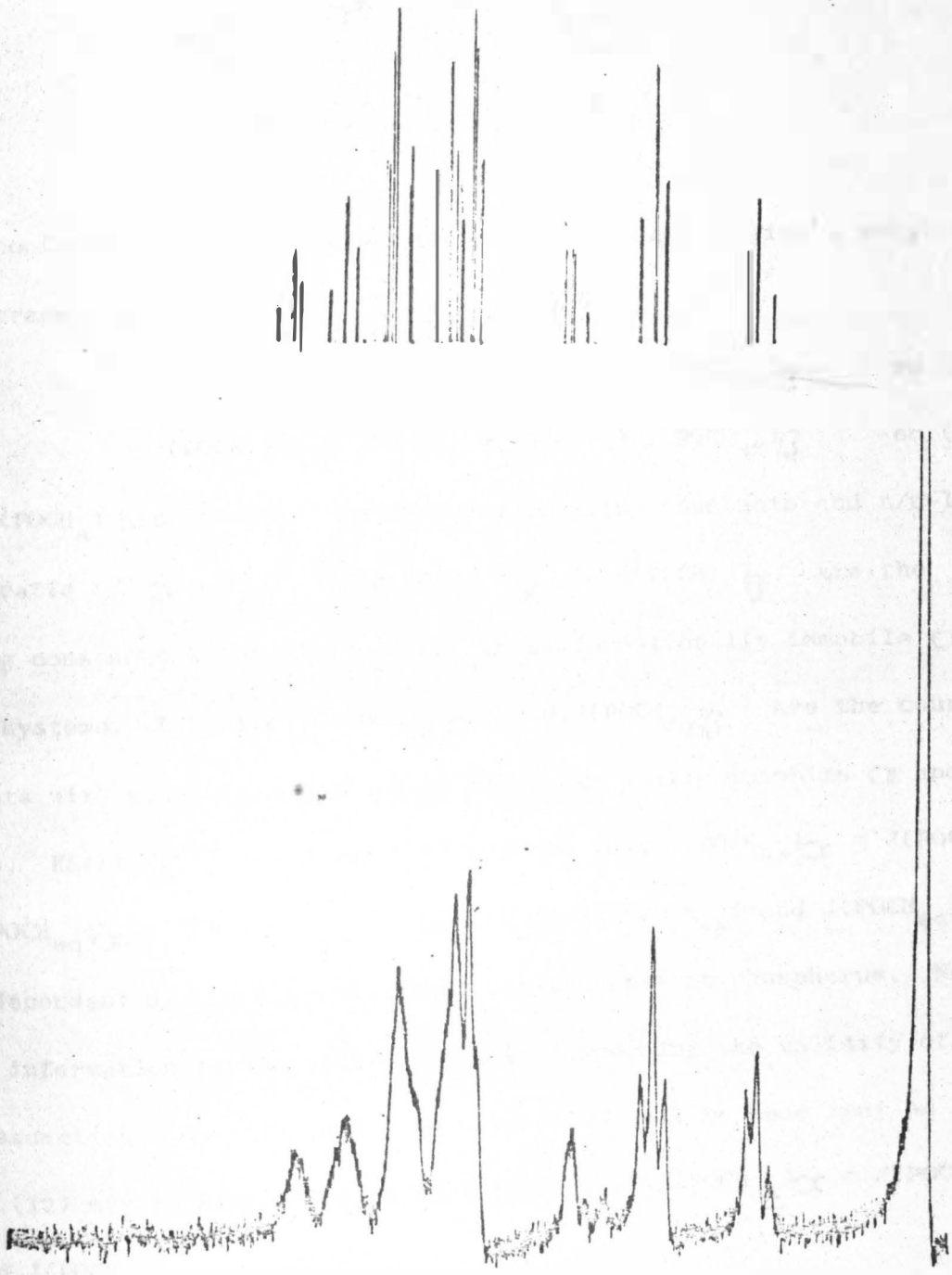
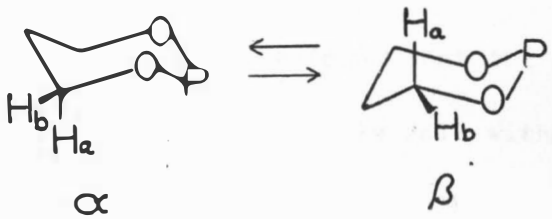


Figure 10

Top: Calculated methylene nmr spectrum

Bottom: Observed spectrum for compound B



α β

If the conformers are interconverting rapidly enough to give a weighted time average then

$$J(POCH_a) = n\ J(POCH_{ax})_{\alpha} + (1-n)\ J(POCH_{eq})_{\beta} \qquad \text{eq (11)}$$

$$J(POCH_b) = n\ J(POCH_{eq})_{\alpha} + (1-n)\ J(POCH_{ax})_{\beta} \qquad \text{eq (12)}$$

where $J(POCH_a)$ and $J(POCH_b)$ are observed coupling constants and n/n-1 is the ratio of α to β .[8,33] $J(POCH_{ax})_{\alpha}$ and $J(POCH_{ax})_{\beta}$ are the coupling constants with axial protons in conformationally immobile α and β systems. Likewise, $J(POCH_{eq})_{\alpha}$ and $J(POCH_{eq})_{\beta}$ are the coupling constants with equatorial protons in conformationally immobile α and β systems. Katritzky[23] and Edmundson[8] assumed that $J(POCH_{ax})_{\alpha} = J(POCH_{ax})_{\beta}$ and $J(POCH_{eq})_{\alpha} = J(POCH_{eq})_{\beta}$, implying that $J(POCH_{ax})$ and $J(POCH_{eq})$ are independent of the disposition of substituents at phosphorus. Not enough information is presently available concerning the validity of this assumption. Nevertheless, the assumption will be made that eq (11) and eq (12) may be simplified by substitution of $J(POCH_{ax})_{\alpha} = J(POCH_{ax})_{\beta} = J_{ax}$ and $J(POCH_{eq})_{\alpha} = J(POCH_{eq})_{\beta} = J_{eq}$.

$$J(POCH_a) = n\ J_{ax} + (1-n)\ J_{eq} \qquad \text{eq (13)}$$

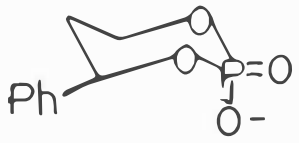
$$J(POCH_b) = n\ J_{eq} + (1-n)\ J_{ax} \qquad \text{eq (14)}$$

The sum of the observed coupling constants $\sum J(POCH) = J(POCH_a) +$

$J(POCH_b)$ is equivalent to $J_{ax} + J_{eq}$.[23]

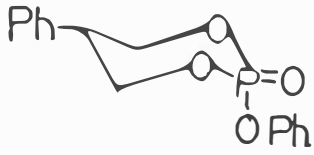
Edmundson[23] and Katritzky[8] have found that the sum of the observed coupling constants ($\sum J(POCH)$) generally fall within the range of 20 to 23 Hz for phosphonate compounds (R_3 = alkyl). Although less information is available for phosphates (R_3 = OR), the range of $\sum J(POCH)$ is approximately 20 to 25 Hz.[30,23] For halogen containing compounds, (R_3 = Cl, Br) the range is generally higher than for phosphates (30 to 35 Hz).[23,30]

Determination of conformer ratios is contingent upon establishing values for J_{ax} or J_{eq}. Katritzky[23] determined J_{ax} and J_{eq} for pyrophosphates utilizing observed coupling constants in $((EtO)_2PO)_2X$ compounds where X = O, S, or Se. The average value of J_{ax} determined by Katritzky is 1.6 Hz.[23] This is in good agreement with the observed value of J_{ax} for (8) determined by M. Tsuboi, et al.[56]



(8)

If (9) is conformationally immobile, the coupling constant reported by Hall and Malcomb, namely 1.4 Hz, is a good approximation of J_{ax}.[38]



(9)

Mujoral, Pujol and Navech assumed that J_{ax} = 1.9 Hz for the purposes of calculating conformer ratios.[53] If seems likely that the true value of J_{ax} for phosphate and phosphonate systems is less than 2.0 Hz and approximately constant. In contrast, J_{eq} appears to vary depending upon the type of substituents attached to phosphorus.[30] J_{eq} may be determined for a given system by eq (15).

$$J_{eq} = J(POCH_a) + J(POCH_b) - J_{ax} \qquad \text{eq (15)}$$

The percent major conformer may be determined by rearrangement of eq (13) or eq (14).

$$n = \frac{J(POCH_a) - J_{eq}}{J_{ax} - J_{eq}} \qquad \text{eq (16)}$$

$$n = \frac{J(POCH_b) - J_{ax}}{J_{eq} - J_{ax}} \qquad \text{eq (17)}$$

Conformer ratios were determined for compounds (IV), A, and B using eq (16) and eq (17) and the observed phosphorus-hydrogen coupling constants given in Table (8). The results of this analysis appear in Table (10).

TABLE 10

DETERMINATION OF CONFORMER RATIOS FROM PHOSPHORUS-HYDROGEN COUPLING-CONSTANTS

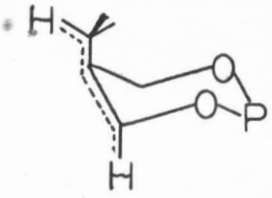
Comp.	Solv.	Temp.	$J(POCH_a)$	$J(POCH_b)$	$\sum J(POCH)$	J_{ax} *	J_{eq} #	Per cent Major Conformer (n) x 100
IV	CCl_4	40	2.7	28.3	31.0	1.5	29.5	96
A	$(CD_3)_2CO$	40	0-3.4	21.4	21.4-24.8	1.5	19.9-23.2	91-100
B	$(CD_3)_2CO$	40	4.7	20.1	23.4	1.5	21.9	85

*See ref. 23,38
#From eq (15)

STEREOCHEMISTRY AT C-5 AND PHOSPHORUS

Relationship of Chemical Shifts and Widths at One-Half Height to the Stereochemistry at C-5

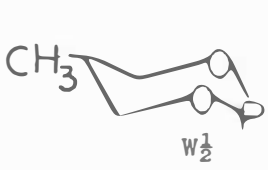
Edmundson has shown by decoupling experiments that the coupling of methyl groups at C-5 with phosphorus is small and non-stereospecific in 1,3,2-dioxaphosphorinans.[35] In contrast, coupling of methyl groups at C-5 with methylene protons at C-4 and C-6 is small but stereospecific.[57] For 5,5-dimethyl diosaphosphorinans which have been assigned chair conformations, the axial methyl group is more strongly coupled to the methylent ring protons than the equatorial methyl group. Furthermore, the axial methyl group is specifically coupled to axial methylene protons.[50] The reason for this is related to the required planar 'W' configuration of atoms for effective coupling through four single bonds.



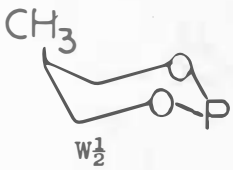
Presumably, rotation of the methyl group will diminish the effectiveness of the planar 'W' configuration. Nevertheless, the resonance peak associated with the axial methyl group will have a greater width at half height ($W_{\frac{1}{2}}$) than the equatorial methyl group due to the increased coupling with axial methylene protons. Table (11) lists examples of compounds in which methyl groups have been given axial and equatorial designations based on the relative values of $W_{\frac{1}{2}}$. Although the chemical shifts of the methyl group are temperature dependent in cases where conformational mobility is

TABLE 11

STEREOCHEMICAL ASSIGNMENTS AT C-5 OF SOME 5,5-DIMETHYL DIOXAPHOSPHORINANS



Narrow



Broad

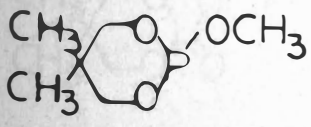
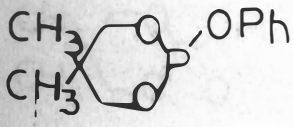
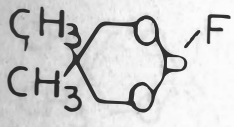
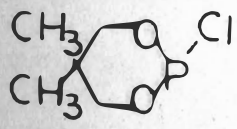
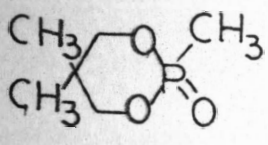
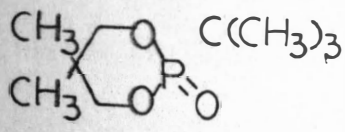
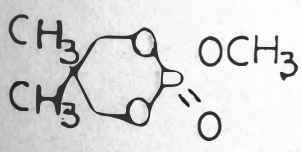
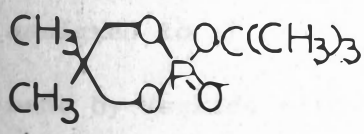
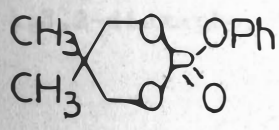
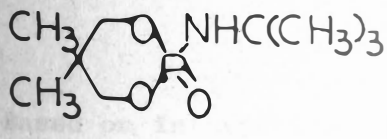
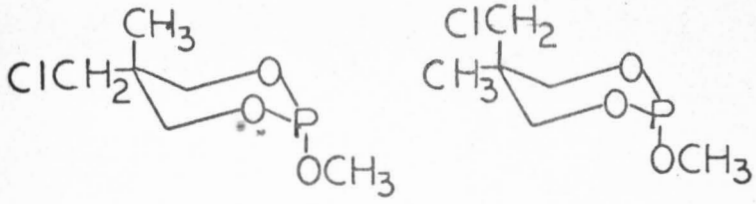
Compound	δ (ppm)	δ (ppm)	Ref.
	0.70	1.25	50
	0.80	1.30	50
	0.80	1.30	50
	0.80	1.25	50
	1.01	1.11	28
	0.87	1.25	28
	0.88	1.20	28

TABLE 11 cont.

Compound	Narrow $W_{\frac{1}{2}}$ δ (ppm)	Broad $W_{\frac{1}{2}}$ δ (ppm)	Ref.
	0.90	1.21	28
	0.97	1.29	28
	0.98	1.16	28

present, in most cases, the chemical shift of the broader methyl signal associated with the axial methyl group is downfield of the equatorial methyl signal.

Stereochemical assignments at C-5 of A, B, and related compounds are given in Table 12. The assignments are based on the relative $W_{\frac{1}{2}}$ values of the methyl signals of each pair of isomers. Therefore, the methyl resonance of (VI) is compared to the methyl resonance of (VII), A with B, (X) with (XI) and so on. In all cases the broader methyl signal is assigned to an axial methyl group. This is analogous to the comparison made by Verkade with the two isomers of 5-chloromethyl-2-methoxy-5-methyl-1,3,2-dioxaphosphorinan.[33]



Based on information given in Table 12, deshielding of axial substituents relative to equatorial substituents might be predicted and based on the trend that all signals from methyl groups designated as axial are downfield of those designated equatorial. If the stereochemical assignments as outlined in Table (12) are correct, the chloromethyl resonance in A should be downfield of the chloromethyl resonance in B, and likewise for each pair of isomers. This prediction is verified by chemical shift values given in Table (13).

It is noteworthy that the stereochemical assignments given for (III) and (VI) in Table (12) are in agreement with X-ray diffraction data.

TABLE 12

RELATIONSHIP OF METHYL CHEMICAL SHIFT AND WIDTH AT ONE-HALF HEIGHT TO THE STEREOCHEMISTRY AT C-5

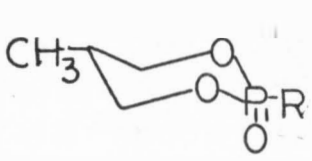
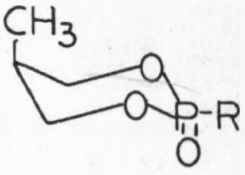
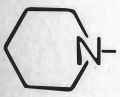
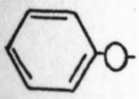
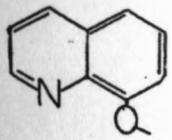
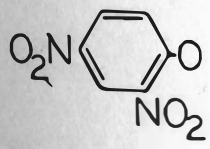
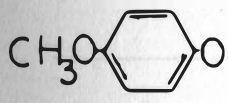
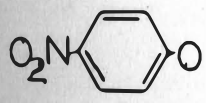
	Methyl Chemical Shift					
						
R	Compd.	$W_{\frac{1}{2}}$(Hz)	δ(ppm)	Compd.	$W_{\frac{1}{2}}$(Hz)	δ(ppm)
Br	(III)	-	0.98			
Cl	(IV)	1.4	0.97			
OH	(V)	-	0.98			
	(VI)	1.6	0.88	(VII)	1.9	1.18
	A	1.2	0.87	B	1.8	1.23
	(X)	1.6	0.85	(XI)	2.0	1.35
	(XII)	1.4	1.02	(XIII)	1.8	1.43

TABLE 12 cont.

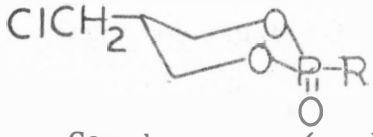
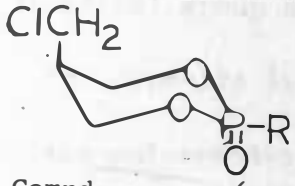
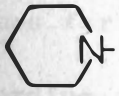
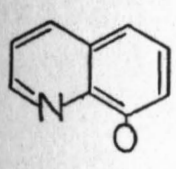
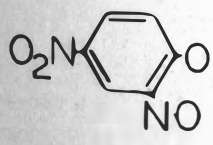
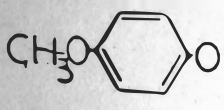
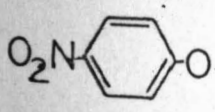
R	Compd.	$W_{\frac{1}{2}}$(Hz)*	δ(ppm)	Compd.	$W_{\frac{1}{2}}$(hz)	δ(ppm)
	(XIV)	1.8	0.90	(XV)	2.2	1.25
	(XVI)	1.4	1.00	(XVII)	1.8	1.36

*All errors estimated at ± 0.2 Hz.

TABLE 13

RELATIONSHIP OF CHLOROMETHYL CHEMICAL SHIFTS TO

THE STEREOCHEMISTRY AT C-5

R	 Compd	(ppm)	 Compd.	(ppm)
	(VII)	3.42	(VI)	3.63
	B	3.26	A	3.68
	(XI)	3.37	(X)	3.68
	(XIII)	3.35	(XII)	3.74
	(XV)	3.32	(XIV)	3.72
	(XVII)	3.42	(XVI)	3.75

The stereochemical assignments at C-5 for (VI) and (VII) are also in agreement with the results of nmr solvent studies conducted by Edmundson.[7] Edmundson contends that the chemical shift difference designated as $\Delta\delta$ and defined as the chemical shift in $CDCl_3$ minus the chemical shift in benzene is greater for the methyl group than the chloromethyl group at C-5 when the methyl groups is equatorially situated. The opposite is true when the methyl group is axial.[8] $\Delta\delta$ values for the chloromethyl and methyl groups in A are 23 Hz and 33 Hz, respectively. The respective values for the chloromethyl and methyl groups in B are 54 Hz and 40 Hz. According to Edmundson's rules, the methyl group in A should be equatorially situated and axial in B. This is also in accord with the stereochemical assignments for A and B in Table (12).

The Stereochemistry At Phosphorus of A and B

The ring geometry and the configuration at C-5 of some dominant conformers are known. All that remains is the assignment of the configuration of groups at phosphorus. For example, the stereochemistry at phosphorus of (IV) is easily deduced from known stereochemical information. The reaction of chlorine with methyl bicyclic phosphite (I) insures that the relationship of the chloromethyl group at C-5 with the phosphoryl oxygen is cis; providing that no subsequent isomerization of (IV) takes place. Analysis of the nmr spectra of (IV) indicates that (IV) is in a dominant chair form in solution. The relative chemical shifts of the chloromethyl and methyl group at C-5 indicates that the chloromethyl group is predominantly axial. This implies that the phosphoryl oxygen of the chair conformer of (IV) must be in an equatorial position.

Similar reasoning applies to (VI). X-ray diffraction data indicates that the relationship of the chloromethyl group and the phosphoryl oxygen in solid state is trans.[5] NMR studies of (VI) in solution indicate that the chloromethyl group at C-5 is primarily axial. If the dominant conformational form of (VI) is chair then the phosphoryl oxygen must be axially situated.

The assignment of the stereochemistry of the dominant conformers of A and B is not as simple as the examples mentioned above. The reason for this is that no prior information is available in regard to the relationship of the configuration at C-5 to the configuration at phos-

phorus. Four things are known, however, about the stereochemistry of A and B.

A) A and B are non-interconvertable geometrical isomers.

B) A and B exist in solution in dominant conformational forms.

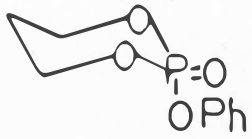
C) The dominant forms of A and B are chair conformers.

D) The configuration at C-5 of the dominant chair conformer of A is with the methyl group primarily equatorially situated and in B axially situated.

This information indicates that the configuration at phosphorus of the conformers of A and B is related in a unique way. The stereochemical assignments at C-5 demand that the phosphoryl oxygen must be axial for both isomers or equatorial for both isomers. They cannot be axial in one isomer and equatorial in the other. If the latter and forbidden case were true, A would be a conformer of B and therefore A and B could not be geometrical isomers. An alternate way of stating this is that since A and B are geometrical isomers and the configuration at C-5 for A is opposite to that of B, the configuration at phosphorus for A and B must be the same. Thus, the relative configuration at phosphorus of the dominant conformers of A and B is related to the relative and similar disposition of the phosphoryl oxygen and phenoxy group in both isomers.

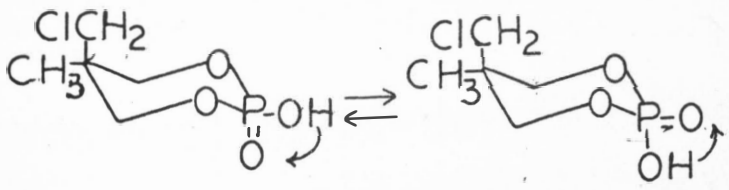
Normally, bulky axial substituents in mobile six-membered ring systems are not favored. The argument that an axial phenoxy group in A and B is less favored because of steric interactions with axial protons at C-4 and C-6 is probably not valid, however. X-ray diffraction

studies of (III) and (VI) have shown that flattening of the phosphate end of the ring greatly reduces 2-4 and 2-6 steric interactions. Likewise, the argument that the phosphoryl oxygen prefers an equatorial position in 2-oxo-1,3,2-dioxaphosphorinans lacks validity. The argument is based on the X-ray diffraction study of (9).[4]

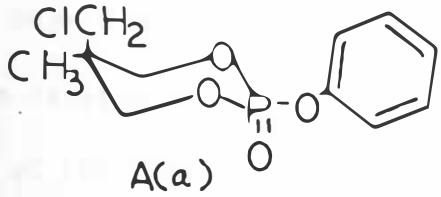
(9) 

(9) is expected to be highly conformationally mobile in solution. There is no apparant reason for believing that the conformational form of (9) in the solid state is the dominant form in solution.

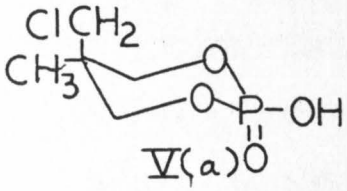
The assignment of configuration of phosphorus for A and B is based on relative chemical shift data. It is assumed that the disposition of substituents at phosphorus will influence the chemical shifts of the axial protons at C-4 and C-6. (V) and A were chosen for a comparitive study of the chemical shifts because each compound has the same stereochemistry at C-5 and because (V) may assume the most stable configuration at phosphorus without changing the configuration at C-5. This is accomplished, presumably, by a simple proton transfer.



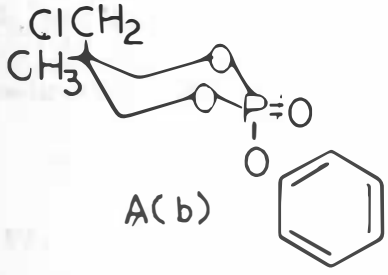
There is no restriction on the relationship of the configuration at phosphorus of A to the configuration of (V). Therefore, A and (V) may have either identical or opposite configurations at phosphorus.



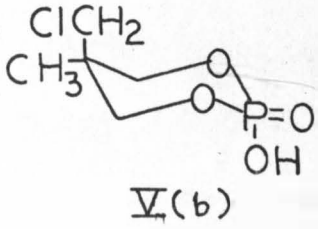
A(a)



V(a)



A(b)



V(b)

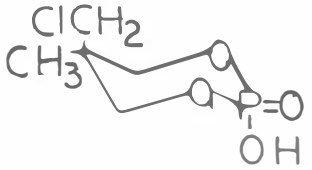
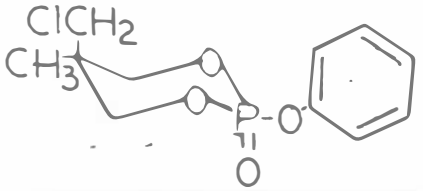
A(a) and V(a) have identical configurations as do A(b) and V(b). If A and (V) have identical configurations with the phosphoryl oxygen axial then the chemical shifts of the axial methylene protons are expected to be similar for both compounds. It is assumed that equatorially disposed phenoxy and hydroxy groups would not have a profound influence on the shielding or deshielding of axial protons. Alternately, if A and (V) have identical configurations with the phosphoryl oxygen equatorial then the chemical shifts of the axial methylene protons are expected to be different. Flattening of the phosphate end of the ring in A should result in a favorable interaction of the axial phenoxy group with the axial protons. One would predict that the benzene ring would shield the axial protons in A relative to those in (V). This prediction is based on the results of solvent studies for 1,3-dioxanes in which it is shown that

the favored orientation of an aromatic ring is perpendicular to axial methylene protons and results in the net shielding of these protons.[83] In summary, if A and (V) have the same configuration at phosphorus one would expect to observe either similar chemical shifts for axial protons or the axial protons in A should be shielded or upfield relative to those of (V). The chemical shifts of axial protons of A and (V) in CD_3COCD_3 are given in Table 14. The relative chemical shifts of (V) and A indicate that the axial protons in A are deshielded relative to those in (V). This means that neither of the above mentioned cases apply to A and (V). The relative difference in the chemical shifts of axial protons in A and (V) have opposite configurations. This means that the phosphroyl oxygen is axial in one but not both compounds.

The location of the phosphoryl oxygen and its ability to form hydrogen bonds and act as a proton acceptor is critical in determining which compound, A or (V), has an axial phosphoryl oxygen. One would predict that the nature of an axial P=O bond is important in influencing the chemical shift of axial methylene protons. Any changes in the axial P=O bond brought about by strong hydrogen bonding or protonation would result in changes in the chemical shifts of axial methylene protons. Table 14 gives the chemical shifts of axial protons of A and (V) in CF_3COOH. CF_3COOH is a relatively strong acid which should result in strong hydrogen bonding if not protonation of the phosphoryl oxygen. If the chemical shifts of the axial methylene protons in CD_3COCD_3 are compared

TABLE 14

CHEMICAL SHIFT VALUES OF AXIAL PROTONS IN ACETONE AND TRIFLUROACETIC ACID

Compound	Assigned Structure	Solvent	
		CD_3COCD_3 H_{ax}(Hz)	CF_3COOH H_{ax}(Hz)
(V)		249*	250*
A		262	256*

*From visual analysis of spectra

to those in CF_3COOH, Compound A demonstrates the most profound changes. This provides evidence that the configuration at phosphorus of A is with the phosphoryl oxygen axially situated. Conversely, the phosphoryl oxygen must be equatorial in (V). If (V) can assume the most stable configuration by a simple proton transfer as suggested earlier, then the opposite configuration of A suggests that other factors are involved in controlling its stereochemistry.

If the phosphoryl oxygen is axial in the dominant conformer of A then it must also be axial in the dominant conformer of B.

RESULTS AND CONCLUSIONS

As a basis for comparison, ΔG values may be calculated for A and B from conformer ratios as given in Table (10). The respective values for A and B are 1.49 kcal/mole and 1.22 kcal/mole. Although these values do not fall within the range of ΔG values given in Table (6), it should be noted that the range given in Table (6) is only approximate. Furthermore, the values calculated for Table (6) are influenced by estimates of solvent-temperature effects which may be erroneous. Likewise, ΔG calculated from conformer ratios in Table (10) is ultimately influenced by the accuracy of the estimation of J_{ax}. In spite of these drawbacks, the agreement of values obtained by both methods is fairly good.

The chief drawback is inherent in the interpretation of the ΔG for A and B. If the low energy conformer of A or B is in equilibrium with more than one high energy form, the exact interpretation of ΔG is obscured. The stereochemistry of the low energy forms of A and B have been assigned. That A and B are in chair conformations in excess of 70% is not surprising in terms of what is known about other phosphate systems. If the assumption is made that both A and B are involved in chair-chair interconversions, then the meaning of ΔG becomes clear. (see Figure 11)

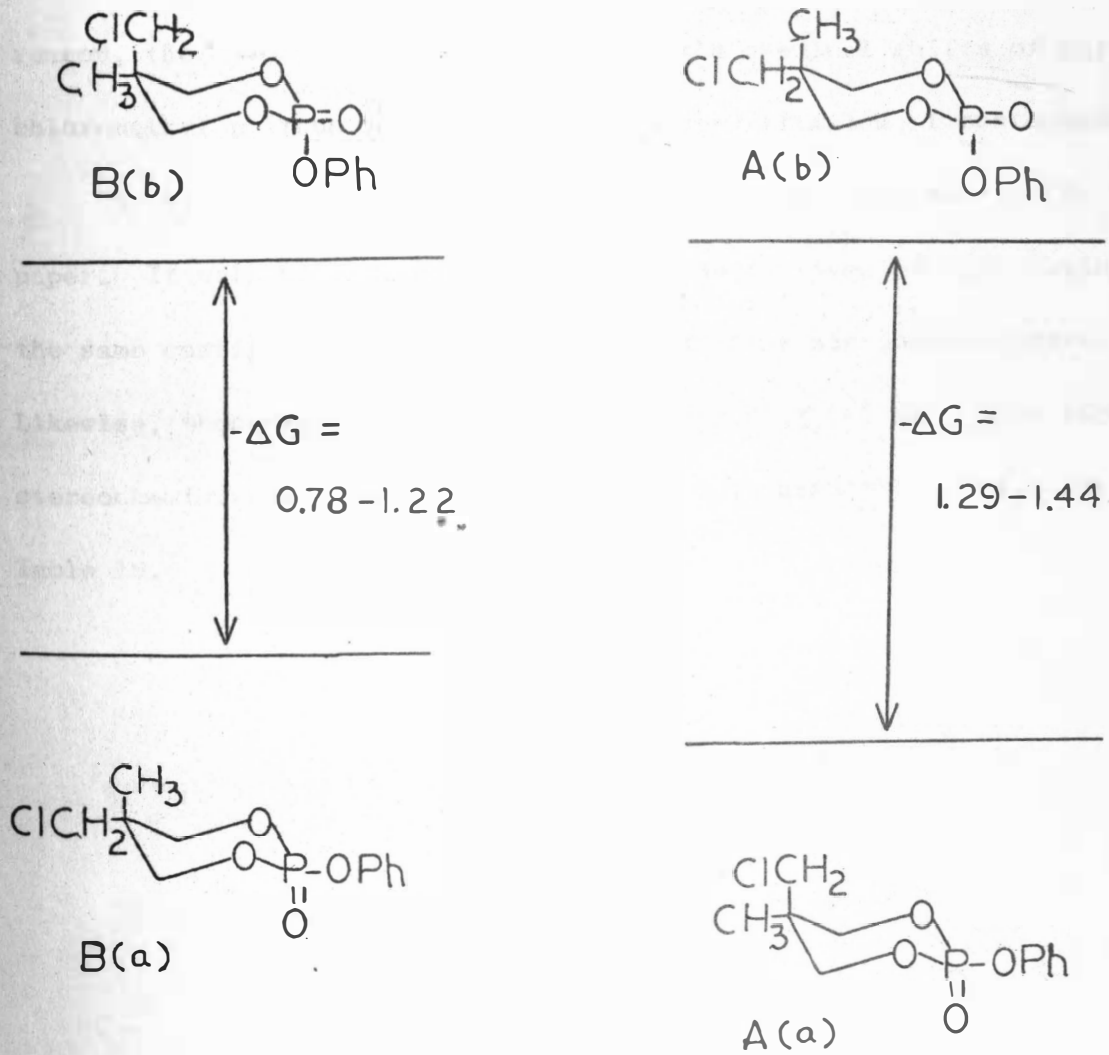
As depicted in Figure (11) there is a significant difference between the free energy difference of the conformers of A compared to those of B. The difference in ΔG for the conformers of A and B is related to their stereochemistry. If B(b) and A(b) have comparable energies then

A(a) may be lower in energy than B(a). Conversly, if B(a) and A(a) have comparable energies then B(b) is lower in energy than A(b). The stabilization of A(b) and B(b) may be related to their configuration at C-5. Verkade suggests that the chloromethyl group is more stable in an axial position than an equatorial position.[32] The data as presented in Figure 11 supports this. The lower energy form of A is stabilized by an axial chloromethyl group relative to the low energy form of B. If the chloromethyl group prefers an axial position, why is B(a) the preferred conformation of B and not B(b)? Verkade suggests that the axial preference of the chloromethyl group is related to diminished steric interactions. This, however is not an adequate explanation of the conformational preference of B, if the stereochemical assignments are correct. This author proposes that the axial preference of the chloromethyl group is related to a favorable dipole vector interaction between the chloromethyl group and the phosphate end of the ring. A favorable dipole interaction would be expected to be sensitive to a change in the configuration at phosphorus. Thus, a diminished or unfavorable dipole interaction may exist for the axial chloromethyl group in B(b) because of a change in configuration at phosphorus relative to A(a). This is a possible explanation of why A(a) is the preferred conformation of A and B(b) is not a preferred conformation of B.

The dipole interaction of an axial chloromethyl group also suggests reasons for the anamolous results obtained from variable temperature

FIGURE 11

COMPARISON OF FREE ENERGY DIFFERENCES OF A AND B

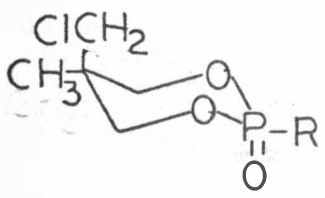


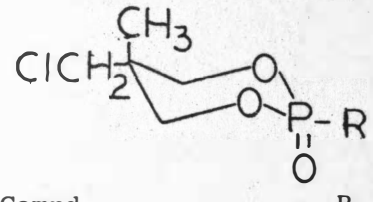
studies of (IV), (V), (VI), and A in Table 5. Each compound which gave erroneous ΔG values was later assigned an axial chloromethyl group at C-5. Since an axial chloromethyl group influenced by dipole interactions is expected to have rotational barriers, the temperature dependent chemical shifts of the chloromethyl protons are expected to be sensitive to these barriers as well as ring barriers to ring inversion. For this reason, the ΔG values calculated from the chemical shifts of axial chloromethyl protons will not give accurate estimates of conformer ratios.

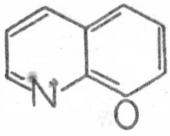
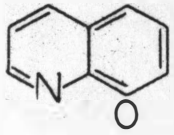
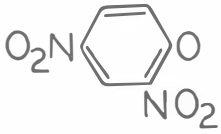
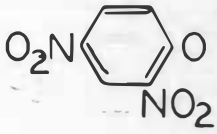
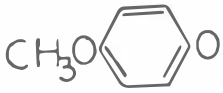
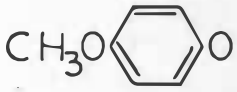
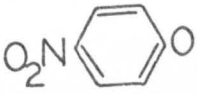
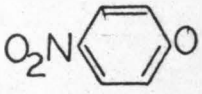
The stereochemistry of A and B have been assigned earlier in this paper. It will be assumed that all aryl derivitives of (IV) having the same configuration at C-5 as A have similar stereochemistries. Likewise, those having the same configuration at C-5 as B have similar stereochemistries. Assignments based on this assumption are given in Table 15.

TABLE 15

STEREOCHEMICAL ASSIGNMENTS OF A, B, AND RELATED COMPOUNDS



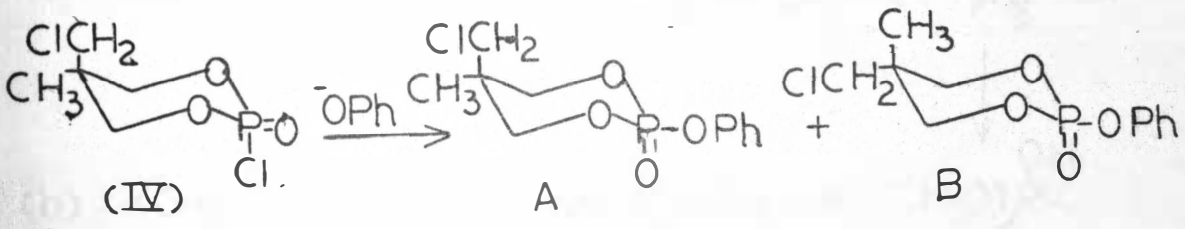


Compd	R	Compd	R
(VI)		(VII)	
A		B	
(X)		(XI)	
(XII)		(XIII)	
(XIV)		(XV)	
(XVI)		(XVII)	

II. THE REACTION OF PHENOXIDE ION WITH 2-CHLORO-5-CHLOROMETHYL-5-METHYL-2-OXO-1,3,2-DIOXAPHOSPHORINAN

INTRODUCTION

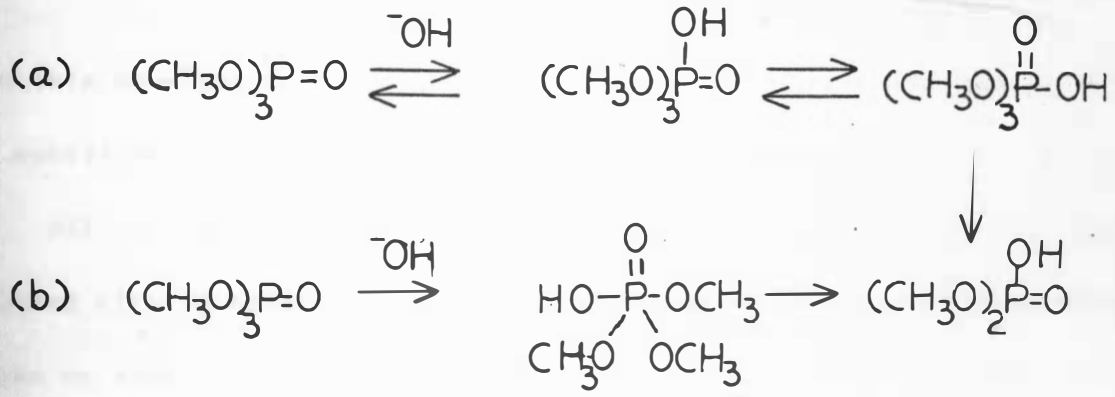
Two isomers are produced in the reaction of phenoxide ion with (IV). The isomers produced in this reaction have been given stereochemical assignments. If these assignments are correct, isomer A has the same configuration at C-5 as (IV) and an opposite configuration at phosphorus. Conversely, isomer B has opposite configurations at C-5 and phosphorus compared to (IV).



The purpose of Part Two of this paper is to discuss the above reaction in terms of what is known about the stereochemistry of reactions at phosphorus. In addition, evidence is provided for a dissociative mechanism in the formation of isomer B.

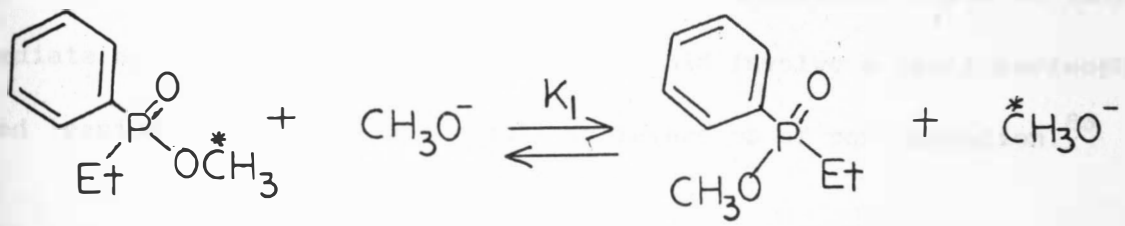
HISTORICAL

Several nucleophilic substitution reactions at phosphorus (IV) esters have been described in terms of associative bimolecular mechanisms. Many of these reaction pathways involve either a five-membered intermediate or a transition state. The alkaline hydrolysis of trimethyl phosphate is an example of a reaction involving a five-membered transition state.[59,60]



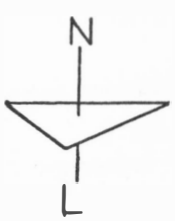
Kinetic studies establish that the hydroxide ion attack at phosphorus is the rate controlling step of the reaction. The reaction is first order in hydroxide ion and first order in phosphate. The formation of an intermediate (reaction pathway a) is ruled out by the failure of the phosphoryl group to exchange oxygen with the solvent (H_2O) prior to hydrolysis.

Bimolecular displacement reactions at phosphorus may proceed with inversion of configuration. Direct proof of an inversion mechanism has been obtained by comparison of the rate of exchange of the labeled methyl group in O-methyl-ethylphenylphosphinate with methoxide ions with the rate of racemization under the same condition.[61,62]

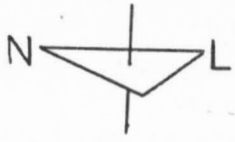


The rate constant for racemization is twice k_1, indicating that each act of substitution proceeds with inversion of configuration.

All nucleophilic reactions with phosphate esters, however, do not proceed with inversion of configuration. The geometry of the transition state or intermediate is crucial in determining the configuration of the products. The degree of hybridization of the empty 3d orbitals at phosphorus with p and s orbitals is important. Electronically, several structures are possible, depending on the particular d orbital used for hybridization. For the d_z2 orbital, pd-sp^2 hybridization results in trigonal bipyramical geometry in which the apical pd bonds are weaker and longer than basal bonds.[62] A transition state or intermediate assuming this type of hybridization would involve apical nucleophile and leaving group and would result in inversion of configuration.[63]



Alternatively, sp^3-d hybridization is possible and would result in trigonal bipyramidal geometry.[62] The basal bonds in this typs of hybridization are weaker than the apical bonds. A transition state or intermediate assuming this type of geometry would involve a basal nucleophile and leaving group and would result in inversion of configuration.[63]

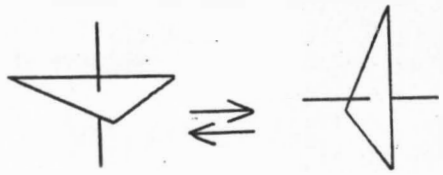


The third alternative for trigonal bipyramidal geometry would involve an apical nucleophile and a basal leaving group or, conversely, an apical leaving group and a basal nucleophile.

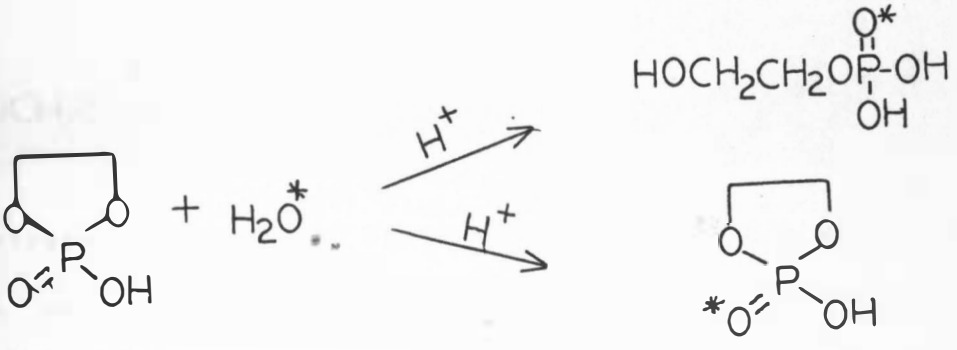
Strictly speaking, these types of transition states are not allowed and violate the law of microscopic reversability.[64] As reaction intermediates, they are allowed, however, and are subject to an interesting type of rearrangement--pseudorotation.[65]

Specifically pseudorotation is a type of intermolecular process in which a trigonal bipyramidal molecule is transformed by deforming angles in such a way that it appears to have been rotated by 90° about

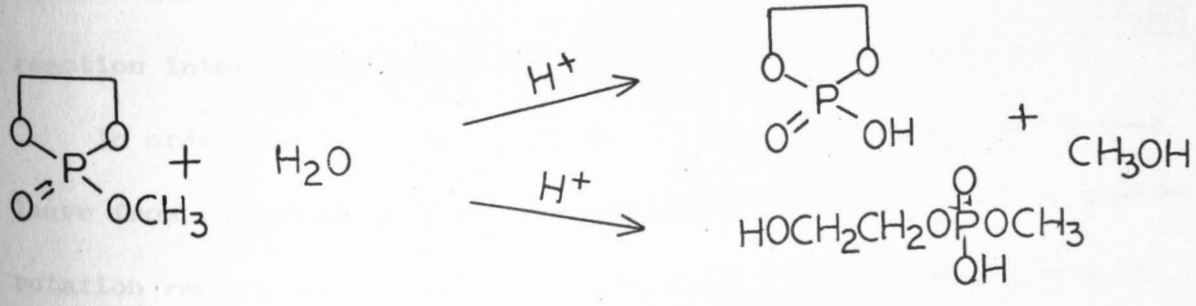
one of the interatomic bonds.[65,66]



The pseudorotation process has been used to explain the results of the rapid hydrolysis of some cyclic phosphate esters. For example, it has been found that the hydrolysis of ethylene hydrogen phosphate is accompanied by rapid oxygen exchange into unreacted ethylene phosphate.[67]

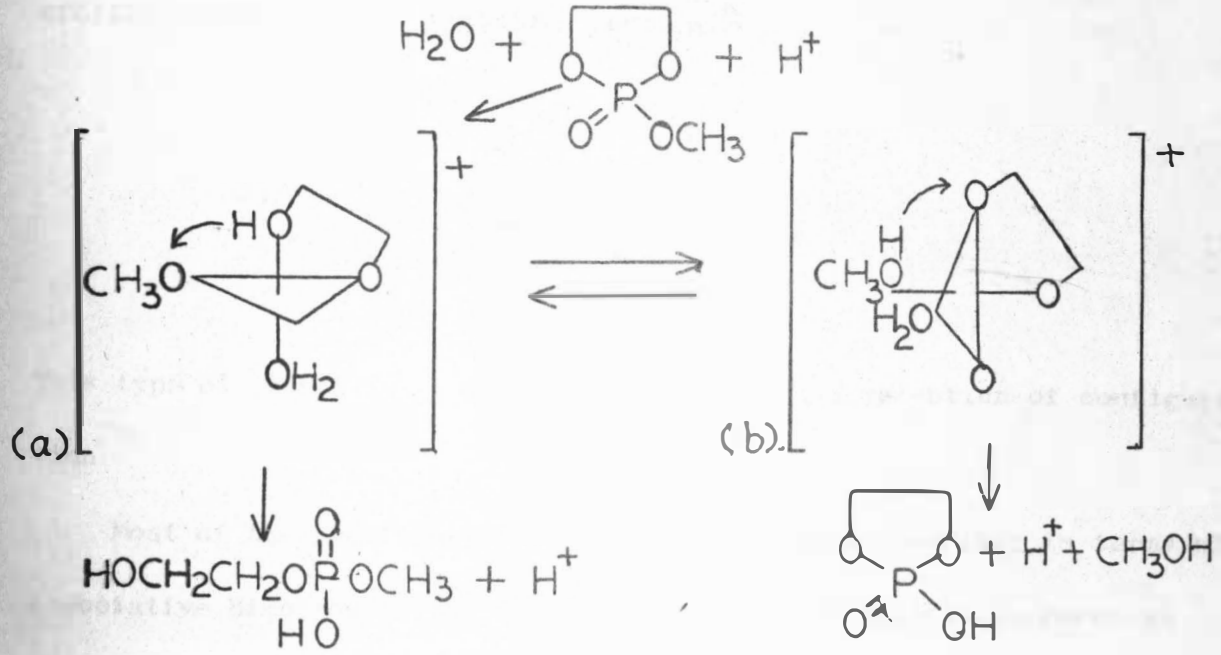


Similarly, the hydrolysis of methyl ethylene phosphate is accompanied by rapid hydrolytic cleavage of the methyl group.[65,68]



Although relief of ring strain can account for the rapid hydrolysis leading to acyclic products it, seemingly, cannot explain the rapid and competitive formation of the cyclized products. Relief of ring strain

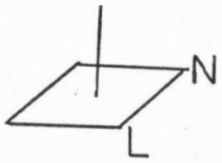
is thought to accompany the formation of a trigonal bipyrimidal intermediate in which one oxygen of the ring occupies a basal position and the other an apical position.[65]



The unstrained intermediate (a) leads to the formation of the acyclic product, but cannot lead to the formation of cyclic product. Presumably, pd-sp^2 hybridization insures that the apical bonds are weaker than the basal bonds. The nucleophile and leaving group are apical and the reaction intermediate proceeds with inversion of configuration.

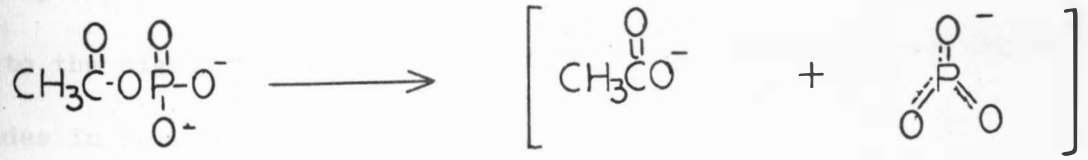
In order for the acyclic product to form, the methoxy group must leave from an apical position. Rearrangement of (a) to (b) via pseudorotation results in an unstrained intermediate and places the nucleophile in the basalplane. Subsequently, bonding to the leaving group in the apical position is weakened. The resultant process proceeds with displacement of the methoxy group.

The trigonal bipyramidal transition state is not the only type of geometry related to d orbital hybridization. For example, $d_{x^2-y^2}p_x p_y$ s hybridization leads to square planar geometry. Participation of the p_z orbital gives a square pyramid structure.[62]

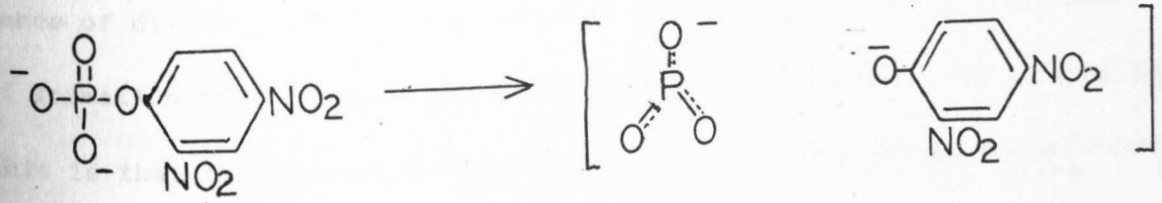


This type of transition state is expected to give retention of configuration.[63]

Most of the reactions so far discussed can be described in terms of associative bimolecular SN_2 type processes. Although displacement at phosphorus can proceed by a dissociative pathway, the number of reliable examples are few.[64,69] A unimolecular mechanism has been proposed for the solvolysis of di-anionic acetyl phosphate.[70]

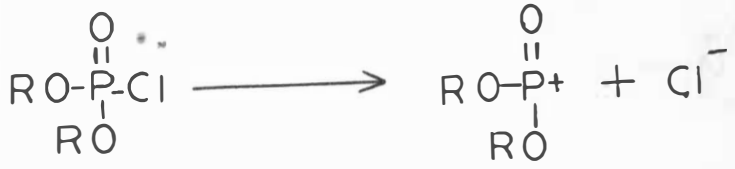


A similar mechanism is proposed for 2,5-dinitrophenyl phosphate.[71]



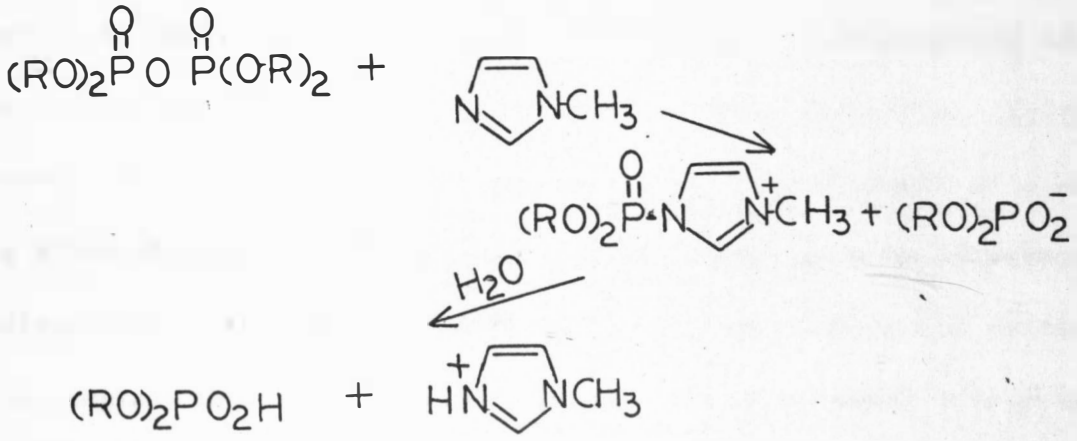
It appears that when the leaving group is the oxy anion of a sufficiently strong acid, the phosphoryl derivitive assumes anhydride character.[64] The phosphoryl intermediate of reduced coordination in the above examples is stabilized by its anionic character.

In contrast, the solvolysis of compounds of the type $(RO)_2POX$ (X = halogen or $PO(OR)_2$ appears to proceed by associative pathways rather than unimolecular of dissociative pathways. The solvolysis of O^{18} labeled diethyl phosphorochlorodate and unlabeled material in H_2O^{18} exclude a mechanism of rapid reversible formation of an intermediate and favor a simple one step displacement.[72] A unimolecular mechanism for the solvolysis of phosphorochlorodates might be favored by solvents of high ionizing ability.

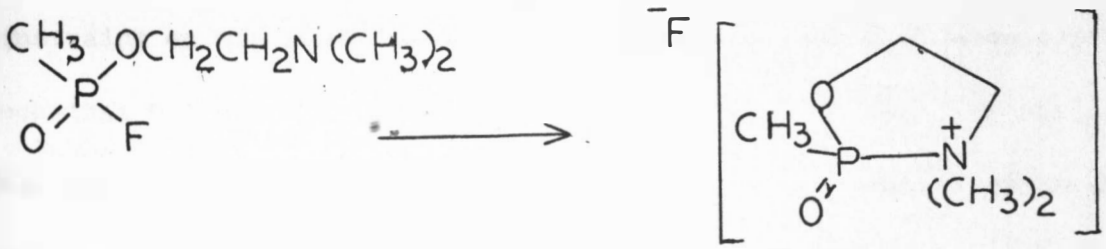


The major participation of a unimolecular mechanism is ruled out, however, due to the significantly different rates of solvolysis of phosphoryl halides in solvents with different nucleophilic properties but with similar ionizing ability.[73-75] A notable exception to this occurs in the solvolysis of di-t-butyl phosphinyl chloride.[76] The relative unimportance of dissociative pathways appears to be related to the reluctance of formation of a positive charge at phosphorus. Perhaps the reason for this is that the loss of P-Cl bond energy is not completely compensated

for by an increase in P=O bond energy.[76] The catalytic effect of certain tertiary amines on the hydrolysis of phosphoryl compounds appears to be related to their ability to stabilize a positive charge at phosphorus.[69,77]



Similarly;[78]



In most cases, unimolecular mechanisms are not favored due to the difficulty of stabilizing positive charge at phosphorus and due to the relative efficiency of bimolecular processes. A discussion of both bi- and unimolecular processes may be found in several sources.[63,64,69,79,80]

DISCUSSION OF RESULTS

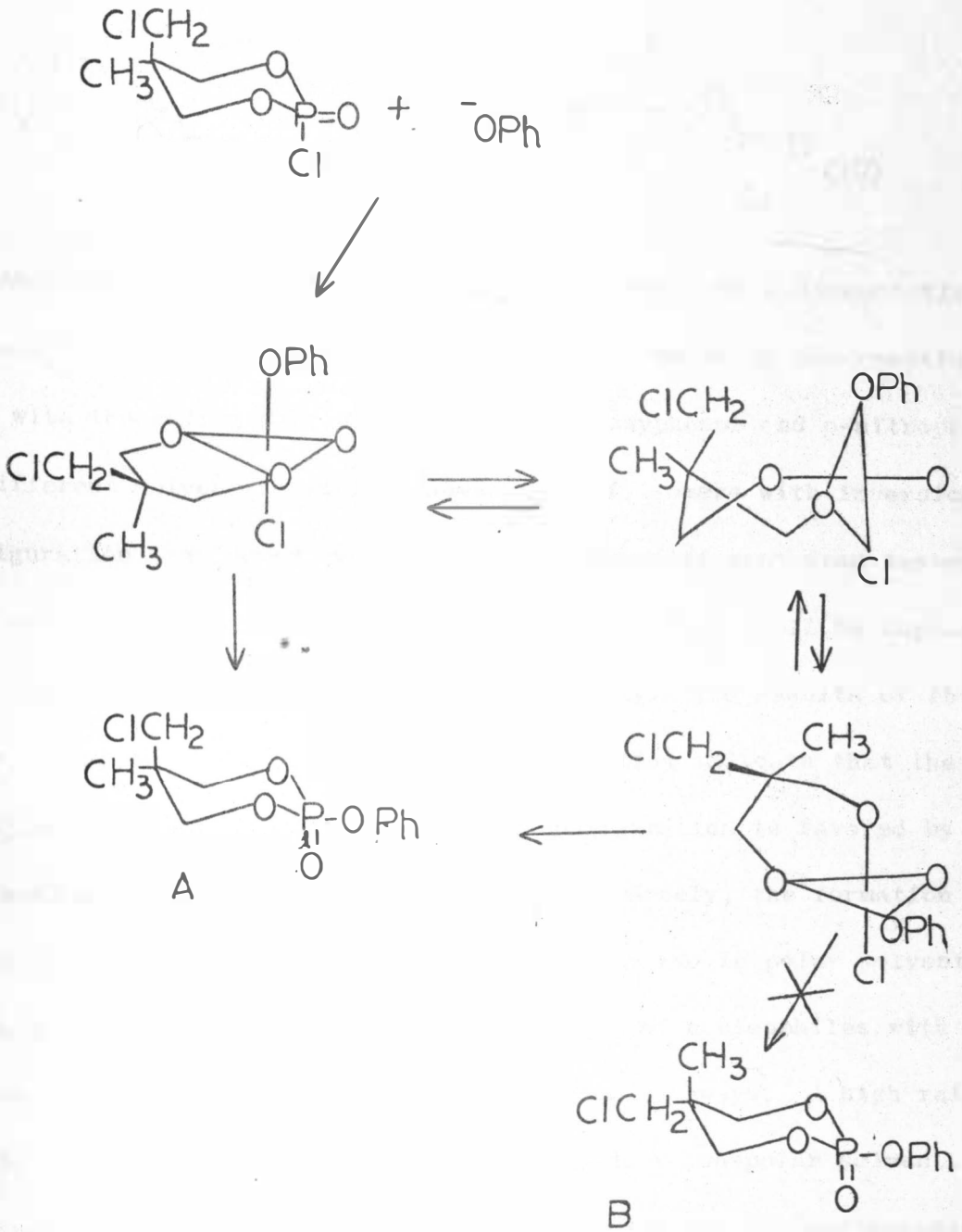
Evidence For A Dissociative Mechanism

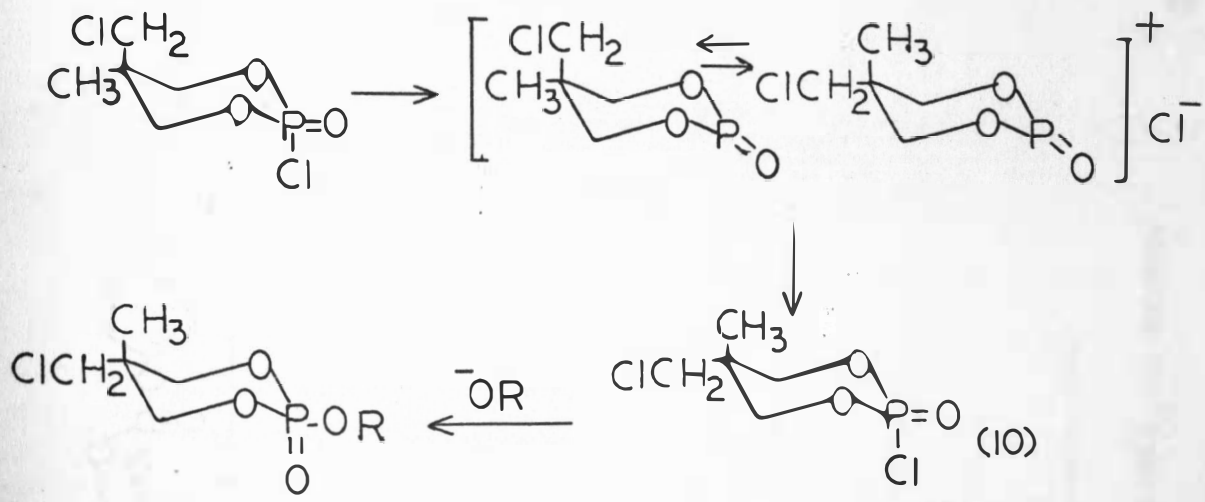
A knowledge of the stereochemistry of A and B, produced in the reaction of phenoxide ion with (IV), is important in determining the nature of the reaction pathway responsible for their formation. If the stereochemical assignments are correct, isomer A is a result of a process which proceeds by inversion of configuration and B by retention of configuration. Although stereochemical evidence alone is not sufficient for a complete description of the reaction pathway, isomer A is probably a result of a bimolecular sequence similar to the one outlined in Figure (12). It should be noted that the six-membered ring places a constraint on the rearrangement of a trigonal bipyramidal intermediate such that O-1 and O-3 cannot occupy apical positions simultaneously. This prevents the formation of isomer B in a trigonal bipyramidal intermediate by pseudorotation. However, isomer B may be formed from an inter-mediate of square pyramidal geometry in which the phenoxy group attacks from a basal position and the chloride leaves from a basal position.

Alternatively, it has been suggested that the formation of products with retention of configuration from the reaction of nucleophiles with (IV) is a result of a dissociative process. Horten suggests that the ionization of (IV) followed by rearrangement results in the formation of isomer (10). Subsequent attack of this isomer by a nucleophile results in the formation of a product with retention of configuration.[82]

FIGURE 12

THE FORMATION OF A IN BIMOLECULAR ASSOCIATIVE PROCESSES INVOLVING PSEUDOROTATION



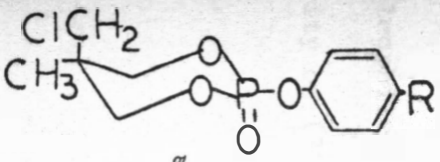


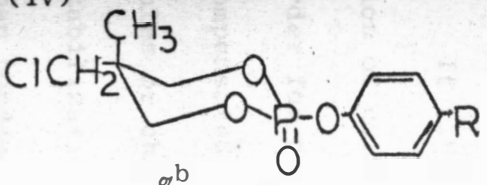
(10)

Additional evidence has been found which supports a dissociative mechanism of (IV). A product study was conducted using the reaction of (IV) with the sodium salt of phenol, p-methoxyphenol and p-nitrophenol in different solvents. It is assumed that if isomers with inversion of configuration are formed by a reaction pathway different from isomers with retention of configuration, the ratio of isomers will be dependent upon nucleophilic strength and solvent polarity. The results of this study are given in Table (16). The isomer ratios indicate that the formation of products with inversion of configuration is favored by good nucleophiles in non-polar solvents. Conversely, the formation of products with retention of configuration is favored in polar solvents. The data appears to indicate that the reaction of nucleophiles with (IV) proceeds by different and competative reaction pathways. A high ratio of A to B, (XIV) to (XV) and (XVI) to (XVII) in a non-polar solvent, i. e. benzene, is favored because reaction conditions are unfavorable toward a dissociative or other types of mechanisms which would result

Table (16)

Phenyl Esters Obtained From (IV)





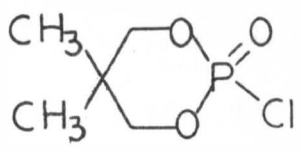
R	Solvent	%	%[b]
H	Benzene	85	15
H	THF[b]	47	53
H	CH_3COCH_3	44	56
H	CH_3CN	48	52
CH_3O	Benzene	88	12
CH_3O	THF	64	36
CH_3O	CH_3COCH_3	58	42
CH_3O	CH_3CN	57	43
NO_2	Benzene	40	60
NO_2	THF	17	83
NO_2	CH_3COCH_3	15	85
NO_2	CH_3CN	6	94

[a]Isomer ratios (%) were obtained by integration of spectra obtained in $CDCl_3$ as solvent

[b]Tetrahydrofuan

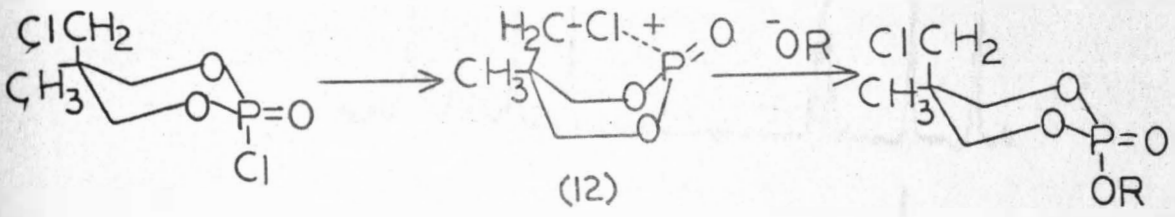
in retention of configuration. One would predict that a dissociative mechanism would be sensitive to solvent polarity and this appears to be supported by the data in Table (16).

If (IV) is involved in dissociative pathway the resultant ionization of chloride ion would place a positive charge on phosphorus. In order for dissociation to occur, the loss of P-Cl bond energy must be compensated for by other factors, perhaps with bonding of solvent molecules or charge delocalization by increased $p_{\pi} - d_{\pi}$ bonding. The stabilization of charge at phosphorus may be involved with factors other than bonding to polar solvents, however. For example, 2-chloro-5,5-dimethyl-2-oxo-1,3,2-dioxaphosphorinan (11) is less reactive toward nucleophiles in polar solvents than one would predict based on the reactivity of (IV).[81]



(11)

For this reason, the dissociation of (IV) may be related to neighboring group effects. Interaction of the chloromethyl group with phosphorus may provide a stabilizing force for the formation of a positive charge in dissociative mechanism.



(12)

Providing the rearrangement of (12) does not occur, nucleophilic attack on (12) would proceed with retention of configuration.

The strongest evidence of a dissociative mechanism is obtained from the isomerization of (XII) and (XIII). (XII) and (XIII) are geometrical isomers which have the same configuration at phosphorus and opposite configurations at C-5. Either isomer is stable at lower temperatures in non-polar solvents. It appears, however, that (XIII) can be converted into (XII) in a polar solvent at higher temperatures. When (XIII) is dissolved in CD_3CN at 55°C, the solution becomes light yellow in color, presumably due to the formation of 2,4-dinitrophenoxy ion. If maintained at this temperature, (XIII) will be converted to (XII). This reaction may be followed by observing changes in the nmr spectra over a period of a few days. The intensity of the methyl resonance associated with (XIII) decreases as the intensity of the methyl resonance associated with (XII) increases. Changes in the nmr spectra of this reaction is given in Figure (13).

The probable reaction sequences responsible in the isomerization of (XII) and (XIII) are outlined in Figure (14). The reaction pathway may involve initial ionization of (XIII) resulting in the formation in 2,4

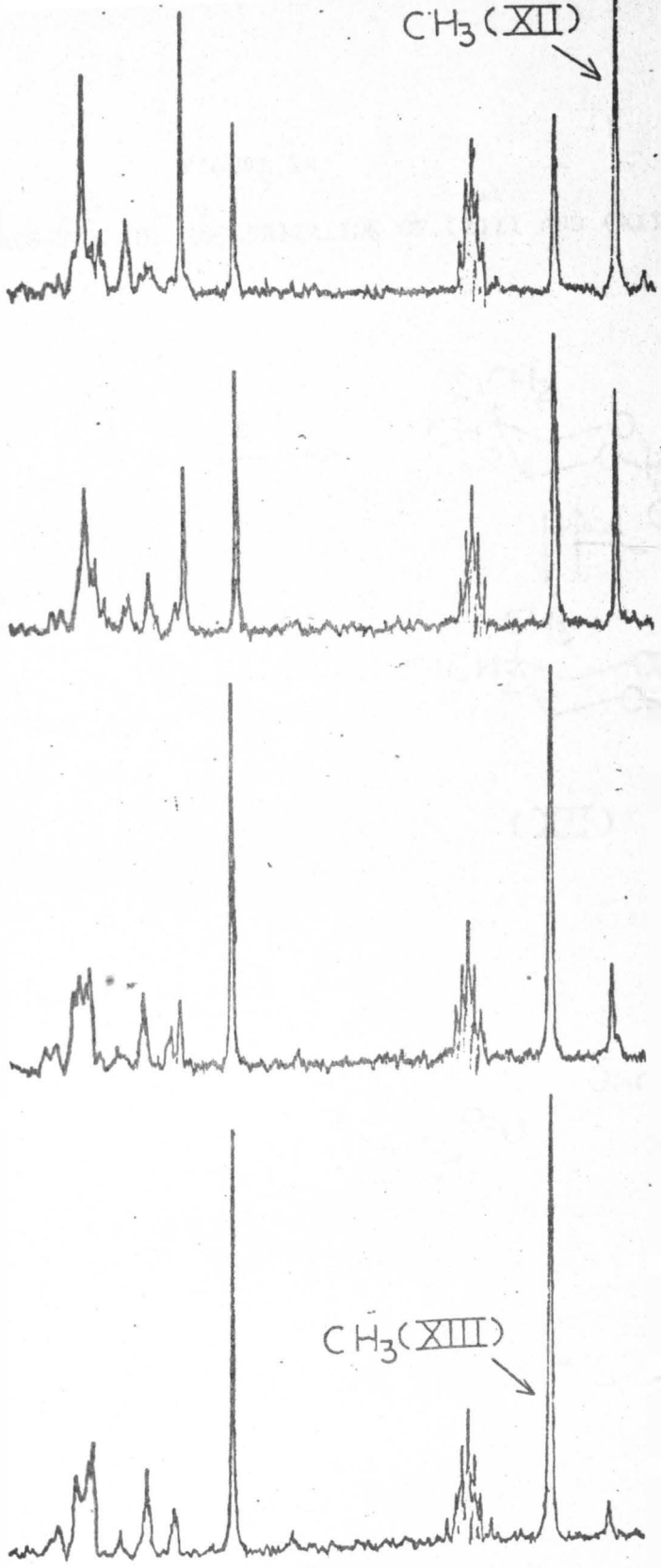
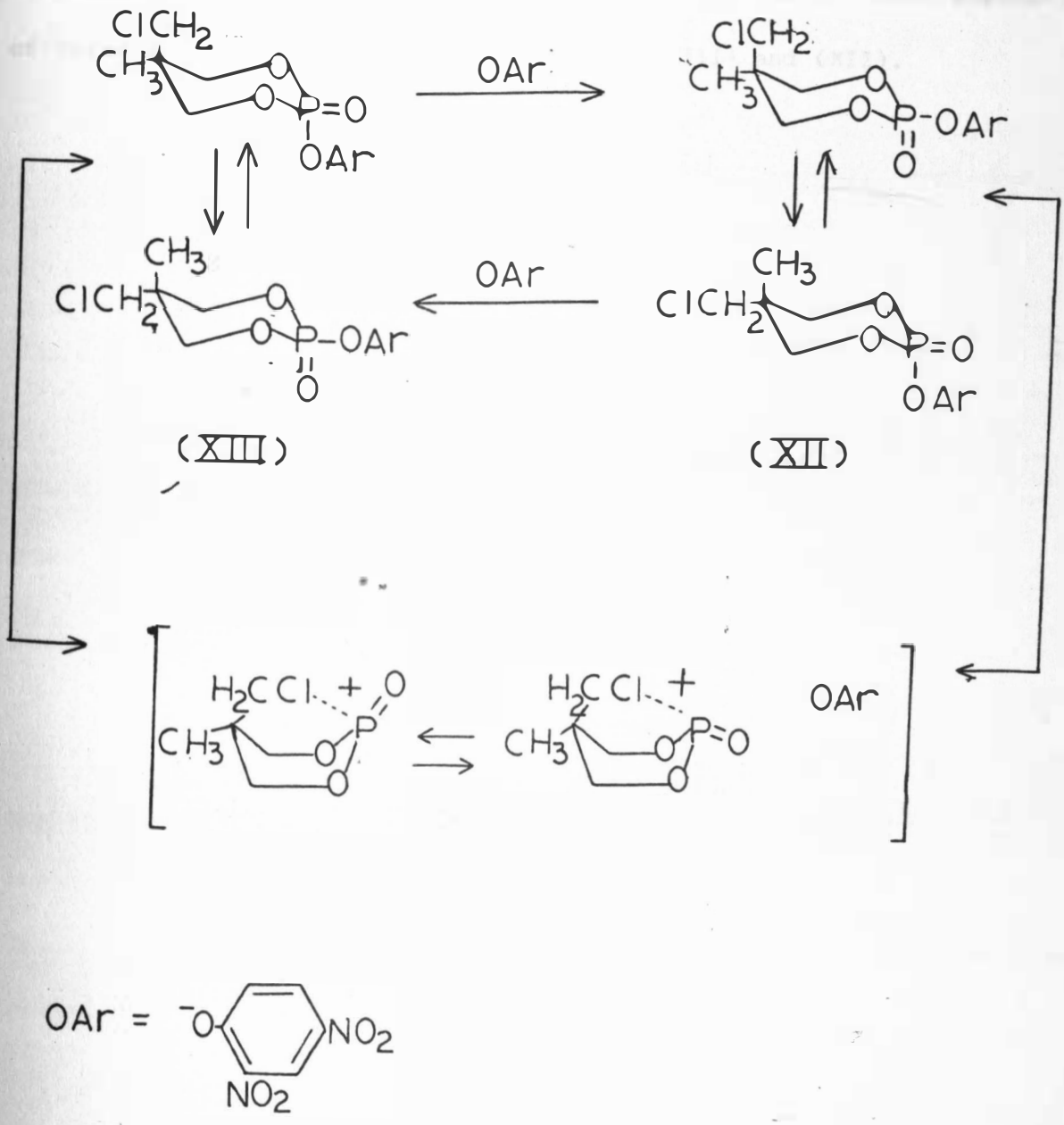


Figure 13
NMR spectra, Conversion of (XIII) to (XII) in CD_3CN at 55 C.
Bottom to top: 0, 3, 6, and 13 days, respectively.

FIGURE 14

REACTION PATHWAYS FOR THE ISOMERIZATION OF (XII) AND (XIII)



dinitrophenoxy ion. The attack of this ion on (XIII) proceeds with inversion of configuration. Subsequent resubstitution reactions at (XIII) result in a mixture of (XIII) and (XII). Alternatively, the reaction pathway may involve the formation of ion pairs. Rearrangement of these ion pairs could give a mixture of (XIII) and (XII).

EXPERIMENTAL

Description of Instrumentation, Materials and Methods

Melting points (mp) are reported in degrees centigrade and are uncorrected. Values under 200° were determined on a Thomas Hoover capillary melting point apparatus. Values above 200° were determined on a Fisher-Johns hot stage melting point apparatus.

Molecular weights (mw) and percent elemental analysis were calculated from proposed molecular formula using standard mass values.

Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, Tennessee.

Ultraviolet (uv) spectra were obtained on a Beckman DK-2A Spectrophotomer. Molar extinction coefficients (ϵ) were calculated from proposed molecular formula and absorption values are reported in nanometers (nm).

Infrared (ir) spectra were obtained from a Perkin-Elmer 521 Grating Infrared Spectrophotometer. Solid samples were run as nujol mulls or in KBr disks. Solution spectra were obtained in a NaCl cavity cell (thickness 0.1 mm) balanced with a Beckman Variable Pathlength Cell (type XL-ON5) with NaCl windows. All spectra were calibrated using polystyrene film versus air. Absorption values are reported in cm^{-1}.

Nuclear magnetic resonance (nmr) spectra were obtained from a Varian A-60A Spectrophotometer at 60 MHz. Unless otherwise stated, spectra were obtained from $CDCl_3$ solutions (0.5 ml) containing approximately 30-60 mg of sample with 1-5% tetramethylsilane (TMS) as internal standard at 40°.

Absorption values are reported in parts per million (δ). High and low temperature nmr spectra were obtained using a V-6040 Variable Temperature Controller with the A-60A Spectrophotometer. The temperature was measured by using either the methanol or ethylene gylcol method. Typical instrument settings at low temperature include: radio frequency 0.01, filter bandwidth 0.1, amplitude 5.0 x 10, sweep time 2500.

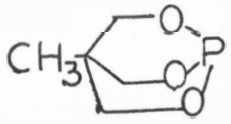
All purified solvents were distilled through a vacuum jacketed distillation column (21 theo. plates) and middle fractions isolated and stored over molecular sieves. Benzene, CCl_4, acetone, and acetonitrile were distilled from P_4O_{10}. Tetrahydrofuran was distilled from $LiAlH_4$. All other chemicals were used without further purification as received from the manufacturer.

Adsorption columns for chromatography were prepared as follows: Silicic acid (500 ml, reagent grade 100 mesh) was stored in an oven for approximately 48 hours at 180°. The powder was allowed to cool in a desiccator and sufficient amounts of chloroform (A.C.S. grade, EtOH present as a stabilizer) were added to produce a thick slurry. This slurry was poured into a glass column (50 cm x 2.5 cm) fitted with a Teflon stopcock and previously plugged with glass wool and sand. It was allowed to rise to a height of 40 cm and excess chloroform was added. The excess chloroform was slowly drained from the column to facilitate packing but at no time was the chloroform allowed to drain below the level of the adsorbent. The majority of columns packed in this way were transluscent and free from air pockets.

Preparation of 1-methyl-4-phospha-3,5,8-trioxabicyclo(2.2.2)octane(Methyl bicyclic phosphite-I)

2-(hydroxymethyl)-2-methyl-1,3-propanediol (60 g, mw 120.15) and trimethyl phosphite (60 g, mw 120.08) were introduced into a single necked round bottom flask. The flask was equipped for distillation using 19/22 TS parts and the receiving vessel connected to a $CaCl_2$ drying tower. Several drops of triethyl amine (1 ml, catalyst) and a magnetic stirring bar were placed in the reaction vessel and this was lowered into an oil bath maintained at approximately 80°. The contents were stirred by a magnetic stirrer and the temperature of the oil bath was allowed to rise 20-30° in 3-4 hours. Methanol began to distill at 90° and after four hours the temperature was maintained at 115 for one hour. During this period 90 percent of the theoretical amount of alcohol (60 ml) was obtained. The temperature was then allowed to rise to 130° and a slight vacuum was applied to obtain the undistilled alcohol and unreacted trimethyl phosphite. Upon cooling, the contents of the flask turned into a white, waxy solid. This material was recrystalized from heptane-benzene (4:1, v/v) yielding 58 g (80% yield) of methyl bicyclic phosphite (mp 91-3 , mw 148.10).[82]

Structure:

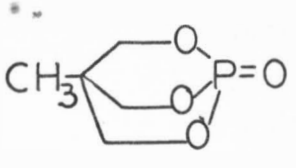


(I)

Preparation of 1-methyl-4-oxaphospha-3,4,8-trioxabicyclo(2.2.2)octane (methyl bicyclic phosphate-II)

Methyl bicyclic phosphite (10 g, 0.067 mole) was dissolved in 300 ml of purified CCl_4 and chilled to 5° in an ice bath. A chilled solution containing tert-butyl hydroperoxide (6.3 g, mw 90.11) and tert-butyl alcohol (50 ml) was added to the phosphite over a period of 40 minutes. The reaction mixture became warm several times and had to be cooled in an ice bath. After standing for several hours, the white microcrystalline methyl bicyclic phosphate was precipitated from the solution. The solid was filtered, washed several times with cold EtOH, and dried in a vacuum at 100°. The yield of methyl bicyclic phosphate was 10 g (91%); mp 251-3; ir (nujol) 1290-1370 (P=O); nmr (acetone-d_6) 0.88 δ singlet (CH_3), 4.41 δ doublet (CH_2).[82]

Structure:



(II)

Analysis: Calculated for $C_5H_9O_4P$: C, 36.6; H, 5.5; P, 18.9. Found: C, 36.5; H, 5.6; P, 18.6.

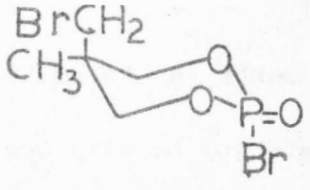
Preparation of Cis -2-bromo-5-bromomethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan(bromodate-III)

Bromine (55 g, mw 159.82) and CCl_4 (300 ml) were placed in a single necked round bottom flask equipped with a 500 ml capacity addition funnel. A CCl_4 solution (300 ml) containing 51 g (0.34 mole) of methyl bicyclic phosphite (I) was added dropwise with cooling and stirring over a period of two hours. During the addition a yellow precipitate formed which re-

dissolved upon warming. The excess solvent and bromine were removed under reduced pressure leaving a light yellow viscous liquid which solidified upon standing. The material was recrystallized from CCl_4 yielding 50 g (47%) of a light yellow solid. This material was recrystallized from benzene-chloroform mixtures until a white crystalline solid was obtained, mp 76-8 ; ir (nujol) 1300 cm^{-1} (P=O); nmr 0.98 δ singlet (CH_3), 3.60 δ singlet ($BrCH_2$), 3.83-4.67 δ multiplet (CH_2).

Structure:

(III)



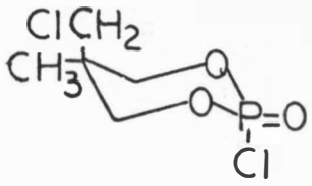
Analysis: Calculated for $C_5H_9Br_2O_3P$: C, 19.5; H, 3.0; P, 10.1 Found: C, 19.7; H, 3.1; P, 10.0.

Preparation of Cis-2-chloro-5-chloromethyl-5-methyl-2-oxo-1,3,2-dioxaphosphorinan(chloridate-IV).

A solution of methyl bicyclic phosphite (74 g, 0.5 mole) and CCl_4 (300 ml) was added dropwise to a solution of CCl_4 (300 ml) and sulfuryl chloride (63 g, mw 134.97). (The procedure was similar to the preparation of the bromodate.) A light yellow solid was isolated and recrystallized from CCl_4 yielding 68 g (62%) of chlorodate (mw 219.01). This material was used without further purification for the synthesis of other compounds outlined in this section. Purification of the chlorodate was otherwise accomplished by recrystallization from benzene-chloroform mixtures and dried in a vacuum at 55°. The chlorodate and bromodate are quite hydroscopic substances and were stored in tightly sealed containers over P_4O_{10}.

This material gave: mp 69-71; ir (nujol) 1300 cm^{-1} (P=O); nmr 0.97 δ singlet (CH_3), 3.60 δ singlet ($ClCH_2$), 3.83-4.67 δ multiplet (CH_2).

Structure:



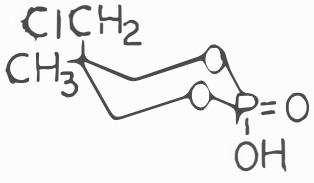
(IV)

Analysis: Calculated for $C_5H_9Cl_2O_3P$: C, 27.43; H, 4.15; P, 14.10. Found: C, 27.32; H. 4.25; P, 14.41.

Preparation of 2-hydroxy-5-chloromethyl-5-methyl-1,3,2-dioxa-phosphorinan (acid-V)

Chlorodate (5 g, 0.023 mole) was added to a solution of H_2O (5 ml) and acetonitrile (30 ml) and stirred for eight hours in a stoppered 50 ml erlenmeyer flask. The solution was reduced to one-half volume under reduced pressure and a small amount of water was added. Upon cooling the solution yielded a white crystalline solid which was dried in a vacuum at 100 ; mp 144-6; ir (nujol) 1270 cm^{-1} and 1190 cm^{-1} (P=O); nmr (MeOH-d_4) 0.98 δ singlet (CH_3), 3.68 δ singlet ($ClCH_2$), 3.84-4.67 δ multiplet (CH_2).[82]

Structure:



(V)

Analysis: Calculated for $C_5H_{10}ClO_4P$: C, 30.0; H, 5.0; Cl, 17.5. Found: C, 30.11; H, 5.14; Cl, 17.54.

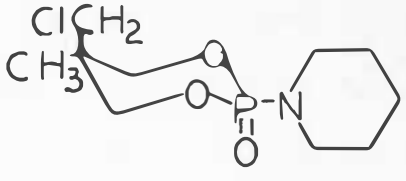
Preparation of trans-5-chloromethyl-5-methyl-2-oxo-2-piperidino-1,3,2-dioxa-phosphorinan(amidate-VI)

A solution of piperidine (10 ml, mw 85.15) and CCl_4 (50 ml) was

added dropwise to a solution of CCl_4 (100 ml) and chlorodate (5 g, 0.023 mole). After the initial exothermic reaction had subsided, piperidine (10 ml) was added and the solution was stirred for one hour. The excess solvent was removed under reduced pressure and the residue was extracted several times using chloroform. The chloroform layer was dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. The residue was recrystallized from benzene-chloroform mixtures; mp 153-4; ir (nujol) 1232 cm^{-1} (P=O); nmr 0.88 δ singlet (CH_3), 1.53 δ complex multiplet (CH_2-piperidine ring), 2.83-3.33 δ complex multiplet (CH_2-piperidine ring), 3.63 δ singlet ($ClCH_2$), 3.66-4.43 δ multiplet (CH_2-phosphorinan ring).[82]

Structure:

(VI)

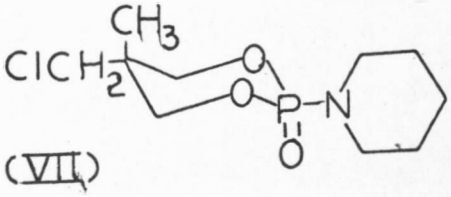


Analysis: Calculated for $C_{10}H_9ClNO_3P$: C, 44.85; H, 7.14; N, 5.17; P, 11.61. Found: C, 44.53; H, 7.12; N, 5.29; P, 11.68.

Cis -5-chloromethyl-5-methyl-2-oxo-2-piperidino-1,3,2-dioxaphosphorinan (amidate-VII)

A sample of this material was kindly supplied by Dr. William S. Wadsworth, South Dakota State University.

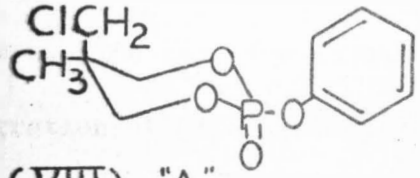
Structure:



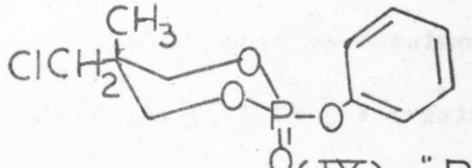
(VII)

Preparation of 5-chloromethyl-5-methyl-2-oxo-2-phenoxy-1,3,2-dioxaphosphorinan (VIII, IX)

Chlorodate (5. g, 0.023 mole) and sodium salt of phenol (3.38 g, mw 146.12) were put into a 125 ml erlenmeyer flask. Purified benzene (50 ml) was added and the mixture was stoppered and stirred for twelve hours. During the course of the reaction a greyish-white precipitate formed which was soluble in H_2O and precipitated Ag ion. At the end of this period the reaction mixture was filtered several times to remove the precipitated material. The filtrate was stripped under reduced pressure and the residue solidified upon standing. The residue was extracted several times with chloroform and the extract was washed with a saturated $NaHCO_3$ solution. The chloroform extract was dried over anhydrous Na_2SO_4. The chloroform was removed under reduced pressure yielding 5 g (78%) of crude product. This material, when eluted through a silicic acid column gave two isomers which have the following proposed structures:



(VIII) "A"



(IX) "B"

VIII: mp 105-7; ir (nujol) 1288 cm^{-1} and 1200 cm^{-1} (P=O); nmr 0.87 δ singlet (CH_3), 3.68 δ singlet ($ClCH_2$), 3.73-4.50 δ multiplet (CH_2) 7.05 δ singlet (Ar); uv (tetrahydrofuran) 268 nm, $\epsilon = 3.78 \times 10^2$, 262 nm 4.82×10^2, 256 nm, $\epsilon = 3.64 \times 10^2$.

IX: mp 130-2; ir (nujol) 1283 cm^{-1} and 1192 cm^{-1} (P=O); nmr 1.23 δ singlet (CH_3), 3.26 δ singlet ($ClCH_2$), 3.66-4.67 δ multiplet (CH_2),

7.05 δ singlet (Ar); uv (tetrahydrofuran) 268 nm, $\epsilon = 3.51 \times 10^2$, 264 nm $\epsilon = 4.48 \times 10^2$, 256 nm $\epsilon = 3.47 \times 10^2$.

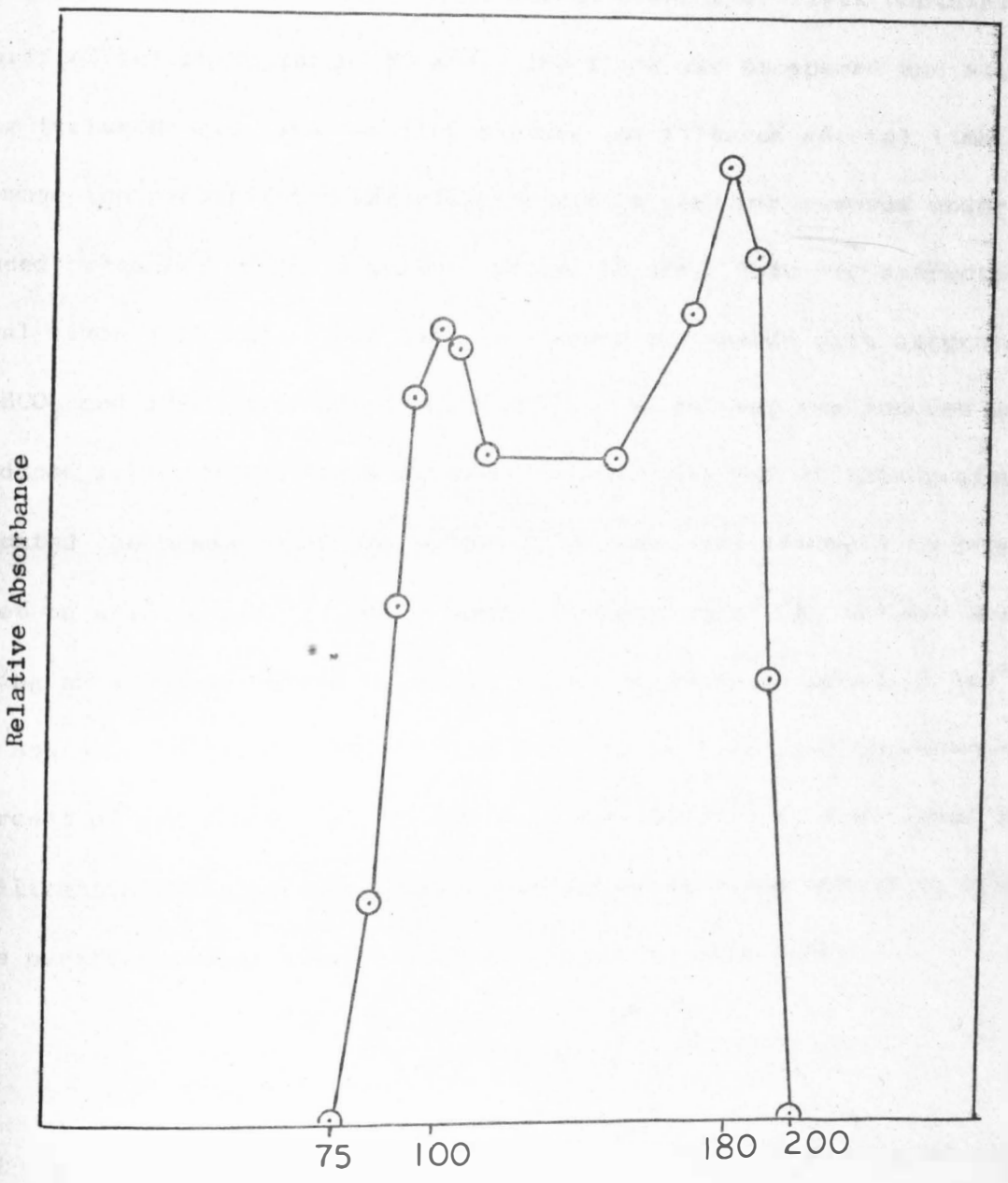
Analysis: Calculated for $C_{11}H_{14}ClO_4P$: C, 47.82; H, 5.07; P, 11.23. Found: C, 47.73; H, 5.12; P, 11.17.

Separation of (VIII) and (IX)

A solution containing chloroform (50 ml) and the above isomers (5 g) was carefully layered into a silicic acid column. The solution was drained into the adsorbent bed but not below it. The column was fitted with a 500 ml reservoir of chloroform and the elution was allowed to proceed at a rate of approximately 60-70 drops per minute. Development of the column could be followed by observing the movement of a large opaque band, but at no time did the isomers separate into distinct bands. Approximately two hundred 10 ml fractions were collected and assayed at 264 nm. It is evident from the elution curve (p. 101) that complete separation was not obtained. The purity of intermediate fractions was determined from nmr spectra. The relative amounts of each isomer could be obtained by the integration of separate methyl signals (0.87 δ, 1.23 δ) arising from each isomer. Intermediate fractions were purified by fractional re-crystallization from heptane-benzene-chloroform mixtures (50:45:5, v/v/v). In all cases, (VIII) was the most difficult isomer to purify. Subsequent separations were performed using slower elution rates (30-40 drops per minute), collecting larger volume fractions (50-100 ml) and the assay procedure was modified to include nmr and melting point data only.

Figure 15

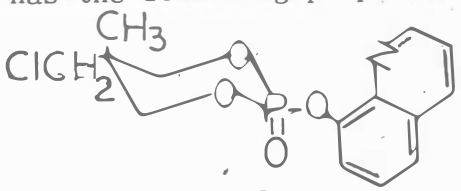
Elution Curve for the Separation of (VIII) and (IX)



Preparation of 5-chloromethyl-5-methyl-2-oxo-2-(8-quinolinoxy)-1,3,2-dioxaphosphorinan (X, XI)

Sodium salt of 8-hydroxyquinoline (3.8 g, 0.023 mole) and chlorodate (5 g, 0.023 mole) were put into a 125 ml erlenmeyer flask containing purified tetrahydrofuran (50 ml). The flask was stoppered and stirred for twelve hours. The reaction mixture was filtered several times to remove the precipitated material and the solvent was removed under reduced pressure leaving a yellow viscous liquid. This was extracted several times with chloroform and the extract was washed with saturated $NaHCO_3$ and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure leaving a viscous residue. The nmr of this residue indicated the presence of two isomers; however, all attempts to separate them on silicic acid failed. Partial separation of (X, XI) was achieved using an aluminia column (aluminum oxide, 80-90 mesh, dried at 180° for 48 hours). Material isolated from this column contained approximately 90 percent of one isomer (XI, by nmr) and was purified by fractional re-crystallization using heptane-benzene-chloroform mixtures (50:45:5, v/v/v). The purified isomer has the following proposed structure:

(XI)



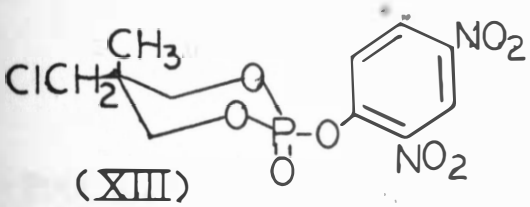
XI: mp 111-3; ir (nujol) 1294 cm^{-1} (P=O); nmr 1.35 δ singlet (CH_3) 3.37 δ singlet ($ClCH_2$), 3.58-4.42 δ multiplet (CH_{eq}), 4.58-5.00 δ multiplet (CH_{ax}), 7.32-8.75 δ multiplet (Ar).

Analysis: Calculated for $C_{14}H_{15}ClNO_3P$: C, 51.31; H, 4.61; P, 9.45.

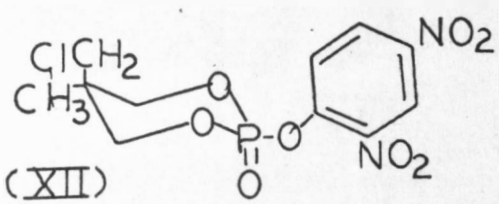
Found: C, 51.54; H, 4.57; P, 9.34.

Preparation of 5-chloromethyl-5-methyl-2-(2,4-dinitrophenoxy)-1,3,2-dioxaphosphorinan (XII, XIII)

The sodium salt of 2,4-dinitrophenol (9.4 g, 0.046 mole) and chlorodate (10 g, 0.046 mole) were mixed with purified benzene (75 ml) in a 125 ml erlenmeyer flask. The flask was stoppered and stirred for twelve hours. The mixture was filtered several times and the solvent evaporated under reduced pressure. The solid residue, 11 g (68% yield), was extracted several times with chloroform. The volume of the extract was reduced to 60 ml and this solution was layered on a silicic acid column. Separation of the two isomers (XII) and (XIII) occurred in a manner similar to the separation of (VIII) and (IX) as described above. The proposed structures are as follows:



(XIII)



(XII)

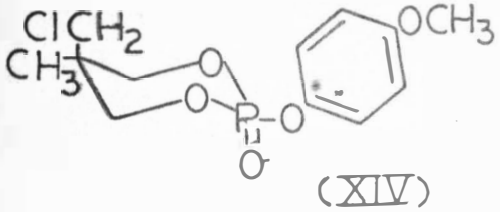
XII: mp 144-8 (impure); ir (nujol) 1344 cm^{-1} (P=O); nmr 1.02 δ singlet (CH_3), 3.74 δ singlet ($ClCH_2$), 4.00-4.67 δ multiplet (CH_2), 7.75-8.70 δ multiplet (Ar).

XIII: mp 118-20; ir (nujol) 1341 cm^{-1} (P=O); nmr 1.43 δ singlet (CH_3), 3.35 δ singlet ($ClCH_2$), 3.76-4.83 δ multiplet (CH_2), 7.67-8.67 δ multiplet (Ar).

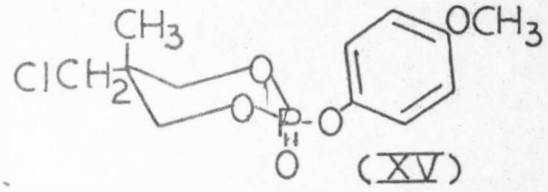
Analysis: Calculated for $C_{11}H_{12}ClN_2O_8P$: C, 36.03; H, 3.30; P, 8.45. Found: C, 36.17; H, 3.36; P, 8.20.

Preparation of 5-chloromethyl-5-methyl-2-(4-methoxyphenoxy)-1,3,2-dioxaphosphorinan (XIV, XV)

Chlorodate (1 g, 0.0046 mole) and the sodium salt of 4-methoxyphenol (0.66 g, 0.0046 mole) were placed in a 125 ml erlenmeyer flask and purified benzene (50 ml) was added. The flask was stoppered and stirred for twelve hours. The precipitated matter was removed with several filtrations and the solvent was evaporated under reduced pressure. The residue was extracted several times with chloroform and the extract was washed with saturated $NaHCO_3$ and dried over Na_2SO_4. The nmr of the chloroform extract indicated the presence of two isomers, (XIV, XV); however, no attempt was made to separate them. It is assumed that their structures are analogous to (VIII) and (IX):



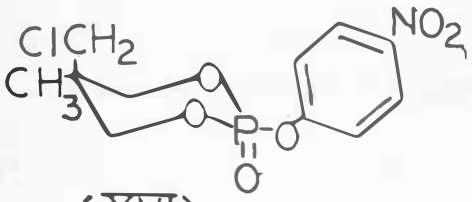
(XIV)



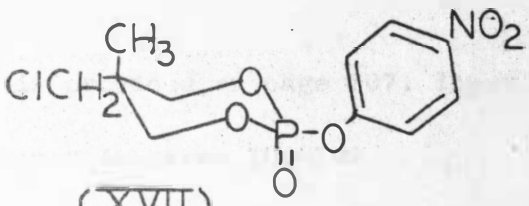
(XV)

Preparation of 5-chloromethyl-5-methyl-2-(4-nitrophenoxy)-1,3,2-dioxaphosphorinan (XVI, XVII)

Chlorodate (1 g, 0.0046 mole) and the sodium salt of 4-nitrophenol (0.7 g, 0.0046 mole) were placed in a 125 ml erlenmeyer flask with purified benzene (50 ml). The residue (1 g, 67% yield) was isolated in a manner similar to the above procedure and the nmr of this material indicated the presence of two isomers. It is assumed that their structures are analogous to (VIII) and (IX):



(XVI)



(XVII)

Analysis: Calculated for $C_{11}H_{13}ClNO_6P$: C, 41.12; H, 4.05: P, 9.65

Found: C, 40.96; H, 4.21; P, 9.47.

APPENDIX

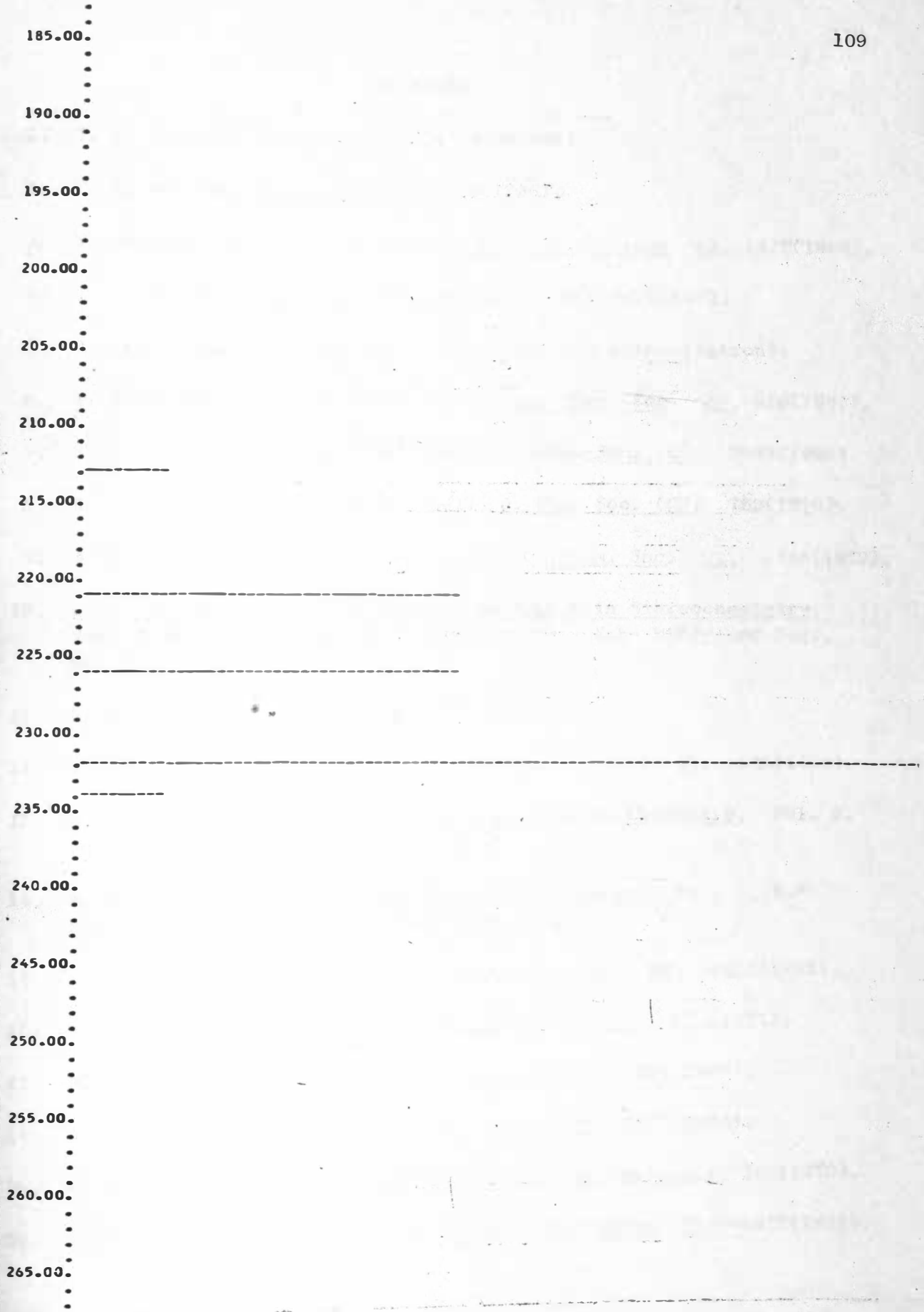
A program listing of OLSVAG is provided on page 107. Input and output information from LAOCN3 is given in pages 108-109.

```
.AN IV 360N-FO-479 3-4          MAINPGM          DATE   10/29/71      TIME     18.45.42

      DIMENSION A(72),T(50),S(50),FX(50),FY(50),FG(250),FXO(250),FXI(250),
     1),FP(250),FE(250)
      COMMON T,S,FX,FY,FG,FXO,FXI,FP,FE
    5 READ(11,100)ID,GI,GF,DG
  100 FORMAT(I2,3F10.4)
      IF(ID .GT. 0) GOTO200
      STOP
  200 READ(11,201)(A(J),J=1,72)
  201 FORMAT(72A1)
      READ(11,202)(T(J),S(J),J=1,ID)
  202 FORMAT(2F10.4)
      WRITE(12,300)(A(J),J=1,72),ID,GI,GF,DG
  300 FORMAT(1H ,23X,72A1,///,1H ,30X,' INITIAL PARAMETERS ',I4,3F10.4,//
     1,1H ,50X, ' EXPERIMENTAL VALUES ',//)
      WRITE(12,301)(T(J),S(J),J=1,ID)
  301 FORMAT(1H ,48X,2F10.4)
      NN=(GF-GI)/DG
      GI=GI-DG
      DO400N=1,NN
      GI=GI+DG
      CALL GFUN(ID,GI)
      CALL ERMB(ID,XO,XI,DE)
      FG(N)=GI
      FXO(N)=XO
      FXI(N)=XI
      FP(N)=EXP(-1.0*GI/(0.001987*(25.0+273.15)))
  400 FE(N)=DE
      WRITE(12,500)
  500 FORMAT(///,2eX,' FREE ENERGY ',' POP. AT 25 DEG. ',' AXIAL SHIFT '
     1,' EQUIT. SHIFT ',' STAND. DEV. ',//)
      WRITE(12,501)(FG(J),FP(J),FXO(J),FXI(J),FE(J),J=1,NN)
  501 FORMAT(1H ,3CX,4F12.4,3X,E12.5)
      GOTO5
      END
RAN IV 360N-FO-479 3-4          GFUN             DATE   10/29/71      TIME     18.46.12

      SUBROUTINE GFUN(ID,GI)
      DIMENSION A(72),T(50),S(50),FX(50),FY(50),FG(250),FXO(250),FXI(250),
     1),FP(250),FE(250)
      COMMON T,S,FX,FY,FG,FXO,FXI,FP,FE
      DO10J=1,ID
      FX(J)=EXP(-1.0*GI/(0.001987*(T(J)+273.15)))
   10 FY(J)=S(J)*(1.0+FX(J))
      RETURN
      END
RAN IV 360N-FO-479 3-4          ERMB             DATE   10/29/71      TIME     18.46.32

      SUBROUTINE ERMB(ID,XO,XI,DE)
      DIMENSION A(72),T(50),S(50),FX(50),FY(50),FG(250),FXO(250),FXI(250),
     1),FP(250),FE(250)
      COMMON T,S,FX,FY,FG,FXO,FXI,FP,FE
      SX=0.0
      SY=0.0
      SXY=0.0
      SX2=0.0
      SMSQ=0.0
      XO=0.0
      XI=0.0
      DE=0.0
      DI=ID
      DO20J=1,ID
      SX=SX+FX(J)
      SY=SY+FY(J)
      SXY=SXY+FX(J)*FY(J)
   20 SX2=SX2+FX(J)*FX(J)
      DE=DI*SX2-SX*SX
      IF(DE .EQ. 0.0) GOTO40
      XI=(DI*SXY-SX*SY)/DE
      XO=(SY*SX2-SX*SXY)/DE
      DO30J=1,ID
      DE=XI*FX(J)+XO-FY(J)
   30 SMSQ=SMSQ+DE*DE
      DE=SQRT(SMSQ/(DI-1.0))
   40 RETURN
      END
```

```
LACCCON III

CASE    6   NMR SPECTRUM TYPE ABX

NN= 3  FREQUENCY RANGE    180.000    300.000  MINIMUM INTENSITY 0.01000

INPUT PARAMETERS

1          W(1)=  230.000
1          W(2)=  225.000
3          W(3)=  100.000
           A(1,2)=   -8.400
           A(1,3)=    3.000
           A(2,3)=   13.600
```

CASE NO 6

LINE	EXP FREQ	CALC FREQ	INTEN	ERROR
2		231.652	1.999	
7		231.647	1.999	
11		225.795	1.632	
12		212.505	0.368	
14		220.904	1.632	
15		234.195	0.368	


185.00.
190.00.
195.00.
200.00.
205.00.
210.00.
215.00.
220.00.
225.00.
230.00.
235.00.
240.00.
245.00.
250.00.
255.00.
260.00.
265.00.

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