Conformational Studies of the Phosphorinane System Based on Low-Temperature ^{31}P Nuclear Magnetic Resonance Spectroscopy[1,2]

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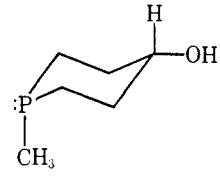
Abstract: 1-R-phosphorinanes (R = CH_3, C_2H_5, i-C_3H_7, or C_6H_5) gave a single proton-decoupled ^{31}P NMR signal at 300°K, but on lowering the temperature, separate sharp signals for the axial-R (upfield) and equatorial-R conformers developed. Peak separations below the coalescence temperatures (°K in parentheses) were: C_6H_5 9.2 ppm (208), CH_3 3.1 (186), C_2H_5 2.1 (177), i-C_3H_7 0.4 (169). From the variation of the equilibrium constant (axial ⇌ equatorial) with temperature, $\Delta H°$ values were derived for the first three compounds. These were in the range −0.6 to −0.7 kcal/mol, revealing that the repulsive nonbonded interactions are considerably smaller than those for similar substituents on the cyclohexane ring. This is largely attributed to the capability of the phosphorinane ring to adjust to the interactions in the axial conformer by flattening of the chair about the phosphorus end. Through an entropy effect, the equilibrium constants diminished to values below unity at room temperature, as seen on extrapolation of the log K vs. $1/T$ plot. For the 1-methyl compound, low-temperature ^1H NMR spectral examination of the P-CH_3 signal confirmed this view, since the $^2J_{PH}$ value (time-averaged) at room temperature (3.0 Hz) was closer to that seen for the axial conformer (3.2) than for the equatorial (1.8). Peak separation in the isopropyl derivative was not adequate to permit calculation of thermodynamic values, but the equatorial preference is greater than that in the other compounds. 1-*tert*-Butylphosphorinane gave only one signal at low temperatures, and is presumed to have a strong preference for the equatorial conformation. The free energy of activation ($\Delta G^{\ddagger}$) for reversal of the phosphorinane ring was in the range 8.3–9.3 kcal/mol. Both the approximate method based on visual determination of the coalescence temperature and complete line-shape analysis were used.

Early in our work on phosphorinanes,[3] it became evident that conformational properties of substituents about phosphorus differed considerably from those about carbon in cyclohexane derivatives. We found, for example, (1) that the conformational equilibria for the cis and for the trans isomers of 1-methyl-4-phosphorinanol were dominated by conformers **1** and **2**, respectively, which implied that the demand for the equatorial position by OH exceeded that by CH_3[3-5]; (2) that the conformational equilibrium for 1-methyl-4-phosphorinanone (**3**) lacked the appreciable bias



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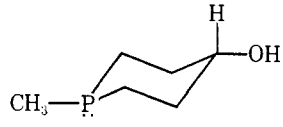

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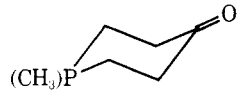

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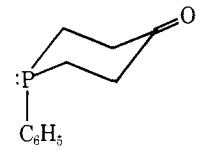

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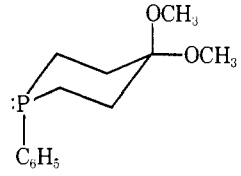
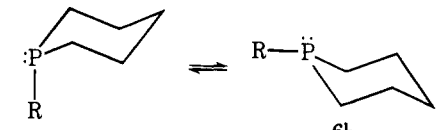


5

for the equatorial conformer,[5] which suggested that the system was able to adjust to the strain imposed by 1,3-nonbonded interactions in the axial conformer; (3) that the phenyl group in 1-phenyl-4-phosphorinanone[6] (**4**) and its dimethyl ketal[7] (**5**) occupied exclusively the axial position in the solid state, as revealed by X-ray analysis. It has also been shown by other workers that in the parent phosphorinane molecule the proton on phosphorus is predominantly in the axial position,[8] and the indication from all of these observations is that there is a remarkably small energy difference between conformers with axial and equatorial P substituent. Indeed, the data are suggestive that the axial conformer could be the energetically favored one, and this raises the question of the operation of attractive, rather than repulsive, 1,3-nonbonded interactions prevailing in this system. Evidence for such interactions has been presented for other heterocyclic systems.[9]

The objective of the present study was to place these qualitative observations of the phosphorinane system on a quantitative basis. Specifically, it was desired to establish the enthalpy difference ($\Delta H°$) between the participants in the conformational equilibrium of **6a** and **6b**, where R rep-



6a **6b**

resents different alkyl or aryl groups, for it appears that this value, along with the entropy change, is the most useful for defining the energetic difference between two conformers.[10] This information could be obtained by determining the effect of temperature on the constant for the conformational equilibrium; with the usual assumption of its independence from temperature changes, $\Delta H°$ is then provided by the slope of the line plotting log K against $1/T$ (the van't Hoff plot). The free energy ($\Delta G°$) and entropy changes ($\Delta S°$) for the process would also be obtained by standard calculations from these experimental data.

The direct observation of the two conformers in the equilibrium of a phosphorinane could, in principle, be accomplished by low-temperature NMR spectroscopic techniques, provided (1) the barrier to ring reversal is high enough so that the equilibration could be slowed down adequately at experimentally feasible temperatures, (2) that useful NMR differences exist between the conformers to permit the determination of their proportion directly from the spectra,

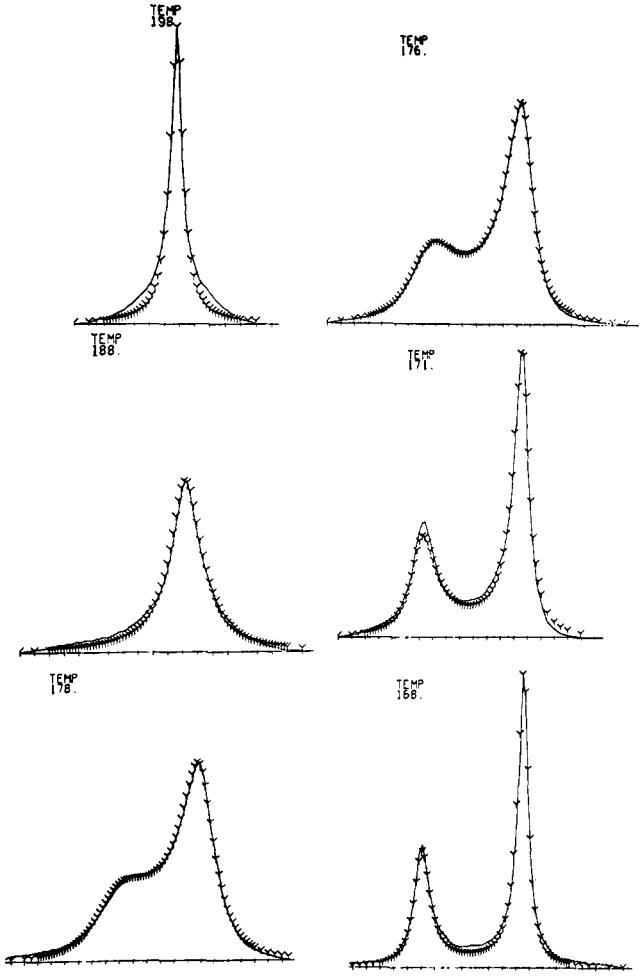
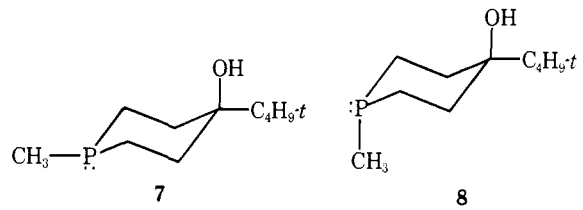


Figure 1. Graphic computer output for experimental (—) and calculated (Y) line shape for the ^{31}P NMR spectrum of 1-ethylphosphorinane at various temperatures (°K). Each division on the horizontal scale is 10 Hz; $H°$ increases from right to left.

and (3) the system does not have such strong bias that the minor conformer is of an unmeasurably low concentration. While no information on the first point was available, we know from earlier observations on conformationally rigid phosphorinanes that the requisite NMR differences do exist. For example, in the cis (**7**) and trans (**8**) isomers of



7 **8**

1-methyl-4-*tert*-butyl-4-phosphorinanol[5,11] the P-CH_3 doublet in the ^1H NMR spectra of the isomers is separated by about 4 Hz in benzene solution. More substantial differences occur for the ^{31}P NMR signals[5] (upfield from H_3PO_4, δ −57.7 and −64.6, respectively), and there are also considerable differences in the ^{13}C NMR signals,[4] notably of the CH_3 group and of $C_{3,5}$. We chose in the present study to make primary use of the ^{31}P NMR spectral differences expected for the axial and equatorial conformers in the mobile system, although no previous report existed on the use of low-temperature ^{31}P NMR spectroscopy for conformational examination of cyclic compounds. The simplicity of the ^{31}P spectra would far exceed that of either ^1H or ^{13}C, especially in compounds bearing a more complex P substituent than methyl. As it turned out, our expectations were fully realized, and low-temperature proton-decoupled ^{31}P NMR spectroscopy proved to be an excellent tool for the study of conformational equilibria in cyclic compounds. We also successfully employed low-temperature ^1H NMR spectroscopy to confirm our findings. We have not yet used low-temperature ^{13}C NMR spectroscopy, but there is little doubt that the technique would be applicable, as has already been shown for cyclohexanes.[12,13]

By using a variety of substituents on phosphorus in such studies, it should be possible to evaluate their relative "size" by comparing $\Delta H°$ values for the equilibria, as has been done so effectively (usually with $\Delta G°$ values) for cyclohexanes.[10] Insight into the nature of the 1,3-interactions could result from these considerations.

Finally, a goal of the present study was to establish energetic parameters for the reversal of the phosphorinane ring, since such data are not available. Analysis of the NMR line-shape changes in the vicinity of the coalescence temperature should provide these data. Barriers are being established for other heterocyclic systems,[9] and a correlation with the torsional energy of the C-X bond has been observed.

Experimental Section

Compounds. The synthesis and characterization of the phosphorinanes used in this study (1-methyl, ethyl, isopropyl, *tert*-butyl, and phenyl) have been reported elsewhere.[14] All sample preparations were conducted in a nitrogen atmosphere in a glove bag.

^{31}P NMR Spectral Measurements. Proton-decoupled (broadband) ^{31}P NMR spectra were obtained in the CW mode with a Bruker HFX-10 Spectrometer at 36.43 MHz. Samples were run in 5-mm tubes with a coaxial 1-mm insert containing the heteronuclear lock (C_6F_6 at ambient temperature; the lower freezing CCl_2F_2 was used down to 129°K, and CCl_3F at temperatures to 163°K, with the latter being preferred). These compounds, especially the chlorides, reacted with the phosphines when present internally in the sample. Phosphoric acid (85%) was run prior to all samples where the chemical shift was to be determined. The sign convention used is that shifts upfield of the standard are negative, those downfield are positive. Variable temperature measurements were made with a Bruker B-ST 100/700 system. Samples were prepared in trimethylethylene or, for the lowest temperatures, vinyl chloride. Measurements were made at 40 Hz/cm sweep width and in some cases at 10 Hz/cm; the rf power employed was kept well below the saturation power, since there have been cases reported of observed equilibrium constants being altered by saturation.[15] As the temperature was lowered, the ^{31}P signal broadened and separated into two singlets, which sharpened as the temperature was lowered further (see Figure 1).

^1H NMR Spectral Measurements. The same instrumentation was used, at a frequency of 90 MHz. The same solvents as used in the ^{31}P measurements sufficed, since their ^1H signals did not interfere with the phosphorinane signal of interest (P-CH_3 at about δ 1); the preferred system was vinyl chloride with CCl_2F_2 lock. Spectral changes observed are illustrated in Figure 2.

Dynamic NMR Measurements. From the ^{31}P peak separation ($\Delta\nu$) at the low-temperature limit and the visually determined coalescence temperature (T_c), the free energy of activation ($\Delta G^\ddagger$) for the ring reversal was calculated for the phosphorinanes from the approximate formula

$$\Delta G^\ddagger_{T_c} = T_c[45.67 + 4.58 \log (T_c/\Delta\nu)]$$

Complete line-shape analysis was performed on the ^{31}P NMR signals for 1-ethylphosphorinane by program ITER,[16] written locally in Fortran IV for an IBM Model 165 Computer. The program provides a plot of the calculated and experimental data by use of a Cal-Comp Plotter. The complete program is available elsewhere.[17] From the mean lifetime of the system (τ), $\Delta G^\ddagger$ can be calculated for any temperature from

$$\Delta G^\ddagger_T = 2.303RT(10.319 + \log T + \log \tau)$$

The slope of the plot of ln τ against $1/T$ can be used to determine $\Delta H^\ddagger_T$ from

Table I. ^{31}P NMR Data for the Phosphorinanes

Phosphorinane	δ,[a] 300°K	$\Delta\delta$, ppm[b]
1-Methyl	−53.7	3.1
1-Ethyl	−38.6	2.1
1-Phenyl	−34.3	9.2
1-Isopropyl	−25.4	0.4
1-*tert*-Butyl	−14.8	*c*

[a] Neat samples. Shifts are ±0.2 ppm. [b] The difference in δ for the two conformers, observed at temperatures below peak coalescence. [c] No separation observed.

Table II. Equilibrium Constants (Axial ⇌ Equatorial) for Phosphorinanes at Various Temperatures

Phosphorinane	T, °K	K_{eq}
1-Methyl	143	2.03
	148	1.76
	153	1.65
	158	1.52
	163	1.51
	168	1.39
	300	0.55[a]
1-Ethyl	151	2.10
	155	1.91
	160	1.85
	165	1.79
	171	1.53
	300	0.65[a]
1-Phenyl	133	2.33
	143	2.21
	148	2.06
	153	1.99
	158	1.84
	163	1.62
	167	1.58
	173	1.42
	300	0.72[a]

[a] Extrapolated value.

$$\Delta H^{\ddagger}_{T} = R\frac{\mathrm{d}\ln\tau}{\mathrm{d}(1/T)} - RT$$

The entropy change ($\Delta S^{\ddagger}$) is calculated from $\Delta H^{\ddagger}$ and $\Delta G^{\ddagger}$ in the usual way.

Results

Low-Temperature ^{31}P NMR Measurements. As the temperature was lowered for 1-methyl, 1-ethyl, and 1-phenylphosphorinane, the ^{31}P NMR signal broadened from a sharp singlet and split into two singlets. These signals sharpened as the temperature was further reduced. Figure 1 illustrates this behavior for the 1-ethyl compound, which occurs over the range 198 to 168°K. The upfield signal was assigned to the conformer with axial P-C_2H_5, in accord with the assignments in the rigid phosphorinanes **7** and **8**. The peaks become sufficiently separated at 168°K to permit analysis of the mixture by measurement of their heights. Cutting and weighing of the paper, or electronic integration, was also used for analysis with equal success. Analysis of the mixture was performed at progressively lower temperatures until the limit imposed by freezing of the system was reached (about 150°K). Phosphorus-31 data are given in Table I, and the results of several analyses at different temperatures are given in Table II. Very similar results are obtained for 1-methyl- and 1-phenylphosphorinanes and data are also recorded in Tables I and II.

A plot of log K against $1/T$ was linear, as is seen in a figure published previously[2] for the case of 1-methylphosphorinane. The other compounds gave similar plots. A least-squares program for a digital computer was used to obtain the best straight line. Values for 1-methylphosphorinane are typical: slope = 155.3, correlation coefficient (R) = 0.957, standard deviation of slope = 27.1. The line was extrapolated to room temperature to find the equilibrium constant. The temperature range covered by the extrapolation is considerable, and a deviation from linearity could introduce error into the constant found at room temperature. This value must therefore be viewed with some caution. There is no doubt that it is less than unity, however, implying an excess of the axial conformer. This point is considered further in the Discussion. For each of the phosphorinanes, the extrapolated line crossed K = 1, and gave the result of an excess axial conformer population at room temperature.

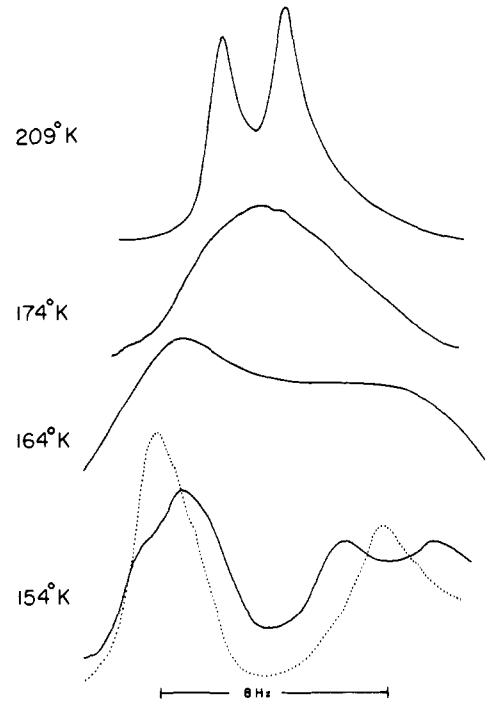


Figure 2. Illustration derived from experimental curves of the effect of temperature on the methyl proton NMR spectrum of 1-methylphosphorinane in vinyl chloride solution. The broken line at 154°K is the spectrum with ^{31}P coupling eliminated. Field strength increases from right to left.

Table III. Thermodynamic Properties for the Phosphorinane Equilibrium (Axial ⇌ Equatorial)

	ΔH°,	ΔG°, kcal/mol		
Phosphorinane	kcal/mol	163°K	300°K	ΔS°, eu
1-Methyl	−0.68 ± 0.05	−0.12 ± 0.06	+0.35 ± 0.07	−3.4 ± 0.7
1-Ethyl	−0.71 ± 0.12	−0.18 ± 0.13	+0.26 ± 0.12	−3.2 ± 1.6
1-Phenyl	−0.58 ± 0.07	−0.16 ± 0.08	+0.19 ± 0.10	−2.6 ± 0.9
1-Isopropyl		ca. −0.5		

The slope of the log K against $1/T$ plot gave ΔH° for the systems (Table III) making the usual assumption that this value is independent of temperature. Free energies could then be calculated ($\Delta G^{\circ} = -RT \ln K$) for the temperature range studied, as well as at the extrapolated temperatures. Sign reversal occurred, of course, as the equilibrium constant became less than unity. Some values are given in Table III for ΔH° and ΔG°, as are ΔS° values.

The reproducibility of the equilibrium constants for a phosphorinane at a certain temperature was quite good, generally ±0.01. The errors expressed in Table III were obtained from the standard deviation of the van't Hoff plot.

An attempt to examine 1-isopropylphosphorinane was unsuccessful; the peak separation of only 14 Hz was not adequate to permit accurate analyses. However, the conformer with the downfield ^{31}P signal was in much greater predominance here than it was for the other three compounds,

Table IV. Free Energy of Activation for the Ring Reversal of Phosphorinanes by the Approximate Method, Using ^{31}P NMR Signals

Phosphorinane	T_c, °K	$\Delta\nu$, Hz	$\Delta G^{\ddagger}_{T_c}$, kcal/mol
1-Methyl	186	113	8.7
1-Ethyl	177	79	8.4
1-Phenyl	208	337	9.3
1-Isopropyl	169	14	8.6

implying that the increased size of isopropyl forces the equilibrium more to the side of the equatorial conformer. An approximate value for K at 163°K is 4.6, which gives $\Delta G^{\circ} = -0.5$. 1-*tert*-Butylphosphorinane gave only one ^{31}P NMR signal over the entire temperature range.

Low-Temperature ^1H NMR Measurements. Only 1-methylphosphorinane had the unique signals necessary for determining the conformer ratio; the P-CH_3 doublet (J = 3.0 Hz at room temperature) was in a clear region of the spectrum. On lowering the temperature, the peak of the doublet merged into a broad unresolved signal (174°K), which then split into two signals at 164°K. At 154°K, the downfield signal was clearly a doublet (J = 3.2 Hz); the upfield signal also had doublet character but was not as well resolved since its coupling constant was significantly smaller (about 1.8 Hz). The two doublets were separated by 8 Hz. That the doublet character for each signal resulted from ^{31}P coupling was demonstrated by a decoupling experiment, whereupon two reasonably symmetrical singlets resulted. Figure 2 illustrates some of these features of the low-temperature spectra.

The signal with J_{PH} = 3.2 Hz was assigned to the axial conformer (cf. 4.0 Hz for **8**) and that with the smaller value to the equatorial (cf. 2.1 for **7**). The relative intensity (peak cutting) of the doublets (about 1:2) as assigned on this basis was consistent with the analysis from the ^{31}P NMR spectra (axial to equatorial 1:2). Since the two doublets were centered only 8 Hz apart, there was some overlap even at the low-temperature limit, and peak area measurements were less precise than those for the ^{31}P signals, which were separated by 113 Hz. The greater separation of the ^{31}P signals also allowed coalescence to occur at a higher temperature (186° vs. 163°K), giving a greater range to determine K at various temperatures. The approximate values for K obtained from the ^1H spectra nevertheless gave a reasonably linear van't Hoff plot, which on extrapolation to room temperature again showed that the axial conformer was predominant (about 4:1).

Dynamic NMR Measurements. The ^{31}P NMR spectra for 1-methyl-, 1-ethyl-, and 1-phenylphosphorinanes allowed a visual estimation of the coalescence temperatures (T_c), and from the peak separation at the low-temperature limit the approximate values for the free energy of activation for ring reversal were calculated. Data are supplied in Table IV. The peak separation varied greatly between the phosphorinanes, causing a spread of some 40° in T_c. To confirm the accuracy of this method, complete line-shape analysis was performed on one phosphorinane (1-ethyl). Values for τ (the mean lifetime of the system) at various temperatures are given in Table V. The least-squares analysis of ln τ vs. $1/T$ gave slope = 4458.3, correlation coefficient 0.999. The following activation parameters were then calculated by standard methods:[18] E_a = 8.8 kcal/mol, log A = 13.2, $\Delta H^{\ddagger}$ = 8.5 kcal/mol, $\Delta S^{\ddagger}$ = +1.2 eu, $\Delta G^{\ddagger}_{177°K}$ = 8.3 kcal/mol.

Figure 1 shows a comparison of the experimentally determined values against the calculated values. The fit is seen to be excellent. The value for $\Delta G^{\ddagger}_{T_c}$ derived from this approach agrees very well with that obtained from the approximate method, pointing to the acceptability of the $\Delta G^{\ddagger}_{T_c}$ values for the other phosphorinanes obtained by this method.

Table V. Mean Lifetime (τ) at Various Temperatures for 1-Ethylphosphorinane

τ, sec	T, °K	τ, sec	T, °K
0.02000	168	0.00310	180
0.01100	171	0.00210	183
0.00740	174	0.00110	188
0.00540	176	0.00057	193
0.00470	177	0.00035	198
0.00420	178		

Discussion

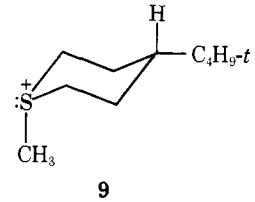
Conformational Preferences of P Substituents. The ^{31}P NMR spectra for the 1-methyl, 1-ethyl, and 1-phenyl derivatives of phosphorinane clearly show that the conformational equilibrium at low temperature lacks the strong bias toward a particular conformer (substituent equatorial) that is so prevalent in cyclohexanes. Nevertheless, at temperatures below peak coalescence there is some inequity in the signal size for the two conformers, and the evidence is compelling that the form in excess is that with the substituent equatorially oriented. This follows from the ^{31}P chemical shift relation (the equatorial isomer has the more downfield ^{31}P signal) and from the magnitude of the P-C-H coupling (the equatorial P substituent has the smaller $^2J_{PH}$ value) as seen on the ^1H NMR spectra. It is therefore true in the phosphorinane system, as it is in the cyclohexane system (but far more pronounced), that repulsive interactions prevail between the P substituent when axial and the 3,5-diaxial protons. The relative size of the two ^{31}P signals changes with increased temperature, however, showing a greater population of the less stable axial conformer. Extrapolation of the plot of log K against $1/T$ allows the prediction of the equilibrium concentrations at room temperature, and the values for all three of the phosphorinanes show the axial conformer to be in excess. The extrapolation takes place over a considerable temperature range, and the size of the error involved is not certain. The values for K at 300°K in Table II must be considered subject to further refinement. Nevertheless, that all three phosphines show the same result on extrapolation is reassuring that the conclusion of an axial excess is sound. The conclusion does not lack for support on other grounds, however. Thus, the time-averaged $^2J_{PH}$ value (3 Hz) for the P-CH_3 group at room temperature is closer to the $^2J_{PH}$ value seen at 129°K for the axial conformer (3.2 Hz) than for the equatorial conformer (1.8 Hz). Also, we have reported elsewhere[14] that the ^{13}C NMR spectra of phosphorinanes possess a sterically dependent feature: $^2J_{PC}$ for ring carbons is greater when the P substituent is equatorial than when it is axial. Thus, for rigid models **7** and **8**, $^2J_{PC_{3,5}}$ is 7 and 0-1 Hz, respectively. The values for the three 1-substituted phosphorinanes are in the range 3-4 Hz, consistent with a largely nonbiased equilibrium.

The axial predominance at room temperature is associated with an entropy difference between the two forms. While not large (−2 to −3 eu), the ΔS° values for the three phosphorinanes are certainly not negligible in these cases where the enthalpy values themselves are rather small (−0.6 to −0.7 kcal/mol). The consequence is that ΔG° is much more temperature dependent than is seen in the cyclohexanes. We include in Table III calculations for ΔG° at 163° and 300°K, and it can be seen that the values differ for the CH_3, C_2H_5, and C_6H_5 cases by 0.47, 0.44, and 0.35 kcal/mol, respectively. Furthermore, these ΔG° values are *negative* at low temperatures but *positive* at room tempera-

ture. In the cyclohexanes, it is common practice to ignore the entropy difference, which is frequently small (<1 eu) and of little consequence compared with the large $\Delta H°$ values (e.g., −1.7 kcal/mol for CH_3), and to consider that $\Delta G°$ and $\Delta H°$ are of quite similar magnitude. In systems such as the phosphorinanes, this approximation could lead to quite erroneous conclusions. Thus, if $\Delta G°$ were determined only at room temperature by some method other than the low-temperature NMR method, the positive sign (and consequent excess of axial conformer) could be taken to indicate that the nonbonded interactions are attractive and not repulsive, and that the equatorial form is in general destabilized relative to axial. The true situation is revealed by the $\Delta H°$ values which as indicated are consistent with the interactions being repulsive. We feel that it is preferable, therefore, to discuss the conformational preferences of P substituents in terms of $\Delta H°$, as has been advocated by others.[10] We do not mean to imply that in other heterocyclic systems the nonbonded interactions will always prove to be repulsive. The case of selenane 1-oxide[9] is particularly striking; at 143°K it is 84% axial and can hardly be considered to have interactions that are repulsive.

Just why the entropy difference in the phosphorinanes is greater than in cyclohexanes is not known. In any case, the difference between $\Delta S°$ values for the two ring systems is not large. The data would have to be refined considerably to get precise $\Delta S°$ values, as the errors in the present measurements (Table III) are relatively large. A recently reported $\Delta S°$ value of −2 eu for another heterocyclic system (4-methylpiperidine 1-nitroxide)[19] suggests that there may be more common departure from the cyclohexane type of value than is presently appreciated.

There are several manifestations of the repulsive nonbonded interactions in the phosphorinane system to back up the conclusion for their presence as reached by the enthalpy values. (1) The ^{13}C NMR spectra[4] of rigid phosphorinane derivatives show the usual chemical shift effects resulting from atoms involved in steric compression. Thus, in the cyclohexane system an axial methyl and the ring carbon in the γ position to this methyl ($C_{3,5}$) are upfield by several parts per million as a result of electron displacement from the steric crowding; in phosphorinane **8**, precisely the same effect is seen relative to the less crowded isomer **7**. (2) The ^{31}P NMR difference between rigid phosphorinanes is in the direction expected from the transmission of the steric compression effect to this atom also. The isomer with axial P substituent has the more upfield signal. The effect is well-known in methylcyclohexanes. (3) The X-ray analysis of P-phenyl compounds **4**[6] and **5**[7] shows that the axial phenyl is crowded to the point that this ring is displaced away from the phosphorinane ring, making the phosphorus atom attached to the phenyl ring lie significantly (0.1-0.3 Å) out of the plane of the phenyl ring. (4) The X-ray studies of the rigid isomers **7** and **8** show that the shape of the ring is dependent on the orientation of the P substituent. When the substituent is axial, the ring adopts a less puckered shape at the phosphorus end. The internal P-C-C bond angles are increased by 5.4° over those in the equatorial isomer, and the torsion angle about the internal P-C bond is decreased by 11° (Table VI). The net effect is to alleviate the crowding that must prevail when the substituent is axial. Precisely



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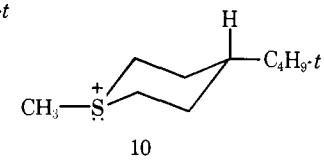

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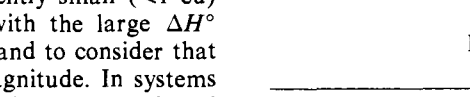
Table VI. Geometric Parameters from the X-Ray Analysis of the Isomeric 1-Methyl-4-*tert*-butyl-4-phosphorinanols



Bond angles	CH_3 equatorial (**7**)[a]	CH_3 axial (**8**)[b]
a/b	110.6	116.0
b/c	112.9	114.6
c/c'	111.2	110.9
a/a'	98.0	97.7
a/d	102.8	101.9
Dihedral angles		
a	57	46
b	62	58
c	60	58

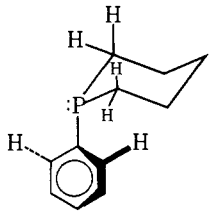
[a] Data taken from the Ph.D. Dissertation of P. A. Luhan, Duke University, Durham, N.C., 1973. Angles in degrees. [b] Reference 11.

the same effect has recently been observed on comparing the rigid isomers **9** and **10** in the thiane system.[20]

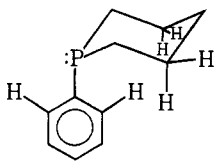
The geometric deformations probably account also for much of the considerable reduction in the energy by which the axial form is destabilized relative to the equatorial, which is seen when both the phosphorinane and thiane systems are compared with the cyclohexane system. For the methyl derivatives of these three-ring systems, $\Delta G°$ values are +0.35 (300°K), −0.275 (373°K; assumed[20] to be the same as found for the *tert*-butyl derivatives **9** and **10**), and −1.7[21] kcal/mol, respectively. The crowding in the axial isomer is relieved in the heterocyclic compounds by the widening of the X-C-C bond angles and the flattening of the ring about the heteroatom. It has been suggested[20] that this adjustment is not possible in the cyclohexane system because of the presence of the hydrogen atom in the equatorial position on the carbon bearing the substituent. The geminal interaction prevents the relief of the steric strain by the torsion angle adjustment.[22] The greater length of the carbon-heteroatom bond may also figure in the existence of diminished steric interaction in the heterocycles.

The room-temperature predominance of the conformer with axial P-alkyl over the equatorial has been noted in the 1,3,2-dioxa-[23] and 1,3,2-dithiaphosphorinanes.[24] It is not known if the same structural changes as seen for the phosphorinane and thiane system occur to relieve the strain in the axial conformer; it is a possibility that deserves consideration, although the extra heteroatoms must alter the shape of these rings considerably. The situation is more complicated here also because of the presence of lone pairs on adjacent atoms that can lead to interactions of another type (the gauche effect[25]). Attractive rather than repulsive 1,3-nonbonded interactions have also been postulated for these systems.[24]

The enthalpy values we have determined for the three different P-substituted phosphorinanes are remarkably similar (methyl, −0.68; ethyl, −0.71; phenyl, −0.58 kcal/mol). This is certainly not the case in the cyclohexanes and suggests the rather small importance of the nonbonded repulsive interactions in the phosphorinane system. The similarity in the "size" of phenyl to that of methyl or ethyl when attached to phosphorus is particularly worthy of comment, for in cyclohexanes phenyl is considered to be a very space-demanding group ($\Delta G°$ = −2.6 to −3.1 kcal/mol[26]). The X-ray studies of **4** and **5** show that phenyl adopts the conformation as shown in **11a** rather than that seen in **11b**, as has been calculated[27] to be the case for axial phenyl on cyclohexane, and recently demonstrated experimentally for a 1,4-disubstituted phenylcyclohexane.[28] This conformation (referred to as the perpendicular;[27] **11b** is parallel) is preferred in order to alleviate interaction of the ortho hydrogen



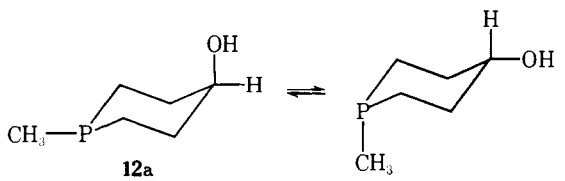
11a



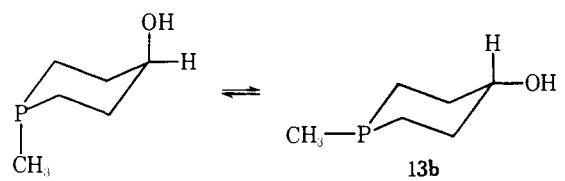
11b

with the axial protons on $C_{3,5}$. The main interactions in the perpendicular conformation are between the ortho hydrogens and the equatorial protons on $C_{2,6}$, or possibly between the π electrons and the 3,5-axial protons. As noted already, the phenyl group is not buttressed by a fourth group on phosphorus and can bend away from the phosphorinane ring to alleviate these interactions. Considerable displacement of the plane of the phenyl ring from the ring-to-phosphorus bond axis was observed in the X-ray analysis of **4**[6] and **5**.[7] Apparently this adjustment is achieved at low-energy cost, causing considerable minimization of the effective size of phenyl when on P relative to that when on -CH. This effect may also prevail for CH_3 and C_2H_5 on P, but it seems to be more pronounced with phenyl. With the bulkier isopropyl and *tert*-butyl groups, it appears that the equatorial conformers predominate even at room temperature. The present study was not successful in obtaining thermodynamic values for these groups, but the qualitative indications from the ^{31}P spectra certainly point this way. Thus, the isopropyl compound had a considerably larger excess (about 4-5 to 1) of equatorial over axial conformer at 163°K, and it seems doubtful in this case that the system would cross the $K = 1$ line. The ^{31}P spectrum of the *tert*-butyl compound showed only one form at the low-temperature limit, and this suggests that the axial conformer is present in too low a concentration to measure by this technique, although the possibility cannot be excluded that insufficient chemical shift difference exists to allow observation of both conformers. These conformational properties are fully supported by ^{13}C NMR measurements,[14] especially from the values for $^2J_{PC}$ (6 Hz for i-C_3H_7, 7 Hz for *tert*-C_4H_9). These agree with the coupling observed for the rigid equatorial model **7** (7 Hz).

From the $\Delta G°$ values for P substituents, combined with conventional $\Delta G°$ values for cyclohexanes, it is now possible to explain the preferred conformations of disubstituted phosphorinanes. This explanation rests on the assumption that $\Delta G°$ values are additive. Consider the case of the 1-methyl-4-phosphorinanols. The $\Delta G°$ value for hydroxy (ax → eq) is −0.89 in benzene,[29] while $\Delta G°_{300°}$ for P-CH_3 (eq → ax) is −0.35; this means that conformation **12b** for this cis isomer will be favored by 1.24 kcal/mol over **12a.** For the trans isomer, conformation **13b** will be preferred over



12a ⇌ 12b



13a ⇌ 13b

13a, but by a smaller amount (0.54 kcal/mol). These energy differences are approximate only, but do suggest that for each isomer conformational control is exerted by the C substituent, and the structure differs about phosphorus. We had come to this conclusion from spectroscopic considerations as early as 1967,[3] and found support for it in later work as well.[5] We can also predict the same result for the 1-phenyl-4-phosphorinanols since $-\Delta G°$ for P-phenyl is small, and indeed we have ^{13}C NMR evidence that these isomers do differ by configuration about phosphorus, with both having an equatorial hydroxy.[17]

Barrier to Ring Reversal in Phosphorinanes. The complete line-shape analysis of the ^{31}P NMR spectral changes accompanying the lowering of the temperature for a sample of 1-ethylphosphorinane gave a value for $\Delta G^‡$ at the coalescence temperature (177°K) of 8.3 kcal/mol. The approximate method gave a value of 8.4 for this compound, 8.7 for the 1-methyl, and 9.3 for the phenyl. This range of values is close to, but less than, the accepted values for ring reversal of cyclohexanes (10-11 kcal/mol[30]). The barrier is significantly less than that for 1-methylpiperidine; this has been expressed as E_a, with a value of 14.4 kcal/mol,[31] while we find E_a for 1-ethylphosphorinane to be 8.8 kcal/mol. It has been found[9] for pentamethylene derivatives of group 6 that the barrier also decreases with size of the heteroatom, and this has been related to the diminished torsional barrier as the size of X in the C-X bond increases. The barrier in 1,1-dimethylsilacyclohexane (5.9 kcal/mol)[32] is well below that in cyclohexane for the same reason.[33] Since the torsional barrier ($\Delta H^‡$) for C-P rotation in $(CH_3)_3P$ is 3.58 kcal/mol,[34] while that for $(CH_3)_3N$ is 4.4,[35] the barrier we have found for ring reversal in the phosphorinane system is quite in line with expectation.

The coalescence temperature varies considerably among the phosphorinanes, and is a function of $\Delta\nu$. The largest $\Delta\nu$ value is seen for the 1-phenyl case (337 Hz), and the coalescence temperature is a comfortably reached 208°K. The isopropyl compound has the smallest $\Delta\nu$ (14 Hz) and the coalescence temperature is some 40° lower than that for phenyl. The diverging $\Delta\nu$ values are a consequence of the different steric influences on the ^{31}P nucleus, as is discussed below.

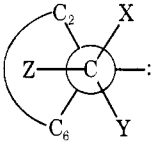
Interpretation of NMR Properties. We have pointed out elsewhere[36] that for five-membered cyclic phosphines the ring makes an additive contribution to the ^{31}P shift just as acyclic substituents do.[37] We later showed[38] that substituent effects of alkyl groups could be treated in much the same way as they are in ^{13}C spectroscopy, and that, for a given phosphorus functional group, adding a carbon β to the phosphorus atom causes deshielding while adding a carbon γ to phosphorus causes shielding. The increments were additive. The series of phosphorinanes prepared for the present study presented the opportunity of exploring the operation of these relations in six-membered rings, where conformational effects have large influences.

The ^{31}P shifts in Table I represent the averaged value for the two equilibrating conformers. In the methyl and ethyl compounds, the value would be closer to that for the predominating axial conformer; for isopropyl it is closer to the predominating equatorial conformer, although $\Delta\delta$ for this compound is only 0.4 ppm. Since methyl and ethyl have rather similar percentages of the conformers and since $\Delta\delta$ for isopropyl is so small, it is possible to ignore conformational aspects of the series and to evaluate the effect on the ^{31}P shift of adding β carbons to the 1-methyl compound. For acyclic tertiary phosphines, an increment of 13.5 ppm accompanies each added β carbon. Knowing the ^{31}P shift for 1-methylphosphorinane to be −53.7 ppm, we then calculate a value of −40.2 ppm for 1-ethylphosphorinane; the

experimental value is a reasonably close −38.6. Similarly, for isopropylphosphorinane we expect a value 27 ppm (two β carbons) downfield from 1-methyl; we find a shift of −25.4, compared to the calculated −26.7. This approach also works for the *tert*-butyl case; three β carbons lead to a calculated value of −14.7, while the experimental value is −14.8.

For four of the phosphorinanes, the ring makes a reasonably constant group contribution (GC)[37] to the ^{31}P shift, as is seen on deducting the GC of each P substituent: methyl GC −21.0, ring GC −32.7; ethyl −7.0, ring −31.6; isopropyl +6.0, ring −31.4; phenyl −3.0, ring −31.1. For *tert*-butyl (GC + 23.0), however, the ring contribution (−37.8) is significantly larger. The greater crowding about phosphorus must be responsible for the increased shielding; the origin of this becomes evident in the discussion to follow. The ring group contributions therefore do not seem reliable for calculating ^{31}P shifts in compounds where large bulky groups are present on phosphorus. The alternative approach of calculating the shift from the number of β carbons gives a much better agreement with the experimental value.

That the conformer with axial P-methyl has a ^{31}P shift upfield from the equatorial follows directly from a recognition of the importance of γ-shielding effects in acyclic compounds,[38] since crowding is more important in the axial conformer.[39] In cyclohexanes, the crowding associated with axial methyl causes electron displacement toward (and shielding of) the ring carbon bearing methyl as well as of the methyl carbon and ring carbons 3 and 5. In phosphorinanes, therefore, the phosphorus atom should be more shielded in the axial conformer. However, as the size of the P substituent increases, another factor must be taken into consideration, for as Table I shows $\Delta\delta$ becomes smaller. We attribute this to the development of shielding effects also in the equatorial conformer. The steric interactions leading to this shielding are evident in the Newman projection along the phosphorus-to-carbon external bond. The number of gauche interactions between the substituents on the external carbon and ring carbons 2 and 6 increases as alkyl groups replace hydrogen at X, Y, and Z. Each of these



gauche interactions, through steric compression, will cause shielding at $C_{2,6}$, and this is clearly evident in the ^{13}C NMR spectra[14] for the series of compounds. The values for $C_{2,6}$ range from δ^{CS_2} 165.8 for P-CH_3 to 171.1 for P-$C(CH_3)_3$. The phosphorus atom in the equatorial conformer experiences the same shielding effect through the compression transmitted from $C_{2,6}$ as it does in the axial conformer through compression of the methyl group. If the P substituent is sufficiently bulky, it is possible that the interactions with $C_{2,6}$ in the equatorial conformer may cause greater shielding at P than the interactions with $C_{3,5}$ in the axial conformer, and reverse the order of signals seen for the smaller groups. There is a suggestion of this in the data in Table I, where $\Delta\delta$ diminishes from 3.1 ppm for methyl to 0.4 for isopropyl. Were data available for *tert*-butyl, they may show that the equatorial conformer was upfield of axial.

We have arrived at a better understanding of some ^1H NMR properties of phosphorinanes as a result of the present studies. We have earlier noted[3] that the equatorial P-methyl when cis to hydroxy was slightly deshielded relative to axial methyl in the trans isomer. This was attributed to a deshielding effect of hydroxy, but since the effect requires the presence of benzene as solvent, it now seems more appropriate to consider it as an example of an aromatic solvent-induced shift effect. The hydroxy group is required for the effect, since it forms a collision complex with the solvent, which then is oriented properly for the deshielding of methyl. The same effect is known among cyclohexanols. In the absence of hydroxy, however, one might expect axial P-methyl protons to be deshielded relative to equatorial, as is true for methyl on cyclohexanes. The low-temperature ^1H NMR of 1-methylphosphorinane shows that this is indeed the case; there is peak separation of 0.09 ppm at 154°K, with the axial methyl downfield. This is entirely consistent with the steric compression argument that explains shielding at C and P; displacement of electron density to carbon in a C–H bond must diminish electron density at hydrogen, and cause deshielding.[40]

Acknowledgment. It is a pleasure to recognize the contributions of Professor Andrew T. McPhail and his associates of this Department in the establishment and interpretation of the important geometric differences in rigid phosphorinanes. Professor Charles G. Moreland, North Carolina State University, is also thanked for his excellent advice and assistance with the complete line-shape analysis.

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Conformational Analysis of Peptides in Oriented Polyoxyethylene by Infrared Dichroism

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Abstract: A new procedure for the determination of infrared dichroic spectra of oligo- and polypeptides is described. The peptide is incorporated in a polyoxyethylene film and partially oriented by uniaxial stretching. The infrared characteristics of the polyoxyethylene support allow measurement of the dichroic spectra of amide N-H stretching bands between 3500 and 3000 cm^{-1}, of amide I and II bands between 1700 and 1500 cm^{-1}, and of far-infrared bands below 800 cm^{-1}. Dichroic spectra of both high molecular weight polypeptides and oligopeptides, whose low molecular weight had hindered their orientation, can be conveniently determined in polyoxyethylene. Procedures for measuring the kinetics of N-H to N-D isotopic exchange reactions of molecules oriented in polyoxyethylene are also described. The infrared dichroic spectra of gramicidin S and of several synthetic oligo- and polypeptides are presented. Gramicidin S exhibits a "cross-β" dichroic spectrum which could arise from extensive association of the β-sheet conformation of Hodgkin-Oughton and Schwyzer into ribbon-like aggregates. Polypeptides were found to be oriented in the α-helical, β-sheet, and "cross-β" conformation in polyoxyethylene films.

We describe here a new technique, based on linear infrared dichroism, for conformational analysis of oligo- and polypeptides. The molecules under investigation are incorporated into a polyoxyethylene film and partially oriented by uniaxial stretching. Infrared dichroic spectra are then recorded using common spectroscopic techniques. The relative orientation of transition dipole moments of various chromophores and their relation to the direction of molecular orientation are derived from the dichroic spectra. This type of important conformational information was previously available only for high polymeric molecules from which oriented films or fibers could be formed; it is now readily obtained for small oligopeptides and for larger molecules which do not form satisfactory films.

The infrared characteristics of the polyoxyethylene (POE) support make it particularly suitable for analysis of the amide N-H stretching band, ν(NH), located near 3300 cm^{-1} and the amide I and II bands between 1700 and 1500 cm^{-1}. Far-infrared bands below 800 cm^{-1} can also be examined. Polyoxyethylene's solubility in water as well as in organic solvents such as chloroform and trifluoroethanol and the ease with which its films can be oriented greatly enhance its usefulness.

Thulstrup, Michl, and Eggers[2a] and Mazur and coworkers[2b] have employed analogous techniques to study the uv dichroism of molecules oriented in stretched polyethylene films. Although polyethylene has infrared windows in spectral regions of important amide absorptions, its low polarity makes it incompatible with most peptides.

We also describe procedures for determining the rates of hydrogen to deuterium isotopic exchange reactions of peptides oriented in POE. The dependence of the dichroism of N-H vibration bands upon extent of N-H to N-D conversion is observed directly during exchange in POE. These experiments allow both the rate of exchange, which reflects accessibility to the solvent medium, and the orientation of each spectrally distinct N-H group to be determined simultaneously. The correlation of exchange kinetics and dichroism greatly enhances the value of the separate measurements for conformational analysis.

The dichroic spectra presented here of gramicidin S and of several synthetic oligo- and polypeptides serve to illustrate the method.

Experimental Section

Materials. Polyoxyethylene (POE), M = 300,000 was purchased from Union Carbide Co. (WSRN) 750 and further purified by repeated methanolic precipitations from chloroform. The polymer was collected and dried under vacuum.

Gramicidin S (Bacillus Brevis) was purchased from Schwarz-Mann, lot No. E V3917, and further recrystallized four times from ethanol: 1 M HCl mp 309° [lit.[3] 277-278°]; $[\alpha]^{20}D$ −290.7° (c 0.43 in 70% ethanol v/v) [lit.[3] −289 (c 0.43 in 70% ethanol v/v].

Poly(γ-benzyl L-glutamate) was purchased from Schwarz-Mann, lot No. PBG-γ-6003, M = 90,000-100,000.

Poly(γ-ethyl L-glutamate) was prepared by polymerization of γ-ethyl L-glutamate N-carboxyanhydride in dioxane with sodium methoxide catalyst (N/I = 15) according to the procedure of Goodman and Hutchison;[4] $\overline{DP}$ = 25.

Poly(L-alanine) was purchased from Pilot Chemical Co., lot No. 6911, M = 35,000.

Z-(γ-ethyl L-glutamate)$_{12}$ ethyl ester (Z, benzyloxycarbonyl) was prepared according to the procedure described by Goodman and Rosen.[5]

Solvents used for preparation of POE stock solutions were Matheson Coleman and Bell spectroquality and were used without further purification.

Preparation of Films. A peptide sample (2-3 mg) was mixed with 0.5 ml of poly(ethylene oxide) stock solution (10% w/v) and the resulting solution was clarified by centrifugation. It was then spread evenly to a 2.5 × 0.7 cm strip on a silanized microscope slide and the solvent was allowed to evaporate at room temperature