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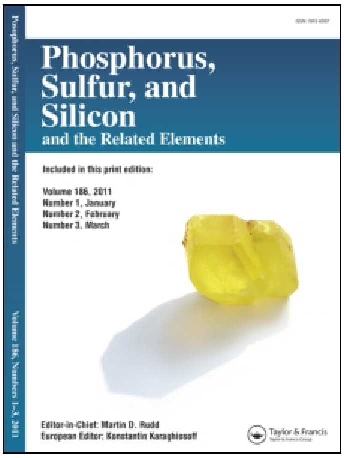

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CYCLIC OXYPHOSPHORANES

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Review

CYCLIC OXYPHOSPHORANES

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(Received September 25, 1989; in final form February 7, 1990)

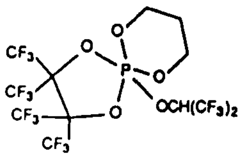
A review on pertinent information on cyclic oxyphosphoranes is presented. Recent X-ray structures and variable temperature ^1H NMR investigations of cyclic pentaoxyphosphoranes reveals a preference for a boat conformation for saturated six-membered rings in apical-equatorial orientations of trigonal bipyramids. These studies include five-, six-, and seven-membered rings and show that the solid state structures are retained in solution. Apical-equatorial ring pseudorotations are more facile for five-membered rings, whereas ligand exchange via diequatorial ring placement is more facile for the larger rings. The importance of the apical-equatorial ring orientation for phosphorinanes appearing as trigonal bipyramidal intermediates in enzymatic reactions of cyclic AMP analogs is emphasized.

Key words: Cyclic oxyphosphorane; trigonal bipyramid; Berry pseudorotation; cyclic AMP.

INTRODUCTION

Pentaoxyphosphoranes are useful models for intermediates in phosphate ester hydrolysis.[1,2] The inclusion of five-membered cyclic substituents in phosphoranes has aided the interpretation of the great acceleration in hydrolysis of similarly constructed cyclic phosphate esters of importance in biological mechanisms. The latter interpretation has been summarized in the Westheimer model.[2]

Although an abundance of structural studies[3] of phosphoranes containing five-membered rings has been performed, little is known about six-membered rings. In the area of pentaoxyphosphoranes, only one structural study had been reported up until our entrance into this field. This concerns compound **1** whose X-ray structure was recently reported by D. Schomburg.[4]



1

Six-membered rings in trigonal bipyramidal arrangements are expected to exert less ring strain than five-membered rings. Whereas, five-membered rings invariably span apical-equatorial sites, six-membered rings might be expected to be located either apical-equatorially or diequatorially with little energy preference between them. A greater knowledge of this preference would be of considerable

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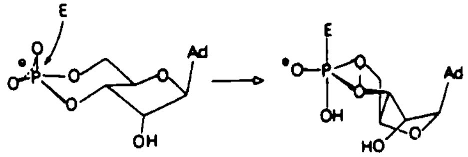
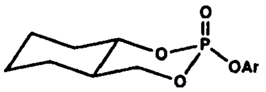
value in assisting in the interpretation of hydrolysis or solvolysis of such ring containing tetracoordinated phosphorus compounds proposed to react via five-coordinated activated states.[5–7]

One important application concerns an understanding of the mechanisms of formation and breakdown of cyclic adenosine 3′,5′-monophosphate (cyclic AMP) catalyzed by adenylate cyclase and cyclic AMP phosphodiesterase, respectively.[8–12] Cyclic AMP is an important effector molecule which regulates a wide variety of biochemical processes. In enzymatic actions, it is not known whether the six-membered ring assumes a diequatorial position in a proposed phosphorane intermediate, an apical-equatorial position, or that the conformation is enzyme dependent. Semi-empirical molecular orbital calculations[10,13] (CNDO/2) on possible pentacoordinated intermediates for the hydrolysis of cAMP indicate a lower energy for diequatorial ring placement in a trigonal bipyramidal compared to an apical-equatorial ring position. In the activation of protein kinases by cAMP, these calculations support diequatorial placement of the cyclophosphate ring which has been proposed to result from attack by a functional group of the enzyme yielding a covalent complex.



The preference for diequatorial placement of a six-membered ring is in agreement with investigations of Ramirez and Ugi[14] and Marquarding *et al.*[15] Also consistent with the above are proposed diquatorial ring trigonal bipyramidal transition states for the hydrolysis of epimeric phosphorinanes,[16,17] e.g.,



Ar = 2,4(NO$_2$)$_2$Ph

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On the basis of an NMR study, Denney and coworkers[18] concluded that seven- and eight-membered rings of monocyclic pentaoxyphosphoranes containing OCH$_2$CF$_3$ groups are situated in diequatorial positions of a trigonal bipyramid (Figure 1).

By way of contrast, Trippett[19] proposed that a phosphorane with a six-membered ring positioned apical-equatorially in a boat conformation has the lowest energy among various ring conformations either situated in diequatorial or apical-equatorial sites of a trigonal bipyramid. In this boat conformation, the lone electron pair on the equatorial oxygen atom residing in a *p* orbital can be located in the equatorial plane, a favorable condition to maximize pi bonding with phosphorus d orbitals. An X-ray study of the tetraoxyphosphorane **2**[20] and the pentaoxyphosphorane **1**[4] supports this hypothesis.

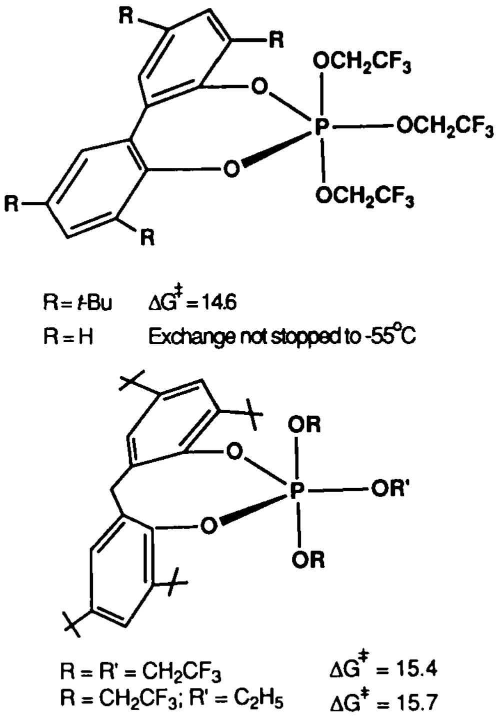
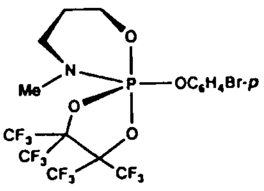
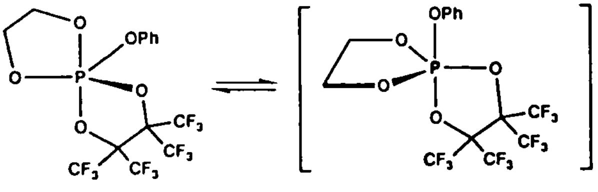


FIGURE 1 Solution state structures and ligand exchange energies, $\Delta G^{\ddagger}$ (kcal/mol), for ring interchanges e–e ⇌ e–a, from an NMR study.[18]



2

On comparison of ligand exchange energies determined from dynamic NMR studies on cyclic oxyphosphoranes where diequatorial exchange activated states are proposed, it is apparent that six-membered rings provide lower barriers than five-membered ring systems.[19,21a] For example, the pseudorotational process postulated for equilibration of CF_3 groups in **3** is accompanied by an exchange barrier of 17.4 kcal/mol compared to only 6.1 kcal/mol for **4**.[19]



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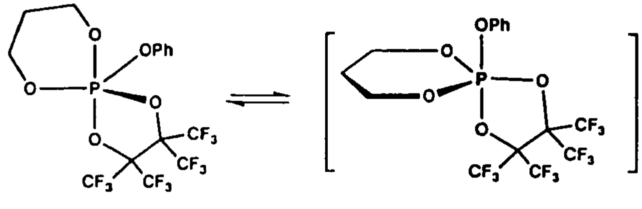

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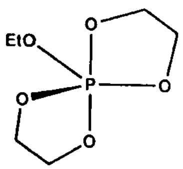
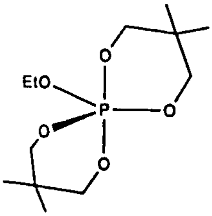
In related NMR studies by Denney and coworkers[21a] on the five- and six-membered ring containing spirocyclic oxyphosphoranes,



A



B

equivalent ring protons and methyl groups were present at room temperature for the six-membered ring derivative but a temperature of 172°C was required to bring about equivalency of the ring protons in the five-membered ring compound. Here as well, exchange via higher energy states with diequatorial rings satisfactorily interprets the data.[21b] Further, apical-equatorial ring exchange is postulated to occur down to the low temperature limit investigated, ~60°C. These pseudorotational processes are summarized in Figure 2, where H is used to represent the acyclic ligand.[22]

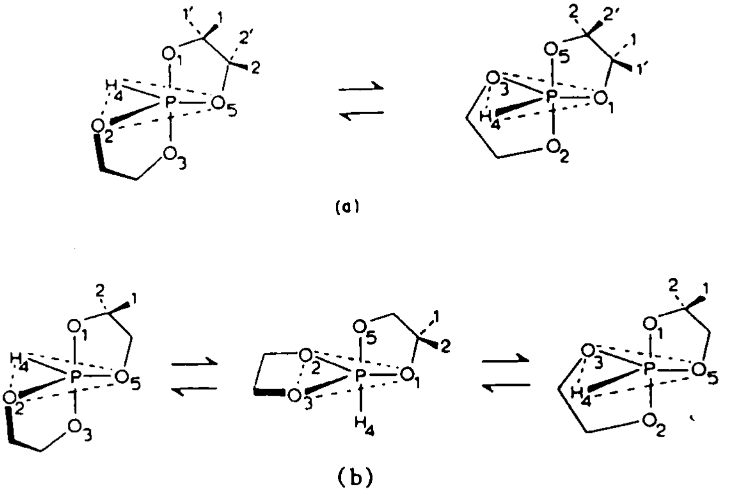


FIGURE 2 (a) Low-temperature exchange process. (b) High-temperature process. Both processes are proceeding by Berry exchange.

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The closeness in energy between apical-equatorial and diequatorial placement of six-membered rings implied by such studies suggests that interpretations of nucleophilic displacements at phosphorus proceeding by way of pentacoordinated states is subject to greater variability compared to that for phosphates containing five-membered rings.

We have carried out X-ray and NMR studies[23] of a series of related cyclic pentaoxyphosphoranes containing ring sizes from five- to seven-membered which have sufficient variability in substituent composition to provide a comprehensive treatment. The studies were undertaken to determine ring site preferences and solution state exchange processes, the knowledge of which should prove useful in interpreting mechanisms of nucleophilic displacement reactions of cyclic phosphorus components. The following reviews the main features resulting from this work and presents a current perspective in relation to existing work.

RESULTS AND DISCUSSION

Synthesis

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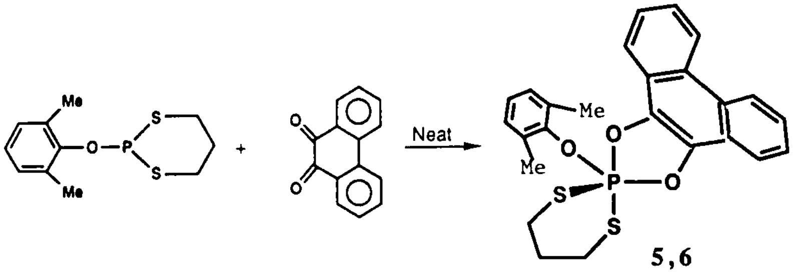
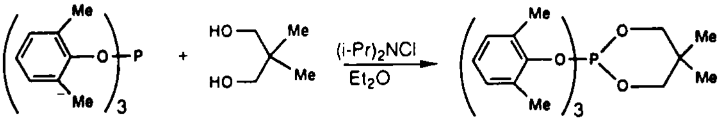
Monocyclic and bicyclic pentaoxyphosphoranes, including two thio derivatives, for which X-ray structures have been obtained are listed in Table I. All of these derivatives were synthesized by oxidative additions of quinones to phosphites or oxidative coupling of diols with phosphites in the presence of chloro diisopropylamine. For example, the synthesis of **5** and **7** by these respective routes are illustrated in Equations (1) and (2). In general, yields varied from 40% to 80% and crystalline products were formed by slow evaporation of the solvent at 25°C. Some of the monocyclic derivatives readily discolored or liquified on standing in air. However, crystals appeared to remain stable indefinitely when sealed in ampoules in the absence of air.



5,6

(1)



7

(2)

TABLE I

Structures of cyclic oxyphosphoranes and their intramolecular exchange processes

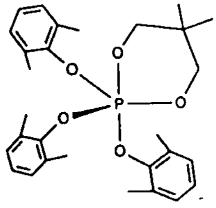
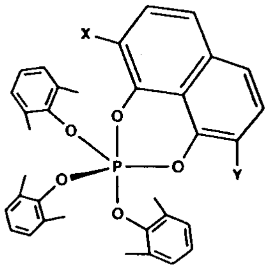
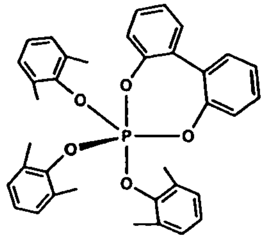
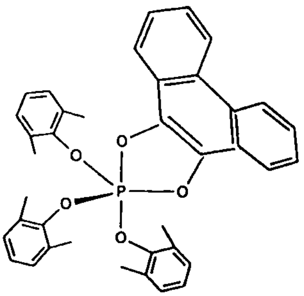
No.	Compound[a]	^{1}H NMR behavior[b]	$\Delta G^\ddagger$ kcal/mol	^{31}P, ppm[c]
7		a–e ⇌ e–a slowed below −50°C	10.6	−77.45
8[d]	 X = Y = H X = Y = Cl X = H, Y = Cl	a–e ⇌ e–a and C—O bond rotation slowed below −60°C		−88.17 −88.32 −88.55
9		a–e ⇌ e–a and C—O bond rotation slowed below 40°C and 15°C, respectively	14.3	−68.34
11		a–e ⇌ e–a and C—O bond rotation not stopped down to −95°C		−57.02

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TABLE I (*continued*)

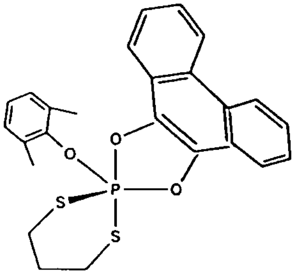
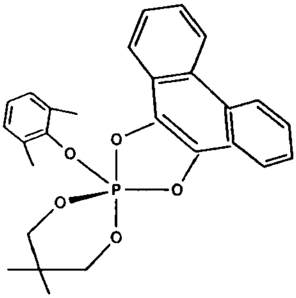
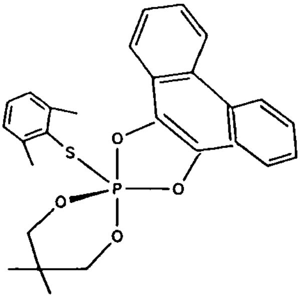
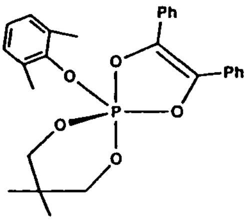
No.	Compound[a]	^{1}H NMR behavior[b]	$\Delta G^{\ddagger}$ kcal/mol	^{31}P, ppm[c]
5, **6**		a–e ⇌ e–a at room temperature		3.96
14[c]		a–e ⇌ e–a and C—O bond rotation not stopped down to −80°C		−48.96
15		a–e ⇌ e–a and C—O bond rotation not stopped down to −60°C a–e ⇌ e–e, above 0°C		−20.30
12		a–e ⇌ e–a and C—O bond rotation not stopped down to −80°C		−53.55

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TABLE I (*continued*)

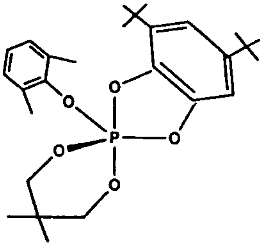
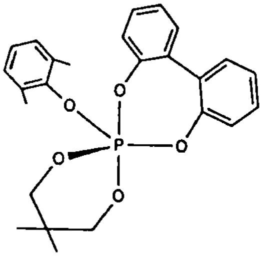
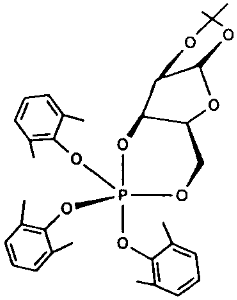
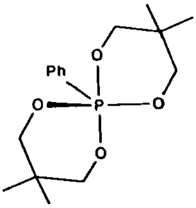
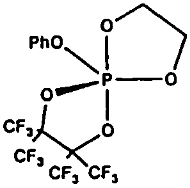
No.	Compound[a]	^{1}H NMR behavior[b]	$\Delta G^{\ddagger}$ kcal/mol	^{31}P, ppm[c]
13		a-e ⇌ e-a and C—O bond rotation not stopped down to −90°C		−51.30
10[f]		a-e ⇌ e-a slowed below −70°C. C—O bond rotation stopped below −60°C		−60.0
		a-e ⇌ e-e above 0°C via seven-membered ring	11.2	
16[g,h]		a-e ⇌ e-a and C—O bond rotation slowed below −20°C	≥11.0	−80.00
17		a-e ⇌ e-a not stopped down to −65°C		−49.15
		a-e ⇌ e-e occurs at room temperature	11.7	
3		a-e ⇌ e-e	17.4	

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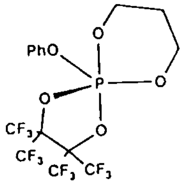
TABLE I (*continued*)

No.	Compound[a]	^{1}H NMR behavior[b]	$\Delta G^{\ddagger}$ kcal/mol	^{31}P, ppm[c]
4		a-e $\rightleftharpoons$ e-e	6.1	

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[a] X-ray structures were obtained in our laboratory for **5–10**, **12–15**, and **17**. All NMR investigations are from our laboratory except for **3**[19] and **4**.[19] Details of the studies reported here will be published elsewhere.[23,24b,27] For **17**, a previous report gave similar NMR results but no activation energy was calculated.[21a]

[b] The pseudorotational process a–e $\rightleftharpoons$ e–a refers to apical-equatorial ring permutations illustrated in Figure 2(a), and that for a–e $\rightleftharpoons$ e–e refers to apical-equatorial to diequatorial ring permutations illustrated in Figure 2(b).

[c] ^{31}P chemical shifts are relative to 85% H_3PO_4 with upfield shifts negative.

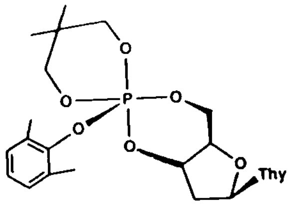
[d] The X-ray structure is consistent with co-crystallization of three compounds.

[e] ^{13}C NMR shows one ring CH_2 group down to −85°C.

[f] ^{13}C NMR shows two ring CH_2 groups at low temperatures which coalesce to one on warming, thus implying cessation of a–e $\rightleftharpoons$ e–a exchange at low temperature.

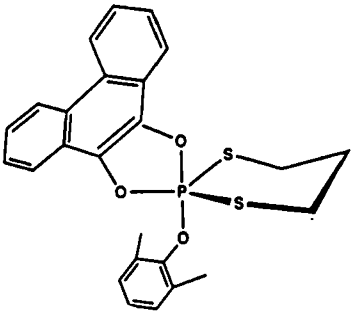
[g] The CH_2OH and OH group in the diol used to synthesize **16** were *cis* to each other, whereas in cAMP, these groups are *trans* to each other.

[h] The *trans*-annelated thymidine (Thy) cyclic monophosphate pentaoxyphosphorane was identified only by ^{31}P NMR at −69.0 ppm. No structural information is available. The representation is consistent with structural information given here.



X-Ray Structures

The dithiaphosphorinane ring compound, **5** and **6**, proves interesting in a number of respects.[23b] It is the first example of a phosphorane structure containing a six-membered ring with the ring sulfur atoms bonded to phosphorus. Also, it is obtained in two crystallographically distinct forms, a monoclinic form, **5**, and a triclinic form, **6**. The principal difference between the molecular geometries of the two forms lies in the orientation of the phenoxy group relative to the remainder of the molecule. Moreover, it is quite unexpected to find the apical-equatorial orientation for the sulfur-containing ring in **5** and **6**. The expected structure would place the more electronegative oxygen atoms in apical positions leaving the sulfur ring atoms in equatorial sites with the ring in a chair conformation.



Packing effects are not indicated since the same structure was obtained in two different crystal systems. However, in view of the comparable apicophilicities of SR and OR groups obtained from NMR studies,[1,19] the observed structure for **5** and **6**, with some gain of ring stabilization in the apical-equatorial orientation, is not unreasonable.

A further feature of the sulfur derivative, which is found in the structures of all of the phosphoranes reported here that conain saturated six-membered rings, is the existence of these rings in a boat conformation of the type discussed by Trippett[19] occupying apical-equatorial sites of a trigonal bipyramid. This conformation is also found in **1** and **2**. A representative arrangement of ring atoms is illustrated here for the sulfur derivative **5** showing a slightly twisted boat.

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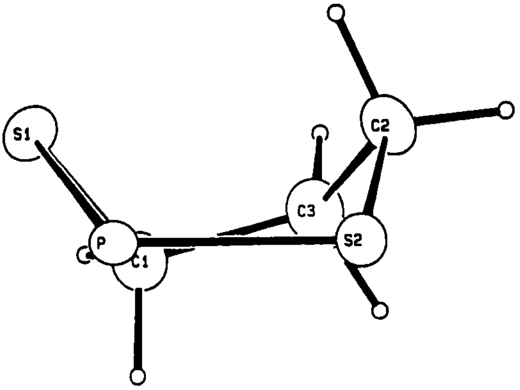

The apical sulfur atom S1 and methylene carbon atom C2 comprise the bow and stern positions of the boat conformation and is the one that allows lone pairs of the equatorial atoms bonded to phosphorus to be placed near the equatorial plane for effective back-bonding.[19]

Additional solid state structural features of interest are found in oxyphosphoranes **8**[23c] and **10**.[23d] With the constraints provided by the dioxanapthalene ligand in **8**, the six-membered ring spans apical-equatorial positions in a planar conformation except for phsphorus which acts as the flap atom. This constraint, however, is insufficient to destabilize the apical-equatorial ring location, nor does it significantly alter the NMR behavior (as discussed in the next section) relative to the boat conformation in the saturated phosphorinane ring in **7**.[23c] An edge on

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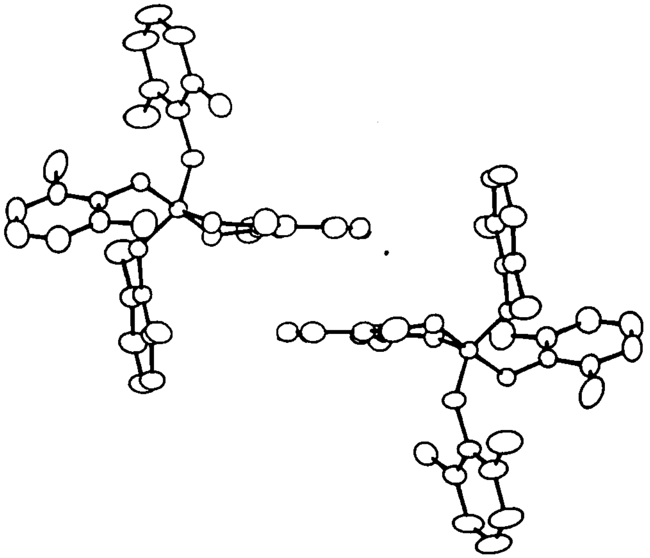


FIGURE 3 Stacking arrangement of **8**.

view of this molecule shows the extent of planarity and indicates the ring stacking arrangement that exists in the crystal (Figure 3).

Both **9**[23c] and **10** contain biphenoxy seven-membered rings in apical-equatorial positions. The bicyclic phosphorane **10** presumably might adopt this configuration due to the presence of the six-membered ring. However, this requirement is not needed since the seven-membered ring of the monocyclic derivative **9** did not adopt a diequatorial location. The extent of puckering in the seven-membered ring for **10** suggests a distorted "rowboat" conformation (Figure 4).

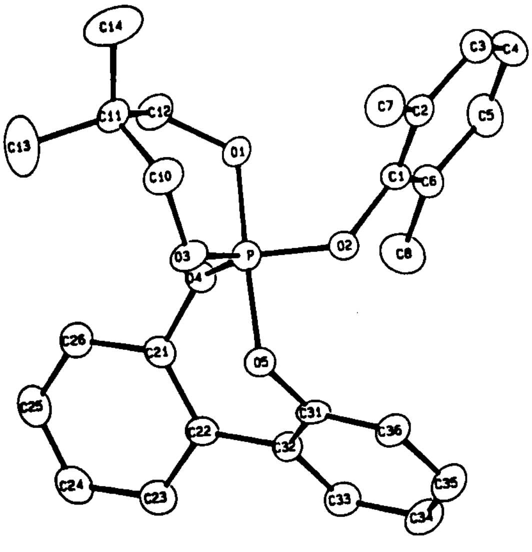
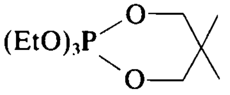


FIGURE 4 Structure of **10**.

Examination of the P—O apical bond lengths for oxyphosphoranes shows that those in the five-membered rings are longer (average, 1.717 Å) than those for six- and seven-membered rings (average, 1.660 Å). The five-membered rings are unsaturated and more rigid and perhaps less easily accommodated in the apical-equatorial sites compared to the larger ring systems.[24a]

^{1}H NMR Studies

Analysis of the variable temperature ^{1}H NMR spectra of the cyclic pentaoxyphosphoranes indicates that the solid state structures are retained in solution. For example, the partial ^{1}H NMR spectrum of the monocyclic phosphorinane derivative, **7**,[23c] given in Figure 5 shows at 19°C a single resonance at 0.50 ppm, a singlet at 2.40 ppm and a doublet at 3.60 ppm. Based on relative intensities, chemical shifts and assigments for related phosphorinanes,[21a] e.g.,  , the peaks observed here are assignable to the methyl protons

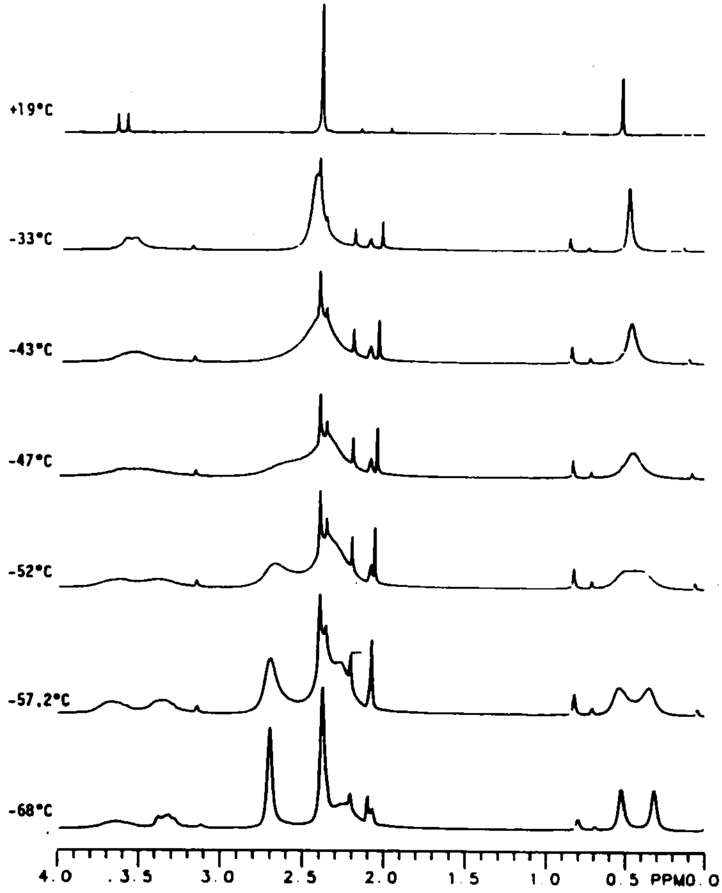


FIGURE 5 Partial ^{1}H NMR spectra of **7** as a function of temperature.

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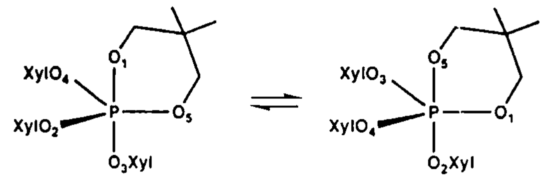
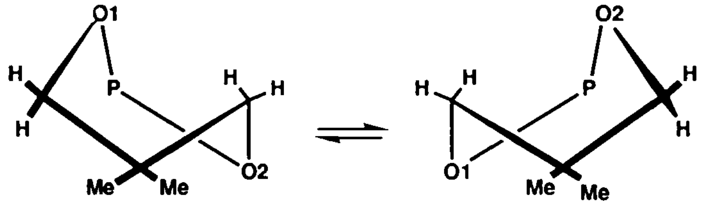
of the phosphorinane ring, the methyl protons of the xylyl groups, and the methylene protons of the phosphorinane ring, respectively. The latter doublet results from phosphorus coupling, $^{3}J\underline{P}\text{–}\underline{H} = 18.3$ Hz. The ^{31}P shift at -77.5 ppm confirms that the compound is pentacoordinated.

The equivalence of the phosphorinane ring methyls, the xylyl methyls, and methylene protons indicated at 19°C, changes to a more complex pattern at −68°C. As an approximation, two types of each of these units are indicated. The integrated intensity of the xylyl methyl groups of 2:1 supports the presence of two equatorial and one apical 2,6-dimethylphenoxy groups. The spectral changes are consistent with the presence of an apical-equatorial ring placement at −70°C, as found for the solid state structure, and the onset of pseudorotation to give the higher temperature spectrum at 20°C where pseudorotation maintains the ring in an apical-equatorial position.



The more complex character shown by the low temperature spectrum in the xylyl methyl group region may indicate a slowing of the C—O bond rotation which causes the appearance of two phosphorinane ring methyl signals. Also, under the assumption that the boat form is retained in solution for the six-membered ring, rapid interchange of boat forms,



which is required to accompany pseudorotation, may be incompletely stopped at low temperatures for phosphorane **7**.

If one considers an alternate structure for **7** with the phosphorinane ring located in diequatorial positions, inconsistencies arise. For this structure, a spectrum indicating one type of ring methyl, one type of ring methylene group, and two types of xylyl methyl groups in the ratio 2:1 should result assuming rapid interchange of ring confirmations. This NMR spectral behavior is not seen at any temperature.

In several of the monocyclic compounds, **8**, **9**, and **16**, six separate resonances assigned to the xylyl methyl groups appear at low temperature compared to the presence of one resonance or closely spaced multiplet at higher temperatures. This suggests that Berry pseudorotation and C—O bond rotation of the xylyl groups are "stopped" at reduced temperatures. The ^{1}H NMR spectrum of the seven-membered ring phosphorane, **9**,[23c] obtained in toluene d_8 at −60°C,

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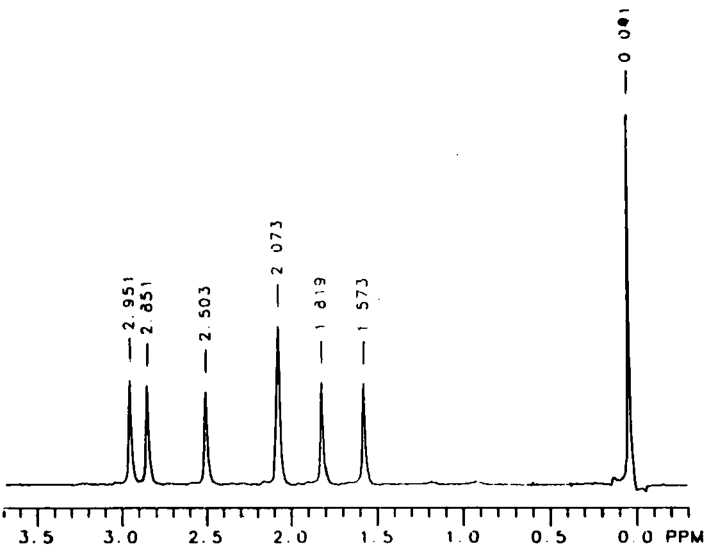

FIGURE 6 Partial ^1H NMR spectrum of **9**.

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illustrates this feature, Figure 6. The resonance at 2.07 ppm is enhanced due to toluene d_8. The signal at 0.0 ppm is due to the reference.

In contrast to the monocyclic pentaoxyphosphoranes, where ^1H NMR indicates that Berry pseudorotation is "stopped" at reduced temperatures for six- and seven-membered ring derivatives (but not for five-membered ring compound **11**[23c]), interpretation of ^1H spectra for bicyclic derivatives[23d] indicates two intramolecular exchange processes occurring at phosphorus. A Berry psuedorotation process appears to operate down to the lowest temperatures studied. At higher temperatures, a trigonal bipyramid with apical-equatorial ring orientations is indicated to undergo exchange via a higher energy trigonal bipyramid that has a six-membered ring in a diequatorial position. This behavior is similar to that discussed in the Introduction for bicyclic oxyphosphoranes containing five-membered rings (Figure 2).

The variable temperature ^1H NMR spectra for phosphorane **10**,[23d] is shown partially in Figure 7. At −68°C the presence of two phosphorinane ring methyl groups, two xylyl methyls, and two multiplets in the methylene region are consistent with the solid state structure of **10** having apical-equatorial ring dispositions. The fact that the methylene protons have not resolved into two ABX patterns suggests Berry pseudorotation is still occurring, Figure 2(a).[24b] The presence of two xylyl methyl groups indicates rotation of the xylyl groups about the C—O bond has ceased. The ^1H spectrum is much simpler at 31°C, now showing one signal for each of the groups. Here onset of the high-temperature process of Figure 2(b) is indicated.

Ligand exchange behavior for monocyclic oxyphosphoranes, summarized in Table I, shows apical-equatorial pseudorotation is not stopped at the low temperature limit of −95°C for **11** which contains a five-membered ring. The latter is consistent with earlier studies, e.g., on the $(EtO)_3\overline{P(OCH_2CH_2O})$ ring

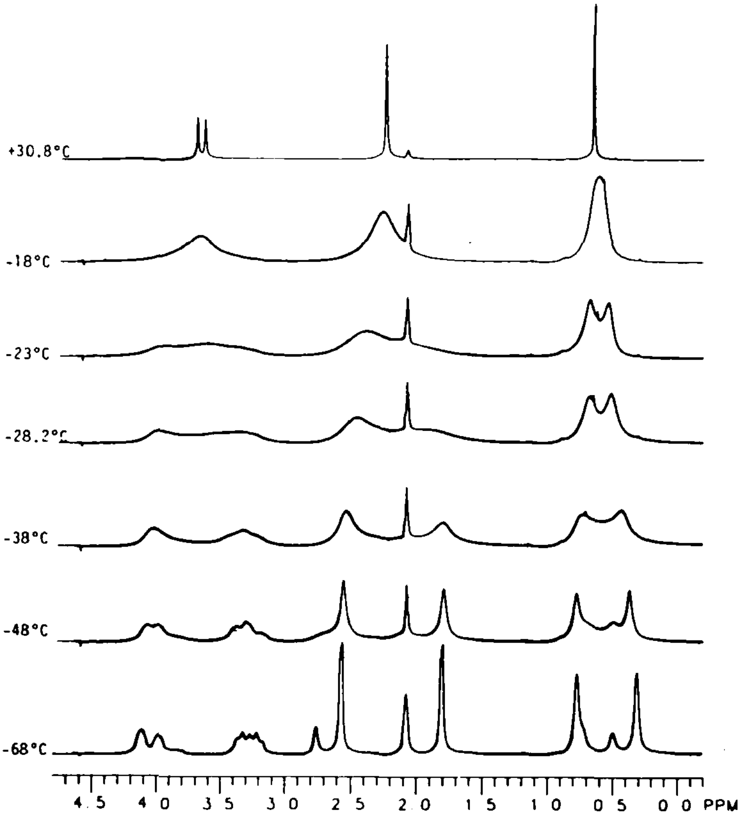

FIGURE 7 Partial ^{1}H NMR spectra of **10** as a function of temperature. Additional signals of possibly another isomer appear at 0.48, 0.77 and 2.75 ppm (−68°C). The peak at 2.1 ppm is due to toluene d_8.

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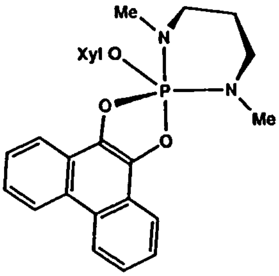
derivative.[21a] In comparison, six- and seven-membered ring compounds, **16**, **7–9**, reveal progressively higher coalescence temperatures for slowing apical-equatorial exchange. Thus, a static structure exists near room temperature for the seven-membered ring derivative, **9**. Cessation of xylyl group rotation and ring puckering motions appear to be coupled to the pseudorotational process in this case. The NMR spectra indicate this as does activation energies calculated from the respective resonances. For example, $\Delta G^\ddagger$ calculated from Equation (3)[25] with the insertion of chemical shift differences in Hz between the decoalesced peaks ($\Delta\nu$) and coalescence temperatures (T_c) for temperature dependent spectra of resonances of **7** assigned to both the ring protons and the methyl substituents of the xylyl groups, and both the methylene protons and methyl groups of the six-membered ring, give the same value within experimental deviations.

$$\Delta G^\ddagger = 4.57 \times 10^{-3} T_c(10.32 + \log(T_c\sqrt{2}/\pi\Delta\nu)). \qquad (3)$$

These respective values were 10.6, 10.9, 10.6 and 10.6 kcal/mol. Consistent with the increasing temperature for the onset of a–e exchange from five- to seven-membered rings is the larger activation energy of 14.3 kcal/mol found for the seven-membered ring derivative, **9**, compared to ≥11.0 kcal/mol calculated for the six-membered ring phosphorane, **16**.[23c]

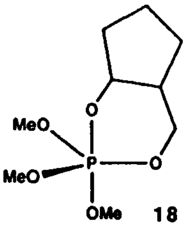
Since the rings are undergoing a–e to e–a exchange (Figure 2(a)) presumably positional reorientation of the rings themselves occurring during this process plays a role. In reaching the square pyramidal transition state, little ring angle change at phosphorus is required. In an ideal TBP this angle is 90° and in the SP, it is 88°.[26] A six-membered ring stabilized in a boat conformation in the ground state TBP, e.g., **7**, most likely reorients to a chair conformation as the special stabilization effect associated with the boat orientation in the TBP is lost in this transition. Although, the phosphorinane ring in **8** exhibits a more planar arrangement (Figure 3), its NMR behavior (Table I) is not measurably different from that for **7**. For this exchange process for a TBP containing apical-equatorially positioned five-membered rings, ring energy changes in reaching the square pyramid should be relatively modest since no special ring puckering changes are required. As the structure of the seven-membered ring phosphoranes, **9** and **10** show, rearrangement of a distorted "rowboat" form must accompany apical-equatorial bond interchange. Figure 4 depicts this ring conformation for **10** and that for **9** is very similar.

The X-ray structure[27] of



shows placement of a ring nitrogen in an apical position in preference to the more electronegative oxygen atom. This suggests a considerable degree of stabilization resulting from apical-equatorial placement of a six-membered ring having a boat conformation.

In the context of our results,[23c] the approximate $\Delta G^{\ddagger}$ value of 10.0 kcal/mol obtained by van Ool and Buck[28] for apical-equatorial psuedorotation of the phosphorinane **18** is entirely reasonable and may not necessarily be associated with any special pseudorotational hindrance cited as a result of the *trans*-fusion of the dioxaphosphorinane ring with the cyclopentane ring. The solution state structure of phosphorinane **19**, closely related to the *cis*-annelated furanose ring system in **16** (Table I), has been suggested[28] to be trigonal bipyramidal with a diequatorially oriented ring.



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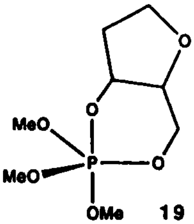

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In contrast to the structures of the seven-membered ring phosphoranes, **9** and **10**, which have apical-equatorial ring orientations, we believe the preference for a diequatorial ring location indicated by NMR spectra[18] of the monocyclic seven- and eight-membered ring compounds, illustrated in Figure 1, is most likely due to the presence of the electronegative OCH_2CF_3 groups whose apicophilicity acts as an overriding feature to any energy gain resulting from an apical-equatorial ring orientation.

In agreement with previous work, a–e ⇌ e–e exchange (Figure 2(b)) is more facile for phosphoranes containing larger rings. Both **10** and **15** undergo exchange via intermediates with diequatorial rings near 0°C, whereas the bicyclic derivative, A, possessing five-membered rings (discussed in the Introduction) required a temperature of 172°C to effect this process[21a] (cf. **3**, **4**, **10** and **15**).

The principal conclusion of the work presented here is that six-membered rings of oxyphosphoranes, like that previously known for five-membered ring derivatives, have an apical-equatorial site preference in a trigonal bipyramid. The preferred ring conformation of saturated six-membered rings is that of a boat. The apical-equatorial site preference also seems to apply to phosphoranes with seven-membered rings. The NMR data also suggest that diequatorial ring placement in activated states becomes easier for the larger sized rings.

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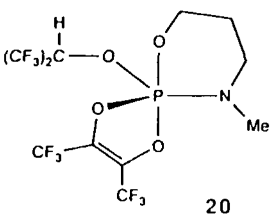
These results support the recent contention of Yu and Bentrude[29] that boat or twist conformations for intermediates in enzymatic reactions of nucleoside 3′,5′-monophosphates should receive serious consideration. Their solution state ^1H NMR studies indicated the presence of the phosphorinane ring in a non-chair (boat and/or twist) conformation for **20**[29] and a twist conformation for **21**.[30]



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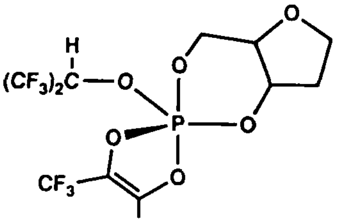

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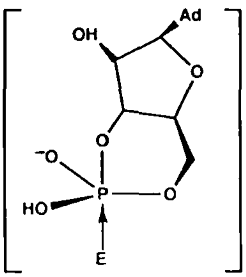
Our studies also lend credence to the theoretical investigation by van Ool and Buck[10] who conclude that hydrolysis of cAMP with phosphodiesterase proceeding by way of a trigonal bipyramidal intermediate must have the intermediate with an apical-equatorial ring orientation, cf. **16** (Table I).



We may anticipate that additional studies focusing on six-membered ring systems in oxyphosphoranes and their sulfur analogs will yield further insight that should prove useful in constructing mechanistic pathways for enzymatic and nonenzymatic nucleophilic displacement reactions of phosphorus.

ACKNOWLEDGEMENT

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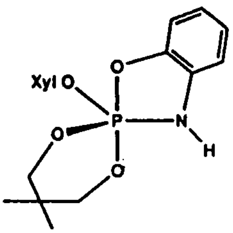

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