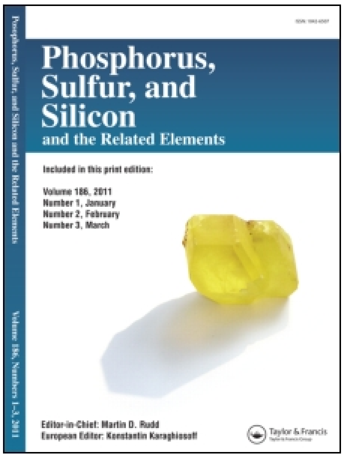


Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

INTERPLAY OF STERIC AND ELECTRONIC INFLUENCES IN THE CHEMISTRY OF MONOCYCLIC AND BICYCLIC PHOSPHORUS ESTERS

J. G. Verkade[a]
[a] Gilman Hall, Iowa State University, Ames, Iowa, USA

To cite this Article Verkade, J. G.(1976) 'INTERPLAY OF STERIC AND ELECTRONIC INFLUENCES IN THE CHEMISTRY OF MONOCYCLIC AND BICYCLIC PHOSPHORUS ESTERS', Phosphorus, Sulfur, and Silicon and the Related Elements, 2: 1, 251 — 281

To link to this Article: DOI: 10.1080/03086647608078956

URL: http://dx.doi.org/10.1080/03086647608078956

Phosphorus and Sulfur
1976, Vol. 2, pp. 251–281

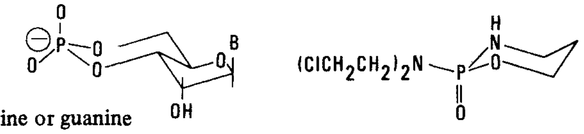
INTERPLAY OF STERIC AND ELECTRONIC INFLUENCES IN THE CHEMISTRY OF MONOCYCLIC AND BICYCLIC PHOSPHORUS ESTERS †

J. G. VERKADE

Gilman Hall, Iowa State University, Ames, Iowa, 50010, USA

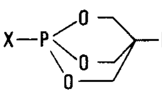
Dedicated to Professor P. E. Verkade on the occasion of his eighty-fifth birthday.

The importance of biologically active cyclic phosphorus systems has become increasingly apparent relatively recently; particularly, for example, with the discoveries of the cellular "second messenger" activities of cyclic 3′, 5′-adenosine and guanosine monophosphates and the powerful cancer therapeutic capabilities of cyclophosphamide and its cyclic metabolites. The earlier recognition that cyclic 2′, 3′-nucleotides formed as intermediates in the hydrolysis of polynucleotides, led to the classic researches of Westheimer and his coworkers on the hydrolysis rates of cyclic and acyclic phosphate esters.[1] Within the few years the extreme toxicities of bicyclic phosphorus esters compared to their acyclic analogues have come to light[2,3] along with the surprising observation that the cholinesterase inhibition of such cages is only negligible.[3,4]



B = adenine or guanine

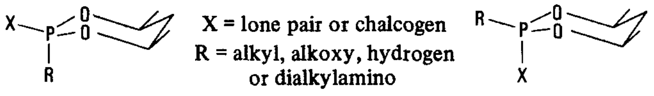
1



X = lone pair, chalcogen
R = alkyl, aryl

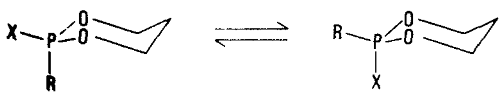
2

The literature contains numerous reports which establish the fact that the steric constraints which occur in mono and bicyclic phosphorus esters result in changes in the basicity and nucleophilicity of the phosphorus atom.[5] These electronic changes are not only meritorious of study in their own right, but they gain special importance when their possible relation to the biological activity of the above systems (1, 2) is considered. An additional feature of six-membered ring phosphorus esters is the isomerism which obtains when equatorial methyl groups are attached to the 4 and 6 positions in the phosphorinane rings (3) in order to minimize concentrations of other conformations. In such systems it has been observed that X does not possess the same Lewis basicity in the axial position as in the equatorial.[5] Moreover, when the ring methyl groups are removed, the position of the conformational equilibrium is found to depend strongly on the nature of R (4).[6]



X = lone pair or chalcogen
R = alkyl, alkoxy, hydrogen or dialkylamino

3



4

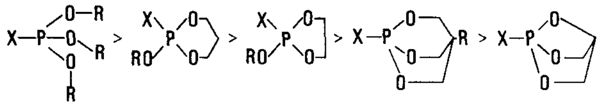
In this paper the experimental approaches, which elucidate conformational preferences influenced by the nature of the exocyclic substituents on phosphorus in six-membered ring esters and which reveal phosphorus basicity variations which are constraint dependent, are summarized. An attempt is also made to rationalize the results on the basis of qualitative bonding considerations.

---

† Plenary Lecture. The Vth International Conference of Organic Phosphorus Chemistry, Gdansk, Poland, September 1974.

I. PHOSPHORUS BASICITY DECREASE UPON MOLECULAR CONSTRAINT

The chemical and spectroscopic evidence discussed below indicates the basicity order shown for the trivalent (X = lone pair) and pentavalent (X = oxygen) phosphorus esters. (5)



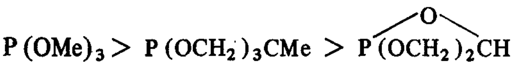
5

A. *Trivalent Phosphorus Esters*

1. *Chemical evidence.* Using proton nmr integrations to study equilibria of the type

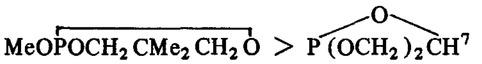
$$H_3BL + L' \rightleftharpoons H_3BL' + L$$

where L and L′ are phosphite esters, it was possible to determine the displacement orders:



$$P(OMe)_3 > P(OCH_2)_3CMe > \overset{O}{P(OCH_2)_2CH}$$

and



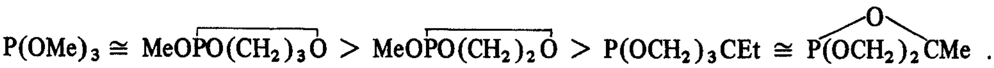
$$MeO\overline{POCH_2CMe_2CH_2O} > \overset{O}{P(OCH_2)_2CH}$$[7]

Because of peak overlaps the basicity of $MeO\overline{POCH_2CMe_2CH_2O}$ with respect to $P(OMe)_3$ and $P(OCH_2)_3CMe$ could not be determined.[7] These results are consistent with the decreased reactivity of constrained phosphites with alkyl halide,[8] acyl halide,[9] chloral[10] and ω,ω,ω-trichloracetophenone[10] which has been attributed[9,10] mainly to increased strain in the four-coordinate intermediate found in the rate-controlling step. Phosphonium salt formation with the 7-norbornadienyl cation appears to lead to decomposition when relatively basic compounds such as $P(OMe)_3$, PR_3 and PPh_3 are used, but this is not a problem with less basic ones such as $P(OCH_2)_3CMe$, PX_3 and $P(C_6F_5)_3$.[11] Potentiometric measurement of the half-wave potentials of phosphites also suggest a decrease in the basicity from $P(OR)_3$ to $P(OCH_2)_3CMe$.[12]

2. *nmr Studies.* Previously it was shown by others[13] that protonation in strongly acid media such as HSO_3F produces a much lower ^1JPH value for phosphines than for $P(OR)_3$. Increased phosphorus effective nuclear charge stemming from augmented substituent electronegativity along with increased lone pair *s* character (arising from the concomitant narrowing of the XPX bond angle) was cited as the source of the trend Table I shows data obtained in our laboratories[14,15] on constrained phosphites and it is seen that the coupling trend confirms the basicity order given earlier. It is clear that when one considers a single class of compounds such as the phosphite esters, the above rationale is insufficient by itself and this will be discussed more fully in section I.C.3.

3. *Infrared studies.* A decrease in the basicity of a phosphorus donor predicts that an sp^2 BH_3 moiety should experience less rehybridization toward sp^3. As a result the BH bonds should retain more *s* character and hence the bond vibration frequency is expected to rise.[16a,b] This expectation is verified in Table II for both the symmetric and asymmetric BH stretching frequencies (as well as their weighted averages) and also by the deuterated derivatives shown.

A decrease in phosphorus donor character also predicts a smaller OH stretching frequency shift for phenol owing to lessened hydrogen bonding to phosphorus. Experimentally the phosphites exhibit two band shifts, one in the 150-190 and one in the 250-320 cm^{-1} range. Which band is indicative of hydrogen bonding to phosphorus is not clear at this time but the trends indicate that the order of hydrogen bonding (and presumably basicities) is roughly



$$P(OMe)_3 \cong MeO\overline{PO(CH_2)_3O} > MeO\overline{PO(CH_2)_2O} > P(OCH_2)_3CEt \cong \overset{O}{P(OCH_2)_2CMe}\ .$$

These results differ[15] only slightly from those reported earlier[16c] owing to the higher phenol concentrations and the poorer resolution in the previous work.

TABLE I
^{1}JPH values for protonated phosphite esters

Compound	^{1}JPH (Hz)	Reference
$H\overset{+}{P}(OR)_3$	795-830	13
$H\overset{+}{P}(OPh)_3$	870	13a
$H(MeO)\overset{+}{\overline{POCH_2CH_2CH_2O}}$	870.0	15
$H(MeO)\overset{+}{\overline{POCH_2CHMeO}}$	890.4	15
$H\overset{+}{P}(OCH_2)_3CMe$	899.2	14
$H\overset{+}{P}\overset{O}{(OCH_2)_2CMe}$	928.8	15

TABLE II
νBH and νBD in borane adducts of phosphite esters[a]

Compound	νBH (D) asym (cm^{-1})	νBH (D) sym (cm^{-1})	Wtd. avg. (cm^{-1})	Reference
$H_3BP(OMe)_3$	2402	2362	2389	7
$D_3BP(OMe)_3$	1795	1691	1760	a
$H_3B\overline{P(OMe)OCH_2CMe_2CH_2O}$	2409	2360	2393	7
$H_3B\overline{P(OMe)OCH_2CH_2CH_2O}$	2411	2364	2395	7
$H_3BP(OMe)OCH_2CH_2O$	2410	2363	2394	7
$H_3BP(OCH_2)_3CMe$	2415	2366	2399	7
$D_3BP(OCH_2)_3CMe$	1810	1705	1775	a
$H_3BP\overset{O}{(OCH_2)_2CH}$	2433	2380	2415	7

[a] C. W. Heitsch and J. G. Verkade, *Inorg. Chem.* 1, 863 (1962).

B. Pentavalent Phosphorus Esters

1. Chemical evidence. Several years ago we showed that, compared to the well known rare earth ion extractant OP (O–n–Bu)$_3$, OP (OCH$_2$)$_3$C–n-Pentyl displays a surprising lack of extraction ability.[17] Thus the retention values using reversed phase partition chromatography are consistently 1.0 for the bicyclic phosphate under a variety of conditions whereas lower values were observed for tributyl phosphate. Thus in spite of the lower bulk and higher dipole moment of a caged phosphate (μ is about two-fold larger than for OP (OR)$_3$, Ref. 18), the basicity of the phosphoryl oxygen is decidedly lower in the bicyclic system.

This conclusion received support when it was shown that the phosphate esters decreased in their affinity for the N-methyl piperidinium ion (as revealed by conductance measurements) in the order

$$OP(O{-}n{-}BU)_3 > n{-}OctylO\overline{PO(CH_2)_3O} > OP(OCH_2)_3CEt$$

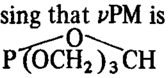
even though the dipole moments of the esters increased from 3.07 D to 5.5 D to 7.10 D.[19] More recently it was observed that in contrast to acyclic phosphates such as $OP(OMe)_3$ and $OP(OEt)_3$, the phosphoryl oxygen of $OP(OCH_2)_3CMe$ could not be alkylated to give the corresponding

$\overset{+}{P}(OR)_4$ ion.[20]

2. *Infrared spectral evidence.* The argument given in section I.A.3 regarding the phenol shift dependence on phosphorus donor character can be extended to include phosphoryl oxygens. The νOH shift differences are seen below to be more satisfying in the case of phosphates.[15,16c]

$OP(OMe)_3$	$MeO(O)\overline{PO(CH_2)_3O}$	$MeO(O)\overline{POCH_2CH_2O}$	$OP(OCH_2)_3C\text{-}n\text{-}Pent$
316 cm^{-1}	276 cm^{-1}	255 cm^{-1}	233 cm^{-1}

A decrease in phosphorus basicity might also be expected to increase pi bonding from the phosphoryl oxygen in phosphates, and LCAO-MO calculations[21] show an excellent correlation of the phosphorus pi bond order as well as the negative charge on the oxygen with νP=O. The νP=O frequencies recorded in Table III indeed do suggest a rise in phosphoryl group pi character upon constraint although distinction between five- and six-membered rings is not possible. Since transition metals in low oxidation states are also very probably capable of pi bonding to electronegative phosphorus ligands,[18] it is perhaps not surprising that νPM is observed to rise from metal complexes of $P(OCH_2)_3CMe$ to analogous

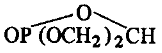


$P\overset{O}{\overbrace{(OCH_2)_3}}CH$

metal compounds.[15]

TABLE III

P=O stretching frequencies for phosphate esters

Compound	νP=O (cm^{-1})	Reference
$OP(O\text{-}n\text{-}Bu)_3$	1260	17
$OP(OMe)_3$	1290, 1271	a
$MeO(O)\overline{PO(CH_2)_3O}$	1312, 1279	a
$MeO(O)\overline{POCH_2CMe_2CH_2O}$	1310, 1270	a
$MeO(O)\overline{PO(CH_2)_2O}$	1302	16c
$OP(OCH_2)_3C\text{-}n\text{-}Pent$	1327	15
 $OP\overset{O}{\overbrace{(OCH_2)_2}}CH$	1346, 1354	16

[a] D. W. White, G. K. McEwen, R. D. Bertrand, and J. G. Verkade, *J. Chem. Soc.* B, 1454 (1971).

3. *Calculational results.* Calculations on phosphate systems do tend to support the experimental findings. Our recent extended Huckel MO calculations yielded about equal phosphoryl oxygen charges for $OP(OMe)_3$ and

$PhO(O)\overline{PO(CH_2)_3O}$

and smaller but still roughly equal charges in the constrained systems

$MeO(O)\overline{PO(CH_2)_2O}$

and $OP(OCH_2)_3CMe$.[22] These results accord with an earlier EHMO calculation in which the same trend in phosphoryl oxygen charge was found from $OP(OMe)_3$ to

$MeO(O)\overline{PO(CH_2)_2O}$ (Ref. 23).

More recently, CNDO/2 calculations suggest a steady rise in phosphorus charge on constraint.

C. A Rationale

1. Structural considerations. From the data summarized in Table IV it is clear from the similar OPO and POC bond angles in meso-$MeO\overline{POCHPhCHPhO}$ and $P(OCH_2)_3CCH_2Br$ that the latter is an unstrained cage.[18,24] Furthermore, attachment of a caged phosphite to a transition metal does not alter these angles appreciably.

In phosphate esters, the OPO angles remain relatively constant while the POC angle is seen to decrease upon constraint from ca. 120° in acyclic systems to 115° in $OP(OCH_2)_3CMe$ (Table V). Not expectedly the average POC angle is still smaller (101.8°) in

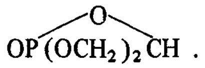

$OP(OCH_2)_2CH$.

TABLE IV
Structural data for phosphites

Compound	POC (°)	OPO (°)	Reference
meso-$MeO\overline{POCHPhCHPhO}$	117.5 (5) [a]	100.8 (4) [b]	c
$(Ni[P(OCH_2)_3CMe]_3NO)BF_4$	118.2 (10)	101.2 (8)	d
$P(OCH_2)CCH_2Br$	117.5 (4)	100.1 (3)	e

[a] This angle refers to the unstrained exocyclic POC linkage.
[b] This is the average of the two relatively unstrained $O_{exo}PO$ ends linkages.
[c] M. G. Newton and B. S. Campbell, *J. Am. Chem. Soc.* **96**, 7290 (1974).
[d] J. H. Meiners, C. J. Rix, J. C. Clardy, and J. G. Verkade, *Inorg. Chem.* **14**, 705 (1975).
[e] D. S. Milbrath, J. P. Springer, J. C. Clardy, and J. G. Verkade, *J. Am. Chem. Soc.*, in press.

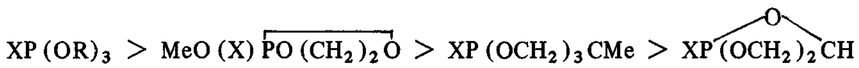
TABLE V
Structural data for phosphates

Compound	POC (°)	OPO (°)	Reference
$OP(OCH_2Ph)_2OH$	120.6 (3)	103.8 (2)	a
$OP(OC_6H_4Cl)_2OH$	121.0 (8)	108.1 (5)	b
$HO(O)\overline{PO(CH_2)_3O}$	119 (1)	104.6 (5)	51a
$HO(O)\overline{POCH_2CMe_2CH_2O}$	115.9 (1.2)	106.1 (8)	51b
$PhO(O)\overline{PO(CH_2)_3O}$	118.8 (9)	105.1 (6)	51c
$MeO(O)\overline{PO(CH_2)_2O}$	104.7 (6)	114.3 (9)	c
$MeO(O)\overline{PO(CMe_2)_2O}$	115.9 (8)	103.2 (6)	d
$OP(OCH_2)_3CMe$	115.2 (1)	103.7 (6)	e
$SP(OCH)_3(CH_2)_3$	113.3 (1.7)	104.5 (1.1)	f
$\overset{O}{OP(OCH_2)_2CMe}$	101.8 (2)	99.9 (1)	g

---

[a] J. D. Dunitz and J. S. Rollett, *Acta Crystallogr.* 9, 327 (1956).
[b] M. Calleri and J. C. Speakman, *Acya Crystallogr.* 17, 1097 (1964).
[c] T. A. Seitz and W. N. Lipscomb, *J. Am. Chem. Soc.* 87, 2488 (1965).
[d] M. G. Newton, J. R. Cox, and J. A. Bertrand, *J. Am. Chem. Soc.* 88, 1503 (1966).
[e] D. M. Nimrod, D. R. Fitzwater, and J. G. Verkade, *Inorg. Chem. Acta* 2, 149 (1968).
[f] P. Anderson and K. E. Hjortass, *Acta Chem. Scand.* 14, 829 (1960).
[g] Ref. e, Table IV.

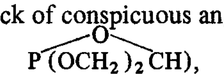
2. Hybridization changes. A major influence in decreasing the basicity of the phosphoryl oxygen in the series



$$XP(OR)_3 > MeO(X)\overline{PO(CH_2)_2O} > XP(OCH_2)_3CMe > XP\overset{O}{(OCH_2)_2}CH$$

is ascribable to the POC angle decrease which shifts the oxygen hybridization from sp^2 towards sp^3. The decrease in pi bonding capability on the part of the alkoxy oxygens which might be expected from the increased hybridization of their p lone pair orbitals would lead to a smaller negative charge on phosphorus and hence also on the phosphoryl oxygen. Even though sp^3 orbitals are capable of entering into pi bonding, their efficiency in doing so is less than that of a p orbital[25] and the trend would therefore still be the same. The flexing of the alkoxy oxygen bond angle has been termed the "hinge effect" and this phenomenon can be expected to manifest itself in other systems as well.[5]

It should be noted that although constrained phosphite esters remain essentially strainless as revealed by a lack of conspicuous angle changes (except possibly in



$P\overset{O}{(OCH_2)_2}CH$),

the alkoxy oxygen "hinge effect" is activated as soon as an electrophile becomes attached to the phosphorus and opens the OPO angle by virtue of phosphorus lone pair polarization.

3. Electron repulsion effects. Because angle changes apparently do not occur from acyclic to six-membered ring phosphates, the hinge effect can not operate here. The conformational arrangement of the alkoxy oxygen p lone pairs with respect to the phosphorus lone pair is very probably not the same in the two types of esters as shown in Figure 1. In this figure conformation (a) is approached in the solid state by acyclic phosphates[26,27] and (b) is taken by a six-membered ring phosphate.[28] If similar conformational differences exist in the phosphite esters, the "α effect" is more pronounced in (a) than it is in (b) since one of the p orbitals in (a) is able to repulsively interact with the phosphorus lone pair, thereby raising the energy of the latter and rendering it more basic. A similar interaction with the phosphoryl oxygen lone pairs and the phosphoryl sigma bond pair leads to the same conclusion for the phosphate esters.

It is now possible to rationalize the trend in ^1JPH coupling values in the phosphite esters (Table I). Electron repulsion effects render the phosphorus lone pair more polarizable in acyclic phosphites compared to six-membered ring systems, and consequently there will be less s character in the P—H bond. In the first bicyclic member of the protonated series, orbital orthogonality (Figure 2) prevents repulsion and the POC hinge effect begins to function. This effect on ^1JPH is augmented in the last member of the series and strain in the OPO angles further increases the coupling by preventing s character from entering the PO links.

4. Phosphorus d orbital effects. Experimental and theoretical studies have shown that there is a chemically important degree of d_π-p_π bonding in the phosphoryl group in that electronic energies and distributions are significantly affected by such multiple bonding, especially when electronegative phosphorus substituents are involved.[18] The shortening of the phosphorus-ester oxygen link in phosphites and phosphates (ca. 1.5 to 1.6 Å, respectively) over the sum of the single-bond covalent radii (1.76 Å) suggests that the ester oxygens are also involved to some degree in multiple bonding. To the extent that phosphorus d orbital participation can occur, therefore, it seems reasonable to suppose that favorable overlap of an ester-oxygen $2p$ lone pair orbital with a phosphorus $3d$ orbital will favor electron delocalization to phosphorus, thereby increasing its basicity as well as that of a phosphoryl oxygen. This approach[29a] was used earlier[26] in rationalizing phosphate ester hydrolysis rate data and here is summarized our extension of this concept to the basicity trends in phosphites and phosphates.[5] It should be mentioned here that recent computations[29b] appear to militate against significant d_π-p_π contribution to basicity changes in these systems.

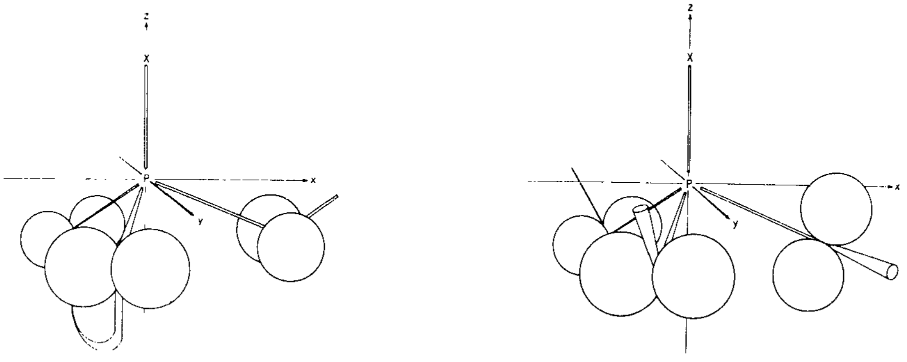


FIGURE 1 Geometric arrangement of the P, O, and C atoms and the ester oxygen p orbitals in acyclic (a), monocyclic (b), phosphorus esters (X = lone pair or oxygen).

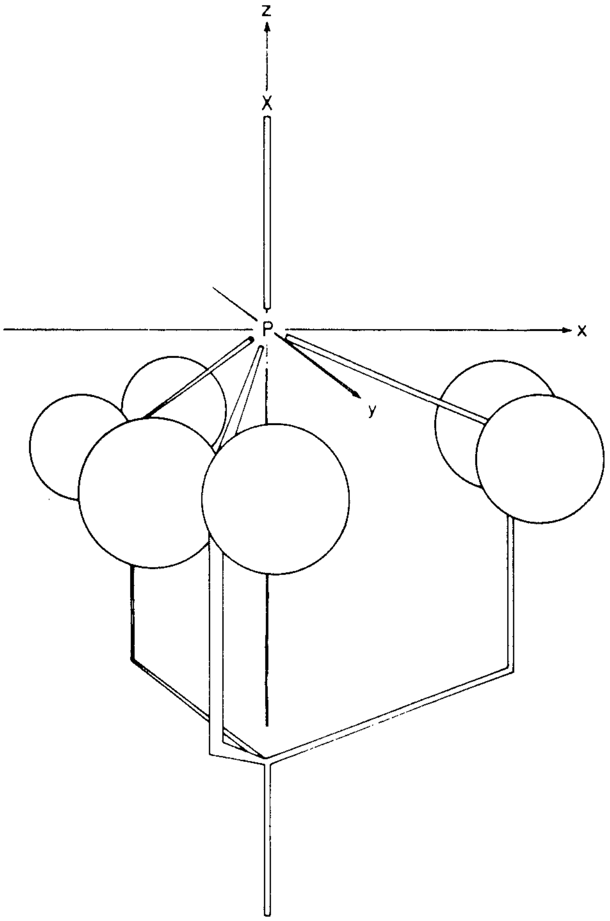
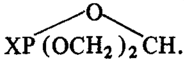


FIGURE 2 Geometric arrangement of the P, O, and C atoms and the ester oxygen p orbitals in a bicyclic phosphorus ester (X = lone pair or oxygen) if sp^2 oxygen hybridization is assumed.

As pointed out earlier, the configurations assumed by acyclic and monocyclic phosphorus esters are those depicted in Figure 1. In Figure 2 is shown the ester oxygen *p* orbital arrangement for a bicyclic system if we assume for a moment that no hybridization of this orbital occurs on these atoms. If we allow two of the phosphorus 3*d* orbitals (*dyz* and *dxz*) to be involved in pi bonding to the phosphoryl oxygen,[26] then the remaining three are candidates for interaction with oxygen *p* orbitals. It can be seen from Figure 3 that the acyclic system can interact with all three of the available phosphorus 3*d* orbitals while only two (the *dxy* and dx^2-y^2) have this property in monocyclic and bicyclic phosphates; the dz^2 being unable to exhibit a net overlap in the latter systems. To the extent that d_π-p_π bonding occurs in the P–O (ester) linkages, these arguments can be extended to include phosphite esters for which parallel conclusions regarding basicity are reached.

The *d* orbital effect and the electron repulsion effect discussed in the preceding section operate in the same direction and both are limited to differentiating only between acyclic and cyclic esters (i.e. both monocyclic and bicyclic). In both rationales, hybridization changes upon constraint are invoked to explain the further decrease in basicity in progressing from six-membered ring systems to



$XP(OCH_2)_2CH$.

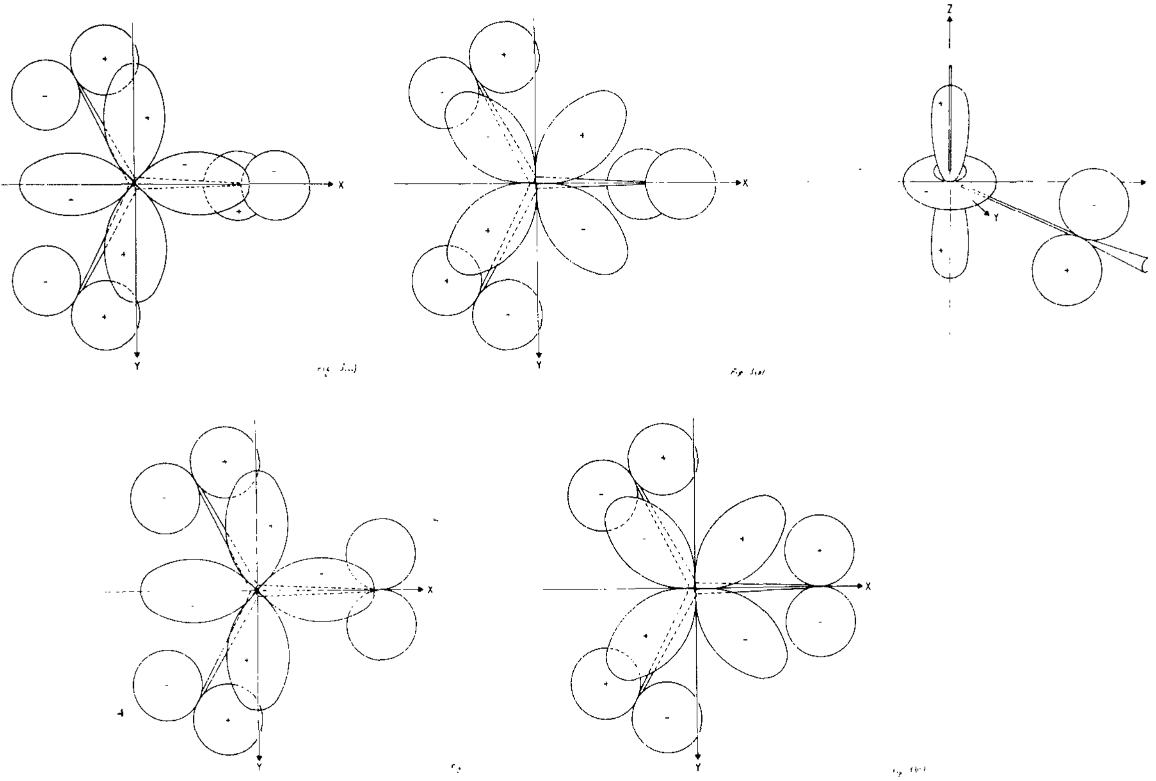
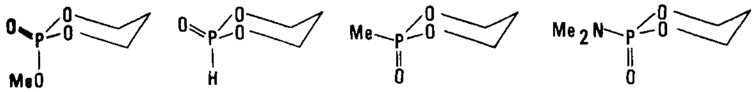


FIGURE 3 View down the *z* axis of the interactions of phosphorus *d* orbitals with oxygen *p* orbitals in acyclic (a, b, and c) and in mono- or bicyclic (d and e) esters.

II. CONFORMATIONS AND BASICITIES IN SIX-MEMBERED RINGS

In this section evidence is summarized which suggests that the dominant conformations in room temperature solutions of six-membered ring systems for the phosphorus substituents shown are **6** and **7**.

6



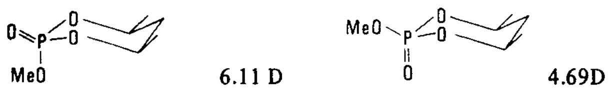
7

Results which establish that the X group (lone pair or oxygen) in conformation (a) is more basic than in conformation (b) are also discussed. Finally a rationale is put forward to account for the conformational preferences and the conformation dependent basicity (**8**).

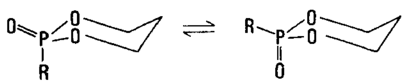
8

A. Conformational Preferences

1. Dipole moment studies. The efficacy of this method for the systems under consideration was established on a firm experimental basis recently by measuring the moments of the rigid isomers shown in **9**.[6c] Although the configurations of these isomers were not unambiguously known, they are based on the following argument. From earlier dipole moment studies in our laboratories on bicyclic phosphorus systems it was demonstrated that the dominant bond moments in $OP(OCH_2)_3CMe$ are those associated with the O=P and OC links as shown in Figure 4 (b).[30] Rearranging the bond dipoles to match the geometry of the six-membered ring conformation shown in Figure 4 (c) indicates that the overall moment is not altered appreciably from the caged geometry. This is also undoubtedly true even when the methoxy group is in the extended position since the O–C bond moment is relatively small. It is clear that the opposite conformation illustrated in Figure 4 (d) will exhibit a smaller overall moment owing to the cancellation of bond moments. An extension of this reasoning leads to the prediction that the substitution of OMe by Me_2N, H and Me in the rigid phosphate isomers above still allows the structure with the equatorial phosphoryl group to retain the higher molecular moment.



9



10

In the equilibrium (**10**) it is assumed that only the chair conformers shown are expected to predominate. If we measure the dipole moment of the equilibrium mixture and if we could determine the molecular moments of both conformers, it becomes possible to calculate the ratio of these conformers in the equilibrium mixture.[6d] The data in Table VI suggest that in the non-rigid systems, the equatorial P=O conformer is favored by OMe and H groups on phosphorus while Me and Me_2N groups enhance the axial P=O conformer.

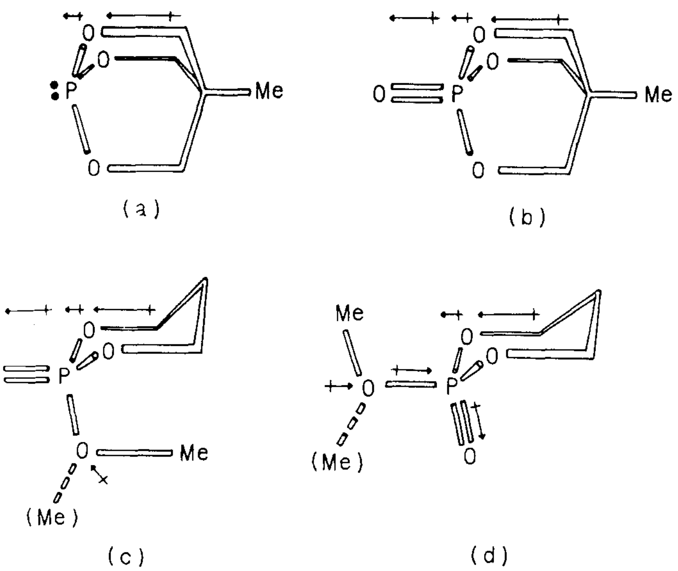
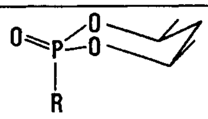
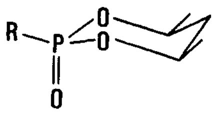
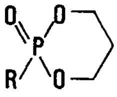


FIGURE 4 Geometrical relationships of dipole vectors in a bicyclic (a and b) and in six-membered ring phosphorus (c and d) esters.

The ratios of the conformers in the non-rigid esters will be discussed in section II.A4.

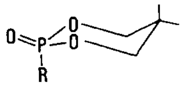
When R = H our measured dipole moments agree rather well with those reported earlier for the semi rigid isomers (11).[31a] On the other hand, our conclusion regarding the dominance of the axial P=O conformer when R=NR$_2$ disagrees with that given in a communication from another laboratory.[32] It was reported that P=O is consistently equatorial in system 12, where R is *inter alia* NEt$_2$ since the measured dipole moments compared favorably with calculated ones when such a conformation was assumed. It should be noted however, that these authors observed a moment of 3.88 D when R = NEt$_2$ which is much closer to our axial P=O isomer value than it is to our equatorial P=O isomer (Table VI). In view of this evidence as well as the x-ray evidence reported in section II.A.5, it appears likely that the axial P=O conformer is favored when R = NMe$_2$ or NEt$_2$.

TABLE VI
Dipole moments (D) for pentavalent phosphorus esters

			
MeO	6.11	4.69	5.63
H	6.37	5.07	5.86
Me	6.42	4.15	4.98
Me$_2$N	5.80	4.05	3.95

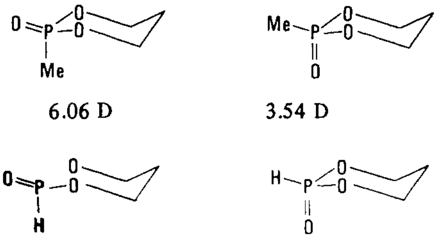
6.1 D 5.1 D

11



12

A few years ago conclusions similar to those implied in Table VI (i.e. the tendency for P=O to be equatorial when R = H and the presence of a conformational equilibrium to arise when R = Me) were arrived at by other workers.[31b] The approach they used was to calculate the dipole moments expected for the conformations (13) from bond moment data and compare them with the measured values. It is interesting to notice that the calculated values of these conformations (13) are substantially lower (ca. 0.3 to 0.6 D) than those for the corresponding 4,6 dimethyl isomers in Table VIII wherein the contribution of the Me groups is only negligible.



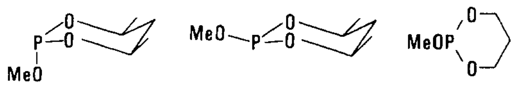
6.06 D 3.54 D Measured: 4.2 D

5.93 D 3.72 D Measured: 5.8 D (for thermodynamically more stable 4-Me isomer)

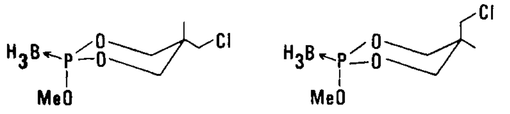
13

Because the phosphorus lone pair moment is not as large as a phosphoryl group moment, the measured moments of the rigid phosphites (14)[33,34] are smaller and their difference is also reduced compared to their phosphate analogs (Table VI). Despite the lower confidence which can be placed in the calculation of the conformer distribution of the non-rigid phosphite, it is gratifying to see that its measured moment implies that the fraction of equatorial phosphorus lone pair conformer in this compound is ca. 0.8.

By introducing a polar B←P bond in the formation of the phosphite BH_3 adducts below, we were able to postulate that the parent phosphites preferred to have their phosphorus lone pairs disposed equatorially.[35] This conclusion was based on a comparison of the vectorial summation of bond moments for the isomers (**15**, **16**) with the measured moment of a 3 to 1 mixture of adducts isomeric at the 5 carbon in which the dominant isomer contained an equatorial Me group. The measured moment of 5.9 D[35] (6.01 and 5.21 D for the dominant and minor isomers respectively) strongly indicated that both isomers contained axial OMe groups. Because adduct formation occurs with retention of configuration at phosphorus (see section II.A.5), the original 3 to 1 phosphite isomer mixture must also have possessed axial OMe groups. Using similar reasoning the configurations at phosphorus in the phosphites (**17**) were deduced from the dipole moments of their corresponding thiophosphate derivatives assuming that the oxidation proceeded with retention of configuration (**18**).[36]

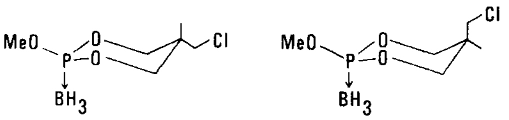


14



4.8 D calculated 5.6 D calculated

15



2.6 D calculated 3.05 D calculated

16

17

5.40 D 3.98 D

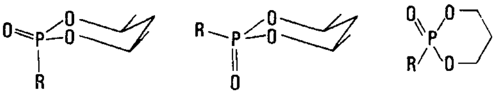
18

Although no values were given, these authors noted that the dipole moments of the parent phosphites were not sufficiently different to permit an assignment of the phosphorus configuration on this basis.

2. *^{31}P chemical shifts.* While proton chemical shift and coupling data, in conjunction with variable temperature studies have proven quite successful in establishing the predominant presence of chair conformers in most systems as well as the ratio of a pair of conformers in several conformationally mobile systems, such techniques by themselves have in general not proven to be reliable for assigning the stereochemistry at phosphorus in a given conformer (see references 37a-c and references quoted therein). The approach we have adopted is to compare the ^{31}P chemical shifts for two rigid model compounds epimeric at phosphorus (**19**, A and B) with $\delta^{31}P$ values for the conformationally non-rigid analogs (**19**, C). The fraction of each conformer present in C (i.e. Y and 1–Y) can then be calculated from the relationship

$$(Y)(\delta_A) + (1-Y)(\delta_B) = \delta_C$$

since δ_C for the rapidly equilibrating conformers will be a weighted average of the two chair forms which almost exclusively comprise the mixture.[6d] From the ^{31}P shifts summarized in Table VII it is easily seen that MeO and H prefer the axial position in contrast to Me_2N which prefers to be equatorial, while the Me group has an intermediate preference. The fractions of each conformer calculated from these data are discussed in section II.A.4. Although it is shown in that section that the conformer ratios calculated by this method are in reasonable agreement with those obtained from other experimental techniques, it should be recognized that the ^{31}P calculations depend on the assumption that the shifts are not very sensitive to substitution of the ring with methyl groups in the 4 and 6 positions. There is some evidence which militates against this assumption in trivalent six-membered ring phosphites[38] as well as phosphates,[33] however.



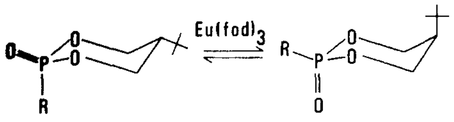
A B C

19

It is to be noted that assignments of epimeric phosphorus stereochemistries from ^{31}P chemical shift comparisons alone are to be viewed with caution since downfield shifts from equatorial to axial P=O groups are not always the case as has been supposed recently.[39] A striking example of an exception is seen in Table VII where R = H and others have also recently published similar results.[40] Our ^{31}P assignments in Table VII are primarily based on x-ray evidence (see section II.A.5) and the dipole moment arguments given in the previous section. Such data are far less dependent upon small changes in electronic character than are ^{31}P shifts.[41]

3. *LIS effects.* Because lanthanide induced shift effects are observed in monocyclic phosphorus esters only when a phosphoryl oxygen is present, this atom must function as the Lewis base for the lanthanide complex.[6c,42] Ascertainment of the equatorial or axial disposition of this group is facile in relatively rigid ring configurations such as the 4-methyl systems[6] wherein the axial methine and methylene protons experience 4 to 5 ppm downfield shifts when the P=O group is axial compared to 2 to 3 ppm when P=O is equatorial.[6] It

would seem therefore that reasonably quantitative estimates of conformation populations in mobile analogs could be obtained from LIS comparisons. Unfortunately the equilibria of 5,5-dimethyl 2-oxo-1,3,2-dioxaphosphorinanes have been shown to shift with concentration to the LIS agent[43] and even the more restricted 5-*t*-butyl isomer (**20**) forms more of the axial P=O conformer in the presence of Eu(fod)$_3$.[44] We will return to this interesting phenomenon in section II.B.2. While considerable information regarding the conformational bias of such compounds can be obtained from such experiments, quantitative estimates of conformer populations are not feasible.



R = Me or Ph

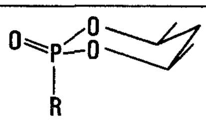
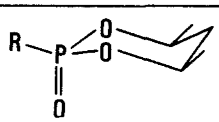
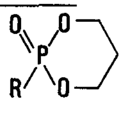
20

4. *P=O stretching frequencies.* The faster time scale of the infrared experiment compared to nmr and dielectric measurements makes it possible to observe separate P=O stretching frequencies in conformationally non-rigid structures. The original assignment of the higher frequency to the equatorial P=O conformer and the lower to the axial[45] was based on dipole moment studies.[32] Since then, numerous investigations have incorporated this criterion for stereochemical assignments[37a,46] and for the calculation of thermodynamic parameters for conformer interconversion.[47] Thus it has been concluded that the phosphates (**21**) predominantly exist as the conformers shown.[37a,46a] The situation proved to be somewhat confusing in the case of the phosphoramidates (**22**) however. The original assignment[46a,e,i] of a major P=O axial conformer was regarded as more tenuous[46b] following the dipole moment work[32] discussed in section II.A.1.

Although our P=O stretching correlations in Table X also ultimately depend on dipole moment studies for the phosphorus stereochemical assignments, it should be realized that the conclusions from the latter investigations rest on *measured* moments of rigid isomers, rather than on vectorial summations of calculated bond moments. Furthermore, as is shown in section II.A.5, there is chemical as well as structural support for our phosphorus stereochemical assignments. Even though the axial P=O phosphate in Table VIII was isomerically pure, two P=O bands of nearly equal intensity appear with a separation similar to that observed in OP(OMe)$_3$ wherein rotational isomerism has been postulated.[48] Severe 1,3 steric interactions may well preclude such isomerism in the P=O equatorial phosphate and indeed the sterically favored exocyclic Me form rather than the endocyclic Me form has been found in the solid state structural analysis of the BH$_3$ adduct (**23**).[49] The axial P=O isomer, however, could well permit rotational isomers involving the sterically unhindered OMe group thus accounting for the two bands.

TABLE VII

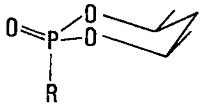
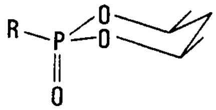
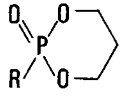
δ^{31} values[a] for pentavalent phosphorus esters

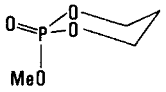
			
MeO	+ 7.1	+ 5.0	6.7
H	−2.9	+ 1.3	−2.26
Me	−19.4	−28.0	−24.2
Me$_2$N	−3.5	−6.6	−6.22

[a] Relative to 85% H$_3$PO$_4$

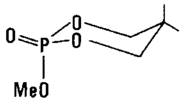
TABLE VIII

P=O stretching frequencies of 2-oxo-1,3,2phosphorinanes

			
MeO	1304 (s)	1289 (m), 1271 (m)	1310 (s)
H	1296 (s)	1267 (s)	1303 (s), 1281 (vw)
Me	1285 (s)	1251 (s)	1288 (m), 1255 (s)
Me_2N	1298 (s)	1270 (s)	1255 (s)



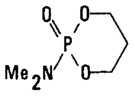
MeO

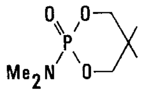


MeO

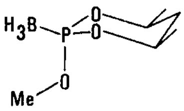
93% in C_5H_5N (Ref. 47a)

21

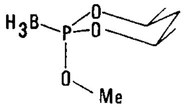




22



exocyclic Me form



endocyclic Me form

23

TABLE IX

Equatorial P=O conformer fractions in $R(O)P(OCH_2)_2CH_2$[a]

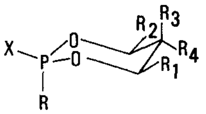
R	From μ	From $\delta^{31}P$	From νP=O
MeO	0.63 (0.09)	0.8 (0.1)	0.8 (0.2)
H	0.58 (0.08)	0.85 (0.1)	0.8 (0.2)
Me	0.32 (0.05)	0.43 (0.02)	0.4 (0.1)
Me_2N	b	0.12 (0.06)	0.19 (0.09)

[a] Error limits are shown in parentheses.
[b] No estimate.

The conformer ratios in Table IX determined from the ir data were calculated assuming that the extinction coefficient of the P=O band in the rigid isomer is the same as that of the corresponding band in the mobile system. The agreement in values produced by the three techniques (Table IX) is reasonable considering the errors and the assumptions involved and lends strong support to the conclusion that when R = MeO and H equatorial P=O is favored, axial P=O dominates when R-Me$_2$N, and competition between the two conformers obtains when R=Me. The equatorial conformer fraction of 0.3 to 0.4 also is in good agreement with the values reported by other workers using a comparison of calculated *versus* experimental dipole moments (0.2-0.3) and Kerr constants (0.2 to 0.4).[31b] These figures are consistently somewhat less than the estimate of 0.5 for this fraction made in another laboratory on the basis of nmr coupling constant measurements.[50]

5. *Chemical and structural evidence.* The stereochemistry at phosphorus as determined from x-ray analyses of 1-X-1-R-1,3,2-dioxaphosphorinanes shown in 24 involve an equatorial phosphoryl oxygen. In all these cases chair conformations are observed except for the derivative wherein R = Ph$_3$C. Here the phosphorus ends of the ring is quite flat, conferring a "chaise longue" conformation owing to the steric requirements of the pseudo axial Ph$_3$C group.[51g,h]

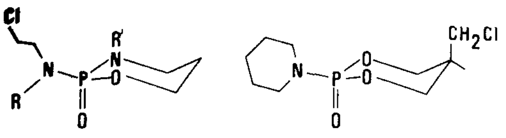
Without evidence from solution experiments, it is not at all safe to assume that the solid state structure implies that the equatorial P=O conformer is preferred in mobile systems. Thus it is quite clear from the solution work presented that, for example, a conformational equilibrium is established when R = Me which is biased toward the axial conformer P=O. Yet the x-ray structure of the equatorial 4-*t*-butyl derivative reveals the equatorial P=O conformer which is actually the less dominant one in solutions of the unsubstituted ring system (Table XI). While the 4-*t*-butyl group would appear to ensure an equatorial P=O disposition in this isomer because of the equatorial preference of the former group, it should be pointed out that a shift in the solution equilibrium toward the opposite conformer is affected by lanthanide shift reagents (see later). X-ray structural results probably do parallel observations in solution when virtually only one conformation is present as in the case for R = MeO or Me$_2$N. The former case is exemplified by the structure of PhO(O)P(OCH$_2$)$_2$CH$_2$,[51a] although even the latter compound, from infrared studies, shows two conformers in solution[46b,e,i] whose ratio is solvent dependent.[52] The x-ray structure of the three powerful anti-cancer mustard derivatives[53] and the piperidino derivative[54] (26) probably reflect the fact that the 2-oxo-1,3,2-dioxaphosphorinane with R = Me$_2$N is found to display only the axial P=O conformer in solution as discussed in previous sections. Historically it is interesting that the crystal structure determination of Br(O)P(OCH$_2$)$_2$C(CH$_2$Br)Me[51d] was prompted by the prediction from a comparison of the measured bond moment with calculated values[55] (an admittedly hazardous procedure) that P=O would be equatorial. Since that time, this structure as well as that of Cl(O)P(OCH$_2$)$_2$CMe$_2$ (Ref. 51e) may be taken as supportive of the finding that a wide variety of non-rigid halophosphonates have been found to be almost purely in the P=O equatorial conformation from solution ir,[37a,46a,b,g,52] nmr[43,56] and dipole moment measurements.[31b]



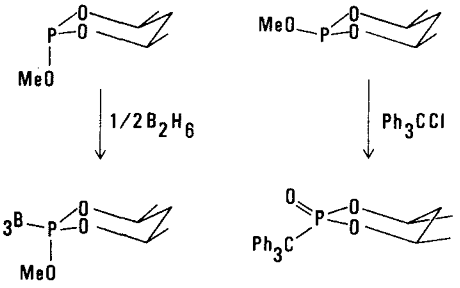
24

R	X	R$_1$	R$_2$	R$_3$	R$_4$	Ref.
HO	O	H	H	H	H	51a
HO	O	H	H	Me	Me	51b
PhO	O	H	H	H	H	51c
MeO	BH$_3$	Me	Me	H	H	49
Br	O	H	H	CH$_2$Br	CH$_3$	51d
Cl	O	H	H	Me	Me	51e
Me	O	H	H	H	*t*-Butyl	51f
Ph$_3$C	O	Me	Me	H	H	51g,h
Ph	O	H	H	Me	Me	51i
H	O	H	Me	H	H	51j

R = ClCH CH , R′ = H (Ref. 53, a,b)
R = ClCH$_2$CH$_2$, R′ = H (Ref. 53, a,b)
R = H, R′ = ClCH$_2$CH$_2$ (Ref. 53c)
R = R′ = ClCH$_2$CH$_2$ (Ref. 53 d)



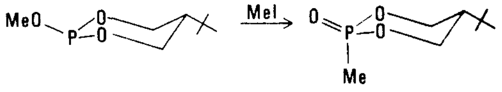
25



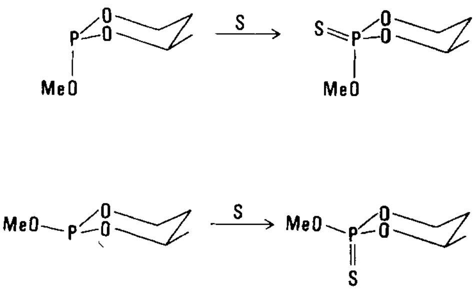
26

Where x-ray structural determinations have been of particular value in our work is in establishing the stereochemistries at phosphorus in the trivalent phosphites (26). Although phosphites of this type are liquids, the BH_3 adduct and the Michaelis-Arbuzov products shown are crystalline and their x-ray structures revealed the configurations above.[49,51g,h] Because the stereochemical course of BH_3 adduct formation at low temperature involves no inversion at phosphorus and since the pathway of the Michaelis-Arbuzov reaction is quite well understood in systems of this type, the parent phosphites must have had the structures shown. The reaction of MeI in reaction (27) to give the phosphonate whose structure has been determined[51f] shows that the thermodynamically less stable parent phosphite possesses an equatorial MeO group and an axial phosphorus lone pair. A report has also appeared[36a] in which the phosphite stereochemical assignments (28) were made on the basis of dipole moment measurements of the products assuming retention of configuration. Although there was considerable disagreement regarding whether the thermodynamically more stably phosphorus stereochemistry in such phosphites possessed an equatorial[35,36a,37b,57] or an axial lone pair,[58] there has been general accord since the structural and dipole moment work has appeared that the methoxy group prefers the axial position.

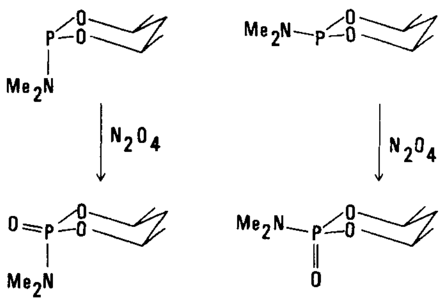
With the structures of the phosphites established it became possible to determine *via* dipole moment (see section II.A.1) and LIS measurements (section II.A.3) whether their N_2O_4 oxidation to the corresponding phosphates occurred with retention or inversion at phosphorus,[6c] since the literature in this regard was not unequivocal.[59] Having shown that this reaction was stereoretentive,[6c] it was applied to the conversion of the corresponding phosphoramidites to the phosphoramidates (29) in order to ascertain which phosphoramidite configuration was thermodynamically more stable.[6c] Since the axial P=O isomer (as shown by dipole moment and LIS studies) arose from the thermodynamically more stable phosphoramidite,[6c] the latter must possess an axial phosphorus lone pair in contrast to equatorial lone pairs in stable phosphites. The same conclusions have been drawn by others for the isomeric systems (30) on the basis of nmr studies of the trivalent compound and of the corresponding phosphoramidates which were obtained by N_2O_4 oxidation assuming stereoretention.[60]



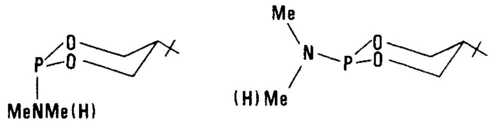
27



28



29



30

During the course of the hydrolyses of the 4,6-dimethyl phosphoramidates formed in the N_2O_4 oxidation above, it was noticed that some prior isomerization of the P=O equatorial isomer to the axial occurred but the reverse process could not be detected for the P=O axial isomer.[6b] This lends further support to our conclusion that in conformationally mobile analogs the P=O axial conformer is the more stable one.

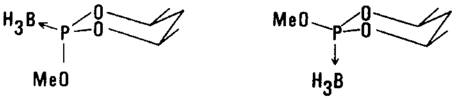
B. *Conformational Dependence of the Basicity of X*

1. Infrared evidence. From the inverse linear relation which has been shown to exist between the P=O stretching frequency and the rare earth extractability of an organophosphorus compound,[61] it might be predicted from the discussion in section II.A.4 that an equatorially disposed phosphoryl oxygen will be less basic than an axially directed one. Strong evidence for this was published a few years ago from phenol shift studies of the compounds (**31**).[31a]

Recently we were able to show from BH stretching frequencies that the parent trivalent ester with an equatorial lone pair was less basic towards BH_3 than the isomer with the axially directed one (**32**).[62] Interestingly, the equatorial preference of a BH_3 in these systems overcomes any tendency to form a stronger axial adduct. This is suggested in the four compounds (**33**) by the similarity of their BH stretching frequencies[62] to the model compound and by the dipole moment studies on the 5-chloromethyl isomers treated in section II.A.1.

It is well known from coordination chemistry that the CO stretching frequencies in phosphine complexes of metal carbonyls generally increase as the sigma basicity decreases and/or the pi acidity increases for the trivalent phosphorus compound in question. Consistent with the expected smaller basicity of an equatorially directed lone pair, the CO frequencies were found to be slightly higher in the equatorially bonded ligand isomer: (**34**).[63]

31



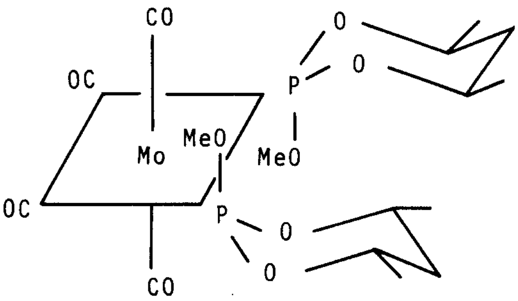
νBH = 2393 cm^{-1} (wtd. avg.) νBH = 2382 cm^{-1} (wtd. avg.)

32

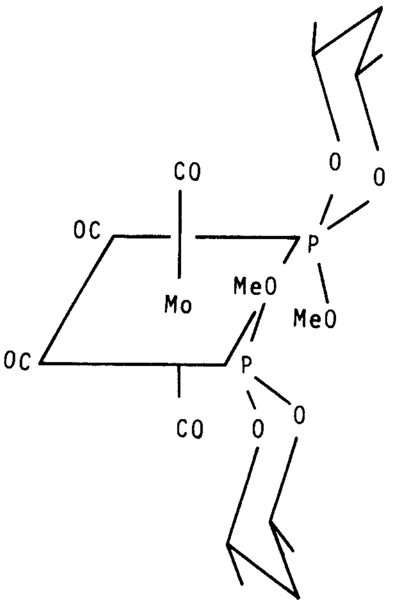
νBH = 2395 νBH = 2393

νBH = 2396 νBH = 2396

33



ν(CO) 2044 1965 1941



ν(CO) 2040 1960 1031

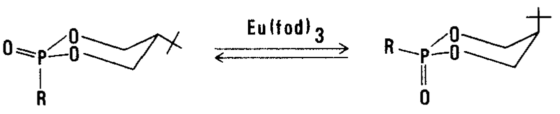
34

2. nmr evidence. From section I.A.2 it will be recalled that decreased sigma basicity is associated with an increase in lone pair *s* character as well as an augmentation of phosphorus positive charge, and this in turn is expected to lead to an increase in the directly bonded PH coupling constant. Measurements of this constant for the protonated species (35) formed in HSO_3F^{22b} confirms the notion that the equatorial lone pair is less basic.

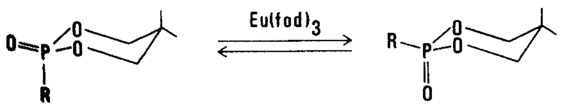
As pointed out in section II.B.1, conformationally mobile trivalent phosphites apparently form the weaker adduct (PBH_3 equatorial). In conformationally mobile phosphonates, however, the equilibrium can be shifted toward the more basic axial P=O conformer in the presence of the LIS shift reagent $Eu(fod)_3$ as shown in the examples (36).[44,45] It appears that if the equilibrium lies strongly toward one of the conformers (equatorial P lone pair or PBH_3 for example) then the stronger axial adduct is not permitted to form. Because alkyl and aryl phosphonates do not have a strong conformational preference, $Eu(fod)_3$ can coordinate to the more basic phosphoryl oxygen and thereby succeed in shifting the equilibrium. Further support for this idea comes from LIS experiments on the 4,4-dimethyl system below (36) where R = Cl. Here the chloro group has a strong tendency to remain axial (see section II.C) and no LIS induced equilibrium shift is detected.[45]

$^1JPH = 865$ Hz $^1JPH = 851$ Hz

35



R = Me, Ph (Ref. 44)

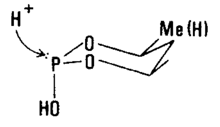


R = Me, Ph, $PhCH_2$ (Ref. 45)

36

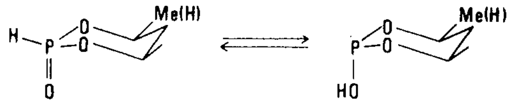
3. *Chemical evidence.* Hydrolysis experiments on the isomers of the hydrogen phosphates (37) have revealed the interesting result that the axial P=O isomer in both cases hydrolyzes easily in acidic media while the equatorial P=O isomers remain intact under the same conditions.[6b] Furthermore, conformationally mobile analogs are also hydrolyzed under these conditions.[6b] A reasonable rationale for this behavior is that the axial POH group in the "enol" tautomer is more stable than an equatorial POH (as is the case with all OR groups in analogous systems), thus facilitating attack of a proton on the equatorial phosphorus lone pair (38).

37

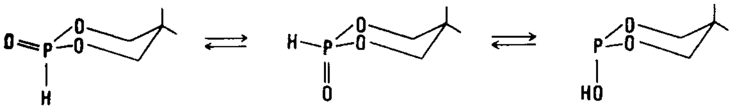


38

Another factor favoring the tautomerization (39) may be the increased basicity of the axial phosphoryl oxygen. Although conformationally mobile analogs would tend to be mainly in the equatorial form P=O, the equilibrium (**40**) is apparently sufficiently important to allow hydrolysis to occur on the final product.



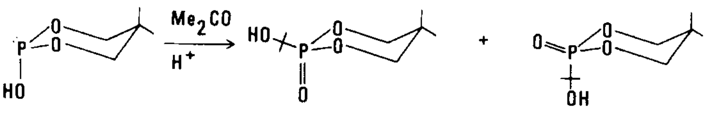
39



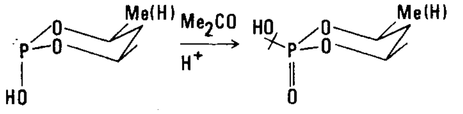
40

The above reasoning also suggests why the acid catalyzed reaction of acetone takes place with conformationally mobile hydrogen phosphonates (**41**) and the P=O axial isomer (**42**) but not with the equatorial P=O isomer.[6b] In the former case, the presence of the two conformations in the product is indicated by the two P=O bonds in the infrared spectrum.[6b]

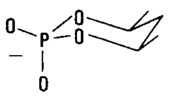
From the evidence presented in the previous discussions in section II.B, it would be predicted that the bulk of the negative charge in the phosphate ion (**43**) would reside on the axial oxygen. The structure of the 5,5 dimethyl derivative (**44**) obtained from an x-ray diffraction study[64] shows the axial bond to be significantly longer (1.542 (11) Å) than the equatorial one (1.457 (14) Å) suggesting the formulation shown. These structural parameters derived in a similar investigation of the unsubstituted derivative (**45**),[66] however, are not as definitive owing to their lower precision.



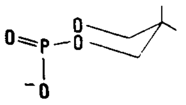
41



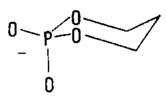
42



43

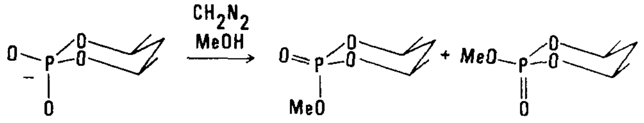


44



45

Recently we were able to approach the relative charge problem chemically by allowing the conformationally rigid ion above to react with diazomethane (**46**).[66] It can be seen that the ratio of isomers is dependent upon the cation and we tentatively put forward the following explanation. With the Na^+, Cs^+ and Me_4N^+ salts axial attack is primarily observed whereas with the others equatorial attack is favored to a larger extent. In the former case the cation is non-coordinating in nature and hence the more basic axial oxygen is free to react. Because Li^+ can coordinate and the $R_{3-X}NH^{+}_{1-X}$ ions can hydrogen bond to the axial oxygen, increasing reaction could occur on the equatorial oxygen. These results coupled with the x-ray results cited earlier[64] suggest that the axial oxygen in the phosphate diester ring of cyclic 3′, 5′-AMP is more basic than its equatorial neighbor. Whether this may be important in the mode of the biological action of this nucleotide is an open question at present. Apparently the isomeric cycle 3, 5′-AMP thiophosphates have similar activities in several *in vitro* experiments[67] which suggests that the axial-equatorial basicity difference in the parent compound may not be significant.



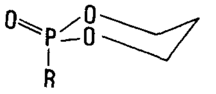
Salt	Ratio		
Na^+	10	to	1
Cs^+	10-20	to	1
Me_4N^+	10-20	to	1
Li^+	2	to	1
NH_4^+	0.7-1	to	1
$C_6H_{11}NH_3^+$	0.6-0.7	to	1
$C_5H_5NH^+$			

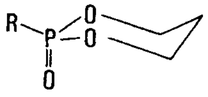
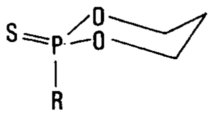
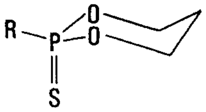
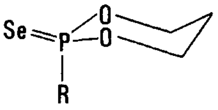
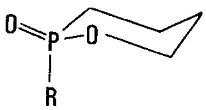
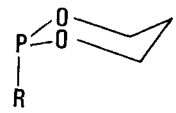
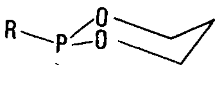
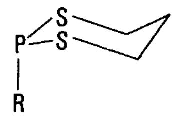
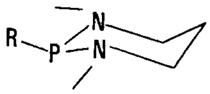
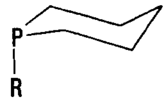
46

C. *A Rationale*

It is desirable to rationalize the conformational tendencies summarized in Table X. A variety of orbital[6c,58,60] as well as steric[6c,31b,60] effects could conceivably be operating which confer the observed conformational properties on 1,3,2-dioxaphosphorinane systems. From the x-ray data given in Tables IV and V it is reasonable to suppose from the ring POC angles (ca. 120°) that the ring oxygens are nearly sp^2 hybridized. The PO bond lengths which are significantly shortened over the sum of their covalent radii indicate that the oxygens are pi bonding to the phosphorus (see appropriate references given in Table IV and V). VII).

TABLE X
Preferred conformations in non-rigid phosphorinanes

	R	References
	H	6d, 31a
	MeO	6c, 6d, 37a, 46a, 47a
	halogen	b, 31b, 37a, 43, 46a, 46b, 46g, 52, 55, 56
	PhNH	70b

	Me	31b, 6d, 44
	2°R	50
	3°R	50
	Ph	44
	Me_2N	6d, 46a, 46e, 46i, section II.A.1
	$C_5H_{10}N$	c
	PhO	d
	Cl	d, e
	Me	d, e
	Ph	d
	H	74
	OEt	f
	Me	g
	i-Pr	60
	Ph	71
	MeO	33-35, 36a, 37b, II.A.2, 49, 51g, 51h, 5
	EtO	36
	Cl	37b
	C_2H_4N	m
	Me_2CCH_2N	m
	Me_2N	6b, 6c, 60
	MeNH	60
	MeO	h
	Me	h
	Ph	h
	Et	h
	Me	i
	Ph	i
	H	j
	Me	k
	Ph	l

---

[a] For convenience, substituents (if any) on the ring are omitted.

[b] W. Stec and M. Mikolajczyk, *Tetrahedron* 29, 539 (1973).

[c] W. S. Wadsworth, S. Larsen, and H. C, Horton, *J, Org. Chem.* 38, 256 (1973).

[d] J. P. Dutasta, A. Grand, J. B. Robert, and M. Tarieb, *Tet. Lett.* 2659 (1974).

[e] B. A. Arbuzov and R. P. Arshinova, *Dokl. Akad. Nauk. SSSR* 195, 859 (1970), Engl.

[f] K. Bergeson and T. Vikane, *Acta Chem. Scand.* 25, 1147 (1971).

[g] W. G. Bentrude, K. C. Yee, R. D. Bertrand, and D. M. Grant, *J. Am. Chem. Soc.* 93, 797 (1971).

[h] R. O. Hutchins and B. E. Maryanoff, *J. Am. Chem. Soc.* **94**, 3266 (1972).

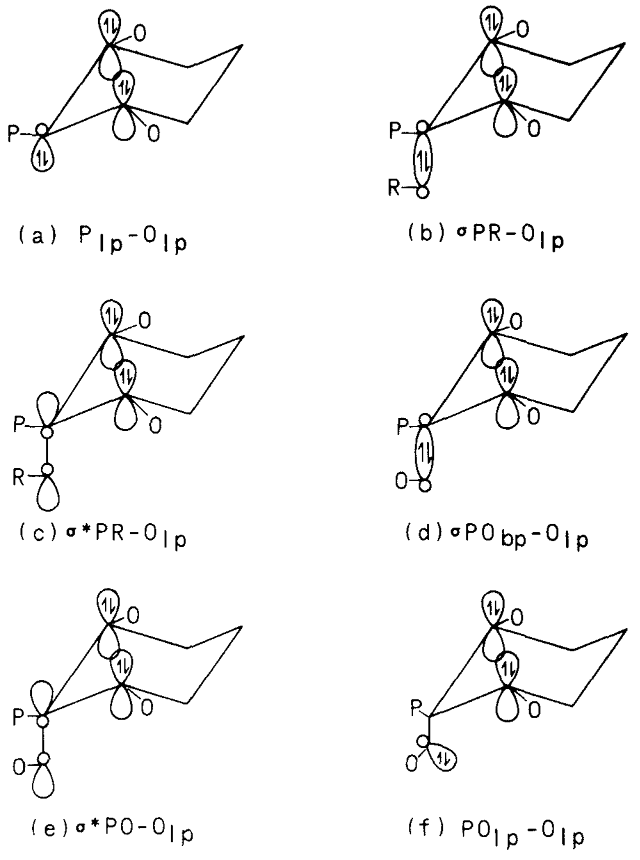
[i] R. O. Hutchins, B. E. Maryanoff, J. P. Albrand, A. Cogne, D. Gagnaire, and J. B. Robert, *J. Am. Chem. Soc.* **94**, 9151 (1972). Because the result implied here is regarded as rather tentative by the authors, it is included here for completeness, but is not discussed in the text.

[j] J. B. Lambert, W. L. Oliver, and G. F. Jackson, *Tet. Lett.* 2027 (1969).

[k] S. J. Featherman and L. D. Quin, *J. Am. Chem. Soc.* **95**, 1699 (1973). While the axial Me conformer predominates at room temperature, the equatorial conformer does so at a low temperature. The ring was unsibstituted in this case.

[l] A. T. McPhail, J. J. Breen, J. H. Somers, J. C. H. Steele, and L. D. Quin, *Chem. Commun.* 1020 (1971). The stereochemistry at phosphorus as shown was found from an x-ray study of the 5,5-dimethoxy derivative. The assumption implied in the table that this is the more stable conformation in solution is very tentative.

[m] A. Cogne, A. G. Guimaraes, J. Martin, R. Nardin, J. B. Robert, and W. J. Stec, *Org. Magn. Res.* **6**, 629 (1974).



(a) P_{lp}-O_{lp}

(b) σPR-O_{lp}

(c) σ^*PR-O_{lp}

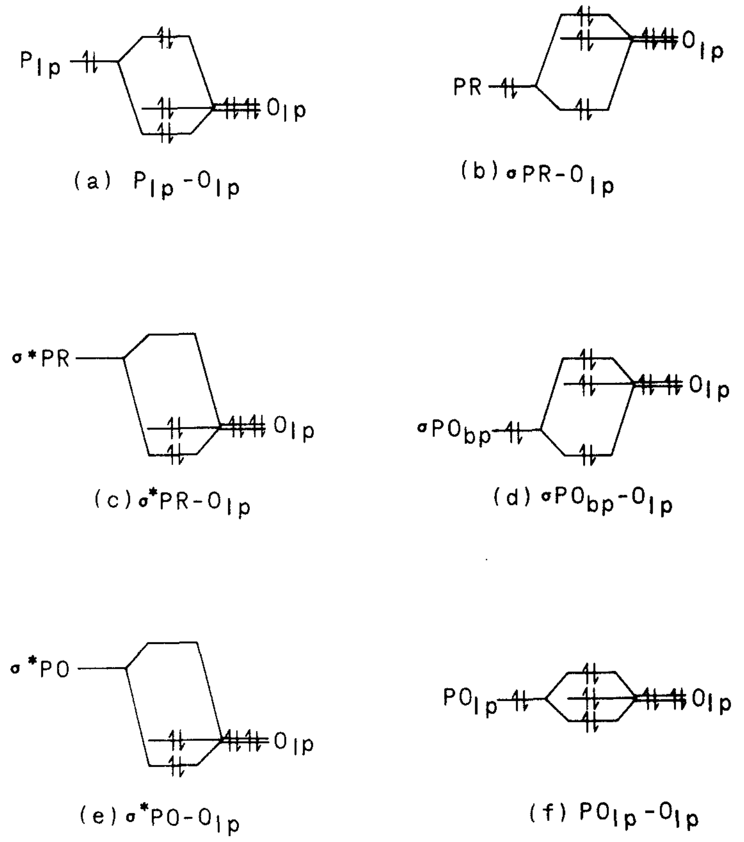
(d) σPO_{bp}-O_{lp}

(e) σ^*PO-O_{lp}

(f) PO_{lp}-O_{lp}

FIGURE 5 Geometrical relationships of dipole vectors in a bicyclic (a and b) and in six-membered ring phosphorus (c and d) esters.

1. Conformational preferences. It now becomes convenient to group the orbital effects into the six types shown in Figure 5, in order to rationalize the conformational preferences. The first three effects are present in trivalent phosphorus esters while all but the first can occur in pentavalent esters. The P_{lp}–O_{lp} and σPO_{bp}–O_{lp} repulsions arise from the modified gauche effect which we put forth earlier[6c] to account for the conformational preference when R = OMe. Thus, in spite of the fact that an axial phosphorus lone pair or pola PO bond would be nearly gauche with respect to the sp^2 lone pairs on the ring oxygens, the axial position of these moieties may well engender significant repulsions from the bottom halves of the PO pi bonds in the ring.[6c] The portion of the following discussion which utilizes the three other terms of Figure 5 arose from a collaborative attempt[68] to further clarify the origins of the conformational and basicity phenomena in these systems. Figure 6 shows the nature of each effect shown in Figure 5 using schematic MO diagrams and it is clear that the repulsions tend to destabilize the system while the attractive hyperconjugative interactions tend to be stabilizing influences. It should be noted that each effect is favored in the conformation shown because of the better orbital overlap which is possible compared to that realized in the opposite conformation.



(a) P_{lp}-O_{lp} (b) σPR-O_{lp}

(c) σ^*PR-O_{lp} (d) σPO_{bp}-O_{lp}

(e) σ^*PO-O_{lp} (f) PO_{lp}-O_{lp}

FIGURE 6 Molecular orbitals formed from orbital interactions in 1,3,2-phosphorinanes possessing an axial X moiety.

When R = MeO or Cl, the equatorial P=X (X = chalcogen) conformer is stabilized whereas when R = alkyl o phenyl the axial P=X conformer dominates. Because of electronegativity differences in the exocyclic phosphorus substituent, the ordering of the P–R MOs could reasonably be that shown in Figure 7a. The interactions (Figure 7b) of these MOs with the ring oxygen $2p$ lone pair (O_{lp}) could then be greater for σPC than POMe axial. A special case is presented when R = H, however, since it would be expected to be equatorial from the foregoing argument. Interactions of the axial P=O group are now probably important and from Figure 7c it can be seen that such a conformation would be repulsive dominent.

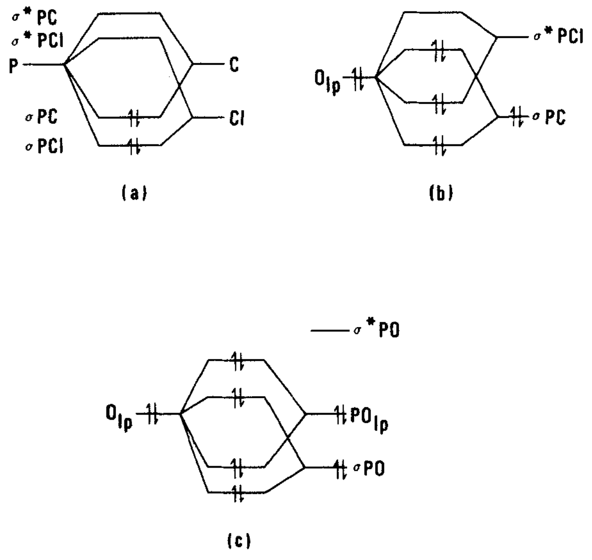
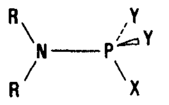


FIGURE 7 Molecular orbitals formed from P and R atomic orbitals (a); O_{1p} and σ^*PCl and σPC orbitals (b); and from σ_{1p} and PO_{1p} (c).

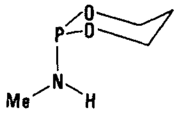
In contrast to the MeO group when X - chalcogen, the Me_2N group prefers to be equatorial suggesting that a steric effect is dominant. Such a steric influence could arise from the necessity for the C_2N plane of an Me_2N group to adopt the conformation shown in (47) in trivalent phosphorus compounds[68] as well as in the pentavalent cyclophosphamides.[53] It is possible in the choice of the two conformations (48), that the P=O axial conformer is the more stable because of prevailing 1,3 syn-diaxial interactions in the other.[6c] Some evidence for this contention is found in trivalent analogs wherein the MeNH,[60] PhNH[70] and *t*-butyl NH[70a] groups favor the axial position to a somewhat greater extent than does Me_2N[6c] in as much as the former are better able to tolerate the steric problem *via* its hydrogen substituent as shown in (49).



47

R	Y	X
Me	F	l*p*
Me	Cl	l*p*
H	F	l*p*
$ClCH_2CH_2$	$NH(CH_2)_3O$	0

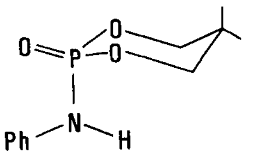
48



49

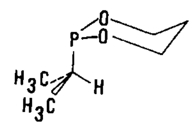
Strong support for this hypothesis comes from the recent x-ray structural investigation of **(50)**[70b] in which the phenylamino group is axial with the sterically unimportant hydrogen located below the ring.

The bulk of the available evidence indicates that a wide variety of groups (Table X) prefer to be axial in trivalent systems, suggesting that electronic effects dominate steric interactions even more so than they do in the pentavalent analogs where alkyl and aryl groups tend to be equatorial, for example. It may seem odd in this regard that the phenyl group does not behave like an Me_2N group since the carbon of the P–Ph bond like nitrogen is sp^2 and might be expected to adopt the equatorial conformation shown **(51)**. nmr data suggest however that, unlike the Me_2N moiety, the phenyl group plane is not constrained to bisect the OPO angles and can adopt the axial conformation **(51)**[71] wherein the 1,3 steric interactions are minimized. While the $\sigma^*PR{-}O_{1p}$ effect can stabilize these systems to some extent, the dominant factor is probably the $P_{1p}{-}O_{1p}$ term. The observation that the i-Pr group like phenyl also prefers the axial position, may be attributable to a preference for the rotamer **(51)** shown below wherein 1,3 steric interactions are minimized.



50

51

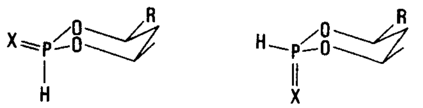


52

2. *Basicity differences.* When a phosphorinane is *forced* to point its phosphorus lone pair (R = MeO) or phosphoryl oxygen (R = H) in the unfavorable axial direction because of alkyl groups which lock the ring, the basicity of these moieties is increased. One reason for this may be that the $P_{1p}{-}O_{1p}$ effect raises the energy of the phosphorus lone pair, rendering it more basic than in an equatorial lone pair where this influence would be greatly decreased. Similar reasoning could apply to the increased basicity of the phosphoryl oxygen lone pairs when the P=O bond is axial, owing to the $PO_{1p}{-}O_{1p}$ and $\sigma PO_{bp}{-}O_{1p}$ terms. These arguments can also be used to account for the preferential axial alkylation of the rigid phosphate anion discussed in section II.B.3.

A second possible influence which can act in concert with the above effects is seen to arise from the interactions which may occur between phosphorus *d* orbitals and the *p* orbital lone pairs on the ring oxygens and R.[5] It was seen in section I.C.4 that for an equatorially directed phosphorus lone pair or P=O bond, the ester oxygen *p* orbitals could interact with two *d* orbitals on phosphorus (Figure 3, d and e). Figure 8 shows the *p* orbital conformation expected for the opposite configuration (axial lone pair or P=O link) and Figure 9 shows that in this geometry three phosphorus *d* orbitals can be involved in pi bonding. The greater pi induction possibilities in the latter situation could be envisioned to lead to a reduction in positive charge on phosphorus (increased basicity).

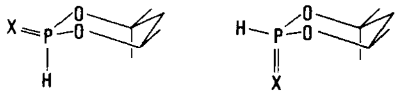
Additional support for the idea that there is increased electron availability in the axial position of 1,3,2-dioxaphosphorinane systems comes from the ^1JPH and ^1JPSe data obtained on the compounds **(53-55)**. It is possible in these rigid isomers, that the $\sigma PR{-}O_{1p}$ effect results in a greater polarizability in the PH bond. The consequent decrease in *s* character could then be responsible for the lower P–H coupling. Because of increased phosphorus polarizability in the P–Se link *via* the $\sigma PSe_{bp}{-}O_{1p}$ term, similar reasoning could be used to rationalize the lower ^1JPSe coupling when this group is axial.



X = O, R = Me ^{1}JPH = 664 (Ref. 6a)
X = O R = H ^{1}JPH = 670 (Refs. 6a, 72)
X = Se R = H ^{1}JPH - 566 (Ref. 73)

X = O, R = Me ^{1}JPH = 719 (Ref. 6a)
X = O R = H ^{1}JPH = 712 (Refs. 6a, 72)
X = Se R = H ^{1}JPH = 618 (Ref. 73)

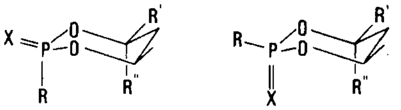
53



X = O ^{1}JPH = 696 (Ref. 74)
X = S ^{1}JPH = 601 (Ref. 75)

X = O ^{1}JPH = 709 (Ref. 74)
X = S ^{1}JPH = 622 (Ref. 75)

54



X = O R = MeSe R'=R''=H ^{1}JPSe = 450 (Ref. 73)
X = O R = ArSe R'=R''=H ^{1}JPSe = 453 (Ref. 73)
X = Se R = MeO R'=R''=H ^{1}JPSe = 978 (Ref. 73)
X = Se R = MeO R'=R''=Me ^{1}JPSe = 984 (Ref. 73)

X = O R = MeSe R'=R''=H ^{1}JPSe = 472 (Ref. 73)
X = O R = ArSe R'=R''=H ^{1}JPSe = 477 (Ref. 73)
X = Se R = MeO R'=R''=H ^{1}JPSe = 941 (Ref. 73)
X = Se R = MeO R'=R''=Me ^{1}JPSe = 975 (Ref. 73)

55

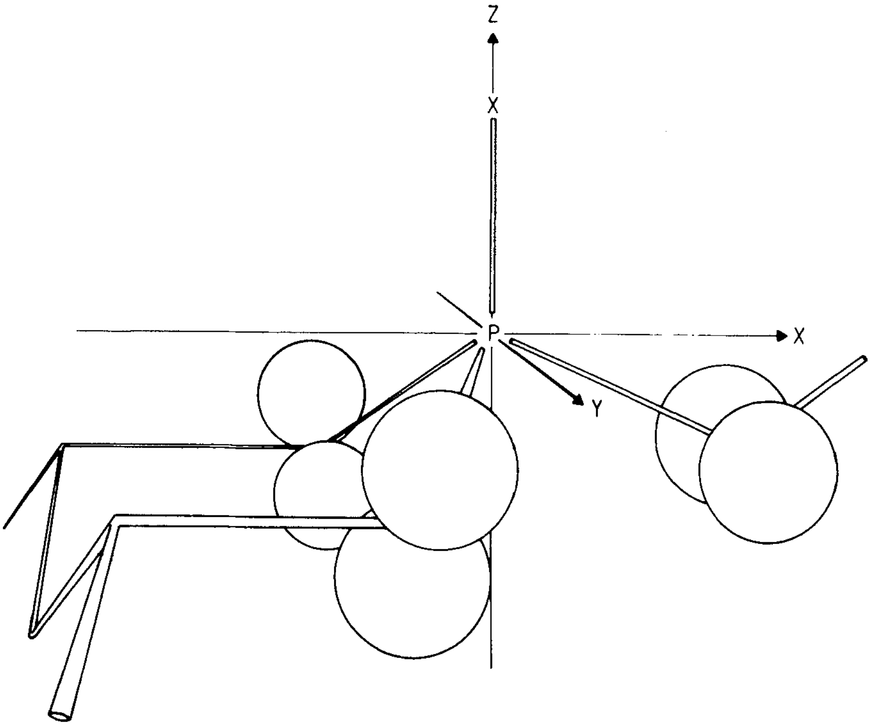


FIGURE 8 Arrangement of *p* orbitals expected in 1,3,2-dioxaphosphorinanes (X = lone pair or oxygen) where R also possesses a *p* orbital lone pair.

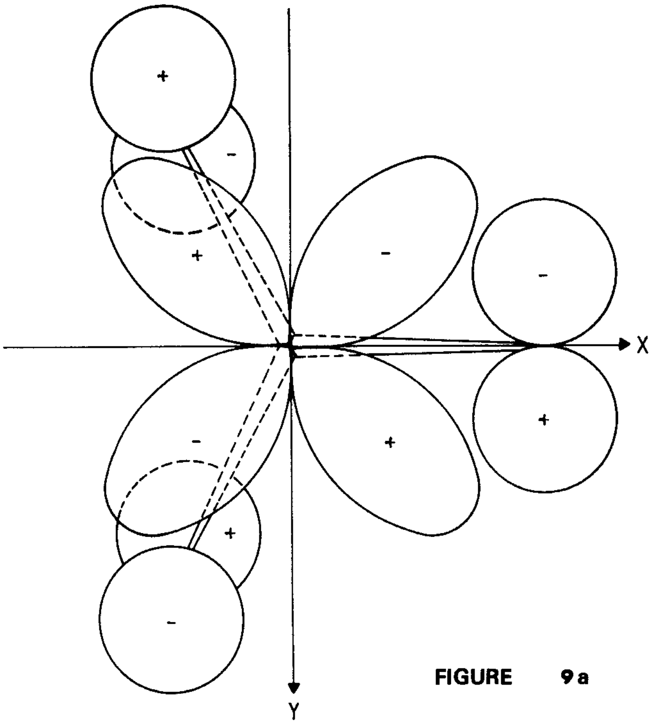
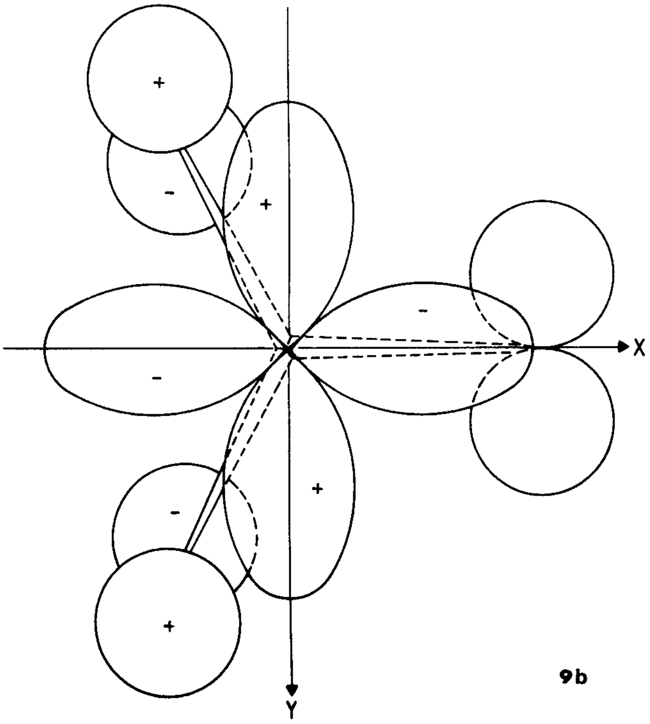


FIGURE 9a



9b

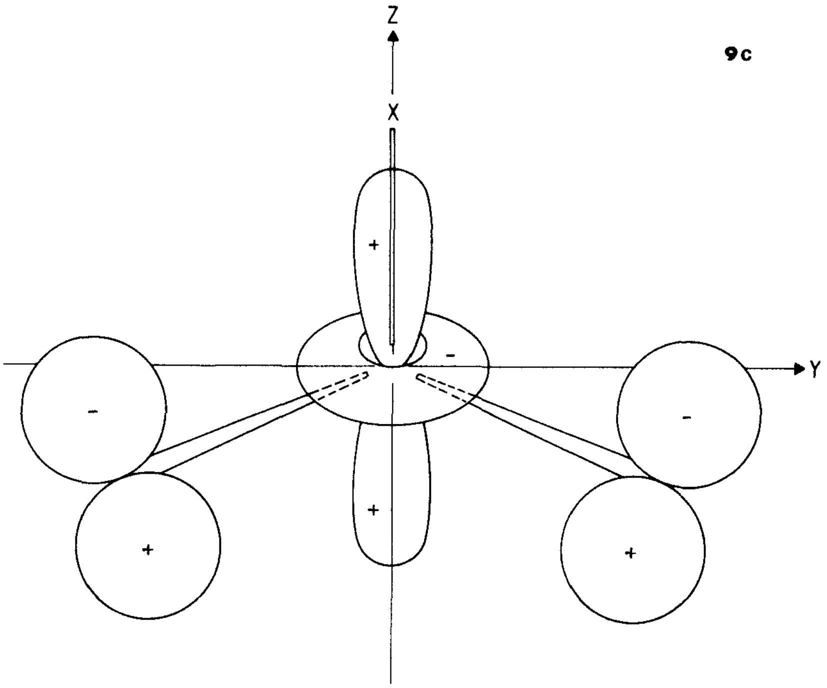


FIGURE 9 View down the *z* axis of the interactions of phosphorus *d* orbitals with oxygen and R *p* orbitals in 1,3,2-dioxaphosphorinanes possessing an axial X moiety (a and b). In (c), the view is down the *x* axis and the *p* orbital lying coplanar with but below the *xy* plane has been omitted.

ACKNOWLEDGEMENTS

The author thanks his many coworkers who contributed to this work and the generous financial support of the National Science Foundation, as well as the National Cancer Institute of the National Institute of Health, is gratefully acknowledged. He also thanks the organizers of this stimulating symposium for the invitation to present researches in this area and Professor R. F. Hudson for several fruitful discussions.

REFERENCES

1. F. H. Westheimer, *Accounts Chem. Res.* **1**, 70 (1968) and references therein.
2. E. M. Bellet and J. E. Casida, *Science* **182**, 1135 (1973).
3. (a) J. Casida M. Eto, A. D. Mosconi, J. L. Engel, D. S. M. Milbath, and J. G. Verkade, *Topical Appl. Pharm.*, in press; (b) J. E. Casida, *Chem. Eng. News* **52**, 56 (1974).
4. R. D. O'Brien, C. Y. Chiu, and J. G. Verkade, to be published.
5. J. G. Verkade, *Bioinorganic Chemistry* **3**, 165 (1974) and references therein.
6. (a) J. A. Mosbo and J. G. Verkade, *J. Am. Chem. Soc.* **94**, 8224 (1972); (b) J. A. Mosbo and J. G. Verkade, *J. Am. Chem. Soc.* **95**, 4659 (1973); (c) J. A. Mosbo and J. G. Verkade, *J. Am. Chem. Soc.* **95**, 4659 (1973) and references cited in these articles; (d) J. A. Mosbo and J. G. Verkade, to be published.
7. D. W. White and J. G. Verkade, *Phosphorus* **3**, 9 (1973).
8. G. Aksnes and R. Eriksen, *Acta Chem. Scand.* **20**, 2463 (1966).
9. (a) R. F. Hudson and C. Brown, *Accounts Chem. Res.* **5**, 204 (1972) and references therein; (b) R. Greenhalgh and R. F. Hudson, *Phosphorus* **2**, 1 (1972).
10. D. A. Denney and F. A. Wagner, *Phosphorus* **3**, 27 (1973).
11. P. Schipper and H. M. Buck, *Phosphorus* **3**, 133 (1973).

12. E. M. Thorsteinson and F. Basolo, *J. Am. Chem. Soc.* **88**, 3929 (1966).
13. (a) W. MaFarlane and R. F. M. White, *Chem. Commun.* 744 (1969) and references therein; (b) G. A. Olah and C. W. McFarland, *J. Org. Chem.* **36**, 1374 (1971).
14. L. J. Vande Griend and J. G. Verkade, *Phosphorus* **3**, 13 (1973).
15. L. J. Vande Griend and J. G. Verkade, to be published.
16. (a) H. Watanabe and K. Nagasawa, *Inorg. Chem.* **6**, 1068 (1967); (b) J. R. Berschied and K. F. Purcell, *Inorg. Chem.* **9**, 624 (1970); (c) L. J. Vande Griend, D. W. White, and J. G. Verkade, *Phosphorus* **3**, 5 (1973).
17. S. C. Goodman and J. G. Verkade, *Inorg. Chem.* **5**, 498 (1966).
18. J. G. Verkade, *Coord. Chem. Rev.* **9**, 1 (1972).
19. A. L. Mixon and W. R. Gilkerson, *J. Phys. Chem.* **75**, 3309 (1971).
20. J. H. Finley, D. Z. Denney, and D. B. Denney, *J. Am. Chem. Soc.* **91**, 5826 (1969).
21. E. L. Wagner, *J. Am. Chem. Soc.* **85**, 161 (1963).
22. (a) J. C. Clardy, D. Truesdale, and J. G. Verkade, unpublished results; (b) J. F. M. Pennings, H. Buck, L. J. Vande Griend, and J. G. Verkade, submitted.
23. D. B. Boyd, *J. Am. Chem. Soc.* **85**, 161 (1963).
24. Unfortunately the published data for $P(OEt)_3$ and $P(OCH{=}CH_2)_3$ are too imprecise to draw any structural conclusions (see Ref. 18 and references therein).
25. M. J. S. Dewar and P. Rono, *J. Am. Chem. Soc.* **91**, 2259 (1969).
26. See reference (g) in Table VII and references therein.
27. W. O. Davies and E. Stanley, *Acta Crystallog.* **15**, 1092 (1962).
28. See reference (e) in Table VII.
29. (a) D. W. J. Cruikshank, *J. Chem. Soc.* 5486 (1961); (b) J.-M. Lehn and G. Wipff, *Chem. Comm.* 800 (1976).
30. A. C. Vandenbroucke, E. J. Boros and J. G. Verkade, *Inorg. Chem.* **7**, 1469 (1968).
31. (a) E. E. Nifant'ev, A. A. Borisenko, I. S. Nasonovskii, and E. I. Matrovsov, *Dokl. Akad. Nauk. USSR* **196**, 28 (1971); (b) B. A. Arbuzov, R. P. Asrchinova, and V. A. Zoroastrova, *Dokl. Akad. Nauk. USSR* **199**, 662 (1971) Engl.
32. M. Kainosho, T. Shimozawa, *Tet. Lett.* 865 (1969).
33. D. W. White, Ph.D. Thesis, Iowa State University, Ames, Iowa, 1970.
34. J. A. Mosbo, Ph.D. Thesis, Iowa State University, Ames, Iowa, 1973.
35. D. W. White, G. K. McEwen, and J. G. Verkade, *Tet. Lett.* 5369 (1968).
36. (a) C. Bodkin and P. Simpson, *Chem. Commun.* 829 (1969); (b) C. Bodkin and P. Simpson, *J. Chem. Soc.* B 1136 (1971).
37. D. W. White, G. K. McEwen, R. D. Bertrand, and J. G. Verkade, *J. Chem. Soc.* B 1454 (1971) and references therein; (b) D. W. White, R. D. Bertrand, G. K. McEwen and J. G. Verkade, *J. Am. Chem. Soc.* **92**, 7125 (1970); (c) J. A. Mosbo and J. G. Verkade, *J. Am. Chem. Soc.* **95**, 4659 (1973).
38. M. Haemers, R. Ottinger, D. Zimmerman, and J. Reisse, *Tetrahedron* **29**, 3539 (1973).
39. D. B. Cooper, J. M. Harrison, T. D. Inch, and G. J. Lewis, *J. Chem. Soc. Perkin I* 1043 (1974).
40. W. Stec and A. Lopusinski, *Tetrahedron* **29**, 547 (1973).
41. See R. D. Bertrand, J. G. Verkade, D. W. White, D. Gagnaire, J. B. Robert, and J. Verrier, *J. Magn. Reson.* **3**, 494 (1970) for a discussion of this problem.
42. K. C. Yee and W. G. Bentrude, *Tet. Lett.* 2775 (1971).
43. A. J. Dale, *Acta Chem. Scand.* **26**, 2985 (1972),
44. W. G. Bentrude, H. W. Tan, and K. C. Yee, *J. Am. Chem. Soc.* **94**, 3264 (1972).
45. M. Kainosho, T. Morofushi, and A. Nakamura, *Bull. Soc. Chem. Japan* **42**, 845 (1969).
46. (a) J. P. Moajoral, R. Pujol, and J. Navech, *Bull. Soc. Chim. France* 606 (1972); (b) J. P. Majoral and J. Navech, *Spectrochim. Acta* **28** A, 2247 (1972); (c) K. Bergesen and T. Vikane, *Acta Chim. Scand.* **26**, 1794 (1972); (d) K. Bergesen and A. Berge, *Acta Chim. Scand.* **26**, 2975 (1972); (e) J. P. Majoral and J. Navech, *Bull. Soc. Chim. France* **95** (1971); (f) J. P. Majoral, J. Navech, and K. Pihlaja, *Phosphorus* **2**, 111 (1972); (g) J. P. Majoral and J. Navech, *Bull. Soc. Chim. France* 1331 (1971); (h) J. P. Majoral and J. Navech, *C. R. Acad. Sci. Paris, Ser. C* **268**, 2117 (1969); (i) J. P. Majoral, R. Kraemer, J. Devillers, and J. Navech, *Bull. Soc. Chim. France* 3917 (1970).
47. (a) J. P. Majoral, R. Pujol, J. Navech, and E. Mathis, *Tet. Lett.* 3755 (1971); (b) J. P. Majoral and J. Navech, *Bull. Soc. Chim. France* 2609 (1971).
48. See M. J. Gallagher and I. D. Jenkins, *Topics in Stereochem.* **3**, 1 (1968); and L. J. Bellamy, *Advances in Infrared Group Frequencies* (Methuen and Co., Ltd., London, 1968) for reviews of this subject.
49. J. Rodgers, D. W. White, and J. G. Verkade, *J. Chem. Soc.* A 77 (1971).
50. A. R. Katritzky, M. R. Nesbit, J. Michalski, Z. Tulimowski, and A. Zwierzak, *J. Chem. Soc.* B, 140 (1970).
51. (a) M-ul-Haque, C. N. Caughlan, and W. L. Moats, *J. Org. Chem.* **35**, 1446 (1970); (b) W. Murayama and M. Kainosho, *Bull. Chem. Soc. Japan* **42**, 1819 (1969); (c) H. J. Geise, *Rec. Trav. Chim.* **86**, 362 (1967); (d) T. A. Beinecke, *Acta Crystallogr.* **413**, 1325 (1969); (e) L. Silver and R. Rudman, *Acta Crystallogr.* **574**, 1328 (1972); M-ul-Haque, C. N. Caughlan, J. H. Hargis, and W. G. Bentrude, *J. Chem. Soc. Abstr.* 1786 (1970); (g) M. G. B. Drew, J. Rodgers, D. W. White, and J. G. Verkade, *Chem. Commun.* 227 (1971); (h) M. G. B. Drew and J. Rodgers, *Acta Crystallogr.* **B 28**, 924 (1972); (i) R. C. G. Killean, J. L. Lawrence, and I. M. Magennis, *Acta Crystallogr.* **B 27**, 189 (1971); (j) W. Saenger and M. Mikolajczyk, *Chem. Ber.* **106**, 3519 (1973).
52. J. P. Majoral, R. Pujol, and J. Navech, *C. R. Acad. Sci. Ser. C* 213 (1972).
53. (a) J. A. Mosbo, J. C. Clardy, and J. G. Verkade, *J. Chem. Soc., Chem. Commun.* 1163 (1972); (b) J. A. Mosbo, J. C. Clardy, and J. G. Verkade, *Phosphorus* **4**, 151 (1974); (c) H. A. Brassfield, R. A. Jacobson, and J. G. Verkade, *J. Am. Chem. Soc.* **97**, 4143 (1975); (d) H. A. Brassfield, J. P. Springer, J. C. Clardy, and J. G. Verkade, *Cryst. Comm.*, in press.

54. R. E. Wagner, W. Jensen, Q. Johnson, and W. Wadsworth, Abstracts, 163rd National ACS Meeting, Boston, April 1972, ORGN 38.

55. R. D. Bertrand, M.S. Thesis, Iowa State University, Ames, Iowa, 1967.

56. R. S. Edmundson and E. W. Mitchell, *J. Chem. Soc.* C 2091 (1968).

57. W. G. Bentrude and J. H. Hargis, *J. Am. Chem. Soc.* **92**, 7136 (1970).

58. (a) D. Gagnaire, J. B. Robert, and J. Verrier, *Bull. Soc. Chim. France* 2392 (1968); (b) J. P. Allbrand, D. Gagnaire, J. B. Robert, and M. Haemers, *Bull. Soc. Chim. France* 3496 (1969); (c) A. V. Bogatskii, A. A. Kolesnik, Yu Yu Samitov, and T. D. Butova, *J. Gen. Chem (USSR)* 37, 1048 (1967).

59. See reference 6c for a summary of this point.

60. W. G. Bentrude and H. W. Tan, *J. Am. Chem. Soc.* 94, 8222 (1972); W. G. Bentrude and H. W. Tan, *J. Am. Chem. Soc.* **95**, 4666 (1973).

61. (a) L. L. Burger, *J. Phys. Chem.* **62**, 590 (1958); (b) J. L. Burdett and L. L. Burger, *Can. J. Chem.* **44**, 111 (1966).

62. D. W. White and J. G. Verkade, *Phosphorus* **3**, 15 (1973).

63. L. J. Vande Griend and J. G. Verkade, *Inorg. Nucl. Chem. Lett.* **9**, 1137 (1973).

64. W. Murayama and M. Kainosho, *Bull. Chem. Soc. Japan* **42**, 1819 (1969).

65. M-ul-Haque, C. N. Caughlan, and W. L. Moats, *J. Org. Chem.* **35**, 1446 (1970).

66. A. P. Hong, J. B. Lee, and J. G. Verkade, *J. Am. Chem. Soc.*, in press.

67. F. Eckstein, private communication.

68. R. F. Hudson and J. G. Verkade, *Tetrahedron Letters* 3231 (1975).

69. (a) E. D. Morris and C. E. Nordman, *Inorg. Chem.* **8**, 1673 (1969); (b) J. R. Durig and J. M. Caspar, *J. Phys. Chem.* **75**, 3837 (1971); (c) A. H. Brittain, J. E. Smith, P. L. Lee, K. Cohn, and R. H. Schwendeman, *J. Am. Chem. Soc.* **93**, 6772 (1971); (d) G. C. Holywell, D. W. Rankin, B. Beagley, and J. M. Freeman, *J. Chem. Soc.* A 785 (1971); (e) P. Fonti, D. Damiania, and P. G. Favero, *J. Am. Chem. Soc.* **95**, 756 (1973).

70. (a) J. B. Robert and W. Stec, private communication. See also Ref. m in Table X; (b) T. S. Cameron, Z. Galdecki, J. Kasolak-Wojciechowska, *Acta Crystallog. B* **31**, 2331 (1975).

71. (a) D. W. White, C. K. McEwen, R. D. Bertrand, and J. G. Verkade, *J. Magn. Reson.* **4**, 123 (1971); (b) W. G. Bentrude and J. H. Hargis, *J. Am. Chem. Soc.* **92**, 7136 (1970).

72. M. Mikolajczyk, *J. Chem. Soc.* D 1221 (1969).

73. W. J. Stec, *Z. Naturforsch* **29** b, 109 (1974).

74. E. E. Nifant'ev, I. S. Nasonovskii, and A. A. Borisenko, *J. Gen. Chem. (USSR)* **41**, 2368 (1971).

75. D. Predivoditeler, D. A. Afanasjewa, J. P. Fillipovich, and E. E. Nifant'ev, *J. Gen. Chem. (USSR)* **43**, 73 (1973).