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Dipole Moment, Nuclear Magnetic Resonance, and Infrared Studies of Phosphorus Configurations and Equilibria in 2-R-2-Oxo-1,3,2-dioxaphosphorinanes

John A. Mosbo* and John G. Verkade*

Departments of Chemistry, Ball State University, Muncie, Indiana 47306, and Iowa State University, Ames, Iowa 50011

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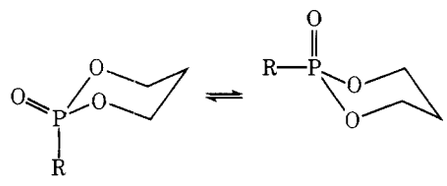
Substantial dipole moment differences (1.3–2.2 D) permit assignment of the stereochemistry at phosphorus in isomeric pairs of 2-R-2-oxo-4,6-dimethyl-1,3,2-dioxaphosphorinanes wherein R = Me (**3a,b**), H (**4a,b**), OMe (**5a,b**), and NMe_2 (**6a,b**) where **a** and **b** denote axial R (equatorial P=O) and equatorial R (axial P=O) relationships, respectively. Analogous assignments were obtained from similar measurements on the isomeric pairs of 2-R-2-oxo-4-methyl-1,3,2-dioxaphosphorinanes wherein R = Me (**7a,b**), H (**8a,b**), OMe (**9a,b**), and NMe_2 (**10a,b**). LIS experiments on **7–10** confirm these assignments. The **a** isomers of **3, 5, 6** and **7, 9, 10** exhibit $\delta^{31}P$ values upfield of those of the **b** isomers whereas the opposite is true for **4a,b** and **8a,b.** Doubling (ca. 19 cm^{-1}) of the phosphoryl stretching frequencies in **5b** and **9b** is attributed to rotational isomerism of the MeO groups while the lack of such doubling in the **a** isomers is attributed to steric restrictions. A more pronounced doubling (ca. 40 cm^{-1}) of this frequency in **6a** and **10a**, on the other hand, may be due to the presence of a second conformer arising as a result of the severe 1–3 steric interactions. The μ and $\delta^{31}P$ values and the extinction coefficients of the P=O stretching frequencies associated with **a** and **b** isomers of the rigid-ring model compounds **3–6** were compared to those of the analogous compounds which were free to attain conformational equilibrium by virtue of the absence of the 4,6-dimethyl substituents. All the data are in accord with a substantial axial R (equatorial P=O) group preference when R = H and MeO, although this preference is slightly reversed for R = Me and strongly opposite when R = Me_2N at room temperature in benzene.

Phosphorus stereochemistries and ring conformations of phosphorinanes, especially the 1,3,2-dioxaphosphorinanes reported here, have received considerable attention in recent years. Several instrumental techniques have been employed, from which conflicting conclusions have been occasionally drawn (vide infra). The purpose of this paper is to report a new approach to the use of solution techniques which eliminates some of the ambiguities.

The investigations reported in the literature for 2-R-2-oxo-1,3,2-dioxaphosphorinanes fall into two broad categories: (1) studies of phosphorus configurations and ring conformational equilibria of conformationally mobile systems such as **1**, and (2) assignments of phosphorus configurations of rings with conformationally reduced mobility such as **2a** and **2b.** It



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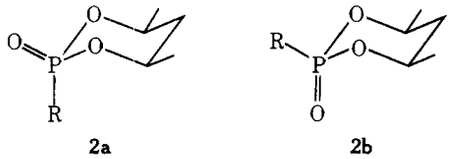


2a **2b**

should be noted that 5,5-dimethyl derivatives are not expected to influence the mobility significantly and they are therefore in the same class with **1.** On the other hand, 4-methyl and 5-*tert*-butyl substituted rings resemble **2** in being more conformationally rigid.

Five instrumental techniques (^1H NMR, ^{13}C NMR, ^{31}P NMR, infrared, and dipole moment experiments) have been used for determinations of phosphorus stereochemistries and ring conformations in solution as is briefly outlined below.

Coupling constants among ring hydrogens and between phosphorus and ring protons have been found to be valuable both for conformer distribution determinations in type **1** compounds and for phosphorus stereochemical assignments.[1] Thus, it has been reported that $^3J_{POCH_{eq}}$ coupling constants are larger for compounds with equatorially oriented substituents in trivalent 1,3,2-dioxaphosphorinanes than for the axial analogues.[2] However, this criterion has been incorrectly applied to 2-oxo analogues[3] which in fact do not exhibit such behavior.[4] Because of this problem in 2-oxo compounds, lanthanide induced shift (LIS) experiments on protons in the molecule become very useful. Mosbo and Verkade have demonstrated that the C4 and C6 axial protons are shifted considerably further downfield in compounds with the **2b** configuration than in those with **2a.**[5] Dale[6] has reported conformer distributions determined from type **1** compounds employing LIS experiments, but the results must be viewed with caution since Bentrude and co-workers[7] have found that the presence of a lanthanide shift reagent can cause conformational changes.

The use of ^{13}C NMR spectra has been reported in only a few instances to identify type **2** isomers. It has been demonstrated that the chemical shift of a carbon atom γ to an axial phosphorus substituent (**b** isomer) is upfield of the **a** isomer.[2b,c]

This technique has not been applied to determinations of conformer distributions in type 1 compounds.

^{31}P NMR data have indicated that chemical shifts of **2a** isomers are generally upfield of the **2b** analogues.[2b,5] A reversal has been found, however, when R = H.[5b,8] No correlations between conformer distributions of type 1 compounds and ^{31}P chemical shifts have been previously reported.

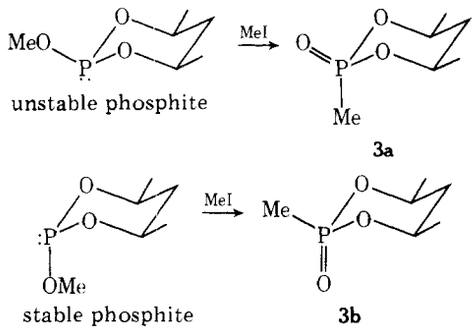
Kainosho et al.[9] first reported that infrared phosphoryl stretching frequencies were indicative of the disposition of the P=O link in the ring. The absorption for the equatorial P=O orientation (**2a**) was found to be at higher energy than that for the axial orientation (**2b**). This technique has been extensively employed for both identification of phosphoryl orientations and determinations of conformer equilibria.[10,11]

Dipole moment data were employed by Kainosho and Shimozawa[12] to deduce phosphorus configurations in type 1 compounds. Their conclusions were tenuous, however, because they were based on comparisons of calculated and observed moments and this method has led to some erroneous assignments by later workers.[11] More recently, dipole moment measurements have been employed to identify the phosphorus configurations of type 2 isomers, where the equatorially oriented P=O of the **a** isomers caused considerably larger molecular moments than the axial P=O[5,13] orientations.

With the exception of infrared spectroscopy, none of the above techniques have been used with any reliability for the determination of both phosphorus configurations and ring conformer distributions of type 1 compounds. In this paper we report quantitative conformer distributions of type 1 compounds, where R = Me, H, OMe, and NMe_2, based primarily on ^{31}P and dipole moment measurements and secondarily on infrared analysis of the P=O region. A new approach to the problem is developed in which ^{31}P chemical shifts and dipole moment measurements of the mobile (type 1) compounds are compared to those of the **2a** and **2b** isomers. The results of these experiments suggest that the infrared phosphoryl stretching frequency criterion is more ambiguous than previously supposed. The 4,6-dimethyl compounds were chosen as excellent representations of conformationally rigid molecules since the presence of the methyl groups renders a second chair form essentially inaccessible.

Results and Discussion

Configurational Assignments of Rigid Compounds. The previously unreported methyl phosphonates **3a** and **3b** were

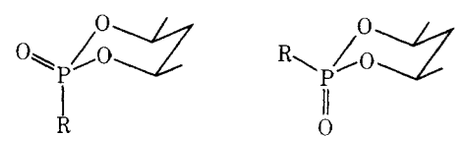


obtained by the reaction of unstable and stable phosphites, respectively, with methyl iodide. The analogous Michaelis–Arbusov reaction to form the 4-methyl compounds **7a** and **7b** has been shown to occur with complete retention of phosphorus configuration.[14] That the 4,6-dimethyl compounds are also obtained through retention of configuration is indicated by the dipole moments of the 4,6-dimethyl substituted compounds **3a,b**, **4a,b**, **5a,b**, and **6a,b** and the 4-methyl substituted compounds **7a,b**, **8a,b**, **9a,b**, and **10a,b** which were derived from the appropriate experimental data (see supplementary material in Table I) and are presented in Table II. Those isomers with equatorial phosphoryl oxygens (**a** isomers)

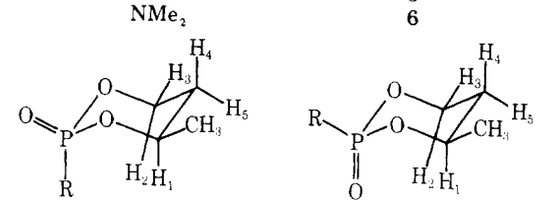
Table II. Dipole Moments, ^{31}P Chemical Shifts, and Phosphoryl Stretching Frequencies of 4-Methyl- and 4,6-Dimethyl-1,3,2-dioxaphosphorinanes[a]

Compd	μ[b]	^{31}P[c]	$\bar{\nu}$(P=O)[d]
3a	6.42	−19.4	1285 s (138)
3b	4.15	−28.0	1251 s (143)
4a	6.37	−2.9	1296 s (79)
4b	5.07	+1.3	1294 vw, 1267 s
5a	6.11	+7.1	1304 s (143)
5b	4.69	+5.0	1289 m, 1271 m
6a	5.80	−3.5	1301 m, 1260 s
6b	4.05	−6.6	1257 s (88)
7a	6.13	−20.4	1284 s (88)
7b	4.07	−27.7	1254 s (110)
8a	6.02	−2.8	1298 s (84)
8b	5.24	+1.7	1293 vw, 1270 s
9a	5.78	+6.8	1309 s (94)
9b	4.93	+5.2	1288 m, 1270 m
10a	5.33	−3.5	1301 m, 1260 s
10b	4.00	−6.6	1257 s (94)

[a] All measurements were made on benzene solutions. [b] Given in Debye units with a precision of ±0.05 D. [c] Given in parts per million relative to external 85% H_3PO_4. Negative and positive signs denote downfield and upfield shifts, respectively, from the standard. [d] Given in cm^{-1}, s = strong, m = medium, w = weak, v = very. The numbers appearing in parentheses are calculated extinction coefficients.



a R	b Compd
Me	3
H	4
OMe	5
NMe_2	6



a R	b Compd
Me	7
H	8
OMe	9
NMe_2	10

are expected to exhibit larger dipole moments than those with axial phosphoryl oxygens (**b** isomers) as has been discussed previously.[5] Lanthanide induced shift (LIS) data for the 4-methyl substitute compounds **8–10** have been presented and rationalized previously[5] and the larger C4 and C6 axial proton shifts (H_1 and H_2) observed for the **b** isomer of **3** (Table III) are consistent with the isomeric phosphorus configurations as shown.

The ^{31}P chemical shifts of the isomeric compounds **3, 5, 6, 7, 9,** and **10** (Table II) are consistent with the previously reported observation that isomers with axially oriented R groups (**a** isomers) have chemical shifts upfield of the equatorial isomers.[2b,5] Because the reverse behavior has been reported

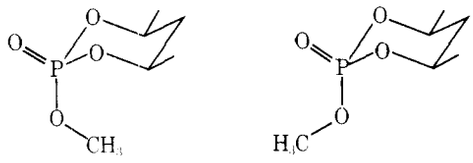
Table III. LIS ^{1}H NMR Shift Data $\Delta\delta^a$ for 2-R-2-Oxo-4-methyl-1,3,2-dioxaphosphorinanes

Compd	R	H_1	Me	H_2	H_3	H_4	H_5
7a	3.64	1.9	1.61	1.9	1.9	1.6	2.6
7b	3.50	4.5	1.09	4.5	1.6	1.4	2.3
8a	*b*	1.6	1.2	1.6	1.6	1.4	2.2
8b	*b*	4.6	1.3	4.1	1.7	2.0	2.6
9a	4.58	3.3	1.30	3.0	2.2	1.5	2.4
9b	3.94	5.1	1.37	4.5	2.2	1.6	2.6
10a	2.64	2.3	1.90	2.3	1.6	1.5	2.6
10b	3.73	5.3	1.19	4.6	2.2	1.4	2.8

^{a} $\Delta\delta$ refers to the chemical shift in the presence of $Eu(fod)_3$ minus that in the absence of $Eu(fod)_3$. ^{b} A very large shift occurred which was out of instrumental range.

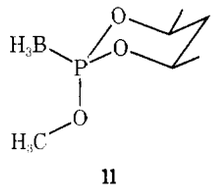
for **8a,b** and **4a,b**,[5b] this criterion must be used with some caution.

The infrared phosphoryl stretching frequencies listed in Table II illustrate that this technique can be misleading unless used with care. Two absorptions of nearly equal intensity for the phosphates **5b** and **9b** and the phosphoramidates **6a** and **10a** were observed even though all four compounds were isomerically pure. The origin of phosphoryl frequency doubling in trialkyl phosphates has been reviewed by several authors.[15] In some cases where the splitting is relatively small (e.g., 15 cm^{-1} for trimethyl phosphate) rotational isomerism has been postulated. However, in other instances a much larger splitting of up to 50 cm^{-1} is observed. In these cases the doubling has been attributed to Fermi resonance of the P=O band with an overtone.[15c] Since splittings for compounds **5b** and **9b** (18 and 19 cm^{-1}, respectively) are similar to that of trimethyl phosphate, it seems reasonable to postulate rotational isomerism of the methoxy group. The apparent absence of such rotational isomers in **5a** and **9a** seems reasonable since Dreiding models of these compounds reveal severe 1–3 steric interactions of the C4 and C6 axial protons when in the folded conformations. The single phosphoryl frequency can thus be attributed to the extended form. Structural support for the extended form of phosphate **5a** comes from the x-ray diffraction study of **11** in which the methyl group was found to be exocyclic to the ring.[16]



folded configuration extended configuration

5a



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For the phosphoramidates the ambiguities in the phosphoryl stretching region are more pronounced. The single frequencies for the **b** isomers of **6** and **10** are very similar in energy to the stronger of the two absorptions of the **a** isomers. This is in contrast to the large difference expected for axial vs. equatorial phosphoryl groups as observed for **3a,b** and **7a,b.** There is much evidence that a nitrogen directly bonded

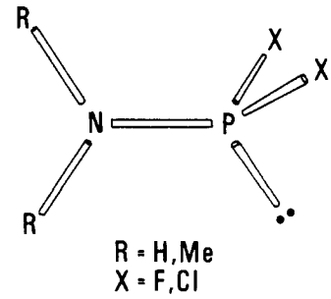
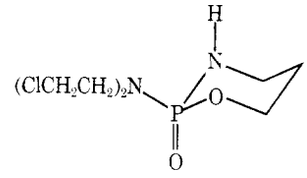


Figure 1. Conformation of compounds of the type R_2NPX_2.

to phosphorus assumes a planar configuration which bisects the X–P–X angle and eclipses the phosphorus lone pair vector[17] in trivalent phosphorus compounds (Figure 1). The crystal structure determinations of cyclophosphamide[18] (**12**)



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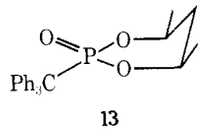
showed a similar phenomenon in the phosphorinane system since the exocyclic nitrogen plane nearly bisects the ring N–P–O angle and eclipses the P=O bond. This apparently stable coplanar relationship of the nitrogen configuration and the phosphorus substituent (oxygen or lone pair) presumably also holds for the phosphoramidates **6a,b** and **10a,b.** The presence of only one type of *N*-methyl group as shown from room temperature ^{1}H NMR spectra indicates rapid rotation about the P–N bond on the NMR time scale in both isomers of each compound. From the structural studies mentioned bove, however, the preferred NR_2 orientation would be as indicated in Figure 1. The single phosphoryl stretching frequency for the **b** isomers could be due to a comparatively low concentration of other rotameric contributions. The situation for the **a** isomers is complicated, however, by the fact that in a chair conformation with the preferred nitrogen orientation [Figure 2(a)], severe steric interactions occur between the *N*-methyl protons and the C4 and C6 axial protons. Two conformational changes could alleviate this problem: (1) rotation about the P–N bond by 90° to produce a stable chair conformation with a disfavored nitrogen configuration [Figure (2(b)] and (2) formation of a half-chair or "chaise longue" (as is found from the x-ray structural determination of **13**[19]). The relatively unstable ring conformation produced by the latter process would preserve the preferred nitrogen conformation [Figure 2(c)]. The presence of two such rotational conformers in isomer **a** of compounds **6** and **10** would be consistent with the appearance of two phosphoryl stretching frequencies. Indeed, the higher energy frequency for each **a** isomer is in the region expected for equatorial P=O and the low energy frequencies are very nearly the same as that observed for **13.**[1a]



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Although temperature variation might be expected to cause a change in such rotamer ratios, this was not observed in the infrared spectra of **7a** in the range of 30–60 °C.

Two phosphoryl stretching frequencies are listed for both **4b** and **8b,** but their origin is not certain. It is not unreasonable to believe that the higher energy peak in the **b** isomers is due

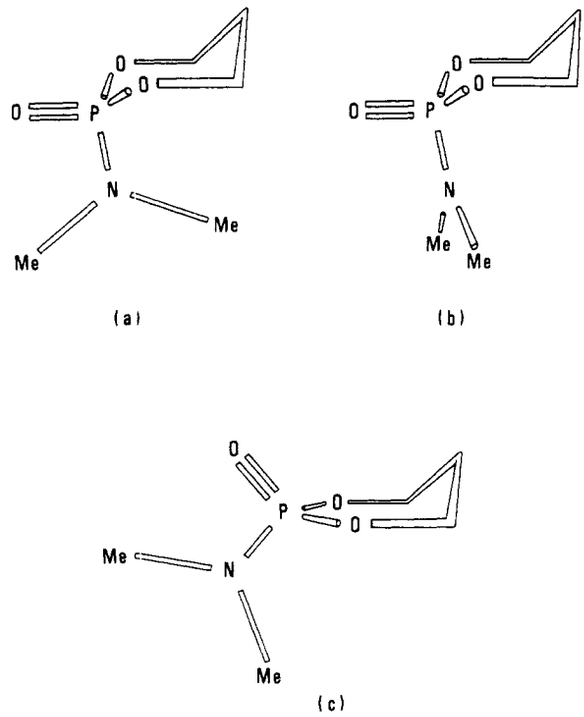
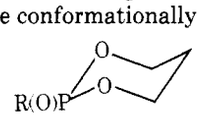


Figure 2. Possible conformations of the **a** isomer of 2-oxo-2-dimethylamino-4,6-dimethyl-1,3,2-dioxaphosphorinane and its 4-methyl analogue.

to a conformer which possesses a more equatorial P=O disposition arising from a twist or boat conformation. Such a conformer could also explain the rather large dipole moment observed for the **b** isomers. As noted in the introduction, it has been postulated that compounds with equatorial phosphoryl oxygens exhibit stretching frequencies at higher energy than those with axial phosphoryl oxygens. The results reported here, however, indicate that care must be exercised in using this criterion for assignment of phosphorus stereochemistry since isomerically pure compounds may display more than one phosphoryl frequency.

Conformational Equilibria. Conformational distributions of the compounds lacking ring carbon substituents were determined by comparison of dipole moments, ^{31}P chemical shifts, and infrared stretching frequencies of compounds **14–17** to those of the analogous isomeric 4,6-dimethyl compounds. The latter served as rigid models of the two chair conformations in the conformationally mobile systems.



R	Compd
Me	14
H	15
OMe	16
NMe_2	17

The first compound considered is the hydrogen phosphonate **15** since the preferred stereochemistry and equilibrium distribution are known for compounds **4a** and **4b** from thermodynamic data.[5b] The dipole moments, ^{31}P chemical shifts, and infrared phosphoryl stretching frequencies are listed in Table IV.

For calculation of the conformer distribution from dipole moment data, the equation $(Y)(\mu_A)^2 + (1 - Y)(\mu_B)^2 = (\mu)^2$ was employed. It was assumed that the dipole moment of **4a** (μ_A) was identical with the dipole moment of the conformer of **15** containing the equatorial P=O orientation, and that the dipole moment of **4b** (μ_B) was the same as that of the opposite

Table IV. Dipole Moments, ^{31}P Chemical Shifts, and Phosphoryl Stretching Frequencies of 2-R-2-Oxo-1,3,2-dioxaphosphorinanes[a]

Compd	μ[b]	$\delta^{31}P$[c]	$\bar{\nu}$(P=O)[d]
14	4.98	−24.2	1288 m, 1255 s
15	5.86	−2.26	1303 s, 1281 vw
16	5.63	6.7	1310 s
17	3.95	−6.22	1255 s

[a] All measurements were made on benzene solutions. [b] Given in Debye units with a precision of ±0.05 D. [c] Given in parts per million relative to external 85% H_3PO_4. [d] Given in cm^{-1}, s = strong, m = medium, w = weak, v = very.

Table V. Conformer Fractions of 2-R-2-Oxo-1,3,2-dioxophosphorinanes[a]

Compd	From μ	From $\delta^{31}P$	From $\bar{\nu}$(P=O)
14	0.32 (0.05)	0.43 (0.02)	0.4 (0.1)[b] 0.35 (0.1)[c]
15	0.58 (0.08)	0.85 (0.1)	0.8 (0.2)
16	0.63 (0.09)	0.8 (0.1)	0.8 (0.2)
17	0.0 (no estimate)	0.12 (0.06)	0.19 (0.09)

[a] The method of calculation is described in the text. The data refer to the fraction of equatorial conformer in solution. The numbers in parentheses are the errors calculated from precision limits. [b] Calculated assuming the extinction coefficient of **3b** to be the same as the lower energy peak of **14**. [c] Calculated assuming the extinction coefficient of **3b** to be the same as the higher energy peak of **14**.

conformation. Knowledge of the measured moment of **15** (μ) therefore allowed calculation of the fraction (Y) of **15** containing equatorial phosphoryl oxygen. The results are given in Table V with estimated precisional errors in parentheses. Since the ring methyl groups of **4a** and **4b** are symmetrically substituted, no ring distortions affecting the dipole moments are expected for these compounds. (Compounds with a single exocyclic methyl group such as **9a,b** were not used in these calculational studies since distortion is more likely and ring conformation changes by way of flipping are sterically less disfavored.) Substitution of a methyl group for a hydrogen does not introduce a significant change in the local dipole moment since the group moment is $(3 \cos 70.5°)(\mu_{C-H}) = (1.004)(\mu_{C-H})$, which is well within the experimental error of the carbon–hydrogen moment. Introduction of the methyl substituents may cause a change in ring angles which would slightly alter dipole moments, but no corrections were made for this possibility. Another possible source of error is the assumption that **4a** and **4b** are conformationally pure. Although there is no reason to believe that this is not the case for **4a, 4b** apparently displays two phosphoryl stretching frequencies indicative of more than one conformation (vide supra). The reasonable assumption that no intermediate conformer of **15** makes a significant contribution to the dipole moment has also been made.

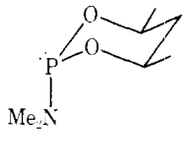
The conformational distribution of **15** was calculated from ^{31}P chemical shift data using the equation $(Y)(\delta_A) + (1 - Y)(\delta_B) = \delta$ (Table V) with similar assumptions to those made for the dipole moment data. The chemical shift of **4a** (δ_A) was assumed to be the same as that of the conformer of **15** containing equatorial P=O, and $\delta^{31}P$ for **4b** (δ_B) was taken to be equal to the axial P=O conformer of **15**. The same two error considerations present in the dipole moment studies also apply here since both are expected to influence the ^{31}P chemical shifts.

The infrared spectrum of **15** displayed two phosphoryl

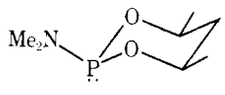
stretching frequencies (Table IV), indicative of two ring conformations. The higher energy absorption was assigned to the equatorial P=O and was assumed to have the same extinction coefficient as that calculated for **4a.** The concentration of this conformer was calculated and the fraction of total compound in that conformation determined (Table V). Any error introduced by assuming identical extinction coefficients is probably overshadowed by the large error in the determination of the absorbances from the nonlinear baselines of the spectra. The equilibrium distribution for **4a** and **4b** at 40 °C is about 90% **4a** and 10% **4b**,[5b] in much better agreement with the results of the ^{31}P and IR methods than with the dipole moment method. All three procedures, however, give the same qualitative result that equatorial phosphoryl is preferred for **15** and this also is consistent with a previous IR study.[10b]

Conformer distributions were calculated for the phosphate **16** (Table V) from the data in Table IV by the same procedures described for **15.** All three methods yield data which qualitatively corroborate the conclusion previously reported for analogous compounds, namely, that equatorial phosphoryl oxygen is preferred.[1c,4g,10c-e,11] Furthermore, the quantitative fractions calculated from ^{31}P and $\bar{\nu}$(P=O) data are in good agreement with those calculated by other workers from phosphoryl stretching frequency data of methyl, ethyl, and phenyl phosphates.[10g]

The dimethylamino substituent in **17** induces a behavior opposite to that of the hydrogen or methoxy compounds in that axial P=O is preferred (Table V). This difference can be ascribed to the same steric problems associated with an axial NMe_2 group in **18a** as described previously.[5a] The tentative



18a

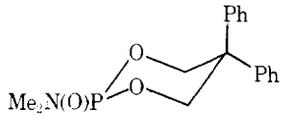


18b

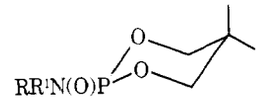
evidence for axial preference of the P=O group from hydrolysis data on **6a,b**[5a] is thus substantiated by the dipole moment, ^{31}P chemical shift, and $\bar{\nu}$(P=O) data for **17.**

An indication of the presence of error in calculating conformer ratios derived from P=O stretching frequency data is now demonstrated with **16** as an example. Only one peak was observed in the spectrum of **16** indicating 100% equatorial P=O. Using the extinction coefficient determined from the P=O mode in **5a** for the analogous peak in **16,** the conformer fraction given in Table V was obtained. Either the peak from the other conformer is so weak as to be unobserved, or the calculations are inaccurate.

Axial P=O preference was initially reported by Majoral and co-workers[10c,e,f,11] for the amino compounds **19** and **20,** but

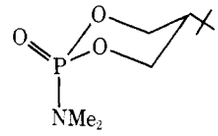


19

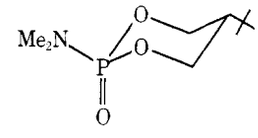


R	R'	Compd
Me	Me	20
n-Pr	H	21
t-Bu	H	22
n-Pent	H	23

they later questioned this conclusion[11] in view of dipole moment studies reported by Kainosho et al.[12] for compounds **20–23** from which the latter authors inferred an equatorial P=O preference. Bentrude and Tan have obtained NMR evidence for the greater stability of axial P=O from compounds **24a,b**[2b,c] and our own results definitely support this conclusion for R_2N substituted derivatives.



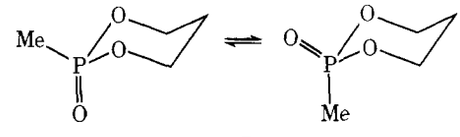
24a



24b

Phosphonates do not appear to display a strong conformational preference[10c,g,11,19,20] and the distributions calculated for the methyl phosphonate **14** (Table V) are consistent with these findings. Two values are calculated from the P=O stretching frequency data; for one it is assumed that the extinction coefficient of **2a** is the same as that of the equatorial P=O conformer of **14** and for the other it is ssumed that the extinction coefficient of **3b** is the same as that of the axial P=O conformer of **14.** All the calculations indicate a somewhat favored axial phosphoryl orientation, which is consistent with previosly reported results.[10g,20]

It is important to note that all of the calculations are based on distributions at or near room temperature with benzene as the only solvent. Indeed, infrared P=O intensities have been reported to be temperature and solvent dependent.[10b,c,g,11] Although benzene was the sole solvent used in the present studies, variable temperature infrared spectra have been obtained for compound **14.** From the data listed in Table VI, values of ΔH and ΔS were calculated to be −1.34 kcal/mol and −5.38 cal/mol·deg, respectively, for the interconversion indicated below, with $\Delta G° = +0.16$ at 25 °C. These



17

values are in reasonable agreement with those reported for phenyl phosphonates calculated from NMR and IR data.[10g] Formation of the equatorial P=O conformer is therefore favored at lower temperature, but the solvent did not permit investigations at temperatures below 5 °C. Low-temperature ^{31}P chemical shifts were essentially unchanged from those measured at 25 °C. The high polarity of $CFCl_3$ as a solvent in this experiment could cause the more polar equatorial P=O conformer to predominate in the low temperature range.

Table VI. Thermodynamic Data for the Conformer Equilibria of 2-Methyl-2-oxo-1,3,2-dioxaphosphorinane (14)[a]

Temp, °C	K_{eq}[b]	Temp, °C	K_{eq}[b]
5	0.76	50	0.53
15	0.68	60	0.52
31	0.62	68	0.47
40	0.57		

[a] Benzene solutions. [b] K_{eq} equals the amount of equatorial phosphoryl conformer divided by the amount of axial phosphoryl conformer.

Conclusions

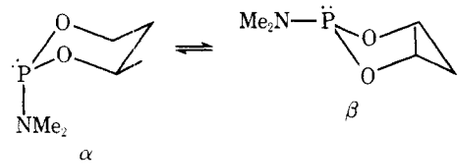
From the results given here, we conclude that the most appropriate instrumental techniques for the determination of phosphorus stereochemistries of conformationally rigid 2-R-2-oxo-1,3,2-dioxaphosphorinanes are dipole moment measurements and LIS experiments. ^{31}P chemical shift and

Table VII. $J(POCCH_3)$ Data for 4-Methyl- and 4,6-Dimethyl-1,3,2-dioxaphosphorinanes

Compd	$J(POCCH_3)$, Hz	Compd	$J(POCCH_3)$, Hz
3a	1.7	**7a**	1.6
3b	1.6	**7b**	1.6
4a	1.7	**8a**	1.9
4b	1.8	**8b**	1.3
5a	2.2	**9a**	2.5
5b	2.2	**9b**	1.9
6a	2.2	**10a**	1.6
6b	2.2	**10b**	2.2

infrared phosphoryl stretching frequency criteria are more ambiguous and can lead to erroneous conclusions. However, for the semiquantitative determination of conformational distributions in equilibria of mobile phosphorinanes, ^{31}P chemical shifts and infrared stretching frequencies may be more accurate if the phosphorous stereochemical assignments have been correctly made. This conclusion is based on the similarity of the thermodynamic data for the equilibrium of **4a** and **4b** and the results for compound **15.**

The isomeric 4,6-dimethyl ring carbon substituted compounds appear to be better representations of conformationally pure compounds than the corresponding 4-methyl compounds for the following reasons. The coupling constants $J(POCCH_3)$ given in Table VII range from 1.6 to 2.5 Hz for all 4,6-dimethyl isomers investigated (**3a,b–6a,b**), for the 4-methyl isomers containing preferred phosphorus configurations (**7b, 8a, 9a,** and **10b**), and also for **7a,** which probably differs little in energy from **7b.** The 4-methyl isomers with unstable phosphorus configurations (**8b, 9b,** and **10a**), however, all have coupling constants which are 0.6 Hz smaller. Although a difference of 0.6 Hz is too small for a meaningful quantitative analysis, it may be indicative of a significant contribution from other conformers arising from ring flipping or twisting. Some evidence for this possibility stems from the recent report of Cogne et al. who found that the trivalent compound **25** exists in the two conformations depicted below



25

with an α/β ratio of 85:15.[2d] The dipole moment data are reasonably consistent with this postulate since compounds **6b** and **10b** have measured moments within experimental error of each other, whereas those of the unstable configurations **6a** and **10a** differ substantially. The same is also true for **3b** and **7b** companed to **3a** and **7a,** although the smaller preference for a specific phosphorus configuration might be expected to produce a smaller difference in moment for **3a** and **7a.** For the hydrogen phosphonates and the phosphates, the 4,6-dimethyl isomers represent dipole moment *extrema* with the 4-methyl isomers intermediate in value. Thus in general, the 4,6-dimethyl isomers are probably better model compounds for axial and equatorial substituents than are the 4-methyl compounds, since the latter are more apt to exist as ring flipped or twisted conformers. Comprehensive NMR spectral analyses of compounds **7a,b–10a,b** are currently underway to determine the extent of chair–chair and chair–nonchair interconversions in 4-methyl compounds.

Experimental Section

The syntheses of the starting materials (*meso*-2,4-pentanediol and 2-chloro-4,6-dimethyl-1,3,2-dioxaphosphorinane) have been described previously.[21] Isomers of the 4,6-dimethyl substituted compounds [2-methoxy-,[5a,20] 2-methoxy-2-oxo-[5a] (**5a,b**), 2-dimethylamino-2-oxo-[5a] (**6a,b**), and 2-hydro-2-oxo-1,3,2-dioxaphosphorinanes[5b] (**4a,b**)] were prepared as previously described. The corresponding 4-methyl-1,3,2-dioxaphosphorinane isomers, as well as the 1,3,2-dioxaphosphorinanes lacking ring substituents, were prepared in a similar manner.

2β-Methyl-2α-oxo-4α,6α-dimethyl-1,3,2-dioxaphosphorinane (3a) and 2α-Methyl-2β-oxo-4α,6α-dimethyl-1,3,2-dioxaphosphorinane (3b). These compounds were synthesized from the equatorial and axial methyl phosphite analogues, respectively. Approximately three times the phosphite volume of methyl iodide was added and the solutions were stirred overnight. The products, obtained in nearly quantitative yields, were sublimed at 55 and 40 °C, respectively (ca. 0.5 mm). Anal. Calcd for $C_6H_{13}O_3P$: C, 43.90; H, 7.98; P, 18.87. Found for **3a:** C, 43.50; H, 8.09; P, 18.44. Found for **3b:** C, 44.23; H, 7.90; P, 18.81.

These compounds were reported earlier[22] as a mixture resulting from the reaction of $OPMeCl_2$ and diol.

2β-Methyl-2α-oxo-4α-methyl-1,3,2-dioxaphosphorinane (7a) and 2α-Methyl-2β-oxo-4α-methyl-1,3,2-dioxaphosphorinane (7b). Syntheses of these compounds were analogous to those described above except that purification was facilitated by vacuum distillation at 93 °C (0.3 mm) and 57 °C (0.15 mm), respectively. Yields were essentially quantitative.

2-Methyl-2-oxo-1,3,2-dioxaphosphorinane (14). This compound was prepared in nearly quantitative yield in the manner described above from the appropriate phosphite and sublimed at 50 °C (0.5 mm). Its melting point (98–99 °C) is in good agreement with that reported earlier for this compound (98–99.5 °C) prepared by reacting $OPMeCl_2$ with 1,3-propanediol.

^{31}P Chemical Shifts. The shifts observed in benzene solution were obtained by standard INDOR techniques employing a Varian Associates HR-60 NMR spectrometer operating at 60 MHz. Positive shifts were assigned to those resonances which appeared at higher field than the external standard, which was 85% H_3PO_4.

Infrared Spectra and Phosphoryl Stretching Frequency Assignments. A Beckman IR-12 operated at sweep speeds of 40 cm^{-1}/s was employed to obtain ambient temperature spectra which were all calibrated with polystyrene. Benzene solutions ca. 0.05 M in solute were used in cells with a 0.1-mm path length and benzene in a 0.1-mm cell was employed in the reference beam. The phosphoryl stretching frequencies of the hydrogen phosphonates were assigned by comparison of samples 80 atom % ^{18}O-enriched in phosphoryl oxygen to normal isotope abundance cmmpounds prepared by the same procedure (vide supra). These were further compared to samples of pure isomers of normal isotope distribution. The phosphoryl stretching frequencies of the other 15 compounds were assigned by comparison of spectra of pure compounds in benzene solution to solutions of compound in benzene saturated with iodine. The weak iodine complex formed caused a decrease in the free phosphoryl absorption with concurrent appearance of a broader absorption about 40 cm^{-1} lower in energy.

Variable-temperature IR spectra were obtained with a Beckman IR-8 spectrometer with a sample cell whose temperature could be controlled with water circulating through a surrounding jacket. Reported temperatures are probably no more accurate than ±3 °C at the extremes.

Dipole Moment Measurements. The instrumentation and data treatment have been described in detail elsewhere.[24] Four solutions of each compound ranging in concentration from about 1 to 10 × 10^{-3} mole fraction in benzene solution prepared under nitrogen were employed.

LIS Experiments. These were carried out on $CDCl_3$ solutions 0.2 M in solute and 0.1 M in tris(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedione)europium(III) [$Eu(fod)_3$] using a Varian Associates HA-100 NMR spectrometer.

Other Instrumentation. Routine ^1H NMR spectra were obtained on either a Varian Associates A-60 NMR spectrometer or an Hitachi Perkin-Elmer R20-B spectrometer operating at 60 MHz. Mass spectra of all the compounds used in this study displayed parent ion peaks at 19 or 70 eV on an Atlas CH-4 single focusing mass spectrometer. Liquid compounds were mixed with powdered molecular sieve before spectra were run.

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Registry No.—**3a,** 61558-34-7; **3b,** 61616-95-3; **4a,** 39762-82-8; **4b,** 39762-83-9; **5a,** 41158-22-9; **5b,** 41158-23-0; **6a,** 41158-15-0; **6b,** 41158-16-1; **7a,** 52265-58-4; **7b,** 52265-59-5; **8a,** 26339-67-3; **8b,** 26339-68-4; **9a,** 33996-03-1; **9b,** 33996-04-2; **10a,** 41158-21-8; **10b,** 41158-20-7; **14,** 13407-03-9; **15,** 16352-21-9; **16,** 33554-05-1; **17,** 61558-35-8; equatorial methyl phosphite, 7735-82-2; axial methyl phosphate, 7735-86-6; 2-methyl-1,3,2-dioxaphosphorinane, 61558-36-9; methyl iodide, 74-88-4.

Supplementary Material Available. A listing of the dielectric, refractive index, and orientation polarization data (1 page). Ordering information is given on any current masthead page.

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Δ^2-1,2,4-Oxadiazolines. 1. Molecular Orbital Calculations, Absorption, and Fluorescence Spectra

Rajendra Mohan Srivastava and Ira M. Brinn*[1]

Departamento de Quimica, Universidade Federal de Pernambuco, Recife, Pernambuco, Brazil

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Molecular orbital calculations of five Δ^2-1,2,4-oxadiazolines and one oxadiazole have been carried out using a CNDO/2 method. The results are in accordance with the experimentally observed values. The calculations strongly support a planar cyclic structure. Striking differences have been observed between the fluorescence spectra of the oxadiazolines and the oxadiazole. An explanation of this behavior is advanced. A facile aromatization of 5-ethyl-3-phenyl-Δ^2-1,2,4-oxadiazoline to 5-ethyl-3-phenyl-1,2,4-oxadiazole is described.

Substituted 1,2,4-oxadiazoles have been found to exhibit various types of biological activity including analgetic, sedative,[2] fungicidal, and insecticidal.[3] Some of them are also anthelmintic when tested against *Nematospiroides dubius.*[4] Δ^2-1,2,4-Oxadiazolines are partially saturated oxadiazoles and comparatively less work has been done on the former. McCowen et al.[4] have tested a few of them for anthelmintic activity although the results were negative. To our knowledge, the molecular orbital calculations and the fluorescence spectra of oxadiazolines have not yet been reported in the literature. We plan to study the following: (a) absorption and fluorescence spectra, (b) the chemistry of the ring, (c) biological activity, and (d) mass spectra. This article deals principally with item a.

We have already prepared six compounds in small quantities. Activity testing will be undertaken as soon as larger quantities are available. This paper deals with the molecular orbital calculations and the absorption and fluorescence spectra of five oxadiazolines, i.e., 5-ethyl-3-phenyl-Δ^2-1,2,4-oxadiazoline (Ia), 5-ethyl-3-(*p*-tolyl)-Δ^2-1,2,4-oxadiazoline (Ib), 3-(*p*-anisyl)-5-ethyl-Δ^2-1,2,4-oxadiazoline (Ic), 3-(*p*-chlorophenyl)-5-ethyl-Δ^2-1,2,4-oxadiazoline (Id), and 5,5-pentamethylene-3-phenyl-Δ^2-1,2,4-oxadiazoline (III), and one oxadiazole, 5-ethyl-3-phenyl-1,2,4-oxadiazole (II). (See Figure 1.) In addition, an easy formation of II from Ia is discussed.

Experimental Section

The solvents used for spectroscopy were chloroform (Merck, Uvasol) and 2-propanol (Aldrich, spectrograde). Neither had detectable fluorescence upon excitation at the wavelengths used.