Conformations of Saturated Six-Membered-Ring Phosphorus Heterocycles Related to Cyclophosphamide. NMR, X-ray, and Infrared Studies of 2-Methoxy-2-oxo-1,3,2-oxazaphosphorinane and 2-Thio-1,3,2-oxazaphosphorinane

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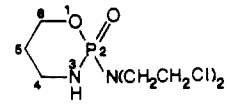
Abstract: The conformations of a series of 2-methoxy-2-oxo- and 2-thio-1,3,2-oxazaphosphorinanes have been investigated. The methoxy substituent on phosphorus causes 5,5-dimethyl-substituted derivatives to populate almost exclusively a chair conformation with MeO axial. The same is true for 5-*tert*-butyl compounds with *t*-Bu and MeO cis. The trans diastereomers, however, depopulate chair conformers in favor of twist forms with pseudoaxial MeO. The population and particular twist conformation favored are dependent on whether the substituent on the ring nitrogen, N(3), is H or Ph. Conversion of chair conformations to the twist form with MeO pseudoaxial is estimated to have a free-energy requirement of only about 2 kcal/mol. X-ray crystallography of 2-methoxy-2-oxo-3-phenyl-1,3,2-oxazaphosphorinane shows the molecule to be in a chair conformation with axial MeO. Certain bond lengths determined when compared with those of other 1,3,2-oxazaphosphorinanes are consistent with the presence of an n–σ^* interaction of the N(3) lone pair with axial substituents on phosphorus which vary with the nature of the N(3) substituent. Infrared results demonstrate clearly the failure of the P=O stretching frequency as an indicator of the P=O orientation without consideration of the substituent at N(3).

The 1,3,2-oxazaphosphorinane ring system is an essential part of the structural features which render cyclophosphamide (**1**) and its congeners, isophosphamide and trophosphamide, active antitumor agents.[1] Microsomal activation of these molecules by C(4) hydroxylation yields potentially diastereomeric products. Furthermore, the diastereomeric *cis*- and *trans*-4-phenylcyclophosphamides have been shown to have efficacies in animal tests which are dependent on the diastereomer employed.[2] A thorough knowledge of the conformational properties of this ring system is vital to an understanding of potential effects of conformation on oxidative activation, the transport properties of metabolites, and metabolite breakdown to cytotoxic products.

Moreover, the 1,3,2-oxazaphosphorinane ring system affords the opportunity to study the effect on the conformational properties of cyclohexane of replacing ring carbon atoms with various heteroatoms. Such replacement results in (1) the alteration of bond angles and lengths, (2) the replacement of ring hydrogen atoms by electron lone pairs attached to heteroatoms, and (3) the introduction of bond and molecular dipoles. 1,3,2-Oxazaphosphorinanes indeed have been found to be very different conformationally from cyclohexanes. Earlier work has pointed out the following: the relative ease energetically for 1,3,2-oxazaphosphorinanes of populating twist conformations,[3] the comparatively small conformational free energy of axial Me_2N on phosphorus when R = H (**2** and **4**),[4] the large increase in conformational free energy of Me_2N with R = Ph (**3** and **5**),[3b,4a] and the progressive increase in the conformational free energies of dialkylamino substituents on phosphorus [Me_2N < Et_2N < $(ClCH_2CH_2)_2N$ < *i*-Pr_2N ($\Delta G°$ to place Z axial rather than equatorial in the equilibrium **12** ⇄ **13**).[4a]



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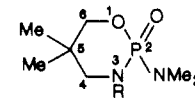
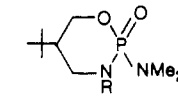
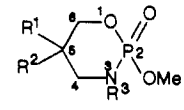


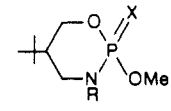
2, R = H
3, R = Ph



4, R = H
5, R = Ph

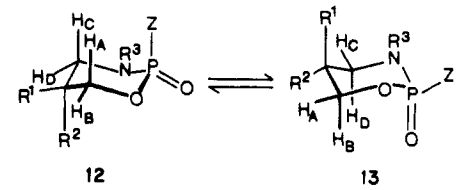


6, R^1 = R^2 = Me, R^3 = H
7, R^1 = R^2 = Me R^3 = Ph



8, R = H, X = O **10**, R = Ph, X = O
9, R = H, X = S **11**, R = Ph, X = S

In contrast to the major measurable effect of the N(3)-substituent change in **2** and **3** on the chair–chair conformational equilibrium **12** ⇄ **13** (Z = Me_2N, R^1 = R^2 = CH_3), we report here that for **6** and **7** (R^1 = R^2 = CH_3, Z = MeO) there is no clearly detectable change in **12**/**13** as a function of R^3 with the very predominant population of **12** in both cases. This result also is in direct contradiction to an earlier report in which **12** ⇄ **13** for the case Z = PhO (R^1 = R^2 = H, Me, and Ph) was said, on the basis of P=O IR frequency changes, to respond dramatically to a change of R^3 from H to Ph,[5] a conclusion we show to be incorrect. Such IR frequencies are demonstrated in the present work to respond to changes in *both* the N(3) substituent and the phosphorus configuration (P=O axial or equatorial). The nature of the N(3) substituent, however, is shown to affect both the specific twist conformer with MeO pseudoaxial formed (**18** or **19**) as well as the extent of the twist form populated.



12 **13**

(1) Two recent reviews by chemists have emphasized both the chemical and pharmacological aspects of cyclophosphamide, its analogues, and related compounds: Zon, G. *Prog. Med. Chem.* **1982**, *19*, 205. Stec, W. *Organophosphorus Chem.* **1982**, *13*, 145. See also: Hill, D. L. *A Review of Cyclophosphamide*; Charles C. Spring: Springfield, IL, 1975. Calvin, M. In *Clinical Pharmacology of Anti-Neoplastic Drugs*; Pinedo, H. M., Ed.; Elsevier: Amsterdam, 1978; pp 245–261. Friedman, O. M.; Myles, A.; Calvin, M. *Adv. Cancer Chemother.* **1979**, *1*, 143.

(2) Boyd, V. L.; Zon, G.; Himes, V. L.; Stalick, J. K.; Mighell, A. D.; Secor, H. V. *J. Med. Chem.* **1980**, *23*, 372.

(3) (a) Bentrude, W. G.; Day, R. O.; Holmes, J. M.; Quin, G. S.; Setzer, W. N.; Sopchik, A. E.; Holmes, R. R. *J. Am. Chem. Soc.* **1984**, *106*, 106. (b) Bajwa, G. S.; Chandrasekaran, S.; Hargis, J. H.; Sopchik, A. E.; Blatter, D.; Bentrude, W. G. *Ibid.* **1982**, *104*, 6385.

(4) I.e., small relative to what it is for 2-oxo-1,3,2-dioxaphosphorinanes: (a) Setzer, W. N.; Sopchik, A. E.; Bentrude, W. G. *J. Am. Chem. Soc.* **1985**, *107*, 2083. (b) Holmes, R. R.; Day, R. O.; Setzer, W. N.; Sopchik, A. E.; Bentrude, W. G. *Ibid.* **1984**, *106*, 2353.

(5) (a) Roca, C.; Kraemer, R.; Majoral, J.-P.; Navech, J.; Brault, J. F.; Savignac, P. *Org. Magn. Reson.* **1976**, *8*, 407. (b) Durrieu, J.; Kraemer, R.; Navech, J. *Ibid.* **1973**, *5*, 407.

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Table I. Coupling Constants (Hz) for ~10% Solutions of 2-Methoxy-1,3,2-oxazaphosphorinanes (**6–11**) at 300 MHz, Ambient Probe Temperature (~25 °C)

compd	solvent	J_{AB}	J_{AX}	J_{BX}	J_{AP}	J_{BP}	J_{CD}	J_{CX}	J_{DX}	J_{CP}	J_{DP}	J_{BD}	J_{POCH_3}
6	C_6D_6	−10.8			0.7	21.0	−13.0			0.5	26.0	3.0	11.0
7	C_6D_6	−10.8			2.4	22.5	−11.9			1.0	20.2	2.1	11.0
cis-**8**	C_6D_6	−11.2	11.0	4.2	2.8	20.7	−12.6	11.6	4.6	4.4	26.6	2.6	10.9
trans-**8**[a]	C_6D_6	−10.9	9.2	3.9	7.6	16.6	−12.0	9.7	5.2	17.2	8.9	<0.2	11.4
cis-**9**	C_6D_6	−11.0	10.8	4.3	4.0	20.9	*b*	11.1	4.5	*b*	*b*	2.3	13.5
	acetone-d_6	−10.8	11.0	3.8	3.6	19.1	−12.4	11.3	4.0	2.1	25.6	2.3	13.8
trans-**9**[a]	C_6D_6	−11.0	9.5	4.4	9.2	18.1	−12.1	8.2	5.9	18.2	9.4	0.7	14.1
cis-**10**	C_6D_6	−11.0	11.2	4.4	4.2	21.4	−11.6	11.2	4.2	2.4	19.6	2.1	11.1
trans-**10**[c]	acetone-d_6	−11.2	9.0	5.4	14.0	11.1	−11.9	9.0	4.7	8.9	12.0	1.0	*c*
cis-**11**	C_6D_6	−10.8	10.6	4.9	7.2	21.3	−12.1	11.0	4.6	4.1	19.4	1.8	13.7
trans-**11**	C_6D_6	−11.1	9.5	5.4	12.0	17.3	−12.0	10.3	4.8	6.9	19.8	0.9	14.1

[a] Iterated and simulated using LAOCN3. [b] H_C and H_D badly overlapped. [c] Analysis done on $POCD_3$ analogue. [d] Additional couplings observed: J_{XP} (−0.7 to −1.1), J_{CY} (Y = proton on N(3)), J_{DY}, and J_{PY}. J_{CP} and J_{DP} were measured under conditions of N(3)H decoupling or following D_2O exchange in key cases.

Table II. ^1H and ^{31}P Chemical Shifts for 2-Methoxy-1,3,2-oxazaphosphorinanes **6–11**[a]

compd	solvent	δ_A[a]	δ_B	δ_C	δ_D	δ_X	δ_{R^1,R^2}[b]	δ_{R^3}[c]	δ_{OMe}[d]	δ ^{31}P
6	C_6D_6	3.47	3.15	2.45	2.27		0.84, 0.84	5.39	3.22	3.8
7	C_6D_6	3.80	3.55	3.28	2.80		0.55, 1.06	6.96–7.47	3.39	0.0[e]
cis-**8**	C_6D_6	3.95	4.11	2.80	3.07	1.64	0.51	5.39	3.58	6.3
trans-**8**	C_6D_6	4.06	4.01	3.06	3.06	1.60	0.70	5.76	3.62	7.8
cis-**9**	C_6D_6	3.93	4.06	3.10–3.15	3.10–3.15	1.49	0.52	2.69	3.51	68.6
	acetone-d_6	4.18	4.30	3.08	3.27	1.79	0.90	2.09	3.61	
trans-**9**	C_6D_6	4.03	3.99	2.79	2.88	1.57	0.56	3.08	3.56	71.6
cis-**10**	C_6D_6	3.90	4.08	3.39	3.28	1.79	0.53	6.99–7.59	3.39	1.2[e]
trans-**10**	acetone-d_6	4.36	4.44	3.62	3.72	2.18	1.01	7.38	*f*	2.5[e]
cis-**11**	C_6D_6	4.00	4.15	3.49	3.29	1.93	0.59	7.00–7.44	3.53	68.0
trans-**11**	C_6D_6	4.21	4.10	3.51	3.28	1.89	0.62	7.00–7.40	3.54	71.5

[a] Measured at 300 MHz. [b] Correspond to substituents at C(5) Me or *t*-Bu. [c] Substituent, H or Ph, on N(3). [d] In $CDCl_3$. [e] δ_Y (H on N(3)) variable. [f] On $POCD_3$ compound.

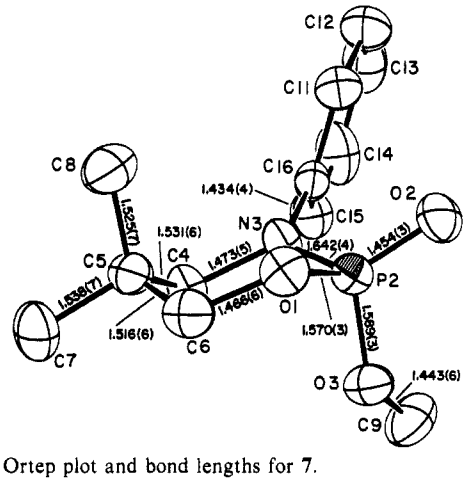


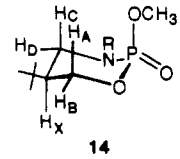
Figure 1. Ortep plot and bond lengths for **7**.

Results

Preparations. The compounds of this study, **6–11**, were prepared following routes analogous to those described for **2–5**.[3b,4] Thus, cyclization of the appropriate amino alcohol with PCl_3/Et_3N, followed by reaction with MeOH and then N_2O_4 or S_8 oxidation, gave the N(3)–Ph compounds **7**, **10**, and **11**. The N(3)–H derivatives resulted in one step from reaction of the amino alcohol with $MeOP(O)Cl_2$ (**6**) or alternatively on treatment with MeOH of the product of a prior reaction of the amino alcohol with $POCl_3$ or $PSCl_3$ (**8** and **9**). Column chromatography effected the separation of the individual diastereomers of **8–11**.

Assignment of Configuration at Phosphorus. A combination of ^1H and ^{31}P NMR techniques along with X-ray crystallography was used to assign the configuration at phosphorus (MeO axial or equatorial) in the predominate conformations populated by **6** and **7** and by the individual diastereomers of **8–11**.

From ^1H NMR couplings, one diastereomer of **8–11** in each case is clearly in the chair conformation with the 5-*t*-Bu equatorial (see below). The assignment of cis geometry (MeO and *t*-Bu, cis) with MeO axial (conformation **14**) to that diastereomer of **8–11** is based on two evidences. First, the order of relative



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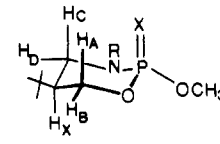

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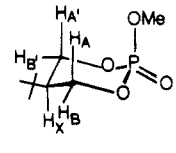
chemical shifts, δ H_A < δ H_B (Table II), is the same as that found for 2-methoxy-1,3,2-dioxaphosphorinane **16** with the established conformation shown[6] as well as other 2-substituted-2-oxo-5-*tert*-butyl-1,3,2-dioxaphosphorinanes.[6a,7] (This order is commonly noted for 5-*tert*-butyl-2-oxo-1,3,2-dioxaphosphorinanes.[8]) Second,



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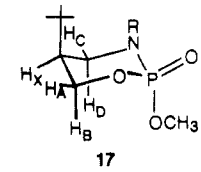

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the ^{31}P NMR chemical shift order based on P–Z orientation, δ ^{31}P (axial) < δ ^{31}P (equatorial), which was noted previously for several 2-oxo- and 2-thio-1,3,2-oxazaphosphorinanes[2,3,9,10] and very

(6) (a) Bentrude, W. G.; Hargis, J. H. *J. Chem. Soc., Chem. Commun.* **1969**, 1113. (b) Bentrude, W. G.; Hargis, J. H. *J. Am. Chem. Soc.* **1970**, *92*, 7136. (c) Warrent, R. W.; Caughlan, C. N.; Hargis, J. H.; Yee, K. C.; Bentrude, W. G. *J. Org. Chem.* **1978**, *43*, 4266 and references therein.

(7) Bentrude, W. G.; Tan, H.-W. *J. Am. Chem. Soc.* **1973**, *95*, 4666.

(8) (a) Bentrude, W. G.; Setzer, W. N. In *^{31}P NMR Spectroscopy in Stereochemical Analysis: Organic Compounds and Metal Complexes*; Verkade, J. G., Quin, L. D., Eds.; VCH: Deerfield Beach, FL, in press. (b) Maryanoff, B. E.; Hutchins, R. O.; Maryanoff, C. A. *Top. Stereochem.* **1979**, *11*, 187–326.

(9) Bajwa, G. S.; Chandrasekaran, S.; Setzer, W. N., unpublished results from this laboratory.

(10) Kinas, R.; Pankiewicz, K.; Stec, W. J.; Farmer, P. B.; Foster, A. B.; Jarman, M. *J. Org. Chem.* **1977**, *42*, 1650.

Table III. Crystal Data for 5,5-Dimethyl-2-methoxy-2-oxo-3-phenyl-1,3,2-oxazaphosphorinane, **7**

molecular formula	$C_{12}H_{18}NO_3P$
M_w	255.25
space group	$P2_{1/c}$ (No. 14)[a]
cell dimensions	
a, Å	14.477 (8)
b, Å	5.939 (4)
c, Å	15.755 (11)
β, deg	105.24 (5)
V, Å^3	1306.9 (14)
Z	4
D_{calcd}, g cm^{-3}	1.30
cryst dimensions, mm	0.4 × 0.4 × 0.4
no. of unique data	2278[b]
absorption coeff (μ_λ), cm^{-1}	1.61

[a] The space group was unambiguously determined by the systematic absences: $h0l$, $l = 2n + 1$; $0k0$, $k = 2n + 1$. [b] All data were used in the calculations.

generally for 2-oxo- and 2-thio-1,3,2-dioxaphosphorinanes,[8b] is observed for **8–11** (Table II). The other diastereomer of **8–11** is thereby the trans one. As noted below, the propensity of the MeO to be axial strongly depopulates chair conformation **15**. However, a fraction of the molecues have the MeO equatorial.

For **7** a single-crystal X-ray structure determination established the axial orientation of the MeO in the chair conformation in the crystal (Ortep perspective view, Figure 1; see Table III for crystal data). ^{1}H NMR (see below) clearly shows a single chair conformation to be very largely populated for both **6** and **7**. In view of the demonstrated strong axial preference in solution of the MeO of *cis*-**8–11**, it is highly probable that **7** is in conformation **12** in solution as well as in the solid phase (X-ray). The relative ^{1}H chemical shift orders, δ $H_A > \delta$ H_B and δ $H_C > \delta$ H_D, are the same for **6** and **7**, showing the MeO orientation to be the same in both molecules.[11] Compounds **6** and **7**, therefore, both have MeO axial in the chair conformation, **12**. [The comparative relative chemical shift orders, δ H_A vs. δ H_B and δ H_C vs. δ H_D, for **6** and *cis*-**8**, for example, would not necessarily be the same even though the MeO is axial in both cases. The presence of a second alkyl (Me) group at the 5-position should have an important influence on chemical shifts.]

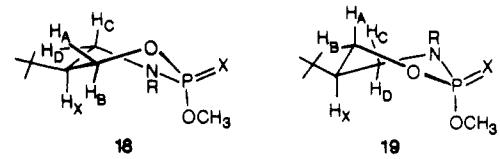
Conformer Populations. Typical of 2-oxo- and 2-thio-1,3,2-oxazaphosphorinanes (as well their 1,3,2-dioxaphosphorinane counterparts), which are very largely in one conformation in solution, is the combination of *large* $^3J_{HP}$ values for those protons equatorial and thus antiperiplanar to phosphorus (e.g., H_B and H_D of **12**) and *small* $^3J_{HP}$ values for axial protons synclinal to phosphorus (e.g., H_A and H_C of **12**).[8a] This situation is in fact observed for **6** and **7** (Table I). The relatively great differences in chemical shifts within the proton pairs H_A/H_B and H_C/H_D at 300 MHz allow an accurate analysis of $^3J_{HP}$ to be made on a first-order basis. For **6** a >95% population of **12** seems certain ($J_{AP} = 0.7$, $J_{BP} = 21.0$ Hz; $J_{CP} = 0.5$, $J_{DP} = 26.0$ Hz). Compound **7** shows more sizable J_{AP} and J_{CP} values, suggestive of greater population of **13**. However, the coupling constants reported[5a] for the PhO analogue of **7** ($J_{AP} = 2.3$, $J_{BP} = 23.5$ Hz; $J_{CP} = 0.7$, $J_{DP} = 21.4$ Hz) are not very different from those for **7** itself. The greater electronegativity of PhO over that of CH_3O should increase the population of **12**. The small, perhaps negligible, difference in $^3J_{HP}$ values between **7** and the phenoxy analogue suggests that the equilibrium **12** $\rightleftarrows$ **13** for **7** is already very nearly anancomeric, i.e., nearly 100% in favor of **12**. The large four-bond couplings, $J_{BD} = 2.1$ and 3.0 Hz, confirm the W arrangement of those protons in **6** and **7**.[8a]

The assignment of chair conformation **14** with *t*-Bu equatorial to the cis diastereomers of **8–11** is clear-cut. The large J_{AX} and J_{CX} values of Table I (10.6–11.6 Hz) combined with small values for J_{BX} and J_{DX} (3.8–4.9 Hz) place the *t*-Bu unmistakably equatorial. Unique for the chair conformation is the combination of large J_{AX} (J_{CX}) and small J_{AP} (J_{CP}) values along with the large J_{BP} (J_{DP}) and small J_{BX} (J_{DX}) combination observed.[6a,8] The J_{BD} values (1.8–3.0 Hz) again are typical of the chair conformation with equatorial H_B and H_D is a W or zigzag configuration.[8a]

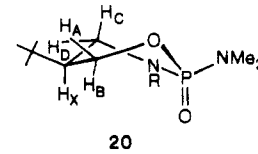
By contrast, for the trans isomers of **8–11**, the axial preference of the MeO manifests itself in a *dramatic depopulation of chair conformation* **15**. (In a number of cases (Table I) computer-assisted LAOCN3 analysis of the spin systems was required because of the chemical-shift close proximity of H_A to H_B and of H_C to H_D.) Thus, throughout the series, J_{AP} and/or J_{CP} values are generally markedly *increased* compared to those of the chair-like cis isomers; conversely, J_{BP} and/or J_{DP} values are strongly *decreased*. Clearly, only minor fractions of *trans*-**8** and -**9** remain in the chair form, **15** (very large J_{CP} relative to J_{DP}). The same is true of *trans*-**10**, although to a lesser degree. Nonetheless, the fact that J_{AP} (14 Hz) is larger than J_{BP} (11 Hz) shows that more than 50% of *trans*-**10** has moved out of conformation **15**. By contrast greater than 50% of *trans*-**11** looks to remain in chair conformer **15**. More precise attempts at assignment of conformer populations for *trans*-**8–11** would be an overinterpretation of the data.

As to the conformers which become population by the trans diastereomers, it is obvious that the 5-*t*-Bu remains largely pseudoequatorial. This conclusion is required by the fact that J_{AX} (9.0–9.5 Hz) and J_{CX} (8.2–10.3 Hz) remain relatively high. (In only one case is J_{CX} below 9.0 Hz.) Assuming reasonable estimated J_{HP} values, approximately 33% of **17** ($J_{BX} \sim 3$ Hz) would be needed to decrease J_{BX} below 9 Hz [(0.67)(11.0) + (0.33)(3) = 8.4 Hz]. Similar arguments can be based on the only minor increases in J_{BX} and J_{DX} noted for *trans*-**8–11**.

Although from the present data precise population assignments to the non-chair conformations occupied by *trans*-**8–11** in preference to **15** to **17** cannot be made, reasonable inferences are possible as to the types of twist forms populated. Earlier work with the trans isomers of **4** and **5** and the 5-phenyl analogue has clearly demonstrated that depopulation of the chair conformation analogous to **14** results in exclusive formation of twist form **20** analogous to **18**.[3] The diagnostic set of coupling constants for



18 **19**



20

20[3] (or **18**) is the combination of large J_{AP} (pseudoequatorial H_A) with simultaneously large J_{AX}. J_{BP} for the pseudoaxial H_B is small, while J_{BX} is somewhat increased. The dihedral angles in the nitrogen side of ring **18** (**20**) are similar to what they are in chair **14** (**15**), i.e., H_C pseudoaxial, H_D pseudoequatorial, and H_X pseudoaxial. Consequently, coupling constants similar to those of chair **14** or **15** are encountered: J_{CX}, large; J_{CP}, small; J_{DX}, small; J_{DP}, large.

Conformer **19** would exhibit opposite effects on observed time-averaged coupling constants. The combination of J_{CX} (large), J_{CP} (large), J_{DX} (small), and J_{DP} (small) is expected. In both **18** and **19**, J_{AX} and J_{CX} should be rather large. However, their precise values will depend on the degree of twisting which occurs. The Karplus relationship for $^3J_{HH}$ predicts that increased twisting should lower J_{AX} and J_{CX} in **18** (**20**) and **19**, respectively.

For *trans*-**8** and *trans*-**9**, compared to those couplings expected for a chair conformation, J_{CP} is markedly *increased* and J_{DP} is *decreased*. This suggests some population of **19**. A smaller increase in J_{AP} and decrease in J_{BP} also is noted as could result from some population of **17** and/or the twist form **18**. By contrast

(11) The relative chemical shifts of H_A/H_B and H_C/H_D are very dependent on the predominant conformer of the **12** $\rightleftarrows$ **13** equilibrium for the series with various R_2N on phosphorus.[4a]

Table IV. Phosphoryl Stretching Frequencies for 2-Methoxy-2-oxo-1,3,2-oxazaphosphorinanes

compd	solvent	$\nu_{P=O}$, cm^{-1}
6	KBr	1260
	CCl_4	1268
7	KBr	1274–1282
	CCl_4	1290
cis-**8**	CCl_4	1267
trans-**8**	CCl_4	1252
cis-**10**	CCl_4	1294
trans-**10**	CCl_4	1261
trans-**4**	KBr	1200
	CCl_4	1220
trans-**5**	KBr	1222
	CCl_4	1236

trans-**10** and *trans*-**11** show greater effects on J_{AP} (increased) and J_{BP} (decreased) than on J_{CP} and J_{DP}. The inference is that twist **18** is the nonchair conformer favored.

Phosphoryl Infrared Frequencies. The infrared stretching frequency for the phosphoryl group (P=O) has been found to correlate in 2-oxo-1,3,2-dioxaphosphorinanes with the axial (lower frequency) or equatorial (higher frequency) orientation of the group.[8b] Recently, this approach was used to attempt to assign the predominant P=O orientation in the POC_6H_5 analogues of **6** and **7** with H, Me, or Ph disubstituted at C(5).[5] The greater stretching frequencies observed for the N(3)Ph compounds were used as evidence to assign their P=O orientations as equatorial, while the lower IR frequencies of the NH counterparts were taken to mean that they possessed axial P=O orientations.

Comparison of the infrared frequencies (Table IV) of *cis*-**8** and *cis*-**10**, both in conformation **14**, shows that substitution of H for Ph at N(3) shifts the absorption strongly to higher frequency *even though the P=O is equatorial (see above) in both cases*. A similar-magnitude higher frequency shift is noted on comparison of **6** and **7**, both in conformation **12**. This leaves little doubt that the 5,5-unsubstituted POPh analogues of **6** and **7** ($R^1 = R^2 = H$) with P=O IR stretching frequencies (KBr) of 1260 and 1282 cm^{-1}, respectively, both also have the P=O equatorial.[5] Conformer **12** is undoubtedly also populated by the reported POPh analogues with $R^1 = R^2 = Me$, $R^3 = Ph$ (IR 1291 cm^{-1}), KBr[5a]) and with $R^1 = R^2 = Ph$, $R^3 = H$ (IR 1265 cm^{-1}, KBr[5b]). The danger in using P=O stretching frequencies alone to assign configuration at phosphorus also is illustrated by looking at those for *trans*-**8** and *trans*-**10**. Both have lower frequency values as compared to their cis counterparts as would be predicted were they primarily in the chair conformation **15** with axial P=O. As pointed out above, this is ruled out by the ^1H NMR results which show twist forms forms to be predominant.

The effect of H or Ph substituent at N(3) on the infrared stretching frequency for *axial* P=O also can be seen (Table IV) for the NH and NPh compounds *trans*-**4** and *trans*-**5**, analogous to *trans*-**8** and *trans*-**10** but with Me_2N in place of MeO, which are indeed almost entirely in conformation **15** with P=O axial.[3] Thus, the effect of substitution at N(3) on IR P=O stretching frequency is operative for *both axial and equatorial P=O*.

Discussion

Studies in Solution. It is evident from the above results that the methoxy group attached to phosphorus in the 2-oxo-1,3,2-oxazaphosphorinane ring system has a marked preference for the axial position. We noted previously that the Me_2N can be more readily accommodated in the axial position of **2** and of *cis*-**4** than in the 2-oxo-1,3,2-dioxaphosphorinane system.[3b,4] However, the very strongly axial preference of the *MeO* of **6**–**11** is exactly parallel to what is known for the 2-oxo-1,3,2-dioxaphosphorinanes.[6,8]

As a consequence of the strong axial preference of MeO, there is no readily discernible, quantifiable effect on the equilibrium **12** ⇄ **13** of replacing the H on N(3) with Ph. A phenyl substituent at N(3) fails as well to measurably depopulate the chair conformer **14** (compare *cis*-**8** vs. *cis*-**10** and *cis*-**9** vs. *cis*-**11**), whereas axial Me_2N on phosphorus in **2**–**5** is strongly destabilized by a Ph at

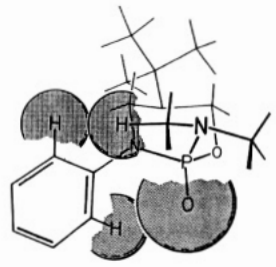
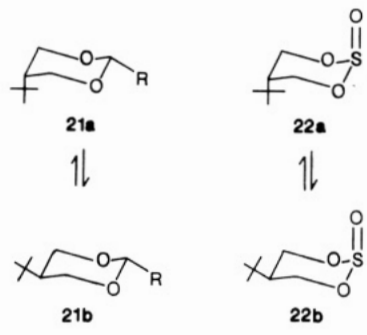


Figure 2. Me_2N/N(3)Ph steric repulsions in *cis*-**5** based on a Dreiding model. Hemispheres approximate atomic radii (taken from ref 3b).

N(3). This is seen in greatly increased populations of conformer **13** and **20**.[3b,4a] According to space-filling molecular models, the latter effect has its origins in the steric interactions shown in Figure 2[3b] which are relieved when the Me_2N is reoriented to become equatorial or pseudoequatorial. Through inductive effects, the phenyl substituent at N(3) may also render the N(3) lone pair less available for stabilizing n–σ^* overlap with the σ^* orbital of the axial substituent, Me_2N or MeO (the anomeric effect[12]). The MeO may be small enough to be relatively unperturbed in the axial positions by steric repulsions involving the phenyl at N(3). In addition, being more electronegative than Me_2N, the MeO likely enhances the n–σ^* interaction enough to offset whatever destabilizing effects the presence of a phenyl at N(3) may have on an axial MeO.

In any event, small changes in the equilibria involving **12**, **13**, and **14** for the MeO compounds would be difficult to discern since the equilibria are in all cases biased toward structures with MeO axial. One cannot attach quantitative figures to the small effects seen on the J_{HP} values. However, it appears very unlikely that the effect of N(3) substitution on $\Delta\Delta G°$ (H vs. Ph) for the **12**/**13** ratio with the MeO compounds is nearly as great as that measured[3b,4a] for the Me_2N derivatives (1.2–1.6 kcal/mol), especially in view of the similarity of coupling constants for **7** and the PhO analogue (see Results). This result is what we would expect for the electronegative, sterically small MeO.

The depopulation of **15** demonstrates clearly the ready accessibility to 1,3,2-oxazaphosphorinanes of twist conformations.[3] Thus, rather than assume conformation **17** with 5-*t*-Bu axial, twist forms with 5-*t*-Bu pseudoequatorial are populated. For 1,3-dioxanes (**21**)[13] and cyclic sulfites (**22**),[14] the axial to equatorial *t*-Bu



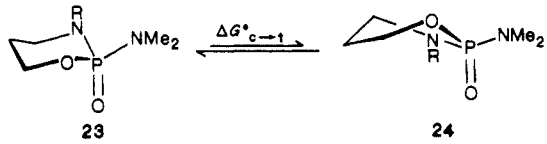
reorientation shown in **21a** → **21b** and **22a** → **22b** gains 1.5–2.0 kcal/mol [$\Delta G°_{25}$ (ax → eq)]. Assuming that $\Delta G°_{25}$ (ax → eq) for the 5-*t*-Bu of **8**–**11** is similar, the inference from the failure of *cis*-**8** and *cis*-**10** to accommodate the axial preference of the MeO by population of **17** to more than a very minor extent is that it costs no more than about 2 kcal/mol to convert the chair conformation of **17** to nonchair conformers such as **18** and **19** with the 5-*t*-Bu pseudoequatorial.

(12) Kirby, A. J. *The Anomeric Effect and Related Stereoelectronic Effects at Oxygen*; Spring-Verlag: West Berlin, Heidelburg, New York, 1983.
(13) (a) Eliel, E. L.; Knoeber, M. C. *J. Am. Chem. Soc.* **1968**, *90*, 3444. (b) Riddell, F. G.; Robinson, M. J. T. *Tetrahedron* **1967**, *23*, 3417.
(14) (a) van Woerden, H. F.; Havinga, E. *Recl. Trav. Chim. Pays-Bas* **1967**, *86*, 341, 353. (b) van Woerden, H. F.; Cerfontain, H.; Green, C. H.; Reijerkerk, R. J. *Tetrahedron Lett.* **1968**, 6107.

Table V. Bond Lengths (Å) in 5,5-Dimethyl-2-methoxy-2-oxo-1,3,2-oxazaphosphorinane, **7**

atoms		atoms	
P(2)–O(2)	1.454 (3)	C(5)–C(7)	1.538 (7)
P(2)–N(3)	1.642 (4)	C(5)–C(8)	1.525 (7)
P(2)–O(1)	1.570 (3)	O(3)–C(9)	1.443 (6)
P(2)–O(3)	1.589 (3)	C(16)–C(11)	1.383 (6)
N(3)–C(16)	1.434 (4)	C(11)–C(12)	1.403 (6)
N(3)–C(4)	1.473 (5)	C(12)–C(13)	1.361 (8)
O(1)–C(6)	1.466 (6)	C(13)–C(14)	1.370 (7)
C(4)–C(5)	1.531 (6)	C(14)–C(15)	1.398 (6)
C(5)–C(6)	1.516 (6)	C(15)–C(16)	1.389 (6)

Our earlier work had demonstrated that $\Delta G°_{25}$ for the chair → twist conversion **23** → **24**, to form the twist conformer with P=O pseudoaxial ($\Delta G°_{c\to t}$), is not greater than 1 kcal/mol.[3] It should be emphasized that converting **15** or **17** to **18** or **19** *requires the formation of a twist form with MeO rather than P=O pseudoaxial.* Bowsprit interactions between pseudoaxial CH_3O and H_X (**18** and **19**) or pseudo 1,3-synaxial repulsions involving CH_3O and a proton at C(4) or C(6) may be larger than those for a pseudoaxial phosphoryl oxygen. It is not surprising, therefore, that the $\Delta G°_{c\to t}$ component of the **15** → **18** (**19**) or **17** → **18** (**19**) conversions should be greater than $\Delta G°_{c\to t}$ for **23** → **24**.



23 **24**

Among the most noteworthy of the conformational findings of this work is the evidence that unlike the case for *cis*-**5**[3b] (and the 5-Ph analogue[3a]), *more than one nonchair conformation* is accessible to *trans*-**8**–**11**. A simple explanation for the population of **18** or **24** by the N(3)–Ph substituted cases, e.g., *cis*-**5** and *trans*-**10** and -**11**, is the fact, shown readily by Dreiding models, that twisting the boat conformation with P and C(5) in the bowsprit positions to form **18** or **24** moves the N(3)–Ph away from the substituents on phosphorus. In **19** or the analogous counterpart of **24**, these substituents retain the closer spacial proximity to N(3) they experience in the boat form. Apparently, this twist form is the more favored one in the absence of the bulky Ph at N(3).

Interestingly, the chair ⇄ non-chair equilibria for *trans*-**10** and *trans*-**11** are different, apparently dependent on whether oxygen or sulfur is attached to phosphorus. The origin of this effect is unknown. This difference is not seen with *trans*-**8** and *trans*-**9**.

Finally, it should be noted that *trans*-**10** and *trans*-**11** with Ph at N(3) not only predominately populate different non-chair conformations than do their N(3)H counterparts, *trans*-**8** and *trans*-**9**, but also appear to remain in the chair form to a greater extent. (Couplings constant comparisons are in Table I.) To become pseudoaxial in the twist conformation **18** or **19**, the axial propensity of MeO ($\Delta G°_{MeO}$) must overcome $\Delta G°_{c\to t}$. The values of $\Delta G°_{MeO}$ and $\Delta G°_{c\to t}$ may be closely enough balanced that MeO/NPh steric and/or electronic factors become important. This contrasts with the observation for *cis*-**10** and *cis*-**11** for which $\Delta G°_{MeO}$, regardless of the presence of Ph at N(3), overwhelms the relatively small 1,3-syn axial repulsions associated with the axial MeO.

X-ray Structure. There are some notable features of the X-ray structure of **7** (Tables V–VII and Figure 1). The endocyclic P(2)–O(1) bond length, 1.570 (3) Å, is comparable to those found in *trans*-2-methoxy-5-*t*-Bu-2-oxo-1,3,2-dioxaphosphorinane (1.568 Å).[6c] The axial P(2)–O(3) bond, 1.589 (3) Å, is longer in **7** than in the above 5-*t*-Bu compound (1.567 Å[6c]). Interestingly, the endocyclic P(2)–N(3) bond, 1.642 (4) Å, is shorter than those found in *cis*-**5**, 1.661 (2) Å,[15] or in the analogous *cis*-2-oxo-2-(dimethylamino)-3,5-diphenyl-1,3,2-oxazaphosphorinane, 1.656 (3) Å,[3a] both of which adopt twist conformations. Both *trans*-4-phenylcyclophosphamide (Ph and mustard, trans)[2,16] and 5,5-dimethyl-2-(dimethylamino)-2-oxo-1,3,2-oxazaphosphorinane (**2**)[4b] adopt chair conformations with the dialkylamino substituent axial in the solid state. The endocyclic P(2)–N(3) bond lengths for these two compounds are 1.620 (3) and 1.626 (5) Å, respectively. These two compounds, having no substituent at N(3) and axial dialkylamino substituents on phosphorus rather than methoxy, have shorter P(2)–N(3) bonds than those found in **7**.

Table VI. Bond Angles (deg) in 5,5-Dimethyl-2-methoxy-2-oxo-1,3,2-oxazaphosphorinane, **7**

atoms		atoms	
O(2)–P(2)–N(3)	115.1 (2)	N(3)–C(16)–C(15)	119.4 (3)
O(2)–P(2)–O(1)	113.5 (2)	C(4)–C(5)–C(6)	109.2 (4)
O(1)–P(2)–N(3)	104.5 (2)	C(4)–C(5)–C(7)	108.4 (4)
O(2)–P(2)–O(3)	115.1 (2)	C(4)–C(5)–C(8)	110.7 (4)
N(3)–P(2)–O(3)	106.9 (2)	C(6)–C(5)–C(7)	107.4 (3)
O(1)–P(2)–O(3)	100.2 (2)	C(6)–C(5)–C(8)	110.4 (4)
O(1)–C(6)–C(5)	112.9 (3)	C(11)–C(12)–C(13)	120.3 (4)
P(2)–N(3)–C(4)	115.9 (2)	C(12)–C(13)–C(14)	120.5 (4)
P(2)–N(3)–C(16)	123.8 (3)	C(13)–C(14)–C(15)	120.6 (4)
P(2)–O(1)–C(6)	118.7 (3)	C(14)–C(15)–C(16)	118.9 (4)
N(3)–C(4)–C(5)	111.7 (3)	C(15)–C(16)–C(11)	120.3 (3)
N(3)–C(16)–C(11)	120.3 (3)		

Table VII. Selected Torsion Angles (deg)[a] in 5,5-Dimethyl-2-methoxy-2-oxo-3-phenyl-1,3,2-oxazaphosphorinane, **7**

atoms	
O(1)–P(2)–N(3)–C(4)	−45.9 (3)
P(2)–N(3)–C(4)–C(5)	56.1 (4)
N(3)–C(4)–C(5)–C(6)	−58.3 (5)
C(4)–C(5)–C(6)–O(1)	56.3 (5)
C(5)–C(6)–O(1)–P(2)	−53.8 (5)
C(6)–O(1)–P(2)–N(3)	44.7 (3)
O(1)–C(6)–C(5)–C(7)	173.7 (4)
O(1)–C(6)–C(5)–C(8)	−65.6 (5)
N(3)–C(4)–C(5)–C(7)	−175.0 (4)
N(3)–C(4)–C(5)–C(7)	63.5 (5)
P(2)–N(3)–C(16)–C(11)	−63.1 (5)
P(2)–N(3)–C(16)–C(15)	119.0 (4)
C(4)–N(3)–C(16)–C(11)	123.1 (5)
C(4)–N(3)–C(16)–C(15)	−54.8 (6)
O(2)–P(2)–O(1)–C(6)	170.8 (3)
O(2)–P(2)–N(3)–C(4)	−171.1 (3)
O(2)–P(2)–N(3)–C(16)	14.9 (4)
O(2)–P(2)–O(3)–C(9)	−71.0 (4)
O(1)–P(2)–O(3)–C(9)	166.9 (3)
N(3)–P(2)–O(3)–C(9)	58.1 (4)

[a] Torsion angles for A–B–C–D are defined as positive for a clockwise rotation of C–D toward A–B while looking down the B–C bond.

The structural comparisons between these compounds are consistent with the stereoelectronic effect deemed primarily responsible for the anomeric effect,[12] i.e., interaction of the N(3) lone pair with the axial P(2)–O(3) σ^* orbital (vide supra). On this basis, ring nitrogen (higher energy, more diffuse lone pair) should be a better π-donor than ring oxygen, and this is manifested in the longer P(2)–O(3) bond length observed in **7** than in analogous 1,3,2-dioxaphosphorinanes. A phenyl-substituted ring nitrogen lone pair, however, due to the inductive electron-withdrawing nature of phenyl, should interact to a lesser degree than the unsubstituted N(3), and this expectation is reflected in the longer P(2)–N(3) bond length in **7** than in the 1,3,2-oxazaphosphorinanes with no N(3) substituents. (The change of R_2N to MeO in the compounds should enhance the N(3)–σ^* interaction and *shorten* the P(2)–N(3) bond. The P(2)–N(3) bond *lengthening* effect, therefore, cannot result from the difference in substituents on phosphorus.) Finally, those 1,3,2-oxazaphosphorinanes (*cis*-**5**, e.g.) which adopt twist conformations (phenyl substituents at N(3)) have pseudoequatorial Me_2N. This essentially turns off the P–N anomeric effect interactions with Z, and the P(2)–N(3)

(15) Unpublished X-ray data and: Bajwa, G. S.; Bentrude, W. G.; Pantaleo, N. S.; Newton, M. G.; Hargis, J. H. *J. Am. Chem. Soc.* **1979**, *101*, 1602.

(16) Himes, V. L.; Mighell, A. D.; Stalick, J. K.; Zon, G. *Acta Crystallogr., Sect. B* **1982**, *B38*, 1009.

bonds are, as expected, longer than that in **7**, in which the anomeric effect is presumably operating. For **7**, a more electronegative MeO is present rather than Me_2N, which may also contribute to the shortening of the P(2)–N(3) bond. These findings suggest that *n-6* interactions as well as steric Z/N(3)R repulsions may be important* in the observed effects on conformation of the nature of the N(3) substituent.

The ring nitrogen in **7** is planar. The sum of the bond angles around N(3) is 359.7°, indicating sp^2 hybridization. There is little, if any, conjugation of the N(3) lone pair with the phenyl substituent as the plane of the phenyl group is nearly perpendicular to the plane formed by P(2), N(3), and C(4). This is evidenced by the P(2)–N(3)–C(16)–C(11) dihedral angle of −63.1°. The phosphorus end of the oxazaphosphorinane ring is flattened to a degree comparable to that observed in 1,3,2-dioxaphosphorinanes with axial substituents at phosphorus.[6c] The angle ϕ between the O(1), P(2), N(3) plane and the O(1), N(3), C(4), C(6) plane is 39.2°, while the angle θ between the planes C(4), C(5), C(6) and O(1), N(3), C(4), C(6) is 51.2°. These are usual for 2-oxo-1,3,2-oxazaphosphorinanes with axial phosphorus substituents.[4b,15] Finally, the dihedral angle C(9)–O(3)–P(2)–O(2) is −71.0°.

Conclusions

The conformational properties of 2-methoxy-2-oxo- and 2-thio-1,3,2-oxazaphosphorinanes are greatly influenced by the strong axial preference of the MeO. 1,3-Syn axial repulsions are easily overcome when chair conformations with MeO axial, such as **12** and **14**, are available. However, depopulation of chair **16** in favor of **17** requires enough energy (~2 kcal/mol) that twist forms, **18** or **19**, are favored instead. This confirms the relative energetic ease of assuming a twist conformation. Whether **18** or **19** predominates depends on the substituent, H or Ph, at N(3). This factor also determines the extent to which conformer **17** is depopulated. Phosphoryl infrared stretching frequency alone is a poor indicator of the axial or equatorial orientation of P=O, as the substituent at N(3) is very important. Comparisons of bond lengths in the X-ray structure of **7** with those of similar 1,3,2-oxazaphosphorinanes are consistent with the idea that stereoelectronic factors (n–σ*) as well as steric effects may be operative in the observed influence of the N(3) substituent on conformational equilibria.

Experimental Section

Methods and Materials. Analyses were carried out by Atlantic Microlab, Inc., Atlanta, GA, and Galbraith Laboratories, Inc., Knoxville, TN. Melting points are uncorrected. Gas chromatograms were routinely performed on an HP 5830 thermal conductivity instrument using silanized 3–4% QF-1 on 80/100 Gas-Chrom Q in 0.25-in. glass columns. Infrared spectra were obtained on a Perkin-Elmer 298 spectrophotometer. ^1H NMR spectra were taken on a Varian SC 300 spectrometer, operated in the FT mode, or on a Varian EM 390 CW instrument. Coupling constants were measured at 300 MHz on 100-Hz expansions, 32K data points, 5.46-s acquisition times, and are probably accurate to ±0.2 Hz. The spectra of *trans*-**8**–**11** were iteratively analyzed with the LAOCN3 program. ^{31}P NMR spectra were taken at 32.2 MHz on a Varian FT-80A spectrometer under proton noise decoupling conditions. Positive ^{31}P chemical shifts are in δ (parts per million) downfield from external 85% H_3PO_4. Mass spectra were obtained on a VG Micromass 7070 double-focusing high-resolution instrument with VG Data System 2000 operated in the EI mode using direct inlet sampling.

2-Methoxy-2-oxo-5,5-dimethyl-1,3,2-oxazaphosphorinane, 6. A solution of methyl phosphorodichloridate (Aldrich Chemical Co., 2.54 mL, 3.78 g, 25.4 mmol) in anhydrous ethyl acetate (50 mL) was added slowly to a rapidly stirred solution of 2-(hydroxymethyl)-2-methylpropylamine[4b] (2.62 g, 25.4 mmol) and anhydrous triethylamine (7.08 mL, 5.14 g, 50.8 mmol) in anhydrous ethyl acetate (100 mL), cooled to 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 2 days. The triethylamine hydrochloride was filtered off, and the solvents were removed from the filtrate. The crude product was recrystallized from ethyl acetate/pentane to give 3.52 g of **1** (79% yield) as a colorless crystalline solid: mp 112–114 °C; ^{31}P NMR (C_6D_6) δ 3.79; IR (KBr) 3265 (N–H), 2960, 1478, 1392, 1260 (P=O), 1094, 1057, 1033, 1000, 960, 875, 840, 786 cm^{-1}; mass spectrum, *m/e* (relative intensity) 179 (5%, M^+), 124 (100%), 94 (21%), 56 (33%), 41 (31%), 30 (91%). Anal. Calcd for $C_6H_{14}NO_3P$: C, 40.22; H, 7.88; P, 17.29. Found: C, 40.25; H, 7.94; P, 17.46.

2-Chloro-3-phenyl-5,5-dimethyl-1,3,2-oxazaphosphorinane. A solution of phosphorus trichloride (6.61 mL, 10.4 g, 7.58 mmol), diluted with anhydrous ethyl ether to 100 mL and a solution of *N*-phenyl-2-(hydroxymethyl)-2-methylpropylamine[4a] (13.6 g, 7.58 mmol) and triethylamine (21.13 mL, 15.34 g, 15.16 mmol), diluted to 100 mL with anhydrous ethyl ether, were added simultaneously, via syringe drive pump, to cooled (0 °C), rapidly stirred ether (300 mL), under argon atmosphere at a rate of 2 mL/min. Upon completion of the addition, the reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction mixture was filtered under argon atmosphere, and the solvents were removed from the filtrate in vacuo. The residue was Kugelrohr distilled from bulb to bulb with an air bath temperature of 90 °C at 0.1 torr to give 14.31 g (77.5% yield) of 2-chloro-3-phenyl-5,5-dimethyl-1,3,2-oxazaphosphorinane as a colorless crystalline solid: ^1H NMR (90 MHz, $CDCl_3$) δ 0.94 (s, 3 H, CCH_3), 1.24 (s, 3 H, CCH_3), 2.76–2.98 (ddd, 1 H, CHN), 3.42–3.78 (m, 2 H, CHO, CHN), 4.14–4.33 (dd, 1 H, CHO), 7.05–7.40 (m, 5 H, Ph); ^{31}P NMR ($CDCl_3$) δ 145.1.

2-Methoxy-3-phenyl-5,5-dimethyl-1,3,2-oxazaphosphorinane. A solution of absolute methanol (0.814 mL, 0.644 g, 20.1 mmol) and anhydrous triethylamine (2.80 mL, 2.04 g, 20.1 mmol) in anhydrous ethyl ether (50 mL) was added slowly to a rapidly stirred solution of 2-chloro-3-phenyl-5,5-dimethyl-1,3,2-oxazaphosphorinane (4.90 g, 20.1 mmol) in anhydrous ethyl ether (250 mL), cooled to 0 °C under an argon atmosphere. The reaction mixture was allowed to warm to room temperature and stirred overnight. The triethylamine hydrochloride was filtered off, and the solvents were removed from the filtrate to give 4.37 g (90.9% crude yield) of 2-methoxy-3-phenyl-5,5-dimethyl-1,3,2-oxazaphosphorinane as a colorless oil which was used without further purification: ^1H NMR (90 MHz, $CDCl_3$) δ 0.80 (s, 3 H, CCH_3), 1.15 (s, 3 H, CCH_3), 2.71–3.94 (ddd, 1 H, CHN), 3.13-3.64 (m, 2 H, CHN, CHO), 3.38 (d, J = 11.4 Hz, 3 H, OCH_3), 3.91–4.08 (dd, 1 H, CHO), 6.88–7.30 (m, 5 H, Ph); ^{31}P NMR ($CDCl_3$) δ 124.6.

2-Methoxy-2-oxo-3-phenyl-5,5-dimethyl-1,3,2-oxazaphosphorinane, 7. A solution of 2-methoxy-3-phenyl-5,5-dimethyl-1,3,2-oxazaphosphorinane (3.92 g, 16.4 mmol) in anhydrous dichloromethane (100 mL) was cooled to −20 °C. The material was oxidized by dropwise addition of a saturated solution of dinitrogen tetroxide in dichloromethane. The reaction mixture was warmed to room temperature and the solvent removed in vacuo to give 4.52 g of a brown oil. A 1.23-g sample of the crude product was chromatographed by MPLC on Merck silica gel 60, eluting with EtOAc/EtOH (9:1) to give 1.08 g (95% yield) of **7** as a pale-yellow crystalline solid, a sample of which was recrystallized from ethyl acetate/pentane: mp 48–50 °C; ^1H NMR (90 MHz, $CDCl_3$) δ 0.86 (s, 3 H, CCH_3), 1.21 (s, 3 H, CCH_3), 2.81–4.10 (m, 4 H, CH_2N, CH_2O), 3.61 (d, J = 12 Hz, 3 H, OCH_3), 6.98–7.30 (m, 5 H, Ph); ^{31}P NMR ($CDCl_3$) δ 0.00; IR (KBr) 3051, 3035, 2971, 2955, 2892, 2876, 1596, 1495, 1467, 1452, 1347, 1329, 1274–1282 (s, P=O), 1196, 1188, 1109, 1072, 1045, 1035, 1025, 1008, 1001, 972, 892, 843, 796, 766, 697, 627 cm^{-1}; mass spectrum, *m/e* (relative intensity) 255 (18%, M^+), 200 (100%), 186 (23%), 106 (63%), 77 (19%). Anal. Calcd for $C_{12}H_{18}NO_3P$: C, 56.46; H, 7.11; P, 12.13. Found: C, 56.30; H, 7.16; P, 12.03.

***cis*- and *trans*-2-Methoxy-2-oxo-5-*tert*-butyl-1,3,2-oxazaphosphorinane, 8.** Phosphorus oxychloride (2.37 g, 15.6 mmol), diluted with anhydrous tetrahydrofuran to 25 mL, and a solution of 2-(hydroxymethyl)-3,3-dimethylbutylamine[3b] (2.0 g, 15.2 mmol) and triethylamine (3.1 g, 30.7 mmol), diluted to 25 mL with anhydrous tetrahydrofuran, were added simultaneously and dropwise to cooled (0 °C), rapidly stirred tetrahydrofuran (100 mL), under a nitrogen atmosphere. The reaction mixture was stirred at 0 °C for 1.5 h and for an additional 2.5 h at room temperature. The triethylamine hydrochloride was filtered off, and the volatile materials were removed from the filtrate in vacuo. The residue was redissolved in anhydrous tetrahydrofuran (50 mL). A solution of absolute methanol (0.5 g, 15.6 mmol) and triethylamine (1.6 g, 15.8 mmol) was added and the reaction mixture stirred for 2 days. The triethylamine was filtered off and the solvent removed in vacuo. The residue (3.15 g) was chromatographed on silica gel using a gravity column, eluting with ethyl acetate/hexane (beginning with 1:1 and increasing the percentage of ethyl acetate), to give 0.127 g of GLC-pure *cis*-**8**, 1.12 g of GLC-pure *trans*-**8**, and 0.703 g of a mixture of the two diastereomers. Anal. Calcd for $C_8H_{18}NO_3P$: C, 46.37; H, 8.76; P, 14.95. Found (mixture of diastereomers): C, 46.17; H, 8.74; P, 15.35.

***cis*- and *trans*-2-methoxy-2-thio-5-*tert*-butyl-1,3,2-oxazaphosphorinane, 9,** were prepared by a procedure analogous to that for **8** using thiophosphoryl chloride (2.58 g, 15.2 mmol), 2-(hydroxymethyl)-3,3-dimethylbutylamine (2.0 g, 15.2 mmol), and triethylamine (3.08 g, 30.4 mmol), followed by methanol (0.73 g, 22.9 mmol) and triethylamine (2.31 g, 22.8 mmol). Chromatographic separation on silica gel, eluting with ethyl acetate/pentane (initially 1:50, increasing percent ethyl acetate to 1:25), gave 0.105 g of GLC-pure *cis*-**9** (mp 63–64 °C), 0.395 of

GLC-pure *trans*-**9** (mp 56–58 °C), and a 2.20-g mixture of the two diastereomers. Anal. Calcd for $C_8H_{18}NO_2PS$: C, 43.04; H, 8.13; P, 13.87. Found (mixture of diastereomers): C, 43.09; H, 8.21; P, 13.77.

***cis*- and *trans*-2-Methoxy-3-phenyl-5-*tert*-butyl-1,3,2-oxazaphosphorinane.** A solution of absolute methanol (2.0 g, 62 mmol) and anhydrous triethylamine (5.0 g, 49 mmol) in anhydrous ethyl ether (50 mL) was added slowly to a cooled (0 °C), rapidly stirred solution of 2-chloro-3-phenyl-5-*tert*-butyl-1,3,2-oxazaphosphorinane[3b] (6.0 g, 22 mmol), in anhydrous ethyl ether (100 mL) under a nitrogen atmosphere. The reaction mixture was allowed to warm to room temperature and stirred for 24 h. The triethylamine hydrochloride was filtered off, the volatile materials were removed by rotary evaporation, and the residue was distilled (bp 140–141 °C/1.5 torr) to give 4.0 g of GLC-pure 2-methoxy-3-phenyl-5-*tert*-butyl-1,3,2-oxazaphosphorinane (68% yield): ^{1}H NMR (90 MHz, $CDCl_3$) δ 0.90 (s, 9 H, $C(CH_3)_3$), 1.69–2.10 (m, 1 H, methine H), 3.42 (d, J_{PH} = 12 Hz, 3 H, OCH_3), 3.29–3.82 (m, 2 H, NCH_2), 3.82–4.33 (m, 2 H, OCH_2), 6.78–7.40 (m, 5 H, aromatic); ^{31}P NMR ($CDCl_3$) δ 133.90 and 130.15 (intensity ratio 15:85).

***cis*- and *trans*-2-Methoxy-2-oxo-3-phenyl-5-*tert*-butyl-1,3,2-oxazaphosphorinane, 10.** A solution of N_2O_4/dichloromethane (9 mL of 3.2% wv) was slowly added to a cooled (−70 °C) solution of *cis*- and *trans*-2-methoxy-3-phenyl-5-*tert*-butyl-1,3,2-oxazaphosphorinane (2.7 g, 10 mmol) in anhydrous dichloromethane (80 mL). The reaction mixture was warmed to room temperature, and the solvent was removed in vacuo to give 2.7 g of a yellow oil. A 0.5-g sample of the crude product was chromatographed on silica gel using a gravity column, eluting with ethyl ether to give 150 mg of GLC-pure *cis*-**10** as a colorless oil [^{31}P NMR ($CDCl_3$) δ 1.21; mass spectrum, *m/e* (relative intensity) 283 (33%, M^+), 201 (13%), 200 (100%), 106 (58%), 77 (10%), 42 (13%)] and 150 mg of GLC-pure *trans*-**10** as a colorless oil [^{31}P NMR ($CDCl_3$) δ 2.47; mass spectrum, *m/e* (relative intensity) 283 (31%, M^+), 201 (11%), 200 (100%), 106 (39%), 105 (10%), 77 (11%), 42 (13%).

Similarly, the $POCD_3$ compound was prepared, and the trans isomer was isolated for ^{1}H NMR analysis.

***cis*- and *trans*-2-Methoxy-2-thio-3-phenyl-5-*tert*-butyl-1,3,2-oxazaphosphorinane, 11.** Sulfur (120 mg, 3.7 mmol) was added to a stirred solution of *cis*- and *trans*-2-methoxy-3-phenyl-5-*tert*-butyl-1,3,2-oxazaphosphorinane (1.0 g, 3.7 mmol) in benzene (40 mL). The reaction mixture was stirred at room temperature for 2 h, heated to 40 °C, and stirred for an additional 2 h. The benzene was removed by rotary evaporation to leave 1.09 g of crude product. A small amount of the crude product was distilled (160 °C/0.4 torr) to give an analytically pure mixture (46:54 by GLC analysis) of *cis*- and *trans*-**11**. Anal. Calcd for $C_{14}H_{22}NO_2PS$: C, 56.17; H, 7.41; P, 10.35. Found: C, 56.32; H, 7.73; P, 10.35. A 1.0-g sample of the crude product was chromatograted on a gravity column of silica gel, eluted with ethyl acetate/hexane (1:20), to give 200 mg of GLC-pure *cis*-**11** and 500 mg of GLC-pure *trans*-**11**.

X-ray Single-Crystal Structure Study of 7. Clear, colorless crystals of **7**, suitable for X-ray, diffraction, were obtained by vapor diffusion of a solution of the compound in diethyl ether with *n*-pentane. A well-formed crystal was mounted on a Syntex P$\bar{1}$ auto diffractometer equipped with a scintillation counter and graphite monochromated Mo Kα radiation. The automatic centering, indexing, and least-squares routines were carried out on 15 reflections in the 2θ range 20–25° to obtain the cell dimensions which are given in Table IV. The data were reduced to F_o and $\sigma(F_o)$. Lorentz and polarization factors were applied to all reflections. The θ–2θ scan mode over the range $3.5 \leq 2\theta \leq 50°$ was used to collect the data, all of which were used in the calculations.

The structure was solved by direct methods and refined by full-matrix least-squares techniques.[17] Hydrogen atoms were added to the model in geometrically ideal positions and refined isotropically. Refinement converged at $R = \sum||F_o| - |F_c||/\sum|F_o| = 0.0614$ and $R_w = \sum w^{1/2}|F_o - F_c|/\sum w^{1/2}|F_o| = 0.0634$.

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Registry No. 6, 103752-08-5; **7**, 103752-09-6; *cis*-**8**, 103752-10-9; *trans*-**8**, 103752-04-1; *cis*-**9**, 103752-11-0; *trans*-**9**, 103752-05-2; *cis*-**10**, 103752-12-1; *trans*-**10**, 103752-06-3; *cis*-**11**, 103752-13-2; *trans*-**11**, 103752-07-4; 2-(hydroxymethyl)-2-methylpropylamine, 26734-09-8; 2-chloro-3-phenyl-5,5-dimethyl-1,3,2-oxazaphosphorinane, 103752-14-3; *N*-phenyl-2-(hydroxymethyl)-2-methylpropylamine, 94844-02-7; 2-methoxy-3-phenyl-5,5-dimethyl-1,3,2-oxazaphosphorinane, 103752-15-4; phosphorous oxychloride, 10025-87-3; 2-(hydroxymethyl)-3,3-dimethylbutylamine, 15521-17-2; thiophosphoryl chloride, 3982-91-0; *cis*-2-methoxy-5-*tert*-butyl-1,3,2-oxazaphosphorinane, 103752-16-5; *trans*-2-methoxy-2-phenyl-5-*tert*-butyl-1,3,2-oxazaphosphorinane, 103752-17-6; 2-chloro-3-phenyl-5-*tert*-butyl-1,3,2-phosphorinane, 83096-42-8; methyl phosphorodichloridate, 677-24-7; phosphorous trichloride, 7719-12-2.

Supplementary Material Available: Tables of fractional atomic coordinates and thermal parameters, and hydrogen atom fractional coordinates for **7** (2); tables of structure factor amplitudes for **7** (10 pages). Ordering information is given on any current masthead page.

(17) All calculations were performed with the Shelxtl program system written by G. M. Sheldrick.

Tritriptycene: A D_{3h} C_{62} Hydrocarbon with Three U-Shaped Cavities†

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Abstract: The first synthesis of tritriptycene **6** (5,7,9,14,16,18,28,33-octahydro-28,33[1′,2′]-benzeno-7,16[2′,3′]-anthraceno-5,18[1′,2′]:9,14[1″,2″]-dibenzenoheptacene) from the readily available pentiptycene **9** in six steps and 11% overall yield is described. Tritriptycene forms a 1:1 crystalline complex with acetone, whose X-ray structure is described. The parallel benzene moieties in **6** are 9.0 Å apart (or 5.5 Å, allowing for the thickness of the π clouds). The carbonyl carbon of the acetone lies near the center of the U-shaped cavity, approximately equidistant (4.5 Å) from the centers of the faces of the four benzene moieties that make up the cavity.

Triptycene (**1**) was first synthesized over 40 years ago by P. D. Bartlett,[1] who prepared it in seven steps and low yield from anthracene and *p*-benzoquinone. Some years later, a one-step synthesis from benzyne and anthracene was developed by Wittig,[2] a discovery that opened up the area of triptycene chemistry.[3]

Despite this substantial history, the considerable potential for extending the rigid triptycene framework to construct larger

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(1) Bartlett, P. D.; Ryan, M. J.; Cohen, S. G. *J. Am. Chem. Soc.* **1942**, *64*, 2649.

(2) Wittig, G.; Ludwig, R. *Angew. Chem.* **1956**, *68*, 40.

(3) For a review, see: Skvarchenko, V. R.; Shalaev, V. K.; Klabunovskii, E. I. *Russ. Chem. Rev.* (*Engl. Transl.*) **1974**, *43*, 951.

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