# Study of the Conformational Equilibria of 2-Z-3-Methyl-1,3,2-oxazaphosphorinanes. Steric and Stereoelectronic Influences on the Orientation of the $Me_2N$ Substituent on Three-Coordinate Phosphorus

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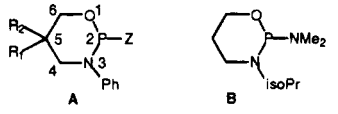
*Received March 2, 1995*[⊗]

The conformations of a series of 1,3,2-oxazaphosphorinanes containing three-coordinate phosphorus, **1–9**, have been determined by the use of $^1H$, $^{31}P$, and $^{13}C$ NMR spectroscopy. The rings were substituted at ring nitrogen, N(3), with a methyl group to compare its effect on conformational energies with those of 1,3,2-oxazaphosphorinanes reported earlier that featured a larger substituent at N(3), Ph or *i*-Pr. Quite expectedly, like those rings previously studied with Ph or *i*-Pr at N(3), a MeO or $(CF_3)_2CHO$ substituent at phosphorus has a strong preference to be axial on a chair-form ring, **1-4**, *cis*-**7**, and *cis*-**8**, or pseudoaxial on a ring in a twist/boat conformation, *trans*-**7**. However, when $Me_2N$ is attached to phosphorus, the newly studied N(3)Me rings display a chair–chair conformational equilibrium, **10** ⇄ **11**, with the $Me_2N$ equatorial ring, **11**, mildly dominant (58/42, **5**; 65/35, **6**). This contrasts with ratios of 17/83 and 20/80 for the corresponding N(3)Ph analogs, **A**, and 23/77 for the N(3)-*i*-Pr compound, **B**. The observed change in the free energy of the equilibrium **10** ⇄ **11**, 1.2–1.3 kcal/mol, is ascribed to the dominant influence of a *decrease* in repulsion experienced in conformation **11** between the *equatorial* $Me_2NP$ and the smaller Me at N(3) ($Me_2N$(eq)/N(3)Me destabilization) compared to that experienced with the N(3)Ph and N(3)-*i*-Pr analogs. This steric influence of N(3) substituents on the equilibrium **10** ⇄ **11** is *opposite* to that found for *four-coordinate* phosphorus containing 1,3,2-oxazaphosphorinanes in which $Me_2NP$(ax)/N(3)Ph repulsions that destabilize **10** appear to be dominant.

## Introduction

The structural properties of 1,3,2-dioxa- and 1,3,2-oxazaphosphorinanes containing three- and four-coordinate phosphorus have been widely studied.[1] In these ring systems, both steric and stereoelectronic factors play important roles in determining the conformations of the six-membered ring and the orientation of the substituent on phosphorus. Recently, we reported on the conformational properties of a series of three-coordinate 2-Z-3-phenyl-1,3,2-oxazaphosphorinanes, **A** ($R_1 = R_2 = H$; Me; *t*-Bu).[2] Unexpectedly, the $Me_2N$ substituent, Z, on phosphorus in this series displayed a 0.8–1.1 kcal/mol axial preference. A similar result, previously reported,[3] was confirmed for 2-(dimethylamino)-3-isopropyl-1,3,2-oxazaphosphorinane, **B**.[2] These findings contrast with the




equatorial preference of the $Me_2N$ group in three-coordinate 1,3,2-dioxaphosphorinanes[1] and four-coordinate 2-oxo-1,3,2-oxazaphosphorinanes substituted at ring nitrogen with phenyl.[4]

These surprising results for **A** and **B** were ascribed tentatively to dominant, destabilizing, vicinal steric repulsions between the 3-phenyl and 3-isopropyl substituents on ring nitrogen and the equatorial $Me_2N$ which are relieved when the $Me_2N$ is axial.[2,3] A second factor that generally favors axial placement of groups on three-coordinate phosphorus in 1,3,2-oxazaphosphorinanes is anomeric stabilization[5] from overlap of the ring nitrogen electron lone pair, n, with the axial PN $\sigma^*$ orbital ($n_N \rightarrow \sigma^*_{PN}$ stabilization). This stabilization likely is enhanced in 1,3,2-oxazaphosphorinanes, compared to their 1,3,2-dioxaphosphorinane counterparts ($n_O \rightarrow \sigma^*_{PN}$ stabilization), by the higher energy of the nitrogen lone pair participant. Furthermore, the X-ray crystal structure of **A** ($R_1 = R_2 = Me$) with axial $PNMe_2$ shows 1,3-syn axial interactions between axial $PNMe_2$ and the axial hydrogens at carbons 4 and 6 to be accommodated by the ring flattening associated with the relatively long C(4)–N(3) and N(3)–P bonds.[2] At the same time, the axial $Me_2N$ assumes a stereoelectronically favorable conformation about the $Me_2N$–P bond that is not available to 1,3,2-dioxaphosphorinanes.

[⊗] Abstract published in *Advance ACS Abstracts,* July 1, 1995.

(1) Reviews may be found in: (a) Bentrude, W. G. In *Conformational Studies of Six-Membered Ring Carbocycles and Heterocycles;* Juaristi, E., Ed.; VCH Publishers: New York, 1995; pp 245–293. (b) Bentrude, W. G. In *Phosphorus-31 NMR Spectral Properties in Compound Characterization and Structural Analysis;* Quin, L. D., Verkade, J. G., Eds.; VCH Publishers: New York, 1994: pp 41–53. (c) Bentrude, W. G.; Setzer, W. N. In *Phosphorus-31 Spectroscopy in Stereochemical Analysis;* Verkade, J. G., Quin, L. D., Eds.; VCH Publishers: Deerfield Beach, FL, 1987; pp 365–389. (d) Maryanoff, B. E.; Hutchins, R. O.; Maryanoff, C. A. *Top. Stereochem.* **1979**, *11*, 187–317.

(2) Huang, Y.; Arif, A. M.; Bentrude, W. G. *J. Org. Chem.* **1993**, *58*, 6235–6246.

(3) Nifant'ev, E. E.; Borisenko, A. B.; Sorokina, S. F.; Grachev, M. K.; Zavalishina, A. I. *Zh. Obshch. Khim.* **1977**, *47*, 2474–2480.

(4) (a) Setzer, W. N.; Sopchik, A. E.; Bentrude, W. G. *J. Am. Chem. Soc.* **1985**, *107*, 2083–2091. (b) Bentrude, W. G.; Day, R. O.; Holmes, J. M.; Quin, G. S.; Setzer, W. N.; Sopchik, A. E.; Holmes, R. R. *Ibid.*, **1984**, *106*, 106–111. (c) Bajwa, G. S.; Chandrasekaran, S.; Hargis, J. H.; Sopchik, A. E.; Blatter, D.; Bentrude, W. G. *Ibid.*, **1982**, *104*, 6385–6392.

(5) (a) Kirby, A. J. *The Anomeric Effect and Related Stereoelectronic Effects at Oxygen*; Springer-Verlag: West Berlin, 1983. (b) Juaristi, E.; Cuevas, G. *Tetrahedron* **1992**, *48*, 5019–5087. (c) For applications to six-membered rings see especially: Juaristi, E. *Introduction to Stereochemistry and Conformational Analysis;* Wiley-Interscience: New York, 1991; Chapters 17 and 18. (d) Juaristi, E.; Cuevas, G. *The Anomeric Effect*; CRC Press, Inc.: Boca Raton, FL, 1994.

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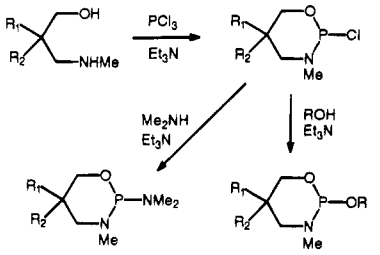
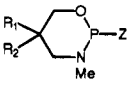
**Scheme 1**



To gain further evidence concerning the role of *equatorial–equatorial* $Me_2NP/N(3)R$ repulsions in determining the axial or equatorial preference of the $Me_2N-P$ bond, a series of 2-Z-3-methyl-1,3,2-oxazaphosphorinanes, **1–9**, has been examined. Indeed, all compounds with Z =



**1** $R_1 = R_2 = Me$, Z = MeO
**2** $R_1 = R_2 = Me$, Z = $(CF_3)_2CHO$
**3** $R_1 = H_Y$, $R_2 = H_X$, Z = MeO
**4** $R_1 = H_Y$, $R_2 = H_X$, Z = $(CF_3)_2CHO$
**5** $R_1 = R_2 = Me$, Z = $Me_2N$
**6** $R_1 = H_Y$, $R_2 = H_X$, Z = $Me_2N$
**7** $R_1$ = *t*-Bu, $R_2 = H_X$, Z = MeO
**8** $R_1$ = *t*-Bu, $R_2 = H_X$, Z = $(CF_3)_2CHO$
**9** $R_1$ = *t*-Bu, $R_2 = H_X$, Z = $Me_2N$

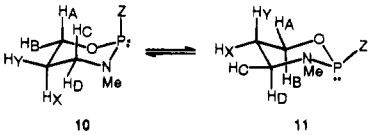
$Me_2N$ displayed a marked preference for the $Me_2N$ to be equatorial. This finding is taken to reflect the reduced equatorial-equatorial repulsions for the pair $Me_2NP/N(3)Me$ compared to the pair $Me_2NP/N(3)$-*i*-Pr (**B**) or $Me_2NP/N(3)Ph$ (**A**) that results from the reduced size of the NMe substituent. This research confirms yet another of the remarkable influences of steric and stereoelectronic influences on heteroatom-containing six-membered rings.

## Results

**Preparations.** The synthetic route to 3-methyl-1,3,2-oxazaphosphorinanes **1–9** is shown in Scheme 1. The kinetic product *trans*-**7** (relation of *tert*-butyl to RO or $Me_2N$) was prepared by a published procedure[2] in a trans/cis ratio of 87/13 ($^{31}P$ and $^1H$ NMR) and converted on distillation to the thermodynamically more stable *cis*-**7**. Compound **9** was isolated by distillation as a 40/60 cis/trans mixture of diastereomers ($^{31}P$ NMR) which slowly changed to a stable, presumably equilibrium, value of 47/53 (cis/trans) at room temperature in $C_6D_6$. Distilled **8** was at least 95% the *cis* isomer.

**$^1H$ NMR Parameters and Conformations of 1–9.** The pertinent $^1H$ NMR coupling constants and chemical shifts for **1–9** are listed in Tables 1 and 2. Protons on the six-membered ring are designated $H_A$, $H_B$, $H_C$, $H_D$, $H_X$, and $H_Y$, as shown in **10**. For the 5,5-dimethyl compounds (**1**, **2**, and **5**), $H_X$ and $H_Y$ are replaced by methyl groups. In *cis*-**7**, **-8**, **-9**, $H_Y$ has been replaced by the *tert*-butyl substituent, while the *tert*-butyl replaces $H_X$ in *trans*-**9**. The NMR data for *trans*-**7** were obtained before purification. Compound **9** was examined as a solution containing both cis and trans diastereomers. Spectra were analyzed on a first order basis. Those for compounds **6** and **9** were also iteratively refined (LAOCN5). The $^1H$ NMR signals for *cis*-**9** and *trans*-**9** were poorly separated in $C_6D_6$ but well-resolved in $CD_3CN$. The lack of influence of solvent on conformational equilibria, as seen in the relative constancy of measured coupling constants (Table 1), was demonstrated for all ring protons of **5** and for certain ring protons of **7** and **9**.

The conformational analyses of the six-membered rings were based on the values of $^3J_{POCH}$ and $^3J_{HCCH}$. Coupling constants $^3J_{PNCH}$ have not been found to be useful in conformational analyses of three-coordinate phosphorus containing heterocyclic six-membered rings,[2,3,6] as they depend strongly on the substituent at N(3).



**10** **11**

The data observed for **1–4**, *cis*-**7**, and *cis*-**8**, (Z = MeO and $(CF_3)_2CHO$) are similar to those seen for previously studied three-coordinate 1,3,2-dioxa- and oxazaphosphorinanes that populate chair conformations analogous to **10** with substituents attached axially to phosphorus. Thus, the small values of $^3J_{AP}$ (3.8–4.2 Hz), $^3J_{BX}$ (3.8–4.5 Hz), and $^3J_{DX}$ (3.9–4.5 Hz) recorded (Table 1) are characteristic of gauche HCCH and HCOP arrangements, while the large values of $^3J_{BP}$ (11.7–13.1 Hz), $^3J_{AX}$ (11.6–12.5 Hz), and $^3J_{CX}$ (11.6–12.5 Hz) observed are typical of antiperiplanar HCCH and HCOP geometries. The relatively large long-range W-configuration couplings recorded, $^4J_{BD}$ (−1.4 to −2.3 Hz), also support the assignment of chair conformation **10** to **1–4**, *cis*-**7**, and *cis*-**8**. By contrast, the data recorded for **5** and **6** demonstrate the presence of a chair–chair equilibrium in solution with conformer **11** (Z = $Me_2N$) dominant, as indicated by the relatively large values of $J_{AP}$ noted (~15 Hz). Chair-form 1,3,2-oxaza- and 1,3,2-dioxaphosphorinanes containing three-coordinate phosphorus with Z equatorial, as in **11**, typically display $J_{AP}$ values of 19–21 Hz.[7] The relatively large values for $J_{BY}$ (8.7 Hz) and $J_{DY}$ (8.5 Hz) also require that **11** be the major conformer populated by **6** (see below for estimates of the populations of **10** and **11**).

*cis*-**9** (Z = $Me_2N$, $H_Y$ = *tert*-butyl) displays a coupling pattern similar to that for *cis*-**7** and *cis*-**8** which were assigned above to the chair conformation **10** (Z = RO, $H_Y$ = *tert*-butyl). The small increase in $J_{AP}$ and decrease in $J_{BP}$ most likely arise from the distortion of the ring (**10**) that was noted previously in the X-ray crystal structure of 5,5-dimethyl-3-phenyl-2-(dimethylamino)-1,3,2-oxazaphosphorinane (**A**, $R_1 = R_2 = Me$).[2] In the same report,[2] values of 5.8 and 11.7 Hz for $J_{AP}$ and $J_{BP}$, respectively, were estimated for **10** from a Karplus plot of $^3J_{HCOP}$ vs dihedral angle. A very minor depopulation of the chair form by *cis*-**9** to occupy a twist/boat conformation may also be in part responsible for the differences in $J_{AP}$ and $J_{BP}$ between *cis*-**9** and its *cis*-**7** and *cis*-**8** counterparts and, along with ring distortion, lead to the observed reductions in $J_{AX}$ and $J_{CX}$ seen in Table 1 for *cis*-**9**.

The coupling constants for *trans*-**9** are very similar to those of *trans*-2-(dimethylamino)-5-*tert*-butyl-1,3,2-dioxaphosphorinane ($J_{AP}$ = 20.2 Hz, $J_{BP}$ = 2.6 Hz, $J_{AY}$ = 4.2

(6) Hutchins, R. O.; Maryanoff, B. E.; Albrand, J. P.; Cogne, A.; Gagnaire, D.; Robert, J. B. *J. Am. Chem. Soc.* **1972**, *94*, 9151–9158.
(7) Bentrude, W. G.; Tan, H.-W.; Yee, K. C. *J. Am. Chem. Soc.* **1975**, *97*, 573–582.

**Table 1. Selected $^1$H NMR Coupling Constants (Hz) for 1–9[a]**

| compd | solvent | $^3J_{AP}$ | $^3J_{BP}$ | $^3J_{CP}$ | $^3J_{DP}$ | $^4J_{BD}$ | $^4J_{AC}$ | $^3J_{AX}$ | $^3J_{BX}$ | $^3J_{CX}$ | $^3J_{DX}$ | $^3J_{AY}$ | $^3J_{BY}$ | $^3J_{CY}$ | $^3J_{DY}$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **1** | $C_6D_6$ | 3.8 | 12.3 | 4.2 | 8.7 | −2.3 | | | | | | | | | |
| **2** | $C_6D_6$ | 4.1 | 13.1 | 4.9 | 9.6 | −2.2 | | | | | | | | | |
| **3** | $C_6D_6$ | 3.8 | 11.7 | 3.9 | 8.4 | −1.4 | | 12.5 | 4.5 | 12.5 | 4.5 | 2.3 | 2.3 | 3.1 | 3.1 |
| **4** | $C_6D_6$ | 4.1 | 12.4 | 4.6 | 12.8 | −1.4 | | 12.5 | 4.3 | 11.7 | 4.7 | 2.3 | 2.7 | 3.4 | 3.3 |
| **5** | $CDCl_3$ | 14.7 | 6.8 | 11.8 | 4.3 | | −1.6 | | | | | | | | |
| **5** | $C_6D_6$ | 14.5 | 6.9 | 11.6 | 4.2 | | −1.6 | | | | | | | | |
| **6**[b] | $CDCl_3$ | 15.3 | 6.0 | 11.8 | 4.0 | | −1.4 | 5.8 | 3.1 | 6.0 | 3.9 | 4.0 | 8.7 | 4.4 | 8.5 |
| *cis*-**7** | $C_6D_6$ | 4.0 | 12.4 | 3.9 | 9.1 | −1.9 | | 11.6 | 3.9 | 11.6 | 3.9 | | | | |
| *trans*-**7** | $C_6D_6$ | 6.7 | 5.8 | 3.4 | 7.0 | | −1.2 | | | | | 3.8 | 8.5 | 5.8 | 8.7 |
| *cis*-**8** | $C_6D_6$ | 4.2 | 12.8 | 4.6 | 10.2 | −1.9 | | 11.6 | 3.8 | 11.6 | 4.0 | | | | |
| *cis*-**9** | $C_6D_6$ | 6.7 | *c* | 4.7 | *c* | *c* | | 10.6 | *c* | 9.8 | *c* | | | | |
| *cis*-**9**[b] | $CD_3CN$ | 6.2 | 11.0 | 4.5 | 7.9 | −1.4 | | 11.0 | 4.5 | 10.1 | 5.3 | | | | |
| *trans*-**9** | $C_6D_6$ | 19.4 | *c* | 15.4 | *c* | | −2.2 | | | | | 4.3 | *c* | 4.6 | *c* |
| *trans*-**9** | $CD_3CN$ | 19.0 | 4.4 | 15.4 | 2.8 | | −2.1 | | | | | 4.5 | 9.7 | 4.9 | 10.7 |

[a] At 300 MHz, ambient temperature. [b] Iteratively refined by use of LAOCN5 program: RMS error, 0.164 Hz (**6**), 0.043 Hz (**9**); probable error, $\delta$ 0.014–0.017 Hz (**6**), 0.005–0.006 Hz (**9**); $J$, 0.021–0.030 Hz (**6**), 0.008–0.011 Hz (**9**). [c] Poorly resolved.

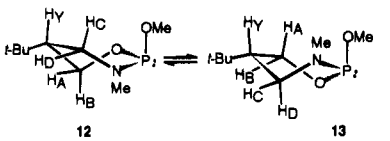
**Table 2. Selected $^1$H NMR Chemical Shifts (ppm) for 1–9[a]**

| compd | solvent | A | B | C | D | X | Y |
|---|---|---|---|---|---|---|---|
| **1** | $C_6D_6$ | 3.74 | 3.00 | 2.86 | 1.82 | | |
| **2** | $C_6D_6$ | 3.79 | 3.08 | 2.73 | 1.84 | | |
| **3** | $C_6D_6$ | 4.02 | 3.50 | 3.16 | 2.32 | 1.98 | 1.12 |
| **4** | $C_6D_6$ | 3.89 | 3.41 | 2.81 | 2.13 | 1.71 | 1.01 |
| **5** | $CDCl_3$ | 3.60 | 3.47 | 2.80 | 2.55 | | |
| **5** | $C_6D_6$ | 3.57 | 3.45 | 2.58 | 2.34 | | |
| **6** | $CDCl_3$ | 4.03 | 3.83 | 3.14 | 2.84 | 1.84 | 1.70 |
| *cis*-**7** | $C_6D_6$ | 3.99 | 3.74 | 3.04 | 2.52 | 1.79 | |
| *trans*-**7** | $C_6D_6$ | 4.03 | 3.63 | 3.03 | 2.55 | | 1.97 |
| *cis*-**8** | $C_6D_6$ | 3.97 | 3.75 | 2.83 | 2.40 | 1.65 | |
| *cis*-**9** | $C_6D_6$ | 3.89 | *b* | 3.03 | *c* | 1.68 | |
| *cis*-**9** | $CD_3CN$ | 3.84 | 3.75 | 3.15 | 2.84 | 1.69 | |
| *trans*-**9** | $C_6D_6$ | 4.03 | *b* | 2.85 | *c* | | 1.81 |
| *trans*-**9** | $CD_3CN$ | 3.99 | 3.66 | 2.96 | 2.68 | | 1.74 |

[a] At 300 MHz, ambient temperature. [b] Cis B and trans A overlapped at 3.7–3.8 ppm. [c] Overlapped with $NMe_2$ signal.

Hz, $J_{BY}$ = 10.8 Hz).[8] The large 19.0 Hz value for $J_{AP}$ is typical of an antiperiplanar HCOP geometry with an axial electron lone pair on phosphorus.[1,7,8] Thus, *trans*-**9** primarily populates the chair conformation **11** ($H_X$ = *tert*-butyl, Z = $Me_2N$) with both $Me_2N$ and *tert*-butyl equatorial. Notably, however, for *trans*-**9**, both $J_{BY}$ (9.7 Hz) and $J_{CY}$ (10.7 Hz) are less than the 11–12 Hz values typical of the analogous axial hydrogens of *cis*-**7** and *cis*-**8** (Table 1). This likely signifies a minor depopulation of the chair conformation. The previously investigated *trans*-5-*tert*-butyl-3-phenyl-2-(dimethylamino)-1,3,2-oxazaphosphorinane populates to a considerable extent boat/twist forms with *tert*-butyl pseudoequatorial and $Me_2N$ pseudoaxial.[2] This suggests that instability in trans chair-form rings in 1,3,2-oxazaphosphorinane systems is most readily relieved in such twist/boat conformations, as will be established for *trans*-**7**. However, the deviations of the key coupling constants for *trans*-**9** from those of the chair (**11**) are not great enough to make an independent, truly definitive assignment of conformation to any minor form populated.

For *trans*-**7**, the observed data deviate strikingly from those expected for chair-form **11** ($H_X$ = *tert*-butyl, Z = MeO). Assuming that $J_{AP}$ should be on the order 19–20 Hz for *trans*-**7** in conformation **11**, the 6.7 Hz value found indicates a strong depopulation of **11**. The alternative chair form **10**, with MeO and *tert*-butyl both axial, would impart 11–12 Hz values to $J_{BP}$. Moreover, to have $J_{AP}$ as low as the observed 6.7 Hz would require essentially total depopulation of **11** in favor of **10**. The observed value for $J_{BP}$ (5.8 Hz), however, is much too low for **10**. Predominant population of **10** would also lead to a greater reduction in observed $J_{BY}$ and $J_{DY}$. The coupling constants obtained are instead more typical of those expected if **11** is predominantly depopulated in favor of approximately equal amounts of rapidly equilibrating twist/boat forms **12** and **13** in which $H_A$ and $H_B$ (as well as $H_C$ and $H_D$) spend equal time in pseudoequatorial and pseudoaxial positions, leading to similar couplings to phosphorus, $J_{AP}$ and $J_{BP}$, as observed. The values of $J_{BY}$




**12** **13**

and $J_{DY}$ in **12** and **13**, as found, should be diminished somewhat but remain nearly equal. Those of $J_{AY}$ and $J_{CY}$, as expected, are slightly increased from those for the chair, **11**. Population of a minor amount of **10** cannot be excluded.

**Chair–Chair Equilibrium Constants for 5 and 6.** The equilibrium constants ($K$, **10** ⇄ **11**) for **5** and **6** were estimated from the observed $J_{AP}$ and $J_{BP}$ values (Table 1) and assumed values for these coupling constants in **10** and **11**. Thus, it is easily shown that (mole fraction **10** = $N$(**10**), mole fraction **11** = $N$(**11**))

$$N(\mathbf{10})J_{AP}(\mathbf{10}) + N(\mathbf{11})J_{AP}(\mathbf{11}) = J_{AP}(\text{obsd})$$

$$N(\mathbf{10}) = 1 - N(\mathbf{11})$$

therefore,

$$N(\mathbf{10}) = \frac{J_{AP}(\text{obsd}) - J_{AP}(\mathbf{11})}{J_{AP}(\mathbf{10}) - J_{AP}(\mathbf{11})}$$

similarly,

$$N(\mathbf{10}) = \frac{J_{BP}(\text{obsd}) - J_{BP}(\mathbf{11})}{J_{BP}(\mathbf{10}) - J_{BP}(\mathbf{11})}$$

Assumed values for **10** noted above, estimated for the analogous 3-phenyl compound ($J_{BP}$ = 11.7 Hz, $J_{AP}$ = 5.8 Hz),[2] along with values for **11** from all-chair-form *trans*-2-(dimethylamino)-5-*tert*-butyl-1,3,2-dioxaphosphori-

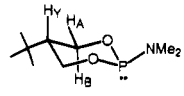
(8) Bentrude, W. G.; Tan, H.-W. *J. Am. Chem. Soc.* **1973**, *95*, 4666–4675. The coupling constants for **14** are revised values ($C_6D_6$) from spectra taken at 300 MHz and iteratively refined by the LAOCN5 program (Y. Huang, unpublished results).

**Table 3. Selected $^{13}C$ NMR Parameters for 1–9[a]**

| | | J, Hz | | | | δ, ppm | | | |
|---|---|---|---|---|---|---|---|---|---|
| compd | solvent | PC4 | PC5 | PC6 | PC′ | C4 | C5 | C6 | C′ |
| **1** | $C_6D_6$ | 5.1 | 1.2 | 3.9 | 29.1 | 56.9 | 31.6 | 67.2 | 37.5 |
| **2** | $C_6D_6$ | 5.5 | <0.5 | 4.5 | 29.0 | 56.9 | 31.1 | 68.7 | 36.5 |
| **3** | $C_6D_6$ | 4.9 | 1.4 | 3.5 | 29.1 | 44.9 | 26.8 | 57.7 | 37.2 |
| **4** | $C_6D_6$ | 5.5 | 1.2 | 4.2 | 29.2 | 45.0 | 26.1 | 59.4 | 36.5 |
| **5** | $C_6D_6$ | 6.2 | 3.1 | 0.7 | 25.3 | 61.9 | 32.6 | 72.8 | 37.4 |
| **6** | $C_6D_6$ | 5.7 | 4.6 | <0.5 | 25.0 | 49.7 | 27.5 | 62.5 | 37.0 |
| *cis*-**7** | $C_6D_6$ | 5.1 | <0.5 | 3.4 | 28.2 | 47.3 | 44.9 | 59.6 | 37.1 |
| *trans*-**7** | $C_6D_6$ | 5.1 | 5.5 | 6.4 | 36.4 | 47.8 | 43.6 | 61.7 | 37.4 |
| *cis*-**8** | $C_6D_6$ | 5.9 | <0.5 | 3.8 | 28.4 | 47.5 | 44.6 | 61.2 | 36.5 |
| *cis*-**9** | $CDCl_3$ | 1.5 | 1.5 | 3.9 | 29.4 | 48.7 | 44.9 | 61.9 | 37.5 |
| *trans*-**9** | $CDCl_3$ | 10.5 | 4.2 | 3.2 | 22.8 | 52.9 | 46.9 | 64.6 | 36.7 |

[a] At 75 MHz, ambient temperature. C′ = N(3)$CH_3$.

nane, **14** ($J_{AP}$ = 20.2 Hz, $J_{BP}$ = 2.6 Hz),[8] were used to estimate $N$(**10**) for **5** and **6** of the present study (this




**14**

approach is the one followed previously for the chair-chair equilibrium of 2-(dimethylamino)-3-phenyl-1,3,2-oxazaphosphorinane and its 5,5-dimethyl congener, **A**, Z = $Me_2N$, $R_1 = R_2$ = H or Me[2]). The percentage of conformer **10** populated by **5** was calculated to be 38%, based on $J_{AP}$, and 46%, based on $J_{BP}$. Similarly, for **6**, the estimated population of conformer **10** was 34%, based on $J_{AP}$, and 37%, based on $J_{BP}$. Averaged mole fractions yield chair-chair equilibrium constants ($K$) of 1.4 for **5** and 1.9 for **6**. These correspond to $\Delta G°$ at 25 °C of −0.19 kcal/mol for **5** and −0.38 kcal/mol for **6**.

**$^{13}C$ NMR Studies.** Pertinent $^{13}C$ NMR coupling constants and chemical shifts are tabulated in Table 3. Contrasts are clearly discernible in the magnitudes of carbon–phosphorus coupling constants for the ring carbons of molecules that $^1H$ NMR shows to be predominantly in conformation **10** (**1**-**4**, *cis*-**7**, and *cis*-**8**) compared to those that populate significant amounts of conformation **11** (**5**, **6**, and *trans*-**9**). Thus, for **5**, **6**, and *trans*-**9**, greater values of $J_{PC5}$ (3.1–4.6 Hz) are found compared to $J_{PC5}$ values for **1**–**4** and *cis*-**7**, -**8**, and -**9** (<0.5–1.5 Hz). This effect of P–Z orientation is seen consistently for 1,3,2-dioxaphosphorinanes featuring three-coordinate phosphorus.[1,9,10] These couplings for the 1,3,2-dioxaphosphorinanes, however, are considerably larger (4–5 Hz, Z axial; 10–11 Hz, Z equatorial) which suggests that there is an attenuation of the coupling through nitrogen compared to oxygen. The 3–5 ppm upfield chemical shifts ($\gamma$-effect[9]) of the resonances of C(4) and C(6) for **1** and **2** compared to **5**, for **3** and **4** compared to **6**, and for *cis*-**7**, -**8**, and -**9** compared to *trans*-**9** are additional evidence for the correctness of the above assignments of orientations (axial vs equatorial) of substituents RO and $Me_2N$ on phosphorus.[9,10]

The large $J_{PC5}$ value (5.5 Hz) for *trans*-**7** is consistent with both conformation **11** and twist structures **12** and **13**. Boat/twist forms similar to **12** and **13** are known to have increased $J_{PC5}$ values for 1,3,2-dioxaphosphorinanes.[10] Caution in applying this generalization, however, should be applied to $^3J_{CP}$ values from CCNP rather than CCOP coupling pathways. Furthermore, such coupling constants also appear to be very susceptible to variations in the CCOP torsion angle, dropping from a maximum near 0° to 1 Hz or less at about 80°.[10a]

**Table 4. $^{31}P$ NMR Chemical Shifts (ppm) in $C_6D_6$ for 1–9[a]**

| compd | δ | compd | δ | compd | δ |
|---|---|---|---|---|---|
| **1** | 129.5 | **5** | 138.6 | *cis*-**8** | 138.0 |
| **2** | 136.1 | **6** | 141.1 | *cis*-**9** | 125.8 |
| **3** | 137.7 | *cis*-**7** | 132.2 | *trans*-**9** | 145.3 |
| **4** | 143.5 | *trans*-**7** | 138.5 | | |

[a] Positive chemical shifts are downfield from external 85% $H_3PO_4$. At 121 MHz, ambient temperature.

Unlike correlations noted for 1,3,2-dioxaphosphorinanes,[9,10] values of $^2J_{CP}$ for C(4) and C(6) of **1**–**9** do not change much with variation in the orientation of Z. Strangely, the noted decrease in $^2J_{PC6}$ for **5** and **6** with $Me_2N$ predominantly equatorial is opposite to the trend noted for 1,3,2-dioxaphosphorinanes.[10a] The differences in couplings between phosphorus and the N(3)$CH_3$ carbon seen in Table 3 presumably are a result of variations in the hybridization at N(3).

**$^{31}P$ NMR Studies.** The $^{31}P$ NMR chemical shifts of compounds **1**–**9** are tabulated in Table 4. The range of chemical shifts (125.8–145.3 ppm) is similar to that found for the corresponding 3-phenyl analogs (**A**) with the same Z substituents on phosphorus.[2] The so-called δ-substituent effect, observed[9b] when there is an equatorial alkyl substituent (often methyl) at the δ-position (C(5)) and an axial P–Z bond of 1,3,2-dioxa-[9b] and 1,3,2-oxazaphosphorinanes[2] containing three-coordinate phosphorus, results in 7.4 and 8.2 ppm upfield chemical shifts for **1** compared to **3** and **2** compared to **4**, respectively. However, the δ-substituent effect between **5** and **6** only is 2.5 ppm. This is presumably because of the predominantly equatorial orientation of the $Me_2N$ group attached to phosphorus in both instances (see above $^1H$ and $^{13}C$ NMR studies). It should be pointed out that, when N(3)Me is replaced by N(3)Ph, the $Me_2N$ group is axially attached to phosphorus in the major conformer. Thus, a larger (6.2 ppm) δ-substituent effect was observed in comparing the 3-phenyl analogs of **5** and **6**.[2]

For *cis*- and *trans*-**7**, a 6.3 ppm difference in $^{31}P$ NMR chemical shifts ($\Delta\delta$) is recorded, which is very similar to that of its 1,3,2-dioxa counterparts ($\Delta\delta$ = 6.9 ppm).[11] The δ-effect chemical shift differentiation is presumably in addition to the $\gamma$-effect (upfield chemical shift) mentioned above for the $^{13}C$ chemical shifts for C(4) and C(6) when Z on phosphorus is axial and normally displayed at phosphorus as well.[1] For *trans*-**7**, a twist conformation with MeO pseudoaxial is highly populated, while the cis conformer is in the chair form with MeO axial. By contrast, for *cis*- and *trans*-**9** (Z = $Me_2N$), a very large effect is noted ($\Delta\delta$ = 19.5 ppm), which is much greater than that reported[8] for their 1,3,2-dioxa counterparts ($\Delta\delta$ = 7.0 ppm). As discussed above, both *cis*- and *trans*-**9** are primarily in chair conformations. By contrast, *cis*-2-(dimethylamino)-5-*tert*-butyl-1,3,2-dioxaphosphorinane populates the twist form to a considerable extent, while its trans diastereomer is entirely in the chair conformation.[7] A large δ-effect on δ-$^{31}P$ depends on the very predominant orientation of the substituent on

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(10) (a) Nifant'ev, E. E. *Zh. Obshch. Khim.* **1986**, *55*, 1481–1496. (b) Quin, L. D. In *Phosphorus-31 Spectroscopy in Stereochemical Analysis*; Verkade, J. G., Quin, L. D., Eds.; VCH Publishers: Deerfield Beach, FL, 1987; pp 391–424.

(11) Unpublished results from this laboratory.

phosphorus being axial in one diastereomer and equatorial in the other, as for *cis*- and *trans*-**9**. The $\Delta\delta$ value of 23.6 ppm reported for *cis*- and *trans*-2-methyl-5-*tert*-butyl-1,3,2-dioxaphosphorinane[9a] also appears to be consistent with this condition.

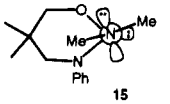
## Discussion

Steric and stereoelectronic interactions are the key factors in determining the orientation of the substituent (Z) on phosphorus and, thereby, the position of the conformational equilibrium **10** ⇄ **11**. For the 1,3,2-oxazaphosphorinanes studied, the steric factors to be considered include: (1) repulsive 1,3-syn axial (Z/H) interactions (destabilizing conformer **10**) and (2) repulsions between vicinal substituents on N(3) and P (i.e. Me/$Z_{eq}$, destabilizing conformer **11**; Me/$Z_{ax}$, destabilizing conformer **10**). Key stereoelectronic factors are potential stabilizing n → $\sigma^*$ interactions (anomeric effects) of electron lone pairs on ring P, N, O, and substituent Z with adjacent antibonding orbitals (PZ, PN, PO).

As shown above for **1**–**4**, **7**, and **8**, MeO and $(CF_3)_2$CHO substituents on three-coordinate phosphorus strongly favor the axial orientation. This is in complete accord with previous findings for three-coordinate 2-Z-3-phenyl-1,3,2-oxazaphosphorinanes[2] and for 2-Z-1,3,2-dioxaphosphorinanes.[1] Anomeric effects featuring small, electron-withdrawing RO substituents on phosphorus outweigh 1,3-syn axial repulsions. Consequently, chair conformations with RO axial are totally populated by **1**–**4** (**10**, Z = RO), *cis*-**7**, and *cis*-**8** (**10**, $H_Y$ = *tert*-butyl, Z = RO). In **10**, n → $\sigma^*_{PZ}$ stabilization involving the 2*p* N(3) and O(1) lone pairs and the axial P–O $\sigma^*$ bond is optimal. Stabilization in **11** can arise only from participation of the lower energy $sp^2$ lone pairs on O(1) with the equatorial $\sigma^*$ P–O bond. The lone pair on N(3) in **11**, regardless of its hybridization, is not favorably oriented with respect to the equatorial POMe for n → $\sigma^*$ overlap.

Likewise, the chair form of *trans*-**7** (**11**, $H_X$ = *tert*-butyl, Z = MeO) with both substituents equatorial is strongly depopulated. Equilibrating, approximately equally populated, twist/boat forms (**12** ⇄ **13**) provide the near equality of $J_{AP}$ and $J_{BP}$ and the reduction in $J_{BY}$ and $J_{CY}$ noted in Table 1. Unlike **11**, conformations **12** and **13** are stabilized by overlap of the 2p electron pair of O(1) or that of N(3) with the adjacent pseudoaxial $\sigma^*$ P–OMe bond. This interaction overcomes the relatively small resistance of these rings[2] to chair to twist conformational change. Interestingly, the corresponding 1,3,2-dioxaphosphorinane (**14**, $Me_2N$ = MeO) also populates twist/boat forms analogous to **12** and **13** but to a somewhat lesser extent than does *trans*-**7**.[7]

When Z is the $Me_2N$ group (**5**, **6**, and **9**), its axial or equatorial preference depends not only on the above steric interactions and stereoelectronic (anomeric) effects but also on the torsional angle about the P–$NMe_2$ bond. Stabilizing stereoelectronic interactions are optimized when the lone pair on $Me_2N$ nitrogen and the lone pair on phosphorus are orthogonal.[12] This orientation is readily attainable when the $Me_2N$ is equatorial in 1,3,2-dioxaphosphorinanes with three-coordinate phosphorus present but evidently blocked by 1,3-syn axial interactions with hydrogens on C(4) and C(6) when $Me_2N$ is axial on phosphorus, leading to a 1 kcal/mol preference for equatorial rather than axial attachment to a chair-form ring.[1c,7,8,13] However, the X-ray crystal structure of 5,5-dimethyl-3-phenyl-2-(dimethylamino)-1,3,2-oxazaphosphorinane displayed a distorted chair structure with the $Me_2N$ axial.[2] Furthermore, the $Me_2N$ was nearly planar and oriented approximately as in **15**. Solution $^1$H NMR



**15**

studies assigned an 13/87 **11/10** ratio to this equilibrium ($\Delta G°$ = 1.1 kcal/mol). For the same molecule unsubstituted at C(5), the **11/10** ratio was 20/80 ($\Delta G°$ = 0.8 kcal/mol). Several factors that may account for the preferred axial orientation were proposed: (1) relief of repulsive, equatorial–equatorial interactions between the phenyl group on N(3) and the equatorial $Me_2N$ on depopulation of the chair conformer comparable to **11** (Me = Ph) to form the chair analogous to **10** (Me = Ph); (2) the deformability of the 1,3,2-oxazaphosphorinane ring, with its bonds to nitrogen longer than those involving only oxygen in the 1,3,2-dioxaphosphorinane ring, that allows axial $Me_2N$ to be more readily accommodated; and (3) the resulting stereoelectronic stabilization of the axial $Me_2N$ in the conformation approximated by **15** (from X-ray structure[2]).

The equatorial–equatorial repulsion between an *i*-Pr at N(3) and equatorial $Me_2N$ had been previously proposed.[3] The axial preference for the $Me_2N$ in that system (**B**, **11/10** = 23/77) was confirmed in our earlier paper on the equilibrium **10** ⇄ **11** with N(3)Ph.[2] The current study was designed to test the effect of a smaller substituent at N(3), the methyl group. Indeed, the equilibrium **10** ⇄ **11** for **5**, **11/10** = 58/42 ($\Delta G°$ = −0.2 kcal/mol), favors **11**. Compared to its N(3)Ph analog (**A**, $R_1 = R_2$ = Me),[2] this amounts to a 1.3 kcal/mol change in $\Delta G°$ for the equilibrium in favor of **11**. The same result for **6** (**11/10** = 65/35, $\Delta G°$ = −0.4 kcal/mol) represents a 1.2 kcal/mol change from $\Delta G°$ for its N(3)Ph analog (**A**, $R_1 = R_2$ = H). These very consistent results suggest that repulsive, equatorial–equatorial interactions between the substituent at N(3) and equatorial $PNMe_2$ are strongly *decreased* in **11** from their magnitude with phenyl[2] or isopropyl[2,3] at N(3). Changes in other interactions between the substituent and lone pair on N(3) and $Me_2N$ in **10** and **11** doubtless also accompany the change at N(3) from phenyl to methyl. The measured $\Delta\Delta G°$ of 1.2–1.3 kcal/mol is a net effect.

Finally, it is significant that, for four-coordinate phosphorus containing 2-oxo-1,3,2-oxazaphosphorinanes, the effect of substituents at N(3) on the equilibrium **10** ⇄ **11** is opposite to that observed for the three-coordinate 1,3,2-oxazaphosphorinanes. With Z = $Me_2N$, $Me_2NP$(ax)/N(3)Ph repulsions dominate such that the $Me_2NP$ is equatorial.[4] For N(3)H, however, $Me_2NP$ is largely axial.[4a,14]

## Conclusion

Substitution at N(3) of the 1,3,2-oxazaphosphorinane ring system containing three-coordinate phosphorus with

(12) Reference 8 and references cited therein.

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(14) Holmes, R. R.; Day, R. O.; Setzer, W. N.; Sopchik, A. E.; Bentrude, W. G. *J. Am. Chem. Soc.* **1984**, *106*, 2353–2358.

the smaller Me substituent in place of Ph or *i*-Pr shifts chair–chair (**10** ⇌ **11**) and chair–twist conformational equilibria for these rings in favor of forms with $Me_2N$ on phosphorus equatorial rather than axial. This effect probably arises from a *reduction* in destabilizing, repulsive interactions between the substituent at N(3) (Me vs Ph or *i*-Pr) and the *equatorial* $Me_2N$ in **11** that are relieved in **10**. This effect contrasts with the previously known[4,14] opposite influence of larger substituents on N(3) of four-coordinate 1,3,2-oxazaphosphorinanes on the equilibrium **10** ⇌ **11** for Z = $Me_2N$.[4,14]

## Experimental Section

**Materials.** Commercial reagents and solvents were used as received unless otherwise noted. Diethyl ether and tetrahydrofuran (THF) were dried over sodium benzophenone and then freshly distilled before use. Other solvents were Omni-Solv grade from EM Industries Inc.

**Spectral and Physical Data.** Details of the recording and referencing NMR, MS, and physical data were reported previously.[2] Designations of $H_X$, $H_Y$, etc. correspond to structures **10** and **11**. Measured coupling constants are considered to have errors of ±0.2 Hz. An APT (Attached proton test) $^{13}C$ NMR spectrum was obtained to aid in the assignments of the resonances of **9**. Only NMR parameters not given in Tables 1–4 are recorded in this section.

**General Procedure for the Preparations of 2-Chloro-3-methyl-1,3,2-oxazaphosphorinanes.** To rapidly stirred THF were added simultaneously and dropwise a solution of *N*-methylamino alcohol and triethylamine in THF and a solution of phosphorus trichloride in THF at room temperature under an argon atmosphere. The resulting mixture was heated at reflux over a period of 2 days and allowed to cool to room temperature. The salt was removed by Schlenk techniques, and the solvent was removed by rotary evaporation. The product was isolated by distillation under vacuum.

**General Procedure for the Preparations of 2-Alkoxy-3-methyl-1,3,2-oxazaphosphorinanes.** To a rapidly stirred solution of 2-chloro-3-methyl-1,3,2-oxazaphosphorinane in diethyl ether was added dropwise a solution of alcohol and triethylamine in diethyl ether at 0 °C under an argon atmosphere. The resulting mixture was allowed to warm to room temperature and then stirred for 3 h. The salt was removed by Schlenk techniques and the solvent by rotary evaporation. Distillation under vacuum gave pure product.

**General Procedure for the Preparations of 2-(Dimethylamino)-3-methyl-1,3,2-oxazaphosphorinanes.** To a stirred solution of triethylamine in diethyl ether, cooled with an ice/salt bath at −12 to −15 °C, was added dropwise a solution of 2-chloro-3-methyl-1,3,2-oxazaphosphorinane in diethyl ether under an argon atmosphere. Dimethylamine gas was simultaneously bubbled through the solution. Following the addition, the admission of dimethylamine gas was continued for another 5 min. The reaction mixture was allowed to warm to room temperature, continuously stirred for 4 h, and then worked up in a manner analogous to the above preparation of the 2-alkoxy derivatives.

**Preparation of *N*-Methyl-2-carbethoxypropionamide.** A mixture of 2-carbethoxy-2-methylpropionic acid[14] (5.08 g, 31.3 mmol) and thionyl chloride (4.02 g, 34.4 mmol) was warmed to 50–55 °C and stirred overnight under an argon atmosphere. The remaining thionyl chloride was removed by rotary evaporation to give the corresponding acid chloride which was taken up with 30 mL of dry diethyl ether and added dropwise to a solution of liquified methylamine (1.90 g, 63.0 mmol) in 300 mL of dry diethyl ether at −78 °C with rapid stirring. The addition took 30 min. The resulting mixture was allowed to warm to room temperature. The white solids were separated by filtration and extracted continuously with ether using a Soxhlet apparatus. The filtrate and the extract were combined. The ether was removed to give a white solid which was recrystallized from *n*-pentane to yield 3.40 g of the title compound as needle-shaped crystals (19.6 mmol, 63% yield): mp 38–40 °C; $^1H$ NMR (300 MHz, $CDCl_3$) δ 1.23 (t, 3 H, *J* = 7.1 Hz), 1.45 (s, 6 H), 2.82 (d, 3 H, *J* = 4.7 Hz), 3.48 (bs, 1 H), 4.19 (q, 2 H, *J* = 7.1 Hz); $^{13}C$ NMR (75 MHz, $C_6D_6$, {$^1H$}) δ 14.0, 23.6, 26.6, 50.3, 61.1, 172.9, 174.3.

***N*-Methyl-2-(hydroxymethyl)-2-methylpropylamine.** To a stirred suspension of lithium aluminum hydride (13.0 g, 343 mmol) in 300 mL of dry THF was added dropwise a solution of *N*-methyl-2-carbethoxypropionamide (19.3 g, 140 mmol) at 0 °C under an argon atmosphere. The resulting mixture was heated at reflux for 4 days and cooled to 0 °C. The reaction was quenched by careful addition of 26 mL of water. The salts were removed by filtration and washed with 300 mL of ether. The filtrate was dried over $MgSO_4$. The solvent was removed by rotary evaporation to give a white solid which was recrystallized from *n*-pentane to yield 9.30 g of white needle-like crystals (79.3 mmol, 57% yield): mp 50–51.5 °C; $^1H$ NMR (300 MHz, $C_6D_6$) δ 0.77 (s, 6 H), 1.98 (d, 3 H, *J* = 1.0 Hz), 2.19 (s, 2 H), 2.95 (bs, 2 H), 3.50 (s, 2 H); $^{13}C$ NMR (75 MHz, $C_6D_6$, {$^1H$}) δ 23.4, 35.4, 37.3, 63.7, 73.7; HRMS calcd for $C_6H_{15}NO$ ($M^+$) 117.1154, found 117.1153.

**Preparation of 2-Chloro-3,5,5-trimethyl-1,3,2-oxazaphosphorinane.** By the above general procedure, the reaction of *N*-methyl-2-(hydroxymethyl)-2-methylpropylamine (3.30 g, 28.4 mmol), triethylamine (5.80 g, 56.8 mmol), and phosphorus trichloride (3.90 g, 28.4 mmol) in THF (200 mL) gave 3.40 g of a colorless liquid (18.7 mmol, 66% yield): bp 62–63 °C (1.2 mmHg); $^{31}P$ NMR (121 MHz, $C_6D_6$, {$^1H$}) δ 152.5 (s); $^1H$ NMR (300 MHz, $C_6D_6$) δ 0.23, 0.76 (two s, 6 H), 1.67 (ddd, 1 H, *J* = −11.6, −2.3, 9.2 Hz), 1.99 (d, 3 H, *J* = 17.7 Hz), 2.52 (dd, 1 H, *J* = −11.6, 10.9 Hz), 3.05 (ddd, 1 H, *J* = −10.8, −2.3, 13.2 Hz), 3.87 (dd, 1 H, *J* = −10.8, 6.5 Hz); $^{13}C$ NMR (75 MHz, $C_6D_6$, {$^1H$}) δ 23.7, 24.2, 31.4, 36.7 (d, *J* = 27.0 Hz), 57.3 (d, *J* = 5.6 Hz), 70.7 (d, *J* = 5.7 Hz).

**Preparation of 2-Chloro-3-methyl-5-*tert*-butyl-1,3,2-oxazaphosphorinane.** By the general procedure, the reaction of *N*-methyl-2-(hydroxymethyl)-3,3-dimethylbutylamine[15] (5.04 g, 34.7 mmol), triethylamine (7.02 g, 69.4 mmol), and phosphorus trichloride (4.86 g, 34.7 mmol) in THF (480 mL) gave 4.15 g of a colorless liquid (19.8 mmol, 57% yield): bp 105–106 °C (1.5 mmHg); $^{31}P$ NMR (121 MHz, $C_6D_6$, {$^1H$}) δ 155.1 (s); $^1H$ NMR (300 MHz, $C_6D_6$) δ 0.56 (s, 9 H), 1.60 (tt, 1 H, *J* = 11.7 , 3.8 Hz), 2.41 (dddd, 1 H, *J* = −11.1 , −1.5, 9.6, 3.8 Hz), 2.18 (d, 3 H, *J* = 18.7 Hz), 2.75 (ddd, 1 H, *J* = −11.1, 11.1, 11.7 Hz), 3.81 (dddd, 1 H, *J* = −11.3, −1.5, 13.2, 3.8 Hz), 4.13 (ddd, 1 H, *J* = −11.3, 6.4, 11.3 Hz); $^{13}C$ NMR (75 MHz, $C_6D_6$, {$^1H$}) δ 27.3 (s, 3 C, $(CH_3)_3C$), 31.1, 36.5 (d, *J* = 27.0 Hz), 44.3, 47.7 (d, *J* = 5.9 Hz), 63.3 (d, *J* = 5.1 Hz).

**Preparation of 2-Chloro-3-methyl-1,3,2-oxazaphosphorinane.** By the general procedure, the reaction of 3-(*N*-methylamino)-1-propanol[16] (6.03 g, 67.7 mmol), triethylamine (13.7 g, 0.14 mol), and phosphorus trichloride (9.48 g, 67.7 mmol) in THF (600 mL) gave 5.01 g of a colorless liquid (32.6 mmol, 48% yield): bp 64–65 °C (1.5 mmHg); $^{31}P$ NMR (121 MHz, $C_6D_6$, {$^1H$}) δ 159.8 (s); $^1H$ NMR (300 MHz, $C_6D_6$) δ 0.79 (ddddd, 1 H, *J* = −14.0, 2.2, 1.7, 3.2, 2.8 Hz), 1.61 (ddddd, 1 H, *J* = −14.0, 13.0, 4.4, 12.2, 4.4 Hz), 1.99 (ddddd, 1 H, *J* = −11.9, −1.6, 8.9, 4.4, 2.8 Hz), 2.02 (d, 3 H, *J* = 18.7 Hz), 2.71 (dddd, 1 H, *J* = −11.9, 10.5, 12.2, 3.2), 3.05 (ddddd, 1 H, *J* = −11.2, −1.6, 12.9, 4.4, 1.7 Hz), 4.06 (dddd, 1 H, *J* = −11.2, 6.3, 13.0, 2.2 Hz); $^{13}C$ NMR (75 MHz, $C_6D_6$, {$^1H$}) δ 26.2 (d, *J* = 1.3 Hz), 36.8 (d, *J* = 27.5 Hz), 45.5 (d, *J* = 5.5 Hz), 61.3 (d, *J* = 5.0 Hz).

**Preparation of 2-Methoxy-3,5,5-trimethyl-1,3,2-oxazaphosphorinane (1).** By the general procedure, the reaction of 2-chloro-3,5,5-trimethyl-1,3,2-oxazaphosphorinane (4.11 g, 22.7 mmol), methanol (0.730 g, 22.7 mmol), and triethylamine (2.30 g, 22.7 mmol) in 100 mL of diethyl ether gave 2.92 g of a colorless oil (16.5 mmol, 73% yield): bp 71–72 °C (7 mmHg); $^1H$ NMR (300 MHz, $C_6D_6$) δ 0.36, 1.01, 1.82 (ddd, 1 H, *J* = −10.9 Hz), 2.30 (d, 3 H, *J* = 15.3 Hz), 2.86 (dd, 1 H, *J* = −10.9 Hz), 3.00 (ddd, 1 H, *J* = −10.4 Hz), 3.20 (d, 3 H, *J* = 11.4 Hz),

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3.74 (dd, 1 H, $J$ = −10.4 Hz); $^{13}$C NMR (75 MHz, $C_6D_6$, {$^1$H}) δ 23.6, 24.6, 37.5 (d, $J$ = 29.1 Hz), 50.5 (d, $J$ = 16.9 Hz); HRMS calcd for $C_7H_{16}O_2NP$ ($M^+$) 177.0919, found 177.0934.

**Preparation of 2-(1,1,1,3,3,3-Hexafluoroisopropoxy)-3,5,5-trimethyl-1,3,2-oxazaphosphorinane (2).** By the general procedure, 2-chloro-3,5,5-trimethyl-1,3,2-oxazaphosphorinane (3.05 g, 16.8 mmol), 1,1,1,3,3,3-hexafluoro-2-propanol (2.82 g, 16.8 mmol), and triethylamine (1.70 g, 16.8 mmol) in 100 mL of diethyl ether gave 3.19 g of a colorless liquid (12.5 mmol, 74% yield): bp 55−55.5 °C (5 mmHg); $^1$H NMR (300 MHz, $C_6D_6$) δ 0.38, 0.95, 1.84 (ddd, 1 H, $J$ = −11.5 Hz), 2.25 (d, 3 H, $J$ = 16.1 Hz), 2.73 (dd, 1 H, $J$ = −11.5 Hz), 3.08 (ddd, 1 H, $J$ = −10.7 Hz), 3.79 (dd, 1 H, $J$ = −10.7 Hz), 4.23 (d of septet, 1 H, $J$ = 6.1, 7.1 Hz); $^{13}$C NMR (75 MHz, $C_6D_6$, {$^1$H}) δ 23.0, 24.0, 36.5 (d, $J$ = 29.0 Hz), 71.0 (d of septets, $J$ = 33.1, 20.3 Hz), 122.2 (q, $J$ = 278.0 Hz). Anal. Calcd for $C_9H_{14}F_6O_2NP$: C, 34.52; H, 4.50; N, 4.47; P, 9.89. Found: C, 34.82; H, 4.56; N, 4.55; P, 9.87.

**Preparation of 2-Methoxy-3-methyl-1,3,2-oxazaphosphorinane (3).** By the general procedure, 2-chloro-3-methyl-1,3,2-oxazaphosphorinane (3.77 g, 24.5 mmol), methanol (0.79 g, 24.5 mmol), and triethylamine (2.48 g, 24.5 mmol) in 70 mL of diethyl ether gave 2.63 g of a colorless liquid (20.2 mmol, 83% yield): bp 55 °C (11.5 mmHg); $^1$H NMR (300 MHz, $C_6D_6$) δ 1.12 (ddddd, 1 H, $J$ = −13.7 Hz), 1.98 (ddddd, 1 H, $J$ = −13.7 Hz), 2.32 (ddddd, 1 H, $J$ = −11.4 Hz), 2.37 (d, 3 H, $J$ = 15.2 Hz), 3.16 (dddd, 1 H, $J$ = −11.4 Hz), 3.31 (d, 3 H, $J$ = 11.5 Hz), 3.50 (ddddd, 1 H, $J$ = −10.7 Hz), 4.02 (dddd, 1 H, $J$ = −10.7 Hz); $^{13}$C NMR (75 MHz, $C_6D_6$, {$^1$H}) δ 37.2 (d, $J$ = 29.1 Hz), 50.4 (d, $J$ = 16.7 Hz); HRMS calcd for $C_5H_{12}O_2NP$ ($M^+$) 149.0606, found 149.0613.

**Preparation of 2-(1,1,1,3,3,3-Hexafluoroisopropoxy)-3-methyl-1,3,2-oxazaphosphorinane (4).** By the general procedure, 2-chloro-3-methyl-1,3,2-oxazaphosphorinane (4.37 g, 28.4 mmol), 1,1,1,3,3,3-hexafluoro-2-propanol (4.78 g, 28.4 mmol), and triethylamine (2.87 g, 28.4 mmol) in 70 mL of diethyl ether gave 7.70 g of a colorless liquid (27.6 mmol, 97% yield): bp 66.5−69 °C (11.5 mmHg); $^1$H NMR (300 MHz, $C_6D_6$) δ 1.01 (ddddd, 1 H, $J$ = −13.9 Hz), 1.71 (ddddd, 1 H, $J$ = −13.9 Hz), 2.13 (ddddd, 1 H, $J$ = −11.7 Hz), 2.21 (d, 3 H, $J$ = 16.1 Hz), 2.81 (dddd, 1 H, $J$ = −11.7 Hz), 3.41 (ddddd, 1 H, $J$ = −11.0 Hz), 3.89 (dddd, 1 H, $J$ = −11.0 Hz), 4.23 (d of septet, 1 H, $J$ = 6.1, = 7.2 Hz); $^{13}$C NMR (75 MHz, $C_6D_6$, {$^1$H}) δ 36.5 (d, $J$ = 29.2 Hz), 70.9 (d of septets, $J$ = 33.0, 20.1 Hz), 122.3 (q, $J$ = 278.0 Hz). Anal. Calcd for $C_7H_{10}F_6O_2NP$: C, 29.48; H, 3.53; N, 4.91; P, 10.86. Found: C, 29.37; H, 3.50; N, 4.61; P, 11.08.

**Preparation of 2-(Dimethylamino)-3,5,5-trimethyl-1,3,2-oxazaphosphorinane (5).** To a solution of dimethylamine (2.00 g, 44.4 mmol, liquified at −78 °C) in 70 mL of diethyl ether was added dropwise a solution of 2-chloro-3,5,5-trimethyl-1,3,2-oxazaphosphorinane (3.40 g, 18.7 mmol) in 30 mL of diethyl ether at 0 °C with rapid stirring. By the general workup procedure given above, 2.80 g of a colorless liquid was obtained (14.7 mmol, 79% yield): bp 52−53 °C (1.1 mmHg); $^1$H NMR (300 MHz, $C_6D_6$) δ 0.75, 0.95, 2.34 (dd, 1 H, $J$ = −11.7 Hz), 2.27 (d, 3 H, $J$ = 11.9 Hz), 2.57 (d, 6 H, $J$ = 8.5 Hz), 2.58 (ddd, 1 H, $J$ = −11.7 Hz), 3.45 (dd, 1 H, $J$ = −10.8 Hz), 3.57 (ddd, 1 H, $J$ = −10.8 Hz); $^1$H NMR (300 MHz, $CDCl_3$) δ 0.91, 1.05, 2.32 (d, 3 H, $J$ = 12.1 Hz), 2.54 (dd, 1 H, $J$ = −11.8 Hz), 2.65 (d, 6 H, $J$ = 8.7 Hz), 2.75 (ddd, 1 H, $J$ = −11.8 Hz), 3.47 (dd, 1 H, $J$ = −11.0 Hz), 3.60 (ddd, 1 H, $J$ = −11.0 Hz); $^{13}$C NMR (75 MHz, $C_6D_6$, {$^1$H}) δ 23.8, 24.5, 36.5 (d, $J$ = 18.5 Hz), 37.4 (d, $J$ = 25.3 Hz). Anal. Calcd for $C_8H_{19}N_2OP$: C, 50.51; H, 10.07; N, 14.73. Found: C, 50.36; H, 10.06; N, 14.51.

**Preparation of 2-(Dimethylamino)-3-methyl-1,3,2-oxazaphosphorinane (6).** By the general procedure, 2-chloro-3-methyl-1,3,2-oxazaphosphorinane (5.01 g, 32.6 mmol), excess dimethylamine, and triethylamine (3.30 g, 32.6 mmol) in 150 mL of diethyl ether gave 3.54 g of a colorless liquid (21.8 mmol, 67% yield): bp 48 °C (1.5 mmHg); $^1$H NMR (300 MHz, $CDCl_3$) δ 1.69 (ddddd, 1 H, $J$ = −13.4 Hz), 1.83 (ddddd, 1 H, $J$ = −13.4 Hz), 2.33 (d, 3 H, $J$ = 12.5 Hz), 2.65 (d, 6 H, $J$ = 8.7 Hz), 2.83 (dddd, 1 H, $J$ = −12.0 Hz), 3.13 (ddddd, 1 H, $J$ = −12.0 Hz), 3.84 (dddd, 1 H, $J$ = −11.3 Hz), 4.03 (ddddd, 1 H, $J$ = −11.3 Hz); $^{13}$C NMR (75 MHz, $C_6D_6$, {$^1$H}) δ 36.5 (d, $J$ = 18.7 Hz), 37.0 (d, $J$ = 25.0 Hz). Anal. Calcd for $C_6H_{15}N_2OP$: C, 44.44; H, 9.32; N, 17.27; P, 19.10. Found: C, 44.36; H, 9.30; N, 17.34; P, 18.59.

**Preparation of 2-Methoxy-3-methyl-5-*tert*-butyl-1,3,2-oxazaphosphorinane (7).** By the general procedure, 2-chloro-3-methyl-5-*tert*-butyl-1,3,2-oxazaphosphorinane (3.02 g, 14.4 mmol), methanol (0.46 g, 14.4 mmol), and triethylamine (1.45 g, 14.4 mmol) in 100 mL of diethyl ether gave 2.17 g of a colorless liquid (10.6 mmol, 73% yield): bp 92−95 °C (6 mmHg). cis diastereomer: $^1$H NMR (300 MHz, $C_6D_6$) δ 0.64, 1.79 (dddd, 1 H), 2.45 (d, 3 H, $J$ = 15.2 Hz), 2.52 (dddd, 1 H, $J$ = −11.0 Hz), 3.04 (ddd, 1 H, $J$ = −11.0 Hz), 3.34 (d, 3 H, $J$ = 11.6 Hz), 3.74 (dddd, 1 H, $J$ = −10.5 Hz), 3.99 (ddd, 1 H, $J$ = −10.5 Hz); $^{13}$C NMR (75 MHz, $C_6D_6$, {$^1$H}) δ 27.6, 31.2, 37.3 (d, $J$ = 28.2 Hz), 50.6 (d, $J$ = 17.3 Hz). trans diastereomer (prepared by the published procedure[2] in a trans/cis ratio of 87/13 ($^{31}$P and $^1$H NMR)): $^1$H NMR (300 MHz, $C_6D_6$) δ 0.74, 1.97 (dddd, 1 H), 2.48 (d, 3 H, $J$ = 14.5 Hz), 2.55 (dddd, 1 H, $J$ = −10.8 Hz), 3.03 (ddd, 1 H, $J$ = −10.8 Hz), 3.35 (d, 3 H, $J$ = 11.2 Hz), 3.63 (ddd, 1 H, $J$ = −10.7 Hz), 4.03 (dddd, 1 H, $J$ = −10.7 Hz); $^{13}$C NMR (75 MHz, $C_6D_6$, {$^1$H}) δ 27.9, 32.0, 37.4 (d, $J$ = 26.3 Hz), 49.9 (d, $J$ = 18.0 Hz); HRMS calcd for $C_9H_{20}O_2NP$ ($M^+$) 205.1232, found 205.1253.

**Preparation of 2-(1,1,1,3,3,3-Hexafluoroisopropoxy)-3-methyl-5-*tert*-butyl-1,3,2-oxazaphosphorinane (8).** By the general procedure, 2-chloro-3-methyl-5-*tert*-butyl-1,3,2-oxazaphosphorinane (1.30 g, 6.20 mmol), 1,1,1,3,3,3-hexafluoro-2-propanol (1.04 g, 6.20 mmol), and triethylamine (0.630 g, 6.20 mmol) in 100 mL of diethyl ether gave 1.93 g of a colorless liquid (5.70 mmol, 91% yield): bp 101−104 °C (7 mmHg); $^1$H NMR (300 MHz, $C_6D_6$) δ 0.53, 1.65 (dddd, 1 H), 2.29 (d, 3 H, $J$ = 16.1 Hz), 2.40 (dddd, 1 H, $J$ = −11.2 Hz), 2.83 (ddd, 1 H, $J$ = −11.2 Hz), 3.75 (dddd, 1 H, $J$ = −10.8 Hz), 3.97 (ddd, 1 H, $J$ = -10.8 Hz), 4.23 (d of septet, 1 H, $J$ = 6.1, 7.1 Hz); $^{13}$C NMR (75 MHz, $C_6D_6$, {$^1$H}) δ 27.2, 31.0, 36.5 (d, $J$ = 28.4 Hz), 70.8 (d of septets, $J$ = 33.0, 19.6 Hz), 122.3 (q, $J$ = 273.0 Hz). Anal. Calcd for $C_{11}H_{18}F_6O_2NP$: C, 38.72; H, 5.32; N, 4.10; P, 9.08. Found: C, 38.71; H, 5.35; N, 4.19; P, 9.13.

**Preparation of 2-(Dimethylamino)-3-methyl-5-*tert*-butyl-1,3,2-oxazaphosphorinane (9).** By the general procedure, 2-chloro-3-methyl-5-*tert*-butyl-1,3,2-oxazaphosphorinane (4.15 g, 19.8 mmol), excess dimethylamine, and triethylamine (2.00 g, 19.8 mmol) in 120 mL of diethyl ether gave 2.89 g of a colorless liquid containing the cis and trans diastereomers (13.3 mmol, 67% yield, bp 94−95 °C (1.5 mmHg)). The cis/trans ratio of 40/60 (distilled, $^{31}$P NMR) was slowly changed to 47/53 (cis/trans) on standing as the neat oil in a freezer over a period of 3 weeks. This ratio did not change further in $C_6D_6$ solution at room temperature after another week. $^{13}$C NMR chemical shift assignments to individual diastereomers are based on relative peak intensities in the 40/60 mixture of diastereomers. cis diastereomer: $^1$H NMR (300 MHz, $CD_3CN$) δ 0.879, 1.69 (dddd, 1 H), 2.48 (d, 3 H, $J$ = 12.6 Hz), 2.62 (d, 6 H, $J$ = 8.5 Hz), 2.84 (dddd, 1 H, $J$ = −11.8 Hz), 3.15 (ddd, 1 H, $J$ = −11.8 Hz), 3.76 (dddd, 1 H, $J$ = −10.7 Hz), 3.84 (ddd, 1 H, $J$ = −10.7 Hz); $^{13}$C NMR (75 MHz, $C_6D_6$, {$^1$H}) δ 27.4, 31.4, 37.3 (d, $J$ = 17.3 Hz), 37.5 (d, $J$ = 29.4 Hz). trans diastereomer: $^1$H NMR (300 MHz, $CD_3CN$) δ 0.877, 1.74 (dddd, 1 H), 2.17 (d, 3 H, $J$ = 12.1 Hz), 2.54 (d, 6 H, $J$ = 8.4 Hz), 2.68 (ddd, 1 H, $J$ = −11.9 Hz), 2.96 (dddd, 1 H, $J$ = −11.9 Hz), 3.66 (ddd, 1 H, $J$ = −11.3 Hz), 3.99 (dddd, 1 H, $J$ = −11.3 Hz); $^{13}$C NMR (75 MHz, $C_6D_6$, {$^1$H}) δ 27.7, 31.2, 35.8 (d, $J$ = 19.7 Hz), 36.7 (d, $J$ = 22.8 Hz). Anal. Calcd for $C_{10}H_{23}N_2OP$: C, 55.02; H, 10.62; N, 12.83; P, 14.19. Found: C, 55.09; H, 10.60; N, 12.78; P, 14.59.

**Acknowledgment.** Support of this research by a grant (2RO1CA11045) from the National Cancer Institute of the Public Health Service is gratefully acknowledged. Funds for the purchase of the Finnigan MAT 95 mass spectrometer were supplied by National Science Foundation Grant CHE-9002690 and the University of Utah Institutional Funds Committee.

JO9504124