Conformations of Saturated Six-Membered Ring Phosphorus Heterocycles. 2-Aryl-1,3,2λ^5-oxazaphosphorinanes

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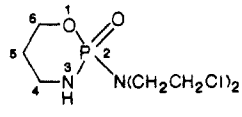
Abstract: A series of 2-aryl-2-oxo- and 2-thioxo-5-*tert*-butyl-1,3,2λ^5-oxazaphosphorinanes has been prepared (**6–12**). Assignments of cis or trans geometries to individual diastereomers were made by ^{31}P and ^{1}H NMR criteria combined with X-ray crystallographic structures for *cis*-**8** and *trans*-**12**. ^{1}H NMR analysis at 300 MHz of chair ⇄ twist equilibria leads to the conclusion, based mostly on the 2-oxo derivatives, that cis chair conformations (**13**) with 5-*tert*-butyl equatorial and Ar substituent on phosphorus axial are strongly destabilized by N3Ph/PAr steric interactions. Thus, one finds an increasingly more favorable estimate of $\Delta G°$ (chair → twist) for the 2-oxo series *cis*-**6**, *cis*-**8**, *cis*-**11**, and *cis*-**12** (N3H/PPh, N3H/PMes, N3Ph/PPh, N3Ph/PMes). Substitution of H on N3 by Ph (*cis*-**11**) changes the $\Delta G°$ (chair → twist) value for the PPh compound (*cis*-**6**) by 0.9 kcal/mol in favor of the twist form. The same substitution for the Mes case (*cis*-**8**) results in an even greater change (≥2.2 kcal/mol) in $\Delta G°$ (chair → twist) with *cis*-**12** in fact essentially completely in twist conformation **15**. Methyl substitution at N3, *cis*-**9**, likewise increases the population of twist conformation, clearly an effect of destabilizing N3Me/PPh interactions in the chair, which are relieved in the twist conformation. These results point to *the major role of N3R/PZ steric repulsive effects* in the equilibria of 1,3,2λ^5-oxazaphosphorinanes. *Excluded is the possibility that Ph substitution at N3 merely reduces the importance of n/σ* anomeric effects involving the N3 lone pair and axial substituent Z (Ar, Me_2N) on phosphorus.* The trans diastereomers also readily depopulate the chair conformation to give twist form **16**, however, instead of **15** (*trans*-**6**, **8**, and **11**). The pseudoaxial-seeking tendencies of substituents on phosphorus for trans diastereomers are shown to be CH_3O > Ph > Me_2N. A notable finding for the *trans*-2-aryl-2-oxo-5-*tert*-butyl-1,3,2λ^5-oxazaphosphorinanes is the destabilizing effect of equatorial PMes compared to equatorial PPh, which results in greater depopulation of the diequatorially substituted chair, **13**.

The 1,3,2λ^5-oxazaphosphorinane ring system, structures **1–5**, is formally derived from cyclohexane by the replacement of three ring carbons by heteroatoms. In so doing, (1) ring hydrogen



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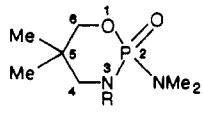
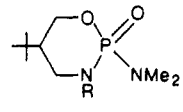


2, R = H
3, R = Ph



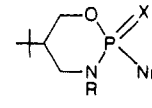
4, R = H
5, R = Ph

atoms are replaced by lone pairs, (2) bond lengths and angles are altered, and (3) bond and molecular dipoles are introduced. The resulting ring system provides an opportunity to study the effects of heteroatoms within the ring on the conformational properties of cyclohexane. Cyclophosphamide (**1**), an important antitumor agent, contains the 1,3,2λ^5-oxazaphosphorinane as an essential element in its biological activity, as do its congeners trophosphamide and isophosphamide.[1] These molecules are activated by a first-step microsomal oxidation in the liver to give 4-OH products, which potentially are diastereomeric. Moreover, in animal tests, the diastereomeric *cis*- and *trans*-4-phenylcyclophosphamides show different efficacies.[2] An understanding of the potential effects of conformation on oxidation, the transport properties of metabolites, and breakdown of metabolites to cytotoxic products depends on a thorough knowledge of the conformational properties of the 1,3,2λ^5-oxazaphosphorinane ring system.

We have reported earlier for a number of 2-oxo- and 2-thioxo-2-(dialkylamino)-1,3,2λ^5-oxazaphosphorinanes the major effects on chair–chair and chair–twist conformational equilibria resulting from substituent changes at N3 and on phosphorus. In particular, from comparison of **4** and **5**, the ~1.6 kcal/mol destabilization of **13** in favor of **15** on replacement of H at N3 by C_6H_5 (X = Me_2N, Y = O) is notable.[3] A similar effect was found on the chair ⇄ chair equilibrium for the 5,5-dimethyl-2-(dialkylamino)-2-oxo-3-R-1,3,2λ^5-oxazaphosphorinanes (**2** and **3**).[4]

The depopulation of chair conformations such as **13** with axial Me_2N was ascribed primarily to *steric repulsions* between the C_6H_5 at N3 and the axial Me_2N. However, the phenyl substituent at N3 is also *inductively* withdrawing and may significantly reduce the stabilization resulting from n/σ* overlap involving the lone pair on N3 and the P–N σ* orbital when the Me_2N is axial. It might indeed be argued that the observed effects of replacement of H by Ph at N3 is primarily a stereoelectronic phenomenon rather than a steric one.

To address this question, we have compared phenyl on phosphorus to the sterically more demanding mesityl substituent (hydrogen, methyl, and phenyl substituents on ring nitrogen) in a series of 5-*tert*-butyl-2-oxo- and 2-thioxo-1,3,2λ^5-oxazaphosphorinanes, **6–12**. *The effects of substituent changes on the*



6: X = O, R = H, Ar = Ph
7: X = S, R = H, Ar = Ph
8: X = O, R = H, Ar = Mes
9: X = O, R = Me, Ar = Ph
10: X = S, R = Me, Ar = Ph
11: X = O, R = Ph, Ar = Ph
12: X = O, R = Ph, Ar = Mes

equilibria involving ***13–16*** *that we report can only be understood*

† University of Utah.
‡ University of Arizona.

(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, The Netherlands, 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) Bajwa, G. S.; Chandrasekaran, S.; Hargis, J. H.; Sopchik, A. E.; Blatter, D.; Bentrude, W. G. *J. Am. Chem. Soc.* **1982**, *104*, 6385.

(4) (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.

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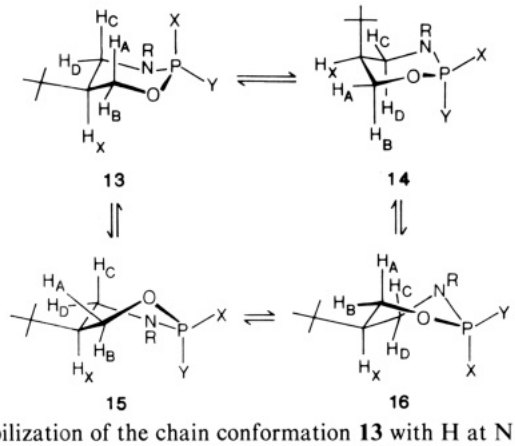
Table I. Proton and Phosphorus Chemical Shifts for **6–12**[a]

compd	solvent	δ(A)	δ(B)	δ(C)	δ(D)	δ(X)	δ(*t*-Bu)	δ(R)[b]	δ(Ar)	δ(^{31}P)[c]
cis-**6**	C_6D_6	3.67	4.17	2.70	3.14	1.76	0.42	6.24	7.19, 8.06	19.47
cis-**7**	C_6D_6	3.71	4.29	2.69	3.09	1.78	0.51	4.05	7.26, 7.97	73.08
cis-**8**	C_6D_6	3.62	4.19	2.65	2.96	1.76	0.42	5.38	6.75, 6.73	20.88
cis-**9**	C_6D_6	3.76	4.13	2.89	2.74	1.91	0.54	2.53	7.19, 7.87	17.33
cis-**9**	tol-d_8, 101 °C	3.86	4.21	3.02	2.84	1.99	0.66	2.56	7.23, 7.85	
cis-**10**	C_6D_6[d]	4.10	4.55	3.13	3.12	2.03	0.59	2.52	7.15, 7.96	82.70
cis-**10**	tol-d_8, 101 °C[d]	3.84	4.28	2.94	2.88	1.81	0.69	2.54	7.19, 7.96	
cis-**11**	C_6D_6[d]	3.82	4.35	3.36	3.39	2.06	0.53	6.86, 7.03	7.55, 7.89	13.33
cis-**12**	C_6D_6	3.81	4.48	3.42	3.49	2.72	0.57	6.57–7.27		14.78
cis-**12**	acetone-d_6	4.20	4.55	3.66	3.70	2.64	1.00	6.80–7.23		
trans-**6**	C_6D_6	4.22	3.94	3.09	3.00	1.63	0.54	5.82	7.18, 8.10	18.96
trans-**7**	C_6D_6	4.39	3.88	2.97	2.67	1.57	0.54	2.11	7.16, 8.04	80.39
trans-**8**	C_6D_6	4.26	3.92	3.05	2.94	1.51	0.53	5.92	6.75, 6.73	20.68
trans-**10**	C_6D_6	4.54	4.06	3.06	2.76	1.98	0.66	2.08	7.18, 8.25	88.75
trans-**11**	C_6D_6	4.37	3.99	3.38		1.93	0.56	6.88, 7.06	7.48, 7.96	15.12
trans-**11**	acetone-d_6[d]	4.48	4.38	3.63	3.76	2.38	0.99	7.06, 7.24, 7.37, 7.48, 7.78		
trans-**12**	C_6D_6	4.65	4.18	3.82	3.38	2.23	0.62	6.61–7.38		19.69
trans-**12**	acetone-d_6	4.55	4.42	3.79	3.60	2.42	1.01	6.82–7.28		

[a] Concentration ~10% w/v. See structure **13** for proton assignments. Measured at 300 MHz. [b] Substituent at N3. [c] In C_6D_6. [d] Simulated and iterated using LAOCN3.

in terms of steric repulsions between R at N3 and axial or pseudoaxial aryl (phenyl or mesityl). An unexpected apparent



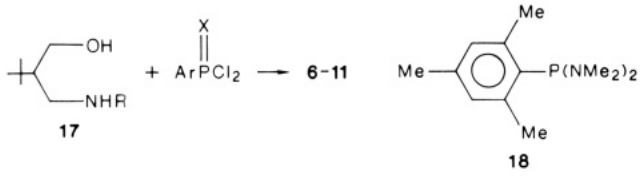
13 **14**

15 **16**

destabilization of the chain conformation **13** with H at N3 and mesityl equatorial on phosphorus also is encountered. Indeed, trans diastereomers (Y = aryl) are seen to readily depopulate conformation **13** in a number of instances.

Results

Preparations. Compounds **6–11** were prepared by reaction of the appropriate amino alcohol with the corresponding phosphoryl dichloride:



17 **18**

Reaction of bis(dimethylamino)mesitylphosphine (**18**) with **17** (R = Ph), followed by oxidation by N_2O_4, gave **12**. Amino alcohol **17** was readily prepared by $LiAlH_4$ reduction of the corresponding amide ester, obtained routinely from diethyl *tert*-butylmalonate.[3]

Assignments of Diastereomers. The designation cis or trans (relationship of *t*-Bu and substituent on phosphorus) to the individual diastereomers of **8** and **12** was made by single-crystal X-ray structure determinations for *cis*-**8** (see Figure 1 and Discussion below) and *trans*-**12** (Figure 2).[5] The cis and trans geometries for the diastereomers of **6**, **7**, and **9–11** were derived from the relative chemical shifts of H_A vs H_B ($\delta(H_A) > \delta(H_B)$ (trans); $\delta(H_B) > \delta(H_A)$ (cis)) and for **7**, **10**, and **11** also from the values of $\delta^{31}P$ ($\delta(^{31}P)$ (trans) > $\delta(^{31}P)$ (cis)), Table I. The ^1H and ^{31}P chemical shift criteria have been validated by X-ray

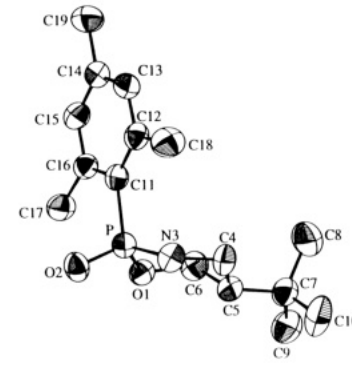


Figure 1. ORTEP plot for *cis*-**8**.

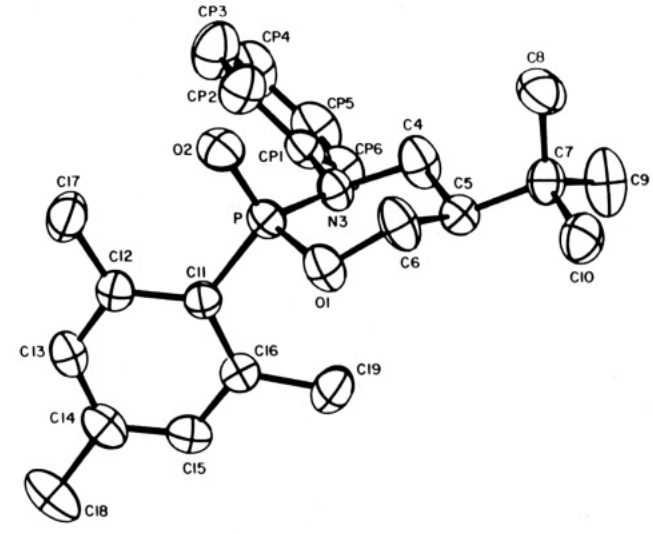


Figure 2. ORTEP plot for *trans*-**12**.[5]

crystallography of six 5-*tert*-butyl-2-oxo- or 2-thioxo-1,3,2λ^5-oxazaphosphorinanes including **8** and **12**.[6] Note that the dia-

(5) Day, R. O.; Holmes, R. R., details to be published elsewhere.

(6) These include, in addition to *cis*-**8** and *trans*-**12**, the following: *cis*-2-(dimethylamino)-2-oxo-5-*tert*-butyl-1,3,2λ^5-dioxazaphosphorinane;[8] *cis*-2-(dimethylamino)-2-thioxo-5-*tert*-butyl-1,3,2λ^5-oxazaphosphorinane;[9] *cis*-2-(dimethylamino)-2-oxo-3-phenyl-5-*tert*-butyl-1,3,2λ^5-oxazaphosphorinane;[3] *cis*-2-(dimethylamino)-2-oxo-3,5-diphenyl-1,3,2λ^5-oxazaphosphorinane.[10] Furthermore, the assignments to the diastereomers of 2-methoxy-2-oxo-5-*tert*-butyl-1,3,2λ^5-oxazaphosphorinanes and their 3-phenyl counterparts,[11] though not done by X-ray crystallography, are unquestioned because of the expected effect of the axial-seeking methoxy on conformation. These compounds as well as their two 2-thio counterparts obey both the ^{31}P and ^1H chemical shift correlation rules.[11] The ^{31}P shift correlation also was found in ref 2 and in: Kinas, R.; Pankiewicz, K.; Stec, W. J.; Farmer, P. B.; Foster, A. B.; Jarman, M. *J. Org. Chem.* **1977**, *42*, 1650.

Table II. Proton Coupling Constants (Hz) for **6–12** at 300 MHz[a]

compd	solvent	T, °C	X	Y	R	J_{AB}	J_{AX}	J_{BX}	J_{AP}	J_{BP}	J_{CD}	J_{CX}	J_{DX}	J_{CP}	J_{DP}	J_{BD}	other[b,e]
cis-**6**	C_6D_6	25	Ph	O	H	−11.4	10.0	4.6	6.8	18.2	−12.7	11.1	4.9	2.3	24.6	2.0	J_{CY} = 3.7, J_{DY} = 6.9, J_{YP} = 6.6
cis-**7**	C_6D_6	25	Ph	S	H	−11.4	10.0	4.6	7.6	20.0	−13.5	11.5	4.7	2.0	25.6	2.0	J_{CY} = 6.8, J_{DY} = 7.1, J_{YP} = 6.8
cis-**8**	C_6D_6	25	Mes	O	H	−11.2	9.1	4.8	9.1	16.9	−12.8	11.2	5.2	2.5	24.5	1.8	J_{CY} = 4.2, J_{DY} = 7.2
cis-**9**	$C_6D_5CD_3$	25	Ph	O	Me	−11.2	9.6	4.9	8.2	16.8	−12.1	11.0	5.7	5.2	15.6	1.4	J_{MeP} = 9.6
cis-**9**	$C_6D_5CD_3$	101	Ph	O	Me	−11.2	9.0	5.3	10.0	14.8	−12.4	10.8	5.6	5.6	15.4	1.2	J_{MeP} = 9.5
cis-**10**[c]	C_6D_6	25	Ph	S	Me	−11.3	7.7	5.1	12.9	16.1	−13.0	9.0	5.6	11.0	14.9	0.0	J_{MeP} = 13.2, J_{XP} = −1.1[d]
cis-**10**[c]	$C_6D_5CD_3$	101	Ph	S	Me	−11.3	7.4	5.6	14.5	14.6	−12.6	9.0	5.6	10.4	15.0	0.7	J_{MeP} = 13.0, J_{XP} = −1.1
cis-**11**[c]	C_6D_6	25	Ph	O	Ph	−11.2	8.3	6.5	15.4	10.7	−12.1	11.2	4.9	1.9	16.6	0.8	J_{XP} = −0.7
cis-**12**	C_6D_6	25	Mes	O	Ph	−10.4	11.4	6.9	18.4	3.3	−11.4[e]	11.4	3.7	1.5	11.4	1.0	
cis-**12**[c]	acetone-d_6	25	Mes	O	Ph	−10.5	11.3	6.6	17.6	4.0	−11.8	11.5	3.3	1.0	12.9	1.1	J_{XP} = −0.7
trans-**6**	C_6D_6	25	O	Ph	H	−10.8	10.8	4.1	5.7	19.4	−11.9	9.6	6.7	14.0	12.7	1.1	J_{CY} = 4.3, J_{DY} = 2.8, J_{YP} = 6.4
trans-**7**	C_6D_6	25	S	Ph	H	−11.2	11.2	4.7	7.2	22.4	−12.4	9.0	5.2	12.4	18.3	1.5	J_{CY} = 3.6, J_{DY} = 5.8, J_{YP} = 9.0
trans-**8**	C_6D_6	25	O	Mes	H	−10.6	10.6	4.2	6.1	19.7	−12.1	9.1	6.8	16.6	8.4	0.9	J_{CY} = 4.8, J_{DY} = 2.6
trans-**10**	C_6D_6	25	S	Ph	Me	−11.2	11.6	4.2	5.5	25.0	−11.4	11.6	4.2	5.8	25.8	2.2	J_{MeP} = 15.9
trans-**11**	C_6D_6	25	O	Ph	Ph	−11.0	11.0	5.7	7.6	19.4	deceptively simple						
trans-**11**	acetone-d_6	25	O	Ph	Ph	−11.0	10.6	5.9	8.4	18.1	−12.2	8.0	6.2	10.7	9.9	0.8	
trans-**12**	C_6D_6	25	O	Mes	Ph	−11.4	11.4	4.2	4.0	21.6	−11.8	11.7	4.5	4.3	18.0	2.0	
trans-**12**	acetone-d_6	25	O	Mes	Ph	−10.9	11.8	4.5	4.4	21.2	−11.2	11.2	4.7	4.3	17.6	1.9	
19[f]	C_6D_6		MeO	O	H	−11.2	11.0	4.2	2.8	20.7	−12.6	11.6	4.6	4.4	26.6	2.6	
20[f]	C_6D_6		MeO	S	H	−11.0	10.8	4.3	4.0	20.9	*h*	11.1	4.5	*h*	*h*	1.9	
20[f]	acetone-d_6		MeO	O	Ph	−10.8	11.0	3.8	3.6	19.1	−12.4	11.3	4.0	2.1	25.6	2.3	
21[f]	C_6D_6		MeO	O	Ph	−11.0	11.2	4.4	4.2	21.4	−11.6	11.2	4.2	2.4	19.6	2.1	
trans-**5**[g]	C_6D_6		O	Me_2N	Ph	−11.8	11.0	4.0	4.0	22.0	−10.5	11.0	3.0	5.0	17.5	2.6	

[a] Concentrations ~10% w/v. See structure **13** for proton assignments. [b] H_Y = proton on N3. [c] Simulated and iterated using LAOCN3. [d] J_{XP} = −0.7 to −1.0 Hz required to correctly simulate H_X spectrum in second-order cases. [e] Closely coupled nature of H_A and H_B reduces the accuracy of these parameters. [f] Reference 11. [g] Reference 3. [h] H_C and H_D overlapped.

stereomers of **8** meet the ^1H shift criterion. (The ^{31}P shifts are too similar to be useful.) Those for **12** are consistent with both the ^1H and ^{31}P chemical shift tests. Although only one diastereomer of **9** was isolated, the assignment is secured by the relative ^1H chemical shifts. Also, the change in conformational behavior of *cis*-**9** compared to *cis*-**6** is parallel to that seen for the thioxo analogues *cis*-**7** and -**10**. Analogous relative ^1H and ^{31}P chemical shift trends have been noted for 5-*tert*-butyl-2-oxo- and 2-thioxo-1,3,2λ⁵-dioxaphosphorinanes.[7] The ^1H shift effect stems from the deshielding influence of the axial P=O on protons cis to it. The above $\delta(H_A)$ vs $\delta(H_B)$ criterion for assigning diastereomers may not work well, however, except for the 5-*tert*-butyl compounds. The ^{31}P shift effect arises from the general correlation that substituents axial on phosphorus in at least some fraction of the conformations populated by a given diastereomer contribute to an upfield shifting of the ^{31}P resonance.[7] The nearly coincidental $\delta(^{31}P)$ values for the diastereomers of **6** and those of **8** cannot be readily explained.

Another corroborative NMR parameter for **6–12** is $\delta(H_X)$. In all cases measured in C_6D_6, the resonance for H_X for the cis diastereomer is *downfield* of that for its trans counterpart. This consistency, along with other chemical shift correlations and the X-ray structures for *cis*-**8** and *trans*-**12**, gives assurance as to the correctness of the assignments.

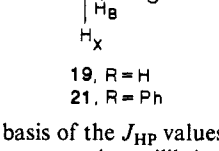
^1H NMR Parameters and Conformations of *cis*-6–12. The conformational equilibria for **6–12** were determined by inspection of $^3J_{HH}$ and $^3J_{HP}$ values obtained mostly by first-order ^1H NMR analysis at 300 MHz. Where second-order spectra were encountered, the parameters were obtained with the aid of the LAOCN3 program. NMR data are summarized in Tables I and II. The cis diastereomers will be discussed first (X = aryl; Y = O, S). The guiding principle in relating $^3J_{HP}$ to conformation is the known Karplus-like relationship for HCOP and HCNP couplings.[7a] For phosphoryl derivatives (2-oxo) individual axial or equatorial couplings are generally independent of whether the phosphoryl oxygen is equatorial or axial. Equatorial protons of 2-thioxo derivatives have coupling constants a few hertz higher when the P=S is axial.[7a]

Table III. Estimated Percentage of **15** in Equilibrium **13** ⇄ **15**

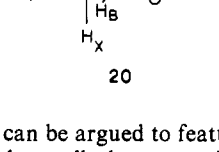
				% **15** based on[a]				
compd	X	Y	R	J_{AP}	J_{BP}	av	$\Delta G°(13 \rightarrow 15)$	$\Delta\Delta G°$
cis-**6**	Ph	O	H	21	25	23	0.68	
cis-**11**	Ph	O	Ph	62	60	61	−0.25	−0.9
cis-**8**	Mes	O	H	32	31	31	0.46	
cis-**12**	Mes	O	Ph			>95	<−1.7	>−2.2
cis-**4**[b,d]	Me_2N	O	H	19	21	20	0.62	
cis-**5**[c,d]	Me_2N	O	Ph	88	96	92	−1.0	−1.6

[a] Assumed J_{HP} values: J_{AP}(**13**) = 2.3 Hz; J_{AP}(**15**) = 23.5 Hz; J_{BP}(**13**) = 23.5 Hz; J_{BP}(**15**) = 2.3 Hz. [b] Observed in C_6D_6: J_{AP} = 6.2 Hz; J_{BP} = 17.0 Hz.[3] [c] Observed in C_6D_6: J_{AP} = 20.0 Hz; J_{BP} = 5.0 Hz.[3] [d] Values assumed for *cis*-**4** and -**5**:[3] J_{AP}(**13**) = 2.8 Hz; J_{AP}(**15**) = 20.7 Hz; J_{BP}(**13**) = 20.7 Hz; J_{BP}(**15**) = 2.8 Hz.

It is evident for *cis*-**6–8** (R = H) that a chair–twist (**13** ⇄ **15**) equilibrium exists in which chair conformation **13** greatly predominates (Table III). J_{AX} in each case is only slightly smaller than that observed for the *cis*-1,3,2λ⁵-oxazaphosphorinanes **19–21**.



19, R = H
21, R = Ph



20

On the basis of the J_{HP} values, all can be argued to feature very nearly anancomeric equilibria with the small, electronegative MeO axial in chair conformation **13**. However, for *cis*-**6–8**, J_{AP} is significantly increased and J_{BP} is somewhat reduced compared to **19–21**.[11] At the same time, J_{CX}, J_{CP}, J_{DX}, and J_{DP} for *cis*-**6–8** are similar to those of **19** and **20**. The data are readily explained by a contribution from twist conformation **15** in which the nitrogen-containing side of the ring is unchanged from **13** (chairlike); but on the oxygen side of **15**, H_A is pseudoequatorial (large J_{AP}) and H_B is pseudoaxial (small J_{BP}).[12] A contribution from **14** is

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(11) Bentrude, W. G.; Setzer, W. N.; Sopchik, A. E.; Bajwa, G. S.; Burright, D. D.; Hutchinson, J. P. *J. Am. Chem. Soc.* **1986**, *108*, 6669.

(12) This is the classic combination of J_{HP} values encountered for twist form **15**: $J_{AP} > J_{BP}$, $J_{AX} > J_{BX}$.[3,10,11]

excluded by the large value of J_{CX} found for all three (J_{CX} = 11.1–11.5 Hz).

The 2-oxo compounds with phenyl substituent at N3, *cis*-**11** and -**12**, show changes in J_{HP} values (compared to **19–21**) like those for *cis*-**6–8** but much greater in degree. This is diagnostic of a larger population of **15**. Most notable is the complete reversal in relative magnitudes of J_{AP} (18.4 Hz) and J_{BP} (3.3 Hz) values for *cis*-**12** in which phenyl on phosphorus (*cis*-**11**) is replaced by the sterically very demanding mesityl group. Twist form **15** is evidently fully populated by *cis*-**12**.[13] The small increase in J_{BX} and decrease in J_{AX} noted for *cis*-**11** (and to a lesser degree for *cis*-**8**) has been seen previously when twist forms are populated.[3,10] A less than maximal degree of twisting reduces the H_ACCH_X dihedral angle below 180° (J_{AX} decreases), and at the same time $\angle H_BCCH_X$ decreases (J_{BX} increases).

The *cis* N3Me 2-oxo derivative, *cis*-**9**, differs from *cis*-**6**, -**7**, -**11**, and -**12** in that both J_{AP} and J_{CP} increase while their opposite couplings, J_{BP} and J_{DP}, decrease. Since J_{AX} and J_{CX} remain large (9.6 and 11.0 Hz) a mixture of twist form **16** as well as **15** appears to be present, but **14** is absent.

The 2-thioxo compound corresponding to *cis*-**9**, i.e. *cis*-**10**, shows much larger changes in the J_{HX} and J_{HP} values. Indeed, the decrease of J_{CX} to 9.0 Hz could mean as much as 40% of the alternative *chair* conformation, **14**, is populated. The remainder would be twist **15** and chair **13**. Reduced J_{CX} would come from a large population of **15**, which is not fully twisted. Another possibility is that increased J_{AP} and J_{CP} result from major populations of twist **15** and **16** (**15** > **16**). In either case chair **13** is strongly depopulated.

^{1}H NMR Parameters and Conformations of *trans*-6–12. For the trans diastereomers, chair–twist equilibria also are evident. Thus, depopulation of chair **13** (X = O, S; Y = aryl) and population of twist **16** by *trans*-**6–8** (R = H) is attested to by the large increases in J_{CP} and major decreases in J_{DP}. These changes are greater in fact than those seen for *cis*-**6–8** for J_{AP} and J_{BP}. Again, the large values of J_{AX} (10.6–11.2 Hz) rule out the presence of chair form **14** in more than very minor quantities. While J_{AP} and J_{BP} are similar to those for **19–21**, J_{AP} is somewhat increased and J_{BP} is decreased, as would be true were a small percentage of twist **15** also present. *Most notable is the fact that the twist conformer largely populated is now* ***16*** *not* ***15***. The small changes in J_{CX} (decreased) and J_{DX} (increased) are readily explained, as were J_{AX} and J_{BX} for *cis*-**9** and -**11**. That is, the ring is not twisted completely into **15**. It structure is somewhere between a boat form, with C5 and P at bowsprit positions, and **15**.

Considering the trans diastereomers of the N3Ph and N3Me derivatives (**10–12**), it is clear that *trans*-**12** is almost entirely in chair conformation **13** with J_{HP} values much like those of *trans*-**5** (Table II). The changes in J_{CP} and J_{DP}, compared to those for **21**, suggest a very minor amount of twist **16** could be present for *trans*-**5** and -**12**. *trans*-**10** also is predominately, if not completely, in the chair form **13** as seen by inspection of its J_{HP} values, which are very close to those of the 2-thioxo analogue of *trans*-**5** (J_{AP} = 5.0 Hz, J_{BP} = 26.0 Hz, J_{CP} = 4.5 Hz, J_{DP} = 24.0 Hz). *trans*-**11**, on the basis of arguments given above for other systems, however, shows the presence of an equilibrium involving chair **13** and both twist forms, **15** and **16**, with **16** predominant. The low value of J_{CX} (8.0 Hz) reflects the lack of complete twisting in **16** seen above for *trans*-**6–8**. The sum of J_{CP} and J_{DP} (20.6 Hz) is considerably reduced as well in comparison to *trans*-**6–8**.

Another parameter, which shows itself useful in these and analogous studies,[3,4,10,11] is J_{BD}. In each instance in which the J_{HP} values confirm the primary population of the chair conformation (*cis*-**6–8**, *trans*-**10** and -**12**, and **19–21**), J_{BD} is of the order of ≥2 Hz. In a chair conformation, only H_B and H_D are in the "W" arrangement required for $^4J_{HH}$ to be relatively large.

X-ray Crystal Structure of *cis*-8. An ORTEP perspective drawing of *cis*-**8**, along with the labeling scheme, is shown in Figure 1. The crystallographic data for *cis*-**8** are listed in Table IV. Atomic coordinates for non-hydrogen atoms appear in Table V. Bond lengths and bond angles are given in Tables VI and VII, respectively. The compound adopts, in the crystalline state, chair conformation **13**. Figure 1 clearly shows the mesityl substituent

(13) Similar coupling constants were found for *cis*-**3**[3] and *cis*-2-(dimethylamino)-2-oxo-3,5-diphenyl-1,3,2λ^5-oxazaphosphorinane,[10] both of which are in the twist form (**15**) in the crystal (X-ray structure studies).

Table IV. Crystallographic Data for *cis*-2-Mesityl-2-oxo-5-*tert*-butyl-1,3,2λ^5-oxazaphosphorinane[a]

mol formula	$C_{16}H_{25}NO_2P$
mol wt	294.36
cryst syst	orthorhombic
space gp	*Pbca* (No. 61)[b]
cell dimens	
a, Å	12.095 (7)
b, Å	11.191 (4)
c, Å	24.525 (13)
V, Å^3	3319 (3)
Z	8
d_{obsd}, g cm^{-3}	1.18 (1)[c]
d_{calcd}, g cm^{-3}	1.18
abs coeff (μ_λ), cm^{-1}	1.72
scan speed, deg min^{-1}	variable (2.0–20.3) as a function of refln intensity
scan range (2θ), deg	−1.0 to +1.0
ratio of bckgd time to peak scan time	0.5
std reflcn	(6,0,0), (0,6,0), (0,0,14) recollcd every 97 reflcn
max dev of stds, %	10, random
no. of data collcd	3456
no. of unique data	3355
no. of data used	1547, $I > 3\sigma(I)$

[a] The estimated standard deviation of the least significant figure is given in parentheses in this table and in the tables that follow. [b] The space group was unambiguously determined from the systematic absences: $0kl$, $k \neq 2n$; $h0l$, $l \neq 2n$; $hk0$, $h \neq 2n$. [c] The density was determined by the flotation method using carbon tetrachloride and *n*-decane.

Table V. Fractional Atomic Coordinates for *cis*-**8**

atom	*x*	*y*	*z*
P	0.56191 (9)	0.40847 (10)	0.07316 (5)
O2	0.63314 (24)	0.43540 (25)	0.02625 (12)
O1	0.62363 (23)	0.43368 (23)	0.12922 (11)
N3	0.45601 (27)	0.4981 (3)	0.07732 (14)
C6	0.5573 (4)	0.4432 (4)	0.17809 (18)
C5	0.4781 (4)	0.5467 (4)	0.17502 (18)
C4	0.3973 (4)	0.5261 (4)	0.12824 (20)
C11	0.5286 (3)	0.2506 (4)	0.07546 (16)
C12	0.4242 (4)	0.2025 (4)	0.6340 (17)
C13	0.4095 (4)	0.0792 (4)	0.06424 (19)
C14	0.4943 (4)	0.0005 (4)	0.07556 (21)
C15	0.5979 (4)	0.0487 (4)	0.08594 (19)
C16	0.6175 (4)	0.1704 (4)	0.08641 (16)
C18	0.3246 (4)	0.2766 (5)	0.04790 (22)
C19	0.4751 (4)	−0.1323 (4)	0.07628 (24)
C17	0.7335 (4)	0.2110 (4)	0.09769 (20)
C7	0.4219 (4)	0.5751 (4)	0.23048 (19)
C9	0.5100 (5)	0.6082 (5)	0.27263 (22)
C8	0.3546 (5)	0.4703 (6)	0.25239 (25)
C10	0.3443 (5)	0.6816 (5)	0.22366 (24)

Table VI. Bond Distances (Å) for *cis*-**8**

P–O2	1.469 (3)	C11–C12	1.404 (6)
P–O1	1.590 (3)	C11–C16	1.426 (6)
P–N3	1.630 (4)	C12–C13	1.392 (6)
P–C11	1.813 (5)	C12–C18	1.511 (6)
O1–C6	1.446 (5)	C13–C14	1.379 (6)
N3–C4	1.471 (5)	C14–C15	1.388 (6)
		C14–C19	1.504 (7)
C6–C5	1.504 (6)	C15–C16	1.382 (6)
C5–C4	1.525 (6)	C16–C17	1.500 (6)
C5–C7	1.554 (6)	N3–HN3	1.139 (3)
C7–C9	1.531 (7)	O2···HN3	1.823 (5)
C7–C8	1.524 (7)		
C7–C10	1.527 (7)		

Table VII. Bond Angles (deg) for *cis*-**8**

O2–P–O1	111.4 (2)	C9–C7–C8	108.7 (5)
O2–P–N3	112.6 (2)	C9–C7–C10	108.2 (4)
O2–P–C11	110.8 (2)	C8–C7–C10	108.1 (5)
O1–P–N3	101.9 (2)	C12–C11–C16	118.5 (4)
C11–P–O1	104.5 (2)	C11–C12–C13	119.4 (4)
C11–P–N3	115.0 (2)	C11–C12–C18	124.1 (4)
P–O1–C6	118.0 (3)	C13–C12–C18	116.5 (4)
P–N3–C4	124.3 (3)	C12–C13–C14	122.8 (4)
P–C11–C12	124.5 (3)	C13–C14–C15	117.4 (4)
P–C11–C16	116.8 (3)	C13–C14–C19	121.2 (4)
C5–C6–O1	111.6 (4)	C15–C14–C19	121.4 (5)
C5–C4–N3	111.2 (4)	C14–C15–C16	118.7 (5)
C6–C5–C4	109.2 (4)	C11–C16–C15	119.3 (4)
C5–C7–C9	109.6 (4)	C11–C16–C17	123.3 (4)
C5–C7–C8	112.7 (4)	C15–C16–C17	117.4 (4)
C5–C7–C10	109.4 (4)	N3–HN3–O2	148.7 (5)

to be axial, while the *tert*-butyl is equatorial. This conformation is the same as that primarily populated in solution. The mesityl group sits crosswise to a vertical plane through atoms P and C5. Thus, ∠C16–C11–P–O_2 = 67.0° and ∠C12–C11–P–O2 = 108.2°. The inequality of these angles is in accord with the differences in the nonbonding distances C11–C4 (3.702 Å) and C11–C6 (3.332 Å). The resulting distances C18–HC4′ (3.568 Å) and C17–HC6′ (2.927 Å) are consistent with the above dihedral angles (C16–C11–P–O2 and C12–C11–P–O2). The very short C17–HC6′ distance has no ready explanation. The atoms O1–P–N3 and C4–C5–C6 define two planes, 1 and 2. The interplane angles between the best plane through atoms N3–C4–C6–O1 and the above planes define the pucker of the chair ring. For plane 1 and N3–C4–C6–O1, a value of 32.9° is found; while for plane 2 and N3–C4–C6–O1, the angle is 51.3°. The flattening seen about phosphorus is typical of 1,3,2-oxazaphosphorinanes and indeed is well within the range found for other structures with axial substituents on phosphorus.[4,9,11] Rings with substituents equatorial show decreased flattening.[14] The interplane angle at the C5 end of the ring for *cis*-**8** is unexceptional. Interestingly, as is typical of P–N bonds,[4b,8–10,14,15] the axial P–C11 bond of *cis*-**8** is longer, 1.813 (5) Å, than the equatorial one of *trans*-**12**, 1.803 (2) Å. Anomeric effect[16] arguments have usually been used to rationalize such differences in the P–N systems. In this regard, the P–N3 bond length in *cis*-**8**, 1.630 (4) Å, is shorter than that in *trans*-**12**, 1.670 (2) Å, as is consistent with the anomeric effect rationale. The phenyl substitution at N3 in *trans*-**12** may, however, also play an important role in lengthening the P–N3 bond. Nonetheless, the suggestion that the P–C (aryl) σ^* orbital is involved with acceptance of adjacent lone pairs (O or N) is somewhat unusual. These effects normally are involved for P–X bonds with X = Cl, O, and N (electronegative substituents).

Discussion

It is clear from the above results that the relative populations of **13**–**16** depend greatly on the particular substituent at N3 and on phosphorus and on whether the diastereomer is cis or trans. In discussing the possible origins of effects of structural changes on the relative energies of conformations, it is useful to cautiously assign approximate conformer populations to those equilibria that involve primarily two structures. This is readily done if reasonable values can be assumed for J_{AP} and J_{BP} in the two structures.

(14) This can be seen in examining the interplane angles or looking at the C4–N3–P–O1 and C6–O1–P–N3 dihedral angles of the compounds with axial substituents (ref 9, and unpublished data, and ref 4b and 11). By comparison for cyclophosphamide with $N(CH_2CH_2Cl)_2$ equatorial, see: Cutbush, S. D.; Neidle, S.; Taylor, G. N.; Gaston, J. L. *J. Chem. Soc., Perkin Trans. 2* **1981**, 980. Adamiak, D. A.; Saenger, W.; Kinas, R.; Stec, W. J. *Z. Naturforsch., C: Biosci.* **1977**, *32C*, 672. Karle, I. L.; Karle, J. M.; Egan, W.; Zon, G.; Brandt, J. A. *J. Am. Chem. Soc.* **1977**, *99*, 4803.

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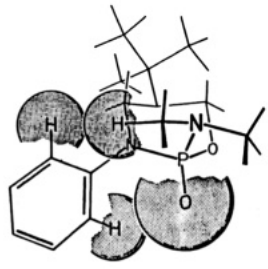


Figure 3. Me_2N/N3Ph steric repulsions in *cis*-**5** based on a Dreiding model. Hemispheres approximate atomic radii (taken from ref 3).

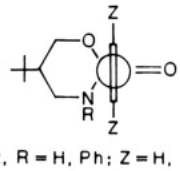
(Because of the obvious effect of the substituent at N3 on J_{CP} and J_{DP}, we generally do not use these parameters.) E.g., for equilibrium **13** ⇄ **15**, as we have shown previously,[3,11] mole fraction **15** can be calculated from the measured J_{AP} using the equation below. A completely analogous equation may be written in terms of J_{BP}.

$$N(\mathbf{15}) = [J_{AP}(\text{obsd}) - J_{AP}(\mathbf{13})]/[J_{AP}(\mathbf{15}) - J_{AP}(\mathbf{13})]$$

Cis Derivatives. As noted in the Results, *cis*-**6**, -**8**, and -**11** all feature the chair–twist equilibrium **13** ⇄ **15**. Since the sum $J_{AP} + J_{BP}$ for these compounds (25.0–26.1 Hz) is greater than that for **19** (23.5 Hz), the values for J_{AP} (23.5 Hz) and J_{BD} (2.3 Hz) for the P–OPh analogue of **3**, which should be entirely in one chair form, were employed ($J_{AB} + J_{BP}$ = 25.8 Hz). It was assumed that the couplings to phosphorus for H_A and H_B are simply interchanged in **13** and **15**. This will be true if **15** is sufficiently twisted. Decreased twisting of **15** would reduce both J_{AP}(**15**) and J_{BP}(**15**) as then ∠H_ACOP is less than 180° and ∠H_BCOP is greater than 60°. Since the sum J_{AP} and J_{BP} in the series *cis*-**6**, *cis*-**8**, and *cis*-**11** does not change, **15** appears to be sufficiently twisted. (As will be noted later, twisting the ring gives rise to J_{AP} and J_{BP} values like those of the chair before this is true of J_{CP} and J_{DP}. A large $J_{AP} + J_{BP}$ sum also is reconciled in this way with the reduced J_{AX} and increased J_{BX} for *cis*-**11**.) Estimates of the populations of **15** for the series of cis diastereomers appear in Table III. Populations based on J_{AP} agree well with those from use of J_{BP}. Clearly, the actual percentage of **15** in each case is only an estimate. However, the trends in populations are certainly valid. Values of $\Delta\Delta G°$ are likely reasonably valid.

What is evident is that when an axial phenyl is on phosphorus, substitution of a phenyl for hydrogen at N3 depopulates chair conformer **13** ($\Delta\Delta G°$(**13** → **15**), *cis*-**6** vs *cis*-**11**, ≅0.9 kcal/mol). This is the same effect noted earlier[3] with Me_2N axial on phosphorus when *cis*-**4** and -**5** are compared. The axial phenyl substituent at phosphorus, however, feels the effect of the N3Ph somewhat less than does the axial Me_2N. *cis*-**5** was earlier reported to be very largely in the twist conformation **15**. This is confirmed in Table III using J_{AP} (20.0 Hz) and J_{BP} (5.0 Hz) values in C_6D_6 previously reported and the slightly different assumed couplings for **13** and **15** of that study, which are more consistent with the lower sum of J_{AP} and J_{BP} for *cis*-**4** and –**5**. Moreover, $\Delta\Delta G°$(**13** → **15**) for *cis*-**4** vs *cis*-**5**, as earlier reported,[3] is 1.6 kcal/mol. (Use of the assumed couplings for **13** and **15** of the present study (Table III) only lowers the estimated percentage of **15** populated by *cis*-**5** to 87%.)

We interpreted[3] the effect of N3Ph on the equilibrium of *cis*-**5** to be a steric one in which conformation **13** is destabilized by repulsive interactions between the N3Ph ortho hydrogens and the Me_2N methyl, Figure 3. The axial Ph at phosphorus of *cis*-**11** cannot bisect the six-membered ring because of interactions with the axial hydrogens at C4 and C6. In the conformation approximated by **22**, which is similar to that depicted in Figure 1,



22, R = H, Ph; Z = H, Me

the ortho hydrogens of the phenyl ring (**22**, Z = H) will experience repulsive interactions with the N3Ph group, which will have an orientation similar to that in Figures 1 and 2. However, in twist conformation **15** such interactions are relieved. According to CPK models the pseudoequatorial phenyl on phosphorus in **15** is relatively free of steric interactions when it is coplanar with the P=O bond. (See also Figure 2.)

The steric nature of the effect of a Ph at N3 is further defined by comparing *cis*-**11** with *cis*-**12** in which the size of the phenyl group on phosphorus is greatly increased by the ortho methyls of the mesityl group, **17** (Z = CH_3). As a result for *cis*-**12** the J_{AP} (18.4 Hz) and J_{BP} (3.3 Hz) values are nearly the reverse of those in **19**, just as expected if a flexible conformation close to **15** is now nearly 100% populated[3,10] ($\Delta\Delta G°$ (**13** → **15**), *cis*-**8** vs *cis*-**11**, ≥2.2 kcal/mol). The J_{CP} (1.5, 1.0 Hz) and J_{CP} (11.4, 12.9 Hz) parameters also are unusual. Although Ph at N3 evidently attenuates the value of $^3J_{HP}$ through nitrogen (see, e.g., **21** vs **19**), the extreme reduction in the sum of J_{CP} and J_{DP} (12.9–13.9 Hz) for *cis*-**12** is exactly what Dreiding models predict if a boat conformation with P and C5 at bowsprit positions indeed were twisted in the direction of **15**, but not fully so (J_{CX} and J_{DX} unperturbed). This pseudorotational twisting motion brings the hydrogens at C4 (H_A and H_B) into approximate 180° (H_A) and 60° (H_B) HCOP dihedral angular relationships with phosphorus before this occurs for H_C, H_D, and ∠HCNP. (See above discussion for *cis*-**6**, **8**, and **11**.) The ∠HCNP angles of <180° for H_C and >60° for H_D reduce both J_{CP} and J_{DP}. The reduction in J_{CP} and J_{DP} is seen to a lesser degree with *cis*-**11**, which strongly populates **15**, but less fully than does *cis*-**12**. *There can be no doubt that the above phenomena have steric origins.*

The very strong steric destabilization of the axial mesityl in *cis*-**12** is dramatized by the fact that a CPK model for chair form **13** cannot even be constructed for *cis*-**12**. With hydrogen at N3, *cis*-**8**, such a model is easily assembled. The only small increase in size for mesityl compared to phenyl noted in Table III (*cis*-**6** vs *cis*-**8**) is completely consistent with what the CPK models reveal.

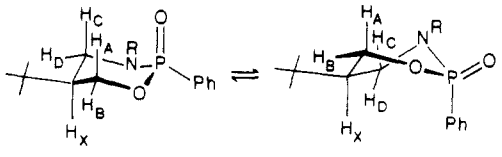
Unlike the phenyl substituent, methyl will not inductively withdraw the N3 lone pair and destabilize **13**. *One may presume, therefore, that the depopulation of* **13** *by* CH_3 *at N3, observed for cis-***9** *and -***10** *(Table II), is totally a steric result.* (Compare *cis*-**6** with *cis*-**9** and *cis*-**7** with *cis*-**10**.) Since more than one twist (**15** and **16**) and for *cis*-**10** perhaps even a second chair form (**14**) are populated in these systems, quantitative numbers like those in Table III cannot be obtained. This is the first instance of relief of strain in a chair conformer like **13** of a cis diastereomer through formation of any other conformer except **15**. Methyl at N3 is evidently not so effective at destabilizing **13** in cis oxides as is phenyl, as simple comparisons of the couplings show. Likewise, it appears not to differentiate so readily the energies of flexible forms, if indeed both **15** and **16** are populated.

Finally, it is worth noting that increasing the temperature of solutions of *cis*-**9** and *cis*-**10** increases the population of the twist conformation (Table II). Though twist forms are readily populated energetically, they are of higher enthalpy than chair conformations.

Trans Derivatives. The trans diastereomers of this study show some unusual conformational properties as well. Most notable is the relative ease with which chair conformers are converted into twist forms. The only P=O compound almost entirely in the chair form **13** is *trans*-**12**. Its J_{HP} values are nearly identical with those of *trans*-**5** listed in Table II. Evidently the pseudoaxial mesityl substituent, like Me_2N, interacts very strongly in twist form **15** or **16** with the Ph at N3.

For *trans*-**6**, **-8**, and **-11**, the values of J_{HP}, compared to those of *trans*-**12**, clearly show depopulation of chair form **13**. The major nonchair form populated by *trans*-**6**, **-8**, and **-11** is twist conformation **16**. This is in contrast to the situation with the corresponding cis diastereomers, which move out of the chair primarily into conformation **15**. A minor amount of **15** is found in the equilibria for the trans isomers as well as evidenced by increases in J_{AP} and decreases in J_{BP} in the order *trans*-**6** ≅ *trans*-**8** < *trans*-**11**. Because of the three-part nature of the equilibrium, calculation of percentages of conformers would be imprecise. A discussion of trends in populations, however, is worthwhile.

Evidently, barring the strong N3 Ph/PMes interaction of *trans*-**12**, the twist forms (**15** < **16**) are quite energetically accessible to the *trans*-**2**-oxo-**1,3,2**λ^5-oxazaphosphorinanes, *trans*-**6**–**8** and **-11**; *all are >50% in the twist conformation* ($J_{CP} > J_{DP}$). The phenyl clearly seeks to be pseudoaxial and provides the driving force for the interconversion **23** → **24**. Earlier it was reported[11]



23 **24**

that the trans analogue of POMe compound **19** is to a great extent in conformation equivalent to **24** (**16**), Ph = MeO. From its coupling constants (J_{AP} = 7.6 Hz, J_{BP} = 16.6 Hz, J_{CP} = 17.2 Hz, J_{DP} = 8.9 Hz), the population of **16** by the trans POMe compound clearly is greater than that for *trans*-**6**. *trans*-**4** was seen to be almost entirely in the chair conformation with *t*-Bu and Me_2N both equatorial.[3] The tendency of phosphorus substituents of *trans*-1,3,2-oxazaphosphorinanes with H at N3 to be pseudoaxial is thus MeO > Ph > Me_2N. The population of twist forms with Ph or Me_2N pseudoaxial is close to negligible in the *trans*-**2**-phenyl- and 2-(dimethylamino)-2-oxo-5-*tert*-butyl-1,3,2λ^5-dioxaphosphorinane series.[7c,d] This is consistent with the generally greater ease of putting substituents axial or pseudoaxial in the 1,3,2λ^5-oxazaphospha series.[4,11]

It is at first surprising that *trans*-**11** (R = Ph) depopulates the chair to about the same extent as does *trans*-**6** (R = H). The twist conformation, **15** or **16**, might be expected to bring into play for *trans*-**11** destabilizing N3Ph/PPh pseudoaxial interactions similar to those discussed above for *cis*-**11**. However, it is important to point out a significant difference between the chair ⇄ twist equilibria for the trans and cis diastereomers. The nonrigid twist forms with a substituent (MeO, Ph, Me_2N, etc.) pseudoaxial are able to flex by pseudorotation to minimize steric interactions within the ring system. Thus, only with the severe N3Ph/PMes case is a strong destabilization of the twist in evidence. By contrast, *cis*-**11** feels the full destabilizing effect of the N3Ph/PPh interaction in the rigid chair **13**.

This flexible feature of the trans twist conformations was noted in the previously reported effect of phenyl substituent on the **15** ⇄ **16** equilibrium for the above-mentioned trans methoxy compound.[11] The N3H compound strongly favors **16**, while the N3Ph compound is largely in conformation **15**. This effect was noted above for *trans*-**11** although it is much less important than for the POMe case.[11] This variation in **15** ⇄ **16** equilibrium most likely involves changes in interactions between substituents on the N3–P bond in different conformations. The influence on **15** ⇄ **16** for the cis diastereomers of substituent at N3 is seen in comparing the NH, NMe, and NPh compounds.

A most unusual observation comes from comparison of *trans*-**6** and **-8**. Clearly, for the cis diastereomers of **6** and **8**, the mesityl is slightly larger (Table III) than phenyl ($\Delta\Delta G°$ ≅ 0.2 kcal/mol). This observation should extrapolate to a lesser depopulation of the trans chair diastereomer **13** by *trans*-**8**. However, the J_{HP} values for *trans*-**6** and *trans*-**8** leave no doubt that *trans*-**8** is less in the chair than is *trans*-**6**. Evidently in this surprising case, the equatorial mesityl is *destabilized* in chair **13**, and this strain is removed in the flexible twist form analogous to **19**. (See above discussion of *trans*-**6** vs *trans*-**11**.) Both Dreiding and CPK models make it clear that the equatorial mesityl, unlike its axial counterpart, experiences severe steric interactions, regardless of the conformation about the P–C (mesityl) bond. Such interactions are clearly evident in the X-ray crystal structure of *trans*-**12**, Figure 3, in the P–C (mesityl) conformation it assumes. (The details of this structure determination will be reported elsewhere.[5]) In twist **16** the pseudoaxial mesityl experiences but one 1,3-synaxial interaction, that with pseudoaxial H_D at C4. Therefore, the Ph and Mes of *trans*-**6** and **-11** should be more nearly equal in steric size in **16** than in the rigid chair **13**. This will allow the desta-

bilization of **13** by equatorial mesityl to be fully expressed in the equilibrium **13** ⇄ **16** for *trans*-**8**. Obviously the steric destabilization of the pseudoequatorial mesityl is not so great as to prevent the near-complete population of the twist conformation by *cis*-**12**.

The trans 2-thioxo compounds, *trans*-**7** and *trans*-**10**, represent an interesting comparison in themselves and also to the 2-oxo series. *trans*-**7** displays an equilibrium composed of the same set of conformers populated by the 2-oxo analogue, *trans*-**6**. Again, the presence of three forms prohibits meaningful quantitation, but comparing J_{CP} and J_{DP} makes it clear that while *trans*-**6** remains <50% in chair conformation **13**, *trans*-**7** is >50% in that form. The methyl at N3 of *trans*-**10** evidently renders twist conformations even less stable than those from *trans*-**7**. The J_{HP} values are very close to those of the thioxo analogue of *trans*-**3**, which is nearly entirely in the chair (J_{AP} = 5.0 Hz, J_{BP} = 26.0 Hz, J_{CP} = 4.5 Hz, J_{DP} = 24.0 Hz).[3] It should be noted that *trans*-2-(dimethylamino)-2-thioxo-5-*tert*-butyl-1,3,2λ⁵-oxazaphosphorinane crystallizes in the chair conformation with Me_2N and *t*-Bu axial.[8] Evidently, crystal packing alone is sufficient to force both substituents axial.

No generalization can be made concerning the relative ease of population of nonchair forms by the corresponding 2-thioxo vs 2-oxo analogues of either the trans or cis diasteromer. Some orderings with respect to depopulation of chair conformation **13** are the following: *cis*-**7** (P=S) ≅ *cis*-**6** (P=O); *cis*-**10** (P=S) > *cis*-**9** (P=O); *trans*-**7** (P=S) < *trans*-**6** (P=O).

Conclusions

The above results demonstrate that the distribution of molecules between conformations **13–16** depends strongly on the following: the nature of the substituent on N3 (H, Me, or Ph); the substituent, Mes or Ph, on phosphorus; and the diastereomer, cis or trans, under consideration. For the cis diastereomers, the primarily N3R/PAr *repulsive steric* nature of effects that destabilize chair **13** is clearly shown by the chair ⇄ twist equilibria comparison for *cis*-**6** vs *cis*-**11** ($\Delta\Delta G°$ = 0.9 kcal/mol) compared to *cis*-**8** vs *cis*-**12** ($\Delta\Delta G°$ = ≥2.2 kcal/mol). The 1.3 kcal/mol difference in $\Delta\Delta G°$ must result from the much greater effective steric size of the axial mesityl interacting with N3Ph compared to that for an axial phenyl. (Any electronic effect of the methyl groups on the mesityl should be similar in *cis*-**8** and -**11**.) Indeed, the effect of N3Ph vs N3H for the axial substituents we have examined so far decreases in the order Mes > Me_2N > Ph (2.2 > 1.6 > 0.9 kcal/mol). The destabilization of **13** in *cis*-**9** and -**10** by a methyl at N3 further confirms the steric origins of the effects of substitution at N3 on chair ⇄ twist since NMe should more readily stabilize an axial phenyl via n–σ*, anomeric effectlike interactions than would NH.

We conclude that the effects noted for the series of cis rings with Ph, CH_3, and H on N3 and Mes, Ph, and Me_2N on phosphorus have largely steric origins. That electronic effects (e.g. the relative energies of N3 lone pairs involved in n–σ* interactions) still could play some minor role in these equilibria is not ruled out. Stereoelectronic effects are under study in this laboratory in systems in which steric effects are constant.

Twist conformations are highly populated by *trans*-**6–8** and -**11**, evidently because the aryl group prefers to be pseudoaxial, and 1,3-synaxial repulsions are minimal in twist conformations. Most surprising is the strong depopulation of chair conformation **13** by *trans*-**8**, apparently as a result of dominant steric repulsions involving the equatorial mesityl of the chair form. For both cis and trans diastereomers, the **15** ⇄ **16** equilibrium is somewhat sensitive to the substituent (H, Ph, or Me) on N3. Overall the tendency of substituents to be pseudoaxial in the trans N3H compounds is MeO > Ph > Me_2N.

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. 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 base, and 5.5-s acquisition times and are probably accurate to ±0.2 Hz. ^{31}P NMR spectra were collected at 32.2 MHz on a Varian FT-80A spectrometer under proton noise decoupling conditions. Positive ^{31}P chemical shifts are (ppm) downfield from external 85% H_3PO_4. The mass spectrometer used was a VG Micromass 7070 double-focusing high-resolution instrument with VG Data System 2000 in the EI mode, direct inlet sampling.

***cis*- and *trans*-2-Phenyl-2-oxo-5-*tert*-butyl-1,3,2λ⁵-oxazaphosphorinane (6).** A solution of phenylphosphonic dichloride (4.46 g, 22.9 mmol) in anhydrous ethyl acetate (45 mL) was added slowly, at room temperature, to a stirred solution of 2-(hydroxymethyl)-3,3-dimethylbutylamine[3] (3.00 g, 22.9 mmol) and anhydrous triethylamine (4.63 g, 45.7 mmol) in anhydrous ethyl acetate (30 mL). The reaction mixture was stirred at room temperture for 48 h. Triethylamine hydrochloride was filtered off. The solvent was removed in vacuo to give a solid residue, which was recrystallized from ethyl acetate to give 5.01 g (86% yield) of a mixture of *cis*- and *trans*-**6**. Anal. Calcd for $C_{13}H_{20}O_2NP$: C, 61.65; H, 7.96; P, 12.23. Found: C, 61.81; H, 8.00; P, 12.30. A 265-mg sample of the purified mixture of diastereomers was chromatographed by MPLC on silica gel, eluting with EtOH/EtOAc (1:20), to give 63 mg of pure *cis*-**6**, 55 mg of pure *trans*-**6**, and 124 mg of a pure mixture of diasteomers. *cis*-**6**: mp 113–115 °C; ^{31}P NMR (C_6D_6) δ 19.47; IR (KBr) 3200 (N–H), 2950, 1625, 1566, 1434, 1365, 1188 (P=O), 1131, 1049, 1030, 996, 800, 740, 690 cm^{-1}. *trans*-**6**: mp 128–130 °C; ^{31}P NMR (C_6D_6) δ 18.96; IR (KBr) 3220 (N–H), 3160, 2945, 1456, 1436, 1360, 1319, 1196 (P=O), 1140, 1122, 1079, 1028, 1003, 843, 793, 739, 692 cm^{-1}.

***cis*- and *trans*-2-Phenyl-2-thioxo-5-*tert*-butyl-1,3,2λ⁵-oxazaphosphorinane (7).** In complete analogy to the preparation of **6**, a solution of dichlorophenylphosphine sulfide (4.83 g, 23 mmol) in anhydrous ethyl acetate (40 mL) was allowed to react with a solution of 2-(hydroxymethyl)-3,3-dimethylbutylamine (3.00 g, 23 mmol) and triethylamine (4.63 g, 46 mmol) to give 5.24 g (85% crude yield) of a mixture of *cis*- and *trans*-**7**. A 500-mg sample of the mixture was chromatographed by MPLC on silica gel, eluting with EtOAc/pentane (1:10) to give 150 mg of pure *trans*-**7**, 200 mg of pure *cis*-**7**, and 120 mg of pure mixture of diastereomers submitted for analysis. *trans*-**7**: mp 78–79 °C; ^{31}P NMR (C_6D_6) δ 80.39. *cis*-**7**: mp 89–90 °C; ^{31}P NMR (C_6D_6) δ 73.08. Anal. Calcd for $C_{13}H_{20}NOPS$: C, 57.97; H, 7.48; P, 11.49. Found: C, 58.07; H, 7.60; P, 11.41.

***N*-Methyl-2-(carbethoxy)-3,3-dimethylbutyramide.** A mixture of 2-(carbethoxy)-3,3-dimethylbutyric acid[3] (16.7 g, 88 mmol) and thionyl chloride (11.6 g, 97 mmol) was heated under reflux for 1.5 h. The excess thionyl chloride was removed under reduced pressure at room temperature. Anhydrous diethyl ether (300 mL) was added to the remaining residue, and anhydrous methylamine was passed into the solution until no more precipitate formed. The precipitate was filtered off and washed with ether (3 × 50 mL). The combined ether solutions were dried ($MgSO_4$) and the ether removed under reduced pressure to yield a crystalline residue, which was recrystallized from ethanol/pentane to give 9.0 g (51% yield) of pure *N*-methyl-2-(carbethoxy)-3,3-dimethylbutyramide as a colorless crystalline solid: mp 109–110 °C; ^1H NMR (60 MHz, $CDCl_3$) δ 1.10 (s, 9 H, *t*-Bu), 1.33 (t, 3 H, $CO_2CH_2CH_3$), 2.86 (d, 3 H, $CONHCH_3$), 3.19 (s, 1 H, methine), 4.22 (q, 2 H, $CO_2CH_2CH_3$).

***N*-Methyl-2-(hydroxymethyl)-3,3-dimethylbutylamine.** A solution of *N*-methyl-2-(carbethoxy)-3,3-dimethylbutyramide (10.0 g, 49 mmol) in anhydrous ethyl ether (250 mL) was added over a 1-h period to a stirred slurry of lithium aluminum hydride (4.72 g, 125 mmol) in anhydrous ethyl ether (100 mL). After 2 days of reflux, the reaction mixture was cooled and then hydrolyzed by the addition of 6 mL of water followed by 45 mL of 15% NaOH solution and another 15 mL of water. The resulting mixture was stirred for 1 h. The ether layer was separated, and the aqueous layer was extracted with ether (3 × 100 mL). The combined ether layers were dried ($MgSO_4$) and filtered, and the ether was removed by rotary evaporation. Distillation at reduced pressure gave 5.1 g (71% yield) of *N*-methyl-2-(hydroxymethyl)-3,3-dimethylbutylamine as a colorless oil: bp 101–102 °C (7.0 torr); ^1H NMR (60 MHz, $CDCl_3$) δ 0.95 (s, 9 H, *t*-Bu), 1.55 (m, 1 H, methine), 2.40 (s, 3 H, NCH_3), 3.10 (m, 2 H, CH_2N), 3.80 (s, 2 H, OH, NH), 3.90 (m, 2 H, CH_2O); IR (thin film) 3200 (br), 2960 (br), 2860, 2800, 1480, 1370, 1240, 1120, 1050 cm^{-1}. Anal. Calcd for $C_8H_{19}NO$: C, 66.16; H, 13.19; N, 9.64. Found: C, 65.93; H, 13.19; N, 9.71.

***cis*-2-Phenyl-2-oxo-3-methyl-5-*tert*-butyl-1,3,2λ⁵-oxazaphosphorinane (9).** By the procedure described for **6**, a solution of phenylphosphonic dichloride (4.79 g, 27 mmol) in ethyl acetate (40 mL) was allowed to react with a solution of *N*-methyl-2-(hydroxymethyl)-3,3-dimethylbutylamine (3.90 g, 27 mmol) and triethylamine (5.42 g, 54 mmol) in ethyl acetate (35 mL) to give 7.1 g (100% crude yield) of product. A 500-mg sample of the mixture was chromatographed by MPLC on silica gel eluting with EtOH/hexane (1:25) to give 213 mg of pure *cis*-**9**: mp

75–76 °C; ^{31}P NMR (C_6D_6) δ 17.54. Anal. Calcd for $C_{14}H_{22}NO_2P$: C, 62.90; H, 8.30; N, 5.24; P, 11.59. Found: C, 61.33; H, 8.57; N, 5.29; P, 11.09.

***cis*- and *trans*-2-Phenyl-2-thioxo-3-methyl-5-*tert*-butyl-1,3,2λ^5-oxazaphosphorinane (10).** Similarly, a solution of dichlorophenylphosphine sulfide (4.37 g, 21 mmol) in ethyl acetate (40 mL) was allowed to react with a solution of *N*-methyl-2-(hydroxymethyl)-3,3-dimethylbutylamine (3.00 g, 21 mmol) and triethylamine (4.19 g, 42 mmol) in ethyl acetate (35 mL) to give 6.23 g (100% crude yield) of a mixture of *cis*- and *trans*-**10**. A 1.50-g sample of the mixture was chromatographed (gravity) on silica gel, eluting with benzene/pentane (1:1) to give 632 mg of pure *trans*-**10**, 612 mg of pure *cis*-**10**, and 49 mg of pure mixture of diastereomers. *trans*-**10**: mp 81–83 °C; ^{31}P NMR (C_6D_6) δ 88.75. *cis*-**10**: mp 84–86 °C; ^{31}P NMR (C_6D_6) δ 82.70. Anal. Calcd for $C_{14}H_{22}NOPS$: C, 59.34; H, 7.83; P, 10.93. Found: C, 59.52; H, 7.87; P, 10.86.

***cis*- and *trans*-2,3-Diphenyl-2-oxo-5-*tert*-butyl-1,3,2λ^5-oxazaphosphorinane (11).** In a similar fashion, a solution of phenylphosphonic dichloride (1.88 g, 9.7 mmol) in ethyl acetate (25 mL) reacted with a solution of *N*-phenyl-2-(hydroxymethyl)-3,3-dimethylbutylamine[3] (2.00 g, 9.7 mmol) and triethylamine (1.95 g, 19 mmol) in ethyl acetate (30 mL) to give 3.30 g (100% crude yield) of a mixture of *cis*- and *trans*-**11**. A 400-mg sample of the mixture was chromatographed by MPLC on silica gel, eluting with EtOAc/hexane (2:3), to give 39 mg of pure *cis*-**11**, 150 mg of pure *trans*-**11**, and 177 mg of a pure mixture of diastereomers for analysis. *cis*-**11**: mp 158–160 °C; ^{31}P NMR (C_6D_6) δ 13.33. *trans*-**11**: mp 126–128 °C; ^{31}P NMR (acetone-d_6) δ 15.12. Anal. Calcd for $C_{19}H_{24}NO_2P$: C, 69.51; H, 7.50; P, 9.43. Found: C, 69.29; H, 7.34; P, 9.40.

Bis(dimethylamino)chlorophosphine was prepared by a modification of the procedure reported by Van Wazer and Maier.[17] Phosphorus trichloride (5.7 mL, 8.9 g, 65 mmol) and hexamethylphosphorus triamide (27.8 mL, 21.2 g, 130 mmol) were mixed at 0 °C. After 15 min the reaction mixture was heated to 100 °C for 30 min. The crude oil was distilled under high vacuum, collecting the product at −78 °C, to give 29.0 g (96% yield) of bis(dimethylamino)chlorophosphine as a clear, colorless liquid, which fumes in air: ^{31}P NMR (C_6D_6) δ 158.4.

Bis(dimethylamino)mesitylphosphine (18). A solution of mesitylmagnesium bromide (100 mmol) in ether, prepared by reaction of magnesium turnings (2.43 g, 0.10 mol) with bromomesitylene (15.3 mL, 19.9 g, 100 mmol) in refluxing anhydrous ether (120 mL) over 5 days, was added slowly at 0 °C to a solution of bis(dimethylamino)chlorophosphine (15.5 g, 100 mmol) in ether (150 mL). The reaction mixture was allowed to warm slowly to room temperature and stirred for 48 h. The reaction mixture was filtered. Solvent removal in vacuo gave a yellow residual oil, which was used without further purification: ^{1}H NMR (90 MHz, C_6D_6) δ 2.20 (s, 3 H, *p*-CH_3), 2.45 (s, 6 H, *o*-CH_3), 2.58 (*d*, J_{PH} = 9.9 Hz, 12 H, *N*-CH_3), 6.95 (*d*, 2 H, aromatic); ^{31}P NMR (C_6D_6) δ 106.2.

Dichloromesitylphosphine. Excess anhydrous HCl was bubbled through a solution of crude bis(dimethylamino)mesitylphosphine (ca. 100 mmol) in anhydrous pentane (200 mL) at room temperature. The reaction mixture was filtered, the pentane removed in vacuo, and the residue distilled from bulb to bulb (Kugelrohr) with an air-bath temperature of 150 °C (0.5 Torr) to give 13.5 g of dichloromesitylphosphine (61% yield from $(Me_2N)_2PCl$) as a colorless crystalline solid: ^{31}P NMR (C_6D_6) δ 167.51.

Mesitylphosphonic Dichloride. A solution of dichloromesityl phosphine (9.73 g, 44.0 mmol) in dichloromethane (100 mL) was oxidizied at −20 °C by dropwise addition of a saturated solution of N_2O_4 in CH_2Cl_2. The reaction mixture was warmed to room temperature. The solvent was removed in vacuo to give 16.54 g of a crude yellow liquid. A 2.88-g sample of the crude product was Kugelrohr distilled at 120 °C (0.2 Torr) to give 1.21 g (67% yield) of mesitylphosphonic dichloride as a colorless crystalline solid: ^{31}P NMR ($CDCl_3$) δ 32.77.

***cis*- and *trans*-2-Mesityl-2-oxo-5-*tert*-butyl-1,3,2λ^5-oxazaphosphorinane (8).** A solution of mesitylphosphonic dichloride (2.64 g, 11.1 mmol) in anhydrous ethyl acetate (30 mL) was added slowly at 0 °C to a stirred solution of 2-(hydroxymethyl)-3,3-dimethylbutylamine[3] (1.46 g, 11.1 mmol) and anhydrous triethylamine (3.10 mL, 2.25 g, 22.2 mmol) in anhydrous ethyl acetate (30 mL). The reaction mixture was allowed to warm to room temperature and then stirred for 5 days. The triethylamine hydrochloride was filtered off. Solvent was removed from the filtrate in vacuo to give 3.21 g of a pale yellow solid (98% crude yield). A 900-mg sample was chromatographed by MPLC on silica gel, eluting with EtOH/EtOAc (1:9), to give 140 mg of pure *trans*-8, which was recrystallized from ethyl acetate/pentane: mp 151–153 °C; ^{1}H NMR (90 MHz, $CDCl_3$) δ 0.90 (s, 9 H, *t*-Bu), 1.35 (m, 1 H, methine), 2.31 (s, 3 H, *p*-CH_3), 2.70 (s, 6 H, *o*-CH_3), 3.1–3.5 (*m*, 2 H, CH_2N), 4.1–4.7 (m, 3 H, CH_2O, NH), 7.08 (d, *J* = 4.8 Hz, 2 H, aromatic); ^{31}P NMR (C_6D_6) δ 20.68; IR (KBr) 3240 (N–H), 2955, 2890, 1610, 1470, 1415, 1397, 1372, 1235, 1208, 1184, 1123, 1100, 1022, 996, 985, 866, 854, 804, 675, 644, cm^{-1}; MS *m/e* 295 (M^+, 29%), 280 (19%), 238 (59%), 210 (33%), 183 (22%), 182 (22%), 69 (23%), 57 (31%), 56 (100%), 41 (40%), 30 (89%). Anal. Calcd for $C_{16}H_{26}NO_2P$: C, 65.06; H, 8.88; P, 10.49. Found: C, 65.11; H, 8.90; P, 10.64. Also isolated was 100 mg of pure *cis*-**8**, which was recrystallized from ethyl acetate/pentane: mp 167–168 °C; ^{1}H NMR (90 MHz, $CDCl_3$) δ 0.86 (s, 9 H, *t*-Bu), 2.06 (*m*, 1 H, methine), 2.32 (s, 3 H, *p*-CH_3), 2.66 (s, 6 H, *o*-CH_3), 2.8–3.6 (m, 2 H, CH_2N), 3.7–4.8 (m, 3 H, CH_2O, NH), 7.10 (d, *J* = 4.5 Hz, 2 H, aromatic); ^{31}P NMR (C_6D_6) δ 20.88; IR (KBr) 3220 (N–H), 2960, 1608, 1480–1440, 1366, 1322, 1242 (P=O), 1137, 1090, 1037, 1005, 850, 800, 781, 629 cm^{-1}; MS *m/e* 295 (M^+, 39%), 238 (75%), 210 (39%), 183 (20%), 182 (21%) 56 (100%), 41 (39%), 30 (82%). Anal. Calcd for $C_{16}H_{26}NO_2P$: C, 65.06; H, 8.88; P, 10.49. Found: C, 65.14; H, 8.94; P, 10.63. Also eluted was 380 mg of pure cis/trans mixture (57:43).

2-Mesityl-3-phenyl-5-*tert*-butyl-1,3,2λ^5-oxazaphosphorinane. A solution of bis(dimethylamino)mesitylphosphine, **18** (6.50 g, 27.3 mmol), and *N*-phenyl-2-(hydroxymethyl)-3,3-dimethylbutylamine[3] (5.65 g, 27.3 mmol) in anhydrous toluene (100 mL) was refluxed under an argon atmosphere for 40 h. The toluene was removed from the reaction mixture in vacuo to give 10.89 g of a crude mixture of diastereomers, which was used without further purification: ^{31}P NMR ($CDCl_3$) δ 125.0, 117.2 (isomer ratio by integration, 1:2.4).

***cis*- and *trans*-2-Mesityl-2-oxo-3-phenyl-5-*tert*-butyl-1,3,2λ^5-oxazaphosphorinane (12).** A sample of crude 2-mesityl-3-phenyl-5-*tert*-butyl-1,3,2λ^5-oxazaphosphorinane (3.00 g, 8.44 mmol) in anhydrous toluene (20 mL) was oxidized at 0 °C by slow addition of *tert*-butyl hydroperoxide (70%, 1.2 mL, 8.44 mmol). The reaction mixture was stirred at 0 °C for 15 min, allowed to warm to room temperature, and stirred for 1 h. The volatile materials were removed in vacuo, to leave 3.49 g of a reddish brown oil: ^{31}P ($CDCl_3$) δ 16.8 (*cis*-**12**); 21.4 (*trans*-**12**) (ratio 2.4:1). A 1.32-g sample of the crude product was chromatographed by MPLC on silica gel. Elution with EtOAc/hexane (1:1) gave, after recrystallization from Et_2O/pentane, 320 mg of pure *cis*-**12** as a colorless crystalline solid: mp 112–113 °C; ^{1}H NMR (90 MHz, C_6D_6) δ 0.58 (s, 9 H, *t*-Bu), 1.86 (s, 3 H, *p*-CH_3), 2.64 (m, 1 H, methine), 2.72 (s, 6 H, *o*-CH_3), 3.19–4.59 (m, 4 H, CH_2N, CH_2O), 6.40–7.32 (m, 7 H, aromatic); ^{31}P NMR (C_6D_6) δ 14.78; IR (KBr) 3042, 3028, 2965, 2912, 2890, 2873, 1600, 1498, 1462, 1296, 1274, 1224 (P=O), 1132, 1082, 1047, 1032, 1013, 976, 862, 854, 807, 783, 758, 700, 649 cm^{-1}; MS *m/e* 372 (M + 1, 25%), 371 (M^+, 100%), 314 (48%), 286 (9%), 259 (10%), 258 (11%), 132 (29%), 106 (38%), 105 (38%), 104 (19%), 93 (11%), 77 (18%), 69 (11%), 57 (11%), 56 (26%), 41 (21%). Anal. Calcd for $C_{22}H_{30}NO_2P$: C, 71.13; H, 8.14; P, 8.34. Found: C, 71.19; H, 8.15; P, 8.57. Also obtained was 700 mg of pure *trans*-**12**, after recrystallization from Et_2O/pentane, as a colorless crystalline solid: mp 133–134 °C; ^{1}H NMR (90 MHz, C_6D_6) δ 0.59 (s, 9 H, *t*-Bu), 1.87 (s, 3 H, *p*-CH_3), 2.29 (m, 1 H, methine), 2.82 (s, 6 H, *o*-CH_3), 3.23–4.79 (m, 4 H, $-CH_2N-$, CH_2O), 6.56–7.44 (m, 7 H, aromatic); ^{31}P NMR (C_6D_6) δ 19.69; IR (KBr) 3060, 2974, 2952, 2912, 2890, 1606, 1594, 1581, 1499, 1462, 1408, 1370, 1366, 1250 (P=O), 1224 (P=O), 1188, 1132, 1086, 1058, 1029, 1015, 948, 856, 836, 813, 788, 764, 717, 702, 643 cm^{-1}; MS *m/e* 372 (M + 1, 16%), 371 (M^+, 61%), 356 (9%), 314 (38%), 286 (11%), 258 (11%), 132 (55%), 106 (75%), 105 (71%), 104 (39%), 77 (66%), 69 (36%), 57 (77%), 56 (56%), 55 (29%), 41 (100%). Anal. Calcd for $C_{22}H_{30}NO_2P$: C, 71.13; H, 8.14; P, 8.34. Found: C, 71.21; H, 8.14; P, 8.59.

X-ray Single-Crystal Structure Study of *cis*-2-Mesityl-2-oxo-5-*tert*-butyl-1,3,2λ^5-oxazaphosphorinane (*cis*-8). Clear colorless crystals of *cis*-**8** were obtained by vapor diffusion of a solution of the compound in ethyl acetate with pentane. A well-formed crystal (plate, cut to cube, 0.3 × 0.3 × 0.3 mm) was mounted on a Syntex $P\bar{1}$ autodiffractometer equipped with a scintillation counter and graphite-monochromated Mo Kα radiation (λ = 0.71073 Å). The automatic centering, indexing, and least-squares routines[18] were carried out on 15 reflections in the 2θ range 8.8°–20.1° to obtain the cell dimensions, which are given in Table IV. The data were reduced to F_o^2 and $\sigma(F_o^2)$. Lorentz and polarization corrections[19] were applied to all reflections. The θ–2θ scan method over the range 4.0° ≤ 2θ ≤ 50.0° was used to collect the data of which those with $I \geq 3\sigma(I)$ were considered observed and were used in the calculations.

The programs used in the course of the structure determination included MULTAN (locally modified, direct methods program by G. Ger-

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(18) Programs used for centering, autoindexing, least-squares refinement of the cell parameters, and data collection were written by Syntex Analytical Instruments, Cupertino, CA.

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Table VIII. Torsional Angles (deg) for *cis*-**8**

O2-P-O1-C6	163.48	C6-C5-C7-C10	179.41
N3-P-O1-C6	43.23	C4-C5-C7-C9	-173.50
C11-P-O1-C6	-76.83	C4-C5-C7-C8	65.39
O2-P-N3-C4	-154.54	C4-C5-C7-C10	-54.89
O1-P-N3-C4	-35.07	P-C11-C12—C13	177.23
C11-P-N3-C4	77.29	P-C11-C12-C18	-1.27
O2-P-C11-C12	-108.17	C16-C11-C12-C13	2.13
O2-P-C11-C16	67.01	C16-C11-C12-C18	-176.37
O1-P-C11-C12	131.70	P-C11-C16-C15	-176.79
O1-P-C11-C16	-53.13	P-C11-C16-C17	2.13
N3-P-C11-C12	20.89	C12-C11-C16-C15	-1.32
N3-P-C11-C16	-163.93	C12-C11-C16-C17	177.61
P-O1-C6-C5	-62.55	C11-C12-C13-C14	-1.22
P-N3-C4-C5	42.52	C18-C12-C13-C14	177.39
O1-C6-C5-C4	62.86	C12-C13-C14-C15	-0.55
O1-C6-C5-C7	-168.83	C12-C13-C14-C19	179.79
C6-C5-C4-N3	-51.49	C13-C14-C15-C16	1.41
C7-C5-C4-N3	-179.21	C19-C14-C15-C16	-178.93
C6-C5-C7-C9	60.80	C14-C15-C16-C11	-0.47
C6-C5-C7-C8	-60.31	C14-C15-C16-C17	-179.46

main, P. Main, and M. M. Woolfson), the Ibers NUCLS (structure factor calculations and least-squares refinement, itself a modification of ORFLS, by R. Busing, K. O. Martin, and H. A. Levy), FORDAP (Fourier summation program, by A. Zalkin), ORFFE (locally modified, calculations of distances, angles, and torsion angles with estimated standard deviations, by Busing, Martin, and Levy), and ORTEP (thermal ellipsoid plotting program, by C. K. Johnson). All calculations were performed on the Control Data Corp. Cyber-175 computer at the University of Arizona Computing Center.

Neutral atomic scattering factors of Cromer and Waber[20a] were used for all atoms except hydrogen, for which the values of Stuart, Davidson, and Simpson[21] were chosen. The effect of the real and imaginary components of anomalous dispersion for the phosphorus atom were included in the structure factor calculations by using the tabulated values of Cromer.[20b]

The structure was refined by full-matrix, least-squares techniques, minimizing the function $w(|F_o| - |F_c|)$.[21] The weights were taken as $w = 4F_o2/[\sigma^2(F_o^2) + (pF_o^2)^2]$ where p, the factor to prevent overweighting of strong reflections, was set equal to 0.03.[22] The discrepancy indices, R and R_w, are defined as $R = \sum||F_o| - |F_c|/\sum|F_o|$ and $R_w = [\sum w(|F_o| - |F_c|)^2/\sum wF_o^2]^{1/2}$. The "goodness of fit" is defined as GOF = $[\sum w(|F_o| - |F_c|)^2/(n - m)]^{1,2}$ where n is the number of reflections used in the refinement and m is the number of variable parameters.

The positions of the phosphorus, nitrogen, oxygens, and three carbon atoms were obtained from an "E-map" based on the solution with the highest combined figure of merit (2.15) generated by the direct methods program MULTAN. A Patterson calculation confirmed the position of the phosphorus obtained from MULTAN. Six cycles of least squares resulted in $R = 0.416$ and $R_w = 0.483$. A total of 10 additional carbon atoms was located in the first difference electron density map. Least-squares refinement resulted in $R = 0.280$ and $R_w = 0.358$. The second difference electron density map revealed the remaining three carbon atoms. Isotropic refinement to convergence resulted in $R = 0.121$ and $R_w = 0.140$. Anisotropic refinement of all non-hydrogen atoms to convergence led to $R = 0.092$, $R_w = 0.114$, and GOF = 3.2. A difference electron density map clearly revealed the positions of all 26 hydrogen atoms, which with the exception of the hydrogen atom bound to the nitrogen, were included as fixed contributors in idealized positions (C-H = 0.95 Å)[23] assuming trigonal geometry about the phenyl carbon atoms and tetrahedral geometry about the methyl and methylene carbon atoms. The hydrogen atom bound to the nitrogen was included as a fixed contributor in the position it was found (N-H = 1.139 (3) Å). Each hydrogen atom was assigned an isotropic thermal parameter 1.0 Å^2 greater than the atom to which it was bound. Full-matrix least-squares refinement of the 181 variables converged with $R = 0.053$, $R_w = 0.060$, and GOF = 2.05. The overdetermination ratio (n/m) was 8.5. The final difference electron density map revealed no peaks greater than 0.27 e Å^{-3} (near TC3).

The final non-hydrogen atomic parameters with their estimated standard deviations are given in Table V, while Tables VI–VIII list bond distances, bond angles, and torsion angles, respectively.

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Registry No. *cis*-**6**, 116005-11-9; *trans*-**6**, 116005-18-6; *cis*-**7**, 116005-12-0; *trans*-**7**, 116005-19-7; *cis*-**8**, 116005-13-1; *trans*-**8**, 116005-20-0; *cis*-**9**, 116005-14-2; *cis*-**10**, 116005-15-3; *trans*-**10**, 116005-21-1; *cis*-**11**, 116005-16-4; *trans*-**11**, 116005-22-2; *cis*-**12**, 116005-17-5; *trans*-**12**, 116025-33-3; **17** (R = H), 15521-17-2; **17** (R = Me), 116005-24-4; **17** (R = Ph), 83096-39-3; **18**, 116005-25-5; MeP(O)Cl_2, 114070-55-2; dichlorophenylphosphine sulfide, 3497-00-5; *N*-methyl-2-(carbethoxy)-3,3-dimethylbutyramide, 116005-23-3; 2-(carbethoxy)-3,3-dimethylbutyric acid, 83096-36-0; bis(dimethylamino)chlorophosphine, 3348-44-5; hexamethylphosphorous triamide, 1608-26-0; mesitylmagnesium bromide, 2633-66-1; bromomesitylene, 576-83-0; dichloromesitylphosphine, 6781-96-0; 2-mesityl-3-phenyl-5-*tert*-butyl-1,3,2λ⁵-oxazaphosphorinane, 116005-26-6.

Supplementary Material Available: Tables of the fixed hydrogen atomic parameters and the thermal parameters for *cis*-**8** (2 pages); listing of observed and calculated structure factors (7 pages). Ordering information is given on any current masthead page.

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