Conformations of Saturated Six-Membered-Ring Phosphorus Heterocycles. Chair–Chair Equilibria for Cyclophosphamide, the 5,5-Dimethyl Derivative, and Related 1,3,2-Oxazaphosphorinanes. Relative Conformational Energies of Nitrogen Mustard and Other R_2N Groups Attached to Phosphorus

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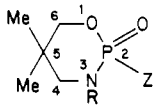
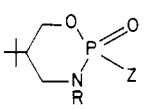
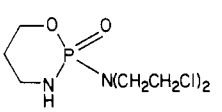
Abstract: A series of 5,5-dimethyl-3-R-2-oxo-2-Z-1,3,2-oxazaphosphorinanes (**1**, R = H, Z = Me_2N; **2**, R = H, Z = Et_2N; **3**, R = H, Z = *i*-Pr_2N; **4**, R = H, Z = $N(CH_2CH_2Cl)_2$; **5**, R = Ph, Z = Me_2N) has been prepared, and their conformations have been studied by ^1H NMR at 300 MHz. The position of the chair $\rightleftarrows$ chair conformational equilibrium (**9** $\rightleftarrows$ **10**) varies with the conformational energy of the group Z in the order *i*-Pr_2N > $(ClCH_2CH_2)_2N$ > Et_2N > Me_2N. Me_2N is predominantly axial (56–65%) and the other Z groups largely equatorial. In C_6D_6 relative to Z = Me_2N, $\Delta\Delta G°$ values (kilocalories/mole) at room temperature for the equilibrium in question are estimated at −0.48 (Et_2N), −0.75 [$(ClCH_2CH_2)_2N$)], and −1.2 (*i*-Pr_2N). For the series Z = Me_2N, Et_2N, and *i*-Pr_2N, a steric effect involving 1,3-synaxial interactions appears operative with R_2N axial. Stereoelectronic factors cannot be totally discounted, however, especially for Z = $(ClCH_2CH_2)_2N$. Dilution and solvent studies show intermolecular H bonding to be a secondary effect for **1–4** favoring the conformer with Z axial at higher solute concentrations. The increase in conformational energy for Z = *i*-Pr_2N compared to Z = Me_2N is confirmed by comparison of the chair $\rightleftarrows$ twist equilibrium for *cis*-2-(diisopropylamino)-2-oxo-5-*tert*-butyl-1,3,2-oxazaphosphorinane (*cis*-**6**) with that of the corresponding 2-dimethylamino compound (*cis*-**7**) studied previously. Knowledge of the chair $\rightleftarrows$ chair equilibrium for **1** and **3** and chair $\rightleftarrows$ twist equilibrium for *cis*-**6** and *cis*-**7** permits the chair $\rightleftarrows$ twist free energy change for the 2-oxo-1,3,2-oxazaphosphorinane ring to be estimated to be only 0.5–0.7 kcal/mol. The destabilizing effect of a phenyl at ring nitrogen N(3) on the conformational energy of axial Me_2N is found by comparison of the chair $\rightleftarrows$ chair conformational equilibria for **1** and **5** ($\Delta\Delta G° \cong 1.2$ kcal/mol). Analyses of J_{HP} for both the CH_2O and CH_2N groups of cyclophosphamide (**8**) in C_6D_6 allow its chair $\rightleftarrows$ chair equilibrium to be determined; $\Delta G° = -0.7$ in favor of $(ClCH_2CH_2)_2N$ equatorial. Comparison with data from another laboratory taken in $CHCl_3$ and H_2O shows the equilibrium to be highly solvent sensitive. It is concluded that cyclophosphamide and its cyclic metabolites should be readily able to assume the chair or twist conformation most advantageous to oxidation, ring-opening of the 4-OH derivative, or transport.

Cyclophosphamide (CPA), **8**, and certain closely related nitrogen mustards containing the 1,3,2-oxazaphosphorinane ring system currently play a key role in cancer chemotherapy. Metabolic oxidation of CPA introduces an OH at C_4, potentially forming two diastereomers.[1] An important effect of diastereomer







1 R = H, Z = Me_2N
2 R = H, Z = Et_2N
3 R = H, Z = *i*-Pr_2N
4 R = H, Z = $(ClCH_2CH_2)_2N$
5 R = Ph, Z = Me_2N

6 R = H, Z = *i*-Pr_2N
7 R = H, Z = Me_2N

8

identity on the efficacies of the *cis*- and *trans*-4-phenylcyclophosphamides in animal tests was recently found.[2] In spite of the potential effect of conformation in these six-membered ring systems on oxidative activation, transport properties, and metabolite breakdown to cytotoxic products, no thorough, systematic study of substituent effects on conformation in the simple chair $\rightleftarrows$ chair system **9** $\rightleftarrows$ **10** has been made. In particular, the relative effective size (or conformational energy) of $(ClCH_2CH_2)_2N$ compared to other R_2N is completely unknown.

The 1,3,2-oxazaphosphorinane system itself if of basic interest relative to the question of the influence on the conformational properties of cyclohexane of replacing ring carbons by various heteroatoms. The 1,3,2-oxazaphosphorinanes have been much less well investigated than have the corresponding 1,3,2-dioxaphosphorinanes.[3] Moreover, recent reports have emphasized the special conformational features of the 1,3,2-oxaza rings, including the importance of the nature or R at N(3) on the chair $\rightleftarrows$ twist equilibria of certain 1,3,2-oxazaphosphorinanes.[4] The preference of the Me_2N for the axial position as in **9** was set forth in a recent X-ray study[5] of **1**. This report also included preliminary ^1H NMR results, suggesting a dominance of **9** over **10** in solution as well. This is in contrast to the very strong equatorial Me_2N preference in 2-oxo-1,3,2-dioxaphosphorinanes.[3]

In the present paper we note the important influence of changing the R substituents on R_2N in **1–4** on the **9** $\rightleftarrows$ **10** equilibrium as well as further support for the axial preference of Me_2N in **1**. The likely effect of both steric and stereoelectronic influences on relative *effective* steric size (relative conformational energies) is seen in the observed order: *i*-Pr_2N > $(ClCH_2CH_2)_2N$ > Et_2N > Me_2N. The remarkable increase in conformational energy of R_2N found in the series **1–3** is confirmed in a study of **6** which is compared to **7**, previously investigated. In addition the major influence of R on conformational energies earlier noted for the chair $\rightleftarrows$ twist

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Table I. Coupling Constants (in Hz) for 2-Oxo-2-(dimethylamino)-5,5-dimethyl-1,3,2-oxazaphosphorinane (**1**) at 300 MHz, Ambient Probe Temperature (~25 °C)

solvent	% conc[a]	J_{AB}	J_{AP}	J_{BP}	J_{CD}	J_{CP}	J_{DP}	J_{AC}	J_{BD}	J_{Me_2N}	ref
C_6D_6[b]	10	−10.5	8.6	14.5	−12.6	10.0	17.8	<1.0	1.8	10.5	*c*
C_6D_6	1	−10.8	9.6	13.6	−12.6	*d*	16.8	<1.0	1.8	10.7	*c*
$CDCl_3$	10	−11.0	9.3	13.9	−12.7	12.0	16.2	<1.0	1.6	10.7	*c*
$CDCl_3$	1	−11.1	10.0	13.1	−12.5	12.5	15.1	<1.0	1.4	10.6	*c*
$CDCl_3$	0.1	−11.4	10.7	12.7	−12.7	~12.5	14.2	<1.0	1.2	10.7	*c*
pyridine-d_5	1	−10.6	8.4	14.2	−12.4	10.2	16.4	<1.0	1.8	10.6	*e*
C_6D_6/Me_2SO-d_6 (1:1)	1	−10.7	8.7	14.1	−12.4	10.5	16.6	<1.0	1.7	10.7	*c*
C_6D_6/CD_3CN (1:1)	1	−10.8	8.8	14.0	*f*	*f*	*f*	*f*	*f*	10.6	*e*

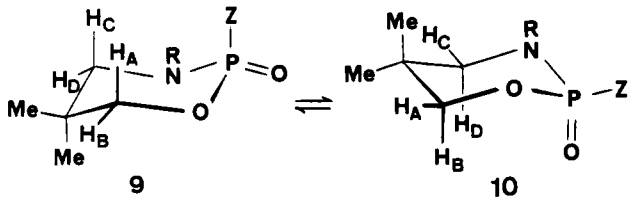
[a] Weight/volume. [b] NH decoupled or D_2O exchanged. Couplings assigned by analogy to NH-decoupled or D-exchanged case in other examples. [c] Reference 3. [d] Obscured by Me_2N peak. [e] This work. [f] $\Delta\nu$ of H_C and H_D only 18 Hz. Strong second-order effects on couplings.

Table II. Coupling Constants (in Hz) for **1–5** and **8** at 300 MHz, Ambient Probe Temperature (~25 °C).

compd	solvent	% conc[a]	J_{AB}	J_{AP}	J_{BP}	J_{CD}	J_{CP}	J_{DP}	J_{AC}	J_{BD}	other
1	C_6D_6[b]	10	−10.5	8.6	14.5	−12.6	10.0	17.8	<1.0	1.8	J_{Me_2N}[c] = 10.5; J_{CNH} = 5.8; J_{DNH} = 5.2
1	C_6D_6	1	−10.8	9.6	13.6	−12.6	*d*	16.8	<1.0	1.8	
1	$CDCl_3$	1	−11.1	10.0	13.1	−12.5	12.5	15.1	<1.0	1.4	
2	C_6D_6	10	−10.6	13.2	10.6	−12.2	16.8	13.8	1.6	<1.0	$J_{HP}(CH_3CH_2)$[c] = 10.8; $J_{HH}(CH_3CH_2)$ = 7.1; J_{CNH} = 4.9; J_{DNH} = 2.9
2	C_6D_6	1	−10.8	14.1	9.5	−11.8	17.5	11.8	1.6	<1.0	
2	$CDCl_3$	10	−11.1	14.7	9.3	*e*	*e*	*e*	1.0	<1.0	
2	$CDCl_3$	1	−10.9	14.8	9.3	−12.0	18.0	*e*	<1.0	1.7	
3	C_6D_6	10	−11.0	18.0	6.0	−11.5	22.2	7.1	2.2	<1.0	$J_{HP}(Me_2CH)$[f] = 18.6; $J_{HH}(Me_2CH)$ = 6.8; J_{CNH} = 5.0; J_{DNH} = 1.8
3	C_6D_6[b,g]	1	−11.0	19.6	4.8	−11.4	24.2	5.0[h]	2.4	<1.0	
3	acetone-d_6	10	−10.9	18.8	5.2	−11.5	23.5	5.4	2.4	<1.0	
3	$CDCl_3$	10	−11.1	18.8	5.5	−11.5	23.2	6.0	2.4	<1.0	
3	$CDCl_3$	1	−11.0	19.4	5.0	−11.7	23.6	5.3	<1.0	2.6	
4	C_6D_6	10	−10.8	*i*	9.6	−12.0	17.1	11.7	1.7	<1.0	$J_{HP}(ClCH_2CH_2)$[f] = 5.0; $J_{HH}(ClCH_2CH_2)$ = 6.8; J_{CNH} = 4.8; J_{DNH} = 2.0
4	C_6D_6	1	−11.0	16.4[i,j]	8.0	−11.6	19.4	9.8	2.0	<1.0	
4	acetone-d_6	10	−10.6	15.0	8.6	−11.7	18.8	10.3	1.7	<1.0	
4	$CDCl_3$[b]	1	−11.1	17.2	7.0	−11.8	21.2	7.9	<1.0	1.8	
5	C_6D_6	10	−10.8	20.7	4.8	−11.9	17.6	5.1	2.4	<1.0	J_{Me_2N} = 9.6
5	acetone-d_6	10	−10.9	18.6	6.7	−12.2	15.4	6.7	2.1	<1.0	
8	C_6D_6	10	−11.1	15.6	7.8	−11.5[h]	16.4[h]	9.9[h,k]	1.0	<1.0	$J_{HH}(ClCH_2CH_2)$ = 7.3[l]; J_{CH} = 4.3; J_{DH} = 3.0
8	C_6D_6[m]	1	−11.0	15.8	7.6	−11.8	17.6	9.6	1.1	<1.0	
8	$CDCl_3$[n]	*o*	*o*	17.7	4.7	*o*	*o*	*o*	*o*	*o*	
8	H_2O[n]	*o*	*o*	13.5	9.9	*o*	*o*	*o*	*o*	*o*	

[a] Weight/volume. [b] NH decoupled or D_2O exchange. [c] At 1% in C_6D_6. [d] Obscured by Me_2N peak. [e] Obscured by overlap with $(CH_3CH_2)_2N$. [f] At 1% in $CDCl_3$. [g] Coupling constants from sample with D_2O added. [h] Couplings of H_C and H_d with ring NH disappear on exchange with D_2O. [i] Obscured by overlap with NCH_2CH_2Cl. [j] Determined from H_A decoupling. [k] H_C and H_D poorly resolved. [l] $J_{HP}(ClCH_2CH_2)$ not determined because of apparent nonequivalence of CH_2P hydrogens. [m] From H_5-decoupled and H_5-decoupled/D_2O added spectra. [n] Values from ref 9. [o] Not reported.

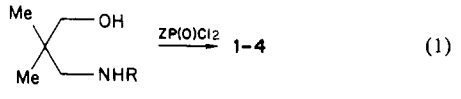
equilibria of **7**[4] is found to apply to **9** ⇄ **10** by comparison of **1** and **5**. Finally, we report a study of the chair ⇄ chair equilibrium



for cyclophosphamide itself which includes an analysis of both CH_2O and CH_2N proton couplings to phosphorus and demonstrates a large effect of solvent on the conformational equilibrium (**9** ⇄ **10**).

Results

Preparation. **1–4** resulted from reaction of the amino alcohol **11** (R = H) with the appropriate $ZP(O)Cl_2$ reagent. Reaction of $(Me_2N)_3P$ with **11** (R = Ph) followed by N_2O_4 oxidation afforded **5**. The two diastereomers of **6**, prepared in a manner



(1)

11

completely analogous to that for **7**,[4] were separated by MPLC. Amino alcohol **11** resulted from $LiAlH_4$ reduction of the amide ester, prepared routinely from the acid chloride of the half ester, which was readily available in two steps from diethyl dimethylmalonate. Assignments of cis and trans geometries (relationship of *t*-Bu to *i*-Pr_2N) to the diastereomers at **6** were made (see below) by analogy to those of **7**[4a] on the basis of the relative upfield ^{31}P NMR shift of the cis isomer compared to that of the trans isomer, the expected chair conformation of the trans isomer (confirmed by ^1H NMR), and the parallel seen in relative chemical shifts of H_A vs. H_B and H_C vs. H_D for the different diastereomers of **6** and **7**.

Proton NMR Parameters and Conformations of 1–5 and 8. In Table I are listed proton coupling constants for **1** (Z = Me_2N) from essentially first-order spectra obtained at 300 MHz under various conditions of solvent and concentration. As concluded previously,[5] we believe chair conformers **9** and **10** are populated (see Table IV) in 60/40 (**9**/**10**) ratio in C_6D_6 at 1% concentration. (The X-ray structure of **1** shows it to be in conformation **9** in the crystal.[5]) A total range of major conformer population of 56–65% in C_6C_6 and $CDCl_3$ at different concentrations is observed. Conformer populations of **1–5** and **8** were estimated on the assumption that only chair conformations **9** and **10** can be populated. This assumption is verified by the relative constancy of the sums of $J_{AP} + J_{BP}$ and $J_{CP} + J_{DP}$ in Tables I and II and parallel changes in J_{AP} and J_{CP} and in J_{BP} and its J_{DP} counterpart.[6] (A boat or

(6) As can be seen from the later discussions, depopulation by the 5,5-dimethyl compounds of **9** in favor of a twist conformer analogous to **14** would keep J_{CP} and J_{DP} similar to what they are in **9**. Simultaneously, J_{AP} and J_{BP} would undergo change in compensating fashion much as in equilibrium **9** ⇄ **10**. This pattern of J_{HP} variation is not observed in Tables I and II.

Table III. ^1H (C_6D_6) at 300 MHz and ^{31}P Chemical Shifts for **1–5** and **8**, Ambient Probe Temperatures (~25 °C)

compd	conc	δ_A	δ_B	δ_C	δ_D	δ_{NH}	δ_{CH_3}	other	^{31}P
1	10	3.54	3.69	2.64	2.83	5.30	0.98, 0.58	2.57 (Me_2N)	13.8[a]
1	1	3.49	3.70	2.56	2.78	4.81	0.89, 0.58	2.54 (Me_2N)	
2	10	3.53	3.93	2.67	3.08	4.93	0.85, 0.80	1.09 (CH_3CH_2); 3.16 (CH_3CH_2)[b]	13.6[a]
2	1	3.47	3.93	2.50	2.97	3.93	0.78, 0.72	1.05 (CH_3CH_2); 3.11 (CH_3CH_2)[b]	
3	10	3.46	4.14	2.52	3.16	3.43	0.95, 0.61	3.54 ($NHCHMe_2$); 1.27, 1.34 ($NCHMe_2$)	13.5[a]
3	1	3.39	4.17	2.29	3.08	2.21	0.94, 0.46	3.49 ($NHCHMe_2$); 1.23, 1.34 ($NCHMe_2$)	
4	1	3.36	3.82	2.31	2.77	*c*	0.69, 0.53	3.17 (NCH_2CH_2Cl);[d] 3.32 (NCH_2CH_2Cl)	12.9[a]
4	10	~3.42[c]	3.80	2.46	2.82	4.14	0.69, 0.66	3.18 (NCH_2CH_2Cl);[d] 3.32 (NCH_2CH_2Cl)	
5	10	3.14	4.14	3.32	2.80		0.99, 0.51	2.42 (Me_2N); 6.69–7.47 (C_6H_5)	8.3[e]
8	10	3.61	3.95	2.63	2.95	4.10	~1.10,[f] ~1.06[f]	3.18 (NCH_2CH_2Cl); 3.39 (NCH_2CH_2Cl)	12.9[a]
8	1	3.59	3.93	2.58	2.92	3.86	~1.10,[f] ~1.06[f]	3.16 (NCH_2CH_2Cl); 3.37 (NCH_2CH_2Cl)	

[a] 1% in $CDCl_3$. [b] Protons nonequivalent. [c] Overlapped with (NCH_2CH_2Cl). [d] Center of CH_2 multiplet. [e] Acetone-d_6. [f] Protons at C_5.

Table IV. Approximate Conformer Populations for **1–8** at 25 °C

			assumed		% 9 based on				$\Delta\Delta G°$	
compd	solvent	conc	J_{AP}	J_{BP}	J_{AP}	J_{BP}	av	$\Delta G°(\mathbf{9} \rightarrow \mathbf{10})$	C_6D_6[a]	$CDCl_3$[b]
1	C_6D_6	10	2.0	22.0	67	63	65	0.35		
1	C_6D_6	1	2.0	22.0	62	58	60	0.23	0	
1	$CDCl_3$	10	2.0	22.0	62	59	61	0.26		
1	$CDCl_3$	1	2.0	22.0	58	54	56	0.14		0
1	$CDCl_3$	1	1.0	23.0	60	56	58	0.18		
1	$CDCl_3$	0.1	2.0	22.0	57	54	56	0.13		
2	C_6D_6	10	2.0	22.0	44	43	43	−0.16		
2	C_6D_6	1	2.0	22.0	40	38	39	−0.25	−0.48	
2	$CDCl_3$	1	2.0	22.0	37	39	38	−0.29		−0.43
3	C_6D_6	10	2.0	22.0	20	20	20	−0.81		
3	C_6D_6	1	2.0	22.0	12	14	13	−1.0	−1.2	
3	$CDCl_3$	1	2.0	22.0	13	15	14	−1.0		−1.1
4	C_6D_6	1	2.0	22.0	28	30	29	−0.52	−0.75	
4	$CDCl_3$	1	2.0	22.0	25	24	25	−0.64		−0.78
5	C_6D_6	10	2.0	23.0	14	12	13	−1.0	−1.2	
8	C_6D_6	1	2.0	22.0	31	28	30	−0.49	−0.72	
8	$CDCl_3$[c]	*d*	2.0	22.0	22	14	18	−0.80		−0.94
8	H_2O[c]	*d*	2.0	22.0	43	40	42	−0.18	−0.41	−0.32

[a] Relative to $\Delta G°(\mathbf{9} \rightarrow \mathbf{10})$ for **1** in C_6D_6 at 1% concentration. [b] Relative to $\Delta G°(\mathbf{9} \rightarrow \mathbf{10})$ for **1** in $CDCl_3$ at 1% concentration. [c] Based on J_{AP} and J_{BP} from ref 9. [d] Not reported.

twist structure is expected to be strongly destabilized by the 5-methyl substituents and, therefore, not to be populated.) For **9** and **10** it is clear that

$$N(\mathbf{9}) \times J_{AP}(\mathbf{9}) + N(\mathbf{10}) \times J_{AP}(\mathbf{10}) = J_{AP}(\text{obsd}) \quad (2)$$

$$N(\mathbf{10}) = 1 - N(\mathbf{9}) \quad (3)$$

Therefore

$$N(\mathbf{9}) = (J_{AP}(\text{obsd}) - J_{AP}(\mathbf{10}))/(J_{AP}(\mathbf{9}) - J_{AP}(\mathbf{10})) \quad (4)$$

Similarly, for J_{BP}

$$N(\mathbf{9}) = (J_{BP}(\text{obsd}) - J_{BP}(\mathbf{10}))/(J_{BP}(\mathbf{9}) - J_{BP}(\mathbf{10})) \quad (5)$$

To obtain rough estimates of molar fractions of **9** and **10** (N(**9**) and N(**10**)) from eq 2–5, one need only have reasonable values for J_{AP} and J_{BP} of **9** and **10**. (Calculations are based on H_A and H_B because of the variation with R in the coupling constant sum for H_C and H_D in **1–5**.) As a reasonable model system, the MeO analogue of **5**,[7] which is almost entirely in one formation with the small, electronegative MeO axial, was used. Values for J_{AP} (22.5 Hz) and J_{BP} (2.4 Hz) were reduced by about 0.5 Hz to 22.0 and 2.0 Hz to give a sum of 24.0 Hz, close to those of $J_{AP} + J_{BP}$ for **1–4** of Tables I and II. It was also assumed that the values of J_{AP} and J_{BP} are interchanges in **9** and **10**, since little effect of phosphorus configuration on couplings is found in the 2-oxo-1,3,2-dioxaphosphorinanes.[3] Values of 2.0 and 23.0 Hz gave for **5** a better match of the experimental sum and closer agreement of the percentages of **9** based on experimental J_{AP} and J_{BP}. As can be seen for **1** in Table IV, small changes in assumed J_{AP} and J_{BP} for **9** and **10** have only a minor effect on the calculated conformer populations. (Compare numbers for **1** in $CDCl_3$ at 1% based on different assumed J_{HP} values.)

(7) Unpublished results from this laboratory.

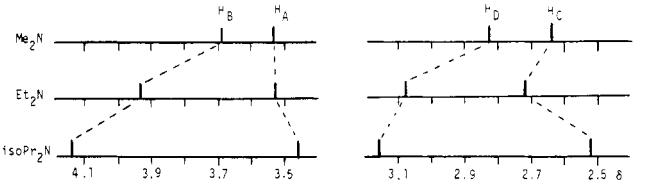


Figure 1. Effects of changing Z on the chemical shifts of H_A, H_B, H_C, and H_D of **1–3**.

Assignments of major conformational populations, **9** or **10**, to **1–3** were made on the basis of two criteria: (1) trends in chemical shifts of protons A–D (Table III), and (2) effects of dilution and solvent change on J_{HP} values (Tables I and II). (Only δ values in C_6D_6 are recorded as parallel though more compressed trends were found in the other solvents.) Most noteworthy for **1–3** is the crossover (for H_A vs. H_B and H_C vs. H_D) in correlation of larger J_{HP} with relative chemical shift between **1** and the others, **2** and **3**; i.e., for **1** the *larger* J_{HP} (J_{BP} or J_{DP}) is associated with the *downfield* proton (H_B or H_D) of the CH_2O or CH_2N, whereas for **2** or **3**, the opposite is true. We interpret this to mean that there is an important change in the conformational population between **1** and **2** and that the major conformation is different in the two cases. Since it is reasonable that Et_2N and *i*-Pr_2N should be larger sterically than Me_2N, it is concluded that for **1** (Table IV), the major conformer populated is **9** (56–65%), while **2** populates **10** to the extent of 57–62%. Moreover, *i*-Pr_2N further destabilizes **9** in favor of **10** which is 80–87% populated.

The trend in chemical shifts for H_A, H_B, H_C, and H_D in Table III is especially notable for H_A and H_B, as shown graphically in Figure 1, and is readily explained. Thus, H_B of **1** is predominantly equatorial (conformer **9**, $J_{BP} > J_{AP}$) and slightly deshielded by the equatorial P=O cis to it; hence $\delta_B > \delta_A$. In the series **1–3**, the progressive shift of equilibrium **9** ⇄ **10** toward **10** moves H_B

Table V. NMR Parameters for 2-(Dialkylamino)-2-oxo-5-*tert*-butyl-1,3,2-oxazaphosphorinanes **6** and **7**

compd[a]	solvent (% conc)	J_{AB}	J_{AX}	J_{BX}	J_{AP}	J_{BP}	J_{CD}	J_{CX}	J_{DX}	J_{CP}	J_{DP}	J_{BD}	J_{CNH}	J_{DNH}	J_{NHP}	ref
cis-**6**	C_6D_6 (1%)	−10.5	9.3	6.2	14.4	10.3	−12.4	10.6	4.8	5.1	19.5	0.6	5.1	6.8	~5	*b*
cis-**6**	$CDCl_3$ (<1%)	−10.8	10.3	5.2	10.9	12.2	−11.9	11.1	5.2	7.9	16.1	1.5	4.4	6.2	~4	*b*
cis-**7**	toluene-d_8 (2%)	−10.4	10.7	4.6	6.5	16.8	−12.8	11.3	4.5	2.7	23.2	2.0	5.8	6.9	6.4	*b*
trans-**6**	C_6D_6 (~10%)	−11.0	11.2	3.8	3.5	21.2	−11.0	11.0	4.2	4.6	23.9	2.4	1.6	4.2	*c*	*d*
trans-**7**	C_6D_6 (1%)	11.0	11.0	3.8	4.0	20.8	−11.0	11.0	4.3	5.4	22.0	2.4	2.4	4.4	*e*	*d*

	δ_A	δ_B	δ_C	δ_D	δ_X	$\delta_{t\text{-Bu}}$	δ_{NH}	other	$\delta^{31}P$ (solvent)	ref
cis-**6**	3.80	4.26	2.73	3.00	1.92	0.59	3.86	1.30, 1.35 (Me_2CH, J_{HH} = 6.8 Hz); 3.74 (Me_2CH, J_{HP} = 18 Hz)	12.1 ($CDCl_3$)	*b*
cis-**6**	3.98	4.36	3.00	3.27	2.10	0.89	2.40	1.21, 1.24 (Me_2CH, J_{HH} = 6.8 Hz); 3.45 (Me_2CH, J_{HP} = 18 Hz)		
cis-**7**	3.78	4.09	2.72	3.08	1.75	0.60	5.14	2.58 (Me_2N, J_{HP} = 10.8 Hz)	14.6 (C_6D_6)	*d*
trans-**6**	4.31	4.02	3.23	2.93	1.66	0.59	3.02	1.31, 1.37 (Me_2CH, J_{HH} = 6.8 Hz); 3.54 (Me_2CH, J_{HP} = 18 Hz)	14.4 ($CDCl_3$)	*b*
trans-**7**	4.24	3.99	3.14	2.92	1.59	0.56	3.62	2.68 (Me_2N, J_{HP} = 9.9 Hz)	14.7 (C_6D_6)	*d*

[a] H_X decoupled and NH exchanged or decoupled spectra run in all cases at this or another concentration. [b] This work. [c] NH region poorly resolved. [d] Reference 4. [e] Partial overlap with H_D.

predominately axial and results in J_{AP} becoming greater than J_{BP} and progressive deshielding of H_B. The latter is predictable from the known large deshielding effect of the axial P=O on syn-axial hydrogens.[8,9] (See relative δ_A and δ_B for *cis*-**6** and *trans*-**6** discussed below.) The environment of H_A is less strongly perturbed, since it is not syn-axial to axial P=O in either **9** or **10** and indeed moves slightly upfield in the series **1–3**, perhaps because of the decreasing influence of the syn-axial polar P–N bond of **9**. The above ideas apply also to the chemical shift trends for H_C and H_D (Table III and Figure I), though less variation in δ_D is seen.

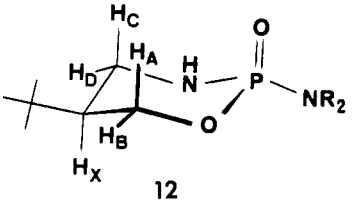
The association of the *larger* J_{HP} of the CH_2O hydrogens of **4** with the upfield proton H_A also is consistent with the assignments of J_{HP} and δ values of Tables I–III and the greater population of **10** (71–75%). The same is true of **5** (87% **10**). The assignment of **4** also is consistent with earlier work on CPA itself.[9]

Tables I and II show the influence of J_{HP} values for **1–3** of changing solvent from C_6D_6 to $CDCl_3$ and of dilution in both solvents from 10% to 1% or less. The changes are small but real. These effects constitute the *second criterion* for assigning the major conformer to **9** or **10**. Dilution of **1** in either solvent and the change to $CDCl_3$ (at a given concentration) cause a decrease in J_{BP} and J_{CP}; i.e., the larger J_{HP} (J_{BP}) is *decreased* as is consistent with depopulation of the major conformation (**9**). Just the *opposite* effects on J_{AP} and J_{BP} occur with **2** and **3** (Table II). Since it is reasonable that the *same* conformation (**9**) is being depopulated in all three cases, *this means that the major conformer is different for* **1** *than it is for* **2** *and* **3**.

Mustard derivative **4** shows (Table II) a response to J_{HP} to solvent change parallel to that seen for **3** at the 10% concentration level. Dilution effects on J_{HP} for **3** and **4** parallel each other as well. However, the same solvent change for 10% solutions of **5** has the *opposite* effect on J_{HP} values. This is likely related to the presence of phenyl rather than hydrogen on ring nitrogen and the lack of H-bonding effects (see below).[10] We judge the criterion based on the relative chemical shifts of H_A and H_B to be reliable for the assignment of **10** as the major conformer for **5**.

Based on relative chemical shifts and J_{HP} values for H_A, H_B, H_C, and H_D, we conclude that the major conformer for CPA (**8**) in C_6D_6 also is **10**, about 70% (Table IV). Indeed, by use of J_{AP} and J_{BP} values reported earlier for CPA,[9] the effect of changing to $CDCl_3$ (Table II) is seen to be parallel to that displayed by **1–4**, though magnified in **8**. Our estimate in Table IV of the population of **9** in $CDCl_3$ (18%) is close to that previously reported (14%, 6.1/1.0 ratio) which was obtained by the use of somewhat different assumed J_{HP} values.[9] (Comment on the large effect of aqueous solvent will be made later.) The previous assignment of an equatorial preference for the nitrogen mustard group of **8** was based on a careful analysis of lanthanide-induced chemical shifts;[9] we are in complete agreement, as noted above. In the earlier report, only J_{AP} and J_{BP} were given. Our results constitute the first ^1H NMR analysis of all J_{HP} for **8**.

^1H NMR Parameters and Conformations of *cis*- and *trans*-6. The identity of *trans*-**6** is firmly established by the relative chemical shift orders $\delta_A > \delta_B$ and $\delta_C > \upsilon_D$ (Table V), which are completely consistent with the other 5-*tert*-butyl-2-oxo-1,3,2-dioxa- and oxazaphosphorinanes we have studied,[4,8] including *trans*-**7**.[4] (Parameters for **7** are also given in Table V for comparison.) It is evident that the axial P=O is strongly deshielding of the syn-axial H_A and H_C. For the cis diastereomers of both **6** and **7**, $\delta_B > \delta_A$, i.e., reversed from the order for the trans isomers. Both *trans*-**6** and -**7** are very largely if not entirely in chair conformation **12** as shown by the large J_{BP} and J_{DP} values for the equatorial hydrogens and small phosphorus couplings for H_A and H_C. These



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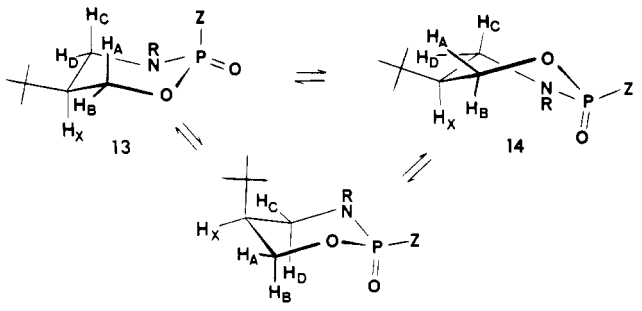
are consistent with the known Karplus-like effects of geometry on $^3J_{HP}$ in such systems.[11] The 2.4-Hz J_{BD} coupling stems from the *W* arrangement of H_B and H_D in **12**. The identities of *cis*-**7** and *trans*-**7**[12] have been proven by X-ray crystallography. The relative ^{31}P NMR chemical shifts for the diastereomers of **6** (Table V) also are confirmatory of their structures. (δ ^{31}P trans > δ ^{31}P cis.[3])

Clearly, however, the major conformation assumed by *cis*-**6** is not a chair. This is best seen by inspection of the coupling constants obtained at 1% in C_6D_6 (Table V). Although chair like values for J_{CX}, J_{DX}, J_{CP}, and J_{DP} can be noted, the corresponding parameters for H_A and H_B feature the combination of large J_{AP} and large J_{AX}, which is diagnostic of a major contribution of twist conformation **14**.[4,13,14] In a case in which **14** is nearly exclusively populated, J_{AP} values of the order 19–20 Hz and J_{BP} diminished to 4–5 Hz have been encountered.[4] An important population of **13** is also present for *cis*-**6** as evidenced by the relatively large time-averaged J_{BP} (10.3 Hz). In **14** the H_BCCH_X dihedral angle

(8) Bentrude, W. G.; Hargis, J. H. *J. Chem. Soc., Chem. Commun.* **1969**, 1113.
(9) White, D. W.; Gibbs, D. E.; Verkade, J. G. *J. Am. Chem. Soc.* **1979**, *101*, 1937.
(10) The increase in population of **9**, the conformer expected to have the larger dipolar moment, is exactly parallel to what is noted for 2-oxo-1,3,2-dioxaphosphorinanes.[3]
(11) See for example: Kung, W.; Marsh, R. E.; Kainosho, M. *J. Am. Chem. Soc.* **1977**, *99*, 5471 and references therein.
(12) Newton, M. G.; Pantaleo, N. S.; Chandrasekaran, S.; Bentrude, W. G., unpublished results.
(13) Sopchik, A. E.; Bentrude, W. G. *Tetrahedron Lett.* **1980**, 4679.
(14) Gorenstein, D. G.; Rowell, R. *J. Am. Chem. Soc.* **1979**, *101*, 4925. Gorenstein, D. G.; Rowell, R.; Findlay, J. *Ibid.* **1980**, *102*, 5077.



13 14 15

is somewhat reduced, and increased J_{BX} values can be encountered, as in Table V. It is notable that J_{AX} (9.3 Hz) for *cis*-**6** is decreased below 10–11 Hz. This could signify the population of perhaps 10% of conformer **15** but more likely only reflects a large degree of twist in **14**, leading to a decreased H_ACCH_X dihedral angle, especially since J_{CX} (10.3 Hz) is not greatly reduced. All *W*-type arrangements of H_A, H_B, H_C, and H_D are lost in **14** as is consistent with the small J_{BD} found *cis*-**6**.

It is possible to estimate the percentage population of **14** for *cis*-**6** (1% in C_6D_6) and **7** (2% in toluene-d_6) by assuming population of both **13** and **14** and use of equations analogous to 2–5 applied above to **1**–**5** and **8**. (Obviously *cis*-**7** populates chair structure **13** to a greater extent than it does twist **14**.) Table VI records values assumed for J_{AP} and J_{BP} in **13** and **14**. In the first set, J_{AP} (**13**) and J_{BP} (**13**) are the values found for the corresponding cis compound with axial MeO in place of R_2N and for which **13** is evidently very highly, if not entirely, populated.[7] For J_{AP} (**14**) and J_{BP} (**14**), the couplings found at −18 °C for the compound analogous to *cis*-**7**, but with R = Ph, are used.[4a] This compound is nearly entirely in a twist conformation like **14**. The second set of parameters arises from assuming that J_{AP} and J_{BP} are simply interchanged in **13** and **14**, which could be true if **14** is sufficiently twisted. Percentage populations of **14** estimated in this manner are recorded in Table VI and show *averaged* numbers of 22% for *cis*-**7** and 63% for *cis*-**6**. The scatter is greater for *cis*-**6**. The greater population of **14** by *cis*-**6** is presumably a result of the increased conformational energy of axial *i*-Pr_2N compared to Me_2N; this effect is exactly parallel to and confirmative to that found for **1** and **3** in which the *i*-Pr_2N shifts the **9** ⇄ **10** equilibrium strongly in favor of **10**.

At <1% in *$CDCl_3$*, *cis*-**6** also populates nonchair conformations, but the actual conformational equilibria involved is not completely clear. Intermolecular hydrogen bonding is completely absent for *cis*-**6** at 1% concentration in $CDCl_3$ (FT-IR). The large values of J_{AX} (10.3 Hz) and J_{CX} (11.1 Hz) show that the *tert*-butyl remains equatorial or pseudoequatorial in all conformations. One notes that J_{CP} is increased and J_{DP} reduced from the values for *cis*-**6** in C_6D_6. Population of the twist conformer with the ring twisted opposite to that of **14** would exchange the position of H_C and H_D, leading to $J_{DP} > J_{CP}$. A small population of this conformer in place of **14** would indeed lead to the reduced J_{DP} and increase J_{CP} noted in Table V. At the same time, the values of J_{AP} (pseudoaxial H_A) and J_{BP} (pseudoequatorial H_B), as observed, would move toward what they would be in the chair, **13**. The same trends in *J* values would occur in response to population of a boat conformer with bowspirit C(5) and P.

Infrared Studies. The hydrogen-bonded NH region (maxima at 3185–3230 cm^{-1}) in the infrared spectra of **1**–**4** and **8** was examined in C_6D_6 and/or $CDCl_3$ to assess what effect *intermolecular* hydrogen bonding might have on conformation populations. Even at 1% in C_6D_6, **1** showed a very intense hydrogen-bonded NH band. This band was less intense though still strong at 5% in $CDCl_3$ but became very weak at 1%. The other compounds, **2**–**4** and **8**, completely lost this absorption at 1% concentration in $CDCl_3$, although it was present at higher concentrations. At 1% solute concentration (0.1% for **1**) the conformational energy order *i*-Pr_2N > $(ClCH_2CH_2)_2N$ > Et_2N > Me_2N still persists (Tables II and IV). Thus, hydrogen bonding does not play the major role in determining conformation. Nonetheless, a *secondary effect* of hydrogen bonding on conformation seems probable, because the percentage of **9** present is greater in all cases at higher concentrations in either solvent. The infrared studies show that at least for **1**, hydrogen bonding is greatly reduced in $CDCl_3$ compared to C_6D_6. The general decrease in population of **9** in $CDCl_3$ compared to C_6D_6 and on dilution in $CDCl_3$ (Table IV) suggests that intermolecular hydrogen bonding is more important in conformation **9** than it is for **10**. Indeed the X-ray structure of **1** (conformation **9**) shows clearly intermolecular P=O·····HN association.[5]

The P=O stretching region of the compounds also was examined, because correlations of frequency with P=O orientations have been useful for 1,3,2-dioxaphosphorinanes[3] and have shown some promise with 1,3,2-oxazaphosphorinanes.[15,16] (See however, refs. 4a,9.) Values are collected in Table VII. Inspection of these numbers makes it clear that for **1**–**5** such correlations are not straightforward, and the IR results only can be interpreted with the aid of NMR data. The number of bands displayed can vary with the medium, as for example with **1**. The series of compounds **1**–**3**, which by ^1H NMR shows a progressive shift in equilibrium from one somewhat favoring **9** to one with **10** very predominant, fail to exhibit faithfully the same trend by IR. Thus, **1** shows only one band in KBr and CCl_4 but two bands in $CDCl_3$. The higher frequency one in $CDCl_3$ (equatorial P=O)[3] is slightly more intense in agreement with ^1H NMR assignments of a 60/40 **9**/**10** population ratio. In $CDCl_3$ **2** shows two bands, and the slightly higher intensity of the 1200-cm^{-1} band fits with the predominance of the P=O axial conformer, in accordance with ^1H NMR. However, **3** which is ca. 85% in conformation **10** (^1H NMR), has an IR spectrum like that of **2** with the 1205-cm^{-1} band only slightly more intense than the one at 1227 cm^{-1}. Moreover, **4** has the band intensities reversed from those at **2** and **3** even though **10** also is favored for **4**. It was previously reported[9] that CPA (**8**) shows five bands in the P=O stretch region when most likely only two conformers are populated.

The increase in P=O frequency in comparing **5** with **3** (KBr) illustrates the effect of replacing a ring hydrogen with a phenyl when both P=O are predominately axial. Both *trans*-**6** and *trans*-**7** (KBr) with P=O axial (structures like **12**) show a low-frequency P=O axial absorption (1200–1205 cm^{-1}) compared to that of the NPh (ring) analogue of **7** with P=O also axial (absorption at 1222 cm^{-1} in KBr, 1236 cm^{-1} in CCl_4). This is clearly an effect of NH vs. NPh rather than a change in P=O orientation, a possibility not always recognized.[16]

The major bands for *cis*-**6** and *trans*-**6** in KBr have similar frequencies as is reasonable, since P=O for *cis*-**6** is pseudoaxial in twist **14** and is axial in *trans*-**6**. (The same is true conformationally in the crystal for *cis*-**7** and *trans*-**7**.) However, *cis*-**7** is largely in the P=O equatorial chair **9** in solution. Yet the more intense band is near that of the axial P=O of *trans*-**7** in CCl_4, a major discrepancy.

^{31}P Chemical Shifts. Typically, for 2-oxo-1,3,2-dioxaphosphorinanes, the axial orientation of a given substituent on phosphorus results in a ^{31}P chemical shift upfield of that for the corresponding equatorially substituted compound.[3] This effect is seen for the oxaza systems as well.[2,4,7,9] *cis*-**6** and *trans*-**6** follow this criterion well (Table V) even though only a fraction of *cis*-**6** is in conformation **13**. To attempt to correlate conformational equilibrium **9** ⇄ **10** with ^{31}P chemical shift for **1**–**4**, however, is not expected to be straightforward as the various alkylamino groups also have different electronic properties. The expected order[3] based purely on conformational equilibrium **9** ⇄ **10**, $\delta_3 > \delta_2 > \delta_1$, is not seen (Table III). Indeed in $CDCl_3$ (1%) the ^{31}P chemial shifts for **1**–**3** are essentially identical. Any attempt to rationalize the very small difference in chemical shifts for **2** and **4**, which are similar conformationally but electronically opposite (and could therefore be very different), is futile. By contrast the

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

(16) Roca, C.; Kraemer, R.; Majoral, J.-P.; Navech, J. *Org. Magn. Reson.* **1976**, *8*, 407. Arshinova, R.; Kraemer, R.; Majoral, J.-P.; Navech, J. *Ibid.* **1975**, *7*, 309. Durrieu, J.; Kraemer, R.; Navech, J. *Ibid.* **1973**, *5*, 407.

Table VI. Estimated Percentage of **14** in Equilibrium **13** ⇄ **14** for **6** and **7**[a]

compd	assumed parameters				% 14 based on		av	$\Delta G°(13 \rightarrow 14)$	$\Delta\Delta G°$
	$J_{AP}(13)$	$J_{AP}(14)$	$J_{BP}(13)$	$J_{BP}(14)$	J_{AP}	J_{BP}			
cis-**7**	2.8	19.6	20.7	4.8	22	24			
cis-**7**	2.8	20.7	20.7	2.8	20	22	22	0.72	
cis-**6**	2.8	19.6	20.7	4.8	70	65			
cis-**6**	2.8	20.7	20.7	2.8	61	58	63	−0.30	−1.0

[a] Using coupling constants from Table V obtained in C_6D_6 (**7**) or toluene-d_8 (**6**).

Table VII. Phosphorphyl Infrared Stretch Frequencies for **1–8**, cm^{-1}

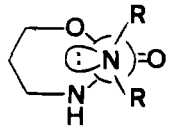
compd	KBr	CCl_4	$CDCl_3$
1	1217	1235	1212, 1229[a]
2	1199,[b] 1220[b]	1200, 1225–1241	1200,[a] 1225
3	1203,[a] 1216	1206,[a] 1217, 1234	1203,[a] 1217
4	1218, 1230	1220, 1225–1240[a,c]	1215,[d] 1230[a]
5	1230,[a] 1261	1236	
cis-**6**	1214		
trans-**6**	1202,[a] 1217		
cis-**7**	1195	1225,[a] 1240	
trans-**7**	1200	1220	
8 (hydrate)	1220–1235[d]	1230,[a] 1239	

[a] More intense. [b] Thin film. [c] Broad. [d] Shoulder.

1,3,2-dioxa systems have been found to be more readily interpretable. In fact it sometimes is possible to correlate ^{31}P chemical shifts roughly with conformer populations.[17]

Discussion

Relative Conformational Energies (Effective Sizes) of R_2N Substituents. The above results establish a substituent conformational free energy order for **1–4**, based on the equilibrium **9** ⇄ **10**, of *i*-Pr_2N > $(ClCH_2CH_2)_2N$ > Et_2N > Me_2N. The respective values of $\Delta\Delta G°$ for Et_2N, $(ClCH_2CH_2)_2N$, and *i*-Pr_2N (compared to Me_2N) are the same within experimental error in $CDCl_3$ and C_6D_6. A total range of free energies of about 1.2 kcal/mol is covered (Table IV). The sterically larger, more branched alkyl substituents in R_2N could destabilize **9** somewhat via increased 1,3-syn-axial repulsions. Thus, a true steric effect is probably at least partially responsible for the phenomena observed here. However, the observed effect is perhaps larger than expected in view of the known pyramidal nature of the axial R_2N in 2-oxo-[5] and 2-thio-1,3,2-oxazaphosphorinanes[18] which moves the R groups away somewhat from the axial ring hydrogens in the preferred P–N conformation with the lone pair directed toward the ring as in structure **16**.[15,18] (Indeed, as discussed below, Me_2N also has a lower conformational free energy in the 1,3,2-oxazaphosphorinanes than in the 1,3,2-dioxaphosphorinane system.)



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It is quite possible that certain stereoelectronic factors also are involved. Thus, in the 2-oxo-1,3,2-dioxaphosphorinanes, it is clear that orbital interactions,[3b,19] including those related to the anomeric effect, favor an axial orientation[3] of sterically small electronegative substituents such as halogen, RO, and PhNH. Perhaps in the series of Me_2N, Et_2N, and *i*-Pr_2N, the progressive decrease in group electronegativities reduces the stabilization of axial R_2N gained from the interaction of ring oxygen and nitrogen lone pairs with the axial P–N σ^* orbital (anomeric effect). This would add to the axial conformational energy of these substituents in the same order *i*-Pr_2N > Et_2N > Me_2N, as the purely steric effect.

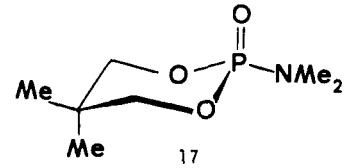
A second, *stabilizing* stereoelectronic effect may be important with R_2N (Z) equatorial as in structure **10**. The optimal geometry of these systems favors coplanarity of the trigonal planar R_2N and P=O.[4b,20,21a] The inability of an axial R_2N to attain this geometry accounts in part for its instability. The favored geometry may be a result of n–σ^* interactions involving the nitrogen lone pair and the bonds to the ring atoms attached to phosphorus.[21] Electron-supplying groups on nitrogen should enhance the lone pair participation in such bonding, leading to a stability order for *equatorial* R_2N of *i*-Pr_2N > Et_2N > Me_2N. Thus, both potential stereoelectronic effects discussed operate in the same direction as the steric repulsions to increase the stability of **10** relative to **9** in the order *i*-Pr_2N > Et_2N > Me_2N. It is also important to point out that apparent steric factors in the group R_2N are a dominant effect in determining P–N rotational barriers in $R_2NP(O)X_2$ and certain P=S compounds both cyclic and noncyclic.[22] Indeed barriers for *i*-Pr_2N rotation are generally larger than for Me_2N. Structure **16** represents, if not the barrier conformation for such rotation, a high-energy rotamer on the rotational pathway.

The relative conformational energies $(ClCH_2CH_2)_2N$ > Et_2N suggest, however, that stereoelectronic effects may not be so simply understood. Thus, electronegative R should *favor* the axial orientation on the basis of both arguments given above and result in the order Et_2N > $(ClCH_2CH_2)_2N$ in opposition to what is found. The steric effect of the β chlorine is not known.

Whatever its precise origins are, the relatively large effective size or conformational energyof the *i*-Pr_2N is confirmed in the chair–twist equilibrium **13** ⇄ **14** when comparing *cis*-**6** with *cis*-**7**. Indeed, as noted in Table VI, the *i*-Pr_2N of *cis*-**6** is about 1 kcal/mol larger than the Me_2N of *cis*-**7**. Considering the error inherent in such estimates, the agreement with the 1.2 kcal/mol effect on equilibrium **9** ⇄ **10** (Table IV) is gratifying.

The effect, discussed earlier, of changing from C_6D_6 to $CDCl_3$ on the conformational equilibrium of *cis*-**6** could reflect differences in the degree of intermolecular hydrogen bonding which was shown by the FT-IR studies of **6** to be absent at 1% concentration in $CDCl_3$. Interestingly, the equilibrium **13** ⇄ **14** for *cis*-**7** showed little or no response to changes in solvent or concentration.[4a] (See also discussion below on solvent effects on **9** ⇄ **10**.)

The ca. 0.2 kcal/mol preference of Me_2N for the *axial* position (**9**) in **1** (Table IV), even though relatively small, is remarkable in view of its 1.1 kcal/mol *equatorial* preference (C_6D_6) in 2-oxo-2-(dimethylamino)-5,5-dimethyl-1,3,2-dioxaphosphorinane, **17**;[23] i.e., Me_2N is more than 1 kcal/mol "smaller" in the oxaza



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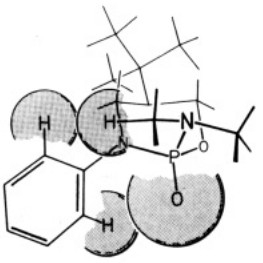


Figure 2. Structure for conformation **13** (Z = NMe_2, R = Ph) based on Dreiding model. Hemispheres approximate atomic radii (taken from ref 4a).

system. Inspection of Dreiding models and X-ray parameters indicates that the ca. 120° CNP bond angle in the ring and longer P–N compared to P–O bond length (both of which are seen in the X-ray structure of **1**[5]) move the axial Me_2N further away from the axial hydrogens at C_4 and C_6 and reduce syn-axial repulsions. The balance of stereoelectronic effects of the type discussed earlier, which favors axial Me_2N and equatorial P=O, is thus dominant. The axial Me_2N of **1** has been shown by X-ray crystallography to have a lengthened P–NMe_2 bond and pyramidal structure about Me_2N nitrogen.[5] Apparently the loss of $PNMe_2$ π stabilization which these X-ray parameters reflect is no longer great enough in the presence of reduced syn-axial repulsions in **1** to force the Me_2N equatorial. Whether the stabilization of equatorial Me_2N is as great in the 1,3,2-oxaza systems as it is with the 1,3,2-dioxa rings and the relative importance of n–σ^* stabilization of axial substituents in the two rings (N vs. O as n–σ^* participation) are at this point matters of speculation only. Even though such stereoelectronic interactions have received considerable experimental and theoretical consideration, it is clear that our understanding of them is as yet incomplete. If indeed reduced steric repulsions are responsible for the decrease in apparent size of Me_2N then the partial role of stereoelectronic effects in accounting for the increased conformational energies (apparent size) of Et_2N and *i*-Pr_2 in **1–3** seems even more probable. Further comparisons of 1,3,2-dioxa- and 1,3,2-oxazaphosphorinanes with substituents at P(2) less susceptible to stereoelectronic effects, e.g., alkyl groups, will be necessary, as will investigation of various ArMeN for which electronic effects alone can be examined. The equilibria **9** ⇄ **10** and **13** ⇄ **14** are ideal for such comparisons, and studies of this type are under way.

Effects of N(3)R on Conformational Equilibria. The remarkable effect of replacing the hydrogen on ring nitrogen with phenyl on the conformational energy of the Me_2N substituent on phosphorus in 1,3,2-oxazaphosphorinanes is very well illustrated in the comparison of **5** with **1**, Table IV. The change in equilibrium amounts to about 1.2 kcal/mol in favor of conformation **10**. In an earlier study[4a] of the effect of R on the equilibrium **13** ⇄ **14** for Z = Me_2N and R = H or Ph, the ring phenyl increased the conformational energy of axial Me_2N in **13** by at least 1.6 kcal/mol.[4a] Since an error in estimated conformer population of 5% (e.g., 40% instead of 35%) will affect $\Delta G°$ by 0.1 kcal/mol for a 60/40 conformer ratio and by 0.2 kcal/mol in the ranges 80/20 to 90/10, the agreement between 1.2 and 1.6 kcal/mol is quite satisfactory. As previously outlined,[4a] we ascribe this effect primarily to steric interactions between the methyl hydrogens of the *axial* Me_2N and the ortho hydrogens of the benzene ring. (See Figure 2 taken from an earlier paper.[4a]) This conformational effect is an important one for 2-oxo-1,3,2-oxazaphosphorinanes which obviously is not present in their 2-oxo-1,3,2-dioxaphosphorinane counterparts. It is not seen with small substituents such as RO on phosphorus.[7] Evidence for the confirmation of the steric importance of such a phenomenon has been found in unpublished work with various combinations of R = Ph and Z = Ph or mesityl.[7] A stereoelectronic component to this effect might also be operative to some degree since the phenyl substitution on nitrogen makes the nitrogen lone pair less available for n–σ^* interactions with axial Me_2N.

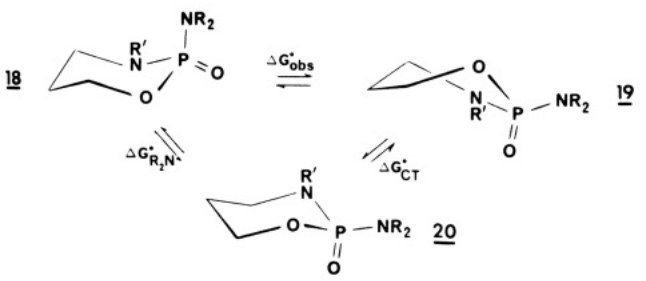
Chair-to-Twist Free Energy Change ($\Delta G°_{CT}$). Further consideration of the equilibrium **13** ⇄ **14** for *cis*-**6** and *cis*-**7** allows a reasonable estimation to be made of the energetic ease with which twist structures are populated. There are two energetic components (eq 6) to the observed $\Delta G°$ for equilibrium **13** ⇄ **14**: the increase in free energy on change from the chair to the twist conformation ($\Delta G°_{CT}$), and the favorable effect of placing the R_2N equatorial ($\Delta G°_{R_2N}$). the $\Delta G°_{R_2N}$ term is approximated by $\Delta G°$ (**9** → **10** or **18** → **19**). The release of steric repulsions is

$$\Delta G°(\mathbf{13} \rightarrow \mathbf{14}) = \Delta G°_{CT} + \Delta G°_{R_2N} \qquad (6)$$

closely similar, although small changes in ring geometry resulting from the 5-*tert*-butyl group could affect $\Delta G°_{R_2N}$ somewhat. Nonetheless, an approximation of $\Delta G°_{CT}$ can be obtained in this way. This dissection is clearly demonstrated by the cycle involving **18**, **19**, and **20**. From $\Delta G°$ (**13** → **14**) for *cis*-**6** (equivalent to $\Delta G°_{obsd}$ for **18** ⇄ **19**), $\Delta G°_{CT}$ (1% in C_6D_6) is 0.7 kcal/mol [−0.30–(−1.0)]. Based on *cis*-**7**, $\Delta G°_{CT}$ (1% in C_1D_6) is 0.5 kcal/mol [0.72–0.23]. The two values, 0.5 and 0.7 kcal/mol, are certainly within experimental error since, as mentioned earlier, $\Delta G°$ (**13** → **14**) and $\Delta G°_{R_2N}$ are normally subject to errors of 0.1–0.2 kcal/mol. Furthermore, the scatter of values of population for **14** for *cis*-**6** in Table VI is large. Both of these estimates are lower than the value of at least 1.6 kcal/mol in our earlier report.[4a] That number was derived from $\Delta G°$(**13** → **14**) for *cis*-**7** by use of an assumed $\Delta G°_{R_2N}$ for Me_2N which was taken to be the same as that for $N(CH_2CH_2Cl)_2$[9] (reported equatorial/axial ratio for $N(CH_2CH_2Cl)_2$ of **8**, 6/1[9]). Similarly, if for the case Z = Me_2N, R = Ph, **14** (**20**) is at least 80% populated (as determined earlier[4a]), then $\Delta G°_{CT}$ can be estimated to be less than 0.5 kcal/mol.

Clearly, the above values of $\Delta G°_{CT}$ are very low for a six-membered ring when compared to cyclohexane (4–5 kcal/mol[24]) and 1,3-dioxane (8 kcal/mol[25]) and similar to the 1 kcal/mol or less figures of $\Delta G°_{CT}$ estimated for 2-oxo-1,3,2-dioxaphosphorinanes[8,26] and 2-oxo-1,3,2-dithiaphosphorinanes.[27] Low $\Delta G°_{CT}$ values seem to be associated with six-membered rings containing lengthened bonds, for example, C–S, P–O, and P–N. Increased bond lengths induce ring flattening and reduced cross-ring steric and torsional repulsions in the twist conformation. One presumes that this is true for the 2-oxo-1,3,2-oxazaphosphorinanes as well. The reason for the apparent population for *cis*-**7** of no other twist conformations except **14** is not known. Nonetheless, the R_2N and NPh are moved further away from each other in **14** than in the other twist conformation directly formed from the boat with C(4) and P(2) in bowspirit positions.

It must emphasized that one refers in these discussions to chair → twist interconversions which correspond to **19** → **20** (Z equatorial or pseudoequatorial) and not to those in which Z is pseudoaxial in the twist conformation. The latter should show



a strong dependence of $\Delta G°_{CT}$ on the steric size of Z. This

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probably is the reason that the trans diastereomers of both **6** and **7** remain totally in the chair conformation with *t*-Bu and R_2N equatorial even though the Me_2N has a small preference for the axial position.

Solvent Effects on Equilibria (9 ⇄ 10). The effect of solvent change on the **9** ⇄ **10** equilibrium for **1–4** is especially interesting in that the change from C_6D_6 to more polar solvents such as $CDCl_3$, acetone, or even C_6D_6/Me_2SO-d_6 or C_6D_6/CD_3CN does not increase the population of the more polar conformation **9** as is common for 2-oxo-1,3,2-dioxaphosphorinanes.[3] In fact $CDCl_3$ and acetone-d_6 favor **10**, as does dilution in C_6D_6 or $CDCl_3$. Both of these effects probably reflect decreased intermolecular hydrogen bonding (Results section) which dominates solute–solvent interactions. Indeed, H bonding seems to be a secondary effect overridden by the steric and electronic effects of R_2N on conformation in all **1–4**. By contrast **5**, with Ph in place of hydrogen on the ring nitrogen, shows a response to increased solvent polarity consistent with the more favorable solvent–solute dipole–dipole interactions expected of conformation **9** which would have a larger dipole moment than **10**.

The **9** ⇄ **10** equilibrium for CPA itself (**8**) is much more susceptible to solvent changes than are those for **1–3** or even **4** to which it is most similar. The effect of water is especially notable. As shown in Tables II and IV, for **8** the percentage of the more stable conformer populated (**10**) ranges from 58 to 82. Local medium effects, e.g., those of enzymes, could be expected to be able to easily perturb the CPA conformational equilibrium in the manner most advantageous to the system whether it be oxidative activation, ring opening of the 4-hydroxy derivative, or transport.

P=O IR Frequencies and Ring Conformation. It should be emphasized that our results show that the use of P=O IR stretching frequencies to assign axial or equatorial phosphoryl oxygen orientation should be considered risky at best. Not only must the substituents Z on phosphorus be very similar (e.g., **1–3**) but no change in substituent on ring nitrogen is allowable. Even then, at least when two conformations are present, the relative intensities of the bands may not be that predicted by conformation population. In certain media the proper number of bands may not be seen. As demonstrated by *cis*- and *trans*-**7**, differently oriented P=O groups occasionally may have the same frequency. As suggested elsewhere,[9] H bonding between molecules may complicate the IR picture where ring NH is present.

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 SW expansions, 32K data base, 5.459-s acquisition times, and are probably accurate to ±0.2 Hz. ^{31}P NMR spectra were made at 32.2 MHz on a Varian FT-80A spectrometer under proton noise decoupling conditions. Positive ^{31}P chemical shifts are in δ parts per million downfield from external 85% H_3PO_4. The mass spectrometer used was a VG Micromass 7070 double-focusing high-resolution instrument with VG Data System 2000 operated in the EI mode using direct inlet sampling. FT-IR work was done on a Nicolet 7199 instrument.

(Bis(2-chloroethyl)amido)phosphoryl Dichloride was prepared by the procedure of White, Gibbs, and Verkade.[9] $Me_2NP(O)Cl_2$, $Et_2NP(O)Cl_2$ and *i*-$Pr_2P(O)Cl_2$ were all made according to Walsh and Toy for $Me_2NP(O)Cl_2$[28] and characterized by ^1H and ^{31}P NMR. Preparations of amino alcohols $HOCH_2C(CH_3)_2CH_2NH_2$ and **3** were reported earlier.[5] The corresponding *N*-phenyl compound, $HOCH_2C(CH_3)_2CH_2NHPh$, **9**, was prepared in parallel fashion except that $EtO_2CC(CH_3)_2COCl$ (0.515 mol in 500 mL of Et_2O) was reacted with $PhNH_2$ (117 g, 1.25 mol in 100 mL of Et_2O), added slowly at room temperature, rather than with NH_3. The reaction mixture was filtered and washed with successive 150-mL portions of H_2O, 10% HCl, H_2O, 10% NH_3, H_2O, and saturated NaCl. The organic layer was dried over $MgSO_4$; the ether was removed and the residue recrystallized from ether/pentane to give *N*-phenyl-2-carboethoxy-2-methylpropionamide, a colorless solid: mp 48–49 °C; (^1H NMR $CDCl_3$), δ 1.30 (3 H, t, CH_3CH_2O), 1.58 (6 H, s, Me_2C), 4.26 (2 H, q, CH_3CH_2O), 7.02–7.59 (5 H, m, C_6H_5), 8.64 (1 H, broad s, NH); IR (KBr) 3250, 2980, 1730, 1660, 1600, 1550, 1495, 1445, 1390, 1324, 1310, 1270 (s, P=O), 1175, 1142, 760 cm^{-1}. Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.29; N, 5.95. found: C, 66.44; H, 7.38; N, 5.97. A solution of this amide (4.71 g, 20.0 mmol) in 50 mL of Et_2O was added slowly to a rapidly stirred suspension of $LiAlH_4$ (1.75 g, 46.0 mmol) in 50 mL of Et_2O. After a 3-day reflux, the mixture was cooled to 0 °C and quenched with a mixture of Et_2O (100 mL) and H_2O (3.8 mL, 212 mmol). This mixture was stirred at room temperature for 1 h; $MgSO_4$ was added and stirring continued for 15 min. Filtration and washing of the solids with Et_2O (4 times), removal of the Et_2O, and bulb-to-bulb Kugelrohr distillation, bp 108–110 °C (0.25 mm), gave 3.50 g (98% yield) of a colorless liquid, **9**: IR (film) 3550, 3390, 3150, 3120, 2930, 2870, 1602, 1508, 1473, 1390, 1366, 1323, 1257, 1181, 1157, 1100, 1042, 994, 750, 697 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.91 (6 H, s, Me_2C), 3.01 (2 H, s, CH_2OH), 3.44 (2 H, s, CH_2NH), 3.61 (2 H, s, NH and OH), 6.74–7.44 (5 H, m, C_6H_5). Anal. Calcd for $C_{11}H_{17}NO$: C, 73.70; H, 9.56. Found: C, 73.70; H, 9.61.

2-(Diethylamino)-2-oxo-5,5-dimethyl-1,3,2-oxazaphosphorinane, 2. A solution of (diethylamido)phosphoryl dichloride (2.45 g, 12.9 mmol) in anhydrous ethyl acetate (50 mL) was added slowly to a rapidly stirred solution of 2-(hydroxymethyl)-2-methylpropylamine (1.33 g, 12.9 mmol) and anhydrous triethylamine (3.60 mL, 2.61 g, 25.8 mmol) in anhydrous ethyl acetate (100 mL), cooled to 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 2 days. The triethylamine hydrochloride was filtered off and the solvents removed from the filtrate to give 3.00 g of a pale yellow oil. A 1.50-g sample of the crude product so obtained was chromatographed by MPLC on silica gel, eluting with EtOAc/EtOH (9:1) to give 760 mg (62.2% yield) of **5** as a clear colorless oil: ^{31}P NMR ($CDCl_3$) δ 13.61; IR (thin film) 3220 (s, br, N-H), 2965, 2935, 2875, 1466, 1382, 1220 (s, P=O), 1199 (s, P=O), 1090, 1035, 1000, 951, 801, 784 cm^{-1}; MS (EI), *m/e* 220 (M^+, 14%), 205 (89%), 165 (19%), 149 (22%) 148 (15%), 122 (10%), 84 (27%), 72 (100%), 69 (14%), 60 (13%), 58 (66%), 56 (12%), 55 (12%), 45 (14%), 44 (21%), 43 (33%), 42 (14%), 41 (24%), 30 (60%), 29 (21%), 28 (30%), 27 (14%); high-resolution MS, *m/e* (M^+) calcd for $C_9H_{21}N_2O_2P$ 220.1340, found 220.1322.

2-(Diisopropylamino)-2-oxo-5,5-dimethyl-1,3,2-oxazaphosphorinane, 3. A solution of (diisopropylamido)phosphoryl dichloride (2.96 g, 14.6 mmol) in anhydrous ethyl acetate (25 mL) was added slowly to a rapidly stirred solution of 2-(hydroxymethyl)-2-methylpropylamine (1.40 g, 13.6 mmol) and anhydrous triethylamine (3.78 mL, 2.75 g, 27.1 mmol) in anhydrous ethyl acetate (100 mL), cooled to 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 6 days. The triethylamine hydrochloride was filtered off and the solvents removed from the filtrate to give 3.94 g of residual yellow oil. A 3.00-g sample of the crude product was purified by MPLC on silica gel, eluting with EtOAc/EtOH (9:1), to give 1.97 g (76.6% yield) of 2-(diisopropylamino)-2-oxo-5,5-dimethyl-1,3,2-oxazaphosphorinane as a colorless crystalline solid, a sample of which was recrystallized from EtOAc hexane for analysis: mp 111–113 °C; ^{31}P NMR ($CDCl_3$), δ 13.46; IR (KBr) 3145 (s, br, N-H), 2957, 2870, 1470, 1411, 1367, 1327, 1216 (s, P=O), 1203 (s, P=O), 1159, 1134, 1086, 1040, 1033, 1013, 990, 948, 784, 673 cm^{-1}; mass spectrum, *m/e* 248 (M^+, 8%), 234 (11%), 233 (100%), 205 (24%), 191 (86%), 135 (15%), 86 (14%), 84 (17%), 69 (16%), 58 (18%), 57 (10%), 56 (16%), 55 (17%), 44 (40%), 43 (31%), 42 (24%), 41 (43%), 40 (41%), 39 (12%). Anal. Calcd for $C_{11}H_{25}N_2O_2P$: C, 53.21; H, 10.15; P, 12.47. Found: C, 53.30; H, 10.19; P, 12.68.

2-(Bis-(2-chloroethyl)amino)-2-oxo-5,5-dimethyl-1,3,2-oxazaphosphorinane, 4. A solution of (bis(2-chloroethyl)amido phosphoryl dichloride (12.1 g, 46.7 mmol) in anhydrous ethyl acetate (100 mL) was added slowly to a rapidly stirred solution of 2-(hydroxymethyl)-2-methylpropylamine[8] (4.82 g, 46.7 mmol) and anhydrous triethylamine (13.0 mL, 9.45 g, 93.4 mmol) in anhydrous ethyl acetate, cooled to 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 3 days. The triethylamine hydrochloride was filtered off and the solvents removed from the filtrate to give 14.7 g of the crude product as a pale yellow oil. A 500-mg sample of this product was chromatographed on silica gel, eluting with EtOH/EtOAc (1:9), to give 350 mg (76% yield) of **4** as a colorless crystalline solid. A sample was recrystallized from ethyl acetate/pentane: mp 90–91 °C; ^1H NMR (90 MHz; $CDCl_3$) δ 0.75 (s, 3 H, CCH_3), 0.80 (s, 3 H, CCH_3), 2.4–3.2 (m, 2 H, ring CH_2N), 3.2–3.5 (m, 8 H, NCH_2CH_2Cl), 3.4–4.1 (m, 3 H, ring CH_2O, NH); ^{31}P NMR ($CDCl_3$) δ 12.92; IR (KBr) 3220 (NH), 2965, 2890, 1465, 1390, 1355, 1333, 1253, 1230 (P=O), 1218 (P=O), 1204, 1139, 1106, 1086, 1036, 1010, 986, 950, 930, 862, 833, 794, 785, 750, 740, 614 cm^{-1}; mass spectrum, *m/e* 288 (M^+, not observed), 241 (32%) 239 (100%), 148 (M – N $(CH_2CH_2Cl)_2$, 35%) 92 (23%); 84 (37%), 56

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(21%), 41 (23%), 30 (51%). Anal. Calcd. for $C_9H_{19}N_2O_2PCl_2$: C, 37.39; H, 6.62; N, 9.69; P, 10.71; Cl, 24.52. Found: C, 37.38; H, 6.65; N, 9.64; P, 10.96; Cl, 24.44.

2-(Dimethylamino)-2-oxo-3-phenyl-5,5-dimethyl-1,3,2-oxazaphosphorinane, 5. A mixture of *N*-phenyl-2-(hydroxymethyl)-2-methylpropylamine[14] (16.3 g, 91.1 mmol) and hexamethylphosphorous triamide (19.5 mL, 17.5 g, 91.1 mmol) in a solution of ethyl acetate (100 mL) and toluene (100 mL) was refluxed for 18 h. The solvents were removed in vacuo, and the residual liquid was dissolved in dichloromethane (250 mL). The reaction mixture was cooled to −20 °C, and the material was oxidized by dropwise addition of a saturated solution of N_2O_4 in CH_2Cl_2. The reaction mixture was warmed to room temperature and the solvent removed in vacuo, leaving a thick brown oil (41.7 g). A 5.75-g sample of the oil was chromatographed on a 20 × 700 mm column of silica gel (Baker, 60–200 mesh, 90 g), eluting with ethyl acetate/hexane (1:1). The first 700 mL of eluent was discarded and the next 400 mL collected. Removal of the solvent by rotary evaporation gave 2.48 g (73.6% yield) of 2-(dimethylamino)-2-oxo-3-phenyl-5,5-dimethyl-1,3,2-oxazaphosphorinane (**5**) as a pale yellow crystalline solid. A small sample of the compound was Kugelrohr distilled from bulb to bulb with an air bath temperature of 120 °C at 0.20 torr and then recrystallized from diethyl ether/pentane to give analytically pure product: mp 60–61 °C; ^{1}H NMR (90 MHz, $CDCl_3$) δ 1.00 (s, 3 H, CCH_3), 1.32 (s, 3 H, CCH_3), 2.63 (d, 6 H, NCH_3, J_{HP} = 10.2 Hz), 3.05–4.50 (m, 4 H, CH_2N, CH_2O), 7.3–7.7 (m, 5 H, C_6H_5); ^{31}P NMR (CD_3COCD_3) δ 8.28; IR (KBr) 2960, 2890, 2845, 2800, 1600, 1500, 1490, 1480, 1305, 1261 (s, P=O), 1230 (s, P=O), 1207, 1190, 1123, 1110, 1080, 1058, 1042, 994, 900, 810, 793, 757, 740, 696 cm^{-1}; mass spectrum, *m/e* 268 (48%, M^+), 213 (81%), 106 (100%), 105 (99%), 104 (29%), 77 (31%), 69 (25%). Anal. Calcd. for $C_{13}H_{21}N_2O_2P$: C, 58.20; H, 7.89; P, 11.54. Found: C, 58.14; H, 7.95; P, 11.68.

2-(Diisopropylamino)-2-oxo-5-*tert*-butyl-1,3,2-oxazaphosphorinanes, 6. A solution of (diisopropylamido)phosphoryl dichloride (6.20 g, 28.4 mmol) in anhydrous ethyl acetate (50 mL) was added slowly to a rapidly stirred solution of 2-(hydroxymethyl)-3,3-dimethylbutylamine (3.73 g, 28.4 mmol) and anhydrous triethylamine (7.92 mL, 5.75 g, 56.9 mmol) in anhydrous ethyl acetate (200 mL), cooled to 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 4 days. The triethylamine hydrochloride was filtered off and the solvents removed from the filtrate to give 8.24 g of a residual yellow solid. A 400-mg sample of this crude product was chromatographed by MPLC on silica gel, eluting with EtOAc/EtOH (9:1) to give 140 mg of pure *trans*-2-(diisopropylamino)-2-oxo-5-*tert*-butyl-1,3,2-oxazaphosphorinane (**6**) as a colorless crystalline solid which was recrystallized from Et_2O/pentane: mp 141 °C; ^{31}P NMR ($CDCl_3$) δ 13.70; IR (KBr), 3270 (s, b, NH), 2962, 2888, 1408, 1364, 1217 (sh), 1202 (s, P=O), 1158, 1130, 1088, 1037, 1030, 1014, 991, 840, 799, 774 cm^{-1}. Anal. Calcd. for $C_{13}H_{29}N_2O_2P$: C, 56.50; H, 10.58; P, 11.21. Found: 56.48; H, 10.61; P, 11.35; MS, (EI) *m/e* 276 M^+ (5.0%), 262 (13%), 261 (100%), 233 (25%), 219 (70%), 135 (28%), 94 (13%), 86 (18%), 69 (11%). In addition 40 mg of the cis diastereomer was obtained and recrystallized from pentane: mp 80–82 °C; ^{31}P NMR ($CDCl_3$) δ 11.52; IR (KBr) 3210 (s, br, NH), 2920, 2870, 1404, 1367, 1249, 1214 (P=O), 1193 (sh), 1160, 1110, 1034, 1000, 968, cm^{-1}; mass spectrum, *m/e* 276 (M^+, 4%), 262 (14%), 261 (100%), 233 (23%), 219 (74%), 135 (29%), 94 (13%), 86 (19%), 69 (27%). Anal. Calcd. for $C_{13}H_{29}N_2O_2P$: C, 56.50; H, 10.58; P, 11.21. Found: C, 56.49; H, 10.54; P, 11.29. A further 160 mg of a pure mixture of diastereomers also was isolated, total 340 mg (89% yield).

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Registry No. 1, 88946-46-7; **2**, 94843-98-8; **3**, 94843-99-9; **4**, 22089-27-6; **5**, 94844-00-5; *trans*-**6**, 94859-54-8; *cis*-**6**, 94844-01-6; **8**, 50-18-0; **9**, 94844-02-7; $Et_2NP(O)Cl_2$, 1498-54-0; *i*-$Pr_2P(O)Cl_2$, 23306-80-1; $EtO_2CC(CH_3)_2COCl$, 64244-87-7; $PhNH_2$, 62-53-3; 2-(hydroxymethyl)-2-methylpropylamine, 76733-32-9; (bis(2-chloroethyl)amido)phosphoryl dichloride, 127-88-8; hexamethylphosphorus triamide, 680-31-9; 2-(hydroxymethyl)-3,3-dimethylbutylamine, 15521-17-2; *N*-phenyl-2-carboethoxy-2-methylpropionamide, 7507-43-9.

Ion Pairing and Reactivity of Enolate Anions. 6. Kinetics and Thermodynamics for Reaction of Alkali Acetylacetonates with Alkyl Halides in Dimethyl Sulfoxide

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Abstract: Rates and heats of reaction are reported for the C-alkylation of alkali salts of various symmetrical β-diketones with methyl and ethyl iodide in dimethyl sulfoxide (Me_2SO). Product analysis by FT-NMR established that the reactions were clean over the concentration range of the kinetic and thermochemical study and, with only one exception, gave 100% carbon alkylation within the limits of detection. The effects of ion pairing, temperature, and alkylating agent were probed to yield an extensive comparison of the effects of structural change on the kinetics of alkylation with methyl or ethyl iodide. The formation of 3-methyl-3-ethylacetylacetone by alternative routes (methylation of potassium 3-ethylacetylacetonate and ethylation of potassium 3-methylacetylacetonate) allows an unprecedented comparison of the energetics of each step along the reaction profile from isomeric reactants in the gas phase, through isomeric transition states, to a common product in Me_2SO solution.

From a pragmatic viewpoint, alkali enolates are probably the most important type of synthetic intermediate since they are involved in the many useful base-promoted alkylation and acylation reactions of carbonyl compounds. However, relatively few systematic physicoorganic studies have been aimed at elucidating the factors which control the rates or product distribution in these important reactions. From what has been done so far, it is clear that practically every variable in the system can influence the outcome. In recent years the sensitivity of many enolate reactions to the choice of alkali counterion has become appreciated and attributed to ion pairing. The notion that dissociated (i.e., "naked") anions are more reactive than those which are paired to alkali cations is attractive and has inspired the use of various strategies such as the use of dipolar nonhydroxylic solvents, polybasic cation ligands, and phase-transfer catalysis to help dissociate the ion pairs. Several excellent recent reviews have organized the literature that

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