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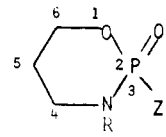
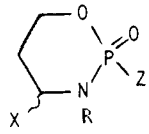
X-ray and NMR Studies of a Cyclophosphamide-like Molecule, *cis*-2-Oxo-2-dimethylamino-3-phenyl-5-*tert*-butyl-1,3,2-oxazaphosphorinane. Twist Conformation in Both Solid Phase and in Solution

Sir:

The 1,3,2-oxazaphosphorinanes cyclophosphamide (**1**), isophosphamide (**2**), and trophosphamide (**3**) are clinically useful anticancer drugs.[1] In vivo oxidation activates these molecules and gives the 4-hydroxy derivatives (**4**) in which the OH and Z may be related either cis or trans. Because of the expected relationship of molecular configuration and conformation to ease of oxidative microsomal potentiation and subsequent efficacy, X-ray studies of a number of such systems have been completed. These include **1**,[2] **2**,[3] and **3**;[4] 4-peroxy-**1**;[5] the 4-hydroperoxy derivatives of **1**[6] and **2**;[4b] and 4-keto-**1**.[7] In addition the enantiomers of **1** have recently been resolved[8] and their absolute configurations assigned by X-ray anomalous dispersion techniques.[9] Indeed, important differences in efficacies and rates of metabolism in humans and mice were ascribed to the two enantiomers.[10] Currently, investigations of



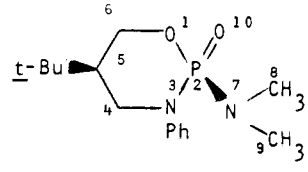
1 R = H; Z = $N(CH_2CH_2Cl)_2$
2 R = CH_2CH_2Cl; Z = $NHCH_2CH_2Cl$
3 R = CH_2CH_2Cl; Z = $N(CH_2CH_2Cl)_2$



4 X = OH; R, Z based on **1**–**3**
5 X = Me; R = H; Z = $N(CH_2CH_2Cl)_2$

the in vivo activities of the *cis*- and *trans*-4-methylcyclophosphamides (**5**) are being pursued.[11]

All of the above systems studied by X-ray crystallographic techniques were shown to possess chair-form conformations. It has been suggested that in solution both cyclophosphamide itself[12] and *trans*-**5** (Me and $N(CH_2CH_2Cl)_2$ trans)[11a] populate more than one conformation. We report here that closely related 1,3,2-oxazaphosphorinane **6** is in a *twist conformation* both in solid state and in solution. Thus, twist forms should receive important consideration in conformational equilibra involving **1**–**5**.



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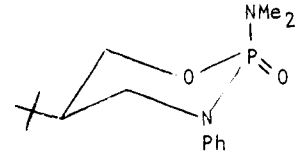

9

A mixture of diastereomeric 2-dimethylamino-2-oxo-3-phenyl-5-*tert*-butyl-1,3,2-oxazaphosphorinanes was synthesized by the N_2O_4 oxidation of the corresponding trivalent phosphorus precursor. The latter was prepared by condensation of the required amino alcohol with $(Me_2N)_3P$ in a refluxing 50:50 mixture of ethyl acetate and toluene as solvent (6 h). The mixture of oxides was separated by column chromatography on silica gel eluted with anhydrous ether. Recrystallization of the cis isomer (**6**) from benzene gave white crystals, mp 165–166 °C (uncorrected). C, H, and P analyses within ±0.3 of calculated values were obtained.

Crystals of **6** belong to space group $P\bar{1}$ with $Z = 2$ (ρ_{calcd} = 1.206, ρ_{measd} = 1.213 g/cm^3) and cell dimensions a = 6.143 (2), b = 11.273 (4), c = 12.423 (3) Å; α = 102.3 (1), β = 95.3 (1), γ = 102.3 (1)°. Data were collected on an Enraf–Nonius CAD-4 diffractometer using Mo K$\bar{\alpha}$ X-radiation with a graphite monochromator and ω–2θ scan technique. The structure was solved by direct methods with the use of MULTAN[1] and refined to R = 0.046 (R_w = 0.035) by full-matrix least squares using the 1754 unique nonzero diffraction maxima. All hydrogen atoms were located and refined isotropically.

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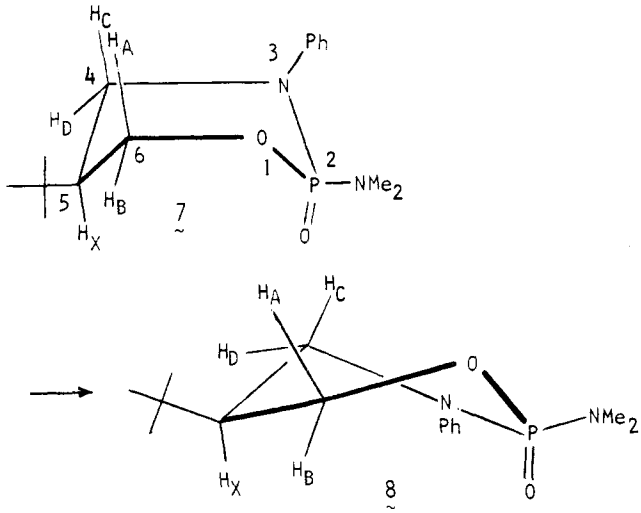
Table I. ^{1}H NMR Parameters for 6

	Chemical Shifts[a]				
solvent	δ_{H_A}	δ_{H_B}	δ_{H_C}	δ_{H_D}	δ_{H_X}
MDCB[b]	3.91	4.34	3.39	3.49	2.24
$CDCl_3$[c]	4.06	4.54	3.50	3.62	2.46

	Coupling Constants[d]									
solvent	J_{AB}	J_{AX}	J_{BX}	J_{AP}	J_{BP}	J_{CD}	J_{CX}	J_{DX}	J_{CP}	J_{DP}
MDCB[b]	−10.5	10.5	6.5	18.1	5.7	−11.1	11.0	3.1	3.5	15.1
$CDCl_3$[c]	−10.6	10.6	6.8	18.0	5.0	−11.0	11.0	4.0	2.6	14.4

[a] In parts per million downfield from internal Me_4Si. [b] Refined values from LAOCN3-assisted iteration in *m*-dichlorobenzene at 90 MHz, 37 °C. [c] First-order analysis of FT spectra at 300 MHz, 25 °C, 1–2% solutions; data acquisition at 3000-Hz sweep width, acquisition time 2.728 s; *J* values were measured on 100-Hz expansions of original 3K acquisition.



The melting point of the crystal used in data collection (mp 168–171 °C) compared favorably with that of the batch sample (mp 164–165 °C).

Figure 1 is an ORTEP drawing of the structure determined for **6**. Only those atoms which define the ring conformation are shown. The basic structure is a twist-form ring with 5-*tert*-butyl and Me_2N pseudoequatorial. The skewing of the ring from the true boat conformation with phosphorus and C-5 at the bow positions is illustrated by **7** → **8**. The resulting twist conformation (Figure 1) is intermediate along the pseudorotation circuit between **7** and the boat form with O-1 and C-4 at the bow positions. The Me_2N (methyls not shown) of **6** is nearly planar ($\measuredangle O_{10}$-P-N_7-C_8, 10.9 (2), and $\measuredangle O_{10}$-P-N_7-C_9, −174.5 (2) °) and rotated only very slightly out of the O_{10}-P-N_7 plane. The plane of the phenyl ring (not shown in Figure 1) is ~30° out of the P-N_3-C_4 plane. Close to trigonal planarity is found about N_3. Bond angles and lengths were not unusal when compared with those of chair forms **1–3** and derivatives thereof previously mentioned. The torsional angles in the ring clearly define its geometry: N_3-P, −12.8 (2); P-O_1, 55.5 (2); O_1-C_6, −35.3 (3); C_6-C_5, −29.0 (3); C_5-C_4, 66.8 (3); C_4-N_3, −42.4 (2)° (errors in parentheses).

The ^{1}H NMR parameters for **6** (Table I) are quite consistent with a very analogous twist form being highly populated in solution as well. Chemical shifts and coupling constants were obtained on a first-order basis at 300 MHz and further refined iteratively at 90 MHz using the LAOCN3 program. Parameter sets obtained by both methods appear in Table I. No notable effect of solvent is found. The small differences in *J* values for H_C and H_D in the two solvents may arise from errors in *J* resulting from the slightly non-first-order nature of the ^{1}H NMR spectrum of H_C and H_D at 300 MHz. Values in *m*-dichlorobenzene are used in the arguments which follow.

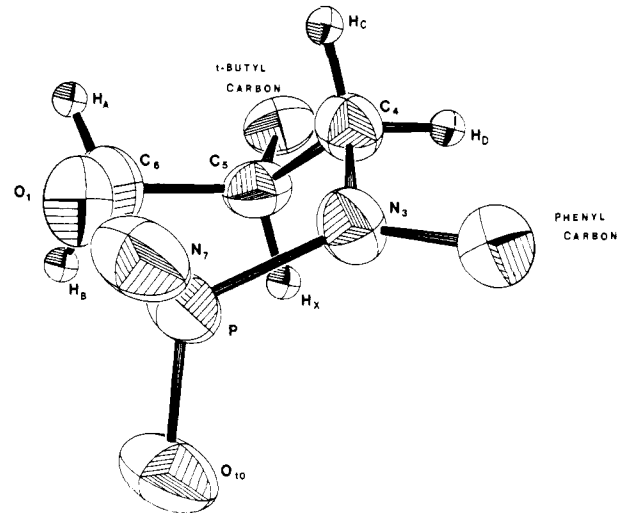


Figure 1. ORTEP drawing of twist **6** from X-ray study.

Noteworthy is the fact that, for each pair of methylene hydrogens, there is one large coupling to phosphorus and one large coupling to the methine hydrogen (H_X). For the CH_2 next to N_3 the values of J_{CX} (11.0 Hz) and J_{CP} (3.5 Hz), along with those for J_{DX} (3.1 Hz) and J_{DP} (15.1 Hz), approach those one would expect for axial H_C and equatorial H_D adjacent to equatorial 5-*tert*-butyl[14] on a chair-form ring. In fact, the skewing deformation **7** → **8** moves these atoms and groups into pseudoequatorial and pseudoaxial positions. The dihedral angles found in the solid state for **6** (Figure 1), $PN_3C_4H_D$ (−160 ± 2), $PN_3C_4H_C$ (83 ± 2), $H_CC_4C_5H_X$ (−174 ± 2), and $H_DC_4C_5H_X$ (67 ± 2°), are consistent with the coupling constants observed.[14] (However, there is no reason to assume that the torsional angles for **6** are *precisely* the same in solution and in the crystal.) The order of chemical shifts, $\delta_{H_D} > \delta_{H_C}$, reflects the deshielding effect of the phosphoryl group cis to H_D noted in the analogous 5-*tert*-butyl-1,3,2-dioxaphosphorinanes[15] and in the trans diastereomer of **6**.[14]

Although the ^{1}H NMR parameters involving H_C and H_D could arise from a chair-form isomer with 5-*tert*-butyl equatorial and Me_2N axial, this is not true for H_A and H_B. Most notably, H_A has a large coupling to H_X (J_{AX} = 10.5 Hz) and to phosphorus (J_{AP} = 18.1 Hz), which is not possible in a chair conformation. (These couplings were confirmed in phosphorus- and H_X-decoupled spectra.) This unusual combination of coupling constants arises because of the large angles $H_AC_6C_5H_X$ and $H_AC_6O_1P$ in the twist conformation. In the solid state these are −153 ± 2 and −158 ± 3°, respectively.[16] Thus the twisting **7** → **8** increases angle $H_AC_6O_1P$ from ~60° in true boat (**7**) to approximate that in the chair conformation with H_A equatorial, without decreasing the $\measuredangle H_AC_6C_5H_X$ drastically. As expected, J_{BX} (6.5 Hz) is large for an axial-

equatorial coupling (angle $H_BC_6C_5H_X$ in the solid, $-34 \pm 3°$). J_{BP} (5.7 Hz) is small (angle H_BC_6OP in the solid, $88 \pm 2°$). Predictably, $\delta_{H_B} > \delta_{H_A}$.[14,15] That **6** should populate a *single* twist form in solution is not surprising, since the 1,3,2-oxazaphosphorinane ring lacks the symmetry of the 2,5-disubstituted-2-oxo-1,3,-2-dioxaphosphorinanes in which two rapidly interconvertible mirror image 2,5-twist forms are populated.[15b,17]

The 1,3,2-oxazaphosphorinane **6** is *primarily* in the twist form (**8**) in solution with no more than minor amounts of chair conformer **9** or *other* twist form populated.[18] This twist preference appears even greater than that of the analogous 1,3,2-dioxaphosphorinane (**6**, PhN = O), 60% of which populates *dl*-pair twist conformers.[15b,19] The relative case of accessibility of twist forms to the 2-oxo-1,3,2-oxazaphosphorinane system is further illustrated by the fact that the trans counterpart of **6** is in a twist conformation in the solid though not in solution.[20]

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(18) Small temperature effects on the ^1H NMR spectra of **6** over the range -50 to $+105$ °C confirm the greater enthalpic stability of **8** over **9**.
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Outer-Sphere Chemical Activation for Electron Transfer in the Mixed-Valence Solid $Cs_2(Sb^{III}_xSb^V_xSn_{1-2x})Cl_6$

Sir:

Resonance Raman studies provide a direct probe of the structural changes required in going from a ground to an excited electronic state.[1] In the case of mixed-valence materials, resonance Raman data obtained when the excitation frequency is tuned to the intervalence transfer (IT) absorption band can clarify the Franck–Condon restrictions for electron transfer.[2-5] Further, those vibrational modes which show resonance enhancement through vibronic coupling to the IT transition are, in principle, the same modes involved in the chemical activation step for thermal electron transfer.[2-4] This is particularly true of outer-sphere mixed-valence solids wherein the coordination spheres of the metal ions involved do not share a common ligand, thereby creating a weak-overlap or localized-valence situation. We report a resonance Raman study of the outer-sphere mixed-valence solid $Cs_2(Sb^{III}_xSb^V_xSn_{1-2x})Cl_6$ where $(SbCl_6)^{-1}$–$(SbCl_6)^{-3}$ pairs have been doped into a host Cs_2SnCl_6 lattice. The results demonstrate resonance enhancement of the *host* Cs_2SnCl_6 vibrational modes due to Raman excitation within the dopant IT band.

In a recent resonance Raman study of the mixed-valence solid $Cs_2(Sb^{III}_{0.5}Sb^V_{0.5})Cl_6$, Clark and Trumble demonstrated the IT resonance enhancement of a combination band involving a lattice mode and the symmetric stretch of the $SbCl_6^{-1}$ ion.[6] This observation of IT enhancement of lattice modes suggests that lattice structural changes accompany the Sb^{III}–Sb^V electron transfer in addition to the expected structural changes of the $(SbCl_6)^{-3}$ and $(SbCl_6)^{-1}$ complex ions. In order to elucidate further the involvement of the lattice structure in solid-state electron transfer, a resonance Raman study of $Cs_2(Sb^{III}_xSb^V_xSn_{1-2x})Cl_6$ has been carried out. The host Cs_2SnCl_6 lattice has no electronic transition in the region of the Sb^{III}–Sb^V IT absorption.

The $Cs_2(Sb^{III}_xSb^V_xSn_{1-2x})Cl_6$ was synthesized using Day's previously reported rapid precipitation method.[7] The Raman spectra were gathered on a Cary-82 spectrometer using Ar^+ and Kr^+ ion lasers. Laser power was typically set at <100 mW to prevent sample decomposition. The excitation profile was obtained by using all available lines of the Ar^+ and Kr^+ lasers. Spectral response of the Cary-82 was calibrated for each point by comparison to a $CaSO_4$ standard. The excitation profile was obtained by plotting the intensity of the sample divided by the intensity of the standard vs. the laser exciting line. The sample was analyzed by X-ray fluorescence and found to contain 36% antimony.

Figure 1 shows the spectra of pure Cs_2SbCl_6, pure Cs_2SnCl_6,

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