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EFFECT OF NITROGEN SUBSTITUENTS ON THE RELATIVE ENERGIES OF TWIST AND CHAIR-FORM CONFORMATIONS OF CIS 2-OXO-2-DIMETHYLAMINO-5-t-BUTYL-1,3,2-OXAZAPHOSPHORINANES

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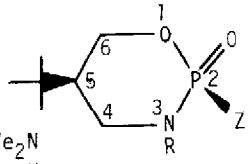
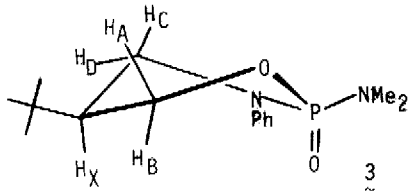
Abstract: Replacement of the phenyl substituent on nitrogen of the 1,3,2-oxaza ring of the title compounds changes the twist-chair equilibrium such that the chair conformation is populated rather than the twist form primarily occupied in the N-phenyl case. A possible rationale based on Me_2N-phenyl interactions is proposed.

Two recent reports have emphasized the propensity of the 1,3,2-oxazaphosphorinane ring to undergo conformational change from the normal chair form to a twist form in response to steric[1] or electronic[2] demands of the substituents on phosphorus. While the principles which govern the conformational effects of substituents on phosphorus may well be like those in the corresponding 1,3,2-dioxaphosphorinanes,[3] the oxaza rings can be perturbed by an additional effect, the nature of the substituent on ring nitrogen. We report here the very important influence on the chair twist-equilibrium in 1,3,2-oxazaphosphorinanes of the identity of the nitrogen substituent.

It was earlier noted[1] that cis-2-oxo-2-dimethylamino-3-phenyl-5-t-butyl-1,3,2-oxazaphosphorinane, 1, is found in solution almost exclusively in a twist conformation, 3. The PMR parameters for 1 are reproduced in Table I. Most important is the combination of large J_{AP} and J_{AX} which can only obtain for the twist conformation shown. However, as shown below, replacement of the 3-phenyl substituent by hydrogen leads to a dramatic change in the relative energies of chair and twist conformations.



1 R=Ph, Z=Me_2N
2 R=H, Z=Me_2N



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The corresponding hydrogen compound, 2, was formed in the usual manner as one of two diastereomers by reaction of the amino alcohol with Me_2NPOCl_2 in the presence of Et_3N. The product diastereomers were separated by column chromatography on SiO_2 and characterized by ^{13}C, ^{31}P, and ^1H NMR and by quantitative elemental analysis for C, H, and P. Assignments of geometries to the individual diastereomers were made by comparisons of ^1H, ^{31}P, and ^{13}C NMR parameters and relative GLC retention times to those of the corresponding P=S diastereomers whose cis and trans geometries had been determined by a single-crystal X-ray study of the cis diastereomer.[4]

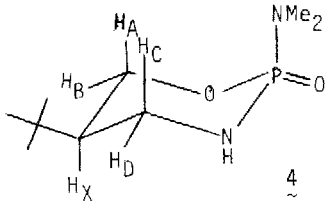
Table I. PMR Parameters for cis-1 and 2

Cmpd	Solvent	Chemical Shifts[a] δH_A	δH_B	δH_C	δH_D	δH_X
1	MDCB[c]	3.91	4.34	3.39	3.49	2.24
2	C_6D_6[d]	3.82	4.15	2.76	3.16	1.81

		Coupling Constants[b] J_{AB}	J_{AX}	J_{BX}	J_{AP}	J_{BP}	J_{CD}	J_{CX}	J_{DX}	J_{CP}	J_{DP}	J_{BD}
1	MCDB[c]	-10.5	10.5	6.5	18.1	5.7	-11.1	11.0	3.1	3.5	15.1	<1.0
2	C_6D_6[d]	-10.8	10.7	4.7	6.2	17.0	-12.6	11.1	4.4	2.4	23.6	2.1

[a] In ppm downfield from internal TMS. [b] In Hz. [c] Refined values from LAOCN3-assisted iteration in m-dichlorobenzene at 90 MHz, 37°. [d] First-order analysis of FT spectrum at 300 MHz, 25°, 10% solution.

Recorded in Table I are the PMR parameters for 2. The couplings J_{AX} (10.7 Hz) and J_{CX} (11.1 Hz) establish the equatorial position of the t-butyl group. Moreover, the combination of large values for J_{BP} (17.0 Hz) and J_{DP} (23.6 Hz) and corresponding small ones for J_{AP} (6.2 Hz) and J_{CP} (2.4 Hz) is that expected for chair conformation 4. Thus while the NPh derivative populates primarily a twist conformation, 3, the NH compound is largely the chair form.



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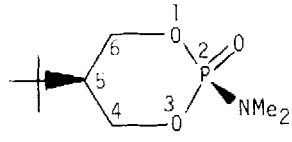

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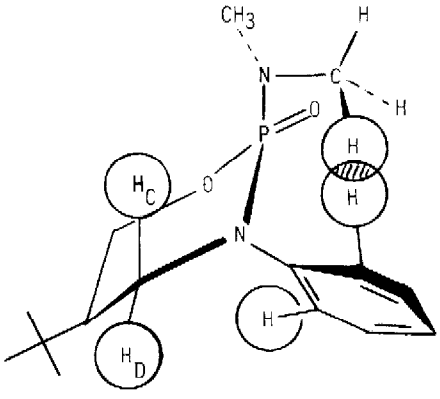
It appears probable to us that the N-phenyl compound, 1, experiences severe destabilizing steric interactions in the chair conformation between the phenyl and dimethylamino groups. These interactions are depicted in structure 5. To avoid interaction of the ortho hydrogens with the equatorial H_D and phosphoryl oxygen the phenyl ring is rotated out of conjugation with the nitrogen lone pair. As a result the ortho hydrogens encounter the Me_2N methyls oriented as shown.[5] These interactions are relieved in the twist form, 3, in which the Me_2N can now assume a conformation with near coplanarity with the P=O. This is seen in the X-ray structure of 1, in which the Ph ring π orbitals are reasonably close to being fully overlapped with the nitrogen lone pair.[1] These sorts of steric problems are absent in the NH compound. Significantly, the N-H and N-phenyl



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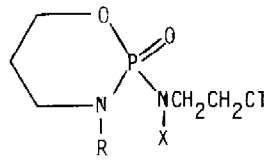


7 R = H, X = CH_2CH_2Cl

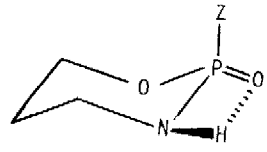
8 R = CH_2CH_2Cl, X = H

9 R = X = CH_2CH_2Cl

compounds with MeO rather than Me_2N on phosphorus both exist in the chair form analogous to 3 in solution.[6] The MeO is both sterically small and strongly axial seeking.

It is notable that the corresponding dioxa compound, cis-2-dimethylamino-2-oxo-5-t-butyl-1,3,2-dioxaphosphorinane, 6, populates a twist conformation to the extent of about 60%.[7] Drieding models show clearly that in the oxaza rings strong ring flattening about nitrogen has increased the non-bonded distances between the axial hydrogens at C-4 and C-6 and the Me_2N methyls compared to those in the 1,3,2-dioxaphosphorinane. Thus reduced 1,3-synaxial interactions could be the source of the apparent greater stabilities of chair conformations such as 4 for the 1,3,2-oxaza rings (in the absence of large groups on nitrogen and phosphorus) compared to the analogous 1,3,2-dioxa compounds.

A potential additional factor favoring axial phosphorus substituent orientation in N-H compounds is shown in structure 10.[8] The importance of such internal hydrogen bonding, available only when phosphoryl oxygen is equatorial, will require careful evaluation by IR studies. The



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conformational properties of 2 are unaffected by intermolecular hydrogen bonding as shown by PMR studies in different solvents with varying sample concentrations.

Biologically, the above findings could be of importance relative to the oxidative activation of cyclophosphamide, 7 (NH), and the related antitumor agents isophosphamide, 8 (NCH_2CH_2Cl), and trophosphamide, 9 (NCH_2CH_2Cl). Microsomal oxidation of these substances in the liver leads to materials with OH functionality at the 4 position which are potentially diastereomeric.[9]

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References:

1. G.S. Bajwa, W.G. Bentrude, N.S. Pantaleo, M.G. Newton, and J.H. Hargis, J. Am. Chem. Soc., 101, 1602 (1979).

2. D.G. Gorenstein and R. Rowell, J. Am. Chem. Soc., 101, 4925 (1979); D.G. Gorenstein, R. Rowell, and J. Findlay, ibid, 5077 (1980).

3. For a recent review see: B.E. Maryanoff, R.O. Hutchins, and C.A. Maryanoff, Topics in Stereochemistry, 11, 187 (1979).

4. M.G. Newton, unpublished results, University of Georgia.

5. That the Me_2N indeed should be oriented as shown in 5 is indicated by the X-ray crystallographic study of the cis P=S compound corresponding to 4.[4]

6. G.S. Bajwa and D.G. Burright, unpublished results from this laboratory.

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8. The possibility of such intramolecular hydrogen-bound structures have been suggested by Verkade et al. (D.W. White, D.E. Gibbs, and J.G. Verkade, J. Am. Chem. Soc., 101, 1937 (1978).

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