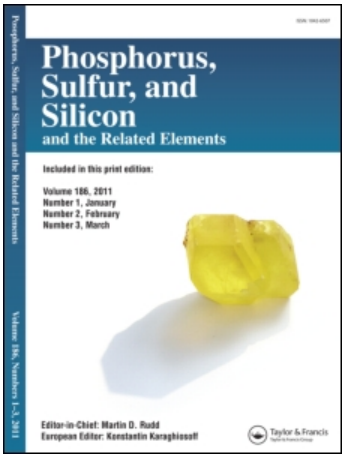

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Conformation of 2-Oxo-2-dimethylamino-1,3,2-λ^5-benzoxazaphosphorinane: X-Ray, NMR, and Ab initio Studies

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*2-oxo-2-dimethylamino-1,3,2-λ^5-benzoxazaphosphorinane **1** was synthesized and characterized by multinuclear NMR and IR spectroscopy, mass spectrometry, and elemental analysis. The structure of **1** was determined by single crystal X-ray diffraction. The conformation of **1** in both solution and in the solid state was studied. According to the results of X-ray, NMR, and ab initio studies, compound **1** adopted a twist conformation with the NMe_2 group in pseudoequatorial orientation.*

Keywords Ab initio studies; benzoxazaphosphorinane; crystal structure; conformational analyses; cyclophosphamide

INTRODUCTION

Cyclophosphamides and structurally related analogues are of interest in different areas of chemistry, e.g., as urease inhibitors,[1] ashless antioxidants, antirust and antiwear additives for lubricating oil,[2] and anticancer drugs.[3] One class of most important derivatives of cyclophosphamides are 1,3,2-oxazaphosphorinanes, which play a key role in cancer chemotherapy.[3] A thorough knowledge of the conformational properties of cyclophosphamides should be beneficial to a detailed understanding of the effect of conformation on pharmacological effects of these compounds.[4] Concerning benzo-annulated derivatives, the preparation and antitumor activity of several compounds has been reported.[5–8] According to our knowledge, this report is the first conformational study of a benzocyclophosphamide derivative. 2-oxo-2-*Z*-

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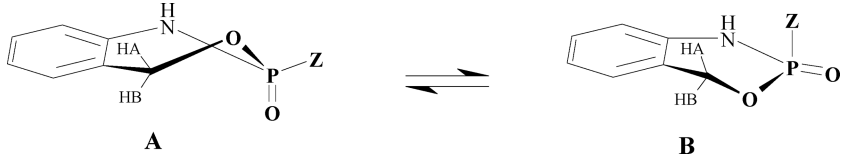
1,3,2-λ^5-benzoxazaphosphorinanes can be viewed as benzocyclohexenes in which carbon atoms have been replaced by oxygen, phosphorus, and nitrogen atoms. Due to benzene ring aromaticity, these compounds in contrast to saturated six-membered rings[9] adopt only two twist conformations, **A** and **B** (Scheme 1).

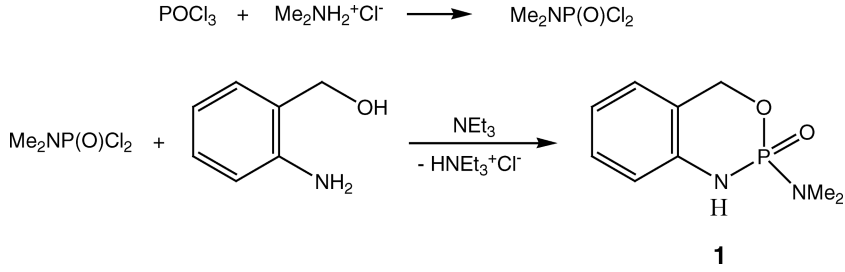


SCHEME 1

Here we report the synthesis of 2-oxo-2-dimethylamino-1,3,2-λ^5-benzoxazaphosphorinane (**1**), which was characterized by ^{1}H, ^{31}P, and ^{13}C NMR; infrared spectroscopy; mass spectrometry; and elemental analysis. The molecular structure of **1** in the crystal was determined by single crystal X-ray diffraction. The structure and relative energies of different conformers of **1** were examined by *ab initio* calculations. These calculations were carried out using the GAUSSIAN 98 program package.[10]

RESULTS AND DISCUSSION

$Me_2NP(O)Cl_2$ was prepared by a literature method[11] using $P(O)Cl_3$ as the starting material. 2-amino benzyl alcohol was reacted smoothly with $Me_2NP(O)Cl_2$ in the presence of triethylamine to afford **1** as a white powder in a high yield (85%).



SCHEME 2

The molecule structure of compound **1** in the crystal, as resulting from single crystal X-ray diffraction studies, is presented in Figure 1. Data collection and structure refinement parameters, as well as selected bond distances, bond angles, and torsion angles, are provided in Tables I and II.

TABLE I Structure Determination of 1

Empirical formula	$C_9H_{13}N_2O_2P$
Formula weight	212.18
Temperature/K	120(2)
Wavelength/Å	0.71073
Crystal system space group	orthorhombic, $P2_12_12_1$
Unit cell dimensions/Å,°	a = 7.552(2)
	b = 7.992(2)
	c = 16.632(5)
	$\alpha = 90$
	$\beta = 90$
	$\gamma = 90$
Volume/Å^3	1003.8(5)
Z, Calculated density/g/cm^3	4, 1.404
Absorption coefficient/mm^{-1}	0.249
F(000)	448
Crystal size/mm	0.08 × 0.12 × 0.3
Theta range for data collection/°	2.45–30.04
Limiting indices	$-10 \le h \le 10$, $-11 \le k \le 9$, $-23 \le l \le 23$
Reflection collected/unique	8368/2899 (R[int] = 0.0194)
Completeness to theta = 30.04	99.2%
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.93 and 0.55
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	2899/0/130
Goodness-of-fit on F^2	1.034
Final R indices (for 2749 refl. with $I \ge 2\sigma[I]$)	R1 = 0.0389, wR2 = 0.1042
R indices (all data)	R1 = 0.0408, wR2 = 0.1061
Absolute structure parameter	0.44(9)
Largest diff. peak and hole eÅ^{-3}	0.772 and −0.244

Figure 1 shows the twist conformation of compound **1**, which is also illustrated by formula **A** (Z=NMe_2, Scheme 1). The phosphoryl oxygen atom O(2) occupies a pseudoaxial position, and the dimethylamino group adopts a pseudoequatorial orientation. Carbon atoms of the NMe_2 group are directed away from the oxazaphosphorinane ring. Coordination at the phosphorus atom is approximately tetrahedral; the average of the six angles around the phosphorus atom is 109.3(7)°. However, the coordination is clearly distorted, since the O(2)P(1)N(1) angle with 115.7(7)° is larger than the O(1)P(1)N(1) angle of 100.9(6)°. The P=O bond length is 1.476(12) A°, in good agreement with the P=O distance in similar compounds.[12,13] The environment of the exocyclic nitrogen atom is nearly planar (sum of the angles at N2: 356.3[12]°).[14] The endocyclic nitrogen atom also displays trigonal planar geometry. The P(1)N(1) bond length is 1.650(14) A° shorter than a single P-N bond, and the an-

TABLE II Selected Structural Parameters of 1

Bond Lengths (Å)		Bond angles (°)	
P1-O2	1.476(12)	O2-P1-O1	1 113.7(7)
P1-O1	1.590(11)	O2-P1-N2	112.1(7)
P1-N2	1.626(14)	O1-P1-N2	106.3(7)
P1-N1	1.650(14)	O2-P1-N1	115.7(7)
O1-C1	1.456(17)	O1-P1-N1	100.9(6)
N1-C7	1.408(2)	C1-O1-P1	116.3(10)
N2-C8	1.462(2)	Torsion angles (°)	
N2-C9	1.468(2)	H_AC(1)O(1)P(1)	173.8
C1-C2	1.503(2)	H_BC(1)O(1)P(1)	55.1

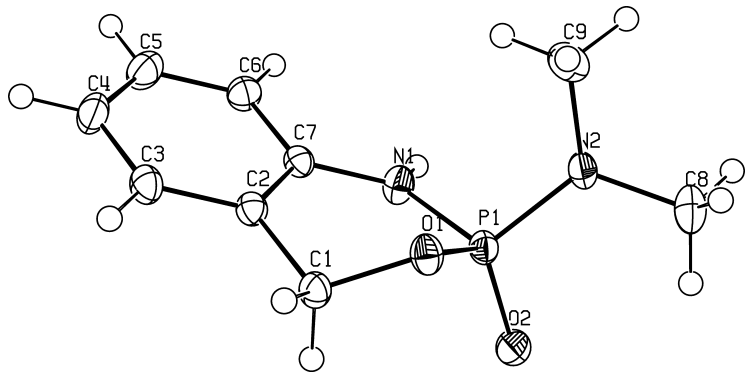


FIGURE 1 ORTEP diagram of the molecular structure of **1** in the crystal; thermal ellipsoids are at 50% probability level.

gle C(7)N(1)P(1) is 124.7(1)° substantially larger than the tetrahedral angle. These values are in accord with partial double-bond properties of the P(1)N(1) bond.[12,14,15] In this conformer the C(1)O(1)P(1) angle is 116.3(10).° This angle is substantially larger than the tetrahedral and is very close to the trigonal,[16] indicating that the endocyclic oxygen atom is prone to change its hybridization from sp^3 to sp^2. Due to benzene ring aromaticity, the carbon atoms C(1), C(2), and C(7) and the nitrogen atom N(1) are coplanar.

Figure 2 shows packing of molecules in the unit cell. Analysis of the intermolecular distances indicate that the crystal is built up of molecules of **1** linked to chains by N—H· · ·O hydrogen bonds (the H· · ·O and N· · ·O distances are 1.96 Å and 2.83 Å respectively, with a N—H· · ·O angle of 170.9°).

The conformation of compound **1** is further characterized by ^{1}H NMR and ^{1}H{^{31}P} NMR spectroscopy. It is well known that the proton (H_B)

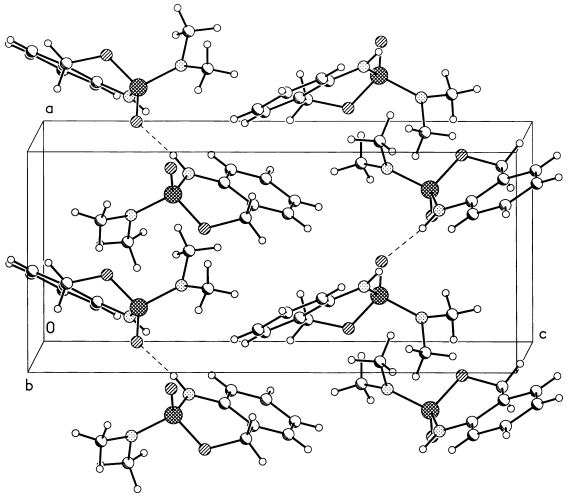


FIGURE 2 Packing of molecules in the unit cell of **1**, showing the hydrogen bonding.

in *cis* position relative to P=O is less shielded than the counterpart (H_A).[4,17] In the ^{1}H NMR spectrum the shielded proton (H_A) shows a larger phosphorus proton coupling constant ($^3J_{PH}$ =23.0 Hz) in accord with the large dihedral angle $H_AC(1)O(1)P(1)$ (173.8°); as expected, the smaller dihedral angle for $H_BC(1)O(1)P(1)$ (55.1°) corresponds to the smaller P,H coupling constant ($^3J_{PH}$ = 7.4 Hz).[18] It is proven that the electronic nature of the substituents at the phosphorus atom is important to rationalize the conformational preference of six-membered phosphorus heterocycles.[15,18–19] When Z is an electron-withdrawing atom or group (i.e., NMe_2), it prefers to occupy the equatorial position,[19] This behavior has been attributed to the repulsive 1,3-synaxial interaction between the methyl groups bonded to the nitrogen atom and the axial hydrogen atom H_B of the oxazaphosphorinane ring,[20] to the maximal $p_\pi(N1)$-$d_\pi(P)$ interaction,[12] and to the stabilizing $p_\pi(O1)$-σ^*(P-Z) endo anomeric interaction.[19] The conversion of **A** to **B** (Scheme 1) involves a change in the $H_BC(1)O(1)P(1)$ and $H_BC(1)O(1)P(1)$ dihedral angles and, consequently, changes in $^3J_{PH}$.[16,17,20] Assignments of conformational population for **A** and **B** (Scheme 1) of compound **1** in solution were made based on three criteria: temperature effect, solvent effect, and concentration effect. Variable temperature-solution NMR experiments (−90–55°C) did not show change in J_{PH} values of diastrotopic protons. When similar checks on the effects of solvent (acetone-d_6 $CDCl_3$) and concentration were made, no important changes in $^3J_{PH}$ values were encountered. Therefore, compound **1** is present in solution and in the

TABLE III Selected Experimental and Calculated (Conformer A) Bond Lengths and Bond Angles for 1

Bond Length (Å)	Exp.	Calcd.	Bond angle (°)	Exp.	Calcd.
P(1)-O(2)	1.48	1.48	O(1)P(1)N(1)	100.9	101.6
P(1)-O(1)	1.59	1.62	P(1)N(1)C(7)	124.7	123.1
P(1)-N(1)	1.56	1.68	C(1)O(1)P(1)	116.8	119.9

solid state as conformer **A**. Pseudoequatorial orientation for the NMe_2 group might be the cause of this conformation.

This interpretation is confirmed by *ab initio* calculations. Geometry optimization was carried out for the conformers of **1**, **A** and **B** (Z=NMe_2) using the HF and the B3LYP levels of theory with 6-31G* and 6-311G** basis sets. The calculated bond lengths and bond angles at B3LYP/6-311G** level of theory are in excellent accord with the experimental values (Table III).

In the structure with the lowest energy, the NMe_2 group is equatorial in agreement with the experiment. Conformational free energy (ΔG°) of these conformers was calculated. At the B3LYP/6-311G** level of theory, after correction for the difference in zero-point energies, the calculated ΔG° for the **A** $\leftrightarrow$ **B** equilibrium was 15.6 kcal/mol. Clearly, the previously discussed value of ΔG° is large when compared to similar compounds.[13,14–17] The result indicates that conformer **A** is more stable than conformer **B**.

In summary, NMR spectroscopy, *ab initio* calculations, and X-ray crystallography showed that compound **1** in both solution and in solid state adopts the twist conformation **A**, with the NMe_2 group in pseudo equatorial position.

EXPERIMENTAL

The melting point was measured on an electrothermal 9100 apparatus and is uncorrected. The IR spectrum was recorded as a KBr pellet on a Shimadzu IR-460 spectrometer. C, H, and N elemental analysis was performed using a Heraeus CHN-O-rapid analyzer. The mass spectrum was recorded with a Finnigan-Matt 8430 mass spectrometer operating at an ionization potential of 70 eV. ^1H, ^{13}C, and ^{31}P NMR spectra were recorded with a Bruker Avance DRX 500 MHz spectrometer in $CDCl_3$ as a solvent. ^1H, ^{13}C, and ^{31}P chemical shifts are given relative to TMS and 85% phosphoric acid, respectively, as external standards. Reagents and solvents used were obtained from Fluka.

Synthesis

N,N-Dimethyl Phosphoramidic Dichloride, ($Me_2NP(O)Cl_2$)

The compound was synthesized and purified according to the reported method.[11]

2-Oxo-2-dimethylamino-1,3,2-λ^5-benzoxazaphosphorinane (1)

To a solution of 2-amino benzyl alcohol (1 g, 8.2 mmol) in CCl_4 were added triethylamine (0.82 g, 8.2 mmol) and $Me_2NP(O)Cl_2$ (1.3 g, 8.2 mmol). The suspension was stirred at -10°C for 12 h, allowed to warm up to r.t., and left for 24 h. After filtration, CCl_4 was evaporated under reduced pressure. The residue was recrystallized from $CHCl_3$, m.p. 176°C, (yield 1.45 g, 85%). Anal. calcd. for $C_9H_{13}N_2O_2P$: C, 50.94; H, 6.18; N, 13.20. Found: C, 50.92; H, 6.18; N,13.21; IR (KBr), υ (cm^{-1}): 3405(m), 2910(w), 1599(w), 1466(s), 1207(vs), 994(s), 927(w), 911(w), 761(m). ^{1}H NMR ($CDCl_3$) $\delta = 2.7$ (d, $^3J_{PH} = 10.3$ Hz, 6H), 4.99 (dd, $J = 13.5$, 23.0 Hz, 1H), 5.38 (dd, $J = 3.5$, 7.4 Hz, 1H), 5.99 (d, $J_{PH} = 7.0$ Hz, 1H), 6.83–7.27 (m, 4H). $^{13}C\{^1H\}$ NMR ($CDCl_3$): $\delta = 36.6$ (d, $J_{PC} = 4.4$ Hz), 67.5 (d, $J_{PC} = 6.9$ Hz), 116.8 (d, $J_{PC} = 9.7$ Hz), 120.9 (s), 121.7 (d, $J_{PC} = 5.00$ Hz), 125.3 (s), 129.1 (d, $J_{PC} = 1.8$ Hz), 140.8 (s). $^{31}P\{^1H\}$ NMR ($CDCl_3$)δ=8.5 (s). MS, m/e (relative intensity) 212 (100%, M^+), 169 (75%), 150 (40%), 104 (50%), 78 (40%), 44 (100%).

Crystal Structure

Data were collected on a Bruker SMART diffractometer with a CCD area detector, using graphite-monochromated Mo-Kα radiation at 120 K. A total of 8,368 reflections were measured. The structure was solved by direct method and refined on F^2 by full-matrix least-squares techniques. The final cycle of least-squares refinement was based on 2,749 observed reflections ($I \geq 2\sigma[I]$). A summary of the crystal data, data collection, and refinement is given in Table I.

Crystallographic data for the structure of **1** have been deposited with the Cambridge Crystallographic Data Center (CCDC). Copies of the data can be obtained free of charge on quoting the number CCDC 242147 from CCDC (12 Union Road, Cambridge CB2 1EZ, UK) (fax: +441223 336033; e-mail: deposit@ccdc.cam.ac.uk).

REFERENCES

[1] M. D. Swerdloff, J. F. Kolc, M. M. Rogic, and L. L. Hendrikson, *U.S. Patent*. **4,** 517, 007 (1985).

[2] D. Abbott, H. Slamon, and R. Sattergood, *Brit. Patent*. 1, **558,** 462 (1980).

[3] G. Zon, *Prog. Med. Chem*., **19,** 205 (1982)
[4] W. N. Setter, A. E. Sopchik, and W. G. Bentrude, *J. Am. Chem. Soc*., **107,** 2083 (1985).
[5] S. M. Ludeman and G. Zon, *J. Med. Chem*., **18,** 1251 (1975).
[6] S. M. Ludeman, G. Zon, and W. Egan, *J. Med. Chem*., **22,** 151 (1979).
[7] G. Zon, S. M. Ludeman, and W. Egan, *J. Am. Chem. Soc*., **99,** 5785 (1979).
[8] Z. Li, J. Han, Y. Jiang, P. Browne, R. J. Knox, and L. Hu, *Bioorg. Med. Chem*., **11,** 4157 (2003).
[9] D. W. White, D. E. Gibbs, and J. G. Verada, *J. Am. Chem. Soc*., **101,** 1937 (1979).
[10] M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, et al., *Gaussian* 98, (Revision A.7), Gaussian Inc., (Pittsburgh, PA, 1998).
[11] E. N. Walsh and A. F. Toy, *Inorg. Synth.,* **7,** 69 (1963).
[12] P. G. Jones, H. Thonnessen, A. Fischer, I. Neda, R. Schmutzler, J. Engel, et al., *Acta Cryst*., **C52,** 2359 (1996).
[13] A. M. Brzozowski and A. Sterpin, *Acta Cryst*., **C46,** 618 (1990).
[14] Y. L. Bennani and S. Hanessian, *Acta Cryst*., **C47,** 1230 (1991).
[15] A. Perales, J. Fayos, and S. Garcia-Blanco, *Acta Cryst*., **B35,** 1620 (1979).
[16] Z. J. Dominguez, M. T. Cortez, and B. Gordillo, *Tetrahedron*, **57,** 9799 (2001).
[17] G. S. Bajwa, S. Chandrasekaran, J. H. Hargis, A. E. Sopchik, D. Blatter, and W. G. Bentrude, *J. Am. Chem. Soc.*, **104,** 6385 (1982).
[18] W. Kung, R. E. Marsh, and M. Kainosho, *J. Am. Chem. Soc.*, **99,** 5471 (1977).
[19] W. G. Bentrude, W. N. Setzer, M. Khan, A. E. Sopchik, and E. Ramli, *J. Org. Chem.*, **56,** 6127 (1991).
[20] G. S. Bajwa, W. G. Bentrude, N. S. Pantaleo, and M. G. Newton, *J. Am. Chem. Soc.*, **101,** 160 (1979).