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Solid-State Conformation of the 1,3,2-Oxazaphospholane Ring in 2-Dialkylamino-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholane Sulfides

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ABSTRACT: *Dialkylamino-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholane sulfides (where the alkyl is an isopropyl, ethyl or methyl group) was obtained by sulfurization of the respective phospholanes. The structures of these compounds were determined by X-ray crystal structure analysis. Five-membered rings exist in the envelope conformation in the crystalline state. The planar part of the 1,3,2-oxazaphospholane rings undergoes twisting with the enlargement of a substituent. The environment of the P atom has the geometry of a distorted tetrahedron.* © 2001 John Wiley & Sons, Inc. Heteroatom Chem 12:146–150, 2001

INTRODUCTION

Five-membered rings are highly fluxional and capable of adopting a range of nonplanar conformations separated by very small energy barriers in solution [1]. In the solid state, one single conformation usually exists, depending on the substituents and crystal packing. Five-membered rings can adopt the envelope or half-chair conformation. There are 91 structures composed of 1,3,2-oxazaphospholane rings described in the literature [1–4], but only for 71 different structures have three-dimensional parameters been determined. Statistically, most preferred is the envelope conformation with carbon bonded to nitrogen at the flap (28 structures), the next most preferred conformation has carbon bonded to oxygen at the flap (19 structures). Moreover, 7 envelope structures exist with N at the flap, 3 with P at the flap, but only 1 with O at the flap, and there are only 5 planar structures. Eight structures have an ideal half-chair conformation. The conformation adopted depends on the substituents both at phosphorus and at the other atoms of the ring [1]. In this article, we attempt to present the influence of substituents at the phosphorus atom on the geometry of 1,3,2-oxazaphospholane rings.

SYNTHESIS

Homochiral chlorophosphoroamidite [(1*R*,2*S*)-*O*,*N*-ephedrine]PCl (**2**) has been synthesized [4,5] by the reaction of the trimethylsilyl derivate of (−)ephedrine (**1**) with phosphorus trichloride. The chloride **2** obtained reacts stereoselectively with trimethylsilyldialkylamines to give liquid 2-dialkylamino-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholanes (**3**),

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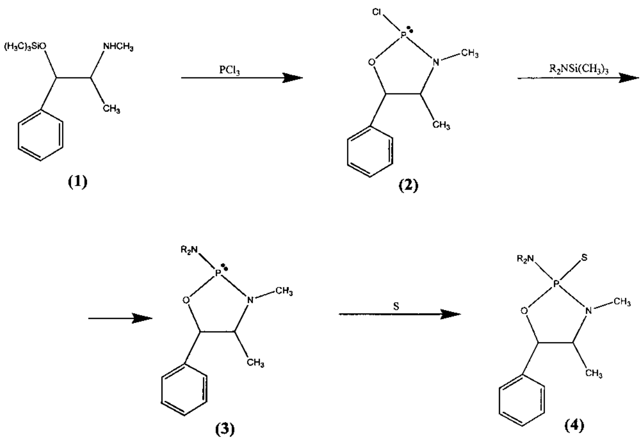

SCHEME 1 Reactions in synthesis.

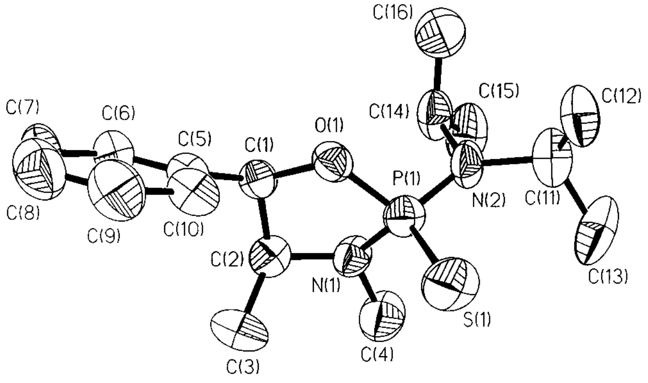

FIGURE 1 The molecular conformation of **4-1** with atom numbering.

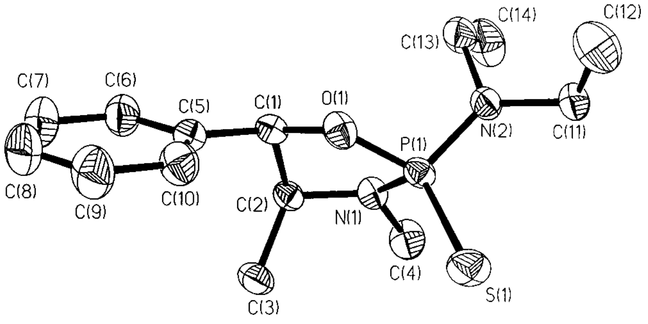

FIGURE 2 The molecular conformation of **4-2** with atom numbering.

which were sulfurized, in a reaction which has been shown to proceed with retention of configuration at phosphorus [4], to give crystalline 2-dialkylamino-3,4-dimethyl-5-phenyl-1,3,2-oxazaphospholane sulphides (4), R = ^{i}Pr (4-1), Et (4-2), Me (4-3) (Scheme 1).

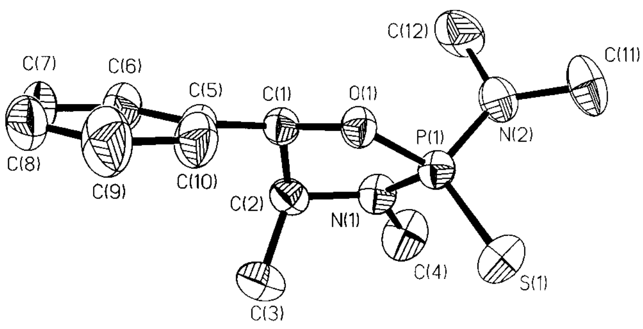

FIGURE 3 The molecular conformation of **4-3** with atom numbering.

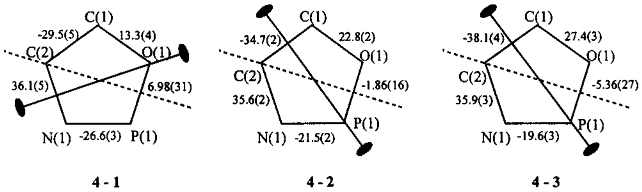

FIGURE 4 Torsion angles (°) and asymmetry parameters.

X-RAY CRYSTALLOGRAPHY

The crystals were mounted in turn on a KUMA-4 automatic four-circle diffractometer and used for data collection. All three-dimensional X-ray intensity data were collected with graphite monochromated Cu-K$_\alpha$ radiation (λ = 1.54178 Å) at room temperature with the ω-2θ scan modes. The unit cell parameters were determined from least-squares refinement of the setting angles of 99 reflections in the θ range 5–60°. Details concerning crystal data and refinement are given in Table 1. Examination of two standard reflections, monitored after each 100 reflections measured, showed 11.6% loss of the intensity for **4-1**, 1.18% for **4-2**, and 3.59% for **4-3**. During the data reduction the decay correction coefficients were taken into account. The transparent, colorless crystals of **4-1**, **4-2**, and **4-3** did not change their appearances during the data collection. Lorentz-polarization correction was applied to the intensity data. The maximum and minimum transmission factors were 0.5989 and 0.5989 for **4-1**, 0.4100 and 0.2687 for **4-2**, 0.5803 and 0.3358 for **4-3**. The structures of the crystals were solved by direct methods and subsequently completed by difference Fourier recycling. All the nonhydrogen atoms were refined anisotropically using full-matrix, least-squares technique on F^2. The hydrogen atoms were treated as riding on the adjacent carbon atom [d(C–H) = 0.96 Å] and refined with the individual isotropic temperature factor

TABLE 1 Crystal Data[a]

	4-1	**4-2**	**4-3**
Empirical formula	$C_{16}H_{27}N_2OPS$	$C_{14}H_{23}N_2OPS$	$C_{12}H_{19}N_2OPS$
Formula weight	326.43	298.37	270.32
Crystal system, space group	Orthorhombic, $P2_12_12_1$	Orthorhombic, $P2_12_12_1$	Monoclinic, $P2_1$
Unit cell dimensions (Å) a	7.481(1)	6.888(1)	6.637(1)
b	11.536(1)	9.420(1)	11.616(1)
c	22.226(2)	25.706(4)	9.565(1)
β			98.94(1)°
Volume (Å^3)	1918.1(4)	1667.9(4)	728.46(15)
Z, Calculated density (mg/m^3)	4, 1.130	4, 1.188	2, 1.232
Absorption coefficient (CuKα) (mm^{-1})	2.28	2.58	2.91
F (000)	704	640	288
Crystal size (mm)	0.25 × 0.25 × 0.25	0.42 × 0.44 × 0.69	0.21 × 0.36 × 0.48
θ range for data collection (°)	3.98–75.19	3.44–80.26	4.68–82.83
Index ranges	$-9 \leq h \leq 9$, $-14 \leq k \leq 14$, $-1 \leq l \leq 27$	$-8 \leq h \leq 1$, $-12 \leq k \leq 1$, $-1 \leq l \leq 32$	$-8 \leq h \leq 8$, $-14 \leq k \leq 14$, $-12 \leq l \leq 5$
Reflections collected/unique	8023/3916	2824/2617	3457/3068
R_{int}	0.1028	0.0609	0.0770
Completeness	99.4% to $2\theta = 75.19°$	100.0% to $2\theta = 80.26°$	96.5% to $2\theta = 96.5°$
Goodness-of-fit on F^2	0.912	1.061	1.110
Final R indices [$I > 2\sigma(I)$] $R1$	0.0466,	0.0390,	0.0576,
$wR2$	0.0944	0.1089	0.1636
R indices (all data) $R1$	0.2215,	0.0433,	0.0645,
$wR2$	0.1439	0.1120	0.1898
No. of parameters	190	173	155
Flack parameter	0.02(4)	0.02(3)	0.06(4)
Extinction coefficient	–	0.0074(8)	0.031(4)
Largest diff. peak and hole (max/min ΔF), eÅ^{-3}	0.143/−0.197	0.416/−0.210	0.409/−0.290

[a] Details in common: diffractometer KUMA4, $T = 293$ K, λ(CuKα) = 1.54178 Å, decay correction coefficient was used, refinement method: full-matrix least-squares on F^2, the hydrogen atom positions were set in calculated positions and were treated as riding on the adjacent carbon, software: SHELXS97, SHELXL97, XP (SHELXTL).

equal to 1.5 times the value of equivalent temperature factor of the parent carbon atom for hydrogen atoms bonded in methyl groups and 1.2 for all other hydrogen atoms. The solutions and refinements were performed with SHELXS97 [6] and SHELXL97 [7]. The graphical manipulations were performed using the XP routine of the SHELXTL [8]. Atomic scattering factors were those incorporated in the computer programs. Bond distances are listed in Table 2 and angles in Table 3. Full crystallographic details have been deposited with CCDC [9].

RESULTS AND DISCUSSION

A perspective view of each of the structures together with their atom numbering scheme are shown in Figure 1, 2, and 3, hydrogen atoms being omitted for clarity. Because the molecules exhibited rather large thermal motion, structures are plotted with 30% probability of thermal ellipsoids.

The molecular geometries of all compounds **4** determined are similar. Only slight differences exist in the bonding pattern of oxazaphospholane rings, mainly in the structure of **4-3**. The greatest difference is found in the length of the bond C(1)–O(1) (Table 2). The bonds P(1)–S(1) and P(1)–N(2) don't depend on substituents and are the same within the range of three standard deviations. The sum of bond angles at the ring C(2) atom increase and at N(1) decrease with an increase of the size of the substituent, which indicates that the atom N(1), gains more of a pyramidal configuration in opposition to C(1), the configuration of which become less pyramidal. This affects the conformation of the oxazaphospholane rings. The rings exist in crystals in the envelope conformation with C(2) at the flap. Maximum deviations from calculated least-squares planes through atoms C(1)–O(1)–P(1)–N(1) are 0.044(2), 0.012(1), 0.034(2) Å in the **4-1**, **4-2**, and **4-3** structures, respectively, and the same also occurs for atom O(1). The flapping atom C(2) deviates from the described least-

TABLE 2 Bond Lengths (Å)

	4-1	**4-2**	**4-3**
P(1)–O(1)	1.608(3)	1.600(2)	1.609(3)
P(1)–N(2)	1.632(4)	1.629(2)	1.628(4)
P(1)–N(1)	1.646(4)	1.645(2)	1.622(4)
P(1)–S(1)	1.921(2)	1.935(1)	1.932(1)
N(1)–C(4)	1.455(6)	1.451(3)	1.452(6)
N(1)–C(2)	1.479(6)	1.466(3)	1.465(5)
O(1)–C(1)	1.459(5)	1.449(3)	1.423(5)
C(1)–C(5)	1.498(7)	1.505(3)	1.507(6)
C(1)–C(2)	1.539(6)	1.538(3)	1.507(6)
C(2)–C(3)	1.518(6)	1.521(3)	1.516(6)
C(5)–C(6)	1.374(7)	1.380(4)	1.370(7)
C(5)–C(10)	1.391(7)	1.378(4)	1.388(8)
C(6)–C(7)	1.362(8)	1.396(5)	1.398(12)
C(7)–C(8)	1.372(10)	1.365(7)	1.369(16)
C(8)–C(9)	1.363(11)	1.363(6)	1.358(16)
C(9)–C(10)	1.401(8)	1.388(4)	1.392(8)
N(2)–C(11)	1.481(7)	1.472(3)	1.446(6)
N(2)–C(14)[a]	1.502(7)		
N(2)–C(13)[b]		1.487(3)	
N(2)–C(12)[c]			1.470(8)
C(11)–C(12)[a]	1.521(7)		
C(11)–C(13)[a]	1.530(8)		
C(14)–C(16)[a]	1.493(7)		
C(14)–C(15)[c]	1.518(8)		
C(11)–C(12)[b]		1.488(5)	
C(13)–C(14)[b]		1.471(5)	

[a] Only for **4-1**.
[b] Only for **4-2**.
[c] Only for **4-3**.

TABLE 3 Bond Angles (°)

	4-1	**4-2**	**4-3**
O(1)–P(1)–N(2)	109.2(2)	109.1(1)	110.3(2)
O(1)–P(1)–N(1)	94.1(2)	94.2(1)	94.7(2)
N(2)–P(1)–N(1)	106.1(2)	107.9(1)	105.2(2)
O(1)–P(1)–S(1)	111.9(1)	113.9(1)	112.1(1)
N(2)–P(1)–S(1)	114.9(2)	111.8(1)	112.5(2)
N(1)–P(1)–S(1)	118.6(2)	118.5(1)	120.6(2)
C(4)–N(1)–C(2)	119.1(4)	119.4(2)	120.6(4)
C(4)–N(1)–P(1)	121.3(4)	121.4(2)	124.4(3)
C(2)–N(1)–P(1)	110.9(3)	111.7(1)	111.0(3)
C(1)–O(1)–P(1)	114.4(3)	113.9(1)	111.9(2)
O(1)–C(1)–C(5)	108.6(4)	110.2(2)	110.2(3)
O(1)–C(1)–C(2)	106.2(4)	105.6(2)	106.4(3)
C(5)–C(1)–C(2)	116.7(4)	115.1(2)	116.4(3)
N(1)–C(2)–C(3)	114.3(4)	113.8(2)	112.4(4)
N(1)–C(2)–C(1)	102.6(4)	101.5(2)	101.2(3)
C(3)–C(2)–C(1)	116.6(4)	114.9(2)	114.6(4)
C(6)–C(3)–C(10)	118.4(5)	119.5(2)	119.3(5)
C(6)–C(5)–C(1)	119.5(6)	118.5(2)	118.6(5)
C(10)–C(5)–C(1)	122.0(6)	121.9(2)	122.1(4)
C(7)–C(6)–C(5)	121.5(7)	119.6(4)	119.2(8)
C(6)–C(7)–C(8)	119.7(8)	120.3(4)	121.4(7)
C(9)–C(8)–C(7)	121.1(8)	120.3(3)	119.3(7)
C(8)–C(9)–C(10)	118.9(8)	120.1(4)	120.4(9)
C(5)–C(10)–C(9)	120.3(6)	120.2(3)	120.3(6)
C(11)–N(2)–P(1)	126.6(4)	124.6(2)	122.5(4)
C(11)–N(2)–C(14)[a]	116.1(4)		
C(14)–N(2)–P(1)[a]	117.0(4)		
N(2)–C(11)–C(12)[a]	114.6(5)		
N(2)–C(11)–C(13)[a]	114.6(6)		
C(12)–C(11)–C(13)[a]	113.2(6)		
C(16)–C(14)–N(2)[a]	112.6(6)		
C(16)–C(14)–C(15)[a]	114.0(6)		
N(2)–C(14)–C(15)[a]	111.0(6)		
C(13)–N(2)–P(1)[b]		119.86(6)	
N(2)–C(11)–C(12)[b]		114.6(3)	
C(14)–C(13)–N(2)[b]		113.1(3)	
C(11)–N(2)–C(13)[b]		115.4(2)	
C(11)–N(2)–C(12)[c]			115.6(5)
C(12)–N(2)–P(1)[c]			118.9(3)

[a] Only for **4-1**.
[b] Only for **4-2**.
[c] Only for **4-3**.

squares planes by 0.506(7), 0.532(3), and 0.547(5) Å, respectively, for **4-1, 4-2**, and **4-3**, which is consistent with an enlargement of the angle between planes C(1)–O(1)–P(1)–N(1) and C(1)–C(2)–N(1). These angles amount to 32.36 (51), 34.12 (20) and 35.62 (31)°. Only the five-membered ring of **4-2** forms an almost ideal envelope with asymmetry parameters ΔC_s = 1.08(16), ΔC_2 = 16.62(19) [3]. In **4-3**, the envelope is slightly distorted (asymmetry parameters ΔC_s = 5.78(35), ΔC_2 = 11.69(28)), and for **4-1**, there is rather a combination of a C(2)-envelope and half chair than only an envelope (asymmetry parameters ΔC_s = 10.50(44), ΔC_2 = 4.93(37)). Moreover, the torsion angle N(1)–P(1)–O(1)–C(1) in **4-1** has an opposite sign to that of **4-3**, which means that the last square plane calculated through these atoms is twisted in the opposite direction. Values of torsion angles and placement of asymmetry parameters are shown in Figure 4. The angle between the least-squares planes calculated through N(1)–P(1)–O(1)–C(1) and the phenyl ring increases with enlargement of the substituent and has values of 37.26(24)° for **4-3**, 42.86(12)° for **4-2**, and 53.11(15)° for **4-1**. The phenyl ring in **4-1** shows symptoms of slight disorder in the region of C(10), which causes a small lengthening of C(10)–C(5) and C(10)–C(9) bonds. With an increase in the size of the substituent, the S(1) atom becomes more equatorial and the N(2) atom becomes less equatorial in relation to the calculated least-square plane through the N(1)–P(1)–O(1)–C(1) atoms, and finally, for **4-3**, the angles between the S(1)-plane and the N(2)-plane are equal within experimental error. The environments of the P atoms in all of the compounds are comparable and have the geometry of a distorted tetrahedron. There is only one angle considerably smaller than tetrahedral: the five-membered ring angle O(1)–P(1)–

N(1), as expected [1,3]. The N(1)–O(1)–N(2) angle is smaller, and the O(1)–P(1)–S(1) and N(1)–P(1)–S(1) angles are slightly larger than tetrahedral. The largest angle is that of N(1)–P(1)–S(1). The N(2)–P(1)–S(1) angle is practically tetrahedral. In the structure of the **4-3** atom, N(1) has nearly a planar coordination, as shows by the sum of angles being equal to 356.0°. This planarity testifies to sp^2 hybridization at nitrogen. This probably causes a shortening of the P(1)–N(1) bond, 1.622(4) Å, as compared with 1.646(4) and 1.645(2) Å for **4-1** and **4-2**, respectively.

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[9] Full crystallographic details have been deposited at Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB1 1EW, United Kingdom and allocated the deposition numbers CCDC 145596, CCDC 145597, and CCDC 145598 for structures **4-1**, **4-2**, and **4-3**, respectively.