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New Chiral Macrocyclic Phosphoramidate Self-Associated by an Intermolecular N–H · · · O = P Hydrogen Bond

Da-Ming Du, Wen-Ting Hua, Zhe-Ming Wang, and Chun-Hua Yan

College of Chemistry and Molecular Engineering, Peking University, Beijing 100871, P. R. China

Peking University, Nonius B. V. Demo Lab for X-Ray Diffraction, Beijing , P. R. China

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ABSTRACT: *New macrocyclic chiral phosphoramidates containing 2,5-diaryl-1,3, 4-oxadiazole and L-alanine methyl ester units were synthesized by a convenient one-pot procedure, X-ray analysis of one chiral macrocycle shows that the phosphoramidate molecules are self-associated by intermolecular N–H · · · O = P hydrogen bonds, the layer stacking along the b axis forming channels parallel to the b axis.* Heteroatom Chem 12:480–484, 2001

INTRODUCTION

The design and synthesis of new functionalized chiral macrocycles for selective recognition of other species is of great interest to chemists [1]. Macrocycles containing phosphorus may also have special application in biological systems and specific recognition for neutral molecules. Friedrichsen reported the synthesis and complexation behavior of phosphine oxide bifunctional macrocycles [2]. Cram has investigated the binding properties of macrocyclic ethers containing the phosphoryl group with alkali metal salts [3]. In order to explore the inclusion behavior of chiral phosphoramidates, we first had to undertake the synthesis, structure, and self-assembly studies of small ring chiral phosphoramidates [4]. In this article, we report the X-ray crystal structure of a new type of chiral macrocyclic phosphoramidate receptor containing L-alanine methyl ester and 2,5-diaryl-1,3,4-oxadiazole units.

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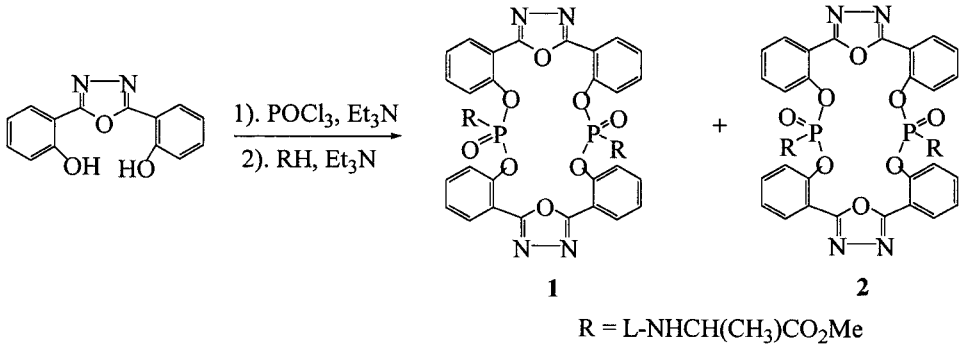
RESULTS AND DISCUSSION

Chiral macrocyclic phosphoramidate receptors **1** and **2** were prepared from 2,5-di(*o*-hydroxyphenyl)-1,3,4-oxadiazole (Scheme 1). 2,5-di(*o*-hydroxyphenyl)-1,3,4-oxadiazole reacted with phosphorus oxychloride in dilute solution at room temperature to form the dichloride, which was treated in situ with L-alanine methyl ester hydrochloride to afford the corresponding [2 + 2] cyclocondensation macrocyclic chiral phosphoramidates **1** and **2** in 9 and 10% yield, respectively. Products **1** and **2** are stereoisomers. The less polar compound **1** may be the *trans* isomer, and the more polar compound **2** is the *cis* isomer, based on the X-ray single crystal diffraction analysis of compound **2**. The two L-alanine substituents are in the *cis* conformation in *cis* isomer **2**. In a previous article, we identified the relative stereochemistry of two isomeric macrocyclic phosphoramidates containing glycine ethyl ester and 2,5-diaryl-1,3,4-oxadiazole moieties by X-ray crystal structure analysis, the less polar isomer having the *trans* configuration and the more polar isomer having the *cis* configuration [5]. The relative

stereo-chemistry of the two isomeric macrocyclic bis-(phosphine oxides) has also been established on the basis of their molecular dipole moments, the less polar isomer having the *trans* stereochemistry [6].

The crystal structure of **2** was determined by X-ray single crystal diffraction analysis. Information concerning the crystallographic data and structure determination of inclusion compound **2** is summarized in Table 1. The fractional atomic coordinates and equivalent isotropic displacement parameters, along with their estimated standard deviations, the bond lengths, and angles for compound **2** are deposited at CCDC [7]. X-ray analysis has shown that compound **2** has C2 symmetry, there being two types of independent molecules (each having two molecules) in the unit cell of the compound **2**: molecule I incorporates atoms C(1) to C(18), and the molecule II incorporates atoms C(19) to C(36) (see Figure 1). Other differences between molecules I and II are the dihedral angles of the aromatic rings. The dihedral an- gles between benzene and oxadiazole rings are 66.56° and 23.97° in molecule I, whereas in molecule



SCHEME 1

TABLE 1 Crystal Data and Structure Refinement for Compound **2**

Empirical formula	$C_{36}H_{32}N_6O_{12}P_2$
Formula weight	802.62
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system, space group	Monoclinic, C2
Unit cell dimensions	$a = 25.7299(5)$ Å $\alpha = 90°$
	$b = 9.3305(3)$ Å $\beta = 117.4834(13)$
	$c = 17.6271(4)$ Å $\gamma = 90°$
Volume	3754.21(16) Å^3
Refls. No. for cell measurement	32334
θ range for cell measurement	3.46 to 29.13°
Z, Calculated density	4, 1.420 Mg/m^3
Absorption coefficient	0.188 mm^{-1}
F(000)	1664
Crystal shape / crystal color	Block / colorless
Crystal size	0.35 × 0.33 × 0.29 mm
Limiting indices	$-35 \le h \le 35$, $-12 \le k \le 12$, $-24 \le l \le 24$
Reflections collected / unique	32334/9906($R_{int} = 0.0521$)
Reflections with $I > 2\sigma(I)$	6575
Completeness to $\theta = 29.13$	99.1%
Decay correction (%)	None
Method for primary solution	Direct
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	9906 / 1 / 518
Goodness-of-fit on F^2	1.013
Final R indices [$I > 2\sigma(I)$]	$R1 = 0.0459$, $wR2 = 0.0901$
R indices (all data)	$R1 = 0.0865$, $wR2 = 0.1020$
Absolute structure parameter	−0.01(7)
Extinction coefficient	0.0025(3)
Largest diff. peak and hole	0.198 and −0.353 e.A^{-3}
Max. and mean shift/sigma	0.001 and 0.000

II, the corresponding dihedral angles are 80.79° and 19.87°, respectively. There are also some difference in the torsion angles around P atoms of molecules I and II: O(2)–P(1)–N(1)–C(15) 44.3(3), O(3)–P(1)–N(1)–C(15) −59.6(3)°, C(1)–O(2)–P(1)–O(3) −63.61(16)° and O(7)–O(3)–P(1)–O(2) 161.85(18)° in molecule I; O(9)–P(2)–N(4)–C(33) 64.0(2)°, O(8)–P(2)–N(4)–C(33) −40.1(2)°, C(19)–O(8)–P(2)–O(9) 65.58(16)°, and O(25)–O(9)–P(2)–O(8) −166.28(17)° in molecule II, respectively. The two O = P double-bond lengths are 1.460(15) and 1.461(15) Å, which are slightly longer than the O = P bond length in the TPPO molecule (1.4554 Å). X-ray analysis of the chiral macrocycle shows that the chiral ligand is rather rigid and constrained. The molecular packing of compound **2** in the unit cell is given in Figure 2. Two independent molecules are disposed alternatively. The two types of molecules are connected by intermolecular N–H · · · O = P hydrogen bonds: An [N(1)–H(16) · · · O(7), 2.876(3)Å, 170(3)°; N(4)–H(32) · · · O(1), 2.919(3)Å, 160(3)°] interaction existing between pairs of related molecules. The phosphoramidate molecules are self-associated by intermolecular N–H · · · O=P hydrogen bonds. The layer structure was formed through the intermolecular hydrogen bond interaction, the layer stacking along the *b* axis forming channels parallel to *b* axis.

In summary, the crystal structure of **2** may be considered in terms of intermolecular N–H · · · O = P interactions. There is no evidence for any significant $\pi \cdots \pi$ interactions between adjacent phenyl rings in this structure.

EXPERIMENTAL

Melting points were measured on an XT-4 melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Varian 200 MHz spectrometer tetramethylsilane (TMS) serving as an internal

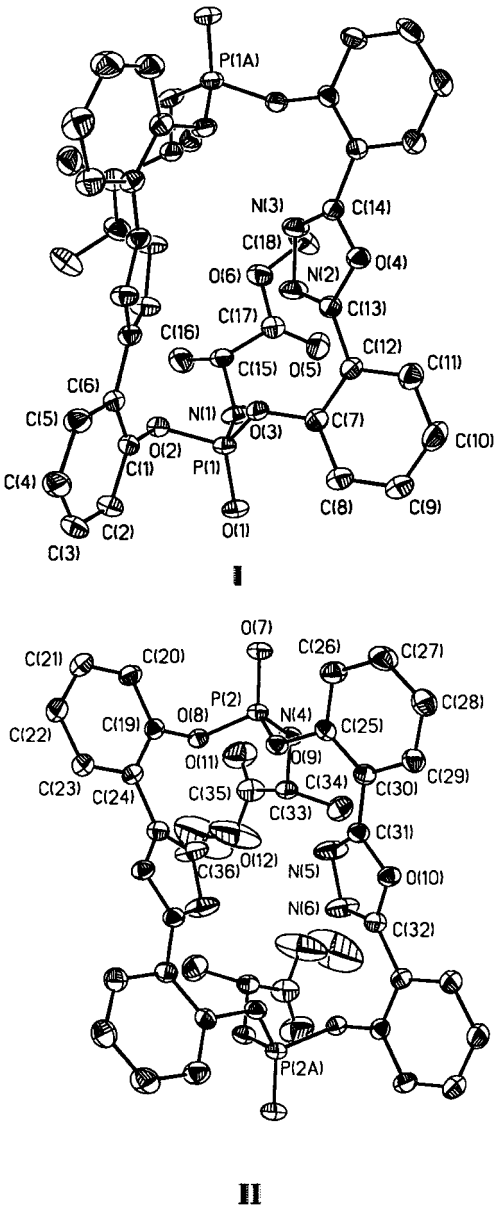


FIGURE 1 Perspective view of compound **2**, showing 30% probability ellipsoids for the nonhydrogen atoms.

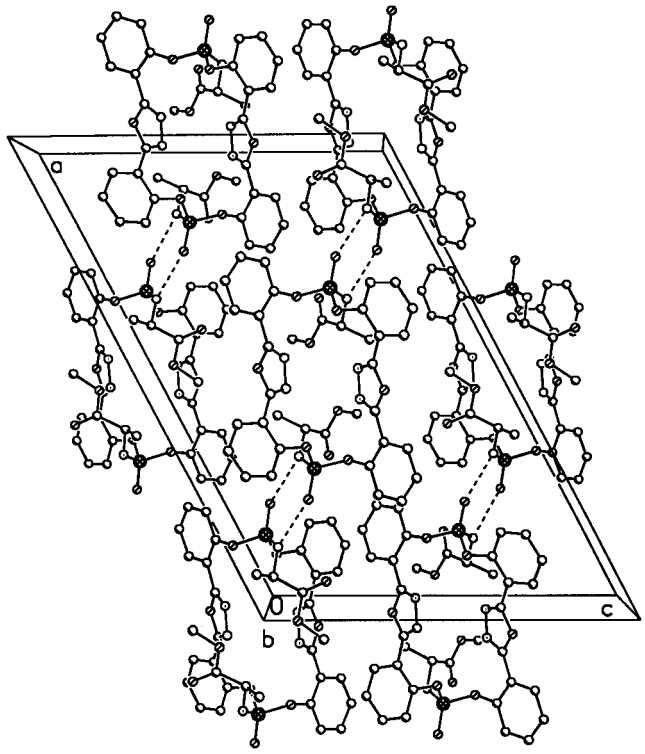


FIGURE 2 The molecular packing of compound **2** in unit cell (view along the *b* axis).

standard, and ^{31}P NMR spectra were recorded using 85% H_3PO_4 as an external standard. Infrared spectra were obtained on a Bruker Vector 22 spectrometer. Mass spectra were obtained on a VG-ZAB-HS mass spectrometer. Optical rotations were measured on a Perkin-Elmer 241 MC spectrometer. Elemental analyses were carried out on an Elementar Vario EL instrument. Solvents used were purified and dried by standard procedures.2,5-di(o-hydroxyphenyl)-1,3,4-oxadizole was synthesized according to a literature produre [8].

Synthesis of Macrocyclic Chiral Phosphoramidates

2,5-di(hydroxyphenyl)-1,3,4-oxadizole (1.0 g, 3.9 mmol) was dissolved in 120 mL of dichloromethane, and phosphorus oxychloride (0.7 g, 4.4 mmol) was added under N_2, followed by the slow addition with stirring of triethylamine (0.8 g, 8.0 mmol). After 1 hour of additional stirring, a solution of L-alanine methyl ester hydrochloride (4.2 mmol) and triethylamine (0.5 g, 4.8 mmol) in dichloromethane (10 mL) was added dropwise with constant stirring into the aforementioned crude acid chloride solution. After the addition, the mixture was stirred at room temperature for 24 hours. The reaction mixture was washed with brine and dried with anhydrous magnesium sulfate. After removal of the solvent under reduced pressure, the crude product was purified by column chromatography on silica gel (elution with ethyl acetate-chloroform 2:1 v/v), products **1** and **2** being obtained. **1**: Yield 9%. m.p. 248–250°C. $[\alpha]_D^{20} = +9.3^\circ$ (c = 0.4, $CHCl_3$). ^{1}H NMR ($CHCl_3$): δ 1.26(*d*, J = 7.2Hz, 6H, CH_3), 3.55 (s, 6H, OCH_3), 4.28–4.45 (m, 2H, CH), 5.34 (t, J = 8.2, 9.6Hz, 2H, NH), 7.30–7.39 (m, 4H, ArH), 7.49–7.58 (m, 4H, ArH), 7.74–7.80 (m, 4H, ArH), 7.96–8.00 (m, 2H, ArH), 8.11–8.15 (m, 2H, ArH). ^{31}P NMR ($CDCl_3$): δ − 0.17. IR(KBr): υ 3412, 3215, 1741, 1611, 1494, 1210, 1147, 924 cm^{-1}. FABMS: *m/z* 803 (M + 1), 700, 599. Anal. for $C_{36}H_{32}N_6O_{12}P_2$, Calcd.: C, 53.87; H, 4.02; N, 10.47. Found: C, 53.80; H, 4.04; N, 10.41. **2**: Yield 10%. m.p. 234–236°C, $[\alpha]_D^{20} = -37.5^\circ$ (c = 0.4, $CHCl_3$). ^{1}H NMR ($CHCl_3$): δ 1.28(d, J = 7.2Hz, 6H, CH_3), 3.48 (s, 6H, OCH_3), 4.24–4.38 (m, 2H, CH), 5.47 (t, J = 9.3Hz, 2H, NH), 7.21–7.32 (m, 4H, ArH), 7.43–7.56 (m, 4H, ArH), 7.67–7.90 (m, 8H, ArH). ^{31}P NMR ($CDCl_3$): δ 0.51, IR(KBr): υ 3450, 3210.8, 1750, 1610, 1494, 1439, 1206, 1147, 920 cm^{-1} . FABMS: *m/z* 803 (M + 1), 700, 599. Anal. for $C_{36}H_{32}N_6O_{12}P_2$, Calcd.: C, 53.87; H, 4.02; N, 10.47. Found: C, 53.80; H, 4.02; N, 10.38.

Compound **2** (20 mg) was dissolved in chloroform:acetone (1:1 v/v) and the resulting solution was allowed to stand at room temperature, colorless crystals suitable for X-ray determination thus being obtained.

X-Ray Data Collection and Structure Analysis of Compound 2

Computing data collection: KappaCCD [9]. Cell refinement: HKL Scalepack [10]. Data reduction: HKL Denzo [10] and maXus [11]. Molecular graphics: Interactive Molecular Graphics XP, version 5.1 for MSDOS [12].

Preliminary examination and data collection for a colorless crystal were performed with Mo Kα radiation (λ = 0.71073 Å) on a Nonius KappaCCD diffractometer equipped with a graphite crystal incident beam monochromator at 293 K. The determination of the crystal class, orientation matrix, and accurate unit-cell parameters was performed according to established procedures [9–11]. Intensities data were corrected for Lorentz and polarization effects. The crystal structure was solved by the direct method using SHELXS-97 [13] and refined by full-matrix least-squares refinement on F^2 with the SHELXL-97 program [14]. All nonhydrogen atoms were refined anisotropically. The positions of hydrogen atoms were generated geometrically and included in the structure factor calculations with assigned isotropic thermal parameters except for H(16) and H(32), which were located by difference Fourier synthesis and refined isotropically with reasonable thermal factors and bonding geometry. International Tables for X-ray Crystallography [15] and molecular graphics from SHELXTL [12] were used. All computations were performed on a PC 586 personal computer.

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