SELECTIVE PROTECTION OF 1,4,8,11-TETRAAZACYCLOTETRADECANE (CYCLAM) IN POSITION 1,4 WITH THE PHOSPHONOTHIOYL GROUP AND SYNTHESIS OF A CYCLAM-1,4-BIS(METHYLPHOSPHONIC ACID). CRYSTAL STRUCTURES OF SEVERAL CYCLIC PHOSPHONOTHIOAMIDES

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Dedicated to Professor Jaroslav Podlaha, who introduced organophosphorus ligands and their coordination chemistry in our Department, on the occasion of his 70th birthday.

A new cyclam-based ligand, 1,4,8,11-tetraazacyclotetradecane-1,4-bis(methylphosphonic acid) (1,4-H_4te2p), was synthesized. Cyclam was protected by the reaction with $PhP(S)Cl_2$ to form exclusively five-membered cyclic phenylphosphonothioic diamide **2** in a moderate yield. The solid-state structures of **2** and several by-products were determined. Compound **2** was isolated as two stable conformers differing in a mutual position of benzene ring and sulfur atom with respect to the cyclam ring. Compound **2** was used for the synthesis of 1,4-dibenzylcyclam. However, the deprotection of the thiophosphoryl-protected bis(methylphosphonate diester) with aqueous HCl under non-optimized conditions led to a mixture of cyclam derivatives differently substituted with methylphosphonic acid groups. The crystal structures of the target product, 1,4-H_4te2p, and also 1,4,8,11-tetraazacyclotetradecane-1,4,8,11-tetrakis(methylphosphonic acid) (H_8tetp) were determined. A similar reaction with cyclen (1,4,7,10-tetraazacyclododecane) led only to hardly purifiable mixtures.

Keywords: Aminophosphonic acids; Azacycle; Azacrown; Cyclam *cis*-protection; Cyclam; Cyclen; Macrocyclic ligands; Phosphonate ligands; Crystal structure determination; TETP; Thiophosphonic amides; Radiopharmaceuticals.

Tetraazamacrocycles and their derivatives have been widely investigated over years as they form very stable complexes with most metal cations. Investigations have led to a number of practical applications of the ligands and their complexes, such as production of MRI contrast agents based on trivalent gadolinium[1], administration of imaging and/or therapeutic radio-

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pharmaceuticals with a range of radiometal isotopes[2], development of luminescent probes based on trivalent lanthanides[3] or preparation of metal-based catalysts for the artificial hydrolysis of RNA or DNA [4]. The ligands used in the complexes are mostly derivatives of two well-known cyclic tetraamines, 1,4,7,10-tetraazacyclododecane (cyclen) and 1,4,8,11-tetraazacyclotetradecane (cyclam), substituted on nitrogen atoms with four coordinating groups (leading to octadentate ligands) such as acetates, acetamides, alkylamines, phosphorus acid derivatives, hydroxyalkyl derivatives, etc. Representatives of polydentate macrocycles are H_4dota and H_4teta (Chart 1). H_4dota is a non-selective ligand forming strong complexes with most divalent and trivalent metal ions, which is particularly suitable for the complexation of trivalent lanthanides. The H_4teta having a larger fourteen-membered ring forms exceptionally stable complexes with ions of metals from the first transition row. However, the metal ions often require the octahedral coordination sphere and octadentate H_4teta (or its phosphonic acid derivative H_8tetp; Chart 1) have more coordinating atoms than necessary. To fulfil the requirement for six coordination sites, several disubstituted derivatives of cyclam have been synthesized and their complexing properties have been investigated[5–8]. The ligands are mostly 1,8-substituted derivatives of cyclam (denoted "*trans*") as they are nowadays relatively easily available[9,10]. Much less is known about properties of ligands and their complexes based on other 1,4- or 1,11-disubstituted cyclam derivatives (denoted "*cis*"). The main reason is that there is no reliable procedure for their synthesis.

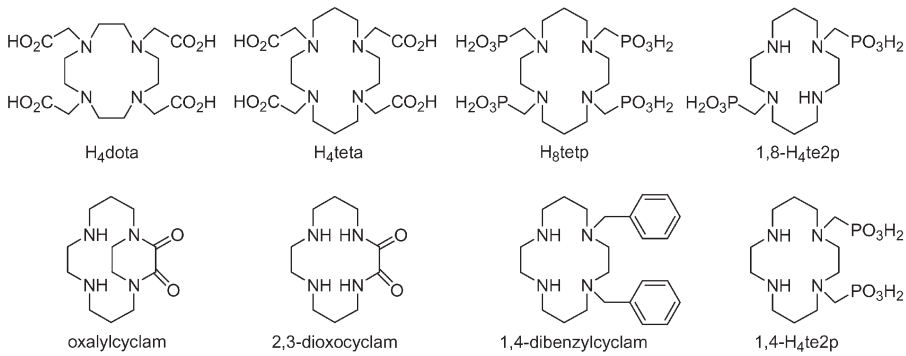


CHART 1
Structures of the compounds mentioned in text

For some years, we have been engaged in study of coordination properties of aminophosphonic acids and macrocycles with phosphorus acid pendant arms[11]. Recently, we have found that 1,8-bis(methylphosphonic acid) derivative[12] (1,8-H_4te2p, Chart 1) of cyclam is an appropriate ligand for divalent transition metal ions[13–15]. The ligand forms thermodynamically very stable complexes[15,16] exhibiting two isomeric forms[13–15]. It is particularly selective for divalent copper[17] and both the isomers of Cu^{2+} complex are highly kinetically inert. However, we have not been able to fully explain the suitable complexing properties of the ligand. The *trans* arrangement of the pendant arms may be responsible for the performance of the ligand. As two other (1,4 and 1,11) regioisomers of bis(methylphosphonic acid) derivatives of cyclam are possible, we decided to synthesize the isomers and investigate their complexing properties to throw more light on coordination chemistry of such ligands. In this paper, we focus on the synthesis of the 1,4-bis(methylphosphonic acid) derivative (1,4-H_4te2p, Chart 1).

The 1,4-protection of cyclam is rather unusual and syntheses of only several cyclam 1,4 derivatives have been described. The 1,4-dibenzylcyclam was prepared by Ni^{2+}-template synthesis[18] but the procedure requires a selectively substituted starting amine (5,8-dibenzyl-1,5,8,12-tetraazadodecane), which is not easily available. Another possibility is 2,3-dioxocyclam (Chart 1) accessible through high-dilution synthesis[19]. Unfortunately, the high-dilution synthetic methods give, in general, rather low yields and reduction of macrocyclic amides is often complicated. More successful was the use of oxalyl protection[20] (Chart 1). However, the deprotection requires very harsh conditions (heating in concentrated alkaline hydroxide)[20,21]. A template synthesis with formation of cobalt(III) complex of cyclam-1,4-diacetic acid followed by reduction to cobalt(II) complex and demetallation led to synthesis of the free ligand[7a]. Some years ago, Majoral et al. used phosphorothioic diamides of cyclam (in 1,4-position) for synthesis of phosphorus-based dendrimers[22]. On the basis of this paper, we decided to test a synthetic route employing easily available phenylphosphonothioic dichloride for 1,4-protection of cyclam as phosphorus acid amides are usually rather easily hydrolyzable.

RESULTS

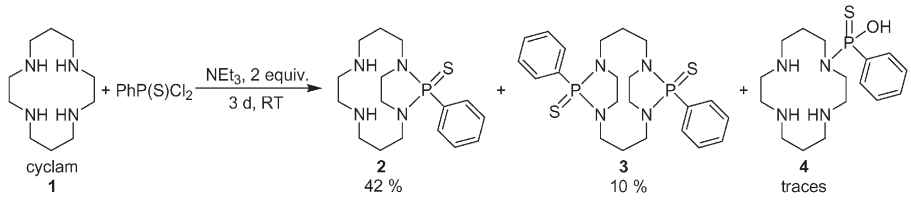
Cyclam Protection

The target product **2** was isolated from the reaction of cyclam **1** with an equivalent amount of phenylphosphonothioic dichloride in chloroform in

the presence of triethylamine as a base. The yields were only moderate (40–50% after column chromatography) and two other by-products were isolated and identified (Scheme 1). Surprisingly, the target product **2** was found to form two chromatographically separable isomers **2a** and **2b**. The isomer **2a** (δ_P ~ 77 ppm) is formed predominantly during the protecting reaction and it was fully characterized by spectroscopic methods (multinuclear NMR, MS). A new peak around 81 ppm which appeared in ^{31}P NMR spectra of some aged solutions after chromatographic purification of reaction mixtures was assigned to the second isomer **2b**. This compound was obtained in pure state after column chromatography of the solutions. Lately, isomer **2b** was identified as the only isomer of **2** present in alkaline aqueous solution of compound **2**. The structures of both isomers were unambiguously confirmed by single-crystal X-ray determination (see below).

The main by-product was isolated by column chromatography and identified as a bis-substituted cyclam **3**. This compound was obtained in a yield of ~10%. The 2:1 intensity ratio of signals of aromatic and aliphatic hydrogen atoms, δ_P ~ 80 ppm falling in the region of phosphonothioic diamides[23] and molecular mass suggested that the product is 2:1 adduct of cyclam and $PhP(S)Cl_2$. Compound **3** was also isolated as a mixture of isomers as it was evidenced by complexity of ^{31}P and ^{1}H NMR spectra of the chromatographically pure product. Finally, one stereoisomer (**3a**) crystallized in pure form from solution of the isomers and its crystal structure was determined (see below).

In some reaction batches, traces of another by-product were identified by TLC. The compound was concentrated in the late fractions from column chromatographies used for isolation of main products **2** and **3** and, finally, it was purified and isolated from the combined late fractions. ^{1}H NMR spectrum of the product showed a full non-equivalence of all ring protons and integration of the spectrum revealed the 1:1 phenyl-to-macrocycle ratio. In ^{31}P NMR spectrum, the compound exhibited a single broad peak at 71 ppm



SCHEME 1
Products of the reaction of cyclam with phenylphosphonothioic dichloride

corresponding to a range of phosphonothioic acid monoamides[23]. Therefore, cyclam derivative **4** with one substituted nitrogen atom was suggested (Scheme 1). This hypothesis was unambiguously confirmed by X-ray structure determination (see below). The occurrence of this product can be attributed to the presence of a trace amount of water in the reaction mixtures.

Crystal Structures of Cyclam Phenylphosphonothioic Amides

We were able to grow single crystals of several phosphonothioic amides and the determination of their structures in the solid state unambiguously confirmed molecular structures of the compounds.

Crystal structure of isomer **2a** consists of two independent molecules; however, both units adopt virtually identical conformations and, thus, only one of them is depicted in Fig. 1. Two adjacent cyclam 1,4-nitrogen atoms are bridged by phosphonothioic group, forming a five-membered C_2N_2P heterocycle (diazaphospholidine ring). The benzene ring is directed above the heterocycle, and the sulfur atom points above the plane formed by the rest of the cyclam ring. The five-membered heterocycle is in an envelope conformation, with the N4 atom turned out from the plane defined by P1, N1, C2 and C3 atoms. Both amide nitrogen atoms significantly share their lone electron pairs with phosphorus atom; it is apparent from the pla-

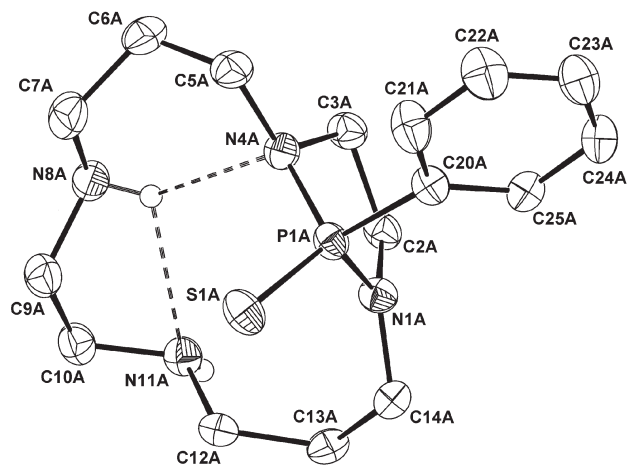


FIG. 1
Molecular structure of **2a**. Hydrogen atoms (except those attached to nitrogen atoms) are omitted for clarity

narity of their neighboring atoms (sum of valence angles on amide nitrogen atoms is 358.3 and 359.4° on N1 atoms and 347.9 and 352.1° on N4 atoms in both independent molecules, respectively). The higher distortion from planarity found for N4 nitrogen atoms is a consequence of the intramolecular hydrogen bond to the nitrogen atom N8 (d(N8···N4) = 3.03 and 3.06 Å in both independent molecules, respectively). Furthermore, nitrogen atom N11 is also involved in hydrogen bonding to N8 (d(N8···N11) = 2.89 and 2.91 Å), stabilizing an endodentate angular conformation typical of non-protonated cyclam ring[24]. The relevant bond lengths and angles are collected in Tables I and II.

In addition to the structure of free base **2a**, crystal structure of its protonated form (H**2a**)$^+$ was also determined. Several single crystals of sulfate of this cation crystallized from chloroform solutions used for NMR characterization. The independent unit in this crystal structure consists of two monoprotonated molecules (H**2a**)$^+$ (Fig. 2), one sulfate dianion and some water molecules. The best refinement of the crystal data was obtained with the assumption of two fully occupied water molecules, and two others with occupancies of 0.5 and 0.25. The structure of both independent macrocyclic ions is almost identical (Tables I and II) and the conformation of the macroring of protonated (H**2a**)$^+$ is essentially the same as that found in the structure of non-protonated **2a** (analogous intramolecular hydrogen bonds (d(N8···N4) = 2.96 and 3.02 Å, and d(N8···N11) = 2.79 and 2.81 Å in both

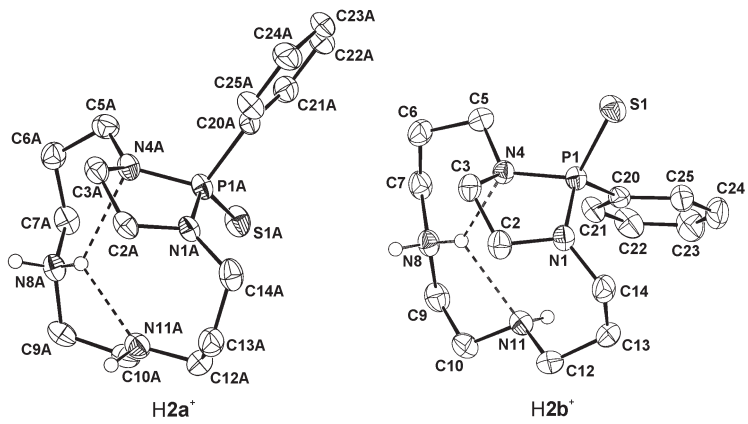


FIG. 2

Molecular structure of (H**2a**)$^+$ (left) and (H**2b**)$^+$ (right) cations in the crystal structures of **2a**·0.5H_2SO_4·1.375H_2O and **2b**·0.5H_2SO_4·3H_2O. Hydrogen atoms (except for those attached to the nitrogen atoms) are omitted for clarity

TABLE I
Geometry of phosphonothioic groups in the crystal structures of **2a**, **2a**·0.5H_2SO_4·1.375H_2O, **2b**·0.5H_2SO_4·3H_2O, **3a** and **4**·H_2O

Bonds	**2a**		**2a**·0.5H_2SO_4·1.375H_2O		**2b**·0.5H_2SO_4·3H_2O	**3b**	**4**·H_2O	
	molecule A	molecule B	molecule A	molecule B				
				Distances, Å				
P1–N1	1.6433(13)	1.6447(13)	1.641(2)	1.638(2)	1.6577(15)	1.6499(15)	P1–N1	1.692(3)
P1–N4	1.6693(13)	1.6625(13)	1.660(2)	1.660(2)	1.6798(14)	1.6765(15)	P1–O1	1.509(3)
P1–S1	1.9368(5)	1.9373(5)	1.9442(7)	1.9446(7)	1.9534(6)	1.9376(7)	P1–S1	1.9678(11)
P1–C20	1.815(2)	1.8192(15)	1.815(2)	1.806(2)	1.807(2)	1.821(2)	P1–C20	1.819(3)
				Angles, °				
N1–P1–N4	93.58(6)	93.55(7)	93.20(9)	93.50(9)	92.97(7)	94.26(7)	N1–P1–O1	106.3(2)
N1–P1–S1	120.06(5)	120.14(5)	122.27(7)	119.61(7)	117.41(6)	120.06(6)	N1–P1–S1	108.17(10)
N1–P1–C20	107.60(7)	107.40(7)	106.00(10)	108.20(10)	111.42(8)	106.88(8)	N1–P1–C20	106.39(14)
N4–P1–S1	116.53(5)	116.40(5)	113.49(7)	115.17(7)	116.67(6)	118.82(6)	O1–P1–S1	118.50(11)
N4–P1–C20	105.31(7)	107.44(7)	112.26(10)	109.76(9)	108.89(7)	106.23(8)	O1–P1–C20	106.98(15)
S1–P1–C20	111.65(5)	110.29(5)	108.79(7)	109.49(7)	108.63(6)	108.98(6)	S1–P1–C20	109.89(12)

TABLE II
Torsion angles in diazaphospholidine rings

Angle	**2a**		**2a**·0.5H_2SO_4·1.375H_2O		**2b**·0.5H_2SO_4·3H_2O	**3b**
	molecule A	molecule B	molecule A	molecule B		
			Distances, Å			
P1–N1–C2–C3	4.31(16)	2.27(17)	13.52(23)	5.54(24)	8.38(19)	2.12(18)
N1–C2–C3–N4	–27.33(17)	–22.36(18)	–29.46(25)	–24.11(25)	–34.74(19)	–28.68(19)
C2–C3–N4–P1	39.96(15)	34.34(16)	35.60(22)	34.33(22)	47.47(16)	43.24(16)
C3–N4–P1–N1	–33.90(11)	–29.85(12)	–25.15(16)	–28.08(16)	–38.17(12)	–38.29(12)
N4–P1–N1–C2	16.93(12)	15.67(12)	6.06(17)	12.71(17)	17.55(14)	21.12(13)
			Angles, °			
C2–N1–P1–S1	140.51(9)	139.11(10)	126.56(14)	134.37(14)	–104.67(12)	148.11(10)
C3–N4–P1–S1	–160.21(9)	–156.18(9)	–152.55(14)	–153.23(13)	84.64(11)	–166.18(9)
C14–N1–P1–S1	–24.43(15)	–32.23(15)	–43.14(21)	–35.64(21)	91.90(16)	–22.52(3)
C5–N4–P1–S1	58.06(13)	55.18(14)	53.12(19)	58.82(18)	–47.89(15)	54.51(16)
C14–N1–P1–C20	104.68(13)	94.80(14)	82.12(20)	90.57(19)	–34.25(18)	102.10(7)
C5–N4–P1–C20	–66.28(13)	–68.99(14)	–70.75(20)	–65.27(19)	75.46(15)	–68.63(15)

the independent molecules of (H**2a**)$^+$, respectively). We were surprised that the single crystals contain the sulfate anions as the sample had no contact with any sulfates. Very probably, these anions originate from the silica gel used for column chromatography due to elution with basic eluent containing ammonia.

The single crystal containing cation (H**2b**)$^+$ was also isolated as a sulfate salt from the sample used for NMR characterization, similarly to the previous case (the origin of the sulfate anion is also the same). The compounds **2a** and **2b** (or (H**2a**)$^+$ and (H**2b**)$^+$ ions) differ in the mutual position of phenyl and sulfur atom on phosphorus atom in respect to the cyclam ring. In the case of **2b**, the sulfur atom is directed above the five-membered C_2N_2P heterocycle. Hence, compound **2b** is a "frozen" conformer of compound **2a**. The independent unit of **2b**·0.5H_2SO_4·3H_2O consists of a monoprotonated (H**2b**)$^+$ ion (Fig. 2), one half of the sulfate anion (with sulfur and two oxygen atoms lying in special positions with half-occupancy) and two fully-occupied and two half-occupied water molecules. The macrocycle conformation in (H**2b**)$^+$ is very similar to that found for **2a** and (H**2a**)$^+$, except that the proton attached to nitrogen N11 points to the opposite direction. Therefore, torsion angles along C9–C10 and C12–C13 bonds are different as well and have the opposite sign. Similarly to the previous cases, molecule of (H**2b**)$^+$ is also stabilized in endodentate conformation by intramolecular hydrogen bonds (d(N8···N4) = 2.82 Å and d(N8···N11) = 2.79 Å). Comparison of both protonated isomeric species (H**2a**)$^+$ and (H**2b**)$^+$ is given in Fig. 2, bond lengths and angles are collected in Tables I and II.

We were also able to determine crystal structures of the isolated byproducts **3a** and **4**. The molecular structure of compound **3a** (one of several possible conformers of **3**) is shown in Fig. 3 and selected bond lengths and angles are given in Tables I and II. The molecule of **3a** is centrosymmetric. The P–S vectors are oriented above the cyclam macrocycle and the benzene rings point above the C_2N_2P heterocycle similarly as in the previous case of **2a**. The identity of compound **4** was unambiguously confirmed by the determination of its crystal structure (Fig. 4, Tables I and II). However, the data quality was rather poor in this case and the final R-factor is high (7.71%), mainly due to a huge disorder in the cyclam macrocyclic unit. Therefore, the exact protonation site of the compound cannot be assigned, but the proton is removed from the phosphonothioic moiety as evidenced by relatively short P–O distance (Table I) and, thus, the proton should be located on an amino group of the cyclam ring.

The geometry around the phosphorus atom in the phenylphosphonothioic moiety in cyclam derivatives **2a**, (H**2a**)$^+$, (H**2b**)$^+$ and **3a** is very similar

(Table I). Bond distances are in the range expected for this moiety[22,25]. The bond angles are highly affected by the formation of the five-membered C_2N_2P heterocycle with a relatively small N1–P1–N4 angle (93–94°). The other bond angles are correspondingly larger than the theoretical tetrahedral ones (Table I). In the case of sterically non-constrained monoamide **4**,

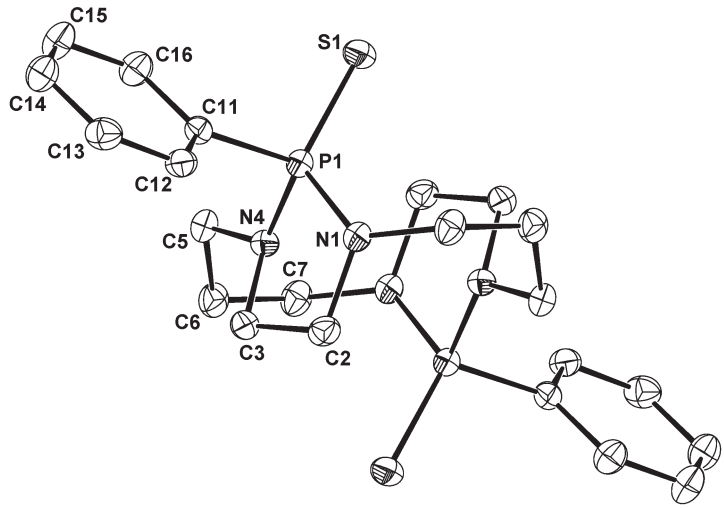


FIG. 3
Molecular structure of **3a**. Hydrogen atoms are omitted for clarity

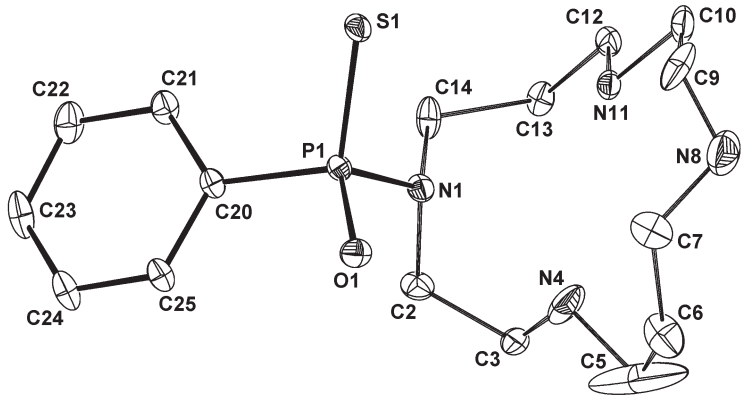


FIG. 4
Molecular structure of **4** in the crystal structure of **4**·H_2O. The disordered macroring is shown in a more abundant position and hydrogen atoms are omitted for clarity

the atoms around the phosphorus atom form almost a regular tetrahedron. Five-membered C_2N_2P heterocycle is in the envelope conformation in all cases, with N4 nitrogen atom (nitrogen atoms in all the structures are labelled consistently in this way) turned away from the plane of the remaining atoms. An exception was found only in the molecule A in the structure of **2a**·$0.5H_2SO_4$·$1.375H_2O$, where C3 carbon atom is the out-of-plane atom of the five-membered C_2N_2P heterocycle. Comparing values of torsion angles along the N1–P1 and N4–P1 bonds, it is clear that the structure of **2b**·$0.5H_2SO_4$·$3H_2O$ remarkably differs from the other as a consequence of different P–S and P–Ph vector orientations in space (Table II).

Cleavage of the Phenylphosphonothioic Moiety

First, we wanted to get some information about stability of the phenylphosphonothioic moiety in **2** and, therefore, we tested several deprotection protocols which can be later used for removal of the group.

To follow acid hydrolysis of the phenylhosphonothioic diamide moiety, compound **2a** was dissolved in aqueous 6 M hydrochloric acid and heated at 70 °C. The course of the reaction was monitored by ^{31}P NMR spectrum; the signal of the starting compound at 76 ppm disappeared while the signal of phenylphosphonic acid (21 ppm) rose. No other phosphorus-containing compounds were identified in the reaction mixture. From the exponential dependence of the integral intensity of the starting compound signal, the half-life time of deprotection was calculated to be ~45 min. It is comparable with the literature data reported for other macrocyclic phosphorus amides[26]. No reaction was observed at room temperature. The assignment of signal of the released $PhPO_3H_2$ was confirmed by addition of the compound to the reaction mixture.

A sample of **2a** was dissolved in the borate buffer (pH 11.0) and heated at 70 °C as in the previous case. ^{31}P NMR spectroscopy revealed a fast conversion of **2a** to **2b** as the signal of **2a** at 77 ppm had only about 1% intensity after dissolution; in the spectra, the major signal of **2b** was observed at 81 ppm. During the reaction, a new signal assigned to phenylphosphonothioic acid at 72 ppm appeared, but the hydrolysis led to a conversion of only ca. 10% after 12 h. The assignments of all the signals were again confirmed by addition of the standard to the reaction mixture.

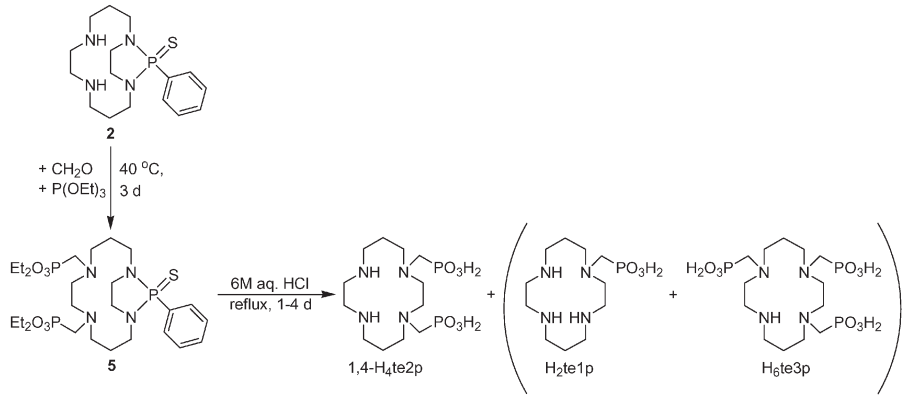
From the attempts to purify the reaction intermediates from the Mannich reaction of **2a** with CH_2O and a phosphorus component (see below), followed that the phenylphosphonothioic diamide **2a** could be hydrolyzed in the presence of a strong cation exchange resin. To illustrate this process, we

loaded ethanolic solution of **2a** onto a column of strong sulfonic cation acid exchanger (Dowex 50) in H^+-form. The column was eluted with water, and the eluate was concentrated by vacuum evaporation. ^{31}P NMR spectroscopy revealed the presence of phenylphosphonothioic acid as a major component and phenylphosphonic acid as a minor one. When the eluate was neutral, the column was washed with 6 M hydrochloric acid. After evaporation of the HCl eluate, the solid product was identified as cyclam hydrochloride (^{1}H and ^{13}C NMR) with no phosphorus-containing admixture (no signal in ^{31}P NMR spectrum).

Syntheses of Selected 1,4-Derivatives

To demonstrate the suitability of the new protecting reagent, we used this approach in preparation of 1,4-substituted cyclams. First, we prepared known 1,4-dibenzylcyclam by the reaction of compound **2a** with a slight excess of benzyl bromide in acetonitrile. After hydrolysis (6 M HCl, 12 h reflux), column chromatography and crystallization, the 1,4-dibenzylcyclam was isolated in 65% yield.

The primary aim of the work was the synthesis of a novel ligand with two methylphosphonic acid pendant arms, 1,4-H_4te2p (Chart 1), as the previous studies of its 1,8-isomer revealed a high potential of such ligand class in coordination chemistry[12–16]. First, this ligand was prepared by a Mannich-type reaction (Scheme 2) between **2a**, triethyl phosphite and paraformaldehyde followed (without purification) by acid hydrolysis of **5** (6 M HCl, 4 days reflux; the long time was necessary to achieve a full hydrolysis of the



SCHEME 2
Synthesis of 1,4-H_4te2p

diesters) and chromatographic separation on cation-exchange columns. The target ligand was isolated as a tetrahydrate in 42% yield together with trisubstituted H_6te3p (12%, Scheme 2) and recently reported[27] monosubstituted H_2te1p (5%, Scheme 2). Fortunately, all three compounds can be easily separated on a weak cation exchanger as they significantly differ in their acid-base properties. When the reaction mixture after the Mannich reaction was purified by silica gel chromatography to obtain pure tetraester **5**, its acid hydrolysis under the conditions given above was surprisingly faster (24 h). The isolated yield of 1,4-H_4te2p was improved to 73%.

The structure of the target ligand, 1,4-H_4te2p, was confirmed by the X-ray structure determination. Single crystals of 1,4-H_4te2p tetrahydrate were formed by slow crystallization of its aqueous solution with diffusion of acetone vapours. The molecular structure of the ligand is shown in Fig. 5. The relevant bond lengths and angles are collected in Table III. The independent unit consists of one ligand and four solvate water molecules. Each phosphonate pendant is monoprotonated and the other protons are bound to both secondary amino groups in the ring. The geometries around the phosphorus atoms are roughly tetrahedral, with significantly longer P–O bonds to the protonated oxygen atoms O11 and O21 (Table III). The macrocycle is in an endodentate conformation typical of a non-fully protonated cyclam ring[24]. The molecular structure is stabilized by rather strong intramolecular

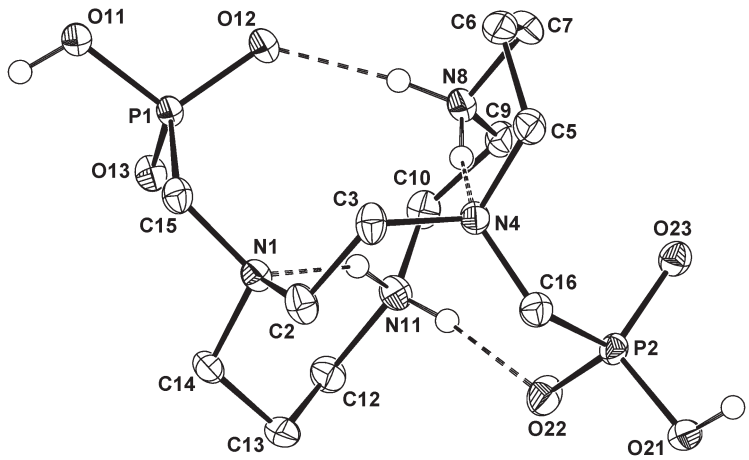


FIG. 5
Molecular structure of 1,4-H_4te2p in the crystal structure of 1,4-H_4te2p·4H_2O. Hydrogen atoms (except for those attached to the nitrogen and oxygen atoms) are omitted for clarity. Intramolecular hydrogen bonds are shown as dashed lines

TABLE III
The geometry of phosphonate groups in the crystal structures of 1,4-H_4te2p·4H_2O and H_8tetp·10H_2O

1,4-H_4te2p·4H_2O				H_8tetp·10H_2O			
Distances, Å							
P1–O11	1.5752(10)	P2–O21	1.5709(10)	P1–O11	1.5712(28)	P2–O21	1.5677(25)
P1–O12	1050.46(9)	P2–O22	1.5032(10)	P1–O12	1.4884(28)	P2–O22	1.4895(25)
P1–O13	1.5107(10)	P2–O23	1.5133(10)	P1–O13	1.4984(28)	P2–O23	1.5008(26)
P1–C15	1.8135(14)	P2–C16	1.8095(14)	P1–C8	1.8316(35)	P2–C9	1.8395(33)
Angles, °							
O11–P1–O12	107.36(5)	O21–P2–O22	108.29(6)	O11–P1–O12	109.76(15)	O21–P2–O22	107.13(15)
O11–P1–O13	111.43(5)	O21–P2–O23	111.52(5)	O11–P1–O13	109.71(17)	O21–P2–O23	112.51(15)
O11–P1–C15	104.24(6)	O21–P2–C16	104.85(6)	O11–P1–C8	102.10(16)	O21–P2–C9	105.82(15)
O12–P1–O13	115.12(5)	O22–P2–O23	114.58(6)	O12–P1–O13	117.29(17)	O22–P2–O23	118.52(15)
O12–P1–C15	108.90(6)	O22–P2–C16	108.07(6)	O12–P1–C8	108.15(16)	O22–P2–C9	106.26(15)
O13–P1–O15	109.21(6)	O23–P2–C16	109.02(6)	O13–P1–C8	108.73(16)	O23–P2–C9	105.73(15)

hydrogen bonds (d(N8···O12) = 2.72 Å, d(N11···O22) = 2.70, d(N8···N4) = 2.79 and d(N11···N1) = 2.76 Å, Fig. 5). Similarly strong $^{+}$N–H···O^{-} hydrogen bonds were observed in 1,8-H_4te2p and its derivatives[12]. Except for these interactions, the whole crystal structure is stabilized by an extended hydrogen bond network between the phosphonate oxygen atoms and the hydrate water molecules (O···O distances in the range 2.56–2.87 Å).

On standing of the acidic reaction mixture from hydrolysis of one batch of ester **5** in an NMR tube for one week, several small colourless prismatic crystals appeared. The X-ray diffraction study revealed these crystals are the well-known tetraphosphonic acid derivative of cyclam[28], H_8tetp (Chart 1 and Fig. 6), which is almost insoluble in acid solutions. The relevant bond lengths and angles are given in Table III. The independent unit is formed by one half of molecule of the ligand and five additional hydrate water molecules. Each phosphonate pendant group is monoprotonated and, correspondingly, all macrocycle nitrogen atoms are protonated. The geometries around phosphorus atoms are roughly tetrahedral, with significantly longer P–O bonds to protonated oxygen atoms O11 and O21 (Table III). The macrocycle adopts (3,4,3,4)-A conformation typical of fully protonated cyclams[24]. The same conformation of the cyclam ring was also observed for trihydrobromide of H_2te1p (ref.[27]). All pendant phosphonate moieties are turned away from the macrocycle and are connected with the neighboring ligand molecules and the solvate water molecules via an extended hydrogen bond network.

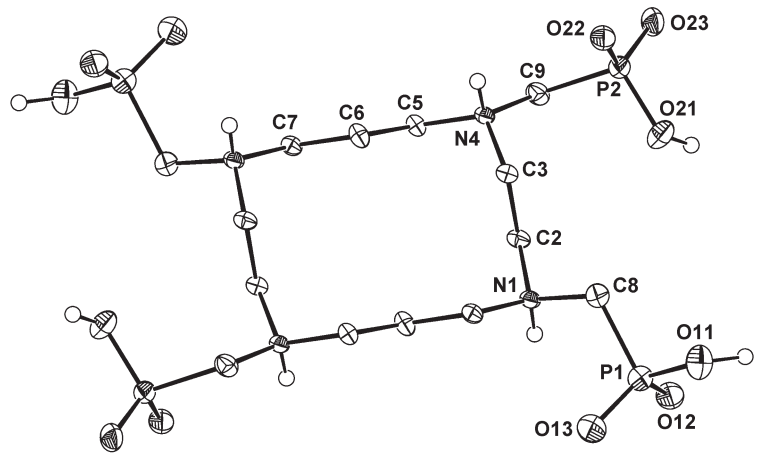
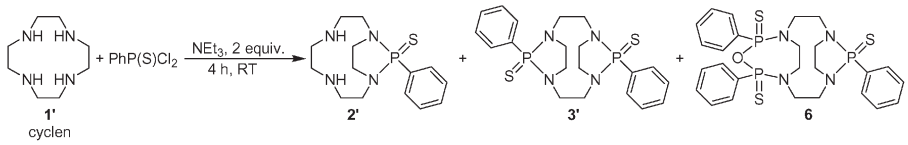


FIG. 6
Molecular structure of H_8tetp in the crystal structure of H_8tetp·10H_2O. Hydrogen atoms (except for those attached to nitrogen and oxygen atoms) are omitted for clarity

Attempts to Protect Cyclen

We tried to apply the method of protection to the cyclen skeleton (Scheme 3). Although the required product **2′** was found in the reaction mixture (NMR and MS), all attempts to find an efficient separation method failed. After repeated chromatographies, pure **2′** was isolated as an oil and in a low yield (~20%). Compound **2′** is present as a mixture of isomers. This was evidenced by complexity of ^{31}P and ^{1}H NMR spectra. However, by standing of its chloroform solution used for NMR characterization for some time, several single crystals appeared. They were found to be **2a′**·0.5H_2SO_4·3H_2O (Fig. 7; the source of sulfate anion is silica gel used for chromatography). The orientation of the sulfur atom and phenyl substituent is analogous to that in the cyclam product **2a**, i.e. with the benzene ring located above the five-membered C_2N_2P heterocycle and sulfur atom directed above the rest of the macrocycle. The independent unit consists of two monoprotonated macrocycles (H**2a′**)$^+$, one sulfate anion and six water molecules. However, both the macrocyclic ions are almost identical and, thus, only one of them is presented in Fig. 7. The monoprotonated cyclen ring is stabilized in endodentate conformation by intramolecular hydrogen bond between protonated amine nitrogen atom N7, unprotonated amine N10 and amide N4 (*d*(N7···N4) = 2.99 and 3.01 Å, and *d*(N7···N10) = 2.71 and 2.72 Å in both independent molecules). The relevant bond lengths and angles are given in Table IV.

In addition, colorless crystals were formed in aqueous ethanol during the work-up. The compound was almost insoluble in all the tested organic solvents (EtOH, acetone, MeCN, toluene, $CHCl_3$, DMSO, DMF) which prevents its spectral characterization. Fortunately, single crystals were formed in several batches and the structure was solved by X-ray diffraction analysis. Surprisingly, the product was identified as compound **6** with the thiophosphoryl–cyclen ratio 3:1 (Fig. 8 and Table IV). The isolated yields of this compound were relatively high (~10%), even from equimolar $PhP(S)Cl_2$–cyclen mixtures. The geometry of the five-membered C_2N_2P heterocycle is similar to that found for the cyclam derivatives (Tables I



SCHEME 3
Isolated products from reaction of cyclen and $PhP(S)Cl_2$

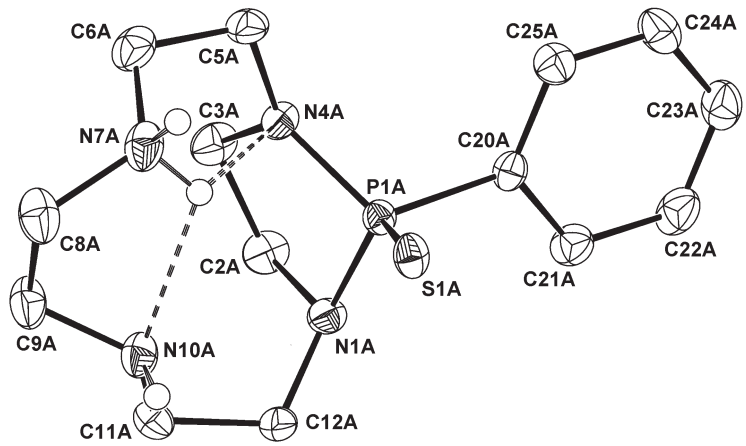


FIG. 7
Molecular structure of $(H\mathbf{2a'})^+$ cation in the crystal structure of $\mathbf{2a'}\cdot 0.5H_2SO_4\cdot 3H_2O$. Hydrogen atoms (except for those attached to the nitrogen atoms) are omitted for clarity

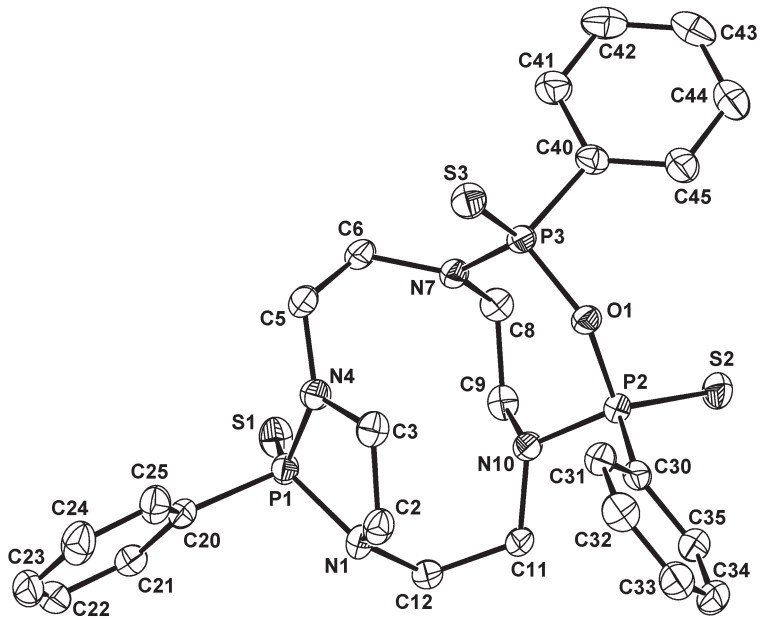


FIG. 8
Molecular structure of **6**. Hydrogen atoms are omitted for the clarity

TABLE IV
The geometry of phosphonothioate groups in the crystal structures of **2a′**·0.5H_2SO_4·3H_2O and **6**

Bond	**2a′**·0.5H_2SO_4·3H_2O		**6**					
	molecule A	molecule B	Five-membered ring		Seven-membered ring			
				Distances, Å				
P1–N1	1.665(2)	1.670(2)	P1–N1	1.672(2)	P2–N10	1.679(2)	P3–N7	1.640(2)
P1–N4	1.650(2)	1.652(2)	P1–N4	1.655(2)	P2–O1	1.6167(13)	P3–O1	1.6156(13)
P1–S1	1.9406(6)	1.9402(6)	P1–S1	1.9396(7)	P2–S2	1.9330(7)	P3–S3	1.9175(7)
P1–C20	1.809(2)	1.815(2)	P1–C20	1.817(2)	P2–C30	1.796(2)	P3–C40	1.804(2)
				Angles, °				
N1–P1–N4	96.90(8)	96.73(8)	N1–P1–N4	95.50(8)	N10–P2–O1	104.57(7)	N7–P3–O1	104.03(7)
N1–P1–S1	119.75(6)	119.82(6)	N1–P1–S1	118.46(6)	N10–P2–S2	116.63(6)	N7–P3–S3	115.32(6)
N1–P1–C20	104.64(8)	105.82(6)	N1–P1–C20	105.13(9)	N10–P2–C30	107.15(8)	N7–P3–C40	108.55(9)
N4–P1–S1	116.47(6)	117.18(6)	N4–P1–S1	118.90(6)	O1–P2–S2	112.18(6)	O1–P3–S3	112.53(6)
N4–P1–C20	108.86(8)	109.08(9)	N4–P1–C20	107.89(9)	O1–P2–C30	100.47(8)	O1–P3–C40	102.03(8)
S1–P1–C20	109.03(6)	107.75(6)	S1–P1–C20	109.43(7)	S2–P2–C30	114.21(7)	S3–P3–C40	113.20(7)
					P2–O1–P3	140.56(9)		

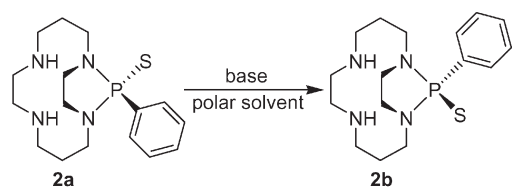
and IV). However, in the seven-membered heterocycle $C_2N_2P_2O$ (hexahydrooxadiazaphosphepine ring), unusually long P–O bonds (1.62 Å) and a very large oxygen valence angle P2–O1–P3 (~140°) were found. To our knowledge, it is the first example of the seven-membered $C_2N_2P_2O$ heterocycle structurally characterized.

From the reaction mixture, another TLC pure compound was also separated. A cluster of peaks in ^{31}P NMR spectrum around 80 ppm, 2:1 integral ratio of aromatic/aliphatic protons in ^{1}H NMR spectrum and mass spectrum the suggest structure of **3′** (Scheme 3). Again, the complexity of the NMR spectra is due to the presence of a number of isomers.

DISCUSSION

The target 1,4-protected cyclam **2** was obtained in a moderate yield of 40–50% employing easily available $PhP(S)Cl_2$. As found, the **2a** isomer is obtained almost exclusively in the protecting reaction and this compound **2a** was used in all subsequent transformations. The minor isomer **2b** is formed from **2a** only under basic conditions and in polar solvent as the isomer **2a** is fully stable in chloroform, chloroform–DABCO mixture or MeOH even under reflux. Formation of **2b** was observed only in MeOH–water mixtures or in water at pH > 10 and at elevated temperature. The rearrangement is irreversible. It was also observed during attempts of alkaline hydrolysis of the protecting moiety (see above). Therefore, the origin of compound **2b** in the oily chromatographic fractions after purification of compound **2a** (standing at room temperature for several hours) can be explained by a presence of ammonia in the eluent; ammonia was not completely removed by evaporation of the fractions.

Thus, both compounds **2a** and **2b** are formally "frozen" conformers. Obviously, penetration of the ethylene bridge (as it is a less sterically constrained group than phenyl) through the rest of the macrocycle must occur during the **2a**→**2b** rearrangement (Scheme 4). The kinetic isomer **2a**



2a **2b**

SCHEME 4
Rearrangement of isomers of **2**

is more stable in neutral and acid solutions, probably due to stabilization through the hydrogen bond between protonated amines and the sulfur atom. In polar solvent, presence of water, high pH and at elevated temperature, the hydrogen bond and the intramolecular hydrogen bond between amine and amide nitrogen atoms are cleaved and, consequently, the thermodynamic isomer **2b** is formed (possibly through a pentacoordinated phosphorus intermediate with participation of hydroxide anion).

By-product **3** (as a mixture of isomers) apparently arose from a further substitution of either isomer **2** with $PhP(S)Cl_2$. The reaction rate of this second substitution is comparable with that of the first step as compound **3** was always present in the reaction mixtures, even at the beginning of the reaction or when a large excess of cyclam was employed. According to these findings, we employed a large excess of triethylamine (up to using it as a solvent) or bases such as DBU or Bu_4NOH. However, only a slightly reduced amount of by-product **3** in the reaction mixtures resulted. Even lowering temperature (down to –20 °C) did not lead to better yields of **2**. In the original report[22], K_2CO_3 was employed as a base. However, the use of carbonates instead of NEt_3 led to much lower yields of **2**. The occurrence of traces of the phosphonothioic monoamide by-product **4** can be attributed to the presence of trace amounts of water in the reaction mixtures. Under the optimized conditions, the target protected cyclam could be isolated in 40–50% yields.

The protection route was also tested in protection of cyclen. However, we found that the reaction is much less clear than that with cyclam. The target product **2′** was isolated only after extensive chromatographic purification as a mixture of two isomers (one isomer **2a′** was characterized structurally). The other two by-products **3′** and **6** were also isolated. The formation of the peculiar heterocyclic compound **6** may be explained by monosubstitution of two $PhP(S)Cl_2$ molecules with adjacent amino groups leading to the formation of a very unusual seven-membered heterocycle after partial hydrolysis and condensation of two P–OH groups. Therefore, one can suggest that the substitution reaction on cyclen is probably faster and more nonselective than that on cyclam and substitution on several nitrogen atoms can proceed independently. According to these findings, the reaction of phenylphosphonothioic dichloride with cyclen can be summarized in Scheme 3.

We also tried to employ commercially available phenylphosphonic dichloride in the reaction with cyclam and cyclen. However, TLC and ^{31}P NMR spectroscopy showed that only very complex mixtures were produced in these reactions. Probably, the reaction between phenylphos-

phonic dichloride and the cyclic polyamines is fast, with no preference for the formation of adducts with a simple stoichiometry.

The crystal structures helped to unambiguously determine molecular structures of the isolated compounds as spectral characterization of chromatographically pure products was rather difficult. There have been only several examples of five-membered C_2N_2P heterocycles presented in literature. Prevote et al.[22] determined crystal structures of similar macrocyclic phosphorothioic triamides having the same five-membered C_2N_2P heterocyclic ring but their compounds were diprotonated on the remaining amine nitrogen atoms. The orientation of sulfur atoms in their five-membered heterocycles corresponds to that in **2a**, $(H\mathbf{2a})^+$, **3a**, **2a′** and **6** where the sulfur is localized above the amine nitrogen atoms of the rest of macrocycle. Bond distances and angles in all heterocycles are similar. The sulfate anion found in some single crystals used for X-ray structure determination obviously came from silica gel used for column chromatography. Sulfates were detected in eluates from washing of the silica gel column with the ammonia-containing eluents under the conditions used in the preparative work.

We tested some selected conditions of removal of the phosphonothioic protecting group. Acid hydrolysis was found to be more effective than the alkaline one in accordance with literature data[26]. Deprotection with a strong cation exchange resin may be used for a selective removal of the protecting group. However, the protecting strategy was not a primary aim of the work and it was not completely explored. The protecting moiety could be easily removed by acid hydrolysis. For our purposes, acid hydrolysis is convenient as ethyl phosphonates are also hydrolyzed under these conditions.

The 1,4-dibenzylcyclam was synthesized starting from **2a**. More importantly, 1,4-bis(methylphosphonate) derivative **5** was easily formed by the Mannich reaction. Direct acid hydrolysis of unpurified ester **5** led to a mixture of several methylphosphonic acid derivatives of cyclam (Scheme 3). The presence of these by-products can be attributed to a mechanism of the Mannich reaction of this kind as it is, in general, reversible. The trace amounts of formaldehyde and phosphite (incompletely removed by filtration and evaporation) can react during the hydrolysis with compound(s) a rising in the reverse Mannich reaction. Purified ester **5** gave the target ligand 1,4-te2p in a high yield. Several H_8tetp crystals were formed on standing of an acid reaction batch. The compound must have arisen from a trace amount of cyclam in the **2a** used for the particular synthetic batch of ester **5**. Probably, a very low concentration of the compound (non-

detectable in ^{31}P NMR spectra of the batch) led to slow crystallization of this ligand in the form suitable for the X-ray diffraction study. The strong intramolecular hydrogen bonds in 1,4-te2p are very similar to those present in the structure of 1,8-te2p (ref.[12]) and are responsible for a high basicity of the amine nitrogen atoms in 1,4-te2p (ref.[29]).

CONCLUSIONS

We synthesized a 1,4-protected cyclam using $PhP(S)Cl_2$. The solid-state structures of the target 1,4-protected cyclam and several by-products were determined by the single-crystal X-ray diffraction. The method is useful for the synthesis of 1,4-substituted cyclam derivatives as it is simple and the phosphonothioic moiety may be removed under milder condition than the oxalate group used previously. The protected cyclam **2a** was successfully used for the synthesis of a new macrocyclic phosphonate ligand, 1,4,8,11-tetraazacyclotetradecane-1,4-bis(methylphosphonic acid). The crystal structure of the ligand showed the presence of strong intramolecular hydrogen bonds which are probably responsible for its high basicity. The crystal structure of H_8tetp was also determined. Despite the only moderate yield of the 1,4-protected cyclam, the method is a reasonable alternative to the existing procedures.

Unfortunately, the method is only partly useful for the synthesis of 1,4-protected cyclen as it led to rather complex mixtures. From the mixtures, the target cyclen derivative was isolated in a low yield together with a cyclen phosphonothioic tetraamide containing a very unusual seven-membered $C_2N_2OP_2$ heterocycle; it is the first example of such heterocycle which was structurally characterized.

EXPERIMENTAL

General

Cyclam[30] (**1**) and phenylphosphonothioic dichloride[31] were synthesized following the literature procedures. Paraformaldehyde was obtained by filtration of aged formaldehyde solutions. Other chemicals were available from commercial sources (Lachema, Fluka, Aldrich, Merck, Acros or Bracco SpA). Solvents were dried by established procedures[32]. Column chromatography was performed on silica gel (60–230 mesh, Merck). TLC was performed on silica gel sheets (Merck TLC aluminium sheets silica gel 60 F_{254}) in the mixtures: (A) propan-2-ol–25% aqueous NH_3 6:1, (B) propan-2-ol–25% aqueous NH_3–water 10:2:7, (C) propan-2-ol–EtOAc 25:1, (D) ethanol–25% aqueous NH_3 1:1, (E) ethanol–25% aqueous NH_3 15:1, detection with aqueous solution of $CuSO_4$ or Draggendorf reagent. Elemental analyses were made in the Institute of Macromolecular Chemistry, Academy of Sciences of

the Czech Republic. Melting points were determined using a Kofler hot-stage apparatus (Boetius) and are uncorrected. NMR spectra (δ, ppm; *J*, Hz) were recorded on a Varian Unity Inova 400 at 399.95 MHz for ^{1}H, 100.58 MHz for ^{13}C and 161.9 MHz for ^{31}P. Internal references for ^{1}H NMR: TMS (δ 0.00 ppm) for $CDCl_3$ solutions, *t*-BuOH (δ 1.25 ppm) for D_2O solutions and CHD_2OD (δ 3.31 ppm) for CD_3OD solutions. Internal references for ^{13}C NMR: $CDCl_3$ (δ 77.0 ppm) for $CDCl_3$ solutions, *t*-BuOH (δ 32.8 ppm) for D_2O solutions and CD_3OD (δ 39.3 ppm) for CD_3OD solutions. External reference for ^{31}P NMR: 85% H_3PO_4 (δ 0.0 ppm). ESI/MS spectra were recorded on a Bruker Esquire 3000 with an ion-trap detector.

Syntheses

Phenylphosphonothioic dichloride. The compound was synthesized according to the literature procedure[31]. Yield 95%. ^{1}H NMR ($CDCl_3$): 7.54–7.70 m, 3 H; 8.10–8.18 m, 2 H. ^{13}C NMR ($CDCl_3$): 128.8 d, 2 C, ^{3}J(P-C) = 18 (PCCH**C**H); 130.2 d, 2 C, ^{2}J(P-C) = 14.5 (PCH**C**H); 133.8 d, 1 C, ^{4}J(P-C) = 3.8 (PC(CH)$_2$**C**H); 138.4 d, 1 C, ^{1}J(P-C) = 117.9 (P–C). ^{31}P NMR ($CDCl_3$): 76.3 t, ^{3}J(P-H) = 19.1.

15-Phenyl-1,5,8,12-tetraaza-15λ^5-phosphabicyclo[10.2.1]pentadecane-15-thione (**2**). Cyclam (**1**; 10.00 g, 50 mmol) was dissolved in dry chloroform (700 ml) and dry triethylamine (10.12 g, 100 mmol) was added. To this solution, phenylphosphonothioic dichloride (10.55 g, 50 mmol) diluted with dry chloroform (5 ml) was added dropwise during 12 h with stirring. The mixture was stirred at room temperature for 3 days. Solvents were evaporated on rotary evaporator to give yellow oil. Four spots were detected by TLC (eluent A, Draggendorf detection): the main product **2a** (R_F 0.2), traces of its isomer **2b** (R_F 0.4), inseparable mixture of isomers of compound **3** (R_F 1.0) and a small amount of compound **4** (R_F 0.15). The products were separated by column chromatography. Because of a low solubility of the reaction mixture in the eluents, the crude product was dissolved in a small amount of chloroform and poured onto a column. The by-product **3** was separated from the other compounds by gradient column chromatography on silica (25% aqueous NH_3–MeOH from 1:6 to 1:3). Compounds **4** and **2a** were separated by another column chromatography using eluent B. Compound **2a** was obtained as a viscous yellow oil solidifying on standing. Yield 7.11 g (42%). For $C_{16}H_{27}N_4PS$ (338.5) calculated: 56.78% C, 8.04% H, 16.55% N, 9.47% S; found: 56.55% C, 7.79% H, 16.13% N, 10.09% S. M.p. 102–107 °C. ^{1}H NMR ($CDCl_3$): 1.60–1.74 m, 2 H ($CH_2C\mathbf{H}_2CH_2$); 1.81–1.95 m, 2 H ($CH_2C\mathbf{H}_2CH_2$); 2.64–2.70 m, 2 H ($C\mathbf{H}_2NH$); 2.74–2.77 m, 2 H ($C\mathbf{H}_2NH$); 2.80–2.86 m, 4 H; 3.00–3.05 m, 4 H ($C\mathbf{H}_2NH$); 3.51–3.62 m, 2 H ($PNCH_2$); 3.77–3.84 m, 2 H ($PNCH_2$); 7.34–7.44 m, 4 H, aryl H); 7.57–7.63 m, 1 H (PCCH). ^{13}C NMR ($CDCl_3$): 25.8 d, 2 C, ^{3}J(P-C) = 3.0 ($CH_2\mathbf{C}H_2CH_2$); 42.8 d, 2 C, ^{2}J(P-C) = 7.6 ($PNCH_2$); 43.3 d, 2 C, ^{2}J(P-C) = 6.4 ($PNCH_2$); 47.6 s, 2 C (CH_2NH); 48.4 s, 2 C (CH_2NH); 128.1 d, 2 C, ^{3}J(P-C) = 13.3 (PCCH**C**H); 129.6 d, 2 C, ^{2}J(P-C) = 11.5 (PC**C**H); 130.5 d, 1 C, ^{4}J(P-C) = 3.0 (PC(CH)$_2$**C**H); 138.1 d, 1 C, ^{1}J(P-C) = 112.5 (P-C). ^{31}P{^{1}H} NMR ($CDCl_3$): 76.6 s. MS, *m/z* (%): 339.3 (100, M + H$^+$).

The main by-product **3** was obtained as a mixture of isomers (yellowish oil, 2.35 g, 10%). NMR spectra were very complex, but the intensity ratio aromatic/aliphatic hydrogens in ^{1}H NMR agrees well with the assumption of 2:1 adduct of the $PhP(S)Cl_2$ and cyclam. Several peaks were observed at about 80 ppm in ^{31}P{^{1}H} NMR spectrum, which is in agreement with the proposed structure as well. Furthermore, one of the isomers (**3a**) crystallized from the oily mixture upon standing and was identified by X-ray analysis.

Compound **4** was isolated in a minute yield. TLC (eluent B, Draggendorf detection): R_F 0.6 (R_F of both the isomers of **2** is 0.8 in the eluent). $^{31}P\{^1H\}$ NMR (D_2O): 71.2 s.

Isomer **2b** was isolated by chromatography (eluent A) of combined highly enriched fractions from several synthetic batches as a light yellow oil in a small yield. ^1H NMR (CD_3OD): 1.40–1.52 m, 2 H ($CH_2CH_2CH_2$); 1.96–2.12 m, 2 H ($CH_2CH_2CH_2$); 2.73 t, 2 H, ^3J(H-H) = 11.4 (CH_2NH); 2.85–3.06 m, 4 H ($PNCH_2$); 2.96–3.00 m, 2 H (CH_2NH); 3.06–3.16 m, 2 H (CH_2NH); 3.16–3.28 m, 4 H; 3.73–3.90 m, 2 H ($PNCH_2$); 7.68–7.76 m, 2 H (PCCHCH); 7.71–7.76 m, 1 H ($PC(CH)_2CH$); 8.06–8.18 m, 2 H (PCCH). ^{13}C NMR (CD_3OD): 26.0 d, 2 C, ^3J(P-C) = 6.0 ($CH_2CH_2CH_2$); 43.9 d, 2 C, ^2J(P-C) = 6.5 ($PNCH_2$); 44.8 s, 2 C ($PNCH_2$); 47.4 s, 2 C (CH_2NH); 49.4 s, 2 C (CH_2NH); 130.0 d, 2 C, ^3J(P-C) = 13.7 (PCCHCH); 130.8 d, 1 C, ^1J(P-C) = 117.9 (P-C); 134.1 d, 2 C, ^2J(P-C) = 11.5 (PCHCH); 134.5 s, 1 C ($PC(CH)_2CH$). $^{31}P\{^1H\}$ NMR (CD_3OD): 81.0 s. MS, *m/z* (%): 339.3 (100, M + H^+).

1,4,8,11-Tetraazacyclotetradecane-1,4-bis(methylphosphonic acid) (1,4-H_4te2p). The Mannich reaction of protected cyclam **2a**, paraformaldehyde and triethyl phosphite was performed by modification of the procedure reported by Sherry et al.[33] Compound **2a** (4.28 g, 12.6 mmol) was dissolved in triethyl phosphite (130 ml, large excess) and paraformaldehyde (total 2.28 g, 76 mmol, 6 equivalents) was added in three portions during three days. Then, the suspension was stirred for another 4–6 days at 40 °C. After cooling, excess of paraformaldehyde was filtered off and volatiles were removed by rotary evaporation. The resulting oil was purified by column chromatography (eluent C). The intermediate **5** was obtained as a viscous yellow oil (6.52 g, 81%). TLC (eluent C, Draggendorf detection): R_F 0.5. $^{31}P\{^1H\}$ NMR ($CDCl_3$): 27.1 s, 2 P (PO_3Et_2); 77.4 s, 1 P (P(S)Ph). MS, *m/z* (%): 639.4 (100, M + H^+); 661.4 (61, M + Na^+); 677.4 (16, M + K^+).

The reaction intermediate **5** (6.52 g, 10.2 mmol) was hydrolyzed in refluxing hydrochloric acid (6 M, 24 h). Solvents were evaporated on rotary evaporator. Excess HCl was removed by co-distillation with water (3×). The resulting product, 1,4-H_4te2p, was purified on a strong acid cation exchange resin (Dowex 50, H^+-form, elution with water followed by 5% aqueous ammonia). The final purification was made by chromatography on weak acid cation exchange resin (Amberlite CG50, H^+-form, water elution). Two compounds were obtained. In the very first fractions, trisubstituted derivative H_6te3p was eluted. It was followed by the target 1,4-H_4te2p. Simple crystallization from water–acetone mixture afforded 1,4-H_4te2p·$4H_2O$ as a small white needles (4.25 g; 91% for the last step, 73% based on **2a**); the product slowly loses water of hydration on standing in air. TLC (eluent D, Cu^{2+} detection): R_F 0.5; m.p. 262 °C (dec.). For $C_{12}H_{30}N_4O_6P_2·4H_2O$ (460.4) calculated: 31.31% C, 8.32% H, 12.17% N; found: 31.48% C, 7.80% H, 12.05% N. ^1H NMR (D_2O, 90 °C): 1.95 p, 4 H, ^3J(H-H) = 5.4 ($CH_2CH_2CH_2$); 2.87 d, 4 H, ^2J(P-H) = 12.4 (PCH_2); 2.92 s, 4 H (NCH_2CH_2N); 3.11 t, 4 H, ^3J(H-H) = 5.4 ($CH_2CH_2CH_2$); 3.24 t, 4 H, ^3J(H-H) = 5.4 ($CH_2CH_2CH_2$); 3.28 s, 4 H (NCH_2CH_2N). ^{13}C NMR (D_2O, 90 °C): 25.0 s, 2 C ($CH_2CH_2CH_2$); 46.8 s, 2 C (NCH_2); 51.5 s, 2 C (NCH_2); 55.4 d, 2 C, ^1J(P-C) = 158.3 (PCH_2); 56.1 s, 2 C (NCH_2); 61.3 s, 2 C (NCH_2). ^{31}P NMR (D_2O, 90 °C): 16.6 t, ^2J(P-H) = 12.6. MS, *m/z* (%): 389.2 (100, M + H^+); 411.2 (88, M + Na^+); 427.2 (22, M + K^+).

The by-product H_6te3p was obtained as a viscous yellow oil, which was crystallized from aqueous 6 M HCl in a small yield as trihydrochloride dihydrate (0.20 g, 2.5% based on **2a**). The crystallization was induced by sonication. TLC (eluent D, Cu^{2+} detection): R_F = 0.2. For $C_{13}H_{33}N_4O_9P_3·3HCl·2H_2O$ (627.8) calculated: 24.87% C, 6.42% H, 16.94% Cl, 8.92% N; found: 25.05% C, 6.64% H, 15.29% Cl, 9.02% N. ^1H NMR (D_2O, 80 °C): 2.57–2.59 m, 4 H ($CH_2CH_2CH_2$); 3.46 d, 2 H, ^2J(P-H) = 11.6 (PCH_2); 3.05 t, 2 H, ^3J(H-H) = 6.0 (NCH_2); 3.54 d,

2 H, ^{2}J(P-H) = 11.6 (PCH_2); 3.56 t, 2 H, ^{3}J(H-H) = 6.8 (NCH_2); 3.62–3.76 m, 6 H, (NCH_2); 3.79 d, 2 H, ^{2}J(H-H) = 12.4 (PCH_2); 3.83 t, 2 H, ^{3}J(H-H) = 5.8 (NCH_2); 3.90 t, 2 H, ^{3}J(H-H) = 8.0 (NCH_2); 4.05 t, 2 H, ^{3}J(H-H) = 6.0 (NCH_2). ^{13}C NMR (D_2O, 80 °C): 24.8 s, 1 C ($CH_2CH_2CH_2$); 25.1 s, 1 C ($CH_2CH_2CH_2$); 45.5 + 47.3 + 52.9 + 53.9 4 × s, 4 × 1 C ($NCH_2CH_2CH_2N$); 53.2 d, 1 C, ^{1}J(C-P) = 150.5 (PCH_2); 53.6 d, 1 C, ^{1}J(C-P) = 143.0 (PCH_2); 54.1 d, 1 C, ^{1}J(C-P) = 149.7 (PCH_2); 55.2 + 55.6 + 56.2 + 56.9 4 × s, 4 × 1 C (NCH_2CH_2N). $^{31}P\{^{1}H\}$ NMR (D_2O, 80 °C): 13.4 s, 1 P; 20.8 s, 1 P; 21.7 s, 1 P. MS, *m/z* (%): 483.2 (100, M + H^+); 521.2 (35, M + K^+); 505.2 (19, M + Na^+).

If ester **5** (prepared from 2.0 g (5.91 mmol) of **2a**) was not purified by chromatography after removal of paraformaldehyde and volatiles, the hydrolysis of the ester groups in refluxing 6 M aqueous HCl took three days. The reaction mixture was processed as above. Crude ligands H_6te3p and 1,4-H_4te2p were eluted from Dowex 50 with diluted ammonia solution while H_2te1p was retained on Dowex 50 after elution with ammonia solution and it was obtained by elution with 6 M aqueous HCl and evaporation of the eluate. The final purification on Amberlite CG50 as above gave first H_6te3p·3HCl·2H_2O (0.45 g, 12% yield based on **2a**) and later 1,4-H_4te2p·4H_2O (1.14 g, 42% yield based on **2a**). The crude H_2te1p was retained on the sorbent and was obtained[27] after elution with 10% aqueous AcOH, evaporation and crystallization from concentrated aqueous HBr as tetrahydrobromide dihydrate (0.19 g, 5% yield based on **2a**).

1,4-Dibenzyl-1,4,8,11-tetraazacyclotetradecane. Compound **2a** (1.02 g, 3.0 mmol) was dissolved in dry acetonitrile (30 ml) and dry solid K_2CO_3 (4.00 g, 28.9 mmol) was added. Benzyl bromide (1.23 g, 7.2 mmol, 2.4 equivalents) was added and the suspension was stirred at room temperature for six days (TLC monitoring, eluent A, Draggendorf detection). Insoluble salts were filtered off and excess benzyl bromide was converted to benzylamine by addition of small amount of aqueous ammonia (10%). The solution was evaporated on rotary evaporator. The protected intermediate was directly hydrolyzed by refluxing in aqueous 6 M HCl (80 ml) for 12 h. Volatiles were removed on rotary evaporator and excess HCl was removed by co-distillation with water (3×). The resulting oil was extracted into chloroform from aqueous K_2CO_3 solution (pH 12). The organic phase was separated, dried (anhydrous Na_2SO_4) and evaporated to obtain a brown viscous oil. The crude product was purified by column chromatography on silica gel (eluent E) giving 1,4-dibenzylcyclam monohydrate (0.78 g, 65%) as a yellow oil and 1,4,8-tribenzylcyclam (trace amount) as an orange-brown oil.

1,4-Bn_2cyclam. For $C_{24}H_{36}N_4 \cdot H_2O$ (398.6) calculated: 72.32% C, 9.61% H, 14.06% N; found: 71.80% C, 9.31% H, 13.85% N. TLC (eluent E, Draggendorf detection): R_F 0.5. ^{1}H NMR ($CDCl_3$): 1.81 m, 4 H (CH_2CHCH_2); 2.37 t, 4 H, ^{3}J(H-H) = 11.2 ($CH_2CH_2CH_2$); 2.39 s, 4 H (NCH_2CH_2N); 2.79 t, 4 H, ^{3}J(H-H) = 10.0 ($CH_2CH_2CH_2$); 2.94 s, 4 H (NCH_2CH_2N); 3.45 s, 4 H, (CH_2Ph); 7.15–7.38 m, 10 H (aryl H). ^{13}C NMR ($CDCl_3$): 25.2 s, 2 C ($CH_2CH_2CH_2$); 46.6 s, 2 C (NCH_2); 46.7 s, 2 C (NCH_2); 51.2 s, 2 C (NCH_2); 51.6 s, 2 C (NCH_2); 57.8 s, 2 C (CH_2Ph); 127.0 s, 2 C (arom. C); 128.1 s, 4 C (arom. C); 129.5 s, 4 C (arom. C); 138.3 s, 2 C (C_{ipso}). MS, *m/z* (%): 381.4 (100, M + H^+); 403.4 (2, M + Na^+).

The more air stable form (1,4-Bn_2cyclam·4HCl·2H_2O) was obtained after crystallization of the free amine from aqueous 6 M HCl. For $C_{24}H_{36}N_4 \cdot 4HCl \cdot 2H_2O$ (562.5) calculated: 51.25% C, 7.88% H, 25.21% Cl, 9.96% N; found: 51.63% C, 8.01% H, 24.52% Cl, 10.38% N. M.p. 167–169 °C (dec.).

The identity of 1,4,8-tribenzylcyclam was confirmed by TLC comparison with authentic[34] sample: R_F 0.7 (eluent E, Draggendorf detection).

13-Phenyl-1,4,7,10-tetraaza-13λ^5-phosphabicyclo[8.2.1]tridecane-13-thione (**2′**). Cyclen (**1′**; 2.50 g, 14.5 mmol) was dissolved in dry chloroform (250 ml). Dry triethylamine (2.94 g, 29.0 mmol) was added and phenylphosphonothioic dichloride (3.06 g, 14.5 mmol) was slowly added to the solution. The mixture was stirred at room temperature for 4 h. Part of cyclen crystallized out in the form of dihydrochloride and was recovered by filtration. The filtrate was extracted with aqueous K_2CO_3 solution (pH 12). The organic phase was evaporated on rotary evaporator to give a yellow semisolid. The residue could not be completely dissolved in common organic solvents (ethanol, acetone, acetonitrile, toluene, chloroform, DMSO, DMF). Ethanol (100 ml) was added, some amount of a solid was filtered off and the filtrate was left standing for 14 days. Then, the crystalline product **6** was collected by filtration (0.79 g, 9%; the crystal suitable for X-ray analysis was isolated before filtration). Two other compounds were detected in the filtrate by TLC (eluent C, Dragendorff detection): the required product **2′** (R_F 0.4) and by-product **3′** (R_F 0.9). The filtrate was concentrated in vacuum and purified by column chromatography on silica gel (gradient of aqueous NH_3–MeOH from 1:6 to 1:3). The red-brown oily **2′** was obtained as a mixture of isomers and (according to ^{31}P NMR spectrum) it was contaminated with a small amount of other inseparable compounds in a yield of 0.90 g (~20%). Surprisingly, a small amount of pure compound **2a′**·0.5H_2SO_4·3H_2O crystallized in NMR tube as white crystals suitable for X-ray analysis. These crystals were used for further characterisation of compound **2a′**.

2a′ TLC (eluent C, Draggendorf detection): R_F 0.4. ^{1}H NMR (CD_3OD): 2.78–2.93 m, 4 H (NHC**H**$_2$); 3.02–3.13 m, 2 H (PNCH_2); 3.14–3.36 m, 6 H (NCH_2); 3.36–3.48 m, 2 H (PNCH_2); 3.77–3.90 m, 2 H (PNCH_2); 7.37–7.47 m, 3 H (aryl H); 7.55–7.63 m, 2 H (aryl H). ^{13}C NMR (CD_3OD): 45.2 d, 2 C, ^2J(C-P) = 10.7 (PNCH_2); 45.5 s, 2 C (NHCH_2); 46.3 s, 2 C (NHCH_2); 46.7 s, 2 C (PNCH_2); 129.4 d, 2 C, ^3J(C-P) = 14.2 (PCCHCH); 130.4 d, 2 C, ^2J(C-P) = 11.5 (PCCH); 131.9 d, 1 C, ^4J(C-P) = 3.0 (PCCHCHCH); 140.8 d, 1 C, ^1J(C-P) = 133.5 (P-C). ^{31}P{^{1}H} NMR (CD_3OD): 89.3 s. MS, *m/z* (%): 311.2 (100, M + H^+).

By-product **3′** was found to be a mixture of isomers as it showed several peaks at ~80 ppm (^{31}P NMR), but the intensity ratio aromatic/aliphatic hydrogens in ^{1}H NMR agrees well with the assumption of 2:1 phosphonothioate-macrocycle adduct. MS, *m/z* (%): 449.5 (100, M + H^+). Yield 0.97 g (~15%).

The compoud **6** was highly insoluble in all common solvents; therefore, attempts at spectral characterization failed. M.p. 224–227 °C (dec.).

X-ray Diffraction Studies

The diffraction-quality single crystals of compound **2a** were grown from its oil overnight. The single crystals of compounds **2a**·0.5H_2SO_4·1.375H_2O, **3a** and **2a′**·0.5H_2SO_4·3H_2O were grown from $CDCl_3$ solutions used for NMR characterization after standing for several days or some weeks. The diffraction-quality single crystals of compound **2b**·0.5H_2SO_4·3H_2O were grown from dichloromethane by slow evaporation. Crystals of compound **4**·H_2O were obtained from chloroform by slow diffusion of hexane vapour. Single crystals of **6** were formed in ethanolic solution of the reaction mixture (see above). Colorless rods of 1,4-H_4te2p·4H_2O were prepared by slow diffusion of acetone vapour into aqueous solution of the ligand. Single crystals of H_8tetp·10H_2O were obtained from HCl–H_2O–D_2O solution on standing of an NMR sample after acid hydrolysis of **5** for several weeks.

The diffraction data were collected at 150(2) K (Cryostream Cooler Oxford Cryosystem) using a Nonius Kappa CCD diffractometer and Mo-K_α radiation (λ = 0.71073 Å). The data

TABLE V
Experimental data for reported crystal structures

Parameter	**2a**	**2a**·0.5H_2SO_4·1.375H_2O	**2b**·0.5H_2SO_4·3H_2O	**3a**	4·H_2O
Formula	$C_{16}H_{27}N_4PS$	$C_{16}H_{30.75}N_4PO_{3.375}PS_{1.5}$	$C_{16}H_{34}N_4O_5PS_{1.5}$	$C_{22}H_{30}N_4P_2S_2$	$C_{16}H_{31}N_4O_2PS$
MW	338.45	412.26	441.53	476.56	374.48
Color	colorless	colorless	colorless	colorless	colorless
Shape	prism	needle	prism	plate	prism
Dimension, mm	0.30 × 0.35 × 0.50	0.05 × 0.10 × 0.40	0.35 × 0.38 × 0.55	0.15 × 0.23 × 0.33	0.38 × 0.40 × 0.63
Crystal system	monoclinic	monoclinic	orthorhombic	monoclinic	monoclinic
Space group	$P2_1/n$ (No. 14)	$C2/c$ (No. 15)	$Pnma$ (No. 62)	$P2_1/c$ (No. 14)	$P2_1/c$ (No. 14)
a, Å	20.5734(4)	40.3036(4)	15.5697(2)	9.4397(3)	14.6198(4)
b, Å	8.23130(10)	7.16660(10)	36.6723(10)	7.9669(2)	7.5902(2)
c, Å	22.9507(5)	30.1557(4)	7.7615(2)	15.2021(6)	18.5187(4)
α, °	90	90	90	90	90
β, °	114.7186(9)	108.1611(5)	90	95.3586(14)	109.1666(16)
γ, °	90	90	90	90	90
V, Å^3	3530.48(11)	8276.26(18)	4431.64(18)	1138.28(6)	1941.06(8)
Z	8	16	8	2	4
D_c, g cm^{-3}	1.273	1.323	1.324	1.390	1.281
T, K	150(2)	150(2)	150(2)	150(2)	150(2)
θ range, °	1.74–27.59	2.89–25.04	2.68–27.47	3.29–27.48	2.31–27.15
Limiting indices	$-26 \le h \le 26$	$-47 \le h \le 47$	$-20 \le h \le 20$	$-12 \le h \le 12$	$-18 \le h \le 18$
	$-10 \le k \le 10$	$-8 \le k \le 8$	$-47 \le k \le 47$	$-10 \le k \le 10$	$-9 \le k \le 9$
	$-29 \le l \le 29$	$-35 \le l \le 35$	$-10 \le l \le 10$	$-19 \le l \le 19$	$-23 \le l \le 23$
μ, mm^{-1}	0.277	0.309	0.299	0.393	0.266
F(000)	1456	3552	1896	504	808
Measured data	8117	7318	5132	2604	4273
Observed data [$I_o > 2\sigma(I_o)$]	6428	5253	3850	2025	3489
Parameters	613	714	397	190	330
GOF on F^2	1.013	1.021	1.032	1.059	1.059
R_1	0.0367	0.0390	0.0370	0.0380	0.0771
wR_2	0.0876	0.0888	0.0893	0.0558	0.2151
R_1 (all data)	0.0530	0.0686	0.0597	0.0916	0.0912
wR_2 (all data)	0.0970	0.1005	0.1010	0.1006	0.2291

TABLE V (continued)
Experimental data for reported crystal structures

Parameter	1,4-H_4te2p·$4H_2O$	H_8tetp·$10H_2O$	**2a′**·$0.5H_2SO_4$·$3H_2O$	**6**
Formula	$C_{12}H_{38}N_4O_{10}P_2$	$C_{14}H_{56}N_4O_{22}P_4$	$C_{14}H_{30}N_4O_5PS_{1.5}$	$C_{26}H_{31}N_4OP_3S_3$
MW	460.40	756.51	413.48	604.64
Color	colorless	colorless	colorless	colorless
Shape	prism	prism	plate	plate
Dimension, mm	0.35 × 0.45 × 0.45	0.10 × 0.18 × 0.30	0.30 × 0.45 × 0.63	0.18 × 0.20 × 0.35
Crystal system	triclinic	triclinic	triclinic	monoclinic
Space group	*P*-1 (No. 2)	*P*-1 (No. 2)	*P*1 (No. 1)	*C*2/*c* (No. 15)
a, Å	8.5744(2)	7.9571(4)	7.10690(10)	34.5543(8)
b, Å	9.3368(2)	9.9506(3)	8.6975(2)	10.9735(2)
c, Å	15.0663(3)	10.7530(5)	16.3963(3)	14.8069(4)
α, °	98.0850(13)	85.266(3)	86.0044(13)	90
β, °	100.0042(11)	71.0241(17)	85.5570(14)	97.6488(10)
γ, °	110.9831(11)	80.769(3)	80.2812(13)	90
V, $Å^3$	1081.73(4)	794.28(6)	994.29(3)	5564.5(2)
Z	2	1	2	8
D_c, g cm^{-3}	1.414	1.582	1.381	1.443
T, K	150(2)	150(2)	150(2)	150(2)
θ range, °	3.06–27.54	2.00–27.50	3.35–27.56	1.95–27.51
Limiting indices	$-11 \le h \le 11$	$-10 \le h \le 10$	$-9 \le h \le 9$	$-44 \le h \le 44$
	$-12 \le k \le 12$	$-12 \le k \le 12$	$-11 \le k \le 11$	$-14 \le k \le 14$
	$-19 \le l \le 19$	$-13 \le l \le 13$	$-21 \le l \le 21$	$-19 \le l \le 19$
μ, mm^{-1}	0.256	0.331	0.328	0.468
F(000)	496	404	442	2528
Measured data	4933	3629	8903	6386
Observed data [$I_o > 2\sigma(I_o)$]	4503	2996	8515	5073
Parameters	389	209	694	458
GOF on F^2	1.037	1.053	1.059	1.023
R_1	0.0318	0.0664	0.0268	0.0351
wR_2	0.0834	0.1912	0.0665	0.0814
R_1 (all data)	0.0352	0.0789	0.0293	0.0526
wR_2 (all data)	0.0857	0.2007	0.0683	0.0894

were analyzed using the HKL DENZO program package[35]. The structures were solved by program SIR92 [36], and refined by program SHELXL97 [37]. All non-hydrogen atoms were refined anisotropically; the hydrogen atoms were located in difference Fourier map and were refined isotropically. In the structures of **4**·H_2O and H_8tetp·10H_2O, hydrogen atoms attached to carbon atoms were placed in theoretical positions using the riding model. Experimental data are given in Table V.

CCDC 287912 (**2a**), 287914 (**2a**·0.5H_2SO_4·1.375H_2O), 287911 (**2b**·0.5H_2SO_4·3H_2O), 287915 (**3a**), 287917 (**4**·H_2O), 287913 (**2a′**·0.5H_2SO_4·3H_2O), 287910 (**6**), 287909 (1,4-H_4te2p·4H_2O) and 287916 (H_8tetp·10H_2O) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge, CB2 1EZ, UK; fax: +44 1223 336033; or deposit@ccdc.cam.ac.uk).

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