Synthesis, Molecular Structure, and Binding Properties of a Hemispherand Incorporating a Phosphoryl Hard Donor Group

Pascale Delangle, Jean-Pierre Dutasta,* Jean-Paul Declercq, and Bernard Tinant

Abstract: Phosphahemispherand **3** was synthesized in 63% yield from its macrocyclic precursor **2** and 1,3-propanediol ditosylate in the presence of NaH in THF. Host **3** exhibited temperature-dependent ^{1}H, ^{13}C, and ^{31}P NMR spectra owing to conformational exchange throughout the molecular framework. *Exo* and *endo* conformers are in equilibrium in solution, and the energy barrier between the two forms is 61 kJ mol^{-1}. Two *exo* conformers, with the P=O bond directed away from the macrocyclic cavity, were predominant at low temperature. The major form was assigned to the C_s symmetry *exo* conformation. The minor *exo* form was assigned to the asymmetric conformation that has one methoxy group on each face of the macroring. The energy barrier for interconversion between the two *exo* forms is 56 kJ mol^{-1}. The binding energies of alkali metal and ammonium cations to **2** and **3** were measured by the picrate extraction technique. The highest K_a values were obtained for the complexes of **3** with K^+ and Rb^+. The conformational changes observed upon complexation were examined by NMR spectroscopy and X-ray analysis and are discussed in terms of preorganization. The formation of 1:1 complexes was only observed with the *endo* conformer.

Keywords: cation complexation · conformation analysis · NMR spectroscopy · phosphorus macrocycles · structure elucidation

Introduction

The majority of the work on molecular hosts for metal and ammonium cations involves structures based on crown ethers and more elaborate systems such as cryptands, spherands, and cavitands. In these systems, the necessary donor atoms are those in oxygen or sulfur ethers or nitrogen binding units, depending on the hard or soft character of the cationic guests involved. Cram et al. introduced the concept of preorganization, which identified the criteria, both structural and electronic, for optimal affinity of guests and hosts.[1] This is exemplified by the spherand structures with enforced conformational strain, which induces high recognition and selectivity towards alkali metals. Hemispherands are a more flexible system, though they include a rigid part. Cram et al. and Reinhoudt et al. have extensively investigated the complexation behavior of hemispherand molecules with various binding sites.[2,3]

[*] Dr. J.-P. Dutasta, Dr. P. Delangle
Stéréochimie et Interactions Moléculaires
UMR CNRS 117, École Normale Supérieure de Lyon
46, Allée d'Italie, F-69364 Lyon Cedex 07 (France)
Fax: Int. code +33 4 7272-8483
e-mail: dutasta@chimie.ens-lyon.fr
Prof. J.-P. Declercq, Dr. B. Tinant
Laboratoire de Chimie physique et de Cristallographie
Université Catholique de Louvain
Place Louis Pasteur 1, B-1348 Louvain-la-Neuve (Belgium)

The P=O phosphoryl group possesses strong binding properties towards cationic guests and is a good hydrogen-bond acceptor. Therefore, incorporation of the phosphoryl unit in preorganized structures can provide powerful hosts for the recognition of cationic guests. Macrocyclic phosphorus ligands have attracted much attention in recent years, and new developments in the synthesis of organized hosts for complexation by means of the phosphorus moieties have been described.[4] Nevertheless, only a few examples of phosphorus ligands bearing a phosphoryl or thiophosphoryl donor group directed towards the interior of a host cavity have been published. Only molecules with cryptand- or cavitand-like structures have been reported to date.[5] Recently, we reported that phosphorus macrocycles could be obtained by the reaction of a diamine with a diaminophosphane and subsequent oxidation of the P^{III} species.[6,7] We have extended this chemistry to rigidified phosphorus molecules,[8,9] and this paper deals with the synthesis and the properties of the first phosphorylated hemispherand **3** and its macrocyclic precursor **2**. The binding activities of **2** and **3** towards alkali metal and ammonium cations were examined to assess the role of the phosphoryl group and of the conformational flexibility in recognition. The solid-state structures of the free ligand **3** and its sodium complex are discussed along with the detailed NMR analysis of the conformational behavior of the host and its complexes. Energy barriers for interconversion between different conformations of the host were determined.

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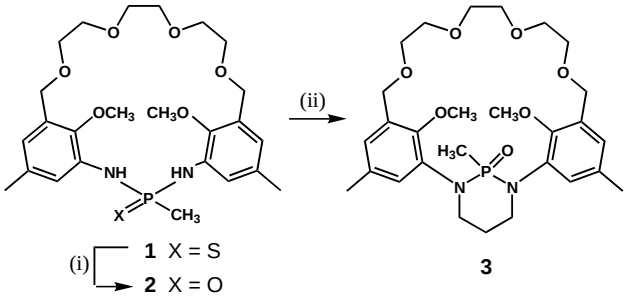
Results and Discussion

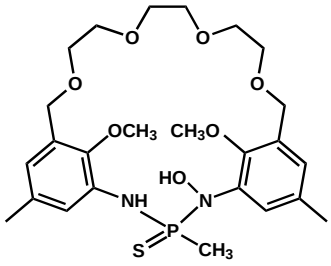
Synthesis: As has already been demonstrated, macrocyclic phosphorus derivatives can be prepared most efficiently by a ring-closure reaction of an appropriate diamine precursor with a diaminophosphane and subsequent oxidation by sulfur.[6–8] There are several simple methods for the oxidation of phosphorus compounds; the most common synthetic procedure requires the in situ oxidation of the P^{III} compounds. The oxidation of thiophosphoryl derivatives to their oxo analogues has been studied extensively and can be conveniently carried out by treatment of the thiophosphonamide with 3-chloroperoxybenzoic acid in dichloromethane. In keeping with this strategy, we developed an efficient route to macrocycles **1**–**3.**

Scheme 1 summarizes the route used to obtain the phosphorylated hemispherand **3**. Macrocycle **1** was produced by



Scheme 1. i) MCPBA in CH_2Cl_2; ii) $TsOCH_2CH_2CH_2OTs$, NaH in THF.

reacting the appropriate aromatic diamine with bis(dimethylamino)methylphosphine, followed by in situ treatment with sulfur by a procedure already described.[7] In this procedure, the macrocyclic phosphorus(III) intermediate was formed but not isolated, although it is of particular interest as a ligand, especially for transition metals. Macrocycle **1** was converted into the corresponding phosphoryl derivative **2** by reaction with 3-chloroperoxybenzoic acid in dichloromethane (yield 85%). Surprisingly, by-product **4** was isolated during the preparation of **2** and was characterized by NMR analysis ($\delta^{31}P = 43.8$). It corresponds to the rather unusual oxidation of one of the two amido groups in **1** by the 3-chloroperoxybenzoic acid to produce hydroxylamine **4**.



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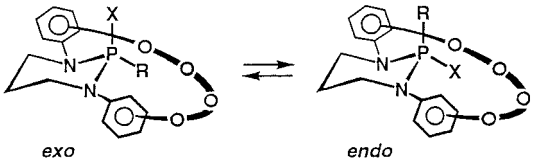
For the rigidification step, the use of the biphasic technique described by Cram,[10] which had proved to be efficient with nonmethoxylated derivatives,[8] failed in the case of the thiophosphorylated and phosphorylated derivatives **1** and **2**. Therefore, we performed the rigidification step under anhydrous conditions. The macrocyclic phosphonamide **2** was mixed under moderate dilution with 1,3-propanediol ditosylate and NaH in dry THF to give the new host **3** in 63% yield. The formation of the phosphoramide anion was indicated by ^{31}P NMR spectroscopy, which gave a broad signal at $\delta = 14.0$; the NMR signal of the starting **2** ($\delta = 23.0$) reappeared when hydrolyzed.

NMR study of phosphahemispherand 3: Phosphahemispherands can exist as two conformers because of their bicyclic structure and the stereochemistry around the phosphorus atom. We defined the *endo* and *exo* forms as the conformers in which the P=O phosphoryl bond is oriented towards or away from the center of the macrocyclic cavity, respectively. A possible *endo*–*exo* exchange pathway is the inversion of the chair conformation of the six-membered diazaphosphorinane ring, which inverts the axial and equatorial orientations of the P=O phosphoryl bond (Scheme 2). This conformational



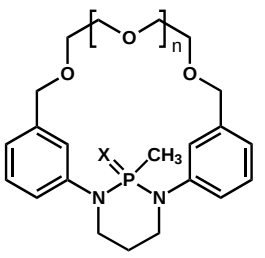
Scheme 2. A possible *endo*–*exo* exchange pathway: inversion of the chair conformation of the diazaphosphorinane ring inverts the orientation of the P=O bond (X = 0, R = CH_3).

behavior is important as it could be involved in the complexing properties of the hosts. An *endo* orientation of the P=O bond allows the phosphoryl group to participate in intracavity complexation, whereas the *exo* conformation does not. Consequently, preorganization of the ligand can only be accomplished with the *endo* conformer and will depend on the relative stability of the preformed cavity in this structure.

Abstract in French: *Le phosphahémisphérand **3** a été synthétisé avec un rendement de 63% à partir du précurseur macrocyclique **2** et du ditosylate de 1,3-propanediol en présence de NaH dans le THF. Les spectres de RMN ^1H, ^{13}C et ^{31}P du récepteur **3** montrent une dépendance avec la température due à des échanges entre plusieurs conformations. La barrière énergétique entre les conformères exo et endo est de 61 kJ mol^{-1}. Deux conformères exo avec la liaison P=O dirigée vers l'extérieur de la cavité macrocyclique prédominent à basse température. La forme majoritaire est attribuée à la conformation exo de symétrie C_s. La forme exo minoritaire est attribuée à la conformation présentant un groupe méthoxy sur chaque face du macrocycle. L'énergie d'interconversion entre les formes exo est de 56 kJ mol^{-1}. La complexation des picrates de cations alcalins et ammoniums par **2** et **3** a été mesurée par une méthode extractive. Les plus grandes valeurs des constantes d'associations K_a ont été obtenues pour les complexes de **3** avec les ions K^+ et Rb^+. Les changements conformationels observés durant le processus de complexation ont été étudiés par spectroscopie de RMN et diffraction des rayons-X, et discutés en terme de préorganisation. La formation de complexes 1:1 n'est observée qu'avec le conformère endo.*

Therefore, it was important to estimate the conformational behavior and the degree of preorganization of **3** before complexation. This was achieved by solution NMR and X-ray structural investigations.

Conformational analysis in solution: In the ^{31}P NMR spectrum of **3** at 300 K in CD_2Cl_2, two signals at $\delta = 31.3$ and 23.3 in a 9:1 ratio indicate the presence of the two slowly exchanging conformers in solution (*exo* and *endo* conformers, respectively). The assignment of the stereochemistry of the conformers was based upon comparison of the NMR data of **3** with those of the corresponding unsubstituted derivatives **5**.[8] The similarity of the NMR data allows the assignment of the highfield signal to the *endo* conformer and the downfield signal to the *exo* one. The proton-decoupled ^{31}P NMR spectrum of **3** (CD_2Cl_2, 80 MHz) is given as a function of temperature in Figure 1, and emphasizes the dynamic nature of the conformational equilibrium. At low temperatures the signal of the *exo* conformer at $\delta = 31.3$ broadens and gives two



5 X = S, O; n = 1, 2

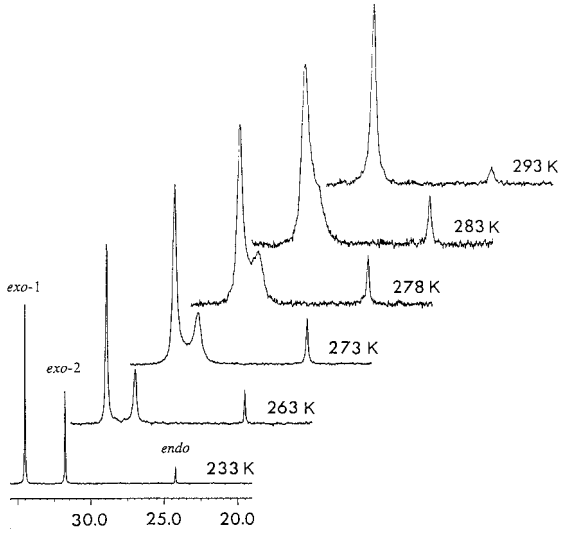


Figure 1. Low-temperature ^{31}P NMR spectra of **3** (CD_2Cl_2, 80 MHz).

resonances (*exo*-1 and *exo*-2) at temperatures below 278 K. The chemical shifts of the different species exhibit a linear temperature dependence, and at 233 K three resonances are observed at $\delta^{31}P = 34.5$, 31.7, and 24.2 (62%, 33%, and 5% respectively). The activation parameter was determined by analysis of the ^{31}P NMR band shape, and gave a barrier $\Delta G^{*} = 56\ kJ\,mol^{-1}$ for the *exo*-1 $\rightleftharpoons$ *exo*-2 process. If the temperature of a $(CDCl_2)_2$ solution of **3** is increased, then a broadening of the ^{31}P resonances is observed. The minor conformer almost disappears in the noise; analysis of the linewidth of the major *exo* species gave a barrier $\Delta G^{*} = 61\ kJ\,mol^{-1}$ for the *exo* – *endo* process.

The conformers in solution were characterized by analysis of the 500 MHz ^1H NMR spectrum. At room temperature, only a broad unresolved proton spectrum of **3** was observed (Figure 2, bottom). Increasing the temperature results in narrowing of the lines to give an averaged spectrum for the rapidly exchanging conformers. More information was obtained from the low-temperature experiments. The 500 MHz ^1H NMR spectrum of **3** at 203 K shows mainly the two *exo* conformers (Figure 2, top). Complete analysis was achieved

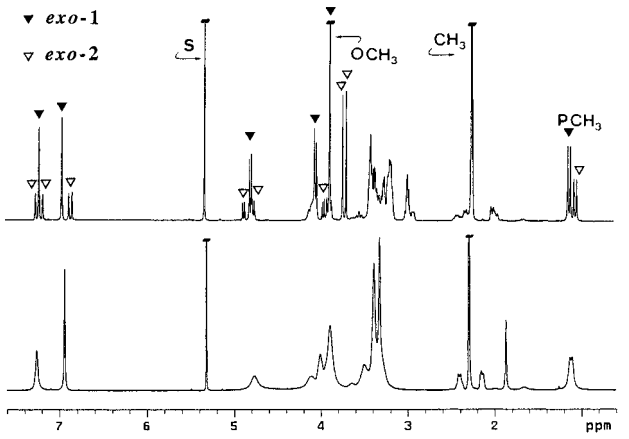


Figure 2. 500 MHz ^1H NMR spectrum (CD_2Cl_2) of phosphahemispherand **3**. Top: 203 K (S = solvent); bottom: 293 K.

by means of two-dimensional correlation experiments. Most of the protons were assigned from the ^1H DQ COSY correlation map at 203 K (a complete assignment of the signals for the two *exo* conformers is given in the experimental section). The methoxy signals, which are not correlated to any other protons through *J* couplings, were assigned from a 2D NOESY experiment run at 203 K. Exchange cross-peaks between the resonance at $\delta = 3.89$ (*exo*-1) and the two signals at $\delta = 3.74$ and 3.69 (*exo*-2) revealed the methoxy signals of both conformers. The major *exo*-1 conformation adopts a C_s averaged symmetry, as evidenced by the two aromatic signals of the anisyl groups. Most of the characteristic signals of the less abundant *exo*-2 species are split up and four different aromatic resonances and two methoxy signals were observed, indicative of an asymmetrical conformation. The similarities of the PCH_3 ^1H chemical shifts are in accord with a similar environment of the phosphorus group in the two *exo* forms; the PCH_3 group of the *endo* conformer resonates at lower field. Selected NMR data for the three conformers are presented in Table 1.

Table 1. Selected NMR data of the three conformers of **3** in CD_2Cl_2 solution.

		exo-1 (sym)	*exo*-2 (unsym)	*endo*
$\delta^{31}P$[a]		34.94	32.02	24.41
	ArH	7.21	7.26; 7.17	–
	ArH	6.95	6.87; 6.84	–
$\delta^{1}H$[b]	OCH_3	3.89	3.74; 3.69	–
	PCH_3	1.13	1.06	1.67
	($^2J_{PH}$/Hz)	(15.5)	(15.5)	(13.5)

[a] 223 K. [b] 203 K.

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We identified the asymmetrical *exo*-2 conformation as the one in which the aromatic rings are in different orientations relative to the phosphorus group. This conformation does indeed lead to the differentiation of the aromatic protons and of the two methoxy groups, which are in different environments. The process mainly involves the rotation of the aromatic rings through the macrocyclic cavity, a process that indicates a relative flexibility of the macrocyclic structure.

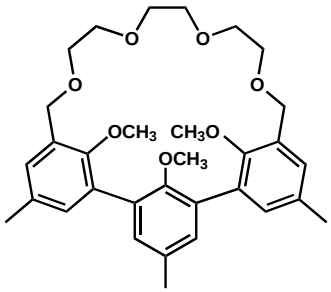
Attempted preorganization by the solvent: The ratio of the two conformers observed at room temperature depends on the polarity of the solvent, so the formation of complexes, which will be favored for only the *endo* conformer, could be modulated by the solvent. In Table 2 the different conformer ratios at 300 K are reported for various solvents whose polarity is expressed through their $E(T)$ factors.[11] The *exo* form is still the major conformation, but the *endo* form is favored more in a polar solvent. The situation in methanol is an exception: the association of the host with methanol molecules through hydrogen bonding could favor the outward orientation of the phosphoryl P=O group (*exo* conformation).

Table 2. *Exo*/*endo* conformers ratio[a] of **3** vs solvent polarity, and ^{31}P NMR chemical shifts (δ).

Solvent	$E(T)$	*exo*/*endo*	δ^{31}P *exo*; *endo*
$CDCl_3$	0.259	95/5	31.2; 24.6
$C_2D_2Cl_4$	0.269	95/5	31.5; 24.6
CD_2Cl_2	0.309	90/10	31.3; 23.3
CD_3COCD_3	0.355	85/15	29.1; 23.3
DMSO	0.444	69/31	28.8; 24.3
CD_3CN	0.460	78/22	28.8; 23.0
CD_3OD	0.762	95/5	35.3; 28.8

[a] Determined from the ^{31}P NMR spectra.

Complexation properties: Hemispherands are very efficient hosts for alkali metal and ammonium ions. They form mainly 1:1 complexes, and solid-state structural analyses show the ion perching above the macrocyclic cavity of the host.[2] In order to assess the role of preorganization of the host molecule during the complexation process, the association constants (K_a) and the free energies of complexation ($-\Delta G^\circ$) for alkali metal and ammonium picrates of phosphahemispherand **3** and its macrocyclic precursor **2** were determined with the picrate extraction technique.[12] They were calculated on the basis of an assumed 1:1 complex formation and are reported in Table 3. For comparison, the values of host **6**, containing three anisyl units, are also included in Table 3.[3]



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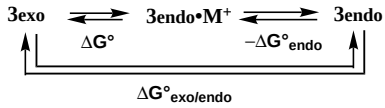
The free energies of binding of the [**3**·cation] complexes are more negative than -25 kJ mol^{-1}, indicating that the phosphahemispherand acts as a good ligand for hard cationic guests. The data in Table 3 show a marked selectivity of **3** for Rb^+ in $CHCl_3$ ($\Delta G^\circ = -40.7$ kJ mol^{-1}). The same trend was observed for the structural analogue hemispherand **6**. The decrease in the binding power of **2** is consistent with the greater conformational freedom of the macrocycle. The most stable complex is obtained with cesium ($\Delta G^\circ = -25.6$ kJ mol^{-1}), clearly indicating poor structural preorganization of the host. The lower affinity of **3** compared with **6** is due to the residual conformational flexibility of the phosphahemispherand. Indeed, as we know, phosphahemispherands can exist as two main conformations, depending on the orientation of the phosphorus substituents. The measured free energy of complexation ΔG° essentially corresponds to the formation of the [**3**·M$^+$] complex, in its *endo* form, from the free ligand in its *exo* conformation (95 % *exo* in $CHCl_3$).

Table 3. Association constants K_a (dm^3 mol^{-1}) and free energies of binding $-\Delta G^\circ$ (kJ mol^{-1}) of picrate salt guests to host **2** and **3** at 293 K in $CHCl_3$ saturated with H_2O.

Cation	**2**		**3**		
	$K_a \times 10^{-6}$	$-\Delta G^\circ$	$K_a \times 10^{-6}$	$-\Delta G^\circ$	$-\Delta G^\circ$ *endo*
Li^+	0.003	19.5	0.027	24.8	32.0 (28.0)[a]
Na^+	0.0078	21.7	0.26	30.4	37.6 (30.9)[a]
K^+	0.017	23.6	14.2	40.1	47.3 (45.6)[a]
Rb^+	0.031	25.1	18.3	40.7	47.9 (46.8)[a]
Cs^+	0.037	25.6	6.6	38.2	45.4 (45.1)[a]
NH_4^+	0.014	23.2	6.7	38.3	45.5
$CH_3NH_3^+$	0.0036	19.9	2.5	35.9	43.0
t-$BuNH_3^+$	0.00069	15.8	0.097	28.0	35.1

[a] Free energies of binding of **6** (ref. [3]).

As depicted in Scheme 3, the free energy of complexation of the preorganized *endo* conformer is given by



Scheme 3. Schematic representation of the thermodynamic equilibria for the formation of the [**3**·cation] complexes.

$\Delta G^\circ_{endo} = -\Delta G^\circ_{exo/endo} + \Delta G^\circ$, where $\Delta G^\circ_{exo/endo}$ is the energy expenditure for the conformational reorganization of **3**. The ΔG°_{endo} values are thus comparable to those of compound **6** (Table 3).

Solid-state structures: Phosphahemispherand **3** crystallized as the **3**·$(CH_3)_2CO$·CH_3OH disolvate. The crystal structure reveals the C_s symmetrical *exo* conformer (Figure 3). The molecule contains a crystallographic plane of symmetry. The two aryl groups are arranged on the same side of the ring, with the methyls of the OCH_3 groups diverging from the cavity and the orbitals of the unshared lone pairs of the oxygens converging on the center of the cavity. The diazaphosphorinane ring is in the chair conformation with the axial P=O bond directed outwards. The macrocyclic cavity is filled by the methyl group of the phosphorus atom and the disordered methylenes C12 and C12* directed inwards.

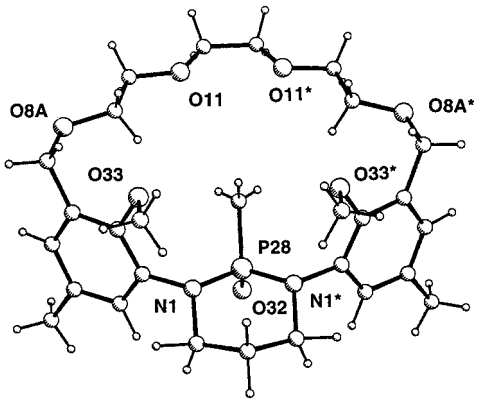


Figure 3. Crystal structure of $\mathbf{3}\cdot(CH_3)_2CO\cdot CH_3OH$.[16] Selected bond lengths [Å] and angles [°]: P28–N1 1.677(3), P28–C31 1.777(6), P28–O32 1.489(4), C28-N1-P28 115.9(2), C5-N1-P28 113.5(2), C5-N1-C28 114.9(2), N1-P28-O32 114.93(13), N1-P28-C31 106.1(2), N1-P28-N1* 101.2(2), C31-P28-O32 112.5(2).

Upon complexation, conformational changes are expected to produce the *endo* conformer with the inward orientation of the P=O bond. Interestingly, the conformational reorganization needed for intracavity complexation is observed in the X-ray structure of the corresponding sodium dihydrate complex $\mathbf{3}\cdot NaSCN\cdot 2H_2O$. In the six-membered heterocycle, the P=O bond adopts an equatorial orientation and is directed towards the macrocyclic cavity. The Na^+ ion is located inside the cavity, and there is an almost planar coordination of Na^+ by four ether oxygens. The coordination sphere of the guest is completed by the phosphoryl oxygen atom and one H_2O molecule (Figure 4). The $O\cdots Na^+$ distances vary from 2.25 to 2.63 Å, with the shortest distance to the phosphoryl oxygen. Atoms O8 and O17 are not coordinated, reflecting the small size of the cation compared to the available macrocyclic cavity.

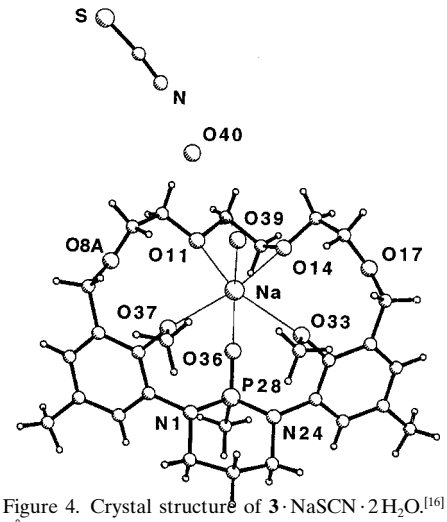


Figure 4. Crystal structure of $\mathbf{3}\cdot NaSCN\cdot 2H_2O$.[16] Selected bond lengths [Å] and angles [°]: P28–N24 1.665(3), P28–N1 1.670(3), P28–C35 1.792(4), P28–O36 1.465(3), Na–O11 2.488(4), Na–O14 2.454(4), Na–O33 2.634(3), Na–O36 2.249(3), Na–O37 2.546(3), Na–O39 2.363(4), C1-N24-P28 119.0(2), C3-N24-P28 116.9(2), C1-N24-C3 116.9(3), C5-N1-P28 117.7(2), C7-N1-P28 115.6(2), C5-N1-C7 115.5(3), N24-P28-O36 114.0(2), N1-P28-O36 114.3(2), N24-P28-C35 109.0(2), N1-P28-C35 108.1(2), N24-P28-N1 100.1(2), C35-P28-O36 110.7(2).

Solution studies: ^{31}P NMR was used to investigate the effects of potassium thiocyanate complexation on the conformational reorganization of host **3**. In acetone solution at 300 K, the free ligand **3** gave two signals corresponding to the two slowly exchanging *exo* and *endo* conformers ($\delta = 29.1$ (85%) and 23.3 (15%) respectively). When potassium thiocyanate is added to the acetone solution of **3**, the ^{31}P NMR signal of the less abundant species reveals an increase in intensity and a lowfield shift (deshielding) with $\delta^{31}P$ varying from 23.3 to 27 when the [guest]/[ligand] ratio reaches 1:1. Concomitantly, the intensity of the lowfield resonance ($\delta^{31}P = 29.1$) decreases with addition of K^+, but its chemical shift is not affected. When exactly one equivalent of salt had been added, the *exo* form disappeared. Even in the presence of an excess of K^+ salt, the $\delta = 27$ resonance remained, and could be unambiguously assigned to the complex $[\mathbf{3}\cdot K^+]$. This indicates that the free and complexed *endo* forms are rapidly exchanging at room temperature. Meanwhile the *exo* conformer, slowly exchanging with its free *endo* partner, disappears in favor of the preorganized *endo* form to allow efficient intracavity complexation of the K^+ cation.

On addition of a large excess of K^+ salt, the signal at $\delta = 27$ does not shift further, indicating that this signal is the resonance of the complex and that there is no more free ligand present after the addition of one equivalent of guest ions. Furthermore, a new signal appears at lower field. This new species increases and its resonance is shifted to lower fields when the concentration of the cation increases. These two signals do not correspond to a conformational equilibrium between two conformers of the complex, as their relative intensities depend on the added salt concentration. They correspond to two slowly exchanging complexes, as demonstrated by ROESY experiments (Figure 5). Investigations of the ^1H and ^{13}C NMR spectra and 2D NMR

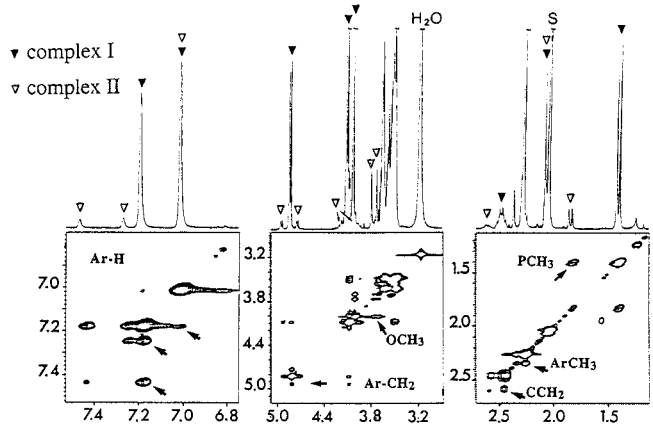


Figure 5. 2D ROESY spectrum (500 MHz) of **3** at 293 K in $[D_6]$acetone with a tenfold excess of K^+ salt showing the two complexes (complex **I** and complex **II**; S = solvent).

correlation experiments of a mixture of **3** and a tenfold excess of KSCN in acetone solution, permitted the identification of the C_s averaged symmetry of complex **I** and the unsymmetrical conformation of complex **II** (Table 4). Under these conditions, the ^{31}P NMR spectrum shows two resonances at

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Table 4. Selected NMR data for the two forms of the complexes [**3**·KSCN] in [D$_6$]acetone and [**3**·CsNO$_3$] in [D$_6$]DMSO at 300 K.

		[**3**·K$^+$] complex I	[**3**·K$^+$] complex II	[**3**·Cs$^+$] complex I	[**3**·Cs$^+$] complex II
δ^{31}P		27.5	29.9	26.1	27.7
	ArH	7.18	7.44; 7.25	7.09	7.35; 7.06
	ArH	7.02	7.02	6.98	6.99; 6.93
δ^{1}H	OCH_3	4.01	3.77; 3.71	3.88	–
	PCH_3	1.41	1.84	1.33	1.65
	($^2J_{PH}$/Hz)	(13.6)	(14.7)	(13.4)	(14.5)
δ^{13}C	PCH_3	5.35	9.50	5.38	9.58
	($^1J_{PC}$/Hz)	(106.2)	(114.1)	(104.9)	(110.5)

$\delta = 27.5$ (88 %, complex **I**) and 29.9 (12 %, complex **II**) for the two slowly exchanging species. However, it is difficult to ascertain the structure of complex **II** based on its NMR data. We suggest the formation of a polynuclear complex for this second species, which could involve the extracavity coordination of a bound cation to the P=O group in an *exo* orientation.

A similar study was performed with cesium nitrate as the guest. The same changes were observed in the ^{31}P NMR spectra on adding increasing quantities of cesium salt to the solution of **3** in [D$_6$]DMSO. After addition of two equivalents of cation, two signals at $\delta = 26.1$ (70 %) and 27.7 (30 %) were observed. The 500 MHz ^{1}H NMR spectrum and 2D COSY, ROESY, and HMQC experiments allowed the characterization of the two [**3**·Cs$^+$] complexes in solution, as described above for the [**3**·K$^+$] complexes (Table 4).

Conclusion

From the viewpoint of its structure and binding abilities, one may regard the macrocyclic phosphonamide **3** as a model for a new family of hemispherand hosts. Furthermore, it emphasizes that, in a sufficiently preorganized structure, the P=O group is an efficient donor unit for the coordination of metal ions in solution. The difficulty of incorporating the phosphoryl hard donor group in a well-defined structure, with convergently arranged binding sites, has been partly reduced with the design of the phosphorylated hemispherand **3**. Preorganization of the ligand is accomplished only with the *endo* conformer. At 300 K, in chloroform solution, the free ligand is mainly in its *exo* conformation ($\Delta G^\circ = 7$ kJ mol^{-1}) so that the host molecule has to be reorganized into its *endo* conformation for intracavity complexation to occur. In the case where the [guest]/[**3**] ratio is ≤ 1, we observe only the *endo* complexed form. The stability of the complexes is close to that of the originally designed hemispherand **6**, if account is taken of the energy expenditure during the structural reorganization of the phosphahemispherand during complexation.

Experimental Section

General: All manipulations involving air-sensitive species were carried out under dry argon. THF was freshly distilled from Na/benzophenone ketyl. Toluene was distilled from Na. Other chemicals were of reagent grade, and were used without further purification. ^{1}H, ^{13}C, and ^{31}P NMR spectra were recorded on Bruker AC200 or Varian Unity 500 spectrometers. Chemical shifts δ are quoted relative to Me$_4$Si (^{1}H and ^{13}C) or 85 % H_3PO_4 (^{31}P). ^{13}C and ^{31}P NMR spectra are proton-decoupled unless otherwise noted. The reported multiplicities of ^{13}C NMR spectra represent ^{31}P–^{13}C couplings. Mass spectra were obtained by the fast atom bombardment (FAB) or electrospray methods. Elemental analyses were performed by the Service Central d'Analyses, CNRS. Melting points were determined on a DSC apparatus or with a Reichert melting point apparatus. Reactions were monitored by ^{31}P NMR and thin-layer chromatography (Merck Kieselgel 60 F_{254}). Silica gel used for column chromatography was Merck Kieselgel 60 (0.040–0.063 mm, 230–400 mesh). The procedure for the preparation of the thiophosphorylated macrocycle **1** has been published previously.[7] 1,3-Propanediol ditosylate was synthesized according to the literature procedure.[13]

3,7,24-Trimethyl-26,27-dimethoxy-11,14,17,20-tetraoxa-2,4,3-diazaphosphatricyclo[20,3,1,1^{5,9}]heptacosa-1(26),5,7,9(27),22,24-hexaene-3-oxide (**2**): A solution of 3-chloroperoxybenzoic acid in CH_2Cl_2 (20 mL) was added dropwise to a solution of macrocycle **1**[7] (0.4 g, 0.76 mmol) in CH_2Cl_2 (75 mL) at 0 °C. The reaction mixture was stirred for 2 h under reflux. After cooling to room temperature, a concentrated aqueous K_2CO_3 solution (100 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (25 mL) and the combined organic extracts were washed with concentrated K_2CO_3 solution (50 mL) and a saturated aqueous solution of NaCl (50 mL), and then dried over $MgSO_4$. The solution was evaporated under reduced pressure and the residue was chromatographed over silica gel (EtOAc, then acetone) to give the oxidized macrocycle **2** in 85 % yield. M.p. 158 °C; ^{1}H NMR (200.1 MHz, $CDCl_3$, 300 K): $\delta = 1.78$ [d, ^2J(P,H) = 15.6 Hz, 3H; PCH_3], 2.16 (s, 6H; CH_3), 3.44–3.54 (m, 12H; OCH_2), 3.57 (s, 6H; OCH_3), 4.39, 4.40 [d_{AB}, $J_{AB} = 10.0$, 4H; $ArCH_2$], 5.46 [d, ^2J(P,H) = 8.3 Hz, 2H; NH], 6.72 (s, 2H; ArH), 7.08 (s, 2H; ArH); ^{13}C NMR (50.3 MHz, $CDCl_3$, 300 K): $\delta = 15.69$ [d, ^1J(P,C) = 119.3 Hz, PCH_3], 20.91 (CH_3), 62.02 (OCH_3), 67.95, 69.35, 70.54, 70.68 (OCH_2), 121.03 [d, J(P,C) = 2.8 Hz, ArCH], 125.27 (ArCH), 130.69, 132.75 (ArC), 134.08 [d, J(P,C) = 2.9 Hz, ArC], 146.90 [d, J(PC) = 7.0 Hz, ArC]; ^{31}P NMR (81.0 MHz, $CDCl_3$, 300 K): $\delta = 23.0$; MS (FAB): $m/z = 509.3$ [M+H]$^+$, 531.3 [M+Na]$^+$; $C_{25}H_{37}N_2O_7P$ (508.54): calcd C 59.05, H 7.33, N 5.51, P 6.09; found C 58.77, H 7.35, N 5.59, P 6.02.

Macrocyclic thiophosphorylated hydroxylamine 4 was isolated during the preparation of **2** by the oxidation of the thiophosphorylated macrocycle **1** with 3-chloroperoxybenzoic acid, and was characterized by NMR spectroscopy. ^{1}H NMR (499.8 MHz, $CDCl_3$, 293 K): $\delta = 1.83$ (s, 3H; CH_3), 1.97 [d, ^2J(P,H) = 14.5 Hz, 3H; PCH_3], 2.34 (s, 3H; CH_3), 3.19 (s, 3H; OCH_3), 3.41–3.65 (m, 12H; OCH_2), 3.61 (s, 3H; OCH_3), 4.17, 4.53 (d_{AB}, $J_{AB} = 10.5$, 2H; $ArCH_2$), 4.44, 4.46 (d_{AB}, $J_{AB} = 12.5$, 2H; $ArCH_2$), 5.07 (s, 1H; OH), 5.78 [d, ^2J(P,H) = 14.0 Hz, 1H; NH], 6.58 (s, 1H; ArH), 6.62 (s, 1H; ArH), 6.74 (s, 1H; ArH), 7.46 (s, 1H; ArH); ^{13}C NMR (50.3 MHz, $CDCl_3$, 293 K): $\delta = 18.19$ [d, ^1J(P,C) = 91.9 Hz, PCH_3], 20.90, 21.21 (CH_3), 61.19, 61.42 (OCH_3), 67.05, 68.83, 69.40, 69.73, 70.40, 70.40, 71.06, 71.15 (OCH_2), 118.24 [d, J(P,C) = 3.6 Hz, ArCH], 114.73, 121.43, 125.28 (ArCH), 130.27, 130.27, 133.12, 134.22, 134.72, 137.99, 144.07 (ArC), 144.88 [d, J(P,C) = 8.7 Hz, ArC]; ^{31}P NMR (81.0 MHz, $CDCl_3$, 300 K): $\delta = 43.8$.

4,21,28-Trimethyl-29,30-dimethoxy-8,11,14,17-tetraoxa-1,24,28-diazaphosphatetracyclo[22,3,1,1^{2,6},1^{19,23}]triaconta-2,4,6(29),19,21,23(30)-hexaene-28-oxide (**3**): A solution of 1,3-propanediol ditosylate (0.292 g, 0.76 mmol, 1.1 equiv) in anhydrous THF (10 mL) was added dropwise to a solution of the phosphorylated macrocycle **2** (0.35 g, 0.69 mmol) and NaH (0.061 g, 1.52 mmol, 60 % in oil) in anhydrous THF (70 mL). The reaction mixture was stirred under reflux for 2 h. After cooling to RT, the mixture was quenched with a minimum amount of water and the THF was evaporated. The residue was taken up in CH_2Cl_2 (80 mL) and H_2O (80 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 40 mL), and the organic extracts were washed with a saturated aqueous solution of NaCl (60 mL) and dried over $MgSO_4$. The solution was evaporated under reduced pressure and the residue then chromatographed over silica gel (EtOAc, then acetone) to give the phosphahemispherand **3** as an oil that was recrystallized from an acetone/hexane mixture (0.24 g, 0.44 mmol, 63 % yield). M.p. 78.1 °C; ^{13}C NMR (50.3 MHz, CD_2Cl_2, 300 K): $\delta = 11.21$ [d, ^1J(P,C) = 119.6 Hz, PCH_3], 20.78 (CH_3), 27.67 (CH_2), 49.12 (NCH_2), 61.46 (OCH_3), 68.38, 69.01, 70.53, 70.76 (OCH_2), 129.6 (ArCH), 130.51 (ArCH), 131.83, 133.90 (ArC), 137.75 (ArC), 154.52 (ArC); ^{31}P NMR (81.0 MHz, $CDCl_3$, 300 K): $\delta = 31.2$, 24.6 (*exo*, *endo*); MS (electrospray): $m/z = 549.7$

$[M+H]^+$, 571.7 $[M+Na]^+$, 587.6 $[M+K]^+$; $C_{28}H_{41}N_2O_7P \cdot H_2O$ (566.61): calcd C 59.35, H 7.65, N 4.94, P 5.47; found C 59.02, H 7.83, N 4.88, P 5.29.

Conformer exo-1: ^{1}H NMR (499.8 MHz, CD_2Cl_2, 203 K): $\delta = 1.13$ [d, ^2J(P,H) = 15.5 Hz, 3H; PCH_3], 2.01 (m, 1H, CH), 2.26 (s, 6H; CH_3), 2.32 (m, 1H, CH), 2.90 – 3.40 (m, 12H; OCH_2), 3.18 (m, 2H, NCH_2), 3.89 (s, 6H; OCH_3), 4.06 (m, 2H, NCH_2), 4.06, 4.80 (d_{AB}, $J_{AB} = 11.5$, 4H; $ArCH_2$), 6.95 (s, 2H; ArH), 7.21 (s, 1H; ArH); ^{31}P NMR (81.0 MHz, CD_2Cl_2, 223 K): $\delta =$ 34.94.

Conformer exo-2: ^{1}H NMR (499.8 MHz, CD_2Cl_2, 203 K): $\delta = 1.06$ [d, ^2J(P,H) = 15.5 Hz, 3H; PCH_3], 1.96 (m, 1H, CH), 2.26 (s, 6H; CH_3), 2.42 (m, 1H, CH), 2.90 – 3.40 (m, 12H; OCH_2), 3.18 (m, 1H, NCH), 3.54 (m, 1H, NCH), 3.69 (s, 3H; OCH_3), 3.74 (s, 3H; OCH_3), 4.11 (m, 2H, NCH_2), 3.87, 4.75 (d_{AB}, $J_{AB} = 12.0$, 2H; $ArCH_2$), 3.94, 4.86 (d_{AB}, $J_{AB} = 11.5$, 2H; $ArCH_2$), 6.84 (s, 1H; ArH), 6.87 (s, 1H; ArH), 7.17 (s, 1H; ArH), 7.26 (s, 1H; ArH); ^{31}P NMR (81.0 MHz, CD_2Cl_2, 223 K): $\delta = 32.02$.

Conformer endo: ^{31}P NMR (81.0 MHz, CD_2Cl_2, 223 K): $\delta = 24.41$.

Crystal structure analysis of $3 \cdot (CH_3)_2CO \cdot CH_3OH$: Crystal size $0.32 \times 0.26 \times 0.14$ mm, orthorhombic, *Pnma*, $a = 9.607(1)$, $b = 14.513(1)$, $c = 24.563(2)$ Å, $V = 3424.7(5)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.24$ g cm^{-3}, $\mu = 1.15$ mm^{-1}, $2\theta_{max} = 135^\circ$, $Cu_{K\alpha}$ radiation, $\lambda = 1.54178$ Å, $\theta - 2\theta$ scan mode, 293 K, 3225 independent reflections, 2385 with $I > 2\sigma(I)$; data corrected for Lorentz polarization but not for absorption; structure solved by direct methods with SHELXS 86,[14] anisotropic least-squares refinement (SHELXL 93[15]) with F^2 values, 256 parameters (12 restraints). H atoms in calculated positions. $R = 0.083$, R(all data) = 0.100, $S = 1.07$, $wR^2 = 0.248$; $w = 1/[\sigma^2 F_o^2 + 0.1609\,P^2 + 1.66\,P]$. Maximum and minimum density in final Fourier synthesis 0.43 and -0.42 e Å^{-3}. Hemispherand **3** and the two solvent molecules lie on a crystallographic mirror plane of symmetry. Two positions for atoms O8 and C12 were refined (site occupation factors 0.76 and 0.24).

Crystal structure analysis of $3 \cdot NaSCN \cdot 2H_2O$: Crystal size $0.28 \times 0.20 \times 0.16$ mm, monoclinic, $P2_1/n$, $a = 10.599(1)$, $b = 23.182(2)$, $c = 13.787(2)$ Å, $\beta = 92.84(1)^\circ$, $V = 3383.4(6)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.31$ g cm^{-3}, $\mu = 1.74$ mm^{-1}, 2θmax = 135°, CuK_α, $\lambda = 1.54178$ Å, $\theta - 2\theta$ scan mode, 293 K, 6100 independent reflections, 3799 with $I > 2\sigma(I)$; data corrected for Lorentz polarization but not for absorption; structure solved by direct methods with SHELXS 86,[14] anisotropic least-squares refinement (SHELXL 93[15]) using F^2 values, 436 parameters (18 restraints). H atoms in calculated positions, those of the water molecules from Fourier difference synthesis (one H not localized). $R = 0.074$, R(all data) = 0.109, $S = 1.08$, $wR^2 = 0.208$; $w = 1/[\sigma^2 F_o^2 + 0.1354\,P^2]$. Maximum and minimum density in final Fourier synthesis 0.67 and -0.49 e Å^{-3}. Two positions for atom O8 (site occupation factors 0.81 and 0.19) and for atoms C17, C18 (site occupation factors 0.53 and 0.47) were refined.

Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited at the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-100210. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (Fax: Int. code + 44 1223 336-033; e-mail: deposit@ccdc.cam.ac.uk).

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