A thiophosphorylated hemicryptophane: structure of the toluene inclusion complex

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The reaction of the tri-(benzaldehyde)-substituted cyclotriveratrylene **6** with phosphotrihydrazide under high dilution conditions gives rise to the novel thiophosphorylated hemicryptophane **1**. **1** is representative of a new family of molecular receptors providing a molecular cavity available for neutral and charged guests. In the crystal, compound **1** encapsulates one toluene molecule.

Un hémicryptophane thiophosphorylé: structure du complexe d'inclusion avec le toluene. La réaction du cyclotrivératrylene **6**, trisubstitué par des groupements benzaldéhyde, avec le phosphotrihydrazide dans des conditions de haute dilution, conduit au nouveau hémicryptophane **1**. **1** représente une nouvelle famille de récepteurs moléculaires contenant une cavité pouvant piéger des substrats neutres ou chargés. Dans le cristal, le composé **1** encapsule une molécule de toluène.

The considerable interest in the design of container molecules[1] is still unabated because of their potential applications in a large area of supramolecular chemistry. Recently, the use of molecular receptors as nanoscale chemical reactors has particularly received much attention.[2] The chemistry of cryptophane is one of the promising routes to design supramolecular receptors that can first encapsulate a substrate and/or a reactant, and second, lead to chemical transformations in the specific environment of the molecular cavity. Our recent approach to the synthesis of cyclotriveratrylene-based ligands suggests that difficulties in combining a catalytic site and a suitable binding pocket for a particular substrate might be overcome by the use of properly designed cryptophanes.[3] The concept of a hemicryptophane that introduces dissymetry at the molecular cavity level can offer such an opportunity.[4] In a first approach we have designed a ditopic host molecule that contains the cyclotriveratrylene building block and the phosphotrihydrazide moiety allowing the formation of a molecular cavity. We thus report the successful synthesis of the thiophosphorylated hemicryptophane **1** and the solid state characterization of its toluene inclusion complex. The new molecule presents a molecular cavity large enough to complex neutral substrates larger than those already investigated with the cryptophanes synthesized so far.

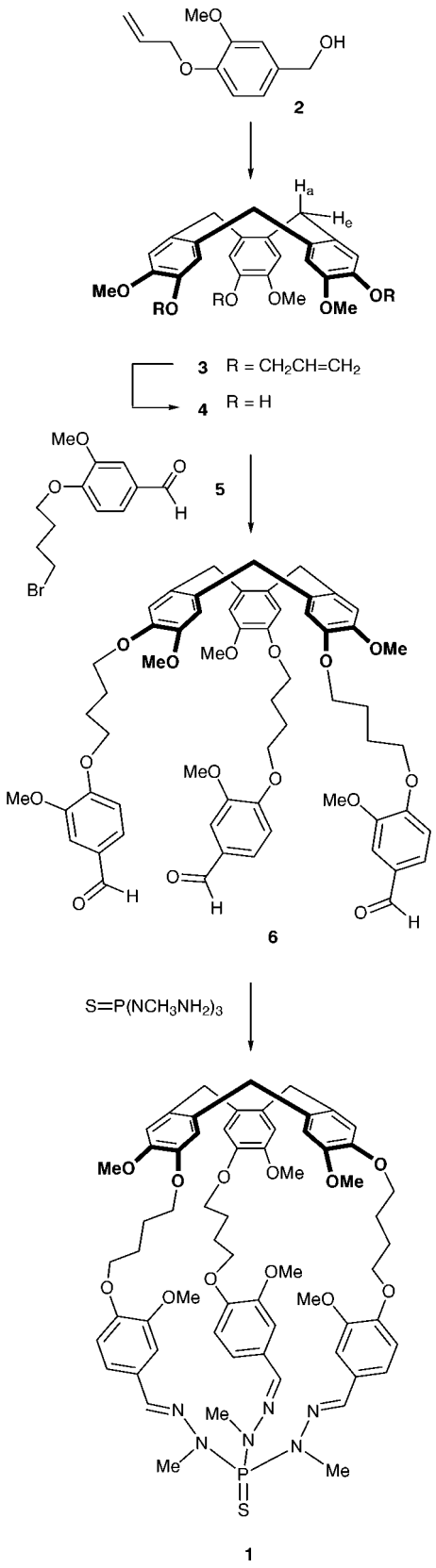
Results and discussion

Synthesis

The synthetic pathway that led to the preparation of **1** is outlined in Scheme 1. The trisallyl cyclotriveratrylene **3** was prepared from the allyl-protected vanillyl alcohol **2** according to the literature method in 62% yield.[5] The cyclotriguaiacylene key precursor **4** was obtained in 90% yield, following a new procedure using a palladium-catalyzed deprotection in the presence of diethylamine. Using triethylammonium formiate as nucleophile gave only hardly reproducible yields of **4**. This method proved to be more convenient than the usual cleavage of the allyl ether groups of **3** in perchloric acid in the presence of Pd on charcoal.[5] The next steps (Scheme 1) were the condensation of the brominated compound **5** with the cyclotriguaiacylene **4** in the presence of aqueous NaOH in DMF–HMPA to give the known cyclotriveratrylene **6**, bearing the three benzaldehyde moieties, in 63% yield.[6] The former compound was obtained in 60% yield from vanillin and 1,4-dibromobutane following the straightforward literature procedure.[6] The condensation of the tri-functionalized cyclotriveratrylene **6** with phosphotrihydrazide, in THF under high dilution conditions, afforded the hemicryptophane **1** in 23% isolated yield. The success of the reaction is partly due to the rather rigid conformation of the phosphorus derivative, which was used by Majoral and colleagues in ring closure reactions for the synthesis of phosphorylated macrocycles and cryptands.[7] Compound **1** was fully characterized by ^{1}H, ^{13}C and ^{31}P NMR in solution, electrospray mass spectroscopy and X-ray crystallography. The recrystallized compound contained two toluene molecules (*vide infra*), which were detected by ^{1}H NMR (Fig. 1).

Characterization of the toluene complex

The molecule can exist as two stereoisomers depending on the orientation of the P=S bond towards or away from the molecular cavity. Only one species was isolated after column chromatography and its structure could not be assigned from the NMR spectra in solution. It was thus of interest to determine the configuration of the molecule in the solid state. **1** was readily recrystallized from toluene to give crystals of X-ray quality of the **1**·(toluene)$_2$ solvated complex. The most striking observations are the outward orientation of the thiophosphoryl bond and the well-preorganized cavity defined by the cyclotriveratrylene and the phosphotrihydrazone moieties. The crystal structure revealed the presence of two toluene molecules. In addition to one disordered interstitial solvent molecule, there is one toluene guest totally encapsulated in the host cavity. To the best of our knowledge, this is the first



Scheme 1 Synthesis of the hemicryptophane **1**.

structure of an aromatic guest imprisoned in the lipophilic cavity of a cryptophane-like receptor. Fig. 2 shows the atomic numbering scheme and Fig. 3 gives a stereoscopic view of the complex. Selected bond lengths and bond angles around the phosphorus atom are given in Table 1.

The whole complex shows an asymmetric structure with respect to the pseudo C_3 axis of the hemicryptophane. The complexed toluene molecule is tilted from the polar axis of the host, which roughly passes through the methyl carbon atom.

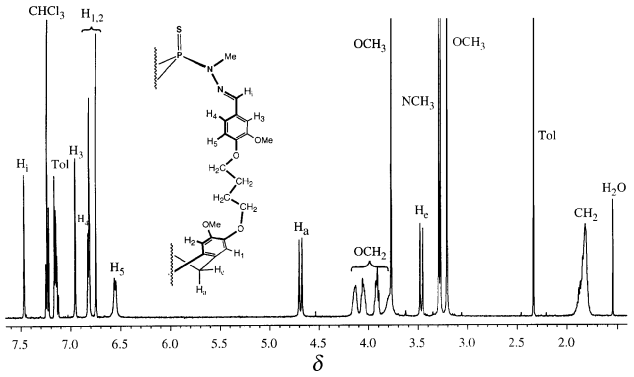


Fig. 1 ^{1}H NMR spectrum ($CDCl_3$, 500 MHz) at 293 K of hemicryptophane **1** (Tol = toluene).

This produces a significant distortion of the cavity. The torsion angles are different within each $O(CH_2)_4O$ bridge [$(g^+ g^+ g^+ a g^-)$, $(g^+ g^+ a a a)$ and $(a g^- g^- a a)$] with O-to-O distances of 5.05, 5.08 and 4.68 Å, respectively. This situation leads to particular structural features between host and guest partners. The aromatic ring of the guest is nested above the cyclotriveratrylene unit while the methyl group is directed toward the phosphorylated cap and wrapped with the three benzyl moieties. In this way, the guest is located within van der Waals contact distance of the host near the aromatic A ring of the cyclotriveratrylene unit and the B′ benzyl ring. Selected short distances, shorter than 3.6 Å, between non-bonded carbon atoms are depicted in Fig. 4. The aromatic guest interacts with the A ring of the cyclotriveratrylene unit through its C(83) and C(92) carbon atoms in an edge-to-face

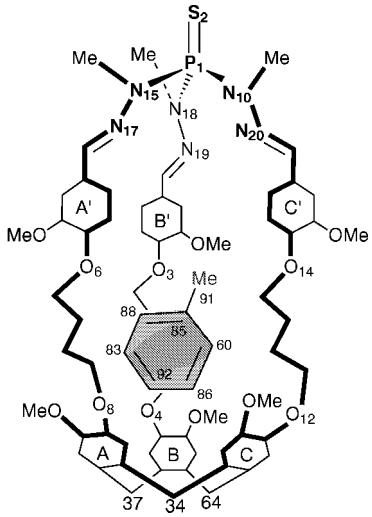


Fig. 2 Atomic numbering scheme for **1**·$(C_7H_8)_2$.

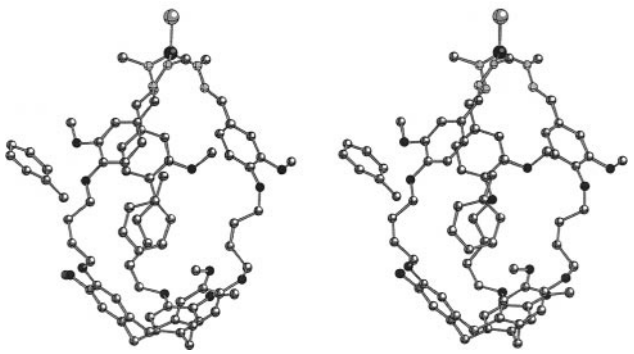


Fig. 3 Stereoview of the complex **1**·$(C_7H_8)_2$.

Table 1 Selected bond lengths (Å) and angles (°) around the phosphorus atom in **1**

P(1)=S(2)	1.929(1)	N(15)—C(81)	1.458(5)
P(1)—N(15)	1.663(3)	N(17)—C(21)	1.279(4)
P(1)—N(18)	1.663(3)	N(18)—N(19)	1.394(4)
P(1)—N(10)	1.677(3)	N(18)—C(68)	1.468(4)
N(10)—N(20)	1.388(4)	N(19)—C(48)	1.276(4)
N(10)—C(67)	1.464(5)		
N(20)—C(23)	1.283(4)		
N(15)—N(17)	1.391(4)		
N(15)—P(1)—N(18)	106.5(1)	C(67)—N(10)—P(1)	119.9(2)
N(15)—P(1)—N(10)	105.3(1)	N(17)—N(15)—C(81)	121.7(3)
N(10)—P(1)—N(18)	105.2(1)	N(17)—N(15)—P(1)	113.6(2)
N(15)—P(1)—S(2)	113.8(1)	C(81)—N(15)—P(1)	121.2(3)
N(18)—P(1)—S(2)	114.3(1)	N(19)—N(18)—P(1)	113.2(2)
N(10)—P(1)—S(2)	112.0(1)	C(68)—N(18)—P(1)	119.9(2)
N(20)—N(10)—C(67)	120.9(3)	N(19)—N(18)—C(68)	120.8(3)
N(20)—N(10)—P(1)	114.8(2)		

Standard deviations are given in parentheses.

arrangement and is nearly parallel to the plan of the aromatic B′ ring. The latter strongly interacts with the methyl group and the quaternary carbon of the guest and, consequently, the corresponding hydrogen atoms are involved in favorable C—H···π interactions (Fig. 4). These contacts probably account for the extended conformation ($a\,a\,a\,g^+\,g^+$) of the O(3)—$(CH_2)_4$—O(4) segment, which forms a zig-zag chain coplanar to the B′ aromatic ring. Both the B′ ring and the planar O—$(CH_2)_4$— unit are involved in a face-to-face stacking with the guest molecule.

These observations reflect that complex stabilization is probably achieved *via* a combination of van der Waals and C—H···π interactions. It is interesting to note that despite the fact that the toluene guest occupies the lipophilic cavity of the hemicryptophane, there is enough room for the inward-turned—(CH_2)— groups of the O(12)—$(CH_2)_4$—O(14) bridge, which adopts the ($g^+\,g^+\,g^+\,a\,g^-$) conformation (Fig. 3 and 4). Moreover, the phosphotrihydrazone moiety defines a small polar cavity that could be used for metal coordination, for example. It is thus tempting to assume that slight modifications of this part of the host could give access to a ditopic metalloreceptor.

Conclusion

The use of the phosphotrihydrazide unit in the hemicryptophane synthesis led with fairly good yields to a new supramolecular receptor that showed affinity for aromatic guest molecules. In the solid, **1** encapsulated one toluene molecule located close to the cyclotriveratrylene unit, that is, in the most lipophilic part of the cavity. The complex was never detected in solution by NMR. The guest is small enough to enter and depart the interior of the host so that mass-law driven exchange of guest with solvent occurs in solution at room temperature. Our strategy as a whole opens the route to the design of a new class of ditopic receptors that differentiate both hemispheres of the molecular cavity. By keeping in mind this background, efforts are presently underway to introduce coordinating sites for a metallic center inside the polar part of the host cavity, which could display catalytic activity. In this sense, hemicryptophane **1** can be viewed as a prototype for a new family of metalloreceptors.

Experimental

General

Anhydrous THF was distilled from sodium benzophenone ketyl. Column chromatography was carried out using silica gel (Merck Kieselgel 60, 230–400 mesh). Melting points were measured on a Reichert melting point apparatus or with a DSC7 Perkin Elmer calorimeter. ^{1}H NMR spectra were recorded at 200.1 or 499.8 MHz on Bruker AC200 or Varian Unity$^+$ 500 spectrometers, respectively. ^{13}C and ^{31}P NMR spectra were recorded on a Bruker AC200 spectrometer at 50.3 and 81.0 MHz, respectively. ^{1}H and ^{13}C chemical shifts are expressed in ppm from TMS; δ ^{31}P is relative to 85% H_3PO_4. ^{13}C assignments were mainly based on DEPT and 2D-correlation spectra. Electrospray mass spectra were performed by the Service Central d'Analyse, CNRS. Allyl-protected benzyl alcohol **2**,[5] triallylcyclotriveratrylene **3**,[5] bromide **5**,[6] trialdehyde **6**,[6] and phosphotrihydrazide[8] were synthesized according to the literature procedures.

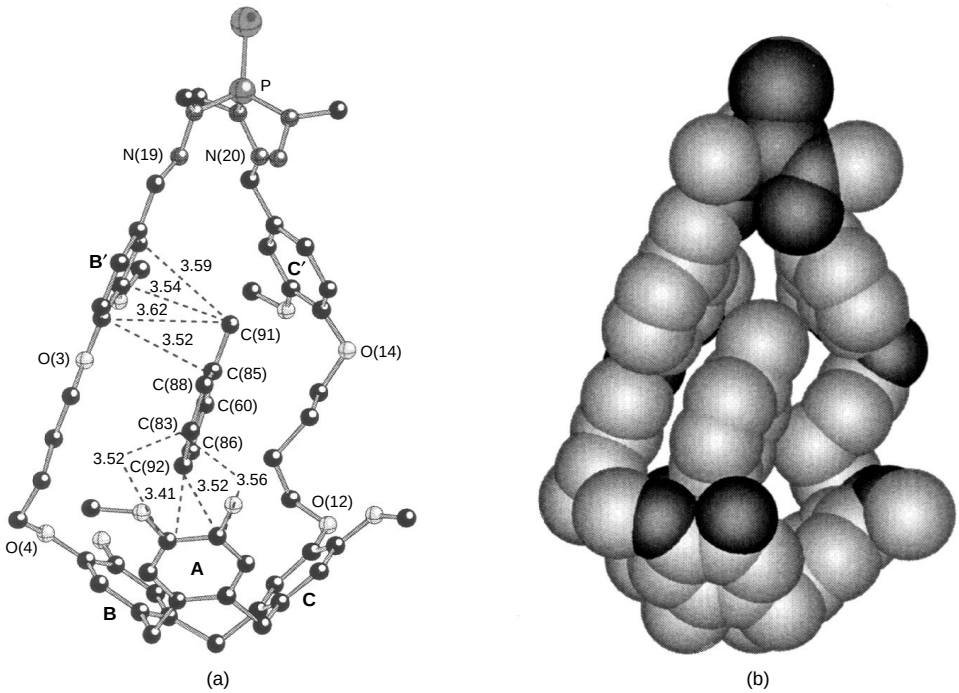


Fig. 4 Partial view of the structure of complex **1**·$(C_7H_8)_2$ showing (a) short contact distances and (b) the corresponding space-filling view.

Table 2 Crystal data and structure refinement for $1\cdot(C_7H_8)_2$

Empirical formula	$C_{63}H_{75}N_6O_{12}PS\cdot 2C_7H_8$
Formula weight	1355.59
Temperature/K	293
Wavelength λ/Å	0.710 70
Crystal system	Triclinic
Space group	$P\bar{1}$
Unit cell dimensions/Å, °	$a = 14.2730(10)$ $\alpha = 82.1390(10)$
	$b = 15.6930(10)$ $\beta = 81.1230(10)$
	$c = 16.7140(10)$ $\gamma = 73.6740(10)$
Volume/Å^3	3532.5(4)
Z	2
D_c/g cm^{-3}	1.274
Absorption coeff/mm^{-1}	0.135
$F(000)$	1444
θ range for data collection	2.81–28.27
Index ranges	$0 \leqslant h \leqslant 18$; $-19 \leqslant k \leqslant 20$; $-21 \leqslant l \leqslant 21$
Reflections collected	14 654
Reflections observed $[I > 2\sigma(I)]$	7426
Parameters/restraints	874/0
Final R/R_w $[I > 2\sigma(I)]$	0.0718/0.1654
R/R_w indices (all data)	0.1615/0.2055
Goodness-of-fit	0.981
$\Delta\rho$ (max/min)/e Å^{-3}	0.685, −0.606
Shift/error (max/mean)	2.104/0.080

Synthesis

(±)-2,7,12-Trihydroxy-3,8,13-trimethoxy-10,15-dihydro-5*H*-tribenzo[a,d,g] cyclononene, 4. To a solution of **3** (1.6 g, 3 mmol) in THF (50 mL) and water (10 mL) were successively added triphenylphosphine (100 mg, 0.38 mmol), $Pd(OAc)_2$ (30 mg, 0.13 mmol) and diethylamine (10 mL, 97 mmol) under argon. The reaction mixture was then stirred at reflux temperature for 4 h. After cooling to room temperature the THF was evaporated under reduced pressure. The residue was taken up with ethyl acetate (2 × 50 mL) and the precipitate that formed was filtered off. The organic phase was washed with water until neutral, dried over Na_2SO_4, and concentrated under vacuum to give a 30 mL solution that was poured into 200 mL of pentane. The resulting solid was filtered, washed with pentane and dried under vacuum to give 1.13 g (88%) of **4**. Mp > 300 °C dec. ^{1}H NMR ($CDCl_3$) δ: 6.82 (s, 3H, ArH); 6.77 (s, 3H, ArH); 5.4 (s, 3H, OH); 4.7 (d, 3H, J = 14 Hz, H_a); 3.80 (s, 9H, OMe); 3.7 (d, 3H, J = 14 Hz, H_e).

Hemicryptophane 1. A solution of **6** (0.4 g, 0.39 mmol) in THF (100 mL) and a solution of the phosphotrihydrazide $S{=}P(NCH_3NH_2)_3$ (0.0772 g, 0.39 mmol) in THF (100 mL) were simultaneously added dropwise at room temperature with stirring to 200 mL of THF under argon. The reaction mixture was further stirred under argon for 3 days. The solvent was evaporated *in vacuo* and the residue was subjected to column chromatography ($CHCl_3$–EtOAc 4 : 1) to yield the hemicryptophane **1** (0.1037 g, 23%). **1** was recrystallized from toluene to afford crystals of the X-ray quality of the complex $1\cdot(toluene)_2$. Mp 235 °C. ^{1}H NMR ($CDCl_3$) δ: 7.47 (s, 3H, H_i); 6.96 (d, 3H, ^4J = 1.6 Hz, H_3); 6.82 (dd, 3H, ^3J = 8.1 Hz, ^4J = 1.6 Hz, H_4); 6.82 (s, 3H, $H_{1,2}$); 6.75 (s, 3H, $H_{1,2}$); 6.56 (d, 3H, ^3J = 8.1 Hz, H_5); 4.69 (d, 3H, ^2J = 13.8 Hz, H_a); 4.13 (br m, 3H, OCH_2); 4.06 (br m, 3H, OCH_2); 3.91 (br m, 3H, OCH_2); 3.79 (br m, 3H, OCH_2); 3.77 (s, 9H, OCH_3); 3.47 (d, 3H, ^2J = 13.8 Hz, H_e); 3.28 (d, 9H, $^3J_{PH}$ = 9.2 Hz, NCH_3); 3.20 (s, 9H, OCH_3); 1.82 (br m, 12H, CH_2). ^{13}C NMR ($CDCl_3$) δ: 149.5, 148.73, 148.23, 146.36, (OC_{arom}); 135.4 (d, $^3J_{PC}$ = 14 Hz, CH=N); 132.2, 131.81, 129.3 (C_{arom}); 119.9, 115.07, 113.57, 112.78, 108.08 (HC_{arom}); 68.22, 68.24 (OCH_2); 56.05, 55.05 (OCH_3); 36.24 ($ArCH_2$); 31.70 (d, $^2J_{PC}$ = 10 Hz, NCH_3); 25.7, 25.1 (CH_2). ^{31}P NMR ($CDCl_3$) δ: 75.9. ES-MS m/z: 1171.5 $(M + H)^+$, 1193.5 $(M + Na)^+$, 1209.5 $(M + K)^+$.

X-ray crystallography

A solution of **1** in toluene was heated until dissolution and cooled slowly to room temperature to afford crystals of the $1\cdot(toluene)_2$ complex, suitable for X-ray analysis. Intensity data were measured at 293 K on a Cappa-CCD Nonius diffractometer using graphite-monochromated Mo-Kα radiation. The structure was solved using direct methods and refined by full-matrix least-squares on F^2 using SHELXTL.[9] Table 2 provides a summary of the crystal data, data collection and refinement parameters.

CCDC reference number 440/108. See http://www.rsc.org/suppdata/nj/1999/545/ for crystallographic files in .cif format.

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