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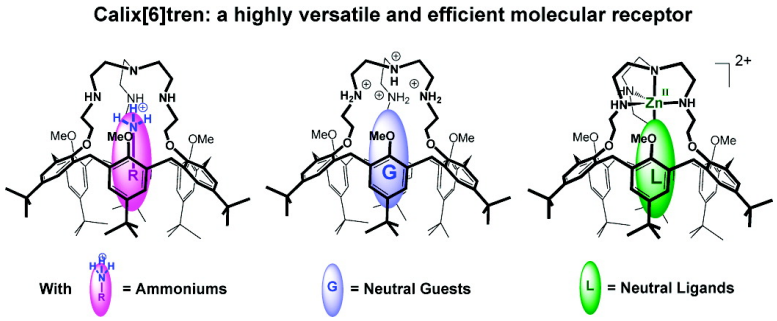

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Polarizing a Hydrophobic Cavity for the Efficient Binding of Organic Guests: The Case of Calix[6]tren, a Highly Efficient and Versatile Receptor for Neutral or Cationic Species

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Abstract: The host−guest properties of calix[6]tren **1** have been evaluated. The receptor is based on a calix[6]arene that is covalently capped at the narrow rim by a tren unit. As a result, the system presents a concave hydrophobic cavity with, at its bottom, a grid-like nitrogenous core. Despite its well-defined cavity and opening to the outside at the large rim, **1** did not behave as a good receptor for neutral molecules in chloroform. However, it exhibited efficient endo-complexation of ammonium guests. By contrast, the *per*-protonated host, **1.4H**$^{+}$, behaved as a remarkable receptor for small organic molecules. The complexation is driven by a strong charge−dipole interaction and hydrogen bonds between the polar guest and the tetracationic cap of the calixarene. Finally, coordination of Zn^{2+} to the tren core led to the asymmetrization of calixarene cavity and to the strong but selective endo-binding of neutral ligands. This study emphasizes the efficiency of a receptor presenting a concave hydrophobic cavity that is polarized at its bottom. The resulting combination of charge−dipole, hydrogen bonding, CH−π, and van der Waals interactions highly stabilizes the supramolecular architectures. Also, importantly, the tren cap allows the tuning of the polarization, offering either a basic (**1**), a highly charged and acidic (**1.4H**$^{+}$), or a coordination (**1.Zn**$^{2+}$) site. As a result, the system proved to be highly versatile, tunable, and interconvertible in solution by simple addition of protons, bases, or metal ions.

Introduction

Molecular receptors are the heart of supramolecular chemistry.[1] They allow the reversible assembly of discrete entities through the establishment of multiple weak interactions between the different components. These phenomena are fundamental in biology. In enzymes, for example, formation of the enzyme−substrate complex is the key for the selectivity and efficiency of the biocatalysis. Also, the knowledge of the major sites of interaction and their relative geometrical positioning is essential for the understanding of the outstanding efficiency of the recognition processes.[2] In the active site of enzymes, these processes, often if not always, combine nonpolar interactions for the recognition of a hydrophobic residue and electrostatic interactions such as charge−charge, charge−dipole, and including of course hydrogen bonding. In some cases also, a metal ion is a ligating center allowing the coordination of the substrate or an intermediate in the catalytic cycle.[3] This is beautifully illustrated by Zn enzymes such as carboxypeptidase.[4] Hence, combining a donor or acceptor site to a hydrophobic pocket is a recurrent strategy encountered in natural systems to efficiently and selectively bind a guest. All this information from Nature has been a major source of inspiration for chemists. On one hand, it has been widely used for the design of new inhibitors. On the other hand, it motivated chemists for the design of artificial hosts useful for selective recognition or catalysis.[1,5]

Among the various molecular platforms that can be used for the construction of such receptors, macrocycles presenting

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(1) (a) Lehn, J.-M. *Supramolecular Chemistry*; Wiley-VCH: Weinheim, 1995. (b) Steed, J. W.; Atwood, J. L. *Supramolecular Chemistry*; Wiley: Chichester, 2000. (c) Reviews on molecular recognition: *Chem. Rev.* **1997**, *97*, 1231−1734.
(2) Dugas, H. *Bioorganic Chemistry: A Chemical Approach to Enzyme Action*, 3rd ed.; Springer-Verlag: New York, 1996; pp 252−387.
(3) (a) Lippard, S. J.; Berg, J. M. *Principles of Bioinorganic Chemistry*, University Science Books: Mill Valley, CA, 1994. (b) Holm, R. H.; Kennepohl, P.; Solomon, E. I. *Chem. Rev.* **1996**, *96*, 2239−2314.
(4) (a) Lipscomb, W. N.; Sträter, N. *Chem. Rev.* **1996**, *96*, 2375−2433. (b) Auld, D. S. *Metal Sites in Proteins and Models*, In *Structure and bonding, Vol. 89*, Sadler, P. J. Ed.; Springer-Verlag: Berlin-Heidelberg, 1997; pp 29−50.
(5) (a) Schneider, H.-J. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1417−1436. (b) Davis, A. P.; Wareham, R. S. *Angew. Chem., Int. Ed.* **1999**, *38*, 2978−2996. (c) Motherwell, W. B.; Bingham, M. J.; Six, Y. *Tetrahedron* **2001**, *57*, 4663−4686.

multiple aromatic units have been widely used. Cavitands[6] such as resorcinarenes,[7] cyclotriveratrilenes,[8] calixarenes,[9] and cyclophanes[10] have been largely developed since the last two decades. Combining such a subunit presenting aromatic walls with a site that bears heteroatoms can lead to an efficient heteroditopic receptor.

We have chosen calix[6]arenes to play the role of the hydrophobic host. Indeed these macrocyclic systems have a size well-adapted for the selective inclusion of small organic molecules,[11] which is not the case of calix[4]arenes that have mostly been used as a platform for the preorganization of a binding site outside of the cavity.[12] However, calix[6]arenes suffer from their great flexibility that must be restricted. Indeed, they must be constrained in the cone conformation to present a concave cavity suitable to include a guest. The second requirement is the implementation of a polarized site. Thus, we have developed different strategies, all based on the introduction of nitrogen functionalities at the narrow rim of the calixarene (Figure 1). For biomimetism purpose in the bioinorganic field, we have first developed systems presenting three coordinating arms[13] such as imidazole groups that, upon binding to a transition metal ion (such as Cu,[14] Zn,[15] Co, Ni[16]), close the entrance on one side and constrain the calixarene cavity in a cone open to outside at the large rim. The so-called *funnel* complexes proved to be remarkable receptors for small organic ligands. However, these systems suffer from possible decoordination leading to the collapse of the conic edifice and the loss of its binding properties. We have also found that the capping of the calix[6]arene cavity can be obtained by ion pairing.[17] Hence, three primary ammonium arms covalently linked at the narrow rim can be efficiently self-assembled by the counteranions in solvents of medium polarity such as chloroform. We showed that the resulting highly polarized edifice quite remarkably behaves as a receptor for neutral molecules presenting a dipolar moment. These supramolecular receptors, however, suffer from disassembly in polar solvents. A way to remedy the weaknesses of the two former systems is to covalently link an aza cap to the calixarene. The first member of the calix[6]azacryptand family that we have described is calix[6]tren **1** (Figure 1).[18] It presents a tren moiety covalently bound to three phenolic units of the calixarene, closing thereby the bottom of the conic cavity by a grid composed by four nitrogen atoms and ethylene groups. Two other members of this new family have been recently described: calix[6]TAC that revealed outstanding properties for hosting ammoniums[19] and calix[6]-PN_3 cryptand,[20] whose binding properties are currently explored.

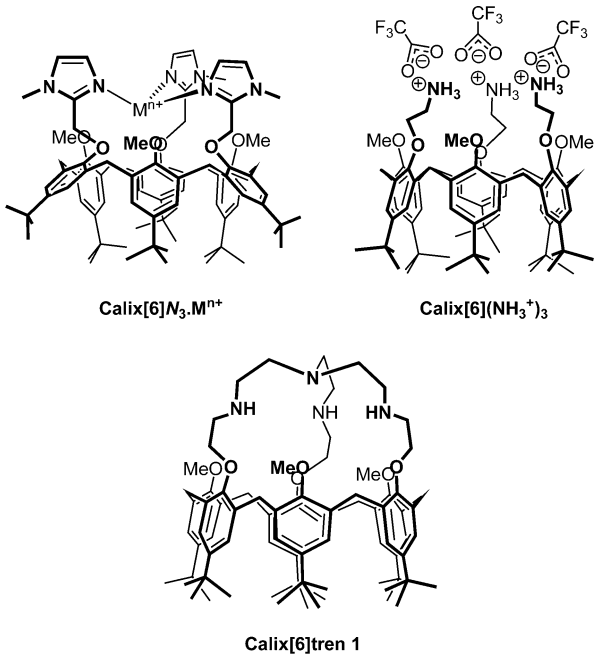


Figure 1. Three calix[6]aza-hosts illustrating different strategies for the capping of the calixarene structure.

Here, we report on the receptor behavior of calix[6]tren that proves to be highly versatile. We describe three different ways of polarizing the edifice. As a result, the host properties of this cryptand can be tuned by the environment. This offers a wide spectrum of binding properties, as the calix[6]azacryptand can respond to cationic species such as ammoniums or metal ions and/or to a variety of neutral molecules as different as acetaldehyde and benzylamine.

Results

A Receptor for Small Ammoniums. The ability of calix[6]tren **1** (Figures 1 and 2a) to include an organic guest was investigated by ^{1}H NMR spectroscopy in chloroform solutions. Whereas cryptand **1** appeared insensitive to neutral molecules

(6) (a) Cram, D. J.; Cram, J. M. *Container Molecules and Their Guests, Monographs in Supramolecular Chemistry*; The Royal Society of Chemistry: Cambridge, 1994. (b) Hof, F.; Craig, S. L.; Nuckolls, C.; Rebek, J., Jr. *Angew. Chemie, Intl. Ed.* **2002**, *41*, 1488−1508. (c) Warmuth, R.; Yoon, J. *Acc. Chem. Res.* **2001**, *34*, 95−105. (d) Higler, I.; Timmerman, P.; Reinhoudt, D. N. *Eur. J. Org. Chem.* **1998**, 2689−2702.
(7) (a) Rudkevich, D. M.; Rebek, J., Jr. *Eur. J. Org. Chem.* **1999**, *9*, 1991−2005. (b) Jasat, A.; Sherman, J. C. *Chem. Rev.* **1999**, *99*, 931−967.
(8) (a) Collet, A. *Tetrahedron* **1987**, *43*, 5725−5759. (b) Collet, A.; Dutasta, J.-P.; Lozach, B.; Canceill, J. *Top. Curr. Chem.* **1993**, *165*, 103−129.
(9) (a) Gutsche, C. D. *Calixarenes, Monographs in Supramolecular Chemistry*; The Royal Society of Chemistry: Cambridge, 1989. (b) Gutsche, C. D. *Calixarenes Revisited, Monographs in Supramolecular Chemistry*; Stoddart, J. F., Ed.; The Royal Society of Chemistry: Cambridge, U.K., 1998. (c) Arduini, A.; Secchi, A.; Pochini, A. *J. Org. Chem.* **2000**, *65*, 9085−9091. (d) *Calixarenes 2001*; Asfari, Z., Böhmer, V., Harrowfield, J., Vicens, J., Eds.; Kluwer Academic Publishers: Dordrecht, Holland, 2001. (e) Mandolini, L.; Ungaro, R., Eds. *Calixarenes in Action*; Imperial College Press: London, 2000. (f) Ikeda, A.; Shinkai, S. *Chem. Rev.* **1997**, *97*, 7, 1713−1734.
(10) Diederich, F. *Cyclophanes, Monographs in Supramolecular Chemistry*; The Royal Society of Chemistry: Cambridge, 1994.
(11) Redshaw, K. *Coord. Chem. Rev.* **2003**, *244*, 45−70.
(12) Except in the case of molecular capsules resulting from the association of two calix[4]arene units. See for example: Shivanyuk, A.; Saadioui, M.; Broda, F.; Thondorf, I.; Vysotsky, M. O.; Rissanen, K.; Kolehmainen, E.; Böhmer, V. *Chem. Eur. J.* **2004**, *10*, 2138−2148. Rebek, J. *Chem. Commun.* **2000**, 637−643.
(13) Sénèque, O.; Rondelez, Y.; Le Clainche, L.; Inisan, C.; Rager, M.-N.; Giorgi, M.; Reinaud, O. *Eur. J. Inorg. Chem.* **2001**, 2597−2604.
(14) (a) Blanchard, S.; Le Clainche, L.; Rager, M.-N.; Chansou, B.; Tuchagues, J.-P.; Duprat, A. F.; Le Mest, Y.; Reinaud, O. *Angew. Chem., Int. Ed.* **1998**, *37*, 2732−2735. (b) Le Clainche, L.; Giorgi, M.; Reinaud, O. *Eur. J. Inorg.* **2000**, 1931−1933. (c) Le Clainche, L., Rondelez, Y.; Sénèque, O.; Blanchard, S.; Campion, M.; Giorgi, M.; Duprat, A. F.; Le Mest, Y.; Reinaud, O. *Comptes Rendus Acad. Sci., Chimie, Série IIc* **2000**, *3*, 811−819. (d) Rondelez, Y.; Sénèque, O.; Rager, M.-N.; Duprat, A. F.; Reinaud, O. *Chem. Eur. J.* **2000**, *6*, 4218−4226. (e) Rondelez, Y.; Rager, M.-N.; Duprat, A.; Reinaud, O. *J. Am. Chem. Soc.* **2002**, *124*, 1334−1340.
(15) (a) Sénèque, O.; Rager, M.-N.; Giorgi, M.; Reinaud, O. *J. Am. Chem. Soc.* **2000**, *122*, 6183. (b) Sénèque, O.; Rager, M.-N.; Giorgi, M.; Reinaud, O. *J. Am. Chem. Soc.* **2001**, *123*, 8442−8443. (c) Sénèque, O.; Giorgi, M.; Reinaud, O. *Chem. Commun.* **2001**, 984−985. (d) Sénèque, O.; Giorgi, M.; Reinaud, O. *Supramol. Chem.* **2003**, *15*, 573−580.
(16) Sénèque, O.; Campion, M.; Giorgi, M.; Le Mest, Y.; Reinaud, O. *Eur. J. Inorg.* **2004**, 1817−1826.
(17) Darbost, U.; Giorgi, M.; Hucher, N.; Jabin, I.; Reinaud, O. *Supramol. Chem.* **2005**, *17*, 243−250.
(18) Jabin, I.; Reinaud, O. *J. Org. Chem.* **2003**, *68*, 3416−3419.
(19) Darbost, U.; Giorgi, M.; Reinaud O.; Jabin, I. *J. Org. Chem.* **2004**, *69*, 4879−4884.
(20) Zeng, X.; Hucher, N.; Reinaud, O.; Jabin, I. *J. Org. Chem.* **2004**, *69*, 6886−6889.

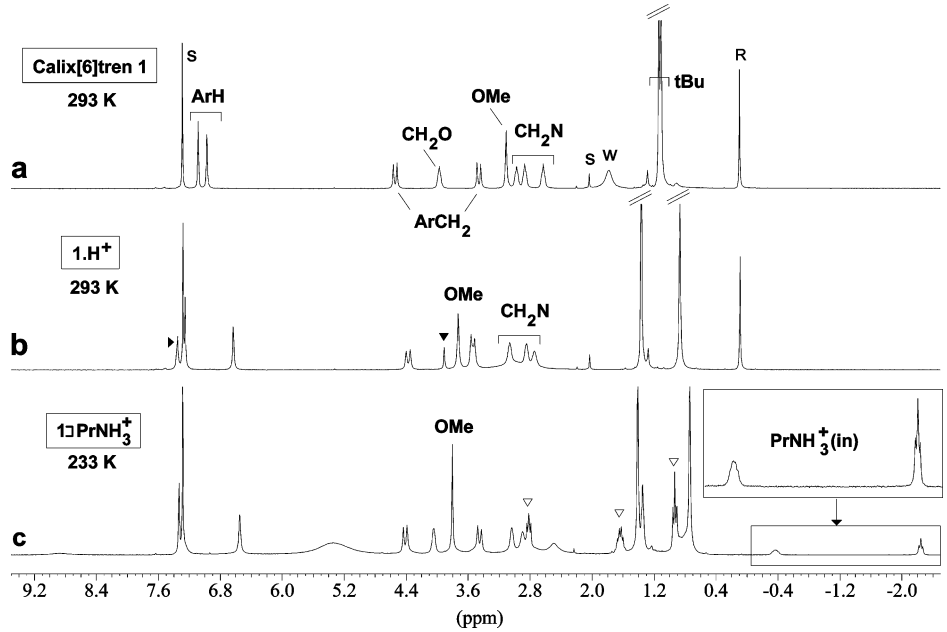


Figure 2. ^{1}H NMR spectra (300 MHz, $CDCl_3$) of calix[6]tren **1** before (a) and after (b) reaction with $BnNH_3^+Cl^-$, 293 K; ▼: signals of free $BnNH_2$. (c) After addition of TFA (4 equiv) and $PrNH_2$ (5 equiv), 233 K; ∇: signals of free $PrNH_3^+$. Residual solvents, water, and reference have been labeled "S", "W", and "R" respectively.

in this solvent, it readily interacted with ammoniums. First of all, calix[6]tren **1** was reacted with excess solid benzylammonium chloride in $CDCl_3$. The resulting solution spectrum displayed new resonances that are characteristic of a new calixarene species presenting C_{3v} symmetry (Figure 2b). Beside resonances denoting the extraction of exactly 1 equiv of benzylamine, no peak in the high field region could be detected. A downfield shift was observed for the methylene protons situated in α-position to the nitrogen atoms (δ_{CH2} = 2.72, 2.83 and 3.04 vs 2.58, 2.82, 2.92 for **1**). This can be rationalized by the monoprotonation by $BnNH_3^+$ of the aza-cap that induces a conformational change of the calixarene structure. Whereas calix[6]tren **1** adopted a straight cone conformation ($\Delta\delta_{tBu}$ = 0.02 ppm and δ_{OCH3} = 3.05 ppm), **1**.$\mathbf{H}^+$ undergoes a more flattened cone conformation due the rejection of the methoxy groups away from the cone (δ_{OCH3} = 3.71), the aromatic units being alternatively in *in* and *out* position ($\Delta\delta_{tBu}$ = 0.49 ppm). Upon decreasing the temperature down to 233 K, no new resonance in the high field region was observed. The calixarene signature only broadened,[21] indicating a restricted conformational mobility that is more pronounced for the *in*-aromatic subunits. Such a behavior has been previously observed with other calix[6]arene derivatives and denotes an empty cavity.[14d,e] By contrast, upon the addition of 1 equiv of propylammonium picrate ($PrNH_3^+Pic^-$) into a $CDCl_3$ solution of **1**, new resonances in the high field region attested to the partial inclusion of the ammonium at 233 K (Table 1). A careful analysis of the spectrum revealed the presence of two species in a ca. 80:20 ratio. The major one was the empty monoprotonated calix[6]tren **1.H**$^+$, whereas the other corresponded to the endo-complex **1**⊃**PrNH$_3^+$**, with a 1:1 calix/ammonium stoechiometry. At room temperature, an average spectrum was observed, showing fast exchange of the amine between two monoprotonated calixarene species.[21] Hence, the addition of 1 equiv of ammonium to calix[6]tren **1** resulted in the competitive endo-complexation of

(21) See the Supporting Information.

Table 1. Relative Affinities of the Ammonium Salts toward Host **1** and NMR Chemical Induced Upfield Shifts (CIS) Observed through Their Endo-Complexation in $CDCl_3$

			CIS (ppm)[b]			
entry	ammonium picrates	relative affinity[a]	α	β	γ	δ
1	$EtNH_3^+Pic^-$	1	−2.47	−2.61	-	-
2	$PrNH_3^+Pic^-$	2.95	n.d.[c]	−2.00	−3.17	-
3	nBuNH$_3^+$Pic$^-$	0.11	−1.55	−1.34	−3.43	−2.88
4	$Me_2NH_2^+Pic^-$	0.05	−2.59	-	-	-

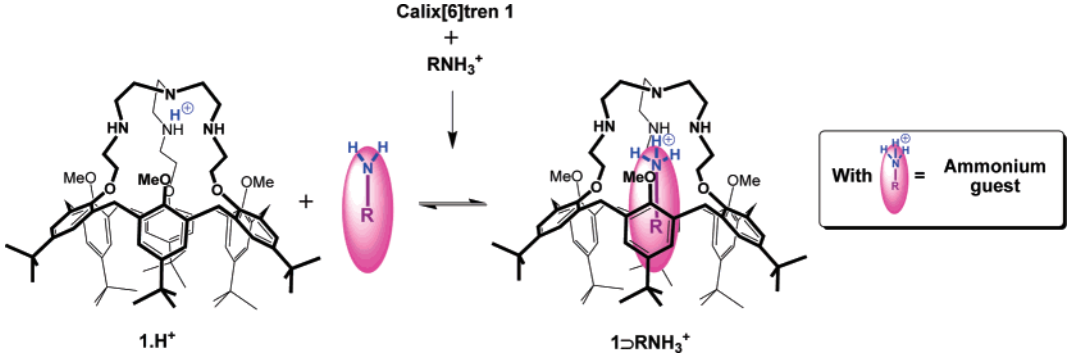
[a] Defined as $[RNH_3^+{}_{in}]/[EtNH_3^+{}_{in}] \times [EtNH_2(H^+)_T]/[RNH_2(H^+)_T]$ where indexes "in" and "T" stand for "included" and "total amount", respectively. Errors estimated ±10%. [b] CIS defined as $\Delta\delta = \delta$(complexed ammonium) − δ(free ammonium). α, β, γ, δ refer to the relative position of the protons to the charged nitrogen atom of the ammonium (i.e. $C_\delta-X_\gamma-X_\beta-X_\alpha-NH_3^+$). [c] Not determined due to overlapping of the host and guest signals.

PrNH$_3^+$ and protonation of the host tren cap (Scheme 1). Similarly, a ca. 1:9 mixture of **1.H**$^+$/**1**⊃**PrNH$_3^+$** was obtained by direct introduction of trifluoroacetic acid (TFA, 4 equiv) and propylamine (5 equiv) into a $CDCl_3$ solution of **1** (see Figure 2c). In all cases, the equilibrium **1**⊃**PrNH$_3^+$** ⇄ **1.H**$^+$ + **PrNH$_2$** could be totally displaced in favor of the formation of inclusion complex **1**⊃**PrNH$_3^+$** by subsequent addition of excess $PrNH_2$. A methoxy resonance at 3.80 ppm showed that **1**⊃**PrNH$_3^+$** adopts the classical flattened cone conformation ($\Delta\delta_{tBu}$ = 0.67 ppm) that is even more pronounced than for **1.H**$^+$ due to its cavity filling.[13]

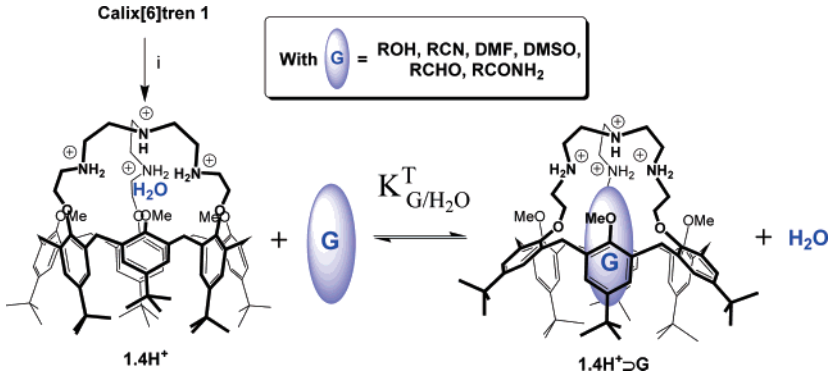
Such a competitive behavior between the binding of a small ammonium guest and the protonation of the host is due to the strong basicity of the tren cap. Indeed, complexes **1**⊃**PrNH$_3^+$** could be also described as resulting from the inclusion of an amine into the monoprotonated host according to the formulation **1.H**$^+$⊃**PrNH$_2$.**

Similar endo-complexes were obtained with the picrate salts of $EtNH_3^+$, nBuNH$_3^+$ or $Me_2NH_2^+$, whereas with $Me_4N^+Pic^-$, no inclusion could be detected. The relative affinities of these ammoniums toward host **1** were determined at 233 K through ^{1}H NMR competitive binding experiments (See the Experimen-

Scheme 1. Complexation of Ammonium Salts by Calix[6]tren **1** in $CDCl_3$



Scheme 2. Synthesis and Host−Guest Properties of **1.4H**$^{+a}$



[a] (i) TFA, CH_2Cl_2, 80 %.

tal Section for the detailed procedures) and the chemical induced shifts (CIS) of the guest proton resonances are reported in Table 1. The protons in γ-positions of the charged nitrogen atom possess the highest shift values, which suggests that they sit in the center of the hydrophobic cavity (entries 2 and 3). The affinity decreases according to the sequence $PrNH_3^+$ > $EtNH_3^+$ > nBuNH$_3^+$ and from primary to secondary ammonium salts. Hence, the stabilization of the host−guest adducts **1⊃RNH$_3^+$** obviously results from a combination of a stabilizing hydrogen bonding network between the included ammonium and the tren cap and a good spatial fit allowing favorable CH−π interactions within the aromatic cavity.[19]

A Tetracationic Receptor for the Complexation of Neutral Molecules. The fully protonated calix[6]tren **1.4H**$^+$ was prepared by reacting trifluoroacetic acid (TFA) in excess with **1** in dichloromethane. Crystallization out of an acetonitrile/ether mixture yielded pure **1.4H**$^+$ (80%) with four trifluoroacetate counteranions as confirmed by elemental analyses (Scheme 2).

The ^{1}H NMR profile of compound **1.4H**$^+$ ($CDCl_3$, 293 K, Figure 3a) is again characteristic of a C_{3v} symmetrical cone conformation that is only slightly flatter than neutral cryptand **1** (δ_{OMe} = 3.07 ppm and $\Delta\delta_{tBu}$ = 0.29). Dissymmetrical broadening of the ^{1}H NMR spectrum occurred at low temperature (233 K) attesting to an empty cavity.[21] Whereas the introduction of a primary amine ($PrNH_2$, 5 equiv) led to the deprotonation of **1.4H**$^+$ with quantitative formation of the above-described monocationic complex **1⊃PrNH$_3^+$**, the addition of a few molar equivalents of nonbasic but polar neutral molecules (G) gave rise to the corresponding host−guest adducts **1.4H**$^+$**⊃G**.

As a representative example, the ^{1}H NMR spectrum of **1.4H**$^+$**⊃EtOH** is displayed in Figure 3b. The NMR profile indicates a C_{3v} symmetry. A normal methoxy resonance at 3.73 ppm for the anisole units shows that they have been expelled from the cavity that became flattened ($\Delta\delta_{tBu}$ = 0.50 ppm). The resonances of free EtOH were very broad. At low temperature, two resonances in the high field region appeared, showing the presence of 1 mol equiv of ethanol included in the aromatic cavity (Figures 3c−e). In the 253−233 K temperature range, a coalescence phenomenon affected the resonances of the complex. At 213 K, a large splitting of the Ar*H* and C*H*$_2$ host resonances was observed whereas the EtOH guest displayed one sharp triplet at δ = −1.78 ppm for its methyl group but two signals at 0.38 and 0.16 ppm for its methylene protons. This phenomenon is due to the freezing of the well-known helical twisting of the three arms of the cap, allowing diastereodifferentiation of the aromatic and methylenic protons of the C_3 edifice.[22,15d,13]

All these observations show the quantitative formation of the endo-complex **1.4H**$^+$**⊃EtOH** with an *in* and *out* exchange of EtOH that is fast at room temperature relative to the NMR time scale but slow at low T. A similar host−guest behavior was observed with a wide variety of small neutral polar molecules (Scheme 2, Table 2). Hence, complexation of nitriles, amides, and even acetaldehyde was observed at low T upon the addition of only a few molar equivalents of guest G in chloroform. DMF, DMSO, and acetamide appeared remarkably strongly complexed since the corresponding sharp signals were observed even at room temperature, which shows a slow exchange rate.[23] On the other hand, no endo-complexation of the bulkier benzamide

(22) Blanchard, S.; Rager, M.-N.; Duprat; A. F.; Reinaud, O. *New J. Chem.* **1998**, 1143−1146.
(23) In this system, the exchange process must be dissociative (see ref 14e). Hence, the stronger bound, the slower the guest exchange.

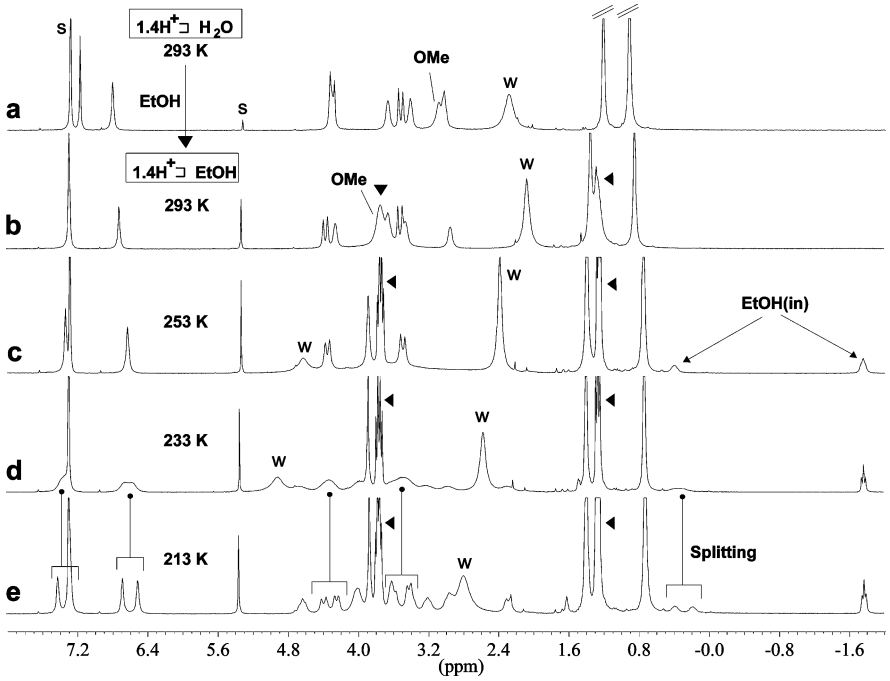


Figure 3. ^{1}H NMR spectra (300 MHz, $CDCl_3$), a: host **1.4H**$^+$ before (a) and after (b−e) addition of EtOH. EtOH(in): included ethanol molecule. ▼: free EtOH (8 equiv). Residual solvents and water have been labeled "S" and "W", respectively.

Table 2. Equilibrium Constants $K^T_{G/H2O}$ and Chemical Induced Upfield Shifts (CIS) Observed through Endo-Complexation of Neutral Organic Molecules (G) by Host 1.4H$^+$ in $CDCl_3$

				CIS (ppm)[b]		
entry	G	$K^{223}_{G/H2O}$[a]	$K^{293}_{G/H2O}$[a]	α	β	γ
1	DMF	680	11.6	−0.98	-	−2.93[c]
2	$AcNH_2$	3030	6.5	-	−3.14	-
3	EtOH	3100	1.7	−3.43[d]	−3.03	-
4	MeOH[e,f]	-	-	−3.26[f]	-	-
5	MeCN	-	-	-	−3.20	-
6	EtCN	-	-	-	−3.34[g]	−3.08[g]
7	MeCHO	-	-	−3.72	−3.16	-
8	DMSO			-	−2.91[h]	-
9	acrylamide	-	-	-	−2.29	−3.54, − 3.21

[a] Defined as [**1.4H**$^+$⊃**G**][H_2O]/[**1.4H**$^+$⊃**H_2O**][G]. Errors estimated ±15%. [b] CIS calculated at 223 K and defined as $\Delta\delta = \delta$(complexed G) − δ(free G). α, β, γ, δ refer to the relative position of the protons to the oxygen atom or the nitrogen atom in the case of nitriles. [c] Average value of the two unequivalent methyl groups. [d] Average value of the diastereotopic protons. [e] The signal of the included OH proton has been identified at − 0.29 ppm (CIS = 3.45 ppm) through a COSY experiment. [f] Determined at 213 K. [g] Determined at 243 K. [h] Determined at 293 K.

could be detected. The guest CIS values (Table 2)[24] show that the polar guests are deeply included in the heart of the cavity. Noteworthy is the different CIS values measured for the CHO protons of DMF and acetaldehyde (entries 1 and 7). This denotes a different binding mode for these two guests, possibly due to hydrogen bonding in the cap for the former, not for the latter.

In view of the large overall charge of the host (4+), we suspected water molecules to participate to the guest exchange. To determine their exact number, a set of two measurements of the T-dependence of the equilibrium between host **1.4H**$^+$, H_2O, DMF, and **1.4H**$^+$⊃**DMF** was undertaken.[25] Curve fitting for a van't Hoff plot[21] clearly showed that the binding of one organic guest is associated to the release of one water molecule according to the equilibrium depicted in Scheme 2. The corresponding thermodynamic parameters ΔH and ΔS were determined for G = DMF. An enthalpy value of $\Delta H = -32(\pm 2)$ kJ·mol^{-1} shows an exothermic process that favors the binding of the organic guest *in* the cavity at low temperature. The associated negative entropy, $\Delta S = -88(\pm 5)$ J·K^{-1}·mol^{-1}, indicates an increasing degree of organization in **1.4H**$^+$⊃**DMF** compared to "free" host **1.4H**$^+$. As shown above, the binding of G, which induces the release of H_2O, leads to a flatter alternate cone conformation that may be associated to a loss of freedom of the system. Indeed, the water molecule in **1.4H**$^+$ most likely sits in the polyammonium cap, the calixarene cavity being essentially empty and thus more flexible. Some equilibrium constants were determined at 293 and 223 K. For G = EtOH and $AcNH_2$, $K^T_{G/H2O}$ were deduced from ^{1}H NMR competitive binding experiments with DMF and $K^T_{DMF/H2O}$ (see Table 2). In agreement with a negative enthalpic contribution for the equilibria, all the values show that the affinity of **1.4H**$^+$ for an organic guest G compared to water increases at low T. At 293 K, this affinity decreases with the dipolar moment of the guest DMF ($\mu = 3.9$ D) > $AcNH_2$ (3.7) > EtOH (1.7) (Table 2, entries 1, 2, and 3), and no complexation of apolar molecules such as alcanes could be observed. This is suggestive of an important contribution of the charge−dipole interaction between the cationic cap and G for the stabilization of the supramolecular edifice, as previously observed in a closely related system.[17] At low-temperature, however, protic guests are better bound than DMF. This is attributable to the participation of hydrogen bonding to their complexation from which stems an even more negative enthalpic value.

Such an endo-complexation of neutral molecules by receptor **1.4H**$^+$ is quite remarkable in view of the lack of response of neutral cryptand **1** under the same experimental conditions. It

(24) In some cases, the attribution of the signals of the included guest was confirmed through 2D NOESY experiments. When TFA was replaced by another acid of close pK_a, i.e., picric acid, similar endo-complexation results were obtained.

(25) Such a study was unsuccessful in the case of **1**⊃**RNH_3**$^+$due to the impossibility to determine with precision the water concentration.

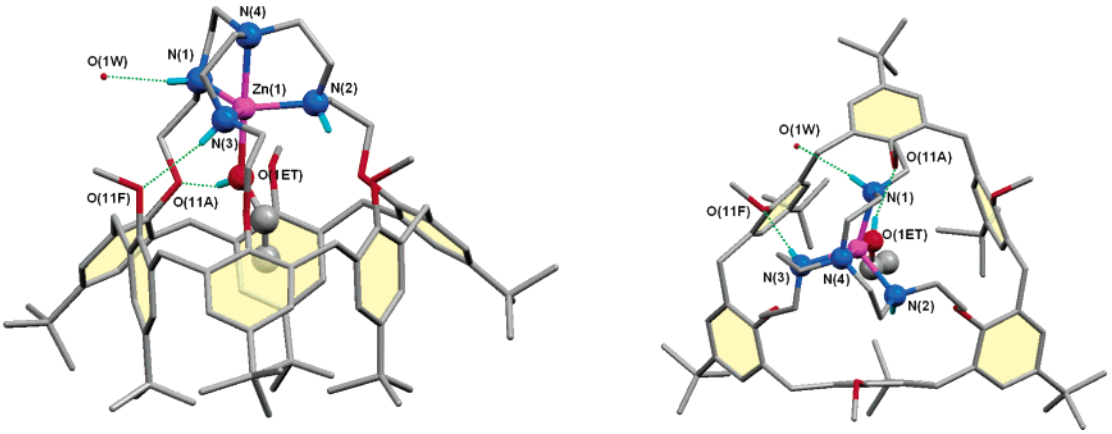


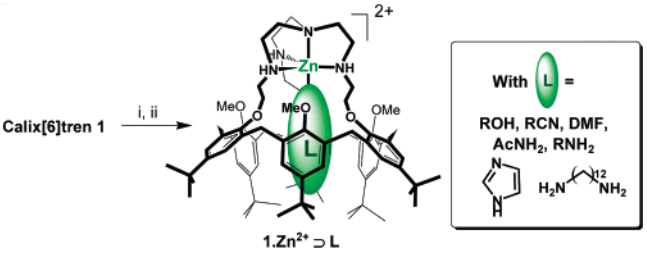
Figure 4. Crystal structures of Zn complex **1.Zn^{2+}⊃EtOH** (left: side view, right: top view). The location of the hydrogen atoms of the amino groups and the ethanol molecule was calculated. Other hydrogen atoms, perchlorate counteranions, and solvents of crystallization were omitted for clarity. Selected bond distances (Å) and angles (deg): [**1.Zn^{2+}⊃EtOH**, Zn(1)−N(3) 2.036(5), Zn(1)−N(2) 2.066(5), Zn(1)−N(1) 2.092(5), Zn(1)−N(4) 2.178(4), Zn(1)−O(1ET) 2.067(5), O(1ET)−O(11A) 2.684(5), N(1)−O(W1) 3.065(5), N(3)−O(11F) 3.134(5), O(1ET)−H−O(11A) 157.8(2), N(1)−H-O(W1) 170.9(2), N(3)−H-O(11F) 171.2(2), N(3)−Zn−N(2) 112.8(2), N(3)−Zn−N(1) 123.9(2), N(2)−Zn−N(1) 119.7(2), N(3)−Zn−N(4) 82.2(2), N(2)−Zn−N(4) 84.9(2), N(1)−Zn−N(4) 84.1(2)].

is rationalized by the electrostatic charge−dipole contribution as the driving force of their inner-cavity binding, CH−π interactions within the cavity, and an additional hydrogen bonding network between the protonated cap and the more basic guests (alcohols and amides). Such a synergistic effect was recently highlighted by us with a calix[6]tris-ammonium receptor that was self-assembled by ion pairing (Figure 1).[17] Indeed, the latter displayed host features similar to **1.4H**$^+$ with, however, much lower binding constants. For DMF at 293 K, it was almost 30 times lower ($K^{293}_{DMF/H2O}$ = 0.43) than with new cryptand **1.4H**$^+$ with a similar enthalpic contribution ($\Delta H = -30$ kJ·mol^{-1}) but a more negative entropy ($\Delta S = -107$ J·K^{-1}·mol^{-1}). Hence the improvement of the host affinity obtained with the covalently capped system stems from a much better preorganization that lowers the entropic cost linked to the binding of an organic guest into the calixarene cavity.

A Heteroditopic Receptor for Metal Ions and Neutral Molecules. The ability of calix[6]tren **1** to coordinate various divalent metal ions such as Zn^{2+}, Cu^{2+}, and Cd^{2+} was explored.[26,27] In all cases, it led to *funnel* complexes with the metal ion coordinated by the tren cap and an exchangeable neutral molecule bound to the metal in the calixarene pocket, as depicted in Scheme 3. We have recently described the synthesis, X-ray, and solution structure of the first Zn^{2+} complex based on calix[6]tren **1**.[26] It displayed a five-coordinate metal ion strongly bound to the tren cap in an asymmetrical environment and to a guest MeCN ligand (**1.Zn^{2+}⊃MeCN**, Scheme 3). In view of these preliminary results, we have undertaken a more detailed study on the host/guest behavior of this dicationic system.

The X-ray structure of the dicationic complex **1.Zn^{2+}⊃EtOH** was obtained through crystallization out of a $CHCl_3$ solution containing a trace of EtOH (Figure 4). The calixarene core stands in a flattened alternate cone conformation with the three *tert*-butyl groups belonging to the anisole units directed toward the entrance of the cavity. The Zn ion is coordinated to the N_4 core of the tren cap and to the guest EtOH molecule. The geometry is trigonal bipyramidal with some tetragonal distortion ($\tau = 0.79$).[28] The Zn−N average distances for the trigonal base of the pyramid are 2.070 Å, the tertiary N atom capping the system being more loosely bound to the metal ion [$d(Zn_1-N_4)$ = 2.178 Å] than the EtOH guest [$d(Zn_1-O_{1Et})$ = 2.067 Å]. The EtOH guest ligand is stabilized through CH−π interactions [d(C···C=C) = 3.8 Å] and by a strong hydrogen bond to one oxygen belonging to the calix funnel [$d(O_{1Et}\cdots O_{11A})$ = 2.684 Å]. Moreover, weak hydrogen bonds take place between the capping secondary amino groups and either a water molecule or a phenoxyl oxygen atom. The three amino arms wrapping the Zn ion adopt an asymmetric conformation with two coordinated arms presenting a relative helical orientation opposite to each other.

Scheme 3. Preparation and Host−Guest Behavior of Complex **1.Zn^{2+}⊃L**[a]



[a] (i) $Zn(ClO_4)_2(H_2O)_6$, CH_2Cl_2, MeOH, 69%.[26] (ii) $CDCl_3$, L.

1.Zn^{2+}⊃EtOH was characterized in solution as well. Upon the addition of a few molar equivalents of EtOH to a $CDCl_3$ solution of Zn-complex **1.Zn^{2+}**,[29] the ^{1}H NMR analyses showed a broad resonance at room temperature[21] that became a sharp triplet at low T ($\delta_{CH3} = -1.64$ ppm, see Figure 5a). The ^{1}H NMR signature of the host structure attested to a dissymmetric conformation (three methoxy resonnances at 3.78, 3.88 and 3.94 ppm), in agreement with the solid-state structure (Figure 4).[30]

(26) Darbost, U.; Zeng, X.; Rager, M.-N. Giorgi, M.; Jabin, I.; Reinaud, O. *Eur. J. Inorg. Chem.* **2004**, 4371−4374.
(27) Calix[6]tren Cu(II) complexes and the study of their redox behavior have been the subject of a different paper: Izzet, G.; Douziech, B.; Prangé, T.; Tomas, A.; Jabin, I.; Le Mest, Y.; Reinaud, O. *Proc. Natl. Acad. Sci. U.S.A.* **2005**, *102*, 6831−6836. Preliminary studies with Cd^{2+} showed that the corresponding complexes behave very similarly to the Zn^{2+} complexes (data not shown).
(28) Addison, A. W.; Rao, T. N.; Reedijk, J.; van Rijn, J.; Verschoor, G. C. *J. Chem. Soc., Dalton Trans.* **1984**, 1349−1356.
(29) The starting material for all the ^{1}H NMR studies was **1.Zn^{2+}⊃**MeOH, which is the resulting complex of the synthesis depicted in Scheme 3 and ref 26. For L = MeOH, $\delta_{CH3} = 0.72$ ppm (EXSY, 213 K, $CDCl_3$).

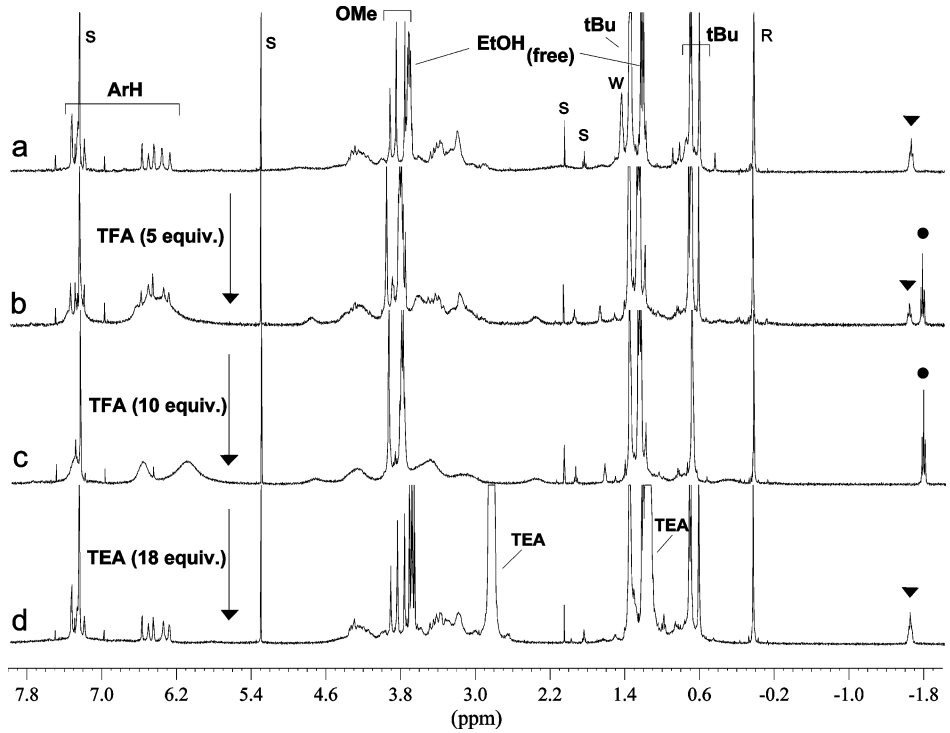


Figure 5. (a) ^{1}H NMR spectrum (400 MHz, 243 K, $CDCl_3$) of complex **1.Zn^{2+}⊃EtOH** in the presence of excess EtOH. (b) Mixture of **1.Zn^{2+}⊃EtOH** and **1.4H$^+$⊃EtOH** obtained upon addition of 5 equiv of TFA. (c) **1.4H$^+$⊃EtOH** obtained after subsequent addition of 10 equiv of TFA. (d) Regeneration of complex **1.Zn^{2+}⊃EtOH** by subsequent addition of TEA (18 equiv). ▼, ●: signals of the included EtOH methyl group of **1.Zn^{2+}⊃EtOH** and **1.4H$^+$⊃EtOH**, respectively. Residual solvents, water, and reference have been labeled "S", "W", and "R", respectively.

Table 3. Chemical Induced Upfield Shifts (CIS) Observed through Endo-Complexation of Neutral Organic Molecules (L) by Host **1.Zn^{2+}** in $CDCl_3$

			CIS (ppm)[b]		
entry	L	relative affinity[a]	α	*β*	*γ*
1	DMF	1	−1.03		−3.12[c]
2	$AcNH_2$	0.39	-	−2.83 [d]	-
3	MeOH	-	−2.78[e]	-	-
4	EtOH	0.41	n.d.[f]	−2.87	-
5	PrOH	-	n.d.[f]	−2.83	−2.91
6	MeCN	-	-	−3.18[e]	-
7	EtCN	-	-	−3.23[g,d]	−2.93[d]
8	$PrNH_2$	1610	n.d.[f]	−3.30	−2.94
9	octylamine	0.95		see ref 31	

[a] Defined as $[L_{in}]/[DMF_{in}] \times [DMF_T]/[L_T]$ and measured at 293 K (indexes "in" and "T" stand for "included" and "total amount", respectively). Errors estimated ±10%. [b] CIS calculated at 243 K and defined as $\Delta\delta = \delta$(complexed L) − δ(free L). α, *β*, *γ*, *δ* refer to the relative position of the protons to the coordinated heteroatom. [c] Average value of the two unequivalent methyl groups. [d] Determined at 253 K. [e] Determined at 213 K. [f] Not determined due to overlapping of the host and guest signals. [g] Average value of the diastereotopic protons.

Similar endo-complexation was also observed with a variety of other small molecules such as nitriles, amides or primary amines. The guest CIS values are given in Table 3.[31] The *δ* shift observed for the C*H*$_2$CH$_3$ protons of the included propylamine is 1.3 ppm more upfield shifted than in the case of **1⊃PrNH$_3^+$**. This indicates a different positioning in the cavity. Indeed, the Zn-coordinated amine is probably hydrogen-bonded to one (or two)[15a] oxygen(s) of the calixarene structure whereas the ammonium is hydrogen-bonded to the nitrogen cap, which moves it up away from the *π*-basic walls of the cavity. The relative affinities, which are reported in Table 3, emphasize the remarkable complexation of propylamine by **1.Zn^{2+}**. Also, interestingly, the low-temperature NMR spectra of complexes **1.Zn^{2+}⊃PrNH$_2$, EtCN** showed a large splitting of the resonances of the diastereotopic methylene protons of the guests.[21] This shows that the calix[6]tren-Zn receptor is chiral and that the asymmetry of the cryptand induced by the Zn coordination is efficiently transmitted through the calixarene host to the bound guest ligand.

The binding of larger basic guests such as imidazole, benzylamine, and dodecyldiamine was also observed[32] under experimental conditions for which the parent calix-N_3 systems (Figure 1) underwent decoordination of Zn. On the other hand, no coordination of bulkier molecules such as phenylethylamine or 4-(dimethylamino)pyridine could be detected, even at low temperature (213 K), which shows that the calixarene *funnel* controls the access to the metal center. Hence, the Zn-complexes **1.Zn^{2+}⊃L** appeared remarkably resistant and neither the addition of AcOH, MeI, Et_3N, nor a stronger base such as NBu_4OH[33] induced decoordination of Zn or deprotonation of the guest. This exceptional robustness is due to both a strong chelate effect and a cavity-controlled access to the metal center.

Facile and Reversible Interconversion of Receptors 1.4H$^+$ and 1.Zn^{2+}. The quantitative interconversion of the

(30) At high temperature (390 K), it was shown that complexes **1.Zn^{2+}⊃L** possess an average C_{3v} symmetrical ^{1}H NMR spectrum due to the fast pyramidal inversion of the coordinated nitrogen atoms, see ref 26.

(31) Resonances of the alkyl chain of the guest for **1.Zn^{2+}⊃CH$_3$(CH$_2$)$_7$NH$_2$** (EXSY, 293 K): $\delta_{CH3} = +0.63$ (CIS = −0.26), $\delta_{CH2} = -1.45, -1.38, -1.25, -0.82, -0.38, +0.46; +0.86$ ppm.

(32) The guest resonances were observed (at 260 K in $CDCl_3$) at 5.28 and 6.29 ppm for **1.Zn^{2+}⊃ImH**. Two sets of signal were obtained (at 293 K in $CDCl_3$) in the case of **1.Zn^{2+}⊃BnNH$_2$**: 5.94, 5.25 ppm and 5.88, 5.13 ppm. This may be due to the formation of two diastereoisomers in this case. Partial resonances of the alkyl chain of the guest for **1.Zn^{2+}⊃H$_2$N-(CH$_2$)$_{12}$NH$_2$** (at 243 K in $CDCl_3$): $\delta_{CH2} = -1.48, -1.04, -0.58, +1.77$ ppm.

(33) AcOH: up to 50 equiv; MeI: ca. 40 equiv, 48 h, reflux; Et_3N or NBu_4OH (0.1 M solution in toluene/methanol), up to 125 and 5 equiv, respectively.

1.Zn^{2+}⊃EtOH and **1.4H^{+}⊃EtOH** host−guest adducts in $CDCl_3$ was evidenced. Indeed, progressive addition of TFA to complex **1.Zn^{2+}⊃EtOH** led to the formation of **1.4H^{+}⊃EtOH** as shown by the appearance of a second high field shifted triplet corresponding to the methyl group of the included ethanol. The overall integration for the EtOH guest remained one versus the calixarene host (Figures 5a,b). With 10 equiv of TFA, **1.4H^{+}⊃EtOH** was obtained as the only species (Figure 5c).[34] Conversely, subsequent addition of TEA (18 equiv) restored the initial NMR profile corresponding to **1.Zn^{2+}⊃EtOH** (Figure 5d). Similar results were obtained when EtOH was replaced by DMF, a nitrile, or $AcNH_2$. In each case, both host−guest adducts were quantitatively interconverted through the acid−base induced Zn decoordination−coordination process. These results indicate that when calix[6]tren **1** is in the presence of 1 equiv of Zn^{2+} and a valuable guest L, only two species (i.e. **1.4H^{+}⊃L** and **1.Zn^{2+}⊃L**) are obtained, their relative proportion depending on the acid−base conditions.

Conclusion

In conclusion, calix[6]tren **1** is a quite remarkable receptor thanks to the combination of a calix[6]arene macrocycle constrained in a cone conformation and an aza cap that closes the narrow rim of the receptacle, leaving a single entrance controlled by a flexible *t*Bu door.[39] The cavity is made out of aromatic walls, highly π-basic, well-adapted for neutral or positively charged guests, reluctant to anions, and size-selective. The cap presents a grid-like nitrogenous moiety that is highly basic. Hence, it can be used to polarize the edifice by protonation, offering an additional number of hydrogen bonding sites. The tren unit also offers a strong binding site for a metal ion that is firmly coordinated at the bottom of the concave cavity thanks to a strong chelate effect. As a result, three different host−guest systems have been described.

- Calix[6]tren **1** itself complexes ammoniums. Here, the cap plays the role of a Brönstedt base, and recognition is based on multiple hydrogen bonding with the ammonium functionality of the guest and a good fit between its organic part and the calixarene cavity with stabilizing CH−π interactions. In the absence of hydrophobic effect (requiring water as a solvent), nonpolar interactions (van der Waals, CH−π) are not strong enough to allow the efficient binding of a neutral guest to **1**.
- In the *per*-protonated host, **1.4H^{+}**, the cap presents four positive charges. This highly polarizes the receptor, yielding strong charge−dipole interactions with the guest and offers multiple hydrogen bond donor sites. The resulting remarkable binding properties toward neutral guest emphasizes the efficiency of combining a polyammonium site and a hydrophobic cavity to build up a receptor for polar neutral molecules.
- The cavity can also be tuned by the coordination of a metal ion. A variety can be used. Zn^{2+} has been deeply explored. A novel X-ray structure confirmed the dissymmetry of the environment provided by the metallo-host, and selectivity is now based on a coordination link in the cap.

The affinity of the host varies according to the way it is polarized. For example, the protonated host does not bind benzylamine, whereas, due to the strength of the coordination bond, the Zn complex does. The versatility of the system is further illustrated by the reversible transformation of one form of the polarized receptor to another in solution. Such interconversion in solution allows the binding properties to be tuned by the environment (more or less basic, presence of metal ions, etc.). In all cases, the systems are highly resistant and thus represent an important improvement compared to the former systems depicted in Figure 1. All these results further illustrate that calix[6]arenes are superb molecular platforms for the construction of efficient, selective, and versatile receptors.[40] Many perspectives are now open: water-solubilization of the edifice, synthesis of optically pure derivatives of calix[6]tren **1** in view of enantioselective recognition, exploration of a possible cooperativity due to the heteroditopic nature of the receptor, tuning of the entrance, i.e. the size of the door,[14e] for catalysis.

Experimental Section

General Procedures. CH_2Cl_2 was distilled over CaH_2 under argon. ^{1}H NMR spectra were recorded at 200, 300, or 400 MHz and ^{13}C NMR spectra at 75 or 100 MHz. Traces of residual solvent or poly(dimethylsiloxane) (R) were used as internal standard. The syntheses were carried out under an inert atmosphere. Elemental analyses were performed at the Service de Microanalyses, (I.C.S.N., Gif sur Yvette, France). Calix[6]tren **1** was synthesized according to ref 18. Picrate salts RNH_3^+,Pic^- were prepared by reacting the amine RNH_2 with picric acid (*o*,*o*′,*p*-trinitrophenol).

Safety Note. ***Caution!*** *Although we have not encountered any problem, it is noted that perchlorate salts of metal complexes with organic ligands are potentially explosive and should be handled only in small quantities with appropriate precautions.*

Characterization of Calix[6]tren 1.H^{+}. An excess of $BnNH_3^+Cl^-$ salt was directly added to a solution of **1** (5 mg, 3.4 μmoL) in 0.6 mL of $CDCl_3$. After 5 min of sonication, the insoluble salt was removed by filtration and ^{1}H NMR spectra of the solution were recorded at 293 and 233 K (see the Supporting Information). They showed that only 1 equiv of the ammonium salt was dissolved leading to **1.H^{+}** and 1 equiv of free $BnNH_2$. ^{1}H NMR (300 MHz, $CDCl_3$, 293 K) δ 0.85 (s, 27H, *t*Bu), 1.34 (s, 27H, *t*Bu), 2.72 (s_b, 6H, OCH_2CH_2), 2.83 (s_b, 6H, CH_2N), 3.04 (s_b, 6H, CH_2N), 3.51 (s_b, 6H, OCH_2), 3.51 (d, J = 15 Hz, 6H, $ArCH_2$eq), 3.71 (s, 9H, OCH_3), 4.35 (d, J = 15 Hz, 6H, $ArCH_2$ax), 6.61 (s, 6H, ArH), 7.23 (s, 6H, ArH).

Synthesis of Calix[6]tren 1.4H^{+}. TFA (0.5 mL) and dichloromethane (1 mL) were added at 0 °C to a flask containing calix[6]tren **1** (99 mg, 0.080 mmol). The reaction mixture was stirred for 15 min.

(34) The broadness of the NMR signature of the calixarene host is due to the coalescence phenomena described above. When recorded either at lower or at higher T, it was superimposable to those shown in Figure 3, thereby demonstrating unambiguously that the species depicted by spectrum c in Figure 5 indeed corresponds to the *per*-protonated receptor.

(35) The experimental XRPD pattern was recorded on a BRUKER D5005 diffractometer with Cu Kα radiation (λ = 1.54178 Å).

(36) SMART for WNT/2000 V5.622 2001, Smart software reference manual, Bruker Advanced X Ray Solutions, Inc., Madison, WI.

(37) SAINT+ V6.02 1999, Saint software reference manual, Bruker Advanced X-ray Solutions, Inc., Madison, WI.

(38) SHELXTL V6.10 2000, Xshell user's manual, Bruker Advanced X-ray Solutions, Inc., Madison, WI.

(39) With a simple tren ligand (i.e. not linked to a hydrophobic cavity), we have not found any report on guest selectivity. Indeed, in the absence of a hydrophobic cavity, the guest binding is very weak and just relies on acid/base and/or donor/acceptor properties.

(40) Tren-capped calix[4]arenes have been previously described.[41] Among them, some present a polyamide binding site that has been shown to complex transition metal ions such as Co^{2+}, Ni^{2+}, Cu^{2+}, and Zn^{2+}.[41a] A polyamine version has been obtained with a *N*-cresol-tren unit capping a calix[4]arene. Beside its coordination to the same divalent metal ion, its tetra-protonated form has been shown to bind anions such as Br^-, I^-, and NO_3^-.[41b] However, complexation of a guest with a lipophilic moiety has not been reported. This is obviously due to the smallness of the calix[4]arene cavity that cannot accommodate an organic guest through its narrow rim.

(41) (a) Rym, A., Oueslati, I.; Amri, H.; Thuéry, P.; Nierlich, M.; Asfari, Z.; Vicens, J. *Tetrahedron Lett.* **2001**, *42*, 1685−1689. (b) Tuntulani, T.; Thavornyutikarn, P.; Poompradub, S.; Jaiboon, N.; Ruangpornvisuti, V.; Chaichit, N.; Asfari, Z.; Vicens, J. *Tetrahedron* **2002**, *58*, 10277−10285. (c) Balàzs, B.; Toth, G.; Horvath, G.; Grün, A.; Csokai, V.; Töke, L.; Bitter, I. *Eur. J. Org. Chem.* **2001**, 61−71.

After concentration, 1 mL of acetonitrile and then 8 mL of ether were added. The resulting precipitate was separated from the solvent and dried under vacuum, giving **1.4H**$^+$ (108 mg, 80%) as a white solid. mp 262 °C (decomp.). IR (KBr): ν 3445, 1682, 722 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, 293 K) δ 0.90 (s, 27H, *t*Bu), 1.19 (s, 27H, *t*Bu), 3.01 (s_b, 6H, $N^+CH_2CH_2N^+$), 3.07 (s_b, 9H, OCH_3), 3.39 (s_b, 6H, N^+-$CH_2CH_2N^+$), 3.50 (d, J = 15 Hz, 6H, $ArCH_2$eq), 3.65 (s_b, 6H, $OCH_2CH_2N^+$), 4.28 (s_b, 6H, $OCH_2CH_2N^+$), 4.28 (d, J = 15 Hz, 6H, $ArCH_2$ax), 6.78 (s, 6H, ArH), 7.15 (s, 6H, ArH), 9.88 (s_b, 4H, N^+H). ^{13}C NMR (75 MHz, $CDCl_3$, rt) δ 29.8 (2 Ar-αCH_2), 31.1; 31.3 (C(CH_3)$_3$), 33.9; 34.3 $C(CH_3)_3$, 45.8; 48.6; 51.0 (CH_2N), 61.6 (OCH_3), 69.1 (OCH_2), 114.6, 118.4 (4 CF_3); 126.1 (2 $C_{Ar}H$); 132.4, 133.1 (C_{Ar}-CH_2), 146.3; 147.8 (C_{Ar}), 151.2; 153.2 ($C_{Ar}O$); 162.1, 162.6 (4 COO^-). Anal. Calcd for $C_{81}H_{118}N_4O_6$, $(CF_3CO_2)_4$, $2H_2O$: C, 61.72; H, 7.10; F, 13.16; N, 3.23. Found: C, 61.79; H, 6.92; F, 13.01; N, 3.34.

Determination of the Relative Affinities of the Ammonium Salts toward Host 1 through ^{1}H NMR Competitive Binding Studies. For a typical procedure: at room temperature, $EtNH_3^+Pic^-$ (2 equiv), $EtNH_2$ (>5 equiv), and $PrNH_2$ (>5 equiv) were successively added in a $CDCl_3$ solution (0.60 mL) containing calix[6]tren **1** (3 mg, 2.4 μmol). A ^{1}H NMR spectrum recorded at 233 K showed the guest resonances of both endo-complexes **1**$\supset$**EtNH$_3^+$** and **1**$\supset$**PrNH$_3^+$** besides the signals corresponding to the free amines. The integrations of the methyl group of the free amines and of the included ammonium guests were used to calculate the relative affinity defined as $[EtNH_3^+{}_{in}]/[PrNH_3^+{}_{in}] \times [PrNH_2(H^+)_T]/[EtNH_2(H^+)_T]$ where indexes "in" and "T" stand for "included" and "total amount", respectively (errors estimated ±10%). Given the large excess of free amines vs the picrate salts and host **1**, the relative affinities were calculated considering that the slight difference of pK_a between the different free amines was negligible.

Determination of the Relative Affinities of the Neutral Guests G toward Host 1.4H$^+$ through ^{1}H NMR Competitive Binding Studies. For a typical procedure: DMF (3 equiv) and EtOH (3 equiv) were successively added in a $CDCl_3$ solution (0.60 mL) containing **1.4H**$^+$ (4 mg, 2.4 μmol). A ^{1}H NMR spectrum recorded at 223 K showed the guest resonances of both endo-complexes **1.4H**$^+\supset$**DMF** and **1.4H**$^+\supset$**EtOH** besides the signals corresponding to the free DMF and EtOH. The integrations of the methyl group of the free guests and of the included guests were used to calculate the relative affinity defined as $[L_{in}]/[DMF_{in}] \times [DMF_T]/[L_T]$ (errors estimated ±10%). Ratio of neutral molecules G used for the other NMR competitive experiment: $DMF/AcNH_2$ = 1.0.

Determination of the Relative Affinities of the Neutral Molecules L toward Complex 1.Zn^{2+} through ^{1}H NMR Competitive Binding Studies. For a typical procedure: at room temperature, DMF (3 equiv) and EtOH (19 equiv) were successively added in a $CDCl_3$ solution (0.60 mL) containing complex **1.Zn**$^{2+}$. A ^{1}H NMR spectrum recorded at 293 K showed the guest resonances of both endo-complexes **1.Zn**$^{2+}\supset$**DMF** and **1.Zn**$^{2+}\supset$**EtOH** besides the signals corresponding to the free DMF and EtOH. The integrations of the methyl group of the free guests and of the included guests were used to calculate the relative affinity defined as $[L_{in}]/[DMF_{in}] \times [DMF_T]/[L_T]$ (errors estimated ±10%). Ratio of neutral molecules L used for the NMR competitive experiments: $DMF/AcNH_2$ = 0.17, DMF/propylamine = 360, DMF/octylamine = 1.80.

X-ray Structure Analysis of 1.Zn$^{2+}\supset$EtOH. X-ray quality crystals were grown at room temperature out of a $CHCl_3$ solution in which complex **1.Zn**$^{2+}\supset$**EtOH** was dissolved in the presence of trace of EtOH. Crystal data: chemical formula = $C_{83}H_{128}Cl_2N_4O_{17.33}Zn$, M_w = 1595.50, trigonal, colorless crystal (0.56 × 0.6 × 0.7 mm^3), a = 26.815(2) Å, b = 26.815(2) Å, c = 23.736(2) Å, γ = 120°, V = 14780(1) Å^3, space group P-3, Z = 6, Z' = 1, D_{calcd} = 1.076 g.cm^{-3}, μ(Mo Kα) = 0.361 mm^{-1}. The experimental[35] and calculated X-ray powder diffraction patterns were compared. The satisfactory agreement between peak positions allowed us to ensure that the selected single crystal is representative of the bulk. A single crystal was stuck on a glass fiber and mounted on the full three-circle goniometer of a Bruker SMART APEX diffractometer with a CCD area detector. Three sets of exposures (1800 frames) were recorded, corresponding to three ω scans, for three different values of ϕ. The cell parameters and the orientation matrix of the crystal were preliminarily determined by using SMART software.[36] Data integration and global cell refinement were performed with SAINT software.[37] Intensities were corrected for Lorentz, polarization, decay, and absorption effects (SAINT and SADABS softwares) and reduced to F_O^2. Refinement details: The program package SHELXTL[38] was used for space group determination, structure solution, and refinement. The space group P-3 was reliably determined from systematic extinctions and relative F_o^2 of equivalent reflections (XPREP). The structure was solved by direct methods (SHELXS). Anisotropic displacement parameters were refined for non-hydrogen atoms. Hydrogen atoms could not be located from subsequent difference Fourier syntheses. Ideal positions were calculated for each one and refined under suitable restraints (SHELXL). The final cycle of full-matrix least-squares refinement on F^2 was based on 20307 observed reflections and 1038 variable parameters and converged with unweighted and weighted agreement factors of: $R_1 = \Sigma(||F_o| - |F_c||)/\Sigma|F_o| = 0.1931$ (0.0925 for 6805 $F_o > 4.0\,\sigma(F_o)$). $wR_2 = [\Sigma[w(F_o^2 - F_c^2)^2]/\Sigma[w(F_o^2)^2]]^{1/2} = 0.3011$. Resolution, refinement steps, and accuracy: Prior to any refinement, the resolution step allowed us to locate all non-H atoms of the Zn−calixarene complex. Two other large peaks would be attributed to chlorine atoms of perchlorate anions. Successive refinement steps led to improve the geometry of the complex, to complete the perchlorate groups, to identify a supplementary chlorine anion located at a special position of the space group, and to identify, but with a poor accuracy, several residual electron density peaks attributed to water molecules. The final R factor is 9.25% (with $F_o > 4.0\sigma(F_o)$). The global electroneutrality is ensured by a partial occupancy of one of the perchlorate anions. The complete formula is actually: $(Zn\text{-}calix)^{2+}/(ClO_4^-)_{1.67}/Cl^-_{0.33}/nH_2O$. The CIF file for the X-ray structure of **1.Zn**$^{2+}\supset$**EtOH** has been submitted to the CCDC with entry number CCDC 232734.

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Supporting Information Available: Crystallographic data of **1.Zn**$^{2+}\supset$**EtOH**, ^{1}H NMR spectra ($CDCl_3$) of **1.Zn**$^{2+}\supset$**EtOH** at room temperature, **1.H**$^+$ at 293 and 233 K, the mixture of **1.H**$^+$ and **1**$\supset$**PrNH$_3^+$** at 293 and 233 K, **1.Zn**$^{2+}\supset$**PrNH$_2$** at 243 K, **1.4H**$^+$ at 223 K, ^{13}C, COSY, HMQC spectra of **1.4H**$^+$ at room temperature, Van't Hoff plot of the equilibrium constant $K^T_{DMF/H2O}$ (PDF, CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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