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A Calix[6]arene Receptor Rigidified by a Self-assembled Triammonium Cap: X-ray and NMR Characterization of the Binding of Polar Neutral Guests

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A calix[6]arene has been rigidified by three primary ammonium arms self-assembled with the counter anions. This supramolecular edifice provides a well-defined conic hydrophobic cavity closed at the narrow rim by a tricationic site. X-ray and NMR analyses show that the resulting polarized host behaves as a remarkable endo-receptor for small molecules such as amides, alcohols and even nitriles. This study highlights the efficiency of a system that associates a cationic site with a hydrophobic cavity to host dipolar neutral molecules.

Keywords: Host-guest; Cationic receptor; Molecular recognition; Calix[6]arene; Self-assembly

INTRODUCTION

Receptors possessing a hydrophobic cavity classically bind neutral molecules through lipophilic or hydrophobic interactions, by coordination to a metal ion or via strong hydrogen bonds [1–11]. Hosts presenting a polyammonium site have been developed for the recognition of anions, such as halides, carboxylates, phosphates, etc. [12,13]. However, little information has been published on the binding of neutral molecules by ammonium-based receptors. Even with receptors featuring ammonium sites associated with a hydrophobic cavity, this aspect appears essentially unexplored [14–16]. By contrast, many neutral receptors have been designed for the binding of ammonium guests [1,2,17–19]. In this paper, we report on the surprising behavior of a calix[6]arene bearing three primary amino arms. Upon protonation in a solvent of medium polarity, it undergoes a self-organization process with the counter anions, leading to closure of the calixarene narrow rim by the ammonium arms. This ion-paired cap rigidifies the whole structure and prevents the cone–cone inversion of the calix[6]arene core. The resulting receptor possesses a polycationic site that displays exceptional affinity for small neutral organic molecules that present a strong dipolar moment.

RESULTS

Calix[6]tris-amine **1** [18] was obtained according to an efficient two-step sequence (overall yield 77%) from the known [20] symmetrically 1,3,5-tris-*O*-methylated calix[6]arene. Upon reaction with trifluoroacetic acid (TFA) in dichloromethane and subsequent crystallization out of an acetonitrile/ether mixture, the corresponding calix[6]tris-ammonium salt **2** was isolated in 85% yield (Scheme 1). This new compound was analyzed by ^{1}H NMR spectroscopy in $CDCl_3$ and all signals were assigned through 2D NMR analyses (HMQC, HMBC). As for the parent tri-amine **1**, the ^{1}H NMR spectrum of **2** recorded at room temperature is characteristic of a C_{3v} symmetrical species (Fig. 3a). However, several features indicate that **1** and **2** possess different conformational properties: (i) both aromatic and both *t*Bu resonances of **2** are very little differentiated ($\Delta\delta = 0.05$ and 0.06 ppm, respectively, compared to 0.25 and 0.22 for **1** [18]), (ii) the methoxy

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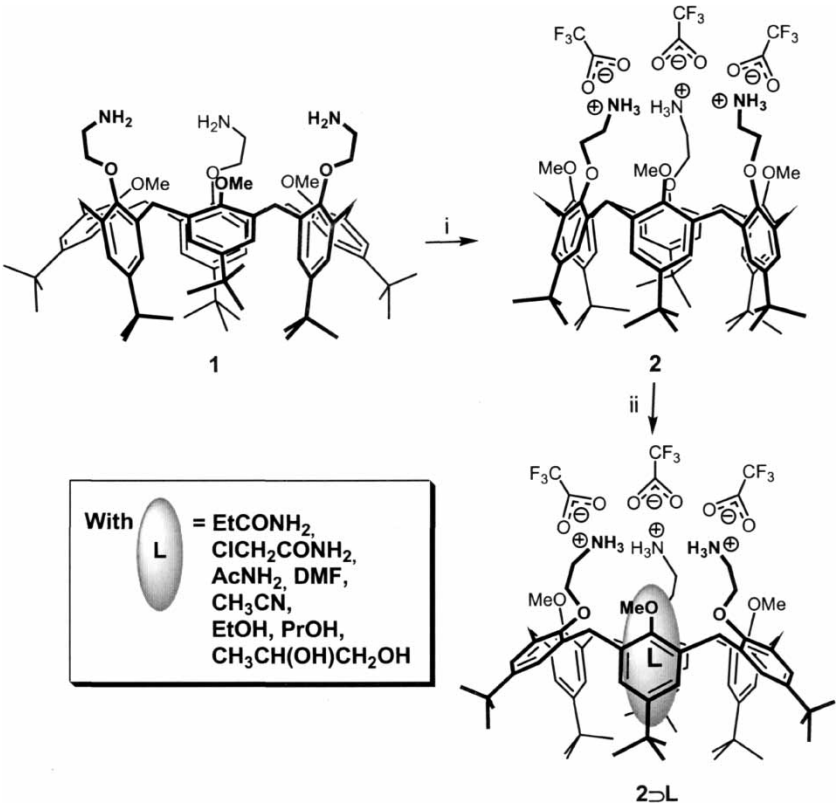

SCHEME 1 (i) TFA, CH_2Cl_2; (ii) L, $CDCl_3$.

groups of **2** display a *quasi*-normal resonance at 3.62 ppm, instead of the upfield shifted one (2.66 ppm) for **1**, (iii) even at 330 K (in $Cl_2CDCDCl_2$) two sharp doublets are observed for the ArCH_2 methylene protons of **2**, showing that cone–cone inversion of the calixarene core is prevented. This clearly contrasts with the single broad peak observed at 3.94 ppm for the ArCH_2 protons in the case of the free tri-amine **1**. This result is quite remarkable because rigidification of the highly flexible calix[6]arenes is usually achieved through covalent bridging between the aromatic moieties [18,19,21–23] or by coordination to a metal ion [5–11]. All these observations indicate that upon protonation, calixarene **1** switches from a classical flattened alternate cone conformation [5–11] to a straight and more rigid cone conformation with the methoxy groups being expelled from the calixarene cavity. By contrast, when recorded in DMSO, the ^{1}H NMR profile of **2** is very similar to that of **1**, with the methoxy groups and the ammonium arms in *in* and *out* positions, respectively[†‡]. These surprising NMR data suggest that, in a solvent of relatively low polarity such as chloroform, the ammonium arms are assembled despite their cationic charge (Scheme 1).

X-ray quality crystals of the endo complex **2** ⊃ **CH_3CN** were grown out of an acetonitrile/ethanol mixture (10:1) upon slow diffusion of ether. When crystallized in the presence of DMF in place of EtOH (CH_3CN/DMF, 10:1), **2** ⊃ **DMF** was obtained. The molecular structures of **2** ⊃ **CH_3CN** and **2** ⊃ **DMF** are shown in Fig. 1. In both cases the calixarene structure is in a cone conformation with the methoxy groups pointing away from the cavity, whereas the ethylammonium groups are directed towards the pseudo C_{3v} symmetry axis. Hence, the three cationic arms are capping the host structure at the narrow rim because of the establishment of a sophisticated hydrogen-bonding network involving the ammonium moieties, the trifluoroacetate anions and either an additional water molecule (in the case of **2** ⊃ **DMF**) or the methoxy groups of the anisole moieties (in the case of **2** ⊃ **CH_3CN**). Interestingly, in each structure a guest molecule (MeCN or DMF) is buried deep in the heart of the calixarene cavity with one methyl group pointing towards an aromatic ring of the calixarene at a perpendicular distance of *ca.* 3.5 Å, denoting stabilizing CH–π interactions. In the case of DMF, the carbonyl group is also involved in the hydrogen-bonding network that caps the host structure [d(O,N) = 2.755 and 2.842 Å in Fig. 1]. By contrast, the included acetonitrile molecule seems to be floating in the host cavity as no hydrogen-bond connection

[†]The ^{1}H NMR spectrum of **2** in DMSO-d_6 showed an upfield shifted resonance for the methoxy groups at 2.04 ppm and the two ArH and *t*Bu signals displayed large $\Delta\delta$ shifts (0.75 ppm and 0.60 ppm, respectively).

[‡]In DMSO-d_6, the conformation adopted by **1** is the same as in $CDCl_3$ as shown by the upfield shifted methoxy resonances (2.20 ppm).

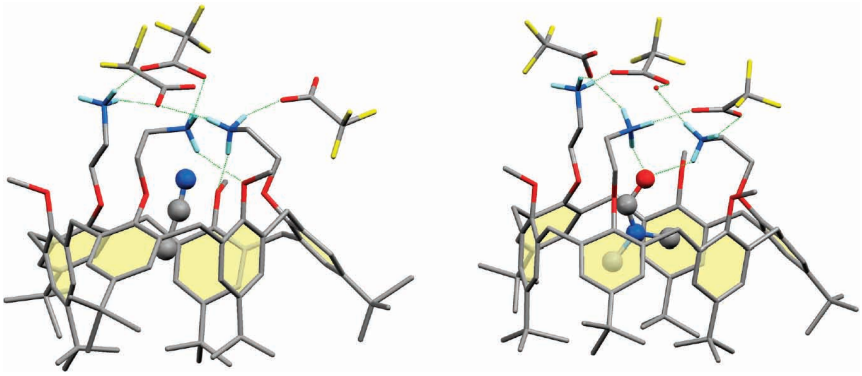

FIGURE 1 Crystal structures of **2** ⊃ **CH_3CN** (left) and **2** ⊃ **DMF** (right). Hydrogen atoms and some crystallization solvent molecules have been omitted for clarity.

with the self-organized cap is observed. Finally, for each structure additional intermolecular hydrogen bonding involving the ammonium and trifluoroacetate groups is observed in the lattice (Fig. 2).

These results and observations prompted us to study the host–guest behavior of **2** in chloroform by ^{1}H NMR spectroscopy. Thus, the addition of DMF (10 equiv.) to a $CDCl_3$ solution containing **2** had two major consequences: the room temperature ^{1}H NMR signals of **2** decreased in intensity and broadened and a novel C_{3v} symmetrical species appeared, which was associated with an extra double resonance in the high-field region, below 0 ppm (Fig. 3a,b). NOESY experiments indicated that these high-field shifted peaks belong to a guest DMF molecule included in the calixarene host in a 1:1 ratio according to their relative integration. At a lower temperature, all the resonances sharpened (Fig. 3c). The guest DMF methyl signals experienced an upfield shift and better splitting, whereas the signal corresponding to the included CHO proton became observable at 6.79 ppm. At 216 K, the new host–guest adduct, namely **2** ⊃ **DMF**, remained the only observable species (Fig. 3d). Its spectrum displays a large splitting of the ArH and *t*Bu signals ($\Delta\delta = 0.70$ and 0.61 ppm, respectively), indicating a conformation change from straight cone in the absence of DMF to flat alternate, upon its inclusion (see Scheme 1 with L = DMF).

The equilibrium between host **2** and **2** ⊃ **DMF** was found to be highly dependent on the water concentration. A set of two measurements of the temperature (T) dependence of the equilibrium showed that one water molecule participates in the host–guest exchange process. Hence, the equilibrium constant K_T was defined by the following equation:

$$\mathbf{2} \supset \mathbf{H_2O} + \mathbf{L} \leftrightarrows \mathbf{2} \supset \mathbf{L} + \mathbf{H_2O}$$

At 300 K, the affinity of receptor **2** for DMF was evidenced by a value $K_{300} = 0.43(5)$. The corresponding thermodynamic parameters were determined from a van't Hoff plot (Fig. 4). In agreement with an exothermic process that favors the binding of DMF at low temperature, the enthalpy value was $\Delta H = -30(3)\,\mathrm{kJ\,mol^{-1}}$. This is of the same order of magnitude as the calculated value for charge–dipole interaction in chloroform[¶]. The associated entropy was found to be negative, with $\Delta S = -107(15)\,\mathrm{JK^{-1}\,mol^{-1}}$. This entropic cost may be attributable to an increasing degree of organization of **2** upon binding DMF compared to water. The comparative ^{1}H NMR spectra of **2** ⊃ **H_2O** and **2** ⊃ **DMF** evidenced a significant conformational change of the calixarene structure from straight to flat alternate cone that may indeed be associated with a loss of freedom of the system. This can be explained by the fact that the associated water molecule in **2** ⊃ **H_2O** sits in the polyammonium cap, the calixarene cavity being essentially empty [24].

A similar host–guest behavior was observed with other polar neutral organic molecules, such as EtOH, PrOH, $AcNH_2$ and the larger $EtCONH_2$ or $ClCH_2CONH_2$ guests[§]. Even the nonhydrogen-bonded MeCN guest could be detected in the cavity with, admittedly, a broader resonance for its methyl group when compared to the other amide and alcohol guests, which indicates a faster exchange process and thus a weaker binding. However, no endo-complexation was

[¶]Considering a distance of *ca.* 4 Å between a tricationic center ($q = +3$e) and a fixed dipole with a dipolar moment $\mu = 3.8$ D (3.82 D for DMF or 3.92 D for MeCN) in chloroform ($\varepsilon = 4.8$), the calculated electrostatic interaction is: $W = -1/(4\pi\varepsilon_0) \times |q|\mu/\varepsilon d^2 = -2.89 \times 3 \times 3.8/(4.8 \times 0.4^2) \approx -40\,\mathrm{kJ\,mol^{-1}}$.

[§]The corresponding guest resonances were: DMF (at 216 K): $\delta_{CH_3} = -0.15$ ppm and -0.53 ppm and $\delta_{HCO} = 6.79$ ppm; $AcNH_2$ (at 223 K): -0.74; EtOH (at 223 K): $\delta_{CH_3} = -1.77$ ppm and δ_{CH_2O} = undetected (signals were overlapped by those of the *t*Bu groups); PrOH (at 213 K): $\delta_{CH_3} = -2.23$ ppm, $\delta_{CH_2} = -1.50$ ppm and δ_{CH_2O} = undetected (signals were overlapped by those of the *t*Bu groups); $CH_3CH_2CONH_2$ (at 263 K): $\delta_{CH_3} = -1.85$ ppm and $\delta_{CH_2} = 0.22$ ppm; $ClCH_2CONH_2$ (at 263 K): $\delta_{CH_2} = 2.00$ ppm; CH_3CN (at 223 K): $\delta_{CH_3} = -1.29$ ppm.

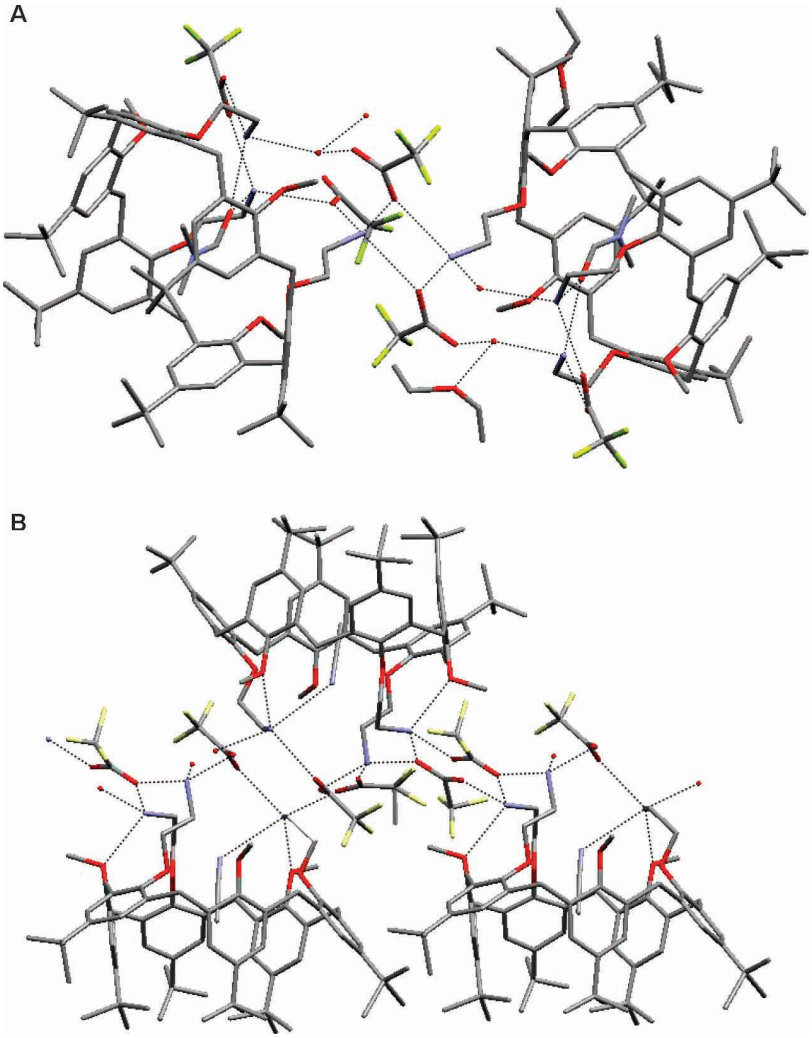

FIGURE 2 X-ray structures displaying the main inter- and intramolecular H-bond interactions within the unit cell. (a) **2** ⊃ **DMF**. (b) **2** ⊃ **CH_3CN**. Some trifluoroacetate as well as the disordered water molecules have been omitted for clarity.

observed at low temperature for the bulkier *N*,*N*-diethylformamide, 2-chloropropionamide molecules or for compounds of low polarity (i.e. CH_2Cl_2, $CHCl_3$, Et_2O, THF, pentane). This remarkable selectivity is due, on the one hand, to the steric control provided by the cavity and, on the other, to the possibility of establishing a crucial charge–dipole interaction between the cap and the guest molecule. Very interestingly, at 220 K, the endo-complexation of a chiral racemic guest [i.e. (±)-propane-1,2-diol] led to a splitting of the resonances of the diastereotopic ArH protons of the calixarene core[‖]. This shows that the asymmetry of the guest can be transmitted to the calixarene host and attests to its tight binding. Competitive NMR binding experiments conducted at 223 K showed relative affinities of 26, 1, 0.75 and 0.04 for $AcNH_2$, DMF, EtOH and CH_3CN, respectively. Hence, acetamide appeared to be the best guest, whereas DMF and EtOH presented similar affinities and the weakest bound is the nonhydrogen-bonded CH_3CN guest. A comparative NMR study has shown that no endo-complexation was observed with neutral calix[6]tris-amine **1** as the receptor. This emphasizes the key role played by the self-assembled cationic cap for the freezing of the calixarene core in the cone conformation and for the binding of neutral guest molecules.

Finally, the stability of the self-organized edifice was tested. Although collapsing in pure DMSO, **2** ⊃ **L** revealed itself to be resistant in a EtOH/$CDCl_3$ (1:4) mixture (L = EtOH). Also, remarkably, when the tris-ammonium salt was generated *in situ* in a $CDCl_3$ solution containing **1** through direct introduction of either H_2SO_4, PTSA, $HClO_4$ or even HCl, the ^{1}H NMR signature of complex **2** ⊃ **DMF** was observed in all cases at low temperature (223 K)[#].

[‖]The resonances for the included (±)-propane-1,2-diol (at 220 K) were: $\delta_{CH_3} = -2.22$ ppm, $\delta_{CH_2O} = 2.03$ and 2.20 ppm, and δ_{CHOH} = undetected (signals were overlapped by those of the *t*Bu groups).

[#]The addition of H_3PO_4 to **1** in $CDCl_3$ led to the precipitation of the salt.

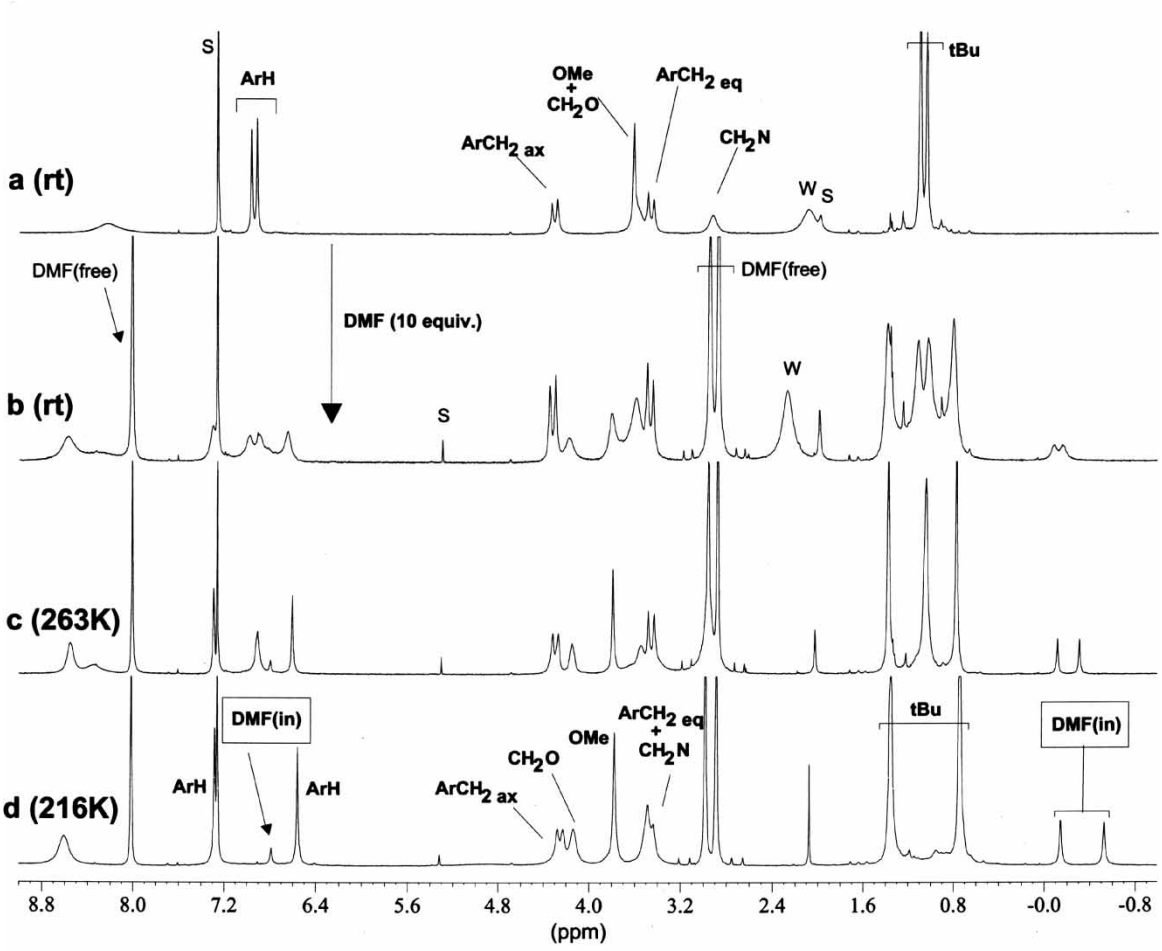

FIGURE 3 ^{1}H NMR spectra of calix[6]tri-ammonium **2** (3 mM in $CDCl_3$) before (a) and after (b–d) the addition of 10 molar equiv. of DMF. Solvent and water are labeled S and W, respectively.

DISCUSSION

From these studies, we can deduce that the stability of the host–guest adducts is a result of four major factors:

i) a strong charge–dipole interaction between the tricationic cap and the guest molecule that is constrained along the C_{3v} axis of the calixarene, thereby optimizing the orientation of its dipole, which unidirectionally points towards the (+3) charge;
ii) a good fit between the lipophilic part of the guest and the calixarene cavity with the establishment of stabilizing CH–π interactions [5–11];
iii) hydrogen bonding between the guest, the protic cap, the counter anions and possibly the oxygen atoms of the calixarene structure in the case of protic guests [25] (although this is not an absolute requirement as demonstrated by the binding of MeCN);
iv) a tight ion-pairing between the cationic arms and the counter anions.

Receptor **2** compares interestingly with the calix[6]tris-imidazole Zn^{2+} system. These Zn-*funnel* complexes also exchanged H_2O for a guest molecule such as DMF in the calixarene structure [24]. However, although the corresponding thermodynamic parameters were of the same order of absolute magnitude, they were of opposite sign ($\Delta H = +33\,\mathrm{kJ\,mol^{-1}}$ and $\Delta S = +91\,\mathrm{JK^{-1}\,mol^{-1}}$). The relative affinities were different as well, with the following order: acetamide (7) ≈ EtOH (5) > DMF (1) > MeCN (0.4). Hence, the molecular recognition processes for the Zn^{2+}-*funnel* complex and for the tricationic receptor **2** are different. Indeed, the exchange process involved two water molecules against one organic guest in the case of Zn, [24] whereas with **2**, a 1:1 exchange occurred. As a result, the Zn complex underwent almost no conformational change upon the exchange of

[#]The addition of H_3PO_4 to **1** in $CDCl_3$ led to the precipitation of the salt.

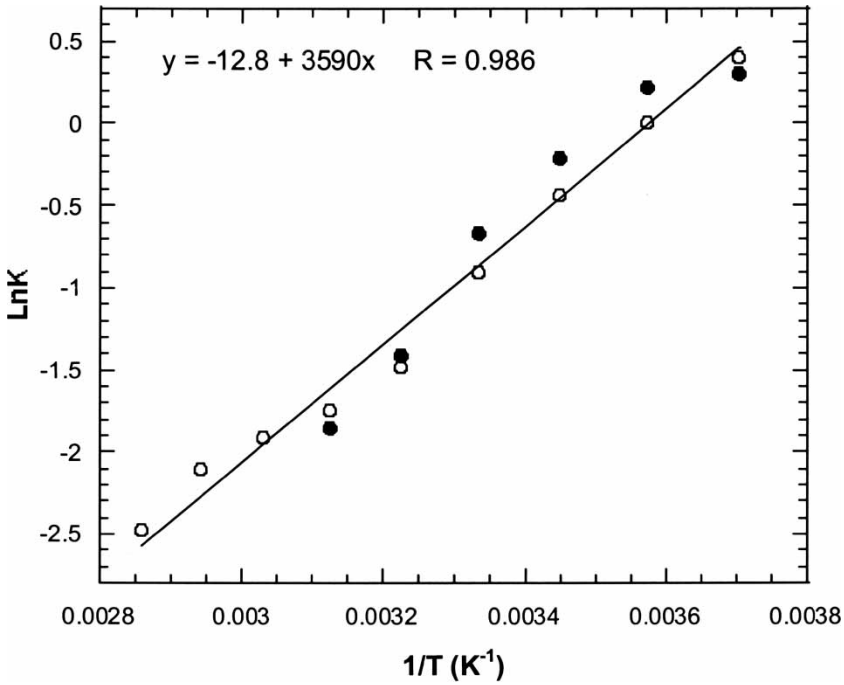

FIGURE 4 van't Hoff plot of the equilibrium constant $K_{DMF/H2O}$ determined by ^1H NMR in $CDCl_3$ solution. [Complex] = 3.1 mM; [DMF] = 31 mM; ○, [H_2O] = 9 mM; •, [H_2O] = 16 mM.

the two water molecules feeding and thus shaping the cavity, whereas the cationic receptor **2** switches from a straight empty cone to an alternate, filled cone conformation. For both systems, similar CH–π interactions between the host and the organic guest were evidenced by X-ray structure analyses. Hence, the differences in the relative affinities for the organic guests are attributable to small variations in their hydrogen bonding and to the absence of a coordination link in receptor **2**.

CONCLUSION

In summary, we have described a very simple self-assembled receptor based on a calix[6]arene. Upon protonation, calix[6]tris-amine **1** undergoes a conformational change with the three ammonium arms becoming sealed together by the counter anions and water molecules in an organic solvent of medium polarity. This produces the new host **2**, which presents a hydrophobic, π-basic concave cavity ended by a tricationic, protic site. The rigidified structure behaves as a selective endo-receptor for small polar neutral molecules in an organic solvent. As revealed by the X-ray structures, the efficiency of the receptor results from the combination of a strong charge–dipole interaction between the polarized guest and the polycationic cap, stabilizing CH–π interactions inside the calixarene cavity and hydrogen bonding in the cap. Until now, strong complexation was observed for amides and alcohol guests. Surprisingly, even MeCN, which lacks a hydrogen-bonding site, could be entrapped by this supramolecular receptor in chloroform. Hence, this study highlights the efficiency of combining a polyammonium site and a hydrophobic cavity to build up a receptor for polar neutral molecules. This may be relevant to biological systems such as enzymes and their Michaelis–Menten complexes. Indeed, if such a system were to be water soluble, it would benefit from additional hydrophobic effects for the trapping of organic molecules. We are currently working in that direction with the design of a water-soluble structure that should fulfill all three requirements.

EXPERIMENTAL

General Procedures

CH_2Cl_2 was distilled over CaH_2 under argon. ^1H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively. Traces of residual solvent or poly(dimethylsiloxane) (R) were used as internal standard. Elemental analyses were performed at the Service de Microanalyse (ICSN, Gif sur Yvette, France).

Calix[6]tris-ammonium Salt (2)

TFA (0.25 ml) and dichloromethane (1 ml) were added to a flask containing calix[6]tri-amine **1** (111 mg, 0.097 mmol). The reaction mixture was stirred for 15 min. After concentrating the mixture, 1 ml of acetonitrile and then 8 ml of ether were

added. The resulting precipitate was separated from the solvent, washed three times with ether and dried under vacuum, giving **2** (122 mg, 85%) as a white solid. Mp 208°C (dec.). ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.04$ (s, 27H; *t* Bu), 1.10 (s, 27H; *t* Bu), 2.93 (s_b, 6H; $OCH_2CH_2N^+$), 3.47 (d, $J = 15$ Hz, 6H; Ar-αCH_{eq}), 3.59 (s_b, 6H; $OCH_2CH_2N^+$), 3.62 (s, 9H; OCH_3), 4.31 (d, $J = 15$ Hz, 6H; Ar-αCH_{ax}), 6.92 (s, 6H; ArH), 6.97 (s, 6H; ArH), 8.23 (s_b, 9H; N^+H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 29.8$ (Ar-αCH_2), 31.2, 31.3 ($C(CH_3)_3$), 34.2 ($C(CH_3)_3$), 39.7 (CH_2N), 61.4 (OCH_3), 68.9 (OCH_2), 114.4, 118.3 (CF_3), 125.7, 126.3 ($C_{Ar}H$), 132.7, 132.9 ($C_{Ar}CH_2$), 146.9, 147.0 (C_{Ar}), 151.4, 152.2 ($C_{Ar}O$), 161.5, 162.0 (COO^-); IR (KBr): $\nu = 3440$, 1679, 722 cm^{-1}. Anal. Calcd. for $C_{75}H_{105}N_3O_6 \cdot 3CF_3COOH \cdot CH_2Cl_2 \cdot CH_3CN$(%): C, 62.56; H, 7.06; N, 3.47. Found: C, 62.67; H, 6.97; N, 3.28. The presence of CH_2Cl_2 and CH_3CN was checked by ^{1}H NMR analysis of the sample used for elemental analysis.

Crystal Data for 2 ⊃ MeCN

$M_w = 3216.89$, monoclinic, colorless crystal (0.4 × 0.3 × 0.2 mm^3), $a = 17.157(1)$, $b = 17.006(1)$, $c = 34.192(2)$ Å, $\beta = 91.51(3)°$, $V = 9972.8(9)$ Å^3, space group Pc, $Z = 2$, $\rho = 1.07$ g cm^{-3}, μ(MoKα) = 0.77 cm^{-1}, 13 628 reflections measured at 178 K (Nonius Kappa CCD diffractometer [26]) in the 0.6–23° θ range, 13 135 unique, 1886 parameters refined on F^2 using 13 128 reflections [SHELXL] [27] to final indices $R[F^2 > 4\sigma F^2] = 0.115$, $wR = 0.282\{w = 1/[\sigma^2(F_o^2) + (0.1813P)^2 + 25.6538P]$, where $P = (F_o^2 + 2F_c^2)/3\}$. Refinement details: two independent molecules of **2 ⊃ MeCN** crystallized in the asymmetric unit. Some trifluoroacetate counter anions were found to be disordered as well as solvent water molecules and a tertiary-butyl. In order to impose a sensible geometry on these disordered parts, as far as possible, the tertiary-butyl, the three F atoms of one trifluoroacetate and the CF_3 moiety of a second one were split on two sites and then refined with rigid body constraints and isotropic displacement parameters. With the same aim the scattering of the solvent water molecules was simulated by assigning oxygen atoms with partial occupancies to the remaining Fourier peaks. The hydrogen atoms of the water molecules were not calculated. No other hydrogen atoms could be found but the distances between the nitrogen atoms of the amines (the donor) and the acceptors (the oxygen atoms of the ligand or the trifluoroacetates) were compatible with hydrogen bonds (these distances were also compatible with those observed in **2 ⊃ DMF** where the hydrogen atoms could be located on the amines). Therefore, we could assign the hydrogen atoms in theoretical positions on the amines, as well as all the other hydrogen atoms of the calixarene (except on the disordered or agitated tertiary-butyls), which were later introduced in the calculations but not refined. The last residual Fourier positive and negative peaks were equal to 0.64 and −0.51, respectively.

Crystal Data for 2 ⊃ DMF

$M_w = 3173.68$, triclinic, colorless crystal (0.3 × 0.3 × 0.25 mm^3), $a = 15.810(6)$, $b = 16.123(8)$, $c = 20.499(9)$ Å, $\alpha = 86.763(3)$, $\beta = 84.046(3)$, $\gamma = 66.734(3)°$, $V = 4773.8(4)$ Å^3, space group $P1$, $Z = 1$, $\rho = 1.1$ g cm^{-3}, μ(MoKα) = 0.86 cm^{-1}, 14 943 reflections measured at 178 K (Bruker–Nonius Kappa CCD diffractometer [26]) in the 2.55–25° θ range, 14 935 unique, 1987 parameters refined on F^2 using 14 935 reflections [SHELXL] [27] to final indices $R[F^2 > 4\sigma F^2] = 0.09$, $wR = 0.231$ [$\{w = 1/[\sigma^2(F_o^2) + (0.1346P)^2 + 6.2747P]$, where $P = (F_o^2 + 2F_c^2)/3\}$. Refinement details: two independent molecules of **2 ⊃ DMF** crystallized in the asymmetric unit. As there was a possibility that a symmetry might exist between the two calixarene moieties, we tried to solve the structure in the *P*1 space group but the refinement was worse than in the *P*1 space group. This lack of symmetry is probably due to the disorder in the crystal, as we had observed previously in structures of this type. Some trifluoroacetate counter anions as well as co-crystallized diethylether molecules were found to be disordered. In order to impose a sensible geometry on the disordered parts, as far as possible, the F atoms of one trifluoroacetate were split on two sites, as well as one diethylether. These moieties were then refined with rigid body constraints and isotropic displacement parameters. All hydrogen atoms on the amines, as well as some on the calixarene moiety, were found experimentally; the remaining ones were assigned in theoretical positions except on some agitated tertiary-butyl where they have been omitted. They all were introduced into the calculations but not refined. The last residual Fourier positive and negative peaks were equal to 0.82 and −0.38, respectively.

Supplementary Material

Crystallographic data for the structures reported in this article have been deposited with the Cambridge Crystallographic Data Centre, CCDC Nos 244800 and 244801. Copies of this information may be obtained free of charge from The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-1223-336-033; E-mail: deposit@ccdc.cam.ac.uk or www.ccdc.cam.ac.uk/conts/retrieving.html).

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