Water-Soluble Calixarene Hosts that Specifically Recognize the Trimethylammonium Group or the Benzene Ring of Aromatic Ammonium Cations: A Combined ^{1}H NMR, Calorimetric, and Molecular Mechanics Investigation

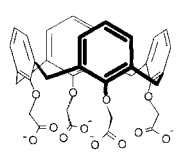
Giuseppe Arena,*[a] Alessandro Casnati,[b] Annalinda Contino,[a] Gaetano G. Lombardo,[a] Domenico Sciotto,*[a] and Rocco Ungaro*[b]

Abstract: The complexation of *N*,*N*,*N*-trimethylanilinium (TMA), benzyltrimethylammonium (BTMA) and *p*-nitrobenzyltrimethylammonium (BTMAN) cations by two different water-soluble calix[4]arenes, **1** and **2**, both fixed in the cone conformation, was studied at neutral pH by ^{1}H NMR spectroscopy and calorimetry. In contrast to the conformationally mobile calix[4]arene tetrasulfonate **3**, host **1** specifically binds the TMA – $\overset{+}{N}(CH_3)_3$ group, whereas **2** recognizes only the aromatic ring of TMA. The introduction of a spacer between the charged polar group and the aromatic residue (BTMA) or an electron-withdrawing group on the aromatic moiety (BTMAN) does not alter this selectivity for host **1**, whereas host **2** selectively recognizes the -$\overset{+}{N}(CH_3)_3$ group of BTMAN, but complexes BTMA unselectively both by the -$\overset{+}{N}(CH_3)_3$ group and the aromatic moiety. The binding constants for all three guests with **1** and **2**, as determined by both ^{1}H NMR spectroscopy and calorimetric titrations, show that inclusion is favored by the presence of the sulfonate groups and that the greater stability observed with **2** mainly arises from a favorable enthalpic contribution. The factors driving inclusion of the ammonium cation by the two hosts are discussed. Molecular mechanics calculations allow determination of the conformational properties of hosts **1** and **2** and of their inclusion complexes.

Keywords: calixarenes · calorimetry · molecular modeling · molecular recognition

Introduction

Water-soluble cyclophanes[1] are becoming increasingly important in supramolecular chemistry because they allow a deeper understanding of the basic forces involved in host–guest recognition processes in a solvent where most biological processes occur. Moreover, these studies permit the design of more sophisticated artificial systems for use in chemical technology. Calixarenes[2] are a special class of cyclophanes which have been used as such, or after functionalization, for the recognition of neutral molecules,[3] metal ions,[3, 4] and, more recently, anions.[5] Calixarene receptors have also been used as active components in mass-sensitive devices for solvent vapors[6] or analytes in aqueous solution.[7] However, despite the versatility of calixarene hosts, few examples of inclusion of organic molecules by calixarenes in aqueous solution have been reported.[2d, 8] Even fewer papers deal with the evaluation of the enthalpy and entropy of association, which are relevant in quantifying binding interactions and in understanding the forces driving the inclusion process in water.[9] Shinkai et al.[8b] previously reported that TMA was unselectively included by the conformationally mobile calixarene **3**.



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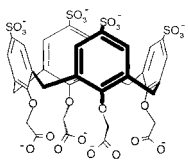

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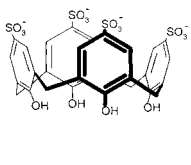

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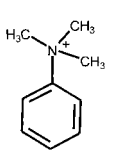
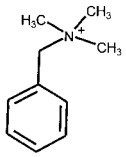
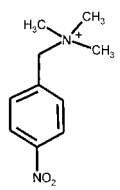


TMA



BTMA



BTMAN

[a] Prof. G. Arena, Dr. A. Contino, Dr. G. G. Lombardo, Prof. D. Sciotto
Department of Chemical Sciences
University of Catania, Viale Andrea Doria 8
I-95125 Catania (Italy)
Fax: (+39) 095-580138
E-mail: garena@dipchi.unict.it

[b] Prof. R. Ungaro, Dr. A. Casnati
Department of Organic and Industrial Chemistry
University of Parma, Viale delle Scienze 78
I-43100 Parma (Italy)
Fax: (+39) 0521-905472
E-mail: ungaro@ipruniv.cce.unipr.it

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We later showed that the rigidification of the calixarene receptor causes the TMA aromatic nucleus to be selectively incorporated into the cavity[10] and that the inclusion of ethanol is assisted by the presence of sulfonate groups at the upper rim of the cavity.[11] Lehn et al. also reported that the sulfonate groups play a role in the binding of the methylammonium group of choline derivatives[8f] by calixarene receptors. On the basis of these findings, we have explored the possibility of inducing selectivity in the recognition of tetraalkylammonium ions by using the conformationally immobilized (cone conformation) calix[4]arenes **1** and **2**. In this paper we report a combined ^{1}H NMR and calorimetric investigation of the inclusion of three methylammonium cations, namely *N,N,N*-trimethylanilinium (TMA), benzyltrimethylammonium (BTMA) and *p*-nitrobenzyltrimethylammonium (BTMAN) by two water-soluble calixarene receptors, **1** and **2**, fixed in their cone conformations.

Results and Discussion

^{1}H NMR studies: ^{1}H NMR spectra of hosts **1** and **2** recorded at different concentrations showed no change in the signals of the various protons, thus ruling out micelle formation in the explored range ($1\times10^{-4}-1\times10^{-2}$ mol dm^{-3}).[12] Figures 1a and 1b show the observed changes ($\Delta\delta_{obs}=\delta_{obs}-\delta_{free\ guest}$) in chemical shifts induced by the complexation of TMA with **1** and **2**, respectively.

No change in the chemical shifts of either host **1** or **2** has been observed. Log *K* values (Table 1) show that the inclusion of TMA is more favorable for **2** than for **1**. In the same table we have also reported the chemical shifts of the uncomplexed guest for the protons used for the fitting procedure. The upfield shifts experienced by TMA protons upon inclusion are due to the ring current effect of the aromatic nuclei of the host;[8a, b, 13] for **1**–TMA a significant complexation-induced shift ($\delta_{complex}-\delta_{free\ guest}$) is observed for the ammonium methyl protons, whereas the signals of the aromatic *para* and *meta* protons do not change. Interestingly, the *ortho* protons show a slight, but still significant, upfield shift. This indicates that the -$\overset{+}{N}(CH_3)_3$ group is selectively included into the cavity, as illustrated in Figure 2a. In contrast, for the **2**–TMA complex

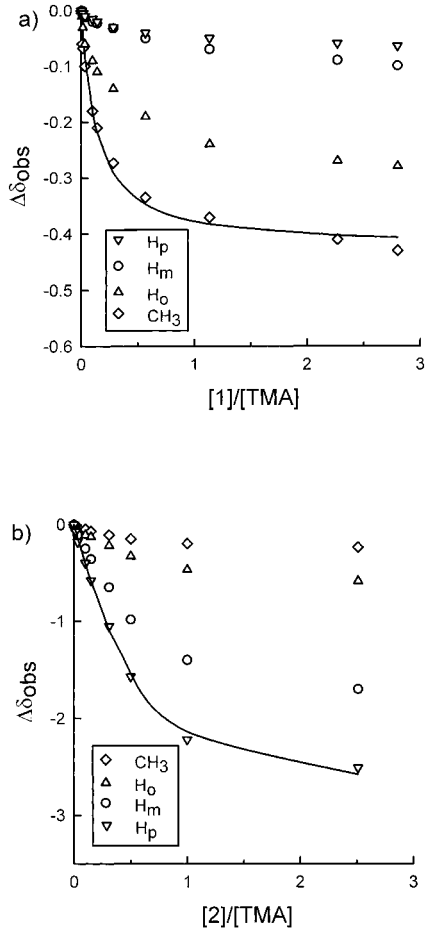

Figure 1. a) Plots of $\Delta\delta_{obs}$ (ppm) versus [**1**]/[TMA] in D_2O, 25 °C, [**1**] = 1×10^{-3} mol dm^{-3}, pD = 7.3 (0.1 mol dm^{-3} phosphate buffer); b) plots of $\Delta\delta_{obs}$ (ppm) versus [**2**]/[TMA] in D_2O, 25 °C, [**2**] = 1×10^{-3} mol dm^{-3}, pD = 7.3 (0.1 mol dm^{-3} phosphate buffer). Solid lines were obtained by applying a curve-fitting procedure to the experimental data used for the evaluation of the association constants.

Table 1. Log *K* and chemical shift limiting values ($\delta_{complex}$) for the complex formation of TMA, BTMA, and BTMAN with hosts **1** and **2**; pD = 7. 3. σ values are given in parentheses.

Reaction	Log *K*	$\delta_{complex}$	[a]	$\delta_{free\ guest}$
1 + TMA → **1**–TMA	2.2 (1)	0.77 (5)	-$\overset{+}{N}(CH_3)_3$	3.64
2 + TMA → **2**–TMA	3.3 (1)	3.36 (5)	H_{para}	7.61
1 + BTMA → **1**–BTMA	1.7 (1)	0.71 (5)	-$\overset{+}{N}(CH_3)_3$	3.05
2 + BTMA → **2**–BTMA	3.3 (1)	1.30 (5)	-$\overset{+}{N}(CH_3)_3$	3.05
1 + BTMAN → **1**–BTMAN	1.7 (1)	1.34 (5)	-$\overset{+}{N}(CH_3)_3$	3.12
2 + BTMAN → **2**–BTMAN	3.4 (1)	1.43 (5)	-$\overset{+}{N}(CH_3)_3$	3.12

[a] Protons used for the fitting procedure.

Abstract in Italian: *La complessazione dei cationi N,N,N-trimetilanilinio (TMA), benziltrimetilammonio (BTMA) e p-nitrobenziltrimetilammonio (BTMAN) da parte di due diversi calix[4]areni solubili in acqua **1** e **2**, entrambi bloccati nella conformazione a cono, è stata studiata a pH neutro mediante ^{1}H NMR e calorimetria. A differenza del calix[4]arene tetrasolfonato **3**, conformazionalmente mobile, il recettore **1** riconosce selettivamente il gruppo -$\overset{+}{N}(CH_3)_3$ del TMA, mentre **2** complessa esclusivamente l'anello aromatico. Introducendo uno spaziatore tra il gruppo carico positivamente e il residuo aromatico (BTMA) o un gruppo elettron-attrattore su quest'ultimo (BTMAN), non si osserva alcuna variazione nel caso del recettore **1** mentre **2** complessa selettivamente il gruppo -$\overset{+}{N}(CH_3)_3$ del BTMAN ma in modo non selettivo il BTMA. Le costanti di associazione di **1** e **2** con tutti e tre i substrati, determinate sia mediante ^{1}H NMR che mediante Calorimetria, mostrano che l'inclusione è favorita dalla presenza dei gruppi solfonici e che la maggiore stabilità dei complessi, osservata nel caso del recettore **2**, è dovuta ad un contributo entalpico piuî favorevole. Sono discussi i fattori che controllano l'inclusione dei cationi ammonio nella cavità dei due recettori. I calcoli di Meccanica Molecolare permettono di avere informazioni sulle proprietà conformazionali dei recettori **1** e **2** e dei loro complessi.*

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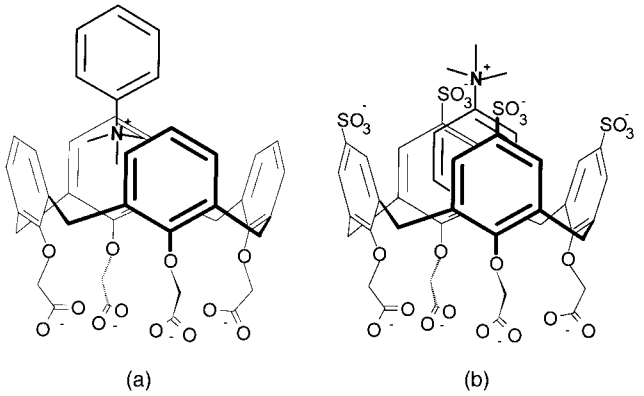

Figure 2. Mode of inclusion of *N*,*N*,*N*-trimethylanilinium ion by: a) host **1**; b) host **2**.

(Figure 1b) only a slight upfield shift is observed for the methyl protons while the aromatic protons experience a CIS that follows the order $H_{para} > H_{meta} > H_{ortho}$. This indicates that the aromatic nucleus of the guest is selectively included in the cavity as illustrated in Figure 2b.

It is noteworthy that in the case of the conformationally flexible calix[4]arene tetrasulfonate **3**, both the ammonium and aromatic moieties of TMA are unselectively bound by the host at pD = 7.3,[8b] while they are selectively recognized by our hosts at the same pD value. In addition, the unique mode of inclusion of TMA remains so even at low pD values; ^{1}H NMR spectra measured for **2** – TMA at pD = 2 (where the carboxylate anions are protonated[14]) show the same trend observed at pD = 7.3. This clearly indicates that the preorganization of the cavity of **1** and **2** plays a key role in determining the selective inclusion of the guest, regardless of the pH. Higher values of log*K*s are also observed for **2**-BTMA compared with **1** – BTMA (Table 1). In the last case the guest is selectively included by the aliphatic moiety only, since both the methyl and methylene protons of BTMA are shifted upfield upon complexation, whereas the resonances of the aromatic protons remain practically unmodified (Figure 3a). Thus inclusion of BTMA into **1** occurs in a manner similar to that illustrated for **1** – TMA (Figure 1a). Instead, in **2** – BTMA all guest protons shift to higher magnetic fields (Figure 3b), thus indicating that there is an equilibrium between the two inclusion modes of the guest as depicted in Figure 4. Titration experiments similar to those recorded in Figure 1 indicate that BTMAN is included only by the ammonium group and that host **2** is more efficient than host **1** (Table 1).

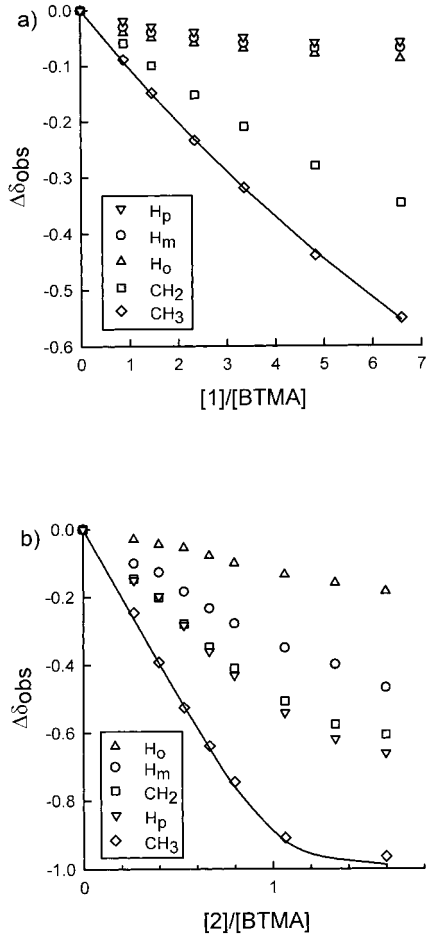

Figure 3. a) Plots of $\Delta\delta_{obs}$ (ppm) versus [**1**]/[BTMA] in D_2O, 25 °C, [BTMA] = 1×10^{-3} mol dm^{-3}, pD = 7.3 (0.1 mol dm^{-3} phosphate buffer); b) plots of $\Delta\delta_{obs}$ (ppm) versus [**2**]/[BTMA] in D_2O, 25 °C, [BTMA] = 4×10^{-3} mol dm^{-3}, pD = 7.3 (0.1 mol dm^{-3} phosphate buffer). Solid lines were obtained by applying a curve-fitting procedure to the experimental data used for the evaluation of the association constants.

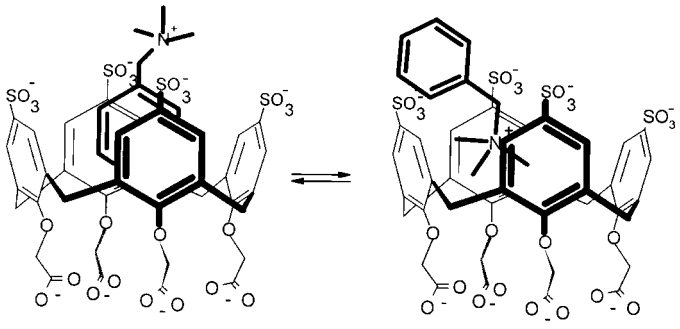

Figure 4. Modes of inclusion of BTMA into host **2**.

Calorimetric investigation: Since ΔH° and ΔS° contributions reveal specific interactions not expressed in the ΔG° term, we determined these quantities by direct calorimetry (Table 2). This allowed us not only to verify the log*K* values obtained by ^{1}H NMR but also to determine ΔH° values directly, thus avoiding the use of van't Hoff plots, which can have the severe limitation[15] of neglecting the ΔC_p contribution, which for inclusion processes may be relevant.[15e, g] The log*K* values obtained by calorimetry (Table 2) are in excellent agreement with those obtained by ^{1}H NMR (Table 1). The thermodynamic data show that, for all three guests, the inclusion complex with **2** is more stable than the analogous complex with **1**, and that this results from a more favorable ΔH° contribution. The sulfonate groups appear to serve as anchoring points for the positively charged ammonium cations, thus leading to a more stable inclusion complex. The process is enthalpically driven for all systems reported here. Interestingly, the inclusion of neutral aromatic guests by cyclophanes in water is also enthalpically driven and has a negative entropic contribution.[15c, g] In contrast, the inclusion

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Table 2. Log K values and thermodynamic parameters of complex formation of TMA, BTMA, and BTMAN with hosts **1** and **2**; pH = 7.0. σ values are given in parentheses.

Reaction	Log K	ΔG° [kcal mol^{-1}]	ΔH° [kcal mol^{-1}]	ΔS° [kcal mol^{-1} K^{-1}]
1 + TMA → **1**–TMA	2.2 (1)	– 3.0 (1)	– 4.9 (2)	– 6.3 (7)
2 + TMA → **2**–TMA	3.3 (1)	– 4.5 (1)	– 8.7 (2)	– 14 (1)
1 + BTMA → **1**–BTMA	1.7 (1)	– 2.4 (1)	– 4.1 (2)	– 6 (1)
2 + BTMA → **2**–BTMA	3.2 (1)	– 4.4 (1)	– 6.4 (1)	– 6.8 (3)
1 + BTMAN → **1**–BTMAN	1.6 (1)	– 2.2 (2)	– 5.0 (5)	– 9 (1)
2 + BTMAN → **2**–BTMAN	3.4 (1)	– 4.6 (1)	– 6.4 (1)	– 6 (1)

of TMA, BTMA, and BTMAN by **1** and **2** is, on average, entropically less unfavored, since the presence of a positive charge leads to greater desolvation. The ΔH° for the interaction of **2** with TMA is much more favorable than that for **1**. This can be ascribed primarily to the stacking interaction between the guest and host aromatic moieties,[15b, c, e, g, 16–18] which is strengthened by the electrostatic interaction between the ammonium group of the guest and the sulfonate groups of the host. The guest molecules are held tightly in the cavity, and the stiffening of the system is also reflected in the ΔS° value, which is more unfavorable than one would expect for classical +/− interactions, since the positive contribution arising from desolvation is partially masked by the tighter binding. This interpretation is strongly supported by the ^{1}H NMR results showing that in the **2**-TMA complex the guest is more deeply included into the cavity of **2** than into the cavity of **1** (vide infra).

A comparison between the three pairs of complexes reveals some interesting aspects of the inclusion process. In such a comparison any differences arising from factors that are difficult to analyze individually (e.g. the solvation of guests, solvation of hosts, etc.) are factored out. The $\Delta\Delta H^\circ$ difference follows the order TMA > BTMA > BTMAN, where $\Delta\Delta H^\circ = \Delta H^\circ_{1-\text{guest}} - \Delta H^\circ_{1-\text{guest}}$. Keeping in mind that BTMAN is bound by both host **1** and **2** by the -$\overset{+}{\text{N}}(CH_3)_3$ group (cation–π[19a] or CH–π[19b] interactions, vide infra) the observed $\Delta\Delta H^\circ$ difference (1.4 kcal mol^{-1}) mainly reflects the difference in complementarity between the two hosts and the guest. For TMA the $\Delta\Delta H^\circ$ difference becomes significantly larger (3.8 kcal mol^{-1}); this results from the involvement in **2**-TMA of a π–π interaction, which is enthalpically more favored than the CH–π interaction.[20] This interpretation is supported by the intermediate $\Delta\Delta$H$^\circ$ difference obtained for the BTMA pair (2.3 kcal mol^{-1}), which reflects the difference between a host–guest system where only a CH–π interaction is taking place (**1**-BTMA) and a system (**2**-BTMA) in which two structures (which give rise to either CH–π or π–π interactions) are in equilibrium (Figure 4).

The calorimetric results obtained with host **1** also help to clarify the so called TMA effect which was proposed after the observation that in several host–guest systems the -$\overset{+}{\text{N}}(CH_3)_3$ group is quite often directed in the interior of the macrocycles, rather than exposed to the aqueous environment.[15b] This phenomenon has been explained as arising from cation–π[19a] or CH–π[19b] interactions between activated methyl groups and the electron-rich macrocyclic cavity. Our data show that, although the enthalpic contribution is dominant, the entropy term is less negative than for other complexes (e.g. **2**-TMA). It is evident that all guests prefer to insert the -$\overset{+}{\text{N}}(CH_3)_3$ group into the cavity of host **1** since, by doing so, they can take advantage of both a CH–π interaction ($\Delta H^\circ < 0$) and the entropically favorable desolvation of the -$\overset{+}{\text{N}}(CH_3)_3$ group following inclusion. If TMA were inserting the aromatic moiety into the cavity of host **1**, this would involve only the π–π interaction, giving rise only to a favorable enthalpic contribution. The above explanation also rationalises the inclusion of the guests by the -$\overset{+}{\text{N}}(CH_3)_3$ group when no additional interactions (i.e. with the negatively charged sulfonate groups) are provided by the host backbone. Since these two different binding modes (aromatic moiety vs. ammonium group) are in competition, it is likely that in BTMAN the presence of a bulky substituent on the aromatic ring favors incorporation via the -$\overset{+}{\text{N}}(CH_3)_3$ group.

Molecular mechanics calculations: Calculations were performed using the MM+ force field of the Hyperchem package[21] after calculation of the atomic charges of each single molecule with the MNDO method,[22] which has been used previously for calixarene host–guest complexes.[23] The optimized structures are shown in Figure 5a–i. Some of the relevant distances are reported in Table 3. They refer to energy minima and are those calculated for the most stable conformations. The distances between the upper-rim carbon atoms of the aromatic rings of the cavities indicate that both free ligands assume approximately the same conformation; that is, they have a C_{2v} elongated shape (Table 3, **1** and **2**). The aromatic rings of the C_2 and C_4 atoms project outwards, whereas the C_1 and C_3 aromatic rings project inwards and lie parallel. As demonstrated for other cone calix[4]arenes by ^{1}H NMR[24] as well as molecular dynamics studies,[8e] each host undergoes a rapid C_{2v}–C_{2v} interconversion, the average structure of which is a C_{4v} cone. The data for free and complexed hosts (Table 3 and Figure 5) show that the inclusion of the -$\overset{+}{\text{N}}(CH_3)_3$ group forces the C_1 and C_3 aromatic rings to move away from one another and the C_2 and C_4 aromatic rings to move inwards, thus rendering the cavity more symmetrical. The cone still maintains a C_{2v} symmetry but with a less elongated shape (Figure 5c–e). In both **2**–TMA and **2**–BTMA* (see Table 3), where inclusion of the guest takes place by the aromatic moiety, the cavity is more elongated, which allows two aromatic rings of the hosts to remain cofacially oriented, accommodating the aromatic residue of the guests in a sandwich-type arrangement, which maximizes the π–π interaction. Figures 5d and 5f and Table 3 also show that in **2**–TMA, as well as in **2**–BTMA*, the guest is not symmetrically included. This is in agreement with results obtained for similar calixarenes by a molecular dynamics study.[8e] The distances between the positively charged ammonium residue and the sulfonate groups (S–N distances) show that the -$\overset{+}{\text{N}}(CH_3)_3$ group tilts towards the negatively charged -SO_3^- group, thus confirming that the sulfonate groups of the upper rim serve as anchoring points. The inclusion of the -$\overset{+}{\text{N}}(CH_3)_3$ group (**1**–TMA, **1**–BTMA, **1**–BTMAN, **2**–BTMA**, and **2**–BTMAN) allows a significantly more symmetrical incorporation of the guests, as indicated by the C–N distances for each of the above systems

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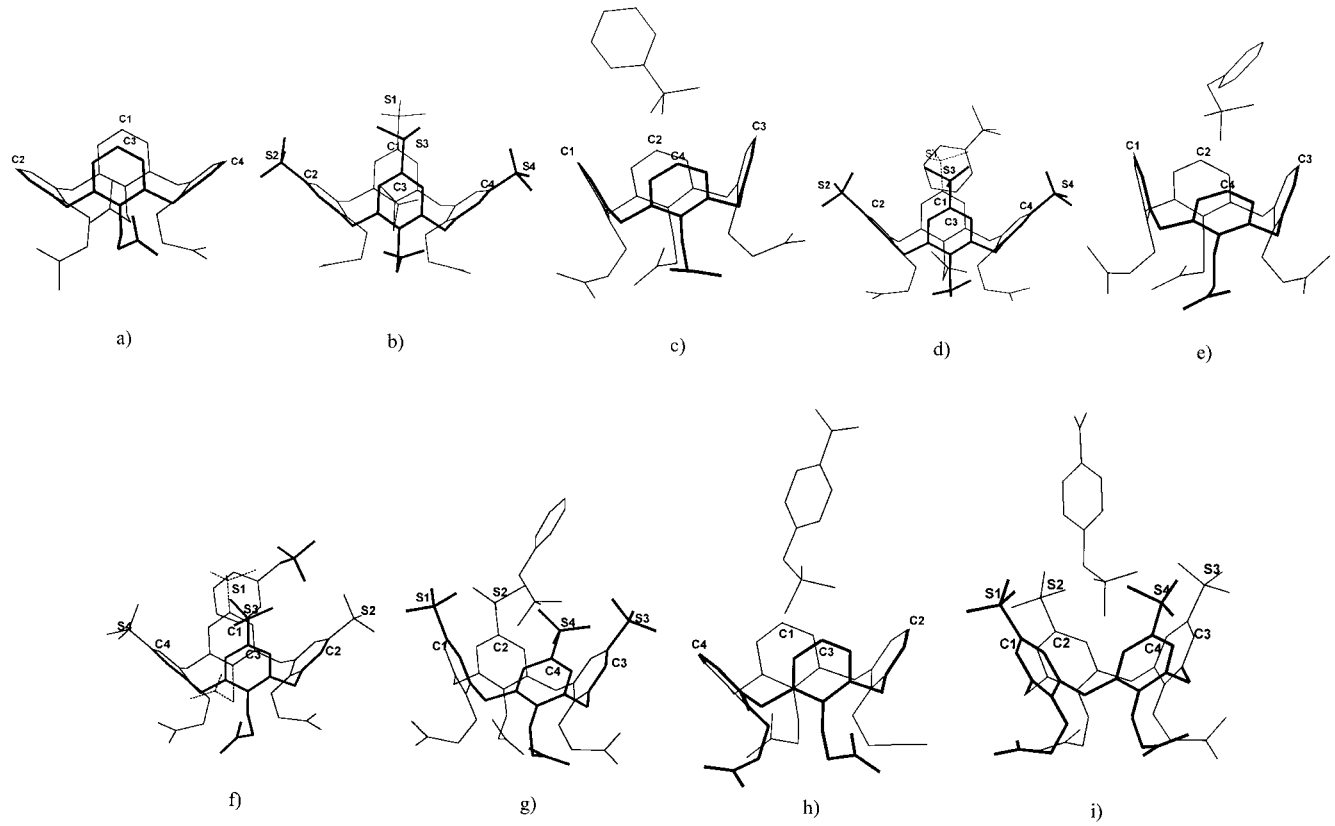

Figure 5. Optimized structures (molecular mechanics) in water, generated for: a) host **1**; b) host **2**; c) **1**–TMA; d) **2**–TMA; e) **1**-BTMA; f) **2**–BTMA*; g) **2**–BTMA**; h) **1**–BTMAN; i) **2**–BTMAN.

(see Table 3). The structures in Figure 5 (MM energy minima) depict frozen images of dynamic systems, as is demonstrated by the NMR equivalence of the four equatorial protons and of the four axial protons of the methylene bridges between the four aromatic rings of the hosts, as well as by the equivalence of the aromatic *meta* protons of the hosts (C_{4v} averaged symmetry). In **2**–TMA and in **2**–BTMA* as well as in all the complexes with host **2**, the $-\overset{+}{N}(CH_3)_3$ group experiences in turn the electric field of each sulfonate group; the guest is tilted away from the C_4 axis but its average position coincides with the C_4 axis, as indicated by the ^{1}H NMR spectra. The signals for the guest reveal the equivalence of the methylammonium protons, of the two *ortho* as well as of the two *meta* protons, and, in the case of **2**–BTMA*, of the two methylene protons. In order to estimate the depth of inclusion of the guest by the two hosts, we have calculated the distance (D) between the center of mass of each guest and the center of mass of the cavity of each host.[25] The shortest distance (5.88 Å) is found for **2**–TMA. This is consistent with the ^{1}H NMR simulation of the shieldings produced by the ring currents of the calixarene cavity. We have also compared the experimental and calculated ^{1}H NMR diamagnetic shifts for both **1**–TMA and **2**–TMA by calculating the shielding values as a function of the depth of guest inclusion along the calixarene C_{4v} symmetry axis (Figure 6). We used Johnson and Bovey's method,[26] taking into account that the experimental shifts ($\delta_{complex} - \delta_{free\ guest}$) result from the ring current effect of four symmetrically placed aromatic rings. For both **1**–TMA and **2**–TMA the experimentally determined shielding values ($\Delta\delta_{CH_3}/4 = -0.717$ and $\Delta\delta_{H_{para}}/4 = -1.062$, respectively) intercept the

Table 3. Relevant distances (in Å) for compounds **1** and **2** and their complexes with TMA, BTMA, and BTMAN obtained by MM+ optimization.

	1	**1**–TMA	**1**–BTMA	**1**–BTMAN	**2**	**2**–TMA	**2**–BTMA*[a]	**2**–BTMA**[a]	**2**–BTMAN
C_1-C_3	4.99	7.57	7.11	7.51	4.92	6.92	6.88	7.99	8.02
C_2-C_4	9.95	8.50	9.04	8.81	10.01	9.32	9.45	8.31	8.42
C_1-N		4.68	4.25	4.25				4.66	4.45
C_2-N		5.16	5.85	4.90				4.87	5.03
C_3-N		4.33	4.22	4.30				4.36	4.53
C_4-N		4.93	4.86	5.19				4.55	4.38
S_1-N						5.13	5.95	5.01	4.88
S_2-N						8.63	4.97	5.45	5.62
S_3-N						5.07	5.10	4.77	5.07
S_4-N						5.40	9.60	4.96	4.94
D		6.75	6.35	6.92		5.88	6.03	6.95	6.79

[a] **2**–BTMA* and **2**–BTMA** indicate the complexes of BTMA with host **2** in which inclusion of the guest takes place by the aromatic moiety or the $-\overset{+}{N}(CH_3)_3$ group respectively.

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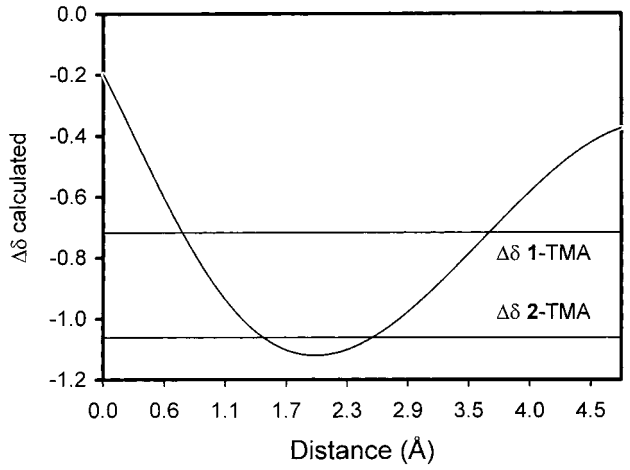

Figure 6. Calculated shielding ($\Delta\delta$, ppm) by an aromatic ring of a calix[4]arene cavity as a function of the distance along the C_{4v} symmetry axis, measured from the geometrical center of the lower rim.

theoretical curve at two different distance values from the center of the lower rim cavity along the C_{4v} axis (0.75 and 3.63 Å for **1**-TMA; 1.52 and 2.59 Å for **2**-TMA). Considering that the lower value obtained for **1**–TMA (0.75 Å) is clearly incompatible with the dimensions of the cavity and the methyl group size, we can reasonably conclude that TMA is more deeply included into the cavity of host **2** than into the cavity of **1**.

Conclusion

In this paper we have shown that the *N*,*N*,*N*,-trimethylanilinium (TMA) cation has a dual binding mode (charged group vs. aromatic moiety inclusion) which occurs in a nonselective fashion with flexible water-soluble calix[4]arene hosts such as **3**. The binding mode can, however, be effectively controlled and turned into a selective process by preorganization of the calixarene cavity into the cone structure.

Host **1** is able to complex the TMA charged group exclusively, while host **2** includes TMA by the aromatic ring, that is, TMA binding occurs in the calixarene cavity in two specific and opposite modes, depending on the presence of sulfonate groups at the upper rim. Besides serving as anchoring points for the positively charged guests, the sulfonate groups significantly deepen the cavity of host **2,** thus improving its inclusion capability.

The combination of ^{1}H NMR, calorimetric, and molecular mechanics data allows us to fully understand the factors controlling the inclusion processes of TMA, BTMA, and BTMAN. In all cases inclusion is enthalpically driven and entropically unfavored. This shows that attractive interaction rather than entropically favorable desolvation is the major driving force for the selective inclusion of these small guests. In line with Diederich's[15g] and our own findings,[17, 18] the thermodynamic characteristics ($\Delta H^\circ < 0$ and $\Delta S^\circ < 0$) for the formation of a tight inclusion complex from small solutes in water differ remarkably from those established for the formation of looser aggregates such as micelles and membranes. In other words, in a tight inclusion complex the number of degrees of freedom of the small binding partners is significantly reduced; this results in a strong entropic loss which masks any gain in desolvation entropy.

Experimental Section

Materials: The synthesis of hosts **1** and **2** has been previously described.[27] The purity of **2** was also checked potentiometrically following the procedure previously described by us.[14, 28, 29] This was not possible for **1**, since this host is not soluble over the entire pH range in which the acid–base titration should be performed. *N*,*N*,*N*-Trimethylanilinium (TMA) chloride, benzyltrimethylammonium (BTMA) chloride and *p*-nitrobenzyltrimethylammonium (BTMAN) chloride were obtained from Aldrich and purified by crystallization either from acetonitrile (TMA) or from an ethanol:acetone mixture (2:5, BTMA and BTMAN). Their analytical concentrations were determined by titration of chloride ions by the Mohr method. NaH_2PO_4 and Na_2HPO_4, used to prepare the buffer solutions, were obtained from Carlo Erba. NaD_2PO_4 and Na_2DPO_4 were prepared by deuteration of the above commercial products. Doubly distilled water and Grade A glassware were used throughout.

^{1}H NMR spectra: Spectra were obtained in D_2O at 25 °C with a Varian Inova 500 MHz spectrometer. Chemical shifts (δ) were externally referenced to DSS (3-trimethylsilyl 1-propanesulfonic acid, sodium salt) in order to avoid any possible interaction of the reference with the calix[4]arene derivatives or with the guest. All experiments were performed in deuterated phosphate buffer (0.1 mol dm^{-3}) with a pD value of 7.3. ^{1}H NMR titrations were carried out in the two following ways: 1) the guest concentration was kept constant (usually 1×10^{-3} mol dm^{-3}) while the host concentration was varied from 1×10^{-4} to 5×10^{-3} mol dm^{-3}; 2) the guest concentration was varied over the concentration range 1×10^{-2} to 3.5×10^{-4} mol dm^{-3} while the host concentration was set at 1×10^{-3} mol dm^{-3}. In all cases the signals of the guest were followed. Each experiment consisted of about ten points.

Calorimetric measurements: The calorimetric runs were performed under both isothermal and isoperibol conditions. The isothermal titrations were carried out in an LKB 2277 microcalorimeter equipped with a perfusion system having a 2.5 mL stainless steel cell; the term *micro* refers to both the volume of titrant used and the amount of heat that can be detected under appropriate conditions. Integration of the power curve gives the heat involved in the reaction, provided the calorimeter has been calibrated by introducing known power values through built-in precision resistors. The isoperibol measurements were performed with a Tronac 450 calorimeter equipped with a 4 mL dewar cell. This calorimeter measures the temperature changes, following the addition of titrant, through a precision thermistor which generates a voltage output; this output is converted into a heat quantity by a precision heater.[30] As recommended,[31] the dewar was calibrated beforehand to ensure that the volume increase resulting from the addition of titrant did not cause an increase in the heat leakage constant of the calorimetric vessel. For the specific cells used for the experiments described here the volume upper limit was found to be 3.4 mL. Consequently, the amount of titrant added was never allowed to exceed 0.3 mL. Usually a 0.2–0.5 mol dm^{-3} solution of the guest (TMA, BTMA, or BTMAN) was added to a $3-5 \times 10-3$ mol dm^{-3} solution of host **1** or **2** buffered at pH 7.0, and 20–30 points recorded for each of the 4–6 independent titrations (see supporting information).

Calculations: In order to obtain *K* values from ^{1}H NMR titrations, the data were treated with a nonlinear least-squares curve-fitting procedure.[32] *K* and ΔH° values were obtained with a modified version of the computer program EQDH.[31] Other details can be found in refs. [25, 26a, and 30].

Molecular mechanics calculations: These calculations were performed with the Hyperchem package.[21] In the first step, the atomic charges of each single molecule were calculated by the MNDO method.[22] In the second step, each calix, with the appropriate trimethylammonium ion, was inserted into a box containing 300 water molecules and a minimum was found. Finally, the ammonium ions were included into the cavity of **1** or **2** and the resulting complexes were inserted into a box containing 300 water molecules and a minimum was also found. The calculations were performed with the MM+ force field, using the standard parameters of the package. The minimization was performed by the conjugate gradient method (Fletcher–Reeves) and was carried out until the RMS gradient reached a value of 0.1 kcal Å^{-1} mol^{-1} (average number of iterations 400).

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