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Guest-induced capsular assembly of calix[5]arenes[†]

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Abstract—Novel dimeric capsules are generated from the non-covalent assembly of cone calix[5]arenes and alkyldiammonium ions $[H_3N\text{-}(CH_2)_n\text{-}NH_3]^{2+}$ featuring an appropriate length of the spacer joining the two charged end groups. ^1H NMR spectroscopy and electrospray ionisation mass spectrometry provide evidence that in the capsule a single ditopic guest holds together a pair of calix[5]arene units, which are oriented rim-to-rim to form a closed cavity encapsulating the shape-complementary dication. © 2002 Elsevier Science Ltd. All rights reserved.

The non-covalent assembly of bowl-shaped hosts leading to discrete molecular assemblies with a well-defined inner cavity capable of size-selective molecular encapsulation is a topic of current interest in supramolecular chemistry.[1] For instance, the reversible dimerisation of tetraurea calix[4]arenes via a seam of intermolecular hydrogen bonds in non-polar media affords capsule-like containers,[2] which resemble Cram's carceplexes[3] in their ability to encapsulate within their interior charged or neutral guest entities. Molecular containers with specific size and shape can be assembled by exploiting intermolecular hydrogen bonding,[4] electrostatic interactions,[5] and metal coordination.[6]

We recently reported that *p*-*tert*-butylcalix[5]arenes locked in a C_{5v}-symmetric cone conformation provide highly preorganised cavities for the formation of strong 1:1 inclusion (*endo*-cavity) complexes with linear alkylammonium ions in organic media.[7] In these hosts, the π-basic cavity acts as the primary binding site by exploiting cation-π interactions,[8] while selectivity of the linear over branched alkylammonium ions is ensured by the presence of the *t*-Bu groups at the wide rim. We have now extended our studies with calixarene hosts to the complexation of the structurally related alkyldiammonium ions, and we wish to report here on the first examples of guest-induced capsular assembly of *p*-*tert*-butylcalix[5]arenes.

Calix[5]arene *penta*-ethers **1**[9] and **2**,[7a] and *penta*-ester **3**,[10] all in the cone conformation but with different affinities for alkylammonium ions,[7] were selected as potential hosts (H) for the dipicrate salts of diammonium guest (G) ions **4**–**7** (Fig. 1).

A rapid screening of the binding affinities of **1**–**3** for the targeted alkyldiammonium ions was provided by the electrospray ionisation mass spectrometry (ESI MS)[11] of 1:1 H/G mixtures ($CHCl_3$/MeOH 2:1, v/v).

The ESI mass spectral behaviour of combinations of *penta*-ethers **1** and **2** with **4**–**7** is quite uniform, and a typical mass spectrum, relevant to calix[5]arene **1** and guest ion **6**, is shown in Fig. 2. Although the spectrum

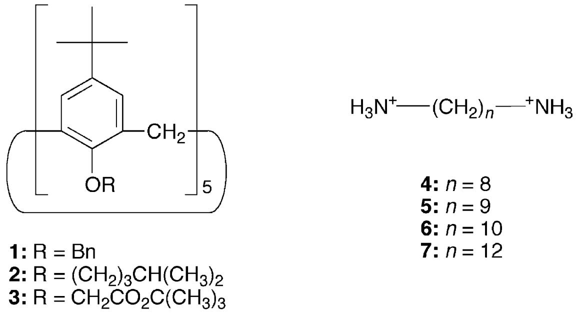

Figure 1. Hosts and guests employed in this study.

Keywords: alkylammonium ions; calixarenes; capsules; diammonium ions; electrospray ionisation; inclusion complexes.

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[†] Dedicated to Professor Volker Böhmer on the occasion of his 60th birthday.

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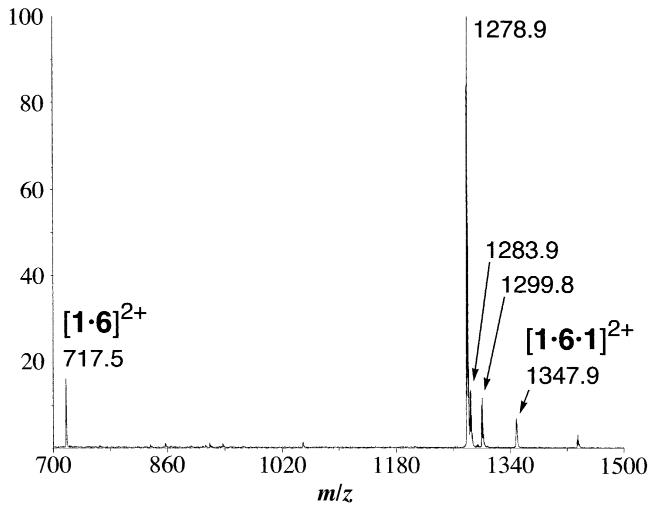

Figure 2. ESI mass spectrum of a 1:1 H/G mixture of **1** and **6** in $CHCl_3/CH_3OH$ 2:1.

shows ion peaks at *m/z* 1278.9 (base peak), 1283.9 and 1299.8, corresponding to $\mathbf{1}\cdot NH_4^+$, $\mathbf{1}\cdot Na^+$ and $\mathbf{1}\cdot K^+$ complexes,[‡] respectively, the formation of 2:1 and 1:1 H/G complexes is clearly evidenced by the presence of moderately intense doubly charged ion peaks at *m/z* 1347.9 and 717.5, corresponding to $[\mathbf{1}\cdot\mathbf{6}\cdot\mathbf{1}]^{2+}$ and $[\mathbf{1}\cdot\mathbf{6}]^{2+}$. Conversely, the spectra of *penta*-ester **3** with **4**–**7** show only prominent peaks corresponding to $\mathbf{3}\cdot NH_4^+$, $\mathbf{3}\cdot Na^+$ and $\mathbf{3}\cdot K^+$ complexes, while no peaks associated with the formation of H/G complexes could be detected.[§][12]

The hypothesis that the $[\mathbf{H}\cdot\mathbf{G}\cdot\mathbf{H}]^{2+}$ ions could possess a capsule-like structure was confirmed by competition experiments (gas-phase formation of hetero-dimers of composition $[\mathbf{1}\cdot\mathbf{G}\cdot\mathbf{2}]^{2+}$) and collision experiments.[13] The latter, performed at different nozzle potentials (50–250 V), showed that the ions of $[\mathbf{H}\cdot\mathbf{G}\cdot\mathbf{H}]^{2+}$ composition are the most stable among those compatible with H/G-containing ions. This strongly supports their capsular nature, ruling out the formation of isobar ions due to unspecifically bound calix[5]arene(s)/diammonium complexes.

The *endo*-cavity nature of both 2:1 and 1:1 H/G complexes between calix[5]arenes **1**–**3** and alkyldiammonium ions **4**–**7** is supported by ^1H NMR titration experiments in $CDCl_3/CD_3OD$ (2:1, v/v). Upon addition of increasing amounts of guest salt (up to 2 equiv.) to a 5×10^{-3} M solution of the host, the ^1H NMR spectra showed distinct signals for the free and complexed host and guest species, in agreement with a slow exchange process on the NMR time scale.[7] With the shorter dication guests **4** and **5**, the high field region of the spectra (0.0 to −2.0 ppm) displays a single set of signals for the complexed guest.[¶] The alkylene proton resonances of the included guest are spread out over a 5 ppm interval, strongly suggesting one-sided inclusion of the dication into the π-basic cavity of the host. The formation of 1:1 H/G complexes generates asymmetrisation of the guest. The degree of complexation, determined by ^1H NMR analysis of equimolar mixtures of host and guest, was relatively low (21–36%) with **1** and quite high (78–93%) with **2** and **3**.

On the other hand, the ^1H NMR titration experiments of calix[5]arenes **1**–**3** with the slightly longer diammonium ions **6** and **7** show the presence of two distinct sets of signals for the included alkylene chain of the guest. This observation is compatible with the formation of both 1:1 and 2:1 H/G inclusion complexes, in accordance with the ESI MS evidence. Fig. 3, relating to a titration experiment of **2** with **6**, typically shows that the relative intensities of the signals associated with the two complexes are strongly dependent on the H/G molar ratio, its progressive decrease causing the merging of the less shielded set (1:1 complex), with consequent depletion of the more shielded one (2:1 complex).

^1H NMR analysis of the 2:1 H/G mixtures with 1,10-decane-diammonium ion **6** has shown that the ratio between the 2:1 and 1:1 complexes is about 28/72 with **1**, 90/10 with **2**, and 63/37 with **3**. Mixtures of calix[5]arenes **1**–**3** with 0.5 equiv. of 1,12-dodecane-diammonium ion **7** showed a similar trend. However, in spite of the longer spacer between the two ammonium heads of the guest, the 2:1 complexes are formed to a lesser extent than with **6**. These results suggest that, among the various host–guest combinations investigated, calix[5]arene **2** and the alkyldiammonium counterpart **6** benefit from optimal shape and length complementarity for the assembly of capsular ternary complexes in high yield. The marked aptitude of **6** to induce a capsular assembly with **2** is further corroborated by an ESI MS competitive complexation experiment of **2** with a cocktail of dicationic guests (**2**:**4**:**5**:**6**:**7** = 40:1:1:1:1, in $CHCl_3$/MeOH 2:1, v/v), which indicates that the binding selectivity of **2** for alkyldiammonium ions (based on signal intensities of the $[\mathbf{H}\cdot\mathbf{G}\cdot\mathbf{H}]^{2+}$ ions formed, see Fig. 4) follows the order **6**>**7**>**5**>**4**.

Our data demonstrate that, beside the expected formation of 1:1 H/G inclusion complexes (Fig. 5a), ditopic α,ω-diammonium ions featuring a spacer of at least ten carbon atoms between the two polar heads display a remarkable tendency to coordinate a pair of calix[5]arene units, which are oriented rim-to-rim to form a closed cavity encapsulating the shape-complementary dication (Fig. 5b). With shorter spacers the formation of the capsule in solution is hindered by severe steric repulsions between the upper rim sub-

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[‡] Inorganic ions, present as impurities in the solvents used, account for the formation of these peaks. A very similar trend is also noticed in the absence of alkyldiammonium guests, ruling out the decomposition of the guest as a possible source of NH_4^+ ions.

[§] Alkali metal ions are known to strongly bind at the lower rim of **3**,[10] and in so doing they switch off the affinity of **3** for alkylammonium ions. This ESI MS observation parallels the reduced activity of **3** as 'sensing agent' for calix[5]arene-based *n*-butylammonium ion selective electrodes in the presence of interfering inorganic ions.[12]

[¶] In the titration experiments of **2** with **5** a second set of high field resonances, associated with the 2:1 complex, could be barely seen for [H]/[G] ≥ 20.

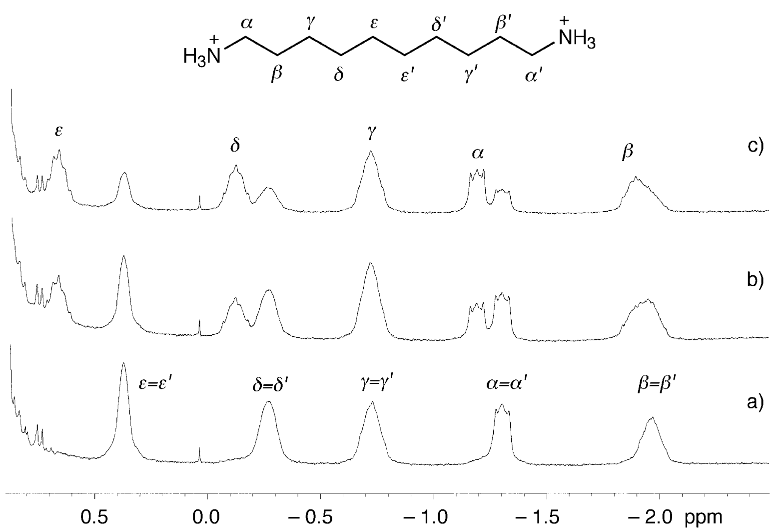

Figure 3. The high field region of the ^1H NMR spectra (300 MHz, 295 K, $CDCl_3/CD_3OD$, 2:1) of mixtures of **2** and **6** at different H/G molar ratios: (a) H/G = 2; (b) H/G = 1; (c) H/G = 0.5.

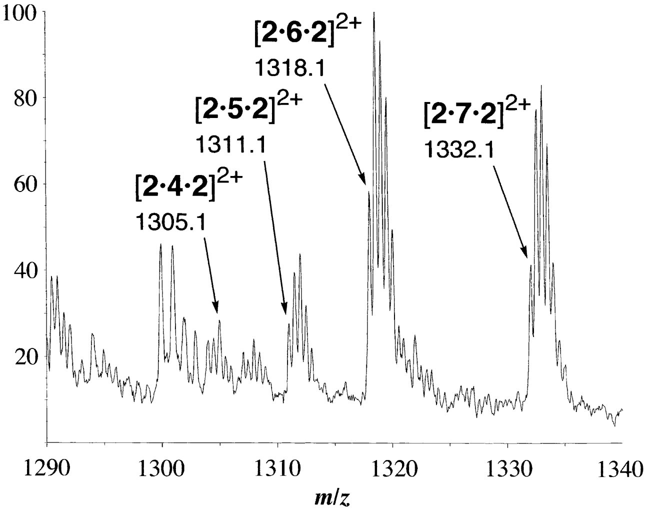

Figure 4. Segment of the ESI mass spectrum of a mixture of **2** and **4**–**7** (**2**:**4**:**5**:**6**:**7** = 40:1:1:1:1, in $CHCl_3$/MeOH 2:1), showing the relative intensities of the peaks accounting for the different capsular assemblies formed.

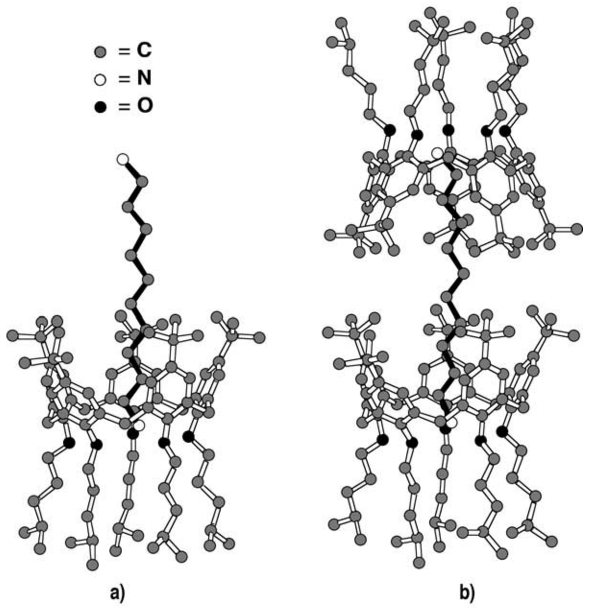

Figure 5. CS Chem3D™ molecular models of (a) the 1:1 inclusion complex and (b) the 2:1 capsular assembly between *penta*-ether **2** and 1,10-decanediammonium ion **6**.

stituents. The trapped guest molecule forms an essential constituent of the capsular assembly of calix[5]arenes. The ternary complex is held together by the cooperative action of a number of weak non-covalent intermolecular forces, including ammonium cation-π[8] and CH-π[14] interactions of the included alkylene chain with the aromatic walls of the calixarene cavity, as well as hydrogen-bond formation between the ammonium head and the ethereal (compounds **1** and **2**) and/or carbonyl oxygen(s) (compound **3**).[15]

The location of the guest within the inner space defined by the capsular assembly of the two calix[5]arene hemicavities can be inferred from a scrutiny of the complexation induced shifts (CISs) experienced by the alkylene chain of the dication upon inclusion, which are reported in Table 1.

CIS values observed for the 1:1 H/G complexes can be regarded as standards to evaluate possible differences in the positioning (degree of penetration) of the ditopic guest in the capsular $H\supset G\subset H$ complexes. In the case of *penta*-ethers **1**, **2** with **7**, the CIS values for the α–δ-CH_2 groups of the guest in both complexes are almost the same, while with **6** the α- and β-CH_2s in the capsule display slightly higher values (up to 0.15 ppm), indicating a lesser degree of penetration than in the 1:1 complexes. However, in spite of the shorter spacer, the ready formation of the capsules from *penta*-ethers **1**, **2** and **6** may imply an extra stabilisation of the ternary complex, probably arising from attractive van der Waals interactions between the two upper rims of the

Table 1. Complexation induced shifts (CISs, $\Delta\delta$ ppm) of methylene groups of α,ω-alkyldiammonium guests **6** and **7** upon formation of *endo*-cavity 2:1 and/or 1:1 H/G complexes with *p*-*tert*-butylcalix[5]arenes **1**–**3** in $CDCl_3/CD_3OD$ (2:1, v/v)[a]

Host	Guest	H/G	α-CH_2	β-CH_2	γ-CH_2	δ-CH_2	ε-CH_2	ξ-CH_2
1	**7**	2:1	4.02	3.59	2.13	1.53	0.77	
		1:1	4.02	3.59	2.13	1.53	0.60	0.38
1	**6**	2:1	4.17	3.69	2.16	1.68	0.95	
		1:1	4.02	3.59	2.16	1.52	0.61	0.37
2	**7**	2:1	4.08	3.51	2.06	1.45	0.69	0.53
		1:1	4.07	3.50	2.03	1.40	0.54	0.24
2	**6**	2:1	4.17	3.55	2.02	1.53	0.84	
		1:1	4.06	3.50	2.02	1.38	0.55	0.33
3	**7**	2:1	3.66	3.41	2.33	1.69	0.83	0.66
		1:1	3.79	3.42	2.21	1.54	0.64	0.38
3	**6**	2:1	4.18	3.51	2.07	1.54	0.86	
		1:1	3.77	3.42	2.22	1.54	0.63	0.37

[a] $\Delta\delta$ values were computed as the difference between the chemical shift of pertinent methylene groups in the free and included guest.

hosts. These additional non-covalent forces have been shown to play an important role in the stabilisation of the 2:1 complexes of calix[5]arenes and Buckminsterfullerene (C_{60}).[16]

The CIS values of the 1:1 H/G complexes with *penta*-ester **3** and **4**–**7** are commensurate with a deeper intrusion of the guest inside the calixarene cavity, because of additional hydrogen bonding of the -NH_3^+ end group with the carbonyl substituent(s). This implies that **6** becomes the shortest guest able to produce capsular assemblies with **3**, the largest CIS deviation from 1:1 complexes being +0.41 ppm for α-CH_2s, while the deepest guest intrusion is noticed in the capsular assembly of **3** with **7** (CIS deviation −0.13 ppm for α-CH_2s). Therefore the formation of the capsules results from a balance between the efficiency of the calixarene host, the length of the spacer and the degree of penetration of the guest inside the cavity.

Future studies will be directed to the design and synthesis of multi-cavity calixarene hosts, possessing either convergent or divergent cavities, and their assemblies with charged ditopic guests.

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