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Synthesis of Upper Rim Covalently Linked Double Calix[6]arenes

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Abstract—A series of new double calix[6]arenes obtained through the 1,3,5-upper rim linkage of two calix[6]arene units with imino or 1,4-phenylendiimino bridges has been synthesised. These compounds were conceived as hosts for selected organic cations but since they are molecular cages with different grades of accessibility of the internal cavity, they gave some insight on the way 1,3,5-trimethoxycalix[6]-arenes interact with guests and, in particular on the pathway guests choose to access the cavity. ^{1}H NMR studies showed that the distance between the two calixarene caps and the dimension of the equatorial portals are the key control elements on the efficiency and selectivity of binding. It was thus hypothesised that the entrance of the guests into the cage takes place exclusively from the equatorial portals and, in general, from the upper rim of the calix[6]arene.

Introduction

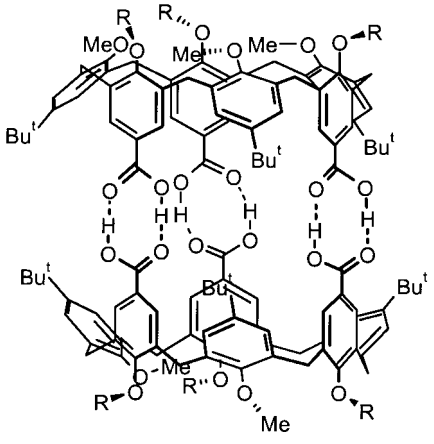
Calixarenes are one of the more extensively studied classes of synthetic hosts. During these last two decades an increasing number of highly selective and efficient receptors for the recognition of metal cations and/or anions and neutral organic molecules have been obtained from these molecular platforms.[1]

More recently several studies dealing with the synthesis of calixarene based hosts able to recognise, through their apolar cavity, organic ammonium cations (especially those involved in biological processes) have been performed.[2] Simple derivatives of calix[4]arene in the *cone* conformation, can recognise quaternary ammonium cations in apolar media, but because of the small size of their cavity they can only efficiently bind guests with small steric demands.[3] In order to increase the host binding surface, rigid double calix[4]arenes[4] or the larger calixarenes (e.g. calix[5],[5] calix[6][6] or homooxacalixarenes[7]) have also been employed. It appears, in general, that calixarene receptors suitable for larger guests show higher binding efficiency toward a potential guest when their conformational mobility is reduced to some extent.

Within the calixarene series, the cavity of calix[6]arene possesses size and symmetry which are probably the best as far as complementarity for quaternary ammonium salts. However, the synthetic problem of controlling the conformational flexibility or fixing it in a rigid *cone* conformation, though documented by several studies, has yet to be fully solved.[8]

Several examples of calix[6]arene derivatives which posses a rigidified skeleton have been reported in the recent literature and some of them show quite interesting recognition properties. The common feature is that in most cases a capping unit was inserted at the 1,3,5-positions of one of the two calix[6]arene rims.[9]

By using a complementary strategy, we have recently verified the possibility of preparing receptors with a rigid and extended cavity having a C_{3v}-symmetry through the self-assembly of the tricarboxy derivative of calix[6]arenes (**I**) (see Fig. 1) and shown its shape selectivity in the binding of *N*-methylpyridinium cations.[10] More recently we have



1 R = C_8H_{17}

Fig. 1. Self-assembled hydrogen bonded molecular cage of calix[6]arene tricarboxylic acid derivative.

Keywords: calixarenes; cage compounds; molecular recognition; quaternary ammonium salts.

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demonstrated for the first time that the calix[6]arene annulus is large enough to allow a dialkyviologen di-cation to thread through the two rims of the calixarene receptor producing a pseudorotaxane.[11]

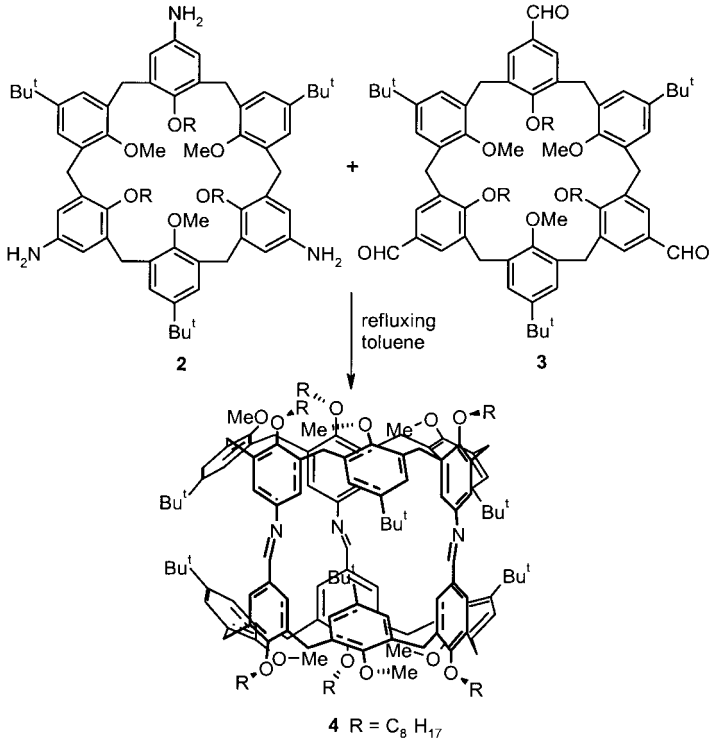
An interesting target was thus to transfer the structural information stored in these hosts to upper rim covalently bridged trimethoxy calix[6]arene derivatives and evaluate the role of both the three methoxy groups and the bridges on the binding properties toward *N*-methylpyridinium cations, thus gaining information whether the access to the cavity of these cages takes place from their poles or from the equatorial portals.

We report herein on the synthesis of a new series of three point head-to-head covalently bridged double calix[6]arenes with bridges that, while maintaining the C_{3v}-symmetry of the cage, span the two calixarene units yielding a host with a bigger cavity; the variation of length and size of these bridges was the parameter used to shield the cage cavity and control the access to the binding site. The binding ability of the hosts were investigated by ^{1}H NMR in $CD_3CN/CDCl_3$ solution, towards a set of *N*-methylpyridinium cations.

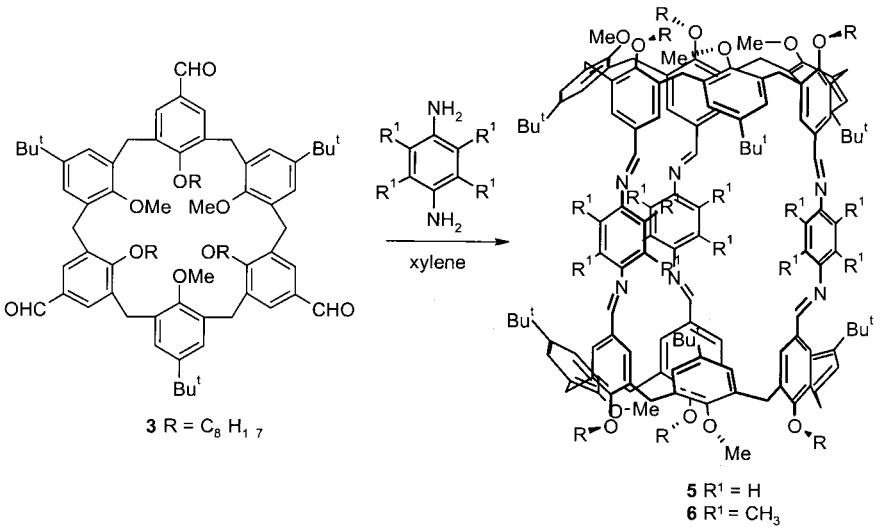
Results and Discussion

Simple molecular mechanics calculations (MM+) indicate that a convenient bridge to connect two calix[6]arene units and maintain them in a fixed conformation was the imino function. For the choice of the synthetic strategy to anchor the two calix[6]arene sub-units, we took advantage of the studies performed by Reinhoudt and co-workers who dimerised two calix[4]arenes through imino bridges obtaining a double calix[4]arene having two different hemispheres.[12] Thus, the double calix[6]arene prototype having short linkers in which access to the cavity should take place only from the calixarene annulus was obtained by reacting the trialdehyde (**3**) with triamino (**2**) derivatives: the three points linked double calix[6]arene **4** was obtained in 26% yield (see Scheme 1). The ^{1}H NMR spectrum of **4** taken in $CDCl_3$ at T=300 K was quite broad and sharpened only in $C_2D_2Cl_4$ at T=353 K. The main feature of the NMR spectrum, taken in these latter conditions, is that while the protons of the aromatic rings bearing the ^{t}Bu groups of both calixarene units resonate as a singlet at δ=7.50 ppm, those involved in the bridges experience two different chemical shifts at δ=7.32 and 6.92 ppm, values that indicate a *pinched cone* conformation. The calixarene methylene protons support the different nature of the two sub-units and resonate as a broad doublet at δ=4.4 ppm for the axial and as a multiplet at δ=3.5 for the equatorial. These data indicate that the linear imino bridges impose a flattened cone conformation to both subunits which thus creates a cavity having the symmetry of a trigonal prism defined by the bridged aromatics and where the nuclei bearing the ^{t}Bu groups are tilted toward the outside. The upfield shift of the six OCH_3 groups of cage **4** (δ=2.60 and 2.53 ppm) indicates that they are oriented inside the cage cavity.

The spanning between the two calixarene units to verify whether the access of the guest to the cavity could take place from the equatorial portals was obtained by introducing three rigid 1,4-diaminobenzene spacers. In particular, reacting the trialdehyde **3** with 1,4-diaminobenzene in a 2:3 molar ratio in refluxing xylene, the corresponding dimer **5** was obtained in 50% yield after precipitation from CH_3OH (see Scheme 2). In a similar manner compound **6**, where the methyl groups on the aromatic bridges could serve to control the access to the inner cavity, was



Scheme 1.



Scheme 2.

synthesised by reacting **3** with tetramethyl-1,4-diaminobenzene in 40% yield.

The ^{1}H NMR spectra of both **5** and **6** taken in $CDCl_3$ show common features. In fact, for both compounds the spectra show sharp signals at room temperature and, as expected, indicate their high symmetry. In **5** and **6** the methoxy groups resonate at δ=2.55 and 2.77 ppm, respectively, indicating that they are oriented inside the cavity.

Binding studies

Because of the different features of the ^{1}H NMR spectra of the double calix[6]arenes synthesised, the binding studies were carried out in $CDCl_3/CD_3CN$=9:1 at 323 K (where they all exhibit sharp signals), with *N*-methylpyridinium (NMP), *N*-methyl-2-picolinium (NM2Pic) and *N*-methyl-4-picolinium (NM4Pic) iodides as guests (see Chart 1).

Preliminarily, the simple calixarene precursors **2** and **3** were tested as hosts and, as expected, they showed negligible complexation ability.

Not totally surprising was the fact that also the double calix[6]arenes **4** and **6** did not show any recognition property toward the guest examined, suggesting that the inward orientation of the methoxy groups at the polar positions, by partially occupying the annulus, prevent the entrance of the guest ion pair into the cavity, which is also shielded from the outside by the short bridges of **4** or by the methyl groups in the portals of **6**.[13]

On the other hand, by adding increasing amounts of a 5×10^{-3} M solution of host **5** to a 5×10^{-4} M solution of the selected guest, a steady upfield shift of the N–CH_3 resonances were observed for all the three guests examined. All NMR spectra showed time-averaged signals for the free and complexed species. Having verified a 1:1 stoichiometry for the association by means of continuous variation methods, the stability constants (K_a), based on monitoring the N–CH_3 group signal, were calculated using methods that have been previously described.[14] It was thus found that the association constants (K_a) for the three guest studied were 447(61), 103(15) and 887(285) M^{-1} for NMP, NM2Pic and NM4Pic, respectively (see Table 1).

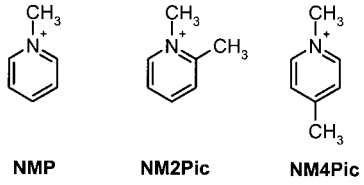


Chart 1.

The different complexation behaviour of hosts **5** and **6** support the hypothesis that the entrance of the guests into

Table 1. Association constants K_a (M^{-1}) and Guest Limiting Shift Values δ_∞ (ppm) for 1:1 complexes measured in $CDCl_3/CD_3CN$=9:1 mixture at T=323 K, of the *N*-methyl pyridinium (NMP), *N*-methyl-2-picolinium (NM2Pic), and *N*-methyl-4-picolinium (NM4Pic) iodides with hosts **5**

Guest	K_a (M^{-1})[a]	δ_∞(N*Me*, ppm)	$\Delta\delta$ (ppm)[b]
NMP	447(61)	3.47(0.06)	+1.1 (N-*Me*) +1.2 (2-*H*) +0.8 (3-*H*) +0.8 (4-*H*)
NM2Pic	103(15)	3.65(0.02)	+0.3 (N-*Me*) +0.3 (2-*Me*) (3-*H*)[c] (4-*H*)[c] +0.3 (5-*H*) +0.5 (6-*H*)
NM4Pic	887(85)	3.09(0.07)	+0.8 (N-*Me*) +0.6 (4-*Me*) +1.1 (2-*H*) +1.0 (3-*H*)

[a] Measured at T=323 by ^{1}H NMR spectroscopy, titrating a solution of the guest [G_0=0.0005 M^{-1}], with a solution of the host [H_0=0.005 M^{-1}], following the *N*-Me signal. All values result from at least duplicate experiments, standard deviations are in brackets.

[b] $\Delta\delta$ Values determined considering the chemical shift of the guest signals at $[G_0]/[H_0]$=0.25 with respect to those of the free guest.

[c] Overlapped peaks.

the cage cavity takes place from the portals present in the equatorial region between the two calixarene units.

Although definitive proof of the structure of the complexes could not be obtained, some features of the geometry of the complexes can be hypothesised by using the analysis of the upfield shifts ($\Delta\delta$) of the various proton signals of the three different *N*-methylpyridinium cations, measured by ^{1}H NMR during complexation. The observation that, although to a different extent, all protons present in the three guests are upfield shifted, indicates that they are in close proximity and are strongly bound in the cage cavity (Table 1) However, the weak upfield shift experienced by the protons in positions 3 and 4 or the 4-CH_3 or 2-CH_3 in the cases of picolinium ions and the constant chemical shift of the calixarenes OCH_3 during titrations[11] probably indicates that these cations are not completely embedded by the host cavity. In agreement with this hypothesis, MM+ calculations suggest that in all the three cases the positively charged portion of the guest is positioned in the equatorial portion of the cage stacked and sandwiched by the bridging aromatic rings in a situation where part of the guest surface is outside of the cavity, while the two calix[6]arene portions only make a minor contribution to the binding site.

Attempts to extend the binding studies to the more elongated viologen cations or to incorporate them inside the cage during synthesis to exploit also the calix[6]arenes cavities failed. It thus appear that the binding property of host **5** derives from the binding ability of the bridges which also control the access of the guest to the cavity.

In conclusion, although a direct comparison of these data with those obtained for the hydrogen bonded dimer **1** is not possible because of the different experimental conditions used, it is reasonable to conclude that the proper choice of the spacer to covalently connect the two calix[6]arene cups results in a substantial increase of efficiency. It also seems clear that in the case of 1,3,5-trimethoxy calix[6]arenes the access to the cavity can take place only through the upper rim.

Experimental

Most of the solvent and all reagents were obtained from commercial supplies and used without further purification. Toluene and *p*-xylene were distilled and stored over $LiAlH_4$ prior to use. ^{1}H and ^{13}C NMR spectra were recorded on Bruker AC300 and AMX400 instruments. Chemical shifts are reported as δ values in ppm from tetramethylsilane as internal standard. Analytical thin-layer chromatography was carried out on silica gel plates (SiO_2, Merck 60 F_{254}). Mass spectra were performed with Finnigan MAT SSQ710 (DCI, CH_4). Melting points were obtained on a nitrogen sealed capillary on an Electrothermal apparatus. All reactions were performed in nitrogen atmosphere unless otherwise specified. 5,17,29-Triamino-11,23,35-tris(1,1-dimethylethyl)-37,39,41-trimethoxy-38,40,42-tri-*n*-octyloxycalix[6]arene (**2**) and 5,17,29-triformyl-11,23,35-tris(1,1-dimethylethyl)-37,39,41-trimethoxy-38,40,42-tri-*n*-octyloxycalix[6]arene (**3**) were synthesised according to literature procedures.[15]

As observed by other authors,[16] the elemental analysis of calixarenes are very often incorrect. Nevertheless, the spectral data were in full agreement with the proposed structure of these new compounds.

Synthesis of cage 4. Calix[6]arene derivatives **2** (0.5 g, 0.4 mmol) and **3** (0.5 g, 0.4 mmol) were dissolved in dry toluene (500 mL) and poured into a round-bottomed flask equipped with a Dean–Stark apparatus. The resulting mixture was refluxed for three days, then the solvent was completely removed by distillation in vacuo. Purification of the residue by column chromatography (ethyl acetate/hexane, 5:95) gave 0.26 g (26%) of **4**; mp: 170–173°C; ^{1}H NMR (300 MHz, $C_2D_2Cl_4$, T=353 K): δ=8.05 (s, 3H, N=C*H*), 7.50 (s, 12H, Ar*H*), 7.32 (s, 6H, Ar*H*), 6.92 (s, 6H, Ar*H*), 4.45 (bd, 12H, $ArCH_2Ar$ ax), 3.96 (m, 12H, $OCH_2(CH_2)_7CH_3$), 3.5–3.6 (m, 12H, $ArCH_2Ar$ eq), 2.60 (bs, 9H, OCH_3), 2.53 (bs, 9H, OCH_3), 2.00 (m, 12H, $OCH_2CH_2(CH_2)_5CH_3$), 1.67 (m, 12H, $O(CH_2)_2CH_2(CH_2)_4CH_3$), 1.51–1.34 (m, 78H, $O(CH_2)_3(CH_2)_4CH_3$, $-C(CH)_3$), 0.96 (bt, 18H, $O(CH_2)_7CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ=191.5, 157.0, 155.8, 154.8, 153.6, 146.1, 145.8, 144.4, 135.2, 133.4, 132.3, 127.7, 127.5, 120.7, 73.6, 61.1, 34.4, 31.8, 30.6, 29.7, 29.3, 26.4, 22.7, 14.1; MS (DCI) *m/z*: 2442 (M^+, 100). Anal. Calcd for $C_{165}H_{225}N_3O_{12}$: C, 81.13; H, 9.28; N, 1.72. Found: C, 80.54; H, 9.30; N, 1.71.

General procedure for the synthesis of cages 5 and 6

Compound **3** (1.00 g, 0.84 mmol) was dissolved in xylene (25 mL) in a round-bottomed flask equipped with a Dean–Stark apparatus and the bridging spacer unit (1.31 mmol) was then added to the solution. After 24 h at 120°C the solvent was removed under reduced pressure: the crude product was dissolved in the minimum amount of CH_2Cl_2 and precipitated with methanol yielding the final product as a yellow-brown solid.

Compound 5. Bridging unit: *p*-phenylenediamine (yield 50%). mp: 194–196°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ=8.05 (s, 6H, N–CH), 7.43 (s, 12H, ArH), 7.40 (s, 12H, ArH), 6.91 (s, 12H, ArH), 4,63 (d, ^2J(H,H)=15 Hz, 12H, $ArCH_2Ar$ ax), 3.93 (t, ^3J(H,H)=6.5 Hz, 12H, $OCH_2(CH_2)_6CH_3$), 3.47 (d, ^2J(H,H)=15 Hz, 12H, $ArCH_2Ar$ eq), 2.55 (bs, 18H, OCH_3), 1.93(m, 12H, $OCH_2CH_2(CH_2)_5CH_3$), 1.58 (m, 12H, $O(CH_2)_2CH_2(CH_2)_4CH_3$), 1.43(s, 54H, $C(CH_3)_3$), 1.35 (m, 48H, $O(CH_2)_2CH_2(CH_2)_4CH_3$), 0.91 (t, ^3J(H,H)=6.8 Hz, 18H, $O(CH_2)_7CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ=158.7, 157.2, 154.6, 149.4, 146.1, 135.0, 132.6, 131.5, 128.1, 127.7, 121.3, 73.6, 61.0, 34.3, 31.8, 31.6, 30.3, 29.5, 29.3, 29.2, 26.1, 22.6, 14.0; MS (DCI) *m/z*: 2750 (MH^+, 100), 2637 (49). Anal. Calcd for $C_{186}H_{240}N_6O_{12}$ (2751.97): C, 81.18; H, 8.79; N, 3.05. Found: C, 80.68; H, 8.83; N, 3.02.

Compound 6. Bridging unit: 2,3,5,6-tetramethyl-1,4-diaminobenzene (yield 40%). mp: 212–215°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ=7.61 (s, 6H, N=CH), 7.39 (s, 12H, ArH), 7.27 (s, 12H, ArH), 4.57 (d, ^2J(H,H)=15 Hz, 12H, $ArCH_2Ar$ ax), 3.94 (t, ^3J(H,H)=6.5 Hz, 12H, $OCH_2(CH_2)_6CH_3$), 3.50 (d, ^2J(H,H)=15 Hz, 12H, $ArCH_2Ar$ eq), 2.77 (bs, 18H, OCH_3), 1.93(m, 12H, $OCH_2CH_2(CH_2)_5CH_3$), 1.62 (s, 36H, $ArCH_3$) 1.60 (m, 12H, $O(CH_2)_2CH_2(CH_2)_4CH_3$),

1.43(s, 54H, $C(CH_3)_3$), 1.35 (m, 48H, $O(CH_2)_2CH_2(CH_2)_4CH_3$), 0.90 (t, ^3J(H,H)=6.8 Hz, 18H, $O(CH_2)_7CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ=161.4, 157.0, 154.3, 147.1, 146.1, 134.8, 132.8, 131.9, 127.8, 127.2, 123.3, 73.4, 60.6, 34.2, 31.8, 31.6, 30.4, 29.5, 29.2, 26.2, 22.6, 14.6, 14.0; MS (DCI) *m/z*: 2920 (M^+, 100), 2806 (38). Anal. Calcd for $C_{198}H_{264}N_6O_{12}$ (2920.29): C, 81.44; H, 9.11; N, 2.88. Found: C, 80.45; H, 9.16; N, 2.83.

References

1. Gutsche, C. D. Calixarenes Revisited. In *Monographs in Supramolecular Chemistry*; Stoddart, J. F., Ed.; The Royal Society of Chemistry: Cambridge, 1998; Vol. 6.
2. Dalla Cort, A.; Mandolini, L. In *Calixarenes in Action*; Mandolini, L., Ungaro, R., Eds.; Imperial College: London, 2000; pp 85–110.
3. Arduini, A.; McGregor, W. M.; Paganuzzi, D.; Pochini, A.; Secchi, A.; Ungaro, R. *J. Chem. Soc., Perkin Trans. 2* **1996**, 839–846.
4. Arduini, A.; Pochini, A.; Secchi, A. *Eur. J. Org. Chem.* **2000**, 2325–2334.
5. (a) Arnecke, R.; Böhmer, V.; Cacciapaglia, R.; Dalla Cort, A.; Mandolini, L. *Tetrahedron* **1997**, *53*, 4901–4908. (b) Arnaud-Neu, F.; Fuangswasdi, S.; Notti, A.; Pappalardo, S.; Parisi, M. F. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 112–114.
6. (a) Takeshita, M.; Nishio, S.; Shinkai, S. *J. Org. Chem.* **1994**, *59*, 4032–4034. (b) Casnati, A.; Jacopozzi, P.; Pochini, A.; Ugozzoli, F.; Cacciapaglia, R.; Mandolini, L.; Ungaro, R. *Tetrahedron* **1995**, *51*, 591–598. (c) Araki, K.; Akao, K.; Otsuka, H.; Nakashima, K.; Inokuchi, F.; Shinkai, S. *Chem. Lett.* **1994**, 1251–1254. (d) Magrans, J. O.; Ortiz, A. R.; Molins, M. A.; Lebouille, P. H. P.; Sànchez-Quevada, J.; Prados, P.; Pons, M.; Gago, F.; de Mendoza, J. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1712–1715.
7. (a) Masci, B. *Tetrahedron* **1995**, *51*, 5459–5464. (b) Masci, B.; Finelli, M.; Varrone, M. *Chem. Eur. J.* **1998**, *4*, 2018–2030.
8. Gutsche, C. D.; Alam, I. *Tetrahedron* **1988**, *44*, 4689–4694.
9. See e.g. Ikeda, A.; Shinkai, S. *Chem. Rev.* **1997**, *97*, 1713–1734 and references therein.
10. Arduini, A.; Domiano, L.; Ogliosi, L.; Pochini, A.; Secchi, A.; Ungaro, R. *J. Org. Chem.* **1997**, *62*, 7866–7868.
11. Arduini, A.; Ferdani, R.; Secchi, A.; Pochini, A.; Ugozzoli, F. *Angew. Chem., Int. Ed. Engl.* **2000**, in press.
12. Struck, O.; Chrisstoffels, A. J.; Lugtenberg, R. J. W.; Verboom, W.; van Hummel, G. J.; Harkema, S.; Reinhoudt, D. N. *J. Org. Chem.* **1997**, *62*, 2487–2493.
13. To exclude the problems associated with slow complexation processes, 1:1 host-guest solutions were refluxed up to 48 h without evidence of complexation. Attempts to utilise this cage as carcerand by adding the guests examined during its synthesis invariably gave the 'empty' host.
14. (a) Wilcox, C. S. In *Frontiers in Supramolecular Chemistry and Photochemistry*; Schneider, H-J., Dürr, H., Eds.; VCH: Veinheim, 1991; pp 123–143. (b) Tsukube, H.; Furuta, H.; Odani, A.; Takeda, Y.; Kudo, Y.; Inoue, Y.; Liu, Y.; Sakamoto, H.; Kimura, K. In *Comprehensive Supramolecular Chemistry*; Atwood, J. L., Davies, J. E. D., MacNicol, D. D., Vögtle, F., Eds.; Pergamon: Oxford, 1996; Vol. 8, pp 123–143.
15. Casnati, A.; Domiano, L.; Pochini, A.; Ungaro, R.; Carramolino, M.; Magrans, J. O.; Nieto, P. M.; López-Prados, J.; Prados, P.; de Mendoza, J.; Janssen, R. G.; Verboom, W.; Reinhoudt, D. N. *Tetrahedron* **1995**, *51*, 12699–12720.
16. (a) Böhmer, V.; Jung, K.; Schon, M.; Wolff, A. *J. Org. Chem.* **1992**, *57*, 790–792. (b) Gutsche, C. D.; See, K. A. *J. Org. Chem.* **1992**, *57*, 4527–4539.