Dimeric Capsules by the Self-Assembly of Triureidocalix[6]arenes through Hydrogen Bonds

Juan J. González,[a] Riccardo Ferdani,[a,b] Emanuela Albertini,[a,b] José M. Blasco,[a] Arturo Arduini,[b] Andrea Pochini,[b] Pilar Prados,[a] and Javier de Mendoza*[a]

Dedicated to Professor José Elguero on the occasion of his 65th birthday

Abstract: A number of calix[6]arenes bearing ureas at the upper rim positions of alternate rings 1, 3 and 5 were prepared and studied in detail by NMR spectroscopy and gel permeation chromatography. *N*-Unsubstituted ureas were shown to dimerize through a cyclic array of hydrogen bonds to give cylindrical cavities capable of encapsulating small molecules such as dichloromethane, benzene and fluorobenzene. Slow equilibria between dimer and monomer were observed in $[D_6]$DMSO-$CDCl_3$ mixtures. By contrast, *N*-substituted ureas are monomeric. All urea monomers with bulky *O*-substituents display a solvent-dependent, slow equilibrium between C_{3v} and C_s cone conformations.

Keywords: calixarenes · host-guest chemistry · hydrogen bonds · inclusion compounds · self-assembly

Introduction

The chemical properties and behaviour of supramolecular entities are governed exclusively by the information stored in their molecular architectures. When two or more identical subunits are geometrically and functionally complementary, they may self-assemble to form a supermolecule that is held together by noncovalent contacts, such as hydrogen bonds or hydrophobic, electrostatic and van der Waals interactions.[1, 2] Several instances of self-complementary molecules that form dimers in solution have been reported. The most interesting examples occur when the molecular subunits have hemispherical or curved structures, because the resulting assembly possesses a defined cavity that may encapsulate guest molecules of appropriate dimensions. In the recent literature a number of calixarenes have been reported to undergo self-assembly through multiple hydrogen bonds in nonpolar solvents. Dimerization of calix[4]arenes that contain urea substituents at the upper rim has been independently and extensively studied by Rebek and Böhmer (Figure 1, left).[3, 4]

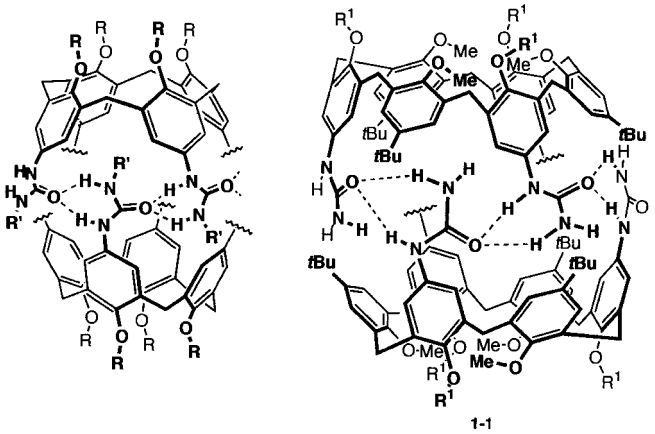


Figure 1. Structure of a tetraureidocalix[4]arene dimer (left) and a 1,3,5-triureidocalix[6]arene dimer **1-1** (right). Some hydrogen bonds that form the cyclic array are depicted. Urea groups at the back have been omitted for clarity.

The cavities produced by tetraureidocalix[4]arenes are not very large. Guests the size of common organic solvents, simple benzene derivatives or cubane can be accommodated in the almost spherical hole, but substrates larger than toluene (i.e., *p*-xylene) are simply too large to penetrate efficiently into these calixarene cages.[3] At first sight, it seems likely that use of other members of the calixarene family, such as calix[5]- or

[a] Prof. Dr. J. de Mendoza, Prof. Dr. P. Prados, Dr. J. J. González, J. M. Blasco
Departamento de Química Orgánica
Universidad Autónoma de Madrid
Cantoblanco, E-28049, Madrid (Spain)
Fax: (+34) 91-397-3966
E-mail: javier.demendoza@uam.es

[b] Prof. Dr. A. Arduini, Prof. Dr. A. Pochini, R. Ferdani, E. Albertini
Dipartimento di Chimica Organica e Industriale
Università degli Studi, Parco Area delle Scienze 17/A
I-43100, Parma (Italy)

Supporting information for this article is available on the WWW under http://www.wiley-vch.de/home/chemistry/ or from the authors.

  0947-6539/00/0601-0073 $ 17.50+.50/0

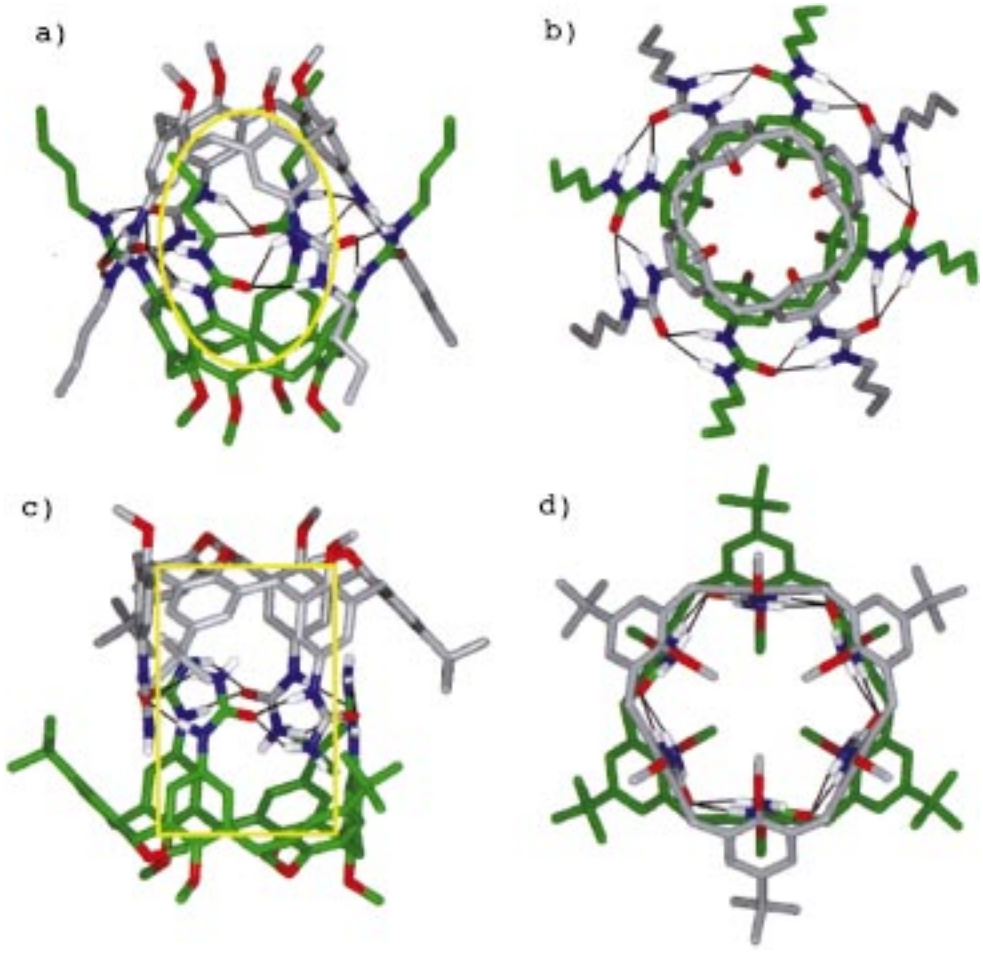


Figure 2. Energy-minimized structures of tetrabutyl-ureidocalix[4]-arene a) side view b) top view, and of 1,3,5-triureidocalix[6]arene c) side view d) top view (InsightII/Discover, cvff force field). In the figures, *O*-alkyl chains have been reduced to methyl groups for clarity. Also, most hydrogen atoms, except those of the ureas, have been omitted. Yellow lines have been used to highlight the approximate size and shape of the resulting cavities.

Abstract in Spanish: *Se han preparado y estudiado en detalle por RMN y cromatografía de permeación de gel varios calix[6]arenos con ureas en las posiciones para de anillos alternados (1,3,5). Los compuestos con ureas N-no sustituídas dimerizan dando lugar a cavidades cilíndricas unidas por un circuito cerrado de enlaces de hidrógeno, capaces de encapsular pequeñas moléculas como diclorometano, benceno o fluorobenceno. En mezclas de [D$_6$]DMSO-CDCl$_3$ se observa un equilibrio lento entre monómero y dímero. Por el contrario, las ureas N-sustituídas son monoméricas. Todas las ureas monoméricas con O-sustituyentes voluminosos muestran un equilibrio lento, dependiente del disolvente, entre conformaciones cono de simetría C_{3v} y C_s.*

Abstract in Italian: *Sono stati preparati e caratterizzati in maniera approfondita mediante NMR e permeazione su gel nuovi calix[6]areni recanti gruppi urea nelle posizioni para di anelli alternati (1,3,5). I composti con uree non sostituite dimerizzano dando origine a cavitá cilindriche, attraverso la formazione di legami ad idrogeno multipli, capaci di incapsulare piccole molecole neutre come diclorometano, benzene o fluorobenzene. In miscele [D$_6$]DMSO-CDCl$_3$ si osserva un equilibrio lento tra monomero e dimero. Al contrario le uree N-sostituite sono monomeriche. Tutte le uree monomeriche con un O-sostituente voluminoso mostrano un equilibrio lento, dipendente dal solvente, tra conformazioni a cono di simmetria C_{3v} e C_s.*

even calix[6]arenes would permit the trapping of larger substrates.[5] However, pentaureideocalix[5]arenes do not dimerize,[6] probably due to steric hindrance caused by the *N*-substituents at the urea termini. In the succesful calix[4]-arene case, the substituents interlock and protrude away from the hydrogen-bonded groups on top of each wide-open conical platform (Figure 2a,b). This is increasingly difficult in the more cylindrical, flexible cone conformation of calix[5]arenes, and almost impossible in the wider and even more flexible calix[6]arenes, for which a perfect cone conformation is difficult to achieve.

A cone conformation with a threefold symmetry axis has been described for many 1,3,5-tri-*O*-methoxycalix[6]arene derivatives, in which three rings point away from the axis; this allows the *O*-methoxy groups to be included in the cavity and thus occupy a substantial part of the cavity space.[7] As a result, the remaining rings lie almost parallel to the threefold central axis of symmetry; this provides a suitable edge for a predictable dimerization by means of sticky contacts between small substituents, for example, carboxylic acid groups.[4c] Because of these steric restrictions, the use of ureas should be limited to *N*-unsubstituted derivatives. Here we describe the synthesis, the encapsulation studies and the conformational behaviour of 1,3,5-triureidocalix[6]arenes **1** (Figure 1, right). Some *N*-substituted derivatives, which were unlikely to dimerize, were also studied for comparison. In our representation (Figure 2c,d), the dimer adopts a quasi-cylindrical

0947-6539/00/0601-0074 $ 17.50+.50/0 *Chem. Eur. J.* **2000**, *6*, No. 1

shape (more precisely, a hexagonal prism) capped by the two flexible calixarene platforms.

Results and Discussion

Synthesis: Triureas **1** and **5** were synthesized by a three-step procedure. Precursors **4a–c** were obtained by alkylation of trinitrocalix[6]arene **2**[8] (38–54% yields) followed by reduction of the resulting **3a–c** by using either H_2/PtO_2 in THF or $NH_2NH_2 \cdot H_2O$/Pd–C in $MeOH/CH_2Cl_2$, which proceeds with almost quantitative yields. Precursors **3d** and **4d** have been described previously.[8] *N*-Substituted ureas **5** were obtained in 50–56% yields from **4** by reaction with the appropriate isocyanate in CH_2Cl_2. *N*-Unsubstituted ureas **1** were prepared in 35–55% yields by reaction of aminocalix[6]arenes **4** with triphosgene or phosgene in toluene followed by treatment of the resulting isocyanate with aqueous ammonia (Scheme 1).

Monomeric calix[6]arenes: The presence of phenyl or *n*-butyl groups prevents dimerization of model 1,3,5-triureidocalix[6]-arenes **5** and these compounds should be monomeric with C_{3v} symmetry.[7] Accordingly, only one aromatic signal for the ureido-substituted ring and homotopic OCH_2R protons were observed in the ^1H NMR spectra ($CDCl_3$) of **5**. Furthermore, an average molecular weight of 1860 ± 300 amu was obtained for **5a** by vapor pressure osmometry (VPO) in chloroform (37 °C, calix[6]arene **6** as standard). This value is in good agreement with that calculated for monomeric **5a** (MW = 1586 amu).

N-Unsubstituted 1,3,5-triureidocalix[6]arenes **1** are also monomeric in polar, competitive solvents, such as [D_6]DMSO. In addition to the expected C_{3v} conformation, a second conformation with a C_s symmetry was observed in the spectra of derivatives **5** (in [D_6]DMSO, [D_6]acetone or [D_3]acetonitrile) and **1** (in [D_6]DMSO), but only for compounds bearing three bulky lower rim *O*-substituents (i.e., larger than *O*–CH_2CH_2OEt) attached to the rings that contain the urea groups. Thus, while the ^1H NMR spectrum of nonrigid compounds **5d** and **1b** (in [D_6]DMSO) showed only the presence of C_{3v} conformation, those of compounds **5a, 1a** and **1c** indicated a mixture of C_{3v} and C_s conformers in ca. 1:1 ratios. The amount of C_s conformer decreased both with decreasing solvent polarity, that is, [D_6]DMSO > [D_6]acetone > [D_3]acetonitrile, and also upon addition of a less polar solvent, such as [D_6]benzene or $CDCl_3$. Reciprocally, the C_s conformation in calixarene **5a** increased on the addition of D_2O to a [D_6]acetone solution of the compound.

Both conformers of compound **1a** were fully assigned by COSY, HMQC and ROESY experiments in a 5:2 [D_6]DMSO/[D_6]benzene mixture at 50 °C, in which signal resolution was best. Connectivities observed in the COSY and ROESY experiments are summarized schematically in Figure 3.

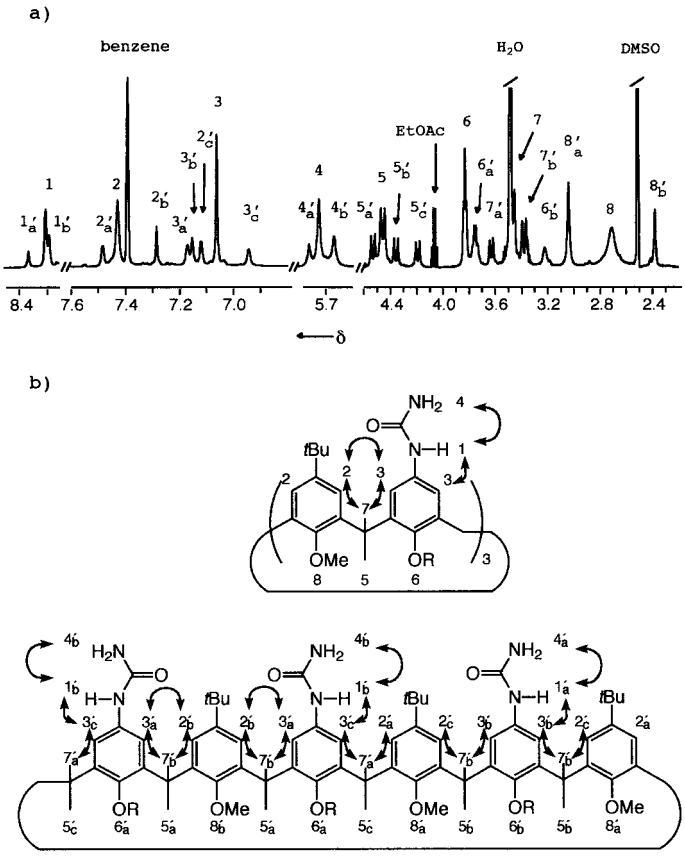
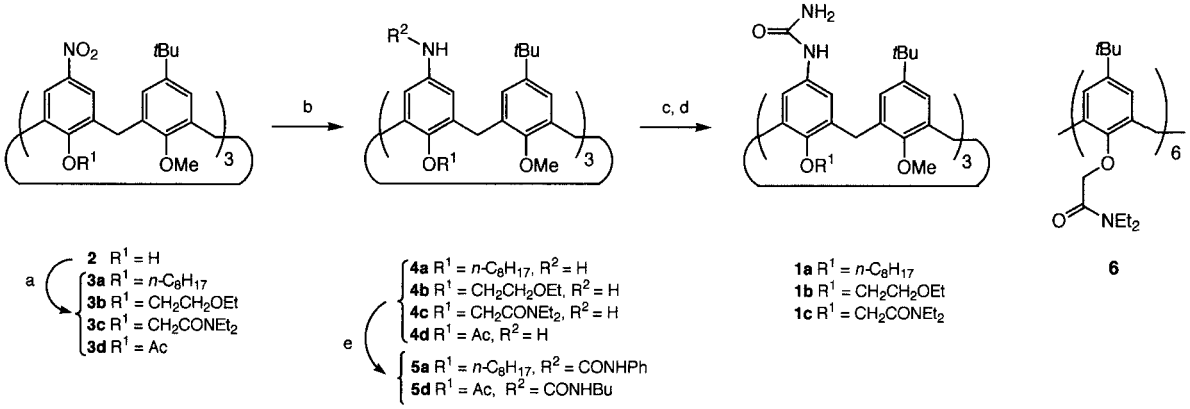


Figure 3. a) ^1H NMR spectrum (500 MHz, [D_6]DMSO/[D_6]benzene 5:2, 50 °C) of **1a** (a dash is used to differenciate C_s conformer signals from C_{3v} conformer signals and subscript letters to differenciate between signals of nonequivalent protons of C_s conformer. b) Connectivities obtained for C_{3v} and C_s conformers of compound **1a** from COSY and ROESY experiments.



Scheme 1. Synthesis of triureidocalix[6]arenes: a) R^1X, NaH, DMF, 75 °C or R^1X, K_2CO_3, CH_3CN, 80 °C. b) H_2, PtO_2, THF or $NH_2NH_2 \cdot H_2O$, Pd/C, CH_2Cl_2/MeOH. c) Triphosgene, $PhCH_3$, 110 °C. d) NH_4OH aq 30%, THF/$PhCH_3$, 25 °C. e) R^2NCO, CH_2Cl_2, 25 °C.

As for other 1,3,5-trimethoxycalix[6]arene derivatives, the C_{3v} conformer of **1a** displays a flattened cone structure, with the methoxy groups inside the calix[6]arene annulus; this was deduced from the two-dimensional NMR spectrum and from the strongly shielded methyl signals ($\delta = 2.65$).[7] On the other hand, the C_s conformation is a flattened cone with two conformationally restricted ureido groups related by a plane of symmetry, and a third urea in the plane freely rotating on the NMR timescale. Such a structure is supported by the diastereotopicity of the OCH_2R ($6'_a$) protons.

A ROESY experiment of **1a** in a 5:2 [D_6]DMSO/[D_6]benzene mixture at 50 °C showed exchange peaks between the C_{3v} and C_s conformers, as well as between signals of the C_s conformer itself, namely, i) for the protons of the same aromatic ring, ii) for the protons of the three nonequivalent *tert*-butyl-substituted rings and iii) for the protons of the three nonequivalent ureido-substituted rings. These exchanges, as well as the dependence of conformer ratios on solvent polarity or on addition of water, can be tentatively explained by a solvent molecule (or H_2O) bridging the conformationally restricted urea groups in the C_s conformer (Figure 4). Thus, this unprecedented slow exchange at room temperature between two cone calixarene conformations not related by ring inversion can be accounted for by the cleavage of hydrogen bonds between the bridging unit and the ureido groups, which leads to the C_{3v} conformer. Conversely, the bridging of two out of the three mobile ureido groups in the C_{3v} conformer by a solvent molecule would be expected to force the structure back to C_s symmetry.

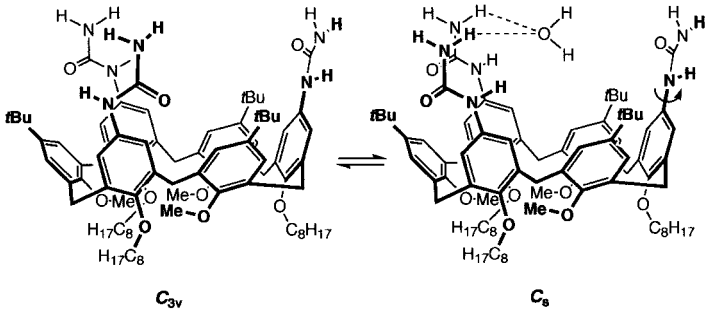


Figure 4. Proposed structures for C_{3v} and C_s conformers of compound **1a**.

Self-assembly: In agreement with our initial predictions, we noticed that *N*-unsubstituted calixarenes **1**, but *not* the *N*-substituted analogues **5**, self-assembled to give dimers (**1-1**) when the competitive polar solvents mentioned above were replaced by less polar ones, such as [D_6]benzene, [D_8]toluene, CD_2Cl_2, $CDCl_3$, CCl_4 or $CDCl_2CDCl_2$. In the dimers, each subunit must display a C_3 symmetry, owing to the circular array of hydrogen bonds that keep the ureas of both rings firmly linked together. As for the calix[4]arene tetraureas,[3] urea rotations are "frozen" in the dimer, so two enantiomeric subunits give rise to a *meso* capsule. The global symmetry of dimers **1-1** is therefore S_6. This was fully consistent with the ^{1}H NMR spectra of either **1a-1a**, **1b-1b** or **1c-1c** in any of the nonpolar solvents mentioned above. For instance, two clearly differenciated aromatic signals at about $\delta = 7.10$ and 6.30 with a characteristic *meta* coupling (assigned unambiguously by a COSY experiment on the aromatic protons of the rings bearing the urea functions) were observed for dimer **1a-1a** in $CDCl_3$. Furthermore, a typical pattern of a triplet of doublets at $\delta = 3.80$ was displayed by the O–CH_2–R protons at the lower rim, which become diastereotopic in the dimer as a result of the loss of the planes of symmetry bisecting each aromatic nucleus in the monomeric subunits that contain freely-rotating urea groups. Irradiation of the CH_2 signal of the *O*-octyl chain at δ 1.87 converted the O–CH_2–R signal into an AB system with a geminal coupling.

The structure of dimer **1a-1a** was also confirmed by gel-permeation chromatography (GPC) in chloroform, using polystyrenes as standards.[9] Compound 5a, (monomer MW = 1580, see above) was used as a model for a monomeric calixarene of similar shape to monomeric **1a**. This compound gave a symmetrical peak at MW = 1293. The unsubstituted urea dimer **1a-1a** (calcd MW = 2715) gave a tailed peak at MW = 1793 and a small peak at MW = 968 corresponding to monomeric **1a** (calcd MW = 1358).[10] Dimer **1b-1b** (calcd MW = 2464) gave a sharp, symmetrical peak at MW = 2656.

Further evidence for dimer **1a-1a** came from dilution experiments and by recording the spectra in mixtures of solvents: a broad signal at about $\delta = 4.9$ from the "free" monomeric urea NH_2 protons gradually emerged as a 2.5×10^{-3} M solution in $CDCl_3$ was diluted to 1.25×10^{-4} M. Dimer **1a-1a** was also studied in mixtures of $CDCl_3$ and [D_6]DMSO. With a 20% v/v of [D_6]DMSO, a slow conversion from dimer to monomer was noted; the two individual species were observed simultaneously in the spectrum (Figure 5).[11]

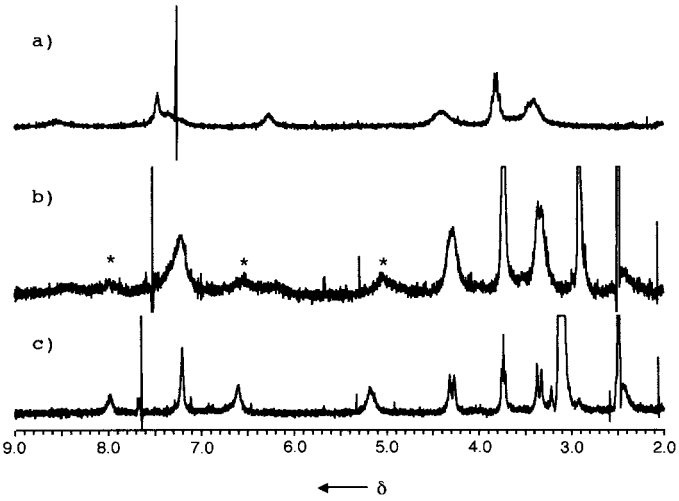


Figure 5. a) ^{1}H NMR spectrum (300 MHz, $CDCl_3$, 25 °C) of **1a-1a**. b) Same sample 30 min after addition of 20% v/v [D_6]DMSO (monomer signals are labelled with an asterisk). c) Two days later.

The flexibility of the calix[6]arene platforms caused the spectra of dimers **1a-1a** and **1b-1b** at 25 °C to be rather broad and poorly resolved. Variable temperature spectra of **1a** in $CDCl_2CDCl_2$ from 25 to 125 °C again showed the transition from dimer to monomer. However, the ^{1}H NMR spectra in $CDCl_3$, $CDCl_2CDCl_2$ and [D_8]toluene were very complex at low temperatures (from −40 to 0 °C); the loss of symmetry was probably caused by the poor fit of these solvents into the

0947-6539/00/0601-0076 $ 17.50+.50/0 *Chem. Eur. J.* **2000**, *6*, No. 1

cavity. By contrast, low-temperature spectra in CD_2Cl_2 (from -70 to $-30\,^{\circ}C$) showed sharply split signals and a change of symmetry from S_6 to C_i (Figure 6).

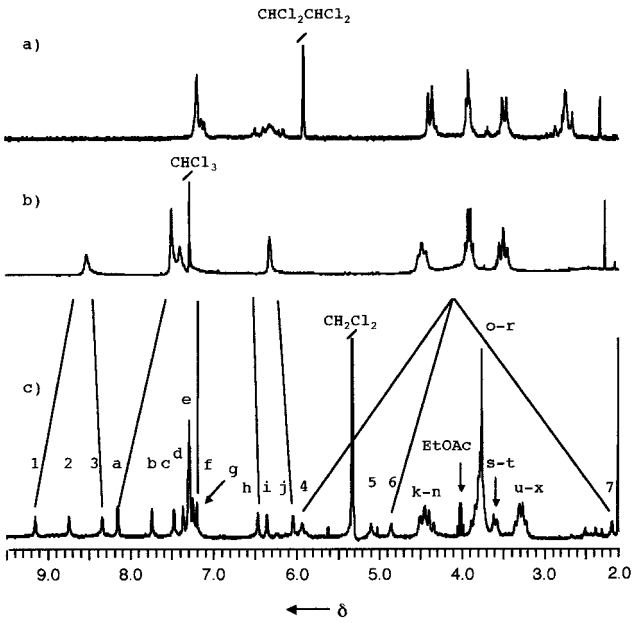


Figure 6. a) ^1H NMR spectrum (300 MHz, $C_2D_2Cl_4$, 125 °C) of **1a**. b) ^1H NMR spectrum (300 MHz, $CDCl_3$, 45 °C) of **1a-1a**. c) ^1H NMR spectrum (300 MHz, CD_2Cl_2, $-40\,^{\circ}C$) of **1a-1a**. For numbering see Figure 7.

Since the ^1H NMR spectrum of monomeric **1a** in a 5:2 CD_2Cl_2/CD_3OD mixture at $-40\,^{\circ}C$ is typically broad and only shows two signals at $\delta = 7.21$ and 6.40 for the aromatic protons,[12] this splitting suggests that the dimerization process freezes the conformational inversion of the calixarene in the range -70 to $-30\,^{\circ}C$.[13]

COSY experiments in CD_2Cl_2 at $-30\,^{\circ}C$ were initially used to correlate protons of the same aromatic rings, or pairs of methylene protons in the calixarene skeleton. A HMQC experiment infers a *syn* arrangement of the aromatic rings, since methylene carbons appeared in the range $\delta = 30.0$–31.5.[14] A ROESY spectrum showed close contacts between protons of contiguous aromatic rings (i.e., c–e, g–j, e–d and e–i) and between those of the adjacent methylene protons (i.e., h–t, c–w–e, g–u, e–x–d, i–v, f–s, a–o and b–p; see Figure 7). These ROEs and the information from the COSY spectrum provided the connectivity around the calixarene units; this can be extended to the urea protons by consecutive correlations between aromatic-NH and NH–NH for two ureido groups (h–2, j–3, i–1, 2–5 and 3–4). The third urea was assigned by elimination. The relative disposition of calixarene units was established by the observation of three intermolecular ROE contacts between aromatic protons in the skeleton of one calixarene and the urea protons of the opposite calixarene (d–5, i–7 and f–4). Finally, the structure for the dimer depicted in Figure 1 (right) was clearly supported by the strong shielding of one of the urea NH_2 protons (namely 7, $\delta = 2.10$, see Figure 7) that is forced to lie in front of the aromatic rings of the complementary subunit.

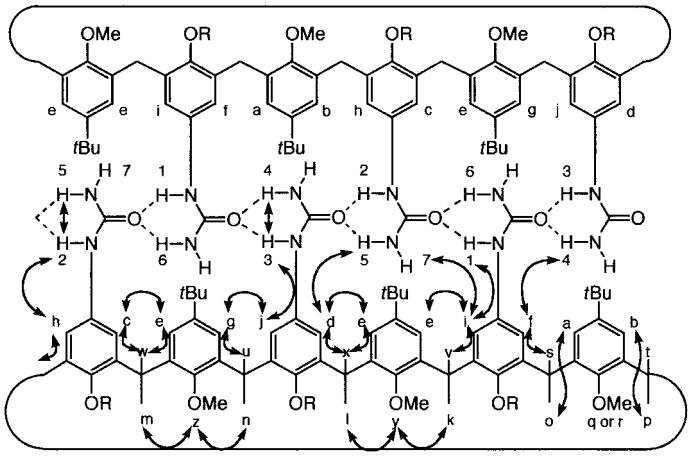


Figure 7. Connectivities obtained for dimer **1a-1a** from COSY and ROESY in CD_2Cl_2 at $-30\,^{\circ}C$.

Guest encapsulation: The well-resolved low-temperature spectrum of dimer **1a-1a** in CD_2Cl_2, in contrast to the broad signals observed with larger solvents (see preceding section) could be interpreted as a sign of solvent encapsulation. Indeed, a new signal appeared at $\delta = 3.67$ when the spectrum was recorded in nondeuterated CH_2Cl_2 at $-50\,^{\circ}C$. The signal was unambiguously assigned to encapsulated CH_2Cl_2 by a HMQC spectrum: a ^{13}C peak was observed at $\delta = 52.3$ (for nonencapsulated CH_2Cl_2 ^1H and ^{13}C NMR peaks appear at $\delta = 5.33$ and 54.0, respectively).

Closer inspection of the two-dimensional NMR spectra of dimer **1a-1a** in CD_2Cl_2 at $-30\,^{\circ}C$ indicates a flattened cone conformation for each subunit, in close agreement with the initial predicted structure (Figure 2c), although somewhat more flexible. For instance, the *tert*-butyl-substituted aromatic rings are wide open, almost in the plane of the methylene bridges with one of them in an intermediate position between a *syn* and an *anti* conformation. The chemical shifts of the corresponding methoxy groups ($\delta = 3.80$, 1.83 and 1.70) clearly show that only two methoxy groups are inside the cavity, the third being directed away. The shape of the capsule was quite sensitive to the size and shape of the solvent. Thus, the spectrum of **1a** in $[D_{10}]p$-xylene at 25 °C was asymmetric, but returned to the typical S_6 symmetry at 50 °C, while the spectrum in $[D_{12}]$mesitylene, a solvent much too big to be encapsulated, was also asymmetric (NH signals at $\delta = 8.10$ and 8.32) but insensitive to temperature changes. Most likely, **1a** forms aggregated oligomers of undefined structure in $[D_{12}]$mesitylene and other large-molecule solvents. Therefore, $[D_{12}]$mesitylene was used as a noncompetitive solvent for the encapsulation studies. This bulky solvent has also been used by Rebek et al. in related systems.[5] Addition of increasing amounts of benzene (1 or 20 equiv with respect to dimer, or 5 mol% with respect to solvent) to a solution of **1a** in $[D_{12}]$mesitylene lead to a new signal at $\delta = 6.16$ that corresponds to encapsulated benzene. This assignment was confirmed by a spectrum of **1a-1a** in nondeuterated benzene ($\delta = 6.0$) and by a HMQC experiment (^{13}C peak at $\delta = 127.0$; ^1H and ^{13}C NMR peaks for nonencapsulated benzene at $\delta = 7.15$ and 128.5, respectively). One benzene molecule per capsule

was included, as evidenced from the NMR integrals.[15] Interestingly, addition of CD_2Cl_2 caused the signal of encapsulated benzene to vanish rapidly, probably due to the flexible nature of the capsule. Furthermore, the ^{19}F NMR spectrum of fluorobenzene (3 mol% relative to solvent) in a solution of dimer **1a-1a** in [D_{12}]mesitylene showed a new signal (shielded 2.8 ppm relative to free fluorobenzene) for the encapsulated guest (Figure 8).

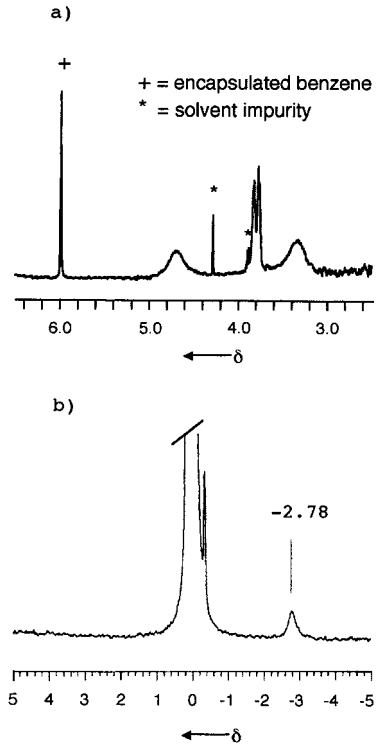


Figure 8. a) Section of a ^1H NMR spectrum of **1a-1a** (500 MHz, [H_6]benzene, 25 °C). b) ^{19}F NMR spectrum (470.5 MHz, [D_{12}]mesitylene, 25 °C) of a solution of **1a-1a** in [D_{12}]mesitylene/fluorobenzene 97:3.

Conclusions

Monomeric triureidocalix[6]arenes are flexible platforms that display cone conformations of C_{3v} symmetry at room temperature in polar solvents, such as [D_6]DMSO. A second conformation of C_s symmetry was present in variable amounts, depending on the solvent polarity. In less polar solvents, triureidocalix[6]arenes form dimeric capsules held together by a cyclic array of hydrogen bonds. These dimers are also flexible and give rise to well-defined NMR signals at low temperatures. Interestingly, monomers and dimers were observed simultaneously in appropriate solvent mixtures. This should enable us to carry out a more in-depth study on the kinetics and thermodynamics of the dimerization process, presumably in both calix[6] and calix[4]arenes. We will report on these findings in due time.

The resulting dimeric cavities are about the same size as those arising from tetraureidocalix[4]arenes, although somewhat different in shape. Thus, guests the size of benzene are easily included into the cavity. HMQC two-dimensional NMR experiments were carried out to unequivocally assign peaks that correspond to encapsulated species.

Experimental Section

Solvents were dried before use by standard methods. Unless otherwise stated all reactions were carried out under argon. Flash chromatography was performed with grade silica gel (Chromagel 60A CC). ^1H and ^{13}C NMR spectra were recorded on Bruker AC200, AMX300 and DRX500 spectrometers, ^{19}F NMR spectra were recorded on a Varian Unity 500 spectrometer. Chemical shifts are reported as δ values in ppm from the residual solvent peak. Mass spectra were performed with a VG AutoSpec mass spectrometer. Elemental analyses were obtained with a Perkin–Elmer 2400 CHN analyzer. Melting points were taken with a Gallenkamp apparatus. Vapor pressure osmometry measurement was obtained with a Knauer mod 11.00 osmometer. Calixarenes **2**,[8] **3d**,[8] **4d**[8] and **6**[16] were obtained by known procedures.

5,17,29-Tri-*tert*-butyl-38,40,42-trimethoxy-37,39,41-tri-*n*-octyloxy-11,23,35-trinitrocalix[6]arene (3a): A suspension of **2** (850 mg, 0.87 mmol) and NaH (450 mg, 11.25 mmol, 60% in mineral oil) in DMF (150 mL) was stirred at 50 °C for 15 min and was treated with 1-iodooctane (3.8 mL, 21.05 mmol) at 75 °C for 3 days. The reaction mixture was partitioned between CH_2Cl_2 and HCl (aq 10%). The organic layer was dried (Na_2SO_4) and evaporated. The residue was subjected to chromatography (hexane/EtOAc 9:1) and triturated (EtOH) to give **3a** as a yellow solid (534 mg, 51%). M.p. 176–17 °C; ^1H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 7.70$ (br s, 6H; ArH), 7.20 (br s, 6H; ArH), 4.60–4.10 (br s, 6H; $ArCH_2Ar$), 3.83 (br s, 6H; CH_2), 3.90–3.40 (br s, 6H; $ArCH_2Ar$), 2.88 (s, 9H; CH_3), 1.84 (br s, 6H; CH_2), 1.50 (br s, 6H; CH_2), 1.30 (br s, 51H; CH_2, CH_3), 0.89 (t, $^3J(H,H) = 7.0$ Hz, 9H; CH_3); $^{13}C\{^1H\}$NMR (75 MHz, $CDCl_3$, 25 °C, DEPT): $\delta = 161.4$, 154.0, 146.8, 143.5, 136.1, 132.2 (ArC), 126.5, 123.9 (ArCH), 73.9 (OCH_2), 60.0 (OCH_3), 34.2 ($(CH_3)_3C$), 31.8 ($ArCH_2Ar$), 31.5 ($(CH_3)_3C$), 30.2, 29.6, 29.4, 29.2, 26.0, 22.6 (CH_2), 14.0 (CH_3); MS (CI): *m*/*z* (%): 1318 (100) $[M]^+$; $C_{81}H_{111}N_3O_{12}$ (1318.80): calcd C 73.77, H 8.48, N 3.19; found C 73.40, H 8.87, N 3.23.

5,17,29-Tri-*tert*-butyl-37,39,41-tris(2-ethoxyethoxy)-38,40,42-trimethoxy-11,23,35-trinitrocalix[6]arene (3b): A solution of **2** (421 mg, 0.43 mmol), K_2CO_3 (366 mg, 2.60 mmol) and KI (ca. 20 mg) in CH_3CN (70 mL) at 80 °C was treated with $EtOCH_2CH_2OTs$[17] (730 mg, 2.90 mmol) for 3 days. The reaction mixture was partitioned between EtOAc (50 mL) and HCl (aq 10%). The organic layer was dried (Na_2SO_4) and evaporated. The residue was subjected to chromatography (hexane/EtOAc 2:1) and triturated (MeOH) to give **3b** as a pale yellow solid (196 mg, 38%). M.p. 219–222 °C; ^1H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 7.70$ (s, 6H; ArH), 7.17 (s, 6H; ArH), 4.00 (br s, 12H; $ArCH_2Ar$), 3.93 (t, $^3J(H,H) = 4.1$ Hz, 6H; CH_2), 3.68 (t, $^3J(H,H) = 4.1$ Hz, 6H; CH_2), 3.47 (q, $^3J(H,H) = 7.0$ Hz, 6H; CH_2), 2.93 (s, 9H; CH_3), 1.29 (s, 27H; CH_3), 1.13 (t, $^3J(H,H) = 7.0$ Hz, 9H; CH_3); $^{13}C\{^1H\}$NMR (75 MHz, $CDCl_3$, 25 °C, DEPT): $\delta = 160.0$, 154.3, 146.8, 143.6, 136.0, 132.2 (ArC), 127.3, 123.2 (ArCH), 72.8, 69.4 (OCH_2CH_2O), 66.6 (OCH_2CH_3), 59.9 (OCH_3), 34.2 ($(CH_3)_3C$), 31.4 ($(CH_3)_3C$), 30.8 ($ArCH_2Ar$), 15.1 (CH_3); $C_{69}H_{87}N_3O_{15}$ (1198.47): calcd C 69.15, H 7.32, N 3.51; found C 69.35, H 6.81, N 3.30.

5,17,29-Tri-*tert*-butyl-37,39,41-tris(*N*,*N*-diethylaminocarbonylmethoxy)-38,40,42-trimethoxy-11,23,35-trinitrocalix[6]arene (3c): A solution of **2** (200 mg, 0.20 mmol) and K_2CO_3 (171 mg, 1.24 mmol) in CH_3CN (40 mL) was stirred at 70 °C for 2 h and was treated with 2-chloro-*N*,*N*-diethylacetamide (0.20 mL, 1.24 mmol) at 70 °C for 5 days. The reaction mixture was partitioned between EtOAc and HCl (aq 10%). The organic layer was dried ($MgSO_4$) and evaporated. The residue was subjected to chromatography (CH_2Cl_2/MeOH, 40:1) to give **3c** as a yellow solid (146 mg, 54%). M.p. 165–168 °C; ^1H NMR (200 MHz, $CDCl_3$, 25 °C): $\delta = 7.50$ (br s, 6H; ArH), 7.19 (s, 6H; ArH), 4.59 (s, 6H; CH_2), 4.40–3.60 (br s, 12H; $ArCH_2Ar$), 3.39 (q, $^3J(H,H) = 7.0$ Hz, 6H; CH_2), 3.37 (q, $^3J(H,H) = 7.0$ Hz, 6H; CH_2), 2.91 (s, 9H; CH_3), 1.31 (s, 27H; CH_3), 1.15 (t, $^3J(H,H) = 7.0$ Hz, 18H; CH_3); $^{13}C\{^1H\}$NMR (75 MHz, $CDCl_3$, 25 °C): $\delta = 166.2$ (CO), 159.4, 154.5, 147.1, 144.0, 135.4, 131.6 (ArC), 127.8, 122.7 (ArCH), 71.5 (OCH_2), 60.0 (OCH_3), 41.5, 40.3 (NCH_2CH_3), 34.2 ($(CH_3)_3C$), 31.4 ($ArCH_2Ar$), 31.3 ($(CH_3)_3C$), 14.3, 12.8 (NCH_2CH_3); MS (FAB^+, *m*-nitrobenzyl alcohol matrix): *m*/*z* (%): 1322 (100) $[M+H]^+$; $C_{75}H_{96}N_6O_{15} \cdot H_2O$ (1339.64): calcd C 67.24, H 7.37, N 6.27; found C 67.33, H 7.72, N 6.45.

General procedures for the synthesis of 4a–c

Method A: A suspension of **3** and PtO_2 (0.33 equiv) was stirred under H_2 (1 atm) for 18 h. The reaction mixture was filtered through Celite and evaporated to give **4**.

0947-6539/00/0601-0078 $ 17.50+.50/0 *Chem. Eur. J.* **2000**, *6*, No. 1

Method B: A suspension of **3**, $NH_2NH_2 \cdot H_2O$ (100 equiv) and Pd/C (0.5 equiv) in MeOH/CH_2Cl_2 7:2 was stirred at 60 °C for 24 h. The reaction mixture was filtered through Celite and evaporated. The residue was partitioned between CH_2Cl_2 and water. The organic layer was dried (Na_2SO_4) and evaporated to give **4**.

11,23,35-Triamino-5,17,29-tri-*tert*-butyl-38,40,42-trimethoxy-37,39,41-tri-*n*-octyloxycalix[6]arene (4a): Reduction of **3a** by method A or B gave **4a** as a pale yellow solid (99% yield). M.p. 147–148 °C; ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): $\delta = 7.18$ (s, 6H; ArH), 5.86 (s, 6H; ArH), 4.30–3.30 (brs, 12H; $ArCH_2Ar$), 3.86 (t, $^3J(H,H) = 6.5$ Hz, 6H; CH_2), 3.01 (s, 9H; CH_3), 1.88 (m, 6H; CH_2), 1.56 (m, 6H; CH_2), 1.33 (s, 51H; CH_2, CH_3), 0.91 (t, $^3J(H,H) = 7.0$ Hz, 9H; CH_3), the NH_2 signal was not observed; ^{13}C{^{1}H}NMR (75 MHz, $CDCl_3$, 25 °C, HMQC): $\delta = 154.7$, 147.3, 146.0, 141.5, 135.0, 133.4 (ArC), 127.1, 114.1 (ArCH), 73.2 (OCH_2), 60.2 (OCH_3), 34.1 ($(CH_3)_3C$), 31.9 ($ArCH_2Ar$), 31.5 ($(CH_3)_3C$), 30.8, 30.5, 29.6, 29.3, 26.3, 22.6 (CH_2), 14.1 (CH_3); MS (FAB^+, *m*-nitrobenzyl alcohol/trifluoroacetic acid matrix): *m*/*z* (%): 1251 (20) $[M+Na]^+$, 1229 (100) $[M+H]^+$; HR-MS (FAB^+, *m*-nitrobenzyl alcohol/trifluoroacetic acid matrix): *m*/*z*: calcd 1250.8840; found 1250.8881; $C_{81}H_{117}N_3O_6 \cdot 3H_2O$ (1282.88): calcd C 75.84, H 9.66, N 3.28; found C 75.91, H 9.67, N 3.10.

11,23,35-Triamino-5,17,29-tri-*tert*-butyl-37,39,41-tris(2-ethoxyethoxy)-38,40,42-trimethoxycalix[6]arene (4b): Reduction of **3b** by method A gave **4b** as a pale yellow solid (100% yield). M.p. 165–168 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 7.10$ (s, 6H; ArH), 5.85 (s, 6H; ArH), 4.20–3.80 (brs, 12H; $ArCH_2Ar$), 3.96 (t, $^3J(H,H) = 4.5$ Hz, 6H; CH_2), 3.77 (t, $^3J(H,H) = 4.5$ Hz, 6H; CH_2), 3.60 (q, $^3J(H,H) = 7.0$ Hz, 6H; CH_2), 3.04 (s, 9H; CH_3), 2.90–2.50 (brs, 6H; NH_2), 1.25 (s, 27H; CH_3), 1.22 (t, $^3J(H,H) = 7.0$ Hz, 9H; CH_3); ^{13}C{^{1}H}NMR (75 MHz, $CDCl_3$, 25 °C, DEPT): $\delta = 154.7$, 147.0, 146.0, 141.8, 135.0, 133.3 (ArC), 126.9, 114.2 (ArCH), 72.1, 69.8 (OCH_2CH_2O), 66.7 (OCH_2CH_3), 60.2 (OCH_3), 34.1 ($(CH_3)_3C$), 31.5 ($(CH_3)_3C$), 30.9 ($ArCH_2Ar$), 15.2 (CH_3); $C_{69}H_{93}N_3O_9 \cdot 0.5H_2O$ (1117.53): calcd C 74.16, H 8.48, N 3.76; found C 74.33, H 8.78, N 3.72.

11,23,35-Triamino-5,17,29-tri-*tert*-butyl-37,39,41-tris(*N*,*N*-diethylaminocarbonylmethoxy)-38,40,42-trimethoxycalix[6]arene (4c): Reduction of **3c** by method A gave **4c** as a white solid (98% yield). M.p. 192–194 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 7.13$ (s, 6H; ArH), 5.69 (s, 6H; ArH), 4.54 (s, 6H; CH_2), 4.40–3.90 (brs, 12H; $ArCH_2Ar$), 3.46 (q, $^3J(H,H) = 7.0$ Hz, 6H; CH_2), 3.43 (q, $^3J(H,H) = 7.0$ Hz, 6H; CH_2), 2.96 (s, 9H; CH_3), 1.31 (s, 27H; CH_3), 1.25 (t, $^3J(H,H) = 7.0$ Hz, 9H; CH_3), 1.17 (t, $^3J(H,H) = 7.0$ Hz, 9H; CH_3), the NH_2 signal was not observed; ^{13}C{^{1}H}NMR (75 MHz, $CDCl_3$, 25 °C, DEPT): $\delta = 167.6$ (CO), 154.9, 147.2, 146.2, 142.1, 134.9, 132.9 (ArC), 127.5, 113.6 (ArCH), 72.4 (OCH_2), 60.2 (OCH_3), 41.6, 40.0 (NCH_2CH_3), 34.1 ($(CH_3)_3C$), 31.5 ($(CH_3)_3C$), 31.1 ($ArCH_2Ar$), 14.4, 12.8 (NCH_2CH_3); MS (FAB^+, *m*-nitrobenzyl alcohol matrix): *m*/*z* (%): 1232 (100) $[M+H]^+$; HR-MS (FAB^+, *m*-nitrobenzyl alcohol matrix): *m*/*z*: calcd 1231.7787; found 1231.7757.

5,17,29-Tri-*tert*-butyl-38,40,42-trimethoxy-37,39,41-tri-*n*-octyloxy-11,23,35-tris-(*N*′-phenylureyl)-calix[6]arene (5a): A solution of **4a** (386 mg, 0.32 mmol) in CH_2Cl_2 (10 mL) was treated with phenylisocyanate (100 μL, 0.95 mmol) at 25 °C for 5 h. The reaction mixture was evaporated and subjected to chromatography (3:2 hexane/EtOAc) to give **5a** as a white solid (279 mg, 56%). M.p. 150–154 °C; ^{1}H NMR (300 MHz, CD_2Cl_4, 97 °C): $\delta = 7.16$ (s, 6H; ArH), 7.07–7.02 (brm, 15H; ArH, NH), 6.91 (brm, 3H; ArH), 6.70 (brs, 3H; NH), 6.25 (s, 6H; ArH), 4.38 (AB system, part B, $^2J(H,H) = 15.4$ Hz, 6H; $ArCH_2Ar$), 3.93 (t, $^3J(H,H) = 6.5$ Hz, 6H; CH_2), 3.52 (AB system, part A, $^2J(H,H) = 15.4$ Hz, 6H; $ArCH_2Ar$), 2.77 (s, 9H; CH_3), 1.90 (m, 6H; CH_2), 1.65–1.45 (m, 6H; CH_2), 1.40–1.20 (m, 51H; CH_3, CH_2), 0.89 (t, $^3J(H,H) = 7.0$ Hz, 9H; CH_3); ^{13}C{^{1}H}NMR (75 MHz, $CDCl_3$, 25 °C, DEPT): $\delta = 154.9$ (CO), 154.6, 152.3, 146.7, 138.3, 135.7, 133.1, 132.3 (ArC), 128.9, 127.6, 123.4, 123.0, 120.5 (ArCH), 73.1 (OCH_2), 60.2 (OCH_3), 34.2 ($(CH_3)_3C$), 31.8 ($ArCH_2Ar$), 31.5 ($(CH_3)_3C$), 30.9, 30.4, 29.5, 29.3, 26.3, 22.6 (CH_2), 14.1 (CH_3); MS (FAB^+, *m*-nitrobenzyl alcohol matrix): *m*/*z* (%): 1608 (100) $[M+Na]^+$, 1586 (81) $[M+H]^+$; $C_{102}H_{132}N_6O_9 \cdot 0.5CH_2Cl_2$ (1628.69): calcd C 75.59, H 8.23, N 5.16; found C 75.20, H 8.39, N 5.43.

37,39,41-Triacetoxy-5,17,29-tri-*tert*-butyl-11,23,35-tris-(*N*′-butylureyl)-38,40,42-trimethoxycalix[6]arene (5d): A solution of **4d** (100 mg, 0.10 mmol) in CH_2Cl_2 (15 mL) was treated with *n*-butylisocyanate (0.13 mL, 1.18 mmol) at 25 °C for 24 h. The reaction mixture was partitioned between CH_2Cl_2 and H_2O. The organic layer was dried (Na_2SO_4) and evaporated. The residue was triturated (Et_2O) to give **5d** as a white solid (67 mg, 55%). M.p. >300 °C; ^{1}H NMR (300 MHz, [D_6]DMSO, 25 °C): $\delta = 8.28$ (brs, 3H; NH), 7.22 (brs, 6H; ArH), 6.84 (brs, 6H; ArH), 6.05 (brt, $^3J(H,H) = 7.0$ Hz, 3H; NH), 3.90–3.50 (brs, 12H; $ArCH_2Ar$), 3.34 (s, 9H; CH_3), 3.10 (q, $^3J(H,H) = 7.0$ Hz, 6H; CH_2), 2.00–1.50 (brs, 9H; CH_3), 1.42–1.23 (m, 12H; CH_2), 1.10 (brs, 27H; CH_3), 0.80 (t, $^3J(H,H) = 7.0$ Hz, 9H; CH_3); ^{13}C{^{1}H}NMR (75 MHz, [D_6]DMSO, 25 °C, DEPT): $\delta = 168.6$ ($COCH_3$), 155.2 (NHCONH), 152.8, 145.1, 141.1, 137.6, 133.3, 131.8 (ArC), 124.7, 118.1 (ArCH), 60.1 (OCH_3), 38.6 (NCH_2), 33.7 ($C(CH_3)_3$), 31.9 (CH_2), 31.1 ($C(CH_3)_3$), 30.6 ($ArCH_2Ar$), 19.5 (CH_2), 13.7 (CH_3), the CH_3CO signal was not observed at this temperature; however, it was observed at 100 °C (HMQC, $\delta = 21.1$); MS (FAB^+, *m*-nitrobenzyl alcohol matrix): *m*/*z* (%): 1316 (100) $[M+H]^+$; $C_{78}H_{102}N_6O_{12} \cdot 2H_2O$ (1351.75): calcd C 69.31, H 7.90, N 6.22; found C 69.37, H 8.24, N 5.86.

5,17,29-Tri-*tert*-butyl-38,40,42-trimethoxy-37,39,41-tri-*n*-octyloxy-11,23,35-triureylcalix[6]arene (1a): A solution of **4a** (124 mg, 0.10 mmol) in toluene (3 mL) was treated with a solution of triphosgene (30 mg, 0.10 mmol) in toluene (1 mL) at 110 °C for 2 h, warmed to 25 °C and treated with NH_4OH (30% aq, 4.30 mL, 7.52 mmol) in THF (1 mL) for 16 h. The organic layer was evaporated and triturated (EtOAc) to give **1a** as a white solid (80 mg, 53%). M.p. 246–252 °C; FT IR (KBr): $\tilde{\nu} = 3497$, 3384, 3207, 3147, 1673 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 8.70–8.40$ (brs, 6H; NH), 7.60–7.10 (m, 18H; ArH), 6.35–6.20 (brs, 6H; ArH), 4.60–4.20 (brs, 12H; $ArCH_2Ar$), 3.90–3.20 (brs, 12H; NH_2), 3.88–3.70 (m, 12H; CH_2), 3.50–3.30 (brs, 12H; $ArCH_2Ar$), 1.87 (m, 12H; CH_2), 1.56 (m, 12H; CH_2), 1.40–1.20 (m, 102H; CH_2, CH_3), 0.88 (t, $^3J(H,H) = 7.0$ Hz, 18H; CH_3), the CH_3O signal was not observed; MS (FAB^+, *m*-nitrobenzyl alcohol matrix): *m*/*z* (%): 1380 (29) $[M+Na]^+$, 1358 (100) $[M+H]^+$; $C_{84}H_{120}N_6O_9 \cdot 0.5CHCl_3$ (1417.62): calcd C 71.59, H 8.57, N 5.93; found C 71.45, H 8.56, N 5.69.

5,17,29-Tri-*tert*-butyl-37,39,41-tris(2-ethoxyethoxy)-38,40,42-trimethoxy-11,23,35-triureylcalix[6]arene (1b): A solution of **4b** (110 mg, 0.10 mmol) in toluene (3 mL) was treated with a solution of triphosgene (35 mg, 0.12 mmol) in toluene (1 mL) at 110 °C for 2 h, warmed to 25 °C and treated with NH_4OH (30% aq, 4.2 mL) in THF (4 mL) for 16 h. The organic layer was evaporated and triturated (EtOAc) to give **1b** as a white solid (68 mg, 55%). M.p. 270–272 °C; FT IR (KBr): $\tilde{\nu} = 3493$, 3375, 3202, 3147, 1673 cm^{-1}; ^{1}H NMR (300 MHz, CD_2Cl_2, 25 °C): $\delta = 8.62$ (brs, 6H; NH), 7.46 (s, 6H; ArH), 7.50–7.30 (brs, 12H; ArH), 6.24 (brs, 6H; ArH), 4.44 (brs, 12H; $ArCH_2Ar$), 4.03 (m, 12H; CH_2), 3.84 (brs, 12H; CH_2), 3.62 (q, $^3J(H,H) = 7.0$ Hz, 12H; CH_2), 3.59–3.37 (brm, 12H; $ArCH_2Ar$), 2.50–1.90 (brs, 18H; CH_3), 1.37 (s, 54H; CH_3), 1.20 (t, $^3J(H,H) = 7.0$ Hz, 18H; CH_3), the NH_2 signal was not observed; MS (FAB^+, *m*-nitrobenzyl alcohol matrix): *m*/*z* (%): 1260 (33) $[M+Na]^+$, 1238 (100) $[M+H]^+$; HR-MS (FAB^+, *m*-nitrobenzyl alcohol matrix): calcd 1237.7164; found 1237.7170.

5,17,29-Tri-*tert*-butyl-37,39,41-tris-(*N*,*N*-diethylaminocarbonylmethoxy)-38,40,42-trimethoxy-11,23,35-triureylcalix[6]arene (1c): A solution of **4c** (116 mg, 0.09 mmol) and pyridine (0.1 mL, 1.22 mmol) in CH_2Cl_2 (8 mL) was treated at 0 °C with phosgene (0.18 mL, 0.34 mmol, 1.89 M in toluene) for 2 h. The reaction mixture was treated with a solution of NH_4OH (30% aq, 4.00 mL, 7.00 mmol) in THF (3 mL) and stirred for 24 h. The solvent was evaporated and the crude product was partitioned between CH_2Cl_2 and H_2O. The organic layer was dried (Na_2SO_4) and evaporated. The residue was triturated (EtOAc) and the filtrate was evaporated and triturated with Et_2O to give **1c** as a white solid (40 mg, 35%). M.p. >300 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): $\delta = 8.50$ (brs, 6H; NH), 7.48 (d, $^4J(H,H) = 2.7$ Hz, 6H; ArH), 7.40–7.10 (brm, 12H; ArH), 6.13 (d, $^4J(H,H) = 2.7$ Hz, 6H; ArH), 4.70–4.30 (m, 24H; OCH_2, $ArCH_2Ar$), 3.90–3.33 (m, 36H; $ArCH_2Ar$, NCH_2CH_3), 2.70–2.10 (brs, 18H; CH_3), 1.36 (s, 54H; CH_3), 1.25 (t, $^3J(H,H) = 7.0$ Hz, 18H; CH_3), 1.10 (t, $^3J(H,H) = 7.0$ Hz, 18H; CH_3), the NH_2 signal was not observed; ^{13}C{^{1}H}NMR (75 MHz, $CDCl_3$, 25 °C, DEPT): $\delta = 167.0$ (CH_2CONEt_2), 157.0 ($NHCONH_2$), 149.2, 146.9, 136.2, 135.4, 135.0, 134.4, 132.0 (ArC), 128.2, 115.7, 114.2 (ArCH), 73.0 (OCH_2), 60.9, 60.3 (OCH_3), 41.8, 40.1 (NCH_2CH_3), 34.3 ($(CH_3)_3C$), 31.6 ($(CH_3)_3C$), 29.7 ($ArCH_2Ar$), 14.5, 12.8 (NCH_2CH_3); MS (FAB^+, *m*-nitrobenzyl alcohol matrix): *m*/*z* (%): 1383 (100) $[M+Na]^+$, 1361 (43) $[M+H]^+$; $C_{78}H_{105}N_9O_{12} \cdot 3H_2O$ (1414.81): calcd C 66.22, H 7.91, N 8.91; found C 66.19, H 8.26, N 8.60.

Acknowledgments

We are grateful to CICYT (project PB93-0283) and to MURST for financial support, to Dr. Jose González de la Campa (CSIC, Madrid) for the GPC analyses, to Dr. Miquel Pons (Univ. Barcelona), Dr. Jesús Jiménez Barbero (CSIC, Madrid) and Dr. Ana Poveda (Univ. Autónoma Madrid) for assistance with NMR experiments.

[1] For review articles, see a) D. Philp, J. F. Stoddart, *Angew. Chem.* **1996**, *108*, 1242 – 1286; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1154 – 1196; b) M. M. Conn, J. Rebek, Jr., *Chem. Rev.* **1997**, *97*, 1647 – 1668; c) J. de Mendoza, *Chem. Eur. J.* **1998**, *4*, 1373 – 1377.

[2] For leading designs based on metal coordination, see: a) N. Takeda, K. Umemoto, K. Yamaguchi, M. Fujita, *Nature* **1999**, *398*, 794 – 796; b) B. Olenyuk, J. A. Whiteford, A. Fechtenkötter, P. J. Stang, *Nature* **1999**, *398*, 796 – 799.

[3] a) K. D. Shimizu, J. Rebek, Jr., *Proc. Natl. Acad. Sci. USA* **1995**, *92*, 12403 – 12407; b) B. C. Hamann, K. D. Shimizu, J. Rebek, Jr., *Angew. Chem.* **1996**, *108*, 1425 – 1427; *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1326 – 1329; c) R. K. Castellano, D. M. Rudkevich, J. Rebek, Jr., *J. Am. Chem. Soc.* **1996**, *118*, 10002 – 10003; d) O. Mogck, V. Böhmer, W. Vogt, *Tetrahedron* **1996**, *52*, 8489 – 8496; e) O. Mogck, E. F. Paulus, V. Böhmer, I. Thondorf, W. Vogt, *Chem. Commun.* **1996**, 2533 – 2534; f) O. Mogck, M. Pons, V. Böhmer, W. Vogt, *J. Am. Chem. Soc.* **1997**, *119*, 5706 – 5712; g) R. K. Castellano, J. Rebek, Jr., *J. Am. Chem. Soc.* **1998**, *120*, 3657 – 3663; h) M. S. Brody, C. A. Schalley, D. M. Rudkevich, J. Rebek, Jr., *Angew Chem.* **1999**, *111*, 1738 – 1742; *Angew. Chem. Int. Ed.* **1999**, *38*, 1640 – 1644; i) C. A. Schalley, R. K. Castellano, M. S. Brody, D. M. Rudkevich, G. Siuzdak, J. Rebek, Jr., *J. Am. Chem. Soc.* **1999**, *121*, 4568 – 4579.

[4] For assemblies based on other H-bonded structural motifs, see a) K. Koh, K. Araki, S. Shinkai, *Tetrahedron Lett.* **1994**, *35*, 8255 – 8258; b) R. H. Vreekamp, W. Verboom, D. N. Reinhoudt, *J. Org. Chem.* **1996**, *61*, 4282 – 4288; c) A. Arduini, L. Domiano, L. Ogliosi, A. Pochini, A. Secchi, R. Ungaro, *J. Org. Chem.* **1997**, *62*, 7866 – 7868; d) J. J. González, P. Prados, J. de Mendoza, *Angew. Chem.* **1999**, *111*, 546 – 549; *Angew. Chem. Int. Ed.* **1999**, *38*, 525 – 528.

[5] For a larger cavity based on resorcinarenes containing imido groups see: a) T. Heinz, D. M. Rudkevich, J. Rebek, Jr., *Nature* **1998**, *394*, 764 – 766; b) T. Heinz, D. M. Rudkevich, J. Rebek, Jr., *Angew. Chem.* **1999**, *111*, 1206 – 1209; *Angew. Chem. Int. Ed.* **1999**, *38*, 1136 – 1139; c) F. C. Tucci, D. M. Rudkevich, J. Rebek, Jr., *J. Am. Chem. Soc.* **1999**, *121*, 4928 – 4929.

[6] V. Böhmer, O. Mogck, M. Pons, E. F. Paulus, in *NMR in Supramolecular Chemistry* (Ed.: M. Pons), Kluwer, Dordrecht, **1999**, pp. 45 – 60.

[7] J. P. M. van Duynhoven, R. G. Janssen, W. Verboom, S. M. Franken, A. Casnati, A. Pochini, R. Ungaro, J. de Mendoza, P. M. Nieto, P. Prados, D. N. Reinhoudt, *J. Am. Chem. Soc.* **1994**, *116*, 5814 – 5822.

[8] A. Casnati, L. Domiano, A. Pochini, R. Ungaro, M. Carramolino, J. O. Magrans, P. M. Nieto, J. López-Prados, P. Prados, J. de Mendoza, R. G. Janssen, W. Verboom, D. N. Reinhoudt, *Tetrahedron* **1995**, *51*, 12699 – 12720.

[9] The GPC chromatograms were obtained with three on-line PLgel columns of 10^4, 10^3 and 500 Å (MW range 500000 – 50) in $CHCl_3$.

[10] The tailing of the peak is due to the slow dissociation of the dimer on the column. See: M. Mammen, E. E. Simanek, G. M. Whitesides, *J. Am. Chem. Soc*, **1996**, *118*, 12614 – 12623.

[11] The simultaneous observation of monomer and dimer has been reported previously in resorcinarene based capsules. See, for example: a) S. Ma, D. M. Rudkevich, J. Rebek, Jr., *J. Am. Chem. Soc.* **1998**, *120*, 4977 – 4981. b) R. G. Chapman, J. C. Sherman, *J. Am. Chem. Soc.* **1995**, *117*, 9081 – 9082.

[12] The ^{1}H NMR spectrum of **1a** in 10:3 CD_2Cl_2/[D_4]methanol at -50 °C showed a mixture of dimer **1a-1a** and monomer **1a;** the monomer was the most abundant species.

[13] For the conformational control in a tetramethoxy calix[4]arene through self-assembly see ref. [3c].

[14] C. Jaime, J. de Mendoza, P. Prados, P. M. Nieto, C. Sánchez, *J. Org. Chem.* **1991**, *56*, 3372 – 3376.

[15] This 2:1 stoicheometry was further assessed by examination of encapsulated benzene in a mixture of equimolar amounts of **1a-1a** and 5,11,17,23 tetrakis-(*N*′-octylureyl)-25,26,27,28-tetrapropoxycalix[4]arene dimer (tetraureido calix[4]arene dimers encapsulate a single benzene molecule, see ref. [3b]). Identical integrals were observed for encapsulated benzene signals about $\delta = 6.0$ and 4.2.

[16] A. Casnati, P. Minari, A. Pochini, R. Ungaro, W. F. Nijenhuis, F. de Jong, D. N. Reinhoudt, *Isr. J. Chem.* **1992**, *32*, 79 – 87.

[17] R. S. Tipson, M. A. Clapp, L. H. Cretcher, *J. Org. Chem.* **1947**, *12*, 133 – 137.

Received: May 25, 1999 [F 1805]