Hydrogen-Bonding Effects in Calix[4]arene Capsules

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Abstract: The synthesis and spectroscopic characterization of self-assembling calix[4]arene based capsules **1a·1a** and **1b·1b** are described. These compounds feature four urea substituents at the upper rims and four secondary amide fragments at the lower rims that can participate in inter- and intramolecular hydrogen bonding in apolar solution. Communication between the calixarene rims in **1a, b** influences the self-assembled cavity's size and shape. Specifically, dimerization results in a *perfect cone* conformation of the calixarene skeleton in **1a, b** and stabilizes a seam of intramolecular amide C=O···H-N hydrogen bonds at the lower rim. This seam is cycloenantiomeric, with either clockwise or counterclockwise arrangements of the head-to-tail amides. Complexation of Na^+-cation breaks hydrogen bonds at the lower rim but maintains the capsular assembly. Encapsulation properties of **1a·1a** and **1b·1b** were studied in nonpolar solvents and their binary mixtures as well as through heterodimerization experiments. The presence of amide groups at the lower rim causes notable differences in the capsule's binding affinities when compared to the corresponding tetraester capsules **1c·1c** and **1d·1d**. In the monomeric state calixarenes **1a, b** are in a *pinched cone* conformation. The solid state X-ray crystallographic studies with monomeric **1a** reveal only two intramolecular C=O···H-N hydrogen bonds between the adjacent amides at the lower rim, and an extensive network of intermolecular hydrogen bonds between urea groups at the upper rim.

Keywords: calixarenes · encapsulation · hydrogen bonding · self-assembly · supramolecular chemistry

Introduction

Hydrogen bonding donor and acceptor sites, properly positioned on a concave molecular platform, result in the self-assembly of capsules.[1] Calixarenes with four urea substituents on their upper rims, for example, dimerize through a cyclic array of *intermolecular* C=O···H-N hydrogen bonds[2, 3] and the resulting systems feature well-defined cavities that reversibly encapsulate smaller molecules. Open-ended molecules, the cavitands, can have their host–guest properties controlled by *intramolecular* hydrogen bonding.

In unsubstituted calixarenes[4] the four phenols form a cooperative, cyclic array of O···H-O bonds that maintain the cone conformation; similarly, in unsubstituted resorcinarenes the eight phenols stabilize the crown conformation.[5] In elaborated resorcinarene cavitands a cyclic array of eight secondary amides enforces a vase-like shape and determines the dynamics of guest exchange.[6] Herein, we describe the synthesis and structural studies of *hybrid* molecules **1a, b** – calix[4]arenes capable of simultaneous participation in *both* inter- and intramolecular hydrogen bonding processes, and report on their interplay (Figure 1). The communication between the sites influences the self-assembled cavity's size and shape and may also lead to transmission of stereochemical information to the cavity from a remote site.

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Results and Discussion

Calix[4]arenes exhibit a number of conformational possibilities but we are concerned here with only two: the perfect cone C_{4v} and the pinched cone C_{2v} conformations (Figure 2). In tetra-*O*-alkylated cone-shaped calix[4]arenes, the perfect cone conformation can not be easily achieved.[7, 8] In the pinched cone calixarene structures two opposite aromatic rings are parallel in a face to face arrangement while the other two are flipped outward. This arrangement minimizes solvent exposed surface and internal cavities, so the C_{2v} symmetrical structure is energetically preferred in solution. Usually the interconversion between the two identical pinched structures is fast on the NMR time scale (Figure 2). The barrier,

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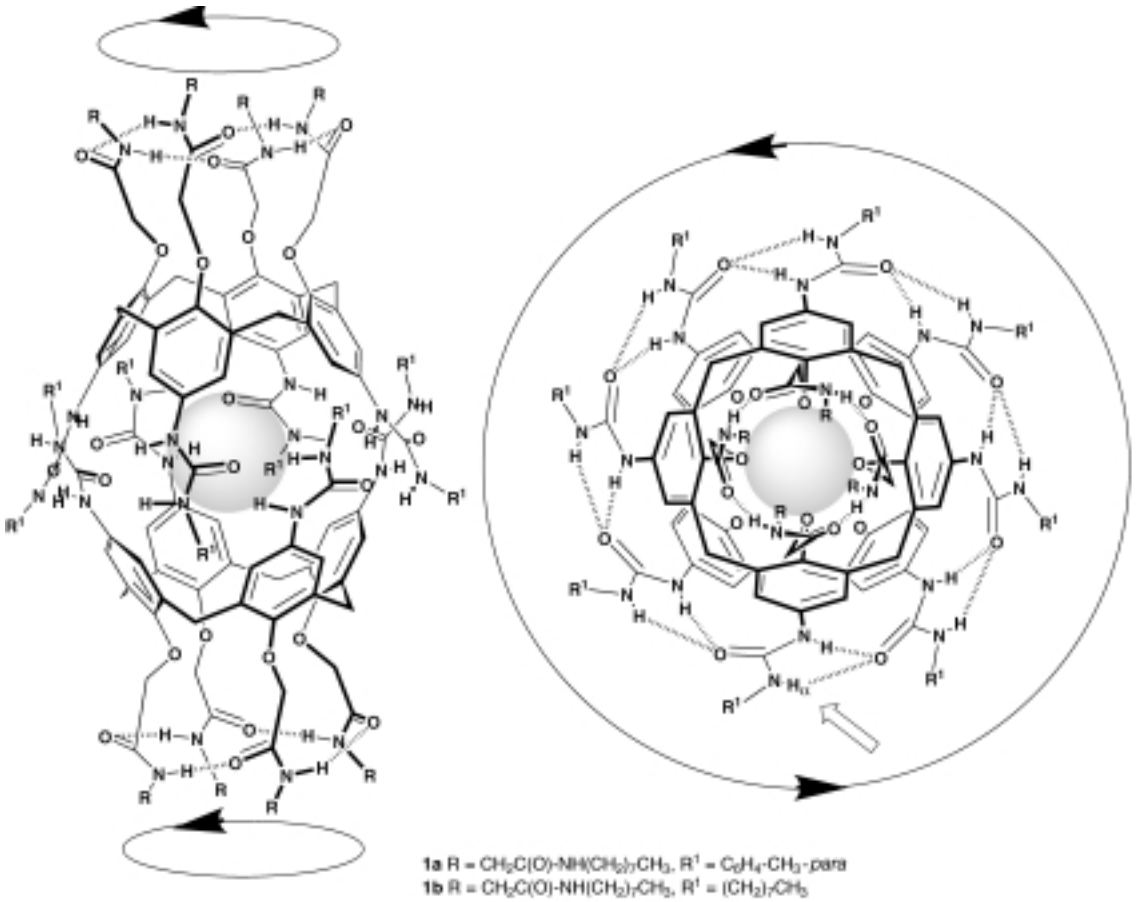


Figure 1. Self-assembly and structure of capsules **1a·1a** and **1b·1b**. Hydrogen bonding is indicated by arrows; only one cycloenantiomeric arrangement is depicted.

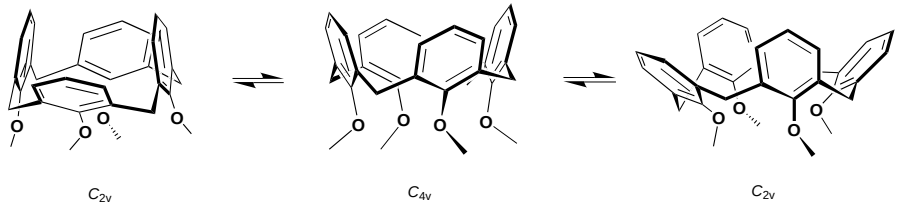


Figure 2. Schematic representation of the $C_{2v} \rightleftharpoons C_{4v} \rightleftharpoons C_{2v}$ conformational equilibria in calix[4]arenes.

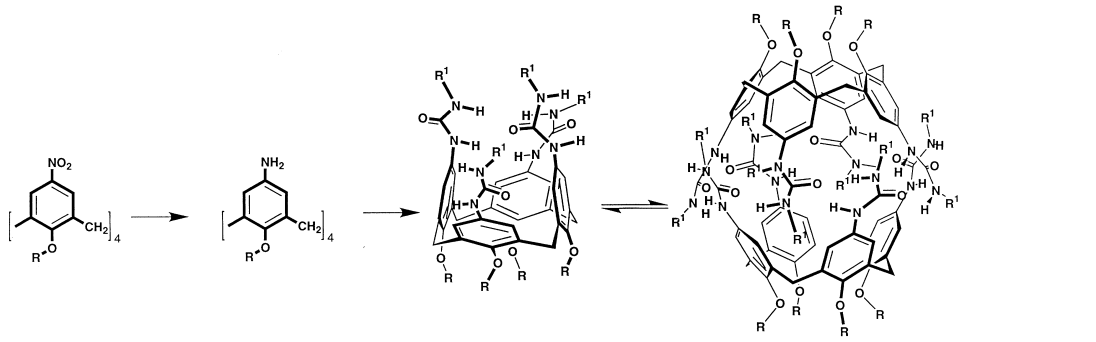
however, can be increased when acid, amide or urea sites are positioned at the upper rim and engage in transannular hydrogen bonding.[8]

A few tactics are available to stabilize the perfect cone shaped calixarenes. They can be rigidly fixed in this conformation through the covalent bridging of proximal phenolic oxygens at the lower rim[7] or by bridging of the distal aromatic rings at the upper rim.[9] Tetraesters and tetra-*N*,*N*-dialkylamides on the lower rim also exist as C_{4v} conformers when they are in contact with cations such as sodium and potassium.[10] The remaining examples are calix[4]arene tetraurea dimeric capsules (for example, **1**).[2, 3] In these, a seam of intermolecular hydrogen bonds at the upper rim and an encapsulated guest molecule stabilize the perfect cone conformer of each calixarene halves.

The combination of four ureas at the upper rim and four secondary acetamide groups at the lower rim was yet unknown. Such structures offer both types of hydrogen bonding—intermolecular assembly and intramolecular folding—and we used this to expose information flow from the upper rim to the lower rim of the calixarene.

Synthesis (Scheme 1): Tetranitrocalix[4]arene tetraester **2**[11] was saponified with aqueous NaOH, activated with $SOCl_2$ then used to acylate *n*-octylamine in $CHCl_3$, giving tetraamide **3**. Reduction of the nitro groups with molecular H_2 and Raney/Ni in toluene at 70 °C afforded tetraamine **4b**, which was directly coupled with either *p*-tolyl- or *n*-octylisocyanate in CH_2Cl_2. The tetraureas **1a** and **b** were obtained in 78 and 48 % yields, respectively. Tetraureas **1c, d** were prepared as descibed in literature[3, 19] from tetraamine **4a**[3] and *p*-tolyl- or *n*-octylisocyanate. Tetraamide **5** was prepared from the corresponding tetraester **6**[12] by a sequence parallel to that used for **3**.

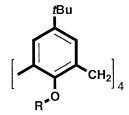
Intramolecular hydrogen bonding at the lower rim: In tetraamides **3** and **5** the lower rim's secondary C(O)−NH groups show spectroscopic evidence of hydrogen bonding.[13] The corresponding ^{1}H-NMR spectra in $CDCl_3$ possess down-



2 R = $CH_2C(O)$-OC_2H_5
3 R = $CH_2C(O)$-$NH(CH_2)_7CH_3$

4a R = $CH_2C(O)$-OC_2H_5
4b R = $CH_2C(O)$-$NH(CH_2)_7CH_3$

1a R = $CH_2C(O)$-$NH(CH_2)_7CH_3$, R^1 = C_6H_4-CH_3-*para*
1b R = $CH_2C(O)$-$NH(CH_2)_7CH_3$, R^1 = $(CH_2)_7CH_3$
1c R = $CH_2C(O)$-OC_2H_5, R^1 = C_6H_4-CH_3-*p*
1d R = $CH_2C(O)$-OC_2H_5, R^1 = $(CH_2)_7CH_3$
1e R = $CH_2C(O)$-$NHC^*H(CH_3)C_6H_5$, R^1 = $(CH_2)_7CH_3$



5 R = $CH_2C(O)$-$NH(CH_2)_7CH_3$
6 R = $CH_2C(O)$-OC_2H_5

Scheme 1. Synthesis of tetraurea **1a–e**, tetraamide **5**, and tetraester **6**.

field N-H triplets at $\delta = 7.33$ and $\delta = 7.57$ for nitrated **3** and butylated **5**, respectively (at 295 K). One set of signals was observed at millimolar concentration ranges. However, on cooling to 213 K, the ^{1}H-NMR spectrum of **5** resolved into two sets of signals for all groups of protons. In particular, two aromatic C-H at $\delta = 7.13$ and 6.36 and two amide N-H at $\delta =$ 7.80 and 7.49 were seen, which is consistent[7] with the pinched cone C_{2v} structure. Apparently, the spectra observed at room temperatures are time-averaged, reflecting fast interconversion between two C_{2v} conformations on the NMR time scale. The signals of tetraamide **5** coalescence at $\approx$233 K in $CDCl_3$. For comparison the tetraester **6** shows fast interconversion between the two C_{2v} conformations on the NMR time scale in the temperature range 210–295 K. Accordingly, intramolecular hydrogen bonding of the lower amides stabilizes the pinched cone conformations and raises the barrier to their interconversion.

Solid-state structures: Further structural information came from the single crystal X-ray analysis of tetraamide **3** and tetraurea **1a** (see Table 6, Table 1). Diffraction quality crystals were obtained from **3** and **1a** by recrcrystallization from MeCN and MeOH/$CHCl_3$, respectively. In the crystalline state molecule **3** adopts a pinched cone conformation (Figure 3). The arrangement of the amido fragments at the lower rim of the calixarene is chiral since the carbonyls are oriented either clock- or counterclockwise. The crystal is a racemate containing both enantiomers related through a center of symmetry. Two intramolecular C=O···H-N hydrogen bonds bridge pairs of neighboring acetamido fragments (Table 1) while the remaining C=O and NH groups form intermolecular hydrogen bonds; the infinite chains of calixarene molecules result (Figure 4). Three MeCN molecules, one of which is disordered over two positions, fill voids in the crystal.

Table 1. Geometry of hydrogen bonding in **3**·3MeCN and **1a**·2MeOH [Å, °].

D-H···A	d(D···A)	∢(DHA)
	3·3MeCN	
N(4)-H(4)···O(7)	2.814(5)	139.5
N(3)-H(3)···O(5)	2.806(4)	139.6
N(1)-H(1)···O(8)[a]	2.869(4)	170.8
N(2)-H(2)···O(6)[b]	2.861(5)	162.8
	1a·2MeOH	
N(5)-H(5)···OZ1	2.853(4)	156.2
N(6)-H(6)···OZ1	3.089(4)	150.6
N(1)-H(1)···OZ2	2.955(4)	143.5
N(2)-H(2)···OZ2	2.985(4)	155.3
N(11)-HZ2···O(12)	2.926(3)	139.7
N(9)-HZ1···O(8)	2.914(3)	140.5
N(3)-H(3)···O(1)[c]	2.963(4)	155.1
N(4)-H(4)···O(1)[c]	3.031(4)	156.1
N(10)-HZ3···O(6)[d]	2.878(4)	162.1
N(7)-H(7)···O(3)[e]	2.808(4)	173.7

Symmetry transformations used to generate equivalent atoms: [a] $-x$, $-y+2$, $-z+1$. [b] $-x$, $-y+2$, $-z$. [c] $-x+\frac{1}{2}$, $y+\frac{3}{2}$, $-z+1$. [d] $x+\frac{1}{2}$, $-y+\frac{1}{2}$, z. [e] $-x+\frac{1}{2}$, $y+\frac{3}{2}$, $-z$.

The molecule of tetraurea **1a** also exists in the pinched cone conformation in the solid state (Figure 5). The carbonyl groups of acetamido and urea fragments are oriented in opposite directions making the whole structure chiral; two enantiomeric conformations are found in the crystal which are related through a center of symmetry.

The amido groups at the lower rim form the hydrogen bonding array similar to that of **3** (Figure 6). No intramolecular hydrogen bonds are found between the urea fragments at the upper rim. Instead, the neighboring ureas form intermolecular hydrogen bonds to two methanol molecules. In addition several H_2O and MeOH molecules with occupancy factors between 0.7 and 0.2 are found in the crystal. The unsaturated C=O and N-H groups form intermolecular

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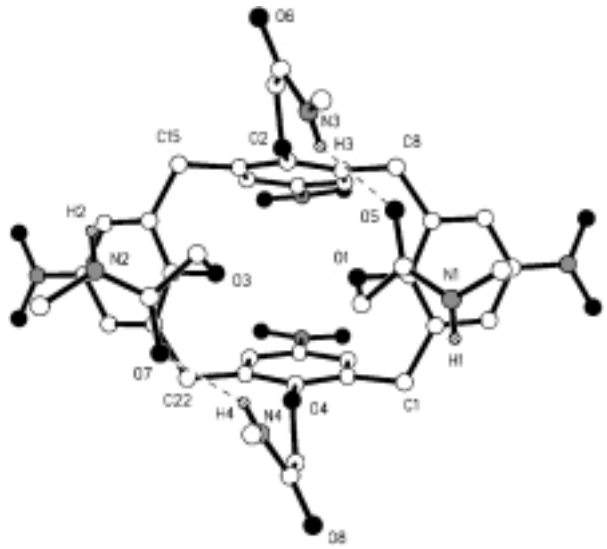

Figure 3. Molecular conformation of **3**. Intramolecular hydrogen bonds are shown in dotted lines. Only the first carbon atoms of pendant butyl chains are shown. Nitrogen and oxygen atoms are darkened.

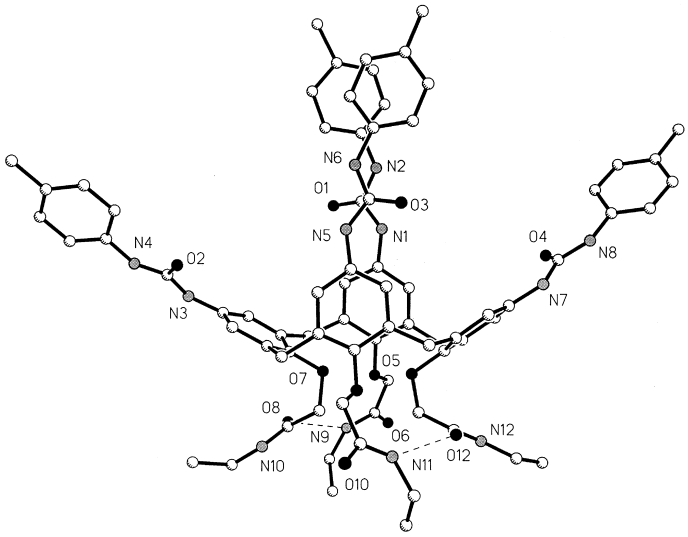

Figure 5. Molecular conformation of **1a**. Intramolecular hydrogen bonds between acetamido groups are indicated. Only the first two carbon atoms of the octyl chains are shown.

hydrogen bonds resulting, again, in infinite chains. Two octyl chains of **1a** and the solvent molecules are highly disordered causing rather high *R* values.

Intermolecular hydrogen bonding at the upper rim: In nonpolar aprotic solvents all tetraureas **1a–d** assembled into dimeric capsules (Figure 7, Figure 8). Characteristic[2, 3] downfield signals for the urea NH_α signals and two *m*-coupled doublets (^4J(H,H) $\approx$2 Hz) of the calixarene aromatics were clearly observed in $CDCl_3$, $C_2D_2Cl_4$, and [D_6]benzene.

Further evidence of dimerization was obtained from the ^{1}H-NMR experiments in two-solvent mixtures, for example $CDCl_3$ with either [D_6]benzene, [D_8]toluene, [D_{10}]*p*-xylene,or $C_2D_2Cl_4$ (Tables 2, 3 and Figure 8). Two sets of signals were observed, one for capsules occupied with one solvent and another for those occupied by the second solvent. Such experiments have been useful to establish the solvent occupancy and exchange rates for other capsules,[14] but had not been reported for calix[4]arene tetraurea dimers. Further, when mixed in a 1:1 ratio, compounds **1a–d** formed heterodimeric assemblies along with the corresponding homodimers in roughly the expected distributions (Table 4). Also as expected,[2, 3] only monomeric species **1a–d** were observed in the competitive solvent [D_6]DMSO.

Remote effects of hydrogen bonding—lower rim to upper rim: Tetraurea tetraamides **1a, b** show different dimerization properties than the corresponding tetraesters **1c, d**. Primary observations came from the analysis of the dimeric capsules distribution in binary solvent mixtures (Table 2, Table 3). When compared with tetraester capsules **1c·1c** and **1d·1d**, tetraamides **1a·1a** and **1b·1b** show somewhat larger affinity towards smaller (volume 76 Å^3) $CDCl_3$ versus [D_6]benzene and $CDCl_2CDCl_2$. This implies that the internal cavity in capsules **1a·1a** and **1b·1b** is smaller than in **1c·1c** and **1d·1d**. Molecular modeling also indicates that the volume of **1a·1a** is $\approx$20 Å^3 less than for **1c·1c**.

The capsule stabilities are also different. While $\approx$2% (vol) of [D_6]DMSO in $CDCl_3$ is needed to dissociate dimer **1c·1c**, capsule **1a·1a** takes less than 1% (vol) of [D_6]DMSO. We propose that intramolecular C=O···H-N hydrogen bonds at the lower rim are responsible for these features.

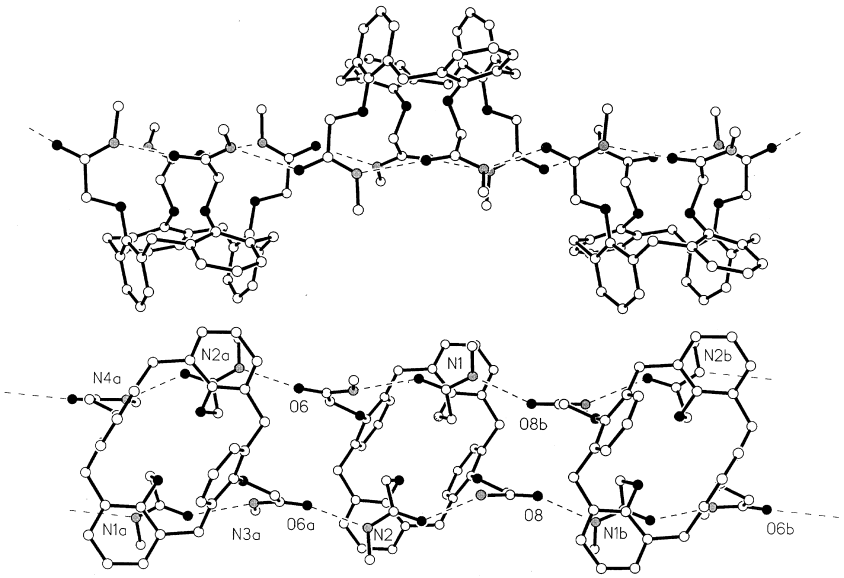

Figure 4. Packing of **3** in crystal. Top: the side view. Bottom: the lower rim view. The nitro groups are omitted for clarity.

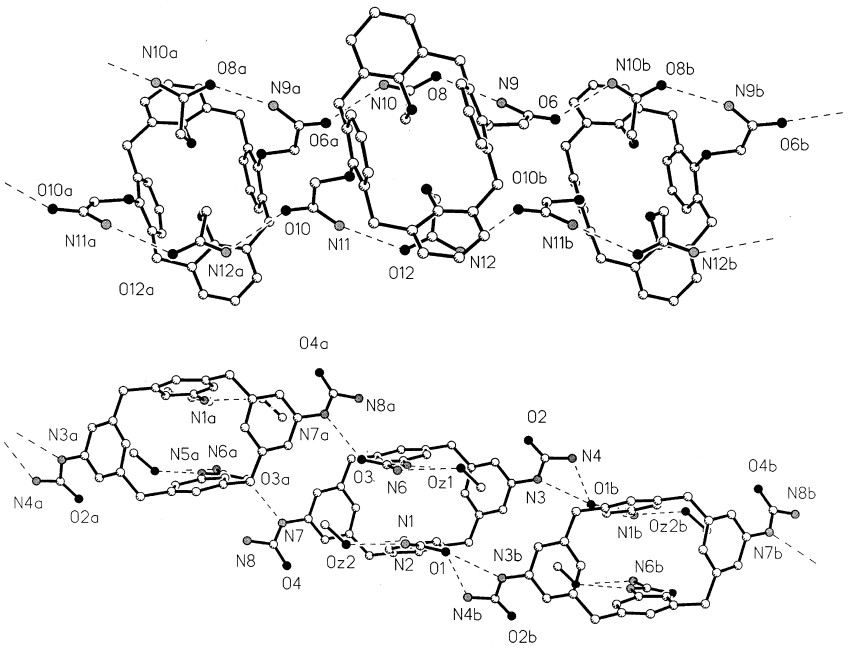

Figure 6. Top: infinite hydrogen bonded chains formed by the acetamido group in calixarene **1a**. Urea fragments and octyl chains are omitted for clarity. Bottom: intermolecular hydrogen bonds between the urea fragments in **1a**. Acetamido groups and *p*-tolyl rings are omitted for clarity.

Remote effects of hydrogen bonding: **upper rim to lower rim**: The arrangement of the lower rim hydrogen bonds in dimeric capsules **1a·1a** and **1b·1b** is different from that of monomeric tetraamides **1a, b, 3**, and **5**. The corresponding portion of the ^{1}H-NMR spectra of **1a** (Figure 8) and **1b** in $CDCl_3$ possess the amide NH signal at $\delta = 6.79$ and $\delta = 6.88$, respectively (at 295 K), which is $\Delta\delta = 0.5$ further upfield than signals of model tetraamides **3** and **5**. From the variable temperature ^{1}H-NMR spectra in $C_2D_2Cl_4$, the temperature coefficient $\Delta\delta/\Delta T$ values[15] of 3.1×10^{-3} and 3.3×10^{-3} were calculated for the amide NH signals of **1a·1a** and **1b·1b**, respectively. These are lower than for tetraamide **5** ($\Delta\delta/\Delta T = 5.2 \times 10^{-3}$) but higher than for both urea N-H protons ($\Delta\delta/\Delta T = 0.2 - 1.7 \times 10^{-3}$) (Table 5). The FT-IR spectra of tetraamide **5** in $CHCl_3$ showed both hydrogen-bonded ($\tilde{\nu} = 3350\ cm^{-1}$) and free ($\tilde{\nu} = 3435\ cm^{-1}$) absorptions ($5 \times 10^{-4} - 1 \times 10^{-2}$ M concentration range) which is consistent with the solid-state structures discussed above. At the same time, the $CHCl_3$ solution of **1a** showed only the hydrogen-bonded stretching at $\tilde{\nu} = 3360\ cm^{-1}$ ($0.5 \times 10^{-3} - 1 \times 10^{-2}$ M concentration range).

Molecular modeling[16] suggests that each amide N-H hydrogen atom in capsules **1a·1a** and **1b·1b** forms an intramolecular hydrogen bond with the adjacent carbonyl with the C=O···H-N distances of ≈2 Å; a cyclic seam of intramolecular hydrogen bonds is imposed on the amides. Moreover, modeling also indicates that *no* such seam can be formed if the calixarene skeleton adopts a C_{2v} pinched conformation. This was further confirmed by ^{1}H-NMR spectroscopy (Figure 9). Specifically, the H_C-C-H_D protons of the methylene unit adjacent to the C(O)-NH at the lower rim appear diastereotopic (in $CDCl_3$, $C_2D_2Cl_4$, etc.), which is an expected consequence of the cycloenantiomeric arrangement of the amides.[17, 18] Both COSY and homonuclear *J*-resolved 2D correlation experiments confirmed the presence of two, nonequivalent protons in the C(O)-NH-CH_CH_D multiplet. In the competitive [D_6]DMSO the cyclic arrangement is interrupted, and only a doublet of triplets (coupled on the adjacent CH_2 and NH) was seen. Addition of D_2O (≈10% vol) further simplifies the picture, and eliminates the coupling on the N-H proton, so that a triplet is observed. In the ^{1}H-NMR spectra of monomeric calixarenes **3** and **5**, the CH_2 protons of the methylene unit adjacent to the C(O)-NH at the lower rim are not diastereotopic ($CDCl_3$, etc.). Furthermore, the CH_2 protons of the EtO-C(O)- group in capsules **1c·1c** and **1d·1d** are not apparently diastereotopic: the seam of the upper rim urea's hydrogen bonds is probably too distant to cause diastereotopism in this case.

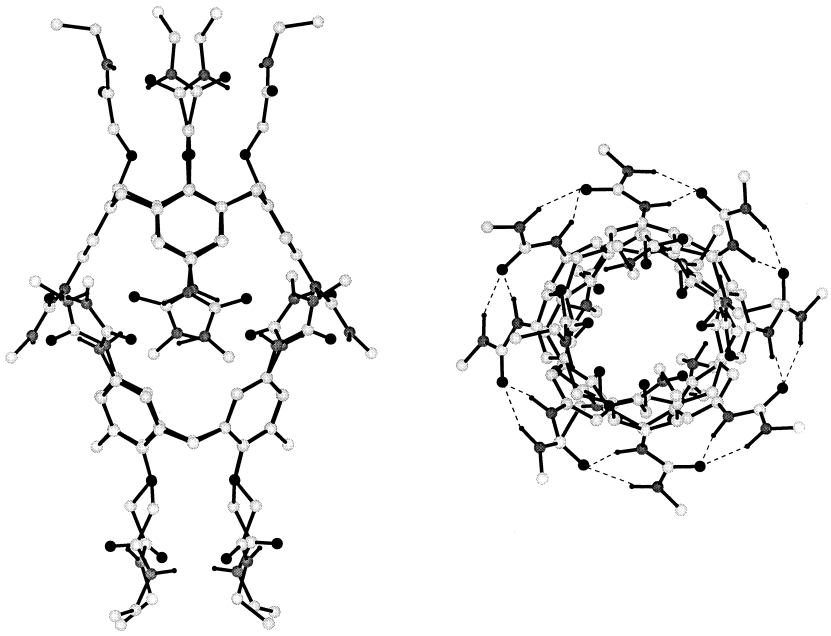

Figure 7. The energy-minimized (MacroModel 5.5, Amber* force field) structure of dimeric capsules **1a·1a** and **1b·1b**. The long alkyl chains and CH hydrogens are omitted for viewing clarity.

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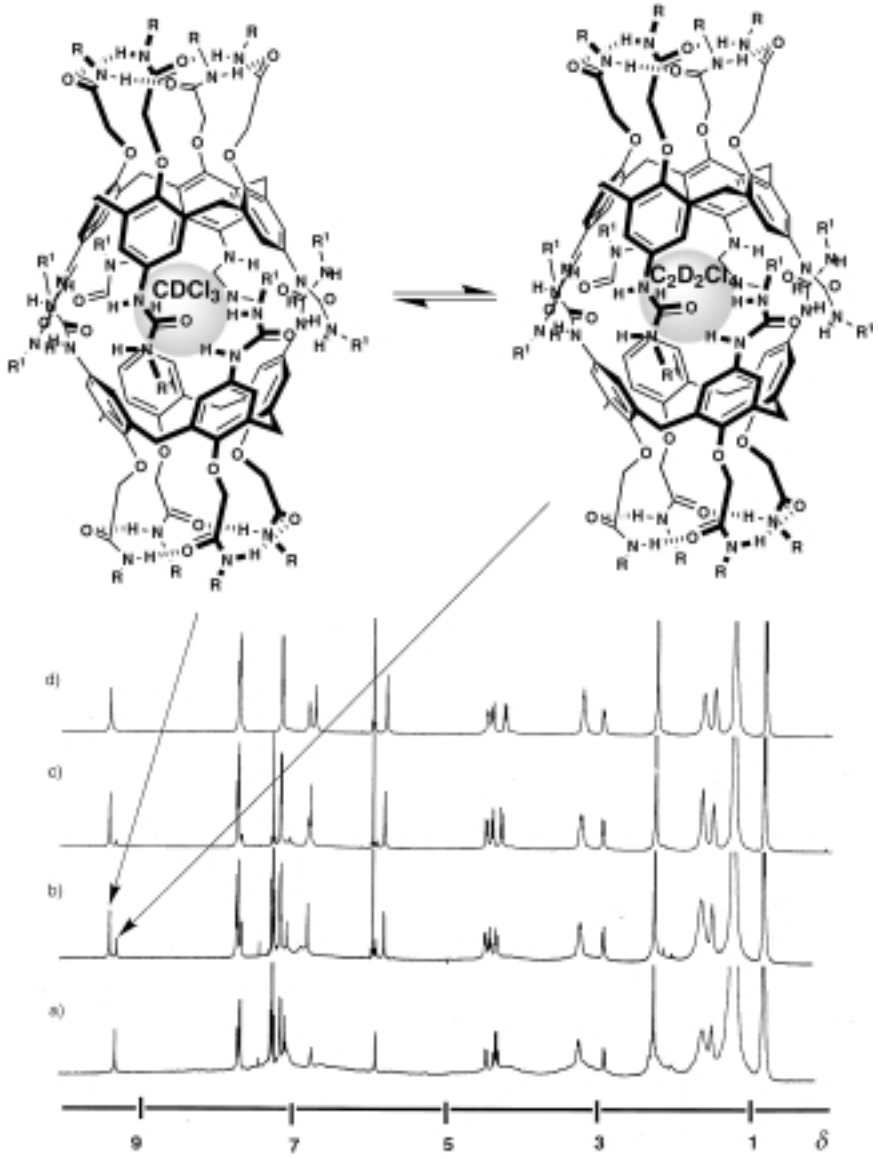

Figure 8. Two-solvent experiments. The ^{1}H-NMR spectra of **1a·1a** (600 MHz, 295 K) in: a) $CDCl_3$; b) $CDCl_3/C_2D_2Cl_4$ 1:3; c) $CDCl_3/C_2D_2Cl_4$ 1:1; d) $C_2D_2Cl_4$. The capsule's urea N-H is situated in downfield region of $\delta = 9-10$.

In short, the lower rim cyclic arrangement of intramolecular hydrogen bonds are observed only when the calix[4]arene skeleton adopts a perfect cone conformation, as is the case of capsules **1a·1a** and **1b·1b**. In the monomeric models, not a seam but two proximal, lower rim intramolecular hydrogen bonds are formed, stabilizing a pinched cone conformation of the skeleton.

Complexation of sodium salts: Addition of a Na^+ source as $NaClO_4$ or NaPic to the $CDCl_3$ or CD_2Cl_2 solutions of **1a, b** results, as expected, in its strong complexation at the lower rim.[10, 13, 19] As a consequence, it breaks the intramolecular amide hydrogen bonding; the amide carbonyls turn inward to coordinate the cation. For both **1a** and **1b**, the amide NH signals shift $\Delta\delta \sim 0.15$ upfield. The protons of the C(O)-$NHCH_2$ methylene unit at the lower rim become apparently magnetically equivalent ($CDCl_3$) (Figure 9). The upper rim urea hydrogen bonding is not disrupted in this case;[19] the NMR spectra of the sodium complexes **1a·**Na^+ and **1b·**Na^+ showed characteristic for the calix[4]arene capsules S_8 symmetrical features. Accordingly, unlike polar competitive solvent (e.g. DMSO, MeOH, DMF, etc.) sodium cation *selectively* controls the hydrogen bonding only at the lower rim.

Conclusion

In the molecules presented here, the upper rims communicate with the lower rims through conformational changes in the skeleton. The lower rim cyclic arrays in dimers **1a·1a** and **1b·1b** are cycloenantiomeric, with either clockwise or counterclockwise arrangements of the head-to-tail amides. This results in diastereomeric relationships in the alkyl chains, attached to the amide nitrogens, in capsules **1a·1a** and **1b·1b** but not in the corresponding monomers. We are currently exploring this phenomenon to achieve such diastereoselection through chiral amide residues attached to the lower rim of tetraures **1**. The Na^+-bound capsules also showed different encapsulation properties than the corresponding cation-free dimers. We will report on the results in the sequel.

Experimental Section

General: Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. ^{1}H-NMR (600 MHz) and ^{13}C-NMR (151 MHz) spectra were recorded on a Bruker DRX-600 spectrometers. The chemical shifts were measured relative to residual non-deuterated solvent resonances. Electrospray (ESI) mass-spectra were obtained with a Finnigan LCQ ion trap mass spectrometer. High resolution matrix-assisted laser desorption/ionization (HRMS-MALDI-FTMS) mass spectrometry experiments were performed on a IonSpec HiResMALDI fourier transform mass spectrometer. For high-resolution mass spectral data, for compounds with molecular weight ≤ 500, the measured masses always agreed to ≤ 5 ppm with the calculated values. For compounds with significantly higher molecular weight (≤ 1500), slightly lower resolution (≤ 10 ppm) was achieved.[20] FT-IR spectra were recorded on a Perkin–Elmer Paragon 1000 PC FT-IR spectrometer. Flash chromatography was performed with silica gel 60 (EM Science or Bodman, 230–400 mesh). All experiments with moisture- or air-sensitive compounds were performed in anhydrous solvents under a dry nitrogen atmosphere. Compounds **2**,[11] **4a**,[3] **1c**,[3] **1d**,[19] and **6**[12] were synthesized in accord with the literature protocols. Molecular modeling was performed using the Amber* force field

Table 2. Distribution of dimeric tetrakis(*p*-tolyl)urea capsules **1a·1a** and **1c·1c** in binary solvent mixtures.[a]

Solvents 1:1	Volume ratio [Å^3]	**1a·1a**	**1c·1c**
[D_6]benzene/$CDCl_3$	83:76	2:1	5:1
[D_8]toluene/$CDCl_3$	100:76	< 1:10	2:3
$CDCl_2CDCl_2$/$CDCl_3$	108:76	10:1	13/1
[D_{10}]*p*-xylene/$CDCl_3$	117:76	< 1:10	< 1/10

[a] Determined by ^{1}H-NMR spectroscopy by integration of the corresponding urea NH and aromatic CH signals. Estimated error 5%.

Table 3. Distribution of dimeric tetrakis(octyl)urea capsules **1b·1b** and **1d·1d** in binary solvent mixtures.[a]

Solvents 1:1	Volume ratio [Å^3]	**1b·1b**	**1d·1d**
[D_6]benzene/$CDCl_3$	83:76	1:2	2:3
[D_8]toluene/$CDCl_3$	100:76	< 1:10	< 1:10
$CDCl_2CDCl_2$/$CDCl_3$	108:76	1:3	2:3
[D_{10}]*p*-xylene/$CDCl_3$	117:76	< 1:10	< 1:10

[a] Determined by ^{1}H-NMR spectroscopy by integration of the corresponding urea NH and aromatic CH signals. Estimated error 5%.

Table 4. Heterodimerization of calix[4]arene tetraureas **1a–d** in $CDCl_3$.[a]

Compounds	[two homodimers]:[heterodimer] /%
1a·1a + **1b·1b**	45:55
1a·1a + **1d·1d**	38:62
1c·1c + **1b·1b**	53:47
1c·1c + **1d·1d**	43:57

[a] Determined by ^{1}H-NMR spectroscopy by integration of the corresponding urea NH and aromatic CH signals. Estimated error 5%.

Table 5. Temperature coefficients ($\Delta\delta/\Delta T \times 10^3$) for the N-H signals of calix[4]arenes **1a, b** and **5** in $C_2D_2Cl_4$.[a]

Compounds	NH_α	NH_β	NH_{amide}
1a[b]	– 1.7	1.3	– 3.1
1b[c]	0.6	– 0.2	– 3.3
5[d]	–	–	– 5.2

[a] Negative values assigned when the chemical shift decreased with temperature. [b] Temperature interval 245–355 K. [c] Temperature interval 275–335 K. [d] Temperature interval 255–355 K.

in the MacroModel 5.5 program.[16] Molecular volume calculations were performed using Grasp program.[21]

25,26,27,28-Tetrakis(*N*-*n*-octylcarbamoyl)methoxy-5,11,17,23-tetra-nitrocalix[4]arene (3): An NaOH (15 g, 0.38 mol) solution in water (150 mL) was added to a suspended solution of tetraester **2** (27.5 g, 29.0 mmol) in MeOH (150 mL), and stirred for 3 h at rt. After been diluted with water (500 mL), the mixture was stirred for another hour. The solution was acidified with conc HCl and filtered, the resulting precipitate was dried in vacuo to afford the corresponding tetraacid as yellow solid (17.1 g, 70%), which was used without further purification. M.p. 214–215 °C; ^{1}H NMR ([D_6]DMSO): $\delta = 12.98$ (s, 4H; COOH), 7.66 (s, 8H; ArH), 4.92 (d, ^2J(H,H) = 14.2 Hz, 4H; $ArCH_2Ar$), 4.77 (s, 8H; OCH_2) 3.69 (d, ^2J(H,H) = 14.2 Hz, 4H; $ArCH_2Ar$); ^{13}C NMR ([D_6]DMSO): $\delta = 170.5$, 161.4, 142.3, 135.7, 123.9, 71.1, 30.5; FT-IR (film): $\tilde{\nu} = 3378$ (COOH), 2947, 2836, 1738 (CO), 1526 (NO_2), 1350, 1248, 1027 cm^{-1}; ESI-MS: *m*/*z*: calcd for $C_{36}H_{28}N_4O_{20}\cdot Na^+$: 859; found: 859 $[M+Na]^+$, 835 $[M-H]^-$. The above tetraacid (4.38 g, 5.23 mmol) was slowly added to a solution of $SOCl_2$ (100 mL) and DMF (2 mL), and the reaction mixture was refluxed for 6 h. After cooling the solution was poured into diethyl ether (200 mL) at ≈0 °C, the precipitate was filtered to obtain the acid chloride as pale yellow solid. To the solution of *n*-octyl amine (12 mL) and triethylamine (10 mL) in CH_2Cl_2 (100 mL), was slowly added the crude acid chloride, and the

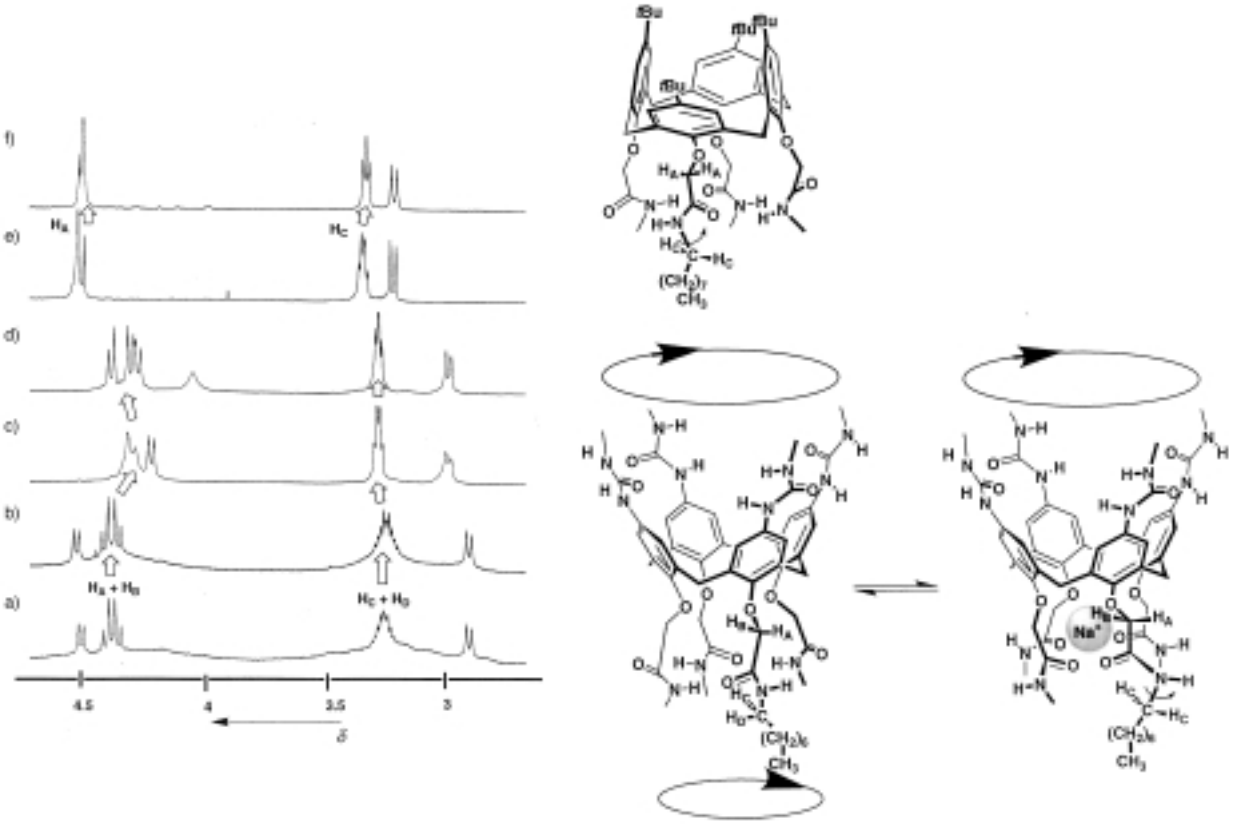

Figure 9. Portions of the ^{1}H-NMR spectra (600 MHz, 295 K): a) capsule **1a·1a** in $CDCl_3$; b) same in $CDCl_3/D_2O$; c) Na^+ complex with **1a·1a** in CD_2Cl_2 after solid–liquid extraction of $NaClO_4$; d) Na^+ complex with **1a·1a** in $CDCl_3/D_2O$ after liquid–liquid extraction of $NaClO_4$; e) tetraamide **5** in $CDCl_3$; f) same in $CDCl_3/D_2O$. The assignments of the methylene H_A, H_B, H_C, and H_D protons is shown on the structures on the right.

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reaction mixture was stirred at rt for 3 h. Water (100 mL) was added, the organic layer was separated, washed with water, 1N HCl, water, and dried over $MgSO_4$. The solvent was evaporated in vacuo to give crude product which was further purified with flash column chromatography (EtOAc/hexanes, 1:1) to afford **3** as a pale yellow powder (2.33 g, 35%). M.p. 207–209 °C; ^{1}H NMR ($CDCl_3$): $\delta = 7.59$ (s, 8H; ArH), 7.33 (brs, 4H; NH), 4.71 (d, $^2J(H,H) = 14.3$ Hz, 4H; $ArCH_2Ar$), 4.56 (s, 8H; OCH_2), 3.49 (d, $^2J(H,H) = 14.3$ Hz, 4H; $ArCH_2Ar$), 3.35–3.31 (m, 8H; NCH_2), 1.58–1.55 (m, 8H; CH_2), 1.31–1.26 (m, 40H; CH_2), 0.88 (t, $^3J(H,H) = 6.9$ Hz, 12H; CH_3); ^{13}C NMR ($CDCl_3$): $\delta = 168.1$, 161.1, 143.6, 135.4, 124.7, 74.5, 40.0, 32.0, 31.2, 29.8, 29.6, 29.5, 27.3, 22.9, 14.3; FT-IR (film): $\tilde{\nu} = 3301$ (NH), 2928, 2856, 1655 (CO), 1533 (NO_2), 1350, 1100 cm^{-1}; ESI-MS: *m*/*z*: calcd for $C_{68}H_{96}N_8O_{16}$: 1281; found 1282 $[M+H]^+$, 1280 $[M-H]^-$.

25,26,27,28-Tetrakis(*N*-*n*-octylcarbamoyl)methoxy-5,11,17,23-tetra-aminocalix[4]arene (4b): Tetranitrocalixarene **3** (2.32 g, 1.81 mmol) was added to a suspension of Raney Nickel in toluene (50 mL). The mixture was stirred under H_2 atmosphere at 60–70 °C for 3 h, cooled and filtered through a celite pad. The filtrate was evaporated in vacuo to give **4b** as a pale brown solid (1.89 g, 90%) which was used without further purification. M.p. 188–189 °C; ^{1}H NMR ($CDCl_3$): $\delta = 7.39$ (brs, 4H; NH), 6.03 (s, 8H; ArH), 4.32 (d, $^2J(H,H) = 13.5$ Hz, 4H; $ArCH_2Ar$), 4.31 (s, 8H; OCH_2), 3.31–3.29 (m, 8H; NCH_2), 2.99 (d, $^2J(H,H) = 13.5$ Hz, 4H; $ArCH_2Ar$), 1.55 (brs, 8H; NH_2), 1.28–1.26 (m, 48H; CH_2), 0.88 (t, $^3J(H,H) = 6.9$ Hz, 12H; CH_3); ^{13}C NMR ($CDCl_3$): $\delta = 170.0$, 149.6, 141.6, 134.9, 116.4, 74.5, 39.7, 32.1, 31.3, 29.9, 29.6, 29.5, 27.3, 22.9, 14.3; FT-IR (film): $\tilde{\nu} = 3322$ (NH), 2957, 2856, 1651 (CO), 1472, 1210 cm^{-1}; HRMS-MALDI-FTMS: *m*/*z*: calcd for $C_{68}H_{104}N_8O_8$: 1160.8050; found 1161.8016 $[M+H]^+$.

25,26,27,28-Tetrakis(*N*-*n*-octylcarbamoyl)methoxy-5,11,17,23-tetra-kis[*N*-(*p*-tolyl)aminocarbamoyl)calix[4]arene (1a): Solution of **4b** (0.253 g, 0.218 mmol) and *p*-tolylisocyanate (0.34 mL, 2.7 mmol) in CH_2Cl_2 (20 mL) was refluxed for 10–12 h, evaporated in vacuo, triturated with cold MeOH and filtered to afford **1a** as a pale yellow solid (0.170 g, 78%). M.p. 185–186 °C; ^{1}H NMR ($CDCl_3$): $\delta = 9.28$ (s, 4H; NH-urea), 7.72 (d, $^4J(H,H) = 2.2$ Hz, 4H; ArH), 7.69 (d, $^3J(H,H) = 8.3$ Hz, 8H; ArH), 7.17 (d, $^3J(H,H) = 8.3$ Hz, 8H; ArH), 7.11 (s, 4H; NH-urea), 6.79 (brt, 4H; NH-amide), 5.93 (d, $^4J(H,H) = 2.2$ Hz, 4H; ArH), 4.48 (d, $^2J(H,H) = 12.3$ Hz, 4H; $ArCH_2Ar$), 4.38 (d, $^2J(H,H) = 14.4$ Hz, 4H; OCH_2), 4.33 (d, $^2J(H,H) = 14.4$ Hz, 4H; OCH_2), 3.31–3.24 (m, 8H; NCH_2), 2.93 (d, $^2J(H,H) = 12.3$ Hz, 4H; $ArCH_2Ar$), 2.29 (s, 12H; $ArCH_3$), 1.69–1.27 (m, 48H; CH_2), 0.90–0.86 (m, 12H; CH_3); ^{13}C NMR ([D$_6$]DMSO): $\delta = 168.7$, 152.4, 150.2, 137.3, 134.2, 134.1, 130.2, 129.0, 118.2, 118.0, 73.6, 38.5, 31.4, 29.3, 29.0, 28.9, 26.7, 22.2, 20.3, 13.9; FT-IR (film): $\tilde{\nu} = 3328$ (NH), 2984, 2928, 1666 (CO), 1552, 1203, 1018 cm^{-1}; HRMS-MALDI-FTMS: *m*/*z*: calcd for $C_{100}H_{132}N_{12}O_{12}$: 1693.0088; found 1716.0042 $[M+Na]^+$.

25,26,27,28-Tetrakis(*N*-*n*-octylcarbamoyl)methoxy-5,11,17,23-tetra-kis[*N*-(*n*-octyl)aminocarbamoyl)calix[4]arene (1b): A solution of **4b** (0.256 g, 0.220 mmol) and *n*-octylisocyanate (0.45 mL, 2.55 mmol) in CH_2Cl_2 (20 mL) was stirred at rt for 10–12 h. It was then evaporated in vacuo, triturated with cold MeOH and filtered to give **1b** as a pale yellow solid (0.187 g, 48%). M.p. 205–207 °C; ^{1}H NMR ($CDCl_3$): $\delta = 7.62$ (d, $^4J(H,H) = 1.9$ Hz, 4H; ArH), 7.51 (s, 4H; NH-urea), 6.88 (brt, 4H; NH-amide), 6.74 (brt, 4H; NH-urea), 6.29 (d, $^4J(H,H) = 1.9$ Hz, 4H; ArH), 4.57 (d, $^2J(H,H) = 12.2$ Hz, 4H; $ArCH_2Ar$), 4.43 (d, $^2J(H,H) = 14.6$ Hz, 4H; OCH_2), 4.38 (d, $^2J(H,H) = 14.6$ Hz, 4H; OCH_2), 3.55–3.50 (m, 4H; urea-NCH_2), 3.33–3.29 (m, 8H; amide-NCH_2), 3.25–3.21 (m, 4H; urea-NCH_2), 3.12 (d, $^2J(H,H) = 12.2$ Hz, 4H; $ArCH_2Ar$), 1.68–1.64 (m, 8H; CH_2), 1.43–1.27 (m, 88H; CH_2), 0.91–0.86 (m, 24H; CH_3); ^{13}C NMR ($CDCl_3$): $\delta = 169.5$, 157.9, 150.3, 135.4, 134.3, 134.1, 118.5, 117.6, 75.4, 40.6, 39.9, 32.1, 32.0, 30.4, 29.9, 29.6, 29.5, 27.4, 27.2, 22.8, 14.3; FT-IR (film): $\tilde{\nu} = 3319$ (NH), 2928, 2856, 1651 (CO), 1557, 1473, 1215; MALDI-FTMS: *m*/*z*: calcd for $C_{104}H_{172}N_{12}O_{12}$: 1782; found 1783 $[M+H]^+$, 1805 $[M+Na]^+$; ESI-MS: *m*/*z*: 1804 $[M+Na]^+$, 1816 $[M+Cl]^-$.

25,26,27,28-Tetrakis(*N*-*n*-octylcarbamoyl)methoxy-5,11,17,23-tetra-*tert*-butylcalix[4]arene (5): A suspension of *tert*-butylcalix[4]arene (2.51 g, 3.87 mmol), Na_2CO_3 (4.0 g, 38 mmol), and 2-bromo-*N*-(*n*-octyl)acetamide (7.7 g, 31 mol) in MeCN (100 mL) was refluxed for 2 d, evaporated in vacuo and redissolved in CH_2Cl_2 (100 mL). The organic layer was washed with water (2 × 100 mL), 1N HCl (2 × 100 mL), water (2 × 100 mL), dried over $MgSO_4$ and then evaporated. The mixture was triturated with cold MeOH and filtered to afford calixarene **5** as a white solid (4.73 g, 92%). M.p. 206–207 °C; ^{1}H NMR ($CDCl_3$): $\delta = 7.57$ (brt, 4H; NH), 6.78 (s, 8H; ArH), 4.49 (s, 8H; OCH_2), 4.48 (d, $^2J(H,H) = 13.0$ Hz, 4H; $ArCH_2Ar$), 3.38–3.34 (m, 8H; NCH_2), 3.24 (d, $^2J(H,H) = 13.0$ Hz, 4H; $ArCH_2Ar$), 1.60–1.57 (m, 8H; CH_2), 1.35–1.23 (m, 40H; CH_2), 1.08 (s, 36H; CH_3) 0.89 (t, $^3J(H,H) = 6.9$ Hz, 12H; CH_3); ^{13}C NMR ($CDCl_3$): $\delta = 169.7$, 153.1, 145.9, 132.9, 126.0, 74.8, 39.8, 34.1, 32.1, 31.7, 31.5, 30.0, 29.6, 29.5, 27.4, 22.9, 14.3; FT-IR (film): $\tilde{\nu} = 3302$ (NH), 2927, 2856, 1652 (CO), 1479, 1195, 1126, 1046; HRMS-MALDI-FTMS: *m*/*z*: calcd for $C_{84}H_{132}N_4O_8$: 1325.0045; found 1347.9980 $[M+Na]^+$.

Single crystal X-ray analysis: Crystallographic data measurements at 173.0(2) K. Direct methods (G. M. Sheldrick, *Acta Crystallogr.* **1990**, *A46*, 467), refinement with full matrix versus F^2 (G. M. Sheldrick, SHELXL-97, Programm for the Refinement of Crystal Structures. *Universität Göttingen*, *Germany*, **1997**). Geometrical restraints were imposed on the disordered parts of octyl chains of **1a.** These parts and some solvent molecules were refined isotropicaly.

Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-141 172/141 173. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

Table 6. Crystallographic data for calixarenes **3** and **1a**.

	3·3MeCN	**1a**·2MeOH
empirical formula	$C_{77}H_{105}N_{11}O_{16}$	$C_{102}H_{140}N_{12}O_{14}$
formula weight	1439	1756
crystal system	triclinic	monoclinic
space group	$P\bar{1}$	$P21/a$
a [Å]	13.301(5)	18.7606(3)
b [Å]	13.376(5)	27.062(1)
c [Å]	19.284(6)	21.632(5)
α [°]	75.97(2)	90
β [°]	85.65(2)	96.644(2)
γ [°]	69.32(2)	90
V [Å^3]	3113.9(4)	10909.3(5)
Z	2	4
D [g cm^{-3}]	1.53	1.10
μ [mm^{-1}]	0.094	0.077
$F(000)$	1364	4128
crystal size [mm]	0.3 × 0. 2 × 0.15	0.45 × 0.32 × 0.2
$2\theta_{max}$ [°]	49.98	49.96
h	−15 to 14	−22 to 22
k	−15 to 15	−30 to 32
l	−22 to 21	−25 to 25
refln. collected	19259	32396
refln. unique	10861	18706
R(int)	0.0321	0.0584
No. of parameters	814	1217
No. of restraints	0	24
S	1.085	1.097
$R1$ ($I > 2\sigma(I)$)	0.0920	0.1321
$wR2$ ($I > 2\sigma(I)$)	0.2583	0.3167
$R1$ (all data)	0.1114	0.2061
$wR2$ (all data)	0.2734	0.3595
$\Delta\rho$ [e Å^{-3}]	0.7/−0.4	0.7/−0.5

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