The Pinched Cone Conformation of Calix[4]arenes: Noncovalent Rigidification of the Calix[4]arene Skeleton

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Calix[4]arenes at the upper rim substituted with two (thio)urea moieties, **2a–c** and **4**, or substituted with two acetamido groups, **5**, adopt a pinched cone conformation in CDCl₃ solution. The pinched cone conformation is the result of *diametrical*, *intramolecular* hydrogen bonds and was studied by ¹H NMR dilution and variable-temperature experiments, NOESY spectroscopy, and FTIR experiments. The pinched cone conformation in these novel calix[4]arenes is stable in C₂D₂Cl₄ up to at least 120 °C. The bis(ureido)calix[4]arenes **2b,c** give a hydrogen-bonded dimer in the pinched cone conformation.

Introduction

Calix[4]arenes¹ can adopt four extreme conformations in solution, *viz.* cone, partial cone, 1,2-alternate, and 1,3-alternate. The conformational interconversion of calix[4]arenes in solution can be blocked by alkylation of the phenolic oxygens at the lower rim with substituents larger than ethyl.² However, even such tetra-*O*-alkylated calix[4]arenes still have some flexibility of the skeleton, and computational studies predict that a structure with *C*_{2v} symmetry is more stable than the more symmetrical *C*_{4v} structure.³ The *C*_{2v} symmetrical structure has two opposite aromatic rings almost parallel, while the other two adopt a flattened position.⁴ This extreme conformation is called the pinched cone conformation. Crystal structures of calix[4]arenes show that in the solid state most derivatives adopt a pinched cone conformation.⁵ In solution the two conformations having *C*_{2v} symmetry interconvert via a *C*_{4v} symmetrical cone conformation (Scheme 1). Usually, this interconversion is fast on the NMR time scale, and as a result a time-averaged structure is observed in the ¹H NMR spectra, *viz.* the *C*_{4v} symmetrical cone conformation.

Regen *et al.*⁶ reported that the presence of four carboxylic acid groups or four primary carboxamide groups at the upper rim of calix[4]arenes increases the barrier for the interconversion considerably. They suggested that this increase results from *intramolecular* hydrogen

bonding between the two opposite carboxylic acid or primary carboxamide groups. Arduini *et al.*⁷ reported a calix[4]arene substituted with two carboxylic acid groups at the upper rim that forms in solution hydrogen-bonded dimers in which the calix[4]arenes adopt a pinched cone conformation. Recently, Shinkai *et al.*⁸ showed that the interconversion between the pinched cone conformations can be blocked by the interaction of the aromatic rings with Ag⁺.

The pinched cone conformation may influence the properties of calix[4]arene-based receptors. Hence, it is important to understand the nature of the pinched cone conformation. The effect of the pinched cone conformation on the result of an alkylation reaction was reported by Timmerman *et al.*⁹ Reaction of a tetra-*O*-alkylated calix[4]arene derivative functionalized at the upper rim with two chloroacetamide groups in the diametrical (1,3) positions with tetrahydroxyresorcin[4]arene occurs at the 1 and 2 positions of the tetrahydroxyresorcin[4]arene and not at the 1 and 3 positions.⁹

In this paper, we report diametrically functionalized calix[4]arenes which adopt the pinched cone conformation *in solution* and provide evidence that this conformation results from *intramolecular* hydrogen bonding. In this way the calix[4]arene skeleton is rigidified via noncovalent interactions.¹⁰

Results and Discussion

Synthesis. Starting from the 1,3-diaminocalix[4]arene tetraethyl ester **1**,¹¹ the bis(ureido) derivatives **2a–c** (Chart 1) were prepared in 36–44% yield by the

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Scheme 1

Table 1. Selected ^1H NMR Chemical Shifts (ppm) of **2a–c**, **4**, and **5** in CDCl_3 at Room Temperature

calix	NH ^a	NH ^b	ArH _{unsub} ^a	ArH _{sub}	ArCH ₂ Ar (<i>J</i> , Hz)
2a	5.08	6.04–6.10	7.01, 6.89	6.09	4.82, 3.20 (14.0)
2b	<i>b</i>	6.63	<i>b</i> , 6.98	6.04	4.92, 3.09 (12.7)
2c	5.09	6.27	6.96, 6.81	6.01	4.82, 3.21 (14.2)
4	6.50	7.10	7.03–6.93 ^c	6.04	4.89, 3.23 (13.9)
5^d		7.03	6.93–6.76 ^e	6.31	4.43, 3.13 (13.3)

^a The first δ value represents a doublet, the second a triplet.
^b Signal coincides with the signals for the aromatic hydrogens of the calix[4]arene skeleton and of the phenyl substituent at the urea moiety. ^c Broad signal. ^d $\leq 5\%$ of a minor conformer is present. ^e Multiplet.

Chart 1

addition of 2 equiv of the appropriate isocyanates to a solution of 1,3-diaminocalix[4]arene **1** in CHCl_3 . In addition, 1,3-diaminocalix[4]arene **1** was treated with thiophosgene¹² to give the 1,3-diisothiocyanatocalix[4]arene **3** in 87% yield. Subsequent addition of *n*-octylamine gave the bis(*n*-octylthioureido)calix[4]arene **4** in 68% yield. The characteristic ^1H NMR data of the bis((thio)ureido)calix[4]arenes **2a–c** and **4** are summarized in Table 1. In addition, bis(acetamido)calix[4]arene **5**¹³ has been included in this study.

The four aromatic hydrogens of the substituted aromatic rings of the calix[4]arene skeleton (ArH_{sub}) give one signal in the ^1H NMR spectrum of bis((thio)ureido)calix[4]arenes **2a–c** and **4**. The six aromatic hydrogens of the unsubstituted aromatic rings of the calix[4]arene skeleton (ArH_{unsub}) give a doublet and triplet in the ^1H

Chart 2

NMR spectrum. The signals at 5.08 and 6.50 ppm in the ^1H NMR spectra of bis(*n*-octyl(thio)ureido)calix[4]arenes **2a** and **4**, respectively, are triplets and can be assigned to the NH^a hydrogens which couple with the neighboring methylene hydrogens of the *n*-octyl groups. Consequently, for **2a**, the broad signal at 6.04–6.10 ppm can be assigned to the NH^b hydrogens. Along this line, for bis(*tert*-butylureido)calix[4]arene **2c** the most upfield positioned signal (5.09 ppm) is assigned to NH^a and the most downfield positioned signal (6.27 ppm) to the NH^b hydrogens. The assignment of the urea hydrogens of bis(phenylureido)calix[4]arene **2b** is based on NOESY spectroscopy. On the basis of NOE connectivities between the signal for ArH_{sub} and the signal at 6.63 ppm this resonance is assigned to NH^b.

Conformational Behavior. The ^1H NMR spectra of the bis((thio)ureido)calix[4]arenes **2a–c** and **4** show two different signals for the aromatic hydrogens of the calix[4]arene, as can be expected on the basis of the diametrical substitution pattern. However, the signals for the aromatic hydrogens of the substituted aromatic rings (ArH_{sub}) are at unusually high field (Table 1). In addition, the ^1H NMR spectrum of bis(*n*-octylureido)calix[4]arene **2a** shows two signals for the NH^aCH₂ hydrogens. Bis(acetamido)calix[4]arene **5** exhibits a spectroscopic behavior similar to that of calix[4]arenes **2** and **4** with the signal for the aromatic hydrogens of the substituted aromatic rings at 6.31 ppm.

The distances between the equatorial calix[4]arene bridging methylene hydrogens (H_{eq}) and the two adjacent aromatic hydrogens (H_1 and H_2 , Chart 2) provide information about the structure of the calix[4]arene skeleton in solution. When the calix[4]arene skeleton adopts a (time-averaged) C_{4v} symmetrical cone conformation these distances are equal, but they differ substantially when the calix[4]arene skeleton adopts a structure that deviates from the C_{4v} symmetrical cone conformation. The distances between the equatorial calix[4]arene bridging methylene hydrogens and the two adjacent aromatic hydrogens were determined by NOESY^{14–16} spectroscopy. The distances (Table 2) were determined using the initial rate approximation¹⁷ in which the distance of 1.79 Å

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Table 2. Calculated Distances (Å) between the H_{eq}^a and the Adjacent Aromatic Hydrogens in **2a–c**, **4**, and **5**^{b,c}

calix	2a	2b	2c	4 ^d	5
H ₁ ^e	2.3	2.5	<i>f</i>	2.5	2.5
H ₂ ^e	3.2	3.0	<i>f</i>	3.1	2.8

^a H_{eq} are the equatorial calix[4]arene bridging methylene hydrogens. ^b CDCl₃, 303 K. ^c ±0.2 Å. ^d Determined at 218 K. ^e For H₁ and H₂ see Chart 2. ^f Not determined quantitatively, but ROESY spectroscopy clearly indicates a longer distance (factor 1.2) for H₂ in comparison to H₁.

Chart 3. Pinched Cone Conformation of **2a** and **4** (Left) and the Proposed Hydrogen-Bonded Dimer Formed by **2b,c** (Right)

between the equatorial and axial bridging methylene hydrogen atoms (Chart 2) was used as a reference.

The difference between the distances of equatorial methylene hydrogens to the two adjacent aromatic hydrogens indicates that the bis((thio)ureido)calix[4]arenes **2a–c**, **4**, and **5** adopt a pinched cone conformation in CDCl₃ solution at room temperature.¹⁸

The pinched cone conformation in the bis((thio)ureido)calix[4]arenes **2a–c** and **4** explains the upfield shift of the aromatic hydrogens of the substituted aromatic rings (H₁). The hydrogen bonding between the urea moieties (Chart 3, *vide infra*) brings the two opposite aromatic rings in close proximity with the result that the aromatic hydrogens of these aromatic rings are shielded.

In bis(ureido)calix[4]arenes **2a–c** and **4** the distance between H_{eq} and H₂ is larger than the distance between H_{eq} and H₁ (Chart 2), indicating that the aromatic rings functionalized with the (thio)urea moieties are oriented toward each other and that the other two aromatic rings are flattened. The pinched cone conformation in **2a** and **4** is depicted in Chart 3.

The NOESY spectrum of bis(phenylureido)calix[4]arene **2b** shows NOE connectivities between the signals for the aromatic hydrogens of the phenyl substituents

Table 3. Presence of Intermolecular NOE Connectivities and the Cross Relaxation Constants (σ , s⁻¹) Observed for the Methylene Bridging Hydrogens in **2a–c** and **4**^a

calix	2a	2b	2c	4
inter NOE	no	yes	yes	no
σ	+0.12	-1.8	-0.6	+0.3

^a CDCl₃, 303 K.

and the aromatic hydrogens of the calix[4]arene skeleton (H₁ and H₂, Chart 2), while the NOESY spectrum of bis-(*tert*-butylureido)calix[4]arene **2c** shows an NOE connectivity between the signals for the hydrogens of the *tert*-butyl groups and the aromatic hydrogens H₁ and H₂. These connectivities cannot result from through-space interactions within a single molecule since in the same molecule these hydrogens are not close enough.¹⁹ Consequently, these NOE connectivities must result from intermolecular interactions (Table 3).

Furthermore, the sign of the NOE connectivities in the NOESY spectra of calix[4]arenes **2b** and **2c** is positive (*i.e.*, negative cross relaxation constants), suggesting that slow tumbling entities, *i.e.*, with increased molecular mass (≥ 2000 g·mol⁻¹) are present.²⁰ Bis(*n*-octylthioureido)calix[4]arene **2a** and bis(*n*-octylthioureido)calix[4]arene **4** do not show any indication of association because no intermolecular NOE connectivities are observed between the hydrogens of the *n*-octyl substituent at the urea moieties and the aromatic hydrogens H₁ and H₂.

Using the initial rate approximation,¹⁷ cross relaxation constants (σ) between the bridging methylene hydrogens were determined (Table 3).²¹ The σ values are an indication for the degree of aggregation of the two atoms involved.¹⁵ The negative σ values for **2b,c** suggest aggregation and are in agreement with the presence of intermolecular NOE connectivities. The positive σ values for **2a** and **4** suggest that no aggregation occurs and support the absence of intermolecular NOE connectivities.

The intermolecular NOE connectivities may result from a dimeric hydrogen-bonded structure formed by two bis-(ureido)calix[4]arenes in the pinched cone conformation as depicted in Chart 3. Such a structure brings the substituents at the urea moieties close to the aromatic hydrogens of the substituted aromatic rings (ArH), and the increased molecular mass of this dimer can explain the negative σ values.

The proposed hydrogen-bonded dimer shows that of the eight urea hydrogens present in the dimer **four urea hydrogens** are involved in intermolecular hydrogen bonding and four urea hydrogens are not involved in hydrogen bonding which is supported by concentration dependent FTIR measurements (*vide infra*).

In the case of bis(acetamido)calix[4]arene **5** ¹H NMR dilution experiments show an upfield shift of the amide hydrogens, but this shift is not accompanied by a significant downfield shift of the aromatic hydrogens of the substituted aromatic rings of **5**. An association constant of 3.8 M⁻¹ was determined by a dilution experi-

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(18) The distances between the equatorial bridging methylene hydrogens (H_{eq}) and the two adjacent aromatic hydrogens (ArH) of tetrakis(*n*-octylureido)calix[4]arene, which adopts a C_{4v} symmetrical cone conformation in CDCl₃ solution, are equal, 2.7 Å. Scheerder, J. Ph. D. Thesis, University of Twente, 1995.

(19) NOE connectivities can be observed when the through-space distance between two hydrogens is smaller than 4.5 Å.¹⁵

(20) Positive NOE connectivities ($\omega\tau_c > 1$) are observed for large molecules, viscous solution, low temperature, or strong magnetic fields. Negative NOE connectivities ($\omega\tau_c < 1$) are observed for small molecules, nonviscous solutions, high temperature, and weak magnetic fields. See ref 15.

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ment²² which is comparable to the oligomerization of *N*-alkylated linear carboxamides.²³ V.P.O. molecular weight determinations²⁴ in CDCl₃ gave a molecular mass of $845 \pm 80 \text{ g}\cdot\text{mol}^{-1}$ which is slightly higher than the calculated molecular mass of the monomer ($707 \text{ g}\cdot\text{mol}^{-1}$). The slight deviation may result from weak intermolecular association.²⁵

The pinched cone conformation in bis(ureido)calix[4]arene **2a**, and on the basis of its analogy to **2a** probably also in bis(thioureido)calix[4]arene **4**, is the result of intramolecular hydrogen bonding between the two opposite (thio)urea moieties (Chart 3), whereas the pinched cone conformation of **2b,c** results from hydrogen bonding between the two monomers in the dimer (Chart 3). The role of hydrogen bonding in the formation of the pinched cone conformations is supported by the ¹H NMR spectra of the bis(ureido)calix[4]arenes **2a–c** in DMSO-*d*₆ which show the signal for the aromatic hydrogens of the substituted aromatic rings more downfield than in the ¹H NMR spectra in CDCl₃. Due to the breaking of the hydrogen bonding in this solvent **2a–c** adopt a time-averaged *C*_{4v} symmetrical cone conformation. Bis(acetamido)calix[4]arene **5** shows a similar behavior. In the ¹H NMR spectrum in CDCl₃ the signal for the aromatic hydrogens of the substituted aromatic rings is positioned at 6.31 ppm while in DMSO-*d*₆ this signal is present at 7.04 ppm. The opposite is observed for the aromatic hydrogens of the unsubstituted aromatic rings: 6.93–6.76 ppm in CDCl₃ versus 6.41 ppm in DMSO-*d*₆. The pinching in CDCl₃ is also expressed by the chemical shift of the OCH₂ hydrogens, which are 0.26 ppm apart in CDCl₃, while in DMSO-*d*₆ the difference is 0.11 ppm.²⁶

The nature of the hydrogen bonds was studied with FTIR spectroscopy. Concentration-dependent FTIR measurements of bis(ureido)calix[4]arenes **2a–c** in CDCl₃ (1–20 mM) reveal a broad, concentration-independent NH stretching band at 3336 cm^{−1}, attributed to intramolecular NH···O=C hydrogen bonds in monomeric **2a** or intermolecular NH···O=C hydrogen bonds in dimeric **2b** and **2c**. In addition, a weak, sharp NH stretching band at 3420 cm^{−1}, attributed to non-hydrogen-bonded NH stretch, was observed for **2a–c**.

Variable-temperature ¹H NMR experiments with **2a–c** and **4** in a range of −60 to +120 °C and with **5** in a range of −60 to +145 °C show no interconversion between the pinched cone conformation and the *C*_{4v} symmetrical cone conformation.

Molecular Modeling. Molecular modeling (quanta/CHARMm)²⁷ of the pinched cone conformation of bis(*n*-octylureido)calix[4]arene **2a** in *vacuo* shows a bifurcated NH···O=C hydrogen bond ($r(\text{H}^b\cdots\text{O}) = 1.797$ and $r(\text{H}^a\cdots\text{O}) = 2.374$ Å; $r(\text{N}\cdots\text{O}) = 2.735$ and 3.168 Å; $\alpha(\text{NH}^b\cdots\text{O}) = 153.6^\circ$ and $\alpha(\text{NH}^a\cdots\text{O}) = 135.9^\circ$) (Figure 1).^{28,29} Hydrogen bonds can be described using three parameters, $\alpha(\text{NH}\cdots\text{O})$, $r(\text{H}\cdots\text{O})$, and $r(\text{N}\cdots\text{O})$ (Figure

Figure 1. Energy-minimized structure of the pinched cone conformation of **2a**. Nonpolar hydrogen atoms are omitted. Nitrogen atoms are colored black, and carbonyl atoms are colored gray.

Figure 2. Geometry of the bifurcated hydrogen bonding motif in **2a**. Distances are given in Å.

2),³⁰ in which $\alpha(\text{NH}\cdots\text{O})$ is the hydrogen bond angle that varies between 90 and 180°, $r(\text{N}\cdots\text{O})$ is the hydrogen atom–hydrogen bond acceptor–atom distance and is generally smaller than 3 Å, and $r(\text{N}\cdots\text{O})$ is the hydrogen bond donor atom–hydrogen bond acceptor atom distance and generally is between 2.4 and 3.2 Å.³¹ The values obtained with molecular modeling are in accordance with these values. The average values for the parameters for NH···O=C hydrogen bonds have been determined on the basis of a survey of the Cambridge Structural Database (CSD) by Taylor *et al.*^{30,32} These average values for intramolecular hydrogen bonds are $\alpha(\text{NH}\cdots\text{O}) = 146.8^\circ$ and $r(\text{H}\cdots\text{O}) = 2.004$ Å.

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The values obtained from the molecular modeling are in reasonable agreement with the average values derived from the CSD. One of the hydrogen bonds of the bifurcated hydrogen bonding motif in **2a** as depicted in Figure 2 has a smaller $\alpha(\text{NH} \cdots \text{O})$ angle and a larger $r(\text{H} \cdots \text{O})$ distance, indicating that this hydrogen bond is weaker than an averaged bifurcated hydrogen bond. The other hydrogen bond has a larger $\alpha(\text{NH} \cdots \text{O})$ angle and a shorter $r(\text{H} \cdots \text{O})$ distance, indicating that this hydrogen bond is stronger than an averaged bifurcated hydrogen bond. The values for $\alpha(\text{NH} \cdots \text{O})$, $r(\text{N} \cdots \text{O})$, and $r(\text{H} \cdots \text{O})$ are in agreement with the values obtained from crystal structures of *N,N'*-diarylated derivatives.³³

Conclusions

Calix[4]arenes functionalized at the upper rim with two (thio)ureido moieties adopt a pinched cone conformation in CDCl_3 due to hydrogen bonding between the urea hydrogens and the urea carbonyl atoms. The pinched cone conformation is stable up to at least 120 °C in $\text{C}_2\text{D}_2\text{Cl}_4$. The bis(ureido)calix[4]arenes **2b** and **2c** most likely form a hydrogen-bonded dimer, while bis(*n*-octyl(thio)ureido)calix[4]arenes **2a** and **4** are present as monomers. A calix[4]arene functionalized with two acetamido groups (**5**) adopts a pinched cone conformation due to intramolecular hydrogen bonding between the two opposite acetamido groups. The pinched cone conformation is stable up to at least 145 °C. These results imply that due to hydrogen bonding in the pinched cone conformation in **2a–c**, **4**, and **5**, the calix[4]arene skeleton is rigidified.

Experimental Section

All melting points are uncorrected. ^1H NMR and ^{13}C NMR spectra were recorded with a 250 MHz spectrometer in CDCl_3 with Me_4Si as an internal standard unless stated otherwise. NOESY, ROESY, and temperature-dependent ^1H NMR spectra were recorded on a 400 MHz spectrometer. The temperature-dependent experiments were performed in $\text{C}_2\text{D}_2\text{Cl}_4$ with intervals of 10 °C. In the NOESY and ROESY experiments the mixing times varied between 30 and 225 ms. For the calculation of the distances NOESY spectra were recorded with three different mixing times. FAB mass spectra were obtained using *m*-nitrobenzyl alcohol (NBA) as a matrix. FTIR spectra were recorded with 32 scans and a resolution of 2 cm^{-1} . Molecular weight determinations were carried out on a vapor pressure osmometer in glass-distilled HPLC-grade CHCl_3 at 29 °C in a concentration range of 4.6–65.3 $\text{g}\cdot\text{kg}^{-1}$. Benzil was used as calibration standard. CHCl_3 was distilled from CaCl_2 and stored over molecular sieves 3 Å, toluene was distilled over Na and stored over molecular sieves 3 Å. All other solvents and chemicals were used without purification. Silica gel (particle size 0.040–0.063 mm, 230–240 mesh) was obtained from Merck. All reactions were carried out under an argon atmosphere. For reasons of clarity and to reduce space the name calix[4]arene was used instead of the original IUPAC name: pentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacos-1(25),3,5,7-(28),9,11,13(27),15,17,19(26),21,23-dodecane. Before the elemental analysis the samples were dried overnight over P_2O_5 at a minimum of 75 °C. The presence of solvent in the analytical samples was confirmed by ^1H NMR spectroscopy. 1,3-Diaminocalix[4]arene **1** was synthesized according to a literature procedure.¹¹ The synthesis of bis(acetamido)calix[4]arene **5** was reported previously.¹³ Molecular Modeling was

performed with CHARMm²⁷ version 22.0 as implemented in Quanta version 3.3.³⁴ Energy minimizations were carried out (Adopted Based Newton–Raphson) until the root mean square of the gradient was $< 0.01 \text{ kcal}\cdot\text{mol}^{-1}\cdot\text{\AA}^{-1}$. A distance-dependent dielectric constant was applied. No cut-offs on the nonbonded interactions were used. Charges on atoms were calculated from point charge templates. The resulting net charges were smoothed over nonpolar carbonyl and hydrogen atoms.

5,17-Bis[*N*-(*R*)ureido]-25,26,27,28-tetrakis(ethoxycarbonyl)methoxycalix[4]arene **2a–c.** To a solution of 1,3-diaminocalix[4]arene **1** (0.96 g, 1.03 mmol) in CHCl_3 (20 mL) was added 2 equiv of the appropriate isocyanate (4.42 mmol), and the mixture was stirred at room temperature for 3 h. Then H_2O (20 mL) was added, and the organic layer was separated; the crude products were purified as described below.

2a: *R* = *n*-octyl. The crude product was triturated with diisopropyl ether followed by recrystallization from CHCl_3 /diisopropyl ether: yield 44%; mp 92–94 °C; IR (KBr) ν 3366 (NH), 1762 ($\text{C}=\text{O}_{\text{ester}}$), 1653 ($\text{C}=\text{O}_{\text{urea}}$) cm^{-1} ; ^1H NMR δ 7.01 (d, 4 H, J = 7.1 Hz), 6.89 (t, 2 H, J = 6.9 Hz), 6.1–6.0 (br s, 2 H), 6.02 (s, 4 H), 5.1–5.0 (br t, 2 H), 4.9–4.8 (m, 8 H), 4.52 (s, 4 H), 3.78, 3.71 (2 s, 8 H), 3.20 (d, 4 H, J = 14.0 Hz), 3.09 (q, 4 H, J = 5.9 Hz), 1.4–1.1 (m, 30 H), 1.12 (t, 6 H, J = 5.1 Hz), 0.88 (t, 6 H); ^{13}C NMR ($\text{DMSO}-d_6$) δ 8.02 (s, 2 H), 6.90, 6.47 (2 s, 8 H), 5.9–5.8 (br t, 2 H), 4.70, 4.60 (2 s, 8 H), 4.65 and 3.11 (ABq, 8 H, J = 12.0 Hz), 4.15 (q, 8 H, J = 7.3 Hz), 3.05 (q, 4 H, J = 5.9 Hz), 1.4–1.1 (m, 36 H), 0.86 (t, 6 H, J = 6.7 Hz); ^{13}C NMR δ 171.0 and 170.0 (s), 157.1 (s), 156.3 (s), 151.8 (s), 135.7 (s), 134.5 (s), 133.1 (s), 129.4 (d), 123.1 (d), 121.6 (d), 71.3 (t), 70.9 (t), 68.3 (t), 51.8 (t), 51.4 (t), 40.2 (t), 31.9 (t), 31.4 (t), 30.2 (t), 29.4 (t), 29.3 (t), 26.9 (t), 22.9 (t), 22.7 (q), 14.1 (q); FAB mass spectrum, positive m/z 1131.7 ($[\text{M} + \text{Na}]^+$, calcd 1132.3), negative m/z 1108.0 ($[\text{M} - \text{H}]^-$, calcd 1108.3). Anal. Calcd for $\text{C}_{62}\text{H}_{84}\text{N}_4\text{O}_{14}\cdot 0.5\text{H}_2\text{O}$: C, 66.59; H, 7.65; N, 5.01. Found: C, 66.59; H, 7.42; N, 5.08.

2b: *R* = phenyl. The crude product was triturated with CHCl_3 /diisopropyl ether: yield 50%; mp 141 °C; IR (KBr) ν 3392 (NH), 1734 ($\text{C}=\text{O}_{\text{ester}}$), 1653 ($\text{C}=\text{O}_{\text{urea}}$) cm^{-1} ; ^1H NMR δ 7.3–7.1 (m, 10 H), 6.98 (d, 6 H, J = 7.0 Hz), 6.87 (t, 2 H, J = 7.1 Hz), 6.63 (s, 2 H), 6.04 (s, 4 H), 4.92 and 3.09 (ABq, 8 H, J = 12.7 Hz), 4.95, 4.47 (2 s, 8 H), 4.3–4.0 (m, 8 H), 1.3–1.1 (m, 12 H); ^{13}C NMR ($\text{DMSO}-d_6$) δ 8.46 (s, 2 H), 8.28 (s, 2 H), 7.35 (d, 4 H, J = 8.0 Hz), 7.22 (t, 4 H, J = 7.6 Hz), 6.91 (t, 8 H, J = 7.4 Hz), 6.56 (s, 4 H), 4.7–4.6 (m, 8 H), 4.2–4.1 (m, 8 H), 3.15 (ABq, 4 H, J = 13.4 Hz), 1.22 (t, 12 H, J = 7.1 Hz); ^{13}C NMR δ 170.6 (s), 169.5 (s), 156.9 (s), 156.8 (s), 154.4 (s), 152.3 (s), 138.5 (s), 135.6 (d), 134.3 (s), 132.1 (d), 129.3 (d), 128.9 (d), 123.0 (d), 122.9 (d), 122.4 (d), 119.3 (s), 71.5 (t), 70.9 (t), 60.7 (t), 60.3 (t), 31.4 (t), 14.2 (q), 14.2 (q); FAB mass spectrum, positive m/z 1060.3 ($[\text{M} + \text{Na}]^+$, calcd 1060.1), negative m/z 1035.8 ($[\text{M} - \text{H}]^-$, calcd 1036.0). Anal. Calcd for $\text{C}_{58}\text{H}_{68}\text{N}_4\text{O}_{12}\cdot \text{H}_2\text{O}$: C, 66.03; H, 5.92; N, 5.31. Found: C, 66.07; H, 5.74; N, 5.35.

2c: *R* = *tert*-butyl. The crude product was purified by column chromatography (SiO_2 ; CH_2Cl_2 :EtOAc = 1:1): yield 36%; mp 131–133 °C; IR (KBr) ν 3390 (NH), 1759 ($\text{C}=\text{O}_{\text{ester}}$), 1653 ($\text{C}=\text{O}_{\text{urea}}$) cm^{-1} ; ^1H NMR δ 6.96 (d, 4 H, J = 7.2 Hz), 6.81 (t, 2 H, J = 7.4 Hz), 6.27 (s, 2 H), 6.01 (s, 4 H), 5.09 (s, 2 H), 4.82 and 3.21 (ABq, 8 H, J = 14.2 Hz), 4.80, 4.52 (2 s, 8 H), 4.3–4.1 (m, 8 H), 1.3–1.2 (m, 48 H); ^{13}C NMR ($\text{DMSO}-d_6$) δ 7.95 (s, 2 H), 6.94 (s, 4 H), 6.40 (s, 6 H), 5.81 (s, 2 H), 4.73, 4.54 (2 s, 8 H), 4.2–4.0 (m, 8 H), 1.3–1.1 (m, 30 H); ^{13}C NMR δ 170.4 (s), 169.8 (s), 156.5 (s), 156.6 (s), 152.2 (s), 135.2 (s), 134.7 (s), 133.5 (s), 129.0 (d), 123.0 (d), 122.2 (d), 71.4 (t), 71.1 (t), 60.6 (t), 60.4 (t), 31.4 (t), 29.7 (s), 29.5 (q), 14.2 (q); FAB mass spectrum, positive m/z 997.2 ($[\text{M}]^+$, calcd 997.1), 1019.6 ($[\text{M} + \text{Na}]^+$, calcd 1020.1); negative m/z 994.9 ($[\text{M} - 2\text{H}]^-$, calcd 995.1). Anal. Calcd for $\text{C}_{54}\text{H}_{68}\text{N}_4\text{O}_{14}\cdot 0.5\text{H}_2\text{O}$: C, 64.47; H, 6.90; N, 5.57. Found: C, 64.41; H, 6.49; N, 5.48.

5,17-Diisothiocyanato-25,26,27,28-tetrakis(ethoxycarbonyl)methoxycalix[4]arene (3). 1,3-Diaminocalix[4]arene **1** (0.66 g, 0.83 mmol) was dissolved in toluene (50 mL).

(32) (a) Taylor, R.; Kennard, O.; Versichel, W. *J. Am. Chem. Soc.* **1983**, *105*, 5761. (b) Taylor, R.; Kennard, O.; Versichel, W. *Ibid.* **1984**, *106*, 244.

(33) Etter, M. C.; Urbaniak-Lipowska, Z.; Zia-Ebrahimi, M.; Pannuto, T. W. *J. Am. Chem. Soc.* **1990**, *112*, 8415.

(34) Quanta was purchased from Molecular Simulations, Inc., Burlington, MA.

Thiophosgene (0.31 mL, 4.13 mmol)³⁵ was added followed by Et₃N (0.53 mL, 4.13 mmol), and the mixture was refluxed for 3 h. The reaction mixture was evaporated thoroughly and the residue was taken up in CH₂Cl₂ (100 mL), washed with H₂O (2 × 50 mL), and dried with MgSO₄. After filtration and evaporation of the solvent the crude product was purified by column chromatography (SiO₂; CH₂Cl₂:MeOH = 99:1) to give **3** as a brown oil: yield 89%; IR (CDCl₃) ν 2131 (NCS) cm⁻¹; ¹H NMR δ 6.68 (t, 6 H, *J* = 7.2 Hz), 6.50 (s, 4 H), 4.87 and 3.17 (ABq, 8 H, *J* = 15.0 Hz), 4.72 and 4.68 (2 s, 8 H), 4.3–4.2 (m, 8 H), 1.3–1.2 (m, 12 H); ¹³C NMR δ 169.7 (s), 167.3 (s), 156.7 (s), 152.4 (s), 133.7 (s), 131.3 (s), 128.8 (s), 126.4 (d), 125.5 (s), 123.5 (s, NCS), 123.0 (d), 71.2 (t), 68.3 (t), 60.6 (t), 58.1 (t), 31.2 (t), 14.1 (q), 11.7 (q); FAB mass spectrum, positive *m/z* 881.9 (M⁺, calcd 882.9), 905.0 ([M + Na]⁺, calcd 905.2).

5,17-Bis(*N*-*n*-octylthioureido)-25,26,27,28-tetrakis[(ethoxycarbonyl)methoxy]calix[4]arene (4**)** was prepared as described for **2a–c** starting from 1,3-diisothiocyanatocalix[4]arene **3** using 2 equiv of *n*-octylamine: yield 68%; mp 149 °C; IR (KBr) ν 3290 (NH) cm⁻¹; ¹H NMR δ 7.0–6.9 (m, 8 H),

6.6–6.5 (br t, 2 H), 6.04 (s, 4 H), 4.89 and 3.23 (ABq, 8 H, *J* = 13.9 Hz), 4.83, 4.57 (2 s, 8 H), 4.3–4.1 (m, 8 H), 3.49 (q, 4 H, *J* = 5.7 Hz), 1.6–1.5 (m, 4 H), 1.3–1.2 (m, 36 H), 0.88 (t, 12 H, *J* = 6.6 Hz); ¹³C NMR δ 180.5 (s), 170.4 (s), 169.5 (s), 156.7 (s), 153.6 (s), 135.7 (d), 135.1 (s), 131.9 (d), 129.4 (d), 124.0 (s), 123.5 (s), 71.6 (t), 71.0 (s), 60.9 (t), 60.4 (t), 45.3 (t), 31.8 (t), 31.5 (t), 29.3 (t), 29.3 (t), 28.9 (t), 27.0 (t), 22.7 (t), 14.2 (q), 14.1 (q); FAB mass spectrum, positive *m/z* 1141.8 (M⁺, calcd 1141.4), negative *m/z* 1139.2 ([M – 2H]⁻, calcd 1139.4). Anal. Calcd for C₆₂H₈₄N₄O₁₂S₂: C, 65.24; H, 7.40; N, 4.91. Found: C, 64.86; H, 7.40; N, 4.94.

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(35) A small excess of thiophosgene was used to prevent the formation of *N,N*-disubstituted thioureas.¹²