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 CDCl$_3$ solution. The pinched cone conformation is the result of *diametrical, intra*molecular hydrogen bonds and was studied by ^{1}H NMR dilution and variable-temperature experiments, NOESY spectroscopy, and FTIR experiments. The pinched cone conformation in these novel calix[4]arenes is stable in C$_2$D$_2$Cl$_4$ 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]arenes[1] 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 ^{1}H 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 *intra*molecular 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 *intra*molecular 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

[†] Laboratory of Organic Chemistry.
[‡] Laboratory of Chemical Analysis.
[⊗] Abstract published in *Advance ACS Abstracts,* April 15, 1996.
(1) (a) Gutsche, C. D. In *Calixarenes Monographs in Supramolecular Chemistry*; Stoddart, J. F., Ed.; The Royal Society of Chemistry: Cambridge, 1989; Vol. 1. (b) Vicens, J., Böhmer, V., Eds. *Calixarenes: a Versatile Class of Macrocyclic Compounds*; Kluwer Academic Publishers: Dordrecht; 1991. (c) Böhmer, V. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 713.
(2) (a) Araki, K.; Iwamoto, K.; Shinkai, S.; Matsuda, T. *Chem. Lett.* **1989**, 1747. (b) Iwamoto, K.; Araki, K.; Shinkai, S. *J. Org. Chem.* **1991**, *56*, 4955.
(3) (a) Grootenhuis, P. D. J.; Kollman, P. A.; Groenen, L. C.; Reinhoudt, D. N.; van Hummel, G. J.; Ugozzoli, F.; Andreetti, G. D. *J. Am. Chem. Soc.* **1990**, *112*, 4165. (b) Harada, T.; Rudzinski, J. M.; Osawa, E.; Shinkai, S. *Tetrahedron Lett.* **1993**, *49*, 5941.
(4) (a) Yamada, A.; Murase, T.; Kikukawa, K.; Matsuda, T.; Shinkai, S. *Chem. Lett.* **1990**, 455. (b) Yamada, A.; Murase, T.; Kikukawa, K.; Arimura, T.; Shinkai, S. *J. Chem. Soc., Perkin Trans. 2* **1991**, 793.
(5) Andreetti, G. D.; Ugozzoli, F.; Ungaro, R.; Pochini, A. In *Inclusion Compounds*; Atwood, J. L., Davies, J. E. D., MacNicol, D. D., Eds.; Oxford University Press: Oxford 1991; Vol. 4, p 64.
(6) Conner, M.; Janout, V.; Regen, S. L. *J. Am. Chem. Soc.* **1991**, *113*, 9670.

(7) Arduini, A.; Fabbi, M.; Mirone, L.; Pochini, A.; Secchi, A.; Ungaro, R. *J. Org. Chem.* **1995**, *69*, 1454.
(8) Ikeda, A.; Tsuzuki, K.; Shinkai, S. *J. Chem. Soc., Perkin Trans. 2* **1994**, 2073.
(9) Timmerman, P.; Nierop, K. G. A.; Brinks, E. A.; Verboom, W.; van Veggel, F. C. J. M.; van Hoorn, W. P.; Reinhoudt, D. N. *Chem. J. Eur.* **1995**, *1*, 132.
(10) For recent examples of covalent rigidification of the calix[4]-arene skeleton, see: (a) Arduini, A.; Fanni, S.; Manfredi, G.; Pochini, A.; Ungaro, R.; Sicuri, A. R.; Ugozzoli, F. *J. Org. Chem.* **1995**, *60*, 1448. (b) Arduini, A.; Fanni, S.; Pochini, A.; Sicuri, A. R.; Ungaro, R. *Tetrahedron* **1995**, *51*, 7951. For stabilization of the pinched cone conformation via upper rim bridging, see: (c) Goldmann, H.; Vögt, W.; Paulus, E.; Böhmer, V. *J. Am. Chem. Soc.* **1988**, *110*, 6811. (d) Böhmer, V.; Vögt, W.; Goldmann, H.; McKervey, A. M.; Owens, M.; Cremin, S.; Collins, E. M. *J. Org. Chem.* **1990**, *55*, 2569.
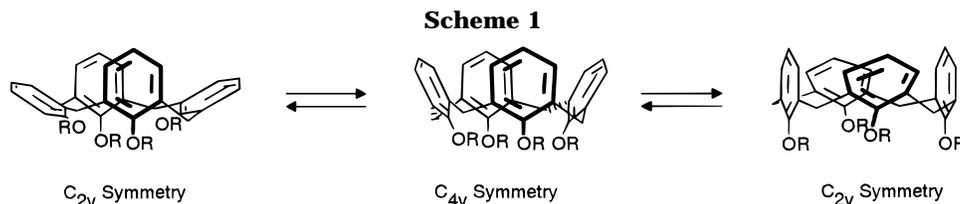(11) Rudkevich, D. M.; Verboom, W.; Reinhoudt, D. N. *J. Org. Chem.* **1994**, *59*, 3683.

Scheme 1

C_{2v} Symmetry C_{4v} Symmetry C_{2v} Symmetry

Table 1. Selected ^{1}H 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_2Ar (J, Hz)
2a	5.08	6.04−6.10	7.01, 6.89	6.09	4.82, 3.20 (14.0)
2b	b	6.63	b, 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} ≤5% of a minor conformer is present. ^{e} Multiplet.

Chart 1

1 X=NH$_2$
3 X=NCS

X=O **2a** R=n-octyl
 **b** R=phenyl
  c R=$tert$-butyl
X=S **4** R=n-octyl

5
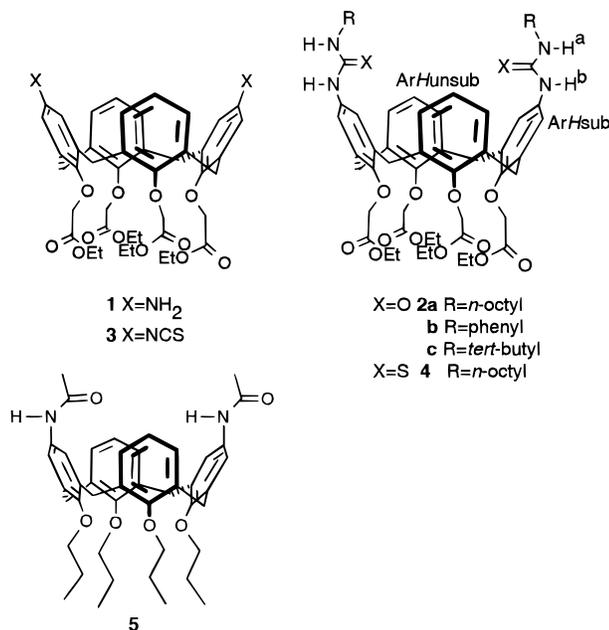
addition of 2 equiv of the appropriate isocyanates to a solution of 1,3-diaminocalix[4]arene **1** in CHCl$_3$. In addition, 1,3-diaminocalix[4]arene **1** was treated with thiophosgene^{12} to give the 1,3-diisothiocyanatocalix[4]-arene **3** in 87% yield. Subsequent addition of n-octyl-amine gave the bis(n-octylthioureido)calix[4]arene **4** in 68% yield. The characteristic ^{1}H 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 (ArHsub) give one signal in the ^{1}H 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 (ArHunsub) give a doublet and triplet in the ^{1}H

Chart 2
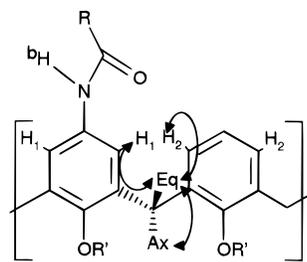
NMR spectrum. The signals at 5.08 and 6.50 ppm in the ^{1}H NMR spectra of bis(n-octyl(thio)ureido)calix[4]arenes **2a** and **4**, respectively, are triplets and can be assigned to the NH^a hydrogens which couple with the neighboring methylene hydrogens of the n-octyl groups. Consequently, for **2a**, 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 ArHsub and the signal at 6.63 ppm this resonance is assigned to NH^b.

Conformational Behavior. The ^{1}H 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 (ArHsub) are at unusually high field (Table 1). In addition, the ^{1}H NMR spectrum of bis(n-octylureido)calix-[4]arene **2a** shows two signals for the NH^{a}CH_2 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 approximation^{17} in which the distance of 1.79 Å

(12) Drobnica, L.; Kristián, P.; Augustín, J. in *The Chemistry of Cyanates and their Thio Derivatives*; Patai, S., Ed.; John Wiley & Sons: New York, 1977; Part 2, p 1032.
(13) Verboom, W.; Bodewes, P.; van Essen, G.; Timmerman, P.; van Hummel, G. J.; Harkema, S.; Reinhoudt, D. N. *Tetrahedron* **1995**, *51*, 449.

(14) Jeener, J.; Meier, B. H.; Bachmann, P.; Ernst, R. R. *J. Chem. Phys.* **1979**, *71*, 4546.
(15) Neuhaus, D.; Williamson, M. P. *The Nuclear Overhauser Effect in Structural and Conformational Analysis*; VCH Publishers: Cambridge, U.K., 1989.

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	f	2.5	2.5
$H_2{}^e$	3.2	3.0	f	3.1	2.8

[a] H_{eq} are the equatorial calix[4]arene bridging methylene hydrogens. [b] CDCl$_3$, 303 K. [c] ±0.2 Å. [d] Determined at 218 K. [e] For H_1 and H_2 see Chart 2. [f] Not determined quantitatively, but ROESY spectroscopy clearly indicates a longer distance (factor 1.2) for H_2 in comparison to H_1.

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

R=CH$_2$C(O)OCH$_2$CH$_3$
X=O, S

R=CH$_2$C(O)OCH$_2$CH$_3$
R'=phenyl, *tert*-butyl
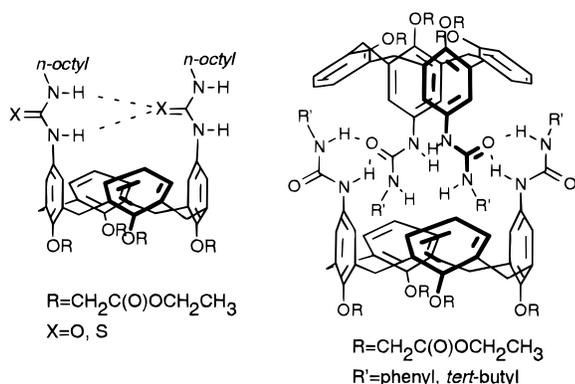
between the equatorial and axial bridging methylene hydrogen atoms (Chart 2) was used as a reference.

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 CDCl$_3$ 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 (H$_1$). 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 H$_2$ is larger than the distance between H$_{eq}$ and H$_1$ (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] CDCl$_3$, 303 K.

and the aromatic hydrogens of the calix[4]arene skeleton (H$_1$ and H$_2$, 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 H$_1$ and H$_2$. 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 *inter*molecular 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 ($\geq$2000 g·mol^{-1}) are present.[20] Bis(*n*-octylureido)-calix[4]arene **2a** and bis(*n*-octylthioureido)calix[4]arene **4** do not show any indication of association because no intermolecular NOE connectivities are observed between the hydrogens of the *n*-octyl substituent at the urea moieties and the aromatic hydrogens H$_1$ and H$_2$.

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 *inter*molecular NOE connectivities. The positive σ values for **2a** and **4** suggest that no aggregation occurs and support the absence of *inter*molecular NOE connectivities.

The *inter*molecular 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 (Ar*H*), 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 *inter*molecular 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** ^{1}H 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-

(16) (a) For an early study of the conformations of calix[4]arenes in solution using NOESY spectroscopy, see: Alfieri, C.; Dradi, E.; Pochini, A.; Ungaro, R. *Gazz. Chim. Ital.* **1989**, *119*, 335. (b) Exchange connectivities in the NOESY spectrum were identified by ROESY experiments where ROE and exchange connectivities have opposite signs. For an introduction to ROESY spectroscopy, see: Bothner-By, A. A.; Stephens, R. L.; Lee, L.; Warren, C. D.; Jeanloz, R. W. *J. Am. Chem. Soc.* **1984**, *106*, 811.

(17) Ernst, R. R.; Bodenhausen, G.; Wokaun, A. *Principles of Nuclear Magnetization Resonance in One and Two Dimensions*; Breslow, R., Goodenough, J. B., Halpern, J., Rowlinson, D., Eds.; International Series of Monographs on Chemistry; Clarendon Press: Oxford, 1987; Vol. 14, pp 490−538.

(18) The distances between the equatorial bridging methylene hydrogens (H$_{eq}$) and the two adjacent aromatic hydrogens (Ar*H*) of tetrakis(*n*-octylureido)calix[4]arene, which adopts a C_{4v} symmetrical cone conformation in CDCl$_3$ 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.

(21) Isotropic tumbling and pure dipole−dipole relaxation is assumed. Wüttrich, K. *NMR of Proteins and Nucleic Acids*; John Wiley & Sons, Inc.: New York, 1986; Chapter 6.

ment[22] which is comparable to the oligomerization of N-alkylated linear carboxamides.[23] V.P.O. molecular weight determinations[24] in CDCl$_3$ gave a molecular mass of 845 ± 80 g·mol^{-1} which is slightly higher than the calculated molecular mass of the monomer (707 g·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 *intra*molecular 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 ^{1}H 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 ^{1}H NMR spectra in CDCl$_3$. 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 ^{1}H NMR spectrum in CDCl$_3$ 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 CDCl$_3$ versus 6.41 ppm in DMSO-d_6. The pinching in CDCl$_3$ is also expressed by the chemical shift of the OCH$_2$ hydrogens, which are 0.26 ppm apart in CDCl$_3$, 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 CDCl$_3$ (1−20 mM) reveal a broad, concentration-independent NH stretching band at 3336 cm^{-1}, attributed to *intra*molecular NH- - -O=C hydrogen bonds in monomeric **2a** or *inter*molecular 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 ^{1}H 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(H^b- - -O) = 1.797 and r(H^a- - -O) = 2.374 Å; r(N- - -O = 2.735 and 3.168 Å; α-(NH^b- - -O = 153.6° and α(NH^a- - -O) = 135.9°) (Figure 1).[28,29] Hydrogen bonds can be described using three parameters, α(NH- - -O), r(H- - -O), and r(N- - -O) (Figure
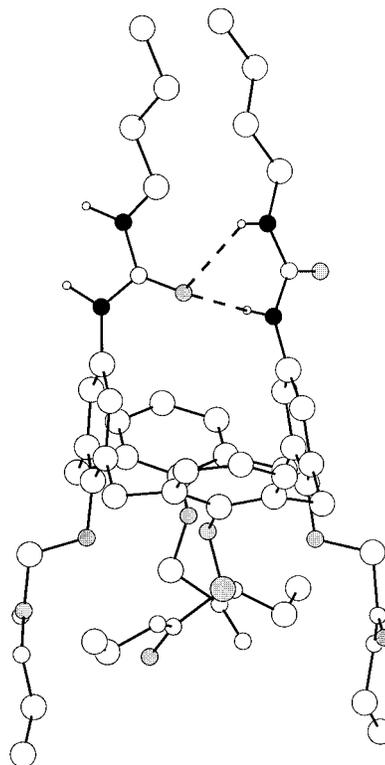

Figure 1. Energy-minimized structure of the pinched cone conformation of **2a**. Nonpolar hydrogen atoms are omitted. Nitrogen atoms are colored black, and carbonyl atoms are colored gray.
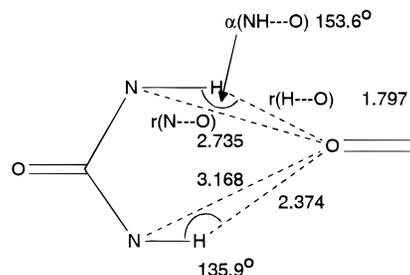

Figure 2. Geometry of the bifurcated hydrogen bonding motif in **2a**. Distances are given in Å.

2),[30] in which α(NH- - -O) is the hydrogen bond angle that varies between 90 and 180°, r(N- - -O) is the hydrogen atom−hydrogen bond acceptor−atom distance and is generally smaller than 3 Å, and r(N- - -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 *intra*molecular hydrogen bonds are α(NH- - -O) = 146.8° and r(H- - -O) = 2.004 Å.

(22) In the ^{1}H NMR dilution experiments the NH signal was used as a probe. The data were treated using the linear regression method as described: Horman, I.; Dreux, B. *Helv. Chim. Acta* **1984**, *67*, 754.

(23) Krikorian, S. E. *J. Phys. Chem.* **1982**, *86*, 1875.

(24) When the V.P.O. data were treated according to the method of Schrier the best fit was found for the model assuming oligomerization; see: Schrier, E. E. *J. Chem. Ed.* **1986**, *55*, 176.

(25) ^{1}H NMR studies and MO calculations suggest that formation of higher linear aggregates is preferred over dimerization; see: Graham, L. L.; Chang, Y. C. *J. Phys. Chem.* **1971**, *75*, 776.

(26) The behavior in acetonitrile-d_3 and acetone-d_6 resembles the behavior in DMSO-d_6 concerning the shifts of the aromatic hydrogens.

(27) Brooks, B. R.; Bruccoleri, R. E.; Olafson, B. D.; States, D. J.; Swaminthan, S.; Karplus, M. *J. Comput. Chem.* **1983**, *4*, 187.

(28) (a) Etter, M. C. *Acc. Chem. Res.* **1990**, *23*, 121. (b) Etter, M. C.; Panuto, T. W. *J. Am. Chem. Soc.* **1988**, *110*, 5896.

(29) The two aromatic rings are almost parallel and their closest distance is 4.51 Å, indicating that π−π stacking is unlikely to contribute to the stability of the pinched cone conformation. Hunter, C. A.; Sanders, J. K. M. *J. Am. Chem. Soc.* **1990**, *112*, 5525.

(30) Taylor, R.; Kennard, O.; Versichel, W. *Acta Crystallogr.* **1984**, *B40*, 280.

(31) Picard, B.; Baudoux, G.; Durant, F. *Acta Crystallogr.* **1995**, *B51*, 103.

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 α(NH- - -O) angle and a larger *r*(H- - -O) distance, indicating that this hydrogen bond is weaker than an averaged bifurcated hydrogen bond. The other hydrogen bond has a larger α(NH- - -O) angle and a shorter *r*(H- - -O) distance, indicating that this hydrogen bond is stronger than an averaged bifurcated hydrogen bond. The values for α(NH- - -O), *r*(N- - -O), and *r*(H- - -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 CDCl₃ 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 C₂D₂Cl₄. 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 *intra*molecular 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 ¹³C NMR spectra were recorded with a 250 MHz spectrometer in CDCl₃ with Me₄Si 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 C₂D₂Cl₄ 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 CHCl₃ at 29 °C in a concentration range of 4.6−65.3 g·kg⁻¹. Benzil was used as calibration standard. CHCl₃ was distilled from CaCl₂ 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[19.3.1.1³,⁷.1⁹,¹³.1¹⁵,¹⁹]octacosa-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 P₂O₅ 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 CHARMm[27] 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 kcal·mol⁻¹·Å⁻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)methoxy]calix[4]arene 2a−c. To a solution of 1,3-diaminocalix[4]arene **1** (0.96 g, 1.03 mmol) in CHCl₃ (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 H₂O (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 CHCl₃/diisopropyl ether: yield 44%; mp 92−94 °C; IR (KBr) υ 3366 (NH), 1762 (C=O_ester), 1653 (C=O_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); ¹H NMR (DMSO-*d₆*) 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); ¹³C 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 ([M + Na]⁺, calcd 1132.3), negative *m/z* 1108.0 ([M - H]⁻, calcd 1108.3). Anal. Calcd for C₆₂H₈₄N₄O₁₄·0.5H₂O: 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 from CHCl₃/diisopropyl ether: yield 50%; mp 141 °C; IR (KBr) υ 3392 (NH), 1734 (C=O_ester), 1653 (C=O_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); ¹H NMR (DMSO-*d₆*) 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); ¹³C 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 ([M + Na]⁺ calcd 1060.1), negative *m/z* 1035.8 ([M − H]⁻ calcd 1036.0). Anal. Calcd for C₅₈H₆₈N₄O₁₁₂·H₂O: 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 (SiO₂; CH₂Cl₂:EtOAc = 1:1): yield 36%; mp 131−133 °C; IR (KBr) υ 3390 (NH), 1759 (C=O_ester), 1653 (C=O_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); ¹H NMR (DMSO-*d₆*) 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); ¹³C 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 ([M]⁺, calcd 997.1), 1019.6 ([M + Na]⁺, calcd 1020.1); negative *m/z* 994.9 ([M − 2 H]⁻, calcd 995.1). Anal. Calcd for C₅₄H₆₈N₄O₁₄·0.5H₂O: 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)methoxy]calix[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.; Urbañczyk-Lipowska, Z.; Zia-Ebrahimi, M.; Panuto, 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 CH_2Cl_2 (100 mL), washed with H_2O (2 × 50 mL), and dried with $MgSO_4$. After filtration and evaporation of the solvent the crude product was purified by column chromatography (SiO_2; CH_2Cl_2:MeOH = 99:1) to give **3** as a brown oil: yield 89%; IR ($CDCl_3$) v 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) v 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 spectum, positive m/z 1141.8 (M⁺, calcd 1141.4), negative m/z 1139.2 ([M − 2H]⁻, calcd 1139.4). Anal. Calcd for $C_{62}H_{84}N_4O_{12}S_2$: 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]