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Enhanced Thermodynamic and Kinetic Stability of Calix[4]arene Dimers Locked in the Cone Conformation

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Wide rim tetraurea derivatives (**2a,b**) have been prepared from a calix[4]arene rigidified in the cone conformation by two diethyleneglycol ether bridges between adjacent oxygens. In comparison to the analogous tetraurea derivatives (**3a,b**) of a tetrapentoxy calix[4]arene, **2a,b** show an increased thermodynamic stability in mixtures of $CDCl_3$ and DMSO-d_6. Their kinetic stability as expressed by the rate of guest exchange (benzene or cyclohexane against the solvent benzene-d_6) is also strongly increased by factors of 30−38. Noticeable differences for the inclusion of selected guests are found.

Introduction

Previously, we[1,2] had shown that calix[4]arene tetraethers in the *cone* conformation substituted by urea functions on the wide rim reversibly dimerize in apolar solvents to form capsules.[3] These dimers show large association constants ($K_a \approx 10^6-10^8$ M^{-1})[4] and appear kinetically stable on the ^{1}H NMR time scale. Both X-ray structure[2b] and ^{1}H NMR studies[2c] demonstrate that this association occurs via the formation of a seam of 16 (eight strong and eight weak) hydrogen bonds between overall eight urea groups. However, these capsules dissociate upon the addition of small amounts of hydrogen-bonding competitors such as DMSO. Initial attempts to improve their stability by forming an unimolecular capsule[5] met with little success.

The kinetic stability of a capsular assembly, characterized for instance by the rate of the guest release or exchange, strongly depends on the solvent and on the included guest. Half-life times of more than 1000 h have been observed in cyclohexane-d_{12} when such inert guests as tetrachloromethane, 1,4-difluorobenzene, methyl-cyclohexane, or cyclohexane are encapsulated in tetratolylurea dimers.[6] Half-life times are shorter in benzene, but the introduction of bulkier residues (tritylphenyl instead of tolyl) at the urea functions[7] effectively increased the kinetic stability by several orders of magnitude, e.g., half-life times up to 60 h for the exchange of the included benzene.[8] In the special case of the homodimer of a tetratritylurea, the formation of which could be induced only by the tetramethylammonium cation as guest, the half-life time could be increased even in DMSO-d_6 to about 90 h.[9]

O-Alkyl groups, Y ≥ propyl, fix the calix[4]arene in one of four possible conformations: *cone*, *partial cone*, 1,3-*alternate*, or 1,2-*alternate*. The apparent C_{4v} symmetry expressed by the NMR spectrum of the *cone* conformer is due to a rapid interconversion of two identical C_{2v}-symmetrical *pinched cone* conformations. Connection of adjacent oxygens at the narrow rim by two di(ethylene glycol) tethers[10] leads to a more rigid calixarene skeleton with a nearly C_{4v} symmetrical shape, as shown by several X-ray structures.[11] This improved the complexation properties of calixarene-based receptors designed for the inclusion of both neutral organic molecules[11b,12] and cations.[13] We therefore concluded that the stability of tetraurea capsules could be increased as well. Here we

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(2) (a) Mogck, O., Böhmer, V., Vogt, W. *Tetrahedron* **1996**, *52*, 8489−8496. (b) Mogck, O.; Paulus, E. F.; Böhmer, V.; Thondorf, I.; Vogt, W. *Chem. Commun.* **1996**, 2533−2534. (c) Mogck, O.; Pons, M.; Böhmer, V.; Vogt, W. *J. Am. Chem. Soc.* **1997**, *119*, 5706−5712.

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(7) There is also an influence of the ether residues, which is not yet entirely explored.

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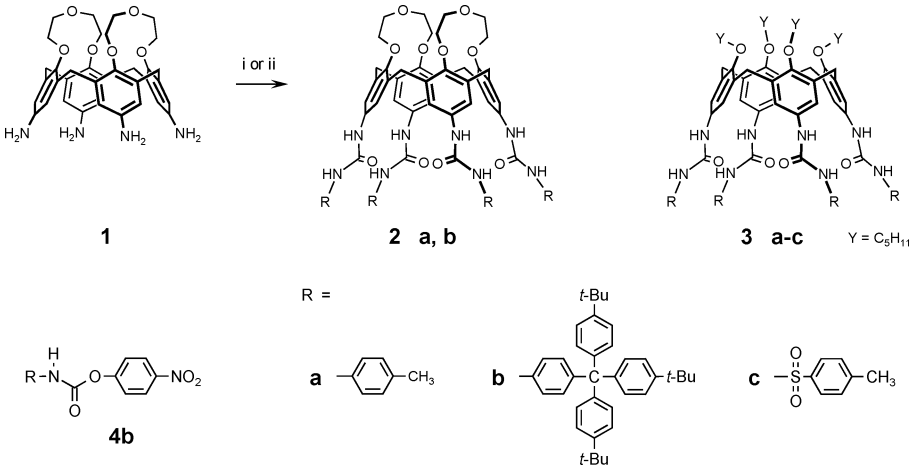
SCHEME 1. Calix[4]arene Tetraurea Derivatives[a]



[a] Reagents and conditions: (i) RNCO, $CHCl_3$, 20 °C, 12 h; (ii) **4b**, $(i\text{-Pr})_2EtN$, DMF, 70 °C, 15 h.

report thermodynamic and kinetic properties of tetraureas derived from this calix[4]arene with a *rigidified cone* conformation.

Results and Discussion

Coupling of the tetraamine **1**,[13] available in three steps from *tert*-butyl calix[4]arene (O-alkylation by diethyleneglycol ditosylate,[10,14] ipso-nitration with fuming nitric acid in refluxing acetic acid, reduction with hydrazine (or hydrogen)), with excess tolyl isocyanate gives **2a** in 60% yield (Scheme 1). Yields of tetraurea calixarene **2b** were lower (5−7%) as a result of severe problems during purification. Better results were obtained in this case with the active urethane **4b** as reagent (an alternative also for the preparation of **2a**), since **2b** precipitates from the solution.[15] The compound **3b** can be prepared in two ways starting either from the tetrapentyl ether tetraamino calix[4]arene[16] and urethane **4b** or from the active urethane of tetraamino calix[4]arene[17] and 4-(tris(4′-*tert*-butyl-phenyl)methyl)aniline. The compounds **2a,b**, **3b**, and **4b** were fully characterized by all standard methods.

The behavior of **2a** was studied by ^1H NMR in $CDCl_3$ (Figure 1), in which it dutifully assembles as the dimeric capsule **2a·2a**. As a result of two short bridges connecting the proximal oxygens of the calix[4]arene skeleton, the *monomeric* tetraurea **2a** has C_{2v}-symmetry. The two symmetry planes intersect two pairs of opposite methylene bridges. When two of those tetraureas **2a** are combined into a homodimer, the symmetry observed by ^1H NMR is reduced to C_2. This is clearly indicated by the four urea N−H singlets between δ = 9.1 and 9.4 corresponding to the eight strongest hydrogen bonds, by four pairs of *meta*-coupled doublets for calixarene protons A to b′, and by four pairs of doublets for $ArCH_2Ar$ protons (Figure 1). Tetraurea **2b** with bulky 4-(*tert*-butyl-trityl)-phenyl units attached to the urea functions showed in $CDCl_3$ and benzene-d_6 also the expected spectrum of a C_2-symmetrical dimer.

It is worthwhile to note that these dimers are already chiral by virtue of the two C_{2v} symmetrical calix[4]arenes (D_2-symmetry). The directionality of the hydrogen bonded belt further reduces the symmetry from D_2 to C_2 but does not lead to additional stereoisomers. This contrasts with chiral C_4-symmetrical heterodimers, where the chirality is due only to the directionality of the hydrogen bonded belt and the change of this directionality leads to the opposite enantiomer.[18]

Disproportionation experiments between dimers of the rigid cone calixarenes **2a**,**b** and dimers of the arylurea of the flexible cone **3a** were used to judge the selectivity of the self-assembly process. Only the substituents attached to the narrow rims differ. Usually, the heterodimerization between two simple arylurea calixarenes is entropically driven and gives a statistical mixture of products,[2a] whereas arylurea **3a** and sulfonylurea **3c** heterodimerize exclusively. This has been explained by the matching of the acid/base properties of their hydrogen bonding side, although the phenomenon is not yet totally understood.[19]

Equimolar solutions of **2a·2a** and **3a·3a** were combined and allowed to come to equilibrium over 20 h. The ^1H NMR spectrum (Figure 2) showed only the sets of peaks from each of the homodimers **2a·2a** and **3a·3a** and *no* peaks for the heterodimer **2a·3a**. Another spectrum acquired after an additional 40 h was identical to the first, indicating that this was indeed the thermodynamically favored state. In fact, even after addition of 8 equiv of **3a**, no new signals for the heterodimer appeared in

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(14) Compound **1** is prepared according to the procedure in ref 10. We found that prewashing the NaH was crucial for successful alkylation.

(15) Obviously the rigidified calix[4]arene skeleton causes steric problems, since a *tert*-butyl-trityl-substituted tetra urea could not be obtained reproducibly.

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(19) More detailed studies of the heterodimerization between **2a** and **3a** and the corresponding tetratosyl-ureas are presented in a forthcoming article.

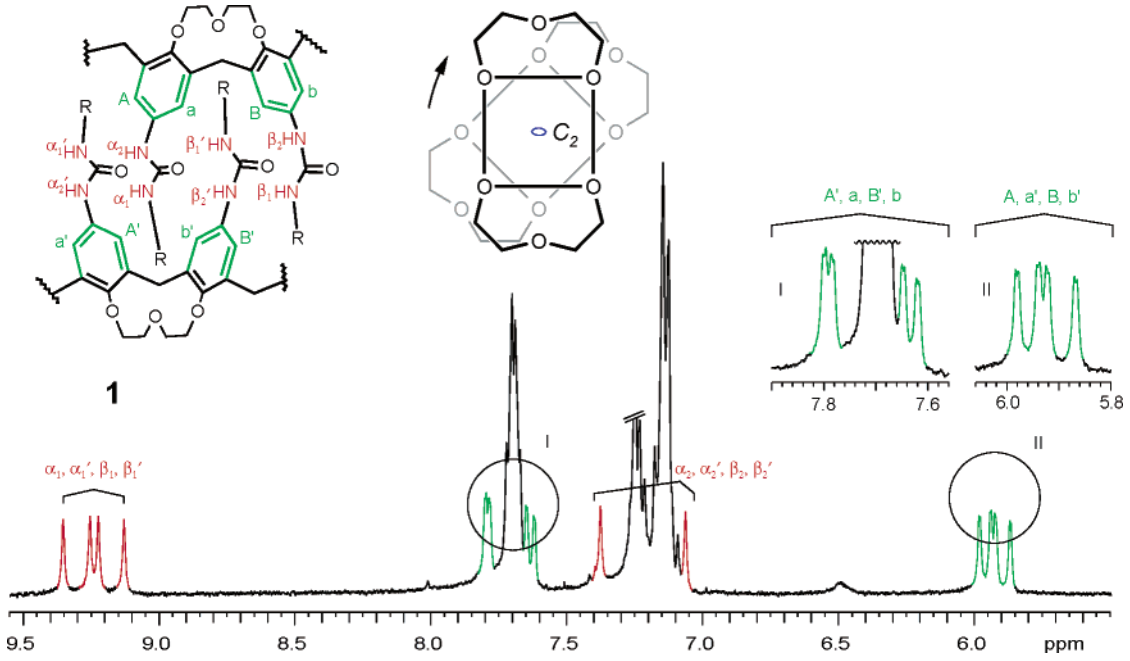

FIGURE 1. Section of the ^{1}H NMR spectrum of **2a·2a** 400 MHz, $CDCl_3$, 25 °C).

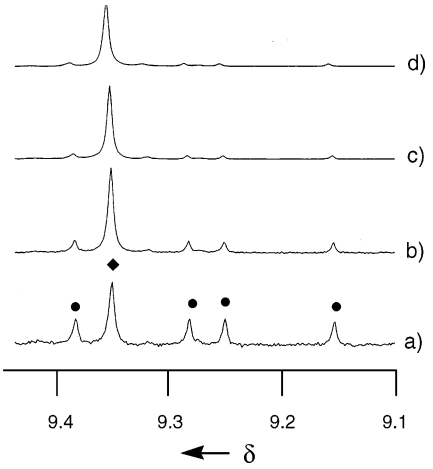

FIGURE 2. Downfield window of the ^{1}H NMR spectra observed for the attempted heterodimerization between **2a·2a** (●) (0.7 mM) and **3a·3a** (Y = $C_{10}H_{21}$) (◆) (600 MHz, $CDCl_3$, 25 °C): (a) 1 equiv of **3a·3a**; (b) 2 equiv of **3a·3a**; (c) 4 equiv of **3a·3a**; (d) 8 equiv of **3a·3a**.

the ^{1}H NMR. The behavior of mixtures of **2b** and **3a** was similar, i.e., no heterodimerization was observed.

Denaturation of **2a·2a** with DMSO-d_6 (Figure 3) was done to measure its tolerance toward hydrogen bond competitors.[20] DMSO-d_6 was titrated into a solution of **2a** or **2b** (at c = 1 mmol) in $CDCl_3$ until a 1:1 ratio of assembly to dissociated monomer (as observed in ^{1}H NMR) was reached. The capsule **2a·2a** did not reach this equilibrium point until the solution contained 8 vol % DMSO. This is roughly four times the amount of DMSO-d_6 tolerated by the conformationally flexible calixarene dimers, which exist solely as the monomer in 10 vol % DMSO-d_6. The homodimers **2b·2b** are more resistant to DMSO-d_6, showing only 4% of the monomer at 11 vol % of DMSO-d_6 and 40% of the monomer at 18% of DMSO-d_6 in the mixture (see Supporting Information, Figure S1).

Because the signals of dimers and monomers in the ^{1}H NMR spectra can be separately integrated (Figure 3) it is possible to estimate and to compare the equilibrium constants for the dimerization at a given composition of the mixed solvent. For 11.7% DMSO-d_6 in $CDCl_3$ a value of K_a = 13−23 M^{-1} was found for **2a** at $c = 1.40 \times 10^{-2} - 3.3 \times 10^{-3}$ M, and K_a = 8000−10000 M^{-1} was derived for **2b** where a lower concentration of $c = 1.2 \times 10^{-4}$ to 2.0×10^{-4} M had to be chosen to observe meaningful amounts of monomer and dimer in equilibrium. Thus, the stability of **2b** is about 500 times higher than of that of **2a**. However, this ratio can be taken only as a rough estimate, since in both cases the K_a values increased with decreasing concentration of the tetraurea. This may be due to the fact that the description as a simple equilibrium **2** ⇌ **2·2** is oversimplified and that further species (leading eventually to broad signals in the NMR-spectrum) are involved. The sensitivity of these measurements to traces of water may be an additional factor influencing the accuracy.

Kinetic measurements were carried out in benzene-d_6 for the exchange of encapsulated benzene (C_6H_6) or cyclohexane (C_6H_{12}) against the solvent to characterize the kinetic stabilities of the dimers. When the benzene complex of a dimer of **2a** or **2b** is dissolved in benzene-d_6, the intensity of the signal of encapsulated benzene (Figure 4a) decreases according to a first-order rate law (Figure 4b). The half-life time of this process is 82 s for **2a**·C_6H_6·**2a** (at 25 °C) and 2460 s for the **2b**·C_6H_6·**2b**. For the flexible tolyl urea **3a** the rate of exchange (benzene for benzene-d_6) was too fast to be measured in this way,[21] whereas $t_{1/2}$ = 550 s was found for **3b**·C_6H_6·**3b**. Because tetraurea dimers with included cyclohexane show a much

(20) For the studies on double-rosettes motif thermodynamically stable in mixtures with DMSO-d_6 (up to 70%), see: Felix, O.; Crego-Calama, M.; Luyten, I.; Timmerman, P.; Reinhoudt, D. N. *Eur. J. Org. Chem*. **2003**, 1463−1474.

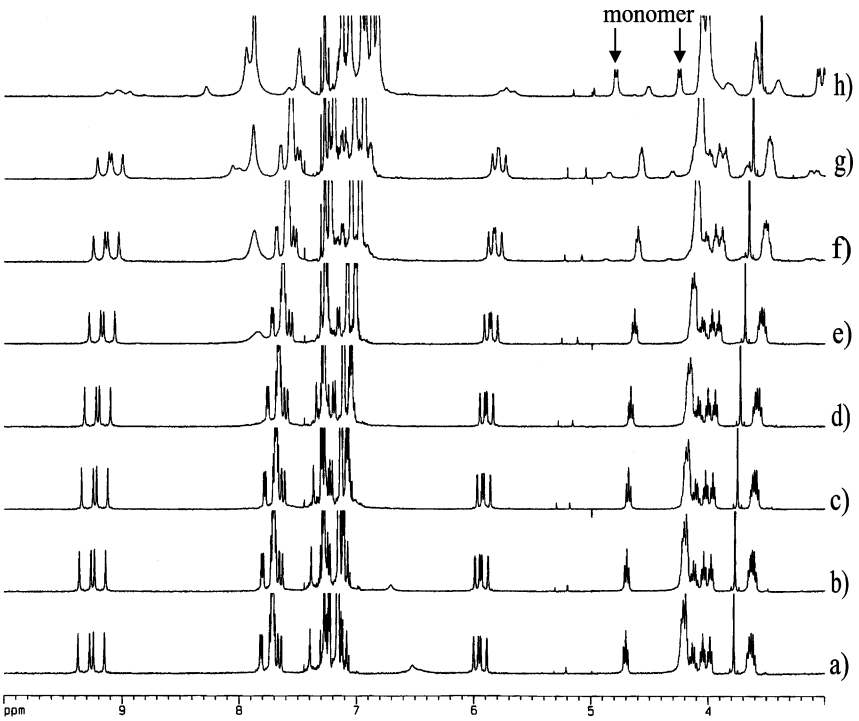

FIGURE 3. Denaturation experiments of the dimer **2a**·**2a** in $CDCl_3$/DMSO-d_6 mixtures (600 MHz, 25 °C, [**2a**] = 1 mmol): (a) pure $CDCl_3$; (b) 0.4% DMSO; (c) 1.4% DMSO; (d) 2.3% DMSO; (e) 4.2% DMSO; (f) 6.0% DMSO; (g) 7.7% DMSO; (h) 11% DMSO.

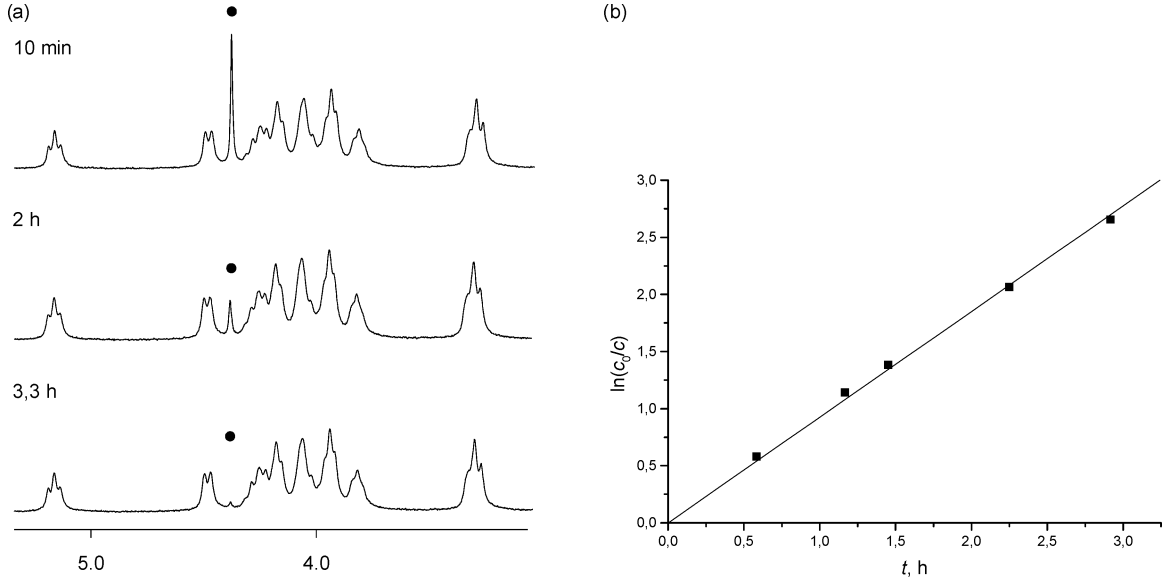

FIGURE 4. (a) Time-dependent ^{1}H NMR spectra (400 MHz, benzene-d_6) of the **2b**·C_6H_6·**2b**. (b) First-order kinetic plot of the guest exchange reaction C_6H_6 vs C_6D_6.

higher kinetic stability, we planned to carry out similar kinetic experiments with cyclohexane as guest. However, C_6H_{12} could not be encapsulated by refluxing **2b**·C_6H_6·**2b** in cyclohexane for 48 h; under the same conditions **2b**·$CHCl_3$·**2b** was converted in only ~30% to **2b**·C_6H_{12}·**2b**.[22] Half-life times found for the cyclohexane complexes of a tetraurea **3a** (with four pentyl groups at the narrow rim) and of **2a** are 6.3 and 245 h, respectively.

In further experiments we were able to verify the consequences of the rigidification of the *cone* conformation on the inclusion of selected guests (G, methyl-substituted cyclohexanones and cyclopentanones) in comparison to methylcyclopentane (M). Ratios of binding constants K_G/K_M were determined for the dimers of **2a** and **3a** in $CDCl_3$ in the presence of an excess of a 1:1 mixture of both guests by integration of the methyl signals of the included guests in the ^{1}H NMR spectra (examples in Figure 5, see also Figures S2 and S3). The

(21) For a similar dimer derived from a mixed tetraether bearing two pentyl and two methyl groups on distal oxygens the rate of guest exchange (benzene, $k = 0.47$ s^{-1}) is comparable to the rate of the dissociation/recombination; see ref 2c.

(22) The observation that no heterodimers are found when **2a** and **2b** are mixed in a 1:1 ratio in benzene-d_6 (even after 15 h at 60 °C) may be explained in a similar way by kinetic problems.

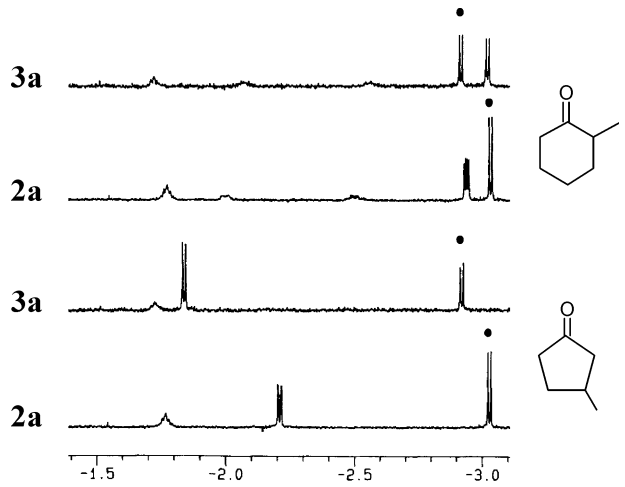

FIGURE 5. High-field window of ^{1}H NMR spectra (600 MHz, chloroform-*d*, 25 °C) recorded for ureas **2a** and **3a** in the presence of mixtures of the indicated guest and methylcyclopentane. The signals of the methyl group of the included methylcyclopentane are indicated (●). [Host] = 1 mM, [guest] = 20 mM, [methylcyclopentane] = 20 mM.

TABLE 1. Relative Binding Constants K_G/K_M of Dimers of Rigid and Flexible Tetraurea Calix[4]arenes 2a and 3a (Y = $C_{10}H_{21}$) for Different Guests vs Methylcyclopentane[a]

guest	**2a·2a**	**3a·3a**
4-methylcyclohexanone	0.28	1.10
3-methylcyclohexanone	1.10	0.71
2-methylcyclohexanone	0.60	0.76
3-methylcyclopentanone	0.59	1.10
2,2-dimethylcyclopentanone	2.00	1.90
2-methylcyclopentanone	1.50	2.60

[a] [host] = 1 mM, [guest] = 20 mM, [methylcyclopentane] = 20 mM; K_G and K_M = binding constants for the guest and for methylcyclopentane, respectively.

values collected in Table 1 show the differences in the relative binding constants for calixarenes **2a** and **3a**, which, however, are difficult to rationalize. Most probably they are not only caused by differences in size and shape of the cavity due to the different flexibility of the host. From the chemical shift of the methyl signals also changes in the preferred orientations of the guest can be deduced that cause differences in the magnetic shielding experienced by the guest. These factors cannot be teased apart.

Conclusions

Rigidification of the calix[4]arene skeleton by two di(ethylene glycol) bridges between adjacent oxygen atoms leads to remarkable changes in the properties of the respective tetraurea derivatives. Dimeric capsules formed by **2a** and **2b** show increased thermodynamic and kinetic stabilities in comparison with the more flexible analogues **3a** and **3b**. In both pairs the stability is higher for bulky urea residues (**2b**/**3b** vs **2a**/**3a**). Differences in the selectivity of guest inclusion are also noticed between both types of tetraurea calix[4]arenes. Most remarkable is the exclusive formation of both homodimers and the complete absence of heterodimers in a solution containing a 1:1 mixture of a flexible and a rigidified tetraurea. This observation will be further discussed in the sequel.

Experimental Section

The tetraamine **1**[13,23] and the tetratolylurea calix[4]arenes **3a** (Y = C_5H_{11},[2a] $C_{10}H_{21}$[1c]) were synthesized in accordance with the published procedures.

5,11,17,23-Tetratolylurea-25,27,26,28-biscrown-3-calix[4]arene (2a). Tolyl isocyanate (0.193 g, 1.45 mmol) was added to a solution of amine **1** (0.280 g, 0.447 mmol) in chloroform (20 mL), and the reaction mixture was stirred for 12 h at 20 °C. Methanol (50 mL) was added, and a white precipitate formed was filtered off, washed with methanol (3 × 10 mL), and crystallized additionally from a chloroform/methanol mixture, yielding a white crystalline compound (0.310 g, 60%): mp >300 °C dec; ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.41 (s, 4H, NH), 8.17 (s, 4H, NH), 7.27 (d, 8H, $^3J_{H,H}$ = 8.3 Hz, CH), 7.11 (br d, 4H, CH_{cal}), 7.08 (br d, 4H, CH_{cal}), 7.03 (d, 8H, $^3J_{H,H}$ = 8.3 Hz, CH), 4.92 and 3.19 (two d, 4H, $^2J_{H,H}$ = 11.7 Hz, $ArCH_2Ar$), 4.40 and 2.92 (two d, 2H, $^2J_{H,H}$ = 11.8 Hz, $ArCH_2$-Ar), 4.20−4.13 (m, 12H, OCH_2CH_2O), 3.64−3.59 (m, 4H, OCH_2-CH_2O), 2.21 (s, 12H); ^{1}H NMR (400 MHz, $CDCl_3$, integration is given for a dimeric species): δ 9.35 (s, 2H, NH), 9.26 (s, 2H, NH), 9.22 (s, 2H, NH), 9.13 (s, 2H, NH), 7.80 (d, 2H, $^4J_{H,H}$ = 2.0 Hz, ArH), 7.78 (d, 2H, $^4J_{H,H}$ = 2.0 Hz, ArH), 7.72−7.67 (m, 16H, ArH), 7.64 (d, 2H, $^4J_{H,H}$ = 2.0 Hz, ArH), 7.61 (d, 2H, $^4J_{H,H}$ = 2.0 Hz, ArH), 7.38 (s, 2H, NH), 7.23−7.06 (m, 22H, ArH and NH), 5.98 (d, 2H, $^4J_{H,H}$ = 2.0 Hz, ArH), 5.94 (d, 2H, $^4J_{H,H}$ = 2.0 Hz, ArH), 5.92 (d, 2H, $^4J_{H,H}$ = 2.0 Hz, ArH), 5.86 (d, 2H, $^4J_{H,H}$ = 2.0 Hz, ArH), 4.69 (d, 2H, $^2J_{H,H}$ = 11.8 Hz, $ArCH_2Ar$), 4.67 (d, 2H, $^2J_{H,H}$ = 11.6 Hz, $ArCH_2Ar$), 4.23−3.94 (m, 28H, $^2J_{H,H}$ = 11.8 Hz, $ArCH_2Ar$ and OCH_2), 3.65−3.56 (m, 8H, OCH_2), 2.88−2.77 (m, 8H, $ArCH_2Ar$), 2.26 (s, 24H, $ArCH_3$); ^{13}C NMR (75 MHz, DMSO-d_6) δ 153.4; 151.2, 149.6, 138.1, 136.0, 135.4, 134.7, 131.1, 129.9, 129.4, 120.3, 119.3, 118.9, 77.3, 74.9, 21.1; ESI/MS *m/z* (relative intensity, %) 1179.5 (M + Na^+, 100).

4-[Tris(4′-*tert*-butylphenyl)methyl]phenyl Carbamic Acid 4-Nitrophenyl Ester (4b). A solution of 4-(tris(4′-*tert*-butyl-phenyl)methyl)aniline[24] (1.525 g, 3.03 mmol) and 4-nitrophenylchloroformiate (0.671 g, 3.33 mmol) in chloroform (20 mL) was stirred for 3 h at 20 °C. Then hexane (50 mL) was added, and the precipitate formed was filtered off, washed with hexane (3 × 10 mL), and dried, yielding a white crystalline compound (1.59 g, 78%): mp 218−223 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.26 and 7.36 (two d, 4H, $^3J_{H,H}$ = 8.8 Hz), 7. 29 and 7.20 (two d, 4H, $^3J_{H,H}$ = 8.9 Hz), 7.25 and 7.08 (two d, 12H, $^3J_{H,H}$ = 8.5 Hz), 6. 95 (s, 1H), 1.30 (s, 27H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 155.40, 150.07, 148.51, 145.03, 143.84, 143.70, 134.15, 132.07, 130.66, 125.21, 124.16, 122.08, 117.70, 63.30, 34.29, 31.36. ESI/MS *m/z* (relative intensity, %) 691.5 (M + Na^+, 25).

5,11,17,23-Tetra{4-[tris(4′-*tert*-butylphenyl)methyl]-phenyl}urea-25,27,26,28-biscrown-3-calix[4]arene (2b). Diisopropylethylamine (76 μL, 0.411 mmol) was added in one portion to a solution of tetraamine **1** (42.8 mg, 0.069 mmol) and active urethane **4b** (229 mg, 0.343 mmol) in DMF (25 mL) and chloroform (1 mL). The solution was stirred at 70 °C for 15 h. After cooling to room temperature, a precipitate was filtered off, washed with DMF (3 × 5 mL), and dried. The resulting solid was dissolved in chloroform (2 mL) and precipitated by adding methanol (20 mL). A white crystalline compound was filtered off, washed with methanol (4 × 5 mL), and dried, yielding 66.5 mg (35%) of the desired compound: mp >330 °C dec; ^{1}H NMR (400 MHz, benzene-d_6, integration is given for a dimeric species) δ 9.88 (s, 2H, NH), 9.86 (s, 2H, NH), 9.62 (s, 2H, NH), 9.60 (s, 2H, NH), 8.18 and 5.94 (two d, 4H, $^4J_{H,H}$ = 1.8 Hz, CH_{cal}), 8.14 and 5.91 (two d, 4H, $^4J_{H,H}$ = 1.8 Hz, CH_{cal}), 8.07 and 7.55 (two d, 8H, $^3J_{H,H}$ = 8.8 Hz, CH), 8.07 and 7.51 (two d, 8H, $^3J_{H,H}$ = 8.8 Hz, CH), 7.97 and 5.81

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(two br d, 4H, CH_{cal}), 7.96 and 5.81 (two br d, 4H, CH_{cal}), 7.93 and 7.44 (two d, 8H, $^3J_{H,H}$ = 8.8 Hz, CH), 7.93 and 7.41 (two d, 8H, $^3J_{H,H}$ = 8.8 Hz, CH), 7.37 and 7.13 (two d, 24H, $^3J_{H,H}$ = 8.8 Hz, CH), 7.36 and 7.12 (two d, 24H, $^3J_{H,H}$ = 8.8 Hz, CH), 7.35 and 7.23 (two d, 24H, $^3J_{H,H}$ = 8.8 Hz, CH), 7.34 and 7.21 (two d, 24H, $^3J_{H,H}$ = 8.8 Hz, CH), 7.01 (s, 2H, NH), 6.88 (s, 2H, NH), 6.82 (s, 2H, NH), 6.76 (s, 2H, NH), 5.18 and 3.31 (two d, 4H, $^2J_{H,H}$ = 10.4 Hz, $ArCH_2Ar$), 5.14 and 3.28 (two d, 4H, $^2J_{H,H}$ = 10.4 Hz, $ArCH_2Ar$), 4.48 and 3.30 (two d, 8H, $^2J_{H,H}$ = 10.0 Hz, $ArCH_2Ar$), 4.3−3.7 (m, 32H, OCH_2CH_2O), 1.28 (s, 54H, $C(CH_3)_3$), 1.27 (s, 54H, $C(CH_3)_3$), 1.22 (s, 108H, $C(CH_3)_3$); MALDI-TOF/MS *m*/*z* (relative intensity, %) 2461.5 ($M + Na^+$, 10).

5,11,17,23-Tetra{4-[tris(4′-*tert*-butylphenyl)methyl]-phenyl}urea-25,26,27,28-tetrapentoxy calix[4]arene (3b). Method a. A solution of the respective tetraamino calix[4]-arene[16] (0.101 g, 0.132 mmol), the active urethane **4b** (0.396 g, 0.592 mmol), and diisopropylethylamine (145 μL, 0.789 mmol) in THF (25 mL) was refluxed for 6 h. After cooling, the mixture was evaporated under reduced pressure, and the residue was passed through a silica column (ethyl acetate/hexane mixture 1:5, R_f = 0.93). The crude product was treated first with ethyl acetate and crystallized from a chloroform/methanol mixture, giving a white powder, which is the chloroform complex of the desired tetraurea dimer (0.207 g, 54%): mp 274−276 °C; ^{1}H NMR (400 MHz, chloroform-*d*, integration is given for a dimeric species) δ 9.56 (s, 8H, NH), 7.83 and 7.14 (two d, 32H, $^3J_{H,H}$ = 8.8 Hz, CH), 7.78 and 5.59 (two d, 16H, $^4J_{H,H}$ = 2.1 Hz, CH_{cal}), 7.08 and 6.93 (two d, 96H, $^3J_{H,H}$ = 6.9 Hz, CH), 6.45 (s, 4H, NH), 4.22 and 2.89 (two d, 16H, $^2J_{H,H}$ = 11.4 Hz, $ArCH_2Ar$), 3.61 and 3.53 (two q, 16H, $^2J_{H,H}$ = $^3J_{H,H}$ = 8.7 Hz, OCH_2), 1.93 (quintet, 16H, $^3J_{H,H}$ = 7.8 Hz, OCH_2CH_2), 1.24 (s, 216H, $C(CH_3)_3$), 1.30−1.15 (m overlapping with the previous singlet, 32H, $CH_2CH_2CH_3$), 0.86 (t, 24H, $^3J_{H,H}$ = 7.8 Hz, CH_2CH_3); ^{13}C NMR (100 MHz, chloroform-*d*) δ 153.78, 151.15, 148.11, 143.76, 142.41, 137.72, 134.90, 134.74, 133.48, 132.67, 130.72, 123.89, 117.66, 116.22, 116.11, 75.64, 63.03, 34.20, 31.38, 30.01, 29.81, 28.23, 22.80, 14.26; ESI/MS *m*/*z* (relative intensity, %) 1465.1 ($M + 2Na^+$, 100), 1945.9 ($2M + 3Na^+$, 19.7), 2907.3 ($2M + Na^+$, 82.01).

Method b. A solution of the active urethane of the tetraamino calix[4]arene[17] (0.543 g, 0.404 mmol) and 4-(tris-4′-*tert*-butyl-phenyl)methyl)aniline (1.041 g, 2.02 mmol) in a mixture of DMF (30 mL) and chloroform (2 mL) was stirred at room temperature for 0.5 h. Then diisopropylethylamine (0.744 mL, 4.04 mmol) was added in one portion, and the solution was stirred at 70 °C for 12 h. After cooling, the solvent was evaporated under reduced pressure, and the residue was dissolved in 250 mL of chloroform. which was washed with 1 M solution of potassium carbonate (3 × 50 mL) and water (3 × 50 mL), dried over $MgSO_4$, and evaporated. The solid obtained after treatment with ethyl acetate was additionally crystallized from a chloroform/methanol mixture, giving a white crystalline compound (0.75 g, 64%), which is the chloroform complex of the desired tetraurea dimer.

Denaturation Experiments with DMSO. Tetraurea derivatives were dried in high vacuum (0.5 mbar) at 100 °C over 3 h and stored in a desiccator over diphosphorus pentoxide and sodium hydroxide. $CDCl_3$ was treated with aluminum oxide (basic) for at least 12 h prior to all measurements. DMSO-d_6 was used without any additional purification. ^{1}H NMR denaturation experiments were carried out directly in a NMR tube by adding a solvent mixture to a solution of the tetraurea calix[4]arene in chloroform-*d*.

Kinetic Studies. Benzene complexes of dimeric capsules were prepared as follows. The tetraurea calix[4]arene was dissolved in benzene (p.a.), stirred with aluminum oxide (basic, 50 mg per 10 mg of the substance) for 15 min, filtered, and evaporated to dryness. Complexes with cyclohexane were prepared from benzene (or chloroform) complexes by heating them up in cyclohexane till a clear solution was formed. The solvent was evaporated under reduced pressure, and the residue was dried (0.5 mbar). Benzene or cyclohexane complexes of dimeric capsules were dissolved in benzene-d_6 and transferred to a NMR tube, and a series of ^{1}H NMR spectra (25 °C) was immediately recorded in appropriate time intervals using an automated procedure for the spectra acquisitions. Kinetic runs for each complex were repeated three times, leading to deviations of less than ±10% from the averaged value.

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Supporting Information Available: Denaturation experiments with urea **2b** in chloroform-*d*/DMSO-d_6 mixtures (^{1}H NMR) and competitive inclusion of methylcyclopentane vs selected guests into the rigid-calix dimer **2a·2a** and into the flexible-calix dimer **3a·3a** (^{1}H NMR). This material is available free of charge via the Internet at http://pubs.acs.org.

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