New Molecular Topologies by Fourfold Metathesis Reactions within a Hydrogen-Bonded Calix[4]arene Dimer

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Abstract: A calix[4]arene tetrapentyl ether in the cone conformation substituted at its wide rim by four *m*-(ω-octenyloxy)phenyl urea groups forms hydrogen-bonded dimeric capsules in dichloromethane/benzene (95:5). Metathesis reaction with Grubbs' catalyst under high-dilution conditions (1.1×10^{-4} M) followed by hydrogenation leads to a covalent connection of all the urea groups within a dimer. Three topologically different products may be expected in such a reaction: a bis[2]catenane, a doubly bridged monocatenane and a tetrabridged capsule. All three possible reaction products could be isolated in an overall yield up to 60% for the separated and purified compounds. Their identification was based on the NMR patterns which reflect the characteristic symmetry properties of the isomeric products especially in the region of the hydrogen-bonded NH protons and were further confirmed by MALDI-TOF mass spectra. Further structural support for the bis[2]catenane comes from a single-crystal X-ray structure, although severe disorder prevents the localization of all atoms in the aliphatic chains connecting the two calix[4]arenes. Kinetic studies for the guest release/exchange (cyclohexane against the solvent [D$_6$]benzene) do not show remarkable differences between the starting dimer and the additionally linked dimers, while the mobility of an included tetraethylammonium cation is obviously more restricted.

Keywords: calixarenes · catenanes · inclusion compounds · metathesis · self-assembly

Introduction

Topologically intriguing molecules[1] such as catenanes,[2] rotaxanes,[3] knots[4] and Möbius strips[5] continue to attract the interest of scientists. This is not only due to simple curiosity or the challenge to synthesize more and more sophisticated structures; there are also relationships to natural products (catenated or super-coiled DNA[6]), new materials and nanometre-sized functional devices or machines.[7] The construction of "knotaxanes" by using (chiral) knots as stoppers in a rotaxane was recently proposed.[8]

The topologically correct covalent connection of molecular fragments can be efficiently assisted by a proper pre-organization through reversible (noncovalent) links, a process currently described by "self-assembly". Various rotaxanes, catenanes and knots have been synthesized by using the pre-organization of functionalized building blocks by metal–ligand interactions,[9] inter/intramolecular hydrogen bonding,[10] π–π stacking[11] or hydrophobic interactions.[3, 12]

It is now well established that calix[4]arenes substituted on their wide rim by four urea functions (**1**) form dimeric capsules which are held together by a seam of intermolecular hydrogen bonds.[13] The inclusion of a suitable guest, often a solvent molecule, is a necessary condition and may be used to induce the formation of the capsule. In these dimers the two calixarenes are turned by 45° (time average) around their common main axis with respect to each other, while the interpenetrating urea residues R point in different directions (Figure 1).

Since these dimers show high thermodynamic[14] and often also high kinetic stability,[15] this is an ideal situation to construct various covalently linked biscalix[4]arenes by reaction between suitable functional groups in the residues R/R′. An appropriate reaction for such a covalent connection is the metathesis of CH=CH$_2$ groups followed by hydrogenation to obtain a saturated CH$_2$–CH$_2$ link, thereby avoiding all complications caused by *cis*–*trans* isomerism. This strategy

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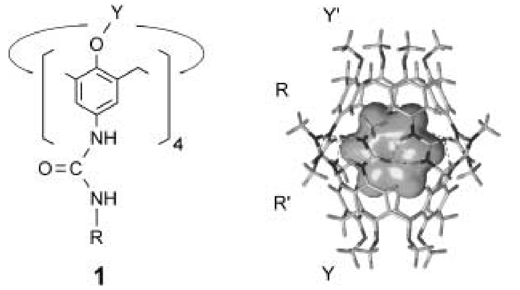

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Figure 1. General formula of a tetraurea calix[4]arene and stick representation of a dimeric capsule with benzene (space filling) as guest, demonstrating the relative orientation of the urea residues R and R′.

has been successfully used to synthesize [2]catenanes[16] and knots.[17, 18] Further examples of its application are the covalent linking of pre-organized building blocks of hydrogen-bonded assemblies like dimers of cyclopeptides[19] and rosettes,[20] as well as the connection of residues on the surface of dendrimers.[21] Here we report our first results on metathesis reactions carried out with dimers formed by **2** (see Figure 3), a tetraurea calix[4]arene with urea residues bearing alkenyl groups.

General topological considerations: In principle, two possibilities exist for the covalent connection of residues attached to the urea functions within a dimeric complex. They are schematically indicated for a dimer of a tetraphenyl urea in Figure 2.

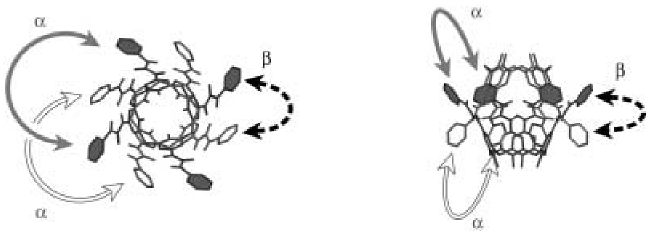
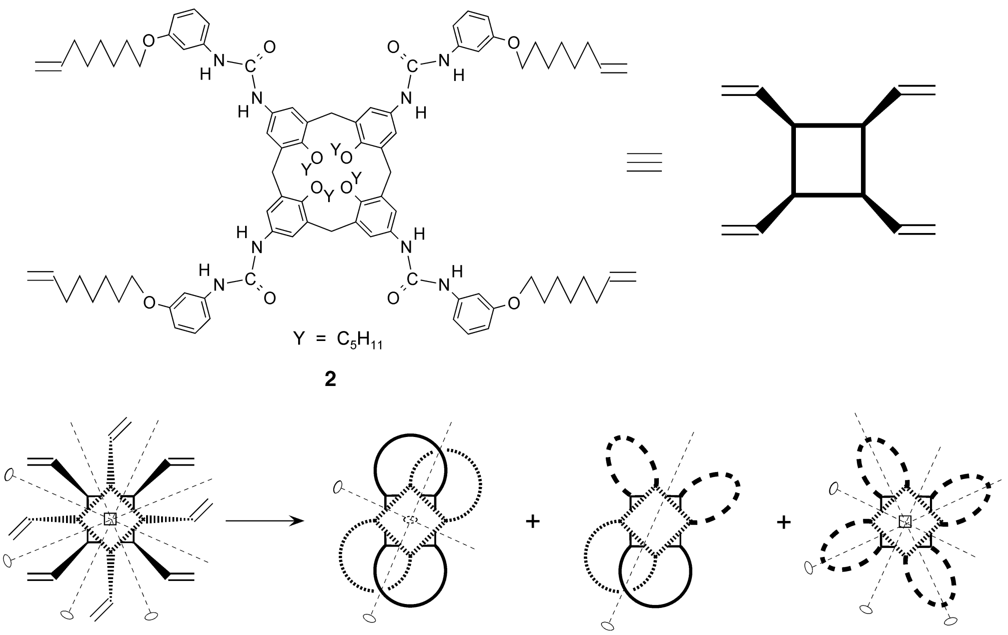


Figure 2. Two possible connections (indicated by arrows) between the urea residues of the same (α) or different calix[4]arenes (β) within a hydrogen-bonded dimer. The two (identical) calixarenes of the homodimer are distinguished by filled and unfilled phenyl urea units; ether groups Y are omitted for clarity.

Thus, three reaction products must be considered for a quantitative conversion, provided the metathesis reaction can be entirely restricted to a single capsule and reactions between capsules do not occur: 1) exclusive connection of adjacent residues within *one* calixarene (α: R – R and R′ – R′; Figure 1 and Figure 2) leads to the bis[2]catenane **3**, 2) exclusive connection of adjacent residues belonging to *different* calixarenes (β: R – R′) results in the formation of the tetrabridged unimolecular capsule **5**,[22] and 3) both connections are realised in the mono[2]catenane **4** which has structural similarities to a pretzelane.[23, 24]

The situation is schematically illustrated in Figure 3 in which the single calix[4]arenes within a dimer are represented by a regular square. The urea functions attached to the *para* positions of the phenolic units extend from the corners of these squares. The "equatorial" plane of the dimer, the "hydrogen-bonded" belt, corresponds to the drawing plane.



	2·2	**3**	**4**	**5**
a	D_{4d}	D_2	C_2	D_4
b	S_8	C_2	C_1	C_4

Figure 3. Schematic representation of the dimer **2·2** and of the potential products of a metathesis reaction. The single calix[4]arenes are symbolized by regular squares (solid and dashed lines) from the corners of which the urea functions extend. Two and fourfold axes are indicated; the symmetry groups without (a) and with directionality (b) of the hydrogen-bonded belt of urea functions are listed.

To discuss the symmetry properties of the species we first will concentrate on the "molecular skeleton" or "molecular assembly" itself, that is, on the mutual arrangement and covalent connection of the two calixarenes (case **a** in Figure 3 in which there is no directionality of the hydrogen-bonded belt). A homodimer of two calix[4]arenes consisting of four identical phenolic units possesses a C_4 axis (perpendicular to the drawing plane in Figure 3), four C_2 axes (within the drawing plane, which means perpendicular to the C_4 axis) and four symmetry planes (σ planes) intersecting the C_4 axis. This corresponds to the *achiral* symmetry group D_{4d}. No symmetry plane is present in all the potential products **3**–**5**, which possess two, one and four C_2 axes lying in the drawing plane of Figure 3. As indicated, a C_2 and a C_4 axis perpendicular to the drawing plane are present in compounds **3** and **5**, respectively. Thus, all three potential reaction products are *chiral*, with symmetry groups D_2, C_2, and D_4 for **3**–**5**, and this chirality is independent of the direction of the hydrogen-bonded belt.[25] It should be observed also for capsules with cationic guests for which the directionality usually changes rapidly on the NMR time scale.[26] With neutral guests, for which a hydrogen-bonded belt is "kinetically stable on the NMR time scale", the C_2 axes in the drawing plane do not exist, and the symmetry reduces to S_8 for the homodimer **2·2** and to C_2, C_1 and C_4 for **3**–**5**.

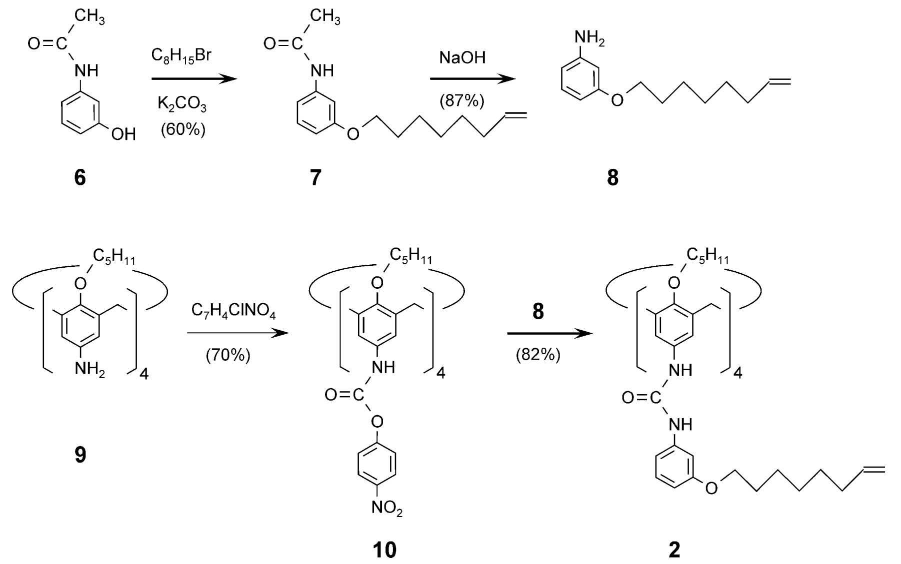
Synthesis: The tetraurea **2** was easily obtained in 82% yield from the active tetraurethane of calix[4]arene **10** by reaction with the aniline **8** in the presence of Hünig's base. The aniline **8** was prepared (in two steps) from commercially available *m*-hydroxyacetanilide (**6**) by *O*-alkylation followed by alkaline hydrolysis in 52% overall yield (Scheme 1).

The commercially available Grubbs' catalyst was used under standard conditions (dichloromethane, room temperature, 48 h) for the metathesis reaction. Since CH_2Cl_2 is not a good template for the dimerization of **2**, benzene was added in a concentration of 0.55 M, while the concentration of **2** was kept at 1.1×10^{-4} M to suppress reactions *between* capsules. A complete conversion was easily verified by the disappearance of the ^1H NMR signals for the $CH{=}CH_2$ protons. After hydrogenation (Pd/C, THF, 30–35 °C)[27] the resulting mixture of products was separated by flash chromatography. Three compounds could be isolated with an overall yield of up to 60% which gave MALDI-TOF spectra with peaks at *m*/*z* 3389.0 (MH^+) and 3411.5 (MNa^+). These correspond to the expected masses of the isomeric compounds **3**–**5**, present as a dimer without guest.

NMR spectra: One of the characteristics of hydrogen-bonded dimers of type **2·2** is a strong hydrogen bond between the NH_α, attached to the urea residue R, and the carbonyl oxygen atom of the adjacent urea function. This hydrogen bond, the presence of which was confirmed by X-ray analysis,[28] shifts the respective NMR signal(s) to very low field (approximately 10 ppm in [D$_6$]benzene), while the hydrogen bond of the NH_β attached to the calixarene skeleton is weaker and its signal(s) appear in the region of the aromatic protons (approximately 6.3 ppm in [D$_6$]benzene).

According to the symmetry classes C_2, C_1, and C_4 one has to expect four, eight, and two signals, respectively, for the eight NH_α groups of capsules formed by compounds **3**–**5**, if the hydrogen-bonded belt keeps its directionality on the NMR time scale. Indeed, this is exactly what is observed in ^1H NMR spectra measured in [D$_6$]benzene. For comparison, Figure 4 also shows the dimer **2·2** for which a single signal is found owing to its S_8 symmetry.

Four, eight, and two different aromatic units of the calix[4]arene skeletons and the same number of different methylene bridges have to be expected in capsules formed by compounds **3**–**5**. The aromatic protons appear as *m*-coupled doublets under conditions where the directionality of the hydrogen-bonded belt persists, and four, eight and two pairs of doublets ($J = 2.0–2.8$ Hz) could be clearly identified from the gs-COSY spectra. The protons of the methylene bridges appear as doublets with geminal coupling ($J = 11–13$ Hz), and four and two pairs of doublets could be distinguished for **3** and **5** (see Table 1). Only in the case of **4** are some of these doublets overlapping.



Scheme 1. Synthesis of the tetraurea calix[4]arene (**2**).

Taken together with the mass spectrometric data, these ^1H NMR results give unambiguous evidence that the structures of the compounds are bis[2]catenane **3** (isolated in 5–12%), doubly bridged mono[2]catenane **4** (26–32%) and tetrabridged dimer **5** (10–15%).[29]

Single-crystal X-ray analysis: Single crystals of **3** were obtained from chloroform/methanol and the structure was solved after numerous attempts (Figure 5). However, the best crystal diffracted to a resolution of just 1.65 Å. Due to severe disorder, which obviously is an intrinsic property of the given structure, not all the

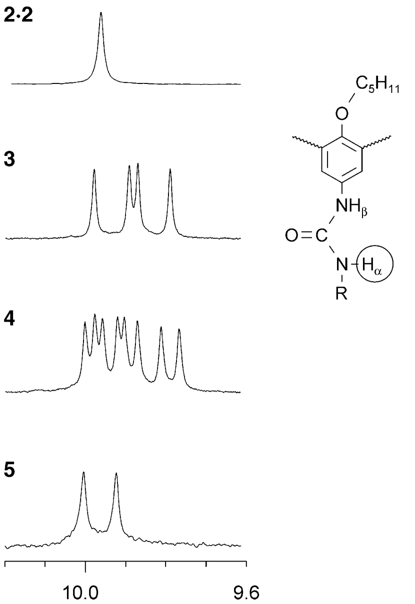


Figure 4. Low-field region (NH$_\alpha$ protons) of the ^{1}H NMR spectra (room temperature, [D$_6$]benzene) of capsules **2**·**2**, **3**, **4**, and **5**.

atoms of the chains connecting the urea residues could be found. Thus, the topology of the bis[2]catenane cannot be evidenced directly by the interlocking macrocycles.

The two calixarene parts form a hydrogen-bonded dimer with 16 hydrogen bonds, assuming as arbitrary limits a distance of N$\cdots$O < 3.50 Å and an angle of N–H$\cdots$O > 135°. Eight hydrogen bonds may be considered as "strong" (average distance N$_\alpha\cdots$O = 2.86 Å) and eight as "weak" ones (average distance N$_\beta\cdots$O = 3.29 Å). The pole-to-pole distance of the capsule, determined between centroids of methylene bridges (ArCH$_2$Ar) is 10.1 Å, which is slightly longer than the distance found in a benzene complex (9.7 Å),[28] but shorter than the one found in a capsule with the tetraethylammonium cation as guest (10.5 Å).[30] The oxygen atoms attached to the urea phenyl groups point exactly in the direction expected for **3**, while these directions should be different for structures **4** and **5**. This may be considered as an indirect proof for the topology of a bis[2]catenane.

Internal mobility and exchange of guests: If benzene is replaced by the tetraethylammonium cation as guest, the symmetry of **3** changes from C_2 to D_2 due to the rapid reorientation of the hydrogen-bonded urea belt in the **3**·Et$_4$N$^+$ complex.[26] Lowering of the temperature to −40 °C leads again to a spectrum reflecting C_2 symmetry (Figure 6) which may be seen as an additional confirmation of the topological considerations developed above.[31] This temperature dependence of the ^{1}H NMR pattern can be used to determine the respective energy barrier $\Delta G^{\ddagger}$ for the reorientation of the hydrogen-bonded belt. Due to the overlapping peaks, this is best done by lineshape analysis and respective studies are in progress.

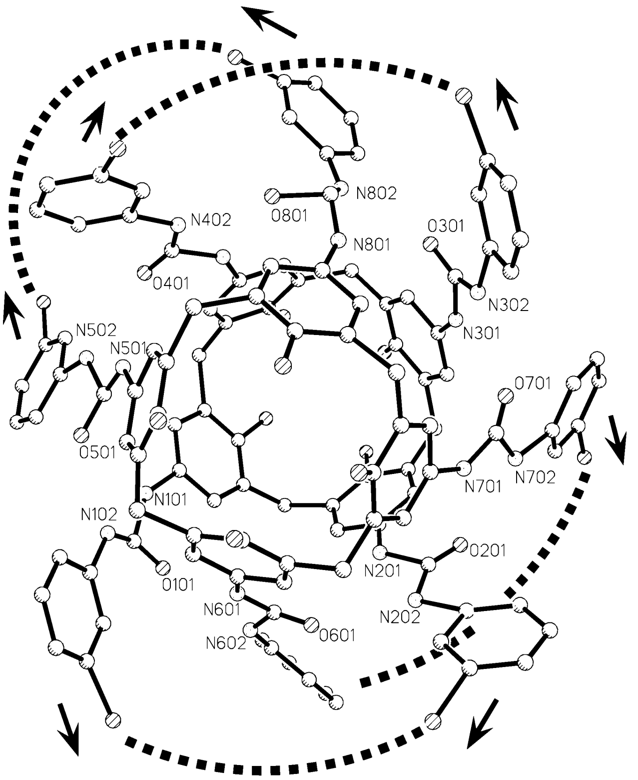


Figure 5. Top view of the X-ray molecular structure of the catenane **3**. Due to severe disorder only fragments of alkyl chains were found which are omitted for clarity. These connecting chains are symbolized by dashed lines while the directions of the ether bonds are indicated by arrows. Distances [Å] between urea residues are: 3.426 (O101–N601), 3.015 (O101–N602), 3.432 (O201–N701), 3.030 (O201–N702), 3.357 (O301–N801), 2.843 (O301–N802), 3.160 (O401–N501), 2.780 (O401–N502), 3.350 (O501–N101), 2.803 (O501–N102), 3.007 (O601–N201), 2.832 (O601–N202), 3.334 (O701–N301), 2.792 (O701–N302), 3.353 (O801–N401), 2.768 (O801–N402).

Table 1. Selected ^{1}H NMR data for **3**–**5** ([D$_6$]benzene, 400 MHz).

Compound	NH protons[a]	Aromatic protons of calix[4]arene[b]	ArCH$_2$Ar protons of calix[4]arene[c]
3	10.01 (2H), 9.93 (2H), 9.91 (2H), 9.82 (2H)	8.16 and 6.35 (4H), 8.15 and 6.29 (4H), 7.93 and 6.32 (4H), 7.92 and 6.24 (4H)	4.58 and 3.33 (4H), 4.53 and 3.27 (4H), 4.50 and 3.26 (4H), 4.47 and 3.20 (4H)
4	10.03 (1H), 10.01 (1H), 9.99 (1H), 9.96 (1H), 9.94 (1H), 9.92 (1H), 9.86 (1H), 9.82 (1H)	8.16 and 6.35 (2H), 8.11 and 6.31 (2H), 8.10 and 6.29 (2H), 8.09 and 6.28 (2H), 8.08 and 6.33 (2H), 8.07 and 6.32 (2H), 7.99 and 6.31 (2H), 7.96 and 6.23 (2H)	4.56 and 3.27 (8H),[d] 4.55 and 3.31 (2H), 4.51 and 3.28 (4H),[d] 4.47 and 3,21 (2H)
5	10.01 (4H), 9.93 (4H)	8.11 and 6.32 (8H), 8.07 and 6.32 (8H)	4.57 and 3.27 (8H), 4.53 and 3.24 (8H)

[a] Only the signals of 8 NH hydrogens which form strong hydrogen bonds are listed. [b] Pairs of doublets correlated by gs-COSY spectra, ^4J = 2.0–2.8 Hz. [c] Pairs of doublets correlated by gs-COSY spectra, ^2J = 11–13 Hz. [d] Overlapping doublets.

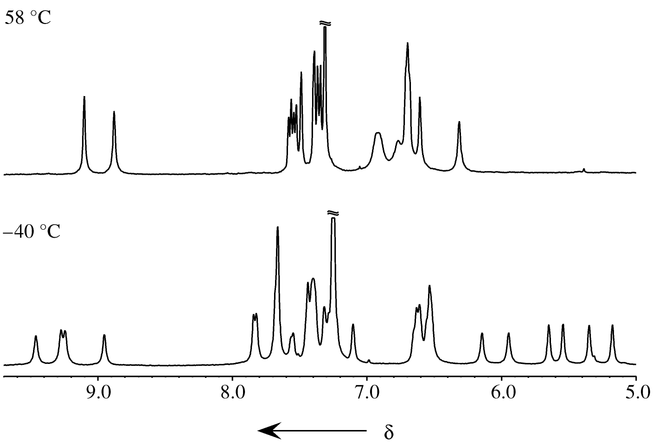


Figure 6. Low-field region of the complex **3** · $Et_4N^+BF_4^-$ in [D_1]chloroform at 58 °C (D_2 symmetry) and −40 °C (C_2 symmetry). Signals at $\delta > 8.6$ ppm belong to NH_α protons of the urea groups.

Lowering of the temperature leads also to a splitting of the signal observed for the methyl groups of the included tetraethylammonium cation at $\delta = -1.62$ ppm (58 °C, Figure 7) into two broad signals at $\delta = -3.30$ and -0.17 ppm.[32] This has to be attributed to the freezing of the rapid rotation of the included Et_4N^+ cation around a pseudo-C_2 axis in the equatorial plane, by which "equatorial" and "polar" methyl groups change their place.[26a] In this case the energy barrier $\Delta G^{\neq}$ can be derived from the coalescence temperature (T_c) and the frequency difference $\Delta\nu$ by using the Gutowsky–Holm equation.[33] These values are collected in Table 2. Evidently, the energy barriers $\Delta G^{\neq}$ for the rotation of the guest are slightly higher for **3**–**5** than for the starting urea **2**. The observed increase in the order **2** < **5** < **4** < **3** is in agreement with an increasingly tighter connection of the two calixarenes.

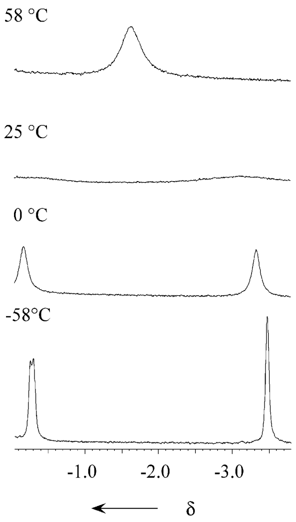


Figure 7. High-field section of the guest signal for (**3** · Et_4N^+) BF_4^- at different temperatures.

Table 2. Energy barriers of the hindered rotation of the included tetraethylammonium cation $\Delta G^{\neq}$ [kJ mol^{-1}] within corresponding complexes, rate constants k (h^{-1}) and half-life times $\tau_{1/2}$ [h] of cyclohexane complexes in [D_6]benzene (25 °C).

Compound	$\Delta G^{\neq}$ (T_c [K])	k[a] [h^{-1}]	$\tau_{1/2}$ [h]
2	47 (265)	0.090	7.7
3	55 (306)	0.045	15
4	52 (292)	0.048	14
5	50 (278)	0.059[b]	12

[a] Averaged from three independent experiments; deviation ±15%. [b] Deviation ±25%.

Preliminary kinetic studies have also been done for the guest exchange. If a capsule containing cyclohexane as guest is dissolved in [D_6]benzene the signal for the included C_6H_{12} at $\delta = -0.97$ ppm slowly disappears, since it is replaced by the deuterated solvent as guest. This process can be conveniently monitored by NMR spectroscopy. First-order rate constants thus obtained are also given in Table 2. The differences between **3**–**5** and **2•2** are not strong, but the tendency is the same as for the rotation of an included guest.[34] Evidently, the connecting chains are too long for an effective hindrance of the guest exchange.

Molecular modeling: Molecular dynamics simulations[35] have been carried out for **3**–**5** including either benzene or a tetraethylammonium cation as guests in order to establish whether a specific compound should be favored.[36] A comparison of the average geometrical parameters of **3**–**5** to those obtained in the same way for **1** (R = H, Y = Et) reveals that the shape of the capsules is very similar (Table 3). The differences of the interaction energies of the calixarene monomers in **3**–**5** (the alkyl chains were omitted from this calculation) as well as the host–guest interaction energies vary only within the standard deviation (Table 4). Thus, from molecular modelling investigations a more or less statistical product distribution (1:2:1) should be expected, as was indeed observed.

Table 3. Summary of average geometric parameters in **1** (R = H, Y = Et) and **3**–**5**.

	1/C_6H_6	**3**/C_6H_6	**4**/C_6H_6	**5**/C_6H_6	**1**/Et_4N^+	**3**/Et_4N^+	**4**/Et_4N^+	**5**/Et_4N^+
number of hydrogen bonds	14	14	14	14	8	8	8	8
extension pole ··· pole [Å][a]	9.6	9.5	9.5	9.5	10.4	10.3	10.2	10.2
equatorial extension [Å][b]	8.0	8.4	8.2	8.2	9.0/10.5	9.0/9.8	9.0/9.7	8.8/10.0
N–H ··· O distance (peripheral)	2.01	2.11	2.11	2.11	2.29	2.36	2.26	2.30
N–H ··· O distance (inner)	2.45	2.39	2.40	2.39	2.82	2.80	2.76	2.74

[a] Distance of the two centroids of the bridging methylene carbon atoms. [b] Measured between opposing van der Waals surfaces. In the case of Et_4N^+ due to the ellipsoidal shape two values for the minimum and maximum diameter are given.

Table 4. Average interaction energies of the calixarene monomers ΔE_{mon} [kcal mol^{-1}] and average energies of host–guest interactions ΔE_{inc} [kcal mol^{-1}] within the capsules (Connecting alkyl chains omitted from the calculation).

	ΔE_{mon}	ΔE_{inc}		ΔE_{mon}	ΔE_{inc}
3/C_6H_6	-62.8 ± 1.1	-20.5 ± 2.5	**3**/Et_4N^+	-50.3 ± 3.2	-59.9 ± 4.4
4/C_6H_6	-62.3 ± 1.1	-20.5 ± 2.7	**4**/Et_4N^+	-51.3 ± 3.0	-59.3 ± 4.1
5/C_6H_6	-62.5 ± 1.1	-20.5 ± 2.4	**5**/Et_4N^+	-51.8 ± 2.9	-58.9 ± 4.2

Conclusion

We have demonstrated that the pre-organization of the two calix[4]arenes in a tetraurea dimer can be used to synthesize topologically interesting molecules. In particular, to the best of our knowledge, the topology of the macrocyclic bis[2]catenane **3** has not been described previously. It should be possible to tune the reaction by an appropriate choice of the reactive urea functions. Thus, the length and place of the spacer could be varied and the incorporation of rigid structural elements could be used to favor the selective formation of one of the possible structures. Bis[2]catenanes of type **3** should be the only product from heterodimers between **2** and a tetraurea derivative in which adjacent urea functions are already covalently connected,[37] while rotaxane-like structures would result from heterodimers between **2** and a bulky tetraurea.[15a] A doubly bridged capsule with D_2 or C_2 symmetry (compare a and b in Figure 2, respectively) would result from homodimers of tetraureas bearing reactive alkenyl residues alternating with nonreactive residues (ABAB type). These examples show that various additional structures with interesting topologies should be available through the metathesis reaction of alkenyl-substituted tetraureas. Studies to explore these possibilities are under way.

Experimental Section

General: [D$_1$]Chloroform (stabilized over silver wool, 99.8 % of deuterium, Fa. Merck) was used for the spectroscopic studies. The ^{1}H NMR spectra were measured on a Bruker DRX400 Avance (400.13 MHz) spectrometer unless otherwise indicated. The 3-hydroxyacetanilide (**6**), *N*,*N*-diisopropylethylamine (both from ACROS), 4-nitrophenylchloroformate (Fluka) and Grubbs' catalyst (Strem) were purchased, while the tetraamine **9** was prepared as described in the literature.[38] Solvents used in syntheses were of a reagent grade (ACS). Reactions were carried out under a nitrogen atmosphere. The complexes with tetraethylammonium tetrafluoroborate for variable temperature ^{1}H NMR measurements were prepared by mixing the corresponding ureas in the NMR tube with an excess of the salt (1:3) in [D$_1$]chloroform (0.7 mL) for 5–10 min in an ultrasonic bath. Cyclohexane complexes of **2**–**5** were prepared by dissolving a sample (3–5 mg) in benzene (3 mL), stirring the resulting solution with aluminium hydroxide (0.1 g, basic, from Merck), filtering, and evaporating to dryness under reduced pressure. The residue (benzene complex) was dissolved in cyclohexane (3 mL) at reflux and evaporated. The last procedure was repeated and the complex thus obtained was dissolved in [D$_6$]benzene (0.6–0.7 mL). A sample was placed in the magnet of the NMR instrument for a whole kinetic run and spectra were recorded automatically every 1–2 h.

Synthesis

3-(7′-Octenyloxy)acetanilide (7): A mixture of 3-hydroxyacetanilide (**6**) (1.125 g, 7.44 mmol), ω-bromoctene-1 (1.565 g, 8.19 mmol), and K_2CO_3 (1.13 g, 8.19 mmol) in DMF (20 mL) were stirred at 70 °C for 6 h. After cooling, the reaction mixture was poured into distilled water (150 mL) and extracted with chloroform (4 × 20 mL). The organic layer was washed with water (2 × 20 mL), dried over $MgSO_4$, and then evaporated under reduced pressure to dryness. Recrystallization from methanol (15 mL) gave the title compound (1.29 g, 60 %) as a white crystalline powder. M.p. 55 °C; ^{1}H NMR ([D$_1$]chloroform, 25 °C): $\delta=7.55$ (br s, 1 H; NH), 7.26 (s, 1 H; CH), 7.16 (t, $J=7.9$ Hz, 1 H; CH), 6.94 (d, $J=7.6$ Hz, 1 H; CH), 6.62 (d, $J=7.6$ Hz, 1 H; CH), 5.80 (m, 1 H; $\mathrm{C}\mathit{H}{=}\mathrm{CH_2}$), 4.99 (dd, $^2J=17.0$ Hz, $^3J=1.8$ Hz, 1 H; $\mathrm{CH{=}C}\mathit{H}_2$), 4.92 (dd, $^2J=11.1$ Hz, $^3J=1.2$ Hz, 1 H; $\mathrm{CH{=}C}\mathit{H}_2$), 3.90 (t, $J=6.4$ Hz, 2 H; OCH_2), 2.14 (s, 3 H; $COCH_3$), 2.03 (q, $J=7$ Hz, 2 H; $\mathrm{C}\mathit{H}_2\mathrm{CH{=}CH_2}$), 1.74 (q, $J=7.0$ Hz, 2 H; CH_2), 1.45–1.30 ppm (m, 6 H; CH_2); ^{13}C NMR ($CDCl_3$): $\delta=168.54$, 159.63, 139.11, 138.98, 129.51, 114.23, 111.80, 110.56, 106.22, 67.92, 33.65, 29.13, 28.79, 28.76, 25.82, 24.57 ppm; elemental analysis calcd (%) for $C_{16}H_{23}NO$: C 73.53, H 8.87, N 5.36; found: C 73.14, H 8.40, N 5.42.

3-(7′-Octenyloxy)aniline (8): A mixture of anilide **7** (0.76 g, 2.9 mmol) and NaOH (4.07 g, 0.102 mol) was heated at reflux in a mixture of ethanol (100 mL) and water (10 mL) for 6 h. After cooling, the mixture was evaporated under reduced pressure, distilled water (300 mL) was added and the mixture was extracted with dichloromethane (4 × 20 mL). The organic layer was washed with water (2 × 30 mL), dried over $MgSO_4$ and evaporated to dryness to give the title compound (0.56 g, 87 %) as a yellow oil. ^{1}H NMR ([D$_1$]chloroform, 25 °C): $\delta=7.08$ (t, $J=7.6$ Hz, 1 H; CH), 6.36 (dd, $^3J=8.2$ Hz, $^4J=1.8$ Hz, 1 H; CH), 6.29 (dd, $^3J=8.2$ Hz, $^4J=1.8$ Hz, 1 H; CH), 6.26 (t, $J=2.4$ Hz, 1 H; CH), 5.86 (m, 1 H; $\mathrm{C}\mathit{H}{=}\mathrm{CH_2}$), 5.07 (dd, $^2J=17.0$ Hz, $^3J=1.8$ Hz, 1 H; $\mathrm{CH{=}C}\mathit{H}_2$), 5.01 (d, $J=10.6$ Hz, 1 H; $\mathrm{CH{=}C}\mathit{H}_2$), 3.94 (t, $J=6.5$ Hz, 2 H; OCH_2), 3.65 (br s, 2 H; NH_2), 2.12 (q, $J=7$ Hz, 2 H; $\mathrm{C}\mathit{H}_2\mathrm{CH{=}CH_2}$), 1.81 (q, $J=8.2$ Hz, 2 H; CH_2), 1.55–1.35 ppm (m, 6 H; CH_2); ^{13}C NMR ($CDCl_3$): $\delta=160.05$, 147.66, 138.78, 129.77, 114.09, 107.49, 104.25, 101.36, 67.44, 33.50, 29.05, 28.65, 28.61, 25.70 ppm; elemental analysis calcd (%) for $C_{12}H_{17}NO$: C 75.35, H 8.96, N 7.32; found: C 75.10, H 9.02, N 7.12.

5,11,17,23-Tetrakis(*N*′-(4″-nitrophenyloxy)carbonylamine)-25,26,27,28-tetrakis(pentyloxy)calix[4]arene (10): A solution of tetraamine **9** (3 g, 3.92 mmol) and 4-nitrophenylchloroformate (3.947 g, 19.6 mmol) in a mixture of chloroform (75 mL) and THF (45 mL) was heated at reflux overnight. After cooling, the reaction mixture was evaporated to dryness under reduced pressure. The residue was heated at reflux in ethyl acetate (40 mL) for 2–3 min. The yellow precipitate was filtered off, washed with hot ethyl acetate and dried to give the title compound (3.69 g, 70 % yield). M.p. > 240 °C (decomp); ^{1}H NMR ([D$_6$]DMSO, 200 MHz): $\delta=9.95$ (br s, 4 H; NH), 8.20 (d, $J=8.8$ Hz; CH), 7.37 (d, $J=8.8$ Hz; CH), 6.90 (br s, 8 H; CH), 4.35 and 3.11 (2 d, $J=12.7$ Hz, 8 H; $ArCH_2Ar$), 3.81 (br t coupling was unresolved, 8 H; OCH_2), 1.87 (m, 8 H; CH_2), 1.50–1.30 (m, 16 H; CH_2), 0.91 ppm (br t, $J=6.3$ Hz; CH_3); ^{13}C NMR ([D$_1$]chloroform, 25 °C): $\delta=155.36$, 152.49, 150.20, 143.78, 134.49, 130.84, 124.26, 121.54, 119.23, 74.47, 30.54, 29.03, 27.60, 22.02, 13.51 ppm.

5,11,17,23-Tetrakis(*N*′-3″-(7‴-octenyloxy)phenyl-*N*-ureido)-25,26,27,28-tetrakis(pentyloxy)calix[4]arene (2): A solution of aniline **8** (0.396 g, 1.81 mmol) and *N*,*N*-diisopropylethylamine (0.467 g, 3.61 mmol) in DMF (5 mL) was added to a solution of the active urethane **10** (0.486 g, 0.361 mmol) in DMF (15 mL) and the reaction mixture was stirred at 70 °C overnight. After cooling to a room temperature (22 °C), the reaction mixture was poured into 1M potassium carbonate (250 mL) and extracted with chloroform (4 × 20 mL). The organic layer was then additionally washed with 1M potassium carbonate (3 × 30 mL), dried over $MgSO_4$, evaporated to dryness and purified twice by column chromatography over silica (ethyl acetate/hexane 1:4) to afford the title compound (0.519 g, 82 %). M.p. 165–170 °C; ^{1}H NMR ([D$_6$]DMSO, 25 °C): $\delta=8.30$ (s, 4 H; NH), 8.16 (s, 4 H; NH), 7.06 (m, 8 H; CH), 6.79 (s, 8 H; CH_{calix}), 6.76 (d, $J=7.6$ Hz, 4 H; CH), 6.46 (d, $J=8.2$ Hz, 4 H; CH), 5.77 (m, 4 H; $\mathrm{C}\mathit{H}{=}\mathrm{CH_2}$), 5.02 (d, $^2J=17$ Hz plus small unresolved long-range couplings, 4 H; $\mathrm{CH{=}C}\mathit{H}_2$), 4.91 (d, $J=10$ Hz plus small unresolved long-range couplings, 4 H; $\mathrm{CH{=}C}\mathit{H}_2$), 4.33 and 3.11 (2 d, $J=12.3$ Hz, 8 H; $ArCH_2Ar$), 3.90–3.75 (m, 16 H; OCH_2), 2.00 (q, $J=6.5$ Hz, 8 H; $\mathrm{C}\mathit{H}_2\mathrm{CH{=}CH_2}$), 1.90 (m, 8 H; CH_2), 1.66 (quintet, $J=7.0$ Hz, 8 H; CH_2), 1.50–1.20 (m, 40 H; CH_2), 0.94 ppm (br t, 12 H; CH_3); ^{1}H NMR ([D$_1$]chloroform, 200 MHz, 25 °C): $\delta=9.43$ (s, 8 H; NH), 7.65 and 5.82 (2 AB d, $^4J=2$ Hz, 16 H; CH_{calix}), 7.58 (br t, small unresolved long-range coupling, 8 H; CH), 7.32 (d, $^3J=8.3$ Hz plus small unresolved long-range couplings, 8 H; CH), 7.21 (t, $^3J=7.8$ Hz, 8 H; CH), 6.88 (s, 8 H; NH), 6.53 (d, $^3J=7.8$ Hz plus small unresolved long-range couplings, 8 H; CH), 5.75 (m, 8 H; $\mathrm{C}\mathit{H}{=}\mathrm{CH_2}$), 4.95 (dd, $^3J=15.6$ Hz, $^4J=2.0$ Hz plus small unresolved long-range couplings, 8 H; $\mathrm{CH{=}C}\mathit{H}_2$), 4.88 (d,

$^3J = 8.8$ Hz plus small unresolved long-range couplings, 8H; CH=CH_2), 4.20 and 2.83 (2d, $^2J = 11.7$ Hz, 16H; ArCH$_2$Ar), 3.90–3.75 (m, 16H; OCH$_2$), 3.65 (t, $^3J = 7.8$ Hz, 16H; OCH$_2$), 2.08–1.79 (m, 32H; CH$_2$), 1.75–1.55 (m, 16H; CH$_2$), 1.45–1.10 (m, 80H; CH$_2$), 0.93 ppm (t, $^3J = 7.3$ Hz, 24H; CH$_3$); ^{1}H NMR ([D$_6$]benzene, 25 °C): $\delta = 10.01$ (s, 8H; NH), 8.13 (s, 16H; CH + CH$_{calix}$), 7.68 (d, $^3J = 7.8$ Hz plus small unresolved long-range couplings, 8H; CH), 7.30–6.90 (m, under solvent peak; CH + NH), 6.62 (d, $^3J = 7.8$ Hz plus small unresolved long-range couplings, 8H; CH), 6.31 (br d, small unresolved long-range coupling, 8H; CH$_{calix}$), 5.77 (m, 8H; C*H*=CH$_2$), 5.04 (br dd, $^3J = 17$ Hz plus small unresolved long-range couplings, 8H; CH=CH_2), 4.99 (br dd, $^3J = 10.1$ Hz plus small unresolved long-range couplings, 8H; CH=CH_2), 4.56 and 3.28 (2d, $^2J = 11.6$ Hz, 16H; ArCH$_2$Ar), 3.90–3.60 (m, 32H; OCH$_2$), 2.07 (quintet, $^3J = 7.1$ Hz, 16H; CH$_2$), 1.94 (q, $^3J = 7.2$ Hz, 16H; CH$_2$), 1.60–1.45 (m, 16H; CH$_2$), 1.40 (quintet, $^3J = 7.5$ Hz, 16H; CH$_2$), 1.30–1.05 (m, 64H; CH$_2$), 0.98 ppm (t, $^3J = 7.5$ Hz, 24H; CH$_3$); ^{13}C NMR ([D$_6$]DMSO, 25 °C): $\delta = 158.96$, 152.25, 151.06, 140.94, 138.63, 134.33, 133.25, 129.21, 118.12, 114.53, 110.07, 107.26, 104.12, 74.71, 67.04, 33.02, 30.54, 29.29, 28.55, 28.15, 28.13, 27.88, 25.25, 22.25, 13.89 ppm; FD MS: m/z: 1747.1 $[M+1]^+$.

Compounds 3–5: Benzene (p.a., 50 mL) was added to a solution of calix[4]arene **2** (0.204 g, 0.117 mmol) in dry dichloromethane (1.00 L). After approximately 15 min a solution of Grubbs' catalyst (0.019 g, 0.0234 mmol) in dry dichloromethane (25 mL) was added. The reaction mixture was stirred for two days at room temperature. DMSO (p.a., 150 µL) was then added, and after 12 h, the solution was washed with water (4 × 100 mL), dried over magnesium sulfate and evaporated to dryness. The residue was passed through a silica column (chloroform as eluant). The mixture of compounds was then hydrogenated (H_2 (1 atm), Pd/C, THF, 30–35 °C, 5 h) until the signal of CH=CH protons at 5.5 ppm had disappeared and the products were separated by flash chromatography (gradient hexane/ethyl acetate 10:1 to ethyl acetate) to yield **3–5** (see Table 1 for selected spectroscopic data). Compound **3** (yield 5–12 %): m.p. (chloroform/methanol) > 300 °C (decomp.), 265–290 ph. tr.; for selected ^{1}H NMR data see Table 1; MALDI-TOF MS: m/z: 3389.0 $[M+1]^+$. Compound **4** (yield 26–32 %): m.p. (chloroform/methanol) > 330 (decomp.), 207–230 and 295–330 ph. tr.; for selected ^{1}H NMR data see Table 1; MALDI-TOF MS: m/z:3390.3 $[M+2]^+$, 3411.3 $[M+\text{Na}^+]$. Compound **5** (yield 10–15 %): > 330 °C (decomp); MALDI-TOF MS: m/z: 3411.5 $[M+\text{Na}^+]$.

X-ray structure analysis: Single crystals of **3** (Figure 5) suitable for an X-ray analysis were obtained from chloroform/methanol. However, the best crystal diffracted to a resolution of just 1.65 Å. Nevertheless, the structure could be solved after numerous attempts by the Shake-and-Bake method (SHELXD, a program for the solution of macromolecular structures; G. M. Sheldrick, University of Göttingen, 1999). It clearly shows the dimeric capsule, but due to the disorder in the four $C_{14}H_{28}$ chains between the oxygen atoms and the low resolution of the data it was impossible to decide how the urea residues are connected. Refinement was performed on F^2 (SHELXL, a program for the refinement of crystal structures; G. M. Sheldrick, University of Göttingen, 1997). All non-hydrogen atoms were kept isotropically and hydrogen atoms were not included. Space group $P2_1/c$, $a = 22.319(2)$, $b = 39.251(6)$, $c = 29.259(3)$ Å, $\beta = 109.465(8)°$, $V = 24167(5)$ Å^3, $Z = 4$, $\mu = 0.08$ mm^{-1} (MoKα), crystal dimensions 0.5 × 0.5 × 0.4 mm^3, 131365 measured intensities, 38492 independent reflections ($R_{int} = 0.20$), 669 parameters, 149 restraints, $R = 0.42$, highest peak and deepest hole in the final difference map: 1.35, −0.67 e Å^{-3}. CCDC-204634 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44)1223-336033; or deposit@ccdc.cam.uk).

MD simulations: MD simulations of **3–5** (in which the *n*-pentyl groups at the narrow rim were replaced by ethyl groups) have been carried out by using the AMBER 6 force field for 9 ns in a rectangular box of chloroform molecules. For details of the protocol see ref. [30].

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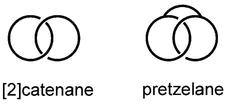

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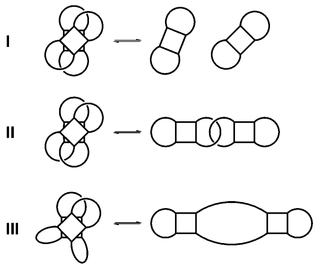

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