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Rotaxanes and Catenanes Derived from Tetra-Urea Calix[4]arenes

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Summary: Calix[4]arenes, substituted by four urea groups at their wide rim, form dimeric capsules in apolar solvents, which are held together by a seam of intermolecular hydrogen bonds. The heterodimerisation of tetra-aryl and tetratosyl ureas was used to synthesize various derivatives, in which adjacent urea residues are connected to form two, three or four loops. The aliphatic connections were tied by olefin metathesis between adjacent alkenyl residues followed by hydrogenation. Heterodimers of tetra-alkenyl substituted tetra-ureas and bis- or tetraloop derivatives were converted analogously to multiple catenanes. Tetra[2]rotaxanes were obtained in a similar manner. In addition to the spectroscopic evidence (NMR, MS) several compounds were confirmed by crystal structures.

Keywords: hydrogen bonding; self-assembly; dimerisation; olefin metathesis; crystal structure

Introduction

Tetraethers of calix[4]arenes bearing four aryl urea groups at their wide rim (**1**) form hydrogen bonded dimers in apolar solvents, such as chloroform, benzene or cyclohexane, while they exist as monomeric species in polar solvents, e.g. ethanol, THF, etc. The two calix[4]arenes are held together by a seam of intermolecular hydrogen bonds alternatingly involving the urea functions of both calix[4]arenes. The internal volume of such a capsule (about 190 Å^3) requires the inclusion of a suitably sized guest, often a molecule of the solvent. In fact, the dimerisation was first concluded from ^{1}H NMR spectra where the guest signals are high-field shifted by 2–3 ppm.[1] Furthermore, the directionality of the hydrogen bonded belt, in which the urea groups simultaneously act as hydrogen bond donor and acceptor, reduces the symmetry of the capsule from C_{4v} to C_4, making the two aryl protons of each phenolic unit different. Thus, they appear as a pair of *m*-coupled doublets, high and downfield shifted, in comparison to the spectrum of the single calixarene (Figure 1). A similar splitting is observed for the NH-signals,[2] since the H-bonding occurs mainly via H_α, the hydrogen attached to the urea residue.

The structure of the dimers was entirely confirmed by an early crystal structure[3] (Figure 2), which was completely in agreement with the predictions based on the NMR results.

Homo- and Heterodimers

If two tetra-ureas **1a** and **1b** bearing different ureas residues form dimers **1a** · **1a** and **1b** · **1b**, their mixture should contain under analogous conditions also the heterodimer **1a** · **1b**. In fact this is the case,[4] as shown by Figure 3. This heterodimerisation was not only an additional proof for the dimerisation, it is also the basis for many syntheses described in the following.

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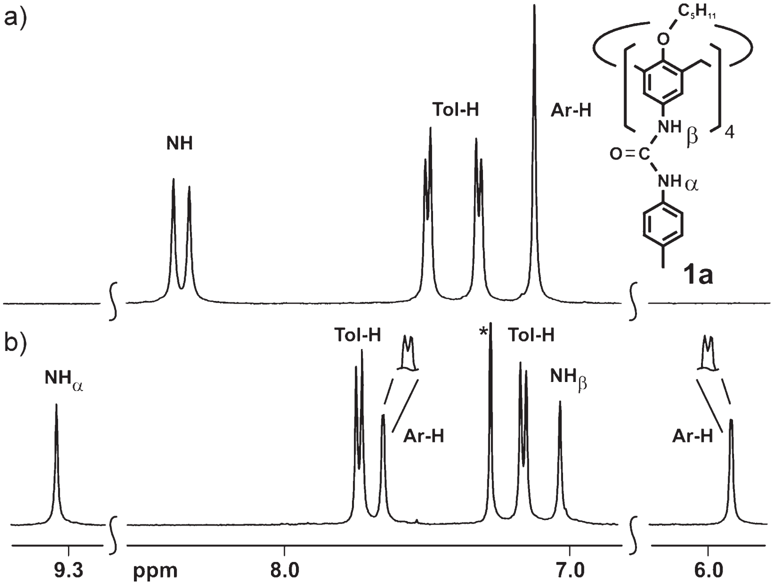

Figure 1.
Sections of the ^{1}H MNR spectra of the tetra-urea **1a** in a) DMSO-d_6 and b) $CDCl_3$.

In addition to the (more or less) statistical dimerisation, the mixture of two tetra-ureas may contain *only* the two homodimers[5] or *only* the heterodimer.[6] The first example for the *exclusive* heterodimerisation involves tetratolyl **1a** (more general tetra-aryl) and tetratosyl ureas **2**, both of which form readily homodimers alone. This observation was used already to form selectively assemblies, such as alternating copolymers[7] via self-assembly although the exact reason was unknown for a long time. MD-simulations recently suggested, that one of the two tetratosyl ureas has to assume a sterically unfavorable conformation in the homodimer, which is not necessary in the heterodimer with aryl ureas.[8] This explanation was subsequently confirmed by two crystal structures[9] (see Figure 4).

Tetra-Ureas with Loops

Adjacent aryl-urea residues may be covalently connected by aliphatic chains to "loops" (see Figure 5). Before we show, that this will create additional selectivities for their dimerisation, we shortly will discuss possibilities to synthesize such derivatives.

As connection we have chosen aliphatic ether chains (-O-$(CH_2)_n$-O-) between the

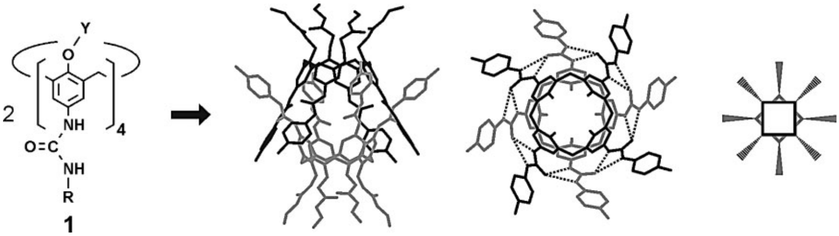

Figure 2.
Two different views of the X-ray structure of the dimeric capsule **1·1** and its schematic representation.

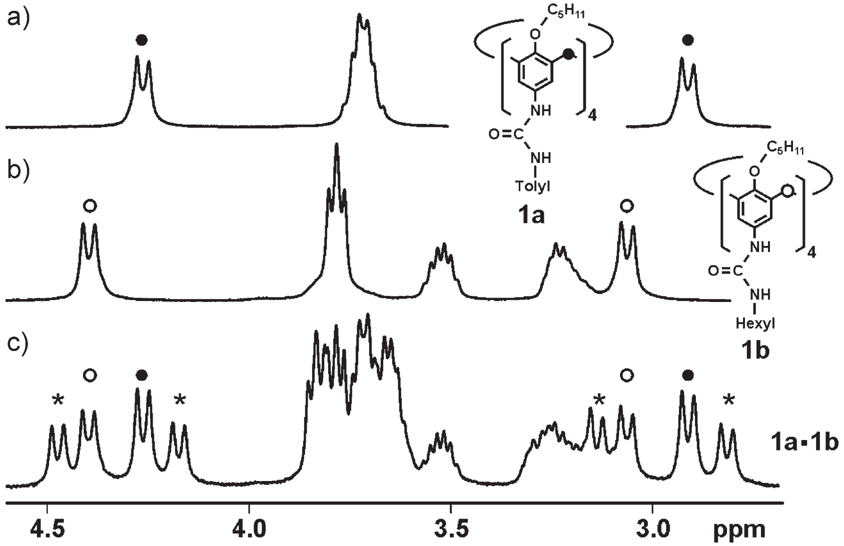

Figure 3.
Sections of the ^{1}H NMR spectra of the a) tetratolyl urea **1a**, b) tetrahexyl urea **1b** and c) stoichiometric mixture of **1a** and **1b**.

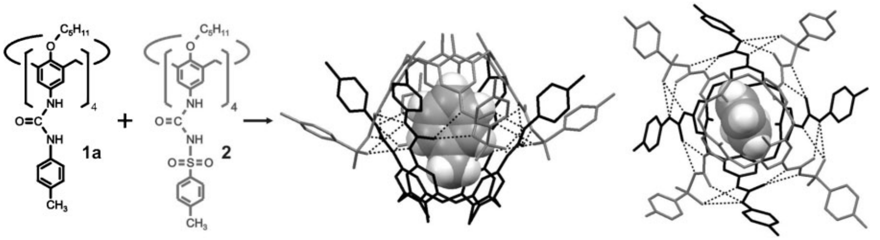

Figure 4.
Single crystal X-ray structure of the heterodimer **1a** · **2**.[9b]

meta-positions of the phenyl residues attached to the urea functions.

Starting from tetra-amines tetra-ureas may be obtained by acylation with activated di-esters under high dilution conditions. In fact, first examples for mono- and bisloop compounds were prepared in this way.[10] However, the synthesis of tetra-urea calix[4]arenes with ω-alkenyl ether chains and their connection by olefin metathesis (followed by hydrogenation) was synthetically more economic. Like all reactions connecting functional groups in *p*-position of calix[4]arenes, it may be troubled by the formation of a bridge across the cavity, instead or at least aside of the desired connection of the adjacent units. This undesired reaction can be entirely avoided using the heterodimers of the alkenyl urea with tetratosyl urea **2**. Bis- and tetraloop compounds (**4**, **7**) with various loops (size, structure) are available in yields of 60–90% as chromatographically pure compounds.[11] (Figure 6). Their ^{1}H NMR spectra show, that for short loops the

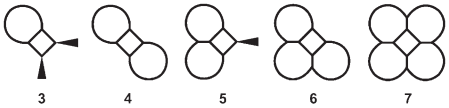

Figure 5.
Schematic representation of the loop-containing tetra-urea calix[4]arenes **3**–**7**.

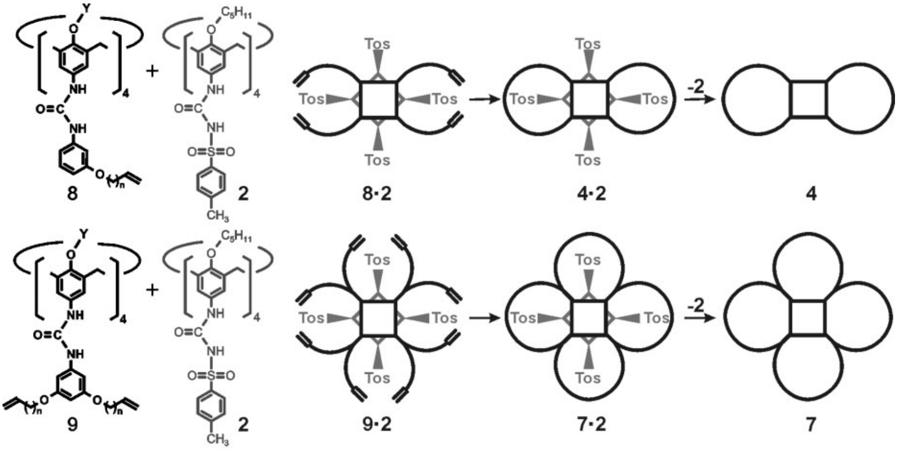

Figure 6.
Template synthesis of bis- and tetraloop tetra-urea calix[4]arenes **4** and **7**.

cone-to-*cone* inversion is impossible also for tetramethylethers. For tetraloop compounds they show the usual, time averaged C_4-symmetry, while a crystal structure finds the molecule in a pinched cone conformation (Figure 7).[12] Cleavage of the urea links to the calixarene was possible in boiling acetic acid, leading to macrocyclic tetra-acetamides.

The synthesis of bis- and trisloop tetraureas **5** and **6** with adjacent loops is also possible and summarized in Figure 8. The partial protection of amino groups in tetraamino calix[4]arenes by Boc[13] or by trityl groups[14] is helpful in these cases.

Bis[2]catenanes

In early experiments we tried to synthesize calix[4]arene based catenanes applying the metathesis reaction directly to homodimers of tetra-alkenyl derivatives of tetra-urea calix[4]arenes **8**.[15] From the resulting product mixture three isomeric compounds could be isolated and identified by their ^{1}H NMR spectra: The desired bis[2]catenane, a doubly bridged monocatenane and a tetrabridged capsule. Obviously not only adjacent alkenyl residues belonging to the same calix[4]arene were connected, but covalent connections occurred also

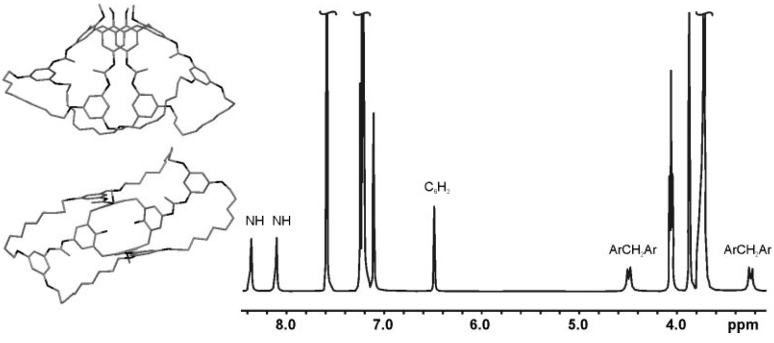

Figure 7.
X-Ray structure of tetraloop **7** (n = 10, Y = CH_3), and section of the ^{1}H NMR spectrum of **7** (n = 14, Y = CH_3) at 100 °C in pyridine.

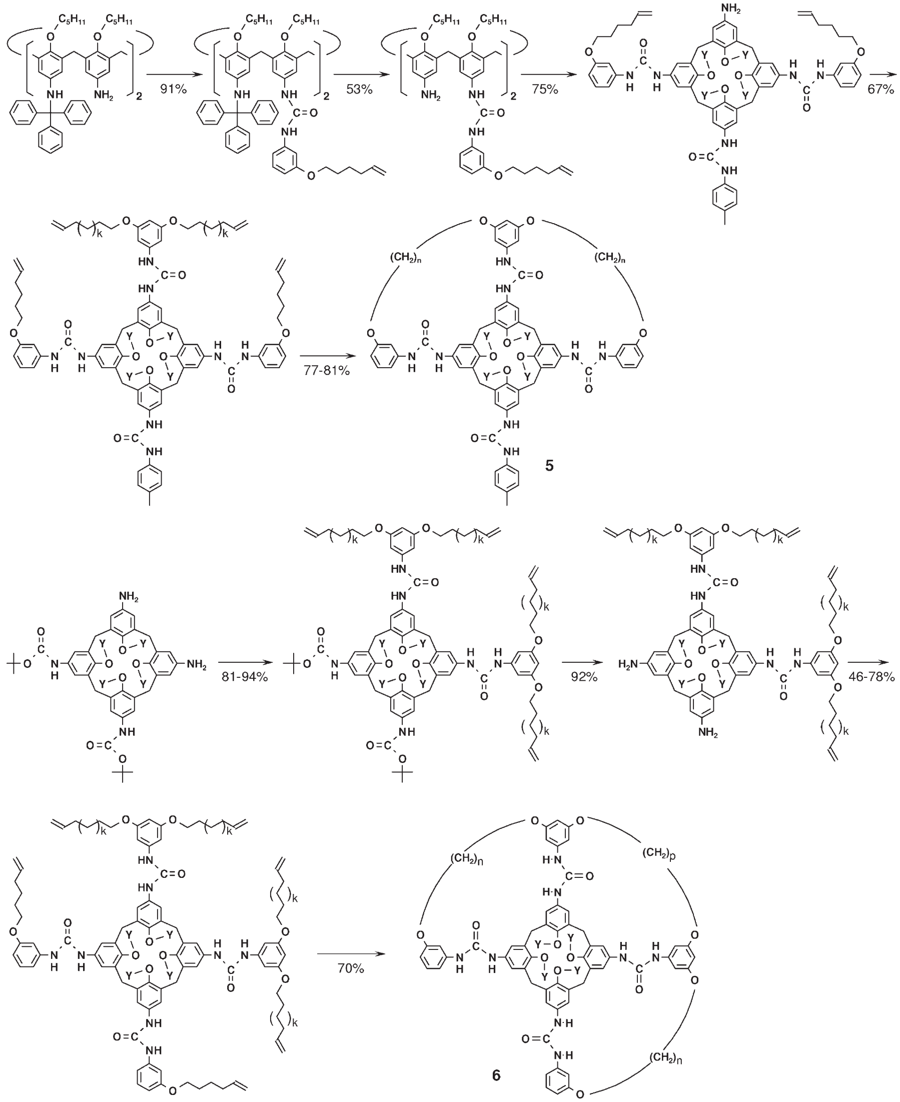

Figure 8.
Examples of multistep syntheses of bis- and trisloop derivatives **5** and **6**.

between adjacent groups of both calixarenes in the dimer.

For an efficient synthesis it is more advantageous to use compounds with “prefabricated” loops. Monoloop compounds **3** form only a single regioisomeric dimer, in which the two loops do not overlap. Since such overlapping loops are sterically unfavorable, bisloop compounds **4** do not dimerize at all, but in mixtures with tetra-alkenyl tetra-ureas **8** they form “quantitatively” heterodimers, since this is the only way, to incorporate all urea functions in a “hydrogen bonded belt” (Figure 9). Various bis[2]catenanes **10** with different ring sizes have been prepared according to this strategy by two “α-connections”[15] homodimers of monoloop compounds still allow a “β-connection” (at least as side reaction)[16] and should be used only in special cases.

Bis[2]catenanes are chiral and their enantiomers could be chromatographically separated on chiral stationary phases. As

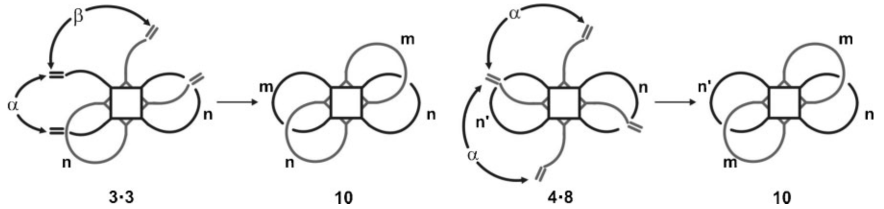

Figure 9.
Schematic representation of the syntheses of bis[2]catenanes **10** starting with homodimer **3 · 3** or heterodimer **4 · 8**.

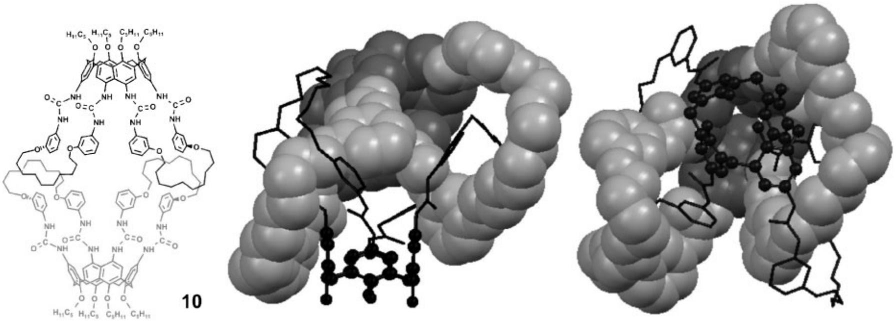

Figure 10.
Single crystal X-ray structure of bis[2]catenane **10** (n = 10) shown from two perspectives.

shown for an example in Figure 10, the catenane structure was also confirmed by an X-ray structure.[17]

Multiple Catenanes

The synthetic principle described above for the preparation of bis[2]catenanes from bisloop compounds can be easily extended to tetraloop compounds **7** and, in principle to bisloop calixarenes with adjacent loops **5** and to trisloop calix[4]arenes **6**.

Combination of bis- (**4**) and tetraloop (**7**) calix[4]arenes leads to bis[3]catenanes **11**, which can be obtained in two ways (Figure 11):

a) from heterodimers between a tetraloop calix[4]arene **7** and a tetra-alkenyl tetraurea **8**,
b) from heterodimers between a bisloop calix[4]arene **4** and an octa-alkenyl tetraurea **9**.

Both ways proved to be possible, and no principal advantage or disadvantage was found.[18] However, for small loops, the passage of bisalkenyl urea functions

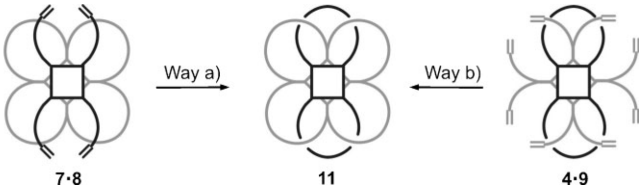

Figure 11.
Schematic representation of the syntheses of bis[3]catenanes **11** starting with heterodimers **7 · 8** or **4 · 9**.

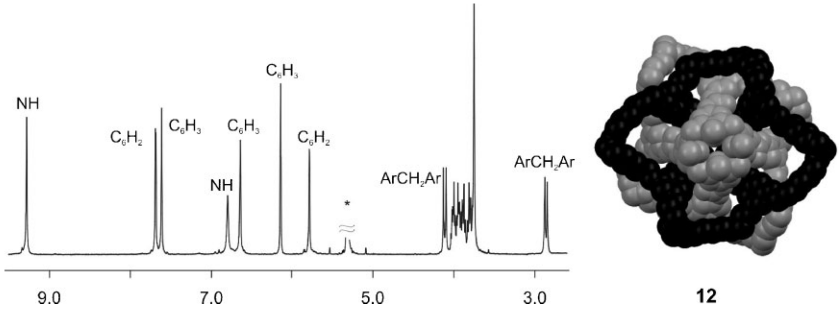

Figure 12.
Section of the ^{1}H NMR spectrum of the cyclic [8]catenane **12** in CD_2Cl_2 (left) and molecular conformation in the crystal.

through the loops may be slowed down for sterical reasons.[19]

The combination of two tetraloop calix[4]arenes **7** was dubbed (cyclo) [8]catenane (**12**), since the molecules contain a structural element of eight interlocked rings in a cyclic arrangement. If all eight loops are identical, the simple ^{1}H NMR spectrum reflects the S_8-symmetry of a simple homodimer (Figure 12). The symmetry is reduced to C_4, if the loops of both calix[4]arenes are different from each other. Bis[3]catenanes **11** are C_2-symmetrical in all cases with identical loops within each calixarene. Additionally to NMR- and MS spectral evidence, crystal X-ray structures prove the pattern of interlocked loops for several examples.

Multiple Rotaxanes

The multiple loop compounds described above can be used also as building blocks for multiple rotaxanes. As usual there are two principal pathways, which have been dubbed as "stoppering" and "clipping".

An example for the first strategy is shown in Figure 13. The tetra-urea **13**, substituted by four maleic acid imide residues (as dienophile) readily forms heterodimers with the tetraloop urea **7** in toluene-d$_8$. Reaction with 1,4,5,8-tetrapentoxy anthracene as diene (105 °C, 72 h) leads to the complete conversion as shown by ^{1}H NMR (disappearance of the signals for maleic imide, new signals for the adduct) and TOF-MS (strong signals for

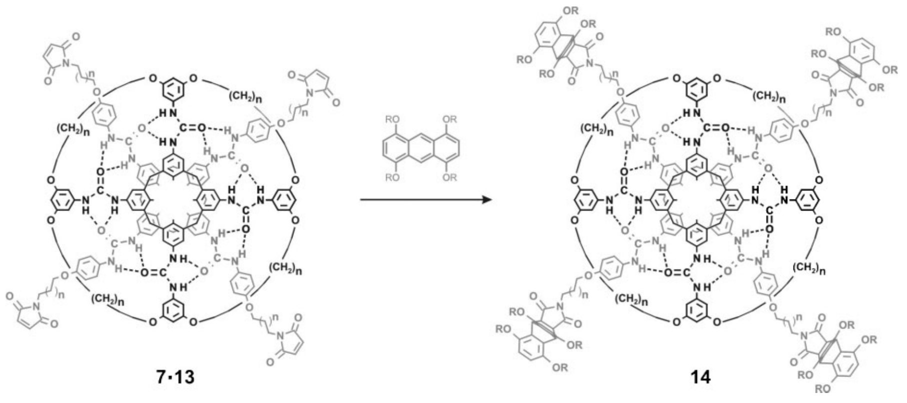

Figure 13.
Synthesis of the rotaxanes **14** (n = 8 or 10, R = C_5H_{11}) by "stoppering" via the introduction of stoppers by Diels-Alder cycloaddition.

the doubly charged species [M+2Na+C_6D_6] and [M+2Na+C_7D_8].[20]

Involuntarily we also found first examples for the formation of tetra[2]rotaxanes by clipping.[21] If the template synthesis for tetraloop compounds **7** described above was attempted for compounds with shorter chains (n = 6, 8) between the arylurea groups, the reaction product could not be split from the tetratosyl urea **2** used as template. This is clearly caused by the tetrahedral arrangement of substituents at the S-atom (N-S-C angle) which prevents the loops from slipping of these hooks.

Conclusions and Outlook

We have shown that various tetra-urea calix[4]arenes in which adjacent urea functions are connected to loops can be prepared in a controlled way, using the tetratosyl urea **2** as template. These and similar syntheses open the door for further studies, some of which will shortly mentioned.

Bis[2]catenanes of type **10** can be synthesized, bearing one carboxyl and one amino group as complementary functions in each bisloop part. Thus they can be converted to oligoamides which in turn can be spanned between a gold substrate and a gold coated AFM tip. Stretching experiments were possible then to characterize the mechanical strength of hydrogen bonded dimeric capsules.[22]

It was shown, that tetra-ureas with loops form only those dimers, where these loops do not overlap. Additional selectivities are obtained by the introduction of bulky residues to (some of) the urea groups. For appropriate combinations of loop size with small and bulky residues it could be shown, that only those dimers form, where a bulky residue has not to penetrate a loop.[23] This enables to establish a sorting scheme for 11 tetra-ureas, where from 35 possible dimers only 6 are formed.[24]

Based on this sorting scheme it will be possible to obtain dendrimers with uniform structure via self-assembly of building blocks in which two, three (or more) tetra-urea molecules are covalently connected via their narrow rim. First examples, using also other motifs (dimerisation of triphenylmethane derived tri-ureas;[25] tetramerisation of calix[4]arenes substituted by three urea groups and one acetamide[26]) have been realized already.[27]

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