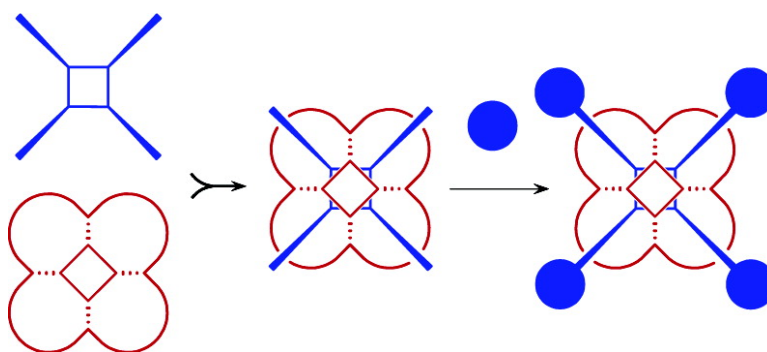


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## Fourfold [2]Rotaxanes Based on Calix[4]arenes

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It is now well established, that calix[4]arenes of type **1** substituted by urea groups at the wide rim form hydrogen-bonded dimeric capsules in apolar solvents.<sup>1</sup> Their structure, first deduced from <sup>1</sup>H NMR spectra, was definitely confirmed by several single-crystal X-ray analyses.<sup>2</sup> The interlocking urea residues of the two calix[4]arenes “roughly” point in opposite directions. Functional groups attached to these urea residues can be covalently connected, e.g. by metathesis between alkenyl groups.<sup>3</sup> If these functional groups are preorganized in heterodimers which are exclusively formed with tetrasoyl ureas<sup>4</sup> as template, multimacrocyclic compounds **2** are available in excellent yield<sup>5</sup> from which the newly formed macrocycles can be detached in a final step.<sup>6</sup>

Macrocyclic tetraureas **2** cannot form homodimers, since this would require a sterically very unfavorable overlap of the “loops” connecting the adjacent urea residues. Therefore, the tendency to form hydrogen bonds leads to the exclusive formation of heterodimers, if an equimolar amount of an “open chain” tetraurea **1** is added,<sup>7</sup> since this is the only way to “saturate” all urea groups. This heterodimerization was successfully applied to construct multiple catenanes by metathesis using again tetraureas of type **1** bearing one or two alkenyl functions per urea residue.<sup>8</sup>

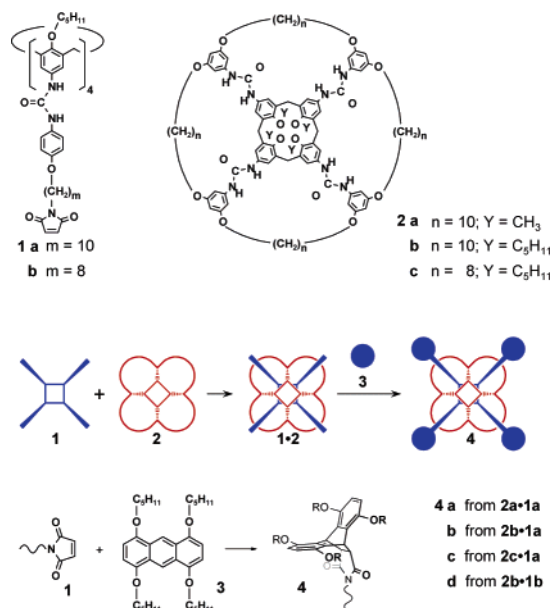
On the other hand, such heterodimers **1·2** can be regarded as pseudorotaxanes,<sup>9</sup> held together by the hydrogen-bonded belt between the urea groups. Attachment of suitably sized stoppers, which cannot pass the macrocycles, would convert them into rotaxanes, also kinetically stable under conditions which break hydrogen bonds.

To realize this general idea, which is illustrated in a sketchy way in Scheme 1, the introduction of the bulky stopper groups must be realized under (aprotic/apolar) conditions, under which the hydrogen bonds between the urea functions are stable. We have chosen for this purpose the Diels–Alder cycloaddition between a maleic imide derivative as dienophile and an anthracene derivative as the diene.

Tetraurea calix[4]arene derivatives **1a,b** bearing four maleic imide functions were obtained from the active tetraurethane<sup>3</sup> by reaction with the corresponding arylamines. These amines were synthesized in five steps by *O*-alkylation of *p*-nitrophenol with *N*-( $\omega$ -bromoalkyl)phthalimide, hydrazinolysis, acylation with maleic acid anhydride followed by dehydration, and reduction of the aryl nitro groups by SnCl<sub>2</sub>. 1,4,5,8-Tetraalkoxy anthracene **3** was prepared in analogy to the synthesis of 1,4,5,8-tetramethoxy anthracene.<sup>10</sup> As expected, **1** forms dimeric capsules in CDCl<sub>3</sub> or benzene-*d*<sub>6</sub>.

Tetra-loop tetraureas **2a,b,c** were synthesized in analogy to the examples described already.<sup>5,7</sup> As expected, their <sup>1</sup>H NMR-spectra in solvents such as CDCl<sub>3</sub> or benzene-*d*<sub>6</sub> are broad and structureless, indicating some association but not the formation of a well-defined

Scheme 1. Synthesis of Tetra[2]rotaxanes **4**



species. However, after the addition of the equimolar amount of **1**, a sharp, well-resolved <sup>1</sup>H NMR spectrum is observed (Figure 1a) which is in complete agreement with the expected spectrum for the heterodimer **1·2**. Especially diagnostic are the low-field shifted signals of the urea functions, indicating the formation of strong hydrogen bonds, and the signals of calixarene phenolic units which appear now as two pairs of meta-coupled doublets.

Addition of 4.1 mol of **3** and refluxing at 110 °C for 72 h leads to the “quantitative” formation of the tetra[2]rotaxane **4** (Figure 1b), which can be deduced from the large upfield shift of the maleic protons H<sup>a</sup> (marked in green) and appearance of the protons H<sup>b</sup> marked in magenta. Additional shifts for the signals of the urea functions indicate changes in the heterodimer in going from the pseudorotaxane to the rotaxane structure.

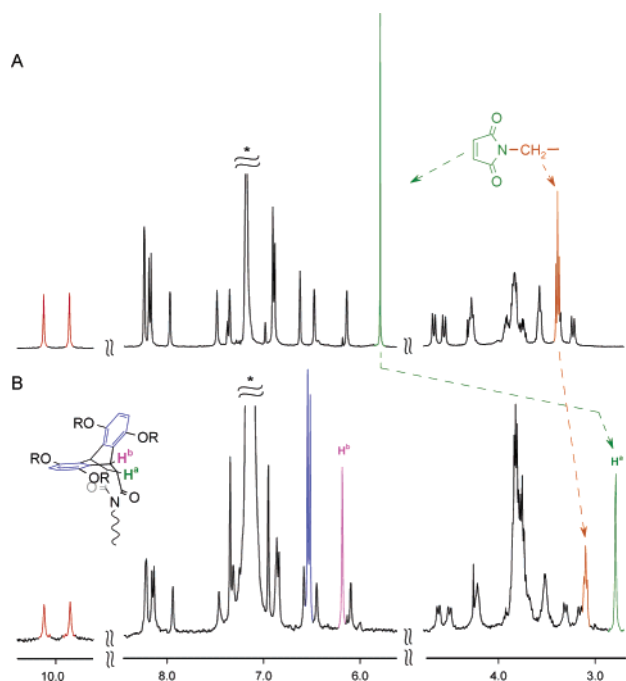
Quantitative conversions were observed for the reaction of **4a** and **4c** on the NMR scale. The isolated yield of pure **4b,d**, however, was only 45–50% since until now a satisfactory purification from the slight excess of **3** was not yet found.

The structure of the tetra[2]rotaxanes was unambiguously confirmed not only by the NMR-spectroscopic changes mentioned above but also by ESI-MS or MALDI-TOF-MS showing the expected molecular peaks.

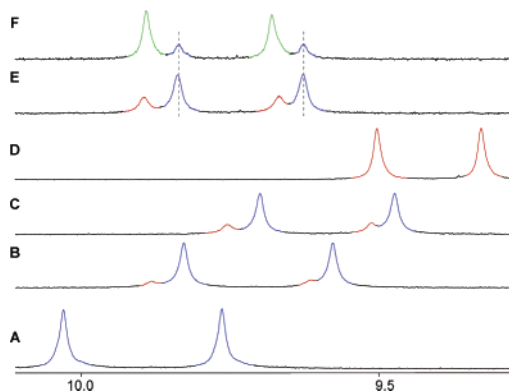
Interesting properties of **4** are evident also from the changes in the <sup>1</sup>H NMR spectra which are observed when increasing amounts of THF are added to a solution in benzene (Figure 2). The low-field signals of the strongly hydrogen-bonded NH-groups are (gradually) shifted to higher field, and a second set appears for these NH signals. The first observation can be explained by

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**Figure 1.** Sections of the  $^1\text{H}$  NMR spectra (benzene- $d_6$ , 400 MHz) of (a) an equimolar mixture of **1a** and **2c** (pseudorotaxane **1a·2c**) and (b) the rotaxane **4c**.



**Figure 2.** Low-field section of the  $^1\text{H}$  NMR spectra of the rotaxane **4b** (A) in benzene- $d_6$ , (B) after addition of 20% THF- $d_8$ , (C) in a 1:1 mixture of benzene- $d_6$  and THF- $d_8$ , and (D) in THF- $d_8$ ; the rotaxane **4d** (E) in a 1:1 mixture of benzene- $d_6$  and THF- $d_8$ , and (F) after addition of 1,4-difluorobenzene.

assuming that the belt of hydrogen-bonded urea functions is more and more “interrupted” by occasional H bonds to THF while its directionality is retained, as indicated also by signals (doublets) for the aromatic protons of each calixarene. The overall structure of the dimeric capsule is also retained, but in addition to capsules with benzene as guest, THF-filled capsules are present which explains the second observation of an additional set of NH signals, increasing in its intensity with increasing amounts of THF. Upon addition of *p*-difluorobenzene, known as a good guest,<sup>11</sup> this second set of NH signals disappears, and also the original set (benzene-filled capsules) shows a lower intensity.

Consequently in pure THF- $d_8$  only one set of low-field NH signals is left, but still one of the NH groups of each calixarene is more strongly hydrogen bonded than the other one. A broadening of Ar–H signals, which nearly coalesce at 50 °C, indicates that directionality of the hydrogen-bonded belt now changes more rapidly. However, the two calixarenes forming the rotaxane **4** remain mechanically connected in contrast to the pseudorotaxane **1·2** which completely dissociates into **1** and **2** under these conditions.

In conclusion, we could show for the first time, that the dimeric assembly formed by tetraurea calix[4]arenes **2a–c** and **1a,b** in aprotic solvents can be fixed by the introduction of bulky stoppers, in the form of a capsule, which may be dubbed a four-fold or tetra-[2]rotaxane.<sup>12</sup> We suggest this name in analogy to the catenanes constructed by the same principle,<sup>7,8</sup> although the whole dimeric capsule consists only of two covalently linked subunits, the two calixarene derivatives. Since the capsular character of **4** persists under hydrogen bond-breaking conditions, it seems feasible also to prepare water-soluble capsules, e.g. by the introduction of  $-\text{CH}_2\text{COOH}$  groups on the narrow rim of the calixarenes and on the anthracene stoppers and to control the guest release in polar solvents by the length of the spacer in the axles.

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**Supporting Information Available:**  $^1\text{H}$  NMR and MALDI-TOF-MS spectra for selected examples of **1** and **4**. This information is available free of charge via the Internet at <http://pubs.acs.org>.

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