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Self Assembly

# A Self-Sorting Scheme Based on Tetra-Urea Calix[4]arenes**

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The generally accepted definition of sorting is a process that achieves some kind of order according to certain criteria or properties such as size, shape, and color. This definition does not hold entirely for the term "self-sorting", which has been defined as the ability to distinguish "self" from "non-self".[1] On the other hand, this term has been used for "the mutual recognition of complementary components in a mixture".[2] In this case, "self" means that the chemical system is able to sort itself based merely on the specific information encoded in the molecules present in the mixture, with no additional external input required. In combination with a driving force such as binding interactions between complementary particles, a more highly ordered state is achieved. In practice, the interaction between the building blocks must be reversible in order to achieve error correction during the sorting progress.

It is evident that the challenge of finding efficient self-sorting systems increases with the similarity of the individual components, because the structural differences, on which the discrimination must be based, become smaller and smaller. Herein, we describe a self-sorting system that consists of eleven structurally very similar compounds. It is based exclusively on calix[4]arenes that are substituted by four urea groups on their wide rim and fixed in the cone conformation by four pentyl ether groups (Scheme 1). All of these calixarenes are thus based on the same scaffold and offer the same hydrogen-bond donors and acceptors. They differ only in peripheral functionalization, that is, the substituents attached to the urea groups are either small or bulky, or adjacent substituents are covalently connected.

In nonpolar, aprotic solvents such as benzene, cyclohexane, or chloroform, tetra-urea calixarenes **1**–**6** dimerize along a seam of 16 hydrogen bonds between interdigitating urea groups.[3] A suitable guest, which is often the solvent, must be included in the cavity that is formed by almost quantitative dimerization of the two halves. Association constants of up to approximately $10^9\,\text{M}^{-1}$ were derived from fluorescence resonance energy transfer (FRET) studies of dye-labeled calixarenes.[4] The monomer–dimer equilibrium is difficult to observe[5] unless more competitive solvents are used.

No restrictions for the dimerization of "open-chain" tetraarylurea groups by the introduction of bulky substituents in the *para* positions of aryl urea groups[6,7] have been reported to date. However, dimerization is obstructed when adjacent urea residues are covalently connected.[8] Tetra-urea calix[4]arenes that bear more than one loop between adjacent urea groups (e.g., **8**–**11**) cannot homodimerize because the loops of the two monomers would obstruct each other.[9] Nevertheless, they still have a strong tendency to dimerize in nonpolar solvents if a suitable partner is available, as only in this case can all urea groups be optimally involved in hydrogen bonding. Therefore, they readily form heterodimers in mixtures with "open-chain" tetra-urea calixarenes[9,10] such as **1**, provided that the urea groups are small enough to penetrate the loops.[11] If those groups, which have to thread through a loop, are too bulky, dimerization does not occur. These observations for the dimerization of tetra-urea calixarene derivatives can be summarized by two general rules: 1) Only dimers that do not require an overlap of loops are formed,[12] and 2) the urea groups that have to pass through loops of the partner must be small enough.

Based on these rules, a library of 11 tetra-urea calix[4]arenes (Scheme 1 and Figure 1) has been designed for which self-sorting is determined by steric factors. The library comprises the complete set of six "open-chain" derivatives **1**–**6**, which bear all possible combinations from four small to four bulky urea groups. The smaller tolyl group can easily pass through the loops, while the (3,5-di-(4-*tert*-butylphenyl)-4-propoxy)phenyl group is too bulky to penetrate them.[13] In addition, five different loop-containing derivatives **7**–**11**, which possess one to four loops within a molecule, have been prepared.[14] All loops have identical $-O-(CH_2)_{10}-O-$ chains that tether the *meta* positions of adjacent phenyl urea groups (Scheme 1).

In general, $N$ objects can combine to form $0.5N(N+1)$ different pairs. Thus, if all possible homo- and heterodimers within the library could be formed, 66 dimers would result.[15] However, the two rules described above exclude some combinations. The first rule makes the formation of 13 dimers (marked "x" in Figure 1) impossible, since loops cannot overlap, which would definitely occur at least once for any of these pairs. The formation of a further 18 dimers labeled "o" in Figure 1 is forbidden by the second rule because the bulky urea groups cannot penetrate the loops.

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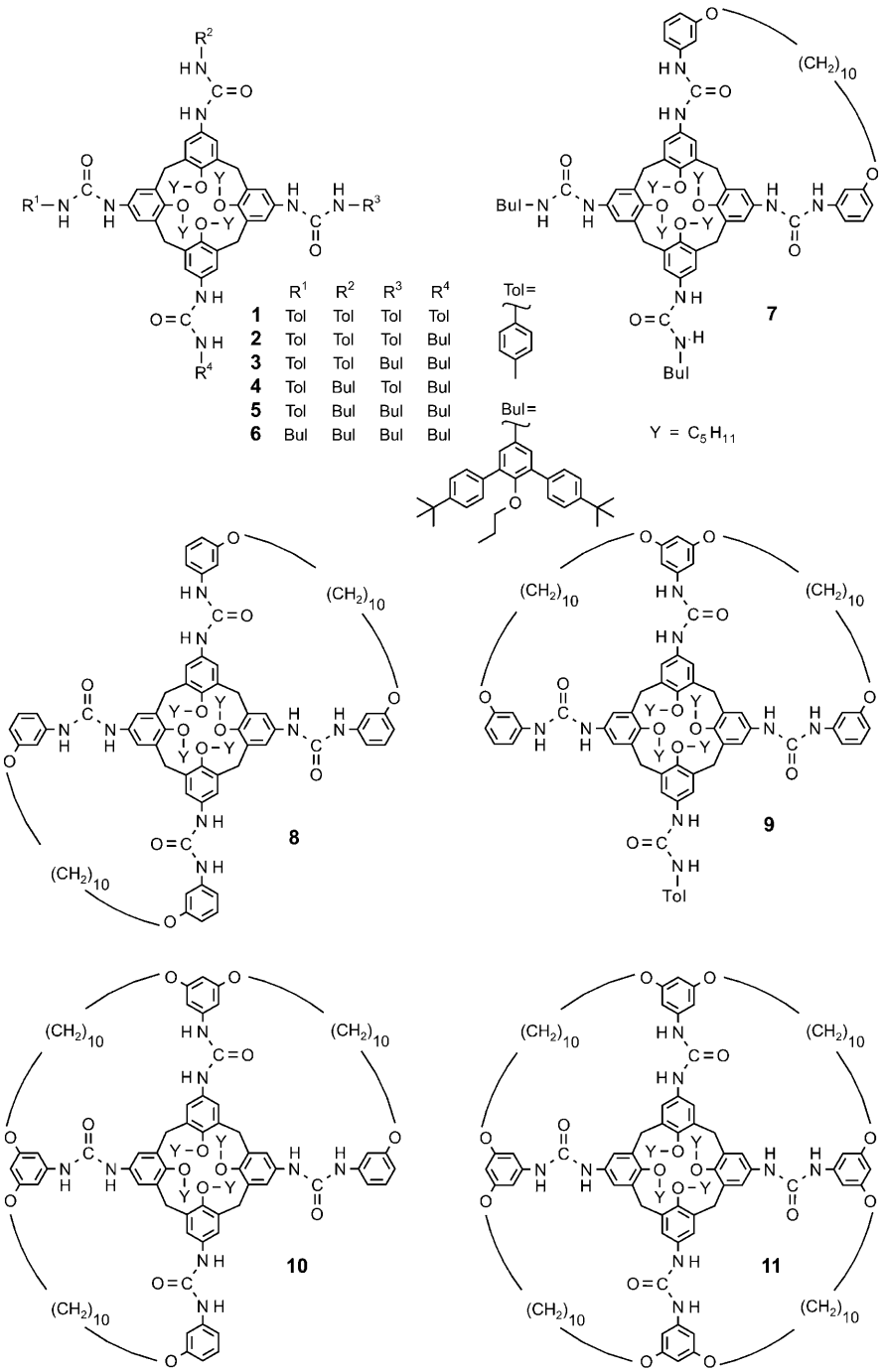


***Scheme 1.*** Tetra-urea calix[4]arenes **1**–**11**.

Among the remaining 35 possible dimers shown in Figure 1, the number of capsules present in a mixture can be further reduced on stoichiometric grounds. In the mixture of compounds **1**–**11**, tetra-tolyl urea **1** can potentially form eleven capsules as its interaction with all the tetra-urea groups present in solution is possible. In contrast, the tetra-loop derivative **11** can dimerize only with **1**. Therefore, if urea derivatives **1** and **11** are present in solution in equimolar amounts, **1** will be completely consumed by **11** to form the dimer **1·11**. Consequently, **1** will be no longer available for dimerization with other partners, and the formation of the remaining ten dimers in the first row is excluded. For the same reasons, tetra-urea calixarene **2** should be consumed by **10**, for which **2** is the only possible partner, once **1** is consumed by **11**. Analogously, **3** and **9**, **4** and **8**, and **5** and **7** should also dimerize quantitatively to leave the homodimerization as the only pairing possibility for **6**. Therefore, an equimolar mixture of all eleven tetra-urea calixarene derivatives should self-sort into only six different dimers: **1·11**, **2·10**, **3·9**, **4·8**, **5·7**, and **6·6**. It is not even necessary that all calixarenes are mixed in stoichiometric amounts, as only the respective pairs must be present in the same quantities.

The aromatic regions of the $^1$H NMR spectra of three dimers are shown in Figure 2 a–c. The homodimer **6·6**, which has the highest symmetry, shows a quite simple set of signals. The NMR spectra of the heterodimers **1·11** and **4·8** are more complex because of their reduced symmetry, although they give evidence of exclusive dimer formation and exclude the presence of further dimers. Mixing equimolar amounts of **1**, **4**, **8**, and **11** leads to the exclusive formation of **1·11** and **4·8** (Figure 2 d). If **6** is added, only the signals for the homodimer **6·6** appear in addition to those already present (Figure 2 e). Consequently, only the three expected dimeric calixarenes are formed, in strict compliance with the two rules discussed above.

However, the $^1$H NMR spectrum in Figure 2 e suggests that such a mixture of five different tetra-urea compounds is essentially the most complicated case that can unambiguously be analyzed by using $^1$H NMR spectroscopy alone. A clear proof that only six dimers are present in the mixture of all eleven tetra-urea calix[4]arenes requires a different analytical technique. In principle, the mixture could be analyzed by using ESI-MS, since the molecular masses of the six dimers—**1·11**, **2·10**, **3·9, 4·8, 5·7**, and **6·6**—are different and differ from all the other possible dimers in Figure 1 (see the Supporting Information). The tetraethylammonium ion is a suitable guest for these experiments.

Indeed, the mass spectra[16] clearly confirm that the expected heterodimers are by far the most abundant ions (Figure 3 a–e). The homodimer $[\mathbf{6}\cdot NEt_4\cdot\mathbf{6}\cdot Na]^{2+}$ is observed

  

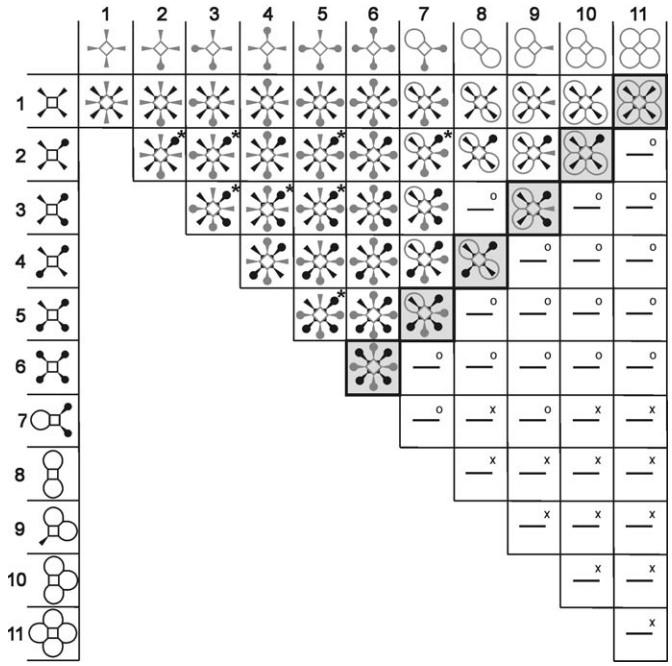


***Figure 1.*** Representation of the self-sorting process in the mixture of eleven tetra-urea calix[4]arene derivatives **1**–**11**. Dimeric combinations marked "x" are impossible because of overlapping loops, while "o" indicates the impossibility of bulky residues to penetrate these loops. Two or three regioisomers are possible for dimers marked "*".

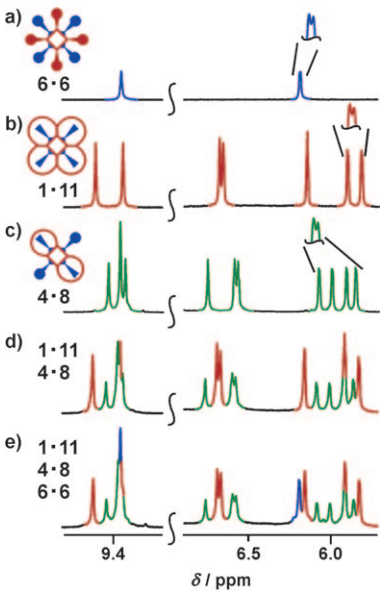


***Figure 2.*** Sections of the $^1$H NMR spectra (400 MHz, 25 °C, $c = 8$ mM, $CDCl_3$) of a) homodimer **6·6**, b) heterodimer **1·11**, c) heterodimer **4·8**, d) a mixture of heterodimers **1·11** and **4·8**, and e) a mixture of tetra-urea calixarenes **1**, **4**, **6**, **8**, and **11**.

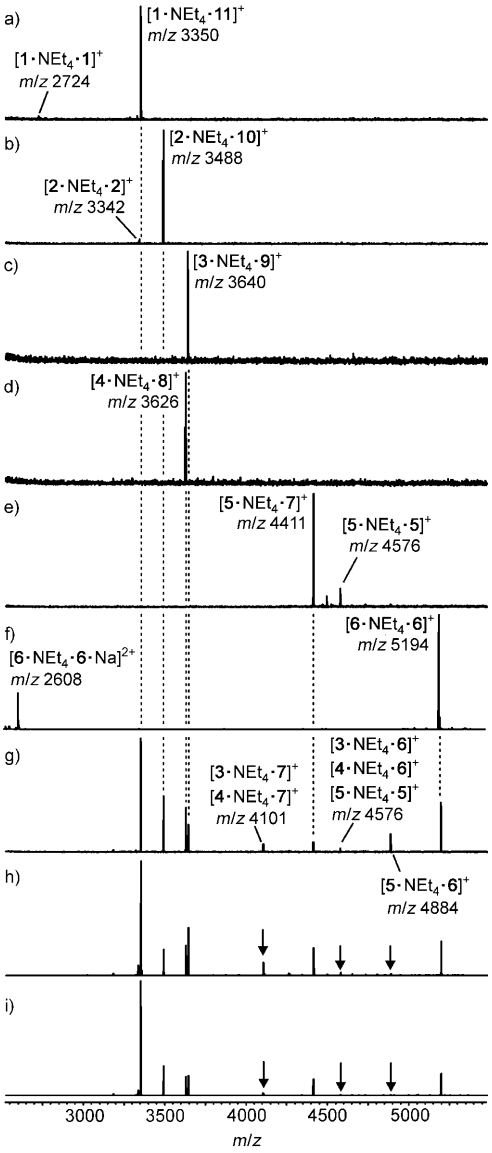


***Figure 3.*** ESI mass spectra (capsule region) of equimolar mixtures of a) **1·11**, b) **2·10**, c) **3·9**, d) **4·8**, and e) **5·7**. f) ESI mass spectrum that reveals the formation of homodimers **6·6**. g) ESI mass spectrum of an equilibrated mixture of all six preformed capsules. h), i) Spectra of the same mixture with 10% and 20% excess of loop-containing monomers **7**–**11**, respectively. Each capsule contains one $NEt_4^+$ ion as the guest. The samples were prepared as described in the Supporting Information and sprayed from $CHCl_3$.

when **6** alone is analyzed by using the same technique (Figure 3 f). Some minor signals (usually $<5\%$) appear for homodimers of **1**–**5**.

Interestingly, the mixtures reach equilibrium only after quite some time, sometimes even days, when the tetraethylammonium ion is present in the sample solutions. In the NMR experiments, $CDCl_3$ is encapsulated and the heterodimers form almost instantaneously. This difference in equilibration rates has been previously reported.[11] It is very likely that the cation contributes additional binding energy arising from cation–π interactions with the aromatic capsule walls.[3e] Thus, the energy requirement for dimer dissociation is raised significantly, which slows down the exchange process.

The mass spectrum of a mixture of all eleven monomers prepared in an analogous fashion was clearly more complex than anticipated. The spectrum showed the presence of unexpected dimers, which should not be formed in a perfectly operating self-sorting process. Even extended equilibration

  

periods of several weeks did not change the final result. To confirm that the equilibrium was indeed reached, the preformed capsules **1**·**11**, **2**·**10**, **3**·**9**, **4**·**8**, **5**·**7**, and **6**·**6** were mixed, equilibrated, and examined by using ESI-MS. Only these six capsules were observed directly after mixing. After one week, however, a spectrum very similar to that directly obtained from the monomers was recorded (Figure 3 g), which confirms the unexpected dimers to be present in the equilibrium mixture.

For a reasonable explanation of this observation, the different concentration regimes of NMR spectroscopy and mass spectrometry must be considered. The final sample concentrations for the MS experiments were lower than those of the NMR experiments by approximately two orders of magnitude. Thus, it is not surprising that the equilibria between the capsule and its components [Eq. (1)] are shifted to some extent to the monomer side compared to those of the NMR samples. This shift leaves some free monomers, which can assemble to yield the undesired capsules. In a complex mixture, the entropy of mixing even supports this process, since each free monomer can form dimers with a number of different partners, thus creating a larger number of different species.

$$\mathbf{1} + \mathbf{11} + NEt_4^+ \rightleftharpoons [\mathbf{1} \cdot NEt_4 \cdot \mathbf{11}]^+$$
$$\mathbf{2} + \mathbf{10} + NEt_4^+ \rightleftharpoons [\mathbf{2} \cdot NEt_4 \cdot \mathbf{10}]^+ \quad (1)$$

etc.

The sorting scheme requires, however, that **1** is completely consumed by **11**, **2** completely by **10**, and so on, since free **1** can combine with all the other tetra-urea calixarenes, free **2** additionally with **2** to **10**, and so on. We thus decided to add the loop-containing compounds **7**–**11**, which cannot dimerize with other members of the group, in a 10 and 20 % excess with respect to **1**–**6**. With this excess, the equilibria would shift back to the expected heterodimeric capsules, thus compensating for the concentration and entropy effects. Indeed, the intensity of the unexpected peaks is already strongly reduced with a 10 % excess of **7**–**11** (Figure 3 h). Upon addition of a 20 % excess of **7**–**11**, they almost completely disappear (arrows in Figure 3 i).

In conclusion, ESI mass spectrometry can provide valuable data on the self-sorting of tetra-urea calixarenes. The self-sorting process presented herein is based on the steric demand of the loops and bulky substituents that are attached to the four urea groups. The formation of only 35 out of 66 potential dimers is geometrically possible. When mixed in appropriate amounts, only six out of the 35 dimers form, because monomers **7**–**11** are unable to dimerize with other members of the group. The importance of component concentrations in self-sorting processes is also shown in this study. Optimum results may not be achieved with stoichiometric amounts as the complexity of the mixture increases. Instead, binding constants and building block concentrations affect the equilibria and determine the optimum composition. A similar effect has been observed for the action of a target molecule on dynamic combinatorial libraries.[17,18] Based on this self-sorting scheme, the formation of much more complex, structurally uniform assemblies will become possible when two or more of the calixarenes are connected with each other.[19,20] More complex self-assembled architectures, for example, oligomers with sequence information or well-defined patterns of cyclic or branched calixarene arrangements, may also become accessible.[21]

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