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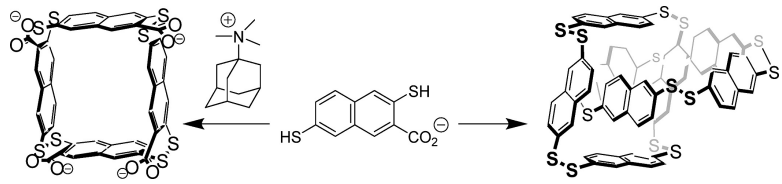

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Dynamic Combinatorial Discovery of a [2]-Catenane and its Guest-Induced Conversion into a Molecular Square Host

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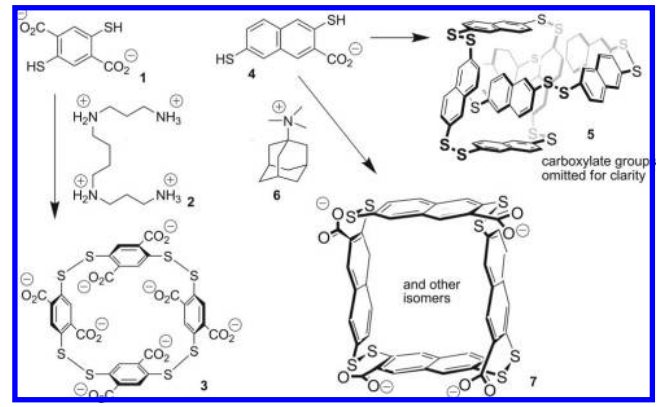
Dynamic combinatorial chemistry[1] has developed into a powerful tool to discover often unexpected interactions between molecules in solution. Dynamic combinatorial libraries (DCLs) have been used to produce new synthetic receptors,[2] interlocked structures,[3] ligands for biomolecules,[4] sensors,[5] and catalysts[6] and for combinatorial resolution.[7] DCLs also provide an exciting entry into the emerging discipline of systems chemistry.[8] Perhaps one of the best examples of dynamic combinatorial chemistry's ability to surprise was the generation of a [2]-catenane, which binds strongly to acetylcholine in organic solvent.[3c,9] We now report how a simple water-soluble naphthalenedithiol building block is converted quantitatively into a series of octameric [2]-catenanes, composed of two interlocked molecular squares. When this mixture is re-equilibrated in the presence of an adamantyl ammonium guest, the catenanes disassemble into their macrocyclic components that bind the guest with nanomolar affinity in water.

DCLs are equilibrium mixtures of compounds formed by connecting building blocks through reversible reactions. Disulfide exchange is currently one of the most popular reversible covalent chemistries and can be operated in water at close to neutral pH, while it is switched off under acidic conditions.[10] It is generally convenient to prepare disulfide DCLs by air oxidation of a solution of thiol-containing building blocks. As part of our successful work with aromatic dithiols,[2a,11] we recently reported the discovery of a macrocyclic nanomolar receptor (**3**) for spermine (**2**) consisting of four units of building block **1**.[11c] We have since prepared the structurally related compound **4** (four steps; 58% yield), which has a comparable orientation of the two thiol groups but features an extended hydrophobic surface area.

Oxidation of an aqueous solution of dithiol **4** at pH 8.0 resulted in a small DCL with a surprising product distribution. Analysis by LC−MS revealed a series of peaks, all with the same mass of 1872, corresponding to eight units of **4** (Figure 1a). Such behavior is highly unusual: the exclusive formation of oligomers as large as octamers is unprecedented in covalent DCLs. Large oligomers are entropically disadvantaged compared to smaller compounds such as trimers and tetramers, which are conspicuous by their absence from this DCL. MS−MS analysis of each of the peaks in Figure 1a showed identical fragmentation patterns consisting of only tetrameric and smaller oligomers (see inset in Figure 1a). This suggests that oligomers with no more than four units are covalently linked, implying that the octamers are in fact [2]-catenanes (**5**) of two mechanically interlocked tetramers. The large number of peaks observed in Figure 1a reflects the very large number of possible structural isomers of the catenane that differ in the arrangement of the carboxylate substituents (separation of the various isomers was deemed impractical). The strongly favored formation of the catenanes in this library is most likely a consequence of the relatively large hydrophobic cavity of a tetramer of **4** which is conveniently filled by another building block. This behavior is similar to previous observations on self-assembled coordination complexes by Fujita et al.[9a]



If the driving force for catenation is avoiding unfavorable exposure of the hydrophobic interior of the tetrameric macrocycles to water, then it should be possible to decatenate the system by introducing a guest that can fill the cavity. Indeed, we found that re-equilibrating the DCL that contained largely catenane in the presence of adamantane derivative **6** resulted in a dramatic change in product distribution: five

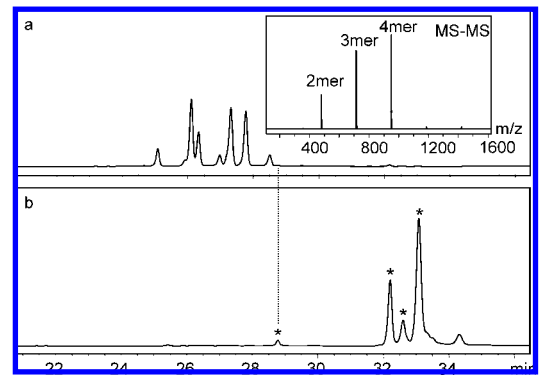


Figure 1. HPLC analysis of a small dynamic combinatorial library made from (a) building block **4** (10 mM) in the absence of guest; (b) building block **4** (1.0 mM) in the presence of adamantane guest **6** (5.0 mM). Peaks due to tetramers **7** are marked with an asterisk. The inset shows the mass spectrum of the daughter ions obtained upon gas-phase fragmentation of the compounds corresponding to the peaks in Figure 1a.

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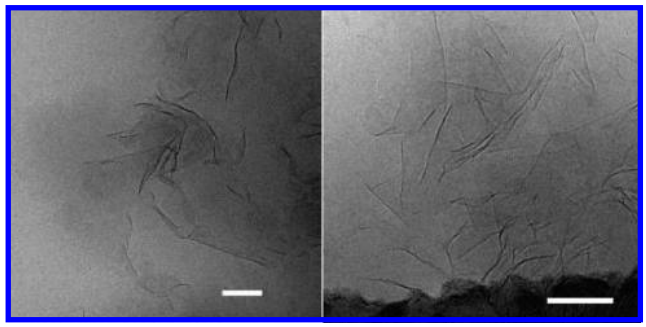

Figure 2. Cryotransmission electron micrographs of the aggregates formed by the **7·6** host−guest complexes in 50 mM borate buffer pH 8.5. [**7**] = 1.25 mM; [**6**] = 5.0 mM. The scale bar corresponds to 100 nm.

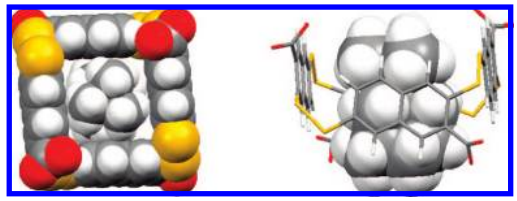

Figure 3. Top and side view of the **7·6** host−guest complex for one of the isomers of **7** obtained by long molecular dynamics simulations. The other isomers gave similar results (see Supporting Information for details).

new peaks appeared, while the catenanes **5** were no longer detectable.[12] Four of the five new signals (marked in Figure 1b) are due to macrocyclic tetramers **7**, differing in the arrangement of the carboxylate groups. The minor fifth peak could not be assigned.

We have isolated the tetramers as a mixture of isomers by preparative HPLC and attempted binding studies using isothermal titration microcalorimetry. Unfortunately, both the free tetramers and the complexes with guest **6** were found to aggregate extensively, complicating the analysis.[13] The aggregates were studied by dynamic light scattering (see Supporting Information) and electron microscopy. Figure 2 shows cryotransmission electron micrographs of the sheetlike aggregates formed by the **7·6** host−guest complexes. These aggregates remain stable in aqueous solution for well over a week and may have potential as a solution-phase analogue of a molecular printboard.[14]

We were nevertheless able to quantify the host−guest binding affinity by immobilizing an analogue of **6** on a polyacrylamide support.[15] On the resin the covalently bound guest molecules are sufficiently far apart to prevent any aggregation of bound hosts. Thus, a 0.22 mM solution of receptor **7** was exposed to the immobilized guest, and the composition of the solution was monitored over time. Host−guest binding equilibrium was reached after five days, and from the amount of **7** remaining in solution the apparent binding constant was estimated[16] to be at least 1.0×10^7 M^{-1}. In control experiments using blank polymer no uptake of **7** from solution could be detected, confirming that all binding to the polymer is due to specific recognition by the adamantane guest.

^{1}H NMR experiments in solution indicated pronounced shifts of the signals of guest **6** upon binding to host **7**, consistent with the nonpolar parts of the guest residing near the naphthalene rings of the host. Molecular modeling indicates that the guest fits well inside the cavity of the host (Figure 3).

In conclusion, we have shown how in the absence of a guest a DCL made from dithiol building block **4** consists entirely of a series of [2]-catenanes built up from eight units of the dithiol. Introduction of adamantane derived guest **6** changes the energy landscape providing an alternative to the [2]-catenanes, prompting them to disassemble to form molecular square tetramers, which act as nanomolar hosts for the guest in water. The exceptionally high affinity of **7** provides further[11c] evidence for the ability of dynamic combinatorial chemistry to produce synthetic receptors with affinities approaching those of their biological counterparts.

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Supporting Information Available: Synthesis of **4**; experimental procedures for the DCLs and isolation of **7**; conditions for HPLC, LC−MS, MS−MS, DLS, and TEM analyses; HPLC and LC−MS data for the mixture of Figure 1; DLS data for the aggregates of **7·6**; estimation of the apparent host−guest binding constant using immobilized guest; complexation induced changes in the ^{1}H NMR resonances of the guest; details of the molecular modeling; ^{1}H NMR spectrum of **5**; amplification data for other guests. This material is available free of charge via the Internet at http://pubs.acs.org.

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