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Amplifying Different [2]Catenanes in an Aqueous Donor−Acceptor Dynamic Combinatorial Library

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We report here the controllable dynamic combinatorial synthesis of two different donor−acceptor (DA) [2]catenanes from a single pair of cysteine-derived dioxynaphthalene (DN) and naphthalenediimide (NDI) building blocks. Either catenane can be obtained in up to 50% yield from a disulfide dynamic combinatorial library (DCL) in water. As an extension of our earlier report,[1] this system highlights the ability of DCLs to generate unexpected and otherwise unattainable [2]catenanes.

Construction of topologically complex structures such as rotaxanes, catenanes, and knots often relies on lengthy syntheses and a precise understanding of the numerous noncovalent interactions involved in the designed 3D structure. In contrast, dynamic combinatorial chemistry (DCC) offers a selection approach in which the assembly process is directed by the system itself under thermodynamic control, so the structure with the lowest free energy is dominant.[2] Unexpected structures with complex geometries are sometimes selected by such dynamic combinatorial methods.[3] Major synthetic challenges can be bypassed through the use of DCC, and furthermore, our understanding of molecular interactions is advanced by studying these newly formed, unexpected complex systems.

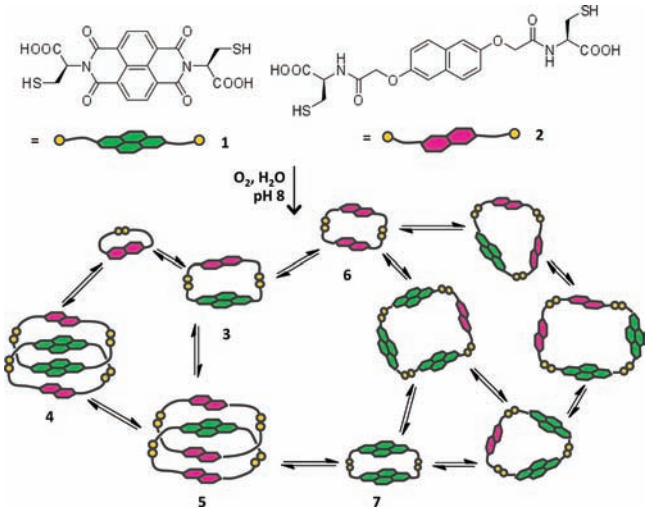

Figure 1. Building blocks NDI **1** and DN **2** and the resulting DCL. Only the species appearing in the discussion are numbered.

We showed recently that in an aqueous DA DCL, the yield of a [2]catenane can be enhanced by increasing the building-block concentration and solvent polarity and by introducing an appropriate template.[1] To further investigate the behavior of DA DCLs, NDI **1** (the acceptor)[4] and the new DN **2** (the donor) were studied under aqueous disulfide exchange conditions (Figure 1). Building block **2**, which was obtained in five simple steps from commercial chemicals [see the the Supporting Information (SI) for details], differs from the donor component of our first DCL DA [2]catenane[1] by the 2,6- versus 1,5-substitution pattern of the naphthalene core and the length of the linker between the cysteine and the DN core (two vs four carbon atoms, respectively).

Dissolving a mixture of **1** and **2** in 1:1 molar ratio in water at pH 8 followed by atmospheric oxidation produced the corresponding disulfide DCL. The DCL was stirred in a close-capped vial for at least 5 days at room temperature when equilibrium had been reached. HPLC/LCMS analyses revealed the presence of a range of macrocycles, including the DA dimer **3** (∼60%) and the [2]catenane **4** (∼10%) at equilibrium. The interlocked nature of **4** was initially recognized in the MS/MS study (Figure 2). Only fragments derived from the DA dimer **3** were observed, and therefore, tetrameric **4** must consist of two identical interlocked macrocycles, each composed of one donor and one acceptor unit.[5] ^{1}H NMR (500 MHz, 300 K, D_2O) analysis of a purified sample of **4** further confirmed the catenated structure, with upfield shifts of 0.48, 0.74, 0.68, and 0.85 ppm observed for the NDI and three DN aromatic signals, respectively, relative to the corresponding peaks of macrocycle **3** (Figure 3). The simplicity of the ^{1}H NMR spectrum of **4**, with one set of aromatic signals for both the NDI and DN units, indicates that **4** adopts a symmetrical conformation in solution with the electron-deficient NDIs stacked in the core of the catenane, similar to the analogous [2]catenane we reported previously.[1] This is the conformation that one would expect to minimize the repulsion between the electron-rich DN units.

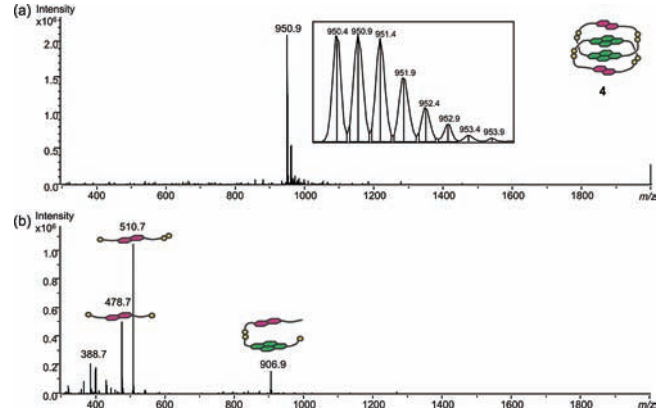

Figure 2. (a) ESI-MS(−) (inset: zoom of the doubly charged molecular ion) and (b) MS/MS molecular ion fragmentation spectra of **4**.

Increasing the ionic strength of the medium shifted the equilibrium toward **4**, which is likely to have the smallest average area of hydrophobic surface exposed to the solvent in comparison with the other components in the DCL.[6] In the presence of 1 M $NaNO_3$, catenane **4** was amplified more than 5-fold, to ∼55%, at the expense of **3** (∼10% vs 60% initially) (Figure 4). The use of other salts such as NaCl, KCl, and KNO_3 produced the same effect.

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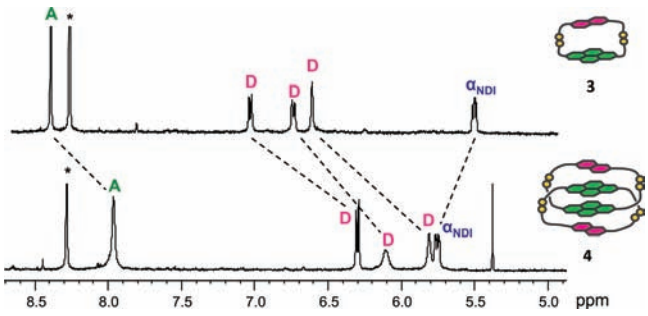

Figure 3. Partial ^{1}H NMR spectra (500 MHz, D_2O, 300 K) of **3** and **4**. Aromatic signals from NDI and DN are labeled with A and D, respectively. Formic acid residue from preparative HPLC is labeled as *.

Further analysis of this new DCL indicated the presence of another [2]catenane, **5**. This library member was present in an insignificant amount (<5%) in the original DCL and amplified to ~10% at high ionic strength. Electrospray ionization mass spectrometry (ESI-MS) and MS/MS analyses of **5** showed fragments of both heterodimer **3** and donor homodimer **6** (Figure 5). This indicates that **5** is an unusual [2]catenane, apparently the first of its kind, in which the DA dimer **3** is interlocked with the donor homodimer **6**.

In order to increase the amount of **5** in the library, we set up a DCL with a biased ratio of **1** and **2**. In a low-salt DCL with a starting **1/2** molar ratio of 1:3, **5** became a significant component in the DCL (~10%). Addition of 1 M $NaNO_3$ to this biased DCL further increased its abundance to ~50%, making **5** the major component. In a DCL with a composition poised midway between those of the two catenanes, i.e. **1/2** = 3:5, **4** and **5** represent ~45% and ~30% of the total DCL material in the presence of 1 M $NaNO_3$, corresponding to an approximately 75% interlocking efficiency (Figure 4e). Addition of DN- and NDI-based templates did not lead to amplification of either of the [2]catenanes, suggesting that the inner cavities of **4** and **5** are too tight for complexation (see the SI for details).

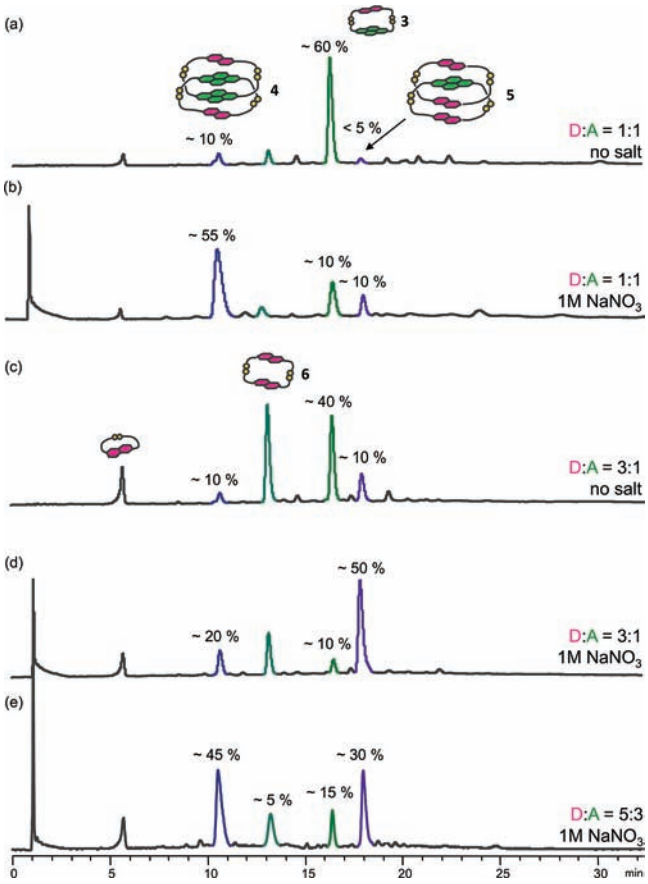

Figure 4. HPLC traces of DCLs under different conditions: (a) **2/1** = 1:1, without salt; (b) **2/1** = 1:1, with 1 M $NaNO_3$; (c) **2/1** = 3:1, without salt; (d) **2/1** = 3:1, with 1 M $NaNO_3$; (e) **2/1** = 5:3, with 1 M $NaNO_3$. Peaks corresponding to **4** and **5** are highlighted in deep blue and purple, respectively, and estimated yields are indicated above the peaks.

The dynamic nature of the catenane synthesis was demonstrated through re-equilibration studies. Addition of a substoichiometric amount of dithiothreitol to a mixture of separately pre-equilibrated DCLs of **1** and **2** reduced some of the disulfides and initiated the exchange (see the SI for details). Building-block interchange was evidenced by the formation of the DA macrocycles, including [2]catenanes **4** and **5**. The formation of both catenanes from separate donor and acceptor DCLs is also indicative that their formation can occur through the threading of linear dimers through cyclic dimers.

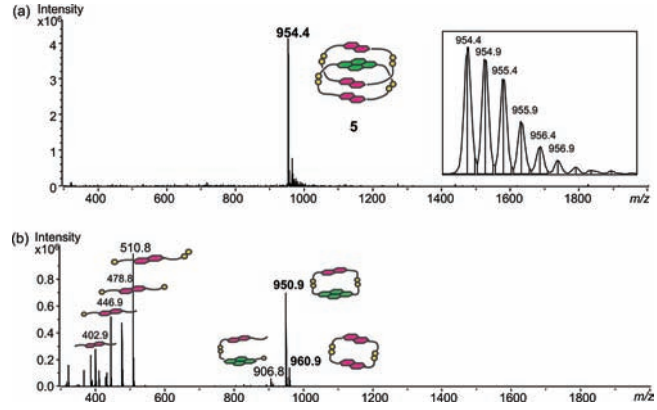

Figure 5. (a) ESI-MS(−) (inset: expansion of the doubly charged molecular ion) and (b) MS/MS molecular ion fragmentation spectra of **5**.

The molecular structure of the unusual three-donor-one-acceptor DA [2]catenane **5** was characterized by various NMR methods. ^{1}H NMR (500 MHz, 300 K, D_2O) analysis of **5** showed nine well-distinguished chemical environments for the DN protons, with the NDI resonances appearing as a pair of coupled doublets. The nine DN resonances can be unambiguously assigned to three groups of signals corresponding to the three different DN environments using correlation spectroscopy (COSY, Figure 6). The geometrical relationship of the four aromatic cores in **5** was probed by nuclear Overhauser effect spectroscopy (NOESY) at different temperatures. At 315 K, no NOEs were observed between different aromatic groups, suggesting that the intramolecular motions of the catenane, such as rocking and rattling, are rapid on the NMR time scale. Lowering the temperature to 298 K led to the appearance of cross-peaks between the NDI and DN for the most upfield proton signals. This indicates that one DN and the NDI are less mobile at this temperature and that they are in the inner position of the catenane. Further cooling to 288 K revealed additional NOEs, including those between the NDI and one of the two outer DNs as well as those between the inner DN and a different outer DN (Figure 7). The D−A−D−D stacking sequence of **5** was therefore established unequivocally. Comparison of the ^{1}H spectra of **3** and **6** showed that all of the aromatic signals of **5** are upfield-shifted by 0.11−0.91 ppm, providing further support that **5** is an interlocked structure analogous to **4**.

The occurrence of **5** is unusual and unexpected, as experience and logic would suggest that the stacking of π-rich donors should

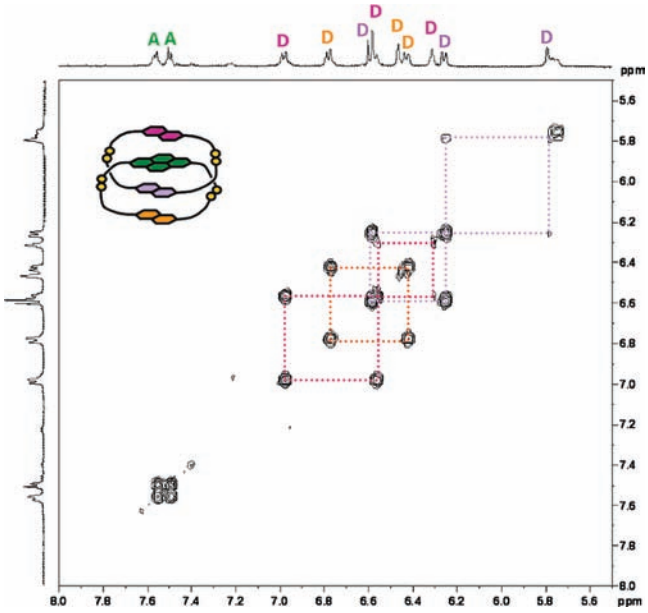

Figure 6. Partial COSY (500 MHz, D_2O, 300 K) spectrum of **5**. Signals from the NDI and DN are labeled with A and D, respectively, and the three sets of donor resonances are colored accordingly.

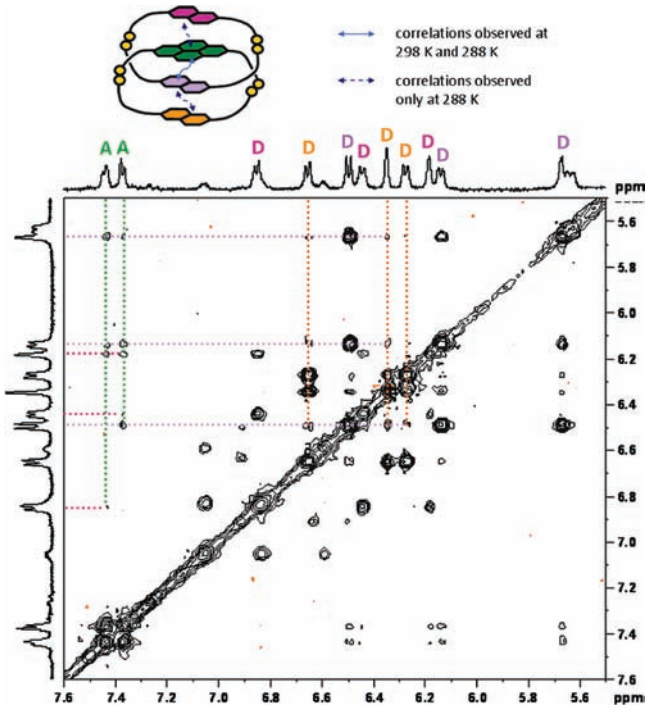

Figure 7. Partial NOESY (500 MHz, D_2O, 288 K, $d_8 = 1200$ ms) spectrum of **5**. Signals from the NDI and DN are labeled with A and D, respectively, and the three sets of donor resonances are colored accordingly.

result in repulsive interactions.[7] Rational designs of DA supramolecular systems, including DA [2]catenanes, therefore incorporate the most favorable alternating DA stacks in the final structures.[3c,8] Hydrophobic interactions seem to play a major role in the formation of **5**, favoring the catenation of **3** and **6** in a polar medium under thermodynamic control (similarly for the interlocking of **3** to form **4**). Stabilization from the D−A−D stacks, however, cannot be ignored, despite not being often considered as the driving force for the formation of other DA catenanes.[9] Indeed, hydrophobic interactions alone do not produce an all-donor [2]catenane from a DCL containing **2** only, irrespective of the amount of salt added.[10] Of course, other factors, such as the geometry and size of the hydrophobic surface as well as electrostatic interactions, could also be involved, but they are difficult to evaluate. Formation of other [2]catenanes with favorable DA stacks from the DCLs, such as D−A−D−A or A−D−A−A, is not possible because of the small cavity of the acceptor homodimer **7**, which prevents the threading of other aromatic molecules.[4]

In summary, we have described the dynamic combinatorial synthesis of two DA [2]catenanes that can be obtained in high yield: the maximum cumulative yield for both catenated species is ∼75%. These two catenanes display stacking structures that are different from those obtained from rational design and are unexpected. The dynamic combinatorial synthesis of these interlocked molecules is not only synthetically efficient from simple acyclic starting materials but also allows unanticipated structures to be selected, thereby complementing and advancing our understanding of molecular interactions.

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Supporting Information Available: Detailed synthetic and DCL setup procedures, HPLC/LCMS methods, and ESI-MS, MS/MS, UV−vis, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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