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Dynamic Combinatorial Donor−Acceptor Catenanes in Water: Access to Unconventional and Unexpected Structures

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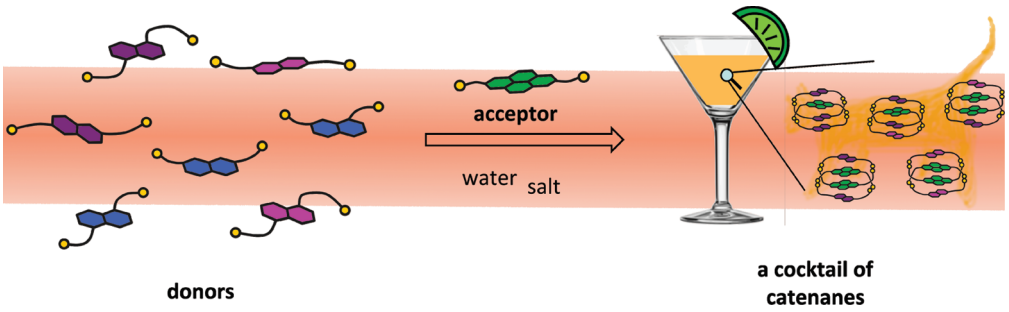

We describe here the assembly of new types of donor−acceptor [2]catenanes from dynamic combinatorial libraries (DCL) in water. These new catenanes contain both the donor and acceptor components in at least one of the interlocked rings, thereby possessing unusual and unexpected DAAD or DADD stacking sequences of the π units in their structures. The efficiency of the catenane assembly process can be enhanced by manipulating the DCL equilibrium in a variety of ways: adding a guest, changing the building block stoichiometries, or increasing the library concentration or the ionic strength of the solvent. The formation of catenanes and their constitutions are found to be dependent on subtle differences in the geometry, dimension, and flexibility of the donor building blocks.

Introduction

From pure laboratory curiosity to their promising potential in the development of molecular devices, catenanes have for many years been intriguing and challenging targets for chemists. With our increasing understanding of intermolecular interactions, a variety of templated catenane syntheses based on metal−ligand coordination,[1] hydrogen bonding,[2] hydrophobic interactions,[3] $\pi-\pi$ interactions,[4] and anion recognition[5] have been developed. As a result of their interlocked structure and the possibility of exerting control on their mechanical motions, catenanes represent a promising class of molecules for incorporation into functional materials,[6] particularly those based on electronically complementary units.

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Stoddart et al. have extensively studied donor−acceptor (DA) catenanes based on the cationic π-deficient paraquat and neutral π-rich systems such as hydroquinone, dioxynaphthalene (DN), and tetrathiafulvalene.[7] We have developed several catenane and rotaxane systems based on neutral acceptor units such as pyromellitic diimide or naphthalenediimide (NDI), initially in organic solvents.[8] Conventional wisdom and current understanding of donor−acceptor interactions have led until now to most of these catenanes being designed and synthesized with the apparently obvious and presumed most favorable alternate parallel arrangement of the π-rich and π-deficient units, to give a DADA stack in the final structure. However, is the apparently obvious conventional wisdom necessarily correct? If one designs and builds only DADA catenanes, then the feasibility and properties of structures with other configurations will remain unknown. We report here a detailed study of donor−acceptor catenane synthesis in water using the dynamic combinatorial approach and show that hitherto unknown and apparently unfavorable configurations are in fact readily accessible. These investigations led us to the discovery of the first nonclassical DA [2] catenanes containing two different donor moieties and allowed us to propose a decisional flowchart that predicts the formation of catenanes as a function of the donor geometry.

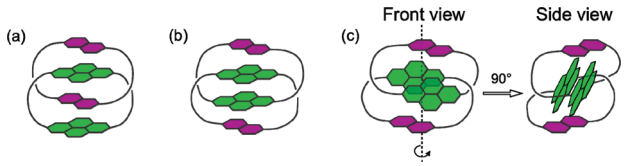

FIGURE 1. Schematic representation of DA [2]catenane in (a) the most usual DADA stacking, (b) the new DAAD stacking, and (c) the ⌶, Gemini, nonparallel conformation. Aromatic π-donor (DN) and π-acceptor (NDI) units are represented by purple and green cartoons, respectively.

We have recently described in preliminary form the use of donor−acceptor interactions in DCL systems[9] and their application in the dynamic combinatorial synthesis of catenanes in water.[10] To our surprise, a [2]catenane containing two interlocked DA dimers was assembled from an NDI and a DN dithiol building block. The interlocking of the two DA units means that the conventional DADA stacking order (Figure 1a) seen in most earlier catenanes is not possible in this molecule. Instead a new DAAD structure (Figure 1b) is formed; this structure is confirmed by NMR studies.[10c] We believe that the conventional DADA [2]catenane cannot form in this system because the small cavity of the acceptor dimer does not allow the threading of a donor moiety through it.[9b] Subsequent studies showed that slight structural modifications

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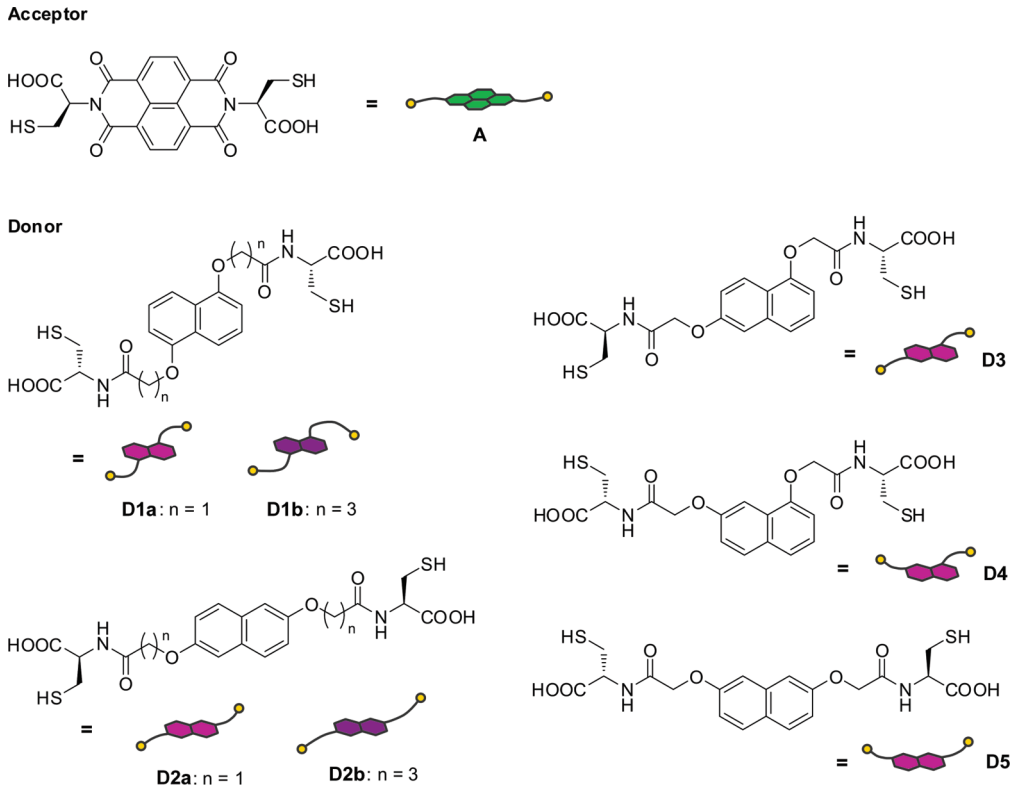

FIGURE 2. Acceptor (**A**) and donor (**D2**−**D5**) building blocks and their cartoon representations.

of the donor building block led to the formation of two new and surprising [2]catenanes. One of the catenanes contains an unexpected stack of three donor and one acceptor units (DADD), whereas the other (DAAD) is conformationally flexible: one of its abundant conformations exhibits an arrangement of the π units that is reminiscent of ♊, the astrological Gemini sign (Figure 1c).

To construct and control supramolecular structures based on donor−acceptor systems, a more detailed understanding of the scope, limitations, and geometries of the underlying donor−acceptor interactions is required. One of the most fruitful ways to uncover subtle supramolecular interactions is by dynamic combinatorial chemistry (DCC).[11] In DCC, building blocks are connected to each other through reversible bonds to form a pool of interconverting compounds, the dynamic combinatorial library (DCL). This reversibility allows the DCL to be under thermodynamic control, the most stable species being selected by the system according to the specific conditions. This selection approach is well-known for its ability to generate unexpected structures[12] that not only bypass the major synthetic challenges of conventional covalent chemistry but also can teach us something new about molecular interactions.

Following our initial communications on the behavior of DCLs containing either acceptors or donors[9] and on the assembly of donor−acceptor catenanes from aqueous DCLs,[10] we now describe the effect of subtle structural changes of the donor component on the resulting DCLs. Donor (D) building blocks with different substitution patterns and linker chain lengths (Figure 2) were prepared and studied in DCLs in the presence of the same NDI acceptor (A) building block. An efficient one-step assembly of donor−acceptor catenanes containing different donor components is also described. Detailed studies were performed on the solution structure and the conformations of the new catenanes.

Results and Discussion

All of the building blocks used in this study follow the same design, with a central flat hydrophobic aromatic surface bearing two cysteine-decorated hydrophilic side arms. While the role of the central aromatic cores is to engage in donor−acceptor and hydrophobic interactions, the amino acid component provides both the thiol functionality for reversible disulfide exchange and the carboxylate group for water solubility. Seven DN-derived donor building blocks were prepared and studied. According to the length of the alkyl chain linking the cysteine with the DN core, these building blocks can be divided into "short" (**D1a**, **D2a**, **D3**, **D4**, and **D5**) and "long" (**D1b** and **D2b**) groups. Five different positional isomers of the "short" donor were synthesized for exploring the effect of the geometry of the building block on catenane assembly in a DCL. The two "long"

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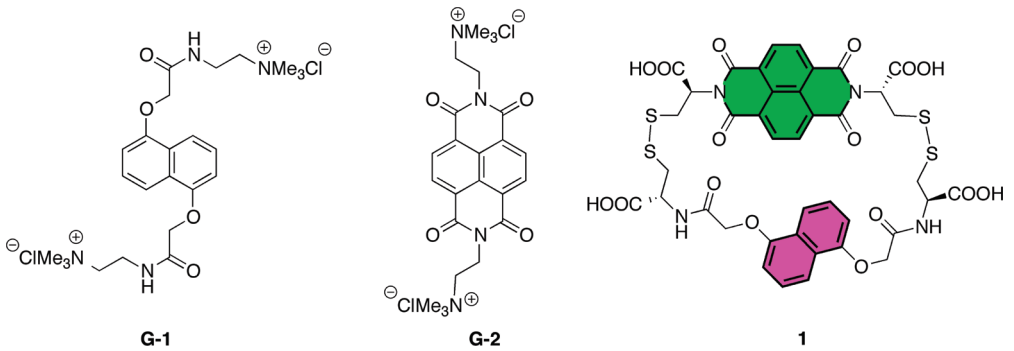

FIGURE 3. Structures of DN- and NDI-guests **G-1** and **G-2** and of heterodimer **1**.

donors were used for the study of the effect of building block flexibility and dimension. The "long" donor building blocks were prepared only for the symmetrical and most commonly used 1,5- and 2,6-DN.

A, **D1a**, **D1b**, **D2a**, and **D2b** were synthesized as previously described.[9,10] Isomeric **D3**, **D4**, and **D5** were prepared by a similar procedure to that for **D1** and **D2** (see Experimental Section and Supporting Information for details). A typical DCL was set up by dissolving a mixture of the NDI acceptor and the appropriate DN donor in water to give a total building block concentration of 5 mM, followed by adjustment of the pH to 8 using aqueous NaOH. The library solution was air-oxidized, equilibrated in a capped vial for 5 days by which time it had reached a stationary state, and analyzed by HPLC/LCMS.

DCL of A and D1a. HPLC and LCMS analyses of the DCL solution prepared from the acceptor **A** and the "short" 1,5-DN donor **D1a** showed the DA dimer **1** (Figure 3) to be the major library member with over 90% yield at stationary state (see Supporting Information). A small amount of the donor monomer was also observed (ca. 5%), but no NDI-only disulfide macrocycles, although the DN and NDI components are present in equimolar quantities and therefore the amount of DN monomer should be matched by an NDI-only species.[13] The high yield of **1** (90%) in the DCL suggests that the mutual recognition of the donor−acceptor building blocks is highly efficient. This library was at thermodynamic equilibrium as demonstrated by reinitiating the disulfide exchange with 15% dithiothreitol (DTT, Figure 4) in a new library composed of a 1:1 mixture of a pre-equilibrated acceptor only DCL with a pre-equilibrated **D1a** only DCL. The library obtained after 15 min of mixing in the presence of DTT mirrored the DCL set up from the unoxidized building blocks.[14] Addition of the DN donor guest **G-1** or the NDI acceptor guest **G-2** as potential templates (Figure 3) did not lead to any change in the library composition.[15] Increasing the solvent ionic strength, which promotes hydrophobic effects and encourages catenane formation[16]

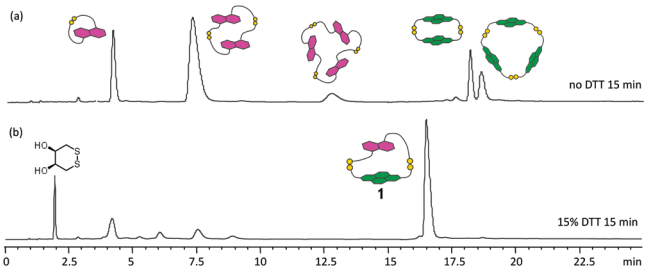

FIGURE 4. HPLC analysis of a 1:1 v/v mixture of 5 mM DCLs equilibrated for 5 days of **A** and of **D1a** after 15 min without (a) and with (b) DTT. Absorbance was recorded at 292 nm.

(see below) also has no influence on the DCL composition. This suggests that the hypothetical larger structures that can be in principle created using **A** and **D1a** are thermodynamically unfavorable relative to the obviously very stable and entropically favorable heterodimer. The cavity of this heterodimer is, as in the case of the NDI dimer, too small to allow threading of an aromatic group, precluding the formation of a simple [2]catenane.

DCL of A and D1b. If the inability to produce a catenane from a DCL of **D1a** and **A** is related to the size of the macrocycles, replacing the donor component with the slightly longer homologue **D1b** should result in catenane formation in the library. A diverse DCL containing at least seven macrocycles was obtained from **A** and **D1b** (1:1 molar ratio, 5 mM, Figure 5).[10c] To our delight, one of the library members (**Cat-1**) was identified as a [2]catenane by mass spectrometry.[17] ESI-MS (negative ion) showed that the doubly charged molecular ions of both **Cat-1** and macrocycle **2** have an m/z of 1007.1, corresponding to a tetramer containing two of each of the building blocks. Different daughter ions, however, were observed in the fragmentation spectra of these two isomers. In the tandem MS spectrum of **Cat-1**, the largest fragment observed has an m/z of 963.0, corresponding to the mass of a decarboxylated heterodimer **3**. No other homodimeric fragments were observed, indicating that **Cat-1** is a [2]catenane consisting of two identical interlocked dimers **3**, each dimer being formed from one of each of the donor and the acceptor units. On the other hand, trimeric fragments (m/z = 1575.1, 1511.1, 1448.1, 1403.0) and heterodimeric but no homodimeric fragments were found in the MS/MS spectrum of **2**, showing that it has a cyclic structure with an alternate [-D-A-D-A-] arrangement.

(13) The absence of an NDI-only library member is probably due to the small quantity and the elution profile that resulted in a small broad signal in the chromatogram, which is masked by the background noise of the UV trace.

(14) A second experiment using the isolated heterodimer **1** as starting point for DCL indicated also that **1** is the thermodynamic and not the kinetic product. See Supporting Information for details.

(15) It was shown previously that the use of guests **G-1** and **G-2** can induce amplifications of the NDI- and DN-only macrocycles in DCLs from the respective building blocks. See ref 9 for details.

(16) (a) Fujita, M.; Ibukuro, F.; Hagihara, H.; Ogura, K. *Nature* **1994**, *367*, 720. (b) Fujita, M.; Ibukuro, F.; Ogura, K. *J. Am. Chem. Soc.* **1995**, *117*, 4175.

(17) (a) Liu, J.; West, K. R.; Bondy, C. R.; Sanders, J. K. M. *Org. Biomol. Chem.* **2007**, *5*, 778. (b) Poulsen, S.-A.; Gates, P. J.; Cousins, G. R. L.; Sanders, J. K. M. *Rapid Commun. Mass Spectrom.* **2000**, *14*, 44.

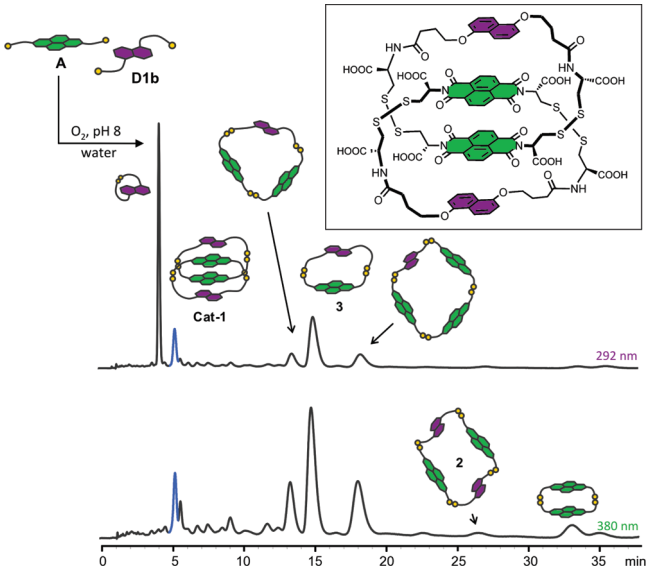

FIGURE 5. HPLC analysis of a DCL from **A** and **D1b** (1:1 molar ratio, 5 mM). The catenane structure is shown in the inset, and its peak is highlighted at 5 min. Absorbance was measured at 292 and 380 nm.

To take full advantage of the dynamic nature of the catenane synthesis, various strategies were used to increase the yield of **Cat-1** in the DCL. One obvious way to promote the formation of **Cat-1** at the expense of smaller products is to exploit Le Chatelier's principle and increase the concentration of the DCL. At 2 mM of total building block concentration (1:1 **A** and **D1b**), no catenane was detected; at 5 mM building block concentration, the catenane corresponds to ca. 10% of the DCL material; the yield of **Cat-1** further increases to ca. 25% at a total concentration of 10 mM. Another way to favor the catenane formation is to increase the solvent ionic strength. Since more hydrophobic surface is buried in the compact catenane than in its constituent dimers **3**, the equilibrium should be shifted toward the formation of the former in a solvent of higher ionic strength. A series of DCLs at different $NaNO_3$ content was prepared. Consistent with our expectation, it was found that the ratio of **Cat-1** in the DCL increases with increasing ionic strength, with ca. 40% of the DCL material observed as the catenane in the library containing 1 M $NaNO_3$. The use of other inorganic salts such as NaCl, KCl, and K_2SO_4 produced a similar effect. This indicates that the increase in concentration of **Cat-1** is due to the increase of the solvent's ionic strength rather than specific interactions with the inorganic ions. Assembly of **Cat-1** in the DCL can also be templated by the donor guest **G-1**. Amplification of **Cat-1** from ~10% to ~15% was observed in the DCL templated by **G-1** (5 mM of equimolar amount of building blocks, 2.5 mM of guest). This observation not only shows that the catenane can be a host for **G-1** but also supports the proposed DAAD π-stacked conformation, whereby intercalation of the donor guest in the catenane central cavity completes the alternate DADAD stacking sequence. On the other hand, no catenane was detected when **G-2** was used as a template. Even though the assembly of **Cat-1** is not favorable in the DCL containing **G-2**, it does not necessarily mean that **Cat-1** does not interact with this guest, but rather that there are other library members that are better receptors for **G-2** and the equilibrium is shifted toward their formation.[18]

(18) A recent simulation study showed that if there are interactions between library members of a DCL, then depending on the strength of the interactions, the relative abundance of the members may be amplified, diminished, or unchanged in the library by a template. See: Orrillo, A. G.; Furlan, R. L. E. *J. Org. Chem.* **2010**, *75*, 211.

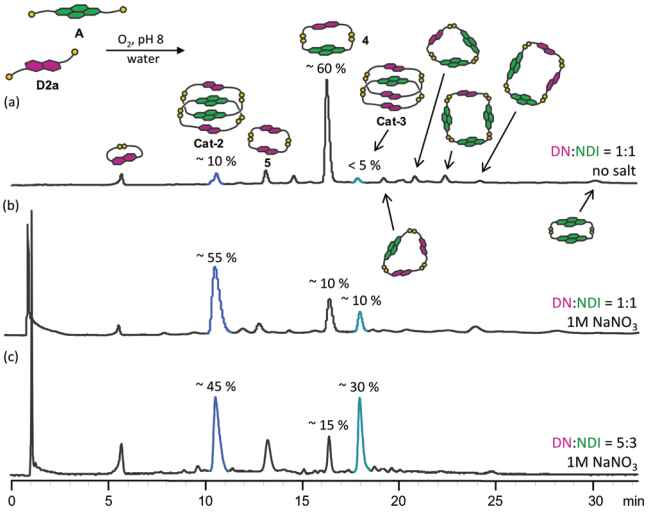

FIGURE 6. HPLC analysis of 5 mM DCLs from **D2a** and **A** in molar ratio of (a) 1:1, (b) 1:1 with 1 M $NaNO_3$, (c) 3:1 with 1 M $NaNO_3$, and (d) 5:3 with 1 M $NaNO_3$. Peaks corresponding to catenanes are highlighted. Absorbance was measured at 260 nm.

DCL of A and D2a. Next, we studied the effect of the geometry of the donor building block on catenane production. In contrast to its 1,5-isomer **D1a**, the 2,6-isomer **D2a** combined with the acceptor **A** gives a diverse DCL containing a range of macrocycles from dimer to tetramer (Figure 6). Surprisingly, the two [2]catenanes **Cat-2** and **Cat-3** were identified in this DCL.[10b] As with catenane **Cat-1**, the interlocked nature of **Cat-2** and **Cat-3** was first revealed by their MS and MS/MS spectra (Figure 7). Analogously to **Cat-1**, **Cat-2** contains two identical interlocked dimers **4**, with each dimer containing both the donor and the acceptor units. By contrast, catenane **Cat-3** is both unusual and unexpected. It contains three donor units and only one acceptor unit: a heterodimer **4** interlocks with a donor homodimer **5** to form a DADD π stacking sequence in its catenated structure. As described above, the proportion of **Cat-2** and **Cat-3** in the DCL can be increased by increasing the solvent polarity. The two catenanes, however, were not amplified by the template **G-1**, presumably because they have smaller cavities than **Cat-1**. The efficiency of catenane assembly in the DCL can also be enhanced by using a building block stoichiometry that favors the formation of both the catenanes. In a DCL prepared with 5:3 mol equiv of **D2a** and **A** (5 mM total concentration, 1 M $NaNO_3$), **Cat-2** and **Cat-3** represent 45% and 30% of the library material, respectively, corresponding to 75% total catenation efficiency.

As interactions between electron-rich donors are repulsive,[19] the formation of catenane **Cat-3** is surprising. For most reported donor−acceptor catenanes, donor−acceptor interactions are not considered as the main driving force for their formation.[8f,20] Hydrophobic effects seem to play an important

(19) Hunter, C. A.; Sanders, J. K. M. *J. Am. Chem. Soc.* **1990**, *112*, 5525.
(20) Houk, K. N.; Menzer, S.; Newton, S. P.; Raymo, F. M.; Stoddart, J. F.; Williams, D. J. *J. Am. Chem. Soc.* **1999**, *23*, 897.

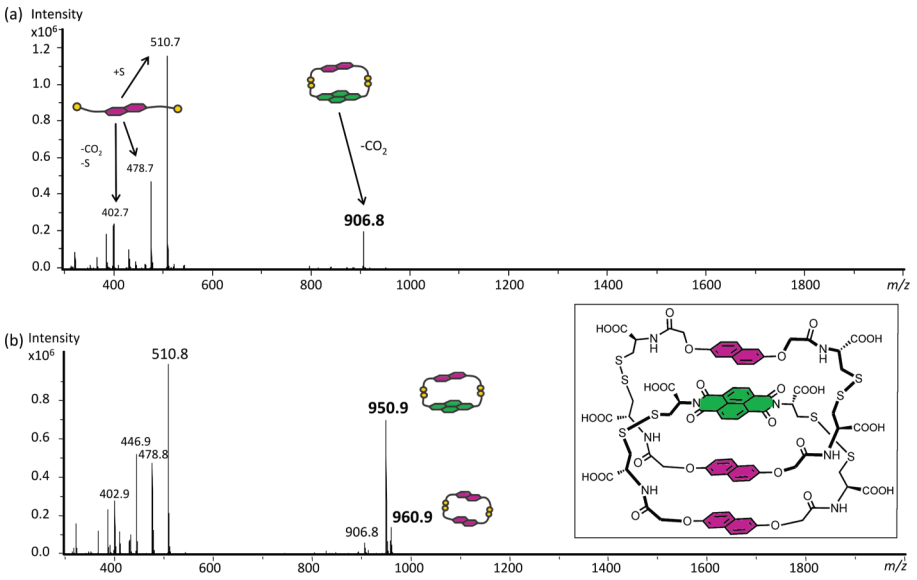

FIGURE 7. Tandem MS fragmentation spectra of molecular ion of (a) **Cat-2** and (b) **Cat-3**. A fragmentation amplitude of 0.3 V was used. The structure of the DADD catenane, **Cat-3**, is presented in the inset.

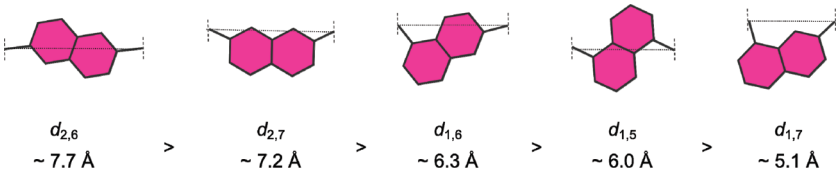

FIGURE 8. Comparison of the dimensions of all of the positional isomers of DN used in this study. The interoxygen distances represent averages of all of the corresponding structures present in Cambridge Structural Database v. 5.31.

role in the formation of **Cat-3** in water. However, no catenane was produced in DCLs containing only the donor building blocks even under high ionic strength condition (5 mM of **D2a**, or 2.5 mM each of **D1a** and **D2a**, 1 M $NaNO_3$).[21] Stabilization from the DAD stacks, therefore, cannot be excluded.

Comparing **D1a** and **D2a**, two very different DCLs with the same acceptor **A** were obtained, although the two donors possess identical thiol side arms. The difference in the geometry of the donor building blocks (1,5- vs 2,6-positions of the naphthalene) is therefore responsible for the difference in DCL distribution. First, because of the different geometry of the two donors, the catenane formation from the DA dimer **1** may be unfavorable because of steric clash of the flexible straps in the catenane. The steric repulsion is likely to be relieved in the case of the isomeric **4** because the disulfide side chains now have a different orientation with respect to the DA units. Second, because the side arms lie on the long axis of the naphthalene, the disulfide macrocycles from **D2a** are slightly larger than those from **D1a** (Figure 8). This slight expansion may allow catenation of the dimer **4** for which **1**, its isomer, may be just too tight. Third, the difference in the stereo- and electronic properties of the two donors also affects the stacking with the NDI acceptor, which in turn alters the stability and relative ratio of different macrocycles

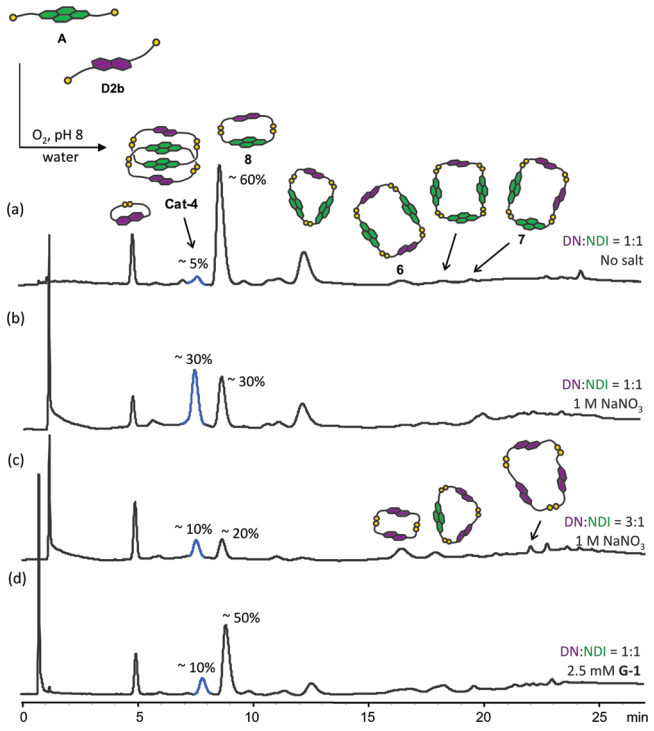

FIGURE 9. HPLC analysis of 5 mM DCLs from **D2b** and **A** in molar ratio of (a) 1:1, (b) 1:1 with 1 M $NaNO_3$, (c) 3:1 with 1 M $NaNO_3$, and (d) 1:1 with 2.5 mM of **G-1**. Peaks corresponding to **Cat-4** are highlighted. Absorbance was measured at 260 nm.

(21) A DCL of 5 mM of **D1a** in the presence of 1 M $NaNO_3$ did not produce an all-donor catenane either (see Supporting Information). Mixed DCLs of both 1,5- and 2,6-DN building blocks were used to maximize the possibility of assembly of an all-donor catenane.

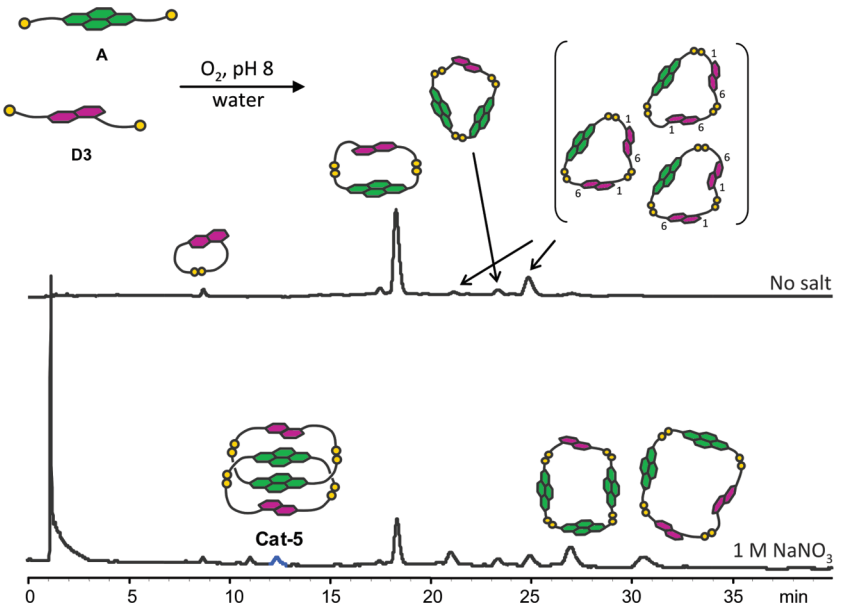

FIGURE 10. HPLC analysis of DCLs of **A** and **D3** (1:1 molar ratio, 5 mM) in (a) the absence of salt and (b) the presence of 1 M $NaNO_3$. The [-D-A-D-] trimer is illustrated in the three possible isomers with the connecting positions on the DN labeled. Absorbance was measured at 283 nm.

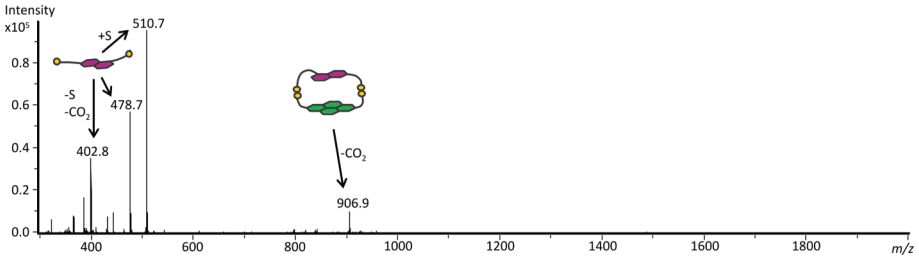

FIGURE 11. MS/MS fragmentation spectra of the molecular ion of **Cat-5**.

in the DCL.[22] Similar arguments govern the formation of [2]catenanes from the other "short" DN building blocks used in this study (see below).

DCL of A and D2b. Parallel to the comparison between **D1a** and **D1b**, the corresponding DCL of **D2b** was studied. In the DCL from **A** and **D2b** (1:1, 5 mM, Figure 9), in addition to several monomer, dimers, and trimers, four tetramers were detected at stationary state. MS showed that three of these four tetramers (**Cat-4**, **6**, and **7**) are composed of two each of the building blocks. The three isomers showed different fragmentation behavior and were differentiated by tandem MS: molecular ion of **Cat-4** directly fragmented into the dimer **8**, and therefore is a [2]catenane. NMR studies showed that **Cat-4** has a ♊, the astrological Gemini sign, arrangement of the π units as one of the observed conformations along with the parallel DAAD stacked one.[10a] Compounds **6** and **7** showed sequential fragmentations, consistent with the cyclic [-D-A-D-A-] and [-D-D-A-A-] structures, respectively, as suggested by the presence of homodimeric daughter ions in the MS/MS spectrum of the latter. As with its isomer **Cat-1**, **Cat-4** was amplified by the guest **G-1** and under high ionic strength condition (1 M $NaNO_3$).

Unlike the DCL from the homologue **D2a**, only one catenane containing two of each of the DA units was produced from the library of the more flexible **D2b**. No DADD catenane analogous to **Cat-3** was detected in the DCL even with 3 equiv of the donor building block under high ionic strength (Figure 9c). Presumably, the favorable interactions that lead to the formation of this catenane are outweighed by the increased entropic cost of incorporating three of the flexible donor building blocks in an interlocked structure, and therefore its formation is unfavorable in the thermodynamically controlled DCL.

DCL of A and D3. The 1,6-DN, **D3**, may be viewed in terms of connectivity as "intermediate" between the 1,5- and 2,6-DNs (**D1a** and **D2a**). In the DCL (1:1 **A** and **D3**, 5 mM), four library members (one cyclic monomer, one cyclic dimer and two cyclic trimers) were observed at stationary state (Figure 10, MS/MS data Figure 11).[23] The diversity of the DCL increased with the solvent ionic strength, when seven different macrocycles including the [2]catenane **Cat-5**[24] were observed. Amplification of the [-D-A-D-] cyclic trimer at

(22) Asakawa, M.; Ashton, P. R.; Boyd, S. E.; Brown, C. L.; Gillard, R. E.; Kocian, O.; Raymo, F. M.; Stoddart, J. F.; Tolley, M. S.; White, A. J. P.; Williams, D. J. *J. Org. Chem.* **1997**, *62*, 26.

(23) As a result of the asymmetry of the 1,6-DN, there are different structural isomers for macrocycles containing more than one donor unit.

(24) As a result of the directionality of the DA dimer, there should be a pair of diastereoisomers of **Cat-5**. The small quantity of the compound in the DCL, however, limited its efficient preparation and purification in sufficient amount for further studies.

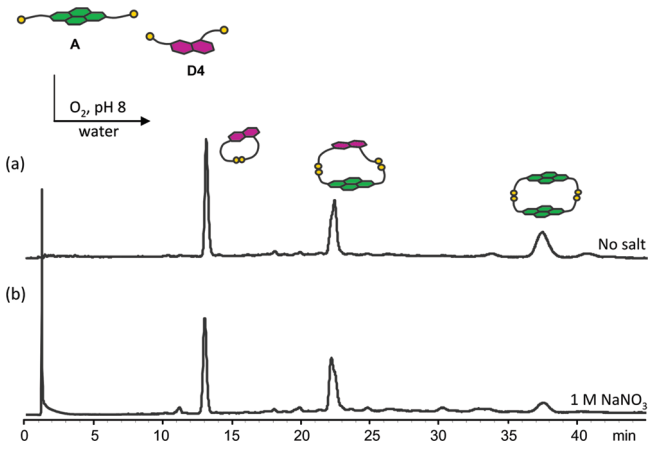

FIGURE 12. HPLC analysis of DCL of **A** and **D4** (1:1 molar ratio, 5 mM) in (a) the absence of salt and (b) the presence of 1 M $NaNO_3$. Absorbance was measured at 292 nm.

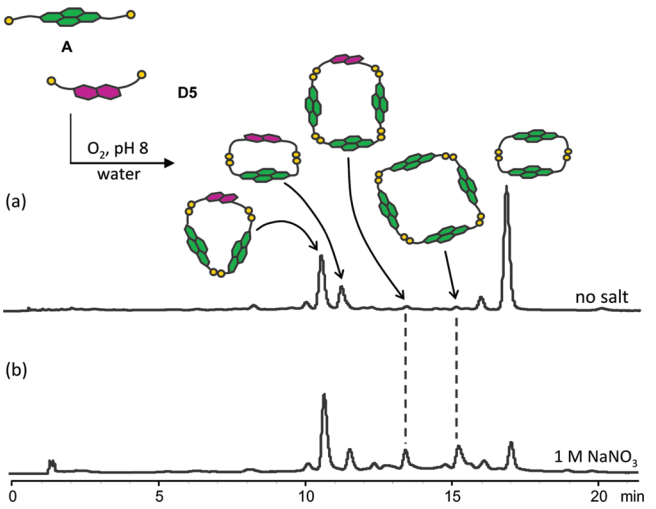

FIGURE 13. HPLC analysis of DCL of **A** and **D5** (1:1 molar ratio, 5 mM) in (a) the absence of salt and (b) the presence of 1 M $NaNO_3$. Absorbance was measured at 380 nm.

ca. 22 min was also observed, probably indicating that this trimer can fold and adopt a more compact and stable structure under high ionic strength condition.

While the DCL of **D1a** and **A** is limited to two library members with no catenane and that of **D2a** and the same NDI building block is diverse with 10 library members containing catenanes **Cat-2** and **Cat-3**, the "intermediate" **D3** produced a DCL with an intermediate diversity (4 and 7 library members at low and high salt content, respectively) and an intermediate propensity for catenane formation, i.e., only under conditions of high ionic strength.

DCL of A and D4. Similar to the DCL containing **D1a**, the heterodimer was identified as the major macrocycle containing both building blocks, in a DCL of the 1,7-DN, **D4**, and **A** (1:1 **D4**:**A**, 5 mM). No catenane or significant change in library composition was observed under high ionic strength conditions (1 M $NaNO_3$, Figure 12). The yield of the DA dimer was around 50%, the remaining material in the DCL being present as the donor monomer and acceptor dimer. The closer spatial arrangement of the two thiol side chains in the 7-DN perhaps results in less ring strain in the corresponding cyclic monomer, and therefore the favorable interactions present in the mixed macrocycles do not provide enough energy to compensate for the entropic costs of intermolecular reactions.

DCL of A and D5. The DCL derived from the 2,7-DN, **D5**, is again quite different: in a low-salt DCL (1:1 **D5**:**A**, 5 mM), the most abundant donor−acceptor macrocycle at stationary state is the [-A-D-A-] cyclic trimer, instead of the dimer seen in all the other DCLs under the same conditions (Figure 13). Donor−acceptor interactions play a less significant role in this library as only around one-third of the library material is incorporated into donor−acceptor macrocycles, the remaining components being found in the donor monomer and acceptor dimer (see Supporting Information). No catenane was formed by increasing the solvent ionic strength, but amplifications of the acceptor tetramer and the [-A-D-A-A-] tetramer were observed.

DCL of A and Mixture of Ds. The ability to generate more diverse catenane structures from DCLs was investigated by mixing more than one donor building block in a DCL; in particular, catenanes containing more than one type of donor unit were possible products. Such catenanes usually require a lengthy synthesis in which different donor units are incorporated stepwise. The selective binding of the acceptor to different donors is used as a handle for controlling molecular motions in such systems.[4a,e−h,7b,7i,7k−7m] To facilitate catenane formation and analytical efficiency, we selected to prepare the DCLs from a mixture of **A**/**D1b**/**D2a** and **A**/**D2a**/**D2b** building blocks. The three donor building blocks were chosen for their efficient catenane formation, and the combination of donors of different masses in a library enabled easy LCMS characterization, avoiding difficulties of creating isomers.

In a DCL containing the 1,5- and 2,6-DNs with respectively the "long" and "short" linkers (1:1:1 of **A**/**D1b**/**D2a**, 5 mM), a diverse range of macrocycles including the previously described catenanes **Cat-2** and **Cat-3** from the "short" 2,6-DN were obtained (Figure 14). No catenane containing **D1b** was observed in this low-salt DCL, presumably due to the higher entropic cost of incorporating the flexible building block into an interlocked structure. Increasing the ionic strength by addition of 1 M $NaNO_3$ to the library resulted in the formation of two new catenanes **Cat-6** and **Cat-7**, both containing all three types of building blocks.[25] Catenane **Cat-6** has two of each of the acceptor and donor units and is composed of two interlocked DA dimers, one from the "long" 1,5-DN and the other from the "short" 2,6-DN. On the other hand, **Cat-7** is another DADD [2]catenane, with a donor homodimer from the "short" 2,6-DN interlocked with a DA dimer from the "long" 1,5-DN.

The catenane **Cat-6** containing two different DN building blocks was isolated from the DCL and purified for NMR characterization. The asymmetry of this system provides an eloquent set of ^{1}H and COSY spectra, allowing detailed conclusions to be drawn about the structure (Figure 15).

In the DCL prepared from **A** and the two 2,6-DNs, the "short" **D2a** and the "long" **D2b** (1:1:1, 5 mM), no significant amounts of interlocked library members were observed under low-salt conditions (Figure 16). However, addition of 1 M

(25) Molecular modeling studies were carried out at molecular mechanics level using the Amber99 and OPLS forcefields. See Supporting Information for details.

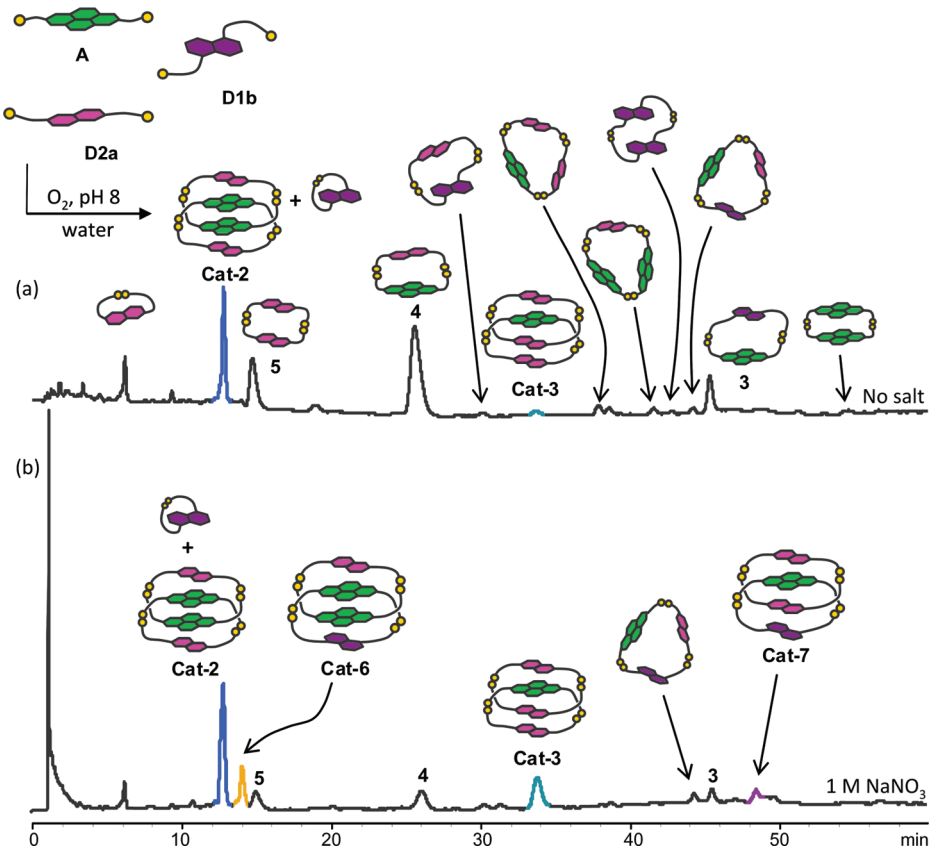

FIGURE 14. HPLC analysis of a 5 mM DCL of **A**, **D1b**, and **D2a** in 1:1:1 molar ratio in (a) the absence of salt and (b) the presence of 1 M $NaNO_3$. Absorbance was measured at 260 nm. Peaks corresponding to catenanes are highlighted.

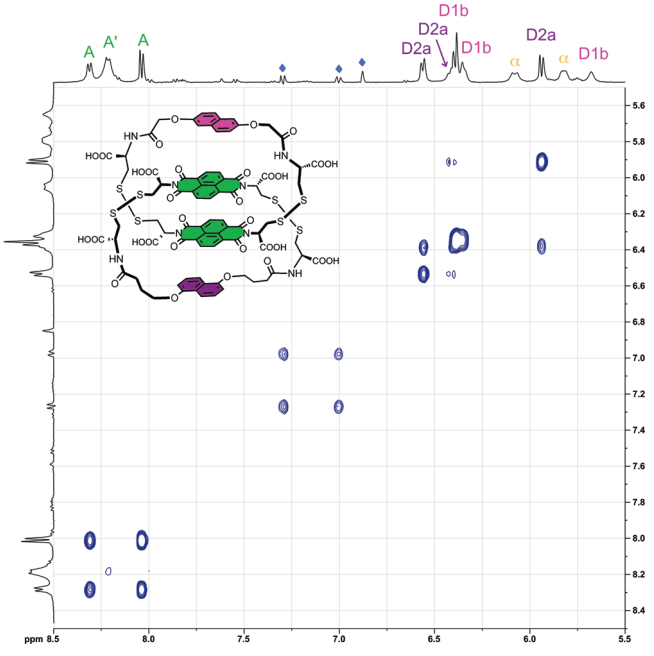

FIGURE 15. Partial COSY spectrum (500 MHz, D_2O, 317 K, 5.5−8.5 ppm) of **Cat-6**. Signals from a DA dimer [-**A**-**D1b**-] impurity are labeled by a blue diamond. The structure of the DADD catenane, **Cat-6**, is presented in the inset.

$NaNO_3$ led to the amplifications of five different catenanes. Three of these (**Cat-2**, **Cat-3**, and **Cat-4**) are derived from only one kind of donor building block and have been described above. The new DAAD [2]catenane **Cat-8** is composed of two different interlocked DA dimers, one from **D2a** and the other from **D2b**, as indicated by tandem MS (Figure 17). **Cat-9** is again another DADD [2]catenane, with a donor homodimer from the "short" 2,6-DN (**D2a**) interlocked with the DA dimer from the "long" **D2b**.[25]

The successful formation of the four [2]catenanes **Cat-1**−**4** described in previous sections indicates that the dimers **3**, **4**, **5**, and **8** are suitable for interlocking; therefore the formation of the four new mixed-DNs catenanes **Cat-6**−**9** is perhaps predictable as these represent the other possible combinations arising from interlocking of these dimers. No catenanes from only the "long" **D1b**, **D2b**, or both were observed in either DCLs, indicating the relatively higher entropic cost of interlocking two of these flexible dimers in the DCLs. Because of the lack of efficient determination of precise abundances of different macrocycles in these complex libraries, it was not possible to determine whether the distribution of the catenanes is statistical or biased toward some of the catenated structures. Nevertheless, the efficient formation of such asymmetrical catenanes, which otherwise requires stepwise functionalization, in just one step using a dynamic combinatorial method has been demonstrated, highlighting the attraction of thermodynamically controlled synthesis.

Conclusion

The efficient assembly of nine donor−acceptor [2]catenanes in aqueous dynamic combinatorial libraries from simple

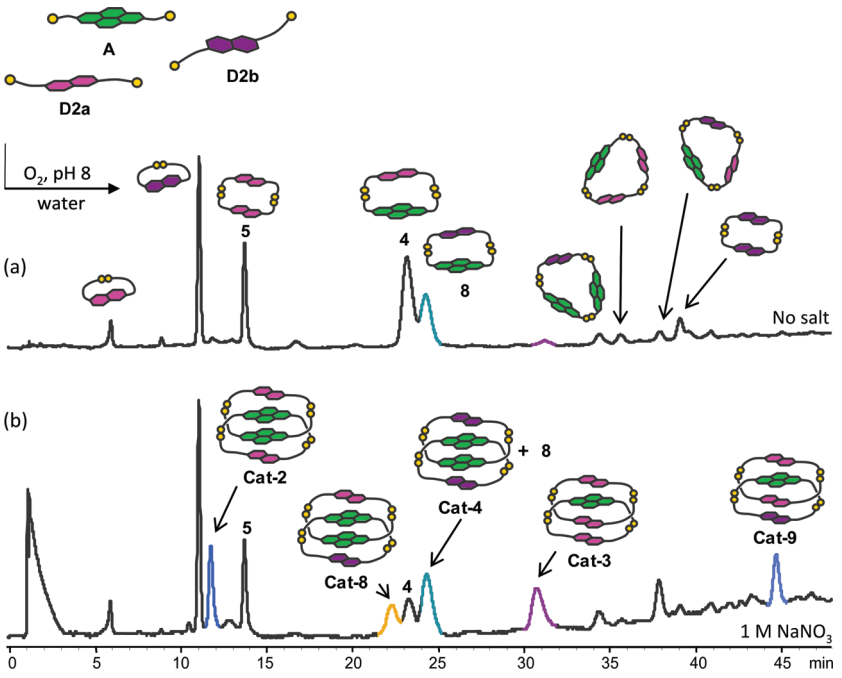

FIGURE 16. HPLC analysis of a 5 mM DCL of **A**, **D2a**, and **D2b** in 1:1:1 molar ratio in (a) the absence of salt and (b) the presence of 1 M $NaNO_3$. Absorbance was measured at 260 nm. Peaks corresponding to catenanes are highlighted.

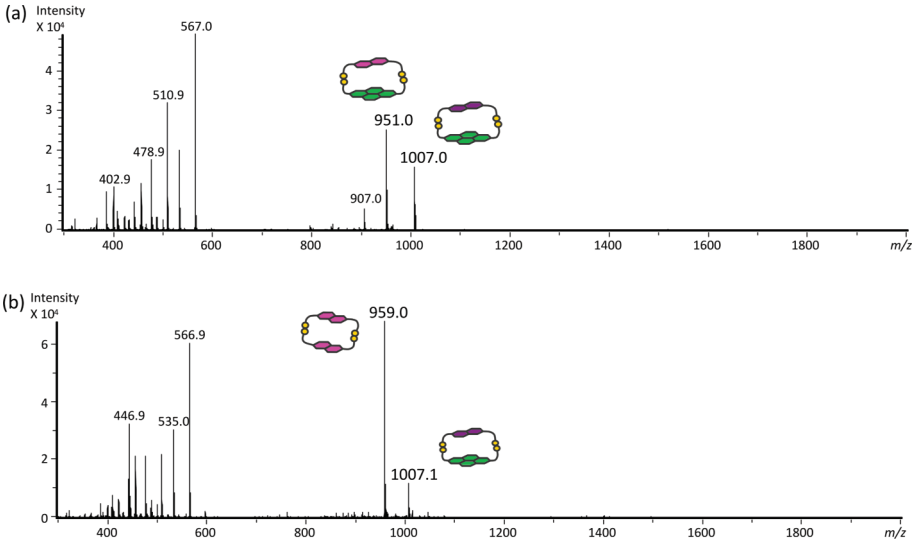

FIGURE 17. Tandem MS spectra of (a) **Cat-8** and (b) **Cat-9**.

acyclic dithiol building blocks has been described. None of these catenanes has the conventional alternating DADA structure, possessing instead either a DAAD or DADD arrangement of the π units. The yield of these interlocked structures can be enhanced by increasing solvent ionic strength through addition of an inorganic salt to the aqueous DCLs. Some of the flexible catenanes (**Cat-1** and **Cat-4**) can also be templated by an appropriate guest. By systematically varying the substitution positions and the linker length of the donor building blocks, we discovered that subtle changes in geometry, dimension, and flexibility of the building block can have significant effects on the DCL diversity, product type, and properties of the resulting catenanes. A fine balance of all these structural features has to be taken into account when designing building blocks for successful catenane assembly in DCL. For the "short"-DN building blocks used in this study a decisional flowchart can be used to describe the DCL behavior of these π-rich isomers when mixed with the same NDI building block (Figure 18). The catenane formation is predicated by presence in the library of either the heterodimer (for the DAAD structures) and donor homodimer (for the DADD ones). The presence of an acceptor unit, **A**, which forms a very tight homodimer that does not allow threading through its cavity is required for the formation of [2]catenanes displaying unconventional arrangements of the π units. We are currently investigating how acceptor moieties with longer side chains interact with the donor building blocks described here.

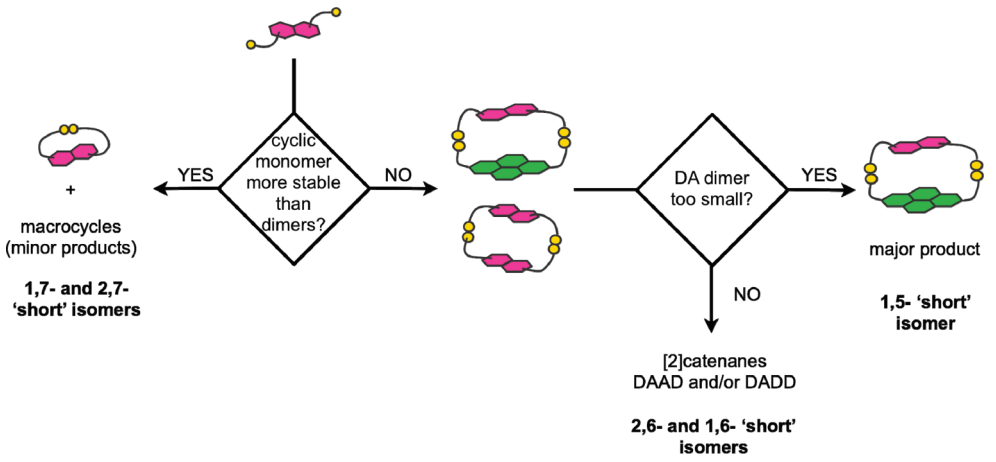

FIGURE 18. Decisional flowchart describing the determinants for [2]catenane formation for libraries containing one "short"-**DN** and one **NDI** building blocks.

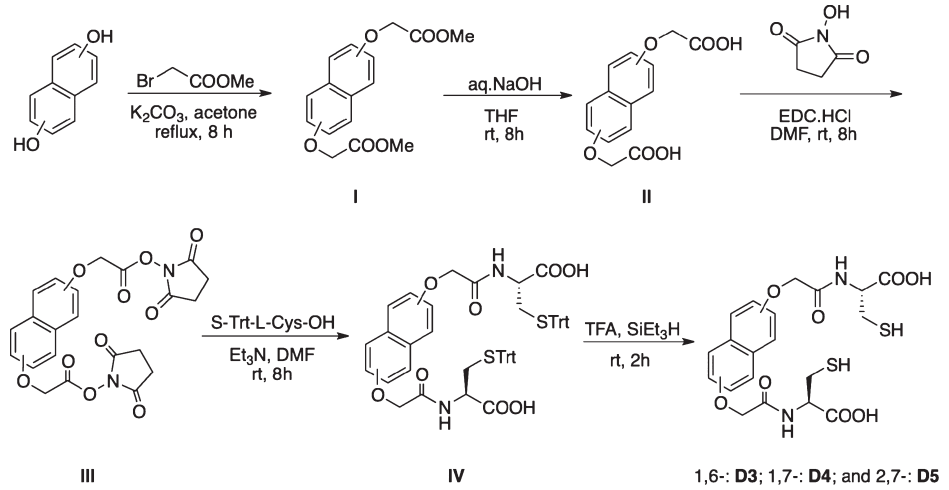

FIGURE 19. Synthesis of building blocks **D3**, **D4**, and **D5** (precursors **I**, **II**, **III**, and **IV** follow the same nomenclature, in which **I3** is the 1,6-, **I4** is the 1,7-, and **I5** is the 2,7-isomer).

The dynamic combinatorial synthesis of catenanes we have discussed here not only represents an efficient alternative for the preparation of these topologically interesting and complex molecules but also highlights the discovery of unexpected structures and advances and complements our understanding of weak donor−acceptor interactions.

Experimental Section

General Procedures for the Synthesis of the DN Methyl Ester I3, I4, and I5 (see Figure 19)[26]. To a solution of dihydroxynaphthalene in acetone (200 mL) were added finely ground K_2CO_3 and methyl bromoacetate. The mixture was heated to reflux for 8 h. The resulting solution was filtered, and Et_2O (100 mL) was added and washed successively with 1 M HCl (50 mL), water (50 mL), and brine (50 mL). Solvents from the organic layer were removed, and the crude solid was used in the next step without further purification. For actual amounts and yields, please see Supporting Information.

General Procedures for the Synthesis of the DN Acid II3, II4, and II5. To a solution of the methyl ester **I** in THF (150 mL) was added 0.5 M NaOH (200 mL). The mixture was vigorously stirred in room temperature for 8 h and poured into 1 M HCl (200 mL). The precipitate formed was collected by filtration, washed with Et_2O, and dried. For actual amounts and yields, please see Supporting Information.

General Procedures for the Synthesis of the Active Ester III3, III4, and III5. A mixture of the DN-acid **II** and *N*-hydroxylsuccinimide was dissolved in DMF (50 mL) and cooled with an ice bath. EDC·HCl was added to the solution, and the mixture was stirred in the melting ice bath for 15 min. Stirring was continued at room temperature for a further 8 h. Volatiles were removed by a rotary evaporator. The residue was redissolved in acetone (10 mL) and added dropwise to a stirring solution of 1 M HCl (200 mL). The precipitate formed was collected by filtration and dried *in vacuo*. For actual amounts and yields, please see Supporting Information.

General Procedures for the Synthesis of the Trityl Protected DNs IV3, IV4, and IV5. To a mixture of the active ester **III** and *S*-trityl-L-cysteine in DMF (50 mL) was added Et_3N. The solution was stirred under N_2 for 8 h at room temperature. Solvent was removed, and the residue redissolved in acetone (10 mL). The acetone solution was added dropwise to a vigorously stirred solution of 1 M HCl (200 mL). The yellowish-brown solid was collected by filtration and dried. For actual amounts and yields, please see Supporting Information.

(26) Hagihara, S.; Gremaud, L.; Bollot, G.; Mareda, J.; Matile, S. *J. Am. Chem. Soc.* **2008**, *130*, 4347.

General Procedures for the Synthesis of Building Blocks D3, D4, and D5. To a Schlenk tube charged with the trityl protected compound **IV** was added degassed TFA under N_2. The solution was stirred at room temperature for 1.5 h, triethylsilane was added, and the mixture was stirred for an additional 30 min. Volatiles were removed *in vacuo*. The yellow solid left was washed with Et_2O (50 mL).

Synthesis of D3. Quantities as follows. **IV3**: 1.0 g, 1.03 mmol. TFA: 10 mL, 130 mmol. $SiEt_3H$: 0.8 mL, 5 mmol. Yield: 0.33 g, 65%. Mp: 87−90 °C (dec). ^{1}H NMR (400 MHz, DMSO-d_6, 300 K): δ (ppm) 8.40 (d, J = 6.0 Hz, 1 H, NH), 8.38 (d, J = 5.8 Hz, 1 H, NH), 8.24 (d, J = 9.2 Hz, 1 H, DN), 7.40−7.34 (m, 2 H, DN, DN), 7.31 (d, J = 2.4 Hz, 1 H, DN), 7.26 (dd, J = 2.6 Hz, 9.2 Hz, 1 H, DN), 6.81 (dd, J = 1.5 Hz, 7.1 Hz, 1 H, DN), 4.76 (s, 2 H, OCH_2), 4.71 (s, 2 H, OCH_2), 4.56−4.49 (m, 2 H, α), 3.00−2.86 (m, 4 H, β, SH). ^{13}C{^{1}H} NMR (125.74 MHz, DMSO-d_6, 300 K): δ (ppm) 171.5, 167.8, 135.5, 126.9, 123.7, 120.3, 120.0, 117.8, 107.5, 104.2, 67.2, 66.8, 54.2, 54.1, 25.5, 25.4. HRMS (ESI+) calcd for $C_{20}H_{23}N_2O_8S_2$ $[M + H]^+$ (m/z) 483.0896, found 483.0926.

Synthesis of D4. Quantities as follows. **IV4**: 0.6 g, 0.62 mmol. TFA: 6 mL, 78 mmol. $SiEt_3H$: 0.4 mL, 2.5 mmol. Yield: 0.17 g, 55%. Mp: 113−115 °C (dec). ^{1}H NMR (400 MHz, DMSO-d_6, 300 K): δ (ppm) 8.63 (d, J = 8.8 Hz, 1 H, NH), 7.92 (d, J = 8.8 Hz, 1 H, NH), 7.84 (d, J = 9.0 Hz, 1 H, DN), 7.49 (d, J = 8.3 Hz, 1 H, DN), 7.45 (d, J = 2.6 Hz, 1 H, DN), 7.30 (t, J = 8.2 Hz, 1 H, DN), 7.27 (dd, J = 2.6 Hz, 9.0 Hz, 1 H, DN), 7.03 (d, J = 7.6 Hz, 1 H, DN), 4.84 (d, J = 16.4 Hz, 2 H, OCH_2), 4.73−4.62 (m, 4 H, OCH_2, α, α), 3.48 (dd, J = 3.5 Hz, 14.8 Hz, 1 H, β), 3.11 (dd, J = 5.0 Hz, 14.1 Hz, 1 H, β), 2.87 (dd, J = 9.4 Hz, 14.2 Hz, 1 H, β). ^{13}C{^{1}H} NMR (125.74 MHz, DMSO-d_6, 300 K): δ (ppm) 171.4, 167.7, 155.4, 152.5, 129.7, 129.4, 125.7, 125.3, 123.9, 120.8, 120.7, 120.0, 118.8, 102.3, 101.4, 67.3, 66.8, 54.2, 541, 25.5, 25.4. HRMS (ESI+) calcd for $C_{20}H_{23}N_2O_8S_2$ $[M + H]^+$ (m/z) 483.0896, found 483.0912.

Synthesis of D5. Quantities as follows. **IV5**: 0.5 g, 0.51 mmol. TFA: 5 mL, 65 mmol. $SiEt_3H$: 0.4 mL, 2.5 mmol. Yield: 0.16 g, 63%. Mp: 94−96 °C (dec). ^{1}H NMR (400 MHz, DMSO-d_6, 300 K): δ (ppm) 12.94 (br, 2 H, COOH), 8.38 (d, J = 8.0 Hz, 2 H, NH), 7.79 (d, J = 8.9 Hz, 2 H, DN), 7.19 (d, J = 2.5 Hz, 2 H, DN), 7.11 (dd, J = 8.9 Hz, 2.5 Hz, 2 H, DN), 4.68 (s, 4 H, OCH_2), 4.51 (dt, 4.6 Hz, 7.7 Hz, 2 H, α), 2.98−2.93 (m, 2 H, β), 2.90−2.83 (m, 2 H, β), 2.43 (t, J = 8.5 Hz, 2 H, SH). ^{13}C{^{1}H} NMR (100.62 MHz, 5:1 acetone-d_6/DMSO-d_6, 300 K): δ (ppm) 168.4, 157.2, 136.6, 130.0, 117.1, 108.1, 67.9, 54.6, 26.4. HRMS (ESI+) calcd for $C_{20}H_{23}N_2O_8S_2$ $[M + H]^+$ (m/z) 483.0896, found 483.0911.

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Supporting Information Available: Detailed procedure for building block synthesis and library preparations, HPLC/LCMS methods, and mass and NMR spectra of isolated macrocycles. This material is available free of charge via the Internet at http://pubs.acs.org.