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Exploring the Formation Pathways of Donor−Acceptor Catenanes in Aqueous Dynamic Combinatorial Libraries

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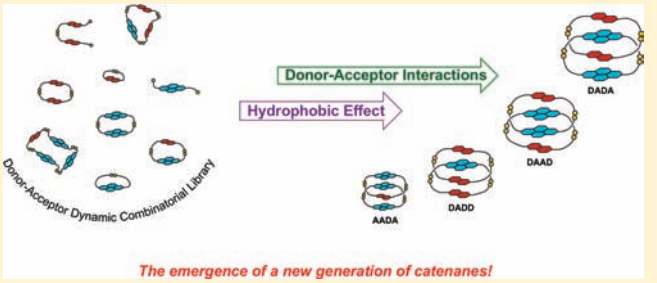
Supporting Information

ABSTRACT: The discovery through dynamic combinatorial chemistry (DCC) of a new generation of donor−acceptor [2]catenanes highlights the power of DCC to access unprecedented structures. While conventional thinking has limited the scope of donor−acceptor catenanes to strictly alternating stacks of donor (D) and acceptor (A) aromatic units, DCC is demonstrated in this paper to give access to unusual DAAD, DADD, and ADAA stacks. Each of these catenanes has specific structural requirements, allowing control of their formation. On the basis of these results, and on the observation that the catenanes represent kinetic bottlenecks in the reaction pathway, we propose a mechanism that explains and predicts the structures formed. Furthermore, the spontaneous assembly of catenanes in aqueous dynamic systems gives a fundamental insight into the role played by hydrophobic effect and donor−acceptor interactions when building such complex architectures.



1. INTRODUCTION

We present here the discovery of new donor−acceptor [2]catenanes assembled from simple electron-donor (D) and electron-acceptor (A) building blocks using disulfide chemistry. Moving on from our previous dynamic combinatorial syntheses of catenanes with unusual DAAD and DADD stacking arrangements, we now describe the formation of catenanes with DADA and unprecedented AADA stacks under the same conditions. These four types of catenanes form a complete set and can be viewed as a whole new generation of donor−acceptor [2]catenanes (Figure 1). More importantly, perhaps, we outline a mechanism that explains and predicts the formation of each of these catenanes, which turn out to be kinetic bottlenecks on the reaction pathway.

Interactions between aromatic molecules are mainly described in term of electrostatic interactions between electron-deficient and electron-rich π-systems.[1] The complementary alternating stack of donor and acceptor aromatic moieties, leading to the optimum electronic overlap, has always been thought to be the most favorable arrangement. Alternating D−A stacks adopt a parallel and compact face-to-face geometry and have been extensively used as scaffolds for complex structures such as foldamers,[2] rotaxanes,[3] and catenanes.[4]

The formation of stacked structures reduces the total solvent-exposed surface area, so efficient desolvation of the aromatic systems plays a crucial role in this process. Iverson et al.[5] showed that the effective strength of donor−acceptor interactions is closely related to the solvent environment: association constants between the electron-rich 1,5-dialkoxynaphthalene (DN) and the electron-deficient 1,4,5,8-naphthalenetetracarboxylic diimide (NDI) vary with the polarity of the solvent, from ca. 2 M^{-1} in chloroform to ca. 2000 M^{-1} in water. As expected, alternating donor−acceptor interactions are clearly dominant over weaker acceptor−acceptor (K_a < 1 M^{-1} in chloroform, ca. 200 M^{-1} in water) or donor−donor interactions (K_a < 1 M^{-1} in chloroform, ca. 20 M^{-1} in water).[5] From these results it is generally believed that the strong solvophobic component of aromatic interactions can be used to dramatically increase the magnitude of electrostatic interactions and that the alternating D−A stack is favored in any solvent.

In the light of these numbers, it is perhaps surprising that in recent years A−A and D−D stacks have spontaneously emerged from the self-assembly of donor and acceptor units in polar media.[6−8] In these cases, the solvophobic effect seems to overcome, at least partially, pure electrostatic interactions between donor and acceptor units, although it remains difficult to evaluate to what extent the two phenomena cooperate and/or compete. To our knowledge, only three examples of these unconventional architectures have been reported in the literature. The first contribution to this field was that of Li and co-workers, who reported the synthesis of an AAAA [2]catenane based on perylenediimide.[6] Most recently, Fujita et al. showed that discrete ADDA and AADA stacks could be obtained within a box-shaped cavity.[7] We reported the dynamic combinatorial synthesis of DAAD and DADD catenanes[8] at the expense of

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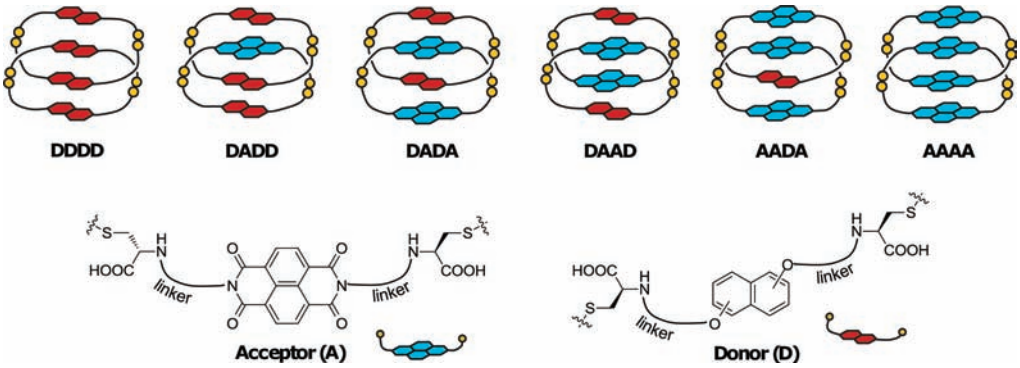

Figure 1. Possible arrangements of the π units of a donor−acceptor [2]catenane. Aromatic π-donor and π-acceptor are represented by red and blue cartoons, respectively.

the expected DADA structure. According to the D−A stacking model, the DADD stack would be unlikely to be formed in significant quantities in competition with the more obvious D−A stacks. By expanding the range of building blocks, we now open the possibility of accessing a larger variety of donor−acceptor catenanes, such as DDDD, DADD, DADA, DAAD, AADA, or AAAA (Figure 1).

Each catenane presented in Figure 1 represents a major synthetic challenge for the classical approach but can, in principle, be achieved using dynamic combinatorial chemistry (DCC).[9,10] We show here that we were able to obtain four out of the six possible arrangements, with the AAAA and DDDD stacks remaining elusive at present. The size and geometry of the building blocks influences dramatically the composition of the dynamic combinatorial libraries (DCLs) such that it allows a precise control over the type of catenane formed on the basis of its structural requirements.

The new generation of donor−acceptor [2]catenanes reported in this work not only constitutes a success in the synthesis of topologically complex targets but it may also open new horizons for the use of catenanes as molecular machines, as one of the DAAD catenanes was recently shown to exhibit two switchable conformations, with a parallel arrangement of the π-units or a Gemini-sign-like conformation.[8b] Hence, these catenanes present a major advance in understanding, designing, and using complex architectures based on donor and acceptor units. These systems also represent a complex environment in which both thermodynamic and kinetic factors play a role in determining the composition of the library.

We present first a proposed mechanistic pathway for the synthesis of the donor−acceptor [2]catenanes which rationalizes our earlier results and predicts the composition of new libraries. The remainder of this paper explores and confirms these predictions experimentally.

2. MECHANISM OF FORMATION OF DONOR−ACCEPTOR CATENANES IN AQUEOUS DCLS

Contrary to our initial thoughts,[8] the dithiol building blocks used in this work are fully oxidized into disulfide and stop exchanging before the libraries reach thermodynamic equilibrium.[11] The kinetics of formation of the library members consequently play a major role, allowing us to map out the pathways leading to the different types of catenanes. For each of these pathways, we can trace the intermediates involved and evaluate the role played by hydrophobic and donor−acceptor interactions in each step of the catenation process.

We propose that the formation of catenanes in aqueous donor−acceptor DCLs occurs through three successive steps: formation of a dimer, threading of a linear species into the dimer's cavity, and closing of the catenane. The key elements in the formation of catenanes are the donor−acceptor interactions and the polarity of the medium, manipulated by the addition of salt.

In pure water, DCLs composed of donor and acceptor building blocks do not usually lead to the formation of catenanes, although traces can be observed in some isolated cases (see the Supporting Information). This indicates that in water, in the time frame of the libraries' oxidation, the sum of donor−acceptor and hydrophobic interactions is insufficient to bring stacks of building blocks into the close proximity necessary for catenation.

In high salt[8,12] (1 M $NaNO_3$) libraries, the increased polarity of the medium promotes the decrease of solvent-exposed hydrophobic surfaces; this is achieved by either a building block or a linear oligomer[14] sliding into the hydrophobic cavity of a preformed cyclic dimer. This threaded species is the first intermediate in the formation of a catenane. Besides the threading mechanism described above, it can also be formed by the templated cyclization of a linear precursor in the presence of a complementary linear template.[13] If the donor−acceptor interactions have a significant role, then the [−A−A−] cyclic dimer should preferentially bind a donor over an acceptor unit; similarly, the [−D−D−] and the [−A−D−] cyclic dimers are more likely to interact with an acceptor rather than a donor moiety. Each of the three favorable threaded species corresponds to the initial step of a different pathway for formation of catenanes, pathways I, II, and III, respectively (Figure 2).

Once a threaded complex is formed through pathway I, II, or III, linking a fourth building block completes the catenane formation. The factors involved in the closing step are more difficult to predict, but electrostatic interactions are expected to play a lesser role than in the threading step: in the closing step, there are only two π surfaces interacting, while in the threading step there are four. The catenanes can then be closed with either an acceptor or a donor building block, depending on which event leads to the maximum stabilization. Therefore, each pathway should lead to a characteristic pair of catenanes: DADD and DADA catenanes from pathway I, DAAD and AADA catenanes from pathway II, and DADA and AADA catenanes from pathway III (Figure 2).

This mechanism predicts that no homocatenane (AAAA or DDDD) will be formed in this system: although the formation of catenanes is dominated overall by the hydrophobic effect, donor−acceptor interactions play a determining role in the first step of threading. However, further increasing the polarity of our

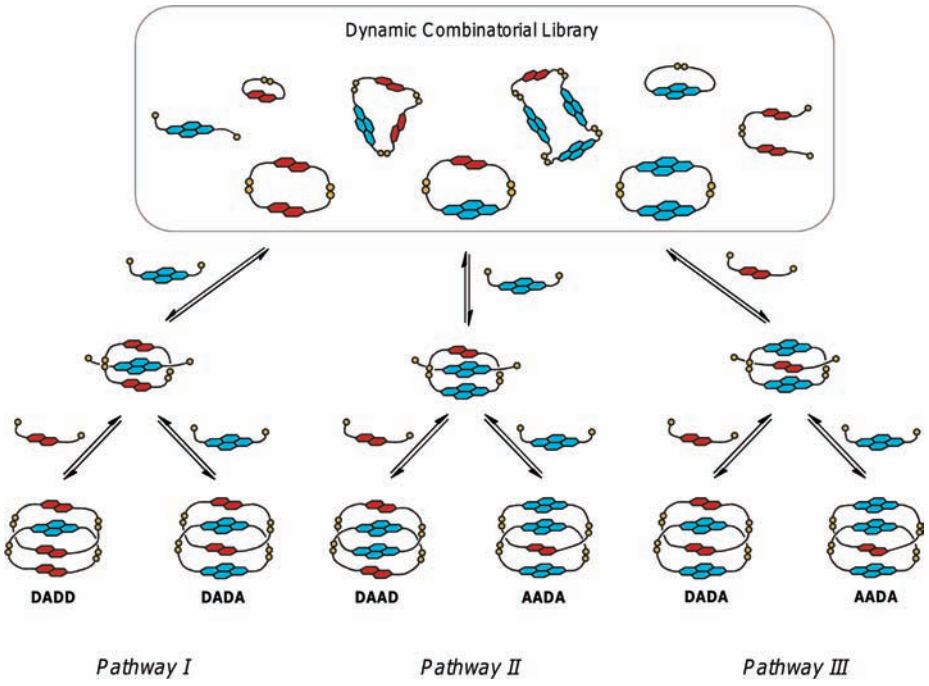

Figure 2. Proposed mechanism for formation of dynamic combinatorial donor−acceptor [2]catenanes. For clarity, the mechanistically equivalent possibilities of threading a linear oligomer through each cyclic dimer or of forming complexes between linear dimers before cyclization are not shown.

medium or increasing the surface area of the hydrophobic core[6] could potentially lead to the formation of homocatenanes.

On the basis of this set of intermediates and interactions involved in the mechanism, it is possible to identify the parameters allowing efficient formation of the catenanes in the libraries. First, the [−A−D−], [−D−D−] and [−A−A−] dimers constitute the cornerstone for the formation of any catenane, so their abundance in the DCL is paramount. To form a catenane, a dimer needs to fulfill two requirements: it must be formed efficiently in the library and be large enough to accommodate an aromatic thread. Catenane formation will be favored when an optimum overlap of the aromatic moieties favors both donor−acceptor and hydrophobic interactions in the two steps of threading and closing. This happens when each ring forming the catenane is tight; when the rings are too flexible, the enthalpic gain is low and cannot compensate for the entropic costs derived from the catenation process, so the catenane is not formed.

We can take advantage of these factors by designing carefully the libraries, not only to form selectively one type of catenane but also to select the pathway by which it will be formed.

3. RESULTS AND DISCUSSION

All building blocks in this study (Figure 3) are constructed on a similar design: a large hydrophobic π-surface, either NDI as electron-acceptor (A) or DN as electron-donor (D), to which are attached two cysteine-terminated hydrophilic side chains of various lengths. The cysteine-derived side chains provide easy access to building blocks of different sizes, along with the thiol necessary for the initiation of disulfide exchange and carboxylic acids for water solubility.

The donor building blocks **D1a**,[13a] **D1b**,[8d] **D2a**,[8c] and **D2b**[8b] were synthesized following previously reported procedures. They differ in the substitution pattern of the central core (1,5- or 2,6-) and the length of the side chains. Syntheses of the acceptor building blocks NDI(Cys)$_2$ (**A1**),[13b,15] NDI(GlyCys)$_2$ (**A2**),[13a] and NDI(GSH)$_2$ (**A5**)[13a] have already been published, while NDI(DMGlyCys)$_2$ (**A3**) and the asymmetrically substituted NDI(Cys)(GSH) (**A4**) were prepared using similar methods (see the Supporting Information). The acceptor building blocks differ in the length, hydrophilicity, and bulk of the side chains. Screening of libraries containing different combinations of these donor and acceptor building blocks allows us to investigate the extent to which all of these parameters play a role in the formation of catenanes.

Aqueous disulfide DCLs were created by dissolving the building blocks to a total concentration of 5 mM in water at pH 8. The pH was adjusted with aqueous NaOH, and the libraries were stirred under air in capped vials to allow oxidation of the thiol building blocks. After 5 days, the libraries were fully oxidized and analyzed by HPLC and LC−MS. Absorbance was recorded at the optimum wavelength for each building block: acceptor units at 383 nm and donor units at 292 nm (1,5-substituted **D1a** and **D1b**) or 260 nm (2,6-substituted **D2a** and **D2b**).

3.1. Exploring Pathway I. The efficient formation of a [−D−D−] dimer required in pathway I (Figure 4) is achieved by using donor building blocks with short side chains.[8a,8c,13a] The short side chains of the building block result in a [−D−D−] dimer whose small cavity size enables a relatively good interaction with an acceptor moiety, favoring the threading mechanism described above. The geometry of the 1,5-isomer **D1a** favors the formation of the [−D−] cyclic monomer over the [−D−D−] dimer and does not lead to the formation of any catenane (see the Supporting Information). On the other hand, the 2,6-isomer **D2a** forms a stable [−D−D−] dimer, which leads to the formation of catenanes through pathway I. Hence, all the following libraries were prepared with the **D2a** donor building block and different acceptor building blocks or mixtures of acceptor building blocks (see the Supporting Information). To summarize the results described in this section, three DADA catenanes were identified,

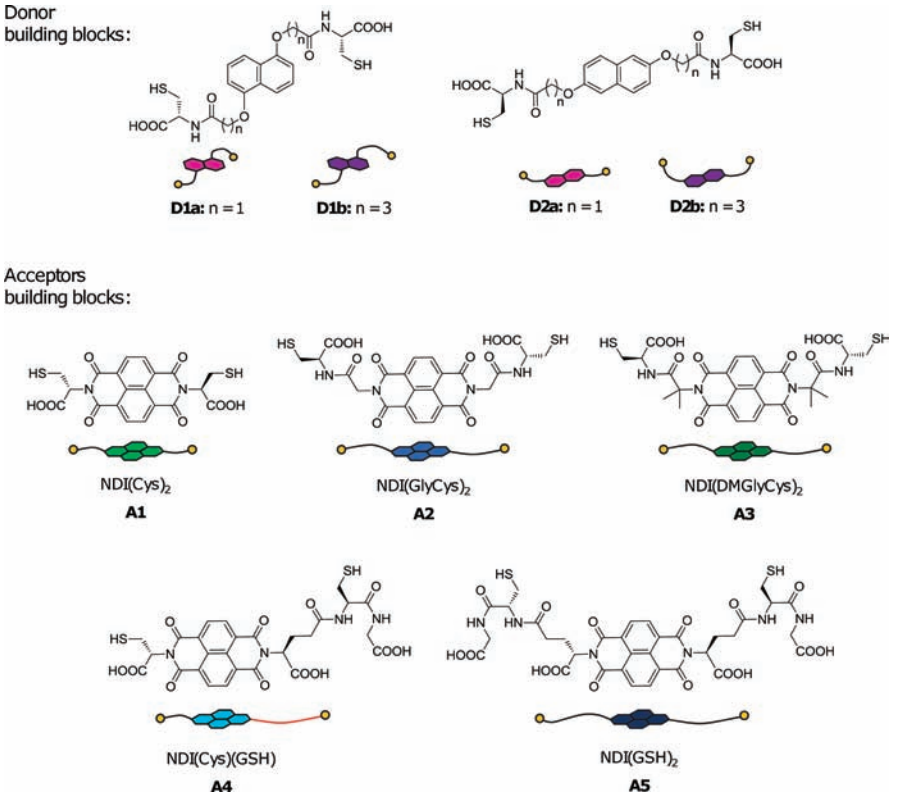

Figure 3. Donor (D) and acceptor (A) building blocks used and their cartoon representations.

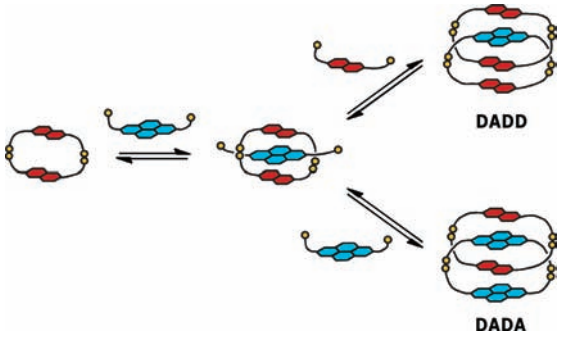

Figure 4. Formation of catenanes via pathway I.

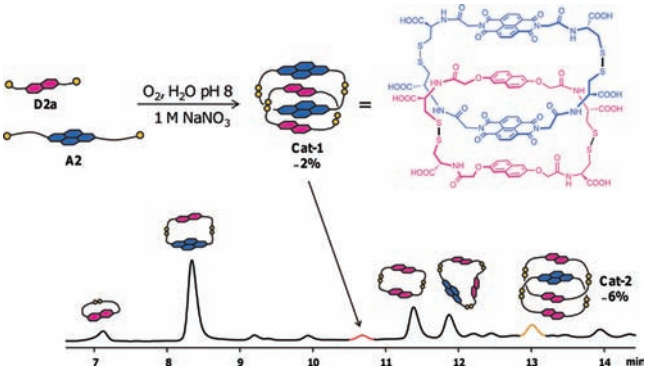

Figure 5. HPLC analysis of an aqueous library composed of **D2a** and **A2** (1:1 molar ratio, 5 mM total), in the presence of 1 M of $NaNO_3$. Absorbance was recorded at 260 nm. The minor species present in the library are described in the Supporting Information.

all containing a [−**D2a**−**D2a**−] dimer interlocked with either [−**A2**−**A2**−], [−**A1**−**A2**−], or [−**A1**−**A4**−] acceptor dimers. Their respective paired DADD catenanes were also identified. The different yields of DADA catenanes suggest that the size of the acceptor dimer influences their efficiency of formation, with the tightest dimer [−**A1**−**A4**−] leading to a 70% yield of the corresponding [2]catenane. Below we present a detailed discussion of the libraries that follow pathway I.

Acceptor **A1**, with short side chains, forms an extremely tight [−**A1**−**A1**−] dimer, which cannot possibly lead to the formation of alternating DADA catenanes.[8,13] Hence, the first DADA catenane (**Cat-1**) was identified, along with its predicted DADD paired catenane (**Cat-2**), in a library containing the slightly longer acceptor **A2** and **D2a** (Figure 5).

Cat-1 was characterized by mass spectrometry (MS and MS/MS), as shown in Figure 6. The ESI-MS (negative ion) shows a doubly charged molecular ion (m/z of 1065.0), corresponding to the mass of a tetramer composed of two donor and two acceptor units. The largest fragments observed in MS/MS have an m/z of 1171.0 and 959.0, corresponding to the mass of the acceptor homodimer and the donor homodimer, respectively. This fragmentation pattern is characteristic of a catenane and it follows the expected fragmentation for a DADA catenane, i.e., a ring containing two acceptors interlocked with another ring consisting of two donors.

The presence of the two paired catenanes (**Cat-1** and **Cat-2**) supports the proposed mechanism, whereby the choice of the threaded building block is directed by donor−acceptor interactions, while the closing step of catenation is driven by hydrophobic

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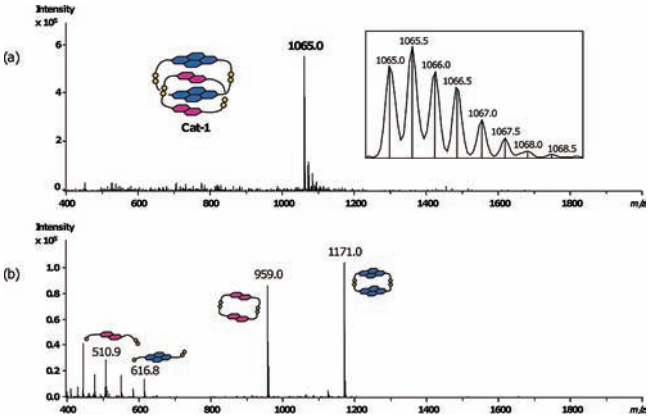

Figure 6. Tandem (a) MS and (b) MS/MS fragmentation of DADA catenane **Cat-1**.

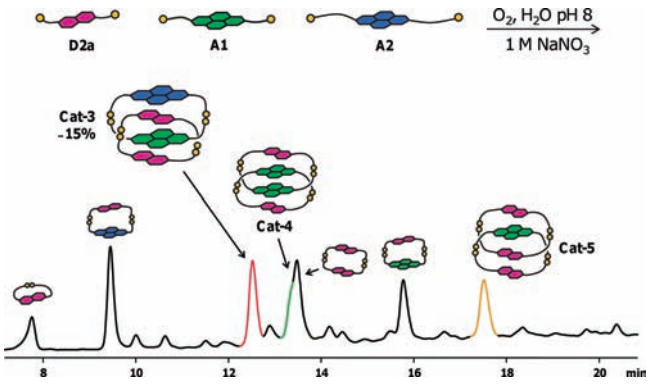

Figure 7. HPLC analysis of an aqueous library composed of **D2a**, **A1**, and **A2** (2:1:1 molar ratio, 5 mM total), in the presence of 1 M of $NaNO_3$. Absorbance was recorded at 260 nm. The minor species present in the library are described in the Supporting Information.

effects. The low yield of both catenanes (**Cat-1**, 2% and **Cat-2**, 6% of the library) is unsurprising, as their respective rings are relatively large, reducing the likelihood of a strong interaction between the aromatic units. Furthermore, even though the building block ratio (1:1) should not favor the formation of a structure containing three donor units, the DADD catenane **Cat-2** is more efficiently formed, indicating that the overall catenation process is not dominated by donor−acceptor interactions.

Considering the size of the [−A−A−] dimer, if [−**A1**−**A1**−] is too tight, the larger [−**A2**−**A2**−] dimer is already too loose to allow formation of a DADA catenane efficiently. Therefore, it was not surprising to observe that replacing **A2** by similarly sized **A3** did not bring much improvement. The behavior of the longer **A4** is relatively complex and will be discussed in the end of this work, but as expected, in the case of the acceptor building block with the longest side chains, **A5**, no catenane was observed: only a limited number of small macrocycles, including the cyclic acceptor monomer, were present at the stationary state (see the Supporting Information).

Introducing two acceptor building blocks in the presence of donor **D2a** allowed easy access to [−A−A−] dimers of intermediate sizes to explore further the formation of catenanes via pathway I. This is illustrated by a library composed of **D2a**, **A1**, and **A2** in a 2:1:1 molar ratio, shown in Figure 7. In this library, the only DADA catenane formed is **Cat-3**, which contains the tight mixed acceptor dimer [−**A1**−**A2**−]. The yield (15%) of

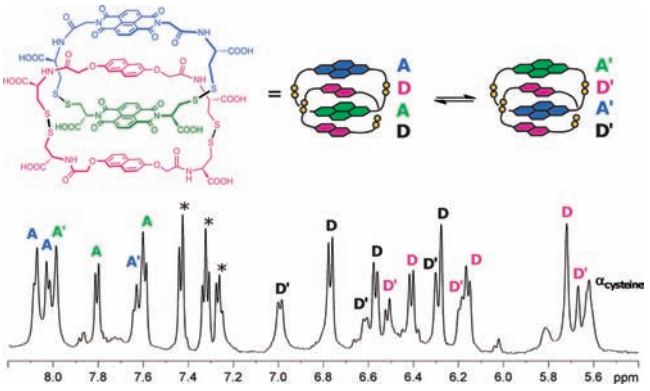

Figure 8. Partial ^{1}H NMR spectrum (D_2O, 298 K, 500 MHz) of DADA catenane **Cat-3** (the peaks labeled with * are associated with a [−**A1**−**A2**−] dimer impurity). The outer NDI, corresponding to the singlet at 8.0 ppm, was assigned arbitrarily to **A1**.

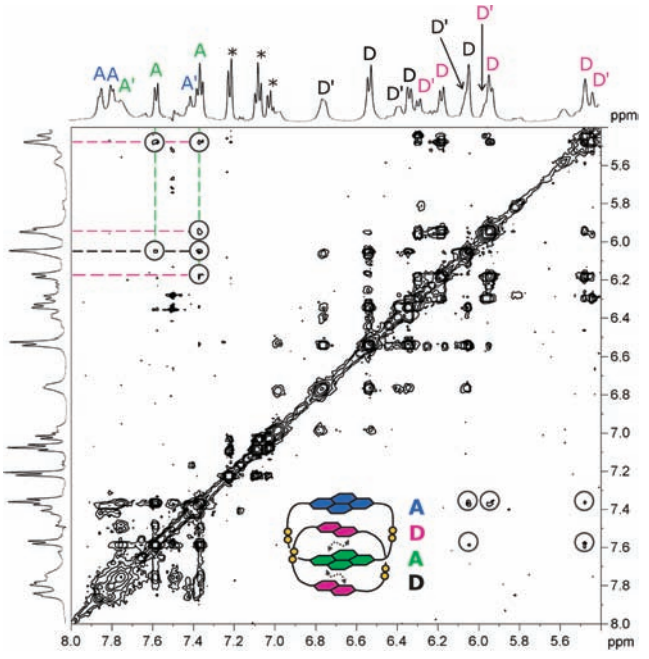

Figure 9. Expanded region of the NOESY spectrum (D_2O, 278 K, 500 MHz, evolution time: 800 ms) of DADA catenane **Cat-3** (the peaks labeled with * are associated with a [−**A1**−**A2**−] dimer impurity). The outer NDI, corresponding to the broad singlet at 7.8 ppm, was assigned arbitrarily to **A1**.

this catenane is higher than that of **Cat-1**. Once again, the DADD paired catenane, **Cat-5**, is present in the library, supporting the proposed formation pathway.

Naturally, increasing the complexity of the DCLs opens the possibility for other pathways to compete with pathway I. This explains the formation of other types of catenanes, such as the DAAD **Cat-4** (Figure 7), and will be discussed later.

Cat-3 was isolated and characterized by ^{1}H NMR (Figures 8 and 9). It displays two conformations in a molar ratio of 2:1, as either **A1** or **A2** can be situated in the inner or outer positions of the catenane. ^{1}H NMR (500 MHz, 298 K, D_2O) shows two sets of signals for each conformation in the acceptor region (7.55−8.15 ppm), assigned by correlation spectroscopy (COSY): one upfield shifted (inner NDI) and one downfield shifted (outer

NDI). A similar pattern, with two sets of signals for each conformation, was observed in the donor region (5.55−7.05 ppm). At low temperature (278 K), cross-peaks between the donor and acceptor units of the major conformation were observed in NOESY spectra, confirming the alternating DADA structure of **Cat-3** (Figure 9).

A library composed of **D2a**, **A1**, and **A4** in a 2:1:1 molar ratio (Figure 10) further illustrates the link between the size of the acceptor ring and the efficiency of the formation of DADA catenanes in the libraries. The [−**A1**−**A4**−] acceptor ring is very tight, and the corresponding catenane **Cat-6** is now formed in the unusually high yield of 70%. The DADD paired catenane **Cat-5** is still present, but is now a minor product. The formation of **Cat-6** in such high yield indicates a combination of optimal donor−acceptor and hydrophobic interactions and their efficient cooperation, leading to this particularly favorable catenane.

Because of its lack of symmetry, **Cat-6** is produced as a pair of diastereomers, each having two conformers, as either acceptor can be situated in the inner or outer positions of the catenane. The ^{1}H NMR of **Cat-6** is consequently extremely complex. However, analysis of the acceptor region by a combination of the COSY and NOESY spectra (7.10−8.15 ppm) allowed correlation of the signals expected from a mixture of four isomeric catenanes (see the Supporting Information).

In conclusion, the **D2a** donor building block forms a stable [−D−D−] dimer, which is the key intermediate for the formation of DADA and DADD catenanes via pathway I. The efficiency of the DADA catenane formation is directly linked to the tightness of the acceptor ring (Figure 11), as reflected by the yields that vary from 2% to 70% of the library. **Cat-3** and **Cat-6** are deep red in color in aqueous solution, which is indicative of the presence of charge-transfer interactions between the complementary aromatic units.

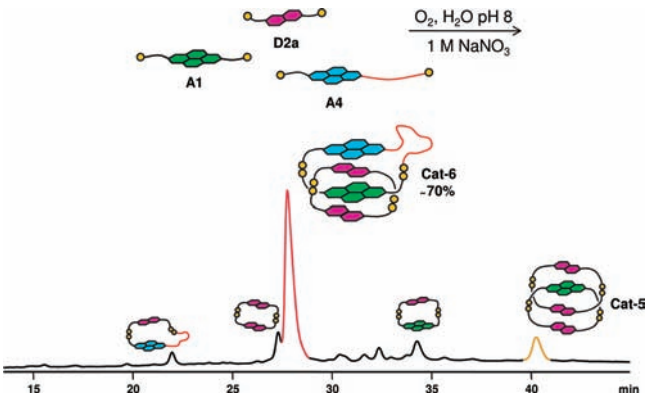

Figure 10. HPLC analysis of an aqueous library composed of **D2a**, **A1**, and **A4** (2:1:1 molar ratio, 5 mM total), in the presence of 1 M of $NaNO_3$. Absorbance was recorded at 260 nm. The minor species present in the library are described in the Supporting Information.

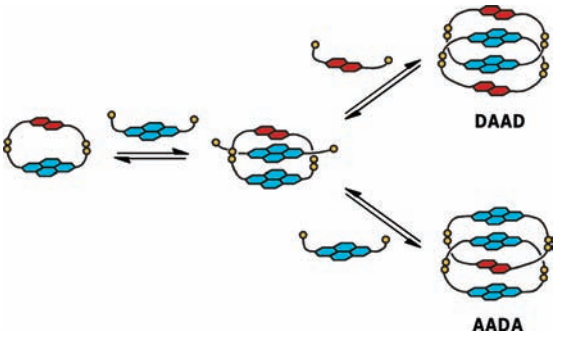

Figure 12. Formation of catenanes via pathway II.

3.2. Exploring Pathway II. Pathway II (Figure 12) occurs under two circumstances. First, the donor building block must have rather long side chains (**D1b** or **D2b**) so that it favors the formation of the [−D−] cyclic monomer and restricts the formation of a stable [−D−D−] dimer,[8a,8b,8d,13] thus preventing the formation of catenanes through pathway I. Second, the formation of the threaded complex into the cavity of the [−A−A−] dimer must be prevented, blocking the formation of catenanes via pathway III. This is the case when using **A1**: as the [−**A1**−**A1**−] dimer is too tight to allow threading through its cavity,[8,13] the [−D−A−] heterodimer becomes the only species that can potentially form a catenane. Composed of a long donor building block and a short acceptor, the [−D−A−] dimer has a relatively small cavity, suitable for strong interactions with an acceptor building block. A pair of ADAA and DAAD catenanes should be formed through pathway II. However, the necessity of having a tight [−A−A−] dimer implies that the ADAA catenane cannot actually be formed; hence, only one type of catenane, DAAD, was observed.

Many of those DAAD catenanes have previously been published by our group[8] and now find their place in the generic mechanism described here, such as **Cat-7**, formed in a library of **D1b** and **A1** (1:1 molar ratio),[8d] (Figure 13a). A similar catenane was observed when replacing **D1b** by its 2,6-isomer **D2b**.[8b]

The short donor **D2a** is also suitable for the formation of a DAAD catenane via pathway II when mixed with **A1** (Figure 13b).[8c] However, we have previously shown that the use of **D2a** also favors pathway I, and the two pathways now compete. According to our mechanism, pathways I and II should

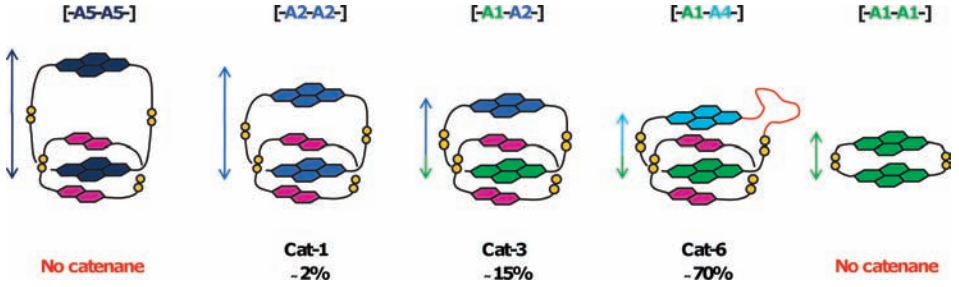

Figure 11. Relationship between the size of the acceptor ring and the efficiency of DADA catenane formation. The donor ring is [−**D2a**−**D2a**−] in each case.

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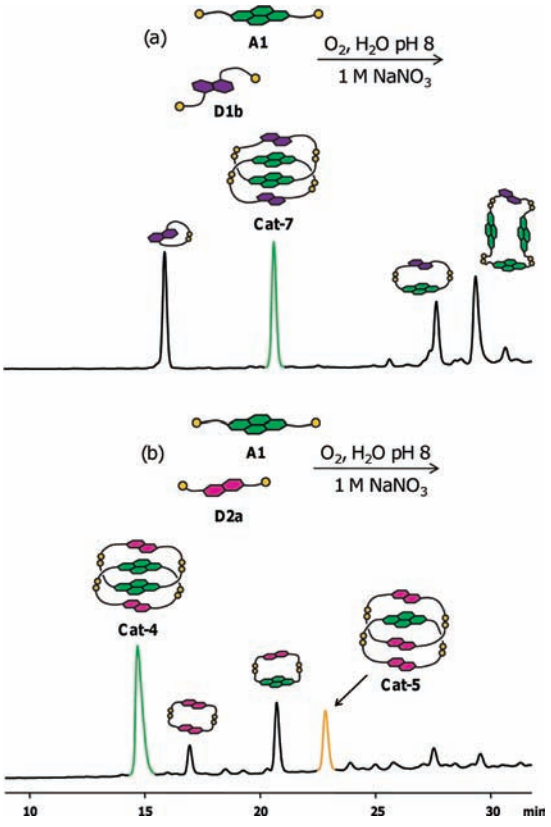

Figure 13. HPLC analysis of aqueous libraries composed of (a) **D1b** and **A1** (1:1 molar ratio, 5 mM total) and (b) **D2a** and **A1** (1:1 molar ratio, 5 mM total). The libraries were prepared with 1 M of $NaNO_3$. Absorbance was recorded at (a) 292 nm and (b) 260 nm.[8c,8d]

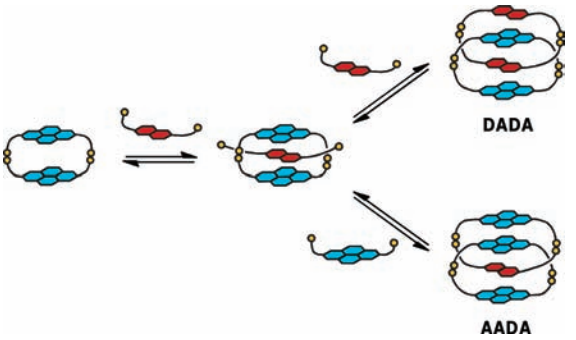

Figure 14. Formation of catenanes via pathway III.

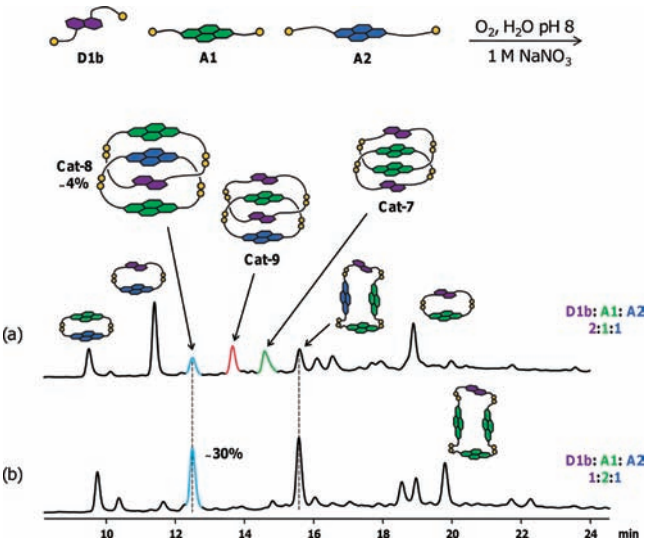

Figure 15. HPLC analysis of aqueous libraries composed of **D1b**, **A1**, and **A2** (5 mM total): (a) 2:1:1 molar ratio and (b) 1:2:1 molar ratio. DCLs were prepared with 1 M of $NaNO_3$. Absorbance was recorded at 383 nm. The minor species present in the libraries are described in the Supporting Information.

lead to two pairs of two catenanes, respectively DADD/DADA, and DAAD/ADAA. Once again, because the [−**A1**−**A1**−] does not allow threading of an aromatic group through its cavity, only one type of catenane can actually be observed for each pathway: DAAD **Cat-4** (pathway II) and DADD **Cat-5** (pathway I). Both catenanes, composed of short donor and acceptor building blocks, are the tightest catenanes obtained to date for these two types of structures and are consequently formed in the best yields (55% for DAAD **Cat-4** in a D:A = 1:1 molar ratio and 50% for DADD **Cat-5** in a D:A = 3:1 molar ratio). This agrees with our previous observation that tight rings are necessary for the efficient formation of catenanes.

The two catenanes were isolated and characterized. Interestingly, the green DAAD catenane **Cat-4** and the orange DADD catenane **Cat-5** exhibit different UV−vis spectra[8c,8d] from the DADA catenanes described above, due to the particular arrangement of their donor and acceptor units.

3.3. Exploring Pathway III. Pathway III (Figure 14), which leads to the formation of the new pair of catenanes DADA and AADA, occurs under particular conditions. The donor building block must have long side chains (**D1b** or **D2b**), to limit the formation of the [−D−D−] dimer. The acceptor building block must also have long enough side chains so that the [−D−A−] dimer is too loose to form any stable threaded complex. However, it must be able to form a [−A−A−] dimer tight enough to allow a favorable interaction with a donor moiety. Therefore, the size of the acceptor building block is critical to the formation of catenanes through pathway III. Unfortunately, it is not the only limitation for this mechanism. In the previous cases described (pathways I and II), the smallest and most rigid donor and/or acceptor building blocks were necessary to lead efficiently to the most compact catenanes. The libraries were consequently quite simple, composed of catenanes and small macrocycles. To access catenanes through pathway III, more flexible building blocks are necessary, increasing the complexity of the libraries: large macrocycles, such as trimers or tetramers, which can fold and thus bury some of their large hydrophobic surfaces, become serious competitors for the formation of the catenanes.

The first library that follows pathway III was composed of donor **D1b** with the acceptor building blocks **A1** and **A2** in a 2:1:1 molar ratio (Figure 15a). The DADA **Cat-9** is formed from the tightest possible acceptor ring in this system [−**A1**−**A2**−], interlocked with the donor ring that is much larger than in previous catenanes of this type, leading to a very low yield. This shows that both the size of the acceptor and the donor rings play a role in the efficiency of formation of the DADA catenane. Its paired AADA catenane **Cat-8** is observed for the first time and identified by tandem MS and MS/MS (Figure 16). The library also contained the DAAD **Cat-7** formed via pathway II.

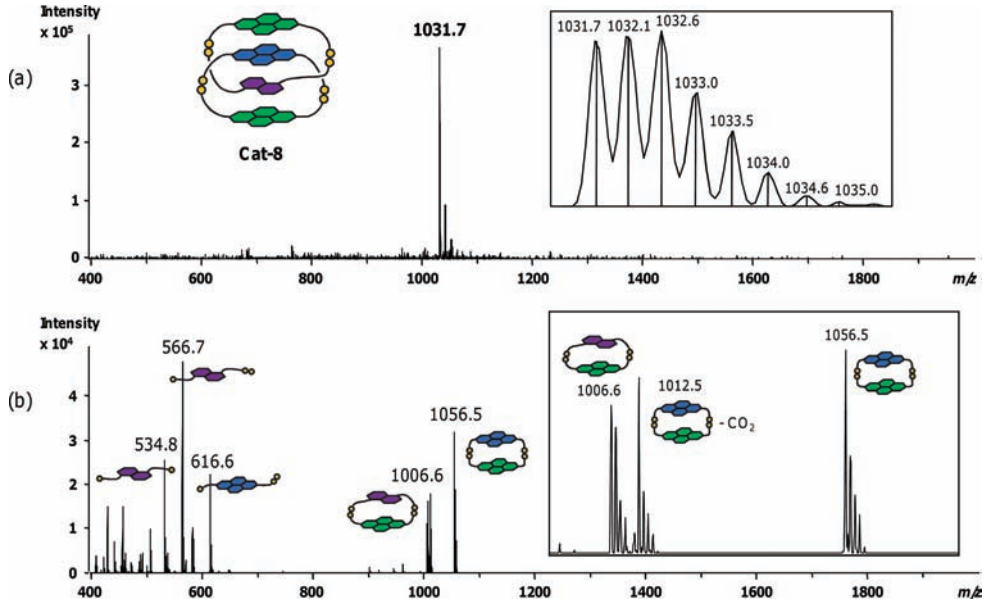

Figure 16. Tandem (a) MS and (b) MS/MS fragmentation of AADA catenane **Cat-8**.

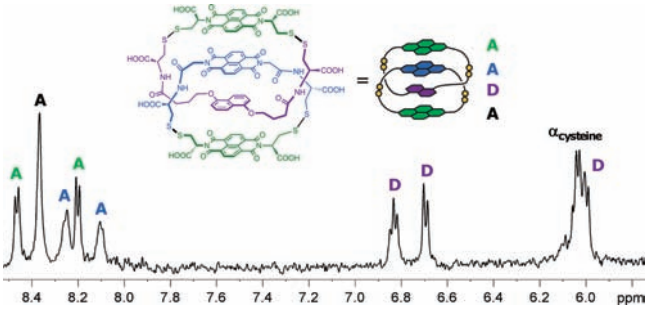

Figure 17. Partial ^{1}H NMR spectrum (D_2O, 298 K, 500 MHz) of AADA catenane **Cat-8**. The inner NDI, corresponding to the doublets at 8.25 and 8.10 ppm, was assigned arbitrarily to **A2**.

ESI-MS (negative ion) of **Cat-8** shows a doubly charged molecular ion (m/z of 1031.7), corresponding to the mass of a tetramer containing only one donor and three acceptor units. The largest fragments observed in MS/MS have an m/z of 1056.5 and 1006.6, corresponding to the mass of the [−**A1**−**A2**−] homodimer and the [−**D2b**−**A1**−] heterodimer, respectively.

The AADA **Cat-9** could be amplified up to 30% yield, along with its isomeric macrocycle [−**A2**−**D1b**−**A1**−**A1**−], by using a biased ratio of building blocks (Figure 15b). The amplification of this tetramer clearly shows that large macrocycles can fold to minimize hydrophobic exposure and be in direct competition with the formation of the corresponding catenanes.

Both **Cat-8** and its corresponding tetramer were isolated and analyzed by ^{1}H NMR spectroscopy (Figure 17 and Supporting Information). The two compounds exhibit significantly different ^{1}H NMR spectra (500 MHz, D_2O), with the spectrum of the catenane displaying the expected upfield shifts for the aromatic protons due to the stacked structure. Only one conformation was observed for the AADA catenane **Cat-8**. Three sets of signals were correlated by COSY in the acceptor region (8.05−8.50 ppm), corresponding to the two outer and one inner NDIs. Only one set of signals corresponding to one DN unit was found in the

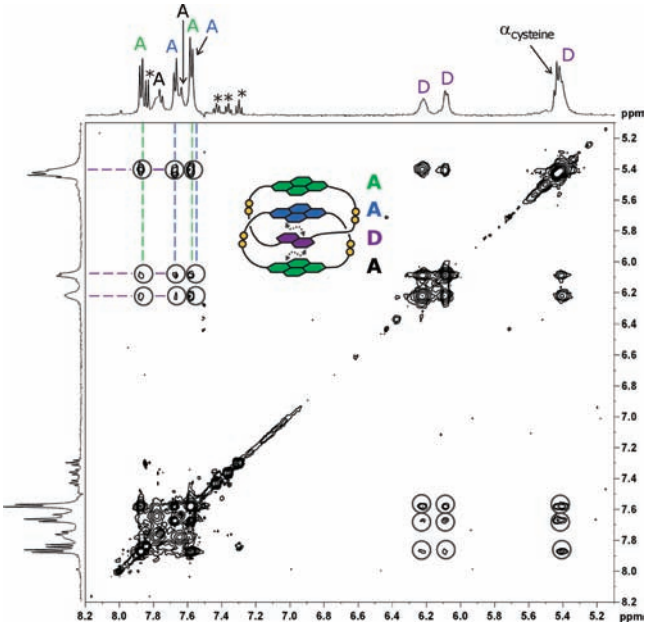

Figure 18. Expanded region of the NOESY spectrum (D_2O, 278 K, 500 MHz, evolution time: 800 ms) of AADA catenane **Cat-8** (the peaks labeled with * are associated with a [−**A1**−**A2**−] dimer impurity).

donor region (5.95−6.90 ppm). At 278 K, cross-peaks between the aromatic units were observed by NOESY, confirming the unusual AADA structure of **Cat-8** (Figure 18).

As expected, a library composed of **D2b**, **A1**, and **A2** (2:1:1 molar ratio, Figure 19) contains the DADA catenane **Cat-11** and its paired AADA catenane **Cat-10**. The presence of **Cat-9** again indicates that pathway II is competing with pathway III.

In a biased library with a ratio of **D2b**:**A1**:**A2** of 1:2:1, the yield of this catenane increased up to 10% of the library, allowing for its isolation (see the Supporting Information). Other AADA catenanes were identified in libraries based on either long donors **D1b** or **D2b**. Only the smallest acceptor rings lead to the

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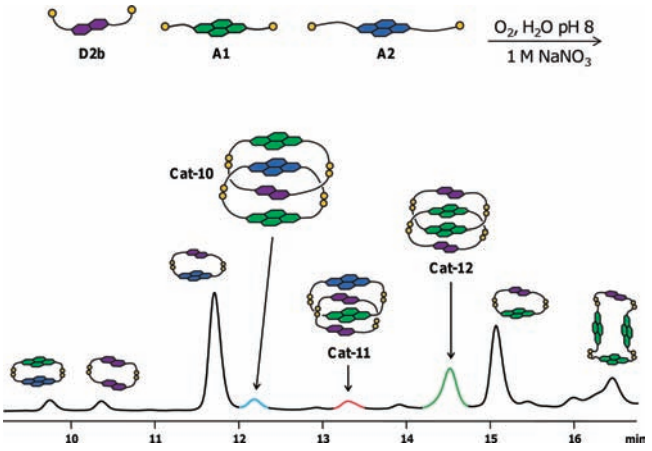

Figure 19. HPLC analysis of an aqueous library composed of **D2b**, **A1**, and **A2** (2:1:1 molar ratio, 5 mM total), in the presence of 1 M of $NaNO_3$. Absorbance was recorded at 383 nm. The minor species present in the library are described in the Supporting Information.

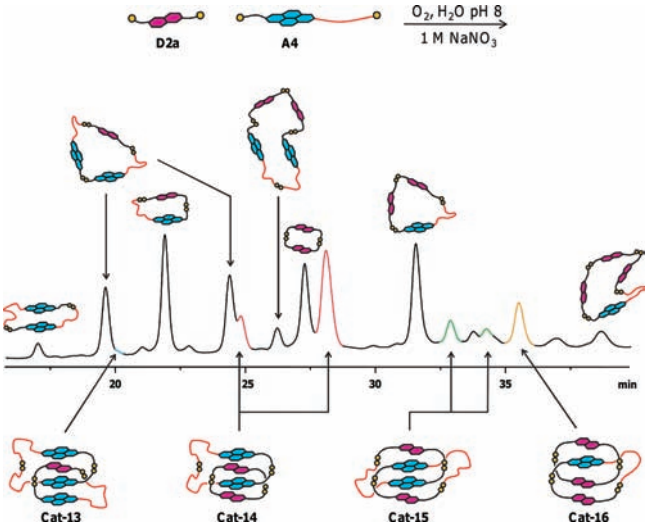

Figure 20. HPLC analysis of an aqueous library composed of **D2a** and **A4** (1:1 molar ratio, 5 mM total), in the presence of 1 M of $NaNO_3$. Absorbance was recorded at 260 nm.

formation of AADA catenanes, but most of the libraries are relatively complex, and the formation of large macrocycles seems to be favored over the formation of the catenanes, which are only present, in most cases, as traces (see the Supporting Information).

To conclude, using flexible donors **D1b** or **D2b** leads to the formation of DADA and AADA catenanes through pathway III. The formation of DADA catenane is not favored through this mechanism, because the donor ring is too large to allow an optimum overlap of the complementary aromatic units. There is a delicate balance in the formation of AADA catenanes, as they are in competition with the formation of large macrocycles such as trimers and tetramers. However, AADA catenane **Cat-8** can be amplified up to 30% by optimizing the choice of the building blocks used in order to access the tightest possible acceptor and donor rings. **Cat-8** and **Cat-10** were isolated as yellow-brown products, showing that AADA catenanes exhibit different optical properties than the other types of catenanes described above.

3.4. Competing Pathways. We have described above design protocols that access catenanes selectively via pathway I, II, or III, but we also observed in the most complex systems that catenanes can be formed via two simultaneous pathways. It is therefore conceivable that a library fulfilling the conditions of all three Pathways will generate all the types of catenanes. This is beautifully illustrated in Figure 20 by a library containing the short donor building block **D2a** and the asymmetric acceptor building block **A4** (1:1 molar ratio, 5 mM). The behavior of **A4** is driven by its shorter side chain, making the formation of a DAAD catenane possible (pathway II). However, the [−A−A−] homodimer is now large enough to allow the formation of DADA and AADA catenanes (pathway III), and the use of **D2a** allows the formation of a DDAD catenane (pathway I). Indeed, all the four possible catenanes DAAD (**Cat-15**), DADD (**Cat-16**), DADA (**Cat-14**), and AADA (**Cat-13**) were observed in the same library.

The presence of two peaks on the HPLC trace for each of **Cat-14** and **Cat-15** can be explained by the existence of different isomers or of slowly interconverting conformations. The synthesis of all four types of catenanes in the same library clearly shows that there is little energetic difference between them. This allows us to conclude beyond a doubt that the formation of the unusual AADA, DAAD, and AADA stacked catenanes is not significantly disfavored when compared to the typical DADA catenane.

4. CONCLUSIONS

A total of 22 new donor−acceptor [2]catenanes with different arrangements of the aromatic units (DAAD, DDAD, DADA, and AADA) have been identified by dynamic combinatorial chemistry (see the Supporting Information). The observation that complete oxidation freezes exchange in such a way that the catenanes become kinetic bottlenecks (or traps) takes this work away from pure dynamic combinatorial chemistry into a hybrid realm where there is a complex interplay of kinetics and thermodynamics. While this is in some sense disappointing, it is not entirely surprising and it also provides an opportunity to probe reaction pathways that are necessarily invisible in a truly thermodynamic equilibrium.

Donor−acceptor interactions, which conventionally lead to DADA catenanes only, were partially overcome by using a highly polar medium, allowing efficient access to catenanes with unusual DADD, DAAD, and ADAA stacking sequences. The formation of these previously exotic catenanes in the DCLs can be convincingly explained by taking into account the relative contributions of donor−acceptor and hydrophobic effects in their assembly. A close analysis of the DCLs studied allowed us to propose a mechanistic pathway for their synthesis and also to predict the outcome of libraries a priori. Donor−acceptor interactions are crucial in the mechanism, but the hydrophobic effect determines the overall outcome of catenation process. Catenanes containing different stacking sequences of the donor and acceptor units can be selectively formed following one of the three synthetic pathways proposed simply by choosing the correct building blocks in the DCL setup.

These results challenge conventional thinking that has limited the scope of donor−acceptor [2]catenanes to strictly alternating stacks of donor and acceptor aromatic units. They indicate that an approach to catenane synthesis that takes into account only donor−acceptor interactions is unnecessarily limiting. To date, aromatic interactions have been satisfactorily described in terms of electrostatic interactions, which can only be enhanced by a solvophobic effect. We have shown here that the solvophobic

effect can overcome and direct syntheses based on supramolecular interactions between aromatic moieties. This observation will allow chemists to design and indeed synthesize complex structures that were previously inaccessible.

■ ASSOCIATED CONTENT

Supporting Information. Detailed procedure for building block synthesis, library preparations, HPLC/LC−MS methods and data, and UV−vis and NMR spectra of isolated catenanes and macrocycles. This material is available free of charge via the Internet at http://pubs.acs.org.

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