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# Structural Parameters Governing the Dynamic Combinatorial Synthesis of Catenanes in Water

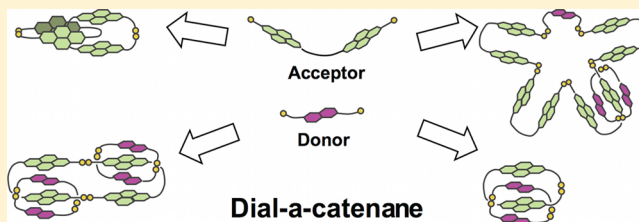
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## S Supporting Information

**ABSTRACT:** We report the first dynamic combinatorial synthesis in water of an all-acceptor [2]catenane and of different types of donor–acceptor [2] and [3]catenanes. Linking two electron-deficient motifs within one building block using a series of homologous alkyl chains provides efficient and selective access to a variety of catenanes and offers an unprecedented opportunity to explore the parameters that govern their synthesis in water. In this series, catenane assembly is controlled by a fine balance between kinetics and thermodynamics and subtle variations in the building block structure, such as the linker length and building block chirality. A remarkable and unexpected odd–even effect with respect to the number of atoms in the alkyl linker is reported.



## INTRODUCTION

We report here the synthesis of a family of [2] and [3]catenanes, assembled from homologous linear building blocks in water. Until now, the low solubility of organic molecules in water and the ability of aqueous media to suppress weak supramolecular interactions have challenged the synthesis of interlocked molecules in water. Catenanes, for example, have mainly been assembled and studied in organic solvents,<sup>1</sup> an approach that has restricted their utility in biological contexts. Following the synthesis of the first water-soluble interlocked molecules,<sup>2</sup> notably pioneered by Fujita et al.,<sup>3</sup> we<sup>4,5</sup> and others<sup>6</sup> have recently begun to develop strategies to access catenanes in water.

Our strategy, based on a dynamic combinatorial approach,<sup>7,8</sup> presents many attractions, especially to explore the potential synthesis of unprecedented structures. We use simple and readily available dithiol building blocks containing either an electron-donor (D) or an electron-deficient (A) aromatic unit functionalized with amino acid residues. The presence of polar amino acid residues not only renders the catenanes water soluble but also permits the introduction of new functionalities, such as carboxylates or amides, which can be used in the context of molecular recognition<sup>5</sup> and could also be utilized for catalysis or post-synthetic modifications.

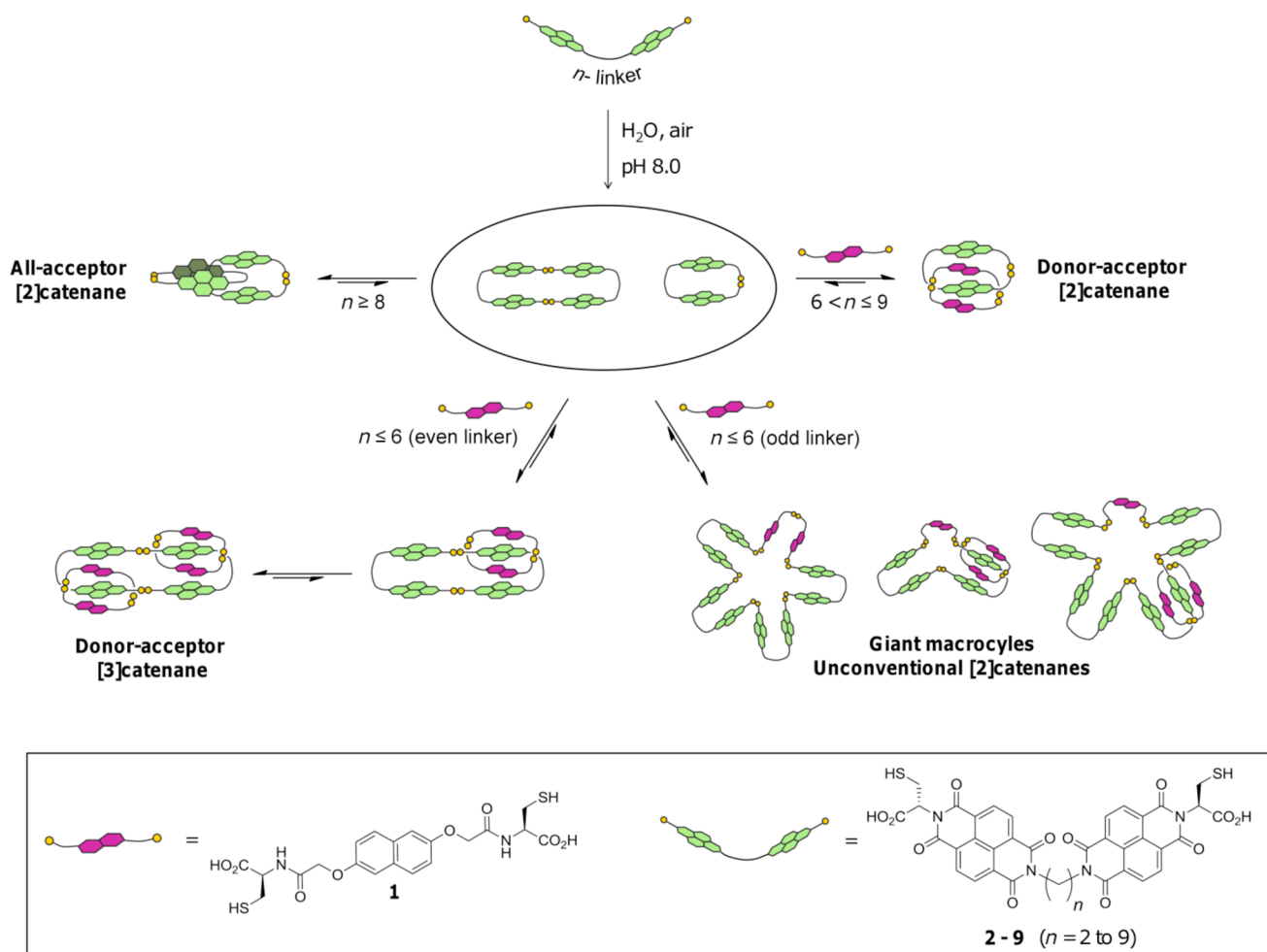
More importantly, we have shown that the hydrophobic effect could be exploited to control the arrangement of the stacked donor and acceptor aromatic groups,<sup>4</sup> allowing us to synthesize [2]catenanes with the conventional alternating DADA stacking sequence as well as with the previously unknown DADD, AADA, and DAAD motifs. The assembly of these catenanes is not driven purely by the hydrophobic effect: donor–acceptor interactions still play an important role,

rendering the formation of the all-acceptor (AAAA) and all-donor (DDDD) catenanes elusive. Building on these results, we showed in an earlier communication<sup>5</sup> that the entropic penalty associated with the formation of larger structures such as [3]catenanes could be overcome by linking two electron-deficient units within one building block, using a butyl linker.

In the current study, we generalize our strategy by using a series of building blocks composed of two electron-deficient units linked with homologous alkyl chains ((–CH<sub>2</sub>–)<sub>*n*</sub> where *n* = 2–9). First, using libraries composed of only electron-deficient building blocks, we demonstrate that the hydrophobic effect alone can be used to direct the synthesis of all-acceptor [2]catenanes. The formation of these all-acceptor [2]catenanes is driven by the intercalation of the hydrophobic alkyl chain between the electron-deficient units and therefore does not contradict our earlier study which showed that, under our dynamic combinatorial conditions (water pH 8.0, 1 M NaNO<sub>3</sub>), the formation of all-acceptor catenanes with four electron-deficient aromatic units stacking in a conventional fashion was improbable.

In the second part of this work, we show that addition of an electron-rich building block to the above-mentioned electron-deficient building blocks shifts the library distribution toward the formation of the smallest accessible donor–acceptor catenane, which may be either a [2] or a [3]catenane depending on the length of the aliphatic linker. These results reveal the operation of an odd–even effect with respect to the number of CH<sub>2</sub> units, *n*, of the linking alkyl chain. This trend is clearly noticeable for short alkyl linkers and vanishes when the

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**Figure 1.** Different types of [2] and [3]catenanes formed in dynamic combinatorial libraries from electron-rich **1** and electron-deficient **2–9** building blocks. The cartoon yellow dots represent the sulfur atoms of the building blocks.

chain length increases. Odd–even effects are often observed in the solid state<sup>9</sup> but appear to be less common in solution state.<sup>10</sup> We, therefore, discuss the possible origins of this effect, which seems to be associated with kinetically controlled processes and tends to disappear when the library progresses toward thermodynamic equilibrium. Finally, we also demonstrate that the catenane synthesis can be influenced by differences in the building block chirality.

Overall, these catenanes constitute a model from which synthetic rules can be extracted. Our results provide an insight into the kinetics and thermodynamics governing the library distribution and highlight the role of various parameters directing catenane synthesis, particularly hydrophobicity, flexibility, and chirality. Representative samples of each type of catenanes were isolated by preparative HPLC and fully characterized as individual compounds by <sup>1</sup>H NMR and UV–vis in addition to the LCMS analyses. This work, which is summarized in Figure 1, therefore constitutes a benchmark for the easy and versatile synthesis of different types of water-soluble [2] and [3]catenanes.

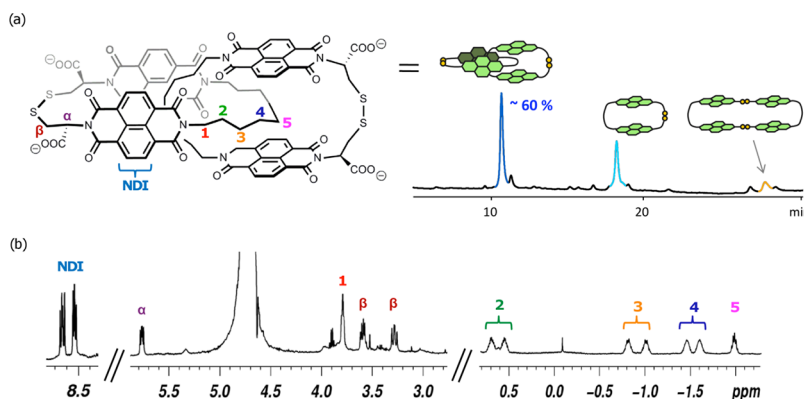
## RESULTS AND DISCUSSION

The synthesis of catenanes was achieved in water in one pot from simple linear building blocks: an electron-rich dialkoxynaphthalene building block (**1**) and a series of homologous acceptor building blocks (**2–9**, Figure 1). The acceptor

building blocks **2–9** are all based on the same design: two large hydrophobic electron-deficient  $\pi$ -systems (1,4,5,8-naphthalenetetracarboxylic diimide) are connected via a flexible aliphatic chain and terminated by L-cysteine hydrophilic side chains.<sup>11</sup> Eight consecutive diamines, from 1,2-diaminoethane to 1,9-diaminononane, were used to produce flexible aliphatic linkers of systematically increasing length. The notation **2–9** refers both to the acceptor building block and to the corresponding number  $n$  of CH<sub>2</sub> of the alkyl chain linking the two aromatic moieties. Some of the results related to building block **4** have been previously published in preliminary form;<sup>5</sup> they are presented here as a part of a more general picture.

**Exploiting the Hydrophobic Effect to Assemble All-Acceptor Catenanes.** The first set of libraries was prepared by dissolving each acceptor **2–9** at a concentration of 5 mM in water at pH 8 in the presence of 1 M NaNO<sub>3</sub> and was analyzed by reverse-phase HPLC. Absorbance was recorded at 383 nm, the optimum wavelength for the naphthalenediimide, and the library members were unambiguously identified by tandem ESI-MS and MS/MS.

Libraries prepared from the short-linker building blocks ( $n < 7$ ) are dominated by the cyclic dimer, while the proportion of cyclic monomer increases with longer linkers ( $7 \leq n \leq 9$ , see SI). For  $n = 8$ , we observed trace amount of a new species that corresponded to an all-acceptor [2]catenane composed of two



**Figure 2.** (a) Reverse-phase HPLC trace of a library prepared by dissolving **9** in water 1 M NaNO<sub>3</sub>, pH 8, and structure of the all-acceptor [2]catenane. (b) <sup>1</sup>H NMR (500 MHz, 298 K) spectrum of the all-acceptor [2]catenane in D<sub>2</sub>O.

interlocked monomeric rings. The yield of this all-acceptor catenane is significantly higher for the linker length  $n = 9$  (60% of the library composition, Figure 2a). The catenane was first characterized by MS (see SI). The MS displays a singly charged molecular ion ( $m/z$  1723.7) corresponding to the mass of a dimer, while the MS/MS fragmentation pattern is characteristic of an interlocked structure, the loss of one ring resulting in the formation of the cyclic monomer ( $m/z$  861.7) and smaller fragments.

The <sup>1</sup>H NMR spectrum (500 MHz, 298 K, Figure 2b) of the all-acceptor [2]catenane in D<sub>2</sub>O exhibits resonances corresponding to a single highly symmetric conformation: four doublets were assigned to the four inequivalent aromatic protons of each naphthalenediimide unit. The chemical shifts of these protons ( $\delta = 8.7$  to 8.5 ppm) are consistent with the proposed geometry of the all-acceptor [2]catenane, where the aromatic units are not stacked and therefore do not experience shielding. On the other hand, the diastereotopic aliphatic protons sandwiched between two aromatic units experience a strong shielding environment and thus appear at very low chemical shift values (from 0.9 to −2.0 ppm). We identified nuclear Overhauser effect (NOE) correlations between the naphthalenediimide protons and aliphatic protons H<sub>1</sub> to H<sub>4</sub> confirming that the aliphatic protons are in close proximity to the aromatic units. Only the most shielded aliphatic proton H<sub>5</sub>, deeply buried within the cavity of the catenane, does not display any NOE correlations with the aromatic protons. Moreover, NOE cross peaks were only observed between alternating protons of the alkyl chain, (H<sub>1</sub>, H<sub>3</sub>, and H<sub>5</sub>) or (H<sub>2</sub> and H<sub>4</sub>), indicating that the alkyl chain is confined to a staggered zigzag geometry within the core of the catenane.

The formation of this all-acceptor catenane appears to be purely driven by the need to minimize solvent exposed surface area. The hydrophobic surfaces are efficiently buried, and the hydrophilic cysteine side chains are exposed to the solvent. This structure highlights the importance of hydrophobic effects in the synthesis of interlocked and folded structures in water. Although we did not investigate the possibility of synthesizing an all-donor catenane, this result, along with previous ones,<sup>4</sup> suggests that such catenanes might be accessible.

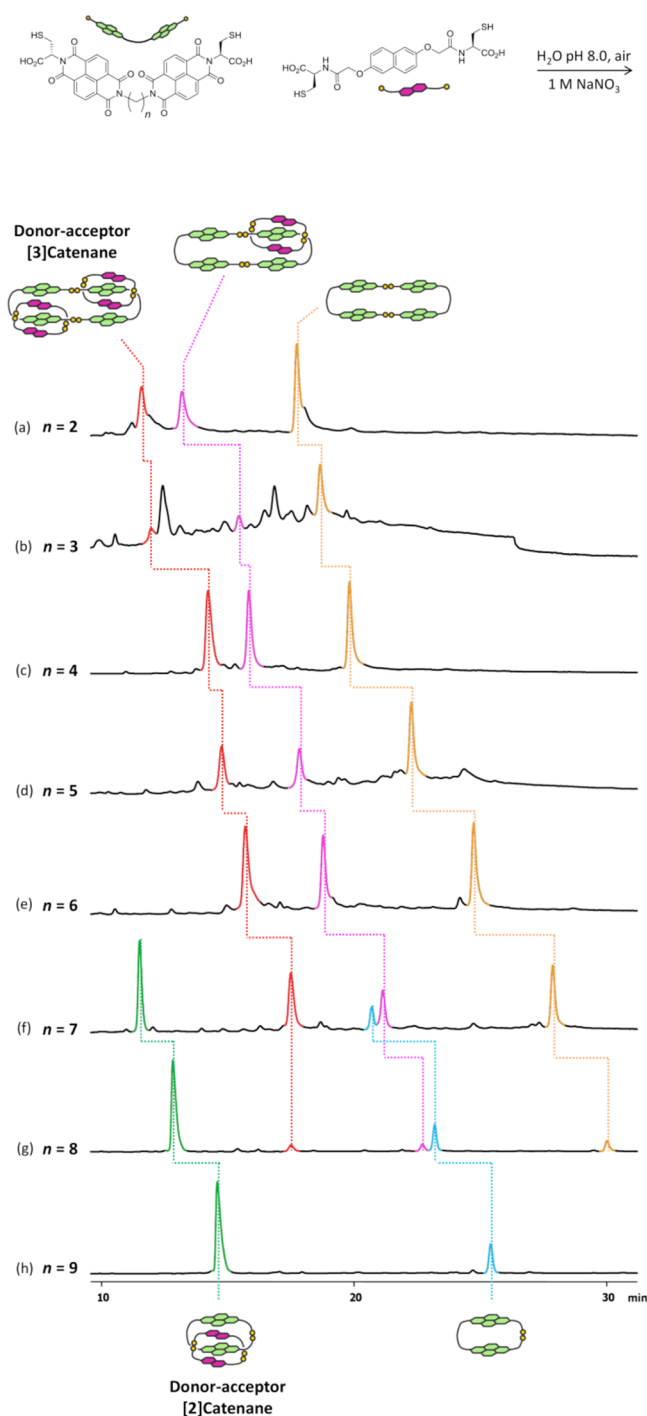
**Combining the Hydrophobic Effect with Donor–Acceptor Interactions: Synthesis of [2] and [3]-Catenanes.** The second set of libraries was prepared by dissolving each acceptor **2–9** in the presence of donor **1** to give a total concentration of 5 mM (1:2 molar ratio) in water at pH 8 (1 M NaNO<sub>3</sub>). Absorbance was recorded at the optimum

wavelength for each building block (donor units at 260 nm, and acceptor units at 383 nm), allowing for easy estimation of the quantity of catenane formed. The presence of the donor building block **1** results in a shift in the equilibrium toward the formation of donor–acceptor [2] and [3]catenanes. Results are shown in Figures 3 and 4.

**Short Linkers ( $n \leq 6$ ): Synthesis of Donor–Acceptor [3]Catenanes and Manifestation of an Unexpected Odd–Even Effect.** For short aliphatic linkers ( $n \leq 6$ ), an unexpected odd–even effect dictates the library behavior, leading to the formation of either simple or extremely complex libraries. Acceptor building blocks with an even-numbered linker ( $n = 2, 4$ , and 6) produced simple libraries containing significant quantities of [3]catenane (Figures 3a,c,e). Kinetic experiments showed the formation of the [3]catenane to be a stepwise process in which the acceptor dimer is formed first and then successively threaded by the donor units.<sup>4</sup> No other macrocycles than the [3]catenane and the intermediate species (the noninterlocked dimers and the intermediate [2]catenane) were observed. The [3]catenane is likely to be the thermodynamic product of the libraries, and its yield is therefore relatively good; however, the residual presence of intermediates suggests that the libraries are fully oxidized and that disulfide exchange stops before the library reaches thermodynamic equilibrium.

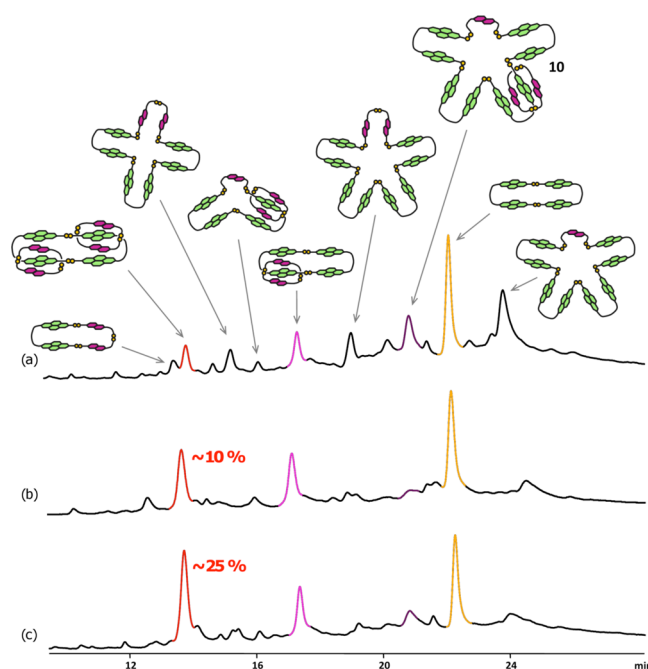
In stark contrast, libraries consisting of acceptor building blocks with an odd-numbered linker ( $n = 3$  and 5) displayed little selectivity for any particular library member. The  $n = 3$  library is the most striking example, while the effect is less pronounced with the more flexible ( $n = 5$ ) before disappearing when the length of the linker is further increased. In the odd-numbered libraries, the [3]catenane is clearly not the dominant species, and we observed the formation of many giant macrocycles.

The odd–even effect is even more pronounced when the libraries are prepared in a 1:1 molar ratio of the two building blocks. Figure 4a illustrates the complexity of the  $n = 5$  library in a 1:1 molar ratio. The library is characterized by the formation of a variety of surprisingly large macrocycles and catenanes, such as **10** ( $m/z$  1555.0, triply charged, Figure 5). The fragmentation pattern generated by MS/MS is consistent with that of a giant [2]catenane. The soft fragmentation at 0.4 V shows fragmentation into the separated rings at  $m/z$  1852.0 and 958.8. Smaller fragments were also detected, but no evidence of linkage between these two rings could be identified, suggesting that they were not covalently bonded to each other.



**Figure 3.** Reverse-phase HPLC analysis of aqueous libraries composed of **1** and (a) **2**, (b) **3**, (c) **4**, (d) **5**, (e) **6**, (f) **7**, (g) **8**, and (h) **9**. These libraries were prepared in a 1:2 molar ratio (5 mM total) in water at pH 8 in the presence of 1 M of NaNO<sub>3</sub>. Absorbance was recorded at 383 nm.

The libraries are fully oxidized after a few hours and may not reach thermodynamic equilibrium. We showed, however, that the library distribution can be shifted toward thermodynamic equilibrium if the reversible process of disulfide exchange is reinitiated by adding fresh thiol to an oxidized library.<sup>4</sup> Therefore, addition of the 2 equiv of building block **1** in one pot or in successive fractions may lead to a different library distribution. In all the libraries, stepwise addition of **1** (two batches of 1 equivalent added at an interval of 2 h) led to an



**Figure 4.** Reverse-phase HPLC analysis of aqueous libraries composed of **1** and **5** in the presence of 1 M of NaNO<sub>3</sub> in a: (a) 1:1 molar ratio, (b) 2:1 molar ratio prepared in one pot, and (c) 2:1 molar ratio after stepwise addition of **1**. The total concentration of building block is 5 mM in every case. Absorbance was recorded at 383 nm.

increase of the catenane yield, which is thermodynamically more stable. Stepwise addition to the  $n = 5$  library is a good example of this behavior (Figure 4b,c). Adding another equivalent of fresh thiol **1** to a library prepared in a 1:1 molar ratio dramatically simplified the library in favor of the [3]catenane. While the final ratio between the building blocks in the ‘stepwise’ library is equal to the ratio in the ‘one pot’ library, the stepwise procedure led to an increase of the [3]catenane yield from 10% to 25%. On the other hand, the giant catenanes, such as **10**, disappear in the ‘stepwise’ library, implying that their formation is mainly kinetically controlled.

The origin of the odd–even effect remains unclear. From our results, it seems that the [3]catenane is the thermodynamic product in all the libraries, regardless of the aliphatic linker length. Although the odd–even effect might influence the stability of the [3]catenane itself, it seems that it mainly controls the stability of the intermediates and competing species met along the kinetic pathways leading to the catenane formation.

**Long Linkers ( $n > 6$ ): Synthesis of Donor–Acceptor [2]Catenanes.** When the aliphatic linker is long enough ( $n > 6$ ), templating by the electron-rich building block favors intramolecular closure of the acceptor building block and results in the formation of donor–acceptor [2]catenanes that are entropically favored over the larger [3]catenane. Our previous studies suggest that the formation of these [2]-catenanes is possible when the aliphatic linker is longer than a cysteine–cysteine linkage, which roughly corresponds to a hexyl chain ( $n > 6$ ).<sup>4</sup> In the  $n = 7$  library, the presence of the two catenanes (Figure 3f) in the same library suggests that the [2]catenane might be relatively strained and that each catenane, being a kinetic trap, is persistent once it is formed. For  $n = 8$  and 9, the [2]catenane is generated in yields of roughly 70% in otherwise simple libraries. The formation of these [2]catenanes



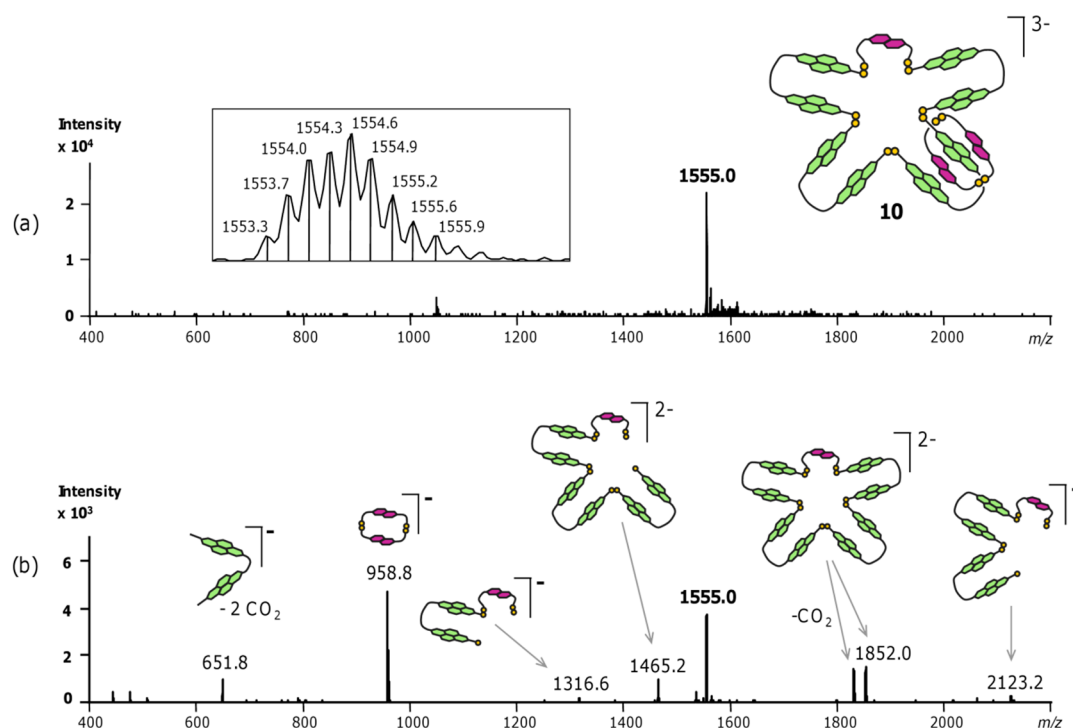


Figure 5. Tandem (a) MS and (b) MS/MS fragmentation of catenane **10**.

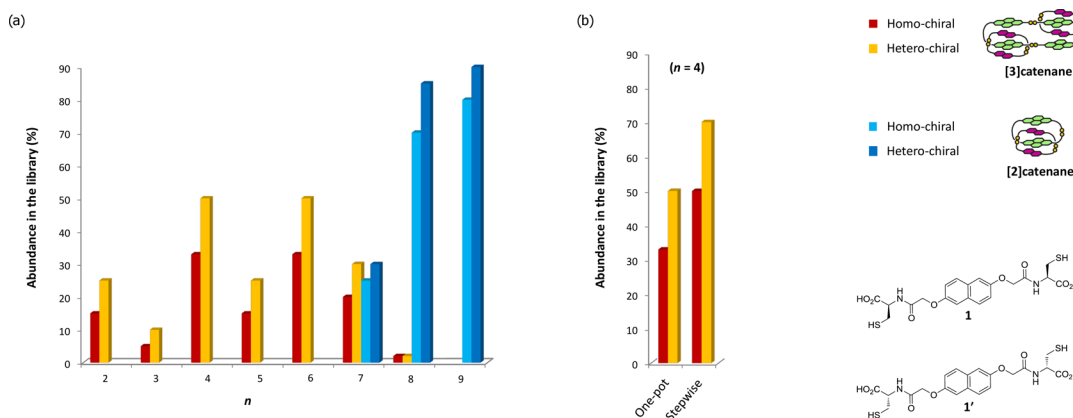


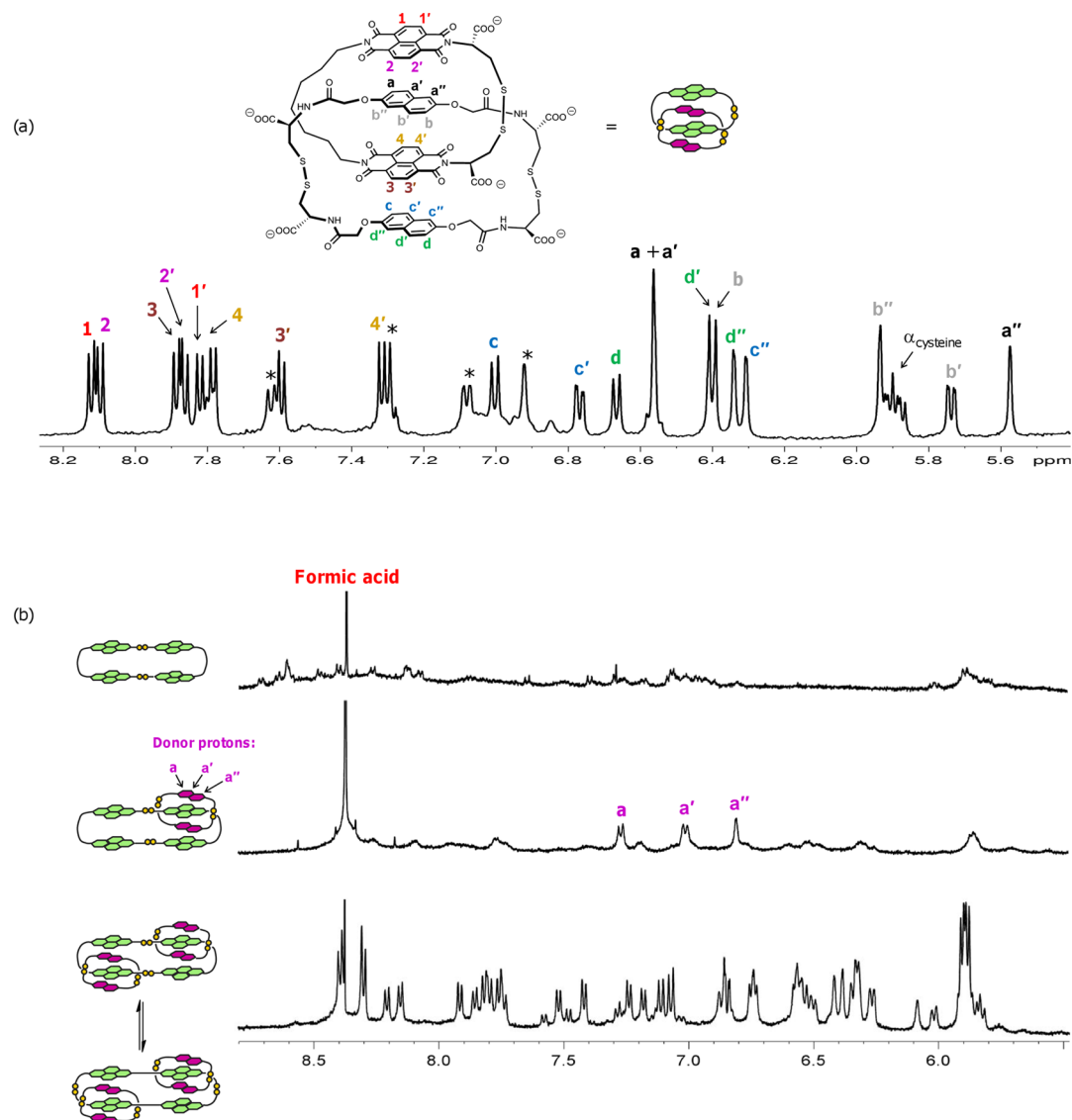
Figure 6. Comparison of the yield of: (a) homo and heterochiral catenanes and (b) homo and heterochiral catenane following the one pot and the stepwise procedures (in the case of  $n = 4$ ).

is highly favored by the tightness of the acceptor cyclic monomer derived from the building blocks of this study ( $7 \leq n \leq 9$ ), in full agreement with our previous observations and mechanistic proposal.

**Influence of Chirality on Catenane Formation.** The aliphatic linker length of the building block is not the only feature that can be used to control catenane synthesis. In compact structures, such as catenanes, the negatively charged carboxylates accumulate around the disulfide bridges, potentially having an adverse effect on their formation. The geometry of the carboxylates is dictated by the cysteine chiral center in the building blocks. Therefore, a change in chirality can be used to influence the energy landscape of the library. Toward this end, we analyzed libraries composed of **2–9** in the presence of the enantiomeric building block **1'**, derived from D-cysteine (Figure 6). Indeed, the libraries distribution is dramatically affected by the change in chirality. Despite the formation of overall more complex libraries, the odd–even effect is still

observable (see SI). Although the effect of chirality on the behavior of complex dynamic systems is difficult to rationalize,<sup>12</sup> comparative kinetic studies suggest that chirality influences the whole energy landscape of the libraries. The formation of heterochiral catenanes seems to be recurrently preferred compared to the formation of catenanes with homochirality. In the most impressive example, the assembly of the [2]catenane becomes nearly quantitative for  $n = 9$  (homochiral [2]catenane: 70%, heterochiral [2]catenane: 90%). The formation of the [3]catenanes is also improved and reaches 50% for  $n = 4$  (homochiral [3]catenane: 33%). Once again, this yield can be further improved to 70% when **1'** is added in a stepwise fashion. To date, these are the best yields obtained for the synthesis of these dynamic combinatorial catenanes.

**<sup>1</sup>H NMR Characterization of a Family of Catenanes ( $n = 7$ ).** The  $n = 7$  library provides a unique opportunity to isolate



**Figure 7.** <sup>1</sup>H NMR spectrum (D<sub>2</sub>O, 298 K, 500 MHz) of the catenanes formed from **1** and **7**. (a) Partial spectrum of the [2]catenane. (b) Partial spectra of the [3]catenane and the macrocyclic intermediates on the pathway to its formation. An impurity is labeled by \*.

and compare by <sup>1</sup>H NMR (500 MHz, 298 K, D<sub>2</sub>O) a [2] and [3]catenane produced from the same building blocks, **1** and **7**.

The <sup>1</sup>H NMR spectrum of the [2]catenane is characteristic of a fully asymmetric catenane in which each of the aromatic protons is inequivalent (Figure 7a). In the acceptor region (7.2–8.2 ppm), eight doublets were assigned by correlation spectroscopy (COSY) to the eight protons of the naphthalene-diimide units: four upfield-shifted (inner acceptor) and four downfield-shifted (outer acceptor). A similar pattern was observed in the donor region (5.5–7.1 ppm).

Figure 7b shows the NMR spectra of the corresponding [3]catenane and of each of the macrocyclic intermediates leading to this [3]catenane. These spectra clearly illustrate how, during the process of the [3]catenane formation, increasing rigidity arising from the successive threading of donor dimers around the acceptor dimer progressively sharpens the NMR signals. The acceptor dimer displays broad resonances characteristic of large, conformationally flexible macrocycles.<sup>3</sup> Threading of one donor ring does not significantly constrain the flexibility of the acceptor dimer: its signals are consequently broad and cannot be assigned. On the other hand, the donor

dimer displays the expected sharp signals of a rapidly rotating ring. Upon threading a second donor ring, the NMR signals sharpen remarkably due to the high level of organization of the aromatic units within the [3]catenane.

The complexity of the [3]catenane structure, with two possible conformations, renders its full characterization difficult by NMR. However, it is important to point out that the exchange between the two conformations can be restricted by both the length of the aliphatic linker and the building block chirality. Indeed, for  $n = 4$ , the homochiral [3]catenane exhibits only one conformation, while the heterochiral [3]catenane exhibits two conformations in a molar ratio of 2:1 (see SI). Of course, the effect of ring size on the energy barrier between the two conformations is more pronounced, and for  $n = 7$ , the two conformations are present in equal proportions.

## CONCLUSIONS

We have shown here that the length of the aliphatic linker, the chirality of the building blocks, and kinetic and thermodynamic parameters can be efficiently manipulated to synthesize a variety of [2] and [3]catenanes in high yields.

In libraries consisting only of the acceptor building blocks connected via long linkers ( $n \geq 8$ ), the hydrophobic effect drives the formation of all-acceptor [2]catenanes. In the libraries composed of acceptor and donor building blocks, changing the length of the linker leads to dramatic variations in library distributions. For short-linkers ( $n \leq 6$ ) we can distinguish two characteristic types of energy landscapes highlighting an odd–even effect. In the first situation (even libraries,  $n = 2, 4, 6$ ), the formation of the [3]catenane is largely favored over the other possible macrocycles. In the second situation (odd libraries,  $n = 3$  and  $5$ ), many other macrocycles compete with the formation of the [3]catenane: the yield of the [3]catenane is low, and the libraries are dominated by the presence of many large macrocycles, some of which are also catenated. Reinitiation of the reversible process through stepwise addition of **1** leads to the production of the thermodynamically more stable [3]catenane at the expense of the unusually large catenanes. Furthermore, changing the building block chirality influences the library distribution in favor of catenane formation.

While the origins of the observed odd–even effect are still unclear, it seems to affect both the shape and the relative energy of the macrocycles formed in solution and the kinetic pathways leading to the formation of [3]catenanes. The right balance between flexibility and rigidity, partially controlled by the odd–even effect, constitutes an important component of the self-assembly of complex structures in dynamic systems.

## ■ ASSOCIATED CONTENT

### ■ Supporting Information

Detailed procedure for building block synthesis, library preparations, HPLC/LC-MS methods and data, 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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### Author Contributions

<sup>§</sup>These authors contributed equally.

### Notes

The authors declare no competing financial interest.

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