Radial Hetero[5]catenanes of Isomeric Peripheral Sequences of the Interlocked Macrocycles

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Abstract: A pair of radial [5]catenanes with an isomeric cyclic –AABB– or –ABAB– type sequence of the interlocked β-cyclodextrin (β-CD) and cucurbit[6]uril (CB[6]) have been efficiently synthesized via CB[6]-mediated azide-alkyne cycloaddition of strategically designed building blocks. Due to a marked difference in the binding strength and interlocking sequence of the peripheral macrocycles, interesting sequence-dependent properties characteristic to mechanically bonded macrocycles were realized. Variable ^{1}H NMR studies showed that the –ABAB– isomer has a more independent β-CD dynamics whereas the β-CD motions in the –AABB– isomer are coupled. Dynamics of the pH-insensitive β-CD can also be further modulated upon a base-triggered mobilization of the CB[6]. Moreover, scission of the central ring in tandem MS experiment led to the dethreading of both β-CD from the –AABB– isomer, but one β-CD is mechanically protected from slippage by the strongly bound CB[6] in the –ABAB– isomer. These unique properties of the mechanical bond expressed in a sequence-specific fashion and the transmission of the control on the macrocycle dynamics from one interlocked component to another highlight the potential of complex hetero[n]catenanes that combine the properties of different macrocycles in an inter-dependent manner, which will be implicated in the design of advanced, multi-component molecular machines.

Introduction

Sequence-specific polymeric molecules are of fundamental importance to life. Most notable examples include nucleic acids that encode genetic information as linear arrays of nucleobases and proteins in which the primary amino acid sequence determines the protein high-order structure, activity and stability.[1,2] In these biomolecules, while the biological information is encoded by sequences of covalently linked monomers, sequence-specific non-covalent interactions, from the complementary hydrogen bonds in protein synthesis machineries[3] to the inter- and intramolecular forces for protein folding,[4] are central to the transfer and expression of the information. These unique features of sequence-specific molecules also hold great promise in data storage[5] and information processing[6] if replicated in synthetic molecules. Although the synthesis and control of sequence-encoded synthetic polymers is still a great challenge,[7] there are few examples of oligomeric systems that display sequence-encoded recognition[8] and duplex formation properties.[9] Sophisticated molecular machines can also be developed when sequence-specific covalent structures are incorporated in mechanically interlocked molecules (MIMs). For example, an artificial peptide synthesizer has been developed based on a [2]rotaxane featuring a thiol-appended, mechanically interlocked macrocycle that can "walk" along an axle containing amino acid side chains that are ordered in a specific sequence.[10]

Exhibition of sequence-specific properties, however, is not exclusive to molecules with components that are covalently linked in a specific order. High-order MIMs, such as [n]rotaxanes and [n]catenanes, with multiple macrocycles that are mechanically interlocked in a specific order, can also display sequence-specific properties, and diverse functions and applications can be envisaged when combined with the unique flexibility, mechanical strength, co-conformational and stereochemical properties of the MIMs.[11] Depending on the topology, there will be a minimum number of macrocycles in a particular MIM to be interlocked to give different sequences. For example, sequence isomerism could be displayed by a linear [3]catenane when there are at least two types of interlocked macrocycles.[12] Due to the challenges in the synthesis of high-order MIMs,[13] reported examples of hetero[n]rotaxanes[14] and hetero[n]catenanes[15] have mostly been prepared as a single isomer, and no comparison and studies on the properties brought by the different sequences of the interlocked macrocycles have been realized. The most representative example of sequence isomerism in MIMs was reported by Leigh and co-workers, in which a pair of [3]rotaxane sequence isomers were prepared by clipping two pyridyl-2,6-diamide macrocycles bearing different substituents onto an unsymmetrical axle in different order.[12] A pair of rotacatenane isomer consists of an dumbbell interlocked on the two different sides of an unsymmetrical [2]catenane has also been recently prepared and characterized by Saito.[16] Despite the importance and high potential of exploiting sequence-specific properties that are due to mechanical interlocking, MIMs of other topology that contain isomeric sequences of the interlocked macrocycles are yet to be realized.

Here we report the efficient and selective synthesis of a pair of isomeric radial [5]catenanes featuring cucurbit[6]uril (CB[6]) and β-cyclodextrin (β-CD) interlocked on a central macrocycle in two different sequences. In spite of the highly similar structures of the [5]catenane isomers, different macrocycle dynamics and mass spectrometric fragmentation behavior were observed as a result of the specific arrangement of the tightly bound CB[6] and the loosely bound β-CD on the periphery, providing an attractive and reliable design strategy for paving the way towards future sequence-specific encoding possibilities.

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Results and Discussion

Design and Synthesis of Radial [5]Catenanes with Different Peripheral Sequences. Radial catenanes were chosen in our study over other catenane types such as linear and branched catenanes because it involves minimally one new macrocycle formation and could be more easily accessible.[17] To realize radial catenanes with isomeric sequences of the peripheral macrocycles, there should either be at least four of two constitutionally different macrocycles interlocked on a central large ring (i.e. radial [n≥5]catenanes) or three constitutionally different macrocycles interlocked on a central ring with directionality (Figure 1). It is noteworthy that radial [n≥5]catenanes have always been prepared with identical peripheral macrocycles[18] and the control on the macrocycle sequence in catenane has not been achieved so far.

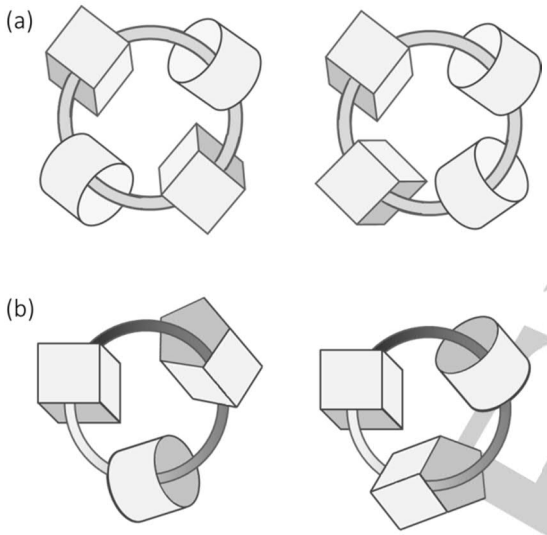


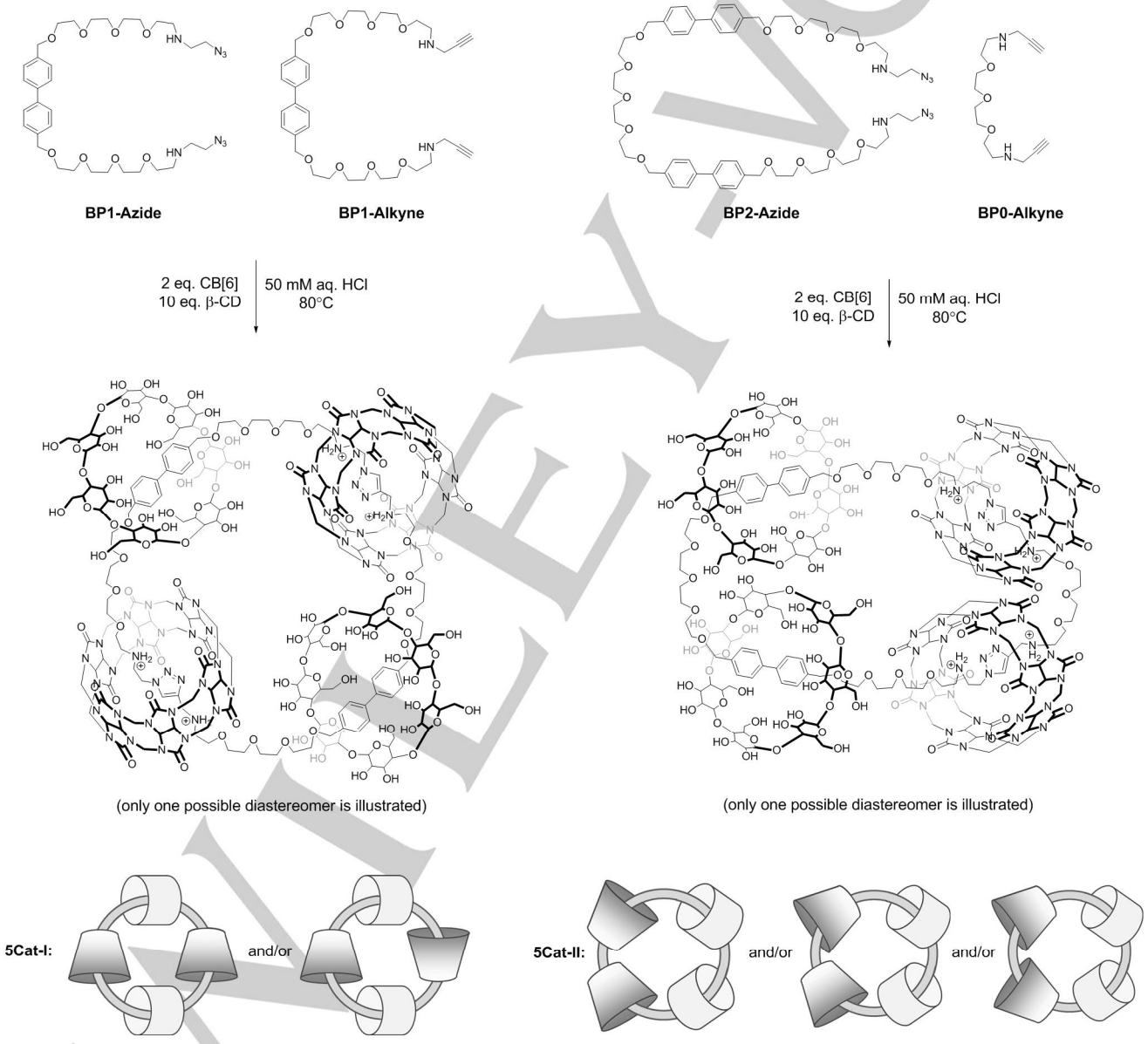
Figure 1. Sequence isomers of radial catenanes: (a) [5]catenanes with two types of peripheral macrocycles; (b) [4]catenanes with three types of peripheral macrocycles interlocked on a central large ring with directionality.

We have been studying new strategies for efficient multi-ring [n]catenane synthesis so as to realize different interesting properties and applications of the mechanical bonds.[19] In particular, by using cucurbit[6]uril-mediated azide-alkyne cycloaddition (CBAAC) to couple the preorganization and macrocyclization in one single step, formation of unwanted, low-order side products is eliminated and the [n]catenane can be obtained efficiently.[19b,19c] If the central macrocycle of a radial catenane is to be formed from a [1+1] cyclization of a bis(2-aminoazide) and a bis(3-aminopropyne) building block by CBAAC, the positions of the two CB[6] will be pre-defined by the positions of the newly formed triazoles, and interlocking another type of macrocycles at selected positions will then give isomeric radial catenanes. β-Cyclodextrin (β-CD), which is known to form stable inclusion complex with aromatic units like biphenylene, was chosen as the second type of peripheral macrocycle because of its compatibility and orthogonality to ammonium–CB[6] binding in aqueous medium.[20] In addition, due to the much stronger CB[6]-bis(ammonium) binding (log K ≈ 5–7)[21] than that of β-CD to biphenylene (log K ≈ 2–3),[22] the significantly different stability and dynamics of the two macrocycles could result in different inter-component interactions and obvious sequence-dependent properties when these macrocycles are interlocked in different sequences.

Bis(2-aminoazide) **BPn-Azide** (n = 1 or 2) and bis(3-aminopropyne) **BPn-Alkyne** (n = 0 or 1) that contain zero, one or two biphenylenes were designed and synthesized. Flexible tetra(ethylene glycol) linkers were incorporated between the recognition units to endow flexibility for macrocycle formation. All the building blocks were prepared from tetra(ethylene glycol) and 4,4'-biphenylenedimethanol via iterative activation and nucleophilic substitution (see SI). The synthesis can therefore be extended to building blocks that contain more biphenylene units for higher order catenane synthesis. The [5]catenanes were facilely obtained by CBAAC of a 2:1 inclusion complex of either building block with CB[6] and the partner building block in the presence of 10 eq. of β-CD. Formation of the CB[6] complex will enhance its solubility and avoid unwanted cycloaddition outside the CB[6] cavity. LCMS analysis of the crude reaction mixture revealed both [5]catenanes were produced in over 80% yield, and pure samples of the [5]catenane were obtained by preparative HPLC in 72% (**5Cat-I**) and 82% (**5Cat-II**) yield (Scheme 1). Despite the strong CB[6]-ammonium binding, β-CD can be successfully interlocked on the biphenylene. In fact, **5Cat-I** can also be obtained in comparable yield from CBAAC using the 1:1 CB[6]·**BP1-Alkyne** and 1:1 CB[6]·**BP1-Azide** complexes in the presence of 10 eq. of β-CD, showing that the CB[6]–ammonium binding is dynamic under the CBAAC conditions to allow self-correction in the case when two 2-aminoazides or two 3-aminopropynes are bound in the same CB[6] cavity (see SI).

There are two possible cyclic sequences of a radial [5]catenane with two β-CD and two CB[6] as the peripheral macrocycles. **5Cat-I** features a cyclic –ABAB– sequence which is a result of the use of **BP1-Alkyne** and **BP1-Azide** that both contain one biphenylene, and hence one each of β-CD was interlocked between the two CB[6] units. On the other hand, **5Cat-II** has a cyclic –AABB– sequence as **BP0-Alkyne** and **BP2-Azide** contain respectively zero and two biphenylenes. In both cases, the cyclic sequence is a result of the orthogonal CB[6]-ammonium and (β-CD)-biphenylene recognition. Such mechanical interlocking of macrocycles with sequence-specific information encoded in the covalent framework of the central large ring via orthogonal non-covalent interactions is conceptually related to and reminiscent of the polypeptide synthesis by ribosomal machineries via complementary hydrogen bonds.[1] Of note, the two central large rings in **5Cat-I** and **5Cat-II** are constitutional isomers with different atom connectivity; the two [5]catenanes are therefore not strictly mechanical sequence isomers which should only be different in their sequence of the mechanically interlocked macrocycles.[12]

In addition, because of the lack of plane symmetry of β-CD and that the two β-CD in the [5]catenanes are not exchangeable due to the presence of the tightly bound CB[6], there could also be two and three diastereoisomers for **5Cat-I** and **5Cat-II** respectively (Figure 2). The two [5]catenane isomers have been characterized in details by various NMR and MS experiments which are described below.



Scheme 1. Synthesis of radial [5]catenanes with isomeric sequences of the interlocked CB[6] and β-CD on the periphery by CBAAC. Only one possible diastereomer is shown for each [5]catenane.

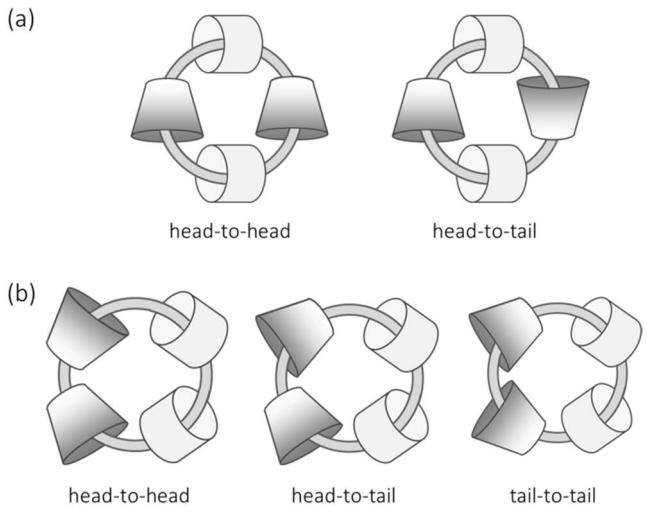


Figure 2. Structures of the possible diastereoisomers of (a) **5Cat-I** and (b) **5Cat-II** due to the different orientation of the β-CD.

NMR Structural Characterization. The ^{1}H NMR spectra of both **5Cat-I** and **5Cat-II** showed one set of resonances at room temperature and are almost identical with no distinguishable features, suggesting both isomers are overall symmetrical and highly similar in their structures (Figure 3). The triazole proton H_z appears as a singlet at 6.56 ppm (for **5Cat-I**) or 6.55 ppm (for **5Cat-II**), which are consistent with other reported chemical shifts of CB[6]-bound triazoles.[14b,14k,14l,19b,19c] NOE cross-peaks between H_z and $H_{CB2}/H_{CB2'}$ on the CB[6] were observed in the 2D NOESY spectra of both [5]catenanes that further support the stationing of the CB[6] units at the triazoles (Figure S19 and S24). The two broad, uncoupled signals observed for $H_a/H_{a'}$ and $H_b/H_{b'}$ of the biphenylene aromatic protons at 298 K for both [5]catenanes are slightly upfield shifted when compared with a related [3]catenane that contains no interlocked β-CD.[19c] The broadness of these peaks also suggests that the two β-CD are more dynamic than the CB[6] in the [5]catenanes and are stationing at slightly different positions around the biphenylene to give co-conformers that are exchanging at a rate close to the NMR timescale. In addition, the NOE cross-peaks between the more upfield broad resonance with H_4 and H_5/H_6 further confirms the interlocking of β-CD at the biphenylene units (Figures S19 and S24). Moreover, the measured diffusion coefficients of 1.71 x 10^{-5} cm^2s^{-1} for **5Cat-I** and 1.77 x 10^{-5} cm^2s^{-1} for **5Cat-II** from the DOSY spectra are also very similar (Figures S20 and S25), showing that the isomeric [5]catenanes are of comparable size in solution.

As discussed above, there could be different diastereomers for the [5]catenanes featuring different relative orientations of the two β-CDs. For a previously reported [3]catenane that contained two interlocked cyclodextrins, the two diastereoisomers with a head-to-head or head-to-tail orientations were obtained as a mixture in equal amount. The two isomers can be differentiated in the ^{1}H NMR spectrum on a symmetry argument due to the rapid circumrotation and exchange of the cyclodextrins[23] For **5Cat-I**, the two triazoles and CB[6] are essentially equivalent and only one resonance was observed for H_1 of the β-CD despite the overall C_1 symmetry of both diastereoisomers,

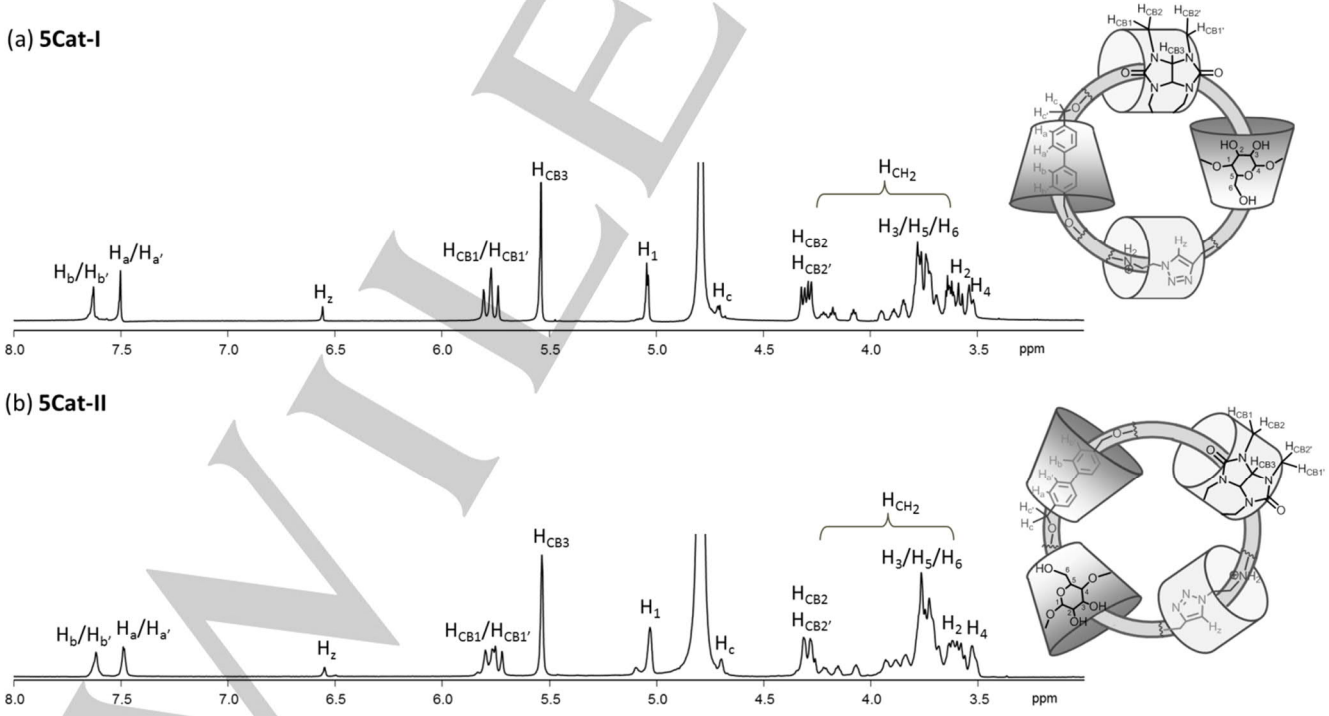


Figure 3. ^{1}H NMR (500 MHz, D_2O, 298 K) spectra of (a) **5Cat-I** and (b) **5Cat-II**. Shown on the right are the labelings of the respective protons. One possible diastereoisomer is shown for each [5]catenane.

showing the interlocked macrocycles exert little to no effect on the chemical environment of each other. The $^{13}C\{^1H\}$ NMR spectrum of **5Cat-I** is fully consistent with the ^1H NMR data and showed that only one chemical environment for the interlocked CB[6] and β-CDs (Figure S17). As a result, no information related to the diastereoisomers can be obtained. Similar ^1H and $^{13}C\{^1H\}$ NMR spectral features that showed the interlocked CB[6] and β-CD are equivalent were observed for **5Cat-II** and no information related to the possible existence of diastereoisomers could be deduced. Of note, in (pseudo)rotaxane systems that contain both cyclodextrins and CB[6] as the interlocked components, a particular orientation of the cyclodextrin with respect to the CB[6] can be more stable due to hydrogen bonds between the macrocycles,[14b,24] and a stereoselective (pseudo)rotaxane formation is possible.[14l,24a] For catenanes with a cyclic structure, the possible existence and effects of the cyclodextrin-CB[6] hydrogen bonds on the stability and stereochemical properties of the catenanes are yet to be explored.

Dynamic Behavior of the [5]Catenane Isomers. Macrocycle dynamics is one of the most important features of MIMs because the translocation of the interlocked macrocycles and switching between different co-conformations are directly related to the properties and potential of the MIMs for their development into functional molecules such as molecular switches and molecular machines.[10,11] Cyclodextrin-containing catenanes have been shown to display dynamic motions such as circumrotation due to the moderate to weak cyclodextrin binding to the template.[22a,23,25] CB[6]-bis(ammonium) binding, on the other hand, can be strong to render a relatively static structure.[14b,14k,19b,19c,26] As a result, **5Cat-I** and **5Cat-II** would represent a pair of interesting examples in which the position and motion of the two β-CDs are separated by two "static" CB[6] in **5Cat-I**, but the β-CD dynamics could be coupled in **5Cat-II** as they are on the same "track" along the central macrocycle.

The dynamic properties of the [5]catenane isomers was first studied by variable temperature ^1H NMR spectroscopy (VT-NMR). At 298 K, two broad signals were observed for the aromatic protons of the biphenyl units of the two [5]catenanes at about 7.5 ppm and 7.6 ppm. Becasue of the asymmetry of the β-CD, four sets of coupled doublets are expected for the aromatic protons of the included biphenyl when the β-CD is relatively static.[14b,20b,27] If the β-CD is able to exchange its position, in the slow exchange regime, multiple sets of signals are to be expected. The two broad signals suggestive of an oscillating motion of the β-CD around the biphenyl unit at a rate comparable to the NMR timescale, corresponding to the coalescence of the different sets of signals to one set of not-completely-resolved signal. Increase in temperature and exchange rate to the fast exchange regime will further resolve the broad signal of the biphenyl to four clear doublets again due to the assymmetry of the β-CD.[23]

Upon increasing the temperature, no significant difference in the chemical shifts was observed for both [5]catenanes. Due to the strong CB[6]-bis(ammonium) binding, the two CB[6] remain at the triazoles and no noticeable change in the peak shape of H_{CB1}/H_{CB2} and H_z was observed. However, resolution of the broad biphenyl aromatic signal at 7.49 ppm of **5Cat-I** was first observed at 328 K, and the signal became completely resolved to two doublets at 348 K (Figure 4a). Some degree of sharpening of the resonance at 7.61 ppm was also observed. These spectral changes are consistent with a more rapid exchange due to a faster β-CD dynamics at a higher temperature, showing that the β-CDs can indeed shuttle along the biphenylene "tracks" separated by two relatively static CB[6] stations. For **5Cat-II**, although some changes in the peak shape of the aromatic signals were observed upon increasing the temperature, no complete resolution of the broad signals was observed at 348 K, which is the highest temperature limit of the NMR spectrometer used. The need of a higher energy to interconvert the conformers of **5Cat-II** compared to those of **5Cat-I** is consistent with the proposal that the dynamics of the two β-CD are coupled in the cyclic –AABB– isomer but are independent of each other in the cyclic –ABAB– isomer, directly demonstrating the effect of the sequence of the peripheral macrocycles on the dynamic properties of the [5]catenanes. Although one may also argue that the different dynamic behavior could arise from the different degree of inter-component interactions due to the possible presence of diastereomers with different β-CD orientations, this would be less probable because such interactions would be stronger in **5Cat-I** than in **5Cat-II** with respectively four and two CB[6]/β-CD interfaces for interactions, which is not consistent with the observation that more energy is required to interconvert the conformers of **5Cat-II** than those of **5Cat-I**.[24]

The macrocycle dynamics were also studied under basic conditions in which the CB[6] are no longer tightly bound upon deprotonation of the ammoniums. Indeed, pH-mediated CB[6] shuttling and co-conformational switching have only been previously studied in rotaxane systems but not in catenanes.[25] Upon addition of NaOH to **5Cat-I**, a slight upfield shift of H_z by ~0.09 ppm was observed along with a change of the peak shape of H_{CB1} signal from two closely spaced to clearly separated doublets (Figure S28). Shifts of some of the aliphatic protons, probably those CH_2 close to the triazole although they cannot be unambiguously assigned, were also noticed with two uncoupled peaks upfield shifted to 3.16 and 3.05 ppm. Similar spectral changes were also observed for **5Cat-II** (Figure S29). These spectral changes showed that the triazoles are still being included inside the CB[6] cavity but the positions of the CB[6] were slightly adjusted upon "unlocking" by deprotonation. This slight adjustment of the CB[6] positions is in great contrast to those observed in CB[6]-based rotaxanes in which complete translocation of the macrocycle is generally observed when the pH is increased.[26] Interestingly, VT-NMR of the deprotonated **5Cat-I** and **5Cat-II** both revealed a resolution of one broad biphenylene aromatic signals, similar to those observed before the addition of base, at a lower temperature than that before deprotonation and the resonance can be completely resolved at 338 K and 348 K for **5Cat-1** and **5Cat-II** respectively (Figures 4b, S30 and S31). These observations suggest that "unlocking" the tightly bound CB[6] by deprotonation could mobilize the CB[6]

and in turn influence the β-CD dynamics, although the latter is not expected to be pH-responsive. The CB[6] in the deprotonated state could be more mobile and accommodating to the shuttling of the β-CDs, and thus less energy is needed for the conformer interconversion. Notably, the modulation of the dynamics of a macrocycle through the stimulated modulation of the dynamics of another macrocycle may be conceptually similar to the transmission of the mechanical motions via different toothed wheels in a gear system. The different β-CD dynamics from the isomeric arrangements of the interlocked macrocycles that can be modulated by pH displayed by the [5]catenane isomers will therefore be implicated in the design of advanced molecular machines based on complex multi-component MIMs. The delicate interplay of the binding strength, dynamics and pH-responsiveness of CB[6] and β-CD in the [5]catenanes also highlights the new potentials of interlocking different macrocycles in a single high-order hetero[n]catenanes.

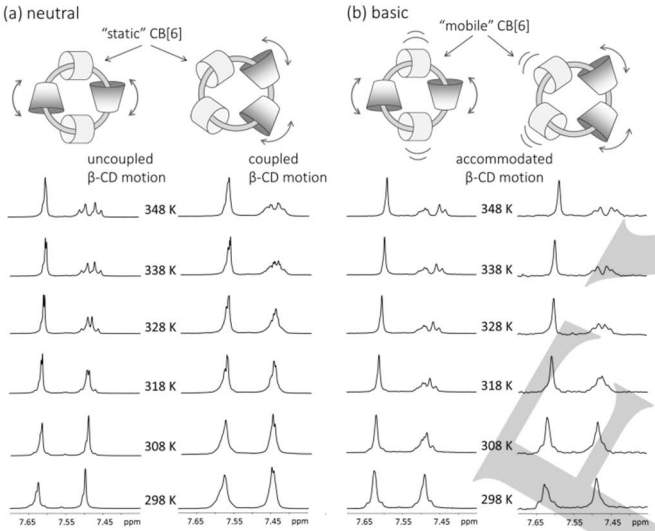


Figure 4. Partial ^{1}H NMR (500 MHz, D_2O) spectra showing the biphenylene aromatic resonances of **5Cat-I** (left) and **5Cat-II** (right) at increasing temperature under (a) neutral conditions and (b) after addition of 10 eq. of NaOH.

Sequence-dependent MS Fragmentation. High resolution ESI-MS analysis of the [5]catenane isomers showed similar molecular ions respectively at *m/z* = 1402.7709 and *m/z* = 1402.7880 for **5Cat-I** and **5Cat-II**, which correspond to the molecular ion at the +4 charge state and their isotopic patterns are both consistent with those simulated for the molecular formulas of $C_{226}H_{322}N_{58}O_{110}$ (Figures S34 and S35). The presence of the +4 ion as the only major species in the MS is also consistent with the strong CB[6]-bis(ammonium) binding that preserves the ammoniums under the MS conditions.

Intriguingly, the isomeric **5Cat-I** and **5Cat-II** displayed very different fragmentation behavior in tandem mass spectrometry experiment. In MS/MS, collision induced dissociation (CID) of the $[M]^{4+}$ parent ion of **5Cat-I** first gave a daughter ion at *m/z* = 1119, corresponding to a loss of one β-CD, at a normalized collision energy of 19% (Figure 5a). A trace amount of another daughter ion at *m/z* = 835, from the loss of both β-CDs, was also observed. On the other hand, both the daughter ions at *m/z* = 1119 and *m/z* = 835 were observed at comparable intensity when the parent $[M]^{4+}$ ion of **5Cat-II** was subjected to the same CID conditions (Figure 5b). No daughter ions resulting from the loss of the CB[6] was observed as a result of the strong CB[6]-bis(ammonium) binding. The different MS^2 fragmentation behavior is again a result of the different sequence of the tightly bound CB[6] and loosely bound β-CDs in the isomeric [5]catenanes. With a cyclic –ABAB– sequence in **5Cat-I**, slippage of one β-CD can be prevented due to the mechanical protection provided by two tightly bound CB[6] upon scission of the central macrocycle. The loss of both the β-CDs will therefore requires scission of at least two covalent bonds and hence a lower signal intensity of *m/z* = 835 was observed in the MS^2 spectrum of **5Cat-I**. For **5Cat-II**, on the other hand, because the two loosely bound β-CDs are adjacent to each other, scission of the central macrocycle at a position between the CB[6] and β-CD, or between the two β-CDs, would create an opening for the slippage of one or both β-CDs to give the daughter ions at *m/z* = 835 and *m/z* = 1119. The comparable intensity of these two daughter ions may also suggest that the central macrocycle was cleaved at a position close to the CB[6], such that the slippage of the inner β-CD is less efficient. Preferred cleavage of the ammonium C–N bond has indeed been reported.[14d,28]

If scission of the β-CD is considered, the different fragmentation pattern of **5Cat-I** and **5Cat-II** could imply a different degree of inter-component interactions in the [5]catenane isomers. In **5Cat-I**, a β-CD could possibly be stabilized by the two adjacent CB[6], whereas a β-CD in **5Cat-II** could only interact with one CB[6]. Although interactions between CB[6] and β-CD have only been reported in linear (pseudo)rotaxane but not macrocyclic systems,[14b,20a,24] the fragmented species may not maintain a cyclic/curved structure and the possible effect of such inter-component interactions could not be ruled out. In fact, further CID of the daughter ion at *m/z* = 1119 showed the remaining β-CD in the fragment derived from **5Cat-I** is more stable than that in **5Cat-II**. At a normalized collision energy of 19%, no further fragmentation was observed in the MS^3 spectrum of **5Cat-I**, but the smaller fragment at *m/z* = 835, from the loss of the remaining β-CD, was observed at a significant intensity in the MS^3 spectrum of **5Cat-II** (Figures S37 and S38). Further scission of these fragments were observed to give distinctive MS^3 spectra for the [5]catenane isomers upon increasing the collision energy. These distinctive fragmentation patterns that provide additional information on the possible inter-component interactions may also help further understanding the macrocycle stability and dynamics, in addition to be an effective characterization method for the highly similar, high-order [n]catenane isomers.

Although no precise information about the bond scission is available, the different fragmentation patterns of the [5]catenane isomers is certainly a result of the different sequences of the interlocked CB[6] and β-CDs on the periphery. Notably, complete dissociation of an entire macrocycle (e.g. β-CD) as a

result of the simultaneous breaking of the covalent and mechanical bonds is characteristic to mechanically interlocked macrocycles.[29] The different MS fragmentation of **5Cat-I** and **5Cat-II** can therefore be considered as a combined feature when the CB[6] and β-CDs are interlocked in a specific order, highlighting the new and unique features that can be generated only when the properties of mechanical bonds are expressed in the context of sequence-specific molecules.

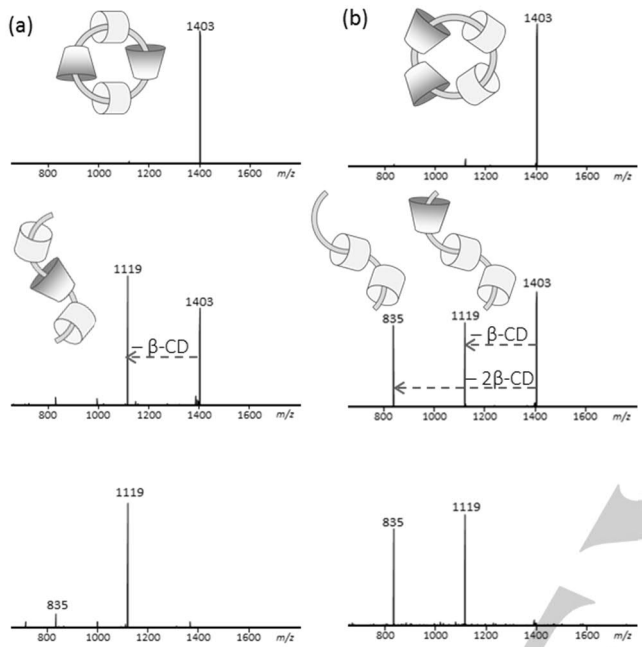


Figure 5. Collision-induced dissociation experiment conducted with mass-selected ions at *m/z* = 1403 ($[M]^{4+}$) of (a) **5Cat-I** and (b) **5Cat-II**, with the suggested fragments at an increasing normalized collision energy (from top to bottom: 17%, 19% and 21%).

Conclusion

In summary, the challenging synthesis of high order [n]catenanes featuring isomeric sequences of the interlocked macrocycles is accomplished by CBAAC of strategically designed building blocks that can engage in orthogonal preorganization. A pair of isomeric [5]catenanes of different cyclic sequences of CB[6] and β-CD interlocked on periphery were synthesized in high yield. Other high-order, multi-component MIMs of a well-defined structure and unprecedented complexity could also be produced using a similar strategy. By arranging the loosely bound β-CD and tightly bound CB[6] in different cyclic sequences, the [5]catenane isomers display very different pH-dependent β-CD dynamic properties and mass spectrometric fragmentation behavior which are unique to molecules possessing mechanical bonds. The preparation of [5]catenane isomers reported in this work not only is a first demonstration of realizing sequence-specific properties in complex molecular links, but also has huge implication in the future exploitation of sequence-specific properties for the design and synthesis of MIMs-based, information-enabled molecular machines and functional materials that combine the unique properties of the mechanical bond in a sequence-specific fashion. Further studies on the applications of these sequence-specific high-order MIMs are currently underway in our laboratory.

Experimental Section

See the Supporting Information for synthetic procedures and supporting figures.

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Keywords: Catenanes • Cucurbiturils • Cyclodextrins • Supramolecular chemistry

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