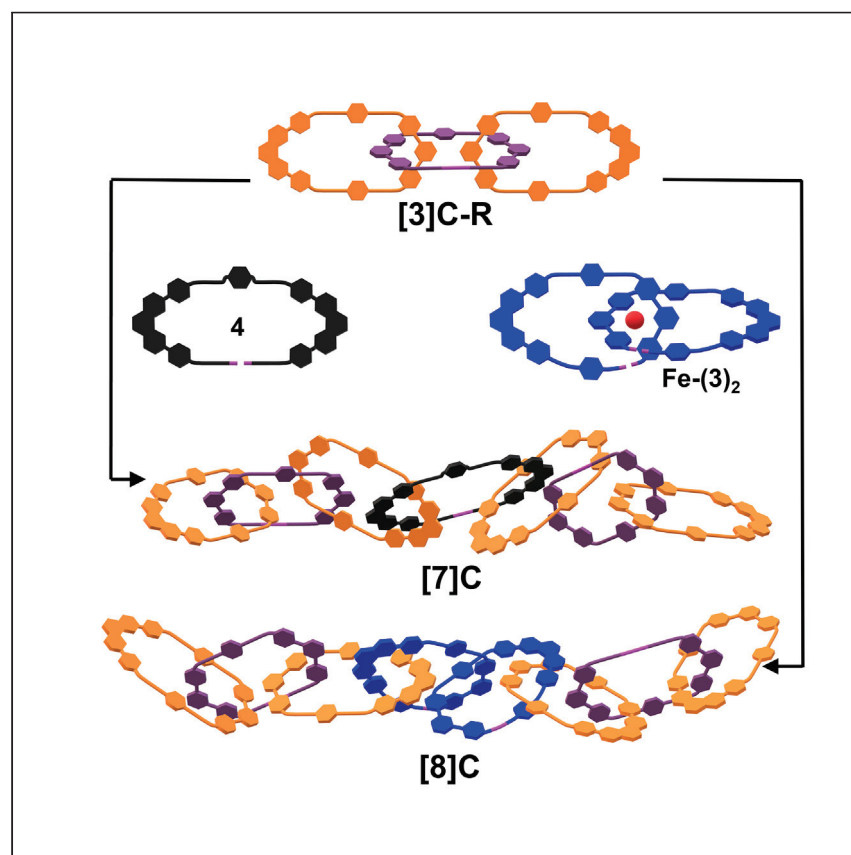


Article

Synthesis of linear [7]- and [8]catenanes



A long-standing goal in polymer science is a flexible and soluble polymer containing all-interlocked molecular rings, but this goal has been difficult to achieve, as many approaches yield mixtures of products. Harlan et al. demonstrate the synthesis of an [8]catenane comprising eight interlocked rings, approaching that of low-molecular-weight polymers.

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Highlights

Concerted “zip-tie” synthesis of discrete linear [7]- and [8] catenanes

Ring-closing metathesis reactions yield multiple mechanical bonds in one reaction

[8]C weighs over 10 kDa and is close to molar masses of low-molecular-weight polymers

Both catenanes contain open metal-binding sites, allowing for further growth

Harlan et al., Cell Reports Physical Science 5, 101767

January 17, 2024 © 2023 The Author(s).

<https://doi.org/10.1016/j.xcrp.2023.101767>



Article

Synthesis of linear [7]- and [8]catenanes

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SUMMARY

Catenanes are a family of mechanically interlocked molecules that consist of molecular rings that can be interlocked to give linear, radial, or cyclic structures. Although chemists have pursued extended linear poly[*n*]catenane architectures for many decades, there still exists a fundamental gap between the synthesis of well-defined, linear oligomers and that of disperse polymers that are often produced as a mixture of architectures. Here, we report two convergent one-pot syntheses that “zip-tie” together two pre-made [3]catenanes by first using orthogonal metal templation with phenanthroline (Cu(I)) and terpyridine (Fe(II)) ligands. These pre-catenate complexes were subjected to a ring-closing metathesis step to afford discrete, linear [7]- and [8]catenanes. The successful synthesis and isolation of the discrete [7]- and [8]catenanes were confirmed using multiple methods of characterization. Because these record-setting linear [*n*]catenanes possess open phenanthroline metal-binding sites at each end, further expansion to all-interlocked linear poly[*n*]catenanes is a realistic proposition.

INTRODUCTION

Mechanically interlocked molecules (MIMs)¹ are defined as having two or more molecular structures interlocked in space that cannot be separated without cleaving a covalent bond.² The two most frequently investigated MIM architectures are [*n*]rotaxanes³ and [*n*]catenanes,⁴ where *n* refers to the number of molecular components that make up each MIM. The former comprises a linear rod- or dumbbell-shaped molecule ensconced by one or more molecular rings or macrocycles that can undergo translational motion along the linear molecular track. Catenanes, however, go one step further and can be formed by linking together the ends of an unstoppered pseudorotaxane (i.e., a ring-closing step), thus creating an interlocked pair of molecular rings. The ease of synthesis and scalability of [*n*]rotaxanes has allowed them to be studied extensively in functional materials—such as in daisy-chain-^{5,6} and slide-ring-based^{7,8} materials, which can undergo significant changes in properties upon activation. However, [*n*]catenanes⁹ are typically more challenging to synthesize due to potential byproduct formation that often occurs during the ring-closing step.^{10,11} Moreover, multiple [*n*]catenane architectures are possible—namely, linear, radial, and cyclic—which presents additional synthetic challenges. Nevertheless, linear [*n*]catenanes, particularly higher-order ones, have extended architectures that hold great potential when integrated into functional materials because the linear arrangement of the interlocked molecular rings maximizes their degrees of freedom (e.g., rotation, translation, and rocking), which could enhance molecular motion within the material and therefore contribute to its overall flexibility and energy dissipation pathways, to name a few potential material benefits.

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<https://doi.org/10.1016/j.xcrp.2023.101767>



Most reported syntheses of $[n]$ catenanes have used some form of templation, which brings two molecular components together in an enthalpically favorable process. Various forms of template-directed syntheses have been investigated over the years, including donor-acceptor,^{12–14} hydrogen-bonding,^{15,16} anion-dipole interactions,¹⁷ etc., but the use of metals has been shown to be the most efficient method of templation¹⁸ to generate smaller $[n]$ catenanes as well as larger oligo-^{19,20} and poly $[n]$ catenanes.^{21,22} For example, Sauvage and co-workers developed²³ an orthogonal metal templation strategy to selectively form asymmetric $[n]$ catenanes. In their approach, ternary tetracoordinate complexes were formed from phenanthroline (phen) ligands and a mono-valent metal (Cu(I)), whereas ternary hexacoordinate complexes were possible using terpyridine (terpy) ligands and a bivalent metal (Ru(II)). Recently, this orthogonal metal templation strategy was used by us to synthesize and isolate a family of discrete $[n]$ catenanes,^{20,24} ranging from 2 to 6 interlocked molecular rings, with the latter [6]catenane representing the largest isolated linear $[n]$ catenane reported to date. Others have used metal templation strategies to prepare discrete higher-order non-linear $[n]$ catenanes. For example, Au-Yeung and co-workers demonstrated²⁵ the synthesis of a branched [8]catenane via a one-pot reaction involving the formation of a bis-phen Cu(I) ternary complex that also served as a template for the addition of four cucurbit[6]uril and two cyclodextrin macrocycles through favorable ion-dipole interactions and hydrophobic binding, respectively. Once assembled, ring-closing metathesis (RCM) chemistry was used to close the phen-based macrocycles, locking the eight molecular rings in place. It is important to note that in nearly all these examples of well-defined $[n]$ catenanes, the terminal molecular rings were essentially dead ends, meaning that further growth to higher-order products or use as a (cross)linker²⁶ is not possible.

Alternatively, polydisperse $[n]$ catenanes have also been produced using an elegant one-pot metal templation strategy through the formation of metallocsupramolecular polymers followed by many simultaneous RCM reactions. Notably, this approach was implemented previously by Rowan and co-workers,^{21,22} who produced disperse poly $[n]$ catenanes with up to 27 subunits. Di Stefano and co-workers²⁷ also used a one-pot approach to make disperse poly $[n]$ catenanes by instead starting from an unsaturated phen-based [2]catenane that was ring opened in the presence of Grubbs catalyst to yield a mixture of catenane architectures. Although each of these methods to make poly $[n]$ catenanes required fewer steps to generate high-molecular-weight products, it remains a challenge to control the type of $[n]$ catenane architecture—i.e., linear, branched, or cyclic—that is produced during the critical ring-closing steps to make poly $[n]$ catenanes.

From these examples, it is clear that a trade-off exists between making disperse yet high-molecular-weight poly $[n]$ catenanes of variable architectures and those of lower-molecular-weight yet well-defined oligo $[n]$ catenanes with dead ends. Here, we describe concerted syntheses involving pre-made [3]catenane building blocks that are assembled with open macrocycle precursors using orthogonal metal templation of mono-valent (Cu(I)) and bivalent (Fe(II)) metals, followed by RCM reactions to make well-defined [7]- and [8]catenanes. Both the [7]- and [8]catenanes represent records for discrete linear $[n]$ catenanes. Also, unlike our previous efforts (Figure 1A), the terminal molecular rings of the [7]- and [8]catenanes are not dead ends (Figure 1B) and therefore may be used for additional growth as needed. Each product was purified using recycling preparative gel permeation chromatography (prep-GPC) after demetallation and then characterized by 1D and 2D proton nuclear magnetic resonance (¹H NMR) spectroscopy as well as matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) and analytical

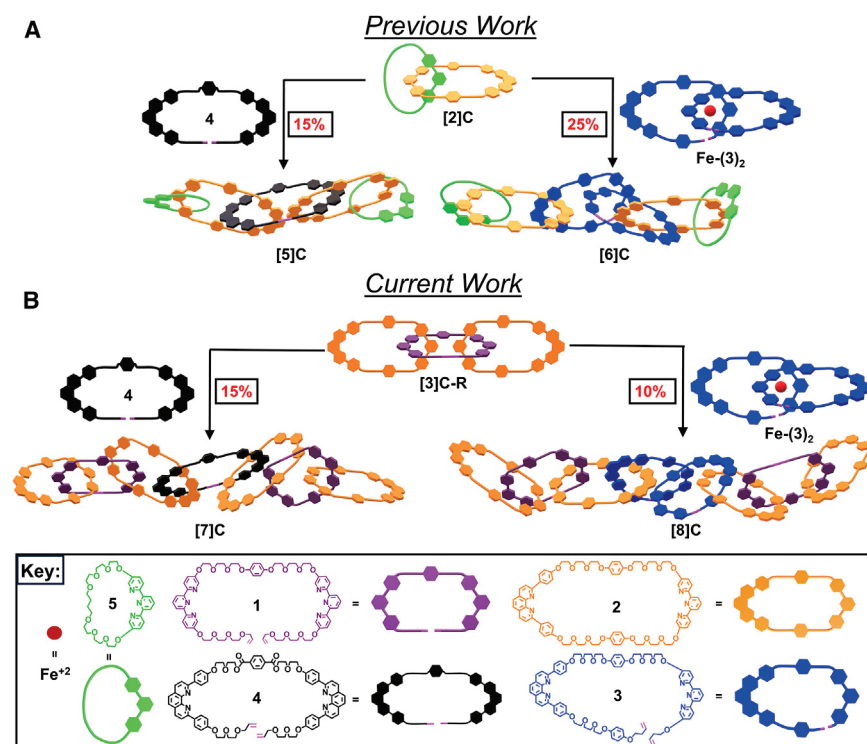


Figure 1. Overview of the concerted zip-tie method used to synthesize higher order linear [n]catenanes

(A) Previous work by us demonstrated the use of a zip-tie method to synthesize well-defined linear [5]- and [6]catenanes ([5]C and [6]C) through orthogonal metal templation and ring-closing metathesis (RCM) reactions. In both cases, each product was terminated by smaller molecular rings, which were incapable of additional RCM steps to make higher-order [n]catenanes.

(B) The current work implemented larger, dual-ligand macrocycles to synthesize and isolate well-defined linear [7]- and [8]catenanes ([7]C and [8]C), both of which represent records for the largest-ever isolated discrete linear [n]catenanes. Moreover, each of these products maintains open phenanthroline coordination sites at each terminus and thus is capable of further expansion in the future.

GPC. We envision that this concerted growth strategy to synthesize [n]catenanes can serve as a blueprint for the synthesis of well-defined, linear poly[n]catenanes.

RESULTS AND DISCUSSION

Synthesis of a [3]catenane building block

Previously, our group demonstrated the use of a “zip-tie” method as an efficient procedure (Figure 1A) to synthesize pure linear oligo[n]catenanes,^{20,24} where *n* ranged from 2 to 6 molecular rings. This method involved the ring closure of pseudo[n]rotaxanes that were first assembled using orthogonal metal templation of a pre-made [2]catenane and open macrocyclic linkers. Here, instead of using a [2]catenane with one dead end, the zip-tie approach was implemented to make a [3]catenane ([3]C). The synthesis of [3]C began (Figure 2A; Scheme S27) with the selective metalation of the terpy ligands of open and closed macrocycles 1 and 2, respectively, using Fe(BF₄)₂·6H₂O. It is important to note that a 1:8 stoichiometric ratio of 1:2 was selected to avoid the potential formation of a metallocsupramolecular polymer comprising mostly 1. Instead, by using a large excess of 2 during the metal templation step (Figure 2A), the phen ligands of 2 were positioned at each terminus and thus favored the formation of a pre-[3]catenane complex consisting of one equiv 1 and two equiv 2. Moreover, we previously demonstrated²⁰ how terpy ligands in a

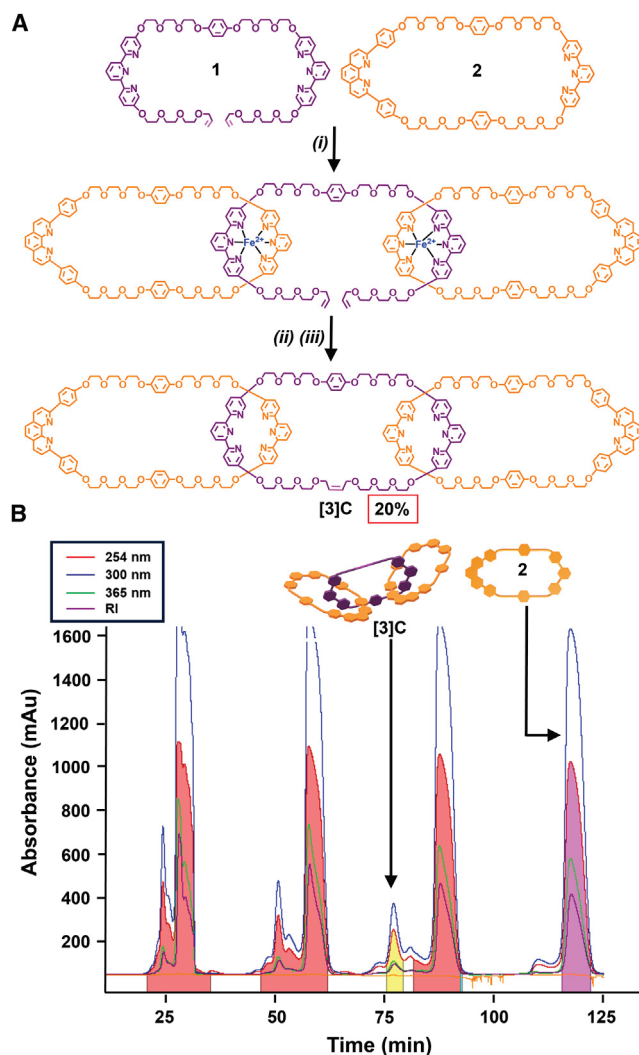


Figure 2. Synthetic scheme and purification of [3]C building block used to synthesize higher-order [n]catenanes

(A) Synthesis of [3]C from precursors 1 (1 equiv) and 2 (8 equiv): (i) $\text{Fe}(\text{BF}_4)_2 \cdot 6\text{H}_2\text{O}$ /THF/ H_2O /3 h/55°C, (ii) Grubbs second-generation catalyst/ CH_2Cl_2 /24 h/reflux, and (iii) K_2CO_3 /DMF/55°C/12 h. (B) Recycling prep-GPC data showing the purification of [3]C, which was performed at 25°C in DMF at 8 mL min⁻¹ flow rate. The product [3]C was isolated in the third cycle at 80 min as indicated by the yellow fraction. Macrocycle 2 was isolated and recovered as indicated by the purple fraction (91 min).

See also Figure S27.

macrocycle have a tendency to flip out of plane and form metal-coordinated dimers of 2 (i.e., $\text{Fe}-(2)_2$; Scheme S28) in the presence of a bivalent metal (e.g., Fe(II)). This dimerization process would disfavor the formation of the desired pre-[3]catenate complex and is likely to occur to some extent in the current syntheses. Thus, a statistical method was required to establish the metal-templated precursor to [3]C, while nearly all the excess 2 that was added to the reaction was recovered using prep-GPC. After the formation of the pre-[3]catenate complex, 1 was ring closed using Grubbs second-generation catalyst. We propose that the yield for the RCM reaction may be slightly lower than expected due to the possibility that the ring may re-open to some extent in the presence of the catalyst, which is well known in [n]catenane

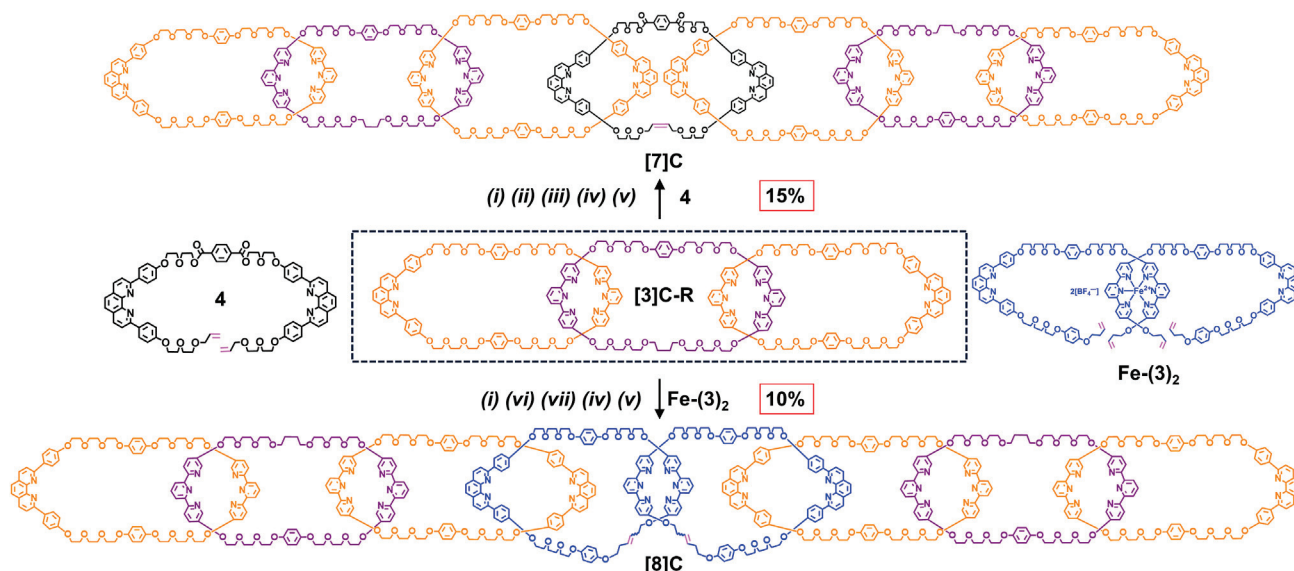


Figure 3. Synthesis of [7]C and [8]C starting from [3]C-R and open macrocycle linkers 4 and Fe-(3)₂, respectively

(i) $\text{Fe}(\text{BF}_4)_2 \cdot 6\text{H}_2\text{O}/\text{THF}/\text{H}_2\text{O}/2\text{ h}/55^\circ\text{C}$. (ii) $\text{Cu}(\text{MeCN})_4\text{PF}_6/4/\text{MeCN}:\text{CH}_2\text{Cl}_2$ (4:11)/24 h/room temperature (RT). (iii) Grubbs second-generation catalyst/ $\text{CH}_2\text{Cl}_2/18\text{ h}/\text{reflux}$. (iv) $\text{K}_2\text{CO}_3/\text{DMF}/24\text{ h}/55^\circ\text{C}$. (v) $\text{KCN}/\text{MeCN}/\text{H}_2\text{O}/1\text{ h}/\text{RT}$. (vi) $\text{Cu}(\text{MeCN})_4\text{PF}_6/\text{Fe}-(3)_2/\text{MeCN}:\text{CH}_2\text{Cl}_2$ (4:1)/24 h/RT. (vii) Hoveyda-Grubbs catalyst/ $\text{CH}_2\text{Cl}_2/18\text{ h}/\text{reflux}$. See also Figures S30 and S31.

syntheses employing RCM chemistry.²⁸ After ring closure, the Fe(II) was removed using K_2CO_3 and DMF, and the product [3]C was purified using prep-GPC (Figure 2B). Additionally, the overall yield to make [3]C depended greatly on the ratio of 1 to 2 during formation of the pre-[3]catenane complex. For example, when a 1:5 ratio of 1:2 was used, the overall yield to make [3]C after ring closing and demetallation was 10%, whereas the 1:8 ratio resulted in a 20% overall yield for [3]C. Lastly, the purity of [3]C was confirmed by analytical GPC (Figure 4C) and high-resolution MS (HR-MS; Figure S31) as well as tandem MS (i.e., MS/MS) (Figure S36).

Next, the synthesis of higher-order [*n*]catenanes was conducted using the pre-made [3]catenane; however, before doing so, the unsaturated olefin of [3]C needed to be reduced (Scheme S29) to prevent deleterious ring-opening reactions that could compete against productive ring-closing ones. Although the most oft-used hydrogenation reaction is $\text{H}_2(\text{g})$ in the presence of Pd/C, these conditions reduced some of the phen ligand's aromatic double bonds. Thus, a diimide hydrogenation was employed *in situ* using *p*-toluenesulfonyl hydrazide and tripropyl amine while keeping the temperature under 130°C . These conditions allowed for selective saturation of the olefin while not dearomatizing any of the phen ligands. The conversion for this reaction was nearly quantitative, as confirmed by ^1H NMR spectroscopy. The isolated yield for the reduced [3]catenane, i.e., [3]C-R, was ~80%.

Synthesis of linear [7]- and [8]catenanes using a concerted zip-tie approach

In contrast to our previous syntheses to prepare [5]- and [6]catenanes bearing smaller, dead-end macrocycles at each terminus, [3]C-R consisted of three larger molecular rings, each bearing two ligands per macrocycle. This molecular architecture opened the door to synthesize higher-order oligo[*n*]catenanes (Figure 3; Schemes S30 and S31) by allowing for metalation at the empty peripheral phen metal-binding sites after first adding Fe(II) to the internal terpy ligands. Mono-metalation of the phen ligands of $(\text{Fe})_2\text{-[3]C-R}$ was achieved using ~1.5 equiv of a Cu(I) source ($\text{Cu}(\text{MeCN})_4\text{PF}_6$) with respect to [3]C-R. It is important to note that the

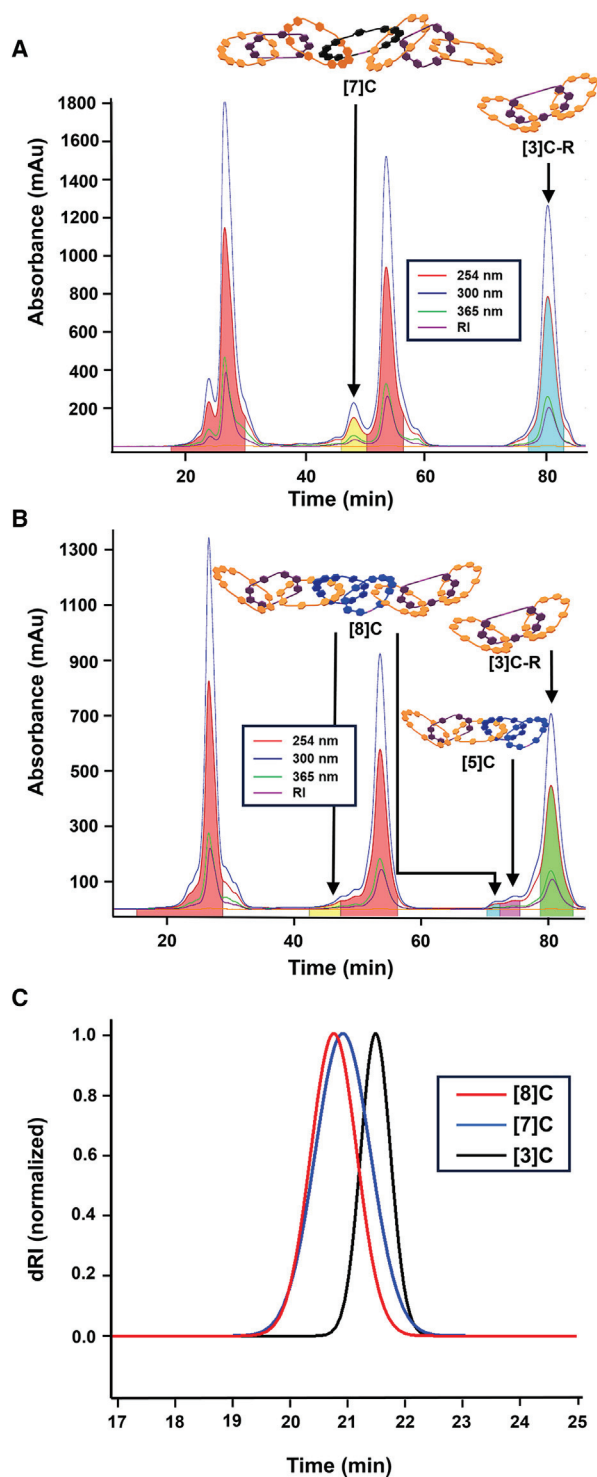


Figure 4. Preparative and analytical GPC data for [7]C and [8]C

(A and B) Recycling prep-GPC data for the crude reactions of [7]C (A) and [8]C (B) in a DMF mobile phase at 8 mL min^{-1} . Pure [7]C was isolated in the yellow fraction at 48 min. Pure [8]C was isolated in the yellow and blue fractions at 47 and 71 min, respectively.

(C) Overlay of analytical GPC traces (normalized and baseline corrected differential refractive index (dRI)) of isolated [3]C, [7]C, and [8]C in DMF with 0.025 M LiBr at 60°C and a 1 mL min^{-1} flow rate.

bis-Cu(I)-metalated species, $(\text{Fe})_2\text{-(Cu)}_2\text{-[3]C-R}$ (data not shown), may also be generated during the Cu(I)-metalation step, and this could potentially lead to formation of a metallocupramolecular polymer and, ultimately, unwanted byproducts. However, the reason why 1.5 equiv Cu(I) was added to $(\text{Fe})_2\text{-[3]C-R}$ instead of 1.05 equiv, for example, is because $(\text{Fe})_2\text{-(Cu)}_{1,2}\text{-[3]C-R}$ are not stable until a bis-phen complex is formed in the next step. Moreover, an excess of $(\text{Fe})_2\text{-(Cu)}_{1,2}\text{-[3]C-R}$ was used (3–4 equiv) to decrease the likelihood of forming the undesired metallocupramolecular polymer, regardless of whether $(\text{Fe})_2\text{-[3]C-R}$ was mono- or bis-Cu(I) metalated. After the Cu(I) addition step, either linker **4** or Fe-(3)_2 was added to produce the pre-catenate form of **[7]C** or **[8]C**, respectively. Next, Grubbs catalyst was added to close the central ring(s) of each complex (i.e., **4** and Fe-(3)_2) to produce each linearly interlocked product. Demetalation using a combination of K_2CO_3 and KCN treatments was performed to remove both Fe(II) and Cu(I) atoms from each terpy-terpy and phen-phen binding site, respectively, prior to purification of each crude product by prep-GPC.

Purification by prep-GPC in DMF was carried out to isolate **[7]C** and **[8]C**. The GPC trace for the crude **[7]C** reaction (Figure 4A) appeared to show less byproducts and a cleaner peak for the desired product. The GPC trace for the crude **[8]C** reaction (Figure 4B), however, showed formation of more byproducts, such as a **[5]catenane**, which was identified by MALDI MS (Figure S41) and resulted from successful ring closing of the Fe-(3)_2 complex but with only one of the premade **[3]C-R** building blocks instead of two. It should be noted that our previous syntheses to prepare linear **[5]-** and **[6]catenanes** (Figure 1A) gave higher yields than that for **[7]C** and **[8]C** (15% and 25% vs. 15% and 10%, respectively). We hypothesize that this difference is because the pre-made **[2]catenane** (**[2]C**) building blocks to make the **[5]-** and **[6]catenanes** used a smaller, single-ligand macrocycle, **5**, that was interlocked with **2**, which, when threaded onto **4** or Fe-(3)_2 followed by ring closing, gave a higher product yield. The higher yield is presumably due to greater stability of the pre-catenate complex during the ring-closing step, which we attest is related to the difference in molecular weight between **[2]C** and **[3]C**, as well as the fact that **[2]C** could be mono-metalated without any concern for bis-metalated **[3]C** intermediates. Concerning the difference in isolated yields between **[7]C** and **[8]C** (15% vs. 10%, respectively), each crude GPC trace (Figures 4A and 4B) shows a lower-molecular-weight peak that elutes after the excess **[3]C** peak that is likely a mixture of starting material (**4** or Fe-(3)_2) and potentially ring-closed products of **4** and Fe-(3)_2 . To verify the purity of each isolated **[n]catenane** product (**[3]C**, **[7]C**, and **[8]C**), analytical GPC (Figure 4C) of each sample was performed. As expected, lower retention times for elution were observed for the higher-molecular-weight **[n]catenanes**, and each peak was unimodal.

For complete details related to the synthesis of each catenane and corresponding precursor compounds, please see Schemes S1–S31.

Characterization of linear **[7]-** and **[8]catenanes**

Next, the identity of each linear **[n]catenane** product was verified using MALDI-TOF-MS. The MS data for **[7]C** (Figure 5) showed peaks for **[4]-**, **[5]-**, and **[6]catenanes** (labeled as fragments i–iii), as well as the parent peak for the **[7]C** product at $m/z = 8,869.94$ $[\text{M}+\text{H}]^+$ (expected: 8,858.79 $[\text{M}+\text{H}]^+$). The fragments resulted from ring-opening events of the terminal rings that occurred during the MS experiment, which is consistent with previous MS characterization of linear oligo**[n]catenanes**.¹⁹ The MS data for **[8]C** (Figure 6) also confirmed the successful synthesis and isolation of the linear **[8]catenane** product, as evidenced by the parent ion peak (vii) at $m/z = 10,147.98$ $[\text{M}+\text{H}]^+$ (expected: 10,139.40 $[\text{M}+\text{H}]^+$). However, in contrast to

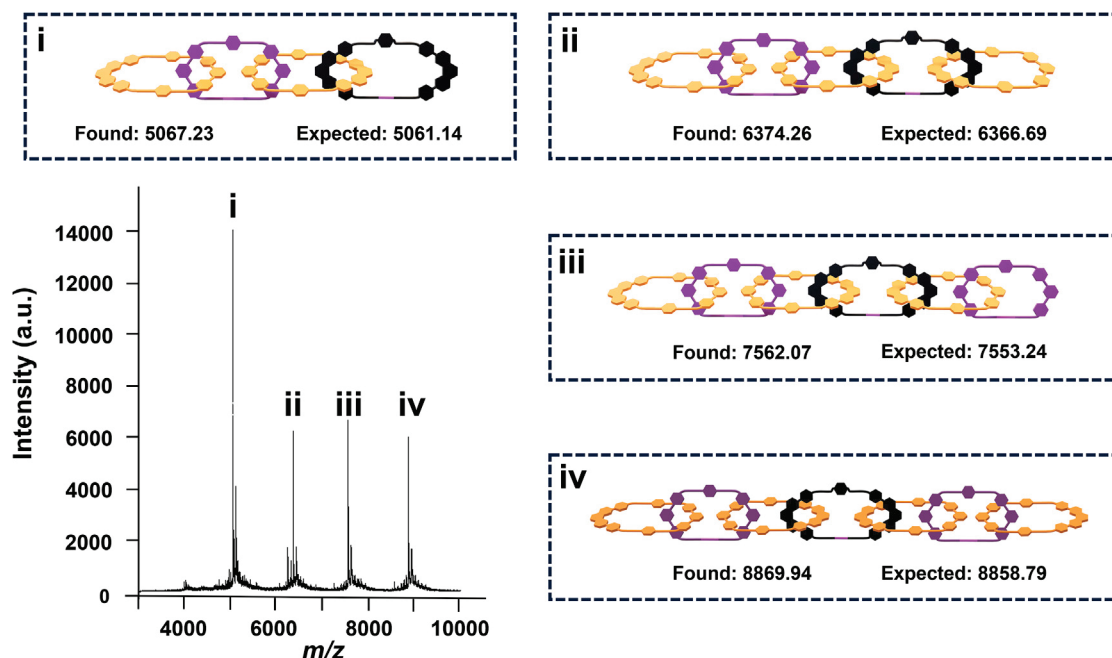


Figure 5. MALDI-TOF-MS spectrum of [7]C was obtained using an α -cyano-4-hydroxycinnamic acid matrix

The parent peak (iv) as well as various fragments (i–iii) were detected plus a proton (H^+) with minor instrumental error ranging from 0.1170% to 0.1260%. Each value provided for “found” and “expected” is the parent or fragment mass plus a proton, e.g., $[M+H]^+$.

the MS spectrum for [7]C, the MS data for [8]C (Figure 6) gave a different fragmentation pattern (i–vi) that originated from ring opening primarily of the inner-most interlocked macrocycles ($(3)_2$) during the MS experiment instead of predominantly the outer macrocycles (i.e., ring-closed 1 and 2). Moreover, the fragmentation data for [8]C produced peaks that included closed macrocycle 3, which is evidence that “figure-of-eight” $[n]$ catenate architectures, which have been observed previously for some double ring-closing catenation reactions, did not form during the RCM step.^{29–32} It should also be noted that all the fragments of [8]C displayed a peak for a Cu(I) ion adduct, presumably due to the propensity of this compound to bind and retain exogenous metals during the MS experiment.

To corroborate the MS data, 1H NMR spectroscopic analysis was performed (Figures S8–S11). Although the 1D 1H NMR spectra for [7]C and [8]C were complex due to the large number of proton resonances that originate from each molecular ring, the spectra clearly represented a combination of proton resonances from each building block ([3]C-R, 4, and 3), and clear upfield and downfield shifting of proton resonances was observed when comparing the spectrum for [3]C-R to that for [7]C and [8]C. Identification of most peaks was made easier by stacking the respective 1H NMR spectra (Figures S12–S14) for [3]C-R, 4, and 3, as well as precursors 1 and 2. Moreover, 2D 1H – 1H NMR analysis (correlated spectroscopy [COSY] or total correlation spectroscopy [TOCSY]; Figures S15–S18) further helped assign the proton resonances in the complex spectra of [7]C and [8]C. Since macrocycle 4 has a pair of ester groups on the central terephthalate ring of its linker, the aromatic proton resonances were easy to distinguish from the aromatic resonances associated with the phenyl rings of 1 and 2. The difference in chemical shift for these protons therefore made it possible to determine the relative ratio of each molecular ring in [7]C, providing further confirmation of the interlocked product structure. For [8]C, the integration of the phen and terpy ligands matched the values that were expected for the combination of each

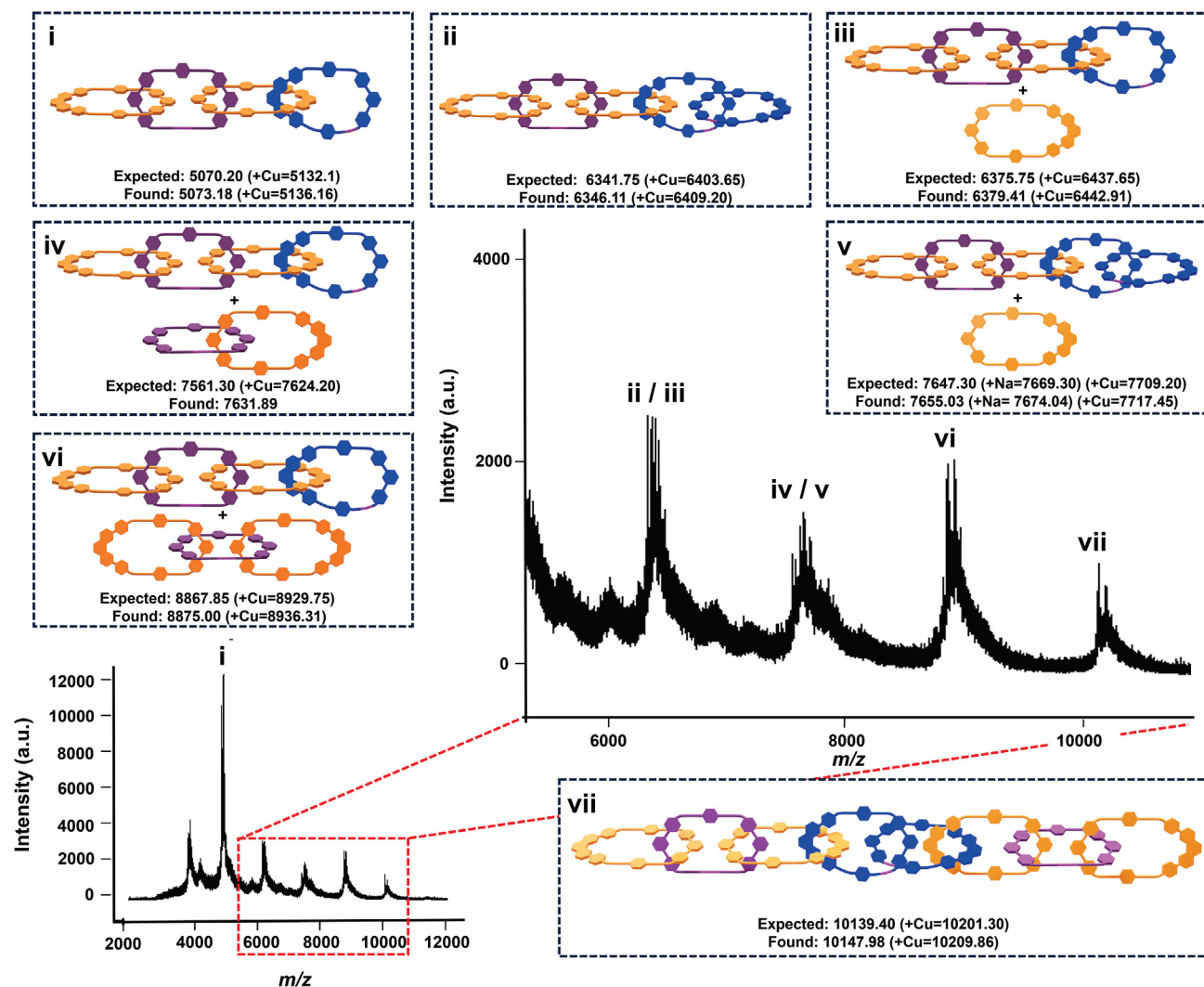


Figure 6. MALDI-TOF-MS spectrum of [8]C was obtained using an α -cyano-4-hydroxycinnamic acid matrix

The parent peak (vii) as well as various fragments (i–vi) plus a proton (H^+) were detected with minor instrumental error ranging from 0.0574% to 0.1011%. Each value provided for “found” and “expected” is the parent or fragment mass plus a proton, Na^+ , or Cu^+ : $[M+H]^+$, $[M+Na]^+$, or $[M+Cu]^+$, respectively.

macrocycle’s proton resonances. Additionally, variable-temperature 1H NMR analysis was conducted (Figure S15) on [8]C in the range of 25°C–70°C to determine if ring circumrotation and simpler spectra could be observed at higher temperatures. However, only shifting and some coalescence of proton resonances associated with the hydroquinone linkers were observed, meaning the ligands were not passing through the cavities of adjacent rings, even at 70°C. Taken together, the NMR spectroscopic analysis, in conjunction with the MS data, supported the assignment of each interlocked product, namely [7]C and [8]C, as well as the corresponding [3]C building block and linkers 4 and 3.

Next, ultraviolet-visible (UV-vis) spectroscopy was used to verify the ability of each [n]catenane to undergo rapid re-metalation. All three [n]catenanes ([3]C, [7]C, and [8]C) showed clear increases in absorbance (Figure S24) after the introduction of an excess of Cu(I) (i.e., one equiv $Cu(MeCN)_4PF_6$ per ligand). Both [7]C and [8]C, as well as their metalated forms, [7]C-M and [8]C-M, respectively, exhibited a higher

absorbance across the entire visible region of the spectrum relative to that for [3]C and [3]C-M. These results are likely because of the larger number of chelated metals and related metal-ligand charge-transfer interactions present in the higher-order [n]catenanes, giving the compounds a more intense color overall. The most substantial absorption before and after metalation was observed for [7]C, an outcome that is most likely due to it possessing electron-withdrawing aromatic ester groups in the terephthalate rings of linker **4**, which extended the overall conjugation length. This hypothesis was verified by assessing the absorption of **4** by itself, which showed a similar absorbance profile.

For complete details related to the characterization of each catenane and corresponding precursor compounds, please see [Figures S1–S42](#).

Conclusions

The [7]- and [8]catenanes described herein represent, to the best of our knowledge, the highest number of linearly interlocked molecular rings synthesized to date for a discrete [n]catenane. The longest, [8]C, weighs over 10 kDa, which is approaching molar masses commonly associated with low-molecular-weight polymers. Moreover, unlike our previous work, where we successfully demonstrated the syntheses of [5]- and [6]catenanes bearing so-called dead-end macrocycles, the [n]catenanes reported here possess dual-ligand molecular rings at each terminus, leaving open the possibility in future efforts to expand beyond 7–8 linearly interlocked molecular rings. Each of these [n]catenane products, [3]C, [7]C, and [8]C, were synthesized using a zip-tie method. The preparation of the higher-order [n]catenanes followed a convergent synthesis approach involving the coupling together of two pre-made [3]C-R molecules using orthogonal metal templation and either a bis-phen-containing open linker, **4**, or a pre-assembled linker, Fe-(**3**)₂, consisting of two terpy-phen-containing open macrocycles as an Fe(II) complex, respectively. Each pre-catenate complex was interlocked after the addition of Grubbs catalyst and subsequent RCM reactions. Purification by recycling prep-GPC proved to be critical in isolating pure [n]catenane, the identities of which were confirmed by MS and 1D/2D ¹H NMR spectroscopy. From a mechanistic perspective, many previous [n]catenane syntheses reported in the literature have encountered issues during the ring-closing step that produced branched, cyclic, or random linear oligomerization byproducts. However, our previous efforts, and this work, have demonstrated the ability to mitigate the formation of any observable cyclic and branched byproducts. We hypothesize that the lack of formation of these byproducts is made possible because the ring closure takes place in the middle of the metalated pre-catenate complex, where the pre-made [3]catenanes created a steric barrier that deterred the formation of unwanted cyclic and branched byproducts. However, as the yields from the one-pot reactions to make [7]C and [8]C would suggest, this approach is not without limitations. If longer, well-defined, higher-molecular-weight poly[n]catenanes, with all interlocked molecular rings, are the ultimate goal, then the yields (currently 10%–15% for [7]C and [8]C) will need to be improved. We hypothesize that much of the hit toward the yields may result from the inherent instability of the olefin bond of the larger [n]catenanes when Grubbs catalyst is present. To overcome this potential issue, we propose that more dilute conditions, which could potentially slow down the ring closure, may be needed to mitigate the competing ring-opening pathway. If successful, this strategy should improve the overall yields and scalability and is therefore a focus of our future research endeavors.



EXPERIMENTAL PROCEDURES

Resource availability

Lead contact

Further information and requests for resources should be directed to and will be fulfilled by the corresponding author, Jonathan C. Barnes (jcbarnes@wustl.edu).

Materials availability

All materials generated in this study are available from the [lead contact](#) upon reasonable request.

Data and code availability

All data supporting the findings of this study are included within the article and its [supplemental information](#). This paper does not report on original code or datasets.

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at <https://doi.org/10.1016/j.xcrp.2023.101767>.

ACKNOWLEDGMENTS

Support for this research was provided by the National Science Foundation (CHE-2204184) and J.C.B.'s David and Lucile Packard Foundation Fellowship.

AUTHOR CONTRIBUTIONS

J.C.B., G.H.H., and N.D.C. contributed to the overall molecular and experimental designs. G.H.H., S.L.T., N.D.C., and M.A.N. synthesized all the reported compounds. G.H.H. and Y.Z. performed characterization and corresponding data analysis. G.H.H. and J.C.B. co-wrote the manuscript. All authors reviewed and revised the manuscript.

DECLARATION OF INTERESTS

The authors filed a non-provisional patent containing part of the work described in this manuscript.

Received: August 12, 2023

Revised: November 27, 2023

Accepted: December 11, 2023

Published: January 5, 2024

REFERENCES

1. Stoddart, J.F. (2017). Mechanically Interlocked Molecules (MIMs)—Molecular Shuttles, Switches, and Machines (Nobel Lecture). *Angew. Chem., Int. Ed.* 56, 11094–11125.
2. Stoddart, J.F. (2009). The chemistry of the mechanical bond. *Chem. Soc. Rev.* 38, 1802–1820.
3. Xue, M., Yang, Y., Chi, X., Yan, X., and Huang, F. (2015). Development of pseudorotaxanes and rotaxanes: from synthesis to stimuli-responsive motions to applications. *Chem. Rev.* 115, 7398–7501.
4. Gil-Ramírez, G., Leigh, D.A., and Stephens, A.J. (2015). Catenanes: fifty years of molecular links. *Angew. Chem., Int. Ed.* 54, 6110–6150.
5. Goujon, A., Lang, T., Mariani, G., Moulin, E., Fuks, G., Raya, J., Buhler, E., and Giuseppone, N. (2017). Bistable [c2] Daisy Chain Rotaxanes as Reversible Muscle-like Actuators in Mechanically Active Gels. *J. Am. Chem. Soc.* 139, 14825–14828.
6. Iwaso, K., Takashima, Y., and Harada, A. (2016). Fast response dry-type artificial molecular muscles with [c2]daisy chains. *Nat. Chem.* 8, 625–632.
7. Jiang, L., Liu, C., Mayumi, K., Kato, K., Yokoyama, H., and Ito, K. (2018). Highly Stretchable and Instantly Recoverable Slide-Ring Gels Consisting of Enzymatically Synthesized Polyrotaxane with Low Host Coverage. *Chem. Mater.* 30, 5013–5019.
8. Liu, C., Kadono, H., Yokoyama, H., Mayumi, K., and Ito, K. (2019). Crack propagation resistance of slide-ring gels. *Polymer* 181, 121782.
9. Au-Yeung, H.Y., and Deng, Y. (2022). Distinctive features and challenges in catenane chemistry. *Chem. Sci.* 13, 3315–3334.
10. Mena-Hernando, S., and Pérez, E.M. (2019). Mechanically interlocked materials. Rotaxanes and catenanes beyond the small molecule. *Chem. Soc. Rev.* 48, 5016–5032.
11. Belfrekh, N., Dietrich-Buchecker, C., and Sauvage, J.-P. (2000). Unexpected Synthesis of an 8-Shaped Macrocyclic System Instead of an Interlocking-Ring System. *Inorg. Chem.* 39, 5169–5172.

12. Amabilino, D.B., Ashton, P.R., Reder, A.S., Spencer, N., and Stoddart, J.F. (1994). *Angew. Chem. Int. Ed. Engl.* **33**, 1286–1290.
13. Griffiths, K.E., and Stoddart, J.F. (2008). Template-directed synthesis of donor/acceptor [2] catenanes and [2] rotaxanes. *Pure Appl. Chem.* **80**, 485–506.
14. Amabilino, D.B., Ashton, P.R., Balzani, V., Boyd, S.E., Credi, A., Lee, J.Y., Menzer, S., Stoddart, J.F., Venturi, M., and Williams, D.J. (1998). Oligocatenanes Made to Order. *J. Am. Chem. Soc.* **120**, 4295–4307.
15. Iwamoto, H., Tafuku, S., Sato, Y., Takizawa, W., Katagiri, W., Tayama, E., Hasegawa, E., Fukazawa, Y., and Haino, T. (2016). Synthesis of linear [5] catenanes via olefin metathesis dimerization of pseudorotaxanes composed of a [2] catenane and a secondary ammonium salt. *Chem. Commun. (Cambridge, U. K.)* **52**, 319–322.
16. Xing, H., Li, Z., Wu, Z.L., and Huang, F. (2018). Catenane crosslinked mechanically adaptive polymer gel. *Macromol. Rapid Commun.* **39**, 1700361.
17. Vickers, M.S., and Beer, P.D. (2007). Anion templated assembly of mechanically interlocked structures. *Chem. Soc. Rev.* **36**, 211–225.
18. Lewis, J.E.M., Beer, P.D., Loeb, S.J., and Goldup, S.M. (2017). Metal ions in the synthesis of interlocked molecules and materials. *Chem. Soc. Rev.* **46**, 2577–2591.
19. Weck, M., Mohr, B., Sauvage, J.-P., and Grubbs, R.H. (1999). Synthesis of Catenane Structures via Ring-Closing Metathesis. *J. Org. Chem.* **64**, 5463–5471.
20. Colley, N.D., Nosiglia, M.A., Tran, S.L., Harlan, G.H., Chang, C., Li, R., Delawder, A.O., Zhang, Y., and Barnes, J.C. (2022). Topologically Controlled Syntheses of Unimolecular Oligo[n] catenanes. *ACS Cent. Sci.* **8**, 1672–1682.
21. Tranquilli, M.M., Wu, Q., and Rowan, S.J. (2021). Effect of metallosupramolecular polymer concentration on the synthesis of poly[n] catenanes. *Chem. Sci.* **12**, 8722–8730.
22. Wu, Q., Rauscher, P.M., Lang, X., Wojtecki, R.J., De Pablo, J.J., Hore, M.J.A., and Rowan, S.J. (2017). Poly[n]catenanes: Synthesis of molecular interlocked chains. *Science* **358**, 1434–1439.
23. Cárdenas, D.J., Gaviña, P., and Sauvage, J.-P. (1997). Construction of interlocking and threaded rings using two different transition metals as templating and connecting centers: Catenanes and rotaxanes incorporating Ru (terpy) 2-units in their framework. *J. Am. Chem. Soc.* **119**, 2656–2664.
24. Colley, N.D., Nosiglia, M.A., Li, L., Amir, F., Chang, C., Greene, A.F., Fisher, J.M., Li, R., Li, X., and Barnes, J.C. (2020). One-Pot Synthesis of a Linear [4]Catenate Using Orthogonal Metal Templation and Ring-Closing Metathesis. *Inorg. Chem.* **59**, 10450–10460.
25. Ng, A.W.H., Lai, S.K.M., Yee, C.C., and Au-Yeung, H.Y. (2022). Macrocyclization Dynamics in a Branched [8]Catenane Controlled by Three Different Stimuli in Three Different Regions. *Angew. Chem., Int.* **61**, e202110200.
26. Nosiglia, M.A., Colley, N.D., Danielson, M.K., Palmquist, M.S., Delawder, A.O., Tran, S.L., Harlan, G.H., and Barnes, J.C. (2022). Metalation/Demetalation as a Postgelation Strategy To Tune the Mechanical Properties of Catenane-Crosslinked Gels. *J. Am. Chem. Soc.* **144**, 9990–9996.
27. Berrocal, J.A., Pitet, L.M., Nieuwenhuizen, M.M.L., Mandolini, L., Meijer, E.W., and Di Stefano, S. (2015). Ring-Opening Metathesis Polymerization of a Diolefinic [2]-Catenane–Copper(I) Complex: An Easy Route to Polycatenanes. *Macromolecules* **48**, 1358–1363.
28. Guidry, E.N., Cantrill, S.J., Stoddart, J.F., and Grubbs, R.H. (2005). Magic Ring Catenation by Olefin Metathesis. *Org. Lett.* **7**, 2129–2132.
29. Fuller, A.-M.L., Leigh, D.A., Lusby, P.J., Slawin, A.M.Z., and Walker, D.B. (2005). Selecting topology and connectivity through metal-directed macrocyclization reactions: a square planar palladium [2] catenane and two noninterlocked isomers. *J. Am. Chem. Soc.* **127**, 12612–12619.
30. Loren, J.C., Gantzel, P., Linden, A., and Siegel, J.S. (2005). Synthesis of achiral and racemic catenanes based on terpyridine and a directionalized terpyridine mimic, pyridyl-phenanthroline. *Org. Biomol. Chem.* **3**, 3105–3116.
31. Leigh, D.A., Lusby, P.J., McBurney, R.T., Morelli, A., Slawin, A.M.Z., Thomson, A.R., and Walker, D.B. (2009). Getting harder: cobalt (III)-template synthesis of catenanes and rotaxanes. *J. Am. Chem. Soc.* **131**, 3762–3771.
32. Yee, C.-C., Ng, A.W.H., and Au-Yeung, H.Y. (2019). Control over the macrocyclization pathway and product topology in a copper-templated catenane synthesis. *Chem. Commun. (Cambridge, U. K.)* **55**, 6169–6172.