Poly[n]catenanes: Synthesis of molecular interlocked chains

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As the macromolecular version of mechanically interlocked molecules, mechanically interlocked polymers are promising candidates for the creation of sophisticated molecular machines and smart soft materials. Poly[n]catenanes, where the molecular chains consist solely of interlocked macrocycles, contain one of the highest concentrations of topological bonds. We report, herein, a synthetic approach toward this distinctive polymer architecture in high yield (75%) via efficient ring closing of rationally designed metallosupramolecular polymers. Light-scattering, mass spectrometric, and nuclear magnetic resonance characterization of fractionated samples support assignment of the high-molar mass product (number-average molar mass ~21.4 kilograms per mole) to a mixture of linear poly[7–26]catenanes, branched poly[13–130]catenanes, and cyclic poly[4–7]catenanes. Increased hydrodynamic radius (in solution) and glass transition temperature (in bulk materials) were observed upon metallation with Zn2+.

Mechanically interlocked molecules (MIMs) such as catenanes, rotaxanes, and knots are attracting increasing attention on account of their aesthetic topological structures (1–3) and their potential applications that range from molecular machines (4) to catalysis (5), drug delivery (6), and switchable surfaces (7). An impressive array of small-molecule MIMs has been successfully synthesized, primarily through proper orientation of the precursor components via a noncovalent templating event that employs, for example, metal-ligand (1, 2, 8–10), donor-acceptor (11), or hydrogen bonding (12) interactions or the hydrophobic effect (3), followed by a covalent fixing step. High molar mass MIMs, or mechanically interlocked polymers (MIPs), such as polyrotaxanes and polycatenanes, offer access to useful properties for functional soft materials platforms (13). Perhaps the most notable example to date is provided by the slide-ring gels (a subset of polyrotaxanes), where the mechanically interlocked rings act as mobile cross-linking sites. These materials exhibit anti-scratch and healing characteristics and, generally, dispersity D > 1. These interlocked polymers contain a very high concentration of topological bonds and can be considered the molecular equivalent of a macroscopic chain (Fig. 1A). Such structures retain their flexibility no matter the stiffness of their ring components on account of the conformational mobility of their topological structures, allowing access to both high strength and excellent flexibility. Figure 1B shows the main conformational mobilities (rotational, elongational, and rocking motions) in the backbone repeat unit of such a chain for appropriate ring sizes (13). Theoretical studies have suggested that poly[n]catenanes with such mobility elements could exhibit a large loss modulus and a low activation energy for flow and could potentially act as superior energy-damping materials and/or elastomers with excellent toughness and stimuli-responsive mechanical properties (13, 15, 16).

The synthesis of poly[n]catenanes, however, represents a major challenge. The confirmed synthesis of these polymeric topologies of high molar mass has yet to be reported. Most of the earlier work on polycatenanes has focused on poly[2]catenane)s (generally accessed by polymerizing a bis-functionalized [2]catenane) (15, 17–23), poly- and oligocatenanes with unclearly defined architectures (24, 25), and polymeric [2]catenanes (i.e., two interlocked cyclic polymers) (26). These materials have afforded insights into the potentially useful properties of MIPs. For example, poly(2)catenane)s have shown conformational flexibility along the polymer chain in solution (indicated by a Kuhn segment length that is shorter than the length of its [2]catenane moiety) (15) and temperature-dependent motion of the rings in solution (18) or in bulk materials (22). However, on account of the covalent linking units present in the poly([2]catenane) backbone, the degree of rotation of the ring components in the catenane moieties is limited (Fig. 1C). Poly[n]catenanes, on the other hand, have rings linked solely by topological bonds, allowing full rotational mobility of every ring (with sufficient ring size), and, as such, should exhibit more conformational flexibility. One of the most successful attempts to access oligo[n]catenanes with at least seven interlocked rings was recently achieved via the ring-opening polymerization of metallo-[2]catenane by Meijer, Dii Stefano, and co-workers (25). However, the specific architecture of the product could not be clearly defined. To date, the longest interlocked molecular chain with clearly defined structure is a linear [5]catenane (olympiadane) reported by Stoddart and co-workers (27) and, more recently, by Iwamoto et al. (28), both via stepwise approaches. Stoddart and co-workers have also used a similar strategy to access a branched [7]catenane (29). These step-wise strategies, however, are not efficient methodologies for the synthesis of long-chain poly[n]catenanes. One key challenge in the synthesis of poly[n]catenanes is the conflicting reaction conditions for accessing macrocycles (requiring low concentration) and polymers (requiring high concentration). Takata, Kihara, and co-workers proposed an elegant solution to this conflict by converting a bridged poly([2]catenane) into poly[n]catenane (20), but to date there is no report of a poly[n]catenane synthesized via this route.

The synthetic strategy toward poly[n]catenanes outlined herein, and illustrated in Fig. 1D, aims at decoupling the above-mentioned conflicting synthetic requirements through the preassembly of a metallosupramolecular polymer (MSP) as a template, followed by an efficient ring-closing reaction and demetallation of the resulting metalated poly[n]catenane. Pioneered by Sauvage and co-workers, metal-ligand coordination has been one of the most successful synthetic routes toward MIMs (1, 2, 8, 9). The terdentate ligand, 2,6-bis(N-alkyl-benzimidazolyl)pyridine (Bip) (Fig. 1E), which binds transition metal ions such as Zn2+ or Fe2+ in a 2:1 stoichiometry, was chosen because it has already been shown to access a wide selection of functional metallosupramolecular polymers that exhibit photo-healing (30), stimuli-responsive (31), shape-memory (32), and actuation properties (33). Furthermore, we have recently shown that [3]catenanes can be accessed via a near quantitative ring-closing reaction of a pseudo[3]rotaxane assembles from a monotropic Bip-containing macrocycle, Zn2+, and a ditopic thread (1 with R = hexyl) in a ratio of 2:2:1 (9).

Building on these studies, we targeted the MSP assembly of the rationally designed 68-membered ditopic Bip macrocycle 2 with the threading molecule 1 and the subsequent ring closing of 1 (Fig. 1E). Upon the addition of 2 equivalents of Zn2+ to...
the 1:1 mixture of 1 and 2, the components self-assembled into the alternating supramolecular copolymer [Fig. 1D; monitored by $^1$H nuclear magnetic resonance (NMR), see fig. S1]. The alternation is a consequence of the principle of maximal site occupancy (34): Two Bip moieties in the same (or different) macrocycle 2 cannot bind the same Zn$^{2+}$ ion; therefore, each Bip unit in 2 must form a 2:1 Bip/Zn$^{2+}$ ion complex with a Bip unit in 1 to maximize enthalpic gain (fig. S2). The formation of an MSP was confirmed by diffusion-ordered spectroscopy (DOSY) (fig. S3). The large binding constant (~10$^6$ M$^{-1}$) in acetonitrile between Bip and Zn$^{2+}$ (35) maintains the MSP under the relatively dilute conditions required to favor the ring-closing reaction (although cyclic MSPs should be favored under very dilute conditions). The ring-closing metathesis reaction showed excellent olefin conversion at 2.5 mM (with respect to Bip). According to the $^1$H NMR chemical shift, the relatively dilute conditions required to favor the formation of an MSP was confirmed by diffusion-ordered spectroscopy (DOSY) (fig. S1). The alternating poly[n]catenane structure. The interlocked structure is further confirmed by nuclear Overhauser effect spectroscopy (NOESY) (Fig. 2C). Lowering the temperature (~17°C) to diminish the ring motions in the poly[n]catenane gives rise to numerous NOE cross peaks in dilute (1% w/v) solutions of 3. Of particular interest are intercomponent NOE cross peaks between protons in the different macrocycles (2 and 4). At least four intercomponent NOE cross peaks—including, for example, one between H$_2$ of 4 and H$_{18}$ of 2—were observed in 3 (Fig. 2C) but not in the simple mixtures of 2 and 4 or 2 and 5 (figs. S11 and S12). Given that NOE signals normally require the protons to be <0.5 nm apart, these data strongly suggest that macrocycles 2 and 4 have to be interlocked and that 3 is a poly[n]catenane.

Having confirmed the interlocked structure, we next used gel permeation chromatography coupled to a multangle light scattering (GPC-MALS) detector to measure the absolute molar mass of the polymers (37). The GPC chromatogram of 3 (Fig. 3A, black line) shows a broad peak consistent with a average molar mass $M_n = 21.4$ kg/mol and dispersity $D = 1.44$ (Table 1). At each elution volume, the absolute molar mass is shown as the red dotted line, indicating that the product distribution 3 contains species with molar mass up to ~200 kg/mol, which corresponds to a poly[130]catenane. Deconvolution of the broad peak in the chromatogram yields three subpeaks (I to III), implying that the poly[n]catenane product may contain three different architectures. The measured absolute molar masses (from MALSS) of these three peaks are about 20 to 200, 10 to 40, and 6 to 10 kg/mol, which would correspond to poly[13–130]catenanes, poly[7–27]catenanes, and poly[4–7]catenanes, respectively. The relative percentage of the three peaks is estimated (on the basis of peak areas) to be 28, 61, and 11%, respectively.

One possible explanation for peaks I to III is the formation of branched, linear, and cyclic architectures, respectively, as illustrated in Fig. 3B.

**Fig. 1. Structure and conformational mobility of and synthetic approach to poly[n]catenanes.** (A) Schematic representation of the poly[n]catenane architecture, which can be thought of as the molecular equivalent of a robust and flexible metal chain. (B) Common conformational motions observed in catenanes. (C) Comparison of the ring rotational mobilities in a poly[2]catenate versus a poly[n]catenane. (D) Targeted synthesis of poly[n]catenane via assembling 1 and 2 into a metallosupramolecular polymer (MSP), followed by ring-closing to yield a poly[n]catenate (i.e., metallated poly[n]catenane) and demetallation. (E) Structure of 1, 2, and 4 (ring-closed product of 1). A few key protons are labeled with blue capital letters in 4 and red lowercase letters in 2. The box highlights the structure of the Bip ligand moiety.
In addition to the targeted linear poly[n]catenanes, it is certainly possible that interchain reactions (dimerization and oligomerization of 4) can occur, leading to higher molar mass branched poly[n]catenanes. Furthermore, it is also possible that a percentage of the MSPs are lower molar mass cyclic structures, which in turn would lead to cyclic poly[n]catenanes. One piece of evidence suggestive of cyclic poly[n]catenanes is the observed transition peak between peaks II and III in the absolute molar mass measurement (Fig. 3A, at ~9.2 ml). If peak III corresponds to a cyclic geometry, we would expect these more compact structures to co-elute with lower molar mass linear polymers (3b).

To more fully characterize the poly[n]catenane mixture, we performed preparative GPC on 3, obtaining four fractions 3a to 3d. 1H NMR studies confirmed that all four fractions contain ~50% of macrocycle 2, consistent with them all being poly[n]catenanes (Fig. S14). GPC-MALS of each fraction confirmed successful size-based separation (Fig. 3C and fig. S15), and the four fractions showed decreasing molar mass (Table 1) with relatively narrow D (1.11 to 1.18) (Table 1). On the basis of the elution times, fractions 3a and 3b mostly correspond to peak I, 3c predominantly corresponds to peaks II and III. Matrix-assisted laser desorption/ionization-time-of-flight (MALDI-TOF) mass spectrometry confirmed the presence of high molar mass poly[n]catenanes with molecular ion peaks corresponding up to a poly[53]catenane in 3d (Fig. 3D) and up to a poly[27]catenane for 3c (Fig. S16).

One way to characterize the architectures (branched, linear, or cyclic) of the poly[n]catenanes in fractions 3a to 3d is to elucidate the average number of chain ends (N_C) of the polymers in each fraction. By definition, N_C equals 0 for cyclic poly[n]catenanes, 2 for linear poly[n]catenanes, and 2 + 4 for branched poly[n]catenanes (Fig. 3B). With absolute molar mass of each fraction available from MALS, their degrees of polymerization (DPs, which we define here as equivalent to n) can be readily calculated by MALS/1544 (results listed in Table 1), where M_MALS is the molar mass from GPC-MALS and 1544 g/mol is the mean molar mass of 2 and 4 (assuming a 1:1 ratio in the polymer). It is then possible to calculate N_C by combining these data with NMR chain-end analysis (eq. S1). The key for such calculations is to find diagnostic chain-end peaks of poly[n]catenanes in the 1H NMR spectra. To do this, a (predominantly) [3]catenane 6 was targeted and synthesized by reacting 1 in the presence of two equivalents of 2 and Zn2+ ions (fig. S17), and its NMR spectrum was compared with 3a to 3d in Fig. 3E. The three groups of peaks for H_Aa of 6 with ~1:1:1 peak areas (fig. S17) were observed and defined as regions a (8.235 to 8.270 ppm), b (8.195 to 8.235 ppm), and c (8.150 to 8.195 ppm), respectively. The lower intensity of region b in 3a to 3d, compared with the intensity in 6, along with the longer NMR relaxation time of the protons in region c (fig. S18), confirms that this region corresponds to the chain end (see supplementary materials). With this assignment, the average number of chain ends, N_C, can be calculated by Eq. 1

\[ N_C = \frac{2f_a}{I_{Aa}} \]

where I_Aa is the total peak integration of H_Aa and f_a is the chain-end peak integration of H_Aa (i.e., region a; see eqs. S1 to S3 for derivation details). The results of the N_C calculations for 3 and

<table>
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<tr>
<th>Sample</th>
<th>3</th>
<th>3a</th>
<th>3b</th>
<th>3c</th>
<th>3d</th>
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<tr>
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<td>Linear/cyclic</td>
<td>Linear/cyclic</td>
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<td>M_n (kg/mol)</td>
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<td>38.5</td>
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3a to 3d are summarized in Table 1. Fractions 3a \((N_C = 8.7)\) and 3b \((N_C = 4.7)\) are predominantly branched, whereas 3c \((N_C = 1.7)\) and 3d \((N_C = 1.2)\) appear to contain different amounts of cyclic poly[n]catenanes that result in \(N_C < 2\). To identify the proportion of cyclic poly[n]catenanes in these latter fractions, additional studies were undertaken to specifically target a cyclic poly[n]catenane 7. This was achieved by carrying out the MSP formation (using Fe\(^{2+}\) as the metal ion) and ring-closing reaction at much lower concentrations (see supplementary materials and fig. S19).

Comparison of the \(H_{A/a}\) region in the \(^1\)H NMR spectra (Fig. 3E) of the cyclic poly[n]catenate–containing fractions (3c, 3d, and 7) shows an additional upfield shift to 8.06 to 8.15 ppm (Fig. 3E, green region), which is defined as region \(\delta\). In contrast, the acyclic poly[n]catenate–containing samples (3a, 3b, and 6) do not have any peaks in this region. Therefore, it is reasonable to conclude that region \(\delta\) is specific for cyclic poly[n]catenanes. Compared with the acyclic poly[n]catenanes (3a and 3b) or [3]catenane 6, it appears that ~50% of the A/a peaks of the cyclic poly[n]catenane 7 are shifted more upfield. One possible explanation is that the cyclic architecture restricts the conformational mobility, resulting in a more compact molecule (fig. S19E) and allowing additional shielding effects from neighboring aromatic moieties. Given that the integral of the \(H_{A/a}\) in 7 shows that ~50% of its \(H_{A/a}\) protons are present in the \(\delta\) region (fig. S20), it is possible to determine the average number of chain ends for the acyclic poly[n]catenanes \((N_{E_x})\) present in each fraction by Eq. 2 (for derivation, see eqs. S3 to S5)

\[
N_{E_x} = DP \times \frac{2I_\delta}{I_{A/a} - 2I_\delta}
\]  

where \(I_\delta\) is the peak integration of the \(\delta\) region in the NMR spectra (Fig. 3E). The results of these calculations show that both 3c and 3d have \(N_{E_x} \approx 2\) (with \(N_C < 2\)), consistent with the fact that they both contain a mixture of linear and cyclic poly[n]catenanes with the percentage of cyclic poly[n]catenanes in 3c and 3d being ~15 and ~34%, respectively (calculated via eq. S6).

Table 1 summarizes the molar mass and architectural data of 3 and the four fractions 3a to 3d. The fraction with the highest molar mass (3a) is assigned to highly branched poly[32–130]catenanes (on the basis of MALSS analysis) (fig. S15A) with an average \(DP = 55\). Fraction 3b consists of a lower degree of branching poly[n]catenanes with an average \(DP = 25\). Fractions 3c and 3d contain mainly linear (with some cyclic) poly[n]catenanes with up to 27 (average \(DP = 11\)) (fig. S15C) and 20 (average \(DP = 8\)) (fig. S15D) interlocked rings, respectively. Based on the data from the four fractions, we can estimate that the overall percentage of branched, linear, and cyclic poly[n]catenanes is ~24, ~60, and ~16%, respectively, which matches well with the GPC peak deconvolution result (28, 61, 11%, respectively) (Fig. 3A).

Taken together these data are consistent with the poly[n]catenane 3 being a mixture of branched poly[13–130]catenanes, linear poly[7–27]catenanes, and cyclic poly4–7catenanes, in approximately the aforementioned ratios.

It is known that catenanes prepared via metal templating exhibit metallo-responsive behavior.
As such, the metallo stimuli–responsive properties of these poly[n]catenanes were investigated in both solution and bulk, by measuring the hydrodynamic radius $R_h$ [with dynamic light scattering (DLS)] (Fig. 4A and fig. S21) and the glass transition temperature ($T_g$) (Fig. 4B and fig. S22), respectively. Addition of Zn\textsuperscript{2+} ions into poly[n]catenanes should lock the conformational motions of the rings, thereby inducing a switch from a highly flexible polymer to a semi-rigid polymer, where the flexibility comes primarily from the tetrachloroethylene glycol (TEG) moieties (Fig. 4A). For predominantly linear poly[n]catenanes (3c, average $DP = 11$), the addition of Zn\textsuperscript{2+} shows a substantial (~70%) $R_h$ increase from 3.9 to 6.6 nm (Fig. 4A). This result agrees well with all-atom molecular dynamics simulations of metallated linear poly[n]catenane (see supplementary materials). Molecules were simulated with the OPLS (optimized potentials for liquid simulations) all-atom force field (39) with 1,1,2,2-tetrachloroethane as the solvent, and the properties of the polymer were probed using a force-extension experiment. To model a poly[n]catenane under tension, an [8] catenane was connected to itself through periodic boundary conditions (Fig. 4C); the extension was enforced through the system (box) length, which is systematically varied; and the corresponding tension follows from the pressure tensor (eq. S9). The force-extension behavior is well described by the extensible worm-like chain (EWLC) model (40), as shown in Fig. 4C. According to this interpretation, each macrocycle’s contribution to the contour length, $l = 2.40 \pm 0.03$ nm, is considerably smaller than the persistence length, $\xi = 7.46 \pm 2.88$ nm, which is characteristic of a semi-rigid polymer. Again, this flexibility can be primarily attributed to the TEG segments of macrocycle 2, as evidenced by larger fluctuations in the intermetal distances for 2 versus 4 (figs. S28 and S29). Based on simulations of a nonperiodic metallated [4]catenane, $R_h$ is ~34% of the end-to-end distance ($R_{ee}$). For a metallated poly[n]catenane of arbitrary $DP$, $R_{ee}$ can be calculated using worm-like chain statistics (eq. S15) and the results of the force-extension simulations. $R_h$ for an average poly[n]catenane in fraction 3c is thereby estimated at 6.89 ± 1.38 nm, in good agreement with DLS results (6.6 nm), further supporting the conclusion that fraction 3c is primarily linear poly[n]catenane (see supplementary materials). The simulated structure of a metallated linear poly[n]catenane under ~15 pN tension is illustrated in Fig. 4D, showing a segment of 12 interlocked rings.

Similar to linear poly[n]catenane, metallation of branched poly[n]catenane (3b, average $DP = 24.9$) with Zn\textsuperscript{2+} shows a ~50% increase in $R_h$ upon metallation (5.0 to 7.6 nm) (fig. S21B), presumably as a consequence of an extension of its arms. Metallation of cyclic poly[n]catenane 7 (average $DP = 6$) shows only a relatively small change of $R_h$ (~10%, from 2.4 to 2.6 nm) (fig. S21C), which is consistent with its cyclic architecture restricting chain extension. In the bulk, the $T_g$ values of poly[n]catenane with predominantly linear (3c) and branched architectures (3b) were found to be 97° and 104°C, respectively, compared with 137°C for 5 (the linear ADMET polymer of 1) (Fig. 4B and fig. S22, determined by differential scanning calorimetry (DSC)). In general, polymers with greater freedom of segmental motion show lower $T_g$ values, which is consistent with the more facile conformational molecular motions expected throughout the poly[n]catenane backbones. Metallation with Zn\textsuperscript{2+} keeps these conformational motions and substantially reduces the flexibility of the poly[n]catenane; as such, no $T_g$ values are observed upon heating up to 160°C for both linear and branched samples (Fig. 4B and fig. S22).

In conclusion, the successful synthesis of mainchain poly[n]catenanes via an MSP templated strategy has been achieved in ~75% yield. The isolated product mixture encompasses linear poly[7–27]catenanes, branched poly[13–130]catenanes, and cyclic poly[4–7]catenanes. This synthetic strategy opens the door to the design and synthesis of a variety of new interlocked polymers.

REFERENCES AND NOTES
SUPPLEMENTARY MATERIALS

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Materials and Methods
Supplementary Text
Figs. S1 to S29
Tables S1 to S3
References (41–93)

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RESEARCH REPORT

Wu et al., Science 358, 1434–1439 (2017) 15 December 2017 6 of 6

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A little zinc makes the rings all link
Although polymer strands are often informally called chains, molecular topologies that actually resemble extended macroscopic chain links have proven surprisingly challenging to make. Most approaches have settled for tethering pairs of interlocked rings amid spacer segments. Wu et al. now report successful synthesis of polycatenanes in which tens of rings are consecutively interlinked. The key was using zinc ions to template the threading of one macrocycle precursor through flanking preformed macrocycles, after which metathesis catalysis closed up the first ring, and the metal could be flushed out.
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