Dynamic Self-Assembly

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Cyclic [2]Catenane Dimers, Trimers, and Tetramers

*Yi-Wei Wu, Shun-Te Tung, Chien-Chen Lai, Yi-Hung Liu, Shie-Ming Peng, and Sheng-Hsien Chiu**

Abstract: *Dimeric, trimeric, and tetrameric cyclic [2]catenanes have been prepared directly through one-pot sodium-ion-templated dynamic imine formation from a diamine and a tetraaldehyde. NaBH$_4$ mediated reduction of the labile imino bonds of these cyclic [2]catenane oligomers, followed by methylation of the resulting secondary amino groups enabled the isolation and characterization of oligomeric cyclic [2]catenanes as stable, covalently linked compounds.*

Although great success has been achieved in the preparation of topologically novel and aesthetically appealing interlocked and interwoven structures, including catenanes,[1] rotaxanes,[1a,2] trefoil knots,[3] Solomon links,[4] Borromean rings,[5] and Stars of David,[6] our ability to construct cyclic [2]catenane oligomers remains limited. To the best of our knowledge, only a few examples of covalently linked cyclic [2]catenane dimers have appeared,[7] with no reports of higher-order systems, primarily because the cyclization of the requisite sizable linear precursors is largely entropically disfavored in the absence of any template effect. A one-pot assembly of oligomeric cyclic [2]catenanes from linear building blocks would require three different cyclization reactions to be performed at different hierarchical levels: 1) the formation of macrocycles from linear components, 2) the construction of [2]catenanes from [2]pseudorotaxanes, and 3) the generation of cyclic [2]catenanes from linear oligomers incorporating [2]catenanes. One approach to ensure reasonable efficiency in the synthesis of cyclic [2]catenane oligomers would be the application of dynamic reversible (thermodynamically controlled) reactions with self-correcting properties.[8] Herein, we report the one-pot assembly of cyclic [2]catenane oligomers through sodium-ion-templated dynamic imine formation from suitably functionalized diamines and tetraaldehydes, and the isolation and characterization of the corresponding cyclic [2]catenane di-, tri-, and tetramers in their reduced amino forms.

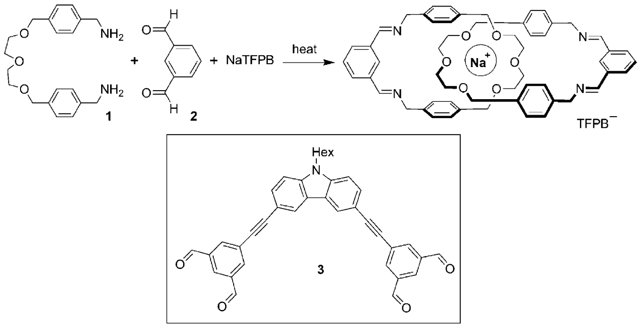

Figure 1. Dynamic templated assembly of a [2]catenane; chemical structure of tetraaldehyde **3**.

Previously, we reported that Na$^+$ ions can template the orthogonal alignment of two di(ethylene glycol)-containing diamines **1**, which can then react with two units of isophthalaldehyde **2** to generate [2]catenanes (Figure 1).[9] We wished to use this approach as the basis for the dynamic synthesis of cyclic [2]catenane oligomers. Therefore, we synthesized tetraaldehyde **3**, which features two rigid extended dialdehyde arms presented at an approximately 90° angle from a carbazole core, for the corresponding reaction with diamine **1**. Expecting that the templating Na$^+$ ions would, to some extent, favor a linear structure for each [2]catenane subcomponent (i.e., separating its two isophthalimine units in a nearly 180° arrangement), we anticipated that the 90° kink in the structure of tetraaldehyde **3** would allow the generation of higher-order cyclic [2]catenane oligomers.

The ^{1}H NMR spectrum of a mixture of diamine **1** (10 mM), tetraaldehyde **3** (5 mM), and NaTFPB (5 mM; TFPB = tetrakis[3,5-bis(trifluoromethyl)phenyl]borate) in (CDCl$_2$)$_2$ displayed reasonably sharp signals after heating at 333 K for ten hours, suggesting that polymers were not the predominant species in this solution (Figure 2b). The negligible signals for residual aldehyde units and the two unequal sets of signals between $\delta = 2.5$ and 3.1 ppm [representing di(ethylene glycol) protons located within the shielding zones of the *para*-xylene units of the [2]catenane subunits] implied the formation of more than one cyclic oligomer under the reaction conditions (Scheme 1). DOSY NMR spectroscopy[10] confirmed that these two sets of signals belonged to molecules of different sizes; we assigned the major and minor sets of signals to the larger and smaller molecules, respectively, based on their diffusion coefficients (see the Supporting Information). The electrospray ionization (ESI) mass spectrum of the solution featured intense peaks near *m*/*z* 1202.6, corresponding to the doubly charged cyclic [2]catenane dimer $[\mathbf{M}_2+2\,\mathrm{Na}]^{2+}$, and relatively weak signals near *m*/*z* values of 1792.4, 1595.7, and 1497.5, corresponding to the $[\mathbf{M}_3+2\,\mathrm{Na}]^{2+}$, $[\mathbf{M}_4+3\,\mathrm{Na}]^{3+}$, and $[\mathbf{M}_5+4\,\mathrm{Na}]^{4+}$ ions, respectively, suggesting that di-, tri-, tetra-, and pentameric cyclic [2]catenanes had been generated in this reaction mixture.

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[*] Y.-W. Wu,[+] S.-T. Tung,[+] Y.-H. Liu, Prof. S.-M. Peng, Prof. S.-H. Chiu
Department of Chemistry, National Taiwan University
No. 1, Sec. 4, Roosevelt Road, Taipei, 10617 (Taiwan, R.O.C.)
E-mail: shchiu@ntu.edu.tw

Prof. C.-C. Lai
Institute of Molecular Biology, National Chung Hsing University and Department of Medical Genetics, China Medical University Hospital
Taichung (Taiwan, R.O.C.)

[+] These authors contributed equally to this work.

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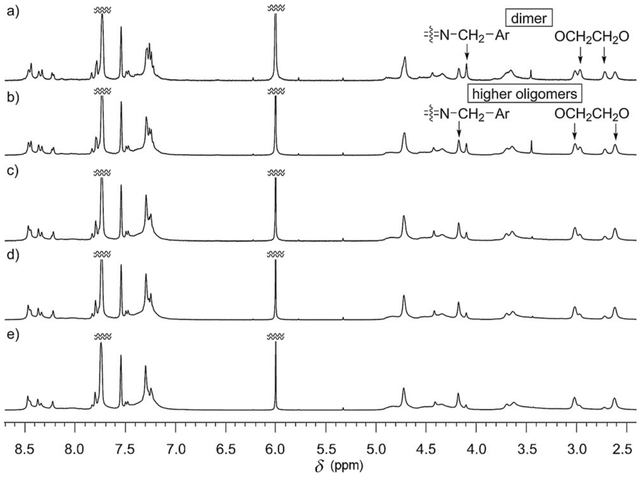
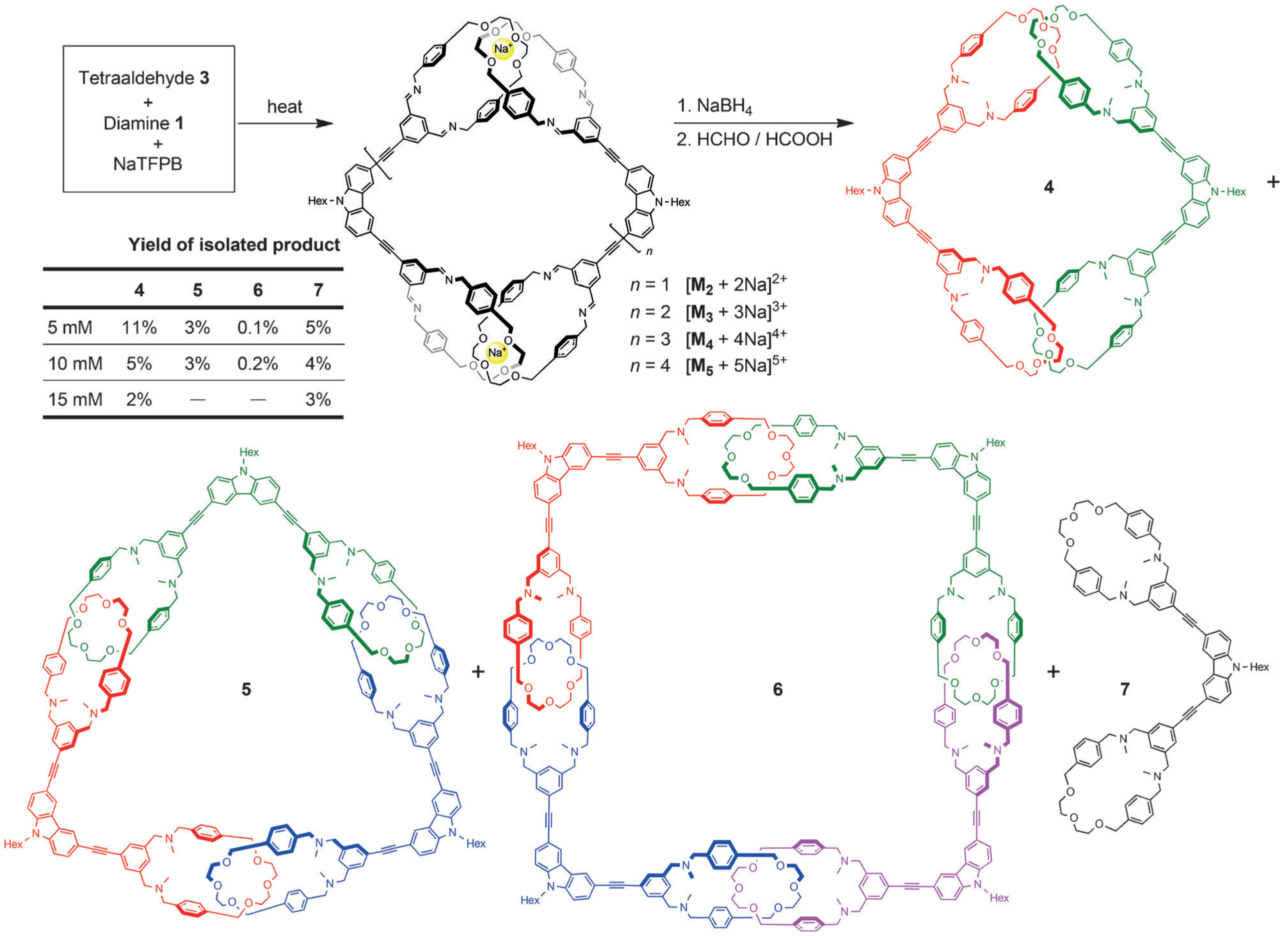


Figure 2. ^{1}H NMR spectra (400 MHz, $CDCl_2CDCl_2$, 298 K) of mixtures of diamine **1**, tetraaldehyde **3**, and NaTFPB (2:1:1) after heating at 333 K for ten hours; concentration of **3**: a) 2.5, b) 5, c) 10, d) 15, and e) 20 mM.

To unambiguously confirm the formation of these novel interlocked structures, we added $NaBH_4$ to a similar, larger-scale mixture to reduce the imino bonds of any cyclic [2]catenane oligomers; after methylation (HCHO/HCOOH)[11] of the crude mixture of reduction products (secondary amines), we isolated the cyclic [2]catenane dimer **4**, trimer **5**, and tetramer **6** by column chromatography in yields of 11, 3, and 0.1 %, respectively (Scheme 1). The linear monomeric unit of the cyclic [2]catenane oligomers, **7**, which may also have been generated through decomposition of cyclic and acyclic [2]catenane oligomers during the reduction process, was isolated in 5 % yield.

In ^{1}H NMR spectra of mixtures formed from **1** and **3** in the presence of Na^+ ions, the intensities of the signals between $\delta = 2.5$ and 3.1 ppm (for the two sets of xylene-shielded ethylene glycol units) varied with respect to the concentration, with those assigned to the cyclic [2]catenane dimer decreasing in intensity upon proceeding from a low (2.5 mM) to a high (20 mM) concentration of the tetraaldehyde, which is consistent with a general preference for the formation of smaller molecular aggregates at lower concentrations. Nevertheless, the signals near m/z 1202.6 for the doubly charged [2]catenane dimer $[\mathbf{M_2}+2Na]^{2+}$ remained by far the most intense in the ESI mass spectra recorded at higher concentrations, relative to those for the tri-, tetra-, and pentameric cyclic [2]catenanes. We reasoned that under the conditions of ESI mass spectrometry, the labile imino bonds of the higher-order [2]catenane oligomers may have cleaved to release the



Yield of isolated product

	4	5	6	7
5 mM	11%	3%	0.1%	5%
10 mM	5%	3%	0.2%	4%
15 mM	2%	—	—	3%

Scheme 1. Dynamic self-assembly, with reduction/alkylation, of cyclic [2]catenane dimer **4**, trimer **5**, and tetramer **6**.

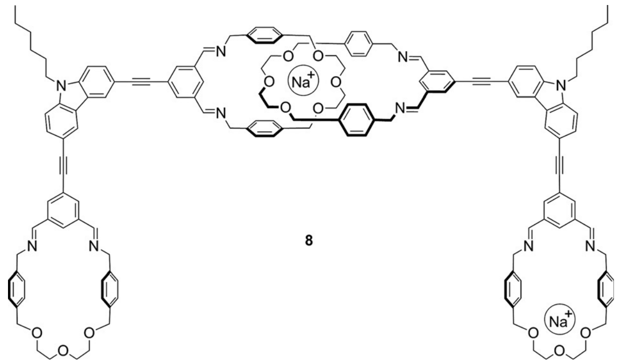


Figure 3. Chemical structure of the acyclic imino [2]catenane dimer **8**.

acyclic [2]catenane dimer **8** (Figure 3), which has the same *m*/*z* ratio as the cyclic dimer **4**. We did not observe any signals corresponding to hexameric or other higher-order oligomers in these mass spectra. Therefore, to confirm the formation of the higher-order [2]catenane oligomers in the higher-concentration solutions, we applied the same reduction conditions to mixtures of diamine **1**, tetraaldehyde **3**, and NaTFPB at concentrations of 10/5/5 and 15/7.5/7.5 mM. Interestingly, we isolated dimer **4**, trimer **5**, and tetramer **6** in yields of 5, 3, and 0.2 %, respectively, from the first reaction mixture, whereas the second did not afford trimer **5** or tetramer **6** at all and only 2 % of dimer **4**.

The significantly lower yields of isolated dimer **4** at higher concentrations are consistent with the observation of lower intensities for the signals of the imino dimer in the ^{1}H NMR spectra of the dynamic mixtures; nevertheless, the combined yields of trimer **5** and tetramer **6** did not increase significantly upon increasing the concentration. We suspect that at concentrations of 15/7.5/7.5 mM (**1**/**3**/NaTFPB), the mixture favored the formation of even higher-order oligomeric cyclic [2]catenanes (pentamers and beyond) and polymers, where the greater number of labile imino bonds limited the efficiency of the subsequent reduction and methylation reactions; therefore, such large species could not be isolated. Possibly for the same reason, we could not isolate the pentameric cyclic [2]catenane from any of our reaction mixtures. As the acyclic form of this pentamer has exactly the same mass as its cyclic form, we are reluctant to confirm the successful assembly of the cyclic [2]catenane pentamer based only on its mass-spectral data. Although the yield of isolated monomer **7** did not increase significantly upon increasing the concentration of the reactants, the yields of the isolated side products (likely a mixture of acyclic [2]catenane oligomers) increased significantly, supporting the notion of partial hydrolysis of the oligomeric and/or polymeric cyclic [2]catenanes during the reduction/methylation process.

After vapor diffusion of hexanes into a toluene solution of cyclic [2]catenane dimer **4**, we obtained single crystals suitable for X-ray crystallography.[12] The solid-state structure in Figure 4 reveals the expected interlocked geometry, with the two [2]catenane subunits linked through carbazole bridging units.

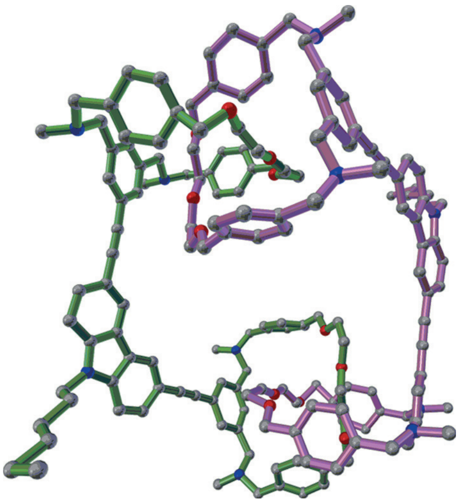


Figure 4. Ball-and-stick representation of the solid-state structure of cyclic [2]catenane dimer **4**. Carbon gray, nitrogen blue, oxygen red.

As structures **4** to **6** all feature a plane of symmetry, with each [2]catenane unit able to freely rotate around the axis defined by its acetylene units (most obviously in our depiction of the cyclic [2]catenane tetramer **6** in Scheme 1), the cyclic [2]catenane oligomers all possess D_{nh} symmetry, which simplifies their ^{1}H NMR spectra. Relative to the ^{1}H NMR spectrum of the linear monomer **7**, the spectrum of each of the oligomeric cyclic [2]catenanes featured two upfield-shifted signals in the range of $\delta = 2.70$–2.90 ppm, corresponding to the di(ethylene glycol) protons shielded by the xylene rings in the [2]catenane subunits (Figure 5). The ^{1}H NMR spectrum of the cyclic [2]catenane trimer **5** is very similar to that of the cyclic dimer **4**, except for slight offsets in the positions of the signals of the di(ethylene glycol) protons ($\delta = 2.70$–2.90 ppm) and their adjacent benzylic protons ($\delta = 3.90$ ppm for **4**; $\delta = 3.93$ ppm for **5**), allowing us to differentiate them but also to make it possible to perform DOSY NMR spectroscopy

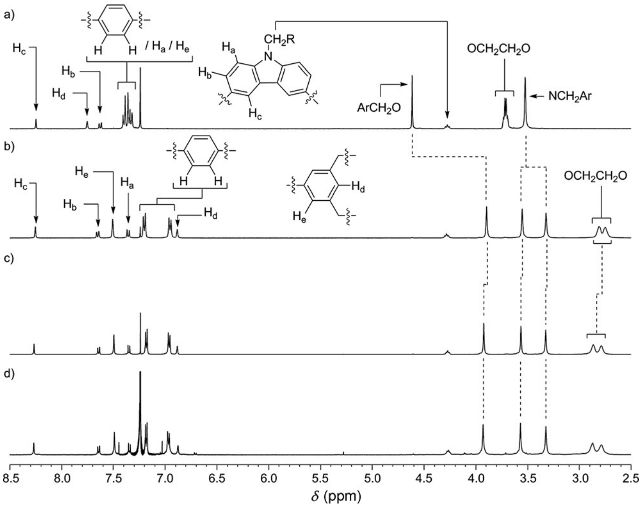


Figure 5. Partial ^{1}H NMR spectra (400 MHz, CDCl$_3$, 298 K) of a) the linear monomer **7** and the cyclic [2]catenane b) dimer **4**, c) trimer **5**, and d) tetramer **6**.

experiments on their equimolar mixture to confirm that the diffusion coefficient of the trimeric cyclic [2]catenane **5** was indeed lower than that of the cyclic dimer **4**. The ESI mass spectrum of the cyclic [2]catenane trimer **5** displayed signals at *m/z* 1867.1, 1245.1, and 934.0, which correspond to the ions $[\mathbf{5}+2\,H]^{2+}$, $[\mathbf{5}+3\,H]^{3+}$, and $[\mathbf{5}+4\,H]^{4+}$, respectively; good matches between the observed and calculated isotope patterns for these ions confirmed the successful synthesis of **5** (Figure 6a). We suspect that the discernable differences in the positions of the ^{1}H NMR signals of the di(ethylene glycol) protons and adjacent benzylic protons for the dimeric and trimeric cyclic [2]catenanes (**4** and **5**, respectively) reflect the different bend angles in their [2]catenane subunits and, therefore, different degrees of shielding of these protons by the xylene rings. Any strain created from such structural bending away from linearity in the dynamic imine-containing cyclic oligomers (favoring higher-order analogues) was presumably balanced by the entropic preference for smaller structures (favoring lower-order analogues).

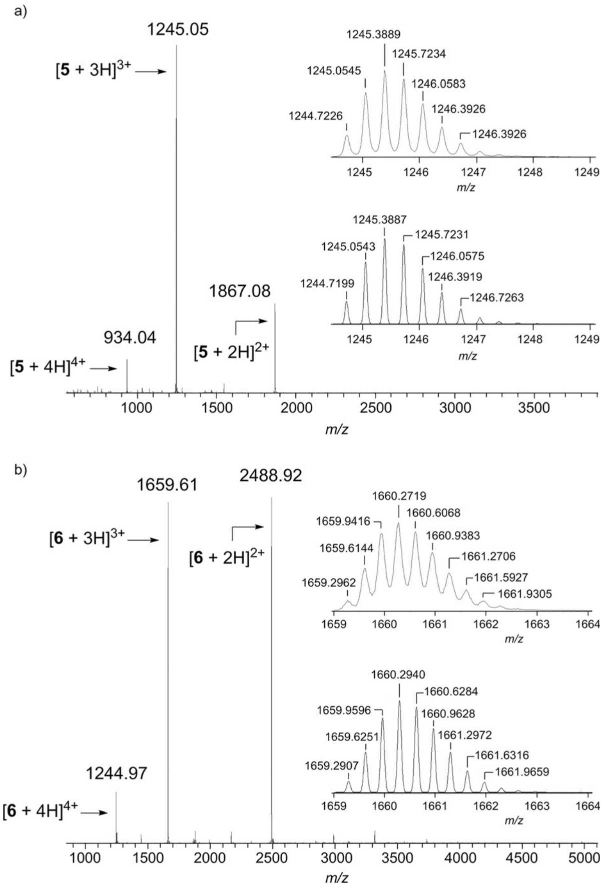


Figure 6. ESI mass spectra of a) the cyclic [2]catenane trimer **5** (exhibiting peaks corresponding to the molecular ions $[\mathbf{5}+2\,H]^{2+}$, $[\mathbf{5}+3\,H]^{3+}$, and $[\mathbf{5}+4\,H]^{4+}$) and b) tetramer **6** (exhibiting peaks corresponding to the molecular ions $[\mathbf{6}+2\,H]^{2+}$, $[\mathbf{6}+3\,H]^{3+}$, and $[\mathbf{6}+4\,H]^{4+}$). The top and bottom insets display the observed and calculated isotopic distributions, respectively.

In contrast, the differences in the ^{1}H NMR spectra of cyclic [2]catenane trimer **5** and tetramer **6** were negligible (Figure 5c,d), making it impractical to differentiate them through DOSY NMR spectroscopy. To confirm that they were indeed two different compounds, we analyzed them by HPLC. The HPLC trace of their mixture, monitored at $\lambda = 254$ nm, revealed two intense signals at retention times of approximately 13 and 21 min, corresponding to trimer **5** and tetramer **6**, respectively (Figure 7). The ESI mass spectrum of the tetrameric cyclic [2]catenane **6** featured intense signals near *m/z* 2488.9, 1659.6, and 1245.0, which correspond to the ions $[\mathbf{6}+2\,H]^{2+}$, $[\mathbf{6}+3\,H]^{3+}$, and $[\mathbf{6}+4\,H]^{4+}$, respectively; again, the observed isotope patterns for these ions matched the calculated ones well (Figure 6b). These results confirm our successful synthesis and isolation of the cyclic [2]catenane tetramer **6**.

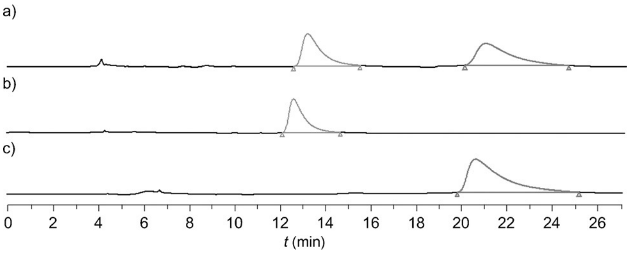


Figure 7. HPLC traces of a) a mixture of cyclic [2]catenane trimer **5** and tetramer **6**, b) trimer **5**, and c) tetramer **6** [Chromatorex column; 5 μm diol; eluent: 0.1% diethylamine in EtOAc/hexanes (1:1); flow rate: 0.75 mL min^{-1}; detection: 254 nm].

We have demonstrated that dimeric, trimeric, and tetrameric cyclic [2]catenanes can be assembled directly from eight (two tetraaldehydes, four diamines, two Na$^+$ ions), twelve (three tetraaldehydes, six diamines, three Na$^+$ ions), and sixteen (four tetraaldehydes, eight diamines, four Na$^+$ ions) components, respectively. Using NaBH$_4$ to reduce the labile imino bonds of the cyclic [2]catenane oligomers, followed by methylation of the resulting secondary amines, allowed us to isolate and characterize these oligomeric cyclic [2]catenanes, including the first examples of trimeric and tetrameric systems, as stable, covalently linked compounds.

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Keywords: catenanes · dynamic self-assembly · imines · supramolecular chemistry · template synthesis

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[12] Crystal data for **4**: $[C_{184}H_{186}N_{10}O_{12}]$; $M_r = 2489.22$; monoclinic; space group *P21/n*; $a = 14.1638(10)$, $b = 27.5488(13)$ (4), $c = 21.9012(14)$ Å; $V = 8545.6(9)$ Å^3; $\rho_{calcd} = 0.967\ g\,cm^{-3}$; $\mu(Cu_{K\alpha}) = 1.54178\ mm^{-1}$; $T = 150(2)$ K; colorless plate; 15558 independently measured reflections; F^2 refinement; $R_1 = 0.1449$; $wR_2 = 0.4183$. The program PLATON/SQUEEZE was applied to account for the residual electron density. CCDC 1408062 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

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