

# New Molecular Topologies Beyond Catenanes and Rotaxanes

Theresa Chang

Department of Chemistry and Biochemistry, University of California, Los Angeles,  
405 Hilgard Avenue, Los Angeles, CA 90095-1569.

tchang@chem.ucla.edu

## ABSTRACT



Not content with interlocked molecules such as catenanes, rotaxanes, and carceplexes, chemists of different persuasions have recently been striving to realize exotic molecular compounds with even more complex topologies and structures. The utilization of appropriate recognition motifs has resulted in the template-directed syntheses of compounds whose molecules resemble trefoil knots, figure eight knots, composite knots and Borromean rings.

Knots and other interlocking and intertwining designs have been prevalent<sup>1</sup> in human artistry and culture since ancient times. However, recent investigations show that the most ancient and complex knots have already been created in Nature, from proteins<sup>2</sup> and DNA.<sup>3</sup> Under appropriate conditions, these macromolecules can form intricate knotted and interlocked structures. Even though molecules with novel topologies and structures have been of great interest to synthetic chemists, it is only recently that it has been possible to construct intertwined and interlocked molecules by design. The discipline<sup>4</sup> of ‘chemical topology’ started to gather momentum at the beginning of the 1960s with Wasserman’s report<sup>5</sup> of his ingenious design and synthesis of the first [2]catenane.<sup>6</sup>

(1) For example, knotworks as decorations were found in *The Book of Kells*, which gave evidence of this fascination in the 8th century. “*Celtic Art. The Methods of Construction*”, Dover Publications, New York, 1973.

(2) See, for example: Liang, C.; Mislow K. *J. Am. Chem. Soc.* **1994**, *116*, 11189–11190.

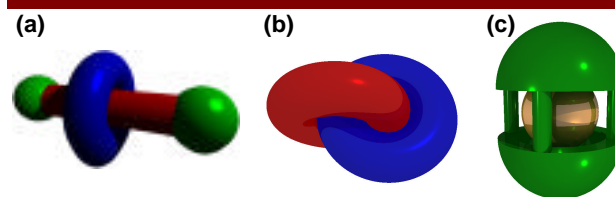
(3) For an example, see: Dean F. B.; Stasiak, A.; Koller, T.; Cozzarelli, N. R. *J. Biol. Chem.* **1985**, 4975–4983.

(4) (a) Frisch, H. L.; Wasserman, E. *J. Am. Chem. Soc.* **1961**, *83*, 3789–3795. (b) Tauber, S. J. *J. Res. Nat. Bur. Stand., Sect. A.* **1963**, *67A*, 591–599. For a recent review, see: (c) Breault, G. A.; Hunter, C. A.; Mayers, P. C. *Tetrahedron* **1999**, *55*, 5265–5293.

(5) Wasserman, E. *J. Am. Chem. Soc.* **1960**, *82*, 4433–4434.

(6) A catenane is composed of mechanically interlocked rings. A rotaxane is composed of a dumbbell and one or more ring(s) that are interlocked mechanically. The prefix [n] before the words ‘catenane’

The early approaches to such molecules, however, relied on statistics—the chance that the macrocyclization of a



**Figure 1.** Diagrammatic representations of some mechanically interlocked molecules such as (a) a rotaxane, (b) a catenane, and (c) a carceplex.

linear molecule occurs while it is threaded through another macrocycle, hence, the yields were inherently poor. Spurred on by this early success, the syntheses of such fascinating molecules moved from mere speculation to the laboratory and many elegant strategies have since been developed<sup>7</sup> for the synthesis of interlocked molecules such

or ‘rotaxane’ signifies the number of mechanically interlocked components in the molecule.

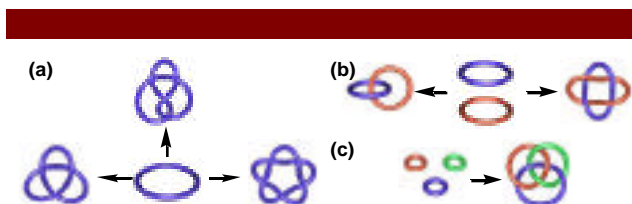
(7) (a) Cram, D. J.; Cram, J. M. *Container Molecules and their Guests*; Stoddart, J. F., Ed.; RSC: Cambridge, 1994. (b) Amabilino, D. B.; Stoddart, J. F. *Chem. Rev.* **1995**, *95*, 2725–2828. (c) Sauvage, J.-P. *Molecular Catenanes, Rotaxanes, and Knots*; Wiley-VCH: Weinheim, 1999. (d) Hubin, T. J.; Kolchinski, A. G.; Vance, A. L.; Busch, D. H. *Adv. Supramol. Chem.* **1999**, *5*, 237–357, and references therein.

as rotaxanes,<sup>5</sup> catenanes,<sup>5</sup> and carceplexes<sup>5,8</sup> (Figure 1). The utilization of covalent templating and metal coordination, as well as a multitude of noncovalent interactions such as hydrogen bonding, cation- and -stacking interactions, has enabled chemists to prepare these, previously elusive, molecular compounds in appreciable quantities. This field has advanced so rapidly that the syntheses of catenanes and rotaxanes are now considered trivial.

Chemists have quickly set their sights on the design and construction of other interlocked and intertwined molecules of more complex topologies. This essay will focus upon the recent developments in the construction of these intriguing molecular architectures—beyond catenanes, rotaxanes, and carceplexes—which have been based on directed syntheses utilizing templating effects and the manipulation of DNA superstructures.

### Supramolecular Topology

A macrocycle as well as a trefoil, figure eight, and composite knots (Figure 2a) can contain the same atoms and connectivities but cannot be interconverted from one to another without (i) the breaking of a covalent bond, (ii) rearrangement of the molecule, and (iii) the subsequent reformation of a covalent bond. They are, hence, termed topological isomers.<sup>4</sup> Topological isomers consisting of two components include noninterlocking macrocycles, [2]catenanes and doubly-interlocked [2]catenanes (Figure 2b) as well as other multiply interlocking [2]catenanes and knots. Examples of three component topological isomers include Borromean rings<sup>9</sup> and its component macrocycles (Figure 2c), as well as singly or multiply interlocking [3]catenanes.



**Figure 2.** Schematic representation of some interlocked and intertwined molecules and their topological isomers. These include—(a) normal (center) or knotted cycles, such as trefoil (left), figure eight (above) and pentafoil (right) knots, (b) a [2]catenane (left) and a doubly interlocked [2]catenane (right), and (c) Borromean rings (right) and the three component macrocycles.

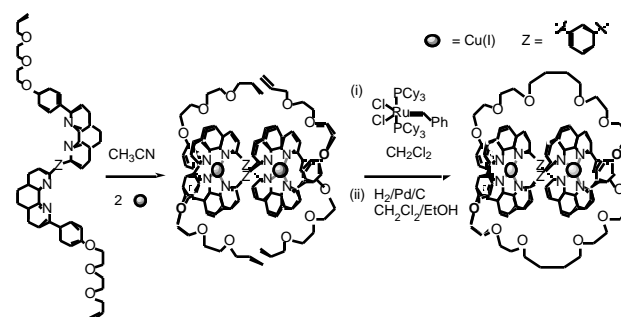
### Metal Templating

The coordination of ligands about transition metal centers has often been utilized for assorted template-directed syntheses because of their specific coordination geometries. These ligands commonly coordinate in a

(8) A carceplex consists of a guest and a host where the guest is trapped within the cavity of the host.

(9) Borromean rings consist of three rings. Although these rings are interlocked as a whole, no two rings are catenated. Hence, if one ring in the set is cleaved, the entire ensemble dismantles.

tetrahedral or octahedral fashion, making the use of metal templating ideal for the construction of three-dimensional architectures. However, metal templates were not always exploited to their fullest potential as they were often employed only as two dimensional templates, for the syntheses of macrocycles. Sauvage played a major role in extending this methodology to the third dimension. Sauvage's monumental discovery<sup>10</sup> in the early 1980s of the assembly of two 2,9-disubstituted-1,10-phenanthrolines about Cu(I) in a pseudotetrahedral fashion enabled the construction of a myriad of mechanically-interlocked molecules.



**Scheme 1.** A dicopper trefoil knot obtained via a double helical intermediate in an overall yield of 35 % (seven steps).

Sauvage utilized his Cu(I)-phenanthroline catenane template for the fabrication of complex molecular knots and interlocked molecules—the first of which was a trefoil knot. Copper(I) ions self-assemble with bidentate 1,10-phenanthroline ligands, separated by 1,3-phenylene spacers, in a double-helical fashion. With this strategy in mind, Sauvage incorporated two coordinating fragments—each bearing two chelating phenanthroline units—into a complex around two metal centers to give a double-helical intermediate. The most efficient trefoil knot synthesis<sup>11</sup> thus far utilizes ring closing metathesis (RCM) with a ruthenium catalyst to bring together the termini of the double helices, resulting (Scheme 1) in an impressive 35 % overall yield (seven steps) of the desired product.<sup>12</sup> The knotted products formed under these conditions exist as a mixture of topological stereoisomers since both right-handed and left-handed double-helical intermediates are equally likely to be formed in the absence of any chiral inducing agents.

Extending the phenanthroline/Cu(I) chelation motif, Sauvage<sup>13</sup> synthesized a composite knot based on the self-assembly of a long tetrachelating thread (Figure 3) by the

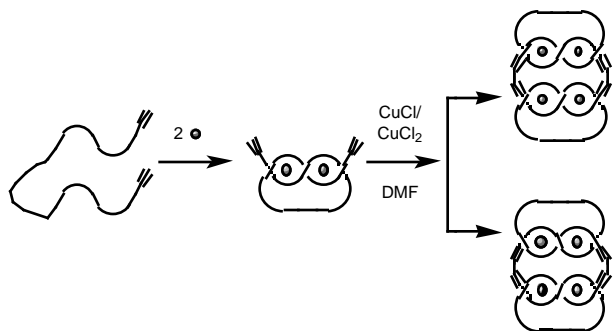
(10) Dietrich-Buchecker, C. O.; Marnot, P. A.; Sauvage, J.-P.; Kirchhoff, J. R.; McMillin, D. R. *J. Chem. Soc., Chem. Commun.* **1983**, 513-515.

(11) Dietrich-Buchecker, C. O.; Rapenne, G.; Sauvage, J.-P. *Chem. Commun.* **1997**, 2053-2054.

(12) Recently, a molecular trefoil knot had been constructed using Fe(II) as the metal template. Rapenne, G.; Dietrich-Buchecker, C.; Sauvage, J.-P. *J. Am. Chem. Soc.* **1999**, *121*, 994-1001.

(13) Carina, R. F.; Dietrich-Buchecker, C.; Sauvage, J.-P. *J. Am. Chem. Soc.* **1996**, *118*, 9110-9116.

addition of Cu(I). Glaser-Eglinton coupling of the terminal acetylenes, followed by demetallation, yields composite knots as a pair of topological enantiomers and a meso isomer.



**Figure 3.** A schematic representation of the synthesis of a composite knot. The long thread is preorganized by the coordination of the four phenanthroline units to Cu(I) ions. Using Glaser coupling, two of these subunits are brought together to give the molecular composite knot.

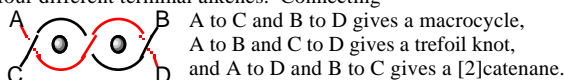
The synthesis of a doubly-interlocking [2]catenane has also been achieved by Sauvage and Fujita,<sup>14</sup> in almost quantitative yield! This system differs from the trefoil knot synthesis only by an additional metal template and a trischelating thread instead of a bischelating thread. Following this trend, we can imagine that a pentafoil knot could, in principle, be constructed by the addition of yet another coordination site, to form a double-helical intermediate consisting of four half-twists (Figure 4). It is worthwhile noting that a double helical intermediate with an odd number of half-turns, once cyclized,<sup>15</sup> results in a multiply interlocked [2]catenane, whereas an even number results in a one component molecular knot of increasing complexity.

### Other Noncovalent Interactions

The exponential growth in the field of supramolecular chemistry is, in part, a direct consequence of self-assembly<sup>16</sup> and its use of noncovalent bonding interactions such as  $\pi$ -stacking, C–H $\cdots$ O hydrogen bonding and C–H $\cdots$  interactions. Since these interactions are each relatively weak, complex formation is reversible. This feature thus enables the system to find the most thermodynamically favorable co-conformation. Using noncovalent forces, Stoddart and coworkers<sup>17</sup> have

(14) Ibukuro, F.; Fujita, M.; Yamaguchi, K.; Sauvage, J.-P. *J. Am. Chem. Soc.* **1999**, *121*, 11014-11015.

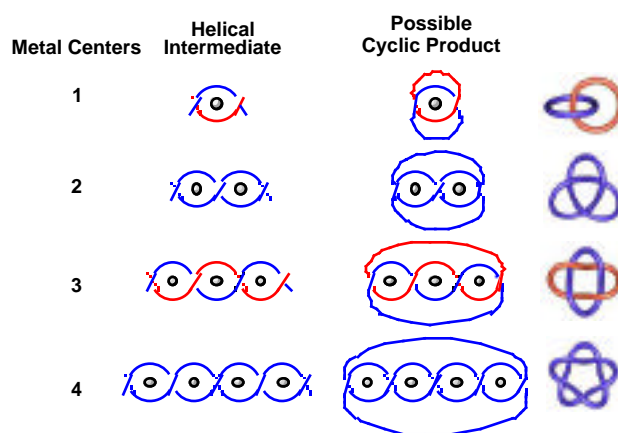
(15) There are three different ways of cyclization by RCM with four different terminal alkenes. Connecting



(16) (a) Whitesides, G. M.; Mathias, J. P.; Seto, C. T. *Science* **1991**, *154*, 1312-1319. (b) Philp, D.; Stoddart, J. F. *Angew. Chem., Int. Ed.* **1996**, *35*, 1155-1196

(17) Ashton, P. R.; Matthews, O. A.; Menzer, S.; Raymo, F. M.; Spencer, N.; Stoddart, J. F.; Williams, D. J. *Liebigs Ann. Recueil* **1997**, 2485-2494.

constructed a molecular trefoil knot. The key feature in this strategy is the self-assembly of a complex, governed by thermodynamic control, which is subsequently converted into its final molecular structure *via* a kinetically controlled covalent bond formation step.



**Figure 4.** Interlocking and intertwining molecules which can be constructed by the self-organization of the threads into double-helical arrangements via metal templates.

This method utilizes the recognition between the  $\pi$ -electron-rich 1,5-dioxynaphthalene-based polyether and a  $\pi$ -electron-deficient bipyridinium-based tetracation to template the formation of the molecular knot. The 1,5-dioxynaphthalene containing thread and the bipyridinium-based compound self-assemble (Scheme 2) to form a complex where two 1,5-dioxynaphthalene units are sandwiched between the three bipyridinium moieties. Employing ultrahigh pressure conditions at ambient temperature, the trefoil knot, as well as a trivial knot (unknotted macrocycle), and an acyclic byproduct, were formed. The presence of the trefoil knot is evidenced by a red/purple color, which is characteristic of charge transfer interactions between these electron-poor/electron-rich systems.

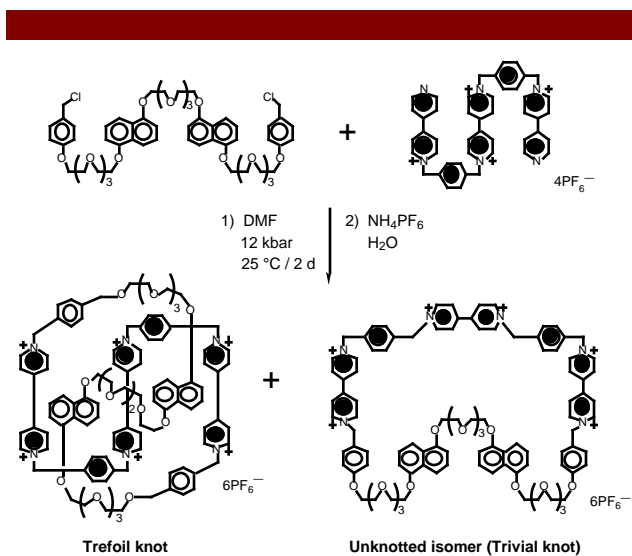
Vögtle has recently reported<sup>18</sup> his fortuitous discovery of a one-step synthesis of a molecular trefoil knot. Starting from 2,6-pyridinedicarbonyl dichloride and a bisamine compound, the trefoil knot—as a result of a 3 + 3 macrocyclization—was obtained in 20 % yield instead of the expected unknotted macrocycle. This reaction is templated by hydrogen bonding interactions with four of the twelve NH hydrogen atoms participating in intramolecular hydrogen bonds.

### DNA Nanoconstruction

The inter- and intramolecular interactions of DNA macromolecules have been studied extensively, leading to the possibility of reliably predicting the three-dimensional structure of various sequences. The ease of synthesis of DNA as a result of solid-phase synthesis make DNA an

(18) (a) Safarowsky, O.; Nieger, M.; Fröhlich, R.; Vögtle, F. *Angew. Chem., Int. Ed.* **2000**, *39*, 1616-1618. (b) Zurer, P. *Chem. Eng. News* **2000**, *78*, 14.

ideal building block for the construction of compounds possessing various complex knotted topologies. By careful design, utilizing hydrogen bonding interactions of complementary base pairs, a DNA strand can assemble to form the desired structure. DNA can also be modified easily by a variety of different enzymes available from Nature. For example, DNA ligase has been used in Nature, and in the laboratory, to anneal DNA fragments.



**Scheme 2.** A trefoil knot synthesis based on the 1,5-dioxynaphthalene/bipyridinium recognition motif.

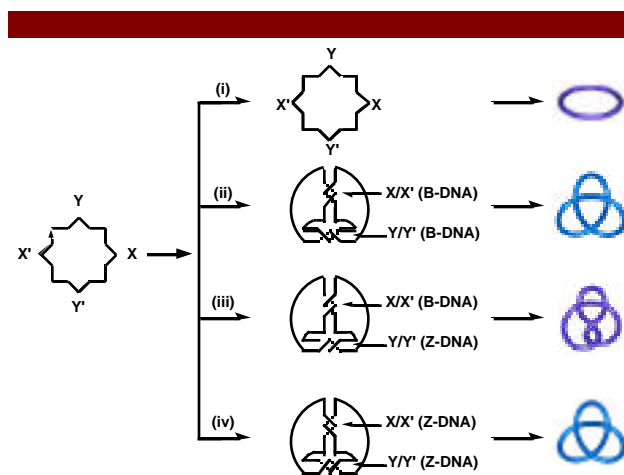
One important feature of DNA is its chiral double-helical structure. Depending on the nucleotide sequence and solvent conditions, the handedness<sup>19</sup> of a particular sequence of DNA can be accurately programmed. Based on these principles, Seeman and coworkers<sup>20</sup> synthesized a series of knotted structures. The formation of four topological isomers—a macrocycle, trefoil knots with positive or negative nodes and a figure eight knot—is possible from just one single strand of DNA. By varying ligation conditions, thereby switching between B- and Z-DNA conformations, a product of the desired topology can be acquired following ligation using DNA ligase. This experiment is illustrated schematically in Figure 5. The starting DNA strand consists of two pairs of complementary sequences which are uncomplexed at low ion concentration but form right-handed double-helices (B-DNA) at with higher ion concentration (0.3 mM Mg<sup>2+</sup>). The two double-helices are capable of a B to Z transition under different conditions, 10 mM Mg<sup>2+</sup> for the first and 10 mM Mg<sup>2+</sup> plus 3 mM Co(NH<sub>3</sub>)<sub>6</sub><sup>3+</sup> for the second. The DNA strand can then self-assemble in the desired arrangement. Ligation of the DNA strand, when

(19) Two types of DNA used extensively in nanoconstruction are B and Z-DNA. From a topological point of view, B-DNA and Z-DNA are mirror images: where B-DNA is a right-handed helix which consists of negative nodes, Z-DNA is left-handed with positive nodes. The handedness of a DNA strand is dependent on the sequence of nucleotides and ion concentrations as well as on solvent conditions.

(20) Du, S. M.; Stollar, B. D.; Seeman, N. C. *J. Am. Chem. Soc.* **1995**, *117*, 1194-1200.

uncomplexed, results in, not unsurprisingly, the unknotted macrocycle. With both of the double helices in the B-DNA or Z-DNA conformations, trefoil knots with negative and positive nodes, respectively, are formed. When the double helices adopt opposite conformations, a figure eight knot is produced. Once ligated, these knots cannot interconvert unless a DNA topoisomerase is present to catalyze the interconversion via the cleavage of the knot, followed by a reorganization of the strand and subsequent reformation of a covalent bond.

Using DNA, Seeman was also able to design and synthesize the first molecular Borromean rings which have yet to be realized by synthetic supramolecular chemists. Seeman was also able to fabricate<sup>21</sup> other molecules and networks of varying complexity including a DNA cube, a truncated octahedron as well as a warp and mesh network.



**Figure 5.** Construction of knots by ligation of a single strand of DNA. Sequences at X and X' as well as Y and Y' are complementary. (i) A macrocycle results in 0.1 mM Mg<sup>2+</sup>, (ii) a trefoil knot (negative nodes) in 0.3 mM Mg<sup>2+</sup>, (iii) a figure eight knot in 10 mM Mg<sup>2+</sup>, and (iv) a trefoil knot with positive nodes in 10 mM Mg<sup>2+</sup> and 3 mM Co(NH<sub>3</sub>)<sub>6</sub><sup>3+</sup>.

## Conclusions

The realization of molecules with knotted topologies exhibits the power of noncovalent templating,<sup>22</sup> molecular recognition<sup>23</sup> and self-assembly.<sup>16</sup> Many of these interlocked molecules can now be prepared in multigram quantities. Their vast potential for use as molecular machines and devices<sup>24</sup> remains—as yet—untapped.

(21) Seeman, N. C.; Wang, H.; Yang, X.; Liu, F.; Mao, C.; Sun, W.; Wenzler, L.; Shen, Z.; Sha, R.; Yan, H.; Wong, M. H.; Sa-Arduyen, P.; Liu, B.; Qi, H.; Li, X.; Qi, J.; Du, S. M.; Zhang, Y.; Mueller, J. E.; Fu, T. -J.; Wang, Y.; Chen, J. *Nanotechnology* **1998**, *9*, 257-273.

(22) Diederich, F.; Stang, P. J., "Templated Organic Synthesis", Wiley-VCH: Weinheim, **2000**.

(23) *Comprehensive Supramolecular Chemistry*, eds. Atwood, J. L.; Davies, J. E. D.; MacNicol, D. D.; Vögtle, F.; Pergamon, Oxford, **1996**, Vol. 1.

(24) (a) Balzani, V.; Credi, A.; Venturi, M., "Molecular-Level Devices", In *Supramolecular Science: Where We Are and Where We Are Going*, Ungaro, R., Dalcanale, E., Eds.; Kluwer: Dordrecht, **1999**. (b) Rouhi, M. *Chem. Eng. News* **1999**, *77*, 13.