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Open Problems in Chemical Topology

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The historical origins of chemical topology are highlighted and seven open problems in the discipline are defined. The current state of experimental work towards their solutions is reviewed. Open problems discussed include size and tightness limits on molecular knots, synthesis of knots more complex than the trefoil, measurement of the enantiomerization barrier of a topological rubber glove, and syntheses of a polyethylene trefoil knot, a stable open knot with stoppers, and a molecular Whitehead link.

1. Introduction

Chemical topology is concerned with molecules that have non-planar graphs. Molecular knots and links (catenanes) are common examples of such compounds (Figure 1). There have been many milestones in the development of the field including the syntheses of molecular trefoil[1] and composite knots,[2] Solomon[3] and Borromean links,[4,5] a Möbius strip,[6] and K_5[7] and $K_{3,3}$[8] molecules.[9] Despite these achievements many open problems remain. After a brief overview of topology and the historical origins of chemical topology, seven problems in the discipline are defined and the current state of experimental work towards their solution is outlined.

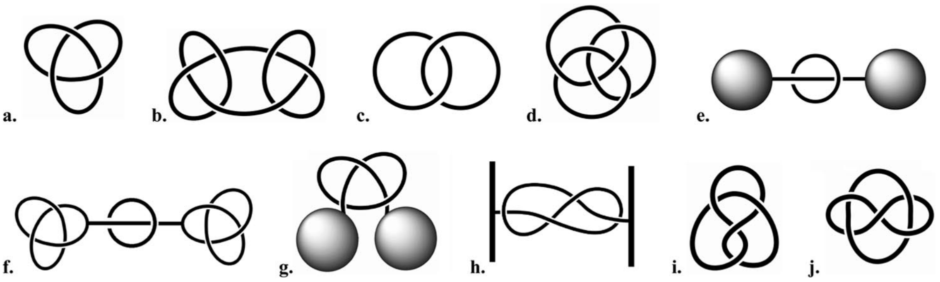

Figure 1. Structures with non-trivial topologies. **a**: trefoil knot, **b**: square knot, **c**: [2]-catenane (Hopf link), **d**: Borromean rings, **e**: rotaxane, **f**: knotaxane, **g**: trefoil rotaxaknot, **h**: Figure eight rotaxaknot, **i**: Figure eight knot, **j**: Whitehead link. Non-DNA molecular versions of structures **a**–**f** have been prepared, whereas syntheses of structures **g**–**i** remain open problems.

This microreview focuses on the chemical topology of small molecules to the exclusion of DNA and proteins. Thetopologies that can be achieved with the latter, in particular DNA, are significantly more advanced. Topoisomer-

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Edward Emmett Fenlon was born in 1968 in Albany, New York, USA. In 1990 he graduated from St. Lawrence University and began graduate studies at the University of Illinois at Urbana-Champaign where he focused on the synthesis of nitrogen heterocycles for self-assembly under the guidance of Prof. Steven C. Zimmerman. He obtained his PhD in 1995 and began a two-year Dreyfus postdoctoral fellowship with Prof. Robert J. Kempton at Northern Kentucky University. He then commenced his independent career at Xavier University in Cincinnati, Ohio. In 2003 he was promoted to Associate Professor with tenure at Xavier. In the same year he moved to his current Assistant Professor position at Franklin & Marshall College in Lancaster, Pennsylvania. One of his research areas involves the synthesis of nucleoside analogues to study nucleic acids, most recently by vibrational spectroscopy of nitrile probes. A second research area is the synthesis and analysis of molecular knots. His research as been supported by Research Corporation, the Dreyfus Foundation, Project SEED, and the US National Science Foundation. In 2000 he received the Joan G. McDonald award for Excellence in Science Teaching. He resides in Lancaster with his wife Stephanie and their son Ethan.

ases naturally form a multitude of complex knots in double stranded DNA plasmids[10] and phage capsids,[11] and molecular biology techniques can be used for the design and synthesis of topologically interesting targets. DNA versions of the figure eight[12] and endless knots[13] have been prepared and DNA-based Borromean rings[4] were synthesized seven years prior to a small molecule version.[5] The rich chemistry of DNA knots has been previously reviewed. For example, Seeman[14] has reviewed synthetic *single*-*stranded* DNA knots and Sumners et al.[15] have reviewed *double-stranded* DNA topology. Naturally occurring proteins also form knots,[16] and Taylor reviewed this area last year.[17] However, many protein knots are "open knots," and therefore are not considered true knots from a mathematical point of view (vide infra).

Numerous reviews of small molecule chemical topology have been published. The reviews[18–22] from 1960–1974 defined the field and Walba's extensive 1985 review[23] fills the gap between this early work and more recent reviews[24] on interlocked and intertwined complexes,[25] supramolecular topology,[26] interlocked and entangled structures,[27] and molecular knots.[28,29] Monographs by Schill[30] in 1971 and a 1999 volume[31] edited by Sauvage and Dietrich-Buchecker are each devoted to catenanes, rotaxanes, and knots and provide excellent overviews of the field at the time they were written. Finally, for detailed mathematical analyses of non-DNA molecular knots and links, the reader is referred to the monograph by Flapan[32] and the work of Liang and Mislow[33–37] and others.[20,22,23,38,39]

2. Topology and Chemical Topology

When topologists consider a geometric object they assume it is infinitely flexible and cannot be broken during deformation. Under these rules the shape of a coffee cup and a doughnut are considered equivalent because one can be deformed into the other.[40] It follows from this that topologists define a knot as a closed loop because a linear object containing a "knot" in the middle can easily untie itself.[41] Applying topology to molecular species involves using a *molecular bond graph* embedded in three-dimensional space (3-space). The vertices of such a graph are atoms or groups of atoms which are connected by edges that are chemical bonds.[32] A molecule has nontrivial topology if its bond graph is nonplanar. Under topological rules molecular properties that are due to rigidity, such as stereocenters, lose their meaning.[40] Also, these conditions would allow four of the objects in Figure 1 to come apart; namely, the central link of the rotaxane or knotaxane would unthread itself and the rotaxaknots would simply untie themselves no matter how large the stopper groups. It is important to note that these topological rules do not apply to real molecules which have finite limits on bond lengths and angles and that rotaxanes and related compounds are stable due to these limitations.

The mathematical analysis of knots began as a way to understand the nature of chemical elements. In the 1860's Lord Kelvin (William Thompson) put forth his vortex theory, which held that each element was a different knot in the æther.[42] This led Scottish physicist Peter Guthrie Tait to start a systematic examination and classification of knots.[43] The development of an algebraic method to study knots came in the 1920's when Alexander developed his polynomial.[44] Another major breakthrough in knot theory was the Jones polynomial[45] in 1984.

Topologists classify knots in various ways. The first is to determine if the structure in question is a composite or prime knot. A *composite* knot is formed by taking two nontrivial knots, cutting them, and joining the ends to make a single knot. For example, combining two enantiomeric trefoils gives a square knot (Figure 1, **b**). In the reverse process, a composite knot is decomposed into its factor knots. A *prime* knot (Figure 2) is one that cannot be further decomposed.[41]

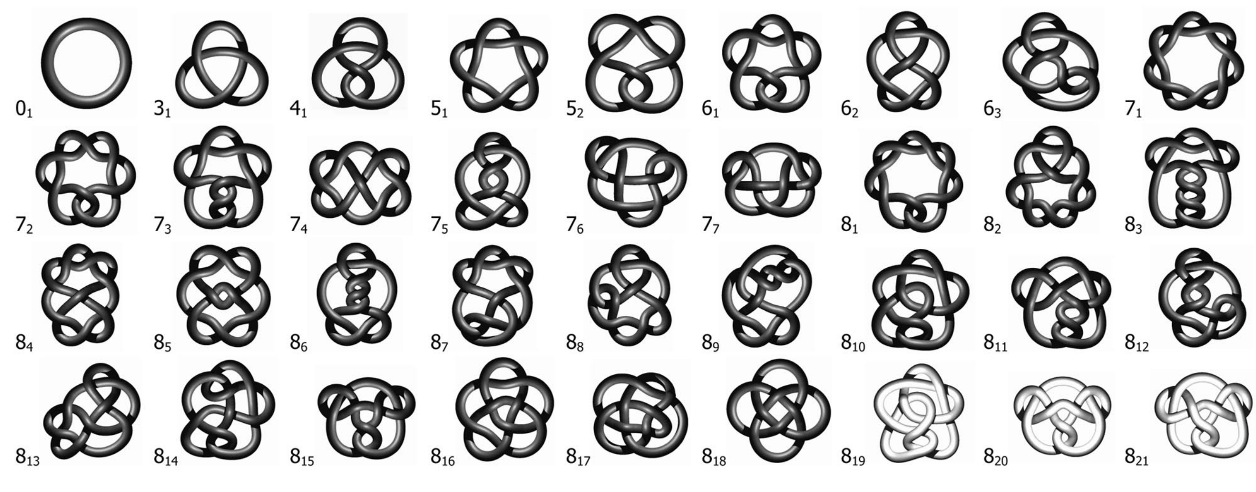


Figure 2. Knot table depicting all prime knots with up to eight crossings. Several prime knots also have common names; e.g., unknot (trivial knot) (0_1), trefoil (3_1), figure eight (4_1), pentafoil (5_1), three-twist (5_2), and endless (7_4). Dark grey knots are alternating and white knots are nonalternating. Face inverted renderings of these knots can appear remarkably different, see Figure 2S in the Supporting Information.

Knots are also classified by crossing number which is the number of times the backbone crosses over itself when projected onto a two-dimensional surface. However, different conformations of a knot result in projections with different crossing numbers, so the knot is identified by the conformation that results in the *minimum* number of crossings. Knots are drawn in this conformation and labeled with the crossing number and a subscripted index number that denotes the knot's position in the standardized Table (Figure 2). So, 0_1 (the unknot) represents a simple ring with no crossings and 6_1, 6_2, and 6_3 represent the three knots with six crossings.

Another way knots are characterized is by chirality. Most prime knots are chiral but others are amphicheiral, meaning that one enantiomer can be deformed into the other. The amphicheiral knots shown in Figure 2 are 4_1, 6_3, 8_3, 8_9, 8_{12}, 8_{17}, and 8_{18}.[41,45] Knots are also classified by whether or not the over/under crossing pattern alternates as a path is made around the knot projection. The nonalternating knots shown in Figure 2 are 8_{19}, 8_{20}, and 8_{21}, all others are alternating knots. The number of knots grows rapidly with increasing crossing number. There are 165 knots with 10-crossings, 46,972 with 14-crossings, and 1,388,705 with 16-crossings.[46] For crossing numbers greater than 17, only the number of alternating knots has been determined; e.g., there are 128,564,665,125 alternating knots with 24 crossings.[47]

Knots are actually a subclass of links that contain only one component. Links can also be classified by crossing number, chirality/amphicheirality, and alternating/nonalternating crossings. The topological convention for representing links uses the crossing number followed by a superscripted number denoting the number of components in the link and a subscripted index number.

3. Historical Origins of Chemical Topology

The origins of the field are most often traced to Frisch and Wasserman's seminal 1961 "Chemical Topology" article in the *Journal of the American Chemical Society*.[19] Indeed, many important concepts are introduced in this paper. However, as the authors note, the genesis of the field goes back further, although there has not always been a written record of these early origins (Table 1).

For example, the idea of a linked ring compound (catenane) can be traced to a seminar by Willstätter between the years 1906–1912.[48] The mention of a rotaxane molecule in the literature can be traced to a 1958 paper by Lüttringhaus et al.,[49] but in a footnote they state that experimental work on a cyclodextrin system was first attempted in 1950. The first known reference to a molecular knot is from a paper written by Ambs in 1952 while he was an undergraduate at Villanova College.[50] The manuscript,[51] which contained a

Table 1. Historical origins of chemical topology.

Structure[a]	Earliest reference[b]	Year	Ref.	First Example[c]	Year	Ref.
Catenane	Willstätter	1912	[48]	Wasserman	1960	[56]
Rotaxane	Lüttringhaus	1950	[49]	Harrison[d]	1967	[57]
Trefoil knot	Ambs	1952	[50]	Sauvage	1989	[1a]
Rotaxaknot	Schill	1974	[22]	n.a.[e]	–	–
Knotaxane	Vögtle	2003	[54]	Vögtle	2003	[55]

[a] See Figure 1. [b] Earliest known mention of the concept of a molecular version of the structure. [c] First non-DNA molecular example. [d] Schill cites an unpublished rotaxane synthesis in 1962 by Stetter and Lihotzky.[58] [e] Not applicable, because a stable rotaxaknot has yet to be prepared.

Table 2. Published synthetic strategies for a trefoil knot.

Year(s)	Method	Group	Experimental work?[a]	Success?[b]	Ref.
1960	Möbius strip	van Gulick	no	n.a.[c]	[18]
1961–1962	random knotting	Wasserman	yes	no	[61]
1961	Möbius strip	Wasserman	no	n.a.[c]	[19]
1971–1983	Möbius strip	Schill	yes	no	[62]
1971–1979	internal threading	Schill	yes	no	[22,63]
1973	octahedral metal	Sokolov	no	n.a.[c]	[21]
1980s	Möbius strip	Walba	yes	no	[23,64]
1987–1992	hook & ladder	Walba	yes	no	[65]
1989	Cu^I double helix	Sauvage	yes	yes	[1a]
1997	π-stacking	Stoddart	yes	yes	[1b]
2000	int. template/H-bonding[d]	Vögtle	yes	yes	[1c]
2001	octahedral metal	Hunter	yes	yes[e]	[1d,66]
2001	bascule beam	Siegel	yes	no	[67]
2006	int. template/H-bonding[d]	Feigel	yes	yes	[1e]
2006–present	thread & cut/solvophobic	Fenlon	yes	–[f]	[68]

[a] Was experimental work undertaken? [b] Has the strategy been successful in producing a trefoil knot? [c] Not applicable, because experimental work was not undertaken. [d] Internal template with hydrogen bonding. [e] An open-knot metal complex was published[1d] but unpublished work reveals that a closed-knot metal complex was also prepared.[66] [f] Structural proof is needed to confirm preliminary results that suggest knot formation.

review of relevant literature,[52–53] was published the following year. The concept of an open knot that cannot untie itself due to bulky stoppers (a molecular rotaxaknot) appears to have been introduced by Boeckmann and Schill in their 1974 review.[22] The concept for a knotaxane (a rotaxane with knots as stoppers) was proposed[54] and the molecule prepared[55] by Vögtle in 2003.

The first published non-DNA molecular manifestation of each of these species is noted in Table 1, with Wasserman,[56] Harrison,[57] Sauvage,[1a] and Vögtle[55] being the first to report a catenane, rotaxane, trefoil knot, and knotaxane, respectively. In the rotaxane case there is some discrepancy about precedence, however, because Schill cites the 1962 unpublished work of Stetter and Lihotzky as the first rotaxane synthesis.[58] A stable rotaxaknot has yet to be prepared and is one of the open problems reviewed below.

In terms of nomenclature, *catenane* was independently proposed by Wasserman[56] and van Gulick[18] in 1960 and is derived from the Latin *catena*, chain; *rotaxane* was introduced by Schill[59] and is based upon the Latin words for wheel and axle, *rota* and *axis*, respectively; *rotaxaknot* was proposed by Busch,[27] and *knotaxane* by Vögtle.[54] Numerous systematic nomenclature systems for topologically interesting compounds such as catenanes, rotaxanes, and knots have been proposed.[18,20,30,60]

A brief examination of the historical efforts toward the trefoil knot highlights the difficulties in preparing compounds with novel topologies. This target has attracted the attention of many synthetic chemists over the past 45 years with 15 literature reports describing approaches to it (Table 2). Only five of these have been successful to date and only two of the trefoil knot systems, those of Sauvage and Vögtle, have been extensively studied.[28,29]

4. What Are the Lower Size Limits for Molecular Knots?

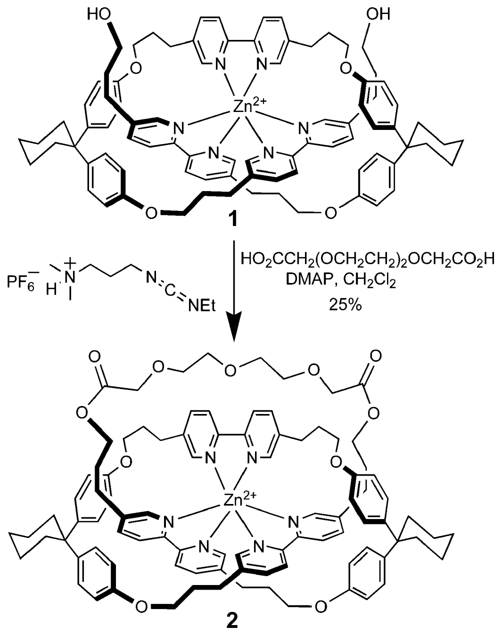
The minimal size required to form polyethylene knots has been addressed by use of space filling molecular models[69] and calculations (Table 3). Wasserman first addressed this issue in 1960 when he predicted the polyethylene trefoil would require "more than 50 carbon atoms."[56] This estimate was made based upon examination of Fisher–Hirschfelder–Taylor (FHT) molecular models.[19] In later years he also published minimal sizes for all prime knots through six-crossings (Table 3).[61,70] van Gulick[18] also used FHT models and his results for the trefoil agree well with Wasserman's, however their pentafoil estimates differ significantly. Boeckmann and Schill[22] used Stuart–Briegleb (SB) models for their size estimates, although they do not address which of the five-crossing and six-crossing knots they examined. Data reported herein show that Corey–Pauling–Koltun (CPK) models estimate minimal knot sizes intermediate between the FHT and SB values.[71] It is not surprising that the CPK models give larger values compared to SB models because Vögtle has noted that CPK models tend to be too rigid and SB models too flexible when compared to experimental data on molecules.[72] Two studies have approached the question using calculations.[73,74] Dhaliwal and Weinberg developed a simple tubular model of knots and also did calculations at the UFF and AM1 levels.[73] For the tubular model, the diameter of the tube was fixed at 3.6 Å and the bond lengths and bond angles were constrained to maintain the values of the secondary carbon atoms in *n*-decane. Using this model the minimal size was found to be 59-, 73-, and 86-atoms for the trefoil, figure eight, and pentafoil knots, respectively. These values provide a fairly close match to those found using FHT molecular models. The UFF and AM1 calculations on the trefoil both showed that a 59-atom backbone was the minimal size for which there was no energy difference between the trefoil and the unknot. The smallest stable trefoil knot found by the AM1 method contained 43 carbon atoms. A more recent study used Hartree–Fock RHF/3-21G$^{(*)}$ level calculations to investigate polyethylene trefoils ranging in size from 25 to 28 carbon atoms.[74] It was concluded that the 27-atom trefoil is the minimal size for a stable knot. This was based on the fact that it was the smallest knot that did not yield imaginary bond vibrational frequencies or broken bonds during the optimization. However, the calculated C–C bond lengths ranged from 1.612 to 1.813 Å, so the compound appears to contain bonds beyond the upper limits of $C(sp^3)$–$C(sp^3)$ bond length. Although several cyclobutenes with C–C bond lengths of 1.71–1.73 Å have been reported, these compounds represent special cases and these are among the longest C–C bonds known.[75]

Table 3. Minimal number (*N*) of methylenes in polyethylene knots $(CH_2)_N$.

Knot[a]	FHT[b]	S-B[c]	CPK[d]	Calculations[e]
3_1	50 (48[f])	45	47	59 (43[g], 27[h])
4_1	74	57	66	73
5_1	83 (72[f])	67	74	86
5_2	92		77	
6_1	100	80	93	
6_2	102		95	
6_3	105		93	

[a] Standard knot nomenclature is used, see Figure 2. [b] Fisher–Hirschfelder–Taylor molecular models.[19,56,61,70] [c] Stuart–Briegleb molecular models.[22] [d] Corey–Pauling–Koltun molecular models, this work.[71] [e] Theoretical calculations based upon a tubular model.[74] [f] Van Gulick's FHT model results.[18] [g] AM1 minimal size.[73] [h] Hartree–Fock RHF/3-21G$^{(*)}$ minimal size.[74]

It is unknown whether molecular knots can approach these modelled limits. The smallest knot in the published literature is a trefoil with 80 backbone atoms.[76] This was prepared by the Sauvage group as part of a systematic study of phenanthroline knots in which a series of trefoils ranging from 80- to 90-backbone atoms were prepared. In this case yield optimization was the goal of the work, not testing the lower limits of knot size. However, unpublished results show that trefoil knots smaller than 80 atoms are feasible. The Hunter group at Sheffield[66] prepared trefoil knot **2** by macrocyclization of open knot **1**[1d] with 3,6,9-trioxaundecanedioic acid (Scheme 1). Mass spectral (M^{2+} peak = 767 Da) and ^1H NMR spectroscopic data support the formation of **2** which contains a 77-atom backbone. Further evidence for the closed knot structure of **2** comes from demetallation experiments. In contrast to the facile demetallation of **1** with chloride ion, efforts to demetallate **2** under the same conditions failed. The highly preorganized metal binding cavity of **2** results in a stronger affinity for the metal and provides steric shielding from the demetallation reagent.



Scheme 1. Preparation of a 77-atom knot by Mayers and Hunter.[66]

Preliminary experimental work from our group suggests that trefoil knots with backbones containing 63- or 72-atoms are feasible (vide infra). Systematic investigation of the lower limits of knot size should be possible with TLC (thread, link, and cut) knots[68] due to a modular design with the ability to adjust the size of the knots produced simply by varying the length of linker 1, linker 2, or the tail (Figure 3). The knot-tying (linking) step is a ring-closing olefin metathesis[77] (RCM) under high dilution during which threading of the tails through the macrocycles can occur. After the RCM, the labile ester bonds are hydrolyzed (cut) to give the knot products. Productive threading occurs when a tail threads through the opposing macrocycle;[78] e.g., tail **a** threads through macrocycle **B** (Figure 3). When productive threading occurs from the same face of the macrocycles (e.g., both top-down) the trefoil knot results after the cutting step. However, with longer tails threading of the two tails can occur from opposite faces leading to the figure eight knot.[68]

The TLC knot method takes advantage of solvophobic interactions by conducting the RCM reaction in a polar solvent such as acetone. This should increase the probability of threading and knot formation by promoting a collapsed conformation of the knot precursor. Meanwhile, second generation iterations of the method are being pursued. These systems encourage tail threading by employing more rigid macrocycles, which should remain in an open conformation, and incorporation of molecular recognition elements between the tail and the macrocycle. These rigid second-generation systems are also expected to be more crystalline which may allow structural proof by X-ray crystallography. Once knot formation has been optimized, the lower limit on knot size will be explored by variation of the size of the macrocycles and the length of the tails.

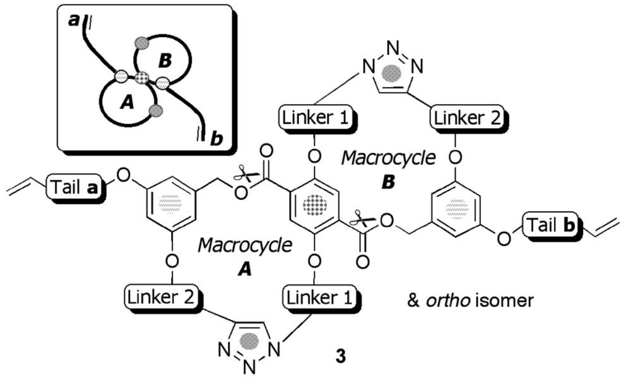


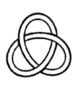
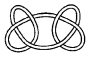
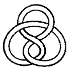
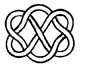
Figure 3. Chemical and schematic (inset) structures of the generalized form of the meta isomer[79] of a TLC molecular knot precursor. Tail and linker length can be varied to place constraints on the RCM knot-tying step. The scissors indicate the ester bond to be hydrolyzed (cut) after the knot-tying step.[68]

5. Knot and Link Tightness

5.1. How Can Knot Tightness Be Assessed? The Backbone Crossing Ratio (BCR)

There are many advanced mathematical methods for studying the energy and/or tightness of a knot.[80–92] These methods include parameters for assessing factors such as the thickness and length of the backbone, number of crossings, writhe, and global radius of curvature. However, there is no simple method for analyzing the tightness of molecular knots and links that have been prepared. Therefore, a

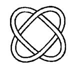
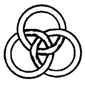
Table 4. Backbone crossing ratios (BCR) for molecular knots.

Knot	Structure	Backbone[a]	BCR[b]	Ref.
Trefoil (3_1)		77	25.7	[66]
		80	26.7	[76]
		94	31.3	[1b]
		96	32.0	[1c]
		102	34.0	[1e]
Square ($3_1\#\bar{3}_1$)		152	25.3	[2]
Figure 8 (4_1)		396 (66 nt[c])	99.0	[12]
Endless (7_4)		720 (120 nt[c])	102.9	[13]

[a] Number of atoms in the knot backbone. [b] Backbone crossing ratio in atoms/crossing. [c] nt = nucleotides in DNA knot.

metric termed the *backbone-crossing ratio* (BCR) has been developed. The BCR is calculated by dividing the number of atoms in the backbone of the knot or link by the total number of crossings. For example, Sauvage's original trefoil knot[1a] had 86 backbone atoms and three crossings for a BCR of 28.7 atoms/crossing (a/c). The BCR values of selected knots are shown in Table 4 and link BCR values are given in Table 5.

Table 5. Backbone crossing ratios (BCR) for molecular links.

Link	Structure	Backbone[a]	BCR[b]	Ref.
Solomon (4_1^2)		100 100 120	25 25 30	[3c] [3d] [3a]
Borromean (6_2^3)		150 3708 (618 nt[c])	25 618	[5] [4]
Olympiadane $(2_1^2\#2_1^2\#2_1^2\#2_1^2\#2_1^2)$		194	24.3	[93]

[a] Total number of atoms in the backbones of all link components. [b] Backbone crossing ratio in atoms/crossing. [c] nt = nucleotides in DNA link.

5.2. What Are the Tightness Limits for Knots and Links?

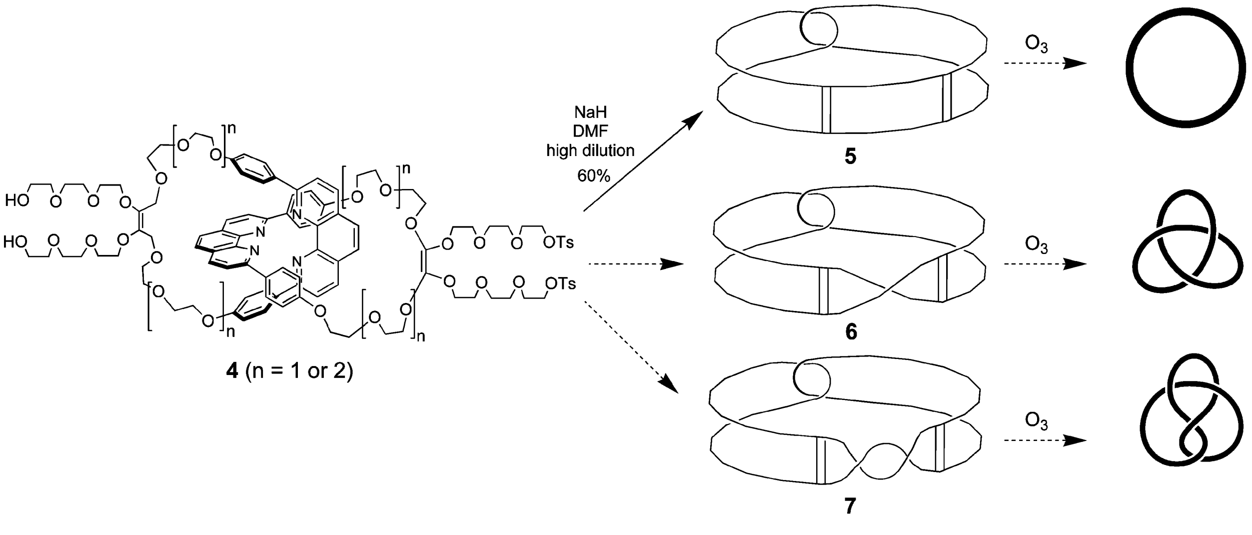
Sauvage's square knot[2] is the tightest of all known knots with a BCR of 25.3 a/c, whereas Stoddart's Olympiadane[93] catenane has the smallest BCR value (24.3 a/c) among the links examined. A typical BCR value for synthetic DNA-based knots appears to be 100 a/c.[94,95] A logical question to ask is: how tight can a molecular knot be? That is, what is the lower limit for the BCR? Using the minimal sizes for knots determined from CPK models (Table 3), BCR values of 15.7, 16.5, 14.8, and 15.5 a/c are obtained for the tightest knots containing three, four, five, and six crossings, respectively. Thus, it appears that the tightest knots have a BCR value of ca. 15 a/c. In terms of what is practical to synthesize, the author conjectures that BCR values less than 20 a/c will not be possible because of the additional steric demands of templates. The figure eight knot that would result from a TLC knot precursor **3**[68] has a BCR of 22.5 a/c, a value that is lower than any known knot or link.

6. Can Prime Knots More Complex Than the Trefoil Be Prepared?

Synthetic efforts and strategies toward prime knots beyond the trefoil have been reported. The figure eight (4_1) knot was a synthetic target of the Walba group in the late 1980's and early 1990's.[23,64,65] Their approach involved incorporation of a phenanthroline-based catenane into a Möbius ladder and the strategy was dubbed the "hook and ladder" approach (Scheme 2).[65] Macrocyclization of precursor **4** could result in three possible products depending upon the degree of intertwining of the tails. No crossings, one crossing, and two crossings result in compounds **5**, **6**, and **7**, respectively. These three knot precursors would, in turn, provide the unknot, trefoil, and figure eight after the proposed cutting (ozonolysis) of the alkenes in the ladder. When the macrocyclization was conducted, only **5** could be isolated. It is interesting to note that thin layer chromatographic analysis of the reaction mixture indicated that other minor products were produced. Sauvage has also published a proposed route to the figure eight knot.[96] The approach involves orthogonal coupling of two bis-phenanthroline copper(I) chelates. It is unclear whether experimental work on this approach was undertaken. The TLC knot method can also produce the figure eight knot and this target is actively being pursued.[68]

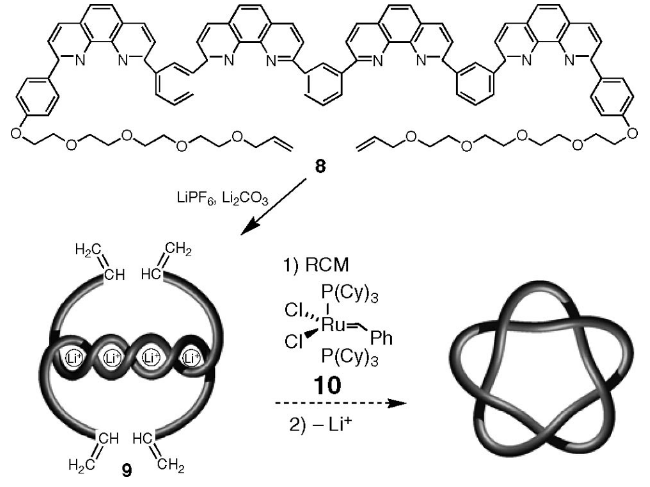
Extensive synthetic efforts towards a pentafoil (5_1) knot have recently been described in a publication by the Sauvage group.[97]

This work builds upon the phenanthroline metal chelates that Sauvage has successfully employed in the past. The hel-



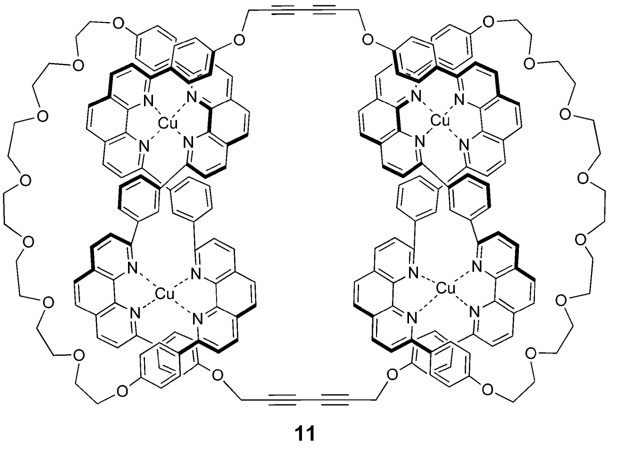
Scheme 2. Walba's hook and ladder approach to the unknot (0_1), trefoil (3_1) knot, and figure eight (4_1) knot.[65]

icates with four phenanthroline units and two copper(I) ions allowed the first successful synthesis of a trefoil knot.[1a] A system with six phenanthroline units and three copper(I) ions then provided the first Solomon's link.[3a] In an effort to further extend this methodology, phenanthroline ligands that are capable of complexing four (**8**) and five metal ions were prepared. The resulting helicate complexes could lead to the pentafoil knot (Scheme 3) and Star of David link (6_1^2), respectively. In these longer systems clean formation of the copper(I) complexes was impossible–insoluble and intractable complexes were produced instead. However, efficient formation of lithium complexes such as **9** was possible. Macrocyclization was then attempted using RCM, but the target knot and link could not be isolated.



Scheme 3. Sauvage's approach to the pentafoil (5_1) knot.

Although only the unknot and trefoil *prime* knots are known, a *composite* knot has been prepared by Sauvage.[2] The synthesis involved modification of his original trefoil route and produced six products, two of which were the desired composite knots. A mixture of the granny knot (racemic) and square knot **11** (*meso*) was isolated in 2.5% yield. This synthesis and that of the Borromean rings[5] stand out as remarkable achievements in small molecule chemical topology.



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7. Can the Enantiomerization Barrier of a Topological Rubber Glove Be Measured?

The term *topological rubber glove* was coined by Walba[65,98] to describe a compound that contains no rigidly achiral representation but has an allowed enantiomerization that occurs through a chiral pathway. Such a compound is topologically achiral even though it is rigidly chiral in every possible conformation.[99] Put another way, a topological rubber glove is chiral racemic and non-resolvable. Two such compounds have been prepared, but it remains an open problem whether the energy barrier for the enantiomerization of a topological rubber glove can be determined.

Shortly after Walba posed the question of whether a topological rubber glove was possible, it was mathematically shown that such compounds could exist. Specifically, Flapan proved that knot 8_{17} (Figure 2) and six of the 10-crossing knots fit the definition.[100,101] However, the syntheses of such complex knots is currently impossible outside of the DNA realm. The figure eight knot was also examined as a potential topological rubber glove since Listing pointed out in 1849 that this knot is amphicheiral; i.e., it can be deformed to its mirror image.[102] The figure eight knot also contains a symmetry presentation (S_4) and therefore the uncolored (uniform backbone) version does not satisfy the definition.[103] The S_4 symmetry is broken by a non-uniform backbone that does not repeat itself exactly four (or 4n) times. Thus, a figure eight knot colored in such a way is also a topological rubber glove (Figure 4). Such a molecule has been prepared from single-stranded DNA.[12,104] Although this DNA figure eight knot is topologically achiral, it is not *chemically* achiral because of the 198 sugar stereocenters.

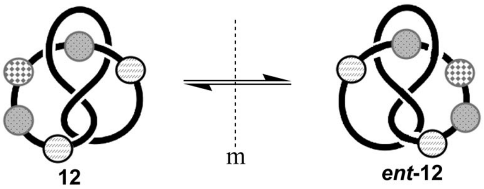


Figure 4. Enantiomorphous conformations of an amphicheiral colored figure eight knot. This knot is a topological rubber glove.

A [2]catenane that is a chemically achiral topological rubber glove was prepared in 1997 by Sauvage.[105] Catenane **13** is converted into its mirror image by rotation of the 1,5-dioxynaphthalene unit (Figure 5). The time-averaged symmetry of **13** is C_S but no individual conformation of the compound belongs to this point group. The compound was fully characterized and dynamic NMR was used in an attempt to determine the enantiomerization barrier. But, even at –90 °C, only peak broadening was observed. It is promising to note that the same workers were able to measure the enantiomerization barrier of a related rotaxane copper(I) complex. This compound showed a coalescence temperature of –78 °C corresponding to a barrier of 46 kJ/mol. The metal-free version of this rotaxane is a Euclidean rubber glove.[105b]

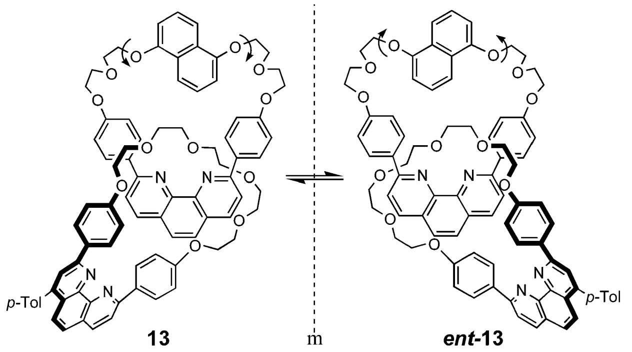


Figure 5. Enantiomorphous conformations of Sauvage's topological rubber glove catenane.

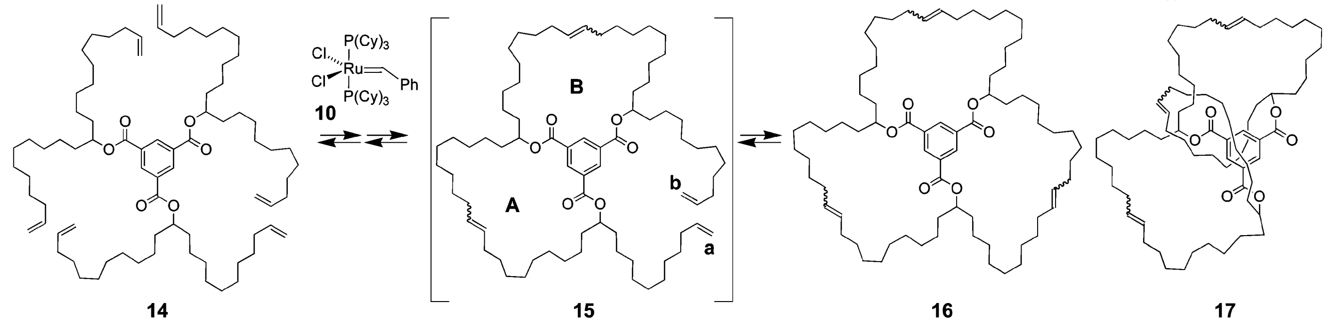
The figure eight knot that would result from the TLC knot method[68] is also a chemically achiral topological rubber glove (Figure 4). If such a knot is sufficiently tight, then the self-threading (slithering) enantiomerization process may be sterically restricted enough to allow the energy barrier to be determined. In general, even if a colored figure eight knot is loose, the enantiomerization barrier may still be measurable if other factors are involved. That is, non-covalent backbone crosslinks (e.g., hydrogen bonds) may provide stabilization to a particular conformation. In this situation the energy barrier for the deformation between the two enantiomers of this favored conformation may be sufficiently high to allow experimental measurement.

8. Can a Polyethylene Trefoil Knot Be Deliberately Prepared?

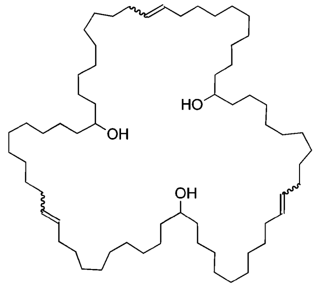
The possibility of knots spontaneously forming in polymers was suggested over 45 years ago when it was conjectured[19,106] that the probability of knot formation approaches 1.0 as the length of the polymer chain approaches infinity. This conjecture was later proven[107] and knots in organic polymers have been studied by a number of theoretical methods.[80,83,85,90,92,108,109] The question of how the knots affect the polymer has also been addressed. A knot is known to weaken a rope and the breaking point is always at the entrance to the knot.[110] Theoretical calculations suggest that the same is true of knotted polyethylene,[111] but this has never been tested experimentally. Polyethylene is perhaps the most important plastic in use today with a worldwide annual consumption of 80 billion pounds.[112] It is used in the production of milk bottles, grocery bags, and pipes. Polyethylene is a linear hydrocarbon polymer with varying amounts of branching determining the density. Recently, Grubbs synthesized and patented a cyclic version of polyethylene with unusual properties that may prove useful.[113] In terms of preparing knotted polyethylene, Frisch and Wasserman were optimistic in 1961 when they noted its synthesis should be "interesting and feasible,"[19] but reality had set in by 1999 when Sauvage et al. noted "the synthesis of such a compound seems to be presently out of reach."[28]

Most of the existing knot strategies (Table 2) cannot easily be incorporated into a polyethylene knot synthesis due to the need for an all-carbon backbone. However, the solvophobic interactions employed in the TLC method may promote polyethylene trefoil knot formation. Experimental work at Franklin & Marshall College toward the polyethylene knot has employed thread and cut precursor **14**, a trimesic acid template with three diene substituents for RCM (Scheme 4).[114,115] At least five products (**18**–**22**) are possible from the RCM/ester hydrolysis sequence on **14**. The discussion below focuses on how a trefoil knot can result from this process. Once **14** reacts with the Grubbs catalyst several possible ring-closing reactions can occur, including the formation of intermediate **15**, which resembles knot-precursor **3** in that it contains two macrocycles (**A**, **B**) and two terminal alkene tails (**a**, **b**).[116] Intermediate **15** can undergo two possible RCM paths; one involves no tail threading to give **16** and the other involves double threading in which tail **a** threads top-down through **B** and tail **b** threads bottom-up through **A** to give **17**. Single-threading followed by RCM results in **16** after conformational rearrangement. Double-threading from the same side (tail **a** top-down through **B** and tail **b** top-down through **A**) appears to be sterically inaccessible based upon examination of CPK models. If this latter mode of threading does occur it will produce **18** after ester hydrolysis. Alternatively, trefoil **17** can form through a route in which a tail becomes threaded not by impaling through a preformed macrocycle but, rather, by macrocycle formation around it. In this scenario, **15** (as drawn) is not an intermediate along the pathway to **17**. After the RCM reaction the esters are hydrolyzed which completely removes the trimesic acid core.[116] At this stage a mixture containing four to six alcohol products was typically produced. These compounds were separable by preparatory thin-layer chromatography (prep-TLC) and/or preparatory size-exclusion chromatography. The stereocenters in **18**–**22** are removed by Dess–Martin oxidation to the corresponding ketones. Independent synthesis and spectroscopic data allowed assignment of small macrocycle **22** and its corresponding ketone. These compounds were exclusively (*E*) isomers as opposed to a ca. 2:1 *E*/*Z* isomer ratio for all other compounds. NMR and IR spectroscopic data for the remaining isolated alcohol **18**–**21** or the ketone products are nearly identical. These compounds do not ionize well for mass spectral analysis. Field desorption ionization worked best, giving weak molecular ion peaks at 924.6 Da for three different alcohol products isolated from one synthesis batch. Unequivocal structural assignment of these products was difficult, but a product that is tentatively assigned as a 63-atom trefoil knot was synthesized and identified by the following sequence.

RCM of **14** in acetone was followed by ester hydrolysis. The alcohol mixture was then hydrogenated to reduce the alkenes and oxidized to the ketones. Purification by prep-TLC led to four bands being isolated. ^{1}H NMR spectra of each was taken in the absence and presence of Pirkle's chiral shift reagent, (*R*)-2,2,2-trifluoro-1-(9-anthryl)ethanol.[117] Only one product showed peak-doubling in the chiral envi-



Scheme 4. Ring-closing metathesis pathway resulting in macrocycle **16** and a trefoil knot **17**.



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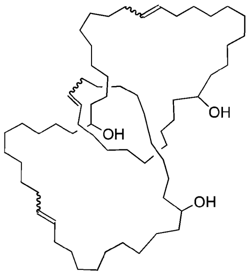

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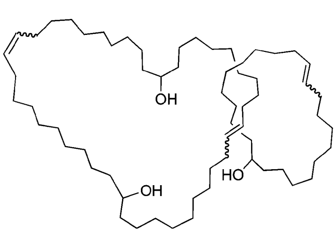

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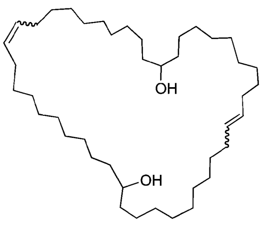

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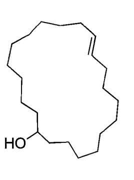

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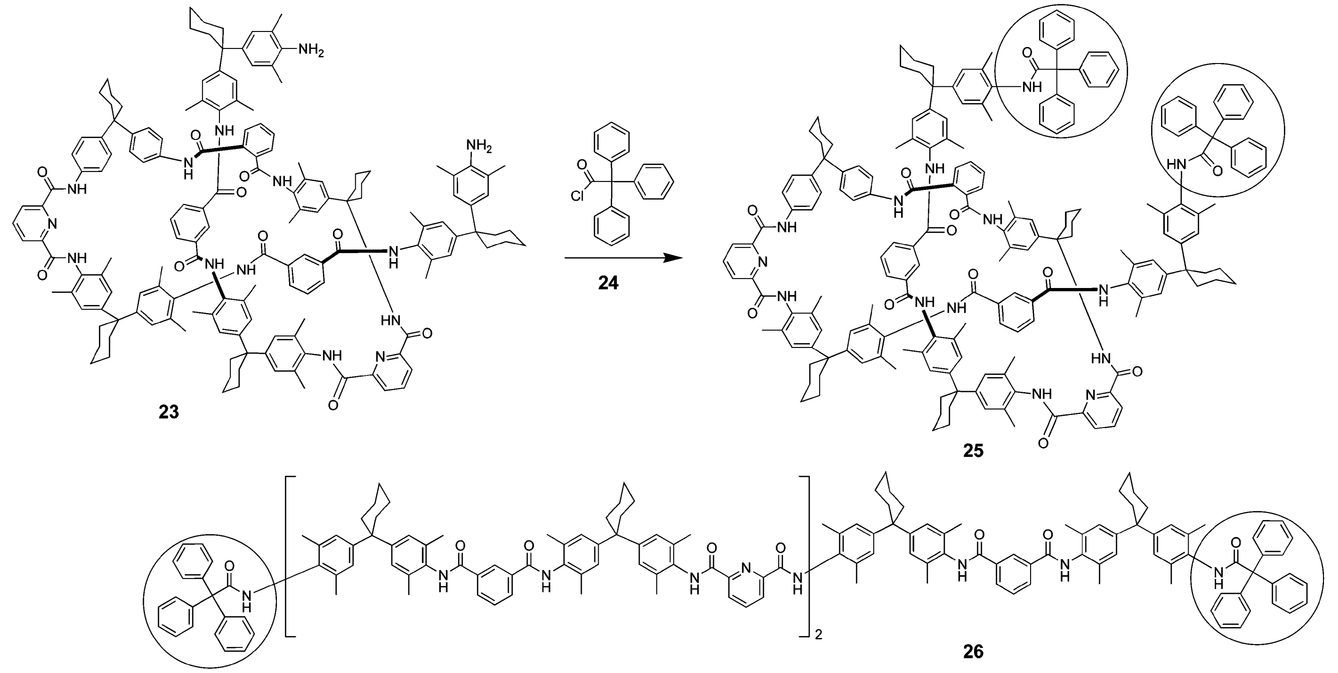
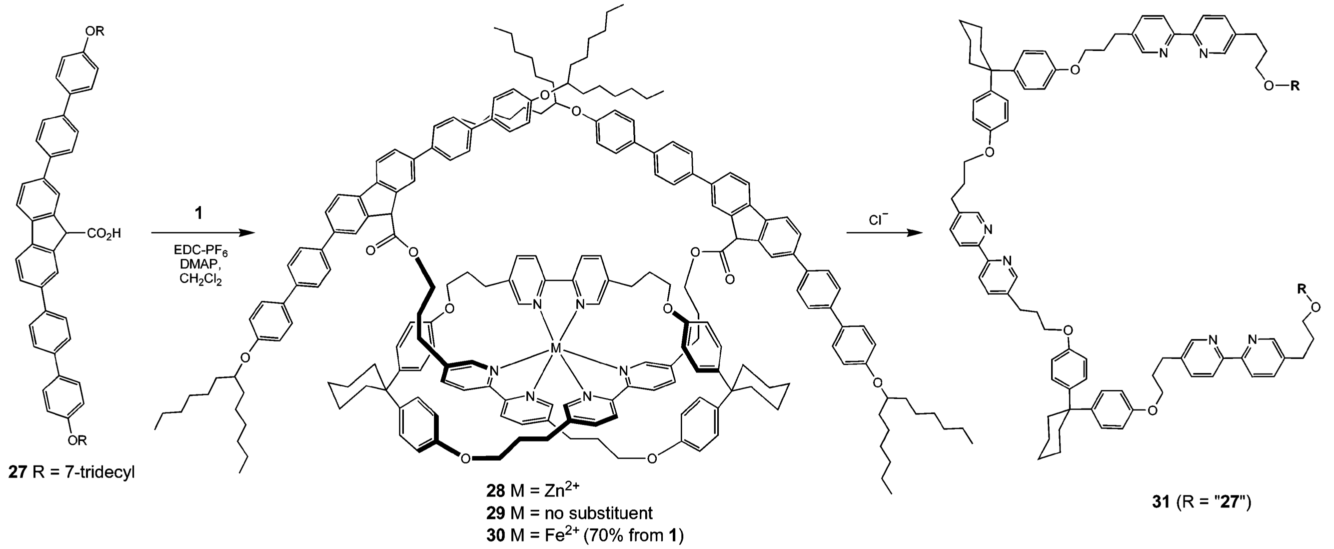
ronment which is evidence of the formation of diastereomeric complexes. Because no stereocenters are present the chirality detected is presumably from the racemic 63-carbon atom trefoil knot. Experiments on a homologous series leading to a 75-carbon atom trefoil have also been conducted.[114] A metal chelation strategy to a polyethylene trefoil knot can also be envisioned.[118]

9. Can a Stable Rotaxaknot Be Prepared?

Synthetic work towards the first rotaxaknot, an open knot that cannot untie itself due to bulky stopper groups, has been undertaken in the Vögtle and Hunter groups. The Vögtle work[119] involved modification of his original route to oligoamide trefoil knots in order to produce decaamide



Scheme 5. Vögtle's approach to rotaxaknot **25**.[119]



Scheme 6. The Hunter/Mayers strategy for rotaxaknot **29**.[66]

precursor **23** which is capable of adopting an open trefoil conformation by hydrogen bonding (Scheme 5). Capture of this intermediate was attempted by reacting the terminal amino groups with trityl acid chloride (**24**) to form either trefoil rotaxaknot **25** or its trivial isomer (**26**). A pure compound with a mass corresponding to **25/26** was obtained in 29% yield. The same product could also be obtained in ca. 0.5% yield by the original direct knot synthesis method when stopper **24** was slowly added to the reaction mixture after a one-hour period. Efforts to identify which isomer formed took advantage of the fact that **25** is chiral racemic and **26** is achiral; but chiral HPLC failed to detect a chiral material. In the end the researchers were unable to prove which isomer was formed, and the possibility that the two were in equilibrium was considered. It was concluded that the steric demand of the stopper was likely inadequate to maintain rotaxaknot **25**, a conclusion that is consistent with the results from Hunter's group.

Mayers in the Hunter group was exploring similar experiments approximately a decade prior to Vögtle's work.[66] In this system open trefoil **1** is formed through the coordination of three bipyridine units around an octahedral zinc ion. The terminal alcohols of **1** were then esterified with bulky rigid aromatic stopper **27** providing metal-rotaxaknot **28** (Scheme 6). When the zinc ion was removed by chloride treatment, rotaxaknot **29** readily untied to form its trivial isomer (**31**). Zinc-rotaxaknot **28** could be converted to iron-rotaxaknot **30** upon treatment with a slight excess of iron(II) perchlorate. This experiment shows that the unknotting process is slower than the transmetallation reaction. Rotaxaknot **30** could also be prepared by first forming the iron complex of the open knot followed by esterification with stopper **27**. Efforts to reform rotaxaknot **28** upon addition of Zn^{2+} to **31** were unsuccessful.

Both of these synthetic efforts suffered from a lack of steric bulk of the stopper group vis-à-vis the large macrocycle in the rotaxaknot and, as a result, unknotting of the initially formed rotaxaknot appears to have occurred. In this regard, the figure eight rotaxaknot (Figure 1, h) may offer an advantage because the macrocycle size is limited by the additional backbone crossing.

10. Can a Whitehead Link Be Prepared?

The Hopf (2_1^2),[56] Solomon (4_1^2),[3] and Borromean (6_2^3)[5] links have been prepared in molecular form. An unrealized classical target in chemical topology is the Whitehead link (5_1^2) (Figure 6). This link was first proposed[120] by topologist J. H. C. Whitehead in 1935 as a counterexample to his earlier theorem on the infamous Poincaré conjecture.[121]

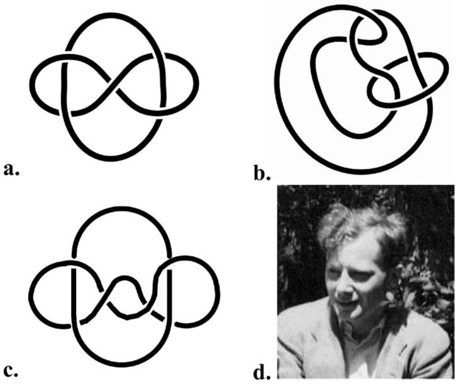


Figure 6. **a**–**c**: Various conformations of the Whitehead link. **d**: J. H. C. Whitehead (ca. 1934).[125]

When planning synthetic approaches to flexible molecules with nontrivial topologies it is helpful to consider multiple conformations. For example, several conformations of the Borromean rings were considered in retrosynthetic analyses.[5,27,35,122–124] One traditional representation of the Whitehead link is shown in Figure 6 (a); this conformation contains the minimal five crossings. Part b of Figure 6 shows another classical representation of the Whitehead link; in this case a nugatory crossing[95] has been introduced. An alternate conformation of this six-crossing version is shown in part c of Figure 6. This latter conformation is perhaps the most palatable from a synthetic stand point. It is unknown whether experimental work towards this challenging target has been attempted.

11. Conclusions

This microreview highlighted progress toward several open problems in small molecule chemical topology. A common thread among these problems is the difficulty in controlling topological stereochemistry; i.e., the tertiary structure of organic molecules. This stands in stark contrast to the high levels of control over regiochemistry and Euclidean stereochemistry (stereocenters) enjoyed in the synthesis of natural products. Synthetic efforts toward figure eight, pentafoil, and polyethylene trefoil knots, as well as a stable trefoil rotaxaknot, were discussed. The minimal size limits of molecular knots were reviewed and the backbone-crossing ratio was introduced as a measure of knot and link tightness. The open problems of whether the energy barrier for the enantiomerization of a topological rubber glove can be measured and whether a Whitehead link can be prepared were also examined. As a final thought, it is humbling to consider that of the *billions* of prime knots known to the mathematicians,[46,47] only *two* have been deliberately prepared in non-DNA molecular form, with one of them being the unknot!

Supporting Information (see also the footnote on the first page of this article): Scheme 1S showing the formation and decomposition of a composite knot. A colored version of the Figure 2 knot Table and face inverted representations of these knots (Figure 2S). Scheme 2S showing additional expected products from the RCM of **14**. Additional information about an alternate approach to a polyethylene trefoil knot.

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