

Chemical Topology: Complex Molecular Knots, Links, and Entanglements

Ross S. Forgan, Jean-Pierre Sauvage,* and J. Fraser Stoddart*

Center for the Chemistry of Integrated Systems and the Department of Chemistry, Northwestern University, 2145 Sheridan Road, Evanston, Illinois 60208-3113, United States

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1. INTRODUCTION

1.1. History and Background

Knots and links are all around us (Figure 1). Be they functional or decorative, we encounter them constantly, when, for example, tying simple bow knots in our shoelaces or the four-in-hand knot in a necktie. These entangled and interlocked entities have also developed strong spiritual and symbolic meanings as human culture has advanced from prehistory, and now embody many tenets of both religious and secular societies. For example, Alexander the Great's cutting¹ of the Gordian Knot over 2000



Figure 1. Photographs of knots in cultural settings taken by R.S.F. (a) The Celtic Knot, a public house decorated with examples of Trefoil Knots and located near to Northwestern University. (b) An early 20th Century French glass paperweight inlaid with a Pentafoil Knot design, currently displayed in the Chicago Art Institute. (c) A commemorative 19th Century plaque, carved into the sandstone wall of the Landmark Hotel, Dundee, Scotland, displays a Solomon Link. (d) A complex interlinked design found on the label of a popular brand of Scottish Whisky.

years ago has come to represent a bold solution to an intractable problem. Particularly prominent in Celtic,² Islamic,³ and Chinese⁴ cultures, interwoven assemblies have persisted into the modern era, artistically and functionally, and, in recent times, have also become the focus of much scientific interest.

1.2. Knot Theory

Pioneering studies in mathematical knot theory were inspired by the erroneous assumption of Lord Kelvin⁵ that the elements were comprised of knots in the all-pervading ether. Persuading his good friend and physicist Peter Guthrie Tait that, should he tabulate all known types of knots, he may be tabulating the chemical elements, Tait set about this challenge with voracity, publishing numerous papers^{6–14} in the 1870s and 1880s. Tait also considered the unconditional chirality of certain knots, those whose graph cannot be deformed in three-dimensional space to their mirror images, and used the term amphicheiral¹⁰ to describe knots with no chirality. A fascinating history of topology in the 19th Century has been recorded by Eppe¹⁵ and includes a beautiful reproduction of a tabulation of over 150 knots from one of Tait's trailblazing papers.¹³ Although the so-called Michelson–Morley experiment consigned¹⁶ the ether to scientific history, knot theory remains a well-studied branch of mathematics to this day.¹⁷

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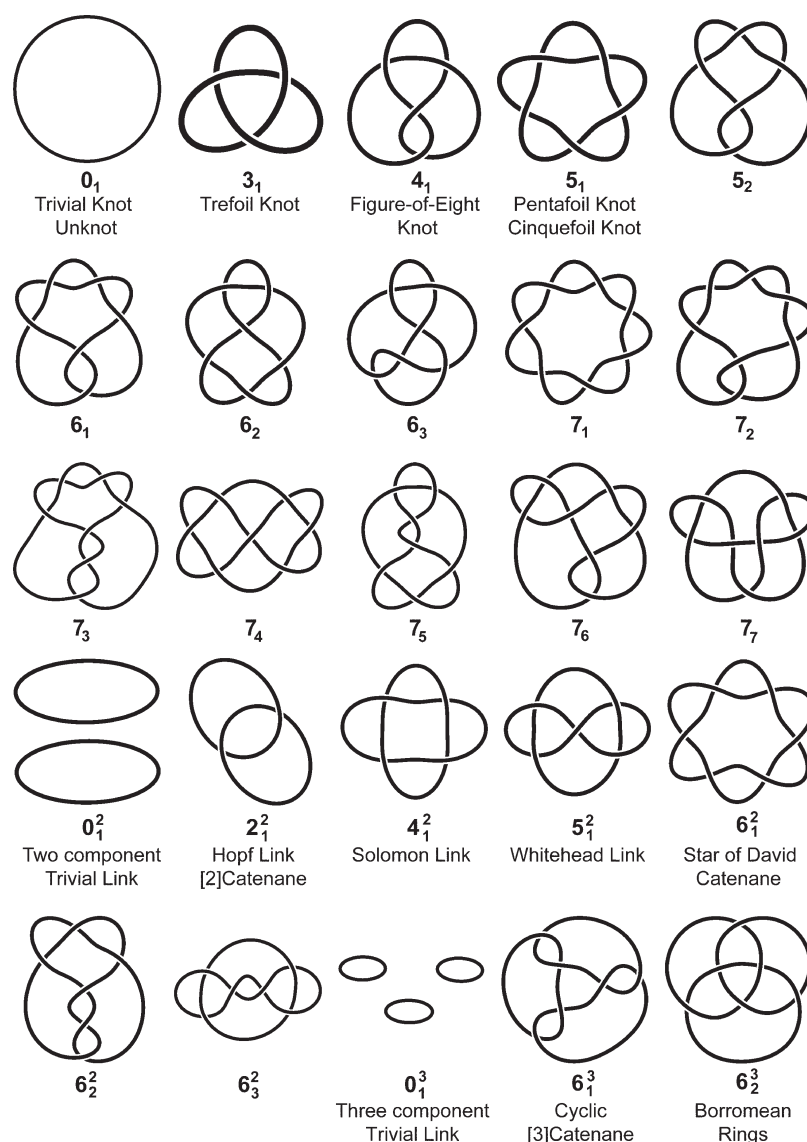


Figure 2. A schematic tabulation of simple knots and links, accompanied by their trivial names and descriptors using the Alexander–Briggs notation.¹⁸ Prepared using KnotPlot.¹⁹

The Alexander–Briggs notation¹⁸ is used to distinguish between different knots and links. The descriptor x_z^y represents a knot, or link, where x is the minimum number of nodes, or crossing points of any projection of the knot or link, y is the number of components (in a knot, $y = 1$ and is usually not displayed in the Alexander–Briggs notation), and z is the order of the knot among its peers with the same number of nodes and components, which describes, when embedding the knot or link on a sphere, the number of handles that must be added such that no crossings are observed. In a manner similar to that of integer numbers, knots can be classified as prime knots or composite knots. Taking two nontrivial knots, cutting them, and joining the ends to afford a single knot forms a composite knot. In the reverse process, a composite knot is decomposed into its factor knots. A prime knot, on the other hand, is one that cannot be further decomposed, in the same way as a prime number cannot be divided by numbers other than one and itself.⁵ Aside from the simplest knots, it can be extremely difficult to determine whether a knot is a prime knot or a composite knot. All prime knots with

seven or less crossings, alongside a collection of interesting links, are displayed¹⁹ in Figure 2, together with their descriptors based on the Alexander–Briggs notation and some trivial names applied to the interlocked species in both artistic and chemical contexts.

Chirality is ubiquitous in chemistry. This is also the case in knot theory. A knot is referred to as being achiral if it can be deformed continuously into its mirror image. If this procedure is not possible, the knot is said to be topologically chiral. For example, the unknot (0_1) and the Figure-of-Eight Knot (4_1) are both achiral, whereas the Trefoil Knot (3_1) is chiral. Knot invariants are mathematical descriptors that are associated with a knot without having to draw it and that are associated with a precisely defined knot, generally in a bijective fashion. A knot polynomial is a knot invariant in the form of a polynomial whose coefficients encode some of the properties of the given knot. The first knot polynomial was introduced by Alexander²⁰ in 1923. More than 60 years later, a very important improvement, which allowed one to associate a polynomial to a knot and also detect

chirality, was proposed: the so-called Jones polynomial, which was discovered by Vaughan Jones²¹ in 1984. Finally, since it is a highly difficult task to find an invariant able to recognize the chirality of a knot, Mislow and Liang²² also tackled this chemistry-oriented problem. A method for partitioning topologically chiral knots was developed by these authors,²³ based on the concept of “writhe profiles”.

1.3. Naturally Occurring Molecular Knots

While knots and links have provoked mathematical discussion for over 100 years, they are also particularly relevant in the field of biology. The discovery^{24–26} in 1967 of the first naturally occurring catenated DNA prompted the beginnings of a field that was later defined by Wasserman and Cozarelli²⁷ as “Biochemical Topology”. Soon after, Trefoil Knots were discovered in both single-stranded²⁸ and double-stranded²⁹ DNA. Subsequently, a wealth of highly complex knotted DNA architectures, including composite knots, were discovered³⁰ and imaged (Figure 3) by electron microscopy. Gel electrophoresis has also proven to be a remarkably useful tool in separating these entities as a result of the differences in compactness of knots as they become more complex.³¹ DNA topoisomerases,^{32–38} the enzymes that are responsible for the formation of these topological constructs, have been studied intensively and extensively; faulty versions are implicated^{39,40} in many forms of cancer. These enzymes can be employed to prepare DNA knots, but not in a controlled manner; many species are generated, rather than one specific target.

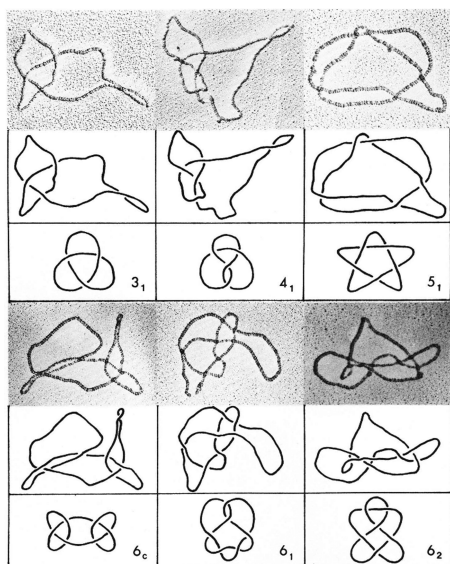


Figure 3. Electron micrographs of knotted DNA, prepared by the action of DNA topoisomerases, at 80 000 \times magnification. Retraced representations of the DNA are shown below the micrograph along with idealized diagrams of the knot and their descriptors using the Alexander–Briggs notation. Redrawn with permission from ref 30. Copyright 1985 American Society for Biochemistry and Molecular Biology.

Knotted proteins are of less common occurrence.⁴¹ In 1994, both Mislow^{42,43} and Mansfield⁴⁴ realized independently that many proteins must exist in their knotted states, and soon thereafter, Tagusakawa^{45,46} reported the structural characterization of (S)-adenosylmethionine synthetase, which contains a linear knot. Recent advances in the X-ray crystallographic

analysis of proteins have uncovered further examples, including (i) a Trefoil Knot deep in the active site of an RNA 2'-O-ribose methyltransferase,⁴⁷ (ii) a light-sensing Trefoil Knot in the chromophore binding domain of a phytochrome,⁴⁸ and (iii) a Figure-of-Eight Knot in plant acetohydroxy acid isomeroreductase.⁴⁹ The most complex protein knot identified to date is a Stevedore's, or double Figure-of-Eight Knot (6₁), which was identified⁵⁰ retrospectively in the crystal structure of α -haloacid dehalogenase DehI.⁵¹ This particular example draws attention to the emergence of the Protein Data Bank (PDB) structural depository⁵² as a valuable resource for those who continue to devise methods^{53–55} to hunt down previously unidentified protein knots. Although the reasons for the existence of knotted proteins remain obscure, in an excellent review on the subject, Taylor⁵⁶ comments that all known knots occur in enzymatic proteins and predominantly in the catalytic domain or in the active site itself. Advances in this area will no doubt continue apace, as exemplified by the recent report⁵⁷ of the synthesis of a protein which was designed and observed to form a Trefoil Knot upon folding.

1.4. Chemical Topology and Topological Chemistry

The importance of topology in naturally occurring biological systems has played a significant role in the expanding field of designing and synthesizing mechanically interlocked compounds in a laboratory setting. The synthesis of molecular knots and links represents a significant challenge in the realm of template-directed synthesis,^{58–69} a problem that has spurred efforts on the part of synthetic chemists for the past 50 years now. The field of Chemical Topology was defined, in 1961, in a seminal paper by Wasserman and Frisch,⁷⁰ wherein they introduced concepts such as topological isomerism—two objects containing the same atoms and chemical bond connectivities, but that cannot be interconverted by any deformative action in three-dimensional space—to a general chemical audience. This 1961 paper also described potential approaches to interlocked compounds and knots. In a mathematical sense, the simplest prime knot, the humble macrocycle or the unknot, was already prevalent in the chemical literature. Although the sheer volume of work in the field of macrocyclic chemistry and its underpinning of the development of supramolecular chemistry^{71–75} precludes its discussion in this Review, interested readers are directed toward a number^{76–85} of seminal papers, reviews, and books for further reading.

Similarly, the unlink, mathematically the simplest link, consists of two unconnected rings. The next simplest link, the Hopf or 2₁² link, has also been expressed chemically for a number of years as the [2]catenane. Following Wasserman's⁸⁶ first synthesis of a [2]catenane by statistical methods, these links remained exotic entities until the Cu(I)-template directed synthesis⁸⁷ of metallocatenanes in 1983 heralded a new era wherein interlocked molecules and the mechanical bond^{88–91} moved into the mainstream of chemical science. There now exists a wide variety of methodologies (Figure 4) for templating the assembly of [*n*]catenanes (*n* denoting the number of interlocked rings) including, but not limited to, metal templation,^{87,92–95} hydrogen-bonding^{96–100} and donor–acceptor^{101,102} interactions, anion coordination,^{103,104} radical templation,^{105,106} and DNA recognition.^{107,108} It should be noted that, in many cases, it is a combination of multiple attractive interactions, be they dynamic covalent, coordinative or noncovalent, which assist in the self-assembly of such species. The seminal examples cited here only

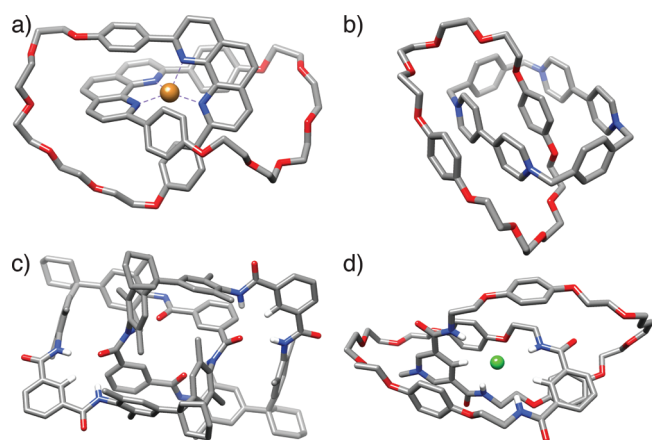


Figure 4. Tubular representations of the solid-state structures of some [2]catenanes, which constitute seminal examples of the particular methods employed in their syntheses. The recognition motif(s) at the heart of the templation methods are as follows: (a) Coordination⁹² of a transition metal, in this case Cu(I) around two phenanthroline ligands, with π - π stacking interactions also lending a hand. (b) Donor-acceptor interactions,¹⁰¹ for example, between π -donating hydroquinone rings in an electron-rich crown ether and π -accepting bipyridinium units in an electron-poor tetracationic cyclophane, with $\text{CH}\cdots\text{O}$ interactions also providing a major (the lion's share) contribution to the templated self-assembly process, which is also aided and abetted by weak $\text{CH}\cdots\pi$ interactions. (c) Hydrogen bonding⁹⁸ between amide bonds in two identical neutral bis-isophthalamide macrocycles. (d) Anion-coordination,¹⁰³ wherein amide N-H bonds are interacting with a chloride ion supported by secondary donor-acceptor interactions between electron-rich hydroquinone rings and electron-poor pyridinium rings. In all four cases, counterions, solvent, disorder, and hydrogen atoms not involved in hydrogen bonding have been removed for clarity. Carbon atoms are gray, oxygen atoms red, nitrogen atoms blue, hydrogen atoms white, Cu(I) ions orange, and chloride anions green. Compounds have been redrawn from CCDC depositions CUFHEQ, KEBKUX, YONCOT, and FAHXAO, respectively.

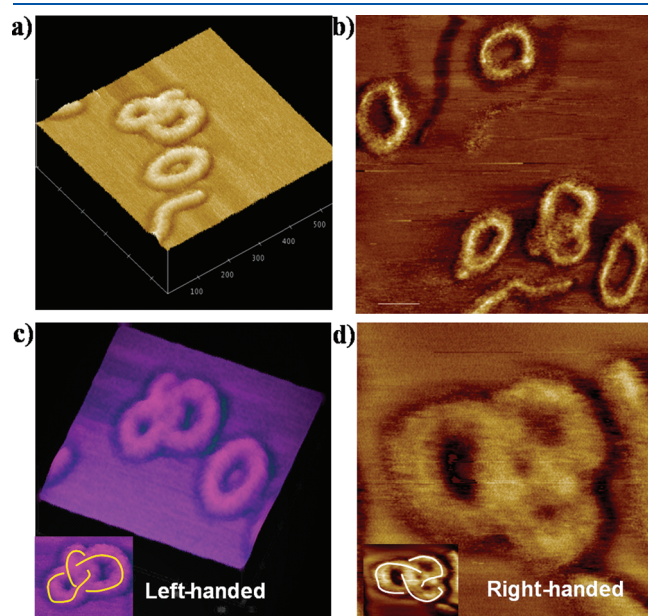


Figure 5. Topographic (a,c) and phase (b,d) AFM images of polymeric Trefoil Knots prepared by the cyclization of triblock copolymers. Note that images (c) and (d) are left- and right-handed versions of the Trefoil Knot, respectively. Reproduced with permission from ref 115. Copyright 2009 Wiley-VCH Verlag GmbH & Co. KGaA.

scratch the surface of a vibrant research field, which, as a result of constraints on length, will not be discussed further in this Review.

As methods to prepare catenanes and their interlocked siblings, the rotaxanes, were developed and fine-tuned, the question arose: how does one prepare more complex molecular knots and links? An unexpected answer was proposed^{109–112} as long ago as 1975, with calculations suggesting that, in the preparation of polymers, linear knots are statistically probable in long polymer strands. This finding is particularly important, given that both theory¹¹³ and experiment¹¹⁴ show a weakening of knotted molecular strands at the entry point of the knot, in comparison to their unknotted analogues. Similarly, on the macroscale, when one wishes to break a sewing thread at a particular point, one can tie a knot at that point and pull on both ends of the thread, rather than reach for a pair of scissors. Recently, Deffieux¹¹⁵ reported a particularly pleasing proof of polymer knotting, employing AFM imaging (Figure 5) of cyclized triblock copolymers to unequivocally illustrate catenanes and Trefoil Knots on the order of hundreds of nanometers. It has also been shown to be possible to tie micrometer-scale knots in fibrous bundles of carbon nanotubes.¹¹⁶

As the nascent field of chemical topology has blossomed, knots and links on the molecular scale moved from being theoretical curiosities to becoming synthetic realities, many of which can be prepared on large scales and studied in depth. The rational design and preparation of these interlocked species, alongside some serendipitous discoveries, have been described previously^{65,117–131} in a number of reviews and accounts. Two reviews give particular insight into the transition metal templating¹²⁸ and hydrogen-bond templating¹²⁹ approaches to the preparation of molecular knots and links. The intriguing aspects of topological stereochemistry^{132–138} and the chirality of many of these species have also been areas of focus for researchers. This comprehensive Review addresses the various synthetic strategies and approaches to preparing complex molecular knots, links, and entanglements, with the aim of introducing the general reader to the field of chemical topology and the elegant template-directed synthetic protocols that underpin its current and future rapid development. In particular, the differing results from stepwise synthetic approaches, involving covalent bond formation under kinetic control, will be compared to those of “all-in-one” strategies, which utilize reversible self-assembly carried out under thermodynamic control.

2. TREFOIL KNOTS

2.1. Background and Proposed Synthetic Routes

The Trefoil Knot (Figure 6) represents the simplest example of a nontrivial knot, i.e., one that cannot be untied in three dimensions without scission, and, as such, is the cornerstone of mathematical knot theory, comprising the 3_1 prime knot, as well as being a prominent historical and cultural symbol. Named after the three-leaved clover, or trefoil plant, the knot comprises a simple overhand knot where the two ends have been connected. A common representation of the knot found in many cultural settings is the triquetra (Figure 6b) wherein sharp vertices are present on the three loops of the knot. The triquetra, and a related version with an intertwined circle, adorn early Germanic currency and runestones, are found in early Christian Celtic art,² such as the spectacular Book of Kells, a ninth Century Irish Book of Gospels, and also signify the Holy Trinity of the Christian faith.¹³⁹ A recent revival in Celtic culture has seen the symbol used in decorative settings, particularly in jewelry (Figure 6d),

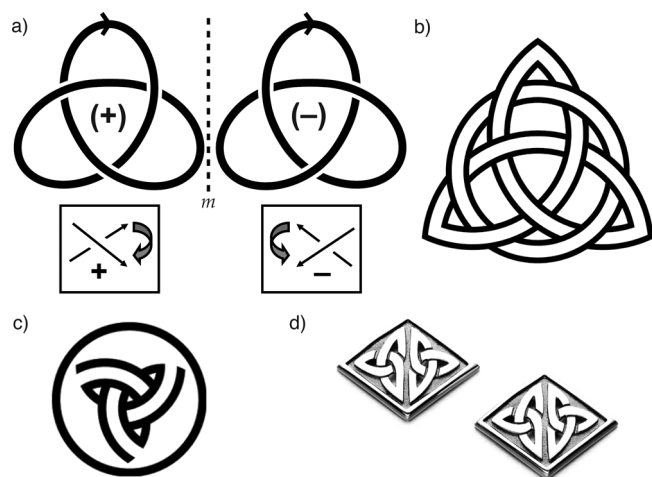


Figure 6. (a) A visualization^{132,133,141} of the inherent topological chirality of Trefoil Knots, wherein the two nonsuperimposable mirror images which comprise the (+) and (−) isomers are displayed side-by-side about a mirror plane, *m*. (b) The triquetra, a stylized version of the Trefoil Knot with sharp corners instead of loops, often displayed with an interlaced circle. (c) A version of the triquetra, which is employed by the Illinois Department of Transportation as its logo. (d) A pair of Celtic-inspired cufflinks, belonging to R.S.F., which display the Trefoil motif. Trefoil Knots are a common feature of Celtic art.

and a triquetra is also found on the artwork of the rock band Led Zeppelin,¹⁴⁰ alongside a representation of the Borromean Rings (vide infra), which members of the band have adopted as their personal symbols.

As the simplest prime knot, the Trefoil Knot was the focus of early interest in the field of chemical topology, with various synthetic strategies having been proposed in the past for the making of its molecular counterpart. It should be noted that Trefoil Knots can exist in left-handed and right-handed forms; that is, they are chiral objects. A molecular Trefoil Knot therefore displays inherent topological chirality, any representation of its graph cannot be deformed in 3D space to its mirror image, and exists as two enantiomers. To determine the chirality of the Trefoil Knot, when moving in a clockwise direction along the knot surface, arrows are projected onto the crossings (Figure 6a). When traveling from the bottom arrowhead to the top arrowhead generates a clockwise movement, the crossing is positive (+), and if the movement is anticlockwise, it is a negative crossing (−). In the particular case of the Trefoil Knot, the crossings of one enantiomer are always of the same descriptor, giving (+) and (−) enantiomers.^{132,133,141}

Attempts to calculate¹⁴² the optical rotations of hypothetical enantiopure molecular Trefoil Knots were described in 1969. To prepare such species, a molecular “Möbius strip”¹⁴³ underpinned many of the early suggested strategies (Figure 7a) and was proposed as early as 1961 by Frisch and Wasserman,⁷⁰ and also by van Gulick¹⁴⁴ in a paper that was rejected at the time (ca. 1961) by *Tetrahedron* and published much later in the *New Journal of Chemistry* in 1993 under the editorship of David Walba. Twists in the ladder-shaped compound **1** provide the appropriate crossing points of the eventual knot, with “rungs” in place near the termini. Upon cyclization to afford **2**, followed by subsequent cleavage of the rungs, a Trefoil Knot **3** should result. Although Walba^{145–147} has synthesized such a Möbius strip compound (**5** in Figure 7b) because it contained only one twist, an

interlocked species would not result after cleavage of the rungs. In concert with this approach, Walba¹⁴⁸ also proposed a “hook and ladder” motif (Figure 7e), wherein tetrahedral transition metal binding sites are incorporated into Möbius strip molecules **11** with the aim of preparing the 4_1 or Figure-of-Eight knot. Again, although a precursor was isolated, it could not be converted into the knot.

Schill,^{149–153} building upon his earlier successful approaches in synthesizing covalently templated catenanes and rotaxanes, devised^{154,155} a Möbius strip molecule wherein the twists are provided by doubly bridged tetraamino-*p*-benzoquinone moieties (**6** in Figure 7c). The synthetic complexity in making these species hampered attempts to prepare the target molecular knots. A related strategy,^{156,157} using benzo-acetal groups (**9** in Figure 7d) to hold the knot pieces in place covalently, also suffered from the difficulties experienced in preparing the appropriate molecular precursors. DNA has recently been utilized¹⁵⁸ in the preparation of a Möbius strip with one twist. It could be excised linearly to form a [2]catenane, and it has been suggested that a similar assembly with two twist turns could be used to prepare a DNA Trefoil Knot.

More recently, Fenlon¹³⁰ has described attempts (Figure 8a) in his research group to prepare a polyethylene knot by a covalently templated approach. Compound **14**, comprised of a trimesic acid core with six pendant alkene-terminated arms, was prepared and cyclized by ring-closing alkene metathesis to yield a pre-knot **15**. Subsequent removal of the trimesate template, followed by reduction of the alkenes and oxidation of the free hydroxyl groups to ketones, generated a variety of macrocycles, one of which was tentatively assigned to be the Trefoil Knot **16**. These preliminary results were reported as part of a review on chemical topology, and a subsequent paper has not yet been published. Fenlon¹⁵⁹ is also pursuing molecular knots by a related “thread-and-cut” strategy. The 3-fold symmetry of 1,3,5-trisubstituted benzene rings also underpins an approach (Figure 8b) suggested by Siegel,^{160a} wherein six bipyridine units are arranged around the aromatic core to yield a ligand **17**, which, when coordinated to Cu(I) ions, forms a “triskelion” knot precursor **18**. The solid-state structure of the tris-copper(I) complex reveals a chiral structure wherein appropriate connections of the six termini and removal of the central core would generate a Trefoil Knot. Just prior to the publication of this review, Siegel^{160b} reported the cyclization of a related triskelion scaffold. A derivative of **17** equipped with six pendant alkynes was prepared and shown to form a complex similar to **18** when three Cu(I) cations, in the form of $[\text{Cu}(\text{MeCN})_4\text{PF}_6]$, were added to this derivative of **17**. Ring-closing was achieved by refluxing with an excess of Cu(II) in MeCN and the complex was characterized by X-ray crystallography, which confirmed the topology and revealed that the complex is present as a racemic modification. Removal of the central core remains the final step in the synthesis of this particular Trefoil Knot.

2.2. Octahedral Metal Cation Templation

Of the synthetic strategies proposed in the early days of chemical topology, only one,¹⁶¹ and very recently at that, has been brought through to fruition and afforded a Trefoil Knot. In 1973, Sokolov¹⁶² proposed, as part of a review on chemical topology in the Russian literature, a motif wherein three bidentate ligands arranged around an octahedral metal center could be linked by appropriate connections of their termini to form a Trefoil Knot. This elegant approach should also allow access to

both topological enantiomers of the Trefoil Knot, as long as the precursor tris-chelate complex is isolated as either the Λ or the Δ isomer. Appropriate arrangement of the ligands is essential in the forming of the entanglement, which acts as the knot precursor. 3,3'-Biisoquinoline ligands, substituted in the 8 and 8' positions, have been utilized^{163,164} to form octahedral entanglements with Fe(II) and Ru(II). While these topological synthons have been used to prepare^{165,166} [3]rotaxanes, wherein two rods are threaded through one ring, no progress has yet been

reported on the synthesis of molecular knots based on this particular motif.

Constable et al.¹⁶⁷ have prepared Fe(II) and Ru(II) octahedral complexes of bipyridine ligands with pendant alkene functions, with the intention of performing ring-closing metathesis to prepare a Trefoil Knot. It was found upon metathesis, however, that large macrocyclic ligands with exocyclic bipyridine moieties constituted the outcome of the reaction, rather than any knotted products. The fact that the six terminal alkene functions must be

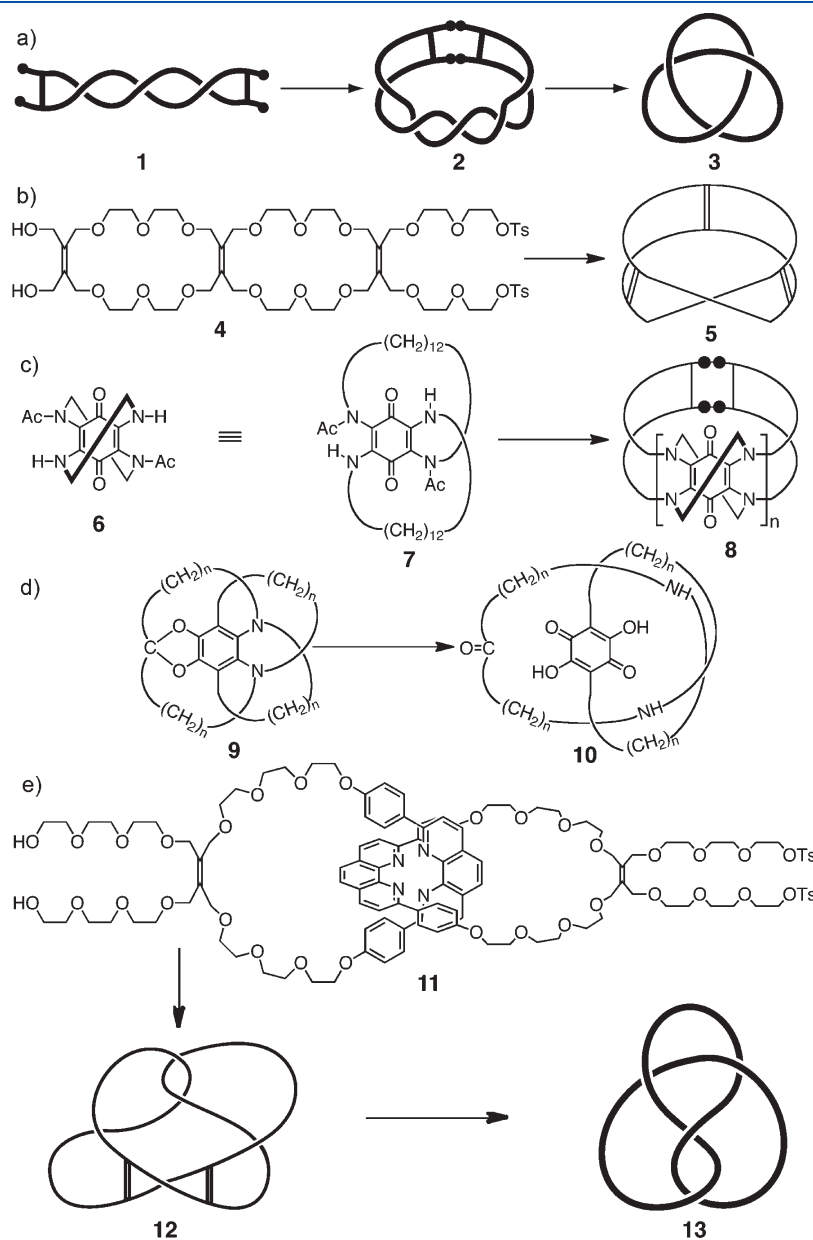


Figure 7. A smorgasbord of covalently templated routes to molecular knots, which have been proposed in the chemical literature. (a) Schematic diagram illustrating a synthetic strategy^{70,144} for making a Trefoil Knot, **3**, from a molecular ladder **1** containing three half twists, which is cyclized to form a Möbius strip, **2**, leading ultimately to a Trefoil Knot after cleavage of the two rungs. (b) Suggested^{145–147} synthesis of a molecular Möbius strip from a so-called THYME compound, **4**, by cyclization. This example, wherein a strip **5** with only one-half twist is generated, is not capable of forming an interlocked species. (c) A proposal^{154,155} for incorporating half twists into a Möbius strip using a doubly bridged tetraamino-*p*-benzoquinone compound **6**. A dodecyl-bridged compound, **7**, was postulated as a synthetic target, which would form the twists of a Möbius strip, **8**. (d) A proposed^{156,157} covalently directed route to a molecular Trefoil Knot **10** via benzo-acetal compounds, **9**, which utilize aromatic central units to hold components of the knot in a strictly preorganized geometry. (e) A "hook-and-ladder" approach¹⁴⁸ to preparing a Figure-of-Eight Knot, **13**. Interlocked compounds such as **11**, with crossings introduced by Cu(I) coordination of phenanthroline units, have incorporated rungs and can be cyclized into molecular ladder-type compounds **12**, with the aim of forming **13** on cleavage of the rungs.

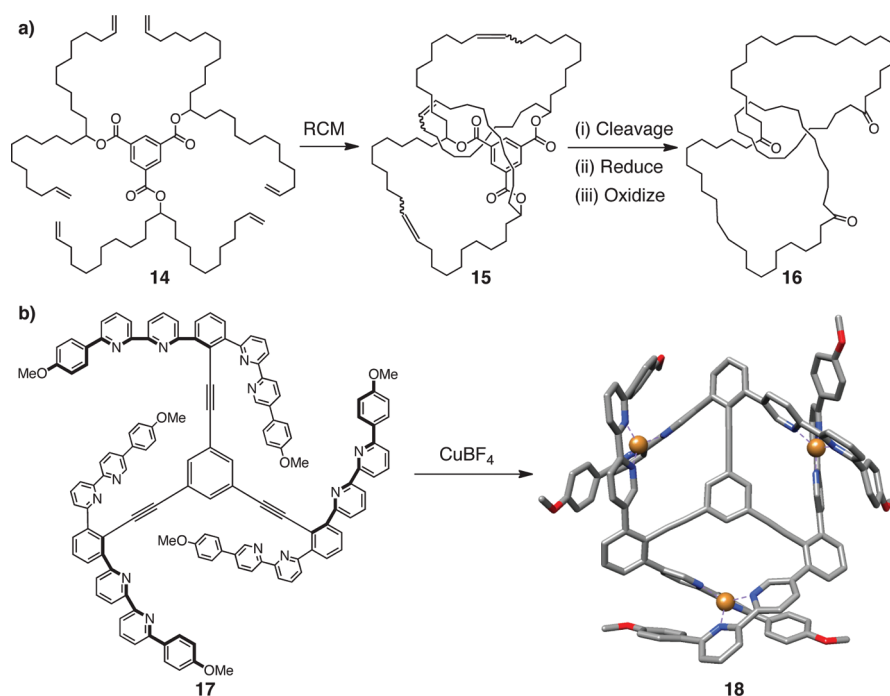


Figure 8. Two examples of synthetic strategies which have been employed in the attempted synthesis of Trefoil Knots based on a 1,3,5-trisubstituted benzene scaffold. (a) A compound 14, wherein the three substituents support two oligomethylene arms terminated by alkene functions that could undergo ring-closing metathesis (RCM) to give the intermediate 15, among other products, has been prepared.¹³⁰ Subsequently, steps i–iii generate a triketone compound, which is expected to be the Trefoil Knot 16. (b) The assembly^{160a} of a triskelion knot precursor based on Cu(I) coordination of a trigonal hexakis-bipyridine ligand, 17. The solid-state structure of the complex 18 is displayed in a tubular representation, with the Cu(I) ions rendered as orange spheres. Redrawn from CCDC deposition 148213.

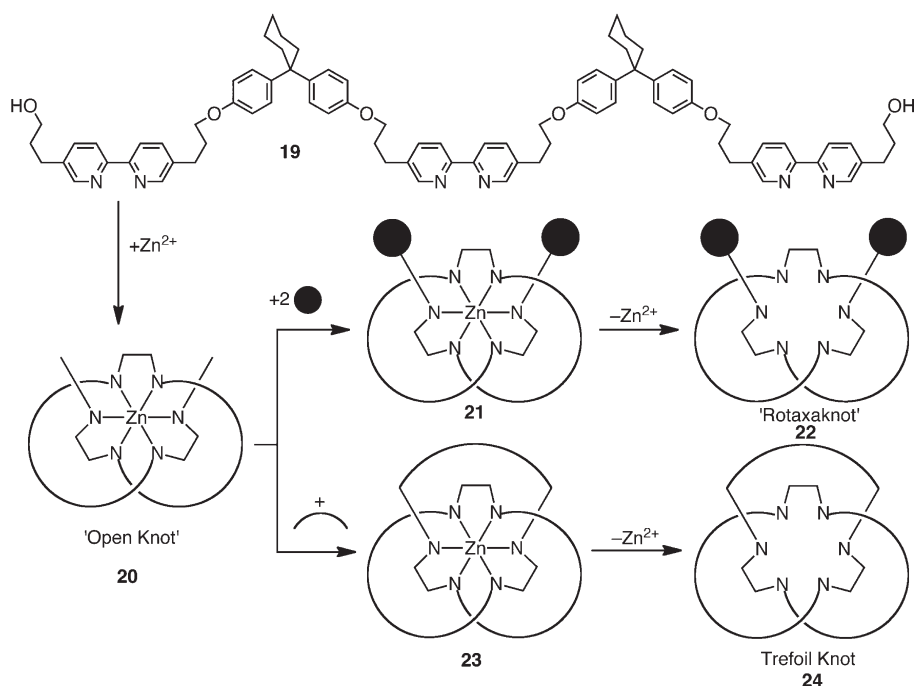


Figure 9. The transition metal templated route utilized by Hunter^{161,169,170} to form a Trefoil Knot, wherein a linear tris-bipyridine ligand 19 is assembled around a $\text{Zn}(\text{II})$ cation to form an "open knot" precursor 20. This complex can then be stoppered to form a metal-templated rotaxaknot, 21, or cyclized to form a Trefoil Knot 23. Demetalation of 21 should result in a metal-free rotaxaknot 22 if the stoppers are large enough, but may also lead to a linear, unentangled species. Compound 23 can be demetalated to the corresponding metal-free Trefoil Knot, 24, which cannot disentwine.

connected in the appropriate manner renders this strategy a high-risk one. An alternative strategy toward this final ring-closing step was proposed recently by Kepert et al.,¹⁶⁸ using metal coordination to effect knot formation. This example further demonstrates the major disadvantage inherent to connecting six termini in the final step, as a topologically trivial metallomacrocyclic was again the outcome, and not its topological isomer, the Trefoil Knot.

Hunter et al.¹⁶⁹ have conceived (Figure 9) an approach utilizing a linear tris-bipyridine ligand **19**, which, when complexed with Zn(II), forms quantitatively an entanglement wherein the ligand wraps itself around the metal center to form an "open knot" **20**. The interlaced species has a crossing pattern that is very similar to that observed when crossing one's arms. This assembly leaves only two termini to be connected in a single step to form the metalated Trefoil Knot **23**, and this step was achieved¹⁶¹ recently by two means, a high dilution diesterification in 25% yield and a ring-closing alkene cross-metathesis on substituted derivatives in up to 68% yield. Both Trefoil Knots were demetalated and studied by ¹H NMR spectroscopy. These examples represent the first and only Trefoil Knots assembled around an octahedral metal center to date.

The metal-templated open knot can be thought of as a precursor to a "rotaxaknot", an exotic species in which bulky stoppers are attached to the ends of a knotted thread such that disentanglement is not possible without the breaking of a covalent bond. Mayers¹⁷⁰ prepared a metal-templated rotaxaknot **21** by attaching bulky stoppers to the ends of both Zn(II)- and

Fe(II)-templated open knots. Upon demetalation, however, dethreading occurs to yield the dumbbell-shaped topological isomer. Attempts to reform the metalated species failed, because the size of the stopper was seemingly insufficient to prevent dethreading, yet appeared to hinder subsequent reknitting.

2.3. Transition Metal Helicate Templatation

Prior to Hunter's realization¹⁶¹ of a near 40-year-old synthetic proposal, an alternative method of transition metal templation had led to the preparation of various Trefoil Knots. The well-defined¹¹⁹ coordination synthon derived from the chelation of Cu(I) cations by two 2,9-substituted-1,10-phenanthroline ligands had already been used⁸⁷ successfully in the preparation of [2]catenanes by a template-directed approach. Coordination of these ligands to Cu(I) cations generates the required crossover point, or node, and, provided the following step is a ring-closing bis-alkylation, produces the [2]catenate—the term catenate⁹² describes a catenane formed around a transition metal template, while the term catenand¹⁷¹ refers to the metal-free derivative—in a one-pot synthesis in 27% yield.

In an extension¹⁷² of this principle (Figure 10), two 1,10-phenanthroline units could be connected by a tetramethylene linker, generating the ligand **25**, which is capable of forming double-stranded helical complexes with Cu(I). Formation of the helicate **26** was not quantitative, however, probably because the flexibility of the linker allows formation of the mononuclear complex. Although high dilution ring-closing alkylation with hexaethylene glycol produced significant amounts of the [1 + 1]

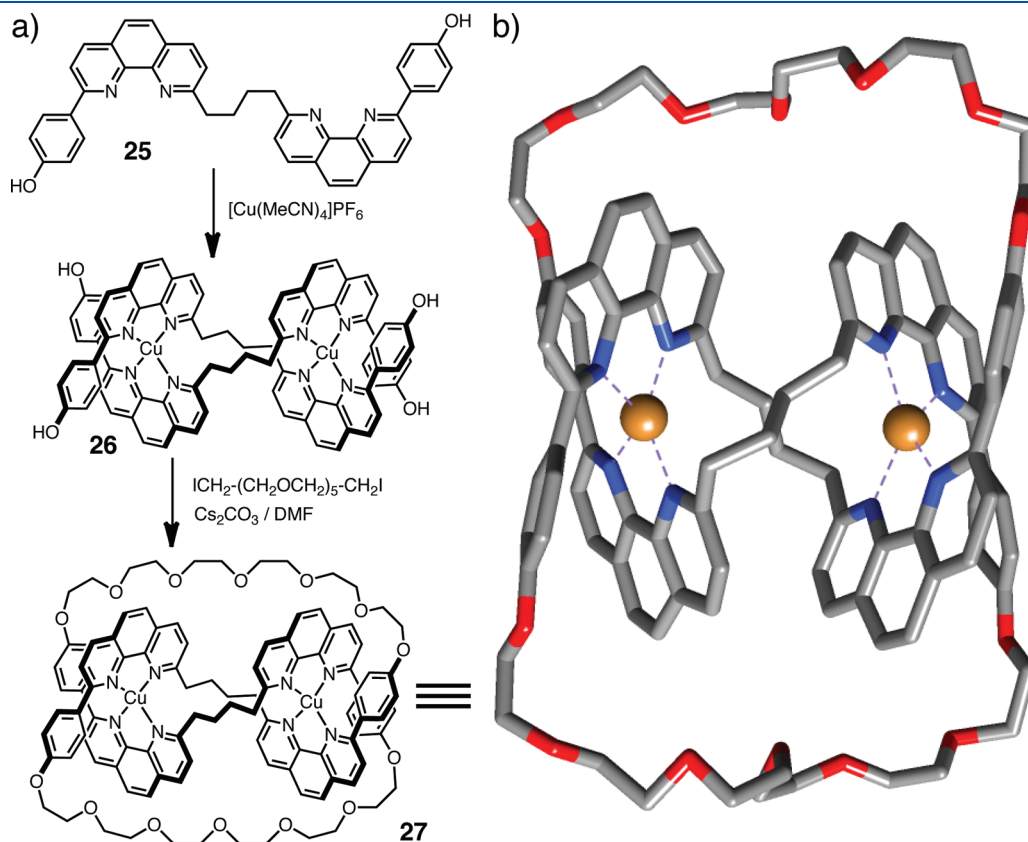
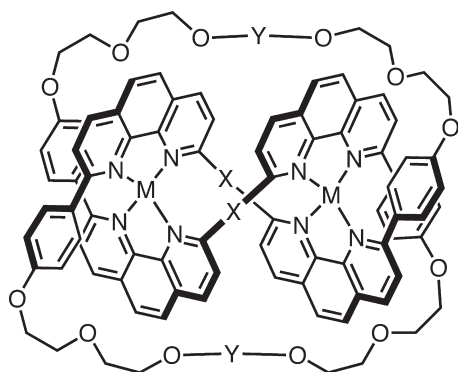


Figure 10. (a) The Cu(I)-templated synthesis¹⁷² of the prototypical molecular Trefoil Knot **27**. Coordination of two Cu(I) cations by two bis-phenanthroline ligands, **25**, forms a double helical precursor complex **26**, which can be cyclized with oligoethylene glycol units to form **27**. (b) The solid-state structure¹⁷⁴ of one topological enantiomer of the Trefoil Knot **27**, shown in a tubular representation with the Cu(I) ions as orange spheres. Hydrogen atoms and counterions are removed for clarity, redrawn from CCDC entry KICHAF.

Table 1. The Range (27–39) of Trefoil Knots Synthesized via the Bis-Phenanthroline Dinuclear Double Helical Precursor System^a



entry	X	Y	metals	yield ^b	reference
27	(CH ₂) ₄	–(C ₂ H ₄ O) ₆ –	Cu ^I /Cu ^I	3%	172
28	(CH ₂) ₂	–(C ₂ H ₄ O) ₆ –	Cu ^I /Cu ^I	0.5%	177
29	(CH ₂) ₄	–(C ₂ H ₄ O) ₅ –	Cu ^I /Cu ^I	0.75%	177
30	(CH ₂) ₆	–(C ₂ H ₄ O) ₅ –	Cu ^I /Cu ^I	2.5%	177
31	(CH ₂) ₆	–(C ₂ H ₄ O) ₆ –	Cu ^I /Cu ^I	8%	177
32	<i>m</i> -C ₆ H ₄	–(C ₂ H ₄ O) ₆ –	Cu ^I /Cu ^I	29%	179
33	<i>m</i> -C ₆ H ₄	–(C ₂ H ₄ O) ₇ –	Cu ^I /Cu ^I	22%	192
34	<i>m</i> -C ₆ H ₄	–(C ₂ H ₄ O) ₂ CH ₂ CH=CHCH ₂ (C ₂ H ₄ O) ₂ –	Cu ^I /Cu ^I	74% ^c	180
35	<i>m</i> -C ₆ H ₄	–(C ₂ H ₄ O) ₆ –	Cu ^I /–	n/a ^d	187
36	<i>m</i> -C ₆ H ₄	–(C ₂ H ₄ O) ₆ –	Cu ^I /Ag ^I	n/a ^d	187
37	<i>m</i> -C ₆ H ₄	–(C ₂ H ₄ O) ₆ –	Cu ^I /Zn ^{II}	n/a ^d	187
38	<i>m</i> -C ₆ H ₄	–(C ₂ H ₄ O) ₆ –	Ag ^I /Ag ^I	n/a ^d	188
39	<i>m</i> -C ₆ H ₄	–(C ₂ H ₄ O) ₆ –	Li ^I /Li ^I	n/a ^d	189

^a The increasing yields illustrate the advances made in the synthesis of this type of knot. ^b The yield displayed is for the final ring-closing step.

^c Ring-closing step achieved by Ru-catalyzed ring-closing alkene metathesis. ^d These knots were prepared by quantitatively remetalating the parent knot, from which the original Cu(I) templates were previously removed.

macrocycle, the desired Trefoil Knot **27** was also present and could be isolated in 3% yield. The unconditional chirality of the Trefoil Knot was demonstrated by ¹H NMR spectroscopy carried out on a mixture of **27** with Pirkle's alcohol¹⁷³ as a chiral shift reagent: peak separation was observed for several of the probe protons. Subsequently, the crystal structure (Figure 10b) of **27** was solved¹⁷⁴ and provided unequivocal evidence for the knotted topology. Interestingly, crystals grown by vapor diffusion of CH₂Cl₂ into a C₆H₆ solution of **27** showed spontaneous resolution; that is, each single crystal contained only one of the two topological enantiomers. Crystals of both enantiomers resulted, leading to the formation of a conglomerate. The unknotted topological isomer was also isolated and characterized¹⁷⁵ crystallographically, while spectroscopic comparison¹⁷⁶ of both compounds provided further evidence of the knotted nature of the target compound.

The low yielding prototypical synthesis of **27** led to efforts to prepare larger amounts of molecular knots in order to study their properties. It transpired¹⁷⁷ that the group used to link the 1,10-phenanthroline moieties is of utmost importance, because of its effect on the extent of formation of the dinuclear double-helical precursor. By simply extending the tetramethylene linker to a hexamethylene one, helix formation increases dramatically, and

subsequent ring-closing alkylation with pentaethylene glycol gave a new Trefoil Knot **31** in 8% yield. It appears that the longer hexamethylene linker is well adapted to allow knot formation, generating a helical complex more efficiently than its shorter analogues.¹⁷⁸ Varying the length of the linker and the ring-closing oligoethylene glycol chain also considerably influences the yield of the knots (**27**–**31** in Table 1).

A significant increase in knot yields was achieved by replacing¹⁷⁹ the polymethylene linker with a *meta*-phenylene bridge, a change of design that resulted in the quantitative assembly of the precursor double helical complex. This increase in stability of the helical species led to the isolation of knots in 22% and 29% yields, when heptaethylene glycol (**33**) and hexaethylene glycol (**32**), respectively, were employed in the final ring-closing alkylation step. Having refined the self-assembly of the double helical complex, the final ring-closing step¹⁸⁰ was investigated in an attempt to improve yields yet further. Ru-catalyzed ring-closing alkene metathesis¹⁸¹ (RCM), which had previously been shown¹⁸² to be extremely efficient in synthesizing some related [2]catenanes in up to 92% yield, was chosen as the final knot-forming reaction. When a *meta*-phenylene-bridged bis-phenanthroline ligand bearing terminal alkene functions was prepared and used as a precursor, knot formation by RCM occurred in 74% yield to give **34**. Alkene metathesis is particularly suited¹⁸³ to macrocyclizations involving Cu(I)-templated species as it is a thermodynamically controlled reaction. It also avoids the need for addition of destabilizing bases, such as NaH, which are required when alkylation is the final step in the reaction sequence. In the case of **34**, the alkene was formed with a *cis*:*trans* ratio of approximately 4:1. The double bonds, however, can be hydrogenated catalytically, removing the complexities associated with a mixture of configurational isomers.¹⁸⁴

The isolation of gram-scale quantities of this new family of molecular Trefoil Knots has enabled their properties to be investigated in an unprecedented manner. The electrochemical and luminescent characteristics of a series of polymethylene-linked knots were examined.¹⁸⁵ The lengths of both the linker and the polyether loops were found to affect significantly the local geometry of the Cu(I) cations and, as such, the physical properties of the knots. In comparison with their unknotted analogues, the behavior of the Cu(I) centers in the knots, including the kinetics of demetalation, is altered drastically. Although it is possible to remove¹⁸⁶ each Cu(I) cation quantitatively in a stepwise manner from the knots, demetalation of the topologically trivial macrocycles is not possible. Indeed, the kinetic inertness of the monocopper knot **35** has led to the preparation¹⁸⁷ of heterodinuclear knots, that is, combinations of Cu(I) and both Ag(I) (**36**) and Zn(II) (**37**) cations, and the study of their electronic properties. Full demetalation of the Cu(I) knots requires the addition of an excess of KCN in refluxing MeCN, and the free knotted ligand that results can then be remetalated¹⁸⁸ with either Ag(I) or Li(I) cations.¹⁸⁹ The dilithium knot **39** exhibits surprising stability, with Li(I) cations showing high affinities for the phenanthroline chelating units, forming an even tighter helical core within the knot than in the analogous Cu(I)-templated knot in the solid state.

All of the knots that have been synthesized using the helical complexation method have been isolated as a racemic modification of two topological enantiomers. The preparation of large quantities of these knots has facilitated their resolution into optical isomers. The fact that the Cu(I) cations have associated

counterions allowed the use^{190,191} of an optically pure anion, (S)-(+)-binaphthylphosphate (BNP[−]), to generate diastereoisomers that could be separated by fractional crystallization. ¹H NMR spectra of both diastereoisomers revealed that the interactions between the aromatic counterions were strongest with the *meta*-phenylene spacer, rather than with the periphery of the knot, an observation that might explain the utility of the BNP[−] anion in the resolution process: its axial chirality arises from the twisted binaphthyl core, in a manner similar to the helical twist, which is the source of chirality of the knot. The circular dichroism (CD) spectra of each diastereoisomer are mirror images, because the BNP[−] anion does not absorb at wavelengths ($\lambda > 280$) that were experimentally accessible. The knots have also shown¹⁸⁸ enantioselective discrimination in the quenching of luminescence of racemic mixtures of Ln(III) complexes, an observation that indicates that topologically chiral species can express their chiral bias.

The successful approach to preparing large quantities of Trefoil Knots has led to the isolation¹⁹² of a more complex species, a composite knot (Figure 11a). A helical “open knot” precursor with terminal alkyne functionalities was prepared, and dimerized by oxidative acetylenic coupling,^{193,194} leading to the formation of the molecular composite $3_1\#3_1$ knot, **40**, which can also be described as $3_1\#3_1$ and $3_1\#3_1^*$. The notations 3_1 and 3_1^* indicate that these two Trefoil Knot fragments are topological enantiomers, and so linking these two knotted components together generates a mixture of the two enantiomers, (+/+) and (−/−), as well as the *meso* isomer (+/−). Although the diastereoisomers could not be separated, they were identified by ¹H NMR spectroscopy. The statistically expected ratio of these isomers was not observed, however, indicating some stereoselective bias in the coupling reaction which led to the composite knots in the first place.

Two further molecular Trefoil Knots have been prepared utilizing alternative helical ligand systems. Linking two terpyridine moieties with a bismethylene bridge, followed by

complexation with Fe(II) cations, generated a dinuclear double helix in the solid state. Upon derivatizing a variant with pendant polyether arms terminated with alkene functions, Fe(II) coordination, followed by RCM, produced¹⁸⁴ (Figure 11b) the Trefoil Knot **41** in 20% yield. Once again, the C=C double bonds were hydrogenated catalytically to remove the *cis/trans* source of isomerism.

The enantioselective synthesis of a Trefoil Knot, i.e., the selective preparation of only one topological enantiomer, has been achieved by an elegant synthetic approach involving CHIRAGEN¹⁹⁵ ligands: optically pure pinene-fused bipyridine chelates. Connection¹⁹⁶ of two of these chelates with a *meta*-phenylene bridge gave a ligand that formed dinuclear double helical Cu(I) complexes with the (*M*) configuration only, and substituted derivatives with alkene-terminated oligoethylene glycol chains could be cyclized (Figure 11c) via RCM to give only the left-handed (−) knot **42** in 74% yield.

2.4. DNA and RNA Trefoil Knots

The success of metal template-directed synthesis lies in utilizing the helical twists induced by the metal complexes as the crossing points, or nodes, that are inherent in knots. Perhaps the most well-known molecular helices are those found in double-stranded DNA, the reproducibility and programmability of which have been exploited extensively by Seeman^{123,197} in the synthesis of DNA nanoarchitectures, including a truncated octahedron of approximately 790 kDa, which, topologically, corresponds to a [14]catenane.¹⁹⁸ The remarkable size and complexity of these mechanically interlocked molecular entities results from the reliability of the Watson–Crick hydrogen-bonded pairs within DNA. The nucleic acid double-helical half twist is a perfect molecular representation of the topological crossover point, node, or unit tangle, which is a basic constituent of every knot and link.¹⁰⁸ By using right-handed B-DNA, it is possible to prepare negative (−) nodes, while left-handed Z-DNA allows access to positive (+) nodes (Figure 12). It is important to note that B-DNA is the more common, naturally

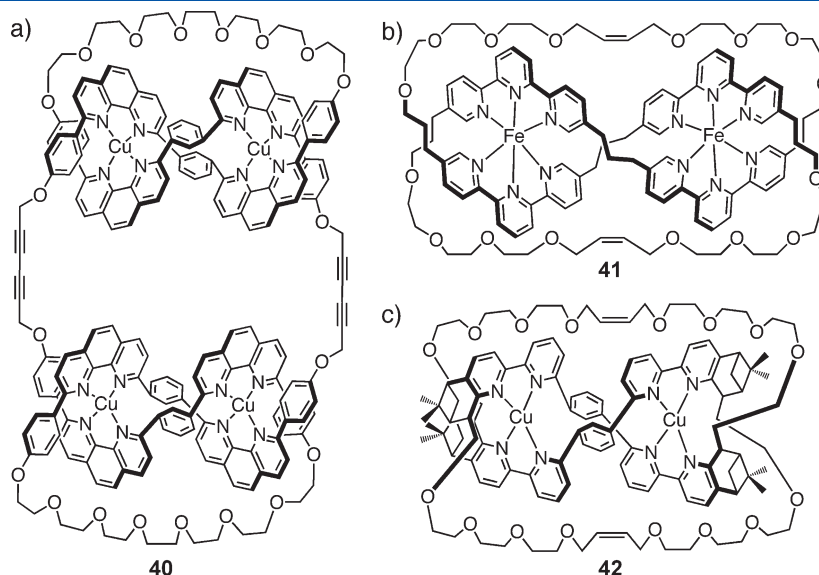


Figure 11. (a) A molecular composite $3_1\#3_1$ knot **40**, formed¹⁹² by conjugation of two 3_1 segments, and prepared by oxidative acetylenic coupling of two alkyne-terminated “open knots”. (b) A molecular Trefoil Knot **41** prepared¹⁸⁴ from Fe(II) terpyridine double helicate complexes and cyclized by alkene metathesis. (c) A molecular Trefoil Knot **42**, based on the CHIRAGEN ligand system, which can be synthesized enantioselectively¹⁹⁶ from optically pure precursor helicates.

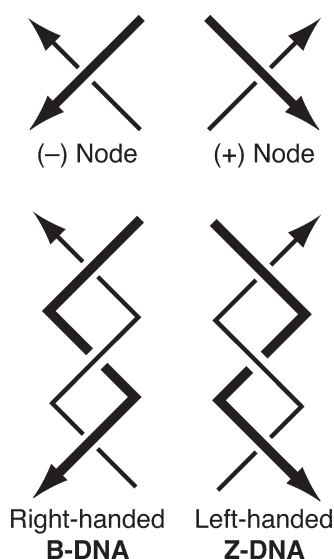


Figure 12. Schematic diagram illustrating the negative (–) and positive (+) nodes inherent to the double helical conformations of B-DNA and Z-DNA, respectively. Redrawn with permission from ref 201. Copyright 1992 American Chemical Society.

occurring motif, yet, if the strand is capable of conversion, solutions of high ionic strength or cationic effectors such as $[\text{Co}(\text{NH}_3)_6]^{3+}$ can convert¹²³ B-DNA into Z-DNA.

This approach led to the synthesis of a right-handed DNA Trefoil Knot by Seeman et al.,¹⁹⁹ utilizing a single B-DNA strand with two sets of complementary 11-mer pairing regions, comprising one full helical turn each, connected by unstructured oligodeoxythymidine (oligo-dT) units. Connecting the ends of the strand, by ligation with T4 DNA ligase, yielded the target knot, which was characterized extensively by gel electrophoresis and sedimentation analysis. A similar Trefoil Knot was prepared²⁰⁰ by a motif with shorter complementary pairing sections, and both of these knots contained negative nodes as a result of the use of B-DNA. By replacing one of the pairing regions with DNA capable of transforming to Z-DNA, Seeman et al.^{201,202} were able to prepare a single strand of DNA, which could again be ligated under regular conditions to give a Trefoil Knot. By contrast, when the cationic effector $[\text{Co}(\text{NH}_3)_6]^{3+}$ was introduced during ligation of this particular DNA strand, a Figure-of-Eight knot, the 4_1 knot, was the result. The 4_1 knot requires two positive and two negative nodes, which are provided, in this case, by the Z-DNA and B-DNA sections, respectively.

The versatility and adaptability of DNA in the preparation of topologically interesting molecules is further demonstrated by one final example (Figure 13). Seeman and co-workers^{203,204} extended the previous concept to the preparation of a single strand of DNA, again containing two complementary pairing regions, but, in this case, both were capable of undergoing transformation from B-DNA to Z-DNA, and one with a greater propensity than the other. Careful control of ligation conditions allowed the preparation of four separate products: (i) the trivial unknot, or macrocycle, (ii) a Trefoil Knot with all negative nodes, containing all B-DNA, ligated at low ionic strength, (iii) a Figure-of-Eight knot with two positive and two negative nodes, comprising a mixture of B-DNA and Z-DNA, ligated at high ionic strength, and (iv) a Trefoil Knot with all positive nodes,

comprising only Z-DNA, ligated at high ionic strength and in the presence of $[\text{Co}(\text{NH}_3)_6]^{3+}$. The two Trefoil Knots are topological enantiomers, while this particular Figure-of-Eight knot represents an exotic species, the topological rubber glove.²⁰⁵ The molecular rubber glove is a topologically achiral object whose molecular graph can be deformed to its mirror image, yet, on the conversion pathway, no achiral presentation can be formed.²⁰⁶ A laboratory-based analogy of this process is the turning inside out of a rubber glove when removing it from one's hand. A Figure-of-Eight Knot with a labeled molecular graph, such as that prepared by Seeman in ref 205, meets these criteria. A further molecular rubber glove has been realized^{207,208} in the form of an asymmetric [2]catenane. The precise control over molecular architecture exhibited by Seeman contrasts strongly with the earlier methods of DNA knot preparation, wherein the action of DNA topoisomerases generated various knotted species with no regulation of the outcomes of the process.

RNA can also be coaxed²⁰⁹ into forming a Trefoil Knot in a similar fashion. A combination of factors, however, renders RNA a much more difficult material to work with, for example, its inherent instability when compared to DNA and the lack of efficient modifying enzymes to perform relatively simple tasks such as exonucleation and ligation. As such, DNA remains the preeminent biological material used^{210–213} in nanotechnological applications, although a recent report²¹⁴ of a polyhedral tRNA

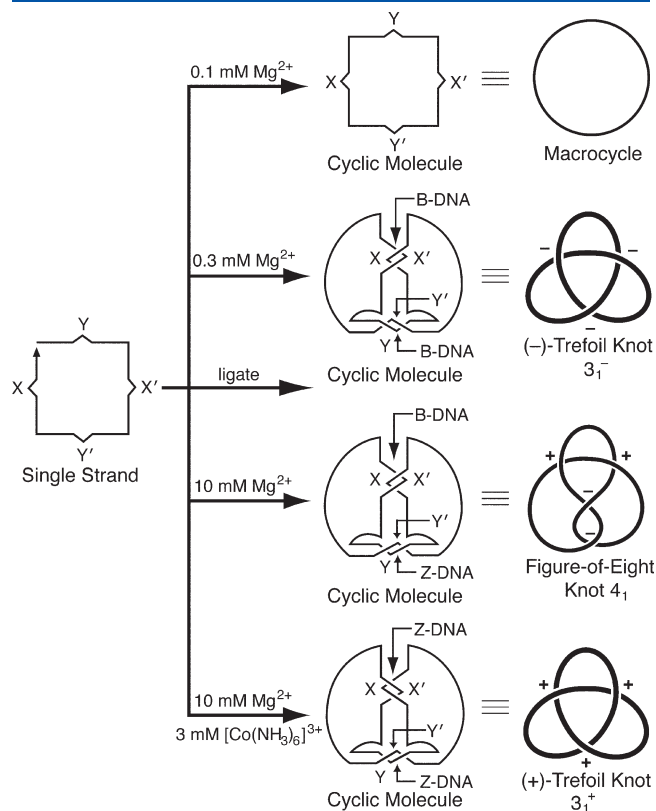


Figure 13. A schematic diagram illustrating the synthesis²⁰³ of four topologically distinct entities from one single strand of DNA. The strand has four pairing regions, denoted by bulges in the square, with X complementary to X' and Y to Y', and the arrowhead indicates the 3' end. The various ligation conditions used, which induce structural changes to certain areas of the molecule from B- to Z-DNA, are shown alongside the resultant helical handedness and topology. Redrawn with permission from ref 203. Copyright 1995 American Chemical Society.

antiprism suggests a future for this material, perhaps in conjunction²¹⁵ with DNA itself. Indeed, Seeman²¹⁶ has reported very recently that single-stranded DNA can be woven into braided assemblies, and one of these constructs has the topology of a Solomon Link. This latest discovery, allied with the synthesis of Borromean Rings (see section 4.3) from DNA double strands, illustrates the versatility of DNA in assembling complex topological entities.

2.5. Hydrogen-Bond Templatation

Just as the first molecular Trefoil Knot resulted¹⁷² from an extension of template-directed synthetic protocols utilized in the preparation of catenanes, the serendipitous discovery, in 2000, of a hydrogen-bond templated Trefoil Knot by Vögtle et al.,²¹⁷ came about during investigations^{126,218,219} into the synthesis of hydrogen-bond templated catenanes. While attempting to scale up the synthesis of the [1 + 1] macrocycle, which results from the bis-amide condensation of **43** with **44** (Figure 14a), a colorless solid representing a [3 + 3] addition product was isolated in 20% yield. X-Ray crystallographic analysis (Figure 14b) revealed the molecular Trefoil Knot **45**, connected by 12 amide bonds and with prodigious intramolecular H-bonding. The simplicity of the synthesis and the ready availability of the precursors have allowed a comprehensive study to be carried out on this range of molecular Trefoil Knots. Numerous derivatives have been prepared^{220,221} with substituents in the R¹ and R²

positions (Figure 14c) located on the pyridinecarboxamide and the isophthalimide moieties, respectively. In most cases, the resolution of both topological enantiomers of the knots was possible using a chiral HPLC protocol developed by Okamoto.²²¹ His procedure employs a column wherein the chiral stationary phase is bound covalently to silica gel, leading to separation factors as high as 11.32 and allowing the examination of the chiroptical properties of the knots.

The mechanism of formation of the knots was also examined in detail. The use of polar solvents, such as dimethylformamide, during the synthesis inhibits hydrogen bonding and, as such, does not lead to the production of detectable amounts of molecular knots, a clear indicator that a hydrogen-bonded supramolecular precursor is an intermediate in the synthesis. Moreover, hydrogen bonds between the amide protons and pyridine nitrogen atoms live on inside the knot itself. To investigate this hypothesis further, Vögtle et al.²²² prepared a series of oligoamide threads (Figure 15) from knot precursors and attempted to carry out "knot-closing" macrocyclizations. It was argued that, should a hydrogen-bonded template be the reason for knot formation, only certain oligoamides would then lead to knotted products. When a decaamide-diamine long thread **46** was prepared, it underwent spontaneous self-knotting to yield an open knot **47** in a fashion similar to that of Hunter's¹⁶⁹ metal-templated open knot described in section 2.2. Simple ring-closing alkylation with the pyridine diacid chloride **44** gave the Trefoil Knot **45** in a

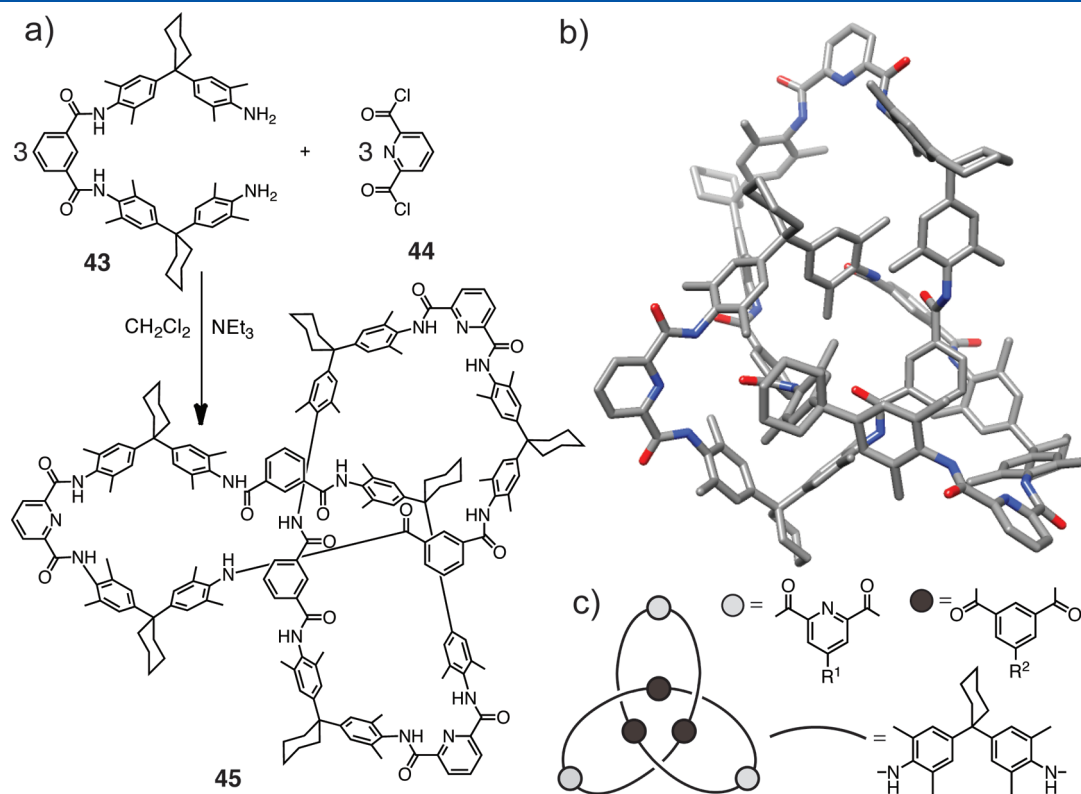


Figure 14. (a) The one-pot synthesis,²¹⁷ as a result of a [3 + 3] macrocyclization of the precursors **43** and **44**, of Vögtle's prototype hydrogen-bonded Trefoil Knot, **45**. (b) Tubular representation of one (+) of the topological enantiomers of **45** found²¹⁷ in its solid-state structure; both enantiomers are present within the unit cell. Hydrogen atoms and solvent molecules are omitted for clarity. Redrawn from CCDC deposition 139484. (c) Graphical representation of the core structure of the hydrogen bonded knots described in this section. The light gray circles represent the pyridinecarboxamide moieties at the extremities of the knots, the dark gray circles the isophthalimide moieties in the center of the knot, and the curved lines the cyclohexylidene-linked bis-aniline linker groups. Substituents can be introduced at both the pyridinecarboxamide groups (R¹) and the isophthalimide groups (R²). Adapted with permission from ref 217. Copyright 2000 Wiley-VCH Verlag GmbH & Co. KGaA.

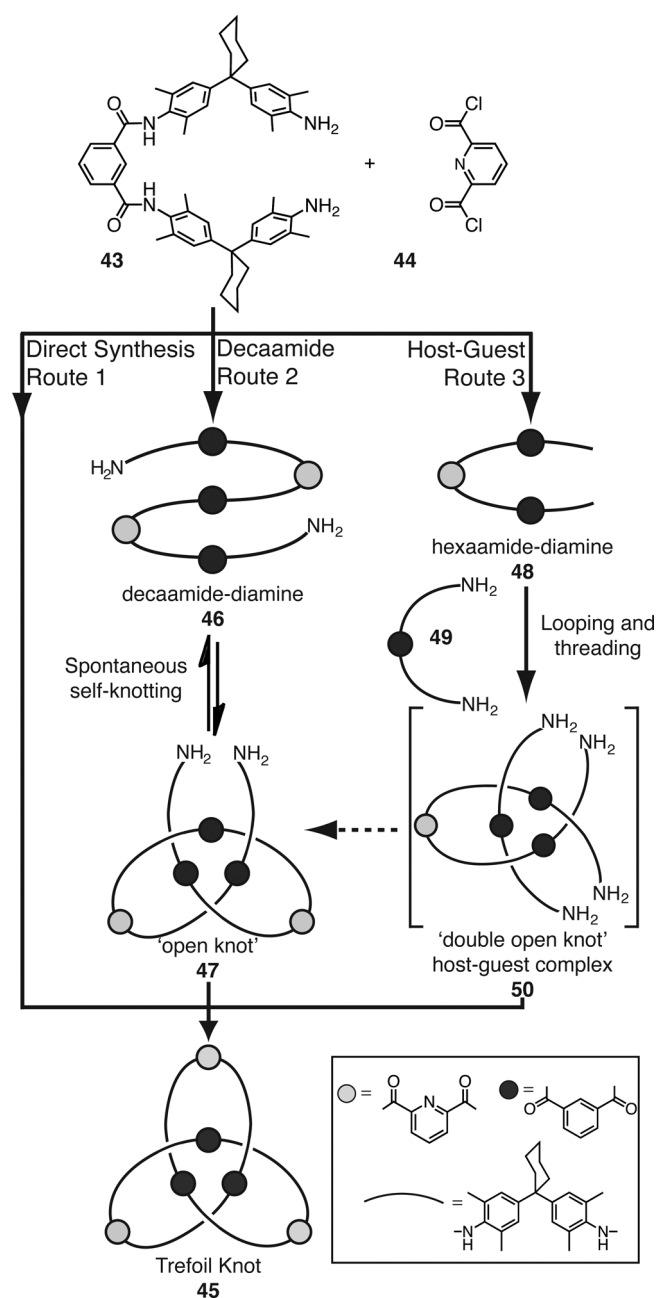


Figure 15. Synthetic strategies for the preparation²²² of hydrogen-bonded Trefoil Knots. Route 1 is the one-pot protocol utilized in the initial synthesis of **45**. Route 2 involves the prior synthesis of a linear precursor **46** capable of self-knotting spontaneously to form an “open knot” compound **47**, which can subsequently be cyclized to the target knot **45** by alkylation. Route 3 shows the possibility that a host–guest complex **50** is involved when two oligomeric thread molecules **48** and **49** are mixed, which may be the reason for knot formation in route 1. Redrawn with permission from ref 222. Copyright 2007 Wiley-VCH Verlag GmbH & Co. KGaA.

stepwise manner, in contrast with the one-pot approach, which first yielded the knot. Subsequently, this stepwise route allowed the preparation of asymmetrical knots, wherein substituted pyridine diacids are utilized in the knot-closing step, giving access to monofunctionalized molecular Trefoil Knots. Difunctionalized knots can also be accessed, from a disubstituted thread and an unsubstituted diacid. Similarly, a hexaamide diamine thread

48 was prepared and, when mixed with 2 equiv of the diamide diamine precursor **49**, is believed to form a supramolecular host–guest complex **50**, which is reminiscent of an open knot. Alkylation with 2 equiv of the pyridine diacid chloride **44** afforded the knot **45**, probably by a route that involves the previously described decaamide diamine open knot **47**.

The synthesis²²² of a rotaxaknot, by stoppering **47** with bulky trityl-based groups, was also attempted. Although a bis-alkylated product was isolated in 29% yield from the open knot, all attempts to prove that the compound comprised a rotaxaknot, rather than a dumbbell, the unraveled topological isomer, failed. In principle, this rotaxaknot should exhibit topological chirality in the same way as does its related Trefoil Knot. The fact that a chiral compound, however, could not be isolated has led to speculation that an equilibrium between the untangled dumbbell and the rotaxaknot prevails in solution.

Mono-, di-, and trisubstituted knots (Figure 16a) can also be prepared²²³ by the selective deprotection of the allyloxy groups of the functionalized knot **51** by $n\text{BuSn}_3\text{H}$ in the presence of a palladium catalyst. This synthetic approach allows access to knots with one, two, and three hydroxy groups (**52–54**) to which different appendages can be attached. For example, solubilizing groups assisted in the study of the dynamics and conformations of these knots in solution by NMR spectroscopy. In CD_3SOCD_3 , a nonsymmetric conformation similar to that present in the solid-state structure of **45** was identified, whereas an average D_3 symmetrical conformation exists in other solvents.

The ability to synthesize substituted Trefoil Knots has led to the preparation, in Vögtle's group, of a series of functionalized knots. Dendritic arrays can be incorporated²²⁴ on the three edges of the knot, improving the solubilities of the compounds, and the mono-, di-, and trisubstituted knots have all been prepared. Interestingly, the isolation of the topological enantiomers was once again achieved, and some chiral induction was observed from the topologically chiral knot to the propeller-like dendritic groups, influencing their orientations in each enantiomer. Vögtle et al.²²⁵ also investigated the combination of topological and point chiralities, by preparing (1*S*)-(+)-camphor-10-sulfonyl-substituted knots and ending up eventually with diastereoisomers, which could be separated by chiral HPLC. Fluorescent dansyl and pyrenesulfonyl groups have been attached²²⁶ to the knots and shown to act as fluorescent molecular acid/base switches. Large alkyl and oligoethylene glycol chains can also be introduced onto the periphery of the knots, making it possible to form Langmuir–Blodgett thin films from them. Interestingly, terminal alkene functions were shown to undergo Ru-catalyzed alkene metathesis to form a novel “double knot”, wherein two Trefoil Knots are linked at each vertex, forming a triply bridged cage-like species. Unfortunately, purification of this double knot could not be achieved, and its identification²²⁷ relies solely on mass spectrometry.

The ease of substitution of these hydrogen-bonded knots has led Vögtle to prepare many topologically complex compounds incorporating the Trefoil motif. Two monosubstituted knots were linked²²⁸ by a biphenyl-4,4'-disulfonyl bridge, forming a dumbbell-shaped molecule with two terminal Trefoil Knots in 75% yield. The combination of two topologically chiral knots means that it is possible to separate the (+/+), (−/−), and *meso* forms of the dumbbell by chiral HPLC, all adding up to a neat demonstration of topological chirality. By linking two knots with an isophthaloyldiamido moiety, a dumbbell with a potential hydrogen-bonding station for a ring is formed; when the linking

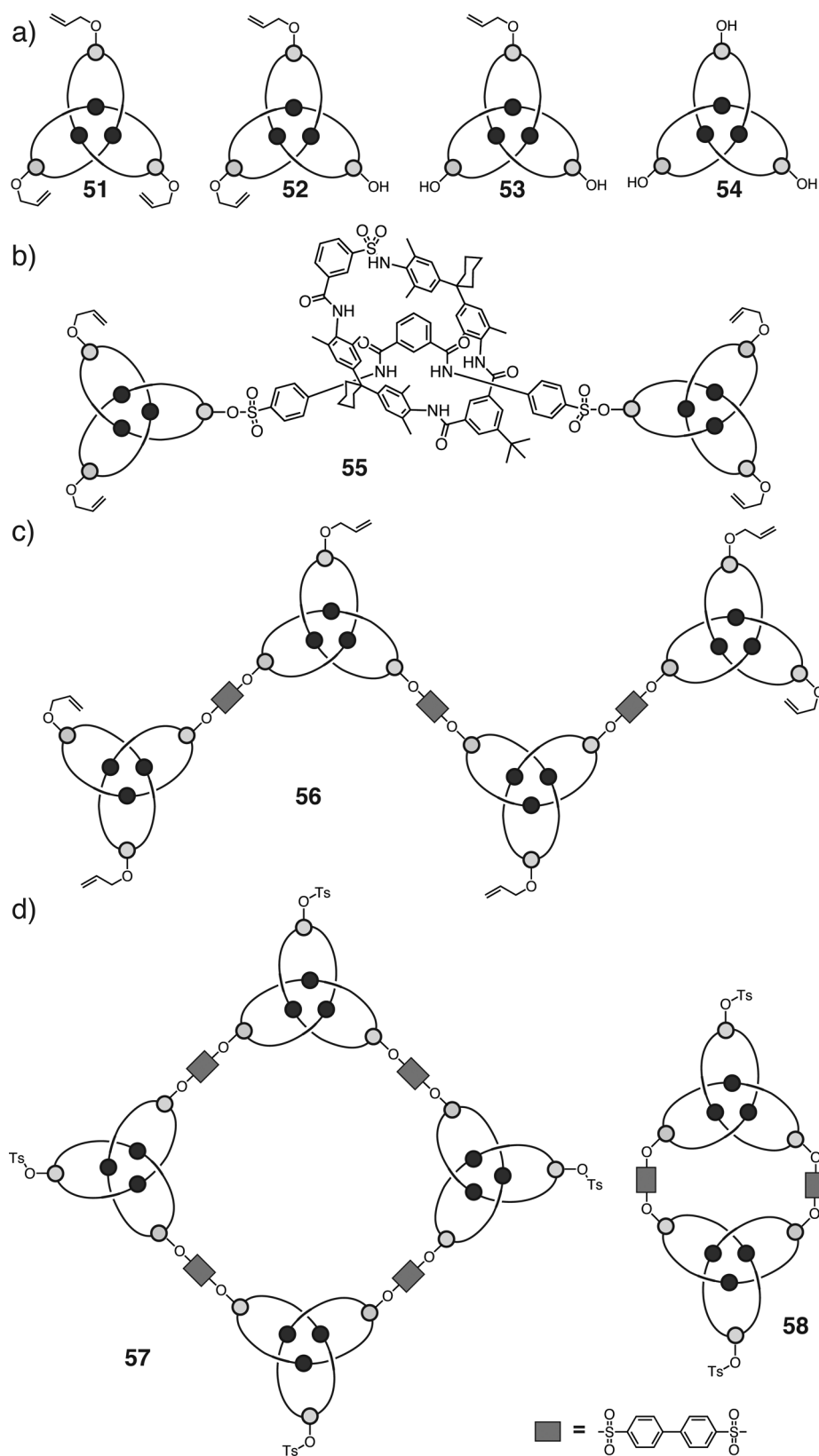


Figure 16. Schematic diagrams of substituted hydrogen-bonded knots and connected assemblies. (a) The synthesis²²⁸ of the tris-allyloxy-substituted knot **51** allows access to mono-, di-, and tri-substituted knots (**52–54**) by selective stepwise deprotection of the allyloxy groups. (b) A "knotaxane" **55**, a rotaxane with two Trefoil Knots as stoppers.²²⁹ (c) A linear tetra-knot molecule **56** prepared²³⁰ by covalently linking four Trefoil Knots. (d) "Knotanophanes",²³⁰ cyclic molecules consisting of more than one linked knot molecule, with the tetra- and diknotanophanes **57** and **58**, respectively, shown.

reaction is carried out in the presence of an appropriate macrocycle, a “knotaxane” **55** is the result²²⁹ (Figure 16b), that is, a rotaxane wherein the stoppers are knots. This knotaxane can also exist in (+/+), (−/−), and *meso* forms, but separation of these isomers has not yet been achieved. Finally, knots have been linked²³⁰ into more complex forms, generating (Figure 16c) linear and branched “oligoknots” **56** containing up to four Trefoil motifs and also “knotanophanes” (Figure 16d), that is, cyclic oligomers (**57** and **58**) up to four units in size. The inclusion of many topologically chiral moieties generates a large number of diastereoisomers, which proved fiendishly difficult to separate.

The topologically exotic, highly complex compounds prepared by Vögtle et al. represent significant advances in the field of topological chemistry. Despite the facile synthesis and the toleration to structural modification of this hydrogen-bonded motif, only one further Trefoil Knot based on amide bond formation has been reported to date. When coupling the steroid 3- α -aminodeoxycholic acid with the amino acid L-valine, Feigel et al.²³¹ discovered an unexpected molecular Trefoil Knot (**59**) in admixture with macrocyclic compounds. The solid-state structure of the Trefoil Knot **59** contains three external and three internal steroid units, linked by six valines, which comprise the chain-crossing regions, or nodes. Hydrogen bonding between the two valine residues of each node is thought to direct the formation of the knot. Because both the L-valine and the 3- α -aminodeoxycholic acid are chiral, the topological isomers of **59** are diastereoisomers. Only the (+)-isomer was detected, indicating that the hydrogen bonding between the two valine units favors the crossing pattern associated with the (+)-isomer.

In one further example, donor–acceptor interactions have been used, in concert with hydrogen bonds, as the source of templation to prepare²³² a molecular Trefoil Knot (Figure 17b), albeit it in very low yield. High-pressure alkylation of an electron-rich dioxynaphthalene thread with an electron-poor bipyridinium one formed both the Trefoil Knot **60**, presumably through the intermediacy of a donor–acceptor double helical precursor “complex”, and the topologically isomeric trivial macrocycle. Both **60** and the macrocycle were characterized by HPLC and mass spectrometry. The low yield was attributed to the small association constant (400 M^{-1}) for the precursor molecules.

2.6. “All-in-One” Approaches – The Future?

The molecular Trefoil Knots prepared to date have mostly arisen through stepwise synthetic strategies, wherein the appropriate crossing points of the knot are designed into a precursor molecule, by virtue of coordinative and/or supramolecular interactions, which is subsequently cyclized to form the knot. The one-step strategies that have been successful so far have relied, for the most part, on covalent bond formation and are not reversible. Their formation most likely proceeds mechanistically through knot precursors; it may be more prudent to describe these routes as “one-pot stepwise syntheses” rather than truly reversible “all-in-one” methods where the knot is the thermodynamically stable product of a reversible self-assembly process. The refining of reaction conditions and the introduction of thermodynamically controlled ring-closing reactions have, however, led to the large-scale preparations of knots. While DNA and RNA have been exploited to form knots in a quantitative manner, their syntheses are not scaleable, despite their elegance and simplicity. It is perhaps surprising, therefore, that no “all-in-one” methods of synthesis have been devised. The synthetic complexity of the knots and links described in the subsequent sections dictates the increasing importance of this preparative approach.

3. SOLOMON LINKS

3.1. Background

The Solomon Link is another assembly that has inspired humanity since ancient times. Named after the biblical King Solomon, it is said to represent his wisdom and knowledge and appears (Figure 18a) in numerous archeological settings across the globe, dating from the Roman Empire and beyond. The two intertwined rings have also been interpreted²³³ as a manifestation of immortality, eternity, and even love. Referred to historically as “Solomon’s Knot”, mathematically, the correct description of the topology is a link. More accurately, the assembly is a 4_1^2 link, as it comprises two components and four crossings.^{5,17,234} The subscript 1 indicates that the Solomon Link can be represented on a torus without any crossing points between the rings. Chemically, it has been described as a four-noded link, and as a “doubly interlocking”,²³⁵ “doubly braided”,²³⁶ or “four-crossing”²³⁷ [2]catenane. The simple [2]catenane, itself a representation of

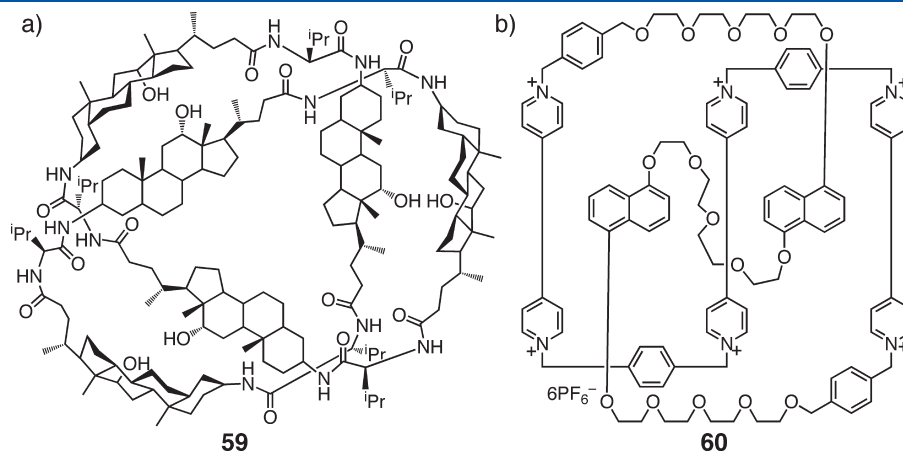


Figure 17. (a) Schematic diagram of the hydrogen-bonded Trefoil Knot **59** formed²³¹ during coupling of L-valine and 3- α -aminodeoxycholic acid. (b) Schematic diagram of a donor–acceptor Trefoil Knot **60**.²³²

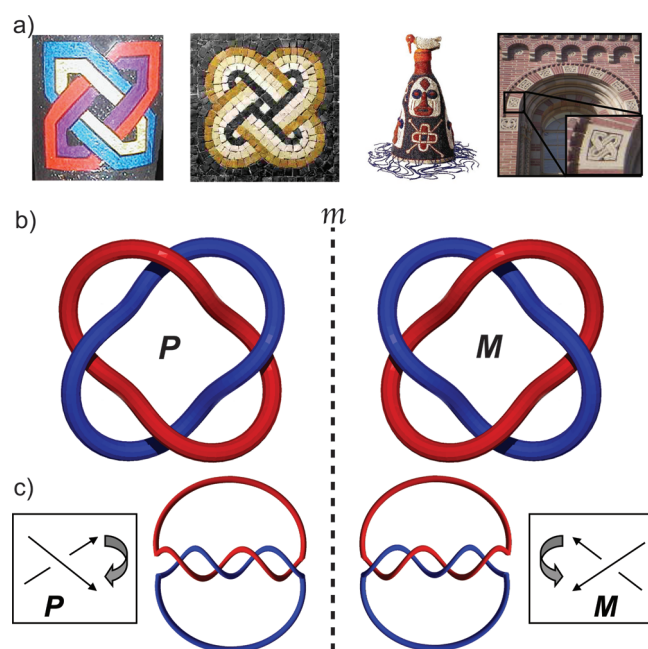


Figure 18. Various representations and examples of Solomon Links. (a) Examples of decorative Solomon Links (from left to right) on a British glass painting, an Italian mosaic tile, an African headpiece, and a carving above a window of Moore Hall, at the University of California, Los Angeles. (b) A schematic diagram of the two topological enantiomers, (*P*) and (*M*), inherent to Solomon Links. (c) Graphical representation of the skew-line system used to determine the chirality of Solomon Links. Adapted with permission from ref 242. Copyright 2007 Wiley-VCH Verlag GmbH & Co. KGaA.

the Hopf link, has the descriptor 2^2_1 , as the two rings cross over at two points rather than the four of the Solomon Link, and here, again, it can be embedded on a torus without crossings as specified by the subscript 1.

In common with the Trefoil Knot, the Solomon Link is unconditionally topologically chiral (Figure 18b). By using the skew-line system,^{132,133,141} it is possible to assign *P* and *M* descriptors to the two enantiomers. In Figure 18c, the two rings are oriented to elucidate the double helix arising from the four crossings of the rings, and arrows are pointed down each helical strand of the link, facing the same direction. If linking the head of the bottom (lower) arrow to the top (above) arrow comprises a clockwise movement, the crossing is assigned the plus (*P*) descriptor, and if the movement is anticlockwise, the minus (*M*) descriptor is assigned to it.

3.2. Transition Metal Helicate Templatation

Truly molecular Solomon Links are considerably less prevalent than molecular Trefoil Knots, possibly as a consequence of the added complexity of linking two components together to form the doubly interlocked motif when compared to the single knotted component of the Trefoil Knot. Two main strategies have realized molecular Solomon Links: (i) the linking of metal-templated helical systems in a stepwise manner, wherein the helicity provides the crossover points inherent to the Solomon Link, and (ii) an all-in-one approach, reliant on template-directed self-assembly of the components into the interlocked architecture. The former approach was utilized²³⁵ in 1994 in the first synthetic preparation of a molecular Solomon Link. Because helical copper(I) complexes of oligophenanthroline ligands had been exploited to constitute topological crossover nodes in the

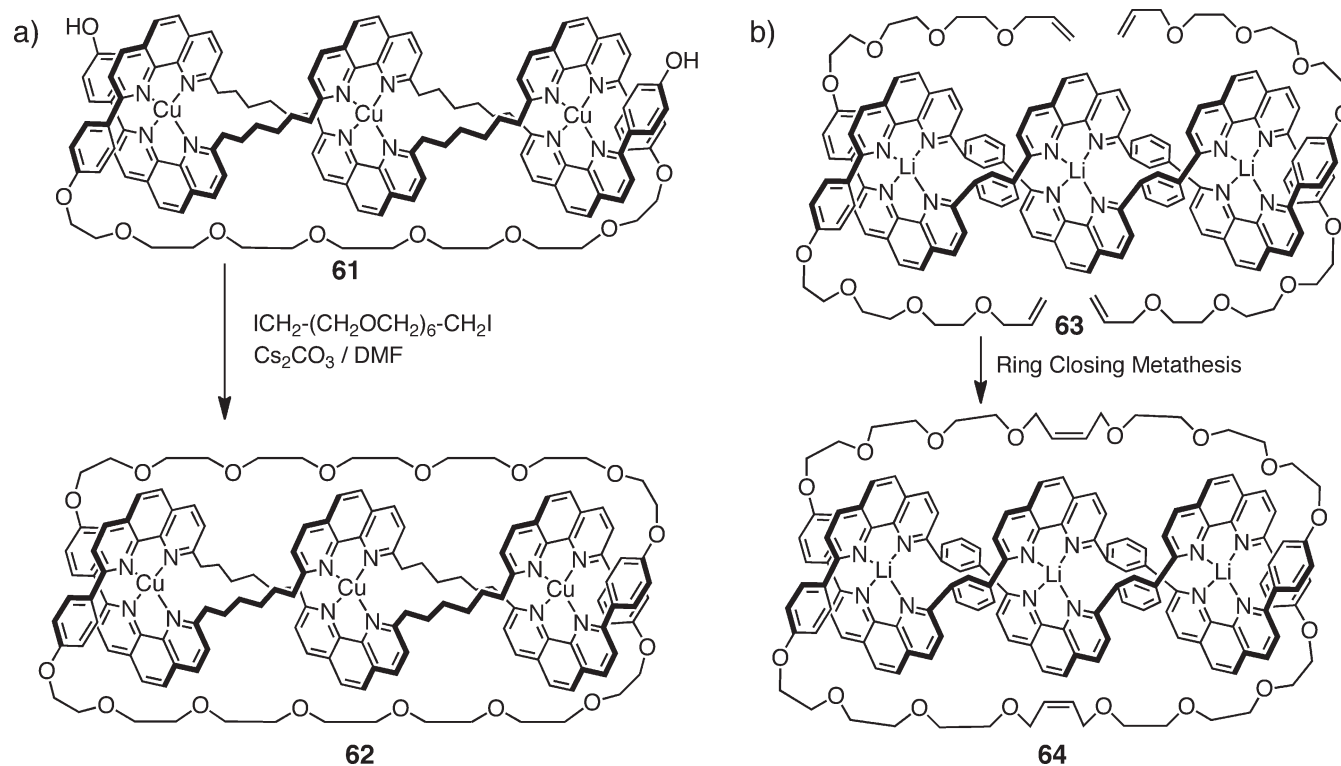


Figure 19. Synthetic routes to metal helicate templated Solomon Links. (a) Alkylation²³⁵ of a Cu(I)-templated trinuclear helical complex **61** comprised of a preformed macrocycle and a thread gave the corresponding Solomon Link **62** in 1.8% yield. (b) Ring-closing alkene metathesis of a Li(I) templated trinuclear helicate **63** comprised of two threads gave the analogous Solomon Link **64** in 30% yield.²³⁹

preparation of both [2]catenanes⁸⁷ (containing one Cu(I) cation) and Trefoil Knots¹⁷² (containing two Cu(I) cations), the next step, anticipated¹¹⁸ in the literature in 1990, was to design a system wherein two rings are linked by three Cu(I) cations in a doubly interlocked manner, to yield a molecular Solomon Link.

The first successful synthesis²³⁵ was dependent (Figure 19a) on the prior preparation of one of the macrocyclic components, comprising three 1,10-phenanthroline moieties linked by hexamethylene groups and cyclized with a heptaethylene glycol chain. Addition of a linear tris-phenanthroline oligomer, again with the three coordinating units linked by hexamethylene groups, and three equivalents of Cu(I) led, not only to the desired helical precursor **61**, but also to additional complexes, which could not be separated. Cyclization with heptaethylene glycol gave the molecular Solomon Link **62** in 1.8% yield, alongside other macrocyclic compounds, but only after extensive chromatography had been carried out on demetalated reaction mixtures. Attempts²³⁷ to prepare the same species by forming a trinuclear double helix from 2 equiv of the linear

tris-phenanthroline ligand and 3 equiv of Cu(I), followed by a double macrocyclization, were not successful.

The structure of **62** was confirmed by comparison with its topological isomer, the singly interlocked [2]catenane, which was also isolated from the reaction mixture. While the ESI mass spectra of both compounds are very similar, subjecting²³⁸ the materials to FAB-MS, which involves a harsher ionization source, results in much more pronounced fragmentation of the more highly strained Solomon Link in comparison with the [2]catenane. The ¹H NMR spectra of each species are also significantly different; the restricted motion of the rings of the strained and crowded Solomon Link in CD₃SOCD₃ leads to a very broad room temperature ¹H NMR spectrum, which can only be resolved at 390 K, whereas the spectrum of the [2]catenane in CD₃SOCD₃ is sharp and well resolved at room temperature.²³⁷

The 1.8% yield of the prototypical link **62** was bettered²³⁹ by an order of magnitude, by employing (Figure 19b) Li(I) cations in the formation of the helical precursor and utilizing Ru-catalyzed ring-closing alkene metathesis in the macrocyclization step. The influence¹⁷⁹ of the subtle modification of the spacer in the bis-phenanthroline ligand on the yield of related Trefoil Knots was already known to be significant. Replacing the hexamethylene groups of the linear tris-phenanthroline compound with *meta*-phenylene bridges gave a ligand that formed a trinuclear double helical complex **63** quantitatively with three Li(I) cations. The appended terminal alkene functions allowed the use of ring-closing alkene metathesis¹⁸¹ to generate, in 30% yield, the lithiated Solomon Link **64**, which was purified after ion-exchange with Cu(I) cations. Reduction of the C=C double bonds, present as a mixture of *cis* and *trans* configurations, resulted in a mixture of (*P*) and (*M*) topological enantiomers of the link.

The above example represents the best yielding synthesis of a molecular Solomon Link by a stepwise protocol reported in the literature to date. To increase the yield and simplify the synthetic procedures, several “all-in-one” approaches have been conceived and implemented.

3.3. “All-in-One” Approaches to Molecular Solomon Links

Subsequently, molecular Solomon Links have been prepared by “all-in-one” approaches, which rely upon the reversibility and error-checking inherent to coordination-driven dynamic self-assembly processes. A collaboration between Fujita and the Strasbourg group²⁴⁰ utilized the structure-directing properties of bis-phenanthroline-copper(I) moieties in concert with pyridine coordination to ethylenediamino-palladium(II) units to form (Figure 20) a doubly interlocking [2]catenane quantitatively. An eight-component self-assembly process in CD₃CN solution generates the Solomon Link **68**, while the competing formation of the singly interlocked [2]catenane **67** is disfavored because of its highly strained nature.

The use of dialkynyldigold(I) compounds in forming macrocyclic species underpins a remarkable study by Puddephatt,^{236,241} which led to the solution of the first crystal structure (Figure 21a) of a Solomon Link. A series of versatile, alkyne-substituted bisphenol ligands were prepared, and, in combination with chelating phosphine ligands, macrocyclic Au(I) complexes were synthesized. Simple modification in the “hinge” region of the bisphenol ligands has a dramatic effect on the topological construct that is formed: five different hinge groups provide two simple macrocycles, two [2]catenanes, and, when a

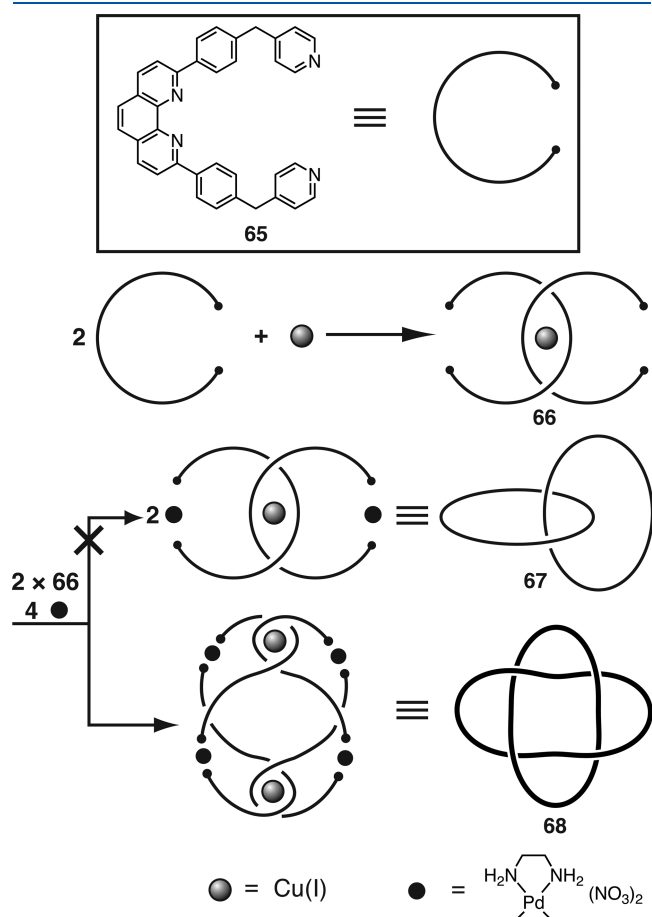


Figure 20. Simplified scheme for the “all-in-one” preparation²⁴⁰ of Cu(I) and Pd(II)-templated Solomon Links by a self-assembly process involving four ligands **65**, four Pd(en) corners, and two Cu(I) ions. Two ligands can form a tetrahedral complex **66** with one Cu(I) cation, but the pendant pyridine groups cannot be linked by Pd(en) corners to form the corresponding [2]catenane **67**, presumably because the resultant geometry is highly strained. Instead, two molecules of **66** complex with four Pd(en) corners to form the Solomon Link, **68**. Redrawn with permission from ref 240. Copyright 1999 American Chemical Society.

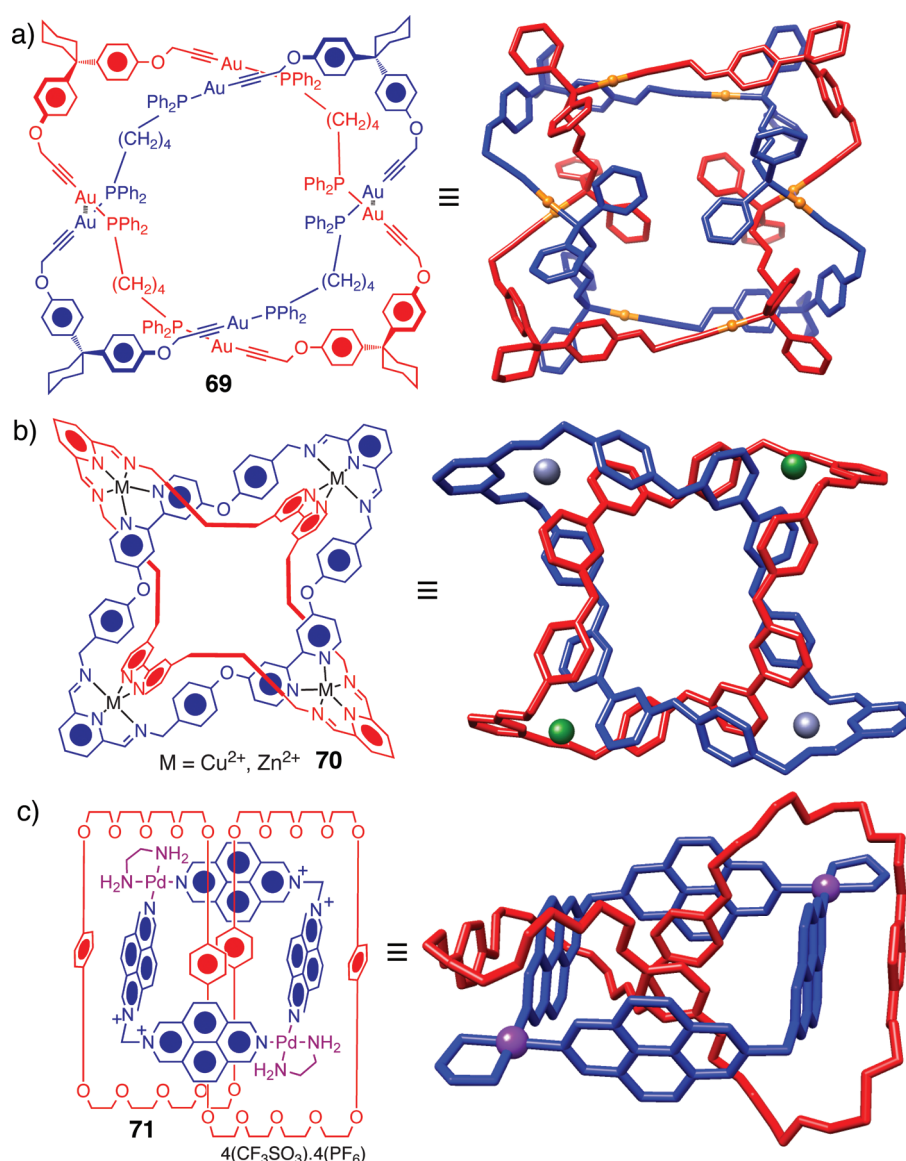


Figure 21. Examples of Solomon Links prepared by the "all-in-one" approach, with schematic diagrams on the left and tubular displays of the corresponding solid-state structures on the right. Counterions and hydrogen atoms are removed for clarity, and the two rings of the link have been depicted in red and blue. Au(I), Zn(II), Cu(II), and Pd(II) ions are represented as yellow, silver, green, and purple spheres, respectively. (a) The Au(I)-templated Solomon Link **69** prepared by Puddephatt.²³⁶ Crystal structure redrawn from CCDC deposition 145603. (b) A Solomon Link **70**, which was templated²⁴² by a mixture of Cu(II) and Zn(II) ions and crystallized from a dynamic library of interlocked species. Redrawn from CCDC deposition 617801. (c) A donor–acceptor Solomon Link **71**, which is also templated by Pd(II) coordination chemistry, prepared by Peinador and Quintela.²⁵⁴ Redrawn from CCDC deposition 728058.

cyclohexylidene hinge is employed, one doubly braided [2]catenane **69**. Inspection of the solid-state structure (Figure 21a) of **69** shows aurophilic interactions between the Au(I) cations of each ring of the assembly. It also exposes the effect of the hinge group on the orientation of the aryl units of the bisphenol linker; changes in geometry imposed by the hinge affect the capacity for attractive aryl–aryl interactions and are more than likely responsible for the formation of the different species in both solution and solid states. The crystal structure of **69** also illustrates perfectly the chirality of the molecular Solomon Link; both enantiomers are present in equal proportions in the solid-state structure.

In 2007, the isolation²⁴² of a Solomon Link was reported utilizing a versatile ligand system, which had previously been used

to synthesize molecular Borromean Rings (vide infra). By harnessing the reversibility and thermodynamically controlled error-checking of both dynamic covalent chemistry^{243–248} and transition metal templating,^{249–252} a compound, wherein two identical macrocycles present four *exo*-bidentate bipyridyl and four *endo*-tridentate diiminopyridyl ligands to four divalent transition metal cations and which exhibited the doubly interlocking topology characteristic of the Solomon Link, was prepared. When a mixture of Zn(II) and Cu(II) was used to template the assembly, a methanolic solution was shown to contain a dynamic interconverting library of molecular Solomon Links and Borromean Rings, from which the Solomon Link **70** (Figure 21b) crystallized preferentially. Although the paramagnetic Cu(II) ion precluded characterization by ¹H NMR spectroscopy, the structure was

unambiguously determined by X-ray crystallography, with supporting evidence from ESI-MS. When the diamagnetic Zn(II) cation was used²⁵³ as the sole source of metal template, the Borromean Ring compound was the predominant product, with a small amount of the molecular Solomon Link also in admixture, as indicated by ¹H NMR spectroscopy in CD₃OD. When crystals were grown from a 3:1 (v/v) mixture of *n*PrOH and MeOH, the Solomon Link compound could be isolated as crystalline octahedra. The distinct difference in crystal habit of each species allowed isolation of the Solomon Link by manual separation and subsequent full characterization by ¹H NMR spectroscopy, ESI-MS, and X-ray crystallography; the solid-state structure is isomorphous with the mixed metal species 70.

Peinador and Quintela²⁵⁴ have used a combination of donor–acceptor interactions and Pd(II) coordination chemistry to prepare a molecular Solomon Link (Figure 21c). When the electron rich crown ether, tetrakis-*para*-phenylene[64]crown-20, is combined with 2 equiv each of a diazapyrene-based ligand and [Pd(en)(OTf)₂] in CD₃CN, an electron-deficient metallocyclophane self-assembles around the crown ether quantitatively to form the doubly interlocked [2]catenane 71. The solid-state

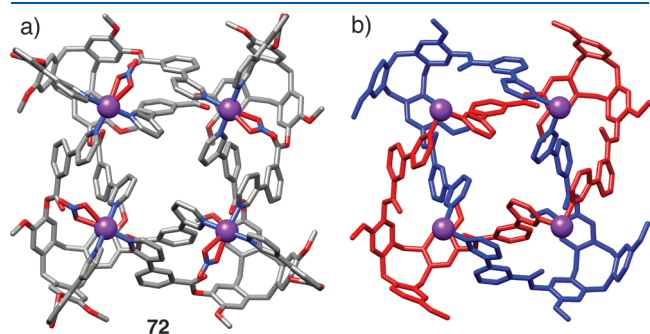


Figure 22. (a) A tubular rendition of the solid-state structure²⁵⁸ of Hardie's Pd(II)-templated "Solomon's Cube" 72. (b) A pared-down version of the solid-state structure illustrating the Solomon linkage, with the loops colored blue and red and the Pd(II) cations rendered as purple spheres. One arm of the cyclotriguaiaacylene ligand and the nitrate ligands have been removed for clarity. Solvent molecules and hydrogen atoms are removed in both cases for clarity. Redrawn from CCDC deposition 710515.

structure reveals multiple CH \cdots O contacts between the two rings, complementing the π – π stacking interactions which template the assembly.

The four-crossing [2]catenane motif has also been identified in more complex settings; a small number of infinite structures that contain the Solomon Link motif as part of their extended frameworks have been solved.^{255–257} In addition, Hardie²⁵⁸ has prepared (Figure 22a) the topologically complex compound 72, based on Pd(II) coordination to a tris-pyridyl cyclotriguaiaacylene ligand, which reveals a doubly interlocked [2]catenane motif (Figure 22b) with further links between the interlocking rings. The sides of the complex are replete with figure-of-eight motifs and, because the assembly resembles a cube, it has been described as a "Solomon's Cube". Three sources of chirality exist within the molecule, (i) the cyclotriguaiaacylene ligand itself, which is used as a racemic mixture, (ii) the Solomon linkage, and (iii) the figure-of-eight rings, and the solid-state structure contains two isomers displaying opposite handedness of all three chiral elements; that is, they are enantiomers. Interestingly, the complex cations pack into a hexameric stellated octahedral assembly, which is homochiral.

This final example illustrates the power of the all-in-one approach for preparing complex interlocked architectures, although in some cases the outcome may be the result of serendipity, rather than of rational design. With few examples arising from stepwise synthetic approaches to date, it is clear that the added complexity of the molecular Solomon Link necessitates the use of all-in-one strategies. All of the examples to date utilize the directionality and reversibility of metal-templation in their assembly: these features remain powerful tools in the arsenal of topologically minded chemists. Although further molecular Solomon Links will no doubt arise using this protocol, a challenge for the future is to prepare molecular Solomon Links employing alternative methods of templation.

4. BORROMEAN RINGS

4.1. Background

The Borromean Rings represent yet another example of a link that has been adopted into human iconography. The three interlocking, but noncatenated, macrocycles that comprise the Borromean Rings²⁵⁹ are arranged in a Brunnian link, wherein

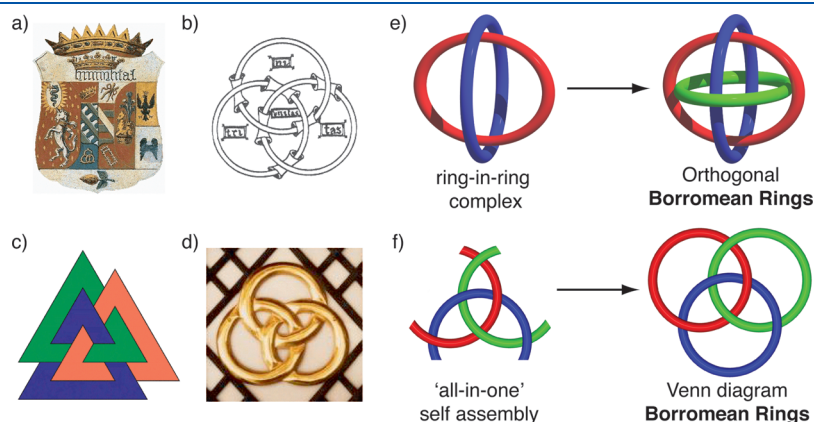


Figure 23. Examples of Borromean Rings depicted²⁶² in art, religion, and science. (a) As the symbol of the Borromeo family of Renaissance Italy, the topology appears on their family crest. (b) The three interlocked rings represent the Christian Holy Trinity. (c) The Norse Walkknot of the slain has the Borromean topology. (d) Shinto Buddhism visualizes the three realms of earth, heaven, and the underworld within the three rings. (e) Schematic diagram illustrating the stepwise ring-in-ring approach to preparing molecular Borromean Rings. (f) Schematic diagram showing the "all-in-one" approach to synthesizing molecular Borromean Rings. Modified with permission from ref 262. Copyright 2005 American Chemical Society.

scission of one ring leads to the dissociation of the other two. In the Anderson–Briggs notation, the Borromean Rings are described as a 6^3_2 link. While their name derives from their association with the Borromeo family of Renaissance Italy—the assembly can be identified as part of their family insignia—the Borromean Rings date from a much earlier period.²⁶⁰ The three rings embody (Figure 23a–d) the intertwining of the Holy Trinity of Christian iconography, they comprise the Norse Walkknot of the slain, and they are also found in ancient Asian cultures.¹²⁷ In a more frivolous and modern context, Borromean Rings are found on the company logo of Ballantine's beer, linking the purity, body, and flavor of the alcoholic beverage.²⁶¹

The aesthetic beauty of the assembly, which has inspired its rich culture and history, has also led to attempts to synthesize molecular Borromean Rings, a not insignificant challenge. Once again, two main strategies (Figure 23e,f) have been explored²⁶² toward the assembly of molecular Borromean Rings: (i) the

stepwise “ring-in-ring” approach, wherein one macrocycle is threaded perpendicularly through another, followed by the appropriate threading and closing of the final ring, and (ii) the “all-in-one” approach, wherein a strict self-assembly protocol allows the threading and knitting of all three rings together in one fell swoop. Other potential methods of synthesis have been proposed, but, to our knowledge, have not been put to the test.

4.2. The “Ring-in-Ring” Approach to Molecular Borromean Rings

Early attempts to prepare Borromean Rings relied on the “ring-in-ring” approach. It is important to note that the geometry associated with the ring-in-ring complex, which is formed in the first step, is of particular significance if the components of the third ring are to be threaded through the assembly in a topologically appropriate manner; the two rings must be perpendicular to one another, and not just a simple macrocycle-in-macrocycle complex,

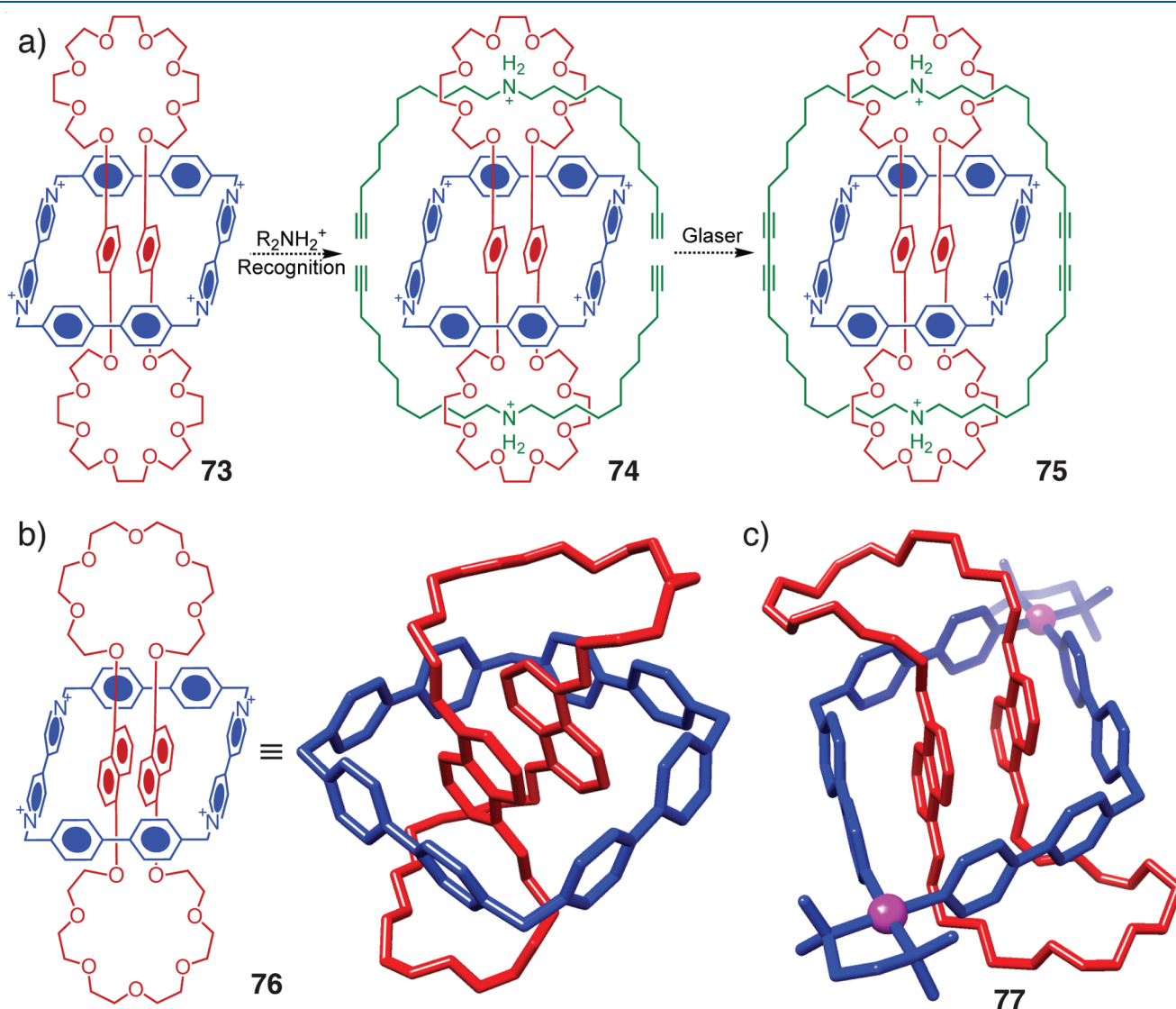


Figure 24. (a) A hypothetical ring-in-ring synthetic route to molecular Borromean Rings first proposed by Busch et al.,⁶⁴ which involves a donor–acceptor ring-in-ring complex 73. The complex constrains long polyether loops that could, in an idealized world, subsequently bind dialkylammonium ion components of a third ring to form 74, which could, at least in principle, be cyclized into molecular Borromean Rings 75. (b) Schematic diagram and tubular representation of the solid-state structure²⁷⁷ of a related ring-in-ring complex 76. (c) Tubular representation of the solid-state structure²⁷⁸ of a similar ring-in-ring complex 77 wherein a self-assembling metallomacrocycle comprises one of the rings.

of which there are many examples in the literature.^{263–273} A “ring-in-ring” strategy was, we believe, first proposed in the literature in 1999 by Busch⁶⁴ as part of a review addressing template-directed synthesis. The strategy (Figure 24a) relies on the formation of a donor–acceptor ring-in-ring complex **73** wherein the electron-deficient cyclophane, cyclobis(paraquat-4,4'-biphenylene),²⁷⁴ encircles two electron-rich aromatic units of a large crown ether, such as bis-*para*-phenylene[52]crown-16. The polyether loops of the crown ether are expected to be located above and below the cyclophane, constrained in a manner similar to the smaller crown ethers, which have a well-established propensity^{275,276} to encircle secondary dialkylammonium ions. Ideally, threading of alkyne-terminated dialkylammonium units, followed by oxidative acetylenic coupling^{193,194} of the appropriate ends of each unit, would comprise the final threading and ring-closing steps to afford the molecular Borromean Rings **75**.

Despite the early release of this proposed synthetic scheme, no progress has been reported until the very recent publication describing the assembly²⁷⁷ of the ring-in-ring complex **76** formed between cyclobis(paraquat-4,4'-biphenylene) and bis-1,5-dinaphtho[50]crown-14. A ring-in-ring complex (Figure 24b) was indeed formed both in solution as well as in the solid state, but

the crystal structure reveals features that suggest that threading of the dialkylammonium components of the final ring would not be highly favored. Numerous CH \cdots O interactions between the polyether loops of the crown ether and the rim of the cyclophane result in the folding down of the crown ether framework onto the cyclophane. Clearly, these interactions would have to be broken to permit the threading of the dialkylammonium ions as a first step toward molecular Borromean Ring formation. A similar ring-in-ring complex **77** has also been prepared²⁷⁸ using an electron-deficient metallocyclophane, not unlike that employed by Peinador and Quintela²⁵⁴ in their synthesis of the Solomon Link **71**. The crystal structure (Figure 24c) of **77** is once again dominated by CH \cdots O interactions, which mask the potential recognition site that could be associated with the polyether loops. These examples demonstrate the necessity of a strategy with wholly orthogonal binding motifs to allow sequential binding of the various components of the molecular Borromean Rings.

Ring-in-ring complexes have also been prepared successfully using transition metal templated approaches (Figure 25a,b). Schmittel²⁷⁹ has employed the tetrahedral bis-phenanthroline copper(I) coordination synthon to assemble **78**. Further modifications of the design would be required, however, to provide

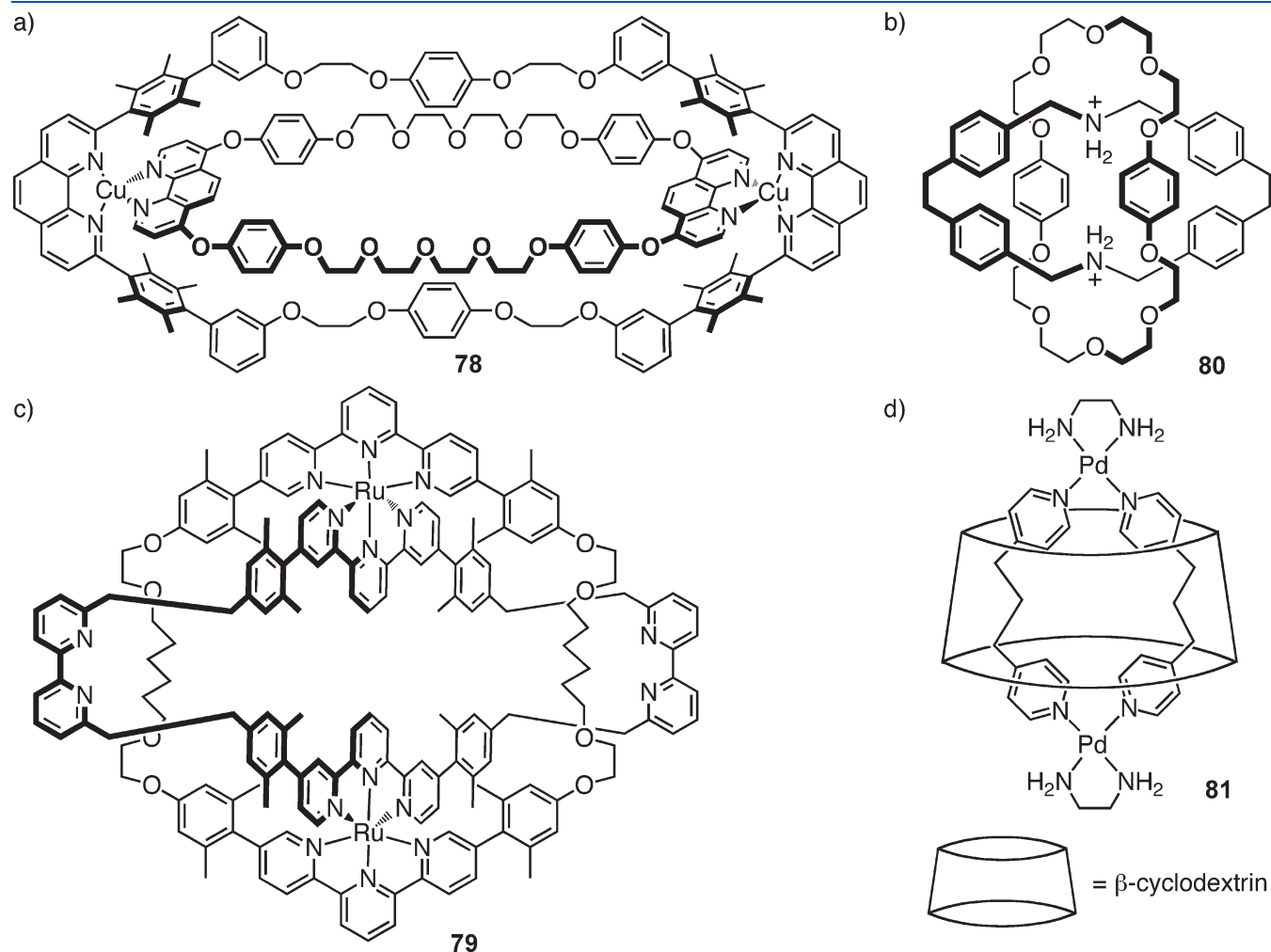


Figure 25. Schematic diagrams of ring-in-ring complexes. (a) A Cu(I)-templated²⁷⁹ ring-in-ring complex **78**. (b) A Ru(II)-templated²⁸⁰ species **79** with auxiliary binding sites for threading a third macrocycle to form Borromean Rings. (c) A ring-in-ring complex **80** based on the hydrogen-bonding interaction between dibenzylammonium cations and crown ethers.²⁸¹ (d) A self-assembled Pd(II) macrocycle that is encapsulated by β -cyclodextrin to form²⁸² the ring-in-ring complex **81**.

recognition motifs for the final macrocycle. Siegel²⁸⁰ has also prepared the Ru(II)-templated ring-in-ring complex **79**. A bis-terpyridine macrocycle was synthesized, and, when two linear Ru(II) terpyridine complexes are bound following the loss of labile chloride ligands, a [3]pseudorotaxane is formed. Capping both ends of the linear threads of the assembly with bipyridine units completed the ring-in-ring assembly, leaving a free coordination site through which to arrange the components of a third ring with the appropriate geometry and topology. Despite this initial foray, there have been no reports of further progress toward molecular Borromean Rings using this particular recognition motif.

Hydrogen-bonding interactions can also be invoked to form ring-in-ring complexes. In the knowledge²⁷⁶ that the crown ether bis-*para*-phenylene[34]crown-10 can accommodate two dibenzylammonium cations, the bis-dibenzylammonium macrocycle was prepared²⁸¹ and shown to form a ring-in-ring complex **80** with the crown ether in solution as well as in the solid state (Figure 25c). Liu²⁸² has also prepared a ring-in-ring complex **81** by utilizing the labile Pd–N bond and the binding properties of β -cyclodextrin. Two flexible bis-pyridyl ligands can be simultaneously encapsulated within the β -cyclodextrin macrocycle, forming a [3]pseudorotaxane bearing pyridyl units that are free to coordinate to Pd(en) synthons, forming (Figure 25d) the ring-in-ring assembly.

As ring-in-ring complexes become more prevalent in the literature, it will become increasingly likely that molecular Borromean Rings will be the outcome of this nascent area of research. Appropriate design of the assembly is vital to a successful synthesis; each recognition motif must be fully orthogonal from the others to allow the required self-assembly processes to occur.

4.3. “All-in-One” Approaches to Borromean Rings

The “all-in-one” approach has provided the only successful routes to the synthesis of molecular Borromean Rings reported in the literature so far. Borromean linkages^{283–297} have been identified in framework solids, largely as a result of the diligence of Ciani and co-workers²⁸³ in identifying these and other complex motifs retrospectively in coordination networks previously described in the literature. Discrete molecular Borromean Rings, however, represent a much more challenging research goal. Seeman,²⁹⁸ following on from his early accomplishments in preparing Trefoil and Figure-of-Eight Knots from DNA, once again exploited the predictability of the Watson–Crick base-pair interactions and the helical turns inherent to DNA in the preparation of molecular Borromean Rings. When projecting a three-dimensional image of the Borromean Rings with mutually perpendicular rings on a surface, the six crossover points of the three rings, the nodes, arrange themselves as complementary alternating $+/-/+/-$ sequences. The double helical turn of DNA can be represented as a crossing point, or node, and Seeman’s design (Figure 26) replaced each node, or “unit tangle”, with three half-turns of DNA rather than one, because the resulting oligonucleotides are more tractable on this length scale.²⁹⁹ By redrawing the Venn diagram of the Borromean Rings in this manner, one can appreciate the fact that the inner three helices are right-handed, corresponding to B-DNA, and the three outer helices are left-handed, corresponding to Z-DNA. The opposite handedness of the helical turns also corresponds to the equal number of positive and negative crossings that constitute the Borromean Link. The synthesis of two sets of three DNA strands, which were combined separately into two

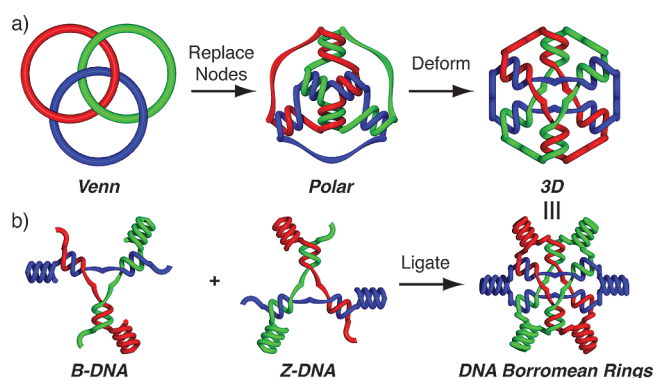


Figure 26. (a) Deformation of a Venn diagram representation of Borromean Rings into a 3D structure with double helical regions. (b) The synthetic approach employed by Seeman et al.²⁹⁸ in the synthesis of DNA Borromean Rings by the ligation of two three-arm junctions comprised of B-DNA and Z-DNA. Modified with permission from ref 262. Copyright 2005 American Chemical Society.

appropriate junctions and then combined and annealed, led to the formation²⁹⁸ of the DNA Borromean Rings.

This particular topology contains a total of 18 crossings—the simplest Borromean link contains six—making it the third member of a family of Borromean links.²⁵⁹ In an elegant demonstration (Figure 27) of the Borromean topology, specifically targeted enzymes allowed exclusive cleavage of each ring of the assembly in a series of experiments, with gel electrophoresis showing the results of ring scission to be the two remaining, noncatenated DNA macrocycles and the linear elements of the cleaved ring.

Metal-templation is also capable of underpinning an “all-in-one” strategy wherein the complementary alternating $+/-/+/-$ sequences of the rings are replaced by *exo/endo/exo/endo* chelation sites. The directionality^{249–252} resulting from transition metal templation, combined with the reversibility and thermodynamic error checking associated with dynamic covalent chemistry,^{243–248} led to the design³⁰⁰ of a Zn(II)-templated compound (Figure 28a) with 12 reversible imine bonds wherein three identical macrocycles present, diagonally in pairs, (i) six *exo*-bidentate bipyridyl chelates and (ii) six *endo*-tridentate diimino-pyridyl ligands to six divalent metal cations in a Borromean topology. Using Zn(II) as the source of the metal template, the molecular Borromean Rings **84** are indeed formed in the remarkable yield of 95%. They were characterized by ¹H NMR spectroscopy and ESI MS, and the Borromean topology was confirmed beyond doubt by X-ray crystallography (Figure 28b). Depending on the nature of the crystallization solvents, a small amount of a related Solomon Link can also be obtained and separated by fractional crystallization.²⁵³

The simplicity of this design, along with the ease of access to the precursors **82** and **83**, has led to the gram-scale preparation³⁰¹ of molecular Borromean Rings in a setting suitable for introduction into undergraduate teaching laboratories. The ability to synthesize large quantities of **84**, along with many substituted derivatives (Table 2), has also initiated a significant appraisal of the properties of this new architecture. In deference to the terminology wherein metal-templated catenanes, which retain their metal cation(s), are referred to as “catenates”⁹² while the demetalated analogues are called “catenands”,¹⁷¹ it has been proposed³⁰² that molecular Borromean Ring compounds containing transition metal templates be known as “Borromeates”

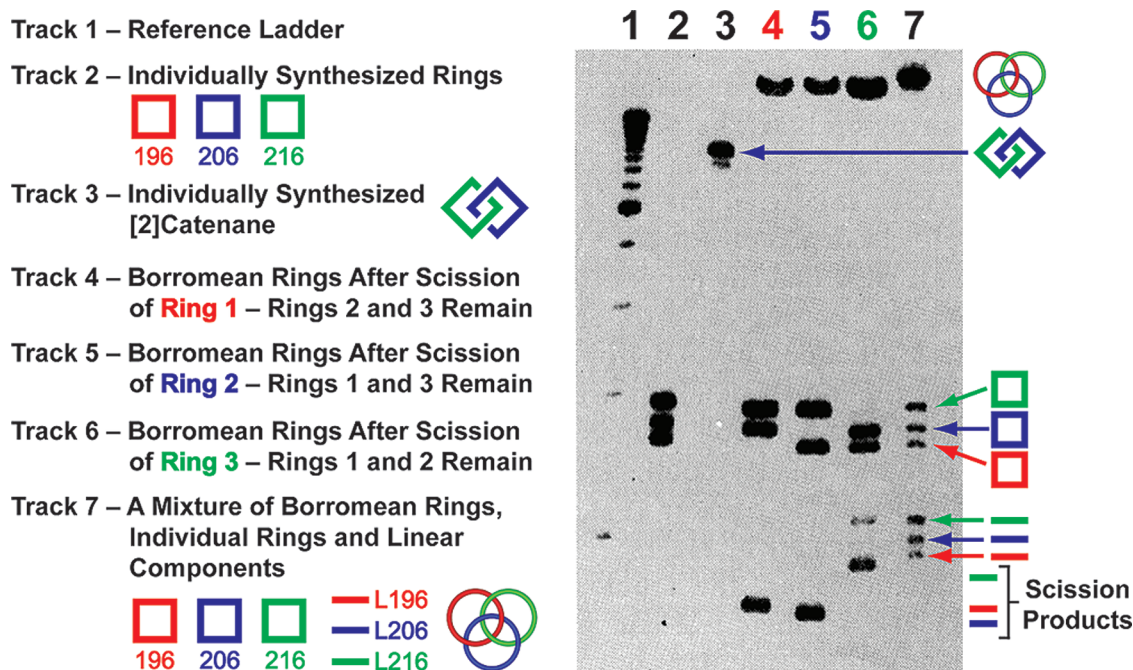


Figure 27. Analysis, by gel electrophoresis, of the DNA Borromean Rings prepared by Seeman et al.²⁹⁸ Track 1 is a reference ladder, while track 2 is a mixture of the three individually synthesized rings of 196, 206, and 216 nucleotides, rendered red, blue, and green, in turn. Track 3 is the [2]catenane formed from the latter two oligonucleotide macrocycles. Tracks 4, 5, and 6 show the DNA Borromean Rings and the products of the targeted digestion of one of the constituent DNA macrocycles. When one ring is excised, all that remains is the other two rings and the linear scission product of the cleaved ring, i.e., no catenated products result, elegantly demonstrating the Brunnian topology of the DNA Borromean Rings. Finally, track 7 is a mixture of the DNA Borromean Rings, the component macrocycles, and their linear precursors. Adapted with permission from ref 298. Copyright 1997 Macmillan Publishers Ltd.

while their metal-free analogues be referred to as “Borromeands”. Borohydride reduction of the imine bonds of **84**, followed by removal, using EDTA, of zinc from the resulting structure, led to the formation³⁰² of the Borromeand, which was analyzed by ¹H NMR spectroscopy and ESI-MS. Interestingly, the fully reduced single ring could also be identified upon reduction, while, as expected, no catenated products resulted, a further chemical proof of the Borromean Ring topology.

The dynamic nature of the Borromean Ring topology was also investigated, with particular focus being placed on the

reversibility resulting from imine bond formation and hydrolysis. Many factors influence the solution equilibria, most dramatically the competitive formation²⁴² of a molecular Solomon Link when, for example, equal amounts of Cu(II) and Zn(II) are utilized as the metal templates. The mixed-metal Solomon Link **70** and the analogous Borromean Rings (which could not be isolated) interchange at room temperature in methanol, as shown by ESI-MS, but no equilibrium between the two topologies exists when only Zn(II) is used as a template. The stability of Zn(II)-only Borromeates becomes evident when derivatives

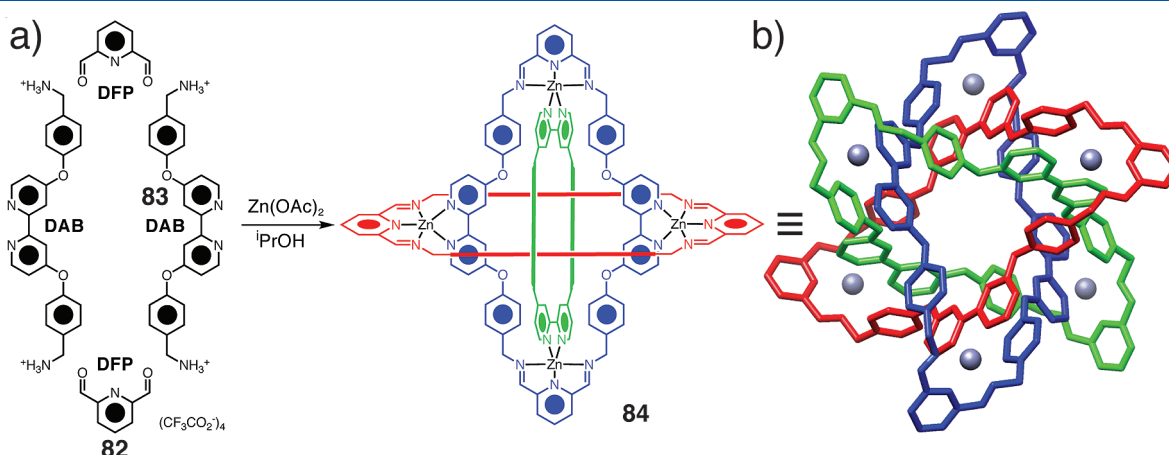
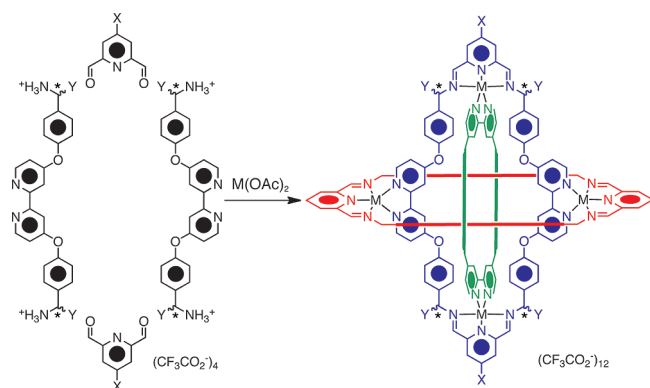


Figure 28. Molecular Borromean Rings.³⁰⁰ (a) Schematic diagram to illustrate the synthesis in *i*PrOH of the Zn(II)-templated assembly **84** from Zn(OAc)₂, diformylpyridine (DFP, **82**), and the diaminobipyridine compound (DAB, **83**), which is generated in situ from its Boc-protected precursor (Boc-DAB) by deprotection with trifluoroacetic acid. (b) Tubular representation of the solid-state structure of **84** with each individual ring colored red, blue, and green and the Zn(II) cations depicted as silver spheres. Hydrogen atoms, solvents, and counterions are removed for clarity, generated from CCDC deposition 231701.

Table 2. The Range (84–99) of Borromeanates Prepared to Date^a

Entry	Metal	X	Y	Yield	Reference
84	Zn(II)	H	H	95%	300
85	Cu(II)	H	H	85%	253
86	Co(II)	H	H	36%	253
87	Mn(II)	H	H	70%	253
88	Cd(II)	H	H	80% ^b	253
89	Zn(II)	Cl	H	95%	303
90	Zn(II)	Br	H	95%	303
91	Zn(II)	Cl/Br (1:1)	H	95%	303
92	Zn(II)		H	97%	304
93	Zn(II)		H	89%	304
94	Zn(II)		H	85%	306
95	Zn(II)		H	83%	306
96	Zn(II)	Cl	(<i>R, R</i>) CH ₂ OH	83%	307
97	Zn(II)	H	(<i>S, S</i>) CH ₂ OH	86%	307
98	Zn(II)	H	(<i>R, R</i>) CH ₂ OH	85%	307
99	Zn(II)	Cl	(<i>S, S</i>) CH ₂ OH	57%	307

^a Variables include substitution of both precursor ligands and changing the transition metal template employed in the synthesis. ^b The value is the crude yield, which also contained appreciable amounts of a Solomon Link byproduct.

with chloro (89) and bromo (90) substituents on the *endo*-diiminopyridyl ligand (position X in Table 2) are mixed together.³⁰³ Combining the two Borromeanates in methanolic solution at room temperature for 2 weeks resulted in no exchange of the diiminopyridyl ligands. In fact, heating the methanolic solution at 60 °C for 5 days, along with the addition of small amounts of trifluoroacetic acid, is required to bring about the scrambling of the *endo* ligands.

The propensity of this Borromean Ring topology to undergo substitution³⁰⁴ has led to the preparation of many derivatives, including a thioether-bearing Borromeanate 92, whose conductance in gated double-barrier tunneling junctions formed using the electrical breakjunction technique on gold nanowires has been investigated.³⁰⁵ A Borromeanate 94, bearing pendant alkene groups on the *endo* ligands, has been prepared and can be post-synthetically modified³⁰⁶ by olefin metathesis. It has also been possible to introduce³⁰⁷ substituents into the *exo* bipyridyl ligand (position Y in Table 2) in the form of stereogenic centers. The enantiopure Borromeanates 96–99 were prepared as both the (*S*) and the (*R*) enantiomers, starting from the corresponding (*S*)

and (*R*) ligands, and display strong and opposite circular dichroism behavior. The crystal structure of the (*R*)-Borromeanate 96 demonstrates that the chirality of the 12 stereogenic centers is transferred to the coordination sphere of the six Zn(II) templates, which show significant distortion from the near-perfect octahedral environment observed in the solid-state structure of the prototypical, unsubstituted Zn(II)-Borromeanate 84.

Related solid-state structures have been observed independently by Schröder³⁰⁸ and Schmittl³⁰⁹ when Cu(I) cations are used to link pyridine appended bipyridine and phenanthroline ligands, respectively. In each case, three rings appear to be linked in a Borromean topology. On closer inspection of the crystal structures, however, each Cu(I) cation was found to be an intrinsic component of one ring while being coordinated to an adjacent ring, meaning that, while they are reminiscent of Borromean Rings, the complexes have a different topology.

The complexity of molecular Borromean Rings is such that the only reported syntheses that fulfill the topological requirement have been as a result of DNA and transition metal templation. To the best of our knowledge, the only stepwise strategy that has been pursued is the ring-in-ring approach. The prevailing opinion seems to be that threading of two rings together is reasonably easy to achieve, while assembling the final third ring is a much more daunting task. New, ingenious architectures will no doubt result as this goal is realized.

5. MORE COMPLEX ENTITIES

Despite the significant advances in chemical topology over the past 50 years, the most complex knot prepared to date remains a DNA Figure-of-Eight Knot. Moreover, there exist no more than a handful of molecular Solomon Links, and only one non-DNA approach has produced molecular Borromean Rings. Obviously, as the complexities of the knots and links grow along with their number of nodes, the design and syntheses of their molecular analogues become several orders of magnitude more difficult. Symmetrical systems simplify the design process, with a prime example being the synthesis²⁵³ of both a Solomon Link and Borromean Rings from the same macrocycle. We can speculate that future synthetic achievements will no doubt center on targets of this nature.

Despite the difficulties involved, reports of more complex interlocked species, which cannot be classified as simple links or knots, continue (Figure 29) to appear in the literature. Triply interlocked cages have been prepared by metal cation^{310,311} and sulfate anion³¹² templation, and they have also been self-assembled covalently³¹³ during crystallization without the apparent need for an external template. A quadruply interlocked metallohelicate has also been reported,³¹⁴ while Böhmer et al.^{315,316} have prepared spectacular quadruply interlocked assemblies from urea-functionalized calix[4]arene scaffolds. Vögtle et al.³¹⁷ have assembled a self-complexing figure-of-eight molecule, essentially a [2]rotaxane wherein the termini of the encircled rod are attached covalently to the opposite ends of the ring component. Ravels have also been proposed³¹⁸ as novel interlocked topological entities, which do not correspond either to knots or links: they are composed of single vertices of three or more degrees, with mutual weaving of the edges emerging from the vertex. Lindoy et al.³¹⁹ reported very recently the isolation of a molecular universal 3-ravel through Fe(III)-templated self-assembly of linked β -diketonato ligands, a discovery that will no

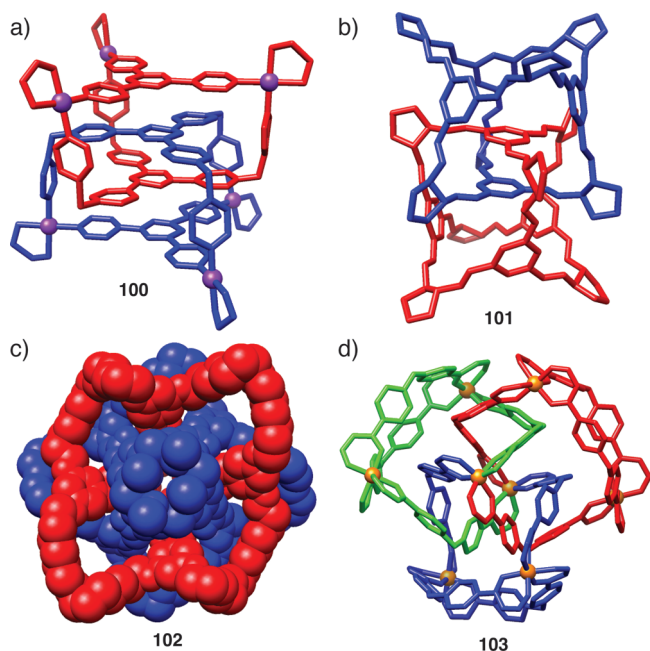


Figure 29. Highly complex interlocked species, which cannot mathematically be described as simple knots or links. (a) Tubular representation of the solid-state structure of a triply interlocked $[2]$ catenane **100** prepared by Fujita.³¹⁰ Each ring shown in blue and red, Pt(II) cations as purple spheres. Hydrogen atoms, solvent molecules, and counterions have been removed for clarity. Redrawn from CCDC deposition EDIBOI. (b) Tubular representation of the solid-state structure of a triply interlocked $[2]$ catenane **101**, which self-assembles³¹³ without the need for an external template by virtue of reversible imine bonds. Each ring shown in blue and red, hydrogen atoms and solvent removed for clarity. Redrawn from CCDC deposition 765992. (c) Space-filling representation of the solid-state structure of a quadruply interlocked species **102** templated³¹⁶ by hydrogen-bonding interactions between urea-modified calix[4]arenes. Each ring shown in blue and red, hydrogen atoms and solvent removed for clarity. Redrawn from CCDC deposition 791999. (d) Tubular representation of the solid-state structure of a molecular universal 3-ravel **103** prepared³¹⁹ from linked β -diketonato ligands and templated by Fe(III) cations, with each “arm” of the ravel colored individually red, blue, and green, and the Fe(III) cations colored orange. Counterions, hydrogen atoms, solvent, and terminal *t*-Bu groups of the ligands have been removed for clarity. Redrawn from CCDC deposition 230612.

doubt prompt further investigation into these complex yet beautiful interlocked entities.

Synthetic routes toward higher order knots and very complex woven species have been suggested,⁶⁵ but attempts to synthesize more complex knots remain few and far between. The double helical approach employed successfully in the making of Trefoil Knots and Solomon Links could feasibly be used to prepare species of higher complexity (Figure 30).¹¹⁸ For ligands with n metal coordination units, if n is an even number, knots with the Alexander–Briggs notation $(n+1)_1$ result, and if n is an odd number, $(n+1)_1^2$ links are the outcome. In the wake of the synthesis of $[2]$ catenanes, Trefoil Knots, and Solomon Links from n -oligophenanthroline ligands where $n = 1, 2$, and 3 , in turn, attempts have been made to synthesize molecular versions of the Pentafoil Knot, 5_1 , and the so-called “Star of David” catenane, the 6_1^2 link that comprises a star-shaped, triply interlocked $[2]$ catenane with six crossing points. These species require ligands where $n = 4$ and 5 , respectively, molecules that represent considerable synthetic challenges in themselves. During

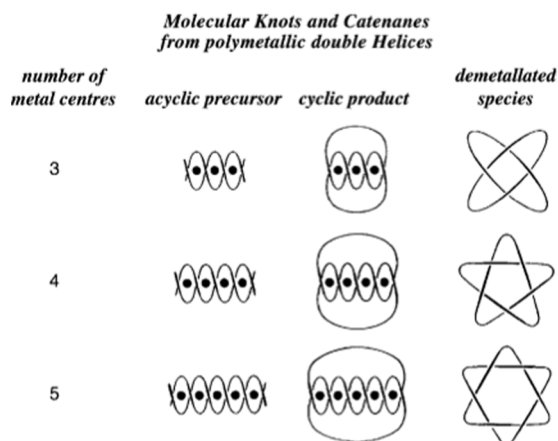


Figure 30. Schematic diagram illustrating the various knots and links, which can be prepared from oligo-helicate molecules. This diagram was first published¹¹⁸ in 1990, but, as far as we are aware, the Solomon Link remains the most complex species prepared by this strategy, to date. Reprinted with permission from ref 118. Copyright 1990 American Chemical Society.

the preparation³²⁰ of the tetrakis- and pentakis-phenanthroline oligomers, it was found that the Cu(I) complexes of the tetrakis ligand constituted a mixture of inseparable compounds, reflecting the relative kinetic inertness of the metal centers. When Li(I) was used to form the helical complexes, both ^1H NMR spectroscopy and ESI-MS analysis indicated the formation of tightly wound tetranuclear and pentanuclear double helices; the ease of loss of a Li(I) cation in the pentanuclear species during electrospray ionization was particularly indicative of the strained nature of the helix. Attempts to form the molecular Pentafoil Knot and Star-of-David catenane, by ring-closing metathesis of alkene-terminated double helical Li(I) complexes, were unsuccessful, perhaps due to the length (28 Å for the pentanuclear double helix) of the helices, which distances the alkene functions that must be linked. Attempts to prepare these more complex topological entities continue.

Another topologically interesting species that may be amenable to synthesis is the Whitehead Link, otherwise described as the 5_2^2 link. Proposed initially by the mathematician J. H. C. Whitehead,³²¹ it is related to the Solomon Link in that it contains one further node or crossing point: it can be regarded as a five-crossing $[2]$ catenane. Fenlon¹³⁰ has speculated that this species could be obtained synthetically in a molecular form, and the differing graphical representations of the link point to synthetic strategies centered on metal coordination or a “ring-in-ring” approach.

6. CONCLUSIONS

The case histories discussed in this Review illustrate the wealth of covalent, coordinative, and supramolecular interactions utilized by chemists and biochemists when they are assembling molecular knots and links. Despite the numerous molecular topologies that have been described to date, it is clear that chemists have only scratched the surface in terms of the vast number of knots and links that are available for chemical synthesis. Obviously, the less complex topologies are much more amenable to molecular expression, and it seems likely that future synthetic efforts will be focused on those topologies that display higher degrees of symmetry.

In terms of the synthetic strategies that may be employed in the preparation of more complex interlocked topologies, we can build on

the experience of those who pioneered the synthesis of molecular Trefoil Knots, Solomon Links, and Borromean Rings. It is noteworthy that, as the complexity and number of crossing points increases, the synthetic approaches have relied much more heavily on the reversibility and error-checking inherent to thermodynamically controlled processes, be they reversible covalent, coordinative, or noncovalent bonds that are being formed and broken. It seems more than likely that future advances in topological chemistry will result from “all-in-one” approaches, rather than from the step-wise strategies that have served the field so effectively in the past. In any event, a wealth of topologically intriguing molecular compounds awaits the ingenuity and skill of forthcoming generations of synthetic chemists.

AUTHOR INFORMATION

Corresponding Authors

*Fax: (847) 491-1009. E-mail: j-sauvage@northwestern.edu (J.-P.S.); stoddart@northwestern.edu (J.F.S.).

BIOGRAPHIES



Ross Forgan received his MChem (Hons) degree from the University of Edinburgh, UK in 2004. He obtained his Ph.D. from the University of Edinburgh, UK in 2008 under the guidance of Prof. Peter Tasker, which included a stint at Massey University, Palmerston North, New Zealand, in the group of Dr. Paul Plieger. He is currently a postdoctoral fellow in the group of Prof. Fraser Stoddart at Northwestern University, U.S., where his interests include self-assembly, coordination chemistry, molecular topology, and metal–organic frameworks.



Jean-Pierre Sauvage was born in Paris (1944). He studied at the University of Strasbourg and earned his Ph.D. under the guidance of Prof. Jean-Marie Lehn in 1971. After postdoctoral research in Oxford, UK, with Prof. Malcolm Green, he came back to Strasbourg as a CNRS researcher. He founded his research group in 1980 and has been both a University Professor and a CNRS Director of Research. His research interests span from artificial photosynthesis and electron transfer, to porphyrin chemistry, molecular topology (catenanes and knots), and transition metal-based molecular machines. He is presently a Professor Emeritus of the University of Strasbourg and a Distinguished Visiting Scholar at Northwestern University, U.S.



Fraser Stoddart received all (B.Sc., Ph.D., D.Sc.) of his degrees from the University of Edinburgh, UK. Presently, he holds a Board of Trustees Professorship in the Department of Chemistry at Northwestern University, U.S. His research has opened up a new materials world of mechanically interlocked molecular compounds and, in doing so, has produced a blueprint for the subsequent growth of functional molecular nanotechnology.

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