A remarkable example of an optically pure molecular single helix that forms a supramolecular double helix in the solid state has been reported. Cyclopropanation of an enantiomerically pure 1,1′-bis(dispiro-[2.0.2.1]heptylidene-methanol) gives the enantiomerically pure di-ol **10.132**. The intrinsic molecular chirality of the helix results in a substantial optical rotation $[\alpha]_D^{20}$ of +691.2°. In the solid state two such helices come together by hydrogen bonding of the terminal alcohol units to give a supramolecular double helix, Figure 10.83a.[95] It is well established that particular heterocycles, notably series of directly connected pyridine and pyrimidine rings incorporated into a single molecule fold into extended helical structures (helical foldamers, *s.a.* Section 10.2.2). Lehn's group have reported a single helical foldamer shown in Figure 10.83b based on hydrazone, an isomorphic analogue of a pyridine group in such systems and much more readily incorporated from a synthetic standpoint. The example shown possesses $3^1/_3$ turns in the molecular helix and is held together by direct π-π stacking and hydrogen bonding.[96]

10.9 Molecular Knots

🗝 Lukin, O. and Vogtle, F., 'Knotting and threading of molecules: Chemistry and chirality of molecular knots and their assemblies', *Angew. Chem., Int. Ed.* 2005, **44**, 1456–1477.

10.9.1 The Topology of Knots

Chemical interest in knots dates back to a hypothesis of Lord Kelvin who suggested the atoms may be knotted forms of the aether – the undetectable substance postulated to form the medium through which light waves travel. This led the Scottish mathematician Tait to attempt a list of all possible knots and thus create a version of the periodic table of the elements. While Kelvin's theory turned out to be wrong, knot theory rapidly became assimilated into mathematics as part of the field of topology. It is ironic that 100 years after Kelvin's death (1907) cosmologists are again turning to knotted *superstrings* in attempts to explain the properties of fundamental sub-atomic particles.[97] Outside the chemical field, knots and interwoven figures have a long and distinguished history, often resulting in beautiful designs, such as the multiply interwoven lettering of the eighth century Celtic *Book of Kells*. The knot is the symbol of unbreaking links, as in the triply interlocked symbol of the powerful Italian Borromeo family, the Borromeo link, while the works of Dutch artist Cornelius Escher evoke superb (sometimes impossible) knotted geometric patterns, many of which are increasingly to be found in modern chemistry (Figure 10.84).

We have already encountered the field of chemical topology in our discussion of catenanes in Section 10.7.1. A [2]catenane is a *topological isomer* of two separated macrocycles and is characterised by having crossing points in its 2D graph set. We can distinguish topological isomers by imagining that the molecule of interest is placed on an infinitely flexible flat rubber sheet. The

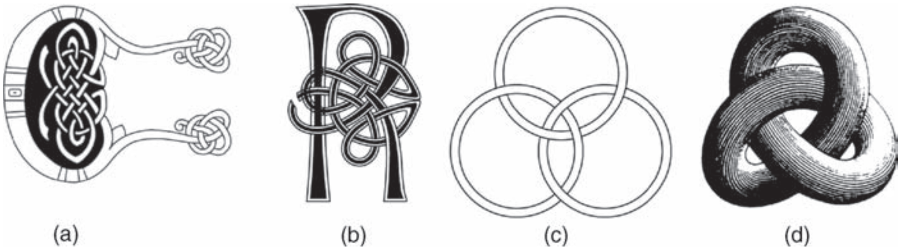


Figure 10.84 (a) and (b) Interlocked lettering from the eighth century *Book of Kells*. (c) The Borromeo family symbol. (d) The trefoil knot as viewed by Dutch artist M. C. Escher. (Copyright Wiley-VCH Verlag GmbH & Co. KGaA. Reproduced by permission).

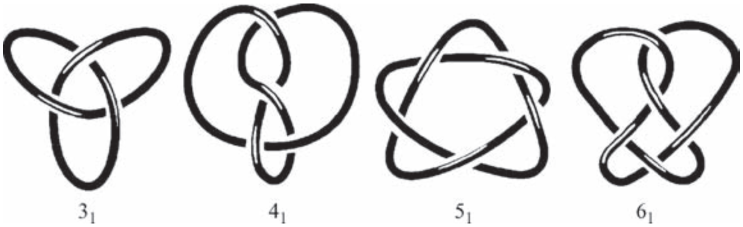


Figure 10.85 The first four prime knots. The number denotes the number of crossings, while the subscript is the order of the knot. (Reprinted with permission from [98]).

sheet and object can be stretched or bent in any way but lines (bonds) cannot be broken and no line can pass through another. Thus a square, triangle and circle are topologically equivalent to one another and even a [2]rotaxane can in principle (albeit not in practice) be unthreaded by infinite expansion of the ring so that it fits over the stopper. A catenane is, however, fundamentally different and cannot be untangled in this way. A similar situation pertains for knots which represent a fascinating intellectual challenge for chemists and give access to new structural motifs with interesting properties.

The auxiliary linkage approach to the synthesis of catenanes such as **10.103** (Section 10.7.5) in combination with the expanding body of knowledge concerning the related helicates (Section 10.8) has enabled the high-yield synthesis of a range of multiply interpenetrated complexes termed *molecular knots*. Unlike catenanes, prime knots are based upon a single-stranded loop. Knots are therefore topological isomers of macrocycles (Figure 10.54). We have already seen the early attempt by Schill and co-workers to prepare a molecular trefoil knot from the auxiliary **10.97**, which, while possibly successful, was plagued by difficulties associated with low yields in the multiple cyclisation steps. In fact, the trefoil knot is the first of many prime knots, the first four of which are shown in Figure 10.85. In addition to the directed approach of Schill, a number of early statistical and semi-statistical approaches to knot formation were proposed and attempted, without significant yield of knotted products being obtained.

In the natural world, numerous knotted and entwined forms of DNA strands are known and have been imaged by electron microscopy (Figure 10.86).[99] Knotted proteins such as lactoferrin and ascorbinic acid

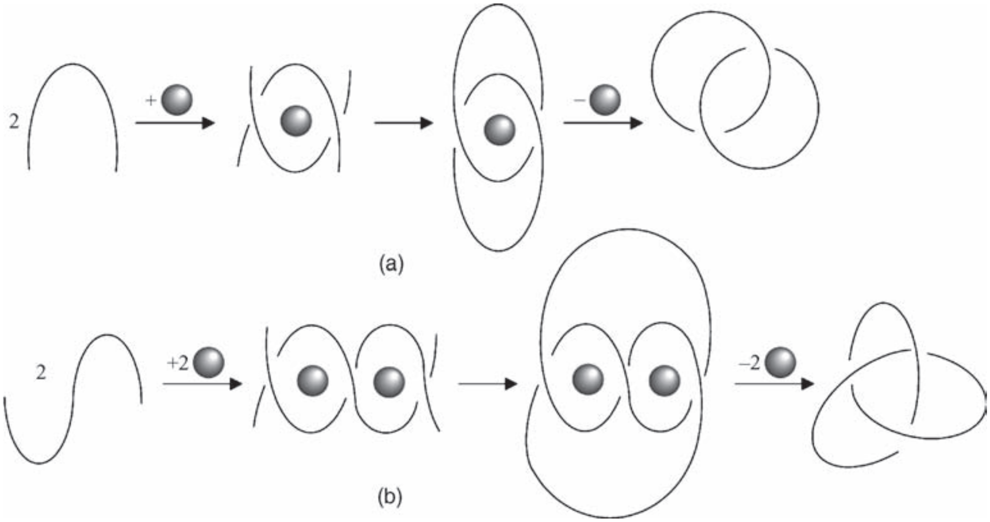
Figure 10.86 Electron microscope image of a loose DNA knot (reproduced from [99] with permission from AAAS).

oxidase possess remarkable biological activity in comparison to analogous linear proteins, respectively in iron(III) transport and in enzymatic oxidation. Modern synthetic polymers often derive mechanical strength from their intertwined nature. On the other hand, molecular modelling studies by Wasserman at the DuPont company have led to the suggestion that the strain at knot cross-overs in polymer strands may result in the entrance to the knot being the mechanical weak points in some polymer materials.[100] Clearly, if large enough macrocycles can be prepared, then there is no reason why knots should not be chemically stable, in the same way that catenanes are.

10.9.2 Trefoil Knots

Following on from the preparation of [2]catenate **10.103** (Scheme 10.27a), Sauvage realised[101] that replacing the single Cu(I) core in $[Cu(\mathbf{10.102})_2]^+$ with a bimetallic double helicate would result in a precursor that, if it was stable enough to be cyclised, would immediately give a trefoil knot *via* a double auxiliary linkage approach (Scheme 10.27b).

Accordingly, the diphenol helicand (**10.133a**) was designed with a flexible $—(CH_2)_4—$ linker between the two bonding domains. The ligand was prepared from 1,10-phenanthroline and $Li(CH_2)_4Li$ in several steps and then reacted with $[Cu(MeCN)_4]^+$ to give the helicate (**10.134a**). Following their catenane synthesis methodology, Sauvage then performed a double cyclisation reaction under high-dilution conditions to isolate the first synthetic trefoil knot (**10.135a**), after a lengthy chromatographic work-up, in 3 % overall yield. The knot was characterised by mass spectrometry and NMR spectroscopy. However, the closure of such a large ring (86-membered) is a statistically unlikely process, and a number of by-products were also present, all of them based on a chiral double helix. The definitive characterisation of the trefoil knot rested, therefore, on the removal of the metal centres with KCN to give the free ligands. Under these circumstances, only the knotted 86-membered ring possesses unconditional chirality, which was demonstrated. The other products, 86- and 43-membered macrocycles,



Scheme 10.27 **(a)** Schematic diagram of the synthesis of a [2]catenane *via* the auxiliary linkage approach. **(b)** Extension of this approach to the formation of a trefoil knot *via* a bimetallic double helicate.[101]

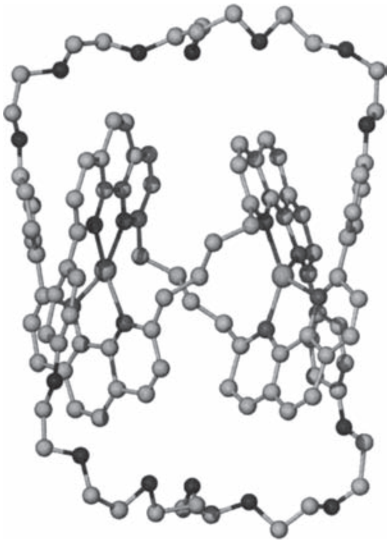
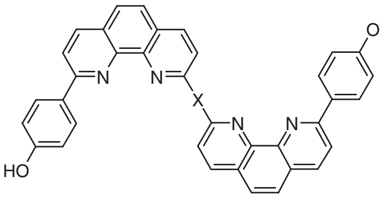


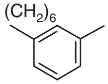
Figure 10.87 X-ray molecular structure of the trefoil knot **10.135a**.[102]

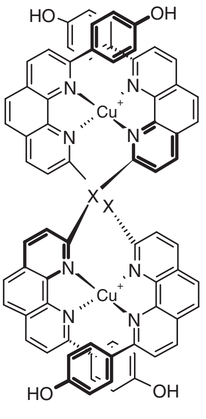
are achiral in the absence of the helix-templating metals. The formation of the knot was confirmed later by an X-ray crystal structure determination (Figure 10.87).[102]



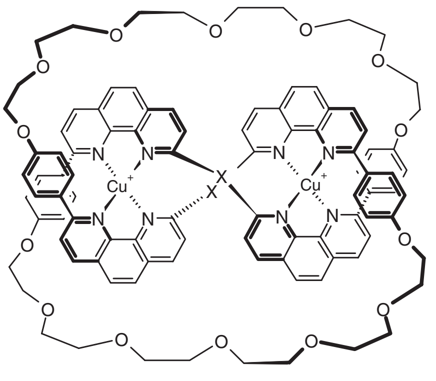
10.133

a X = $(CH_2)_4$
b X = $(CH_2)_2$
c X = $(CH_2)_6$
d X =





10.134



10.135

While ingenious, the low yield of **10.135a** left significant room for improvement. Particular problems identified were the competing formation of non-helical face-to-face 2 : 2 complexes during the helicate-formation step, and the spatial arrangement of the four reaction ends of **10.134**. Accordingly, Sauvage's group tried a number of other helicand ligands with a variety of spacers 'X' (**10.133b–d**) in the hope of improving overall yields. They also varied the length of the polyethyleneglycol chain used in the cyclisation step. Virtually all of the compounds tried yielded knots of type **10.135**. For **10.133b** and **10.133c**, yields were again low, the best being 8 %, obtained for X = $(CH_2)_6$ with a pentaethyleneglycol chain, to give an overall 84-membered knotted macrocycle. In contrast, yields of up to 24 % were obtained for the unknotted macrocyclic topological isomers. The more rigid ligand **10.133d** proved much more promising,

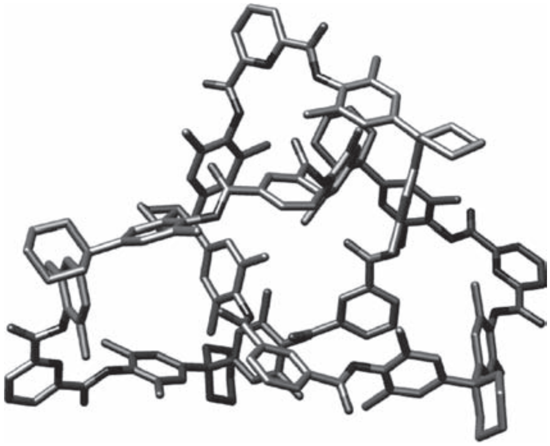


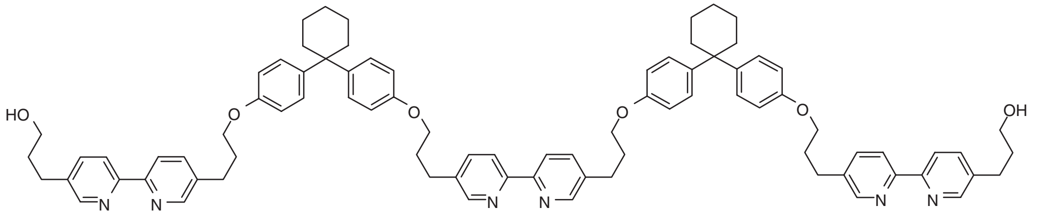
Figure 10.88 X-ray crystal structure of a hydrogen-bonded trefoil knot produced in a one-pot synthesis.[104]

giving the trefoil knot **10.135d** in an overall 29 % yield after chromatography. This is a sufficient yield to allow the study of some of the knotted compound's properties and the full characterisation by NMR and FAB (fast atom bombardment—a relatively gentle ionisation technique) mass spectrometry. The reason for this greatly improved yield is not entirely clear, but it may well be related to the compound's compact geometry. The X-ray crystal structure of the precursor **10.134d** gives a Cu···Cu separation of 4.76 Å, compared to values of 6.30 and 7.00 Å for the knots with $(CH_2)_4$ and $(CH_2)_6$ spacers, respectively.

In principle a trefoil knot could also be templated using a single, octahedral metal centre and indeed this has been achieved by self-assembly of a linear tris(bidentate) strand about octahedral Zn(II). Thus reaction of the linear ligand **10.136** gives an 'open' trefoil knot based on a tris(bidentate) zinc centre. The knot has been characterised in solution and in the solid state and its formation is fully reversible, consistent with the principles of self-assembly. Thus, addition of chloride which coordinates to the Zn^{2+} centre regenerates the free ligand **10.136**, while the trefoil knot re-forms upon removal of the chloride with Ag^+ (to give insoluble AgCl).[103]

A remarkable one-pot self-assembling synthesis of a 96-atom backbone trefoil knot was reported in 2000 by the group of Fritz Vögtle (Bonn, Germany). The knot comprises just twelve amide functionalities and is derived from essentially the same reaction discussed in chapter 6 as a synthesis of a *p*-quinone host (Scheme 6.13). The reaction is carried out under high dilution with a pre-formed diamide arising from the reaction of two diphenylmethane derived diamines with 2,6-pyridine dicarboxylic acid dichloride and gives the covalent knot in 20 % yield along with the 2+2 and 4+4 macrocycle products. The X-ray structure of this knot, which is templated *via* intramolecular hydrogen bonding without the use of a metal template, is shown in Figure 10.88.[104]

Finally, a trefoil knot has also been reported based on Stoddart's 'blue box' donor-acceptor stacking templating methodology (Section 10.7.3).[105]



10.136

10.9.3 Other Knots

The potential exists of using the highly versatile helicate-based approach of Sauvage to continue to prepare more and more highly knotted and interlinked species. As a general rule, we can show that, in this approach, if the number of metal centres is even, then the number of crossings of the molecular loop will be odd. In this case, odd numbers of crossings are necessary in order to generate a knot. Thus two metal centres give the trefoil knot, four a pentafoil, six a heptafoil *etc.* On the other hand, odd numbers of metal centres will generate even numbers of crossings and give rise to doubly interlocked [2]catenanes (Figure 10.89).

Synthetically, Sauvage's group have been able to extend this work as far as three metal centres, giving rise to the (unconditionally chiral) doubly interlocked [2]catenate **10.137**.[106] The synthetic procedure is similar to those employed for the trefoil knots **10.135** and singly interlocked [2]catenane **10.103**, and involves a double high-dilution ring-closure of two 60-membered rings by Cs_2CO_3-catalysed reaction of the two diphenol precursor threads with $ICH_2(CH_2OCH_2)_6CH_2I$ in dimethyl formamide at 60°C. Unsurprisingly, the reaction is not very clean. It is a tribute to the consummate skill of the researchers involved that, after extensive chromatographic work-up, a 2 % yield of the product was isolated and characterised by NMR spectroscopy and careful mass spectrometry. Similar careful work has resulted in the synthesis of some composite knots as diastereomeric mixtures, including a double trefoil.[107]

The scope of synthetic 'higher knots' is relatively limited at present because of the tremendous synthetic challenges involved. However, we have already seen that natural system forms knots readily and DNA is a particular good candidate as a knot template because of its double helical nature. The knot-forming tendencies of DNA have been exploited particularly by the group of Nadrian C. Seeman (New York, USA) to produce by design using both self-assembly and deliberate manipulation (*e.g.* by

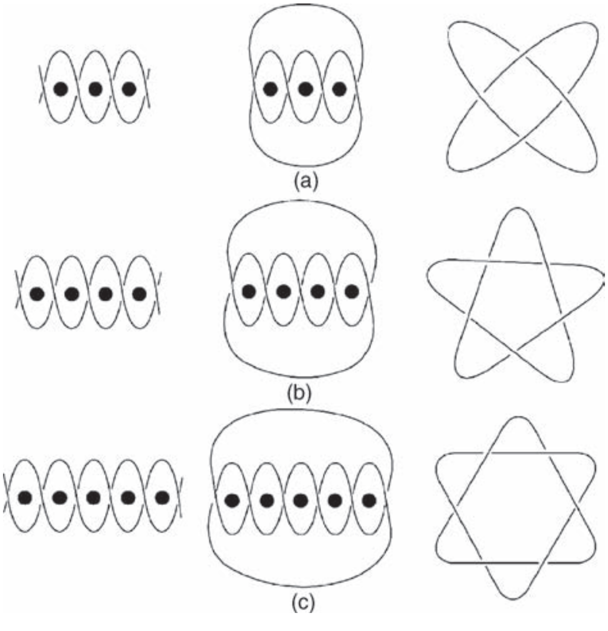
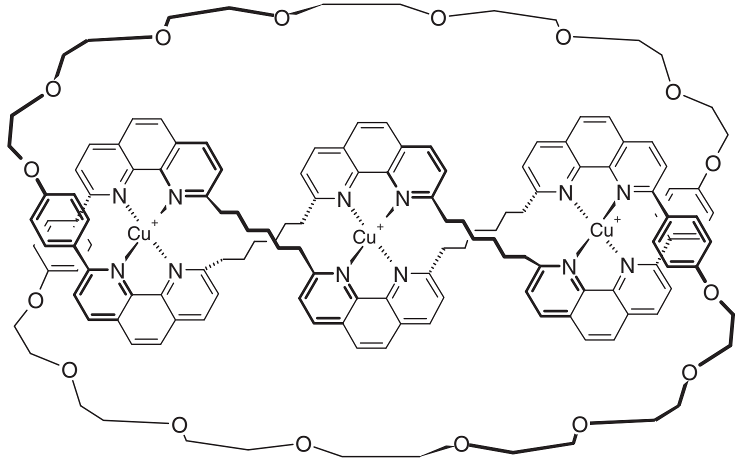


Figure 10.89 Conceptual production of increasingly interlocked species through the use of multimetallic helicates. (a) Doubly interlocked [2]catenane from three metal centres. (b) Pentafoil knot from four metal ions. (c) Triply interlocked [2]catenane. (Reproduced with permission from [98]).



10.137

optical tweezers) DNA-based knotted and topologically complex structures. It is well established that DNA forms well-behaved right- (B-form) or left-handed (Z-form) double helical structures depending on the base sequence (*cf.* Section 2.9). Seeman's group designed and prepared a DNA single strand comprising a total of 104 nucleotide bases. The strand contains regions (A, A′, B and B′) with 11 or 12 complementary base pair sequences (*i.e.* A is complementary to A′, B is complementary to B′) that cause it to self-assemble into specifically either B- or Z-helices.[108] The sequences are linked by oligo-thymidine spacers. Self-assembly is induced and controlled by the concentration of Mg^{2+} ions in conjunction with the inert $[Co(NH_3)_6]^{3+}$ resulting in the formation of a DNA macrocycle, a left- and a right-handed trefoil knot and a figure-of-eight knot (Figure 10.90). This work makes clever use of restriction enzyme cleavage strategies to confirm the topological properties of the products since conventional spectroscopic or diffraction methods are not useful in studying these very large assemblies. This basic approach has been used to give other very sophisticated DNA assemblies such as a cube, a truncated octahedron and even a Borromeo ring arrangement. We will look at other self-assembling strategies towards the enduringly popular Borromeo rings in the next section.[109]

Finally another interesting class of entanglement, *ravels*, distinct from knots has recently been recognised as at least a theoretical possibility. A ravel tangles a planar graph in the vicinity of a vertex whereas knots lie within cycles in the graph. The simplest kind of ravel is shown in Figure 10.91. It is postulated that ravels may be recognised in MOFs or DNA type structures in the future and they offer a tantalising new challenge to the synthetic chemist.[110]

10.9.4 Borromean Rings

🗝 Cantrill, S. J., Chichak, K. S., Peters, A. J. and Stoddart, J. F., 'Nanoscale Borromeo rings', *Acc. Chem. Res.* 2005, **38**, 1–9.

The three interlocked rings of the Borromeo symbol (Figure 10.84c) are an enduring and popular symbol of unity that features widely in heraldry and iconography. None of the three rings penetrates either of the other two in the way a catenane does, nevertheless they are topologically interlocked and cannot be separated without breaking one of the rings. However, if any one ring is removed the other two can be immediately separated intact. The Borromeo rings represent a particularly difficult

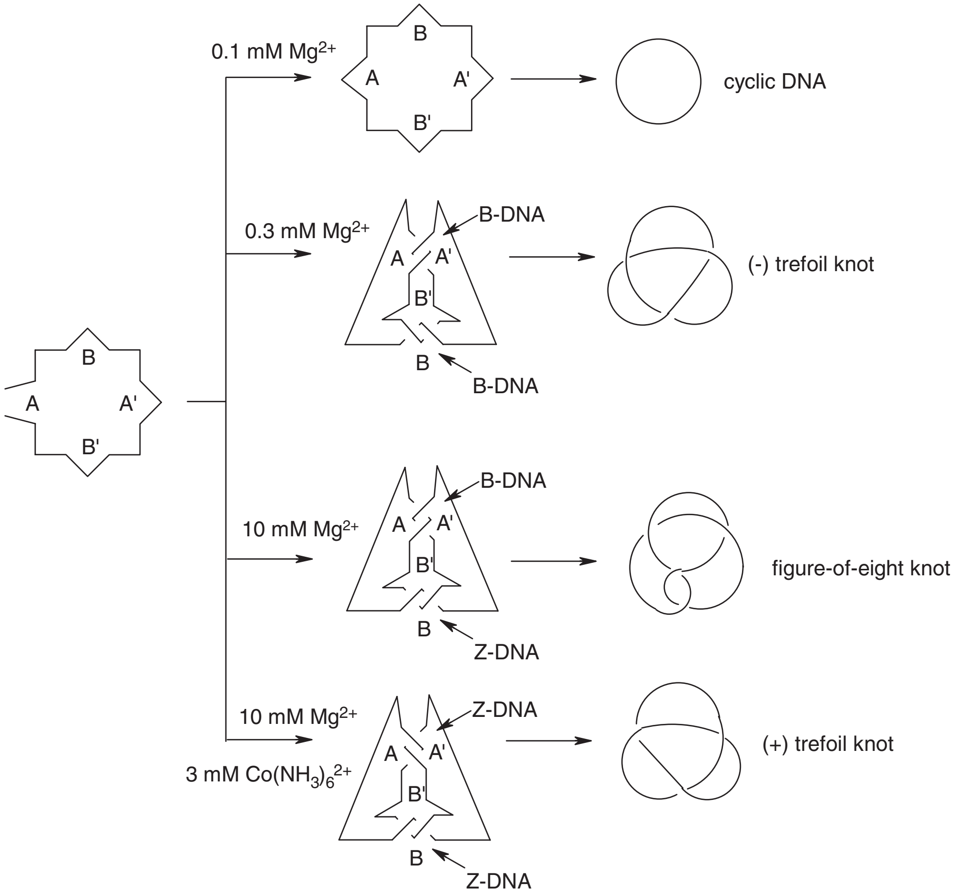


Figure 10.90 Self-assembly of DNA knots.[108]

synthetic challenge since three separate macrocycles must be interlocked simultaneously. While DNA-based Borromeo rings were first synthesised in 1997,[109] it was not until 2004 that the self-assembly of a discrete artificial Borromeo ring compound (a zinc(II) based 'Borromeate') was realised by Stoddart's group at UCLA. The synthesis is based on the thermodynamic assembly of two kinds of error-checking,

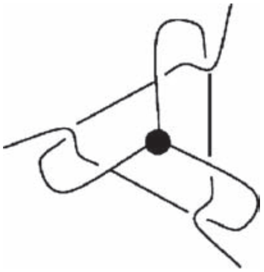
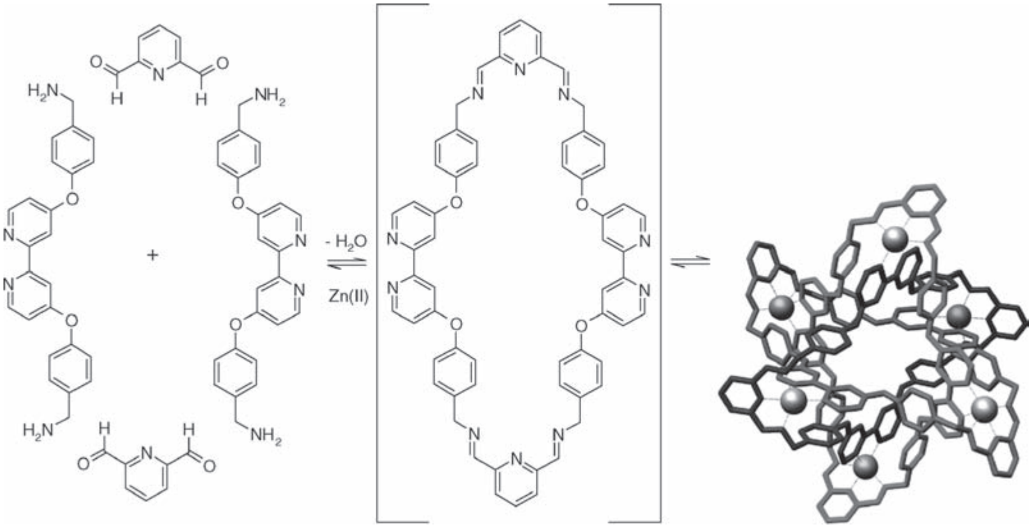


Figure 10.91 The simplest kind of ravel based on a 3-connected vertex. While none of the three threads are knotted or catenated, pulling on all three of them simultaneously results in an entangled unit distinct from the analogous unravelled 3-connected node.[110]



Scheme 10.28 Self-assembly of a 2.5 nm wide Borromeo ring complex showing the product's X-ray molecular structure.[112]

reversible interaction – coordination of ligands to relatively labile Zn^{2+} ions and reversible imine bond formation by Schiff base condensation, Scheme 10.28. The system was designed to give complete cross complementarity between the exo (bidentate) and endo (tridentate) sites in the final complex such that exo only matches with endo and *vice versa*. The use of Zn^{2+} is important too since zinc(II) commonly forms five-coordinate complexes. The assembly proceeds in a remarkable 80 % yield in the final one-pot self-assembly step to give the hexanuclear Borromeate, which was characterised by X-ray crystallography, Scheme 10.28. There is some evidence for the templation of the assembly by a seventh Zn(II) ion situated at the centre of the assembly. Interestingly, while the Borromeo complex is the major product, carrying out the reaction with a 1:1 mixture of zinc(II) and copper(II) acetates gives a product of different topology – a tetrametallic *Solomon knot*, Figure 10.92. The Solomon knot can be isolated by careful crystallisation because it is less soluble then the Borromeo complex.[111]

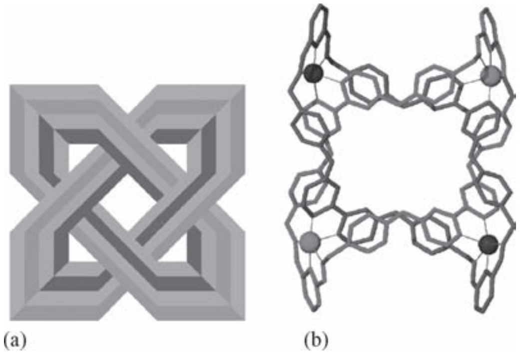


Figure 10.92 (a) a stylistic rendering of a Solomon knot and (b) X-ray structure of the chemical Solomon's knot.[111]

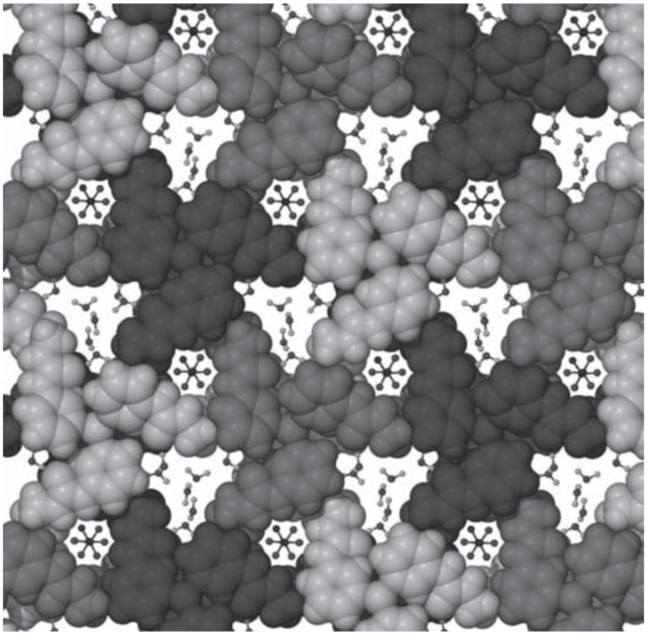


Figure 10.93 A coordination polymer Borromeo weave containing water guests in the open cavities and supported by saturated hydrogen bonding to nitrate anions.[113] See plate section for colour version of this image.

In addition to DNA-based and discrete coordination complex systems, the Borromeo rings also make an appearance in a few coordination polymers. As discussed in Section 9.5.6 it is possible to isolate crystalline solids comprising three separate, distinct interlocked infinite coordination polymer mesh sheets in which the holes in one mesh are occupied by the strands of the other two sheets in a Borromeo fashion. Such motifs are termed 'Borromeo weaves'. In the last chapter we saw in Figure 9.38 a Borromeo weave linked together by argentophilic interactions. A Borromeo weave able to contain guests such as discrete water clusters or solvents such as methanol or acetonitrile, all supported by saturated hydrogen bonding to nitrate anions is shown in Figure 10.93.

Summary

- Self-assembly is the *spontaneous and reversible association of molecules or ions (tectons) to form larger, more complex supramolecular entities according to the intrinsic information contained in the molecules themselves.*
- Fundamentally self-assembly is a *convergent* process in which a number of components assemble into, ideally, a single final, stable structure. Self-assembly is thus very distinct from chemical *emergence* which is a divergent process in which complexity evolves over time.
- Self-assembly can comprise a number of hierarchical levels, *j*. The lifetime of each self-assembled stage (τ) is inversely proportional to its position in the hierarchy, thus the highest stages are much longer lived than the stages below them, *i.e.* $\tau_j >> \tau_{j-1}$.
- Self-assembly can be divided into a number of classes; 1. strict self-assembly, 2. irreversible self-assembly, 3. precursor modification followed by self-assembly, 4. self-assembly with post-modification, 5. assisted self-assembly, 6. directed self-assembly, 7. self-assembly with intermittent processing.