Pergamon

Tetrahedron 55 (1999) 5265–5293

TETRAHEDRON

Tetrahedron report number 490

Supramolecular Topology

Gloria A. Breault,[b] Christopher A. Hunter [a,*] and Paul C. Mayers [a]

[a] Krebs Institute for Biomolecular Science, Department of Chemistry, University of Sheffield

Sheffield S3 7HF, UK

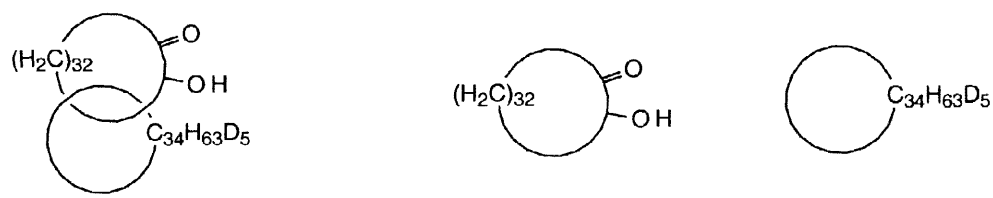
[b] Zeneca Pharmaceuticals, Mereside, Alderley Park, Macclesfield, Cheshire SK10 4TG, UK.

Received 9 March 1999

Contents

AN INTRODUCTION TO CHEMICAL TOPOLOGY

Traditionally, chemists have described the structure of organic molecules in terms of the number and types of atoms they contain and the sequence and nature of bonding between those atoms. It was soon realised that two molecules could contain the same atoms linked in a different sequence and such a pair of molecules are described as constitutional isomers. Somewhat later, it became clear that even when molecules contained the same atoms and bonds, it was still possible for isomers to exist. Variations in the spatial arrangement around an atom or other centre can lead to stereoisomers.[1] Over the years, many special forms of isomerism have been identified as the range of molecules prepared has become more complex, but almost all are variants upon one of these fundamental types. The first molecule whose structure could not be absolutely described by considering these factors was reported by Frisch and Wasserman in 1961.[2] They synthesised a molecule consisting of two interlocked rings,



1 **2** **3**

Figure 1. The catenane **1** is a topological isomer of the two macrocycles **2** and **3**.

* *E-mail: C.Hunter@Sheffield.ac.uk FAX: +44 114 2738673*

PII: S0040-4020(99)00282-3

which they termed a catenane (Figure 1). The two rings in the linked catenane structure did not differ in any way from the unlinked macrocycles in terms of the atoms or bonds they contained, yet clearly the two systems were chemically distinct. It was to describe this difference that the term topological isomerism was introduced. The two structures were then said to be topological isomers. The synthesis and study of such topologically complex molecules is often referred to as topological stereochemistry,[3] and here we review progress in this field over the past 40 years.[4,5]

Before going on to discuss topology in chemistry, it is worth briefly considering some of the basic ideas underlying the mathematics of topology. Topology is an area of mathematics that allows one to decide upon the equivalence or inequivalence of two geometric forms.[6] It is important at this stage to separate the two distinct ideas of Euclidean and topological geometries. It is the concepts of Euclidean geometry that we are most familiar with in the everyday world, properties such as size, length, angles, etc. that we use to describe a given object. For example, let us consider some of the simple objects in Figure 2. In Euclidean geometry, squares A and B; which have the same side lengths and areas, would be said to be equivalent (or *congruent* in mathematical terminology). Square C, which differs in size, is not equivalent but is said to be *similar*. Clearly, triangle D and circle E are entirely different objects.

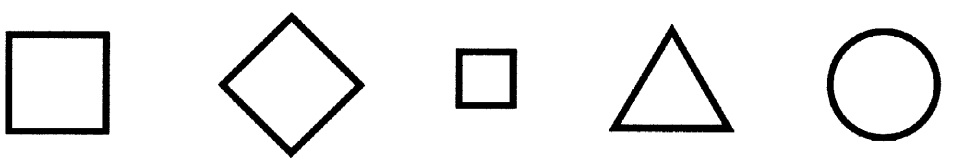


Figure 2. Some simple objects for the consideration of Euclidean and topological geometry.

In topological geometry however, we consider different properties. To understand these, we must consider the object of interest on the surface of an extremely flexible rubber sheet.[7] Properties of interest in topological geometry are those that remain unchanged during any twisting or stretching of the rubber sheet. In general, this can be considered to be the connectivity of the object: lengths, angles and size are no longer considered. If we now look again at the objects in Figure 2, we can see that in terms of topology they are all equivalent, since given complete freedom to distort lengths and angles, any one object can be transformed into any other. Indeed, they are all simply different representations of the same topological object, a closed curve. When considering the transformation of any object into another in topological geometry, one may consider the object to be totally flexible with no restriction on length and angle changes. However, connectivity is a property that must remain unchanged. A line cannot be broken or a line may not pass through another during the deformation.

If we apply these rules to the two structures in Figure 1, it is clear that the catenane cannot be converted into two separate macrocycles by a continuous deformation. The two systems are topologically distinct. This is also true of the circle and knot in Figure 3: both are closed curves, but they are topologically distinct. So we can see that while normal chemical isomerism such as stereoisomerism arises from the consideration of Euclidean properties (bond types, angles), to classify topological isomers, we must consider topological geometry.

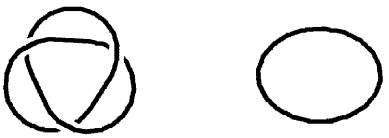


Figure 3. Two topologically distinct closed curve structures.

Although we have already referred to the synthesis and study of topologically complex molecules as topological stereochemistry, the use of the word stereochemistry must not be taken to imply that such molecules are inherently chiral. Some simple systems, for example catenanes, are achiral although they can be made chiral by defining a direction around each of the rings (Figure 4(a)). Also, while the trefoil knot is indeed chiral (Figure 4(b)), the closely related figure-of-eight knot is achiral (Figure 4(c)).

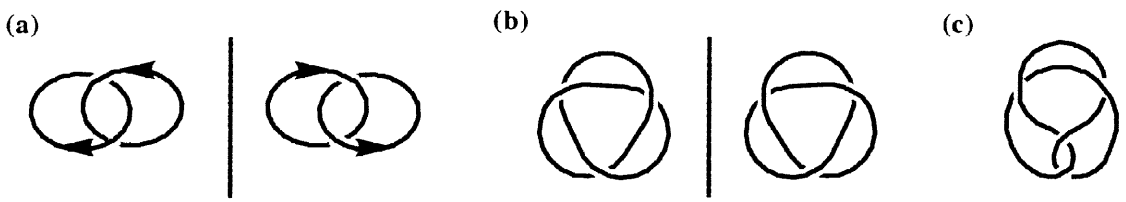


Figure 4. (a) A chiral catenane and its non-superimposable mirror image. (b) A right- and left-handed trefoil knot. (c) An achiral figure-of-eight knot.

APPROACHES TO THE SYNTHESIS OF TOPOLOGICALLY COMPLEX MOLECULES

We now turn to the problem of synthesising molecules with non-trivial topologies. As in asymmetric synthesis where absolute stereochemistry is controlled, control of topological stereochemistry has required the development of new synthetic strategies. The key step in any synthesis is the generation of an intermediate that contains latent topological properties: the latent topology is realised by macrocyclisation of this intermediate (Figure 5).

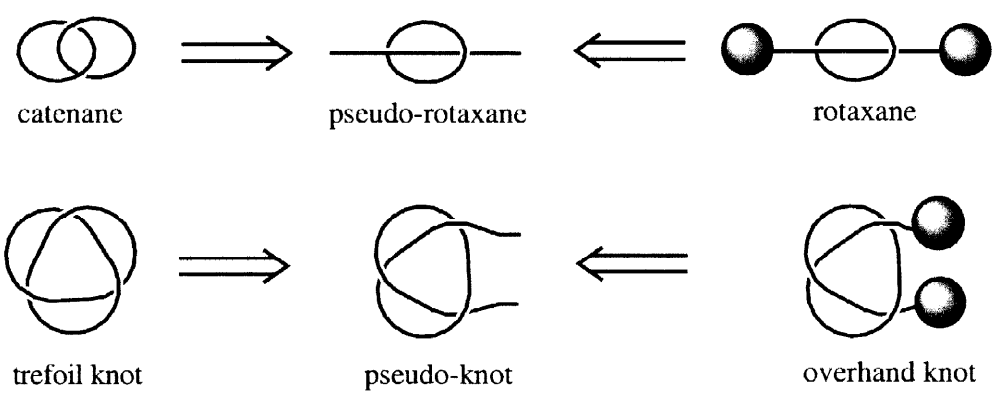


Figure 5. The pseudo-rotaxane and pseudo-knot are the key intermediates in the synthesis of complex topologies.

For example, the topologically trivial pseudo-knot (or twist) is the key intermediate required for the synthesis of the topologically complex closed trefoil knot. Similarly, the synthesis of the topologically complex catenane must proceed via the topologically trivial pseudo-rotaxane. These intermediates are often not isolated and may only be present in the reaction mixture in very small amounts, but it is their properties that define the limits on the yields of catenane and knot syntheses.

Chemists working in this field soon realised that it was possible to trap the latent topological properties of the pseudo-rotaxane by capping the ends of the linear molecule with two bulky stopper groups to prevent unthreading. Since the rules of topological geometry apply only to closed systems, it is not possible to define the topology of a rotaxane in a precise mathematical sense: with infinitely flexible molecules, the macrocycle could easily slip over the stoppers to generate the two separate components, the macrocycle and the linear strand. However, molecules are not infinitely flexible, and so it is possible to prepare rotaxanes that can only be converted to their component parts by breaking bonds. In the absence of rigorous topological definitions, nomenclature has become a problem in this area: there is clearly a relationship between the size of the stopper, the diameter of the macrocycle and the difference between a rotaxane and a pseudo-rotaxane,[8] but the question is where do we draw the line ? There are all the associated problems of defining temperature, timescale and bond strength, which we will not discuss further.

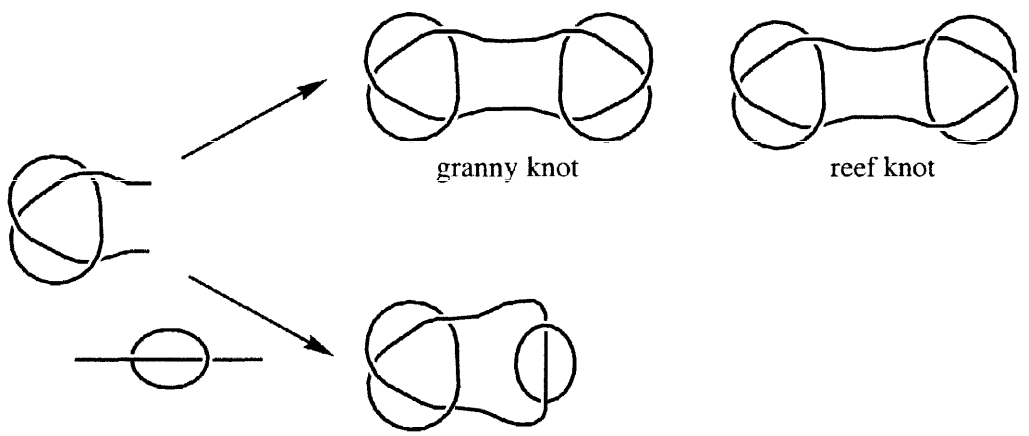


Figure 6. Interesting topologies accessible from pseudo-knots and pseudo-rotaxanes.

The overhand knot is related to the trefoil knot and pseudo-knot in the same way as the rotaxane is related to the catenane and pseudo-rotaxane. As yet there are no examples of a synthetic overhand knot, but it can clearly be prepared by capping the ends of a pseudo-knot with two bulky stopper groups. The pseudo-rotaxane and pseudo-knot can be used in various combinations for the construction of more complex topologies (Figure 6). Dimerisation of a pseudo-knot gives two composite knots, the reef knot and granny knot, which are related as diastereoisomers, reflecting the fact that the pseudo-knot can adopt two enantiomeric conformations. It is also possible to envisage more sophisticated intermediate structures with richer latent topological properties, but as yet such systems have not been realised, and so we will concentrate on the synthesis of catenanes and knots.

TOPOLOGICAL STEREOCHEMISTRY IN NATURE

Although examples of synthetic topological isomers are still somewhat rare, there are numerous examples of such structures in nature. It was during the 1960s, a time which coincided with the first serious attempts at the preparation of synthetic systems, that the first examples of topological complexity were discovered in DNA. The first DNA catenane was discovered in the mitochondria of human cells in 1967 by Vinograd, who used electron microscopy to image DNA.[9,10] Although such catenane structures are common, DNA knots are relatively rare and were first observed somewhat later: the first single stranded DNA knot from bacteriophage fd in 1976, and the first double stranded DNA knot from bacteriophage P2 DNA in 1981.[11-14] At first DNA catenanes were nothing more than curiosities, but it quickly became apparent that these structures had important implications for the biological function of DNA. Catenanes form during the replication of circular DNA, for example in the animal virus SV40.[15] If parent and daughter molecules are interlocked in a catenane, the replication process cannot proceed further. To solve this problem, nature has a class of enzymes called topoisomerases that are capable of effecting the required topological transformations upon DNA.[16] We have seen that for simple objects changes in Euclidean properties cannot produce a change in topology, so the mechanism of action of topoisomerases must involve the breaking of a DNA strand followed by the passage of another strand through the gap so formed, followed by a resealing process (Figure 7).[17] Type I topoisomerases carry out transformations that require the breaking of only one DNA strand, while type II topoisomerases effect reactions that require the breaking of two strands.[18]

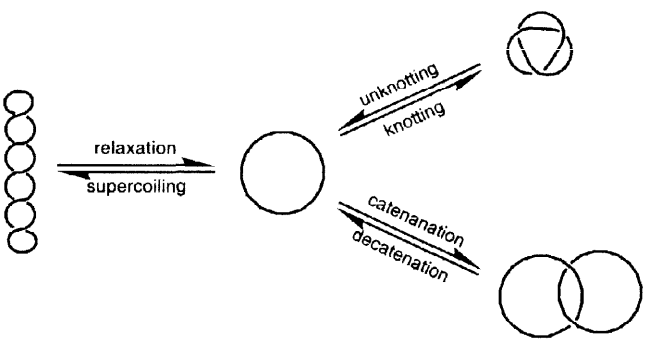


Figure 7. Some topological transformations of double stranded DNA effected by topoisomerase II enzymes.

Topology and topoisomerases play an even more important role in the biology of DNA in a process known as supercoiling. If one considers taking circular double stranded DNA, cutting both strands, twisting through 360° and then resealing the strands it may appear that exactly the same structure has been reformed. However, the product is in fact a topological isomer which is related to the initial material in the same way that a Möbius strip is related to a simple band: a Mobius strip is a topological object possessing only one surface, prepared by cutting a band, introducing a twist and sealing the ends together (Figure 8). As a consequence, the overall three-dimensional DNA structure may be significantly changed. In fact, highly supercoiled DNA, i.e. DNA containing a large number of such twists, adopts a very compact structure rather than the fairly open structure that would otherwise exist. In this way, the availability of DNA for replication or transcription can be controlled via its topology.[19,20]

Figure 8. A Möbius strip.

Given this variety of functions for the topoisomerases, it is not surprising that they are vitally important within the cell. In fact, all cells contain such enzymes, and if their function is inhibited, the cell dies. This has made both type I and type II topoisomerases attractive drug targets, and a number of antibacterial drugs have been shown to target bacterial topoisomerases inhibiting various stages of the cutting - strand passage - resealing process.[21,22] Drugs that target eukaryotic topoisomerases are highly cytotoxic and include many anti-cancer drugs.

As well as naturally occuring topologically complex structures in DNA, linear DNA has been used by Seeman in designed syntheses of topologically complex molecules. These syntheses utilise the fact that DNA forms well-behaved right- (B-form) or left-handed (Z-form) double helical structures depending on the base sequence.

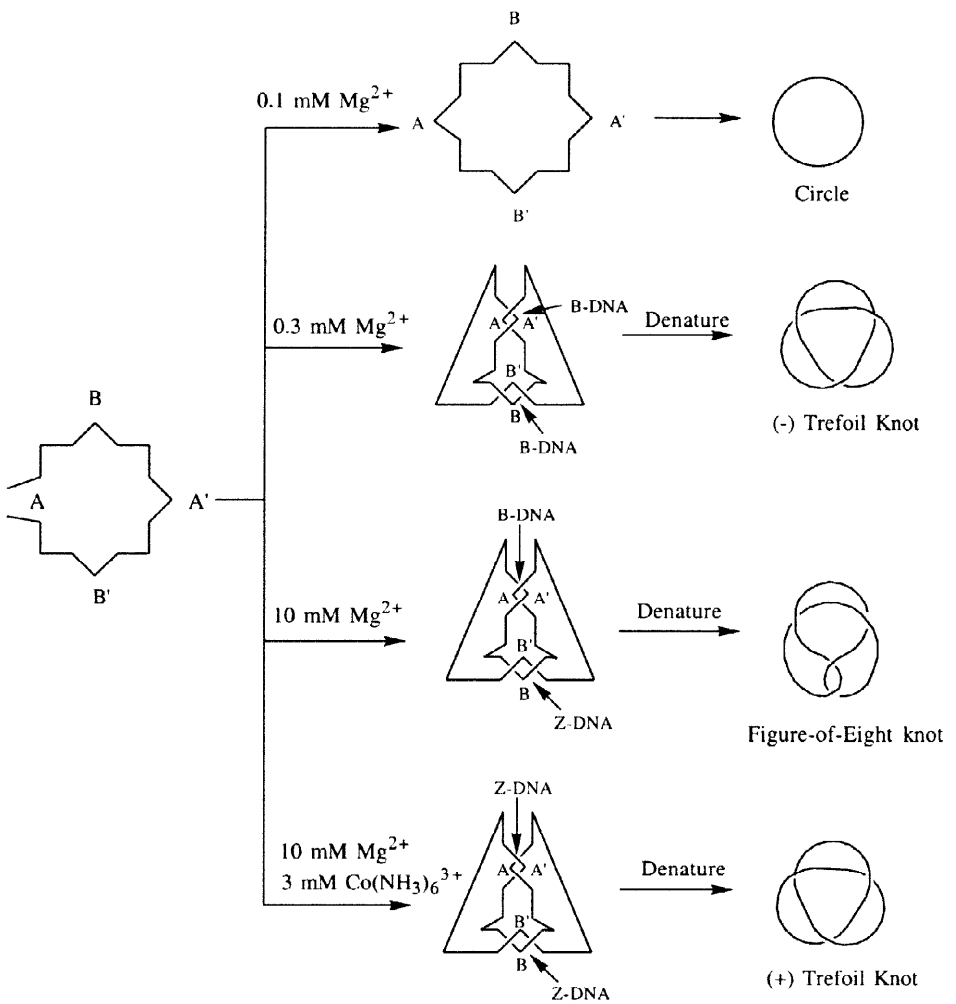


Figure 9. Seeman's synthesis of DNA knots.

Figure 9 shows how Seeman has used the same single strand of DNA containing 104 nucleotides to prepare a circle, a left- and a right-handed trefoil knot as well as a figure-of-eight knot.[23] A-A' and B-B' represent 11 or 12 base-pair complementary sequences that have been designed to produce specific sections of double helix. These sequences are joined by oligo-thymidine linkers. Addition of various concentrations of Mg^{2+} and $Co(NH_3)_6^{3+}$ induces the formation of either B- or Z-helices in various parts of the structure and hence controls the topology and chirality of the products. One of the interesting aspects of this work is the use of restiction enzyme cleavage strategies to confirm the topological properties of the products, which can not be characterised by conventional spectroscopic or diffraction methods. Seeman has used this basic approach to assemble astonishly complex structures from multiple strands of DNA such as a DNA cube [24] and a truncated octahedron.[25]

While DNA exhibits a large number of topologically complex structures, until very recently there were no reports of similar phenomena in proteins. The first claims of knotted protein structures were made by Liang and Mislow in 1994 following a search of crystallographic structures in the Brookhaven Protein Data Bank.[26,27] They claimed that a number of proteins exhibited knotted substructures, but a topologically significant connectivity could only be found if metal-histidine interactions and disulphide bonds were used to link various points on the polypeptide chain. In 1996, Takusagawa reported that the structure of (S)-adenosylmethionine synthetase (MAT) contained an open knot (Figure 10).[28] Open structures such as this pseudo-knot do not satisfy the mathematically rigorous definition of a knot, and this makes identification somewhat subjective. However, open structures that contain latent topological properties have assumed increasing significance in the development of strategies for the synthesis of topologically complex molecules as explained above. Topologically, the native folded form of MAT is identical to that of the linear unfolded protein, and this clearly has important implications for reversible folding of the protein which does not require making or breaking peptide bonds.

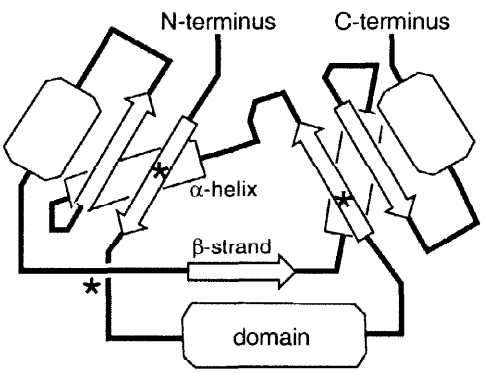


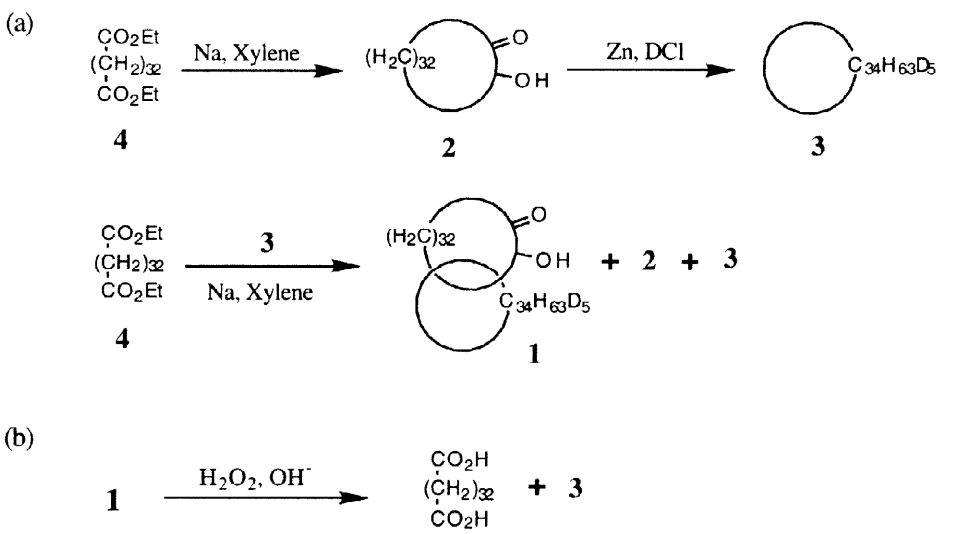
Figure 10. The pseudo-knot structure of the polypeptide chain of (S)-adenosylmethionine synthetase. Crossing points are indicated by asterisks.

STATISTICAL METHODS FOR GENERATING COMPLEX TOPOLOGIES

Before strategies for preparing the key intermediates were developed, some syntheses were attempted that relied on the low statistical probability of chance encounters in concentrated solutions to yield complex topologies. Nowadays this seems rather hopeful, but it was surprisingly successful. In 1960, Van Gulick and Wasserman

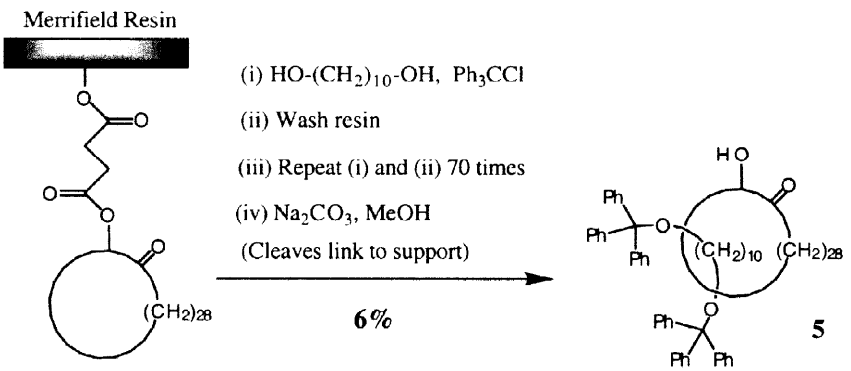
independently began to consider the problem of the synthesis of two linked rings, a system for which they both proposed the name catenane. Van Gulick's discussion of the problem was surprisingly never published at the time although it has been much referenced by other workers in the field. His manuscript was reputedly rejected for "not being chemistry"[29] although it was finally published in 1993.[30] Wasserman went on to publish a low yielding catenane synthesis in late 1960 as outlined in Scheme 1(a).[2] He estimated that for a simple cycloalkane, a ring of at least C_{20} would be required before another alkane chain could thread through it.[31] The larger the ring, the easier the threading, but the lower the cyclisation yield. His initial system was a compromise using two 34-membered rings. His early terminology was to denote this as a 34,34-catenane, although later, with the advent of multi-ring systems, such compounds came to be called simply [2]-catenanes. The number in square brackets denotes the number of interlocked rings. Diester **4** was subjected to an acyloin condensation followed by a Clemmensen reduction in DCl to give the deuterium labelled cyclic hydrocarbon **3**. A further molecule of diester **4** was then cyclised in the presence of **3** and produced a mixture of products, which by a random threading of **4** through **3** during the cyclisation contained some catenane **1**. The yield was very low and the presence of **1** could only be inferred spectroscopically as outlined below. Such low yields from so called statistical reactions are a consequence of the very small amounts of psuedo-rotaxane present in the reaction mixtures and are in marked contrast to the almost quantitative yields in the templated reactions that will be discussed later.

Wasserman's proof of structure consisted of chromatographing the crude product on silica. Pentane was used to elute the non-polar cyclic hydrocarbon while the more polar acyloin functionality remained on the silica. When the product remaining on the column was removed, it was shown by IR spectroscopy to still contain deuterium - evidence for the mechanical linking of the deuterated and acyloin rings. Further evidence came from oxidative cleavage of the acyloin function in the product followed by chromatography. Now after eluting with pentane, the product remaining on the silica was shown to contain no deuterium. This was attributed to cleavage of the catenane as shown in Scheme 1(b).



Scheme 1. (a) Wasserman's statistical catenane synthesis, and (b) the evidence for catenane formation based upon cleavage of the product.

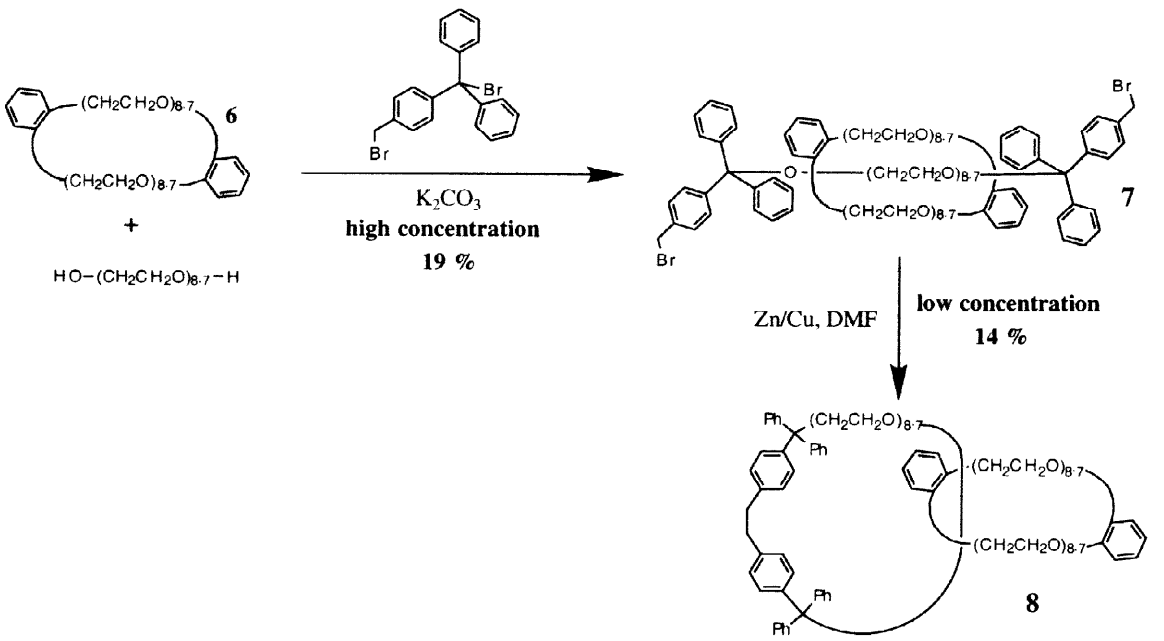
In a 1961 paper, Wasserman also considered the possibility of a statistical approach to a molecular knot.[32] He calculated that at least a C_{50} chain would be required and prepared a C_{66} diester, which he subjected to a similar acyloin condensation to that used successfully in his catenane synthesis. Not surprisingly, no results were ever published, and one can envisage many problems associated with such a scheme. The desired product could only ever be produced in a very low yield, and the spectroscopic proof used in the catenane characterisation was not applicable to this system. As Wasserman appreciated, the only hope of identifying a knot in the product mixture was to utilise the fact that a trefoil knot exhibits chirality. However, since both enantiomers would form in equal amounts, the product would still be optically inactive. This left the proposal of adding an optically active species that would bind to the knot to produce diastereoisomers for chromatographic separation or spectroscopic identification. Again, no results were forthcoming, and it seems that the yield of knot was simply too low to have any hope of detecting it among the products. A further 30 years would pass before the first synthetic knot was isolated and characterised.



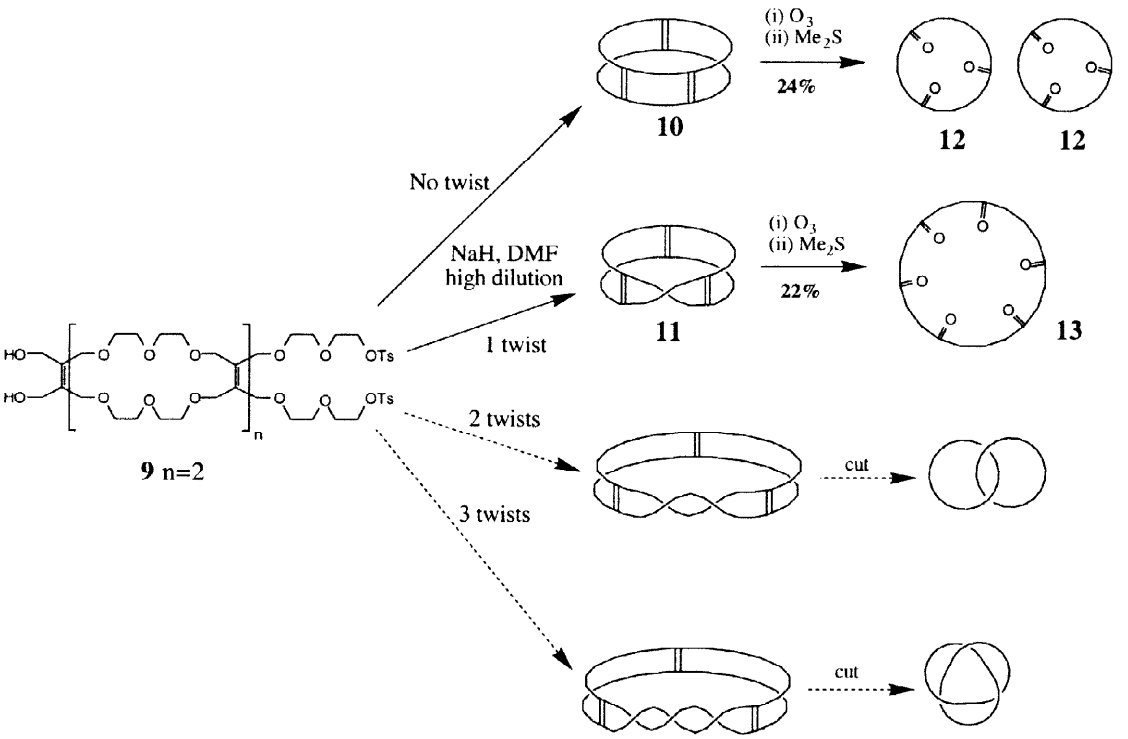
Scheme 2. Harrison and Harrison's rotaxane synthesis.

Although a molecular knot was to remain beyond the scope of such early work, the 1960s did also see the first successful rotaxane synthesis. In 1967 Harrison and Harrison reported the synthesis of rotaxane **5** in 6% yield using the statistical threading approach outlined in Scheme 2.[33] This ingenious route partly surmounted the problem of a low yield in statistical reactions by repeating the threading and capping step 70 times. Although they proposed the name "hooplane" for such systems, rotaxane is the term that has become generally accepted.

The work of Zilkha and Agam[34, 35] in the mid-1970s saw the only real improvement in the yields of catenanes by the statistical method. They realised that the conditions favouring the required threading processes, i.e. high concentration, were inconsistent with those conditions favouring macrocyclisation, i.e. low concentration. To overcome this problem in their catenane synthesis, they divided the synthesis into two stages (Scheme 3). They prepared a mixture of crown ethers, dibenzo-58.2-crown-19.4 **6** from polyethylene glycol with an average molecular weight of 400 (PEG 400). In a high concentration reaction, a further molecule of PEG 400 was stoppered using two derivatised trityl groups in the presence of the crown macrocycle to give rotaxane **7** in 19 % yield. **7** was isolated and then subjected to a high dilution macrocyclisation to yield catenane **8** in 14% yield (3 % overall). They called this method the double-stage approach, and the synthesis still represents one of the few examples of the direct conversion of a rotaxane into a catenane.



Scheme 3. Zilkha and Agam's double-stage rotaxane-catenane synthesis.



Scheme 4. Topologies accessible via Möbius strips.

A different statistical route to topologically complex molecules is the preparation of molecular Möbius strips. If Möbius strips with various numbers of twists are cut down the centre, a whole range of interesting topologies are accessible (Scheme 4).[3] The idea that such a strategy could give access to a molecular knot was

suggested by Frisch and Wasserman in 1961.[32] Much experimental work towards realising these possibilities has been carried out by Walba who synthesised a number of molecular strips such as **9** based upon tetra(hydroxymethyl)ethene (THYME) polyethers (Scheme 4).[36] Cyclisation of **9** yielded two products identified as the cylinder **10** and the single half-twist Möbius strip **11**. Walba has demonstrated that cutting of the strip down its centre can be achieved in the chemical sense via ozonolysis of the THYME double bonds.[37] Cylinder **10** gave two molecules of triketone **12** and the half-twist Möbius strip **11** gave the hexaketone macrocycle **13**. So far, the double and triple half-twist Möbius strips required for the formation of a catenane and trefoil knot respectively have not been characterised. It seems that the chance of so many twists occurring during the cyclisation reaction is remote. Other workers have attempted to incorporate units that template the formation of a half-twist in such systems, and these systems will be considered below.

Although these methods produced interesting and novel molecules, it was clear that both the yields and the topological complexities of the systems produced were always going to be severely limited by the statistical approach. A radically different synthetic strategy was required for useful preparative routes to topologically complex systems, and template methodology provided the answer.

TEMPLATES IN CHEMICAL SYNTHESIS

When Watson and Crick elucidated the structure of the DNA double helix in 1953, it was soon realised that when DNA replicated, one strand acted as a template for the formation of a new molecule.[38] Since that time, chemists have developed many systems whose synthesis depends on a template effect, and this approach provides the key to the preparation of the pseudo-rotaxane and pseudo-knot structures required to control topological stereochemistry. In Busch's definition, "a chemical template organises an assembly of atoms with respect to one or more geometric loci in order to achieve a particular linking of atoms".[39] Bonding between template and substrate(s) is often via weak non-covalent interactions, although some systems do use covalent bonds that can be readily cleaved or form reversibly. There are many different forms of template, but a convenient classification is that introduced by Sanders (Figure 11).[40] For topological stereochemistry, it is clearly interweaving and cyclisation templates that are of greatest importance, so linear-type templates leading to phenomena such as self-replication will not be considered here.[41]

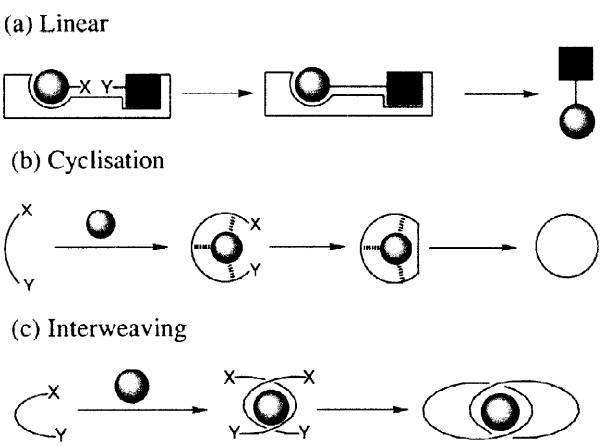
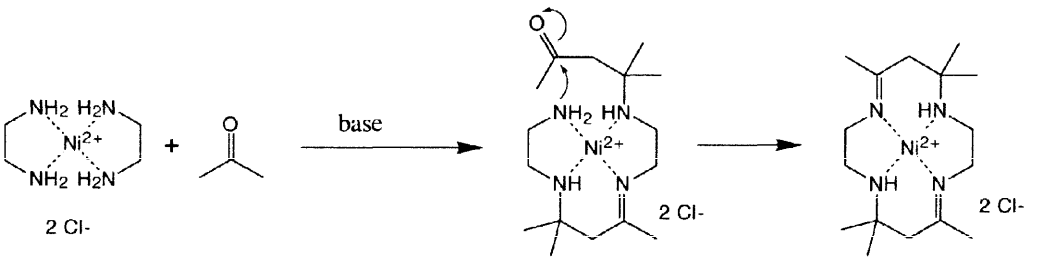


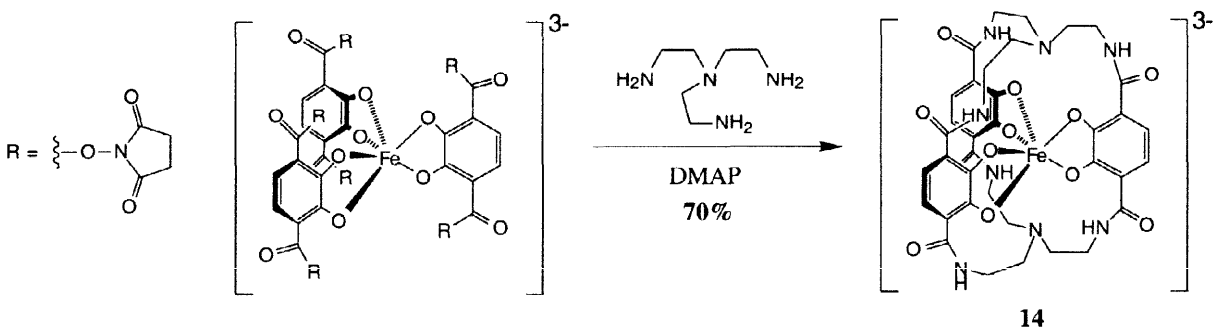
Figure 11. Classification of template effects according to Sanders.

By far the most common class of templated macrocyclisations are those templated by metal ions. It was the discovery that metal ions can act in such a manner during the 1960s that initiated the serious study of template effects in synthesis. Curtis reported the first templated synthesis of a Schiff's base macrocycle in 1961 (Scheme 5): a macrocyclic product was only isolated in the presence of nickel.[42] Busch subsequently made use of this template effect to prepare a range of macrocyclic ligands.[43] In 1967, Pedersen reported his templated crown ether synthesis:[44] his initial yields were very low, but Greene obtained much improved results during the early 1970s.[45] He found that if tetra-*n*-butylammonium hydroxide was used as base, mainly polymer was obtained along with only a very low yield of the expected crown ether. However, if potassium *t*-butoxide was substituted as base, the yield increased dramatically to 93%, and the product was isolated coordinated to potassium as its tosylate salt.



Scheme 5. Curtis' templated macrocycle synthesis.

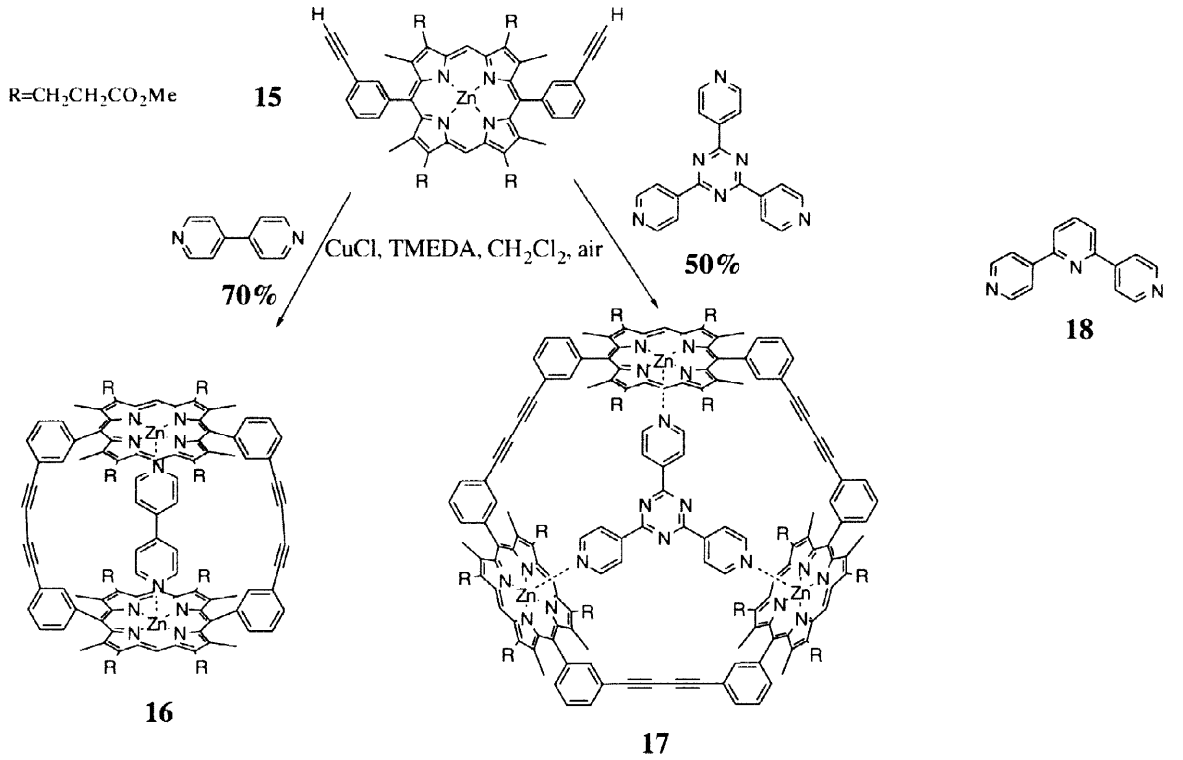
The metal template effect has now been used in countless examples of macrocycle synthesis. Removing the metal ion after the synthesis to obtain the free macrocycle can be problematical, but this is the only real drawback of this very useful technique. The method is not limited to simple macrocycles, but has been used extensively to build up more complex cage molecules, such as Raymond's iron sequestering agent (Scheme 6).[46] Using high dilution conditions to minimise polymerisation, it is only possible to obtain a 4 % yield of **14**, but in the presence of iron (III), the yield increases to 70 %.



14

Scheme 6. Templated synthesis of Raymond's iron sequestering agent.

Although metal ions are by far the most common templates for macrocyclisation reactions, other methods do exist. Sanders has prepared a number of macrocycles using a neutral organic molecule coordinated to zinc porphyrins to provide a template effect.[47,48]

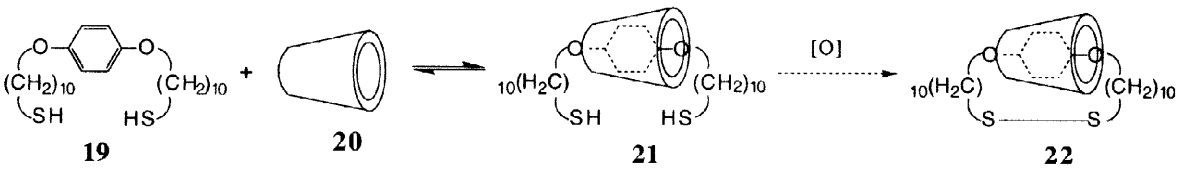


Scheme 7. Sanders' templated synthesis of porphyrin macrocycles.

The porphyrin monomer **15** can be cyclised in good yield to either dimer **16** or trimer **17** depending upon the presence of a small organic molecule to provide the relevant template effect (Scheme 7). 4,4'-Bipyridine acts as a positive cylisation template producing a three-fold increase in the yield of **16** relative to the untemplated reaction. However, tripyridyltriazine plays a rather different role in the formation of the trimer **17**. It increases the yield of trimer by a factor of 1.5 relative to the untemplated reaction by inhibiting the formation of dimer **16**: it is a negative template for dimer formation. A similar yield of trimer is obtained in the presence of **18**, which is clearly not capable of acting as a positive cyclisation template, since it lacks the third binding site.

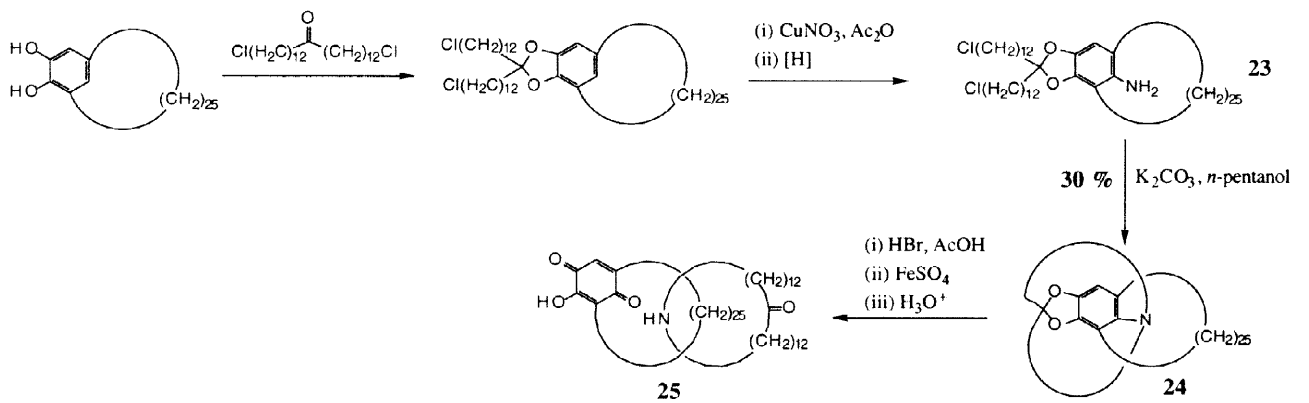
TEMPLATED SYNTHESIS OF CATENANES AND ROTAXANES

The use of template methods have transformed the field of topological stereochemistry, because they provide excellent tools for the preparation of the key pseudo-rotaxane and pseudo-knot intermediates. Although it is only in the last ten years that template synthesis has made preparative scale chemistry on topologically complex systems viable, one of the earliest attempted catenane syntheses to appear in the literature was based on a template strategy (Scheme 8).[49] In 1958, Lüttringhaus utilised the hydrophobic effect to form an inclusion complex between **19** and cyclodextrin **20**. The intermediate **21** is what we now know as a pseudo-rotaxane, and in theory, intramolecular oxidative coupling of the thiols should give catenane **22**. However, only starting material was ever isolated.



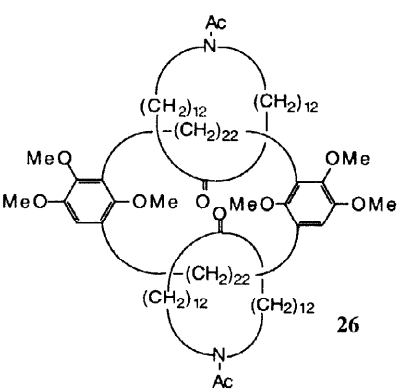
Scheme 8. Lüttringhaus' attempted catenane synthesis. **20** = cyclodextrin.

Four years after the first catenane synthesis by Wasserman, Schill and Lüttringhaus published the first templated catenane synthesis.[50] They used a covalently attached template to ensure that the two rings produced were interlocked. The main points of their rather lengthy synthesis are illustrated in Scheme 9.



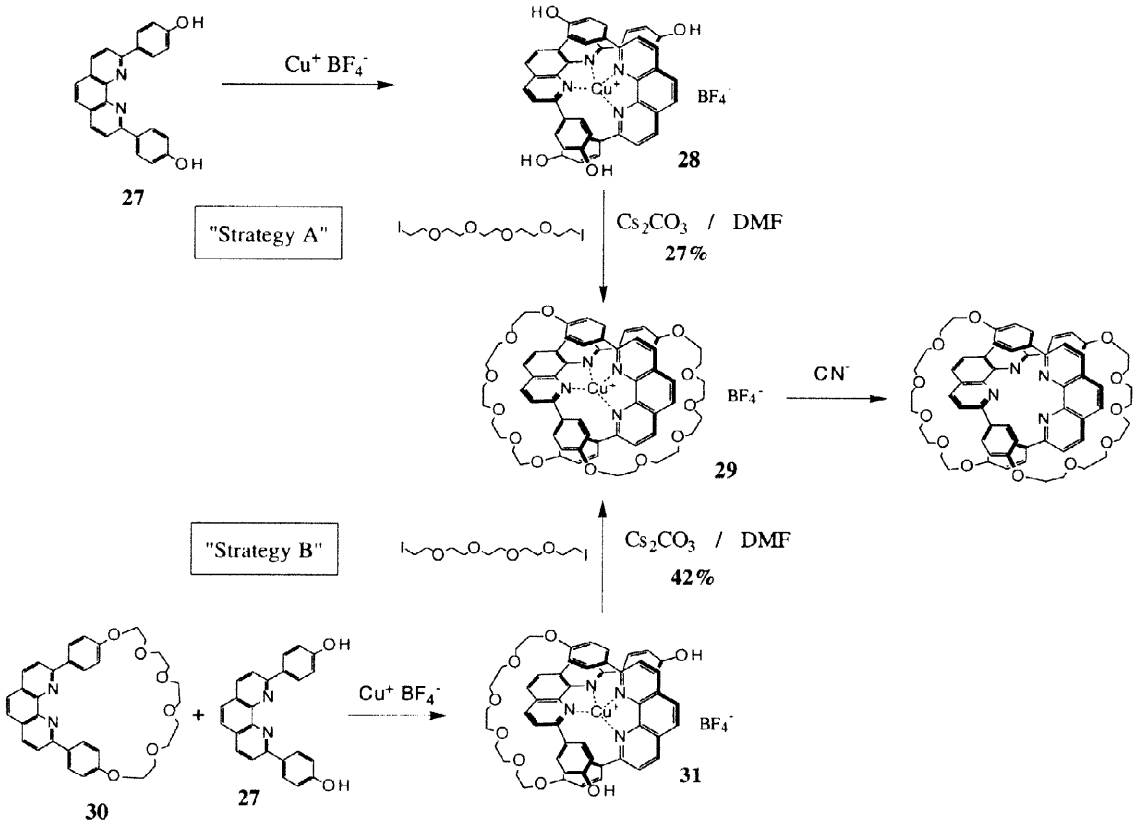
Scheme 9. Schill and Lüttringhaus's covalently templated catenane synthesis.

The key intermediate is the dichloride **23**. Cyclisation via intramolecular alkylation of the amine is constrained by the tetrahedral geometry of the acetal carbon to give only the catenane precursor **24**.The veratrole core of the molecule templates the cyclisation to give the required topology. Acetal hydrolysis and cleavage of the aryl-nitrogen bond gave the catenane structure **25** which was characterised as its N-acetyl derivative. This methodology has been extended to the first synthesis of a [3]-catenane **26.**[51]



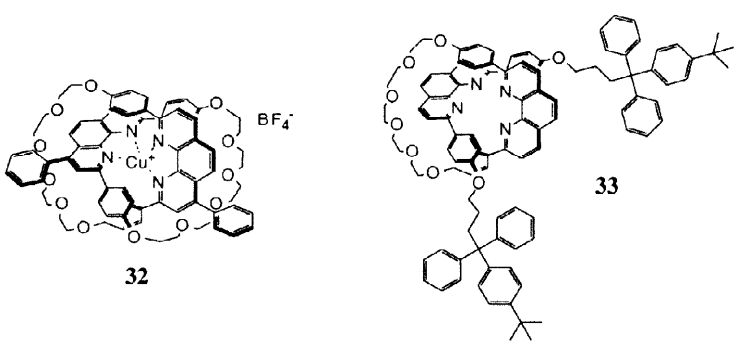
During the 1980s, Sauvage developed a powerful metal-ion templating strategy,[52] which initially gave access to catenanes and rotaxanes, and has since been expanded to give the first synthetic molecular trefoil knot.[53] The catenane synthesis is illustrated in Scheme 10.[54] In Strategy A, the phenanthroline unit **27** is coordinated to Cu(I). Macrocyclisation of complex **28** under high dilution conditions gave the required catenane **29** in 27% yield. Strategy B is simply a variant on this. Here, the macrocycle **30** is synthesised first. Upon mixing **30**, **27** and Cu(I), the pseudo-rotaxane **31** is formed. Complexation of two **30** units to Cu(I) is steric blocked, and so equilibration results in quantitative formation of the key intermediate **31**. Macrocyclisation gives catenane **29** in 42% yield. Although the Cu(I) ion is an interweaving template and ensures the interlocking of the two

macrocycles, it is not a cyclisation template. The macrocyclisation reactions must therefore be carried out under high dilution conditions to maximise intramolecular cyclisation and reduce any intermolecular reactions. However, the use of ring-closing methathesis has recently increased the yield of catenane to over 90%.[55]

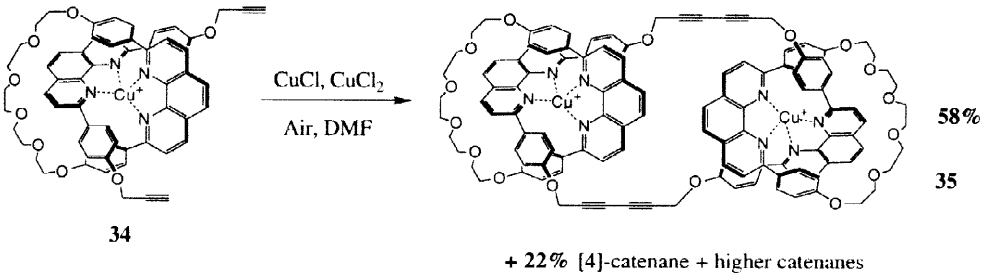


Scheme 10. Sauvage's templated catenane synthesis.

Sauvage has extended this strategy to prepare a number of other novel systems such as **32**.[56,57] As explained earlier, a catenane becomes chiral when it is possible to define a direction around the rings. The catenane **32** has been demonstrated to be chiral by NMR experiments.[56] This type of template effect has also yielded a number of rotaxanes such as **33**, which was reported by Gibson in 1991.[58]



Sauvage has gone on to use pseudo-rotaxane **34** to prepare [3]-catenane **35** [59] (Scheme 11) and has identified higher oligomers up to a [7]-catenane in mass spectra of the reaction byproducts.[60] A large number of different catenanes and rotaxanes have now been reported using the Sauvage copper-phenanthroline template strategy, but these will not be discussed further here.[57]



Scheme 11. Sauvage's [3]- and higher order catenane synthesis.

A second important template strategy was developed during the 1980s by Stoddart. He has used aromatic stacking interactions to template the synthesis of a host of catenanes and rotaxanes.[61] The key building blocks are the two pseudo-rotaxane complexes shown in Figure 12.[62,63] Application of the paraquat-dialkoxybenzene stacking interaction as an interweaving template is illustrated in the classic [2]-catenane synthesis in Scheme 12.[64]

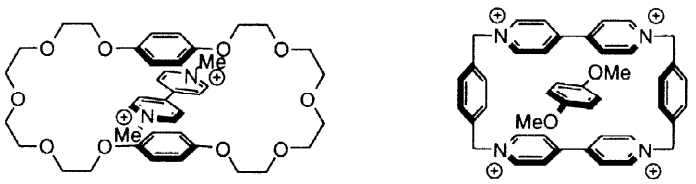
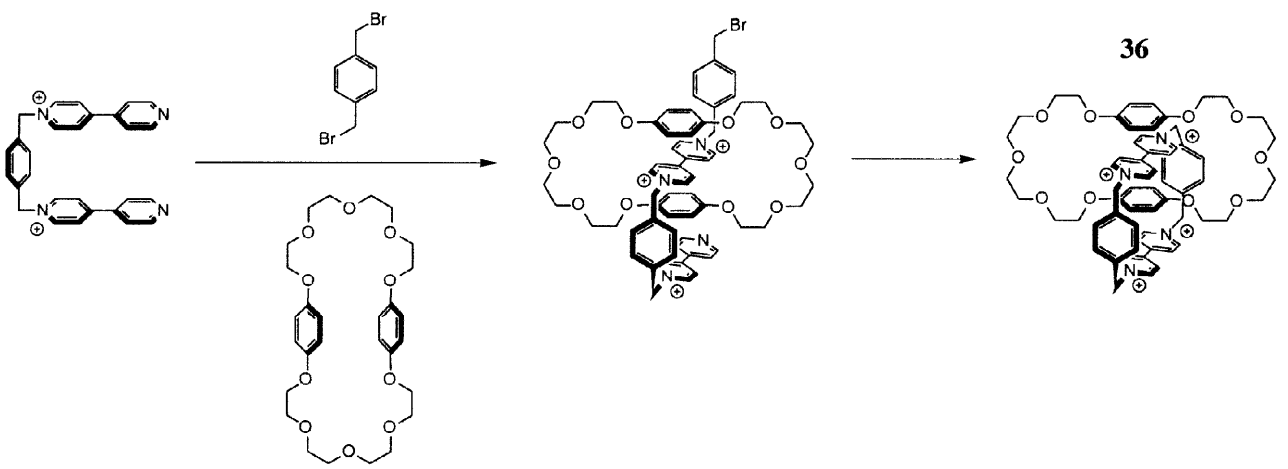
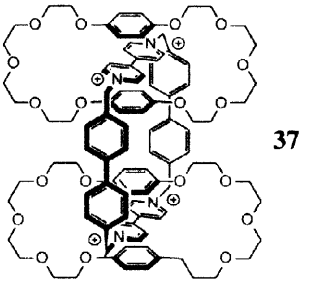


Figure 12. Paraquat-dialkoxy benzene complexes which form the basis of Stoddart's template strategy.

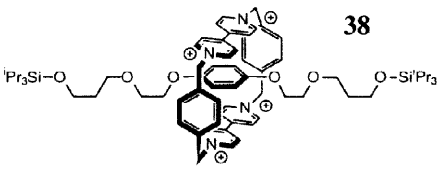


Scheme 12. Stoddart's [2]-catenane synthesis.

This template strategy has provided access to multi-ring catenanes such as **37** [65] and numerous rotaxanes (e.g. **38**).[66] Stoddart has explored three distinct routes for rotaxane synthesis: the threading approach where the linear component is threaded through the macrocycle, and the pseudo-rotaxane produced is then stoppered; the slippage approach where the stoppered linear strand can slip through the macrocycle at elevated temperature but cannot slip out again at room temperature; [67] and the clipping appoach where the macrocycle is formed around the stoppered linear strand (Figure 13).These synthetic strategies have been used to prepare some remarkably complex systems, for which applications are envisaged in the emerging field of molecular devices.[68] The Stoddart template methodology has since been used by a large number of other groups to prepare a wide range of different systems too numerous to mention here. [69]



37



38

In a related approach, Sanders has recently used aromatic stacking interactions between dihydroxynaphthalene and naphthalenediimide derivatives to prepare a [2]-catenane.[70]

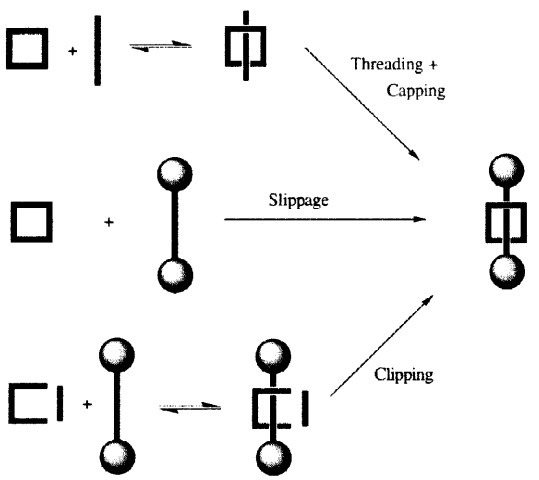
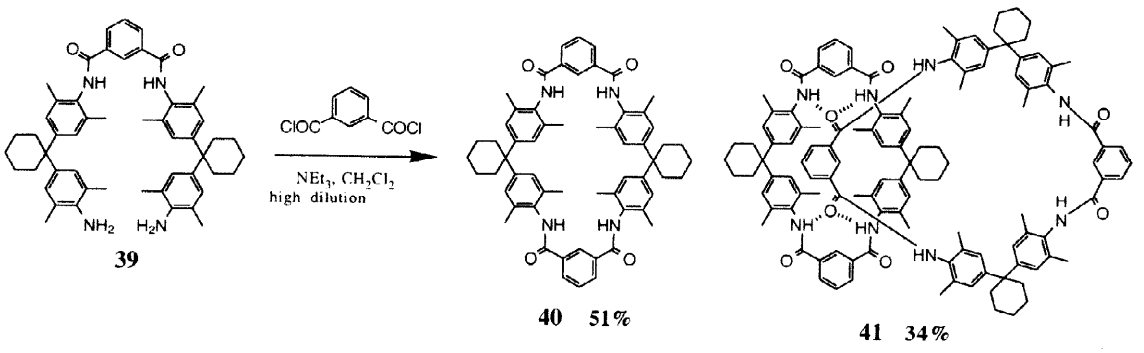
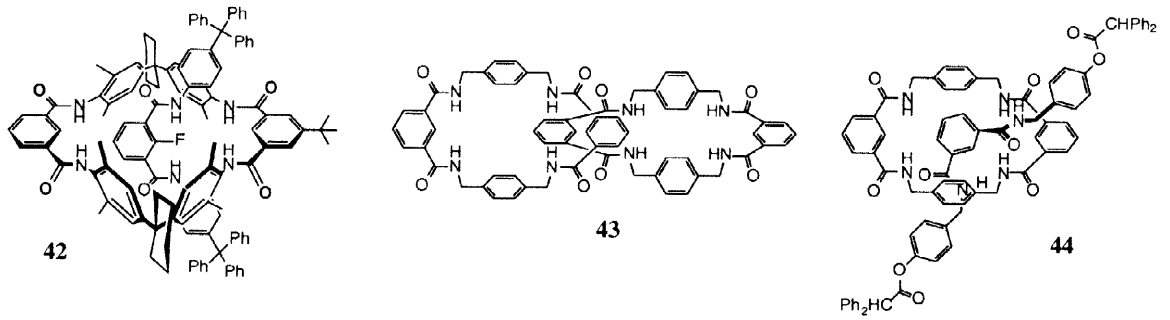


Figure 13.Three different routes to a [2]-rotaxane.

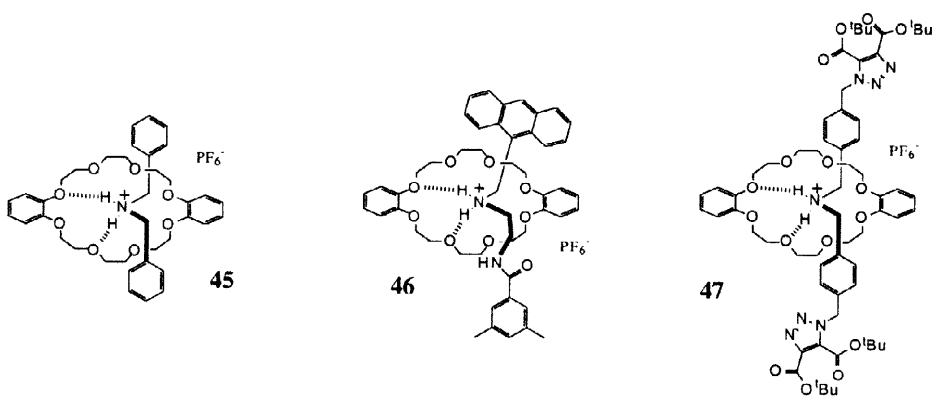
The first example of a catenane templated by hydrogen-bonding was reported by Hunter in 1992 (Scheme 13).[71-73] High dilution macrocyclisation of **39** and isophthaloyl dichloride gave not only the expected macrocycle **40** in 51% yield but also the [2]-catenane **41** in 34% yield. Vögtle has described a number of related catenanes [74,75] and has gone on to use the same methodology to prepare rotaxanes such as **42**.[76] Leigh also reported the synthesis of a catenane templated by hydrogen-bonding interactions. **43** is formed in a remarkable 20% yield from eight separate components in one pot.[77] The reaction is so efficient that the simple macrocyclic target molecule, required as a receptor for carbon dioxide, could not be prepared directly. Leigh has since published a strategy based upon the preparation and subsequent cleavage of rotaxane **44** to access the simple macrocycle.[78]



Scheme 13. Hunter's serendipitous [2]-catenane synthesis. The hydrogen-bonding interactions shown in **41** are presumed to template catenane formation.

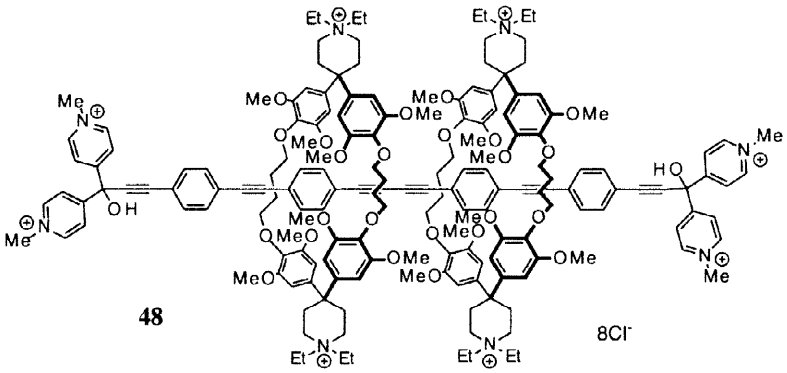


Stoddart discovered that H-bonding interactions between secondary amines and crown ethers lead to the formation of pseudo-rotaxane complexes such as **45**.[79] This motif has been used to assemble multi-component pseudo-rotaxanes, and some of these have been stoppered to yield rotaxanes, **46** and **47**.[80]

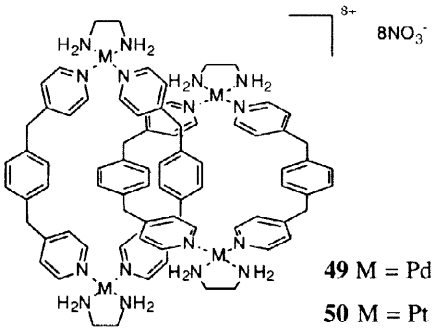


Anderson has successfully used the hydrophobic effect to template the synthesis of water-soluble [3]-rotaxane **48** in reasonable yield.[81] Also of interest are Fujita's catenanes **49** and **50**,[82] which represent one of the few examples of the incorporation of a metal ion into the cyclic components of a catenane structure. Again, aromatic interactions provide the molecular recognition to favour catenane formation. In the palladium system, the catenane is in equilibrium with the free macrocycle, so the amount of catenane present depends on concentration. At high concentration, **49** exists almost entirely in the form of catenane. For the less kinetically labile platinum

system, the free macrocycles are stable at room temperature and do not equilibrate to catenane **50**. However, upon heating in highly polar media, catenane can form. Cooling to room temperature traps the macrocycles in the catenane structure, and this has led Fujita to describe this system as a "molecular lock".[83]



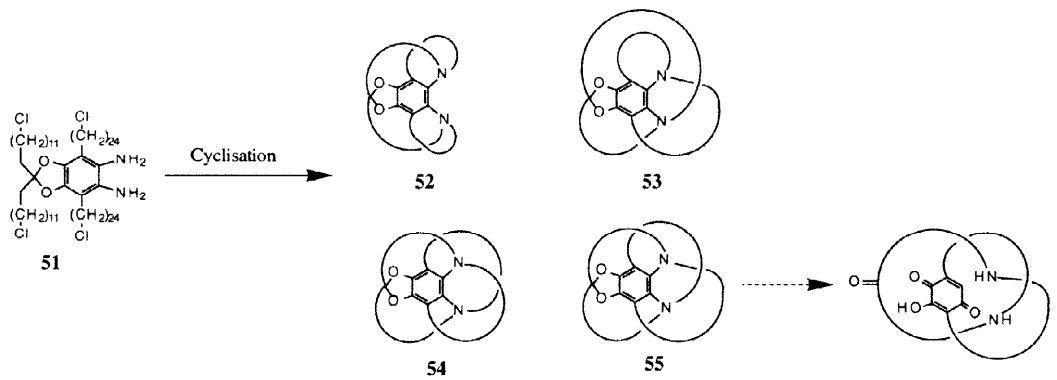
48



49 M = Pd
50 M = Pt

TEMPLATED SYNTHESIS OF KNOTS

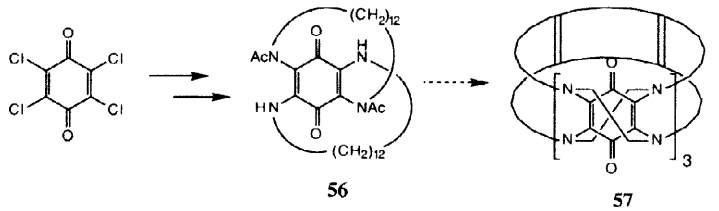
We have already discussed Schill and Lüttringhaus's covalently templated catenane syntheses. Schill also attempted to extend this methodology to a trefoil knot as outlined in Scheme 14.[84] Here, the key intermediate is **51**, where the geometry of the tetrahedral acetal carbon limits the number of possible products from intramolecular cyclisation. There are four different products that could arise from complete intramolecular cyclisation of **51**, and **55** is the precursor to a trefoil knot via the acetal hydrolysis and aryl-nitrogen bond cleavage discussed earlier. Schill obtained three cyclised products in a total yield of 2 % but could not confidently assign structures, so it is unclear whether **55** was produced or not.



Scheme 14. Schill's attempted trefoil knot synthesis.

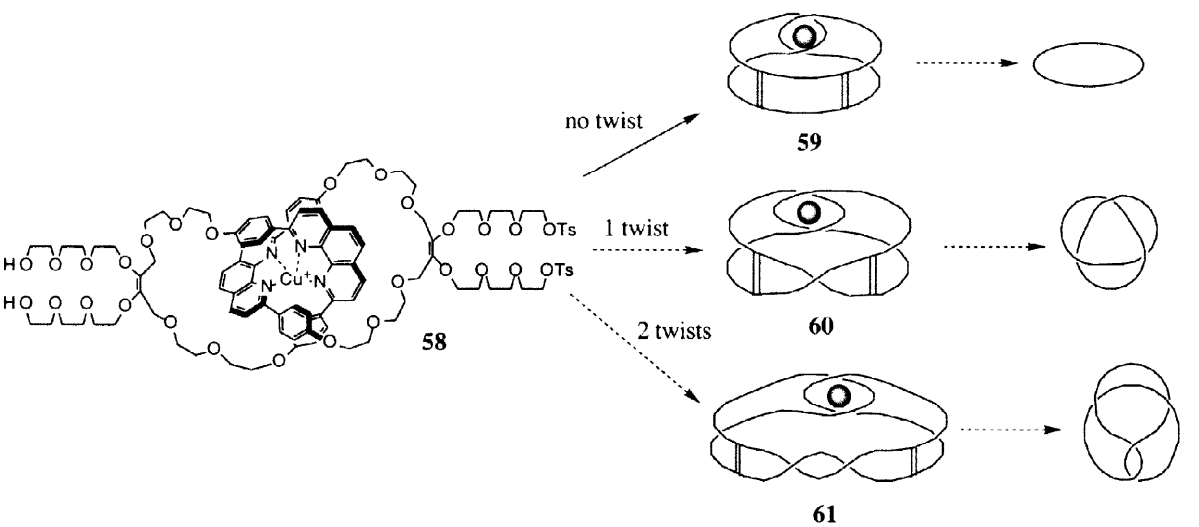
We have also discussed attempted strategies using molecular Möbius strips to obtain topologically complex molecules. We observed that such methods must be considered to be statistical in nature since only random chance can result in the formation of the twists required to give objects with complex topologies upon cleavage. Schill attempted to template a half-twist using a covalent method as shown in Scheme 15. He prepared the doubly bridged system **56** in a number of steps from tetrachlorobenzoquinone.[85,86] This can be considered to

template a half-twist, such that if three units were linked together followed by a cyclisation reaction, the triple half-twist Möbius strip **57** would result. Cleavage of the aryl-nitrogen bonds would effectively cut the strip in half and yield a trefoil knot as discussed earlier. However, no positive results were ever published.



Scheme 15. Schill's attempted templated synthesis of a triple half-twist Möbius strip.

A further scheme for at least a partial templating of twists in a molecular strip is the "hook and ladder" approach developed by Walba (Scheme 16).[87] By making use of the Sauvage template, only one half-twist has to be introduced statistically in the cyclisation of **58** in order to get the knot precursor **60**. If two half-twists could be introduced, then **61** would be a precursor for a figure-of-eight knot, a structure for which no other synthetic route has been proposed. However, only untwisted **59** was isolated and characterised from the cyclisation of **58**.[88]



Scheme 16. Walba's attempted "hook and ladder" knot synthesis.

We have discussed a number of different templating strategies for the synthesis of catenanes and rotaxanes, and the ultimate extension of this came in 1989 when Sauvage published the first synthesis of a molecular trefoil knot, using an ingenious extension of his copper-phenanthroline catenane template.[53] If a double helical structure is subjected to an intramolecular double macrocyclisation, there are three possible products, one of which is a trefoil knot (Figure 14).

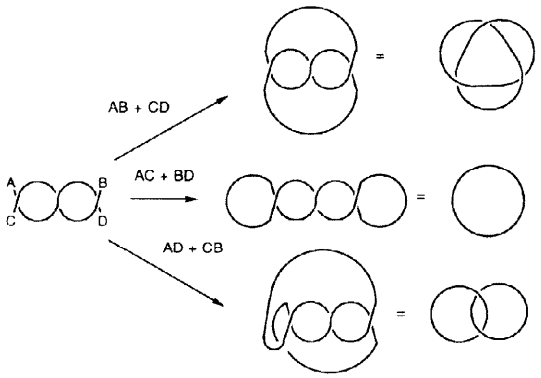
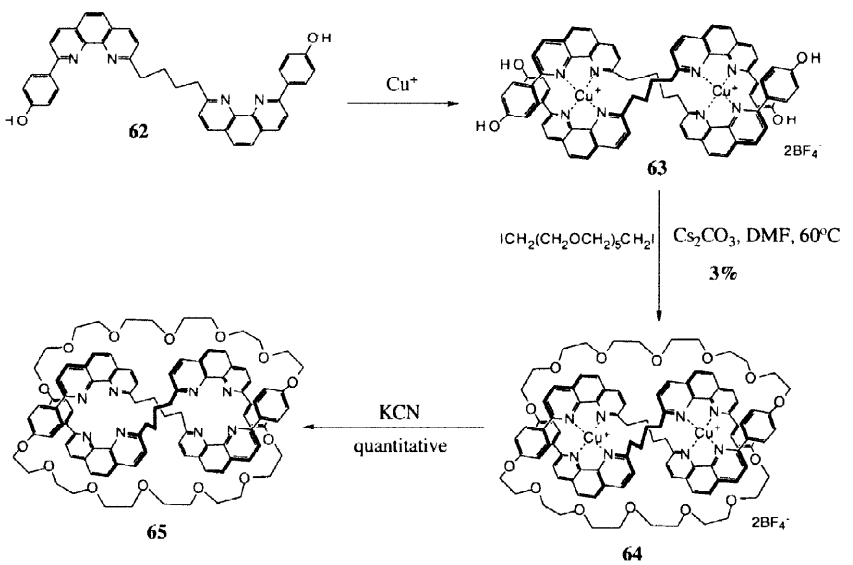


Figure 14. Sauvage's double helix approach to a trefoil knot.

Lehn has shown that double helical structures can be assembled from bipyridine oligomers using metal ion coordination.[89] Combining such structures with Sauvage's interweaving template strategy produced the synthetic sequence in Scheme 17. Addition of $Cu(MeCN)_4^+BF_4^-$ to bisphenanthroline **62** gave the double helical complex **63**,which was not isolated. Macrocyclisation under high dilution conditions yielded a mixture of products, and the metallo-knot **64** was isolated in 3 % yield after careful chromatography. Demetallation gave the free knot **65**. A small amount of the unknotted topological isomer was also isolated. Although the yield was very low,[90] variation of the group linking the two phenanthroline units [91] and the use of ring-closing metathesis in the macrocyclisation step resulted in a yield of 74 %.[92]



Scheme 17. Sauvage's trefoil knot synthesis.

Sauvage has proposed that this knot is just the second in a series of topologies available using this strategy, the first member being the catenane discussed earlier (Figure 15).[90] Recently, the group has indeed published the first synthesis of a doubly interlocked [2]-catenane in 2% yield using this strategy.[93] The doubly interlocked catenane exhibits remarkably different properties to its singly interlocked isomer: the two compounds

have very different R_f values and undergo different fragmentation in the FAB mass spectrum because of the more highly strained nature of the doubly interlocked system.[94] It remains to be seen if the group is now engaged in extending this methodology further to a pentafoil knot.

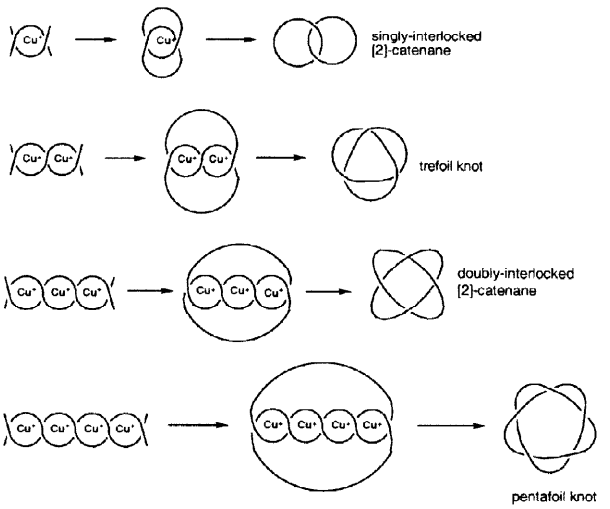
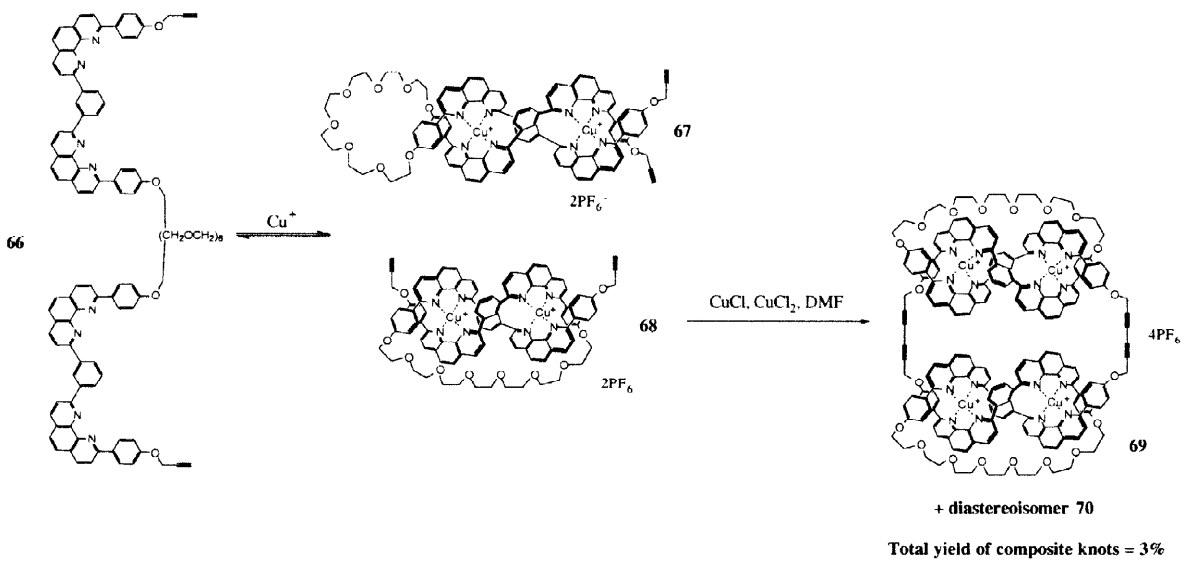


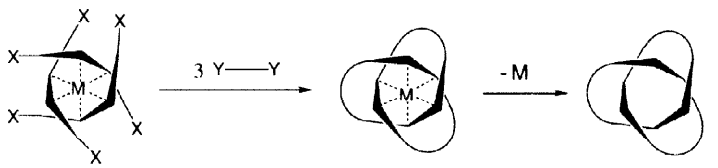
Figure 15. A series of interesting topologies accessible via Sauvage's double helix strategy.

Most recently, Sauvage has extended his methodology further to the synthesis of composite knots, that is to say knots made up of more than one subunit as opposed to the prime trefoil knot (Scheme 18, cf Figure 6).[95] The precursor **68** is the first example of a synthetic pseudo-knot to appear in the literature, and as explained above this structure represents a key intermediate for the preparation of knots. However, the pseudo-knot cannot be isolated: it is the minor component in an inseparable mixture with **67**, and so the yield of the diastereomeric composite knots **69** and **70** is low.



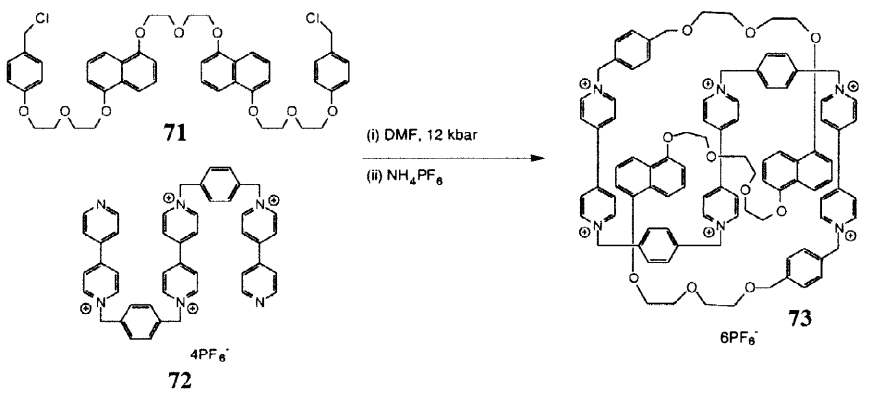
Scheme 18. Sauvage's synthesis of composite knots.

In 1973, Sokolov suggested a templating strategy based upon an octahedral metal centre with three coordinated bidentate ligands.[96] If three functionalised ligands are arranged around an octahedral metal ion, they are disposed in such a way that connection of the appropriate ends leads to a trefoil knot (Scheme 19). However, the probability of linking the ends in the correct manner is fairly remote, when one considers the numerous wrong connections that could be made. Not surprisingly, nearly 25 years after the original proposal, no experimental results have been reported using such a strategy. We are currently pursuing a strategy based on the Sokolov proposal in our laboratory.



Scheme 19. Sokolov's strategy for a trefoil knot synthesis via an octahedral metal ion template. X and Y represent groups that can react together to form a new bond.

Stoddart has reported the synthesis of a trefoil knot utilising the aromatic interactions used so successfully in his catenane and rotaxane syntheses. Macrocyclisation of **71** and **72** gave a complex mixture of products: two of the fractions isolated by hplc gave a molecular ion corresponding to **73** in the mass spectrum, and these were tentatively assigned as the trefoil knot and the unknotted topological isomer (Scheme 20).[97]



Scheme 20. Stoddart's trefoil knot synthesis.

REFERENCES

(1) For a discussion of optical activity and stereoisomerism, see March, J. *Advanced Organic Chemistry*, 4th Edition; Wiley: New York, 1992; pp. 94-127.

(2) Wasserman, E. *J. Am. Chem. Soc.* **1960**, *82*, 4433.

(3) Walba, D.M., *Tetrahedron* **1985**, *41*, 3161.

(4) Amabilino, D.B.; Stoddart, J.F. *Chem. Rev.* **1995**, *95*, 2725.

(5) (a) Sauvage, J.-P. *Acc. Chem. Res.* **1990**, *23*, 319. (b) Dietrich-Buchecker, C.O.; Sauvage, J.-P. *Chem. Rev.* **1987**, *87*, 795.
(6) Turro, N.J. *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 882.
(7) Arnold, B.H. *Intuitive Concepts in Elementary Topology*; Prentice-Hall: Englewood Cliffs, NJ, 1962.
(8) Ashton, P.R.; Baxter, I.; Fyfe, M.C.T.; Raymo, F.M.; Spencer, N.; Stoddart, J.F.; White, A.J.P.; Williams, D.J. *J. Am. Chem. Soc.* **1998**, *120*, 2297.
(9) Hudson, B.; Vinograd, J. *Nature* **1967**, *216*, 647.
(10) Clayton, D.A.; Vinograd, J. *Nature* **1967**, *216*, 652.
(11) Liu, L.F.; Depew, R.E.; Wang, J.C. *J. Mol. Biol.* **1976**, *106*, 439.
(12) Liu, L.F.; Perkocha, L.; Calendar, R.; Wang, J.C. *Proc. Natl. Acad. Sci. USA* **1981**, *78*, 5498.
(13) Kreuzer, K.N.; Cozzarelli, N.R. *Cell* **1980**, *20*, 245.
(14) Krasnow, M.A.; Stasiak, A.; Spengler, S.J.; Dean, F.; Koller, T.; Cozzarelli, N.R. *Nature* **1983**, *304*, 559.
(15) Jaenisch, R.; Levine, A.J. *J. Mol. Biol.* **1973**, *73*, 199.
(16) Wang, J.C. *J. Mol. Biol.* **1971**, *55*, 523.
(17) Bates, A.D.; Maxwell, A. *DNA Topology*; Oxford University Press: Oxford, 1993.
(18) Maxwell, A.; Gellert, M. *Adv. Prot. Chem.* **1986**, *38*, 69.
(19) Hayashi, Y.; Hayashi, M. *Biochemistry* **1971**, *10*, 4212.
(20) Tse-Dinh, Y.-C. *Nucleic Acids Res.* **1985**, *13*, 4751.
(21) Drlica, K.; Franco, R.J. *Biochemistry* **1988**, *27*, 2253.
(22) Liu, L.F.; Wang, J.C. *Proc. Natl. Acad. Sci. USA* **1987**, *84*, 7024.
(23) Du, S.M.; Stollar, B.D.; Seeman, N.C. *J. Am. Chem. Soc.* **1995**, *117*, 1194.
(24) Chen, J.; Seeman, N.C. *Nature* **1991**, *350*, 631.
(25) Zhang, Y.; Seeman, N.C. *J. Am. Chem. Soc.* **1994**, *116*, 1661.
(26) Liang, C.; Mislow, K. *J. Am. Chem. Soc.* **1994**, *116*, 11189.
(27) Liang, C.; Mislow, K. *J. Am. Chem. Soc.* **1995**, *117*, 4201.
(28) Takusagawa, F.; Kamitori, S. *J. Am. Chem. Soc.* **1996**, *118*, 8945.
(29) Walba, D.M. *New J. Chem.* **1993**, *17*, 618.
(30) Van Gulick, N. *New J. Chem.* **1993**, *17*, 619.
(31) Wasserman, E. *Sci. Am.* **1962**, *207*, 94.
(32) Frisch, H.L.; Wasserman, E. *J. Am. Chem. Soc.* **1961**, *83*, 3789.
(33) Harrison, I.T.; Harrison, S. *J. Am. Chem. Soc.* **1967**, *89*, 5723.
(34) Agam, G.; Zilka, A. *J. Am. Chem. Soc.* **1976**, *98*, 5212.
(35) Agam, G.; Zilka, A. *J. Am. Chem. Soc.* **1976**, *98*, 5214.
(36) Walba, D.M.; Richards, R.M.; Haltiwanger, R.C. *J. Am. Chem. Soc.* **1982**, *104*, 3219.
(37) Walba, D.M.; Armstrong, J.D.; Perry, A.E.; Richards, R.M.; Homan, T.C.; Haltiwanger, R.C. *Tetrahedron* **1986**, *42*, 1883.
(38) Watson, J.D.; Crick, F.H.C. *Nature* **1953**, *171*, 737.
(39) Busch, D.H. *J. Inclusion Phenom.* **1992**, *12*, 389.
(40) Anderson, S.; Anderson, H.L.; Sanders, J.K.M. *Acc. Chem. Res.* **1993**, *26*, 469.
(41) For a short review and further references, see Vögtle, F.; Hoss, R. *Angew. Chem. Intl. Ed. Engl.* **1994**, *33*, 375.

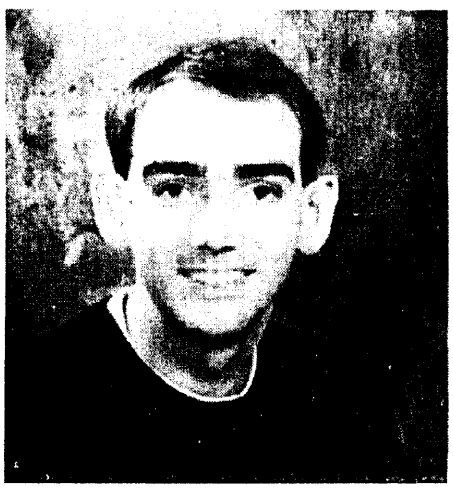
(42) Curtis, N.F.; House, D.A. *Chem. Ind.* **1961**, *42*, 1708.
(43) Curry, J.D.; Busch, D.H. *J. Am. Chem. Soc.* **1964**, *86*, 592.
(44) Pedersen, C.J. *J. Am. Chem. Soc.* **1967**, *89*, 7017.
(45) Greene, R.N. *Tetrahedron Lett.* **1972**, 1793.
(46) McMurry, T.J.; Rodgers, S.J.; Raymond, K.N. *J. Am. Chem. Soc.* **1987**, *109*, 3451.
(47) Anderson, H.L.; Sanders, J.K.M. *J. Chem. Soc. Chem. Commun.* **1992**, 1163.
(48) Anderson, H.L.; Sanders, J.K.M. *Angew. Chem. Intl. Ed. Engl.* **1990**, *29*, 1400.
(49) Lüttringhaus, A.; Cramer, F.; Prinzbach, H.; Henglein, F.M. *Liebigs Ann. Chem.* **1958**, *185*, 613.
(50) Schill, G.; Lüttringhaus, A. *Angew. Chem. Intl. Ed. Engl.* **1964**, *3*, 546.
(51) Schill, G.; Rissler, K.; Fritz, H.; Vetter, W. *Angew. Chem. Intl. Ed. Engl.* **1981**, *20*, 187.
(52) Dietrich-Buchecker, C.O.; Sauvage, J.-P. *Chem. Rev.* **1987**, *87*, 795.
(53) Dietrich-Buchecker, C.O.; Sauvage, J.-P. *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 289.
(54) (a) Dietrich-Buchecker, C.O.; Sauvage, J.-P. *Tetrahedron Lett.* **1983**, *24*, 5091. (b) Dietrich-Buchecker, C.O.; Sauvage, J.-P., Kintzinger, J.P. *Tetrahedron Lett.* **1983**, *24*, 5095. (c) Dietrich-Buchecker, C.O.; Sauvage, J.-P.; Kern, J.-M. *J. Am. Chem. Soc.* **1984**, *106*, 3043.
(55) Mohr, B.; Weck, M.; Sauvage, J.-P.; Grubbs, R.H. *Angew. Chem. Intl. Ed. Engl.* **1997**, *36*, 1308.
(56) Mitchell, D.K.; Sauvage, J.-P. *Angew. Chem. Intl. Ed. Engl.* **1988**, *27*, 930.
(57) For further examples, see (a) Chambron, J.-C.; Heitz, V.; Sauvage, J.-P. *J. Chem. Soc. Chem. Commun.* **1992**, 1131. (b) Chambron, J.-C.; Dietrich-Buchecker, C.O.; Nierengarten, J.F.; Sauvage, J.P.; Solladie, N.; Albrecht-Gary, A.M.; Meyer, M. *New J. Chem.* **1995**, *19*, 409. (c) Momenteau, M.; LeBras, F.; Loock, B. *Tetrahedron Lett.* **1994**, *35*, 3289. (d) Chambron, J.-C.; Heitz, V.; Sauvage, J.-P. *Bull. Soc. Chim. Fr.* **1995**, *32*, 340. (e) Jorgensen, T.; Becher, J.; Chambron, J.-C.; Sauvage, J.-P. *Tetrahedron Lett.* **1994**, *35*, 4339. (f) Sauvage, J.-P.; Ward, M. *Inorg. Chem.* **1991**, *30*, 3869.
(58) Wu, C.; Lecavalier, P.R.; Shen, Y.X.; Gibson, H.W. *Chem. Mater.* **1991**, *3*, 569.
(59) Dietrich-Buchecker, C.O.; Hemmert, C.; Khémiss, A.-K.; Sauvage, J.P. *J. Am. Chem. Soc.* **1990**, *112*, 8002.
(60) Bitsch, F.; Dietrich-Buchecker, C.O.; Hemmert, C.; Khémiss, A.-K.; Sauvage, J.P. *J. Am. Chem. Soc.* **1991**, *113*, 4023.
(61) Stoddart, J.F. *Chem. Brit.* **1991**, 714.
(62) Stoddart, J.F. *Pure Appl. Chem.* **1988**, *60*, 467.
(63) Odell, B.; Reddington, M.V.; Slawin, A.M.Z.; Spencer, N.; Stoddart, J.F.; Williams, D.J. *Angew. Chem. Intl. Ed. Engl.* **1988**, *27*, 1547.
(64) Ashton, P.R.; Goodnow, T.T.; Kaifer, A.E.; Reddington, M.V.; Slawin, A.M.Z.; Spencer, N.; Stoddart, J.F.; Vicent, C.; Williams, D.J. *Angew. Chem. Intl. Ed. Engl.* **1989**, *28*, 1396.
(65) Ashton, P.R.; Brown, C.L.; Chrystal, E.J.T.; Goodnow, T.T.; Kaifer, A.E.; Parry, K.P.; Slawin, A.M.Z.; Spencer, N.; Stoddart, J.F.; Williams, D.J. *Angew. Chem. Intl. Ed. Engl.* **1991**, *30*, 1039. For further examples of multi-ring catenanes, see Amabilino, D.B.; Ashton, P.R.; Brown, C.L.; Córdova, E.; Godinez, L.A.; Goodnow, L.A.; Goodnow, T.T.; Kaifer, A.E.; Newton, S.P.; Pietraszkiewicz, M.; Philp, D.; Raymo, F.M.; Reder, A.S.; Rutland, M.T.; Slawin, A.M.Z.; Spencer, N.; Stoddart, J.F.; Williams, D.J. *J. Am. Chem. Soc.* **1995**, *117*, 1271. Amabilino, D.B.; Ashton, P.R.; Reder, A.S.; Spencer, N.; Stoddart, J.F. *Angew. Chem. Intl. Ed. Engl.* **1994**, *33*, 433. Amabilino, D.B.; Ashton, P.R.; Reder, A.S.; Spencer, N.; Stoddart, J.F. *Angew. Chem. Intl. Ed. Engl.* **1994**, *33*, 1286.

(66) Ashton, P.R.; Johnston, M.R.; Stoddart, J.F.; Tolley, M.S.; Wheeler, W. *J. Chem. Soc. Chem. Commun.* **1992**, 1128.
(67) Ashton, P.R.; Belohradsky, M.; Philp, D.; Stoddart, J.F. *J. Chem. Soc. Chem. Commun.* **1993**, 1269.
(68) (a) Ashton, P.R.; Brown, C.L.; Chrystal, E.J.T.; Parry, K.P.; Pietraszkiewicz, M.; Spencer, N.; Stoddart, J.F. *Angew. Chem. Intl. Ed. Engl.* **1991**, *30*, 1042. (b) Stoddart, J.F. *Chem. Brit.* **1991**, 714.
(69) (a) Ashton, P.R.; Ballardini, R.; Balzani, V.; Boyd, S.E.; Credi, A.; Gandolfi, M.T.; GomezLopez, M.; Iqbal, S.; Philp, D.; Preece, J.A.; Prodi, L.; Ricketts, H.G.; Stoddart, J.F.; Tolley, M.S.; Venturi, M.; White, A.J.P.; Williams, D.J. *Chem. Eur. J.* **1997**, *3*, 152. (b) Anelli, P.L.; Asakawa, M.; Ashton, P.R.; Bissell, R.A.; Clavier, G.; Gorski, R.; Kaifer, A.E.; Langford, S.J.; Mattersteig, G.; Menzer, S.; Philp, D.; Slawin, A.M.Z.; Spencer, N.; Stoddart, J.F.; Tolley, M.S.; Williams, D.J. *Chem. Eur. J.* **1997**, *3*, 1113.
(70) Hamilton, D. G.; Sanders, J. K. M.; Davies, J. E.; Clegg, W.; Teat, S. J. *Chem. Comm.* **1997**, 897.
(71) Hunter, C.A. *J. Am. Chem. Soc.* **1992**, *114*, 5303.
(72) Carver, F.J.; Hunter, C.A.; Shannon, R.J. *J. Chem. Soc. Chem. Commun.* **1994**, 1277.
(73) Adams, H.; Carver, F.J.; Hunter, C.A. *J. Chem. Soc. Chem. Commun.* **1995**, 809.
(74) Vögtle, F.; Meier, S.; Hoss, R. *Angew. Chem. Intl. Ed. Engl.* **1992**, *31*, 1619.
(75) Ottens-Hildebrandt, S.; Nieger, M.; Rissanen, K.; Rouvinen, J.; Meier, S.; Harder, G.; Vögtle, F. *J. Chem. Soc. Chem. Commun.* **1995**, 777.
(76) Vögtle, F.; Händel, M.; Meier, S.; Ottens-Hildebrandt, S.; Ott, F.; Schmidt, T. *Liebigs Ann. Chem.* **1995**, 739.
(77) Johnston, A.G.; Leigh, D.A.; Pritchard, R.J.; Deegan, M.D. *Angew. Chem. Intl. Ed. Engl.* **1995**, *34*, 1209.
(78) Johnston, A.G.; Leigh, D.A.; Murphy, A.; Smart, J.P. *Bull. Soc. Chim. Belges* **1996**, *105*, 721.
(79) Ashton, P.R.; Campbell, P.J.; Chrystal, E.J.T.; Glink, P.T.; Menzer, S.; Philp, D.; Spencer, N.; Stoddart, J.F.; Tasker, P.A.; Williams, D.J. *Angew. Chem. Intl. Ed. Engl.* **1995**, *34*, 1865.
(80) (a) Ashton, P.R.; Glink, P.T.; Stoddart, J.F.; Tasker, P.A.; White, A.J.P.; Williams, D.J. *Chem. Eur. J.* **1996**, *2*, 729. (b) Kolchinski, A.G.; Busch, D.H.; Alcock, N.W. *J. Chem. Soc. Chem. Commun.* **1995**, 1289.
(81) Anderson, S.; Anderson, H.L. *Angew. Chem. Intl. Ed. Engl.* **1996**, *35*, 1956.
(82) Fujita, M.; Ibukuro, F.; Hagihara, H.; Ogura, K. *Nature* **1994**, *367*, 720.
(83) Fujita, M.; Ibukuro, F.; Yamaguchi, K.; Ogura, K. *J. Am. Chem. Soc.* **1995**, *117*, 4175.
(84) Schill, G.; Doerjer, G.; Logemann, E.; Fritz, H. *Chem. Ber.* **1979**, *112*, 3603.
(85) Schill, G.; Tafelmair, F. *Synthesis* **1971**, *10*, 546.
(86) Schill, G.; Keller, U.; Fritz, H. *Chem. Ber.* **1983**, *116*, 3675.
(87) Walba, D.M. In *Graph Theory and Topology in Chemistry*, Ed. King, R.B.; Elsevier: Amsterdam, 1987; pp23-42.
(88) Walba, D.M.; Zheng, Q.Y.; Schilling, K. *J. Am. Chem. Soc.* **1992**, *114*, 6259.
(89) Lehn, J.M.; Pigault, A. *Angew. Chem. Intl. Ed. Engl.* **1988**, *27*, 1095.
(90) Dietrich-Buchecker, C.O.; Sauvage, J.P. *New. J. Chem.* **1992**, *16*, 277.
(91) (a) Dietrich-Buchecker, C.O.; Nierengarten, J.F.; Sauvage, J.P.; Armaroli, N.; Balzani, V.; De Cola, L. *J. Am. Chem. Soc.* **1993**, *115*, 11237. (b) Dietrich-Buchecker, C.O.; Sauvage, J.P.; De Cian, A.; Fischer, J. *J. Chem. Soc. Chem. Commun.* **1994**, 2231.

(92) Dietrich-Buchecker, C.O.; Rapenne, G.N.; Sauvage, J.P. *Chem. Comm.* **1997**, 2053.
(93) Nierengarten, J.F.; Dietrich-Buchecker, C.O.; Sauvage, J.P. *J. Am. Chem. Soc.* **1994**, *116*, 375.
(94) Dietrich-Buchecker, C.O.; Leize, E.; Nierengarten, J.F.; Sauvage, J.P.; Van Dorsselaer, A. *J. Chem. Soc. Chem. Commun.* **1994**, 2257.
(95) Carina, R.F.; Dietrich-Buchecker, C.; Sauvage, J.-P. *J. Am. Chem. Soc.* **1996**, *118*, 9110.
(96) Sokolov, V.I. *Russ. Chem. Rev.* **1973**, *42*, 452.
(97) Ashton, P.R.; Matthews, O.A.; Menzer, S.; Raymo, F.M.; Spenver, N.; Stoddart, J.F.; Williams, D.J. *Liebigs Ann. Recueil* **1997**, 2485.

Biographical sketch

Christopher A. Hunter



Paul C. Mayers

Chris Hunter studied at Churchill College, University of Cambridge, where he received his BA in 1986 and PhD in 1989 under the supervision of Professor J. K. M. Sanders in the Department of Chemistry. He then moved to a lectureship at the University of Otago, New Zealand. In 1991, he moved to the University of Sheffield, where he is currently the Lister Institute Professor of Chemistry and head of Organic Chemistry. His research interests are based around the chemistry of non-covalent interactions and include template synthesis, self-assembly of chromophore arrays, quantitative studies of molecular recognition, DNA structure and computer modelling. Chris Hunter is a Lister Institute research fellow. He has received the Meldola medal from the Royal Society of Chemistry and the Zeneca Research Award for Organic Chemistry.

Paul Mayers was born in Chester, England in 1972. He received a BSc degree from the University of Sheffield in 1994 and remained at Sheffield for PhD studies with Professor C. A. Hunter working on the metal ion templated synthesis of molecular knots. He is currently carrying out postdoctoral work with Dr M. Hannon and Dr P. Taylor at the University of Warwick on dendrimer-based metalloenzyme mimics.