

Figure 10.51 Melamine-cyanuric acid derivatives arranged according to their relative stability as measured by the $HB/(N - 1)$ parameter. (Reprinted with permission from Section Key Reference © 1995 American Chemical Society).

10.7 Catenanes and Rotaxanes

➔ Raymo, F. M. and Stoddart, J. F. 'Interlocked macromolecules', *Chem. Rev.*, 1999, **99**, 1643–1666.

10.7.1 Overview

➔ Breault, G. A., Hunter, C. A. and Mayers, P. C., 'Supramolecular topology', *Tetrahedron* 1999, **55**, 5265–5293.

A catenane is a compound consisting of two or more rings that are interlocked mechanically without there being necessarily any chemical interaction between the two. Generally, the rings cannot be separated without breaking a chemical bond. Catenanes are named according to the number of interlocked rings, *e.g.* a [2]catenane consists of two interlocked rings (Figure 10.52). The 'ane' ending is by analogy with *alkanes* and, generally, a catenane is taken to be an organic fragment, although it rarely consists solely of hydrocarbon moieties. The terms [n]catenand and [n]catenate are also used, by analogy with *cryptand* and *cryptate*, in circumstances where the interlocked ring system is capable of acting as a ligand for a metal centre. The catenand is the free ligand that forms a catenate complex in the presence of a metal centre.

Rotaxanes consist of a long, fairly linear molecule threaded through a macrocyclic ring, like cotton through the eye of a needle. Again, true rotaxanes cannot decompose back to a separate ring and chain without breaking chemical bonds, and hence the linear, chain part of the molecule is terminated frequently by bulky groups that are too large to fit through the cyclic fragment. Rotaxanes without such physical barriers, in which the 'thread' can slip out of the 'needle', are termed *pseudorotaxanes*. Pseudorotaxanes are frequently necessary precursors to both rotaxanes and catenanes. Typical synthetic procedures consist of the templated self-assembly of a pseudorotaxane (a kind of host-guest complex)

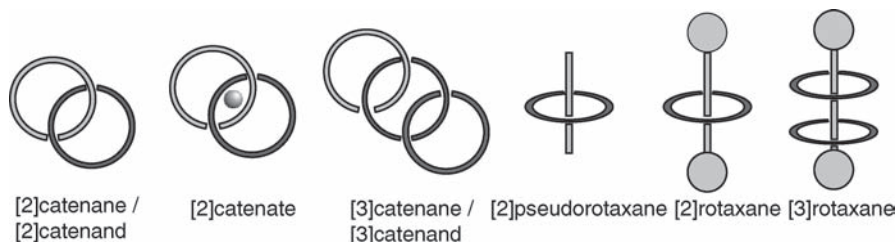


Figure 10.52 Nomenclature of catenanes, rotaxanes and pseudorotaxanes.

via the intermediary of a metal ion, electrostatic or hydrogen bonding forces, followed by ring closure (catenanes) or termination at one or both ends with a bulky end group (rotaxanes) (Figure 10.53). Formation of these species is, to some extent, an academic curiosity, although as we saw in Chapter 2 they are models of some biological molecular machinery such as ATP synthase, which which couples the rotation of an axle in a wheel with the endergonic production of ATP, and DNA polymerisation by enzymes such as DNA polymerase III. However, the long-term possibilities for their application include the formation of sophisticated switchable molecular devices, development of materials with new physical properties, and surface immobilisation of catalytically photo or redox active species without the need to alter their properties by chemical modification.

The chemical composition of a catenane or rotaxane is identical to the two (or more) separate components, yet the threading of one component through another has important consequences for the physical and chemical properties of the resulting aggregate. This observation classes the formation of interlinked and threaded species as a form of isomerism (different from traditional chemical isomerism, such as *cis/trans* and *fac/mer*). Catenanes are termed 'topological' isomers of their separated ring components. In this context, we understand the topology of the aggregate to mean the number and type of crossing points if the structure is drawn out in two dimensions (*e.g.* on a piece of paper – this 2D representation is termed a *molecular graph*). We cannot draw a [2]catenane without at least two crossing points, whereas two separated macrocycles do not require any crossing points. The two structures are thus fundamentally different. Formally, they are *homeomorphic* (*i.e.* have the same form) without being *isotopic* (same structure and composition) and we say that their molecular graph is *non-planar* and their topology is *non-trivial*. Interestingly, following this strict definition, rotaxanes are not topological isomers of their individual components since, conceptually at least, the ring of the rotaxane can always be slipped over the end of the linear portion to give the separated constituents by infinitely expanding the ring. Chemically, while

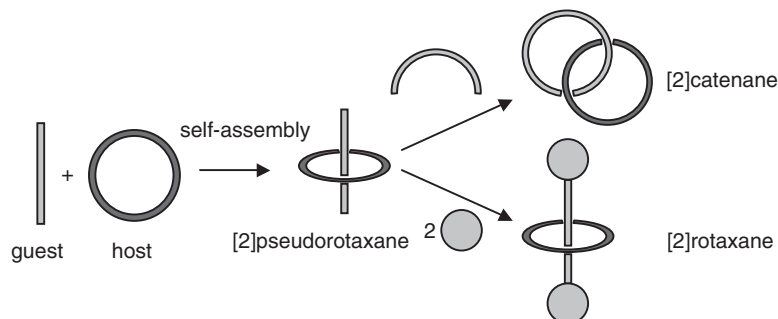


Figure 10.53 Synthesis of catenanes and rotaxanes via host-guest chemistry.

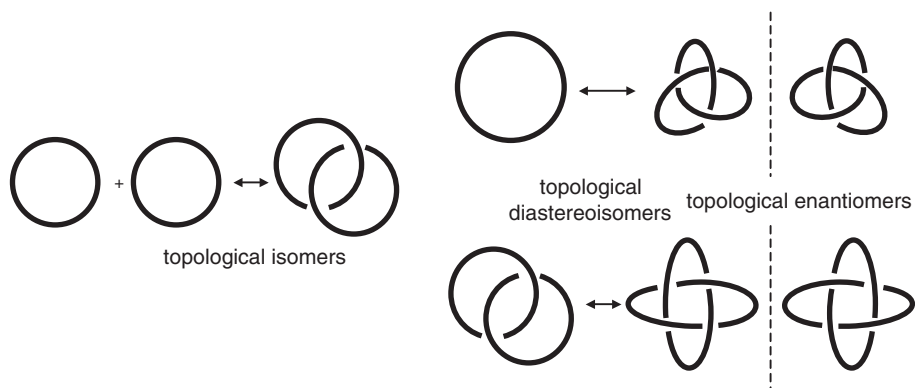


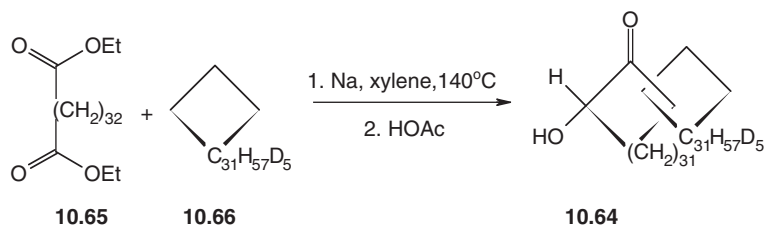
Figure 10.54 Topological isomerism, diastereoisomerism and chirality as related to a [2]catenane, a trefoil knot and a doubly interlocked [2]catenane.

this is true for a pseudorotaxane, it cannot occur in practice for a true rotaxane because the stoppers (end groups) are too large. The difference between the real molecule and the topological definition is that, in topology, all of the components are infinitely stretchable as long as they are not broken. The existence of topological isomers also implies the existence of topological enantiomers in which a chiral catenane or other molecularly knotted system is chiral by virtue of its interlinkage as opposed to any intrinsic chirality of any of the components (Figure 10.54).

10.7.2 Statistical Approaches to Catenanes and Rotaxanes

➔ Amabilino, D. B. and Stoddart, J. F. 'Interlocked and intertwined structures and superstructures', *Chem. Rev.*, 1995, **95**, 2725–2828.

There are two distinct approaches to catenane synthesis: the statistical approach, and approaches relying on self-assembly, so-called 'directed synthesis'. The statistical approach relies on the small chance that macrocyclisation may occur while a linear precursor is threaded through a macrocyclic component. Because this is a rather unlikely eventuality, it naturally results in low yields of interlinked product and is chiefly of historical interest. It was this kind of statistical approach that resulted in the first synthesis of a [2]catenane by Wasserman in 1960 (**10.64**), from cyclisation of the long-chain diester **10.65** while threaded through the annulus of a deuterated C_{34} cycloalkane **10.66** (Scheme 10.11).⁵⁷ Although the overall yield of the catenation reaction was less than 1 %, the existence of the catenane was firmly established. The relatively polar [2]catenane product, along with other polar macrocyclisation reaction products and



Scheme 10.11 The first catenane synthesis *via* the statistical approach.⁵⁷

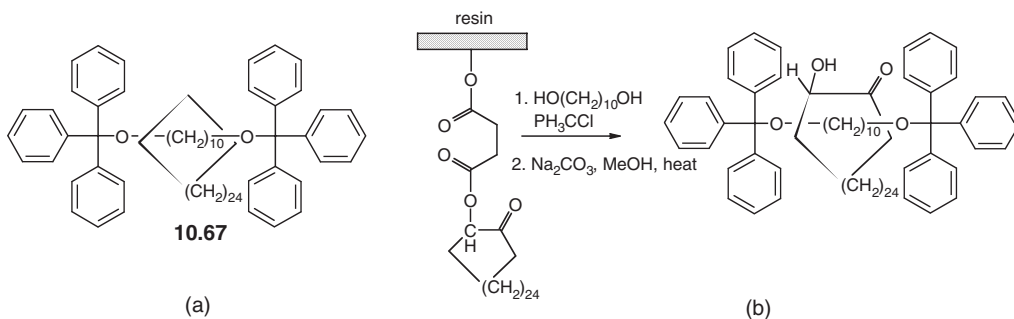


Figure 10.55 Statistical rotaxane synthesis (a) product from solution and (b) analogue prepared in higher yield (6 %) on a solid support.

starting materials, was separated from ‘free’ cycloalkane. The acyloin ring was then cleaved and the nonpolar fraction collected. The presence of the deuterated macrocycle in this reaction fraction, it was argued, could arise only from a catenated product.

Statistical approaches have also been applied to rotaxane synthesis. Rotaxanes and pseudorotaxanes have been prepared by refluxing a range of cyclic hydrocarbons of between 11 and 39 $-\text{CH}_2-$ groups with a linear triphenylmethyl-stoppered component at 120°C . At this elevated temperature, larger rings are occasionally able to ‘slip’ over the end of the triphenylmethyl stopper groups, forming low yields (less than 2 %) of rotaxanes (**10.67**) on cooling. At room temperature, the rotaxane containing the C_{29} macrocycle is stable with respect to slippage back to the constituent components, whereas macrocycles with chain lengths of C_{33} and upwards are extremely labile. It is possible to increase statistical yields by repetitive reaction with the cyclic component immobilised on a solid support. Covalently attaching a C_{28} macrocycle to the surface of a resin and treating it with the dumb-bell components a total of 70 times gives a stable rotaxane that can be cleaved from the resin and purified to give an overall yield of 6 % (Figure 10.55).

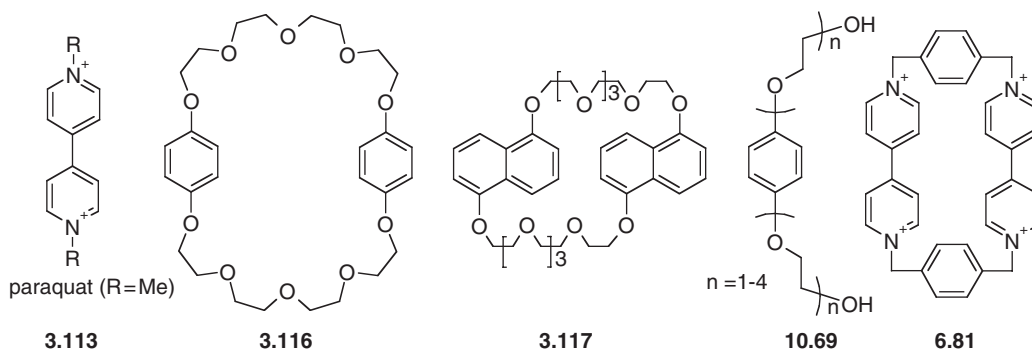
10.7.3 Rotaxanes and Catenanes Involving π - π Stacking Interactions

➔ Schalley, C. A., Beizai, K. and Vögtle, F., ‘On the way to rotaxane-based molecular motors: Studies in molecular mobility and topological chirality’, *Acc. Chem. Res.* 2001, **34**, 465–476.

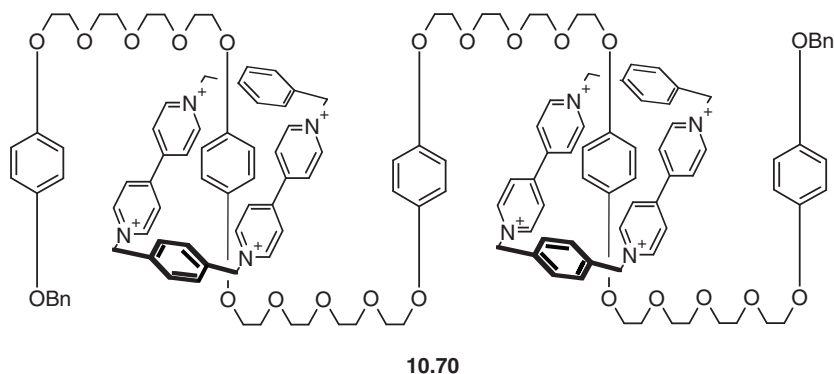
Clearly the low yields obtained in the statistical approach to catenane and rotaxane synthesis suggest that a much more directed approach is very much needed, in which the chemist does not, in effect, rely on luck to thread molecular components together. The obvious strategy towards a directed rotaxane and catenane synthesis is to encourage the threading (self-assembly) of the reactants before the cyclisation or stoppering reaction that covalently fixes the array together. If the reactants are predominantly associated in solution as a self-assembled host–guest complex (*i.e.* relatively large binding constant), there is a much greater probability that they will be associated in the desired fashion when they react. Generally the pre-reaction host–guest complex is a pseudorotaxane and constitutes a self-assembled template for the covalent synthesis of the rotaxanes and catenanes proper (Figure 10.53).

We have already seen (Section 3.12.6) how strong π -stacking interactions occur with the aryl corands **3.116** and **3.117** and the herbicide paraquat (**3.113**) (*e.g.* **3.116** + **3.113**, $K_{11} = 730 \text{ M}^{-1}$ in Me_2CO), resulting in solid-state and solution incorporation of the electron-deficient guest within the corand ring. This inclusion of paraquat within the macrocycle is effectively the formation of a [2]pseudorotaxane, and this

system has formed the basis of extensive work by the group of Sir J. Fraser Stoddart (now at Northwestern University, USA) on the use of such interactions to generate a vast range of interpenetrated molecules. In the case of paraquat, it is the guest that is electron-deficient and the host that is electron-rich. Generally, the stability of the pseudorotaxanes increases with increasing chain length, thus for $R=Me$, $K_{11}(Me_2CO) = 17 M^{-1}$, whereas for $R = H(OCH_2CH_2)_3$, $K_{11} = 2520 M^{-1}$. Either approach is of great synthetic utility in the syntheses of rotaxanes and catenanes. Compare this assembly to Figure 10.12 in which a electron-rich podands of type ROC_6H_4OR ($R = Me$, **10.68**; $R = H(OCH_2CH_2)_n$, $n = 1-4$, **10.69**) are incorporated into a rectangular box made up of two paraquat derivatives (**6.81**) to give another [2]pseudorotaxane. Compound **6.81** is famous as Stoddart's 'little blue box' (Section 6.5.8).



Based on the former approach, Stoddart *et al.* have constructed higher pseudorotaxanes such as the [3]pseudorotaxane **10.70** rather like threading beads on to a string. The tetracationic cyclophane is stabilised by π -stacking and charge-transfer interactions between the aryl rings, the 'solvation' of the positive charge on the 'blue box' by the crown oxygen atoms, and $C-H \cdots O$ hydrogen bonds from the relatively acidic aryl $C-H$ protons to the crown oxygen atoms. The charge-transfer interactions give rise to a characteristic orange colour for all the complexes containing this kind of binding motif.



The most obvious way to prepare a rotaxane from a pseudorotaxane is to attach a bulky substituent group to the open end of the threaded molecule. The overall procedure is termed 'threading' (Figure 10.56). For example, reaction of the [2]pseudorotaxanes formed from di-ols **10.68** and **10.69** and bis(bipyridinium) receptor **6.81** with tri-*iso*-propylsilyl trifluoromethanesulfonate (triflate) in the presence of lutidine gives the corresponding tri-*iso*-propylsilylated [2]rotaxanes (**10.71**) in about

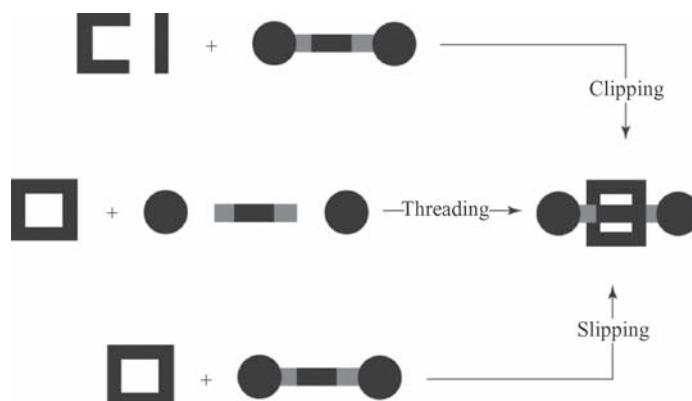
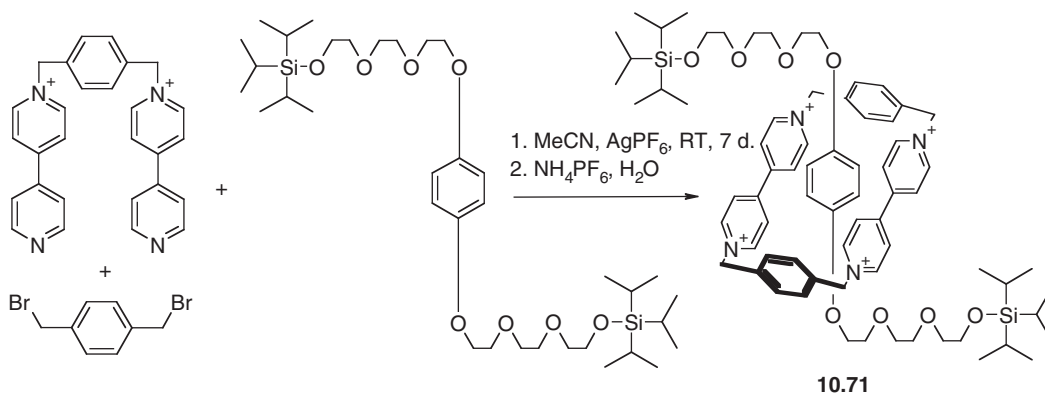


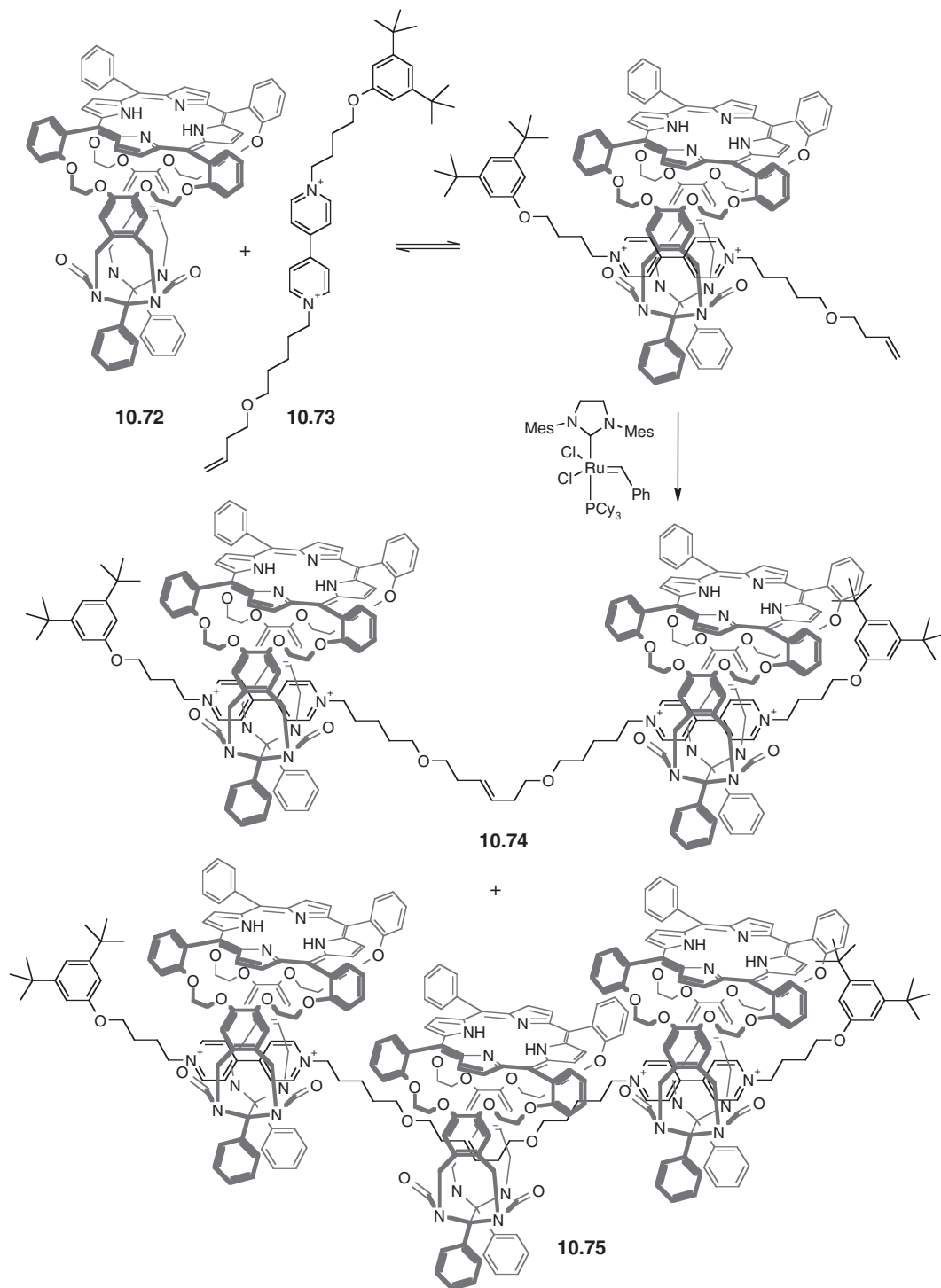
Figure 10.56 Synthesis of rotaxanes *via* self-assembly of electron-rich and electron-poor aryl fragments. (Reproduced with permission from [58]).

21 % yield. The same compound can also be made by the ‘clipping’ route (Figure 10.56) in 14 % yield, using a preformed tri-*iso*-propylsilylated thread according to the reaction shown in Scheme 10.12. The final approach to rotaxanes, slipping, involves the use of a terminator group that is just small enough to pass through the macrocyclic ring upon careful heating/refluxing, but lacks sufficient energy to break through the conformational barrier at lower temperatures, as seen in the statistical approach to rotaxanes such as **10.67**.

A remarkable synthesis of [3]- and [4]rotaxanes has been achieved by Alan Rowan at the University of Nijmegen (Netherlands) using an alkene metathesis approach. Porphyrin-derived macrocycle **10.72** has a very strong affinity for bipyridinium derivatives such as **10.73** ($K_a > 10^6 \text{ M}^{-1}$ in dichloroethane). Combining the two gives a [2]pseudorotaxane with a terminal alkene, ripe for alkene cross-coupling using Grubbs’ catalyst. The coupling reaction gives only a 25 % yield of [3]rotaxane **10.74** and in an attempt to improve yields Rowan’s group added an excess of macrocycle **10.72**. To their surprise this resulted in the formation of the [4]rotaxane **10.75** as well as **10.74**, implying that the thread **10.73** can bind two macrocycles before the coupling stage (Scheme 10.13).⁵⁹ The manganese(II) complex of the porphyrin-containing macrocycle **10.72** is a very good catalyst for epoxidation (addition of an oxygen



Scheme 10.12 Synthesis of a [2]rotaxane *via* the clipping approach.



Scheme 10.13 Synthesis of [3]- and [4]rotaxanes using alkene cross-coupling.⁵⁹

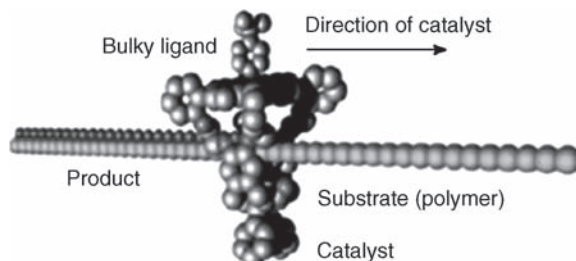


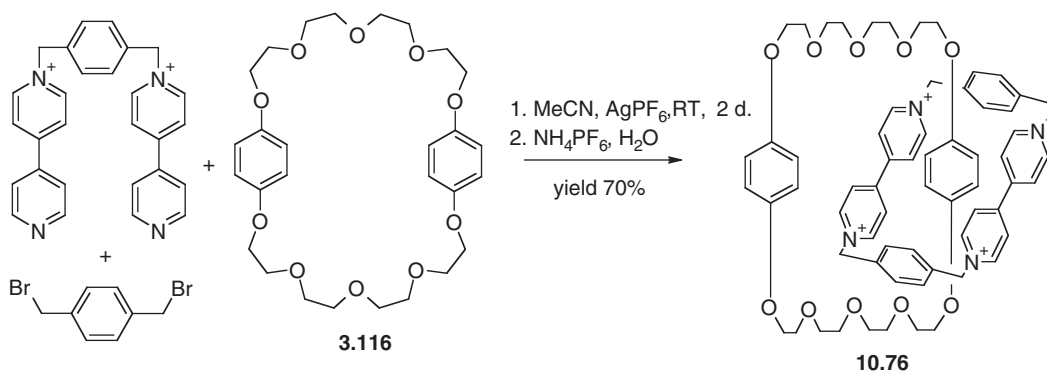
Figure 10.57 Cartoon representation of the Mn(II) complex of **10.72** acting as an epoxidation processing catalyst (reprinted with permission from Macmillan Publishers Ltd).

atom to an alkene to give a three-membered C-O-C ring) of alkenes in the presence of oxidising agents such as iodosylbenzene (PhIO). The toroidal complex can act as a processing catalyst analogous to DNA polymerase (Section 2.9.5) which adds oxygen atoms to a threaded polybutadiene substrate. The process is shown schematically in Figure 10.57.⁶⁰ Rotaxanes are of considerable interest as molecular machines in this kind of way and we will return to this topic in the next chapter (Section 11.5).

By analogy with their use of charge-assisted π - π stacking interactions in rotaxane synthesis, Stoddart's group prepared a [2]catenane by a planned template approach.⁶¹ Again, the preparation involved the electron-deficient blue box **6.81** and followed a procedure in which the cation precursor was first threaded through the electron-rich crown ether **3.116** before ring closure to generate the [2]catenane **10.76** via a clipping approach (Scheme 10.14).

It is a tribute to the templating effect of the electronically matched pairs of reactants that the [2]catenane **10.76** is produced in 70% overall yield. Even the analogous five-component self-assembly reaction in which **3.116** is reacted with two equivalents of 4,4'-bipyridyl and two equivalents of α,α' -dibromo-*p*-xylene proceeds in 42% overall yield. The X-ray crystal structure of this compound (Figure 10.58) shows clearly the interlocking nature of the two rings, with the π -electron-rich quinone and π -electron-deficient bipyridinium rings stacked some 3.5 Å apart. Moreover, this same stacking interaction is seen between one [2]catenane molecule and the next within the solid-state structure, to give an infinite donor-acceptor array, reinforcing the evidence for the templated nature of the synthesis.

[2]Catenane **10.76** displays some very interesting dynamic properties, which may be followed by ¹H NMR spectroscopy. In particular, at 81°C the hydroquinone ring protons appear as a singlet signal



Scheme 10.14 Template synthesis of the [2]catenane **10.76**.⁶¹

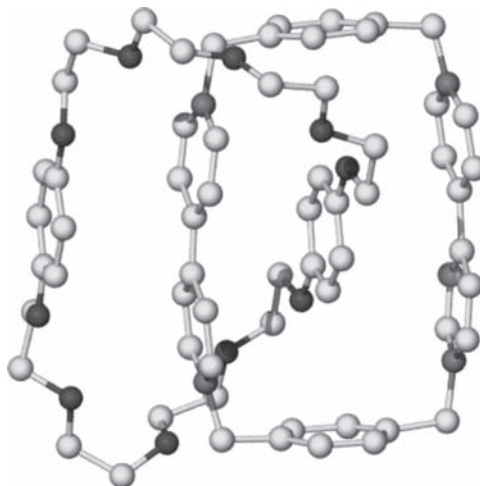


Figure 10.58 X-ray crystal structure of the [2]catenane **10.76**.

at δ 4.57 ppm. At room temperature, slow circumrotation of the crown ether through the bipyridinium macrocycle (process I, Figure 10.59) results in two separate signals at δ 3.45 and 6.16 ppm, the former clearly affected significantly by the shielding effect of the inner surface of the bipyridinium cyclophane **6.81**. Using the coalescence method (Box 3.3), the energy barrier for the rotation can be calculated as 65.3 kJ mol^{-1} . The analogous circumrotation of the cyclophane through the crown ether may be monitored similarly (process II, Figure 10.59). Coalescence calculations give an energy barrier to rotation of 51.1 kJ mol^{-1} with coalescence occurring at -45°C in acetone solution. Two further processes termed rattling and rocking have also been identified.

The excellent synthetic results obtained for **10.76** can be compared with preparative yields obtained for various other π -donor crown ether ring sizes (Table 7.3). Clearly, the 34-membered ring is optimum, with yields dropping off very rapidly with smaller crowns as a function of poor fit. Lower yields are also observed for larger crowns as a result of increased conformational freedom. The greater flexibility of the rings is also reflected in the activation energy for ring rotation by process II, which was lowered by some 10.5 kJ mol^{-1} for the larger crown ethers.

The electrochemistry of catenane **10.76** can be studied by cyclic voltammetry (Box 4.1). The compound possesses very different redox properties in comparison with the two isolated components.

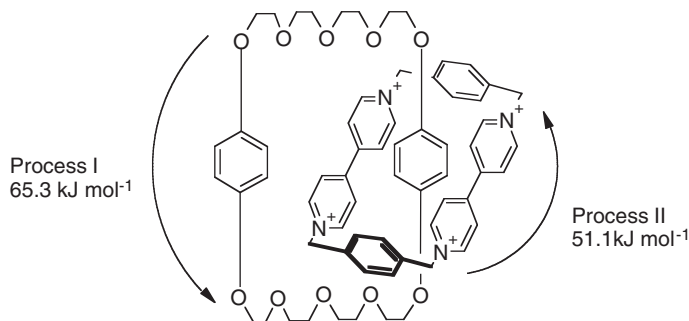


Figure 10.59 Dynamic processes associated with [2]catenane **10.76**.

This difference is a direct result of the close π -stacking interactions. Electrochemical reduction of the bis(bipyridinium) cyclophane occurs in three distinct stages:

1. One-electron reduction of the more accessible, less stabilised bipyridinium moiety outside the crown ether cavity (this bipyridinium moiety acts as an acceptor to just one stabilising hydroquinone unit).
2. A second one-electron reduction corresponding to the bipyridinium moiety inside the cavity.
3. Finally, a two-electron reduction corresponding to the neutralisation of both bipyridinium rings.

In contrast, the bis(bipyridinium) macrocycle component (**6.81**) undergoes only two discrete two-electron reductions. The reason that four distinct reductions are not observed for **10.76** is that following the initial two reductions, the ring circumrotation process (process II, Figure 10.59) becomes fast on the cyclic voltammetric time scale and so the distinction between the 'inner' and 'outer' bipyridinium units is lost. The cyclic voltammetric waves are shown in Figure 10.60.

The self-assembling approach to catenane synthesis adopted by Stoddart *et al.* has proved to be extremely versatile, and since the preparation of **10.76** in 1989, these workers have been able to go on to construct [3]-, [4]- and even [5]- and [7]-catenanes using this methodology. Synthesis of [n]catenanes for values of $n > 2$ must necessarily be based upon larger-ring compounds that can accommodate portions of two interlocked rings within their cavities. Initial studies with this aim focused upon the dimer of **3.116**, tetrakis(*p*-phenylene)-[68]crown-20 (**10.77**). When the bis(bipyridinium) macrocycle is closed around it under relatively mild conditions similar to those shown in Scheme 10.14, only a [2]catenane (**10.78**) is produced, in a poor yield consistent with the large size of the crown ring (*cf.* Table 10.4). However, under 10 kbar pressure, a modest yield of the analogous [3]catenane (**10.79**) is obtained (Scheme 10.15). The low yields are a result of the high degree of flexibility of the 68-membered ring.⁶²

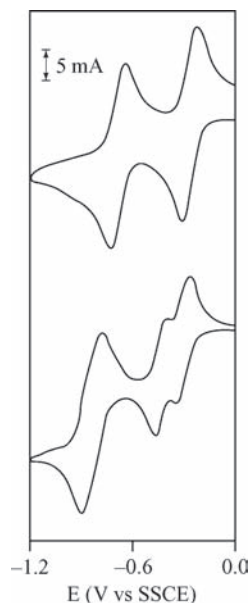
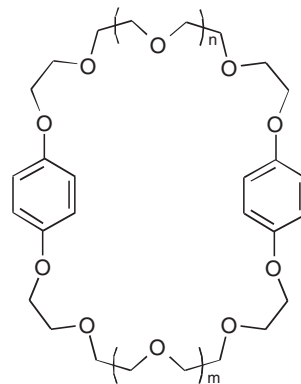


Figure 10.60 Cyclic voltammograms of the cyclophane **6.81** (top) and [2]catenane **10.76** (bottom). (Reprinted with permission from [62] © 1995 American Chemical Society).

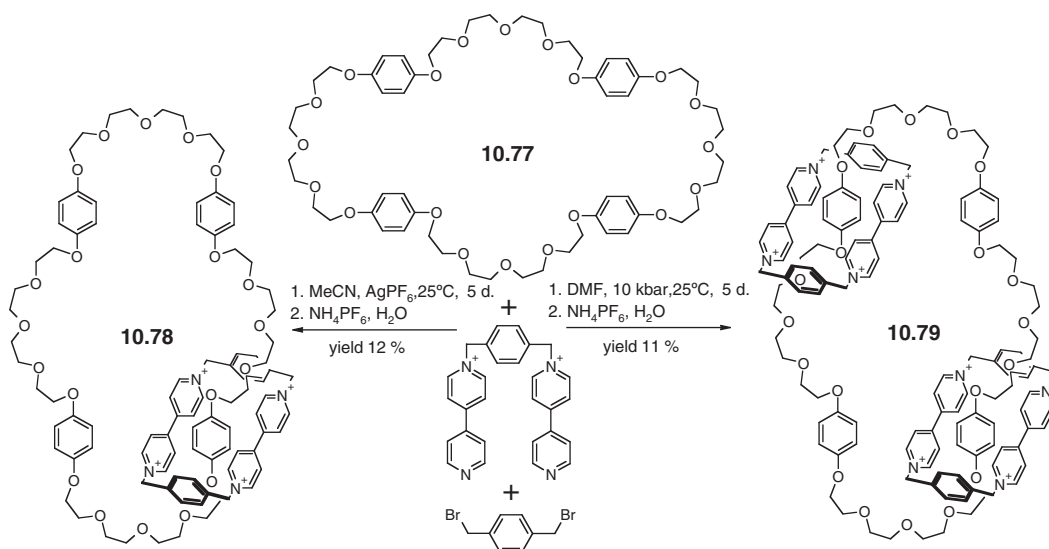
Table 10.4 Yields of [2]catenanes produced *via* the type of reaction shown in Scheme 10.14 as a function of crown ether ring size.

n	m		Yield of [2]catenane (%)
0	1	[31]crown-9	10
1	1	[34]crown-10	70
2	1	[37]crown-11	55
2	2	[40]crown-12	54
3	2	[43]crown-13	40
3	3	[46]crown-14	49

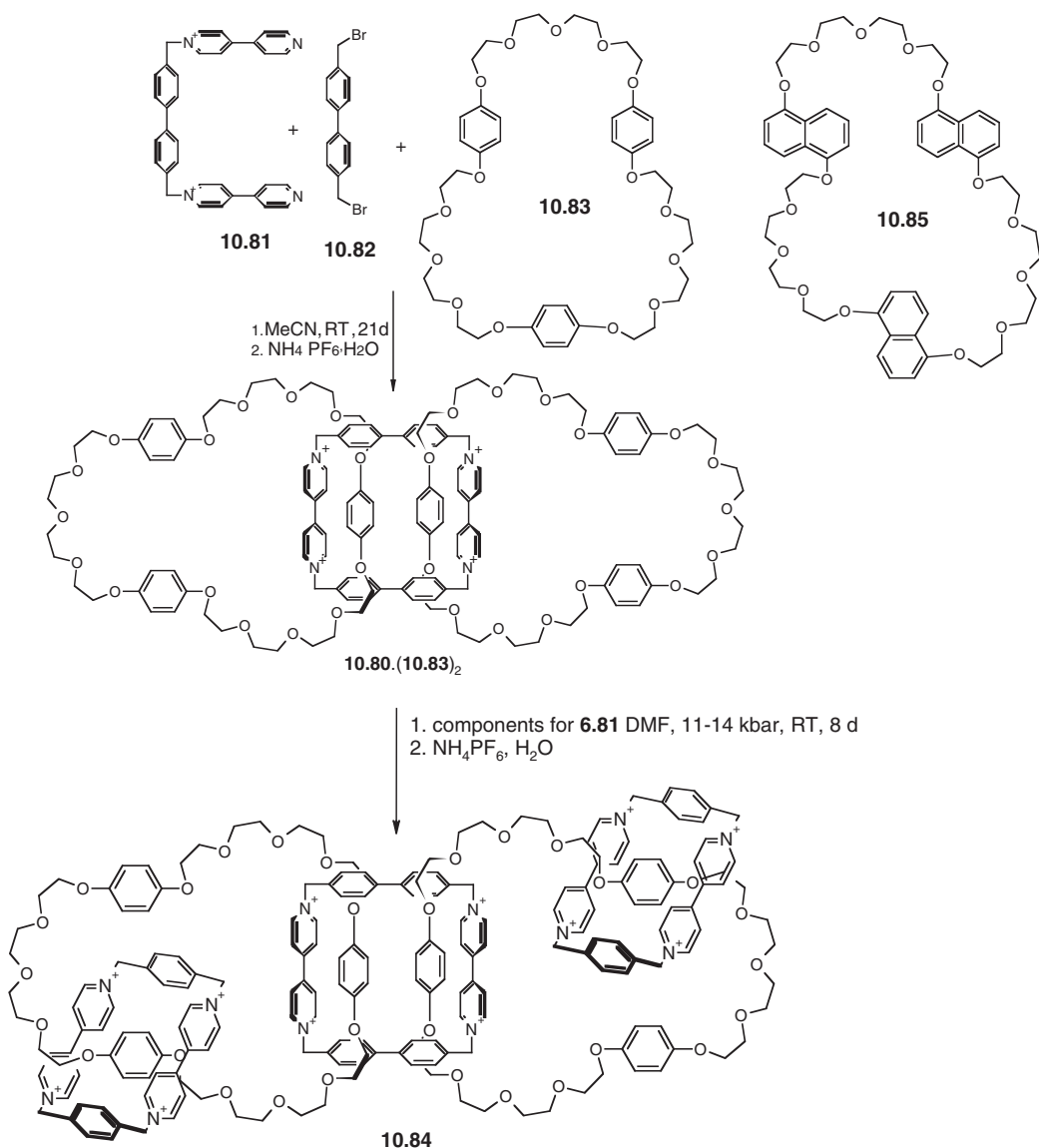


Like its smaller [2]catenane analogues, compound **10.78** exhibits some very interesting dynamic behaviour in which the smaller cationic cyclophane ring behaves like a molecular ‘train’, travelling around the four hydroquinone stations of the crown ring at a rate of 300 times per second, corresponding to an activation energy of 59.0 kJ mol^{-1} . If the [2]catenane is a molecular train, the [3]catenane **10.79** may be described as a molecular ‘merry-go-round’. In solution, the symmetry of the crown ring is maintained indicating that even though both bipyridinium cyclophanes (**6.81**) are travelling around the crown ring (activation energy 57.0 kJ mol^{-1}), they do so in a concerted fashion, remaining at diametrically opposed hydroquinone stations.

Following the success of this work, Stoddart realised that in order to construct even larger catenanes, cyclophane **6.81** would have to be replaced by a larger acceptor ring capable of incorporating two hydroquinone units from separate crown ethers. A combination of a large-ring crown ether electron-donor and large cyclophane cations then allows access to ever larger catenanes and ultimately catenane polymers. The synthesis of a larger electron-acceptor was addressed by the preparation of the tetracationic cyclophane **10.80**, which simply replaces the *p*-xylyl spacer in **6.81** with a *p*-biphenyl group.

**Scheme 10.15** High-pressure synthesis of a [3]catenane.

Stoddart's group anticipated that a two-step process involving clipping of the precursors **10.81** and **10.82** around two molecules of **10.77** to give a [3]catenane centred upon **10.80**, followed by clipping on two molecules of **6.81**, would give the desired [5]catenane. Unfortunately, this ambitious scheme ended in failure, ascribed to the conformational mobility of crown ether **10.77**. Undeterred, they attempted the same strategy with the intermediate-sized crown ether **10.83**. Under atmospheric pressure, this reaction gave the intermediate [3]catenane **10.80**·(**10.83**)₂ in 3.5 % yield which they carried forward to the second stage. Under ultra-high pressure conditions, clipping **6.81** around this [3]catenane gave a 22 % yield of a [4]catenane and just a trace of the desired [5]catenane (**10.84**), Scheme 10.16. This low yield was frustrating, but encouraged the



Scheme 10.16 First synthesis of a [5]catenane.⁶³

researchers to continue with their strategy to prepare macroscopic amounts of a [5]catenane. Their objective was finally achieved by yet another change of crown ether, this time substituting the aryl rings in **10.83** for the 1,5-dioxynaphthalene analogue **10.85**. The strategy shown in Scheme 10.16 produced the expected [5]catenane in an acceptable yield of 5 % without the use of high pressure. The resulting molecule was dubbed ‘olympiadane’ because of its resemblance to the international Olympic Games symbol. The analogous [4]catenane was also produced in 31 % yield.⁶³

Olympiadane was characterised by ¹H NMR spectroscopy, which shows the molecule to be highly symmetric at 60 °C due to fast interannular circumrotation of all the components. The spectrum is significantly broader at room temperature, while at 0 °C the resonances assigned to the smaller cyclophanes (**6.81**) split into two signals corresponding to the freezing out of the rotation of these components. The mass spectrum of the [5]catenane is also highly definitive, with a clear peak at *m/z* 5072 corresponding to olympiadane in conjunction with seven, eight, nine and ten (of a possible 12) PF₆⁻ anions and analogous peaks for the [4]catenane. Also, in a remarkable feat of supramolecular crystallography, the crystal structure of olympiadane has been determined by the group of David Williams at Imperial College, London, revealing a very compact structure. Remarkably Stoddart went on to prepare a [7]catenane by clipping four molecules of **6.81** to the intermediate **10.80**·(**10.83**)₂. The X-ray crystal structure of this enormous supermolecule was also determined by Williams, Figure 10.61.⁶⁴

The charge-assisted $\pi - \pi$ stacking methodology has proved to be enormously versatile and has led to an enormous variety of catenated species. Of particular interest is the chiral bis([2]catenane) **10.86** arising from clipping two equivalents of the bis(pyridinium) precursor with the tetrabromo derivative **10.87** in the presence of crown ether **3.116**. Note that this compound is not a [3]catenane because it does not possess a central ring that interpenetrates with two others. It is simply a covalently linked pair of [2]catenanes. The chirality of the compound is readily evident in its ¹H NMR spectrum, which gives a characteristic AB quartet for the diastereotopic CH₂N⁺ protons of the octacationic cyclophane. Clearly there is little chance (on steric grounds) of the cyclophane cation rotating through the crown ether ring (process II), but the crown rotation (analogous to process I) is observed with an activation energy of 67.0 kJ mol⁻¹, very similar to the [2]catenane analogue **10.76**. At low temperature in acetone-*d*₆, NMR spectroscopy shows that **10.86** exists as two translational

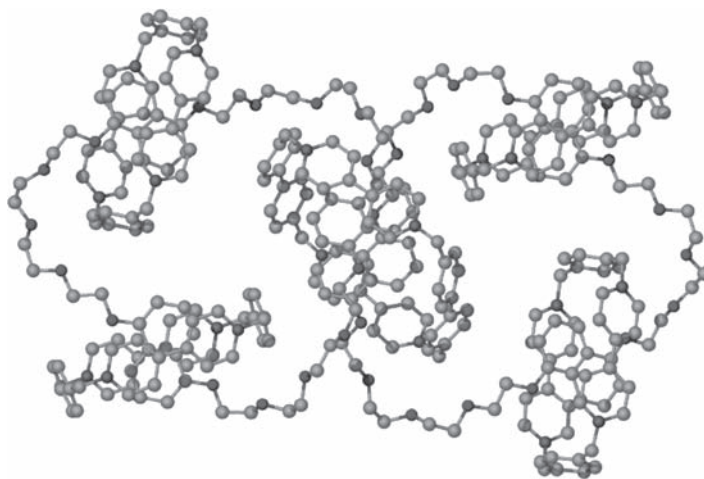
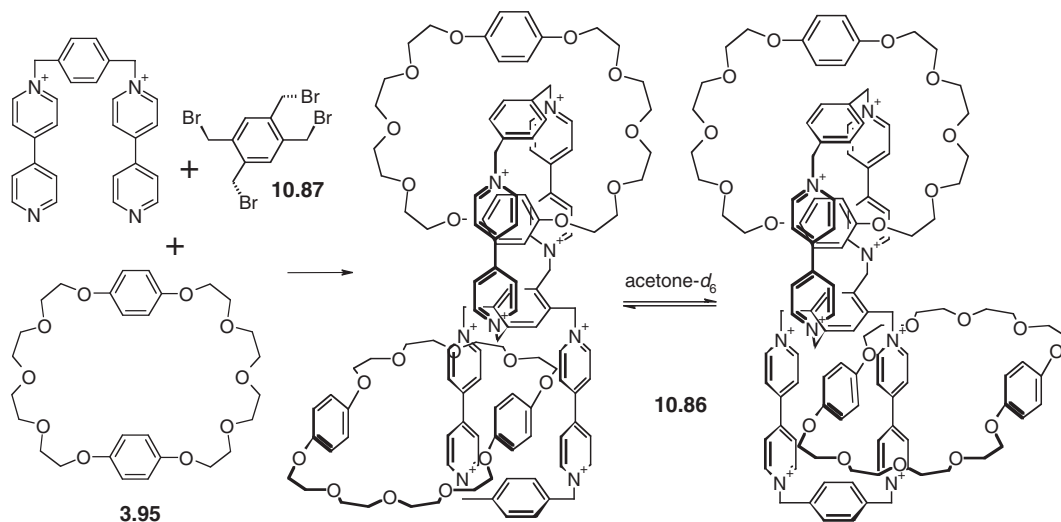


Figure 10.61 X-ray crystal structure of the [7]catenane analogue of olympiadane.⁶⁴ See plate section for colour version of this image.



Scheme 10.17 Synthesis and conformational equilibria of *bis*([2]catenane) **10.86**.⁶⁵

isomers, each of equal population (Scheme 10.17).⁶⁵ *Bis*([2]catenane) **10.86** was prepared in 13 % yield from the one-step self-assembly of five components. Interestingly, the free octacationic cyclophane has not yet been isolated, clearly suggesting that the presence of the electron-rich crown ethers templates the reaction. In general, yields of these types of *bis*([2]catenanes) increase significantly when the length of the covalent spacer between the two rings of the cyclophane cation is increased.

A novel variant on the mechanical interlinking approach is to tether the two interlocked components together. This process results in a single knotted covalent molecule termed a *pretzelane* after the baked savory snack particularly popular in the US. Compound **10.88** is an example of a *pretzelane* (Figure 10.62) which is formed simultaneously with its dimer, a cyclic *bis*([2]catenane).⁶⁶ Use of a longer spacer between the two macrocycles gives exclusive formation of the *pretzelane* in 49 % yield. The *pretzelane* has both helical and plane chirality and hence exists as a mixture of two diastereoisomers, each of which has two enantiomers.

The versatility of this approach to interlocked molecules make it very attractive as a means towards nanoscale molecular machines in which the motions of the individual components are beginning to be translated into molecular logic operations and mechanical switches. We will return to this subject in the next chapter.

10.7.4 Hydrogen Bonded Rotaxanes and Catenanes

➔ Kay, E. R. and Leigh, D. A., 'Hydrogen bond-assembled synthetic molecular motors and machines', *Top. Curr. Chem.* 2005, **262**, 133–177.

While attempting to prepare a simple amide-based macrocycle according to the reaction shown in Scheme 10.18, David Leigh (now of the University of Edinburgh, UK) and co-workers stumbled upon the [2]catenane **10.89** which is formed spontaneously. The two interpenetrated rings completely fill one another's cavity and the complex is held together by amide NH...O hydrogen bonding. These hydrogen bonds give a clue to the reason why catenane formation is so facile and occurs in reasonable yield. The assembling amide precursor is included within a second macrocycle by this same double

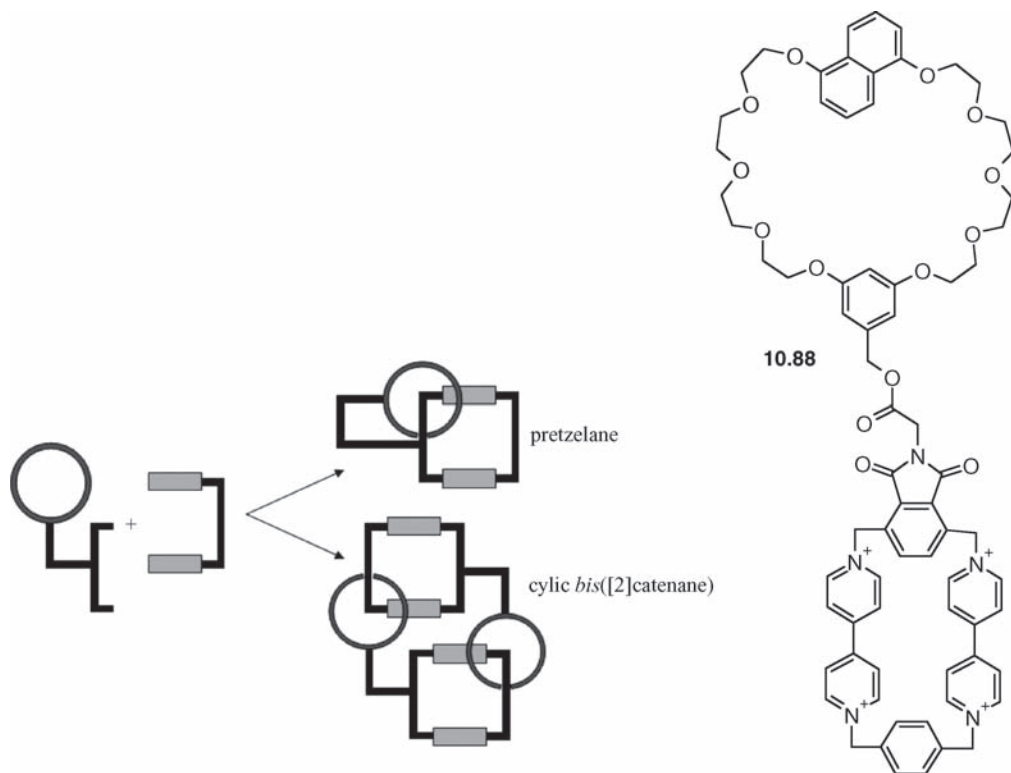
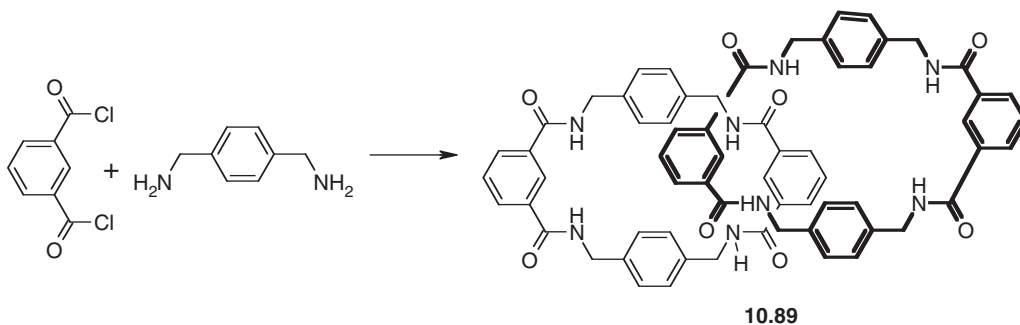


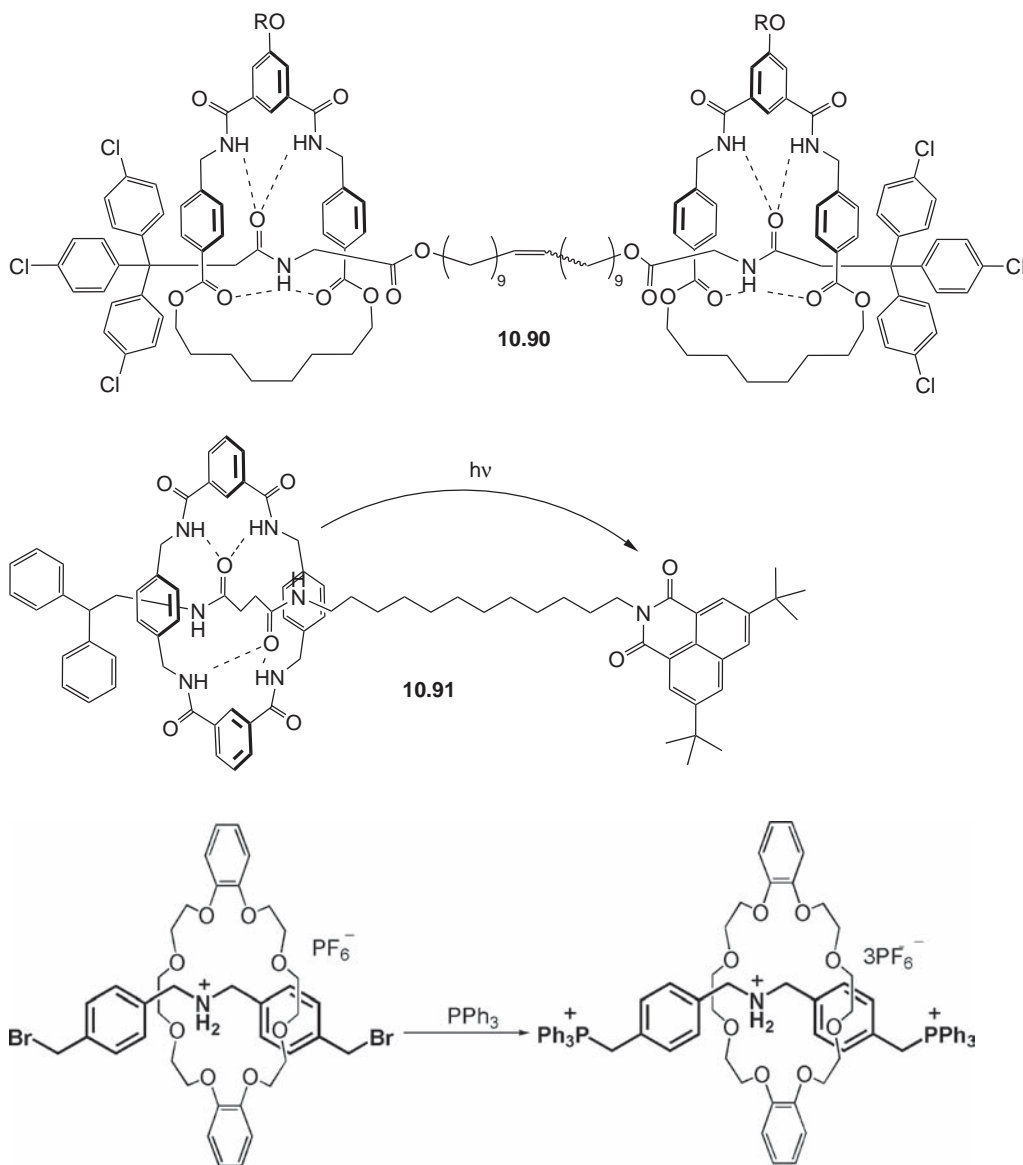
Figure 10.62 Cartoon and 2D molecular representation of *pretzelane* **10.88** and the alternative bis([2]catenane).⁶⁶

NH...O=C hydrogen bonding interaction causing cyclisation to occur on the included acid chloride. We saw a similar effect in Section 6.5.7 when we looked at amide-based macrocycles as hosts for *p*-quinone. This use of hydrogen bonding to template the formation of interlocked molecules has proved to be very useful and has also been applied to rotaxanes, as in the [3]rotaxane **10.90** which is synthesised under thermodynamic control using alkene metathesis (which causes the central double bond to break and re-form, allowing the macrocycles to thread on to the axel by a 'slipping' process).⁶⁷



Scheme 10.18 Accidental synthesis of an amide-based [2]catenane.⁷⁰

Use of an asymmetric thread in conjunction with one of the macrocycles from **10.89** gives a bistable molecular machine, **10.91**. The hydrogen bonding is stronger to the succinamide diamide portion of the thread in the initial state in this complex. However photoexcitation of the naphthalimide followed by reduction of the resulting hole with an external donor makes a naphthalimide radical anion which is a much stronger hydrogen bonding site. As a result the macrocycle moves to the opposite end of the thread on the timescale of about 1 μ s. Following charge recombination over *ca.* 100 μ s the system returns to the ground state and the macrocycle moves back to its original position. The ensemble somewhat resembles a molecular piston with the macrocycle shuttling back and forth about 10,000 times per second and generating 10^{-15} W of power per molecule!⁶⁸



Scheme 10.19 Formation of a rotaxane by capping a secondary ammonium guest.⁶⁹

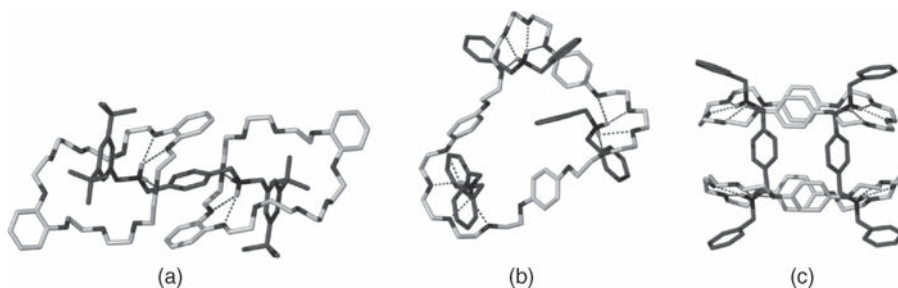


Figure 10.63 Crown ether ammonium ion based rotaxane type hydrogen bonded complexes (a) [3]rotaxane, (b) three threads in one ring and (c) two threads linking two rings.

The hydrogen bonding of ammonium ions to crown ethers has also been used to assemble a range of rotaxanes and *pseudorotaxanes*. The inclusion of a secondary ammonium thread into dibenzo[24]crown-8 followed by covalent capping to give a rotaxane is shown in Scheme 10.19.⁶⁹ This kind of approach can result in some interesting multiply threaded rotaxane type compounds, Figure 10.63.

10.7.5 Metal and Auxiliary Linkage Approaches to Catenanes and Rotaxanes

➔ Lankshear, M. D. and Beer, P. D., 'Strategic anion templation', *Coord. Chem. Rev.* 2006, **250**, 3142–3160.

The beauty of the methodology of catenane synthesis pioneered by Stoddart and co-workers lies in its relative simplicity, high yields and versatility. By designing self-assembling host–guest systems, the reaction becomes preprogrammed towards catenane synthesis and the interpenetration brought about by self-assembly methods is fixed by covalent modification. The host–guest concept behind catenane synthesis may be generalised to the idea of an 'auxiliary linkage' in which there is no distinction between host and guest in the initial self-assembled complex, nor any distinction between the forces holding it together, which may be electrostatic, covalent, coordination interactions, hydrogen bonding *etc.* The auxiliary linkage is simply an organisational device that holds the reactants in the correct relative orientations or positions in order to give the desired catenated product (Figure 10.64) (*cf.* the synthesis of insulin by self-assembly with covalent modification, Section 10.3.2).

The earliest use of the auxiliary linkage approach was the employment of a steric barrier as an auxiliary linkage in the directed synthesis of hydrocarbon catenanes by Schill and Lüttringhaus. One of the most elegant examples of this approach is shown in Scheme 10.20.⁷¹ The procedure involves the construction of a corand ring containing a primary amino substituent (**10.92**). The auxiliary linkage effect in this precursor is provided by a negative steric template that holds the two chloroalkane arms apart and forces them to point in opposite directions. The two arms are thus forced to attack the amino group from opposite directions resulting in the high-yield formation of the double ansa compound (**10.93**). Once this crucial cyclisation step has been accomplished, the auxiliary linkage is no longer necessary and is hydrolysed away with HBr in acetic acid to give the ketone (**10.94**). Finally, cleavage of the bond between the nitrogen atom and the aromatic ring liberates catenane **10.95**.

The existence of interlocked molecules such as **10.95** can be established by a variety of spectroscopic techniques. Most importantly, mass spectrometry provides very characteristic patterns for catenanes. The mass spectra for catenated species are very different from those of covalently linked precursors (such as **10.94**) but are more than the sum of their two individual components. Catenane mass spectra are characterised by the appearance of peaks at high m/z corresponding to the parent species as well as fragments corresponding to the transfer of hydrogen atoms from one macrocycle to the functional

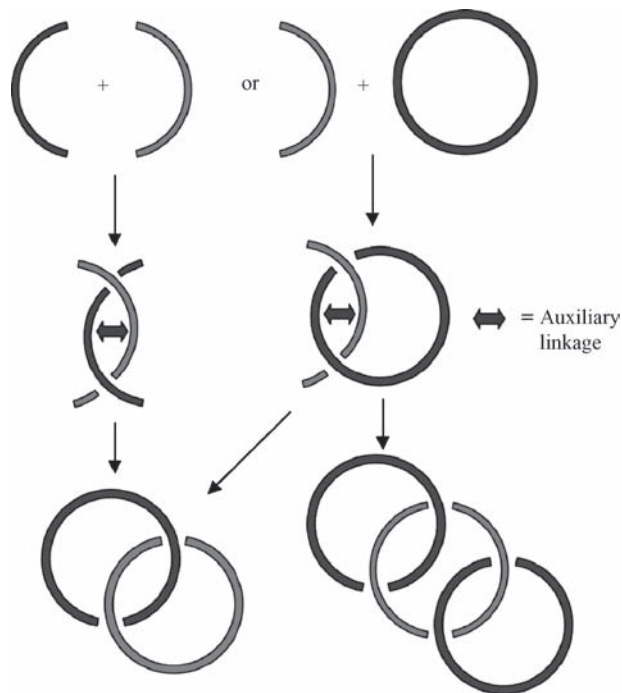
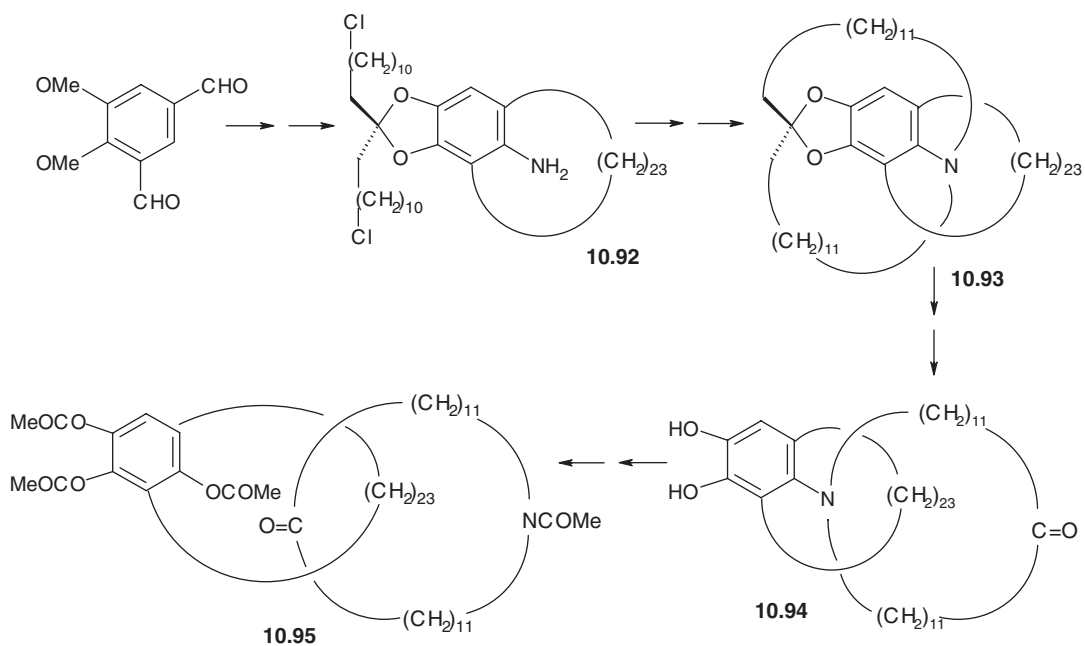


Figure 10.64 The auxiliary linkage approach to the synthesis of [2] and [3]catenanes. The auxiliary linkage may be a covalent, coordinate or noncovalent bond.



Scheme 10.20 Directed synthesis of a [2]catenane by use of a negative templating steric barrier as an auxiliary linkage.⁷¹

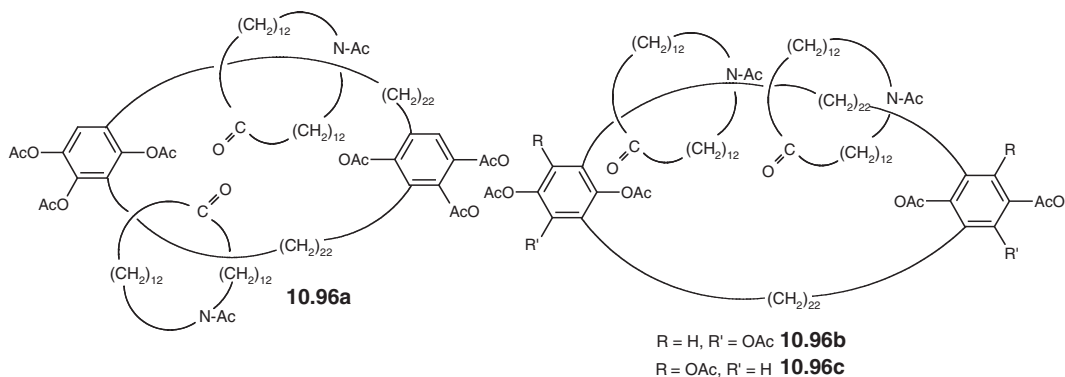


Figure 10.65 [3]catenane translational isomers.⁷²

group of the other. The first degradation process then seems to consist of disconnection of the two rings since there are then very few peaks until clear fragmentation peaks of the individual components, resembling the spectra of the individual macrocycles.

Generally, both ^1H and ^{13}C NMR spectroscopy reveal shifts to low field in resonances arising from nuclei within the interlocked structure. This shift has been attributed to van der Waals interactions between the two catenane components. Spin-lattice (T_1) relaxation time measurements in NMR spectra have also been used in related systems to establish that the motions of the interlocked rings are more restricted than the motions of the free species. Similar controlled methodology has been used to prepare a [3]catenane (**10.96**) that exists as a total of three isomers (Figure 10.65).⁷² In addition to carcerism (Section 6.7.4) and topological isomerism that we have already encountered, this type of isomerism represents a further example of the way in which the mechanical arrangement of the fragments of a molecular aggregate can result in the formation of physically different compounds. The isomers differ in the placing of the nitrogen-containing rings with respect to one another, and in the substituents on the larger, central cyclophane ring. Compound **10.96a** proved sufficiently different in terms of polarity from the other two isomers that it could be separated from them chromatographically. The presence of the aryl rings prevents the mutual interconversion of **10.96a–c** under ambient conditions.

Attempts have also been made to carry out multiple sterically directed cyclisations on closely related systems with a view to generating multiply interlocked materials. Compound **10.97** was prepared and subjected to a triple ring closure reaction. Unfortunately, the inherent low yields of the crucial reaction steps resulted in immense difficulty in characterising the reaction products. Compound **10.97** is prepared in nine steps, and following multiple cyclisation, a total of only 1.7 % of product was obtained, which proved to be an isomeric mixture of three different interlocked species.

In general, because the molecule possesses two-fold symmetry, there are only two ways of connecting the chloro substituents 1–4 with amines 5 and 6: linking of 1 and 2 with 5 (and 3 and 4 with 6) or linking 1 and 3 with 5 (and 2 and 4 with 6). However, the various possibilities for topological isomerism and diastereoisomerism result in four different possible products (not counting enantiomers). The former connectivity results ultimately in [2]catenane formation, whereas the latter can produce a macrocyclic compound or a complicated knotted structure termed a trefoil knot, which was the original target of the synthesis (*cf.* Section 10.9) (Figure 10.66). A total of three products were obtained, and NMR spectroscopic results suggested that the precursor to the trefoil knot may have been produced as one of the products. The final steps to generate the noncovalently interlocked structures were not reported.⁷³

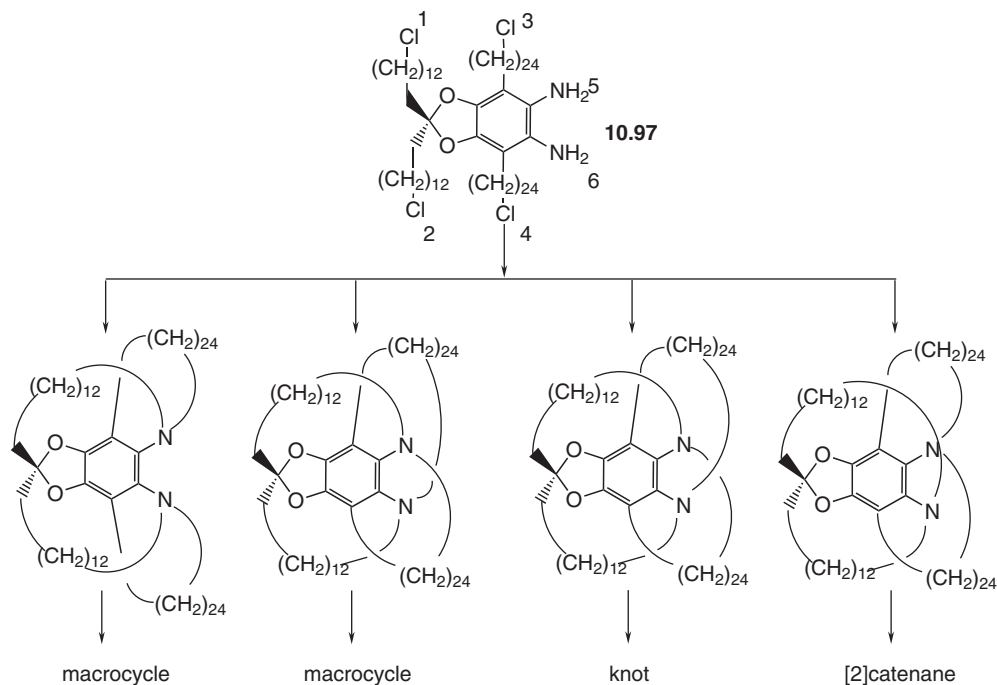
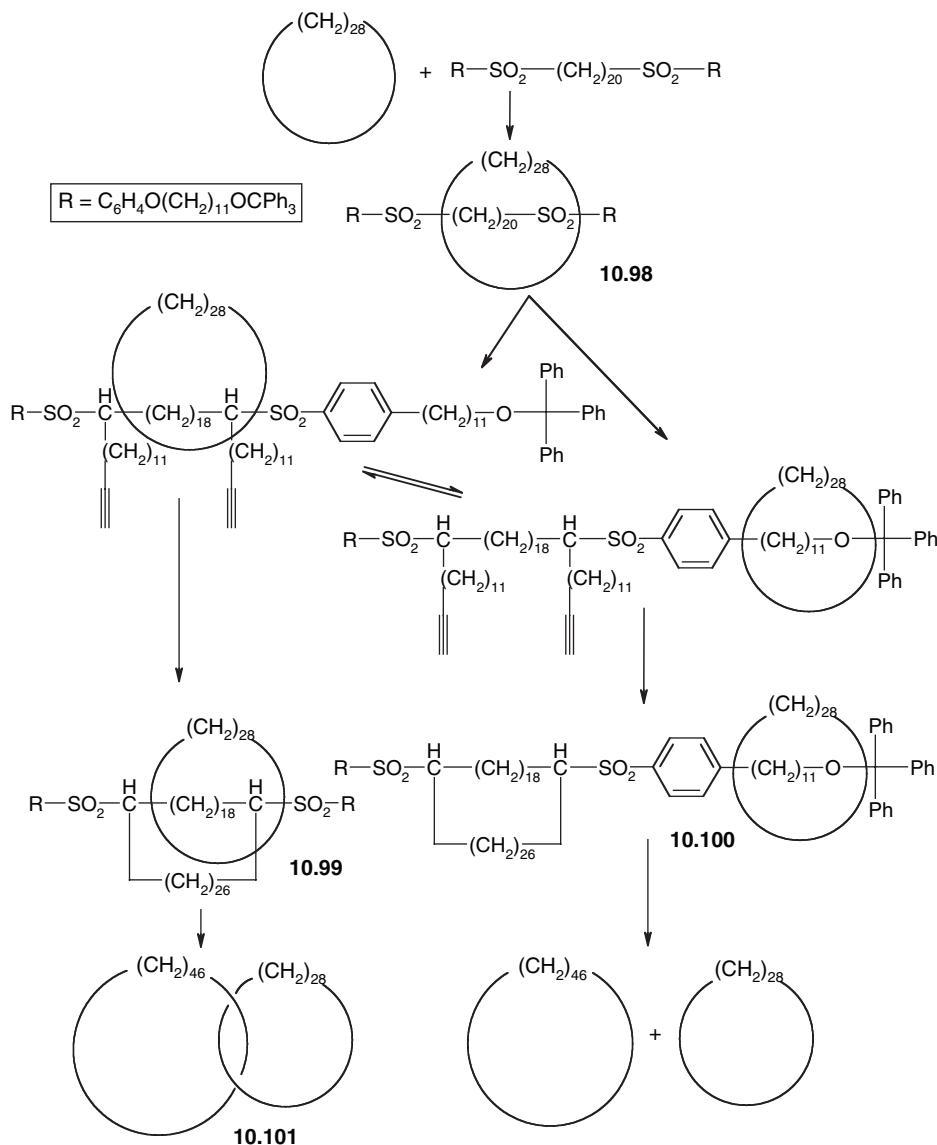


Figure 10.66 Possible triply cyclised intermediates from **10.97**.⁷³

In all cases examined so far, the precursors and resulting catenanes contain a number of functional groups necessary in order to ‘direct’ the synthesis. Since the beginning of catenane synthesis however, it had remained a goal, at least for the sake of academic interest, to prepare a purely hydrocarbon catenane consisting of two interlocked cycloalkanes. Clearly, with the severely limited strength of van der Waals interactions between alkane precursors, a purely statistical approach was unlikely to give appreciable yields. On the other hand, a directed approach was liable to result in the incorporation of a large number of functional groups that might be difficult to remove. This showcase feat of supramolecular chemistry was accomplished by a combination of statistical and then directed approaches (Scheme 10.21). Initially, the translationally isomeric [2]rotaxanes **10.98** were prepared by statistical slipping methods. The bulky triphenylmethyl (trityl) stoppers proved sufficient to prevent the unthreading of the rotaxanes at room temperature. The methylene groups alpha to the sulfonyl functionalities proved sufficiently acidic to deprotonate in the presence of alkyl lithium reagents and the resulting lithium salt was used to elaborate the rotaxanes with alkynyl substituents capable of undergoing cyclisation *via* Glaser coupling to give either a [2]rotaxane **10.99** or a [2]catenane **10.100**. Reduction of the resulting alkyne macrocycle and removal of the redundant blocking groups gave either the uncatenated macrocycles or the all-hydrocarbon catenane **10.101**.

The directed approach of Schill is a subtle manifestation of the auxiliary linkage approach, which, while extremely elegant, is highly intensive of synthetic effort and ultimately low-yielding because it relies on robust covalent linkages to force the reactants into a suitable conformation to optimise interlinked product formation. A more obvious and accessible example of an auxiliary linkage is coordination to a metal cation, in a variation of the kinetic template synthesis approach used in the simple macrocyclisation reactions studied in Chapter 3. This approach has been adopted with enormous success by Jean-Pierre Sauvage (Strasbourg, France). The Sauvage approach⁷⁵ relies upon the observation



Scheme 10.21 Statistical and directed synthesis of the first hydrocarbon catenane.⁷⁴

(firmly established by a detailed NMR spectroscopic study) that transition metal ions such as Cu(I) generally adopt a tetrahedral coordination geometry and, in the presence of bidentate ligands such as a 1,10-phenanthroline derivative **10.102**, are able to organise those ligands in a mutually orthogonal fashion (Figure 10.67).

Sauvage realised immediately that functionalisation of the methoxy substituents and cyclisation with a long polyethylene glycol chain would inevitably result in catenanes under high-dilution macrocyclisation conditions. Deprotection of the anisole derivative **10.102** with pyridinium chlorohydrate gave a bis(phenol) compound that was cyclised with 1,14-diiodo-3,6,9,12-tetraoxatetradecane in dimethylformamide (DMF) to give directly the [2]catenane **10.103** in 27 % yield, along with a 20 %

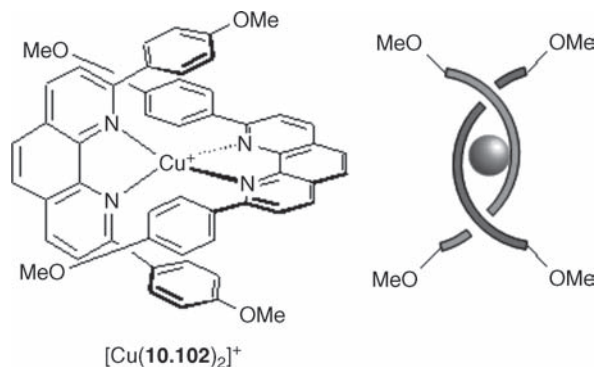
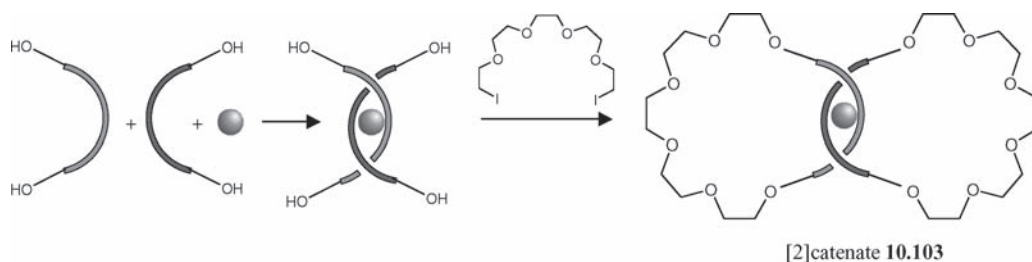
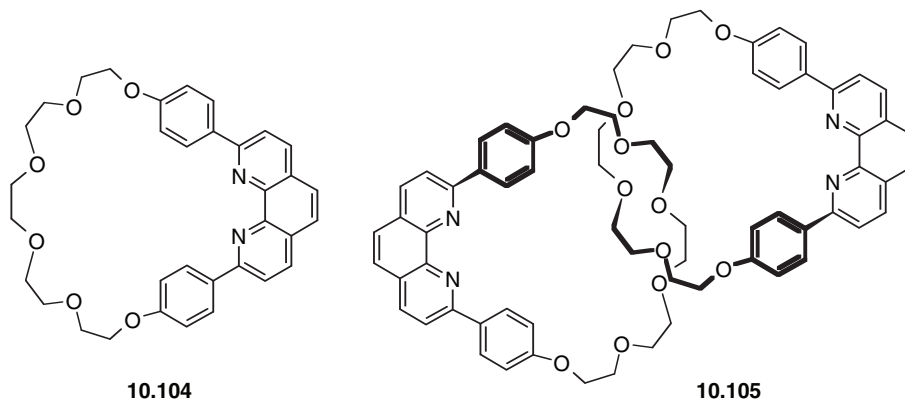


Figure 10.67 The 2:1 complex between 1,10-phenanthroline derivative **10.102** and Cu(I) along with cartoon schematic.⁷⁵



Scheme 10.22 Metal templated synthesis of catenate **10.103**.⁷⁵

yield of macrocycle **10.104** and polymeric products. In recognition of the fact that the two catenated phenanthroline units in **10.103** are acting as ligands for the Cu(I) centre, the complex as a whole was christened a *catenate*, by analogy with the cation *cryptates*. The free catenated ligand is thus referred to as a *catenand* (*cf. cryptand*) (Scheme 10.22).



The yield of **10.103** is improved further by adopting a stepwise approach in which the preformed corand **10.104** is reacted with $[\text{Cu}(\text{MeCN})_4]^+$ and one equivalent of the deprotected **10.102** to give an intermediate pseudorotaxane. Cyclisation as before gives the catenate **10.105** in an impressive 42 % yield.

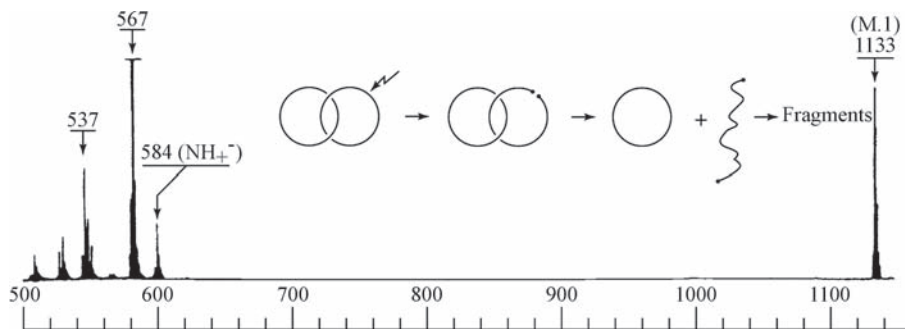


Figure 10.68 Mass spectrum of catenand **10.105** showing molecular ion peak and fragmentation into the separated macrocycle. (Reprinted with permission from [76] © 1987 American Chemical Society).

As a final stage, the catenate was then treated with CN^- (an excellent ligand for Cu^+) in order to remove the Cu(I) centre as $[\text{Cu}(\text{CN})_4]^{3-}$ to give the free catenand, **10.105**. The catenand was characterised by mass spectrometry, with the molecular ion observed at m/z 1133. The mass spectrum shows the characteristic feature of catenands, namely that the first fragmentation is ascribable to the decoupling of the two interlocked rings and so no fragmentation peaks are observed until the signal for uncatenated **10.104** at m/z 567 (Figure 10.68). Also of interest is the ^1H NMR spectrum of the compound, which indicates that in the free state, without the Cu(I) centre to bind the two phenanthroline moieties together, the catenand undergoes a significant conformational change to relocate the bulky, electron-rich phenanthroline groups as far apart as possible, as indicated in the diagram of **10.105**. Both structures were confirmed by X-ray crystallography (Figure 10.69).

Interestingly, the kinetics of the metal decomplexation reaction from the catenate, both intrinsic and assisted by CN^- , as shown below, are particularly slow. Direct comparison of kinetic data for $[\text{Cu}(\mathbf{10.102})_2]^+$ and $[\text{Cu}(\mathbf{10.104})_2]^+$ (*i.e.* **10.103**) showed that the intrinsic decomplexation rate is 2500 times slower for the catenate than its open analogue, despite the fact that steric congestion around the metal centre is similar in both cases. The cyanide-assisted rate is 40 times faster in the uncatenated complex $[\text{Cu}(\mathbf{10.102})_2]^+$. This observation suggests that the presence of the polyether chain results in significant distortions as part of the decomplexation process, significantly raising the activation energy barrier.

Also of interest are the cyclic voltammetric (Box 4.1) properties of the two Cu(I) complexes, $[\text{Cu}(\mathbf{10.102})_2]^+$ and $[\text{Cu}(\mathbf{10.104})_2]^+$. The uncatenated bis(chelate) complex exhibits an entirely irreversible reduction at about -1.7 V (versus saturated calomel electrode reference, SCE), consistent with

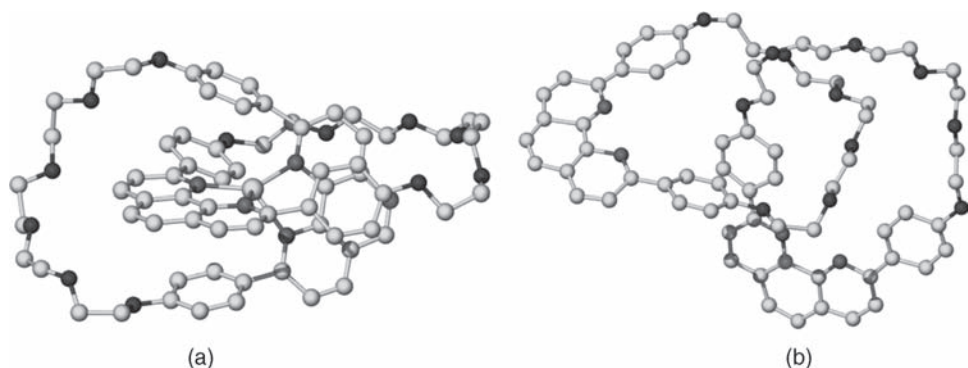
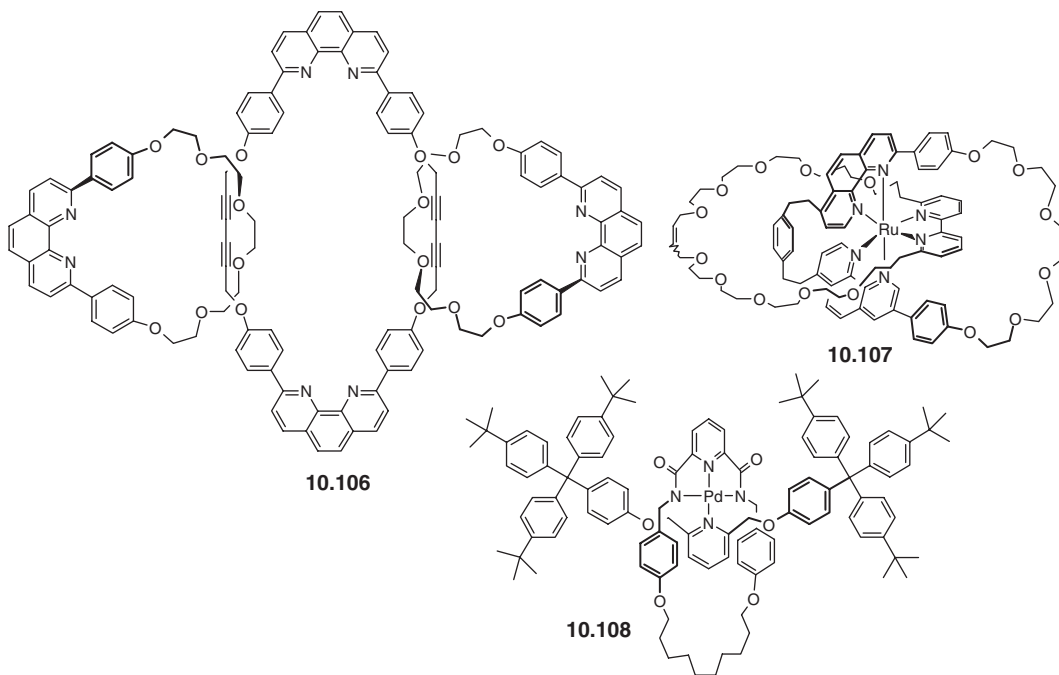


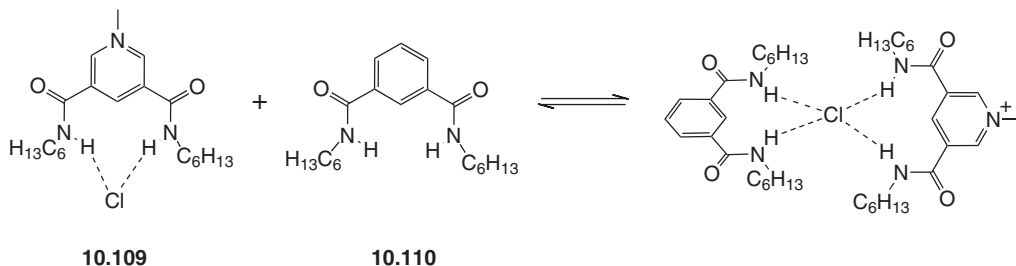
Figure 10.69 X-ray crystal structures of (a) the catenate **10.103** and (b) the free catenand **10.105**.⁷⁶

the decomposition of the complex to free **10.102** and copper metal when the Cu(I) centre is reduced to Cu(0). In contrast, an entirely reversible reduction wave at similar potential is seen for the catenate. This suggests that the fact that the complex is catenated (and therefore the two phenanthroline-binding domains cannot move apart from one another) stabilises the Cu(0) complex. Indeed, deep blue solutions of $[\text{Cu}(\mathbf{10.104})_2]_0$ are stable under argon for days. It is likely that the compound is only formally Cu(0); in reality, the added electron resides on one of the phenanthroline moieties to give an organic radical anion.

Sauvage and co-workers have gone on to prepare [3]- and [4]catenates such as **10.106** using a similar method with the greatly enlarged bis- and tris(phenanthroline) derivatives acting as the central macrocycles. Analogous systems have also been prepared with three larger chelating ligands around octahedral metal centres such as Fe(II) and Ru(II), resulting in three-component entanglements.⁷⁷ While these entanglements have yet to be transformed into complex interlocked compounds (but see Section 10.9 for a description of an ‘open’ trefoil knot produced in this way), an octahedral ruthenium(II) system has been used to produce a hetero-[2]catenane **10.107** based on a bis(phenanthroline) ligand on one ring and a bipyridyl on the other using ring-closing alkene metathesis.⁷⁸ Square planar metals such as Pd(II) have also been used as auxiliary linkages to template the formation of [2]rotaxanes as in **10.108**.⁷⁹ The bulky tetraphenylmethane-derived thread is linked to an open macrocycle precursor by coordination of the Pd(II) centre. The ring is then closed by alkene metathesis followed by reduction of the resulting double bond. Once the rotaxane is formed the palladium(II) ion can be removed by addition of cyanide to give the free rotaxane. Yields for the complexation and decomplexation steps are almost quantitative while the combined macrocyclisation and reduction step proceeds in 69 % yield.

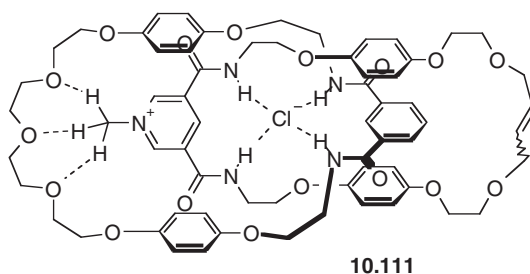


In addition to metal centres and covalent approaches, anions such as Cl^- may also be used as templating auxiliary linkages.⁸⁰ Paul Beer and co-workers from the University of Oxford, UK, recognised that ion pairing in non-polar solvents such as acetone allowed the coordination of a neutral hydrogen bond donor such as **10.110** to the pyridinium salt **10.109**, with a binding constant



Scheme 10.23 Strong ion-pairing in the pyridinium salt in non-polar solvents allows the coordination of a neutral hydrogen bond donor and hence the creation of the precursor to a ‘crossover’ in a catenane using the chloride ion as an auxiliary linkage.⁸⁰

of *ca.* 100 M⁻¹ (Scheme 10.23). This association creates a mutually orthogonal crossover point with the Cl⁻ ion playing a role analogous to that of the Cu(I) centre in [Cu(**10.102**)₂]⁺. Transferring this chemistry to cyclic species, Beer’s group prepared a crown-ether derived macrocycle capable of interacting with the acidic pyridinium –CH₃ hydrogen bond donor and a pyridinium derivative capable of undergoing cyclization using ring closing metathesis once complexed. The result is [2]catenane **10.111**, formed in 45 % yield along with 5 % of a [3]catenane byproduct. The concept has also been used to prepare [2]rotaxanes similar to **10.108**. What is particularly interesting about these systems is that the templation is particularly effective even though the binding constants are not all that large. It is simply necessary to have a significant majority of the linked species in solution when the cyclization occurs.



10.7.6 Molecular Necklaces

☞ Kim, K., ‘Mechanically interlocked molecules incorporating cucurbituril and their supramolecular assemblies’, *Chem. Soc. Rev.* 2002, **31**, 96–107.

Before we leave catenanes we should mention one final class of compound, namely molecular necklaces, in which a number of macrocycles are looped onto a single central ring like beads onto a string. The concept is illustrated in Figure 10.70a and an example involving a metallomacrocycle threaded through three cucurbit[6]uril ‘beads’ (compound **6.38**, Section 6.2.4) is shown in Figure 10.70b. Because there is a total of four different rings this compound is described as a [4]molecular necklace or [4]MN. The large ring that forms the ‘thread’ is commonly linked using self-assembly of a coordination compound, in this case square planar platinum(II) ethylene diamine complex (*cf.* molecular squares and boxes, Section 10.5.3) and takes advantage of the affinity of cucurbituril for protonated diamine guests as in

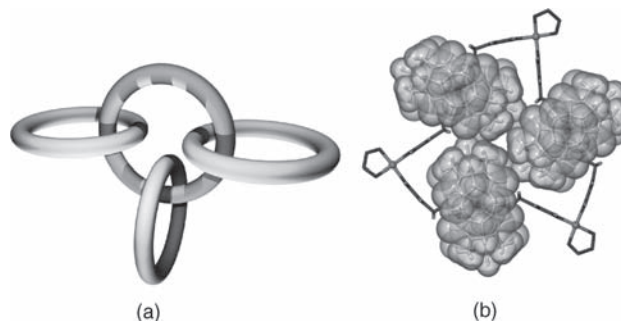


Figure 10.70 (a) schematic representation of a [4]MN and (b) linking of three cucurbit[6]uril molecules around a platinum(II) based metallomacrocycle.⁸¹

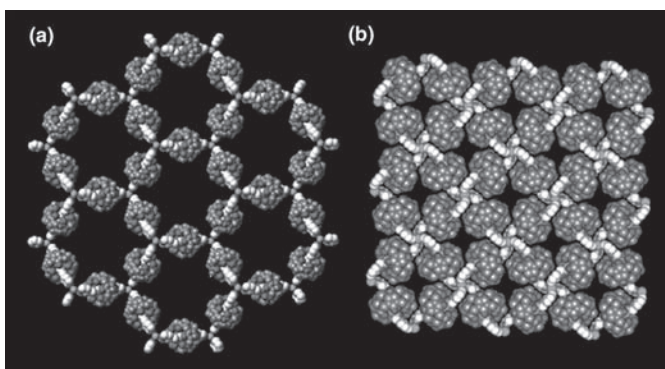
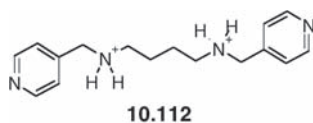


Figure 10.71 Molecular necklace type coordination polymer rotaxanes (a) hexagonal 2D polyrotaxane net and (b) square-grid shaped 2D polyrotaxane net (reproduced by permission of The Royal Society of Chemistry). See plate section for colour version of this image.

the ligand **10.112** which links the Pt(II) centres together. Using the 3-pyridyl isomer of **10.112** the system can also be expanded to give a square 'string' able to bind four cucurbiturils (a [5]MN). A number of polymeric necklace-type systems are also known in which a coordination polymer network is ringed by cucurbiturils as in Figure 10.71.



10.8 Helicates and Helical Assemblies

➔ Piguet, C., Borkovec, M., Hamacek, J., Zeckert, K., 'Strict self-assembly of polymetallic helicates: the concepts behind the semantics', *Coord. Chem. Rev.* 2005, **249**, 705–726.

10.8.1 Introduction

The self-assembling double-helical structure of DNA has provided the inspiration for a further area of supramolecular self-assembly, namely the use of metal ions to template the assembly of organic threads into