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Template routes to interlocked molecular structures and orderly molecular entanglements

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Contents

Abstract

This review discusses the synthesis of mechanically interlocked molecules where templates orient the reactants to produce permanent structures as the result of new linkages. An introduction outlines the concepts and opportunities of the field, paying special attention to the components of chemical templates. Next, the chemical template types most successfully

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applied to the synthesis of new interlocked molecular structures, metal ion templates, hydrogen bonded templates, cyclodextrin templates, and π-donor π-acceptor templates, are described. The progress each template type has made towards the goal of true polymeric interlocked structures is noted. The conclusion summarizes the current state of the field and points out new directions that appear ripe for future exploration. © 2000 Elsevier Science S.A. All rights reserved.

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1. Introduction

1.1. Concepts and opportunities

Since their inception [1,2], chemical templates have provided exciting new molecular topologies [3,4], beginning with macrocycles and macropolycycles, and then proceeding to simple and complicated knots, monomeric and polymeric rotaxanes, simple and oligomeric catenanes and varieties of putative molecular switches. We suggest that these are only the beginnings of a vast new research subject and that the intricate ordered entanglements that characterize the use of macroscopic fibers and the production of common and uncommon fabrics, throughout the history of human-kind, should all be subject to micro replication using molecular strands [5,6]. Today this pre-emergent realm of orderly molecular entanglements is mostly a vision, but that vision encompasses a melange of interlocked molecular architectures, a virtual molecular macrame, including the well known interlocked molecules mentioned above, but, ultimately, also molecular braids and the molecular equivalents of various kinds of cloth — the products of weaving, knitting, and crocheting — and even their three-dimensional counterparts. The subject has unlimited and very compelling appeal. Consider an embroidered message of molecular dimensions on the surface of molecular cloth, readable only by an atomic force microscope.

The basic science of orderly molecular entanglements offers unique challenges in the most subtle and demanding aspects of stereochemistry and mechanisitic control. Geometry, symmetry and topology unite in chemical templates to forge reaction pathways leading to intricate extended molecular architectures. The proposed new structures raise new questions about property–structure relationships, and serendipitous discovery is expected. Entirely new classes of materials will be synthesized and some of their properties are likely to be both novel and useful, reflecting, for example, the effects of greatly enhanced flexibility, while retaining the strength associated with chemical bonds. This suggests strength and deformability, a combination that has many traditional uses; imagine tough yet malleable plastics. Intricate molecular patterns, both indelible and rewriteable, suggest applications ranging from art, information storage, and security to switches and other parts for molecular machines.

History assures us that the challenge of producing these new interlocked architectures must eventually yield to focused fundamental research. The foundation of a

science and technology based on orderly molecular entanglements will be the fundamental understanding of the elementary steps that facilitate the necessary manipulation of molecular strands. In our view, the vision presented here becomes incrementally achievable through the applications of chemical templates. It follows that the elements of chemical templates and the elementary steps they control provide the fundamental avenue of opportunity.

A chemical template organizes an assembly of atoms, with respect to one or more geometric loci, in order to achieve a particular linking of atoms [5,7]. In this review, the 'particular linking of atoms' will be limited to those that generate interlocked assemblies between otherwise independent molecules; e.g. rotaxanes, catenanes, separate knots, knots joining strands, mechanically linked oligomers and polymers, and braided, knitted or woven materials constructed by the interlocking of linear molecules. Further, the ambition to create continuous and intricate molecular architectures requires that the achieving of a particular linking of atoms establish a permanent interlocking between the molecules. This will usually require formation of one or more chemical bonds while the template organizes the assembly of atoms. Equally important, the template may involve components that, like catalysts, do not become permanent parts of the molecular architectures. Early on, we recognized two classes of chemical templates: kinetic templates that influence the mechanistic pathway and thermodynamic or equilibrium templates that select and bind certain complementary structures from among an equilibrating mixture of structures [1]. Kinetic templates are of primary importance in generating molecularly interlocked structures.

It is appropriate to judge the effectiveness of template synthesis by comparison with so-called statistical threading. This provides the appropriate baseline methodology because statistical threading is what is left if a template is not used; it depends on the probability that a linear molecule will penetrate and occupy the space within a macrocycle without the benefit of any particular intermolecular attraction. Further, threading is a simple elemental step of great importance to the formation of interlocked structures, and the first interlocked molecular structures were prepared by routes involving statistical threading [8]. As we discuss at length below, it is well known that chemical templates can organize molecular cross-overs, through the use and location of their turns and anchors, but producing the first interlocked polymers and the first molecular cloth constitute daunting challenges that can be partially addressed in terms of the yields of single steps of the sequential chemical reactions. Early on, Wasserman estimated the statistical probability for threading a linear molecule through a macrocycle to be something less than 0.01, and supported his estimate with experimental findings [9,10]. Similarly, the classic study by Harrison and Harrison of rotaxane formation with the ring component bound to a Merrifield resin revealed that 70 successive applications of the statistical threading and blocking reactions resulted in only 6% of the rings being converted to rotaxane [11]. In contrast, template threading is based on mutually attracting participants (to form a template complex). Many studies involving single threadings using various templates (vide infra) give much higher yields — up to 92% in the best case [12]. It is essential that the yields of these elementary steps be increased to virtually

quantitative or large numbers of sequential steps cannot succeed in producing significant amounts of the envisioned new materials.

Gibson and co-workers [13–15] have pointed out the compelling fact that statistical threading can be used with most systems comprised of a linear molecule and a macrocyclic molecule. His work exemplified the use of statistical threading in the formation of polyester polyrotaxanes by polymerizing sebacoyl chloride and 1,10-decanediol in the presence of [30]crown[10] followed by a capping reaction with 3,3,3-triphenylpropionyl chloride (Fig. 1). The resulting polymer had 16% by weight of the trapped macrocycle, showing the statistical method to be effective, since no template interaction occurs to aid threading [15]. It is Gibson's view that the special functionalities and complementary geometries required for effective template threading greatly limit the applicable systems. The disadvantages are great when the desired product involves a continuous structure such as a polyrotaxane or polycatenane because of the necessary repetition of many stages of complicated interactions. From the standpoint of the template enthusiast, this further emphasizes the need for simple templates having components that serve catalytic functions.

1.2. Components of chemical templates — anchors, turns, threadings, and cross-overs

In order to achieve template-directed assembly of extremely complicated and/or highly extended, interlocked molecular architectures it is necessary to achieve an intimate understanding of how chemical templates function and how they can control vast cascading sequences of templating steps in polymerization processes [7]. Consequently, predictable and reliable routes to the goals presented here require the understanding of the essential components of an efficacious template and of the elemental steps that constitute its function. We begin by recognizing the fundamental elements of chemical templates, their general roles, and the range of their variations. Attention is also directed to the interrelationships between the parts and to the elemental processes they guide.

In any chemical template, an anchor constitutes the first component (a metal ion, ion pair complement, partial charge complement, or hydrogen bonded partner); this
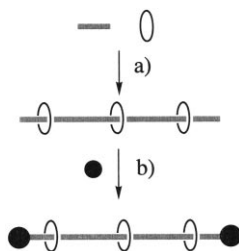

Fig. 1. A cartoon example of statistical threading for polyrotaxane formation: (a) polymerization of linear segments in the presence of a macrocycle, (b) a stoppering reaction to trap the rings.

anchor holds an appropriate conjugate component, or components. One important role performed by such an anchor-constrained component is to build a turn into the emerging structure; appropriately, such a component is called a molecular turn. Molecular turns have two or more terminal, or near terminal, reactive groups, each pointed in a critical, often the same, direction. This simple kind of molecular template is composed of an anchor and a molecular turn, and the turn may be intrinsic in the structure of the conjugate component or, in the case of a more flexible conjugate component, it may be caused by the anchor (Fig. 2). Examples of turns forced by the anchor include the first clearly demonstrated template synthesis [1,2], numerous studies on the synthesis of macrocycles [16–19], and, a variety of studies by Amabalino and Stoddart [20]. In contrast, the conjugates used by Dietrich-Buchecker and Sauvage [31] in their ground breaking studies of catenanes and knots are themselves molecular turns.

Molecular threading [9–11,22] and molecular cross-overs must be added to molecular turns and anchors as common elements in chemical templates. The
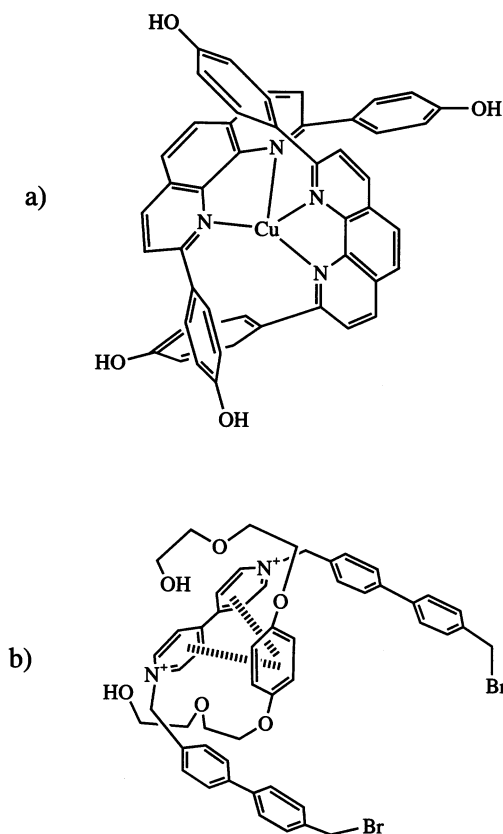

Fig. 2. Examples of anchor/turn template complexes: (a) Sauvage's Cu^I anchor and phenanthroline turn, (b) Stoddart's π-donor and π-acceptor conjugate.

combination of an anchor with two non-parallel molecular turns produces a molecular cross-over (Fig. 3(a)). This template is one of the two that organizes elements essential for catenane and rotaxane synthesis. Catenanes are produced by two ring closings on a molecular cross-over, each ring closing process making use of a single molecular turn. Rotaxanes are produced by one ring closing on a single molecular turn and the addition of blocking groups to the other conjugate. Finally, macrobicycles are formed by fused closings on a fused cross-over (= fused pair of turns) (Fig. 3(b)). Molecular threading provides the second route to catenane formation and is broadly demonstrated in rotaxane formation. A template for molecular threading requires anchoring a cyclic molecule and a linear molecule, or a molecular turn, that is inserted through the center of the large ring. Sauvage's template for formation of the trefoil knot uses two cross-overs with two pairs of
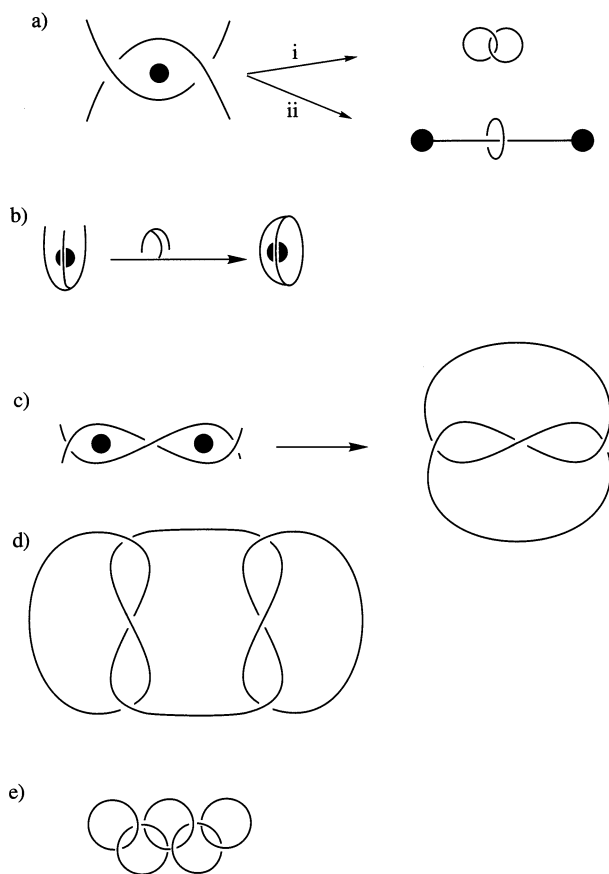

Fig. 3. (a) A simple cross-over gives (i) a catenane upon two ring closures or (ii) a rotaxane upon one ring closure and blocking, (b) a fused turn can be used for macrobicycle syntheses, (c) use of two anchors and ditopic turns to form a trefoil knot, (d) a composite knot from two two-anchor templates, (e) an oligocatenane resulting from multiple cross-overs on the same anchor.

linked turns [23]. The turns within a linked pair are mutually inverted so that when two linked pairs are combined with the two anchors in the template, a double helical motif forms (Fig. 3(c)). Sauvage and associates used four cross-overs (eight mutually inverted linked pairs of turns and four metal ion anchors) in the template synthesis of complicated knots, specifically, the square knot and the granny (Fig. 3(d)) [24]. Stoddart's templates for oligocatenanes also provide multiple crossovers by placing multiple anchor positions on a large macrocycle. When several turns bind the anchor, a multi-crossover template is formed, which leads to the oligocatenane product [25] (Fig. 3(e)) (although the assignment of anchor and turn in Stoddart's templates is more ambiguous than in other cases).

It is clearly true that, today, scientists are controlling intricate sequences of steps (threadings, cross-overs, ring closings, and other linkages) in order to form complicated orderly molecular entanglements. The many structural motifs that have been achieved through chemical templates are displayed in Fig. 4. A goal of high priority is the ability to produce polymers by the control of a continuum of sequential steps. From there, the goals explode into more intricate continuous interlocked structures; e.g. molecular braids and molecular cloth. The power of chemical templates becomes obvious when one realizes that the marvelous array of structural motifs so briefly summarized above has been achieved with a remarkably small number of distinct chemical templates. Basic types of interlocked structures are used below to illustrate important, extensively studied templates, but no attempt is made either to treat the applications of a given template exhaustively or to recommend which templates are best for the generation of particular interlocked motifs. These templates have all been found to be versatile. When a class of interlocked structure is first discussed, the related principles are presented. Also in this section, we will describe progress toward mechanically linked polymers for the different template types. In the last section, we will offer conclusions and suggestions for the future.

2. The classic chemical templates

Although it will eventually become clear that the template anchor, as defined above, may not always be obvious, it remains true that the various kinds of heavily used templates are readily classified in terms of their anchors, and outstanding examples of each kind will be discussed. The nature of the template will be presented, followed by an indication of the range of interlocked structures that have been prepared using the template, and an indication of the potential it presents. On this basis, the most obvious category is the metal ion anchor since the metal ion constitutes a multifunctional center about which molecular turns of various kinds are readily oriented. Under this heading we will discuss Sauvage's highly successful templates as well as alternative metal ion templates that are currently under investigation. Hydrogen bonding anchors for templates are almost as diverse as are metal ion anchors, but they differ sharply in that they generally involve multicentric interactions. Examples include Busch/Stoddart secondary ammonium ion anchors and the Hunter/Vogtle/Leigh diamide templates. Cyclodextrin templates will be
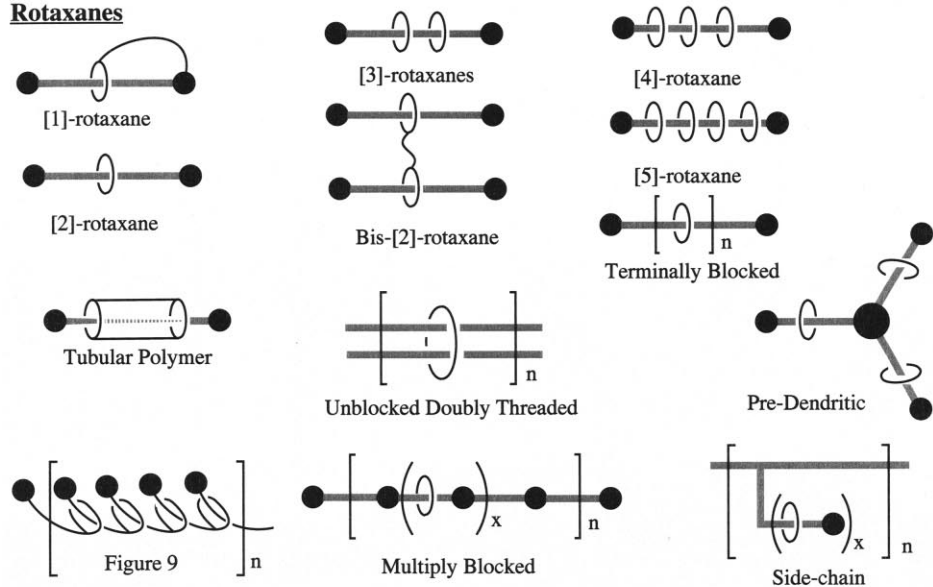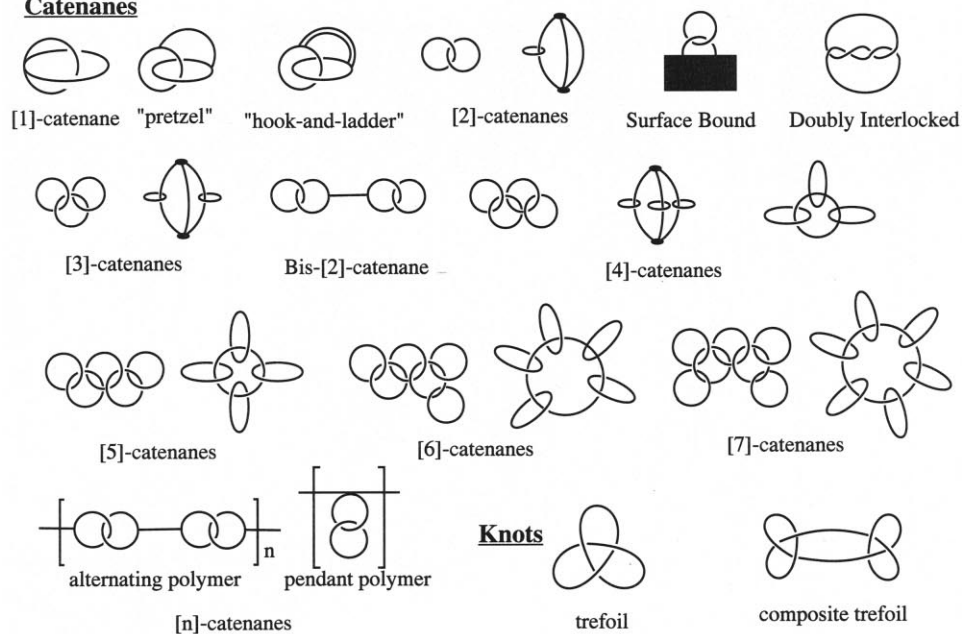
Rotaxanes

[1]-rotaxane

[2]-rotaxane

[3]-rotaxanes

Bis-[2]-rotaxane

[4]-rotaxane

[5]-rotaxane

Terminally Blocked

Tubular Polymer

Unblocked Doubly Threaded

Pre-Dendritic

Figure 9

Multiply Blocked

Side-chain

Catenanes

[1]-catenane   "pretzel"   "hook-and-ladder"   [2]-catenanes   Surface Bound   Doubly Interlocked

[3]-catenanes   Bis-[2]-catenane   [4]-catenanes

[5]-catenanes   [6]-catenanes   [7]-catenanes

alternating polymer   pendant polymer

[n]-catenanes

Knots

trefoil

composite trefoil

Fig. 4. The various interlocked structures which have resulted from template syntheses: rotaxanes, catenanes, and knots.

presented separately because of the complexity of their template interactions (which often include significant hydrogen bonds). We oversimplify by labeling Stoddart's template, formed between electron rich aromatic ether moieties and paraquat-containing moieties, as π-donor/acceptor templates. These important templates include π–π stacking, ion–dipole attractions and unusual, but undeniable, hydrogen bonding interactions, which combine to force molecular strands into turns.

2.1. Metal ion templates

Templates based on metal ion anchors are prototypical of the concept and historically important since they provided the seminal examples. A single metal ion anchor acts as a unique point around which the construction of new molecules that cannot be made by other known pathways can be achieved. Metal ion templates played a key role in the development of macrocyclic ligand chemistry and its derivative chemistries. In the early 1960s, the Busch group demonstrated the first rational syntheses of macrocycles around metal ion templates [1,2,26–28]. The planar nickel(II) ion in Fig. 5 forces a tetradentate ligand into a turn, bringing its two reactive terminal groups into adjacent positions, in that way facilitating cyclization by their reaction with a reagent that is a second molecular turn, α,α'-dibromo-o-xylene [1]. This venerable example demonstrates the ultimate significance of the kinetic template effect, the ability of the metal ion anchor to predictably control the spatial orientation of reactive groups during the formation of critical linkages. Metal ion anchors offer the additional advantage that they are often readily removed, leaving the interlocked structure intact, or as stated by Sauvage, "The novelty of this approach… is that the chelating ligands collected by the metal, and organized in its coordination sphere, are not covalently linked to each other after the cyclization reaction" [29]. Innumerable examples have been reported of macrocycles, macrobicycles, macrocycles with appendages, appended macrocycles, ditopic, tritopic, etc., macrocycles in the voluminous literature. Here we are restricted to interlocked structures generated by molecular template reactions.

The potential of metal ion templates for the production of interlocked structures were first widely recognized through their success in the preparation of catenanes, molecules made up of two or more mechanically interlocked, or interpenetrating rings, the simplest being the two component [2]-catenane. Several conceptually different routes for catenane synthesis have appeared, including statistical threading [8], direct organic synthesis [30], and various template methods, which have been by
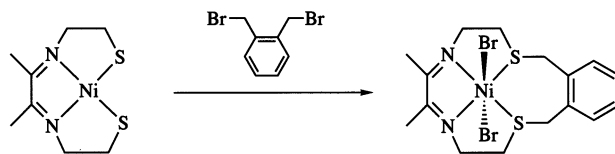

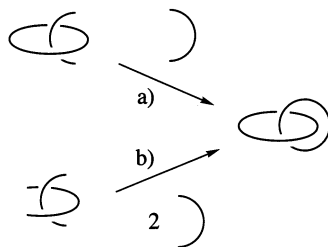Fig. 5. The seminal metal ion template macrocyclization.

Fig. 6. Two strategies for template catenane formation: (a) the ring-turn approach, (b) the two-turn approach.

far the most successful. There are multiple template routes to catenane formation. The first, the ring-turn approach (Fig. 6(a)), forms a macrocycle initially by reaction of a turn and a second difunctional reactant — this is simply macrocyclization. Complexation of this macrocycle with an anchor and another equivalent of the turn gives the threaded template, in effect a pseudorotaxane. The second ring can then be closed about the first to produce the [2]-catenate [31]. The second, two-turn approach (Fig. 6(b)) cyclizes both turns of a template composed of a single cross-over, using difunctional reagents. The same pseudorotaxane is a likely intermediate. This method requires fewer steps, yet often leads to lower yields [32].

In the 'three-dimensional' realm required for interlocked structures, non-planar geometries are templated by selection of appropriate nonplanar metal ions as anchors. By coordination, the metal ion anchors two conjugate molecular turns which are thereby oriented in accord with the metal ion coordination sites they occupy. For a tetrahedral metal ion anchor, didentate ligands/molecular turns are held in mutually orthogonal positions with respect to each other. The molecular turn/ligand, 2,9-bis(p-hydroxyphenyl)-1,10-phenanthroline (Fig. 7(a)), has critical structural features that have made it highly successful — it provides the necessary geometric control over terminal reactive groups that extend well beyond the metal center and can form the copper(I) complex (Fig. 7(b)), which was found to exhibit
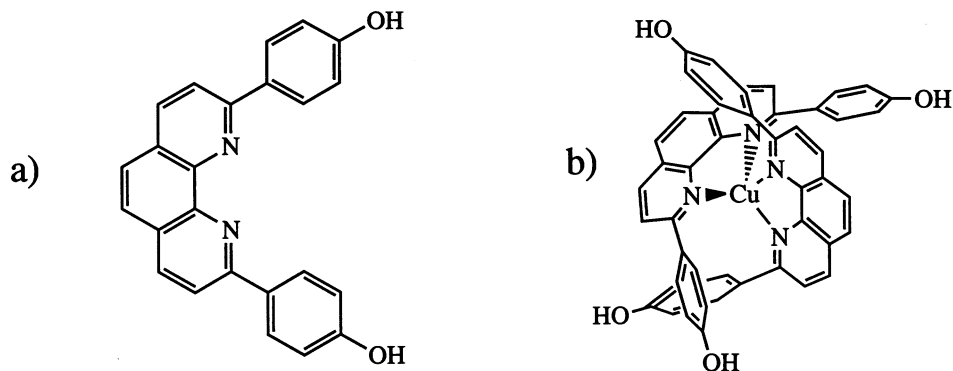

Fig. 7. (a) Sauvage's molecular turn, (b) the resulting two-turn complex of Cu[I].

precisely the geometry and binding strength needed [33]. Sauvage used copper(I) to exploit the '3D' nature of tetrahedral metal complexes to provide the first template directed synthesis of catenanes, a subject that provides dramatic demonstration of the old saw that the devil is in the details. In the first reported template synthesis of catenanes, where the bifunctional ring closing reagents were pentaethylene glycol dihalides, only 27% of the product was obtained by the two-turn approach [32], while the ring-turn approach yielded 42% [31]. Recently, using the Grubbs' ring-closing metathesis reaction and moving the ring closure reaction to a much greater distance for the metal-anchored cross-over, the Sauvage group has prepared simple [2]-catenanes in 92% yield [34]. From this and other examples it is apparent that for interlocking turns, choosing and locating the terminal functional groups so that no additional linking atoms (or a minimum number) are required to complete the ring greatly facilitates the efficiency of catenane formation — a hypothesis that will prove to be of great generality. The advantage probably derives in large part from the reduced competition between the formation of intramolecular and intermolecular linkages. Other advantages should stem from reclaiming the ability to use a large excess of a second reagent and the fact that no additional atoms are needed to form the final ring. For the purposes of discussion we will call this the principle of least reagent [4].

Using various modifications of this template system, the Sauvage group and others have compiled a most impressive array of interlocked molecular systems, including many rotaxanes and catenanes of varying complexity: rotationally constrained [35] and topologically chiral [2]-catenanes [36] achieved by substitution of one or both rings by organic groups, a 'hook-and-ladder' topologically and covalently linked 2-catenane [37], [3]- and[4]-catenanes from the joining of multiple ring-turn templates to form a large macrocycle with smaller ones trapped on it [38,39], and [2]-, [3]-, and[5]-rotaxanes formed by blocking the reactive terminals on mono- or multifunctional ring-turn templates [40–42]. These and many other important developments are directly attributable to the design and use of a highly effective molecular turn providing the required geometric control and the requisite reactive groups that extend beyond the metal center. But this template has been uniquely successful among small molecule templates in the syntheses of molecular knots.

Mathematicians describe a 'knot' as a cord that is intertwined with itself, with its loose ends joined so that it cannot become untangled. This definition makes a macrocycle a rudimentary knot, or the 'unknot'. If two or more knots are interlocked with each other, the result is called a 'link'. A [2]-catenane is a link composed of two unknots [43]. Mathematical knot theory, the formal discipline dealing with knots and links, evolved from the early work of chemists in the middle of the 19th century. Having been shown Peter Tait's experiment in which colliding smoke rings do not comingle but rebound from each other, William Thompson (Lord Kelvin) suggested that each chemical element is composed of a permanent and unique knot in the ether (the universal fluid filling all space). Since simplification of a knot without breaking the continuous cord that contains it is impossible, their correlation with the immutable elements was rational. Accordingly, Thomp-

son catalogued the prime (non-composite, vide infra) knots having up to nine crossovers as he sought to assign knots to the elements [44]. Subsequently, mathematicians adopted and dominated the field of knot theory, and only recently, have chemists redirected their attention to this intriguing field. The synthesis of molecules sharing the topologies of true knots (excepting the use of macromolecular DNA [45–49]) has been achieved only by template syntheses, mostly in the laboratories of Sauvage and his collaborators.

The trefoil knot is the simplest knot (outside of the unknot) and Sauvage began synthesis of the first molecular example by linking two of his phenanthroline-based molecular turns together with a methylene group, producing a pair of linked turns. Complexation of such a ligand/conjugate with copper(I) gave a mixture of products, and, in the structure of greatest interest, two ligands combine with two copper(I) ions to form a double helical complex (Fig. 8). The pair of didentate turns constituting a single ligand are twisted orthogonally (with respect to each other) at the linkage between the two copper ions. Creating two new links between each ligand in the double helical complex and the other by a pair of polyglycol chains produces a trefoil knot in 3% yield [23]. Removal of the metal ion gives a molecule having the same linkages as a large macrocycle made up of two molecules of the double-turn and two molecules of the bridging unit. However, the new molecule is a knot and topologically very different from the simple macrocycle — the two topological isomers cannot be interconverted without breaking at least one chemical bond.

The yield of the trefoil knot is remarkably improved (29%) by replacing the methylene group connecting the pair of turns with a *m*-phenylene group [50]. This improvement was traced to quantitative formation of the double helical precursor
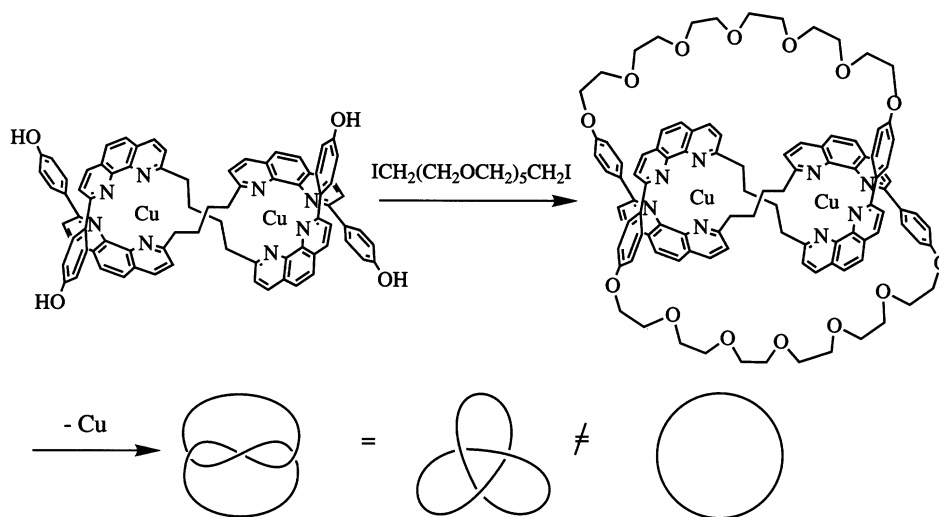

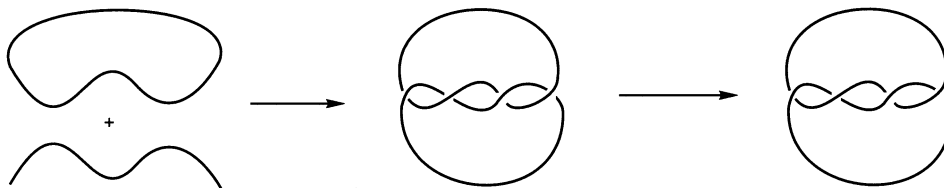Fig. 8. Synthesis of the first trefoil knot using a two-anchor helical template.

Fig. 9. A cartoon representation of the synthesis of the first doubly wound [2]-catenane from a three-anchor helical template.

complex, instead of a mixture of complexes. This favorable yield has made further studies possible, including, separation of the enantiomers of this chiral knot [51]. Similarly, the extension of this helical approach to larger linear arrays of copper ions became thinkable. In his analysis of the subject, Sauvage points out the fascinating facts that even numbers of cross-overs (i.e. tetrahedral copper(I) plus pairs of turns) always produces increasingly complex knots while odd numbers of cross-overs lead to increasingly complex multiply interlocked [2]-catenanes (Fig. 9) [21].

According to theory, a composite knot is formed when the cord of a single knot is cut and the two free ends are joined to those of a second severed knot, producing a large knot that is composed of smaller, simpler knots [43]. The first composite knots were prepared using a 4-crossover template comprised of four tetrahedral copper ion anchors and two conjugate components, each composed of four linked turns of the Sauvage type [24]. This 4-turn conjugate was fashioned by connecting two of the *m*-phenylene ditopic ligands (used for trefoil knot synthesis) with a polyglycol chain. Acetylene functions were then affixed to the ends of the linear tetra-topic ligand. Complexation in a copper(I)/ligand ratio of 2:1 produced a familiar double helical species, but a polyether chain now spans between distant ends of the linked tetrahedra. Two of these double helical species were joined by cyclodimerization producing the familiar composite knots sailors and scouts recognize as the square knot and granny (3% yield, Fig. 10).
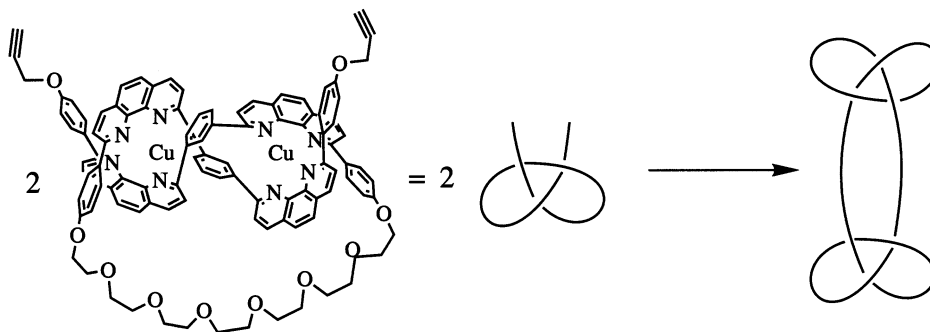

Fig. 10. The first composite knot utilized two two-anchor helical templates.

The use of templates to synthesize interlocking structures with multiple components is both exciting in its possibilities and challenging to present technology. Therefore, it is perhaps justifiable to view the ultimate goal of such syntheses as a 'holy grail of unnatural product synthesis'. As stated in the introduction, polymers of interlocked rings might have remarkable properties of strength and flexibility due to their interlocked structure [5]. Polymerization dependent on the catenane or rotaxane formation remains unattained, although rotaxanes of polymers have been studied substantially. Such a polyrotaxane produced by a metal ion template used a phenanthroline containing macrocycle as the ring group, a new polymerizable axle, and Zn^{II} as the metal ion anchor. The bipy turn axle group was terminated by sulfur-containing functional moieties and threaded into the ring by complexation with zinc(II) (Fig. 11). The crystal structure of this pseudorotaxane monomer has been determined and NMR studies in $CDCl_3$ indicate it is fully associated in solution (no signals for the free components are seen). Electrochemical polymerization of the pseudorotaxane gives the polyrotaxane with the zinc anchor still in place, but the polymer can be shown to reversibly bind both Zn^{II} and Cu^I [52].

Based on the concept of alternating mechanical and covalent bonds, a collaborative effort between Geerts and Sauvage has produced polymeric catenanes which contain alternating units of [2]-catenanes prepared by the usual Sauvage template chemistry and covalently linked spacer groups [53]. The collaborators prepared the
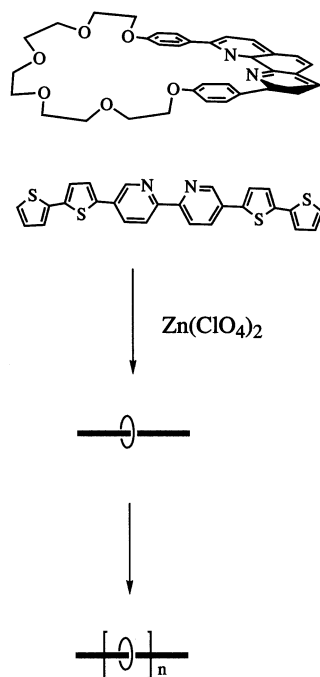

Fig. 11. A polyrotaxane based on a Zn^{II} metal ion anchor, a bipy containing threading unit and a phenanthroline containing macrocycle.

now commonplace templated [2]-catenane, but in this case each ring contained a reactive peripheral hydroxyl group. Polycondensation with a diacid spacer yielded the poly-[2]-catenane polymer (Fig. 12). Characterization studies support the structure of the product as a linear polymer, with a molecular weight on the order of 10^6 Da. This is clearly an example of a polymer held together by catenane linkages, although catenane formation was not the polymerization process. Study of the properties of this new polymer is on-going.

We take this opportunity to point out that most of the above templates and topologically distinct products are the result of the clever use of a single metal/ligand anchor/turn pair or template. This fact demonstrates how powerful such templates can be, yet how few distinct types of true templates for interlocked structures now exist can be seen in our table of contents. It is clear that when a new template type is developed, the possibilities for its use are only restricted by the imagination of its users. Other metal ion anchored templates have been hinted at
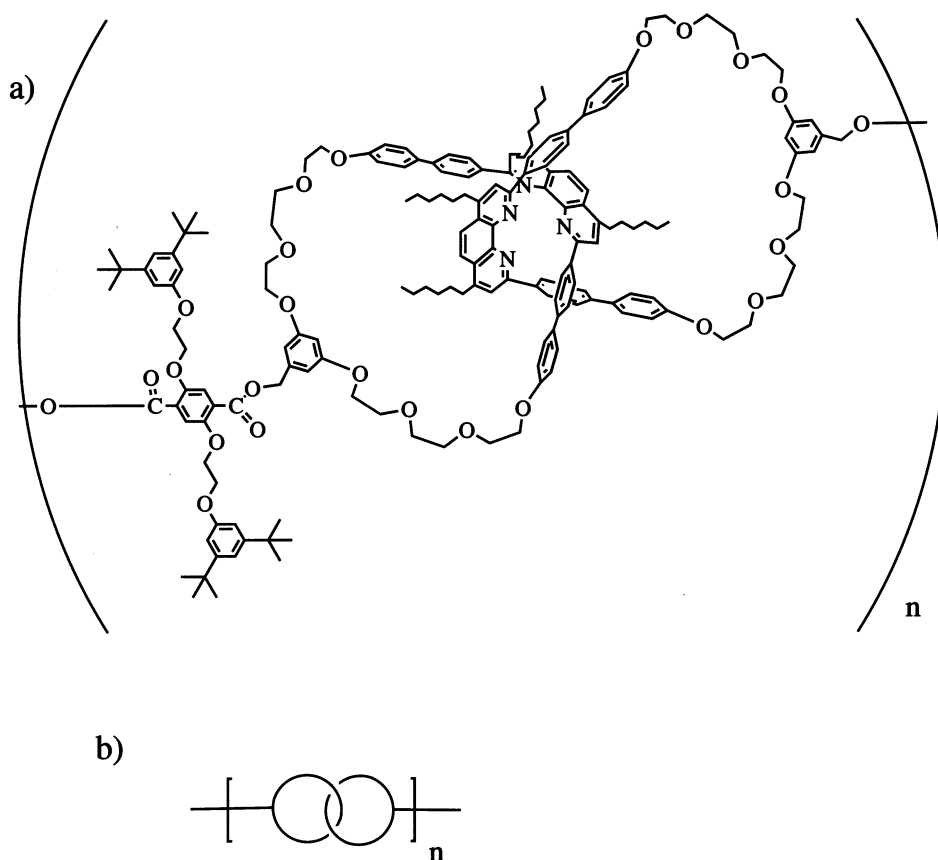

Fig. 12. (a) The polycatenane with alternating covalent and mechanical bonds synthesized by Geerts and Sauvage, (b) a cartoon representation of the structure.

and they will be briefly discussed below. In fact, octahedral metal ions have been used in exciting cases of template syntheses, but those systems have not yet been so fully exploited. A [2]-catenate based on octahedral Ru^{II} utilizing a 5,5′-disubstituted terpy ligand as the turn for the octahedral anchor has been synthesized by the Sauvage group [54]. The geometry of the two tridentate chelates around an octahedral metal atom anchor, are similar to the orthogonal chelation of two bidentate ligands about tetrahedral copper(I). An 11% yield of the [2]-catenate was isolated upon cyclization with hexaethylene glycol diiodide (Fig. 13(a)).

Work in our own laboratory on octahedral transition metal complexes of Schiff base ligands has led to a new family of potential molecular templates [55]. A distinct advantage of these systems is their ease of synthesis; complexes of tridentate Schiff base ligands derived from 2,6-dicarbonyl pyridines and *para*-substituted anilines can be made in high-yield, one-pot reactions. The terminal functional groups of the ligand may be changed without altering the basic structure of the template complex by simply varying the aniline derivatives. Complexes of the type shown in Fig. 13(b) have been prepared and crystallographically characterized, where R = OH, NH$_2$, CO$_2$H, CH$_2$OH, CH$_2$CO$_2$H, CH$_2$CH$_2$OH. Reactions at the terminal groups have succeeded in high yields while retaining the geometry about the octahedral metal ion anchor. Suitable difunctional bridging reagents ought to produce rotaxanes and catenates, and preliminary results give reason for optimism.
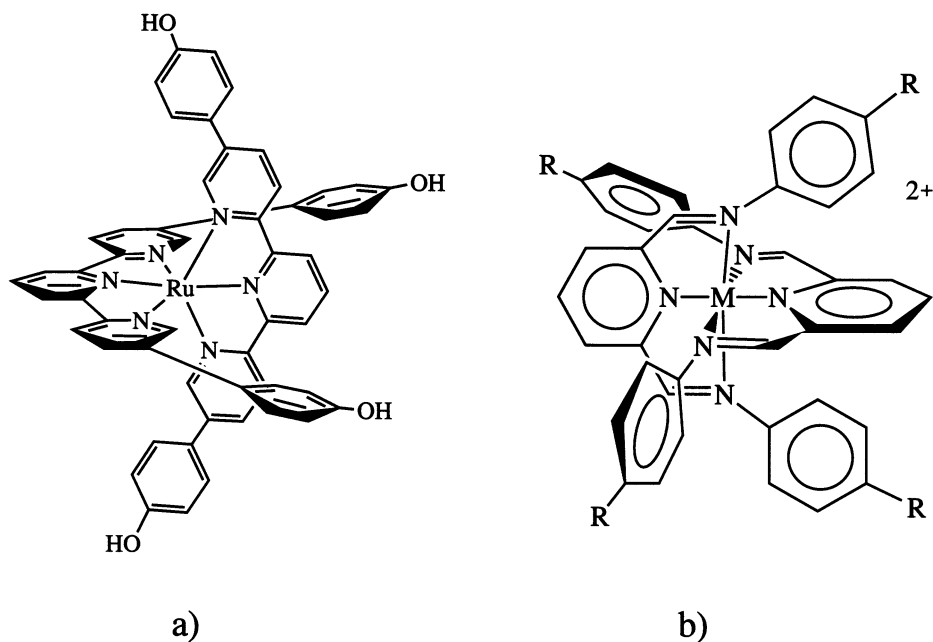

Fig. 13. (a) Sauvage's Ru-terpy octahedral template complex, (b) Vance's Schiff-base octahedral template complex.

2.2. Hydrogen bonded templates

Typically, hydrogen bonds are much weaker than covalent bonds, even those in many metal complexes. Another trait of hydrogen bonds is that they tend to produce bicentric linkages, even though a single proton can hydrogen-bond to multiple centers in some cases. Accordingly, effective hydrogen bonded templates generally are composed of multiple binding sites, for strong complexation to occur. For hydrogen bonded templates, the stereochemical requirements that are typical are rather more flexible than those for many transition metal templates, yet still more specific than those of spherical alkali and alkali earth metal ions. For effective complexation, a rigid molecular framework (i.e. preorganization) is often required to provide stable juxtapositioning of the binding sites for anchor-turn interactions based on the formation of several hydrogen bonds. Because of their relative rigidity and appropriate array of donor atoms, the functionalized macrocycles, such as crown ethers and their analogs, that are often used in supramolecular architecture naturally satisfy this requirement. Many different functional groups may participate in hydrogen bond formation; amine and amide nitrogens, carbonyl and ether oxygens, as well as hydroxyl groups, are the most frequently used fragments.

2.2.1. Ammonium–crown ether templates

Because of their importance in the study of the threading process, rotaxanes dominate our discussion of hydrogen bonded templates involving ammonium cations and crown ether macrocycles. Pseudorotaxanes, formed between linear molecules threaded into their macrocycle partners in the absence of blocking groups, are precursors of true rotaxanes, interlocked molecules formed when bulky blocking groups on the linear molecule's extremities prevent unthreading. Pseudorotaxanes exist as equilibrium mixtures of threaded and unthreaded states, while true rotaxanes are topologically linked moieties requiring covalent bond breakage for dissociation.

Numerous conceptually different methods for rotaxane preparation exist (Fig. 14), several of which can be template directed [3,4]. One linear component organizes another so that cyclization occurs around the first in the clipping approach, resulting in the familiar wheel-through-axle topology of a rotaxane [56], though the template closely resembles that for simple macrocyclization. In the snapping mechanism, the linear component is terminated by two bulky substituents, and dissociates into two fragments, one of which then forms a complex with the cyclic component. Reconstitution of the linear molecular fragments then produces the rotaxane [57]. Threading is unquestionably split into both template directed and statistical methods. 'Template threading involves an attractive interaction between the linear species and the macrocycle, such as metal chelation, charge transfer interaction, H-bonding, π-stacking interaction, or the like. Hence, the equilibrium… is enthalpically driven…' [22]. As discussed above, statistical threading counts on the random distribution of axis and wheel molecules to produce the required 'pseudorotaxane' prior to blocking group addition.

a) clipping   b) threading

c) snapping   d) slipping
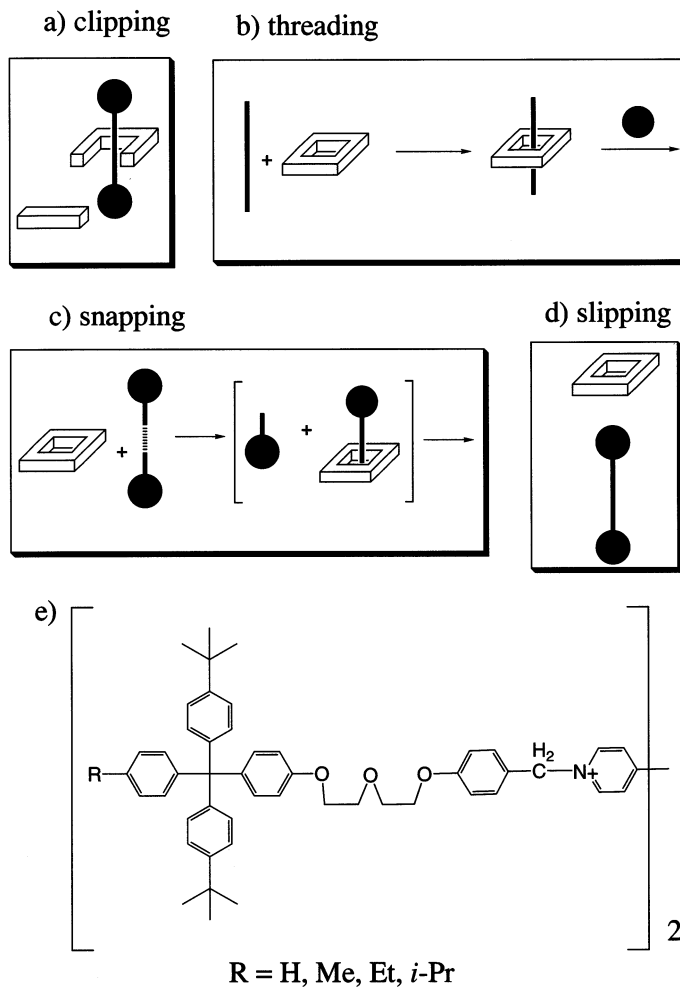
e)

R = H, Me, Et, *i*-Pr

Fig. 14. Various approaches to rotaxane formation (a) clipping, (b) threading, (c) snapping and (d) slipping, (e) Stoddart's axle component for slipping formation of a rotaxane with bis-*p*-phenylene-34-crown-10.

Slippage, the fourth mechanism, is never template directed. Here, independently synthesized cyclic and pre-blocked linear molecules with bulky substituents of just the right size already in place, are associated by heating them together. Slippage cannot be template directed because no further bond formation reaction occurs after the complex is formed. The distribution of the rotaxane and the separate reactants shifts toward the former through a combination of two factors: (1) complexation of cyclic and threaded linear components and (2) bulkiness of the blocking groups on the linear chain [58]. Intuitively, the size of the bulky blocking group should have the most definitive effect — if it is too big, it will never 'slip'

into the macrocycle. Even so, it is surprising how subtle this effect is. The Stoddart group has explored the mechanism of the slippage reaction of bis-*p*-phenylene-34-crown-10 and bipyridinium linear components blocked by 4-R-phenyl-bis(4-*tert*-butyl-phenyl)methane units where R = H, Me, Et, and *i*-Pr (Fig. 14(e)). Yields of the 2-rotaxane are around 50% for reactions where R = H, Me, and Et, yet when R = *i-Pr*, no rotaxane at all is isolated [59]. Such a large difference in results is attributed to a change in the rate determining step as R changes from Et to *i-Pr*.

Here, we must emphasize that the distinction between slippage to form a rotaxane and threading to form a pseudorotaxane is ambiguous. Clearly, exceedingly large endgroups entirely prevent a linear molecule from entering (or exiting) a macrocycle, yet the specific criteria for size exclusion are unknown. Somewhere along the continua of size and temperature in each system, slippage can start to occur. In addition to the bulk of the end groups, the extent of non-topological binding between the axle molecule and the ring must exert some influence, just as this binding forms the pseudorotaxane template prior to rotaxane formation by the addition of blocking groups. Shouldn't this binding stabilize the rotaxane even if its mode of formation is slippage? To preserve the concepts of slippage and pseudorotaxanes, it might be useful to invent some arbitrary parameter such as 'percentage yield at a given temperature' to distinguish between threading to form a pseudorotaxane and slippage to form a true rotaxane. The purist might maintain that any such species that could form or dissociate at any temperature without the breaking of a covalent bond is merely a pseudorotaxane. Yet, formation of rotaxanes by the slippage pathway has figured heavily in the history of rotaxane synthesis. We suggest no such system of classification is necessary at this time, but it is important to recognize the ambiguity of some of the terms used in the field. Stoddart and co-workers have invoked the use of fuzzy logic [60] to describe the intersection of the two sets, rotaxanes versus completely dissociated ring and axle components, as something that is 'inherently vague'.

Pedersen's seminal paper [61] illuminated the ability of crown ethers to form complexes with ammonium salts, and other early studies using relatively small rings indicated that primary ammonium salts form the most stable complexes [62]. X-ray structures of primary ammonium ion complexes with large crown ethers showed that the ammonium group can penetrate deeply into crown-ethers, suggesting that threading of secondary amines might be possible. This viewpoint was strongly supported by the fact that polymeric polyamine molecules serve as multifunctional anchors, threading many cyclodextrin rings spontaneously, thereby forming poly-pseudorotaxanes [63]. In this work, poly(iminoundecamethylene) and poly-(iminotrimethylene–iminoundecamethylene) were threaded by α-CD molecules by stirring their solutions until equilibrium was reached. Nicotinoyl blocking groups were then added to lock the CD rings permanently on the polymer. Intriguingly, the polyamine having pairs of nitrogens close to each other achieved a distinctly higher coverage, up to 67 mol% based on CD units per amino group (37 CDs per molecule) compared with only 10 mol% for the polymer in which all nitrogens are separated by 11 carbons.

The association of pairs of nitrogens with higher yielding rotaxane synthesis has recently been applied to our own work. Because the polyrotaxane formation observed by Wenz and Keller was far more successful than that reported earlier for small molecules, we suggested the possibility that the presence of multiple binding sites on the polyammonium axle molecules greatly favors threading. The smallest model for such a polymeric axle appeared to be a diamine and this was put to the test successfully, leading to the first example of a stoichiometric rotaxane, based on an ammonium ion/crown ether template (Fig. 15) [64]. The primary ammonium group was expected to provide the initial coordination of the end group to the cyclic receptor facilitating penetration of the ring. Competition for H-bonding with the crown ether oxygens by the secondary amine was then expected to complete the threading process. Comparison of rotaxane formation between the diamine of Fig. 15 and the structural analog having a methylene group in place of the secondary amine showed that only the diamine formed substantial yields of the rotaxane. Movement of the crown ether from the primary to the secondary amine completes the threading process, forming a pseudorotaxane. Then, acylation of the primary amine produces the [2]-rotaxane. The closeness of the primary and secondary ammonium groups was expected to facilitate the switching of the coordination position, a competition that might be critical in determining the success of the blocking reaction. Optimized yield of rotaxane at this point was 15%. In the absence of any previously successful amine/crown ether templated rotaxane synthesis, this was viewed as highly promising. Reasoning that competitive complexation by the primary amine group, over the secondary amine group, may be limiting the yield, the system was redesigned to favor binding of the secondary amine. Since both the diammonium axle molecule and the [24]crown8 macrocycle have only very limited solubilities in water but substantial solubilities in many organic solvents, a water soluble acylating agent was chosen to retain that reagent in water, and the reaction was then conducted at a water/chloroform interface; this doubled the yield of rotaxane (Fig. 15).

Subsequent reports verified the strong complexation of secondary ammonium salts with crown ethers to give threaded pseudorotaxanes [65–67], indicating that the complexing ability of the secondary amines provides adequate templating for rotaxane formation. Stability constants measured for these pseudorotaxanes range from minimal in DMSO to $\sim 10^4$ in $CDCl_3$. More complicated arrays, such as doubly encircled, and double and triple-stranded pseudorotaxanes have been characterized crystallographically [65,67].

Stoddart's group also applied a secondary ammonium/crown ether template to the preparation of [2]- and [3]-rotaxanes (Fig. 16) [68,69]. Terminal azido-groups were added to the ammonium salts that serve as axle molecules to facilitate a blocking reaction. Transformation into substituted 1,2,3-triazole stoppers proceeded by cycloaddition with di-*tert*-butyl acetylenedicarboxylate. The yields of [2]-rotaxanes were about 30%, and that of a [3]-rotaxane was about 10%. We viewed these yields as supporting a consideration that is critical to the ultimate achievement of high molecular weight polymers by rotaxane formation. In the simplest sense, the formation of the [3]-rotaxane requires two steps that depend on
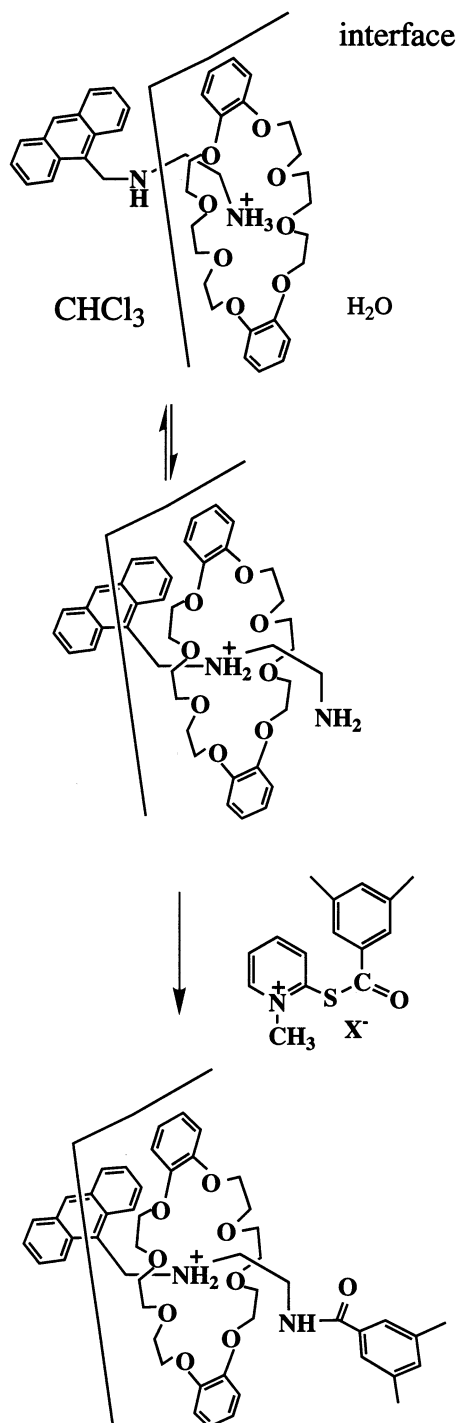
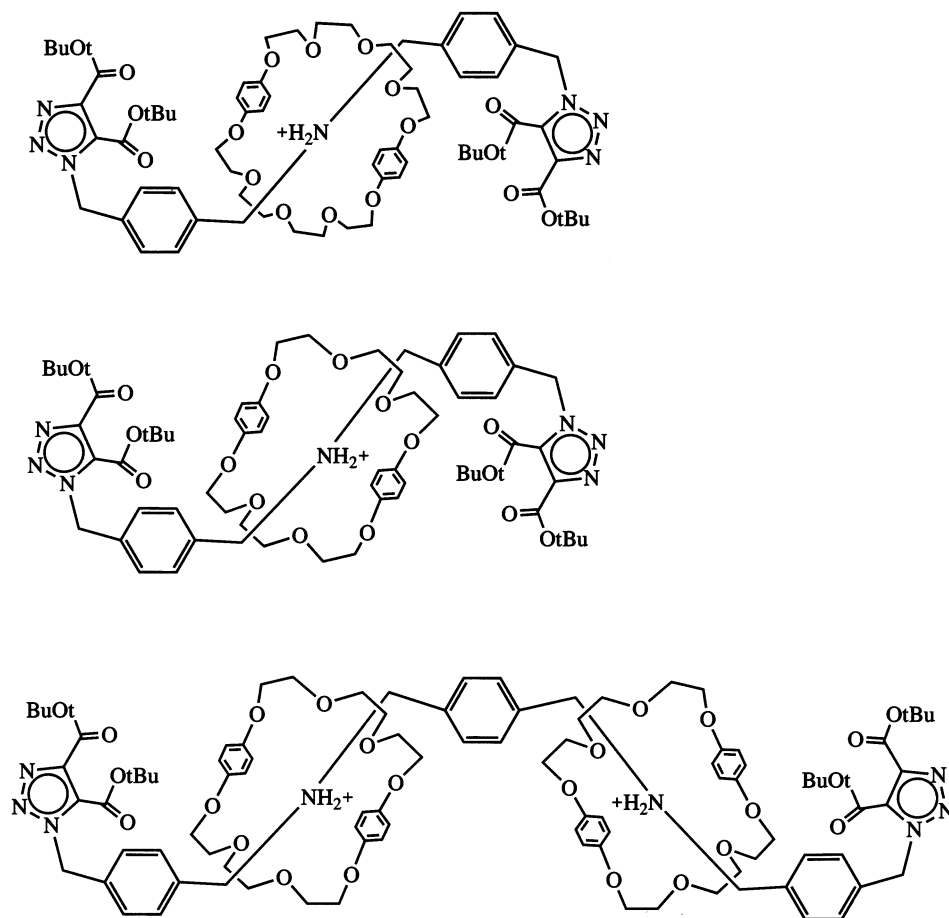Fig. 15. Kolchinski and Busch's use of relay threading and a solvent interface to enhance rotaxane formation.

Fig. 16. Stoddarts [2]- and [3]-rotaxanes from ammonium-crown templates.

the same factors that determine the single step yield of the closely related [2]-rotaxane. Indeed the yield of Stoddart's [3]-rotaxane is approximately the square of the yield of the [2]-rotaxane. Obviously, the expected yields of high molecular weight oligomers would be expected to be very small. This and other arguments create the demand for templates leading to high yield rotaxane formation. From this point of view, the study of [3]-rotaxanes becomes particularly important in the quest to produce high yielding templates; i.e. the greatest yield loss along the road to polyrotaxanes probably occurs at the second step, [3]-rotaxane formation.

Both the threading and blocking processes must be highly effective for successful rotaxane syntheses. As mentioned above, however, incomplete threading of crown ether/secondary ammonium ion complexes is indicated in many cases by NMR studies revealing the presence of free crown and ammonium moieties in solution [65–67]. Specifically, the variable success of the Stoddart group at achieving stable

pseudorotaxanes, combined with our evidence that the primary ammonium ion may compete too effectively with the secondary amine inspired redesign of our axial ligand. Preserving the idea that a 'relay threading' process may be advantageous we sought a more weakly hydrogen bonding terminal functional group to replace the primary ammonium ion; the thiol group appeared ideal for that purpose (Fig. 17). Not only should threading be improved, formation of the disulfide by oxidation of the pseudorotaxane offered a novel route to [3]-rotaxane formation. Iodine oxidation of the corresponding pseudorotaxane showed remarkable success and afforded the [3]-rotaxane (Fig. 17) in a record high yield of 84%, which, by the reasoning above, implies threading and formation of a pseudorotaxane precursor in greater than 90% yield [70].

Pursuit of an early holy grail of supramolecular architectures, mechanically linked polyrotaxanes, has involved a healthy competition between the Stoddart, Busch, and Gibson groups. At the 22nd International Macrocyclic Conference in Seoul, Korea in 1997 [71], we reported the oligomerization by rotaxane formation of a novel type of rotaxane in which the axle and ring components are both parts of a single monomer molecule (Fig. 18(a)). GPC showed oligomeric rotaxanes as high as the nonamer. The corresponding pseudorotaxane was also found to exist in oligomeric form by the mass spectrometry. We suggested the name 'figure 9' polyrotaxane for this motif. In 1998, Stoddart et al. reported the synthesis of a crown ether molecule having a benzylamino group as a substituent on dibenzo[24]crown8, a species that might be capable of forming the same molecular motifs (Fig. 18(b)) [72]. The polymeric motif was labeled a daisy chain polymer, but the compound itself formed only a cyclic dimer of a mutually interpenetrating motif that may better be described as the 69 pattern. Again searching only for pseudo oligorotaxanes, but bringing forward the famous Stoddart template, three examples of self-complementary monomers of the same class were synthesized (Fig. 18(c)) [72,73]. As before, a crystal structure revealed the 69 motif in the solid state, but
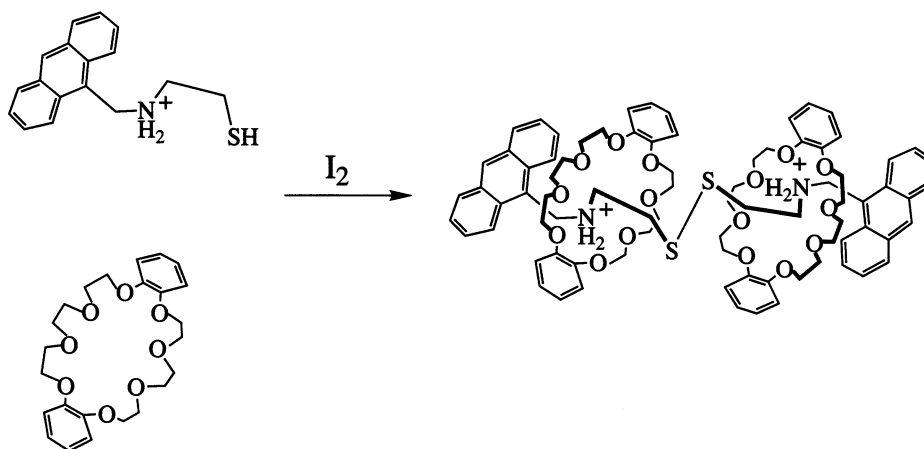

Fig. 17. Relay threading of thiol and amine groups results in the record 84% yield of a [3]-rotaxane.
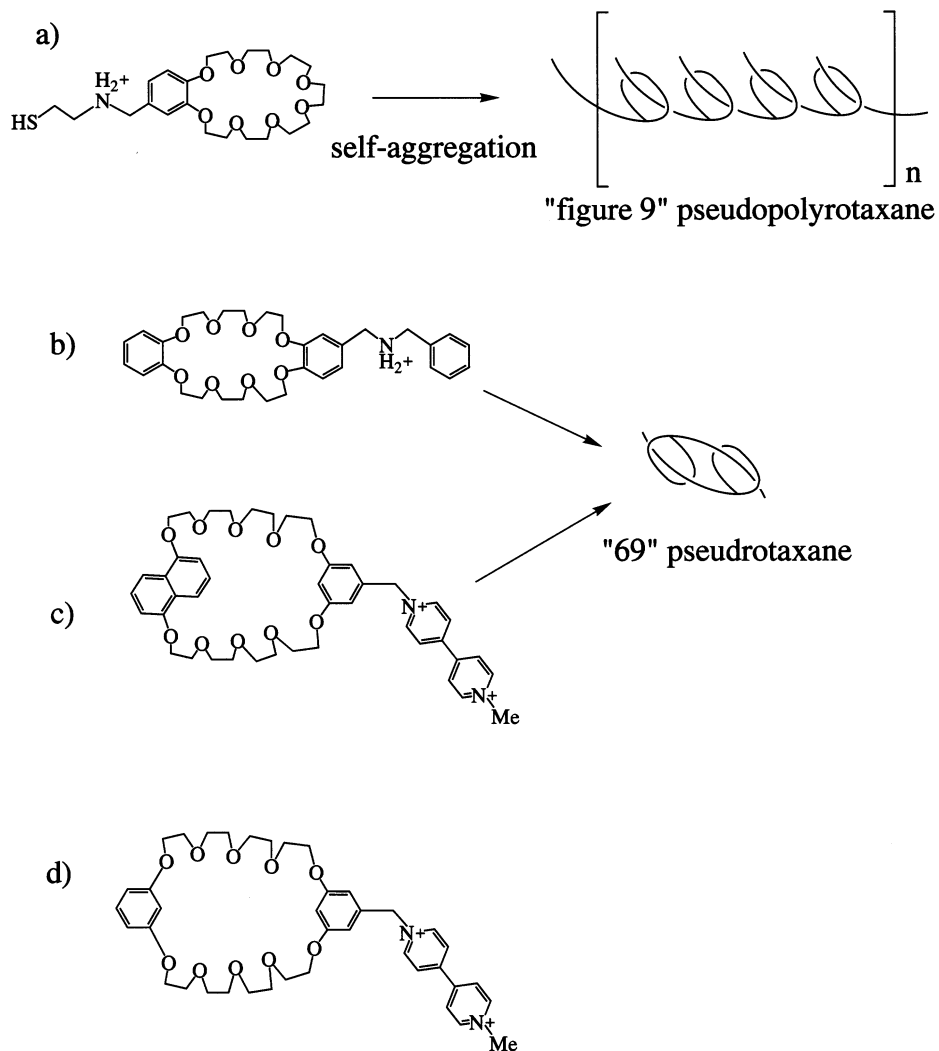
Fig. 18. Development of the figure 9 polyrotaxane concept, (a) Kolchinski and Busch's original figure 9 pseudopolyrotaxane, (b) and (c) Stoddart's attempts at figure 9 polyrotaxanes have yielded a new motif, the 69 dimer, (d) Gibson's figure 9 precursor.

mass spectral data provided evidence for oligomers as high as pentamers. The authors also assumed that failure of spectroscopic data on solutions to fit simple linear models indicated oligomerization in solution.

Gibson has previously applied a motif similar to the figure 9 monomer as a supramolecular connector in cross-linked polymers [74]. His group has more recently reported figure 9 pseudorotaxane oligomers formed in solution where the number of monomeric units has been calculated at 50 when the concentration of

the paraquat-crown difunctional monomer reaches 2.0 M in acetone (Fig. 18(d)). ^{1}H-NMR methods based on the chemical shift of an internal hydrogen of the crown moiety were used to estimate the extent of oligomerization. Spectra of related completely free and completely complexed crown ethers were used to calibrate the chemical shift change as a function of complexation. 2D-NMR spectra were consistent with the assignment of the pseudorotaxane formation in the oligomers. If blocking technology can be applied to these highly associated pseudorotaxanes to give the true rotaxanes, the goal of truly topologically interlocked polymers may be close at hand [75].

2.2.2. Diamide templates

In 1992, a new type of H-bond templated [2]-catenane was serendipitously discovered by Hunter [76]. Reaction of the incomplete product of a macrocyclization reaction, with *iso*-phthaloyl chloride at high dilution gave the unexpected [2]-catenane in 34% yield (Fig. 19). Mass spectrometry and extensive variable temperature and two-dimensional ^{1}H-NMR spectroscopy initially determined the interlocked nature of the product. A crystal structure removed the remaining ambiguities regarding conformation and the exact number of H-bonds involved [77]. Six H-bonds between the two identical rings are present in the solid state and are assumed, along with possible aromatic interactions, to be responsible for the formation of the interlocked structure in solution. Those hydrogen bonds provided the anchor and cause the turn in the linear molecule for the template process to occur.

Geerts et al., preceding their collaboration with Sauvage (vide supra), exploited the ease of functionalization at the position *meta* to the amides in Hunter's starting bis-amine to form the first polymers having alternating mechanically interlocked and covalently bound components [78]. The dibromo-functionalized amide catenane was combined with two different rigid spacer molecules, leading to oligomeric products (see Fig. 12(b)). Oligomers of up to 8 units were identified by gel permeation chromatography and FAB-MS.

Using templates with substituents on the 1,3-phenylene linker, but which are otherwise like Hunter's prototype, Vögtle has probed the mechanism of amide H-bond catenane formation [79]. From the route-dependent selective formation of the in/in and out/out isomers, Vögtle concluded that the critical intermediate for catenane formation is the macrocycle (Fig. 20(a)), where appropriate diacid chlorides can complex orthogonally to the ring plane, giving template complexes (Fig. 20(b)). The two different binding sites present in the unsymmetric templates lead to two isomeric products for each kind of diacid chloride and provide a basis for understanding the route-dependent formation of the in/in and out/out isomers (Fig. 20(c)). Vögtle has cleverly exploited these templates to reproduce many of the various interlocked structures previously seen in metal ion template chemistry: topologically chiral [2]-catenanes [80], [2]- and [3]-rotaxanes [81,82], and covalently as well as topologically linked [2]-catenanes [83] and rotaxane assemblies [84]. New rotaxanes have also been prepared in which the threading moiety no longer contains an arene group, but is an aliphatic amide, thus showing that H-bonding is more important to the template formation than potential $\pi-\pi$ interactions [85].
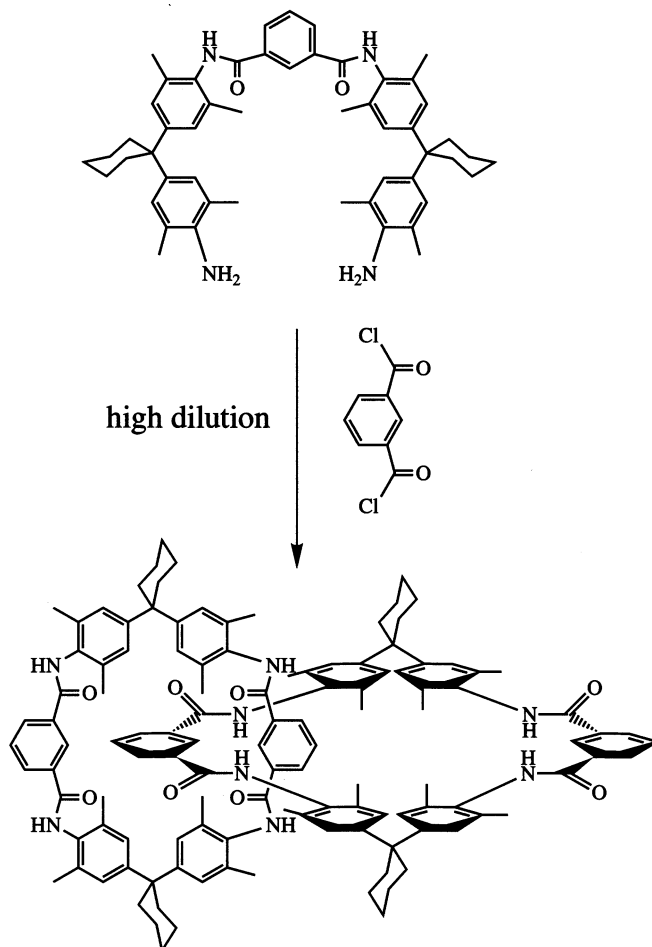
Fig. 19. The synthesis of Hunter's first amide [2]-catenane.

A facile [2]-catenane synthesis by Leigh et al., based on simpler amide H-bond templates appeared in 1995. *iso*-Phthaloyl chloride and 1,4-bis(amino-methyl)benzene were combined at high dilution (Fig. 21), to give an unexpected product (20% yield) which precipitated readily from the reaction medium. Characterization revealed that the product was the [2]-catenane of two $2 + 2$ macrocycles formed from the readily available and inexpensive starting materials [86]. At the same time, this research group showed how tolerant to variation this new catenane approach is [87]. A large range of [2]-catenanes form in similar one pot reactions from many different aromatic 1,3-dicarbonyl compounds and benzylic diamines. The inexpensive and facile synthesis coupled with the flexibility of this design for interlocked molecules are clear advantages over most of the templates we have seen so far. Leigh has applied this template to rotaxane
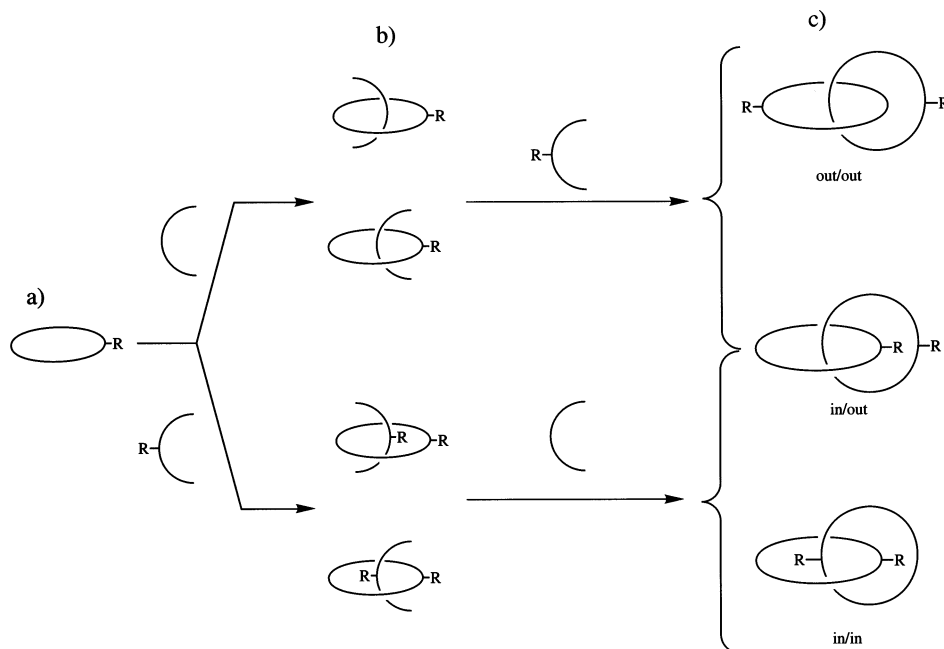
Fig. 20. Vogtle's study of the mechanism of amide catenanes: (a) substituted macrocycles form various template complexes (b) with substituted or unsubstituted turns and eventually yield path-dependent product [2]-catenanes (c).

formation [88], and to the study of the ring rotation kinetics in his 2-catenanes [89] as well.

2.3. Cyclodextrin templates

Groundbreaking research [90–93] has exploited the 'supermolecules' that are cyclodextrin inclusion complexes. Cyclodextrins, or CDs, consist of six (α), seven (β), or eight (γ) α-(1-4)-linked D-glucose units arranged in a torus, which results in
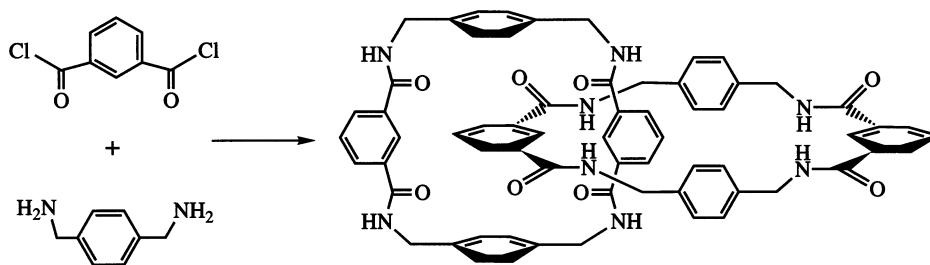

Fig. 21. Leigh's simple and flexible synthesis of amide [2]-catenanes.

rigid conical structures within which hydrophobic cavities exist. Made by the enzymatic degradation of starch, cyclodextrins are readily available as raw material macrocycles for supramolecular architecture construction. Their hydrophobic cavities have been used to bind a myriad of guest molecules [94]. Many of these host–guest complexes will be considered pseudorotaxanes for the purposes of this discussion.

Cyclodextrins act as anchors in templates by binding linear organic molecules within their hydrophobic cavities, allowing the protruding functionalized termini to undergo further reaction. Through the accumulation of multiple weak intermolecular interactions, such as hydrophobic effects, van der Waal's interactions, and hydrogen bonds, CDs can bind guest molecules quite strongly, occasionally even as strongly as a covalent bond [95]. While this binding is very complicated, the interactions are very general in that a wide range of guest types form complexes with CDs, suggesting that CDs may be among the most non-specific, of templating agents available. CDs do 'select' for molecules having at least some low polarity fragment, yet virtually any molecule having a polymethylene chain or aromatic ring is a potential 'turn' for an appropriately sized cyclodextrin 'anchor' to form a pre-interlocked template. This flexibility should prove vital as CD templated supramolecular architectures are explored further.

Threading an α,ω-diaminoalkane, diaminohexaethylene (DAHE) through (2,6-di-*O*-methyl)-α-CD, followed by a stoppering reaction with the sodium salt of 2,4,6-trinitrobenzenesulfonic acid (TNBS) gave the first completely non-ionic cyclodextrin [2]-rotaxane only as recently as 1997 (Fig. 22) (TNBS and DAHE react easily in water to give the covalent C–N bond). The reaction yielded 42% of the product, which was characterized by elemental analysis, UV–vis, NMR, and FAB-MS techniques [96]. Ironically, the first report of CD polyrotaxanes occurred more than 20 years earlier, in 1976 [97]. It was the result of the condensation of inclusion complexes (pseudorotaxanes) of aliphatic and aromatic diamines and β-CD with *iso*-phthaloyl or *tere*-phthaloyl chloride in water. Called 'tunnel polymers,' these new types of polyrotaxanes were predicted to '…develop a new and broad field of polymer materials'.

The development of that field has been most accelerated by Harada and his colleagues, concentrating their efforts on polyrotaxanes formed from poly(ethylene
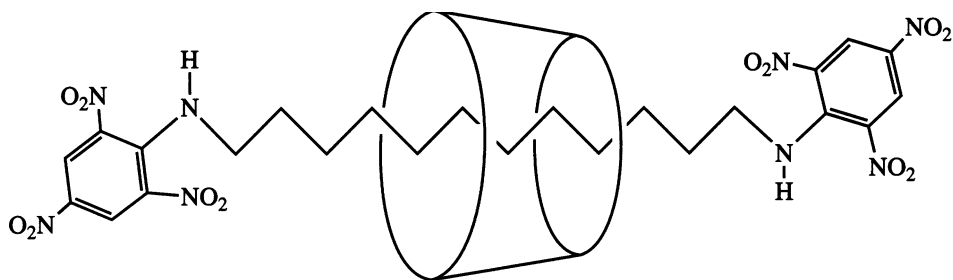

Fig. 22. The first covalent [2]-rotaxane using cyclodextrins as the ring component.

glycol), or PEG, and cyclodextrins. Aqueous solutions of 400–10 000 Da PEGs can be added to saturated solutions of α-CD to give stoichiometric complexes in yields up to 90% [98]. Quantitative experiments have indicated that two ethylene glycol units are bound in each α-CD cavity (the cavity and the two ethylene glycol units are both about 7 Å long). Poly(propylene glycol), or PPG does not form complexes with α-CD, but does so easily with the slightly larger β- and α-CDs, implying that there is some selectivity in CD templates [99]. Rotaxanes called 'molecular neck-laces' form when α,ω-bisamine PEGs thread CDs before reaction of the amines with 2,4-dinitrofluorobenzene stopper the polyrotaxanes (Fig. 23(a)) [100]. Begin-ning with PEGs averaging 3350 Da, polyrotaxanes have been isolated with an average mass of 23 200, indicating ca. 20 α-CD units had been captured in each polymer molecule; i.e. a [21]-rotaxane had been formed.

Harada's tubular polymer is a stunning example of a template generated supramolecular architecture. In this unusual material, covalent bonds tie together the α-CDs trapped on the molecular necklace molecule described above [101]. The hydroxyl groups of each CD on the polyrotaxane combined with epichlorohydrin, giving the covalent linkages between them (Fig. 23(b)). Strong base removes the stopper groups, releasing (by an undescribed mechanism) the tubular polymers, which had an average mass of nearly 20 000 Da, in 92% yield. Smaller than, but reminiscent of, tubular or fibrillar structures found in living organisms, these tubular polymers might be used in separation technologies, or perhaps as 'organic zeolites' [102].

In contrast to the successes of cyclodextrins in rotaxane formation, it is surprising how difficult their use in catenane formation has been. The pioneer in investigation of interlocked structures, Luttringhaus, planned the first experiment aimed at incorporating a cyclodextrin into a catenane [103]. The proposed template was a bis(8-mercaptooctyl) derivative of hydroquinone in a complex with α-CD; however, no catenane was isolated (Fig. 24(a)). Stoddart finally succeeded in making the first cyclodextrin catenanes some 35 years later [104]. A bitolyl unit between te-traethylene glycol groups terminated by amino functionalities was used to thread (2,6-di-O-methyl)-β-CD. Reaction of this template complex with *tere*-phthaloyl chloride gave a mixture of catenanes (Fig. 24(b)) in low yield. The nature of the molecules that typically thread cyclodextrins probably contributes to their lack of success as catenane components. They are poor turns — the threading molecules are often flexible and their terminals are not specifically oriented. An oriented turn is not so important to rotaxane formation, but to close a turn into a ring, it is vital.

2.4. π-Donor π-acceptor templates

The discussion of the architectures arising from π–π templates revolves around the creative and voluminous work of Stoddart and his productive co-workers. Stoddart's constructs developed from investigations of the host–guest complexes of the π-deficient herbicide paraquat and π-donating macrocycles, such as bis-*p*-phen-ylene-34-crown-10, (BPP34C10) [20]. In relatively polar solvents, strong complexes form with the herbicide bound between the electron rich hydroquinone units
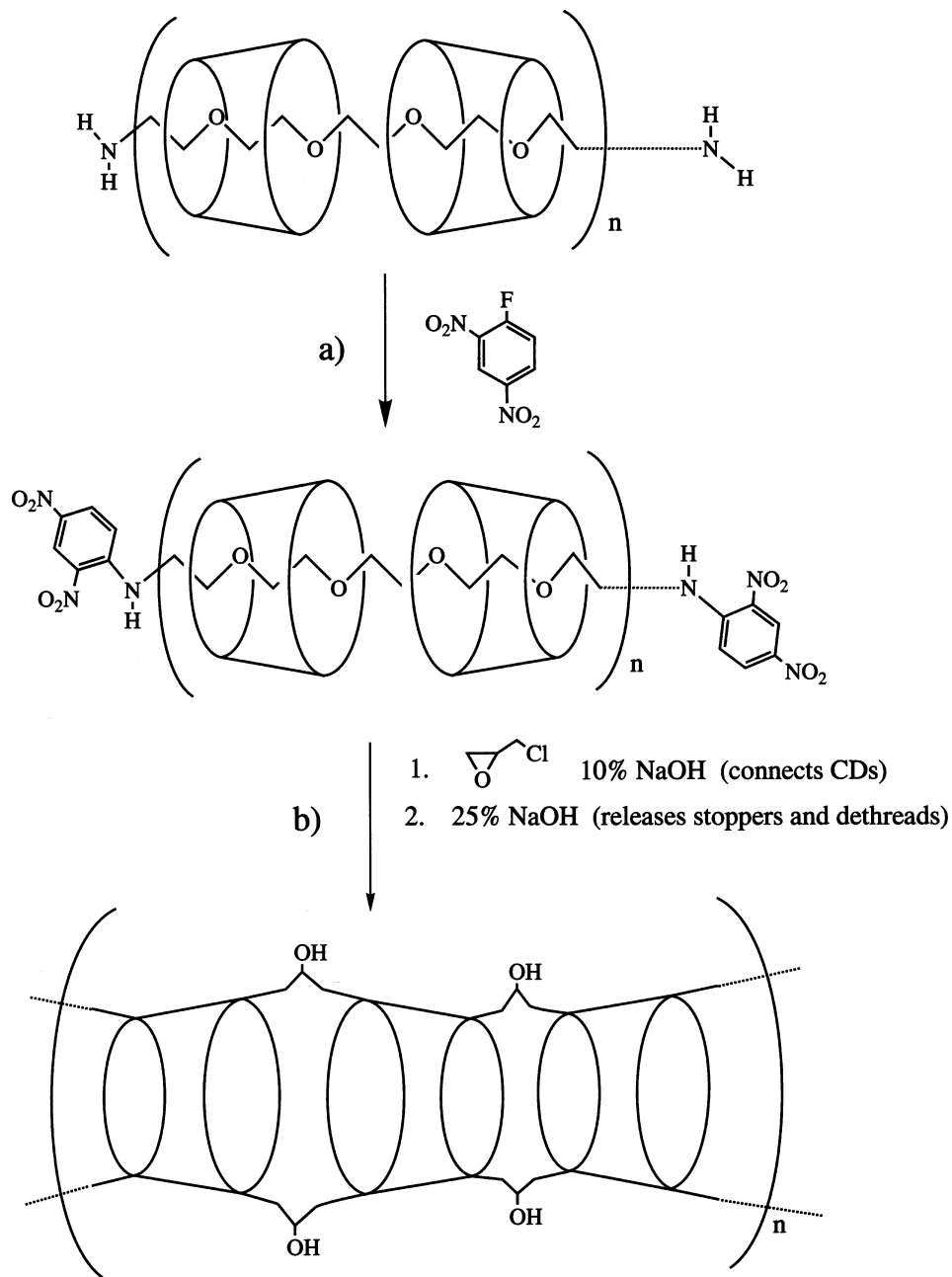
Fig. 23. (a) Formation of Harada's molecular necklace and (b) tubular polymer using template synthesis with cyclodextrin components.
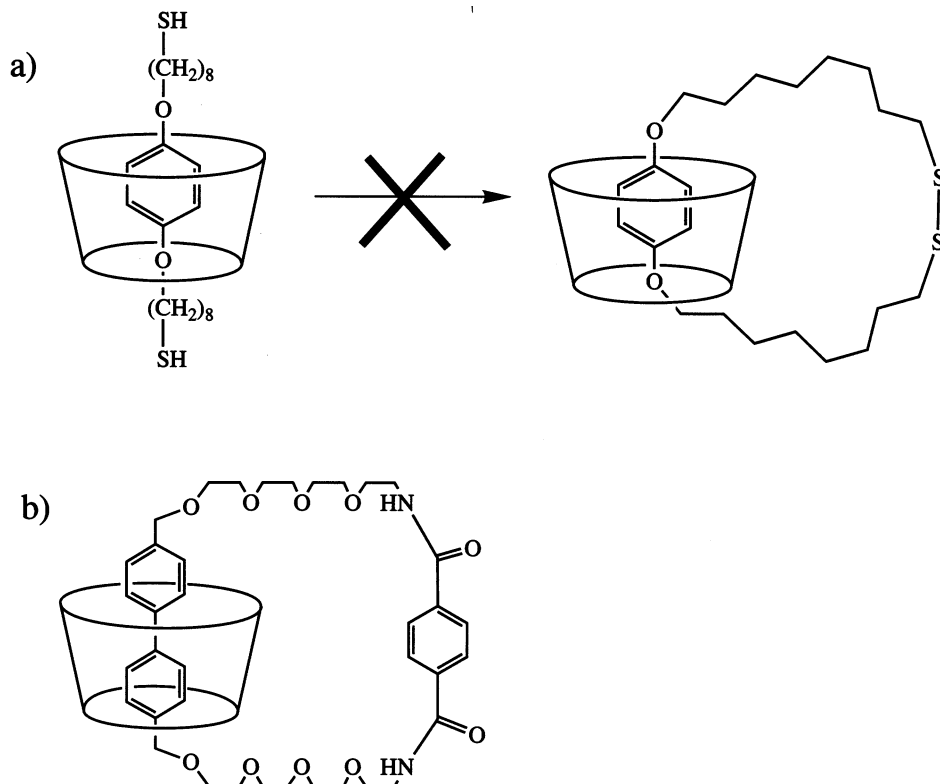
Fig. 24. (a) Luttringhaus' failed cyclodextrin catenane reaction and (b) Stoddart's first successful cyclodextrin [2]-catenane.

of BPP34C10 [105,106]. These studies revealed, a nearly ideal system for the template synthesis of interlocked molecules: strong non-covalent interactions, with predictable complexation products, that have geometries favorable for closing rings or stoppering rotaxanes. Although the combination of interactions involved in Stoddart's templates (vide supra) is more complex and more interesting, it is convenient to refer to such systems as involving π–π interactions, or as making use of a π–π template, and we use such shorthand jargon to facilitate communication.

Another interesting consideration about the π–π templates is the designation of its common parts, the anchor and the turn. It is intuitive in Sauvage's chemistry (vide supra) that the metal ion always serves as the anchor and the ligand is always the turn. However, in the case of π–π templates, either the π-donor or the π-acceptor might have been designated as the anchor or the turn (see Fig. 2). However, we conclude that the anchor is best regarded as the cumulative forces that bind and orient the two π-systems, and that it may be regarded as located at the point in space directly between those systems. Additional interactions are associated with inducing the molecular turn. In any case, no separately definable

physical entity is behaving as the anchor. In this and related situations, it is best to define the anchor as the dominating force that orients the individual molecular units so that they can collectively perform the templating function.

In order to take full advantage of the π–π system's characteristics, Stoddart developed a turn to accompany the interesting anchor technology he had discovered — a phenylene-linked bis-paraquat that, when complexed with BPP34C10, underwent reaction with *p*-xylene dibromide, to produce the desired template product, the [2]-catenane, in a remarkable 70% yield (Fig. 25) [107]. This simple [2]-catenane provided the breakthrough that has led to the synthesis of much more complex structures using the same general kind of template strategy: formation of the π–π complex, followed by further reaction to close rings or stopper rotaxanes.

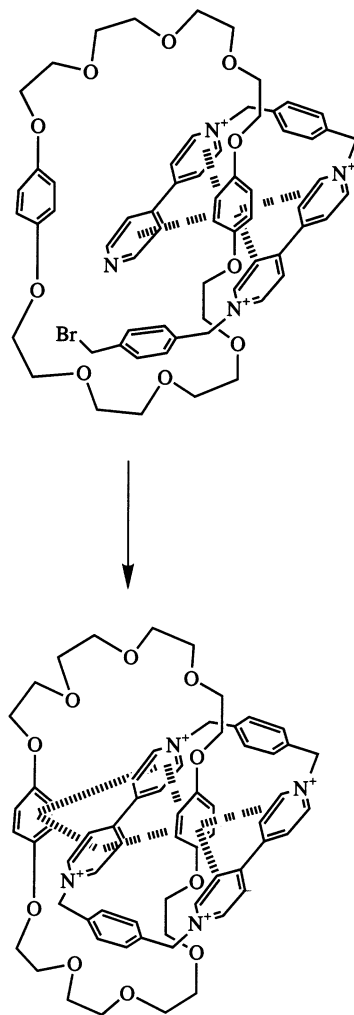Fig. 25. The π–π template synthesis of Stoddart's prototypical [2]-catenane.

A stated goal of the research conducted by the Stoddart group is to create polycatenanes [20]. Again, we emphasize that extremely interesting properties may occur in such polymers because the individual molecules from which the polymer is formed are joined by mechanical interlinkages, rather than by covalent bonds as in typical polymers. The first step in developing such polymers was the extension of the π–π template to the synthesis of a [3]-catenane [108]. To do so, a slightly larger paraquat cyclophane unit was synthesized, linking the paraquat units through a bitolyl group. The [3]-catenane, shown in Fig. 26(a) was obtained in 30% yield from the reaction of this π-acceptor turn and the usual macrocyclic π-donor.

Progress towards mechanically linked polymers proceeded in Stoddart's group with the 1994 publication of a linear chain of five linked rings, an array appropriately named Olympiadane (Fig. 26(b)) [109]. Successive reactions lead first to the [3]-catenane, by making use of the new larger paraquat-turn to link two newly designed multi-site π-donor macrocycles, then to the [5]-catenane Olympiadane by reaction with two more of the smaller π-acceptors turns, templated onto unoccupied π-donor sites.

This same strategy has now been extended to produce a [7]-catenane [110] (Fig. 26(c)), which conveniently illustrates the concepts of branched as compared with linear catenanes. In a linear catenane, each ring is coupled only to its two sequential neighbors, whereas, in a branched catenane, the ring at the node of the branch is attached to both its two sequential neighbors and to the branching ring. The Stoddart group used their larger aromatic macrocycle as the center link in a base chain of five rings with their smaller aromatic macrocycle as end groups and branches (which are indistinguishable in this case), and the large crown ether as the nodal ring. The order of the node was determined by the number of electron donor sites in the nodal macrocycle.

Polycatenanes via another strategy required the synthesis of bis-catenanes and bis-rotaxanes [111,112]. These effectively difunctional, mechanically bonded molecules were prepared from bis-linkers and bis-macrocycles, which contained the requisite π-acceptor or π-donor aromatic groups. Clipping of the complementary aromatic system produced the bis-[2]-rotaxane (Fig. 27(a)) and threading (which forms bis-[2]-pseudorotaxanes) was followed by cyclization to produce the bis-[2]-catenanes (Fig. 27(b)). Polymers resulting from polymerization or copolymerization of related functionalized bis-catenanes have been reported [113], giving polymers of up to 25 repeat units and M_n values of up to 45 kg mol^{-1}. Little data on the properties of the new polymers is available, though it is hoped they would display interesting properties. From one perspective, it is unfortunate that such polymers would not contain only mechanical interlinks (Fig. 27(c)), our aforementioned 'holy grail'. There are earlier reports of polymers with alternating mechanical and covalent linkages in the main chain but synthesized using other kinds of templates and different strategies (vide supra).

An interesting molecule which could be called a [1]-catenane has recently been developed by the Stoddart group [114]. A clever synthesis yields a benzocrown in which the benzo group is disubstituted with paraquat arms. These arms can then self-complex with the napthyl group on the other side of the crown ether. Ring
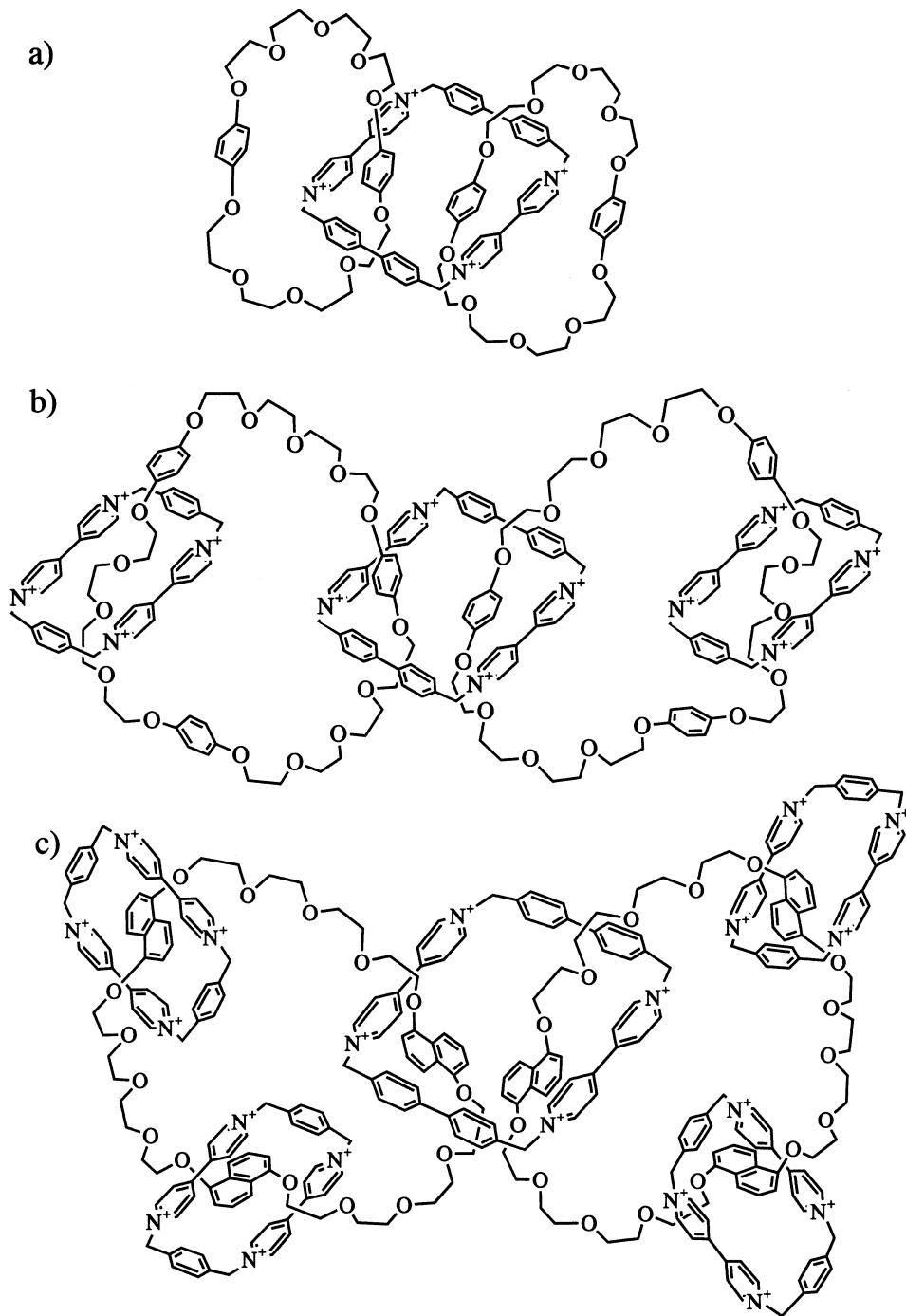
Fig. 26. Advancement of the π–π template oligocatenanes from (a) the first [3]-catenane to (b) the [5]-catenane Olympiadane and finally to (c) a branched [7]-catenane.
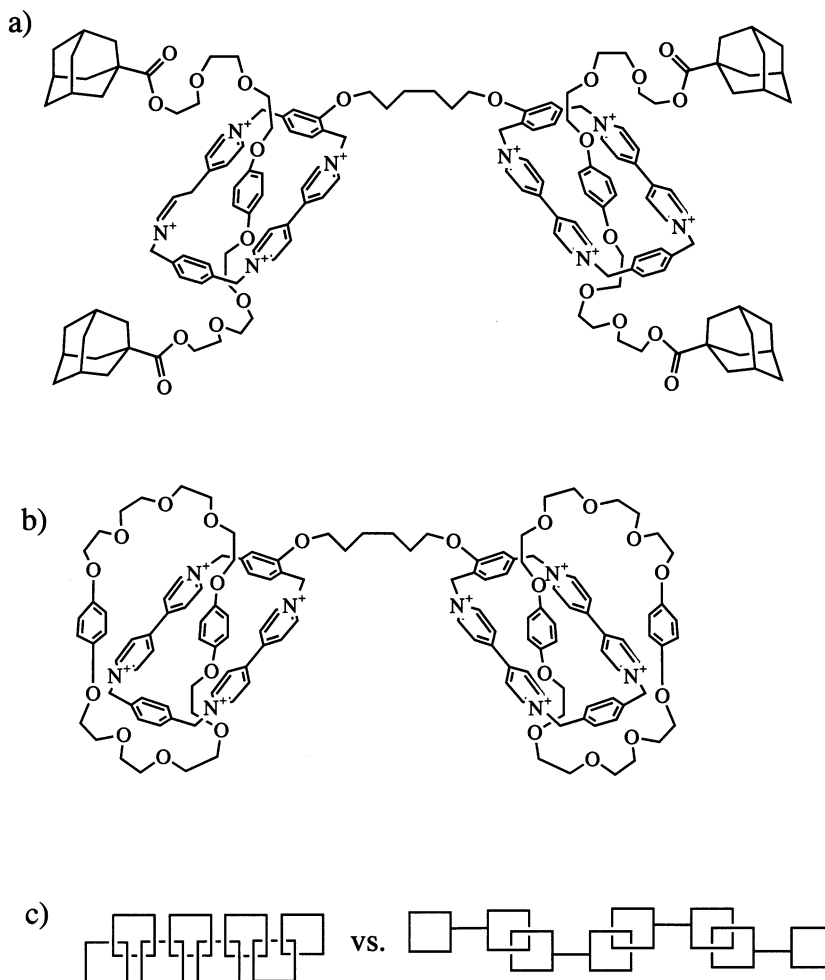
Fig. 27. Bis-[2]-rotaxanes (a) and bis-[2]-catenanes, which can be used in the formation of (c) polycatenanes with alternating covalent and mechanical bonds (compared with a polymeric catenane of only mechanical bonds).

closure with *p*-dibromoxylene gives topological interlocking of the two rings emanating from the benzo group (Fig. 28(a)). This molecule is topologically similar to Walba's hook-and-ladder molecule [37] and Vögtle's pretzel [83], where chains covalently connect [2]-catenane rings. But, here the covalent connection has been reduced to zero intervening atoms that aren't part of the rings themselves. In related work [115], Stoddart's group has polymerized [2]-catenanes in which a single ring is difunctionalized, resulting in pendant poly[2]-catenanes (Fig. 28(b)). Again, the goal of truly interlocked polymers has not quite been met, since the mechanical bond is only present in side-chains in this case.
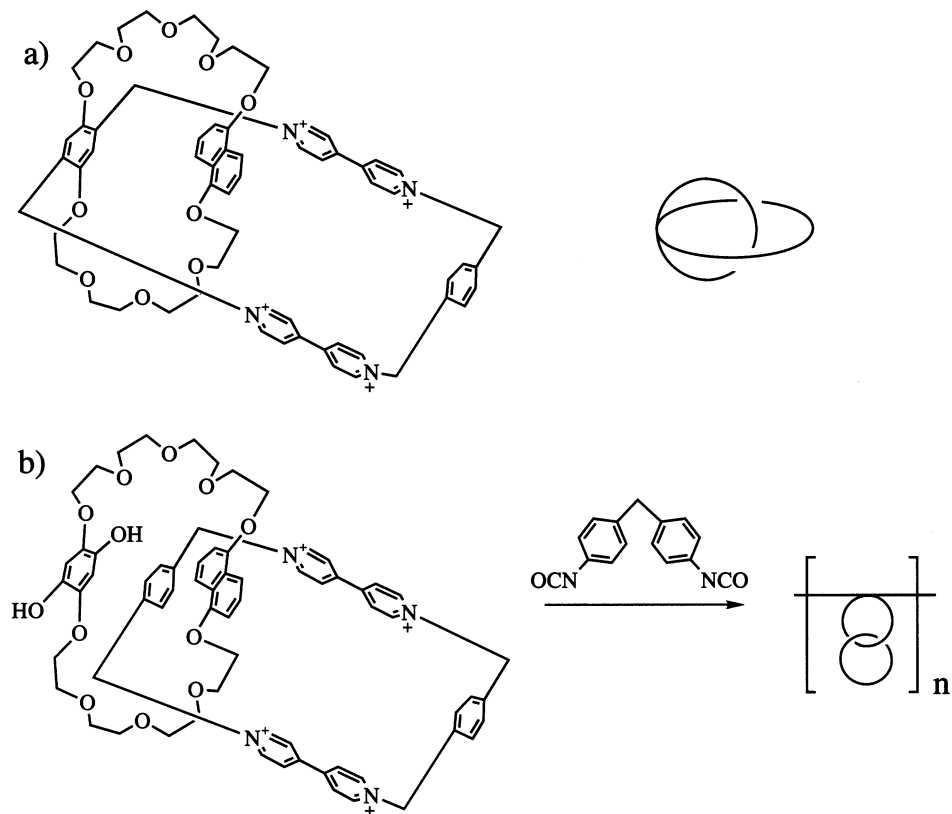
Fig. 28. Difunctionalization of one ring can lead to (a) a novel [1]-catenane or (b) the first pendant polycatenanes.

Stoddart's group claims to have forced their template system to yield a trefoil knot [116] although not as successful in yield or characterization as we have seen from Sauvage earlier. The method for the knot preparation is shown in Fig. 29 and uses polyfunctional π-donor and π-acceptor linear molecules to intertwine with each other before their reactive terminals are joined to produce the trefoil knot. Unfortunately, the yield of the trefoil knot is reported at only 0.6% and its characterization remains ambiguous. The assignment of the trefoil structure is based on mass spectrometry, the color of the product, which indicates both π-donor and π-acceptor systems are present, and the fact that the other isolated product, assumed to be the simple macrocycle of the same components, binds ammonium cation while the tentative knot product fails to do so. The interpretation of the authors is that the knotted structure sterically precludes ammonium binding and therefore, the product that doesn't bind ammonia is the knot. ^{1}H-NMR studies could not confirm the suggested structures of the two isolated products and no suitable crystals have been obtained for structural analysis.
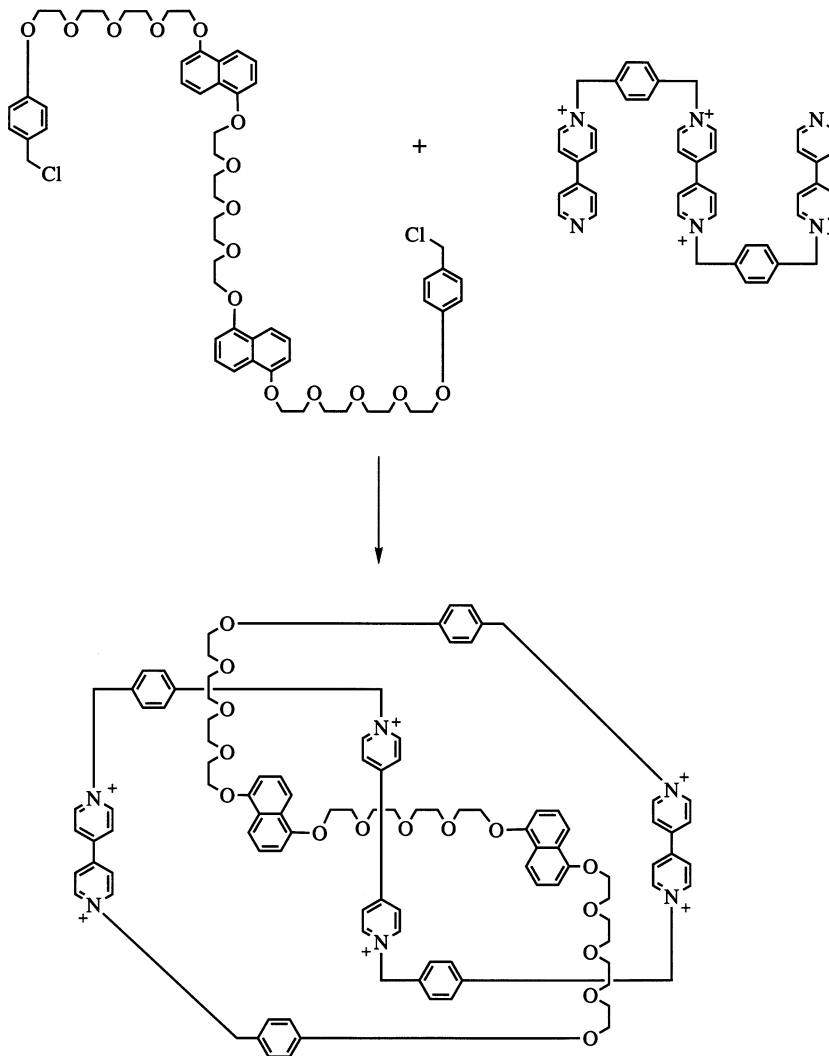
Fig. 29. Stoddart's synthesis of a trefoil knot utilized polyfunctional π–π template precursors.

Finally, we must point out the recent work of Sanders et al., who have developed [2]-catenanes based on neutral π–π templates [117,118] in yields as high as 52%. The template now consist of electron-rich aromatic crown-ether macrocycles and an electron-deficient aromatic diimide derivative (Fig. 30). This system shows that neutral components can yield similar results to what is found in Stoddart's work, where the electron-deficient component is generally a charged paraquat derivative.

In closing this section, we must point out how powerful these so-called π–π templates can be in contrast to the seeming modest strength of the binding forces that make them possible. Also, we should observe the apparent necessity of
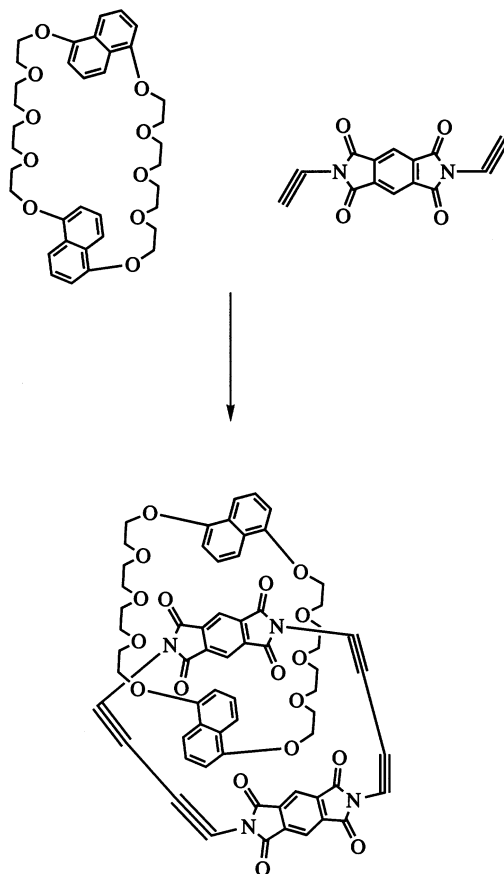
Fig. 30. Sander's use of neutral π–π template pairs to form a [2]-catenane.

preserving all aspects of the template, from the obvious and easily overemphasized π–π stacking and electrostatic anchoring, to the C–H hydrogen bonds that are always built into the components. The combination of these features seem critical to the formation of the templates which produce the high yields and complex molecular architectures that have become associated with this area of chemistry. Yet, as Sanders has shown, not all of the features are vital, but some may be replaced with suitable substitutions. The total range of variations that is functional remains an open question.

3. Conclusions and suggestions for the future

Unquestionably, exceptional advancement has taken place in the generation of new interlocked molecular architectures, both in the diversity and complexity of the

supermolecules that have been synthesized and in the interpretation of the empow-ering correlations, generalizations and principles. Sophistication has proceeded even to composite knots based on four templating centers, branched oligomeric cate-nanes with at least seven interlocked rings, polymers with repeating catenane linkages, polyrotaxanes with multiple rings impaled on single linear molecules, rotaxanes with rings on branched polymeric structures and rotaxanes as cross-link-ing strategies. Template chemistry has played a large role in this maturation. The assortments of interactions that create template behavior have grown and it is proper to conclude that any constraining force at the molecular level could feasibly serve the role of anchor in the anchor/turn combination that is so pivotal to template behavior. Major growth areas are metal ions, multiple hydrogen bonds, the interactions of aromatic rings, hydrophobic interactions, and amalgamations of the above. It is amazing how powerful a single model of a molecular turn can be in generating new chemistry if it arises in a favorable environment; e.g. Sauvage's or Stoddart's turn in either of their labs. The rousing success that has been achieved offers promise that even more fascinating and facilitative advances will be made. It is not yet credible to describe the equivalent of a molecular sewing, knitting, or weaving machine, but many alluring opportunities are being revealed as chemists remove the overburden of ignorance from the underlying wealth of new chemistry. The enormous potential of the field has hardly been perceived and, even within the currently visible realm, many challenging supramolecular architectures are yet to be achieved. Before closing we will consider a few real possibilities.

3.1. A new fundamental element for templates

The divergent molecular turn is an under-appreciated structure that is not itself an interlocked molecule, but rather a type of template element. New interlocked structures, new architectures, and new routes to known architectures should follow from proper use of divergent turns. Convergent turns, like those described previ-ously in this review (e.g. Sauvage's, Stoddart's), fold across the anchor in the template complex. A divergent turn, on the other hand, folds away from the anchor in its template complex [3]. A simple shift of the phenol units in Sauvage's turn from the 2 and 9 positions of phenanthroline to the 4 and 7 positions, would create such a divergent turn (Fig. 31(a)).

The power of a divergent turn lies in the diverse template targets it makes possible, especially in its combination with a convergent turn on the same anchor. For example, the union of two such templates could result in a ring-in-ring structure, a pseudorotaxane of sorts (Fig. 31(b)). This complex may act as an intermediate in the synthesis of a Borromean ring structure [119]. Sterically blocking one terminus of the divergent turn in a mixed-turn template, could produce, remarkably, an 'overhand knot', tied in a [1]-rotaxane fashion (Fig. 31(c)). Mathematically, this overhand crossing isn't a true knot; its ends are not joined. But, if the blocking groups are large enough to prevent unthreading, the structure will be interlocked and the new architecture might be called a 'rotaxaknot'. A single molecule constituting a fused turn by merging convergent and divergent features
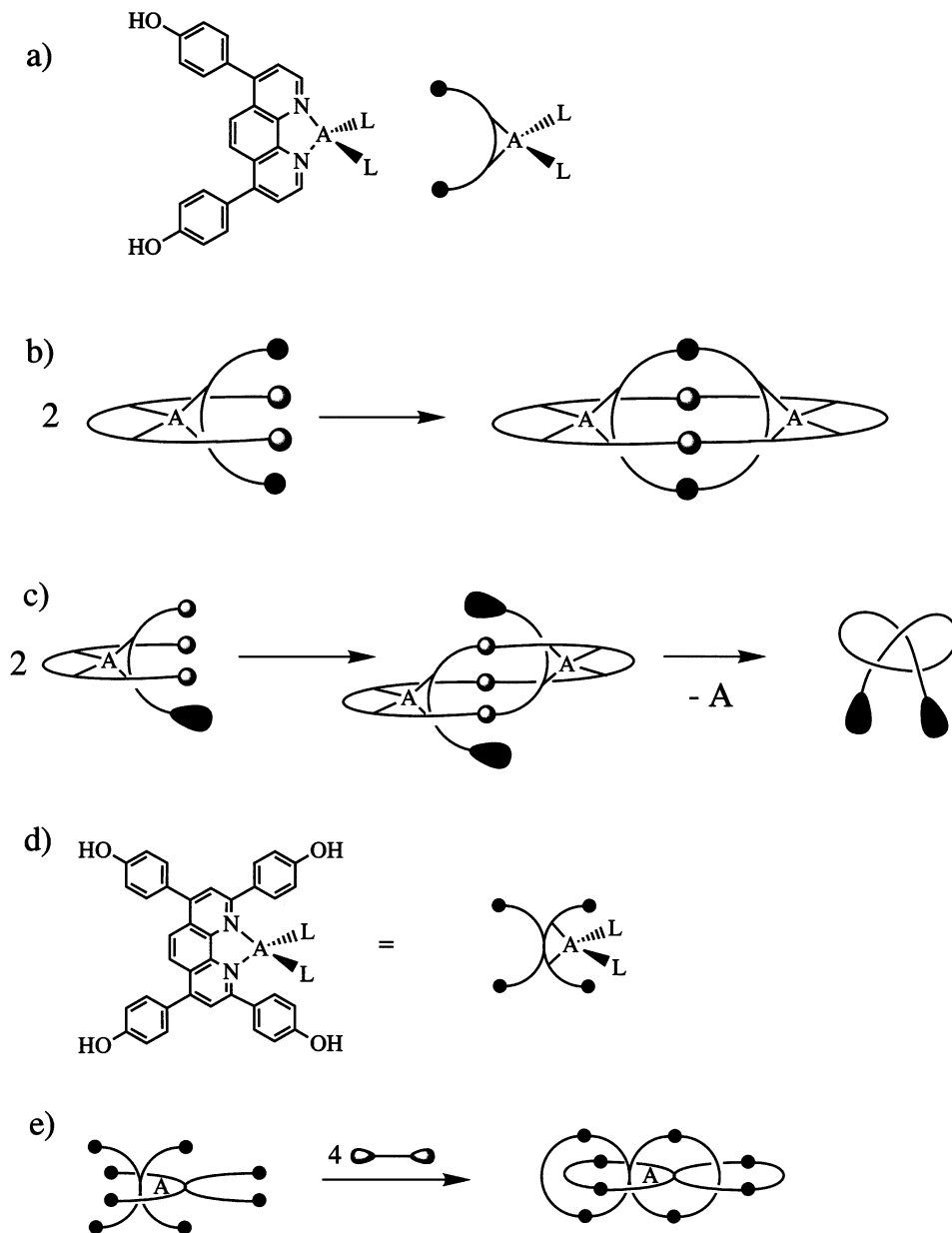
Fig. 31. (a) A hypothetical divergent turn and its cartoon representation (b) combining divergent and convergent turns on the same template complex could lead to a ring-in-ring complex or (c) an overhand rotaxaknot (d) a hypothetical convergent/divergent turn and its cartoon representation could be used to form (e) an interlocked set of figure eight's.

(Fig. 31(d)) could give even more interesting interlocked structures, such as two interlocked figure eights (Fig. 31(e)). In this hypothetical molecule, the second ring prevents the first from rotating. From these few, simple examples, it is clear that the addition of the divergent turn to the supramolecular chemist's toolbox should importantly augment the types of interlocked structures he or she can build. As we strive toward the most challenging goals of orderly molecular entanglements, such as the weaving or knitting of polymer strands [6], such tools will be of critical importance.

Schmittel and Ganz have illustrated the concept of divergent turns by constructing mixed convergent/divergent turn template precursors like those discussed above (Fig. 32(a)) [120,121]. Incorporating one or two divergent turns into macrocycles prior to complexation results in model starting materials for the [2]-catenane and ring-in-ring structures, respectively, as discussed above (Fig. 32(b)). Three separate groups have already incorporated *ex*-facing bipy groups into at least one ring of $\pi-\pi$ templated catenanes in order to provide binding sites for metal ions [122–124]. Divergent turn template reactions would result if these binding sites were used for further reaction of the resulting metal complexes.
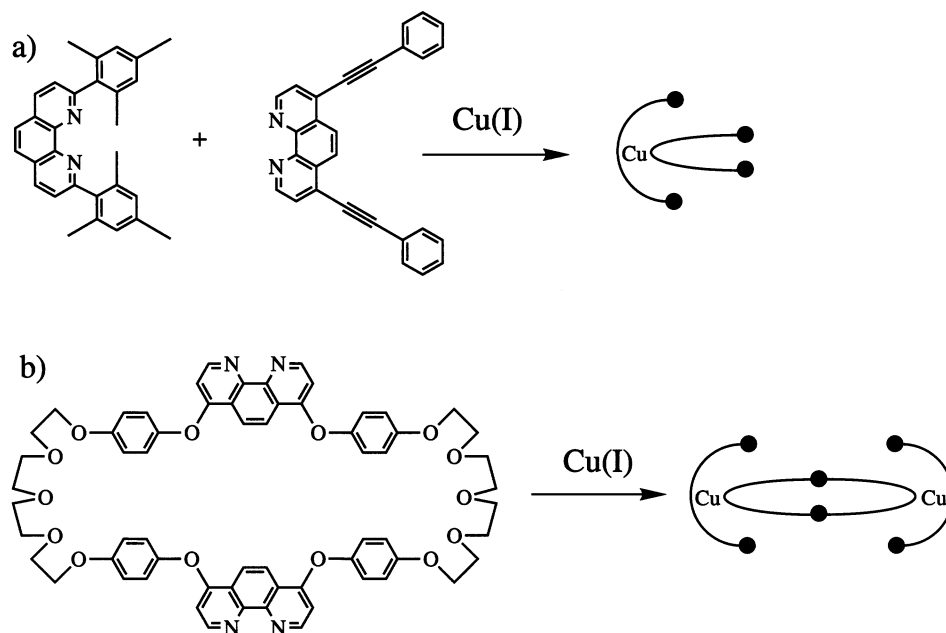

Fig. 32. Model complexes prepared by Schmittel and Ganz contain (a) convergent and divergent turns on the same complex and (b) precursors to a ring-in-ring complex.

3.2. Molecular weaving

The ultimate aspiration of chemists working on interlocked structures might be to weave molecules as if they were macroscopic threads. Although this goal seems distant, progress is being made. To avoid confusing the aspirations of this noble field, the use of the word 'weaving' should be reserved for covalently linked molecular strands mechanically interlocked by multiple crossovers (interfacings) with multiples of other strands. 'Weaving' should not be used to describe solid state
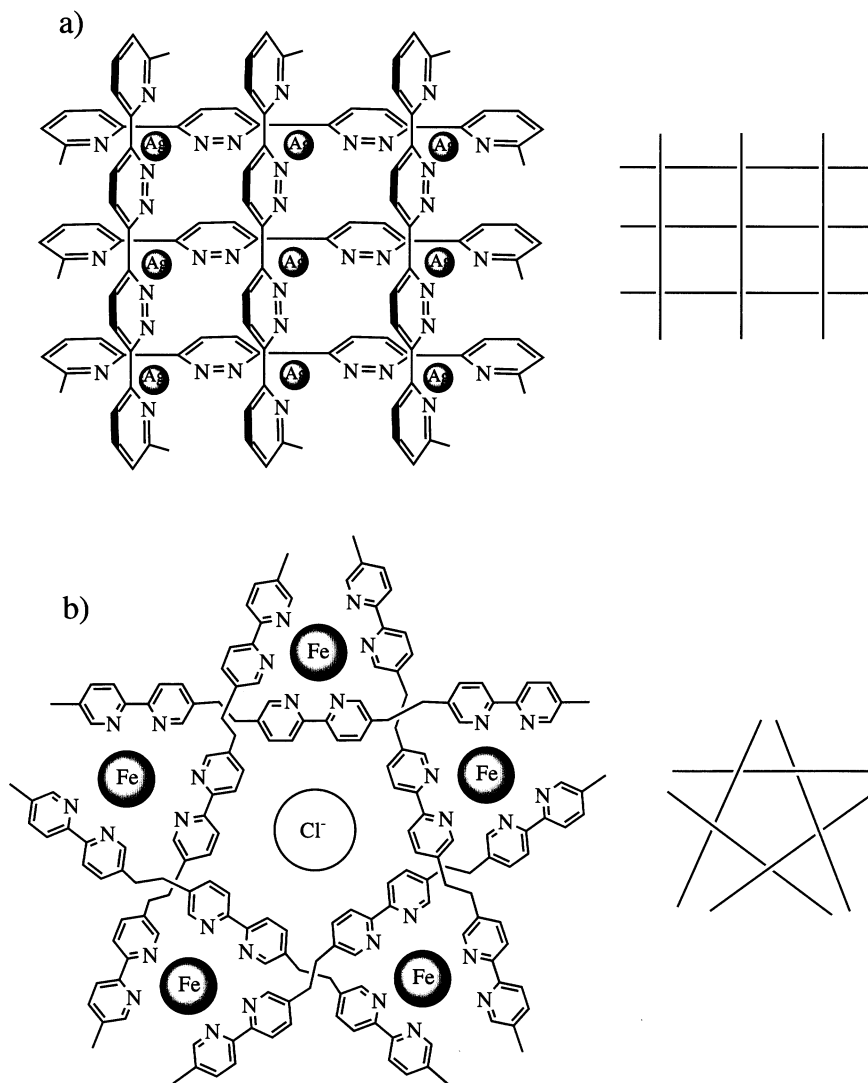
Fig. 33. Lehn's (a) rack complexes and (b) circular double helicates hint at the possibilities of molecular weaving.

structures where hydrogen bonds or other weak interaction mimic truly covalently interlocked motifs. Lehn's rack-type complexes (Fig. 33(a)) [125,126] may foreshadow true molecular weaving and his circular double helicates (Fig. 33(b)) [126–128] do actually meet the requirements of our definition. These structures rely on self-assembly of multi-functional ligands around multiple metal ions.

While flexible linear ligands with multiple binding sites seem predisposed to form helical dimers or trimers around multiple metal ions [129], more rigid ligand strands prevent helication and form the rack-like assemblies of Lehn. A weaving architecture could likely be achieved by making even more rigid ligand oligomers where the binding sites are constrained to opposite sides of the strand (Fig. 34). Rigidly built in binding sites on both sides of the ligand strand might program in the necessary interlacing property of weaving. Truly functional ligand oligomers for woven molecules will have to be determined experimentally, but several qualities appear to be essential: rigid constraint of adjacent binding sites to opposite sides of the ligand (flexibility, i.e. rotation, could result in helices or rack-like complexes), thermodynamically strong metal complexes formed by relatively kinetically labile mechanisms (to facilitate the assembly of multiple components), and spacer units of sufficient length to accommodate the metal ion in the space in between the woof and the warp. Geometry and dimension will limit the choice of metal ions to those that can be maintained within the weave (for example, tetrahedral ions will require that the ligand strands be perpendicular to each other) further requiring that adjacent bidentate donor sites be located at distances approximating the van der Waal's diameter of one metal ion. Appropriate early targets for the development of this chemistry, such as model systems of three, four, or nine metal ions containing difunctional or trifunctional ligand strands would lay the groundwork for polymeric woven sheets. Some of these hypothetical model systems and their possible template synthesized interlocked products are shown in Fig. 35. Truly polymeric
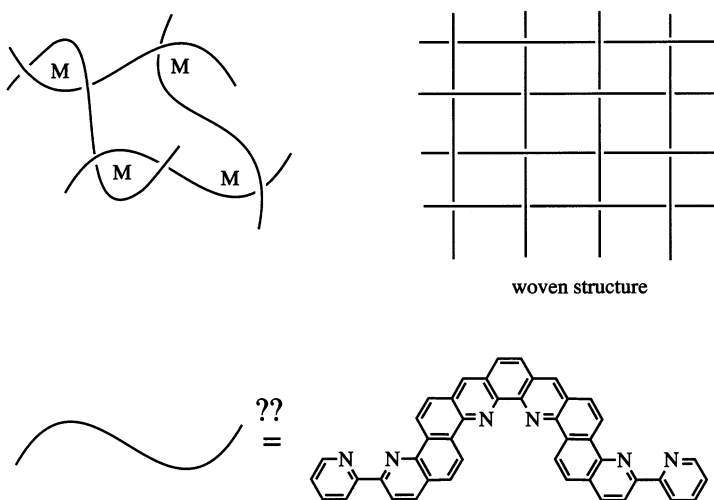

Fig. 34. The authors' concept of true molecular weaving and a potential weaving ligand.
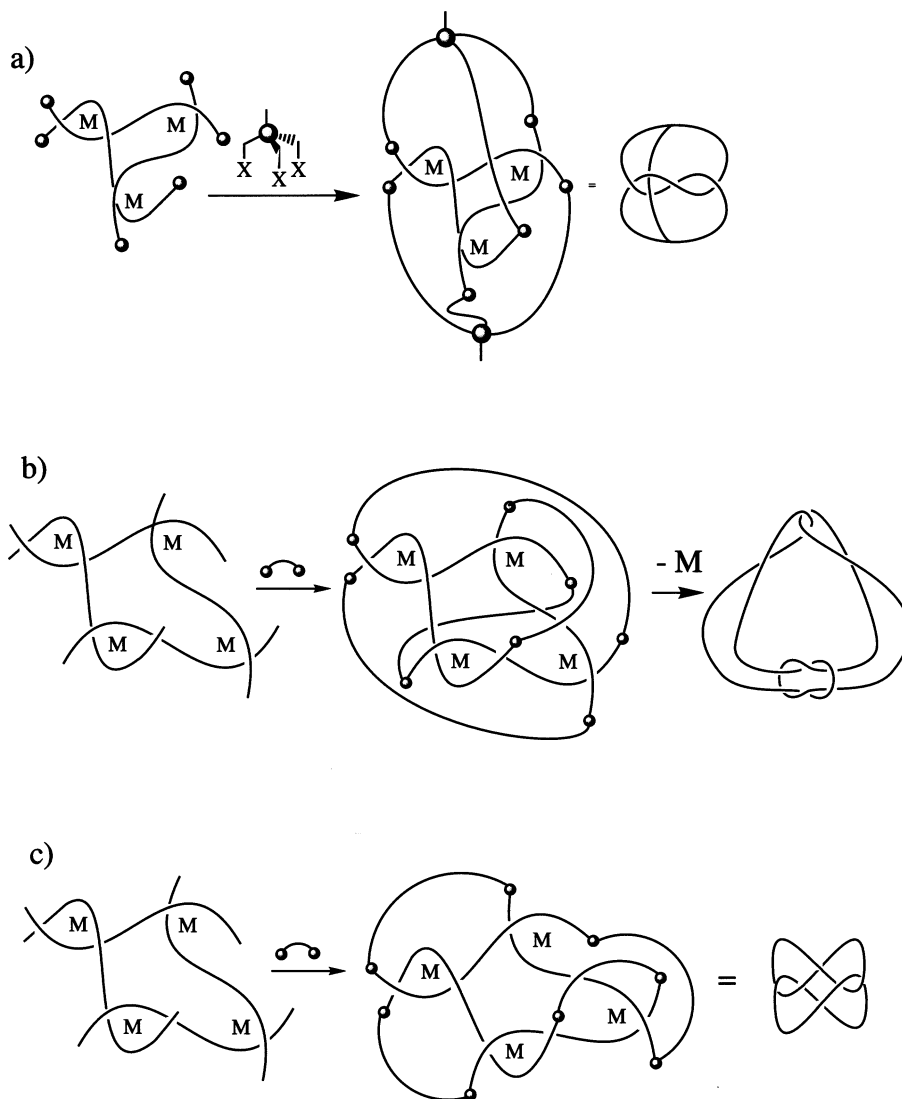
Fig. 35. The authors' vision of weaving model complexes (a) a molecular braid from a trinuclear weaving model complex (b) and (c) complicated links from possible tetranuclear weaving model complexes.

template-assembled products will be derived from 'intelligent' subunits and can be considered interlocked due to their 'infinite' size, as in unblocked polyrotaxanes. For the first low molecular weight prototypes, 'pseudointerlocked' is an appropriate descriptive term.

3.3. A final word

We have confined this discussion to the synthesis of mechanically interlocked molecules, where templates orient the reactants to produce permanent structures as the result of new linkages. Such template chemistry has produced an extensive array of often previously unknown molecular architectures and these are summarized in the line drawings of Fig. 4. While all of these may be described as orderly molecular entanglements, most can also be described as discreet molecules that constitute landmarks along the road to mechanically interlocked polymers, of one, two, and three dimensions; the goal itself remains barely touched. Through the appealing vision of new interlocked architectures that many of us perceive and the preparative routes that we can design, the advances in the realm are as evident as grain standing in a field. The harvest season is at hand.

This review discusses the synthesis of mechanically interlocked molecules where templates orient the reactants to produce permanent structures as the result of new linkages. An introduction outlines the concepts and opportunities of the field, paying special attention to the components of chemical templates. Next, the chemical template types most successfully applied to the synthesis of new interlocked molecular structures, metal ion templates, hydrogen bonded templates, cyclodextrin templates, and π-donor π-acceptor templates, are described. The progress each template type has made towards the goal of true polymeric interlocked structures is noted. The conclusion summarizes the current state of the field and points out new directions that appear ripe for future exploration.

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