

# Topologically complex molecules obtained by transition metal templation: it is the presentation that determines the synthesis strategy†

Jean-Claude Chambron<sup>\*a</sup> and Jean-Pierre Sauvage<sup>b</sup>

Cite this: *New J. Chem.*, 2013, **37**, 49

Received (in Montpellier, France)  
29th June 2012,  
Accepted 25th September 2012

DOI: 10.1039/c2nj40555e

[www.rsc.org/njc](http://www.rsc.org/njc)

Topological constructions made from closed curves range from simple links to intricate knots and started to capture the chemists' attention in the early sixties. These mathematical objects result from particular embeddings of a single or a set of closed curves in the three-dimensional space that show an infinite variety of presentations. Simple catenanes, higher order interlocked macrocycles, and molecular knots can be synthesized *via* the metal template approach, just as simple macrocycles. However, this requires that rigid presentations with appropriate geometrical characteristics be identified prior to molecular design, and those selected for the metal-templated synthesis of some of these fascinating molecules are reviewed here.

<sup>a</sup> ICMUB (UMR CNRS No. 6302), Université de Bourgogne, 9 Avenue Alain Savary, BP 47870, 21000 Dijon, France. E-mail: [jean-claude.chambron@u-bourgogne.fr](mailto:jean-claude.chambron@u-bourgogne.fr); Fax: +33 (0)3 80 39 61 17; Tel: +33 (0)3 80 39 61 16

<sup>b</sup> ISIS, Université de Strasbourg, 8 Allée Gaspard Monge, 67000 Strasbourg, France. E-mail: [jpsauvage@unistra.fr](mailto:jpsauvage@unistra.fr); Fax: +33 (0)3 68 85 51 40; Tel: +33 (0)3 68 85 51 43

† This article is included in the All Aboard 2013 themed issue.

## Introduction

Knotted and intertwined patterns have fascinated mankind and artists for centuries, because of the beauty and the symbolism they convey. Therefore it is not surprising if they can be found in the cultural production of virtually all civilizations across time and space.



**Jean-Claude Chambron**

*interactions and the self-assembly of chiral molecular capsules by dynamic covalent chemistry.*

*Jean-Claude Chambron has been a CNRS Research Director of the University of Burgundy at Dijon since 2001. He received his PhD from the University of Strasbourg with Prof. Jean-Pierre Sauvage and worked in his group as a CNRS Research Associate on topological chirality and porphyrin-incorporating catenanes and rotaxanes. His current research interests concern the induction of chirality by non-covalent*



**Jean-Pierre Sauvage**

*combining porphyrins and ruthenium or iridium complexes. He was awarded the Izatt-Christensen Award in Macrocyclic Chemistry in 1991, the Prelog Gold Medal, ETH-Zürich (Switzerland) in 1994, the RB Woodward Award in Porphyrin Chemistry in 2008 and the Japan Coordination Chemistry Award in 2009 as well as numerous Named Lectureships.*

*Jean-Pierre Sauvage is presently a Professor Emeritus and a CNRS Research Director Emeritus of the University of Strasbourg as well as a Distinguished Visiting Scholar at Northwestern University. With his group, he has contributed to the fields of molecular topology (knots and catenanes), rotaxanes and molecular machines. He is also interested in artificial photosynthesis and multicomponent systems*

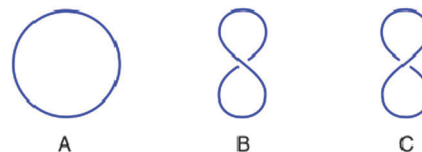
In fact, knotting and intertwining are very common but non-trivial manual acts in nautical and weaving techniques. The latter could be even rendered mechanical by the use of looms as early as in the 18th century. Although the first molecules made with two intertwined macrocycles were designed and synthesized in the sixties,<sup>1</sup> that is, more than 50 years ago, the fabrication of topologically complex molecules still remains a challenging task. As a matter of fact, so far only the simplest non-trivial knot (the trefoil knot)<sup>2–5</sup> has been the subject of extensive investigations, not to mention the recent report of the covalent capture of the pentafoil knot.<sup>6</sup>

Several synthetic strategies<sup>‡</sup> have been imagined and developed for making interlocked and knotted molecules, which all rely on template effects.<sup>7</sup> The latter can be classified either as kinetic or as thermodynamic. Kinetic template effects operate in the course of a reaction when molecular precursor fragments take up well defined geometrical and/or topological arrangements (preorganisation), which foreshadow the geometry and/or the topology of the target molecule. By contrast, a thermodynamically templated reaction involves a mixture of species in equilibrium, the latter being displaced towards the formation of the most stable product. Strictly speaking, a template is an auxiliary chemical species (atom, ion, or molecule) that is engaged in bonding interactions with the precursors (kinetic template) or the final product (thermodynamic template), and that can be removed once the reaction is complete. However, the operation of an external species may not be required, the interactions take place directly between the precursors or within the product. Templating interactions include covalent and coordination bonds, hydrogen bonding,  $\pi$ - $\pi$  donor-acceptor and van der Waals interactions, and solvophobic effects, which influence reaction enthalpies and entropies to various extents. The concept of transition metal templating, which relies on coordination bonds, was initially developed for making simple macrocycles.<sup>7</sup> It turned out to lend itself wonderfully for the rational synthesis of topologically complex molecules, as advantage was taken not only from stereoelectronic but also from chemical properties of transition metal cations.<sup>8</sup> In this “Perspective” article we shall show that the implementation of metal-templating in the synthesis of these exotic molecular systems results from the interplay between topology and geometry. We hope that this observation will help researchers interested in this topic to carry out the synthesis of more and more complex knotted and intertwined chemical structures.

## Molecular topology

As three-dimensional objects at the nanometric scale, molecules are characterized by topological and geometrical properties.<sup>1b,9</sup> Whereas the latter are well mastered by the chemist, as they are at the heart of stereochemistry, the former are usually limited to atom connectivity, as it is the source of constitutional isomerism. This topological property is sometimes qualified as “intrinsic”,

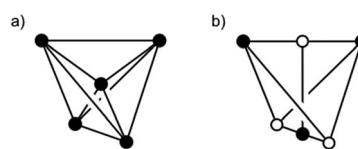
<sup>‡</sup> The earliest claimed catenane formation was based on statistical threading. See: E. Wasserman, *J. Am. Chem. Soc.* 1982, **82**, 4433.



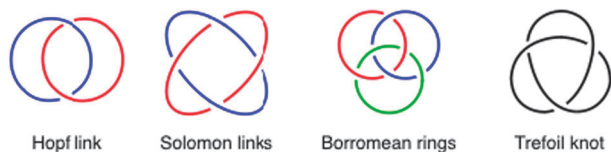
**Fig. 1** Different presentations of the embedding of the circular graph in the three-dimensional space. Note that **B** and **C** are chiral and are enantiomorphs.

since it is fully described by the molecular graph. However, as well as its geometry, the topology of a molecule may stem from embedding of its molecular graph in the three-dimensional space, in which case it is qualified as “extrinsic”. For example, whereas the topology of a macrocycle is a property of the corresponding circular molecular graph, the topology of two interlocking rings is described by their mutual embedding in the three dimensional space. The geometrical properties of molecules are characterized by distances between atoms and angles between bonds. However, contrary to solid objects at the human scale, most of the molecules display a number of differing geometries, the so-called conformations. Interchange between conformations is possible insofar as variations of bond angles and interatomic distances are physically possible. Importantly, contrary to geometry, the topology of a molecule remains unchanged whatever the deformations it undergoes, so long as they are continuous, even if they are impossible physically. The infinite variety of rigid figures formed by the embedded graphs are called “presentations”.<sup>9</sup> They are drawn either with 3-D effect or as a selected projection on the plane. For the trained eye the latter can be regarded as conveying as much information as the former. Minimal presentations are those that barely express the extrinsic topology. Whereas all the presentations of a given molecular object are topologically equivalent, those displaying particular shapes and symmetries, that is, remarkable geometrical characteristics, must be recognized and identified by the chemist interested in synthetic molecular topology, as the knowledge of these very presentations is necessary for the design and implementation of synthetic strategies. As an illustration Fig. 1 shows two remarkable presentations of the circular graph (the one of macrocyclic molecules): the circle of  $C_\infty$  symmetry (**A**) and the “figure of eight” of  $D_2$  symmetry (**B** and **C**). Indeed, there exist macrocyclic molecules, the conformations of which are close to these symmetrical presentations.<sup>10</sup>

A molecule can be considered as topologically complex when none of the projections in the plane of all possible presentations of its embedded graph can be drawn without at least a crossing point. Particular in this respect is the case of molecules, the graph of which cannot be drawn in the plane without crossing points. Such graphs are qualified as intrinsically non-planar, and the minimally non-planar graphs, that is, those displaying only



**Fig. 2** Presentations of remarkable embeddings of the Kuratowski's non-planar graphs (a)  $K_5$  and (b)  $K_{3,3}$  in the three-dimensional space.



**Fig. 3** The four minimal presentations of a Hopf link and the Solomon links, the Borromean rings, and the trefoil knot. Note that the Solomon links and the trefoil knot are chiral. Only one enantiomer is represented here.

one crossing point are Kuratowski's graphs  $K_5$ , the complete graph built on five vertices, and  $K_{3,3}$ , the complete bipartite graph on six vertices, three of which connect to each of the other three. Rigid presentations of embeddings of these graphs in the three-dimensional space that have been used for the design of molecules with intrinsically non-planar graphs are given in Fig. 2. Noteworthy, molecular representatives of either  $K_5$  or  $K_{3,3}$  non-planar graphs have been synthesized in the past.<sup>11,12</sup>

In the following discussion, we shall consider only molecules that are topologically complex according to the most general criterion, that is, molecules with intrinsically non-planar graphs will be ignored here. The simplest topologically complex molecules belong to either the family of links, which result from interlocking of rings, or the family of knots, which result from tying a string and linking its two ends. Common and minimal presentations of the prototypical members of these families of molecules are represented in Fig. 3.

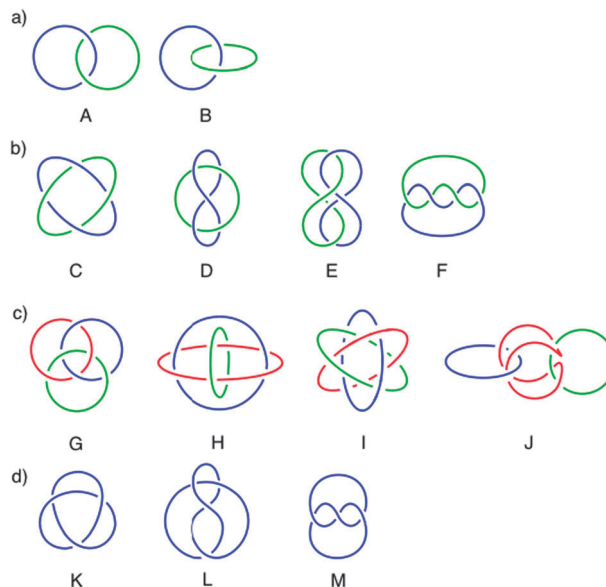
In the family of links, [2]catenanes (topological figure: Hopf links) are made from two interlocked rings, doubly-interlocked [2]catenanes (topological figure: Solomon links) show four crossings, and the Borromean rings are made of three interdependent rings, yet any two of them are not interlocked. Strictly speaking, [2]rotaxanes made of a ring encircling a dumbbell-like fragment are not topologically complex since unthreading could easily be carried out mentally by shrinking the voluminous groups attached at the ends of the dumbbell – an operation which is of course impossible from an experimental viewpoint – however if the stoppers are large enough to prevent ring unthreading under any physically-accessible conditions (which comes down to having an infinitely long string component), the corresponding molecules behave as [2]catenanes. Therefore [2]rotaxanes can be treated as [2]catenanes, and the link making the two components interdependent is qualified as mechanical.<sup>13</sup>

It is the family of knots that contains the most topologically complex figures, the trefoil knot (denoted  $3_1$ ) being the first of the series of prime knots. Therefore, it is not at all surprising that most of the research in this field has focussed on devising methods for making molecules displaying this topology.<sup>2–5</sup>

All these figures are realized chemically using macrocyclic organic components, or, in a few instances metallo-organic macrocycles that incorporate a metal in their atom sequence.

## Topological equivalence

Presentations of the same object are equivalent, that is, they can be converted into each other by continuous deformation. Remarkable presentations of the topological constructions



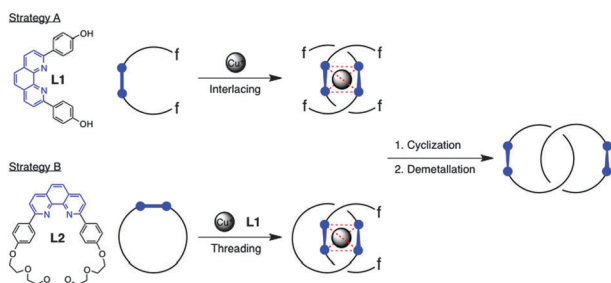
**Fig. 4** Presentations of remarkable embeddings in the three-dimensional space of selected links and knots. (a) Hopf links, (b) Solomon links, (c) Borromean rings, (d) Trefoil knot.

discussed here are presented in Fig. 4, the minimal presentations are shown first (**A**, **C**, **G**, and **K** correspond to those shown in Fig. 3). Hopf links (Fig. 4a) display a remarkable rigid presentation, the  $D_{2d}$ -symmetric one (**B**), in which the planes of the two interlocking rings are orthogonal, and which was used for the transition metal-templated synthesis of [2]catenanes. The minimal presentation can also be viewed as a general chiral  $D_2$  (**A**) presentation, in which the angle between the planes of the rings is  $>0^\circ$  and  $<90^\circ$ . In the case of the chiral “Solomon links”, all four presentations **C**, **D**, **E**, and **F** have been effectively used for the synthesis of doubly-interlocked [2]catenanes. They are drawn in Fig. 4b. The minimal presentation **C**, which corresponds to the classical drawing of the Solomon links, can also be viewed as that of a  $D_4$ -symmetric presentation. The  $D_2$ -symmetric presentation **D** features a “relaxed” ring that is interlocked with a figure-eight twisted ring, while twisting of both rings produces the  $D_2$ -symmetric presentation **E**. Finally, the  $D_2$ -symmetric presentation **F** is based on a central double helical structure. The “Borromean rings” (from the coat of arms of the Borromeo family) also feature a remarkable topological assembly of rings. They are constructed from three rings that are not interlocked with each other, yet any ring makes the other two interdependent. Selected drawings of geometrically well-defined presentations are reproduced in Fig. 4c. The minimal presentation (**G**) derives from the classical view of the Borromean rings. Its  $D_3$ -symmetric embedding in 3D space requires that none of the rings be planar. **H** is a drawing of the achiral  $D_{2h}$  ring-in-ring presentation constructed from three elliptic rings, which can be deformed to a  $S_6$ -symmetric presentation (**I**). Finally, the achiral  $C_{2v}$  presentation (**J**) is made of two orthogonal rings that are threaded each along a boat-shaped ring (in the stereochemical sense). Whereas all three rings in the former presentations are

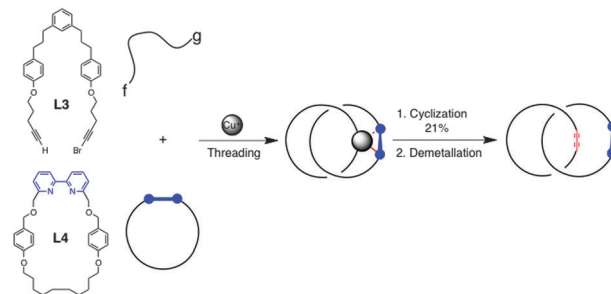
equivalent to each other, this is not the case for the latter one that differentiates the outer rings from the central one. Unlike Hopf links, Solomon and Borromean rings that use two or more closed lines (*i.e.*, circuits), knots are topological constructions made of a single closed line. The simplest one is the trefoil knot, which owes its name to the  $D_3$ -symmetric presentation (**K**) shown in Fig. 4d. In the variant **L** of  $C_2$  symmetry the upper lobe of **K** has been given a clockwise twist so that the corresponding diagram has four crossings. This presentation has been notably used for the active metal template synthesis of the trefoil knot.<sup>5</sup> Another remarkable presentation of the trefoil knot is the  $D_2$ -symmetric one (**M** in Fig. 4d), which is based on a central double helical structure that shows three crossing points, whereas that of the Solomon rings has four crossings. Besides, presentations **K** and **M** were used for the standard transition metal-templated synthesis of knots.<sup>2,4</sup>

## [2]Catenanes

[2]Catenanes were the very first chemical realizations of the Hopf links that used transition metal templation.<sup>14</sup> The original idea was to place two horseshoe-shaped bidentate ligands (**L1**) around a metal with tetrahedral coordination demands ( $\text{Cu}(\text{I})$ ), the extremities of one ligand extending beyond the chelate part of the other ligand, in order to generate the two required crossings (Fig. 5). Each curved ligand was subsequently locked into a ring structure by macrocyclization (Strategy A). A variation of this strategy consisted of using a preformed macrocycle (**L2**) that incorporated one of the two chelates, the metal driving the threading of the functionalized ligand **L1** through the macrocycle (Strategy B). Greater than 90% yields were observed upon cyclization *via* intramolecular alkene metathesis.<sup>14b</sup> The transition-metal templated approach to the [2]catenanes was not limited to tetrahedral metal templates. Other coordination geometries involving the appropriate ligands and metals were used: linear (two monodentate and  $\text{Au}(\text{I})$ ),<sup>15</sup> square planar (one monodentate and one terdentate and  $\text{Pd}(\text{II})$ ),<sup>16</sup> square pyramidal (one bidentate and one terdentate and  $\text{Zn}(\text{II})$ ),<sup>17</sup> and octahedral (two terdentate and  $\text{M}(\text{II})$ ,  $\text{M} = \text{Mn, Fe, Co, Ni, Cu, Zn, Cd, Hg}$ , and



**Fig. 5** Synthesis of a [2]catenane from linear (**L1**) and cyclic (**L2**) precursors incorporating bidentate chelates for complexation of a tetrahedral metal cation template. The disk-ended bold blue lines represent 1,10-phenanthroline chelates and their N-donor atoms. The grey sphere is the  $\text{Cu}^+$  cation and *f* is a function that reacts either inter- or intramolecularly. The metal coordination geometry is enhanced by dotted red lines, as well as in the subsequent figures.



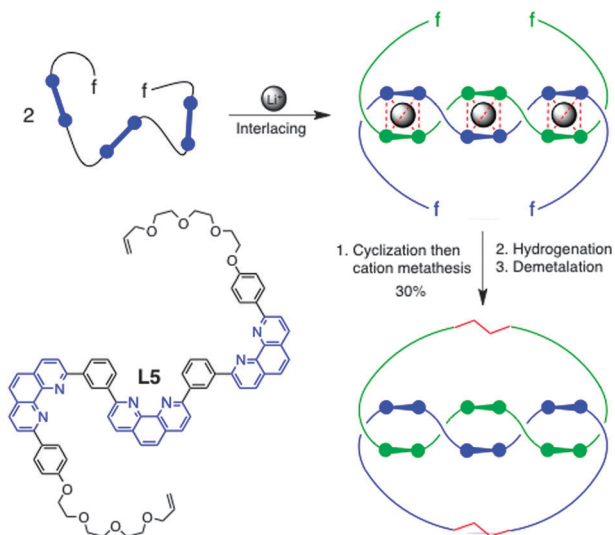
**Fig. 6** Synthesis of a [2]catenane *via* "active metal template" strategy from linear (**L3**) and cyclic (**L4**) precursors. The disk-ended blue bold lines represent a chelate and its donor atoms, and the grey sphere is  $\text{Cu}^+$ . The functions *f* (terminal alkyne) and *g* (bromoalkyne) react at the metal to form the new C–C bond sequence shown in red.

$\text{Ru}$ ;<sup>18</sup> or one bis-bidentate and one bidentate and  $\text{Ru}(\text{II})$ ).<sup>19</sup> As in classical templation, the role of the metal cation is to arrange the ligands in such a way that the geometry of the desired presentation is readily attainable using standard cyclization reactions. In the last decade however, Leigh and co-workers as well as others introduced the so-called "active-metal template" technique, in which the template in the geometrical sense is also involved in the cyclization reaction, either stoichiometrically or catalytically (Fig. 6).<sup>20</sup> This very elegant route follows strategy B in Fig. 5 with the difference that only the macrocycle incorporates the chelate for metal capture. The reactive functions *f* and *g* of the species to be threaded are involved both in the metal complexation and in the metal-directed cyclization reaction, the latter taking place inside the preformed macrocycle. Fig. 6 illustrates the case in which the catalyzed reaction is the intramolecular copper-mediated Cadiot–Chodkiewicz coupling of a bromoalkyne with a terminal alkyne forming a C–C bond. The catenane was obtained in 21% yield. Yields as high as 53% could be reached when the cyclization reaction was the  $\text{Cu}(\text{I})$  catalyzed azide-alkyne Huisgen cycloaddition.<sup>20a</sup>

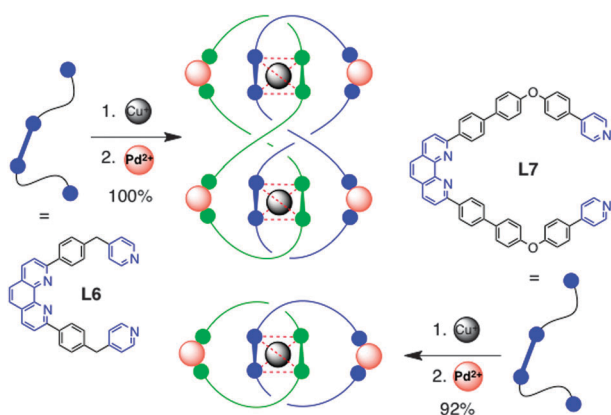
## Solomon rings

The doubly interlocked [2]catenanes were at first rationally synthesized by Dietrich-Buchecker *et al.*,<sup>21</sup> by homologation of the double helix route to the trefoil knot that these authors had developed earlier (see section Molecular knots). Accordingly, a one and a half turn double helix was formed by mixing two equiv. of tris-phenanthroline ligand **L5** with three equiv. of  $\text{Li}^+$ . The resulting trinuclear double helix was closed on both sides by RCM, purified after exchange of  $\text{Cu}^+$  for  $\text{Li}^+$ , and the resulting bis-copper(I) complex was isolated in 30% yield. The template-free doubly-interlocked [2]catenane was obtained quantitatively after catalytic hydrogenation followed by demetallation with cyanide (Fig. 7).

Interestingly, other reported examples of Solomon rings were obtained by *serendipity*. All proceeded under thermodynamic equilibrium conditions, using reversible, either covalent or metal–ligand bonds. For example mixing dpp-based chelates carrying pyridyl end groups **L6** with  $\text{Cu}^+$  and  $\text{Pd}(\text{en})(\text{ONO}_2)_2$



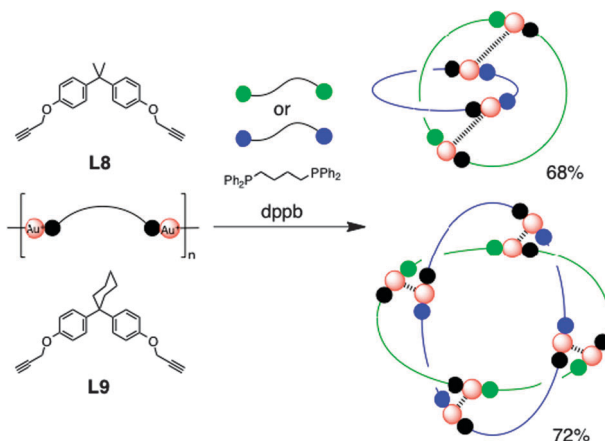
**Fig. 7** Rational synthesis of a doubly-interlocked [2]catenane. The disk-ended coloured bold lines represent 1,10-phenanthroline chelates and their N-donor atoms, the grey sphere is the  $\text{Li}^+$  cation, and f represents reactive functions, in that case the terminal olefin fragments of trisphenanthroline **L5**.



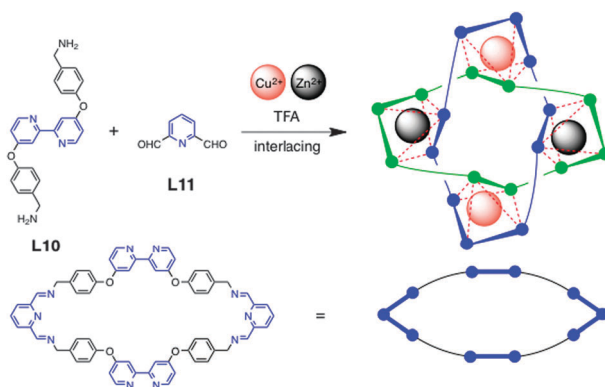
**Fig. 8** Formation of a doubly interlocked [2]catenane by simultaneous  $\text{Cu}(\text{i})$  templation and capture by  $\text{Pd}(\text{II})$  metal complex fragment. The disk-ended coloured bold lines represent 1,10-phenanthroline chelates and their N-donor atoms, the isolated disks pyridyl ligands, the grey sphere is the  $\text{Cu}^+$  cation, and the brown sphere  $\text{Pd}^{2+} = [\text{Pd}(\text{en})]^{2+}$  metal complex fragment.

afforded quantitatively doubly-interlocked [2]catenane  $[\text{Cu}_2\text{L6}_4\text{Pd}_4(\text{en})_4]^{10+}$  rather than the anticipated [2]catenane  $[\text{CuL6}_2\text{Pd}_2(\text{en})_2]^{5+}$  that would have resulted from capture of two pyridyl ligands of the same dpp chelate by  $[\text{Pd}(\text{en})]^{2+}$  complex subunits (Fig. 8).<sup>22</sup> Such a transition metal-locked [2]catenane was indeed obtained in 92% isolated yield by using extended 4-pyridyl-substituted dpp ligands, such as **L7**, in which the pyridyl end groups of the *same* dpp can effectively clamp  $\text{Pd}^{2+}$  cations.<sup>23</sup> Remarkably, the structure of this doubly interlocked [2]catenane corresponds to presentation E (Fig. 4b) of the Solomon rings.

Similarly, Puddephatt and co-workers had shown that breaking the organometallic polymer based on  $\text{Au}(\text{i})$  complexation of a bis-propargyl derivative of bisphenol A (**L8**) with  $\text{Ph}_2\text{P}(\text{CH}_2)_4\text{PPh}_2$  (dppb) led to a [2]catenane made of organometallic  $[(\text{L8-2H})\text{Au}_2(\text{dppb})]$



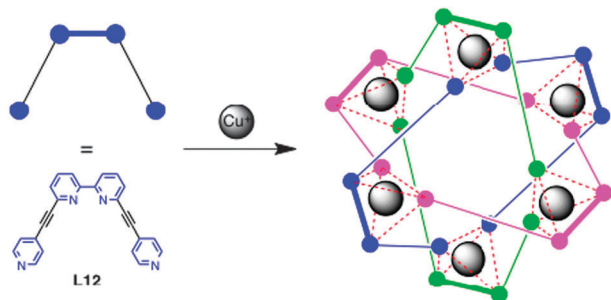
**Fig. 9** Formation of a doubly-interlocked [2]catenane (one enantiomer shown) against a [2]catenane using auriphilic inter-metallomacrocyclic interactions. The brown spheres are  $\text{Au}^+$  cations, the black and coloured disks represent carbyne and phosphorus binding atoms, respectively. For a given diphosphine the outcome of the reaction depends on the chemical nature of the bridge connecting the carbyne ligands (**L8** vs. **L9**).



**Fig. 10** Self-assembly of a doubly-interlocked [2]catenane (one enantiomer shown) by mixed  $\text{Cu}^{2+}$ - $\text{Zn}^{2+}$  metal templation. The coloured bold lines represent a 2,6-pyridine diimine tridentate chelate and a 2,2'-bipyridine bidentate chelate, with the coordinating N atoms represented as disks. The brown and grey spheres represent  $\text{Cu}^{2+}$  and  $\text{Zn}^{2+}$  cations, respectively. A sixth binding site (not represented) is occupied by a trifluoroacetate anion, which makes the coordination spheres of the metal cations actually octahedral.

macrocyclic subunits held together by auriphilic interactions in 68% yield (Fig. 9).<sup>24</sup> Quite interestingly, just changing the two methyl groups of the bisphenol A subunit by a cyclohexyl substituent (in **L9**) switched the equilibrium to the formation of the organometallic doubly interlocked [2]catenane  $[(\text{L9-2H})_2\text{Au}_4(\text{dppb})_4]$  in 72% yield. Note that this latter system corresponds to the classical presentation (A) of the Solomon rings.<sup>25</sup> It is worth mentioning that shorter diphosphines led to organometallic macrocycles.

Finally, Stoddart and co-workers reported the formation in the solid state of a doubly-interlocked [2]catenane resulting from mixed  $\text{Cu}(\text{II})$ - $\text{Zn}(\text{II})$  Schiff-base condensation of diamine **L10** incorporating the 2,2'-bipyridyl chelate, and 2,6-pyridine dialdehyde **L11** (Fig. 10).<sup>26</sup> These Solomon rings are constructed from two macrocycles incorporating alternating *exo* bipyridyl and *endo* pyridyl diimine chelates, respectively, so that



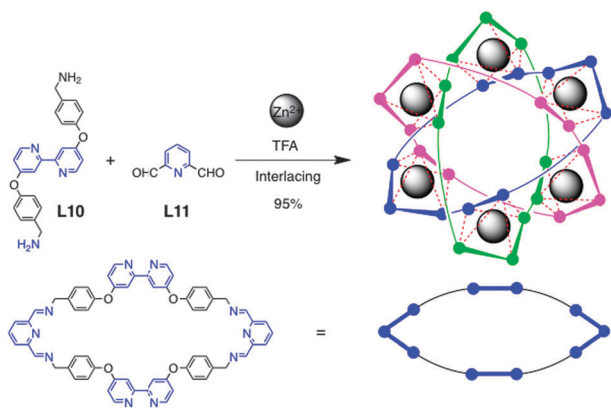
**Fig. 11**  $\text{Cu}^+$ -templated formation of the metallo-organic Borromean rings structure constructed from ligand **L12**. The grey sphere is the  $\text{Cu}^+$  cation, the disk-ended coloured bold lines represent the 2,2'-bipyridyl chelate and the isolated disks stand for the nitrogen atoms of the pyridyl end-groups of **L12**.

each metal template cation has an octahedral coordination sphere made from a bidentate, a terdentate, and a monodentate triflate ligand. Therefore they also correspond to presentation **A** of the Solomon rings. The doubly interlocked catenane is one of the unexpected possible reaction products that is in equilibrium, in particular, with the corresponding Borromean rings.

We note that Solomon links derived from presentation **D** (Fig. 4b) have been reported by Quintela *et al.* However they will not be further discussed here as their formation relies also on donor-acceptor  $\pi$ - $\pi$  stacking interactions.<sup>27</sup>

## Borromean rings

The very first molecular compound displaying the topology of Borromean rings was obtained serendipitously by Schröder *et al.* in 2003, by mixing equimolar amounts of  $\text{Cu}(\text{I})$  and the “extended” 2,6-di(4-pyridyl)bipyridine chelate **L12**, and it was characterized in the solid state (Fig. 11).<sup>28</sup> The hexanuclear



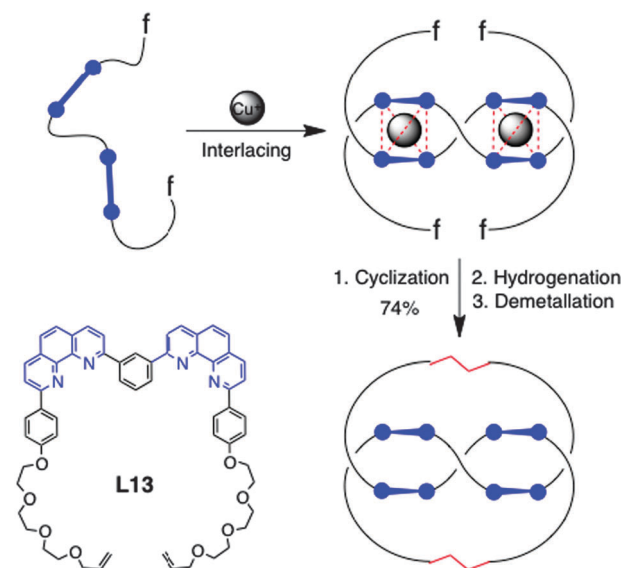
**Fig. 12**  $\text{Zn}^{2+}$ -templated Schiff-base condensation of 2,2'-bipyridine **L10** functionalized with primary amine end groups and pyridine-2,6-dicarboxaldehyde **L11** affords nearly quantitatively the hexanuclear Borromean rings structure. The grey sphere is the  $\text{Zn}^{2+}$  cation, the coloured bold lines represent a 2,6-pyridine diimine tridentate chelate and a 2,2'-bipyridine bidentate chelate, respectively, with the coordinating N marked as disks. A sixth binding site (not represented) is occupied by a trifluoroacetate anion, which makes the coordination spheres of the metal cations actually octahedral.

complex is composed of metallo-organic rings that leave a central cavity for anion encapsulation ( $\text{BF}_4^-$ ).

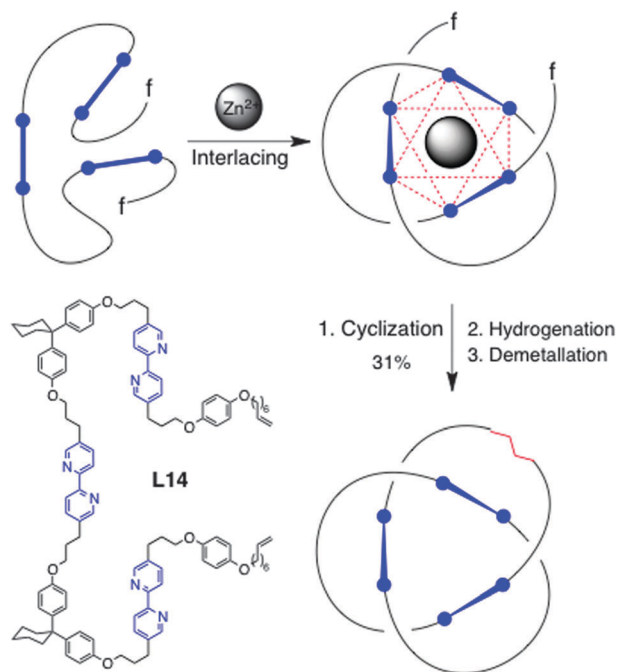
Various attempts using rational approaches for the synthesis of Borromean rings featuring fully organic rings were undertaken. They all relied either on the “ring-in-ring” presentation **H** or the “rack” presentation **J**.<sup>29</sup> In spite of these efforts however, only a one-pot metal template synthesis using Schiff-base condensation of **L10** and **L11**, but in the presence of  $\text{Zn}(\text{II})$ , afforded the spectacular hexanuclear “Borromean rings”  $\text{Zn}(\text{II})$  complex (Fig. 12) in 95% yield.<sup>30</sup> This was generalized to the synthesis of the so-called Borromean rings using divalent metals such as  $\text{Cu}(\text{II})$ ,  $\text{Ni}(\text{II})$ ,  $\text{Cd}(\text{II})$ ,  $\text{Mn}(\text{II})$ , and  $\text{Co}(\text{II})$ .<sup>30b</sup> This remarkable achievement constitutes another example of how variations (even quite subtle) in ligand structure or nature of the template metal cation can be inferred in the topological outcome of the reaction product. This is of course the case when the reactions are thermodynamically controlled. In the present case, the newly created bonds can be considered as “covalent dynamic” bonds.<sup>31</sup>

## Molecular knots

The very first synthesis of a molecular trefoil knot was achieved by Dietrich-Buchecker *et al.* in 1989,<sup>2a</sup> who homologated the metal template effect of  $\text{Cu}(\text{I})$  that had successfully led to the simpler catenanes.<sup>14</sup> The strategy employed is unique in that it was based on presentation **M** in Fig. 4d and relied on the successful formation of a double helical  $\text{Cu}(\text{I})$  dinuclear complex with bis-phenanthroline ligands in which the two chelates are connected by various bridges. The best yields (74%) were observed when a *meta*-phenylene connector was used (Fig. 13).<sup>2d</sup> The most efficient covalent sealing of the



**Fig. 13**  $\text{Cu}(\text{I})$ -templated synthesis of a trefoil knot based on the double helical presentation **M** in Fig. 4. The disk-ended blue bold lines represent 1,10-phenanthroline chelates and their N-donor atoms. The grey sphere is the  $\text{Cu}^+$  cation and **f** is the allyl function for cyclization by intramolecular metathesis reaction.

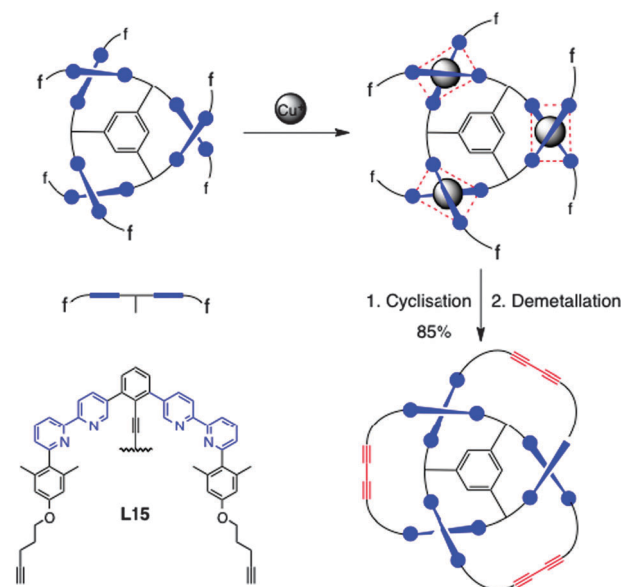


**Fig. 14**  $\text{Zn}^{2+}$  templated synthesis of a trefoil knot from tris-bipyridine ligand **L14** carrying allyl groups at its extremities. The disk-ended blue bold lines represent 2,2'-bipyridine chelates and their N-donor atoms. The grey sphere is the  $\text{Zn}^{2+}$  cation and f the allyl function for cyclization by intramolecular metathesis reaction.

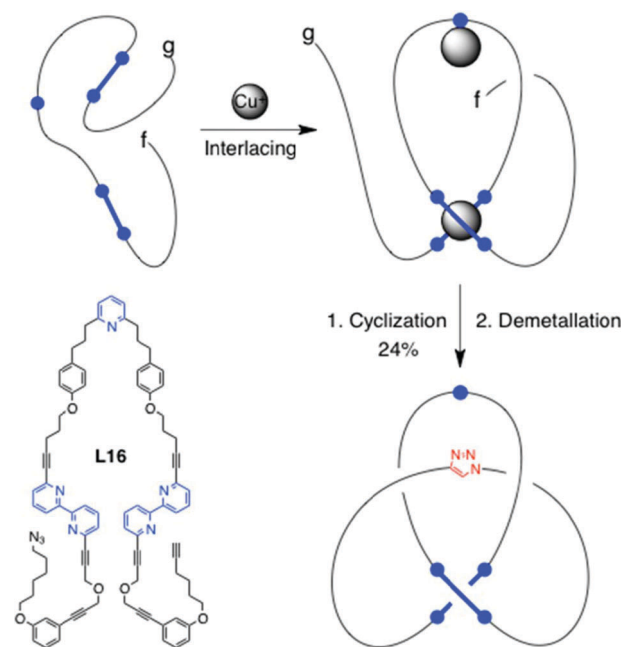
dangling arms used the Grubbs metathesis reaction, which had been also used for making  $\text{Cu}(\text{I})$  catenates in nearly quantitative yields (see Fig. 5).<sup>14b</sup> It should be noted that a double helical precursor based on a bis-terpyridyl analogue of **L13** and  $\text{Fe}(\text{II})$  as templating ion also led to a molecular knot.<sup>2d</sup> Catalytic hydrogenation of the olefinic double bonds, followed by demetallation with cyanide afforded the template-free trefoil knot.

The approach taken by Hunter and co-workers,<sup>4</sup> that is the one relying on presentation **K** in Fig. 4d and an octahedral metal template, had been actually devised in the 1970's by Sokolov in a seminal paper dealing with molecular topology.<sup>32</sup> It remained to those authors to design and synthesize the tris-bipyridyl ligand (**L14**) that would form the appropriate interlaced structure in the presence of  $\text{Zn}^{2+}$  cations (Fig. 14). Because of its demonstrated efficiency in numerous cyclization reactions, the Grubbs metathesis reaction was again employed as a means of covalent sealing of the intermediate open knot structure, and this afforded the knot in Fig. 14 in 31% yield. Up to 68% yield was obtained when allyl functions were used. Catalytic hydrogenation followed by demetallation with lithium sulfide afforded the template-free trefoil knot.

The so-called triskelion approach of Siegel and co-workers also uses the  $C_3$ -symmetric presentation **K** in Fig. 4d, however, instead of placing the template in the center of the topological figure in an octahedral environment, it creates pseudotetrahedral ones at its three crossing points.<sup>33</sup> Strictly speaking, this approach does not entirely rely on transition metal templating, the bipyridine chelates being held by a central benzene ring



**Fig. 15** The triskelion approach to the molecular trefoil knot. The disk-ended blue bold lines represent 2,2'-bipyridine chelates and their N-donor atoms. The grey sphere is the  $\text{Cu}^+$  cation and f the propargyl function for cyclization by intramolecular Glaser reaction.



**Fig. 16** Active metal templated synthesis of a molecular knot. The grey sphere is the  $\text{Cu}^+$  cation. The disk-ended blue bold lines represent the 2,2'-bipyridyl chelates and the isolated disk stand for the nitrogen atom of the pyridyl central fragment. The functions f and g stand for the azide and the terminal alkyne groups that are used in the  $\text{Cu}(\text{I})$ -catalyzed azide-alkyne Huisgen cycloaddition.

that plays the role of a permanent organic template. The three arms of the triskelion **L15** spontaneously take up a  $C_3$ -symmetric, helical arrangement because of steric hindrance. This produces the three required crossings, which are further fixed by  $\text{Cu}(\text{I})$  coordination (Fig. 15).

Triple cyclisation by Glaser coupling reaction of the dangling extremities produces the knotted structure in 85% yield.<sup>34</sup> The template metal could be removed by reaction with cyanide.

The most recent transition metal-templated route to a molecular trefoil knot uses the “active metal” template concept invented and developed by the group of Leigh for making rotaxanes and catenanes (see Fig. 6).<sup>20</sup> As in the approach of the group of Hunter the authors have developed a molecular thread (**L16**) incorporating binding sites (a pyridine and two bipyridines) in programmed positions, which in the presence of Cu(I) gives the knotted structure shown in Fig. 16 in 24% overall yield after removal of the metal template with EDTA.<sup>5</sup> Two metal templates are required: the first fixes a loop by defining a crossing point at the bipyridine chelates, the second, bound to the pyridine located inside the loop, reacts with the functionalized extremities of the molecular thread, which simultaneously defines the two other crossing points and covalently fixes the knotted structure. The cyclization reaction chosen was the azide-alkyne Huisgen cycloaddition, because it is catalyzed by the same metal cation (Cu<sup>+</sup>) as the one used as geometrical template.

## Perspectives

This overview has shown that all kinds of topologically complex molecules, from catenanes to knots, can be synthesized using transition metal templation, and has highlighted the importance that the topological concept of presentation has in the design of rational syntheses of catenanes and knots in particular. Identification of rigid presentations with well defined geometrical features, insertion of metal cation binding sites in these frameworks in such a way that they offer simple coordination geometries (such as tetrahedral or octahedral) either at crossing points or inside loops, and selection of cyclization reactions are the key steps in the programmed transition metal-templated synthesis of all kinds of catenanes and other interlocked ring structures, and knots.

Although it is not the purpose of this Perspective article to discuss and analyse the fascination that interlocking or knotted objects have exerted and continue to exert on molecular chemists, we would like to mention that the synthetic work done on such compounds has partly been motivated by their beauty, in relation to their topological properties and to their shape. The trefoil knot, for example, has been the object of many discussions for many decades before it was made at the molecular level. The synthetic challenge has also stimulated synthetic teams to tackle the problem. Before starting an actual preparation of these molecules, to design a convincing strategy was of utmost importance. As highlighted in this review article, the topological presentation of the object to be made was and still is determining and represents the best source of inspiration for conceptually elaborating a route to the target species. Looking back to the past, what has been realised in the course of the last decade or so was difficult to imagine twenty or twenty-five years ago. This success is to a large extent due to the power of the transition metal-based approaches proposed and implemented by the various research teams working in the field of topological chemistry. In twenty years virtually all conceivable

approaches to the molecular trefoil knot have been explored, and a first synthesis of the pentafoil knot has been recently proposed. However the Borromean rings resisted so far controlled, stepwise assembly and the borromeanes could not be obtained in metal-free form. In spite of these difficulties, there is no doubt that the synthesis of more complex knots and catenanes than those known today will be achieved within the next few years. Beyond these achievements, another point concerns the applications of interlocked and knotted molecules. Mechanical bonds have been used now for more than fifteen years for designing, fabricating and actuating molecular switches and motors, and the field of supramolecular polymers based on interlocked components is currently being developed spectacularly. By comparison, with very few exceptions properties associated with intentionally made knotted structures have yet to be identified or imagined, and much work remains to be done in this field.

## Notes and references

- (a) A. Lüttringhaus, F. Cramer, H. Prinzbach and F. M. Henglein, *Liebigs Ann.*, 1958, **613**, 185; (b) H. L. Frisch and E. Wasserman, *J. Am. Chem. Soc.*, 1961, **83**, 3789; (c) G. Schill and A. Lüttringhaus, *Angew. Chem., Int. Ed. Engl.*, 1964, **3**, 546; (d) N. van Gulick, *New J. Chem.*, 1993, **17**, 619, and other articles of this special issue of the *New Journal of Chemistry* dedicated to “Topology in Molecular Chemistry”.
- (a) C. O. Dietrich-Buchecker and J.-P. Sauvage, *Angew. Chem., Int. Ed. Engl.*, 1989, **28**, 189; (b) C. O. Dietrich-Buchecker, J.-P. Sauvage, J.-P. Kintzinger, P. Malt ese, C. Pascard and J. Guilhem, *New J. Chem.*, 1992, **16**, 931; (c) C. O. Dietrich-Buchecker, J.-F. Nierengarten, J.-P. Sauvage, N. Armaroli, V. Balzani and L. De Cola, *J. Am. Chem. Soc.*, 1993, **115**, 11237; (d) G. Rapenne, C. Dietrich-Buchecker and J.-P. Sauvage, *J. Am. Chem. Soc.*, 1999, **121**, 994; (e) C. Dietrich-Buchecker, G. Rapenne, J.-P. Sauvage, A. De Cian and J. Fischer, *Chem.-Eur. J.*, 1999, **5**, 1432.
- (a) O. Safarowsky, M. Nieger, R. Fr hlich and F. V gtle, *Angew. Chem., Int. Ed.*, 2000, **39**, 1616; (b) F. V gtle, A. H nten, E. Vogel, S. Buschbeck, O. Safarowsky, J. Recker, A.-H. Parham, M. Knott, W. M. M ller, U. M ller, Y. Okamoto, T. Kubota, W. Lindner, E. Francotte and S. Grimme, *Angew. Chem., Int. Ed.*, 2001, **40**, 2468; (c) M. Feigel, R. Ladberg, S. Engels, R. Herbst-Irmer and R. Fr hlich, *Angew. Chem., Int. Ed.*, 2006, **45**, 5698; (d) J. Br ggemann, S. Bitter, S. M ller, W. M. M ller, U. M ller, N. M. Maier, W. Lindner and F. V gtle, *Angew. Chem., Int. Ed.*, 2007, **46**, 254.
- (a) H. Adams, E. Ashworth, G. A. Breault, J. Guo, C. A. Hunter and P. C. Mayers, *Nature*, 2001, **411**, 763; (b) J. Guo, P. C. Mayers, G. A. Breault and C. A. Hunter, *Nat. Chem.*, 2010, **2**, 218.
- P. E. Barran, H. L. Cole, S. M. Goldup, D. A. Leigh, P. R. McGonigal, M. D. Symes, J. Wu and M. Zengerle, *Angew. Chem., Int. Ed.*, 2011, **50**, 12280.



- 6 J.-F. Ayme, J. E. Beves, D. A. Leigh, R. T. McBurney, K. Rissanen and D. Schultz, *Nat. Chem.*, 2012, **4**, 15.
- 7 (a) S. Anderson, H. L. Anderson and J. K. Sanders, *Acc. Chem. Res.*, 1993, **26**, 469; (b) D. H. Busch, A. L. Vance and A. G. Kolchinskii, in *"Comprehensive Supramolecular Chemistry"*, ed. J. L. Atwood, J. E. D. Davies, D. D. MacNicol and F. Vögtle, Elsevier Science Ltd, 1996, vol. 9, pp. 1–42.
- 8 (a) J.-C. Chambron, C. Dietrich-Buchecker and J.-P. Sauvage, in *"Comprehensive Supramolecular Chemistry"*, ed. J. L. Atwood, J. E. D. Davies, D. D. MacNicol and F. Vögtle, Elsevier Science Ltd, 1996, vol. 9, pp. 43–84; (b) J. E. Beves, B. A. Blight, C. J. Campbell, D. A. Leigh and R. T. McBurney, *Angew. Chem., Int. Ed.*, 2011, **50**, 9260.
- 9 D. M. Walba, *Tetrahedron*, 1985, **41**, 3161.
- 10 (a) J.-Y. Shin, H. Furuta, K. Yoza, S. Igarashi and A. Osuka, *J. Am. Chem. Soc.*, 2001, **123**, 7190; (b) S.-Y. Chang, M.-C. Um, H. Uh, H.-Y. Jang and K.-S. Jeong, *Chem. Commun.*, 2003, 2026; (c) E. Vogel, M. Michels, L. Zander, J. Lex, N. S. Tuzun and K. N. Houk, *Angew. Chem., Int. Ed.*, 2003, **42**, 2857; (d) J.-i. Setsune, A. Tsukajima, N. Okazaki, J. M. Lintuluoto and M. Lintuluoto, *Angew. Chem., Int. Ed.*, 2009, **48**, 771.
- 11 (a) H. E. Simmons, III and J. E. Maggio, *Tetrahedron Lett.*, 1981, **22**, 287; (b) L. A. Paquette and M. Vazeux, *Tetrahedron Lett.*, 1981, **22**, 291; (c) D. Kuck and A. Schuster, *Angew. Chem., Int. Ed. Engl.*, 1988, **27**, 1192.
- 12 (a) D. M. Walba, R. M. Richards and R. C. Haltiwanger, *J. Am. Chem. Soc.*, 1982, **104**, 3219; (b) C.-T. Chen, P. Gantzel, J. S. Siegel, K. K. Baldrige, R. B. English and D. M. Ho, *Angew. Chem., Int. Ed. Engl.*, 1995, **34**, 2657.
- 13 D. B. Amabilino, P. R. Ashton, C. L. Brown, E. Córdova, L. A. Godínez, T. T. Goodnow, A. E. Kaifer, S. P. Newton, M. Pietraszkiwicz, D. Philp, F. M. Raymo, A. S. Reder, M. T. Rutland, A. M. Z. Slawin, N. Spencer, J. F. Stoddart and D. J. Williams, *J. Am. Chem. Soc.*, 1995, **117**, 1271.
- 14 (a) C. O. Dietrich-Buchecker and J.-P. Sauvage, *Chem. Rev.*, 1987, **87**, 795; (b) B. Mohr, M. Weck, J.-P. Sauvage and R. H. Grubbs, *Angew. Chem., Int. Ed. Engl.*, 1997, **36**, 1308.
- 15 S. M. Goldup, D. A. Leigh, P. J. Lusby, R. T. McBurney and A. M. Z. Slawin, *Angew. Chem., Int. Ed.*, 2008, **47**, 6999.
- 16 (a) Y. Furusho, T. Matsuyama, T. Takata, T. Moriuchi and T. Hirao, *Tetrahedron Lett.*, 2004, **45**, 9593; (b) D. A. Leigh, P. J. Lusby, A. M. Z. Slawin and D. B. Walker, *Chem. Commun.*, 2005, 4919.
- 17 C. Hamann, J.-M. Kern and J.-P. Sauvage, *Inorg. Chem.*, 2003, **42**, 1877.
- 18 (a) D. A. Leigh, P. J. Lusby, S. J. Teat, A. J. Wilson and J. K. Y. Wong, *Angew. Chem., Int. Ed.*, 2001, **40**, 1538; (b) L. Hogg, D. A. Leigh, P. J. Lusby, A. Morelli, S. Parsons and J. K. Y. Wong, *Angew. Chem., Int. Ed.*, 2004, **43**, 1218; (c) J.-P. Sauvage and M. Ward, *Inorg. Chem.*, 1991, **30**, 3869.
- 19 (a) P. Mobian, J.-M. Kern and J.-P. Sauvage, *J. Am. Chem. Soc.*, 2003, **125**, 2016; (b) F. Arico, P. Mobian, J.-M. Kern and J.-P. Sauvage, *Org. Lett.*, 2003, **5**, 1887.
- 20 (a) S. M. Goldup, D. A. Leigh, T. Long, P. R. McGonigal, M. D. Symes and J. Wu, *J. Am. Chem. Soc.*, 2009, **131**, 15924; (b) Y. Sato, R. Yamasaki and S. Saito, *Angew. Chem., Int. Ed.*, 2009, **48**, 504.
- 21 (a) J.-F. Nierengarten, C. O. Dietrich-Buchecker and J.-P. Sauvage, *J. Am. Chem. Soc.*, 1994, **116**, 375; (b) C. Dietrich-Buchecker and J.-P. Sauvage, *Chem. Commun.*, 1999, 615.
- 22 F. Ibukuro, M. Fujita, K. Yamaguchi and J.-P. Sauvage, *J. Am. Chem. Soc.*, 1999, **121**, 11014.
- 23 (a) C. Dietrich-Buchecker, N. Geum, A. Hori, M. Fujita, S. Sakamoto, K. Yamaguchi and J.-P. Sauvage, *Chem. Commun.*, 2001, 1182; (b) C. Dietrich-Buchecker, B. Colasson, M. Fujita, A. Hori, N. Geum, S. Sakamoto, Y. Yamaguchi and J.-P. Sauvage, *J. Am. Chem. Soc.*, 2003, **125**, 5717.
- 24 (a) C. P. McArdle, M. J. Irwin, M. C. Jennings and R. J. Puddephatt, *Angew. Chem., Int. Ed.*, 1999, **38**, 3376; (b) C. P. McArdle, S. Van, M. C. Jennings and R. J. Puddephatt, *J. Am. Chem. Soc.*, 2002, **124**, 3959; (c) N. C. Habermehl, F. Mohr, D. J. Eisler, M. C. Jennings and R. J. Puddephatt, *Can. J. Chem.*, 2006, **84**, 111.
- 25 (a) C. P. McArdle, J. J. Vittal and R. J. Puddephatt, *Angew. Chem., Int. Ed.*, 2000, **39**, 3819; (b) C. P. McArdle, M. C. Jennings, J. J. Vittal and R. J. Puddephatt, *Chem.-Eur. J.*, 2001, **7**, 3572.
- 26 C. D. Pentecost, K. S. Chichak, A. J. Peters, G. W. V. Cave, S. J. Cantrill and J. F. Stoddart, *Angew. Chem., Int. Ed.*, 2007, **46**, 218.
- 27 C. Peinador, V. Blanco and J. M. Quintela, *J. Am. Chem. Soc.*, 2009, **131**, 920.
- 28 O. V. Dolomanov, A. J. Blake, N. R. Champness, M. Schröder and C. Wilson, *Chem. Commun.*, 2003, 682.
- 29 (a) M. Schmittel, A. Ganz and D. Fenske, *Org. Lett.*, 2002, **4**, 2289; (b) J. C. Loren, M. Yoshizawa, R. F. Haldimann, A. Linden and J. S. Siegel, *Angew. Chem., Int. Ed.*, 2003, **42**, 5702.
- 30 (a) K. S. Chichak, S. J. Cantrill, A. R. Pease, S. H. Chiu, G. W. V. Cave, J. L. Atwood and J. F. Stoddart, *Science*, 2004, **304**, 1308; (b) C. D. Meyer, R. S. Forgan, K. S. Chichak, A. J. Peters, N. Tangchaivang, G. W. V. Cave, S. I. Khan, S. J. Cantrill and J. F. Stoddart, *Chem.-Eur. J.*, 2010, **16**, 12570.
- 31 S. J. Rowan, S. J. Cantrill, G. R. L. Cousins, J. K. M. Sanders and J. F. Stoddart, *Angew. Chem., Int. Ed.*, 2002, **41**, 898.
- 32 V. I. Sokolov, *Russ. Chem. Rev.*, 1973, **42**, 452.
- 33 C. R. Woods, M. Benaglia, S. Toyota, K. Hardcastle and J. S. Siegel, *Angew. Chem., Int. Ed.*, 2001, **40**, 749.
- 34 K. I. Arias, E. Zysman-Colman, J. C. Loren, A. Linden and J. S. Siegel, *Chem. Commun.*, 2011, **47**, 9588.