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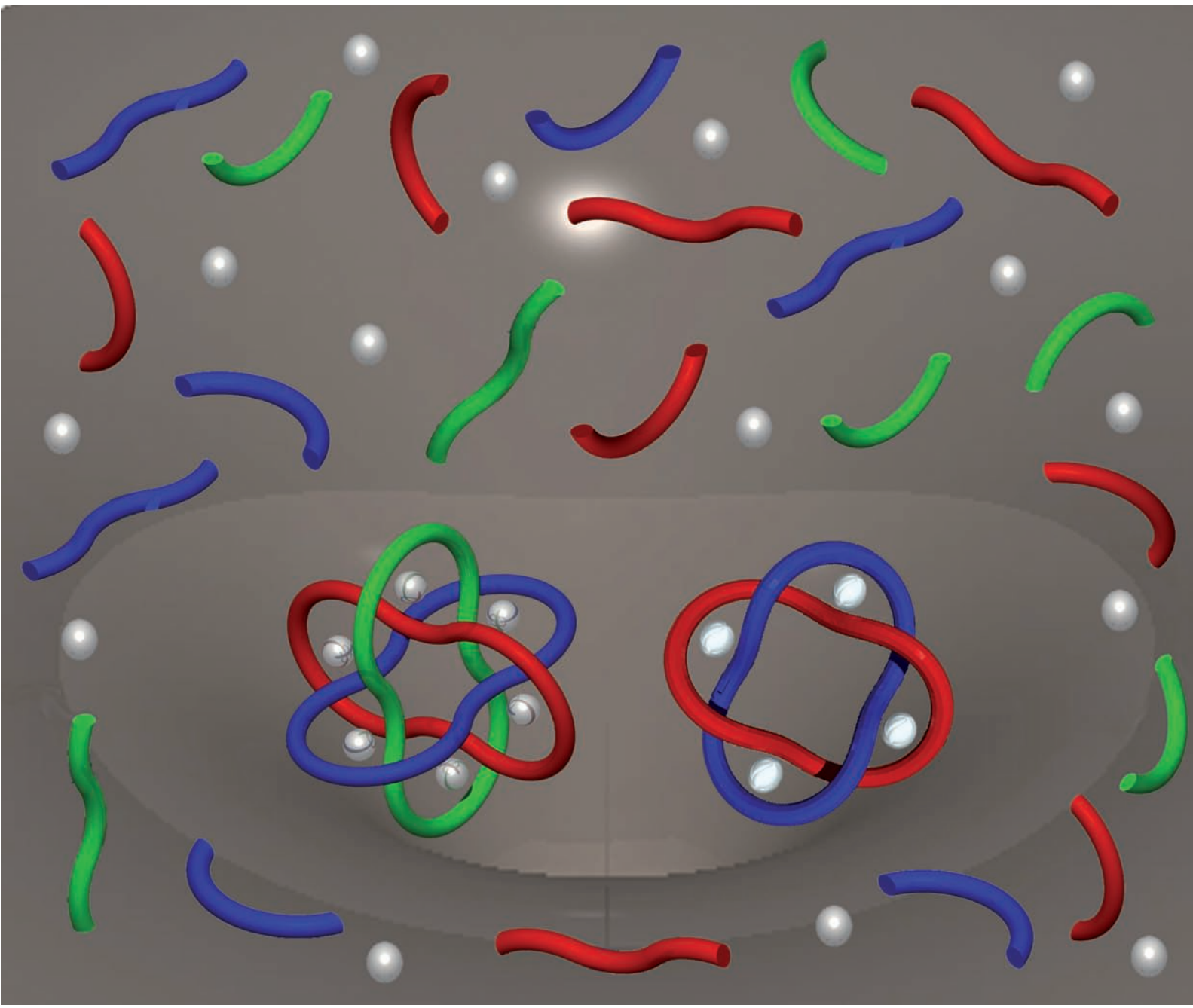

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Template-directed synthesis employing reversible imine bond formation

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The imine bond – formed by the reversible condensation of an amine and an aldehyde – and its applications as a dynamic covalent bond in the template-directed synthesis of molecular compounds, will be the focus of this *tutorial review*. Template-directed synthesis – or expressed another way, supramolecular assistance to covalent synthesis – relies on the use of reversible noncovalent bonding interactions between molecular building blocks in order to preorganise them into a certain relative geometry as a prelude to covalent bond formation to afford the thermodynamically preferred product. The use of this so-called dynamic covalent chemistry (DCC) in templated reactions allows for an additional amount of reversibility, further eliminating potential kinetic products by allowing the covalent bonds that are formed during the template-directed reaction to be 'proofread for errors', thus making it possible for the reaction to search out its thermodynamic minimum. The marriage of template-directed synthesis with DCC has allowed chemists to construct an increasingly complex collection of compounds from relatively simple precursors. This new paradigm in organic synthesis requires that each individual piece in the molecular self-assembly process is preprogrammed so that the multiple recognition events expressed between the pieces are optimised in a highly cooperative manner in the desired product. It offers an extremely simple way of making complex mechanically interlocked compounds – *e.g.*, catenanes, rotaxanes, suitanes, Borromean rings and Solomon knots – from relatively simple precursors.

1 Background

The reversible condensation between amino and carbonyl groups to form imine bonds is one of the most fundamental and ubiquitous reactions in chemistry. It is hardly surprising therefore that, Hugo Schiff (Fig. 1), the German chemist,[1] who discovered the reaction in 1864, has since been immortalised in the common name for compounds – they are now known routinely as "Schiff's bases" – containing imine bonds.

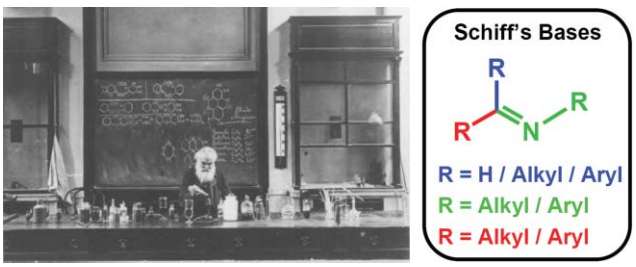

Fig. 1 Schiff and his bases.

The definition[2,3] of a Schiff's base – also known as an azomethine or anil, as well as an imine – which is designated constitutionally as $RR^1C{=}NR^2$, requires that R is an aryl

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group, R^1 is a hydrogen atom, or an alkyl or aryl group, and R^2 is either an alkyl or aryl group which contains[4] an alkyl- or aryl-substituted carbon atom at the point of attachment to the nitrogen atom. There are a handful of other functional groups that deviate slightly from this definition and hence display analogous reactivity and will be excluded from further discussion in this *tutorial review*: they include hydrazones ($R^2 = NR_2$) and oximes ($R^2 = OH$).

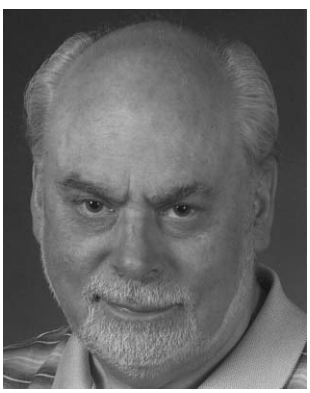
Imine bond formation is a simple reaction which involves loss of H_2O within a single molecule, or between two molecules containing amino and carbonyl groups, such that a C=N double bond is formed either intra- or inter-molecularly. Adding H_2O to an imine leads to hydrolysis and drives the condensation in the opposite direction, leading to the recovery of the starting material(s). The reaction (Fig. 2(a)), which is acid-catalysed, is executed typically by refluxing the starting material(s) under azeotropic conditions.

Many external considerations, including solvent, concentration, pH and temperature, as well as steric and electronic factors, can influence the equilibrium shown in Fig. 2(a). As such, there are many parameters that can be altered in order to drive the reaction forward – or indeed backwards. For a dynamic reaction, like imine bond formation, to proceed in the direction of products, *i.e.*, imines, the change in the free energy during the reaction must be favourable, *i.e.*, ΔG° in eqn (1) must be less than zero.

$$\Delta G^\circ = \Delta H^\circ - T\Delta S^\circ \quad (1)$$

Since imine bond formation occurs under equilibrium control, it is common to drive the reaction towards completion by removing H_2O as it is formed, either (1) by separating it physically in a Dean–Stark apparatus, or (2) by adding a drying agent that adsorbs H_2O from the reaction mixture. Conversely, the dynamic nature of imine bond formation can be exploited by adding H_2O, along with a catalytic amount of an acid to favour hydrolysis. In addition to hydrolysis, imines commonly participate in another two types of equilibrium-controlled reactions shown in Fig. 2. In summary, imines can participate in:

(a) *Hydrolysis* – The imine reverts back to the original compound(s) containing amino and carbonyl groups by addition of *water* (Fig. 2(a)).



J. Fraser Stoddart

Fraser Stoddart was born in Edinburgh, Scotland, in 1942. He received all (BSc, PhD and DSc) of his degrees from the University of Edinburgh, UK. Presently, he holds the Fred Kavli Chair in NanoSystems Sciences at the University of California, Los Angeles (UCLA). His research has opened up a new materials world of mechanically interlocked molecular compounds and, in so doing, has produced a blueprint for the subsequent growth of functional molecular nanotechnology.

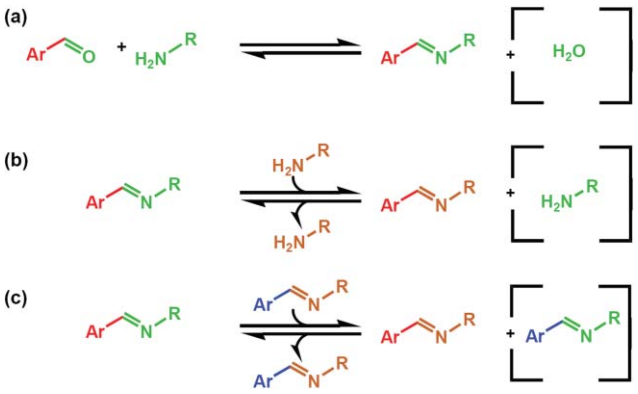


Fig. 2 The three fates involving imine reactants: (a) imine condensation, (b) exchange and (c) metathesis.

(b) *Exchange* – Upon introduction of a second *amine*, the original imine may undergo transimination where the R groups are exchanged (Fig. 2(b)).

(c) *Metathesis* – Upon introduction of a second *imine*, the two imines can undergo a reaction in which the two R groups are exchanged (Fig. 2(c)).

Once the desired imine is obtained, it can be 'fixed' by reducing the imine bond to a secondary amine function, thus trapping the product in a kinetic manner. While this strategy is a useful attribute of the imine bond, it is really the reversibility associated with an imine's formation that makes Schiff's discovery especially significant – particularly since relatively few covalent bonds are capable of being formed, broken and reformed under equilibrium control. If this equilibration process is relatively fast, then so-called dynamic covalent chemistry[5] (DCC) leads to the formation of the most thermally stable product in a relatively short period of time. Given that the relative stabilities of reactants and products dictate their proportions at equilibrium, we can control these proportions in at least two different ways: (1) we can *drive* the equilibrium in one direction or the other by adjusting the reaction conditions, *e.g.*, adding or removing reactants or products, or (2) we can *design* the starting materials to encourage the formation of a particular product, *e.g.*, by incorporating certain steric or electronic recognition features into the starting materials that favour the formation of the desired product.

Template-directed synthesis,[6–9] or the incorporation of molecular recognition motifs into starting materials with the intention of targeting one specific product, relies on other types of reversible noncovalent forces, such as hydrogen bonding, electrostatic interactions, metal coordination, donor–acceptor interactions, and π–π stacking interactions. Like DCC, supramolecular chemistry is equilibrium-controlled, and thus dynamically generates the most thermodynamically stable molecular assembly. Since both DCC and supramolecular chemistry each have a set of parameters that can be tuned according to the desired product, the chemist can play the part of an engineer in judiciously designing the construction of a molecular architecture by considering the structural features of both the template and building blocks of the superstructure, as well as the ideal combination of conditions that will most efficiently form the desired product. The triumphant marriage

of these two orthogonal approaches to dynamic chemistry has proven to be a most powerful combination, allowing for subcomponents to first self-assemble using noncovalent interactions, followed by reversible covalent bond formation, achieving elegant, mechanically interlocked structures that would be otherwise inconceivable using traditional, kinetically controlled synthetic methodology. This *tutorial review* will focus on the exploitation of the kinetically labile imine bond employed in the template-directed synthesis of compounds with sophisticated molecular architectures.

2 Metal-templated formation of imine macrocycles

Although a macrocycle is one of the simplest molecular structures, it is quite a challenge to synthesise selectively a macrocycle of a specific size. While many macrocyclic ring sizes are kinetically accessible, calling upon DCC can reduce this pool size down somewhat by selection of a thermodynamically accessible library.[10] In order, however, to construct exclusively just one macrocycle, a template is often required to amplify the desired product. Transition metal ions have proven to be suitable templates to organise imine-containing fragments and to do so with geometrical precision. The addition of a metal template to an imine condensation mixture allows the imine bonds to form around the template, thus stabilising the metal ion by surrounding it with nitrogen donor atoms, while simultaneously obtaining one chelated macrocycle, precisely proportioned according to both the metal's optimal coordination geometry, and the size and shape of the linkers between the newly formed imine functions. This 'template effect' was popularised in the mid-1960s by Busch,[11] who investigated the condensation of *o*-aminobenzaldehyde in the presence of nickel(II) or copper(II) metal ions to form (Fig. 3(a)) the closed macrocyclic, tetrameric condensates. As early as 1962, Curtis[12] had already described (Fig. 3(b)) the condensation of a pair of aliphatic amines with two aliphatic ketones in the presence of nickel and copper dications to give a macrocycle, a result which was confirmed by infrared (IR) spectroscopy and the subsequent identification of degradation products. Later on in the 1960s, macrocycles were produced (Fig. 3(c)) by Jäger[13] from two components, by allowing a tetradentate linear ligand, terminated with ketones, to wrap itself around copper(II) or nickel(II), followed by a ring-closing condensation upon the addition of 1,3-diaminopropane. During the 1970s, Fenton[14] showed that divalent metal cations are not the only templates capable of producing macrocycles. He templated the formation – and obtained the X-ray crystal structures – of a series of quinquedentate macrocyclic ligands (Fig. 3(d)) using lead(II) and even the alkaline earth metal dications, such as magnesium(II), calcium(II), strontium(II) and barium(II), as templates. This series of macrocycles made in the 1960s and 1970s can, in retrospect, be viewed as landmarks in template-directed synthesis. The highly effective formation of simple macrocycles from judiciously designed building blocks was to act as a spur to chemists to synthesise even more exotic compounds, some with rather unique topologies.

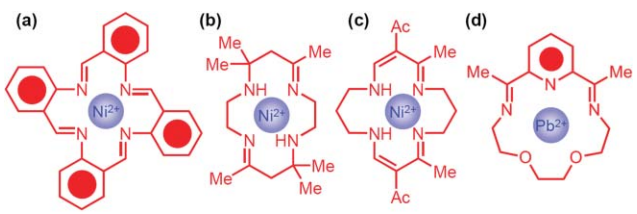


Fig. 3 Some early examples of metal-templated imine-containing macrocyles, including (a) Busch's macrocylic tetrameric condensate, (b) the Curtis macrocycle, (c) a diaminopropane-derived macrocycle, (d) a lead-templated macrocycle.

3 Metal-templated formation of imine helicates

Altering the shape and size of the linkers between the imine bond chelation sites could conceivably lead to an infinite number of different topologies. The Curtis macrocycle (Fig. 3(b)), for example, is derived from six small organic building blocks with concave shapes that adapt to form a closed loop when ordered around a metal. However, by using the considerably longer isobutylene linker between a diamino building block, a twisted macrocyle (Fig. 4(a)) was formed.[15] Mixing a bisbenzaldehyde, linked by an isobutylene chain, with a bisaniline component, linked by a diethylene glycol chain, dinuclear nickel(II) and copper(II) complexes were formed selectively in the shape of a closed-loop double helix, as confirmed by X-ray crystallography.

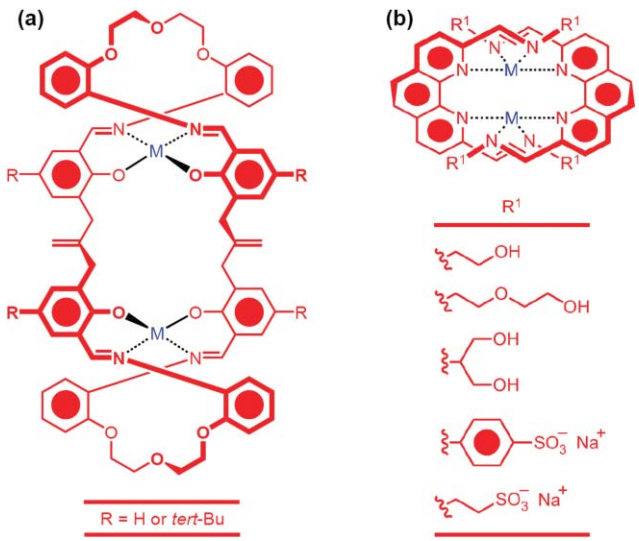


Fig. 4 (a) A twisted macrocycle, templated by Ni(II) and Cu(II). (b) A phenanthroline-based helicate templated by Cu(I).

Another degree of freedom lies in the choice of the template. Metals are among some of the best templates for imine bond formation. Moreover, they can align imines, according to the coordination geometry specific to the metal – and the metal's oxidation state. Copper(II) and other metals, which have octahedral coordination spheres, have proved to be ideal for aligning ligands in a perpendicular orientation, thus allowing the spatially selective condensation of imines to take place. In contrast, Cu(I) prefers tetrahedral coordination geometry, and as such, the ligands are preorganised in a more flattened arrangement, which, upon imine condensation, allows for interwoven architectures to be formed. Two

diformylphenanthroline units can organise around two Cu(I) centers, and, in the presence of certain primary amines, imine condensation occurs (Fig. 4(b)) at each end of the phenanthroline residues to create[16] a helicate. The helical shape of the final assembly is a consequence of both the crescent shape of the spacer between the chelation sites, and the preference for the Cu(I) template to preorganise the chelation sites into a tetrahedral arrangement. It should be noted that these helicates, confirmed by X-ray crystallographic analyses, were formed in aqueous media, which is usually believed to prevent imine bond formation. In many cases, however, aqueous solvents can actually drive imine bond formation owing to the hydrophobic interactions that compress reactants together around the template, thus increasing their effective molarities. By varying the stereoelectronics associated with the selection of primary amine starting materials, the authors monitored the limits of helix formation by ^{1}H and ^{13}C NMR spectroscopies and were able to develop a set of selection rules for double-helicate complex formation, based upon steric interactions, charge, pH, and solvent effects on imine bond formation. Certain patterns were clearly established: for example, amines bearing three alkyl groups on the α-carbon are not "allowed" presumably because of steric hinderance. Likewise, in all cases, a greater extent of helicate formation was observed in H_2O than in MeCN. The effects of creating a pH differential were also investigated during the acid titration of copper helicates, establishing that an imine-constituted helicate containing aniline moieties was stable down to pH 2, while an alkylamine-based helicate was only stable down to pH 5. The difference in pK_as between the two amine starting materials was then exploited in a competition experiment, in which the aniline was added to a previously formed helicate constructed from an alkyl amine. Equilibrium favoured the displacement of the aliphatic amine with the incorporation of the aniline residue. This pK_a-driven substitution of imine bonds illustrates one way in which control can be gained over imine exchange. The selection rules[17] provide the chemist with more opportunities to predict and fine tune reaction conditions employing imine bond formation, exchange and metathesis reactions.

4 Metal-templated formation of catenanes

Just as crescent-shaped ligands have led successfully to the self-assembly of double helicates, so one can envision connecting the tails of each ligand using DCC once the double helicate is formed to yield two interlocked rings, *i.e.*, a catenane. Leigh *et al.*[18] have used this approach to make a [2]catenate (Fig. 5) by simultaneously organizing two concave-shaped 2,6-diformylpyridine ligands in a mutually orthogonal manner around octahedral metals, while their ends are linked together by reaction with a diamine. The same catenate can also be formed using another dynamic covalent reaction – namely olefin metathesis – where a Schiff's base ligand with two terminal olefins is allowed to first coordinate to the metal, and thereafter, the resulting complex is subjected to double macrocyclisation by ring-closing metathesis (RCM) using a Grubbs' catalyst. It transpires that closing the ring *via* imine metathesis gives "uniformly higher," yet unoptimised yields, in comparison with the RCM route. It takes four imine bonds to bring the five components together to form a catenate. It happens to be the lowest energy means by which the metal templates can satisfy their coordination geometry. The formation of the catenate was followed by ^{1}H NMR spectroscopy and confirmed by X-ray crystallography.

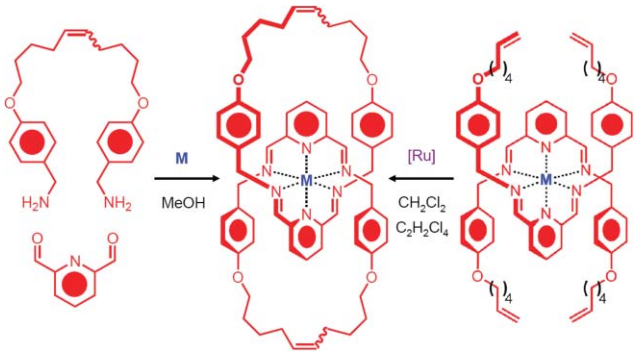


Fig. 5 A mutually orthogonal complex templated by the octahedral transition metals, Mn(II), Fe(II), Co(II), Ni(II), Cu(II), Zn(II), Cd(II) and Hg(II) followed by one of two ring-closing steps – (1) imine condensation or (2) RCM – to obtain a [2]catenate.

5 Dynamic rotaxanes

5.1 Rotaxanes formed by imine clipping

Imine bonds can also be used in the template-directed synthesis of rotaxanes, which are similar to catenanes, except that one of the linked macrocycles in a catenane is severed and then the resulting linear component, or thread, is stoppered with bulky end-groups to prevent the intact macrocycle from dethreading. Rotaxanes can be formed in a variety of different ways, including clipping and threading-followed-by-stoppering. The first [2]rotaxane, formed by the clipping process and employing template-directed imine formation, was synthesised[19] as shown in Fig. 6. In synthesising this [2]rotaxane, a library of macrocyclic and linear compounds was first of all prepared by the condensation between tetraethylene glycol bis(2-aminophenyl)ether and 2,6-diformylpyridine. When the reaction was monitored by ^{1}H NMR spectroscopy, it was found to have reached equilibrium with 50% of the precursors condensing in a 1 : 1 reaction to form the [24]crown-8 macrocycle and the other 50% forming higher order macrocycles and linear compounds, with a *cis*/*trans* mixture of isomers being formed around the C=N bonds. Upon addition of one equivalent of the dumbbell, bis(3,5-dimethoxybenzyl)ammonium hexafluorophosphate – the ^{1}H NMR spectrum revealed that an equilibrium between the [2]rotaxane (indicated by sharp ^{1}H NMR resonances) and the other compounds (indicated by broad ^{1}H NMR signals) was reached in only four minutes. The presence of the [2]rotaxane in the equilibrium mixture was confirmed by fast atom bombardment mass spectrometry (FAB-MS). The sharpness of the [2]rotaxane signals suggested that it is thermodynamically stable on the 360 MHz ^{1}H NMR timescale. The ammonium center of the dumbbell component serves two purposes – one is to template the formation of the [24]crown-8 derivative using weak acid catalysis and the other is to stabilise the resulting structure through hydrogen bonding.

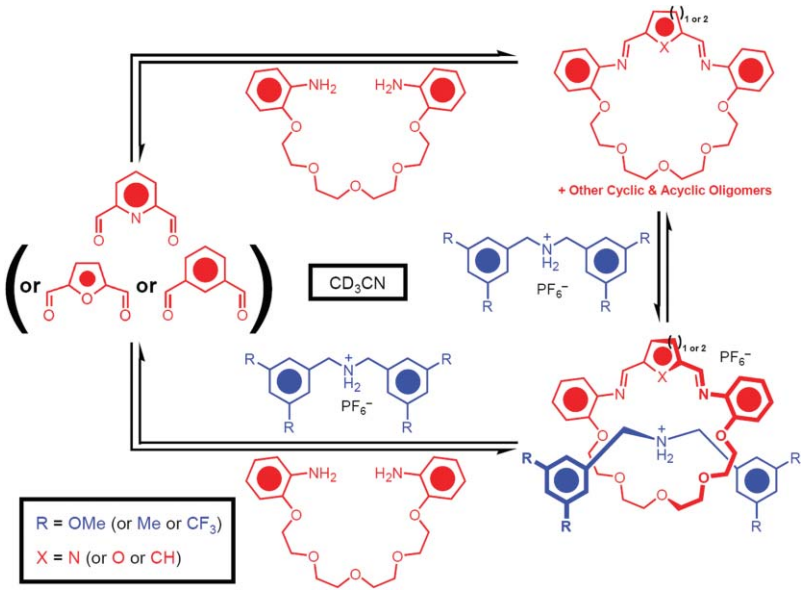


Fig. 6 A collection of [2]rotaxanes formed through a clipping process in which either a diformyl aromatic derivative is used to clip an ethylene glycol-linked diamine around a dibenzyl ammonium dumbbell, or in which a single rotaxane is amplified from a library of cyclic and acyclic oligomers.

Since the [2]rotaxane is still in equilibrium with other macrocyclic and linear species, the crown ether was reduced with a slight excess of BH_3·2,6-lutidine in CD_3CN. The stepwise reduction was observed by ^{1}H NMR spectroscopy. Signals for the starting [2]rotaxane were observed to disappear and signals corresponding to the singly-reduced [2]rotaxane were observed to appear, and then eventually disappear, giving rise finally to signals for the fully reduced [2]rotaxane. Interestingly, ^{1}H NMR resonances for the free dumbbell were also observed to disappear, indicating that reduction of the [2]rotaxane is faster than reduction of the macrocyclic and linear imines, and that the equilibrium is being driven toward formation of the fully reduced [2]rotaxane. After two days, the reaction came to completion and the ^{1}H NMR spectrum revealed that all of the precursors had been converted kinetically into the fully reduced [2]rotaxane, the structure of which was confirmed by FAB-MS and X-ray crystallography. The time required to complete this reaction was shortened[20] to 2 h, using the less toxic BH_3·THF.

The experiment was repeated[21] to form (Fig. 6) a total of nine [2]rotaxanes, resulting from the use of three different diformyl derivatives and three different dialkylammonium dumbbells. In all cases, sharp signals were observed at equilibrium in the ^{1}H NMR spectrum, indicating that the [2]rotaxanes are thermodynamically stable on the ^{1}H NMR timescale at room temperature. The length of time required to reach equilibrium varied, depending on the nature of the components, and ranged from a few minutes up to three days in the case of 2,5-diformylfuran and the dumbbell carrying four methyl substituents. For each dumbbell, it was observed that equilibrium was attained fastest when the dialdehyde was 2,6-diformylpyridine and slowest when it was 2,5-diformylfuran. For a given dialdehyde, the reactions reached equilibrium fastest in the case of the dumbbell carrying four trifluoromethyl substituents. This observation can be rationalised by examining the electronic properties of the dumbbells and the dialdehydes. Pairing the most π-electron deficient dialdehyde (diformylpyridine) with the most π-electron rich dumbbell (tetramethoxy) or pairing the most π-electron rich dialdehyde (diformylfuran) with the most π-electron deficient dumbbell (tetra(trifluoromethyl)) resulted in relatively rapid formation of [2]rotaxanes, while pairing the most π-electron rich dialdehyde and dumbbell resulted in the slowest formation of all.

However, the rate of formation under kinetic control does not relate to thermodynamic stability. The macrocycles formed from the diformylpyridine and diformylfuran contain more hydrogen bond acceptors than the macrocycle formed from 1,3-diformylbenzene, and the corresponding rotaxanes were shown to be more stable, as determined by integration of the [2]rotaxane signals in their ^{1}H NMR spectra. Competition experiments between pairs of dialdehydes or between pairs of dumbbells were used to determine the relative thermodynamic stabilities of the [2]rotaxanes. Each of the competition experiments was carried out in three different ways: (1) by combining all of the components in equimolar ratios and then allowing equilibrium to be reached, or (2) by, first of all, allowing each of the two possible [2]rotaxane mixtures to reach equilibrium separately and (3) by then introducing one equivalent of either dialdehyde or dumbbell and allowing each of these new systems to equilibrate once again. Generally, it took longer for the preformed [2]rotaxane mixtures to reach equilibrium than for the mixtures in which all components were added simultaneously. For each dialdehyde, it was determined that the dumbbell carrying four trifluoromethyl substituents leads to the most stable [2]rotaxane, while the dumbbell containing four methoxy substituents leads to the least stable [2]rotaxane, demonstrating that the dumbbell is indeed a more efficient template when it is more π-electron deficient. As expected, the [2]rotaxanes formed from

diformylbenzene are the least stable, and for a given dumbbell, the ones formed from the diformylfuran are found to be more stable than those formed from diformylpyridine. This result was explained by the enhanced basicity of the π-electron stabilised imino and phenoxy units on the furan-containing macrocycle, allowing them to act as better hydrogen bond acceptors, despite the greater basicity of the pyridine nitrogen which one might have expected to be a better hydrogen bond acceptor than the furan oxygen.

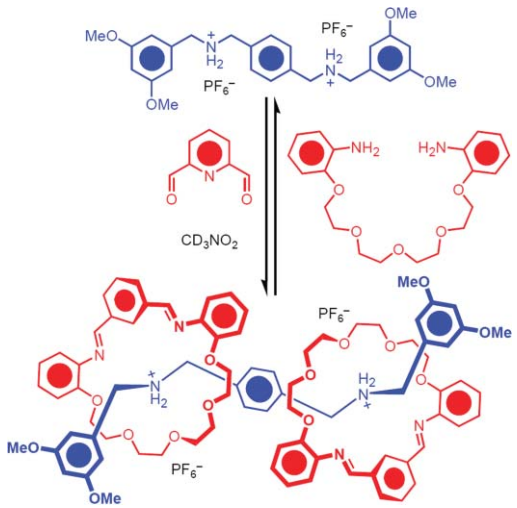


Fig. 7 A [3]rotaxane synthesised by means of a dual clipping process.

Employing this thermodynamic imine-based clipping process, a variety of mechanically interlocked molecules have been obtained using template-directed protocols.[20,22,23] The first of these, a [3]rotaxane, was synthesised[20] (Fig. 7) by using a two-station bis(dialkylammonium) dumbbell. The reduced [3]rotaxane was obtained in CD_3NO_2 in an 80% yield by driving the reaction kinetically, using BH_3·THF. Its structure was confirmed by ^{1}H NMR spectroscopy and X-ray crystallography.

Next, a branched [4]rotaxane (Fig. 8(a)) was synthesised[20] by using a trifurcated three-station tris(dialkylammonium) template. The reaction was driven kinetically using BH_3·THF to give the desired product in 87% yield. The structure was confirmed by ^{1}H NMR spectroscopy and high resolution electrospray ionization mass spectrometry (HR-ESI-MS). This branched rotaxane has also been employed[22] as a core for the convergent synthesis of mechanically interlocked dendrimers. Dendridic dialdehydes (Fig. 8(b)–(d)) from generation zero to generation two were clipped to the trifurcated template using imine condensation under thermodynamic control, and ^{1}H NMR spectroscopy showed yields in excess of 90%, stable for more than 24 h. The imine bonds could be reduced, the mechanically interlocked dendrimers were isolated, and these structures were confirmed by HR-ESI-MS and ^{1}H NMR spectroscopy. In principle, the dynamic convergent synthesis of dendrimers allows components to be mixed and matched on the basis of a larger system under equilibration, which would allow the dendrimer to adapt to its environment. The dynamic nature of these dendrimer systems was demonstrated[23] by mixing preformed dendrimers and allowing them to come to equilibrium, forming dynamic combinatorial libraries where the ratio of the constituents in the library can be controlled by varying the conditions under which the library is prepared.

The third class of higher-order rotaxanes investigated[20] was based (Fig. 9) on a tetraaldehyde formed by linking two of the diformylpyridine derivatives. First, this tetraaldehyde was exposed to a single-station dialkylammonium thread and the bis[2]rotaxane was observed by ^{1}H NMR spectroscopic analysis to form in quantitative yield. The tetraaldehyde was then exposed to a two-station template, and a cyclic

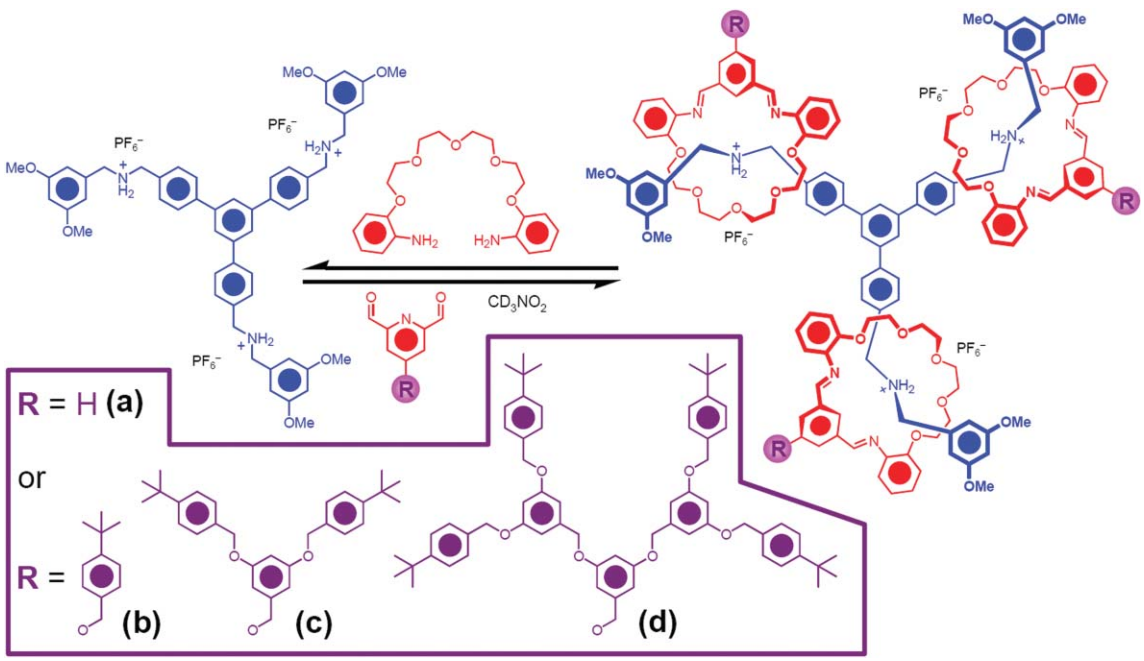


Fig. 8 (a) A branched [4]rotaxane synthesised by means of a triple clipping process and modified with (b) generation zero, (c) generation one, and (d) generation two dendrons.

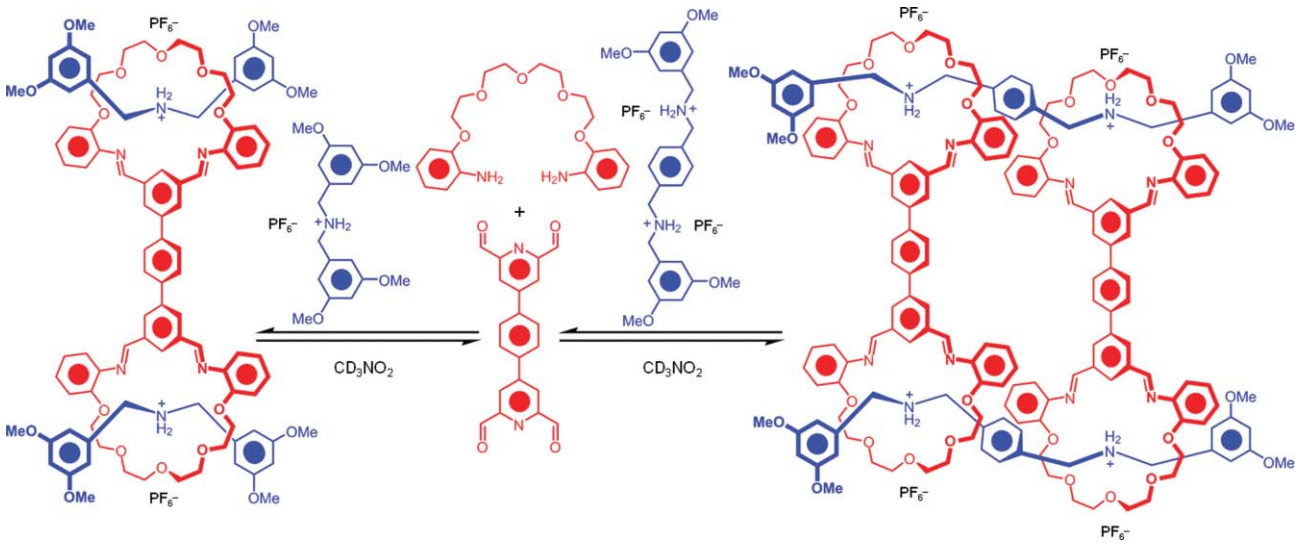


Fig. 9 A bis[2]rotaxane and cyclic [4]rotaxane formed, respectively by clipping a tetraaldehyde onto a pair of single- and double-station dialkylammonium threads.

[4]rotaxane was formed in quantitative yield, as determined by ^{1}H NMR spectroscopy, despite the possibility for formation of oligomeric or higher order macrocyclic structures. The imines in both products were reduced using BH_3·THF, the products were isolated, and the structures were confirmed by HR-ESI-MS, ^{1}H NMR spectroscopy, and, in the first case, X-ray crystallography.

5.2 Rotaxanes formed by imine stoppering

Using imine bonds to form thermodynamically stable [2]rotaxanes is, by no means, limited to the clipping process. Stoppers can also be added dynamically to the ends of a rod, entrapping a threaded macrocycle. An amine-terminated stopper has been added (Fig. 10) to a diformyl-substituted dialkylammonium template[24] and the system was allowed to equilibrate, yielding 73% by ^{1}H NMR integration of the doubly-stoppered template, 23% of the singly-stoppered template, and 4% of free template. Dibenzo[24]crown-8 (DB24C8) was added to this equilibrated mixture and the system was again allowed to come to equilibrium. The final reaction mixture revealed 47% of the doubly-stoppered [2]rotaxane, 26% of the singly-stoppered [2]pseudorotaxane, 4% of the unstoppered [2]pseudorotaxane, 16% of the doubly-stoppered template, 6%

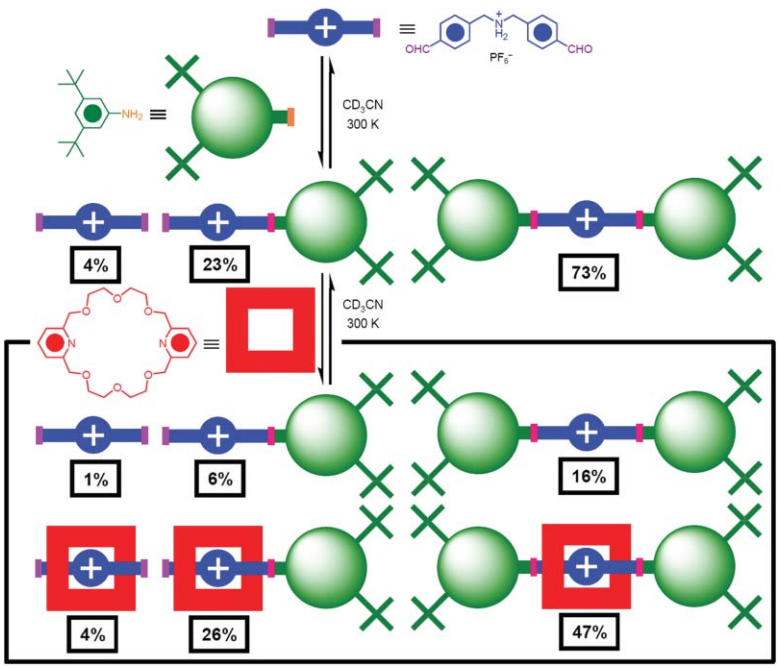


Fig. 10 Free and singly-stoppered threads and a dumbbell are formed under thermodynamic control from a diformyldibenzylammonium template. Upon introduction of dipyridyl[24]crown-8, free and singly-stoppered [2]pseudorotaxanes and a [2]rotaxane are observed to form in yields exceeding the sum of the yields of the initial threads.

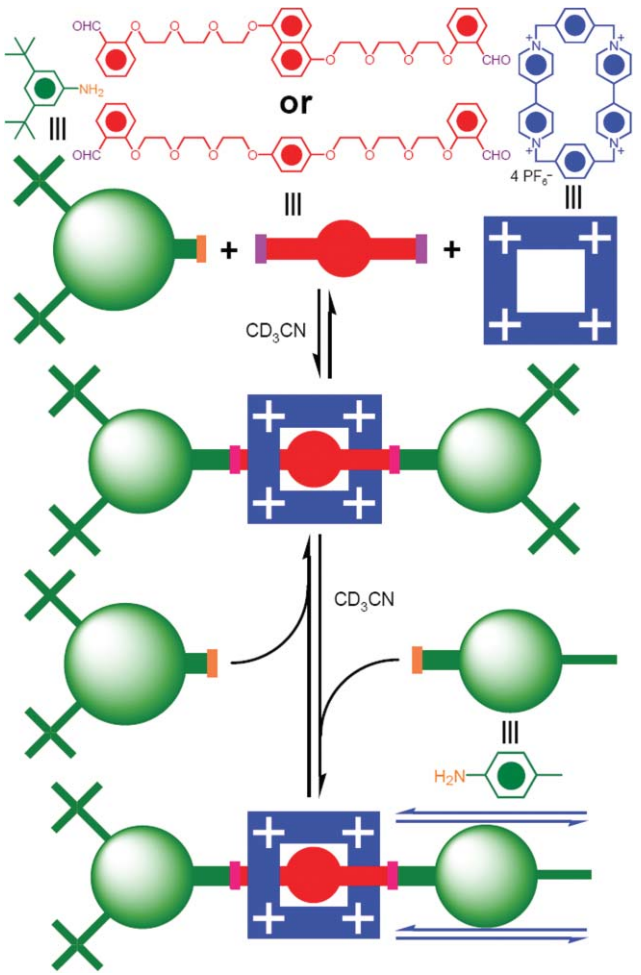


Fig. 11 A dynamically stoppered [2]rotaxane is formed from an electron-poor macrocycle encompassing an electron-rich recognition site. Upon subsequent imine exchange of one or more stoppers with *p*-toluidine, the macrocycle is observed to dethread.

of the singly-stoppered template, and 1% of the free template. It follows that the stoppers must be dynamically labile, since it is not possible for the DB24C8 to thread onto the doubly-stoppered template. If these stoppers were not labile, no more than 23 + 4 = 27% of the [2]rotaxane could have been formed, yet it makes up 47% of the dynamic combinatorial library (DCL). The imine bonds in the equilibrated reaction mixture were subsequently reduced with PhSeH and the 'fixed' [2]rotaxane was isolated and characterised by FAB-MS and ^{1}H NMR spectroscopy.

Additional dynamically-stoppered rotaxanes (Fig. 11) were investigated[25] in which the macrocycle employed was cyclo-bis(paraquat-*p*-phenylene) and the recognition unit on the diformyl thread was either 1,5-dioxynaphthalene or 1,4-dioxybenzene. When two amino-terminated stoppers were added to reaction mixtures containing the macrocycle and one or other of the two threads, [2]rotaxanes and [2]pseudorotaxanes were formed and observed by ^{1}H NMR spectroscopy. This mixture was then exposed to *p*-toluidine, which is not a stopper for the macrocycle, and the stoppers were observed by ^{1}H NMR spectroscopy to undergo imine exchange with *p*-toluidine, in the absence of an acid catalyst, resulting in the formation of an additional class of pseudorotaxanes containing one or more *p*-toluidine residues. In addition, competition experiments between the dioxynaphthalene and dioxybenzene threads showed, as expected, that the dioxynaphthalene-based [2]rotaxane is the preferred thermodynamic product by a 6 : 1 ratio.

It should be noted that the two threading-followed-by-stoppering examples of rotaxane syntheses,[24,25] presented so far in this tutorial review, do not actually rely on template-directed imine formation. On the contrary, the macrocycle is templated onto a thread, to which stoppers are added and removed dynamically. Since the imine bonds are under constant dynamic equilibration, the presence or absence of the macrocycle should not greatly affect the equilibrium concentrations of the free, singly-stoppered, and doubly-stoppered templates. However, a family of [2]rotaxanes has been synthesised[26] in which the stoppering of the thread also templates the threading of the ring. In this system (Fig. 12), an octahedral metal ion is treated with a 2,6-diaminopyridine-derived macrocycle and 2,6-diformylpyridine in the presence of aniline-derived stoppers. The macrocycle acts as a tridentate ligand for the complexation of the metal ion, and imine formation between the diformylpyridine and two of the aniline stoppers allows for the templated formation of the [2]rotaxane in near quantitative yields with many metal ions. The [2]rotaxane is the only metal-containing product observed in all cases by ^{1}H NMR spectroscopy, FAB-MS, and X-ray crystallography, probably as a direct

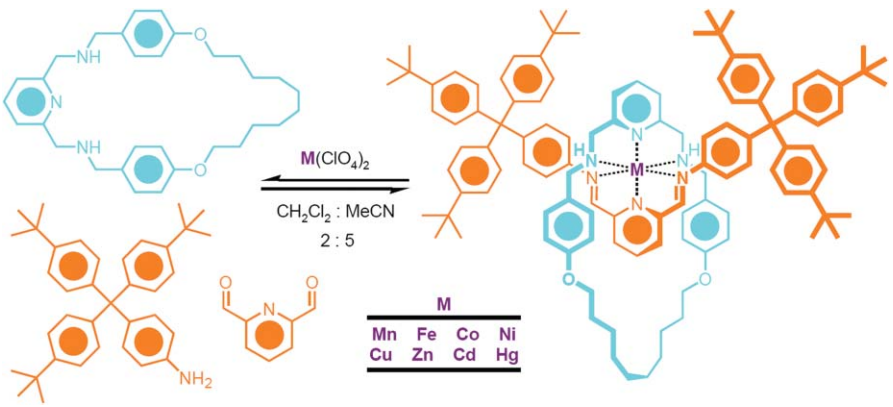


Fig. 12 Octahedral metal template-directed imine-stoppering of [2]rotaxanes.

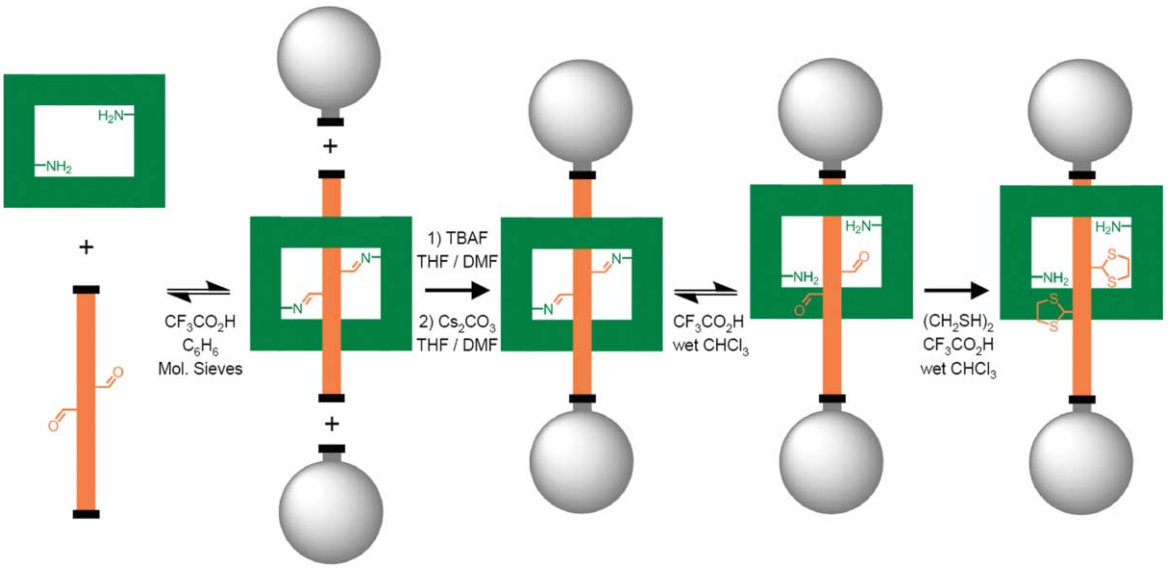


Fig. 13 Schematic representation of a [2]rotaxane templated by dynamic imine bond formation in which stoppers are added while the macrocycle is covalently bound to the thread using imine bonds, which are subsequently hydrolysed to free the macrocycle, followed by dithioacetylation of the formyl groups to yield a [2]rotaxane.

consequence of the fact[26] that imine N donors form stronger dative bonds with metals than amine N donors. As a result, the strongest metal-containing complex should be a bis-thread complex, followed by a thread-ring complex, and finally a bis-ring complex. However, in the bis-thread complex, the aniline-derived stoppers are held in a geometry in which there can be no π-stacking interactions, so the thread-ring complex – in which these interactions are observed by ^{1}H NMR spectroscopy and in the solid state by X-ray crystallography – becomes the thermodynamic minimum and is the main product of the reaction.

5.3 Rotaxanes templated by imine bond formation

Recently, Kawai *et al.*[27] have reported the synthesis of a rotaxane in which imine bond formation was used as a template (Fig. 13) in order to connect covalently the ring component to the thread component. Once these subunits are covalently assembled, and the stoppers added to the rotaxane precursor through standard covalent chemistry, the imine bonds can be hydrolysed to free the ring, thus forming the [2]rotaxane. In order to ensure that the system did not re-equilibrate to the covalent species, the aldehydes were subjected to dithioacetylation. This concept of using reversible covalent chemistry as a templation method for making mechanically interlocked compounds may lead to a class of compounds where weak interactions between the components are not present in the resulting assembly.

6 Suitanes

Compounds called suitanes, which rely heavily upon the dynamic template-directed formation of imine bonds, have been synthesised recently.[28] Suitanes consist of a 'torso' from which appendages extend and onto which rings can be threaded to form pseudorotaxanes. The rings can then be

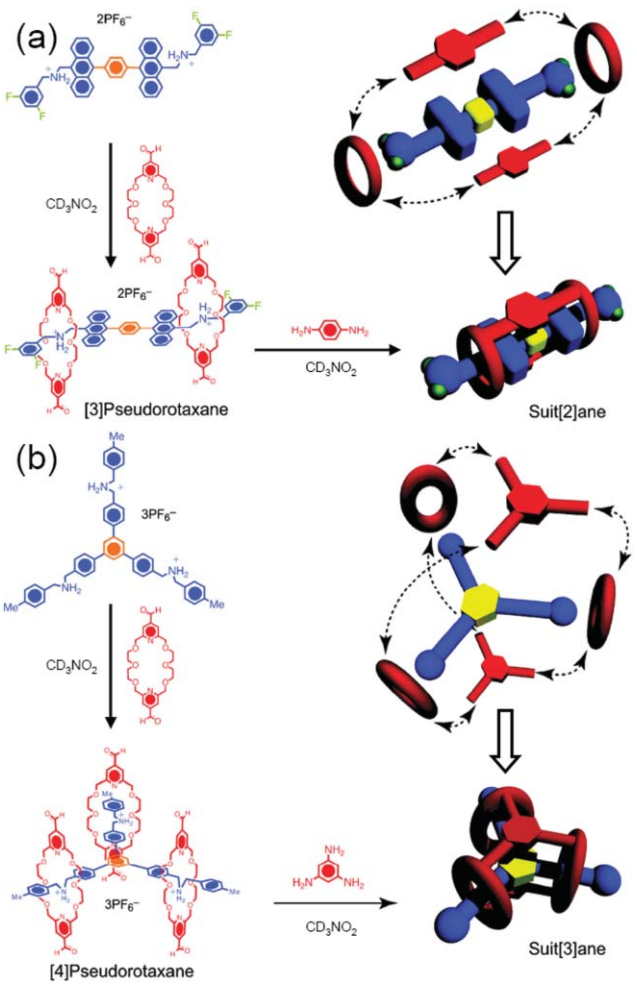


Fig. 14 Templated dynamic covalent synthesis of suit[2]ane and suit[3]ane.

linked together to form a close-fitting 'suit' around the torso. This suit is designed in such a way that it is internally stoppered so that the appendages emanating from the torso cannot be removed from their associated rings. A number is placed between 'suit' and 'ane' to indicate the number of appendages that protrude from the suit.

In the reported versions[28,29] of these mechanically interlocked compounds, both a suit[2]ane and a suit[3]ane rely on dynamic imine-bond formation (Fig. 14) to connect the crown ether rings together around the torso. Each of the crown ether rings bear two aldehyde groups, one on each side of the crown ether. After these crown ethers are threaded onto the torso bearing the appendages with dialkylammonium centres, the crown ethers are linked using a di- or triamino-substituted benzene ring. The dynamic nature of this synthesis allows for the requisite proofreading to take place so that the most thermodynamically stable compounds – namely suitanes – are formed in exceptionally high yields and have been characterised by X-ray crystallography.

7 Metal-templated formation of molecular grids

Given that transition metals with octahedral coordination geometries can align ligands orthogonally, molecular grids can be envisaged as a result of using octahedral coordination sites to organise ligands that have linear, rigid shapes, as well as a coordination site for every crossing. The components of a linear ligand containing two coordination sites, derived from a central pyrimidine dialdehyde bridging unit, have been linked[30] laterally to aminophenol endgroups using imine chemistry in the presence of zinc ions as templates. The utility of the imine bond as the linker of choice has been tested under amplification conditions, when the same grid-building protocol was applied to a mixture of different aminophenol and carbonyl components. The resulting [2 × 2] molecular grid was amplified with a selectivity of over 99%, and its structure elucidated by X-ray crystallography. The reversible connectivity of imine bonds, and

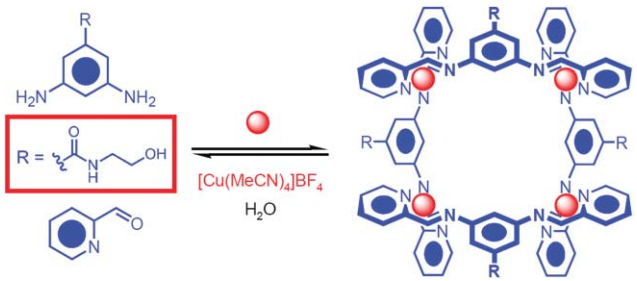


Fig. 15 A [2 × 2] copper grid derived from a central diaminobenzamide condensing with pyridinecarbaldehyde endgroups.

their ability to allow self-correction to occur upon environmental change, has also been demonstrated in exchange reactions, where an aminophenol was added in ten-fold excess to exchange out a nitrated – hence more deactivated – aminophenol derivative. When another environmental change, namely that of pH, was inflicted upon this grid, the dynamic imine bonds responded by undergoing hydrolysis, leading to complete break down of the grid in acidic medium. Upon making the medium basic, the same grid reformed.

A [2 × 2] copper grid (Fig. 15) has been formed[31] in quantitative yields from a mixture of diaminobenzamide, pyridinecarbaldehyde and $[Cu(MeCN)_4]BF_4$. The formation of this tetrameric structure is undoubtedly encouraged by the linear shape of the ligand subcomponents – namely an aldehyde and an amine – which makes it unlikely for any closed loop structure or helix to be formed. However, the bisimine ligand formed would theoretically have oblique coordinate vectors that are not conducive to grid formation, a structure which requires parallel coordinate vectors. In the event, the strained grid is only formed successfully in one solvent, that is deuterated water. Although H_2O is often used to hydrolyse imines, it has been suggested that water actually facilitates grid formation on account of hydrophobic effects, thereby increasing the effective molarity of reactants and

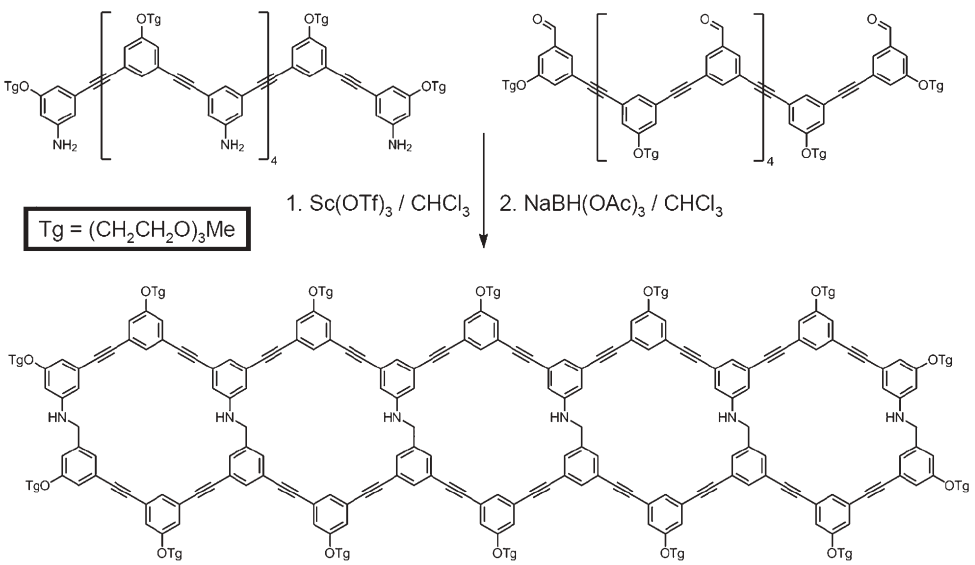


Fig. 16 A [6]-rung molecular ladder formed by using imine bonds to cross-link an aldehyde-bearing hexamer with an amino-bearing hexamer, followed by irreversible reduction of the imine bonds.

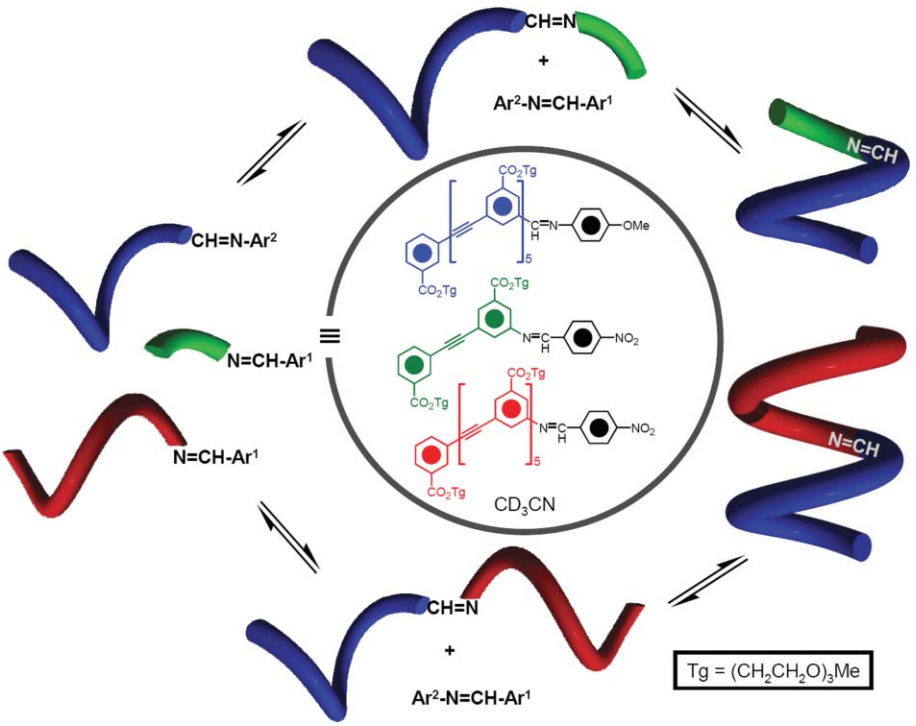


Fig. 17 The imine metathesis of *meta*-connected phenyleneethynylene oligomers, resulting in the formation of foldamers.

enabling the otherwise unlikely grid to snap together as a result of imine condensations. An X-ray crystal structural analysis of a single crystal verified the formation of the strained grid.

8 Covalent assembly of molecular ladders

Recently, Moore and co-workers[32] have demonstrated the self-assembly of [*n*]-rung molecular ladders using imine bond formation to cross-link discrete (n = 3–6) *m*-phenylene ethynylene oligomers. The rungs are constructed (Fig. 16) upon imine bond formation in $CHCl_3$ between an oligomer bearing *n* aldehyde functions and a complementary oligomer functionalized with *n* amino groups. The ladders can be trapped by irreversible reduction of the imine bonds with $NaBH(OAc)_3$. Despite their large aromatic surface area, the molecular ladders exhibit good solubilities. Although matrix-assisted laser desorption/ionization mass spectrometry (MALDI-MS) provides clean evidence of the formation of the desired molecular ladder, gel permeation chromatography (GPC) shows the formation of high molecular weight oligomeric by-products. The yields of the desired molecular ladders, n = 3–6, ranged from 71 to 10%, respectively. The authors offer two possible reasons for this trend toward lower yields with higher *n*. Longer oligomers, may be more prone to misassemble, and the products of this misassembly could be trapped easily by the large number of imine bonds that form. Alternatively, the equilibrium distribution may be less populated with the desired [*n*]-rung ladder as *n* increases.

9 Oligomers driven by folding

Polymerisations can provide a wide range of compounds by altering the structure of the monomers, the sequence in which they are assembled, and the overall chain length of the polymer. These parameters can be manipulated so that it is favourable to form oligomers with a well-defined folding pattern – often referred to as foldamers – by using monomers that interact by means of noncovalent bonding interactions, and a linker between the monomers of an appropriately determined length. In a sense, these interactions indicate that the template for foldamer construction can be programmed into the monomer units. Moore and co-workers[33] have demonstrated, for example, that folding can drive a ligation reaction, enabling the preferential synthesis of certain sizes of oligomers, when the ligation is executed by means of imine bond metathesis. Starting with two selected imine-terminated *meta*-connected phenyleneethynylene short chain segments, one with an N-terminated imine bond, and the other with a C-terminated imine bond, the chain lengths with the greatest folding capacity (when paired) lead to the formation (Fig. 17) of the corresponding imine-containing foldamer. If the number of monomer units (*i.e.*, chain length) of each component is sufficiently large, a foldamer with two turns will be formed upon imine bond metathesis. However, if the chain length is too small, no helix will be formed, and so there is no driving force for imine metathesis. This observation supports the notion that folding is stabilised by the contact areas between turns. It has been determined that there is a critical chain length at which folding will occur – at least one turn. In this case, the oligomer must be a hexamer. This critical chain length was determined by mixing monofunctionalized subunits that contain from one (monomer) to six (hexamer) aromatic rings. The corresponding K_{eq} (294 K, CD_3CN) values – determined from the integration of the peaks in ^1H NMR spectra – were shown to increase markedly from 1.1 to 62,

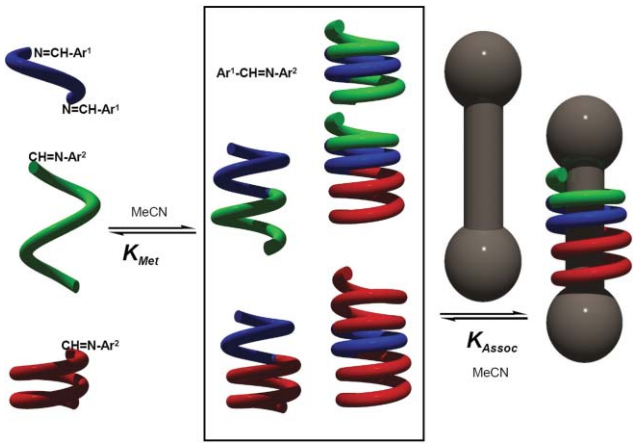


Fig. 18 Cartoon representation of the imine metathesis between a bis *C*-terminated tetramer with a pair of N-terminated oligomers to form a library of foldamers. Upon addition of a dumbbell guest, a single foldamer was amplified in keeping with the length of the rod.

respectively. Thus, in this series, the most energetically favourable outcome is the formation of the largest helix formed, the dodecamer, or two turns of the helix. Conversely, when placed in solvents that do not favour folding, the K_{eq} (294 K, $CDCl_3$) only varies from 1.2 (monomer) to 1.9 (hexamer), reinforcing the hypothesis that imine bond formation – or helix ligation – is templated by folding. Competitive metathesis experiments were then performed between two N-terminal imines of different lengths that compete for the ligation to a C-terminal imine to form either an octomer or dodecamer. In CD_3CN, ^1H NMR spectra and GPC traces revealed that the dodecamer is preferred by a molar ratio of 3.6 : 1. To increase the size-selectivity of the formation of larger oligomers, a dumbbell-shaped guest was used[34] as an additional driving force to template imine ligation of oligomers of certain sizes selectively. Three starter sequences were added into one pot – a tetramer having two N-terminal imines, along with a hexamer and a dodecamer, both of which have one C-terminal imine. With this starting mixture, many sizes of oligomers are possible, so a hydrophobic rod capped with bulky triphenylmethyl groups, was added to this mixture to select from this library just the one helix with the number of turns that can wrap (Fig. 18) around the dumbbell enough to extend from one stopper to the other. The binding affinity was found to be at a maximum for oligomers with 20–22 aromatic ring repeat units. HPLC Traces revealed once again that, in a solvent ($CHCl_3$) not conducive to folding, the product distribution is statistical. In solvents (MeCN) that favour folding, the 20–22-mer is formed in 72% yield. Furthermore, in MeCN, the addition of the guest amplifies the oligomer from the library in yields of 85%.

10 Bio-applications of template-directed imine formation

Perhaps the best-known template-directed reaction is the one which involves the assembly of mono-nucleotides along each single strand of a double helix of DNA in the *in vivo* DNA replication reaction to form a pair of DNA double helices. The imine bond has, in fact, been used[35] to model this replication process by substituting the static phosphodiester bonds found in the DNA backbone with a dynamic imine bond. In this process, one end of a set of short oligonucleotides was modified with an aldehyde, while the other end of a different set of oligonucleotides was modified with a primary amine to allow for imine bond formation between pairs of oligonucleotides to take place. These short oligonucleotides were then shown (Fig. 19) to form a small library of longer imine-coupled oligonucleotides, which were then fixed with $NaBH_3CN$ and the ratios of products were identified by reverse-phase HPLC. Upon addition of a template oligonucleotide to the dynamic library, the corresponding template-preferred imine-containing oligonucleotide was amplified by a 30-fold ratio at low temperature over other products, demonstrating the power of the DNA-template.

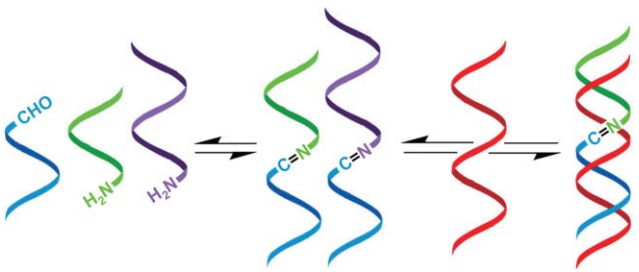


Fig. 19 A small library of imine-containing oligonucleotides formed from formyl- and amino-terminated oligonucleotides being driven to a single product upon the introduction of a complementary oligonucleotide template mimicking *in vivo* DNA replication.

Living organisms rely on thousands of template-directed reactions, and in recent years, dynamic combinatorial chemistry (DCC)[10] – the coupling of a group of related precursors using a repetitive set of reversible covalent reactions to form a diverse library of molecules – has been used to exploit these templates by finding the compound, out of a library of compounds, with the highest binding affinity to a given host or guest. DCC relies on reversible reactions to create a large number of possible structures in dynamic equilibrium in a

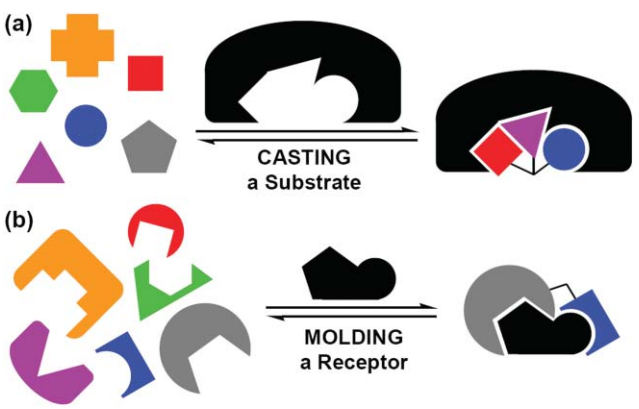


Fig. 20 Dynamic combinatorial chemistry, starting from a library of components in dynamic equilibrium, being used for (a) the casting of a substrate from a given receptor and (b) molding a receptor to a given substrate.

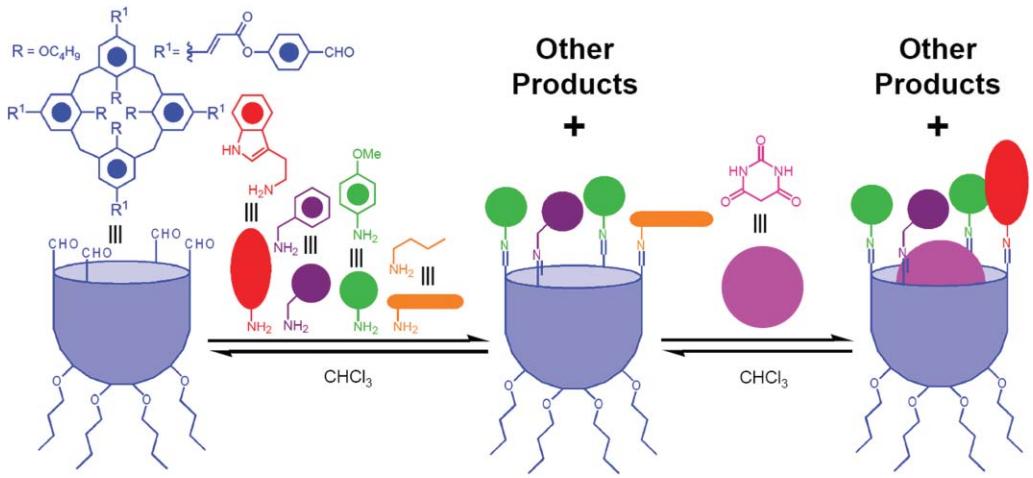


Fig. 21 A tetraformyl cavitand-based dynamic combinatorial library in which the hydrophobic guest bound by the hydrophobic cavity of the cavitand influences the nature of the major product.

single pot, starting from a set of specific precursors in a ratio dictated by the thermodynamic and kinetic properties of the components and their interactions.[36] This library can then be used for either *casting* a substrate that fits a given receptor (Fig. 20(a)) or for *molding* a receptor for a given substrate (Fig. 20(b)). Imine bonds are ideal for the generation of DCLs because they are rapidly reversible under physiological conditions and can be irreversibly fixed. In one example,[36] a substrate for Carbonic Anhydrase II (CA II) was cast from a set of amines and aldehydes that were chosen so that analogous components would have comparable reactivities (to avoid bias), but so that the library could exhibit large variability – nonpolar versus polar versus charged, for example. After the DCL reached equilibrium in the presence of CA II, $NaCNBH_3$ was added to reduce the imine bonds, and CA II was thermally denatured and removed. The dynamic library was analysed by HPLC to determine the identity of any amplified species, which were also identified by synthesising each possible component in the library separately and determining retention times for each candidate on the HPLC.

The DCL approach can also be used to mold receptors for specific guests to occupy. One example[37] of this concept involves deep cavity tetraformyl calix[4]arenes, which contain hydrophobic cavities that can be used to attract a hydrophobic guest. Tetraformyl guests were exposed to a mixture of four aromatic and aliphatic amines and – despite the fact that there are 251 possible isomers, including all possible mono-, di-, tri- and tetra-substituted calix[4]arenes with all possible regioisomers considered – one major product (Fig. 21) was observed by ^{1}H NMR spectroscopy and liquid secondary ion mass spectrometry tandem mass spectrometry (LSIMS-MS). While one of the amines can presumably act as a template for this reaction, if a hydrophobic guest is added to the library, a different receptor can be molded since this substrate shifts the thermodynamic preference of the DCL. This preference was shown by exposing the system to two different guests – barbituric acid and biotin (not shown) – whereupon new hosts were amplified and observed by LSIMS-MS and ^{1}H NMR spectroscopy. In the case of barbituric acid, the amplified receptor was not detected at all in the library formed with no guest present. The guests were shown to be in the cavity of the calix[4]arene by diffusion NMR spectroscopy.

11 Dynamic hemicarcerands

When two cavitands are brought together so that their cores form a cavity that can be used to incarcerate a guest, the molecule is called a carcerand and when it holds a guest, the

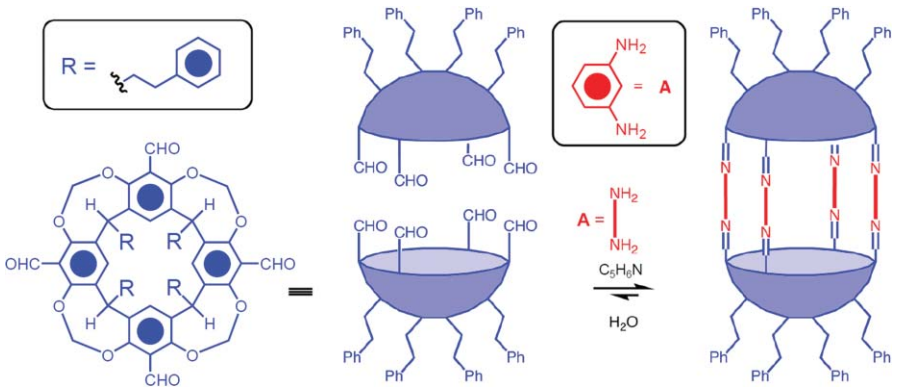


Fig. 22 A dynamic hemicarcerand formed the eight-fold condensation of four diamino linkers with two tetraformyl cavitands.

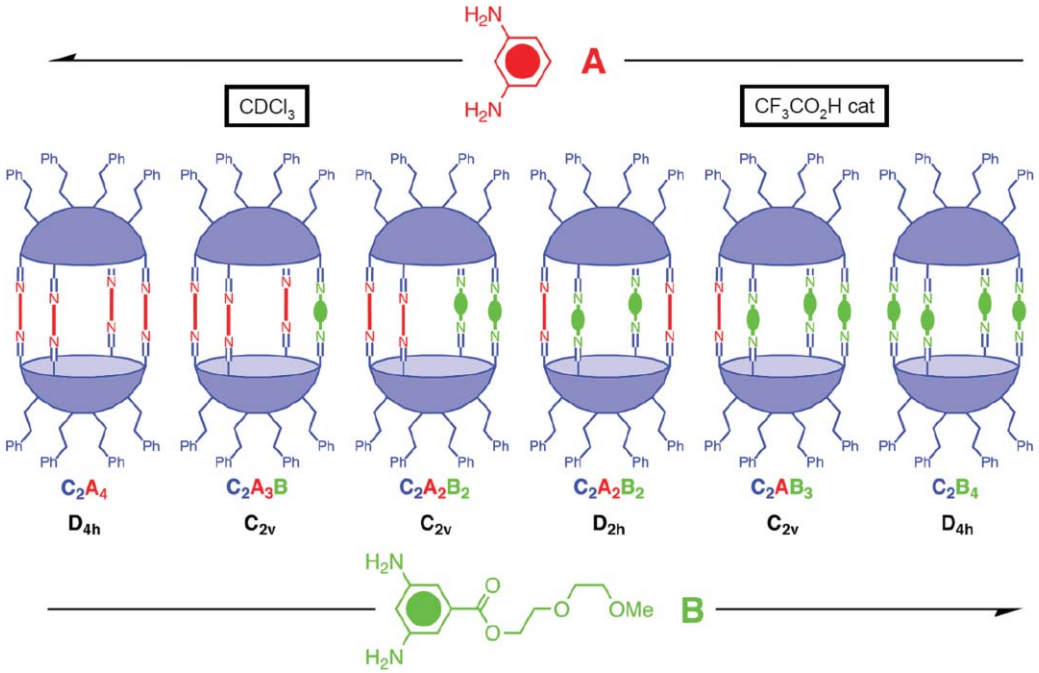
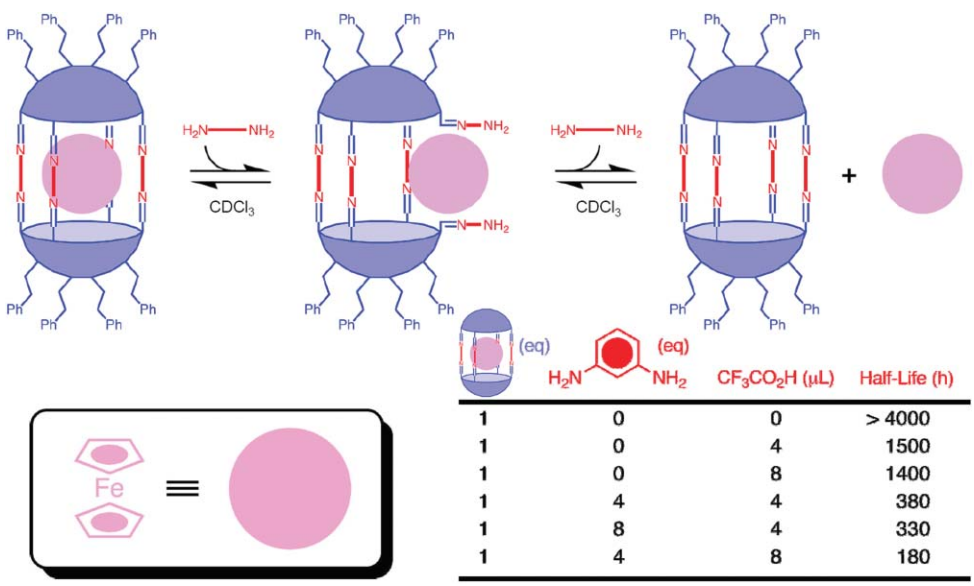


Fig. 23 Dynamic exchange of diamino linkers to form a collection of hemicarcerands.

complex is known as a carceplex. When the linkers that are used to connect the two cavitands together, however, provide a large enough portal for guests to escape from the core at higher temperatures, then the structure is known as a hemicarcerand and the host–guest complex is known as a hemicarceplex. In order to control the rate at which a guest can be complexed and decomplexed from the hemicarcerand, Quan and Cram[38] have employed two imine bonds in each of the four linkers between two cavitands by condensing two equivalents of a tetraformyl cavitand that is structurally similar to a calix[4]-arene with four equivalents of a diamine in the presence of an acid catalyst and $MgSO_4$ to act as a water scavenger, to give (Fig. 22), in near-quantitative yield in less than an hour, the hemicarcerand. The efficiency of this reaction suggests that the hemicarcerand which is formed is the thermodynamic product. The dynamic nature of the hemicarcerand was investigated by exchanging (Fig. 23) the diamine bridging units with ones carrying an ^{1}H NMR probe, and the equilibrated mixture was further analysed by FAB-MS, revealing a statistical mixture of the six possible hemicarcerands. This equilibrium could be adjusted statistically by varying the amount of each ligand added to the solution.



(eq)	(eq)	CF_3CO_2H (μL)	Half-Life (h)
1	0	0	> 4000
1	0	4	1500
1	0	8	1400
1	4	4	380
1	8	4	330
1	4	8	180

Fig. 24 Acid-catalysed complexation/decomplexation using imine exchange by means of a bar-opening/bar-closing mechanism requires the presence of an excess of both the diamino linker and an acid catalyst.

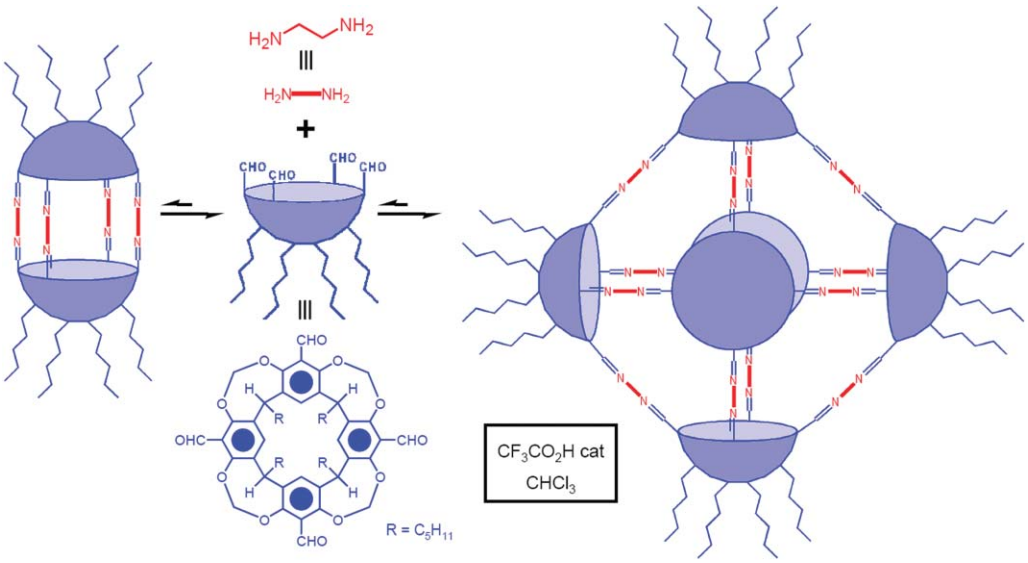


Fig. 25 A 24-fold imine condensation between six tetraformyl cavitands and twelve ethylenediamine molecules, leading to the formation of an octahedral nanocontainer in near quantitative yield.

It was postulated that the ligands were exchanged by means of a bar-opening/bar-closing mechanism which involves successive imine exchange reactions on each end of the diamine. In order to study this mechanism in operation, ferrocene was encapsulated[39] in the hemicarceplex, and the half-life of the reaction was investigated by ^{1}H NMR spectroscopy by observing (Fig. 24) the sharp singlets for the complexed and uncomplexed ferrocene at δ 3.66 and 4.16, respectively, under a variety of conditions. In the absence of an acid catalyst and an excess of diamine, the half-life of the hemicarceplex was >4000 h at room temperature. Addition of an acid catalyst reduced the half-life to 1500 h, but doubling the concentration of the catalyst did not increase significantly the rate of decomplexation. A full kinetic analysis of these data suggests that hydrolysis is the rate-determining step of the reaction in the absence of any free diamine. However, upon addition of 4 equivalents of diamine in the presence of an acid catalyst, the half-life of the hemicarceplex was found to drop to only 380 h. Although doubling the concentration of diamine did not reduce the rate of decomplexation significantly, doubling the concentration of acid catalyst further reduced the half-life of the complex to 180 h. Kinetic analysis of the data reveals that the bar-opening step of the reaction is the rate determining step, and the rate of decomplexation is fastest when excess of diamine is present along with acid to catalyse the imine exchange reaction. It should be noted, however, that even with four equivalents of diamine present, the rate of reaction suggests that the likelihood of two gates being open at any given time is fairly low, and three or four gates being open becomes increasingly less likely. Therefore, decomplexation can occur with a very low probability of the cavitands becoming fully separated.

While studying alternative diamines and cavitand substituents, Warmuth and co-workers[40] discovered the spontaneous assembly of an octahedral nanocontainer (Fig. 25) consisting of six cavitands held together with 24 imine bonds. This reaction, which prefers the hexamer as a result of a near-quantative thermodynamic reaction, produces a nanocontainer with a cavity that is approximately 17 nm^3. The imine bonds were reduced, and the structure of the nanocontainer was confirmed by ^{1}H and ^{13}C NMR spectroscopies, and HR-ESI-MS. In order for 18 components to self-assemble spontaneously in near-quantative yield, the authors calculated that the yield for each individual imine condensation must be in excess of 99%. Such a high-yielding synthesis is generally only achievable if an ideal template is used to preorganise the reactants prior to bond formation or, as in this case, if proofreading can occur in a dynamic system until the thermodynamic product is formed. As an illustration of the dynamic nature of these nanocontainers, it was shown[41] that, by varying the reaction conditions, two other types of nanocontainers were formed – a tetramer and an octamer – in addition to the hexamer, but it was not possible to separate the homologues by GPC.

12 Molecular Borromean Rings

The nontrivial link, known as the Borromean Rings (BRs), has fascinated scholars of all persuasions for centuries.[42] For chemists, they represent a formidable synthetic challenge, as they are comprised of three mutually interlocked, yet non-catenated rings. The BR topology can be viewed as a three-ring system – as described in knot theory – with the sole requirement that the scission of any one of the rings severs the union of the three. Calling upon the dynamic covalent chemistry of the imine bond, the equilibrium-based methods of imine formation have been successfully exploited,[43] in conjunction with the templation power of zinc(II), to effect (Fig. 26) a one-step total synthesis of a molecular Borromean link in over 95% yield, on a gram scale, from 18 precursors. Conceptually, the synthesis of Borromeates[44] can be attributed to three phenomena – (1) pairing recognition units, (2) alternating nodes, and (3) employing dynamic covalent bonds. The strategy uses a set of six *endo*

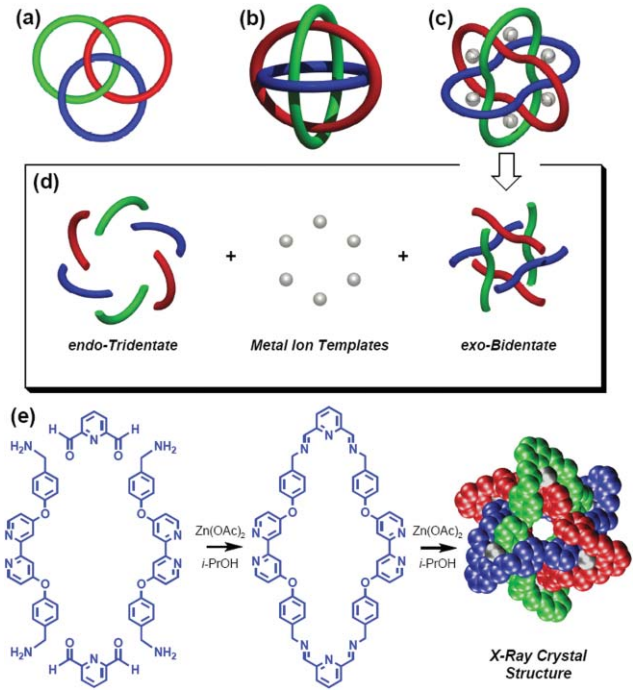


Fig. 26 The BRs can be depicted in several representations including (a) a Venn diagram, (b) an orthogonal arrangement, or (c) the molecular cartoon representation featuring the metal ion templates embedded in each of the six crossing points. (d) The retrosynthesis of the BR self-assembly process anticipates the use of an *exo* tridentate ligand, templated by metal ions to an *exo* bidentate ligand. (e) In chemical terms, the ligands employed in the BR synthesis involve the *exo* diamino bipyridyl ligand undergoing an imine condensation with the *endo* diformyl pyridine in the presence of a metal template in yields exceeding 95%.

tridentate and six *exo* bidentate oriented ligands designed to form the nodes in an oriented trigonal bipyramidal unit around the zinc ions, six of which are incorporated into the Borromean link topology by the formation of 12 imine bonds and 30 dative bonds. The X-ray crystal structure revealed the BRs are stabilised by a total of 12 π–π stacking interactions.

These Borromeates[44] can be demetallated by reducing all 12 imine bonds and then removing the six Zn(II) ions. Reduction and demetallation results[44] in a true or real Borromean link – or the so-called Borromeands – since the molecules remain intact without the presence of the templating Zn(II) ions (Fig. 27). The reduction was established to follow two pathways – 60% of the BRs were reduced to give the corresponding Borromeand, while 40% of the BRs had a macrocycle cleave during the course of reduction, and, true to the topological properties of the BRs, the assembly unraveled to give two free macrocyles and one linear component. Peaks corresponding to both the free macrocycle and the Borromeand were evident in the ^{1}H NMR spectrum. The HR-ESI-MS likewise confirmed the presence of the reduction products, and additionally confirmed the presence of the linear component, whose terminal aldehyde function had reacted with the reaction solvent – namely, EtOH – to give the corresponding acetal.

It has also been demonstrated that the BR framework can be modified[45,46] by pre-assembly modification of one of the building blocks – by employing pyridine diimine precursors with functional groups attached to the 4-position on the pyridine ring – to yield hexasubstituted BRs.

The mechanism of formation of the molecular BRs has been probed[47] by labeling the 4-position of the pyridine diimine precursors with chlorine and bromine atoms, to make them easy targets for observation by mass spectrometry. The lability of at least some of the 30 dative bonds and 12 imine bonds stabilising and constituting the BR framework were assessed (Fig. 28) by stirring a methanolic solution of both the hexachlorinated BR (homo-Cl_6) and the hexabrominated BR (homo-Br_6) at 60 °C in the presence of catalytic amounts of trifluoroacetic acid. Under these conditions, the BRs underwent imine metathesis, and consequently scrambled to form a statistical distribution of the possible halogenated products, all observed using HR-ESI-MS.

Molecules with interlocked and intertwined structures have non-planar molecular graphs and can exhibit topological chirality. Although the classic example is the trefoil knot, catenanes can also display topological chirality, provided both rings possess structural directionality. The BRs are topologically achiral (amphicheiral), and remain so even after orientation. Thus, the only way by which BRs can be rendered chiral is to introduce chirality in the form of elements that are planar, axial or point (stereogenic) in nature. Hence, two enantiomeric pairs of Borromean linked compounds (Fig. 29) we prepared[48] using Zn(II) ions to template their formation from chiral diaminobipyridine ligands with one of two like stereogenic centers – *i.e.*, (*RR*) or (*SS*) – and either 2,6-diformylpyridine or its 4-chloro derivative to give the (*R*)^{12} and (*S*)^{12} enantiomers of the Borromean link compounds. It transpires that, as a consequence of introducing four stereogenic centres into each of three identical rings in these chiral Borromeates, such that they pair up in locations close to the six ions, these metal ions are surrounded by chiral coordination spheres as revealed by one X-ray crystal structure and several circular

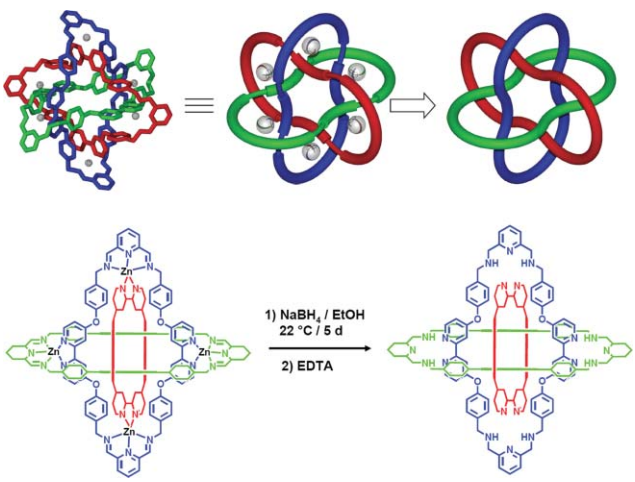


Fig. 27 Reduction of BRs using $NaBH_4$, followed by demetallation with EDTA.

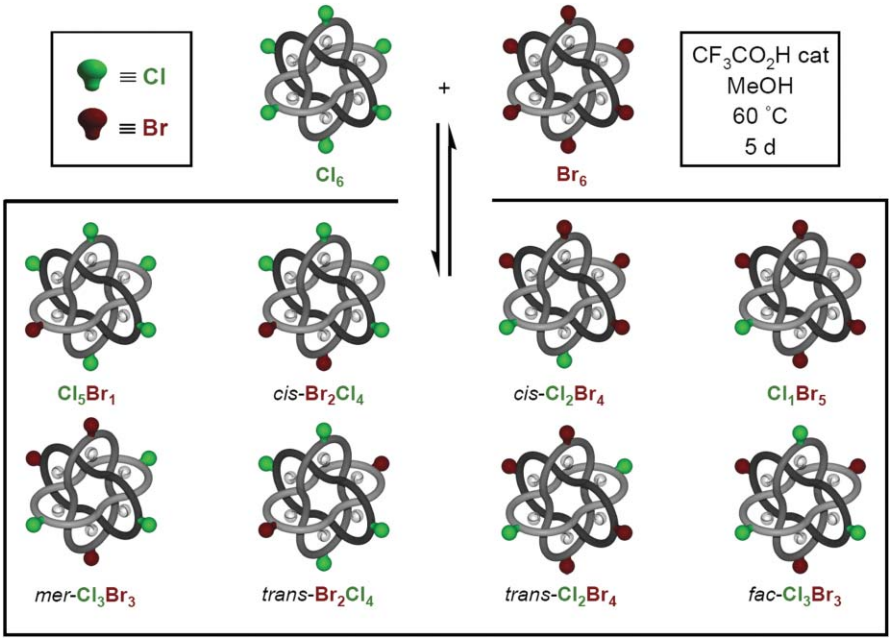


Fig. 28 Homo-Br_6 and homo-Cl_6 BRs were mixed in a methanolic solution in the presence of an acid catalyst to undergo imine metathesis. Under these conditions, the two BRs scrambled to produce a dynamic library containing a statistical distribution of halogenated BRs.

dichroism (CD) spectra. The CD spectra of the chiral Borromeates show intense Cotton effects at 224 and 239 nm, attributed to the stereogenic centres appended to the bipyridyl ligand. Most unusual are the intense bands that are also evident at 272 and 310 nm, at which the free ligand is optically inactive. These high-energy absorptions are a consequence of the chiral coordination sphere around the zinc ions, induced by the nearby chiral centres on the bipyridyl ligand. These chiral coordination spheres were most easily observed in the X-ray crystal data, where the chiral ligands appear to wrap around the metal in a helical, hence chiral fashion. Furthermore, the distorted octahedron around each of the six zinc ions deviates substantially from the ideal octahedron observed, in the X-ray crystal data, around each of the zinc ions in the achiral Borromeates.

13 A molecular Solomon link

The topology holding the common name of King Solomon's 'Knot', is described mathematically as a 'link' – or, more precisely, the 4_1^2 link – since it contains four crossings and is comprised of two components. The template-directed synthesis (Fig. 30) of a molecular Solomon link was recently obtained[49] from a 12-component self-assembly process that exploits dynamic covalent chemistry to form eight imine bonds and 24 dative bonds associated with the coordination of two doubly interlocked macrocycles, each tetranucleating and decadentate overall to a total of two Zn(II) and two Cu(II) ions on the average. The two macrocycles present, diagonally in pairs, four *exo*-bidentate bipyridyl and four *endo*-diimino-pyridyl ligands to the four metal ions. This unexpected topology was obtained by altering the conditions of the highly

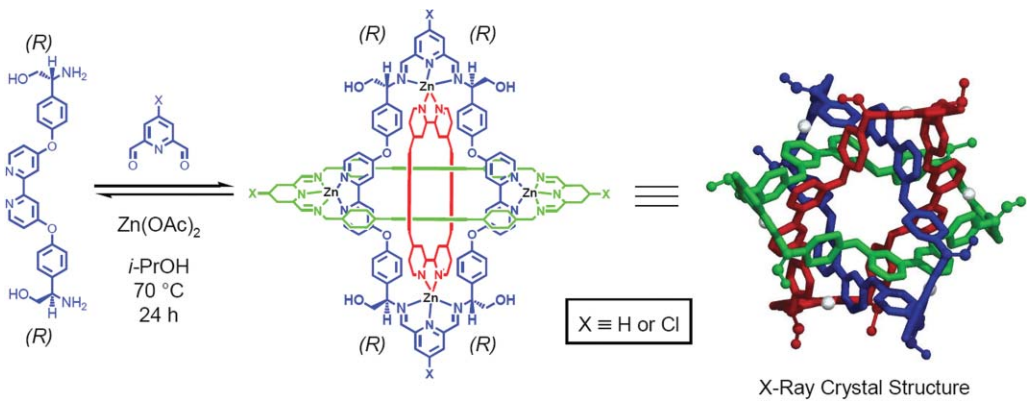


Fig. 29 Synthesis and X-ray crystal structure of a chiral Borromeate formed from the zinc(II)-templated imine condensation between a chiral *exo* diaminobipyridyl ligand and an *endo* diformylpyridine ligand.

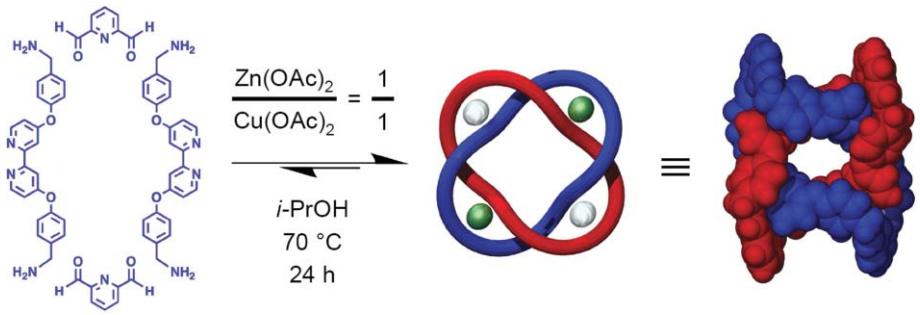


Fig. 30 In the presence of Cu(II) and Zn(II) in a 1 : 1 ratio, diaminobipyridine and diformylpyridine form a molecular Solomon knot, which can be amplified and isolated upon crystallisation.

successful molecular BR synthesis templated by Zn(II) ions to incorporate a mixed template protocol. Specifically, in the presence of *equimolar amounts* of Zn(II) and Cu(II) ions, the molecular Solomon Knot becomes one of the thermodynamic products in solution, and the exclusive product in the solid state. Upon obtaining single crystals, X-ray crystallographic data were obtained repeatedly for the Solomon Knot, yet upon dissolving each crystal in MeOH, the HR-ESI-MS revealed that the mixed-metal Cu/Zn Borromeates are competing with the Cu/Zn Solomon Knots in solution. These experimental results led to the conclusion that the molecular Solomon link was amplified by the act of kinetically-controlled crystallisation from a DCL of molecular knots.

14 Summary

Although the chemistry of Schiff's bases has been investigated to the point of near exhaustion over more than a century now, it is only very recently that the dynamic character of the imine bond has been exploited in organic synthesis. The imine bond is one of the very few covalent bonds to extol the virtues of reversibility, proofreading and error checking. The coupling of the dynamic covalent chemistry of the imine bond with the dynamic nature of dative and noncovalent bonds allows a template-directed protocol to be applied to the synthesis of some quite complex and exotic molecular compounds in extraordinary high yields under thermodynamic control. The rediscovery of the chemistry of the imine bond in the context of dynamic covalent chemistry will bring many new and complex molecular compounds into being in the next few years.

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