

Locking self-assembly: strategies and outcomes

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In the last ten to fifteen years, self-assembly has been increasingly employed to construct discrete supramolecular structures. In most cases, due to the thermodynamic factors that drive the self-assembly process, the final architectures produced by this approach are not kinetically robust. Thus, when robust structures are required a “self-assembly followed by covalent modification” strategy has been commonly applied. However, over the last decade an alternative strategy has emerged. Several methods for “locking” self-assembly, and thus yielding kinetically inert products have been developed. This review outlines the main strategies that have been employed towards such aims and describes some of the properties that result from the enhanced stability of product architectures.

1 Introduction

As far back as the 1950s it was suggested that, to maximize efficiency and minimize errors, growth of biological systems must involve a process similar to motor-vehicle assembly, whereby sub-assembled molecular components are fitted together into a “final product.” However the concept of molecular self-assembly as physical scientists understand it today first emerged from molecular biology studies on viruses in the 1960s and it was subsequently used to explain the formation of structures as diverse as membranes and bacterial flagella.¹

The most fundamental definition of self-assembly is the spontaneous formation of higher order structures from simpler building blocks. This definition implies a thermodynamically driven process close to, or at, equilibrium. In contrast with the kinetic regime familiar to standard covalent syntheses, these conditions - where entropy-enthalpy compensation effects predominate - often yield discrete highly complex, architectures.² In many ways, the paradigm of this process is presented

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structure of functional molecular architectures.

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by the much studied self-assembly of the tobacco mosaic virus, TMV.

TMV virions were the first systems to be shown to self-assemble *in vitro*. They consist of a single RNA strand, around 6400 nucleotides long, surrounded by a right-handed single helix coat protein made up of approximately 2130 protein sub-unit building blocks – Fig. 1. These components only assemble into the “correct” structure at specific pH, ionic strengths and temperatures, and a move away from these conditions results in their disassembly.³ Clearly, such processes involve kinetically labile components.

In the last few decades, many of the lessons learnt from systems such as TMV have been applied to the abiotic architectures created by supramolecular chemistry. This work is developing in the context of attempts to access what has now become known as nanotechnology – the design of devices and materials at the molecular scale. As the multiple possibilities inherent in this approach have been realised, exploration of possible “bottom-up” construction strategies has burgeoned. For the reasons outlined above, much of this work has

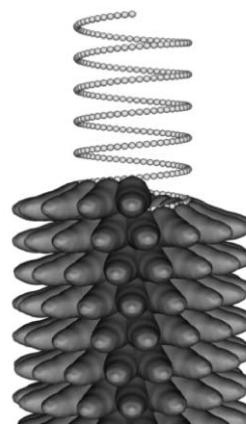
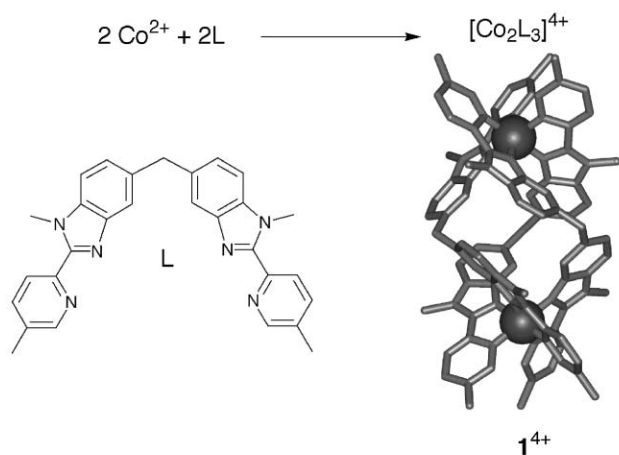


Fig. 1 Details of the structure of TMV, showing protein coat cut away to reveal the encapsulated single RNA strand. Image courtesy of Dr Peter Sforza, Virginia Polytechnic Institute and State University.



Scheme 1 Synthesis of a triple helicate based on Co^{II} metal ion templates.

involved kinetically labile moieties. However in many cases – for example, the construction of molecular hosts, sensors, and components for molecular electronics and devices – it would be advantageous to allow labile building blocks to assemble and then, when the target structure is obtained, “lock” to create a kinetically robust architecture.

The first method exploited in pursuit of this latter goal, involving self-assembly followed by covalent modification, has been pursued, amongst others, by the Stoddart and Sauvage groups who have used this strategy to construct interlocked functional molecular architectures.^{4,5} However, this method often requires judicious selection of specific reactions and very careful, not to say demanding, design of components that participate in the final covalent steps.

An emerging alternative strategy involves construction by self-assembly followed by whole-system switching into the kinetic regime, thus “locking” the resultant architecture into a structurally resilient entity.

This review restricts itself to self-assembling systems that are plainly under thermodynamic control, producing locked products that can be easily isolated. The various strategies

that have been used for locking and examples of the novel properties that arise from such systems are also discussed.

2 Locking strategies involving coordination chemistry

2.1 Electrochemical locking

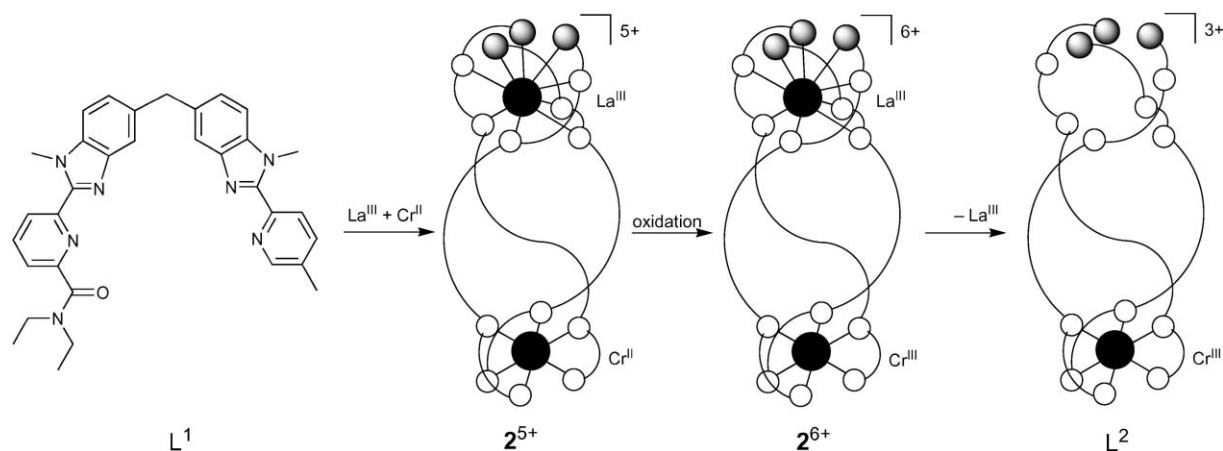
The first example of intentional kinetic locking came from the work of Williams and co-workers⁶ during their studies on helicate complexes.

In their research the Swiss based group found that by using relatively simple achiral ligands with more than one metal binding site, and various classically labile metal ion templates, the targeted assembly of both double and triple helicates could be realized. This process resulted in racemic mixtures of both right- and left-handed helices. In 1994, a method for the separation of enantiomers of the triple helicates was described, using a well-known characteristic of cobalt coordination chemistry often alluded to in undergraduate text-books: as a d^7 metal centre, Co^{II} is a labile octahedral system, whereas Co^{III} has a low spin d^6 electron configuration and is a classical example of an inert octahedral metal centre.

Using Co^{II} templates, a triple helicate, $\mathbf{1}^{4+}$, was assembled in high yield – Scheme 1. Subsequent oxidation yielded the Co^{III} based helicate, $\mathbf{1}^{6+}$. The enantiomers of this complex are kinetically locked and readily separated using simple chromatographic techniques.⁶

By extending this approach, Piguet and co-workers⁷ have isolated chirally pure triple helicates incorporating lanthanide ions. Using the compartmental ligand \mathbf{L}^1 , a racemic mixture of the heterodinuclear $\text{Ln}^{\text{III}}/\text{Cr}^{\text{II}}$ triple helicate $\mathbf{2}^{5+}$ was prepared in one step – Scheme 2. Aerial oxidation results in the formation of $\text{Ln}^{\text{III}}/\text{Cr}^{\text{III}}$, $\mathbf{2}^{6+}$, in which the d-metal centre, and consequently the coordination geometry around it, is kinetically locked.

Ln^{III} decomplexation produced a kinetically locked, optically active, triple-helical ligand, \mathbf{L}^2 with a pre-organised nonadentate coordination site. This ligand was resolved using cation exchange chromatography and reaction of the separated enantiomers with Ln^{III} ($\text{Ln} = \text{Eu}, \text{Gd}$ and Tb) resulted in



Scheme 2 Self-assembly of heterobimetallic triple helicates $\mathbf{2}^{5+}$, followed by oxidation to give inert $\mathbf{2}^{6+}$, and Ln^{III} decomplexation to give a preorganised nonadentate coordination site in \mathbf{L}^2 .

the synthesis, isolation, and structural characterisation of enantiomerically pure d-f helicates.⁷

2.2 Thermal unlocking of inert metal centres

In a number of specific cases, conditions that “unlock” normally kinetically inert metal centres have been developed. In 1995 Fujita and co-workers described the first example of this approach.

2.2.1 Pt^{II} systems. Previously, using a suitably hindered Pd^{II} template, *i.e.*, [Pd(en)]²⁺ (where en = ethylenediamine) the Japanese group had reported on the self-assembly of a square macrocycle, **3a**, which is a host for electron rich aromatic molecules in water. The fact that the complex is the genuine thermodynamic product of a rapidly equilibrating mixture was illustrated by its disassembly on changes in the stoichiometry of construct components.

Using the same metal ion “assembler”, but different ligand “connects,” Fujita *et al.* have used the same approach to assemble a spectacular array of 2-D and 3-D cages and molecular architectures, including interlocked macrocyclic structures such as catanane **4a** and a large M₆L₄ cage **5a** – Scheme 3. Like **3a**, all these structures were found to be kinetically labile. So, for example **4a** is only seen in solution at high concentration regimes, while at lower concentrations, unlinked macrocycles are observed.⁸ In contrast, use of a Pt^{II} template produced considerable changes in the conditions required for self-assembly and the kinetic properties of the final products.⁹

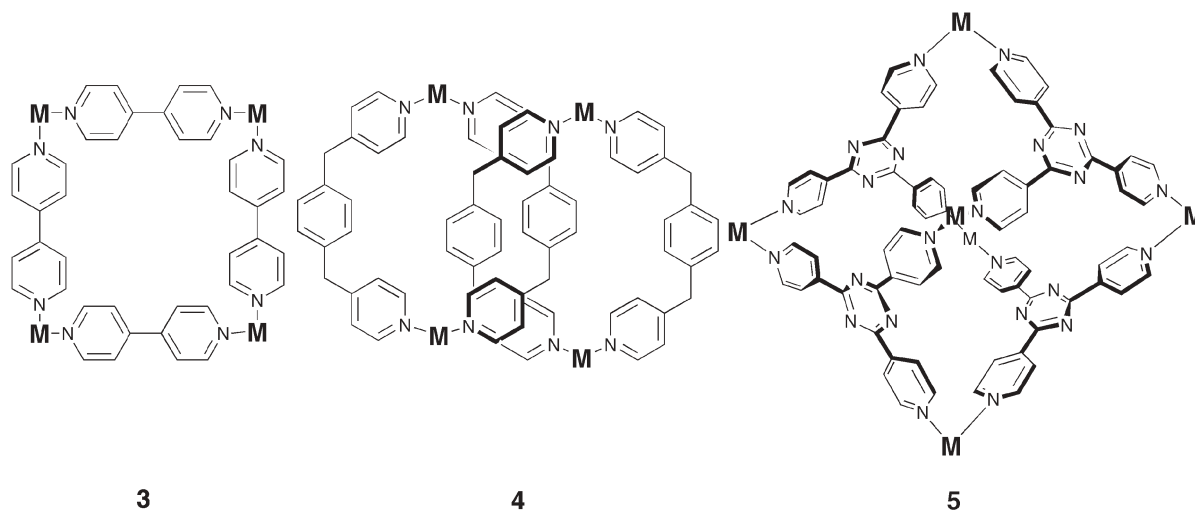
As a third-row transition metal centre Pt^{II} is considerably more kinetically inert than Pd^{II}; while Pd^{II}-N bonds to nitrogen heterocycles such as pyridine are fluxional, the equivalent Pt^{II}-N bonds are kinetically robust and at room temperature they form an irreversible linkage. However, at elevated temperatures and in high ionic strength solvents, such as aqueous 5 M sodium nitrate solutions, the Pt^{II}-N bond becomes sufficiently labile for equilibration towards thermodynamic products to occur. Consequent cooling and lowering of ionic strength “relocks” the Pt^{II}-N linkage thus producing

kinetically robust molecular architectures. This approach was initially used to construct locked macrocycle **3a** and catanane **4b**. The kinetic stability of these structures was confirmed by the observations that in contrast to **3a**, complex **3b** does not disassemble on addition of reaction components, and that **4b** can be isolated from solution as a crystalline product whose structure was confirmed by X-ray studies.^{9a} A variation on this method was employed to construct cage **5b**.

Initially it was found that, even at high temperatures, self-assembly of **5b** was not high yielding with significant amounts of oligomeric kinetic products also being produced. In this case efficient assembly also requires guest templating. In the presence of sodium adamantancarboxylate, a known guest for **5a**, self-assembly preceded smoothly in a high-yielding manner. Once **5b** was locked through cooling to room temperature, the guest could be removed and the empty cage was isolated in good yields. In contrast to **5a**, which decomposes in the presence of acids or bases, **5b** is structurally resilient over a large pH range from pH < 1 to pH > 11. This has allowed **5b** to display a number of unusual functions; for example, the nanocage acts as a pH responsive host.

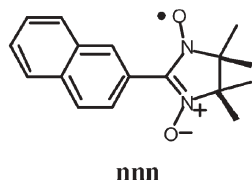
In neutral solutions, the guest *N,N*-dimethylaniline is included into the macrocyclic cavity in a 1 : 4 host : guest ratio, but when the solution is strongly acidified, NMR studies reveal that decapsulation of the protonated guest occurs. This phenomenon, which is thought to occur due to cation-cation repulsion and a decrease in favourable hydrophobic interactions, is reversible as lowering pH results in re-encapsulation of the guest.^{9b} An extension of this work has led to systems with switchable spin states.

After it was found that two molecules of the radical 2-naphthyl nitronyl nitroxide, **nnn**, are so closely enclathrated by host **5** that their singlet spin states interact to produce a triplet state, the effect of pH on the **5b**·(**nnn**)₂ assembly was investigated. Below pH 1.4 the triplet signal is completely repressed because at low pH the radical is protonated. The cation **nnn**H⁺ is thus expelled from the central cavity of **5b** due to unfavourable coulombic interactions and a decrease in hydrophobicity. However, the triplet signal returns if the pH is

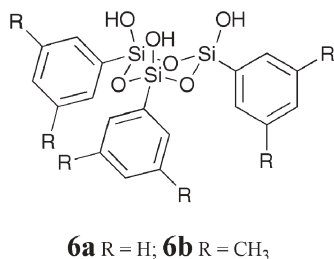


Scheme 3 Square-planar metal-ion templated cages **3a**, **4a** and **5a**, M = Pd^{II}; **3b**, **4b** and **5b**, M = Pt^{II}.

raised to 6.5 as deprotonated **nnn** is regenerated.¹⁰ Other studies on **5b** involved ‘ship-in-a-bottle’ syntheses within the macrocyclic cage.



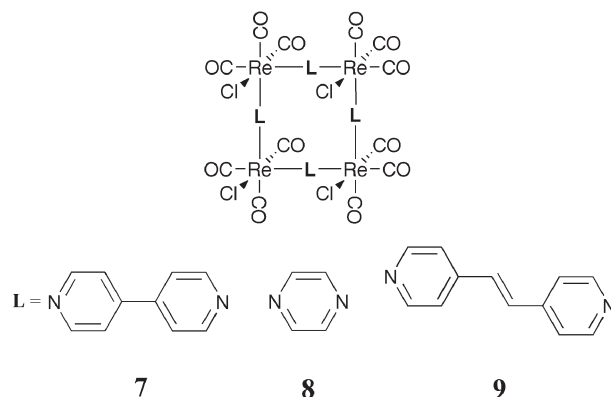
Cyclic siloxanes are unstable, short-lived intermediates in the polycondensation of trialkoxysilanes. Their isolation is important in the understanding of the condensation process and also as models of silica-gel surfaces. However, the instability of these species means that they have rarely been isolated. In direct contrast to this usual behaviour, the hydrolysis of phenyltrimethoxysilane in aqueous solutions of **5b**, results in the production of cyclic siloxane **6a**, as part of a host–guest complex **5b·6a** that can even be isolated as an air-stable solid. The entrapment of **6a** within the host cavity of **5b** was confirmed by unsuccessful attempts at solvent extraction using chloroform. Furthermore, when a bulkier aromatic unit is attached to the Si, ¹H NMR studies revealed that the rotation of the resulting cyclic siloxane, **6b**, within the host is highly restricted. Thus the **5b·6b** assembly displays C₃ symmetry.



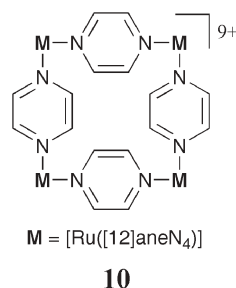
Remarkably, in stark contrast with the usual properties of these short-lived highly reactive species, the encapsulated cyclic siloxane are not only stable in solution for periods over a month, they are also tolerant of very acidic (pH < 1) conditions.¹¹

2.2.2 Re^I systems. As a low-spin d⁶-system of a third-row transition metal Re^I is a classically inert metal centre. However, despite this fact, Re^I moieties are some of the most used metal templates in the construction of discrete metallo-macrocyclic architectures.

Although the Hupp group first reported the assembly of kinetically-locked Re^I building blocks using Pd^{II} centres (*vide infra*), the conditions required for the construction of macrocycles exclusively containing Re units were rapidly delineated. Hupp and colleagues reported that the 1 : 1 reaction of [ReCl(CO)₅] with suitable ditopic pyridyl based bridging ligands at high temperatures in toluene–THF solvent mixtures yields analytically pure macrocyclic squares such as **7–9**.¹² Given that the yields are in excess of 95% it seems likely that these squares are the product of true thermodynamically driven self-assembly, indicating that in these conditions the metal centre is kinetically labile.



There are a number of factors that enhance the lability of the Re^I-centre in these reactions. Firstly, the carbonyl groups are classically strong *trans*-labilising ligands. Secondly, the reaction is carried out at high temperature and thirdly the solvent contains THF, which is capable of weakly coordinating to Re^I-centres and so stabilize unsaturated intermediates in the self-assembly process. A large number of studies have been carried out on such systems. Unlike many other architectures, the metallomacrocycles assembled using these building blocks are neutral and, since they do not require any charge compensating anions that may block the central aperture, they are particularly suited to the construction of thin-films that have been used for molecular sieving and nano-filtration.¹³



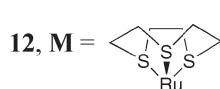
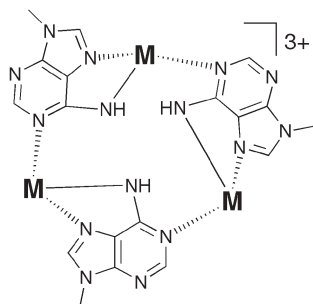
2.2.3 Ru^{II} systems. Despite their rich electrochemistry and photophysics, much less work has involved self-assembling Ru^{II}-based systems; this is probably due to a lack of suitable building blocks. However, there are a few notable examples involving macrocycle coordinated metal centres.

In 2002, the Long group reported on the use of the nitrogen donor macrocycle ligand 1,4,7,10-tetraazacyclododecane as a blocking group for four sites of octahedral Ru^{II}. By imposing a *cis*-coordination geometry onto the two remaining sites of the metal centre and employing the ditopic ligand pyrazine complex **10** a tetranuclear macrocyclic square analogue of the much studied Creutz–Taube ion was isolated in almost quantitative yield. Crystallographic studies revealed that although macrocycle [10]Cl₉ is formally a mixed valent, MV, [Ru^{II}₃Ru^{III}] system, each metal centre has identical coordination geometry. This indicates that **10**⁹⁺ is actually valence delocalised with four equivalent Ru^{2.25+} centres. Electrochemical studies revealed that it was possible to access the two other MV states available to this system; **10**¹⁰⁺ (formally [Ru^{II}₂Ru^{III}₂]) and **10**¹¹⁺ (formally [Ru^{II}₃Ru^{III}]).

Comproportionation constants derived from the electrochemical data are also consistent with the postulate that 10^{9+} is valence delocalised Robin and Day class III system ($K_c \approx 10^9$) while 10^{10+} and 10^{11+} seem to display a much lower degree of interaction ($K_c = 10^2$ and 10^3 respectively). However, optical studies on this system were less conclusive, with IR spectroscopy offering ambiguous evidence of valence delocalisation and no definitive intervalence charge transfer, IVCT, in the near-infrared being observed.¹⁴

In analogous work, the Thomas group has employed the facially blocked octahedral fragment $[Ru^{II}([9]aneS_3)]$ which incorporates a thiacycrown ligand in self-assembly processes. In this case, for steric and electronic reasons, pyridyl-based ligands coordinated to this moiety are unusually labile, particularly at high temperatures. However, in ambient conditions, structures incorporating this building block can be kinetically robust. This is illustrated by recently reported work on Ru^{II} bowls, architectures that were inspired by the elegant studies of Fish and co-workers on the self-assembly of trinuclear rhodium-based metallomacrocycles.¹⁵

In aqueous solutions, using $[cp^*Rh^{III}]$ moieties ($cp^* =$ pentamethylcyclopentadienyl) as templates and suitably hindered nucleobases such as 9-methyladenine as bridging ligands the Fish group observed that over a specific pH range self-assembly of trinuclear bowls, **11**, took place at room temperature. Further studies on these and related Ru and Ir triangular structures confirmed that such metallomacrocycles are indeed kinetically labile¹⁶ and can even be used to construct dynamic combinatorial libraries, DCLs¹⁷—for further information on the DCL concept *vide infra*.

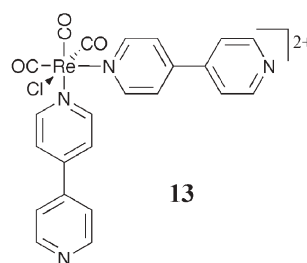


In contrast to these observations, self-assembly of similar structures templated by the $[Ru^{II}([9]aneS_3)]$ fragment only occurs at elevated temperatures after more prolonged reaction times. Furthermore, in contrast to the previous reported macrocycles, which show irreversible electrochemistry, complex **12**—which is isolated as a $[Ru^{II}_3]$ system—can be oxidised at ambient temperatures in three reversible steps, thus producing two different MV states. Again, comproportionation constants derived from the electrochemical data suggest that these two states have contrasting electronic properties, with K_c for 12^{4+} , which is formally a $[Ru^{II}_2Ru^{III}]$ state being 8×10^2 , and K_c for 12^{5+} , which is formally a $[Ru^{II}Ru^{III}_2]$ state being 3×10^6 . However, in this case, spectroelectrochemistry

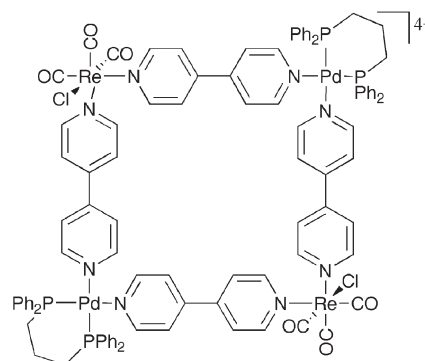
studies reveal clearly resolved IVCT bands in the near-infrared for both 12^{4+} and 12^{5+} . Analysis of the IVCTs using Hush theory confirms that 12^{4+} is a valence localised, electron hopping, Robin and Day class II system, while 12^{5+} is a valence delocalised class III system. Clearly, systems such as **10** and **12** have potential as prototypical multistate electron transfer switches.¹⁸

2.3 Self-assembly of pre-synthesized locked components

In this approach kinetically locked metal complexes with the required connective geometry and/or function are synthesised as a building block for self-assembly and then using a “complexes as ligands” approach another metal centre is used as the templating “assembler.” One of the first examples of the intentional use of this strategy comes from the early work of the Hupp group on Re^I based metallomacrocycles.



13



14

Following the synthesis of complex **13** through the reaction of $[Re(CO)Cl]$ with 4,4'-bipyridine, 4,4'-bpy, this locked “corner” was reacted with $[Pd(dppp)(tf)_2]$ ($dppp =$ 1,3-(diphenylphosphino)propane; $tf =$ triflate) to yield the cationic macrocycle **14**. The incorporation of luminescent corners into this complex results in a functional architecture. Addition of anions to acetone solutions of **14** produces an increase in luminescence intensity that is dependent on the binding affinity for a given anion, with BF_4^- ($K_b = 6000 M^{-1}$) producing much larger intensity change than ClO_4^- ($K_b = 900 M^{-1}$).¹⁹ In this case it should be emphasised that although the Re^I moiety is inert, the Pd^{II} -linking motif is a kinetically labile “weak-link.” However, using a similar strategy, more structurally complex systems showing higher kinetic stabilities have been constructed.

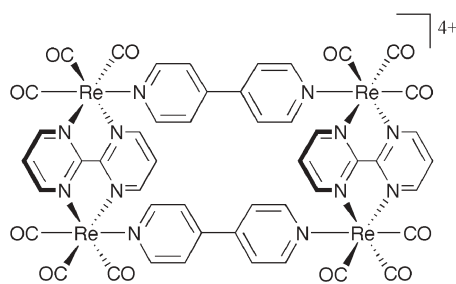
To enhance selectivity and binding affinities for planar aromatic guests, the synthesis of molecular rectangles was investigated. Initial attempts to synthesize tetrametallic

rectangles from mixtures of bridging ligands such as pyrazine and 4,4'-bipy together with $\text{Re}(\text{CO})_5\text{Cl}$, yielded a mixture of two squares rather than mixed bridging ligand rectangles. Therefore, a strategy involving the synthesis of dinuclear complexes as preformed, kinetically inert, 'edges' was investigated.

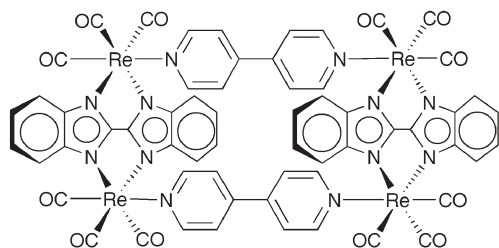
Preliminary studies involved $[\text{Re}(\text{CO})_4(\mu\text{-SR})]_2$ complexes as edges. These easily synthesized complexes are conveniently purified by column chromatography and reaction with suitable ditopic bridges, for example 4,4'-bipy, results in the assembly of molecular rectangles such as **15** – Scheme 4.

Unfortunately, X-ray crystallography studies revealed that the interplanar spacing in these systems is too small to permit the resulting cavity from functioning as receptor sites, even for planar molecules such as benzene.²⁰

However, by using dinuclear 2,2'-bipyrimidine (bpym) and 2,2'-bisbenzimidazolone (bibzim) based edges, a series of cationic and neutral rectangles such as **16** and **17** with larger cavities were produced.²¹ While both these latter macrocycles bind to aromatic guest molecules, the kinetically inert nature of the rectangles has also meant that in-depth electrochemical and electrooptic studies can be carried out on these architectures.

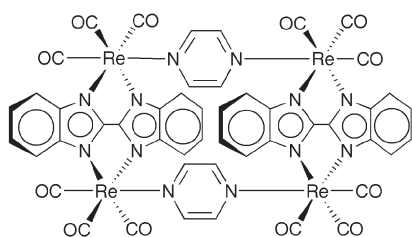


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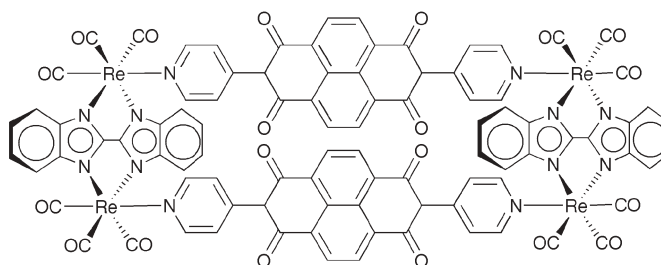


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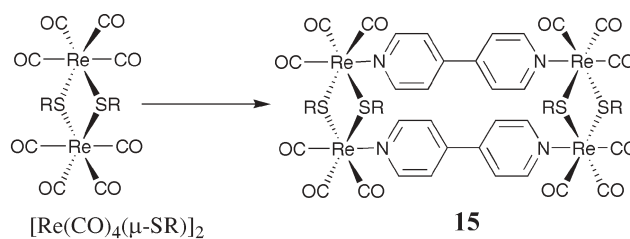
It was found that, in non-coordinating solvents, reversible bridging ligand-based reductions of these macrocycles occurs, involving the ditopic, monodentate bridges. This leads to the



18



19



Scheme 4 Synthesis of molecular rectangles using pre-synthesised $[\text{Re}(\text{CO})_4(\mu\text{-SR})]_2$ edges.

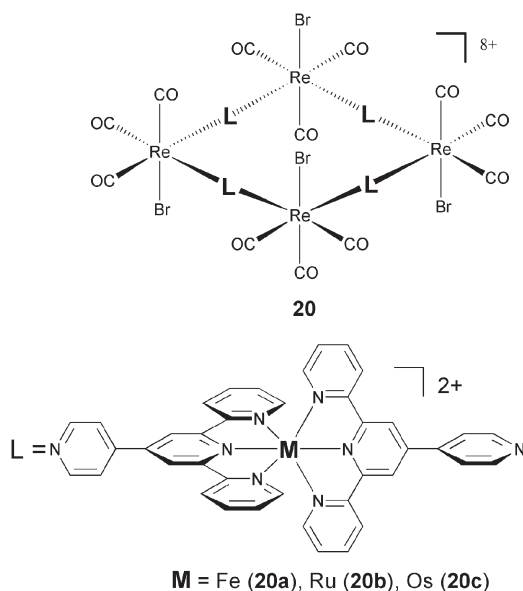
formation of *ligand-centred* MV (LCMV) states, as opposed to the more usually studied metal-based systems.

Electrochemical and optical studies on the LCMV rectangles, such as **17**⁻, revealed that, unlike metal-based systems where interactions are chiefly mediated by through-bond super-exchange mechanisms, electronic coupling between ligands involves direct donor orbital/acceptor orbital overlap. Thus although ligand positioning in **17** and its analogues is nominally identical, being defined by the $[\{\text{Re}(\text{CO})_3\}_2(\text{bibzim})]$ edge units, the extent of electron delocalization within the rectangles was found to be highly dependent on small changes in ligand orientation and separation distances. For example, although the LCMV state of **17** is a Class II system approaching valence delocalization, the LCMV-state of **18** is only weakly coupled as constraints imposed by ligand size and rigidity restrict favourable van der Waals contact between pyrazine units, while a decrease in cofacial overlap of ligands in the LCMV state of **19** means that it is effectively a Class I, non-communicating, fully valence-localized, system. In contrast, for rectangle **15**, co-facial distances between the redox active ligands approaches full van der Waals contacts and as a consequence its LCMV state is completely valence delocalised.²²

Rectangles **15**–**19** are all non-luminescent, however similar strategies involving the self-assembly of other suitable d^6 metal centres has led to kinetically locked heterometallic luminescent systems.

Lees and colleagues investigated the properties of molecular squares, **20**, that incorporate Fe^{II} , Ru^{II} , and Os^{II} centres coordinated to terpyridyl-based ligands as edges and are assembled using the standard Re^{I} -corner template. In this case, although it was found that the macrocycles display reversible metal-based oxidations and ligand-based reductions, there was no evidence of electronic coupling between the components. As has been reported for many terpyridyl-based complexes of d^6 metal centre, **20a** and **20b** are not emissive, although **20c** does display Os^{II} -based metal-to-ligand, ³MLCT,

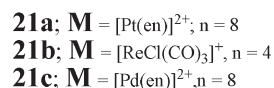
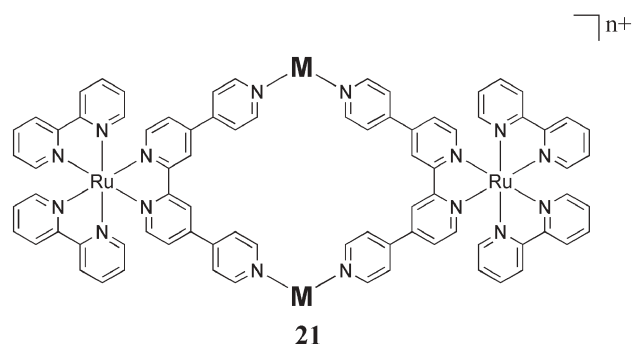
luminescence. These observations can be explained by a consideration of the energy gap between the emissive $^3\text{MLCT}$ state and a low-lying non-emissive ^3MC excited state, which is relatively accessible for **20a** and **20b**. Thus, the MLCT excited states of these latter complexes are deactivated *via* efficient nonradiative decay. In contrast, the stronger ligand field and lower oxidation potential of Os^{II} compared to Fe^{II} and Ru^{II} results in an increased energy gap between the $^3\text{MLCT}$ and ^3MC states. Therefore, because the ^3MC excited states of **20c** are not readily populated, emission from the $^3\text{MLCT}$ state is facilitated. These studies also revealed that the emission of **20c** is independent of the excitation wavelength, implying that energy transfer from higher lying excited states to the lowest energy Os -based $^3\text{MLCT}$ state is highly efficient. Despite these distinctive electrochemical and photophysical properties, it was found that none of the macrocycles functioned as host for anions in a manner analogous to complex **14**.²³



In more recent work, the Thomas group have investigated the properties of metallamacrocycles that contain luminescent units related to the much-studied $[\text{Ru}(2,2'\text{-bpy})_3]^{2+}$ cation embedded in their structure.²⁴ Using $[\text{Pt}^{\text{II}}(\text{en})]$ and $[\text{Re}^{\text{I}}(\text{CO})_3\text{Cl}]$ as “assembler” templates macrocycles **21a** and **21b** were obtained. NMR spectroscopy and electrochemistry studies confirmed that, in contrast to the Pd^{II} templated structure **21c**,^{24a} these former complexes are kinetically robust. As for **20c**, it is clear that energy transfer within all three systems is highly efficient, with Ru -based $^3\text{MLCT}$ luminescence occurring independent of the excitation wavelength.

Depending on the counter-anion employed the macrocycles can be rendered soluble in aqueous or organic solutions. Preliminary studies revealed that while they function as hosts for polyaromatic molecules in water and there are considerable changes in the absorbance spectra of the complexes on binding, there is no modulation in emission properties.^{24a}

In acetonitrile it was found that the macrocycle **21b** behaves in a manner that is somewhat similar to **14**, functioning as luminescence-based sensors for anions. A comparison of three anions, BF_4^- , BPh_4^- , and SO_4^{2-} , with similar tetrahedral



symmetry but differing charge or size reveals distinct binding preferences. As might be expected, electrostatic interactions play an important role in this recognition process, with SO_4^{2-} being bound with a much higher affinity ($K_b \approx 7200 \text{ M}^{-1}$) than BF_4^- ($K_b = 1575 \text{ M}^{-1}$). Nonetheless, the relatively high affinity for BPh_4^- ($K_b \approx 3000 \text{ M}^{-1}$) suggests that π - π interactions can also contribute to the binding process.^{24b}

3 Locking organic chemistry

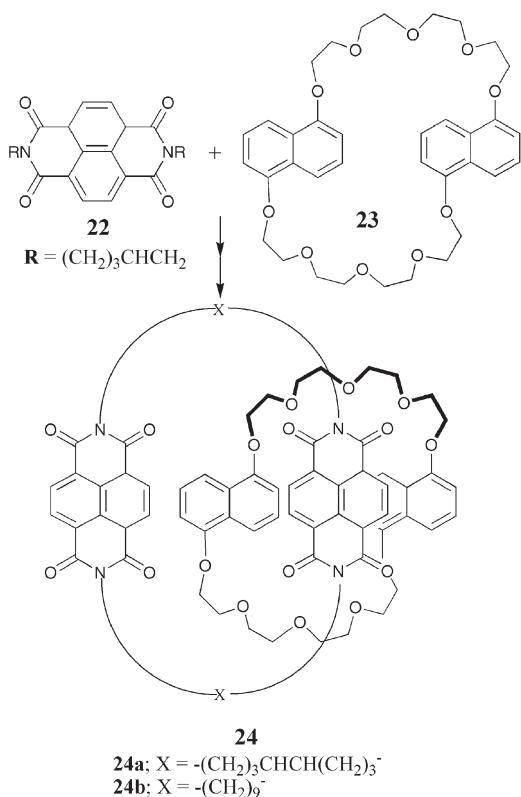
As previously outlined, most covalent chemistry – typified by traditional organic synthesis – is in the kinetic regime and therefore, until recently, the isolation of thermodynamically driven products was not common. However, in recent years several groups have outlined strategies involving switchable covalent linkages.

Dynamic covalent chemistry, DCC, is an area of rapidly expanding interest that has been facilitated through the judicious selection of specific reactions used in the creation of intra-assembly linkage. For an authoritative and exhaustive account of this approach the interested reader is directed to a recent review.²⁵ Herein, examples of the reactions typically employed for DCC are outlined.

The first intentional approaches to locked self-assembly *via* DCC involved the use of an olefin metathesis catalyst to control reversible ring closing (RCM) reactions in the construction of catananes. In 1998 Sanders and co-workers outlined how Grubb’s catalyst could be used to prepare neutral π -associated [2]catenanes under thermodynamic control.²⁶

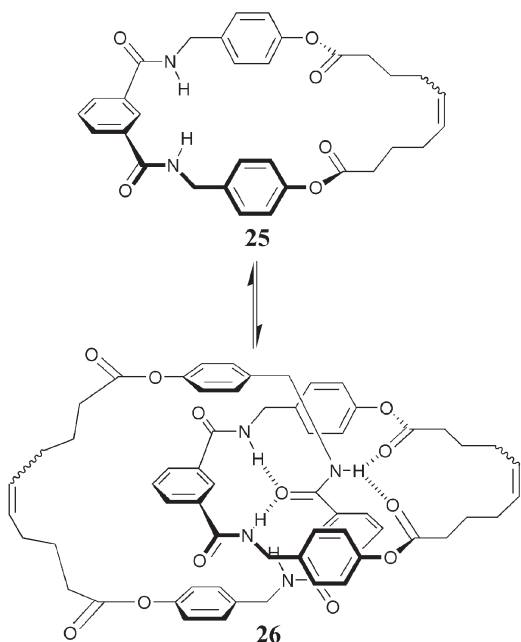
The group synthesised electron deficient aromatic diamides, such as **22**, containing olefin-terminated alkyl substituents. When two equivalents of **22** were added to macrocycle **23** in the presence of Grubb’s catalyst the formation of catananes such as **24a** (as a mixture of the *cis/cis cis/trans* and *trans/trans* isomers) was observed, which yielded a single saturated catanane, **24b**, on catalytic hydrogenation – Scheme 5.

In somewhat related work the Leigh group investigated a “magic ring” system where Grubb’s catalyst was used to mediate ring-opening and ring-closing metathesis and thus equilibrate macrocycle **25** with locked catanane **26** – Scheme 6. It was found that product ratios in this reaction were concentration dependent: at low concentrations only the simple macrocycle was detected, but at a concentration of $0.2 \text{ M} > 95\%$ of the mixture was found to be the catanane.



Scheme 5 Aromatic building blocks and resultant catananes constructed using dynamic covalent chemistry.

As might be expected, removal of the catalyst suppresses olefin metathesis and therefore locks the reaction, freezing the product distribution at the ratio obtained in the presence of the catalyst. However dilution followed by addition of catalyst does result in a redistribution of the product mixture. The

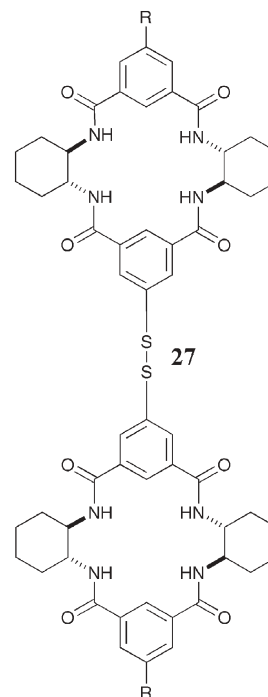


Scheme 6 "Magic ring" synthesis of catananes by DCC, catalysed by Grubb's catalyst.

catanane can also be disassembled at any concentration by trifluoroacetylation of the macrocycle amide bonds before the introduction of catalyst, as this switches off the inter-macrocycle hydrogen bonding used to assemble the catanane. These observations confirm that such catalysed assembly processes are truly under thermodynamic control.²⁷

Another linker that lends itself well to DCC systems is the disulfide bond, which is readily formed from thiols in the presence of oxygen and small amounts of base, and although disulfide exchange takes place efficiently under mild conditions in the presence of a catalytic amount of thiol the linkage is locked in acidic conditions where exchange becomes negligible. The Still group first exploited these properties for DCC showing that the concentration of a disulfide linked ditopic receptor, **27**, for tripeptides could be amplified from a simple equilibrating mixture of three different disulfides.²⁸

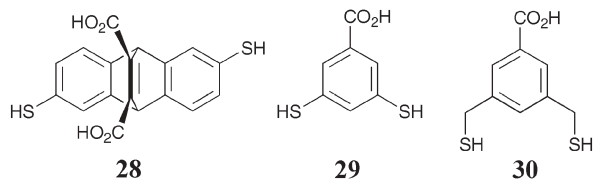
More recently Otto and Sanders have extended this approach to construct DCLs, in water.



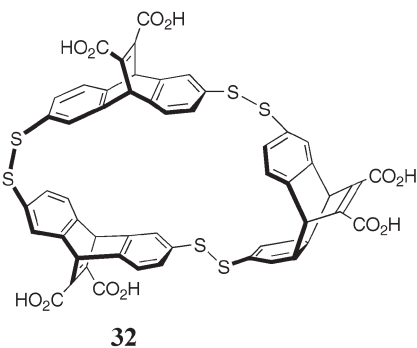
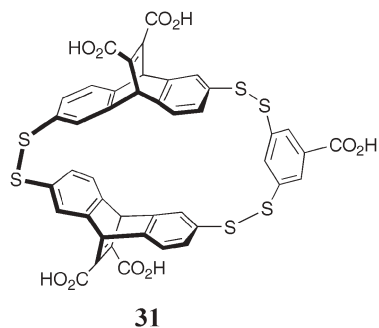
Put simply a DCL is a mixture of compounds that are undergoing continuous interconversion. Since the building blocks of a dynamic combinatorial library are labile, the molecular constructs of the library and its composition are governed by thermodynamics rather than kinetics.²⁹ Therefore, a DCL responds to external influences: a molecular recognition event selective for one member of the library will stabilize this member and amplify its presence within the library. For example, in Otto and Sanders work on disulfide based linkages, by mixing the three building blocks **28–30** a DCL consisting of at least 45 different detectable macrocyclic structures was created.

On addition of the anionic guest 2-methylisoquinolinium iodide diastereomers of one macrocyclic structure, **31**, are amplified. In contrast, addition of a structurally more complex guest, *N*-methylated morphine, leads to amplification of a

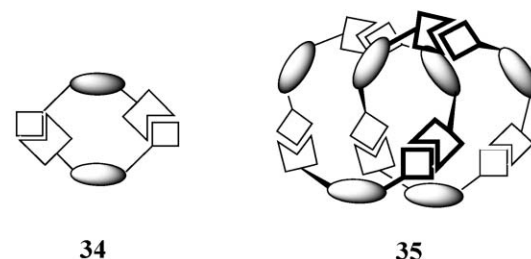
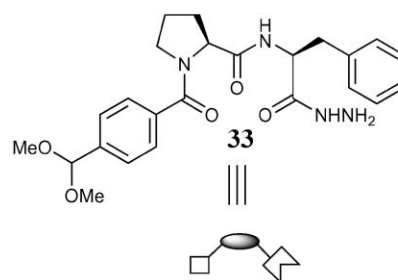
second macrocyclic host, **32**. In both cases, after self-assembly in the presence of the relevant host, a change in reaction conditions allows these hosts to be locked and isolated in good yields.³⁰



One of the most studied linkages for DCC and DCL construction is the C=N bond. Although Schiff bases have been investigated, the high sensitivity of such bonds towards hydrolysis means that a final step involving reduction to amines is often required.³¹ This may affect the structure and rigidity of the assembly; for this reason other more hydrolytically stable bonds such as oximes and hydrazones,^{29,32} where bond exchange only occurs in acidic conditions, have also been investigated. A recently reported study using such linkages is illustrative of the power of the DCL approach in revealing new and unpredicted recognition architectures.



The relatively simple peptide building block, **33**, results in a DCL containing a number of cyclic structures. Addition of acetylcholine to this dynamic system initially amplifies the [1 + 1] macrocycle, **34**. However, over a period of days an entirely new component, **35**, comes to dominate the library, eventually making up 70% of the equilibrating mixture. Spectroscopic studies on the locked and isolated product revealed that **35** is a single diastereoisomer of a catanane, composed of two interlocked [3 + 3] macrocycles! This structure is selected due to its high binding affinity for acetylcholine ($K_b = 1 \times 10^7 \text{ M}^{-1}$ in 95 : 5 CHCl_3 –DMSO).³³

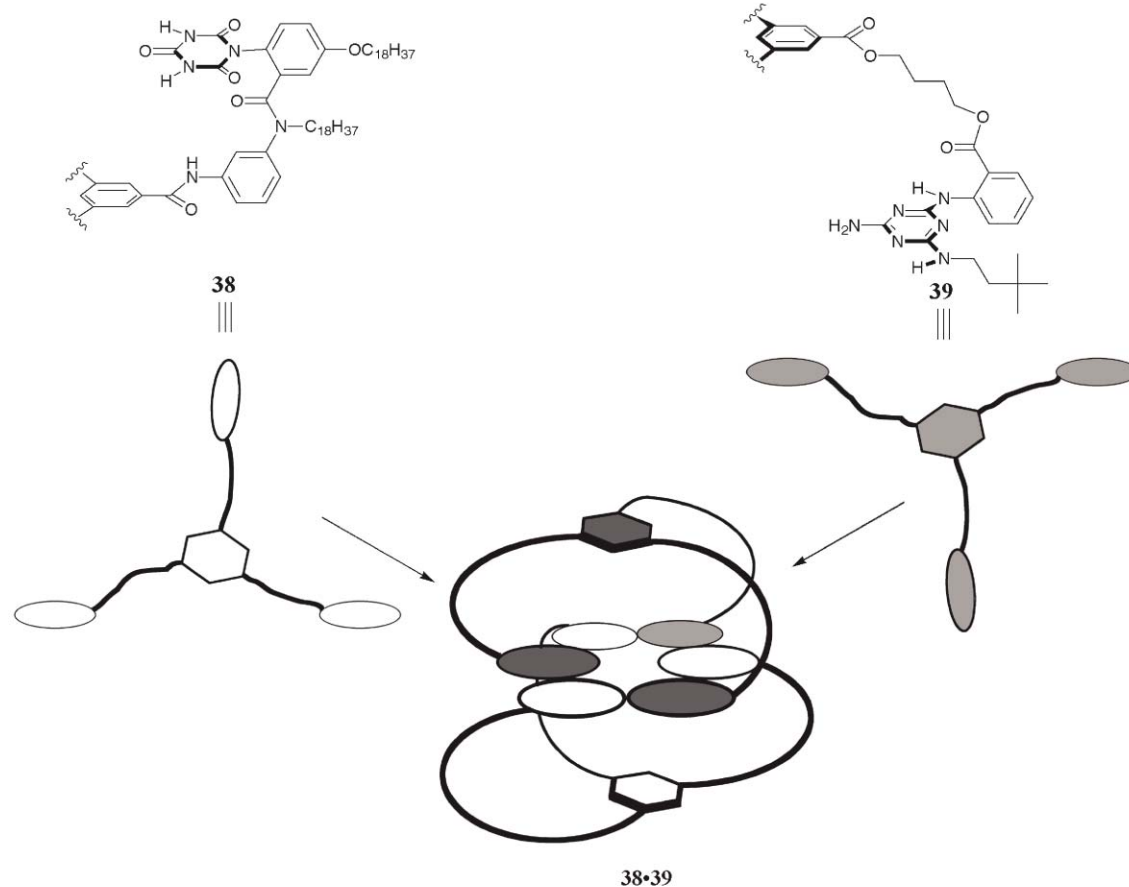
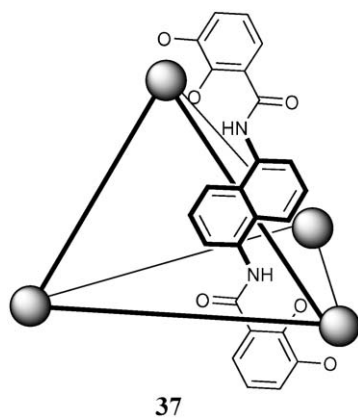
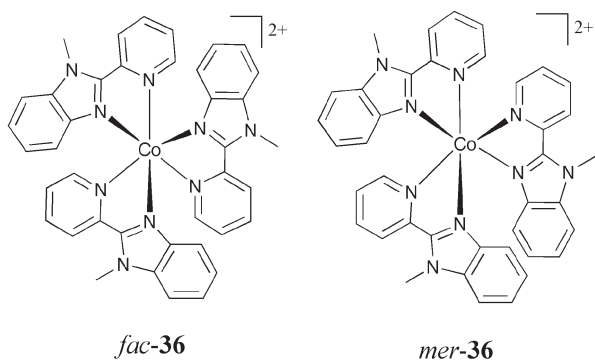


4 Locking *via* cooperativity

The most elegant examples of locked self-assembly occur when cooperativity between reversible interactions used to construct a thermodynamically selected assembly provides the locking mechanism in the final product. A macroscale analogy to this effect is seen in the behaviour of Velcro, where individual, easily reversible, interactions (between nylon hooks and loops) are collectively capable of providing firm fastening for garments.

The first suggestion that cooperative locking was possible in abiotic systems came from the Lehn group's work on metal ion templated helication processes. In 1993, the group reported on the Ni^{II} templated assembly of an oligonuclear triple helicate complexes. It was found that this system partially resolved into Λ - and Δ -enantiomers on crystallization and that racemisation of the normally labile Ni centre occurred 500 times more slowly than normally observed for monomeric systems.³⁴ Later studies on the previously discussed Co^{II} -based helicate, **1⁴⁺**, revealed more profound effects.

In a detailed NMR spectroscopy study, the Williams group discovered that the rate of racemisation of **1⁴⁺** is 10^5 slower than the rate of interconversion of the *mer* and *fac* isomers of the mononuclear analogue, **36²⁺**. This effect was attributed to the enhanced cooperativity inherent in the rigid **1⁴⁺** architecture, which means that each metal centre creates a preorganised site for coordination to a second metal ion.³⁵ This effect is observed to a still greater degree in a tetranuclear complex reported by the Raymond group. Using Ga^{III} metal ion templates to assemble inflexible C_2 symmetric bis-catecholate ligands, the group produced the chiral tetrahedral $[\text{M}_4\text{L}_6]$ assembly **37**. The ditopic rigid bridging ligands were designed so that if one metal centre is coordinated in an Λ or Δ configuration then a second metal centre must coordinate with the identical chirality. Thus, **37** is obtained as a racemic mixture of $\Lambda\Lambda\Lambda\Lambda$ and $\Delta\Delta\Delta\Delta$. In the presence of the chiral anion, *N*-methylnicotinium, which is encapsulated within the cluster cavity, homochiral $\Lambda\Lambda\Lambda\Lambda$ -**37** and $\Delta\Delta\Delta\Delta$ -**37** clusters were completely resolved.

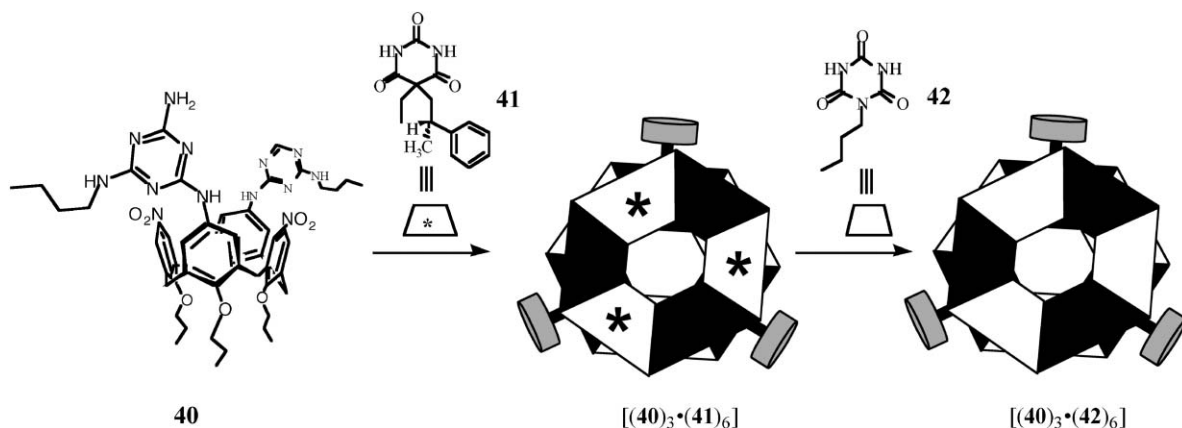


Furthermore, the entire tetrahedral assembly is so rigid that, in contrast to mononuclear tris(catecholate)gallium(III) complexes – where racemisation rapidly takes place *via* a Bailar twist mechanism – alkali aqueous solutions of homochiral **37** retain enantiopurity even when boiled.³⁶

Although the above examples are driven by coordination chemistry, hydrogen-bonding systems can display similar effects; for example, in 1993 Seto and Whitesides, reported on the properties of the [**38·39**] dimer whose assembly is driven by an array of 18 hydrogen bonds formed by melamine and cyanurate moieties – Scheme 7. Using ¹H NMR spectroscopy the exchange process between the dimer and a close structural analogue of **39** was monitored. It was found that [**38·39**] was extremely kinetically robust: at room temperature, even after a period of 16 h, exchange of **39** with its analogue was only 5% complete.³⁷

In more recent work, using related melamine–cyanurate hydrogen bonded motifs, the Reinhoudt group has isolated chirally pure assemblies from achiral building blocks. Starting with calix[4]arene **40**, the addition of the chiral barbiturate derivative **41** led to the enantiospecific assembly of [(**40**)₃·(**41**)₆]. The chirality of this assembly was retained even when **41** was replaced by achiral cyanurates such as **42** – Scheme 8. Indeed, it was found that racemisation of the [(**40**)₃·(**42**)₆] array is extremely slow with a half-life of 4.5 days being observed at room temperature.³⁸

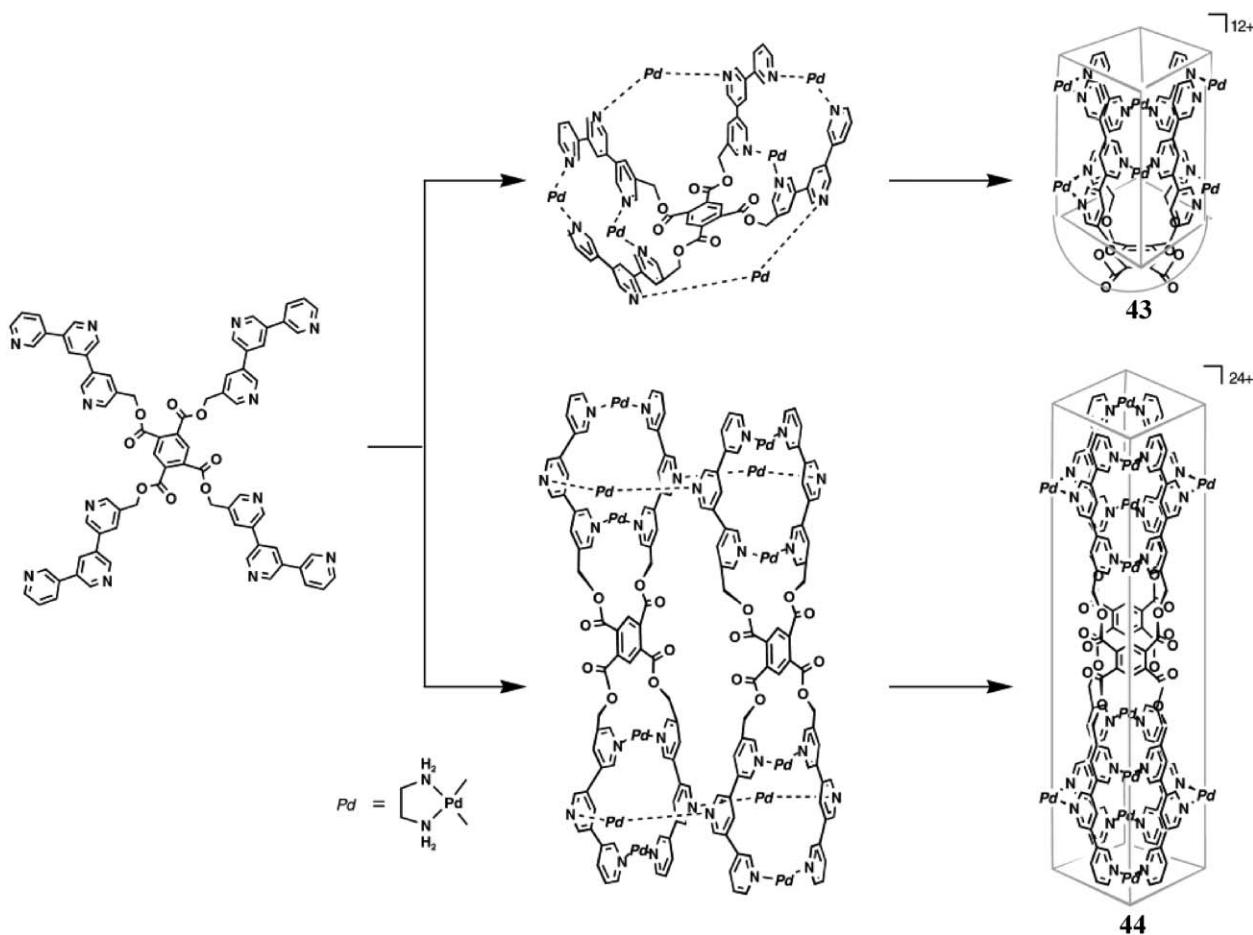
Scheme 7 Hydrogen-bonding drives the self-assembly of a dimer [**38·39**] that displays high kinetic stability. Adapted with permission from ref. 37.



Scheme 8 Two-step assembly of a chiral hydrogen bond assembly composed of achiral building blocks. (Adapted with permission from ref 38b. Copyright 2000, Macmillan Publishers Ltd: Nature.)

Finally, a fascinating example of the complex interaction between thermodynamics and kinetics in self-assembly processes comes from the Fujita group's work on nanotubes. In an extension of previous work that had led to the assembly of open tubes,³⁹ and using the previously mentioned Pd^{II} template, the group targeted the construction of an end-capped structure, **43**, from a specifically designed ligand – Scheme 9. It

was found that assembly of this structure requires templating by the guest, 4,4'-dimethylbiphenyl. Once assembled, the host is kinetically robust: exchange with the asymmetric guest sodium biphenylcarboxylate occurs efficiently with the hydrophobic biphenyl group of the new guest included deep within the tube and the hydrophilic carboxylate group exposed to the solvent. When this exchange was carried out at high



Scheme 9 Self-assembly of a kinetically robust end-capped structure **43** occurs in the presence of the template 4,4'-dimethylbiphenyl. However, under certain specific conditions, a second kinetically trapped species, **44**, can also be isolated from the reaction mixture. (Reprinted with permission from ref. 40, Copyright 2003, Wiley-Interscience.)

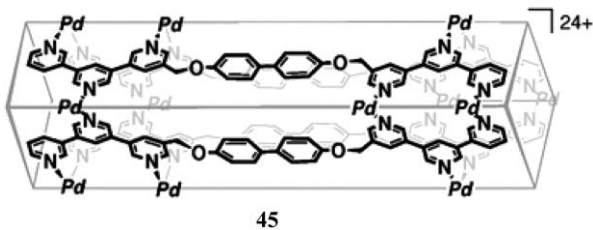


Fig. 2 Adapted with permission from ref. 41.

concentrations NMR spectroscopy revealed the presence of a new minor component, **44**, in solution.

Slow evaporation of the reaction mixture led to isolation of single crystals of **44** and an X-ray analysis revealed that this product is in fact a 3.0 nm double open tube composed of two ligands linked together by twelve metal centres in which the central cavity is filled by two molecules of biphenylcarboxylate, each with their carboxylate residue pointing out of the tube. Surprisingly, when crystals of this structure are dissolved in water no conversion back to **43** occurred even over a period of a month. The researchers concluded that *both* **43** and **44** are kinetically trapped structures that assemble from the component mixture under specific conditions.⁴⁰ Both these structures are only kinetically stable while hosting a molecular guest within their central cavity, but by extending this approach the Japanese group have more recently reported on a related assembly, **45** (Fig. 2), that is kinetically robust at room temperature even after removal of the guest required to template its assembly.⁴¹

Conclusions

The concept of locking self-assembled structures, which has only been applied to abiotic systems in the last decade or so, is now an established strategy for the construction of complex molecular architectures. As the examples outlined above illustrate, it has already been applied to a wide range of organic and inorganic systems. This approach has led to assemblies with novel electronic and photophysical properties as well as new hosts for molecular recognition. Notably, it has become one of the key features in the rapidly developing field of dynamic combinatorial libraries. While many locking strategies involve assembler functionalities that can be switched *via* changes in temperature, pH or redox chemistry, examples of assemblies locked by cooperative interactions alone show that even kinetically labile building blocks can be used in the construction of kinetically robust systems.

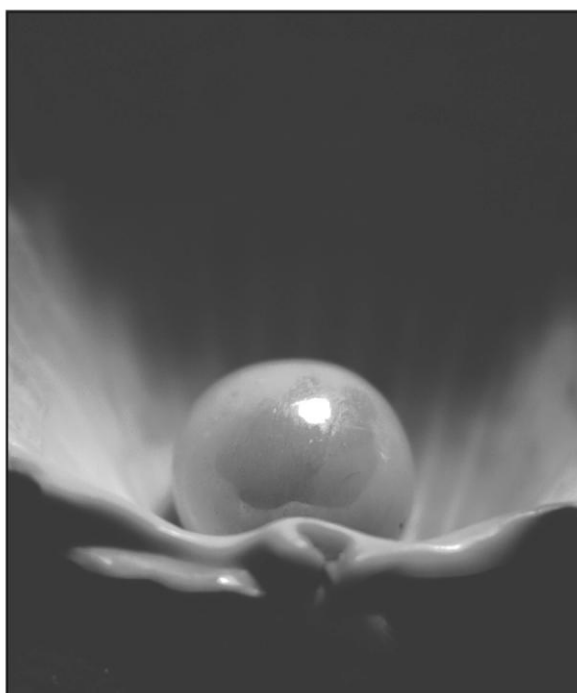
As the drive towards functional nano-architectures gathers pace it seems likely that bottom-up abiotic self-assembly and locked-assembly will play an increasingly important role.

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