The Palladium(II) Templated Syntheses of Interlocked Architectures

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September 2007
Dedicated to Patrick and my Family
"If we knew what it was we were doing, it would not be called research, would it?" - Albert Einstein
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Abstract

Over the past quarter century transition metal ions have been used to template the formation of interlocked architectures such as catenanes and rotaxanes, due to their well-defined geometrical preferences and their ability to direct the orientation of ligands in three-dimensional space. Until recently, square planar, one of the classic transition metal geometries, had yet to be exploited for the construction of such structures. Herein, the application of palladium(II) combined with a “3+1” pyridine-2,6-dicarboxamido and pyridine heteroligand set is described. While it may seem reasonable to expect that a two-dimensional coordination geometry would not be well suited for the synthesis of inherently three-dimensional interlocked architectures, the reverse has been shown to been true. Indeed, it has proven itself to be a very proficient and versatile template motif, exemplified by the syntheses of various multi-component architectures. Initially, this template was applied to the synthesis of the first [2]rotaxane whose formation was directed by a metal ion with a square planar geometrical preference. Importantly, the heteroleptic nature of the motif enabled a clipping strategy, which would not have been possible using a homoleptic system; this particular trait being essential for the synthesis of more intricate structures.

Subsequently this template was used for the assembly of a [2]catenane together with two isomers of this interlocked structure: a single tetradebate macrocycle which adopted a “figure of eight” conformation encapsulating the metal, and a complex in which two macrocycles of the catenane are not interlocked. The three isomers were selectively formed depending on how the building blocks were assembled and cyclised. The efficacy of this palladium(II) template was further demonstrated by its application to the construction of increasingly complex architectures such as multi-ring rotaxanes. It provided fundamental control over the addition to a thread of individual macrocycles, which could be sequentially clipped-on using only one template site, by the iteration of three simple steps - complexation, macrocyclisation and demetallation. This impressive control has also allowed the syntheses of a unique pair of [3]rotaxanes that exhibit sequence isomerism through the use of two different macrocycles.
Declaration

The scientific work described in this thesis was carried out in the School of Chemistry at the University of Edinburgh between October 2003 and September 2006. Unless otherwise stated, it is the work of the author and has not been submitted in whole or in support of an application for another degree or qualification of this or any other University or institute of learning.

Signed.

Date 30th May 08
Lectures and Meetings Attended

   Oral presentations: a) “*[n]*Rotaxanes from sequential isomers to molecular barcodes”; b) “Palladium Directed Syntheses of Interlocked Architectures”


8. **School of Chemistry, Organic Section Firbush Symposium**, Firbush Point Centre, University of Edinburgh, Scotland, April 2005. Poster presentation entitled: "Order is the Key to Selectivity"


Poster presentation entitled: "Metal-Directed Syntheses of [n]Rotaxanes and Mechanically Interlocked Sequential-Isomers"
Acknowledgements

I would like to thank a whole host of people for their assistance and encouragement throughout my PhD. Thank you Prof. David. Leigh for giving me the opportunity to work in the magnificent Leigh group, for providing all the resources I ever needed and for teaching me the importance of presenting work so that it tells a story. I would like to give a very special and well deserved “go raibh mile maith agat” (that’s a thousand thank yous in Irish) to Dr. Paul Lusby, who mentored me throughout my PhD and was always there in my times of need. I would also like to thank the following people: Prof. Alex Slawin for all her work solving the X-ray crystal structures that are presented in this thesis. Dr. Barney Walker for his contribution to parts of the work described in this thesis and for the nickname “Lamo”. Louise Hogg for her preparation of copious amounts of ‘stopper’ and ‘U-shape’ and for all her work keeping Lab 29 going. Thanks to the guys (you know who you are) for looking after our NMR and all the staff at the University of Edinburgh School of chemistry for their help and assistance over the years, especially John Millar who was always there to lend a hand.

A hearty thanks to Dr. Steve Goldup for all your keen insights and support over the final leg of the PhD journey and to all my lab mates along the way – you truly made it worth it – Nick, Euan, Drew, Byran, James, Manashi, Isabel, Julia, Vivi, Weiquan, Jeff, Emilio, Diego, José, Ale, Laure, Roy, Andrea, Popi, Claire, Pepe, Bill, Smilja, Steve M., Vince, Chin Fa, Raman, Steph, Ai-Lan, Stuart, Marius, Vicki, Kevin, Aurelian – I hope I haven’t missed anyone out!

And to the possie – Dot, Anna, Fiona, Maria, Jemma, Christine, Rachel, Allan, Pete, Graham, Iain, Damien, Sanjay and Tom - thank you for your friendship and all the wonderful memories of the time spent during my PhD.

Finally, thank you to my family for all your support and encouragement that lifted me though to the end and last but not least thank you, thank you, thank you, to my dearest Paddy who has always been there to experience this rollercoaster journey with me!
List of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tr>
<td>Å</td>
<td>Angstrom</td>
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<tr>
<td>δ</td>
<td>Chemical shift</td>
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<tr>
<td>bipy</td>
<td>Bipyridine</td>
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<tr>
<td>Calcd.</td>
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<tr>
<td>CPK</td>
<td>Corey-Pauling-Koltun</td>
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<tr>
<td>DB24C8</td>
<td>Dibenzo-24-crown-8</td>
</tr>
<tr>
<td>DIAD</td>
<td>Diisopropylazodicarboxylate</td>
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<tr>
<td>DMAP</td>
<td>4-dimethylaminopyridine</td>
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<tr>
<td>DMF</td>
<td>( N,N' )-dimethylformamide</td>
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<tr>
<td>DMSO</td>
<td>Dimethylsulfoxide</td>
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<td>DNA</td>
<td>Deoxyribonucleic acid</td>
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<tr>
<td>E</td>
<td>( E ) trans isomer</td>
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<tr>
<td>EDCI</td>
<td>1-(3-dimethylaminopropyl)-3-ethyl-carbodiimide hydrochloride</td>
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<td>EDTA</td>
<td>Ethylenediamine tetraacetic acid</td>
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<td>equiv</td>
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<td>ESI</td>
<td>Electrospray Ionisation</td>
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<tr>
<td>FAB</td>
<td>Fast Atom Bombardment</td>
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<td>Hydrogen bonding</td>
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<tr>
<td>HRMS</td>
<td>High Resolution Mass Spectrometry</td>
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<tr>
<td>J</td>
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<td>Low Resolution Mass Spectrometry</td>
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<td>Melting point</td>
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<tr>
<td>MS</td>
<td>Mass Spectrometry</td>
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<tr>
<td>m/z</td>
<td>Mass-to-charge ratio</td>
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<tr>
<td>NMR</td>
<td>Nuclear Magnetic Resonance</td>
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<tr>
<td>phen</td>
<td>Phenanthroline</td>
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<tr>
<td>ppm</td>
<td>Part per million</td>
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<tr>
<td>RCM</td>
<td>Ring Closing Metathesis</td>
</tr>
<tr>
<td>terpy</td>
<td>Terpyridine</td>
</tr>
<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
</tr>
<tr>
<td>TFA</td>
<td>Trifluoroacetic acid</td>
</tr>
<tr>
<td>TfOH</td>
<td>trifluoromethanesulfonic acid</td>
</tr>
<tr>
<td>TLC</td>
<td>Thin Layer Chromatography</td>
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<tr>
<td>TM</td>
<td>Transition Metal</td>
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<tr>
<td>VT</td>
<td>Variable Temperature</td>
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<tr>
<td>E</td>
<td>cis isomer</td>
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General Comments on Experimental Data

Unless stated otherwise, all reagents and anhydrous solvents were purchased from Aldrich Chemicals and used without further purification. Column chromatography was carried out using Kiesegel C60 (Merck, Germany) as the stationary phase, and TLC was performed on precoated silica gel plates (0.25 mm thick, 60F254, Merck, Germany) and observed under UV light. All $^1$H and $^{13}$C NMR spectra were recorded on a Bruker AV400 instrument at a constant temperature of 25 °C. Chemical shifts are reported in parts per million from low to high field and referenced to TMS. Coupling constants ($J$) are reported in hertz (Hz). Standard abbreviations indicating multiplicity were used as follows: m = multiplet, br = broad, d = doublet, q = quadruplet, t = triplet, s = singlet. All melting points were determined using Sanyo Gallenkamp apparatus and are reported uncorrected. ESI mass spectrometry was performed with a Micromass Platform II mass spectrometer controlled using Masslynx v2.3 software while FAB mass spectrometry was carried out by the laboratory services at the University of Edinburgh.
Chapter 1: Metal-Templated Syntheses of Interlocked and Entangled Architectures
1.1 Introduction

Nature harnesses the power of intramolecular and intermolecular non-covalent interactions, such as hydrogen bonding, π-π interactions, metal-ligand coordination, hydrophobic forces, van der Waals interactions and electrostatics to control specific recognition events and assemble biological structures. As the scientific community’s understanding of these processes has developed, chemists have recognised that this approach may be utilised, in much the same way, to assemble a variety of structures with potentially very interesting properties or applications. These interactions now form the basis of the chemist’s molecular engineering toolbox, enabling ever-more sophisticated structures to be developed as for example prototypes for molecular devices and machines. Indeed it was the advent of the field of supramolecular chemistry and the advancements therein, coupled with improvements in analytical chemistry (which now allows us to fully characterise these structures) that has provided the impetus for the development of such complex and functional molecular architectures. These advancements in supramolecular chemistry have greatly improved our understanding of events such as molecular recognition, host-guest complexation, self-assembly and molecular structural assembly and notably, the founding fathers of this field, Cram, Pedersen, and Lehn, of this field were duly recognised for their contributions when they were awarded the Nobel Prize for chemistry in 1987.

Mechanically interlocked structures such as catenanes (Figure 1.1a) and rotaxanes (Figure 1.1b), originally a synthetic curiosity, have now become viable synthetic targets due to these advances in supramolecular chemistry and analytical chemistry. Catenanes, whose name derives from the Latin catena meaning chain, consist of two or more interlocked rings. Rotaxanes, named from the Latin rota meaning wheel and axis meaning axle, consist of a ring trapped on a dumbbell-shaped component that is often called a thread or axle. However, it should be noted that although modern syntheses of catenanes and rotaxanes rely on supramolecular concepts, they are not classed as supramolecular assemblies since they are single molecules; their multiple components are intrinsically held together via “mechanical bonds” that can only be
separated from one another by the cleavage of one or more covalent or other non-labile bonds.\textsuperscript{6} The nomenclature used to describe these architectures involves prefixing (in square brackets) the number of interlocked components in the particular species; for example, a [2]rotaxane consists of one ring threaded onto one dumbbell-shaped component and a [3]rotaxane consists of two macrocycles threaded onto a single dumbbell-shaped component or two axles threaded through one large macrocycle. Similarly, a [2]catenane consists of two interlocked rings. An [n]rotaxane or [n]catenane therefore consists of n interlocked components; in the former case this commonly (although not necessarily) means that n-1 rings are threaded onto the dumbbell shaped component.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{images/Figure1.1.png}
\caption{Cartoon representations of (a) a [2]Catenane, (b) a [2]Rotaxane, (c) a Trefoil knot and (d) Borromean rings.}
\end{figure}

Other comparable structures that are not strictly interlocked but that are often grouped together with catenanes and rotaxanes, not least because of the synthetic challenge they pose, are knots (Figure 1.1c) and Borromean rings (Figure 1.1d). Knots hold interest for several reasons; “Knot Theory” is an area of mathematics devoted to their study and interestingly these geometries can often be seen in nature, for instance, duplex circular DNA is twisted into highly knotted forms.\textsuperscript{7} Knots have long held a general fascination for people, as evidenced in historic artwork such as the “Book of Kells”, an impressively illustrated manuscript fashioned by 8\textsuperscript{th} century Irish Monks, which includes very intricate knotted designs. Similarly, the Borromean symbol has also been depicted in artwork dating back to this period; however the actual name “Borromean Rings” only came into popular use when the 15th century Italian aristocratic Borromeo family adopted it for their coat of arms. Like catenanes and rotaxanes, these structures can only be disentangled through the cleavage of a
covalent bond. Of note is the fact that the rings of the Borromean structure are all locked together rather than interlocked with each other; consequently cleavage of just one of the three rings results in complete dissociation of all three fragments. Knots and Borromean rings are also of interest due to their topologically complex nature, since they also cannot be unraveled or converted to another isomeric form by continuous deformation, of their molecular graph structure, in three dimensional space.\textsuperscript{8} In the same way, catenanes and their non-interlocked counterpart rings are topological isomers. Rotaxanes however, are topologically trivial since their component parts can be dissociated from each other by continuous deformation of one or other of the components (i.e. the ring can be stretched and/or the stoppers shrunk so that slippage can occur).

Efficient syntheses of mechanically interlocked architectures usually exploit combinations of different non-covalent interactions to template the formation of nascent components in the desired architecture. Of these, metal-ligand interactions are probably the most versatile; one need only look to the number and variety of metals listed on the periodic table whose different properties can be utilised. Depending on the choice of metal-ligand combination a range of properties can be engineered. Kinetic stability can be imparted, locking all the components together in a fixed well-defined structure; alternatively, the most thermodynamically stable structure can be biased by choosing a metal-ligand combination that affords the components kinetic lability thus allowing error-checking and correction, a process characteristically associated with supramolecular chemistry. Additionally, compared to other types of bonding interactions (such as hydrogen bonding) that generally persist in the interlocked product whose assembly they facilitated, metal-ligand interactions can be conveniently and simply ‘switched-off’ by removing the metal. The pre-eminence of the metal template approach has been exemplified by the syntheses of a diverse range of structures; from the very first template-assisted synthesis of a catenane to the some of the most challenging and complex structures constructed to date, trefoil knots and Borromean rings.\textsuperscript{9}
As early as 1964, metal ions with octahedral geometrical preferences had been exploited for their organising abilities in the synthesis of macrocycles. Furthermore, the premise of using them to assemble topologically complex and other interlocked architectures was discussed in 1973 by Sokolov. However, it was the exploitation of metal-ligand interactions in the assembly of a rotaxane by Ogino and a catenane by Sauvage in the early eighties that heralded an important paradigm shift that paved the way for the subsequent revolution in the template-directed syntheses of interlocked architectures, such as the ammonium/crown ether and π-acceptor-π-donor systems pioneered by Stoddart, amide based hydrogen-bonding systems developed by Hunter, Leigh and Vögtle, and metal incorporating systems by Fujita. Prior to the reports by Sauvage and Ogino, catenanes and rotaxanes had been assembled in very low yields either via lengthy covalent bond-based synthetic routes (that essentially used covalent templates) or statistical methods (that relied on the chance threading of pre-components).

Metal ions have been utilised in the construction of interlocked structures in mainly three different ways. The distinction between these methods lies in the type of interactions that drive the interlocking processes. The distinguishing aspect of the first method (method 1) is the kinetic assembly of the structure via the metal-chelation of pre-formed ligands. For this, the metal ion assumes a predominant templating role driving the attraction of the components whilst also directing their orthogonal alignment. This method exploits features of coordination chemistry such as the kinetic stability of multidentate ligands with metal ions (the "chelate effect") and the well-defined geometrical preferences of different transition metals, which allows the components to be suitably aligned, ready for a covalent bond forming reaction to generate the interlocked product. The common geometrical metal preferences have been exploited for the assembly of interlocked and entangled structures are tetrahedral (Figure 1.2a), square planar (Figure 1.2b), square pyramidyl (Figure 1.2c), trigonal bipyramidyl (Figure 1.2d) and octahedral (Figure 1.2e). Particular features of method 1 include the use of relatively non-labile metal ions and often the ability to isolate acyclic intermediates (which cannot be done with other
template approaches), which facilitates the synthesis of structures of greater complexity and structural diversity. In addition, the interlocked structure remains intact in the event that the metal is removed.

The second method (method 2) provides for the self-assembly of interlocked and entangled structures under thermodynamic control by exploiting dynamic covalent chemistry in concert with the well-defined geometrical alignment afforded by metal ions. In this case the multidentate coordination sites may be assembled in situ and the driving forces that promote the assembly of the structure are the “chelate effect” and in addition the formation of other favourable inter-component interactions such as \( \pi-\pi \) interactions or hydrogen bonding. The effect of the metal ion directing the alignment of the ligands and the reversibility of the covalent bonds selects against the formation of side-products and indeed facilitates the formation of the most thermodynamically stable product, through a process of proof-reading and error-checking. An important characteristic of this method is that the often reversible nature of this assembly process can be switched off by halting the dynamic exchange reaction thus fixing the interlocked structure such that it does not disassemble upon removal of the metal-ion(s).

In contrast, the third method (method 3) exploits the often reversible nature of monodentate metal-ligand bonding allowing multicomponent systems to self-assemble and attain thermodynamic equilibria, while other non-covalent interactions
such as \(\pi-\pi\) interactions, hydrophobic forces or hydrogen bonding drive the three-dimensional alignment of the components. Compared to the other strategies this method generally employs simple building blocks since usually they need only form monodentate bonds with the metal ion. An intrinsic aspect of the resulting systems is that the metal ion is located within the backbone of the structure and consequently its removal results in collapse of the overall structure. In essence, the stability of structures assembled \textit{via} this method is determined by the weakest metal-ligand bond.

\begin{scheme}
(a) \hspace{2cm} (b) \hspace{2cm} (c) \hspace{2cm} (d)
\end{scheme}

\textbf{Scheme 1.1. Method 1} - Cartoon schematic showing general kinetic metal-template strategies used for the assembly of a catenane, routes (a) and (b), and a rotaxane, routes (c) and (d). The purple parts of the components indicate metal binding sites and are incorporated into the middle of the components. The structures can be assembled in a few simple steps where (i) is a complexation step (with the metal pre-complexed to one of the components), (ii) is a cyclisation step, (iii) is a demetallation step, and (iv) a complexation step (with the metal complexing both components in the same reaction.)
There are several different synthetic routes available for forming catenanes and rotaxanes that utilise method 1 (see Scheme 1.1); for example, a metal-complexed catenane (ML5) can be assembled by either single (Scheme 1.1a) or double (Scheme 1.1b) cyclisation routes of appropriate pre-catenane intermediates. Metal-free catenane (L5) is then afforded simply by demetallation of the metal-catenane (ML5). Likewise, metal complexed rotaxanes (ML9) can be assembled by the cyclisation of an appropriate acyclic pre-rotaxane (L7ML6) (Scheme 1.1c) or additionally by the so-called ‘threading-and-stoppering’ approach (Scheme 1.1d), which involves the simultaneous complexation and threading of a non-stoppered thread (L8) through a preformed metal-macrocycle complex (ML1) to give the pseudo-rotaxane (L8ML1). This threading step is similar to that of the catenane strategy outlined in Scheme 1.1a and often the macrocycle component is first complexed with the metal-ion. This pre-complexation ensures that, in the case where the metal is non-lablile and the components have similar ligating sets, only one product is obtained; homoleptic species are not obtained. Again, the free rotaxane (L9) is afforded easily by removal of the metal from the metal-rotaxane (ML9).

\[
\text{Scheme 1.2. Method 2 - Cartoon schematic showing general thermodynamic metal-template strategies for the assembly of (a) a catenane and (b) a rotaxane. The purple parts of the components indicate metal binding sites and are incorporated into the ends and middle of the components. The syntheses include (i) the self-assembly of the structure from various components through the formation of dynamic covalent bonds and (ii) “fixing” of the reversible covalent bonds and demetallation (which can occur in the same or in separate steps).}
\]
Metal-free catenanes and rotaxanes can also be constructed via a self-assembly approach using method 2 (see Scheme 1.2). The formation of metal catenane (ML\textsubscript{12}) arises from the reaction of "u-shape" precursor (L\textsubscript{10}) with a smaller acyclic metal-binding unit (L\textsubscript{11}) in the presence of a metal ion. These components can be designed to have complementary end-functionalities capable of forming dynamic covalent bonds, which once formed have the ability coordinate to the metal ion. In order to fully satisfy the metal's coordination sphere, two such ligand sets are required, meaning that the [2]catenane often represents the thermodynamic minimum. The dynamic and reversible nature of the bonds can then be switched off and the metal removed to afford an entirely organic catenane (L\textsubscript{12}). Similarly, metal-rotaxanes (ML\textsubscript{16}) may be afforded by reaction of appropriately end-functionalised stopper (L\textsubscript{13}) and metal binding groups (L\textsubscript{15}) with a multidentate macrocycle (L\textsubscript{14}) in the presence of a metal ion. Subsequent fixing of the reversible bonds and demetallation gives the metal-free rotaxane (L\textsubscript{16}).

The main synthetic approaches applied to the assembly of catenanes and rotaxanes using method 3 are illustrated in Scheme 1.3. As with most self-assembly reactions, the metal ions need only be stirred with suitable ligands to afford catenane or rotaxane structures, which can often self-assemble from several components. Catenanes and rotaxanes that self-assemble with the metal ion incorporated into the backbone of the macrocycles are depicted in Schemes 1.3a and 1.3c respectively. Alternatively, they can assemble via pseudorotaxane monomers that either coordinate together to form a "molecular necklace" type catenane (Scheme 1.3b) or be stoppered with a suitably bulky metal complex to afford a rotaxane (Scheme 1.3d). Rotaxanes may also be constructed via another strategy that results in the metal being integrated into the middle of the thread (Scheme 1.3e). In this situation rotaxanes can form from a half-thread (L\textsubscript{22}) and a preformed macrocycle (C\textsubscript{1}) affording either a [2]rotaxane (C\textsubscript{1}M{L\textsubscript{15}L\textsubscript{12}) or a [3]rotaxane M[C\textsubscript{1}L\textsubscript{2}]\textsubscript{2} that assembles from the complexation of two semi-rotaxane precursors.
Scheme 1.3. Method 3 - Cartoon schematic showing general thermodynamic self-assembly strategies that utilise metal ions but non-metal templating interactions for the assembly of catenanes as shown in routes (a) and (b), and rotaxanes as shown in routes (c)-(e). The purple parts of the components indicate metal binding sites and are incorporated into the ends of the components. The structures assemble in a single step from several individual components and are held together by metal-ligand interactions. Removal of the metal results in disassembly of the structure.

The remaining sections of this chapter focus on published examples of the metal-templated syntheses (i.e. methods 1 and 2) of catenanes, rotaxanes and structures such as knots and Borromean rings. The historical background section is provided to help put into perspective the more recent developments, which are subsequently discussed in this chapter, and ultimately the work described in this thesis in chapters two to five. Syntheses where the metal ions play a largely ancillary role in the formation of interlocked and locked architectures (i.e. method 3) will not be discussed in further detail here. However, a significant body of work has been
published in this area and it is fitting to provide illustrations of architectures assembled via this method (see Figure 1.3).

Figure 1.3. Examples of catenanes and rotaxanes assembled via method 3 showing (a) a [2]catenane by Fujita; (b) a “molecular necklace” [4]catenane by Kim; (c) a [2]rotaxane by Jeoung where a metal ion is incorporated into the macrocycle’s “backbone”; (d) Ogino’s metal-complex stoppered rotaxane; (e) a [2]rotaxane where the metal ion is incorporated into the middle of the thread by Wisner and (f) a [3]rotaxane by Anderson where the metal is also incorporated into the centre of the thread.

Numerous catenanes have been constructed via the strategy outlined in Scheme 1.3a, including an eminent example (Figure 1.3a) of a palladium metalloccatenane from Fujita. Kim and co-workers have published several examples of ‘molecular necklace’ type catenanes assembled via the catenane strategy depicted in Scheme
1.3b, one example of which is shown in Figure 1.3b. Compared to their analogous catenanes, there are relatively few examples of rotaxanes that incorporate metals in the backbone of their macrocycles (this is not surprising since the formation of the catenane could be a significant side reaction); the example of this type of rotaxane illustrated in Figure 1.3c was published by Jeoung. The first metal containing interlocked architecture is depicted in Figure 1.3d, a rotaxane assembled via the strategy outlined in Scheme 1.3d, was published by Ogino in 1981 and exploited cobalt(III) metal complexes as stoppers. Figures 1.3e and 1.3f show rotaxanes from the groups of Wisner and Anderson respectively, which illustrate structures assembled via the strategy outlined in Scheme 1.3f.

Extended metal-templated supramolecular assemblies such as metal-organic frameworks, polyrotaxanes, molecular grids and ladders, molecular devices, shuttles and machines will not be covered in this chapter as these are covered extensively in other reviews and are not within the scope of this thesis.

1.2 Background

The following section, which describes the growth of the area of metal-directed templated syntheses of catenanes, rotaxanes and knots is dominated by the work of Sauvage and co-workers. Sauvage's realisation that the three-dimensional templating effect of a Cu(I) metal ion could be exploited to assemble a catenane has had a profound influence on this area. The synthesis of this first metal-templated catenane was based on the combination of a copper(I) ion with a 2,9-diphenyl 1,10-phenanthroline ligand, whereby the tetrahedral geometric preference of the copper ion was used to direct the orthogonal alignment of two bidentate ligands. What is particularly noteworthy is that they showed that they could successfully assemble copper catenane via two different strategies (see Scheme 1.4).

The first approach published in 1983 followed strategy A (which incidentally was one step longer than strategy B) and followed a route whereby the preformed phenanthroline macrocycle 1 was reacted with [Cu(MeCN)₄]BF₄ salt to form an
unsaturated metal-macroyclic complex that was subsequently stirred with the macrocyclic precursor 2 to afford the hetero-di-phenanthroline copper complex 3. Finally, reaction with an iodide terminated pentaethylene glycol chain afforded catenane 4 in 42% from 1. The second approach followed strategy B and commenced with the complexation of two equivalents of acyclic phenanthroline ligand 2 with copper(I), to give precursor 5, followed by a double cyclisation reaction to afford catenane 4 in 27%.13

\[
\text{Strategy A}
\]

\[
\text{Strategy B}
\]

\[
\text{Scheme 1.4. Sauvage's original tetrahedral Cu(I) catenane}
\]

The yields for both single and double macrocyclisation strategies based on a copper(I) phenanthroline core have since been significantly improved through the employment of ring closing metathesis (RCM) using Grubbs’ I catalyst; by using alkene-terminated macrocyclic precursors, yields of 92% for the catenane forming steps were achieved.33 Whilst the double macrocyclisation route, using either ring-closing metathesis (RCM) or Williamson-ether bond forming reactions, seems favourable as it has fewer steps, this route can sometimes lead to non-interlocked products (excluding oligomers). However, this type of problem can be overcome by following the single macrocyclisation route.
Sauvage and co-workers also showed that the copper ion could be removed from metal-catenane 4 by simply reacting with an excess of potassium cyanide to quantitatively affording the free catenane 6 (see Scheme 1.5). The interlocked nature of the metal catenane and its demetallated counter-part were proven conclusively through X-ray crystallographic analysis. In the metal containing catenane 4, the copper(I) ion is centrally bound via the four nitrogen atoms of the two phenanthroline components in a pseudo-tetrahedral geometry. In contrast, the metal-free catenane 6 adopts a very different co-conformation; the phenanthrolines, no longer held in a convergent fashion by coordination to the copper metal ion, have swung to the periphery of the structure and now point away from each other. This is possibly due to lone-pair repulsion or crystal packing energy effects, although clearly the non-coordinated phenanthroline components can rotate rapidly at room temperature.

Scheme 1.5. Demetallation of Sauvage’s Cu(I) bis-phenanthroline catenane and re-metallation with a variety of alternative metal ions.

The properties of the free catenane as a ligand were methodically studied and it was found that a range of metal ions, Li(I), Ag(I), Co(II), Ni(II), Zn(II), Cd(II) and Fe(II) could be inserted into the empty cavity to generate new metal containing catenanes (7a-g). Some interesting properties were apparent, most notably; these metal ions adopt a distorted tetrahedral coordination geometry when complexed to the catenane, presumably enforced by the steric requirements of the two interlocked phenanthroline components. In addition, the enhanced stability inherent to interlocked macrocycles (termed the “catenand effect”) was demonstrated by the isolation of catenanes of lithium, nickel, cadmium and zinc (7a, 7d, 7e and 7f), whereas respective non-interlocked analogues were not stable enough to be
isolated.\textsuperscript{36b} Interestingly, while it was also found that Pd(II) could coordinate with 6, this $d^8$ metal circumvented the adoption of a tetrahedral coordination geometry by undergoing orthometallation with one of the macrocycles.\textsuperscript{37}

Rather surprisingly, it was not until eight years after the publication of the first copper-templated [2]catenane 4 that the first metal-templated synthesis of a [2]rotaxane 8 was published by Gibson (see Scheme 1.6).\textsuperscript{38} This synthesis exploited the Cu(I) bis-phenanthroline based motif pioneered by Sauvage\textsuperscript{32} and even used the same precursor complex, 3, as Sauvage’s earlier catenane synthesis (see Scheme 1.4). Gibson found that by simply subjecting 3 to another Williamson-ether type reaction, this time with an iodide-terminated trityl-derived blocking group, the first metal-complexed rotaxane, 8, could be isolated. Subsequent reaction with Amberlite-CN resin afforded its metal-free counterpart 9 in a 42\% yield.

\begin{center}
\textbf{Scheme 1.6.} Gibson’s tetrahedral Cu(I) templated [2]rotaxane.
\end{center}

The stopper groups in rotaxane 8 perform the sole purpose of preventing the de-threading of the macrocycle. However, stoppers can also be used to impart electrochemical and photochemical properties on the interlocked structure (see Figure 1.4). With this in mind Sauvage and co-workers prepared a Cu(I) templated [2]rotaxane 10 utilising zinc(II) and gold(III) phorphyrins as stoppers.\textsuperscript{39} Following this, in an effort to mimic the electron transfer properties of a bacterial photosynthetic reaction centre porphyrins were attached to the 2,9-diphenyl 1,10-phenanthroline macrocycle; for example catenane 11 was assembled with pendant
zinc(II) and gold(II) tetraarylporphyrins attached to each macrocycle. Analogous [2]rotaxanes with porphyrin stoppers and macrocycles with pendant porphyrins have also been prepared. Other electro-active subunits that have used include a tetrathiafulvalene moiety incorporated into a catenane and fullerenes employed as rotaxane stoppers as for example in 12.

Sauvage has published a wide body of work exemplifying the versatility of the Cu(I) phenanthroline template, such as its successful application to the synthesis of higher order catenanes and rotaxanes. In 1985 the synthesis of a [3]catenane using the established Williamson ether reaction for the cyclisation step was reported; unfortunately the yield was very low (~2%). However, a short time later an alternative approach, which relied on the oxidative coupling of terminal acetylene groups, was used to afford [3]catenane 13 (Figure 1.5) in 58% yield. In addition, the synthesis also resulted in the formation of a tri-metallic complex, in 22% yield,
which was proposed as [4]catenane 14 (Figure 1.5), which consists of a central hexayne 66-membered ring with three peripheral 30-membered rings. These catenanes were also successfully demetallated using KCN and crystal structures of both the Cu(I) [3]catenane\textsuperscript{46} 13 and its metal-free counterpart were published\textsuperscript{47}. Furthermore, higher order homologues of these catenanes were also afforded by this synthetic approach, with electrospray mass spectrometry of a crude reaction mixture identifying multi-ring catenanes up to n=7\textsuperscript{48}.

![Figure 1.5. Examples of multi-ring catenanes assembled via the Cu(I) di-phenyl bis-phenanthroline coordination motif.](image)

Having extended the templating strategy to [3]catenanes, Sauvage found that analogously to the [2]catenanes, the copper metal ions could also be systematically replaced by other metal ions such as Ag(I), Zn(II), Co(II) and Ni(II). This gave rise to homo-dinuclear\textsuperscript{49} and heterodinuclear\textsuperscript{50} [3]catenanes whose electrochemical, photochemical and photophysical properties were comprehensively studied\textsuperscript{49, 50, 51}. Another interesting multi-ring structure assembled via the copper(I) phenanthroline tetrahedral motif was a [4]catenane, in which three macrocycles encircle the three respective spokes of a bicyclic skeleton\textsuperscript{52}. 

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Interestingly, procedures for the assembly of higher order rotaxanes were not developed until into the 1990’s. The synthesis of pseudo [3]rotaxane complexes were first explored by Sauvage and shortly afterwards rigid rack pseudo[4]rotaxane complexes were also assembled by Lehn and co-workers by utilising three of Sauvage’s ubiquitous Cu(I) phenanthroline macrocycles to complex a thread with three consecutive bipyridyl units. Intriguingly, the only \( [n] \)rotaxanes, where \( n \) is greater than 2, that have been synthesised using the Cu(I) bis-phenanthroline template use porphyrins as stoppers. For example, several [3] and [5]rotaxanes with various metallated and non-metallated porphyrins have been prepared by Sauvage and as an artefact of the syntheses, each macrocycle is compartmentalised between two porphyrins throughout the thread. Compartmentalised bis-copper [3]rotaxane 15

*Figure 1.6. Examples of Cu(I) templated “compartmentalised” multi-ring rotaxanes.*
(Figure 1.6) was synthesised in 32% yield from a reaction that also afforded a [2]rotaxane in 25% yield.\textsuperscript{55a} Similarly, the synthesis of a [3]rotaxane with additional butyl spacer groups between phenanthroline units also led to the formation of [5]rotaxane 16 in 8% yield.\textsuperscript{55b}

Although the syntheses of higher order rotaxanes can be synthetically challenging; unlike catenanes, they are nevertheless topologically non-trivial. The first topologically chiral catenane 17 (Figure 1.7) was published by Sauvage in 1988.\textsuperscript{56} Even though each macrocycle is achiral overall the catenane is chiral due to the non-symmetrical nature of the macrocycles. This asymmetry imparts directionality to each ring and consequently topological chirality to the interlocked catenane due to the alternate orientations the rings can adopt relative to one another. Evidence of this chirality was shown by taking a $^1$H NMR of the catenane in the presence of Pirkle’s chiral reagent, which resulted in the spectrum peaks being split. Although originally isolated as a racemate, the isomers were later resolved by HPLC on a chiral stationary phase.\textsuperscript{57} Interestingly, catenane 18 exhibits conformational topological chirality - each conformation is chiral but in dynamic equilibrium due to the presence of the 1,5-dihydroxynaphthalene, which is free to rotate thus allowing the rapid interconversion of all possible enantiomers.

\textbf{Figure 1.7.} Examples of catenanes with non-symmetrical macrocycles, one of which (17) is chiral.

Unlike singly-interlocked [2]catenanes, their doubly-interlocked analogues possess inherent topological chirality, without the need to introduce directionality into either of the rings. The doubly interlocked [2]catenane (also known as a Solomon knot) 19 (Figure 1.8), which contains four cross-over points was first synthesised, although in
a very modest 2% yield, using the copper(I) phenanthroline motif.\textsuperscript{58} Notably, it was found that 19 could be distinguished from its isomeric singly interlocked [2]catenane using mass spectrometry.\textsuperscript{59} Later however, Sauvage also found that they could use the alkali metal ion lithium(I) to template the formation of the required double-stranded helical precursor and that this lithium complex was stable enough to allow the doubly-interlocked catenane 20\textsuperscript{a} to form under mild RCM conditions. Unfortunately, due to purification issues the lithium catenane was not isolated but could instead be converted (albeit with some difficulty) to the copper analogue 20\textsuperscript{b}, which allowed isolation of the doubly-entwined catenane in a much improved 30% yield.\textsuperscript{60}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{sauvage.png}
\caption{Solomon and Trefoil Knots.}
\end{figure}

An eminent synthetic achievement by the group of Sauvage was the successful application of the 1,10 phenanthroline Cu(I) motif to the synthesis of trefoil knot 21 (Figure 1.8),\textsuperscript{9a} the structure of which was unambiguously confirmed shortly after by X-ray crystallographic analysis.\textsuperscript{61} The cornerstone of this synthesis was the formation of the helicoidal dinuclear complex and although the synthesis of the trefoil knot was a triumph in terms topologically complex methodology, the yield was only 3%. However, modifications to the design of the trefoil knot, most notably to the small group that links the 2-substituted phenanthroline rings, have led to an improvement in yields; initially by replacing the butyl linkage with a hexyl group\textsuperscript{62} and more recently through the use of a rigid 1,3-isothaloyl spacer which improved the yield to around 30%.\textsuperscript{63}
Due to this enhanced rigidity, the most recent knot 23a proved inert to demetallation using the usual reaction conditions. Nonetheless, the two metal ions could be extracted in a stepwise manner using KCN in refluxing acetonitrile giving first a monocopper species and subsequently the free knotted ligand. This artefact of the synthesis also enabled heterodinuclear copper/zinc 23b and copper/silver 23c knotted complexes to be formed. Fascinatingly, it became apparent that the metal-free knotted species strives to regenerate its more thermodynamically stable entwined conformation at the slightest opportunity; evidenced by its ready re-metalation when it came into contact with lithium ions. In 1997 the synthetic strategy was adapted to exploit ring-closing metathesis for the key cyclisation step and the trefoil knot 24 was isolated in 74% yield. Recently, a stereoselective synthesis of a trefoil knot has been achieved. 

\[ 
\begin{align*}
\text{Scheme 1.7. Cu(I) templated syntheses of a "Hybrid" rotaxane and catenane exploiting Ru(II) terpyridine coordination.}
\end{align*}
\]

Further to their work where they utilised porphyrins as stoppers, Sauvage and co-workers adopted an approach similar to that of method 3 whereby metal complexes are used as stoppers to form a "hybrid" type structure 27 (Scheme 1.7). Two
different metals are used; Cu(I) to template the formation of pseudorotaxane 25 via bis-phenanthroline coordination and Ru(II) to form bis-terpyridine stopper coordination complexes.\textsuperscript{68a} Due to the high affinity of the Cu(I) for the phenanthroline ligands, the reaction is selective with no evidence that any competition for the terpyridine units takes place. Interestingly, catenane 29 could be selectively formed from the same precursor 25 and the Cu(I) template could be removed from both rotaxane and catenane to give 28 and 30 respectively using KCN, conditions that the stoppers proved inert to.\textsuperscript{68b}

As is evident there are numerous examples of tetrahedral metal templated catenanes and rotaxanes, but up until the turn of the millenium there were very few examples where transition metals with preferred octahedral geometry (or indeed other geometries) were utilised in the metal-templated syntheses of catenanes or rotaxanes. The first catenane successfully assembled around an octahedral metal ion 34 (Scheme 1.8) was published in 1991 by Sauvage.\textsuperscript{69} The synthesis exploited Ru(II) 5,5''-disubstituted terpyridine precursor 31, rather than a 6,6''-disubstituted analogue, since it provides a less hindered binding site for the metal ion. Due to solubility issues, the protected phenol tridentate unit, 31, was first reacted with RuCl\textsubscript{3} to afford the bis-terpyridine complex 32 which could easily be deprotected under mild conditions with boron tribromide to afford complex 33. Double cyclisation of this precursor complex 33, using the procedures developed originally for the copper catenane system, afforded the bis(terpyridine)ruthenium(II) catenane 34 in a modest 11\% yield.\textsuperscript{69}

\textit{Scheme 1.8.} Ru(II) octahedral templated synthesis of a catenane.
Unfortunately, the stability of the ruthenium catenane prevented its demetallation and attempts to make the iron analogue, which would have been more susceptible to demetallation, proved unsuccessful. Later attempts to make the iron analogue employing mild ring-closing metathesis conditions that precluded the disassembly of the Fe(II) precursor complex, resulted instead in the formation of a large macrocyclic complex pinched into a ‘figure-of-eight’ shape through its coordination to the metal.\textsuperscript{34a} However Fe(II) was later used by Piguet and co-workers to template the formation of a “hybrid” catenane, which self-assembled from Fe(II) and Ag(I) and a multidentate ligand containing both tridentate and bidentate sites (Figure 1.9).\textsuperscript{70} In this catenane the Fe(II) shows distorted-octahedral coordination to two tridentate binding units while two Ag(I) ions show distorted-tetrahedral coordination to two bidentate units. Analogous to other self-assembly approaches, demetallation would result in the collapse of the structure.

**Figure 1.9.** Piguet’s octahedral metal templated “hybrid” catenane

Magnesium and gold have been used to template the self-assembly of several catenanes and rotaxanes and whose structures would also disentangle should the metal ions be removed (Figure 1.10). Magnesium self-assembles rotaxane \textsuperscript{36} and catenane \textsuperscript{37} by interacting with a crown-ether based macrocycle while simultaneously aligning and forming organometallic bonds to the required components.\textsuperscript{71} Alternatively, the self-assembly of gold organometallic catenane \textsuperscript{38}, published by Mingos and co-workers, where each macrocycle contains six gold atoms connected via $\eta^1$ and $\eta^2$ coordinated ethynl ligands, is believed to be directed by “aurophilic” interactions.\textsuperscript{72}
1.3 Recent Developments

1.3.1. Tetrahedral

The last few years have seen the established Cu(I) phenanthroline template applied to the construction of new types of structures as well as its exploitation by groups other than Sauvage’s. New template motifs that exploit Cu(I) in combination with different ligands have also been developed. Scheme 1.9 shows the assembly of “hermaphrodite” molecule 40, so called because each monomer 39 of this dimeric species contains two complementary parts, a female chelating ring attached to a male coordinating linear part. Remarkably, assembly of 40 is quantitative despite being a double threading process. Its structure was unambiguously confirmed by examination of the X-ray crystal data, which showed the linear extended nature of the molecule, with a distance of 36.6 Å between the two terminal phenolic oxygens.
A trimer and a tetramer species assembled from hermaphrodite molecules have also recently been reported. These were formed by adapting the hermaphrodite architecture such that the male linear part is connected directly to the middle of the phenanthroline unit via an oxazole spacer, which ensures the phenanthroline coordinating units are orthogonal to one another. It was expected that the tetramer would be the sole product, however, the two species have the ability to interconvert and it was observed that the tetramer was only dominant in concentrated solutions, whereas the trimer was the dominant species in dilute solutions.

**Figure 1.11.** Rotaxane and Catenane with porphyrins incorporated into the backbone of their macrocycles.

Further to their previous work whereby catenanes and rotaxanes were constructed containing porphyrins attached to the macrocycles in a pendant-like fashion, Sauvage and co-workers have assembled rotaxanes and catenanes such as 41 and 42 respectively (Figure 1.11), whose structures have porphyrins incorporated directly into the backbone of their macrocycles. One of the advantages of interlocked
structures in general is that their intrinsic mechanical bonds afford the study of through-space rather than through bond electron transfer. In these structures the copper metal ion can selectively be removed and/or replaced with other metal ions such as silver(I) and lithium(I) in order to probe the electron transfer processes of these molecules.\textsuperscript{77}

Other groups have also employed the Cu(I) phenanthroline motif to assemble rotaxanes and catenanes for the study of electron-transfer processes. These include Swager whose work involved assembling rotaxanes \textbf{43} with Cu(I) phenanthroline based macrocycles and bidentate bipyridyl unit based threads (Figure 1.12).\textsuperscript{78} They found that metal binding in the tetrahedral pocket of the rotaxane quenched the fluorescence, and interestingly they also found that alkali metal ions such as Li(I) and Na(I) bound to the rotaxane through the bipyridyl unit and the oxygens of the ethylene glycol units of the macrocycle giving new photophysical properties. Schuster and co-workers have also employed Sauvage’s Cu(I) template to assemble rotaxanes and catenanes with both porphyrin and fullerene appendages.\textsuperscript{79} One such example is [2]rotaxane \textbf{44} (Figure 1.12), which has fullerene stoppers and a pendant porphyrin attached to the macrocycle.

\textbf{Figure 1.12.} Rotaxanes with electron transfer properties.

In 2004, Sauvage published a new chiral [2]catenane 45 (Figure 1.13), in which each macrocycle incorporated the intrinsically chiral 1,1'-binaphthyl motif. Interestingly, the CD measurements showed that chirality transfer could take place between the 1,1'-binaphthyl groups and the copper complex core. More recently, chiral catenanes with integrated phosphine oxide units prepared via the Cu(I) phenanthroline motif have been reported. The chirality of catenane 46 is attributed to the stereogenic centres incorporated into the phosphine oxide-functionalised macrocycle, which was isolated as the enantiometrically pure S,S. In addition, a pair of diastereomeric catenanes were assembled with the phosphine oxide moiety incorporated into both macrocycles.

![Figure 1.13](image.png)

Figure 1.13. Examples of chiral catenanes recently assembled using Sauvage’s generic Cu(I) template motif.

In 2005, Sauvage and co-workers published another novel structure, a handcuff-like compound 51 (Scheme 1.10), assembled via their standard Cu(I) tetrahedral template. The structure consists of a fused bis-macroyclic core with a larger macrocycle threaded through each macrocycles cavity. The bis-macrocylic core 48, which contains two back to back bis-phenanthroline units, was prepared by homocondensation of 47 in melted ammonium acetate. This was subsequently complexed to copper and then the di-butenylic derivative 49 to yield 50 quantitatively. A “1+1” cyclisation of the two acyclic components, via RCM of terminal alkene groups of 50, with Grubbs (I) as catalyst, afforded the final handcuff compound 51 in 80% yield. The bis-macroyclic structure 48 has also been employed in the synthesis of a pseudo-rotaxane tetramer. The grid-like structure was formed by threading two bis-bidentate rods, through two of the fused bis-macrocycles in the presence of Cu(I).
Bäuerle and co-workers have also chosen to exploit the efficient and versatile properties of Sauvage’s Cu(I) phenanthroline motif to assemble π-conjugated catenanes. This unit was chosen not only for its established catenane forming tendencies but also for the conjugated nature of the phenanthroline backbone. The assembly of a fully conjugated structure enforces a high degree of rigidity on the structure, posing an increased challenge for the cyclisation step, which usually relies on a certain amount of flexibility in the macrocycle precursor. The fully π-conjugated system of the macrocycles of catenane 56 (Scheme 1.11) are composed of quaterthiophene, phenanthroline and diacetylene units. Catenane 56 was assembled via a double cyclisation strategy (see Scheme 1.1b). This strategy first involves the complexation of acyclic compound 52 with [Cu(CH3CN)4]BF4 to afford the homoleptic complex 53, which was subsequently cyclised, via a novel approach using Pt(II) corners, to form the Cu(I) diplatina catenane 54. Subsequent reaction with iodine afforded 55 in 74% yield, via the 1,1-reductive elimination of the Pt(II) corners with concurrent carbon-carbon bond formation. The metal-free catenene 56 (with 34-membered macrocycles) was obtained successfully by reaction of 55 with KCN. Previous to this Bäuerle and co-workers had assembled a similar Cu(I)

\[ \text{Scheme 1.10. Cu(I) templated synthesis of "Handcuff" type compound by the group of Sauvage.} \]
catenane with 28-membered macrocycles;\textsuperscript{85} unfortunately the steric constraints imposed by these smaller macrocycles prevented its demetallation.

Another d\textsuperscript{8} metal ion has been used to facilitate the ring-closing of a copper templated catenane (Scheme 1.12). Sauvage and Fujita collaborated on the synthesis of catenane 58, which exploited Sauvage’s bis-phenanthroline Cu(I) motif to assemble precursor 57. This acyclic complex was subsequently cyclised via palladium(II) coordination, a method developed in Fujita’s group for the thermodynamic self-assembly of catenanes.\textsuperscript{56} Previous to this, a similar strategy had resulted in the formation of a doubly interlocked [2]catenane.\textsuperscript{22a}

\textit{Scheme 1.11}. Bäuerle’s \pi-conjugated catenane assembled using Sauvage’s bis-phenanthroline Cu(I) template.

29
Recently Nitschke and co-workers published the synthesis of a novel Cu(I) templated catenane that also contained functionalised phenanthroline units as chelating groups. However, unlike Sauvage’s earlier syntheses, which proceed via kinetically stable intermediates, copper catenane 61 (Scheme 1.13) was self-assembled under thermodynamic control via the condensation reaction of dianiline 59 and 1,10-phenanthroline-2,9-dialdehyde 60, in the presence of [Cu(CH₃CN)₄]BF₄. Interestingly, two copper ions are bound per catenane; each metal ion presumably datively bonded to two imine nitrogens and two phenanthroline nitrogens. In the absence of an X-ray crystal structure the catenated structure was corroborated via molecular mechanics calculations, a mass spectrometric study and the observation of NOE signals between the phenanthroline protons and the alkyl protons.

Scheme 1.12. Example of a Cu(I) templated hybrid catenane incorporated Pd(II)metal ions in the “backbone” of the macrocycles.

In addition, the catenane was successfully demetallated to afford 62, firstly by reducing the imine bonds (which is essential since it stops the exchange and kinetically fixes the interlocked structure) and secondly by reacting with EDTA under basic conditions to remove the copper ions. As part of this work it was shown that control over product topology could also be achieved by the appropriate selection of the reaction components, based on properties such as rigidity and length. Reaction of 60 with a diamine analogue of 59, which is shorter and more flexible, results in the self-assembly of a macrocycle twisted into a dimeric helical structure through the coordination of two copper metal ions.

Scheme 1.14. Leigh’s “Click Rotaxane”.

Until this point, all the previously described metal-directed template syntheses have relied on the use of stoichiometric amounts of metal ion with ligands that have strongly bonding, pre-organised binding sites that facilitate interlocking. In contrast, in a unique example by Leigh and co-workers, the metal ion Cu(I) is not only used in sub-stoichiometric amounts, it is also bi-functional, aiding the templated formation of [2]rotaxane 66 and simultaneously catalysing the formation of its thread from precursors 64 and 65 via a 1,3-cycloaddition or “click” reaction (Scheme 1.14). In this case the only preceding binding site is in the macrocycle 63, whose endotopic pyridine nitrogen weakly binds the Cu(I) ion and directs the catalysed reaction inside its cavity. The key to the use of sub-stoichiometric amounts of copper was the addition of excess pyridine, which acted as a competing ligand; under such conditions it proved possible to isolate rotaxane 66 in 82% yield using only 4 mol % Cu(I), with respect to 64 and 65. Sauvage and co-workers have also employed the
"click reaction", however in this case it was used to attach stoppers to a pseudorotaxane assembled via their generic Cu(I) phenanthroline template. 89

1.3.2. Square Planar

Up until 2004 there were no examples of interlocked structures whose assembly was directed by a metal ion with a square planar geometrical preference. The closest example, again from Sauvage, was the palladium(II) templated synthesis of pseudo[2]rotaxane 70 (Scheme 1.15). 90 This square-planar template uses a 3+1 approach, the tridentate unit, a 2,2'6',2''-terpyridine (terpy), is incorporated into the macrocycle 67, which is pre-coordinated with the palladium metal ion affording 68. Subsequent reaction with the monodentate, pyridine-functionalised thread 69 gives the square planar palladium pseudorotaxane 70 in quantitative yield. Further to this work (and the work described in chapter 2), an example of a [2]rotaxane templated about a palladium(II) metal ion was published by Takata and Hiraro. 91

Scheme 1.15. Synthesis of a pseudorotaxane assembled via a square planar palladium (II) template.

1.3.3 Trigonal Bipyramidyl

There are also limited examples of architectures assembled via a 5-coordinate metal template and not surprisingly, the first example hails from Sauvage who used Zn(II), a metal ion that will readily adopt either 4, 5 or 6 coordinate complexes, to assemble catenane 75 from a combination of tridentate and bidentate components (Scheme 1.16). 92 The trigonal bipyramidyl catenane 75 was formed via initial metal complexation of terdentate macrocycle 71 with Zn(OTf)₂ to form 72, which was then further complexed with the phenanthroline bidentate unit 73 to afford 74. Cyclisation
of 74's olefin-terminated phenanthroline ligand via RCM and subsequent hydrogenation of its internal double bond afforded the penta-coordinated zinc(II) catenane 75. The free catenane 76 was achieved simply by stirring a dichloromethane solution of the metalated catenane with an aqueous base solution. Analogous to their work with the tetrahedral template, they found that catenane 76 could be remetallated with Zn(II) and other metal ions such as Cu(II) and Fe(II) forming 77a and 77b respectively.

Scheme 1.16. Zn(II) templated synthesis of a catenane with a trigonal bipyramidal geometry about its metal centre.

One of the most significant metal-template syntheses to exploit the penta-coordination preference of Zn(II) was the remarkable one-pot synthesis published by Stoddart and co-workers (Scheme 1.17). It used six Zn(II) metal ions to help direct the self-assembly of Borromean rings 80, in near quantitative yield, from six exo-bidentate bipyridyl ligands 78 and six endo-diiminopyridyl ligands 79. The assembly of such an intricate molecule from eighteen discrete building blocks was made possible by the reversible nature of both imine bond formation and Zn-N coordination, which enabled the system to reach a thermodynamic minimum through continual error-checking and error-correction steps. The impressive structure was
unambiguously confirmed upon elucidation of the X-ray crystal data, which also illustrated that other non-covalent forces played a part in the assembly process, evidenced by the fact that each bipyridyl unit is flanked by a pair of phenolic rings at a distance ideally suited for π-stacking. Further studies have shown that the Borromean ring organic ligand is stable in the absence of the Zn(II) ions following reduction of the imines (as we have previously seen in an example from Nitschke, reducing the imine bonds ‘fixes’ the interlocking) and that cleavage of any one of the links results in complete dissociation of the two remaining rings. Stoddart and co-workers subsequently synthesised a range of Borromean rings templated by other transition metals ions such as Cu(II), Ni(II), Cd(II), Mn(II) and Co(II). Intriguingly, when they used a mixed metal template of Zn(II) and Cu(II), with the same ligands and reaction conditions, they found that instead of forming a Borromean ring system a doubly interlocked catenane (or Solomon Knot) was formed.

Scheme 1.17. The one-pot thermodynamic self-assembly synthesis of Borromean rings by Stoddart.

1.3.4 Octahedral

Further to Sauvage and co-workers use of ruthenium(II)-terpyridine derived ligands to template the formation of a catenane (Scheme 1.8), these same terdentate ligands were applied to the construction of the first octahedral metal templated knot 81 (Figure 1.14) using the first-row transition metal Fe(II). The synthesis also benefited
from the application of the a ring-closing metathesis approach, which had previously been applied to the synthesis of the Cu(I) tetrahedral templated knot.\textsuperscript{67a} Unfortunately, as previously mentioned, this coordination motif could not be successfully applied to the syntheses of catenanes.\textsuperscript{34a} Another interesting example of an open knotted structure with an octahedral metal centre (Figure 1.14) was reported by Hunter in 2001.\textsuperscript{95} A multidentate ligand containing three bipyridyl units coordinates to a Zn(II) ion in a fashion that entwines the biphenyl units such that open knot complex 82 is formed. The folding process is also fully reversible; addition of excess chloride ion regenerates the free ligand.

![Figure 1.14. Metal templated knots with octahedral geometries about their metal centres.](image)

That same year, Leigh reported the first general method for preparing catenanes using a variety of octahedral transition metals (Scheme 1.15).\textsuperscript{96} The ligand system used in this study was based on a tridentate 2,6-diiminopyridine coordination motif, 83. Two distinct methods were used for preparing the same catenanes. The first, a kinetically controlled approach, involved forming the precatenane metal complex 84, by simple addition of the ligand 83 to the precursor metal reagent, while subsequent ring-closing metathesis of the terminal alkenes generated the interlocked products in good yields.
In the second method, the catenanes could be assembled *in situ* by treatment of a bis-amine with 2,6-pyridinedicarbaldehyde and the metal reagent in methanol. Further study of the zinc catenane 85f revealed the remarkable stability of the complexed catenane, which could not be demetallated using EDTA/disodium salt; it was only when the imine bonds had been reduced, labilising the metal, that these demetallation conditions could be used to afford free catenane 86.

Slight adaptation of this system was required in order to make the analogous rotaxanes 90a-h (Scheme 1.16), since using the imine macrocycle precursor ligand 83 in conjunction with a similar tridentate thread would have lead to the formation of
unwanted thread-thread and catenane complexes. Instead by using a preformed bis-amine macrocycle 88, rotaxanes could be formed in virtually quantitative yields by simply mixing with bulky aniline 87, 2,6-diformylpyridine 89 and the appropriate metal perchlorate salt. The fact that the rotaxane is the thermodynamically favoured product was further demonstrated by pre-forming the double-thread complex, which fully rearranged to the interlocked product when exposed to the macrocycle. This preference was attributed to the presence of π-stacking between the thread and macrocycle in the rotaxane, which is absent in the double-thread complex.

In 2003, Sauvage published the synthesis of catenane 94 (Scheme 1.17) assembled via a new Ru(II) coordinated octahedral template with a 4+2 binding motif.98 The tetradeionate ligand, constructed by covalently linking two bidentate 1, 10-phenanthrolines units, was cyclised to give the pre-formed macrocycle 91. Following complexation of this macrocycle with ruthenium, the bidentate 2,2'-bipyridine acyclic ligand 92 was simultaneously complexed and threaded to give the pre-catenane 93, which was subsequently cyclised to afford catenane 94.

Scheme 1.17. New octahedral coordination motif from Sauvage.
In contrast to the previous Ru(II) bis-terpy catenane 34 (see Scheme 1.8) which could not be demetallated, this new coordination motif affords the advantage that the ruthenium metal ion can be photochemically de-coordinated from the bipyridine unit giving a structure, in this case catenane 95, where the two ligands are held together by only a mechanical bond. This system has shown some versatility; catenanes can also be assembled using a double macrocyclisation approach\textsuperscript{98c} and additionally, Rhodium(II), another second-row transition metal, has also been employed in the synthesis of an analogous catenane.\textsuperscript{99} Unfortunately, this set of ligands has met with limited success when employed with first-row transition metals such as Zn(II) and Fe(II).\textsuperscript{98b}


This ruthenium "4+2" approach has also been adapted slightly and applied to the synthesis of rotaxanes (Scheme 1.18).\textsuperscript{100} In these syntheses the set-up of the
threading partners is reversed compared to that of the synthesis of the catenane in Scheme 1.17. The tetradeative unit now forms part of acyclic thread 96 whereas the bidentate bi-pyridyl unit is incorporated into macrocycle 97. Initially, the synthesis of a rotaxane using the exact same Ru(II)(diamine)₃ core as catenane 94 was attempted, but it led to a mixture of interlocked and non-interlocked isomers that could not be separated. However, this problem was overcome by altering the bidentate macrocyclic structure to incorporate two phenyl groups, making it more rigid. The synthesis then followed a rotaxane strategy of threading and complexation, to form pseudorotaxane 98, and a subsequent stoppering reaction with trityl blocking groups to form the Ru(II) [2]rotaxane 99. In an analogous fashion to the synthesis of the catenane, the macrocycle and thread could be separated from each other by irradiation with UV light to afford 100.

\[ \text{Scheme 1.19. Seigel's octahedral coordination motif for the metal templated synthesis of catenanes.} \]
Siegel and co-workers have also developed an octahedral template strategy for the assembly of catenanes that has roots in Sauvage’s early octahedral work. This study employed manisyl-substituted tridentate 2,2’; 6’, 2” terpyridine and 2-pyridin-2-yl-1,10-phenanthroline based ligands for the syntheses of catenanes (Scheme 1.19).34b

Their initial synthetic strategies involved the double macrocyclisation of the Ru(II)terpyridine derivative of 102 via the ring-closing metathesis of alkene terminated polyethers; however, this led to the formation of a mixture of catenane and macrocyclic figure of eight complex in a 1:2 ratio respectively. Further to this they switched to a copper-mediated acetylenic cyclisation of 102; but this time a mixture of catenane 103 and “figure of eight” complex 104 persisted in the same ratio for both types of tridentate ligands with polyether R groups. Altering the R group to include a biphenyl linker provided increased rigidity and improved the ratio to a 1:1 mixture. Intriguingly, when the metal was switched to Fe(II) 105 and they reverted to ring-closing metathesis conditions for the cyclising step, exclusive formation of catenane 106 resulted. This is in contrast to the work of Sauvage who found that a double RCM of their Fe(II) terpyridine complex resulted solely in figure of eight complex. The thermodynamic stability of the ruthenium octahedral complexes prevented demetalation, as expected but removal of the more labile iron metal ion from catenane 106 was accomplished by oxidation, using hydrogen peroxide under basic conditions, to afford demetallated catenane 107.

1.4 Summary

Upon reflection of the previously mentioned work, one can see that the metal-template approach provides access to a wide variety of interlocked and entangled structures. There are numerous structures that are assembled about a tetrahedral metal core geometry, most of which exploit Sauvage’s Cu(I) bis-phenanthroline motif. There are also an increasing number of examples that utilise transition metal ions with octahedral metal preferences. However, development of ligand coordination motifs for metals with a square planar geometrical preference has been limited. Palladium(II), which been used extensively in the formation of catenanes and some rotaxanes assembled via method 3, has only rarely been used to template
the assembly of interlocked architectures; when work for this thesis began there were no examples of rotaxanes or catenanes whose assembly was templated by a metal ion with square planar coordination. The work described in the following chapters aims to fill this knowledge gap, exemplified by the application of a palladium(II) square planar coordination motif to a broad spectrum of interlocked and entangled structures. Proof of concept is demonstrated in Chapter 2 by the successful application of the template to the assembly of a [2]rotaxane. Chapter 3 outlines how this template can additionally be utilised for the synthesis of [2]catenanes and that it can be used to selectively control the assembly of specific products based on the order in which the components are cyclised. The modular and versatile nature of this palladium(II) coordination motif is exemplified in Chapter 4, where it is used to selectively assemble multi-ring rotaxanes using only a single metal-binding site in the thread. Finally, Chapter 5 describes how this palladium(II) coordination motif can be applied to the selective syntheses of a unique pair of sequence isomers.

1.5 References


Burchell, T. J.; Eisler, D. J.; Puddephatt, R. J. *Dalton Trans.* **2005**, 268-272. (q) 


[72] (a) Michael, D.; Mingos, P.; Yau, J.; Menzer, S.; Williams, D. J. *Angew. Chem. Int. Ed.* **1995**, *34*, 1894-1895. (b) "Aurophilic" interactions are the attractive forces between gold atoms; they are of similar strength to hydrogen-bonds.


Chapter 1


Chapter 2: Structural Requirements for the Assembly of a Square Planar Metal-Coordinated [2]Rotaxane


Acknowledgements

The following people are gratefully acknowledged for their contribution to this chapter: Dr. P. Lusby and Dr. D. Barney Walker for the synthesis of rotaxanes Pd6 and 6H2 and analogous compounds; Dr I. D. H. Oswald and Dr. S. Parsons solved the X-ray crystal structure of Pd6.
2.1 Introduction

The starting point for the revolution in catenane and rotaxane synthesis that occurred during the last part of the 20th century was Sauvage's realisation that metal-ligand coordination geometries could fix molecular fragments in three-dimensional space such that they were predisposed to form mechanically interlocked architectures through macrocyclisation or 'stoppering' reactions.1 Efficient synthetic methods to rotaxanes were subsequently developed based on four2 (tetrahedral), five3 (trigonal bipyramidal and square pyramidal) and, most recently, six4 (octahedral) coordinate metal templates (Figure 2.1).5

![Figure 2.1](image)

Figure 2.1. Exploiting transition metal-ligand geometries in the synthesis of mechanically interlocked architectures: (a) tetrahedral, (b) square pyramidal and trigonal bipyrimidal, (c) octahedral and (d) square planar coordination motifs.

One of the benefits of using specific coordination motifs for such assemblies is that the resulting interlocked ligands often do not permit other metal geometries in their binding site, which can consequently be exploited either to lock a metal in an unusual geometry for its oxidation state6 or to bring about large amplitude 'shuttling' of the ligand components.3,7 Here we show that three-dimensional interlocked architectures can also be assembled from two-dimensional coordination templates, using steric and electronic restrictions to direct the synthesis in the third dimension. The resulting [2]rotaxane is the first example of a mechanically interlocked ligand that forms a four-coordinate square planar metal complex.8
2.2 Results and Discussion

The square planar [2]rotaxane ligand design consists of a tridentate benzylic amide macrocycle and a monodentate thread (Figure 2.1d). The macrocycle incorporates a 2,6-dicarboxyamidopyridine unit in order to exploit palladium chemistry recently developed\textsuperscript{9} by Hirao. The thread contains a pyridine donor substituted either 2,6- or 3,5- with appropriately bulky stoppers. It was envisioned that in the key intermediate, Pd(1)(2-5) (Scheme 2.1), the geometry of the precursor to the macrocycle (previously used to direct hydrogen bond assembly processes\textsuperscript{10}) would promote intercomponent π-π stacking, causing the pyridine donor of the thread to bind the metal orthogonally to the N\textsubscript{3}-ligand (complimenting the normally preferred orientation\textsuperscript{11}) thus directing the assembly in the third dimension. A series of readily available threads 2-5 was investigated during the study.

The rotaxane synthesis was carried out according to Scheme 2.1. Treatment of 1H\textsubscript{2} with Pd(OAc)\textsubscript{2} in acetonitrile smoothly generated a complex Pd(1)(CH\textsubscript{3}CN) in which the metal’s fourth coordination site is occupied by a normally labile acetonitrile molecule. Nevertheless, displacement of the acetonitrile by bis-ester pyridine ligand 4 was unsuccessful (vide infra). However, simple combination of 5 or either of the bis-ether pyridine threads, 2 and 3, with Pd(1)(CH\textsubscript{3}CN) in either dichloromethane or chloroform gave the desired complexes Pd(1)(5/2/3) in 97, 63 and 96% yields, respectively.
Scheme 2.I. Reagents and conditions: (i) Pd(OAc)$_2$, CH$_3$CN, 76%; (ii) CHCl$_3$, 50 °C; 2 63%, 3 96%, 4 0%, 5 97%; (iii) 1. Grubbs' catalyst (0.1 equiv), CH$_2$Cl$_2$; 2. H$_2$, Pd-C, THF, 6H$_2$ 98%, 3 + 7H$_2$ 63%, 5 + 7H$_2$ 69% (over 2 steps); (iv) KCN, MeOH, CH$_2$Cl$_2$, 20 °C, 1 h and then 40 °C, 0.5 h, 97%.
The $^1$H NMR spectrum of Pd(1)(2) is shown in Figure 2c. Comparison with the spectra of Pd(1)(CH$_3$CN) and 1H$_2$ (Figure 2.2b and 2.2a, respectively) shows features clearly indicative of metal coordination (the absence of H$_C$ and shifts in H$_A$ and H$_B$) and the anticipated aromatic stacking between the tridentate and monodentate ligands (particularly H$_E$ and H$_F$). Similar chemical shift differences were observed for Pd(1)(3) and Pd(1)(5), however, ring closing olefin metathesis (RCM) followed by hydrogenation (Scheme 2.1, step iii) of the three complexes produced very different results. Whilst cyclisation of Pd(1)(2) gave the corresponding [2]rotaxane Pd6 in 77% yield following hydrogenation of the olefin, no [2]rotaxane was produced from RCM of Pd(1)(3) or Pd(1)(5), the only products in each case being uninterlocked macrocycle and thread. Why does only one of the four threads direct rotaxane synthesis in the desired manner?

Figure 2.2. $^1$H NMR spectra (400 MHz, 9:1 CDCl$_3$:CD$_3$CN, 298 K) of: (a) 1H$_2$, (b) Pd(1)(CH$_3$CN), (c) Pd(1)(2), (d) [2]rotaxane Pd6. The lettering refers to the assignments in Scheme 1.1.
The $^1$H NMR spectra of the [2]rotaxane (Pd6, Figure 2.2d), mass spectrometry and the preserved association of the organic fragments upon demetallation, unambiguously confirmed the interlocked structure. In addition to the loss of the terminal olefin protons, some subtle differences in the $^1$H NMR spectrum of Pd6 compared to Pd(1)(2) (Figure 2.2c) indicates that some rearrangement of the ligands does occur on rotaxane formation. Single crystals of Pd6 suitable for X-ray crystallography$^{[12]}$ were grown by slow cooling of a warm, saturated solution of the [2]rotaxane in acetonitrile.

![Figure 2.3. X-ray crystal structure of rotaxane Pd6 showing: (a) staggered and (b) side-on views.$^{[12]}$ Carbon atoms of the macrocycle are shown in light blue and those of the thread in yellow; oxygen atoms are red, nitrogen dark blue, palladium grey. Selected bond lengths [Å]: Pd-N15 1.95, Pd-N25 1.86, Pd-N32 2.04, Pd-N59 2.02; other selected distance [Å]: N15-N25 3.81; macrocycle bite angle [°]: N59-Pd-N32 160.0. The macrocycle is disordered over two similar sites (50:50), but one is omitted for clarity together with the hydrogen atoms.](image)

The solid state structure (Figure 2.3) shows the interlocked architecture and the pseudo- (the N$_3$-bite angle is 160.0°) square planar geometry of the palladium. The
\[ \pi \]-stacking between the macrocycle and the pyridine of the thread so apparent in solution from the \(^1\)H NMR shifts is significantly offset in the solid state (side-on view, figure 2.3b). The co-conformation adopted by the macrocycle and thread in the rotaxane crystal structure clearly illustrates why RCM of the complexes formed with the 3,5-disubstituted threads (Pd(1)(3) and Pd(1)(5)) can lead to uninterlocked products; even with both fragments attached to the metal, cyclisation of 1 can readily occur without encircling a 3,5-substituted pyridine thread. Similarly, the conformation of the thread suggests a possible reason for the lack of reactivity of the 2,6-bis-ester thread, 4, towards Pd(1)(CH\(_3\)CN). In the crystal structure the electron density of the ether oxygen atoms of the thread is directed away from the occupied \(d_{2z}\) orbital lobes which lie above and below the plane of the square planar geometry \(d^8\) palladium. Chelation by 4 to Pd1 has to occur orthogonally for steric reasons. Such an arrangement would force electron density from the ester carbonyl groups into this high energy space.

**Figure 2.4.** \(^1\)H NMR spectra (400 MHz, CDCl\(_3\), 298 K) of: (a) macrocycle 7H\(_2\), (b) demetallated [2]rotaxane 6H\(_2\), (c) thread 2. The lettering refers to the assignments in Scheme 1.1.
Demetallation of Pd6 with potassium cyanide (Scheme 2.1, step iv) generates the free [2]rotaxane 6H2 in 97% yield confirming that once formed the coordination bonds are not required to stabilise the interlocked architecture. The 1H NMR spectrum of 6H2 and its uninterlocked components in CDCl3 are shown in Figure 2.4. The shielding of the benzyl groups in the rotaxane compared to the free macrocycle, together with the large (1.7 ppm) downfield shift in the amide protons (Hc), indicate that specific hydrogen bonding interactions between the thread and the macrocycle are 'switched on' by the demetallation-protonation procedure. It appears that the amide groups of 6H2 simultaneously hydrogen bond to the pyridine groups in both macrocycle and thread.

In conclusion, we have described methodology for assembling a three-dimensional interlocked molecular architecture from a two-dimensional metal template. A combination of steric and electronic factors direct the synthesis in the third dimension, either promoting or preventing interlocking. The resulting [2]rotaxane is the first derived from a square planar coordinated metal and completes the series of mechanically interlocked ligands for common transition metal geometries started by Sauvage in 1983.

2.3 Experimental Section

Unless stated otherwise, all reagents and anhydrous solvents were purchased from Aldrich Chemicals and used without further purification. (p-hydroxyphenyl)tris(p-tert-butylphenyl)methane16 and 4-(hex-5-enyloxy)benzylamine17 were prepared according to literature procedures.
**N,N’-Bis[4-(hex-5-enyloxy)benzyl]-2,6-pyridinedicarboxamide 1H2**: To a solution of 4-(hex-5-enyloxy)benzylamine (2.18 g, 10.6 mmol) and triethylamine (1.07 g, 10.6 mmol) in dichloromethane (50 mL) at 0 °C under an atmosphere of nitrogen was added slowly 2,6-pyridinedicarbonyl dichloride (1.08 g, 5.30 mmol). The reaction was then stirred at room temperature for 18 h. The solvent was removed under reduced pressure and the crude residue purified by column chromatography (1:9 EtOAc/CH2Cl2) and then recrystallised from acetonitrile to yield the title compound as a colourless crystalline solid (2.61 g, yield = 91%). m.p. 141.2-143.0 °C; ¹H NMR (400 MHz, CDCl3, 298 K): δ = 1.46 (m, 4H, H_{alkyl}), 1.68 (m, 4H, H_{alkyl}), 2.02 (m, 4H, H_{alkyl}), 3.81 (t, 4H, J = 6.6 Hz, H_{C}), 4.44 (d, 4H, J = 6.3 Hz, H_{D}), 4.90 (m, 4H, H_{D}), 5.73 (m, 2H, H_{D}), 6.68 (d, 4H, J = 8.8 Hz, H_{F}), 7.11 (d, 4H, J = 8.8 Hz, H_{E}), 7.90 (t, 1H, J = 7.8 Hz, H_{A}), 8.22 (d, 2H, J = 7.8 Hz, H_{B}), 8.62 (t, 2H, J = 6.3 Hz, H_{C}); ¹³C NMR (100 MHz, CDCl3, 298 K): δ = 25.3, 28.7, 33.4, 42.9, 67.8, 114.6, 114.8, 125.2, 129.0, 129.9, 138.5, 138.9, 148.8, 158.5, 163.5; LRFAB-MS (3-NOBA matrix): m/z = 541 [M]⁺, 564 [MNa]⁺; HRFAB-MS (3-NOBA matrix): m/z = 541.29425 (calcd. for C_{33}H_{39}N_{3}O_{4}, 541.29406).
[(N,N’-Bis[4-(hex-5-enyloxy)benzyl]-2,6-pyridinedicarboxamido)palladium(II) (acetonitrile)] Pd(1)(CH₃CN): To 1H₂ (0.480 g, 8.86x10⁻¹ mmol) and palladium(II) acetate (0.199 g, 8.86x10⁻¹ mmol) was added anhydrous acetonitrile (50 mL). The reaction was stirred at room temperature under an atmosphere of nitrogen for 4 h. The resulting suspension was filtered off, washed with excess acetonitrile (25 mL), and dried in air to yield the title compound as a yellow/green solid (0.465 g, yield = 76%). m.p. 120 °C (dec); ¹H NMR (400 MHz, 9:1 CDCl₃:CD₃CN, 298 K): δ = 1.47 (m, 4H, H₄), 1.69 (m, 4H, H₄), 1.93 (s, 3H, Pd–NCC₃), 2.03 (m, 4H, H₄), 3.85 (m, 4H, J = 6.3 Hz, H₆), 4.38 (s, 4H H₂D), 4.89 (m, 4H, H₂), 5.74 (m, 2H, H₂), 6.73 (d, 4H, J = 8.6 Hz, H₂), 7.13 (d, 4H, J = 8.6 Hz, H₂), 7.65 (d, 2H, J = 7.6 Hz, H₂), 8.00 (t, 1H, J = 7.6 Hz, H₂); ¹³C NMR (100 MHz, 9:1 CDCl₃:CD₃CN, 298 K): δ = 0.5, 27.4, 32.1, 48.1, 66.5, 112.9, 113.3, 115.3, 123.4, 127.1, 132.1, 137.2, 139.8, 151.8, 156.4, 156.5, 169.1; LRFAB-MS (3-NOBA matrix): m/z = 646 [Pd1H]⁺, HRFAB-MS (3-NOBA matrix): m/z = 646.18925 (calcd. for C₃₃H₃₈N₃O₄Pd, 646.18943).
To a THF solution (50 mL) of (p-hydroxyphenyl)tris(p-tert-butylphenyl)methane, (1.50 g, 2.97 mmol), 2,6-pyridinedimethanol (0.21 g, 1.49 mmol) and triphenylphosphine (0.778 g, 2.97 mmol), under an atmosphere of N₂ at 0 °C, was added dropwise DIAD (0.70 mL, 2.97 mmol). The solution was allowed to warm to room temperature and stirred for 18 h. The solvent was then removed under vacuum, and methanol (50 mL) added to the crude residue. The resulting white solid was filtered off, and purified by column chromatography (CDCl₃) to yield the title compound as a colourless solid (0.952 g, yield = 64%). m.p. 277 °C (dec); ¹H NMR (400 MHz, CDCl₃, 298 K): δ = 1.29 (s, 54H, Hₘ), 5.18 (s, 4H, Hₙ), 6.84 (d, 4H, J = 8.8 Hz, Hₚ), 7.08 (m, 16H, Hₚ + H₟), 7.22 (d, 12H, J = 8.8 Hz, Hₚ), 7.48 (d, 2H, J = 7.6 Hz, Hₚ), 7.76 (t, 1H, J = 7.6 Hz, Hₙ); LRFAB-MS (3-NOBA matrix): m/z = 1112 [MH]⁺; HRFAB-MS (3-NOBA matrix): m/z = 1112.72910 (calcd. for C₂₈₂H₂₉₄NO₂, 1112.72846).

To a THF solution (50 mL) of (p-hydroxyphenyl)tris(p-tert-butylphenyl)methane, (0.725 g, 1.44 mmol), 3,5-pyridinedimethanol (0.100 g, 7.2x10⁻¹ mmol) and triphenylphosphine (0.415 g, 1.60 mmol), under an atmosphere of N₂ at 0 °C, was added dropwise DIAD (0.3 mL, 1.6 mmol). The solution was allowed to warm to
room temperature and stirred for 18 h. The solvent was then removed under vacuum, and methanol (50 mL) added to the crude residue. The resulting white solid was filtered off, and purified by column chromatography (CDCl₃) to yield the title compound as a white solid (0.480 g, yield = 60%). m.p. 265 °C (dec); ¹H NMR (400 MHz, CDCl₃, 298 K): δ = 1.28 (s, 54H, Hₙ), 5.08 (s, 4H, Hₑ), 6.83 (d, 4H, J = 9.2 Hz, Hₑ), 7.06 (d, 12H, J = 8.6 Hz, Hₑ), 7.11 (d, 4H, J = 9.2 Hz, Hₐ), 7.22 (d, 12H, J = 8.6 Hz, Hₑ), 7.92 (m, 1H, Hᵢ), 8.65 (m, 2H, Hₐ); ¹³C NMR (100 MHz, CDCl₃, 298 K): 29.4, 32.4, 111.3, 122.1, 128.8 (x2), 130.5, 133.5, 138.6, 142.0, 146.4, 151.3, 154.1, 155.9, 205.1; LRFAB-MS (3-NOBA matrix): m/z = 1112 [MH]⁺; HRFAB-MS (3-NOBA matrix): m/z = 1112.72797 (calcd. for C₈₁H₉₄NO₂, 1112.72846).

3-{4-[Tris-(4-tert-butyl-phenyl)-methyl]-phenoxy}-propan-1-ol:
(p-hydroxyphenyl)tris(p-tert-butylphenyl)methane (1.00 g, 2 mmol), 3-bromopropan-1-ol (0.268 g, 2.00 mmol), potassium carbonate (2.7 g, 20 mmol) and sodium iodide (0.01 g 0.07 mmol) were dissolved in butanone (100 mL) and the mixture was heated at reflux for 18 h. The solution was then filtered and the solvent was removed under vacuum. The crude residue was purified by column chromatography (1:9, EtOAc:CH₂Cl₂) to give the title compound as a white solid (0.991 g, yield = 88%). m.p. 290 °C (dec); ¹H NMR (400 MHz, CDCl₃, 298 K): δ = 1.29 (s, 27H, Hᵢ), 2.02 (m, 2H, Hₐ), 3.85 (t, 2H, J = 6.0 Hz, Hₑ), 4.10 (t, 2H, J = 6.2 Hz, Hₑ), 6.76 (d, 2H, J = 9.0 Hz, Hₑ), 7.07 (m, 8H, Hᵢ+ Hₐ), 7.22 (d, 6H, J = 8.5 Hz, Hₑ); ¹³C NMR (100 MHz, CDCl₃, 298 K): δ = 25.4, 28.1, 28.4, 28.7, 42.9, 67.4, 114.7, 125.3, 129.2, 129.8, 148.8, 158.6, 163.3, 169.7; LRFAB-MS (3-NOBA matrix): m/z = 562 [M]⁺; HRFAB-MS (3-NOBA matrix): m/z = 562.38039 (calcd. for C₄₀H₅₀O₂, 562.38108).
4: EDCI (0.182 g, 0.95 mmol) was added to a solution of pyridine-2,6-dicarboxylic acid (0.072 g, 4.3x10^{-1} mmol) and 3-\{4-[Tris-(4-tert-butyl-phenyl)-methyl]-phenoxy\}-propan-1-ol (0.484 g, 8.6x10^{-1} mmol) in dichloromethane (50 mL) and the mixture was cooled to 0 °C. A solution of DMAP (0.021 g, 1.7x10^{-1} mmol) in dichloromethane (10 mL) was added dropwise and the mixture was stirred for 3 h. The solution was then washed with, 1 M hydrochloric acid (20 mL), saturated aqueous sodium bicarbonate (20 mL) and saturated aqueous sodium chloride (20 mL). The dichloromethane washings were combined and dried with sodium sulfate and the solvent was removed under reduced pressure to yield the title compound as a white solid, (0.430 g, yield = 84%). m.p. 281-282 °C; \(^1\)H NMR (400 MHz, CDCl\(_3\), 298 K): \(\delta = 1.28\) (s, 54H, H\(_i\)), 2.25 (m, 4H, H\(_d\)), 4.03 (t, 4H, \(J = 6.0\) Hz, H\(_e\)), 4.52 (t, 4H, \(J = 6.4\) Hz, H\(_c\)), 6.79 (d, 4H, \(J = 8.6\) Hz, H\(_g\)), 7.28 (m, 16H, H\(_f\)+ H\(_i\)), 7.21 (d, 12H, \(J = 8.4\) Hz, H\(_b\)), 7.90 (t, 1H, \(J = 8.0\) Hz, H\(_a\)), 8.18 (d, 2H, \(J = 8.0\) Hz, H\(_b\)); \(^{13}\)C NMR (100 MHz, CDCl\(_3\), 298 K): \(\delta = 31.4, 34.3, 60.8, 65.8, 112.9, 124.1, 127.9, 130.7, 132.3, 138.2, 139.8, 144.1, 148.3, 148.5, 156.5, 157.9, 164.6, 183.8); LRFAB-MS (3-NOBA matrix): \(m/z = 1257\) [MH]+; HRFAB-MS (3-NOBA matrix): \(m/z = 1256.76819\) (calcd. for C\(_{87}H_{102}NO_{6}\), 1256.77072).
5: EDCI (0.182 g, 9.5x10^{-1} mmol) was added to a solution of pyridine-3,5-
dicarboxylic acid (0.072 g, 4.3x10^{-1} mmol) and 3-{4-[tris-(4-tert-butyl-phenyl)-
methyl]-phenoxy}-propan-1-ol (0.484 g, 8.6x10^{-1} mmol) in dichloromethane (50 
ml) and the mixture was cooled to 0 °C. A solution of DMAP (0.021 g, 1.7x10^{-1} 
mmol) in dichloromethane (10 mL) was added dropwise and the mixture was stirred 
for 3 h. The solution was then washed with, 1 M hydrochloric acid (20 mL), 
saturated aqueous sodium bicarbonate (20 mL) and saturated aqueous sodium 
chloride (20 mL). The dichloromethane washings were combined and dried with 
sodium sulfate and the solvent was removed under reduced pressure to yield the title 
compound as a white solid, (0.40 g, yield = 83%). m.p. 276-277 °C; \textsuperscript{1}H NMR (400 
MHz, CDCl\textsubscript{3}, 298 K): \( \delta = 1.28 \) (s, 54H, \( H_j \)), 2.25 (m, 4H, \( H_d \)), 4.08 (t, 4H, \( J = 6.0 
Hz, H_e \)), 4.57 (t, 4H, \( J = 6.4 \) Hz, \( H_c \)), 6.74 (d, 4H, \( J = 8.6 \) Hz, \( H_g \)), 7.06 (m, 16H, \( H_f + H_h \)), 7.21 (d, 12H, \( J = 8.4 \) Hz, \( H_b \)), 8.81 (s, 1H, \( H_i \)), 9.35 (s, 2H, \( H_a \)); \textsuperscript{13}C NMR 
(100 MHz, CDCl\textsubscript{3}, 298 K): \( \delta = 26.8, 29.6, 32.1, 61.0, 62.0, 111.0, 122.4, 124.2, 
128.5, 130.4, 136.1, 138.0, 142.2, 146.4, 152.3, 154.5, 155.9, 162.5 \); LRFAB-MS (3-
NOBA matrix): \( m/z = 1257 \) [MH\textsuperscript{+}]; HRFAB-MS (3-NOBA matrix): \( m/z = 
1256.77142 \) (calcd. for \( \text{C}_{87}\text{H}_{102}\text{NO}_{6} \), 1256.77072).
Pd(1)(2): 2 (0.344 g, 3.09x10^{-1} mmol) and [Pd(1)(CH_3CN)] (0.255 g, 3.71x10^{-1} mmol) were gently heated (50 °C) in CHCl_3 (25 mL) for 10 minutes, and then stirred for a further 1 h at room temperature. The solvent was removed under reduced pressure, and the crude residue purified by column chromatography (1:24 EtOAc:CH_2Cl_2) to give the title compound as a yellow solid (0.344 g, yield = 63%).

m.p. 172 °C (dec); \(^1\)H NMR (400 MHz, CD_2Cl_2, 298 K): \(\delta\) = 1.28 (s, 54H, H_h), 1.38 (m, 4H, H_{alkyl}), 1.54 (m, 4H, H_{alkyl}), 2.00 (m, 4H, H_{alkyl}), 3.53 (t, 4H, J = 6.3 Hz H_C), 3.94 (s, 4H, H_D), 4.90 (m, 4H, H_I), 4.93 (s, 4H, H_c), 5.74 (m, 2H, H_H), 6.39 (s, 8H, H_E + H_F), 6.76 (d, 4H, J = 8.8 Hz, H_e), 7.12 (m, 16H, H_d + H_g), 7.25 (d, 12H, J = 8.8 Hz, H_D), 7.63 (d, 2H, J = 7.8 Hz, H_b), 7.77 (d, 2H, J = 7.8 Hz, H_b), 8.01 (t, 1H, J = 7.8 Hz, H_a), 8.09 (t, 1H, J = 7.8 Hz, H_A); \(^{13}\)C NMR (100 MHz, CD_2Cl_2, 298 K): \(\delta\) = 25.7, 29.1, 31.5, 33.8, 34.6, 48.9, 63.5, 67.8, 69.5, 114.0, 114.5, 114.7, 122.6, 124.6, 125.0, 128.4, 130.8, 132.4, 133.3, 139.0, 140.1, 141.2, 141.2, 144.7, 148.9, 153.2, 155.7, 158.2, 159.3, 171.3; LRFAB-MS (3-NOBA matrix): \(m/z = 1757\ [M]^+\); HRFAB-MS (3-NOBA matrix): \(m/z = 1757.90693\) (calcd. for \(^{12}\)C_{113}^{13}\)CH_{130}N_4O_6^{106}\)Pd, 1757.90559).
Pd(1)(3): 3 (0.100 g, 9x10^{-2} mmol) and [Pd(1)(CH3CN)] (0.062 g, 9x10^{-2} mmol) were gently heated (50 °C) in dichloromethane (10 mL) for 10 minutes, and then stirred for a further 1 h at room temperature. The solvent was removed under reduced pressure to give the title compound as a yellow solid (0.152 g, yield = 96%). m.p. 187 °C (dec); \textsuperscript{1}H NMR (400 MHz, CDCl3, 298 K): δ = 1.28 (s, 54H, H_{b}), 1.41 (m, 8H, H_{alyl}), 1.97 (m, 4H, H_{alyl}), 3.71 (t, 4H, J = 6.5 Hz, H_{G}), 4.15 (s, 4H, H_{e}), 4.69 (s, 4H, H_{D}), 4.90 (m, 4H, H_{l}), 5.70 (m, 2H, H_{il}), 6.49 (d, 4H, J = 8.5 Hz, H_{F}), 6.58 (d, 4H, J = 8.5 Hz, H_{B}), 6.80 (d, 4H, J = 8.5 Hz, H_{e}), 7.05 (d, 12H, J = 8.5 Hz, H_{g}), 7.15 (d, 4H, J = 8.5 Hz, H_{d}), 7.21 (d, 12H, J = 8.5 Hz, H_{j}), 7.73 (s, 1H, H_{a}), 7.76 (s, 2H, H_{b}), 7.85 (d, 2H, J = 8.0 Hz, H_{b}), 8.09 (t, 1H, J = 8.0 Hz, H_{d}); \textsuperscript{13}C NMR (100 MHz, CDCl3, 298 K): δ = 25.3, 28.7, 31.4, 33.4, 34.3, 48.0, 65.6, 67.7, 113.1, 113.9, 114.8, 124.1, 124.8, 127.8, 130.7, 132.6, 133.0, 134.9, 135.1, 138.4, 140.6, 141.1, 143.9, 148.5, 153.1, 155.4, 157.3, 157.8, 157.9, 170.8; LRFAB-MS (3-NOBA matrix): \textit{m/z} = 1758 [M]; HRFAB-MS (3-NOBA matrix): \textit{m/z} = 1757.90303 (calcd. for $^{\text{12}}$C_{113}$^{\text{13}}$CH_{130}N_{4}O_{5}$^{\text{106}}$Pd, 1757.90559).
Pd(1)(5): 5 (0.268 g, 2.1x10⁻¹ mmol) and [Pd(1)(CH₃CN)] (0.147 g, 2.1x10⁻¹ mmol) were gently heated (50 °C) in dichloromethane (20 mL) for 10 minutes, and then stirred for a further 1 h at room temperature. The solvent was removed under reduced pressure to give the title compound as a yellow solid (0.386 g, yield = 97%). m.p. 193 °C (dec); ¹H NMR (400 MHz, CD₂Cl₂, 298 K): δ = 1.22 (s, 54H, Hj), 1.42 (m, 4H, H_{allyl}), 1.64 (m, 4H, H_{allyl}), 2.00 (m, 4H, H_{allyl}), 2.21 (m, 4H, H_d), 3.69 (t, 4H, J = 6.5 Hz, H_G), 4.03 (t, 4H, J = 6.0 Hz, H_c), 4.15 (s, 4H, H_D), 4.45 (t, 4H, J = 6.5 Hz, H_e), 4.88 (m, 4H, H_i), 5.68 (m, 2H, H_H), 6.37 (d, 4H, J = 8.5 Hz, H_F), 6.50 (d, 4H, J = 8.5 Hz, H_E), 6.77 (d, 4H, J = 8.6 Hz, H_g), 7.02 (m, 16H, H_f+ H_i), 7.14 (d, 12H, J = 8.5 Hz, H_h), 7.79 (d, 2H, J = 8.0 Hz, H_b), 8.04 (t, 1H, J = 8.0 Hz, H_d), 8.42 (s, 2H, H_a), 8.55 (s, 1H, H_b); ¹³C NMR (100 MHz, CD₂Cl₂, 298 K): δ = 23.3, 26.6, 27.8, 29.4, 31.5, 32.3, 46.2, 62.0, 65.7, 110.9, 112.2, 112.9, 122.1, 123.0, 125.3, 125.5, 126.4, 128.7, 130.4, 130.6, 131.2, 136.4, 138.1, 138.9, 142.1, 146.4, 151.1, 152.2, 154.4, 155.6, 156.0, 160.0, 168.8; LRFAB-MS (3-NOBA matrix): m/z = 1902 [M]+; HRFAB-MS (3-NOBA matrix): m/z = 1901.94173 (calcd. for ¹²C₁₁₉¹³CH₁₃₈N₄O₁₀¹⁰⁶Pd, 1901.94785).
Pd6: (a) To an anhydrous degassed dichloromethane solution (400 mL) of Grubbs’(I) catalyst (0.031 g, 3.74x10^{-2} mmol) under an atmosphere of N₂, was added via a double ended needle, Pd(1)(2) (0.657 g, 3.74x10^{-1} mmol) in anhydrous degassed dichloromethane (100 mL). The solution was stirred at room temperature for 18 h. The solvent was removed under vacuum and the crude residue purified by column chromatography (1:24 EtOAc:CH₂Cl₂) to give a yellow solid (0.50 g).
(b) A mixture of the yellow solid obtained in part (a) (0.50 g) in THF (50 mL), and 10% w/w Pd-C (0.100 g) was stirred under an atmosphere of H₂ for 18 h. The Pd-C was then removed by filtration through a plug of Celite, and the solvent was removed under reduced pressure to give the title compound as a yellow solid (0.499 g, yield =77% over 2 steps). m.p. 292 °C (dec); ¹H NMR (400 MHz, CD₂Cl₂, 298 K): δ = 1.21 (m, 8H, Hₐₖᵢₙ), 1.29 (s, 54H, Hₖ), 1.41 (m, 4H, Hₐₖₖ), 1.55 (m, 4H, Hₐₖₖ), 3.71 (t, 4H, J = 6.3 Hz, Hₐ), 4.11 (s, 4H, Hₐ), 5.19 (s, 4H, Hₐ), 6.30 (d, 4H, J = 8.3 Hz Hₕ), 6.35 (d, 4H, J = 8.3 Hz, Hₕ), 6.85 (d, 4H, J = 8.8 Hz, Hₖ), 7.18 (m, 16H, Hₐ + Hₕ), 7.26 (d, 12H, J = 8.3 Hz, Hₕ), 7.43 (d, 2H, J = 7.8 Hz, Hₕb), 7.77 (d, 2H, J = 7.8 Hz, Hₕb), 7.90 (t, 1H, J = 7.8 Hz, Hₕb), 8.09 (t, 1H, J = 7.8 Hz, Hₕb); ¹³C NMR (100 MHz, CD₂Cl₂, 298 K): δ = 24.7, 27.7, 27.8, 28.6, 30.3, 33.3, 48.8, 62.4, 66.4, 69.2, 113.8, 114.0, 121.1, 123.6, 123.9, 127.2, 129.6, 131.2, 132.1, 138.6, 140.0, 140.5, 143.6, 147.6, 152.0, 154.5, 156.9, 158.0, 170.5; LRFAB-MS (3-NOBA matrix): m/z = 1730 [M⁺]; HRFAB-MS (3-NOBA matrix): m/z = 1731.89199 (calcd. for ¹²C₁₁₁¹³CH₁₂₈N₄O₈Pd, 1731.88994).
Ring closing metathesis and hydrogenation of Pd(1)(3)

(a) To an anhydrous degassed dichloromethane solution (60 mL) of Grubbs' (I) catalyst (0.031 g, 3.74x10⁻² mmol) under an atmosphere of N₂, was added via a double ended needle, Pd(1)(3) (0.140 g, 8.0x10⁻² mmol) in anhydrous degassed dichloromethane (30 mL). The solution was stirred at room temperature for 18 h. The solvent was removed under vacuum to give a dark green solid (0.20 g).

(b) A mixture of the green solid obtained in part (a) (0.20 g) in THF (20 mL), and 10% w/w Pd-C (0.020 g) was stirred under an atmosphere of H₂ for 18 h. The Pd-C was then removed by filtration through a plug of Celite, and the solvent was removed under reduced pressure. The crude mixture was purified using column chromatography to give two colourless compounds that were identified as 3 (0.056 g yield = 63% over 2 steps) and macrocycle 7H₂ (0.027 g, yield = 65% over 2 steps).

Macrocycle (7H₂); m.p. 258-260 °C; ¹H NMR (400 MHz, CDCl₃, 298 K): δ = 1.30 (m, 12H, H₆), 1.70 (m, 4H, H₄), 3.86 (t, 4H, J = 6.0 Hz, H₂), 4.52 (d, 4H, J = 6.0 Hz, H₃), 6.71 (d, 4H, J = 8.5 Hz, H₄), 7.10 (d, 4H, J = 8.5 Hz, H₅), 7.94 (m, 3H, H₆); ¹³C NMR (100 MHz, CDCl₃, 298 K): δ = 25.4, 28.1, 28.4, 28.7, 42.9, 67.4, 114.7, 125.3, 129.2, 129.8, 138.9, 148.8, 158.6, 163.1; LRFAB-MS (3-NOBA matrix): m/z = 516 [MH⁺]; HRFAB-MS (3-NOBA matrix): m/z = 516.28550 (calcd. for C₁₂H₃₈N₃O₄, 516.28623).
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Ring closing metathesis and hydrogenation of Pd(1)(5)

(a) To an anhydrous degassed dichloromethane solution (200 mL) of Grubbs’ (I) catalyst (0.016 g, 1.9x10⁻² mmol) under an atmosphere of N₂, was added via a double ended needle, Pd(1)(5) (0.367 g, 1.93x10⁻¹ mmol) in anhydrous degassed dichloromethane (50 mL). The solution was stirred at room temperature for 18 h. The solvent was removed under vacuum to give a dark green solid (0.352 g).

(b) A mixture of the yellow solid obtained in part (a) (0.33 g) in THF (30 mL), and 10% w/w Pd-C (0.033 g) was stirred under an atmosphere of H₂ for 18 h. The Pd-C was then removed by filtration through a plug of Celite, and the solvent was removed under reduced pressure. The crude mixture was purified using column chromatography to give two colourless compounds that were identified as 5 (0.17 g yield = 69% over 2 steps) and 7H₂ (0.071 g, yield = 71% over 2 steps).

6H₂: To Pd6 (0.131 g, 7.56x10⁻² mmol) in dichloromethane (10 mL) and methanol (10 mL) was added potassium cyanide (0.075 g, 1.15 mmol) in methanol (2 mL). The solution was stirred for 1 hour at room temperature and then heated gently to reduce the overall volume to less than 5 mL. The resulting mixture was portioned
between dichloromethane (25 mL) and water (25 mL). The organic layer was collected and the water extracted with further dichloromethane (10 mL). The combined organic extracts were washed with further water (25 mL) and then dried over anhydrous sodium sulfate. After filtration, the solvent was removed under reduced pressure and the crude residue purified by column chromatography (1:99 EtOAc:CH₂Cl₂) to give the title compound as a colourless solid (0.119 g, yield = 97%). m.p. 157 °C (dec); ¹H NMR (400 MHz, CDCl₃, 298 K): δ= 1.32 (m, 8H, Hₐₜ), 1.37 (s, 54H, Hₖ), 1.46 (m, 4H, Hₐₜ), 1.71 (m, 4H, Hₐₜ), 3.76 (t, 4H, J = 6.3 Hz, Hₖ), 4.31 (d, 4H, J = 6.1 Hz, Hₜ), 3.38 (s, 4H, Hₜ), 6.30 (d, 4H, J = 8.6 Hz, Hₜ), 6.48 (d, 4H, J = 8.8 Hz, Hₚ), 6.63 (d, 4H, J = 8.6 Hz, Hₚ), 7.06 (d, 4H, J = 8.8 Hz, Hₚ), 7.14 (m, 14H, Hₜ + Hₚ), 7.31 (d, 12H, J = 7.3 Hz, Hₜ), 7.63 (t, 1H, J = 7.8 Hz, Hₜ), 7.97 (t, 1H, J = 7.8 Hz, Hₜ), 8.43 (d, 2H, J = 7.8 Hz, Hₚ), 9.49 (t, 2H, J = 6.1 Hz, Hₚ); ¹³C NMR (100 MHz, CDCl₃, 298 K): δ= 24.4, 27.3, 27.4, 28.2, 30.4, 33.3, 41.6, 62.0, 65.8, 67.6, 111.9, 112.0, 119.1, 123.1, 124.3, 127.6, 128.4, 129.6, 131.1, 136.1, 137.6, 139.2, 143.0, 147.3, 148.1, 154.6, 155.2, 156.8, 162.8; LRFAB-MS (3-NOBA matrix): m/z = 1627 [M⁺]; HRFAB-MS (3-NOBA matrix): m/z = 1628.00326 (calcd. for ¹²C₁₁₁¹³CH₁₃₀N₄O₆, 1628.00239).

### 2.4 References and Notes


[12] **L6Pd**: C$_{121}$H$_{141.5}$N$_{8.5}$O$_{6}$Pd, $M = 1917.33$, yellow block, crystal size 0.47 x 0.31 x 0.27 mm$^3$, triclinic, $P\bar{1}$, $a = 15.7840(10)$, $b = 15.9967(10)$, $c = 22.8029(14)$ Å, $\alpha = 84.9850(10)$, $\beta = 71.8430(10)$, $\gamma = 80.5460(10)^\circ$, $V = 5392.5(6)$ Å$^3$, $Z = 2$, $\rho_{\text{calcd}} = 1.193$ Mg m$^{-3}$; Mo $K\alpha$ radiation (graphite monochromator, $\lambda = 0.71073$ Å), $\mu = 0.231$ mm$^{-1}$, $T = 150(2)$ K. 34043 data (15412 unique, $R_{\text{int}} = 0.0331$, $2.06 < \theta < 23.26^\circ$), were collected on a Brucker SMART CCD diffractometer using narrow frames (0.5 ° in $\omega$), and were corrected semiempirically for absorption and incident beam decay. Data beyond 0.9 Å were weak and were not used for refinement. The structure was solved by direct methods (SIR92)$^{[13]}$ and refined by full-matrix least-squares against $F^2$.$^{[14]}$ Phenyl groups were constrained to be rigid hexagons and hydrogen atoms were placed in calculated positions. The whole macrocyclic component, inclusive of the Pd atom, is disordered (50:50) over two positions. The alkyl chain is further disordered and the refinement of this portion of the structure was controlled by application of restraints to both 1, 2 and 1, 3 distances and use of a common isotropic displacement parameter for all C-atoms forming the chain. The only disorder present in the thread is in two of the t-butyl groups. That based on C244 is rotationally disordered (70:30) with the central carbon atom (C244) fully occupied and the two alternative sets of methyl positions related by a 60° rotation about the C244-C243 bond. All atoms in the groups were refined with anisotropic displacement parameters (adps), those of 'opposite' C-atoms being constrained to be equal. The t-butyl group attached to C263 is disordered (70:30) over two positions and was refined isotropically. Similarity restraints were applied to chemically equivalent 1,2 and 1,3 distances in both disordered
t-butyl groups. In the latter stages of refinement there was still significant unassigned electron density associated with diffuse solvent. This density was modelled using the procedure of van der Sluis and Spek,\cite{15} comprising 199 electrons per unit cell, which corresponds to approximately 4.5 MeCN solvent molecules per asymmetric unit; values of $M$, $F(000)$, $\mu$ etc. have been calculated on this assumption. $wR = \left\{\Sigma[w(F_o^2-F_c^2)^2]/\Sigma[w(F_o^2)^2]\right\}^{1/2} = 0.2527$, conventional $R = 0.0806$ for $F$ values of 15412 reflections with $F_o^2 > 2\sigma(F_o^2)$, $S = 1.115$ for 885 parameters. Residual electron density extremes were 1.03 and -0.94 eÅ$^{-3}$. Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-229418. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033; or deposit@ccdc.cam.ac.uk.


\cite{14} Sheldrick, G. M. University of Göttingen, Germany, 1997.


Acknowledgements

The following people are gratefully acknowledged for their contribution to this chapter: Dr. P. Lusby for his work on the synthesis of 11H₂ and the investigation of the interconversion of the two atropisomers Pd(7)(exo-8):Pd(7)(endo-8); Dr. D. Barney Walker for his work on Pd(7)(10); and Prof. A. M. Z. Slawin solved the X-ray crystal structures of Pd9, Pd11 and Pd(7)(10).
3.1 Introduction

The use of transition metal ions to direct the synthesis of interlocked architectures remains amongst the most efficient strategies available. In addition to exploiting reversible coordination chemistry to deliver high yields of thermodynamically privileged catenanes incorporating metals in their ring frameworks, catenates – metal complexes of organic interlocked macrocyclic ligands – can be formed through metal template macrocyclisation reactions. However, whilst the use of tetrahedral copper(I) geometry to hold bidentate ligands in a geometry suitable for subsequent interlocking macrocyclisation reactions has been extensively developed over a twenty year period, the transposition of this basic concept to other coordination modes has been slow to develop. Although Sokolov alluded to the possibility of using octahedral ions to template catenane synthesis as early as 1973, attempts to prepare interlocked architectures in this way initially met with limited success and it is only recently that efficient synthetic routes based on octahedral coordination have been developed. There is also a single example of 5-coordinate zinc(II) being used to direct the formation of a [2]catenate and a remarkable crown ether-threaded organometallic catenate templated about a magnesium atom that also forms part of one ring.

At first sight the use of a template strategy to produce interlocked macrocyclic ligands for metals with a square planar coordination geometry might appear somewhat counter-intuitive. Square planar coordination obviously involves a 2D donor set, whilst interlocking of the two rings requires two crossing points (one positive, one negative) necessitating control over the nature of covalent bond formation in the third dimension. However, by using a tridentate-monodentate ligand combination, the relative orientation of the ligands coordinated to the metal can be varied (formally by rotation about the monodentate ligand-metal bond) and therefore, in principle, systems can be designed to extend above and below the plane of the square planar coordination mode and direct a subsequent ring closure reaction. Indeed, there are several examples of the orthogonal alignment of organic fragments using such a ‘3+1’ donor set of ligands and we recently found it was
Chapter 3

Since the attempted simultaneous double macrocyclisation strategy had given rise to intercomponent bond formation, we sought to exclude this possibility\textsuperscript{20} by pre-forming one or other of the rings prior to the second, metal-directed, cyclisation reaction (Scheme 3.3, Routes II and III).

**Route II – Metal-directed RCM of 8**

Tridentate macrocycle 7H\textsubscript{2} was prepared in 57% yield by treatment of pyridine-2,6-dicarbonyl dichloride with the appropriate diamine under high dilution conditions (see Experimental Section). Subsequent complexation with palladium(II) acetate afforded Pd(7)(CH\textsubscript{3}CN) (93%, scheme 3.3, v). Threading of 8 through the cavity of Pd(7)(CH\textsubscript{3}CN) via the substitution of the coordinated acetonitrile was attempted by simple mixing of the two in dichloromethane at room temperature (Scheme 3.3, vi). While mass spectrometry confirmed the ligand exchange, the \textsuperscript{1}H NMR spectrum of the crude product was unexpectedly complex. Closer inspection of the thin layer chromatographic analysis of the reaction mixture revealed two products with very similar R\textsubscript{f} values in a ratio of approximately 2:3. Despite their proximity, these proved amenable to separation by preparative thin layer chromatography on silica gel-coated plates (CH\textsubscript{2}Cl\textsubscript{2}:MeOH, 98.5:1.5 as eluent). The isolated complexes gave indistinguishable fragmentation patterns by electrospray ionisation mass spectrometry, the molecular mass ion suggesting they were both isomers of Pd(7)(8). However, the \textsuperscript{1}H NMR spectra exhibited important differences between the two products. When compared to the spectra of the starting materials, the minor isomer (lower R\textsubscript{f}, Figure 3.4d), showed significant shielding of the 7 benzyl rings (H\textsubscript{E} and H\textsubscript{F}) indicative of aromatic stacking with the pyridine group of 8. In contrast, the major isomer (higher R\textsubscript{f}, Figure 3.4b), showed no evidence of stacking interactions but a greater degree of complexity in both the 8 signals (two sets of non-equivalent H\textsubscript{b}, H\textsubscript{c}, H\textsubscript{d}, H\textsubscript{e} and H\textsubscript{f} resonances) and the H\textsubscript{D} methylene groups (an AB system with a 2.5 ppm separation between the two proton environments) of 7. From this we tentatively assigned the two products as ‘non-threaded’ (major isomer) and ‘threaded’ (minor isomer) atropisomers,\textsuperscript{21} Pd(7)(exo-8) and Pd(7)(endo-8) respectively (Scheme 3.3).
Figure 3.4. $^1$H NMR spectra (400 MHz, CD$_2$Cl$_2$, 298 K) of (a) Pd(7)(10); (b) Pd(7)(exo-8); (c) 8; (d) Pd(7)(endo-8); (e) Pd(1)(10); (f) Pd11. The lettering refers to the assignments shown in Scheme 3.

Intriguingly, CPK models suggested that cyclisation of 8 could occur with each atropisomer of Pd(7)(8), suggesting that two compounds of identical connectivity but different conformations\textsuperscript{22} are predisposed to form topological isomeric products upon RCM – the [2]catenate, B, and the analogous non-interlocked double macrocycle structure, C. Sure enough, treatment of the 2:3 mixture of atropisomers with Grubbs’ catalyst in CH$_2$Cl$_2$, followed by hydrogenation and demetallation (Scheme 3.3, vii (three steps – the mixtures of topological and olefin isomers preventing the isolation of pure products until the end of the reaction sequence)) afforded three products: macrocycles 7H$_2$ (44%) and 10 (41\textsuperscript{\%}\textsuperscript{23}) arising from complex Pd(7)(10), and a
further compound, which mass spectrometry confirmed to be a different isomer of 9H$_2$, in 25% overall yield for the three steps.

$^1$H NMR spectroscopy of the new compound in CDCl$_3$ (Figure 3.2b) revealed shielding of most resonances compared to the free macrocycles 7H$_2$ (Figure 3.2a) and 10 (Figure 3.2d) characteristic of interdigitation, suggesting that it was indeed the [2]catenand 11H$_2$. The exception to the upfield trend in shifts were the amide protons (H$_C$), which were shifted significantly downfield (ca. 1.3 ppm) in the catenand compared to those of 7H$_2$, indicative of a significant hydrogen-bonding interaction between the amide protons of one ring and the pyridine nitrogen of the other. In contrast, the analogous amide protons in the 58-membered free macrocycle 9H$_2$ occur at 8.11 ppm in CDCl$_3$ (Figure 3.2c), only slightly downfield of their position in 7H$_2$ (7.88 ppm, Figure 3.2a), meaning that little intramolecular hydrogen bonding is occurring in the large flexible macrocycle. Why is this internal hydrogen bonding absent when it is so clearly present in the mechanically bonded isomer 11H$_2$? Firstly, the size and nature of the solvent-exposed surfaces of the compact [2]catenane structure and the large, relatively open, macrocycle must be very different, making desolvation of the amide and pyridine residues in the catenane a significantly less energetically costly process. Secondly, with the 2,6-bis(oxyethylene)pyridine and 2,6-pyridinecarboxamide groups on different components, the macrocycles in 11H$_2$ can orientate themselves for inter-residue hydrogen bonding with little more than the loss of a single rotational degree of freedom. In contrast, alignment of the groups to enable a similar interaction within 9H$_2$ would significantly restrict the number of conformations accessible by the alkyl chains in the large flexible ring, the resulting losses in degrees of freedom raising the energy of the hydrogen bonded structure. This unusual orthogonal double bifurcated bis-pyridine hydrogen bonding interaction is also observed in the related [2]rotaxane system.$^{17}$

Re-introduction of Pd(II) into the free ligand systems (9H$_2$→Pd9, Scheme 3.3, xii; 11H$_2$→Pd11, Scheme 3.3, xiii; 7H$_2$→Pd(7)(CH$_3$CN) + 10→Pd(7)(10), Scheme 3.3,
v, viii) proceeded smoothly in each case, the last two providing pure samples of complexes formed previously as intermediates during each pathway of the Route II syntheses. ESI mass spectrometry initially identified the formation of Pd(7)(10), confirming that both macrocycles could simultaneously bind to palladium without being interlocked. $^1$H NMR spectroscopy (Figure 3.4a) corroborated this result and showed significant similarity (a diastereoptopic environment for H$_b$, H$_c$, H$_d$, H$_e$, H$_f$ and H$_g$) to the presumed ‘non-threaded’ isomer of Pd(7)(8) (Figure 3.4b). These spectral features are consistent with orthogonal binding of the rings to the square planar geometry metal, with neither macrocycle being able to pass through the cavity of the other nor rotate (at least not rapidly on the NMR time scale in the case of the monodentate ligand) about the plane of the square planar coordination geometry. This means both macrocycles are perforce desymmetrised in the plane that they coordinate to the metal, i.e. top from bottom in 7 and left from right in 10 (as Pd(7)(10) is depicted in Figure 3.5a).

Pleasingly, the pure samples of Pd(7)(10) and Pd11 both provided single crystals suitable for structure elucidation by X-ray crystallography (Figure 3.5 and Figure 3.6, respectively). Between them, the X-ray crystal structures of Pd9, Pd(7)(10) and Pd11 not only confirm the identity of the metal complexes – a unique set of topological (Pd(7)(8) and Pd11) and constitutional (Pd9 and Pd(7)(10)/Pd11) isomers – but also the structural assignments of the free ligands inferred by the earlier $^1$H NMR and mass spectrometry analysis.
Figure 3.5. X-ray crystal structure of non-interlocked double macrocycle complex Pd(7)(10) grown from a saturated solution of the complex in acetone. a) Side-on and b) top views. Carbon atoms of the 7 macrocycle are shown in light blue and those of the 10 macrocycle in yellow; oxygen atoms are red, nitrogen dark blue, palladium grey. Selected bond lengths [Å]: N2-2.032, N5-Pd 1.943, N11-Pd 2.032, N41-Pd 2.077; tridentate fragment bite angle [°]: N2-Pd-N11 160.8.

Figure 3.6. X-ray crystal structure of palladium [2]catenate Pd11 grown by slow cooling of a warm, saturated solution of the complex in acetonitrile. a) Side-on and b) top views. Carbon atoms of the 7 macrocycle are shown in light blue and those of the 10 macrocycle in yellow; oxygen atoms are red, nitrogen dark blue, palladium grey. Selected bond lengths [Å]: Pd-N2 1.934, Pd-N5 2.041, Pd-N11 2.036, Pd-N41 2.079; tridentate fragment bite angle [°]: N2-Pd-N11 160.2.
Atropisomer-specific synthesis of different topological isomers

Although RCM (and subsequent hydrogenation and demetallation) of the mixture of the two Pd(7)(8) atropisomers gives a ratio of isolated interlocked to non-interlocked products similar to the starting atropisomer ratio, it does not necessarily follow that one atropisomer leads solely to one product. The interconversion of the two Pd(7)(8) atropisomers in solution was investigated by $^1$H NMR spectroscopy. The initial ‘threaded’:‘non-threaded’ ratio of ca. 2:3 remained unchanged over 7 days in CD$_2$Cl$_2$ at RT. Similarly, spectra of pure samples of each of the compounds were invariant under these conditions, demonstrating that the atropisomers are kinetically stable at room temperature in a non-coordinating solvent. However, addition of ~10% CD$_3$CN to either of the pure atropisomer solutions or the 2:3 mixture led to a gradual change in the ‘threaded’:‘non-threaded’ ratio, rising to ca. 7:3 after 4 days. This suggests that the ‘threaded’ isomer is thermodynamically favoured and that atropisomer interconversion can take place via the dissociation of 8 from either form of Pd(7)(8), the vacant coordination site being temporarily filled by a molecule of CD$_3$CN. Accordingly, the reaction between 8 and Pd(7)(CH$_3$CN) was repeated in refluxing acetonitrile. After several hours, $^1$H NMR spectroscopy showed a 7:3 ratio of the ‘threaded’:‘non-threaded’ forms of Pd(7)(8). Heating over two days increased the ratio to 8:1 after which no further change occurred.

RCM of single atropisomer samples of Pd(7)(8) in CH$_2$Cl$_2$ did, indeed, generate a single new species in each case. The product of RCM of the presumed Pd(7)(endoo-8) complex was hydrogenated to give solely the [2]catenate, Pd11; the product of RCM of presumed Pd(7)(exo-8) proved unstable to hydrogenation, so the metal was removed instead (KCN, MeOH, CH$_2$Cl$_2$, 20 °C, 1 h and then 40 °C, 0.5 h), liberating two different macrocycles, 7H$_2$ (96%) and the unsaturated olefin analogue of 10 (93%).
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**Route III - Metal-directed RCM of 1**

Finally, we investigated the product distribution arising from pre-forming the monodentate macrocycle and applying metal-directed cyclisation of the tridentate ligand (Scheme 3, Route III). Pd(1)(CH$_3$CN) and 10 were stirred together in dichloromethane at room temperature (Scheme 3.3, ix) and, in contrast to the analogous step in Route II, reacted to give a single product rather than a mixture of atropisomers. The $^1$H NMR spectrum of Pd(1)(10) (Figure 3.4e) suggests the two ligands are threaded, the upfield shift of H$_E$ and H$_F$ compared to similar protons in the non-threaded Pd(7)(10) and Pd(7)(exo-8) complexes (Figure 3.4a and 3.4b, respectively) indicating π-stacking of the benzyl groups of 1 with the pyridine unit of 10. It is difficult to distinguish between whether Pd(1)(10) can exist as threaded/non-threaded atropisomers but is formed solely as the Pd(exo-1)(10) isomer, or rather threaded and non-threaded forms of Pd(1)(10) are in equilibrium with the threaded conformation being thermodynamically preferred by several kcal mol$^{-1}$. In any event, RCM of Pd(1)(10) and subsequent hydrogenation (Scheme 3.3, x) afforded exclusively the [2]catenate, Pd11, in 78% yield, making this route both synthetically efficient and completely selective for the mechanically interlocked topological isomer.

In conclusion, a [2]catenate and the isomeric single macrocycle and double macrocycle metal complexes can each be efficiently assembled about a palladium(II) template via RCM. The order in which the tridentate and monodentate ligand cyclisation reactions and coordination steps are performed determines the outcome of the synthetic pathway, providing selective routes to each of the three topological and constitutional isomers. In one case, pre-forming the tridentate macrocycle followed by its coordination along with the acyclic monodentate ligand to the Pd, produces threaded and non-threaded atropisomers. These can be isolated and, whilst the individual forms are stable in dichloromethane, they can be interconverted in a coordinating solvent through ligand exchange. Each atropisomer was shown to be a true intermediate to a different topological product meaning that, in this reaction, the choice of solvent can determine whether the [2]catenate is formed or its non-
interlocked isomer. It is remarkable to see how topology and connectivity can be selected so exquisitely – in three different forms – using just one set of organic building blocks and a metal atom with a two dimensional coordination geometry.

3.3 Experimental Section

Unless stated otherwise, all reagents and anhydrous solvents were purchased from Aldrich Chemicals and used without further purification. 1,10-bis[p-(aminomethyl)phenoxy]decane,\textsuperscript{24} \textbf{1H\textsubscript{2}}\textsuperscript{25} and \textit{Pd(1)}(CH\textsubscript{3}CN)\textsuperscript{25} were prepared according to literature procedures.

\textbf{Scheme 3.4.} Reagents and conditions: i) 6-bromohex-1-ene, K\textsubscript{2}CO\textsubscript{3}, NaI, butan-2-one, \(\Delta\), 18 h, 70%; ii) 2, 6-bis(bromomethyl)pyridine, NaH, THF, \(\Delta\), 18 h, 70%; iii) 1,10-dibromodecane, K\textsubscript{2}CO\textsubscript{3}, NaI, butan-2-one, \(\Delta\), 18 h, 75%; iv) NaBH\textsubscript{4}, CHCl\textsubscript{3}/MeOH, \(\Delta\), 4 h, 73%; v) 2, 6-bis(bromomethyl)pyridine, NaH, THF, \(\Delta\), 18 h, 60%; vi) 1,10-bis[p-(aminomethyl)phenoxy]decane, 2,6-pyridinedicarbonyl dichloride, Et\textsubscript{3}N, CH\textsubscript{2}Cl\textsubscript{2}, 0 °C then warm to r.t., 18 h, 57%; vii) Pd(OAc)\textsubscript{2}, CH\textsubscript{3}CN, r.t., 1 h, 93%.
S1: To a solution of 4-hydroxybenzyl alcohol (1.32 g, 10.6 mmol) and 6-bromohex-1-ene (1.73 g, 10.6 mmol) in butan-2-one (75 mL), were added potassium carbonate (7.32 g, 53.0 mmol) and a catalytic amount of sodium iodide. The suspension was refluxed for 18 h under an atmosphere of nitrogen. After cooling, the potassium carbonate was removed by filtration and the filtrate concentrated in vacuo. The resultant oil was re-dissolved in dichloromethane (50 mL) and washed with water (2 x 25 mL), followed by a saturated aqueous solution of sodium chloride (25 mL). The water layers were combined and re-extracted with dichloromethane (25 mL). The combined organic layers were dried over anhydrous magnesium sulfate, concentrated in vacuo and the crude product purified by column chromatography (CH₂Cl₂) to yield S1 as a colourless oil (1.54 g, yield = 70%). $^1$H NMR (400 MHz, CDCl₃, 298 K): $\delta = 1.61$ (m, 2H, $H_{alkyl}$), 1.84 (m, 2H, $H_{alkyl}$), 2.18 (m, 2H, $H_{alkyl}$), 2.77 (s, 1H, OH), 3.98 (t, 2H, $J = 6.5$ Hz, $H_g$), 4.56 (s, 2H, $H_d$), 5.06 (m, 2H, $H_i$), 5.88 (m, 1H, $H_h$), 6.90 (d, 2H, $J = 8.3$ Hz, $H_f$), 7.27 (d, 2H, $J = 8.3$ Hz, $H_e$); $^{13}$C NMR (100 MHz, CDCl₃, 298 K): $\delta = 25.1, 28.5, 33.3, 64.5, 67.6, 114.3, 114.6, 128.4, 132.8, 138.3, 158.4$; LRFAB-MS (3-NOBA matrix): $m/z = 206$ [M]$^+$; HRFAB-MS (3-NOBA matrix): $m/z = 206.13060$ (calcd. for C₁₃H₁₈O₂, 206.13068).
8: To a solution of Si (1.11 g, 5.38 mmol) in anhydrous THF (20 mL), under an atmosphere of nitrogen at 0 °C was added sodium hydride (0.174 g, 7.25 mmol) (60% dispersion in oil). After 30 minutes a solution of 2, 6-bis(bromomethyl)pyridine (0.713 g, 2.69 mmol) in anhydrous THF (15 mL) was added using a transfer needle and the suspension refluxed under an atmosphere of nitrogen for 18 h. Upon cooling the reaction mixture was filtered, concentrated in vacuo and the resultant crude oil re-dissolved in dichloromethane, washed with water (2 x 25 mL), and a saturated aqueous solution of sodium chloride (25 mL). The water layers were combined and re-extracted with dichloromethane (25 mL). The combined organic layers were dried over anhydrous magnesium sulfate, concentrated in vacuo and the crude product purified by column chromatography (95:5 CH₂Cl₂:EtOAc) to yield 8 as a colourless oil (0.970 g, yield = 70%).

$^1$H NMR (400 MHz, CDCl₃, 298 K): $\delta = 1.49$ (m, 4H, H$_{a,i}$), 1.72 (m, 4H, H$_{a,i}$), 2.05 (m, 4H, H$_{a,i}$), 3.88 (t, 4H, $J = 6.4$ Hz, H$_g$), 4.49 (s, 4H, H$_d$), 4.57 (s, 4H, H$_d$) 4.94 (m, 4H, H$_d$), 5.76 (m, 2H, H$_h$), 6.80 (d, 4H, $J = 8.6$ Hz, H$_f$), 7.22 (d, 4H, $J = 8.6$ Hz, H$_e$), 7.31 (d, 2H, $J = 7.8$ Hz, H$_b$), 7.62 (t, 1H, $J = 7.8$ Hz, H$_a$); $^{13}$C NMR (100 MHz, CDCl₃, 298 K): $\delta = 25.2$, 28.6, 33.4, 67.7, 72.6, 72.7, 114.3, 114.7, 119.9, 129.4, 129.8, 137.2, 138.5, 157.9, 158.7; LRFAB-MS (3-NOBA matrix): $m/z = 516$ [MH]$^+$; HRFAB-MS (3-NOBA matrix): $m/z = 516.31141$ (calcd. for C$_{33}$H$_{42}$NO$_4$, 516.31138).

S2 (4,4'-decanediylidioxy-dibenzaldehyde)$^{[26]}$: The synthesis of S2 was carried out as for S1 but using 4-hydroxybenzaldehyde (1.62 g, 13.3 mmol), 1,10-dibromodecane (2.00 g, 6.66 mmol), potassium carbonate (9.20 g, 66.6 mmol) and a catalytic amount of sodium iodide. The crude residue was recrystallised from methanol to yield the title compound as a colourless solid (1.91 g, yield = 75%). m.p. 78-79 °C (lit. 78-80 °C)$^{[26]}$ $^1$H NMR (400 MHz, CDCl₃, 298 K): $\delta = 1.21$-1.47 (m,
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12H, $H_{alkyl}$), 1.81 (m, 4H, $H_{alkyl}$), 4.02 (t, 4H, $J = 6.6$ Hz, $H_{g}$), 6.97 (d, 4H, $J = 8.6$ Hz, $H_{j}$), 7.81 (d, 4H, $J = 8.6$ Hz, $H_{e}$), 9.86 (s, 2H, $H_{d}$); $^{13}$C NMR (100 MHz, CDCl$_3$, 298 K): $\delta = 25.9, 29.0, 29.3, 29.4, 68.3, 114.7, 129.7, 132.0, 164.2, 190.8$; LRFAB-MS (3-NOBA matrix): $m/z = 383$ [MH$^+$]; HRFAB-MS (3-NOBA matrix): $m/z = 383.22211$ (calcd. for C$_{24}$H$_{31}$O$_4$, 383.22223).

S3 (4,4'-[decane-1,10-diylbis(oxy)]bis[benzenemethanol])$^{[27]}$: To a solution of S2 (1.80 g, 4.70 mmol) in chloroform (50 mL) and methanol (10 mL), was slowly added sodium borohydride (1.78 g, 47.0 mmol). The reaction mixture was then heated at reflux for 4 h, cooled to 0 °C and quenched with 1 M hydrochloric acid. The product was then extracted with dichloromethane (3 x 50 mL) and the combined organic extracts dried over anhydrous magnesium sulfate and concentrated in vacuo to yield S3 as a colourless solid (1.33 g, yield = 73%). m.p. 131-132 °C; $^1$H NMR (400 MHz, DMSO, 298 K): $\delta = 1.24-1.47$ (m, 12H, $H_{alkyl}$), 1.71 (m, 4H, $H_{alkyl}$), 3.94 (t, 4H, $J = 6.6$ Hz, $H_{g}$), 4.42 (d, 4H, $J = 4.8$ Hz, $H_{d}$), 5.02 (t, 2H, $J = 4.8$ Hz, OH) 6.87 (d, 4H, $J = 8.6$ Hz, $H_{j}$), 7.22 (d, 4H, $J = 8.6$ Hz, $H_{e}$); $^{13}$C NMR (100 MHz, DMSO, 298 K): $\delta = 25.4, 28.6, 28.6, 28.8, 62.4, 67.2, 113.9, 127.8, 134.3, 157.2$; LRFAB-MS (3-NOBA matrix): $m/z = 386$ [M$^+$]; HRFAB-MS (3-NOBA matrix): $m/z = 386.24509$ (calcd. for C$_{24}$H$_{34}$O$_4$, 386.24571).
10: To a solution of S3 (1.29 g, 3.34 mmol) and 2,6-bis(bromomethyl)pyridine (0.885 g, 3.34 mmol) in anhydrous THF (1 L) was added sodium hydride (0.176 g, 7.35 mmol, 60% in oil suspension) under an atmosphere of nitrogen. The reaction was refluxed under nitrogen for 18 h. Upon cooling, the suspension was filtered and the filtrate concentrated in vacuo. The crude residue was re-dissolved in dichloromethane, washed with water (25 mL), dried over anhydrous magnesium sulfate and concentrated in vacuo. The crude residue was purified by column chromatography (95:5 CH₂Cl₂:EtOAc) to yield 10 as a colourless crystalline solid (0.981 g, yield = 60%). m.p. 61-62 °C; ¹H NMR (400 MHz, CDCl₃, 298 K): δ = 1.22-1.48 (m, 12H, H_{alkyl}), 1.73 (m, 4H, H_{alkyl}), 3.97 (t, 4H, J = 6.3 Hz, H₂γ), 4.43 (s, 4H, H₂δ), 4.60 (s, 4H, H₂ζ), 6.80 (d, 4H, J = 8.6 Hz, H₂η), 7.23 (d, 4H, J = 8.6 Hz, H₂η), 7.36 (d, 2H, J = 7.8 Hz, H₂b), 7.69 (t, 1H, J = 7.8 Hz, H₂b); ¹³C NMR (100 MHz, CDCl₃, 298 K): δ = 25.6, 28.5, 28.6, 29.3, 67.3, 71.2, 72.2, 114.5, 119.9, 129.2, 130.0, 137.1, 157.7, 158.7; LRFAB-MS (3-NOBA matrix): m/z = 490 [MH⁺]; HRFAB-MS (3-NOBA matrix): m/z = 490.29495 (calcd. for C₃₁H₄₀NO₄, 490.29573).
7H₂: *Method 1*: To a solution of 1,10-bis[p-aminomethyl]phenoxy]decane (5.00 g, 13.0 mmol) in anhydrous dichloromethane (2950 mL), at 0 °C under an atmosphere of nitrogen, was added triethylamine (2.93 g, 29.0 mmol). A solution of 2,6-pyridinedicarbonyl dichloride (2.65 g, 13.0 mmol) in anhydrous dichloromethane (50 mL) was slowly added dropwise over 3 h, while keeping the solution at 0 °C. The solution was then allowed to warm to room temperature and stirred for 18 h before being concentrated *in vacuo*. The crude residue was purified by column chromatography (50:50 CH₂Cl₂:EtOAc) and recrystallised from acetonitrile to yield colourless crystals of the title compound (3.80 g, yield = 57%). m.p.259-260 °C; ¹H NMR (400 MHz, CD₂Cl₂, 298 K): δ = 1.23-1.46 (m, 12H, H₆&i), 1.71 (m, 4H, H₄&y), 3.91 (t, 4H, J = 6.3 Hz, H₃), 4.55 (d, 4H, J = 6.1 Hz, H₂D), 6.77 (d, 4H, J = 8.6 Hz, H₄F), 7.17 (d, 4H, J = 8.6 Hz, H₄E), 8.00 (t, 1H, J = 7.8 Hz, H₄A), 8.10 (br, 2H, H₄C) 8.31 (d, 2H, J = 7.8 Hz, H₂B); ¹³C NMR (100 MHz, CD₂Cl₂, 298 K): δ = 25.7, 28.4, 28.7, 29.1, 42.7, 67.6, 114.7, 125.2, 129.2, 130.6, 139.1, 149.2, 158.8, 163.5; LRFAB-MS (3-NOBA matrix): m/z = 516 [MH⁺]; HRFAB-MS (3-NOBA matrix): m/z = 516.28550 (calcd. for C₃₁H₃₅N₃O₄, 516.28623).

*Method 2* Synthesis as for 9H₂ using Pd(7)(CH₃CN) (0.050 g, 7.6x10⁻² mmol) and potassium cyanide (0.05 g, 7.7x10⁻¹ mmol). The crude residue was purified by column chromatography (50:50 CH₂Cl₂:EtOAc) to yield 7H₂ (0.037 g, 95%).
Pd(7)(CH$_3$CN): To a solution of 7H$_2$ (1.55 g, 3.00 mmol) in anhydrous acetonitrile (50 mL), was added palladium(II) acetate (0.674 g, 3.00 mmol) and the reaction stirred at room temperature for 1 h under an atmosphere of nitrogen. The resulting precipitate was filtered, washed with acetonitrile (25 mL) and dried under suction to yield a yellow solid (1.84 g, yield = 93%). m.p. 240 °C (decomp.); $^1$H NMR (400 MHz, 9:1 CD$_2$Cl$_2$:CD$_3$CN, 298 K): $\delta$ = 1.22-1.77 (m, 16H, H$_{alkyl}$), 1.95 (s, 3H, Pd-NCCCH$_3$), 3.92 (t, 4H, $J$ = 6.3 Hz, H$_G$), 4.41 (s, 4H, H$_D$), 6.77 (d, 4H, $J$ = 8.3 Hz, H$_P$), 7.13 (d, 4H, $J$ = 8.3 Hz, H$_E$), 7.71 (d, 2H, $J$ = 7.8 Hz, H$_I$), 8.07 (t, 1H, $J$ = 7.8 Hz, H$_A$); $^{13}$C NMR (100 MHz, 9:1 CD$_2$Cl$_2$:CD$_3$CN, 298 K): $\delta$ = 0.5, 25.7, 28.4, 28.8, 29.3, 49.5, 67.4, 114.5, 115.5, 125.0, 128.5, 133.7, 141.4, 153.4, 158.2, 170.7; LRFAB-MS (3-NOBA matrix): $m/z$ = 620 [MH-CH$_3$CN]$^+$; HRFAB-MS (3-NOBA matrix): $m/z$ = 660.19089 (calcd. for C$_{33}$H$_{38}$N$_4$O$_4$Pd, 660.19251).

Pd(1)(8): A solution of 8 (0.520 g, 1.01 mmol) and Pd(1)(CH$_3$CN) (0.687 g, 1.00 mmol) in anhydrous dichloromethane (25 mL) was stirred for 1 h at room
temperature. The solution was concentrated in vacuo and the crude residue purified by column chromatography, (95:5 CH$_2$Cl$_2$:EtOAc) to yield Pd(1)(8) as a yellow, gummy solid (1.08 g, yield = 93%). m.p. 120 °C (decomp); $^1$H NMR (400 MHz, CD$_2$Cl$_2$, 298 K): $\delta = 1.38-1.83$ (m, 16H, $H_{alkyl}$), 1.99-2.15 (m, 8H, $H_{alkyl}$), 3.77 (t, 4H, $J = 6.6$ Hz, $H_G$), 3.85-3.95 (m, 8H, $H_g + H_D$), 4.29 (s, 4H, $H_d$), 4.57 (s, 4H, $H_c$), 4.99 (m, 8H, $H_f + H_i$), 5.82 (m, 4H, $H_H + H_h$), 6.46 (d, 4H, $J = 8.6$ Hz, $H_E$), 6.57 (d, 4H, $J = 8.6$ Hz, $H_F$), 6.85 (d, 4H, $J = 8.6$ Hz, $H_J$), 7.24 (d, 4H, $J = 8.6$ Hz, $H_J$), 7.47 (d, 2H, $J = 7.8$ Hz, $H_b$), 7.81 (d, 2H, $J = 7.8$ Hz, $H_b$), 7.91 (t, 1H, $J = 7.8$ Hz, $H_d$), 8.13 (t, 1H, $J = 7.8$ Hz, $H_d$); $^{13}$C NMR (100 MHz, CDCl$_3$, 298 K): $\delta = 25.3, 25.3, 28.7, 28.7, 33.4, 33.4, 48.7, 67.7, 67.8, 71.8, 73.2, 114.1, 114.3, 114.7, 114.7, 121.8, 124.7, 128.5, 128.9, 129.3, 133.0, 138.4, 138.5, 139.1, 140.5, 152.8, 157.9, 158.9, 160.5, 171.0. LRFAB-MS (3-NOBA matrix): $m/z = 1161$ [MH$^+$]; HRFAB-MS (3-NOBA matrix): $m/z = 1161.49253$ (calcd. for C$_{66}$H$_{79}$N$_4$O$_8$Pd, 1161.49299).

**Pd9: Method 1** (a) A solution of Pd(1)(8) (0.452 g, 0.390 mmol) in anhydrous degassed dichloromethane (150 mL) was added via a double ended needle to a solution of first generation Grubbs’ catalyst (0.064 g, 7.8x10$^{-2}$ mmol) in anhydrous degassed dichloromethane (500 mL) under an atmosphere of nitrogen. The solution was stirred at room temperature for 18 h, concentrated in vacuo and the crude residue purified by column chromatography (96:4 CH$_2$Cl$_2$:EtOAc) to yield a yellow solid (0.33 g). (b) To a stirred solution of the yellow solid obtained in part (a) (0.33 g) in THF (50 mL), was added 10% w/w Pd-C (0.050 g) and the resultant suspension stirred under an atmosphere of hydrogen for 18 h. The suspension was filtered through a plug of Celite, and the solution concentrated in vacuo to yield Pd9 as a yellow solid (0.32 g, yield = 75% over 2 steps). m.p. 196 °C (decomp); $^1$H NMR
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(400 MHz, CD$_2$Cl$_2$, 298 K): $\delta = 1.09$-1.84 (m, 32H, $H_{alyl}$), 2.70 (d, 2H, $J = 14.4$ Hz, $H_D$), 3.64 (m, 4H, $H_C$), 4.0-4.13 (m, 8H, $H_g + H_c + H_d$), 4.39 (d, 2H, $J = 10.6$ Hz, $H_d$), 5.04-5.14 (m, 4H, $H_c + H_d$), 6.38 (d, 4H, $J = 8.6$ Hz, $H_E$), 6.49 (d, 4H, $J = 8.6$ Hz, $H_F$), 6.84 (d, 4H, $J = 8.6$ Hz, $H_G$), 7.20 (d, 4H, $J = 8.6$ Hz, $H_h$), 7.45 (d, 2H, $J = 7.8$ Hz, $H_b$), 7.76 (d, 2H, $J = 7.8$ Hz, $H_B$), 7.88 (t, 1H, $J = 7.8$ Hz, $H_a$), 8.08 (t, 1H, $J = 7.8$ Hz, $H_b$), 13C NMR (100 MHz, CDCl$_3$, 298 K): $\delta = 23.7$, 25.2, 25.5, 27.5, 27.5, 27.5, 28.6, 29.5, 48.5, 67.1, 68.1, 71.8, 73.2, 114.0, 114.8, 121.2, 124.8, 128.5, 128.7, 129.5, 132.8, 139.1, 140.7, 152.8, 158.1, 158.6, 160.6, 171.1; LRFAB-MS (3-NOBA matrix): $m/z = 1109 [MH]^+$; HRFAB-MS (3-NOBA matrix): $m/z = 1109.46275$ (calcd. for C$_{62}$H$_{75}$N$_4$O$_8$Pd, 1109.46169).

**Method 2**

To a stirred solution of 9H$_2$ (0.050 g, 5.0x10$^{-2}$ mmol) in anhydrous acetonitrile (10 mL) and dichloromethane (10 mL), palladium(II) acetate (0.011 g, 5.0x10$^{-2}$ mmol) was added and the solution refluxed for 18 h under an atmosphere of nitrogen. The resulting precipitate was filtered, washed with acetonitrile (25 mL) and dried under suction to yield Pd9 (0.047 g, 85%).

9H$_2$: To a solution of 9Pd (0.100 g, 9.00x10$^{-2}$ mmol) in dichloromethane (10 mL) and methanol (10 mL) was added potassium cyanide (0.091 g, 1.4 mmol) in methanol (2 mL). The solution was stirred at room temperature for 1 h, until it was colourless, and then heated gently to reduce the overall volume to less than 5 mL. The resultant mixture was dispersed in water (25 mL) and washed with dichloromethane (3 x 25 mL). The combined organic extracts were washed with further water (25 mL) and dried over anhydrous magnesium sulfate. After filtration, the solution was concentrated in vacuo and the crude residue purified by column chromatography (85:15 CH$_2$Cl$_2$:EtOAc) to give the title compound as a colourless
solid (0.085 g, yield = 94%). m.p. 186 °C (decomp); \(^1\)H NMR (400 MHz, CD₂Cl₂, 298 K): \(\delta = 1.17-1.78\) (m, 32H, \(H_{alkyl}\)), 3.84-3.96 (m, 8H, \(H_G + H_E\)), 4.48-4.54 (m, 12H, \(H_D + H_d + H_e\)), 6.76-6.84 (m, 8H, \(H_F + H_J\)), 7.15-7.24 (m, 8H, \(H_E + H_e\)), 7.30 (d, \(2H, J = 7.8\) Hz, \(H_B\)), 7.66 (t, 1H, \(J = 7.8\) Hz, \(H_a\)), 8.02 (t, 1H, \(J = 7.8\) Hz, \(H_d\)), 8.11 (br, 2H, \(H_C\)), 8.32 (d, \(2H, J = 7.8\) Hz, \(H_B\)).

\(^1^3\)C NMR (100 MHz, CDCl₃, 298 K): \(\delta = 25.9, 25.9, 29.0, 29.1, 29.2, 29.3, 29.3, 29.3, 43.0, 67.9, 68.0, 72.4, 72.4, 114.4, 114.7, 120.3, 125.2, 129.0, 129.6, 129.7, 129.8, 137.2, 139.0, 148.8, 157.9, 158.6, 158.8, 163.3; LRFAB-MS (3-NOBA matrix): \(m/z = 1006 [MH]^+\); HRFAB-MS (3-NOBA matrix): \(m/z = 1005.57406\) (calcd. for \(C_{62}H_{77}N_{10}O_8\), 1005.57414).

Pd(7)(endo-8)/Pd(7)(exo-8): The synthesis of Pd(7)(8) was carried out as for Pd(1)(8) but using 8 (0.300 g, 5.82x10⁻¹ mmol) and Pd(7)(CH₃CN) (0.384 g, 5.82x10⁻¹ mmol) as reactants. The crude residue was purified using column chromatography (85:15 CH₂Cl₂:EtOAc) to yield a 2:3 mixture of the two atropisomers as a yellow solid (0.587 g, 89%). The atropisomers were separated using preparative thin layer chromatography (98.5:1.5 CH₂Cl₂:MeOH).

**Threaded atropisomer, Pd(7)(endo-8).** \(^1\)H NMR (400 MHz, CD₂Cl₂, 298 K): \(\delta = 1.18-1.82\) (m, 24H, \(H_{alkyl}\)), 2.10 (m, 4H, \(H_{alkyl}\)), 3.80 (t, 4H, \(J = 6.6\) Hz, \(H_G\)), 3.90 (t, 4H, \(J = 6.6\) Hz, \(H_E\)), 4.01 (s, 4H, \(H_D\)), 4.42 (s, 4H, \(H_d\)), 4.69 (s, 4H, \(H_c\)), 4.98 (m, 4H, \(H_I\)), 5.83 (m, 2H, \(H_h\)), 6.24-6.35 (m, 8H, \(H_E + H_F\)), 6.80 (d, 4H, \(J = 8.6\) Hz, \(H_J\)), 7.15 (d, 2H, \(J = 7.8\) Hz, \(H_B\)), 7.23 (d, 4H, \(J = 8.6\) Hz, \(H_e\)), 7.66 (t, 1H, \(J = 7.8\) Hz, \(H_d\)), 7.77 (d, 2H, \(J = 7.8\) Hz, \(H_B\)), 8.10 (t, 1H, \(J = 7.8\) Hz, \(H_A\)). \(^1^3\)C NMR (100 MHz, CD₂Cl₂, 298 K): \(\delta = 25.7, 25.8\) (x2), 28.8, 29.1 (x2), 29.8, 33.8, 49.9, 67.6, 72.3, 73.7, 114.6,
114.7, 114.8, 121.8, 124.8, 128.4, 129.6, 130.4, 132.0, 139.0, 139.1, 140.9, 153.2, 157.9, 159.4, 160.2, 171.5; LRESI-MS m/z = 1157 (M + Na⁺). **Non-threaded atropisomer**, Pd(7)(exo-8) \(^1\)H NMR (400 MHz, CD\(_2\)Cl\(_2\), 298 K): \(\delta = 0.73\text{-}1.81\) (m, 24H, \(H_{\text{alkyl}}\)), 2.11 (m, 4H, \(H_{\text{alkyl}}\)), 2.49 (d, 2H, \(J = 14.4\) Hz, \(H_D\)), 3.33 (s, 2H, \(H_d\)), 3.39 (s, 2H, \(H_c\)), 3.93 (m, 8H, \(H_G + H_g\)), 4.68 (s, 2H, \(H_d\)), 5.00 (m, 6H, \(H_f + H_E\)), 5.63 (s, 2H, \(H_c\)), 5.83 (m, 2H, \(H_f\)), 6.74 (m, 8H, \(H_F + H_f\)), 6.85 (m, 4H, \(H_F + H_F\)), 7.28 (m, 5H, \(H_e + H_e + H_b\)), 7.72 (d, 1H, \(J = 7.8\) Hz, \(H_b\)), 7.82 (d, 2H, \(J = 7.8\) Hz, \(H_b\)), 7.88 (t, 1H, \(J = 7.8\) Hz, \(H_g\)), 8.13 (t, 1H, \(J = 7.8\) Hz, \(H_d\)); \(^{13}\)C NMR (100 MHz, CD\(_2\)Cl\(_2\), 298 K): \(\delta = 25.7, 25.9, 29.0, 29.1, 29.1, 29.2, 29.8, 33.9, 49.0, 67.9, 68.2, 68.3, 71.4, 72.2, 72.4, 73.8, 114.5, 114.7, 114.8, 114.8, 122.2, 122.5, 125.1, 128.6, 129.6, 130.1, 130.2, 130.5, 133.44, 139.1, 140.2, 141.25, 153.1, 158.3, 159.2, 159.5, 159.7, 162.3, 171.6; LRESI-MS m/z = 1157 (M + Na⁺).

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**Preparation of 7H\(_2\), 10 and 11H\(_2\) from the mixture of Pd(7)(exo-8) and Pd(7)(endo-8)**

(a) A solution of Pd(7)(8) (0.362 g, 3.19 x10\(^{-1}\) mmol) in anhydrous degassed dichloromethane (150 mL) was added \textit{via} a double ended needle to a solution of first generation Grubbs’ catalyst (0.030 g, 3.6x10\(^{-2}\) mmol) in anhydrous degassed dichloromethane (500 mL) under an atmosphere of nitrogen. The solution was stirred at room temperature for 18 h, after which it was concentrated \textit{in vacuo} and the crude residue purified by column chromatography (9:1 CH\(_2\)Cl\(_2\):CH\(_3\)COCH\(_3\)) to yield a yellow solid. (b) To a solution of the yellow solid obtained from part (a) in THF (20
mL) was added PdEnCatTM (0.080 g, 3.2 x10⁻² mmol) and the resulting suspension stirred under an atmosphere of hydrogen (50 bar) for 18 h. The suspension was then filtered and the solution concentrated in vacuo.\[28\] (c) To a solution of the crude product obtained from part (b) in dichloromethane (10 mL) and methanol (10 mL) was added potassium cyanide (0.311 g, 4.79 mmol) in methanol (4 mL). The solution was stirred at room temperature for 1 h, until it was colourless, and then heated gently to reduce the overall volume to less than 5 mL. The resulting mixture was dispersed in water (25 mL) and washed with dichloromethane (3 x 25 mL). The combined organic extracts were washed with further water (25 mL) and dried over anhydrous magnesium sulfate. After filtration, the solution was concentrated in vacuo and the crude residue purified by column chromatography (99:1 CH₂Cl₂:MeOH) to give 7H₂ (0.12 g), 10 (0.020 g) and 11H₂ (0.081 g) in 73%, 13% and 25% yields respectively (over three steps). 11H₂: m.p.125-126 °C; \(^1\)H NMR (400 MHz, CD₂Cl₂, 298 K): \(\delta\) = 1.22-1.55 (m, 24H, Hₐₖₖ), 1.63-1.76 (m, 8H, H₉ₖₖ), 3.75-2.89 (m, 12H, H₆ + H₅ + H₆), 4.02 (d, 4H, \(J = 6.3\), H₇), 4.16 (s, 4H, H₈), 6.32-6.42 (m, 8H, H₉ + H₈), 6.48 (d, 4H, \(J = 8.6\) Hz, H₆), 6.74 (d, 4H, \(J = 8.6\) Hz, H₅), 6.85 (d, 2H, \(J = 7.8\) Hz, H₆), 7.40 (t, 1H, \(J = 7.8\) Hz, H₅); \(^1\)C NMR (100 MHz, CDCCl₃, 298 K): \(\delta\) = 25.6, 25.8, 28.3, 28.5, 28.6, 28.7, 29.2, 29.4, 42.2, 67.0, 67.1, 70.0, 72.6, 113.6, 114.1, 118.9, 124.1, 128.3, 128.8, 129.8, 130.4, 136.5, 137.3, 148.6, 157.3, 157.5, 158.4, 163.2; LRFAB-MS (3-NOBA matrix): \(m/z = 1006 [MH]^+\); HRFAB-MS (3-NOBA matrix): \(m/z = 1005.57494\) (calcd. for C₆₂H₇₇N₄O₈, 1005.57414).
The synthesis of Pd(1)(10) was carried out as for Pd(1)(8) but using 10 (0.279 g, 5.70 x10⁻¹ mmol) and Pd(1)(CH₃CN) (0.392 g, 5.70 x10⁻¹ mmol) as reactants. The resulting crude residue was purified by column chromatography (95:5 CH₂Cl₂:EtOAc) to yield Pd(1)(10) as a yellow solid (0.446 g, yield = 69%). m.p. 58-60 °C; ¹H NMR (400 MHz, CD₂Cl₂, 298 K): δ = 1.19-1.48 (m, 12H, Hₐₖₖₙ), 1.50-1.82 (m, 12H, Hₐₖₖₙ), 2.13 (m, 4H, Hₐₖₙ), 3.55 (s, 4H, Hₜₙ), 3.80-3.91 (m, 8H, Hₐ + Hₜ), 4.18 (b, 4H, Hₐ), 4.39 (s, 4H, Hₜ), 5.00 (m, 4H, Hᵢ), 5.86 (m, 2H, Hᵢᵢ), 6.21 (br, 4H, Hₐₖ), 6.41 (d, 4H, J = 8.0 Hz, Hₚ), 6.52 (d, 4H, J = 8.3 Hz, Hᵢᵢ), 7.07 (d, 4H, J = 8.3 Hz, Hₚ), 7.25 (d, 2H, J = 7.8 Hz, Hᵢᵢ), 7.71-7.78 (m, 3H, Hₐₖ+Hₐ), 8.11 (t, 1H, J = 7.8 Hz, Hₐ). ¹³C NMR (100 MHz, CD₂Cl₂, 298 K): δ = 25.7, 26.0, 28.9, 29.0, 29.1, 29.9, 33.8, 48.5, 67.6, 68.1, 70.4, 73.1, 114.2, 114.4, 114.8, 123.5, 124.3, 128.6, 131.4, 133.6, 139.1, 139.3, 140.4, 153.0, 157.9, 158.2, 159.3, 159.8, 170.8; LRFAB-MS (3-NOBA matrix): m/z = 1135 [MH⁺]; HRFAB-MS (3-NOBA matrix): m/z = 1135.47843 (calcd. for C₆₄H₇₇N₄O₈Pd, 1135.47734).
Method 1

(a) The synthesis of Pd11 was carried out as for Pd9 (method 1) but using Pd(1)(10) (0.352 g, 3.10x10⁻¹ mmol) as the starting material and (0.030 g, 3.6x10⁻² mmol) of Grubbs’ catalyst. The crude residue was purified by column chromatography (96:4 CH₂Cl₂:EtOAc) to yield a yellow solid (0.34 g). (b) The yellow solid obtained from part (a) (0.34 g) was treated with 10% w/w Pd-C (0.050 g) over H₂ in THF (20 mL) as for Pd9, yielding Pd11 (0.268 g, 78% over 2 steps). m.p. 134-135 °C; ¹H NMR (400 MHz, CD₂Cl₂, 298 K): δ = 1.04-1.50 (m, 24H, H₁₄), 1.60 (m, 4H, Hₐ), 1.70 (m, 4H, Hₖ), 3.60 (s, 4H, H₄), 3.81 (t, 4H, J = 6.3 Hz, H₅), 3.89 (t, 4H, J = 6.3 Hz, H₆), 4.36-4.42 (m, 8H, Hₗ), 5.94 (d, 4H, J = 8.6 Hz, Hₗ), 6.10 (d, 4H, J = 8.6 Hz, Hₖ), 6.63 (d, 4H, J = 8.6 Hz, H₉), 7.05 (d, 2H, J = 7.8 Hz, H₇), 7.15 (d, 4H, J = 8.6 Hz, H₈), 7.60 (t, 1H, J = 7.8 Hz, H₉), 7.76 (d, 2H, J = 7.6 Hz, H₈), 8.13 (t, 1H, J = 7.6 Hz, H₉); ¹³C NMR (100 MHz, CD₂Cl₂, 298 K): δ = 25.8, 26.0, 28.5, 28.7, 28.9, 29.2, 30.0, 30.1, 49.4, 67.1, 67.7, 69.6, 72.9, 114.5, 114.8, 121.2, 124.5, 128.2, 128.6, 131.7, 132.9, 138.8, 140.6, 153.1, 157.4, 159.5, 160.0, 171.1. LRFAB-MS (3-NOBA matrix): m/z = 1109 [MH]+; HRFAB-MS (3-NOBA matrix): m/z = 1109.46152 (calcd. for C₆₂H₇₅N₄O₅Pd, 1109.46169).

Method 2

The synthesis of Pd11 was carried out as for Pd9 (method 2) but using 11H₂ (0.050 g, 5.0x10⁻² mmol) as the starting complex and (0.011 g, 5.0x10⁻² mmol) of palladium(II) acetate to yield Pd11 (0.044 g, 79%).
7Pd10: The synthesis of Pd(7)(10) was carried out as for Pd(1)(8) but using 10 (0.110 g, 2.25x10^{-1} mmol) and Pd(7)(CH3CN) (0.149 g, 2.25x10^{-1} mmol) as reactants. The crude residue was purified by column chromatography (97.5:2.5 CH2Cl2:MeOH) to yield Pd(7)(10) as a yellow solid. (0.194 g, yield = 78%). m.p. 181 °C (decomp); 1H NMR (400 MHz, CD2Cl2, 298 K): δ = 0.81-1.74 (m, 32H, H_{alkyl}), 2.50 (d, 2H, J = 14.8 Hz, H_{D'}), 3.34-3.44 (m, 4H, H_{D'} + H_{E'}), 3.78-4.02 (m, 6H, H_{G'} + H_{G'} + H_{D}), 4.09 (t, 2H, J = 6.3 Hz, H_{G}), 4.72 (s, 2H, H_{D}), 5.08 (d, 2H, J = 14.8 Hz, H_{D}), 5.67 (s, 2H, H_{E}), 6.64-6.84 (m, 12H, H_{F'} + H_{F'} + H_{F} + H_{D}), 6.92 (d, 1H, J = 7.8 Hz, H_{D}), 6.99 (d, 2H, J = 8.6 Hz, H_{E}), 7.12-7.22 (m, 3H, H_{B} + H_{E}), 7.38 (t, 1H, J = 7.8 Hz, H_{D}), 7.83 (d, 2H, J = 7.8 Hz, H_{B}), 8.13 (t, 1H, J = 7.8 Hz, H_{D}); 13C NMR (100 MHz, CD2Cl2, 298 K): δ = 25.6, 25.9 (x2), 28.5, 29.0, 29.1, 29.3, 29.4, 29.6, 29.8, 29.9, 49.2, 67.8, 67.9, 68.3, 72.1, 72.8, 73.4, 76.3, 114.8, 114.9, 115.4, 122.0, 122.7, 125.1, 128.3, 129.9, 130.3, 130.5, 131.4, 133.0, 138.4, 141.3, 153.0, 158.2, 158.7, 159.6, 160.6, 161.9, 171.6; LRESI-MS m/z = 1131 (M + Na^+).

11H2: The synthesis of H211 was carried out as for 9H2 but using Pd11 (0.210 g, 1.90x10^{-1} mmol) as the starting complex and potassium cyanide (0.190 g, 2.92 mmol). The crude residue was purified using column chromatography (85:15 CH2Cl2:EtOAc) to yield 11H2 as a colourless solid (0.185 g, yield = 97%).

X-ray Crystallographic structure determinations. Pd9: C_{62}H_{74}N_{10}O_{8}Pd, M = 1109.65, yellow prism, crystal size 0.3 x 0.2 x 0.15 mm, monoclinic, P2(1)/n (# 14), a = 11.839(17), b = 17.17(2), c = 27.07(8) Å, β = 92.689(19)°, V = 5497(19) Å^3, Z = 4, ρ_{calc} = 1.341 Mg m^{-3}; MoKα radiation (confocal optic, λ = 0.71073 Å), μ = 0.397
mm$^{-1}$, $T = 93(2)$ K. 25519 data (8839 unique, $R_{int} = 0.0352$, 2.37$<\theta<$25.35$^\circ$), were collected on a Rigaku MM007/Mercury CCD diffractometer and were corrected for absorption. The structure was solved by direct methods and refined by full-matrix least-squares on $F^2$ values of all data (G. M. Sheldrick, SHELXTL, Bruker AXS Madison WI, USA, 2001, version 6.1) to give $wR = \{\Sigma[w(F_0^2 - F_c^2)^2]/\Sigma[w(F_0^2)^2]\}^{1/2} = 0.2821$, conventional $R = 0.0919$ for $F$ values of reflections with $F_0^2 > 2\sigma(F_0^2)$, [6956 observed reflections] $S = 0.919$ for 677 parameters. Residual electron density extremes were 2.085 and -1.443 eÅ$^{-3}$.

Pd(7)(10).0.5CH$_3$COCH$_3$: C$_{63.5}$H$_{77}$N$_4$O$_{8.5}$Pd, $M = 1138.69$, yellow plate, crystal size 0.2 $\times$ 0.1 $\times$ 0.02 mm, triclinic, $P-1$, $a = 16.191(15)$, $b = 24.30(2)$, $c = 30.6665(5)$ Å, $\alpha = 105.54(5)$, $\beta = 101.08(5)$, $\gamma = 90.607(11)^\circ$, $V = 11381(24)$ Å$^3$, $Z = 848$ (four independent molecules), $\rho_{calc} = 1.329$ Mg m$^{-3}$; CuMo$_{K\alpha}$ radiation (confocal optic, $\lambda = 0.71073$ 1.54178 Å), $\mu = 3.109$ mm$^{-1}$, $T = 173(2)$ K. 143757 data (38597 unique, $R_{int} = 0.0354$, 2.08$<\theta<$68.13$^\circ$), were collected on a Rigaku MM007/Saturn9270 CCD diffractometer and were corrected for absorption. The structure was solved by direct methods and refined by full-matrix least-squares on $F^2$ values of all data (G. M. Sheldrick, SHELXTL, Bruker AXS Madison WI, USA, 2001, version 6.1) to give $wR = \{\Sigma[w(F_0^2 - F_c^2)^2]/\Sigma[w(F_0^2)^2]\}^{1/2} = 0.1198$, conventional $R = 0.0452$ for $F$ values of reflections with $F_0^2 > 2\sigma(F_0^2)$ [38597 observed reflections], $S = 1.068$ for 2803 parameters. Residual electron density extremes were 1.879 and -1.247 eÅ$^{-3}$.

Pd11: C$_{62}$H$_{74}$N$_4$O$_8$Pd, $M = 1109.65$, yellow prism, crystal size 0.3 $\times$ 0.2 $\times$ 0.15 mm, monoclinic, $P2(1)$ (# 4), $a = 11.3837(6)$, $b = 36.2251(19)$, $c = 13.6178(8)$ Å, $\beta = 97.838(3)^\circ$, $V = 5563.2(5)$ Å$^3$, $Z = 4$, $\rho_{calc} = 1.325$ Mg m$^{-3}$; MoK$_{\alpha}$ radiation (confocal optic, $\lambda = 0.71073$ Å), $\mu = 0.392$ mm$^{-1}$, $T = 93(2)$ K. 37193 data (16752 unique, $R_{int} = 0.0600$, 2.57$<\theta<$25.34$^\circ$), were collected on a Rigaku MM007/Saturn70 CCD diffractometer and were corrected for absorption. The structure was solved by direct methods and refined by full-matrix least-squares on $F^2$ values of all data (G. M. Sheldrick, SHELXTL, Bruker AXS Madison WI, USA, 2001, version 6.1) to give $wR = \{\Sigma[w(F_0^2 - F_c^2)^2]/\Sigma[w(F_0^2)^2]\}^{1/2} = 0.1571$, conventional $R = 0.0624$ for $F$ values
of reflections with $F_0^2 > 2\sigma(F_0^2)$ [16035 observed reflections], $S = 1.066$ for 1353 parameters. Residual electron density extremes were 0.811 and -1.526 eÅ$^{-3}$.

### 3.4 References and Notes


Chapter 3


[20] At least as long as the RCM reaction is not under thermodynamic control. However, metathesis of internal olefins is generally much slower than terminal olefins. See, for example, Kidd, T. J.; Leigh, D. A.; Wilson, A. J. J. Am. Chem. Soc. 1999, 121, 1599-1600.

[21] The term ‘atropisomerism’ technically refers to conformers which can be isolated as separate chemical species as a result of restricted rotation about a single bond [IUPAC Compendium of Chemical Terminology 2nd Edition, 1997]. We stretch this definition slightly in applying it to Pd(7)(endo-8) and Pd(7)(exo-8), which are isolable as a result of restricted rotation about various single bonds in particular ligand orientations.

[22] The term “co-conformation” is generally used to refer to the relative positions of mechanically interlocked components with respect to each other[Fyfe, M. C. T.; Glink, P. T.; Menzer, S.; Stoddart, J. F.; White, A. J. P.; Williams, D. J.
However, since the two components in Pd(7)(endo-8) and Pd(7)(exo-8) are connected by a continuous sequence of covalent and coordination bonds, in this case “conformation” is a sufficient descriptor.

The hydrogenation conditions employed in Routes I and III led to a complex mixture when applied to the products of metathesis in Route II. Not only was significant decomplexation of the somewhat strained non-interlocked double macrocycle complex observed, but the resulting free monodentate ligand, 10, was degraded, presumably by hydrogenolysis of the benzyl ether moieties. Although the use of Pd EnCat™ did not prevent the ligand decomplexation during the hydrogenation step, it reduced the degradation of the free monodentate macrocycle [Bremeyer, N.; Ley, S.; Ramarao, C.; Shirley, I. M.; Smith, S. C. *Synlett* 2002, 1843-1844].


Chapter 4: Controlled Iterative Addition of Macrocycles onto a Single Binding Site Rotaxane Thread

Published as "One Template, Multiple Rings: Controlled Iterative Addition of Macrocycles onto a Single Binding Site Rotaxane Thread" A.-M. L. Fuller, Prof. D. A. Leigh, Dr. P. J. Lusby Angew. Chem. Int. Ed. 2007, 46, 5015-5019.
4.1 Introduction

The introduction\(^1\) and subsequent spectacular growth\(^2\text{-}^8\) of template strategies\(^2\) to molecules with multiple mechanically interlocked components (rotaxanes,\(^3\text{-}^4\), \(^8\) catenanes\(^5\text{-}^6\), \(^8\) and Borromean rings\(^7\)) has revolutionised approaches to their synthesis. However, despite the many different template systems and innovative assembly processes developed thus far, a feature common to all current methods is that they each employ at least one binding site per macrocycle, i.e. a minimum of \(n-1\) templates per \(n\) interlocked components.

![Diagram of rotaxane synthesis](image)

**Scheme 4.1.** An iterative \([n]\)rotaxane synthesis utilising a single template unit (shown in purple) and the repetition of three simple steps: (i) complexation of an acyclic ligand (shown in light blue) to the template site; (ii) macrocyclisation; (iii) demetallation.

Here we describe a strategy (Scheme 4.1) for assembling multi-ring rotaxanes in which just a single ligation site is used to clip-on as many macrocycles as required (and the length of the thread will permit), through the repetition of three simple steps. The method (Scheme 4.2) involves the repetitive coordination and macrocyclisation of a tridentate ligand for palladium about stoppered molecular thread \(12\), sequentially forming rings of type \(7H_2\) to iteratively\(^{5b}\) generate \([2]\), \([3]\) and \([4]\)rotaxanes.
Overcoming the restriction of only one ring per template unit—especially the ability to re-utilise the template despite the proximity of a previously cyclised component—should aid the synthesis of increasingly complex higher order interlocked assemblies (e.g. defined sequences of different rings on a molecular strand).

The single template site iterative assembly of multiple ring rotaxanes utilises a square planar geometry Pd(II)-based ‘clipping’ methodology previously developed as a ‘classical’ (i.e. one macrocycle per binding site) template synthesis of rotaxanes and catenanes. The metal is first bound to a tridentate 2,6-pyridinedicarboxamide ligand (significantly this involves deprotonation of the ligand amide groups) and the resulting complex, Pd(1)(CH$_3$CN), is coordinated to a monodentate pyridine unit on a thread such that subsequent macrocyclisation via ring closing metathesis (RCM) occurs around the thread to generate an interlocked architecture. The key to extending this protocol so that further ligands can be cyclised around the template after the first is decomplexed, is the observation that whilst Pd(1)(CH$_3$CN) will readily exchange its labile coordinated acetonitrile molecule for a pyridine unit (e.g. Scheme 4.2, step i), it does NOT undergo tridentate ligand exchange with protonated (i.e. metal free) versions of the 2,6-pyridinedicarboxamide system (e.g. 13H$_2$, 14H$_2$, Scheme 4.2, steps iv and vii). Thus a pyridine group on a thread can repetitively be used to replace acetonitrile ligands of Pd(1)(CH$_3$CN), with the resulting complexes then being macrocyclised, one at a time.

### 4.2 Results and Discussion

To demonstrate the effectiveness of this strategy in a multi-ring rotaxane synthesis, a suitable thread, 12, was prepared (see experimental section 4.4), with a single pyridine unit as the only potential template site and sufficient space—provided by a C$_{11}$ alkyl chain—between the stoppers to accommodate several macrocycles. As anticipated, stirring 12 with Pd(1)(CH$_3$CN) in dichloromethane resulted in rapid formation of Pd(1)(12) (92%, Scheme 2, step i). Macrocyclisation with Grubbs’ first generation RCM catalyst and subsequent hydrogenation gave the saturated palladium [2]rotaxane Pd13 (72%, Scheme 2, step ii). Treatment with potassium
cyanide (Scheme 4.2, step iii) then afforded the metal-free [2]rotaxane, 13H₂, in 62% overall yield for the first iterative cycle.

Scheme 4.2. The controlled iterative synthesis of [2], [3] and [4]rotaxanes 13H₂, 14H₂ and 15H₂. CPK models confirm that the threaded rings cannot pass through the cavities of each other and so the color of each fragment of a structure reflects its origin in the synthetic sequence. (i) Pd(1)(CH₃CN), CH₂Cl₂, 5 h, RT, 92%; (ii) a. Grubbs’ catalyst (0.12 equiv), CH₂Cl₂; b. o-Nitrobenzenesulfonylhydrazide (NBSH), Et₃N, CH₂Cl₂, 72% (over 2 steps); (ii) KCN, CH₂Cl₂, MeOH, 94%; (iv) Pd(1)(CH₃CN), CH₂Cl₂, 5 h, RT, 96%; (v) a. Grubbs’ catalyst (0.12 equiv), CH₂Cl₂; b. NBSH, Et₃N, CH₂Cl₂, 84% (over 2 steps); (vi) KCN, CH₂Cl₂, MeOH, 98%; (vii) method A: Pd(1)(CH₃CN), CH₂Cl₂, 3 days, RT, Pd(1)(14H₂) 51%, iso-[Pd(1)(14H₂)] 37%. method B: Pd(1)(CH₃CN) (3eq), CH₂Cl₂, Δ, 7 days, Pd(1)(14H₂) 81%, iso-[Pd(1)(14H₂)] 5%; (viii) a. Grubbs’ catalyst (0.12 equiv), CH₂Cl₂; b. NBSH, Et₃N, CH₂Cl₂; 3. KCN, CH₂Cl₂, MeOH, 70% (over 3 steps) (ix) a. Grubbs’ catalyst (0.12 equiv), CH₂Cl₂; b. NBSH, Et₃N, CH₂Cl₂, 87% (over 2 steps); (x) KCN, CH₂Cl₂, MeOH, 97%.

A comparison of the room temperature ¹H NMR spectrum of 13H₂ in CD₂Cl₂ (Figure 4.1c) with that of the free components, macrocycle 7H₂ and thread 12 (Figure 4.1a
and b, respectively), confirms the interlocked nature of the product. The most significant differences in the spectra are for the signals of the methylene protons adjacent to the thread pyridine group (H_e and H_g), which are shifted significantly upfield in the [2]rotaxane. The macrocycle phenyl resonances (H_{EI} and H_{FI}) are also shielded in the [2]rotaxane while the amide protons (H_{CI}) move 1.3 ppm downfield, indicative of intercomponent hydrogen bonding with the pyridine unit. However, small upfield shifts in nearly all the axle signals in the rotaxane, including the alkyl region, show that this interaction is rather weak and the macrocycle is able to access the full length of the thread in CD_2Cl_2.

For the second iterative cycle, starting from [2]rotaxane 13H_2 repetition of the three steps (complexation, macrocyclisation and demetallation, Scheme 4.2, steps iv-vi) smoothly afforded [3]rotaxane 14H_2 in 79% overall yield. The crucial complexation of Pd(1)(CH_3CN) to the free pyridine group of 13H_2 to give Pd(1)(13H_2) (Scheme 4.2, step iv) proceeds in 96% yield in 5 h with no trace of transmetallation to the rotaxane macrocycle. Comparison of the ^1H NMR spectrum of Pd(1)(13H_2) in CD_2Cl_2 (Figure 4.2b) with that of Pd(1)(12) (Figure 4.2a) indicates that the displaced macrocycle in the [2]rotaxane spends a significant amount of time over the ether unit furthest from the palladium coordination sphere (1.2 ppm upfield shift in thread methyleneoxy resonance H_m), presumably at least in part as a result of amide-ether oxygen H-bonding. The ^1H NMR of the demetallated [3]rotaxane 14H_2 in CD_2Cl_2 is shown in Figure 4.1d. The occurrence of the amide signals at 9.4 and 8.6 ppm (H_{C2} and H_{CI}) suggest that the amide-pyridine hydrogen bonding is appreciably stronger than the amide-ether hydrogen bonding interaction.
Figure 4.1. $^1$H NMR Spectra (400 MHz, CD$_2$Cl$_2$, 298 K) of the metal-free rotaxanes and their non-interlocked components. (a) macrocycle 7H$_2$; (b) thread 12; (c) 2]rotaxane 13H$_2$; (d) 3]rotaxane 14H$_2$; (e) 4]rotaxane 15H$_2$. The italicised letters and numbers refer to the assignments in Scheme 4.2 and the component sequences indicated in the cartoons.

The final iterative cycle commenced with the reaction of 3]rotaxane 14H$_2$ with Pd(1)(CH$_3$CN) (Scheme 4.2, step vii, method A). However, the reaction proved
extremely sluggish using the conditions previously employed (CH₂Cl₂, 293 K) and after three days the product mixture was separated by column chromatography to give, somewhat unexpectedly, two new kinetically stable products in a ratio of 2:3. Mass spectrometry suggested that the products were isomers of Pd(1)(14H₂) (see Scheme 4.2), in which the two macrocycles are restricted to different regions of the thread by Pd(1) coordination to the pyridine unit. The major product was assigned by \(^1\)H NMR as isomer Pd(1)(14H₂). Its spectrum (Figure 4.2c) shows increased shielding of the alkyl region with respect to the similarly derivatised \([2]\)rotaxane Pd(1)(13H₂) (Figure 4.2b), suggesting that both macrocycles are located over the C₁₁ region of the thread. In contrast, the \(^1\)H NMR spectrum (Figure 4.2d) of the minor isomer showed no increase in shielding of the alkyl region compared to Pd(1)(13H₂). Rather, significant shifts of the thread methyleneoxy (Hₑ) and stopper protons Hₐ and Hₑ occur indicating that this isomer is \(iso\)-\([Pd(1)(14H₂)]\), in which the two macrocycles are separated by the coordinated Pd(1) unit.

Whilst the formation of this second isomer appears surprising given the steric demands of the macrocycle and the very limited space available between the pyridine ligation site and the closest bulky stopper, it presumably reflects the fact that an ether oxygen atom is available on that part of the thread for one of the two amide macrocycles to spend significant time hydrogen bonding to. Complexation of Pd(1) to the pyridine unit traps that proportion of macrocycles in that region of the thread and the kinetic stability of the pyridine-palladium bond inhibits equilibration to the less sterically hindered isomer. In agreement with this rationalisation, carrying out the reaction at reflux for 7 days (Scheme 4.2, step vii, method B) to induce some reversibility in the pyridine-palladium bond formation gave 81% of Pd(1)(14H₂) with only a small amount of the minor isomer. The final macrocyclisation and demetallation steps to give \([4]\)rotaxane 15H₂ could be carried out on either the single isomer Pd(1)(14H₂) (Scheme 4.2, steps ix and x) or on the mixture of Pd(1)(14H₂)/\(iso\)-[Pd(1)(14H₂)] isomers (Scheme 4.2, step viii). The \([4]\)rotaxane obtained from these reactions—in both case single species—had identical physical properties and indistinguishable \(^1\)H NMR spectra (Figure 4.1e), again supporting the
structural assignments of Pd(1)(14H₂) and iso-[Pd(1)(14H₂)]. The ¹H NMR spectrum of 15H₂ in CD₂Cl₂ (Figure 4.1e) shows three sets of amide signals, and further shielding of both the C₁₁ alkyl chain of the thread and in particular the methyleneoxy resonances (Hₖ, H₇, H₈). The overall yield for the iterative cycle to add the third ring to generate the [4]rotaxane is a pleasing 68% (via single isomer Pd(1)(14H₂)).

Figure 4.2. ¹H NMR Spectra (400 MHz, CD₂Cl₂, 298 K) of the coordination complexes of Pd(1) with the thread, [2]rotaxane and [3]rotaxane. (a) Pd(1)(12); (b) Pd(1)(13H₂); (c) Pd(1)(14H₂); (d) iso-[Pd(1)(14H₂)]. The italicised letters and numbers refer to the assignments in Scheme 4.2 and the component sequences indicated in the cartoons.
In conclusion, we have described methodology for preparing multi-ring rotaxanes through the iterative addition of macrocycles to a rotaxane thread bearing a single ligation site. Using this efficient and effective strategy both the number and the order in which macrocycles are assembled onto a thread can be controlled with unprecedented precision.

4.3 Experimental Section

Synthesis of 12

Scheme 4.4. Reagents and conditions: (a) 2,6-pyridinedimethanol, PPh₃, DIAD, CH₂Cl₂, 62%; (b) SOCl₂, CH₂Cl₂, 99%, (c) 11-bromo-1-undecanol, K₂CO₃, NaI, butan-2-one, 90%, (d) NaH, THF, 95%.
S1: To a suspension of (p-hydroxyphenyl)tris(p-tert-butylphenyl)methane\textsuperscript{13} (7.57 g, 15.0 mmol), 2,6-pyridinedimethanol (10.4 g, 75.0 mmol) and triphenyl phosphine (4.72 g, 18.0 mmol) in dichloromethane (200 mL) at 0 °C under an atmosphere of nitrogen, was added diisopropyl azodicarboxylate (DIAD, 3.54 mL, 18.0 mmol) dropwise. The suspension was allowed to warm to room temperature and stirred for 18 h. The suspension was then filtered and the solvent removed under reduced pressure. The crude residue was stirred in methanol (200 mL) for 30 min, after which time the solid was filtered off and purified by column chromatography (ethyl acetate:dichloromethane 1:24 as eluent) to yield S1 as a colourless solid (5.82 g, 62%). M.p. 249-251 °C; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): \(\delta = 1.30 (s, 27H, H_a), 3.80 (b, 1H, OH), 4.78 (s, 2H, H_j), 5.19 (s, 2H, H_i), 6.85 (d, 2H, \textit{J} = 9.0 Hz, H_e), 7.08-7.12 (m, 8H, H_{d+c}), 7.17 (d, 1H, \textit{J} = 7.7 Hz, H_h), 7.23 (d, 6H, \textit{J} = 8.6 Hz, H_b), 7.46 (d, 1H, \textit{J} = 7.7 Hz, H_g), 7.73 (t, 1H, \textit{J} = 7.7 Hz, H_h); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}): \(\delta = 31.4, 34.3, 63.0, 63.8, 70.2, 113.3, 119.3, 119.9, 124.1, 130.7, 132.4, 137.7, 140.2, 144.0, 148.3, 156.1, 156.4, 158.2; LRMS (FAB, NOBA): \textit{m/z} = 626 [MH]\textsuperscript{+}; HRMS (FAB, NOBA): \textit{m/z} = 626.39990 [MH]\textsuperscript{+} (calc. for C\textsubscript{44}H\textsubscript{52}NO\textsubscript{2}, 626.39981).
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S2: To a solution of S1 (5.01 g, 8.00 mmol) in anhydrous dichloromethane (125 mL) was added thionyl chloride (1.50 mL, 20.7 mmol) and the reaction mixture stirred overnight, after which the solvent and excess thionyl chloride were removed under reduced pressure to yield S2 as a colourless solid (5.10 g, 99%). M.p. 260 °C (decomp); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = 1.30\) (s, 27H, H\(_a\)), 4.68 (s, 2H, H\(_i\)), 5.18 (s, 2H, H\(_f\)), 6.85 (d, 2H, \(J = 9.0\) Hz, H\(_e\)), 7.05-7.13 (m, 8H, H\(_{d+e}\)), 7.23 (d, 6H, \(J = 8.6\) Hz, H\(_b\)), 7.41 (d, 1H, \(J = 7.7\) Hz, H\(_i\)), 7.51 (d, 1H, \(J = 7.7\) Hz, H\(_g\)), 7.76 (t, 1H, \(J = 7.7\) Hz, H\(_h\)); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta = 31.4, 34.3, 46.5, 63.0, 70.3, 113.2, 120.5, 121.6, 124.0, 130.7, 132.3, 137.9, 140.1, 144.0, 148.3, 155.9, 156.1, 157.4\); LRMS (FAB, NOBA): \(m/z = 644\) [MH]\(^+\); HRMS (FAB, NOBA): \(m/z = 644.36595\) [MH]\(^+\) (calc. for C\(_{44}H_{51}^{35}\)ClNO, 644.36592).

S3: To a solution of (p-hydroxyphenyl)tris(p-tert-butylphenyl)methane (7.57g, 15.0 mmol) and 11-bromo-1-undecanol (3.77 g, 15.0 mmol) in butan-2-one (200 mL), were added potassium carbonate (10.4 g, 75.0 mmol) and a catalytic amount (~50 mg) of sodium iodide. The suspension was refluxed for 18 h under an atmosphere of nitrogen. Upon cooling, the potassium carbonate was removed by filtration and the
filtrate concentrated under reduced pressure. The resultant oil was dissolved in dichloromethane (150 mL) and washed with water (2 x 50 mL), followed by a saturated solution of brine (50 mL). The water layers were combined and re-extracted with dichloromethane (50 mL). The combined organic layers were dried over anhydrous magnesium sulfate, concentrated under reduced pressure and the crude residue subjected to column chromatography (ethyl acetate: petroleum ether (40:60); 1: 9) to yield S3 as a colourless solid (9.11 g, 90%). M.p. 172-174 °C; \[ \text{\(^{1}H\) NMR (400 MHz, CD\textsubscript{2}Cl\textsubscript{2}): } \delta = 1.24-1.59 \text{ (m, 43H, } H_{i+m+n+o+p+r+s+z+2}), 1.71-1.82 \text{ (m, 2H, } H_{e}), 3.60 \text{ (t, 2H, } J = 6.6 \text{ Hz, } H_{k}), 3.93 \text{ (t, 2H, } J = 6.6 \text{ Hz, } H_{u}), 6.76 \text{ (d, 2H, } J = 9.0 \text{ Hz, } H_{r}), 7.12-7.21 \text{ (m, 8H, } H_{x+y-w}), 7.28 \text{ (d, 6H, } J = 8.6 \text{ Hz, } H_{y}); \text{\(^{13}C\) NMR (100 MHz, CD\textsubscript{2}Cl\textsubscript{2}): } \delta = 26.1, 26.4, 29.7, 29.8 (x2), 29.9, 30.0 (x2), 31.5, 33.3, 34.6, 63.2, 63.5, 68.3, 113.5, 124.6, 130.8, 132.2, 139.8, 144.9, 148.7, 157.4; \text{LRMS (FAB, NOBA): } m/z = 674 [M]^+; \text{HRMS (FAB, NOBA): } m/z = 674.50626 [M]^+ \text{ (calc. for } \text{C}_{48}\text{H}_{66}\text{O}_{2}, 674.50628).}

12: To a solution of S3 (4.45 g, 6.60 mmol) in anhydrous THF (50 mL) under an atmosphere of nitrogen, was added sodium hydride (0.53 g, 13.2 mmol, 60% dispersion in oil). The reaction was refluxed for an hour and then allowed to cool to room temperature, after which S2 (3.54 g, 5.50 mmol) was added and the mixture refluxed overnight. The reaction was then filtered, concentrated under reduced pressure and the residue re-dissolved in dichloromethane (150 mL), washed with water (2 x 50 mL), and then a saturated solution of brine (50 mL). The water layers were combined and re-extracted with dichloromethane (50 mL). The combined organic layers were then dried over anhydrous magnesium sulfate, concentrated under reduced pressure and the crude product subjected to column chromatography.
using a gradient solvent system, (ethyl acetate: petroleum ether (40:60), 5:95 to 15:85 as eluent) to yield 12 as a colourless solid (6.71 g, 95%). M.p. 180-182 °C; \(^1\)H NMR (400 MHz, CD\(_2\)Cl\(_2\)): \(\delta = 1.25-1.48\) (m, 68H, \(H_{a+z+m+n+o+p+q+r+s}\)), 1.58-1.68 (m, 2H, \(H_j\)), 1.70-1.80 (m, 2H, \(H_g\)), 3.54 (t, 2H, \(J = 6.6\) Hz, \(H_k\)), 3.92 (t, 2H, \(J = 6.6\) Hz, \(H_a\)), 4.58 (s, 2H, \(H_f\)), 5.12 (s, 2H, \(H_l\)), 6.75 (d, 2H, \(J = 9.0\) Hz, \(H_a\)), 6.87 (d, 2H, \(J = 9.0\) Hz, \(H_a\)), 7.10-7.20 (m, 16H, \(H_{c+x+d+w}\)), 7.24-7.30 (m, 12H, \(H_{b+y}\)), 7.34-7.43 (m, 2H, \(H_i+z\)), 7.73 (t, 1H, \(J = 7.7\) Hz, \(H_e\)); \(^{13}\)C NMR (100 MHz, CD\(_2\)Cl\(_2\)): \(\delta = 26.5, 26.6, 29.7, 29.8, 29.9, 30.0\) (x3), 30.2, 31.5 (x2), 34.6 (x2), 63.5 (x2), 68.3, 71.1, 71.6, 74.0, 113.5, 113.9, 120.1, 120.4, 124.7, 124.7, 130.8 (x2), 132.2, 132.4, 137.6, 139.8, 140.5, 144.8, 144.9, 148.7, 148.8, 156.8, 157.0, 157.4, 159.1; LRMS (FAB, NOBA): \(m/z = 1282\) [M]; HRMS (FAB, NOBA): \(m/z = 1282.89269\) [M] \(^+\) (calc. for \(^{12}\)C\(_{91}\)\(^{13}\)CH\(_{115}\)NO\(_3\), 1282.89105).

Pd(1)(12): A solution of 12 (2.57 g, 2.00 mmol) and Pd(1)(CH\(_3\)CN)\(^{9a}\) (1.37 g, 2.00 mmol) in anhydrous dichloromethane (30 mL) was stirred for 5 h at room temperature under an atmosphere of nitrogen. The solution was then concentrated under reduced pressure and the crude residue purified by column chromatography (ethyl acetate: petroleum ether (40:60) 1:2 as eluent) to yield Pd(1)(12) as a yellow solid (3.55 g, 92%). M.p. 152 °C (decomp); \(^1\)H NMR (400 MHz, CD\(_2\)Cl\(_2\), 293 K): \(\delta = 1.12-1.81\) (m, 80H, \(H_{a+z+t+s+r+q+p+o+n+m+l+i+H LI+H l}\)), 2.07 (m, 4H, \(H_{j+}\)), 3.35 (t, 2H, \(J = 6.6\) Hz, \(H_k\)), 3.61-3.77 (m, 4H, \(H_{GJ+GJ}\)), 3.83-3.96 (m, 4H, \(H_{DI+DI}\)), 4.02 (d, 2H, \(J = 14.3\) Hz, \(H_{DI}\)), 4.55 (s, 2H, \(H_j\)), 4.87 (s, 2H, \(H_{j+}\)), 4.91-5.04 (m, 4H, \(H_{LI}\)), 5.74-5.86
Pd13: Step 1. To a solution of first generation Grubbs’ catalyst (0.148 g, 0.180 mmol) in anhydrous degassed dichloromethane (1150 mL) under an atmosphere of nitrogen, was added a solution of Pd(1)(12) (2.90 g, 1.50 mmol) in anhydrous degassed dichloromethane (350 mL). The solution was stirred for 18 h at room temperature, concentrated under reduced pressure and the crude residue subjected to column chromatography (ethyl acetate: petroleum ether (40:60) 2:3 then 1:1 as the product eluted) to yield a yellow solid (2.42 g). Step 2. To a solution of the product obtained from Step 1 in anhydrous dichloromethane (15 mL) under an atmosphere of nitrogen were added o-nitrobenzenesulfonylhydrazide (NBSH)\textsuperscript{11} (2.22 g, 10.2 mmol) and triethylamine (1.78 mL, 12.8 mmol) and the suspension stirred overnight. The resultant orange/brown solution was then washed with sodium bicarbonate (3 x 75
The combined organic layers were then dried over anhydrous magnesium sulfate, concentrated under reduced pressure and the crude product purified by column chromatography using a gradient solvent system (ethyl acetate: dichloromethane; 0: 1 to 1: 1) to yield Pd13 (as a yellow solid (2.06 g, 72% over 2 steps). M.p. 154 °C (decomp); $^1$H NMR (400 MHz, CD$_2$Cl$_2$): $\delta$ = 1.16-1.49 (m, 80H, H$_{a+z+m+n+o+p+q+r+s+ll+JI+KI}$), 1.54-1.86 (m, 8H, H$_{HI+Il}$), 3.54 (d, 2H, J = 14.3 Hz, H$_{DI'}$), 3.59-3.85 (m, 6H, H$_{k+gi+g'i}$), 3.92 (t, 2H, J = 6.6 Hz, H$_{u}$), 4.66 (d, 2H, J = 14.3 Hz, H$_{DI}$), 4.80 (s, 2H, H$_{j}$), 5.02 (s, 2H, H$_{f}$), 6.34 (s, 8H, H$_{EI+F'I}$), 6.70-6.79 (m, 4H, H$_{e+y}$), 7.11-7.21 (m, 17H, H$_{c+x+d+g+w}$), 7.23-7.31 (m, 12H, H$_{b+y}$), 7.49 (d, 1H, J = 7.8 Hz, H$_{i}$), 7.79 (d, 2H, J = 7.8 Hz, H$_{BJ}$), 7.85 (t, 1H, J = 7.8 Hz, H$_{h}$), 8.10 (t, 1H, J = 7.8 Hz, H$_{AI}$); $^{13}$C NMR (100 MHz, CD$_2$Cl$_2$): $\delta$ = 25.8, 26.0, 26.5 (x2), 28.9 (x2), 29.7, 29.8 (x2), 29.9, 30.0 (x3), 31.5 (x2), 34.6 (x2), 49.9, 63.5 (x2), 67.5, 68.3, 70.0, 72.4, 73.2, 113.5, 115.0, 115.3, 121.5, 122.2, 124.7 (x2), 125.0, 128.4, 130.8 (x2), 132.1, 132.2, 133.2, 139.5, 139.8, 141.1, 141.4, 144.8, 144.9, 148.7, 148.8, 153.2, 155.5, 157.4, 158.0, 159.9, 160.0, 171.6; LRMS (FAB, NOBA): m/z = 1903 [MH]$^+$; HRMS (FAB, NOBA): m/z = 1903.06386 [MH]$^+$ (calc. for $^{12}$C$_{122}^{13}$CH$_{151}$N$_4$O$_7$Pd, 1903.06483).

13H$_2$: To a solution of potassium cyanide (0.977 g, 15.0 mmol) in methanol (50 mL) was added a solution of Pd13 (1.90 g, 1.00 mmol) in dichloromethane (50 mL). The solution was heated gently until it was colourless and then the overall volume allowed to reduce to less than 5 mL. The resultant mixture was dispersed in water (150 mL) and washed with dichloromethane (3 x 50 mL). The combined organic
extracts were washed with more water (50 mL) and dried over anhydrous magnesium sulfate. After filtration, the solution was concentrated under reduced pressure to yield 13H2 as a colourless solid (1.69 g, 94%). M.p. 132-136 °C; 1H NMR (400 MHz, CD2Cl2): δ = 1.01-1.50 (m, 82H, H_a+z+l+m+n+o+p+q+r+s+I1+JJ+K1), 1.53-1.71 (m, 6H, H_{H1+l}), 3.22 (t, 2H, J = 6.6 Hz, H_k), 3.65-3.81 (m, 6H, H_{u+G1}), 3.89-3.98 (dd, 2H, J = 5.0, 14.5 Hz, H_{D1/l}), 4.23 (s, 2H, H_i), 4.28 (s, 2H, H_j), 4.50-4.60 (dd, 2H, J = 7.5, 14.5 Hz, H_{D1/l}), 6.33-6.45 (m, 6H, H_{F1+e}), 6.63-6.75 (m, 6H, H_{E1+s}), 6.97-7.07 (m, 3H, H_{g+r+}), 7.11-7.22 (m, 15H, H_{c+x+i+w}), 7.24-7.32 (m, 12H, H_{b+y}), 7.58 (t, 1H, J = 7.8 Hz, H_h), 8.00 (t, 1H, J = 7.8 Hz, H_d), 8.36 (d, 2H, J = 7.8 Hz, H_{B1}), 9.25-9.32 (m, 2H, H_{C1}); 13C NMR (100 MHz, CD2Cl2): δ = 25.8, 26.3, 26.4, 28.7, 28.8, 29.6, 29.7, 29.8 (x2), 29.9 (x4), 31.4 (x2), 34.5 (x2), 42.7, 63.4, 63.5, 67.2, 68.2, 69.2, 71.8, 73.1, 113.4, 113.6, 114.4, 120.1, 120.3, 124.6, 124.7, 125.3, 129.0, 130.4, 130.7 (x2), 132.0, 132.2, 137.7, 139.0, 139.8, 140.3, 144.9 (x2), 148.7 (x2), 150.0, 156.2, 156.5, 157.1, 158.2, 163.8; LRMS (FAB, NOBA): m/z = 1801 [MH3]+; HRMS (FAB, NOBA): m/z = 1799.17444 [MH]+ (calc. for 12C_{122}^{13}CH_{153}N_{4}O_{7}, 1799.17728).

Pd(1)(13H2): The synthesis was carried out as described for Pd(1)(12) but using 13H2 (0.900 g, 0.500 mmol) as the replacement ligand and Pd(1)(CH3CN) (0.344 g, 0.501 mmol) in anhydrous dichloromethane (30 mL). The resultant crude residue was purified by column chromatography (ethyl acetate: petroleum ether (40:60), 2:1 as eluent) to yield Pd(1)(13H2) as a yellow solid (1.17 g, 96%). M.p. 140 °C (decomp); 1H NMR (400 MHz, CD2Cl2): δ = 0.54-0.66 (m, 2H, H_a), 0.76-1.74 (m,
Pd14: Step 1 of the synthesis was carried out as described for Pd13 but using Pd(1)(13H2) (1.10 g, 0.450 mmol) as the metal complex and 0.074 g (0.090 mmol) of Grubbs’ catalyst in anhydrous degassed dichloromethane (400 mL). The crude residue was purified by column chromatography using a gradient system (ethyl acetate: petroleum ether (40:60); 2:1 to 1:0 as eluent) to yield a yellow solid (0.947 g). Step 2 was carried out as for Pd13 by using the product obtained in Step 1 above (0.947 g), NBSH (0.684 g, 3.14 mmol) and Et3N (0.550 mL, 3.99 mmol) in...
dichloromethane (5 mL). The crude residue was purified by column chromatography using a gradient system (ethyl acetate: dichloromethane; 0:1 to 1:1 as eluent) to yield Pd14 as a yellow solid (0.914 g, 84% over two steps). M.p. 162 °C (decomp); \(^1\)H NMR (400 MHz, CD2Cl2): \(\delta = 0.55-0.65\) (m, 2H, \(H_x\)), 0.78-0.99 (m, 6H, \(H_{t+r+q}\)), 1.03-1.47 (m, 86H, \(H_{e+z+m+n+o+p+j1+l+j2+j1+k1+k2}\)), 1.54-1.73 (m, 10H, \(H_{d2+h1+i}\)), 1.85 (t, 2H, \(J = 7.7\) Hz, \(H_u\)), 2.16 (d, 2H, \(J = 14.3\) Hz, \(H_{d2}\)), 3.57-3.91 (m, 12H, \(H_{k+G2+G2'+D1'+G1}\)), 4.69-4.78 (m, 4H, \(H_{D2+f}\)), 4.84-4.92 (dd, 2H, \(J = 8.3, 14.5\) Hz, \(H_{DI}\)), 5.07 (s, 2H, \(H_j\)), 6.34 (s, 8H, \(H_{F2+E2}\)), 6.47-6.56 (m, 6H, \(H_{v+F1}\)), 6.72 (d, 2H, \(J = 8.9\) Hz, \(H_c\)), 6.80 (d, 4H, \(J = 8.5\) Hz, \(H_{E1}\)), 7.11-7.21 (m, 11H, \(H_{c+d+g+w}\)), 7.23-7.35 (m, 18H, \(H_{b+y+z}\)), 7.52 (d, 1H, \(J = 7.8\) Hz, \(H_i\)), 7.79 (d, 2H, \(J = 7.8\) Hz, \(H_{B2}\)), 7.85 (t, 1H, \(J = 7.8\) Hz, \(H_h\)), 8.02-8.14 (m, 2H, \(H_{A1+A2}\)), 8.41 (d, 2H, \(J = 7.8\) Hz, \(H_{B1}\)), 8.49-8.56 (m, 2H, \(H_c\)), \(^13\)C NMR (100 MHz, CD2Cl2): \(\delta = 25.6, 25.8\) (x3), 26.5, 28.7, 28.8 (x3), 28.9, 29.7 (x2), 29.8, 29.9 (x2), 30.0 (x2), 31.4 (x2), 34.5, 34.6, 43.0, 49.9, 63.5, 63.6, 67.3, 67.5, 67.9, 70.0, 72.4, 73.2, 113.1, 114.6, 115.0, 115.3, 121.4, 122.1, 124.7, 124.8, 125.0, 125.6, 128.4, 129.7, 130.3, 130.7 (x2), 132.0, 132.2, 133.1, 139.1 139.5, 140.4, 141.1, 141.4, 144.7, 144.9, 148.7, 148.8, 149.7, 153.1, 155.4, 155.9, 158.0, 158.5, 159.8, 160.0, 163.7, 171.6; LRMS (FAB, NOBA): \(m/z = 2419\) [MH\(^+\)]; HRMS (FAB, NOBA): \(m/z = 2418.34192\) [MH\(^+\)] (calc. for \(^{12}\)C\(^{153}\)\(^{13}\)CH\(_{188}\)N\(_7\)O\(_{11}\)Pd, 2418.34324).

14H\(_2\): The synthesis was carried out as described for 13H\(_2\) but using Pd14 (0.847 g, 0.350 mmol) as the metal complex and 0.342 g (5.25 mmol) of potassium cyanide in
methanol (20 mL) and dichloromethane (20 mL), to yield 14H2 as a colourless solid (0.794 g, 98%). M.p. 138-140 °C; 1H NMR (400 MHz, CD2Cl2): δ = 0.55-0.66 (m, 2H, H2), 0.78-1.48 (m, 94H, H3+H+I+J+K+L+M+N+O+P+Q+R+S+T+U+V+W+X+Y+Z), 1.55-1.73 (m, 8H, H12+H13), 2.49 (t, 2H, J = 7.6 Hz, H12), 3.15 (t, 2H, J = 6.8 Hz, H13), 3.69-3.95 (m, 12H, H112+H113), 4.01 (s, 2H, H1), 4.26 (s, 2H, H1), 4.52-4.61 (dd, 2H, J = 7.5, 14.5 Hz, H12), 4.78-4.88 (dd, 2H, J = 8.1, 14.5 Hz, H13), 6.28-6.34 (m, 6H, H16+H17+H18+H19), 6.46-6.54 (m, 6H, H14+H15), 6.62 (d, 4H, J = 8.5 Hz, H10), 6.78 (d, 4H, J = 8.5 Hz, H9), 6.91 (d, 1H, J = 7.8 Hz, H8), 7.01 (d, 2H, J = 8.8 Hz, H7), 7.11-7.21 (m, 9H, H6+H7+H8), 7.23-7.36 (m, 18H, H4+H5), 7.56 (d, 1H, J = 7.8 Hz, H6), 7.97-8.07 (m, 2H, H16+H17), 8.33-8.42 (m, 4H, H112+H113), 8.50-8.56 (m, 2H, H14+H15), 9.38-9.47 (m, 2H, H18+H19); 13C NMR (100 MHz, CD2Cl2): δ = 25.6, 25.8 (x2), 25.9, 26.4, 28.7 (x3), 28.8, 29.7 (x4), 29.8, 29.9, 30.0 (x2), 31.4 (x2), 34.5, 34.6, 42.6, 43.0, 63.5 (x2), 67.2, 67.3, 67.9, 68.9, 72.0, 73.0, 113.1, 113.5, 114.4, 114.6, 120.2 (x2), 124.7, 124.8, 125.2, 125.5, 128.9, 129.7, 130.2, 130.4, 130.7 (x2), 131.9, 132.2, 137.5, 139.0, 139.1, 140.3, 140.4, 144.9 (x2), 148.6, 148.8, 149.7 (x2), 155.9, 156.0, 156.4, 158.1, 158.3, 158.5, 163.7, 163.8; HRMS (FAB, NOBA): m/z = 2314.45543 [MH]+ (calc. for 12C153 13C153 15N70 11, 2314.45569).
**Method A**

A solution of 14H₂ (0.301 g, 0.130 mmol) and Pd(1)(CH₃CN) (0.090 g, 0.131 mmol) in anhydrous dichloromethane (30 mL) was stirred at room temperature for 3 days under an atmosphere of nitrogen. The solution was then concentrated under reduced pressure and the crude residue purified by column chromatography (ethyl acetate: dichloromethane, 1:1 then 1:0, as eluent) to yield two yellow solids; higher rf - *iso-*[Pd(1)(14H₂)] (0.142 g, 37%), lower rf - Pd(1)(14H₂) (0.196 g, 51%). Pd(1)(14H₂):

**¹H NMR (400 MHz, CD₂Cl₂):** \( \delta = 0.29-0.63 \) (m, 8H, \( H_{m+n+r+s} \)), \( 0.70-1.00 \) (m, 4H, \( H_{l+i} \)), \( 1.06-1.49 \) (m, 88H, \( H_{a+z+y+z+y+z+y+j+I+j+I+j+I+j+I+j+I} \)), \( 1.50-1.76 \) (m, 12H, \( H_{l+i}+j+I+j+I+j+I+j+I+j+I \)), \( 1.98-2.07 \) (m, 4H, \( H_{l+i} \)), 2.32 (t, 2H, \( J = 7.6 \) Hz, \( H_{a} \)), 2.94 (t, 2H, \( J = 7.1 \) Hz, \( H_{b} \)).

Hz, H₂), 3.42-3.70 (m, 6H, H₁D₁⁺G₁⁺G₃), 3.76-3.94 (m, 10H, H₁D₁⁺G₁⁺G₂), 4.20-4.30 (dd, 2H, J = 7.5, 14.5 Hz, H₁D₂), 4.46 (d, 2H, J = 14.1 Hz, H₂D₃), 4.56 (s, 2H, H₂), 4.78-5.02 (m, 10H, H₁J₁⁺D₁⁺D₂⁺L₃), 5.70-5.82 (m, 2H, H₃K₃), 6.36-6.55 (m, 14H, H⁺F₃⁺E₃⁺F₁), 6.60-6.80 (m, 10H, H⁺F₂⁺E₁), 7.04-7.20 (m, 14H, H₂E₂+d+w+c), 7.25-7.35 (m, 18H, H_{b+y+z}), 7.53 (m, 3H, H₂), 7.83 (d, 2H, J = 7.8 Hz, H₃B₂), 7.95-8.17 (m, 6H, H₁+a+c₂+AJ+A₂+A₃), 8.38-8.45 (m, 4H, H₁B₁+B₂), 8.52-8.59 (m, 2H, H₁C₁); ¹³C NMR (100 MHz, CD₂Cl₂): 25.6 (x2), 25.8, 26.0, 26.2, 28.7 (x2), 28.8, 28.9, 29.0, 29.1, 29.7, 29.9, 30.1 (x2), 30.2 (x2), 31.4 (x2), 33.8, 34.5, 34.6, 34.9, 42.9, 43.2, 49.2, 63.4, 63.6, 67.1, 67.2, 67.7, 67.9, 69.1, 72.5, 73.2, 113.1, 113.9, 114.5 (x2), 114.8 (x2), 122.1 122.2, 124.6, 124.8, 125.1, 125.7, 125.8, 128.5, 129.5, 129.6, 130.0, 130.7, 130.8, 130.9, 132.1, 132.2, 133.1, 139.0, 139.1, 139.2, 140.0, 140.4, 140.9, 141.4, 144.6, 145.0, 148.7, 148.8, 149.5, 149.7, 153.1, 155.4, 155.7, 158.3, 158.5, 158.8, 160.1, 160.2, 163.6, 163.7, 171.3; LRMS (FAB, NOBA): m/z = 2960 [MH⁺]; HRMS (FAB, NOBA): m/z = 2959.62842 [M]⁺ (calc. for ¹²C₁₈₅¹³C₂H₂₂₆N₁₀O₁₅Pd, 2959.63283). iso-[Pd(1)(14H₂)]: ¹H NMR (400 MHz, CD₂Cl₂): δ = 0.55-0.70 (m, 2H, H₃), 1.06-1.49 (m, 11H, Hₐ+z+i+m+n+o+p+r+s+t+H₁H₂+H₃+H₁+H₂+H₁+J₁+J₂+K₁+K₂), 2.07-2.16 (m, 4H, H₁J₃), 2.43 (t, 2H, J = 7.6 Hz, H₄), 2.65-2.80 (m, 4H, H₁D₁⁺G₃), 3.48-3.62 (m, 4H, H₁G₂), 3.70 (s, 2H, H₂), 3.73-3.92 (m, 10H, H₁D₁⁺G₁⁺G₃), 4.46-4.60 (m, 4H, H₂D₂⁺D₂), 4.88-5.15 (m, 8H, H₁D₁⁺L₃⁺D₃), 5.31 (s, 2H, H₂), 5.76-5.89 (m, 2H, H₃K₃), 6.13 (d, 4H, J = 8.6 Hz, H₁F₂), 6.20 (d, 2H, J = 8.7 Hz, H₃), 6.41-6.60 (m, 14H, H₁F₃⁺E₃⁺F₁⁺v), 6.72-6.84 (m, 8H, H₂F₂⁺E₁), 6.95 (d, 2H, J = 8.7 Hz, H₄), 7.13-7.39 (m, 28H, H₁b+c+i+g+w+x+y), 7.64 (d, 1H, J = 7.9 Hz, H₅), 7.86 (d, 2H, J = 7.8 Hz, H₃B₂), 7.98-8.10 (m, 4H, H₂C₂⁺A₁⁺A₂), 8.15 (d, 1H, J = 7.8 Hz, H₄D₃), 8.40-8.46 (m, 4H, H₁B₁+B₂), 8.55-8.63 (m, 2H, H₁C₁); ¹³C NMR (100 MHz, CD₂Cl₂, 293 K): 25.6, 25.7 (x2), 25.8, 26.6, 28.8 (x3), 29.0, 29.2 (x2), 29.6, 29.7 (x2), 30.0 (x2), 30.1, 30.2 (x2), 31.5 (x2), 33.9, 34.6 (x2), 43.1 (x2), 50.3, 63.5, 63.7, 67.3 (x2), 67.8, 68.1, 68.6, 71.3, 71.8, 113.1 (x2), 114.4 (x2), 114.6, 114.8, 121.2, 122.2, 124.8, 125.0, 125.2, 125.6, 125.9, 128.6, 129.3, 129.7, 129.8, 130.2, 130.4, 130.8, 131.6, 132.2, 133.1, 139.0, 139.1, 139.3, 139.7, 140.5, 141.3, 141.4, 145.0 (x2), 148.7, 148.8, 149.8, 149.9, 153.0, 154.5, 155.8, 156.8, 158.4 (x2), 158.5, 163.5, 163.8 (x2), 171.4; LRMS (FAB, NOBA): m/z = 2958 [M-H⁺]; HRMS
Method B

A solution of $14\text{H}_2$ (0.301 g, 0.130 mmol) and Pd(1)(CH$_3$CN) (0.267 g, 0.390 mmol) in anhydrous dichloromethane (30 mL) under an atmosphere of nitrogen, was refluxed for 7 days. The solution was then concentrated under reduced pressure and the crude residue purified by column chromatography, (ethyl acetate:dichloromethane; 1:1 then 1:0, as eluent) to yield Pd(1)(14H$_2$) (0.312 g, 81%) and iso-[Pd(1)(14H$_2$)] (0.019 g, 5%) as yellow solids.

Pd15: Step 1 of the synthesis was carried out as described for Pd13 using Pd(1)(14H$_2$) (0.296 g, 0.100 mmol) as the metal complex and 0.010 g (0.012 mmol) of Grubbs’ catalyst in anhydrous degassed dichloromethane (100 mL). The crude residue was purified by column chromatography using a gradient system (ethyl acetate: petroleum ether (40:60); 3:1 to 1:0, as eluent) to yield a yellow solid (0.264 g). Step 2 was carried out as described for Pd13 using the product obtained from Step 1 above (0.264 g) with NBSH (0.157 g, 0.720 mmol) and Et$_3$N (0.125 mL, 0.900 mmol) in dichloromethane (2 mL). The crude residue was purified by column chromatography using a gradient system (ethyl acetate:dichloromethane, 0:1 to 1:0, as eluent) to yield Pd15 as a yellow solid (0.255 g, 87% over two steps). M.p. 142 °C (decomp); $^1$H NMR (400 MHz, CD$_2$Cl$_2$): $\delta$ = 0.32-2.08 (m, 120H, H$_{a+z+l+m+n+o+p+q+r+s+t+H1+H2+H3+I+I2+I3} +J1+J2+J3+K1+K2+K3$), 2.37 (t, 2H, $J = 7.6$ Hz,
H₄), 3.02 (t, 2H, J = 7.4 Hz, H₃), 3.16 (d, 2H, J = 14.2 Hz, H₅), 3.66-3.96 (m, 14H, H₂G₁+G₂+G₃+D₁'), 4.42-4.50 (dd, 2H, J = 6.0, 14.6 Hz, H₆₂'), 4.56 (s, 2H, H₇), 4.69-4.79 (dd, 2H, J = 7.0, 14.6 Hz, H₆₁), 4.84-4.94 (dd, 2H, J = 7.0, 14.6 Hz, H₆₁'), 5.02-5.11 (m, 4H, H₇₁+D₁), 6.34 (s, 8H, H₈₁+G₃), 6.44 (d, 2H, J = 8.9 Hz, H₈), 6.51 (d, 4H, J = 8.6 Hz, H₉), 6.66 (d, 2H, J = 8.9 Hz, H₉), 6.71-6.82 (m, 8H, H₁₀₂+G₂), 7.07 (d, 1H, J = 7.7 Hz, H₉), 7.11-7.23 (m, 14H, H₁₀₂+d+u+e), 7.26-7.36 (m, 18H, H₁₁+e+y), 7.52 (d, 1H, J = 7.7 Hz, H₉), 7.80-7.87 (m, 3H, H₁₂+G₂), 7.97-8.16 (m, 5H, H₁₂₁+G₁₁+G₂₁), 8.40-8.46 (m, 4H, H₁₂₁+D₂), 8.56-8.59 (m, 2H, H₁₂₁), 13C NMR (100 MHz, CD₂Cl₂): 25.7, 25.8 (x2), 26.0, 26.2, 26.5, 26.6, 27.2, 27.3, 28.7 (x2), 28.8, 28.9, 29.0, 29.2, 29.6, 29.7, 29.9, 30.1, 30.2, 30.4, 31.4 (x2), 34.5, 34.6, 43.0, 43.1, 50.1, 63.4, 63.6, 67.1, 67.2, 67.5, 67.7, 69.8, 72.7, 73.4, 113.1, 114.5, 114.8, 115.0, 115.5, 121.4, 121.8, 124.7, 124.8, 125.1, 125.6, 128.7, 128.3, 129.5, 129.6, 130.0, 130.7 (x2), 130.8, 131.9, 132.1, 133.0, 139.1, 139.3, 139.5, 140.5, 141.3, 141.4, 144.7, 144.9, 148.7, 148.7, 149.6, 149.7, 153.1, 155.3, 155.7, 158.1, 158.5, 158.8, 160.8 (x2), 163.5, 163.7, 171.5; HRMS (FAB, NOBA): m/z = 2933.61040 [M⁺]⁺ (calc. for 12C₁₈₃ 13C₂H₂₂₄N₁₀O₁₅Pd, 2933.61718).

15H₂:

**Method 1 – from Pd15**

The synthesis was carried out as described for 13H₂ using Pd15 (0.220 g, 0.075 mmol) as the metal complex and 0.074 g (1.12 mmol) of potassium cyanide in dichloromethane (4 mL) and methanol (4 mL) to yield 15H₂ as a colourless solid (0.206 g, 97%). M.p. 140-144 °C; ¹H NMR (400 MHz, CD₂Cl₂): δ = 0.13-0.86 (m,
12H, H_{m+n+r+s+t}), 1.02-1.49 (m, 96H, H_{a+z+o+p+q+I+I2+B+J+I/J+I2+B+J3+K+Kl+K2+K3}), 1.58-1.77 (m, 12H, H_{B3+H2+Hl}), 2.25-2.29 (m, 4H, H_{u+k}), 3.58-3.99 (m, 20H, H_{D3+G3+f+D1+G1+D2+D2'}), 4.23 (s, 2H, H_{j}), 4.81-5.03 (m, 6H, H_{D3+D1+D2}), 6.11 (d, 2H, J = 8.8 Hz, H_{x}), 6.21 (d, 4H, J = 8.5 Hz, H_{F3}), 6.41-6.53 (m, 6H, H_{v+F1}), 6.58 (d, 4H, J = 8.5 Hz, H_{E3}), 6.65 (d, 4H, J = 8.5 Hz, H_{F2}), 6.76 (d, 4H, J = 8.5 Hz, H_{E1}), 6.87 (d, 1H, J = 7.7 Hz, H_{g}), 6.93-7.04 (m, 6H, H_{E2+d}), 7.10-7.37 (m, 27H, H_{w+b+c+x+y+z}), 7.55 (d, 1H, J = 7.7 Hz, H_{h}), 8.00-8.14 (m, 3H, H_{A1+A2+A3}), 8.37-8.48 (m, 8H, H_{B1+B2+B3+C2}), 8.53-8.60 (m, 2H, H_{C1}), 9.26-9.31 (m, 2H, H_{C3}); \textsuperscript{13}C NMR (100 MHz, CD_{2}Cl_{2}): \delta = 25.6, 25.7 (x2), 25.8 (x2), 28.6, 28.7 (x3), 28.8 (x2), 29.0, 29.5 (x3), 29.6 (x2), 30.0 (x2), 30.1, 30.3, 31.4 (x2), 34.5, 34.6, 42.8, 42.9, 43.1, 63.5, 63.6, 67.2 (x3), 67.7, 68.1, 72.4, 73.2, 113.1, 113.4, 114.3, 114.5, 114.8, 119.3, 120.2, 124.8 (x2), 125.5, 125.6, 125.7, 128.8, 129.4, 129.6, 129.8, 130.1, 130.7 (x2), 130.8, 131.7, 132.1, 137.7, 139.1, 139.2 (x2), 140.2, 140.5, 144.9 (x2), 148.6, 148.8, 149.6, 149.7, 149.8, 155.6, 155.7, 156.4, 158.1, 158.2, 158.5, 158.7, 163.5, 163.7 (x2); LRMS (FAB, NOBA): m/z = 2830 [MH]+; HRMS (FAB, NOBA): m/z = 2829.72691 [M]+ (calc. for \textsuperscript{12}C\textsubscript{183}\textsuperscript{13}C\textsubscript{2}H\textsubscript{226}N\textsubscript{10}O\textsubscript{15}, 2829.72963).

**Method 2** – from a mixture of Pd(1)(14H\textsubscript{2}) and iso-[Pd(1)(14H\textsubscript{2})]  
Step 1 of the synthesis was carried out as described for Pd\textsubscript{13} using a mixture of Pd(1)(14H\textsubscript{2}) and iso-[Pd(1)(14H\textsubscript{2})] (0.296 g, 0.100 mmol) as the metal complex and 0.010 g (0.012 mmol) of Grubbs’ catalyst in anhydrous degassed dichloromethane (100 mL). The crude residue was purified by column chromatography using a gradient system (ethyl acetate: petroleum ether (40:60), 3:1 to 1:0, as eluent) to yield a yellow solid (0.252 g). Step 2 was carried out as described for Pd\textsubscript{13} using the product obtained in Step 1 above (0.252 g), NBSH (0.157 g, 0.720 mmol) and NEt\textsubscript{3} (0.125 mL, 0.90 mmol) in dichloromethane (2 mL). The crude residue was purified by column chromatography (ethyl acetate: dichloromethane, 0:1 to 1:0, as eluent) to yield a yellow solid (0.245 g). Step 3 was carried out as described for 13H\textsubscript{2} using the product obtained in Step 2 above (0.245 g) as the metal complex and 0.081 g (1.25 mmol) of potassium cyanide in methanol (4 mL) and dichloromethane (4 mL) to yield 15H\textsubscript{2} as a colourless solid (0.198 g, 70% over three steps).
4.4 References and Notes


[2] For reviews which highlight various aspects of template strategies to 
mechanically interlocked architectures, see: (a) Amabilino, D. B.; Stoddart, J. 
d) _Templated Organic Synthesis_ (Eds.: Diederich, F.; Stang, P. J.), Wiley-VCH, 
Badjić, J. D.; Cantrill, S. J.; Flood, A. H.; Leung, K. C.-F.; Liu, Y.; Stoddart, J. 
M. O.; Böhmer, V. _Chem. Commun._ **2006**, 2941-2952. (m) Vickers, M. S.; 

[3] For examples of [4]rotaxanes (at least three ring template sites), see: (a) 
Ashton, P. R.; Balladini, R.; Balzani, V.; Bélohrodký, M.; Gandolfi, M. T.; 
Philp, D.; Prodi, L.; Raymo, F. M.; Reddington, M. V.; Spencer, N.; Stoddart, 
Amabilino, D. B.; Ashton, P. R.; Balzani, V.; Brown, C. L.; Credi, A.; Fréchet, 
J. M. J.; Leon, J. W.; Raymo, F. M.; Spencer, N.; Stoddart, J. F.; M. Venturi, J. 


[8] Higher interlocked oligomers, up to a [7]catenane [(a) Bitsch, F.; Dietrich-Buchecker, C. O.; Khémiss, A.-K.; Sauvage, J.-P.; Van Dorsseelaer, A. J. Am. Chem. Soc. 1991, 113, 4023-4025] and a [6]rotaxane [(b) Parham, A. H.; Schneider, R.; Vögtle, F. Synlett, 1999, 1887-1890], have been detected in various reaction mixtures by mass spectrometry. The latter example, which features six template sites on the thread for up to five macrocycles, was termed an ‘iterative rotaxane synthesis’ by the authors but is essentially a standard
one-pot ‘threading-and-stoppering’ strategy. For high order catenanes and rotaxanes in which the threaded rings are covalently connected together, see:


[11] The 12 component proved unstable to hydrogenation using H₂ over Pd/C, although this method had been previously employed successfully on Pd(II)-coordinated interlocked architectures. Various alternative reagents and conditions were investigated of which o-nitrobenzenesulfonylhydrazide (NBSH) proved the most efficacious [see Myers, A. G.; Zheng, B.; Movassaghi, M.; J. Org. Chem. 1997, 62, 7507].


Chapter 5: Sequence Isomerism in Rotaxanes
Chapter 5

5.1 Introduction

Nature employs polymeric sequences of only four DNA bases to encode the genetic information that contains the instructions for the workings of the cell. This type of "sequence isomerism" is also found in RNA and proteins and is fundamental to the transfer of information in biological systems. The order of the sequence is crucial; even slightly different sequences can have very different meanings and therefore disastrous consequences for the cell. In fact, any polymer comprised of two or more monomer units can exhibit sequence isomerism, but unfortunately, controlling the order of these units still poses a significant challenge for the synthetic chemist. Specifically, the sequence isomerism expressed by these types of polymers, be they biological or artificial, arises from the different orders in which the various building blocks can be covalently linked.

Interlocked molecules, such as multi-ring catenanes and rotaxanes that contain at least two different macrocycles, can exhibit "sequence isomerism" that arises from the "mechanically" bonded nature of their component rings which can adopt distinct arrangements relative to one another. "Chain" catenanes (see Figure 5.1a) composed of at least two distinguishable rings exhibit sequential isomerism analogous to their covalently linked counterparts.

However multi-ring rotaxanes and "molecular necklace" catenanes can display an alternative, unique form of sequence isomerism that arises from the order of interlocked components around a cyclic or linear "backbone" component, be it the central ring in the molecular necklace catenane or the thread in a rotaxane. In these cases, diastereotopic mechanically interlocked sequence isomers can arise (see Figure 5.1b-e) and since the rings all have the same connectivity the isomers are only distinguishable by the sequence of their different rings on the backbone component, provided their order is conserved, i.e. the rings are sufficiently small or rigid that they are prevented from slipping past one another.
In the circumstances where all the interlocked components of a molecular necklace rotaxane (Figure 5.1b) and a catenane (Figure 5.1c) are symmetrical there need only be two distinct types of macrocycle (shown as blue and green) all interlocked with one “backbone” component (orange). The fewest number of rings that must be linked onto the backbone component in order for a pair of sequence isomers to arise is four (two of each type, blue and green) in the case of a catenane\(^9\) whereas for the rotaxane the fewest number required is three.\(^{10}\) Significantly, when directionality is incorporated into the central component (orange component, Figure 5.1d and e), the number of threaded macrocycles needed to form interlocked sequence isomers decreases by one to three in a catenane and two in a rotaxane.\(^{11}\) Nevertheless, the syntheses of a discrete pair of [4]catenane sequence isomers (Figure 5.1d) now requires three distinctly different interlocked macrocycles,\(^{12}\) (green, blue and red) and the pair of rotaxane sequence isomers (Figure 5.1e) still requires only two distinct macrocycles (green and blue).\(^{12}\)

*Figure 5.1.* Minimum structural requirements for pairs of mechanically interlocked sequence isomers, showing (a) “chain” linked [3]catenane isomers, (b) [4]rotaxane and (c) [5]catenane sequence isomers, and (d) [4]catenane and (e) [3]rotaxane sequence isomers with respective unsymmetrical central ring and thread.
Surprisingly, there appear to be only a few examples of rotaxanes that contain constitutionally different macrocycles;\textsuperscript{13} An early example from the group of Stoddart\textsuperscript{13a} relied on using the same templating interaction (π-acceptor-π-donor) to add two differently sized macrocycles to the thread using two distinct strategies, the smaller \textit{via} a “threading” strategy and the larger \textit{via} a “slippage” strategy.\textsuperscript{14} However, a symmetrical thread was employed and consequently this structure displays no isomerism. More recently, the group of Li exploited two different templating interactions to assemble a [3]rotaxane with two constitutionally different rings.\textsuperscript{13b} The thread incorporated a site capable of π-π interactions site as well as a hydrogen-bonding templating site and as a result two macrocycles one specific for each site, were interlocked around the unsymmetrical thread in a particular order. An intrinsic limitation of this approach of course, is that the synthesis of a pair of sequence isomers is not possible (even though at first glance it may look feasible) since for example aligning two macrocycles in “different orders” would require the synthesis of two different threads with non-indentical stoppers, i.e the threads would always need to be constitutionally different. Furthermore, applying this approach to control the order of different macrocycles on a rotaxane thread requires that their sequence be pre-programmed directly into the thread (essentially reducing the problem to that of conventional covalently linked sequence isomerism).

Herein, we describe a general method by which constitutionally different macrocycles can be assembled onto a non-symmetrical rotaxane thread with precise sequence control, exemplified through the syntheses of a pair of [3]rotaxane isomers corresponding to those represented in Figure 5.1e. Uniquely, this pair of diastereoisomers did not result from the statistical reaction of a non-symmetrical thread with different macrocycle precursors, but rather they were afforded separately from a different sequence of reactions. The cornerstone of this method is the so-called “3+1” approach, which is based upon the coordination of a tridentate pyridine-2,6-dicarboxamide ligand and monodentate pyridine ligand to a palladium(II) ion. While this coordination motif had initially been applied to the synthesis of a [2]rotaxane\textsuperscript{15} and a [2]catenane,\textsuperscript{16} the non-labile ligand exchange properties of this
In this approach (Scheme 5.1) the metal-complexed tridentate unit, incorporated into the benzylic bis-olefin-terminated macrocyclic precursor Pd(I)(CH$_3$CN) (shown in blue), is further complexed with the monodentate unit (shown in purple) built into the thread 12. The geometrical preference of palladium(II) which effects a square planar ligand coordination mode in concert with π-stacking interactions between the aromatics, aligns the ligands orthogonal to one another such that macrocyclisation via ring-closing metathesis (RCM) afforded an interlocked structure. Demetallation regenerated the monodentate pyridine binding site permitting complexation of another macrocyclic precursor Pd(I)(CH$_3$CN) unit. This previous work shows that by iteratively recycling a particular set of reactions it is possible to control the number of macrocycles added to a thread. It will now be shown that this non-symmetrical thread 12, where the pyridine binding site is situated proximal to one stopper, can be exploited to control the sequence of two constitutionally different macrocycles ultimately affording a pair of mechanically interlocked sequence isomers.

Scheme 5.1. Iterative syntheses of multi-ring rotaxanes. Synthesis of a [4]rotaxane by the iteration of the following steps (i) complexation of Pd(I)(CH$_3$CN), (ii) macrocyclisation, (iii) demetallation; using a single binding site to add all three macrocycles.
5.2 Results and Discussion

In order to adapt the iterative synthesis strategy to access a pair of [3]rotaxane sequence isomers a second distinct tridentate macrocycle precursor was required. This new building block needed to be constitutionally different enough to be distinguishable from Pd(1)(CH$_3$CN) by $^1$H NMR, but similar enough that the templating approach and the synthetic methodology could be conserved. These requirements were satisfied by Pd(18)(CH$_3$CN), synthesised in four steps from chelidamic acid (16)(see Scheme 5.2).

Scheme 5.2. Synthesis of second type of "U-shape" and its use in the synthesis of a [2]rotaxane. Reagents and conditions: (i) a. Pentafluorophenol, EDCI, CH$_2$Cl$_2$, 0°C; b. (4-(hex-5-enyloxy)phenyl)methanime, CHCl$_3$, 0°C, 89% (over two steps); (ii) PrI, K$_2$CO$_3$, butan-2-one, A, 95%; (iii) Pd(OAc)$_2$, CH$_3$CN, 70%; (iv) CH$_2$Cl$_2$, 97%; (v) a. Grubbs' (I) catalyst (0.12 equiv), CH$_2$Cl$_2$; b. o-nitrobenzene-sulfonylhydrazide (NBSH), NEt$_3$, CH$_2$Cl$_2$, 70% (over 2 steps); (vii) KCN, CH$_2$Cl$_2$/MeOH, 98%.

The synthesis of the [2]rotaxane 19H$_2$ was now straightforward using the previously developed strategy (Scheme 5.2; steps iv-vi). Combination of the monodentate thread
with the palladium coordinated ligand Pd(18)(CH$_3$CN) in dichloromethane, lead to the facile replacement of the labile acetonitrile molecule and the formation of the complex Pd(18)(12) as a single species (97%, Scheme 5.2, v). Subjecting Pd(18)(12) to RCM using Grubbs’ first generation catalyst, followed by hydrogenation of the resultant internal double bond afforded the corresponding Pd[2]rotaxane Pd19 in 70% isolated yield over these two steps. On regarding the $^1$H NMR spectrum (Figure 5.2b) the signature resonances (H$_{B}$, H$_{H}$ and H$_{t}$) of the new macrocycle are apparent. Also evident, are the characteristic shifts resulting form the interaction of the macrocycle with the thread, such as the expression of the thread’s asymmetry evidenced by the signals for the diastereotopic benzylic protons (H$_{D}$ and H$_{D'}$)$^{17}$ and the convergence and upfield shift by 1ppm and 0.5 ppm of the benzyl ring protons (H$_{E}$ and H$_{F}$) respectively due to $\pi$-stacking with the pyridine moiety of 12 (not shown here)$^{15-17}$. The removal of the metal from Pd19 to generate the [2]rotaxane 19H$_2$ as a single species (Scheme 5.2, vii) was affirmed by the appearance of the amide protons (H$_{C}$) at 9.3 ppm in the $^1$H NMR spectrum (Figure 5.2c); their large downfield shift indicative of intramolecular H-bonding to the pyridine of the thread.$^{15-17,21}$ In addition, the removal of the palladium ion had a noticeable effect on the macrocyclic pyridine protons (H$_{B}$) which have shifted downfield ($\Delta\delta = 0.5$ ppm). Also of note are the benzylic protons (H$_{D}$ and H$_{D'}$), which now free to couple to the amide protons, show a distinctive ABX multiplet system resonating at 4.6 ppm and 3.9 ppm respectively.
Figure 5.2. $^1$H NMR Spectra (400 MHz, CD$_2$Cl$_2$, 298 K) of (a) 12; (b) Pd19; (c) 19H$_2$. The lettering refers to the assignments in Scheme 5.2.

Now with two different [2]rotaxanes 19H$_2$ and 13H$_2$ already in hand from the previous syntheses of multi-ring rotaxanes the syntheses of the pair of [3]rotaxane isomers proceeded smoothly (see Scheme 5.3). Pd(1)(19H$_2$) was easily afforded as a single product by complexation of the original macrocycle precursor Pd(1)(CH$_3$CN) (see Scheme 5.1) with 19H$_2$ under the usual conditions (Scheme 5.3, i). RCM of Pd(1)(19H$_2$) and subsequent hydrogenation gave the palladium coordinated [3]rotaxane Pd20 (Scheme 5.3, ii). Its counterpart Pd21 was similarly synthesised starting from the combination of [2]rotaxane 13H$_2$ with isopropyl macrocycle precursor Pd(18)(CH$_3$CN) (Scheme 5.3, iv-v).
Scheme 5.3. Parallel syntheses of two mechanically interlocked "sequence isomers". Reagents and conditions (i) Pd(1)(CH$_3$CN), CH$_2$Cl$_2$, 97%; (ii) a. Grubbs’ catalyst (0.12 equiv), CH$_2$Cl$_2$; b. NBS, NEt$_3$, CH$_2$Cl$_2$, 72% (over 2 steps); (iii) KCN, CH$_2$Cl$_2$/MeOH, 98%; (iv) Pd(18)(CH$_3$CN), CH$_2$Cl$_2$, 95%; (v) a. Grubbs’ catalyst (0.12 equiv), CH$_2$Cl$_2$; b. NBS, NEt$_3$, CH$_2$Cl$_2$, 82% (over 2 steps); (vi) KCN, CH$_2$Cl$_2$/MeOH, 98%.

On first appearance the $^1$H NMR spectra of Pd20 and Pd21 (Figure 5.3a and d respectively) are remarkably similar, however there are distinct differences that pertain to the signals of the pyridine in the palladium-coordinated macrocycles. In Pd20, the non-functionalised macrocycle (blue) is coordinated to palladium and its pyridine protons (H$_B$) resonate at 7.8 ppm, whereas in Pd21 the same protons of this macrocycle (blue) resonate at 8.4 ppm in the absence of the metal. Analogously, the pyridine protons H$_{*B}$ of the non-complexed isopropyl macrocycle (green) appear at 7.9 ppm in Pd20 but in Pd21 the protons are affected by the metal’s presence and are upfield shifted to 7.2 ppm. As expected, the resonances of the alkyl region of the
thread in Pd20 and Pd21 show increased shielding due to the presence of metal-free macrocycle and in particular, the aliphatic protons are significantly shifted nearly 1 ppm upfield compared to the [2]rotaxane analogues (compare Figure 5.2).

Now all that remained was the removal of the palladium metal ion from Pd20 and Pd21 (Scheme 5.3, iii and vi) finally affording the pair of [3]rotaxane sequence isomers 20H2 and 21H2 in 98% yield each. At first glance the 1H NMR spectra of the individual respective isomers (Figure 5.3b and c) seem identical, closer inspection reveals very subtle differences in the shifts of certain protons; for instance, the aromatic stopper protons (Hb) are shifted slightly downfield in 20H2 compared to 21H2. In addition, the benzylic resonances of both macrocycles appear at slightly different shifts in each isomer.

Figure 5.3. 1H NMR Spectra (400 MHz, CD2Cl2, 298 K) of a) Pd20; b) 20H2; c) 21H2; d) Pd21. The lettering refers to the assignments in Schemes 5.2 and 5.3.
Intriguingly, the sequence isomers $20H_2$ and $21H_2$ also have slightly different FAB mass spectroscopy fragmentation patterns. Both spectra show the daughter ion peaks (m/z = 1800 and 1858) pertaining to the [2]rotaxanes $13H_2$ and $19H_2$ respectively. However, the spectral data of $20H_2$ shows a peak for m/z = 1858 ion which is 40% higher than that of the peak for the m/z = 1800 ion, in contrast these peak intensities are reversed for $21H_2$: the peak height of the m/z = 1800 ion is 73% greater than that of the m/z = 1858 ion. This seems to suggest that the macrocycle that resides over the pyridine is more likely to fragment and be lost. This behaviour can be compared to that of constitutionally identical polypeptide chains with different amino acid sequences, which also show different fragmentation patterns.

In conclusion, the challenge of precisely controlling the order and number of constitutionally different macrocycles in rotaxane syntheses has been addressed through the synthesis of a unique pair of [3]rotaxane sequence isomers; achieved by the application of a methodology employing a “3+1” palladium(II) template. A process of successive ligand complexation, ring-closing and demetallation reactions was effectively used to clip the different macrocycles onto an asymmetric thread in alternate orders. Significantly, this approach is a general method for adding any number of different rings (in different orders) to a rotaxane thread and thus can be exploited for the syntheses of isomerically pure higher order rotaxanes; implicitly providing access to a greater number of available isomeric permutations and thus “chemically-encoded” molecules.

5.3 Experimental Section

Unless stated otherwise, all reagents and anhydrous solvents were purchased from Aldrich Chemicals and used without further purification. 4-(hex-5-enyloxy)phenyl)methamine,$^{15}$ Pd(I)(CH$_3$CN)$^{15}$ and o-nitrobenzenesulfonylhydrazide$^{17}$ were prepared according to literature procedures.
17: To a suspension of chelidamic acid (3.0 g, 15 mmol) and pentafluorophenol (PFP) (6.1 g, 33 mmol) in dichloromethane (75 mL) at 0°C, a solution of 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide (EDCI) (6.3 g, 33 mmol) in dichloromethane (75 mL) was added drop-wise. The reaction mixture was stirred for several hours until the solution became homogenous, after which it was concentrated _in vacuo_ and passed through a short plug of silica (ethyl acetate: 40-60 petroleum ether; 2: 3). The resultant colourless solid was then dissolved in chloroform (25 mL) and the solution cooled to 0°C, after which a solution of 4-(hex-5-enyloxy)phenyl)methamine\(^1\) (6.0 g, 29 mmol) in chloroform (25 mL) was added drop-wise. The resultant solid was filtered off and recrystallised from acetonitrile to yield 17 as a colourless solid (7.4 g, 89\%). Mp. 182-184 °C; \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta = 1.48-1.59\) (m, 4H, H\(_{d1}\)), 1.69-1.80 (m, 4H, H\(_{d2}\)), 2.05-2.15 (m, 4H, H\(_{d3}\)), 3.83 (t, 4H, \(J = 6.5\) Hz, H\(_{d4}\)), 4.40 (d, 4H, \(J = 5.7\) Hz, H\(_{d5}\)), 4.93-5.07 (m, 4H, H\(_{d6}\)), 5.75-5.88 (m, 2H, H\(_{d7}\)), 6.71 (d, 4H, \(J = 8.6\) Hz, H\(_{d8}\)), 7.10 (d, 4H, \(J = 8.6\) Hz, H\(_{d9}\)), 7.77 (s, 2H, H\(_{d10}\)), 8.61 (bs, 2H, H\(_{d11}\)), 10.87 (bs, 1H, H\(_{d12}\)); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta = 25.3, 28.7, 33.4, 43.1, 67.7, 112.9, 114.5, 114.7, 129.0, 129.4, 138.5, 149.9, 158.5, 164.1, 167.1; LRMS (FAB, NOBA): \(m/z = 558\) [MH]\(^+\); HRMS (FAB, NOBA): \(m/z = 558.29898\) [MH]\(^+\) (calc. for C\(_{33}\)H\(_{40}\)N\(_3\)O\(_5\), 558.29680).
18H₂: To a solution of 17 (1.7 g, 3.0 mmol) and iodopropane (0.4 mL, 4.0 mmol) in butan-2-one (75 mL), potassium carbonate (2.1 g, 15 mmol) was added. The suspension was then heated at 70°C, for 18 h, under an atmosphere of nitrogen. Upon cooling, the potassium carbonate was removed by filtration and the filtrate concentrated in vacuo. The resultant oil was re-dissolved in dichloromethane (100 mL) and washed with water (2 x 50 mL), followed by a saturated aqueous solution of sodium chloride (50 mL). The water layers were combined and re-extracted with dichloromethane (50 mL). The combined organic layers were dried over anhydrous magnesium sulfate, concentrated in vacuo and the crude product purified by flash chromatography (dichloromethane) to yield 18H₂ as a colourless gummy solid (1.7 g, 95%).$^1$H NMR (400 MHz, CDCl₃): δ = 1.38 (d, 6H, J = 6.0 Hz, H₄), 1.50-1.66 (m, 4H, H₂), 1.72-1.84 (m, 4H, H₂), 2.07-2.17 (m, 4H, H₂), 3.93 (t, 4H, J = 6.4 Hz, H₂), 4.57 (d, 4H, J = 6.0 Hz, H₂), 4.72-4.84 (m, 1H, H₃), 4.92-5.08 (m, 4H, H₄), 5.75-5.89 (m, 2H, H₅), 6.83 (d, 4H, J = 8.5 Hz, H₆), 7.22 (d, 4H, J = 8.5 Hz, H₇), 7.82 (s, 2H, H₈), 7.99 (t, 2H, J = 5.7 Hz, H₉),$^{13}$C NMR (100 MHz, CDCl₃): δ = 21.7, 25.3, 28.7, 33.4, 42.9, 67.8, 71.2, 112.1, 114.6, 114.8, 129.1, 130.0, 138.5, 150.7, 158.5, 163.5, 166.9; LRMS (FAB, NOBA): m/z = 600 [MH]$^+$; HRMS (FAB, NOBA): m/z = 600.34331 [MH]$^+$ (calc. for C$_{36}$H$_{46}$N$_3$O$_5$, 600.34375).
Pd(18)(CH₃CN): To a solution of 18H₂ (1.5 g, 2.5 mmol) in anhydrous acetonitrile (50 mL), palladium(II) acetate (0.56 g, 2.5 mmol) was added and the reaction was stirred at room temperature for 6 h under an atmosphere of nitrogen during which time the solution turned a dark green colour. The resultant black precipitate was filtered off, the filtrate concentrated to ~10 mL and triturated with ether. The resultant yellow solid was filtered under suction to afford Pd(18)(CH₃CN) (1.3 g, 70%). Mp. 132 °C (decomp); ¹H NMR (400 MHz, CDCl₃/CD₃CN: 9/1): δ = 1.49 (d, 6H, J = 6.0 Hz, H*₉), 1.59-1.70 (m, 4H, H₂), 1.80-1.96 (m, 4H, H₂), 2.10 (s, 3H, HMeCN), 2.16-2.25 (m, 4H, H₂), 4.02 (t, 4H, J = 6.5 Hz, H₆), 4.54 (s, 4H, H₄), 4.81-4.91 (m, 1H, H₇), 5.01-5.16 (m, 4H, H₂), 5.85-5.98 (m, 2H, H₈), 6.30 (d, 4H, J = 8.6 Hz, H₉), 7.30 (d, 4H, J = 8.6 Hz, H₈), 7.39 (s, 2H, H₇); ¹³C NMR (100 MHz, CD₂Cl₂/CD₃CN: 9/1): δ = 1.9, 21.6, 25.6, 29.0, 33.8, 49.6, 68.0, 72.8, 111.5, 114.3, 114.6, 117.0, 128.5, 134.0, 139.0, 154.7, 158.0, 168.9, 170.6; LRMS (FAB, NOBA): m/z = 704 [M-CH₃CN]⁺ (calc. for C₃₈H₄₆N₄O₅Pd, 745).
Pd(18)(12): A solution of 12 (1.0 g, 0.78 mmol) and Pd(18)CH₃CN) (0.58 g, 0.78 mmol) in anhydrous dichloromethane (25 mL) under an atmosphere of nitrogen, was stirred for 5 h at room temperature. The solution was then concentrated in vacuo and the crude residue purified by column chromatography, (ethyl acetate: 40-60 petroleum ether; 2: 3) to yield Pd(18)(12) as a yellow solid (1.5 g, 97%). Mp. 158 °C (decomp); ¹H NMR (400 MHz, CD₂Cl₂): δ = 1.24-1.53 (m, 78H, Hₐ+ₙ+q+p+o+n+m+*f+*M), 1.56-1.71 (m, 6H, Hₐ+*n), 1.72-1.83 (m, 2H, H₂), 2.04-2.12 (m, 4H, Hₐ), 3.37 (t, 2H, J = 6.6 Hz, Hₖ), 3.62-3.79 (m, 4H, H*₄G+*G'), 3.83-3.96 (m, 4H, H*₃D+*D'), 4.01 (d, 2H, J = 14.2 Hz, H*₃D), 4.56 (s, 2H, H*₂J), 4.82-5.05 (m, 7H, H*₃N+*f+*L), 5.75-5.88 (m, 2H, H*K), 6.40-6.52 (m, 8H, H*₃E+*R), 6.77 (m, 4H, H*₂v), 7.12-7.21 (m, 16H, H*₁d+*w+x), 7.24-32 (m, 14H, H*₂b+*y+*B), 7.52 (d, 1H, J = 7.8 Hz, H₁), 7.59 (d, 1H, J = 7.8 Hz, H₂), 7.98 (t, 1H, J = 7.8 Hz, H₃); ¹³C NMR (100 MHz, CD₂Cl₂): δ = 21.8, 25.7 (x2), 26.4, 26.6, 29.1, 29.7 (x2), 29.8, 30.0 (x2), 30.1, 31.5 (x2), 33.9, 34.5 (x2), 48.9, 63.4 (x2), 67.8, 68.2, 69.3, 72.1, 72.4, 72.7, 111.6, 113.4, 114.0, 114.3, 114.8, 121.9, 122.0, 124.6 (x2), 128.5, 130.7, 130.8, 132.2, 132.3, 133.4, 139.0, 139.7, 141.0 (x2), 144.7, 144.9, 148.6, 148.8, 154.5, 155.6, 157.3, 158.2, 159.1, 161.4, 168.9, 171.3; LRMS (FAB, NOBA): m/z = 1988 [MH⁺]; HRMS (FAB, NOBA): m/z = 1987.12805 [MH⁺] (calc. for ¹²C₁₂⁷¹³CH₁₅₉N₄O₈Pd, 1987.12235).
Pd19: (a) To a solution of first generation Grubbs' catalyst (70 mg, 0.08 mmol) in anhydrous degassed dichloromethane (400 mL) under an atmosphere of nitrogen, Pd(18)(12) (1.3 g, 0.65 mmol) in anhydrous degassed dichloromethane (250 mL) was added. The solution was stirred at room temperature for 18 h, concentrated in vacuo and the crude residue purified by column chromatography (ethyl acetate: 40-60 petroleum ether; 1: 2) to yield a yellow solid (1.1 g). (b) To a solution of the product obtained in step (a) in anhydrous dichloromethane (7 mL), under an atmosphere of nitrogen, o-nitrobenzenesulfonyl-hydrazide (NBSH) (1.2 g, 5.5 mmol) and triethylamine (1.0 mL, 7.2 mmol) were added and the suspension stirred overnight. The resultant orange/brown solution was then washed with sodium bicarbonate (3 X 75 mL). The combined organic layers were then dried over anhydrous magnesium sulfate, concentrated in vacuo and the crude product purified by column chromatography (ethyl acetate: 40-60 petroleum ether; 1: 2) to yield Pd19 as a yellow solid (0.89 g, 70% over 2 steps). Mp. 150 °C (decomp); $^1$H NMR (400 MHz, CD$_2$Cl$_2$): $\delta$ = 1.13-1.49 (m, 86H, H$_{a}+m+n+o+p+q+r+s+t+u+v+w+x+y+z), 1.54-1.80 (m, 8H, H$_{a+n+i+u}$), 3.50 (d, 2H, J = 14.3 Hz, H$_{a}$), 3.59-3.85 (m, 6H, H$_{a+n+i+u}$), 3.92 (t, 2H, J = 6.6 Hz, H$_{a}$), 4.66 (d, 2H, J = 14.3 Hz, H$_{a}$), 4.79 (s, 2H, H$_{a}$), 4.81-4.90 (m, 1H, H$_{a+n+i+u}$), 5.04 (s, 2H, H$_{a}$), 6.33 (s, 8H, H$_{a+n+i+u}$), 6.70-6.79 (m, 4H, H$_{a+n+i+u}$), 7.11-7.31 (m, 31H, H$_{a+n+i+u}$), 7.48 (d, 1H, J = 7.8 Hz, H$_{a}$), 7.83 (t, 1H, J = 7.8 Hz, H$_{a}$); $^{13}$C NMR (100 MHz, CD$_2$Cl$_2$): $\delta$ = 21.8, 25.8, 26.4, 26.5, 28.8, 28.9, 29.7 (x2),
29.8, 29.9 (x2), 30.0 (x3), 31.4 (x2), 34.5 (x2), 50.0, 63.4, 63.5, 67.4, 68.2, 70.0, 72.4, 72.7, 73.2, 111.6, 113.4, 114.9, 115.3, 121.3, 122.0, 124.6, 124.7, 128.4, 130.7 (x2), 132.0, 132.2, 133.3, 139.3, 139.7, 141.4, 144.8, 144.9, 148.7 (x2), 154.5, 155.5, 157.3, 157.9, 159.9, 160.0, 168.8, 171.6; LRMS (FAB, NOBA): m/z = 1959 [M-H]+;
HRMS (FAB, NOBA): m/z = 1960.10257 [M]+ (calc. for $^{12}$C$_{125}^{13}$CH$_{156}$N$_4$O$_8$Pd, 1960.09876).

19H$_2$: To a solution of potassium cyanide (0.35 g, 5.4 mmol) in methanol (20 mL) Pd19 (0.71 g, 0.36 mmol) in dichloromethane (20 mL) was added. The solution was heated gently until it went colourless, and then the overall volume was allowed reduce to less than 5 mL. The resultant mixture was dispersed in water (100 mL) and extracted with dichloromethane (3 x 50 mL). The combined organic extracts were washed with a further portion of water (50 mL) and dried over anhydrous magnesium sulfate. After filtration, the solution was concentrated in vacuo to yield 19H$_2$ as a colourless solid (0.64 g, 98%). Mp. 144-146 °C; $^1$H NMR (400 MHz, CD$_2$Cl$_2$): $\delta = 1.13$-$1.48$ (m, 88H, H$_{a+z+l+m+n+o+p+q+r+z+y+y+y+y+y+m}$), 1.56-1.70 (m, 6H, H$_{ha}$), 3.25 (t, 2H, $J = 6.8$ Hz, H$_k$), 3.68 (t, 2H, $J = 6.7$ Hz, H$_a$), 3.72-3.82 (m, 4H, H$_B$), 3.85-3.94 (dd, 2H, $J = 4.9$, 14.5 Hz, H$_D$), 4.23 (s, 2H, H$_f$), 4.30 (s, 2H, H$_i$), 4.51-4.60 (dd, 2H, $J = 7.5$, 14.5 Hz, H$_F$), 4.81-4.91 (m, 1H, H$_N$), 6.35 (d, 4H, $J = 8.6$, H$_{y+y}$), 6.45 (d, 2H, $J = 8.9$, H$_e$), 6.64 (d, 4H, $J = 8.6$, H$_{xy}$), 6.71 (d, 2H, $J = 8.9$, H$_d$), 7.00 (d, 1H, $J = 7.8$, H$_g$), 7.06 (d, 2H, $J = 8.9$, H$_d$), 7.11-7.21 (m, 15H, H$_{c+x+l+w}$), 7.24-7.32 (m, 12H, H$_{b+y}$), 7.58 (t, 1H, $J = 7.8$ Hz, H$_a$), 7.85 (s, 2H, H$_b$), 9.20-9.28 (m, 2H, H$_C$).
\(^{13}\)C NMR (100 MHz, CD\(_2\)Cl\(_2\)): \(\delta = 21.9, 25.8, 26.3, 26.4, 28.7, 28.8\) (x2), 29.6, 29.7, 29.8, 29.9 (x4), 31.4 (x2), 34.5 (x2), 42.7, 63.4 (x2), 67.3, 68.2, 69.2, 71.4, 71.8, 73.1, 112.1, 113.4, 113.6, 114.4, 120.1, 120.2, 124.6, 124.7, 129.0, 130.4, 130.7 (x2), 132.0, 132.2, 137.4, 139.8, 140.3, 144.9 (x2), 148.6, 148.7, 151.6, 156.2, 156.6, 157.1, 158.2, 158.5, 163.9, 167.1; LRMS (FAB, NOBA): \(m/z = 1859\) \([\text{MH}^+]\); HRMS (FAB, NOBA): \(m/z = 1857.21925\) \([\text{MH}^+]\) (calc. for \(^{12}\)C\(_{125}\)^{13}\)CH\(_{159}\)N\(_{40}\)O\(_{8}\), 1857.21915).

Pd(1)(19H\(_2\)): Synthesis as per Pd(1)(12) using 19H\(_2\) (0.56 g, 0.30 mmol) and Pd(1)(CH\(_3\)CN) (0.21 g, 0.30 mmol). The resultant crude residue was purified by column chromatography (ethyl acetate: 40-60 petroleum ether; 1: 1) to yield Pd(1)(19H\(_2\)) as a yellow solid (0.73 g, 97%). Mp. 151 °C (decomp); \(^1\)H NMR (400 MHz, CD\(_2\)Cl\(_2\)): \(\delta = \) 0.56-0.68 (m, 2H, H\(_a\)), 0.76-1.74 (m, 100H, H\(_a+z+l+m+n+o+p+q+r+t+*H+H+*l+*j+*k+*m\)), 2.00-2.10 (m, 4H, H\(_d\)), 2.46 (t, 2H, \(J = 7.6\) Hz, H\(_u\)), 3.37 (t, 2H, \(J = 6.6\) Hz, H\(_d\)), 3.59-3.90 (m, 12H, H\(_G+G'+*D'+*D'+*G\)), 4.08 (d, 2H, \(J = 14.3\) Hz, H\(_D\)), 4.60 (s, 2H, H\(_J\)), 4.77-5.03 (m, 9H, H\(_F+*H+*N+*L\)), 5.73-5.85 (m, 2H, H\(_k\)), 6.39-6.55 (m, 14H, H\(_F+*F+*F\)), 6.70-6.82 (m, 6H, H\(_e+*E\)), 7.10-7.20 (m, 10H, H\(_c+d+w\)), 7.22-7.36 (m, 18H, H\(_b+y+z\)), 7.51-7.60 (m, 2H, H\(_g+i\)), 7.80 (d, 2H, \(J = 7.8\) Hz, H\(_b\)), 7.87 (s, 2H, H\(_e\)), 7.98 (t, 1H, \(J = 7.9\) Hz, H\(_h\)), 8.12 (t, 1H, \(J = 7.8\) Hz, H\(_d\)), 8.48-8.56 (m, 2H, H\(_e\)); \(^{13}\)C NMR (100 MHz, CD\(_2\)Cl\(_2\)): \(\delta = 21.9, 25.7\) (x2), 25.8, 26.6, 28.7 (x2), 28.8, 29.1, 29.7, 29.9 (x2), 30.0 (x2), 30.1 (x2), 31.4 (x2), 33.8, 34.5, 34.6, 43.1, 48.8, 63.5, 63.6, 67.3, 67.8, 67.9, 69.3, 71.4, 72.2, 72.6, 112.3,
113.1, 113.9, 114.4, 114.6, 114.8, 122.0, 122.2, 124.6, 124.8, 124.9, 128.5, 129.6, 130.3, 130.7, 130.8, 132.1, 132.3, 133.3, 139.0, 139.9, 140.3, 141.0, 141.1, 144.7, 145.0, 148.8 (x2), 151.7, 153.2, 155.6, 155.9, 158.3, 158.5, 159.2, 161.2, 163.8, 167.0, 171.3; LRMS (FAB, NOBA): m/z = 2500 [M-H]⁺; HRMS (FAB, NOBA): m/z = 2502.40106 [MH]⁺ (calc. for \textsuperscript{112}C\textsubscript{158}\textsuperscript{13}CH\textsubscript{196}N\textsubscript{7}O\textsubscript{12}Pd, 2502.40076).

Pd\textsubscript{20}: (a) Synthesis as per Pd\textsubscript{19} using Grubbs' (I) catalyst (23 mg, 0.028 mmol) and Pd(1)(19H\textsubscript{2}) (0.58 g, 0.23 mmol). The crude residue was purified by column chromatography using a gradient system (ethyl acetate: 40-60 petroleum ether; 1:1 to 5:2) to yield a yellow solid (0.49 g). (b) Synthesis as per Pd\textsubscript{19} using the product obtained in step (a) (0.49 g), NBSH (0.44 g, 2.0 mmol) and NEt\textsubscript{3} (0.35 mL, 2.5 mmol). The crude residue was purified by column chromatography using a gradient system (ethyl acetate: dichloromethane; 0:1 to 1:1) to yield Pd\textsubscript{20} as a yellow solid (0.41 g, 72% over two steps). Mp. 249 °C (decomp); \textsuperscript{1}H NMR (400 MHz, CD\textsubscript{2}Cl\textsubscript{2}): δ = 0.59-0.71 (m, 2H, H\textsubscript{a}), 0.80-1.50 (m, 98H, H\textsubscript{a}+z+m+n+o+p+q+r+t+u+v+w+x+y+z+*J+K+*M), 1.54-1.76 (m, 10H, H\textsubscript{a}+H\textsubscript{b}+H\textsubscript{c}), 2.54 (t, 2H, J = 7.4 Hz, H\textsubscript{a}), 3.49 (d, 2H, J = 14.3 Hz, H\textsubscript{D}), 3.58-3.92 (m, 12H, H\textsubscript{a}+H\textsubscript{b}+H\textsubscript{c}+H\textsubscript{d}+H\textsubscript{e}), 4.70-4.92 (m, 7H, H\textsubscript{D}+H\textsubscript{E}+H\textsubscript{F}+H\textsubscript{G}), 5.09 (s, 2H, H\textsubscript{D}), 6.35 (s, 8H, H\textsubscript{F}+H\textsubscript{E}), 6.47-6.58 (m, 6H, H\textsubscript{a}+H\textsubscript{b}+H\textsubscript{c}+H\textsubscript{d}+H\textsubscript{e}+H\textsubscript{f}), 6.73 (d, 2H, J = 8.9 Hz, H\textsubscript{D}), 6.82 (d, 4H, J = 8.5 Hz, H\textsubscript{E}), 7.11-7.36 (m, 29H, H\textsubscript{a}+H\textsubscript{b}+H\textsubscript{c}+H\textsubscript{d}+H\textsubscript{e}+H\textsubscript{f}+H\textsubscript{g}+H\textsubscript{h}+H\textsubscript{i}+H\textsubscript{j}+H\textsubscript{k}+H\textsubscript{l}+H\textsubscript{m}+H\textsubscript{n}+H\textsubscript{o}+H\textsubscript{p}+H\textsubscript{q}+H\textsubscript{r}+H\textsubscript{s}+H\textsubscript{t}+H\textsubscript{u}+H\textsubscript{v}+H\textsubscript{w}+H\textsubscript{x}+H\textsubscript{y}+H\textsubscript{z}), 7.53 (d, 1H, J = 7.7 Hz, H\textsubscript{i}), 7.76-7.92 (m, 5H, H\textsubscript{b}+H\textsubscript{c}+H\textsubscript{d}+H\textsubscript{e}+H\textsubscript{f}+H\textsubscript{g}+H\textsubscript{h}+H\textsubscript{i}+H\textsubscript{j}+H\textsubscript{k}+H\textsubscript{l}+H\textsubscript{m}+H\textsubscript{n}+H\textsubscript{o}+H\textsubscript{p}+H\textsubscript{q}+H\textsubscript{r}+H\textsubscript{s}+H\textsubscript{t}+H\textsubscript{u}+H\textsubscript{v}+H\textsubscript{w}+H\textsubscript{x}+H\textsubscript{y}+H\textsubscript{z}), 8.08 (t, 1H, J = 7.8 Hz, H\textsubscript{a}), 8.49-8.57 (m, 2H, H\textsubscript{C}); \textsuperscript{13}C NMR (100 MHz, CD\textsubscript{2}Cl\textsubscript{2}): δ = 21.9, 25.7, 25.8 (x2), 26.6, 28.8 (x3), 28.9, 29.7,
29.7, 29.8 (x2), 29.9, 30.0 (x4), 31.5 (x2), 34.6 (x2), 43.1, 49.9, 63.5, 63.6, 67.3, 67.5, 67.9, 70.0, 71.5, 72.5, 73.3, 112.4, 113.2, 114.6, 115.0, 115.3, 121.4, 122.1, 124.8 (x2), 125.0, 128.4, 129.7, 130.3, 130.7 (x2), 132.1, 132.2, 133.4, 139.5, 140.3, 141.1 (x2), 144.8, 145.0, 148.7, 148.8, 151.7, 153.2, 155.5, 156.0, 158.0, 158.5, 159.8, 160.0, 163.8, 167.1, 171.6; HRMS (FAB, NOBA): LRMS (FAB, NOBA): m/z = 2478 [MH+]; HRMS (FAB, NOBA): m/z = 2476.38402 [M]+ (calc. for \(^{12}\text{C}_{156}^{13}\text{CH}_{194}\text{N}_{7}\text{O}_{12}\text{Pd}, 2476.38511)

**20H**₂: Synthesis as per **19H**₂ using Pd₁₉ (0.30 g, 0.12 mmol) and potassium cyanide (0.12 g, 1.8 mmol) to yield **20H**₂ as a colourless solid (0.28 g, 98%). Mp. 132-136 °C; \(^1\text{H} \text{NMR (400 MHz, CD}_{2}\text{Cl}_2\): } \delta = 0.58-0.69 (m, 2H, H₃), 0.80-1.51 (m, 100H, Hₐ₋ₚ+p+q+r+t+*L+*J+*K+*M), 1.59-1.72 (m, 8H, H*ₘ₋ₙ), 2.51 (t, 2H, J = 7.5 Hz, Hₜ), 3.16 (t, 2H, J = 6.9 Hz, Hₜ), 3.69-3.95 (m, 12H, H_D₋₄+*G+*G), 4.02 (s, 2H, Hᵢ), 4.27 (s, 2H, Hᵢ), 4.35-4.62 (dd, 2H, J = 7.7, 14.5 Hz, H_D), 4.75-4.90 (m, 3H, H*₄₋₅), 6.28-6.35 (m, 6H, Hₐ₋ₙ), 6.46-6.55 (m, 6H, H*ₘ₋ₙ), 6.63 (d, 4H, J = 8.6 Hz, Hₜ), 6.79 (d, 4H, J = 8.5 Hz, Hₚ), 6.91 (d, 1H, J = 7.7 Hz, Hₚ), 7.02 (d, 2H, J = 8.8 Hz, Hₜ), 7.12-7.21 (m, 9H, H₁₋₉), 7.23-7.35 (m, 18H, H₀₋₁₉), 7.56 (d, 2H, J = 7.7 Hz, Hₚ), 7.87 (s, 2H, Hₐ), 8.01 (t, 1H, J = 7.8 Hz, Hₚ), 8.37 (d, 2H, J = 7.8 Hz, Hₚ), 8.47-8.54 (m, 2H, Hₐ), 9.38-9.45 (m, 2H, Hₐ); \(^{13}\text{C} \text{NMR (100 MHz, CD}_{2}\text{Cl}_2\): } \delta = 21.8, 25.7, 25.8 (x3), 26.4, 28.7 (x3), 28.8, 29.7 (x3), 29.9 (x3), 30.0 (x2), 31.4 (x2), 34.5, 34.6, 42.6, 43.0, 63.4, 63.6, 67.2, 67.3, 67.8, 68.8, 71.5, 71.9, 73.0, 112.3,
113.1, 113.5, 114.4, 114.6, 120.1, 120.2, 124.7, 124.8, 125.2, 128.9, 129.6, 130.3, 130.4, 130.7 (x2), 131.9, 132.1, 137.5, 138.9, 140.3 (x2), 144.9, 145.0, 148.6, 148.7, 149.7, 151.7, 156.0, 156.4, 158.1, 158.3 (x2), 158.5, 163.8 (x2), 167.0; LRMS (FAB, NOBA): $m/z = 2370 \ [M-H]^+$; HRMS (FAB, NOBA): $m/z = 2372.49443 \ [MH]^+$ (calc. for $^{12}\text{C}_{156}^{13}\text{CH}_{196}\text{N}_7\text{O}_{12}$, 2372.49756).

Pd(18)(13H$_2$): Synthesis as per Pd(18)(12) using 13H$_2$ (0.63 g, 0.35 mmol) and Pd(18)(CH$_3$CN) (0.26 g, 0.35 mmol). The resultant crude residue was purified by column chromatography (ethyl acetate: 40-60 petroleum ether; 1:1) to yield Pd(18)(13H$_2$) as a yellow solid (0.83 g, 95%). Mp. 152 °C (decomp); $^1$H NMR (400 MHz, CD$_2$Cl$_2$): $\delta = 0.55-0.67 \ (m, \ 2H, \ H_a), \ 0.77-1.78 \ (m, \ 100H, \ H_{a+z+l+m+n+o+p+q+l+l+m+l+K+*H}), \ 2.02-2.11 \ (m, \ 4H, \ H_a), \ 2.46 \ (t, \ 2H, \ J = 7.6 \ Hz, \ H_a), \ 3.37 \ (t, \ 2H, \ J = 6.6 \ Hz, \ H_b), \ 3.59-3.90 \ (m, \ 12H, \ H_G+G+*D+D+*G), \ 4.08 \ (d, \ 2H, \ J = 14.3 \ Hz, \ H_D), \ 4.60 \ (s, \ 2H, \ H_f), \ 4.80-5.04 \ (m, \ 9H, \ H_j+*D+*N+*L), \ 5.73-5.85 \ (m, \ 2H, \ H_k), \ 6.39-6.56 \ (m, \ 14H, \ H_F+E+E+F), \ 6.71-6.83 \ (m, \ 6H, \ H_e+E), \ 7.10-7.37 \ (m, \ 30H, \ H_{b+c+d+w+x+y+z}), \ 7.50-7.59 \ (m, \ 2H, \ H_{g+i}), \ 7.96 \ (t, \ 1H, \ J = 7.9 \ Hz, \ H_b), \ 8.06 \ (t, \ 2H, \ J = 7.8 \ Hz, \ H_{g}), \ 8.41 \ (d, \ 1H, \ J = 7.8 \ Hz, \ H_{g}), \ 8.51-8.58 \ (m, \ 2H, \ H_c); ^{13}$C NMR (100 MHz, CD$_2$Cl$_2$): $\delta = 21.7, 25.6, 25.7(x2), 25.8, 26.6, 28.7 (x3), 29.1, 29.7, 29.8, 30.0 (x3), 30.1, 31.4 (x2), 33.8, 34.5, 34.6, 43.0, 48.9, 63.4, 63.6, 67.3, 67.9 (x2), 69.3, 72.1, 72.6, 72.7, 111.6, 113.1, 113.9, 114.4, 114.6, 114.7, 121.9, 122.0, 124.6, 124.8, 125.5, 128.5, 129.7, 130.2, 130.7, 130.8, 132.2, 132.3, 133.4, 139.0, 139.1,
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139.7, 140.4, 141.0, 144.7, 148.8 (x2), 148.8, 149.7, 154.51, 155.6, 155.8, 158.3, 158.5, 159.2, 161.3, 163.7, 168.9, 171.3; LRMS (FAB, NOBA): \( m/z = 2503 \) [MH]\(^+\); HRMS (FAB, NOBA): \( m/z = 2502.4037 \) [MH]\(^+\) (calc. for \( ^{12}\text{C}_{158}\text{C}_{196}\text{N}_{7}\text{O}_{12}\text{Pd}, 2502.40076 \)).

Pd21: (a) Synthesis as per Pd19 using Grubbs’ (I) catalyst (0.026 g, 0.032 mmol) and Pd(18)(13H2) (0.66 g, 0.26 mmol). The crude residue was purified by column chromatography using a gradient system (ethyl acetate: 40-60 petroleum ether; 1: 1 to 5: 2) to yield a yellow solid (0.58 g). (b) Synthesis as per Pd20 using the product obtained in step (a) (0.58 g), NBSH (0.50 g, 2.3 mmol) and NEt3 (0.40 mL, 2.9 mmol). The crude residue was purified by column chromatography using a gradient system (ethyl acetate: dichloromethane; 0:1 to 1:1) to yield Pd21 as a yellow solid (0.53 g, 82% over two steps). Mp. 153 °C (decomp); \(^1\text{H NMR} \) (400 MHz, CD2Cl2): \( \delta = 0.58-0.70 \) (m, 2H, \( H_3 \)), 0.80-1.50 (m, 108H, \( H_{a+z+m+n+o+p+q+r+t+*f+*j+*i+*k+*m} \)), 1.55-1.76 (m, 10H, \( H_{+H+H+} \)), 2.54 (t, 2H, \( J = 7.6 \) Hz, \( H_a \)), 3.47 (d, 2H, \( J = 14.3 \) Hz, \( H_{i+D} \)), 3.60-3.93 (m, 12H, \( H_{k+G+G+D+*G} \)), 4.70-4.95 (m, 7H, \( H_{*D+f+D+*N} \)), 5.10 (s, 2H, \( H_j \)), 6.35 (s, 8H, \( H_{**E} \)), 6.49-6.59 (m, 6H, \( H_{v+F} \)), 6.74 (d, 2H, \( J = 8.8 \) Hz, \( H_e \)), 6.82 (d, \( 4H, J = 8.5 \) Hz, \( H_d \)), 7.12-7.37 (m, 31H, \( H_{b+c+d+g+w+x+y+*b} \)), 7.52 (d, \( 1H, J = 7.7 \) Hz, \( H_i \)), 7.84 (t, \( 1H, J = 7.9 \) Hz, \( H_b \)), 8.06 (t, \( 1H, J = 7.8 \) Hz, \( H_d \)), 8.43 (d, \( 2H, J = 7.8 \) Hz, \( H_b \)), 8.51-8.58 (m, \( 2H, H_C \)); \(^{13}\text{C NMR} \) (100 MHz, CD2Cl2): \( \delta = 21.8, 25.6, 25.8 \) (x3), 26.5, 28.7, 28.8 (x3), 28.9, 29.7 (x2), 29.8 (x2), 29.9, 30.0 (x2), 31.5 (x2), 31.6 (x2).
21H₂: Synthesis as per 19H₂ using 21Pd (0.30 g, 0.12 mmol) and potassium cyanide (0.12 g, 1.8 mmol) to yield 21H₂ as a colourless solid (0.28 g, 98%). Mp. 129-131 °C (decomp); 1H NMR (400 MHz, CD₂Cl₂): δ = 0.57-0.70 (m, 2H, Ḣ₅), 0.79-1.51 (m, 100H, Ḣₐ+Ḡ+G), 1.61-1.72 (m, 8H, Ḣ₂), 2.53 (t, 2H, Ḣ₁), 3.20 (t, 2H, Ḣ₂), 3.70-3.93 (m, 12H, Ḣ₁), 4.01 (s, 2H, Ḣ₃), 4.30 (s, 2H, Ḣ₁), 4.30-4.37 (dd, 2H, Ḣ₁), 4.79-4.92 (m, 3H, Ḣ₂), 6.28-6.38 (m, 6H, Ḣ₃), 6.48-6.56 (m, 6H, Ḣ₄), 6.62 (d, 4H, Ḣ₅), 6.80 (d, 4H, Ḣ₆), 6.92 (d, 1H, Ḣ₇), 7.05 (d, 2H, Ḣ₈), 7.13-7.22 (m, 9H, Ḣ₉), 7.25-7.28 (m, 18H, Ḣ₁₀), 7.57 (d, 1H, Ḣ₁₁), 7.86 (s, 2H, Ḣ₁₂), 8.05 (t, 1H, Ḣ₁₃), 8.41 (d, 2H, Ḣ₁₄), 8.51-8.58 (m, 2H, Ḣ₁₅), 9.35-9.43 (m, 2H, Ḣ₁₆); 13C NMR (100 MHz, CD₂Cl₂): δ = 21.9, 25.6, 25.8 (x3), 26.4, 28.7 (x3), 28.8, 29.7 (x3), 29.8 (x2), 29.9, 30.0 (x2), 31.5 (x2), 34.5, 34.6, 42.6, 43.0, 63.5, 63.6, 67.2, 67.3, 67.9, 68.7, 71.4, 71.9, 73.0, 112.1, 113.1, 113.6, 114.4, 114.6, 120.0, 120.1, 124.7, 124.8, 125.6, 128.9, 129.7.
130.3, 130.4, 130.7 (x2), 131.9, 132.2, 137.5, 139.1, 140.2, 140.4, 144.9 (x2), 148.6, 148.8, 149.7, 151.6, 155.9, 156.1, 156.5, 158.1, 158.4, 158.5, 163.7, 163.9, 167.1; LRMS (FAB, NOBA): \( m/z = 2371 \ [M]^+ \); HRMS (FAB, NOBA): \( m/z = 2372.49202 \ [MH]^+ \) (calc. for \( ^{12}\text{C}_{156}^{13}\text{CH}_{196}\text{N}_{7}\text{O}_{12} \), 2372.49756).

### 5.4 References and Notes


[3] The sequence of RNA nucleobases AUG is a start codon, conversely its sequence isomers UAG and UGA are stop codons, see; Caskey, C. T.; Tompkins, R.; Scolnick, E.; Caryk, T.; Nirenburg, M. Science 1968, 162, 135.

[4] For example, the single change of a valine to a glutamic acid residue in the amino acid sequence of the \( \beta \) chain of Haemoglobin can lead to sickle-cell anemia, see; Ingram, V. M. Nature 1957, 180, 326.


[6] Interestingly, of the chain [3]catenanes that have been made using two different interlocked rings only a single isomer appears to have been made in each case: (a) Hubbard, A. L.; Davidson, G. J. E.; Patel, R. H.; Wisner, J. A.; Loeb, S. J.
These types of isomers are topologically non-trivial since the isomers are non-interconvertible through geometrical transformations.
These types of isomer are topologically trivial since infinitely stretching some of the rings would allow scrambling of the sequence.


[12] There do not appear to be any examples of this type of structure in the literature.


[14] Strictly speaking however, a slippage strategy yields a pseudorotaxane.


[19] This compound could also exist as the pyridone form, but seems \textsuperscript{1}H NMR evidence suggests it exists mainly in the pyridine form.


[21] The complex spectra were assigned with the extensive aid of 2-D experiments, namely COSY, TOSCY and ROESY.

[22] Bifuricated H-bonding between the amides and the pyridines of both ligands has also been seen in solid state: Leigh, D. A.; Lusby, P. J.; Slawin, A. M. Z.; Walker, D. B., Angew. Chem. Int. Ed. 2005, 44, 4557
Published Papers
A 3D Interlocked Structure from a 2D Template: Structural Requirements for the Assembly of a Square-Planar Metal-Coordinated [2]Rotaxane

Anne-Marie Fuller, David A. Leigh, Paul J. Lusby, Iain D. H. Oswald, Simon Parsons, and D. Barney Walker

The starting point for the revolution in catenane and rotaxane synthesis that occurred during the last part of the 20th century was the realization by Sauvage and co-workers that metal-ligand coordination geometries could fix molecular fragments in three-dimensional space such that they were predisposed to form mechanically interlocked architectures through macrocyclization or "stoppering" reactions. Efficient synthetic methods to rotaxanes were subsequently developed based on four- (tetrahedral), five- (trigonal bipyramidal and square pyramidal), and, most recently, six-coordinate (octahedral) metal templates (Figure 1). One of the benefits of using specific coordination motifs for such assemblies is that the resulting interlocked ligands often do not permit other metal geometries in their binding site, which can consequently be exploited either to lock a metal in an unusual geometry for its oxidation state or to bring about large-amplitude "shuttling" of the ligand components. Here we show that three-dimensional interlocked architectures can also be assembled from two-dimensional coordination templates by using steric and electronic restrictions to direct the synthesis in the third

[**] This work was supported by the European Union Future and Emerging Technology Program MechMol and the EPSRC.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.
Figure 1. Exploiting transition-metal-ligand geometries in the synthesis of mechanically interlocked architectures: a) tetrahedral, b) square pyramidal and trigonal bipyrimidal, c) octahedral, and d) square-planar coordination motifs.

Scheme 1. Reagents and conditions: a) Pd(OAc)$_2$, CH$_3$CN, 76%; b) CHCl$_3$, 50°C; L2: 63%, L3: 96%, L4: 0%, L5: 97%; c) 1. Grubbs catalyst (0.1 equiv), CH$_2$Cl$_2$; 2. H$_2$, Pd/C, THF, H$_2$L6: 98%, L3+L7: 63%, L5+L7: 69% (over 2 steps); d) KCN, MeOH, CH$_2$Cl$_2$, 20°C, 1 h and then 40°C, 0.5 h, 97%.
dimension. The resulting [2]rotaxane is the first example of a mechanically interlocked ligand that forms a four-coordinate square-planar metal complex.\[8\]

The square-planar [2]rotaxane ligand design consists of a tridentate benzylic amide macrocycle and a monodentate thread (Figure 1 d). The macrocycle incorporates a 2,6-dicarboxyamidopyridine unit to exploit the palladium chemistry recently developed\[9\] by Hirao and co-workers. The thread contains a pyridine donor group substituted with appropriately bulky stoppers in either the 2,6- or 3,5-positions. It was envisioned that in the key intermediate, [Pd(L1)(L2–L5)] (see Scheme 1), the geometry of the precursor to the macrocycle (previously used to direct hydrogen bond assembly processes\[10\]) would promote intercomponent π-π stacking, thus encouraging the pyridine donor of the thread to bind the metal ion orthogonally to the N₃ ligand (complimenting the normally preferred orientation\[11\]) and directing the assembly in the third dimension. A series of readily available threads L2–L5 was investigated during the study.

The rotaxane synthesis was carried out according to Scheme 1. Treatment of H₂L₁ with Pd(OAc)₂ in acetonitrile smoothly generated a complex [Pd(L1)(CH₃CN)] in which the fourth coordination site of the metal is occupied by a normally labile acetonitrile molecule. Nevertheless, displacement of the acetonitrile by bis-ester pyridine ligand L₄ was unsuccessful (see below). However, simple combination of L₅ or either of the bis-ether pyridine threads (L₂ and L₃) with [Pd(L1)(CH₃CN)] in either dichloromethane or chloroform gave the desired complexes [Pd(L1)(L₅/L₂/L₃)] in 97, 63 and 96% yields, respectively. The 'H NMR spectrum of [Pd(L1)(L₂)] is shown in Figure 2c. Comparison with the spectra of [Pd(L1)(CH₃CN)] and H₂L₁ (Figure 2b and 2a, respectively) shows features clearly indicative of metal coordination (the absence of H₇ and shifts in H₄ and H₉) and the anticipated aromatic stacking between the tridentate and monodentate ligands (particularly H₈ and H₉). Similar chemical shift differences were observed for [Pd(L1)(L₃)] and [Pd(L1)(L₅)], however, ring closing olefin metathesis (RCM) followed by hydrogenation (Scheme 1, step c) of the three complexes produced very different results. Whilst cyclization of [Pd(L1)(L₂)] gave the corresponding [2]rotaxane [Pd(L₆)] in 77% yield following hydrogenation of the olefin, no [2]rotaxane was produced from RCM of either [Pd(L1)(L₃)] or [Pd(L1)(L₅)], the only products in each case being the free macrocycle and thread. Why does only one of the four threads direct rotaxane synthesis in the desired manner?

The 'H NMR spectra of the [2]rotaxane ([Pd(L₆]), Figure 2d), mass spectrometric analysis, and the preserved association of the organic fragments upon demetalation, unambiguously confirmed the interlocked structure. In addition to the loss of the terminal alkene protons, some subtle differences in the 'H NMR spectrum of [Pd(L₆)] compared to [Pd(L₁)(L₂)] (Figure 2c) indicates that some rearrangement of the ligands does occur on formation of the rotaxane. Single crystals of [Pd(L₆)] suitable for X-ray crystallography\[12\] were grown by slow cooling of a warm, saturated solution of the [2]rotaxane in acetonitrile. The solid-state structure (Figure 3) shows the interlocked architecture and the

pseudo-square-planar geometry (the N$_3$ bite angle is 160.0°) around the palladium center. The π stacking between the macrocycle and the pyridine ring of the thread so apparent in solution from the $^1$H NMR shifts is significantly offset in the solid state (see the side-on view, Figure 3b). The co-conformation adopted by the macrocycle and thread in the crystal structure of the rotaxane clearly illustrates why RCM of the complexes formed with the 3,5-disubstituted threads ([Pd(L1)(L3)] and [Pd(L1)(L5)]) can lead to uninterlocked products; even with both fragments attached to the metal, cyclization of L1 can readily occur without encircling a 3,5-substituted pyridine thread. Similarly, the conformation of the thread suggests a possible reason for the lack of reactivity of the 2,6-bis-ester thread L4 towards [Pd(L1)(CH$_3$CN)]. In the crystal structure the electron density of the ether oxygen atoms of the thread is directed away from the occupied d$_{π}$ orbital lobes which lie above and below the plane of the square-planar geometry at the d$_{π}$ palladium center. Chelation (Scheme 1, step d) generates the free [2]rotaxane H$_2$L6 in 97% yield, thus confirming that the coordination bonds are not required to stabilize the interlocked architecture once it is formed. The $^1$H NMR spectrum of H$_2$L6 and its uninterlocked components in CDC$_3$ are shown in Figure 4. The shielding of the benzyl groups in the rotaxane relative to the free macrocycle, together with the large (δ = 1.7 ppm) downfield shift of the amide protons (H$_e$), indicate that specific hydrogen-bonding interactions between the thread and the macrocycle are "switched on" by the demetalation/protonation procedure. It appears that the amide groups of H$_2$L6 simultaneously hydrogen bond to the pyridine groups in both the macrocycle and thread.

In conclusion, we have described methodology for assembling a three-dimensional interlocked molecular architecture from a two-dimensional metal template. A combination of steric and electronic factors direct the synthesis in the third dimension, either promoting or preventing interlocking. The resulting [2]rotaxane is the first example derived from a square-planar-coordinated metal center and completes the series of mechanically interlocked ligands for common transition-metal geometries initiated by Sauvage and coworkers in 1983.

Received: December 29, 2003 [Z53622]

Keywords: coordination modes · palladium · rotaxanes · template synthesis


[**Pd(L6)**]: C_{121} H_{141}5 N_{85} O_{6} Pd, M_r = 1917.33, yellow block, crystal size 0.47 x 0.31 x 0.27 mm³, triclinic, space group Pi, a = 15.7840(10), b = 15.9967(10), c = 22.8029(14) Å, α = 84.9850(10), β = 84.9850(10), γ = 80.5460(10)°, V = 3592.5(6) Å³, Z = 2, μ_{calcd} = 1.193 Mg m⁻³; MoKα radiation (graphite monochromator, λ = 0.71073 Å), µ = 0.231 mm⁻¹, Т = 150(2) K. 34043 data (15 412 unique, R =0.0331, 2.06<θ<23.26°), were collected on a Brucker SMART CCD diffractometer using narrow frames (0.5° in 2θ), and were corrected semiempirically for absorption and incident beam decay. Data beyond 0.9 Å were weak and were not used for refinement. The structure was solved by direct methods (SIR92) and refined by full-matrix least-squares against F². Phenyl groups were constrained to be rigid hexagons and hydrogen atoms were placed in calculated positions. The whole macrocyclic component, inclusive of the Pd atom, is disordered (50:50) over two positions. The alkyl chain is further disordered and the refinement of this portion of the structure was controlled by application of restraints to both 1,2 and 1,3 distances and use of a common isotropic displacement parameter for all C atoms forming the chain. The only disorder present in the thread is in two of the tert-butyl groups. That based on C244 is rotationally disordered (70:30) with the central carbon atom (C244) fully occupied and the two alternative sets of methyl positions related by a 60° rotation about the C244-C243 bond. All atoms in the groups were refined with anisotropic displacement parameters (adps), those of "opposite" C atoms being constrained to be equal. The tert-butyl group attached to C263 is disordered (70:30) over two positions and was refined isotropically. Similarity restraints were applied to chemically equivalent 1,2 and 1,3 distances in both disordered tert-butyl groups. In the latter stages of refinement there was still significant unassigned electron density associated with diffuse solvent. This density was modeled by using the procedure of van der Sluis and Spek, comprising 199 electrons per unit cell, and corresponds to approximately 4.5 MeCN solvent molecules per asymmetric unit; values of M_r, F(000), μ etc. have been calculated on this assumption. wR = [Σ[w(Fo-Fc)²]/Σ[w(Fo)²]]¹/² = 0.2527, conventional R = 0.0866 for F values of 15 412 reflections with F² > 2σ(F²), S = 1.115 for 885 parameters. Residual electron density extremes were 1.03 and -0.94 eÅ⁻³. CCDC-229418 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44)1223-336-033; or deposit@ccdc.cam.ac.uk).
Abstract: We report the synthesis of a [2]catenate using a square planar palladium(II) template, together with two isomers of the interlocked structure: a single tetradeptate macrocycle that adopts a "figure of eight" conformation to encapsulate the metal and a complex in which the two macrocycles of the catenate are not interlocked. The three isomers can each be selectively formed depending on how the building blocks are assembled and cyclized. Olefin metathesis of both building blocks while they are attached to the metal gives the single large macrocycle in 77% yield. Cyclizing the monodentate unit prior to attaching both ligands to the metal gives the [2]catenate in 78% yield. Preforming the tridentate macrocycle produces a complex in two atropisomeric forms—threaded and nonthreaded—in a 2:3 ratio, which do not interconvert in dichloromethane at room temperature over 7 days. RCM of the nonthreaded atropisomer affords the complex with two noninterlocked macrocyclic ligands; RCM of the threaded atropisomer generates the topologically isomeric [2]catenate. Heating the acyclic atropisomers in acetonitrile provides a mechanism for their interconversion via ligand exchange, allowing the threaded:nonthreaded ratio to be varied from 2:3 to 8:1. All three fully ring-closed complexes were characterized unambiguously by $^1$H NMR spectroscopy and X-ray crystallography. As far as we are aware, this is the first time such a set of three formal topological and constitutional isomers has been described.

Introduction

The use of transition metal ions to direct the synthesis of interlocked architectures remains among the most efficient strategies available.1-5 In addition to exploiting reversible coordination chemistry to deliver high yields of thermodynamically privileged catenanes incorporating metals in their ring frameworks,2 catenates—metal complexes of interlocked organic macrocyclic ligands—can be formed through metal template macrocyclization reactions. However, the use of tetrahedral copper(I) geometry to hold bidentate ligands in an orientation suitable for subsequent interlocking macrocyclization reactions has been extensively developed over a 20 year period,6-8 the transposition of this basic concept to other coordination modes has been slow to develop. Although Sokolov alluded to the possibility of using octahedral ions to template catenane synthesis as early as 1973,9 attempts to prepare interlocked architectures in this way initially met with limited success.10 and it is only recently11 that efficient synthetic routes based on octahedral coordination have been developed. There is also a single example12 of five-coordinate zinc(II) being used to direct the formation of a [2]catenate and a remarkable crown ether-threaded organometallic catenate templated about a magnesium atom that also forms part of one ring.13

At first sight, the use of a template strategy to produce interlocked macrocyclic ligands for metals with a square planar coordination geometry might appear somewhat counter-intuitive. Square planar coordination obviously involves a 2D donor set, and therefore, in principle, systems can be designed to extend above and below the plane of the square planar coordination mode and direct a subsequent ring closure reaction. Indeed, there are several examples14 of the orthogonal alignment of organic fragments using such a “3 + 1” donor set of ligands, and we recently found that it was possible to exploit this effect to form a mechanically interlocked structure (Scheme 1).15 Through a combination of electronic and steric factors, the square planar palladium holds the monodentate 2,6-

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dimethylenoxy pyridine thread orthogonal to a bis-olefin-terminated tridentate benzylc amide macrocycle precursor such that cyclization by ring closing olefin metathesis (RCM) results in a [2]rotaxane in 77% yield.

However, extending this strategy to catenane synthesis is not straightforward. Even though oligomer and polymer formation could be minimized by metal chelation of the acyclic building blocks, a double macrocyclization strategy could produce three different isomeric products (1–3, Scheme 2), and even preforming one of the rings prior to attaching the building blocks to the metal could still afford either the interlocked (1) or noninterlocked (3) complex. Therefore we explored several potential routes to a square planar coordination [2]catenate, varying the sequence that the rings were cyclized and whether or not the building blocks were attached to the metal prior to

dmacrocyclization. Remarkably, it proved possible to find synthetic routes to each of the isomers 1–3 shown in Scheme 2.

Results and Discussion

Route 1: Simultaneous Metal-Directed Olef in Metathesis of L1 and L2. The first route investigated was the possible


1. 1st generation Grubbs’ catalyst, (Cp*), H2PdC

2. H2, Pd-C

77%
double macrocyclization of the tridentate (H₃L₁) and monodentate (L₂) building blocks, with both ligands already coordinated to a square planar metal, L₁PdL₂ (Scheme 3, Route I). The monodentate ligand L₂ was prepared in two steps from 4-hydroxybenzyl alcohol (see Supporting Information) and when combined with the known L₁Pd(CH₃CN) complex in dichloromethane, this provided the tetra-terminal olefin complex, L₁PdL₂, in 93% yield (Scheme 3, ii). ¹H NMR confirms the exchange of the acetonitrile ligand for L₂ (Figure 1a,b; note the upfield shift of the aromatic resonances of L₁ (H₄ and H₅) by 0.8 and 0.2 ppm, respectively, due to stacking with the pyridine group of L₂).

Subjecting L₁PdL₂ to RCM using the first-generation Grubbs’ olefin metathesis catalyst, followed by hydrogenation of the resulting internal double bond (Scheme 3, iii), gave a single species in 75% isolated yield for the two steps. FAB mass spectrometry confirmed that the complex had the molecular weight (m/z = 1110, MH⁺) necessary to be one of the isomers 1–3, and the ¹H NMR spectrum (Figure 1c) showed significant differences to L₁PdL₂, most notably in the region of 2.5–5.5 ppm, indicating that some change in orientation of the building blocks had occurred upon RCM. Treatment of the complex with potassium cyanide (Scheme 3, iv) gave a single organic compound (confirmed by mass spectrometry and ¹H NMR), ruling out the possibility that the product of the RCM was the two noninterlocked ring isomer, 3; that is, the product of Route I could not be L₄PdL₅.

The ¹H NMR spectrum (Figure 2c) of the demetalated structure did not show the shielding effects characteristic of benzylic amide macrocycle interlocked systems, the chemical shifts being virtually identical to the independently prepared free ligands, H₂L₄ and L₅ (Figure 2a and d, respectively). This suggested that the ligand isomer formed from Route I was probably H₂L₃, the single large macrocycle (2) resulting from intercomponent metathesis between the L₁ and L₂ olefin groups. This assignment was confirmed when single crystals suitable for X-ray crystallography were grown from slow cooling of a hot, saturated acetonitrile solution of the complex formed by Route I. The solid state structure (Figure 3) shows the tetradeinate 58-membered single macrocycle satisfying the square planar coordination geometry of the palladium, with the tridentate 2,6-dicarboxamidopyridine moiety held orthogonally to the monodentate 2,6-bis(oxyethylene)pyridine group. This results in twisting of the macrocycle, providing a single crossover point in a distinctive figure-of-eight conformation (Figure 3b). Although rare, this shape is not unique among coordination complexes of large flexible macrocycles, with other examples—based on octahedral metals—reported by the groups of Sauvage (a 58-membered hexadentate bis-terpy macrocycle bound to iron(II)) and Busch (a 40-membered ring coordinating to nickel(II) via 2,6-diminopyridine groups). In all cases, the metal ion provides the crossover point, imposing helical chirality on what would otherwise be intrinsically achiral macrocycles (for L₃Pd, both enantiomers are observed in the unit cell). Re-examination of the ¹H NMR spectrum (Figure 1c) reveals that the ring conformation of L₃Pd is conserved from the solid state to solution. The low (C₂) symmetry results in the individual protons of the H₂D, H₅ and H₆ methylene groups (H₂D, H₇, H₆, H₅, H₆, and H₇) being held in diastereotopic environments; the magnitude of the splittings following their proximity to the crossover point (H₂ and H₇ are split by nearly 2.5 ppm, H₅ and H₆ by 1.0 ppm, and H₆ and H₇ by just 0.4 ppm). Interestingly, the aromatic region of L₃Pd is virtually identical to that of L₁PdL₂ (Figure 1b), suggesting that while the alkyl residues may be mobile, the rest of the acyclic precursor complex is well-organized for intercomponent olefin metathesis.

Since the attempted simultaneous double macrocyclization strategy had given rise to intercomponent bond formation, we sought to exclude this possibility by preforming one or the other of the rings prior to the second, metal-directed, cyclization reaction (Scheme 3, Routes II and III).

Route II: Metal-Directed RCM of L₂. Trideterminate macrocycle H₂L₄ was prepared in 57% yield by treatment of 2,6-...
pyridinedicarbonyl dichloride with the appropriate diamine under high dilution conditions (see Supporting Information). Subsequent complexation with palladium(II) acetate afforded L4Pd(CH3CN) (93%, Scheme 3, v). Threading of L2 through the cavity of L4Pd(CH3CN) via the substitution of the coordinated acetonitrile was attempted by simple mixing of the two in dichloromethane at room temperature (Scheme 3, vi). While mass spectrometry confirmed the ligand exchange, the 1H NMR spectrum of the crude product was unexpectedly complex. Closer inspection of the thin layer chromatograph of the reaction mixture revealed two products with very similar Rf values in a ratio of approximately 2:3. Despite their proximity, these proved amenable to separation by preparative thin-layer chromatography on silica gel-coated plates (CH2Cl2:MeOH, 98.5:1.5 as eluent).
The isolated complexes gave indistinguishable fragmentation patterns by electrospray ionization mass spectrometry, the molecular mass ion suggesting they were both isomers of L4PdL2. However, the 1H NMR spectra exhibited important differences between the two products. When compared to the spectra of the starting materials, the minor isomer (lower R1, Figure 4d) showed significant shielding of the L4 benzyl rings (H2 and H3), indicative of aromatic stacking with the pyridine group of L2. In contrast, the major isomer (higher R1, Figure 4b) showed no evidence of stacking interactions but a greater degree of complexity in both the L2 signals (two sets of nonequivalent H2, H3, H6, H8, and H7 resonances) and the H2 methylene groups (an AB system with a 2.5 ppm separation between the two proton environments) of L4. From this, we tentatively assigned the two products as “threaded” (minor isomer) and “threaded” (minor isomer) atropisomers,21 L4Pd(exo-L2) and L4Pd(endo-L2), respectively (Scheme 3).

Intriguingly, CPK models suggested that cyclization of L2 could occur with each atropisomer of L4PdL2, suggesting that two compounds of identical connectivity but different conformations22 are predisposed to form topological isomeric products.
upon RCM—the [2]catenate, 1, and the analogous noninterlocked double macrocycle structure, 3. Sure enough, treatment of the 2:3 mixture of atropisomers with Grubbs' catalyst in CH2–Cl2, followed by hydrogenation and demetalation (Scheme 3, vii (three steps—the mixtures of topological and olefin isomers preventing the isolation of pure products until the end of the reaction sequence)), afforded three products: macrocycles H2L4 and L5 arising from complex 3, and a further compound, which mass spectrometry confirmed to be a different isomer of H2L3, in 25% overall yield for the three steps.23

1H NMR spectroscopy of the new compound in CDCl3 (Figure 2b) revealed shielding of most resonances compared to the free macrocycles H2L4 (Figure 2a) and L5 (Figure 2d) characteristic of interdigitation, suggesting that it was indeed the [2]catenand H2L6. The exception to the upfield trend in shifts was the amide protons (Hc), which were shifted significantly downfield (ca. 1.3 ppm) in the catenand compared to those of H2L4, indicative of a significant hydrogen-bonding interaction between the amide protons of one ring and the pyridine nitrogen of the other. In contrast, the analogous amide protons in the 58-membered free macrocycle H2L3 occur at 8.11 ppm in CDCl3 (Figure 2c), only slightly downfield of their position in H2L4 (7.88 ppm, Figure 2a), meaning that little intramolecular hydrogen bonding is occurring in the large flexible macrocycle. Why is this internal hydrogen bonding absent when it is so clearly present in the mechanically bonded isomer H2L6? First, the size and nature of the solvent-exposed surfaces of the compact [2]catenand structure and the large, relatively open, macrocycle must be very different, making desolvation of the amide and pyridine residues in the catenane a significantly less energetically costly process. Second, with the 2,6-bis(oxyethylene)pyridine and 2,6-pyridinocarboxamide groups on different components, the macrocycles in H2L6 can orientate themselves for inter-residue hydrogen bonding with little more than the loss of a single rotational degree of freedom. In contrast, alignment of the groups to enable a similar interaction within H2L3 would significantly restrict the number of conformations accessible by the alkyl chains in the large flexible ring, the resulting losses in degrees of freedom raising the energy of the hydrogen-bonded structure. This unusual orthogonal double bifurcated bis-pyridine hydrogen-bonding interaction is also observed in the related [2]rotaxane system.17

Reintroduction of Pd(II) into the free ligand systems (H2L3 → 1Pd, Scheme 3, xiii; H2L6 → 6Pd, Scheme 3, xiii; H2L4 → 4Pd(CH2CN) + L5 → 4PdL5, Scheme 3, v, viii) proceeded smoothly in each case, the last two providing pure samples of complexes formed previously as intermediates during each pathway of the Route II syntheses. ESI mass spectrometry initially identified the formation of 4PdL5, confirming that both macrocycles could simultaneously bind to palladium without being interlocked. 1H NMR spectroscopy (Figure 4a)

Figure 5. X-ray crystal structure of noninterlocked double macrocycle complex 4PdL5 grown from a saturated solution of the complex in acetone. (a) Side-on and (b) top views. Carbon atoms of the L4 macrocycle are shown in light blue, and those of the L5 macrocycle in yellow; oxygen atoms are red, nitrogen dark blue, and palladium gray. Selected bond lengths [Å]: N2–Pd 2.052, N5–Pd 1.943, N11–Pd 2.032, N41–Pd 2.077; tridentate fragment bite angle [°]: N2–Pd–N11 160.8.

corroborated this result and showed significant similarity (a diastereotopic environment for H3, and two sets of signals for each H6, H5, H4, H3, and H2) to the presumed nonatropisomeric isomer of 4PdL2 (Figure 4b). These spectral features are consistent with orthogonal binding of the rings to the square planar geometry metal, with neither macrocycle being able to pass through the cavity of the other nor rotate (at least not rapidly on the NMR time scale in the case of the monodentate ligand) about the plane of the square planar coordination geometry. This means both macrocycles are perforce desymmetrized in the plane that they coordinate to the metal, that is, top from bottom in L4 and left from right in L5 (as 4PdL5 is depicted in Figure 5a).

Pleasingly, the pure samples of 4PdL5 and 6Pd both provided single crystals suitable for structure elucidation by X-ray crystallography (Figure 5 and Figure 6, respectively). Between them, the X-ray crystal structures of 3Pd, 4PdL5, and 6Pd confirm not only the identity of the metal complexes—a unique set of topological (4PdL2 and 6Pd) and constitutional (3Pd and 4PdL5/6Pd) isomers—but also the structural assignments of the free ligands inferred by the earlier 1H NMR and mass spectrometry analyses.

Atropisomer-Specific Synthesis of Different Topological Isomers. Although RCM (and subsequent hydrogenation and demetalation) of the mixture of the two 4PdL2 atropisomers gives a ratio of isolated interlocked to noninterlocked products similar to the starting atropisomer ratio, it does not necessarily follow that one atropisomer leads solely to one product. The
interconversion of the two L4PdL2 atropisomers in solution was investigated by 1H NMR spectroscopy. The initial threaded:nonthreaded ratio of ca. 2:3 remained unchanged over 7 days in CD2Cl2 at room temperature. Similarly, spectra of pure samples of each of the compounds were invariant under these conditions, demonstrating that the atropisomers are kinetically stable at room temperature in a noncoordinating solvent. However, addition of ~10% CD3CN to either of the pure atropisomer solutions or the 2:3 mixture led to a gradual change in the threaded:nonthreaded ratio, increasing to ca. 7:3 after 4 days. This suggests that the threaded isomer is thermodynamically favored, and that atropisomer interconversion can take place via the dissociation of L2 from either form of L4PdL2, the vacant coordination site being temporarily filled by a tridentate fragment.

Figure 6. X-ray crystal structure of palladium[2]catenate L6Pd grown by slow cooling of a warm, saturated solution of the complex in acetonitrile. (a) Side-on and (b) top views. Carbon atoms of the L4 macrocycle are shown in light blue, and those of the L5 macrocycle in yellow; oxygen atoms are red, nitrogen dark blue, and palladium gray. Selected bond lengths [Å]: Pd—N2 1.934, Pd—N5 2.041, Pd—N11 2.036, Pd—N41 2.079; tridentate fragment bite angle [°]: N2—Pd—N11 160.2.

Route III: Metal-Directed RCM of L1. Finally, we investigated the product distribution arising from preforming the monodentate macrocycle and applying metal-directed cyclization of the tridentate ligand (Scheme 3, Route III).24 L1Pd(CH3CN) and L5 were stirred together in dichloromethane at room temperature (Scheme 3, ix) and, in contrast to the analogous step in Route II, reacted to give a single product rather than a mixture of atropisomers. The 1H NMR spectrum of L1PdL5 (Figure 4e) suggests the two ligands are threaded; the upfield shift of H5 and H3 compared to similar protons in the nonthreaded L4PdL5 and L4Pd(exo-L2) complexes (Figure 4a and b, respectively), indicating π-stacking of the benzyl groups of L1 with the pyridine unit of L5. It is difficult to distinguish between whether L1PdL5 can exist as threaded/nonthreaded atropisomers but is formed solely as the (exo-L1)PdL5 isomer, or rather threaded and nonthreaded forms of L1PdL5 are in equilibrium with the threaded conformation being thermodynamically preferred by several kcal mol⁻¹. In any event, RCM of L1PdL5 and subsequent hydrogenation (Scheme 3, x) afforded exclusively the [2]catenate, L6Pd, in 78% yield, making this route both synthetically efficient and completely selective for the mechanically interlocked topological isomer.

Conclusions

A [2]catenate and the isomeric single macrocycle and double macrocycle metal complexes can each be efficiently assembled about a palladium(II) template via RCM. The order in which the tridentate and monodentate ligand cyclization reactions and coordination steps are performed determines the outcome of the synthetic pathway, providing selective routes to each of the three topological and constitutional isomers. In one case, preforming the tridentate macrocycle followed by its coordination along with the acyclic monodentate ligand to the Pd produces threaded and nonthreaded atropisomers. These can be isolated and, while the individual forms are stable in dichloromethane, they can be interconverted in a coordinating solvent through ligand exchange. Each atropisomer was shown to be a true intermediate to a different topological product, meaning that, in this reaction, the choice of solvent can determine whether the [2]catenate is formed or its noninterlocked isomer. It is remarkable to see how topology and connectivity can be selected so exquisitely—in three different forms—using just one set of organic building blocks and a metal atom with a two-dimensional coordination geometry.

Experimental Section

Selected Spectroscopic Data for the Set of Three Constitutional and Topological Isomers. L3Pd: 1H NMR (400 MHz, CD2Cl2, 298 K): Δ δ = 1.09–1.84 (m, 32H, alkyl-H), 2.70 (d, 2H, J = 14.4 Hz, H5), 3.64 (m, 4H, H6), 4.00–4.13 (m, 8H, H7 + H8 + H9), 4.39 (d, 2H, J = 10.6 Hz, H10), 5.04–5.14 (m, 4H, H14), 5.38 (d, 4H, J = 8.6 Hz, H13), 6.38 (d, 4H, J = 8.6 Hz, H12), 6.49 (d, 4H, J = 8.6 Hz, H11), 6.84 (d, 4H, J = 8.6 Hz, H10).

(23) The hydrogenation conditions employed in Routes I and III led to a complex mixture when applied to the products of metathesis in Route II. Not only was significant decomposition of the somewhat strained noninterlocked double macrocycle complex observed but also the resulting free monodentate ligand, L5, was degraded, presumably by hydrolysis of the benzyl ether moieties. Although the use of Pd EnCat did not prevent the ligand decomplexation during the hydrogenation step, it significantly reduced the degradation of the free monodentate macrocycle [Bremeyer, N.; Ley, S. V.; Ramarao, C.; Shirley, I. M.; Smith, S. C. Synlett 2002, 1843–1844.]

A Square Planar Palladium \[2\]Catenate

\[
\text{H}_2, \quad 7.20 \ (d, \ 4H, \ J = 8.6 \ \text{Hz}, \ H_2), \quad 7.45 \ (d, \ 2H, \ J = 7.8 \ \text{Hz}, \ H_2), \quad 7.76 \ (d, \ 2H, \ J = 7.8 \ \text{Hz}, \ H_2) \ . \]

\[
\text{C} \quad 13 \ 
\]

\[
\text{CNMR (100 MHz, CD}_2\text{Cl}_2, \ 293 \ \text{K}) : \quad \delta = 23.7, \ 25.2, \ 25.5, \ 25.7, \ 27.5, \ 27.5, \ 28.6, \ 29.5, \ 48.5, \ 67.1, \ 68.1, \ 71.8, \ 73.2, \ 114.0, \ 114.8, \ 121.2, \ 124.8, \ 128.5, \ 128.7, \ 129.5, \ 132.8, \ 139.1, \ 140.7, \ 152.8, \ 158.1, \ 158.6, \ 160.6, \ 171.1 \ . \]}

\[
\text{HRMS (FAB, NOBA) : Caled for C}_6\text{H}_7\text{N}_4\text{O}_8\text{Pd} [M + H]^+ \ 1109.46169. \ 
\]

\[
\text{Acknowledgment. This work was supported by the European Union Future and Emerging Technology program, \textit{MechMol}, and the EPSRC.} \]

\[
\text{Supporting Information Available: Experimental procedures and spectroscopic data for all new compounds, and thermal ellipsoids for the crystal structures of L3Pd, L4PdL5, and L6Pd. This material is available free of charge via the Internet at http://pubs.acs.org.} \]

JA053005A
Rotaxane Synthesis

One Template, Multiple Rings: Controlled Iterative Addition of Macrocycles onto a Single Binding Site Rotaxane Thread**

Anne-Marie L. Fuller, David A. Leigh,* and Paul J. Lusby

Dedicated to Sir J. Fraser Stoddart on the occasion of his 65th birthday

The introduction[1] and subsequent spectacular growth[2–5] of template strategies[2] to molecules with multiple mechanically interlocked components (rotaxanes,[3,4,6-8] catenanes,[5,6,8] and Borromean rings[9]) has revolutionized approaches to their synthesis. However, despite the many different template systems and innovative assembly processes developed thus far, a feature common to all current methods is that they each employ at least one binding site per macrocycle, that is, a minimum of \( n-1 \) templates per \( n \) interlocked components. Here we describe a strategy (Figure 1) for assembling multi-

![Figure 1. An iterative [n]rotaxane synthesis utilizing a single template unit (shown in purple) and the repetition of three simple steps: a) complexation of an acyclic ligand (shown in light blue) to the template site; b) macrocyclization; c) demetalation.](image)

ring rotaxanes in which just a single ligation site is used to clip on as many macrocycles as required (and the length of the thread will permit), through the repetition of three simple steps. The method (Scheme 1) involves the repetitive coordination and macrocyclization of a tridentate ligand for palladium about a stopped molecular thread (L1), sequentially forming rings of type \( \text{H}_2\text{L}_2 \) to iteratively[8] generate \([2]_\text{rotaxane}\), \([3]_\text{rotaxane}\), and \([4]_\text{rotaxane}\). Overcoming the restriction of only one ring per template unit—especially the ability to re-utilize the template despite the proximity of a previously cyclized component—should aid the synthesis of increasingly complex higher order interlocked assemblies (for example, defined sequences of different rings on a molecular strand).

The single template site iterative assembly of multiple ring rotaxanes utilizes a square-planar geometry \( \text{Pd}^{II} \)-based "clipping" methodology previously developed[10] as a "classical" (that is, one macrocycle per binding site) template synthesis of rotaxanes and catenanes. The metal atom is first bound to a tridentate 2,6-pyridinedicarboxamide ligand (significantly, this involves deprotonation of the ligand amide groups[9]). The resulting complex \([\text{L}_3\text{Pd(CH}_3\text{CN)}\text{]}\text{]^{II}}\) is coordinated to a monodentate pyridine unit on a thread such that subsequent macrocyclization by ring-closing metathesis (RCM) occurs around the thread to generate an interlocked architecture.[10]

The key to extending this protocol so that further ligands can be cyclized around the template after the first is decomplexed, is the observation that whilst \([\text{L}_3\text{Pd(CH}_3\text{CN)}\text{]}\text{]^{II}}\) readily exchanges its labile coordinated acetonitrile molecule for a pyridine unit (see Scheme 1, step a), it does not undergo tridentate ligand exchange with protonated (that is, metal-free) versions of the 2,6-pyridinedicarboxamide system (for example, \( \text{H}_2\text{L}_4 \) and \( \text{H}_4\text{L}_5 \); Scheme 1, steps d and g). Thus, a pyridine group on a thread can repetitively be used to replace acetonitrile ligands of \([\text{L}_3\text{Pd(CH}_3\text{CN)}\text{]}\text{]^{II}}\), with the resulting complexes then being macrocyclized one at a time.

To demonstrate the effectiveness of this strategy in a multi-ring rotaxane synthesis, a suitable thread \( \text{L}_1 \) was prepared (see the Supporting Information) with a single pyridine unit as the only potential template site and sufficient space—provided by a \( \text{C}_11 \) alkyl chain—between the stoppers to accommodate several macrocycles. As anticipated, stirring \( \text{L}_1 \) with \([\text{L}_3\text{Pd(CH}_3\text{CN)}\text{]}\text{]^{II}}\) in dichloromethane resulted in rapid formation of \([\text{L}_3\text{Pd(L}_1\text{)}\text{]}\) (92%, Scheme 1, step a). Macrocyclization with the Grubbs first-generation RCM catalyst and subsequent hydrogenation[11] gave the saturated palladium \([\text{L}_3\text{Pd(L}_1\text{)}\text{]}\) (Scheme 1, step b). Treatment with potassium cyanide (Scheme 1, step c) then afforded the metal-free \([\text{L}_3\text{Pd(L}_1\text{)}\text{]}\) in 62% overall yield for the first iterative cycle.

A comparison of the room-temperature \(^1\text{H}\) NMR spectrum of \( \text{H}_2\text{L}_4 \) in \( \text{CD}_2\text{Cl}_2 \) (Figure 2c) with that of the free components macrocycle \( \text{H}_3\text{L}_2 \) and thread \( \text{L}_1 \) (Figure 1a and b, respectively) confirms the interlocked nature of the product. The most significant differences in the spectra are...
The controlled iterative synthesis of [2]-, [3]-, and [4]-rotaxanes H₂L₄, H₂L₅, and H₂L₆. CPK models confirm that the threaded rings cannot pass through the cavities of each other and so the color of each fragment of a structure reflects its origin in the synthetic sequence.

**Scheme 1.** The controlled iterative synthesis of [2]-, [3]-, and [4]-rotaxanes H₂L₄, H₂L₅, and H₂L₆. CPK models confirm that the threaded rings cannot pass through the cavities of each other and so the color of each fragment of a structure reflects its origin in the synthetic sequence.

<table>
<thead>
<tr>
<th>Step</th>
<th>Reaction Details</th>
</tr>
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<tbody>
<tr>
<td>a</td>
<td>[L₃Pd(CH₃CN)], CH₂Cl₂, 5 h, RT, 92%</td>
</tr>
<tr>
<td>b</td>
<td>1. Grubbs catalyst (0.12 equiv), CH₂Cl₂; 2. ortho-nitrobenzenesulfonylhydrazide (NBSH), Et₃N, CH₂Cl₂, 72% (over 2 steps)</td>
</tr>
<tr>
<td>c</td>
<td>KCN, CH₂Cl₂, MeOH, 94%</td>
</tr>
<tr>
<td>d</td>
<td>[L₃Pd(CH₃CN)], CH₂Cl₂, 5 h, RT, 96%</td>
</tr>
<tr>
<td>e</td>
<td>1. Grubbs catalyst (0.12 equiv), CH₂Cl₂; 2. NBSH, Et₃N, CH₂Cl₂, 84% (over 2 steps)</td>
</tr>
<tr>
<td>f</td>
<td>KCN, CH₂Cl₂, MeOH, 88%</td>
</tr>
<tr>
<td>g</td>
<td>Method A: [L₃Pd(CH₃CN)], CH₂Cl₂, 3 days, RT, [L₃PdH₂L₅] 51%, iso-[L₃PdH₂L₅] 37%; Method B: [L₃Pd(CH₃CN)] (3 equiv), CH₂Cl₂, Δ, 7 days, [L₃PdH₂L₅] 81%, iso-[L₃PdH₂L₅] 5%; 1. Grubbs catalyst (0.12 equiv), CH₂Cl₂; 2. NBSH, Et₃N, CH₂Cl₂; 3. KNC, CH₂Cl₂, MeOH, 70% (over 3 steps)</td>
</tr>
<tr>
<td>h</td>
<td>1. Grubbs catalyst (0.12 equiv), CH₂Cl₂; 2. NBSH, Et₃N, CH₂Cl₂, 87% (over 2 steps)</td>
</tr>
<tr>
<td>i</td>
<td>KCN, CH₂Cl₂, MeOH, 97%</td>
</tr>
</tbody>
</table>

For the signals of the methylene protons adjacent to the pyridine group of the thread (H and H₈), which are shifted, particularly that of H, upfield in the spectrum of the [2]rotaxane. The macrocycle phenyl resonances (H₉ and H₁₀) are also shielded in the [2]rotaxane while the amide protons (H₁₅) move 1.3 ppm downfield, which is indicative of intercomponent hydrogen bonding with the pyridine unit. However, small upfield shifts in nearly all the axle signals in the rotaxane, including the alkyl region, show that this interaction is rather weak and the macrocycle is able to access the full length of the thread in CH₂Cl₂.

For the second iterative cycle, repetition of the three steps (complexation, macrocyclization, and demetallation, Scheme 1, steps d–f) starting from [2]rotaxane H₂L₄ smoothly afforded [3]rotaxane H₂L₅ in 79% overall yield. The crucial complexation of [L₃Pd(CH₃CN)] to the free pyridine group of H₂L₄ to give [L₃PdH₂L₄] (Scheme 1, step d) proceeds in 96% yield in 5 h with no trace of transmetalation to the rotaxane macrocycle. Comparison of the 'H NMR spectrum of [L₃PdH₂L₄] in CD₂Cl₂ (Figure 3b) with that of [L₃PdL₁] (Figure 3a) indicates that the displaced macrocycle in the [2]rotaxane spends a significant amount of time over the ether unit furthest from the Pd coordination sphere (1.2 ppm upfield shift of the methyleneoxy resonance of the thread H₉), presumably at least in part as a result of hydrogen bonding between the amide and oxygen atom of the ether. The 'H NMR spectrum of the demetallated [3]rotaxane H₂L₅ in CD₂Cl₂ is shown in Figure 2d. The occurrence of the amide signals at δ = 9.4 and 8.6 ppm (H₂ and H₁) suggest that the hydrogen-bonding interaction between the amide and oxygen atom of the ether is appreciably stronger than that between the amide and ether groups.
method A). However, the reaction proved extremely sluggish using the conditions previously employed (CH2Cl2, 293 K), and after three days the product mixture was separated by column chromatography to give, somewhat unexpectedly, two new kinetically stable products in a ratio of 2:3. Mass spectrometry suggested that the products were isomers of [L3PdH2L5] (Scheme 1), in which the two macrocycles are restricted to different regions of the thread by coordination of [L3Pd] to the pyridine unit. The major product was assigned by 1H NMR spectroscopy as isomer [L3PdH2L5]. Its spectrum (Figure 3c) shows increased shielding of the alkyl region with respect to the similarly derivatized [2]rotaxane [L3PdH2L4] (Figure 3b), which suggests that both macrocycles are located over the C11 region of the thread. In contrast, the 1H NMR spectrum (Figure 3d) of the minor isomer showed no increase in the shielding of the alkyl region relative to [L3PdH2L4]. Rather, significant shifts of the thread methyleneoxy (Hr) and stopper protons Hs and Ha occur, which indicates that this isomer is iso-[L3PdH2L5], in which the two macrocycles are separated by the coordinated [L3Pd] unit.

Whilst the formation of this second isomer appears surprising given the steric demands of the macrocycle and the very limited space available between the pyridine ligation site and the closest bulky stopper, it presumably reflects the fact that an ether oxygen atom is available on that part of the thread to which one of the two amide macrocycles can spend significant time hydrogen bonding. Complexation of [L3Pd] to the pyridine unit traps that proportion of macrocycles in that region of the thread and the kinetic stability of the pyridine-palladium bond inhibits equilibration to the less sterically hindered isomer. In agreement with this rationalization, carrying out the reaction at reflux for 7 days (Scheme 1, step g, method B) to induce some reversibility in the formation of the pyridine-palladium bond gave 81% of [L3PdH2L5] with only a small amount of the minor isomer.

The final macrocyclization and demetalation steps to give [4]rotaxane H2L6 could be carried out on either the single isomer [L3PdH2L5] (Scheme 1, steps i and j) or on the mixture of [L3PdH2L5]/iso-[L3PdH2L5] isomers (Scheme 1, step h). The [4]rotaxane obtained from these reactions—in both cases single species—had identical physical properties and indistinguishable 1H NMR spectra (Figure 2e), again supporting the structural assignments of [L3PdH2L5] and iso-[L3PdH2L5]. The 1H NMR spectrum of H2L6 in CD2Cl2 (Figure 2e) shows three sets of amide signals, and further shielding of both the C11 alkyl chain of the thread and in particular the methyleneoxy resonances (Hr, Hs, Ha). The overall yield for the iterative cycle to add the third ring to generate the [4]rotaxane is a pleasing 68% (by way of single isomer [L3PdH2L5]).

In conclusion, we have described methodology for preparing multi-ring rotaxanes through the iterative addition of macrocycles to a rotaxane thread bearing a single ligation site. By using this efficient and effective strategy, both the number and the order in which macrocycles are assembled onto a thread can be controlled with unprecedented precision.
Experimental Section

General procedure for the iterative synthesis of an [n]rotaxane from an [n-1]rotaxane or thread: a) Complexation: A solution of the metal-free 2,6-disubstituted pyridine ligand (L1, H2L4, or H2L5, 0.1-2.0 mmol) and [L3Pd(CH2CN)2] (1 equiv for L1, H2L4; 3 equiv for H2L5) in anhydrous dichloromethane (30 mL) was stirred for 5 h at room temperature (7 days at reflux for H2L5) under an atmosphere of nitrogen. The mixture was then concentrated under reduced pressure and the crude residue purified by column chromatography to yield the corresponding complex [L3PdL1] (92%), [L3PdL4] (96%), or [L3PdH2L5] (81%). b) Macrocyclization: The complex obtained from (a) was dissolved in anhydrous dichloromethane (200 mL for 1 mmol of substrate) and added via a double-ended needle to a solution of the first-generation Grubbs catalyst (0.12 equiv) in anhydrous dichloromethane (850 mL per mmol) under an atmosphere of nitrogen. The solution was stirred at room temperature for 18 h, after which it was concentrated under reduced pressure, and the crude residue subjected to column chromatography to yield the corresponding unsaturated olefin rotaxane-metal complex. This was dissolved in dichloromethane (12 mL for 1 mmol of substrate) and then NBSH (8.0 equiv) and triethylamine (10 equiv) added. The suspension was then stirred overnight. The resultant orange/brown solution was washed with sodium bicarbonate (3 × 75 mL) and the organic layers combined and concentrated to give the saturated solution (typically 0.1-1.0 mmol) in dichloromethane.


Keywords: coordination modes, macrocycles, palladium, polyrotaxanes, rotaxanes, template synthesis

A "threading-and-stoppering" procedure based on a Pd(II) template has also been described: Y. Furusho, T. Matsuura, T. Takata, T. Moriuchi, T. Hira, Tetrahedron Lett. 2006, 45, 9593–9597. The Li component proved unstable to hydrogenation using H2 over Pd/C, although this method had been previously employed successfully on Pd(II)-coordinated interlocked architectures.[9] Various alternative reagents and conditions were investigated of which ortho-nitrobenzenesulfonylhydrazide (NBSH) proved the most efficacious [see A. G. Myers, B. Zheng, M. Movassaghi, J. Org. Chem. 1997, 62, 7507].

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