

Rotaxanes as Molecular Machines - The Work of Professor David Leigh

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The concept, preparation, and development of mechanically interlocked molecules, dates back more than forty years and, as an area, has attracted increasing attention. Those who have made significant contributions include Professor David Leigh of the University of Edinburgh. His activities in working on the synthesis and applications of rotaxanes, in particular, stem from the late 1990s and are the focus of this paper. He began with the development of an active metal template synthesis that offers increased efficiency over the previously used passive template methods; supramolecular chemistry and non-covalent interactions enable the syntheses of rotaxanes in fewer steps and in greater yields. Rotaxanes are of interest to scientists because they exhibit markedly different spectroscopic responses, chemical reactivity, and mechanical properties over their non-interlocked analogues. More recently Leigh has turned to the properties of these molecules as molecular machines.

Rotaxanes are defined by the IUPAC as *molecules in which a ring encloses another rod-like molecule having end-groups too large to pass through the ring opening; the rod-like molecule is thus held in position without covalent bonding*.¹ A rotaxane is thus a mechanically locked architecture which consists of macrocyclic rings trapped on a linear unit, the thread, by two bulky constituents, the stoppers (Fig. 1).² This mechanical interlocking is not a chemical bond; rather, it intrinsically links the backbone components of the molecule and prevents their dissociation without the cleavage of one, or more, covalent bonds. They are named using the format [x]-rotaxane, where *x* indicates the number of components in the molecule; thus, a [2]-rotaxane would consist of one thread and one macrocyclic ring.

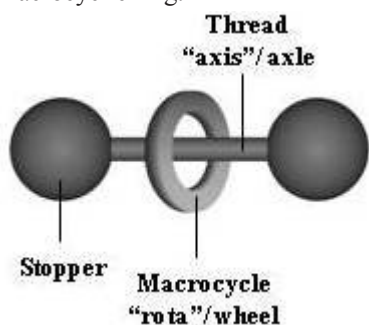


Fig. 1. Graphical representation of a [2]-rotaxane - one thread and one macrocycle.

Rotaxanes are prevalent in biology as molecular motors that produce rotary and linear motion. One such molecular machine is a bacterial flagellum. It is a tail-like structure that projects from bacterial cells and assists in locomotion via a helical motion. The bacterial flagellum is driven by a rotary engine made up of a protein anchored in the inner cell membrane. This protein has the shape of

a [3]-rotaxane with one thread and two macrocyclic components as shown in Fig. 2.³ The engine is powered by an electrochemical proton gradient across the cell membrane set up by the cell's metabolism. This turns the flagellum at a frequency of approximately 1000 Hz, propelling the bacterial cell at 100 $\mu\text{m}/\text{sec}$ with an estimated 100 % fuel efficiency.⁴

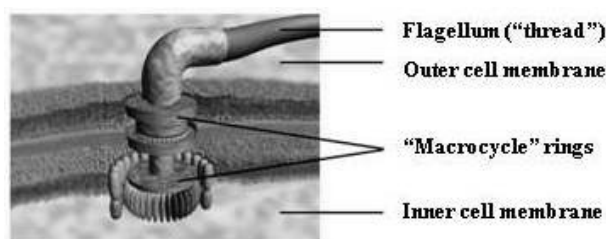


Fig. 2. Bacterial flagella motor of *E. Coli*, which is a [3]-rotaxane.

Rotaxanes are also utilized in DNA replication, including the enzyme DNA polymerase, which is used to catalyse the polymerisation of deoxyribonucleotides into a DNA strand. The polymerase binds to a single strand of DNA, and then directs the incoming deoxyribonucleotides into the correct position to form a sequence complementary to the original single strand. It also keeps the DNA strand in place to greatly reduce errors during synthesis. As the DNA chain does not have stoppers at its end, the complex is not a *true* rotaxane as it is able to separate into its independent components – such molecules are termed pseudo-rotaxanes (Fig. 3).⁵ Both of these biological molecular machines utilize chemical energy through metabolism to generate motion at ambient temperatures. One of the most interesting and important functions of these biological rotaxanes is their ability to assemble in the correct arrangement without the need for an external stimulus. It is this self-assembly which Leigh is trying to replicate out of the biological world using supramolecular chemistry.

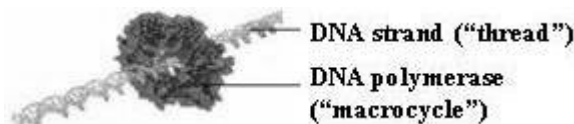


Fig. 3. Pseudo-rotaxane structure of DNA polymerase.

The self-assembly of rotaxanes is an important characteristic of their synthesis. Self-assembly is the spontaneous formation of a thermodynamically stable product from the aggregation of pre-existing components by weak supramolecular, non-covalent interactions into a particular spatial arrangement. This requires architectures that restrict the degrees of freedom of the reactants, and control their motion to encourage the desired product to form. These supramolecular interactions include hydrogen bonding, dipole and ion interactions, π -stacking, and dis-

persion effects. They generally have a high stability and are relatively labile. This self-assembly is also known as bottom-up assembly where smaller components are built into larger, more complex assemblies without the use of an external stimulus. This type of synthesis is beneficial as it enables the formation of complex structures with multiple functional groups in relatively few steps and in good yield. As a thermodynamically stable product is produced, it also increases the likelihood of the desired product being formed as the major product, which decreases the need for separation from side products.

There are three commonly used methods for rotaxane synthesis known as i) capping, ii) clipping, and iii) slipping as illustrated in Fig. 4.⁶ In each, a metal ion complexes with the separate rotaxane components to hold them in the correct orientation for the formation of the interlocked architecture; as the metal ion is unused otherwise in the reaction, these methods are known as *passive* metal template syntheses. The capping method relies strongly on thermodynamics to hold the thread within the macrocycle by non-covalent, supramolecular interactions. The stoppers are then added onto the pseudo-rotaxane to form a rotaxane. Clipping is similar to the capping method, except that the thread and chain are complete and bound to a partial macrocycle. This macrocycle undergoes a ring-closing reaction to form the final rotaxane. The slipping method exploits the kinetic stability of the rotaxane. If the stopper molecules are of an appropriate size one can reversibly thread through the macrocycle at high temperature: that is, it is a dynamic complex. On cooling, the macrocycle becomes kinetically trapped on the thread. These are efficient synthetic methods as they generally result in good yields. However, the removal of the metal ion after the desired mechanically interlocked architecture is made is non-trivial since it has a permanent coordination site on each component. The method also requires stoichiometric quantities of the metal ion, which can be expensive.

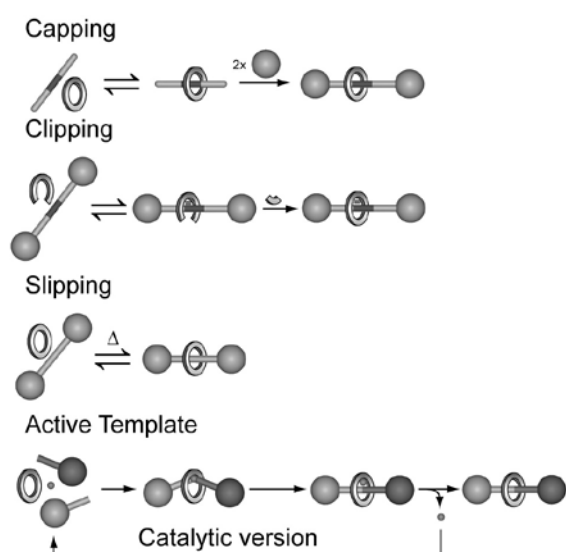


Fig. 4. Rotaxane synthesis by *passive* template mechanisms.

Active template synthesis was developed by Leigh to overcome the limitations associated with passive metal template routes. It utilizes the catalytic properties of metal ions to enhance covalent bond formation, as well as their ability to direct the bond formation; in this way the metal

ion is *active* as it has dual functionality. This synthesis relies on a macrocycle that is able to bind a metal ion endotopically in its cavity, promoting the formation of a covalent bond between two *half-thread* units to form a rotaxane. As the metal ion is locked into position, the mechanical bond is selectively formed through the macrocycle as shown in Fig. 5.⁷ The reaction can occur stoichiometrically with one equivalent of the template, or catalytically when the active template turns over during the reaction. This active route has the advantage over the previously used methods as it enables *traceless* syntheses: it does not require permanent recognition elements on each component of the interlocked product to enable the mechanical bond to be formed. This also enables otherwise *impossible* rotaxanes to be synthesized, as architectures that cannot otherwise be generated become possible, *viz.*, greater structural diversity is achievable.

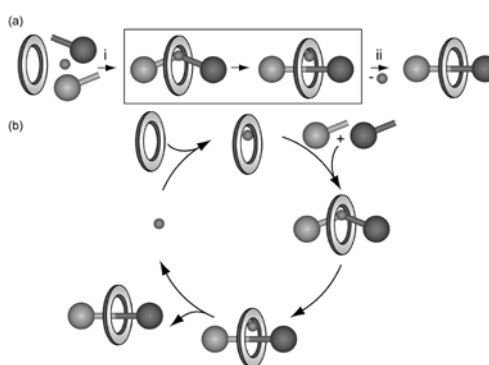
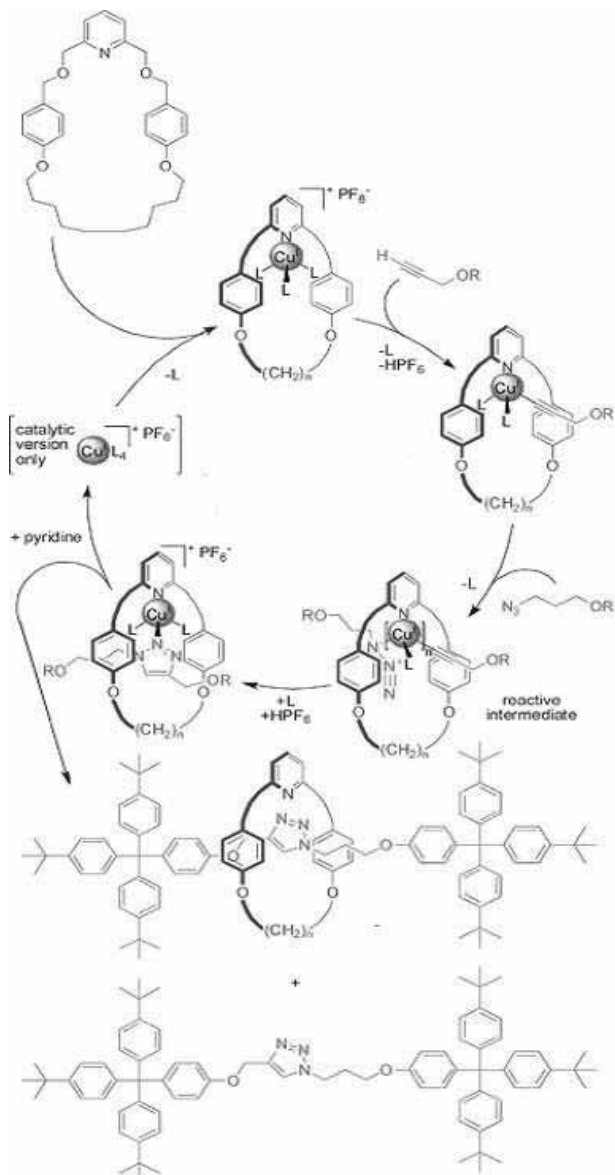


Fig. 5. (a) Non-catalytic, and (b) catalytic active metal template synthesis of a rotaxane.

The active metal template synthesis was first developed in 2006 by Leigh using stoichiometric quantities of copper(I) as the template ion. He evolved a Cu(I)-catalysed terminal alkyne–azide 1,3-cycloaddition (CuAAC) reaction, now termed a *click* reaction,⁸ which as the name suggests involves the 1,3-dipolar addition of an azide to a terminal alkyne to give a 1,2,3-triazole. Leigh used previously developed 2,6-disubstituted pyridine macrocycles in this reaction, as they contained the desired endotopic ligating nitrogen atom required to bind the metal template ion. In this case the Cu(I) source was $\text{Cu}(\text{MeCN})_4\text{PF}_6$ as it does not contain ligands that can competitively bind with the metal (Scheme 1).⁹ Sub-stoichiometric amounts of Cu(I) became possible when pyridine was added to the system. Pyridine acts as a competing ligand and prevents the Cu(I) from being sequestered by the macrocycle during the reaction, thereby allowing its use as a catalyst. The rotaxane yield was optimized by varying, the temperature, solvent, ratios of alkyne/azide to Cu(I), as well as the flexibility, size and steric properties of the macrocycle. The nature of the Cu(I) compound used also altered the kinetics of the CuAAC reaction. Thus, pyridine-based ligands facilitate the oxidation of Cu(I) to non-catalytic Cu(II). So, while they initially increase the rate of reaction, they prevent quantitative conversion because the template ion is removed from the system. The addition of a second equivalent of Cu(I) increases the rate of formation of rotaxane, suggesting that the π -activation of the copper unit is dominant; also, it suggests that the reaction involves an intermediate featuring two metal ions. This primary

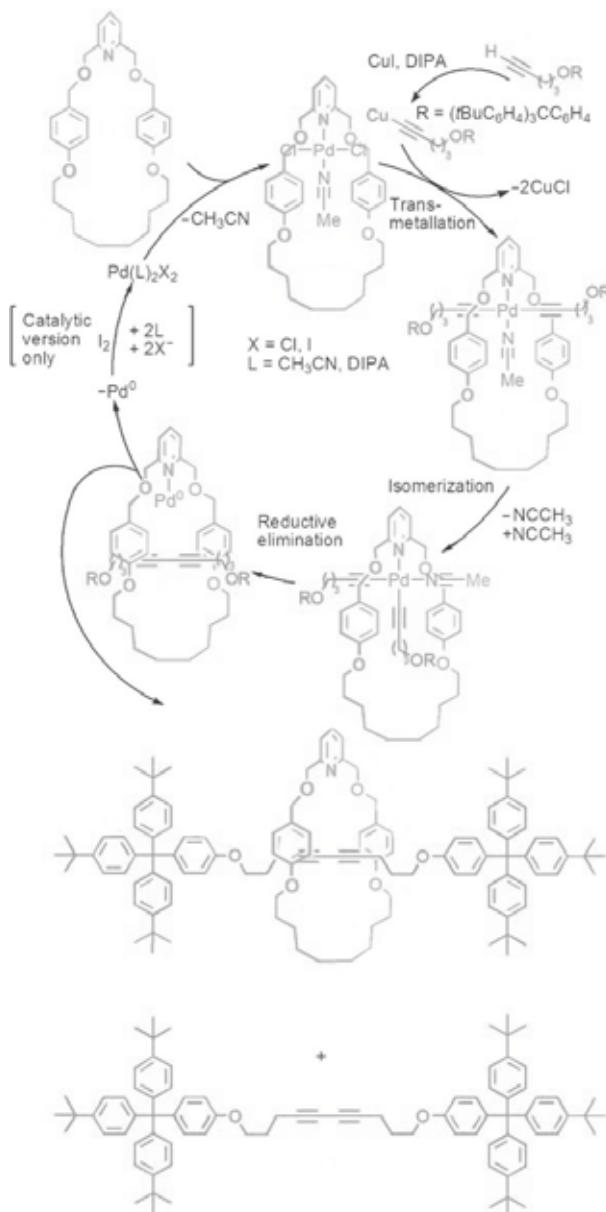
Cu(I) active metal template synthesis has resulted in the development of further rotaxane syntheses using different chemistry, such as Glaser couplings,¹⁰ which couple two alkynes together, and an Ullman biaryl ether condensation by other groups.¹⁰



Scheme 1. CuAAC active metal template synthesis of [2]-rotaxanes.

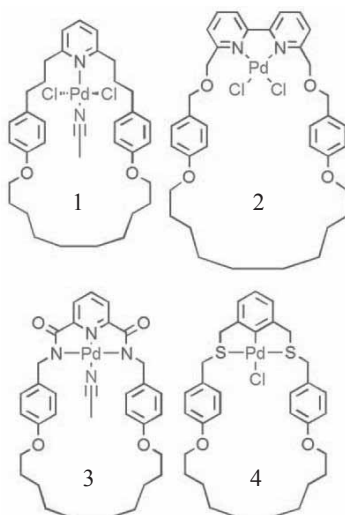
Leigh, however, turned his focus to the use of palladium(II) as a template ion, as processes catalysed by it have led extensively to C-O, C-N, C-S and C-C bond formation. It has proved to be useful in rotaxane synthesis owing to the two-dimensional square planar coordination geometry that gives steric control over the crossover point in the third-dimension: the palladium holds the half-threads in the correct transoid position for an interlocked architecture to form. The homocoupling of half threads carrying terminal alkyne groups was used to form the rotaxane with a monopyridine macrocycle as shown in Scheme 2.¹¹ During the synthesis, Pd(II) is reduced to Pd(0) upon formation of a covalent bond that provides the thread molecule and, thus, the desired rotaxane. In order for the palladium to be catalytic, the Pd(0) must be oxidized back to Pd(II), a process achieved with oxygen and iodine. Optimum product yields were obtained from catalytic quantities

of Pd(II), when the amount of the half thread was increased to three times that of the macrocycle, and the reaction time was increased to 72 hours. Additionally, it was found that catalytic amounts of Pd(II) gave much cleaner conversions and higher yields over use of stoichiometric Pd(II) that is likely to be a result of fewer side reactions. The method was also tested with bidentate and tridentate macrocycles, but the bidentate macrocycles gave lower yields and the tridentate macrocycles no rotaxane at all. This is most likely a result of the cisoid arrangement in which the macrocycles are held by the Pd(II) for transmetallation to occur; it reduces the chance of two alkyne substituents coupling through the macrocycle and forming the rotaxanes (Scheme 3).¹¹



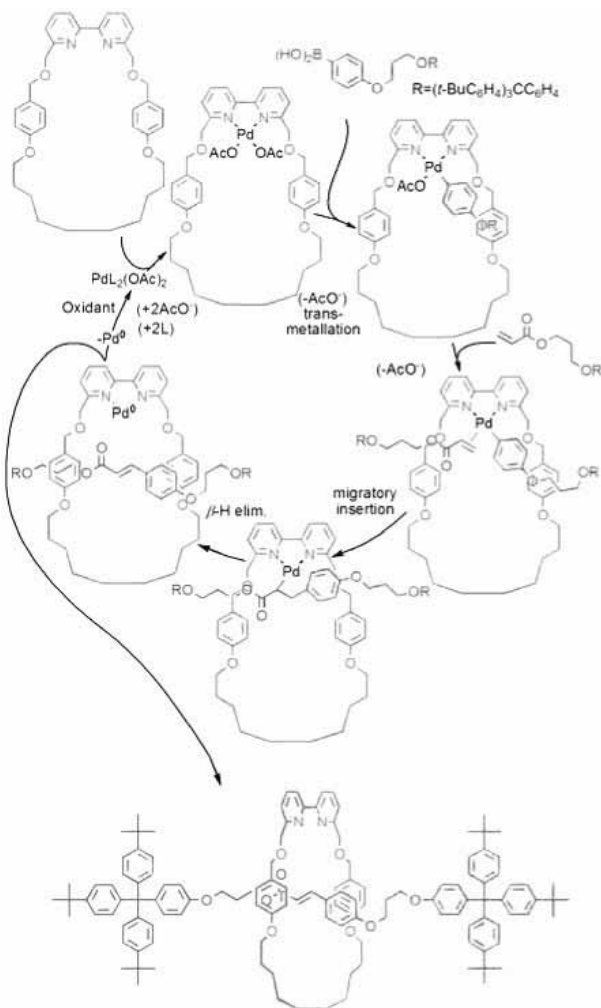
Scheme 2. Palladium(II)-mediated homocoupling of alkynes to form a [2]-rotaxane.

Catalytic quantities of Pd(II) were also used to form a [2]-rotaxane, using oxidative Heck cross-coupling to form the thread of the rotaxane. Here, migratory insertion followed by β -H elimination forms the covalent, and thus mechanical, bonds required. As in the alkyne homocoupling example, Pd(0) needs to be re-oxidized to Pd(II) and is achieved with oxygen and benzoquinone (Scheme



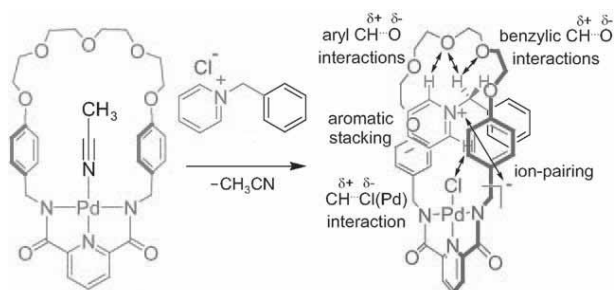
Scheme 3. Coordination geometries of 1: free monodentate, 2: bidentate and 3, 4: tridentate macrocycles to Pd(II).

4).¹² This method has an advantage over the previous ones because the cross-coupling is tolerant of a range of different partners that include vinyl ketones and styrenes as well as the alkenes already shown and, thus, gives rise to a range of rotaxanes with functionalized stoppers. It was also shown that quantitative product yields could be attained with very small amounts of Pd-templating, something that had not been seen previously in the synthesis of small, complex molecules.

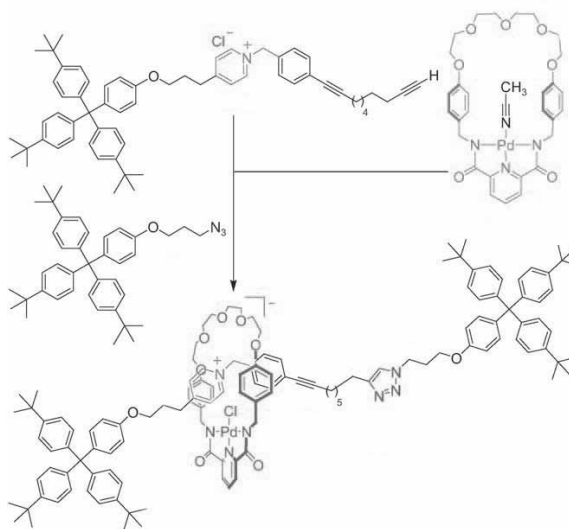


Scheme 4. [2]-Rotaxane synthesis by a Pd(II)-mediated oxidative Heck cross-coupling.

The use of Pd(II) in an ion-pair synthesis has been reported also by Leigh. Here, the Pd(II) does not act as an active template in the same manner as the previous examples. A tridentate macrocycle, which binds Pd(II) endotopically, is used and the remaining coordinative site is occupied by an acetonitrile ligand. This latter ligand is replaced by the chloride ion from benzyl pyridinium chloride in the rotaxane half thread thereby creating a positive charge in the half thread. This is now able to ion pair with the (now) negatively charged Pd(II) complex, thus holding the thread in the correct position for a mechanical bond to be formed. Aromatic π -stacking interactions, and $\text{CH}\cdots\text{O}$ and $\text{CH}\cdots\text{Cl}$ hydrogen bonding between the host and guest molecules also help hold the thread in the correct position. These interactions also stabilize the molecule and enable it to be isolated and characterised (Scheme 5).¹³ As would be expected, these interactions are able to occur only in polar solvents. When the reaction is carried out in DMSO, threading, and thus rotaxane formation, did not occur. CuAAC chemistry was used to connect the two halves of the thread molecule, resulting in a quantitative yield (Scheme 6).¹³ In this rotaxane synthesis, the Pd(II) is used as an anion template, rather than as a metal template; it is the ion-pair interaction between the positively charged thread and negatively charged macrocycle that is the active template component in the synthesis. The presence of charge at a single position of the thread component of the rotaxane invites the possibility for a switchable thread where the macrocycle exhibits positional preference along the thread depending on the conditions of the rotaxane system.



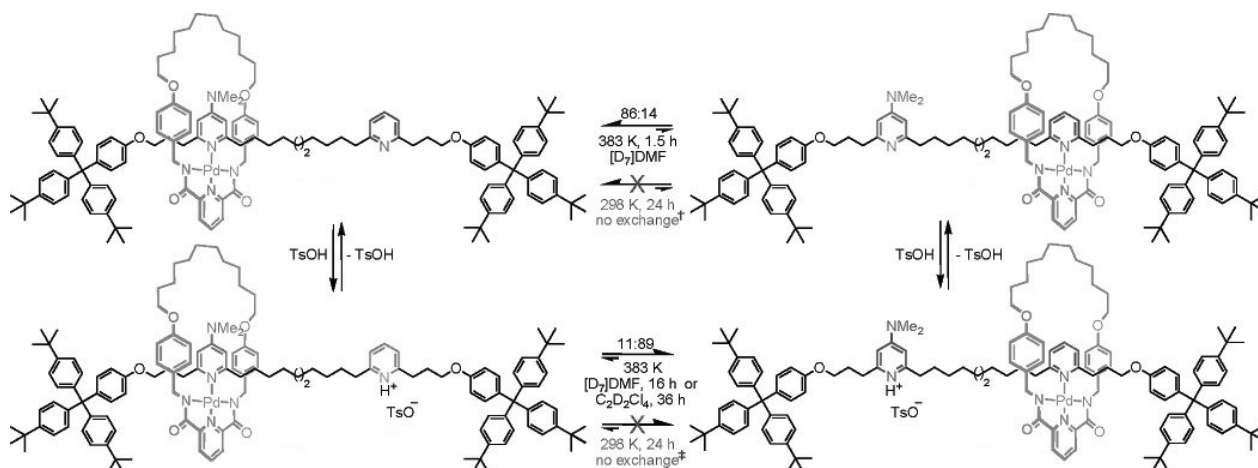
Scheme 5. Synthesis of a pseudorotaxane and the non-covalent interactions present.



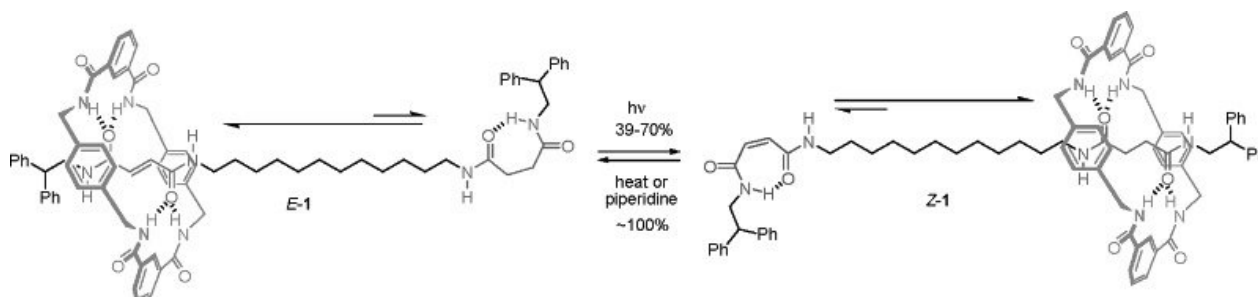
Scheme 6. CuAAC synthesis of a [2]-rotaxane based on an anion template method.

Leigh used the concept of a switchable rotaxane thread in the design of a molecule that has the potential to act as a molecular machine. If two different binding sites (stations) are present on the thread of a rotaxane, the macrocycle, generally, is able to move between the positions under random thermal motion owing to its preference for one over the other. Such rotaxanes are referred to as *molecular shuttles*. The thread of Leigh's rotaxane synthesized using ion-pair interactions contains two such different ligating stations, the other of which is charged (the pyridinium station) and one which is not (the triazole station). When the rotaxane macrocycle is charged, that is, when the chloride ion is bound to the palladium, it prefers to sit over the pyridinium station because of the favourable ion-pair interaction. When AgPF_6 is added, the chloride ion binds to the silver ion, AgCl precipitates, and the macrocycle is uncharged; it moves to be over the neutral triazole station with the PF_6^- acting to balance the charge of the positive pyridinium station. The negative charge can be returned to the macrocycle upon the addition of tetrabutylammonium chloride, which returns the chloride ion to the palladium centre. This molecular shuttle, therefore, demonstrates motion along the rotaxane thread on changes to the macrocycle's charge; this is known as anion switching (Scheme 7)¹³ Although the shuttling is reversible, it cannot be achieved quickly as solvent needs to be added to cause the anion switching and would need to be removed after each step to prevent the system from becoming too large in volume.

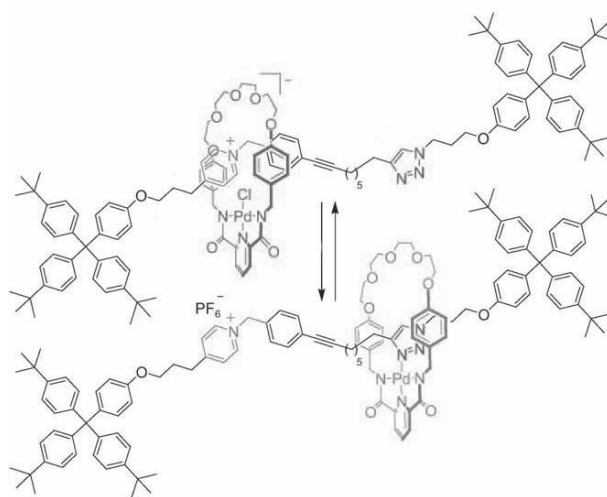
Leigh has also developed a molecular shuttle that uses reversible protonation of the rotaxane stations to drive shuttling of the macrocycle (Scheme 8).¹⁴ The motion of this shuttle is dependent upon variations in the kinetics of binding the palladium to the nitrogen of the two stations.



Scheme 8. Molecular shuttle driven by reversible protonation of the rotaxane stations.



Scheme 9. Molecular shuttle which uses light to induce motion in the rotaxane.



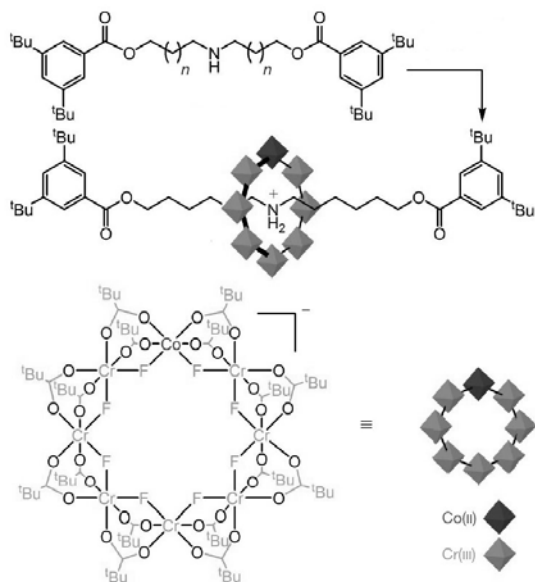
Scheme 7. Molecular shuttle using anion switching to generate motion.

In the case at hand, the macrocycle exhibits a preference for positioning over the more basic dimethylaminopyridine (DMAP). However, this preference is changed when the nitrogen of the group is protonated. Shuttling is driven by preferences in the position of the proton, rather than the palladium differentiating between the two stations, since a N-H bond is much stronger than a N-Pd bond. Therefore, this molecular shuttle could be pH-driven. However, the kinetic stability of the Pd-N bond means that protonation of the stations alone is not sufficient to induce motion; the system must be heated to 100 °C, likely limiting use as a molecular shuttle.

A change in rotaxane thread structure can be induced without the need for a chemical stimulus – light can be used instead. Photoisomerization of the favoured station

can result in a change of the station that the macrocycle prefers. Such isomerisation cannot be undone using light, however, and heat or solvent must be introduced to shuttle the macrocycle back to its original position (Scheme 9).¹⁵ Leigh has shown also that a light stimulus can be used to form a molecular shuttle that has the ability to do work in the macroscopic world. A rotaxane containing two different stations on its thread, one hydrophilic and the other hydrophobic, was deposited as a monolayer on to a gold surface. Upon irradiation, isomerization of the hydrophilic station (the π -bond) occurred, causing the macrocycle to shuttle to the hydrophobic station, thus altering the nature of the surface of the gold film (Fig. 6).¹⁶ This change in surface hydrophilicity can do work by moving a liquid droplet uphill. Thus, a droplet of iodomethane was moved up a gradient of 12° (Fig. 7),¹⁶ although it remains to be seen if this gradient is the maximum at which work can be done. Regardless of this, Leigh envisages that such light-driven molecular machines have the potential to be used as energy storage devices. Alternatively, they could be employed in lab-on-a-chip devices that are being developed for use in medicinal diagnostic testing to control the flow of liquid on a microscopic scale, and enable multiple diagnostic tests on one sample, increasing throughput and lowering costs.

Leigh is also developing rotaxane shuttles as qubits (quantum bits) for quantum computers because of their mechanically linked organic and inorganic componentry (Scheme 10).¹⁷ The inorganic macrocyclic components of such rotaxanes exhibit electronic, magnetic and paramagnetic characteristics as a result of the influence on, and potentially by, the organic portion of the molecule. The rotaxane uses a variety of supramolecular interactions, e.g. hydrogen bonding, ion-pair interactions and metal-to-ligand bonding, to generate motion and cause changes in the physical properties of the metals in the molecule. This is an important development in rotaxane chemistry as it successfully combines inorganic and organic chemistry by mechanical bonds and allows the formation of molecules with composite properties, a concept not previously utilized to any extent.



Scheme 10. A rotaxane with both organic and inorganic sections.

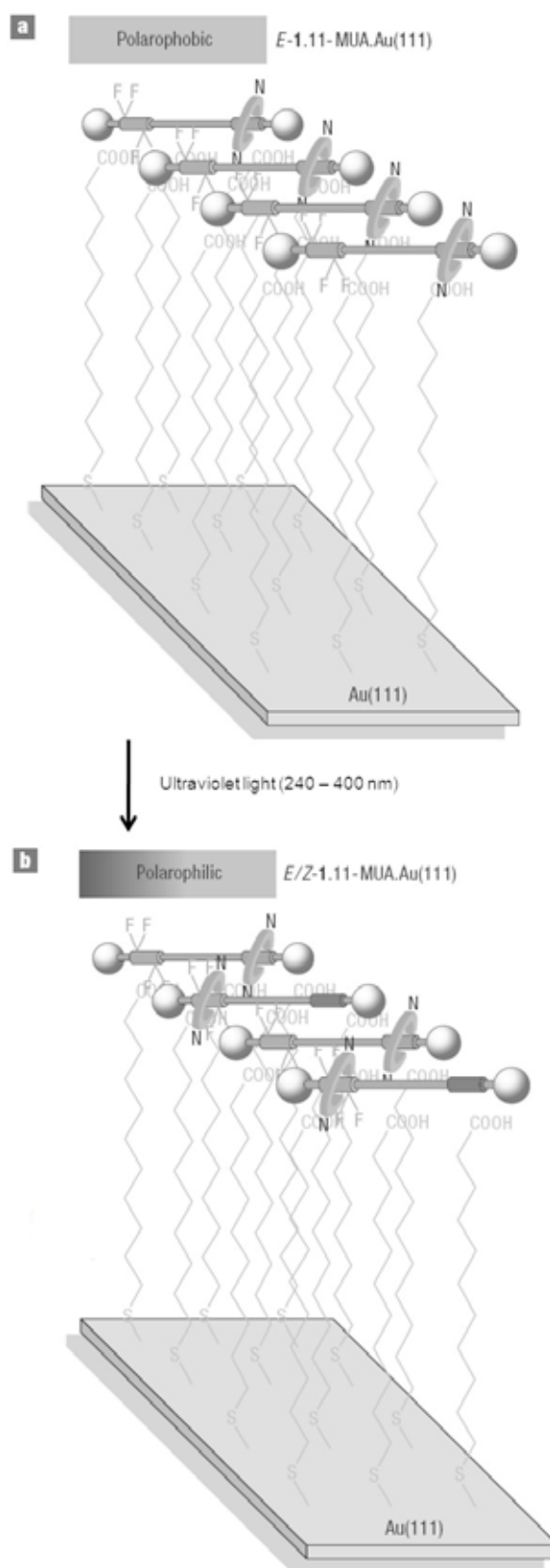


Fig. 6. Photoswitching of surface a. hydrophilicity (polarophilic)/ b. hydrophobicity (polarophobic) of a rotaxane macrocycle. Copyright Nature Publishing Group and reproduced with permission from *Nature Materials* - see ref.16.

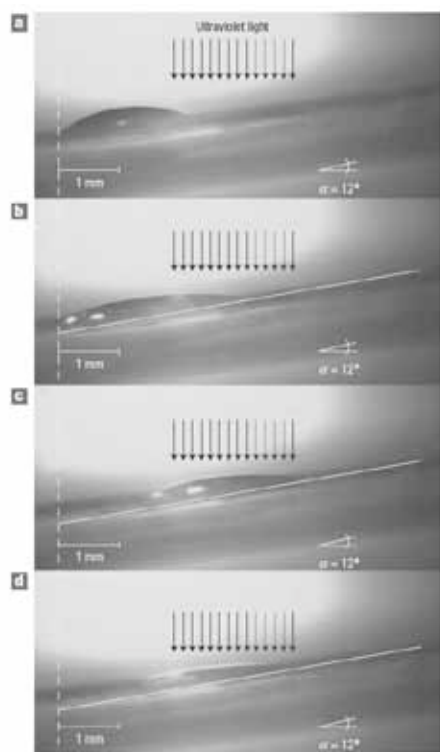


Fig. 7. Movement of a droplet of iodomethane up a gradient of 12° . Copyright Nature Publishing Group and reproduced with permission from *Nature Materials* - see ref.16.

The development of alternative active metal template methods to the original *passive* template methods by Professor David Leigh has been an important step in the synthesis of rotaxanes. The dual functionality of the metal ion in directing covalent bond formation, and catalysing the formation of a rotaxane, allows efficient synthesis with the possibility of synthesizing otherwise inaccessible rotaxane architectures. This success results from combining supramolecular chemistry and non-covalent interactions.

The increased efficiency has allowed Leigh to focus on applications of these rotaxanes as molecular shuttles and the design of such molecular motors with potential in, amongst others, medicine and technology.

References

1. IUPAC. *Compendium of Chemical Terminology*, 2nd ed. (the *Gold Book*). Blackwell Scientific Publications, Oxford (1997).
2. *Molecular Recognition & Self-Assembly* –see: <http://publish.uwo.ca/~jwisner/research.htm> (accessed 17 May 2009).
3. *Primer: Irreducible Complexity in a Nutshell* - see <http://www.ideacenter.org/contentmgr/showdetails.php/id/1142> (accessed 17 May 2009).
4. Berg, H. C. *Ann. Rev. Biochem.* **2003**, *72*, 19-54.
5. Argiriadi, M. A.; Goedken, E. R.; Bruck, I.; O'Donnell, M.; Kuriyan, J. *Struct. Biol.* **2006**, *6*(2), no pp given.
6. Aricó, F.; Badjic, J. D.; Cantrill, S. J.; Flood, A. *et al. Top. Cur. Chem.* **2005**, *249*, 203–259.
7. Aucagne, V.; Berná, J.; Crowley, J. D.; Goldup, S. M., *et al. J. Am. Chem. Soc.* **2007**, *129*, 11950-11963.
8. Tornøe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057-3064.
9. Aucagne, V.; Hänni, K. D.; Leigh, D. A.; Lusby, P. J.; Walker, D. B. *J. Am. Chem. Soc.* **2006**, *128*, 2186-2187.
10. Saito, S.; Takahashi, E.; Nakazono, K. *Organic Lett.* **2006**, *8*, 5133-5136.
11. Berná, J.; Crowley, J. D.; Goldup, S. M.; Hänni, K. D., *et al. Angew. Chem. Int. Ed.* **2007**, *46*, 5709-5713.
12. Crowley, J. D.; Hänni, K. D.; Lee, A.-L.; Leigh, D. A. *J. Am. Chem. Soc.* **2007**, *129*, 12092-12093.
13. Barrell, M. J.; Leigh, D. A.; Lusby, P. J.; Slawin, A. M. Z. *Angew. Chem. Int. Ed.* **2008**, *47*, 8036-8039.
14. Crowley, J. D.; Leigh, D. A.; Lusby, P. J.; McBurney, R. T., *et al. J. Am. Chem. Soc.* **2007**, *129*, 15085-15090.
15. Chatterjee, M. N.; Kay, E. R.; Leigh, D. A. *J. Am. Chem. Soc.* **2006**, *128*, 4058-4073.
16. Berná, J.; Leigh, D. A.; Lubomska, M.; Mendoza, S. M., *et al. Nature Materials*, **2005**, *4*, 704-710.
17. Lee, C.-F.; Leigh, D. A.; Pritchard, R. G.; Schultz, D., *et al. Nature*, **2009**, *458*, 314-318.