MINIREVIEW

Recent Advances in the Synthesis and Application of Hydrogen Bond Templated Rotaxanes and Catenanes

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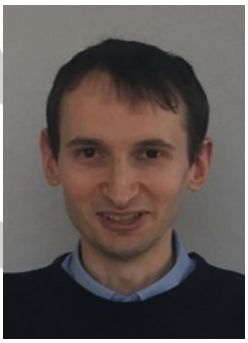
Abstract: Alongside the use of metal cations and π-π stacking, hydrogen bonding is one of the major templating interactions used to prepare rotaxanes and catenanes. In this review, a brief summary of key historical milestones will be followed by discussion of developments from over the last decade in both synthetic methodology and application of hydrogen bond templated interlocked molecules. Hydrogen bond templation can allow for rapid access to interlocked molecules in high yields, with select examples having been put to useful purpose, in applications such as organocatalysis and cellular imaging.

1. Introduction

Rotaxanes[1] (macrocyclic ring(s) trapped on a stoppered axle, Figure 1a), and catenanes[2] (interlocked macrocyclic rings, Figure 1b) represent the two principal classes of interlocked molecules. Such molecules are most well known for their potential to act as components of molecular machines due to the possibility of large amplitude motion of their interlocked components.[3] Furthermore, a range of useful functions of interlocked molecules have been demonstrated,[4] including their use in catalysis[5] and as hosts for ionic and molecular guests.[6]



Nick Evans graduated from Wadham College, University of Oxford with a First Class Masters in Chemistry (2006), before obtaining a DPhil in Inorganic Chemistry (2011), having worked on anion sensing rotaxanes and catenanes in the group of Prof Paul Beer. After undertaking postdoctoral research on luminescent lanthanide complexes with Prof David Parker at Durham University, he became a lecturer at the newly re-opened Department of Chemistry at Lancaster University in 2013. His current research interests are in the area of functional supramolecular chemistry, seeking to exploit hydrogen bond templated rotaxanes and catenanes in useful applications.

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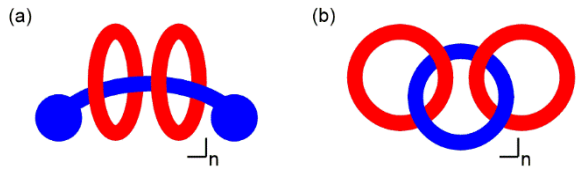


Figure 1. Schematic representations of: a) [n+2]rotaxane and b) [n + 2]catenanes.

The vast majority of such molecules have been and are still prepared by template synthesis.[7] The use of metal cations[8] and π-π stacking[9] to prepare interlocked molecules was first established by the groups of the Nobel laureates, Sauvage[10] and Stoddart[11] in the 1980s. The potential for hydrogen bonding to template the formation of catenanes was discovered soon after by Hunter,[12] Vögtle[13] and Leigh.[14]

This review will discuss recent progress in both the synthesis and application of hydrogen bond templated rotaxanes and catenanes. The focus will be on examples reported in the last decade or so, but to help the non-expert, the article will begin with a brief summary of key historical breakthroughs, dating back to the early nineties.[15] Following this, attention will turn to how some of these well-established synthetic methods have been used to generated interlocked molecules for new applications. Then development of methodologies based on alternative hydrogen bond donor/acceptor arrangements, and their exploitation, will be reviewed.

As a short review, this article cannot be exhaustive, and so a fair degree of selection from amongst the published literature has been necessary. In particular, it has been decided that discussion should be focused on interlocked molecules where the hydrogen bond templated synthesis relies on components that are overall electrostatically neutral, i.e. do not require a discrete counter-ion. Hence examples of ammonium-crown ether[16] and anion[17] templated interlocked molecules are not discussed.

2. Key Early Examples of Hydrogen Bond Templated Rotaxanes and Catenanes

When attempting to prepare a bis-isophthalamide macrocycle by reaction of isophthalamide containing bis-amine **1** and isophthaloyl dichloride under high dilution conditions, Hunter isolated [2]catenane **2** in a respectable 34% yield (Figure 2).[12] In his first report, the interlocked structure of **2** was established by means of NMR experiments, but was subsequently confirmed by single crystal X-ray structure determination.[18] Hunter proposed that catenane **2** arises from the association of an isophthaloyl unit

through a cyclized macrocyclic cavity, templated by a combination of hydrogen bonding and π-π interactions, that are not inhibited by the use of a relatively non-competitive solvent (dichloromethane). In solution, the motion of the interlocked rings of **2** is restricted by the presence of the bulky cyclohexyl groups, meaning that only a limited 90° rocking motion of the internal isophthalamide groups through the macrocyclic cavities is possible.

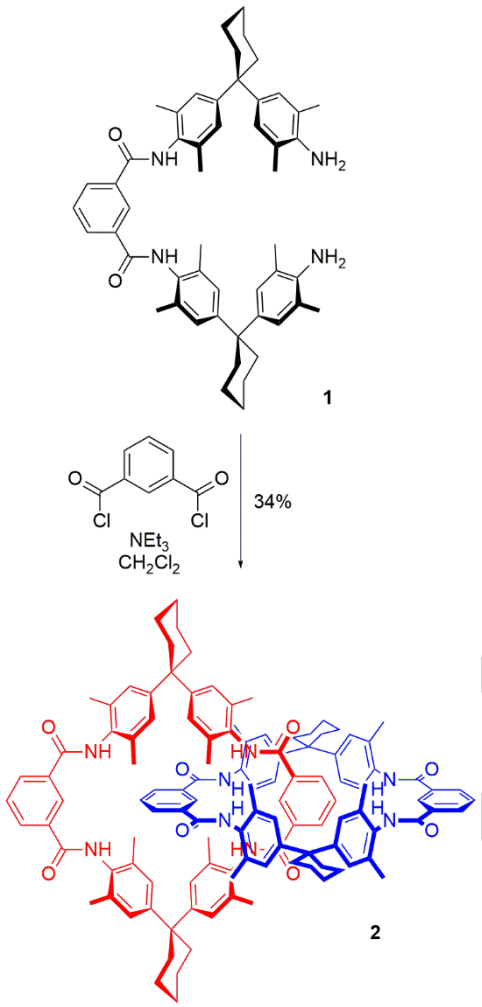


Figure 2. Hunter's seminal synthesis of [2]catenane **2**.

Immediately following Hunter's paper, Vögtle and co-workers reported upon their isolation of analogous [2]catenane **4** (Figure 3).[13] Reacting bis-amine **3** with methoxyisophthaloyl dichloride under high dilution conditions in chlorobenzene led to formation of catenane **4** in a significantly lower yield of 8%, that may be attributed (in part at least) to the higher number of components that come together during the cyclization steps.

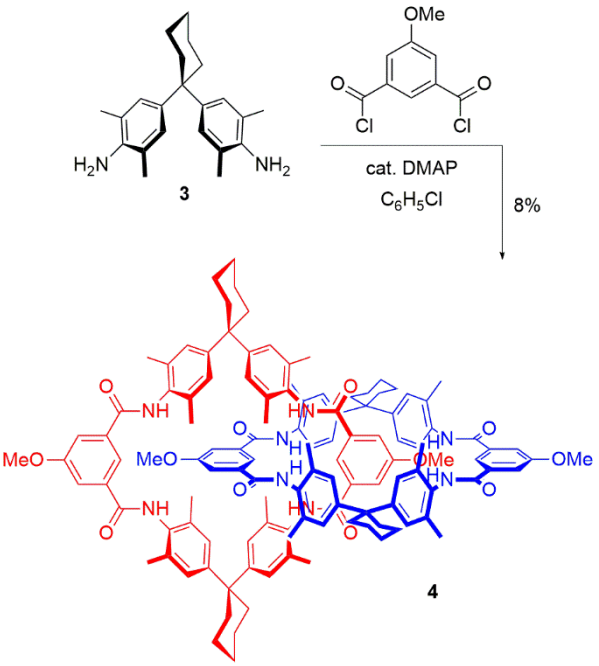


Figure 3. Vögtle's synthesis of [2]catenane **4**.

Shortly after these reports, Leigh and co-workers serendipitously prepared [2]catenane **5** (Figure 4).[14] Simply reacting *p*-xylenediamine and isophthaloyl dichloride led to the catenane **5** in 20% yield. In this case, the rings of the catenane are able to pirouette with respect to one another in solution.

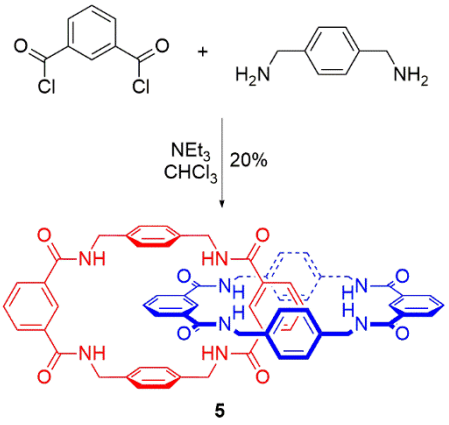


Figure 4. Leigh's synthesis of [2]catenane **5**.

For Vögtle and Leigh these discoveries proved to be the starting points for sustained research programmes focused on interlocked molecules. For example, Vögtle and co-workers soon demonstrated the possibility of preparing hydrogen bond templated [2]rotaxanes by reacting aromatic diacid chlorides threaded through a bis-isophthalamide macrocycle **6** with 4-tritylaniline (Figure 5).[19] While the yield using isophthaloyl dichloride to generate a rotaxane was modest (11%), a yield of 41% was achieved when using 4-(chlorosulfonyl)benzoyl chloride to prepare rotaxane **7**.[20]

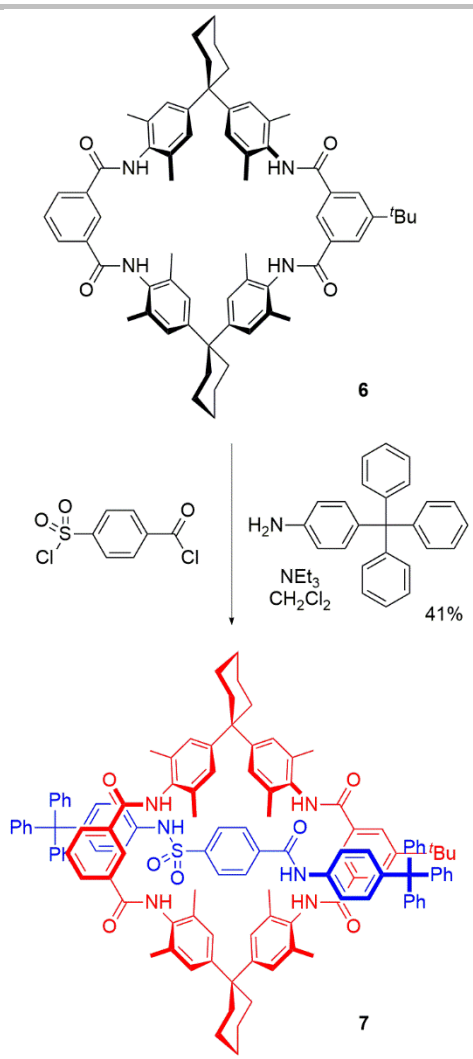


Figure 5. Example of Vögtle's [2]rotaxane synthesis.

While Leigh's group did prepare further examples of catenanes,[21-23] arguably their most influential work from this time arose from investigations into the synthesis of rotaxanes, by reacting *p*-xylenediamine and isophthaloyl dichloride in the presence of appropriate axle components in chloroform (or chloroform majority solvent systems). This was demonstrated first using an isophthalamide axle (28% yield, using 5 equivalents of bis-amine and acid chloride),[24] then a glycylglycine axle (62% yield, using 5 equivalents of bis-amine and acid chloride)[25] and most famously fumaramide axle **8** to generate rotaxane **9** in a very impressive 97% yield (using 4 equivalents of bis-amine and acid chloride, Figure 6).[26] Evidently, the fumaramide functional group appears to be particularly well suited for rotaxane synthesis, with the key carbonyl oxygens being held in appropriate positions to accept hydrogen bonds from N-H groups of the cyclizing macrocyclic component, due in part to the preorganized geometry enforced by the *E* alkene.

Building upon this work, and understanding that different hydrogen bonding motifs on the axle could allow for positional discrimination, a range of rotaxane switches were prepared that could be switched by, for example, light/heat,[27] electrochemical[28] and anion[29] stimuli. To exemplify, the operation of one such switch

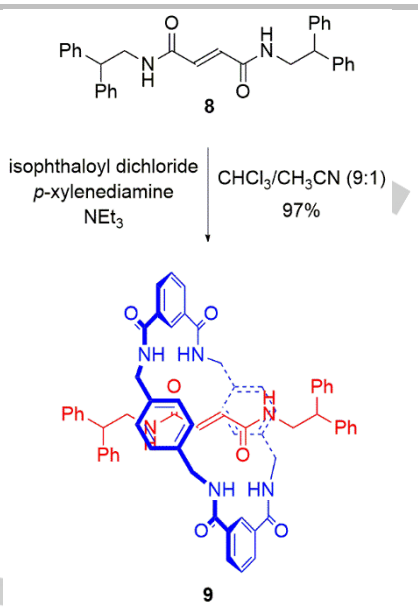


Figure 6. Leigh's synthesis of a fumaramide-containing axle [2]rotaxane **9**.

10 (in chlorinated solvent) is illustrated in Figure 7.[30] When the alkene possesses *E* geometric isomerism (i.e. fumamaride), the macrocycle will reside at this station, rather than the alternative glycylglycine station, as stronger hydrogen bonds can form between the macrocyclic and axle components. Photoisomerism of the C=C bond to *Z* (i.e. to form a maleamide), creates a strong intra-component hydrogen bond, and so disrupts the inter-

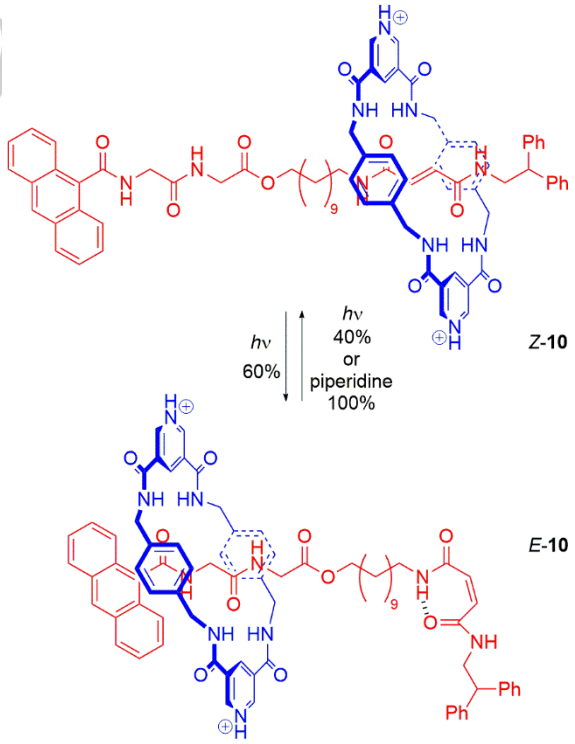


Figure 7. An early example of a Leigh light-operated [2]rotaxane molecular switch.

component hydrogen bonding. As a consequence, stronger inter-component hydrogen bonding will be possible between the macrocycle and axle if the ring resides at the glycylglycine station, and so shuttling occurs. The positively charged bis-pyridinium macrocycle then quenches the fluorescence of the anthracene stopper, that may be detected spectroscopically. This process may be reversed by photoisomerism (or addition of piperidine), thus isomerizing the C=C bond back to the *E* isomer, inducing the macrocycle to shuttle back to the restored fumamaride station, and hence leading to restoration of anthracene fluorescence.

This work on switches was subsequently extended to produce impressive demonstrations of directional rotation in catenane systems.[31,32] For example, as depicted in Figure 8, isomerization of the alkene (*succ-Z*-**11** to *succ-E-11*) generates a fumaramide station that has higher affinity for the macrocycle than the succinimide station. By removal of either of the trityl or silyl blocking groups, then the macrocycle may translate to the fumaramide station, with re-installation of the relevant blocking group generating *fum-E*-**11**. Isomerization of double bond (*mal-Z*-**11**), means that when the other blocking group is removed the macrocycle may then return to the succinimide station (which after the blocking group is restored) re-generates *succ-Z*-**11**.

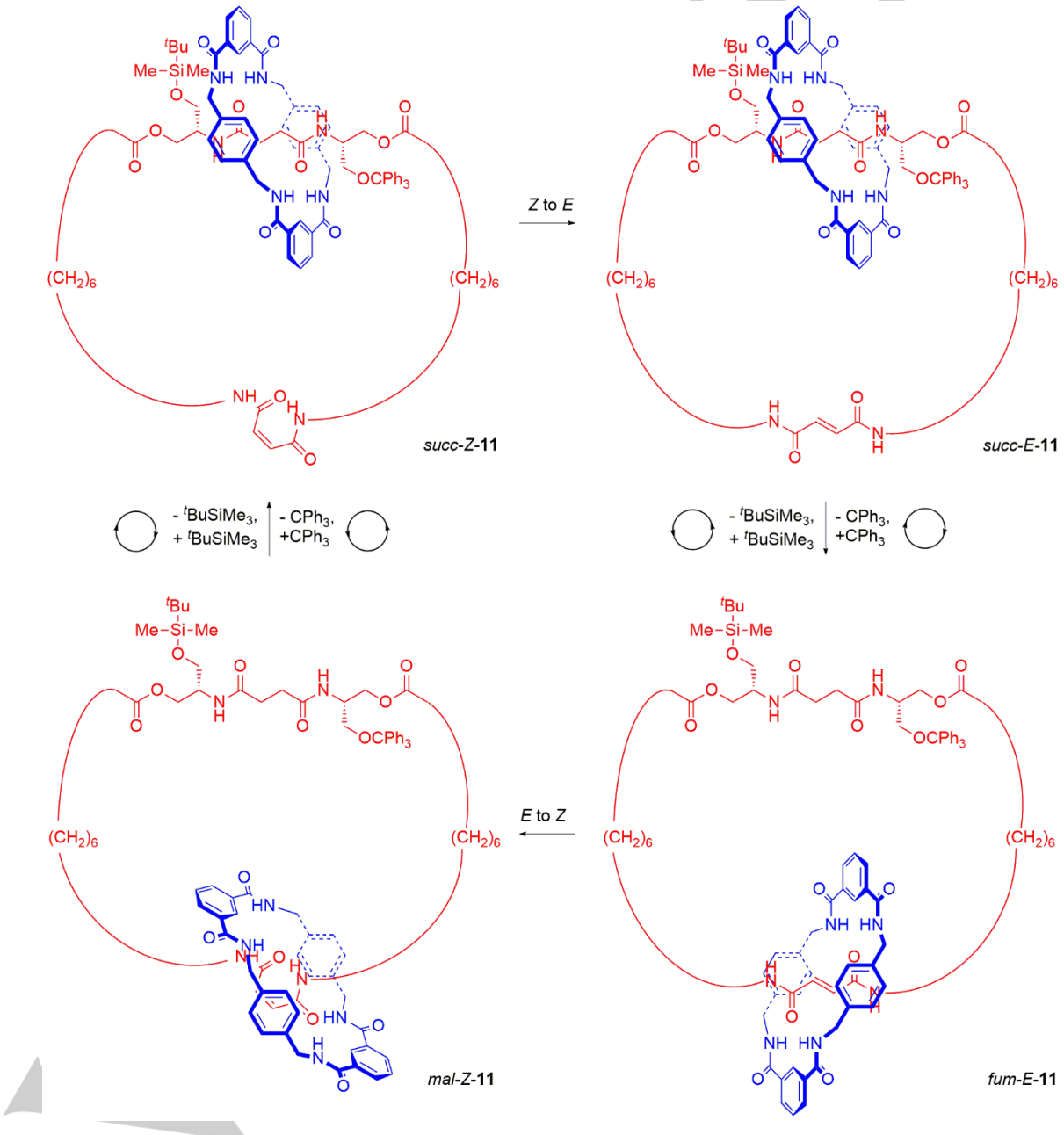


Figure 8. Leigh's reversible rotary molecular motor **11**.

3. Progress in Hydrogen Bond Templated Rotaxanes and Catenanes

3.1. Further application of "Leigh-style" benzylic amide macrocycles with fumaramide and related threading motifs

Rotaxanes incorporating "Leigh-style" benzylic amide macrocycles templated using fumaramide (and other established) hydrogen bond acceptor motifs have continued to be prepared for a wide variety of purposes. For example, looking to build towards the construction of so-called "molecular boxes", Simpkins and co-workers reported on the preparation of three fumaramide [3]rotaxanes (Figure 9).[33] Despite using 24 equivalents of *p*-xylenediamine and isophthaloyl dichloride, yields of rotaxanes **15** and **16** were low (8% and 17%) when using axles **12** and **13** possessing NBn_2 stoppers. However, switching to N(Ph)Bn stoppers on axle **14**, allowed for production of [3]rotaxane **17** in 40% yield. Interestingly, attempts to reduce the macrocyclic amides of **17** using $BH_3{\cdot}SMe_2$ complex led to disassembly of the interlocked structure.

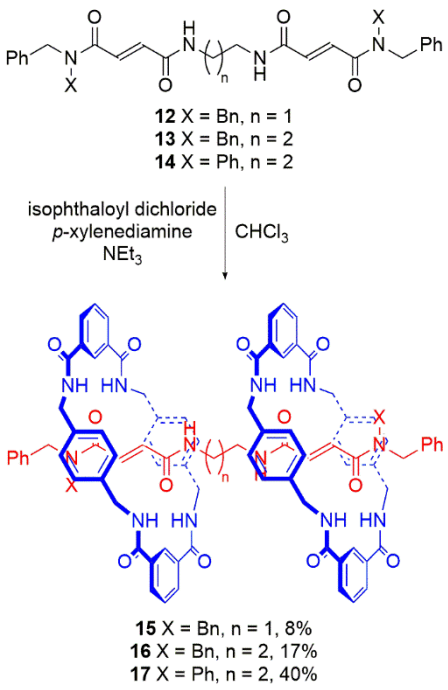


Figure 9. Simpkins' synthesis of fumaramide [3]rotaxanes **15**-**17**.

Leigh, in collaboration with Aucagne and Papot, has constructed a [2]rotaxane-based propeptide **18** (Figure 10).[34] A simple glycylglycine axle motif was used to synthesize an interlocked rotaxane, that possessed a bulky nitrophenol ester stopper group to allow for subsequent extension of the axle to incorporate a pentapeptide sequence with bulky side-chain substituents at the C terminus to prevent dethreading of the macrocyclic component. As part of **18, t**he pentapeptide is stable towards enzymatic degradation, due to the steric protection of the threaded macrocycle. Release of the free peptide sequence **19** was achieved by cleavage of a carbohydrate stopper by a glycosidase enzyme (see Figure 10). A second generation of rotaxane was subsequently reported with ethylene glycol chains to improve aqueous solubility.[35]

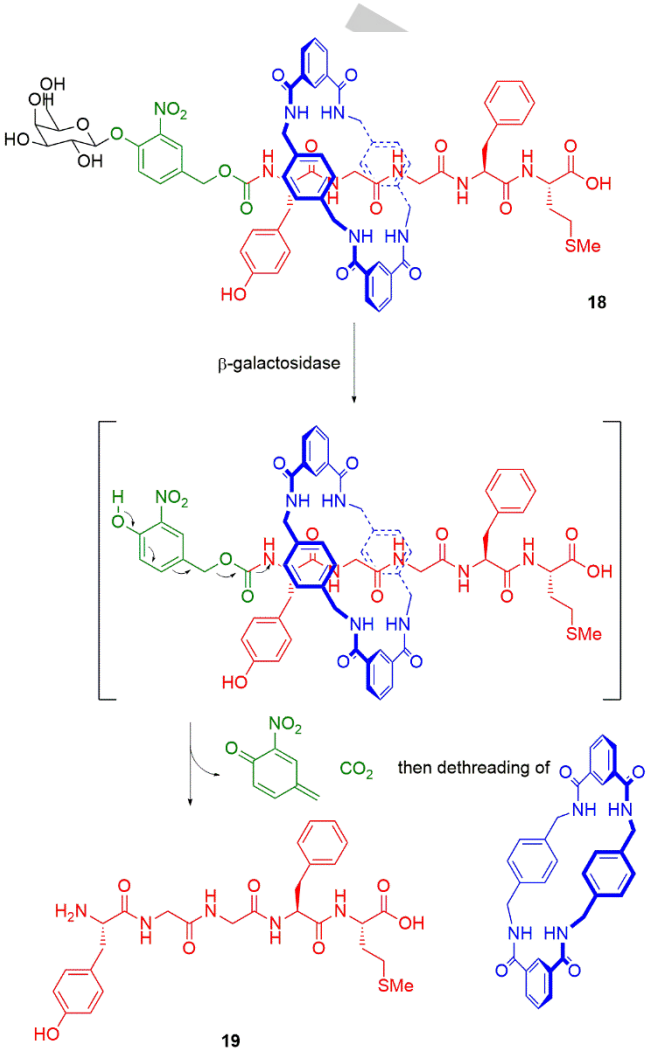
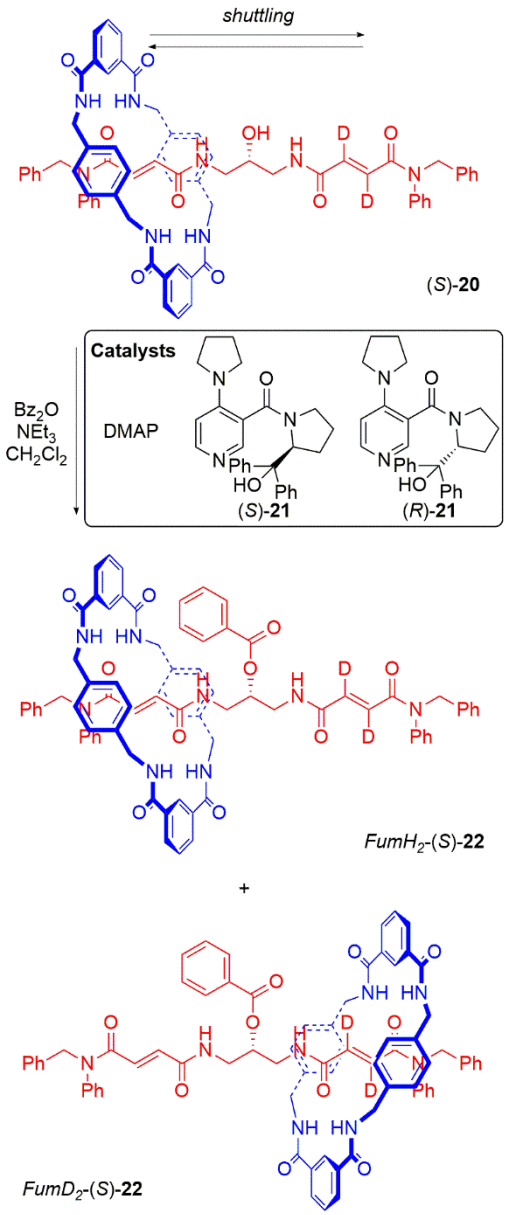


Figure 10. Structure of propeptide [2]rotaxane **18** and the mechanism of degradation to release pentapeptide sequence **19**.

The simple positional changes of the components of a molecular switch are insufficient for directional transport to occur progressively or work to be done cumulatively. A molecular motor requires a ratchet mechanism that prevents the work that is done in one step being undone as the molecule is reset. Leigh and co-workers have prepared rotaxanes that can act as chemically driven molecular information rachets.[36, 37] An example is depicted in Figure 11, where position of the macrocycle is used to affect the rate at which the a group is added between two stations on the axle.[36] Acylation of the alcohol on the axle of [2]rotaxane (*S*)-**20** in the presence of achiral catalyst DMAP leads to a 50:50 mixture of *FumH*$_2$-(*S*)-**22** and *FumD*$_2$-(*S*)-**22**. However, the equivalent acylation using chiral catalyst (*S*)-**21** or (*R*)-**21** leads to 33:67 *FumH*$_2$-(*S*)-**22**/*FumD*$_2$-(*S*)-**22** and 67:33 *FumH*$_2$-(*S*)-**22**/*FumD*$_2$-(*S*)-**22** respectively. This implies that the chiral catalyst is able to discriminate (to a limited extent) between the two pseudo-enantiomeric co-conformers of (*S*)-**20**. Hence, a ratchet mechanism has been demonstrated as the macrocycle distribution has been driven away from its equilibrium position.

Using very similar principles, this concept was also applied to a rotaxane with non-identical stations[36] and to an example of a three-compartment information ratchet, where the axle consists of two end compartments (that are identical aside from isotopic labelling) separated by a third central compartment.[37]



Catalyst	Ratio of *FumH*$_2$-(*S*)-**22**/ *FumD*$_2$-(*S*)-**22**
DMAP	50:50
(*S*)-**21**	33:67
(*R*)-**21**	67:33

Figure 11 An example of a chemically-driven molecular information ratchet.

A very impressive autonomous catenane-based small-molecule motor has subsequently been developed (Figure 12).[38] In [2]catenane **23** a smaller macrocyclic ring may directionally rotate around the larger ring. Critical to achieving this phenomenon is that the rate of attachment of bulky 9-fluorenylmethoxycarbonyl (Fmoc) groups to catenane **24** is faster when the macrocycle is far from the reactive site than when it is near (when using bulky-pyridine-based catalyst (*R*)-**25** and Fmoc-Cl as a fuel) while the rate of detachment of the Fmoc from catenane **23** is independent of macrocycle position.

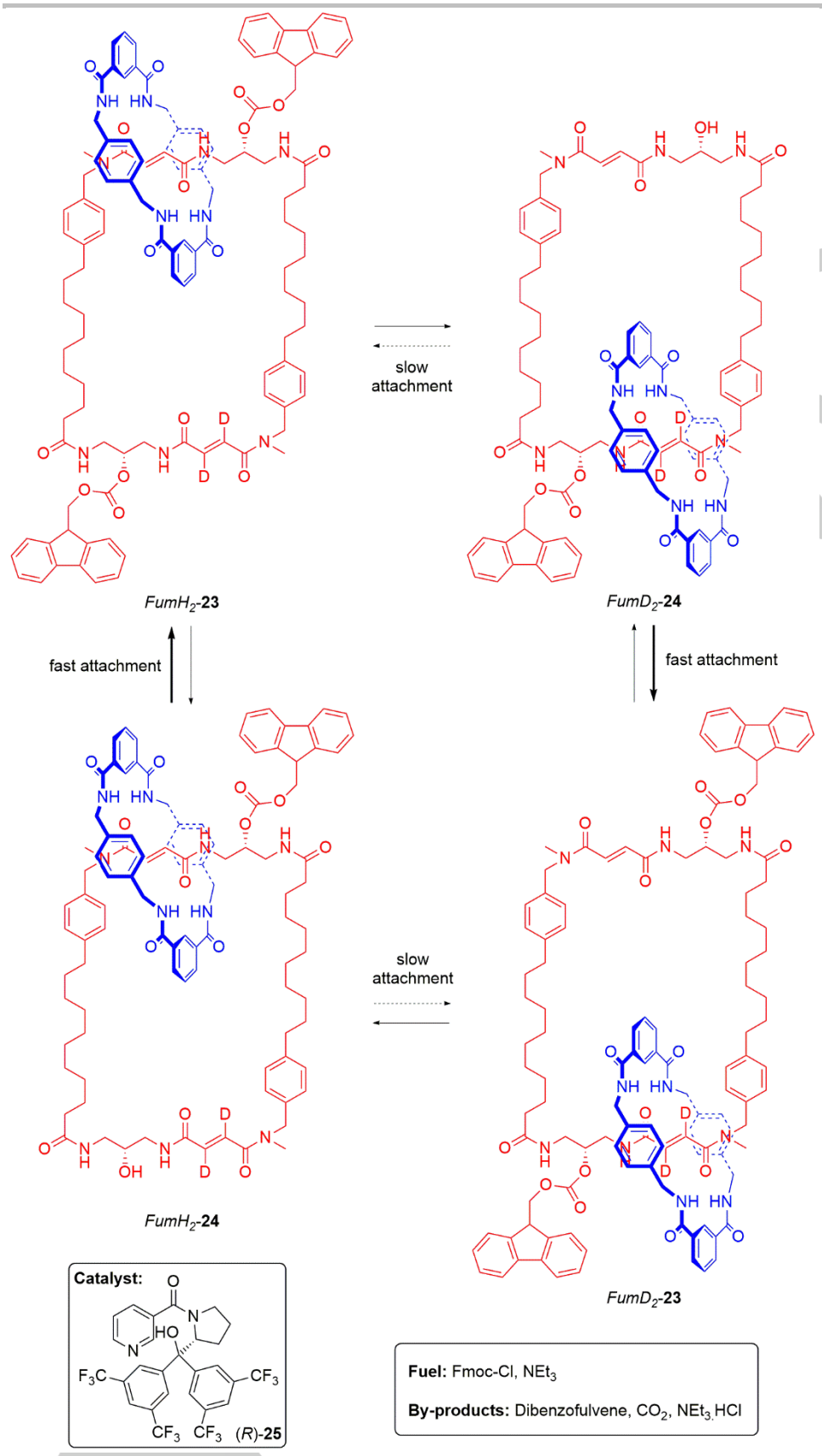


Figure 12 Illustrating the operation of Leigh's chemically-fuelled catenane molecular rotary motor (rotating clockwise as depicted).

A demonstration of how the 3D structures of interlocked molecules can possess interesting properties for asymmetric catalysis is provided by mechanically point-chiral rotaxane (*S*)-**28** (Figure 13).[39] [2]Rotaxane (*S*)-**28** was prepared by first clipping shut of a "Leigh-style" benzylic amide macrocycle around a (chiral) succinamide axle (*R*)-**26** to give [2]rotaxane (*R*)-**27** (in 33% yield using 10 equivalents of *p*-xylenediamine and isophthaloyl dichloride). (*R*)-**27** was then, via a short synthetic sequence, adapted to generate (*S*)-**28** that includes a second succinamide motif in the axle. The chirality of (*S*)-**28** arises from the bulky group at the centre of the axle preventing the macrocycle shuttling between the two succinamide stations. The secondary amine on the axle of (*S*)-**28** may participate in Michael addition and enamine reactions. Modest enantiomeric ratios of products were obtained (the 71:29 *er* for the reaction of **29** and **30** to give **31** was the best reported), reflecting the fact that rotaxane (*S*)-**28** had only been prepared in 84% *ee*. Critically, enantiomeric ratios of 50:50 were observed for products of all reactions where the achiral axle component of (*S*)-**28** was used instead of (*S*)-**28** itself.

Recently, Berna and co-workers have discovered that an interlocked *N*-benzylfumaramide will cyclize to form a β-lactam, in high yields by use of Cs_2CO_3 or CsOH in DMF (as exemplified for fumaramide [2]rotaxane **32** in Figure 14a).[40] Furthermore, this cyclization process proves to be highly regio- and diastereoselective, in contrast to cyclization of the non-interlocked fumaramide. If sufficiently small functionality is used at the termini of the axle, non-interlocked β-lactams may be isolated through thermally induced slippage of the kinetically stable pseudorotaxanes. In a subsequent paper, the same group established a route to the enantioselective formation of β-lactams by use of *N*-(α-methyl)benzyl fumaramides (Figure 14b).[41]

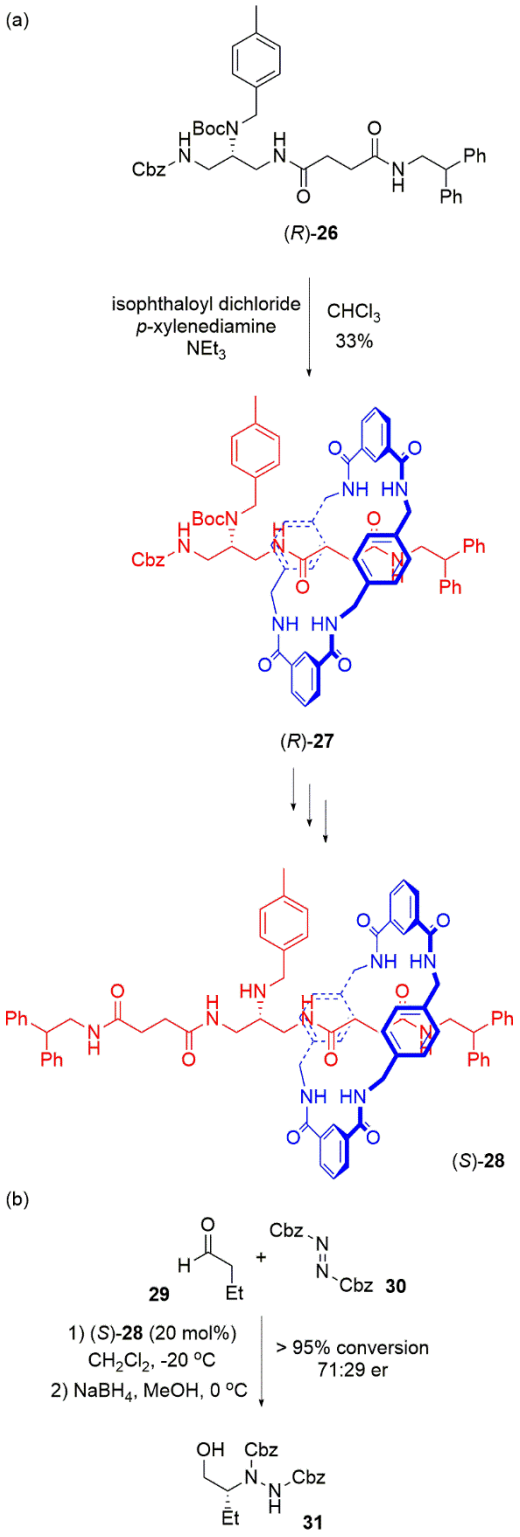


Figure 13 Mechanically point-chiral [2]rotaxane (*S*)-**28** for asymmetric catalysis: (a) synthesis of [2]rotaxane (*S*)-**28**, (b) example of asymmetric catalyzed reaction using (*S*)-**28**.

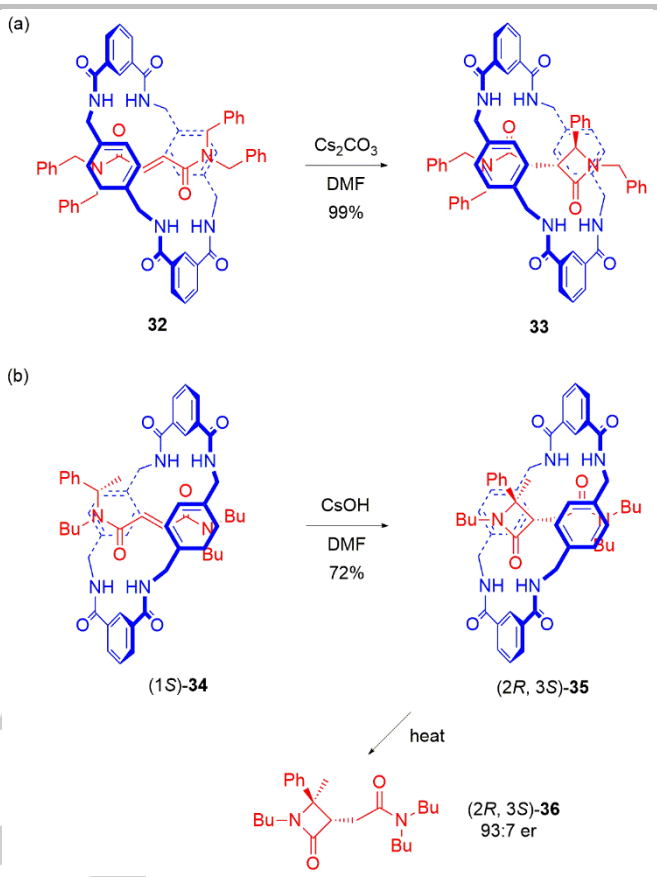


Figure 14 Berna's controlled synthesis of β-lactams using fumaramide [2]rotaxanes: (a) cyclization of fumaramide [2]rotaxane **32**, (b) enantioselective formation of β-lactam **36**.

3.2. New hydrogen bond accepting motifs for rotaxanes and catenanes with "Leigh-style" benzylic amide macrocycles

Considerable work has been undertaken in the last decade, upon alternative hydrogen bond acceptor motifs for rotaxanes using "Leigh-style" benzylic amide macrocycles. In fact, Leigh's group disclosed the existence of bis-nitrone [2]rotaxane **38** in 2000.[42] In a subsequent paper, they disclosed its preparation in a yield of 70% using 6.0 equivalents of isophthaloyl dichloride and 6.6 eq of *p*-xylenediamine to cyclize a macrocycle around bis-nitrone axle **37** (Figure 15).[43] By encapsulating the nitrone groups within in a rotaxane structure leads to some intriguing redox behaviour. While the nitrones are not reducible using $NaBH_4$ (unlike those in the free axle **37**), the bis-nitrone of **38** is activated towards one electron electrochemical reduction.

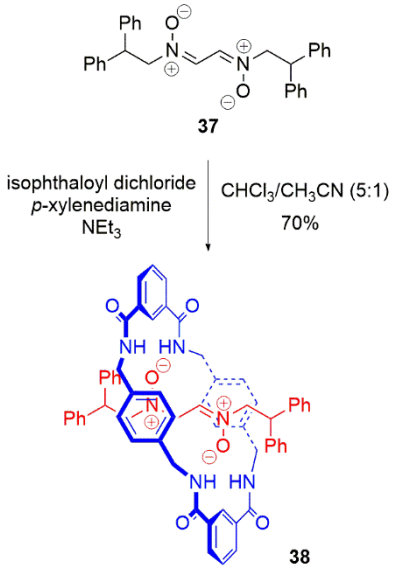


Figure 15 Synthesis of bis-nitrone [2]rotaxane **38**.

Subsequently, investigations turned to axles containing phosphorus and sulfur functional groups.[44, 45] With phosphorus systems, the highest yield of rotaxane formation (60% for **40**, with five-fold excesses of isophthaloyl dichloride and *p*-xylenediamine) was observed with phosphinamide axle **39** (Figure 16).[44]

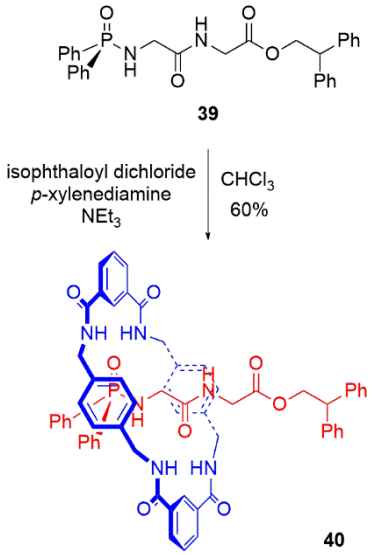


Figure 16 Synthesis of phosphinamide [2]rotaxane **40**.

In a systematic study of sulfur containing rotaxanes, sulfoxide [2]rotaxane **45** was isolated in much greater yield (using five-fold excesses of isophthaloyl dichloride and *p*-xylenediamine) than either of its sulfide and sulfone analogues. This result correlates to the ability of the tested functional groups to act as hydrogen bond acceptors for the forming macrocyclic component (Figure 17).[45] Furthermore, a more rigid vinyl sulfoxide motif in the axle allowed for isolation of a [2]rotaxane in 63% yield.[45]

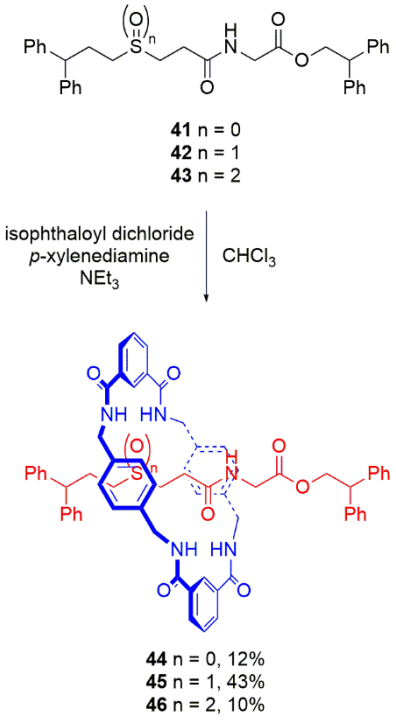


Figure 17 Synthesis of sulfur containing [2]rotaxanes **44**-**46**.

The variation in ability of the different sulfur functional groups to act as hydrogen bond acceptors was then used to prepare a molecular shuttle by using a set of sulfur-succinimide rotaxanes (Figure 18).[45] Sulfide rotaxane **47** was prepared by cyclizing the classic benzylic amide macrocycle around the succinimide functional group. Controlled oxidation using 1 equivalent of *m*CPBA generated sulfoxide rotaxane **48**, which led to translation of the macrocycle to the sulfur containing station. Further *m*CPBA generates sulfone rotaxane **49**. To return to the sulfide rotaxane **47** (from either **48** or **49**), the authors used thiolate $Ph_2CHCH_2CH_2SNa$ to achieve a Michael-retro-Michael substitution at the β-carbon, as reducing agents proved capricious.

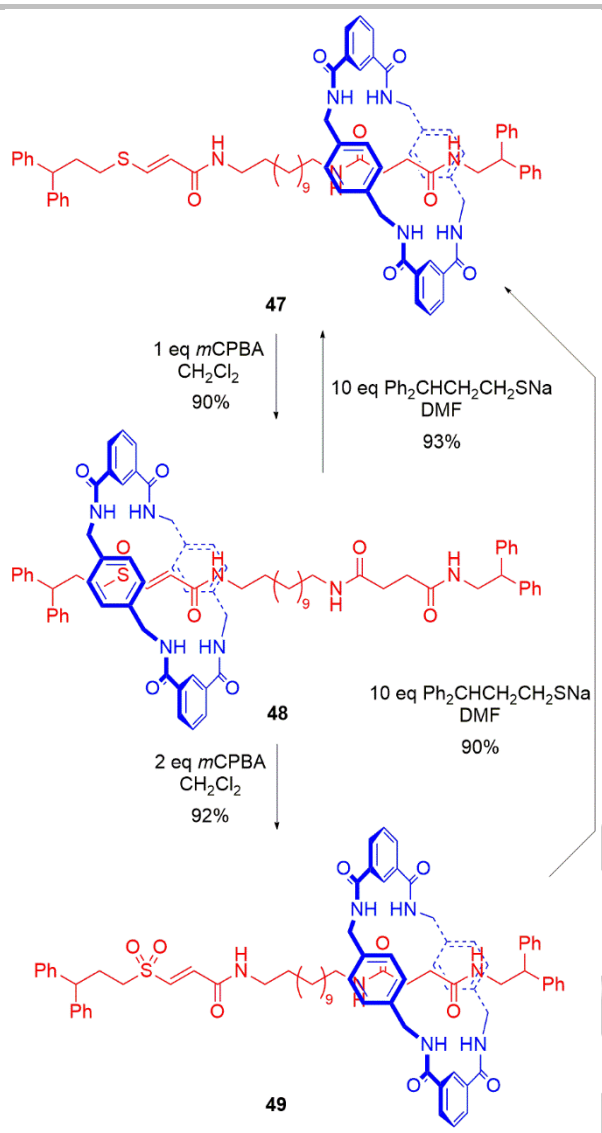


Figure 18 Switching of a sulfur-succinimide molecular shuttle system **47**/**48**/**49**, positions of macrocyclic component as in $CDCl_3$.

Leigh's group has also reported upon the use of pyridyl-acyl hydrazone as a templating motif.[46] Using hydrazone axle **50** allows for generation of the *E* isomer of [2]rotaxane **51** in 70% yield (with 8-fold excess of *p*-xylenediamine and isophthaloyl dichloride, NB: no cyclization occurs around *Z*-**50**). The light switchable nature of the pyridyl-acyl hydrazone was then used to shuttle the position of the macrocycle in **51** (Figure 19). As the *E* isomer, the pyridyl-acyl hydrazone is a better hydrogen bond acceptor than the succinic amide-ester, so the macrocycle resides over the former station. However, switching to the *Z* isomer, leads to a strong intra-component hydrogen bond at the hydrazone meaning the macrocycle translates to the succinic amide-ester, a process reversible by addition of TFA. The positional discrimination of the macrocycle was determined to be greater than 95% for each isomer of **51**.

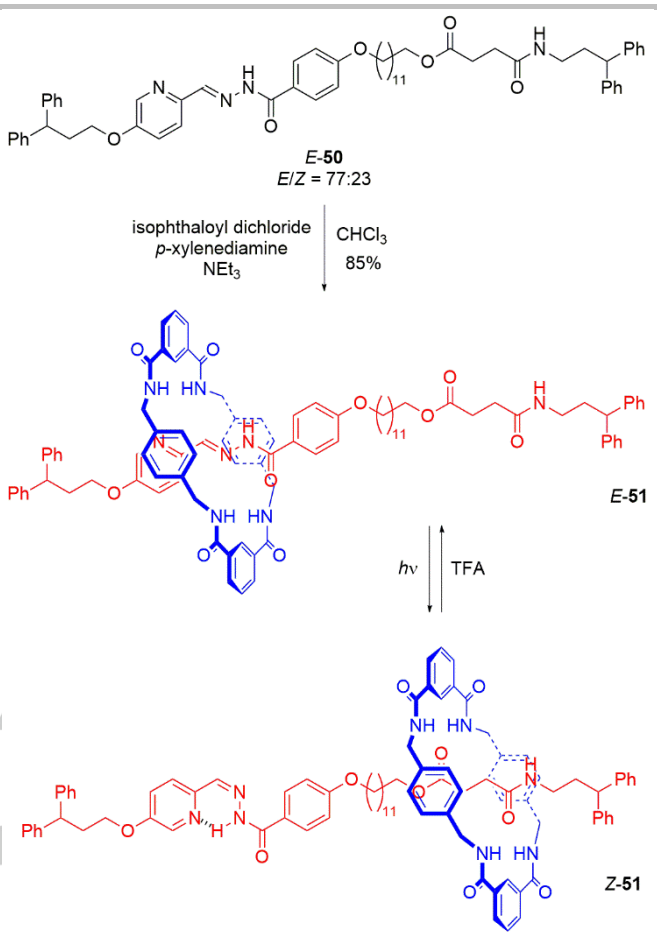


Figure 19 Synthesis and operation (in CD_2Cl_2) of a light switchable [2]rotaxane shuttle **51**.

Berna and co-workers have also studied a range of alternative axles. For example, [2]rotaxane **53** may be prepared from azodicarboxamide axle **52** in 58% yield (using 12 equivalents of isophthaloyl dichloride and *p*-xylenediamine, Figure 20a).[47] The azodicarboxamide motif may be reversibly reduced to the corresponding hydrazodicarboxamide, and the same researchers used this property to generate a molecular shuttle system **54**/**55** that includes a succinic amide-ester group as a second station.[47]

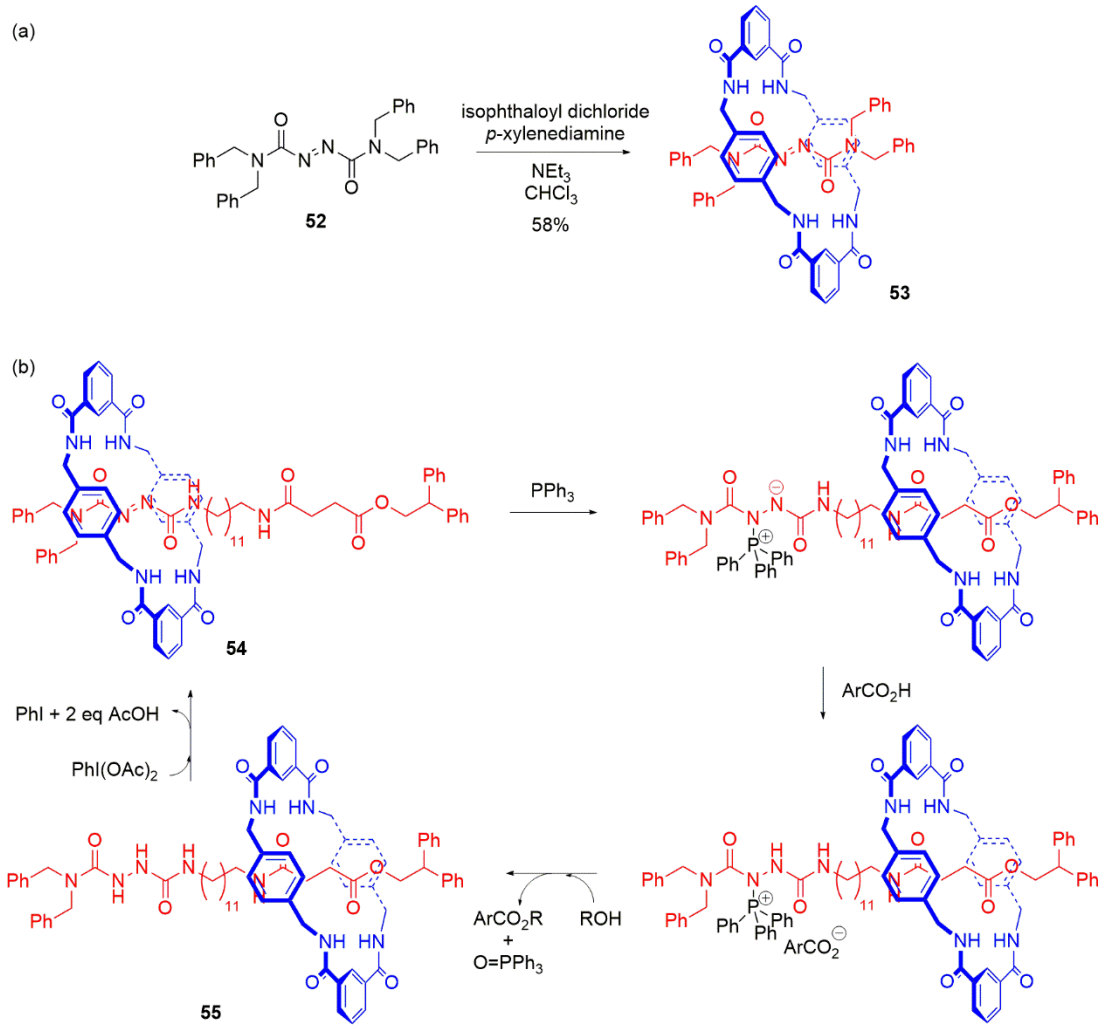


Figure 20 Azodicarboxamide [2]rotaxanes: (a) synthesis of exemplar [2]rotaxane **53**, (b) operation of molecular shuttle system **54**/**55** as an organocatalyst for a Mitsunobu reaction.

Switching the location of the macrocyclic component could be achieved by use of N_2H_4 and NBS/pyridine, but also in a continuous mode, where the rotaxane acts as an organocatalyst for a Mitsunobu reaction in the presence of iodosobenzene diacetate, that re-oxidizes the hydrazodicarboxamide rotaxane **55** back to the azodicarboxamide rotaxane **54** (Figure 20b).[47]

The same group then investigated using di(acylamino)pyridine as a templating motif. In an exemplar synthesis, axle **56** was reacted with 12 equivalents of isophthaloyl dichloride and *p*-xylenediamine to prepare [2]rotaxane **57** in 33% yield (Figure 21a).[48] In the same report, degenerate two station [2]rotaxane **58** was prepared (Figure 21b). In CD_2Cl_2, addition of the hydrogen bond complementary barbital restricted the location of the macrocyclic ring to the alkyl component of the axle between the two di(acylamino)pyridine stations. Shuttling along the full length of the rotaxane axle could be restored by addition of Hamilton-type receptors (e.g. **59** in Figure 21b) that competitively sequester barbital.[48, 49]

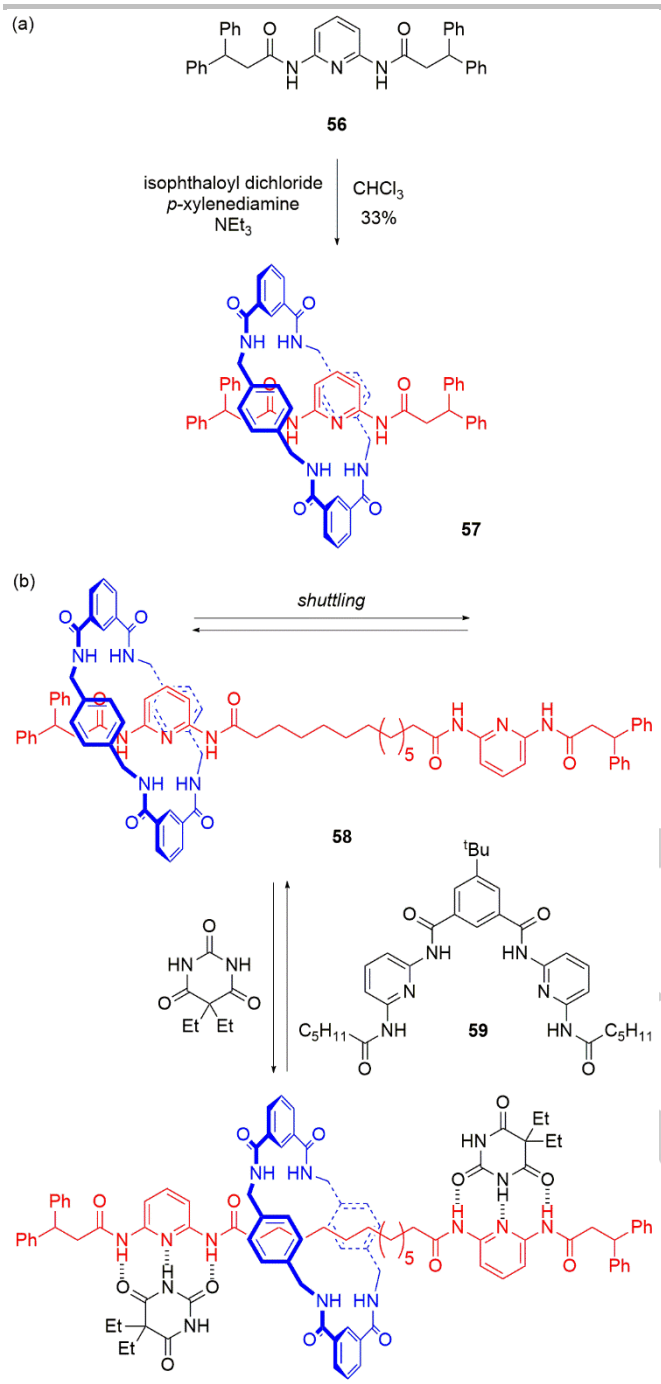


Figure 21 Di(acylamino)pyridine rotaxanes: (a) synthesis of exemplar [2]rotaxane **57**, (b) two station [2]rotaxane shuttle **58**, controllable by reversible complexation of a small molecule..

In a subsequent report, the researchers demonstrated further control of di(acylamino)pyridine-based rotaxanes (Figure 22).[50] While the parent di(acylamino)pyridine [2]rotaxane **60** exhibits an approximate 2:1 ratio of residence of the di(acylamino)pyridine and amide stations in CD_2Cl_2, there was excellent discrimination (at least 98:2) in co-conformational occupation by pyridine-*N*-oxide [2]rotaxane **61** and the protonated pyridine [2]rotaxane **62**, that may be reversibly accessed from **60** as illustrated in Figure 22.

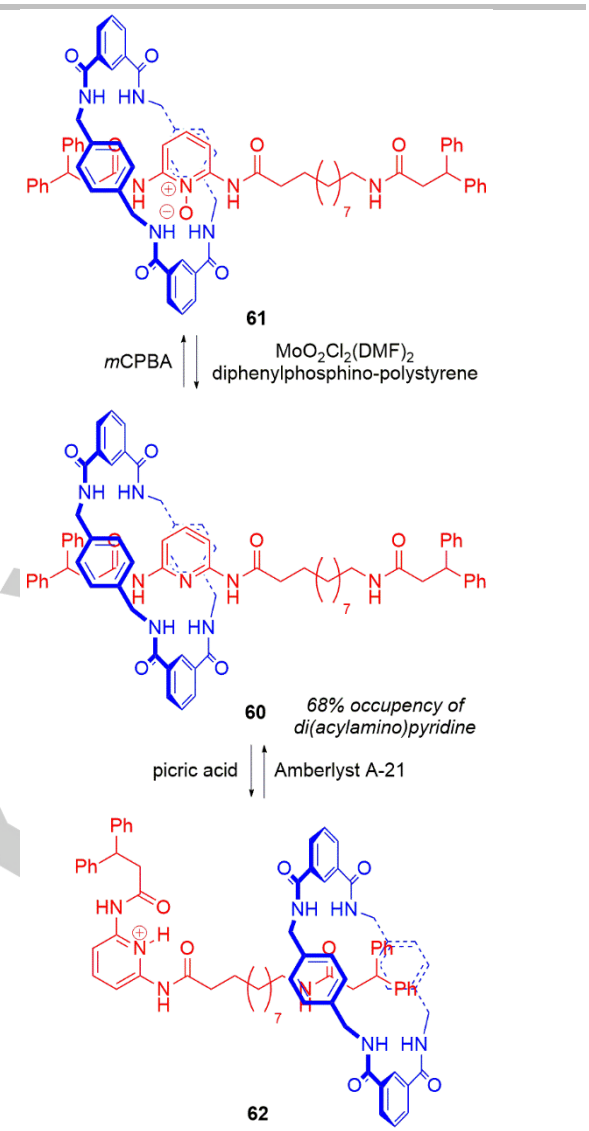


Figure 22 Switching of co-conformational behaviour from a parent di(acylamino)pyridine [2]rotaxane **60**.

More recently, Berna and co-workers have studied thiodigycolamide containing axles for rotaxane formation.[51] In the exemplar synthesis, it proved to be a sub-optimal template motif, as using eight equivalents of *p*-xylenediamine and isophthaloyl dichloride with axle **63** only produced [2]rotaxane **64** in 13% yield (Figure 23a). The subsequent shuttle **67**, was therefore prepared by cyclization around the fumaramide station. With the macrocycle residing at the fumaramide station, the rotaxane **65** may catalyze a chalcogeno-Baylis-Hillman reaction, with a diastereoselective ratio of 80:20 (*E*:*Z*) being observed for the product **68**. Photoisomerization to the malemide leads to translation of the macrocycle to the thiodiglycolamide, preventing it from participating as a catalyst, and so there is a switching off of diastereoselectivity in the Baylis-Hillman reaction (Figure 23b).

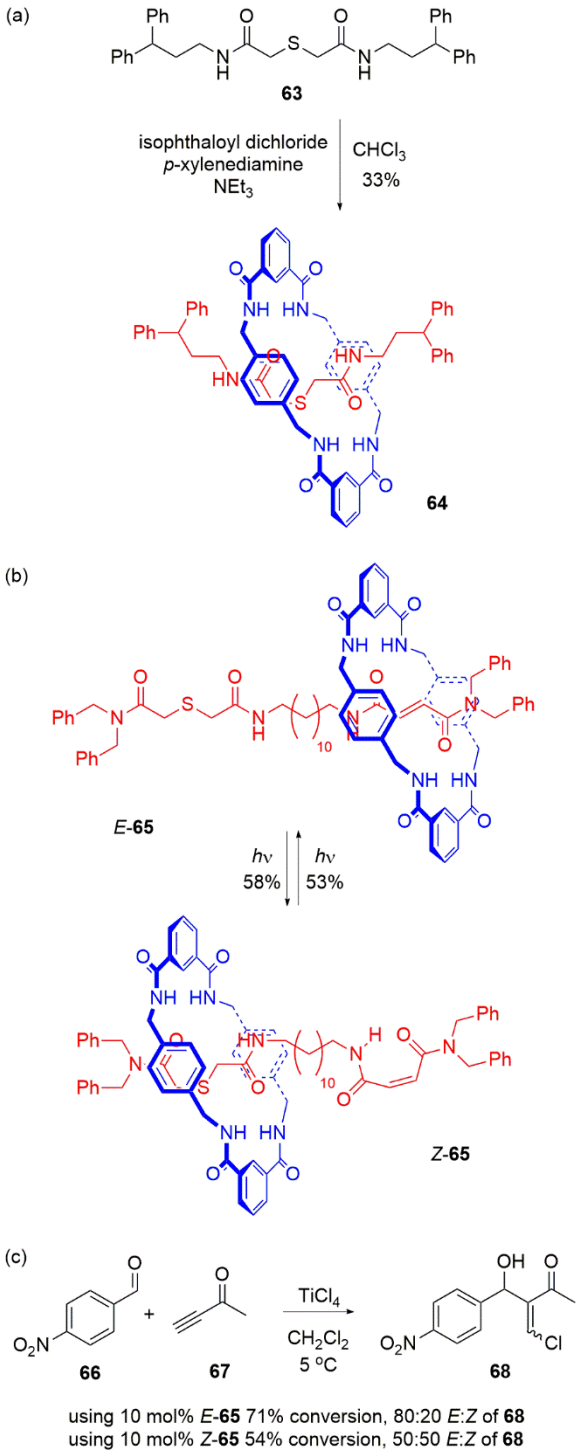


Figure 23 Thiodiglycolamide rotaxanes: (a) synthesis of exemplar [2]rotaxane **64**, (b) photoswitchable [2]rotaxane **65** and (c) chalcogeno-Baylis-Hillman reaction studied using **65** as a catalyst.

An exciting demonstration of the potential real-world impact of interlocked molecules, is provided by the work on squaraine (and more recently croconaine) rotaxanes and catenanes by Smith and co-workers. Squaraines can act as fluorescent near-IR dyes, but they are susceptible to nucleophilic attack and formation of aggregates. Smith's group were able to cyclize "Leigh-style" benzylic amide macrocycles (using four equivalents of bis-acid chloride and *p*-xylenediamine) in reasonable yield around a suitably designed squaraine axle **69** (Figure 24).[52] While the isophthaloyl [2]rotaxane **70** is more stable towards nucleophilic than the free axle **69**, the pyridyl analogue **71** is essentially inert. Subsequently, [2]rotaxane **71** was used in fluorescence microscopy studies, and was found to parallel the cellular location behavior of lipophilic stain Nile red.[53]

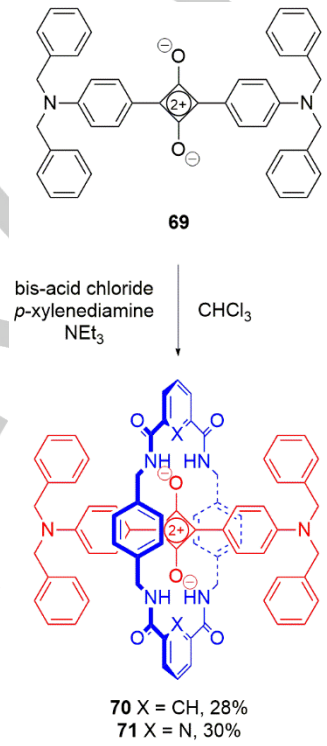


Figure 24 Smith's original squaraine [2]rotaxanes **70** and **71**.

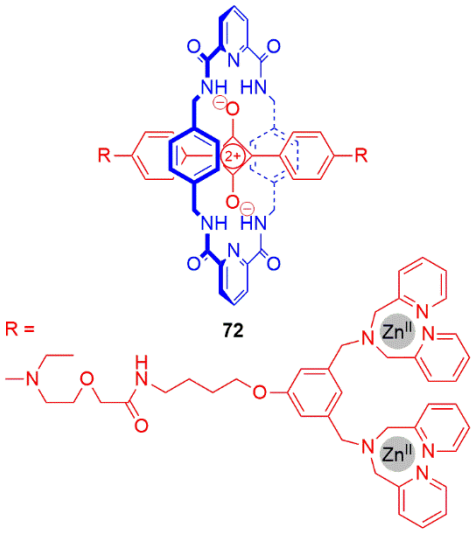


Figure 25 Smith's zinc(II)-dipicolylamine appended squaraine [2]rotaxane **72** used to image bacterial cell division.

Incorporation of zinc(II)-dipicolylamine groups to the stoppers of [2]rotaxane **72** allowed for association of the rotaxane to the anionic surfaces of bacterial cells (Figure 25).[53] The stability

of the encapsulated dye allowed for the real-time recording of fluorescence images of bacteria undergoing cell division.

Switchable squaraine rotaxanes have also been prepared. For example, [2]rotaxane **73** – prepared by stoppering a bis-alkyne appended squaraine threaded through a Hunter/Vögtle-style macrocycle – can act as a reversible optical chloride sensor (Figure 26).[54] Addition of chloride leads to translocation of the macrocycle to allow for simultaneous hydrogen bonding of the chloride anion by a triazole C-H and isophthalamide N-Hs. This process is accompanied by an enhancement in fluorescence emission. Interestingly, the rotaxane could be adsorbed onto silica gel plates to generate prototype dipsticks that allowed for detection of chloride by the naked eye.

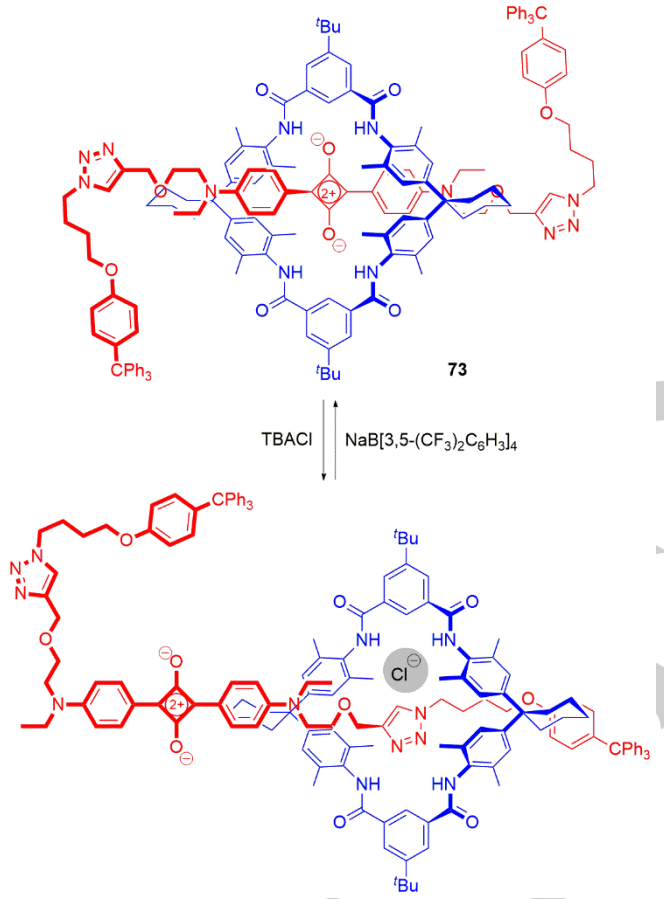


Figure 26 Synthesis and switching of Smith's first generation squaraine [2]rotaxane shuttle **73** that senses chloride.

In a follow-up paper, an improved sensory [2]rotaxane shuttle **74** was reported that incorporates an anthracene analogue of the classic "Leigh-style" benzylic amide macrocycle (Figure 27).[55] The principal advantages of **74**, in comparison to **73** are that it (a) provides a ratiometric fluorescent response to chloride and (b) possesses a dihydroxyl substituted squaraine that is more stable than a simple squaraine when displaced from the steric protection of the macrocycle cavity.

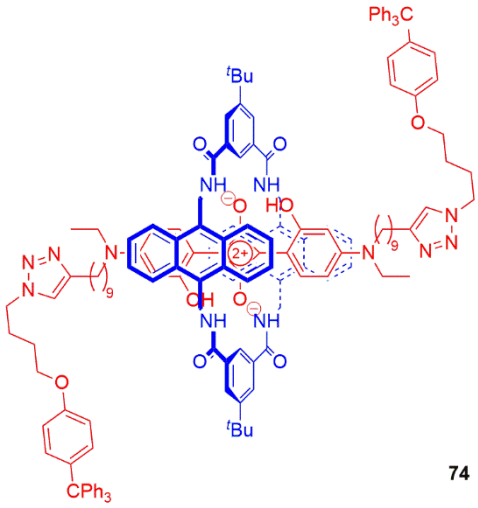


Figure 27 Structure of Smith's second generation squaraine [2]rotaxane shuttle **74** that senses chloride.

Using the same anthracene macrocycle, Smith's group has also managed to prepare a thermally activated, chemiluminescent rotaxane-based imaging dye. [2]Rotaxane **75** may be cleanly converted to the mono(endoperoxide) [2]rotaxane **76**, which at low temperatures is stable, but at body temperature will convert back to **75**, thus emitting near-IR light that can pass through (e.g.) a living mouse (Figure 28).[56]

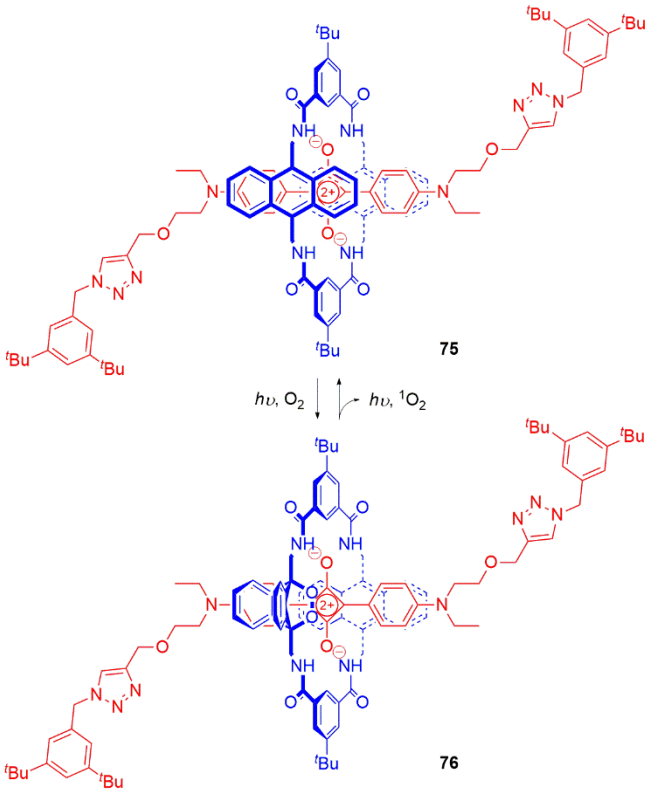


Figure 28 Smith's squaraine endoperoxide [2]rotaxane **76**.

Squaraine catenanes have also been prepared. For example, [2]catenane **78** was synthesized in 35% yield by cyclizing 4.8 equivalents of isophthaloyl dichloride and 9,10-bis(aminomethyl)anthracene around squaraine macrocycle **77** (Figure 29).[57] A bis-*tert*-butyl analogue of **78** has subsequently been used to stain polymeric nanoparticles for *in vivo* imaging.[58]

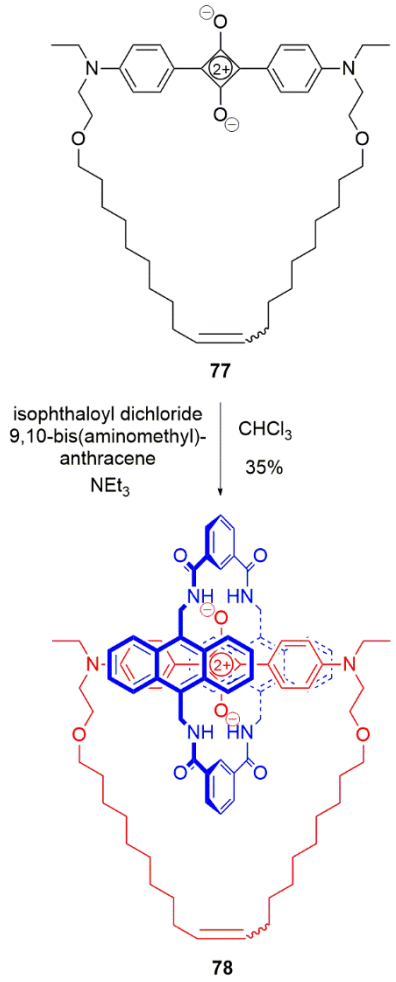


Figure 29 Synthesis of squaraine [2]catenane **78**.

In more recent times, Smith's attention has turned to using croconaine in place of squaraine, croconaines being highly stable both chemically and photothermally. [2]Rotaxane **82** was prepared in 84% yield by stoppering the pseudorotaxane formed between macrocycle **79** and bis-alkyne appended croconaine axle precursor thread **80** with three equivalents of azide **81** (Figure 30).[59] This was then used to dope silicate micelle nanoparticles, where it was found that encapsulating the dye in a rotaxane beneficially minimizes the broadening of the near-IR absorption band.[59] Subsequently a related rotaxane was used for acid activated photothermal heating and for ratiometric photoacoustic imaging of acidic pH in a living mouse.[60]

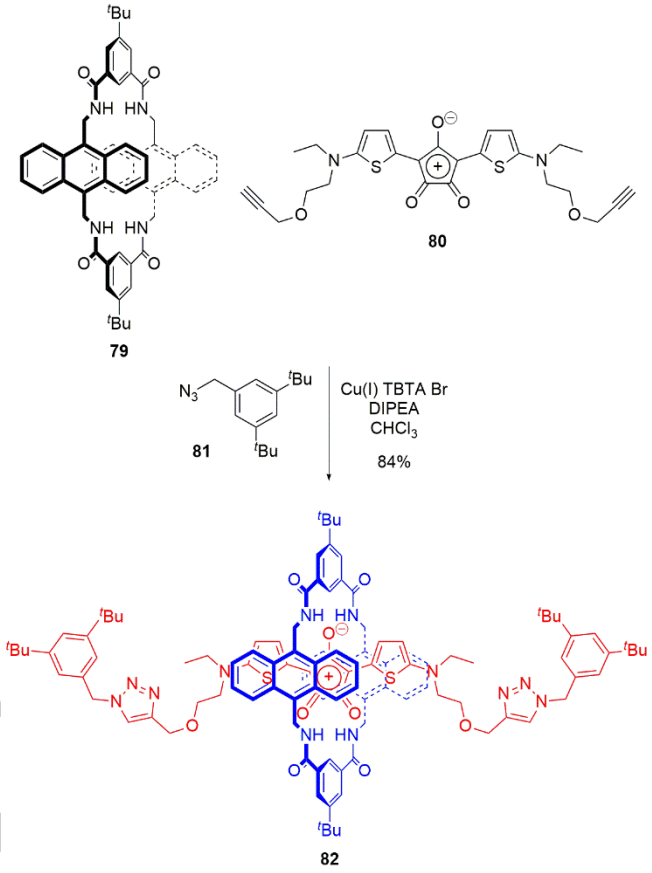


Figure 30 Synthesis of croconaine [2]rotaxane **82**.

3.3. Some alternative templating motifs: barbiturate and pyridine-*N*-oxide containing axles

While the vast majority of hydrogen bond templated interlocked molecules possess a bis-isophthalamide macrocycle, examples without such a component are known. For example, Tucker and McClenaghan prepared [2]rotaxane **86** by stoppering a pseudorotaxane consisting of macrocycle **83** and bis-azide functionalized barbiturate **84**, with bulky terphenyl alkyne stopper **85**, relying on the complementarity of the bis-2,6-diaminopyridyl motif for the barbiturate functionality (Figure 31).[61] The yield was modest at 22%, but the researchers did only use 1.1 equivalents of **83** and 2.1 equivalents of **85** (with respect to the barbiturate **84**).

The same researchers subsequently prepared a similar [2]rotaxane **89** by clipping, using a photochemical anthracene dimerization reaction (Figure 32).[62] This reaction is reversible upon heating, and so the researchers were able to cycle the system through four irradiation-thermal reversion cycles, with a fatigue of 38%.

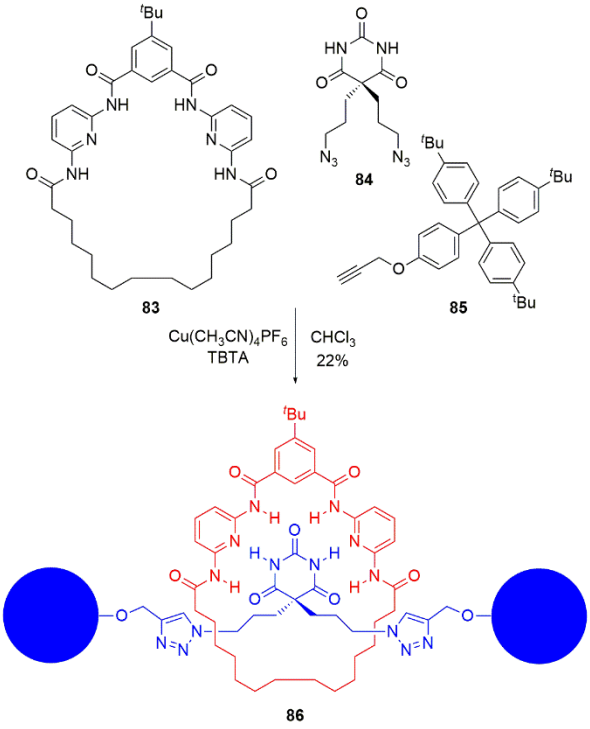


Figure 31 Tucker & McClenaghan's hydrogen bond templated barbiturate [2]rotaxane **86**.

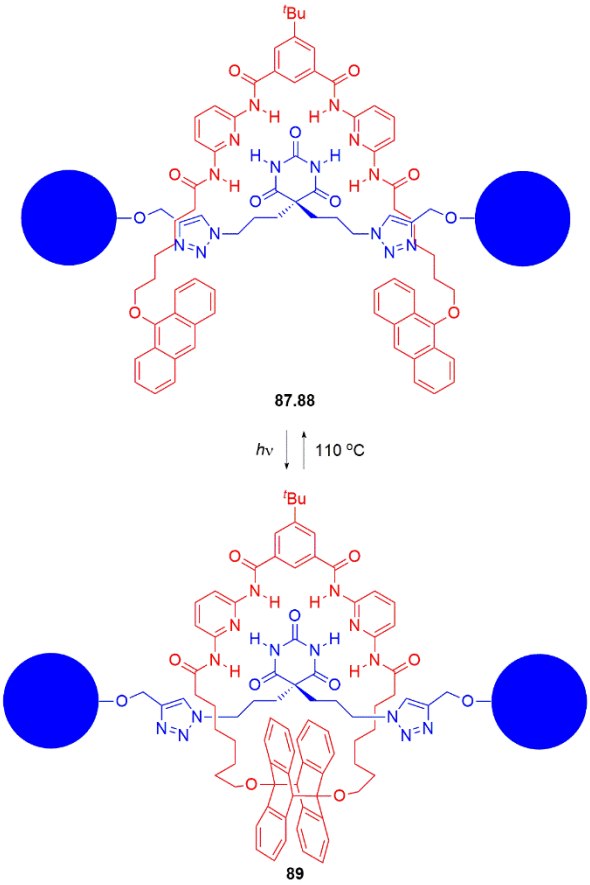


Figure 32 Tucker & McClenaghan's reversible photocapture of hydrogen bond templated barbiturate [2]rotaxane **89**.

Inspired by Jiang's reports of pseudorotaxanes consisting of pyridine-*N*-oxide threads passing through polyether isophthalamide macrocycles,[63] Evans and co-workers used macrocycle **90** to prepare a fully stoppered pyridine-*N*-oxide containing [2]rotaxane **93** in 32% yield, using strictly stoichiometric equivalents of components **90**, **91** and **92** (Figure 33).[64] As part of their study, the authors demonstrated the necessity for the polyether chain within the structure of the macrocycle for successful rotaxane formation.

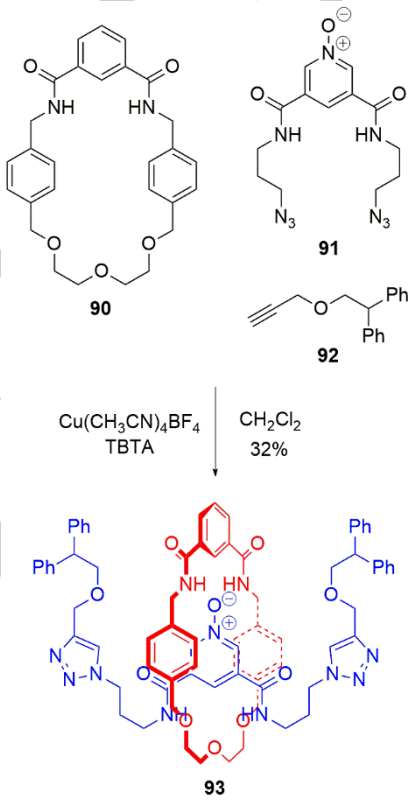


Figure 33 Synthesis of pyridine-*N*-oxide [2]rotaxane **93** using polyether-isophthalamide macrocycle **90**.

More recently, Ballester and co-workers have used bis(calix[4]pyrrole) macrocycle **94**, to prepare pyridine-*N*-oxide [2]rotaxane **97**, also by CuAAC "click" stoppering in 50% yield (using 2 and 4 equivalents of **95** and **96** respectively, Figure 34).[65] Notably attempts to use an anion template to increase the yield of formation, proved unsuccessful, attributed to reduction in performance of the copper catalyst. Rotaxane **97** is able to efficiently bind tetra-alkylammonium salts in chloroform. However, above one equivalent of salt, the 1:1 complex of salt and rotaxane gradually converts to a 2:1 complex, with the authors proposing that binding of the ion pair at each calix[4]pyrrole induces displacement of the pyridine-*N*-oxide motif from the cavity of the macrocycle.

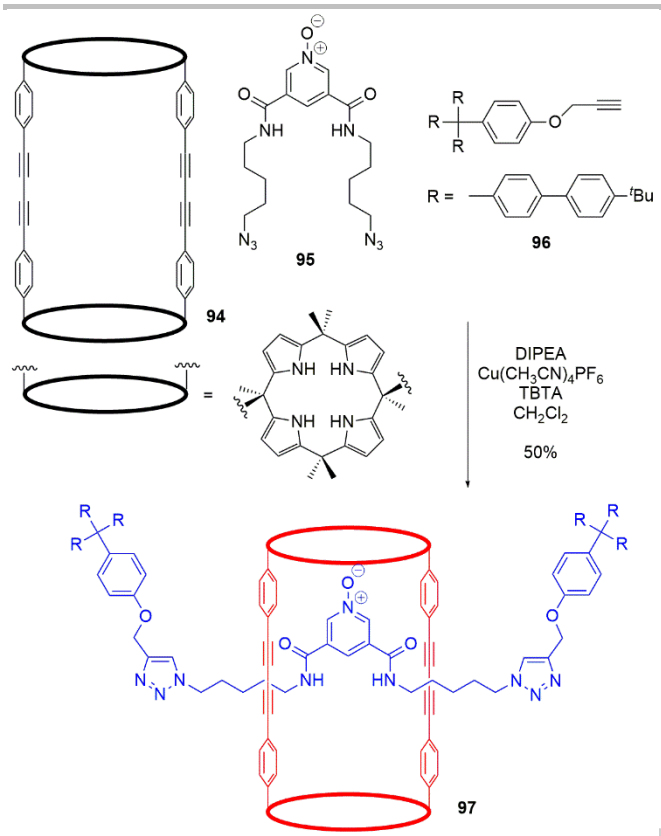


Figure 34 Synthesis of pyridine-*N*-oxide [2]rotaxane **97** using bis(calix[4]pyrrole) macrocycle **94**.

3.4. A single amide (or urea) as a simple – yet effective – hydrogen bond templation motif

The regular use of the "Leigh-style" benzylic amide macrocycle containing systems has arisen from the simplicity and the high yield of the clipping of the macrocycle around (e.g.) a fumaramide axle motif. In fact it is possible to use a single (coumaric) amide as the templating motif on the axle component as demonstrated in the production of [2]rotaxane **99** by Brouwer and Leigh (Figure 35).[66] The authors propose that the axle amide N-H hydrogen bonds to one of the macrocycle amide C=O groups, an arrangement successfully modelled computationally. However, the yield of 14% is rather modest considering eight equivalents of *p*-xylenediamine and isophthaloyl dichloride were used

This example actually follows a previous rotaxane prepared using a single amide motif in its axle component, and a mono-isophthalamide macrocycle. In an unusual "magic rod" synthesis employing Grubbs' catalyst to achieve reversible olefin metathesis, [2]rotaxane **102** was prepared in 15% yield, using equimolar amounts of axle **100** and macrocycle **101** (Figure 36).[67] In this case, the authors propose that the axle amide N-H hydrogen bonds to the macrocycle ester C=O groups in the rotaxane.

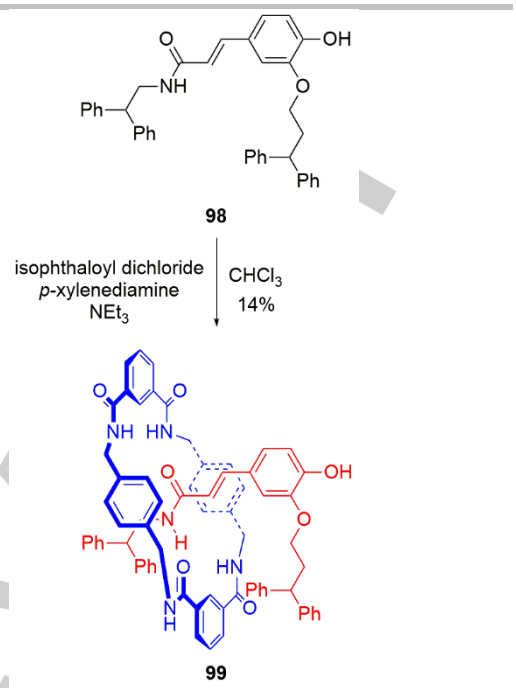


Figure 35 Synthesis of Brouwer & Leigh's coumaric amide [2]rotaxane **99**.

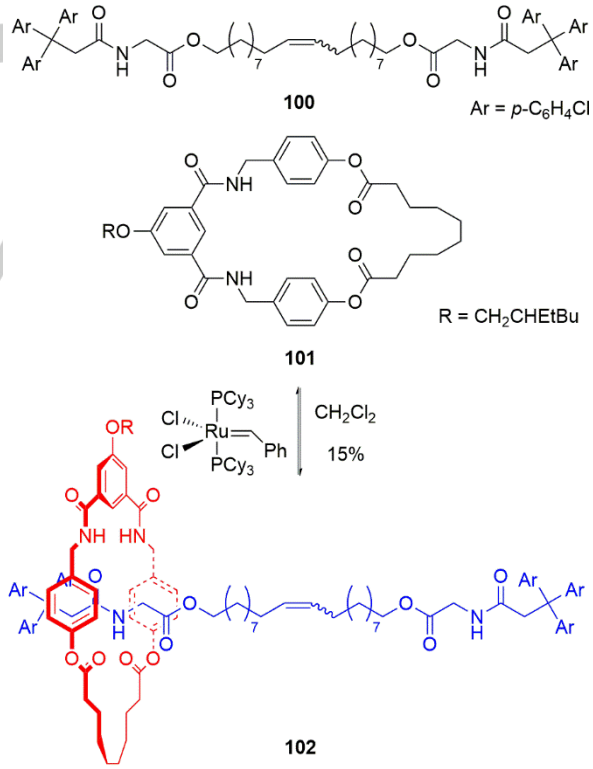


Figure 36 Leigh's magic rod amide [2]rotaxane **102**.

Subsequently, the same group prepared a hydrogen bond templated molecular shuttle with glycylglycine and *N*-benzylaniline stations (Figure 37).[68] Impressively, [2]rotaxane **106** was prepared in 31% yield, when using equimolar amounts of macrocycle **103** and axle components **104** and **105**. As the macrocycle contains only one isophthalamide, only one of the

amide groups of a glycylglycine station can be hydrogen bonding to the macrocycle at a time. Addition of acid to the rotaxane allows for protonation of amine and the macrocycle translates to the protonated ammonium, supported by hydrogen bonding (reversible by the addition of base). Li and co-workers have reported upon a related rotaxane, stoppered using a [2+2] cycloaddition reaction.[69]

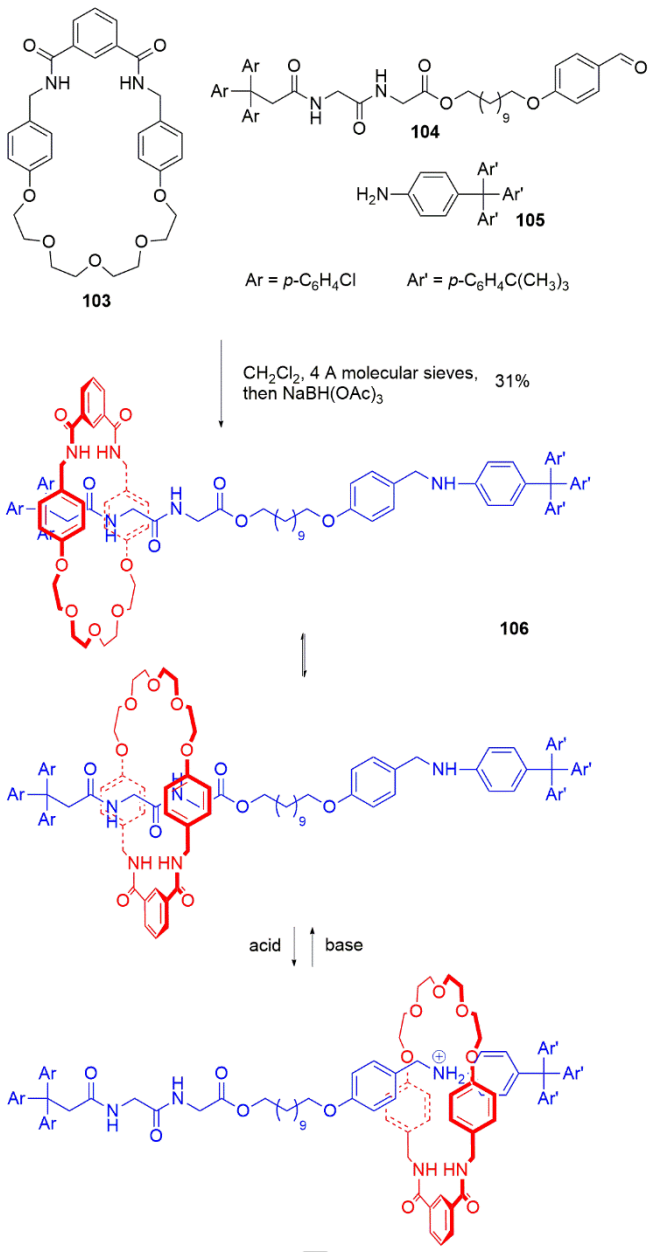


Figure 37 Synthesis and operation (in CD_3CN) of Leigh's rotaxane shuttle **106**.

It transpires that it is possible to access rotaxanes using a single amide templating motif on the axle even more efficiently by use of a smaller macrocycle. This was first demonstrated by Philp and co-workers, where even using equimolar amounts of components **107**, **108** and **109** still furnished [2]rotaxane **110** in a yield of 45%, by use of a nitrone-maleimide stoppering reaction (Figure 38).[70]

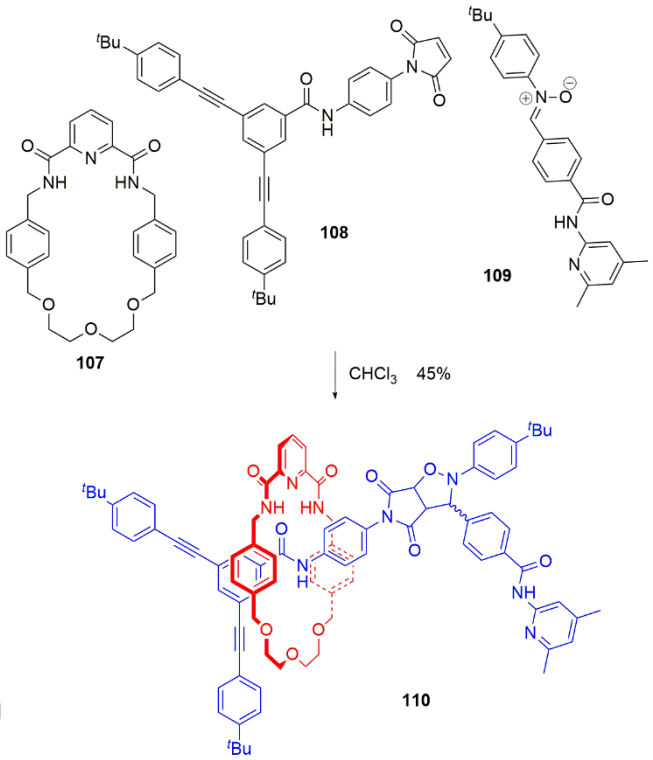


Figure 38 Philp's synthesis of single amide [2]rotaxane **110**.

This exemplar synthesis was part of a study by Philp *et al* to generate self-replicating rotaxanes.[70-72] While first attempts at creating a hydrogen bond directed self-replicating network were not particularly successful (using analogous rotaxanes to **110** with a carboxylic acid that could hydrogen bond to the 2-amino-pyridyl group to direct self-replication),[70] later work has made significant progress towards this very ambitious goal. To illustrate using one of the more successful reported examples, [2]rotaxane **114** (see Figure 39) can act as an auto-catalytic template for its own formation, but the interference between the recognition and reaction processes, causes threading formation to exceed rotaxane formation in this particular case.[71]

Philp's group has also studied the stoppering of such single amide templated rotaxanes using aza-Wittig reactions (Figure 40).[73] The yield of formation of [2]rotaxane **116** was somewhat low at 25%, even when running the covalent capture of pseudorotaxane **107.115** by triphenylphosphine at low temperatures.

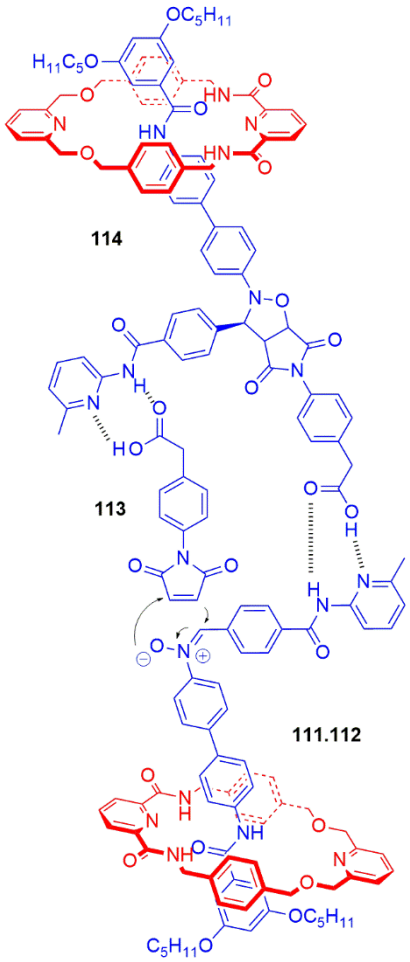


Figure 39 Targeted self-replication synthesis of [2]rotaxane **114**.

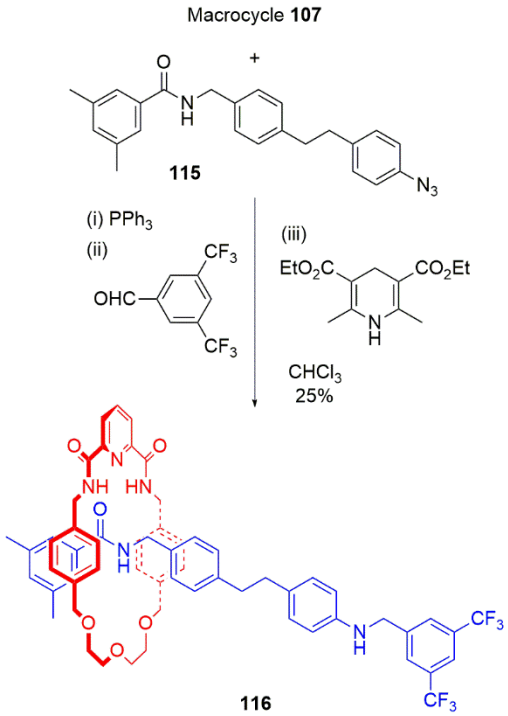


Figure 40 Philp's aza-Wittig stoppered [2]rotaxane **116**.

Inspired by Philp's reports, Evans and co-workers investigated the potential for the popular CuAAC "click" reaction to act as a stoppering reaction to prepare analogous rotaxanes. It proved possible to prepare [2]rotaxane **119** in a yield of 47% when using 1.1 equivalents of **117** and **118** with respect to macrocycle **90** (Figure 41a).[74] This methodology has subsequently been used to generate a [3]rotaxane and a degenerate [2]rotaxane shuttle,[75] and most recently [2]rotaxane **120**, that is mechanically chiral by consisting of rotationally asymmetric macrocyclic and directional axle components (Figure 41b).[76] It is possible to modulate the expression of chirality of **120** (as reported by the diastereotopic behaviour in the ^{1}H NMR spectrum of the CH_2 proton environment adjacent to the axle amide) by varying the solvent polarity or by the addition of acid and base.

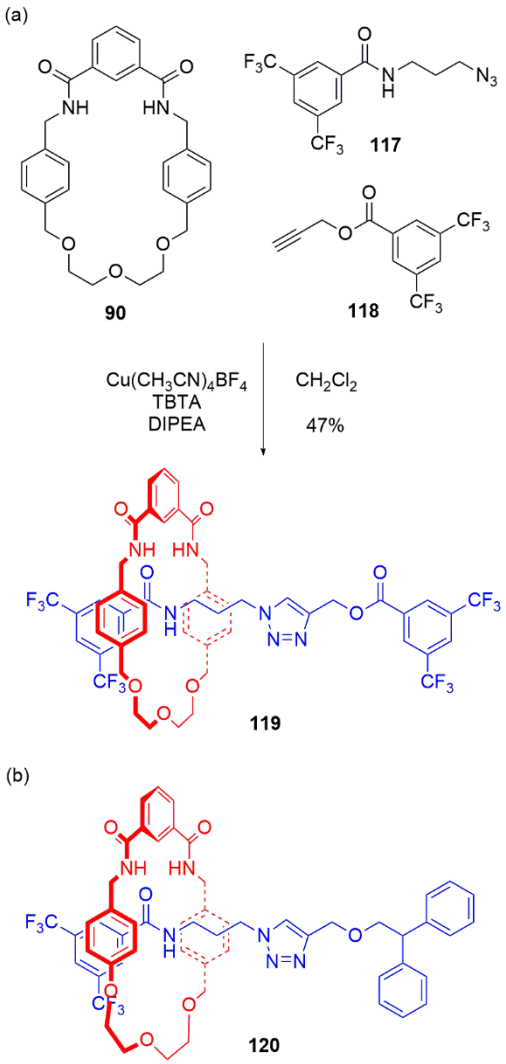


Figure 41 Evans' CuAAC click amide-templated rotaxanes: (a) exemplar synthesis of [2]rotaxane **119**, (b) structure of mechanically chiral [2]rotaxane **120**.

During the initial stages of these investigations, Marrs and Evans had actually serendipitously isolated hydrogen bond templated [2]catenane **122** (Figure 42).[77] Reaction of bis-amine **121** with isophthaloyl dichloride, under pseudo-high dilution conditions, generated catenane **128** in 12% yield. The rings of

catenane **122** may rotate relative to one another, controllable by varying solvent or temperature, as monitored by ^{1}H NMR spectroscopy. A similarly serendipitous [2]catenane **125** has been reported by Gunter *et al*, as a by-product in the preparation of an isophthalamide strapped porphyrin (Figure 43).[78]

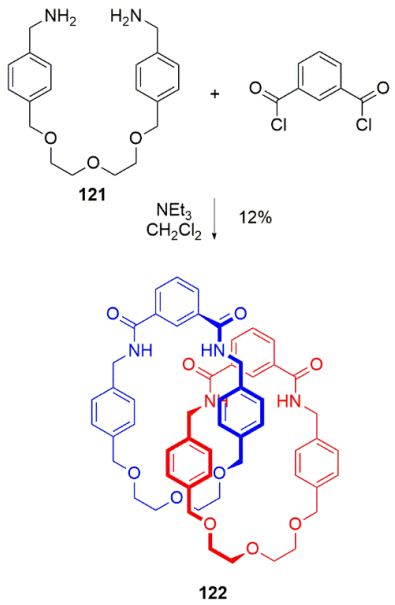


Figure 42 Evans' serendipitous synthesis of [2]catenane **122**.

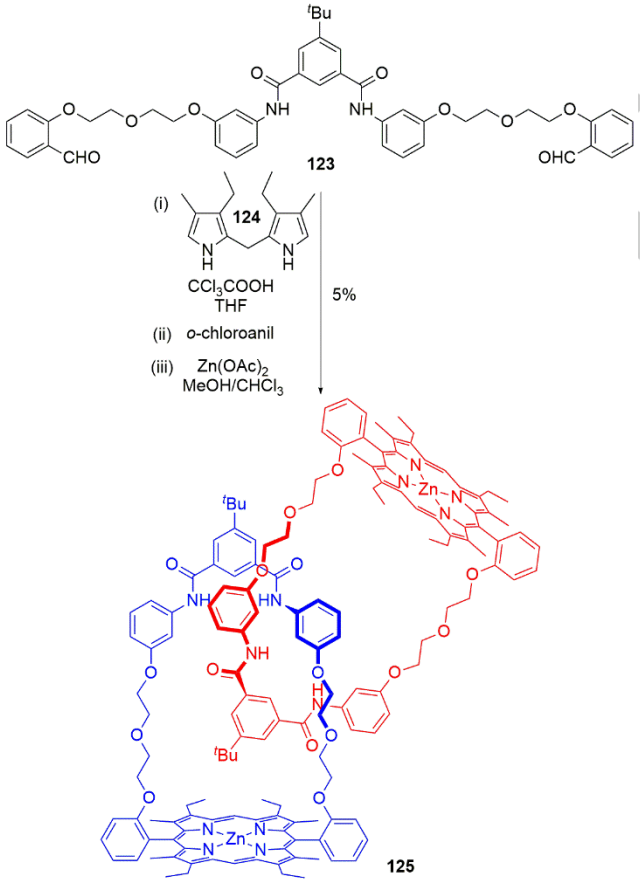


Figure 43 Gunter's serendipitous synthesis of [2]catenane **125**.

It is also possible to use other simple hydrogen bonding functionality to template the formation of interlocked molecules. For example, Chiu and co-workers have reported upon the use of urea.[79] In the representative example depicted in Figure 44 they stoppered urea-alcohol **126** threaded through macrocycle **107**, with the bulky 3,5-di(tert)butylphenylisocyanate. [2]Rotaxane **127** possesses a urea and carbamate on its axle. In 1:1 $CDCl_3/CD_3CN$, addition of acetate leads to translocation of macrocycle, as the anion chelates to the urea. This is reversible upon addition of sodium perchlorate that removes the acetate anion by precipitation.

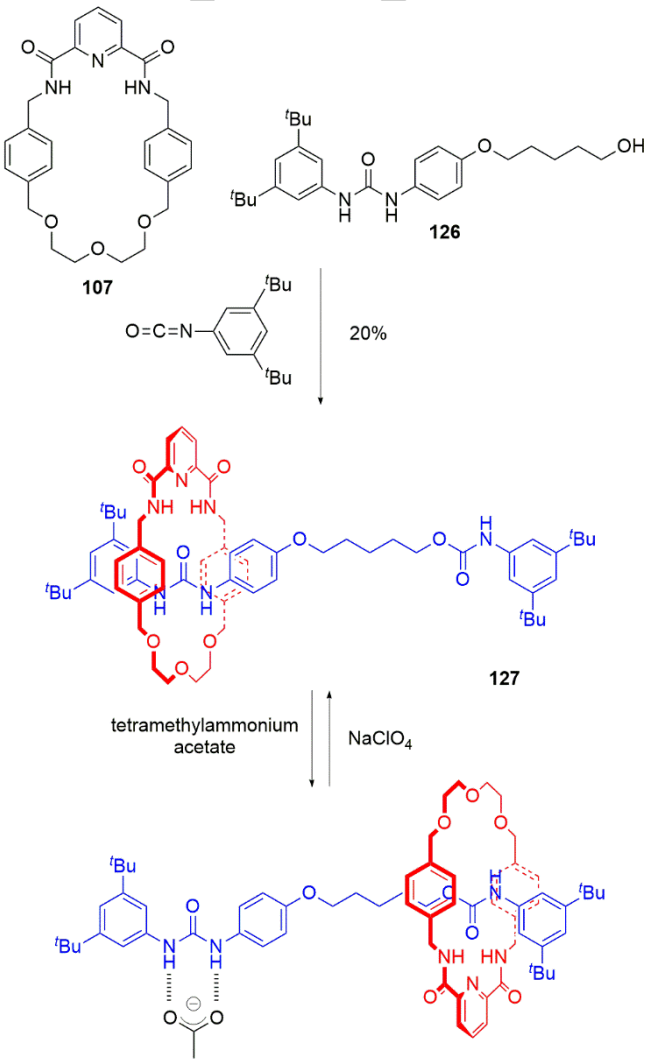


Figure 44 Chiu's urea-templated rotaxane molecular switch **127**.

Leigh's group has used a squaramide to template the formation of [2]rotaxane **131** (Figure 45a).[80] Using 2.35 equivalents of macrocycle **129** and 2.6 equivalents of amine stopper **130** with respect to axle precursor **128**, the Boc-protected version of **131** was formed in 47% yield – which is quite impressive considering the relatively polar solvent system (CH_2Cl_2/THF/CH_3CN 60:35:5) employed. Removal of the Boc protecting group to generate **131** reveals a dibenzylamine station, which when protonated is where the macrocyclic component resides. By switching between neutral and protonated states of

131, control over the reactivity of a mixture of *trans*-β-nitrostyrene and crotonaldehyde, with 1,3-diphenylpropane-1,3-dione can be achieved (Figure 45b). When **131** is deprotonated, the macrocycle resides over the squaramide, so the dibenzylamine station catalyzes Michael addition to crotonaldehyde. When **131** is protonated, the squaramide is revealed, so that it can hydrogen bond to the nitro group of *trans*-β-nitrostyrene, thus activating this substrate preferentially to Michael addition.[81]

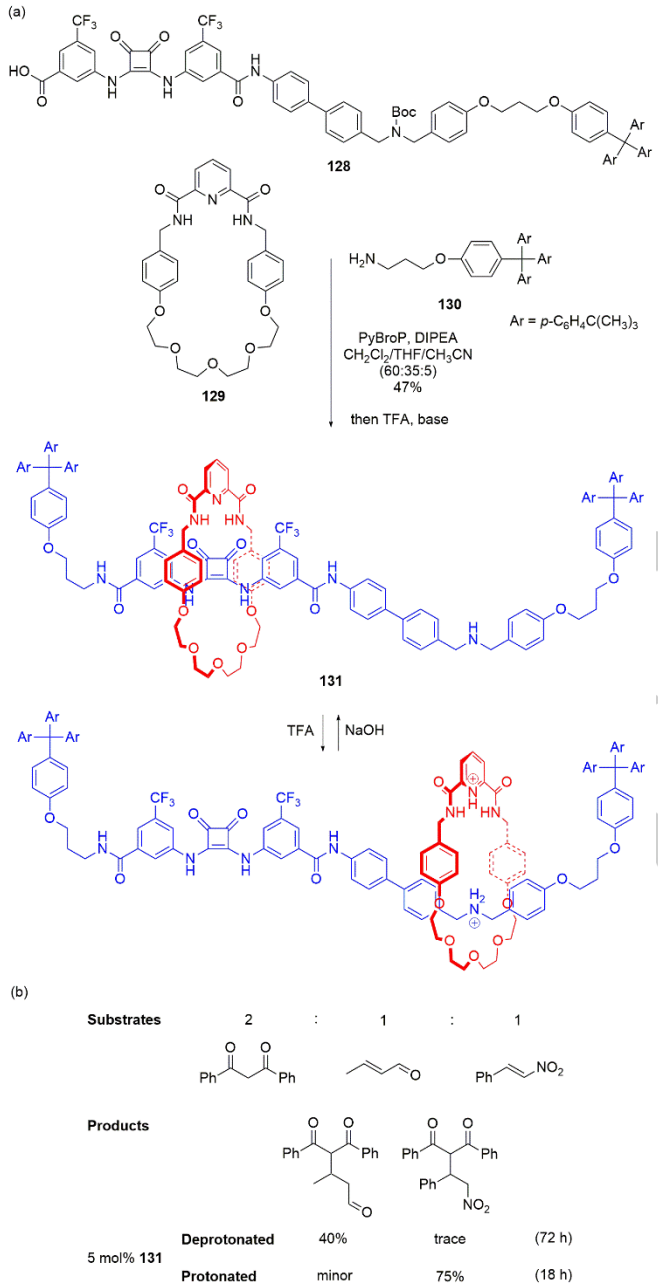


Figure 45 Leigh's squaramide [2]rotaxane **131**: a) synthesis and switching of **131**, b) catalytic behaviour of **131** in Michael additions, dependent on protonation state.

3.5. Hydrogen bond mediated transition state stabilization – a future direction in synthesizing interlocked molecules?

Finally, a very recent development has been the use of hydrogen bond mediated transition state stabilization to generate rotaxanes as pioneered by Leigh and co-workers. In the first of their studies, cyclic sulfate **132** and amine **133** were reacted in the presence of pyridyl-2,6-dicarboxamide macrocycle **129** (Figure 46).[82] With 5-fold excess of the half axle components, a 70% yield of [2]rotaxane **134** was observed after 5 days. Critically neither **132** nor **133** associates strongly with macrocycle **129** (as determined by ^{1}H NMR titration experiments). The researchers therefore propose that the macrocycle stabilizes the transition state: the forming sulfate group hydrogen bonds to the pyridyl-2,6-dicarboxamide, while the developing protonated ammonium hydrogen bonds to the polyether oxygens.

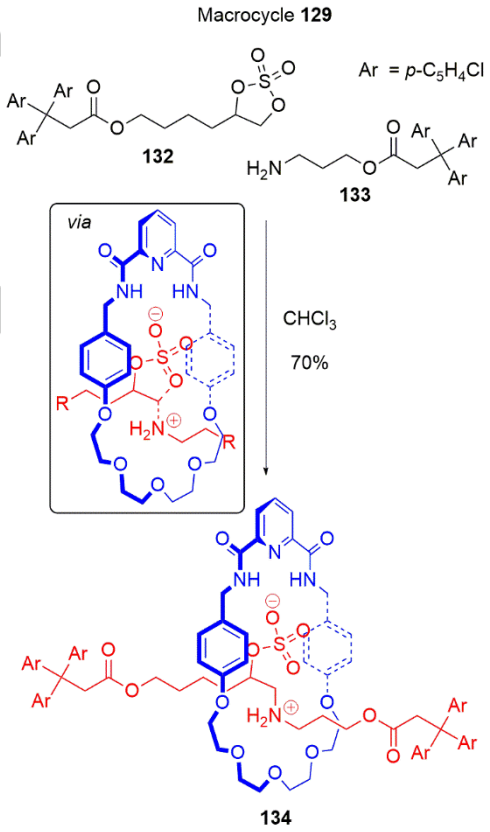


Figure 46 Leigh's [2]rotaxane **134** prepared via the transition state stablized addition of primary amine **133** to cyclic sulfate **132** through macrocycle **129**.

Following this initial report, it has been demonstrated that analogous reactions may be run using commercially available crown ethers as macrocyclic components.[83] It transpires 24-crown-8 (**137**) will stabilize the attack of a primary amine with a variety of electrophilic partners that occur through the macrocyclic cavity. Amongst the most promising results from this work is depicted in Figure 47, where using strictly stoichiometric amounts of **135** and **136**, [2]rotaxane **138** was prepared in 56% yield in a reaction time of 2.5 hours.

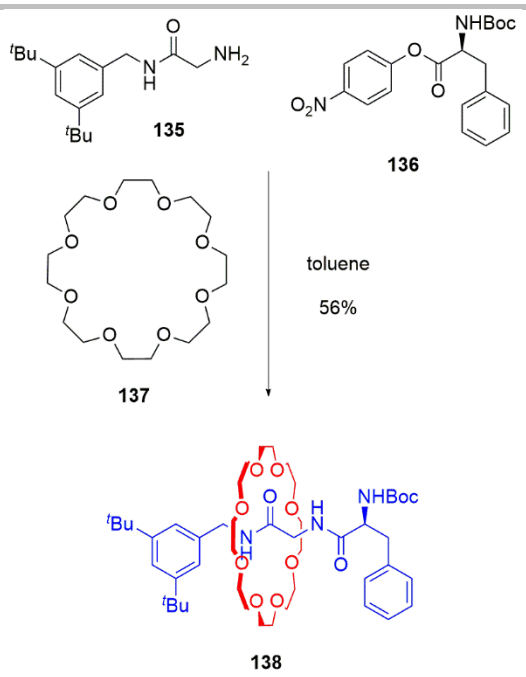


Figure 47 Example of transition stabilized [2]rotaxane synthesis by the reaction of primary amine **135** with electrophilic partner **136** through 24-crown-8 (**137**).

4. Conclusions

Over the last decade or so, the hydrogen bond templated synthesis of interlocked molecules has remained a highly active area of research. The well-established "Leigh-style" benzylic amide macrocycles with fumaramide (and related) threading motifs are being used in an ever expanding range of applications (e.g. peptide delivery, catalysis and molecular-sized motors). Alternative templates to fumaramide have not only been identified but are themselves to be found in rotaxanes and catenanes that have found use in applications including catalysis and cellular imaging, critically benefitting from properties arising from their interlocked structures. It has also proved possible to move away from the classic "Leigh-style" benzylic amide macrocycle. In particular, a simple amide (or urea) is a remarkably efficient templating motif for rotaxane formation. Finally, the very recent results in synthesis by transition state stabilization, hint at opportunities of more exciting discoveries in the synthesis of such rotaxanes.

Considering all these developments, both in synthesis and application, it could well be proposed that in the future functionally useful interlocked molecules that find widespread real-world application may well be prepared by use of hydrogen bond templation.

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Keywords: rotaxanes • catenanes • hydrogen bonding • templated synthesis • molecular machines

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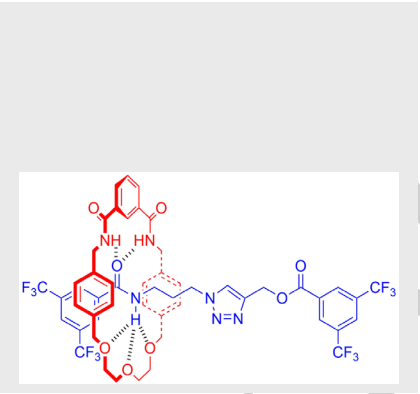
Entry for the Table of Contents (Please choose one layout)

Layout 1:

MINIREVIEW

This review focuses on progress in the field of hydrogen bond templated rotaxanes and catenanes over the last decade. A summary of key historic examples, is followed by discussion of developments in synthetic methodology and useful application of the resulting interlocked molecules.



Interlocked Molecules

*Nicholas H. Evans**

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Recent Advances in the Synthesis and Application of Hydrogen Bond Templated Rotaxanes and Catenanes