From Rotaxane Synthesis to Controlled Submolecular Motion Through Ammonium Ion Binding

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For Karen

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Abstract

This thesis demonstrates ways in which the ammonium group can be used to template the formation of rotaxanes, and to control their submolecular motion.

The first part details the development of a methodology for synthesising rotaxanes from cyclic peptide macrocycles. Cyclic octa- and deca- peptides of the L-ProGly repeat unit are versatile ionophores that are known to bind both metal ions and organic cations. One mode of binding exhibited by this type of macrocycle is to associate a cation on either face of the macrocycle: a so called 'sandwich complex'. If the two cations with which the macrocycle binds are secondary ammonium groups connected by a spacer of suitable length, then an inclusion complex is formed. Trapping of this type of inclusion complex by covalent modification has allowed access for the first time to synthetic rotaxanes of cyclic peptides.

The latter half of this thesis details the synthesis and operation of two different switchable molecular shuttles in which the position of the macrocycle is determined by a change in the protonation level of the molecule. The first of these shuttles operates by a combination of amide-amide and crown ether-ammonium interactions. In its neutral form these amide-amide hydrogen bonds hold the macrocycle over a dipeptide residue. When an amine group in the thread is protonated, polyether-ammonium cation interactions dominate and the macrocycle changes position. The second shuttle relies solely on crown ether-ammonium interactions. In this instance pH controlled movement is achieved by the selective deprotonation of one of two ammonium stations, inducing the macrocycle to reside predominantly on the second, less acidic, station.

Declaration

The scientific work described in this thesis was carried out in the School of Chemistry at the University of Edinburgh between October 2002 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 16/3/2007

Acknowledgements

Thanks first and foremost to Prof. Dave Leigh for giving me the opportunity to work in a superb environment, with all the equipment and resources that a Ph.D. student could possibly hope to have at their disposal.

As for the rest of you, you know who you are. I am not even going to try to thank everyone by name; there are too many, and I don't want to leave anyone out. My time in Lab 29 has been enjoyable, enlightening and rewarding because of the ever-changing group of talented and creative individuals with whom I have had the privilege to work. I thank every last one of you.

Thanks also to my family and friends out in the real world, your support and encouragement have been invaluable.

Thanks finally to Karen, for everything.

List of Abbreviations

Å	Angstrom
Ar	Aryl
BAL	Backbone amide-linking
Calcd	Calculated
CB[n]	Cucurbit[n]uril
CD	Cyclodextrin
CPK	Corey-Pauling-Koltun
DBA^+	Dibenzylammonium
DCC	Dicyclohexylcarbodiimide
DMAP	4-Dimethylaminopyridine
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethylsulfoxide
DNA	Deoxyribonucleic acid
E	*Trans* isomer
EDCI	1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide
equiv	Equivalents
ESI	Electrospray ionisation
Et	Ethyl
FAB	Fast-Atom Bombardment
g	Grams
h	Hours
H-bond	Hydrogen bond
HBTU	*O*-(Benzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium hexafluorophosphate
HOBt	Hydroxybenzatriazole
HR-MS	High resolution mass spectrometry
J	Coupling constant
LR-MS	Low resolution mass spectrometry
Me	Methyl

mg	Milligram
MHz	Megahertz
min	Minutes
ml	Millilitre
mmol	Millimole
m.p.	Melting point
m/z	Mass-to-charge ratio
NMR	Nuclear magnetic resonance
Ph	Phenyl
ppm	Parts per million
rt	Room temperature
δ	Chemical shift
TBTU	*O*-(Benzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium tetrafluoroborate
THF	Tetrahydrofuran
TFA	Trifluoroacetic acid
TfOH	Trifluoromethanesulfonic acid
TLC	Thin-layer chromatography
TsOH	*Para*-toluenesulfonic acid
X^-	Unspecified anion
Z	*Cis* isomer

About the Structure of this Thesis

This thesis has been structured as a series of self-contained chapters. The first chapter is a survey of the relevant literature. The remaining four chapters are structured as journal articles, two of which have been published, and two of which are awaiting submission. Each chapter is therefore necessarily independent, and I apologise for any repetition in the introduction and references between chapters.

Chapter 1

Interlocked Molecular Architectures *via* Ammonium Templates

I: General Introduction

Aims

The aim of this survey is to introduce the reader to the various ways in which the ammonium group has been used to template the formation and to modulate the behaviour of interlocked molecular architectures. A wide variety of interlocked molecular topologies exist or have been proposed as synthetic targets,[1] however this survey will focus on the most common examples of this class of molecule: rotaxanes and catenanes.

Layout and Numbering

The ammonium group is a strong hydrogen bond donor,[2] and as such is frequently used as a recognition element, most commonly for a macrocycle or macrocycle precursor, en route to the synthesis of interlocked molecules. The intention has been to make this review section comprehensive. This survey is subdivided according to the type of macrocycle (or precursor) that has been used to bind the ammonium group. Two main areas make up the bulk of the survey, namely crown ether and cucurbituril systems, which are followed by the few examples that do not fall into either of these categories. Each section begins with a discussion of relevant non-interlocked complexes, before progressing to detail their interlocked counterparts and finally to discuss molecular scale devices. The section describing crown ether systems has been subdivided into two parts. The first part deals with complexes and interlocked molecules incorporating crown ethers based on the widely used [24]crown-8 framework. The second part details complexes and interlocked molecules incorporating crown ether macrocycles of other ring sizes and constitutions.

Compounds have been assigned numbers where the full structure (as opposed to a cartoon or other representation) has been shown, except in the case of simple molecules, for which the systematic name is given. Common crown ethers and the cucurbituril macrocycles are described by (hopefully more informative)

abbreviations based on their chemical names. Inclusion complexes are denoted by the compound numbers or abbreviations of their components, rather than having a separate compound number. Ammonium salts are named as their parent amines followed by the acid by which they have been protonated. Transition metal complexes are considered as single molecules.

1.1: An Introduction to Rotaxanes and Catenanes

1.1.1 Definitions and Terminology

Rotaxanes and catenanes are the most common examples of interlocked molecules.[1] A catenane (Figure 1a) consists of two macrocycles that are locked together like links in a chain. A rotaxane (Figure 1b) consists of a macrocycle threaded onto a linear component, and held there by the presence of two bulky blocking groups. The components of a rotaxane or catenane are held together by a mechanical bond: it is not possible to separate the two components without breaking one or more covalent bonds. It is important to emphasise that a mechanical bond is as significant as a covalent one – two mechanically interlocked components form a single molecule, just as two covalently linked ones do. Rotaxanes and catenanes are sometimes erroneously described as 'supramolecules', but although they are almost always derived from a precursor that is a supramolecular assembly, the rotaxane or catenane is itself a discrete molecular entity, often with dramatically different properties to its non-interlocked components. In addition to rotaxanes and catenanes there are numerous other examples of interlocked molecules including knots,[1, 3] bundles,[4] and the recently realised borromeates.[5]

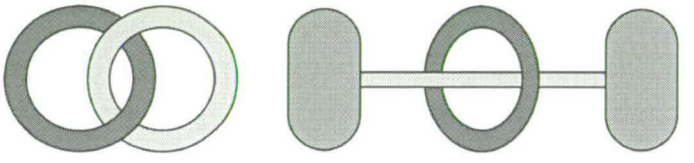


Figure 1. Representations of (a) a [2]catenane and (b) a [2]rotaxane

A number in square brackets prefixing the term 'catenane' or 'rotaxane' is used to denote the number of interlocked components. Thus a chain of four rings is a [4]catenane (Figure 2a), while two macrocycles entrapped on a single thread is a [3]rotaxane (Figure 2d). Note that this terminology does not attempt to describe the nature or connectivity of the interlocked components, therefore three macrocycles locked onto a central ring is also an example of a [4]catenane (Figure 2b). Similarly, two dumbbell shaped threads encircled and entrapped by a single macrocycle is a [3]rotaxane (Figure 2c).

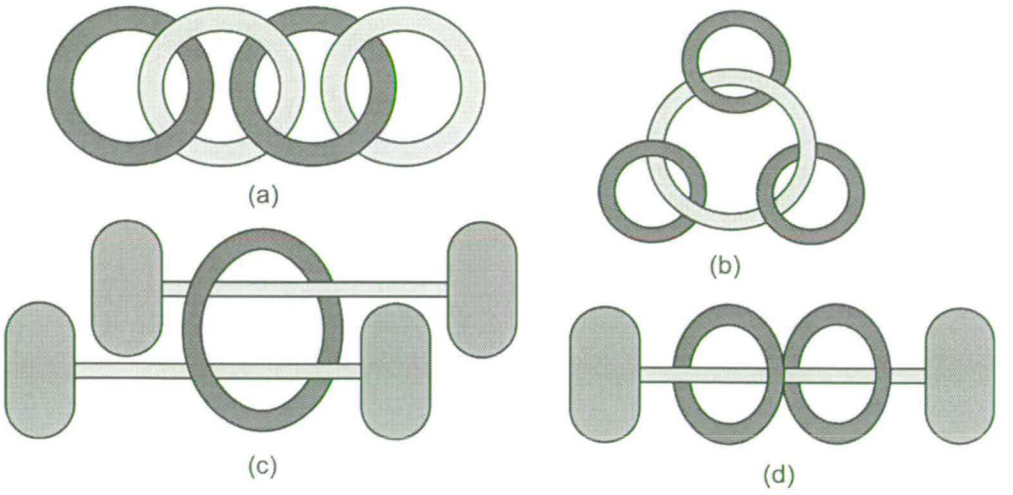


Figure 2. Representations of (a) and (b) [4]catenanes and (c) and (d) [3]rotaxanes

Non-interlocked analogues of rotaxanes or catenanes are often subjects of investigation in their own right, sometimes as a means of gaining insight into the nature of the intercomponent interactions that may be used to assemble an interlocked molecular architecture, and sometimes for the specific properties of the supramolecular assembly itself. The term 'pseudorotaxane' is used to describe a threaded (but not interlocked) assembly of a macrocycle and a linear component (Figure 3). A pseudorotaxane is simply an inclusion complex in which the included species protrudes from either side of the macrocyclic host.

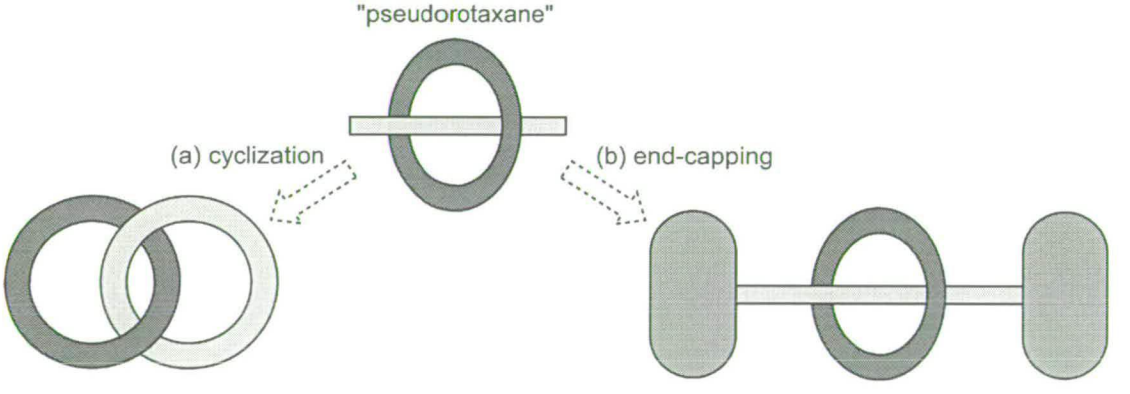


Figure 3: Intermediacy of a pseudorotaxane in the synthesis of rotaxanes and catenanes

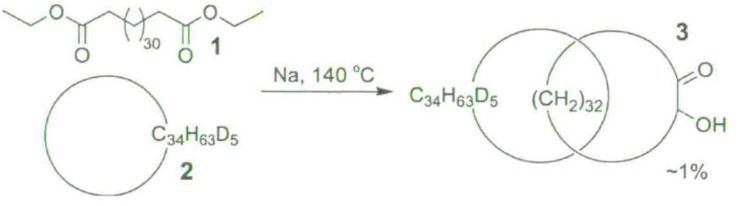
1.1.2 Historical Perspective

1.1.2.1 Statistical Methods

The earliest methods of producing interlocked molecules did not make use of any intercomponent interactions to bring the constituent parts together. Instead, a

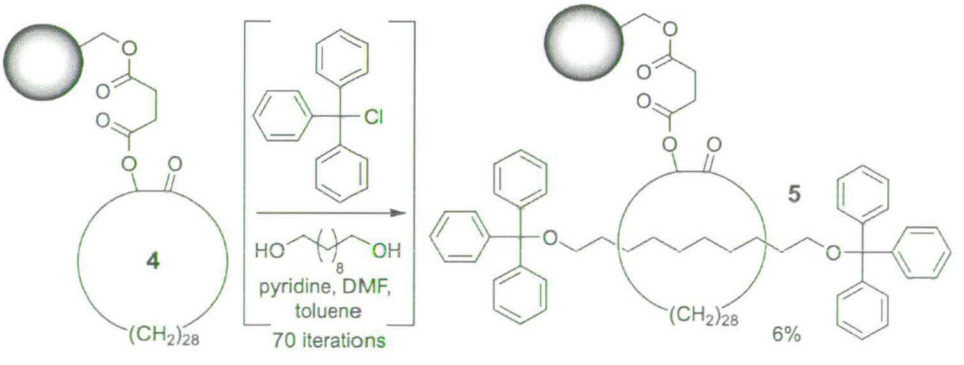
statistical approach was used, where the formation of an interlocked molecule was achieved by the chance interweaving of precursors during the course of a covalent modification. Reliance on such entropically disfavoured events means that statistical methods typically result in very low yields of interlocked products.

The first example of a synthetic catenane was achieved by Wasserman in 1960 (Scheme 1).[6] By conducting an acyloin condensation macrocyclization reaction of **1** in the presence of hydrocarbon macrocycle **2**, trace amounts of catenane **3** were produced.



Scheme 1. Statistical synthesis of a catenane

The first example of a synthetic rotaxane was described by Harrison and Harrison in 1967. The rotaxane was accessed *via* a statistical method, in which 1,10-decanediol was capped with trityl groups in the presence of resin-supported macrocycle **4**, resulting in small amounts of interlocked product.[7] To increase the yield of rotaxane the end-capping reaction was iterated seventy times. Despite this the final yield of rotaxane **5** was only 6%.

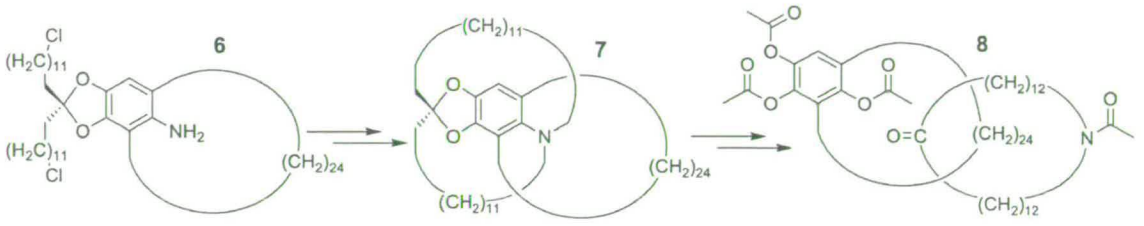


Scheme 2. Iterative statistical synthesis of a rotaxane

1.1.2.2 Directed Synthesis

An alternative approach to statistical methods is to use a covalent scaffold to assemble the elements of an interlocked structure, a method termed 'directed

synthesis'. A report by Schill and co-workers in 1964 describes the synthesis of a catenane by a directed covalent approach.[8] By making use of a central aromatic unit to direct the cyclization of one ring through another, followed by removal of the covalent link a catenane was accessed.



Scheme 3. Synthesis of a catenane by a directed covalent approach

Though this approach represents a leap forward compared to the inevitably low-yielding statistical methods, the large number of synthetic steps involved mean that the overall yield is still rather low at approximately 5%. Following this work various interlocked molecular architectures were produced, including catenanes, rotaxanes and knots.[9]

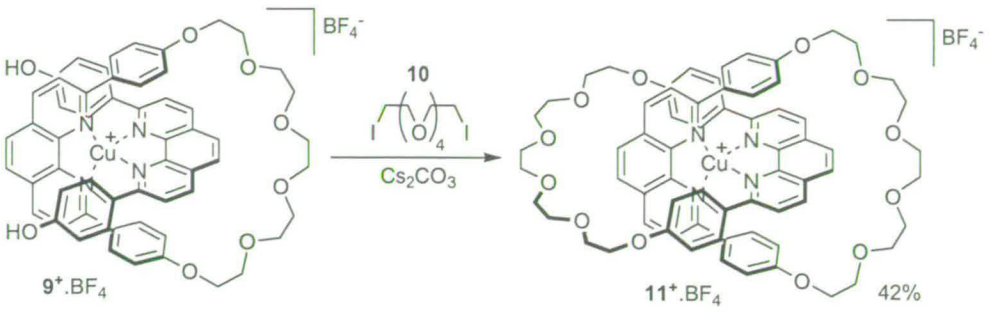
1.1.2.3 Noncovalent Templates

The advent of supramolecular chemistry provided the necessary understanding to make use of non-covalent forces as a means of controlling the spatial arrangement of the precursors to an interlocked structure. Various non-covalent interactions have been used to template the formation of interlocked molecular architectures. Representative examples of the main classes are illustrated below.

1.1.2.3.1 Transition Metal Coordination

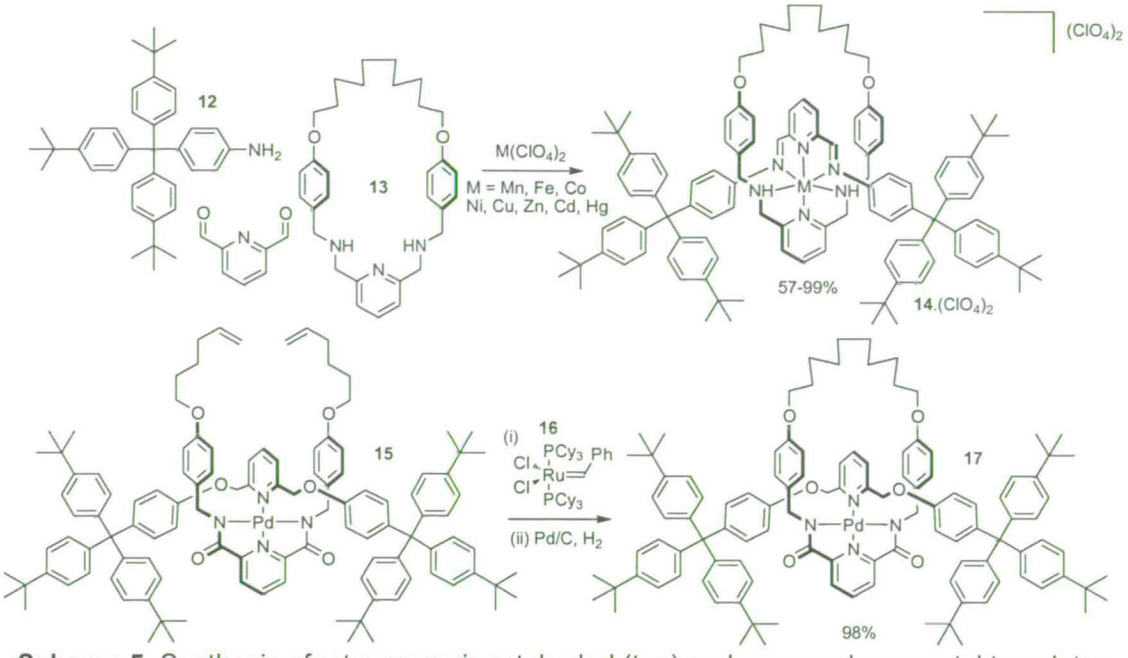
The well-defined geometries afforded by transition metal coordination complexes have been used for the synthesis of interlocked architectures in the ground-breaking work of Jean-Pierre Sauvage *et al.* Sauvage recognised that the mutually orthogonal arrangement of two phenanthroline ligands around a Cu(II) ion could be used to synthesise a catenate (the term 'catenate' is used to denote the metal complex of a catenane, 'catenand' denotes the demetallated ligand).[10] Alkylation of the copper(I) complex $\mathbf{9}^{+}.BF_4$ with diiodide **10** gave the catenate $\mathbf{11}^{+}.BF_4$ (Scheme 4). The Sauvage group has since used templates of this type to synthesise a wide variety of

interlocked molecular structures including molecular knots[11] and prototype 'molecular muscles'.[12]



Scheme 4. A Cu(I) templated catenate

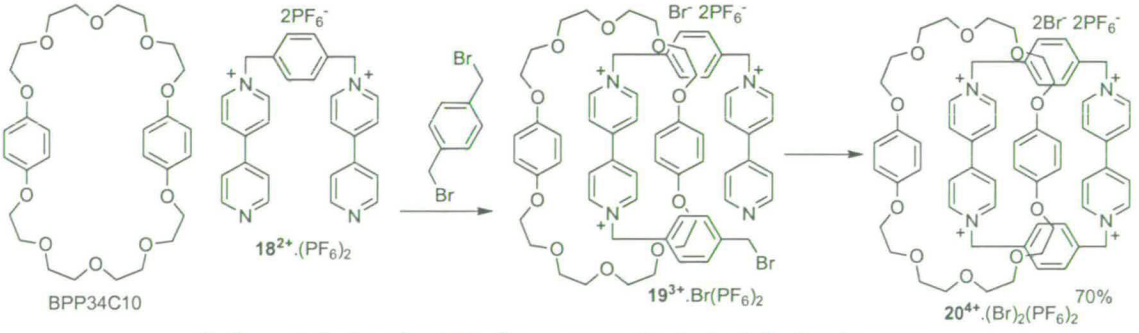
The Leigh group has demonstrated the use of octahedral and square planar coordination motifs in the synthesis of rotaxanes and catenates. Catenates and rotaxanes based on an octahedral coordination geometry were formed under thermodynamic control by the construction of an imine ligand system around a transition metal ion (Scheme 5, top).[13] In the presence of macrocycle **13** and a transition metal ion, two equivalents of bulky amine **12** condense with pyridine-2,6-dicarbonyl to give rotaxane **14**. Rotaxanes based on a square planar coordination system were accessed from complex **15**, in which a monodentate pyridine based ligand and a pyridine-2,6-dicarboxamido macrocycle precursor are coordinated to a Pd(II) ion.[14] Steric and electronic factors result in the ligands adopting a mutually orthogonal arrangement that is necessary for the formation of the interlocked product on ring-closing metathesis of the macrocycle precursor catalyzed by ruthenium species **16**.



Scheme 5. Synthesis of rotaxanes *via* octahedral (top) and square planar metal templates

1.1.2.3.2 Aromatic Interactions

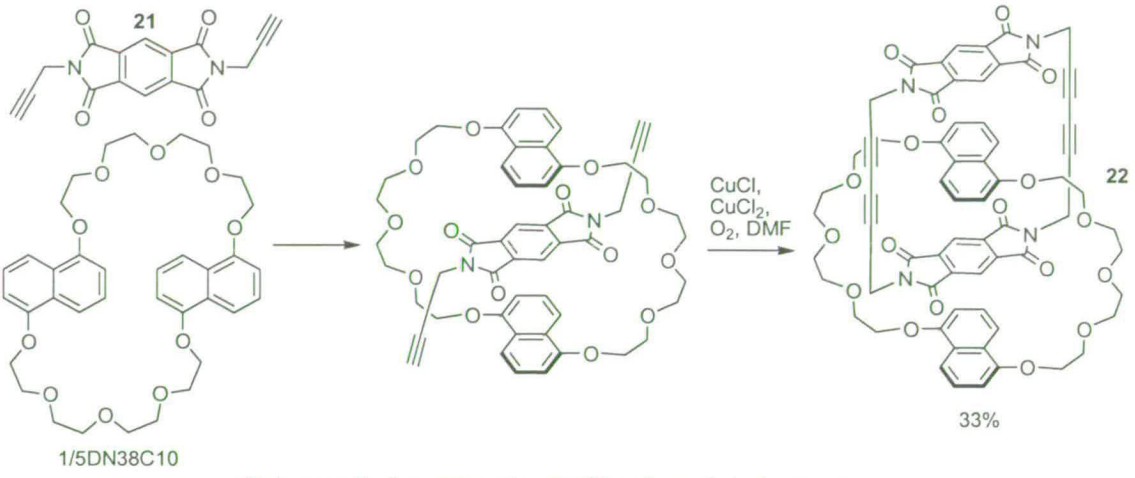
In the early 1990's Fraser Stoddart and co-workers reported the synthesis of a catenane based on an electron-rich crown ether macrocycle and an electron-poor paraquat-based macrocycle (Scheme 6).[15] A complex between *bis-para*-phenyl[34]crown-10 (BPP34C10) and $\mathbf{19}^{3+}.Br(PF_6)_2$ is formed due to a combination of electrostatic interactions, aromatic stacking and hydrogen bonding, allowing the catenane $\mathbf{20}^{4+}.(Br)_2(PF_6)_2$ to form in high yield. This type of donor-acceptor template has since been widely exploited, mainly by the Stoddart research group, for the synthesis of a wide variety of interlocked molecular architectures.[16]



Scheme 6. An electron donor-acceptor templated catenane

Aromatic interactions between neutral species have been exploited by the group of Sanders for the synthesis of a catenane.[17] Diimide units of the type **21** form inclusion

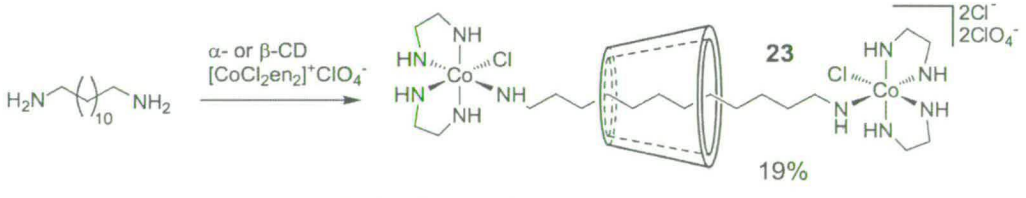
complexes with 1,5-dinaphtho-[38]crown-10 (1/5DN38C10). By carrying out a Glaser coupling of two equivalents of the diimide, catenane **22** is synthesised (Scheme 7).



Scheme 7. An aromatic stacking templated rotaxane

1.1.2.3.3 Hydrophobic Interactions

In 1981 Ogino reported the synthesis of the cyclodextrin–based rotaxane **23** by the end-capping of an inclusion complex between α- or β-cyclodextrin.[18] Hydrophobic interactions favour the inclusion of the hydrocarbon chain of 1,12-dodecylamine within the cavity of the cyclodextrin macrocycle. The amine functionalities of the thread then coordinate to Co(III) complexes, which act as stoppers (Scheme 8).

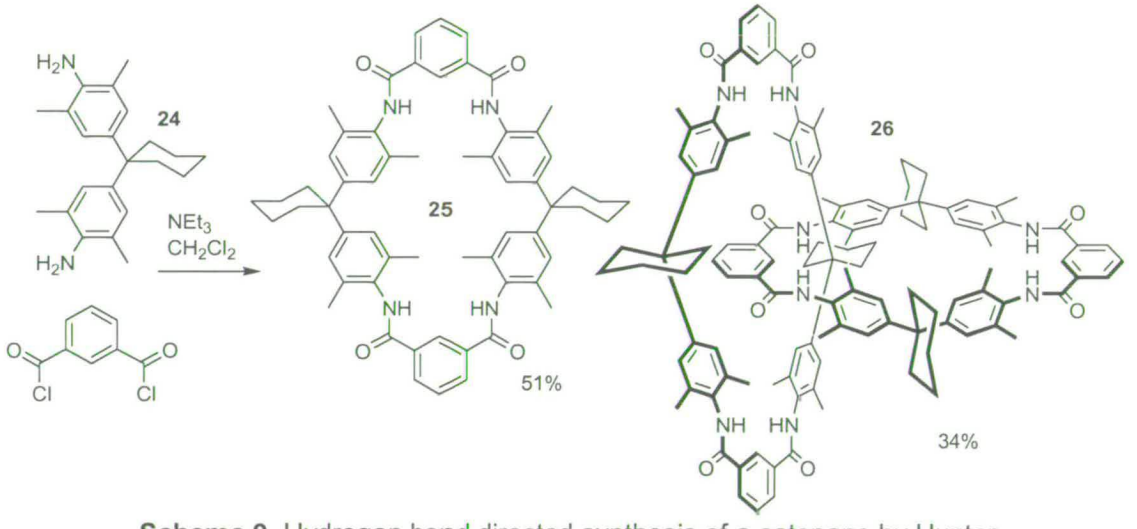


Scheme 8. Synthesis of a cyclodextrin rotaxane

Cyclodextrins have since been used for the synthesis of various discrete rotaxanes, including encapsulated dyes, in which an organic chromophore is protected from degradation by an encircling macrocycle.[19] Cyclodextrin macrocycles have also been used extensively for the formation of polyrotaxanes,[20] including 'insulated molecular wires', in which a linear conducting polymer is encircled by multiple cyclodextrin macrocycles.[21]

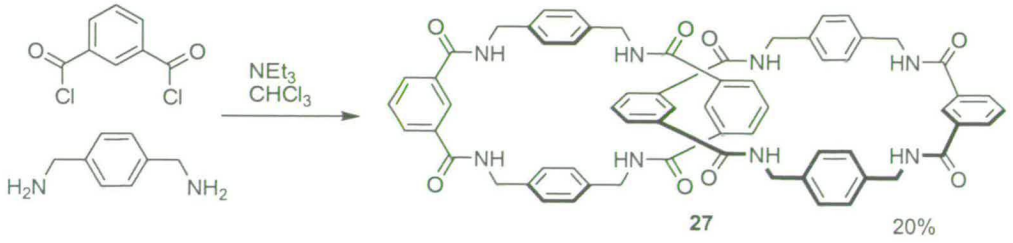
1.1.2.3.4 Hydrogen Bonding

Hydrogen-bond templated catenanes were first accessed in the early 1990's with the serendipitous discovery of a [2]catenane by Hunter.[22] When attempting to synthesise quinone receptor **25** by a macrocyclization reaction between the amine **24** and isophthaloyl dichloride, catenane **26** was formed as a co-product in a yield of 34% (Scheme 9). The interlocked nature of the product was confirmed by an elegant series of NMR experiments, and later by an X-ray diffraction crystal structure.[23] A related catenane was reported soon afterwards by Vögtle and co-workers.[24] The Vögtle group has since reported the synthesis of a variety of interlocked molecular architectures, particularly knots, based on hydrogen bond templates.[25]



Scheme 9. Hydrogen bond directed synthesis of a catenane by Hunter

The hydrogen bond templated synthesis of a structurally very simple catenane was reported by the Leigh group in 1995.[26] Catenane **27** was the unexpected product of an attempt to produce the corresponding macrocycle by a reaction between *para*-xylylenediamine and isophthaloyl dichloride (Scheme 10). The Leigh group has since reported the synthesis of various rotaxanes and catenanes, including various switchable molecular devices, and catenanes in which the direction of circumrotation of one ring about the other can be controlled.[27]



Scheme 10. Hydrogen bond directed synthesis of a catenane by Leigh *et al.*

1.1.2.4 Interlocked Peptides

Though interlocked structures have been well documented in DNA systems for many years,[28] it is only comparatively recently that interlocked structures have been identified in peptides and proteins.[29] This is in part because interlocked motifs are often buried deep within the folds of a protein, and are not immediately apparent; indeed, computational methods have been used to identify knots 'hidden' within proteins.[30]

One of the largest regular catenated structures known is the capsid shell of bacteriophage HK97.[31] This virus is protected by a regular polyhedral peptide shell that has been likened to chain mail armour. The capsid is formed by the self-assembly of an icosahedral structure from 420 identical protein subunits. Ligation of each of the subunits to two of its neighbours results in a catenated structure in which twelve pentameric and sixty hexameric rings are intertwined with an adjacent ring at each vertex. The high stability of this remarkable molecule was shown to be directly attributable to its interlocked nature.

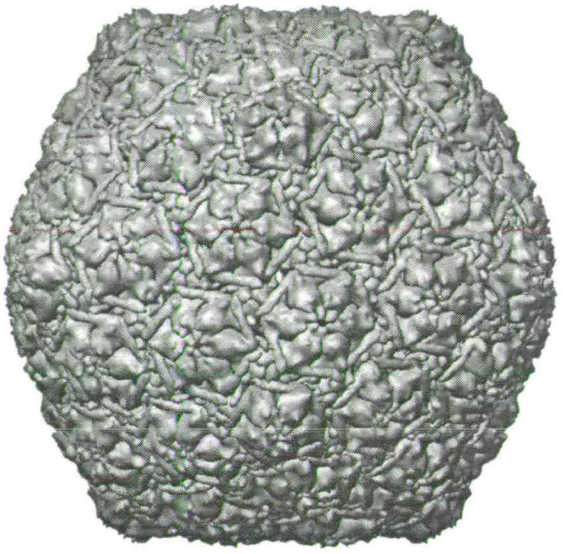


Figure 4. A representation of the HK97 capsid (Reproduced from http://www.cgl.ucsf.edu/Research/virus/capsids/viruses.html)

Probably the most common form of mechanically interlocked motif within proteins is not formed directly from the peptide backbone, but rather by disulfide formation between the side chains of cysteine residues, resulting in a knotted structure. 'Cystine knots' have been found in various proteins,[29, 32] and are a defining and conserved feature of several classes of plant peptides including the cyclotides. Small cystine knots of this type are characterised by a compact knotted structure resulting from the formation of three internal disulfide bonds. The cyclotides are distinguished by also having a head-to-tail cyclized peptide backbone. Cyclotide proteins are found in plants of the *Violacaea*, *Rubiaceae* and *Cucurbitaceae* families and have variously been shown to have anti-tumour,[33] anti-HIV,[34] uterotonic[35] and antimicrobial activities.[36] A characteristic property of this class of peptide is an exceptionally high resistance to chemical, thermal and enzymatic denaturation.

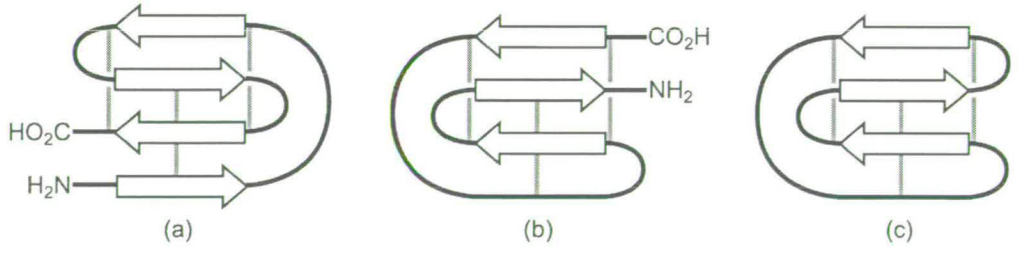


Figure 5. Representations of the structures of growth factor cystine knot (a), inhibitor cystine knot (b) and cyclotide (c). Arrows represent β-sheet regions, disulfide bonds are indicated by grey lines.

Microcin J25 (MccJ25) is a small antimicrobial peptide that is secreted by certain strains of *E.coli* to mediate microbial competition. This peptide was originally thought to be circular,[37] but was later shown to have a more unusual interlocked structure (Figure 6).[38] An octapeptide macrocycle is formed by an amide linkage between the *N*-terminus and the carboxylic acid side chain of the eighth amino acid, a glutamate residue. The *C*-terminus of the peptide is 'threaded' through this macrocycle, and is unable to escape due to the steric bulk of the aromatic side chain groups of a tyrosine residue on one side and a phenylalanine residue on the other. The rotaxane substructure of this peptide has been shown to survive in the absence of the covalent connection between the two components- i.e. the molecule has a true rotaxane substructure.[39] The presence of a mechanical bond is thought to be the source of the remarkable resistance to enzymatic and chemical degradation exhibited by MccJ25. A similar structure has recently been found to exist in the 'lariatin' peptides expressed by a strain of Rhodococcus bacteria.[40]

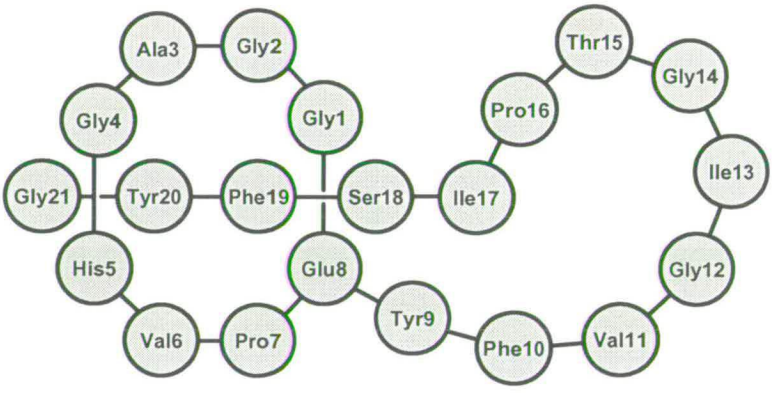
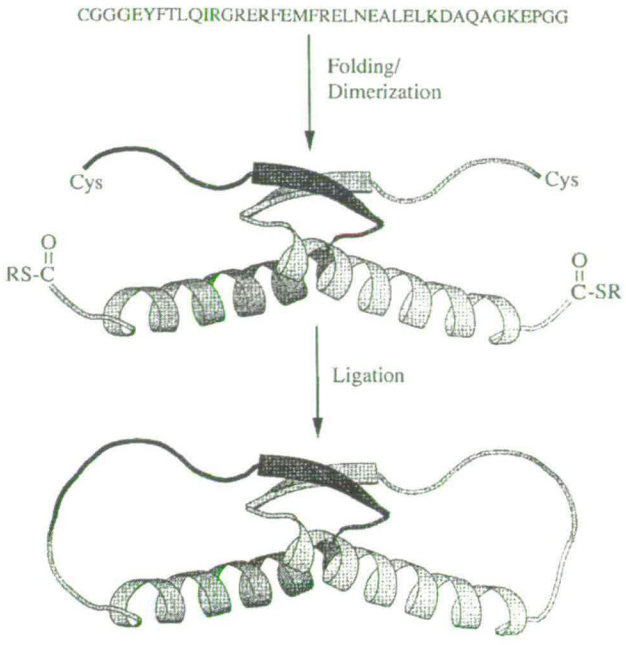


Figure 6. A schematic representation of MccJ25.

The research group of Dawson has reported the synthesis of a catenane based on a dimeric protein.[41] The p53 tumour suppressor protein is known to exist in a dimeric form consisting of two intertwined peptide chains. A modified version of this protein dimer was doubly cyclized by native chemical ligation to produce a catenane (Scheme 11). A later study examined the thermodynamic properties of the catenane, and showed that the apparent melting temperature of the catenane was around 59 °C higher than that of the p53 protein dimer.[42]



Scheme 11. Synthesis of a protein catenane (reproduced from reference 41).

1.2: Crown Ether–Derived Rotaxanes and Catenanes

1.2.1 About Crown Ethers

Crown ethers can be most basically described as cyclic oligomers of the -CH_2CH_2O- repeat unit. First realised by Pedersen in the 1960's, this class of molecule has gone on to become one of the cornerstones of supramolecular chemistry. The first crown ether was isolated as a by-product from a reaction intended to yield the phenolic complexing agent **28** for dications (Figure 7).[43] In addition to the intended molecule small quantities of the macrocyclic product dibenzo[18]crown-6 (DB18C6) were found to crystallise out of the reaction mixture. The macrocyclic product was observed to have a high binding affinity for potassium ions, despite being neutral itself.

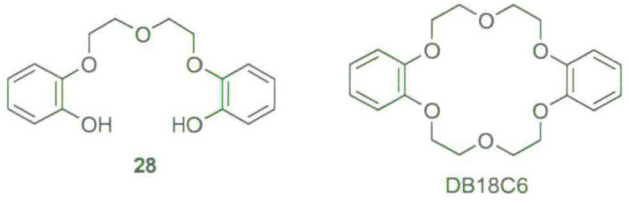


Figure 7. Pedersen's intended target (left) and the actual product, dibenzo[18]crown-6

The ability of crown ethers to bind ammonium ions was recognised during Pedersen's original investigation, though complexes were only reported for primary amines.[43] It was not until 1995, some three decades later, that it was shown that rotaxanes could be accessed by binding a secondary ammonium ion with a suitably sized crown ether macrocycle.[44]

Since the initial development of crown ethers, a bewildering array of related macrocycles have been described.[45] Variation of the size of the ring, the number and type of heteroatoms and the number and type of rigid elements have all been explored extensively. A recent review estimates the number of different crown ether macrocycles in the literature to be in the region of 10,000.[46] A naming convention whereby the name is constructed by taking the number of ring atoms in square brackets followed by 'crown' then the number of electron donor atoms. A prefix

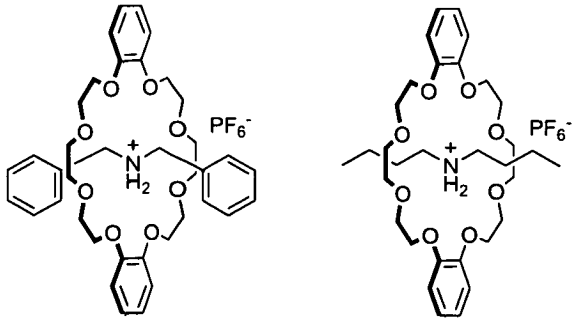
describes any substitution of the assumed basic ethylene glycol repeat unit. This naming system is not perfect, but is less cumbersome than many of the alternatives.

1.2.2 [24]Crown-8 Macrocycles

Of the wide variety of crown ethers employed in the synthesis of interlocked molecules, those with a [24]crown-8 constitution, particularly dibenzo[24]crown-8 (DB24C8), have been investigated the most. These systems are discussed in this section.

1.2.2.1 Pseudorotaxanes

Shortly following the publication of the first crown ether-ammonium rotaxane by the Busch group (*vide infra*) a series of publications from the group of Fraser Stoddart[47-49] provided a more detailed investigation into the nature of the interactions between secondary ammonium salts and DB24C8. The DB24C8 macrocycle was found to form pseudorotaxanes with both dibenzylammonium (DBA^+) and di-*n*-butylammonium salts The pseudorotaxane structure was found in each case to be maintained by a series of N-H and N-C-H to oxygen hydrogen bonds, as well as π-π interactions in the case of DBA^+. The degree of association between ammonium species and macrocycle was found to be strongly dependant on solvent polarity, favouring apolar, noncompeting solvents such as $CHCl_3$, in which association constants in the order of 10^4 M^{-1} are observed. In all solvents investigated the association constant for pseudorotaxane formation was several times higher for DBA^+ than for di-*n*-butylammonium, an effect attributed to the higher acidity and preorganization of DBA^+, as well as its ability to participate in aromatic interactions with the host. The rate of exchange between the free and complexed forms of the ammonium species were slow on the NMR timescale for the more sterically encumbered DBA^+ cation, whereas the di-*n*-butylammonium species exchanged rapidly on the NMR timescale.



(a) (b)

Figure 8. DB24C8 pseudorotaxanes of DBA^+ (a) and dibutylammonium (b) salts.

The Stoddart group has established the existence of a linear free-energy relationship for the complexation of various derivatives of DBA^+ with DB24C8.[50] For a range of symmetrical DBA^+ derivatives, substituted at the *meta* or *para* positions of each ring, the association constants with DB24C8 were determined. The association constants were found to vary according to the Hammett substituent constant (σ), with a 'reaction' constant (ρ) of around +1, indicating that the positive charge on the DBA^+ derivative is partially attenuated on formation of the complex with DB24C8. The range of association constants is attributed to the differing ability of the variously substituted DBA^+ derivatives to act as hydrogen bond donors and to engage in π-stacking interactions with DB24C8. Variation of the structure of the macrocycle was investigated in a later study.[51] It was shown that the ability of a macrocycle with a [24]crown-8 constitution to bind to DBA^+ ions was inversely proportional to the number of benzo substituents on the macrocycle, dropping from a value of 1700 M^{-1} for [24]crown-8 to 320 M^{-1} for DB24C8 for the association of $DBA.HPF_6$ in acetonitrile at 300K. Tetrabenzo[24]crown-8 was later shown to form pseudorotaxane complexes with DBA^+ ions in the solid state but not in solution.[52]

A study by the group of Loeb has introduced the *N*-benzylanilinium group as a recognition motif for the formation of pseudorotaxanes with DB24C8 (Figure 9).[53] A small series of *N*-benzylanilinium salts having different substituents at the *para*-position of each aromatic ring (**29a-d**) were found to form pseudorotaxane complexes with both DB24C8 and [24]crown-8. The nature of the substitution on the aromatic rings of the ammonium species was shown to have an influence on the binding constant, with lower degrees of association where electron donating groups

partially attenuate the positive charge of the anilinium group. The *N*-benzylanilinium threads are much more acidic than their DBA^+ counterparts, and require an excess of a strong acid such as trifluoromethanesulfonic acid to be fully protonated.

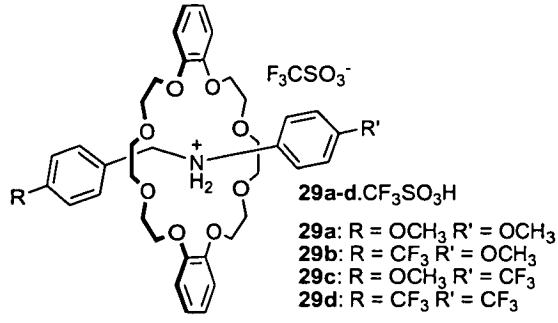


Figure 9. Pseudorotaxane complexes of *N*-benzylanilinium salts

Following an earlier report by the Balzani group detailing the photochemical aspects of binding between DB24C8 and the protonated form of 9-methylaminomethylanthracene[54] a more detailed study was undertaken in collaboration between the Balzani and Stoddart groups.[55] The mode of binding between (9-anthracenyl)methylbenzylammonium hexafluorophosphate and DB24C8 is analogous to that observed previously between DBA^+ salts and the same macrocycle. Formation of the pseudorotaxane has significant photochemical consequences: an intermolecular energy transfer results in quenching of the fluorescence of the macrocycle and a concomitant sensitisation of the anthracene fluorescence. The Stoddart group has further reported the use of a DBA^+/DB24C8 pseudorotaxane motif as one end of a 'molecular extension cable'.[56] The DB24C8 macrocycle of **30** acts as a socket into which a molecular 'wire' $\mathbf{31}^{2+}.H(PF_6)_3$ terminating in a DBA^+ moiety is docked. The ruthenium (II) complex of **30** acts as a photoinduced electron donor to a bipyridinium group further along the 'wire', triggering the dissociation of a 1/5DN38C10 macrocycle.

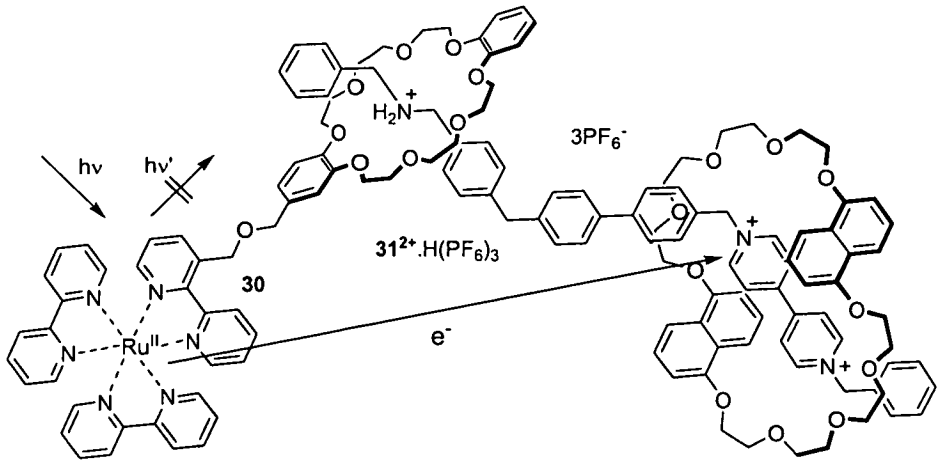


Figure 10. A 'molecular extension cable'.

A thorough investigation of the ability of benzo[24]crown-8 (B24C8) to form pseudorotaxane complexes was carried out by the group of Daryle Busch.[57] A series of secondary ammonium salts, including **32a-l**.HSCN, were found to form pseudorotaxane complexes with B24C8, with association constants in the region of 10-300 M^{-1} in acetone at 25 °C (Figure 11). The ability of the ammonium salts to bind the crown ether macrocycle was found to be reduced when there was steric bulk close to the ammonium ion, and was completely prevented for a *t*-butyl substituted ammonium species. Different length straight chain alkyl substituents were found not to affect the binding constant, but for longer chains the rate of exchange between the bound and free states was observed to be lower, presumably because only certain conformations of the alkyl chain allow passage of the macrocycle.

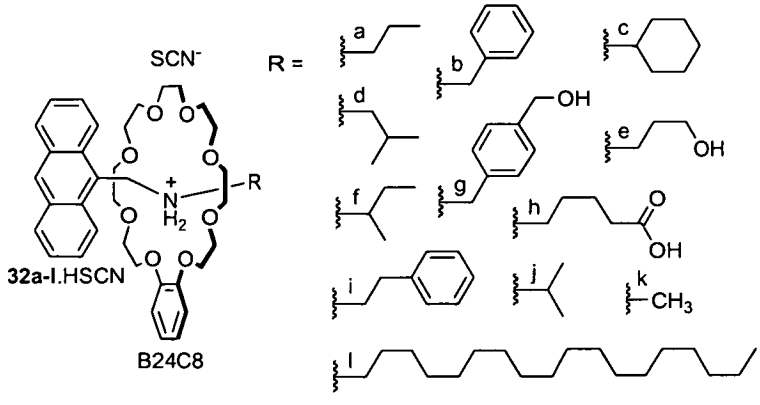


Figure 11. Representative examples of pseudorotaxane structures investigated by Loeb *et al.*

A study by Jones and Gibson investigates the influence of ion pairing on complex formation, taking as a model system the inclusion of a DBA^+ ion by DB24C8.[58] The ability of different DBA^+ salts to form pseudorotaxane complexes with DB24C8 was studied. It was found that in an apolar solvent, a pre-equilibrium ion pair dissociation event must occur before the ammonium ion can be bound by the crown ether. Therefore the ability of different DBA^+ salts to form complexes with DB24C8 was related to the equilibrium constant for those salts to dissociate into solvent separated ion pairs.

A [3]pseudorotaxane has been reported by the Stoddart group.[59] The symmetrical thread **33**.$(HPF_6)_2$ was synthesised in which a central anthracene unit is flanked by two DBA^+ groups. This molecule was found to bind to two DB24C8 macrocycles simultaneously, with slight negative cooperativity due to competition between the two macrocycles for the limited π-stacking interactions afforded by the central anthracene moiety (Figure 12).

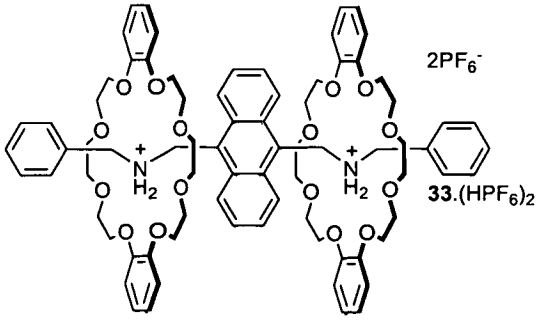
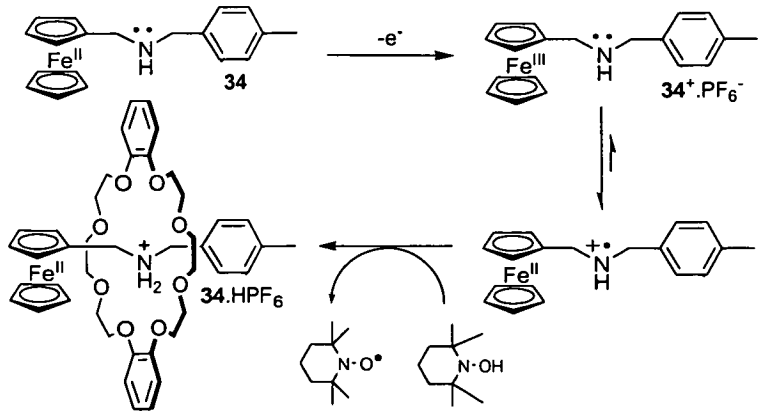


Figure 12. A [3]pseudorotaxane by Stoddart *et al.*

The group of Osakada has reported the formation of pseudorotaxanes *via* the electrochemical oxidation of ferrocene-based thread **34**.[60] Oxidation of the ferrocene unit to the ferrocenium Fe^{3+} species is followed by a single electron transfer from the adjacent amine of the thread. The resultant nitrogen radical cation then abstracts a hydrogen radical from an external source to form protonated thread **34**.HPF_6, and thence the pseudorotaxane.



Scheme 12. Electrochemical formation of a pseudorotaxane

An attempt at making inherently chiral pseudorotaxanes has been described by Lacour *et al.*[61] Unsymmetrical DB24C8 derived macrocycle **35** was found to exhibit no orientational preference in binding chiral secondary ammonium salt **36**.HPF$_6$ due to the distance between the ammonium ion and chiral group (Figure 13). A very slight (~8%) selectivity was detected when the chiral TRISPHAT anion was employed instead of PF_6^-.

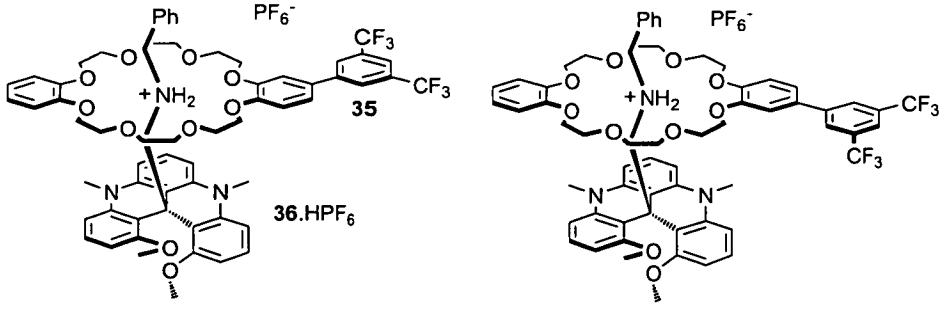


Figure 13. Diastereomeric pseudorotaxanes

A modified DB24C8 macrocycle has been used to create a supramolecular C_{60} dimer.[62] By fusing a C_{60} unit to each component of a DB24C8/DBA$^+$ recognition pair two fullerene groups can be held close in space without being covalently attached to one another. Similarly, the Stoddart group has described the use of a crown ether-ammonium ion binding event to arrange supramolecular dimers of phthalocyanine derivatives (Figure 14).[63] To achieve this end, macrocycle **37** was synthesised, in which a phthalocyanine moiety is fused onto a DB24C8 ring. These crown ether derivatives were found to form a 2:1 complex with *bis*-DBA$^+$ thread

38.$(HPF_6)_2$. The same DB24C8/phthalocyanine hybrid macrocycle was later used for the formation of a supramolecular phthalocyanine/fullerene ensemble.[64]

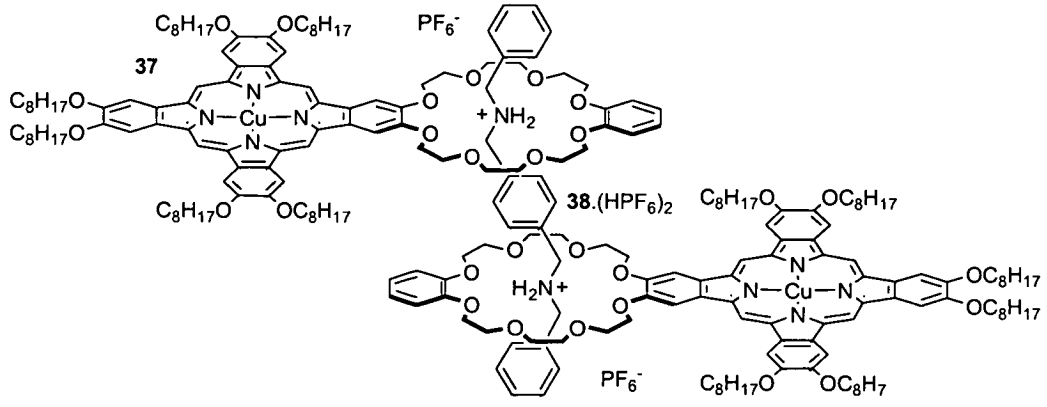


Figure 14. A [3]pseudorotaxane phthalocyanine dimer

Tokunaga and Seo have demonstrated the simultaneous operation of two orthogonal hydrogen bond recognition motifs in the formation of a pseudorotaxane dimer.[65] Macrocycle **39** consists of a DB24C8 unit attached to a self-complementary donor-donor-acceptor-acceptor hydrogen bond motif (Figure 15). The pseudorotaxane of this macrocycle and DBA^+ was shown to dimerize in apolar media. In related work the Stoddart group has shown that by functionalising DBA^+ units with one or more carboxyl groups it is possible to generate arrays of DB24C8 pseudorotaxanes in the solid state.[66]

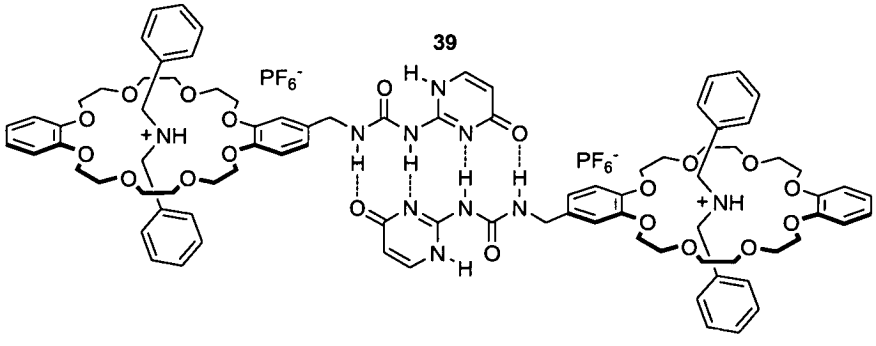
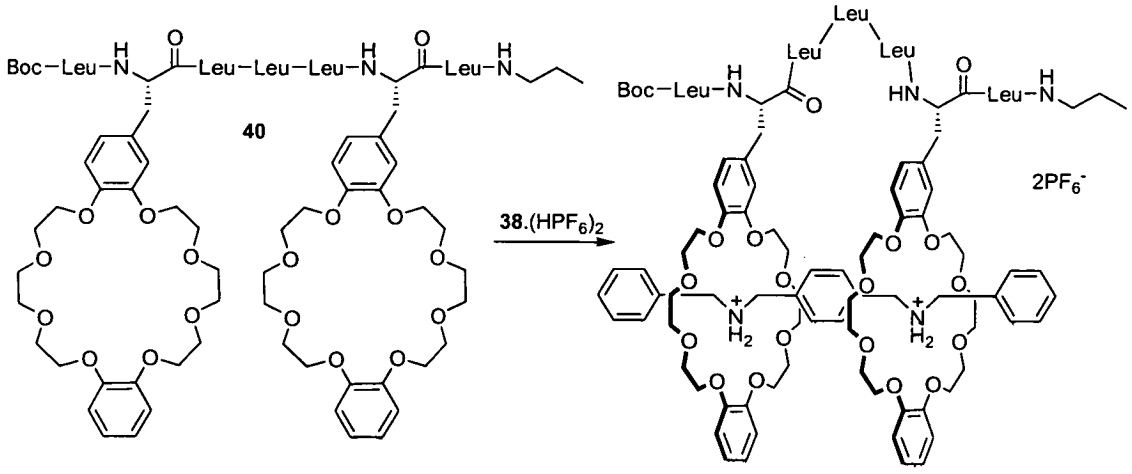


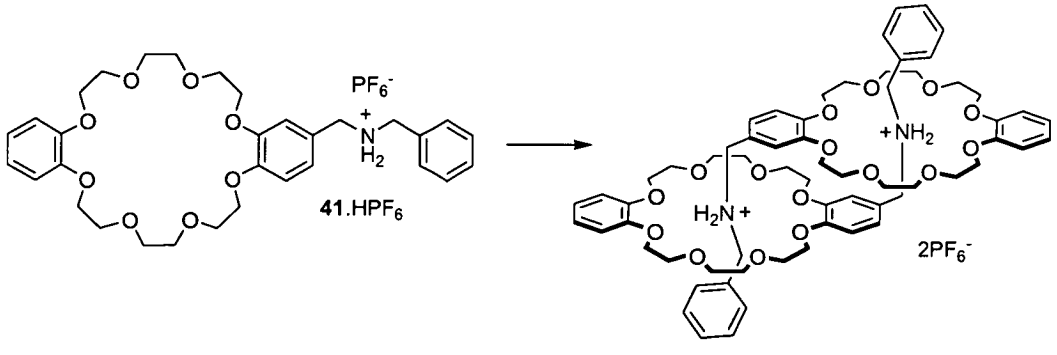
Figure 15. A pseudorotaxane dimer.

The Stoddart group has produced pseudorotaxanes from *bis*-DBA^+ thread **38**.$(HPF_6)_2$ and peptide chain **40**, which is functionalised with two DB24C8 macrocycles (Scheme 13).[67] Changes in the circular dichorism (CD) spectrum of the peptide on formation of the pseudorotaxane indicated that the peptide was induced to adopt a β-turn conformation.



Scheme 13. Conformational change of a peptide by pseudorotaxane formation

The formation of supramolecular 'daisy chain' species has been reported by the Stoddart research group.[68] By directly linking a DBA^+ unit to one of the catechol rings of a DB24C8 macrocycle, these workers created the species **41**.HPF_6 that is self-complementary, but that cannot 'bite its own tail'- *i.e.* bind to its own ammonium group. It was supposed that this molecule could form high order linear or cyclic polymers, but in fact the only species that was observed was the [c2]daisy chain, in which two of the units dimerize (Scheme 14). The absence of higher oligomers is attributed to high enthalpic and entropic costs of forming larger arrays under thermodynamic control.



Scheme 14. Formation of a supramolecular [c2]daisy chain

A report by the Stoddart group describes the formation of a 'supramolecular bundle'.[69] The bundle is a pseudorotaxane formed between triphenylene based *tris*-(crown ether) **43** and *tris*-DBA^+ thread **42**.$(HPF_6)_3$ (Figure 16). The two units were observed to form a [1 + 1] complex in the solid state and in solution, with each of the

ammonium groups of **42**.$(HPF_6)_3$ docked into one of the DB24C8 units of **43**. The decomplexation of the two components was studied by monitoring the changes to the ^1H NMR spectrum while gradually titrating DMSO into an equimolar solution of **42**.$(HPF_6)_3$ and **43** in the otherwise noncompeting solvent mixture of 1:1 $CDCl_3/CD_3CN$. As the percentage of DMSO is increased the bound form of the two components gradually becomes less favoured and new signals appear for the species where one, two, or three of the DBA^+ arms have been dissociated from the crown ether unit. At a DMSO concentration of ~33% the complex is completely disrupted.

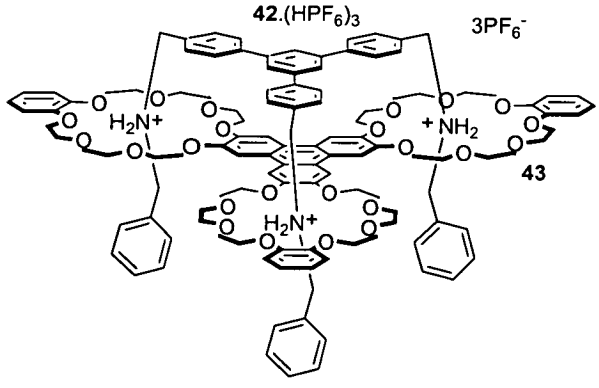


Figure 16. A supramolecular bundle

A report by Han and Chen describes the formation of pseudorotaxanes from a host consisting of two DB24C8 rings fused to a triptycene core.[70] The host was found to bind two DBA^+ units simultaneously, one in each DB24C8 region. A variant of this receptor **44**, in which two DB24C8 macrocycles are fused to two triptycene units, was later used as the core of a dendritic [3]pseudorotaxane structure formed by association of two equivalents of dendron **45**.HPF_6 (Figure 17).[71]

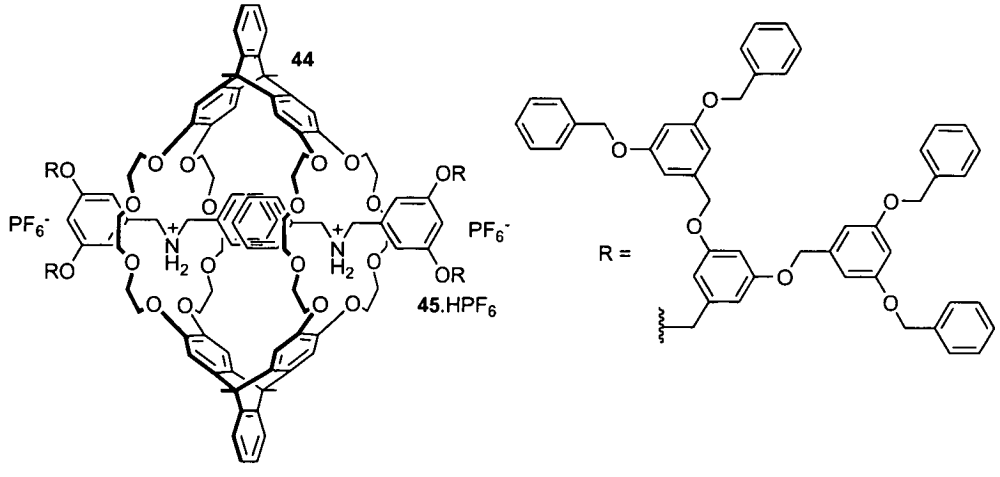


Figure 17. [3]Pseudorotaxane dendrimer.

The Stoddart group has reported the formation of self-assembled 'dendronized polymers'.[72] Polymerisation of suitably functionalised DB24C8 derivatives gave crown ether-appended polystyrene (**46a**) or polyacetylene (**46b**) chains. Formation of pseudorotaxane links between the crown ether polymer and DBA^+ functionalised Frechet-type dendrons **47a-c**.HPF_6 resulted in a supramolecular dendrimer.

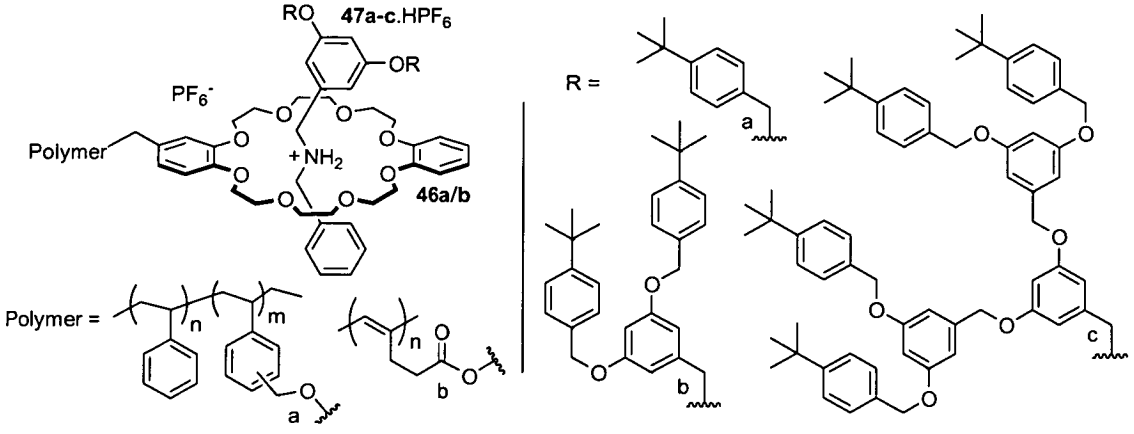
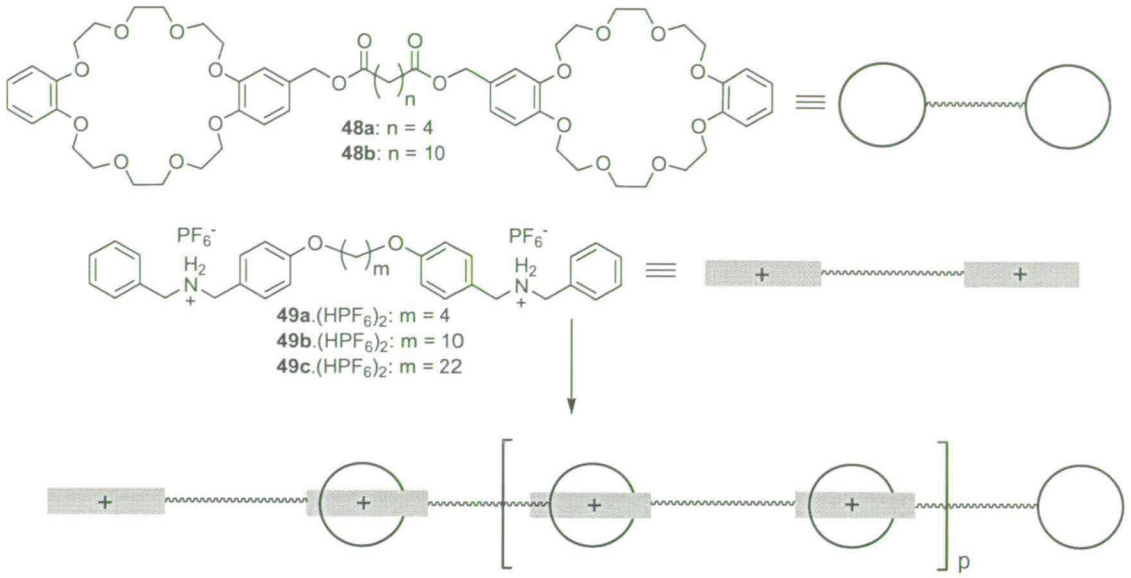


Figure 18. 'Dendronized polymers'

A report by the Gibson group describes the formation of pseudorotaxane polymers from complementary pairs of homoditopic molecules.[73] This work examined the ability of *bis*-crown ethers **48a/b**, consisting of two DB24C8 macrocycles linked by different lengths of flexible spacer, to form complexes with *bis*-ammonium threads **49a-c**.$(HPF_6)_2$, in which two DBA^+ groups are similarly connected by different flexible spacers. It was found that in general, longer spacers diminished the formation of cyclic oligomers in favour of linear species. It was demonstrated that the pseudorotaxane polymers could be cast into thin films or pulled into fibres.



Scheme 15. Formation of pseudorotaxane polymers

Fitzmaurice *et al.* have demonstrated the formation of DB24C8/DBA$^+$ pseudorotaxanes on the surface of a gold nanocrystal.[74] By using DB24C8-derived macrocycle **50** bearing a thiol tether it was possible to adsorb a monolayer onto the surface of gold spheres of around 40 Å diameter, from which pseudorotaxanes were formed after the addition of a DBA$^+$ salt (Figure 19). A further study by the same group describes the controlled aggregation of silver nanoparticles by pseudorotaxane formation.[75]

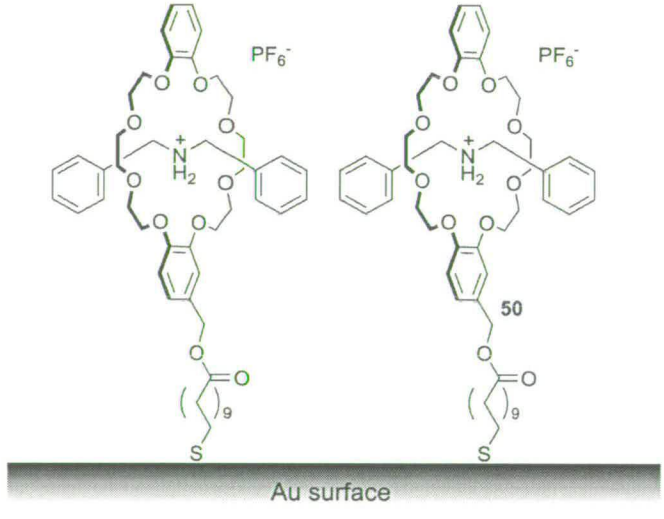
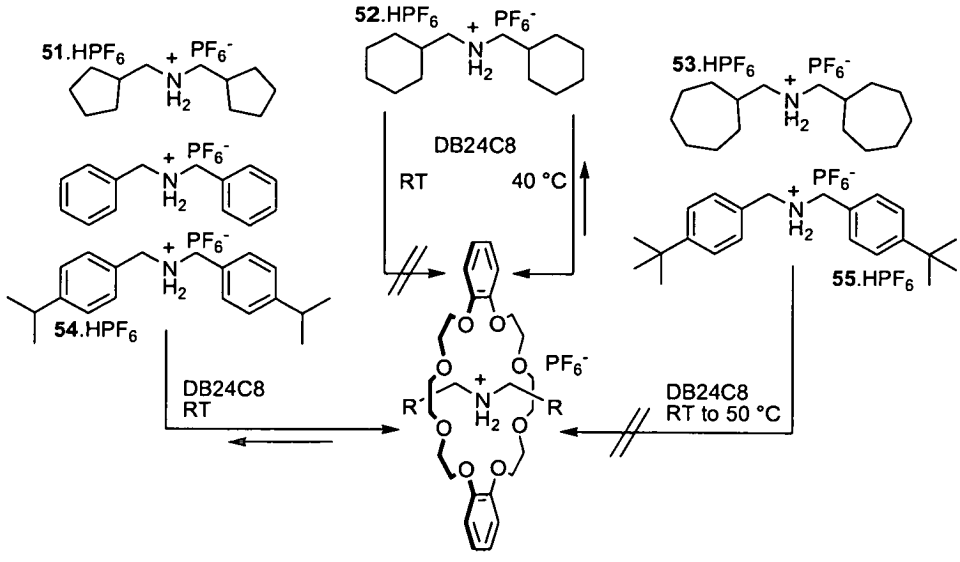


Figure 19. Pseudorotaxanes on the surface of a gold nanoparticle

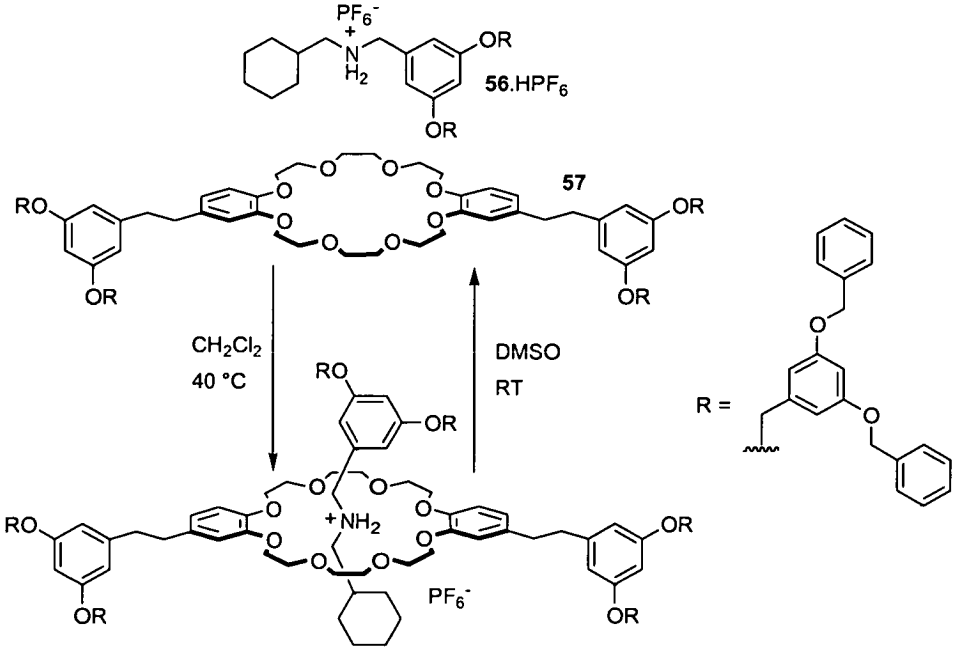
1.2.2.2 The Grey Area: 'Rotaxane-Like Complexes' by Slipping

A study by the Stoddart group has probed the 'grey area' between rotaxanes and pseudorotaxanes by assessing the ability of a range of threads to form complexes with DB24C8 (Scheme 16).[76] The threads all featured the same central -$CH_2NH_2^+CH_2$- unit, but had different cycloalkyl or aryl substituents on either side of this. The degree to which a DB24C8 ring was able to slip over the flanking groups was determined for a range of different conditions for each thread. It was found that the macrocycle is able to slip over a *para*-isopropylbenzyl group of **54**.HPF_6 but not a *para-tert*-butylbenzyl group of **55**.HPF_6. Similarly, the cyclopentyl group of **51**.HPF_6 provided little impediment to the movement of the macrocycle, whereas the cycloheptyl ring of **53**.HPF_6 completely prevented the macrocycle from slipping onto the ammonium group. The intermediate cyclohexyl substituted thread **52**.HPF_6 allowed the exchange of DB24C8 on and off the ammonium group at 40 °C in CH_2Cl_2, but not at 20 °C in the same solvent. The authors conclude that the boundary between rotaxane and pseudorotaxane is not well defined, being strongly dependant on conditions, particularly solvent and temperature, and is better described as a fuzzy transition region in which differing degrees of rotaxane-like character are exhibited. A subsequent report by Tokunaga and co-workers probed the effect of pressure on the kinetics of complexation of DBA^+ or *bis*(cyclohexylmethyl)ammonium salts with DB24C8.[77] The rate of inclusion was found to increase with increasing pressure, an effect attributed to the reduction in free volume on formation of the inclusion complex.



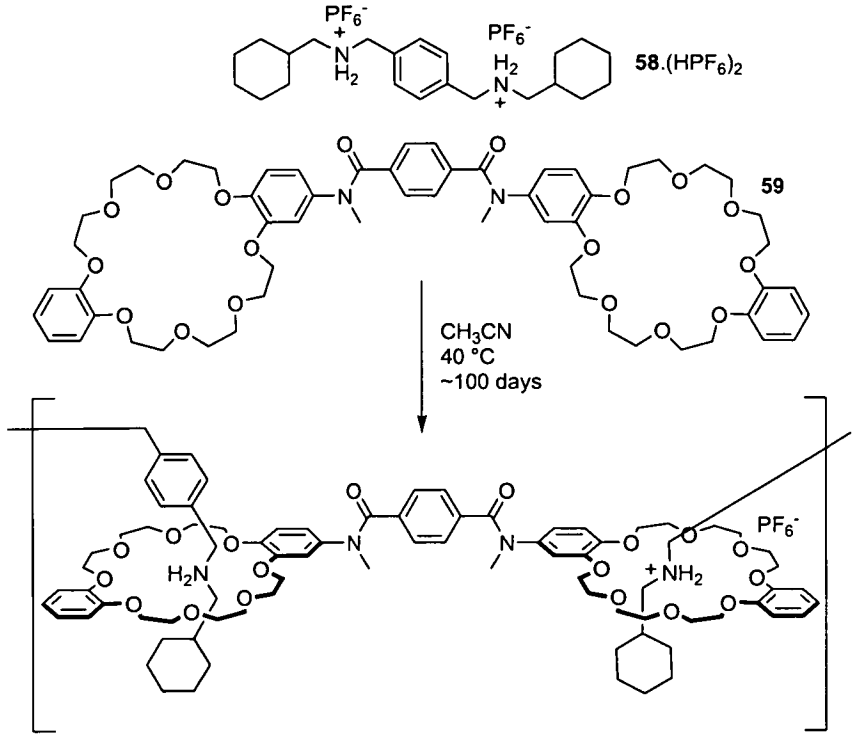
Scheme 16. Pseudorotaxanes and rotaxane-like complexes by slipping

A slippage process has been exploited by the Stoddart research group for the formation of dendrimers linked by rotaxane-like complexes using the DB24C8 macrocycle **57**, which bears two dendritic units (Scheme 17).[78] At 40 °C in CH_2Cl_2 a rotaxane-like structure is formed between the macrocycle and cyclohexylmethylammonium-derived dendritic unit **56**.HPF_6. The resultant dendrimer was stable at room temperature in apolar media, but dissociated into its constituent parts in polar media such as DMSO.



Scheme 17. Formation of a dendrimer linked by a rotaxane-like complex

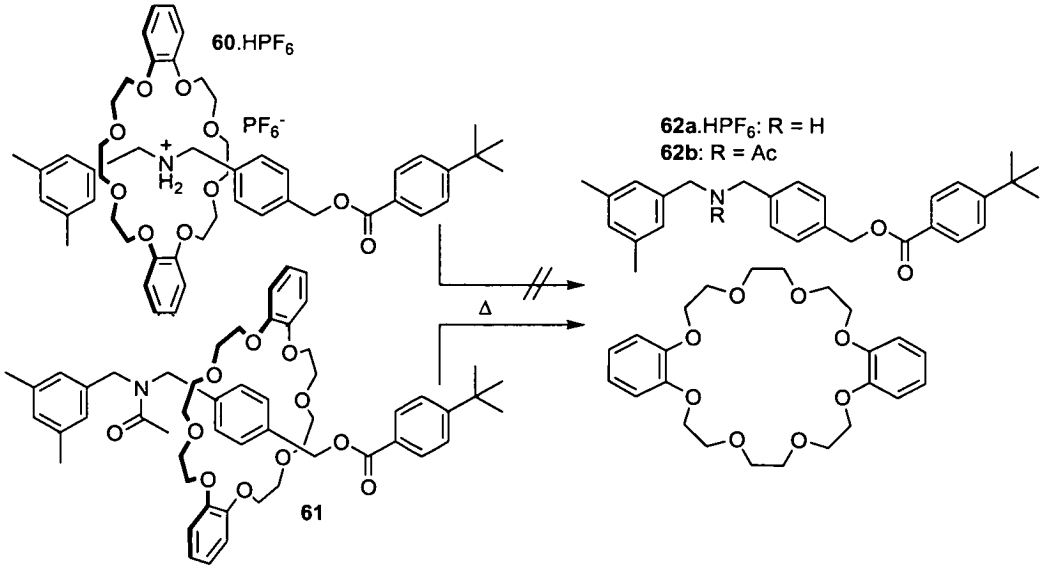
The condition-dependent slipping methodology established by Stoddart has been employed by Takata for the formation of polymeric materials linked by rotaxane-like complexes.[79] By incubating *bis*-ammonium salt **58**.$(HPF_6)_2$ terminating in cyclohexyl groups with *bis*-crown ether **59** an assembly was generated that at room temperature in an apolar solvent behaved as a stable poly[3]rotaxane, but that dissociated rapidly in polar solvents such as DMSO.



Scheme 18. Polyrotaxane-like assembly by slipping

A study by the Takata group has attempted to determine whether or not the *tert*-butyl group is large enough to act as a true stopper for the DB24C8 macrocycle.[80] Though widely employed as a stopper, the *tert*-butyl group appeared (in molecular models) to actually be slightly smaller than the cavity of the DB24C8 macrocycle. The propensity of a *tert*-butyl 'stoppered' rotaxane to dethread under a variety of conditions was therefore studied. Rotaxane **60**.HPF_6, having a DBA^+ template, DB24C8 macrocycle and a *para-tert*-butylphenyl group at one terminus of the thread, was observed to be stable in DMSO at 100 °C for 31 days, with no release of thread **62a**.HPF_6 (Figure 19). The template interaction between thread and macrocycle was then removed by acylation of the thread to give neutral species **61**. A solution of **61** in DMSO at 45 °C was observed to completely dissociate into free

thread **62b** and rotaxane in 5 days. Repeating the same experiment with a 3,5-dimethylphenyl stoppered analogue did not result in dissociation of the components in either the ionic or 'neutralised' (acylated) rotaxanes. It was therefore concluded that the *tert*-butyl group is not large enough to function as a true stopper for DB24C8 under all conditions, and furthermore that the presence of a template interaction between macrocycle and thread can increase the apparent bulk of an end-capping group.



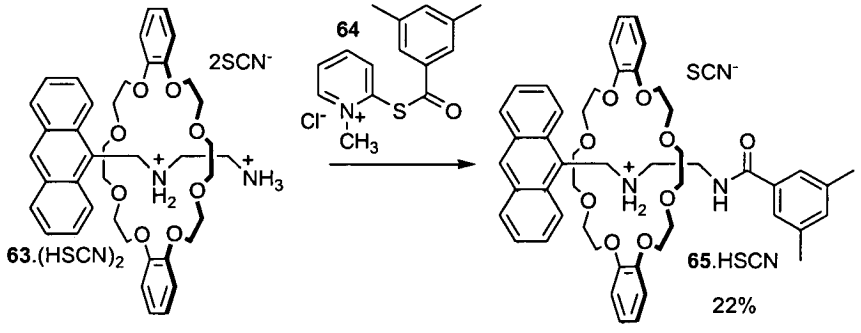
Scheme 19. Dethreading over a *para-tert*-butylbenzyl group

This result may appear to be something of an aporia in light of the earlier slipping experiments by the Stoddart group, and seems to relegate some rotaxanes to mere rotaxane-like complexes. The critical difference in this instance is the lack of template interaction in **61**, which elevates the ground state of the macrocycle with respect to the energy barrier presented by the *tert*-butylphenyl group. The same situation does not apply for slipping *on* to a thread, even in the presence of a template interaction, so this result does not contradict Stoddart's observations. Furthermore, so long as the ammonium template remains in place, a *tert*-butylphenyl stoppered 'rotaxane' should be kinetically inert and behave as a 'true' rotaxane.

1.2.2.3 Rotaxanes by End-Capping

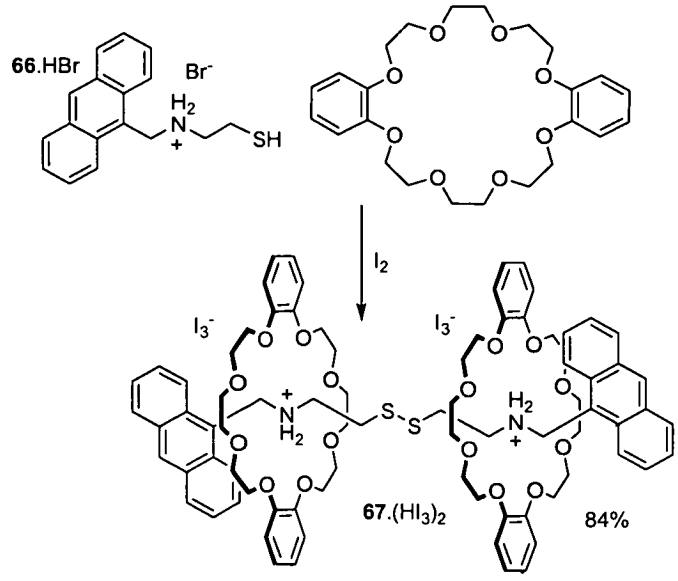
1.2.2.3.1 Interlocking Under Kinetic Control

The first report of the use of ammonium binding by crown ether macrocycles as a basis of interlocked architectures occurs in a publication from the group of Daryle Busch.[44] It was shown that anthracene derivative **63**.$(HSCN)_2$ could be acylated with **64** in the presence of DB24C8 to produce rotaxane **65**.HSCN (Scheme 20). In contrast to later work these workers carried out the acylation reaction in the presence of a molar equivalent of a tertiary amine base (Bu_3N). Comparatively low yields of rotaxane (12%) were obtained when the reaction was carried out as a homogenous process in chloroform. The yield of rotaxane was found to increase to 22% when the analagous reaction was carried out as a biphasic process between water and chloroform. The authors propose that rotaxane formation is favoured in the biphasic case because the intermediate pseudorotaxane may be stabilised at the phase boundary, where acylation is most likely to occur.



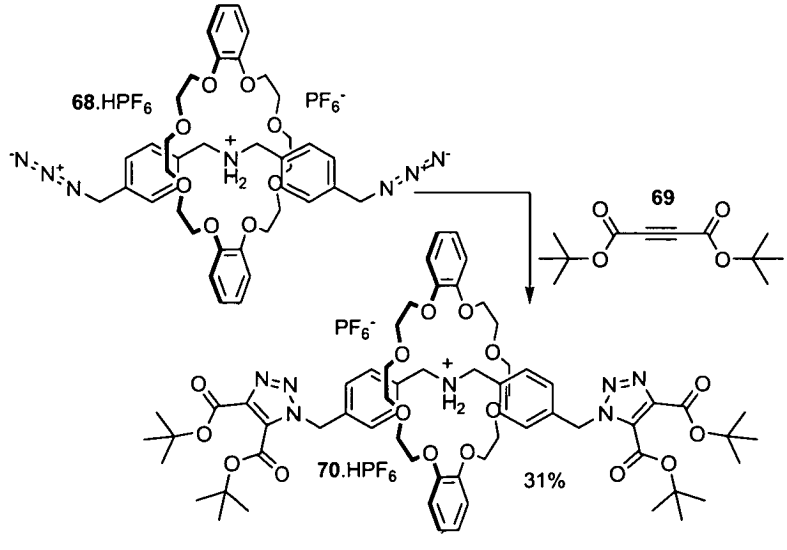
Scheme 20. Synthesis of the first crown ether rotaxane by Busch *et al.*

The Busch group has reported the formation of a [3]rotaxane in high yield by the dimerization of thiol-terminated thread **66**.HBr in the presence of DB24C8 (Scheme 21).[81] Oxidation of the thread with molecular iodine furnished the symmetrical disulfide linked [3]rotaxane **67**.$(HI_3)_2$ in an 84% yield.



Scheme 21. Rotaxane formation by oxidative disulfide formation

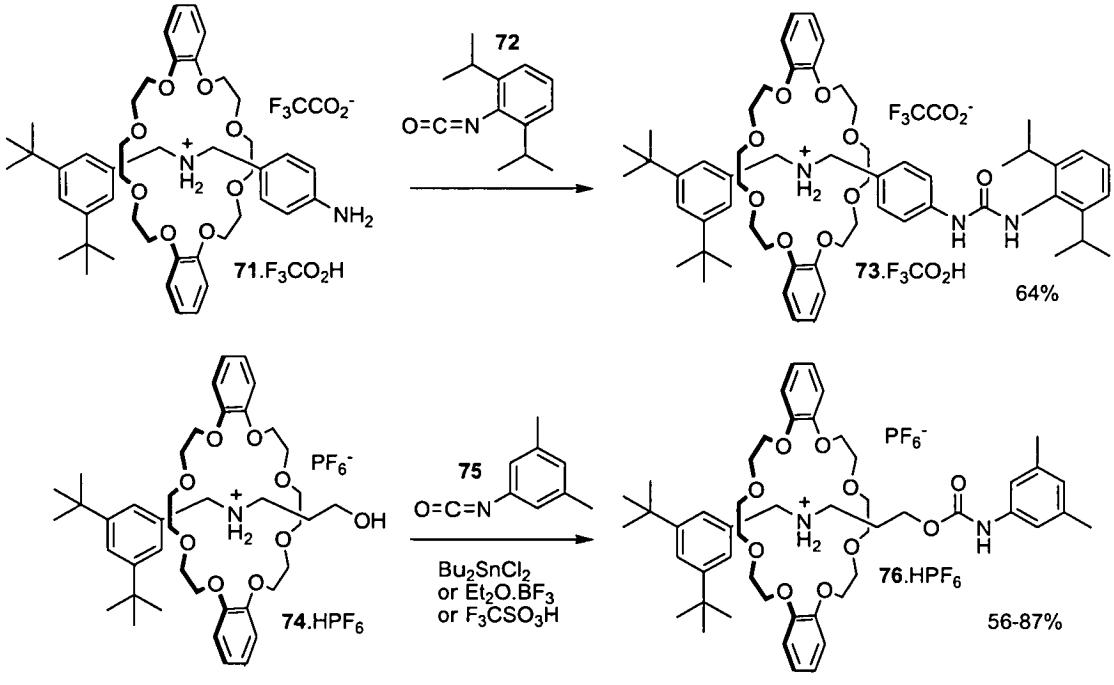
The Stoddart group has made use of a 1,3-dipolar cycloaddition reaction between a bulky alkyne and an azide to synthesise rotaxanes (Scheme 22).[47, 82] The inclusion complex of **68**.HPF_6 with DB24C8 undergoes a thermally activated cycloaddition with alkyne **69** to give rotaxane **70**.HPF_6 in a 31% yield. Using this method [3]rotaxanes were prepared in moderate yields, though attempts at producing a symmetrical two-station [2]rotaxane were unsuccessful. This end-capping protocol was later applied to the synthesis of a mechanically interlocked bundle.[83]



Scheme 22. End-capping by cycloaddition

The Stoddart group has reported the synthesis of a DBA/DB24C8 based rotaxane by a end-capping method in which bulky aryl isocyanate **72** reacts with aniline-

terminated thread **71**.F_3CCO_2H to give the urea-stoppered rotaxane **73**.F_3CCO_2H in a 64% yield (Scheme 23, top).[84] An extension of this method by the Takata group made use of a Lewis or Brönsted acid catalyst to allow the reaction of isocyanate **75** with alcohol-terminated thread **74**.HPF_6 to give the carbamate-stoppered rotaxane **76**.HPF_6.[85]

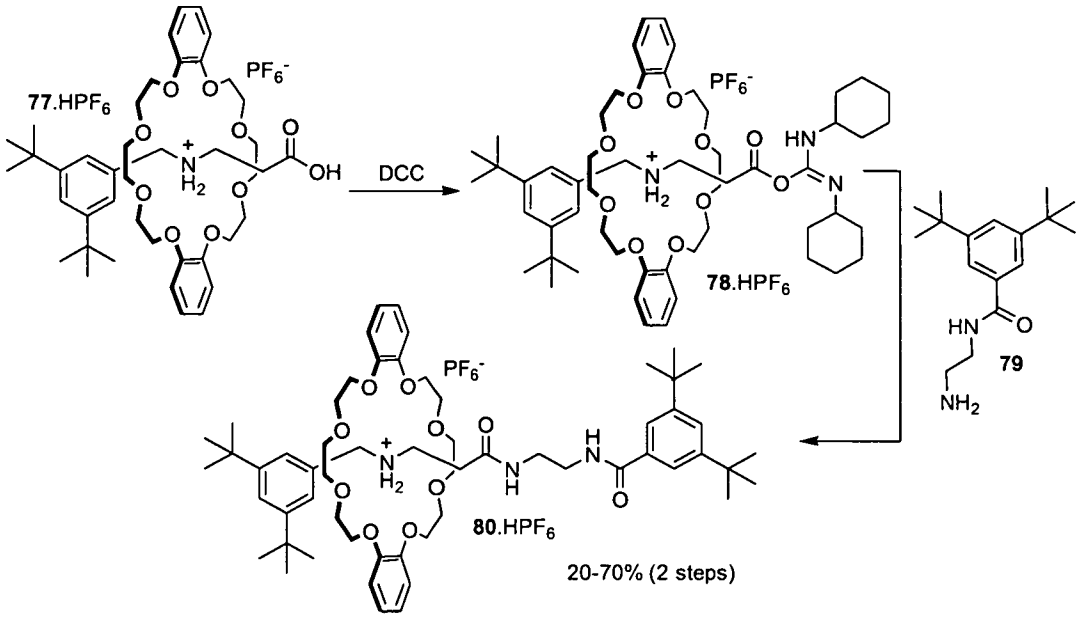


Scheme 23. Urea (top) and carbamate stoppered rotaxanes by addition to isocyanates

The Takata group has used the reaction between a bulky isocyanate and an alcohol-terminated ammonium thread to synthesise a range of rotaxanes in which a fullerene moiety is appended to a DB24C8-type macrocycle.[86] By introducing bulky electron donating groups as stoppers it was possible to study photoinduced intercomponent electron-transfer processes between the fullerene group and the thread.

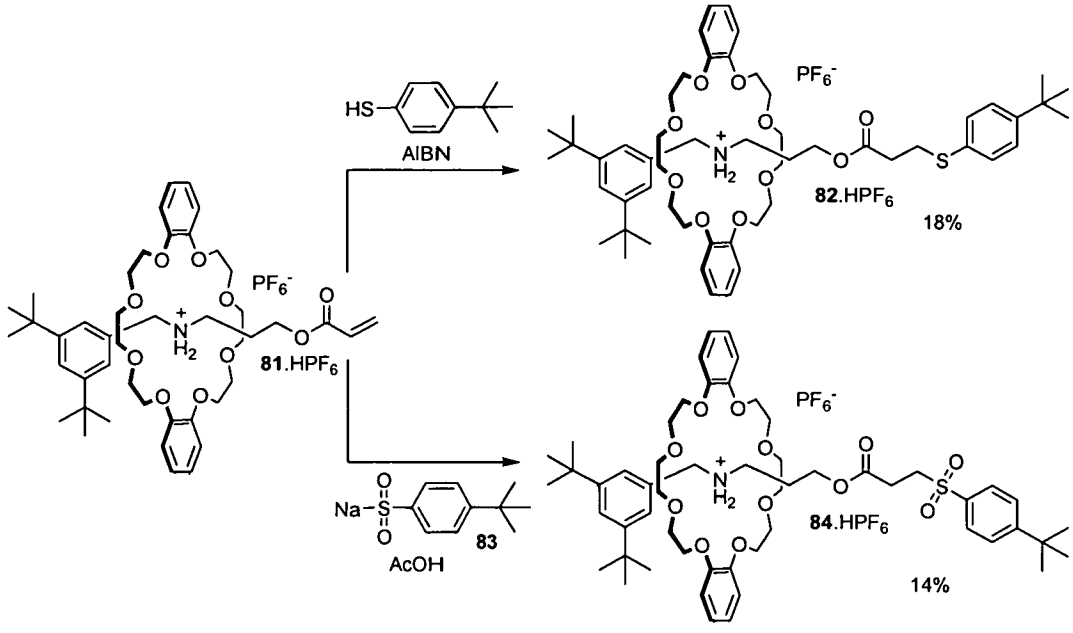
A report by Zehnder and Smithrud details the formation of activated ester-stoppered rotaxanes stoppered by reaction of a carboxylic acid thread with dicyclohexylcarbodiimide (DCC).[87] Mono-stoppered ammonium thread **77**.HPF_6, terminating in a carboxylic acid group, was treated with DCC in the presence of DB24C8 to give activated-ester stoppered rotaxane **78**.HPF_6 (Scheme 24). Subsequent reaction of this rotaxane with amine **79** gave access to the amide-linked rotaxane **80**.HPF_6. This methodology was later exploited to form rotaxanes in which

interactions between amino-acid moeities appended to the thread and macrocycle were examined.[88] The DCC-stoppered rotaxane was also used to synthesise rotaxanes stoppered at one end with a hydrophobic cyclophane as potential cell-transport agents.[89]



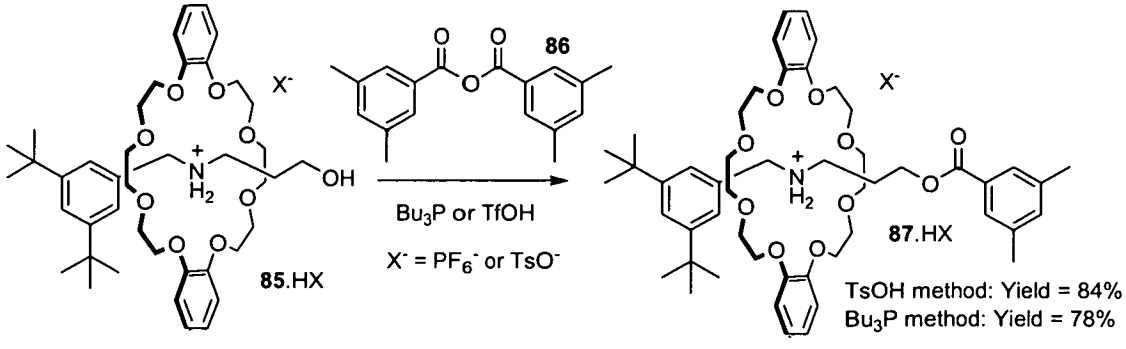
Scheme 24. A DCC-stoppered rotaxane and its subsequent reaction with a bulky amine

The research group of Takata has described the formation of a rotaxane *via* the conjugate addition of *para-tert*-butylthiophenol under radical conditions to mono-stoppered thread **81**.HPF_6 in the presence of DB24C8 to give rotaxane **82**.HPF_6 in an 18% yield (Scheme 25).[90] Addition of bulky sodium sulfinate **83** to the same substrate was carried out under acidic conditions to give rotaxane **84**.HPF_6 in a 14% yield.



Scheme 25. Synthesis of rotaxanes by conjugate addition

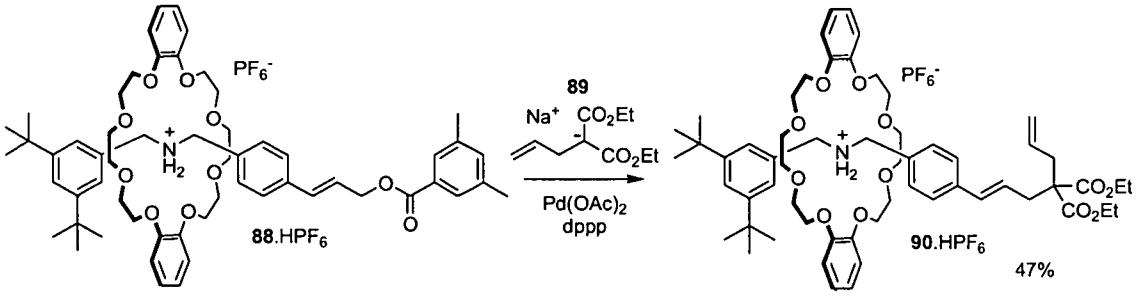
A report by Takata *et al.* demonstrates the direct preparation of a rotaxane from a protonated amino alcohol thread, DB24C8 and a bulky anhydride, and details the sensitivity of this process to the nature of the acid used to form the ammonium template.[91] Trifluoromethanesulfonic acid was found to catalyse the *O*-acylation of thread **85**.TsOH by anhydride **86**, while maintaining complete protonation of the ammonium group, preventing *N*-acylation, to give rotaxane **87**.TsOH (Scheme 26). Tributylphosphine can be used as a nucleophilic catalyst to effect the same transformation, but under milder conditions.[92] Using this methodology rotaxanes were prepared in high yields. A further extension of this methodology was to make use of a thiolester as a mild acylating agent.[93] This modification circumvents some of the problems associated with the use of an anhydride, particularly the epimerization of chiral acids.



Scheme 26. End-capping by *O*-acylation under nucleophilic or acidic catalysis

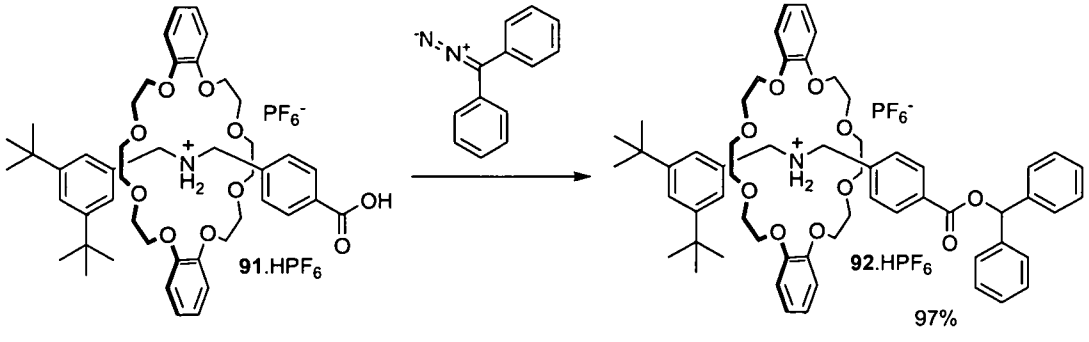
The Takata group have made use of their tributylphosphine catalysed acylation protocol in the synthesis of [3]- and [5]rotaxanes from threads with two or four ammonium sites, respectively.[94] The same methodology has also provided access to a ferrocene-stoppered rotaxane.[95]

The Takata group have detailed a method of exchanging the stoppering group of a rotaxane using the Tsuji-Trost allylation reaction.[96] Rotaxane **88**.HPF_6 (accessed using the Bu_3P catalysed acylative end-capping method described above), in which one of the stoppers is a cinnamyl ester, was treated with malonate ester anion **89** in the presence of a palladium(0) catalyst (Scheme 27). The allylation product **90**.HPF_6 was obtained without any dethreading of the macrocycle, the intermediate palladium π-allyl complex acting as a stopper during the allylation process.



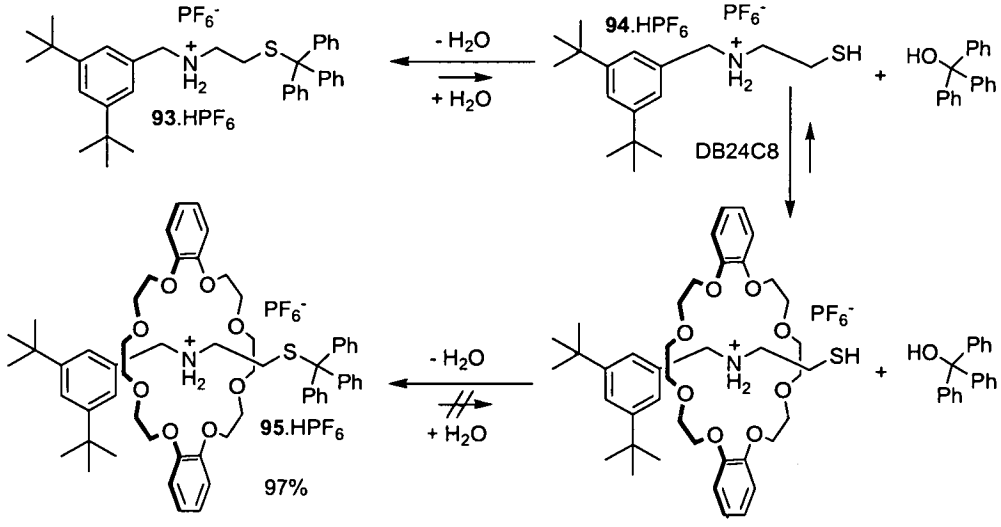
Scheme 27. End-cap exchange of a rotaxane by a Tsuji-Trost reaction

A report by Tokunaga *et al.* describes the formation of rotaxane **92**.HPF_6 in a near quantitative yield by ester formation between the carboxylic acid moiety of thread **91**.HPF_6 and a diphenylmethanediazonium in the presence of DB24C8 (Scheme 28).[97] Rotaxanes were also produced in high yields for a range of different bulky diazo compounds as well as for a substituted DB24C8 macrocycle.



Scheme 28. End-capping with a diazo-compound

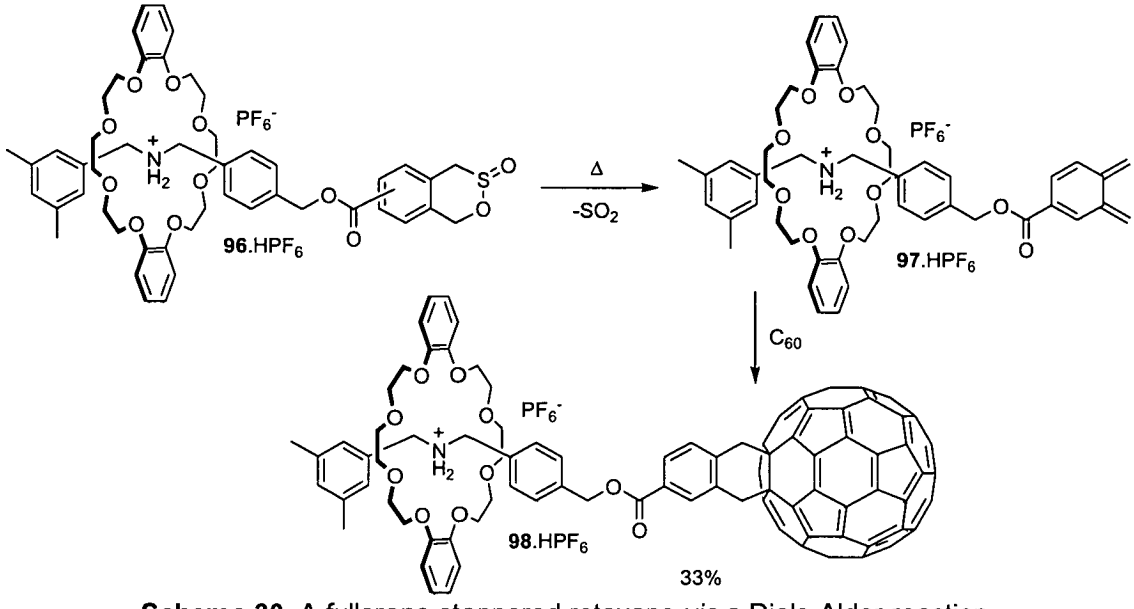
The Takata group has demonstrated the effectiveness of trityl capping as a means of forming rotaxanes.[98] A monostoppered ammonium thread terminating in a thiol group was treated with trityl hexafluorophosphate in the presence of DB24C8 to produce the corresponding [2]rotaxane product in very high yields. A corresponding hydroxyl terminated thread was converted into the [2]rotaxane in a reasonable yield, though the protocol was somewhat complicated by the need to add triethylamine to neutralise the HPF_6 that was generated during the course of the reaction. The same group later showed that the trityl-thioether system was more subtle than first thought: the rotaxane product is the kinetic sink of an otherwise reversible reaction.[99] The mildly acidic ammonium group of thread **93**.HPF_6 is thought to catalyse the reversible capping by the trityl group, allowing the macrocycle access to the ammonium group prior to the reattachment of the stopper to give rotaxane **95**.HPF_6 (Scheme 29). Once the rotaxane is formed the hydrolysis of the trityl thioether linkage is effectively halted, presumably because of the steric encumbrance of the macrocycle. Thus the rotaxane is formed by a reversible reaction, but once the interlocked architecture has been established the reverse reaction is halted, allowing the formation of **95**.HPF_6 in a near quantitative yield.



Scheme 29. Rotaxane formation by semi-reversible trityl capping

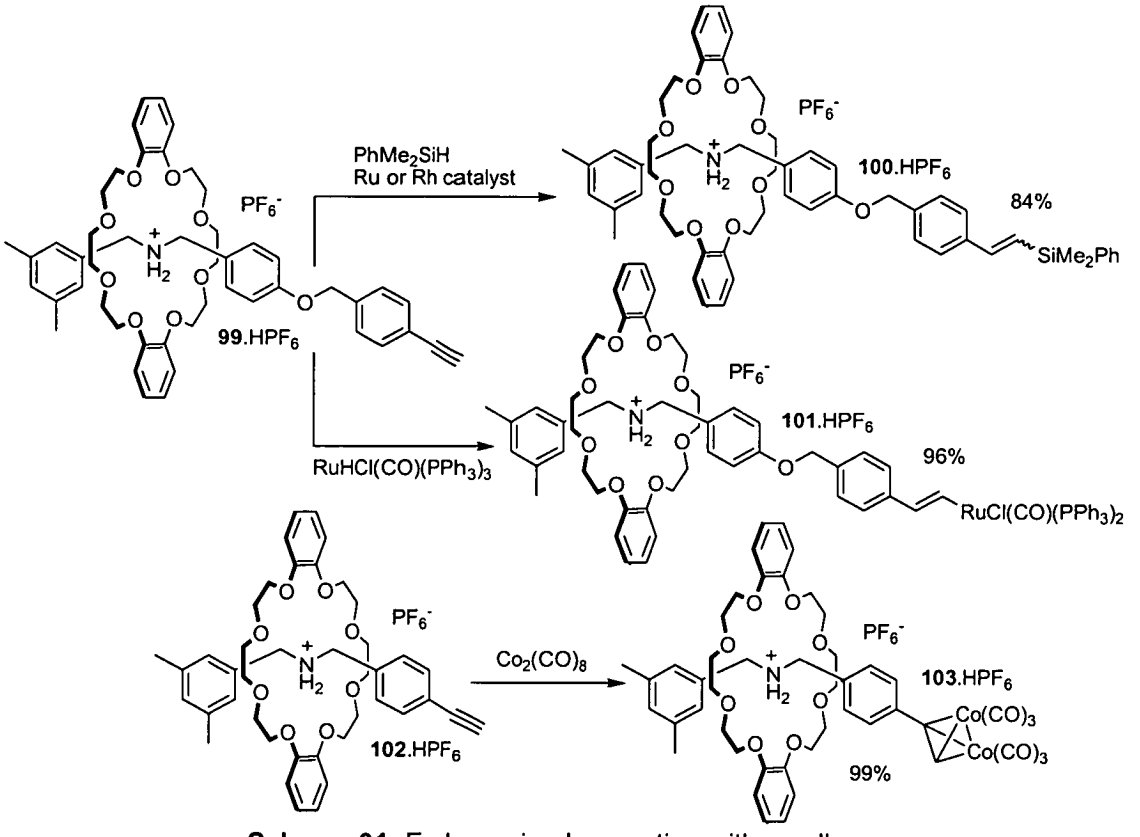
A communication by the Takata group details the use of a Diels-Alder reaction to introduce the stoppers of a rotaxane.[100] Diene-terminated thread **97**.HPF_6 was accessed by the *in situ* decomposition of the sultine moiety of **96**.HPF_6 at elevated

temperatures. Reaction of **97**.HPF_6 with a suitably bulky dieneophile (in this case C_{60}) produced rotaxane **98**.HPF_6 in a yield of 33%.



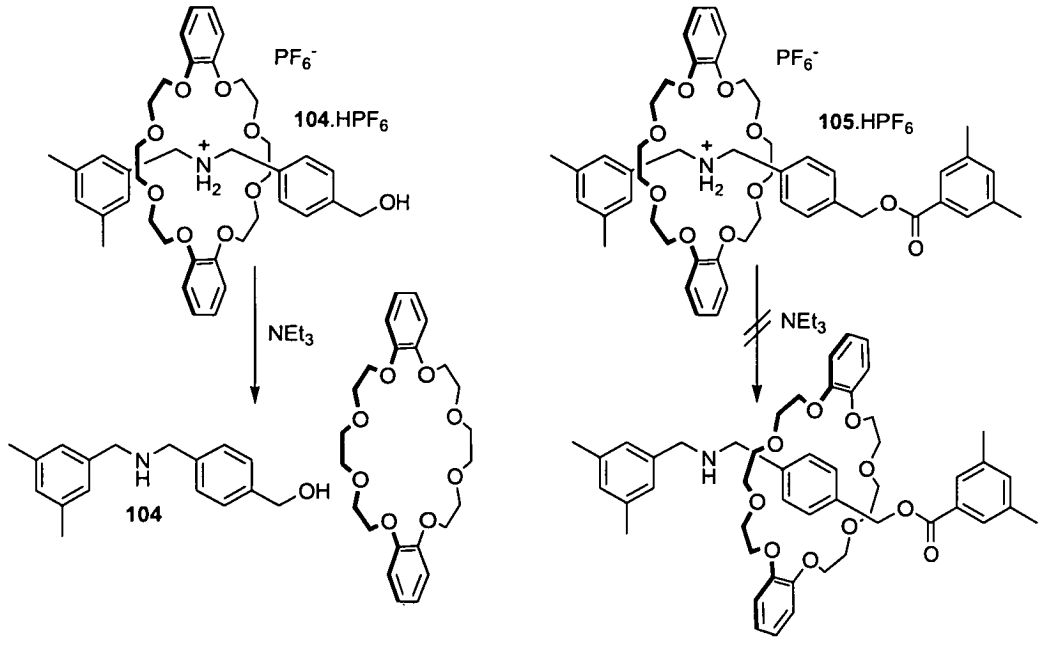
Scheme 30. A fullerene-stoppered rotaxane *via* a Diels-Alder reaction

The groups of Takata and Tokunaga have demonstrated the formation of rotaxane architectures by various reactions of alkyne-terminated threads. A hydrosilylation reaction was used as a means of end-capping thread **99**.HPF_6 in the presence of DB24C8 (Scheme 30).[101] Reaction of the alkyne-terminated ammonium thread with a bulky silane in the presence of DB24C8 and a ruthenium or rhodium catalyst produced the silane-stoppered rotaxane **100**.HPF_6 in a yield of 84%. This process proceeds *via* an intermediate rotaxane stoppered by the transition metal catalyst. In a later publication the ruthenium (II) complex stoppered rotaxane **101**.HPF_6 was isolated.[102] This rotaxane was further elaborated to the η^3-allylruthenium-stoppered rotaxane by reaction with an allene. The related alkyne-terminated thread **102**.HPF_6 was end-capped by reaction of the alkyne group with dicobalt octacarbonyl in the presence of DB24C8 to give acetylene dicobalt hexacarbonyl stoppered rotaxane **103**.HPF_6 in a 99% yield.[103]



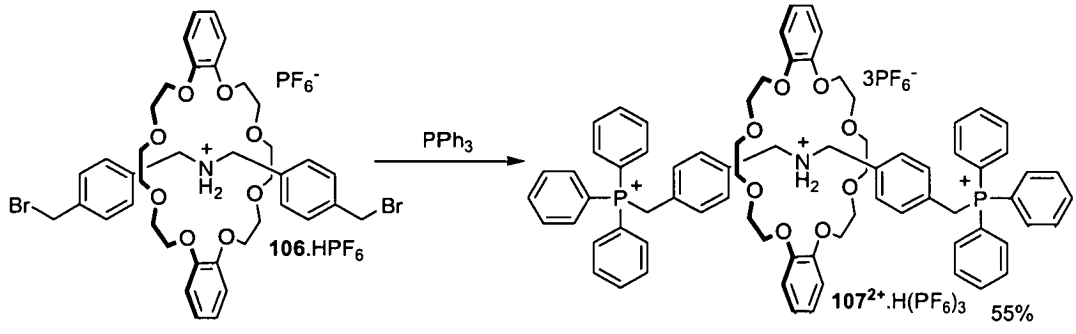
Scheme 31. End-capping by reaction with an alkyne

A paper by the Takata group investigates the effect of the crown ether macrocycle on the acidity of the ammonium thread.[104] It was found that the ammonium group of rotaxane **105**.HPF_6 displayed substantially lower acidity than the equivalent thread **104**.HPF_6 (Scheme 32). Whereas the equivalent pseudorotaxane was readily neutralised with triethylamine, DBU or potassium carbonate, the rotaxane itself remained protonated in the presence of all of these bases, and was also unaffected by calcium hydride. The rate of H/D exchange was measured for the rotaxane, and was found to have a half-life of 17 min, a value larger than that of most alcohols.



Scheme 32. Reduced acidity of a rotaxane (right) compared to its non-interlocked analogue

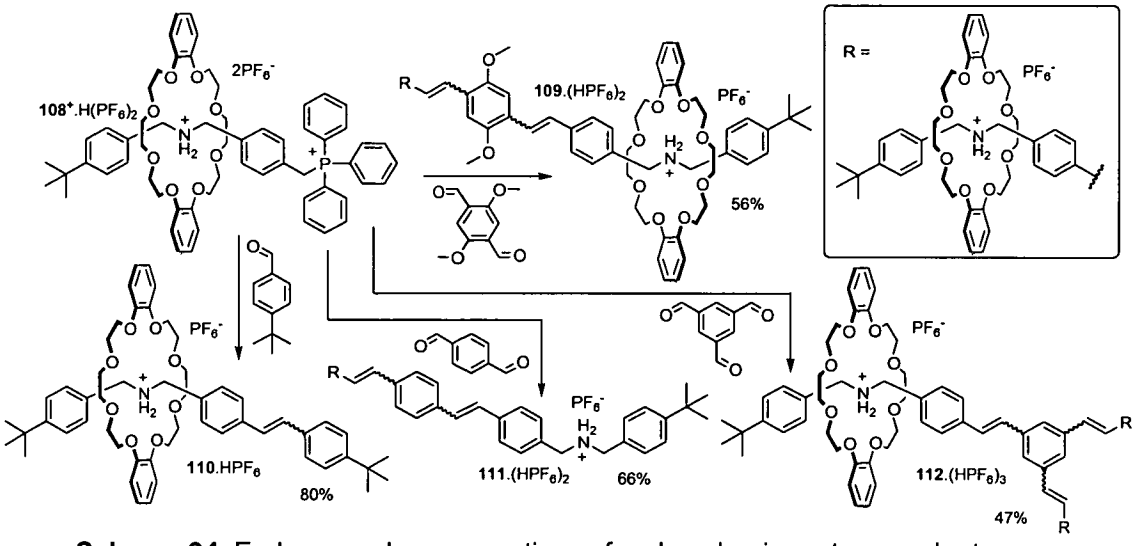
A report by the Stoddart group describes the formation of a phosphonium-stoppered rotaxane.[105] Thread **106**.HPF_6 terminating at each end in benzylic bromide groups was heated in the presence of DB24C8 and triphenylphosphine to give rotaxane **107**$^{2+}$.HPF_6 in a 55% yield (Scheme 33).



Scheme 33. A triphenylphosphonium-stoppered rotaxane

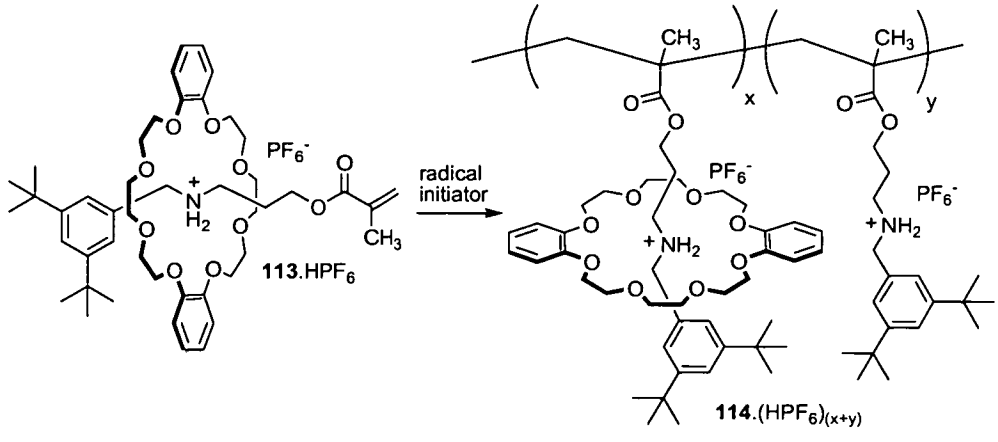
By exploiting the reactivity of phosphonium stoppers the Stoddart group has achieved the synthesis of a variety of interlocked structures by 'end-cap exchange'.[106] Rotaxane **108**$^{+}$.$H(PF_6)_2$, which is stoppered at one end with a phosphonium group, was subjected to Wittig reaction conditions with a number of different aldehydes to give products including [3]rotaxane **109**.$(HPF_6)_2$, [2]rotaxane **110**.HPF_6, degenerate molecular shuttle **111**.$(HPF_6)_2$ and branched [4]rotaxane **112**.$(HPF_6)_3$ (Scheme 34). Providing the aldehyde is sufficiently bulky no

dethreading of the macrocycle can occur, and the rotaxane architecture is maintained in the olefinic product. This methodology was later applied to the synthesis of a four-station [3]catenane and a [3]rotaxane in which two DB24C8 macrocycles are distributed about three DBA^+ stations along the vector of the thread.[107] Further work has seen the synthesis of polyrotaxanes,[108] mechanically linked dendrimers[109] and molecular 'daisy chains'.[110]



Scheme 34. End-cap exchange reactions of a phosphonium-stoppered rotaxane

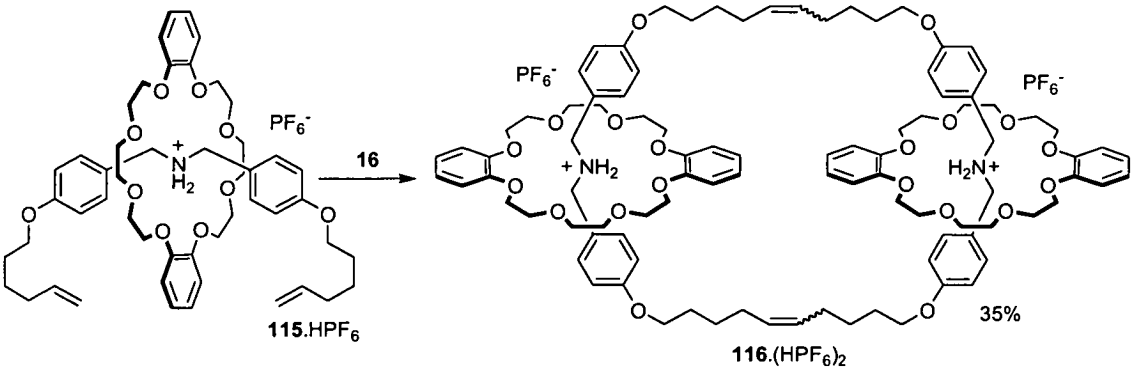
The group of Takata has described the synthesis of side chain polyrotaxanes by the polymerisation of thread **113**.HPF_6, in which the thread is terminated by an acrylyl ester (Scheme 35).[111] Pseudorotaxane monomers were polymerised under radical conditions, both neat and as a copolymer with styrene. The side chains of the resultant polymer were a mixture of rotaxane and non-interlocked thread residues, with a maximum rotaxane incorporation of around 50%.



Scheme 35. Synthesis of a side-chain polyrotaxane

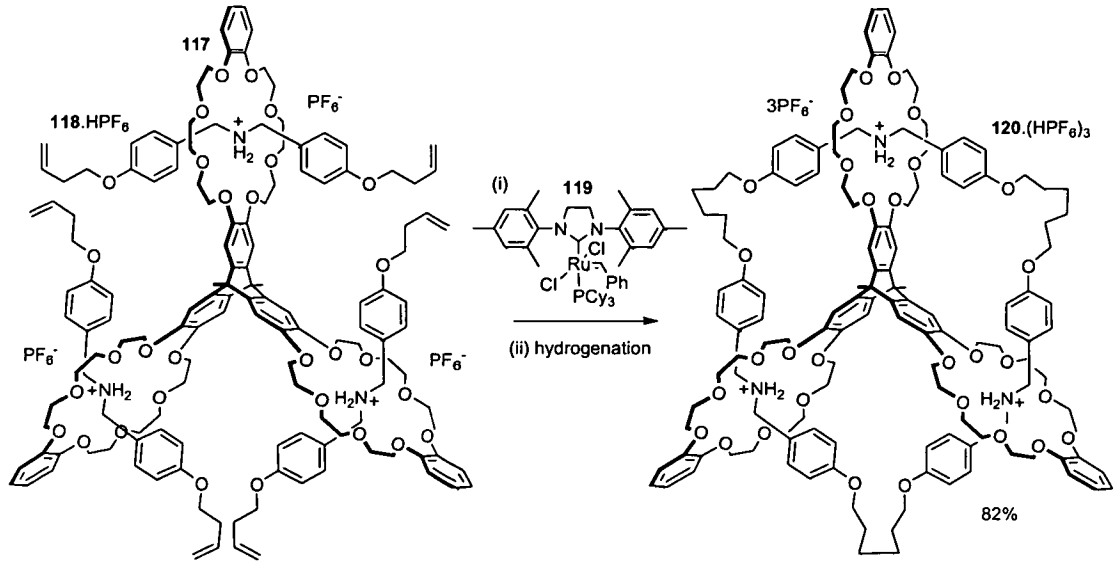
1.2.2.3.2 Interlocking Under Thermodynamic Control

A report by Fukazawa *et al.* details the synthesis of a [3]catenane by an olefin metathesis dimerization protocol.[112] Thread **115**.HPF_6, bearing two terminal olefin groups formed the expected pseudorotaxane complex with DB24C8 (Scheme 36). Olefin metathesis catalyzed by **16** gave symmetrical [3]catenane **116**.$(HPF_6)_2$ in a 35% yield.



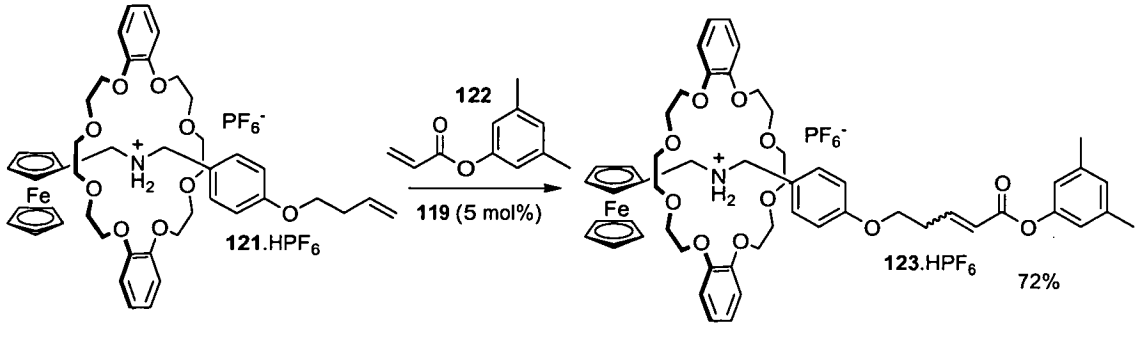
Scheme 36. A [3]catenane by olefin metathesis

A report by Zhu and Chen describes the synthesis of an unusual interlocked '[4]pseudocatenane' structure.[113] Homotritopic host **117** consisting of three DB24C8-type macrocycles fused onto a triptycene core forms a [1 + 3] complex by inclusion of three equivalents of thread **118**.HPF_6 (Scheme 37). This *tris*-[2]pseudorotaxane is pre-organized such that under olefin metathesis conditions catalyzed by **119** each **118**.HPF_6 unit is fused to its neighbours to give an 82% yield of **120**.$(HPF_6)_3$, in which a large *tris*-ammonium macrocycle is threaded through each of the crown ether moeities of the of the host. The same workers later reported the synthesis of a chiral analogue of **120**.$(HPF_6)_3$, with an unusual 'ship's wheel' structure.[114]



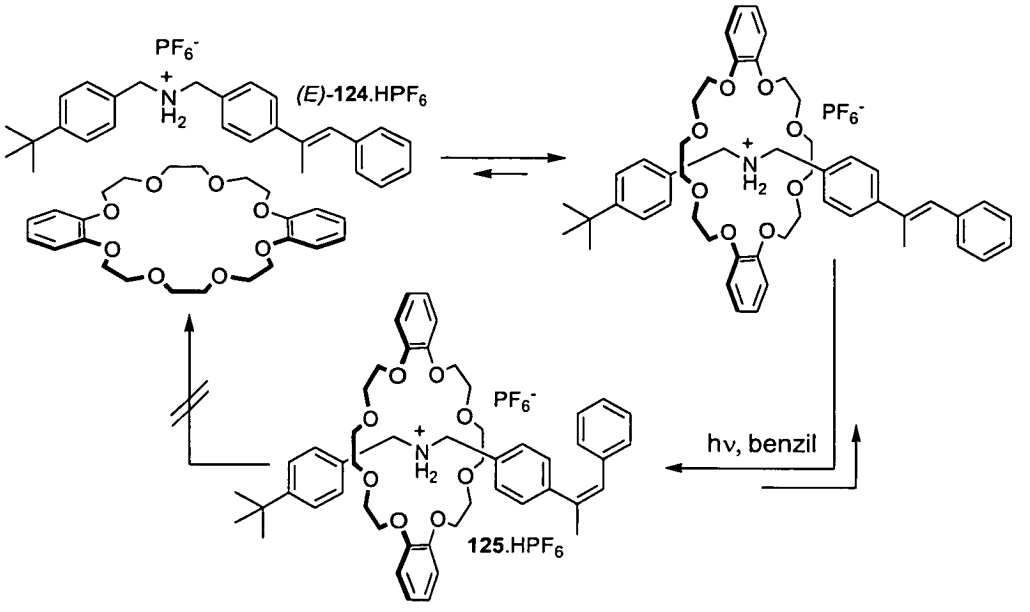
Scheme 37. A [4]pseudocatenane by olefin metathesis

A report by Suzaki and Osakada describes the synthesis of rotaxanes by a cross-metathesis procedure.[115] The DB24C8 complex of thread **121**.HPF_6 was end-capped by reaction with **122**, catalysed by **119**, to give the rotaxane **123**.HPF_6 in 72% yield (Scheme 38).



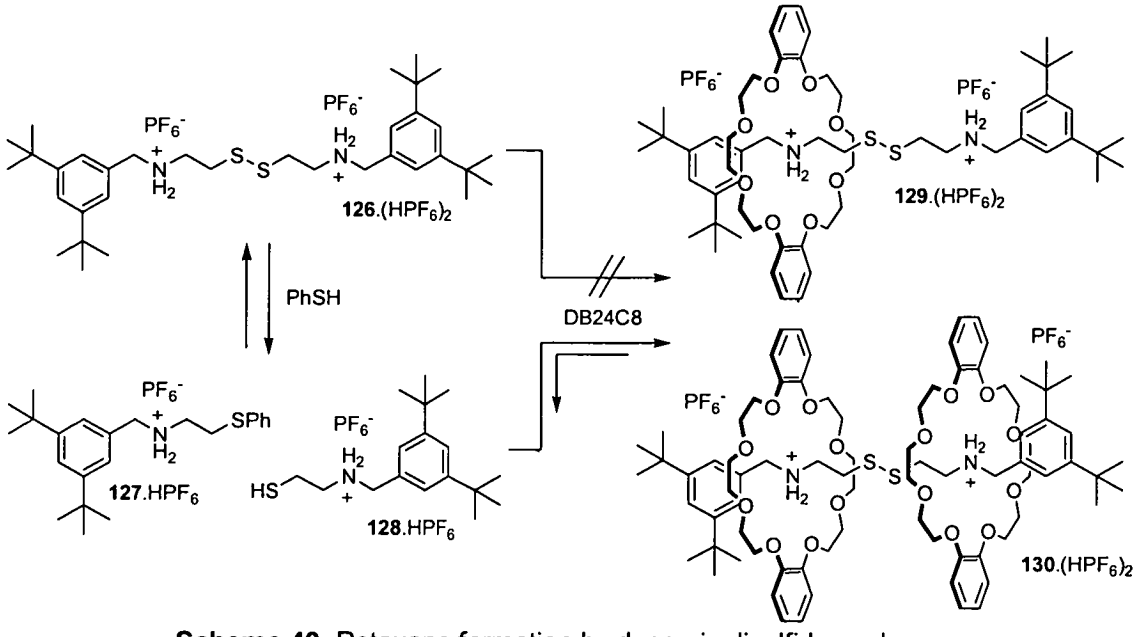
Scheme 38. Rotaxane formation by cross-metathesis

A report from the group of Tokunaga describes the formation of a rotaxane by the *E/Z* isomerization of stilbene-functionalised thread **124**.HPF_6.[116] The two different isomers of the thread present quite different kinetic barriers to the movement of a DB24C8 macrocycle: exchange is possible for *(Z)*-**124**.HPF_6, but not for *(E)*-**124**.HPF_6. Formation of a pseudorotaxane between *(E)*-**124**.HPF_6. followed by photoisomerization to the *Z* isomer gave the rotaxane **125**.HPF_6 in a 73% yield.



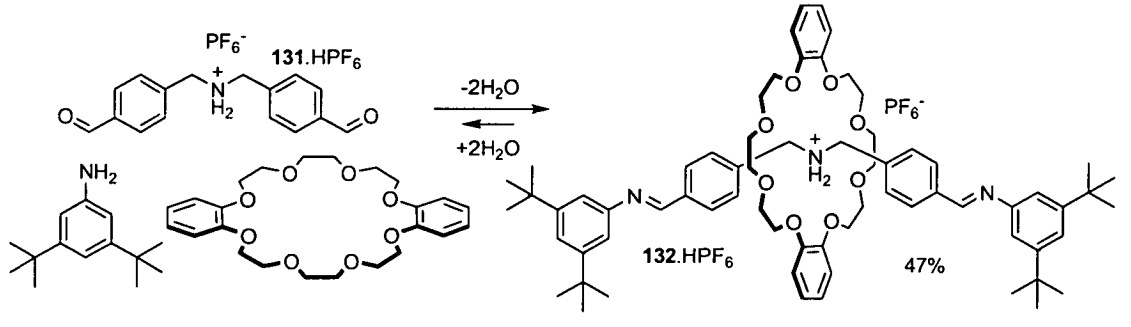
Scheme 39. Rotaxane formation by photoisomerization

Disulfide exchange has been exploited for the synthesis of rotaxanes under thermodynamic control.[117] Nucleophilic attack by thiophenol on symmetrical disulfide thread **126**.$(HPF_6)_2$ yields asymmetric disulfide **127**.HPF_6 and thiol **128**.HPF_6 half threads, both of which can bind to DB24C8 (Scheme 40). Subsequent thiol exchange reforms the full disulfide thread as [2]rotaxane **129**.$(HPF_6)_2$ or [3]rotaxane **130**.$(HPF_6)_2$. The major product in the initial stages of the reaction is **129**.$(HPF_6)_2$, which then depletes as the more thermodynamically favoured (but slow to form) **130**.$(HPF_6)_2$ is produced. The product ratio is condition dependant: at 50 °C in CD_3CN an equilibrium ratio of approximately 2:1 (**130**:**129**) is obtained. While investigating alternative nucleophilic catalysts the Takata group discovered a surprisingly stable thiophosphonium salt formed by addition of hexamethylphosphorustriamide to the disulfide-linked rotaxane.[118] The thiol-mediated dynamic rotaxane forming technique was later used to form poly[3]rotaxanes,[119] and to reversibly cross-link poly(crown ether) chains.[120]



Scheme 40. Rotaxane formation by dynamic disulfide exchange

The formation of a rotaxane under thermodynamic control has also been described by Stoddart *et al.*[121] These workers made use of a reversible imine-forming reaction between **131**.HPF_6 and 3,5-di-*tert*-butylaniline in the presence of DB24C8 to form rotaxane **132**.HPF_6 in 47% yield (Scheme 41). The system was shown to be under thermodynamic control by incorporation of a macrocycle onto a fully equilibrated thread. It was also demonstrated that the exchange process could be halted by addition of a reducing agent that converts the imine linkages to non-labile amines. A later publication by the same workers applied the same methodology to a π-donor/π-acceptor template system, and introduced imine exchange, rather than hydrolysis then reformation, as a means of establishing the rotaxane.[122]

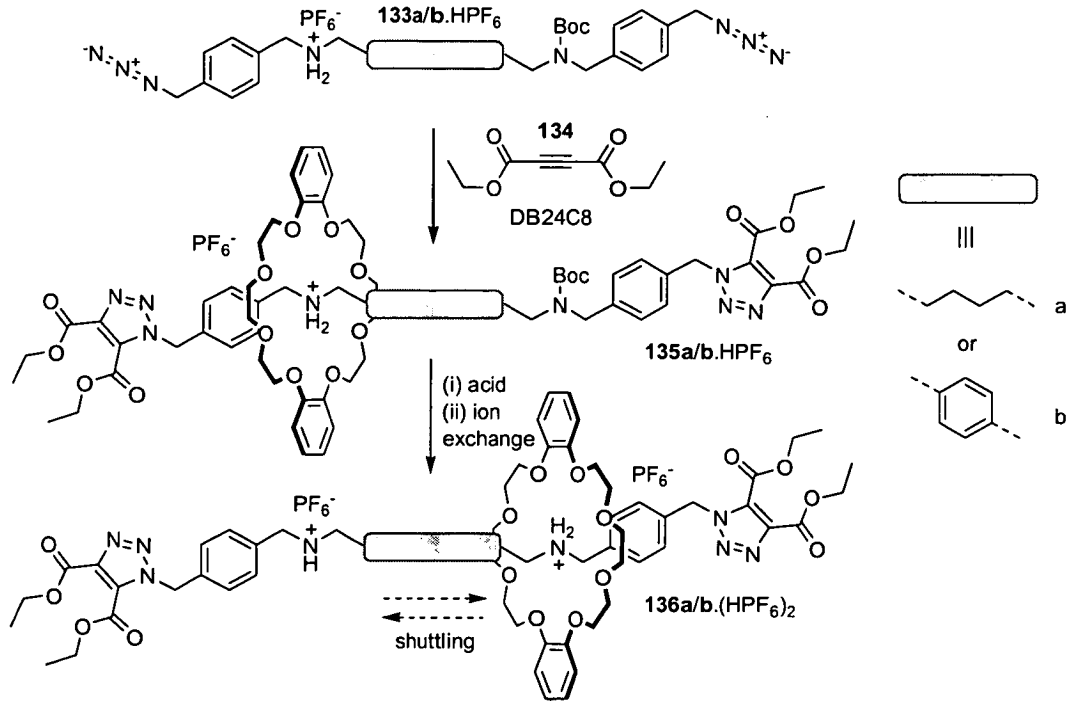


Scheme 41. Synthesis of a rotaxane by dynamic imine formation

1.2.2.4 [24]Crown-8 Molecular Devices

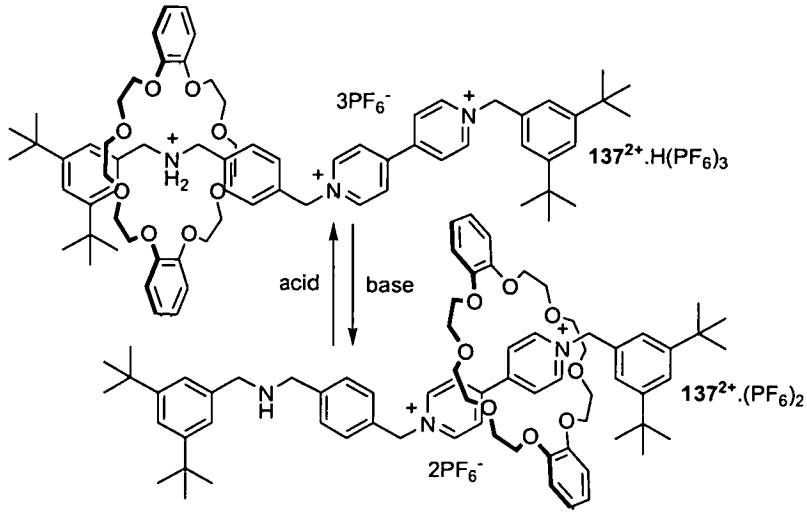
Following the publication of the first molecular shuttle,[123] in which a *bis*-paraquat macrocycle shuttled between two degenerate hydroquinone stations, a wide range of more advanced molecular shuttles have been reported. Molecular switches[124] are now commonplace and prototypes of more complex systems are being described.[125] Ammonium group-based systems have constituted an important part of the progress that this area has already seen. The ammonium template naturally lends itself towards switchable systems that operate through a change in protonation level.

Two related degenerate molecular shuttles have been reported by the Stoddart group.[126] A 1,3-dipolar cycloaddition was used to install the stoppers onto threads bearing one ammonium group and one *t*-Boc protected amine spaced apart by either a hexyl (**133a**.HPF_6) or xylyl (**133b**.HPF_6) unit (Scheme 42). These threads were converted to the [2]rotaxane smoothly by cycloaddition of the azides with alkyne **134** in the presence of DB24C8 to give rotaxanes **135a**.HPF_6 and **135b**.HPF_6 in 29% and 34% yields respectively. Removal of the *t*-Boc groups gave the degenerate molecular shuttles **136a**.$(HPF_6)_2$ and **136b**.$(HPF_6)_2$. In the case of **136b**.$(HPF_6)_2$ shuttling was slow on the NMR timescale due to the steric impediment presented by the xylyl spacer. Shuttling in the case of **136a**.$(HPF_6)_2$ was rapid compared to the NMR timescale, but could be slowed by reducing the temperature of the system and using an apolar solvent. It was also found that treatment of **136a**.$(HPF_6)_2$ with a tertiary amine resulted in the removal of only one ammonium proton, the other being additionally stabilised by the presence of the DB24C8 macrocycle. Singly charged **136a**.HPF_6 was also found to undergo a shuttling process, but *via* a 'proton ferry' mechanism, in which the translocation is not just of the macrocycle but also of the proton. The energy of activation for this process is higher than that for shuttling of the macrocycle alone in **136a**.$(HPF_6)_2$.



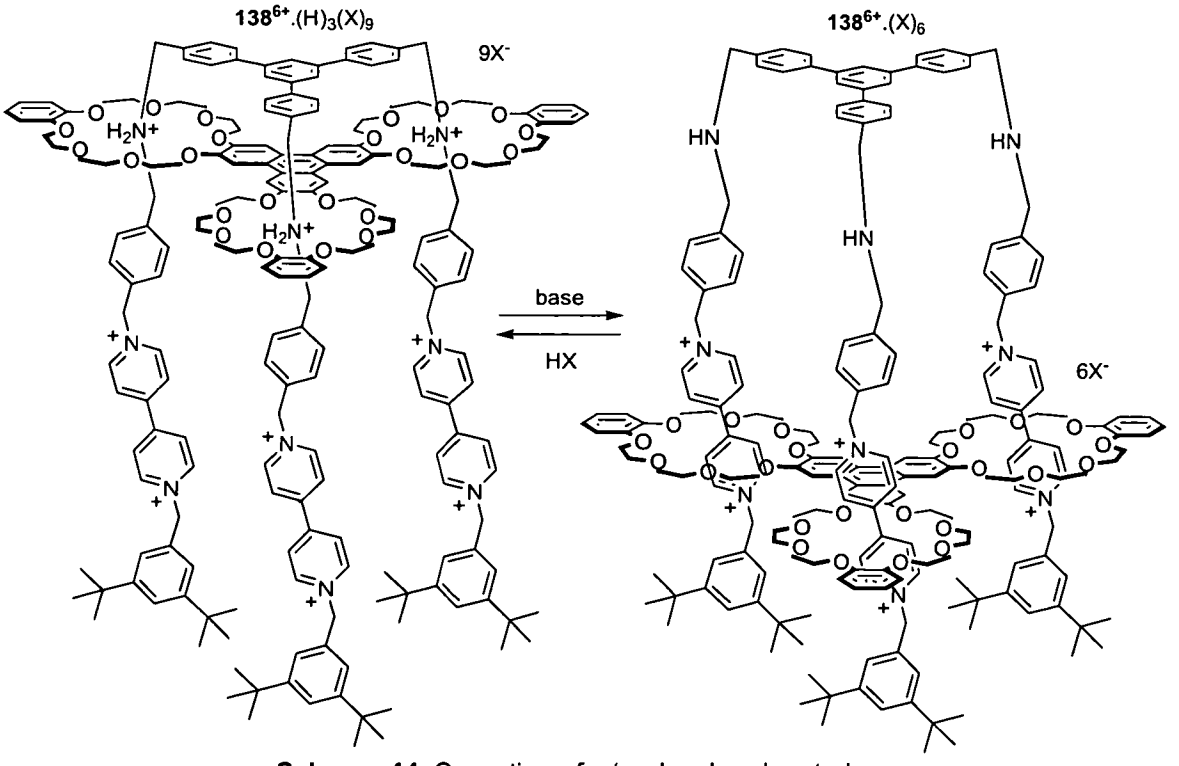
Scheme 42. Degenerate molecular shuttles.

The switchable molecular shuttle $\mathbf{137}^{2+}$ has been reported by the Stoddart research group.[127] This rotaxane has two stations: a DBA^+ group and a bipyridinium group. In its protonated form, $\mathbf{137}^{2+}.H(PF_6)_3$ the DB24C8 macrocycle resides almost exclusively (>98%) on the DBA^+ unit (Scheme 43). Deprotonation of the rotaxane to give $\mathbf{137}^{2+}.(PF_6)_2$ reverses the situation, and the macrocycle moves almost exclusively (>99%) to the bipyridinium station. The authors note that the occupancy of the bipyridinium station by the macrocycle is a phenomenon only observed in the restricted environment of the interlocked architecture: no association is observed between the non-interlocked analogues. A related rotaxane was constructed in which the stopper adjacent to the ammonium station was an anthracene group, allowing the shutting process to be studied by photophysical measurements. The shuttling dynamics of this molecule were studied by stopped flow techniques.[128] A related protonation switchable rotaxane was later reported in which a 1,2-*bis*(pyridinium)ethane station was used in place of the bipyridinium site of the original system.[129]



Scheme 43. Operation of a pH-switchable molecular shuttle

The Stoddart group has described the synthesis of a 'molecular elevator' $\mathbf{138}^{6+}$ (Scheme 44).[130] This work can be thought of as a combination of the mechanically interlocked bundle systems and the DBA^+/bipyridinium shuttle systems both previously reported by the Stoddart group. In the protonated state $\mathbf{138}^{6+}.(H)_3(X)_9$ the *tris*-crown ether unit remains almost exclusively on the DBA^+ stations, but on deprotonation of all three DBA^+ units to give $\mathbf{138}^{6+}.(X)_6$ the crown ether unit moves to reside on the bipyridinium stations. Reprotonation reverses the movement. The crown ether unit is displaced by around 0.7 nm between the two states of the molecule, and the shuttle was calculated to be able to exert a force of 200 pN on moving from the (deprotonated) DBA^+ to bipyridinium stations.



Scheme 44. Operation of a 'molecular elevator'

1.2.3 Other Crown Ether Macrocycles

A wide variety of threaded and interlocked structures have been formed using macrocycles that differ from the [24]crown-8 constitution first used for this purpose. This increase in structural variety has helped to elucidate the nature of the interactions between crown ethers and ammonium species, and has allowed the incorporation of crown ethers with unusual functionalities or characteristics into interlocked structures.

1.2.3.1 Pseudorotaxanes

The group of Harry Gibson has investigated the ability of the *meta*- substituted isomers of the DB24C8 and *bis-para*-phenylene[34]crown-10 (BPP34C10)[131] macrocycles to form pseudorotaxanes.[132] *Bis*(*m*-phenylene)-26-crown-8 (BMP26C8)[133] was shown by NMR spectroscopy not to form pseudorotaxanes with various dialkylammonium species in solution. The presence of some type of 1:1 complex, possibly the pseudorotaxane, was indicated by mass spectrometry, though attempts to grow crystals of such a complex were unsuccessful. *Bis*-

metaphenylene[32]crown-10 (BMP32C10) was shown by X-ray crystallography to form [3]pseudorotaxanes with DBA^+ hexafluorophosphate in the solid state. Later work by the Stoddart group again found no evidence for the formation of pseudorotaxanes between BMP26C8 and dialkylammonium salts.[134] The Stoddart group did find, however, that benzometaphenylene[25]crown-8 (BMP25C8) formed pseudorotaxanes with DBA^+ salts, though with a binding constant lower than that of DB24C8 under comparable conditions.

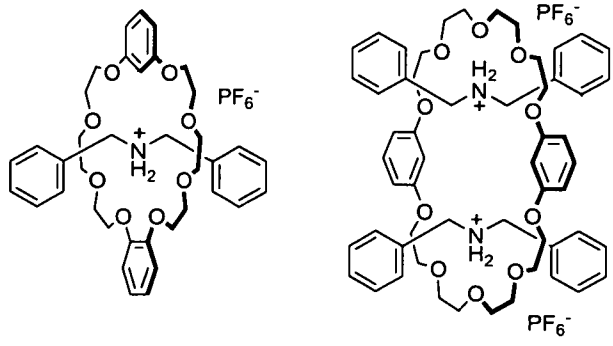
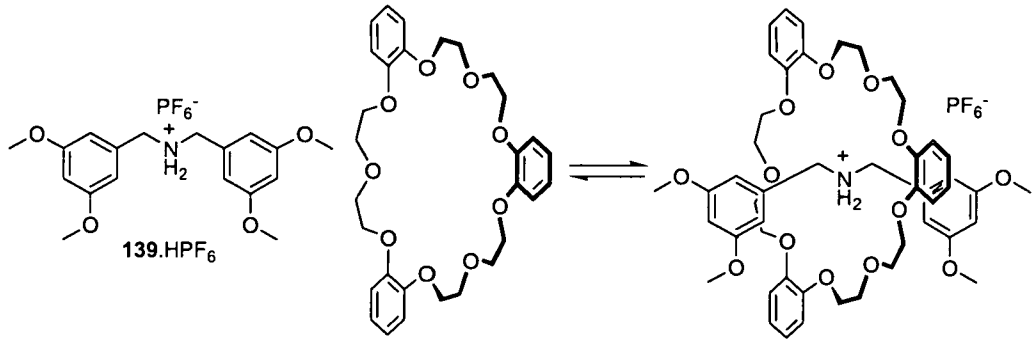


Figure 20. Pseudorotaxanes of BMP25C8 (left) and BMP32C10 with DBA^+

The Stoddart group has reported the use of the tribenzo[27]crown-9 (TB27C9) macrocycle[135] for the formation of pseudorotaxane complexes with DBA^+ derivatives.[136] The macrocycle was found to form DBA^+ complexes in a manner similar to DB24C8, except that the larger size of the TB27C9 macrocycle means that more bulky DBA^+ derivatives such as **139**.HPF_6 are able to thread into its cavity (Scheme 45).



Scheme 45. Formation of a pseudorotaxane of TB27C9

A report by Balzani, Mandolini and co-workers describes the operation of a molecular level 'plug and socket'.[137] (±)Binaphtho[23]crown-7 (**140a**) and (±)binaphtho[26]crown-8 (**140b**) macrocycles[133] were found to form pseudorotaxane

complexes with **32b**.HPF_6 (Figure 21). Macrocycles **140a/b** were found to sensitise the fluorescence of the anthracene thread in a manner that is compared to a macroscopic plug and socket: electronic energy is 'sent' to the macrocycle 'socket' and is transferred to the docked anthracene 'plug'. A subsequent report by Clemente-León *et al.* describes the effect of ion pairing on the formation of the **140b.32b**.HX pseudorotaxane.[138] The ability of **32b**.HX to complex **140b** was sensitive to the nature of the anion X, favouring large, charge dispersed species such as PF_6^-.

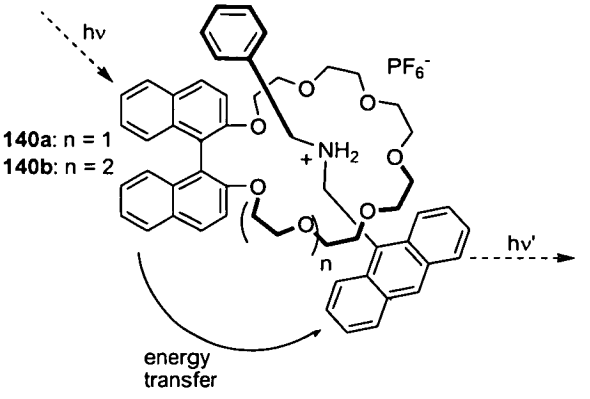


Figure 21. A molecular 'plug and socket'.

During the course of their initial investigations into crown ether/dialkylammonium pseudorotaxanes the Stoddart group found that BPP34C10 can encircle two DBA^+ ions simultaneously (Figure 22a).[49, 139] The ammonium ions were each shown to associate independently to one of the polyether chains of the macrocycle, with additional stabilisation through edge to face aromatic interactions between the benzyl rings of the guest and the hydroquinone rings of the macrocycle. This behaviour has been shown to be quite general, and has been exploited for the formation of various pseudorotaxane structures in which two DBA^+ units are held close in space by association to the same BPP34C10 macrocycle. This dual-binding ability has variously been used for the formation of [2]pseudorotaxanes[140] and [2+2] complexes with diammonium threads,[139] pseudopolyrotaxane structures,[141] supramolecular cage complexes[142] (Figure 22b)- including an analogue of the photosynthetic special pair[143] and a tetrathiofulvalene dimer,[144] as well as an unusual ring-in-ring complex with a diammonium macrocycle (Figure 22c).[145]

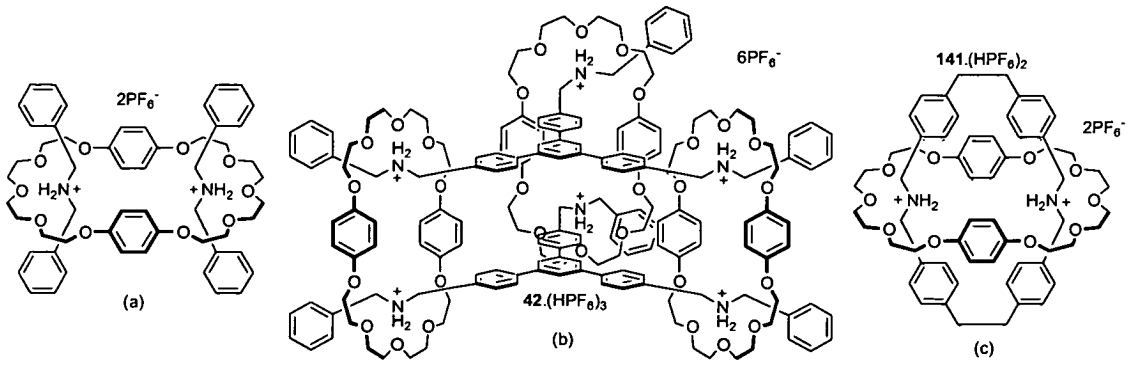


Figure 22. A [2]pseudorotaxane (a), supramolecular cage (b) and ring-in-ring complex (c)

Pseudorotaxane assemblies between very large crown ether macrocycles and several DBA^+ ions have been reported by the Stoddart group.[146] The crown ether macrocycles *tris-para*-phenylene[51]crown-15 (TPP51C15) and *tetrakis-para*-phenylene[68]crown-20 (TPP68C20) were co-crystallised with three or four molar equivalents of DBA^+ hexafluorophosphate respectively, and the crystals were analysed by single crystal X-ray diffraction. The TPP51C15-derived crystals were found to be of a [4]pseudorotaxane, in which one of the PF_6^- counterions is surrounded by three ammonium ions, which are in turn encircled by the macrocycle (Figure 23a). The central PF_6^- ion is partially enveloped in the assembly, and is held in an ordered state in the crystal structure by a series of C–H···F hydrogen bonds donated by the benzylic methylene units of the three DBA^+ ions. A similar arrangement is exhibited in the [5]pseudorotaxane formed between TPP68C20 and four equivalents of DBA^+ hexafluorophosphate (Figure 23b). In this instance the central PF_6^- anion is completely enveloped by the pseudorotaxane, in which the macrocycle adopts a 'tennis ball seam' arrangement.

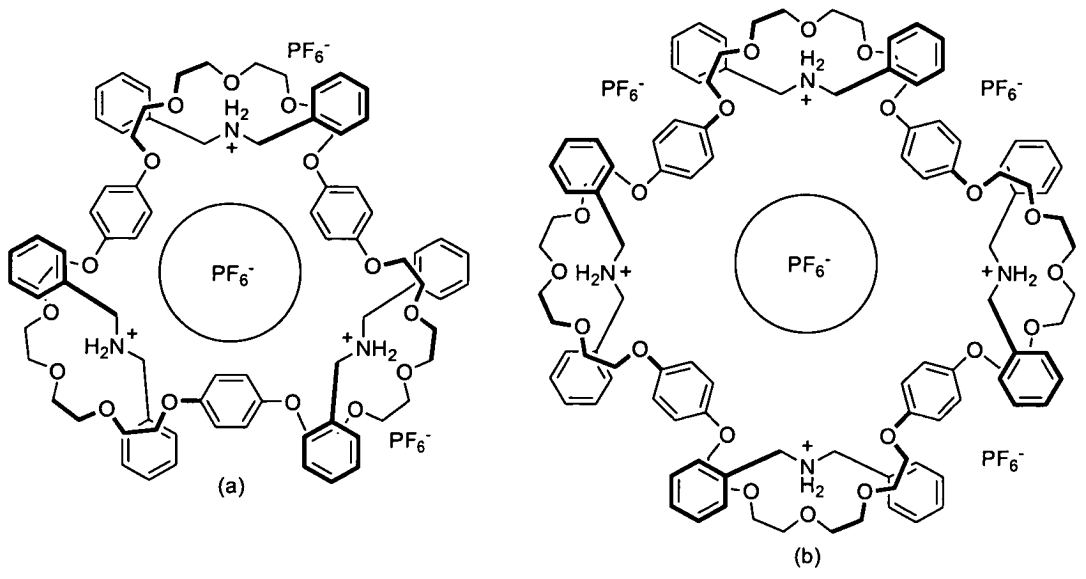
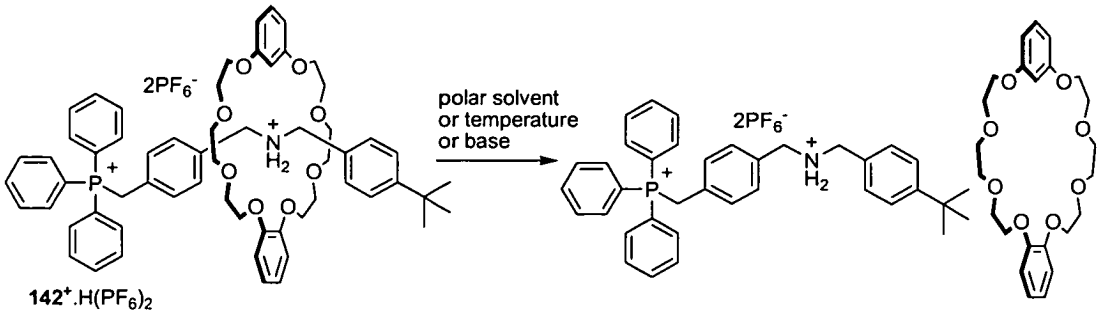


Figure 23. A [4]pseudorotaxane of TPP51C15 (a) and [5]pseudorotaxane of TPP68C20 (b)

1.2.3.2 The Grey Area: Rotaxane-Like Complexes

The 'controlled release' characteristics of a rotaxane-like complex between BMP25C8 and *para-tert*-butyl thread **142**$^{+}$.H(PF$_6$)$_2$ have been investigated by the Stoddart group (Scheme 46).[147] It was found that the 'rotaxane' exhibited solvent-dependant stability: it would partially dissociate during column chromatography when eluted with CH_2Cl_2/MeOH but not when eluted with CH_2Cl_2/MeCN. The kinetics of the dissociation process were investigated in several different solvents and for a range of temperatures. The dissociation of the complex was much more rapid in polar solvents: in CH_2Cl_2 the half-life for dissociation is 1500 h at 25 °C, whereas in a 1:1 mixture of CH_2Cl_2 and DMSO the half-life is just over 10 minutes at the same temperature. The entropy of activation for the dethreading process was also strongly solvent-dependant. In apolar media the $\Delta S^{\ddagger}$ values were positive, reflecting a poorly solvated polar transition state, whereas in polar solvents the $\Delta S^{\ddagger}$ values were negative due to ordering of the solvent around the exposed ammonium group.

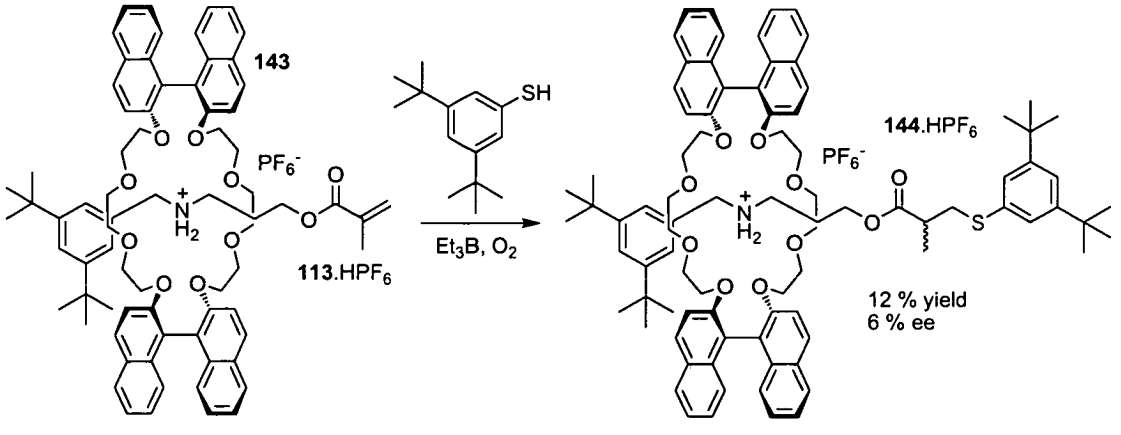


Scheme 46: Deslippage of a BMP25C8 macrocycle over a 4-*tert*-butylbenzyl group

1.2.3.3 Rotaxanes

1.2.3.3.1 Rotaxanes By End-Capping

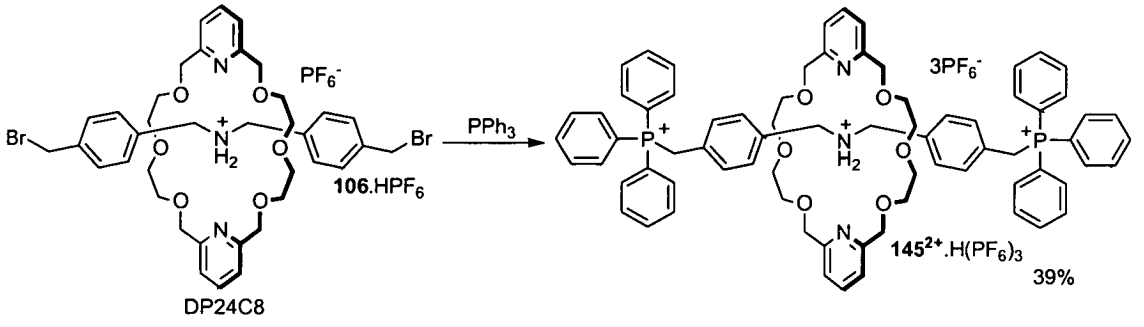
The ability of a chiral crown ether to influence the stereochemical outcome of a end-capping reaction has been investigated by the Takata group.[148] Using **143**, an expanded version of known chiral crown ether, these workers assessed the ability of the macrocycle to affect the radical addition of 3,5-di-*tert*-butylthiophenol to thread **113**.HPF_6. A very slight selectivity for one enantiomer of the rotaxane product **144**.HPF_6 was observed. This work was followed by a later study that gauged the ability of a chiral rotaxane to direct the stereochemical outcome of a benzoin condensation reaction, though again stereoselectivity was slight, with a maximum ee of 32%.[149]



Scheme 47. Enantioselective end-capping

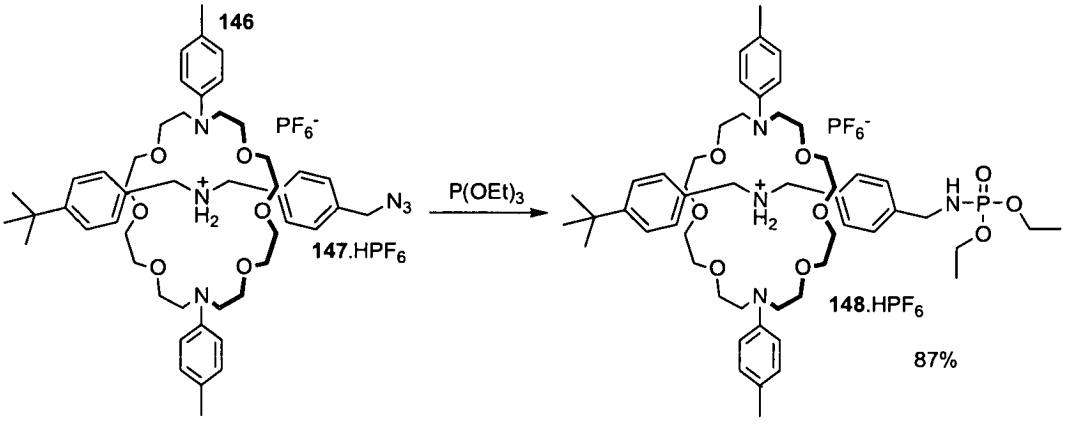
A crown ether macrocycle containing two pyridine groups, dipyrido[24]crown-8 (DP24C8), has been used by the Stoddart group for the synthesis of rotaxanes.[150] The DP24C8 macrocycle was found to bind DBA^+ hexafluorophosphate more strongly

than DB24C8 does, and the DP24C8 complex was found to exchange more rapidly. Rotaxane $\mathbf{145}^{2+}.H(PF_6)_3$ was prepared in a 39% yield by end-capping thread $\mathbf{106}.HPF_6$ with triphenylphosphine in the presence of DP24C8 (Scheme 48).



Scheme 48. Synthesis of a rotaxane of DP24C8

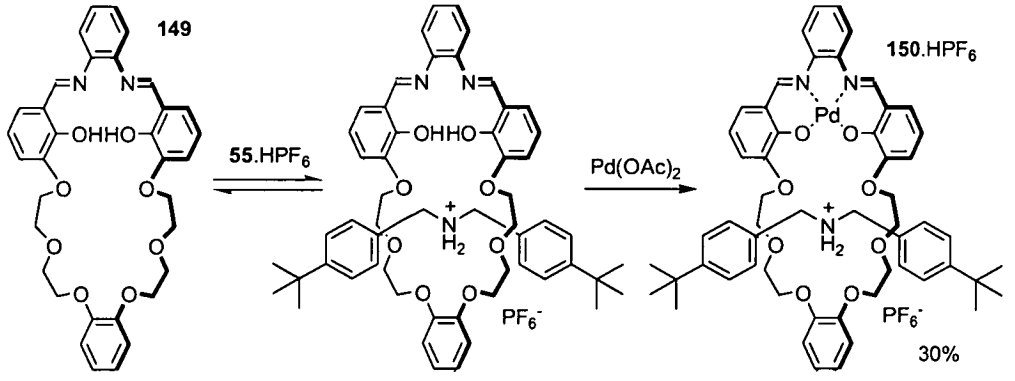
The group of Chiu has prepared a rotaxane from dianilino[24]crown-8 (**146**). The ability of **146** to bind to DBA^+ ions was found to be modest, with no association observed in acetonitrile, and around 50% complexation in a cooled mixture of $CDCl_3/CD_3NO_2$.[151] Macrocycle **146** was subsequently incorporated into a rotaxane architecture by a end-capping protocol in which azide thread $\mathbf{147}.HPF_6$ was reacted with triethyl phosphite in the presence of **146** to give phosphoramidate-stoppered rotaxane $\mathbf{148}.HPF_6$ in 87% yield (Scheme 49).[152]



Scheme 49. Synthesis of a phosphoramidate-stoppered dianilino[24]crown-8 rotaxane

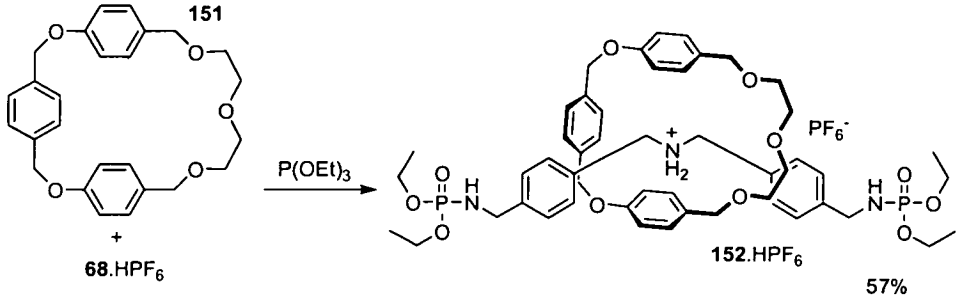
A crown ether macrocycle containing a salophen unit has been investigated by Asakawa *et al.* for the formation of rotaxanes *via* an unusual 'threading followed by shrinking' protocol.[153] Macrocycle **149** has a cavity large enough to allow thread $\mathbf{55}.HPF_6$ to form an inclusion complex by threading (Scheme 50). Addition of

$Pd(OAc)_2$ deprotonates both phenol groups of **149**, installing a Pd(II) ion into the salenophen moiety, effectively reducing the ring size of the crown ether macrocycle. The 'smaller' macrocycle is no longer able to pass over the *tert*-butylbenzyl units of the thread, and hence the pseudorotaxane is converted to a true rotaxane, **150**.HPF_6 in a yield of 30%.



Scheme 50. Rotaxane synthesis by 'threading followed by shrinking'

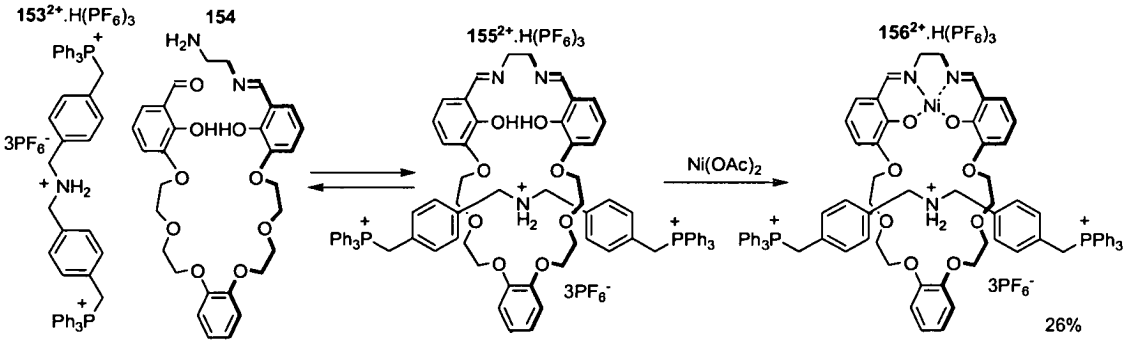
The group of Chiu has investigated the ability of a macrocycle bearing only a small polyether region to form inclusion complexes with DBA^+ ions.[154] These workers sought to determine just how small an oligoethylene glycol region would be sufficient to form inclusion complexes with DBA^+ ions. They therefore synthesised the 'oxygen deficient' macrocycle, **151**, which has only a diethylene glycol chain, the rest of the structure comprising of rigid benzyl spacers. Macrocycle **151** was found to bind DBA^+ ions with association constants comparable to those of DB24C8. Aromatic stacking and cation-π interactions between host and guest are thought to contribute to formation of the complex. Phosphoramidate-stoppered rotaxane **152**.HPF_6 was synthesised to unambiguously establish the threaded mode of binding (Scheme 51). This macrocycle was later incorporated into a pH switchable shuttle[155] based on the same thread as was previously reported by the Stoddart group.[127]



Scheme 51. Rotaxane formation from a diethylene glycol macrocycle

1.2.3.3.2 Rotaxanes by Macrocyclization

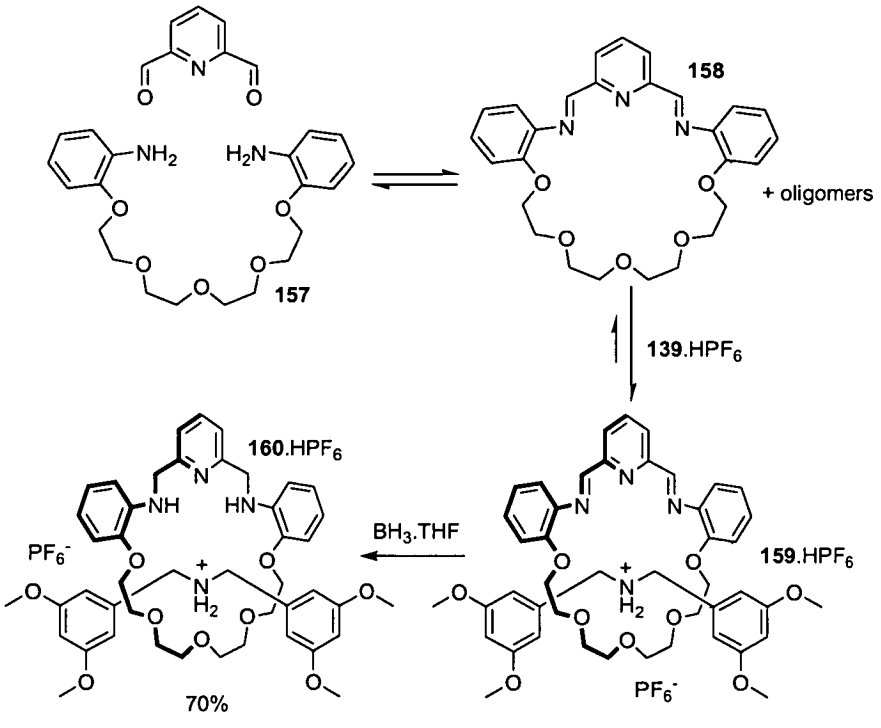
A report by Asakawa *et al.* details the dynamic formation of a rotaxane from a salen-derived crown ether macrocycle.[156] A ditopic macrocycle was designed with a crown ether region and a salen region. When the macrocycle is bound to Ba^{2+} or to Na^{+} the imine bonds of the salen group are dynamic. The ring can therefore open to form **154**, which can wrap around thread $\mathbf{153}^{2+}.H(PF_6)_3$ to form rotaxane $\mathbf{155}^{2+}.H(PF_6)_3$, in which the imine bonds are still kinetically labile (Scheme 52). Addition of $Ni(OAc)_2$ installs Ni(II) into the salen group and coordinatively stabilises the imines, preventing their hydrolysis. In this manner rotaxane $\mathbf{156}^{2+}.H(PF_6)_3$ is produced in a 26% yield.



Scheme 52. Rotaxane formation by imine hydrolysis and reformation

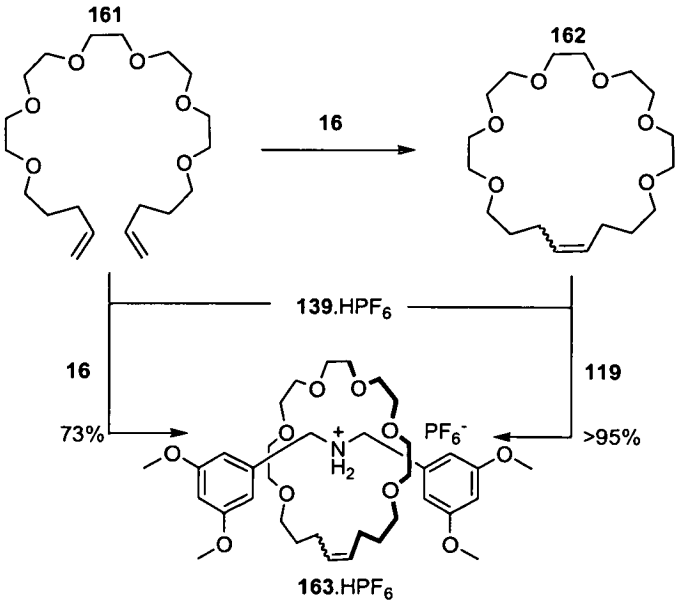
The Stoddart group has reported a versatile methodology for 'clipping' a crown-ether derived macrocycle around an ammonium thread by means of a reversible imine bond hydrolysis/reformation process under thermodynamic control.[157] Macrocycle **158** was devised as an imine-containing analogue of DB24C8 (Scheme 53). An equimolar solution of pyridine-2,6-dicarbonyl and diamine **157** results in a complex mixture of interconverting compounds that includes **158** as well as higher cyclic and linear oligomers. An equimolar solution of pyridine-2,6-dicarbonyl, **157** and $\mathbf{139}.HPF_6$ thread was found to rapidly equilibrate to give rotaxane $\mathbf{159}.HPF_6$ as the major product. The product could be kinetically 'locked' by reduction of the imine bonds to give $\mathbf{160}.HPF_6$ in 70% yield. A subsequent paper by the same workers detailed the kinetic and thermodynamic effects of structural variation of the rotaxane precursors in the clipping reaction.[158] The rapid and high yielding nature of this clipping reaction has led to its application in the synthesis of some challenging interlocked architectures: a mechanically interlocked dendrimer system has been

reported, again by the Stoddart group,[159] as have a variety of higher order rotaxane structures,[160] including a [3]rotaxane, a branched [4]rotaxane, a *bis*[2]rotaxane and a [4]rotaxane consisting of two [3]rotaxanes fused across their macrocycles.



Scheme 53. Rotaxane formation by dynamic imine formation

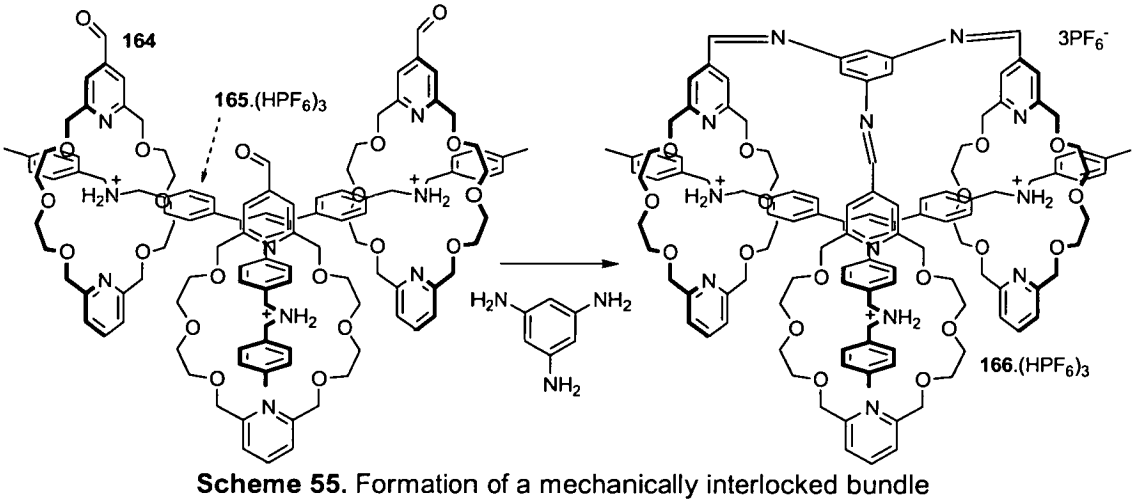
A so called 'magic rings' rotaxane was reported by the Grubbs group.[161] These workers showed that rotaxane architectures can be accessed by subjecting linear di-olefin macrocycle precursor **161** to ring-closing metathesis conditions with catalyst **16** in the presence of thread **139**.HPF_6 (Scheme 54). The presence of the thread increases the yield of cyclic product (as rotaxane) from the ring-closing metathesis reaction compared to when it is carried out in the absence of an ammonium template. An alternative approach to the rotaxane product is the 'magic rings' method, where the macrocycle **162** is formed first, then is subjected to olefin metathesis conditions with catalyst **119** in the presence of thread **139**.HPF_6. In this instance the more active catalyst was needed in order to activate the internal olefin bond. Under these conditions a mixture of thread and macrocycle was converted to >95% rotaxane in less than one hour. This work was followed by a joint publication by the Stoddart and Grubbs groups in which a catenane was produced under analogous conditions.[162]



Scheme 54. Rotaxane formation by olefin metathesis

1.2.3.3.3 Other Interlocked Structures

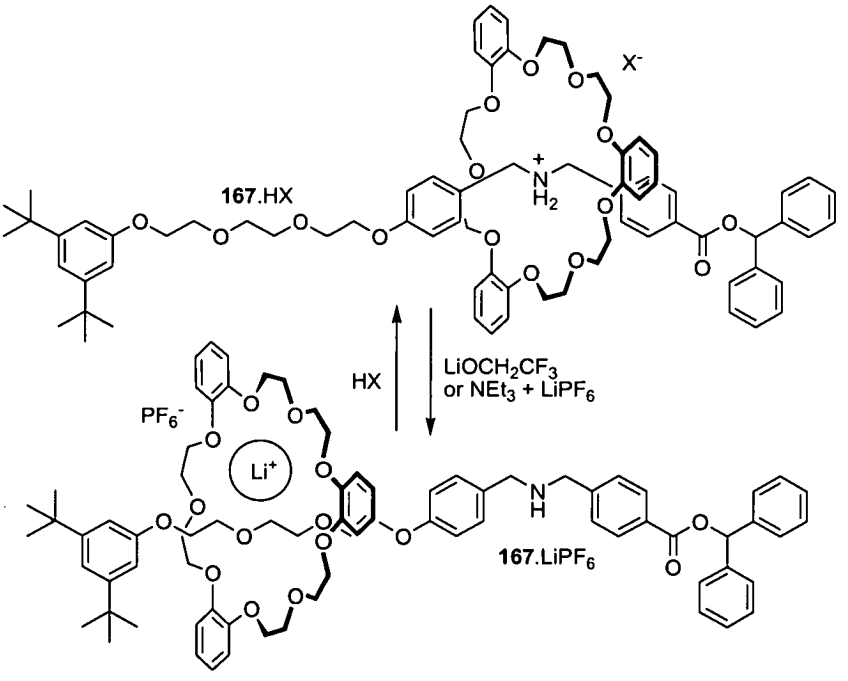
The Stoddart group has reported the synthesis of a novel mechanically interlocked bundle by the capping of a threefold symmetrical [4]pseudorotaxane.[163] A [4]pseudorotaxane is formed by the association of three formyl-substituted dipyrido[24]crown-8 derived macrocycles (**164**) with symmetrical *tris*-ammonium species **165**.$(HPF_6)_3$ (Scheme 55). Imine formation between the formyl groups of the macrocycles and 1,3,5-*tris*-aminobenzene results in the interlocked structure **166**.$(HPF_6)_3$ in which the *tris*-ammonium unit is unable to dissociate.



Scheme 55. Formation of a mechanically interlocked bundle

1.2.3.4 Molecular Devices

Cation binding has been used as a stimulus to trigger the submolecular motion of rotaxane-based molecular switch **167**.[164] The rotaxane has two regions in its thread: a DBA^+ unit and a triethylene glycol chain. The macrocyclic component of rotaxane **167** is tribenzo[27]crown-9. In the absence of any external cations the macrocycle resides almost exclusively over the DBA^+ station (Scheme 56). Similarly, addition of an excess of $LiPF_6$ as a source of Li^+ did not alter the mean position of the macrocycle. It is only when a metal cation and a base are used that the position of the macrocycle is affected: addition of $LiOCH_2CF_3$ results in the translocation of the macrocycle to the polyether region of the thread. Shuttling was also effected by alkali metal salts in the presence of triethylamine, with no observed selectivity for a specific metal ion.

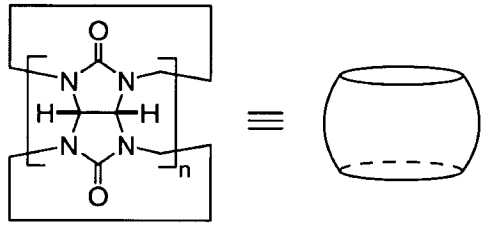


Scheme 56. Operation of a molecular shuttle switched by a metal cation

1.3: Cucurbituril

1.3.1 About Cucurbituril

The cucurbituril (CB) family of macrocycles are cyclic oligomers derived from glycoluril.[165, 166] Originally only the hexamer was known,[165] but in recent years other homologues have been accessed,[167] leading to the introduction of the cucurbit[n]uril (CB[n]) notation, where [n] denotes the number of repeat units. The name 'cucurbituril' derives from the Latin name 'cucurbitaceae' for the family of plants that includes the pumpkin, and was chosen because of the resemblance in shape between the macrocycle and this fruit. Cucurbit[n]uril macrocycles are versatile hydrophobic hosts that have certain similarities to cyclodextrins. In addition to hydrophobic interactions, the cucurbit[n]uril macrocycles are able to interact with guest species *via* the urea carbonyl groups that line each portal of the macrocycle.



n=5,6,7,8,10

Figure 24. Representation of the cucurbit[n]uril series of macrocycles

1.3.2 Pseudorotaxanes of Cucurbituril

There are a great many examples of inclusion complexes of CB[n] macrocycles, many of which could be described as pseudorotaxanes- i.e. a more or less linear component is included within the cavity of a macrocycle. For the purposes of this survey discussion has been restricted to those complexes that are of direct relevance to the understanding of CB[n] derived interlocked systems.

1.3.2.1 Discrete Pseudorotaxanes

The group of Kim has described the formation of CB[6] pseudorotaxane monolayers on a gold surface.[168] The pseudorotaxane complex of 1,4-butanediammonium derivative **168**.$(HBr)_2$ and CB[6] was linked to a gold surface by means of a 1,2-

dithiolane group (Figure 25). The pseudorotaxane monolayer was found to entirely shield the gold surface from being accessed by other species. Treatment of this monolayer with an aqueous sodium hydroxide solution deprotonates the ammonium thread and disrupts the pseudorotaxane. In the absence of the macrocycle the monolayer is significantly less bulky and is unable to shield the gold surface. The de-threading is reversed upon treating the monolayer with a mildly acidic solution of CB[6].

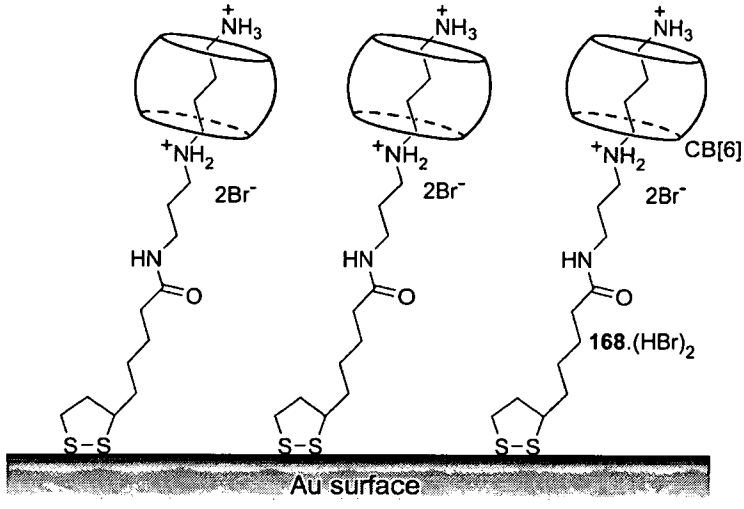


Figure 25. A CB[6] pseudorotaxane on a gold surface

1.3.2.2 Pseudopolyrotaxanes

A report by Tuncel and Steinke describes the threading of CB[6] macrocycles onto a linear polyammonium thread.[169] Gradual threading of CB[6] on to poly(iminiohexamethylene chloride) **169**.$(HCl)_n$ was observed in an acidic aqueous solution of the two components (Figure 26a). The slow formation of the main-chain pseudopolyrotaxane is attributed to the high activation energy for the shuttling of the CB[6] along the chain and that the macrocycles have to 'queue up' in order to thread onto the chain. A maximum thread occupancy of 0.5 CB[6] macrocycles per ammonium group was determined by integration of diagnostic NMR signals. In related work, the group of Kim has reported the formation of side-chain pseudopolyrotaxanes of CB[6].[170] Coordination of CB[6] to polystyrene **170**.$(HBr)_{2n}$ or polyacrylamide chains bearing protonated diaminobutane side-chains furnished the corresponding pseudopolyrotaxanes (Figure 26b). Threading of the polymer side

chains is reversed on deprotonation of the ammonium groups. The presence of CB[6] macrocycles on the side chains was found to affect the bulk properties of both polymers, significantly increasing their rigidity and thermal stability.

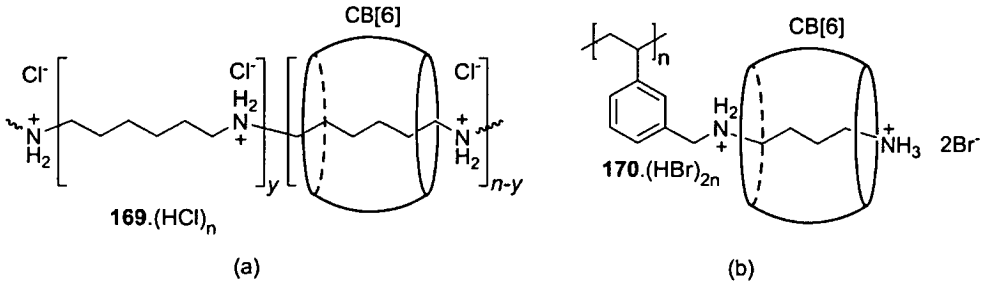


Figure 26. CB[6] (a) main-chain and (b) side-chain pseudopolyrotaxanes

A CB[6] pseudorotaxane-terminated dendrimer has been reported by the research group of Kimoon Kim.[171] The pseudorotaxane formed between dendrimer **171**.$(HBr)_{94}$ and CB[6] was found to have markedly reduced mobility compared to uncomplexed **171**.$(HBr)_{94}$, as a result of a sterically crowded shell of CB[6] pseudorotaxane units around the outer surface of the dendrimer (Figure 27).

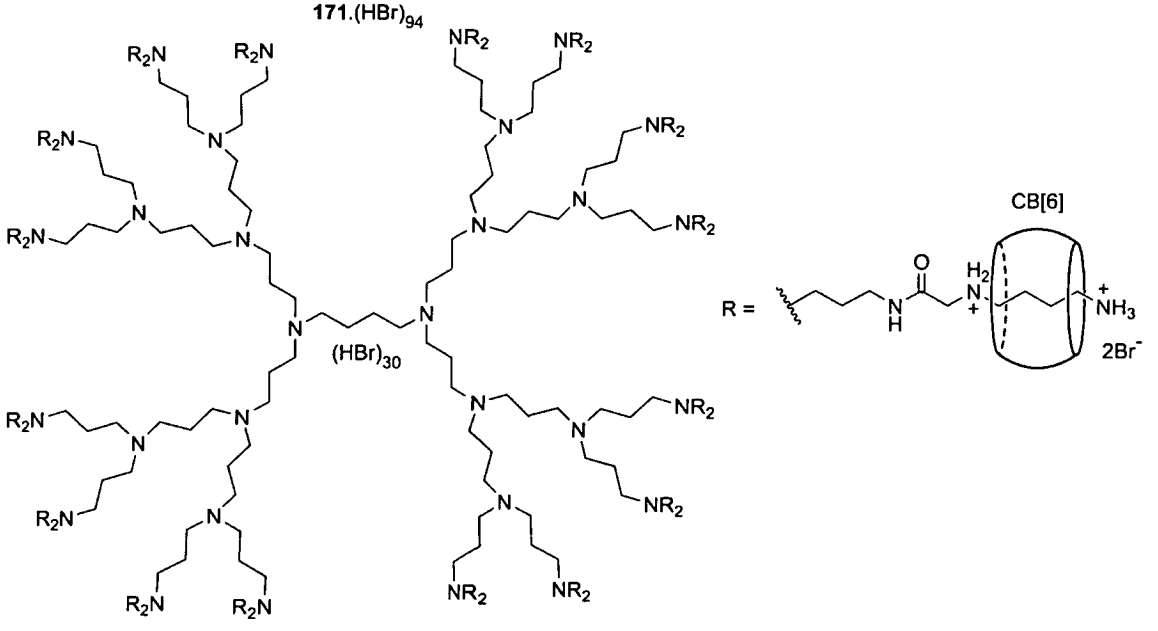


Figure 27. A CB[6] pseudorotaxane terminated dendrimer

A report jointly produced by the research groups of Kim and Yui describes a diblock pseudopolyrotaxane of polymer **172**.$(HX)_{2n}$ incorporating both CB[7] and dimethyl-β-cyclodextrin macrocycles (Figure 28).[172] The polymer was shown to exhibit pH-

responsive movement of the cucurbituril macrocycles onto the polypropylene glycol region on deprotonation of the ammonium groups.

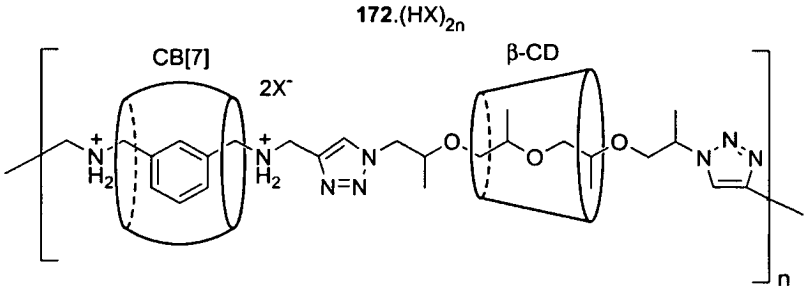
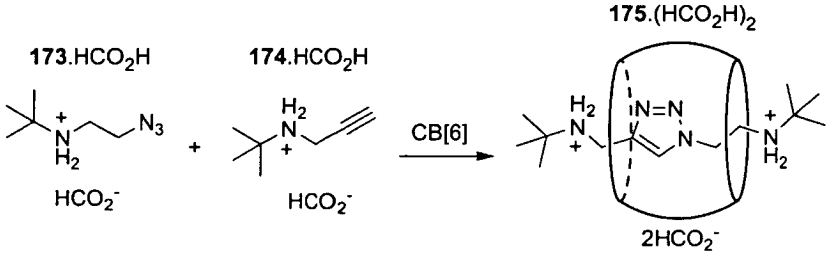


Figure 28. A CB[7]/DM-β-CD diblock pseudopolyrotaxane

1.3.3 Rotaxanes By End-Capping

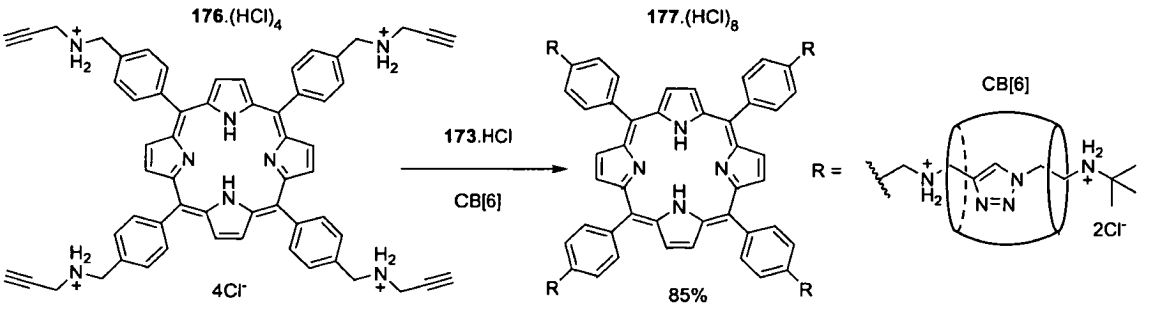
1.3.3.1 Discrete Covalent-Stoppered Rotaxanes

The first example of a rotaxane of CB[6] was reported by Mock and co-workers.[173] These workers discovered that CB[6] is able to catalyse the 1,3-dipolar cycloaddition reaction between an alkyne and an azide, and that this can be used to construct interlocked architectures (Scheme 57). A complex can be formed between CB[6] and (among other combinations) one equivalent each of azide **173**.HCO_2H and alkyne **174**.HCO_2H. Hydrogen bonding and ion-dipole interactions hold the ammonium groups of each guest at either portal of the macrocycle, while hydrophobic interactions induce the alkyne and azide groups to reside within the cavity of the macrocycle. This arrangement leads to steric strain between the groups within the macrocycle cavity, destabilising the substrates compared to the transition state of the cycloaddition reaction, resulting in the formation of rotaxane **175**.$(HCO_2H)_2$. Cycloaddition within the CB[6] macrocycle occurs with a rate acceleration of about 10^5. This methodology has since been elaborated for the synthesis of [2], [3] and [4]rotaxanes by Tuncel and Steinke.[174]



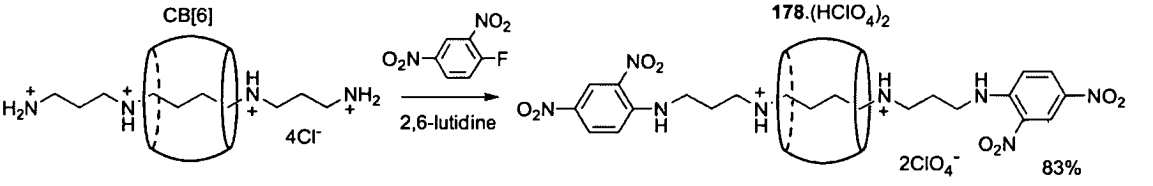
Scheme 57. A CB[6] rotaxane by Mock *et al.*

A report by Tuncel and co-workers describes the formation of a [5]rotaxane incorporating four CB[6] macrocycles.[175] Using the CB[6]-promoted cycloaddition methodology first described by Mock *tetrakis*-ammonium porphyrin derivative **176**.$(HCl)_4$ was converted to the [5]rotaxane **177**.$(HCl)_8$ by reaction with four equivalents of **173**.HCl, promoted by four CB[6] macrocycles (Scheme 58).



Scheme 58. A porphyrin-based [5]rotaxane

A report by Kim and co-workers describes the synthesis of a CB[6] rotaxane by an end-capping approach.[176] The inclusion complex formed between CB[6] and spermine tetrahydrochloride was end-capped by means of a nucleophilic aromatic substitution reaction with 2,4-dinitrofluorobenzene to produce rotaxane **178**.$(HClO_4)_2$ (Scheme 59).The same end-capping procedure has been applied to the synthesis of a rotaxane incorporating a *bis*-phenyl substituted derivative of CB[6] by the research group of Nakamura.[177]

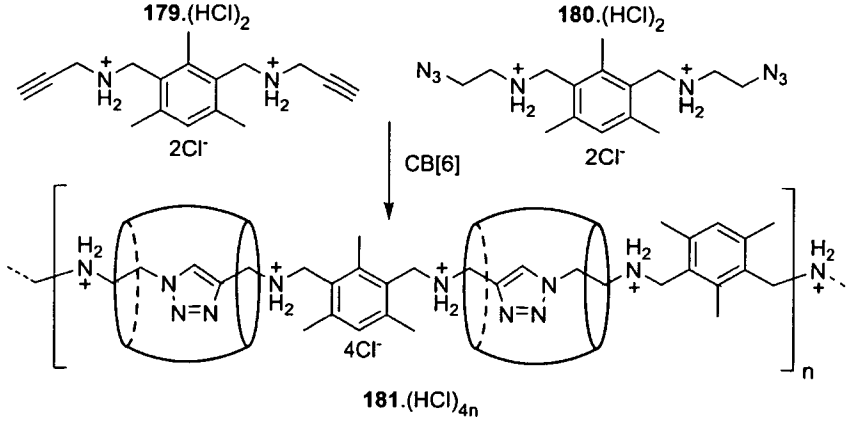


Scheme 59. A CB[6] rotaxane by end-capping

1.3.3.2 Covalent Polyrotaxanes

A report by Steinke and Tuncel details the formation of polyrotaxanes of cucurbituril by a 'catalytic self-threading' methodology.[178] The ability of cucurbituril to promote the 1,3-dipolar cycloaddition reaction between an azide and an alkyne was exploited by Steinke and Tuncel to catalyse the coupling of a diazide **179**.$(HCl)_2$ with dialkyne **180**.$(HCl)_2$ to form polyrotaxane **181**.$(HCl)_{4n}$. It was necessary to use bulky polymerisation partners to prevent the competitive, non-reactive, mode of

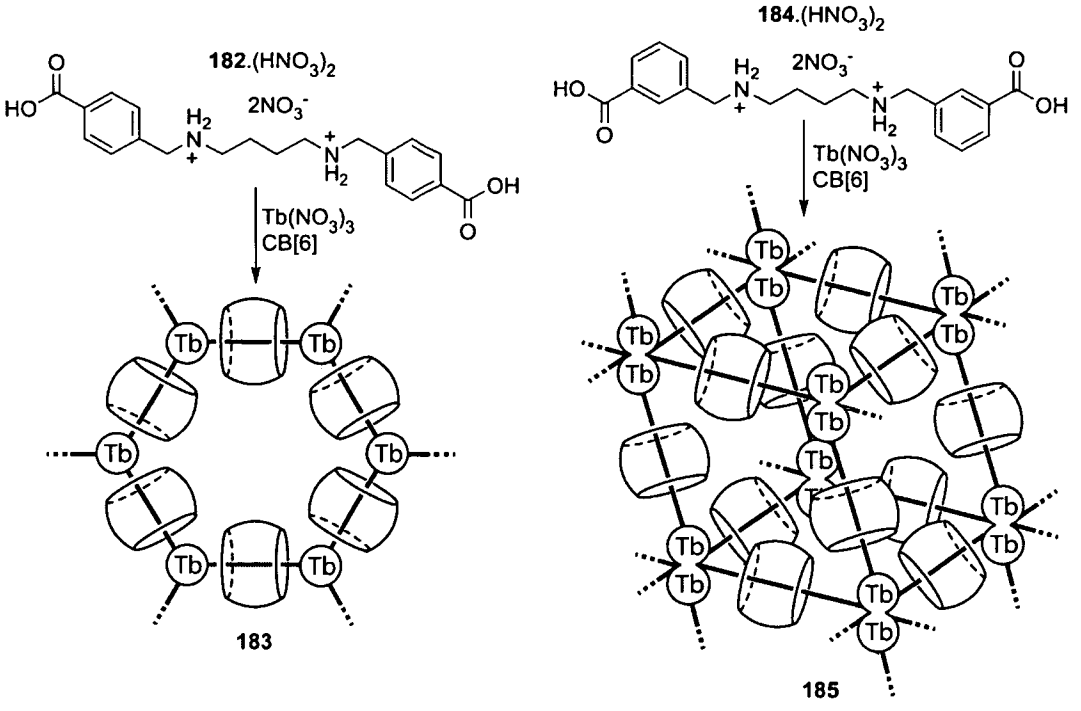
complexation in which a single diazide or dialkyne is included within a CB[6] macrocycle. This restriction means that the polyrotaxanes formed are necessarily 'in-chain stoppered'- i.e. the macrocycles are isolated from one another by bulky units in the polymer chain. 'Perfect' mainchain polyrotaxanes were thus synthesised with a molecular weights of up to 39,000.



Scheme 60. Synthesis of a mainchain polyrotaxane

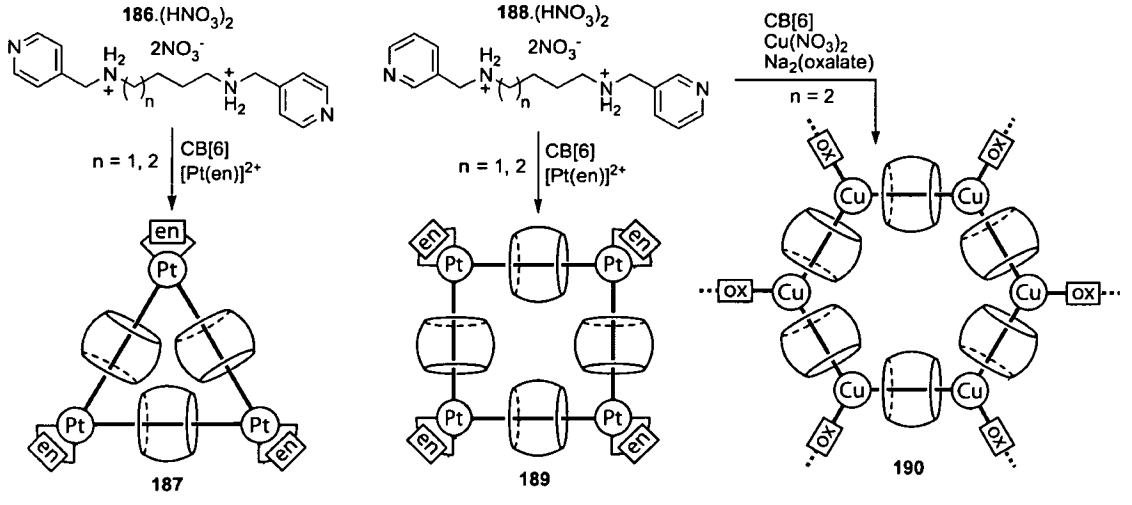
1.3.3.3 Metal Complex Stoppered Rotaxanes and Catenanes

A report by the research group of Kim describes the formation of a three-dimensional polyrotaxane network in which CB[6] pseudorotaxane units are held in a regular array in the solid state by coordination of benzoate residues at each terminus of the thread to a Tb(III) ion.[179] When the para-benzoate thread **182**.$(HNO_3)_2$ is used two-dimensional network **183** is formed, whereas the meta-benzoate unit **184**.$(HNO_3)_2$ results in the formation of three-dimensional network **185** (Scheme 61). Using a similar methodology a two-dimensional hexagonal rotaxane network[180] and a one-dimensional helical rotaxane network[181] were assembled with Au(I) as the linking unit. The same methodology was later used to access other one- and two-dimensional rotaxane networks.[182] Related work by Sun, Chen *et al.* describes the synthesis of one-dimensional CB[6] polyrotaxanes linked by Ag(I) ions.[183]



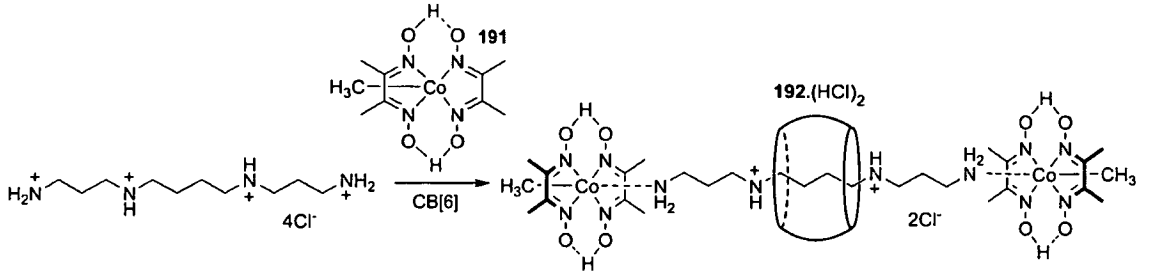
Scheme 61. Formation of two- and three-dimensional CB[6] rotaxane networks

The group of Kim has reported the synthesis of various 'molecular necklace' (MN) catenane systems in which discrete cyclic units are formed from coordinating CB[6] pseudorotaxane units linked to a transition metal ion. The *para*-pyridyl thread **186**.$(HNO_3)_2$ forms [4]MN **187** with an equivalent each of CB[6] and Pt(II) (Scheme 62).[184] The *meta*-pyridyl thread **188**.$(HNO_3)_2$ forms [5]MN **189** with an equivalent of Pt(II) and CB[6],[185] or can form 7[MN] 190 with an equivalent of CB[6] and Cu(II).[186] A Cu(II)-linked [5]MN was accessed by similar methods.[187]



Scheme 61. Synthesis of [4]MN, [5]MN and [7]MN structures *via* transition metal coordination

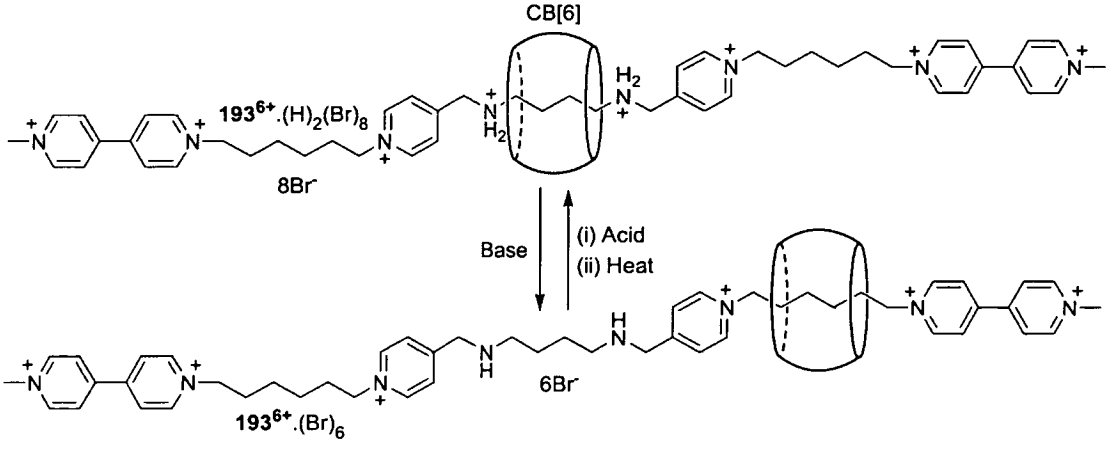
A transition metal-stoppered [2]rotaxane of CB[6] has been reported by Chen and co-workers.[188] The inclusion complex formed between CB[6] and spermine terahydrochloride was treated with Co(III) complex **191** to form rotaxane **192**.$(HCl)_2$ (Scheme 64).



Scheme 64. Synthesis of a cobalt-stoppered CB[6] rotaxane

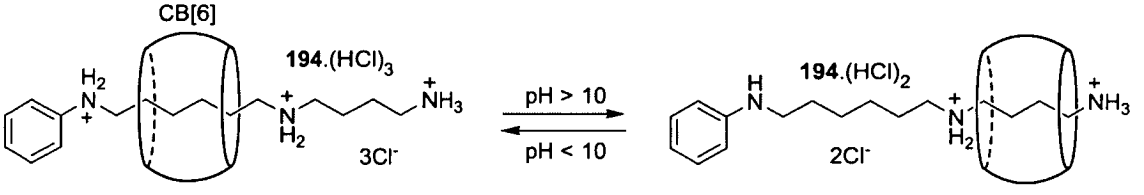
1.3.4 Pseudorotaxane Switches

The research group of Kim has reported the self-assembly of a protonation controlled molecular switch.[189] The pseudorotaxane formed between thread $\mathbf{193}^{6+}.(H)_2(Br)_8$ and CB[6] has a symmetrical thread with a central *bis*-dialkylammonium recognition site- over which the CB[6] macrocycle primarily resides- flanked on either side by *bis*-pyridinium alkyl stations (Scheme 64). On deprotonation to give $\mathbf{193}^{6+}.(Br)_6$ the macrocycle moves rapidly to one of the outer stations. When the system is reprotonated the macrocycle remains on the outer station at room temperature, but on heating returns to the central diammonium station, thus shuttling in one direction requires only a chemical input, but the reverse process requires both chemical and thermal activation.



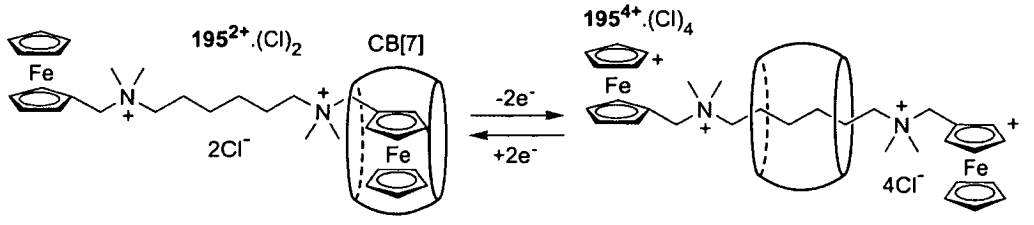
Scheme 64. Operation of a protonation controlled CB[6] molecular switch

A protonation driven CB[6] pseudorotaxane molecular switch has been reported by Mock and Pierpont.[190] In its fully protonated form thread **194**.$(HCl)_3$ presents two possible binding sites for CB[6], in which the ammonium groups are separated by four or six methylene units, the latter presenting the more favourable binding site for CB[6]. On elevating the pH above a threshold value of approximately 10 the aniline nitrogen is no longer protonated and the CB[6] macrocycle moves to the alternative station. A fluorescent derivative of this switch has been reported by Kim *et al.*[191] By incorporating a fluorene unit into the thread it is possible to gauge the state of the switch, although this is an indirect measure of the position of the macrocycle as the change in fluorescence of the fluorene unit is determined by the protonation state of the adjacent amine/ammonium and not by the position of the macrocycle.



Scheme 65. Operation of protonation controlled CB[6] molecular switch

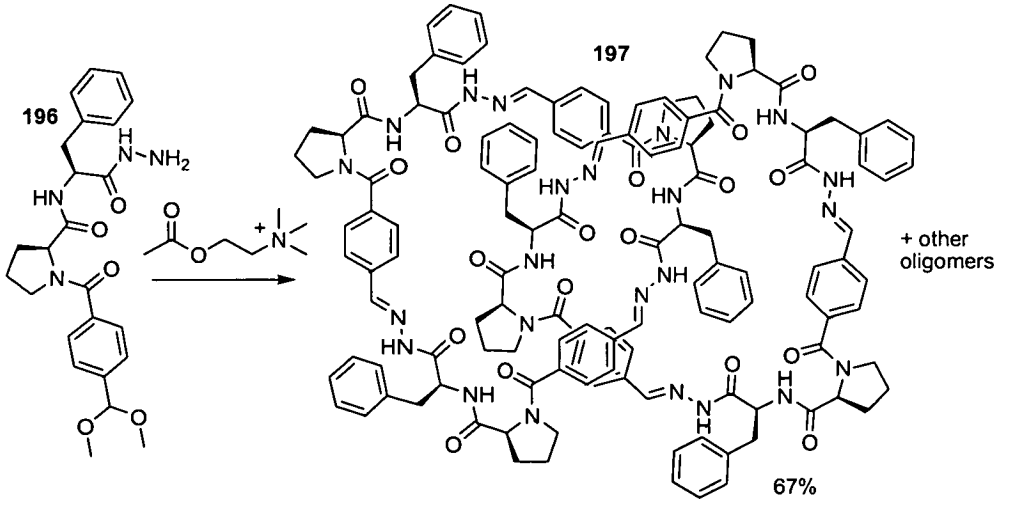
A pseudorotaxane-based molecular switch based on CB[7] has been reported by Sobransingh and Kaifer.[192] The switch consists of the CB[7] pseudorotaxane of thread $\mathbf{195}^{2+}.(Cl)_2$, which has two quaternary ammonium groups in its central region and a ferrocene group at each end (Scheme 66). Due to hydrophobic interactions the CB[7] macrocycle resides over one of the ferrocene groups and interacts with one of the quaternary ammonium groups by hydrogen bonding. Electrochemical oxidation to give thread $\mathbf{195}^{4+}.(Cl)_4$ 'switches off' the hydrophobic interaction afforded by ferrocene and the macrocycle moves to reside over the centre of the thread, where it instead interacts with both of the quaternary ammonium groups.



Scheme 66. Operation of an electrochemically controlled CB[7] molecular switch

1.4 Other Systems

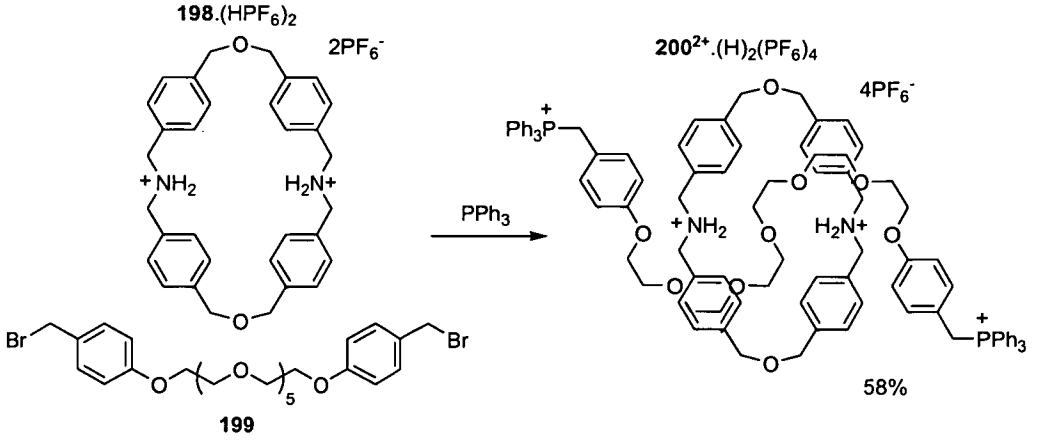
A remarkable ammonium-templated catenane has been reported by the Sanders research group.[193] The Sanders group was investigating the possibility of producing a acetylcholine binding molecule from a dynamic combinatorial library (DCL) in which the peptide-like unit **196** oligomerizes by the formation of hydrazone linkages. In the absence of a molecular template the library forms an equilibrium distribution of products, of which the cyclic trimer is the most abundant. In the presence of acetylcholine chloride the product distribution of the library changes dramatically, and the most abundant product is a hexamer. This hexameric material was isolated from the library and identified as [2]catenane **197**, which consists of two interlinked trimeric macrocycles (Scheme 67). Only one of the two possible diastereomers of the catenane was formed. The catenane was found to bind acetylcholine with an association constant of 1.4×10^7 M^{-1}.



Scheme 67. Spontaneous formation of an acetylcholine binding catenane

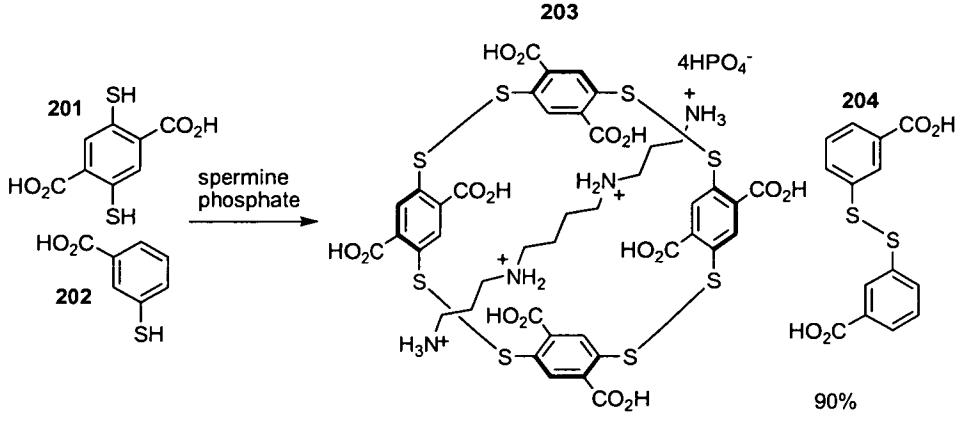
The Stoddart group has described the synthesis of a rotaxane using a 'reversed' version of the widely exploited DBA/DB24C8 recognition pair.[194] In this work macrocycle **198**.$(HPF_6)_2$, consisting of two linked DBA^+ units was threaded by hexaethylene glycol thread **199** (Scheme 68). The association constant for the complex formation was found to be approximately 3000 M^{-1} in CH_3NO_2 at 298 K. The formation of an inclusion complex was confirmed by synthesis of the

corresponding rotaxane $\mathbf{200}^{2+}.(H)_2(PF_6)_4$ by end-capping *via* the addition of triphenylphosphine.



Scheme 68. Synthesis of a 'reversed recognition motif' rotaxane

The research group of Otto has described the selective formation of a macrocyclic receptor for spermine from a dynamic combinatorial library.[195] In the absence of a template, oxidation of thiols **201** and **202** results in a complex dynamic mixture of disulfides including linear and cyclic species (Scheme 69). On addition of spermine to the mixture the product distribution is shifted to give the cyclic tetramer **203** in 90% yield. Macrocycle **203** was found to bind spermine with a dissociation constant of 22 nM, and was shown to be capable of extracting spermine from DNA, its natural host.



Scheme 69. Formation of a spermine receptor by disulfide exchange

1.5 Conclusions and Outlook

The ammonium group has proven to be a versatile and readily accessible template for the synthesis of interlocked molecules. The expedient synthesis allowed by ammonium binding- particularly using 'off the shelf' macrocycles- has allowed ready access to interlocked molecular architectures of increasing complexity. This, coupled with the fact that the hydrogen bond donor ability of the ammonium group can be effectively 'switched off' by deprotonation, has meant that the ammonium group has played a key role in the development of the current generation of interlocked molecules. This is likely to continue into the future, allowing chemists to assemble ever more complex interlocked molecules, and to introduce pH-switchable properties that could drive the motion of prototype molecular machines.

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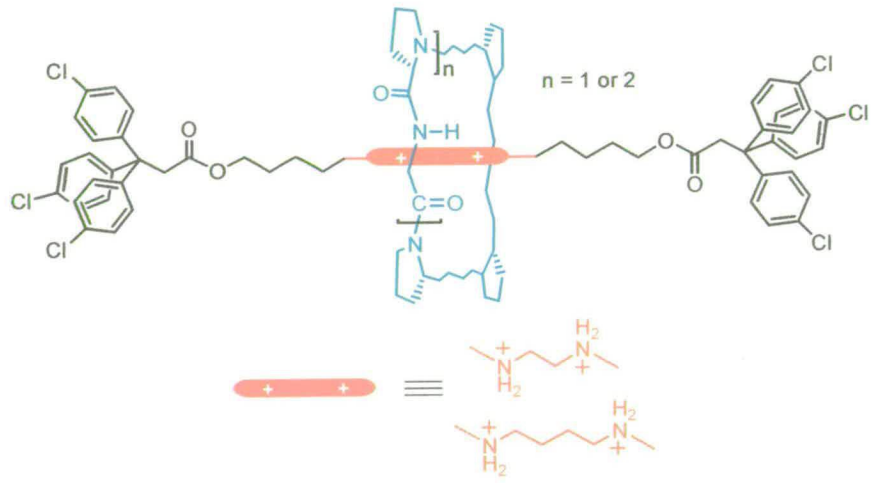
Chapter 2 Synopsis

This chapter describes the synthesis of a new class of rotaxanes in which the macrocyclic component is a cyclic peptide derived from the L-ProGly repeat unit. Macrocycles of this types are known to simultaneously bind two ammonium groups, one on either face of the ring. This mode of binding is exploited to induce a diammonium thread to form an inclusion complex that is then end-capped to give the rotaxane. Association to the ammonium groups of the thread disrupts the internal hydrogen bond network of the macrocycle.



All solid phase peptide synthesis work was carried out by A. Thomson. Diammonium thread compounds and rotaxanes were prepared by J. Lock. Rotaxane products were purified by J. Lock and A. Thomson. The manuscript for publication was prepared jointly between V. Aucagne, D. Leigh, J. Lock and A. Thomson.

Chapter 2

Rotaxanes of Cyclic Peptides

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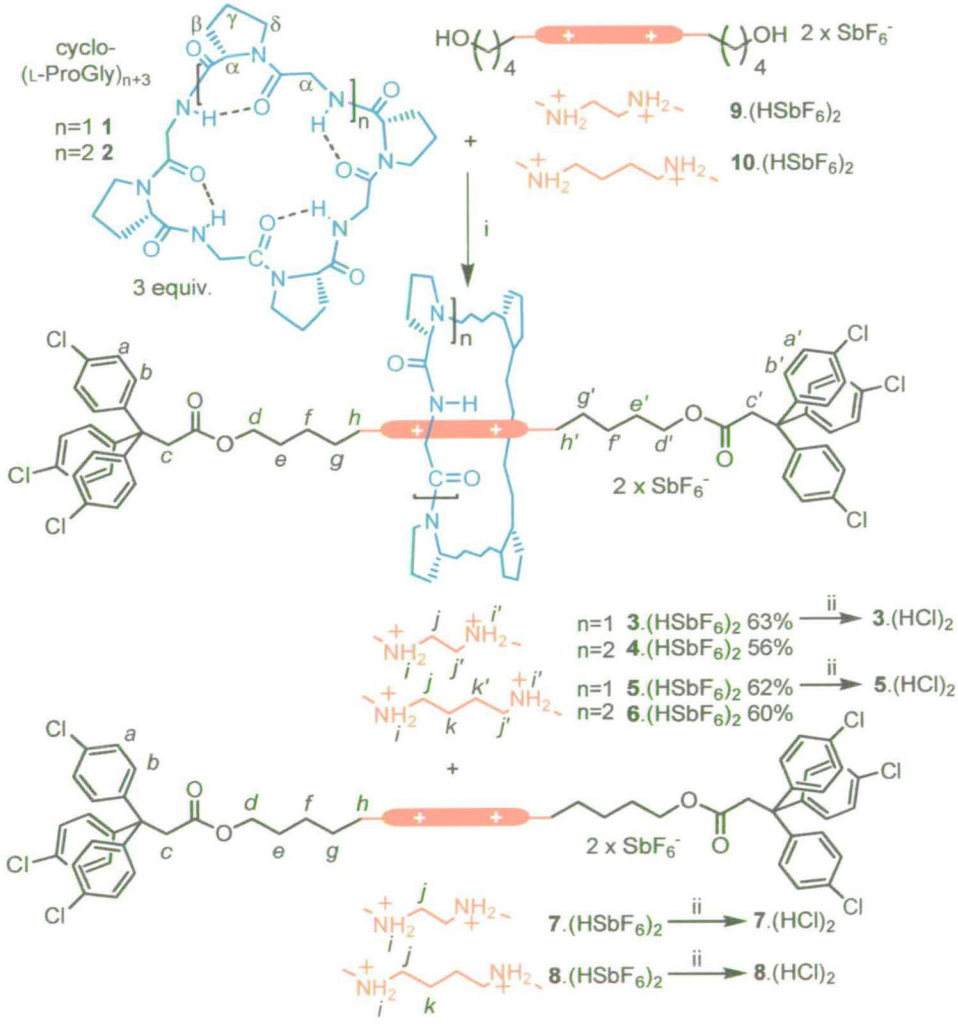
2.1 Introduction

Until recently the existence of mechanically interlocked peptide backbones in nature was far from clear cut. However, in the past few years, first knots,[1] then catenanes[2] and, finally, rotaxanes[3] have been unambiguously characterized in naturally occurring peptides and proteins.[4] Although the implications of kinetically stable entanglements on peptide and protein structure, properties, function and folding remain almost completely unknown, already studies on the few interlocked peptides available have shown them to possess a wealth of intriguing properties, including high resistance to peptidases,[5a] unique modes of antimicrobial and antiviral action,[5b-d] impressive membrane transport characteristics,[5e] and stability to thermal and chemical denaturing.[5f] However, few artificial or simpler analogues have been investigated to date since no methodology yet exists for synthetically interlocking peptide fragments.[6,7] En route to this goal, here we describe the preparation of rotaxanes from a class of well-known cyclic peptides and some nonpeptidic threads.

Efficient synthetic routes to catenanes and rotaxanes generally rely on strong-binding mutual recognition elements on each component to direct a threading or macrocyclization reaction.[8] The problem with applying such a strategy to peptides is that the amide groups of each free component will normally be largely self-satisfied in terms of hydrogen bonding through folding, and little driving force will exist for interlocking. Indeed, several attempts[3b,c] to synthesize microcin J25, a 21-residue oligopeptide with a rotaxane architecture, by conventional peptide synthesis strategies have failed. However, many natural and unnatural cyclic peptides are known to bind cations efficiently. Crown ether-[9] and cucurbituril-[10] organic cation binding provides some of the most effective rotaxane template syntheses known, and we wondered whether a similar interaction could also be used to promote rotaxane formation with peptidic macrocycles. The formation of an inclusion complex between an amide macrocycle and a linear organic cation could provide the required spatial arrangement of components to furnish a rotaxane *via* a stoppering approach. As prototypical systems we investigated cyclic octa- (**1**) and deca- (**2**) peptides derived from the L-ProGly repeat unit.[11] High stability constants (Ka $\approx 10^3$-10^5 M^{-1})

have been reported for 1:1 metal and 1:1 and 1:2 protonated amino acid ester complexes of these cyclopeptides in acetonitrile.[11c] Accordingly, we constructed a series of cationic diol threads and examined their efficacy in rotaxane-forming "stoppering" reactions with a bulky acid chloride and macrocycles **1** and **2** (Scheme 1).[12] Ester formation was chosen as a stoppering reaction because of its tolerance of acidic conditions and lack of by-products.



Scheme 1. Synthesis of cyclic peptide [2]rotaxanes **3**-**6**$(HSbF_6)_2$. Reagents and conditions: i. $(4\text{-}ClC_6H_4)_3CCH_2COCl$, $CHCl_3$:CH_3CN 3:7, RT, 7 days. ii. sat. $NaHCO_3$, then 1 M HCl. For clarity, atom labels are only shown for one repeat unit of the cyclopeptide in [2]rotaxanes **3**-**6**$(HSbF_6)_2$

2.2 Results and Discussion

Cyclo(L-ProGly)$_4$ (**1**) and cyclo(L-ProGly)$_5$ (**2**) were prepared *via* a solid-phase backbone amide-linking approach, which allowed rapid and divergent access to both macrocycles with minimal need for purification. As they are water-soluble, a simple aqueous extraction removes either macrocycle from a rotaxane-forming reaction mixture, and they can easily be recycled. In contrast, the chromatographic separation of the [2]rotaxanes from the corresponding threads is rather difficult and it therefore proved convenient to use an excess of the cyclic peptide to maximize the ratio of rotaxane to thread. Although only traces of interlocked products were formed with monocationic ammonium or pyridinium threads, we were delighted to find that [2]rotaxanes **3**-**6**.(HSbF$_6$)$_2$ were formed in 56-63% yield from ethane-1,2-diammonium and butane-1,4-diammonium templates.[12] The ^{1}H NMR spectra (Figure 1) of the cyclo(L-ProGly)$_4$-based [2]rotaxanes **3**.(HCl)$_2$ and **5**.(HCl)$_2$ and their free components (threads **7**.(HCl)$_2$ and **8**.(HCl)$_2$ and macrocycle **1**) provide some insights into the structure of the rotaxanes and the nature of the template interaction. Cyclo(L-ProGly)$_4$ exists as a mixture of rotamers in acetonitrile,[11c] ~30% as an all-trans conformer (shown in light blue in Figure 1c) in which four γ-turn Gly-to-Gly H-bonds give rise to a relatively planar structure with the glycine carbonyls pointing towards the centre and the proline carbonyls directed away. However, a single set of signals is observed for each constitutionally distinct proton of the macrocycle in both **3**.(HCl)$_2$ (Figure 1b) and **5**.(HCl)$_2$ (Figure 1d). Cyclo(L-ProGly)$_4$ is known[11c] to adopt a geometry in 1:2 host-guest ammonium cation complexes which is also an all-trans rotamer, but is cylindrical rather than flat, with the glycine carbonyls rotated towards one face and the proline carbonyls to the other, destroying the internal hydrogen bond network. The ^{1}H and ^{13}C (see ref 11c) NMR spectra are consistent with a similar structure existing in rotaxanes **3**.(HCl)$_2$ and **5**.(HCl)$_2$. Rapid spinning of the thread in the cavity (the macrocycle resonances remain symmetrical even at 240 K in CD_3CN) enable each of the peptide carbonyls to interact with the two ammonium groups through an alternating network of hydrogen bonds and electrostatic$C{=}O^{\delta-}\cdots N^+$ interactions.

Confirmation of the change in conformation of cyclo(L-ProGly)$_4$ upon rotaxane formation is seen in the changes in the resonances of the glycine methylene groups.

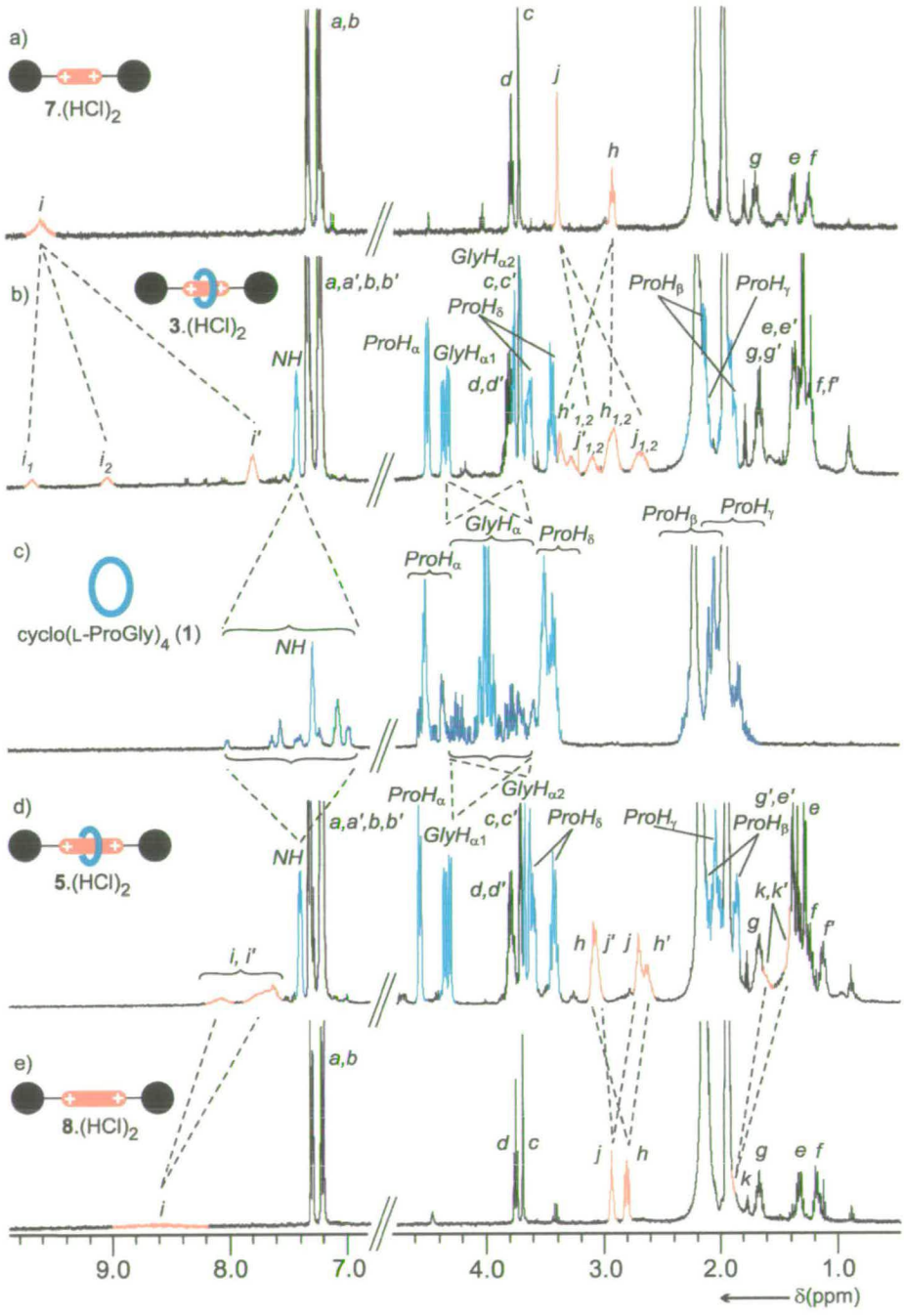


Figure 1. Partial ^{1}H NMR spectra (400 MHz, CD_3CN, 298 K) of a) ethane-1,2-diammonium thread **7**.$(HCl)_2$; b) [2]rotaxane **3**.$(HCl)_2$; c) cyclo(L-ProGly)$_4$ (**1**); d) [2]rotaxane **5**.$(HCl)_2$; e) butane-1,2-diammonium thread **8**.$(HCl)_2$. The labeling corresponds to that shown in Scheme 1. The resonances of the all-trans rotamer of cyclo(L-ProGly)$_4$ are shown in light blue and those from minor rotamers, only present in part (c), in dark blue.

The geminal $GlyH_\alpha$ protons in the H-bonded all-trans rotamer of free **1** are in similar proximities to the shielding region of the adjacent proline carbonyl groups and appear at similar chemical shifts (Figure 1c). However, in both **3**.$(HCl)_2$ and **5**.$(HCl)_2$ H-bonding of the glycine carbonyls to the ammonium groups rotates the NHCO groups, causing the positions of the geminal methylene protons relative to the adjacent proline carbonyls to differ from each other such that the four $GlyH_{\alpha 1}$ protons are shifted downfield by 0.35 ppm whereas the four $GlyH_{\alpha 2}$ protons are shifted upfield by 0.30 ppm. Despite the loss of the internal hydrogen bonding network, the amide resonances still experience a slight net upfield shift in the rotaxanes as a result of the inductive effect from the strong interaction of glycine carbonyls with the ammonium groups.

In the ethane-1,2-diammonium rotaxane, **3**.$(HCl)_2$, it is clear that one ammonium group ($H_{i'}$, Figure 1b) H-bonds principally to the glycine carbonyls and one (H_{i1} and H_{i2}, Figure 1b) to the proline carbonyls. The greater shielding of the $H_{i'}$ protons (indicative of stronger H-bonding) is, again, consistent with the previous studies[12c] on cyclo(L-ProGly)$_4$–ammonium ion host-guest complexes. The fact that the -CH_2N^+- protons internal to the template (H_j) are shielded in the rotaxane compared to the thread, whilst those external to the template (H_h) are deshielded, indicates that each ammonium group is largely H-bonded from just one direction, with the macrocycle located over the central ethane group.

Whilst the shifts of the -H_2N^+- signals in rotaxane **5**.$(HCl)_2$ are less informative, the internal and external -CH_2N^+- groups are both split into shielded and de-shielded resonances indicating that H-bonding with the longer template occurs to each ammonium group from both directions (obviously not simultaneously). In other words, the cyclopeptide is loosely held in **5**.$(HCl)_2$ and able to access the full length of the thread.

The ability of cation-amide interactions to disrupt internal amide-amide H-bonding augurs well for their use to overcome peptide folding and provide a thermodynamic

driving force for the formation of kinetically stable peptide and protein entanglements.

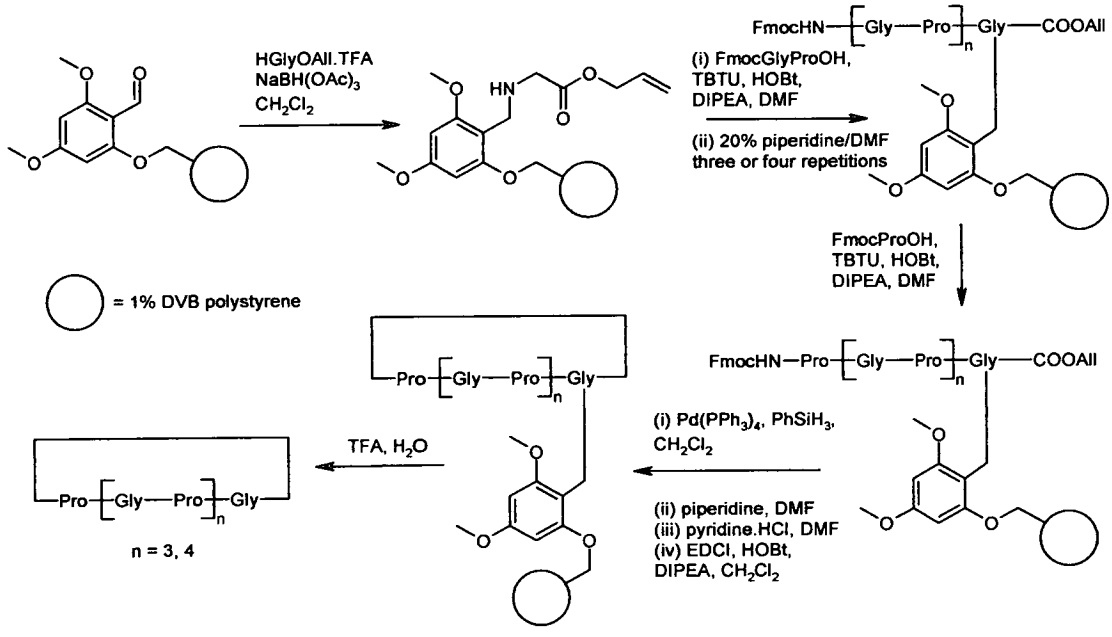
2.3 Experimental Section

General

Unless otherwise stated, all reagents and anhydrous solvents were purchased from Aldrich chemicals and used without further purification. 5-Chloro-1-pentanol was purchased from Lancaster and FmocGlyOH and Boc-L-Pro were purchased from NovaBiochem. All reagents were of at least 98% purity. Column chromatography was carried out using Kieselgel C60 (Merck, Germany) as the stationary phase. Thin layer chromatography was performed on precoated silica gel plates (0.25 mm thick, $60F_{254}$, Merck, Germany) and compounds were visualized under UV light; amine-bearing compounds were visualized by dipping the plate in a 1% w/v solution of ninhydrin in ethanol then heating the plate with a heat gun. Eluent compositions for thin layer chromatography were selected so as to give Rf values of 0.2. Reverse phase chromatography was carried out using Diaion HP-20 resin, which was prepared according to the manufacturer's instructions. All ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AV 400 instrument, at a constant temperature of 298 K. Chemical shifts are reported in parts per million from high to low field and referenced to the residual solvent peak. Standard abbreviations indicating multiplicity are given: m = multiplet, br = broad, d = doublet, q = quadruplet, t = triplet, s = singlet. Coupling constants (*J*) are reported in hertz (Hz). Melting points were determined using a Sanyo Gallenkamp apparatus and are uncorrected. Melting points for literature compounds match to within 1 °C. LCMS was carried out using a Waters 2795 HPLC system and a Phenomenex Luna (5μ) C18 analytical column (250 × 2.0 mm). A solvent gradient of 5-95% acetonitrile/water over a 35 minute interval and a flow rate of 0.2 cm^3/minute were applied. UV-active components eluted from the column were detected using a Waters 486 Tunable Absorbance Detector set to read absorbance at 254 nm. ESI mass spectrometry was performed with a Micromass Platform II Mass Spectrometer controlled using Masslynx v2.3 software. FAB accurate mass spectrometry was carried out by the University of Edinburgh services.

Cyclo(ProGly)$_4$ (1) and Cyclo(ProGly)$_5$ (2)

General: Cyclo(ProGly)$_4$ and Cyclo(ProGly)$_5$ were synthesised *via* a backbone amide linking protocol. The cyclized products were characterised by LC-MS and HRMS. FmocGlyProOH and HGlyOAll.TFA were synthesised using standard protecting group chemistry. Solid phase synthesis work was carried out in a polypropylene syringe tube fitted with frit and tap.



Scheme E1. Solid phase synthesis of **1** and **2**.

Attachment of linker: The 'o-PALdehyde' linker was synthesised according to a literature procedure[13] and was attached to an aminomethyl polystyrene support as follows: Aminomethyl polystyrene (1 mmol) was swelled in DMF (30 ml) for 1 h then drained. A solution of o-PAL linker (2 mmol), TBTU (2 mmol), HOBt (2 mmol) and DIPEA (2 mmol) in DMF (30 ml) was stirred for 5 min then added to the resin. The resin was agitated for 24 h, then drained and washed with DMF (4 × 30 ml) then CH_2Cl_2 (4 × 30 ml). The resin was then treated with an 8:1:1 mixture of CH_2Cl_2:pyridine:acetic anhydride (30 ml) for 1 h. The resin was drained and washed with CH_2Cl_2 (4 × 30 ml).

Loading of first residue: o-BAL resin (1 mmol) was swelled in CH_2Cl_2 (30 ml) then drained and a solution of HGlyOAll.TFA (10 mmol) in CH_2Cl_2 (30 ml) was added

and the mixture agitated for 6 h. $NaBH(OAc)_3$ (5 mmol) was added and the mixture agitated for a further 1 h. The resin was drained and washed with CH_2Cl_2 (4 × 30 ml).

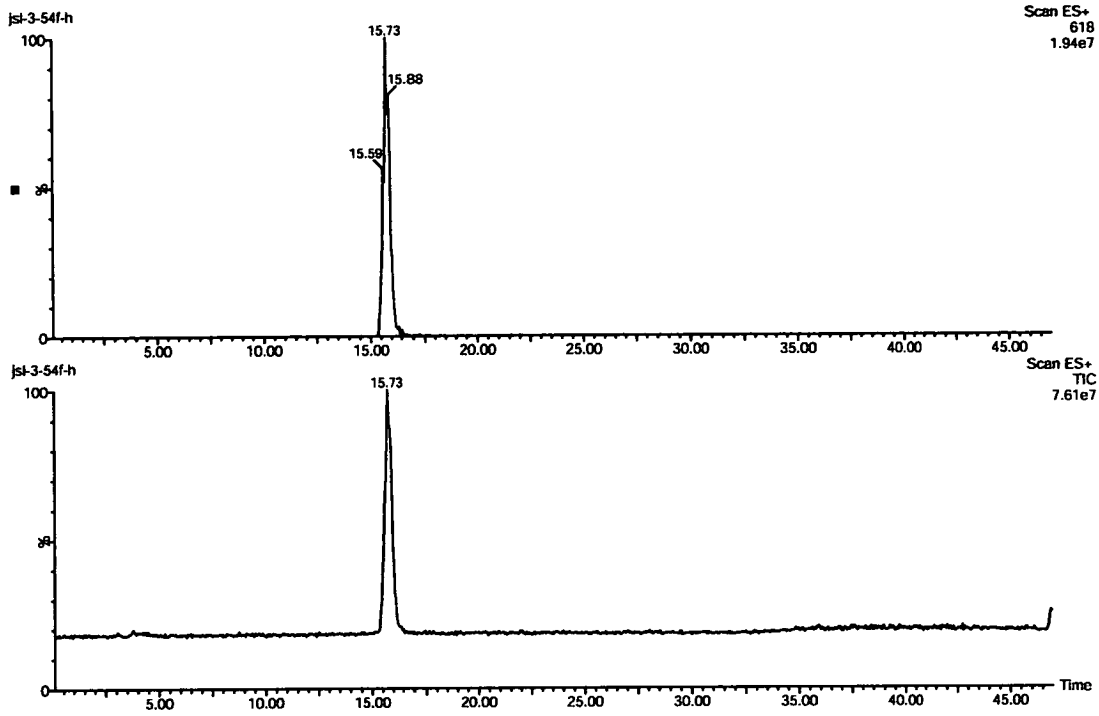
Fmoc SPPS: Where required the resin bound peptide was Fmoc deprotected by treatment of the resin with a 20% solution of piperidine in DMF (4 × 5 min) then washed with DMF (4 × 30 ml). Peptide couplings were carried out according to the following general protocol (quantities assume complete loading of 1 mmol resin): A solution of Fmoc protected amino acid (2 mmol), TBTU (2 eq), HOBt (2 mmol) and DIPEA (2 mmol) in DMF (30 ml) was stirred for 5 min then added to the resin. The resin was agitated for between 4 and 16 h as convenient, then drained and washed with DMF (4 × 30 ml).

Solid-phase macrocyclization reactions

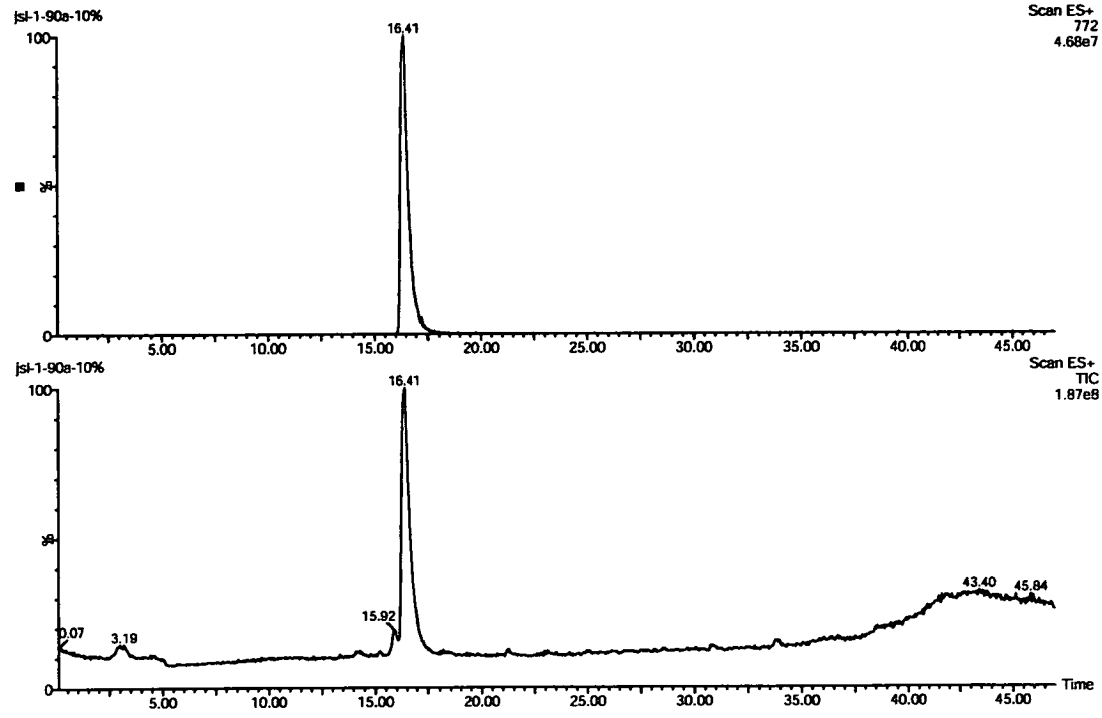
The octa- or deca- peptide was deprotected and cyclized on a 1 mmol scale as follows: The resin was treated with $Pd(PPh_3)_4$ (0.25 mmol) and $PhSiH_3$ (10 mmol) in CH_2Cl_2 (30 ml) for 16 h. The resin was then drained and washed with CH_2Cl_2 (4 × 30 ml) then DMF (4 × 30 ml). The resin was treated with 20% piperidine in DMF (4 × 5 min) then washed with 4 × 30 ml of the following: DMF, 1M pyridine.HCl in DMF, DMF, CH_2Cl_2. The resin was then treated with EDCI (2 mmol), HOBt (2 mmol) and DIPEA (2 mmol) in CH_2Cl_2 (30 ml). After 24 h the resin was drained and washed with CH_2Cl_2 (4 × 30 ml).

Cleavage: The cyclized material was cleaved from the solid support by treatment with TFA containing 5% water (10 ml) followed by washing with a 10% solution of methanol in CH_2Cl_2 (4 × 30 ml). The combined washings were evaporated to dryness and the resultant oil trituated in diethyl ether to give the crude cyclic peptide. The crude material was further purified using reverse-phase chromatography on a 2 × 15 cm column of Diaion HP-20 resin eluting with 0-50% acetonitrile in water. Yields of purified material were: Cyclo(ProGly)$_4$ **1**, 20%; HRMS (FAB, 3-NOBA matrix): *m/z* = 617.3045 $[(M+H)^+]$ (anal. calcd. for $C_{28}H_{41}N_8O_8^+$ *m/z* = 617.3047), and

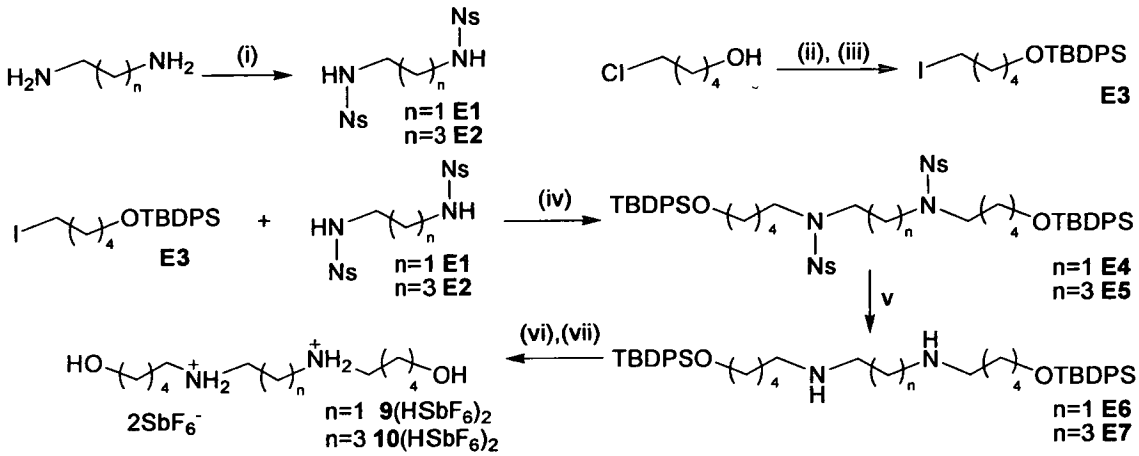
Cyclo(ProGly)$_5$ **2**, 24%; HRMS (FAB, 3-NOBA matrix): *m/z* = 771.3783 [(M+H)$^+$] (anal. calcd. for $C_{35}H_{51}N_{10}O_{10}^+$ *m/z* = 771.3790).



HPLC trace of purified **1**. The upper trace is a scan across the whole data set for the mass of **1**, the lower trace is the total ion count.



HPLC trace of purified **2**. The upper trace is a scan across the whole data set for the mass of **2**, the lower trace is the total ion count.



Scheme E2. Synthesis of the diols $\mathbf{9}(HSbF_6)_2$ and $\mathbf{10}(HSbF_6)_2$. Reagents and conditions: (i) 2-nitrobenzenesulfonyl chloride, triethylamine, dichloromethane, 298K; (ii) TBDPSCl, imidazole, DMF, 298K; (iii) NaI, acetone, reflux; (iv) K_2CO_3, DMF, 353K; (v) mercaptoacetic acid, LiOH, DMF, 298K; (vi) ~1 mol dm^{-3} HCl in H_2O/methanol, 298K; (vii) $AgSbF_6$, methanol, 298K.

N,N'-Bis(2-nitrobenzenesulfonyl)-ethane-1,4-diamine (**E1**) and *N,N'*-bis(2-nitrobenzenesulfonyl)-butane-1,4-diamine (**E2**) were prepared by a literature procedure.[14] Data for **E1**: m.p. 163 °C; ^{1}H NMR (400 MHz, d_6-DMSO) δ = 8.09 (t, 2H, J = 5.6 Hz, NH), 7.94-7.99 (m, 4H, ArH), 7.83-7.88 (m, 4H, ArH), 2.80-2.87 (m, 4H, CH_2N), 1.37-1.42 (m, 4H, alkylH); ^{13}C NMR (100 MHz, d_6-DMSO) δ = 147.7, 133.9, 132.6, 132.5, 129.3, 124.3, 42.1, 26.1; HRMS (FAB, 3-NOBA matrix): m/z = 431.0331 [$(M+H)^+$] (anal. calcd. for $C_{14}H_{15}N_4O_8S_2^+$ m/z = 431.0331).

Data for **E2**: m.p. 189 °C; ^{1}H NMR (400 MHz, d_6-DMSO) δ = 8.17 (br s, 2H, NH), 7.93-7.98 (m, 4H, ArH), 7.83-7.89 (m, 4H, ArH), 3.34 (s, 4H, CH_2N); ^{13}C NMR (100 MHz, d_6-DMSO) δ = 147.9, 134.1, 132.3, 132.2, 129.4, 124.5, 42.31; HRMS (FAB, 3-NOBA matrix): m/z = 459.0634 [$(M+H)^+$] (anal. calcd. for $C_{16}H_{19}N_4O_8S_2^+$ m/z = 459.0644).

1-(*tert*-Butyldiphenylsilyl)oxy-5-iodopentane (E3)

(a) 1-(*tert*-Butyldiphenylsilyl)oxy-5-chloropentane

A solution of 5-chloro-1-pentanol (1.02 g, 8.16 mmol) and imidazole (0.578 g, 8.49 mmol) in *N,N*-dimethylformamide (DMF) (3 cm^3) was cooled to 0 °C and *tert*-butyldiphenylsilyl chloride (2.24 g, 8.15 mmol) was added dropwise. The mixture

was warmed to room temperature and stirred for an additional 3 hours. Water (30 cm^3) was added and the solution was extracted with dichloromethane (2 × 20 cm^3). The combined organic layers were washed with saturated sodium bicarbonate solution (25 cm^3), dried over magnesium sulfate and concentrated under reduced pressure. The residue was subjected to column chromatography (1:9-1:3 dichloromethane/petroleum ether) to yield 1-(*tert*-Butyldiphenylsilyl)oxy-5-chloropentane as a colourless oil (2.61 g, 89%); ^1H NMR (400 MHz, $CDCl_3$) δ = 7.66 (d, *J* = 9.6 Hz, 4H, ArH), 7.35-7.43 (m, 6H, ArH), 3.67 (t, *J* = 6.1 Hz, 2H, $C\underline{H_2}OTBDPS$), 3.51 (t, *J* = 6.8 Hz, 2H, CH_2Cl), 1.72-1.79 (m, 2H, $C\underline{H_2}CH_2OTBDPS$), 1.49-1.60 (m, 4H, alkylH), 1.05 (s, 9H, *t*BuH).

(b) A mixture of 1-(*tert*-butyldiphenylsilyl)oxy-5-chloropentane (1.59 g, 4.40 mmol) and sodium iodide (2.05 g, 13.4 mmol) in acetone (15 cm^3) was heated at reflux for 16 hours. The reaction mixture was filtered and concentrated to dryness under reduced pressure. Water (40 cm^3) and dichloromethane (40 cm^3) were added and the layers were separated. The organic layer was washed with water, dried over magnesium sulfate and concentrated under reduced pressure. The residue was subjected to column chromatography (1:3 dichloromethane/petroleum ether) to yield **E3** as a colourless oil (1.42 g, 85%); ^1H and ^{13}C NMR data were consistent with those reported in the literature.[15]

_N,N'_-Bis(2-nitrobenzenesulfonyl)-_N,N'_-bis-[5-(*tert*-butyldiphenyl-silyanyloxy)-pentyl]-ethane-1,2-diamine (E4)

N,N'-Bis(2-nitrobenzenesulfonyl)-ethane-1,2-diamine (**E1**) (0.145 g, 0.336 mmol) and 1-(*tert*-Butyldiphenylsilyl)oxy-5-iodopentane (**E3**) (0.307g, 0.678 mmol) were dissolved in DMF (1.5 cm^3) and potassium carbonate (0.200 g, 1.45 mmol) was added. The mixture was stirred at 70 °C for 16 hours, cooled to room temperature and water (10 cm^3) was added. The mixture was extracted with dichloromethane (2 × 5 cm^3) and the combined organic layers were washed with water (10 cm^3), dried over magnesium sulfate and concentrated under reduced pressure. NMR spectra of the residue showed it to be >95% pure **E4** (0.363 g, quant); ^1H NMR (400 MHz, $CDCl_3$) δ = 7.93-7.96 (2H, m, ArH), 7.59-7.66 (12H, m, ArH), 7.54-7.56 (2H, m, ArH), 7.34-7.41 (12H, m, ArH), 3.59 (t, *J* = 6.3 Hz, 4H, $C\underline{H_2}OTBDPS$), 3.45 (s, 4H, CH_2NNs),

3.26-3.30 (m, 4H, CH_2NNs), 1.49-1.57 (m, 8H, $C\underline{H}_2CH_2NNs$, $C\underline{H}_2CH_2OTBDPS$), 1.28-1.35 (m, 4H, alkylH), 1.02 (s, 18H, *t*BuH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 148.1, 135.6, 134.0, 133.6, 132.9, 131.7, 130.6, 129.6, 127.6, 124.2, 63.6, 49.1, 46.8, 32.0, 28.2, 27.8, 26.9, 22.8, 19.2.

_N,N'_-Bis(2-nitrobenzenesulfonyl)-_N,N'_-bis-[5-(*tert*-butyldiphenyl-silyanyloxy)-pentyl]-butane-1,4-diamine (E5)

_N,N'_-Bis(2-nitrobenzenesulfonyl)-butane-1,4-diamine (**E2**) (0.500 g, 1.09 mmol) and 1-(*tert*-Butyldiphenylsilyl)oxy-5-iodopentane (**E3**) (0.981 g, 2.17 mmol) were dissolved in DMF (5 cm^3) and potassium carbonate (1.10 g, 7.97 mmol) was added. The mixture was stirred at 70 °C for 16 hours, cooled to room temperature and water (30 cm^3) was added. The mixture was extracted with dichloromethane (2 × 20 cm^3) and the combined organic layers were washed with water (30 cm^3), dried over magnesium sulfate and concentrated under reduced pressure. The residue was subjected to column chromatography (1:2-1:1 ethyl acetate/petroleum ether) to yield **E5** as a colourless gum (2.28 g, 95%); ^1H NMR (400 MHz, $CDCl_3$) δ = 7.95-8.00 (2H, m, ArH), 7.61-7.66 (12H, m, ArH), 7.54-7.58 (2H, m, ArH), 7.35-7.43 (12H, m, ArH), 3.59 (t, J = 6.3 Hz, 4H, $C\underline{H}_2OTBDPS$), 3.23-3.30 (m, 4H, CH_2NNs), 3.18-3.24 (m, 4H, CH_2NNs), 1.48-1.52 (m, 12H, $C\underline{H}_2CH_2NNs$, $C\underline{H}_2CH_2OTBDPS$), 1.25-1.31 (m, 4H, alkylH), 1.05 (s, 18H, *t*BuH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 148.1, 135.5, 133.9, 133.6, 133.4, 131.6, 130.6, 129.6, 127.6, 124.1, 63.6, 47.1, 46.5, 32.0, 27.8, 27.8, 26.9, 25.0, 22.9, 19.2; HRMS (FAB, 3-NOBA matrix): m/z = 1107.4460 $[(M+H)^+]$ (anal. calcd. for $C_{58}H_{75}N_4O_{10}S_2Si_2^+$ m/z = 1107.4463).

_N,N'_-Bis-[5-(*tert*-butyldiphenyl-silyanyloxy)-pentyl]-ethane-1,2-diamine (E6)

_N,N'_-Bis(2-nitrobenzenesulfonyl)-_N,N'_-bis-[5-(*tert*-butyldiphenyl-silyanyloxy)-pentyl]-ethane-1,2-diamine (**S4**) (0.360 g, 0.336 mmol) was dissolved in DMF (1.5 cm^3) and cooled to 0 °C. Mercaptoacetic acid (0.133 g, 1.44 mmol) and lithium hydroxide (0.130 g, 3.10 mmol) were added successively and the mixture was warmed to room temperature. After 3 hours, water (10 cm^3) was added and the mixture was extracted with ethyl acetate (3 × 10 cm^3). The combined organic layers were washed with saturated sodium bicarbonate solution (20 cm^3), dried with

magnesium sulfate and concentrated under reduced pressure. The residue was subjected to column chromatography (0.1:1:9 triethylamine/methanol/chloroform) to yield **E6** as a pale yellow gum (0.140 g, 55%); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.65-7.68 (8H, m, ArH), 7.35-7.42 (12H, m, ArH), 3.65 (t, *J* = 6.6 Hz, 4H, C$\underline{H_2}$OTBDPS), 2.71 (s, 4H, C$\underline{H_2}$NH$_2$), 2.58 (t, *J* = 7.3 Hz, 4H, C$\underline{H_2}$NH$_2$), 1.81 (br s, 2H, NH), 1.53-1.60 (m, 4H, C$\underline{H_2}$CH$_2$OTBDPS), 1.43-1.50 (m, 4H, C$\underline{H_2}$CH$_2$NH$_2$), 1.33-1.40 (m, 4H, alkylH), 1.04 (s, 18H, *t*BuH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 135.6, 134.0, 129.6, 127.6, 63.9, 49.2, 47.6, 32.3, 28.8, 26.9, 23.4, 19.2; HRMS (FAB, 3-NOBA matrix): *m/z* = 709.4586 [(M+H)$^+$] (anal. calcd. for $C_{44}H_{65}N_2O_2Si_2^+$ *m/z* = 709.4585).

***N,N'*-Bis-[5-(*tert*-butyldiphenyl-silyanyloxy)-pentyl]-butane-1,4-diamine (E7)**

N,N'-Bis(2-nitrobenzenesulfonyl)-*N,N'*-bis-[5-(*tert*-butyldiphenyl-silyanyloxy)-pentyl]-butane-1,4-diamine (**S5**) (0.550 g, 0.497 mmol) was dissolved in DMF (2 cm^3) and cooled to 0 °C. Mercaptoacetic acid (0.186 g, 2.01 mmol) and lithium hydroxide (0.175 g, 4.17 mmol) were added successively and the mixture was warmed to room temperature. After 3 hours, water (15 cm^3) was added and the mixture was extracted with ethyl acetate (3 × 10 cm^3). The combined organic layers were washed with saturated sodium bicarbonate solution (20 cm^3), dried with magnesium sulfate and concentrated under reduced pressure. The residue was subjected to column chromatography (0.1:1:9 triethylamine/methanol/chloroform) to yield **E7** as a pale yellow gum (0.319 g, 87%); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.62-7.68 (8H, m, ArH), 7.34-7.42 (12H, m, ArH), 3.62 (t, *J* = 6.3 Hz, 4H, C$\underline{H_2}$OTBDPS), 3.23 (br s, 2H, NH), 2.70-2.76 (m, 4H, C$\underline{H_2}$NH$_2$), 2.63-2.68 (m, 4H, C$\underline{H_2}$NH$_2$), 1.70-1.78 (m, 4H, C$\underline{H_2}$CH$_2$NH$_2$), 1.51-1.61 (8H, C$\underline{H_2}$CH$_2$NH$_2$, C$\underline{H_2}$CH$_2$OTBDPS), 1.32-1.40 (m, 4H, alkylH), 1.05 (s, 18H, *t*BuH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 135.5, 134.1, 129.5, 127.6, 63.8, 49.7, 49.6, 32.4, 29.5, 27.8, 26.9, 23.6, 19.2; HRMS (FAB, 3-NOBA matrix): *m/z* = 737.4895 [(M+H)$^+$] (anal. calcd. for $C_{46}H_{69}N_2O_2Si_2^+$ *m/z* = 737.4898).

***N,N'*-Bis-(5-hydroxypentyl)-ethane-1,2-diammonium hexafluoroantimonate 9(SbF_6)$_2$**

(a) *N,N'*-Bis-(5-hydroxypentyl)-ethane-1,2-diammonium chloride

N,N'-Bis-[5-(*tert*-butyldiphenyl-silyanyloxy)-pentyl]-ethane-1,2-diamine (**E6**) (0.140 g, 0.190 mmol) was dissolved in methanol (2.5 cm^3) and concentrated hydrochloric acid (0.2 cm^3) was added dropwise at room temperature. The mixture was stirred for 4 hours and concentrated to dryness under reduced pressure. The residue was triturated with diethyl ether and dried over P_2O_5 under reduced pressure to yield **9**.$(HCl)_2$ as a pale yellow solid (0.065 g, 100%); m.p. 196-200 °C (dec); ^1H NMR (400 MHz, d_6-DMSO) δ = 9.31 (br s, 4H, NH_2^+), 3.39 (t, J = 6.1 Hz, 4H, $C\underline{H}_2OH$), 3.29 (br s, 4H, $C\underline{H}_2NH_2^+$), 3.23 (br s, 4H, $C\underline{H}_2NH_2^+$), 1.59-1.67 (m, 4H, $C\underline{H}_2CH_2NH_2^+$), 1.40-1.46 (m, 4H, $C\underline{H}_2CH_2OH$), 1.33-1.39 (m, 4H, alkylH).

(b) Anion exchange

N,N'-Bis-(5-hydroxypentyl)-ethane-1,2-diammonium chloride (0.050 g, 0.16 mmol) was dissolved in methanol (1 cm^3) and a solution of silver hexafluoroantimonate (0.109 g, 0.320 mmol) in methanol (0.5 cm^3) was added. The mixture was stirred for 8 hours in the absence of light, filtered through celite and concentrated. The residue was triturated with diethyl ether and dried over P_2O_5 under reduced pressure to give **9**.$(HSbF_6)_2$ as a pale yellow gum (0.085 g, 73%); ^1H NMR (400 MHz, CD_3CN) δ = 6.70 (br s, NH_2^+) 3.52 (t, J = 6.1 Hz, 4H, $C\underline{H}_2OH$), 3.22-3.27 (br s, 4H, $C\underline{H}_2NH_2^+$), 2.02-3.08 (m, 4H, $C\underline{H}_2NH_2^+$), 2.26 (br s, 2H, OH), 1.65-1.73 (m, 4H, $C\underline{H}_2CH_2NH_2^+$), 1.49-1.56 (m, 4H, $C\underline{H}_2CH_2OH$), 1.39-1.47 (m, 4H, alkylH); ^{13}C NMR (100 MHz, CD_3CN) δ = 61.9, 49.4, 44.0, 32.3, 24.7, 23.2; ESI-MS: m/z = 233 [M + H^+].

_N,N'_-Bis-(5-hydroxypentyl)-butane-1,4-diammonium hexafluoroantimonate 10$(SbF_6)_2$

(a) *N,N'*-Bis-(5-hydroxypentyl)-butane-1,4-diammonium chloride

N,N'-Bis-[5-(*tert*-butyldiphenyl-silyanyloxy)-pentyl]-butane-1,4-diamine (**E7**) (0.272 g, 0.366 mmol) was dissolved in methanol (5 cm^3) and concentrated hydrochloric acid (0.5 cm^3) was added dropwise at room temperature. The mixture was stirred for 4 hours and concentrated to dryness under reduced pressure. The residue was triturated with diethyl ether and dried over P_2O_5 under reduced pressure to yield **10**.$(HCl)_2$ as a pale yellow solid (0.110 g, 90%); m.p. 210-212 °C (dec) ^1H NMR (400 MHz, d_6-DMSO) δ = 8.78 (br s, 4H, NH_2^+), 3.39 (t, J = 6.3 Hz, 4H, $C\underline{H}_2OH$),

2.80-2.91 (m, 8H, $C\underline{H}_2NH_2^+$), 1.57-1.68 (m, 8H, $C\underline{H}_2CH_2NH_2^+$), 1.41-1.46 (m, 4H, $C\underline{H}_2CH_2OH$), 1.29-1.35 (m, 4H, alkylH).

(b) Anion exchange

N,N'-Bis-(5-hydroxypentyl)-butane-1,4-diammonium chloride (0.105 g, 0.316 mmol) was dissolved in methanol (1.5 cm^3) and a solution of silver hexafluoroantimonate (0.217 g, 0.632 mmol) in methanol (0.5 cm^3) was added. The mixture was stirred for 3 hours, filtered through celite and concentrated. The residue was triturated with diethyl ether and dried over P_2O_5 under reduced pressure to give **10**.$(HSbF_6)_2$ as a pale yellow solid (0.210 g, 91%); m.p. 120-121 °C (dec) ^1H NMR (400 MHz, CD_3CN) δ = 6.53 (br s, NH_2^+), 3.51 (t, J = 6.4 Hz, 4H, $C\underline{H}_2OH$), 2.92-3.03 (m, 8H, $C\underline{H}_2NH_2^+$), 2.26 (br s, 2H, OH), 1.62-1.70 (m, 8H, $C\underline{H}_2CH_2NH_2^+$), 1.48-1.55 (m, 4H, $C\underline{H}_2CH_2OH$),1.36-1.44 (m, 4H, alkylH); ^{13}C NMR (100 MHz, CD_3CN) δ = 61.9, 49.0, 48.0, 32.4, 26.2, 23.4, 23.3, ESI-MS: m/z = 261 [M + H^+].

General procedure for the analytical scale synthesis of [2]rotaxanes 3-6$(HSbF_6)_2$

Diol **9**.$(HSbF_6)_2$ or **10**.$(HSbF_6)_2$ (~0.004 mmol) was dissolved in a solution of 30% chloroform/acetonitrile to give a concentration of ~10 mmol dm^{-3}, 3 molar equivalents of cyclo(ProGly)$_{n+3}$ (n = 1 or 2) was added and the mixture was stirred for 15 minutes. Acid chloride $(4\text{-Cl-}C_6H_4)_3CCH_2COCCl$ (0.016 mmol) was added, the mixture was stirred at room temperature for 7 days and a sample was analysed by LCMS to determine the degree of formation of [2]rotaxane with respect to the corresponding thread.

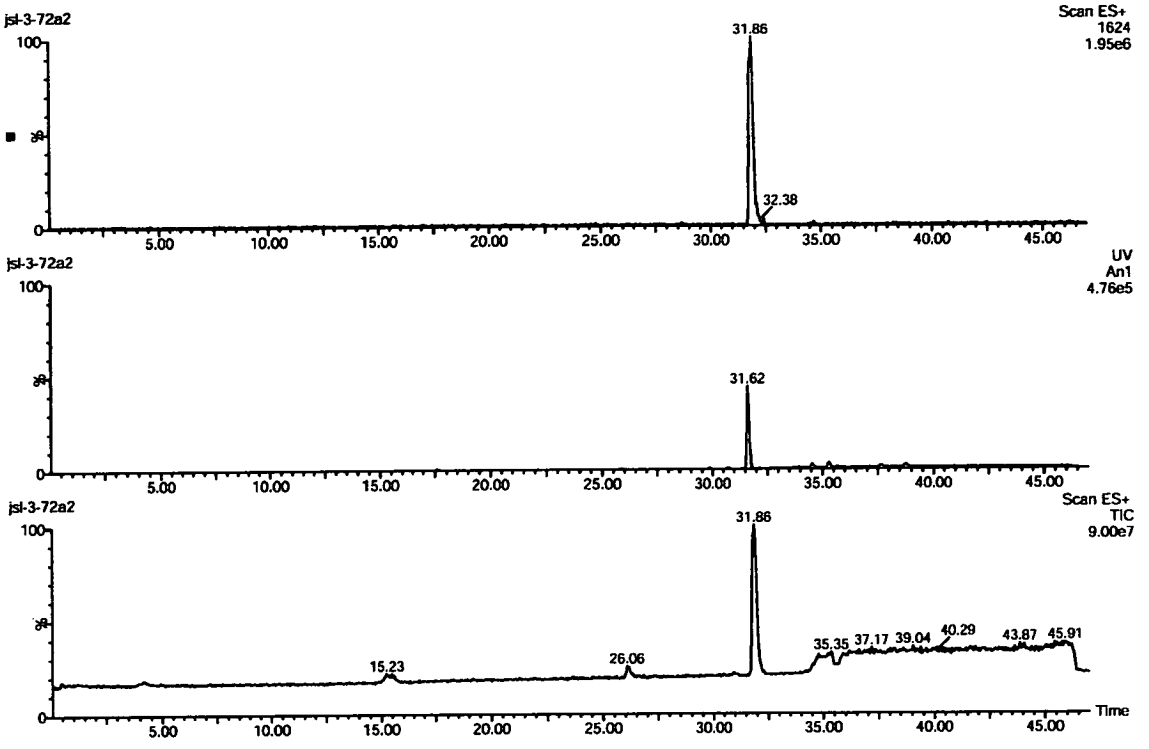
General procedure for the synthesis of [2]rotaxanes 3.$(HCl)_2$ and 5.$(HCl)_2$ and threads 7.$(HCl)_2$ and 8.$(HCl)_2$

The syntheses of **3**.$(HSbF_6)_2$ and **5**.$(HSbF_6)_2$ were repeated on a larger scale, but under the same conditions as described for the analytical scale reactions. Solvent was removed by gentle nitrogen flow and the residue was dissolved in dichloromethane (1 cm^3), washed with water (3 × 1 cm^3), dried over magnesium sulfate and concentrated under reduced pressure. The residue was subjected to column chromatography (1:19-1:9 methanol/dichloromethane) and the material was redissolved in dichloromethane (2 cm^3), washed successively with saturated sodium

bicarbonate solution (2 × 1 cm^3), 1 mol dm^{-3} hydrochloric acid solution (2 × 1 cm^3) and water (1 cm^3), dried over magnesium sulfate and concentrated under reduced pressure. The residue was triturated with diethyl ether and dried over P_2O_5 under reduced pressure to give the rotaxane and thread as white solids. Samples of the threads **5**.$(HSbF_6)_2$ and **6**.$(HSbF_6)_2$ were prepared in an analogous manner, purified by column chromatography (1:19-1:9 methanol/dichloromethane) and converted to the corresponding chloride salts as described above.

[2]Rotaxane 3.$(HCl)_2$

Diol **9**.$(HSbF_6)_2$ (5 mg, 0.007 mmol) was dissolved in a solution of 30% chloroform/acetonitrile (0.65 cm^3), cyclo(ProGly)$_4$ (13 mg, 0.021 mmol) was added and the mixture was stirred for 15 minutes. Acid chloride (4-Cl-C_6H_4)$_3$$CCH_2COCCl$ (12 mg, 0.028 mmol) was added and the mixture was stirred for 7 days at room temperature. After work-up and purification as described in the general procedure above, **3**.$(HCl)_2$ was obtained as a white solid (3 mg, 25%); ^{1}H NMR (400 MHz, CD_3CN) δ = 9.68 (br s, 1H, NH_2^+), 9.04 (br s, 1H, NH_2^+), 7.78 (br s, 2H, NH_2^+), 7.38-7.44 (m, 4H, CONH), 7.28-7.32 (m, 12H, ArH), 7.18-7.23 (m, 12H, ArH), 4.47-4.50 (m, 4H, *L*-ProH$_\alpha$), 4.33 (dd, J_1 = 17.3 Hz, J_2 = 7.9 Hz, 4H, GlyH$_{\alpha 1}$), 3.68-3.84 (m, 12H, H_c, $H_{c'}$, GlyH$_{\alpha 2}$, H_d, $H_{d'}$), 3.60-3.65 (m, 4H, *L*-ProH$_{\delta 1}$), 3.40-3.46 (m, 4H, *L*-ProH$_{\delta 2}$), 3.31-3.37 (m, 1H, $H_{h1'}$); 3.22-3.29 (m, 1H, $H_{h2'}$); 3.02-3.14 (m, 1H, $H_{j1'}$); 2.84-2.99 (m, 3H, H_{h1}, H_{h2}, $H_{j2'}$), 2.60-2.75 (m, 2H, H_{j1}, H_{j2}), 2.06-2.14 (m, 4H + solvent, *L*-ProH$_{\beta 1}$), 1.83-1.96 (m, 12H + solvent, *L*-ProH$_{\beta 2}$, *L*-ProH$_\gamma$), 1.60-1.70 (m, 4H, H_g, $H_{g'}$), 1.31-1.41 (m, 4H, H_e, $H_{e'}$), 1.17-1.28 (m, 4H, H_f, $H_{f'}$); ^{13}C NMR (100 MHz, CD_3CN) δ = 174.2, 171.6, 171.2, 169.2, 145.7, 145.6, 132.8, 131.6, 128.9, 64.7, 61.3, 55.6, 55.4, 48.8, 48.5, 47.3, 46.2, 46.1, 42.4, 30.8, 28.3, 27.5, 26.6, 25.7, 25.2, 23.3, 23.0; ESI-MS: *m/z* = 812-816 [M^{2+}], 1622-1632 [$(M-H)^+$].

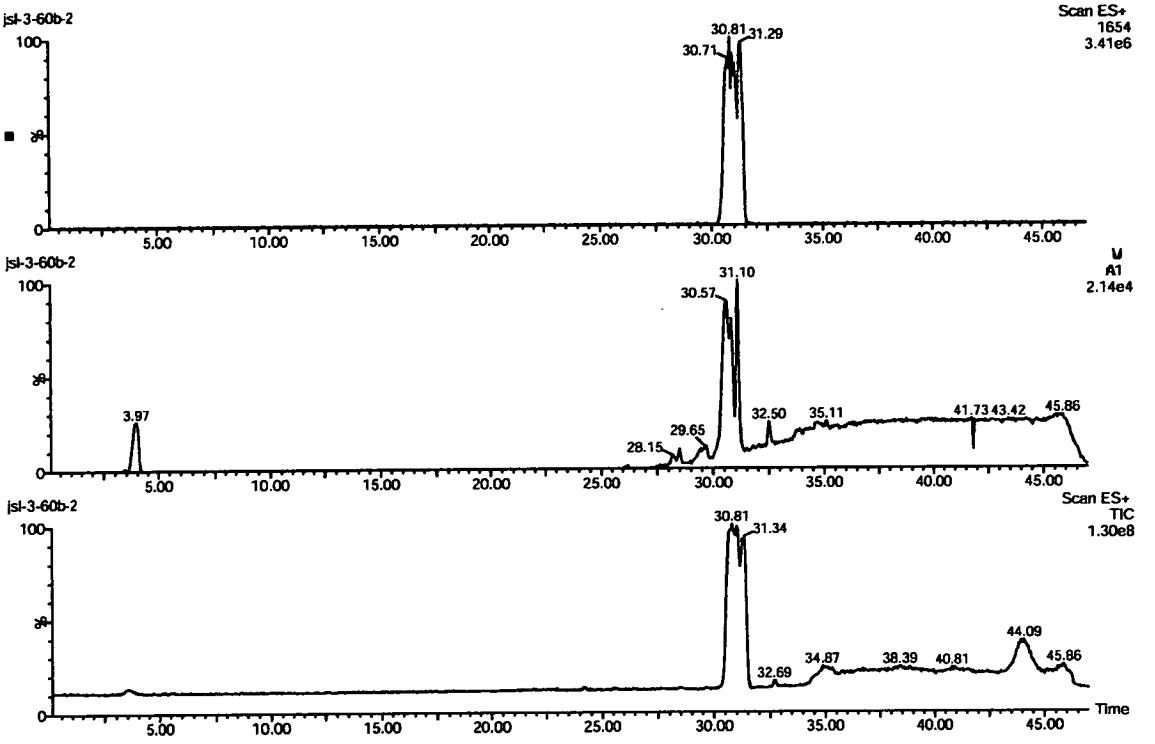


HPLC trace for rotaxane **3**. The upper trace is a scan across the whole data set for the mass of **3**, the middle trace is the UV and the lower is the TIC.

[2]Rotaxane 5.$(HCl)_2$

Diol **8**.$(HSbF_6)_2$ (16 mg, 0.021 mmol) was dissolved in a solution of 30% chloroform/acetonitrile (2.0 cm^3), cyclo(ProGly)$_4$ (40 mg, 0.065 mmol) was added and the mixture was stirred for 15 minutes. Acid chloride (4-Cl-C_6H_4)$_3$$CCH_2COCCl$ (36 mg, 0.084 mmol) was added and the mixture was stirred for 7 days at room temperature. After work-up and purification as described in the general procedure **5**.$(HCl)_2$ was obtained as a white solid (11 mg, 31%); ^{1}H NMR (400 MHz, CD_3CN) δ = 8.20 (br s, 2H, NH_2^+), 7.69 (br s, 2H, NH_2^+), 7.38-7.41 (m, 4H, CONH), 7.29-7.33 (m, 12H, ArH), 7.19-7.23 (m, 12H, ArH), 4.56 (dd, J_1 = 2.8, J_2 = 8.3, 4H, *L*-ProH$_\alpha$), 4.32 (dd, J_1 = 17.43, J_2 = 8.34, 4H, GlyH$_{\alpha 1}$), 3.75-3.83 (m, 4H, H$_d$, H$_{d'}$), 3.71-3.72 (m, 2H, H$_{c'}$), 3.70 (s, 2H, H$_c$), 3.65 (dd, J_1 = 17.43, J_2 = 3.54, 4H, GlyH$_{\alpha 2}$), 3.57-3.62 (m, 4H, *L*-ProH$_{\delta 1}$), 3.30-3.35 (m, 4H, *L*-ProH$_{\delta 2}$), 3.04-3.11 (m, 4H, H$_h$, H$_{j'}$), 2.60-2.72 (m, 4H, H$_j$, H$_{h'}$), 1.96-2.14 (m, 12H, *L*-ProH$_{\beta 1}$, *L*-ProH$_\gamma$), 1.83-1.88 (m, 4H, *L*-ProH$_{\beta 2}$), 1.58-1.71 (m, 4H, H$_g$, H$_{(k \text{ or } k')}$), 1.30-1.41 (m, 6H, H$_{(k \text{ or } k')}$, H$_{g'}$, H$_{e'}$), 1.21-1.29 (m, 4H, H$_e$, H$_f$), 1.07-1.15 (m, 2H, H$_{f'}$); ^{13}C NMR (100 MHz,

CD_3CN) δ = 173.7, 171.4, 171.2, 168.9, 145.7, 145.6, 132.7, 131.2, 128.8, 64.9, 64.7, 60.9, 55.5, 55.4, 48.7, 48.5, 48.1, 47.8, 47.1, 46.1, 42.1, 30.6, 29.3, 26.5, 26.0, 25.1, 24.2, 23.3, 23.2; ESI-MS: *m/z* = 826-830 [M^{2+}], 1650-1660 [$(M-H)^+$].



HPLC trace for rotaxane **5**. The upper trace is a scan across the whole data set for the mass of **5**, the middle trace is the UV and the lower is the TIC.

Thread 7.$(HCl)_2$

Diol **9**.$(HSbF_6)_2$ (3 mg, 0.004 mmol) was dissolved in a solution of 30% chloroform/acetonitrile (0.30 cm^3), acid chloride $(4\text{-}Cl\text{-}C_6H_4)_3CCH_2COCCl$ (8 mg, 0.019 mmol) was added and the mixture was stirred for 7 days at room temperature. After work-up and purification as described in the general procedure above, 7.$(HCl)_2$ was obtained as a white solid (3 mg, 66%); ^1H NMR (400 MHz, CD_3CN) δ = 9.64 (br s, 4H, NH_2^+), 7.28-7.32 (m, 12H, ArH), 7.17-7.21 (m, 12H, ArH), 3.77 (t, *J* = 6.2 Hz, 4H, H_d), 3.70 (s, 4H, H_c), 3.37 (s, 4H, H_j), 2.90 (t, *J* = 6.9 Hz, 4H, H_h), 1.64-1.71 (m, 4H, H_g), 1.32-1.39 (m, 4H, H_e), 1.19-1.26 (m, 4H, H_f); ^{13}C NMR (100 MHz, CD_3CN) δ = 171.3, 145.7, 132.98, 131.5, 128.9, 64.5, 55.4, 48.5, 45.9, 28.7, 26.0, 23.6; ESI-MS: *m/z* = 1006-1014 [$(M-H)^+$].

Thread 8.$(HCl)_2$

Diol **10**.$(HSbF_6)_2$ (5 mg, 0.007 mmol) was dissolved in a solution of 30% chloroform/acetonitrile (0.65 cm^3), acid chloride $(4\text{-}Cl\text{-}C_6H_4)_3CCH_2COCCl$ (12 mg, 0.028 mmol) was added and the mixture was stirred for 7 days at room temperature. After work-up and purification as described in the general procedure **8**.$(HCl)_2$ was obtained as a white solid (6 mg, 80%); ^1H NMR (400 MHz, CD_3CN) δ = 7.28-7.32 (m, 12H, ArH), 7.18-7.22 (m, 12H, ArH), 3.76 (t, J = 6.3 Hz, 4H, H_d), 3.70 (s, 4H, H_c), 2.92-2.95 (m, 4H, H_j), 2.78-2.83 (m, 4H, H_h), 1.92-1.96 (m, 4H, H_k), 1.63-1.70 (m, 4H, H_g), 1.30-1.37 (m, 4H, H_e), 1.14-1.21 (m, 4H, H_f); ^{13}C NMR (100 MHz, CD_3CN) δ = 171.2, 145.7, 132.8, 131.6, 128.9, 64.8, 55.6, 49.2, 46.2, 28.4, 26.1, 23.7, 23.4; ESI-MS: m/z = 1034-1044 $[(M\text{-}H)^+]$.

2.4 References and Notes

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(4) One reason for these architectures remaining unknown for so long is that they are often difficult to spot in heavily folded protein structures.[1d,f] Also Edman degradation does not reveal interlocked character and so such compounds can easily be misassigned.

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Chapter 3 Synopsis

The preceding chapter details our initial investigations into the formation of rotaxanes of cyclic peptides. This chapter consists of a more in-depth discussion of this type of rotaxane. The first section of this chapter is an investigation into the structural variation of the diammonium template used to bind the cyclo(L-ProGly)$_{4/5}$ macrocycle. Analytical scale rotaxane-forming reactions were carried out for threads in which the ammonium groups were separated by different length alkyl spacers. Yields of interlocked product were determined by LC-MS, and the different behaviour of the two macrocycles is discussed. The latter section of this chapter is a comparison of the ^{1}H NMR spectra of the cyclo(L-ProGly)$_4$ and cyclo(L-ProGly)$_5$ rotaxanes of the same thread. Incorporation of these macrocycles into the interlocked structure significantly reduces their conformational freedom. The different constraints imposed on the thread by the encircling macrocycle were found to affect the acidity of the thread ammonium protons.

Chapter 3

Rotaxanes of Cyclic Peptides: Variation of the Template and Macrocycle

3.1 Introduction

Interlocked architectures such as knots,[1] catenanes[2] and rotaxanes[3] have only comparatively recently been recognized in naturally occurring peptides and proteins. Identification of such structures is often difficult, and computational methods have been used to unambiguously identify the presence of knots 'hidden' within the folds of large proteins.[1d] Even in much smaller peptides, topological links can be overlooked, a notable recent example being that of microcin J25 (MccJ25), a natural peptide antibiotic that was originally thought to be circular, but was later shown to have an interlocked 'lassoed tail' structure.[3]

The presence of a mechanical bond confers a number of properties atypical to peptides or proteins. Like covalent crosslinks, interlocked structures are thought to exist in natural peptides and proteins partly because of their ability to enhance the stability of the molecule. This effect is perhaps most dramatically exemplified by the 'protein chainmail' capsid shell that surrounds the HK97 bacteriophage.[2] The virus is protected by an icosahedral shell built up of twelve pentagonal and sixty hexagonal protein units that are mechanically linked at each vertex. A non-interlocked analogue of this shell (expressed by a mutant virus) was found to be dramatically less stable to denaturing conditions.[2a] Similarly MccJ25 has been shown to have a high resistance to many peptidases,[4a] as well as chemical and thermal[4c] denaturing conditions.

Another feature common to many of the known interlocked peptides and proteins is high biological activity. It is likely that this is in part due to the stability afforded by the mechanical bond, but it appears that the well defined structure also contributes directly to the activity of these molecules. The family of cystine-knot peptides contains molecules that, despite being closely structurally related, exhibit activity towards a wide variety of biological targets. Cystine knots have variously been found to have anti-HIV, antibacterial, anticancer and uterotonic properties.[1f] The aforementioned MccJ25 is a potent antibiotic with a completely novel mode of action: the molecule blocks the secondary channel of bacterial RNA polymerase, preventing the uptake of monomers and therefore shutting down the enzyme and

preventing transcription.[4b,d-g] Another family of peptides with the same general 'lassoed tail' structure as MccJ25 are the lariatins, which have recently been found to be active against tuberculosis.[3d]

Despite their unique and desirable properties, little headway has been made in producing interlocked peptides synthetically.[5] Nature makes use of a delicate balance of driving forces including hydrophobic interactions and hydrogen bonding to assemble many of the known examples of interlocked peptides and proteins.[1-4] Folding and intermolecular association processes mediate the self-assembly of the individual protein precursors of the HK97 capsid prior to the structure being interlocked by enzymatic modification.[2] Similarly, cystine knot proteins are thought to form by folding of a precursor followed by the spontaneous formation of disulfide links. [1d-g] Less is known about the formation of MccJ25, but it appears that the required spatial arrangement of a linear precursor is enforced by a processing enzyme and not by spontaneous folding of the peptide, therefore attempts to produce MccJ25 by the chemical cyclization of its linear precursor did not yield any interlocked material. Thus while many interlocked peptides are formed because of their intramolecular interactions, MccJ25 is formed despite these interactions.

The subtle intercomponent networks of hydrogen bonds exhibited in natural systems are extremely difficult to emulate in artificial ones, and are generally highly substrate specific, making them unsuitable as the basis of a general route to artificial interlocked peptides. In the absence of the delicate intercomponent hydrogen bond complementarity of natural systems, hydrogen bonding can become a significant barrier to the association of the components of an interlocked architecture: the components will typically satisfy their hydrogen bonding requirements by forming an internal hydrogen bond network rather than by associating with each other. An alternative strategy more suited to artificial systems is to make intercomponent association more favourable by replacing the internal hydrogen bond network with a small number of strong hydrogen bonds, the geometry of which is much more easily controlled. Ammonium groups are strong hydrogen bonds donors, and are therefore well suited to this purpose.[6] With the ultimate objective of a generic route to entirely peptidic interlocked architectures, this research group recently achieved the hydrogen

bond templated synthesis of the first synthetic rotaxane in which the macrocycle was a cyclic peptide.[7] It is possible to form rotaxanes from cyclic octa- and deca- peptides derived from the L-ProGly repeat unit by covalently 'trapping' the inclusion complexes that these macrocycles form with certain alkylammonium threads. We herein report a more complete investigation of this work.

3.2 Strategy

Our strategy for synthesizing rotaxanes of cyclic peptides took inspiration from two main sources: peptide-cation complexes[8] and cucurbituril derived rotaxanes.[9] Cyclic oligomers of the L-ProGly repeat unit (as well as other structurally related cyclic peptides) are ionophores that are known to form strong 1:1 and 1:2 complexes with metal cations[8c,d] or ammonium salts.[8b] In all cases, binding occurs on the face of the ring (as opposed to within the cavity), hence the 1:2 complexes are described as 'sandwich complexes' (Figure 1a). The first cation is bound *via* the glycine carbonyls, an event that disrupts a network of 1-3 hydrogen bonds (these cyclic peptides can be thought of as a sequence of γ turns) and allows the proline carbonyl groups to form a second binding site on the opposite face of the macrocycle. The propensity of cyclo(L-ProGly)$_n$ macrocycles to simultaneously bind two positive charges on either face of the macrocycle is reminiscent of a similar mode of binding exhibited by cucurbituril (Figure 1b). Cucurbituril is a rigid hexameric macrocyclic derivative of glycoluril that has a hydrophobic cavity, each entrance to which is ringed by six ureido carbonyl groups. These carbonyl groups are directed approximately perpendicular to the plane of the ring, and form a cation binding site on each face of the macrocycle. A combination of hydrogen bonding and hydrophobic interactions can be used to create inclusion complexes between cucurbituril and butyl-1,4-diammonium units, despite the charged units being bound outwith the cavity of the macrocycle. A diverse range of rotaxanes have been prepared from this system by covalent modification of this type of inclusion complex.[9] We reasoned that a similar mode of binding could be used to form inclusion complexes of alkyldiammonium threads and cyclo(L-ProGly)$_n$ macrocycles, and that such an inclusion complex could be end-capped to produce a rotaxane. We

chose to use the acylation of an alcohol with an acid chloride as the means of installing the end-cap groups on to the thread.

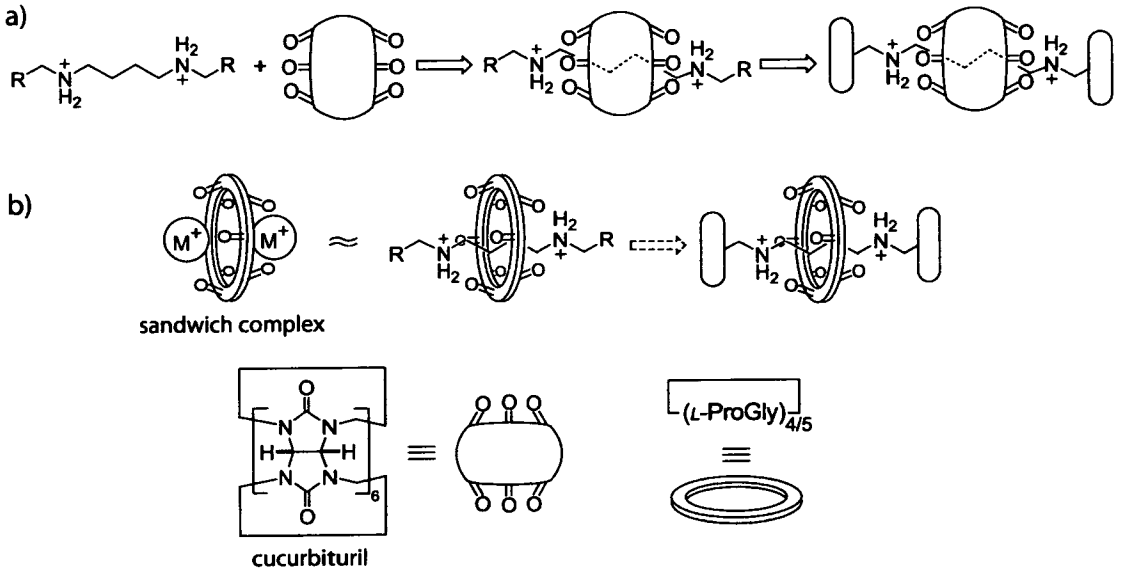
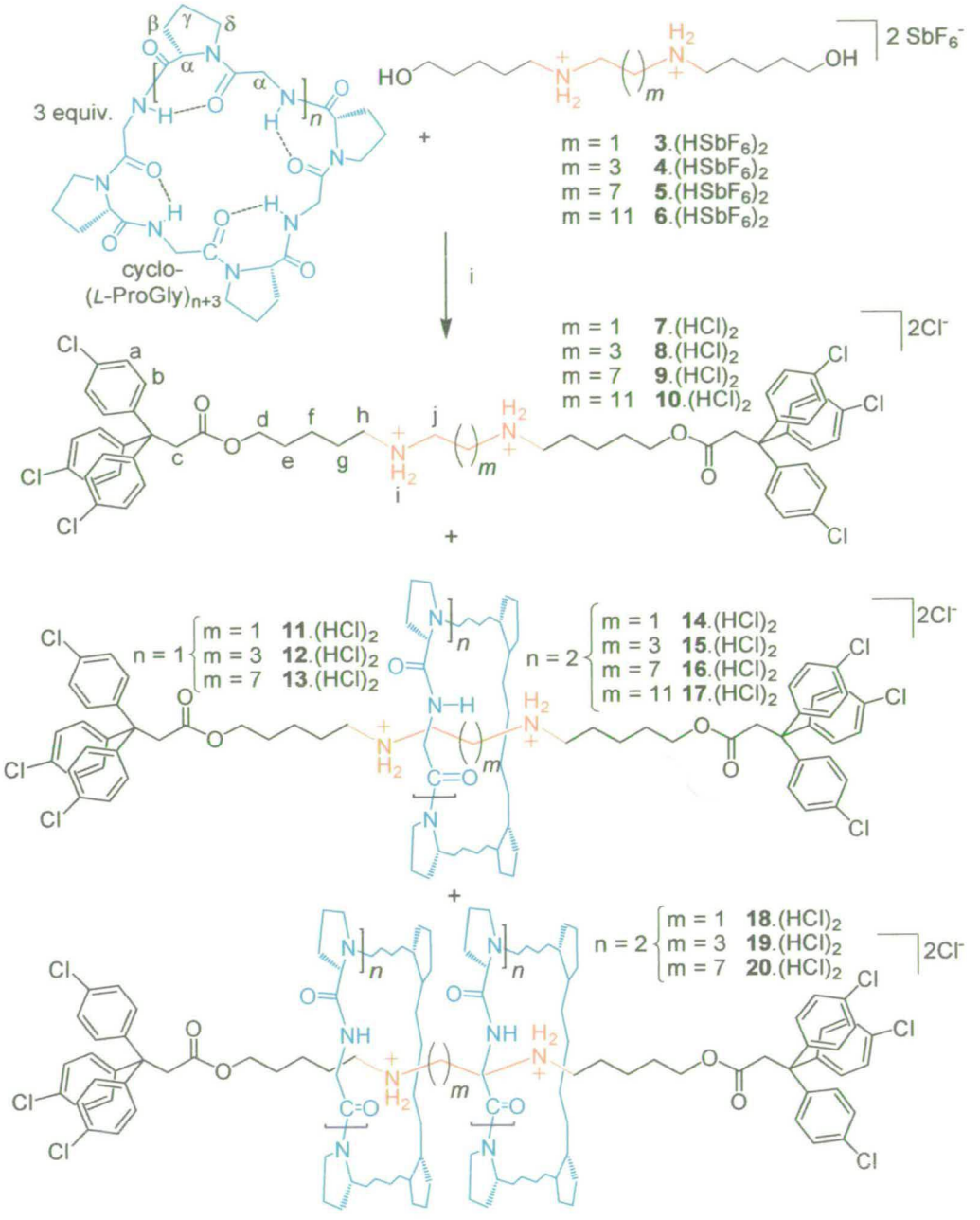


Figure 1. (a) Cucurbituril and (b) cyclic peptide rotaxanes by capping of an inclusion complex

3.3 Analytical Scale Experiments

An inspection of CPK models indicated that cyclo(L-ProGly)$_4$ (**1**) and cyclo(L-ProGly)$_5$ (**2**) are of appropriate sizes to potentially form rotaxanes by binding an alkyldiammonium species. However, the optimal spacing between the ammonium groups of a thread was not obvious from the molecular models. We therefore prepared the small series of threads **3-6**.(HSbF$_6$)$_2$, in which two ammonium groups are spaced apart by 2, 4, 8 and 12 methylene units, respectively (Scheme 1). The non-hydrogen bond competing hexafluoroantimonate anion was used in order to maximize the degree of association between the thread and macrocycle. It was also necessary to select a solvent that was apolar enough not to interfere significantly with the hydrogen-bonding interactions between thread and macrocycle, but that was polar enough to solvate the diammonium thread. A 7:3 mixture of acetonitrile to chloroform was eventually found to be suitable for this purpose. Micromole scale reactions were carried out in vials. To a solution of thread and an excess of macrocycle was added the bulky acid chloride *tris*-(4-chlorophenyl)-propionyl chloride. The reaction progress and product mixture were evaluated by LC-MS analysis. Product yields were estimated by integration of the UV traces, based on the

assumption that the UV absorbance at 254 nm (arising primarily from the aromatic stoppers) was the same for thread and rotaxane.



Scheme 1. The Synthesis of Rotaxanes **7**-**20**.$(HCl)_2$: Reagents and conditions i. (4-$ClC_6H_4)_3CCH_2COCl$, $CHCl_3$:CH_3CN 3:7, rt, 7 days. For clarity, atom labels are only shown for one repeat unit of the cyclopeptide in rotaxanes **11**-**20**.$(HCl)_2$.

Rotaxane products were identified in all of the product mixtures, in quantities varying from traces to a maximum of 63% (Table 1). Quite different trends were observed for macrocycles **1** and **2**. The yield of rotaxane for **1** is at a maximum for

the ethyl spaced thread, and remains nearly the same for the butyl thread. However, the yield falls off sharply for the octyl spaced thread, and only trace amounts of rotaxane were detected for the dodecyl spaced thread. These results show that the two shorter threads have ammonium groups that are ideally spaced to bind to **1**, but that above a certain chain length it becomes unfavourable for the macrocycle to bind the thread as an inclusion complex, and the yield of rotaxane drops accordingly. Earlier experiments had shown that both macrocycles form only trace amounts of rotaxane with a related monoammonium thread. The failure of **1** to form rotaxane with thread **6**.$(HSbF_6)_2$ is unsurprising when considering that the internal cavity of the macrocycle is not large enough to accommodate any folding of the alkyl spacer, preventing it from binding to both ammonium groups simultaneously (at least in the threaded mode of binding). The yield of rotaxane therefore drops to a value similar to that for a thread bearing a single ammonium group.[7] It is important to emphasize that a low yield of rotaxane does not necessarily imply a low degree of association between macrocycle and thread, what it does demonstrate, however, is a low degree of inclusion of the thread within the macrocycle. In the case of **2**, rotaxanes are formed in similar quantities for the ethyl, butyl and octyl spaced threads, with a maximum yield for the butyl spacer. It is only for the dodceyl spacer that the yield of rotaxane falls off markedly. These results indicate that **2** is able to simultaneously bind to both ammonium groups of all of the threads examined, and that only for the longest thread does the interaction become significantly less favourable. These results reflect the different sizes and flexibilities of **1** and **2**: the smaller macrocycle is a comparatively strained structure with few degrees of freedom and a small cavity, and is therefore limited in which threads it is able to bind. By contrast macrocycle **2** has significantly greater flexibility, as well as a larger cavity, and is consequently able to bind more widely spaced ammonium groups.

	cyclo(*L*-ProGly)$_4$		cyclo(*L*-ProGly)$_5$	
m	[2]rotaxane	[3]rotaxane	[2]rotaxane	[3]rotaxane
1	63 (**11**)	trace	46 (**14**)	10 (**18**)
3	62 (**12**)	trace	56 (**15**)	4 (**19**)
7	15 (**13**)	trace	43 (**16**)	15 (**20**)
11	trace	0	15 (**17**)	trace

Table 1. Percentage yields of rotaxanes for different thread and macrocycle size based on LC-MS integration of micromole scale reactions. Compound numbers are shown in brackets. Spacer lengths are m + 1 methylene units as in Scheme 1. 'Trace' indicates that the compound was detectable by mass spectrometry only.

In the rotaxane forming reactions of macrocycle **1** traces of [3]rotaxane were observed for all but the longest thread, suggesting that it is possible for two macrocycles to reside on a single diammonium thread, but that this is not a favourable mode of binding. However in the case of macrocycle **2**, appreciable amounts of [3]rotaxane were also formed with all the spacers except the dodecyl one, the greatest amount being formed with the octyl spaced thread. The formation of appreciable amounts of [3]rotaxane indicates that some type of cooperative binding is in effect: two macrocycles and a diammonium thread result in more rotaxane than one macrocycle does with a monoammonium[7] thread. The formation of [2]- and [3]rotaxane are competitive processes, and the formation of [3]rotaxane is effectively out-competed in the case of the butyl spacer, for which the highest yield of [2]rotaxane, as well as the largest ratio of [2] to [3]rotaxane, is obtained. The mode of binding by which [3]rotaxane is formed is not known, though cyclo(L-ProGly)$_n$ macrocycles are known to form different types of sandwich complex with metal cations, including one referred to as a 'double decker sandwich', in which two macrocycles and two metal ions form an alternating arrangement.[8c] Binding the thread in this manner would result in [3]rotaxane, though it is unclear why this is a competing process in the case of macrocycle **2** but not **1**.

3.4 Preparative Scale Experiments

Following the analytical scale evaluation, selected experiments were carried out on a preparative scale. Using the conditions optimized during the analytical scale experiments rotaxanes **11**, **12**, **14** and **15** were prepared on a larger scale. However, purification of the rotaxane products proved to be problematic. While excess peptide macrocycle could be easily removed by extracting into water, separation of the organic soluble products- thread and rotaxane- proved to be particularly difficult. It was eventually found that the rotaxane products could be purified by preparative TLC on silica plates pretreated with ammonium chloride.

Comparison of the ^{1}H NMR spectra of rotaxanes **11**.$(HCl)_2$ and **14**.$(HCl)_2$ with their non-interlocked components gives some insight into the effects of forming the interlocked structure (Figure 1). In acetonitrile solution, the free macrocycles **1** and **2** adopt a number of conformations by cis-trans isomerization of one or more GlyL-Pro amide bonds. The major conformer of **1** (Figure 1a) is the symmetrical 'all-trans' one (represented in light blue), though a number of other lower symmetry conformations (dark blue) are also present. By contrast **2** (Figure 1e) exhibits greater conformational freedom, existing as a much more complex mixture of conformers, of which the all trans is not the major one.

The macrocyclic components of both **11**.$(HCl)_2$ and **14**.$(HCl)_2$ are significantly conformationally restricted compared to their non-interlocked analogues, the macrocycle of **11**.$(HCl)_2$ being limited to only the symmetrical all trans conformer. The cavity of **1** is small, and it is likely that steric constraints mean that no other conformations are available to the macrocycle once its cavity is occupied by the thread. The all trans conformer is also the major one in **14**.$(HCl)_2$, though in this instance not to the exclusion of other conformations. One result of this conformational freedom is to greatly complicate the NMR spectrum of **14**.$(HCl)_2$ compared to that of **11**.$(HCl)_2$. The additional macrocycle conformations do not have any rotational symmetry, so each constitutionally distinct proton appears as a separate (though often overlapping) signal. The different conformers of the macrocycle

interact differently with the thread, so a large number of overlapping signals are also exhibited by thread protons.

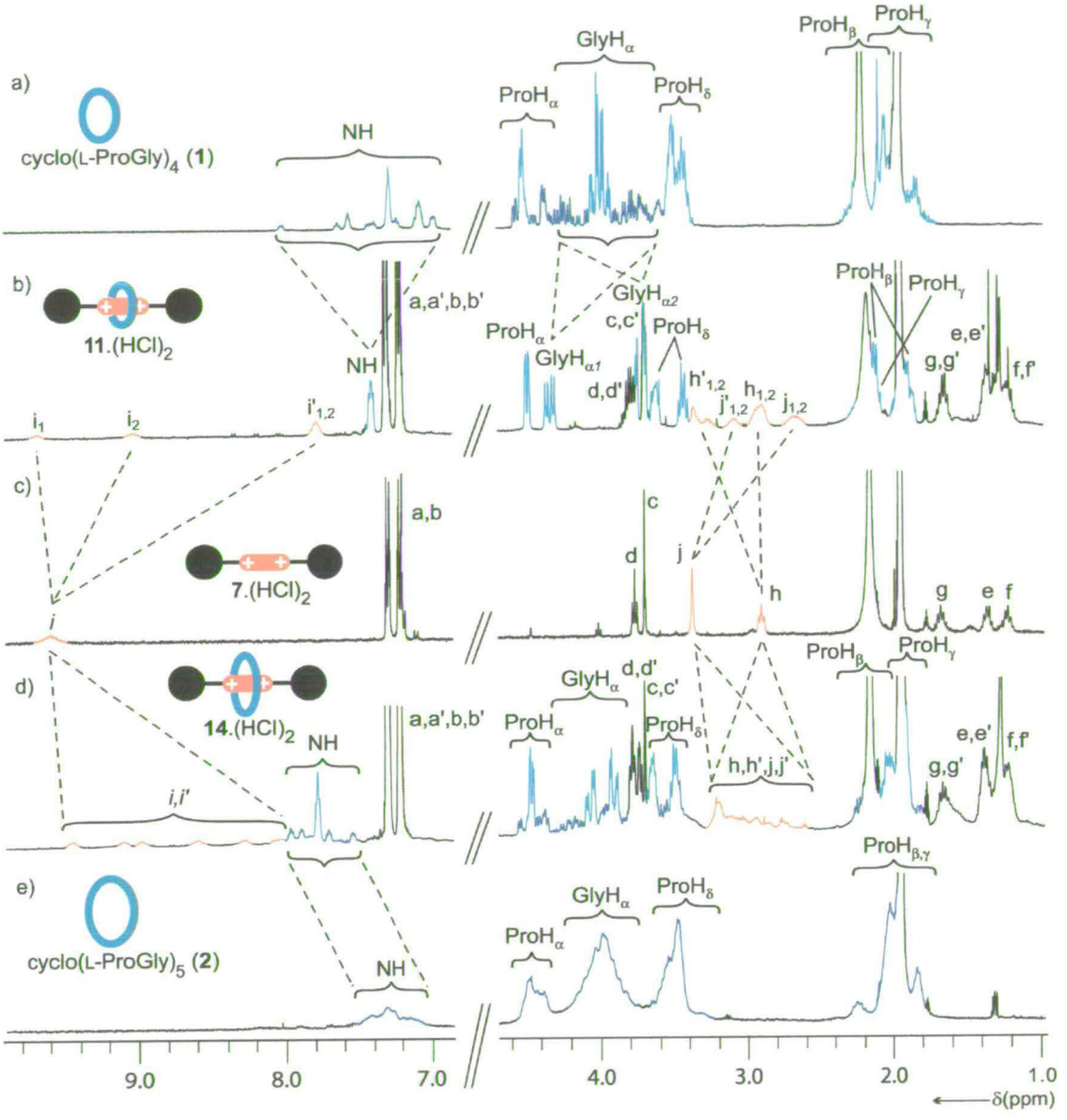


Figure 2. Comparison of partial ^{1}H NMR spectra (400 MHz, CD_3CN, 298 K) of a) **1**, b) **11**.$(HCl)_2$, c) **7**.$(HCl)_2$, d) **14**.$(HCl)_2$ and e) **2**. Atom labels are as shown in scheme 1, in **11**.$(HCl)_2$ and **14**.$(HCl)_2$ the presence of the macrocycle means that the thread no longer has a mirror plane perpendicular to its long axis, therefore pairs of diastereotopic protons related by inversion of the thread are designated a/a' etc. Geminal diastereotopic protons are labelled with a subscript 1 or 2.

Though the all trans conformation dominates in both rotaxanes the macrocycles of **11**.$(HCl)_2$ and **14**.$(HCl)_2$ show some notable differences even within these conformers. In **11**.$(HCl)_2$ there is a ca 0.6 ppm splitting of the $GlyH_\alpha$ resonances

induced by the carbonyl of the adjacent proline residue. The conformational adjustment induced by binding the thread results in one $GlyH_\alpha$ proton being in closer proximity to the shielding region of the L-Pro carbonyl group and the other $GlyH_\alpha$ proton being more distant than in the free macrocycle. This effect is much less pronounced in the **14**.$(HCl)_2$ system (the two $GlyH_\alpha$ resonances are separated by ca 0.2ppm), indicating that the $GlyH_\alpha$ protons experience a more similar environment- i.e. a less rigid conformation is enforced upon the macrocycle and the proline carbonyls are rotated less on average. This suggests that the macrocycle in **14**.$(HCl)_2$ does not bind to the thread with all of its proline carbonyl groups simultaneously. There is also a pronounced difference in the chemical shift of the amide NH resonances in **11**.$(HCl)_2$ and **14**.$(HCl)_2$. For **11**.$(HCl)_2$ the amide NH is a single resonance at ca 7.6 ppm, a value approximately 0.2 ppm downfield of the value for the all trans conformer of **1**. Despite the loss of the internal hydrogen bond network of the macrocycle, the resonance is still shifted slightly downfield by the inductive effect of the glycine amide carbonyls accepting a strong hydrogen bond from the ammonium group. That this effect is even more pronounced for the macrocycle of **14**.$(HCl)_2$ is perhaps surprising considering that same number of hydrogen bond donors are shared between more acceptors, but probably arises as a consequence of the greater conformational freedom of **2** allowing it to more effectively accept hydrogen bonds through the proline carbonyls.

In both cases the presence of the entrapped macrocycle has significant effects on the thread, particularly in the resonances of the ammonium protons and their adjacent methylene units. In the case of **11**.$(HCl)_2$ the ammonium proton resonances are shifted upfield as a consequence of acting as hydrogen bond donors, one set of ammonium protons (H_i) are shifted by ca 2ppm, whereas the other set are shifted to a much smaller degree and are split into a geminal diastereotopic pair. This indicates that one set of amide carbonyls of the macrocycle (presumably the glycyl carbonyls) is free to interact with one of the ammonium groups, whereas the other set of carbonyls is less able to access the other, probably due to the steric and electronic penalties incurred by converging eight carbonyl groups into a small volume of space. A similar situation exists in **14**.$(HCl)_2$, though the spectrum is complicated by the

presence of different rotamers of the macrocycle. The signals for the ammonium protons are split into a complex series of signals between approximately 9.6 ppm to 8 ppm due to differing degrees of hydrogen bond interaction between (and within) the different conformers of the macrocycle. A complex series of signals is also observed for the H_h and H_j protons, reflecting differing degrees of exposure to the shielding/deshielding regions of the encircling carbonyl groups.

The nature of the interactions between the macrocycle and thread in rotaxanes **11**.$(HCl)_2$ and **14**.$(HCl)_2$ was further elucidated by comparison of their ^1H NMR spectra with those of their deprotonated counterparts (Figure 3). Deprotonation of the thread **7**.$(HCl)_2$ using a solid supported base to give **7** results in ca 0.7 ppm and 0.5 ppm upfield shifts of the H_j and H_h resonances respectively. On treating rotaxane **14** with the same solid supported base disappearance of the ammonium NH signal and a similar upfield shift of the H_h and H_j resonances suggest that the rotaxane has been deprotonated, however the H_h and H_j signals remain a complicated and broad set of signals, indicating that even in the deprotonated form the macrocycle remains localized to the central region of the thread, presumably through weak amine NH to amide carbonyl hydrogen bonds. Deprotonation of **14**.$(HCl)_2$ also results in some significant changes to the macrocycle, most notably the splitting of the $GlyH_\alpha$ proton resonances is 'switched off' in the deprotonated rotaxane, as is that of the $ProH_\delta$ resonance. This effect is indicative of a conformational change in the macrocycle whereby the proline carbonyl that was previously rotated towards the central cavity of the macrocycle has instead rotated back towards the outside of the ring, allowing the internal GlyNH to L-Pro carbonyl hydrogen bond network to be re-established. Rotation of the proline carbonyl in this manner places the $GlyH_\alpha$ protons at equal (or in the case of L-$ProH_\delta$ less dissimilar) distances from the L-Pro carbonyl, disrupting its differential shielding effect. It is also worth noting that the macrocycles in **14**.$(HCl)_2$ and **14** display approximately the same degree of rotameric variability: i.e. it is the steric presence of the thread, and not the ammonium-amide interaction that determines which rotamers are available to the macrocycle in either case.

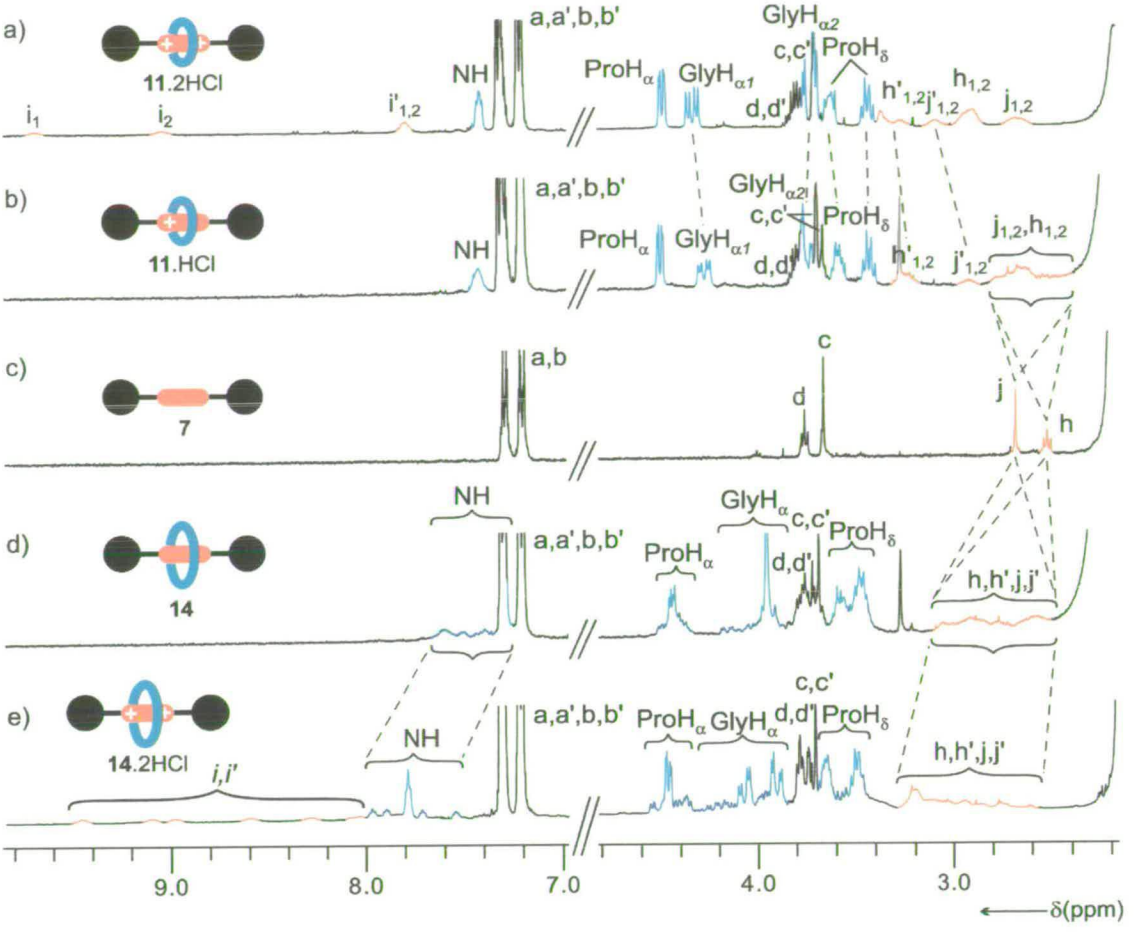


Figure 3. Comparison of partial ^{1}H NMR spectra (400 MHz, CD_3CN, 298 K) of a) **11**.$(HCl)_2$, b) **11**.HCl, c) **7**, d) **14** and e) **14**.$(HCl)_2$. Atom labels are as shown in scheme 1.

Treatment of **11**.$(HCl)_2$, under the same basic conditions did not result in analogous changes to its ^{1}H NMR spectrum. The macrocycle remains in one rotameric form and the splitting of the $GlyH_\alpha$ resonances persists, though the signals converge by approximately 0.1 ppm. The splitting of the L-$ProH_\delta$ resonances is also only marginally (0.05 ppm) attenuated. The H_h and H_j resonances exist as two sets of signals, one set at similar chemical shift to those of **11**.$(HCl)_2$ and one set that has been shifted upfield, suggesting that in this instance only one of the ammonium protons has been removed. Effects of this type, where the acidity of an ammonium thread is reduced by stabilization of the protonated form due by an encircling macrocycle, are well documented in the related crown ether/ammonium based rotaxane systems.[10] In this instance the size of the macrocycle appears to be critical: a CPK model of rotaxane **11** shows that the macrocycle is a 'tight fit' around the thread, and that for steric reasons it is not possible to re-establish the internal γ-turn

hydrogen bonds that exist in the free macrocycle. The inability to form internal hydrogen bonds will destabilize the neutral rotaxane **11** compared to either of its protonated forms, effectively increasing the basicity of the amine.

3.5 Conclusion

In conclusion, we have synthesized a series of [2] and [3]rotaxanes in which the macrocyclic component is an octa- or deca- peptide derived from the L-ProGly repeat unit. The suitability of different diammonium motifs to act as templates for rotaxane formation was investigated for the two different macrocycles. The smaller, more rigid **1** was best suited to more closely spaced ammonium groups, whereas the larger and more flexible **2** showed less discrimination, forming rotaxanes from all of the threads. Macrocycle **2** also produced significant quantities of [3]rotaxane in competition with [2]rotaxane. In all cases the internal hydrogen bond network of the cyclic peptide is disrupted as a consequence of binding to the diammonium thread. The basicity of the thread amine groups was found to be enhanced for one of the cyclo(L-ProGly)$_4$ rotaxanes. These results suggest that it may be possible to tailor a thread to the spatial and hydrogen bonding requirements of a specific peptide macrocycle. We are continuing our investigations in this area, with the ultimate goal of establishing a general synthetic route to natural and unnatural interlocked peptides.

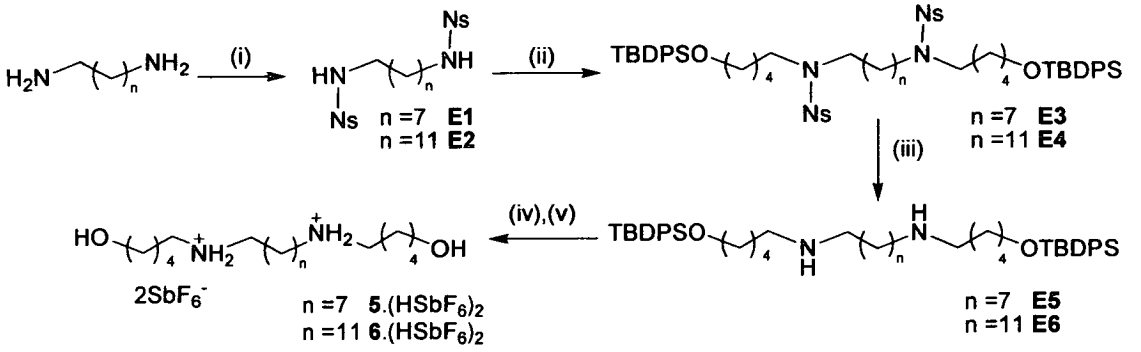
3.6 Experimental Section

General

Unless otherwise stated, all reagents and anhydrous solvents were purchased from Aldrich chemicals and used without further purification. 5-Chloro-1-pentanol was purchased from Lancaster and FmocGlyOH and Boc-*L*-Pro were purchased from NovaBiochem. Column chromatography was carried out using Kieselgel C60 (Merck, Germany) as the stationary phase. Analytical and preparative thin layer chromatography were performed on precoated silica gel plates (0.25 mm thick, 60F$_{254}$, Merck, Germany) and compounds were visualized under UV light; amine-bearing compounds were visualized by dipping the plate in a 1% ninhydrin in ethanol solution then heating the plate with a heat gun. Eluent compositions for thin layer chromatography were selected so as to give Rf values of 0.2. Reverse phase

chromatography was carried out using Diaion HP-20 resin, which was prepared according to the manufacturer's instructions. All ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AV 400 instrument, at a constant temperature of 298 K. Chemical shifts are reported in parts per million from high to low field and referenced to the residual solvent peak. Standard abbreviations indicating multiplicity are given: m = multiplet, br = broad, d = doublet, q = quadruplet, t = triplet, s = singlet. Coupling constants (*J*) are reported in hertz (Hz). Melting points were determined using a Sanyo Gallenkamp apparatus and are uncorrected. LCMS was carried out using a Waters 2795 HPLC system and a Phenomenex Luna (5μ) C18 analytical column (250 × 2.0 mm). For analysis of rotaxane-forming reactions a solvent gradient of 5-95% acetonitrile/water over a 35 minute interval and a flow rate of 0.2 cm^3/minute were applied. UV-active components eluted from the column were detected using a Waters 486 Tunable Absorbance Detector set to read absorbance at 254 nm. ESI mass spectrometry was performed with a Micromass Platform II Mass Spectrometer controlled using Masslynx v2.3 software. FAB accurate mass spectrometry was carried out by the University of Edinburgh services.

1-(*tert*-Butyldiphenylsilyl)oxy-5-iodopentane, cyclo(ProGly)$_4$ (**1**), cyclo(ProGly)$_5$ (**2**), threads **3**.$(SbF_6)_2$ and **4**.$(SbF_6)_2$ and rotaxanes **11**.$(SbF_6)_2$, **12**.$(SbF_6)_2$, **14**.$(SbF_6)_2$ and **15**.$(SbF_6)_2$ were prepared according to the procedures described in chapter 2 of this thesis.



Scheme E1. Synthesis of the diols **5**.$(HSbF_6)_2$ and **6**.$(HSbF_6)_2$. Reagents and conditions: (i) 2-nitrobenzenesulfonyl chloride, triethylamine, dichloromethane, rt; (ii) 1-(*tert*-butyldiphenylsilyl)oxy-5-iodopentane, K_2CO_3, DMF, 80 °C; (iii) mercaptoacetic acid, LiOH, DMF, rt; (iv) ~1 mol l^{-1} HCl in H_2O/methanol, rt; (v) $AgSbF_6$, methanol, rt.

***N,N'*-Bis(2-nitrobenzenesulfonyl)-octane-1,8-diamine (E1)**

A solution of 1,8-diaminooctane (0.398 g, 2.77 mmol) and triethylamine (0.86 ml, 6.1 mmol) in dichloromethane (10 ml) was cooled to 0 °C and 2-nitrobenzenesulfonylchloride (1.23 g, 5.56 mmol) was added in portions. The mixture was allowed to warm to room temperature and stirred for an additional 2 hours. The precipitate was collected by vacuum filtration and washed with dichloromethane and acetone to yield **E1** as a white solid (1.29 g, 90%); m.p. 160 °C; ^{1}H NMR (400 MHz, d_6-DMSO) δ = 8.05 (t, 2H, J = 5.7 Hz, NH), 7.94-7.99 (m, 4H, ArH), 7.83-7.88 (m, 4H, ArH), 2.83-2.87 (m, 4H, CH_2N), 1.32-1.39 (m, 4H, $C\underline{H}_2CH_2N$), 1.04-1.19 (m, 8H, alkylH); ^{13}C NMR (100 MHz, d_6-DMSO) δ = 147.7, 133.9, 132.8, 132.5, 129.5, 124.2, 42.6, 28.9, 28.2, 25.7; HR-MS (FAB) $C_{20}H_{26}N_4O_8S_2$ calcd m/z $[(M + H)^+]$ = 515.1270 found 515.1269.

***N,N'*-Bis(2-nitrobenzenesulfonyl)-dodecane-1,12-diamine (E2)**

A solution of 1,12-diaminododecane (0.492 g, 2.46 mmol) and triethylamine (0.86 ml, 6.1 mmol) in dichloromethane (10 ml) was cooled to 0 °C and 2-nitrobenzenesulfonylchloride (1.09 g, 4.92 mmol) was added in portions. The mixture was allowed to warm to room temperature and stirred for an additional 2 hours. The precipitate was collected by vacuum filtration and washed with dichloromethane and acetone to yield **E2** as a white solid (1.31 g, 93%); m.p. 162 °C; ^{1}H NMR (400 MHz, d_6-DMSO) δ = 8.04 (br s, 2H, NH), 7.94-7.99 (m, 4H, ArH), 7.83-7.88 (m, 4H, ArH), 2.84-2.90 (m, 4H, CH_2N), 1.34-1.43 (m, 4H, $C\underline{H}_2CH_2N$), 1.11-1.23 (m, 16H, alkylH); ^{13}C NMR (100 MHz, d_6-DMSO) δ = 147.6, 133.9, 132.8, 132.5, 129.3, 124.2, 42.5, 29.0, 28.8, 28.7, 28.4, 25.8; HR-MS (FAB) $C_{24}H_{34}N_4O_8S_2$ calcd m/z $[(M + H)^+]$ = 571.1896 found 571.1885.

***N,N'*-Bis(2-nitrobenzenesulfonyl)-*N,N'*-bis-[5-(*tert*-butyldiphenyl-silyanyloxy)-pentyl]-octane-1,8-diamine (E3)**

N,N'-Bis(2-nitrobenzenesulfonyl)-octane-1,8-diamine (**E1**) (0.145 g, 0.987 mmol) and 1-(*tert*-butyldiphenylsilyl)oxy-5-iodopentane (1.00 g, 2.21 mmol) were dissolved in DMF (3 ml) and potassium carbonate (0.498 g, 3.60 mmol) was added. The mixture was stirred at 70 °C for 16 hours, cooled to room temperature and water (20

ml) was added. The mixture was extracted with dichloromethane (2 × 15 ml) and the combined organic layers were washed with water (20 ml), dried over magnesium sulfate and concentrated under reduced pressure. The residue was subjected to column chromatography (1:3-2:3 ethyl acetate/petroleum ether) to yield **E3** product as a pale yellow gum (0.756 g, 66%); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.97-8.00 (m, 2H, ArH), 7.61-7.66 (m, 12H, ArH), 7.55-7.59 (m, 2H, ArH), 7.35-7.44 (m, 12H, ArH), 3.59 (t, *J* = 6.3 Hz, 4H, C$\underline{H_2}$OTBDPS), 3.20-3.27 (m, 4H, CH_2NNs), 1.44-1.54 (m, 12H, C$\underline{H_2}CH_2$NNs, C$\underline{H_2}CH_2$OTBDPS), 1.26-1.35 (m, 4H, alkylH), 1.14-1.21 (m, 8H, alkylH), 1.03 (s, 18H, *t*BuH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 148.1, 135.5, 133.9, 133.2, 131.5, 130.6, 129.5, 127.6, 124.1, 63.6, 47.1, 32.0, 29.0, 28.0, 27.8, 26.9, 26.4, 22.9, 19.2. LR-MS (ESI) m/z = 1163 [$(M + H)^+$]

_N,N'_-Bis(2-nitrobenzenesulfonyl)-_N,N'_-bis-[5-(*tert*-butyldiphenyl-silyanyloxy)-pentyl]-dodecane-1,12-diamine (E4)

_N,N'_-Bis(2-nitrobenzenesulfonyl)-dodecane-1,12-diamine (**E2**) (0.552 g, 0.967 mmol) and 1-(*tert*-butyldiphenylsilyl)oxy-5-iodopentane (0.981 g, 2.17 mmol) were dissolved in DMF (3 ml) and potassium carbonate (0.550g, 3.99 mmol) was added. The mixture was stirred at 70 °C for 16 hours, cooled to room temperature and water (20 ml) was added. The mixture was extracted with dichloromethane (2 × 15 ml) and the combined organic layers were washed with water (20 ml), dried over magnesium sulfate and concentrated under reduced pressure. The residue was subjected to column chromatography (1:3-2:3 ethyl acetate/petroleum ether) to yield **E4** as a colourless gum (0.865 g, 73%); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.97-8.00 (m, 2H, ArH), 7.61-7.67 (m, 12H, ArH), 7.55-7.58 (m, 2H, ArH), 7.35-7.43 (m, 12H, ArH), 3.59 (t, *J* = 6.3 Hz, 4H, C$\underline{H_2}$OTBDPS), 3.21-3.27 (m, 4H, CH_2NNs), 1.45-1.54 (m, 12H, C$\underline{H_2}CH_2$NNs, C$\underline{H_2}CH_2$OTBDPS), 1.27-1.36 (m, 4H, alkylH), 1.16-1.24 (m, 16H, alkylH), 1.03 (s, 18H, *t*BuH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 148.0, 135.5, 133.9, 133.2, 131.4, 130.7, 129.5, 127.6, 124.0, 63.6, 47.1, 47.0, 32.1, 29.4, 29.2, 28.1, 27.8, 26.7, 26.6, 22.9, 21.1, 19.2; LR-MS (ESI) m/z = 1219 [$(M + H)^+$]

_N,N'_-Bis-[5-(*tert*-butyldiphenyl-silyanyloxy)-pentyl]-octane-1,8-diamine (E5)

N,N'-Bis(2-nitrobenzenesulfonyl)-*N,N'*-bis-[5-(*tert*-butyldiphenylsilyanyloxy)-pentyl]-octane-1,8-diamine (**E3**) (0.660 g, 0.567 mmol) was dissolved in DMF (1.5 ml) and cooled to 0 °C. Mercaptoacetic acid (0.210 g, 2.30 mmol) and lithium hydroxide (0.215 g, 5.10 mmol) were added successively and the mixture was warmed to room temperature. After 3 hours, water (15 ml) was added and the mixture was extracted with ethyl acetate (3 × 15 ml). The combined organic layers were washed with saturated sodium bicarbonate solution (40 ml), dried over magnesium sulfate and concentrated under reduced pressure. The residue was subjected to column chromatography (0.1:1:19-0.1:1:12 triethylamine/methanol/chloroform) to yield **E5** as a pale yellow gum (0.322 g, 72%); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.65-7.67 (m, 8H, ArH), 7.35-7.43 (12H, m, ArH), 3.66 (t, *J* = 6.4 Hz, 4H, C$\underline{H_2}$OTBDPS), 2.56-2.60 (m, 8H, C$\underline{H_2}$NH$_2$), 1.53-1.60 (m, 4H, C$\underline{H_2}$CH$_2$OTBDPS), 1.44-1.51 (m, 8H, C$\underline{H_2}$CH$_2$NH$_2$), 1.34-1.41 (m, 4H, alkylH), 1.29-1.32 (m, 8H, alkylH), 1.04 (s, 18H, *t*BuH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 135.5, 134.1, 129.5, 127.6, 63.8, 49.9, 47.6, 32.4, 29.3, 27.3, 26.9, 23.5, 19.2; HR-MS (FAB) $C_{50}H_{76}N_2O_2Si_2$ calcd m/z [(M + H)$^+$] = 793.5524 found 793.5531.

_N,N'_-Bis-[5-(*tert*-butyldiphenyl-silyanyloxy)-pentyl]-dodecane-1,12-diamine (S6)

N,N'-Bis(2-nitrobenzenesulfonyl)-*N,N'*-bis-[5-(*tert*-butyldiphenylsilyanyloxy)-pentyl]-dodecane-1,12-diamine (**E4**) (0.840 g, 0.689 mmol) was dissolved in DMF (2 ml) and cooled to 0 °C. Mercaptoacetic acid (0.251 g, 2.88 mmol) and lithium hydroxide (0.265 g, 6.29 mmol) were added successively and the mixture was warmed to room temperature. After 3 hours, water (20 ml) was added and the mixture was extracted with ethyl acetate (3 × 15 ml). The combined organic layers were washed with saturated sodium bicarbonate solution (40 ml), dried over magnesium sulfate and concentrated under reduced pressure. The residue was subjected to column chromatography (0.1:1:19-0.1:1:12) triethylamine/methanol/chloroform) to yield **E6** as a pale yellow gum (0.461 g, 79%); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.65-7.67 (m, 8H, ArH), 7.35-7.42 (m, 12H, ArH), 3.65 (t, *J* = 6.4 Hz, 4H, C$\underline{H_2}$OTBDPS), 2.56-2.61 (m, 8H, C$\underline{H_2}$NH$_2$), 1.44-1.60 (m, 12H, C$\underline{H_2}$CH$_2$NH$_2$, C$\underline{H_2}$CH$_2$OTBDPS), 1.34-1.41 (m, 4H, alkylH), 1.24-1.32 (m, 16H, alkylH), 1.04 (s, 18H, *t*BuH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 135.5, 134.0,

129.5, 127.5, 63.8, 50.0, 49.9, 32.4, 29.9, 29.6, 29.4, 27.2, 26.9, 23.5, 19.2; HR-MS (FAB) $C_{50}H_{76}N_2O_2Si_2$ calcd m/z $[(M + H)^+]$ = 849.6150 found 849.6130.

_N,N'_-Bis-(5-hydroxypentyl)-octane-1,8-diammonium hexafluoroantimonate 5.$(SbF_6)_2$

(a) _N,N'_-Bis-(5-hydroxypentyl)-octane-1,8-diammonium chloride: _N,N'_-Bis-[5-(*tert*-butyldiphenyl-silyanyloxy)-pentyl]-octane-1,8-diamine (**E5**) (0.310 g, 0.391 mmol) was dissolved in methanol (5 ml) and concentrated hydrochloric acid (0.5 ml) was added dropwise at room temperature. The mixture was stirred for 4 hours and concentrated to dryness under reduced pressure. The residue was triturated with diethyl ether and dried over P_2O_5 under reduced pressure to yield **5**.$(HCl)_2$ as a pale yellow solid (0.150 g, 97%); m.p. 187-190 °C (dec); ^{1}H NMR (400 MHz, d_6-DMSO) δ = 8.67 (br s, 4H, NH_2^+), 3.39 (t, J = 6.2 Hz, 4H, CH_2OH), 2.78-2.88 (m, 8H, $CH_2NH_2^+$), 1.55-1.64 (m, 8H, $CH_2CH_2NH_2^+$), 1.38-1.47 (m, 4H, CH_2CH_2OH), 1.24-1.35 (m, 4H, alkylH).

(b) Anion exchange: _N,N'_-Bis-(5-hydroxypentyl)-octane-1,8-diammonium chloride (0.105 g, 0.268 mmol) was dissolved in methanol (1 ml) and a solution of silver hexafluoroantimonate (0.184 g, 0.536 mmol) in methanol (0.5 ml) was added. The mixture was stirred for 5 hours in the absence of light, filtered through celite and concentrated. The residue was triturated with diethyl ether and dried over P_2O_5 under reduced pressure to give **5**.$(SbF_6)_2$ as a pale yellow gum (0.185 g, 88%); ^{1}H NMR (400 MHz, CD_3CN) δ = 6.44 (br s, 4H, NH_2^+) 3.50 (t, J = 6.2 Hz, 4H, $C\underline{H}_2OH$), 2.92-3.02 (m, 8H, $C\underline{H}_2NH_2^+$), 1.60-1.71 (m, 8H, $C\underline{H}_2CH_2NH_2^+$), 1.46-1.54 (m, 4H, $C\underline{H}_2CH_2OH$), 1.36-1.43 (m, 4H, alkylH), 1.32-1.35 (m, 8H, alkylH); ^{13}C NMR (100 MHz, CD_3CN) δ = 62.0, 49.0, 32.4, 28.9, 26.5, 26.3, 26.2, 23.3; LR-MS (ESI) m/z = 317 $[(M + H)^+]$.

_N,N'_-Bis-(5-hydroxypentyl)-dodecane-1,12-diammonium hexafluoroantimonate 6.$(SbF_6)_2$

(a) _N,N'_-Bis-(5-hydroxypentyl)-dodecane-1,12-diammonium chloride: _N,N'_-Bis-[5-(*tert*-butyldiphenyl-silyanyloxy)-pentyl]-dodecane-1,12-diamine (**E6**) (0.405 g, 0.477 mmol) was dissolved in methanol (6 ml) and concentrated hydrochloric acid (0.6 ml)

was added dropwise at room temperature. The mixture was stirred for 4 hours and concentrated to dryness under reduced pressure. The residue was triturated with diethyl ether and dried over P_2O_5 under reduced pressure to yield **6**.$(HCl)_2$ as a pale yellow solid (0.201 g, 94%); m.p. 221-224 °C (dec); ^{1}H NMR (400 MHz, d_6-DMSO) δ = 8.64 (br s, 4H, NH_2^+), 4.35-4.55 (m, 2H, OH), ~3.4 (t (indistinguishable from HOD peak), 4H, CH_2OH), 2.78-2.87 (m, 8H, $C\underline{H}_2NH_2^+$), 1.52-1.63 (m, 8H, $C\underline{H}_2CH_2NH_2^+$), 1.37-1.46 (m, 4H, $C\underline{H}_2CH_2OH$), 1.20-1.37 (m, 12H, alkylH).

(b) Anion exchange: *N*,*N*'-Bis-(5-hydroxypentyl)-dodecane-1,12-diammonium chloride (0.150 g, 0.335 mmol) was dissolved in methanol (1.5 ml) and a solution of silver hexafluoroantimonate (0.230 g, 0.670 mmol) in methanol (0.5 ml) was added. The mixture was stirred for 3 hours, filtered through celite and concentrated. The residue was triturated with diethyl ether and dried over P_2O_5 under reduced pressure to give **6**.$(SbF_6)_2$ as a pale yellow solid (0.273 g, 96%); m.p. 120-121 °C (dec) ^{1}H NMR (400 MHz, CD_3CN) δ = 6.20 (br s, NH_2^+), 3.50 (t, J = 6.2 Hz, 4H, $C\underline{H}_2OH$), 2.91-3.03 (m, 8H, $C\underline{H}_2NH_2^+$), 1.56-1.71 (m, 8H, $C\underline{H}_2CH_2NH_2^+$), 1.46-1.54 (m, 4H, $C\underline{H}_2CH_2OH$), 1.37-1.44 (m, 4H, alkylH), 1.28-1.35 (m, 16H, alkylH); ^{13}C NMR (100 MHz, CD_3CN) δ = 62.0, 49.0, 48.9, 32.4, 30.1, 29.9, 29.5, 26.8, 26.4, 26.2, 23.3; LR-MS (ESI) m/z = 373 $[(M + H)^+]$.

General procedure for the analytical scale synthesis of [2]rotaxanes 11-20$(HSbF_6)_2$

Diol **9**$(SbF_6)_2$ or **10**$(SbF_6)_2$ (~0.004 mmol) was dissolved in a solution of 30% chloroform/acetonitrile to give a concentration of ~10 mmol dm^{-3}, 3 molar equivalents of cyclo$(ProGly)_{n+3}$ (n = 1 or 2) was added and the mixture was stirred for 15 minutes. Acid chloride $(4\text{-Cl-}C_6H_4)_3CCH_2COCCl$ (0.016 mmol) was added, the mixture was stirred at room temperature for 7 days and a sample was analysed by LC-MS to determine the degree of formation of [2]rotaxane with respect to the corresponding thread.

General procedure for the preparative scale synthesis of rotaxanes 11, 12, 14 and 15.$(HCl)_2$ and threads 7 and 8.$(HCl)_2$

Diol **3**.$(HSbF_6)_2$ or **4**.$(HSbF_6)_2$ (~0.004 mmol) was dissolved in a solution of 30% chloroform/acetonitrile to give a concentration of ~10 mmol dm^{-3}, 3 molar equivalents of cyclo(ProGly)$_{n+3}$ (n = 1 or 2) was added and the mixture was stirred for 15 minutes. Acid chloride (4-Cl-C_6H_4)$_3$$CCH_2COCCl$ (4 molar equivalents) was added, the mixture was stirred at room temperature for 7 days and a sample was analysed by LCMS. If an appreciable amount of 'monostoppered thread' was still evident, a second portion of (4-Cl-C_6H_4)$_3$$CCH_2COCCl$ (2 molar equivalents) was added and the mixture was stirred for an additional 7 days. Solvent was removed by gentle nitrogen flow and the residue was triturated with diethyl ether, dissolved in dichloromethane (1 ml), washed with water (3 × 1 ml), dried over magnesium sulfate and concentrated under reduced pressure. The residue was subjected to preparative TLC on alumina backed plates that had been pretreated with a solution of saturated triethylamine hydrochloride in dichloromethane. Plates were developed with a 1:19 methanol/dichloromethane solution. The product was extracted from the silica with a 1:9 methanol/dichloromethane solution and the solution was washed with 1 mol dm^{-3} hydrochloric acid solution (2 × 1 ml) and water (1 ml), dried over magnesium sulfate and filtered. Dowex-22 chloride ion exchange resin was added to the solution and the mixture was allowed to stand for 1 hour. The mixture was filtered and the filtrate was concentrated under reduced pressure to give the rotaxane as a white amorphous solid.

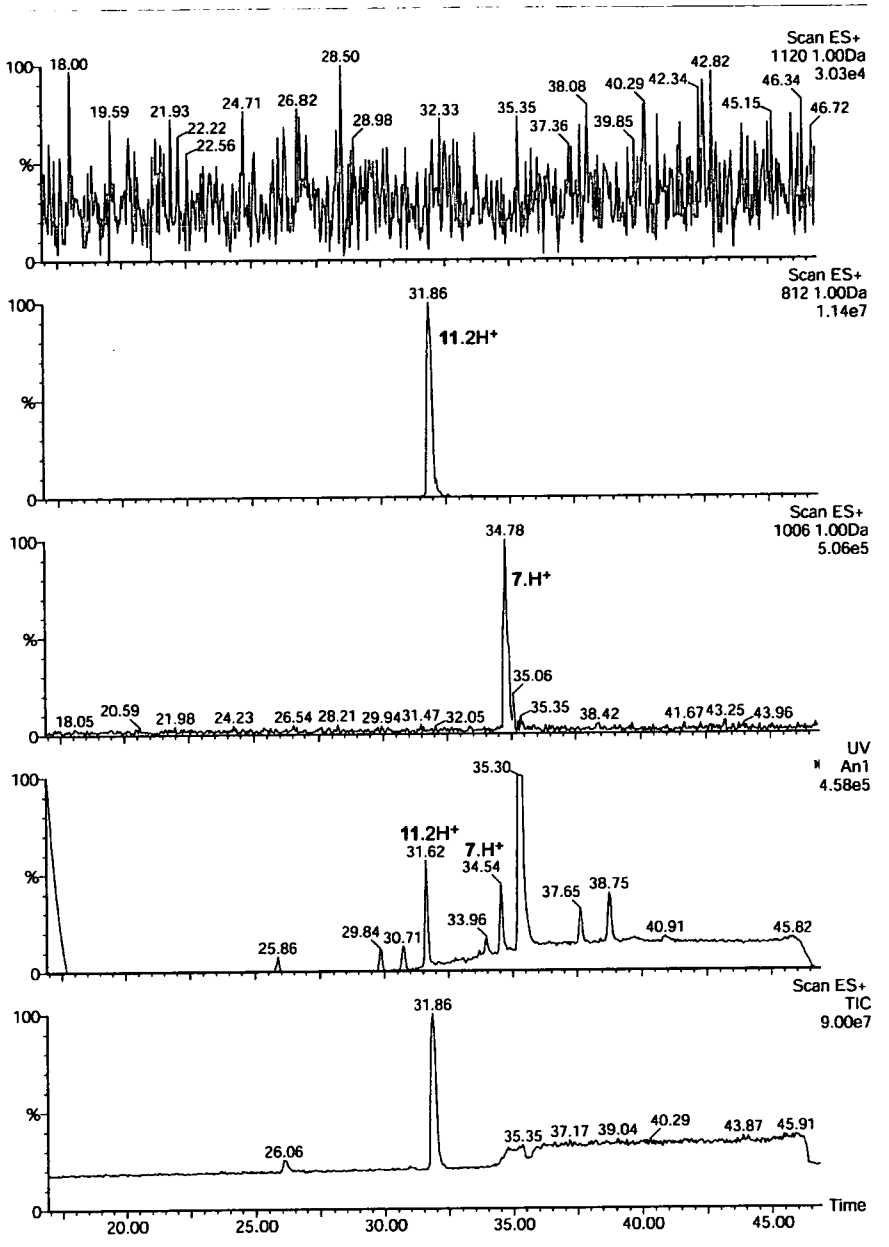
Thread 9.$(HCl)_2$

m.p. 120-121 °C (dec) ^{1}H NMR (400 MHz, CD_3CN) δ = 1.25-1.65 (m, 8H, 4 × CH_2), 1.72-1.86 (m, 4H, 2 × CH_2), 2.81 (br m, 2H, CH_2N), 2.90 (br m, 2H, CH_2N), 3.54 (s, 2H, CH_2CO), 3.71 (t, 2H, J = 6.3, OCH_2), 7.04 (d, 6H, J = 8.8, ArH), 7.17 (d, 6H, J = 8.8, ArH), 9.27 (br s, 4H, 2 × $^+NH_2$); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 23.3, 24.1, 25.1, 25.5, 27.8, 29.7, 45.9, 48.6, 48.7, 54.6, 64.1, 128.3, 130.3, 132.6, 144.1, 170.3; LR-MS (ESI) m/z = 545 $[(M + 2H)^{2+}]$.

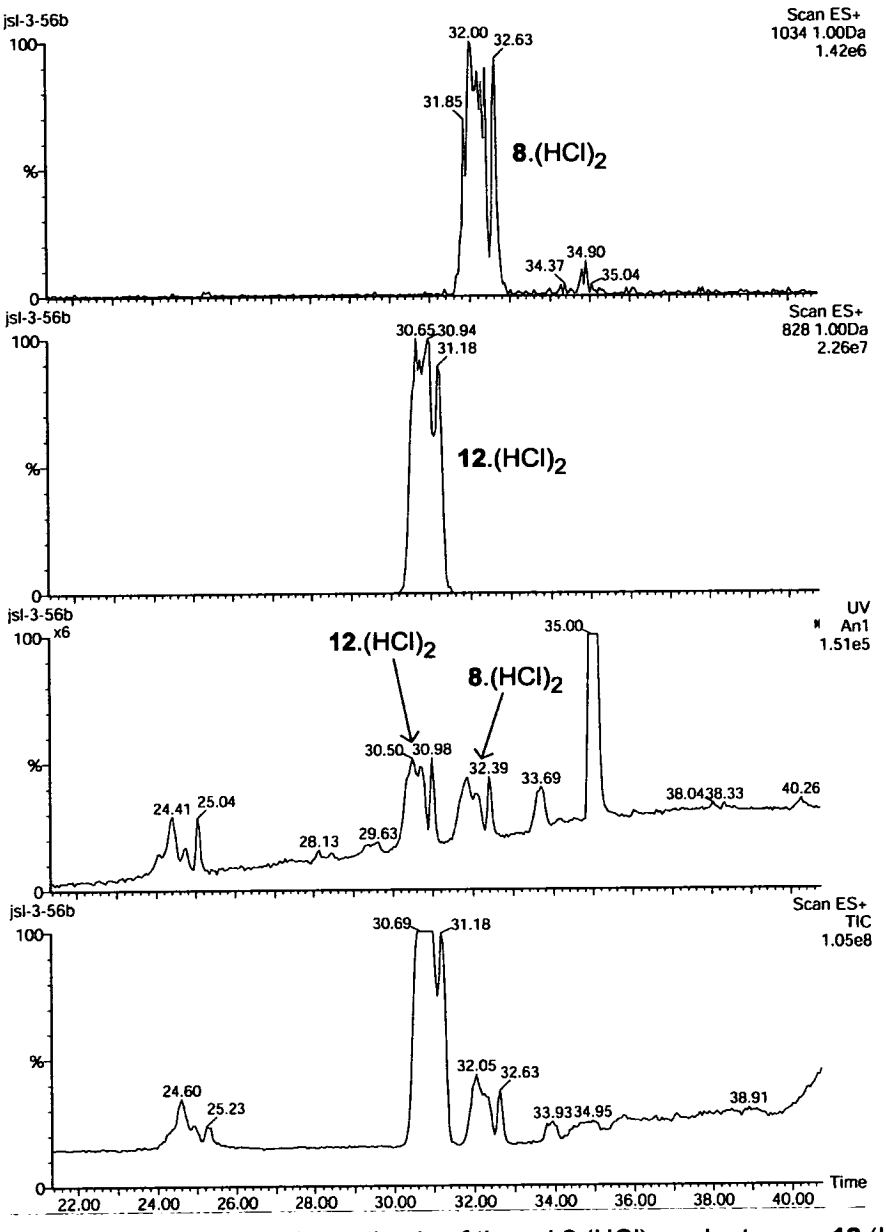
Thread 10.$(HCl)_2$

m.p. 120-121 °C (dec) ^{1}H NMR (400 MHz, CD_3CN) δ = 1.15-1.34 (m, 12H, 6 × CH_2), 1.64, (br m, 2H, CH_2), 1.73 (br m, 2H, CH_2), 2.77 (br m, 4H, 2 × CH_2N), 3.53 (s, 2H, CH_2CO), 3.70 (t, 2H, J = 6.3, CH_2O), 7.04 (d, 6H, J = 8.7, ArH), 7.17 (d, 6H,

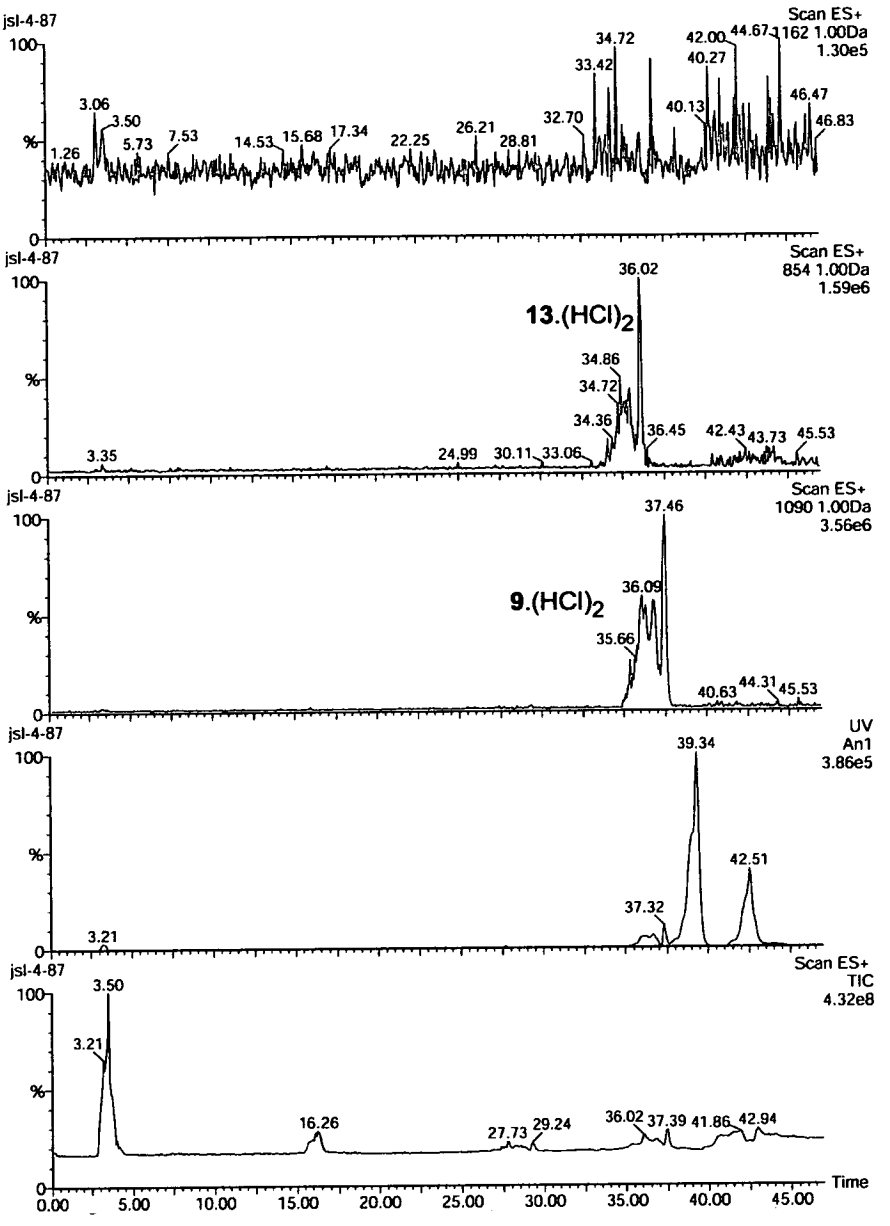
J = 8.7, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 22.8, 23.2, 25.3, 25.4, 25.9, 26.5, 27.3, 27.8, 29.7, 45.9, 47.8, 48.3, 64.1, 128.2, 130.3, 132.6, 144.1, 170.3; LR-MS (ESI) m/z = 573 $[(M + 2H)^{2+}]$.



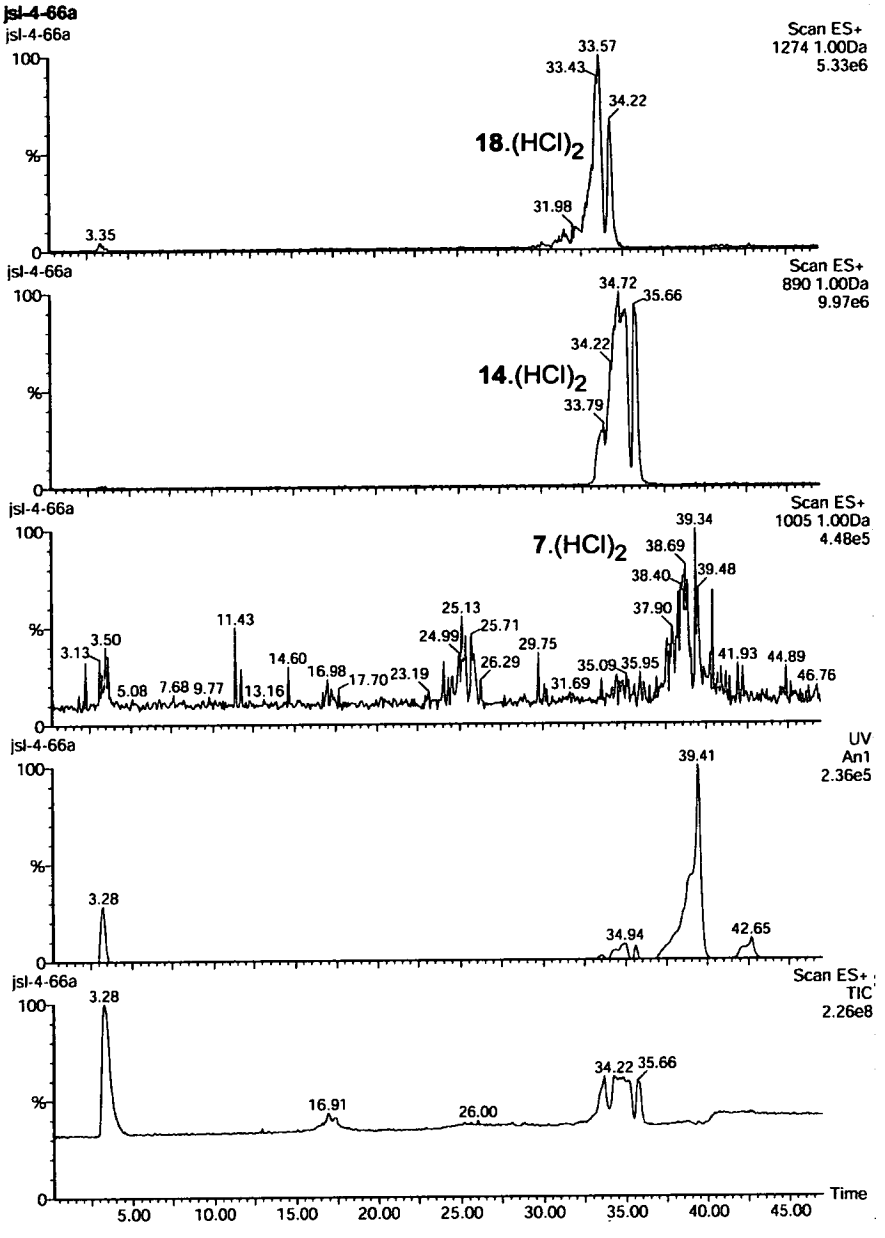
HPLC trace for analytical scale synthesis of thread **7**.$(HCl)_2$ and rotaxane **11**.$(HCl)_2$. The top trace is a scan for the mass of the corresponding [3]rotaxane. Impurities present in the UV trace are due to decomposition of the 'stopper' acid chloride.



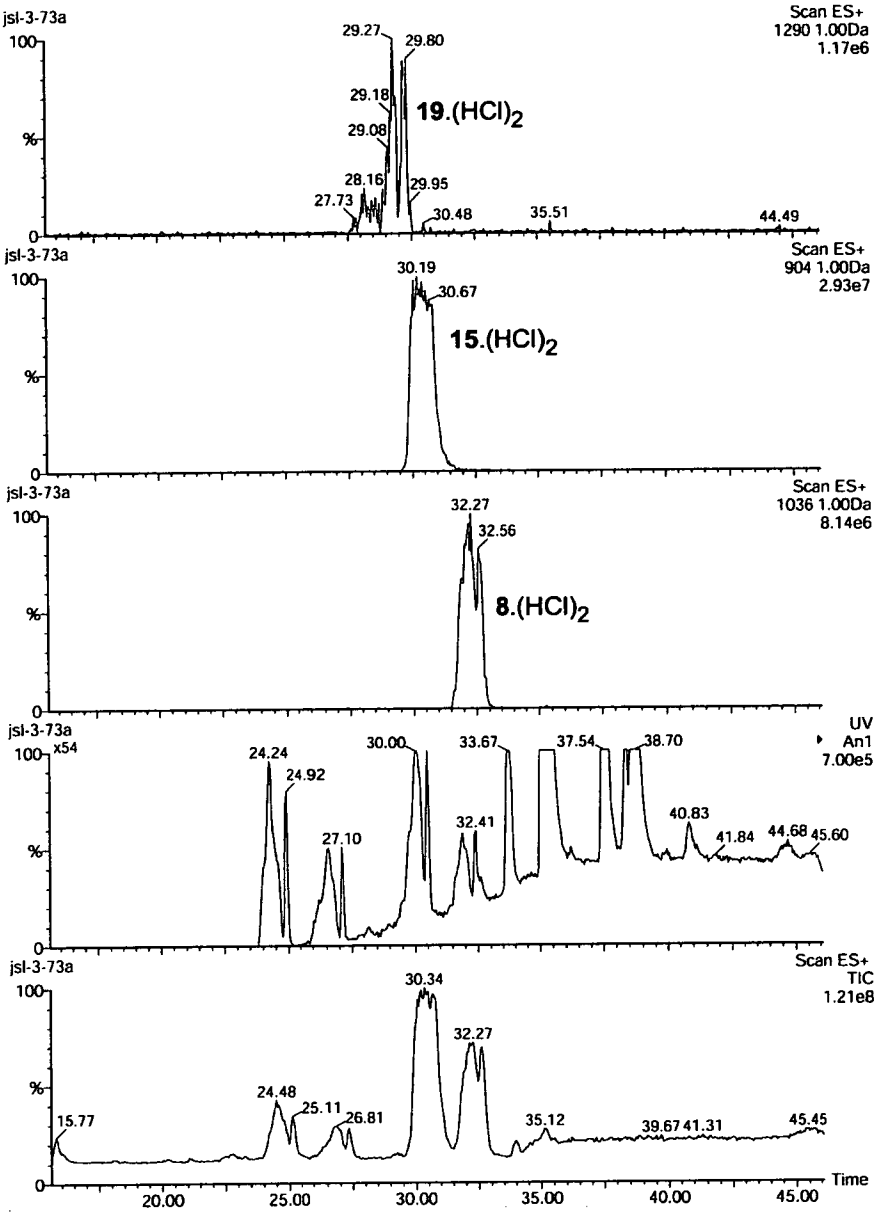
HPLC trace for analytical scale synthesis of thread **8**.$(HCl)_2$ and rotaxane **12**.$(HCl)_2$



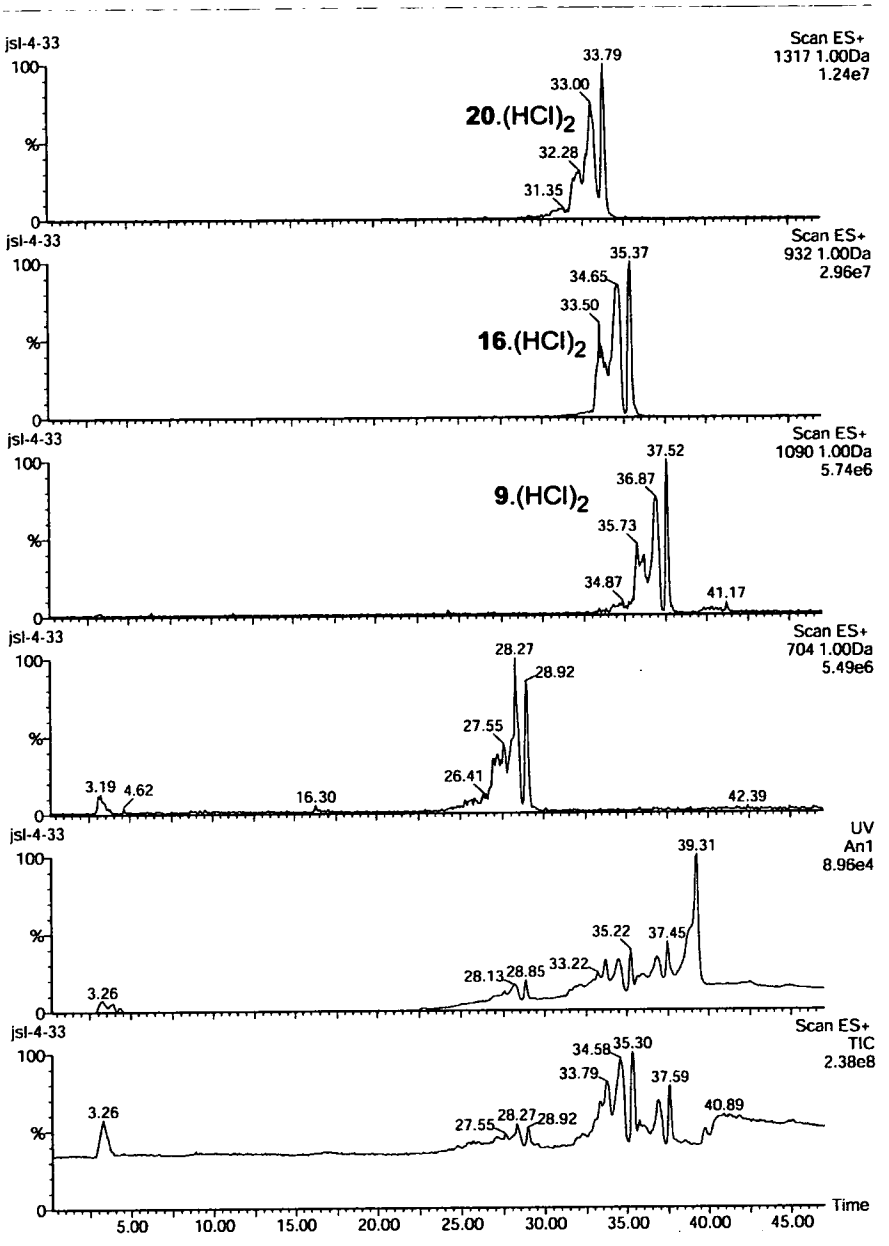
HPLC trace for the analytical scale synthesis of thread **9**.$(HCl)_2$ and rotaxane **13**.$(HCl)_2$. The top trace is a scan for the mass of the corresponding [3]rotaxane.



HPLC trace for the analytical scale synthesis of thread **7**.$(HCl)_2$, [2]rotaxane **14**.$(HCl)_2$ and [3]rotaxane **18**.$(HCl)_2$



HPLC trace for the analytical scale synthesis of thread **8**.$(HCl)_2$, [2]rotaxane **15**.$(HCl)_2$ and [3]rotaxane **19**.$(HCl)_2$



HPLC trace for the analytical scale synthesis of thread **9**.$(HCl)_2$, [2]rotaxane **16**.$(HCl)_2$ and [3]rotaxane **20**.$(HCl)_2$

3.7 References and Notes

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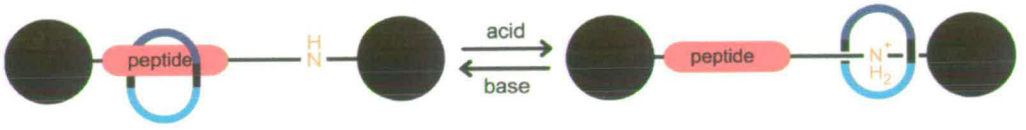
Chapter 4 Synopsis

This chapter describes the synthesis of a rotaxane in which the average position of a 'hybrid' macrocycle can be controlled by altering the protonation state of the molecule. The formation of the rotaxane is templated by amide-amide hydrogen bonding interactions. In the neutral form these amide-amide hydrogen bonds hold the macrocycle over a dipeptide residue; when the thread is protonated, polyether-ammonium cation interactions dominate and the macrocycle changes position.



Chapter 4

A Switchable Dual Binding Mode Molecular Shuttle

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4.1 Introduction

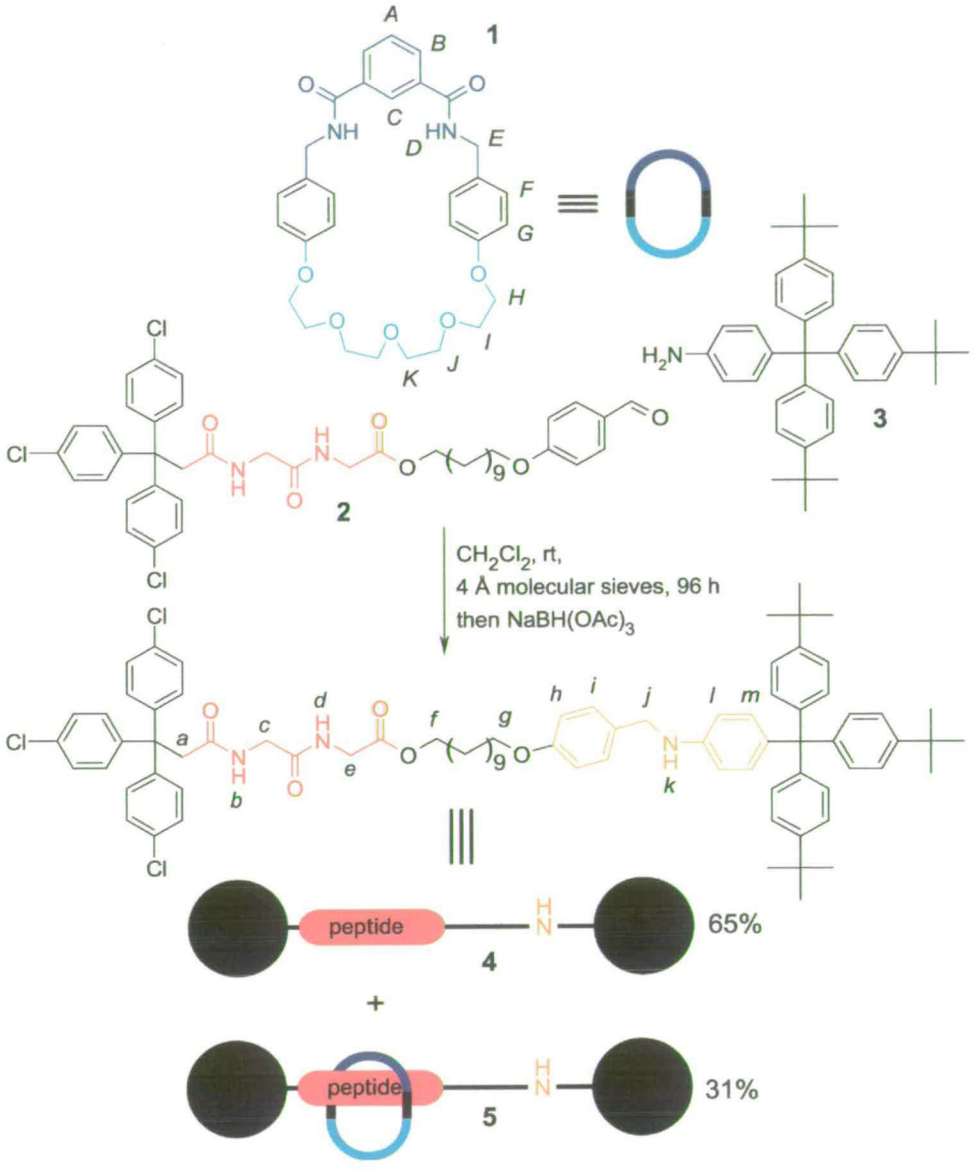
Rotaxanes in which the position of the macrocyclic component can be changed by an external stimulus are amongst the simplest of molecular-scale mechanical devices.[1] Various stimuli have been employed to induce such switching, including metal binding,[2] configurational changes,[3] and alteration of the oxidation state[4] or protonation level[2f,4a,5] of the molecule. Here we report on the synthesis and operation of a pH-switchable molecular shuttle that uses different sets of intercomponent interactions to achieve distinct and differing co-conformations in the neutral and protonated states.

Amide-amide hydrogen bonding of short peptide units with isophthalamide macrocycles is a well-established template route for the synthesis of rotaxanes.[6] Recently the Loeb group, inspired by the ammonium cation-crown ether rotaxane system originally introduced by Busch[7] and Stoddart,[8] demonstrated[9] that a protonated *N*-benzylaniline group can be complexed as a pseudorotaxane by a crown ether. We wondered whether these two recognition motifs could be combined to generate a new type of dual binding mode, protonation-switched, molecular shuttle.

4.2 Results and Discussion

A target rotaxane incorporating glycylglycine and *N*-benzylaniline 'stations' in the thread and an isophthalamide group and polyether chain in the macrocycle was synthesized using reductive amination to simultaneously generate the interlocked architecture and install the *N*-benzylaniline moiety (Scheme 1).[10] In CH_2Cl_2 macrocycle **1** hydrogen bonds to the mono-stoppered glycylglycine thread **2**, forming a pseudorotaxane.[6e] Covalent capture of the threaded intermediate by imine formation with bulky amine **3**, followed by *in situ* reduction with $NaBH(OAc)_3$, afforded the thread **4** and [2]rotaxane **5** in 65 and 31% yields, respectively (see Experimental Section). This synthesis follows earlier work in which an analogous rotaxane was synthesised incorporating a macrocycle that lacked the crown ether functionality of **1**, instead having a sebacoyl ester (unpublished results). Without the

crown ether the yield of rotaxane is higher, but no protonation-dependant behaviour is observed.



Scheme 1. Synthesis of thread 4 and [2]rotaxane 5.

The ^{1}H NMR spectra (Figure 1) of thread **4**, rotaxane **5** and macrocycle **1** confirm the interlocked nature of **5** and show that in the neutral form of the rotaxane the macrocycle is largely localized on the peptide region of the thread (Scheme 2). The upfield shifts of the methylene resonances of the peptide station (H_a 0.20 ppm, H_c 0.32 ppm and H_e 0.46 ppm, Figure 1b cf Figure 1a) in **5** are characteristic[6] of aromatic shielding by the encapsulating macrocycle. The greater shielding of H_e suggests the macrocycle hydrogen bonds primarily to the central glycylglycine

carbonyl unit and only to a lesser extent to the comparatively hindered amide carbonyl adjacent to the stopper (Scheme 2).[6e] The ester carbonyl is a weaker hydrogen bond acceptor than the amides[11] and does not appear to contribute significantly to the intercomponent binding.

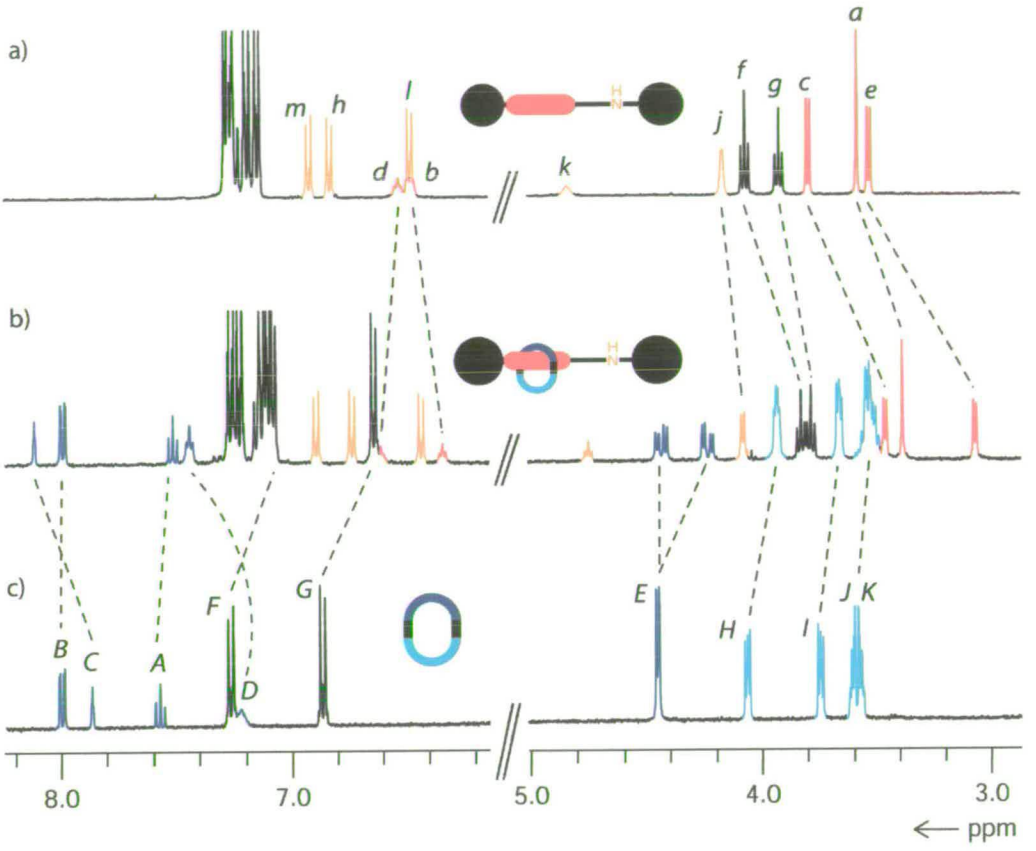
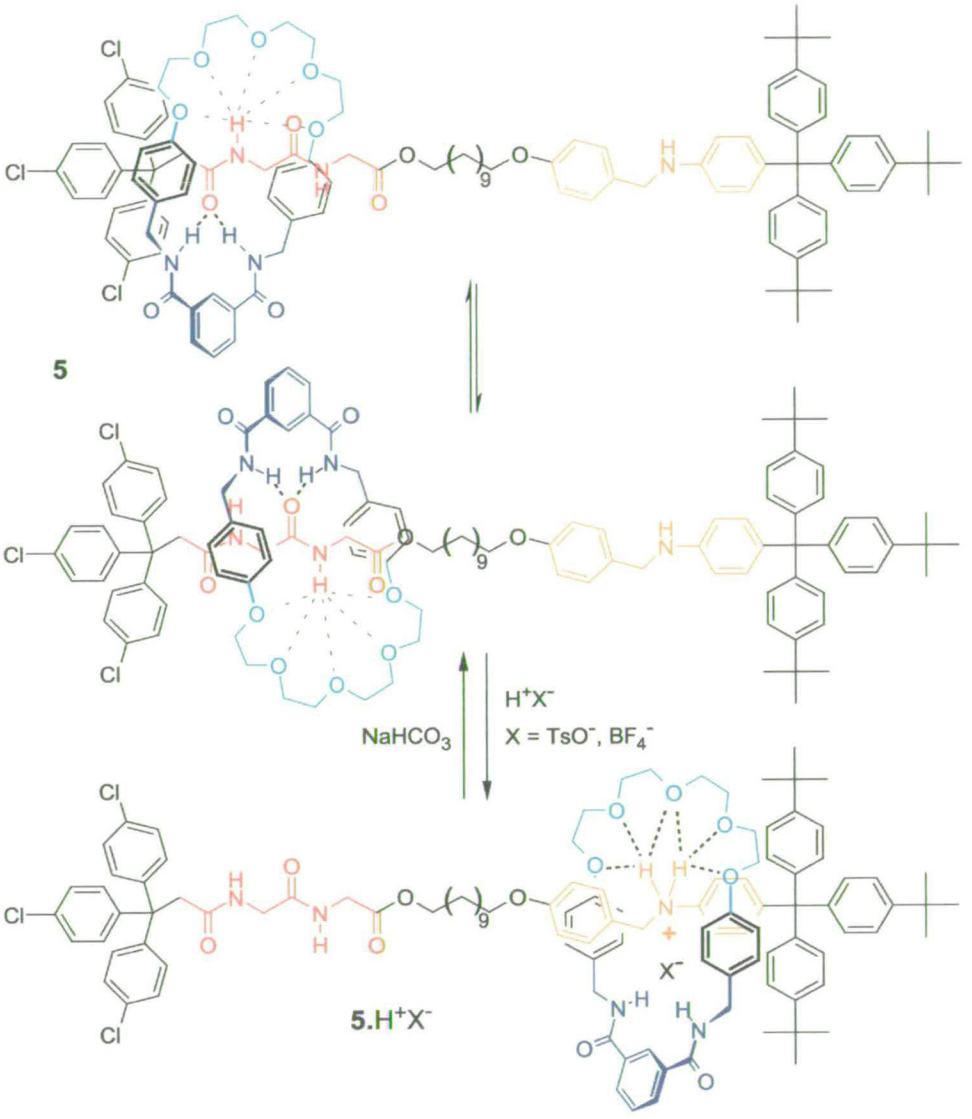


Figure 1. Partial ^{1}H NMR spectra (400 MHz, CD_3CN, 298 K) of a) thread **4**, b) rotaxane **5** and c) macrocycle **1**. The lettering corresponds to the proton assignments shown in Scheme 1.

The thread amide resonances, H_b and H_d, are shifted upfield (0.13 ppm) and downfield (0.10 ppm), respectively, in the rotaxane as a result of the collective influences of (i) aromatic shielding (upfield shift), (ii) hydrogen bonding to the macrocycle polyether oxygens (downfield shift) and (iii) inductive effects of the hydrogen bonding to the thread carbonyl groups (downfield shift). There is no evidence of any interaction between the macrocycle and the secondary amine group. For the rotaxane macrocycle, the 0.22 ppm (Figure 1b cf Figure 1c) downfield shift of the amide protons (H_D) indicates significant amide-amide hydrogen bonding with the thread. The polyether protons (H_H -H_K) are shifted upfield by roughly 0.1 ppm,

confirming that the polyether oxygens accept hydrogen bonds from the thread amides. As the thread is unsymmetrical, the faces of the macrocycle are diastereotopic in the rotaxane. This effect is seen most clearly in the ABX system of H_E (Figure 1b)



Scheme 2. Principal intercomponent binding modes of **5** in its neutral and protonated forms. For $X^- = TsO^-$ the macrocycle amides H-bond to the anion; for $X^- = BF_4^-$ they do not. Dashed lines are used to illustrate time-averaged hydrogen bond positions. The relative strength of the interactions is indicated by the weight of the dashed lines.

Protonation of **5** with one equivalent of *p*-toluenesulfonic acid results in significant changes to the ^1H NMR spectrum in CD_3CN (Figure 2b). Aromatic shielding is observed for the thread protons adjacent to the ammonium unit (H_J) and the macrocycle benzyl groups (H_F and H_G), indicating that the preferred position of the

ring is now over the anilide ammonium station (Scheme 2). Interestingly, the signals for the thread amide protons in the protonated rotaxane appear at 6.6 ppm, almost the same as in the neutral thread (**4**), whereas in the protonated thread these signals occur at 6.9 and 6.95 ppm, suggesting inter- or intramolecular interactions exist with the ammonium group in the protonated unrotaxanated thread. Thus the presence of the macrocycle effectively 'insulates' the amides of the thread from the ammonium centre.

The ring amide protons appear 0.2 ppm downfield in **5**.H^+ (Figure 2b) with respect to **5** (Figure 1b), which is likely due to hydrogen bonding to the tosylate counterion.[12] When an alternative, non-coordinating, acid such as HBF_4 is used, the H_D resonance appears at the same position as in the free macrocycle but the ring still resides over the ammonium group indicating that the macrocycle-anion interaction is not crucial for the shuttling process.

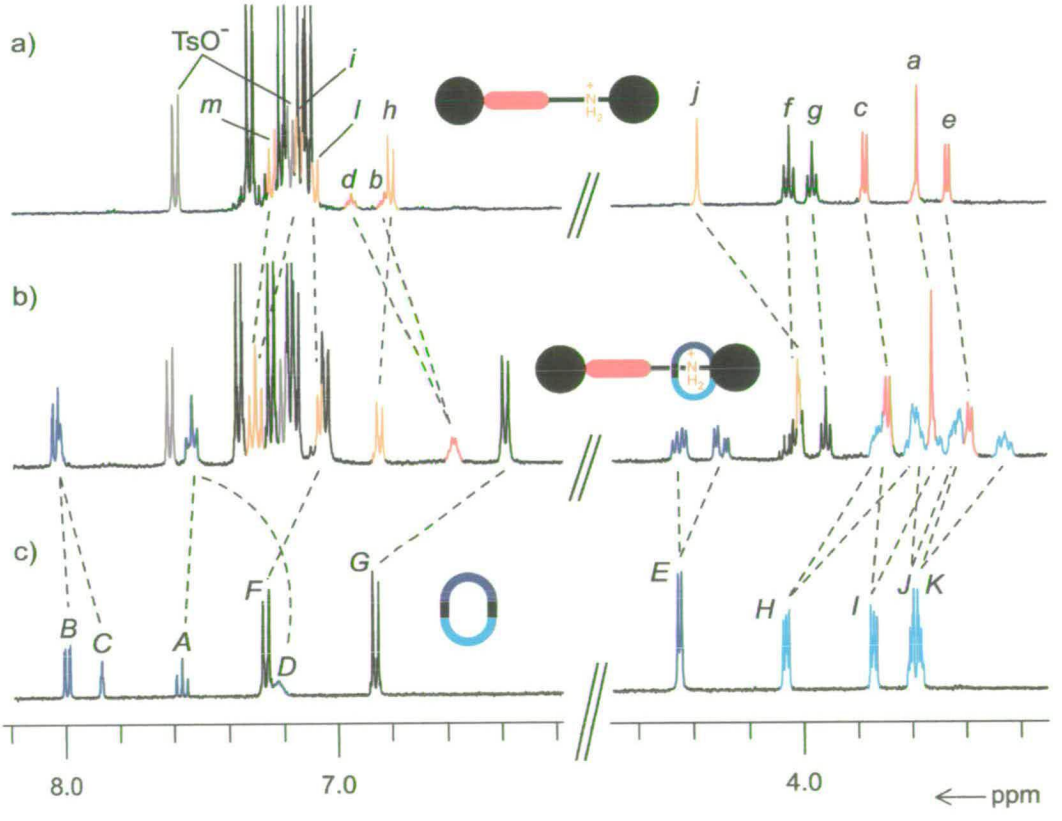


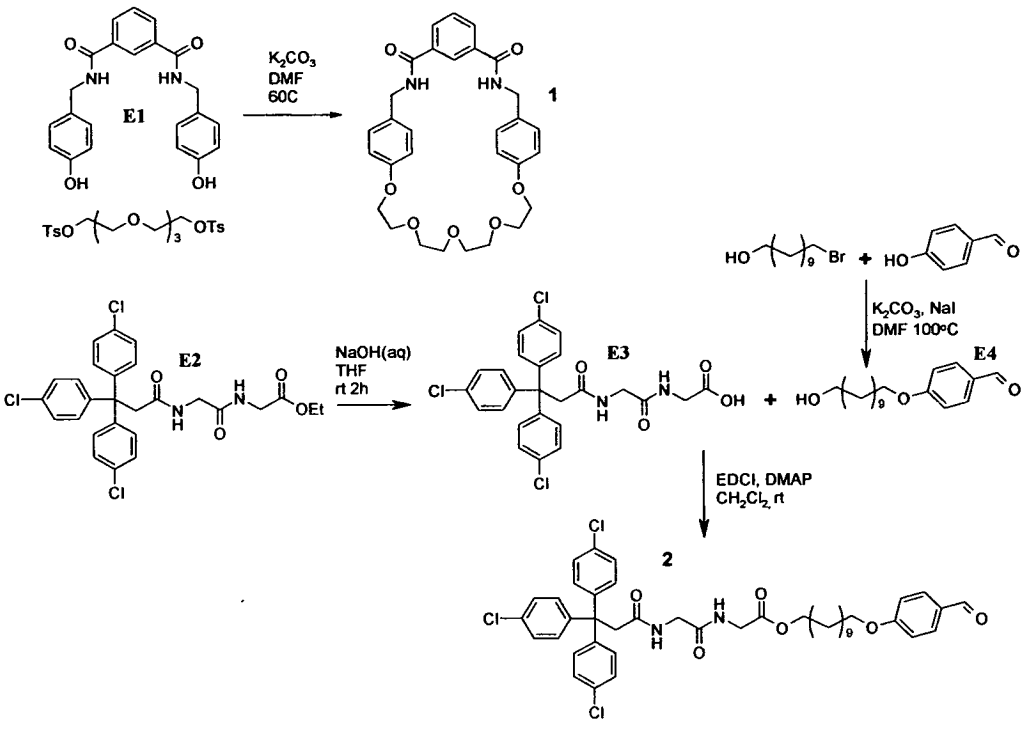
Figure 2. Partial ^{1}H NMR spectra (400 MHz, CD_3CN, 298 K) of a) protonated thread **4**.TsOH, b) protonated rotaxane **5**.TsOH and c) macrocycle **1**. The lettering corresponds to the proton assignments shown in Scheme 1.

In conclusion, rotaxane **5/5**.H^+ is a novel type of molecular shuttle that switches the macrocycle between two distinct translational forms with high positional integrity by exploiting both amide-amide hydrogen bonding and crown ether-ammonium cation interactions. The incorporation of multiple recognition motifs into molecular structures is likely to prove important in controlling relative component motion in systems that are more sophisticated than simple switches.[13]

4.3 Experimental Section

General

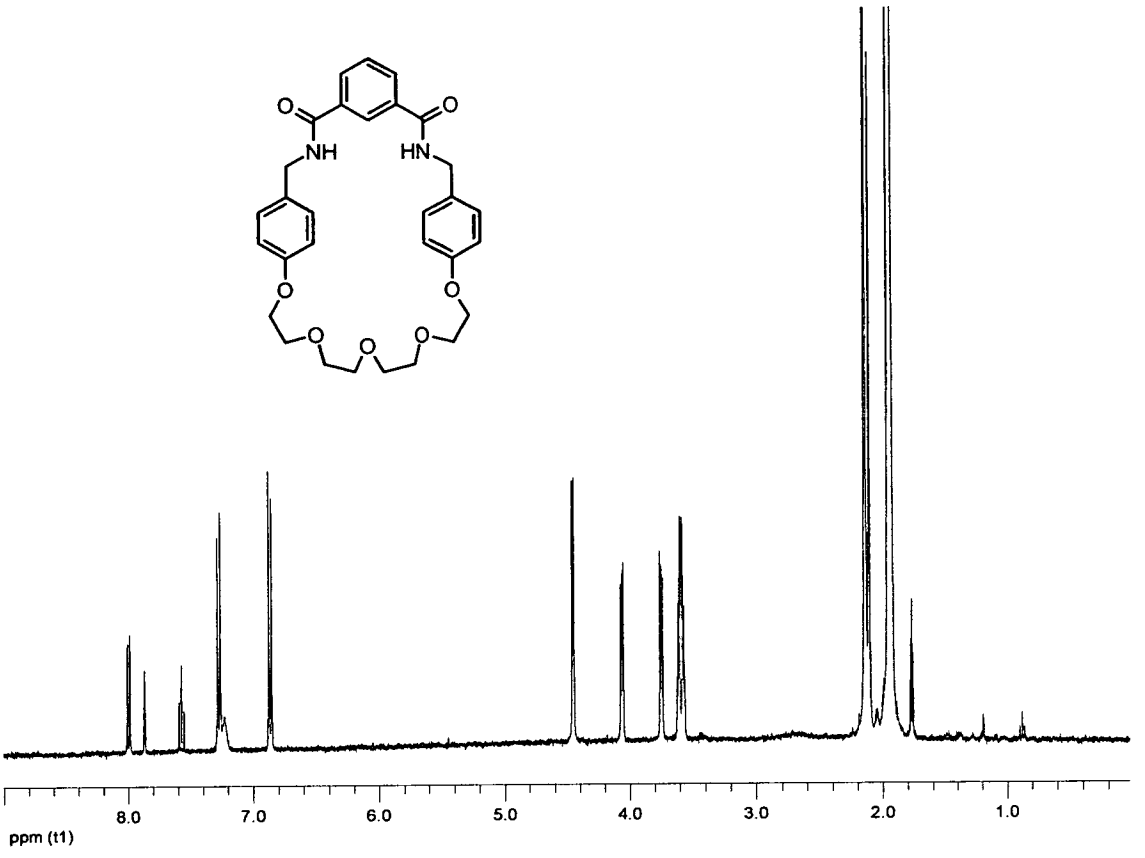
Unless otherwise stated, all reagents were purchased from Aldrich chemicals and used without further purification. Column chromatography was carried out using Kieselgel C60 (Merck, Germany) as the stationary phase. Thin layer chromatography was performed on precoated silica gel plates (0.25 mm thick, $60F_{254}$, Merck, Germany) and compounds were visualized under UV light. Eluent compositions for thin layer chromatography were selected so as to give Rf values of 0.2 unless otherwise indicated. All ^1H and ^{13}C NMR spectra were recorded on a Bruker AV 400 instrument, at a constant temperature of 298 K. Chemical shifts are reported in parts per million from high to low field and referenced to the residual solvent peak. Standard abbreviations indicating multiplicity are given: m = multiplet, br = broad, d = doublet, q = quadruplet, t = triplet, s = singlet. Coupling constants (*J*) are reported in hertz (Hz). Melting points were determined using a Sanyo Gallenkamp apparatus and are uncorrected. ESI mass spectrometry was performed with a Micromass Platform II Mass Spectrometer controlled using Masslynx v2.3 software. FAB accurate mass spectrometry was carried out by the University of Edinburgh services. Macrocycle precursor **E1** was prepared as described in reference 14. Glycylglycine derivative **E2** was prepared as described in reference 15. Bulky aniline derivative **3** was prepared as described in reference 16.



Scheme E1. Synthesis of **1**,**E3**, **E4** and **2**.

Macrocycle 1

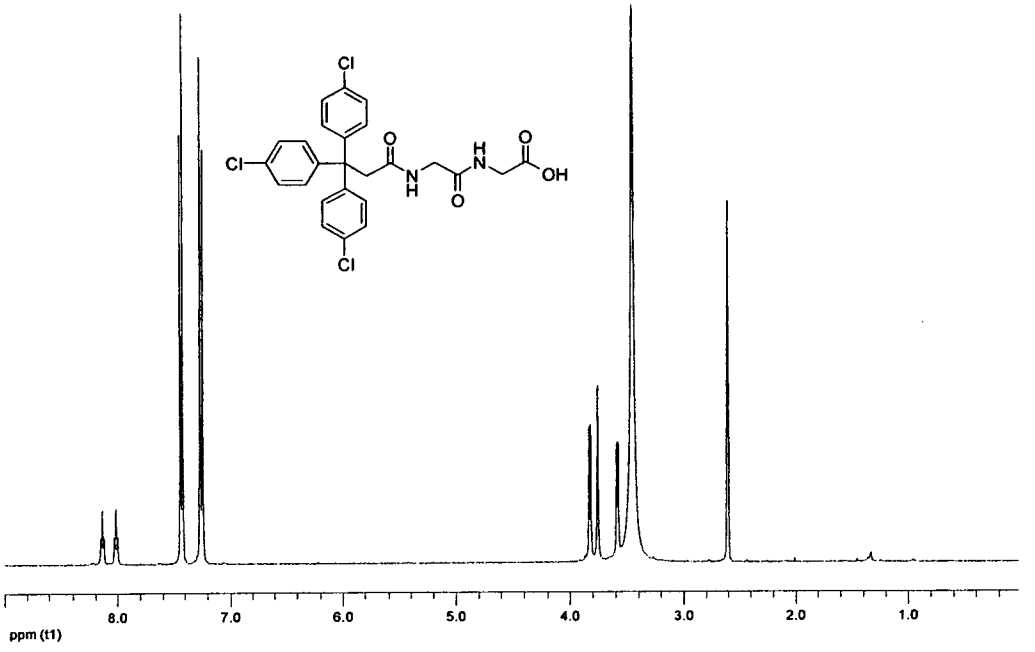
A solution of **E1** (752 mg, 2 mmol) tetraethyleneglycol di-*para*-toluenesulfonate (1.0 g, 2.0 mmol) in *N*,*N*-dimethylformamide (200 ml) containing solid potassium carbonate (2 g) was heated at 60 °C for 24 h. The solvent was removed under reduced pressure and the residue extracted with ethyl acetate (3 × 100 ml). The combined extracts were washed through a short plug of silica with additional ethyl acetate and then the solvent removed under reduced pressure to give macrocycle **1** as a colourless crystalline solid. Yield: 397 mg, 37%; m.p. 238-240 °C, ^{1}H NMR (400 MHz, CD_3CN) δ = 3.57 (m, 4H, OCH_2CH_2O), 3.61 (m, 4H, OCH_2CH_2O), 3.75 (m, 4H, OCH_2CH_2O), 4.06 (m, 4H, OCH_2CH_2O), 4.45 (d, 4H, *J* = 5.4 Hz, $ArCH_2$), 6.87 (d, 4H, J = 8.7 Hz, ArH), 7.22 (br s, 2H, CONH), 7.27 (d, 4H, *J* = 8.7 Hz, ArH), 7.57 (t, 1H, *J* = 7.7 Hz, ArH), 7.86 (s, 1H, ArH), 7.99 (d, 2H, *J* = 7.7 Hz, ArH); ^{13}C NMR (100 MHz, CD_3SOCD_3) δ = 42.2, 67.1, 68.8, 69.8, 69.9, 114.21, 125.5, 128.6, 129.1, 130.0, 131.1, 134.8, 157.4, 166.0; HR-MS (FAB) $C_{30}H_{34}N_2O_7$ calcd m/z $[(M + H)^+]$ = 535.2444, found 535.2445.



^{1}H NMR, 400 MHz, CD_3CN, 298 K

***N-Tris*(4-chlorophenyl)propionyl glycylglycine E3**

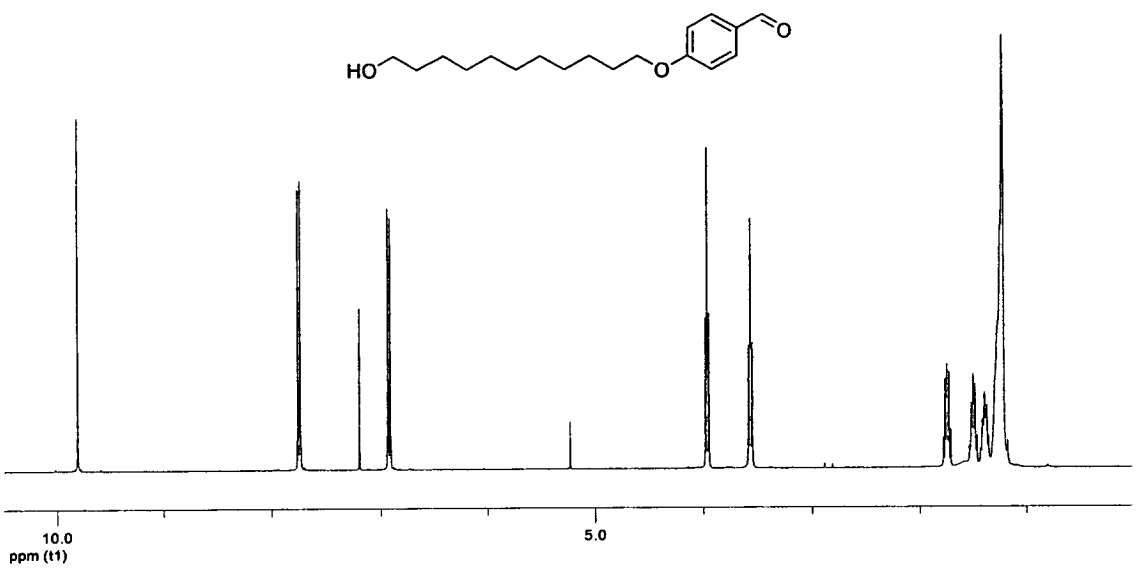
To a solution of *N-tris*(4-chlorophenyl)propionyl glycylglycine ethyl ester (**E2**) (2.74 g, 5.00 mmol) in THF (100 ml) was added 1 M NaOH(aq) (10 mmol). The mixture was stirred for 24 hours at room temperature. After this time the mixture was neutralized by the dropwise addition of 1 M HCl(aq). The solvent was removed under reduced pressure and the resultant solid partitioned between ethyl acetate and water. The organic phase was dried ($MgSO_4$) and the solvent removed under reduced pressure to give **E3** as a colourless solid. Yield: 2.538 g, 98%; m.p. 240 °C (decomp); ^{1}H NMR (400 MHz, CD_3SOCD_3) δ = 3.47 (d, 2H, J = 5.7 Hz CONHC$\underline{H_2}$CO), 3.65 (s, 2H, C$\underline{H_2}$CONH), 3.72 (d, 2H, J = 5.9 Hz CONHC$\underline{H_2}$CO), 7.15 (d, 6H, J = 8.8 Hz, ArH), 7.33 (d, 6H, J = 8.8 Hz, ArH), 12.58 (br s, 1H, COOH); ^{13}C NMR (100 MHz, CD_3SOCD_3) δ = 41.6, 45.7, 54.5, 59.7, 127.6, 130.81, 130.85, 145.3, 156.7, 168.9, 169.6, 171.0; HR-MS (FAB) $C_{25}H_{20}{}^{35}Cl_3N_2O_4$ calcd m/z [(M + H)$^+$] = 519.0645, found 519.0646.



^{1}H NMR, 400 MHz, CD_3SOCD_3, 298 K

4-(11-hydroxyundecyloxy)-benzaldehyde E4

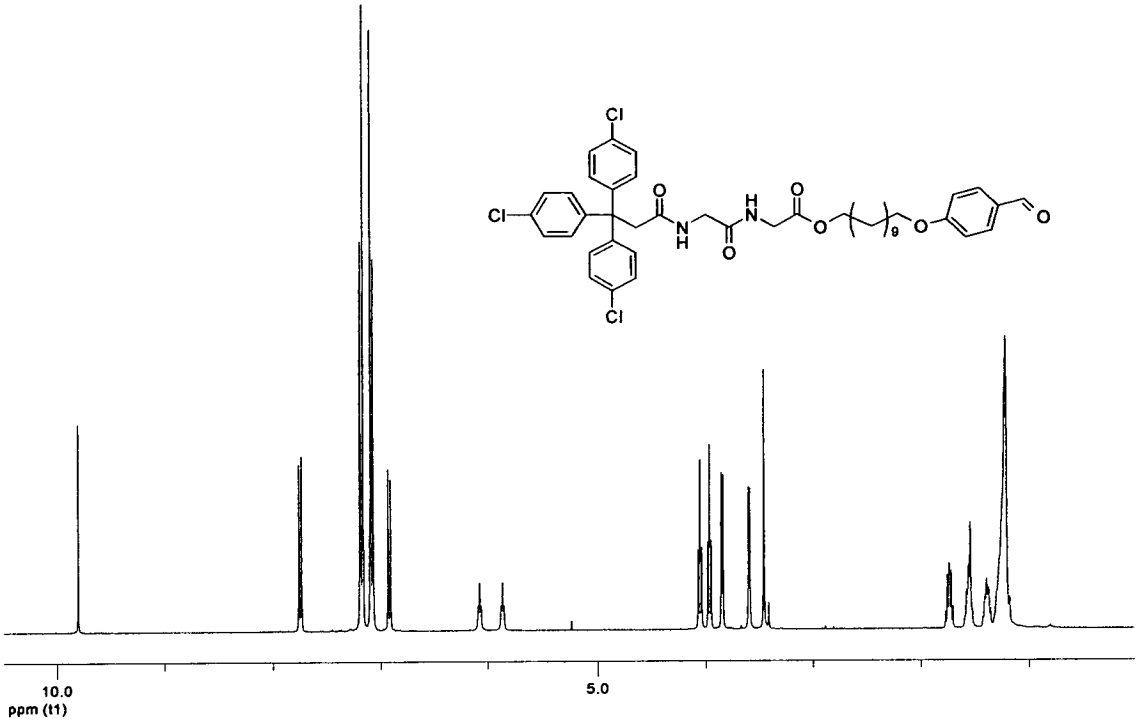
A solution of 4-hydroxybenzaldehyde (1.32 g, 5.00 mmol) and 11-bromoundec-1-ol (1.26 g, 5 mmol) in DMF (50 ml) containing solid potassium carbonate (10 g) and sodium iodide (0.1 g) was heated at 100 °C for 12 h. After this time the solution was filtered and the solvent removed under reduced pressure. The resultant solid was dissolved in CH_2Cl_2 and washed with water. The organic phase was dried ($MgSO_4$) and the solvent removed under reduced pressure to give **E4** as an off-white solid. Yield: 1.508 g, 97%; m.p. 68-70 °C ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.17-1.34 (br m 6 × CH_2), 1.39 (m, CH_2), 1.49 (m, CH_2), 1.74 (m, CH_2), 3.57 (t, 2H, J = 6.6 Hz, $HOC\underline{H}_2$), 3.97 (t, 2H, J = 6.6 Hz, $ArOC\underline{H}_2$), 6.92 (d, 2H, J = 8.7 Hz, ArH), 7.76 (d, 2H, J = 8.8 Hz, ArH), 9.81 (s, 1H, ArCHO); ^{13}C NMR (100 MHz, CD_3Cl) δ = 25.7, 26.0, 29.1, 29.3, 29.4, 29.50, 29.53, 29.6, 32.8, 63.1, 68.4, 114.7, 129.7, 132.0, 164.3, 190.9; HR-MS (FAB) $C_{18}H_{28}O_3$ calcd m/z $[(M + H)^+]$ = 293.2117, found 293.2114.



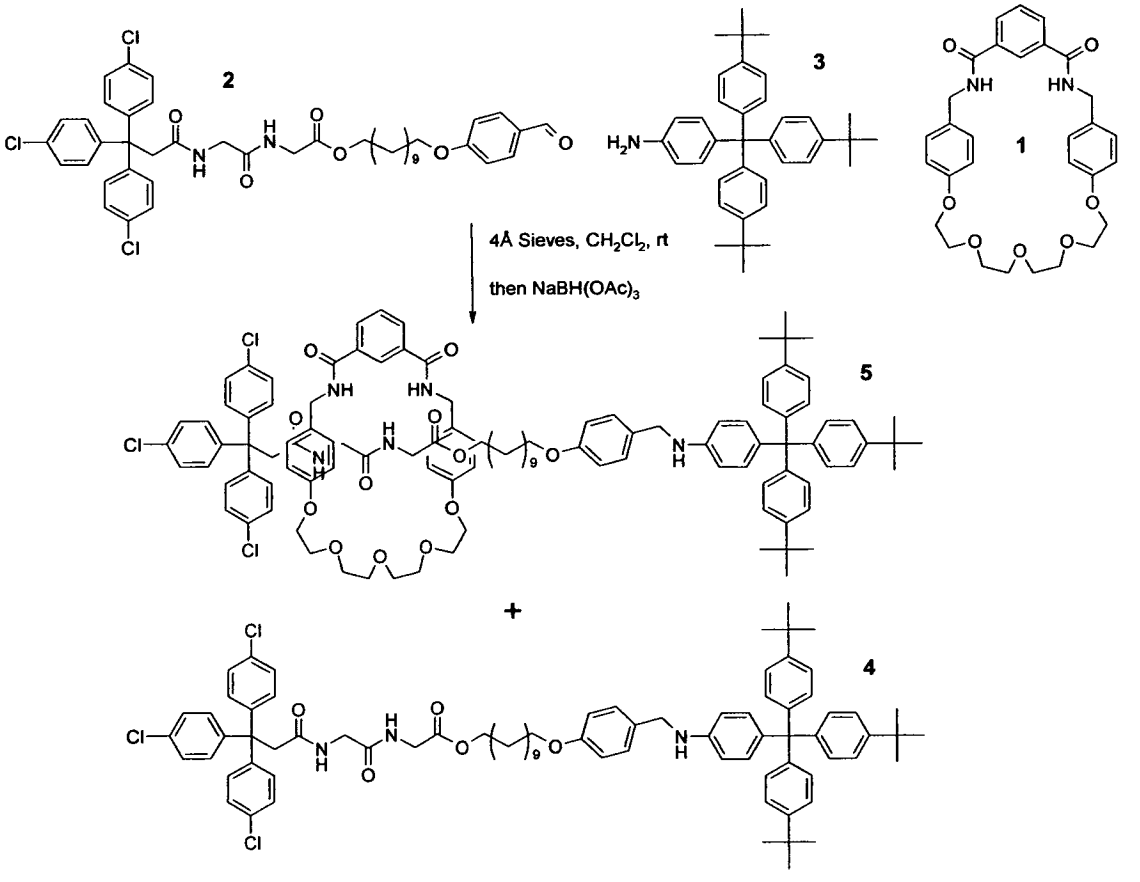
^{1}H NMR, 400 MHz, $CDCl_3$, 298 K. Peak at ca 5.3 ppm is residual CH_2Cl_2.

Mono stoppered thread 2

To a solution of **E3** (518 mg, 1.00 mmol), **E4** (322 mg, 1.10 mmol) and DMAP (1.2 mmol) in acetone (100 ml) at 0 °C was added EDCI (1.2 mmol). The reaction mixture was allowed to warm to room temperature and was stirred for 24 h. After this time the solvent was removed under reduced pressure and the material redissolved in CH_2Cl_2 (200 ml). The solution was washed with 1 M HCl(aq) then brine. The organic layer was dried ($MgSO_4$) then the solvent removed under reduced pressure and the resultant material purified by silica chromatography, using 5% acetone in CH_2Cl_2 as the eluent to give **2** as a colourless solid. Yield: 525 mg, 66%; m.p. 100-106 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 1.23-1.40 (br m 6 × CH_2), 1.46 (m, CH_2), 1.63 (m, CH_2), 1.81 (m, CH_2), 3.53 (s, 2H, C$\underline{H_2}$CONH), 3.67 (d, 2H, J = 5.2 Hz, CONHC$\underline{H_2}$CO), 3.93 (d, 2H, J = 5.3 Hz, CONHC$\underline{H_2}$CO), 4.04 (t, 2H, J = 6.5 Hz, OC$\underline{H_2}$CH$_2$), 4.13 (t, 2H, J = 6.7 Hz, OC$\underline{H_2}$CH$_2$), 5.91 (t, 1H, J = 5.2 Hz, CONH), 6.13 (t, 1H, J = 5.2 Hz, CONH), 6.99 (d, 2H, J = 8.7 Hz, ArH), 7.15 (d, 6H, J = 8.8 Hz, ArH), 7.25 (d, 6H, J = 8.8 Hz, ArH), 7.82 (d, 2H, J = 8.7 Hz, ArH), 9.88 (s, 1H, CHO); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 25.8, 25.9, 28.5, 29.0, 29.2, 29.3, 29.45, 29.48, 29.49, 41.1, 43.1, 47.6, 55.1, 65.8, 68.4, 114.7, 128.3, 129.7, 130.3, 132.0, 132.7, 144.1, 157.8, 164.3, 168.4, 169.6, 170.0, 190.9; HR-MS (FAB) $C_{43}H_{47}{}^{35}Cl_3N_2O_6$ calcd m/z [(M + H)$^+$] = 793.2578, found 793.2571.



^{1}H NMR, 400 MHz, $CDCl_3$, 298 K



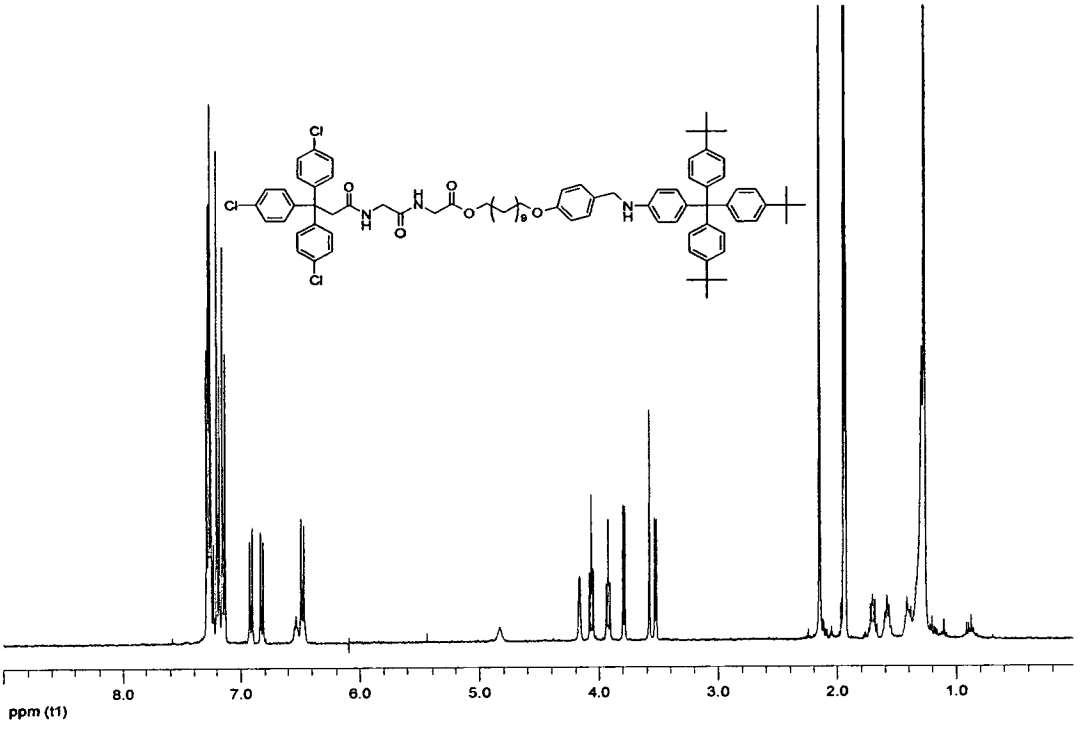
Scheme E2. Synthesis of 4 and 5.

Thread 4 and Rotaxane 5

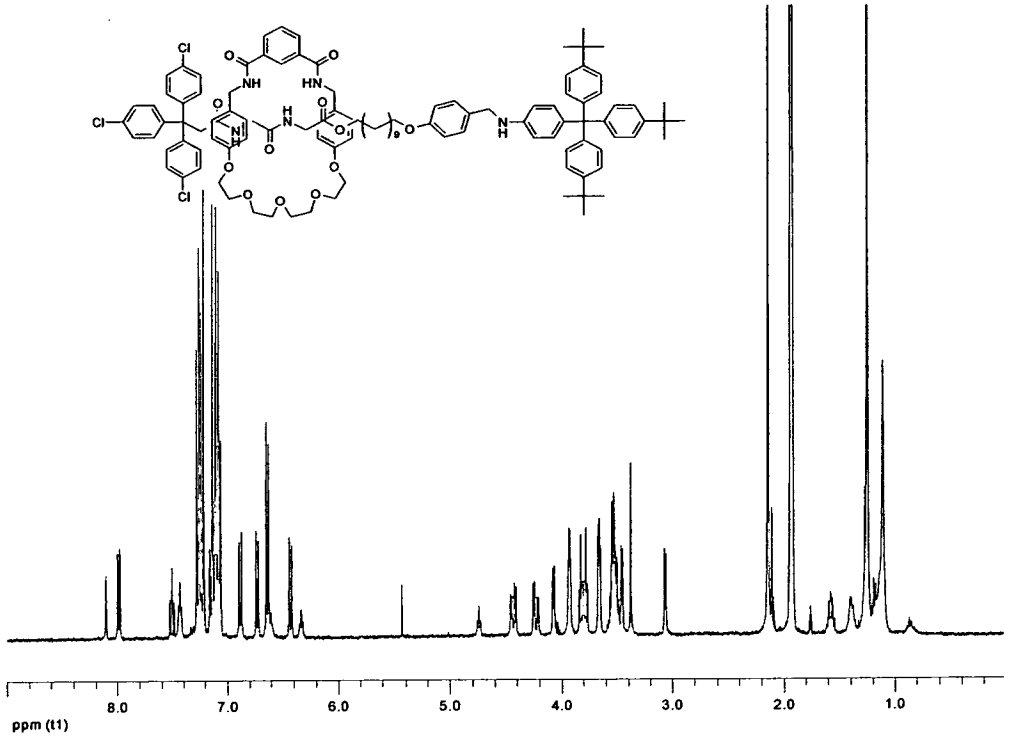
A solution of macrocycle **1** (149 mg, 0.280 mmol), thread precursor **2** (222 mg, 0.28 mmol) and amine **3** (145 mg, 0.280 mmol) in chloroform containing activated 4 Å molecular sieves was stirred for 96 h at room temperature. Sodium triacetoxyborohydride (594 mg, 2.80 mmol) was added and the mixture stirred for a further 4 hours. The reaction mixture was loaded directly onto a silica column and eluted with 2% methanol in chloroform to yield **4** (233 mg, Rf = 0.35, 65%) and **5** (157 mg, Rf = 0.2, 31%). Thread **4**; ^{1}H NMR (400 MHz, CD_3CN) δ = 1.23-1.36 (br m 6 × CH_2), 1.26 (s, 27H, $C(CH_3)_3$) 1.41 (m, CH_2), 1.59 (m, CH_2), 1.71 (m, CH_2), 3.53 (d, 2H, *J* = 5.7 Hz, $CONHC\underline{H}_2CO$), 3.58 (s, 2H, $C\underline{H}_2CONH$), 3.79 (d, 2H, *J* = 5.9 Hz, $CONHC\underline{H}_2CO$), 3.92 (t, 2H, *J* = 6.5 Hz, $OC\underline{H}_2CH_2$), 4.06 (t, 2H, *J* = 6.6 Hz, $OC\underline{H}_2CH_2$), 4.17 (br, 2H, $ArC\underline{H}_2NH$), 4.84 (br, 1H, $ArCH_2N\underline{H}$), 6.47 (br m, 1H, CONH), 6.48 (d, 2H, *J* = 8.8 Hz, ArH), 6.53 (br m, 1H, CONH), 6.83 (d, 2H, *J* = 8.6 Hz, ArH), 6.92 (d, 2H, *J* = 8.8 Hz, ArH), 7.12-7.31 (m, 24H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 25.8, 26.1, 28.5, 29.2, 29.3, 29.4, 29.5, 29.5 29.7, 31.4, 34.3, 41.1, 43.0, 47.6, 55.1, 60.4, 62.9, 65.9, 68.0, 111.5, 114.6, 123.9, 128.3, 129.0, 130.3, 130.7, 131.3, 132.0, 132.7, 136.5, 144.1, 144.4, 145.9, 148.1, 158.4, 168.4, 169.6, 170.0; HR-MS (FAB) $C_{80}H_{92}{}^{35}Cl_3N_3O_5$ calcd m/z [(M + H)$^+$] = 1280.6181, found 1280.6183.

Rotaxane **5**; ^{1}H NMR (400 MHz, CD_3CN) δ = 1.08-1.22 (m, 14H, 7 × CH_2), 1.25 (s, 27H, $C(CH_3)_3$), 1.40 (m, 2H, CH_2), 1.58 (m, 2H, CH_2), 3.07 (d, 2H, *J* = 5.3 Hz, $CONHC\underline{H}_2CO$), 3.38 (s, 2H, $C\underline{H}_2CONH$), 3.46 (d, 2H, *J* = 5.4 Hz, $CONHC\underline{H}_2CO$), 3.48-3.58 (m, 8H, $CH_2OC\underline{H}_2C\underline{H}_2O$), 3.66 (m, 4H, $ArOCH_2C\underline{H}_2O$), 3.78 (t, 2H, *J* = 6.5 Hz, $OC\underline{H}_2CH_2$), 3.82 (t, 2H, *J* = 6.7 Hz, $OC\underline{H}_2CH_2$), 3.93 (m, 4H, $ArOC\underline{H}_2CH_2O$), 4.08 (d, 2H, *J* = 5.7 Hz, $ArC\underline{H}_2NH$), 4.33 (ddd, 4H, J_1 = 64.8 Hz, J_2 = 14.2 Hz, J_3 = 6.1 Hz, $CONHC\underline{H}_2Ar$), 4.75 (t, 1H, $ArCH_2N\underline{H}$), 6.33 (t, 1H, *J* = 5.4 Hz, CONH), 6.43 (d, 2H, *J* = 8.8 Hz, ArH), 6.60 (t, 1H, *J* = 5.0 Hz, CONH), 6.64 (d, 4H, *J* = 8.6 Hz, ArH), 6.74 (d, 2H, *J* = 8.6 Hz, ArH), 6.89 (d, 2H, *J* = 8.7 Hz, ArH), 7.05-7.17 (m, 18H, ArH), 7.20-7.29 (m, 12H, ArH), 7.44 (t, 2H, *J* = 5.8 Hz, CONH), 7.51 (t, 1H, *J* = 7.7 Hz, ArH), 7.99 (d, 2H, *J* = 7.7 Hz, ArH), 8.11 (s, 1H, ArH) ; ^{13}C NMR (100 MHz, $CDCl_3$) δ = 25.8, 26.1, 28.5, 29.3, 29.39, 29.41, 29.6, 29.68, 29.71, 31.4, 34.3, 41.1, 41.3, 44.1, 46.8, 48.0, 54.8, 62.9, 65.5, 67.1, 68.0, 70.0, 70.1, 70.5,

111.5, 114.5, 123.3, 123.9, 124.1, 128.1, 128.4, 129.0, 129.2, 129.8, 130.4, 130.7, 131.3, 131.9, 132.1, 132.5, 133.8, 136.5, 144.3, 144.4, 145.9, 148.1, 158.0, 158.4, 166.0, 169.8, 169.1, 169.3; HR-MS (FAB) $^{12}C_{109}{}^{13}CH_{126}{}^{35}Cl_3N_5O_{12}$ calcd m/z [(M + H)$^+$] =1815.8580, found 1815.8556.



^{1}H NMR, 400 MHz, CD_3CN, 298 K



^{1}H NMR, 400 MHz, CD_3CN, 298 K

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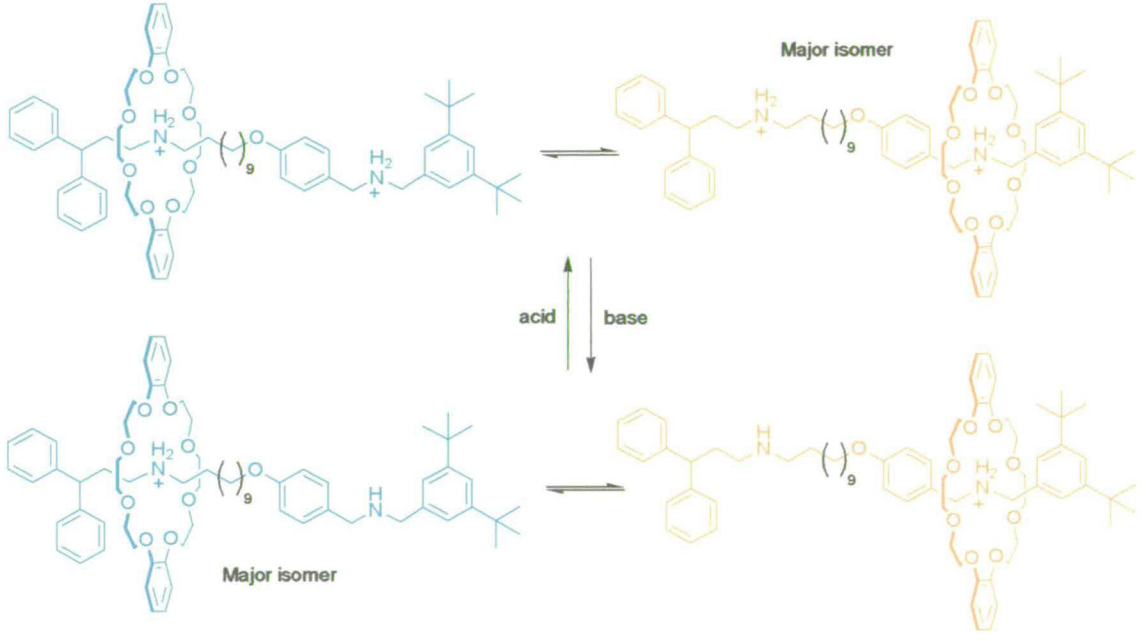
Chapter 5 Synopsis

This chapter details the synthesis and operation of a pH-controllable molecular shuttle in which the average position of a crown ether macrocycle can be varied between two different dialkylammonium stations by protonation or deprotonation. In the doubly protonated form of the shuttle the macrocycle resides primarily on the more acidic dibenzylammonium station, though a proportion of the macrocycle population can be found over the diethylammonium station. In the singly protonated form of the shuttle the situation is reversed, with the majority of the macrocycle population residing over the diethylammonium station. A small proportion of the other translational isomer is still observed, though in this instance it must arise from the translocation of both the macrocycle and the ammonium proton.



Chapter 5

A Bis-Dialkylammonium pH Shuttle

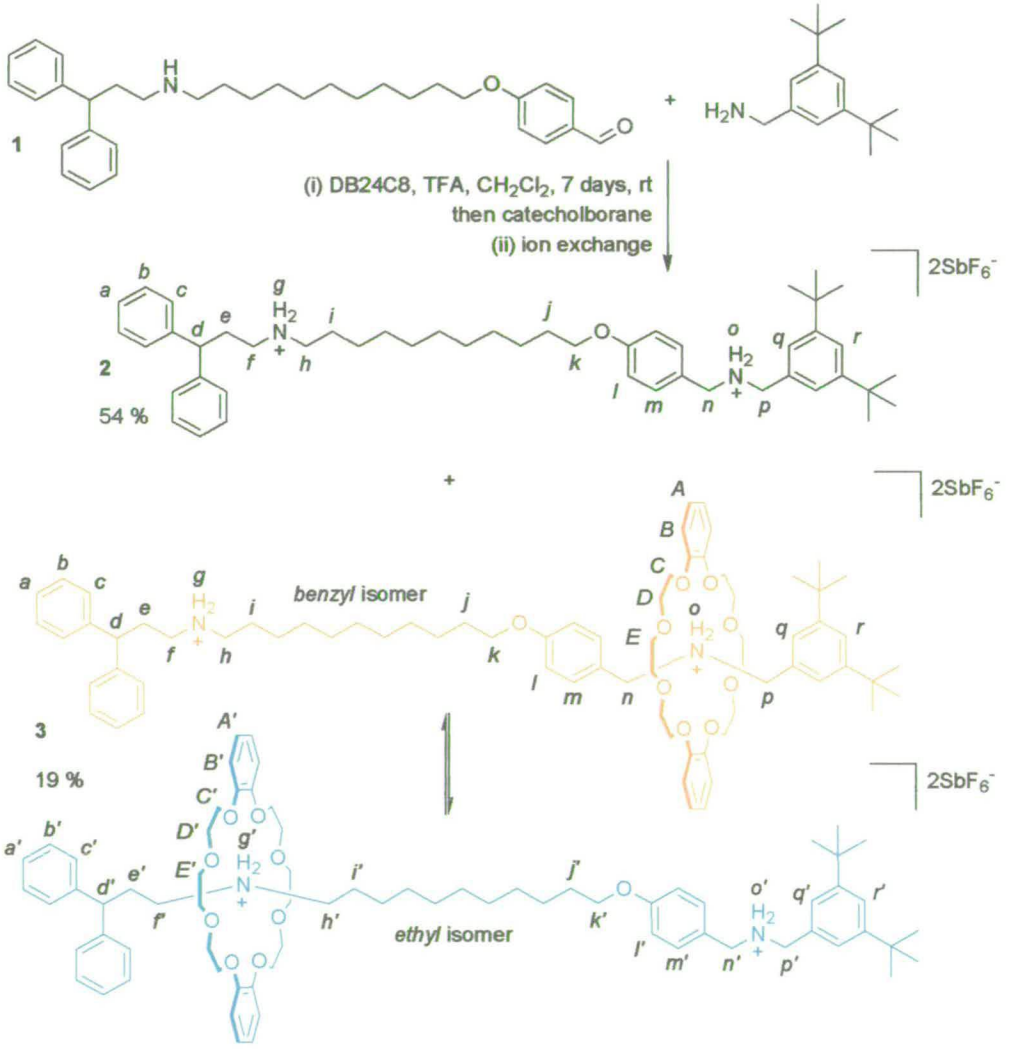
5.1 Introduction

Recent years have seen the synthesis of addressable molecular shuttles[1] that operate *via* a variety of different stimuli. Controlled submolecular motion has been achieved in structurally diverse molecular shuttles using such inputs as changes in conformation,[2] oxidation state,[3] covalent constitution[4] and binding events.[5] One of the chemical stimuli most frequently exploited for this purpose is a change in the protonation level of the molecule.[6] The dialkylammonium-crown ether recognition pair has been widely employed in the synthesis of interlocked molecules,[7] and naturally lends itself to the construction of protonation controlled molecular shuttles.[6a-d,f] Previous examples of this type of shuttle have all functioned by switching the position of a crown ether macrocycle between an amine/ammonium group and another pH independent station derived from an *N*-alkylpyridinium moiety. We herein report the synthesis of a molecular shuttle in which a crown ether macrocycle can be switched between two dialkylammonium binding sites of differing acidities.

The degree of inclusion of a dialkylammonium species within a [24]crown-8 type macrocycle is known to be strongly dependant on ability of the alkyl substituents to moderate the hydrogen-bond donating character of the ammonium group.[8] Early investigations showed that dibenzylammonium (DBA^+) species are bound more strongly than dibutylammonium ones within a dibenzo[24]crown-8 (DB24C8) macrocycle, partly as a consequence of additional favourable aromatic interactions and a higher degree of preorganisation, but primarily because of the disparity in the ability of the two ammonium species to act as hydrogen bond donors. Similarly, DBA^+ species bearing electron donating substituents on their aromatic rings are bound less strongly than those bearing electron withdrawing substituents.[8d] The hydrogen bond acidity and Brönsted acidity of an ammonium species are closely linked, being governed by the same electronic factors. On this basis we decided to investigate whether the difference in hydrogen bond and Brönsted[9] acidity between a DBA^+ and a diethylammonium derived station could be exploited as the basis of a protonation-controlled molecular shuttle.

5.2 Results and Discussion

The rotaxane **3** was designed as a readily accessible target incorporating all of the required structural features. A reductive amination reaction was chosen as the key synthetic step, allowing the introduction of one of the ammonium stations at the same time as forming the rotaxane (scheme 1).[6c,10] Of the two possible disconnections presented by this approach, the one at the DBA^+ station allows the use of the aromatic aldehyde, which is stable and undergoes facile imine-forming reactions. The penalty for this approach is that the lower affinity diethylammonium station must be used as the template for the macrocycle.



Scheme 1. Synthesis of thread **2** and rotaxane **3**.

The aldehyde-terminated half-stoppered thread **1** was prepared in four steps from commercially available materials (see Experimental Section). A solution of **1**,

DB24C8, 3,5-di-*tert*-butylbenzylamine and two equivalents of trifluoroacetic acid in dichloromethane was stirred at room temperature for 1 week. At low pH values imine formation is slow,[11] but an excess of acid is necessary to maintain the ammonium template required for inclusion of the thread in the DB24C8 macrocycle.[12] After one week the imine was reduced to the corresponding amine using catecholborane. Chromatographic purification of the final product proved problematic. It was eventually found that pretreating a silica preparative TLC plate with a solution of ammonium chloride prior to chromatography allowed the separation of the rotaxane product from the non-interlocked thread. Following chromatography the rotaxane was ion-exchanged to the SbF_6 salt to ensure uniformity, giving a pure sample of rotaxane **3**.$(HSbF_6)_2$ in a yield of 19%.

Comparison of the ^1H NMR spectrum of rotaxane **3**.$(HSbF_6)_2$ with its non-interlocked components (Figure 1) confirms the interlocked nature of the product. Rotaxane **3**.$(HSbF_6)_2$ exists as two translational co-conformational isomers that interconvert at a rate slower than the NMR timescale, and therefore appear as separate sets of signals. In the most abundant translational isomer (orange resonances in Figure 1b), the signals for H_p and H_n are shifted downfield by approximately 0.25 ppm compared to those of the non-interlocked thread, an effect characteristic of the DBA^+ station being occupied by the DB24C8 macrocycle. This is further supported by the presence of aromatic shielding effects in the H_l, H_m, H_q and H_r resonances due to intercomponent aromatic stacking between the aromatic rings of the DBA^+ station and the macrocycle. The H_l and H_m resonances are shifted upfield by around 0.3 ppm and 0.1 ppm, respectively, while the resonances for H_q and H_r are shifted upfield to a much smaller degree, presumably as a consequence of the steric interference of the flanking *tert*-butyl groups disfavouring aromatic stacking with the macrocycle. A slight upfield shift is exhibited by the macrocycle catechol protons H_A and H_B compared to the free macrocycle, again indicating the presence of aromatic stacking. The signals for the diethylammonium station of the major translational isomer (H_d, H_e, H_f and H_h) closely resemble the corresponding resonances of the non-interlocked thread. The minor translational isomer of **3**.$(HSbF_6)_2$ (blue resonances in Figure 1b) exhibits a downfield shift of approximately 0.1 ppm for the signals arising from the

methylene units adjacent to the ammonium group of the diethylammonium station ($H_{f'}$ and $H_{h'}$), an effect that is again indicative of hydrogen bonding to the macrocycle. The $H_{A'}$ and $H_{B'}$ resonances of the macrocycle are shifted slightly downfield, indicating that the inductive effects of hydrogen bonding dominate over aromatic stacking interactions. Aromatic shielding effects are evident in

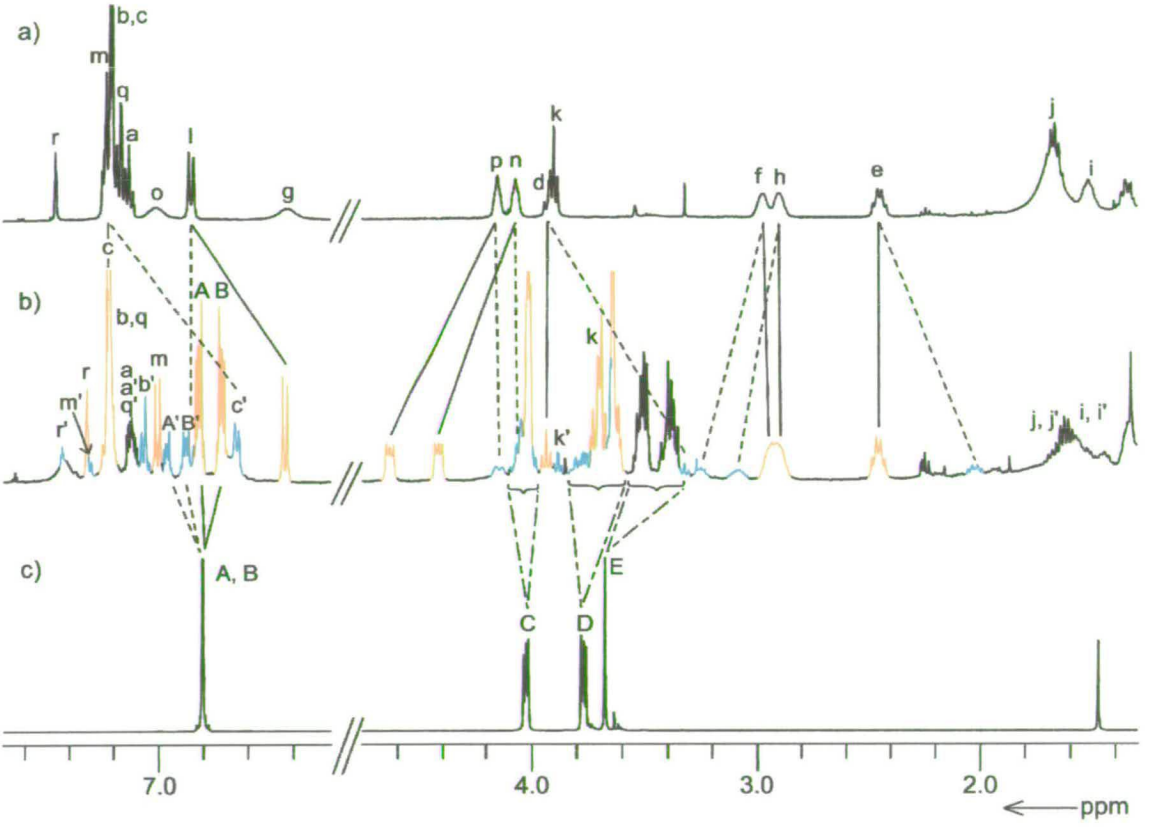


Figure 1. Partial ^{1}H NMR spectra (400 MHz, 298 K, CD_2Cl_2) of a) **2**.$(HSbF_6)_2$, b) **3**.$(HSbF_6)_2$ and c) DB24C8. Peaks corresponding to the *benzyl* translational isomer of **3**.$(HSbF_6)_2$ are coloured orange, and are compared with related signals in spectra a) and c) with solid lines. Signals arising from the *ethyl* isomer are shown in blue, and are marked with dashed lines. Peaks arising from overlapping resonances of both isomers have not been colour coded. Signal assignments refer to the proton labels shown in Scheme 1.

the resonances close to the diethylammonium station, particularly those on the 'stopper side'. The $H_{c'}$, $H_{d'}$ and $H_{e'}$ resonances are shifted upfield by 0.3, 0.3 and 0.25 ppm respectively. Less effect is evident in the $H_{i'}$ resonance, indicating that the macrocycle is held close to the phenyl groups of the stopper by aromatic stacking. The signals for the DBA^+ station ($H_{l'}$, $H_{m'}$, $H_{n'}$, $H_{p'}$, $H_{q'}$ and $H_{r'}$) of the minor isomer

are nearly identical to those of the non-interlocked thread. In both translational isomers the ethylene protons of the macrocycle (H_C, H_D, H_E, $H_{C'}$, $H_{D'}$ and $H_{E'}$) are diastereotopic due to the non-symmetrical nature of the thread, and result in complex and overlapping sets of signals.

These observations are consistent with rotaxane **3**.$(HSbF_6)_2$ existing as a mixture of translational isomers, the major one being that in which the DBA^+ station is occupied (*benzyl* isomer in Scheme 1), and the minor one having the macrocycle over the diethylammonium station (*ethyl* isomer in Scheme 1). The population distribution of approximately 2:1 in favour of the benzyl isomer reflects the differing hydrogen bond-donor strengths of the two ammonium groups. Interconversion of the isomers is slow compared to the NMR timescale due to the steric impediment presented by the benzyl group of the DBA^+ station.[8a] The stations in either translational isomer are effectively isolated from each other, i.e. the unoccupied stations are not perturbed by any folding or intermolecular association with the occupied ones, and therefore resemble the non-interlocked thread.

Rotaxane **3**.$(HSbF_6)_2$ was treated with an excess of a solid-supported tertiary amine base. This was found to result in the loss of only one of the two ammonium protons of the rotaxane, whereas the thread **2**.$(HSbF_6)_2$ was completely neutralised under identical conditions. The reduced acidity of **3**.$(HSbF_6)_2$ is a consequence of the additional stability afforded to the ammonium group by the encircling crown ether macrocycle.[13] The macrocycle is only able to 'protect' a single ammonium group from deprotonation, therefore treatment of **3**.$(HSbF_6)_2$ with base results in the mono-protonated rotaxane **3**.$HSbF_6$. A comparison of the ^1H NMR spectra of the rotaxanes **3**.$(HSbF_6)_2$ and **3**.$HSbF_6$ and the threads **2**.$(HSbF_6)_2$ and **2** illustrates the effect of changing the protonation level of the shuttle (Figure 2).

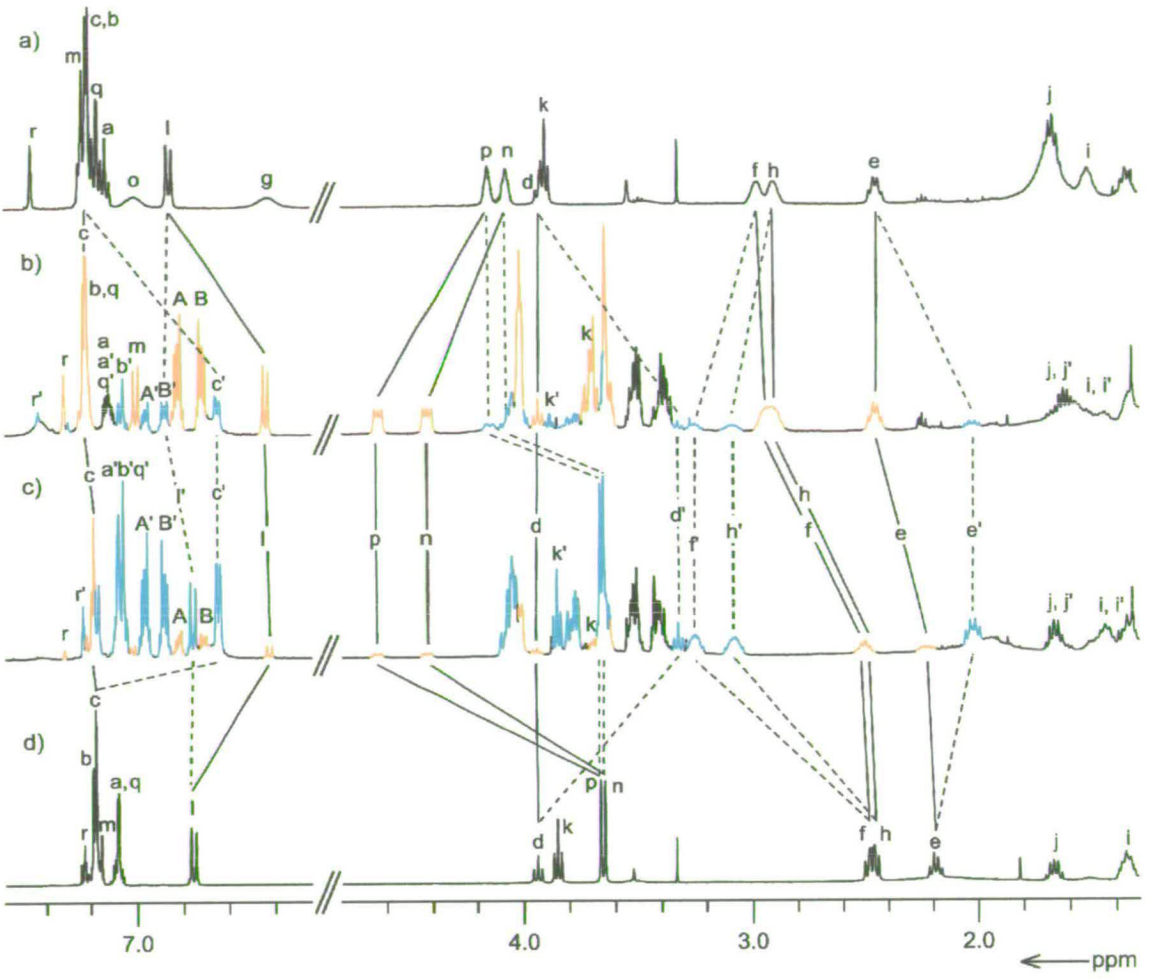
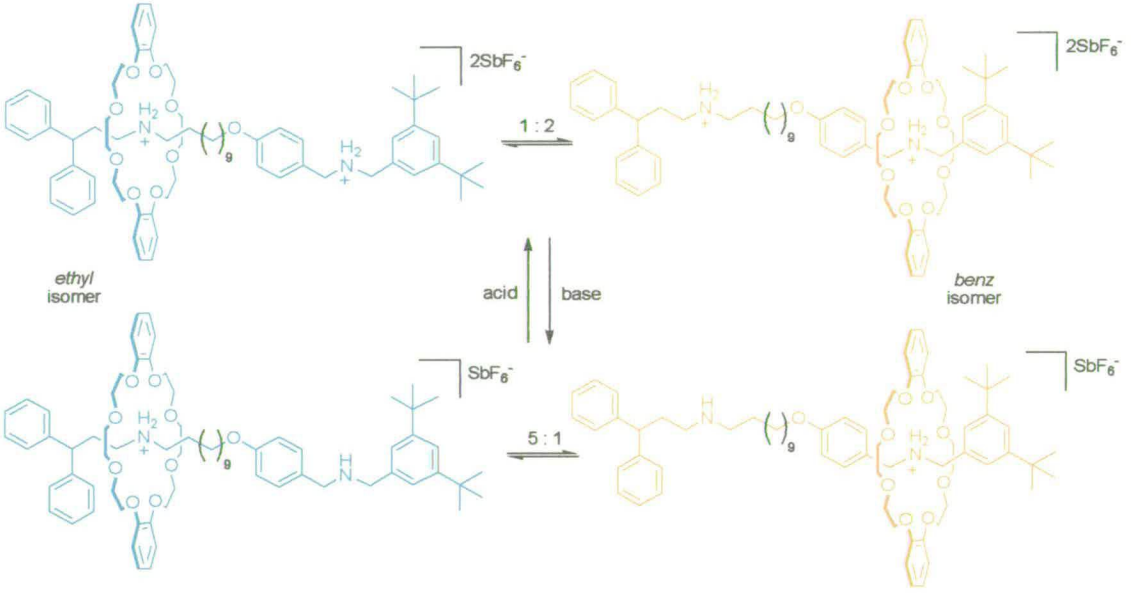


Figure 2. Partial ^{1}H NMR spectra (400 MHz, 298 K, CD_2Cl_2) of a) **2**.$(HSbF_6)_2$ b) **3**.$(HSbF_6)_2$, c) **3**.$HSbF_6$ and d) **2**. Peaks corresponding to the *benzyl* translational isomer of **3**.$(HSbF_6)_2$ and **3**.$HSbF_6$ are coloured orange, and are compared with related signals in spectra a) and c) with solid lines. Signals arising from the *ethyl* isomer are shown in blue, and are marked with dashed lines. Peaks arising from overlapping resonances of both isomers have not been colour coded.

The ^{1}H NMR spectrum of **3**.$HSbF_6$ (Figure 2c) displays two sets of signals, each of which is similar to those of the two translational isomers of **3**.$(HSbF_6)_2$, indicating that counterparts of the *ethyl* and *benzyl* translational isomers are still present in the singly protonated rotaxane. In each set of signals the key resonances for the occupied stations of **3**.$(HSbF_6)_2$ are conserved, whereas the signals for the unoccupied stations in either case match those of the non-protonated thread **2**. For example, the *benzyl* isomer of **3**.$HSbF_6$ has H_l, H_m, H_p, H_n etc. resonances at near identical chemical shifts to those of **3**.$(HSbF_6)_2$, whereas the H_c, H_d, H_e, H_f, H_h etc. resonances lie at similar chemical shifts as those of the corresponding protons of **2**. Similarly the H_d, H_e, H_f

and H_h resonances of the *ethyl* isomer of **3**.$HSbF_6$ match those of **3**.$(HSbF_6)_2$, whereas the H_l, H_m, H_p, H_n etc. resonances match those of **2**. Therefore in either translational isomer of **3**.$HSbF_6$ the macrocycle resides on a protonated station, leaving the other station neutral. No signals are observed for the protonation of an unoccupied station in **3**.$HSbF_6$, suggesting that the macrocycle and ammonium proton are for the most part closely associated with each other. These observations are consistent with shuttling occurring *via* a 'proton-ferry' type mechanism, in which the ammonium proton and macrocycle move in unison from station to station (Scheme 2).[13a]



Scheme 2. Dynamic behaviour of rotaxane 3 in its doubly (top) and singly protonated forms

The most abundant translational isomer in the rotaxane **3**.$HSbF_6$ is the *ethyl* co-conformation, which is approximately five times more abundant than the *benzyl* isomer. The determining factor in this case is the differing abilities of the two stations to compete for the single ammonium proton, and with it the macrocycle. That there is any competition from the benzyl station at all is perhaps surprising, considering that it is less basic by approximately 1.5 pKa units,[9] however the protonated benzyl station binds the macrocycle more strongly than the alkyl one (as demonstrated by the 2:1 preference for this station in **3**.$(HSbF_6)_2$), a factor that presumably acts to offset the disparity between the two stations. Deprotonation of the

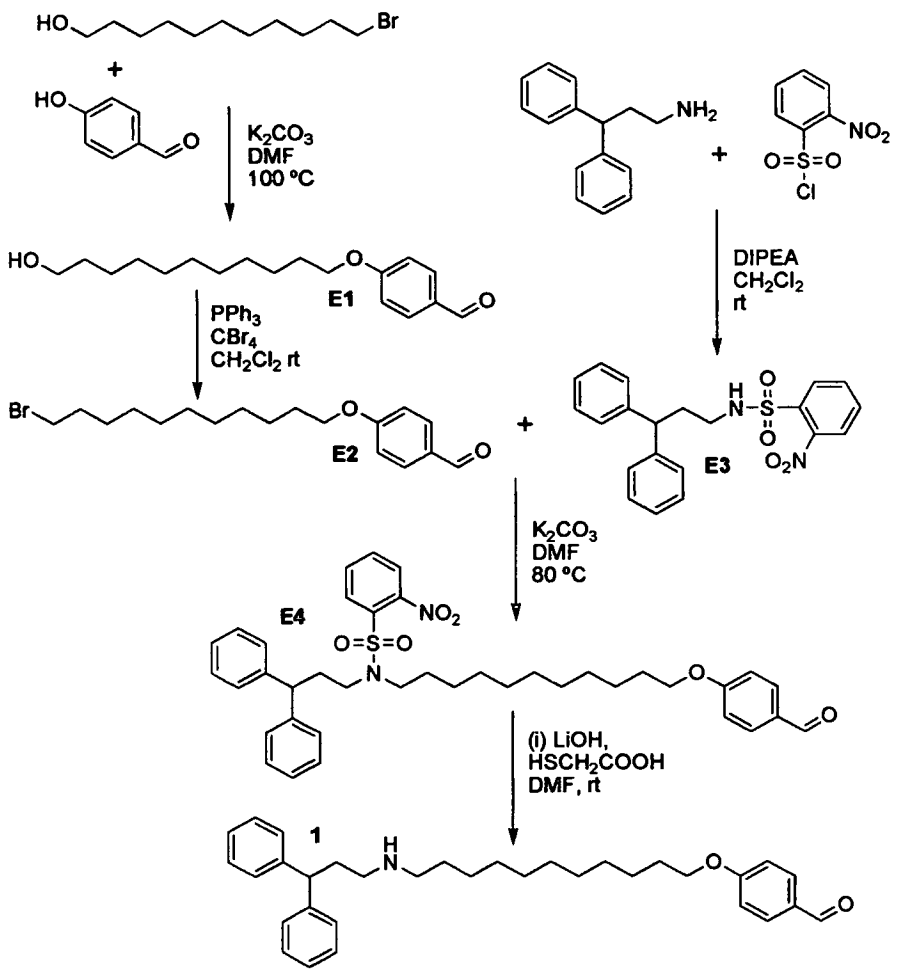
shuttle from **3**.$(HSbF_6)_2$ to **3**.$HSbF_6$ therefore changes preferred co-conformation of the molecule from the *benzyl* to the *ethyl* translational isomer.

In conclusion we have shown that the difference in acidity (hydrogen bond and Brönsted) of two stations differing only in the substituents about the same central $-CH_2NH_2^+CH_2-$ unit is sufficient to form the basis of a switchable molecular shuttle that operates by a change in protonation level. The positional discrimination exhibited by this system is modest compared to that of related shuttles,[6a-d] but there is scope to fine-tune the system by varying the substituents of each station. Fine-tuning of this type is likely to be an essential aspect in the development of such switchable molecular systems into more complex nanoscale devices and machines.

5.3 Experimental Procedures

General

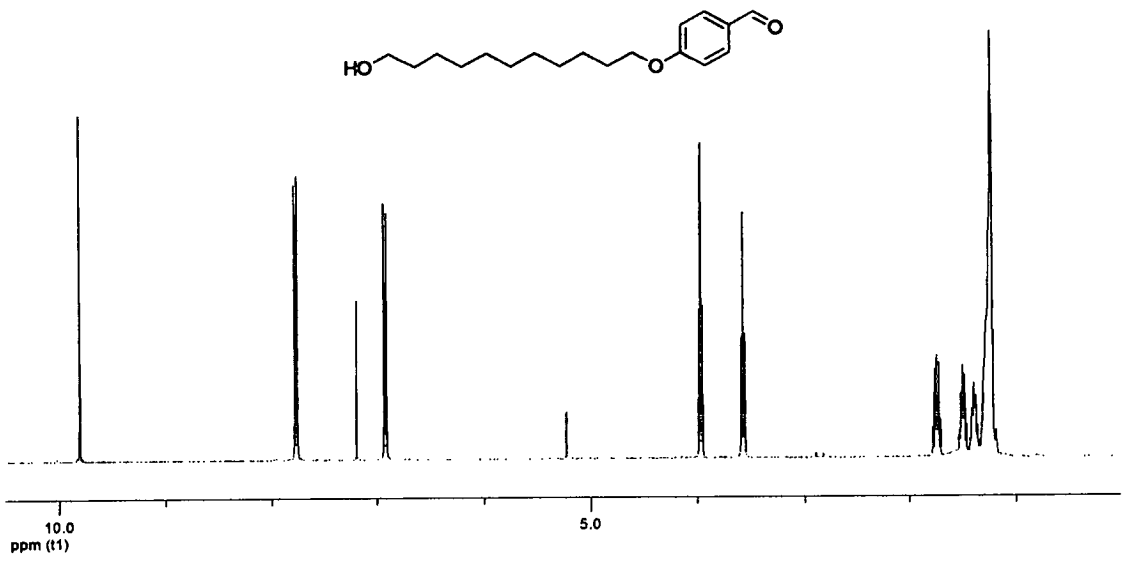
Unless otherwise stated, all reagents were purchased from Aldrich chemicals and used without further purification. Column chromatography was carried out using Kieselgel C60 (Merck, Germany) as the stationary phase. Thin layer chromatography was performed on precoated silica gel plates (0.25 mm thick, $60F_{254}$, Merck, Germany) and compounds were visualized under UV light. Eluent compositions for thin layer chromatography were selected so as to give Rf values of 0.2. All ^1H and ^{13}C NMR spectra were recorded on a Bruker AV 400 instrument, at a constant temperature of 298 K. Chemical shifts are reported in parts per million from high to low field and referenced to the residual solvent peak. Standard abbreviations indicating multiplicity are given: m = multiplet, br = broad, d = doublet, q = quadruplet, t = triplet, s = singlet. Coupling constants (*J*) are reported in hertz (Hz). Melting points were determined using a Sanyo Gallenkamp apparatus and are uncorrected. ESI mass spectrometry was performed with a Micromass Platform II Mass Spectrometer controlled using Masslynx v2.3 software. FAB accurate mass spectrometry was carried out by the University of Edinburgh services. 3,5-Di-*tert*-butyl benzylamine was prepared as described in reference 14.



Scheme E1. Synthesis of **E1**, **E2** ,**E3**, **E4** and **1**.

4-(11-hydroxyundecyloxy)-benzaldehyde E1

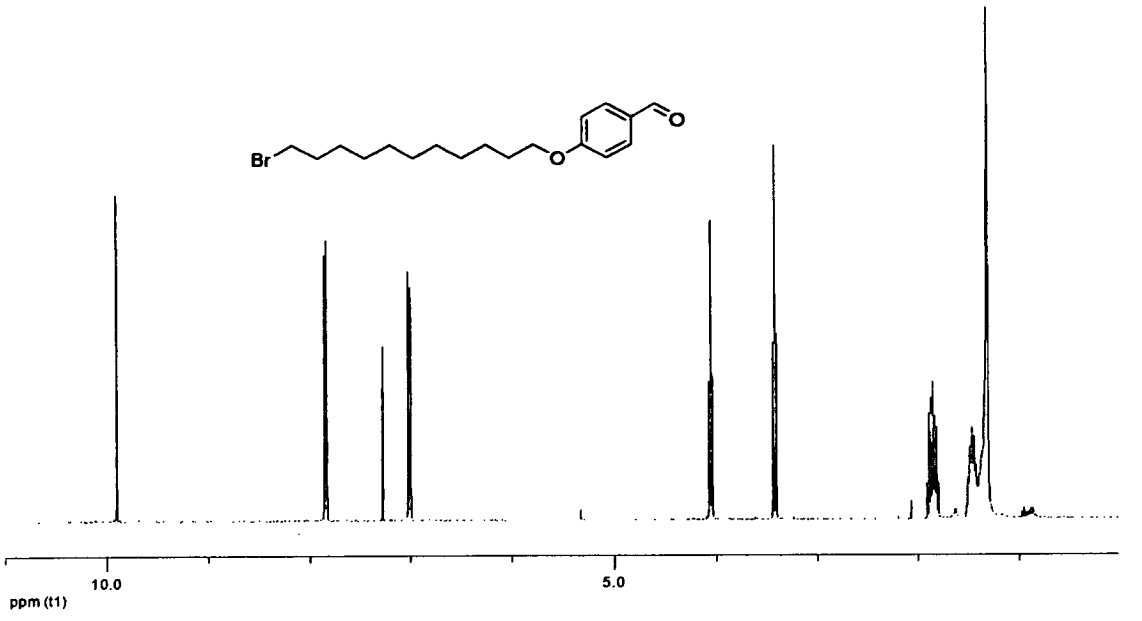
A solution of 4-hydroxybenzaldehyde (1.32 g, 5.00 mmol) and 11-bromoundec-1-ol (5.00 mmol) in DMF (50 ml) containing solid potassium carbonate (10 g) and sodium iodide (0.1 g) was heated at 100 °C for 12 h. After this time the solution was filtered and the solvent removed under reduced pressure. The resultant solid was dissolved in CH_2Cl_2 and washed with water. The organic phase was dried ($MgSO_4$) and the solvent removed under reduced pressure to give **E1** as an off-white solid. Yield: 1.508 g, 97%; m.p. 68-70 °C ^{1}H NMR (400 MHz, CD_3Cl) δ = 1.17-1.34 (br m 6 × CH_2), 1.39 (m, CH_2), 1.49 (m, CH_2), 1.74 (m, CH_2), 3.57 (t, 2H, J = 6.6 Hz, $HOC\underline{H}_2$), 3.97 (t, 2H, J = 6.6 Hz, $ArOC\underline{H}_2$), 6.92 (d, 2H, J = 8.7 Hz, ArH), 7.76 (d, 2H, J = 8.8 Hz, ArH), 9.81 (s, 1H, ArCHO); ^{13}C NMR (100 MHz, CD_3Cl) δ = 25.7, 26.0, 29.1, 29.3, 29.4, 29.50, 29.53, 29.6, 32.8, 63.1, 68.4, 114.7, 129.7, 132.0, 164.3, 190.9; HR-MS (FAB) $C_{18}H_{28}O_3$ calcd m/z $[(M + H)^+]$ = 293.2117 found 293.2114.



^{1}H NMR, 400 MHz, $CDCl_3$, 298 K. Peak at ca 5.3 ppm is residual CH_2Cl_2.

4-(11-bromoundecyloxy)-benzaldehyde E2

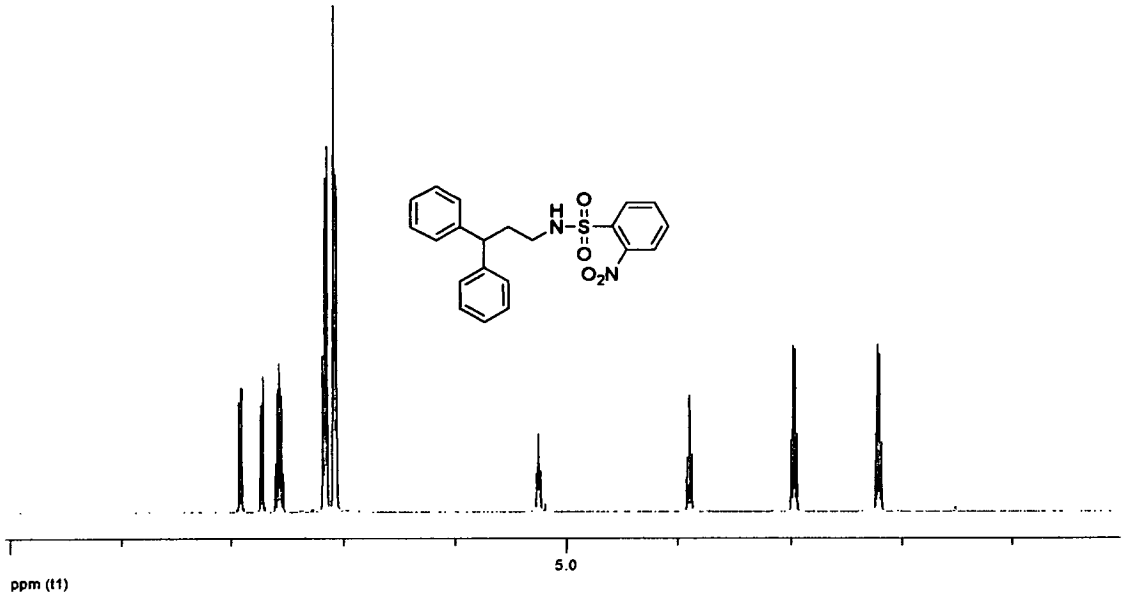
Aldehyde **I** (1.46 g, 5.00 mmol), tetrabromomethane (5 mmol) and triphenylphosphine (5 mmol) were dissolved in dichloromethane (100 ml) at 0 °C. The solution was allowed to warm to room temperature and stirred overnight. The solvent was then removed under reduced pressure and the resultant material was dry loaded onto a silica column and eluted with 25% CH_2Cl_2 in petroleum ether to give **E2** as a yellow oil. Yield: 1.26g, 71 %; ^{1}H NMR (400 MHz, CD_3Cl) δ = 1.25-1.50 (m, 7 × CH_2), 1.83, (m, 2 × CH_2), 3.41 (t, 2H, J = 6.8, CH_2Br), 4.03 (t, 2H, J = 6.5, CH_2O), 6.99 (d, 2H, J = 8.7, ArH), 7.82 (d, 2H, J = 8.8, ArH), 9.87 (s, 1H, CHO); ^{13}C NMR (100 MHz, CD_3Cl) δ = 28.2, 28.8, 29.1, 29.3, 29.4, 29.5, 29.5, 26.0, 32.8, 34.1, 68.4, 114.7, 129.7, 132.0, 164.3, 190.9; HR-MS (FAB) $C_{18}H_{27}BrO_2$ calcd m/z $[(M + H)^+]$ = 355.1273 found.



^{1}H NMR, 400 MHz, $CDCl_3$, 298 K

_N_-(3,3-Diphenylpropyl)-2-nitrobenzenesulfonamide E3

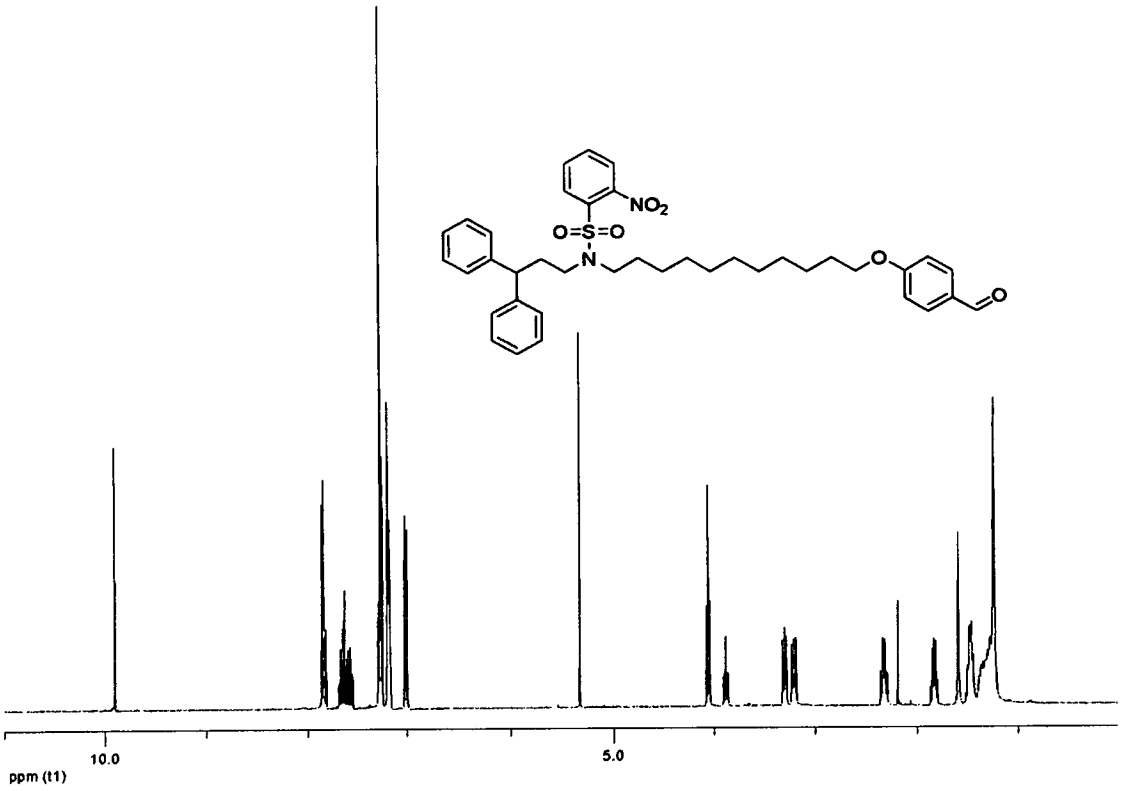
A solution of 3,3-diphenylpropylamine (4.22 g, 20.0 mmol) and *N,N*-diisopropylethylamine in dichloromethane (100 ml) was cooled to 0°C and 2-nitrobenzenesulfonyl chloride (20 mmol) was added portionwise. The solution was allowed to warm to room temperature and stirred overnight. The solution was then washed with 1M aqueous HCl then water, then dried ($MgSO_4$). The solvent was removed under reduced pressure to give **E3** as a white crystalline solid. Yield: 7.80 g, 98 %; m.p. 107-111 °C; ^{1}H NMR (400 MHz, CD_3Cl) δ = 2.21 (q, 2H, J = 7.2 Hz, CH_2), 2.97 (q, 2H, J = 6.7, CH_2), 3.89 (t, 1H, J = 7.9, CH), 5.25 (t, 1H, J = 6.0, NH), 7.05-7.11 (m, 6H, ArH), 7.13-7.19 (m, 4H, ArH), 7.53-7.62 (m, 2H, ArH), 7.71-7.75 (m, 1H, ArH), 7.89-7.93 (m, 1H, ArH); ^{13}C NMR (100 MHz, CD_3Cl) δ = 35.4, 42.3, 48.1, 125.4, 126.6, 127.7, 128.7, 131.1, 132.8, 133.56, 133.60, 143.5, 148.0; HR-MS (FAB) $C_{21}H_{20}N_2O_4S$ calcd m/z $[(M + H)^+]$ = 397.1222 found 397.1231.



^{1}H NMR, 400 MHz, $CDCl_3$, 298 K

_N_-(3,3-Diphenylpropyl)-_N_-[11-(4-formylphenoxy)-undecyl]-2-nitrobenzenesulfonamide E4

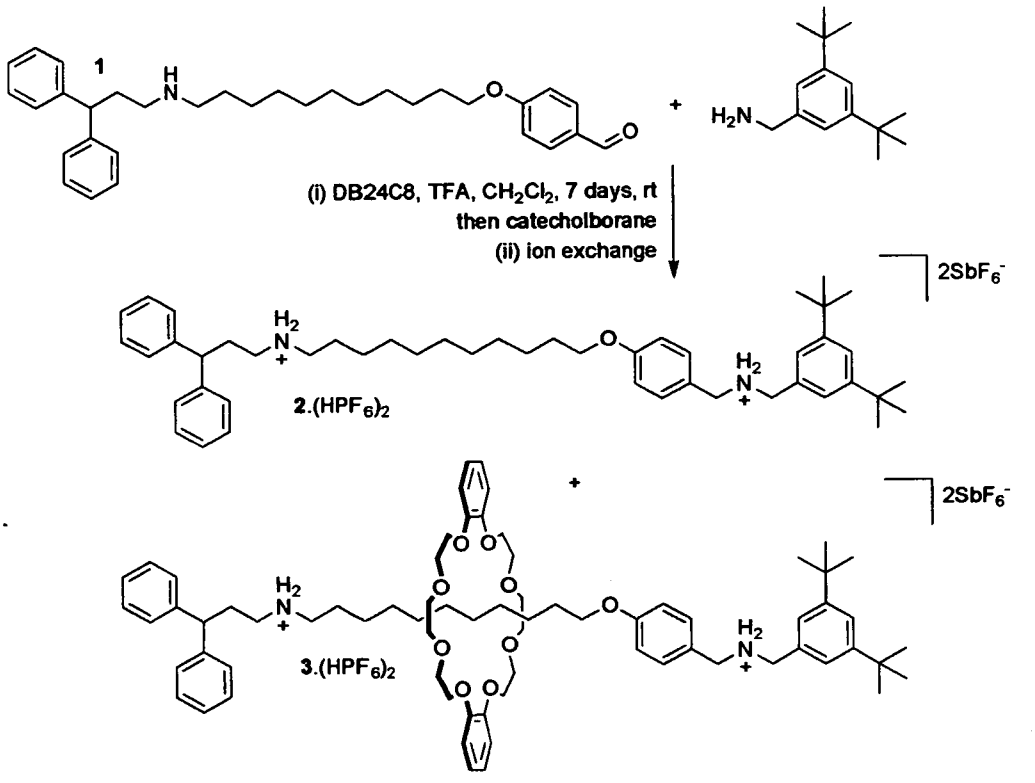
A solution of aldehyde **E2** (1.0 g, 2.8 mmol) and **E3** (2.6 mmol) in butanone (50 ml) containing potassium carbonate (2 g) and sodium iodide (50 mg) was heated at 80 °C overnight. The solution was then filtered and then dry loaded onto a silica column and eluted with a 1:1 mixture of CH_2Cl_2 and petroleum ether to give **E4** as a yellow gum. Yield: 1.33 g, 76 %; ^{1}H NMR (400 MHz, CD_3Cl) δ = 1.20-1.41 (m, 12H, 6 × CH_2), 1.47 (m, 4H, 2 × CH_2), 1.83, (m, 2H, CH_2) 2.33 (q, 2H, J = 7.9, CH_2), 3.21 (m, 2H, NCH_2), 3.30 (m, 2H, NCH_2), 3.88 (t, 1H, J = 7.8, $Ar_2\underline{CH}CH_2$), 4.06 (t, 2H, J = 6.5, OCH_2), 7.01 (d, 2H, J = 8.7, ArH), 7.17-7.23 (m, 6H, ArH), 7.25-7.31 (m, 4H, ArH), 7.54-7.69 (m, 3H, ArH), 7.80-7.87 (m, 3H, ArH), 9.90 (s, 1H, ArCHO); ^{13}C NMR (100 MHz, CD_3Cl) δ = 26.0, 26.5, 28.2, 29.06, 29.12, 29.3, 29.42, 29.43, 29.49, 34.0, 45.9, 47.8, 48.7, 68.4, 114.8, 124.1, 126.5, 127.6, 128.7, 129.7, 130.8, 131.6, 132.0, 133.3, 133.4, 143.7, 147.9, 164.3, 190.9; HR-MS (FAB) $C_{39}H_{46}N_2O_6S$ calcd m/z $[(M + H)^+]$ = 671.3155 found 671.3150.



^{1}H NMR, 400 MHz, $CDCl_3$, 298 K. Peak at ca 5.3 ppm is residual CH_2Cl_2.

4-[11-(3,3-Diphenyl-propylamino)-undecyloxy]-benzaldehyde 1

A solution of **E4** (1.0 g, 1.5 mmol), lithium hydroxide (6 mmol) and mercaptoacetic acid (3 mmol) in DMF (5 ml) was stirred overnight. The solution was diluted with ethyl acetate (100 ml) and washed with water then saturated aqueous sodium hydrogen carbonate. The organic layer was dried ($MgSO_4$) and the solvent removed under reduced pressure to give the title compound as a yellow gum. Yield: 0.513 g, 70 %; ^{1}H NMR (400 MHz, CD_3Cl) δ = 1.21-1.41 (m, 12H, 6 × CH_2), 1.43-1.53 (m, 4H, 2 × CH_2), 1.82 (m, 2H, CH_2), 2.33 (q, 2H, J = 7.5 Hz, $Ph_2CH\underline{CH_2}$), 2.61 (m, 4H, 2 × $\underline{CH_2}N$), 4.01 (t, 1H, J = 7.8, $Ph_2\underline{CH}$), 4.05 (t, 2H, J = 6.5, OCH_2), 7.01 (d, 2H, J = 8.8, ArH), 7.16-7.21 (m, 2H, ArH), 7.24-7.31 (m, 8H, ArH), 7.84 (d, 2H, J = 8.8, ArH), 9.90 (s, 1H, CHO); ^{13}C NMR (100 MHz, CD_3Cl) δ = 25.8, 26.0, 26.7, 28.9, 29.1, 29.3, 29.39, 29.42, 29.5, 29.7, 31.2, 46.4, 47.8, 48.6, 68.4, 114.7, 126.7, 127.7, 128.8, 129.7, 132.0, 142.9, 164.3, 190.9; HR-MS (FAB) $C_{33}H_{43}NO_2$ calcd m/z $[(M + H)^+]$ = 486.3372 found 486.3420.

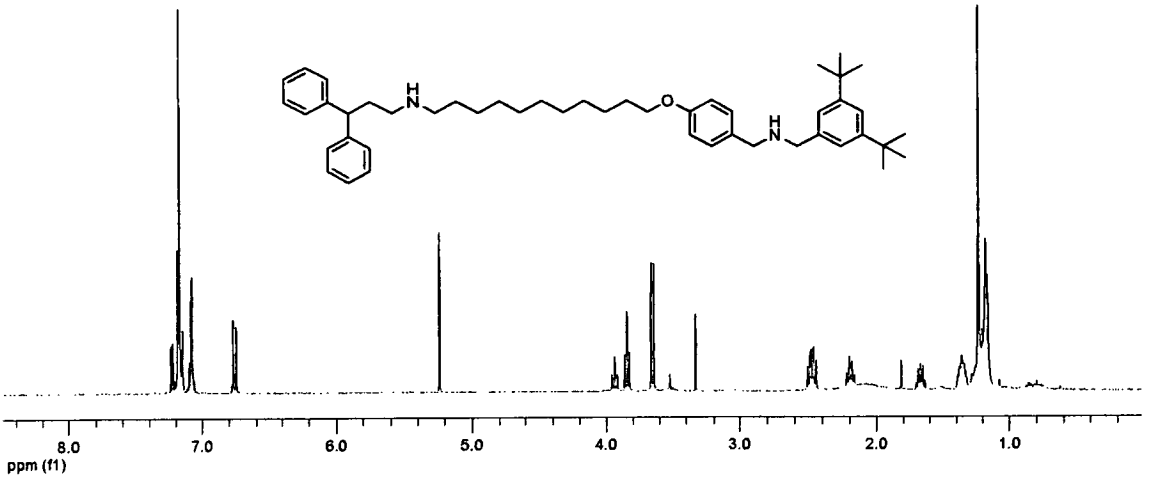


Scheme E2. Synthesis of **2** and **3**.

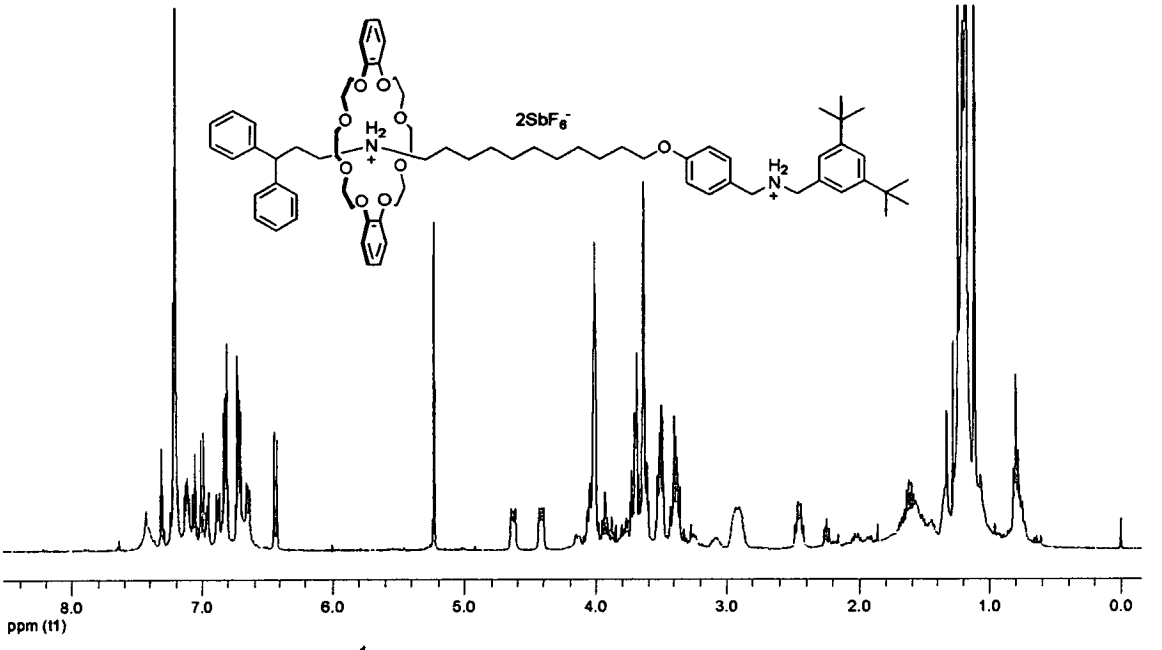
Thread 2 and Rotaxane 3

A solution of **1** (120 mg, 0.2 mmol), di-*tert*-butylbenzylamine (48 mg 0.22 mmol) and dibenzo[24]crown-8 (180 mg, 0.4 mmol) and trifluoroacetic acid (0.44 mmol) in CH_2Cl_2 (5 ml) was stirred for 1 week at room temperature. After this time a 1M catecholborane solution in THF (1 mmol, 1 ml) was added dropwise and the mixture was stirred for 12 h at room temperature. The solution was then diluted with CH_2Cl_2 (50 ml) and washed with 1M HCl (aq) (50 ml), saturated ammonium bicarbonate (aq) (50 ml) then brine (50 ml). The organic phase was dried ($MgSO_4$) and the solvent removed under reduced pressure. The resultant mixture was purified by preparative thin-layer chromatography using silica plates pre-treated by dipping in a saturated solution of ammonium chloride in acetonitrile. The plates were developed using a 5 % solution of MeOH in $CHCl_3$ as eluent to give **2** and **3**, which were treated with the following procedure to ensure uniformity of their counterions: Purified **2** or **3** was dissolved in CH_2Cl_2 and acidified by dropwise addition of a 1M solution of HCl in diethyl ether. The solvent was removed under reduced pressure and the resultant material was redissolved in CH_2Cl_2 then agitated overnight over an excess of Dowex-22 chloride ion-exchange resin. The solvent was removed under

reduced pressure and the residue was redissolved in a 25% solution of MeOH in CH_2Cl_2 then stirred overnight in the presence of excess solid $NaSbF_6$. The resultant suspension was filtered and the solvent removed under reduced pressure. The resultant solids were suspended in CH_2Cl_2 and filtered followed by evaporation of the solvent to yield **2**.$(HSbF_6)_2$ (125 mg, 54%) and **3**.$(HSbF_6)_2$ (61 mg, 19 %). Thread **2**.$(HSbF_6)_2$; ^{1}H NMR (400 MHz, CD_2Cl_2) δ = 1.13-1.29 (m, 30H, 6 × CH_2, 6 × CH_3), 1.35 (m, 2H, CH_2), 1.52 (m, 2H, CH_2), 1.67 (m, 2H, CH_2), 2.45 (m, 2H, CH_2), 2.90 (br m, 2H, $CH_2\underline{CH_2}N$), 2.97 (br m, 2H, $CH_2\underline{CH_2}N$), 3.90 (t, 2H, *J* = 6.5, CH_2O), 3.92 (t, 1H, J = 7.9, $Ph_2\underline{CH}CH_2$) 4.07 (br t, 2H, $Ar\underline{CH_2}N$), 4.15 (br t, 2H, $Ar\underline{CH_2}N$), 6.85 (d, 2H, *J* = 8.5, ArH), 7.10-7.26 (m, 14H, ArH), 7.46 (s, 1H, ArH); ^{13}C NMR (100 MHz, CD_2Cl_2) δ = 25.9, 26.38, 26.45, 28.97, 29.01, 29.1, 29.2, 29.3, 30.1, 31.4, 31.7, 35.3, 48.8, 49.0, 50.0, 51.5, 52.6, 68.5, 115.9, 121.2, 124.3, 124.9, 127.4, 127.8, 128.8, 129.4, 131.6, 143.1, 153.1, 161.0; HR-MS (FAB) $C_{48}H_{68}N_2O$ calcd m/z [$(M + H)^+$] =689.5410, found. Rotaxane **3**.$(HSbF_6)_2$; ^{1}H NMR (400 MHz, CD_2Cl_2) δ = 1.01-1.38 (m, 32H + 32H', 6 × CH_2, 6 × CH_3, 6 × CH'_2, 6 × CH'_3), 1.30-1.71 (m, 4H + 4H', 2 × CH_2, 2 × CH'_2), 2.02 (m, 2H', CH'_2), 2.45 (m, 2H, CH_2), 2.91 (br m, 4H, 2 × CH_2), 3.08 (br m, 2H', CH'_2), 3.25 (br m, 2H', CH'_2), 3.32 (t, H', *J* = 7.6, Ph_2CH'), 3.33-3.44 (m, 4H + 4H', OCH_2 + OCH'_2 diastereotopic signals), 3.46-3.56 (m, 4H + 4H', OCH_2 + OCH'_2 diastereotopic ethylene signals), 3.57-3.83 (m 10H + 8H', OCH_2 + OCH'_2 diastereotopic ethylene signals OCH_2), 3.87 (t, 2H', *J* = 6.6, OCH'_2), 3.93 (t, 1H, *J* = 8.0, Ph_2CH'), 3.96-4.19 (m, 8H + 12H', OCH_2 + OCH'_2 diastereotopic ethylene signals 2 × $ArCH'_2$), 4.41 (m, 2H, $ArCH_2$), 4.63 (m, 2H, $ArCH_2$), 6.43 (d, 2H, *J* = 8.7 ArH), 6.64 (m, 4H', ArH'), 6.71 (m, 4H, ArH), 6.82 (m, 4H, ArH), 6.85-6.90 (m, 6H', ArH'), 6.96 (m, 4H', ArH'), 7.00 (d, 2H, *J* = 8.7 ArH), 7.03-7.15 (m, 2H + 8H', ArH + ArH'), 7.18-7.25 (m, 10H, ArH), 7.29-7.32 (m, H + 2H', ArH + ArH'), 7.43 (s, H', ArH'); ^{13}C NMR (100 MHz, $CDCl_3$) (major translational isomer) δ = 25.5, 26.1, 26.4, 28.4, 28.6, 28.8, 28.9, 29.2, 29.7, 30.2, 31.3, 34.8, 47.1, 48.2, 49.0, 52.4, 52.8, 67.9, 70.1, 70.5, 70.9, 112.6, 114.4, 121.7, 122.6, 123.6, 126.2, 127.2, 127.8, 128.5, 130.6, 131.3, 143.7, 147.3, 151.5, 159.7; $C_{72}H_{99}N_2O_9$ calcd m/z [$(M + H)^+$] =1137.7507, found 1137.7516.



^{1}H NMR, 400 MHz, CD_2Cl_2, 298 K



^{1}H NMR, 400 MHz, CD_2Cl_2, 298 K

Deprotonation of 2.$(HSbF_6)_2$ and 3.$(HSbF_6)_2$:

In a disposable polypropylene reaction tube fitted with a frit and a tap diethylaminopolystyrene resin (200 mg, 0.2 molar equivalents) was swelled in CH_2Cl_2 and the excess solvent drained off. A solution of **2**.$(HSbF_6)_2$ or **3**.$(HSbF_6)_2$ (2 μmol) in CH_2Cl_2 (2 ml) was added and the mixture was agitated on an orbital shaker for 1 h. After this time the reaction mixture was drained and the resin was washed with additional CH_2Cl_2 (3 × 2 ml), the mixture being agitated for five minutes during each wash. The solvent and washes were combined and evaporated to give **2** or **3**.$HSbF_6$ with >95% recovery of material.

5.4 References

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Appendix: Published Papers

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Rotaxanes of Cyclic Peptides

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Until recently the existence of mechanically interlocked peptide backbones in nature was far from clear-cut. However, in the past few years, first knots,[1] then catenanes[2] and, finally, rotaxanes[3] have been unambiguously characterized in naturally occurring peptides and proteins.[4] Although the implications of kinetically stable entanglements on peptide and protein structure, properties, function, and folding remain almost completely unknown, already studies on the few interlocked peptides available have shown them to possess a wealth of intriguing properties, including high resistance to peptidases,[5a] unique modes of antimicrobial and antiviral action,[5b–d] impressive membrane transport characteristics,[5e] and stability to thermal and chemical denaturing.[5f] However, few artificial or simpler analogues have been investigated to date since no methodology yet exists for synthetically interlocking peptide fragments.[6,7] En route to this goal, here we describe the preparation of rotaxanes from a class of well-known cyclic peptides and some nonpeptidic threads.

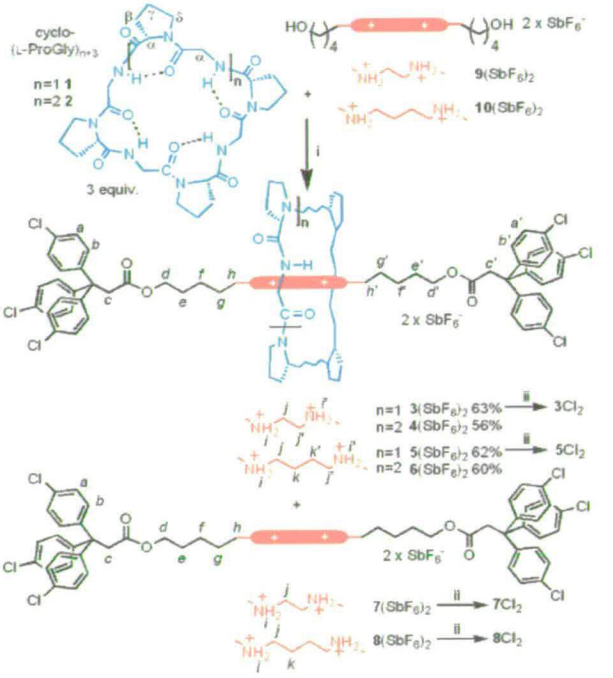
Efficient synthetic routes to catenanes and rotaxanes generally rely on strong-binding mutual recognition elements on each component to direct a threading or macrocyclization reaction.[8] The problem with applying such a strategy to peptides is that the amide groups of each free component will normally be largely self-satisfied in terms of hydrogen bonding through folding, and little driving force will exist for interlocking. Indeed, several attempts[3b,c] to synthesize microcin J25, a 21-residue oligopeptide with a rotaxane architecture, by conventional peptide synthesis strategies have failed. However, many natural and unnatural cyclic peptides are known to bind cations efficiently. Crown ether[9] and cucurbituril[10] organic cation binding provides some of the most effective rotaxane template syntheses known, and we wondered whether a similar interaction could also be used to promote rotaxane formation with peptidic macrocycles. As prototypical systems we investigated cyclic octa- (**1**) and deca (**2**)-peptides derived from the L-ProGly repeat unit.[11] High stability constants ($K_a \approx 10^3-10^5$ M^{-1}) have been reported for 1:1 metal and 1:1 and 1:2 protonated amino acid ester complexes of these cyclopeptides in acetonitrile.[11c] Accordingly, we constructed a series of cationic diol threads and examined their efficacy in rotaxane-forming "stoppering" reactions with a bulky acid chloride and macrocycles **1** and **2** (Scheme 1).[12]

Cyclo(L-ProGly)$_4$ (**1**) and cyclo(L-ProGly)$_5$ (**2**) were prepared via a solid-phase backbone amide-linking approach (see Supporting Information (SI)). As they are water soluble, a simple aqueous extraction removes either macrocycle from a rotaxane-forming reaction mixture, and they can easily be recycled. In contrast, the chromatographic separation of the [2]rotaxanes from the corresponding threads is rather difficult, and it therefore proved convenient to use an excess of the cyclic peptide to maximize the ratio of rotaxane to thread. Although only traces of interlocked products were formed with monocationic ammonium or pyridinium threads, we were delighted to find that [2]rotaxanes **3**–**6**(SbF$_6$)$_2$ were formed in 56–63% yield from ethane-1,2-diammonium and butane-1,4-diammonium templates.[12]

The ^{1}H NMR spectra (Figure 1) of the cyclo(L-ProGly)$_4$-based [2]rotaxanes **3**Cl$_2$ and **5**Cl$_2$ and their free components (threads **7**Cl$_2$ and **8**Cl$_2$ and macrocycle **1**) provide some insights into the structure of the rotaxanes and the nature of the template interaction. Free cyclo(L-ProGly)$_4$ exists as a mixture of rotamers in acetonitrile,[11c] ~30% in the all-trans conformer form (shown in light blue in Figure 1c) in which four γ-turn Gly-to-Gly H-bonds give rise to a relatively planar structure with the glycine carbonyls pointing toward the center and the proline carbonyls directed away. However, a single set of signals is observed for each constitutionally distinct proton of the cyclic peptide in both **3**Cl$_2$ (Figure 1b) and **5**Cl$_2$ (Figure 1d). Cyclo(L-ProGly)$_4$ is known[11c] to adopt a geometry in 1:2 host–guest ammonium cation complexes which is also an all-trans rotamer, but is cylindrical rather than flat, with the glycine carbonyls rotated toward one face and the proline carbonyls to the other, destroying the internal H-bond network. The ^{1}H and ^{13}C (see ref 11c) NMR are consistent with a similar structure existing in rotaxanes **3**Cl$_2$ and **5**Cl$_2$. Rapid spinning of the thread in the cavity (the macrocycle resonances remain symmetrical even at 240 K in CD$_3$CN) enables each of the peptide carbonyls to interact with the two ammonium groups through an alternating network of hydrogen bonds and electrostatic C=O$^{\delta-}$···N$^+$ interactions.

Confirmation of the change in conformation of cyclo(L-ProGly)$_4$ upon rotaxane formation is seen in the changes in the resonances of the glycine methylene groups. The geminal GlyH$_\alpha$ protons in

Scheme 1. Synthesis of Cyclic Peptide [2]Rotaxanes **3**-**6**(SbF$_6$)$_2$[a]



[a] Reagents and conditions: i. (4-ClC$_6$H$_4$)$_3$CCH$_2$COCl, CHCl$_3$:CH$_3$CN 3:7, RT, 7 days. ii. sat. NaHCO$_3$, then 1 M HCl. For clarity, atom labels are only shown for one repeat unit of the cyclopeptide in [2]rotaxanes **3**–**6**(SbF$_6$)$_2$

10.1021/ja057206q CCC: $33.50

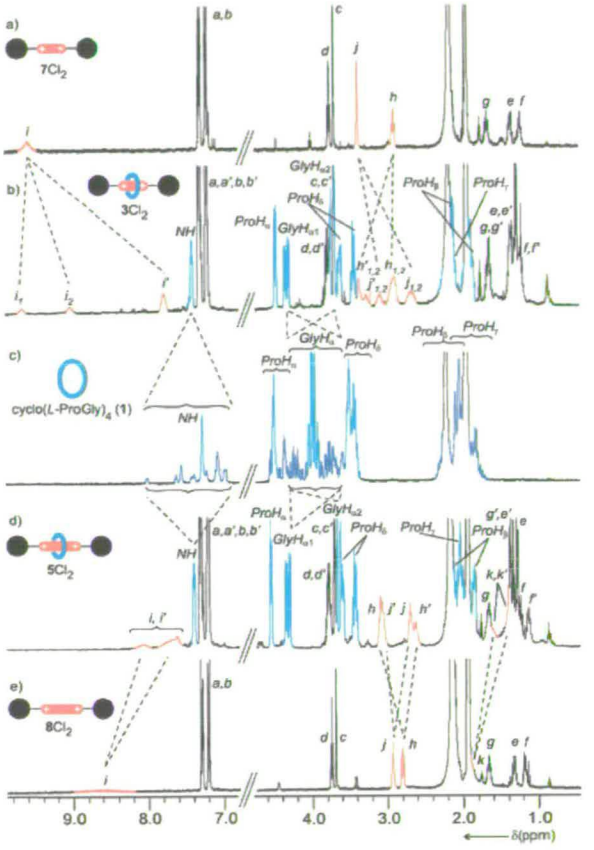


Figure 1. ^{1}H NMR spectra (400 MHz, CD_3CN, 298 K) of (a) ethane-1,2-diammonium thread $\mathbf{7}Cl_2$; (b) [2]rotaxane $\mathbf{3}Cl_2$; (c) cyclo(L-ProGly)$_4$ (**1**); (d) [2]rotaxane $\mathbf{5}Cl_2$; (e) butane-1,2-diammonium thread $\mathbf{8}Cl_2$. The labeling corresponds to that shown in Scheme 1. The resonances of the all-trans rotamer of cyclo(L-ProGly)$_4$ are shown in light blue, and those from minor rotamers, only present in part (c), in dark blue.

the H-bonded all-trans rotamer of free **1** are in similar proximities to the shielding region of the adjacent proline carbonyl groups and appear at similar chemical shifts (Figure 1c). However, in both $\mathbf{3}Cl_2$ and $\mathbf{5}Cl_2$ H-bonding of the glycine carbonyls to the ammonium groups rotates the NHCO groups, causing the positions of the geminal methylene protons relative to the adjacent proline carbonyls to differ such that the four $GlyH_{\alpha 1}$ proton resonances are shifted *downfield* by 0.35 ppm, whereas the four $GlyH_{\alpha 2}$ proton resonances are shifted *upfield* by 0.30 ppm. Despite the loss of the internal H-bonding network, the amide resonances still experience a slight net upfield shift in the rotaxanes as a result of the inductive effect from the strong interaction of glycine carbonyls with the ammonium groups.

In the ethane-1,2-diammonium rotaxane, $\mathbf{3}Cl_2$, it is clear that one ammonium group ($H_{i'}$, Figure 1b) H-bonds principally to the glycine carbonyls and one (H_{i1} and H_{i2}, Figure 1b) to the proline carbonyls. The greater shielding of the $H_{i'}$ protons (indicative of stronger H-bonding) is, again, consistent with the previous studies[12c] on cyclo(L-ProGly)$_4$–ammonium ion host–guest complexes. The fact that the $-CH_2N^+-$ protons internal to the template (H_j) are shielded in the rotaxane compared to the thread, while those external to the template (H_h) are deshielded, indicates that each ammonium group is largely H-bonded from just one direction, with the macrocycle located over the central ethane group.

While the shifts in the $-H_2N^+-$ signals in rotaxane $\mathbf{5}Cl_2$ are less informative, the internal and external $-CH_2N^+-$ groups are both split into shielded and deshielded resonances, indicating that H-bonding with the longer template occurs to each ammonium group from both directions (obviously not simultaneously). In other words, the cyclopeptide is loosely held in $\mathbf{5}Cl_2$ and able to access the full length of the thread.

The ability of cation–amide interactions to disrupt internal amide–amide H-bonding networks augurs well for their use to overcome peptide folding and provide a thermodynamic driving force for the formation of kinetically stable peptide and protein entanglements.

Supporting Information Available: Experimental details for the synthesis of the macrocycles, rotaxanes, threads, and precursors.

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(12) To maintain the ammonium template the "stoppering" reaction must be carried out in the absence of base. HCl is generated during the reaction, autocatalyzing ester formation. Since there is the potential for a mixture of counterions in the initially formed rotaxane salts, anion exchange was performed to ensure uniformity.

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Switchable Dual Binding Mode Molecular Shuttle

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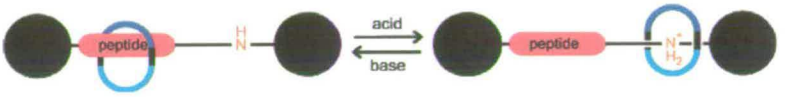
ABSTRACT



Protonation controls the location of a dual binding mode macrocycle in a [2]rotaxane. In the neutral form, amide–amide hydrogen bonds hold the macrocycle over a dipeptide residue; when the thread is protonated, polyether–ammonium cation interactions dominate and the macrocycle changes position.

Rotaxanes in which the position of the macrocyclic component can be changed by an external stimulus are among the simplest of molecular-scale mechanical devices.[1] Various stimuli have been employed to induce such switching, including metal binding,[2] configurational changes,[3] and alteration of the oxidation state[4] or protonation level[2f,4a,5] of the molecule. Here we report on the synthesis and operation of a pH-switchable molecular shuttle that uses different sets of intercomponent interactions to achieve distinct and differing coconformations in the neutral and protonated states.

Amide−amide hydrogen bonding of short peptide units with isophthalamide macrocycles is a well-established template route for the synthesis of rotaxanes.[6] Recently, the Loeb group, inspired by the ammonium cation−crown ether rotaxane system originally introduced by Busch[7] and Stoddart,[8] demonstrated[9] that a protonated *N*-benzylaniline group

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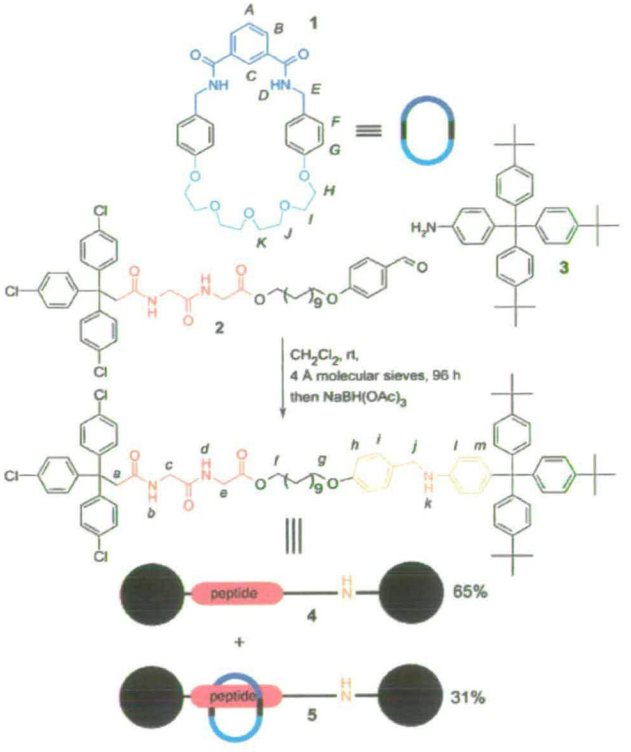
can be complexed as a pseudorotaxane by a crown ether. We wondered whether these two recognition motifs could be combined to generate a new type of dual binding mode, protonation-switched, molecular shuttle.

A target rotaxane incorporating glycylglycine and *N*-benzylaniline "stations" in the thread and an isophthalamide group and polyether chain in the macrocycle was synthesized using reductive amination to simultaneously generate the interlocked architecture and install the *N*-benzylaniline moiety (Scheme 1).[10] In CH_2Cl_2, macrocycle **1** hydrogen

Scheme 1. Synthesis of Thread **4** and [2]Rotaxane **5**



bonds to the monostoppered glycylglycine thread **2**, forming a pseudorotaxane.[6e] Covalent capture of the threaded intermediate by imine formation with bulky amine **3**, followed by in situ reduction with $NaBH(OAc)_3$, afforded the thread **4** and [2]rotaxane **5** in 65 and 31% yields, respectively (see Supporting Information).

The ^1H NMR spectra (Figure 1) of thread **4**, rotaxane **5**, and macrocycle **1** confirm the interlocked nature of **5** and

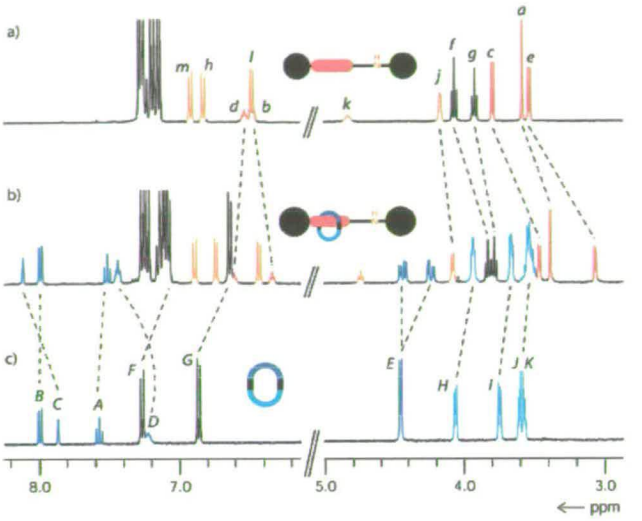


Figure 1. Partial ^1H NMR spectra (400 MHz, CD_3CN, 298 K) of (a) thread **4**, (b) rotaxane **5**, and (c) macrocycle **1**. The lettering corresponds to the proton assignments shown in Scheme 1.

show that in the neutral form of the rotaxane the macrocycle is largely localized on the peptide region of the thread (Scheme 2). The upfield shifts of the methylene resonances of the peptide station (H_a 0.20, H_c 0.32, and H_e 0.46 ppm, cf. Figure 1b and Figure 1a) in **5** are characteristic[6] of aromatic shielding by the encapsulating macrocycle. The greater shielding of H_e suggests the macrocycle hydrogen bonds primarily to the central glycylglycine carbonyl unit and only to a lesser extent to the comparatively hindered amide carbonyl adjacent to the stopper (Scheme 2).[6e] The ester carbonyl is a weaker hydrogen bond acceptor than the amides[11] and does not appear to contribute significantly to the intercomponent binding.

The thread amide resonances, H_b and H_d, are shifted upfield (0.13 ppm) and downfield (0.10 ppm), respectively, in the rotaxane as a result of the collective influences of (i) aromatic shielding (upfield shift), (ii) hydrogen bonding to the macrocycle polyether oxygens (downfield shift), and (iii) inductive effects of the hydrogen bonding to the thread carbonyl groups (downfield shift). There is no evidence of

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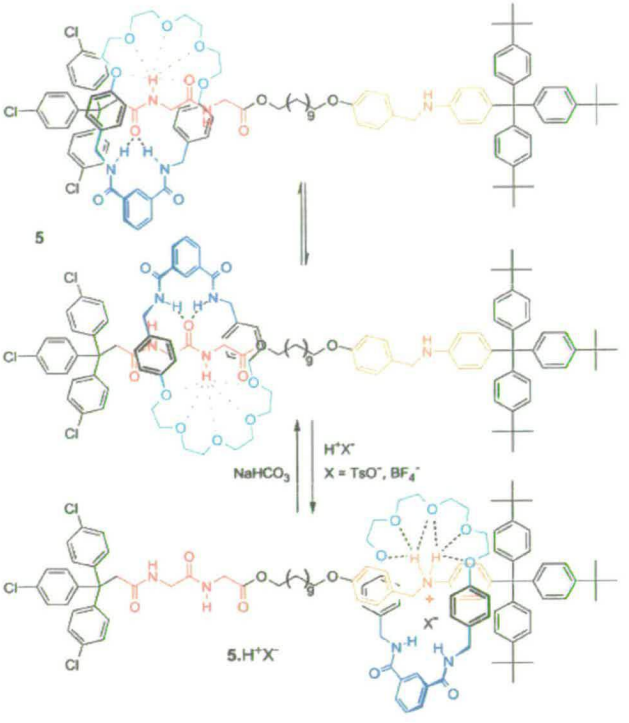
Scheme 2. Principal Intercomponent Binding Modes of **5** in Its Neutral and Protonated Forms[a]



[a] For $X^- = TsO^-$, the macrocycle amides H-bond to the anion; for $X^- = BF_4^-$, they do not.

any interaction between the macrocycle and the secondary amine group. For the rotaxane macrocycle, the 0.22 ppm (cf. Figure 1b and Figure 1c) downfield shift of the amide protons (H_D) indicates significant amide−amide hydrogen bonding with the thread. The polyether protons (H_H−H_K) are shifted upfield by roughly 0.1 ppm, confirming that the polyether oxygens accept hydrogen bonds from the thread amides. As the thread is unsymmetrical, the faces of the macrocycle are diastereotopic in the rotaxane. This effect is seen most clearly in the ABX system of H_E (Figure 1b).

Protonation of **5** with 1 equiv of *p*-toluenesulfonic acid results in significant changes to the ^{1}H NMR spectrum in CD_3CN (Figure 2b). Aromatic shielding is observed for the thread protons adjacent to the ammonium unit (H_j) and the macrocycle benzyl groups (H_F and H_G), indicating that the preferred position of the ring is now over the anilide ammonium station (Scheme 2). Interestingly, the signals for the thread amide protons in the protonated rotaxane appear at 6.6 ppm, almost the same as in the neutral thread (**4**). In the protonated thread, however, these signals occur at 6.9 and 6.95 ppm, suggesting inter- or intramolecular interactions exist between the amide carbonyls and the ammonium group

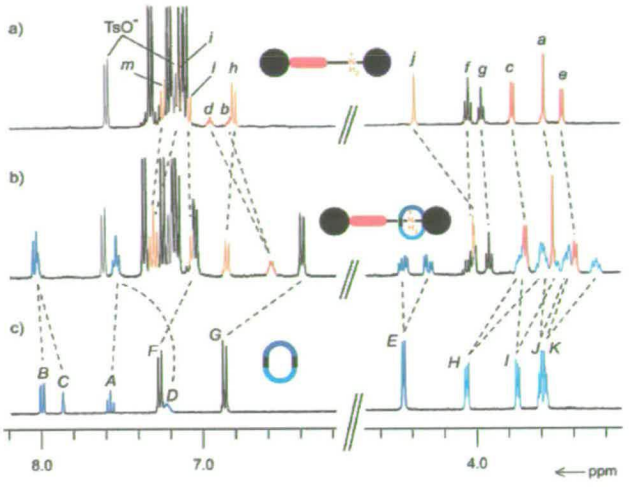


Figure 2. Partial ^{1}H NMR spectra (400 MHz, CD_3CN, 298 K) of (a) protonated thread **4**·TsOH, (b) protonated rotaxane **5**·TsOH, and (c) macrocycle **1**. The lettering corresponds to the proton assignments shown in Scheme 1.

in the protonated unrotaxanated thread. Thus, the presence of the macrocycle effectively "insulates" the amides of the thread from the ammonium center.

The ring amide protons appear 0.2 ppm downfield in **5**·H^+ (Figure 2b) with respect to **5** (Figure 1b), which is likely due to hydrogen bonding to the tosylate counterion.[12] When an alternative, noncoordinating, acid such as HBF_4 is used, the H_D resonance appears at the same position as in the free macrocycle, but the ring still resides over the ammonium group indicating that the macrocycle−anion interaction is not crucial for the shuttling process.

In conclusion, rotaxane **5**/**5**·H^+ is a novel type of molecular shuttle that switches the macrocycle between two distinct translational forms with high positional integrity by exploiting both amide−amide hydrogen bonding and crown ether−ammonium cation interactions. The incorporation of multiple recognition motifs into molecular structures is likely to prove important for controlling component and substrate motion in future generations of molecular-level machines.[13]

Supporting Information Available: General synthetic experimental procedure, characterization, and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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