

INTERLOCKED HOST STRUCTURES FOR ANION RECOGNITION AND METAL NANOPARTICLES FOR CATALYSIS AND SENSING APPLICATIONS

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This thesis describes the synthesis and anion recognition properties of a variety of interlocked host receptors and the application of metal nanoparticles in the areas of catalysis and sensing.

Chapter One introduces the field of anion supramolecular chemistry, with particular emphasis on areas relevant to the research discussed in later chapters. Following this, the synthesis and applications of metal nanoparticles are outlined.

Chapter Two details the synthesis of a range of halo-triazolium based rotaxanes and explores the effects of altering both the halogen bond donor atom and degree of preorganisation on the anion recognition properties of the interlocked host system. A halogen bond containing catenane is also prepared and its anion binding properties investigated.

Chapter Three initially reports the anion-templated synthesis of a series of neutral pyridine *N*-oxide axle containing rotaxanes before their ability to recognise anions in aqueous solvent mixtures is studied. Attempts to enhance anion binding through the incorporation of a positive charge into the macrocyclic component of the rotaxane structure are also explored.

Chapter Four outlines the preparation of β -cyclodextrin functionalised metal nanoparticles and investigations of their catalytic and sensing properties.

Chapter Five describes in detail the synthetic and analytical procedures discussed in chapters two to four.

Chapter Six summarises the conclusions of this thesis.

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Previously published work

Some of the work described in this thesis has already been published.

Peer-reviewed journal article

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J. M. Mercurio, R. C. Knighton, J. Cookson and P. D. Beer, *Halo-triazolium Axle Functionalised [2]Rotaxanes for Anion Recognition: Investigating the Effects of Halogen Bond Donor and Preorganisation*, Chem. Eur. J., 2014, Accepted Manuscript.

Oral presentation

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Glossary of abbreviations

δ	chemical shift
λ	wavelength
λ_{exc}	excitation wavelength
μ	micro
η	viscosity
Δ	change in (a measurement)
$\angle$	bond angle
$^{\circ}$	degree
$^{\circ}\text{C}$	degrees Celsius
$\text{\AA}$	Ångstrom
A^{-}	anion
ADP	adenosine diphosphate
aq.	aqueous
Ar	aryl
atm.	atmosphere
ATP	adenosine triphosphate
br	broad
Bu	butyl
c	centi
calc.	calculated
cat.	catalytic
conc.	concentrated
COSY	homonuclear correlation spectroscopy
d	doublet, diameter
D_{H}	hydrodynamic diameter
dd	double doublet
DEAD	diethyl azodicarboxylate
dec.	decomposed
DIPEA	<i>N,N</i> -diisopropylethylamine
DLS	dynamic light scattering
DMAP	4-(dimethylamino)pyridine
DMF	<i>N,N</i> -dimethylformamide
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid

EDC	<i>N</i> -(3-dimethylaminopropyl)- <i>N</i> '-ethylcarbodiimide
EDTA	ethylenediaminetetraacetic acid
<i>e.g.</i>	<i>exempli gratia</i>
eq., equiv.	equivalent
ESI	electrospray ionisation
Et	ethyl
<i>et al.</i>	<i>et alii</i>
eV	electron volt
FI	field ionisation
g	gram
GC	gas chromatography
Grubbs' II	Grubbs' second generation catalyst
hr	hour
Hz	hertz
I	intensity
IUPAC	International Union of Pure and Applied Chemistry
J	joule
<i>J</i>	coupling constant
k	kilo
<i>k</i>	rate constant
K	kelvin
K_a	association constant
K_{app}	apparent association constant
L	litre
M	mega, molar, molecular ion
m	meter, milli, multiplet
<i>m/z</i>	mass-to-charge ratio
MALDI	matrix-assisted laser desorption/ionisation
Me	methyl
min	minute
mol	mole
mp	melting point
Ms, mesyl	methanesulfonyl
MS	mass spectrometry
n	nano
NMR	nuclear magnetic resonance
NP	nanoparticle

OAc	acetate
P	poise
pH	$-\log_{10}[\text{H}^+]$
Ph	phenyl
$\text{p}K_a$	$-\log_{10}[K_a]$
ppm	parts per million
q	quartet
quin.	quintet
RCM	ring closing metathesis
ref.	reference
RI	refractive index
ROESY	rotating-frame nuclear Overhauser effect correlation spectroscopy
s	second, singlet
sat.	saturated
sept.	septet
SERS	surface enhanced Raman spectroscopy
<i>sic</i>	<i>sic erat scriptum</i>
t	triplet
T	tesla
<i>t</i> , <i>tert</i>	tertiary
TBA	tetrabutylammonium
TBTA	tris[(1-benzyl-1 <i>H</i> -1,2,3,-triazol-4-yl)methyl]amine
TEM	transmission electron microscopy
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
TLC	thin layer chromatography
Ts, tosyl	<i>para</i> -toluenesulfonyl
UV	ultra-violet
V	volts
vis	visible
VT	variable temperature
vs.	<i>versus</i>
wt%	weight percentage
X ⁻	halide
XPS	X-ray photoelectron spectroscopy

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CHAPTER ONE

Chapter One: Introduction

1.1 The importance of anions

Anions impact our everyday lives, with them playing essential roles in biological, medicinal, environmental and chemical processes. All of the genetic information necessary for life to exist is contained within DNA, a polyanionic double helix constructed from a phosphate ester scaffold. ATP and ADP contain phosphate anions at physiological pH and are crucial in the biological storage of energy. In addition, almost 70% of enzyme substrates are negatively charged, while the simple monatomic chloride anion is found extensively in extra-cellular fluid.¹

The disruption of anion transport in the human body is responsible for a number of medical disorders. For example, Alzheimer's disease has been linked to problems with anion exchange procedures² and the misregulation of chloride channels has been implicated in the terminal genetic condition cystic fibrosis,³ which causes severe degeneration of the lungs, and also Best disease⁴ and Dent's disease,⁵ which cause vision loss and renal failure respectively. Environmentally, the overuse of nitrate- and phosphate-based fertilisers to enhance food production in intensive arable farming has had a detrimental impact on aquatic systems and is linked to eutrophication.⁶ Nuclear fuel reprocessing forms the radioactive pertechnetate anion as a by-product, posing a risk to human health,⁷ whilst cyanide and naturally occurring arsenate anions are known to be extremely toxic.

Finally, anions can act as important nucleophiles, bases and catalysts in many chemical processes and altering their coordination properties can modify their efficacy. Given the prevalence of anions in nature and the effects they can have on the environment resulting from anthropogenic activities, it is no surprise that the design and synthesis of hosts and sensors for negatively charged species is now a thriving area of modern chemical research.

1.2 Anion supramolecular chemistry

Supramolecular chemistry was defined as “*the chemistry of the intermolecular bond, covering the structures and functions of the entities formed by the association of two or more chemical species*”⁷ by Jean-Marie Lehn who, together with Pedersen and Cram, was awarded the Nobel Prize in Chemistry in 1987. The origins of synthetic supramolecular chemistry can be traced back to 1967 when Pedersen demonstrated that crown ethers such as dibenzo-18-crown-6 (**Figure 1.1a**) bound alkali metal cations,⁸ a year after which the first anion receptors were reported by Park and Simmons,⁹ who showed that protonated macrobicyclic amine systems (**Figure 1.1b**) encapsulate halide anions in aqueous solvent media.

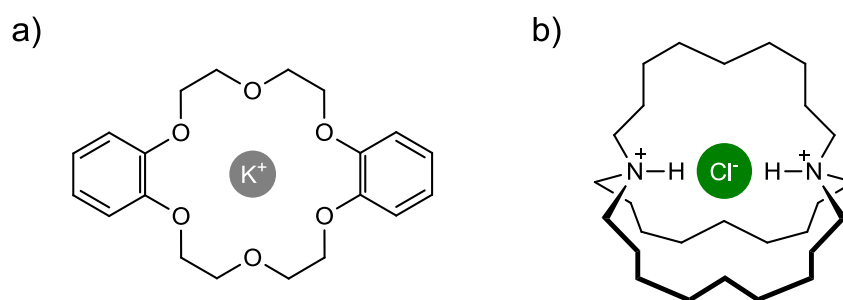


Figure 1.1—a) Pederson's dibenzo-18-crown-6 receptor and b) Park and Simmon's [9.9.9]-'katapinate.'

It was not until the late 1970s and early 1980s however that the field of anion supramolecular chemistry became an established area of research, with early interest in supramolecular chemistry largely focused on cation coordination. This can arguably be attributed to the various inherent properties of anions, discussed in the next section, which result in the design and construction of suitable hosts being very challenging.

1.2.1 The challenge of anions

The recognition and sensing of anions is considered to be more demanding than it is for cations,¹⁰ owing to a number of their fundamental properties:

Size: anions are larger, and hence more charge diffuse, than their isoelectronic cations resulting in the electrostatic interactions employed in many anion receptors being less effective than they would be in the analogous cation receptor.

Geometry: while cations are by definition spherical, anions adopt an array of different geometries (**Figure 1.2**), making the design and synthesis of anion receptors more demanding. However, it should be noted that this property of anions does potentially afford the benefit of selective guest binding *via* host–guest complementarity (**Section 1.2.3**).

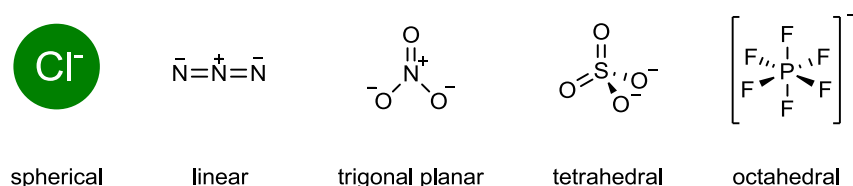


Figure 1.2—Differing geometries exhibited by anions.

pH dependence: many anions of interest only exist over a limited pH range. For example, carboxylates become protonated at low pH, thus losing their characteristic negative charge. It is also worth considering that many anion receptors are positively charged, some of which rely on the protonation of functional groups, such as amines, that can be deprotonated at higher pH. In this case, a potential anion host must operate within a pH window where the anionic guest remains deprotonated and receptor itself remains protonated.

Solvation: anions typically exhibit high free energies of solvation in hydroxylic solvents due to them being able to form strong hydrogen bonds with solvent molecules. As a consequence, achieving strong and selective binding, particularly in aqueous media, can be very challenging. Solvent effects are discussed in more detail in **Section 1.2.5**.

1.2.2 Non-covalent interactions

Numerous intermolecular, or non-covalent, interactions can be exploited to bind anionic guest species:

Electrostatic interactions cover all forms of Coulombic interactions between opposite charges (**Figure 1.3**), with two classes of this type of interaction being utilised to bind anions: *ion–ion interactions* are the stronger of the two but are non-directional and so are often used in concert with other more directional interactions to achieve strong and selective guest binding; *anion–dipole* interactions are considerably weaker, however their utility lies in their directionality which arises from the orientation of the dipole.

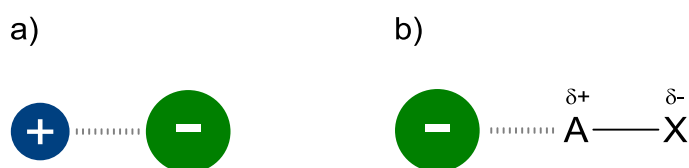


Figure 1.3—a) Ion–ion and b) anion–dipole electrostatic interactions.

Hydrogen bonding is a specific type of dipole interaction where a hydrogen atom covalently bound to a more electronegative atom (e.g. O, N, C) interacts with a neighbouring ion or dipole via its partial positive charge (**Figure 1.4a**). Hydrogen bonds are thought of as directional, with them having bond angles close to 180°, and can be found in a vast array of anion receptors, both synthetic and biotic.

Halogen bonding is closely related to hydrogen bonding, with the hydrogen atom now replaced with a halogen atom (**Figure 1.4b**). Halogen bonds¹¹ arise from the anisotropic distribution of a halogen atom's electron density, when it is attached to an electron-withdrawing group, causing an area of partial positive charge (or *σ-hole*) to exist at the halogen end of the Y–X bond (Y = C, N or O, X = halogen) into which electron density can be donated. The size and polarisation of the *σ-hole* can be enhanced by increasing the electron-withdrawing nature of Y and by employing the larger, more polarisable, halogens (I > Br > Cl). There are countless examples of halogen bonding in the solid state (such as **Figure 1.4c**),^{12, 13} however, despite their comparable strength to hydrogen bonds and

increased directionality, they have only begun to be utilised in solution phase anion recognition as recently as 2010.¹⁴

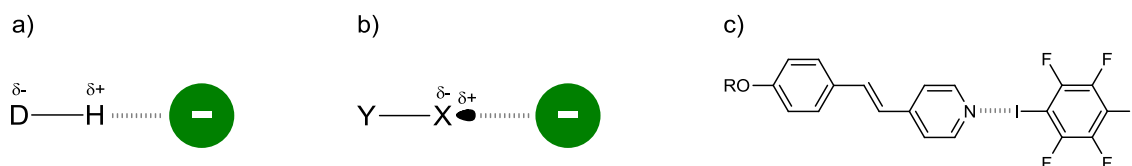


Figure 1.4—a) Anion complexation by hydrogen bonding. b) Schematic representation of halogen bonding and c) halogen bonding as found in liquid crystals (D is an electronegative atom, H is a hydrogen atom, X is a halogen atom and Y is a carbon, nitrogen or halogen atom).

Anion- π interactions are a relatively new type of non-covalent interaction that occur between electron deficient (π -acidic) aromatic systems and anions (**Figure 1.5a**).^{15, 16} The strength of this interaction is largely governed by the π -acidity of the aromatic system, with an increase in electron deficiency enhancing anion interaction.

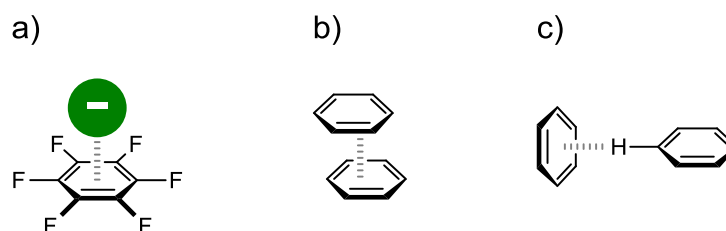


Figure 1.5—a) Schematic representation of an anion- π interaction. b) Face-to-face and c) edge-to-face aromatic donor-acceptor interactions.

Closely related to anion- π interactions are *aromatic donor-acceptor interactions* which, although not strictly used for the complexation of anions, are worth highlighting given their relevance to the research carried out in this thesis. These interactions occur between electron-rich and electron-deficient aromatic rings and can adopt one of two orientations: face-to-face (**Figure 1.5b**) and edge-to-face (**Figure 1.5c**), with the former being considered previously as π - π stacking interactions. Recent work has shown these face-to-face interactions to be dominated by electrostatic and dispersion forces, not π -orbital overlap as previously thought, and so the term π - π stacking is no longer considered accurate.¹⁷

Although they possess a high degree of orbital overlap, and as such cannot be classed as non-covalent interactions, *coordinate bonds* are often utilised in supramolecular chemistry. For example, Lewis acid–base coordination, such as metal–anion complexation, has been exploited in anion receptor design (**Section 1.3.2.3**).

1.2.3 Complementarity

One of the most fundamental principles of supramolecular chemistry is the concept of host–guest complementarity. This allows for the attractive non-covalent interactions between two or more species to be maximised and leads to a stronger association than would be observed if the host was not of complementary size and shape for the guest. The concept of complementarity was initially reflected in the simplistic “*lock-and-key*” model for substrate inclusion by enzymes, proposed by Emil Fischer in 1894 (**Figure 1.6a**).¹⁸ A more accurate representation of this phenomenon, however, is the preferred “*induced fit*” model which accounts for the subtle conformational adjustments that occur upon guest binding (**Figure 1.6b**).¹⁹

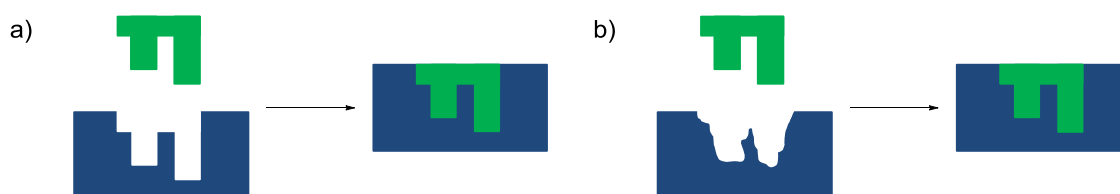


Figure 1.6—Cartoon representations of the a) “lock-and-key” and b) “induced fit” models of complementarity.

The principle of complementarity is exploited in the design of numerous synthetic anion receptors to afford guest selectivity, such as Bowman-James’s tricyclic host²⁰ and Flood’s tetra-triazole macrocycle²¹ that exhibit selective binding of bifluoride and chloride respectively (**Figure 1.7**). Bowman-James’s system discriminates in terms of *shape*: bifluoride is bound far more strongly than chloride, in DMSO ($\log K_a = 3.74$ (HF_2^-), negligible (Cl^-)), due to the host’s cavity being of complementary shape for an anion of linear geometry.

Flood's receptor selectively binds chloride over both fluoride and iodide, in dichloromethane ($K_d(M^{-1}) = 1.1 \times 10^7$ (Cl⁻), 2.8×10^5 (F⁻), 1.7×10^4 (I⁻)), due to chloride being of the correct size to maximise multiple C–H $\cdots$ A⁻ hydrogen bonding interactions within the macrocycle's cavity.

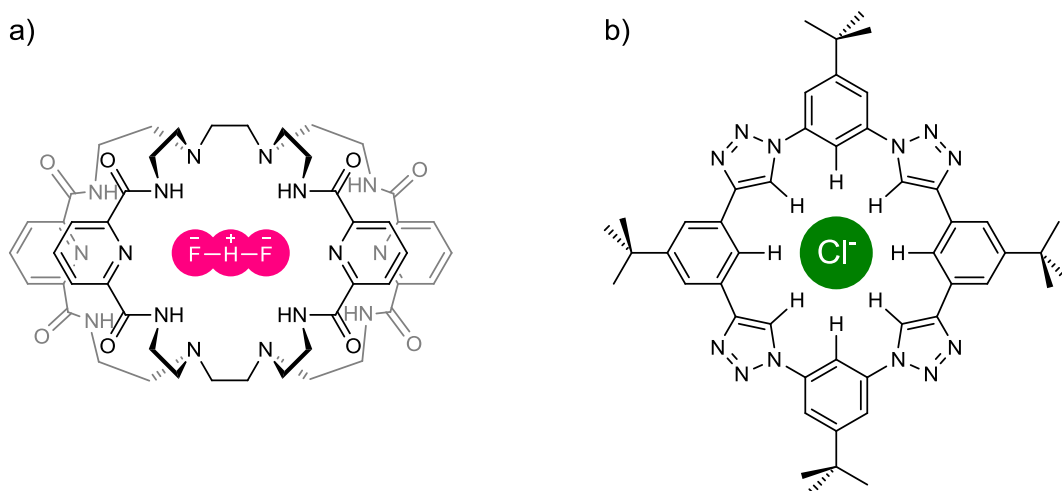


Figure 1.7—a) Bowman-James' bifluoride selective tricyclic host and b) Flood's chloride selective tetra-triazole macrocycle.

1.2.4 The concept of preorganisation and the macrocyclic effect

Preorganisation is another factor that needs to be taken into account when designing anion receptors. This concept was developed by Cram, who stated that “*the more highly hosts and guests are organised for binding and low solvation prior to their complexation, the more stable will be their complexes.*”²² An example of the importance of preorganisation, and the effects it can have on guest binding, was reported by Santacroce and co-workers.²³ They demonstrated that a preorganised isophthalamide receptor (**Figure 1.8a**) complexes chloride an order of magnitude more strongly, in CD₃CN, than its non-preorganised analogue (**Figure 1.8b**). This result arises from intramolecular hydrogen bonding interactions between the hydroxyl and carbonyl groups of the receptor orientating the amide hydrogen bond donors in a convergent manner ideal for guest complexation.

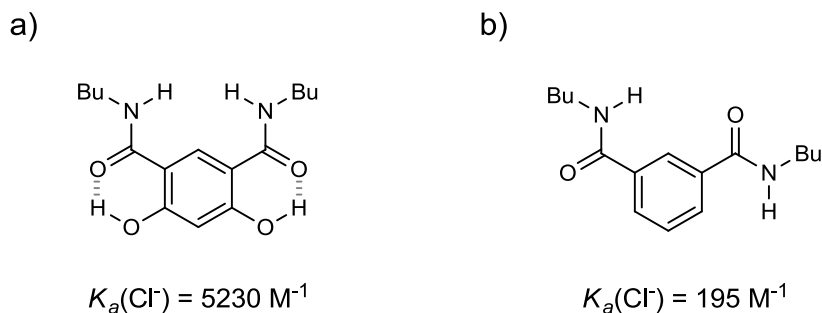


Figure 1.8—Santacrocce and co-workers' isophthalamide receptors as an example of preorganisation.

As a result of preorganisation, macrocyclic hosts exhibit stronger guest binding than their acyclic equivalents. This observation is referred to as the *macrocyclic effect* and has both enthalpic and entropic contributions. Enthalpically, macrocycles are typically less well solvated than their acyclic analogues and so desolvation prior to guest binding requires less energy. Entropically, macrocyclic hosts are less flexible, and so lose fewer degrees of freedom upon complexation, resulting in a lower entropic cost of guest binding. This effect was demonstrated by Hamilton *et al.* who showed that their macrocyclic host bound iodide three orders of magnitude more strongly than its acyclic counterpart in 98:2 $\text{CDCl}_3/\text{DMSO}-d^6$ (**Figure 1.9**).²⁴

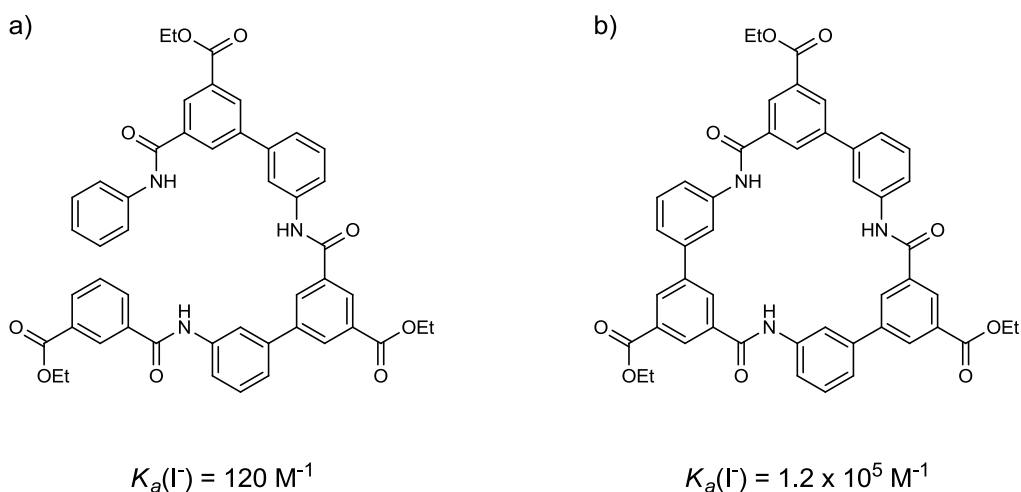


Figure 1.9—a) Hamilton's acyclic and b) macrocyclic receptors as an example of the macrocyclic effect.

1.2.5 Solvent effects

Solvent effects are of great importance in solution phase anion supramolecular chemistry, with them having a significant influence on both the strength and selectivity of a binding event.

In solution, host and guest species are solvated, giving rise to enthalpic and entropic contributions to host–guest complexation. Desolvation of these species is enthalpically disfavoured; however, the release of solvent molecules is entropically favoured, with these preferences reversed for the re-solvation of the host–guest complex.

The extent of solvation of the host and guest is affected by the choice of solvent; protic polar solvents heavily solvate charged species and are able to hydrogen bond to both the anion and receptor, whilst this is not the case with aprotic organic solvents. Furthermore, the degree of solvation can change markedly for different anions in the same solvent media, with this being linked to the *Hofmeister series* of anion hydrophobicity (**Figure 1.10**).¹⁰ Therefore, in aqueous solvent mixtures, hydrophobic anions will tend to be bound more strongly than hydrophilic anions due to their poorer solvation. To observe the opposite trend, or anti-Hofmeister selectivity, a receptor must effectively compete with the solvent, presenting a significant obstacle for the supramolecular chemist to overcome.

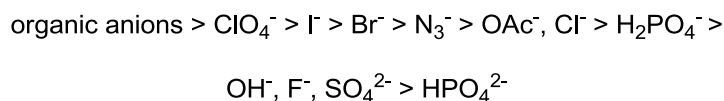


Figure 1.10—The Hofmeister series of anion hydrophobicity.

1.3 Anion receptors

Although the first synthetic anion receptor (**Figure 1.1b**) was reported in the late 1960s, it is only in the past two decades or so that synthetic anion receptors have become prevalent in the

literature. These receptors utilise the fundamental aspects of anion supramolecular chemistry highlighted previously, with inspiration for their design taken from how negatively charged species are recognised in Nature.

1.3.1 Anion recognition in Nature

The most common naturally occurring anion receptors are proteins, which exhibit extremely strong and selective anion recognition through the action of multiple complementary hydrogen bond donor groups arranged in a preorganised manner within their binding domains. Examples include the *sulfate-binding protein* (SBP) and the *phosphate-binding protein* (PBP) (**Figure 1.11**).

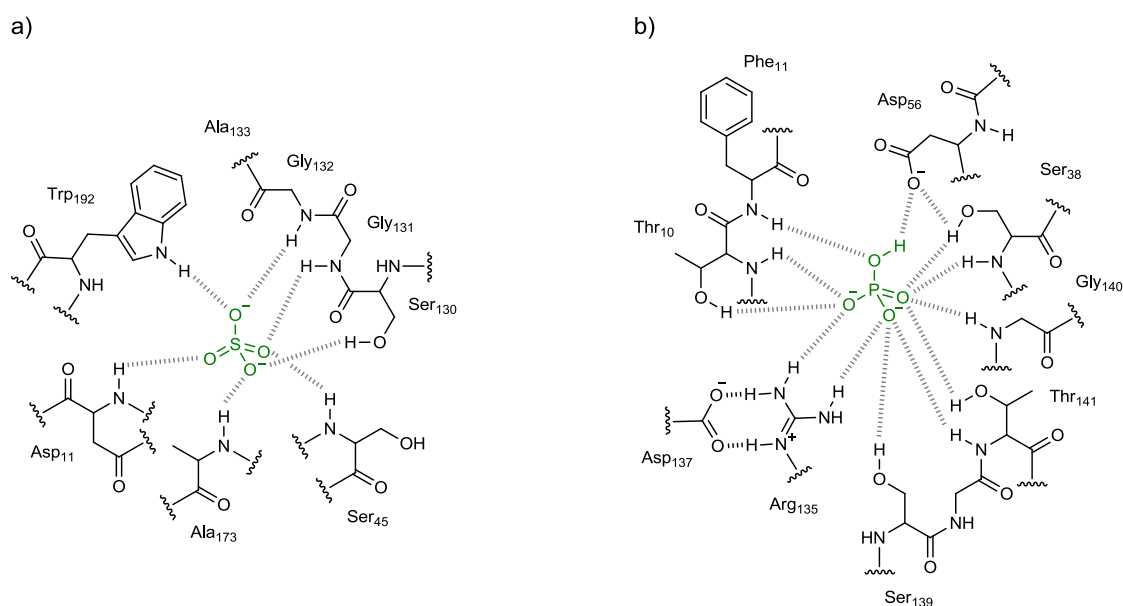
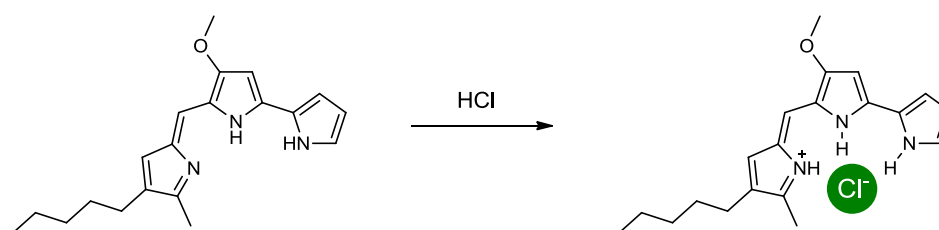


Figure 1.11—Binding domains of a) the sulfate-binding protein and b) the phosphate-binding protein.

The SBP is found in *Salmonella typhimurium* and selectively transports sulfate, binding the anion in a cleft between two globular domains of the protein.²⁵ The selectivity of this cleft is believed to arise from the tertiary structure of the protein giving directionality to the seven hydrogen bond donor groups of the surrounding neutral residues. The PBP is responsible for the transport of phosphate within bacterial cells, with its binding site also situated between

two globular domains that are inaccessible to the surrounding aqueous media.²⁶ Twelve hydrogen bonds are formed between the protein and anion, eleven of which involve protein hydrogen bond donors, with an additional electrostatic contribution to guest binding coming from the guanidinium group of the Arg₁₃₅ residue. In the one remaining hydrogen bond the protein acts as a hydrogen bond acceptor, which accounts for the observed selectivity for mono-hydrogen phosphate as the negatively charged Asp₅₆ residue would repel fully deprotonated anions of similar tetrahedral geometry, such as sulfate.

In addition to proteins, there are a number of small molecule anionophores that play important roles in Nature, such as the prodigiosin family of pyrrole-based anion receptors. These systems are primarily used for the transport of chloride across liposomal membranes,²⁷ with *Prodigiosin 1* transporting chloride via H⁺/Cl⁻ symport²⁸ (**Scheme 1.1**) or an anion exchange mechanism.²⁹



Scheme 1.1—Transport of chloride, as HCl, by Prodigiosin 1.

A final example of anion recognition in Nature is that of the enzyme *Carboxypeptidase-A*, which selectively catalyses protein hydrolysis at the C-terminal amino acid (**Figure 1.12**).³⁰ The anionic carboxylate group of the bound peptide forms two hydrogen bonds with the guanidinium group in the enzyme's active site, holding the substrate in close proximity to the catalytic zinc(II) cation. A hydrophobic pocket also exists within the active site allowing for specific peptide hydrolysis as it preferentially binds hydrophobic side chains, such as phenylalanine.

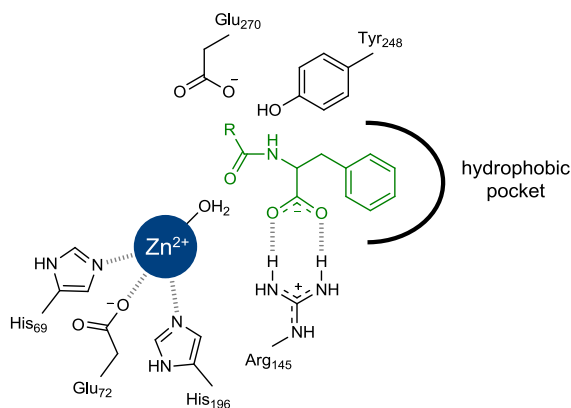


Figure 1.12—The active site of Carboxypeptidase-A.

From these limited set of examples, Nature can be seen to heavily exploit hydrogen bonding and electrostatic interactions to attain strong and selective anion recognition. It is no surprise, therefore, that these interactions are prevalent in synthetic anion receptors, as discussed in the next section.

1.3.2 Synthetic anion receptors

Synthetic anion receptors can be conveniently divided into three broad categories: *neutral*, *positively charged* and *Lewis acidic* anion receptors. Neutral anion receptors bind anions primarily using hydrogen bonding or other non-covalent interactions (excluding electrostatic interactions). Positively charged anion receptors take advantage of electrostatic interactions, however they often employ other non-covalent interactions, such as hydrogen bonding, to achieve binding selectivity due to the inherent lack of directionality of electrostatic interactions. Lewis acidic hosts exploit Lewis acid–base complexation for anion coordination, with them including transition metal-based receptors. These different classifications of anion receptor will be dealt with sequentially in the following three sections.

1.3.2.1 Neutral anion receptors

Neutral anion receptors rely on the complementary effect of multiple weak non-covalent forces, principally hydrogen bonding, to achieve the recognition of anionic guests generally in

polar organic solvents. The directionality of such interactions affords greater selectivity than their positively charged counterparts (**Section 1.3.2.2**). Receptors incorporating amide, urea, thiourea, pyrrole, hydroxyl and triazole functional groups are commonplace, whilst hosts exploiting halogen bonding have only recently been reported (**Figure 1.13**).

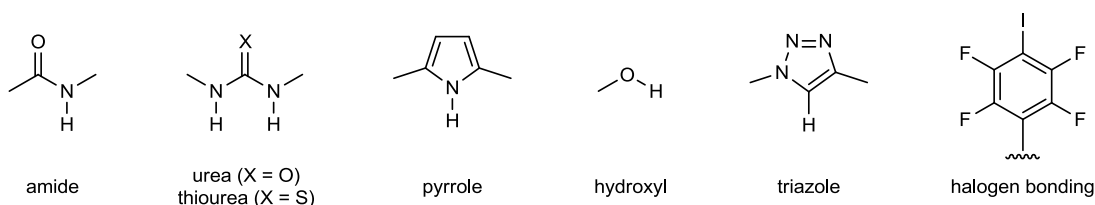


Figure 1.13—Neutral anion binding motifs.

Receptors containing N–H hydrogen bonds account for a great majority of neutral synthetic anion receptors. Much attention has been paid to amide-based receptors, which is not surprising given the prevalence of amide N–H $\cdots$ A[−] hydrogen bonding interactions in Nature. Crabtree and co-workers reported the anion binding capabilities of the isophthalamide motif, which demonstrated 1:1 halide anion recognition in dichloromethane through the action of two convergent amide hydrogen bonds (**Figure 1.14a**).³¹ This work was then expanded by Jurczak who incorporated analogous pyridine-2,6-bis-amide motifs into macrocyclic structures whose size could be fine-tuned to achieve enhanced chloride selectivity (**Figure 1.14b**).³² The $n = 1$ macrocycle bound chloride, in a 1:1 stoichiometric fashion, two orders of magnitude more strongly than its smaller ($n = 0$) and larger ($n = 3$) cyclic analogues in DMSO solution ($K_a = 1930$, 65 and 18 M^{−1} respectively). The same pyridine-2,6-bis-amide functionality has also been exploited by Bowman-James and co-workers who synthesised a tricyclic host (**Figure 1.7a**) possessing a complementary binding cavity for linear anions, in particular bifluoride, which it bound selectively over the halides in DMSO.

Ureas and thioureas are closely related to the amide group, with these moieties instead possessing two parallel N–H hydrogen bond donor groups that are suitably spaced to

recognise Y-shaped anions, such as nitrate and carboxylate. For example, Fabbrizzi has described a urea-based receptor that strongly complexes acetate in acetonitrile solution ($\log K_a = 6.61$), with the binding mode for this system inferred from X-ray crystallography (**Figure 1.14c**).³³ Thiourea N–H protons are generally more acidic than their urea analogues, which can result in thiourea-based receptors being more potent anion binders. However, this increased acidity can also lead to deprotonation of the thio-urea NH groups, as demonstrated by Wu and co-workers.^{34, 35} Their tris-urea receptor (**L**₁) was shown to bind a number of oxoanions, such as PO_4^{3-} and SO_4^{2-} , strongly in 3:1 DMSO/water whereas tris-thiourea receptor (**L**₂) underwent deprotonation by the highly basic anions studied in the same solvent mixture (**Figure 1.14d**).

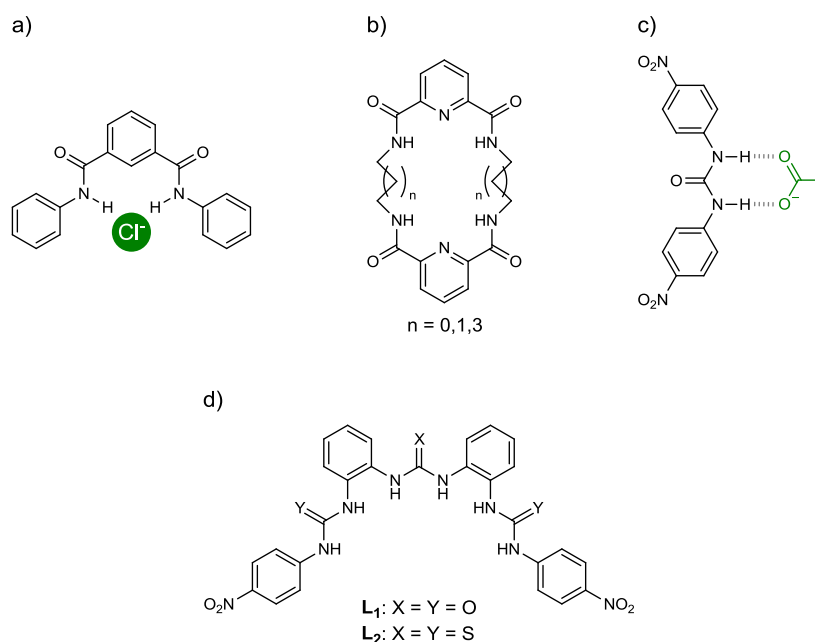


Figure 1.14—a) Crabtree's isophthalamide receptor, b) Jurczak's pyridine-2,6-bis-amide-containing macrocycle, c) Fabbrizzi's urea-based anion receptor and d) Wu and co-workers' urea- and thiourea-based receptors.

The pyrrole group is a potent anion binding motif which has been exploited in numerous receptors such as calixpyrroles, indoles, carbazoles and indolocarbazoles. Calix[4]pyrroles (**Figure 1.15a**) were the first neutral pyrrole-containing receptors to be reported and have

been shown to bind fluoride and chloride strongly in dichloromethane ($K_a = 1.7 \times 10^4$ and $3.5 \times 10^2 \text{ M}^{-1}$ respectively).³⁶ The anion binding properties of this system were developed further by Sessler and co-workers by the incorporation of a pyrrole-containing strap (**Figure 1.15b**), with this additional hydrogen bond donor group resulting in a near hundred-fold improvement of chloride binding strength in acetonitrile.³⁷ Indolocarbazoles are also effective anion complexants, with many examples of their use being reported in the literature, such as Jeong's fluoride selective rigid indolocarbazole-containing macrocycle (**Figure 1.15c**).³⁸

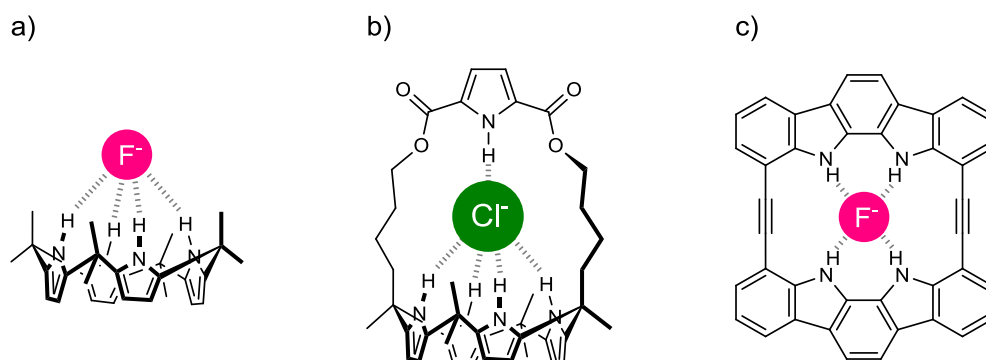


Figure 1.15—a) The first neutral pyrrole-containing anion receptor, b) Sessler's strapped calix[4]pyrrole and c) Jeong's rigid indolocarbazole-containing macrocycle.

Anion receptors utilising hydrogen bond donors other than N–H have also been reported. For example, the simple catechol group has been shown to complex chloride, in acetonitrile solution, via $\text{O–H}\cdots\text{Cl}^-$ hydrogen bonds (**Figure 1.16a**)³⁹ and a number of hosts exploit C–H hydrogen bond donors. Craig and co-workers have shown that a tetra-triazole foldamer can be used to bind chloride in acetone solution (**Figure 1.16b**),⁴⁰ whilst more recently, Flood *et al.* have synthesised a cyanostilbene 'campestarene,' or cyanostar, macrocycle (**Figure 1.16c**) which forms 2:1 sandwich complexes with large anions, such as BF_4^- , ClO_4^- and PF_6^- , in 2:3 $\text{CD}_3\text{OD}/\text{CD}_2\text{Cl}_2$.⁴¹

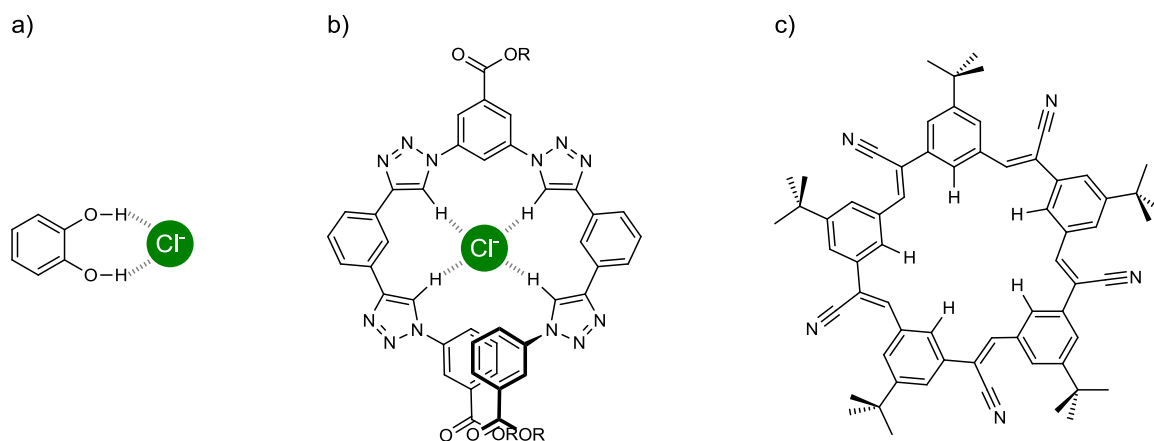


Figure 1.16—a) Chloride binding by catechol, b) Craig's tetra-triazole foldamer and c) Flood's cyanostar macrocycle.

The implementation of halogen bonding interactions in solid state crystal engineering is well known;^{42, 43} however, their use in solution phase anion recognition is still in its infancy. Taylor and co-workers were the first to exploit halogen bonding for solution phase anion recognition with the tripodal receptor **L**₁ (**Figure 1.17a**) being shown to selectively complex chloride over bromide, iodide and various oxoanions in acetone solution.¹⁴ This work has been expanded to elegantly demonstrate how the halogen bond donor ability of a host is dependent upon the polarisability of the halogen atom (**Section 1.2.2**), with bromine and fluorine functionalised receptors **L**₂ and **L**₃ (**Figure 1.17a**) reported to bind chloride over four orders of magnitude more weakly than **L**₁ in the same solvent.⁴⁴ Receptors that incorporate both hydrogen and halogen bonding are also known, with the same group developing a urea-based receptor (**Figure 1.17b**) that complexes anions strongly in acetonitrile.⁴⁵

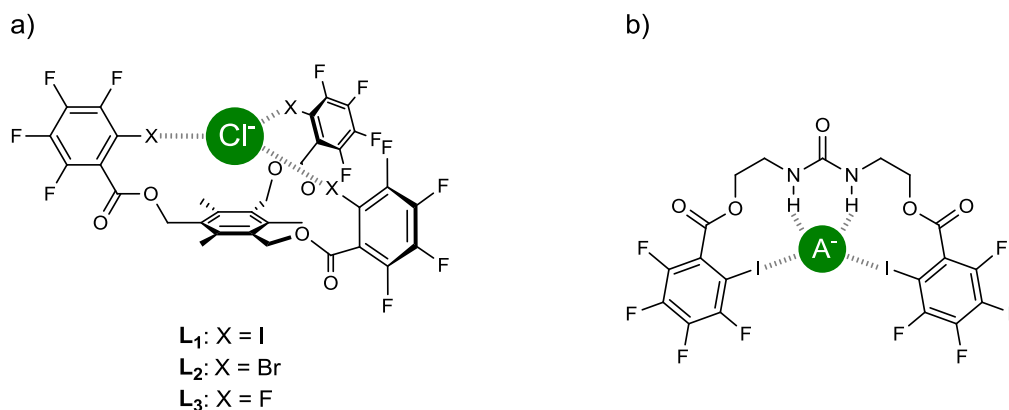


Figure 1.17—Taylor's a) tripodal hosts and b) mixed hydrogen and halogen bonding urea-based receptor.

1.3.2.2 Positively charged anion receptors

The most fundamental property of anions is their negative charge, and so one of the most effective ways to complex an anion is for the receptor to be positively charged, allowing for electrostatic ion–ion interactions to be exploited. Positively charged anion binding motifs found in the literature include ammonium, guanidinium, pyridinium, imidazolium and, more recently, triazolium (**Figure 1.18**).

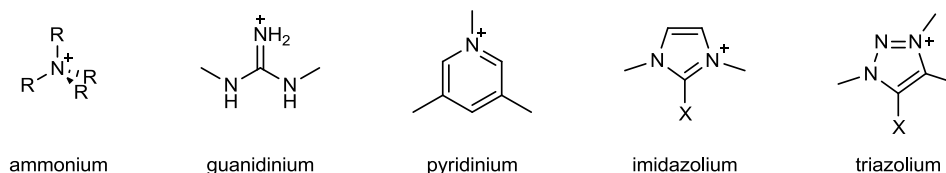


Figure 1.18—Commonly used positively charged anion binding motifs ($X = H, Br$ or I)

After Park and Simmons reported the first anion receptor (**Figure 1.1b**), which used two ammonium moieties to bind halide anions in aqueous trifluoroacetic acid solution,⁹ Lehn and co-workers constructed a series of macrocyclic and macrotricyclic polyammonium-based receptors whose cavity size could be tailored for a specific anion.⁴⁶⁻⁴⁹ For example, their cryptand receptor, which bears six protonated amine groups, was shown to selectively bind the linear azide anion, in aqueous solution, by virtue of its complementary binding cavity (**Figure 1.19a**).⁵⁰ More recently, a similar polyammonium receptor (**Figure 1.19b**) has been

shown to selectively complex the environmentally important pertechnetate anion (**Section 1.1**) in aqueous solution ($\log K_a = 5.50$) through the action of multiple N–H $\cdots$ O hydrogen bonds.⁵¹

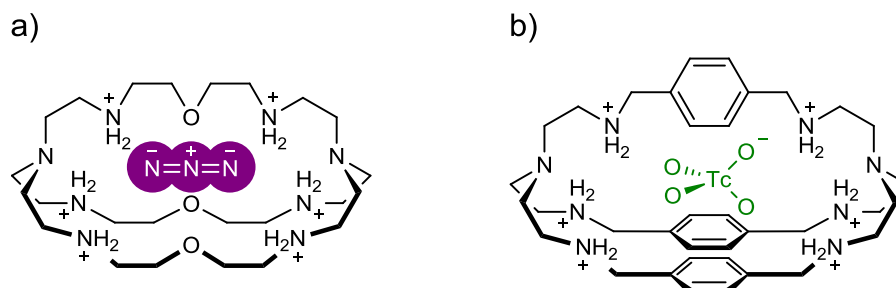


Figure 1.19—a) Lehn's azide selective cryptand and b) Amendola's pertechnetate receptor.

Polyammonium receptors have one major drawback—they are pH dependent, with the host only remaining protonated at low pH, thus restricting their use. One way of overcoming this is by using quaternary ammonium groups which, despite no longer profiting from hydrogen bonding stabilisation, can still utilise electrostatic interactions for anion binding. For example, Schmidtchen incorporated four quaternary ammonium motifs into cage-like receptors (**Figure 1.20a**) which were demonstrated to bind halides in aqueous solvent media.^{52, 53} Quaternary ammonium groups are not directional, however, which led to issues with the counteranion competing with the target guest for the binding cavity. This was overcome by attaching carboxylate⁵⁴ (**Figure 1.20b**) or borate⁵⁵ groups to the periphery of the cage to make zwitterionic receptors, which were shown to exhibit improved halide anion recognition.

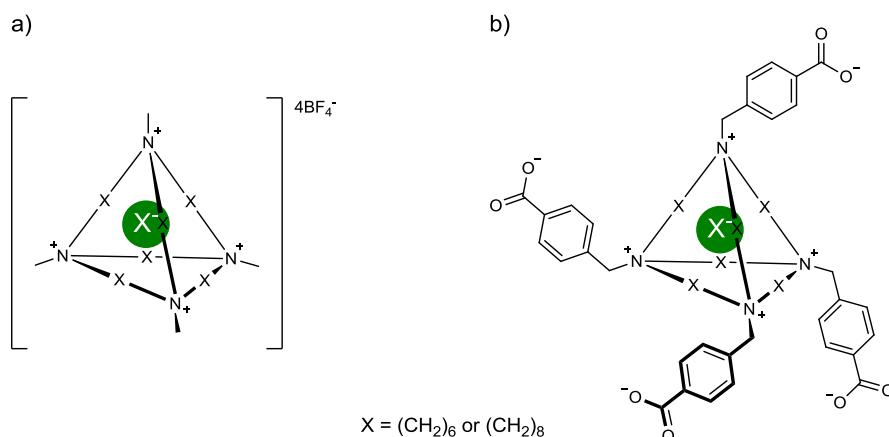


Figure 1.20—Schmidtchen's quaternary ammonium cage-like receptors.

Another strategy for avoiding the pH issues experienced with ammonium-based receptors is to employ a more basic anion recognition motif. Guanidinium has a higher pK_a than ammonium ($pK_a = 13.5$ vs. 9.47), due to charge delocalisation, and so remains protonated over a wider pH range.⁵⁶ This motif is often used to bind oxoanions as it can donate two parallel hydrogen bonds; for example, Hamilton and co-workers' acyclic bis-guanidinium receptor (**Figure 1.21a**) binds diphenyl phosphate in acetonitrile ($K_a = 4.6 \times 10^4 \text{ M}^{-1}$) and Schmidtchen's bipodal receptor (**Figure 1.21b**) recognises hydrogen phosphate strongly in water ($K_a = 970 \text{ M}^{-1}$).⁵⁷

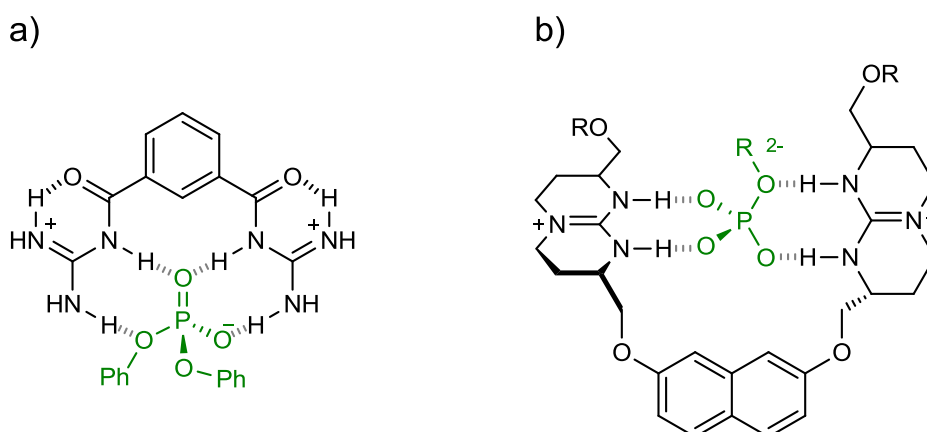


Figure 1.21—a) Hamilton's acyclic bis-guanidinium receptor and b) Schmidtchen's bipodal receptor.

The pyridinium group has been incorporated into numerous positively charged anion receptors, which take advantage of both electrostatic and hydrogen bonding interactions. Shinoda and co-workers have demonstrated that a tetra-pyridinium macrocycle (**Figure 1.22a**) binds tricarboxylate anions in water,⁵⁸ whereas Steed *et al.* synthesised a tripodal tris-pyridinium receptor (**Figure 1.22b**) that complexes bromide in acetonitrile solution ($K_a = 838 \text{ M}^{-1}$).⁵⁹

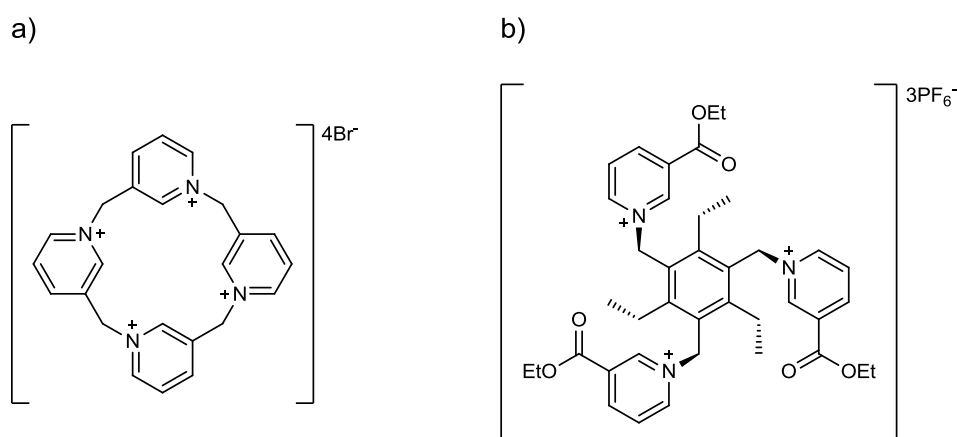


Figure 1.22—a) Shinoda's tetra-pyridinium macrocycle and b) Steed's tripodal receptor.

More recently, imidazolium and triazolium motifs have emerged as important anion binding groups due to their acidic C–H protons, which are capable of participating in charge-assisted hydrogen bonding. The use of two or more of these functional groups within a cyclic structural framework can result in the cooperative complexation of an anionic guest. For example, Alcalde *et al.* described an imidazolium containing macrocycle (**Figure 1.23a**) that selectively binds acetate in DMSO ($K_a = 359 \text{ M}^{-1}$),⁶⁰ whereas a tetrakis-imidazolium macrocycle (**Figure 1.23b**) has been shown to preferentially bind azide in the same solvent ($K_a = 488 \text{ M}^{-1}$).⁶¹

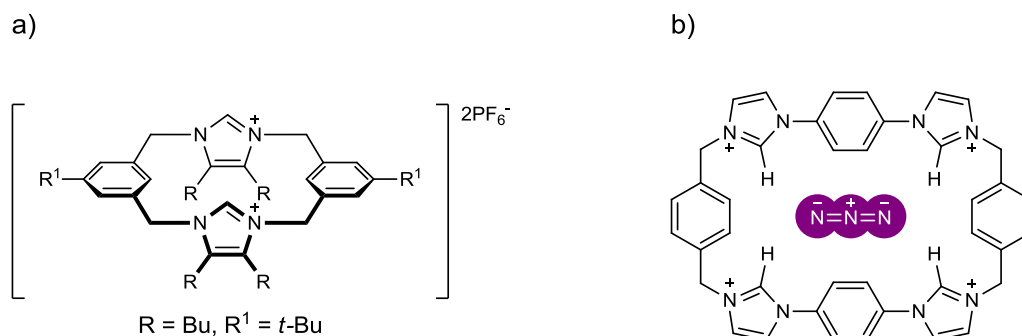


Figure 1.23—a) Alcalde's imidazolophane and b) Beer's tetrakis-imidazolium macrocycle.

The first example of exploiting the 1,2,3-triazolium motif in anion recognition was reported by Pandey *et al.* in 2008.⁶² They synthesised an acyclic steroid-based receptor (**Figure 1.24a**) that exhibits selectivity for dihydrogen phosphate, in chloroform, over halides and acetate. More recently, a tetra-triazolium macrocycle (**Figure 1.24b**) was demonstrated to be capable of complexing anions strongly in the competitive 1:1 DMSO/water solvent mixture.⁶³

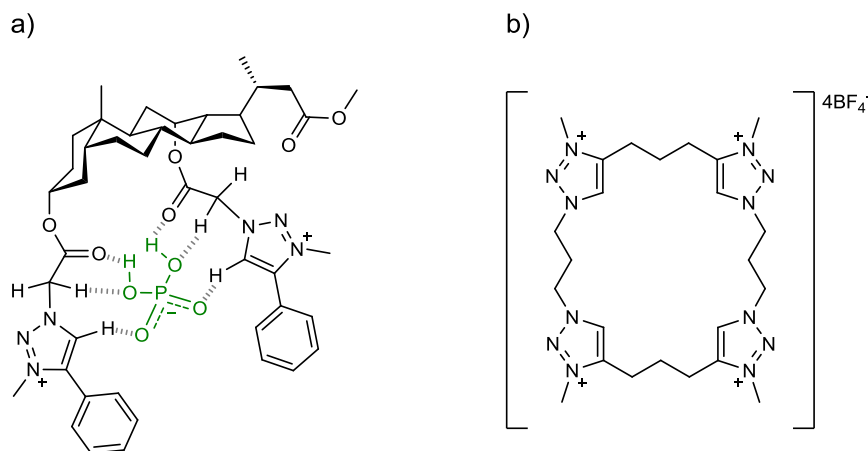


Figure 1.24—a) Pandey's steroid-based triazolium anion receptor and b) a tetra-triazolium macrocycle.

The introduction of halogen bonding as a relatively new non-covalent interaction available to the anion supramolecular chemist has resulted in the synthesis of halo-imidazolium and -triazolium functionalised anion receptors, although their use is still very much in its infancy. Resnati and Metrangolo have shown, through extensive ¹H NMR experiments, that a 2-iodo-imidazolium receptor (**Figure 1.25a**) selectively binds oxoanions over halides in

DMSO solution through the action of charge-assisted halogen bonding ($K_a(M^{-1}) = 1100$ ($H_2PO_4^-$), 260 (OAc^-), 150 (Cl^-), 67 (Br^-), 34 (I^-)).⁶⁴ The halo-imidazolium motif has been utilised by Beer *et al.* in the construction of two halogen bonding imidazolophanes (**Figure 1.25b**) that were found to selectively bind bromide and iodide in 9:1 MeOH/water.⁶⁵ The same group have also pioneered the use of the 5-iodo-triazolium group for halide anion recognition and reported simple 5-iodo-triazolium halide salts (**Figure 1.25c**) that exhibit $C-I \cdots X^-$ halogen bonding interactions in the solid state.⁶⁶

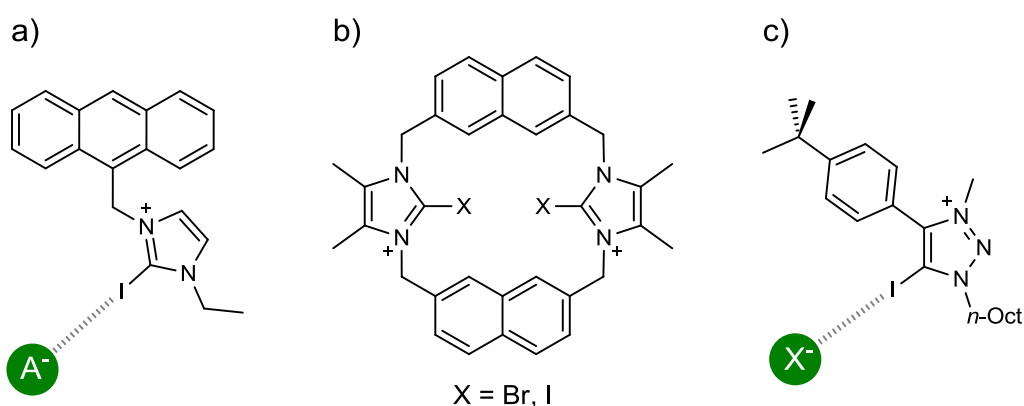


Figure 1.25—a) Resnati and Metrangolo's 2-iodo-imidazolium receptor and Beer's b) 2-halo-imidazolophane and c) 5-iodo-triazolium receptors.

1.3.2.3 Lewis acidic anion receptors

A number of Lewis acidic hosts have been reported in the literature containing heteroatoms such as boron,⁶⁷ silicon,⁶⁸ tin,⁶⁹ and germanium.⁷⁰ These species bind anions *via* donation of electron density from the anionic guest into a vacant orbital, such as Gabbai's boron and mercury containing fluoride receptor (**Figure 1.26a**).⁷¹ Transition metals can also be used to bind anions in an analogous manner,^{72, 73} with an added electrostatic contribution. For example, Jolliffe's bis-zinc(II) host (**Figure 1.26b**)⁷⁴ and Fabbrizzi's bis-copper(II) cage complex (**Figure 1.26c**),⁷⁵ which are selective for pyrophosphate and azide anions respectively, in aqueous solution.

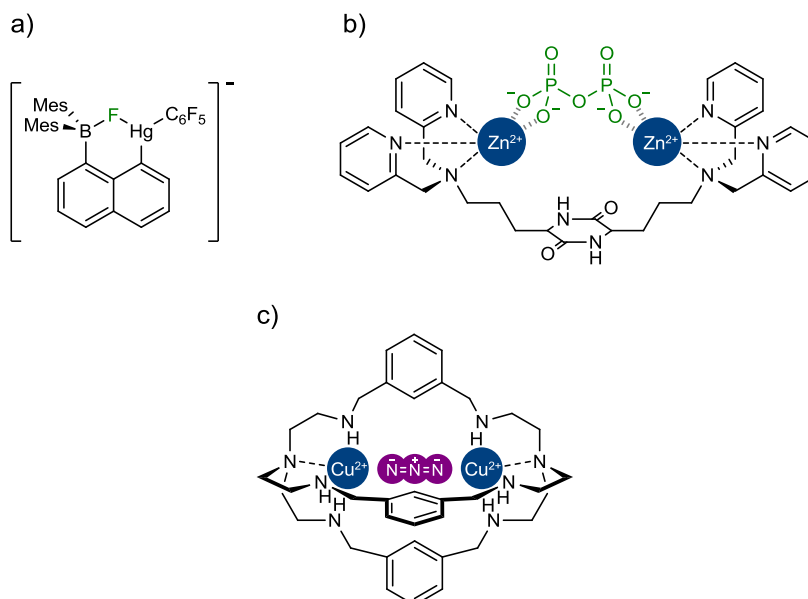


Figure 1.26—a) Gabbaï's boron and mercury-containing receptor, b) Jolliffe's bis-zinc(II) host and c) Fabbri's azide selective bis-copper(II) cage complex.

1.3.3 Applications of anion receptors

Reporter group functionalised anion receptors have been employed for the sensing of negatively charged species for a number of years, with such *anion sensors* often exploiting optical^{76, 77} or electrochemical⁷⁸ responses. More recently, receptors have been designed to act as *anion transporters*^{79, 80} and have also found use in *anion-controlled gelation*.^{81, 82}

One of the most commonly integrated reporter groups used for electrochemical anion sensing is the ferrocene motif. Guest complexation typically causes a cathodic shift in the ferrocene/ferrocenium redox couple, arising from stabilisation of the ferrocenium oxidation state by the nearby bound anion. For example, Tucker and Moody have shown that, in acetonitrile solution, coordination of chiral carboxylate anions by the urea group of their acyclic ferrocene host (**Figure 1.27a**) results in a cathodic shift of the metallocene redox couple of up to 90 mV.⁸³

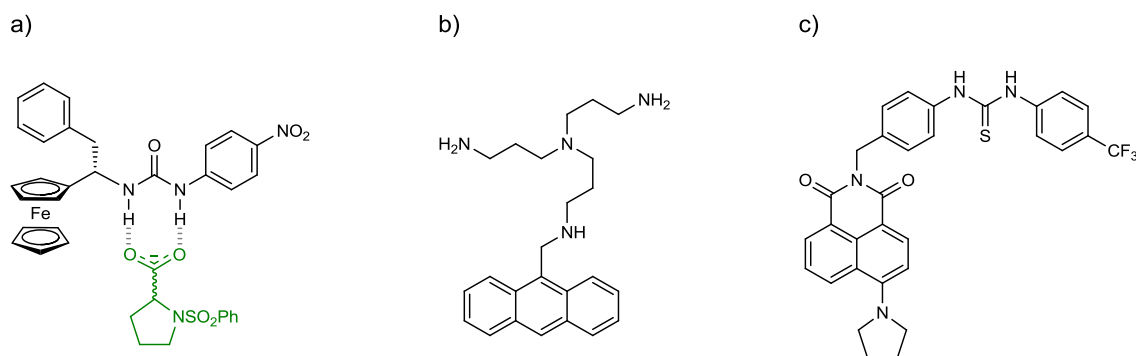


Figure 1.27—a) Tucker and Moody's ferrocene-functionalised anion sensor, b) Czarnik's anthracene-containing fluorescent sensor and c) Gunnlaugsson's naphthalamide-based sensor.

Optical anion sensors can be divided into two distinct classes—*fluorescent* or *colorimetric* sensors. Fluorescent sensors are attractive targets given their ability to detect very low concentrations of guests in solution, whereas the latter have the advantage of offering an optical response detectable by the naked eye. The anthracene group is often incorporated into fluorescent anion sensors, with the first example of its use shown in **Figure 1.27b**.⁸⁴ Binding of phosphate results in fluorescence emission being enhanced due to the inhibition of *photo-induced electron transfer* (PET), which is a mechanism by which a fluorescent group is quenched without the emission of radiation. More recently, Gunnlaugsson and co-workers have reported a naphthalamide thio-urea receptor (**Figure 1.27c**) which, in DMSO solution, undergoes fluorescence quenching upon addition of dihydrogen phosphate, again *via* a PET mechanism.⁸⁵

The preparation of synthetic trans-membrane anion transporters could allow for the action of their naturally occurring analogues to be mimicked, with such systems having the potential to provide cures for diseases such as cystic fibrosis (**Section 1.1**). A recent example of this type of system was reported by Gale and co-workers; their *ortho*-phenylenediamine-based bis-urea receptors (**Figure 1.28a**) were shown to be effective transporters of a variety of anions, including chloride, nitrate and bicarbonate, with the addition of electron-withdrawing groups, such as CN and NO₂, found to enhance anion transport.⁸⁶

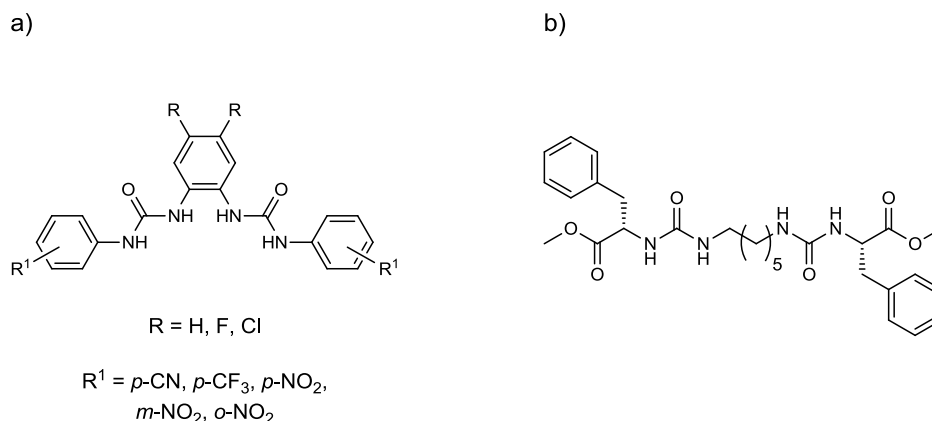


Figure 1.28—a) Gale's bis-urea-functionalised anion transporters and b) Steed's bis-urea gelator.

The application of anion receptors as supramolecular gels is an area of growing modern research. For example, Steed and co-workers have used bis-urea gelators (**Figure 1.28b**) to assist the crystallisation of organic compounds, in particular the anticonvulsant drug carbamazepine.⁸² Their gel matrix slows crystal growth resulting in larger, more uniform crystals which are then recovered by anion-triggered gel dissolution.

1.4 Mechanically interlocked structures

Despite the literature being replete with acyclic and macrocyclic anion receptors, as highlighted previously (**Section 1.3.2**), it has been argued that the challenge of selectively recognising anions in protic solvents, such as water, necessitates the construction of intricately designed three-dimensional mechanically interlocked host structures.⁸⁷ Mechanically bonded molecular systems consist of two or more interlocked components that cannot be separated without the cleavage of a chemical bond. Such systems can display complicated molecular topologies,⁸⁸ the two most common of which are *[n]*rotaxanes (**Figure 1.29a**) and *[n]*catenanes (**Figure 1.29b**), where *n* defines the number of interlocked components. A rotaxane contains one or more rings threaded over an axle component locked in place by two bulky stopper groups, whilst a catenane consists of two or more interlocked rings. A related structure is an interpenetrated *[n]*pseudorotaxane assembly (**Figure 1.29c**)

which, although not interlocked, is an important precursor in the synthesis of catenanes and rotaxanes, as discussed in the next section.

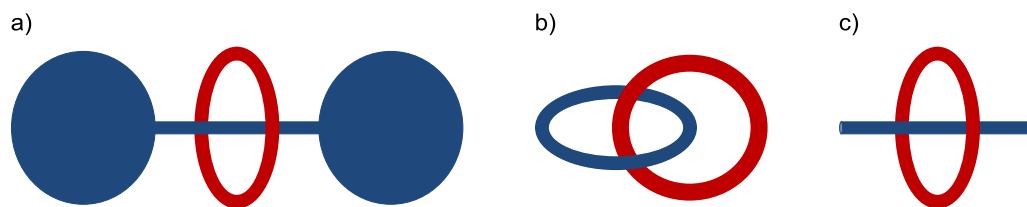


Figure 1.29—Cartoon representations of a) a [2]rotaxane, b) a [2]catenane and c) a [2]pseudorotaxane.

1.4.1 Synthetic strategies

Numerous approaches to the formation of interlocked structures have been reported. Catenanes are synthesised either by *cyclisation* (**Figure 1.30a**) or *double cyclisation* (**Figure 1.30b**) strategies, in which one or both of the ring components are formed in the making of the desired interlocked product. Methods for rotaxane formation include the commonly employed *clipping* (**Figure 1.30c**) and *stoppering* (**Figure 1.30d**) routes. Clipping involves the cyclisation of the macrocycle around the axle component, whereas stoppering involves the appending of bulky stopper groups to a pseudorotaxane assembly.

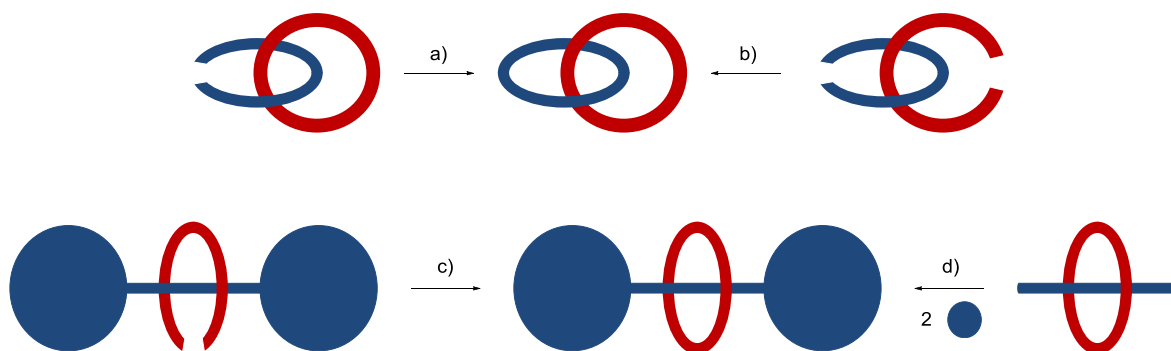


Figure 1.30—Common synthetic routes to mechanically interlocked structures: a) cyclisation and b) double cyclisation syntheses of [2]catenanes; c) clipping and d) stoppering syntheses of [2]rotaxanes.

Other less frequently exploited synthetic pathways to interlocked structures include *magic ring* catenation,^{89, 90} where two macrocycles re-open and then subsequently close in an

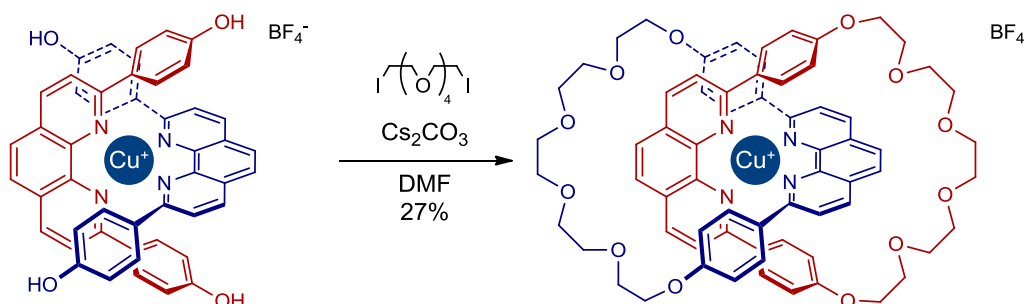
interlocked arrangement, and the *snapping*,^{91, 92} *slippage*,^{93, 94} *shrinkage*^{95, 96} and *swelling*^{97, 98} methods of rotaxane formation. Snapping occurs when two “half-axes” are combined within a macrocycle and slippage arises when the macrocycle component is able to slide over the axle stopper groups. In the swelling strategy the stopper groups are increased in size after the macrocycle has threaded onto the axle, whereas in shrinkage, the macrocycle, which is initially large enough to allow the axle to interpenetrate it, is decreased in size to prevent de-threading.

1.4.2 Templatation

Whilst early attempts at synthesising mechanically interlocked structures relied purely upon low yielding statistical approaches,⁹⁹⁻¹⁰² modern syntheses utilise a templating species that, as defined by Busch, “organises an assembly of atoms, with respect to one or more geometric loci, in order to achieve a particular linking of atoms.”¹⁰³ This type of methodology is referred to as *templatation* and involves the use of cationic, neutral or anionic templating species, as discussed in the following three sections.

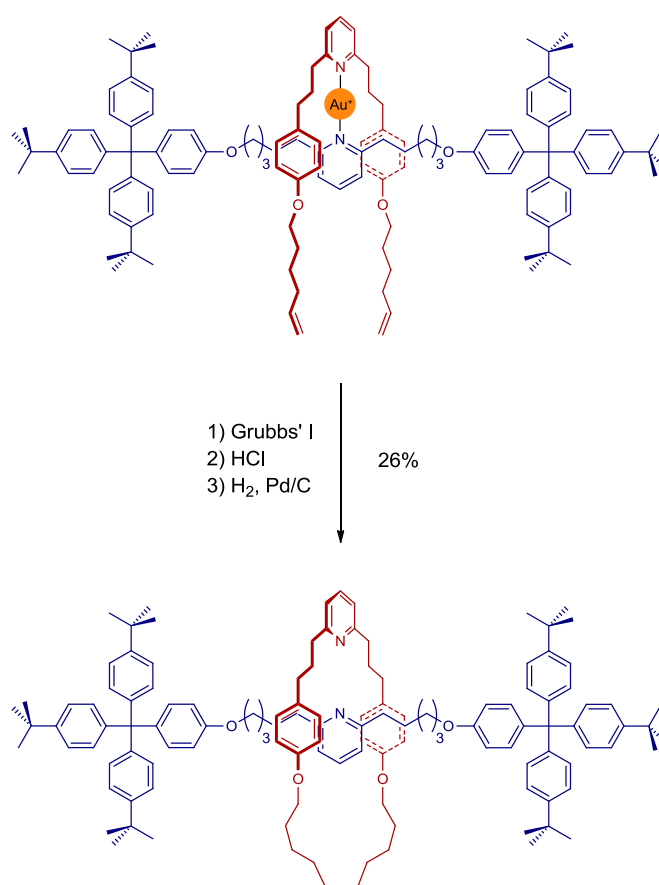
1.4.2.1 Cation templation

The templated synthesis of interlocked structures was pioneered in the 1980s by Sauvage who reported that a copper(I) cation could be used to template the formation of a [2]catenane in an isolated yield of 27% (**Scheme 1.2**)¹⁰⁴



Scheme 1.2—Sauvage's copper(I)-templated double cyclisation [2]catenane synthesis.

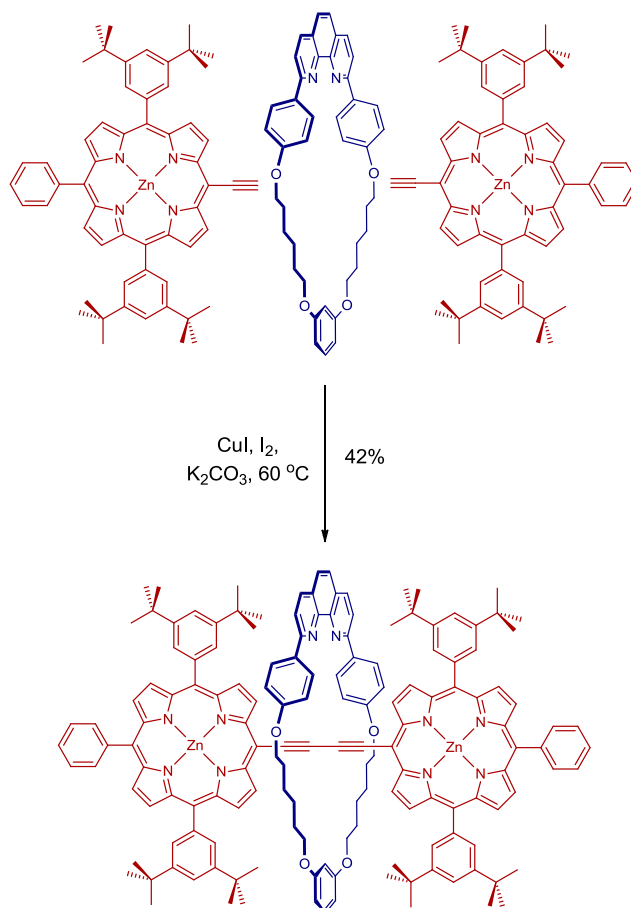
This synthesis relied on the orthogonal arrangement of two bidentate phenanthroline ligands around the tetrahedrally coordinated copper(I) ion, cyclisation of which gave the copper complex of the [2]catenane.¹⁰⁵ Since the publication of this seminal work, a range of transition metals with various coordination geometries have been exploited for the templated synthesis of interlocked systems.¹⁰⁶ For example, Leigh *et al.* have used a linearly directing gold(I) cation to template the synthesis of a [2]rotaxane *via* a clipping methodology (**Scheme 1.3**).¹⁰⁷



Scheme 1.3—Leigh's gold(I)-templated [2]rotaxane synthesis.

The same group were also the first to describe the use of *active-metal templation*, where a catalytically-active metal is bound transiently in the macrocycle's cavity from where it templates covalent bond formation to afford the interlocked product.⁹¹ Since the publication of this work, active-metal templation has become a common route to interlocked structures

with numerous coupling reactions being exploited in the mechanical bond forming step.¹⁰⁸ For example, Anderson *et al.* have used Cu(I)-catalysed Glaser coupling in the synthesis of their porphyrin stoppered [2]rotaxane (**Scheme 1.4**).⁹²



Scheme 1.4—Anderson's porphyrin stoppered [2]rotaxane synthesised via an active-metal-templated Glaser coupling reaction.

Whilst the preceding examples have all involved the use of metal cations, organic cations have also been successfully used as templating reagents in the synthesis of interlocked structures, with two of the most common examples being the 4,4'-bipyridinium and secondary dialkyl-ammonium motifs. Stoddart has pioneered the use of these templating species, with the charge-assisted aromatic donor-acceptor interactions between the 4-4'-bipyridinium motif and a bisoxy-naphthalene derivative facilitating the synthesis of a [2]rotaxane¹⁰⁹ (**Figure 1.31a**) and hydrogen bonding between the dialkyl-ammonium group and a dibenzo-24-

crown-8 macrocycle leading to the construction of a [2]catenane¹¹⁰ (**Figure 1.31b**). More recently, Loeb and co-workers used the benzimidazolium motif to template the formation of a [2]rotaxane (**Figure 1.31c**).¹¹¹

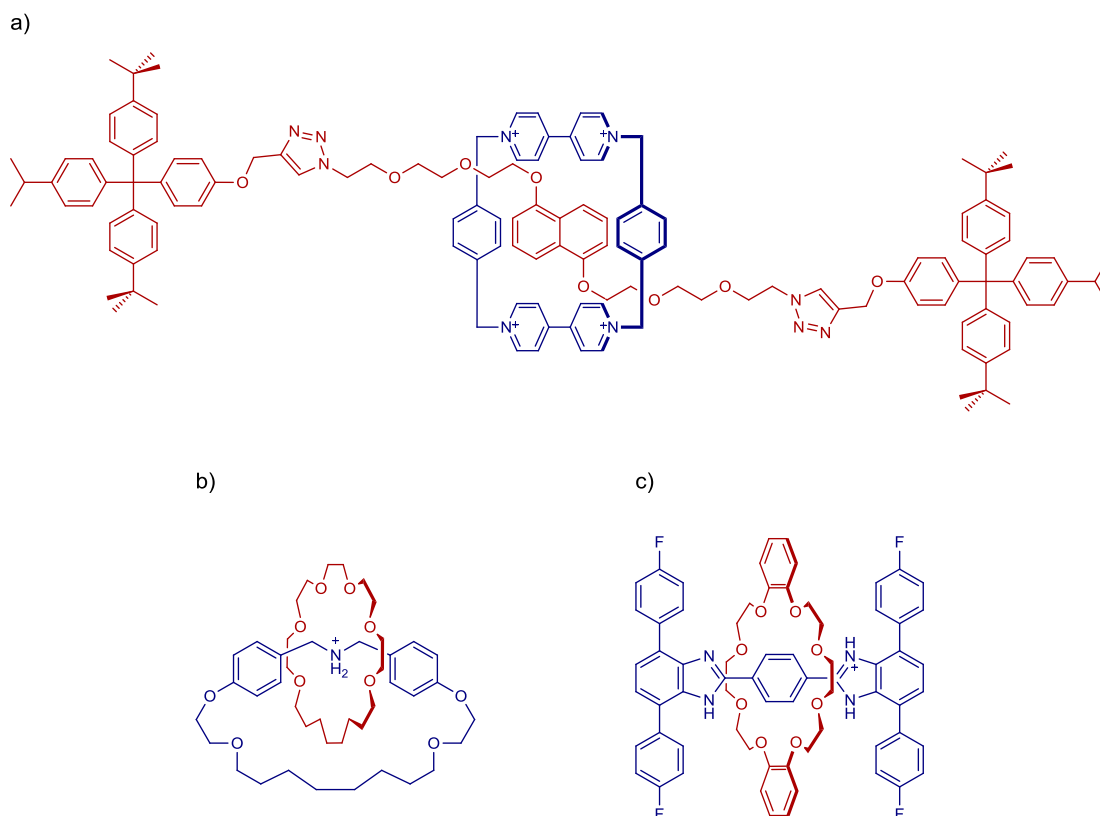


Figure 1.31—Stoddart's a) 4-4'-bipyridinium-containing [2]rotaxane and b) dialkyl-ammonium polyether [2]catenane. c) Loeb's benzimidazolium-templated [2]rotaxane.

1.4.2.2 Neutral templation

Charged groups are not always needed to template the formation of mechanically interlocked structures, as first exemplified by the work of Hunter, in 1992, who showed that favourable inter-component hydrogen bonding between amide motifs was responsible for the synthesis of a neutral octa-amide [2]catenane.¹¹² This work has since been expanded upon by Leigh and co-workers who have reported a series of isophthalamide catenanes^{113, 114} synthesised from isophthaloyl dichloride and a range of simple diamines, and more recently a number of neutral rotaxanes formed *via* inter-component hydrogen bonding, such as **Figure 1.32a**.^{115, 116}

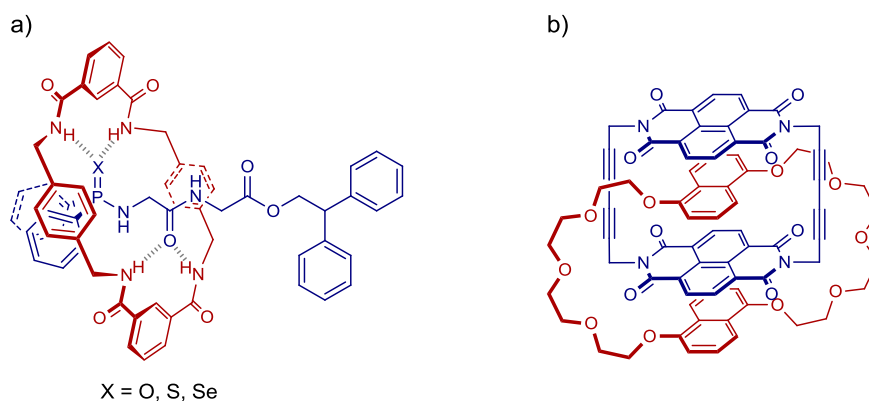
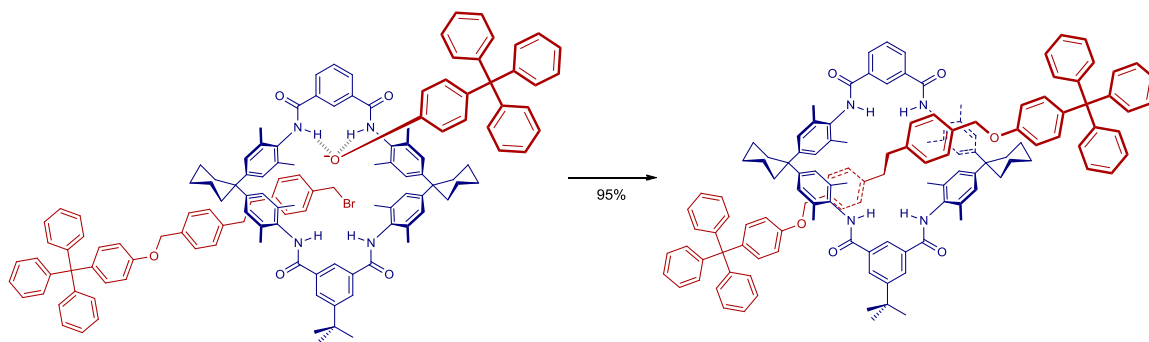


Figure 1.32—a) Leigh's neutral [2]rotaxanes synthesised via inter-component hydrogen bonding and b) Sanders' [2]catenane templated by aromatic donor–acceptor interactions.

Other neutral inter-component interactions have also been used to direct the construction of interlocked systems. For example, Sanders and co-workers have demonstrated that aromatic donor–acceptor interactions (**Section 1.2.2**) can be used to template the formation of a [2]pseudorotaxane between a bisoxy-naphthalene macrocycle and a naphthalene diimide (NDI) component which they can then convert to a [2]catenane (**Figure 1.32b**) via a copper(I)-catalysed alkyne coupling reaction.¹¹⁷ Finally, the hydrophobic effect (**Section 1.2.5**) has also been used for the templated synthesis of interlocked structures, often using cyclodextrin inclusion complexes in aqueous environments, as exemplified by the work of Harada^{118, 119} and Anderson.^{120–122}

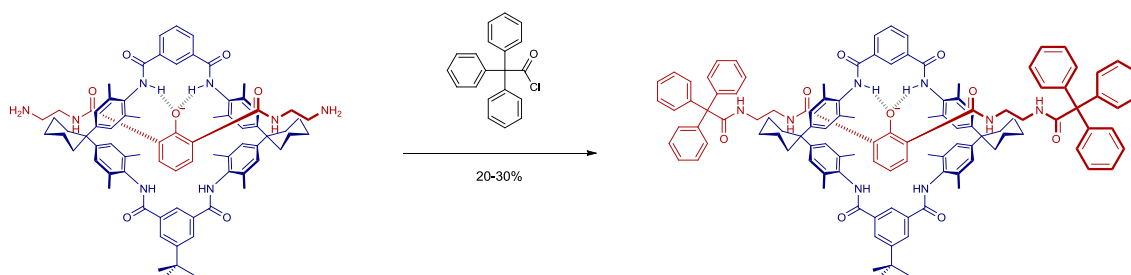
1.4.2.3 Anion templation

Of the three categories of templation, anion templation is historically the least widespread owing to the number of inherent challenges associated with anion complexation (**Section 1.2.1**). This is reflected in the fact that the first mechanically interlocked structure synthesised via anion templation was reported in 1999 by Vögtle,¹²³ sixteen years after Sauvage's seminal cation-templated [2]catenane synthesis (**Scheme 1.2**). Vögtle exploited the association of a phenolate half-axle and a tetra-amide macrocycle to template the formation of a [2]rotaxane in an impressive 95% yield in which the template is consumed (**Scheme 1.5**).



Scheme 1.5—Vögtle's anion-templated [2]rotaxane synthesis.

The phenolate anion has also been used by Schalley in the synthesis of a [2]rotaxane in which the phenolate template remains in the interlocked product (**Scheme 1.6**).¹²⁴ In this case, the isophthalamide–phenolate interaction templates the formation of a pseudorotaxane before stoppering *via* amide condensation affords the [2]rotaxane.



Scheme 1.6—Schalley's phenolate-templated [2]rotaxane synthesis.

In the early 2000s, Beer and co-workers reported the first instances of *discrete anion templation*, in which the template does not form part of the product interlocked structure, making this methodology fundamentally different from the previous examples.¹²⁵⁻¹²⁸ This strategy relies on the “sharing” of a chloride anion between a pyridinium chloride tight ion pair and an isophthalamide macrocycle component, with additional stabilisation coming from aromatic donor–acceptor interactions and hydrogen bonding between the *N*-methylpyridinium protons and polyether chain (**Figure 1.33a**). This pseudorotaxane assembly has since been utilised in the synthesis of numerous interlocked catenane and rotaxane structures,

such as those shown in **Figure 1.33b**¹²⁹ and **Figure 1.33c**.¹²⁶ Importantly, discrete anion templation allows for the template to be removed once the interlocked structure has formed, leaving behind a unique three-dimensional binding pocket, which can be exploited in the selective recognition of anionic guests (see **Section 1.4.3.2**).^{126, 127, 130} Beer has since expanded his methodology to include a number of different anion coordinating groups to replace the pyridinium isophthalamide motif, such as imidazolium (**Figure 1.33d**)¹³¹ and triazolium.¹³²

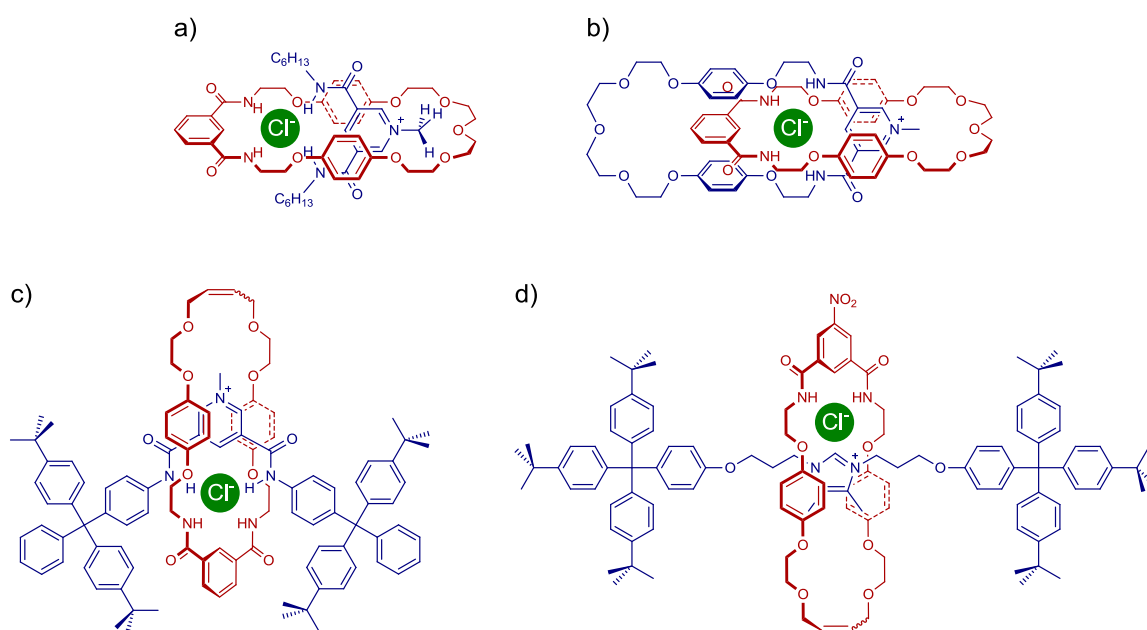


Figure 1.33—Discrete chloride anion templation as used for a) [2]pseudorotaxane assembly, b) [2]catenane synthesis and c) [2]rotaxane synthesis. d) Beer's imidazolium axle-containing [2]rotaxane.

More recent developments include the use of different anion templates, with the first nitrate anion-templated [2]rotaxane (**Figure 1.34a**) having been prepared,¹³³ and the integration of halogen bonding motifs, such as 5-iodo-triazolium (**Figure 1.34b**)¹³⁴ and 2-bromo-imidazolium (**Figure 1.34c**),¹³⁵ as alternative anion complexing groups. Finally, the synthesis of more intricate architectures, including a triply-interlocked capsule¹³⁶ and a “hand-cuff” catenane,¹³⁷ as well as numerous anion sensors¹³⁸⁻¹⁴¹ (**Section 1.4.3.2**) have also been reported, giving evidence for the scope of applications possible for discrete anion templation.

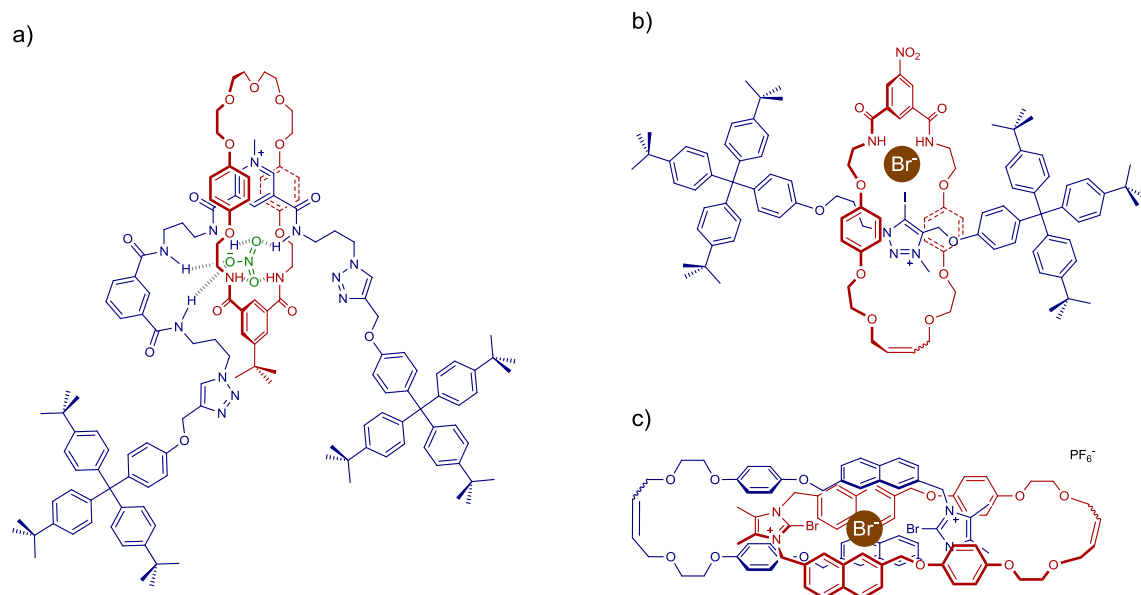


Figure 1.34—Beer's a) nitrate-templated [2]rotaxane, b) iodo-triazolium axle-containing [2]rotaxane and c) 2-bromo-imidazolium functionalised [2]catenane.

1.4.3 Applications of mechanically interlocked structures

With the effective synthesis of interlocked structures now made possible by the various templation methods discussed above, their potential application in a number of important areas of modern day research, including *molecular motion*,¹⁴²⁻¹⁴⁴ *guest recognition*^{145, 146} and *sensing*,^{87, 147} is currently being investigated.

1.4.3.1 Molecular motion

Mechanically bonded structures are ideal candidates for behaving as molecular machines as their multiple components allow for the position of one part of the interlocked molecule to be changed relative to the others. For example, a *pirouetting* motion is possible *via* the rotation of a macrocycle component in catenanes and rotaxanes, whereas *shuttling* behaviour can be exhibited in rotaxanes by the movement of the macrocycle along the axle (**Figure 1.35**).

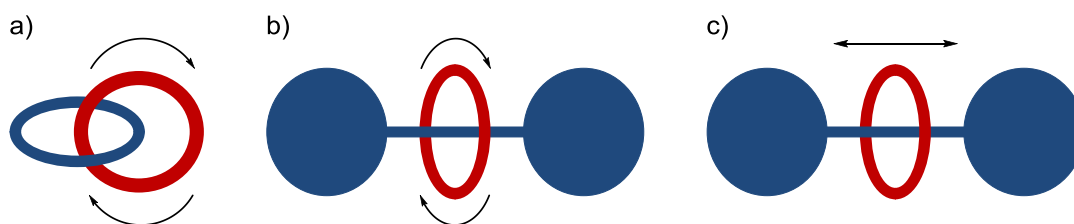
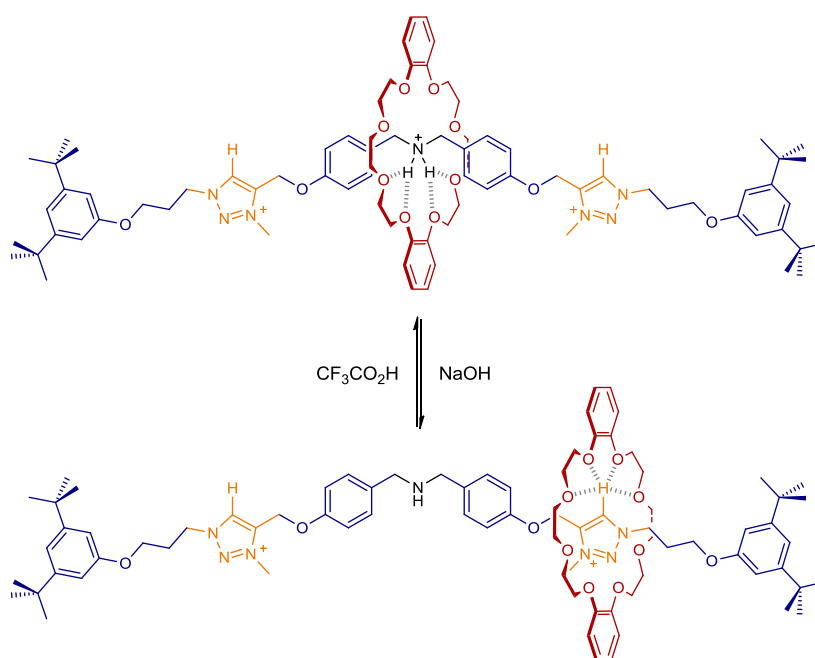


Figure 1.35—Cartoon representations of pirouetting molecular motion in a) catenanes and b) rotaxanes, and c) shuttling molecular motion in rotaxanes.

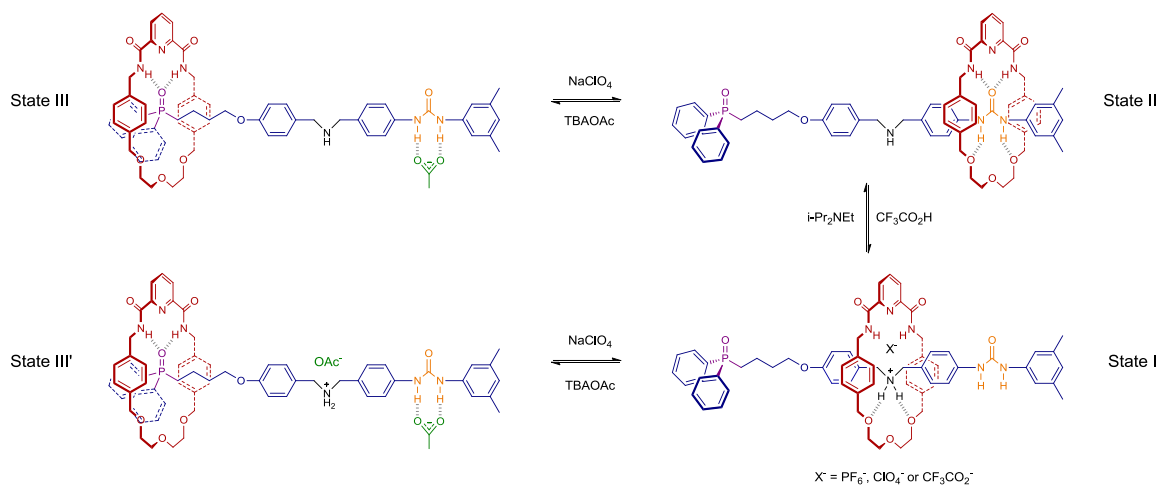
Stoddart and co-workers were the first to report a [2]rotaxane that demonstrated shuttling molecular motion, with this movement being driven either electrochemically or by changes in pH.¹⁴⁸ More recent examples of interlocked molecular machines include Leigh's acid/base switchable [2]rotaxane organocatalyst (**Scheme 1.7**)¹⁴⁹ and Wang's switchable three-station molecular shuttle (**Scheme 1.8**).¹⁵⁰



Scheme 1.7—Leigh's acid/base switchable [2]rotaxane organocatalyst.

In Leigh's system, the macrocycle resides over the triazolium motif when the rotaxane's secondary amine site is deprotonated, allowing the axle amine unit to catalyse Michael addition reactions between a thiol and α,β -ketone. However, upon protonation, the

macrocycle shuttles from the triazolium groups to the resulting dialkyl-ammonium station causing inhibition of catalysis. Wang's three-station shuttle (**Scheme 1.8**) is synthesised in State I with the macrocycle residing over the dialkyl-ammonium motif; subsequent addition of base followed by TBA acetate results in the macrocycle shuttling to the urea (State II) and phosphine oxide (State III) sites due to deprotonation of the dialkyl-ammonium motif and blocking of the urea site by an acetate anion respectively. This motion was shown to be reversible with the addition of NaClO_4 , to precipitate the bound acetate anion as NaOAc , and then trifluoroacetic acid returning the shuttle to its initial conformation (State I). It was also demonstrated that the macrocycle could be reversibly transported from the dialkyl-ammonium site to the phosphine oxide site (State I $\leftrightarrow$ State III') without going through the intermediate State II.



Scheme 1.8—Wang's switchable three-station molecular shuttle.

Although impressive, rotaxane shuttles are amongst the simplest molecular machines found in the literature. More sophisticated systems such as *molecular muscles*,¹⁵¹⁻¹⁵³ *ratchets*,^{154, 155} and *elevators*^{156, 157} have all been reported recently, giving evidence not only for the diverse applications of mechanically interlocked structures but also the scope for supramolecular chemistry to regulate processes at the molecular level.

1.4.3.2 Guest recognition and sensing

With their intricately designed binding cavities, somewhat reminiscent of those found in Nature (**Section 1.3.1**), mechanically interlocked host structures have widespread potential use for the selective recognition and sensing of guest species.

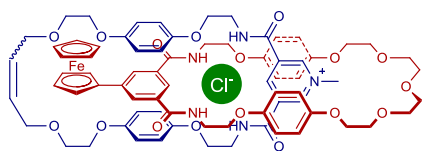
Discrete templation methods often result in the product interlocked system displaying a strong binding affinity for the templating species. For example, Sanders has described an acetylcholine-templated [2]catenane that was shown to bind its template one hundred times more strongly than other acetylcholine derivatives, in 95:5 CHCl₃/DMSO.¹⁵⁸

In keeping with the research interests of this thesis, Beer and co-workers have demonstrated that anion-templated interlocked structures, such as those shown in **Figure 1.33** and **Figure 1.34**, often selectively bind their templating anion over other, more basic anions.¹²⁶⁻¹³³ For example, the [2]rotaxane shown in **Figure 1.33c** binds chloride ($K_a = 1130 \text{ M}^{-1}$) significantly more strongly than both dihydrogen phosphate ($K_a = 300 \text{ M}^{-1}$) and acetate ($K_a = 100 \text{ M}^{-1}$) in 1:1 CDCl₃/CD₃OD¹²⁶ and the nitrate-templated [2]rotaxane (**Figure 1.34a**) was reported to selectively bind its template ($K_a = 430 \text{ M}^{-1}$) over hydrogen carbonate ($K_a = 100 \text{ M}^{-1}$) and dihydrogen phosphate ($K_a = 50 \text{ M}^{-1}$) in 45:45:10 CDCl₃/CD₃OD/D₂O.¹³³ This observed selectivity arises from the interlocked structures possessing binding cavities that are of complementary size and shape for the templating species.

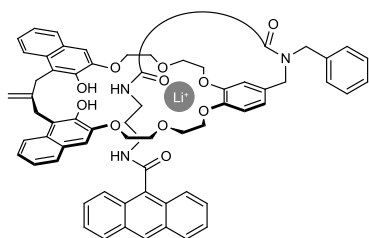
The sensing of guest species can be achieved through functionalising catenanes and rotaxanes with reporter groups, in a similar manner to the anion sensors discussed in **Section 1.3.3**. For example, Beer's ferrocene-appended [2]catenane (**Figure 1.36a**)¹³⁸ is capable of electrochemically sensing chloride in 1:1 dichloromethane/acetonitrile. The maximum cathodic shift in the ferrocene/ferrocenium redox couple of this system was observed after addition of one equivalent of chloride, in contrast to oxoanions, where the addition of many more equivalents of anion was necessary to observe a maximum cathodic perturbation. The

same group have also exploited fluorescence as a means for sensing anionic guests, with the halogen bonding [2]catenane shown in **Figure 1.34c** exhibiting an enhanced fluorescence response upon binding chloride and bromide in acetonitrile solution.¹³⁵

a)



c)



b)

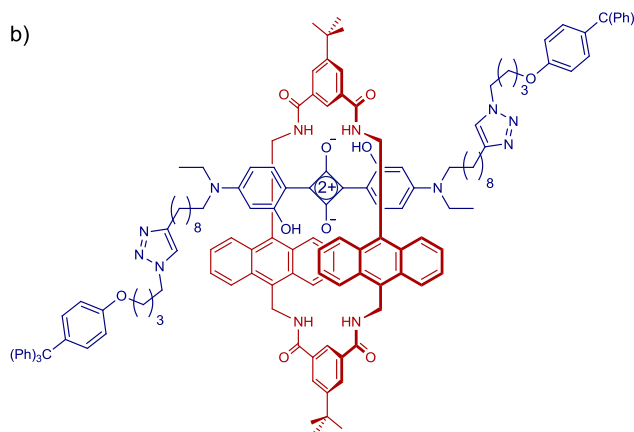


Figure 1.36—a) Beer's ferrocene-appended [2]catenane, b) Smith's chloride sensing squaraine rotaxane and c) Hiratani's [1]rotaxane lithium sensor.

More recently, Smith and co-workers have reported a squaraine rotaxane shuttle (**Figure 1.36b**) that gives an colorimetric response to chloride binding, in acetone solution.¹⁵⁹ The addition of chloride causes the macrocycle to shuttle along the axle and exposes the squaraine station, resulting in a change in its absorption band that is detectable by the naked eye.

Analogous cation sensing is also possible, as demonstrated by Hiratani and co-workers who reported a [1]rotaxane that displays a unique fluorescence response upon binding lithium ions (**Figure 1.36c**).¹⁶⁰ In this system, the binding of Li^+ by the polyether groups restricts the movement of the axle component, resulting in an enhanced fluorescence response due to the naphthalene and anthracene groups being held close together.

1.5 Metal nanoparticles

Whilst the majority of this thesis is concerned with the synthesis of mechanically interlocked structures and their anion recognition properties, the application of metal nanoparticles as new catalysts and sensors is also investigated in a collaborative CASE Award project with Johnson Matthey.

1.5.1 Introduction

Metal nanoparticles are discrete clusters of metal atoms with sizes that range between 1–100 nm. Although often considered a discovery of modern science, their existence can be traced back to Roman times where they were used for decorative purposes.¹⁶¹ Due to the quantum confinement of electrons, nanoparticles display a number of unique chemical and physical properties different from those of the bulk metal.¹⁶² This has resulted in considerable interest for their use in the areas of catalysis,¹⁶³⁻¹⁶⁸ biology¹⁶⁹⁻¹⁷¹ and optics.¹⁷²⁻¹⁷⁴

1.5.2 Methods of synthesis

There are a number of different methods for preparing metal nanoparticles,¹⁶² with most of these being wet chemical routes that rely on the chemical reduction of metal salts to form colloidal suspensions.¹⁷⁵ Due to their high surface energy, these colloids are thermodynamically unstable and prone to agglomeration,¹⁶¹ requiring them to be kinetically stabilised in some way. The two common mechanisms of stabilisation are *steric* and *electrostatic* (**Figure 1.37**). Steric stabilisation is afforded by surrounding the nanoparticles with either a layer of ligands or a polymer shell that prevents them from coming into close contact, whereas electrostatic stabilisation is provided by surrounding the nanoparticles with charged species that prevent agglomeration *via* electrostatic repulsion.

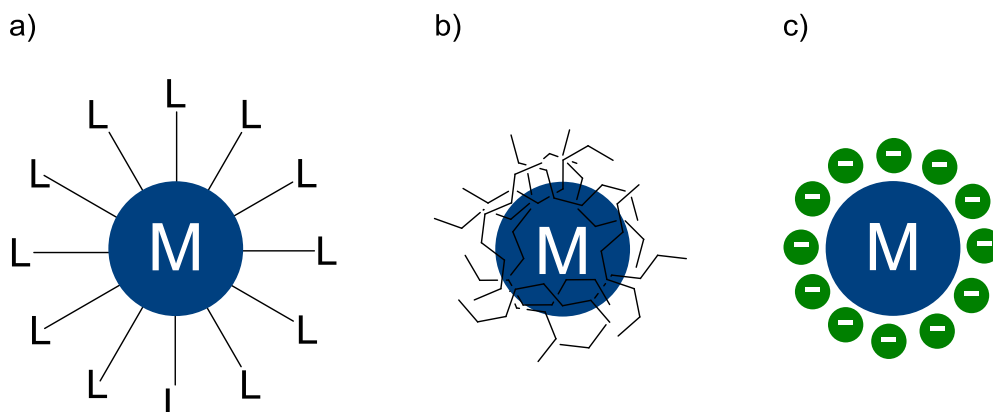


Figure 1.37—Kinetic stabilisation of nanoparticles by a) ligands (steric), b) polymers (steric) and c) charged species (electrostatic).

Examples of well-known metal nanoparticle syntheses are the Turkevich^{176, 177} and Brüst¹⁷⁸ methods. The Turkevich method was discovered in 1951 and can be used to prepare gold nanoparticles roughly 10–20 nm in size from tetrachloroauric acid and aqueous sodium citrate *via* heating. The citrate anions act as both the reducing agent and an electrostatic stabiliser, with changing the amount of citrate present having the effect of altering the size of the produced nanoparticles. The Brüst method was developed in the early 1990s with it producing organic soluble gold nanoparticles approximately 5–6 nm in size. Initially, tetrachloroauric acid is transferred into an organic solvent containing thiol-based ligands by a phase-transfer agent, which is typically an alkyl-ammonium salt. Subsequent reduction by adding an aqueous solution of sodium borohydride results in the formation of organic soluble gold nanoparticles, decorated with the thiol-based ligands, with these able to be easily separated from the aqueous phase. It is important to note that, whilst these original reports outline the synthesis of gold nanoparticles, these methods have also be adapted for use with other metals, such as silver,^{179, 180} platinum¹⁸¹ and palladium.¹⁸²

1.5.3 Applications of metal nanoparticles

Metal nanoparticles possess high surface area/volume ratios and, due to their controlled synthesis, impressive uniformity of size between clusters.¹⁸³ In addition, gold and silver nanoparticles display a structure-dependent *surface plasmon resonance* (SPR) band in their UV-visible spectrum, arising from the collective excitement of surface localised electrons, which results in them being deeply coloured.^{161, 162} Given these properties, it is no surprise that two of the most common applications of metal nanoparticles are in *catalysis* and *sensing*.

1.5.3.1 Catalysis applications

Catalysis is one of the most important areas of modern research, with approximately 90% of all the materials, pharmaceuticals and foodstuffs commonly used in our day-to-day lives being made from catalytic processes.¹⁸⁴ Whilst such products can be manufactured using traditional homo- and heterogeneous catalytic systems, there has been a noticeable shift in recent years to the use of *nanocatalysts*, in which preformed nanoparticles are dispersed onto a solid support. The use of such nanocatalysts has two key advantages: firstly, their large surface area affords optimal substrate contact, ensuring cost-effective use of the catalytic material¹⁸⁵ and enhanced activity and durability;¹⁷⁵ secondly, catalytic activity and selectivity can be fine-tuned by altering the size, shape and/or surface functionality of the nanoparticles.¹⁸⁶⁻¹⁸⁹

With these points in mind, metal nanoparticles have been shown to catalyse a wide array of important chemical reactions (**Figure 1.38**). Gold nanoparticles have been reported to catalyse a number of oxidations,¹⁹⁰ including that of carbon monoxide,¹⁹¹ whereas other metals, such as palladium and platinum, have been exploited in an array of important hydrogenation¹⁹²⁻¹⁹⁶ and coupling reactions.¹⁹⁷⁻¹⁹⁹

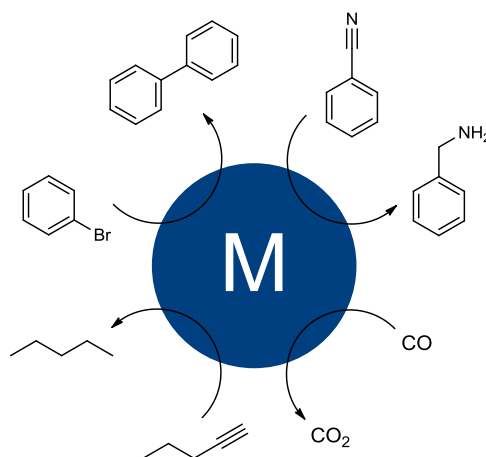
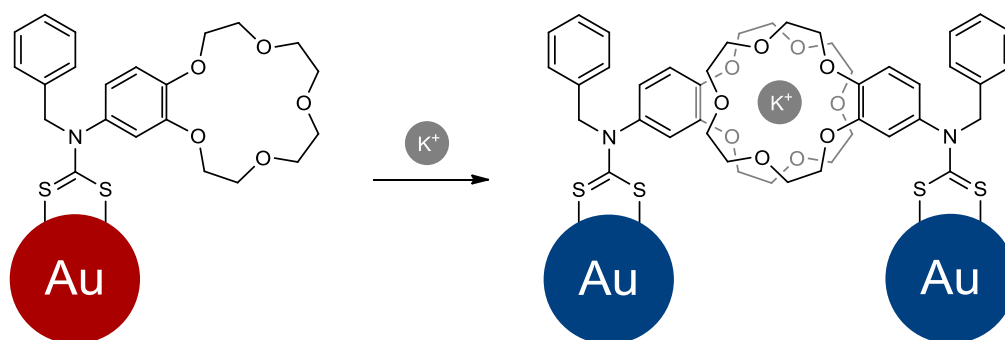


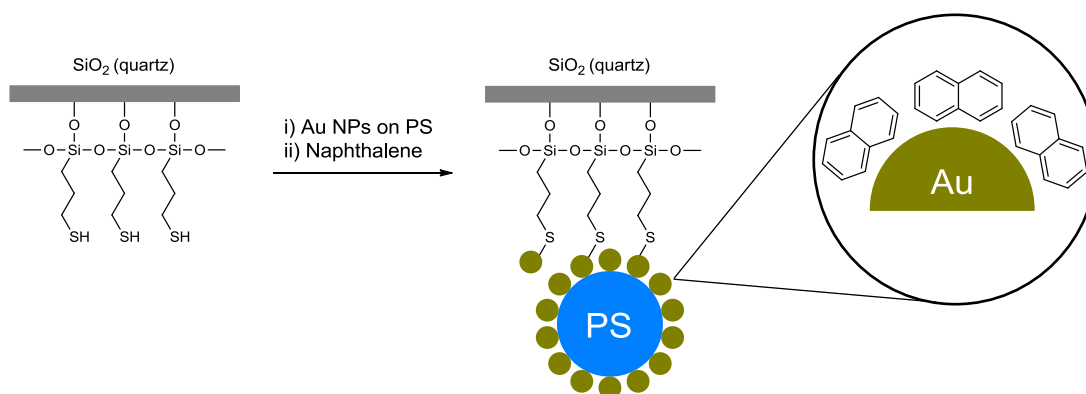
Figure 1.38—Diagrammatic representation of the array of reactions catalysed by metal nanoparticles.

1.5.3.2 Sensing applications

The SPR band of gold and silver nanoparticles is dependent upon their size, shape, composition and the dielectric constant of the surrounding media,²⁰⁰⁻²⁰² resulting in characteristic absorption spectra for different nanoparticles. This property can be used to elucidate the nature of the surrounding or adsorbed species, as demonstrated by a number of colorimetric chemical sensors.²⁰³⁻²⁰⁹ For example, Menon and co-workers have reported that gold nanoparticles decorated with benzo-15-crown-5 moieties are able to colorimetrically detect potassium ions in aqueous solution (**Scheme 1.9**).²⁰⁹ In its unbound state, their system has a red colour, however this changes to blue upon addition of potassium ions as guest complexation gives rise to aggregation of the nanoparticles.



Scheme 1.9—Menon and co-workers' colorimetric potassium sensor.



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1.5.3.3 Biological applications

Whilst the application of metal nanoparticles in the areas of catalysis and sensing is of particular interest to this project, nanoparticles also have important biological applications. The dimensions of nanoparticles make them ideal for incorporation into biological systems; as such, gold nanoparticles have been used as delivery agents for the introduction of proteins²²¹ and small molecules²²² into cells. For example, the active component of the anti-cancer agent oxaliplatin was appended to gold nanoparticles (**Figure 1.39**) which resulted in improved cell and nucleus permeability, thus enhancing drug delivery.²²³ Owing to their unique optical and magnetic properties nanoparticles have also been exploited in bio-imaging,²²⁴⁻²²⁶ with nanoparticle-based contrast agents being used to image cancer cells.^{227, 228}

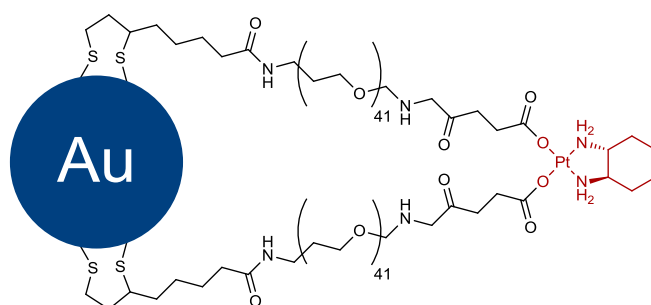


Figure 1.39—Graham and Wheate’s gold nanoparticles functionalised with the active component of oxaliplatin (red) for use as an anti-cancer drug delivery agent.

1.6 Thesis outline

This project is broadly split into two main areas of research—anion recognition by mechanically interlocked structures, synthesised *via* anion templation, and the use of metal nanoparticles for catalysis and sensing applications.

Chapter Two discusses the anion-templated formation of interpenetrated and interlocked structures containing 5-halo-triazolium halogen bond donating motifs. A series of [2]rotaxanes are synthesised and the effects of altering the halogen bond donor, as well as the structure of the axle component, on the anion binding properties of the system investigated.

A halogen bond containing [2]catenane is also synthesised and its ability to recognise anions *via* fluorescence highlighted.

Chapter Three initially reports the synthesis of a series of novel isophthalamide functionalised macrocycles and describes their ability to form pseudorotaxane assemblies with a pyridine *N*-oxide threading component. This observation results in the preparation of four neutral pyridine *N*-oxide containing [2]rotaxanes, which are subsequently found to bind halide anions strongly in aqueous solvent mixtures. An attempt to enhance the anion binding affinity of these systems through the incorporation of a positive charge is also reported.

Chapter Four outlines the preparation of gold and palladium nanoparticles decorated with β -cyclodextrin functionalised ligands for catalysis and sensing applications. The well-documented host–guest inclusion chemistry of β -cyclodextrin not only accounts for the unusual catalytic properties observed by such materials but is also exploited for the controlled aggregation of gold nanoparticles necessary for SERS sensing.

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CHAPTER Two

Chapter Two: Halogen bonding interlocked host structures

2.1 Introduction

2.1.1 The halogen bond

Since the research detailed in this Chapter was begun, the halogen bond has been defined by IUPAC: “a halogen bond occurs when there is evidence of a net attractive interaction between an electrophilic region associated with a halogen atom in a molecular entity and a nucleophilic region in another, or the same, molecular entity.”¹ The definition highlights a number of important features of a typical halogen bond, $R-X\cdots Y$, that are relevant to the work discussed in this Chapter:

- $R-X$ is termed the halogen bond donor and Y the halogen bond acceptor
- The interatomic distance between X and Y tends to be less than the sum of their van der Waals' radii
- The $R-X$ bond length usually increases upon halogen bond formation, owing to donation of electron density by Y into the $R-X$ σ^* anti-bonding orbital
- The halogen bond angle tends to be close to 180°
- Halogen bond strength decreases as the electronegativity of X increases and the electron-withdrawing ability of R decreases

The forces involved in halogen bond formation are primarily electrostatic. However, there are also polarisation, charge transfer and dispersion contributions to consider, with the relative roles of these different forces varying from one halogen bond to another. Density functional theory (DFT) studies of CF_3X molecules have revealed that the electron density around the halogen X atom is anisotropically distributed, giving rise to a region of partial positive charge

(or σ -hole) at the halogen end of the C–X bond^{2, 3} which is able to interact with a Lewis base, such as an anion. The size of this σ -hole increases as the halogen atom becomes less electronegative (or more polarisable), meaning that R–I is a superior halogen bond donor to R–Br, which in turn is better than R–Cl, as shown in **Figure 2.1**.

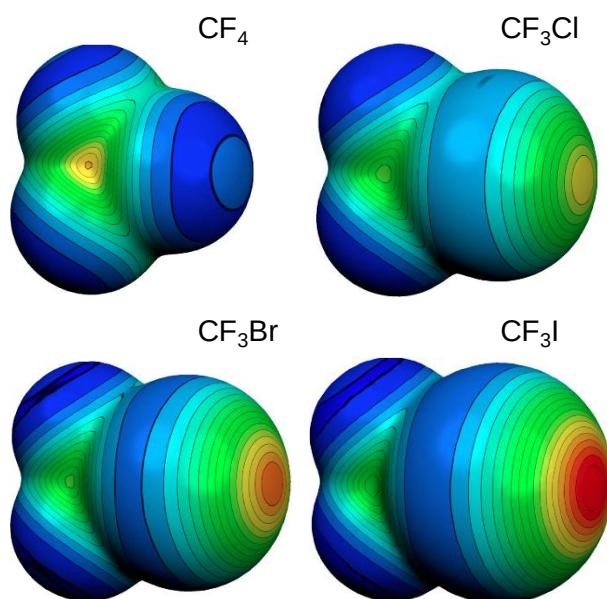


Figure 2.1—DFT analysis of CF_3X molecules (red represents regions of partial positive charge).²

With their comparable strength to hydrogen bonds and increased directionality, it is surprising that the use of halogen bonding in supramolecular chemistry has remained limited until the last ten to fifteen years. During this time, halogen bonds have been exploited for a number of varied applications including crystal engineering,⁴ self-assembly,⁵ and, more recently, solution phase anion recognition (**Sections 1.3.2.1** and **1.3.2.2**) and the assembly of interlocked and interpenetrated structures, as detailed in the next section.

2.1.2 Halogen bonding interlocked and interpenetrated structures

In 2010, Beer and co-workers reported the first use of halogen bonding to direct the assembly of an interpenetrated structure, where chloride templated the formation of a pseudorotaxane between a bromo-imidazolium threading component and an isophthalamide macrocycle

(**Figure 2.2a**).⁶ Interestingly, they found that the halogen bonding bromo-imidazolium pseudorotaxane was more stable than its hydrogen bonded imidazolium analogue ($K_{app}(M^{-1}) = 254$ and 97 respectively, in $CDCl_3$).

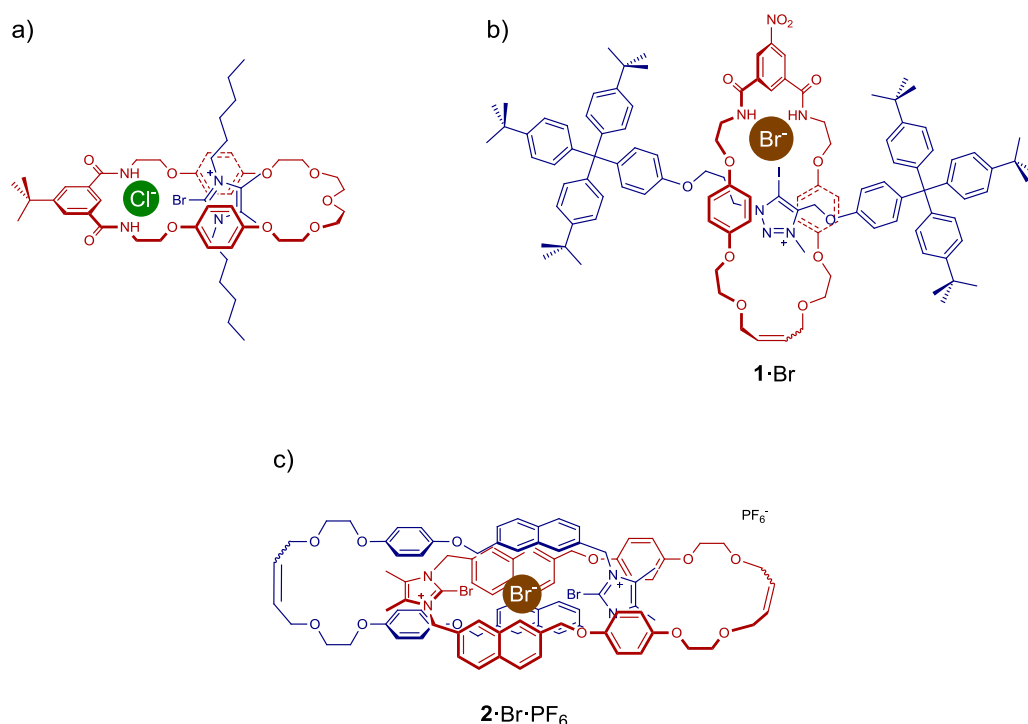


Figure 2.2—Halogen bonding anion-templated interpenetrated and interlocked structures: a) a bromo-imidazolium containing [2]pseudorotaxane, b) an iodo-triazolium axle containing [2]rotaxane and c) a bromo-imidazolium based [2]catenane.

Soon after, the same group exploited solution phase halogen bonding in the bromide anion-templated synthesis of the first halogen bonding interlocked construct **1·Br** (**Figure 2.2b**), consisting of an iodo-triazolium containing axle component.⁷ The incorporation of this halogen bond donating group was found to increase the rotaxane's strength of bromide anion complexation by over two orders of magnitude, in 1:1 $CDCl_3/CD_3OD$, as compared to the previously reported triazolium analogue **3·PF₆** (**Figure 2.3a**)⁸ ($K_a > 10^4 M^{-1}$ vs. $970 M^{-1}$). More recently, the first halogen bonding catenane (**Figure 2.2c**) was synthesised, via bromide anion templation, and shown to bind chloride and bromide anions in acetonitrile solely by $C-Br \cdots X^-$ halogen bonding interactions.⁹

2.1.3 Chapter objectives

Given the impressive anion recognition properties exhibited by the first halogen bonding rotaxane **1**·PF₆ (**Figure 2.2b**), the theme of this chapter focuses on integrating the halo-triazolium motif into interlocked host structures for anion recognition applications.

Attention initially centres on the 5-bromo-1,2,3-triazolium motif and its potential to form anion-templated interpenetrated and interlocked assemblies. The bromo-triazolium axle containing analogue of rotaxane **1**·PF₆ was targeted and its anion binding properties determined and compared to **1**·PF₆.

The anion binding capabilities of a number of triazolium containing [2]rotaxanes have recently been demonstrated to be significantly affected by altering the structure and degree of preorganisation (**Section 1.2.4**) of the axle component.¹⁰ Removing the flexible propylene linker adjacent to the triazolium group in [2]rotaxane **3**·PF₆ (**Figure 2.3a**) resulted in a near three-fold increase in chloride binding affinity in 1:1 CDCl₃/CD₃OD ($K_a(\mathbf{3}\cdot\text{PF}_6) = 424 \text{ M}^{-1}$, $K_a(\mathbf{4}\cdot\text{PF}_6) = 1110 \text{ M}^{-1}$), with this observation attributed to rotaxane **4**·PF₆ (**Figure 2.3b**) being a more preorganised host.

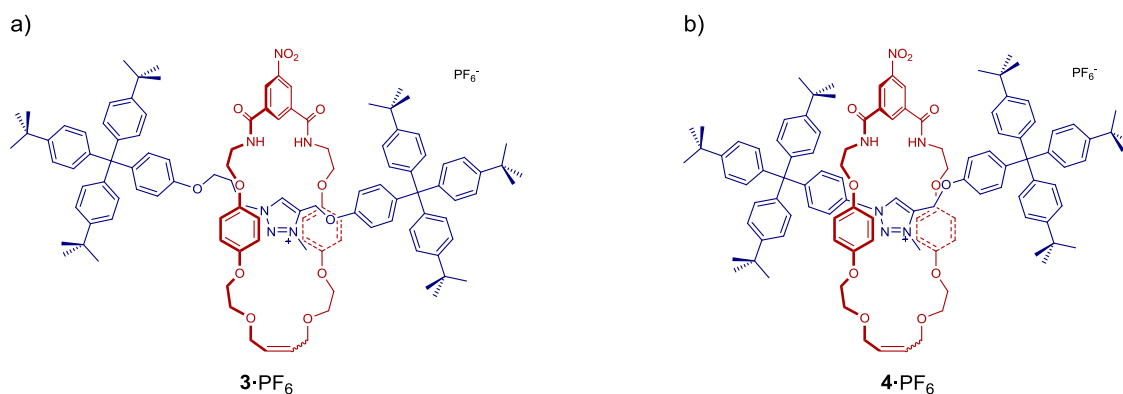


Figure 2.3—Previously reported triazolium axle containing [2]rotaxanes.

With this in mind, the syntheses of the halo-triazolium analogues of **4**·PF₆ were also undertaken with the expectation that the combined effects of preorganisation and halogen

bonding would result in impressive anion recognition properties being exhibited by the target novel halogen bonding hosts.

Finally, attempts at incorporating the iodo-triazolium motif into a [2]catenane structure were carried out.

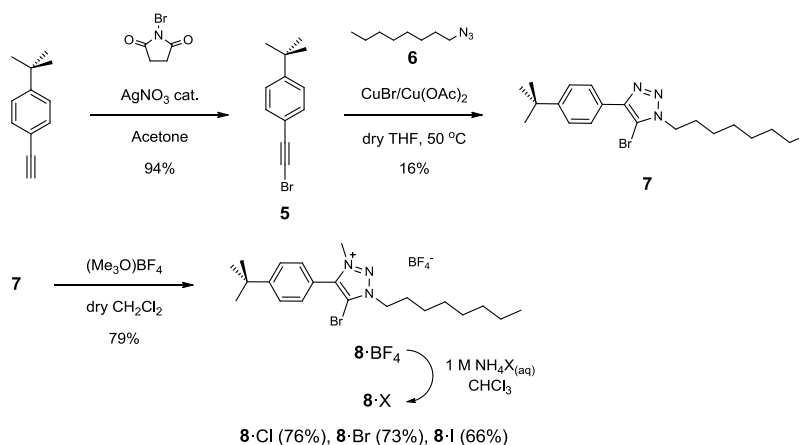
2.2 The bromo-triazolium motif for anion recognition

2.2.1 Bromo-triazolium functionalised model systems

Before attempts at synthesising the targeted 5-bromo-1,2,3-triazolium axle containing rotaxane could be undertaken, the ability of this halogen bonding motif to direct the anion-templated assembly of interpenetrated [2]pseudorotaxane assemblies needed to be investigated. This necessitated the preparation of a simple bromo-triazolium functionalised threading component **8**⁺ and an isophthalamide macrocycle **17**.

2.2.1.1 Bromo-triazolium thread synthesis

The target bromo-triazolium functionalised threading component **8**⁺ was synthesised *via* the three-step pathway shown in **Scheme 2.1**. Commercially available 1-(*tert*-butyl)-4-ethynylbenzene was converted to bromo-alkyne **5**, in 94% yield, *via* a literature procedure involving reaction with *N*-bromosuccinimide and a silver nitrate catalyst in acetone.¹¹ Reaction of **5** with octylazide **6** in the presence of a 1:1 copper(I) bromide/copper(II) acetate catalyst, following a modified literature procedure,¹² gave bromo-triazole **7** in a modest 16% yield. Alkylation of **7** with trimethyloxonium tetrafluoroborate in dry CH₂Cl₂ afforded the bromo-triazolium thread **8**·BF₄ (79%), with the corresponding halide salts **8**·X (X = Cl, Br, I) being obtained *via* repeated washing of a chloroform solution of **8**·BF₄ with 1 M NH₄X_(aq).



Scheme 2.1—Synthesis of bromo-triazolium functionalised threading species $8 \cdot X$.

The new bromo-triazolium halide derivatives were characterised by ^1H and ^{13}C NMR, as well as high resolution mass spectrometry. Crystals of $8 \cdot \text{Br}$ and $8 \cdot \text{I}$ suitable for characterisation by single crystal X-ray diffraction analysis were grown by vapour diffusion of diisopropylether into a chloroform solution of the corresponding halide salt and their structures determined by Dr. C. Serpell ($8 \cdot \text{Br}$) and R. Knighton ($8 \cdot \text{I}$) (**Figure 2.4**). A $\text{C-Br} \cdots \text{Br}^-$ halogen bond is observed in the crystal structure of $8 \cdot \text{Br}$, with a bond length of $3.12 \text{ \AA}$ (fraction of the sum of the van der Waal's radii, $R_{\text{BrBr}} = 0.84$) and a bond angle of 178° . Whereas for the iodide salt, a $\text{C-Br} \cdots \text{I}^-$ bond length of $3.35 \text{ \AA}$ ($R_{\text{BrI}} = 0.87$) and bond angle of 180° are observed. These near linear bond angles and low R values are indicative of a strong halogen bond between the bromo-triazolium bromine atom and the corresponding halide anion (**Section 2.1.1**).

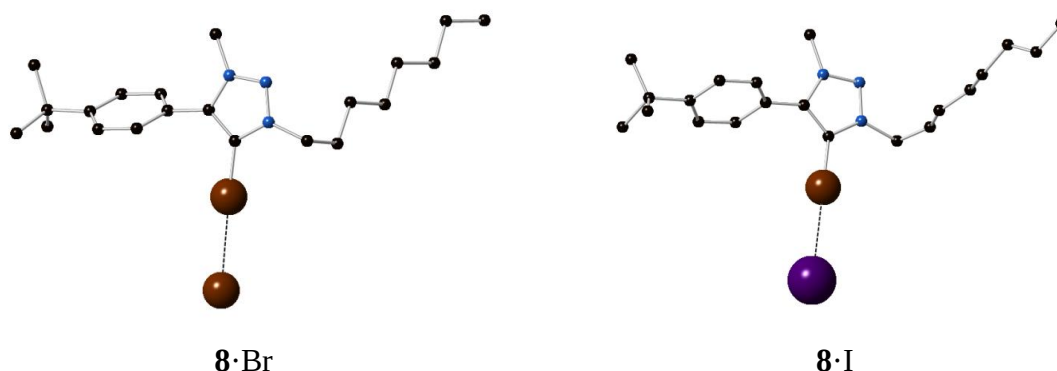
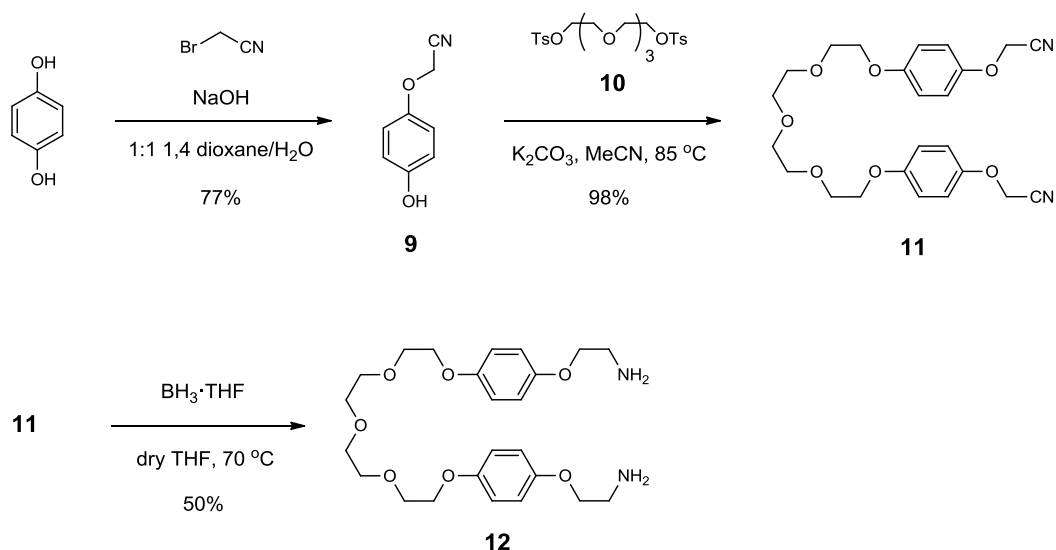


Figure 2.4—Solid state structures of bromo-triazolium halide threads $8 \cdot \text{Br}$ and $8 \cdot \text{I}$ (hydrogen atoms omitted for clarity, black = C, blue = N, brown = Br, purple = I).

2.2.1.2 Isophthalamide macrocycle synthesis

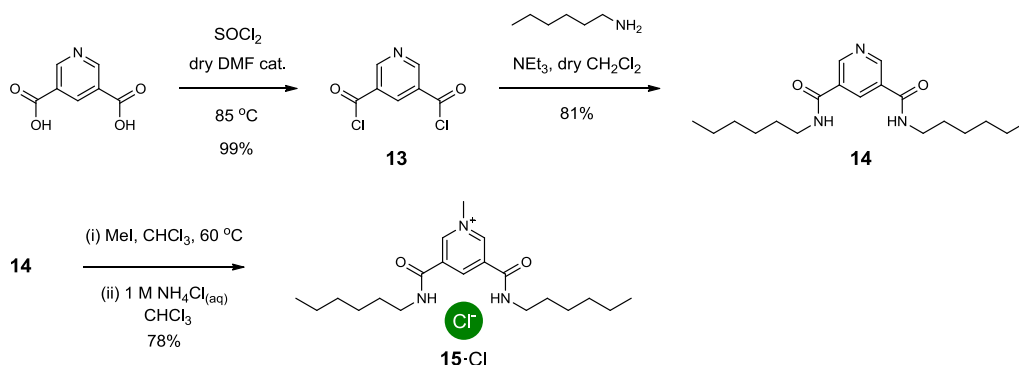
Isophthalamide macrocycle **17** was synthesised *via* a standard in-house and literature template procedure devised by Dr L. Hancock (**Scheme 2.2** and **Scheme 2.4**).¹³ Initially, hydroquinone was mono-functionalised using bromoacetonitrile and NaOH in 1:1 1,4-dioxane/water to give nitrile **9** (77%). Reaction of **9** with half an equivalent of bis-tosylate **10** in refluxing acetonitrile afforded compound **11** in 98% yield. Reduction of the nitrile functionalities with borane in THF solution gave bis-amine polyether macrocycle precursor **12** in 50% yield (**Scheme 2.2**).



Scheme 2.2—Bis-amine polyether macrocycle precursor synthesis.

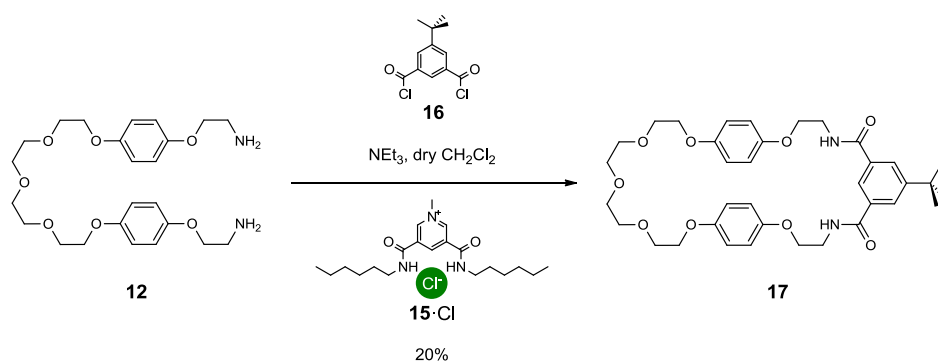
Macrocyclisation of **12** was performed in the presence of an appropriate 3,5-bis-hexylamide-pyridinium template **15**·Cl, which was prepared as shown in **Scheme 2.3**. Commercially available pyridine-3,5-dicarboxylic acid was refluxed in SOCl_2 with one drop of dry DMF catalyst to produce the bis-acid chloride **13** in quantitative yield. This was immediately reacted with two equivalents of hexylamine, in the presence of triethylamine, to give compound **14** (81%). Methylation of the pyridine functionality of **14** by heating with iodomethane in chloroform afforded the iodide salt **15**·I which upon halide anion exchange

via repeated washing of a chloroform solution of the iodide salt with 1 M $\text{NH}_4\text{Cl}_{(\text{aq})}$ gave **15·Cl** in 78% yield.



Scheme 2.3—Synthetic route to 3,5-bis-amide-pyridinium template **15·Cl**.

The desired isophthalamide macrocycle **17** was prepared by condensation of bis-amine macrocycle precursor **12** with 5-*tert*-butylisophthaloyl dichloride **16**, in the presence of pyridinium chloride template **15·Cl** and triethylamine (**Scheme 2.4**). After purification via silica gel column chromatography the macrocycle was isolated in 20% yield, which, disappointingly, is much lower than the 42% yield quoted in the literature.¹³



Scheme 2.4—Synthesis of target isophthalamide macrocycle **17**.

2.2.1.3 Anion-templated pseudorotaxane investigations

Initially, qualitative ^1H NMR investigations were carried out to assess whether bromotriazolium threading species **8⁺** was able to form an anion-templated interpenetrative assembly with macrocycle **17**. Addition of one equivalent of thread **8·Br** to a CDCl_3 solution of **17**

caused diagnostic upfield shifting and splitting of the macrocycle hydroquinone protons δ and ε , arising from aromatic donor–acceptor interactions with the electron-deficient bromotriazolium heterocycle, indicative of pseudorotaxane formation (**Figure 2.5**). Also of note was the downfield shifting of macrocycle isophthalamide protons α and β arising from hydrogen bonding interactions between these protons and the templating bromide anion. Similar perturbations were also observed with **8**·Cl and **8**·I whereas, importantly, no noticeable shifts were observed when a templating halide anion was not present (**8**·BF₄).

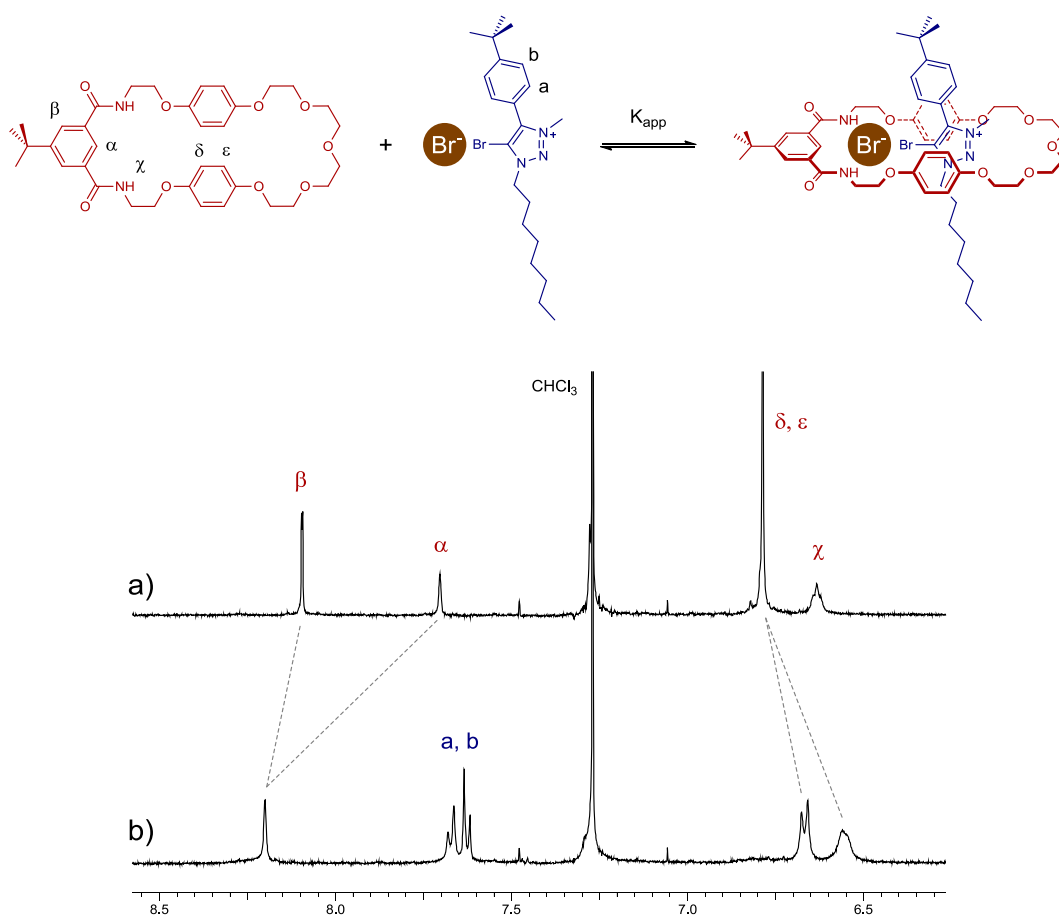


Figure 2.5—Truncated ¹H NMR spectra of a) macrocycle **17** and b) an equimolar mixture of macrocycle **17** and thread **8**·Br (500 MHz, CDCl₃, 293 K).

Further evidence for interpenetration was obtained from two-dimensional ¹H–¹H ROESY NMR, which revealed a number of inter-component through space interactions (**Figure 2.6**). Couplings between the macrocycle hydroquinone protons (δ and ε) and the thread aromatic

protons (*a* and *b*) were observed, together with interactions between the same thread aromatic protons and the macrocycle polyether CH₂ groups.

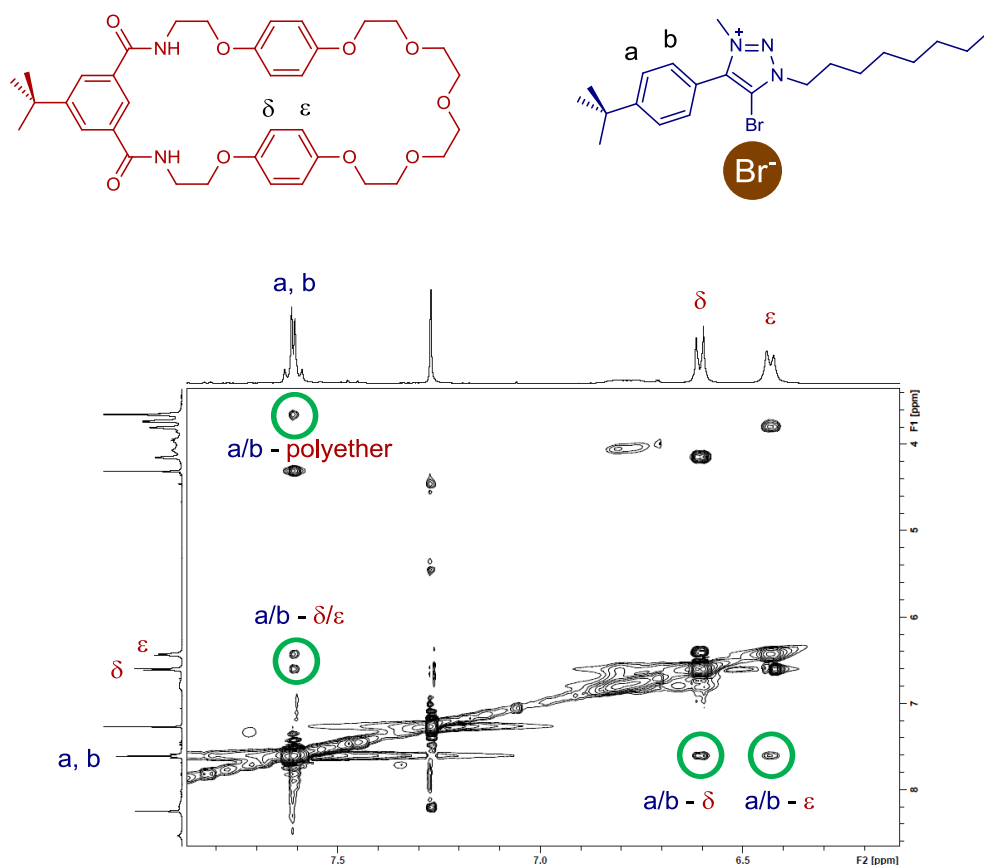


Figure 2.6—Truncated ROESY NMR spectrum of an equimolar mixture of macrocycle **17** and thread **8·Br** (500 MHz, CDCl₃, 293 K).

Given this evidence, quantitative ¹H NMR titration experiments were then performed in order to obtain apparent association constants¹⁴ for anion-templated pseudorotaxane assembly in CDCl₃. Aliquots of a CDCl₃ solution of **8·X** were added to a CDCl₃ solution of macrocycle **17** and the shift of the macrocycle hydroquinone protons ϵ monitored. The resultant titration data (**Figure 2.7**) was then analysed with WinEQNMR2¹⁵ curve fitting software to give the 1:1 stoichiometric apparent association constants shown in **Table 2.1**.

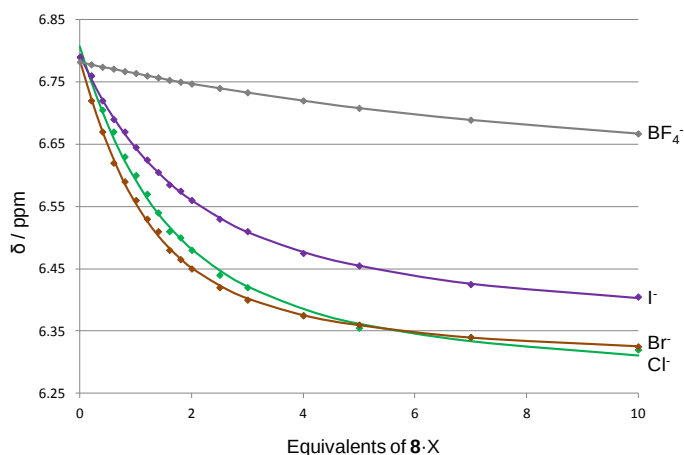


Figure 2.7—Changes in chemical shift of macrocycle **17** hydroquinone protons ϵ upon addition of increasing amounts of threading component **8·X** (500 MHz, CDCl_3 , 293 K, data points represent experimental data, continuous lines represent calculated curves).

Table 2.1—Apparent association constants, $K_{\text{app}} (\text{M}^{-1})$, calculated for pseudorotaxane assembly between macrocycle **17** and thread **8·X** (estimated standard errors in parentheses, CDCl_3 , 293 K).

Anion, X	$K_{\text{app}} (\text{M}^{-1})$
Cl^-	485(37)
Br^-	761(29)
I^-	344(10)
BF_4^-	20(7)

The most stable pseudorotaxane assembly results from using bromide as a template, which is in keeping with the trends observed for the previously reported triazolium and iodo-triazolium analogues of thread **8⁺** (**Table 2.2**).⁷ The incorporation of a halogen bonding donor motif is clearly favourable for this system with the values of K_{app} obtained with a bromide or iodide template being noticeably larger than those for the hydrogen bonding triazolium analogue. Importantly, the halide anions exhibit an obvious templating effect for the formation of an interpenetrative assembly between thread **8⁺** and macrocycle **17**, with their apparent association constants being markedly larger in magnitude than that of BF_4^- .

Table 2.2—Apparent association constants, $K_{\text{app}} (M^{-1})$, for pseudorotaxane assembly between macrocycle **17** and the previously reported triazolium and iodo-triazolium analogues of thread **8**·X (estimated standard errors in parentheses, $CDCl_3$, 293 K).

Anion, X	Triazolium ^[a]	Iodo-triazolium ^[b]
Cl^-	490(38)	538(17)
Br^-	610(31)	1188(93)
I^-	232(8)	392(24)
BF_4^-	—	29(19)

^[a] values taken from ref. 7.

2.2.2 Bromo-triazolium axle containing [2]rotaxane

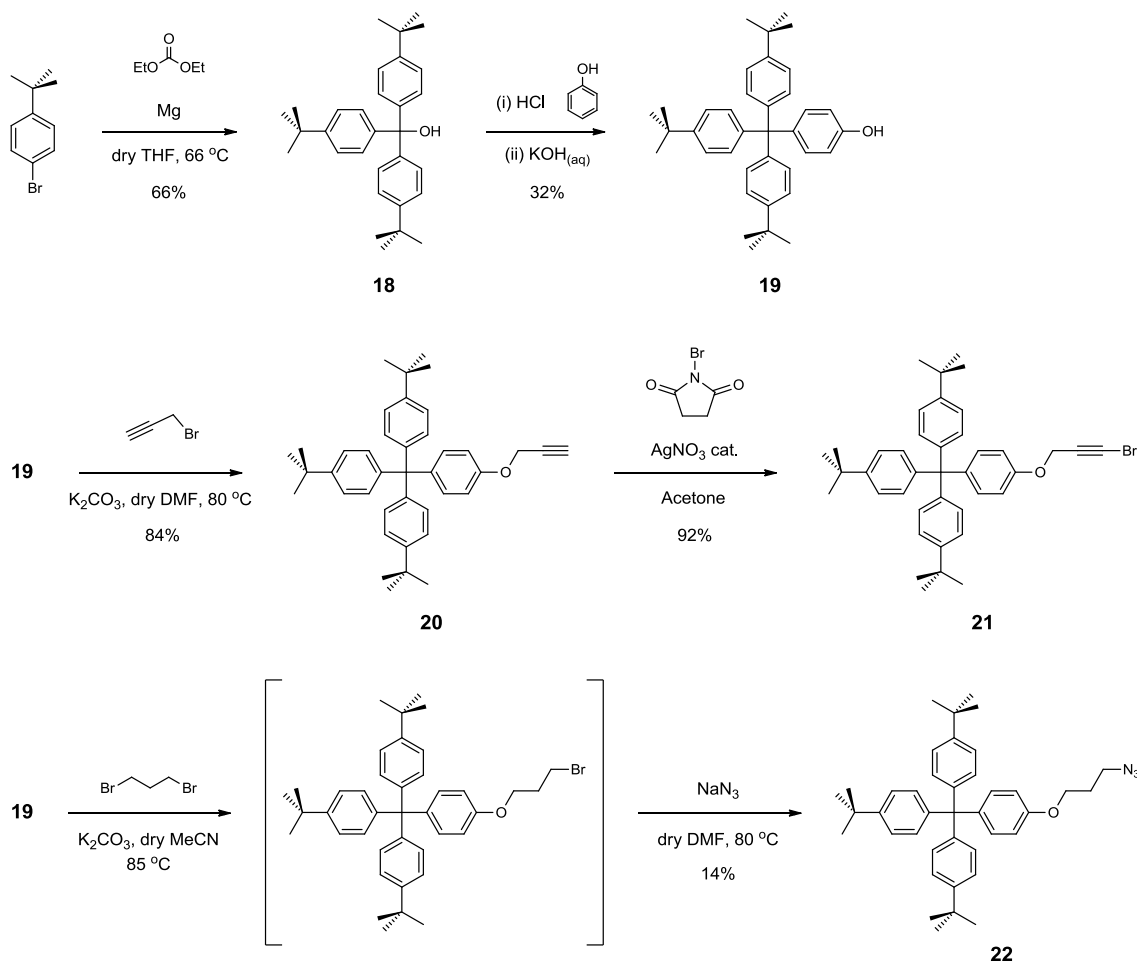
Having demonstrated the halide anion-templated pseudorotaxane formation of simple bromo-triazolium thread **8**⁺ with an isophthalamide macrocycle, it was envisaged that the synthesis of the target bromo-triazolium axle containing [2]rotaxane *via* an anion-templated Grubbs' II-catalysed ring closing metathesis (RCM) 'clipping' strategy would be possible. This required the preparation of an axle component bearing the relevant anion binding motif and a macrocycle precursor that could be cyclised around it.

2.2.2.1 Axle synthesis

The synthesis of bromo-triazolium functionalised axle **24**⁺ (**Scheme 2.6**) required the preparation of two terphenyl-stoppered precursor compounds, bromo-alkyne **21** and azide **22**¹⁶ (**Scheme 2.5**).

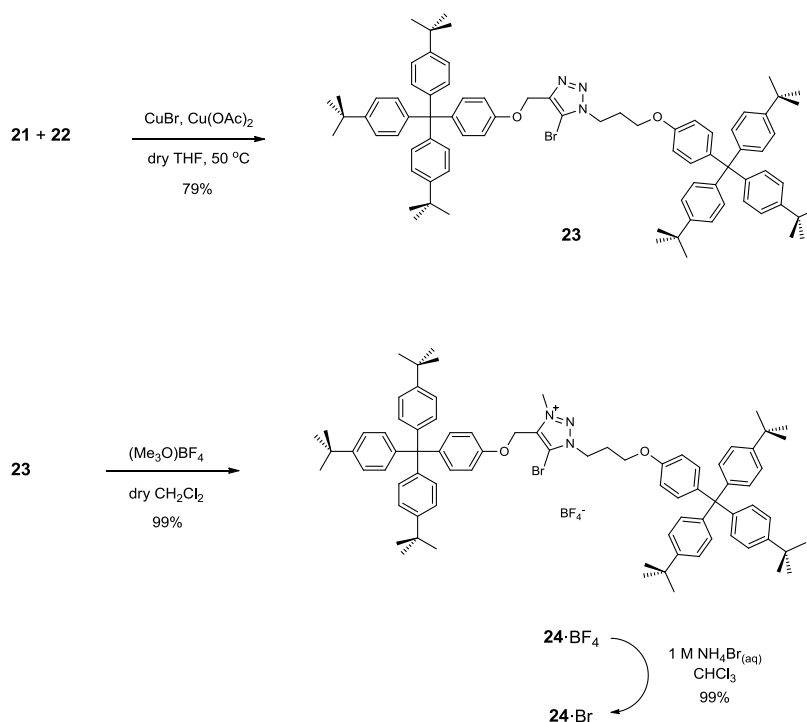
A Grignard reaction between commercially available 1-bromo-4-*tert*-butyl benzene and diethyl carbonate, in dry THF, afforded tris(4-(*tert*-butyl)phenyl)methanol **18** in 66% yield. This was subsequently heated overnight in molten phenol, under acidic conditions, to form terphenyl compound **19** in 32% yield, which was then refluxed with bromoacetonitrile and K_2CO_3 to give terphenyl-stoppered alkyne **20** (84%).¹⁷ This was then converted to the desired bromo-alkyne **21** in 92% yield following a literature procedure.¹¹ Terphenyl-stoppered azide **22** was synthesised in a two-step procedure from compound **19** as previously reported.¹⁶

Initial reaction of **19** with 1,3-dibromopropane and K_2CO_3 in dry acetonitrile afforded an intermediate mono-bromo-propyl functionalised compound that was immediately reacted with sodium azide to give the product terphenyl-stoppered azide **22** in an overall yield of 14%.



Scheme 2.5—Synthesis of terphenyl-stoppered bromo-alkyne and azide axle precursors.

Cycloaddition reaction of bromo-alkyne **21** and azide **22**, following a modified literature procedure¹² involving a mixed copper(I) bromide/copper(II) acetate catalyst system, resulted in the formation of bromo-triazole axle precursor **23** in 79% yield. Methylation with trimethyloxonium tetrafluoroborate in dry CH_2Cl_2 afforded the tetrafluoroborate salt of the target axle **24**· BF_4 in quantitative yield (**Scheme 2.6**).



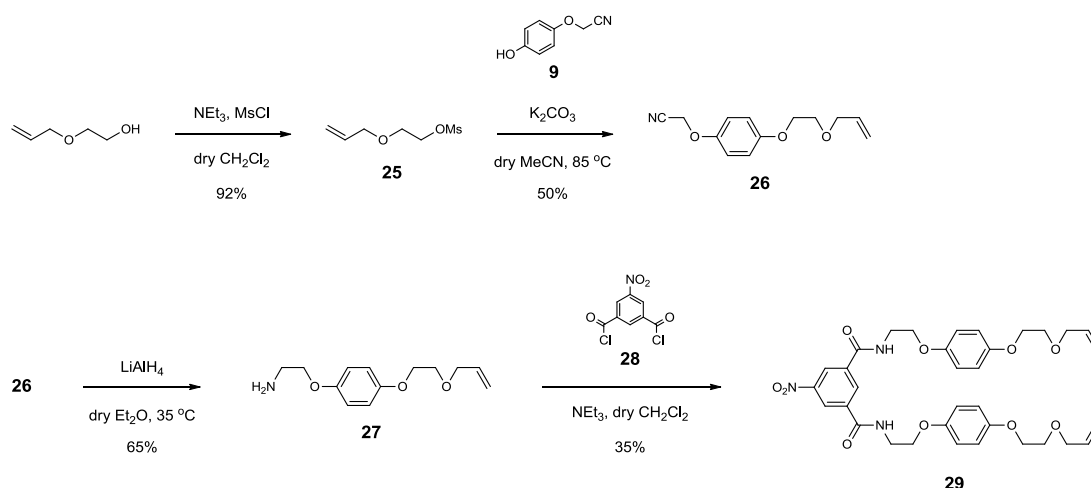
Scheme 2.6—Synthesis of bromo-triazolium functionalised axle **24·Br**.

In **Section 2.2.1.3** the strongest pseudorotaxane assembly between bromo-triazolium thread **8⁺** and macrocycle **17** was observed when a bromide anion was present. This suggested that bromide would be the most suitable anion to template the synthesis of the target [2]rotaxane. Therefore, **24·BF₄** was dissolved in chloroform and washed repeatedly with 1 M $\text{NH}_4\text{Br(aq)}$ to give the axle bromide salt **24·Br** in quantitative yield.

2.2.2.2 Macrocycle precursor synthesis

The target bis-vinyl appended macrocycle precursor **29** was prepared following a literature procedure devised by Dr M. Sambrook (**Scheme 2.7**).¹⁸ 2-(Allyloxy)ethanol was reacted with triethylamine and methanesulfonyl chloride, in dry CH_2Cl_2 , to form mesylate **25** in 92% yield. This was coupled with mono-functionalised hydroquinone **9** under basic conditions to afford vinyl-appended compound **26** (50%), the nitrile group of which was reduced with LiAlH_4 in diethyl ether to give amine **27** in 65% yield. The target macrocycle precursor **29** was then prepared by amide condensation of two equivalents of amine **27** with acid chloride **28**

(formed by reaction of commercially available 5-nitroisophthalic acid with SOCl_2) in the presence of triethylamine. Following purification *via* silica gel column chromatography, **29** was isolated in a disappointing 35% yield, much lower than the 50% yield quoted in the literature.¹⁸



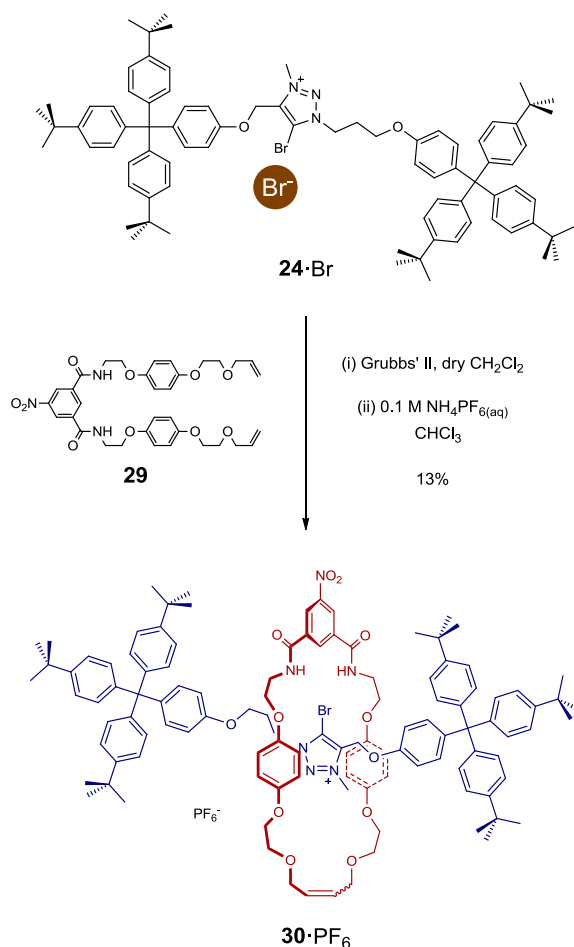
Scheme 2.7—Synthesis of bis-vinyl appended macrocycle precursor **29**.

The design of bis-vinyl appended macrocycle precursor **29** has been specifically tailored for use in a ‘clipping’ rotaxane synthesis. Similar in makeup to isophthalamide macrocycle **17**, with hydroquinone groups present to partake in aromatic donor–acceptor interactions, **29** contains a nitro-isophthalamide motif to increase the acidity of the nearby amide protons for enhanced anion binding strength and, importantly, terminal vinyl groups allowing for cyclisation *via* a Grubbs’ II-catalysed RCM reaction.

2.2.2.3 [2]Rotaxane synthesis and characterisation

Following the successful synthesis of the required components, the target bromo-triazolium axle containing rotaxane was synthesised by reaction of 1.5 equivalents of axle **24**·Br and one equivalent of macrocycle precursor **29**, in dry CH_2Cl_2 , with Grubbs’ II catalyst (**Scheme 2.8**). The product was isolated as its hexafluorophosphate salt **30**· PF_6 in 13% yield, following

purification *via* preparative thin layer chromatography and removal of the bromide template by repeated washing with 0.1 M $\text{NH}_4\text{PF}_6(\text{aq})$.



Scheme 2.8—Synthesis of target bromo-triazolium axle containing [2]rotaxane **30·PF₆**.

The new rotaxane was characterised by ^1H , ^{13}C , ^{19}F and ^{31}P NMR spectroscopy and by high resolution ESI mass spectrometry. The high resolution ESI-MS analysis of the rotaxane gave the expected mass peak at m/z 1843.9143 $[\text{M} - \text{PF}_6]^+$ and the ^1H NMR spectrum of **30·PF₆**, together with that of macrocycle precursor **29**, is shown in **Figure 2.8**. It can be seen that, upon rotaxane formation, the macrocycle hydroquinone protons δ and ϵ have shifted upfield and split due to aromatic donor–acceptor interactions between the macrocycle’s electron-rich hydroquinone units and the electron-deficient bromo-triazolium moiety of the axle, suggesting

the axle interpenetrates the macrocycle. Also, the appearance of a new peak corresponding to the vinyl protons ϕ shows that **29** has now been cyclised.

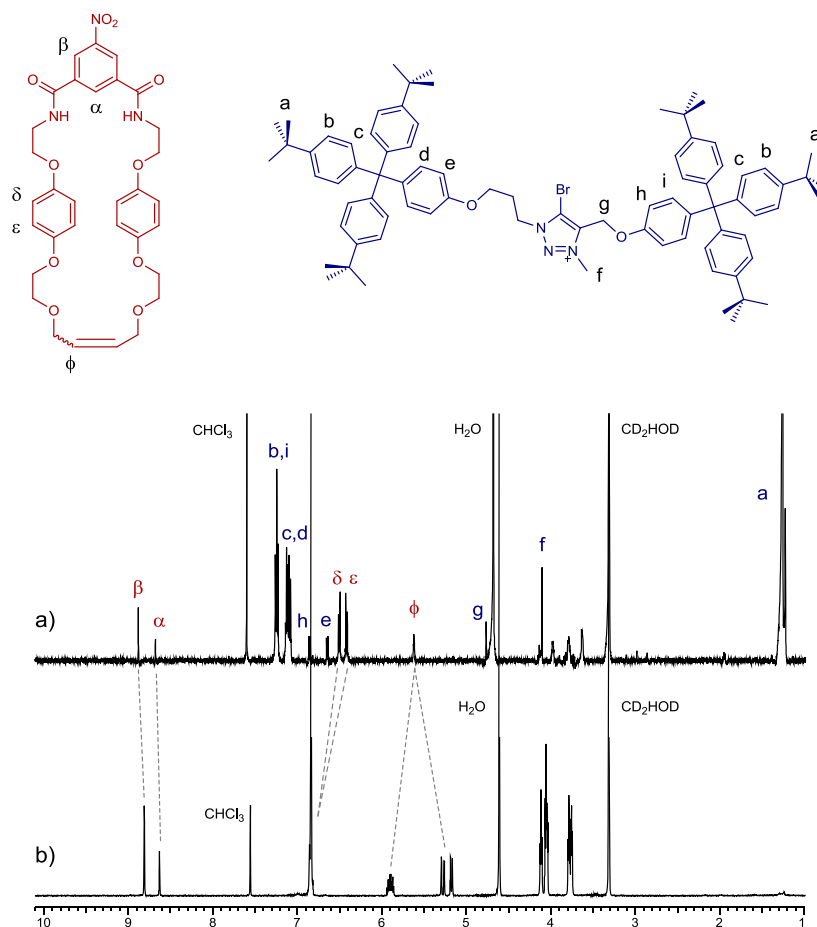


Figure 2.8— ^1H NMR spectra of a) [2]rotaxane **30**· PF_6 and b) macrocycle precursor **29** (500 MHz, 1:1 $\text{CDCl}_3/\text{CD}_3\text{OD}$, 293 K).

Further evidence for interlocked structure formation was obtained from two-dimensional ^1H – ^1H ROESY NMR spectroscopy and X-ray crystallography. The ROESY spectrum of rotaxane **30**· PF_6 revealed several through space couplings between the macrocycle and axle components, consistent with the formation of an interlocked product (**Figure 2.9**). Interactions of the macrocycle hydroquinone protons δ and ϵ with a number of the axle protons are seen, as well as coupling of the macrocycle alkene protons ϕ and the axle triazolium methyl protons f .

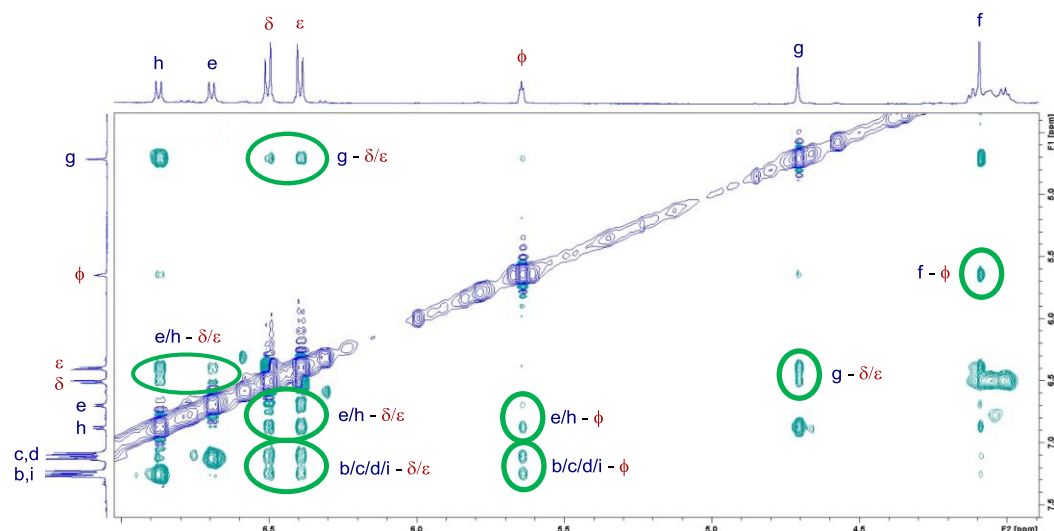


Figure 2.9—Truncated ROESY NMR spectrum of rotaxane **30**·PF₆ (500 MHz, 1:1 CDCl₃/CD₃OD, 293 K, peak assignments taken from **Figure 2.8**).

Conclusive evidence for the interlocked nature of the rotaxane was provided by single crystal X-ray structural analysis of its chloride and acetate salts, **30**·Cl and **30**·OAc. The crystals were grown by vapour diffusion of diisopropylether into a chloroform/methanol solution of the rotaxane and the corresponding anion; their structures were determined by R. Knighton and are shown in **Figure 2.10** and **Figure 2.11**.

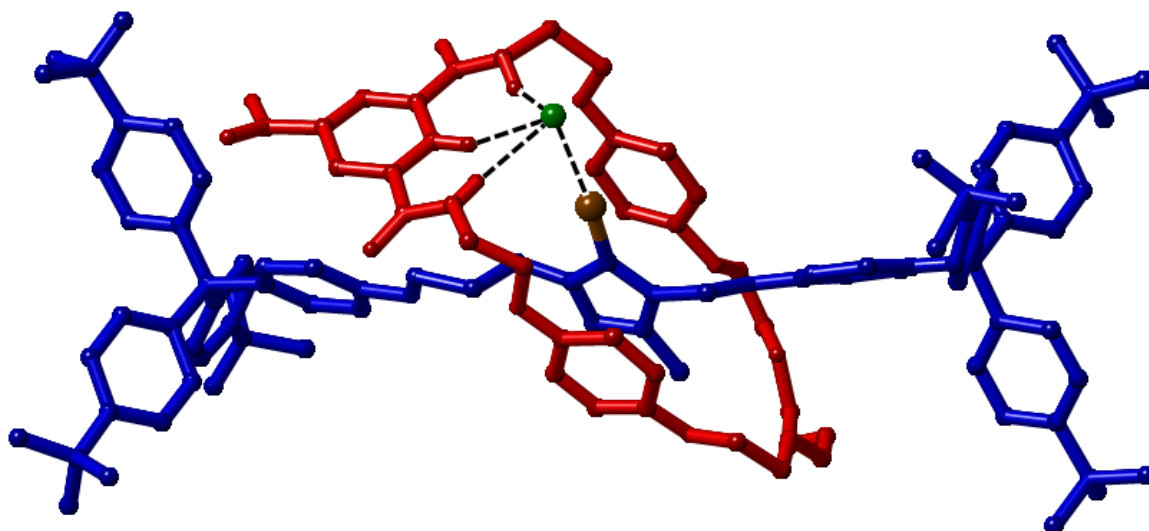


Figure 2.10—Solid state structure of rotaxane **30**·Cl (all non-hydrogen bonding hydrogen atoms omitted for clarity).

Importantly, the existence of a $\text{C}-\text{Br}\cdots\text{Cl}^-$ halogen bond can be seen in the solid state structure of $\mathbf{30}\cdot\text{Cl}$, with a bond length of 2.92 Å ($R_{\text{BrCl}} = 0.81$) and bond angle of 175° , with these values indicative of a strong halogen bond. Three hydrogen bonding interactions are also evident, two being from the amide groups of the macrocycle ($\text{N}\cdots\text{Cl} = 3.28$ and 3.38 Å, $R_{\text{NCl}} = 0.99$ and 1.02 , $\angle\text{N}-\text{H}\cdots\text{Cl} = 164^\circ$ and 141°) and one from the internal isophthalamide aromatic proton ($\text{C}\cdots\text{Cl} = 3.46$ Å, $R_{\text{CCl}} = 1.00$, $\angle\text{C}-\text{H}\cdots\text{Cl} = 150^\circ$). Given the ratios of the van der Waals' radii for these interactions are approximately equal to one and that the bond angles deviate from 180° , these hydrogen bonds can be considered to be weak. This is likely due to the size of the axle bromine atom causing a conformational change of the macrocycle which results in the chloride anion perching on the outside of the rotaxane binding cleft, in a similar manner to that observed with the analogous iodo-triazolium rotaxane $\mathbf{1}\cdot\text{Br}$.⁷ Due to the poor data obtained for $\mathbf{30}\cdot\text{OAc}$ no bond data can be accurately given, and so the solid state structure provides proof of the interlocked nature of $\mathbf{30}^+$ only.

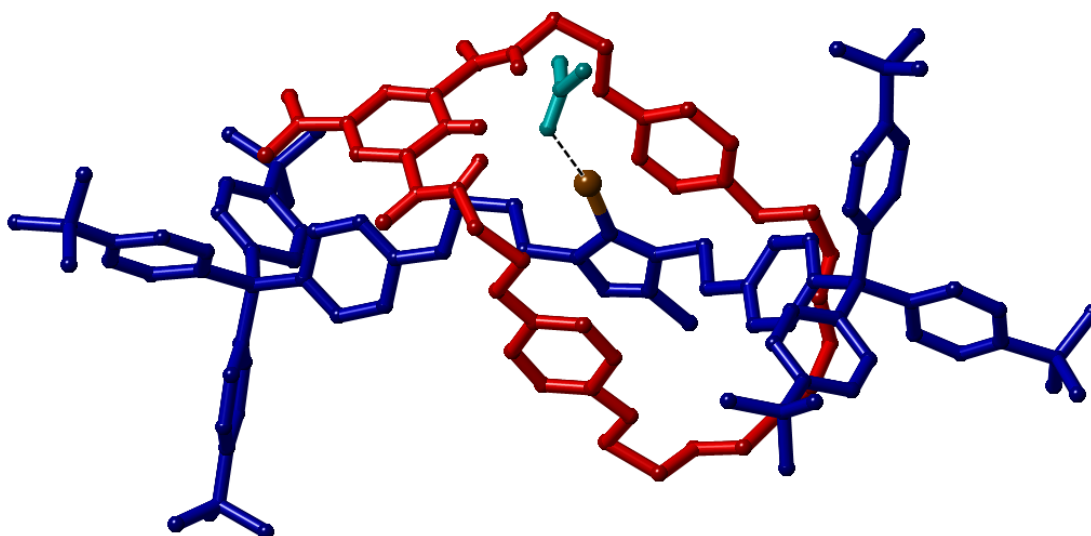


Figure 2.11—Solid state structure of rotaxane $\mathbf{30}\cdot\text{OAc}$ (most hydrogen atoms omitted for clarity).

2.2.2.4 Anion recognition properties

The anion recognition properties of **30**·PF₆ were investigated using ¹H NMR titration experiments. The addition of anions, as their TBA salts, to separate solutions of the rotaxane in 1:1 CDCl₃/CD₃OD caused downfield shifts of the macrocycle isophthalamide protons α and β indicative of hydrogen bonding interactions (**Figure 2.12**). Interestingly, the axle terphenyl protons h were seen to shift downfield suggesting their involvement in anion recognition also.

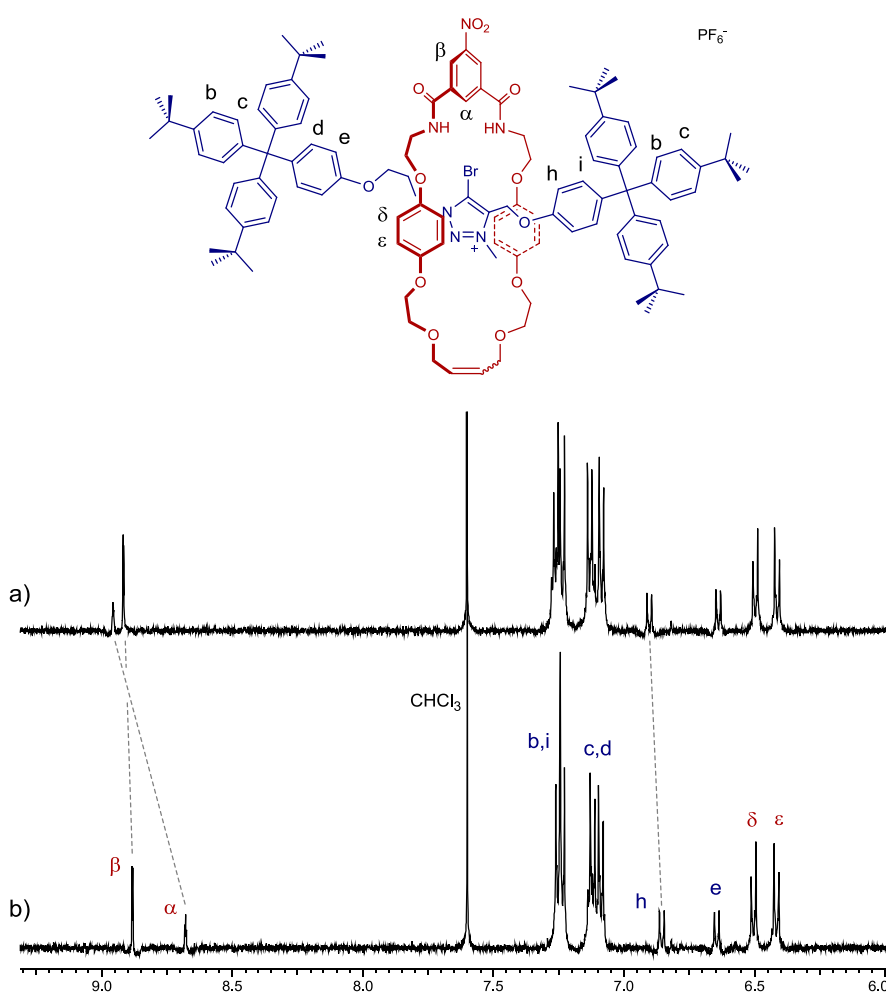


Figure 2.12—Truncated ¹H NMR spectra of a) rotaxane **30**·PF₆ upon addition of one equivalent of TBA·Br and b) rotaxane **30**·PF₆ (500 MHz, 1:1 CDCl₃/CD₃OD, 293 K).

WinEQNMR2¹⁵ analysis of titration data obtained from monitoring the downfield shift of macrocycle proton α (**Figure 2.13**) gave the 1:1 stoichiometric association constants (K_a)

shown in **Table 2.3**. It can be seen that bromo-triazolium rotaxane **30**·PF₆ exhibits a selectivity for the halide anions over the more basic acetate anion, with a particular preference for the larger halides, bromide and iodide. This indicates that the rotaxane binding domain is of a complementary size and shape to encapsulate the spherical halide anions over the trigonal planar acetate anion, which overcomes the basicity of the oxoanion.

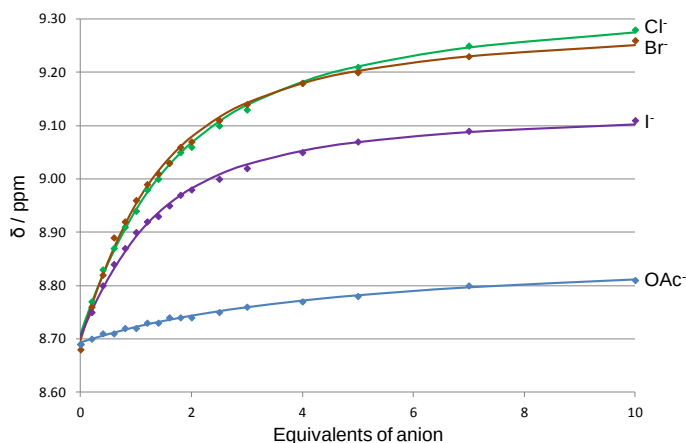


Figure 2.13—Changes in chemical shift of rotaxane proton α upon addition of increasing amounts of different anions (500 MHz, 1:1 CDCl₃/CD₃OD, 293 K, data points represent experimental data, continuous lines represent calculated curves).

Table 2.3—Association constants, K_a (M⁻¹), obtained for rotaxane **30**·PF₆ with various anions (estimated standard errors in parentheses, 1:1 CDCl₃/CD₃OD, 293 K).

Anion	K_a (M ⁻¹)
Cl ⁻	435(27)
Br ⁻	620(44)
I ⁻	648(51)
OAc ⁻	93(14)

Comparison of the association constants obtained for rotaxane **30**·PF₆ with those previously reported for its iodo-triazolium **1**·PF₆⁷ and triazolium **3**·PF₆^{8, 10} analogues (**Table 2.4** and **Figure 2.14**), reveals that incorporation of the halogen bonding bromo-triazolium group into the axle component of the rotaxane structure enhances the bromide and iodide anion recognition strength relative to its protic triazolium rotaxane analogue **3**·PF₆. Interestingly,

the magnitudes of chloride anion association are similar for both rotaxanes. Rotaxane **30**·PF₆ is still some way off matching the potency of iodo-triazolium axle containing rotaxane **1**·PF₆, with this attributed to the superior halogen bond donor ability of iodine as compared to bromine on the basis of their relative polarisabilities.

Table 2.4—Association constants, K_a (M^{-1}), obtained for rotaxanes **1**·PF₆, **3**·PF₆ and **30**·PF₆ with various anions (estimated standard errors in parentheses, 293 K).

Anion	1 ·PF ₆ ^[c]	3 ·PF ₆ ^[a,d]	30 ·PF ₆ ^[a]
Cl [−]	—	457(4) ^[b]	424(20)
Br [−]	>10 ^{4[a]}	1251(10) ^[b]	620(44)
I [−]	—	2228(171) ^[b]	350(16)
OAc [−]	—	—	42(3)

^[a] 1:1 CDCl₃/CD₃OD, ^[b] 45:45:10 CDCl₃/CD₃OD/D₂O, ^[c] values taken from ref. 7, ^[d] values taken from ref. 10.

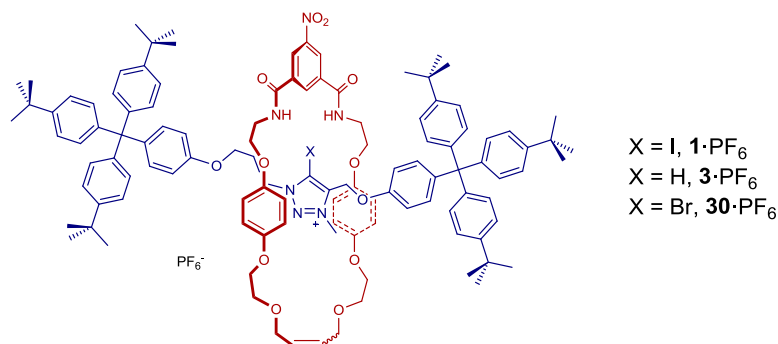


Figure 2.14—Triazolium and halo-triazolium axle containing rotaxanes referred to in **Table 2.3** and **Table 2.4**.

It is noteworthy that the affinity of **30**·PF₆ for iodide is almost double that of protic triazolium containing rotaxane **3**·PF₆. Whilst the iodide selectivity of iodo-triazolium rotaxane **1**·PF₆ can be explained by the Hofmeister series bias observed in aqueous solvent mixtures, where binding of iodide is favoured over both chloride and bromide on the basis of relative ease of desolvation,¹⁹ the same argument cannot be made for **30**·PF₆ given that 1:1 CDCl₃/CD₃OD is the solvent used in this case. It is possible that the larger bromine substituent of the axle forces a conformational change of the rotaxane upon anion binding, similar to that shown in the solid state structure of **30**·Cl (**Figure 2.10**), resulting in the binding cavity being able to

accommodate a larger anion. A similar conformational change was not observed in the solid state structure of triazolium rotaxane **3**·PF₆⁸ and so perhaps explains its preference for the smaller halides.

2.2.3 Summary

The potential for the 5-bromo-1,2,3-triazolium motif to direct the halide anion-templated assembly of interpenetrated and interlocked structures *via* C–Br···X[–] halogen bonds has been demonstrated. A simple bromo-triazolium threading component **8**⁺ was shown to form a halide anion-templated pseudorotaxane with an isophthalamide macrocycle **17**, with the most stable assembly formed in the presence of a bromide template.

This led to the synthesis of the first bromo-triazolium axle containing interlocked rotaxane structure **30**·PF₆ *via* a bromide anion-templated Grubbs' II-catalysed RCM clipping strategy. The presence of the halogen bonding motif was demonstrated to enhance bromide and iodide anion recognition relative to the protic triazolium rotaxane analogue, as well as alter the observed binding selectivity towards the larger halides. Rotaxane **30**·PF₆ was found to be a relatively less potent anion receptor than its iodo-triazolium axle containing rotaxane analogue **1**·PF₆ on the basis of the inferior halogen bond donor ability of its C–Br bond relative to a C–I bond.

2.3 Increasing inter-component preorganisation of halo-triazolium axle containing [2]rotaxanes

2.3.1 Introduction

The concept of preorganisation is one of the most fundamental principles of anion supramolecular chemistry (**Section 1.2.4**). Host systems which have been designed to

minimise conformational rearrangement upon guest binding typically exhibit very stable host–guest complexes resulting from both favourable enthalpic and entropic contributions.

This effect has been exploited recently to enhance the anion binding strength of triazolium axle containing rotaxane $3 \cdot \text{PF}_6$.¹⁰ An analogous rotaxane, containing a shortened axle component, $4 \cdot \text{PF}_6$ (**Figure 2.15**) has been demonstrated to be a superior anion complexant to $3 \cdot \text{PF}_6$ as a result of the shortened axle restricting the movement of the macrocycle component. This restricted movement reduces the number of degrees of freedom in the overall rotaxane structure. Hence $4 \cdot \text{PF}_6$ is more preorganised for guest binding and an almost three-fold increase in chloride and bromide binding affinity was observed (**Table 2.5**).

Table 2.5—Association constants, $K_a (M^{-1})$, obtained for previously reported rotaxanes $3 \cdot \text{PF}_6$ and $4 \cdot \text{PF}_6$ with various anions (estimated standard errors in parentheses, 1:1 $\text{CDCl}_3/\text{CD}_3\text{OD}$, 293 K).

Anion	$3 \cdot \text{PF}_6$ ^[a]	$4 \cdot \text{PF}_6$ ^[a]
Cl^-	424(20)	1110(110)
Br^-	423(14)	1320(21)
I^-	350(16)	566(23)
OAc^-	42(3)	92(15)

^[a] values taken from ref. 10.

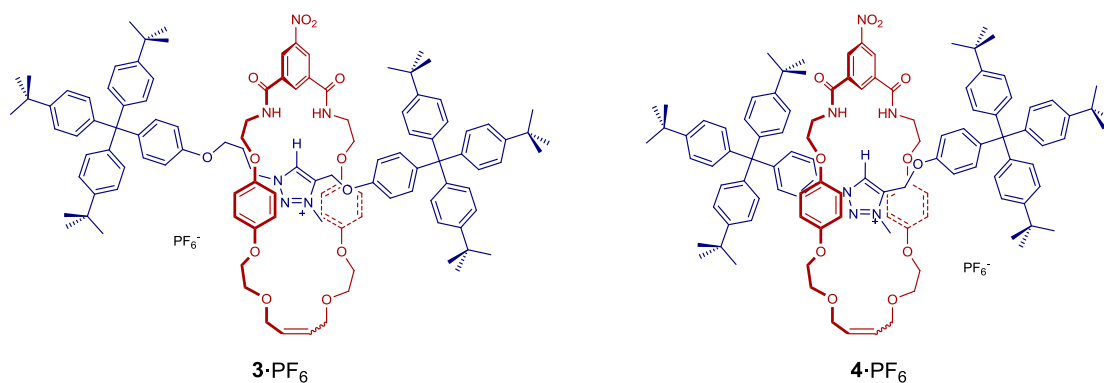
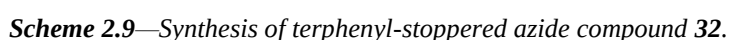


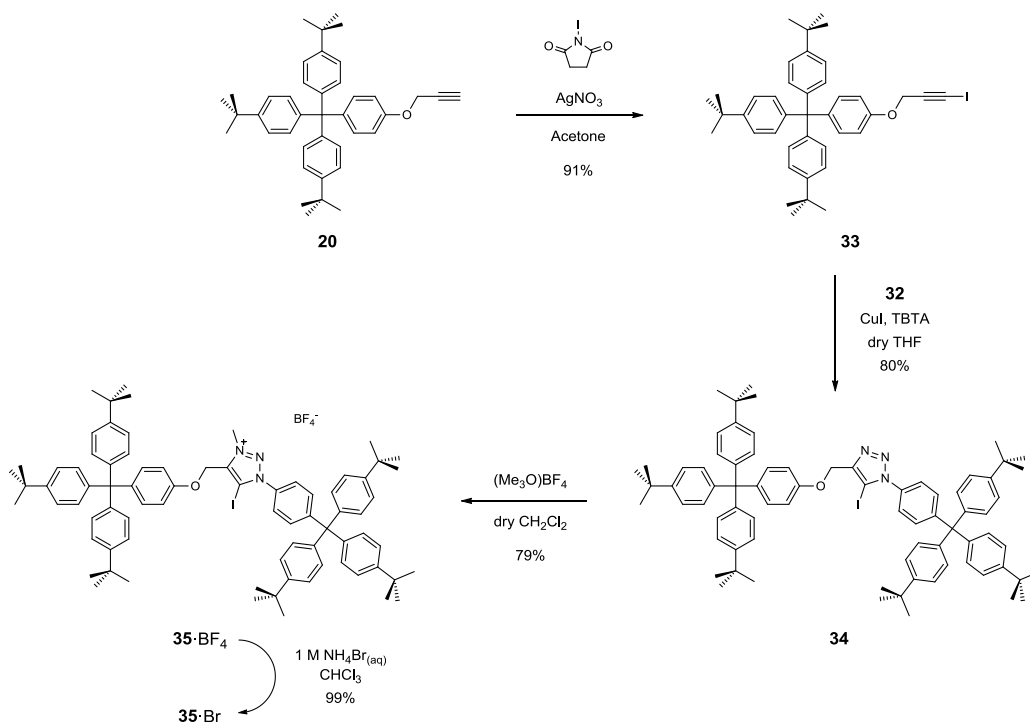
Figure 2.15—Triazolium axle containing rotaxanes referred to in **Table 2.5**.

In the previous section, the bromo- and iodo-triazolium groups were shown to be superior anion binding motifs to triazolium. Therefore, it was anticipated that interlocked [2]rotaxane

In order for the necessary shortened halo-triazolium axles to be prepared, a terphenyl-stoppered azide component **32** in which the azide is directly attached to the terphenyl stopper was required (**Scheme 2.9**). Tris(4-(*tert*-butyl)phenyl)methanol **18** was dissolved in benzene and reacted with acetyl chloride before being heated in aniline overnight to give terphenyl-stoppered amine **31** (48%).²⁰ This was then converted to the desired terphenyl-stoppered azide *via* a diazonium reaction in 69% yield.²¹

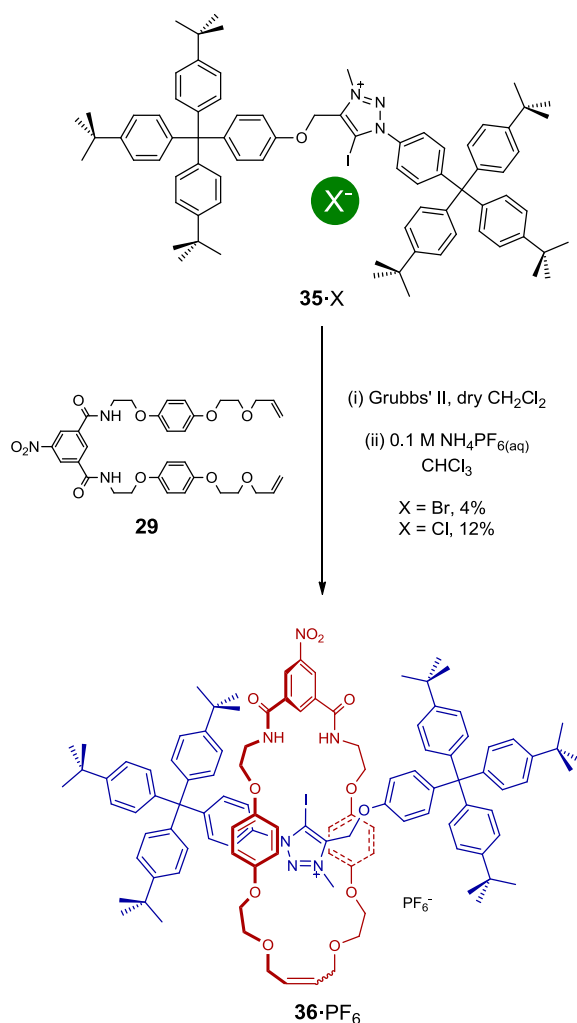


A terphenyl-stoppered iodo-alkyne **33** was synthesised from alkyne **20** in 91% yield by reaction with *N*-iodosuccinimide in the presence of a catalytic amount of silver nitrate (*Scheme 2.10*).¹¹ Compound **33** was then reacted with azide **32** using a literature procedure²² to afford iodo-triazole **34** in 80% yield. Methylation of **34** using trimethyloxonium tetrafluoroborate in dry CH₂Cl₂ gave the tetrafluoroborate salt of the target shortened iodo-triazolium axle **35**·BF₄ (79%). This was then converted to the bromide salt **35**·Br by repeated washing with 1 M NH₄Br_(aq) in preparation for the rotaxane forming reaction.



Scheme 2.10—Synthesis of shortened iodo-triazolium axle **35·Br**.

Following the successful synthesis of iodo-triazolium axle **35·Br**, the target iodo-triazolium functionalised rotaxane was synthesised by reaction of one equivalent of **35·Br** and 1.5 equivalents of macrocycle precursor **29**, in dry CH_2Cl_2 , with Grubbs' II catalyst (**Scheme 2.11**). The product was isolated as its hexafluorophosphate salt **36·PF₆**, in a modest yield of 4%, following purification *via* repeated preparative thin layer chromatography and removal of the bromide template by washing with 0.1 M $\text{NH}_4\text{PF}_6(\text{aq})$. Given the poor yield obtained for this reaction it was decided to repeat the synthesis using the chloride salt of the axle **35·Cl**. Interestingly, the use of a chloride template increased the yield to 12%, which suggests shortening of the axle component results in the smaller halide being a more efficient templating reagent.



Scheme 2.11—Synthesis of shortened iodo-triazolium axle containing rotaxane **36·PF₆**.

The new rotaxane was characterised by high resolution ESI mass spectrometry and by ^1H , ^{13}C , ^{19}F and ^{31}P NMR spectroscopy. A number of important observations can be made from comparison of the ^1H NMR spectra of **36·PF₆** and macrocycle precursor **29** that indicate an interlocked product has been formed (**Figure 2.16**). The hydroquinone protons δ and ϵ of the macrocycle component have shifted upfield and split due to them partaking in aromatic donor–acceptor interactions with the electron-deficient iodo-triazolium group of the axle, suggesting the axle now resides in the macrocycle cavity. In addition, a new peak assigned to the macrocycle vinyl protons ϕ can also be seen confirming the cyclisation of **29**.

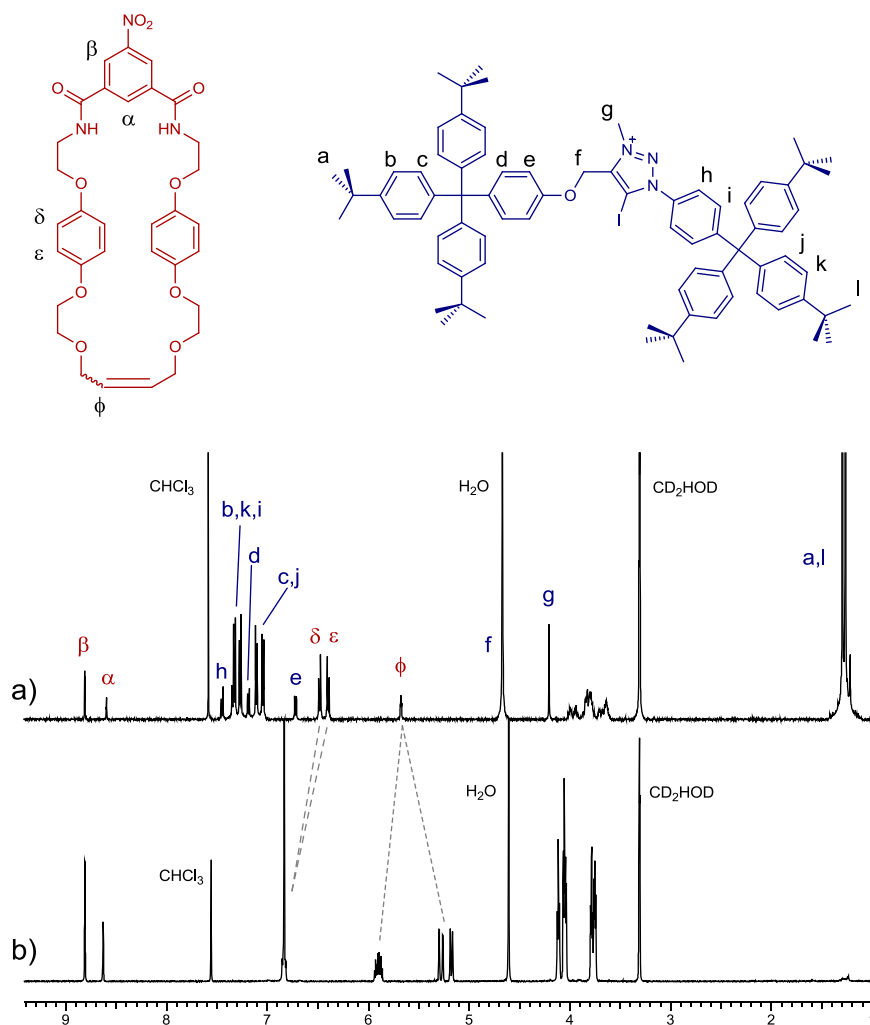


Figure 2.16— ^1H NMR spectra of a) [2]rotaxane **36**·PF₆ and b) macrocycle precursor **29** (500 MHz, 1:1 CDCl₃/CD₃OD, 293 K).

Further evidence for the formation of an interlocked structure was obtained from the two-dimensional ^1H – ^1H ROESY NMR spectrum of **36**·PF₆ (**Figure 2.17**). Through space couplings of the internal and external macrocycle isophthalamide protons (α and β) with a number of the axle terphenyl protons consistent with the formation of an interlocked rotaxane product are observed.

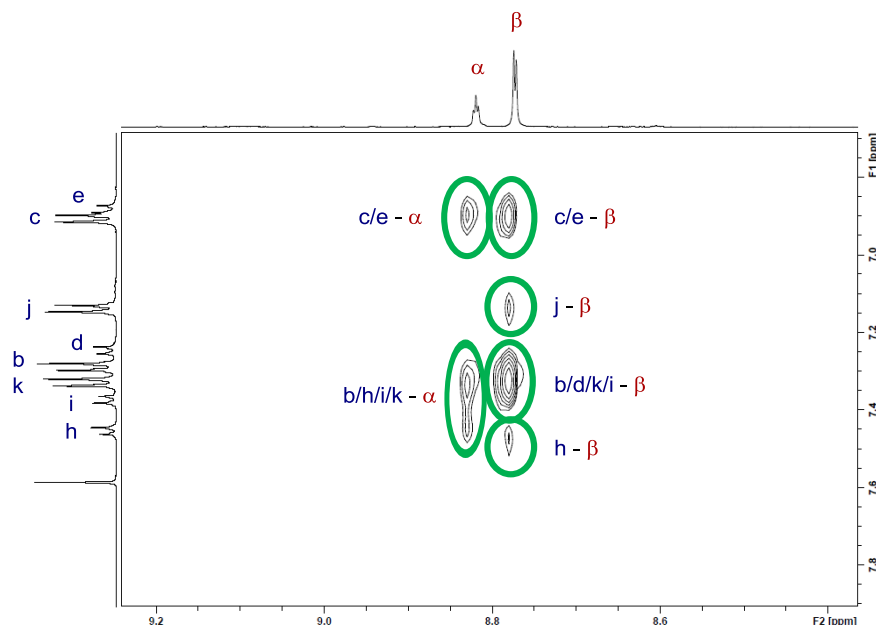
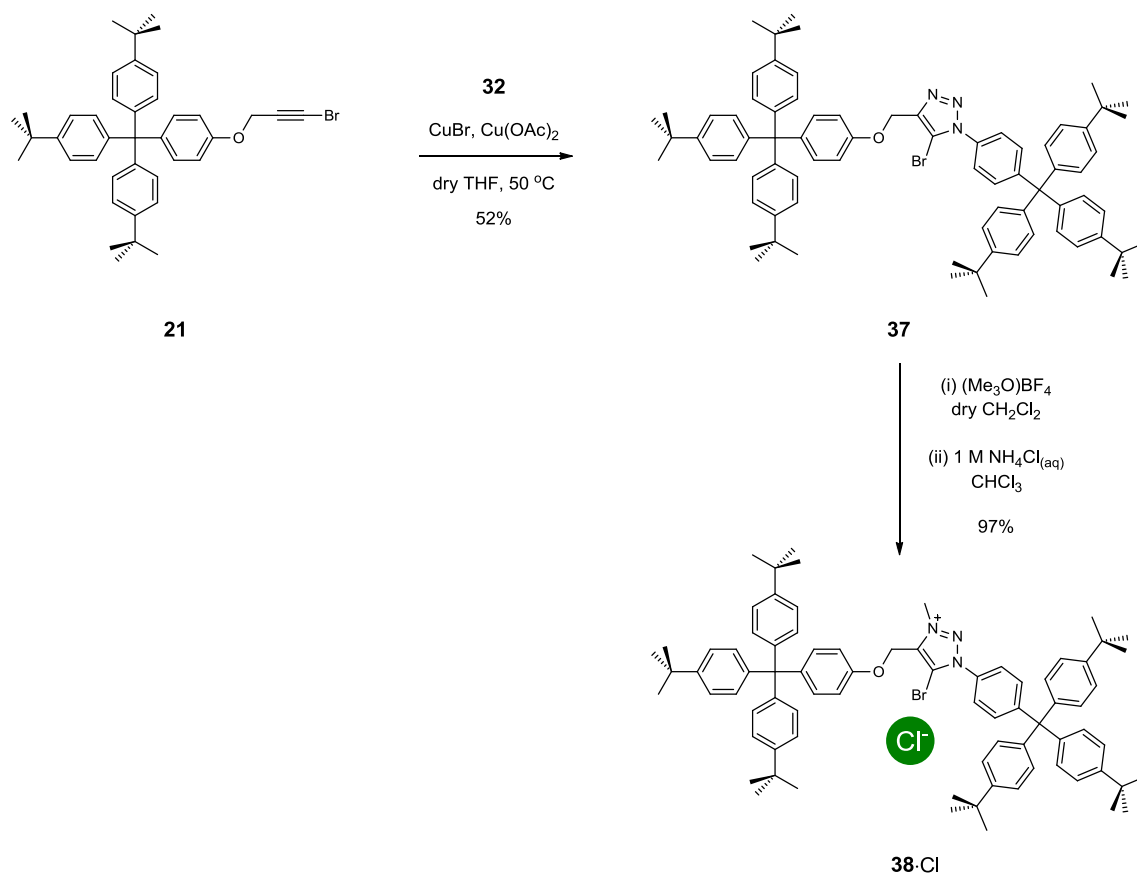


Figure 2.17—Truncated ROESY NMR spectrum of rotaxane **36**·PF₆ (500 MHz, 1:1 CDCl₃/CD₃OD, 293 K, peak assignments taken from **Figure 2.16**).

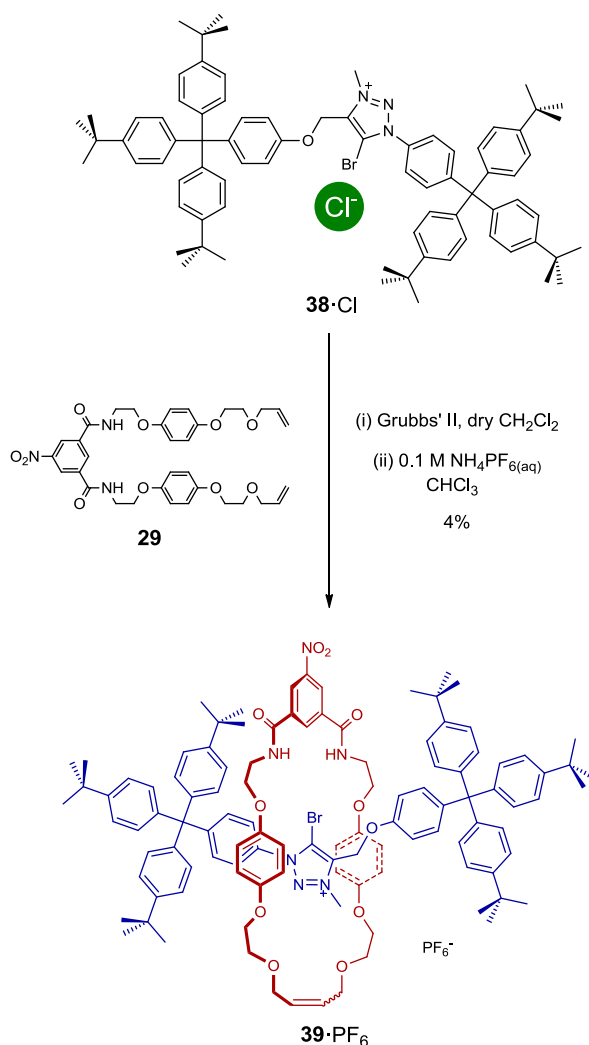
2.3.2.2 Bromo-triazolium axle containing [2]rotaxane

The bromo-triazolium functionalised shortened axle was prepared in an identical manner to axle **24**⁺ except for the substitution of propyl-linked terphenyl azide **22** with azide component **32** (**Scheme 2.12**). A modified literature procedure¹² in which a THF solution of azide **32** and bromo-alkyne **21** was heated in the presence of a mixed copper(I) bromide/copper(II) acetate catalyst afforded bromo-triazole **37** in 52% yield. Methylation with (Me₃O)BF₄ in dry CH₂Cl₂ resulted in the formation of the tetrafluoroborate salt of the target bromo-triazolium axle **38**·BF₄. Given the success of using a chloride anion to template the synthesis of rotaxane **36**·PF₆, **38**·BF₄ was dissolved in chloroform and repeatedly washed with 1 M NH₄Cl_(aq) to form the axle chloride salt **38**·Cl, which was isolated in a yield of 97%.



Scheme 2.12—Synthesis of shortened bromo-triazolium axle **38·Cl**.

With axle **38·Cl** isolated, an analogous synthetic protocol to preparing **36·PF₆** was used to synthesise the target bromo-triazolium axle containing rotaxane **39·PF₆** (**Scheme 2.13**). The product was isolated as its hexafluorophosphate salt **39·PF₆** in a low 4% yield following purification *via* preparative thin layer chromatography and removal of the chloride template by repeated washing with 0.1 M $\text{NH}_4\text{PF}_6(\text{aq})$. This yield is markedly lower than that obtained for iodo-triazolium analogue **36·PF₆** and is attributed to the poorer halogen bond donor ability of bromo-triazolium which results in a weaker interaction with the templating chloride anion. It is noteworthy that attempts at repeating the rotaxane synthesis with a bromide template were unsuccessful.



Scheme 2.13—Synthesis of shortened bromo-triazolium axle containing rotaxane **39·PF₆**.

High resolution ESI-MS analysis of rotaxane **39·PF₆** gave the expected mass peak at m/z 1785.8728 $[M - PF_6]^+$ and further characterisation was obtained from ^1H , ^{13}C , ^{19}F and ^{31}P NMR spectroscopy. As before, perturbations of the macrocycle hydroquinone protons (δ and ϵ) and the appearance of a peak corresponding to the macrocycle alkene protons ϕ in ^1H NMR spectrum of **39·PF₆** (**Figure 2.18**), combined with through space inter-component coupling in its two-dimensional ^1H - ^1H ROESY NMR spectrum (**Figure 2.19**), confirm an interlocked structure has been synthesised.

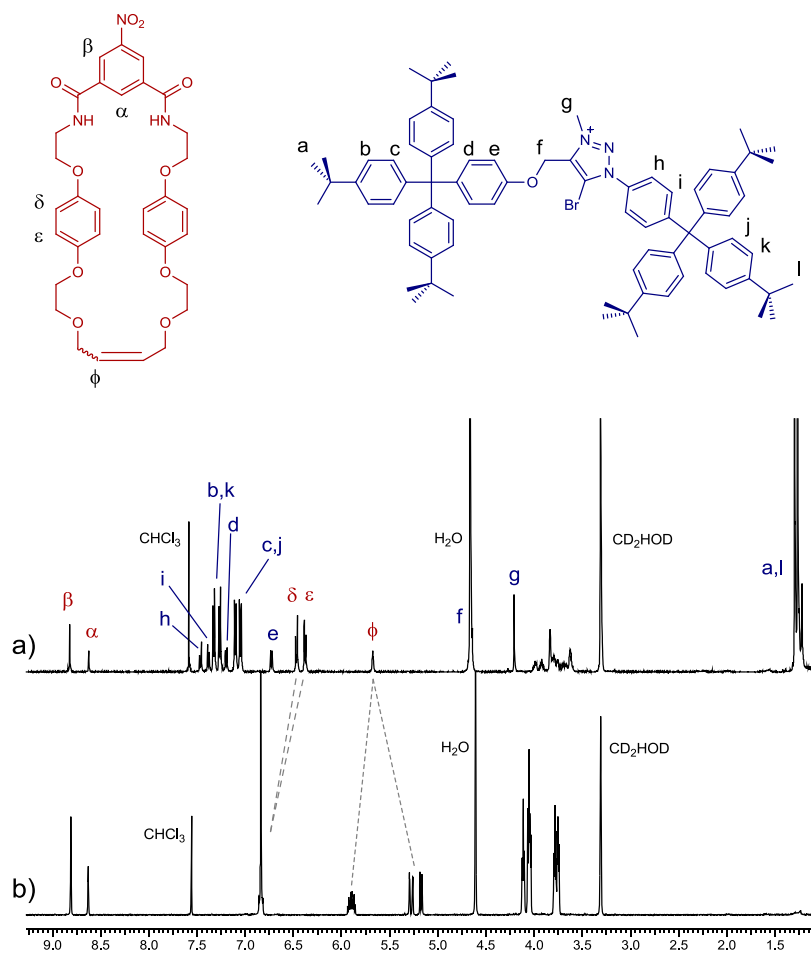


Figure 2.18— ^1H NMR spectra of a) [2]rotaxane $39\cdot\text{PF}_6$ and b) macrocycle precursor **29** (500 MHz, 1:1 $\text{CDCl}_3/\text{CD}_3\text{OD}$, 293 K).

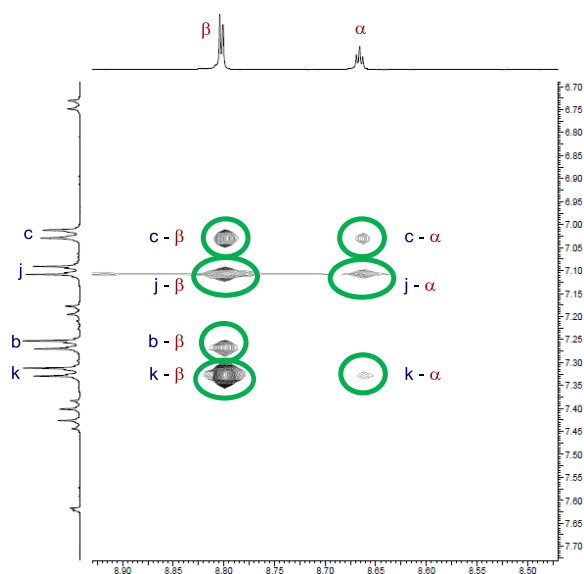


Figure 2.19—Truncated ROESY NMR spectrum of rotaxane $39\cdot\text{PF}_6$ (500 MHz, 1:1 $\text{CDCl}_3/\text{CD}_3\text{OD}$, 293 K, peak assignments taken from **Figure 2.18**).

2.3.3 Anion recognition properties

With the halo-triazolium rotaxanes **36**·PF₆ and **39**·PF₆ successfully isolated, their anion binding properties were investigated by ¹H NMR titrations, with iodo-triazolium rotaxane **36**·PF₆ studied initially. Addition of bromide, as its TBA salt, to a 1:1 CDCl₃/CD₃OD solution of **36**·PF₆ resulted in downfield shifts of the macrocycle isophthalamide proton α and axle terphenyl protons d , e and h , indicative of hydrogen bonding with the halide guest (**Figure 2.20**). Interestingly, macrocycle proton β and axle terphenyl protons c can be seen to move in the opposite upfield direction.

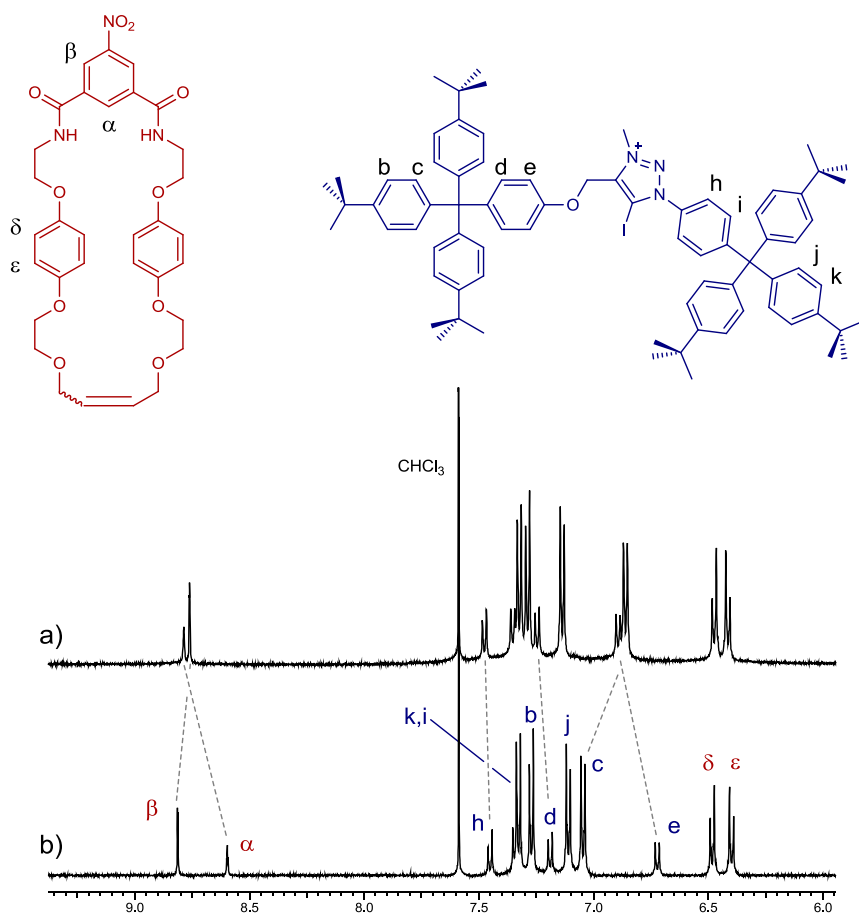


Figure 2.20—Truncated ¹H NMR spectra of a) rotaxane **36**·PF₆ upon addition of one equivalent of TBA·Br and b) rotaxane **36**·PF₆ (500 MHz, 1:1 CDCl₃/CD₃OD, 293 K).

Similar chemical shift perturbations were observed upon addition of other anions although their magnitudes differ; for example, for isophthalamide proton α $\Delta\delta_{10 \text{ equiv.}} = 0.36$ (Cl[−]),

0.27 (Br^-), 0.14 (I^-) and 0.06 (OAc^-). Analogous anion titration experiments with bromotriazolium functionalised rotaxane $39\cdot\text{PF}_6$ led to similar changes being observed in the ^1H NMR spectra.

WinEQNMR2¹⁵ analysis of the titration data obtained by monitoring the movement of the macrocycle component proton α of the respective rotaxanes (**Figure 2.21a** and **2.21b**) gave 1:1 stoichiometric association constants (**Table 2.6**). The halide binding affinities of iodo-triazolium rotaxane $36\cdot\text{PF}_6$ were found to be particularly strong in 1:1 $\text{CDCl}_3/\text{CD}_3\text{OD}$ and so the titrations were repeated in the more competitive 45:45:10 $\text{CDCl}_3/\text{CD}_3\text{OD}/\text{D}_2\text{O}$ solvent mixture (**Figure 2.21c**). The association constants obtained for these titrations are also included in **Table 2.6**.

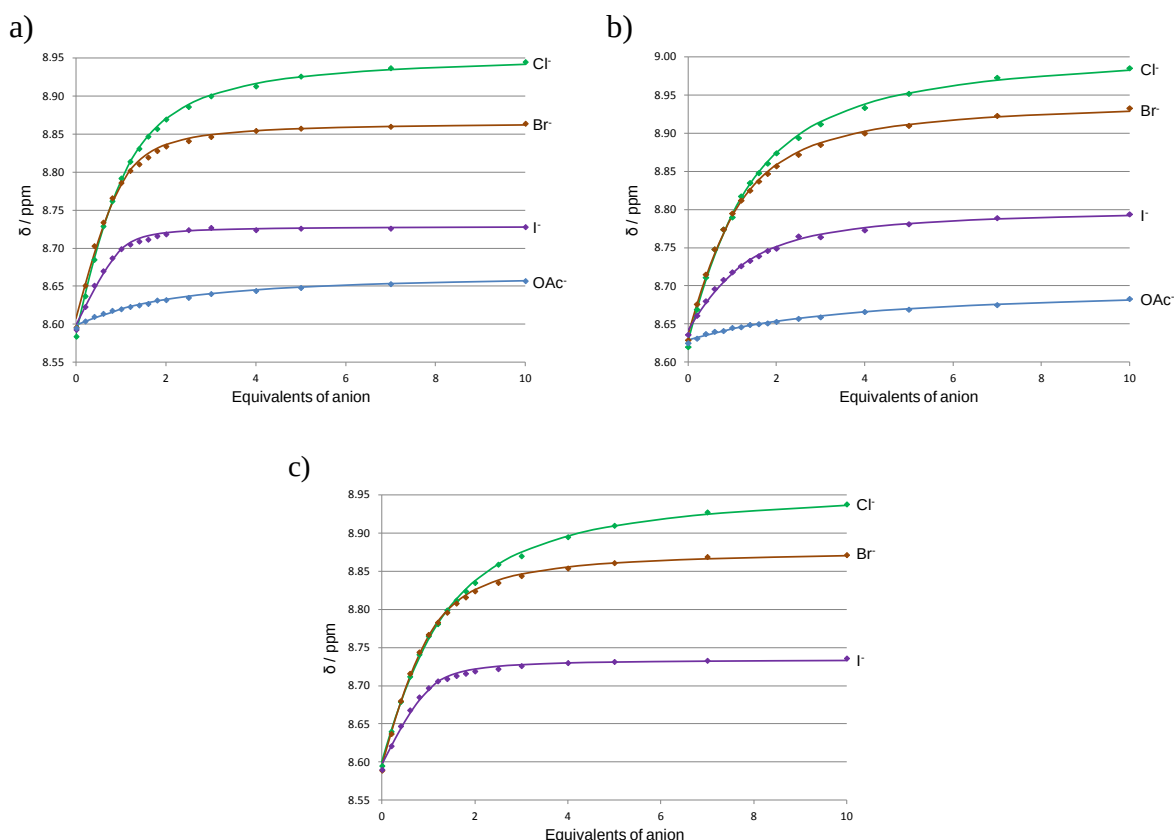


Figure 2.21—Changes in chemical shift of proton α upon addition of increasing amounts of different anions to a) rotaxane $36\cdot\text{PF}_6$ and b) rotaxane $39\cdot\text{PF}_6$ in 1:1 $\text{CDCl}_3/\text{CD}_3\text{OD}$ and c) rotaxane $36\cdot\text{PF}_6$ in 45:45:10 $\text{CDCl}_3/\text{CD}_3\text{OD}/\text{D}_2\text{O}$ (500 MHz, 293 K, data points represent experimental data, continuous lines represent calculated curves).

Table 2.6—Association constants, $K_a (M^{-1})$, obtained for rotaxanes **36**·PF₆ and **39**·PF₆ with various anions (estimated standard errors in parentheses, 293 K).

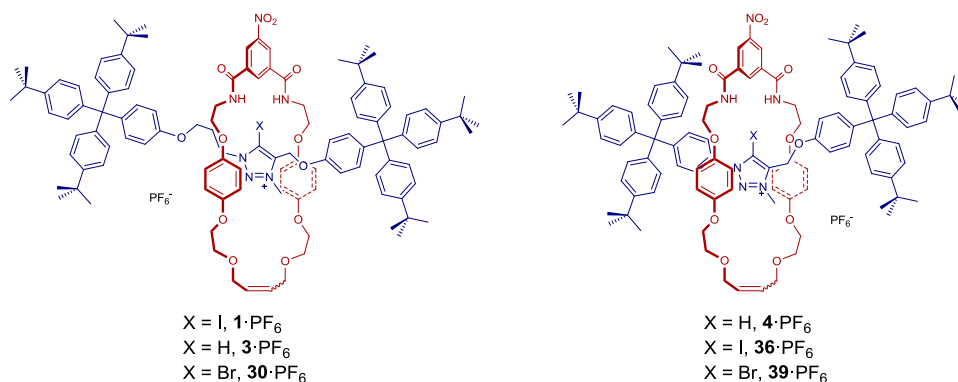
Anion	36 ·PF ₆	39 ·PF ₆ ^[a]	
Cl [−]	1350(50) ^[a]	678(29) ^[b]	640(36)
Br [−]	3510(40) ^[a]	1840(100) ^[b]	993(61)
I [−]	6790(590) ^[a]	4570(510) ^[b]	806(69)
OAc [−]	292(32) ^[a]	—	129(4)

^[a] 1:1 CDCl₃/CD₃OD, ^[b] 45:45:10 CDCl₃/CD₃OD/D₂O.

Table 2.7—Association constants, $K_a (M^{-1})$, obtained for triazolium and halo-triazolium rotaxanes with various anions (estimated standard errors in parentheses, 293 K).

Anion	1 ·PF ₆ ^[c]		30 ·PF ₆ ^[a]	3 ·PF ₆ ^[a,d]	4 ·PF ₆ ^[a,d]
Cl [−]	—	457(4) ^[b]	435(27)	424(20)	1110(110)
Br [−]	>10 ^{4[a]}	1251(10) ^[b]	620(44)	423(14)	1320(21)
I [−]	—	2228(171) ^[b]	648(51)	350(16)	566(23)
OAc [−]	—	—	93(14)	42(3)	92(15)

^[a] 1:1 CDCl₃/CD₃OD, ^[b] 45:45:10 CDCl₃/CD₃OD/D₂O, ^[c] values taken from ref. 7, ^[d] values taken from ref. 10.

**Figure 2.22**—Triazolium and halo-triazolium axle containing rotaxanes referred to in **Table 2.6** and **Table 2.7**.

As was hoped, the more preorganised halo-triazolium rotaxanes **36**·PF₆ and **39**·PF₆ display stronger anion binding affinities than their respective less preorganised rotaxane analogues **1**·PF₆ and **30**·PF₆ (**Table 2.7**).

Direct comparison of rotaxanes **36**·PF₆ and **39**·PF₆ reveals that the iodo-triazolium axle containing rotaxane is the most potent anion receptor. This is unsurprising given that the

iodo-triazolium motif is a superior halogen bond donor to bromo-triazolium on the basis of the relative polarisabilities of the halogen atoms, as discussed in **Section 2.2.2.4**.

The halide anion binding selectivities of **36**·PF₆ and **39**·PF₆ are different to that of their protic triazolium rotaxane analogue **4**·PF₆; iodide and bromide are bound the most strongly by halo-triazolium rotaxanes **36**·PF₆ and **39**·PF₆ respectively, whereas **4**·PF₆ prefers the smaller chloride anion. This is likely due to the halo-triazolium rotaxanes undergoing a conformational change to accommodate their large axle halogen donor atoms which results in their host cavities being more accessible to the larger halide guests. The observed iodide selectivity of iodo-triazolium rotaxane **36**·PF₆ in 1:1 CDCl₃/CD₃OD ($K_a(\text{I}^-)/K_a(\text{Cl}^-) = 5.0$) was found to be enhanced further when 45:45:10 CDCl₃/CD₃OD/D₂O was used as the titration solvent ($K_a(\text{I}^-)/K_a(\text{Cl}^-) = 6.7$), which can be attributed to the Hofmeister series bias favouring binding of iodide over both chloride and bromide on the basis of relative ease of desolvation.¹⁹ Importantly, the use of the iodo-triazolium motif can be seen to dramatically enhance the overall binding strength of the system, with the association constants for **36**·PF₆ with all three halides being larger than those obtained with rotaxane **4**·PF₆. This indicates that the incorporation of this halogen bonding motif has a favourable impact on the anion recognition properties of the rotaxane and that it is a more potent anion binding group than triazolium.

Finally, comparison of halo-triazolium rotaxanes **36**·PF₆ and **39**·PF₆ with the less preorganised protic triazolium rotaxane **3**·PF₆ shows that the effects of halogen bonding and increased inter-component preorganisation result in a more potent anion host which, in the case of **36**·PF₆, is capable of halide guest recognition in aqueous solvent mixtures.

2.3.4 Summary

Two novel halo-triazolium rotaxanes containing shortened axle components have been synthesised and their anion recognition properties investigated. As was hoped, the increased inter-component preorganisation of these systems gave rise to enhanced anion binding strength as compared to their less preorganised analogues.

The effects of altering the rotaxane's halogen bond donor was also investigated, with iodo-triazolium axle containing rotaxane **36**·PF₆ found to bind the halide anions more strongly than the bromo-triazolium rotaxane analogue **39**·PF₆. This is attributed to a C–I bond being a superior halogen bond donor to a C–Br bond due to the greater polarisability of iodine.

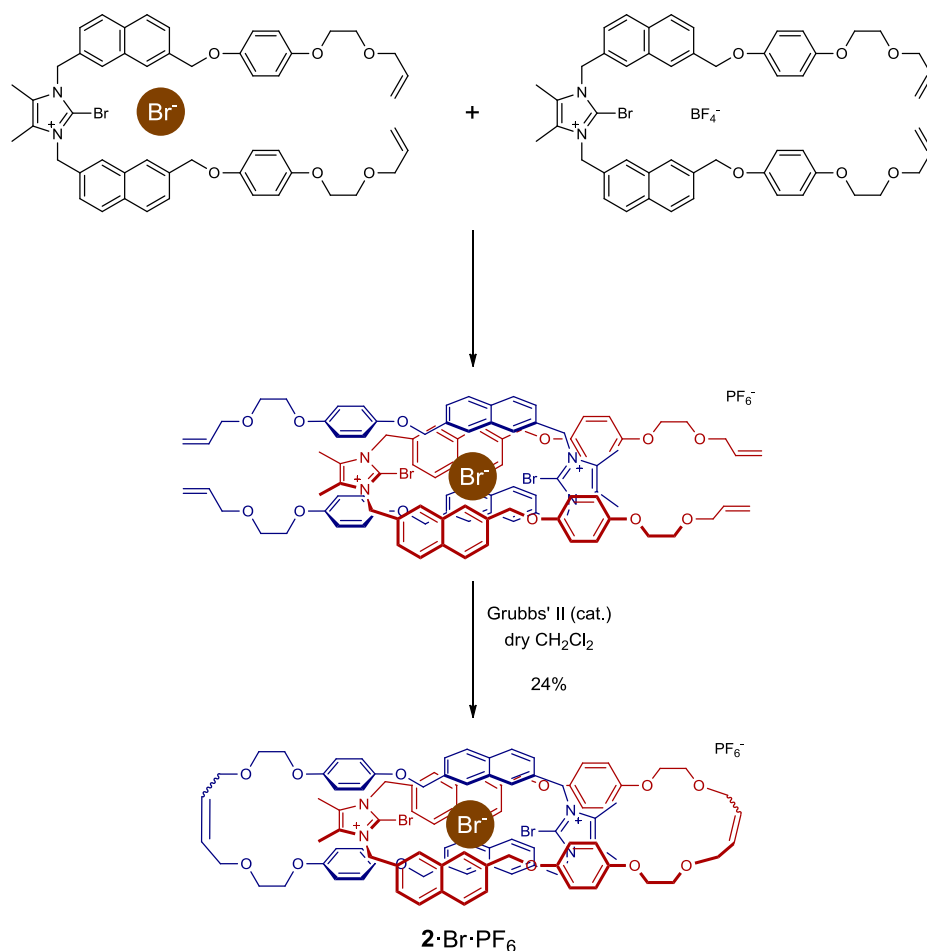
Importantly, it was demonstrated that an interlocked host that combines the effects of halogen bonding and increased inter-component preorganisation, such as **36**·PF₆, is a potent anion receptor capable of halide guest recognition in aqueous solvent media.

Given the impressive anion recognition properties of the iodo-triazolium axle containing rotaxane, the integration of this halogen bonding motif into other interlocked structures, such as a [2]catenane, was seen as a logical progression.

2.4 Iodo-triazolium containing [2]catenane

2.4.1 Introduction

In *Section 2.1.2* the first halogen bonding [2]catenane⁹ was introduced briefly. This interlocked structure was synthesised by a bromide anion-templated Grubbs' II-catalysed RCM “double-cyclisation” strategy (*Scheme 2.14*). Stirring an equimolar solution of the bromide and hexafluorophosphate salts of the bromo-imidazolium bis-vinyl appended precursor compound resulted in the formation of a 2:1 precursor/bromide complex, augmented by two C–Br···Br[–] halogen bonds, which upon double-cyclisation afforded the interlocked homo-[2]catenane **2**·Br·PF₆ in 24% yield.



Scheme 2.14—Grubbs' II-catalysed RCM double-cyclisation synthesis of the first halogen bonding [2]catenane $2 \cdot \text{Br} \cdot \text{PF}_6$.

Upon removal of the bromide template, fluorescence spectroscopic anion binding investigations revealed that, in acetonitrile solution, $2 \cdot (\text{PF}_6)_2$ selectively bound and sensed chloride ($K_a = 3.71 \times 10^6 \text{ M}^{-1}$) and bromide ($K_a = 1.48 \times 10^5 \text{ M}^{-1}$) via cooperative halogen bonding interactions. Importantly, no optical response was detected with F^- , I^- , OAc^- , H_2PO_4^- , NO_3^- and HCO_3^- , highlighting the complementary nature of the catenane host cavity for chloride and bromide anions.

In **Section 2.3.2** it was demonstrated that the iodo-triazolium motif was a superior halogen bond donor to the corresponding bromo-triazolium analogue. Therefore, it was anticipated that integration of the iodo-triazolium group into a homo-[2]catenane would result in a novel interlocked host for anion recognition.

2.4.2 Catenane synthesis and characterisation

Synthesis of the target iodo-triazolium containing [2]catenane initially required the construction of a bis-vinyl appended precursor compound 52^+ (**Figure 2.23b**), which is of similar design to the precursor compound of catenane $2 \cdot (\text{PF}_6)_2$ (**Figure 2.23a**) and contains extra linking groups either side of the naphthalene units to accommodate the larger C–I halogen bond donors.

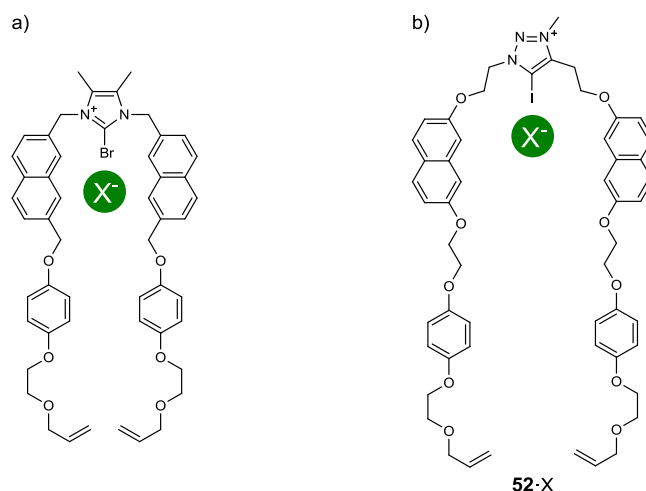
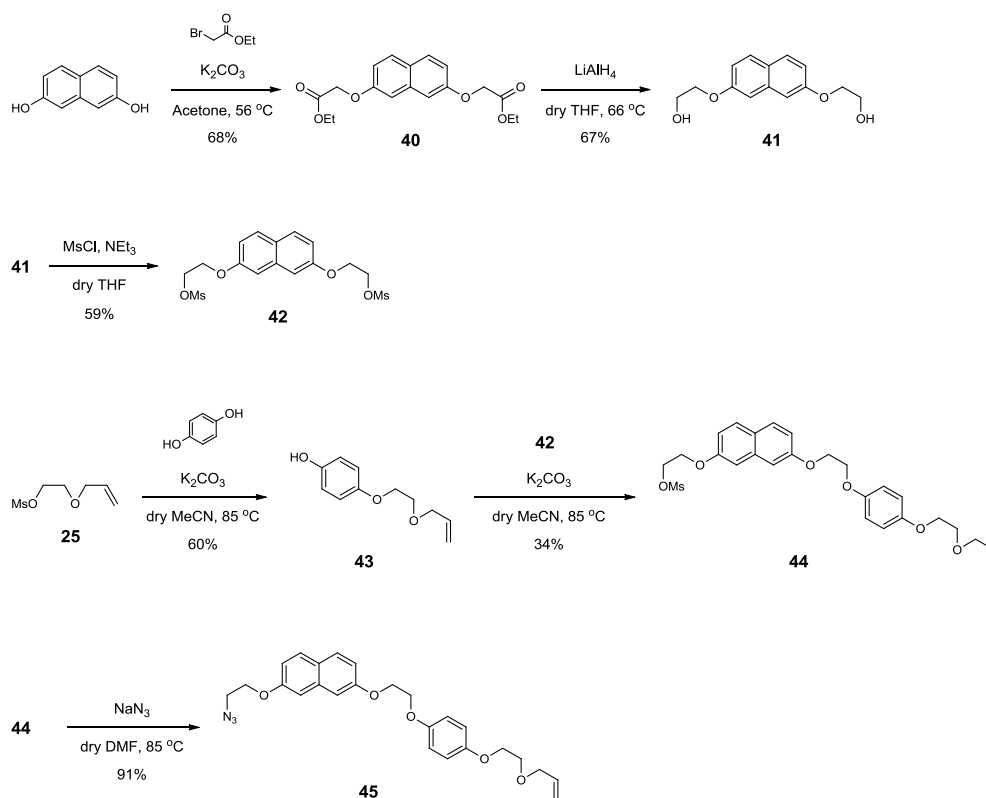


Figure 2.23—a) Bromo-imidazolium functionalised precursor compound to catenane $2 \cdot (\text{PF}_6)_2$ and b) targeted iodo-triazolium containing bis-vinyl appended catenane precursor $52 \cdot \text{X}$.

2.4.2.1 Iodo-triazolium containing bis-vinyl appended precursor synthesis

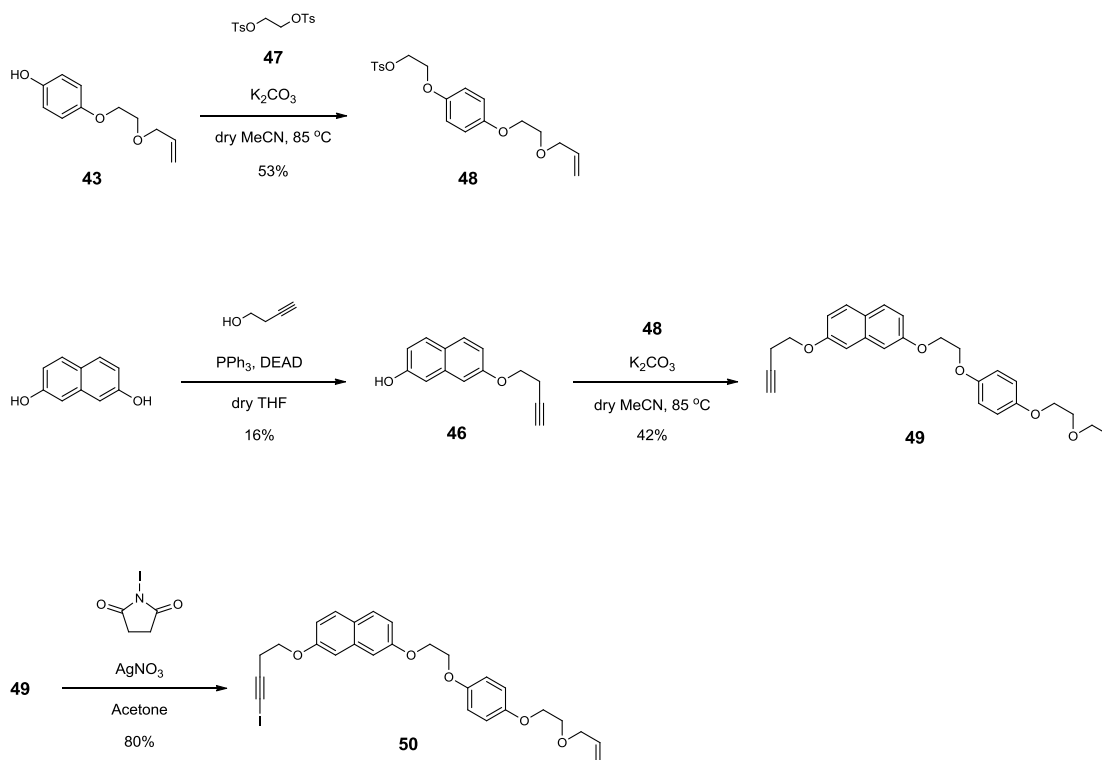
In order to prepare the iodo-triazolium containing bis-vinyl appended compound 52^+ , two precursor compounds, azide and iodo-alkyne components **45** and **50**, needed to be synthesised. Azide **45** was isolated following the multi-step pathway shown in **Scheme 2.15**. 2,7-Dihydroxynaphthalene was reacted with two equivalents of ethyl bromoacetate, in the presence of K_2CO_3 to form compound **40** (68%), which was then converted to diol **41** by reduction with lithium aluminium hydride in dry THF (67%). Reaction of **41** with methanesulfonyl chloride and triethylamine in dry THF afforded bis-mesylate **42** in 59% yield. The reaction of one equivalent of mesylate **25** with hydroquinone under basic

conditions afforded the mono-functionalised derivative **43** in 60% yield. An equimolar reaction of **43** and bis-mesylate **42**, in the presence of K_2CO_3 , in dry acetonitrile gave **44** (34%). Finally, reaction of **44** with sodium azide resulted in the formation of the target azide compound **45** in 91% yield.



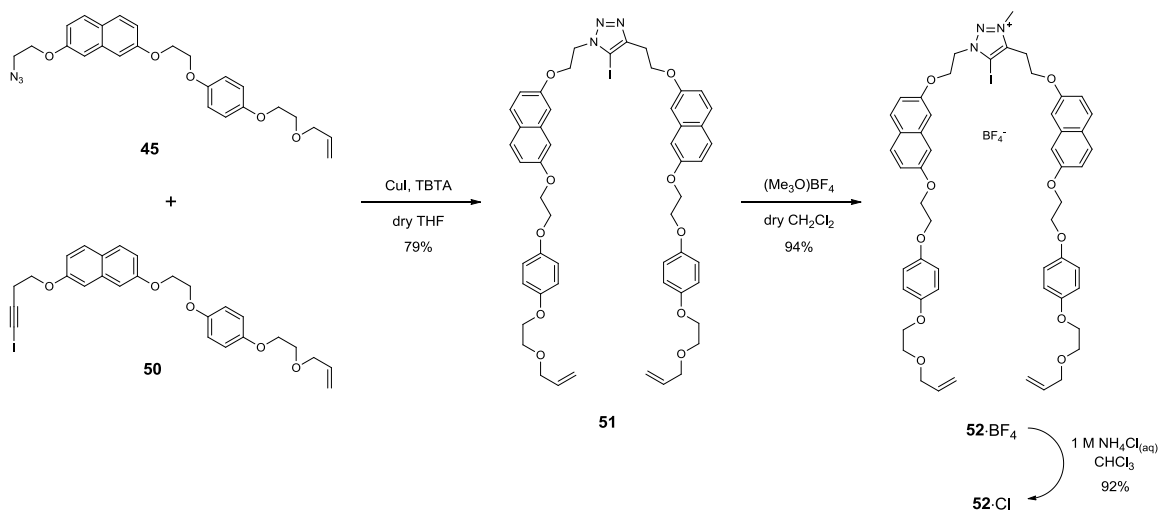
Scheme 2.15—Synthesis of vinyl appended azide compound **45**.

Iodo-alkyne **50** was prepared by the route shown in **Scheme 2.16**. The previously isolated mono-functionalised hydroquinone **43** was reacted with bis-tosylate **47** to form compound **48** (53%). This was then reacted with the product **46** of a Mitsunobu reaction between 2,7-dihydroxynaphthalene and 3-butyne-1-ol to form alkyne **49** in 42% yield. Reaction of **49** with *N*-iodosuccinimide, in the presence of a catalytic amount of $AgNO_3$, afforded the desired iodo-alkyne **50** (80%).



Scheme 2.16—Synthesis of vinyl appended iodo-alkyne **50**.

The iodo-triazolium containing bis-vinyl appended precursor **52**⁺ was then synthesised by a two-step procedure from azide **45** and iodo-alkyne **50** (**Scheme 2.17**). ‘Click’ reaction²² of **45** and **50** afforded the bis-vinyl appended iodo-triazole compound **51** in 79% yield. Methylation with (Me₃O)BF₄ in dry CH₂Cl₂ gave the tetrafluoroborate salt **52**·BF₄ (94%), half of which was dissolved in chloroform and anion exchanged to the corresponding chloride salt **52**·Cl by repeated washing with 1 M NH₄Cl_(aq) (92%).

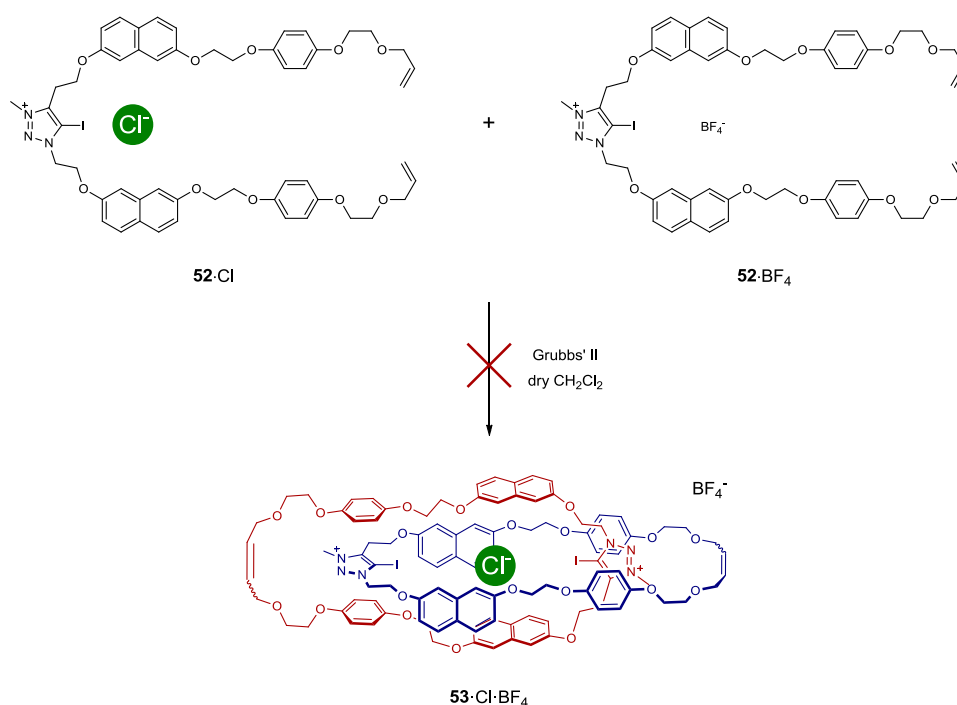


Scheme 2.17—Synthesis of iodo-triazolium containing bis-vinyl appended precursor $52 \cdot X$.

With the tetrafluoroborate and chloride salts of 52^+ isolated, the synthesis of the target iodo-triazolium functionalised homo-[2]catenane could be attempted *via* the previously mentioned Grubbs' II-catalysed RCM double cyclisation strategy, as detailed in the following section.

2.4.2.2 Homo-[2]catenane

Synthesis of the homo-[2]catenane 53^{2+} was attempted by reaction of an equimolar solution of $52 \cdot \text{BF}_4$ and $52 \cdot \text{Cl}$ in dry CH_2Cl_2 with Grubbs' II catalyst (10% by weight) (**Scheme 2.18**). After stirring at room temperature for 24 hours, a fine off-white precipitate formed in the reaction mixture which mass spectrometry and ^1H NMR identified as macrocycle 54^+ (**Figure 2.24**). Disappointingly, no evidence of catenane formation was found in the remaining crude reaction mixture. Analogous observations were made when the reaction was repeated with a bromide template.



Scheme 2.18—Attempted synthesis of iodo-triazolium containing homo-[2]catenane 53^{2+} .

The failure of this reaction is possibly due to the poor solubility of the cyclised product 54^+ (**Figure 2.24**). In a double cyclisation method for catenane formation it is unlikely that both RCM bond forming reactions occur simultaneously. Instead, one macrocyclic component is likely to form before the second precursor compound is cyclised to give the interlocked product. Hence, precipitation of 54^+ prior to the catenane bond forming reaction taking place may account for the interlocked species not being isolated.

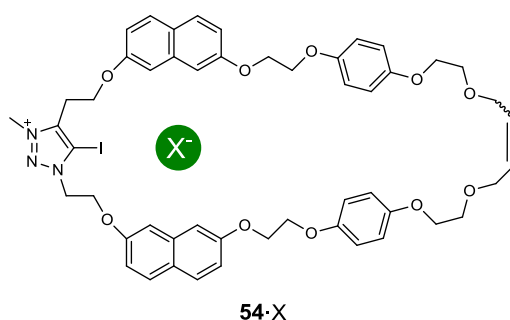


Figure 2.24—Cyclised form of iodo-triazolium containing bis-vinyl appended precursor 52^+ , 54^+ .

2.4.2.3 Hetero-[2]catenane

In **Section 2.2.1.3** it was highlighted that the iodo-triazolium motif was capable of forming a [2]pseudorotaxane with an isophthalamide macrocycle *via* halide anion templation.⁷ With this in mind, it was hoped that iodo-triazolium containing bis-vinyl appended precursor **52**·Cl would form an interpenetrated assembly with a similar isophthalamide macrocycle, which could ultimately be cyclised to form a hetero-[2]catenane.

Initially, a qualitative equimolar ¹H NMR titration experiment was performed to ascertain if there was any evidence for pseudorotaxane formation between **52**·Cl and isophthalamide macrocycle **55** (kindly donated by Dr. L. Gilday). Upon addition of one equivalent of **52**·Cl to a CD₂Cl₂ solution of macrocycle **55**, the macrocycle hydroquinone protons δ and ϵ shifted upfield and split, which is diagnostic of an interpenetrative assembly (**Figure 2.25**). Also, downfield shifts of the macrocycle isophthalamide protons α and β arising from hydrogen bonding with the templating chloride anion were noted. Finally, the signals corresponding to the naphthalene and hydroquinone protons of **52**·Cl split.

With this ¹H NMR evidence of chloride anion-templated interpenetrative assembly, the synthesis of a hetero-[2]catenane was attempted.

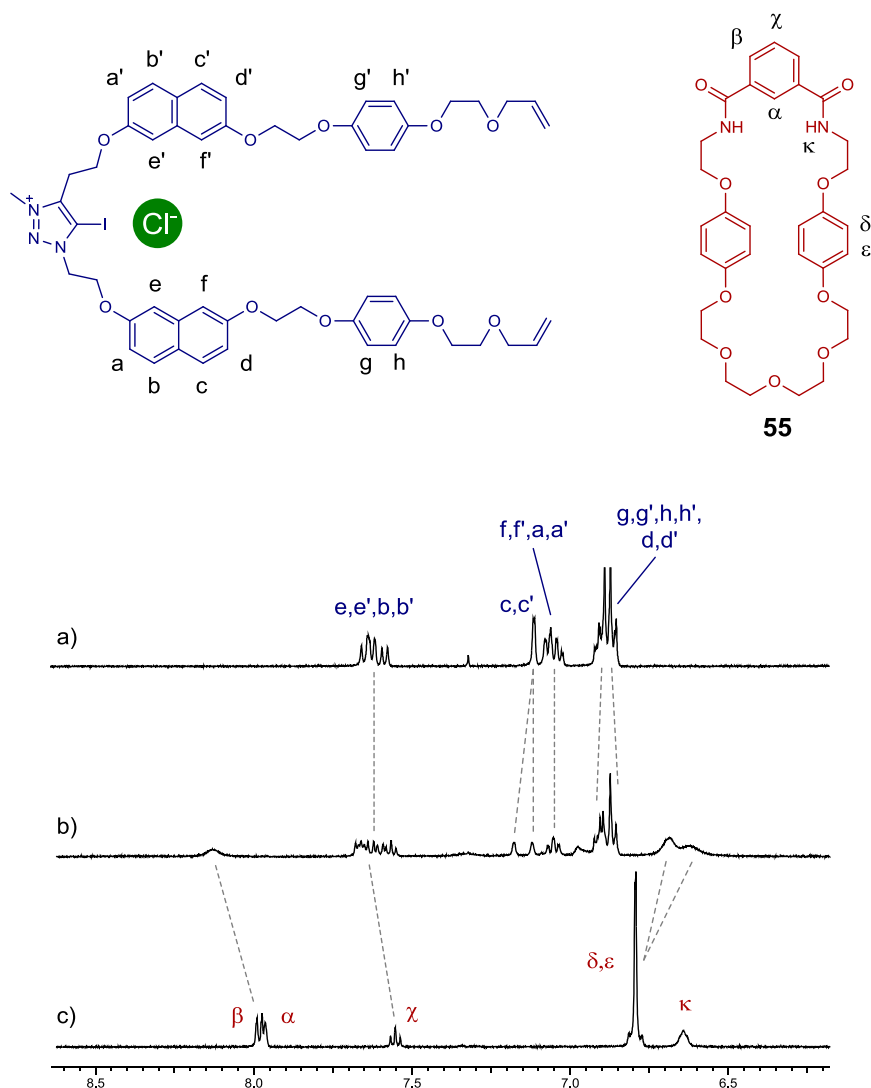
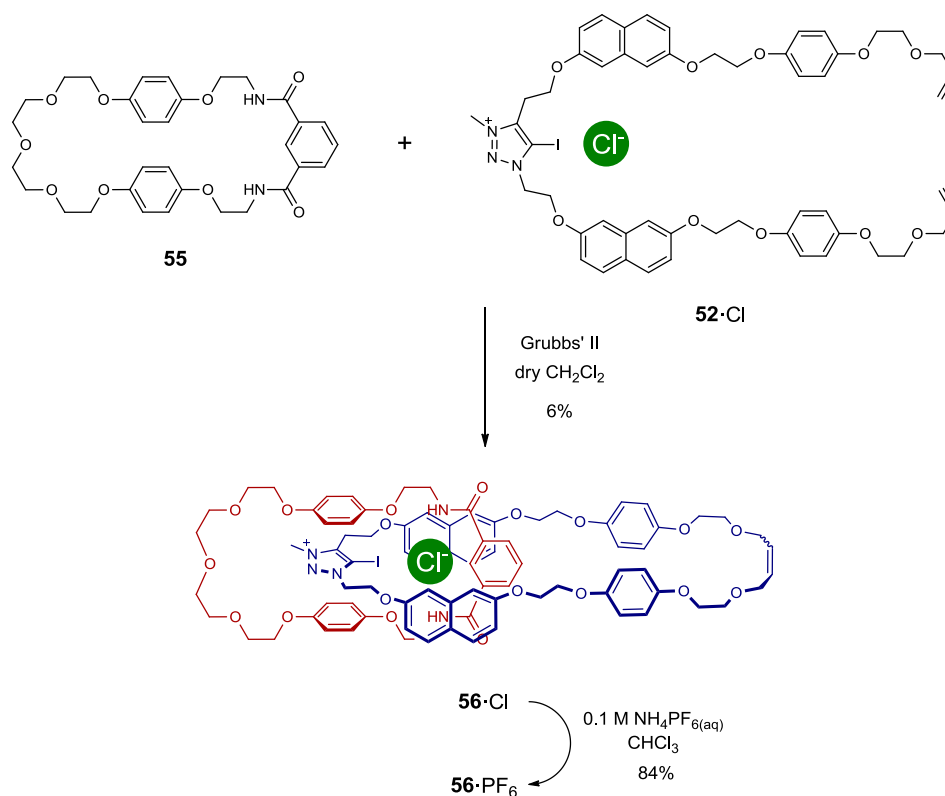


Figure 2.25—Truncated ^1H NMR spectra of a) 52·Cl, b) an equimolar mixture of 52·Cl and isophthalamide macrocycle 55 and c) isophthalamide macrocycle 55 (500 MHz, CD_2Cl_2 , 293 K).

The novel catenane was prepared by reaction of one equivalent of 52·Cl and 1.5 equivalents of macrocycle 55, in dry CH_2Cl_2 , with Grubbs' II catalyst (**Scheme 2.19**). The product was isolated as its chloride salt 56·Cl in 6% yield after purification *via* preparative thin layer chromatography. Repeated washing of a chloroform solution of 56·Cl with 0.1 M $\text{NH}_4\text{PF}_6(\text{aq})$ afforded the hexafluorophosphate salt of the catenane 56· PF_6 (84%).



Scheme 2.19—Synthesis of hetero-[2]catenane **56·PF₆**.

The new catenane **56·Cl** was characterised by ¹H NMR and by high resolution ESI mass spectrometry. High resolution ESI-MS analysis of **56·Cl** gave the expected mass peak at m/z 1588.5346 [M - Cl]⁺ and the ¹H NMR spectrum of **56·Cl**, together with those of precursor **52·Cl** and macrocycle **55**, is shown in **Figure 2.26**. It can be seen that upon catenane formation the macrocycle protons α , β and κ are all shifted downfield, with this attributed to hydrogen bonding with the templating chloride anion. Importantly, the macrocycle hydroquinone protons δ and ϵ have shifted upfield and split due to aromatic donor–acceptor interactions with the electron-deficient iodo-triazolium motif indicative of interlocked structure formation, with this ratified further by the presence of a peak corresponding to the alkene protons i of the closed threading component. The naphthalene region of the catenane's ¹H NMR spectrum (**Figure 2.27**) is complex due to the asymmetric nature of the iodo-triazolium macrocycle component.

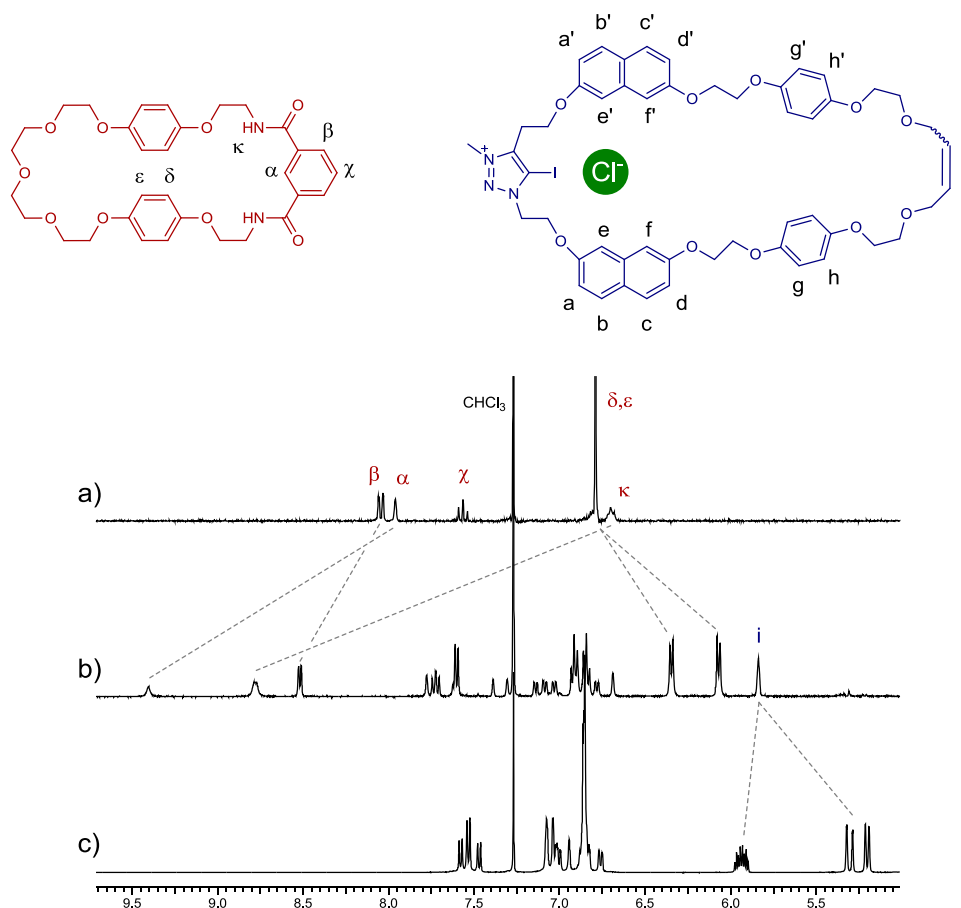


Figure 2.26—Truncated ^1H NMR spectra of a) macrocycle **55**, b) catenane **56**·Cl and c) iodo-triazolium containing bis-vinyl appended precursor **52**·Cl (500 MHz, CDCl_3 , 293 K).

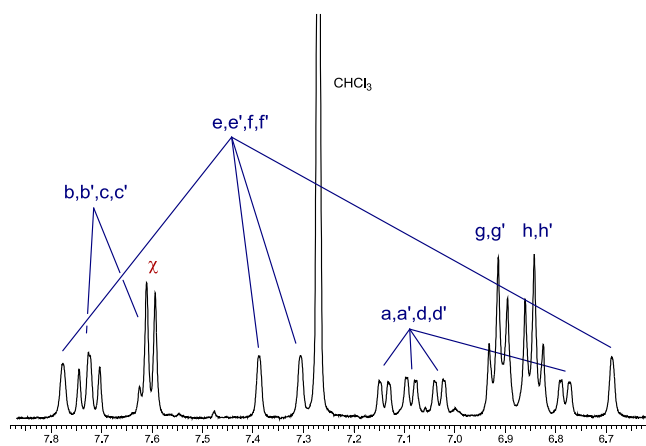


Figure 2.27—Expanded aromatic region of the ^1H NMR spectrum of catenane **56**·Cl (500 MHz, CDCl_3 , 293 K, peak assignments taken from **Figure 2.26**).

The interlocked nature of **56**⁺ was confirmed by two-dimensional ¹H–¹H ROESY NMR, with a number of through space couplings observed between the isophthalamide and iodo-triazolium macrocycle components (**Figure 2.28**).

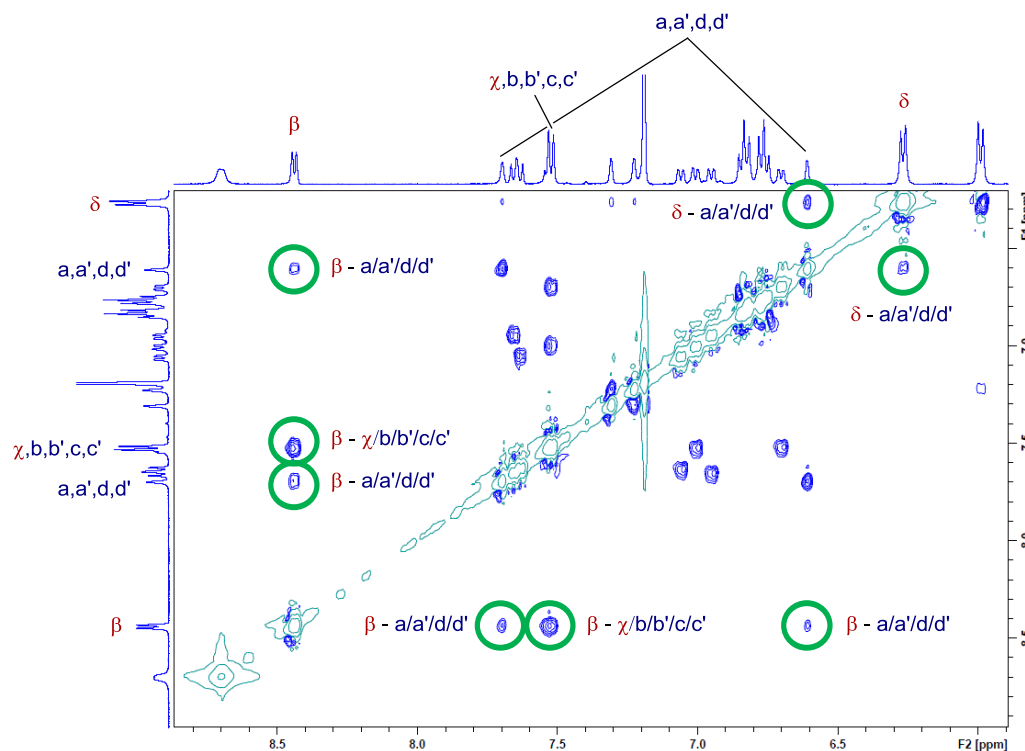


Figure 2.28—Truncated ROESY NMR spectrum of catenane **56**·Cl (500 MHz, CDCl₃, 293 K, peak assignments taken from **Figure 2.26**).

2.4.3 Anion recognition and sensing properties

Due to the low yield and hence limited supply of catenane **56**·PF₆, it was not possible to undertake quantitative ¹H NMR anion titration experiments. A comparison of the ¹H NMR spectra of the chloride and hexafluorophosphate salts of **56**⁺, however, revealed perturbations of a number of protons indicative of halide anion binding (**Figure 2.29**). Downfield shifts of protons α , β and κ of the isophthalamide macrocycle component are a result of hydrogen bonding interactions with the chloride anion. In addition, naphthalene protons e , e' , f , f' also shift downfield revealing they are also involved in anion binding. Hydroquinone protons δ and ϵ are seen to move upfield possibly as a result of chloride anion complexation leading to a

catenane conformation with enhanced aromatic donor–acceptor interactions between the electron-rich isophthalamide macrocycle hydroquinone groups and the electron-deficient iodo-triazolium motif.

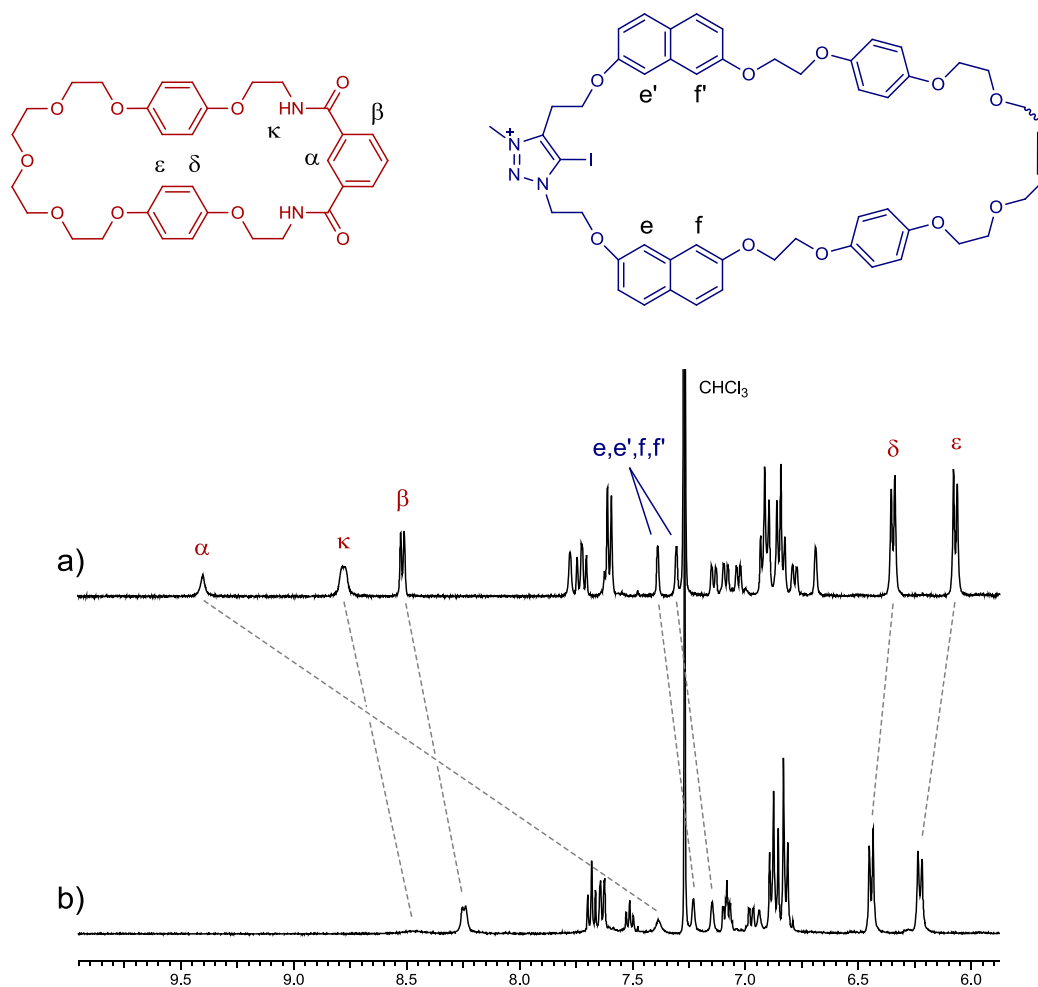


Figure 2.29—Truncated ^1H NMR spectra of a) **56**·Cl and b) **56**·PF₆ (500 MHz, CDCl_3 , 293 K).

Exploiting the naphthalene groups of catenane **56**·PF₆ allowed for fluorescence anion titration experiments to be performed, in acetonitrile solution. Increasing amounts of the TBA salts of chloride, bromide, iodide, acetate and dihydrogen phosphate were added to separate acetonitrile solutions of **56**·PF₆ and the fluorescence emission spectra monitored (**Figure 2.30**).

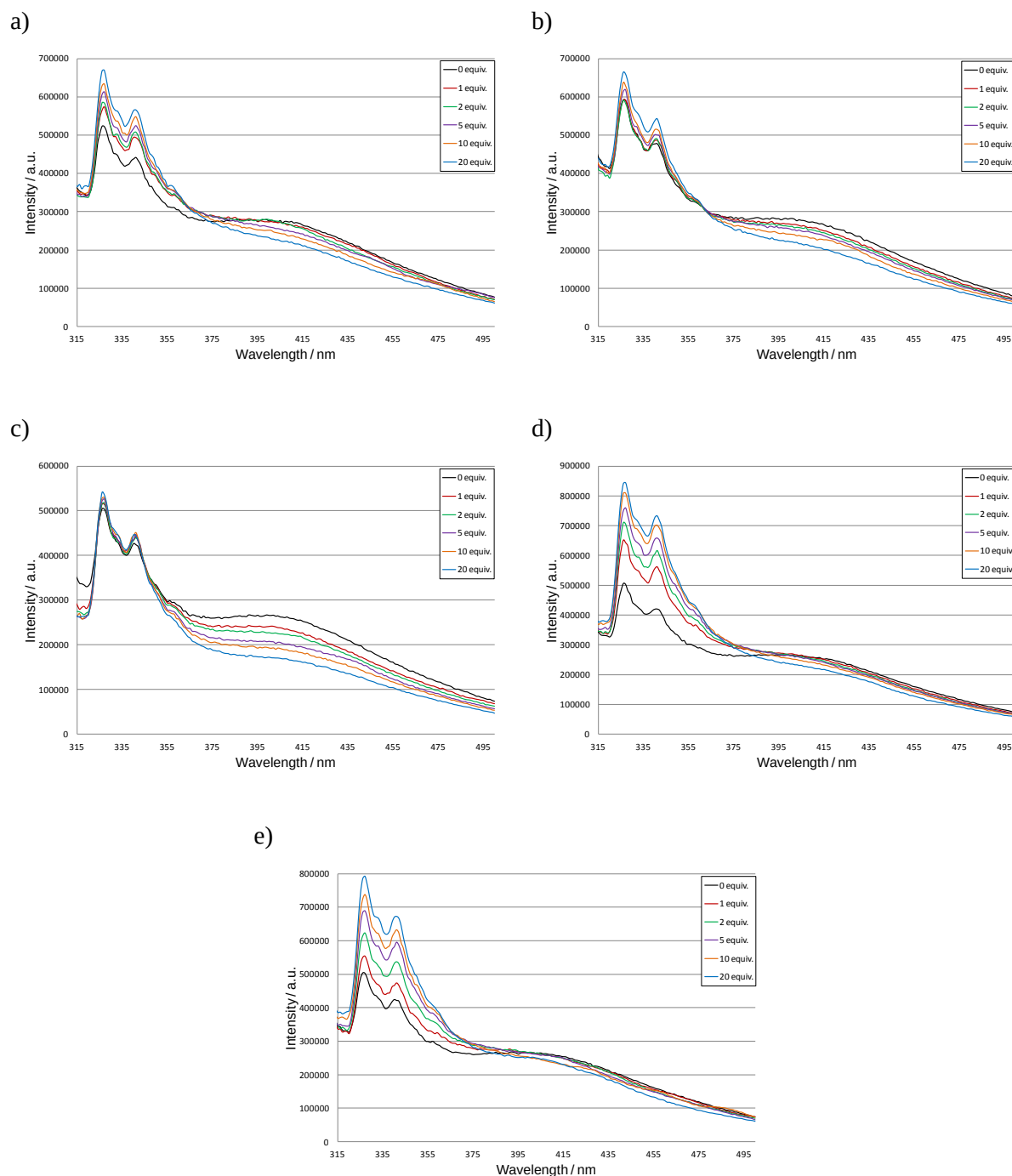


Figure 2.30—Changes in the emission spectrum of catenane **56**·PF₆ in acetonitrile upon addition of a) TBA·Cl, b) TBA·Br c) TBA·I, d) TBA·OAc and e) TBA·H₂PO₄ ([host] = 1 × 10⁻⁵ M, λ_{exc} = 280 nm, 293 K, note different y-axis scales)

In all cases, increases in intensity of the naphthalene monomer emission bands (326 and 340 nm) were observed upon the addition of anions, concomitant with a decrease in intensity of the catenane's broad excimer²³ emission band (centred at 410 nm). The relative

magnitudes of these changes after the addition of 20 equivalents of anion are shown in **Table 2.8** and represented graphically in **Figure 2.31**.

Table 2.8—Percentage changes in emission intensity, ΔI (%), at 326, 340 and 410 nm after the addition of 20 equivalents of various anions to an acetonitrile solution of catenane **56**·PF₆ ($[host] = 1 \times 10^{-5}$ M, $\lambda_{exc} = 280$ nm, 293 K).

Anion	326 nm	340 nm	410 nm
Cl [−]	+28	+29	-20
Br [−]	+12	+13	-23
I [−]	+7	+4	-36
OAc [−]	+66	+73	-14
H ₂ PO ₄ [−]	+56	+58	-7

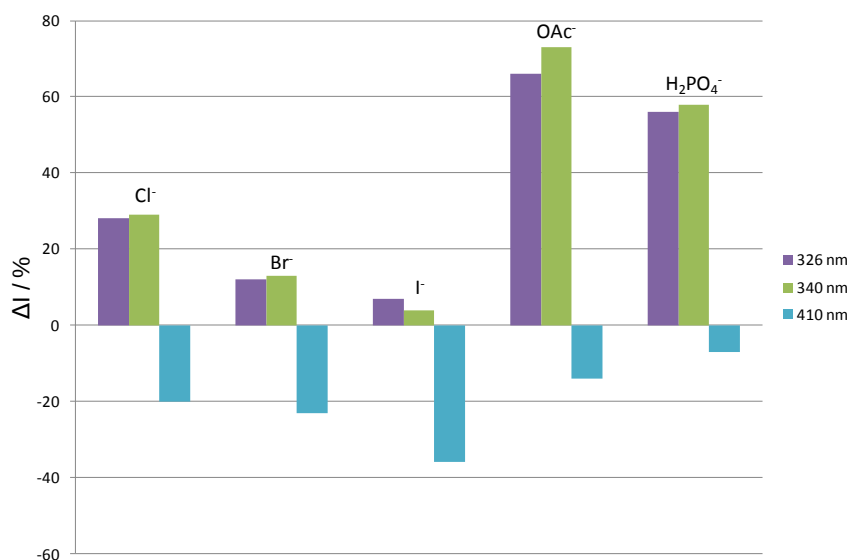


Figure 2.31—Graphical representation of data reported in **Table 2.8**.

The observed increases in intensity of the monomer emission bands are thought to be a result of the rigidity effect, which arises from anion complexation reducing the number of available vibrational and rotational non-radiative decay processes.²⁴ The addition of acetate and dihydrogen phosphate induces much greater percentage increases in emission intensity than the halides, which tentatively suggests the catenane **56**·PF₆ binds the oxoanions the most strongly. The decrease in excimer emission may be attributed to anion binding preventing

intramolecular excimer formation, as the guest would bind in the host cavity between the two naphthalene groups. The most dramatic decrease is observed with iodide, which is likely to be augmented by the effects of heavy atom collisional quenching.²⁵

It was hoped that monitoring the intensity of the monomer emission bands of **56**·PF₆ upon the addition of anions would provide titration data from which anion association constants could be determined. DynaFit²⁶ analysis of the titration data, however, was only able to calculate association constants for acetate and dihydrogen phosphate binding (**Figure 2.32** and **Table 2.9**).²⁷

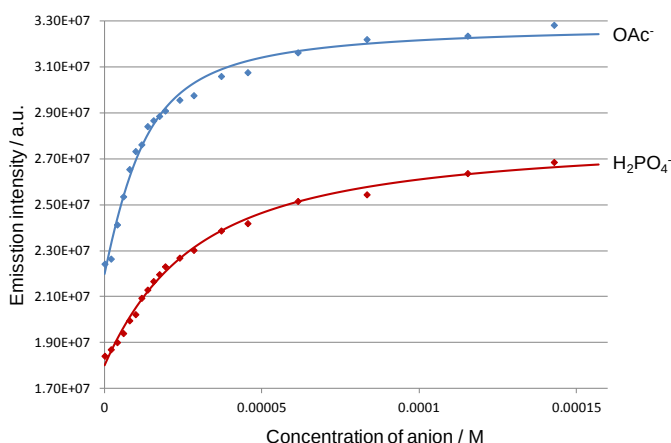


Figure 2.32—Changes in monomer emission intensity upon addition of increasing amounts of acetate and dihydrogen phosphate anions, as their TBA salts, to separate acetonitrile solutions of catenane **56**·PF₆ ([host] = 1×10^{-5} M, λ_{exc} = 280 nm, 293 K, data points represent experimental data, continuous lines represent calculated curves).

Table 2.9—Association constants, K_a (M⁻¹), for catenane **56**·PF₆ with acetate and dihydrogen phosphate anions (CH₃CN, 293 K).

Anion	K_a (M ⁻¹) ^[a]
OAc ⁻	1.5×10^5 [1.3 – 1.8×10^5]
H ₂ PO ₄ ⁻	4.5×10^4 [4.1 – 4.8×10^4]

^[a] 99% confidence intervals given in square brackets, a 1:1 binding model was used in all cases.

Catenane **56**·PF₆ binds acetate and dihydrogen phosphate strongly in acetonitrile solution with a preference for the former more basic oxoanion. Interestingly, this strong oxoanion recognition is in contrast to bromo-imidazolium functionalised catenane **2**·(PF₆)₂, which did

not detect these oxoanions *via* analogous fluorescence titration experiments in the same solvent.⁹

2.4.4 Summary

The initially targeted iodo-triazolium containing homo-[2]catenane was unable to be prepared, with this likely due to precipitation of the intermediate macrocycle **54**⁺ prior to the catenane bond forming reaction taking place. However, an alternative new hetero-[2]catenane **56**·PF₆, containing both halogen and hydrogen bonding macrocyclic components, was successfully isolated. Preliminary ¹H NMR studies revealed the catenane bound chloride and fluorescence anion titrations were performed to quantitatively assess its anion binding properties. Notable fluorescence responses were observed upon the addition of various anions to an acetonitrile solution of **56**·PF₆, with the most dramatic occurring with acetate and dihydrogen phosphate. This suggested the catenane is selective for these oxoanions and Dynafit²⁶ analysis of the titration data revealed that acetate was bound the most strongly.

2.5 Conclusions and future work

The anion recognition and templation properties of the 5-bromo-1,2,3-triazolium motif have been exploited in the bromide-templated synthesis of the first bromo-triazolium containing [2]rotaxane. This interlocked host was shown to bind bromide and iodide anions more strongly than its protic triazolium analogue, indicating that the bromo-triazolium motif is an effective anion binding motif.

Two new halo-triazolium rotaxanes that combined the effects of halogen bonding and increased inter-component preorganisation were synthesised and found to be potent anion receptors. These rotaxanes were demonstrated to bind the halide anions more strongly than their less preorganised analogues, with the iodo-triazolium axle containing rotaxane

exhibiting the most impressive anion recognition properties due to the greater halogen bond donor ability of iodo-triazolium relative to bromo-triazolium.

Integration of the iodo-triazolium motif into an all halogen bonding [2]catenane structure was attempted. The initially targeted homo-[2]catenane could not be prepared, however the successful synthesis of a novel hetero-[2]catenane containing both hydrogen and halogen bonding macrocyclic components was achieved. Fluorescence anion titrations revealed the catenane bound anions in acetonitrile solution, with the host displaying strong binding of acetate and dihydrogen phosphate oxoanions.

This Chapter has shown halogen bonding to have real potential in the areas of anion-templated synthesis of interlocked host structures and anion recognition. In particular, the iodo-triazolium motif has been demonstrated to be an extremely potent anion recognition unit. All of the systems studied in this Chapter involve the use of a single halo-triazolium group and so future work could involve the construction of interlocked structures bearing two or more of these motifs to potentially further enhance the anion binding properties of the host. Moreover, all halogen bonding rotaxane and catenane hosts would be interesting synthetic targets that promise to exhibit anion binding capabilities in aqueous solvent media.

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23. An excimer is a complex formed between a fluorophore in its excited state and an identical fluorophore in its ground state. Excimer formation is common for aromatic species, including naphthalene.
24. P. D. Beer, F. Szemes, V. Balzani, C. M. Salà, M. G. B. Drew, S. W. Dent and M. Maestri, *J. Am. Chem. Soc.*, 1997, **119**, 11864-11875.
25. M. Kasha, *J. Chem. Phys.*, 1952, **20**, 71-74.
26. P. Kuzmič, *Anal. Biochem.*, 1996, **237**, 260-273.
27. The alternative Specfit titration analysis software gave similar association constants for acetate and dihydrogen phosphate binding and was also unable to calculate association constants from the halide titration data.

CHAPTER THREE

Chapter Three: Pyridine *N*-oxide axle containing [2]rotaxanes

3.1 Introduction

3.1.1 The pyridine *N*-oxide motif in supramolecular chemistry

Pyridine *N*-oxides, and their derivatives, have been utilised for a variety of applications such as antiviral agents,¹⁻³ novel coordination ligands⁴⁻⁶ and asymmetric catalysis.⁷⁻⁹ In recent years, their use in the area of supramolecular chemistry has been explored. Ballester has reported a series of calix[4]pyrrole-based receptors (**Figure 3.1a**) that recognise pyridine *N*-oxide functionalised guests in aqueous solvent media through the action of pyrrole N–H hydrogen bonding to the pyridine *N*-oxide oxygen atom and hydrophobic interactions.¹⁰ This work has been expanded recently with the polyatomic anion-assisted assembly of a [2]pseudorotaxane between a bis-calix[4]pyrrole functionalised macrocycle and pyridine *N*-oxide threading species (**Figure 3.1b**).¹¹ In this system, thiocyanate and azide anions were found to be the most effective templates for pseudorotaxane assembly in chloroform solution.

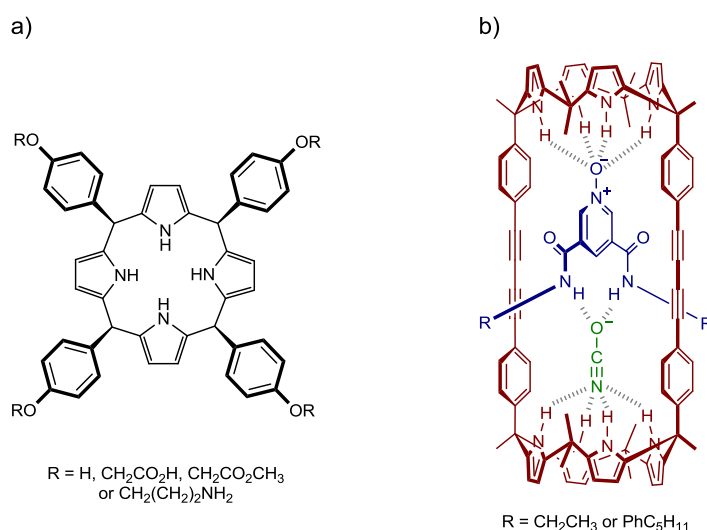
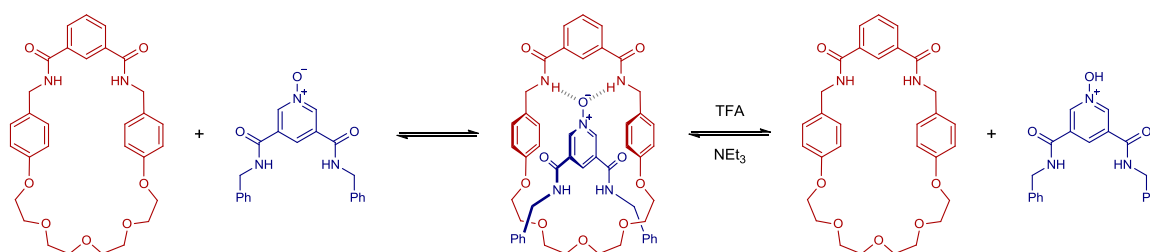


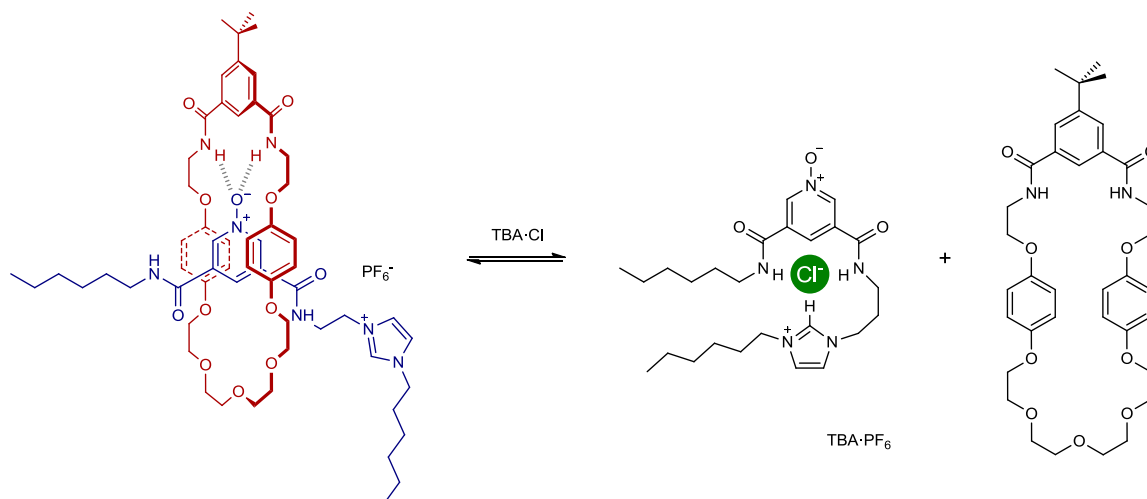
Figure 3.1—Ballester's a) calix[4]pyrrole functionalised pyridine *N*-oxide receptors and b) pyridine *N*-oxide containing [2]pseudorotaxane.

The incorporation of the pyridine *N*-oxide motif into interpenetrated structures has also been demonstrated by Jiang and co-workers. They reported that a pyridine *N*-oxide threading species is capable of forming a stable pseudorotaxane with an isophthalamide macrocycle, in CDCl_3 , through the action of pyridine *N*-oxide–amide $\text{N-H}\cdots\text{O}$ hydrogen bonds and aromatic donor–acceptor interactions (**Scheme 3.1**).¹² It was also shown that threading can be controlled by acid/base stimuli; acidification with TFA protonates the pyridine *N*-oxide oxygen donor atom and results in pseudorotaxane disassembly, with this action reversed upon addition of triethylamine.



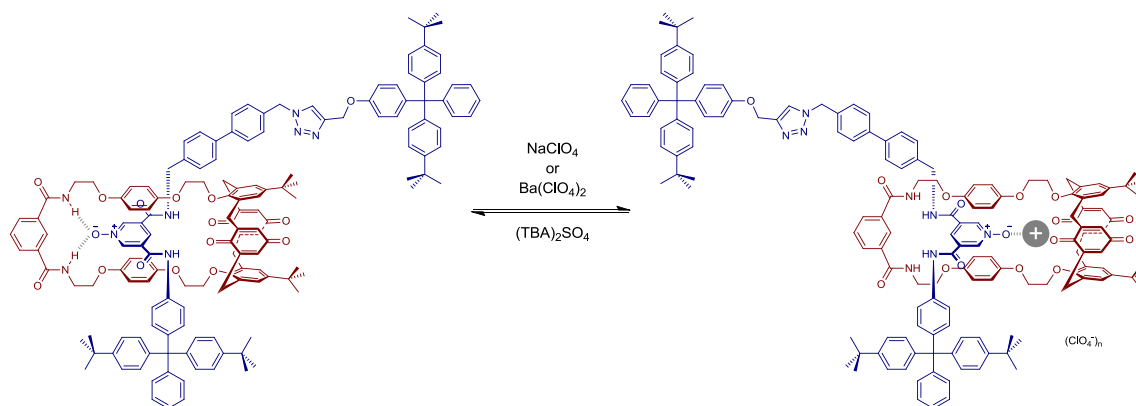
Scheme 3.1—Jiang's pH switchable pseudorotaxane assembly between a pyridine *N*-oxide threading species and an isophthalamide macrocycle.

Recently, Beer and co-workers have reported an example of anion-controlled pyridine *N*-oxide–isophthalamide macrocycle pseudorotaxane assembly and disassembly (**Scheme 3.2**).¹³ Pyridine *N*-oxide–amide $\text{N-H}\cdots\text{O}$ hydrogen bonds and aromatic donor–acceptor interactions again direct interpenetrated assembly, with the addition of chloride reported to induce a conformational change of the threading component that results in pseudorotaxane disassembly.

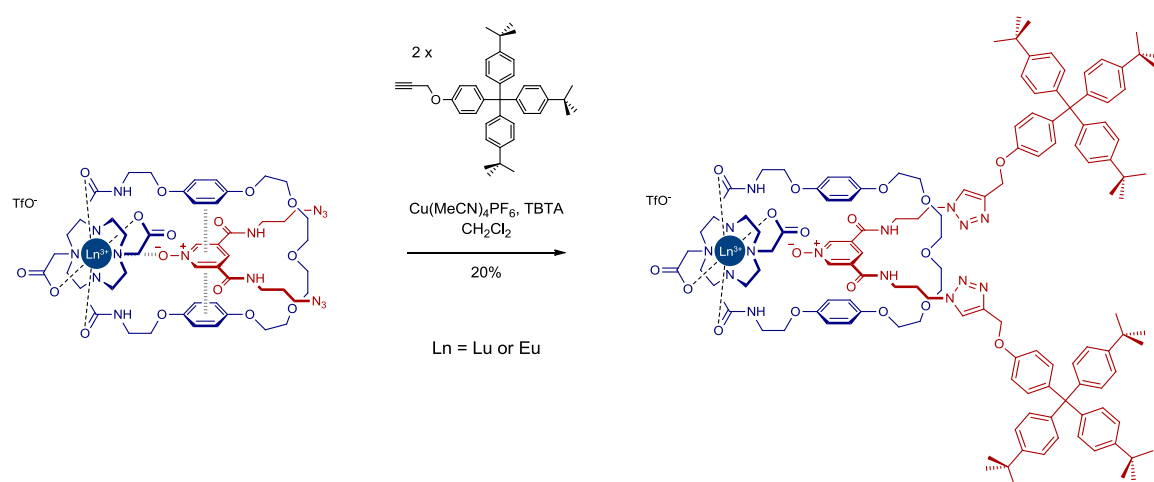


Scheme 3.2—Beer's anion-induced disassembly of a pyridine *N*-oxide containing pseudorotaxane.

The pyridine *N*-oxide motif has also been exploited as an axle component in the synthesis of [2]rotaxane structures. Alkali metal templation was utilised to prepare a [2]rotaxane which exhibits cation-induced pirouetting molecular motion in chloroform solution (**Scheme 3.3**),¹⁴ whereas lanthanide metal cations were described to template the synthesis of the pyridine *N*-oxide axle containing [2]rotaxanes shown in **Scheme 3.4**.¹⁵



Scheme 3.3—Cation-induced pirouetting molecular motion of a pyridine *N*-oxide axle containing [2]rotaxane.



Scheme 3.4—Lanthanide metal cation-templated synthesis of pyridine *N*-oxide axle containing [2]rotaxanes.

3.1.2 Chapter objectives

Whilst alkali metal cations have been demonstrated to template the formation of pyridine *N*-oxide axle containing interlocked structures, the analogous use of anions to synthesise such mechanically interlocked systems is unprecedented. With this in mind, this Chapter focuses on the anion-templated synthesis of pyridine *N*-oxide axle containing [2]rotaxanes and their application in anion recognition.

A series of novel bis-isophthalamide macrocycles are prepared initially whose design has been specifically tailored for anion-templated interpenetrated assembly with a pyridine *N*-oxide functionalised threading species (**Figure 3.2**).

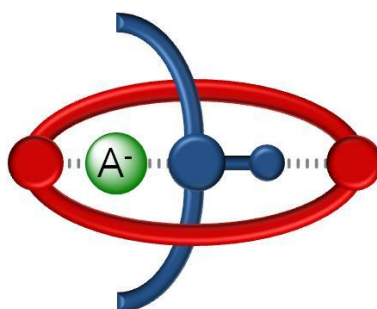


Figure 3.2—Cartoon representation of anion-templated pseudorotaxane assembly involving a bis-isophthalamide macrocycle and a pyridine *N*-oxide threading species.

The two macrocycle isophthalamide groups complement the simultaneous recognition of an anion and pyridine *N*-oxide motif, with anion binding expected to augment pseudorotaxane formation. A series of neutral pyridine *N*-oxide axle containing [2]rotaxanes are then prepared *via* a stoppering strategy (**Section 1.4.1**) and their anion recognition properties studied.

Finally, the effect of incorporating a positively charged pyridinium motif, into the macrocyclic component of the rotaxane, on the anion recognition properties of the interlocked host will be investigated.

3.2 Pyridine *N*-oxide axle containing neutral [2]rotaxanes

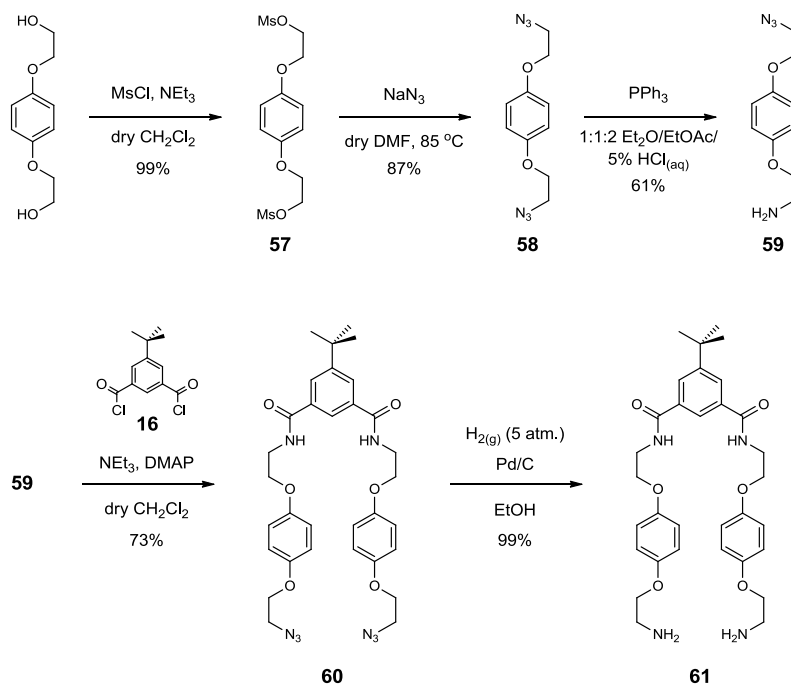
Part of the research discussed in this Section was carried out in collaboration with Part II student Fergus Tyrrell.

3.2.1 Bis-isophthalamide macrocycles

3.2.1.1 Syntheses

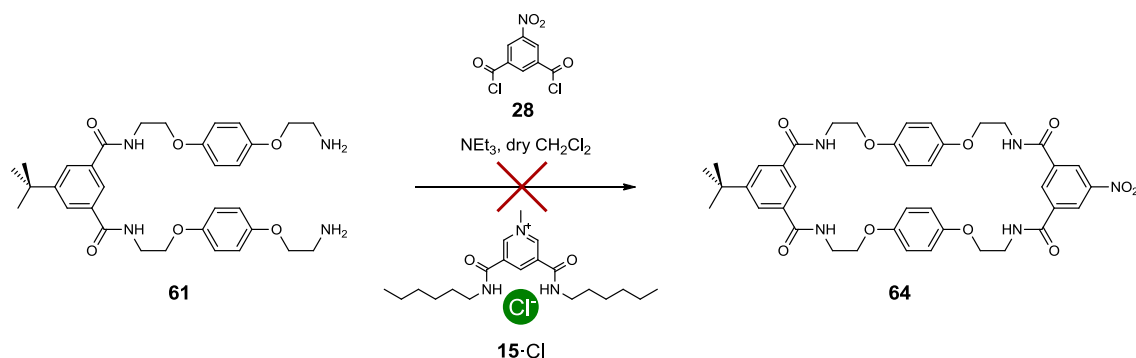
Four new bis-isophthalamide containing macrocycles were synthesised. This involved the initial preparation of a bis-amine precursor derivative **61** that could then be cyclised with an appropriate bis-acid chloride to afford the target macrocycles.

Commercially available hydroquinone bis(2-hydroxyethyl)ether was converted to mono-amine **59** following a three-step literature procedure.¹⁶ This was reacted with half an equivalent of 5-*tert*-butylisophthaloyl dichloride **16** and triethylamine, in the presence of DMAP, to afford bis-azide **60** in 73% yield. Catalytic hydrogenation of **60** gave bis-amine precursor **61** in quantitative yield (**Scheme 3.5**).



Scheme 3.5—Synthesis of bis-amine precursor **61**.

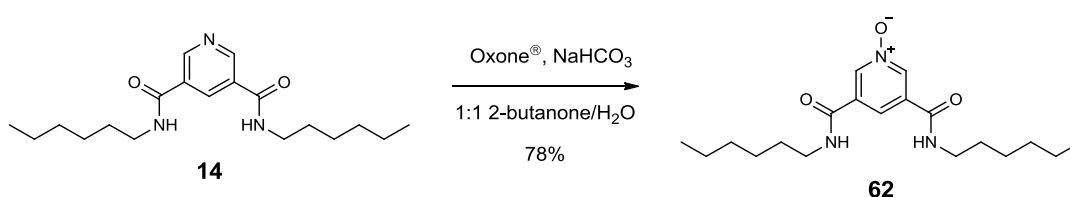
Macrocycle synthesis was initially attempted using pyridinium chloride template **15**·Cl as this species had been previously shown to enhance the yield of acid chloride–bis-amine polyether condensation macrocycle syntheses,¹⁷ such as the synthesis of polyether macrocycle **17** in Chapter Two (**Scheme 2.4**), through the action of stabilising aromatic donor–acceptor and hydrogen bonding interactions. A solution of 5-nitroisophthaloyl dichloride **28** in dry CH₂Cl₂ was added dropwise over one hour to a mixture of bis-amine precursor **61**, triethylamine and pyridinium chloride template **15**·Cl in dry CH₂Cl₂ (**Scheme 3.6**). However, after stirring at room temperature overnight and work up, no evidence for macrocycle formation was found; only insoluble oligomer material was isolated.



Scheme 3.6—Attempted macrocycle synthesis using pyridinium chloride template **15·Cl**.

The failure of this reaction was thought to arise from the steric bulk of the pyridinium methyl protons possibly hindering the cyclisation procedure. This would not occur in the previously reported templated synthesis of polyether macrocycle **17** as hydrogen bonding interactions between the pyridinium methyl protons and the polyether group of the bis-amine precursor would facilitate macrocycle formation.

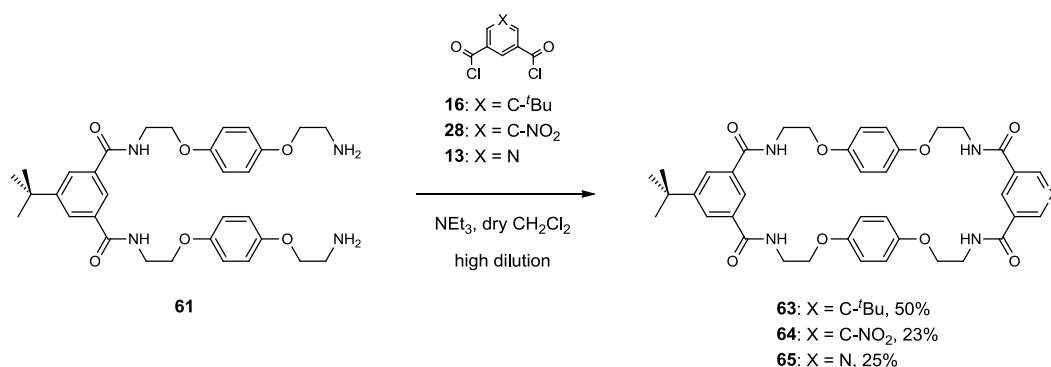
An alternative pyridine *N*-oxide functionalised template was prepared in the hope that its *N*-oxide oxygen donor atom would hydrogen bond to the isophthalamide group of bis-amine precursor **61**. Reaction of the previously synthesised pyridine-3,5-bis-amide compound **14** (Chapter Two, **Scheme 2.3**) with Oxone[®] and NaHCO₃ in 1:1 water/2-butanone afforded the potential template **62** in 78% yield (**Scheme 3.7**).¹⁴



Scheme 3.7—Synthesis of pyridine *N*-oxide thread **62**.

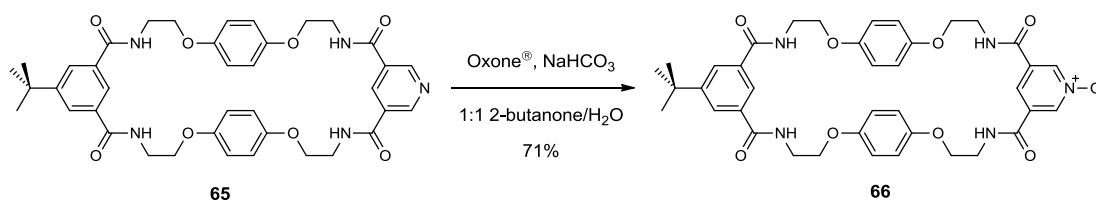
Once again, when the condensation synthesis of nitro-isophthalamide macrocycle **64** (**Scheme 3.6**) was attempted using pyridine *N*-oxide derivative **62** in place of pyridinium chloride template **15·Cl** no macrocycle was detected.

Given the failure to prepare nitro-isophthalamide macrocycle **64** via a templated approach, high dilution conditions were employed instead (**Scheme 3.8**). Equimolar dry CH₂Cl₂ solutions of bis-amine precursor **61** and 5-nitroisophthaloyl dichloride **28** were added dropwise over six hours to a stirred solution of triethylamine in dry CH₂Cl₂ at room temperature. After purification by silica gel column chromatography the target nitro-isophthalamide macrocycle **64** was isolated in 23% yield. Analogous high dilution cyclisation reactions with 5-*tert*-butylisophthaloyl dichloride **16** and pyridine-3,5-dicarbonyl dichloride **13** afforded the corresponding macrocycles **63** and **65** in 50% and 25% yields respectively (**Scheme 3.8**).



Scheme 3.8—Synthesis of isophthalamide macrocycles **63**, **64** and **65** via high dilution.

A pyridine *N*-oxide functionalised macrocycle **66** was also prepared, in 71% yield, by oxidation of the pyridine group of macrocycle **65** with Oxone[®] and NaHCO₃ in 1:1 water/2-butanone (**Scheme 3.9**).



Scheme 3.9—Synthesis of pyridine *N*-oxide functionalised macrocycle **66**.

New macrocycles **63–66** were all characterised by ^1H and ^{13}C NMR spectroscopy and ESI mass spectrometry. The high resolution ESI-MS analyses of **63–66** gave the expected mass peaks at m/z 787.3649 $[\text{M} + \text{Na}]^+$, 788.2706 $[\text{M} + \text{Cl}]^-$, 732.3007 $[\text{M} + \text{Na}]^+$ and 748.2925 $[\text{M} + \text{Na}]^+$ respectively and their ^1H NMR spectra are displayed in **Figure 3.3**. Macrocycles **64–66** possess more complicated aromatic regions than bis-*tert*-butylisophthalamide macrocycle **63** owing to their asymmetric nature and it can be seen that the chemical shifts of protons α and β vary between the macrocycles reflecting the differing electron-withdrawing nature of the X group.¹⁸

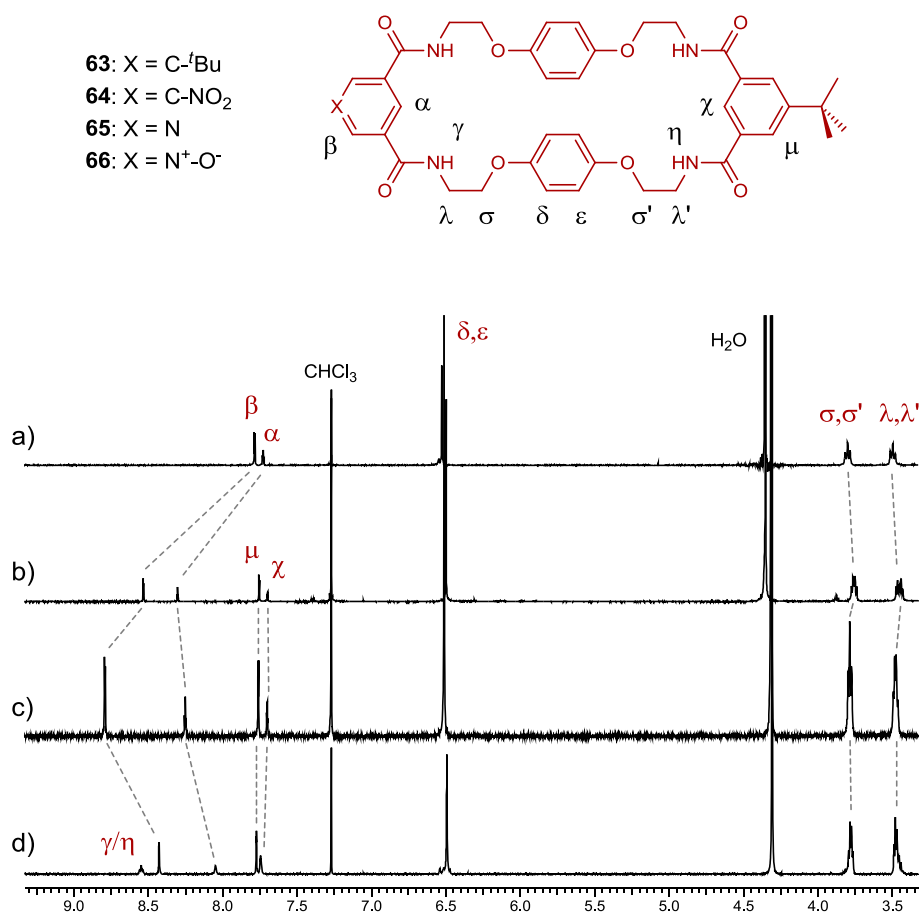


Figure 3.3—Truncated ^1H NMR spectra of macrocycles a) **63**, b) **64**, c) **65** and d) **66** (500 MHz, 1:1 $\text{CDCl}_3/\text{CD}_3\text{OD}$, 293 K).

3.2.1.2 Anion recognition properties

With the target bis-isophthalamide macrocycles successfully isolated, ^1H NMR chloride binding titrations were undertaken to assess the strength of halide recognition and, importantly, determine the binding stoichiometry as macrocycles **63–66** each possess two anion recognition sites.

Nitro-isophthalamide macrocycle **64** was studied initially; increasing amounts of a 1:1 $\text{CDCl}_3/\text{CD}_3\text{CN}$ solution of $\text{TBA}\cdot\text{Cl}$ were added to a solution of **64** in the same solvent mixture and the resultant ^1H NMR spectra recorded. The peaks corresponding to internal isophthalamide protons α and χ , as well as amide protons γ and η , were all observed to shift downfield significantly upon addition of the halide anion (**Figure 3.4**). These observations are indicative of hydrogen bond formation between these protons and the chloride anion.

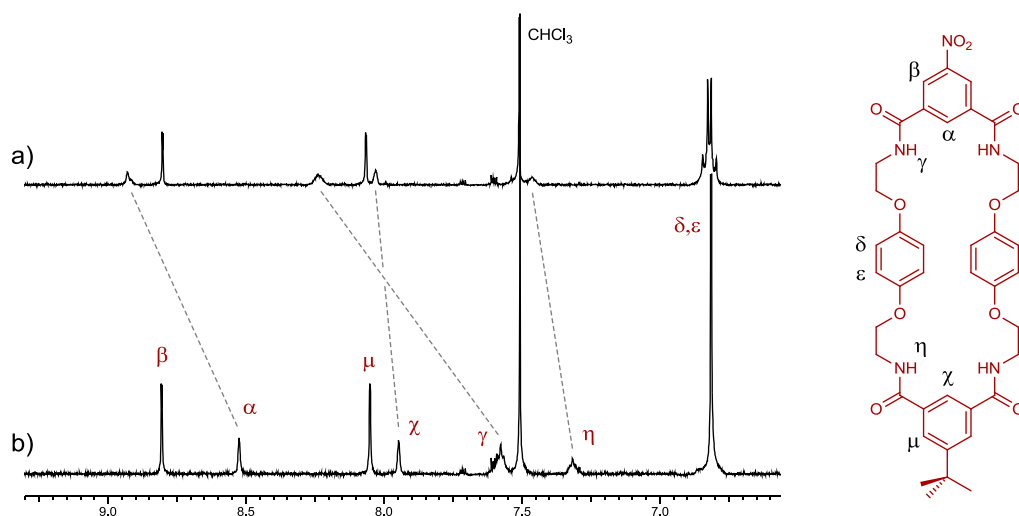


Figure 3.4—Truncated ^1H NMR spectra of a) an equimolar mixture of nitro-isophthalamide macrocycle **64** and $\text{TBA}\cdot\text{Cl}$ and b) nitro-isophthalamide macrocycle **64** (500 MHz, 1:1 $\text{CDCl}_3/\text{CD}_3\text{CN}$, 293 K).

The magnitudes of these perturbations were found to vary, with the largest changes in chemical shift occurring with protons α and γ , suggesting that the anion binds most strongly at the nitro-isophthalamide site: $\Delta\delta_{10 \text{ equiv.}} = 0.93$ (α), 1.51 (γ), 0.22 (χ), 0.46 (η). Hydroquinone protons δ and ϵ shift marginally downfield ($\Delta\delta_{10 \text{ equiv.}} = 0.07$) and noticeably split into an

apparent quartet. This suggests a loss of symmetry within the macrocycle upon the addition of chloride, possibly due to preferential binding of the anion to the nitro-isophthalamide group. Similar changes were observed in the ^1H NMR spectra of macrocycles **63** and **65** upon the addition of chloride, whilst pyridine *N*-oxide macrocycle **66** was unable to be studied due to its insolubility in the titration solvent. The titration data obtained from monitoring amide protons γ and η of the three macrocycles (**Figure 3.5**) was analysed with WinEQNMR2¹⁹ curve fitting software, giving 1:1 stoichiometric association constants (**Table 3.1**).

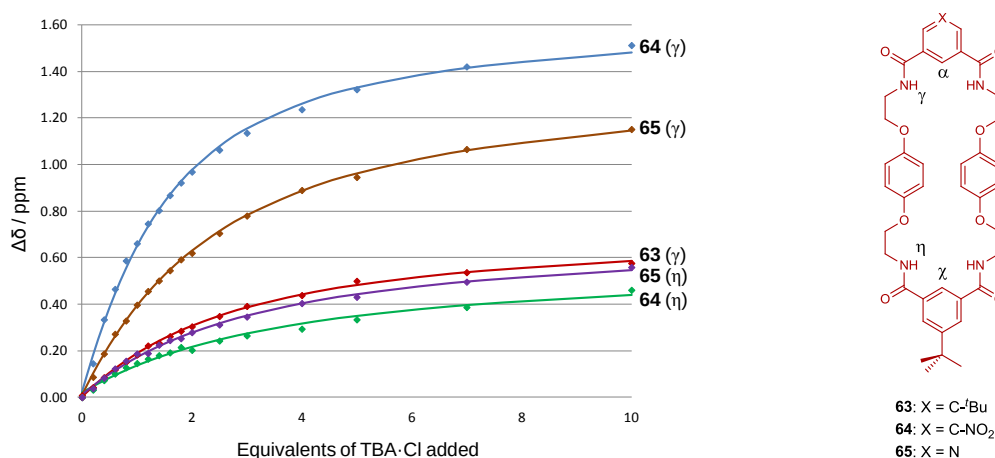


Figure 3.5—Changes in chemical shift, $\Delta\delta$ (ppm), of macrocycle amide protons upon addition of increasing amounts of TBA·Cl (500 MHz, 1:1 $\text{CDCl}_3/\text{CD}_3\text{CN}$, 293 K, data points represent experimental data, continuous lines represent calculated curves).

Table 3.1—Chloride association constants, K_a (M^{-1}), for macrocycles **63–65** calculated from the titration data displayed in **Figure 3.5** (estimated standard errors in parentheses, 1:1 $\text{CDCl}_3/\text{CD}_3\text{CN}$, 293 K).

Macrocycle	Amide protons γ	Amide protons η
63	208(12)	— ^[a]
64	493(12)	139(26)
65	246(8)	176(16)

^[a] no value is given as macrocycle **63** possesses two equivalent tert-butylisophthalamide binding sites.

Different association constant values are obtained depending on which amide proton was monitored, suggesting that chloride is bound at both isophthalamide sites in a dynamic manner on the NMR timescale. It can be seen that chloride is bound more strongly at the nitro-isophthalamide and pyridine sites of macrocycles **64** and **65** respectively as a result of

their more electron withdrawing nature compared to the alternative *tert*-butylisophthalamide binding site. Finally, given the symmetric nature of bis-*tert*-butylisophthalamide macrocycle **63** only one association constant was calculated, with this value found to be lower than those obtained for the nitro-isophthalamide and pyridine sites of **64** and **65** respectively, as expected.

3.2.1.3 Pseudorotaxane investigations

Having demonstrated that macrocycles **63–65** were capable of recognising chloride, their potential to form anion-templated interpenetrated pseudorotaxane assemblies with pyridine *N*-oxide thread **62** was investigated.

Preliminary ^1H NMR titration experiments were performed to assess pseudorotaxane formation between macrocycles **63–65** and pyridine *N*-oxide thread **62** alone, and in the presence of one equivalent of TBA $\cdot$ Cl, in 1:1 $\text{CDCl}_3/\text{CD}_3\text{CN}$. Importantly, both in the absence (**Figure 3.6**) and presence of chloride, the macrocycle hydroquinone protons δ and ϵ were shifted upfield upon addition of thread **62** to the macrocycle. This is a consequence of aromatic donor–acceptor interactions between the two species, indicative of pseudorotaxane formation. It is noteworthy that the magnitude of this perturbation is relatively larger when chloride is present, suggesting a templating effect is observed; for example with nitro-isophthalamide macrocycle **64**, $\Delta\delta_{1\text{equiv.}} = -0.09$ (without Cl^-), -0.49 (with Cl^-). In addition, downfield shifts of the macrocycle internal isophthalamide protons α and χ were also observed in all cases.²⁰ These arise from hydrogen bonding interactions with the pyridine *N*-oxide oxygen donor atom, when chloride is absent, and hydrogen bonding interactions with the same oxygen donor atom and chloride when the halide anion is present.

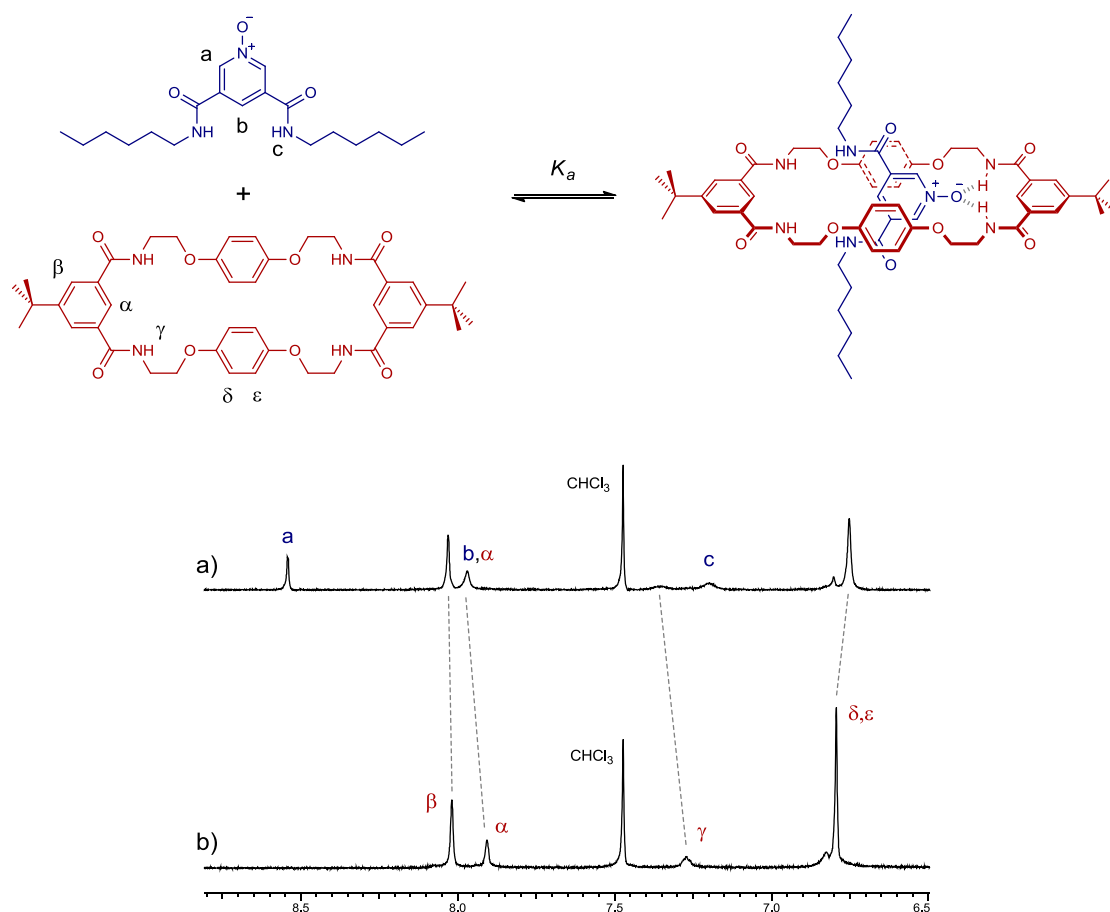


Figure 3.6—Truncated ^1H NMR spectra of a) an equimolar mixture of pyridine *N*-oxide thread **62** and macrocycle **63** and b) macrocycle **63** (500 MHz, 1:1 $\text{CDCl}_3/\text{CD}_3\text{CN}$, 293 K).

Quantitative ^1H NMR titration experiments monitoring the diagnostic shifts of hydroquinone protons δ and ϵ gave titration data (**Figure 3.7**) from which 1:1 stoichiometric association constants were determined using WinEQNMR2¹⁹ (**Table 3.2**). The values obtained for chloride-templated pseudorotaxane assembly with macrocycles **64** and **65** in 1:1 $\text{CDCl}_3/\text{CD}_3\text{CN}$ were found to be $>10^4 \text{ M}^{-1}$ and so these titration experiments were repeated in the more competitive 9:1 $\text{CDCl}_3/\text{CD}_3\text{OD}$ solvent mixture to obtain quantitative K_{app} values.

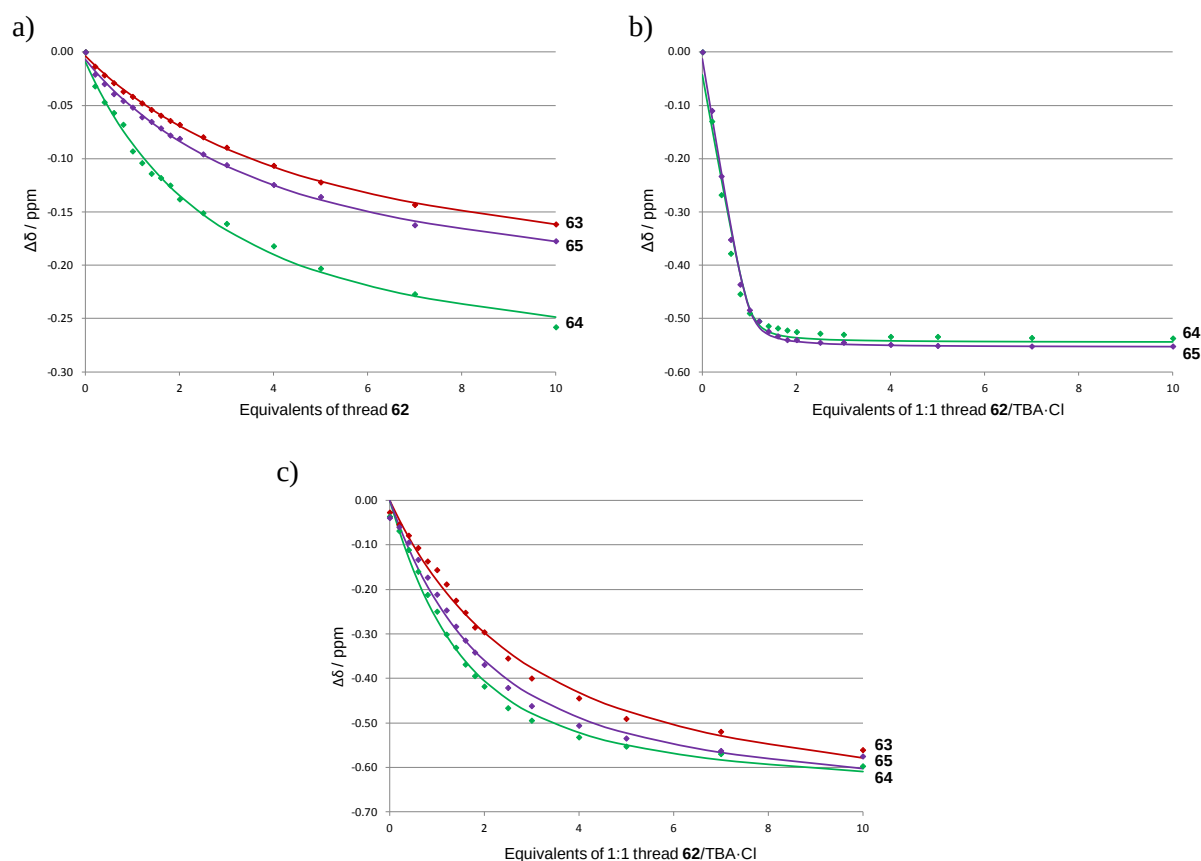


Figure 3.7—Changes in chemical shift, $\Delta\delta$ (ppm), of macrocycle hydroquinone protons δ and ϵ upon addition of a) pyridine *N*-oxide thread **62** and b) an equimolar solution of thread **62** and TBA·Cl in 1:1 $\text{CDCl}_3/\text{CD}_3\text{CN}$, and c) an equimolar solution of thread **62** and TBA·Cl in 9:1 $\text{CDCl}_3/\text{CD}_3\text{OD}$ (500 MHz, 293 K, data points represent experimental data, continuous lines represent calculated curves).

Table 3.2—Association constants, K_a (M^{-1}), and apparent association constants, K_{app} (M^{-1}), calculated from the titration data shown in **Figure 3.7** (estimated standard errors in parentheses, 293 K).

Macrocycle	Thread 62 ^[a]	1:1 Thread 62 /TBA·Cl ^[b]	
63	93(6) ^[c]	—	197(30) ^[d]
64	216(15) ^[c]	$>10^4$ ^[c]	529(47) ^[d]
65	120(12) ^[c]	$>10^4$ ^[c]	337(52) ^[d]

^[a] values reported are association constants (K_a), ^[b] values reported are apparent association constants (K_{app}),²¹
^[c] 1:1 $\text{CDCl}_3/\text{CD}_3\text{CN}$, ^[d] 9:1 $\text{CDCl}_3/\text{CD}_3\text{OD}$.

It can be seen that all the macrocycles form stable interpenetrative assemblies with thread **62** through the combination of favourable pyridine *N*-oxide–isophthalamide macrocycle hydrogen bonding and aromatic donor–acceptor interactions. Comparison of the association constants obtained for pseudorotaxane assembly with macrocycles **64** and **65** in 1:1 $\text{CDCl}_3/\text{CD}_3\text{CN}$ both in the absence and presence of chloride indicates that interpenetration is

enhanced greatly when a chloride anion is present. The values obtained in 9:1 CDCl₃/CD₃OD show that the most stable anion-templated pseudorotaxane assembly is formed with nitro-isophthalamide macrocycle **64** and the weakest with bis-*tert*-butylisophthalamide macrocycle **63**, which is not surprising given the more acidic nitro-isophthalamide motif binds the templating chloride anion the most strongly.

Further evidence for pseudorotaxane assembly was obtained from two-dimensional ¹H–¹H ROESY NMR spectroscopy. The ROESY spectrum of an equimolar mixture of bis-*tert*-butylisophthalamide macrocycle **63**, pyridine *N*-oxide thread **62** and TBA·Cl reveals several through space couplings indicative of pseudorotaxane formation (**Figure 3.8**). Diagnostic inter-component couplings are also observed when similar ROESY spectra are recorded with macrocycles **64** and **65**, both in the absence and presence of chloride.

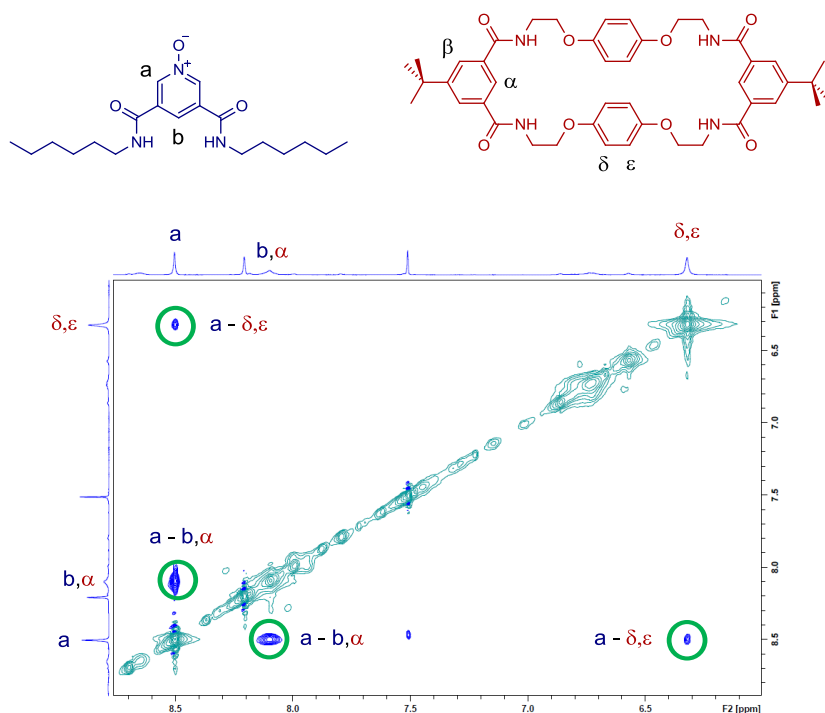


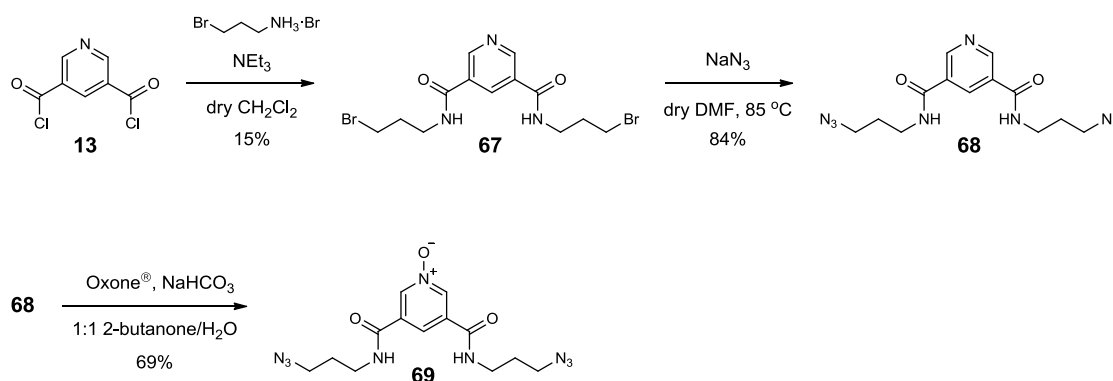
Figure 3.8—Truncated ROESY NMR spectra of an equimolar solution of bis-*tert*-butylisophthalamide macrocycle **63**, thread **62** and TBA·Cl (500 MHz, 1:1 CDCl₃/CD₃CN, 293 K).

3.2.2 Neutral rotaxanes containing pyridine *N*-oxide axle components

3.2.2.1 Syntheses and characterisation

The target interlocked [2]rotaxane systems were successfully synthesised using a chloride anion-templated threading-followed-by-stoppering methodology. This initially required the preparation of a pyridine *N*-oxide functionalised threading species **69** possessing terminal azide functional groups which could then undergo a copper(I)-catalysed azide–alkyne cycloaddition (CuAAC) click stoppering reaction.¹⁵

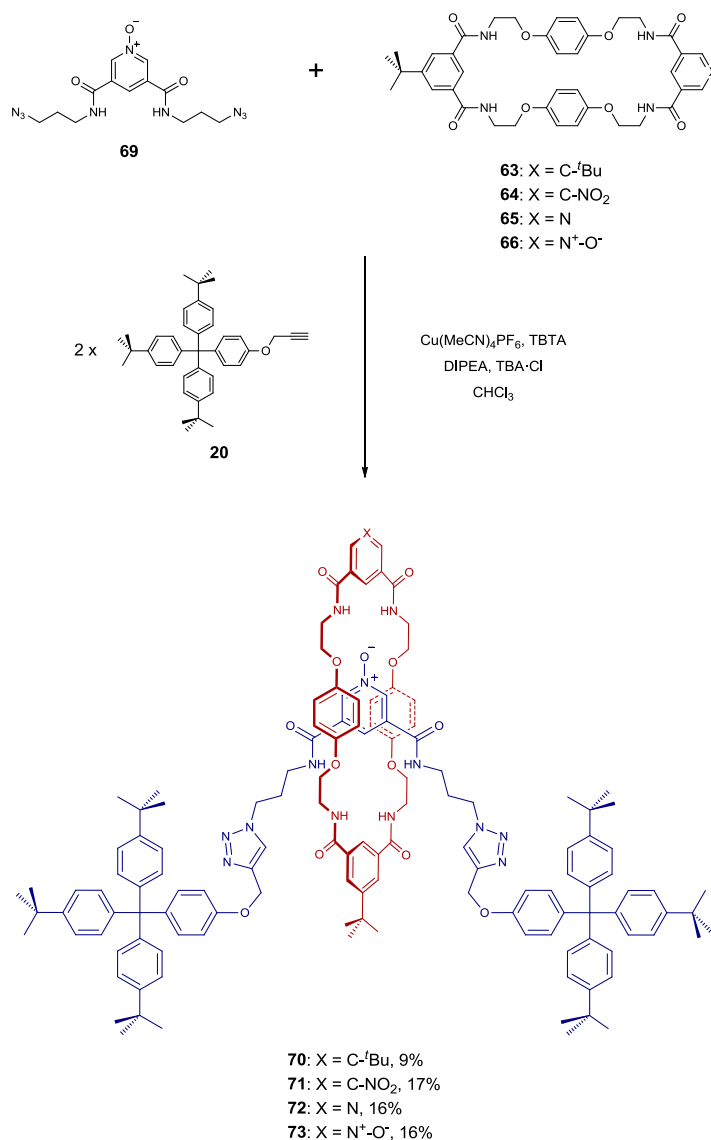
Bis-acid chloride **13** was reacted with two equivalents of 3-bromopropylamine hydrobromide and triethylamine, in dry CH₂Cl₂, to give compound **67** in a modest 15% yield. Reaction with sodium azide in dry DMF at 85 °C afforded bis-azide species **68** in 84% yield. Compound **68** was then reacted with Oxone[®] and NaHCO₃ in 1:1 2-butanone/water to give the pyridine *N*-oxide axle precursor **69** in 69% yield (*Scheme 3.10*).¹⁵



Scheme 3.10—Synthesis of pyridine *N*-oxide axle precursor **69**.

Equimolar amounts of pyridine *N*-oxide axle precursor **69**,¹⁵ the respective macrocycle (**63**–**66**) and TBA·Cl, together with two equivalents of alkyne functionalised terphenyl stopper **20**²² and three equivalents of diisopropylethylamine (DIPEA) were stirred in chloroform solution for 24 hours in the presence of Cu(MeCN)₄PF₆ and TBTA. After washing with water to remove the chloride template (as TBA·Cl) and purification by preparative thin layer

chromatography the target [2]rotaxanes **70–73** were isolated in yields of 9%, 17%, 16% and 16% respectively (**Scheme 3.11**). It is important to note that no rotaxane product was isolated when the syntheses were repeated in the absence of a chloride anion, highlighting the important templating role the halide anion is playing in the mechanical-bond-forming process.



Scheme 3.11—Synthesis of neutral [2]rotaxane **70–73** via a chloride anion-templated threading-followed-by-stoppering strategy.

The novel rotaxanes were all characterised by ¹H and ¹³C NMR spectroscopy and high resolution mass spectrometry. Comparison of the ¹H NMR spectra of rotaxanes **70** and **71**

with those of their respective macrocycles (**63** and **64**) and the free pyridine *N*-oxide axle **74**¹⁵ reveal a number of changes indicative of interlocked structure formation (**Figure 3.9** and **Figure 3.10**). Macrocycle internal isophthalamide protons α , in the case of rotaxane **70**, and α and χ , in the case of **71**, shift downfield, which is indicative of their involvement in hydrogen bonding to the axle *N*-oxide oxygen donor atom. Importantly, macrocycle hydroquinone protons δ and ϵ are seen to move upfield as a result of aromatic donor–acceptor interactions with the pyridine *N*-oxide motif of the axle component, suggesting the axle now interpenetrates the macrocycles. Similar observations were also made with rotaxanes **72** and **73**.

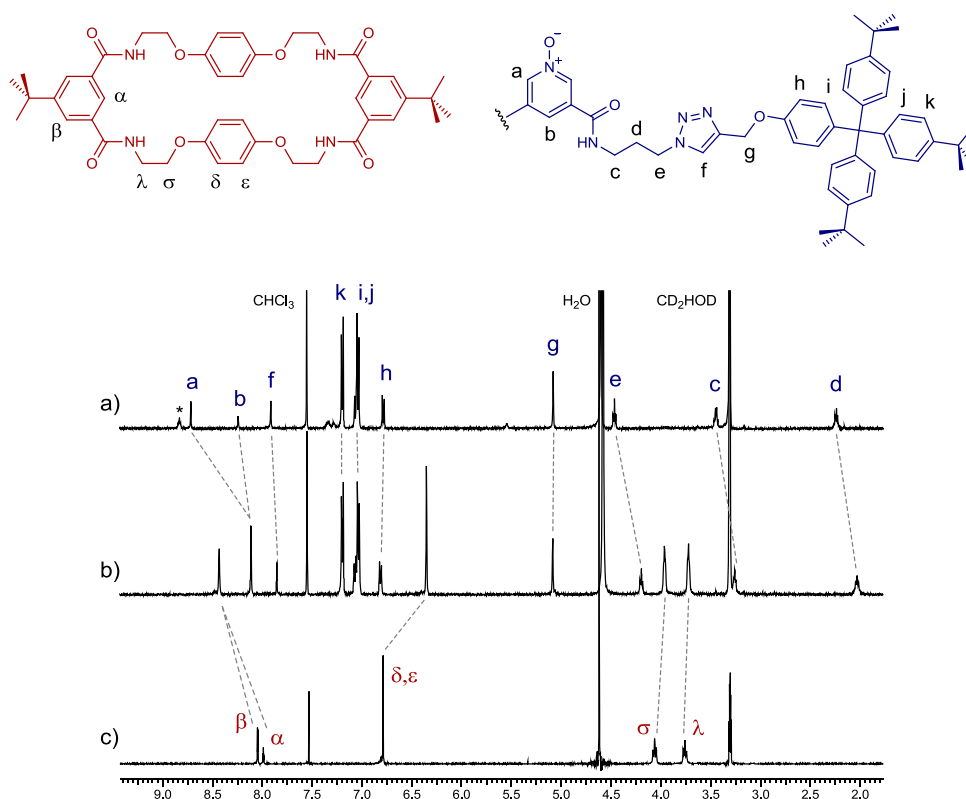


Figure 3.9—Truncated ¹H NMR spectra of a) free pyridine *N*-oxide axle **74**, b) bis-*tert*-butylisophthalamide rotaxane **70** and c) bis-*tert*-butylisophthalamide macrocycle **63** (500 MHz, 1:1 CDCl₃/CD₃OD, 293 K, peak marked * corresponds to unexchanged amide NH protons).

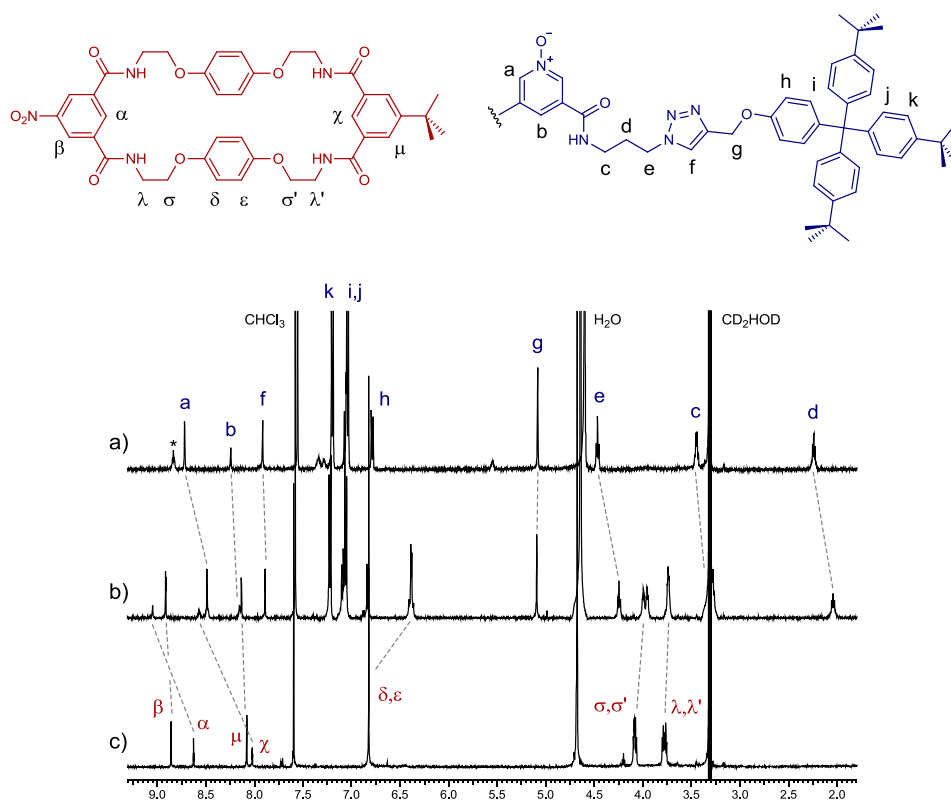


Figure 3.10—Truncated ^1H NMR spectra of a) free pyridine *N*-oxide axle **74**, b) nitro-isophthalamide functionalised rotaxane **71** and c) nitro-isophthalamide functionalised macrocycle **64** (500 MHz, 1:1 $\text{CDCl}_3/\text{CD}_3\text{OD}$, 293 K, peak marked * corresponds to unexchanged amide NH protons).

Two-dimensional ^1H – ^1H ROESY NMR spectroscopy confirmed the interlocked nature of the novel rotaxanes, with the spectra of all four of the rotaxanes revealing a number of through space inter-component couplings. In the ROESY spectrum of nitro-isophthalamide functionalised rotaxane **71** (**Figure 3.11**), couplings of the macrocycle hydroquinone protons δ and ϵ with axle pyridine *N*-oxide protons a and b , as well as axle terphenyl stopper protons i and j are observed. Furthermore, the internal nitro-isophthalamide proton α is seen to interact with pyridine *N*-oxide protons a . Complete characterisation data for rotaxanes **70–73** can be found in the Appendices (**Appendix A.2**).

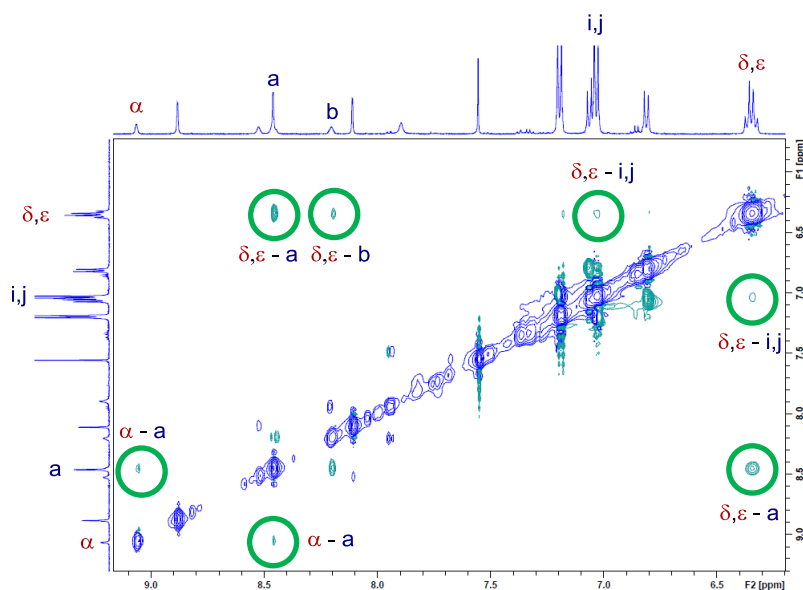
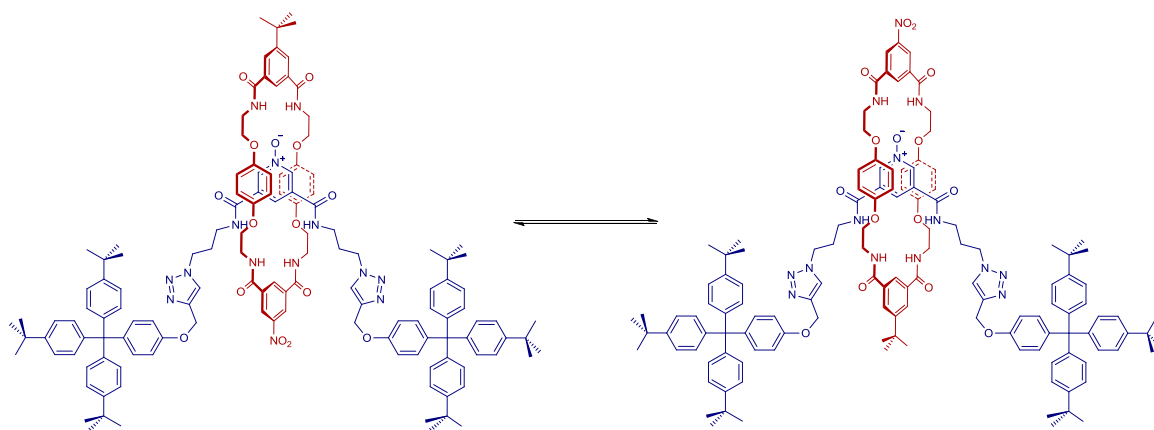


Figure 3.11—Truncated ROESY NMR spectrum of nitro-isophthalamide functionalised rotaxane **71** (500 MHz, 1:1 CDCl₃/CD₃OD, 293 K, peak assignments taken from **Figure 3.10**).

The rotaxanes possess two isophthalamide binding sites that the axle pyridine *N*-oxide oxygen donor atom can hydrogen bond to and so, in principle, can adopt two different conformations via the macrocycle component undergoing a pirouetting motion around the axle (**Scheme 3.12**).



Scheme 3.12—Two possible conformations exhibited by nitro-isophthalamide functionalised rotaxane **71** resulting from molecular pirouetting of the macrocycle component around the pyridine *N*-oxide axle.

Low temperature variable temperature (VT) ¹H NMR was used to investigate this pirouetting motion in nitro-isophthalamide functionalised rotaxane **71**. Significant broadening of both the

macrocycle and axle isophthalamide protons was observed when the sample was cooled from 298 K to 198 K (**Figure 3.12**). Importantly, the macrocycle hydroquinone protons are also seen to broaden, with these observations indicating the interlocked structure is dynamic on the NMR time-scale and at room temperature is switching between the two possible conformations.

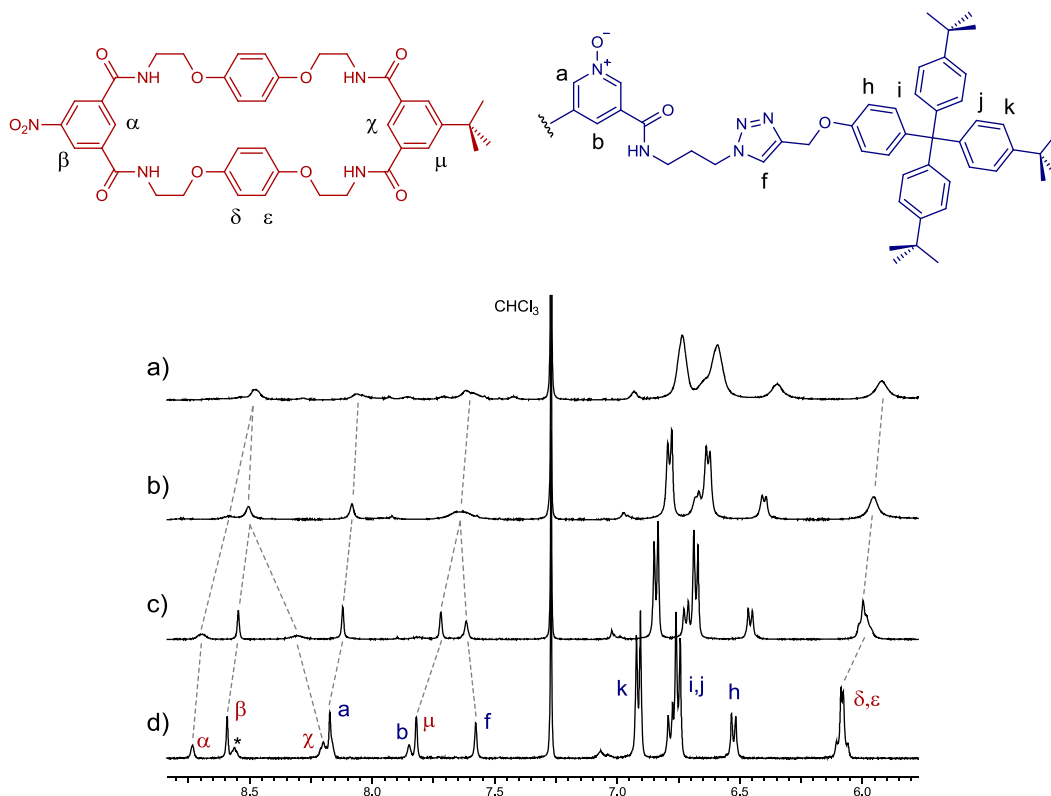


Figure 3.12—Truncated ^1H NMR spectra of nitro-isophthalamide functionalised rotaxane **71** at a) 198 K, b) 223 K, c) 248 K and d) 298 K (500 MHz, 1:1 $\text{CDCl}_3/\text{CD}_3\text{OD}$, peak marked * corresponds to unexchanged amide NH protons).

3.2.2.2 Anion recognition properties

With the four neutral pyridine *N*-oxide axle containing rotaxanes successfully isolated, ^1H NMR anion titration experiments were undertaken to assess their anion binding affinities. Nitro-isophthalamide functionalised rotaxane **71** was studied initially; upon addition of increasing amounts of $\text{TBA}\cdot\text{Cl}$ to a solution of **71** in 1:1 $\text{CDCl}_3/\text{CD}_3\text{OD}$ protons α , χ , b and f

were observed to shift downfield significantly, whereas hydroquinone protons δ and ε are seen to move upfield and split (**Figure 3.13**).

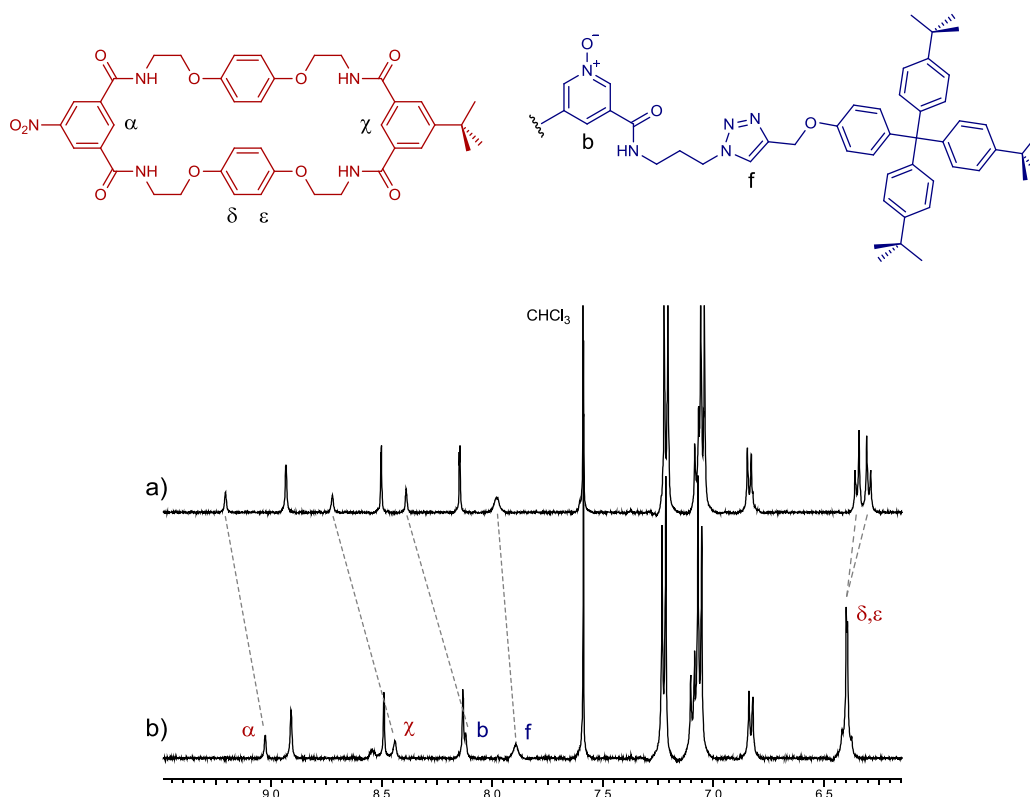


Figure 3.13—Truncated ^1H NMR spectra of a) an equimolar mixture of nitro-isophthalamide functionalised rotaxane **71** and TBA·Cl and b) nitro-isophthalamide functionalised rotaxane **71** (500 MHz, 1:1 $\text{CDCl}_3/\text{CD}_3\text{OD}$, 293 K).

The upfield shift and splitting of these protons suggests that chloride binding results in the rotaxane adopting a conformation that enhances aromatic donor–acceptor interactions between the macrocycle hydroquinone groups and the pyridine *N*-oxide motif of the axle component. Downfield shifts of protons α , χ , b and f are indicative of polarising hydrogen bonding interactions between these protons and the chloride anion. The perturbations of axle pyridine *N*-oxide proton b and triazole proton f suggest that the axle wraps around and encapsulates the anion. The shifting of the macrocycle internal isophthalamide protons α and χ indicates that anion recognition is occurring at both of the macrocycle isophthalamide binding sites of rotaxane **71** in a dynamic manner. To confirm this, low temperature VT ^1H

NMR studies of a 1:1 mixture of nitro-isophthalamide rotaxane **71** and TBA·Cl were performed (**Figure 3.14**). Similar broadening of the aromatic region was observed to that seen in the free rotaxane (**Figure 3.12**), indicating that the conformation of **71** is not locked by chloride binding and both isophthalamide recognition sites are accessible to the halide anion.

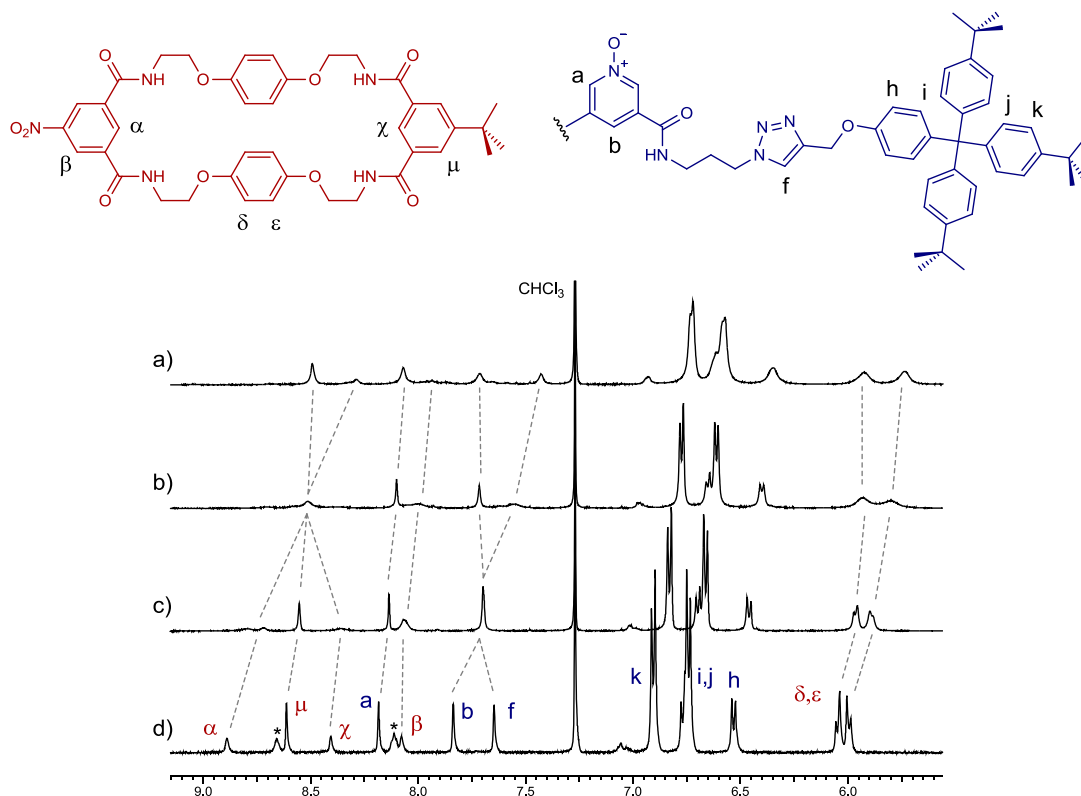


Figure 3.14—Truncated ^1H NMR spectra of an equimolar solution of nitro-isophthalamide rotaxane **71** and TBA·Cl at a) 198 K, b) 223 K, c) 248 K and d) 298 K (500 MHz, 1:1 $\text{CDCl}_3/\text{CD}_3\text{OD}$, peaks marked * are unexchanged amide NH protons).

Similar downfield shifts of protons α , χ , b and f were observed with the other rotaxane systems with chloride and various other anions. The titration data obtained by monitoring the perturbation of internal isophthalamide proton α for each of the rotaxanes (**Figure 3.15**) was analysed using the WinEQNMR2¹⁹ curve fitting software to give the 1:1 stoichiometric association constants reported in **Table 3.3**. It is important to note that the same association constant values, within experimental error, were obtained from analysing the titration data of

macrocycle internal isophthalamide proton χ and axle pyridine *N*-oxide proton *b*. This is a result of the anion being able to bind at both isophthalamide sites, as previously discussed.

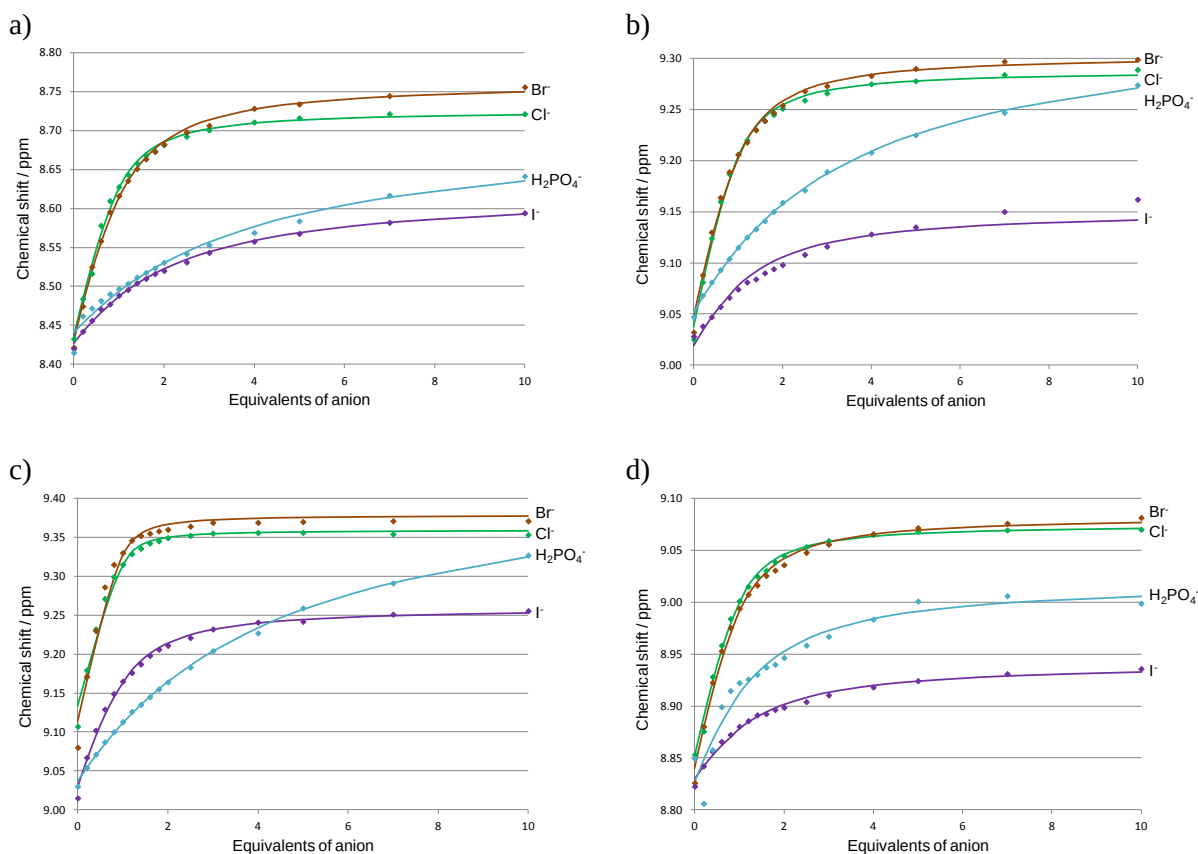


Figure 3.15—Changes in chemical shift of rotaxane proton α upon addition of increasing amounts of various anions to a) rotaxane **70**, b) rotaxane **71**, c) rotaxane **72** and d) rotaxane **73** (500 MHz, 1:1 CDCl₃/CD₃OD, 293 K, data points represent experimental data, continuous lines represent calculated curves).

Table 3.3—Anion association constants, K_a (M^{-1}), for pyridine *N*-oxide axle containing rotaxanes **70–73** (1:1 CDCl₃/CD₃OD, 293 K, estimated standard errors in parentheses).^[a]

Anion	70	71	72	73
Cl [−]	2720(280)	2790(240)	>10 ⁴	3010(340)
Br [−]	1330(90)	2050(280)	>10 ⁴	2090(30)
I [−]	295(22)	667(28)	1700(190)	635(84)
H ₂ PO ₄ [−]	129(33)	152(7)	112(7)	671(54)

^[a] these values were determined from the titration data obtained for proton *a*.

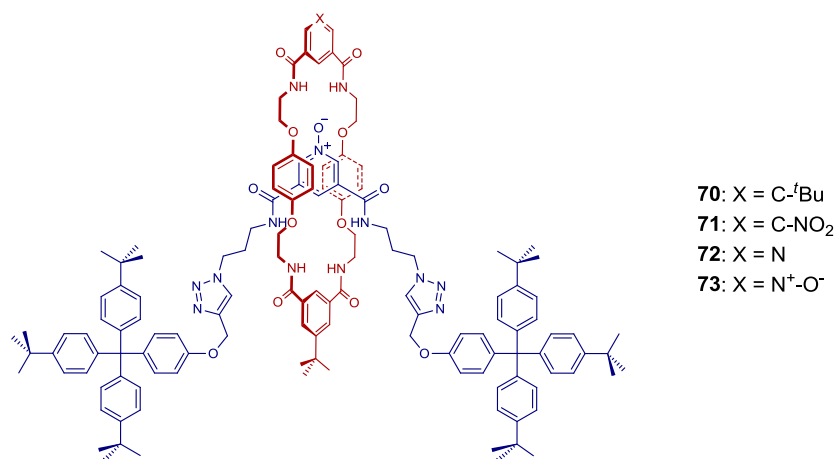


Figure 3.16—Pyridine *N*-oxide axle containing rotaxanes referred to in **Table 3.3**.

All four of the rotaxanes exhibit strong binding of the halides, in particular chloride and bromide, which are bound preferentially over iodide and dihydrogen phosphate.²³ This suggests that the rotaxanes possess interlocked binding clefts of complementary size for the smaller chloride and bromide anions, whereas the larger iodide and dihydrogen phosphate anions are presumably too large to penetrate the binding cavity. Importantly, the strength of chloride binding for these neutral systems is comparable to that of previously reported charged [2]rotaxanes containing pyridinium axle and isophthalamide macrocycle components (**Figure 3.17**).^{24, 25}

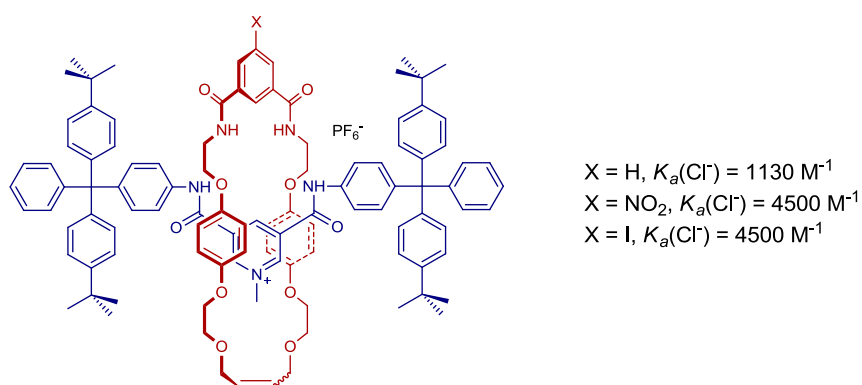


Figure 3.17—Previously reported charged [2]rotaxanes possessing pyridinium axle and isophthalamide macrocycle components (K_a values are for chloride binding in 1:1 CDCl₃/CD₃OD).

Given the strong binding of chloride and bromide by rotaxanes **70–73**, in particular pyridine functionalised rotaxane **72**, the ^1H NMR halide anion titration experiments were repeated in the more competitive 45:45:10 $\text{CDCl}_3/\text{CD}_3\text{OD}/\text{D}_2\text{O}$ aqueous solvent mixture. The internal isophthalamide proton α was again monitored to give titration data (**Figure 3.18**) analysed by WinEQNMR2¹⁹ to give 1:1 stoichiometric association constants (**Table 3.4**). As before, the same association constant values, within experimental error, were obtained from analysing the titration data of macrocycle proton χ and axle proton b .

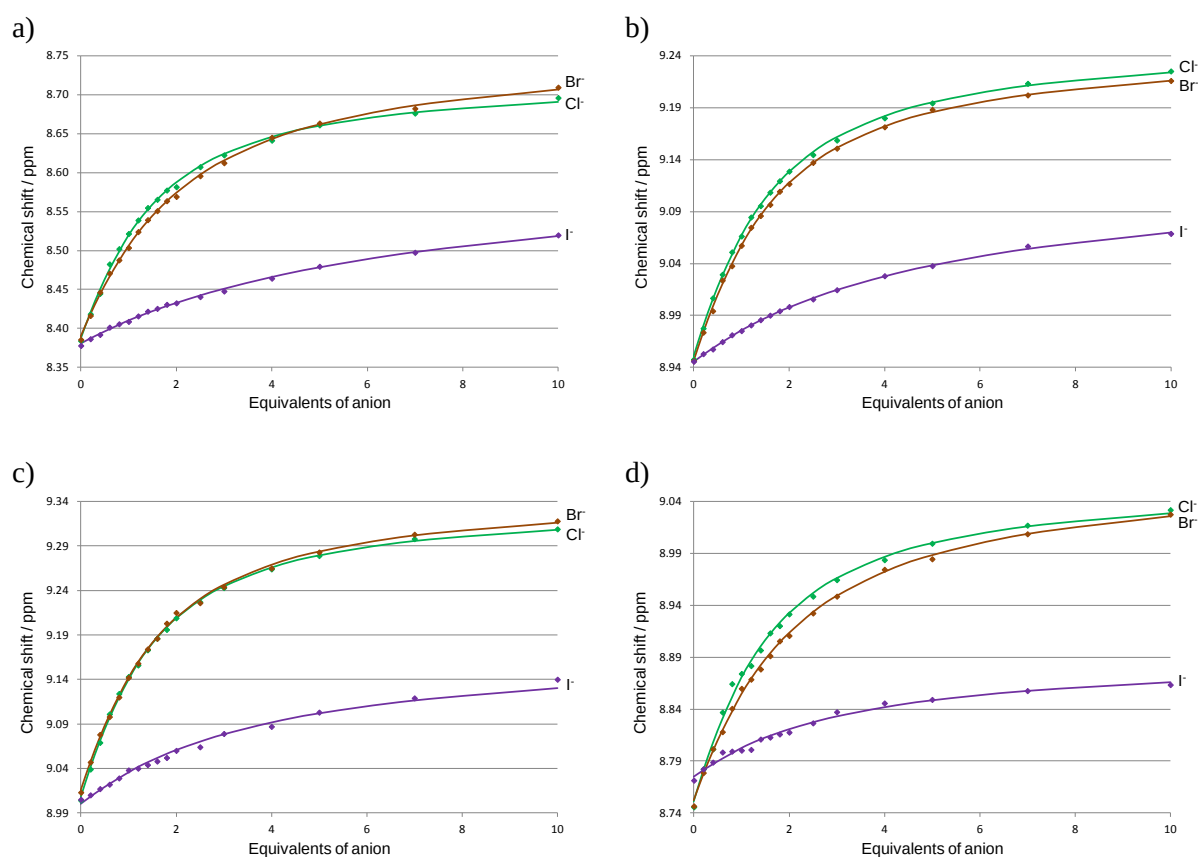
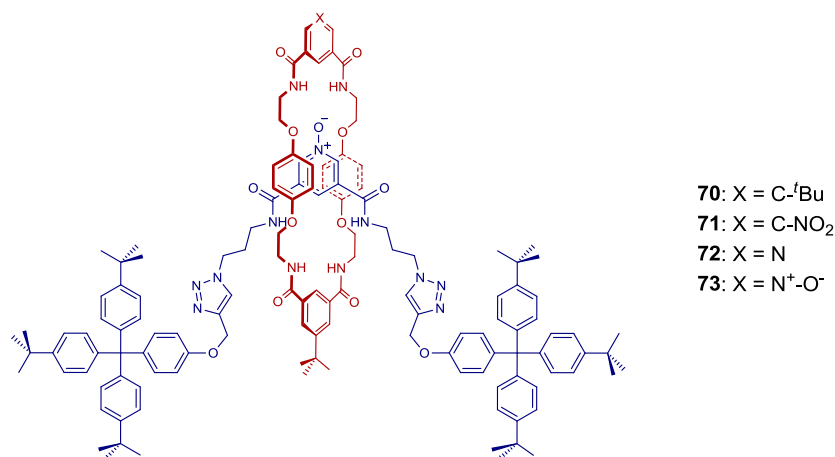


Figure 3.18—Changes in chemical shift of rotaxane proton α upon addition of increasing amounts of various anions to a) rotaxane **70**, b) rotaxane **71**, c) rotaxane **72** and d) rotaxane **73** (500 MHz, 45:45:10 $\text{CDCl}_3/\text{CD}_3\text{OD}/\text{D}_2\text{O}$, 293 K, data points represent experimental data, continuous lines represent calculated curves).

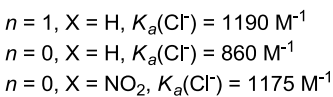
Table 3.4—Anion association constants, K_a (M^{-1}), for pyridine *N*-oxide axle containing rotaxanes **70–73** (45:45:10 $CDCl_3/CD_3OD/D_2O$, 293 K, estimated standard errors in parentheses).^[a]

Anion	70	71	72	73
Cl^-	501(27)	475(15)	552(8)	487(39)
Br^-	311(14)	442(6)	466(9)	324(17)
I^-	59(3)	92(4)	139(10)	175(32)

^[a] these values were determined from the titration data obtained for proton *a*.

**Figure 3.19**—Pyridine *N*-oxide axle containing rotaxanes referred to in **Table 3.4**.

The rotaxanes again display selectivity for the smaller chloride and bromide anions over iodide. This goes against the Hofmeister series bias,²⁶ which favours binding of the larger halide in aqueous solvent media on the basis of relative ease of desolvation, giving further evidence for the rotaxane binding domains being of complementary size for the smaller halides. Impressively, the strength of chloride binding by the neutral rotaxanes **70–73** is again comparable to previously reported charged pyridinium axle containing rotaxane systems (**Figure 3.20**).²⁷



3.3 Pyridine *N*-oxide axle containing positively charged [2]rotaxane

3.3.1 Introduction

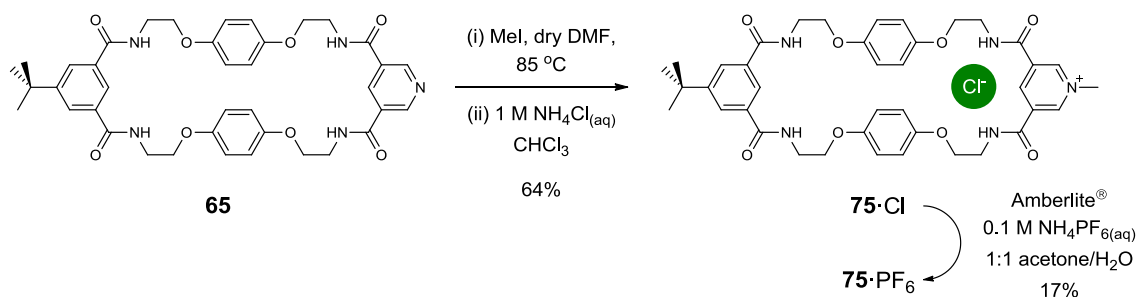
In the previous section, four neutral pyridine *N*-oxide axle containing [2]rotaxanes **70–73** were found to exhibit impressive halide anion recognition in aqueous solvent mixtures, with the strength of chloride binding being comparable to that of previously reported charged systems. It was thought that the methylation of the pyridine motif of rotaxane **72** would further enhance the host's anion recognition properties as a result of the additional electrostatic contribution to anion guest binding.

3.3.2 Pyridinium macrocycle

3.3.2.1 Synthesis

Due to the limited quantity of pyridine functionalised rotaxane **72** available it was decided not to synthesise the target pyridinium rotaxane *via* methylation of **72**. An alternative route, involving methylation of pyridine macrocycle **65**, was undertaken in the hope that a higher yield of the product interlocked structure would result from the macrocycle's positive charge enhancing the chloride anion templating effect.

Pyridine macrocycle **65** was reacted with iodomethane, in dry DMF, at 85 °C to give the iodide salt of the pyridinium macrocycle **75·I**. This was then dissolved in chloroform and washed repeatedly with 1 M $\text{NH}_4\text{Cl}_{(\text{aq})}$ to afford the macrocycle chloride salt **75·Cl** in 64% yield. In order for anion binding and pseudorotaxane studies to be performed the macrocycle was converted to its hexafluorophosphate salt **75·PF₆** in a modest 17% yield by passing a 1:1 acetone/water solution of **75·Cl** through an Amberlite[®] exchange column that had been pre-treated with 0.1 M $\text{NH}_4\text{PF}_{6(\text{aq})}$ (**Scheme 3.13**).



Scheme 3.13—Synthesis of target pyridinium functionalised macrocycle $\text{75}\cdot\text{PF}_6$.

3.3.2.2 Anion recognition properties

The strength of chloride binding to pyridinium functionalised macrocycle $\text{75}\cdot\text{PF}_6$ was determined via a ^1H NMR titration experiment. Increasing amounts of $\text{TBA}\cdot\text{Cl}$ were added to a 1:1 $\text{CDCl}_3/\text{CD}_3\text{CN}$ solution of the macrocycle and pyridinium proton α , internal isophthalamide proton χ and amide protons γ and η were all observed to shift downfield, indicative of polarising hydrogen bonding interactions with the chloride anion (**Figure 3.21**).

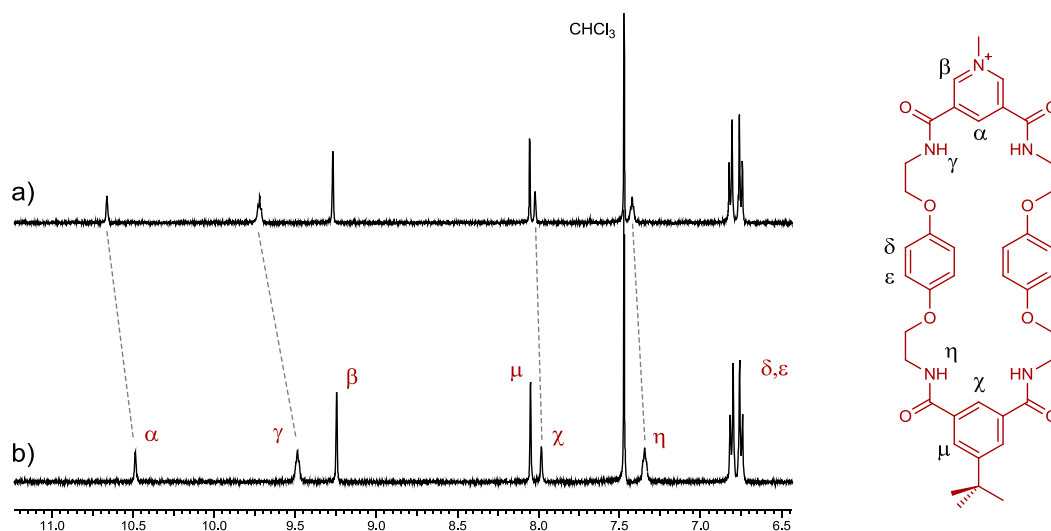


Figure 3.21—Truncated ^1H NMR spectra of a) an equimolar solution of pyridinium macrocycle $\text{75}\cdot\text{PF}_6$ and $\text{TBA}\cdot\text{Cl}$ and b) pyridinium macrocycle $\text{75}\cdot\text{PF}_6$ (500 MHz, 1:1 $\text{CDCl}_3/\text{CD}_3\text{CN}$, 293 K).

The most dramatic downfield shifts occurred for pyridinium proton α and nearby amide protons γ suggesting, as expected, that the chloride anion binds more strongly at the pyridinium site of the macrocycle; $\Delta\delta_{1 \text{ equiv.}} = 0.18$ (α), 0.24 (γ), 0.05 (χ), 0.09 (η).

WinEQNMR2¹⁹ analysis of the titration data obtained from monitoring the downfield shifts of amide protons γ and η (**Figure 3.22**) gave 1:1 stoichiometric association constants for chloride binding at the pyridinium and *tert*-butyl isophthalamide binding site respectively (**Table 3.5**).

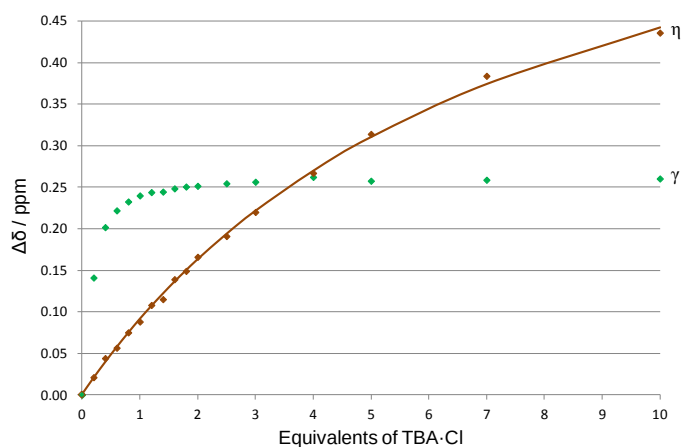


Figure 3.22—Changes in chemical shift, $\Delta\delta$ (ppm), of macrocycle **75**·PF₆ protons γ and η upon addition of increasing amounts of TBA·Cl (500 MHz, 1:1 CDCl₃/CD₃CN, 293 K, data points represent experimental data, continuous lines represent calculated curves).

Table 3.5—Chloride association constants, K_a (M^{-1}), for macrocycles **63–65** and **75**·PF₆ (estimated standard errors in parentheses, 1:1 CDCl₃/CD₃CN, 293 K).

Macrocycle	Amide protons γ	Amide protons η
63	208(12)	— ^[a]
64	493(12)	139(26)
65	246(8)	176(16)
75 ·PF ₆	>10 ⁴	55(4)

^[a] no value is given as macrocycle **63** possesses two equivalent *tert*-butylisophthalamide binding sites.

As the magnitude of the shifts and association constant values suggest, macrocycle **75**·PF₆ binds chloride almost entirely at its pyridinium site. The large association constant value >10⁴ M⁻¹ confirms that the positive charge of the pyridinium motif has enhanced chloride binding significantly when compared to the neutral macrocycle analogues **63–65**.

3.3.2.3 Pseudorotaxane investigations

Given the positively charged nature of pyridinium functionalised macrocycle **75**·PF₆ it was expected that it would form a more stable pseudorotaxane assembly with pyridine *N*-oxide thread **62**, both in the absence and presence of a templating chloride anion, than its neutral macrocycle counterparts **63–65**.

Analogous ¹H NMR pseudorotaxane titrations both in the absence and presence of chloride (**Figure 3.23**) revealed the macrocycle hydroquinone protons δ and ϵ to move upfield, which is diagnostic of pseudorotaxane assembly. As before, protons α and χ are seen to shift downfield, indicating that they are involved with hydrogen bonding to the pyridine *N*-oxide oxygen donor atom, in the absence of chloride, and to the same oxygen donor atom and chloride when the anion is present.

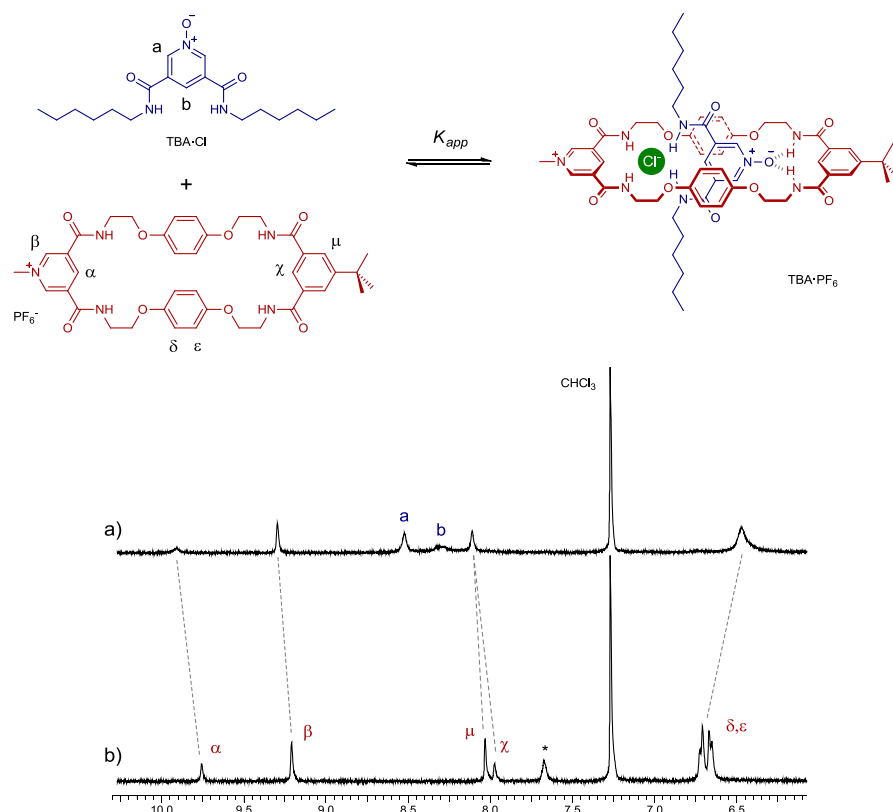


Figure 3.23—Truncated ¹H NMR spectra of a) an equimolar solution of pyridinium macrocycle **75**·PF₆, pyridine *N*-oxide thread **62** and TBA·Cl and b) pyridinium macrocycle **75**·PF₆ (500 MHz, 9:1 CDCl₃/CD₃OD, 293 K, peak marked * corresponds to unexchanged amide NH protons).

The upfield shift of the macrocycle hydroquinone protons δ and ε was monitored to give titration data (**Figure 3.24**) from which 1:1 stoichiometric association constants (**Table 3.6**) were obtained by analysis with WinEQNMR2¹⁹ curve fitting software.

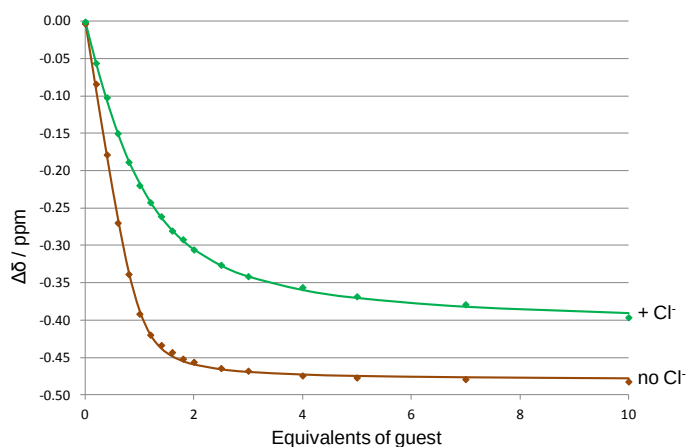


Figure 3.24—Changes in chemical shift, $\Delta\delta$ (ppm) of macrocycle **75**·PF₆ hydroquinone protons δ and ε upon addition of increasing amounts of pyridine *N*-oxide thread **62** both in the absence and presence of TBA·Cl (500 MHz, 293 K, data points represent experimental data, continuous lines represent calculated curves, note different solvent systems used: 1:1 CDCl₃/CD₃CN for un-templated titration data; 9:1 CDCl₃/CD₃OD for chloride anion-templated titration data).

Table 3.6—Association constants, K_a (M⁻¹), and apparent association constants, K_{app} (M⁻¹), for un-templated and templated pseudorotaxane assembly with macrocycles **63–65** and **75**·PF₆ (estimated standard errors in parentheses, 293 K).

Macrocycle	Thread 62 ^[a]	1:1 Thread 62 /TBA·Cl ^[b]	
63	93(6) ^[c]	—	197(30) ^[d]
64	216(15) ^[c]	>10 ^{4[c]}	529(47) ^[d]
65	120(12) ^[c]	>10 ^{4[c]}	337(52) ^[d]
75 ·PF ₆	>10 ^{4[c]}	—	1168(36) ^[d]

^[a] values reported are association constants (K_a), ^[b] values reported are apparent association constants (K_{app}),²⁴
^[c] 1:1 CDCl₃/CD₃CN, ^[d] 9:1 CDCl₃/CD₃OD.

Pyridinium functionalised macrocycle **75**·PF₆ can be seen to form a much more stable interpenetrated pseudorotaxane assembly with pyridine *N*-oxide thread **62** than its neutral macrocyclic analogues, both in the absence and presence of a templating chloride anion. This is as expected, given that electrostatic interactions can now be combined with hydrogen bonding and aromatic donor–acceptor interactions to facilitate interpenetration. The increase

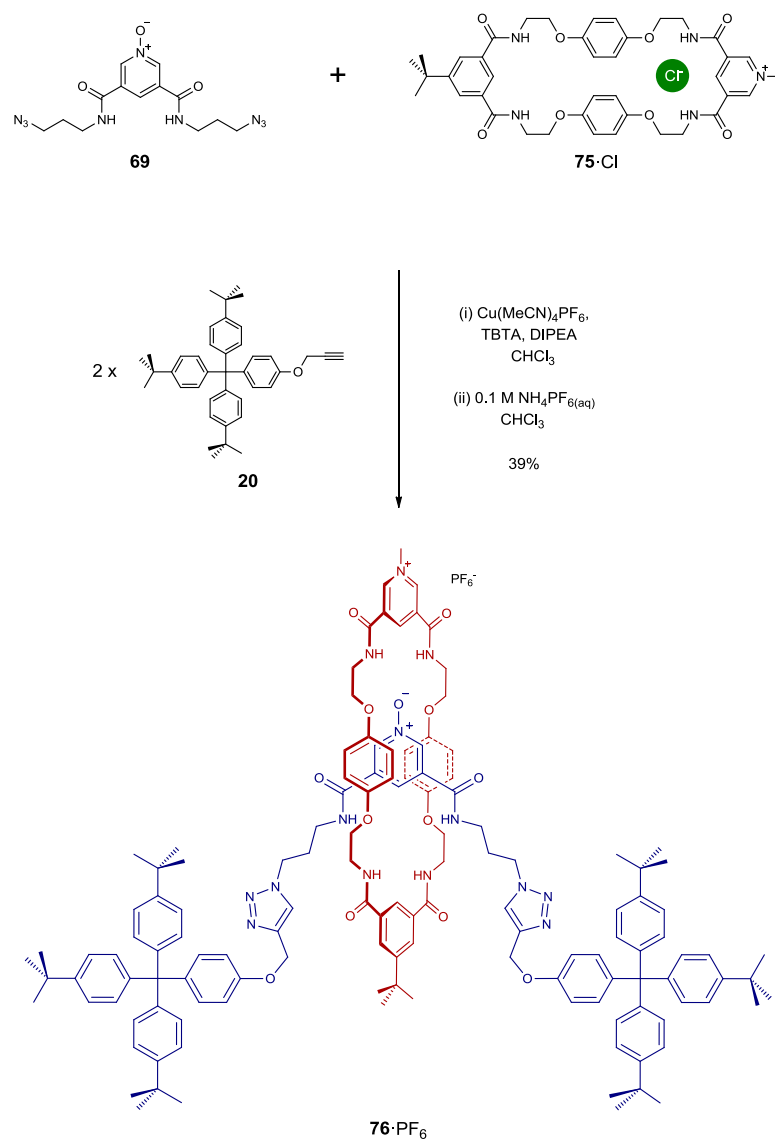
in K_{app} for anion-templated pseudorotaxane assembly suggests that rotaxane synthesis with pyridinium functionalised macrocycle **75**⁺, *via* the same threading-followed-by-stoppering methodology, should result in a higher yield of the interlocked product.

3.3.3 Positively charged rotaxane containing a pyridine *N*-oxide axle component

3.3.3.1 Synthesis and characterisation

Positively charged pyridine *N*-oxide axle containing rotaxane **76**·PF₆ was synthesised using an almost identical methodology to that employed to prepare the neutral rotaxanes **70–73**. In this case, the templating chloride anion was provided by using the chloride salt of the pyridinium functionalised macrocycle **75**·Cl.

A chloroform solution of an equimolar amount of pyridine *N*-oxide axle precursor **69**¹⁵ and pyridinium macrocycle chloride salt **75**·Cl, together with two equivalents of alkyne functionalised terphenyl stopper **20**²² and three equivalents of DIPEA, was stirred at room temperature for 24 hours in the presence of Cu(MeCN)₄PF₆ and TBTA. The crude reaction mixture was purified by preparative thin layer chromatography to give the chloride salt of the target rotaxane **76**·Cl, which was then exchanged to its hexafluorophosphate salt **76**·PF₆ by repeated washing of a chloroform solution of **76**·Cl with 0.1 M NH₄PF_{6(aq)} (**Scheme 3.14**). The overall yield for rotaxane synthesis was 39%, significantly higher than the yields obtained for the neutral rotaxanes **70–73**, as expected.



Scheme 3.14—Synthesis of positively charged pyridine *N*-oxide axle containing rotaxane **76**· PF_6 .

The new rotaxane **76**· PF_6 was characterised by ^1H , ^{13}C , ^{19}F and ^{31}P NMR spectroscopy and by high resolution ESI mass spectrometry. The high resolution ESI-MS analysis gave the expected mass peak at m/z 1089.5877 corresponding to $[\text{M} + \text{Na}]^{2+}$ and the ^1H NMR spectrum of **76**· PF_6 is shown in **Figure 3.25**, together with those of pyridinium functionalised macrocycle **75**· PF_6 and the free pyridine *N*-oxide axle **74**.¹⁵

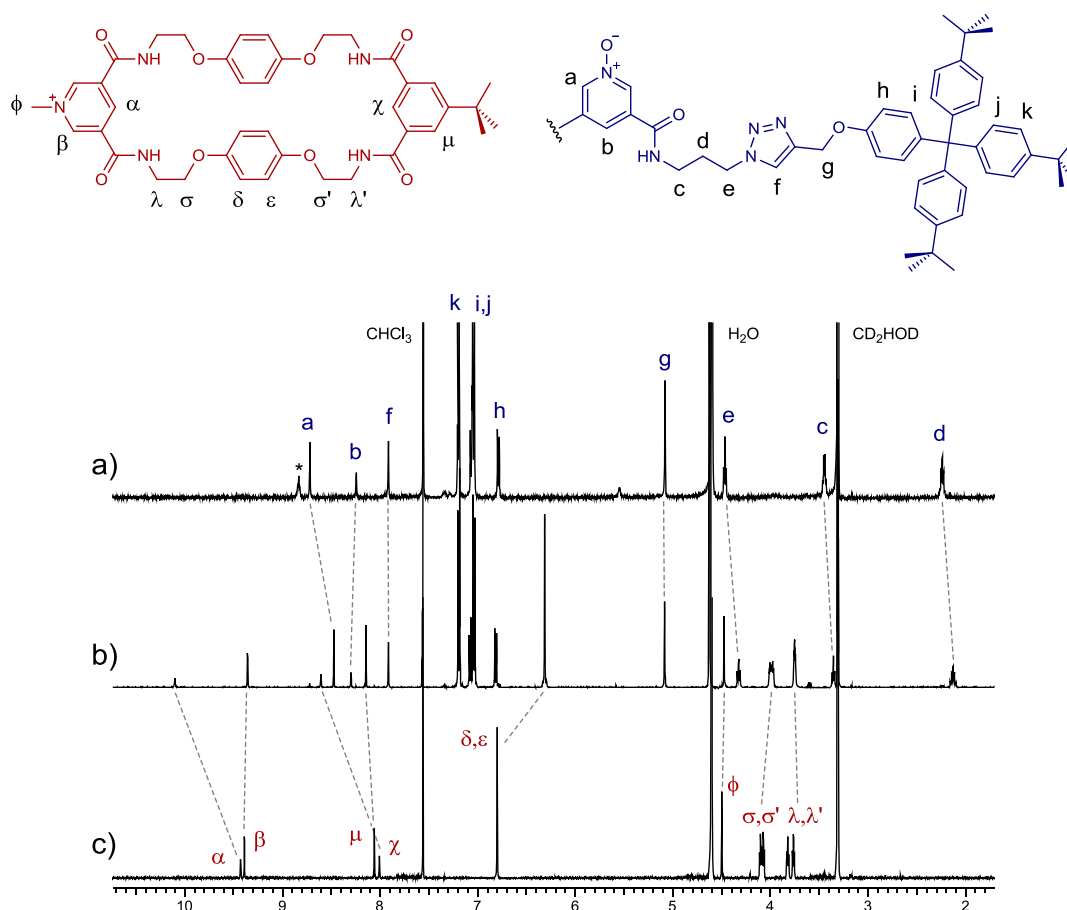


Figure 3.25—Truncated ^1H NMR spectra of a) free pyridine *N*-oxide axle **74**, b) rotaxane **76**· PF_6 and c) pyridinium functionalised macrocycle **75**· PF_6 (500 MHz, 1:1 $\text{CDCl}_3/\text{CD}_3\text{OD}$, 293 K, peak marked * corresponds to unexchanged amide NH protons).

As with neutral rotaxanes **70–73**, the macrocycle internal pyridinium and *tert*-butylisophthalamide protons, α and χ respectively, have shifted downfield as a result of hydrogen bonding interactions with the axle pyridine *N*-oxide oxygen donor atom. An upfield shift of the macrocycle hydroquinone protons δ and ϵ is also observed, arising from aromatic donor–acceptor interactions between the macrocycle hydroquinone groups and the pyridine *N*-oxide motif of the axle, diagnostic of interlocked structure formation.

Definitive evidence for the formation of rotaxane **76**· PF_6 was obtained by ^1H – ^1H two-dimensional ROESY NMR spectroscopy. Through space couplings of macrocycle hydroquinone protons δ and ϵ with axle protons a , b and f are observed, together with interaction of pyridine *N*-oxide protons a with pyridinium proton α (**Figure 3.26**).

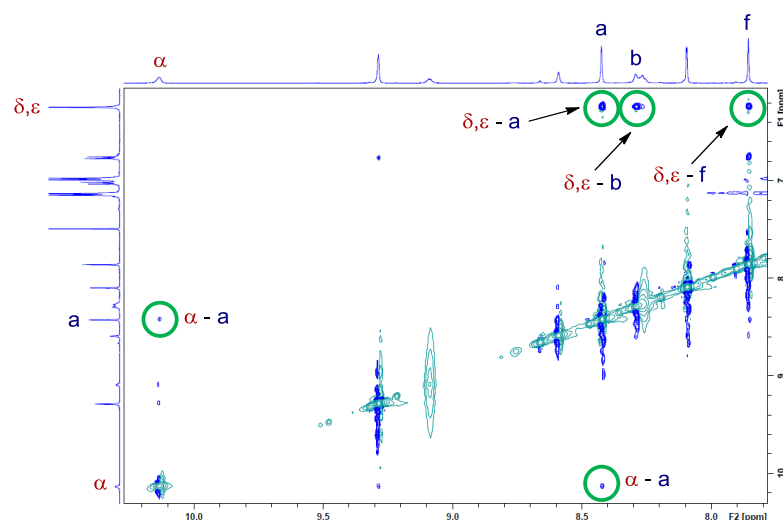


Figure 3.26—Truncated ROESY NMR spectrum of rotaxane **76**·PF₆ (500 MHz, 1:1 CDCl₃/CD₃OD, 293 K, peak assignments taken from **Figure 3.25**).

The coupling of pyridine *N*-oxide proton *a* and pyridinium proton α tentatively suggests that, in 1:1 CDCl₃/CD₃OD, the rotaxane adopts a conformation in which the axle pyridine *N*-oxide oxygen donor is directed towards the more acidic pyridinium amide groups of the macrocycle component (**Figure 3.27**).

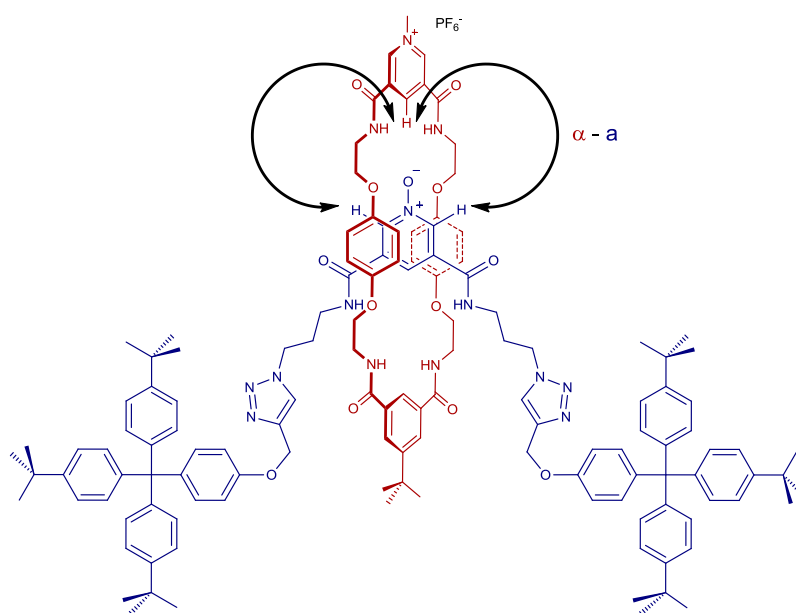
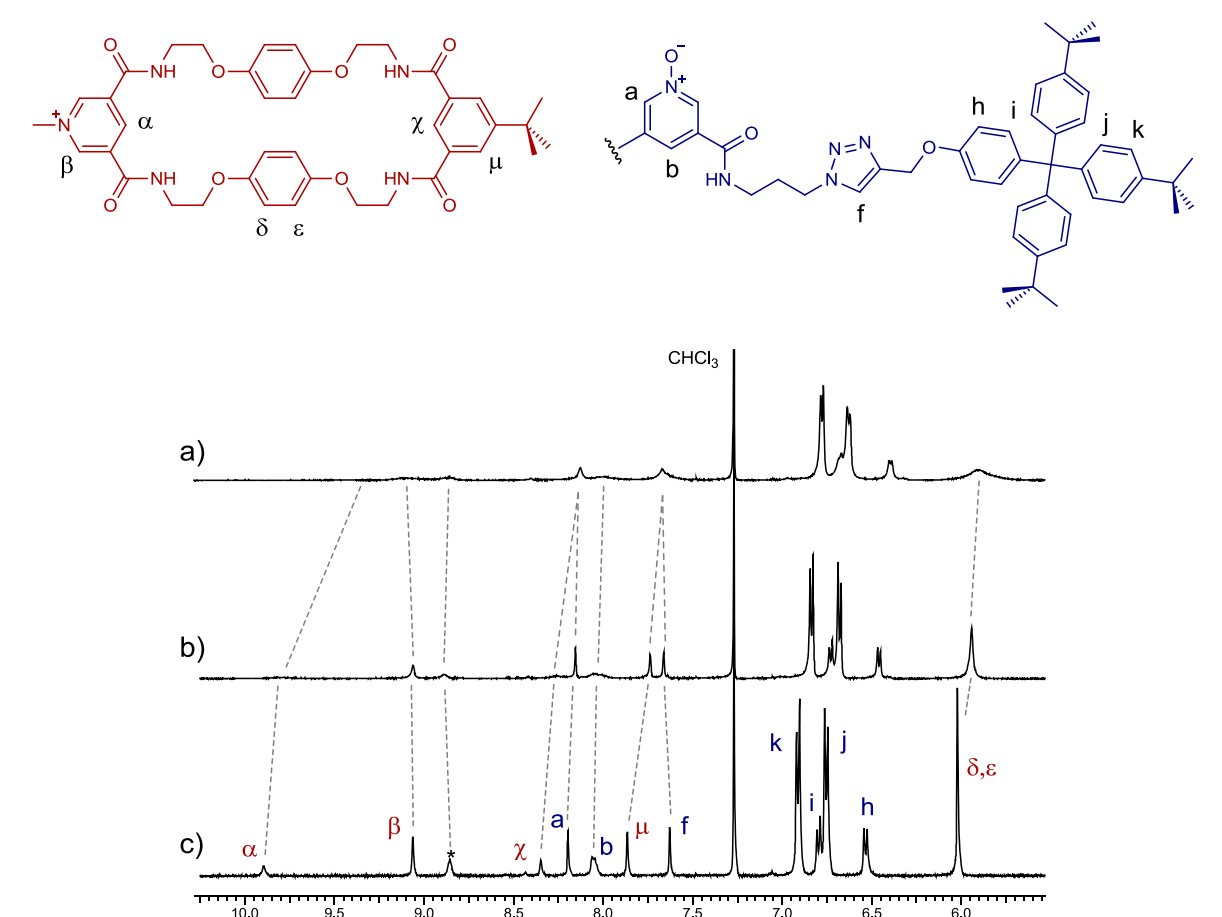
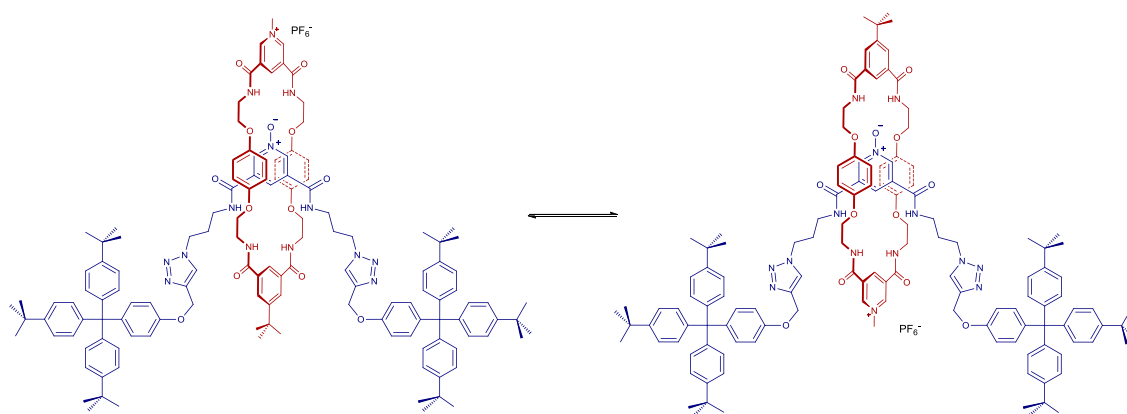


Figure 3.27—Conformation of rotaxane **76**·PF₆ suggested by couplings in its ROESY spectrum.



This indicates that despite the previous DOESY evidence, which suggests the contrary,



Scheme 3.15—Two possible conformations exhibited by positively charged rotaxane **76**·PF₆ resulting from molecular pirouetting of the macrocycle component around the pyridine *N*-oxide axle.

3.3.3.2 Anion recognition properties

With the positively charged rotaxane **76**·PF₆ successfully isolated, ¹H NMR anion titration experiments were undertaken to assess its anion recognition properties.

Initially, aliquots of a solution of TBA·Cl in 45:45:10 CDCl₃/CD₃OD/D₂O were added to a solution of rotaxane **76**·PF₆ in the same solvent mixture and the ¹H NMR spectra recorded. Macrocycle pyridinium proton *α* and *tert*-butylisophthalamide proton *χ* shift downfield upon the addition of chloride, as do axle pyridine *N*-oxide proton *b* and triazole protons *f*. Hydroquinone protons *δ* and *ε* are seen to move upfield, suggesting that chloride binding enhances the aromatic donor–acceptor interactions between the macrocycle hydroquinone units and the axle pyridine *N*-oxide group (**Figure 3.29**).

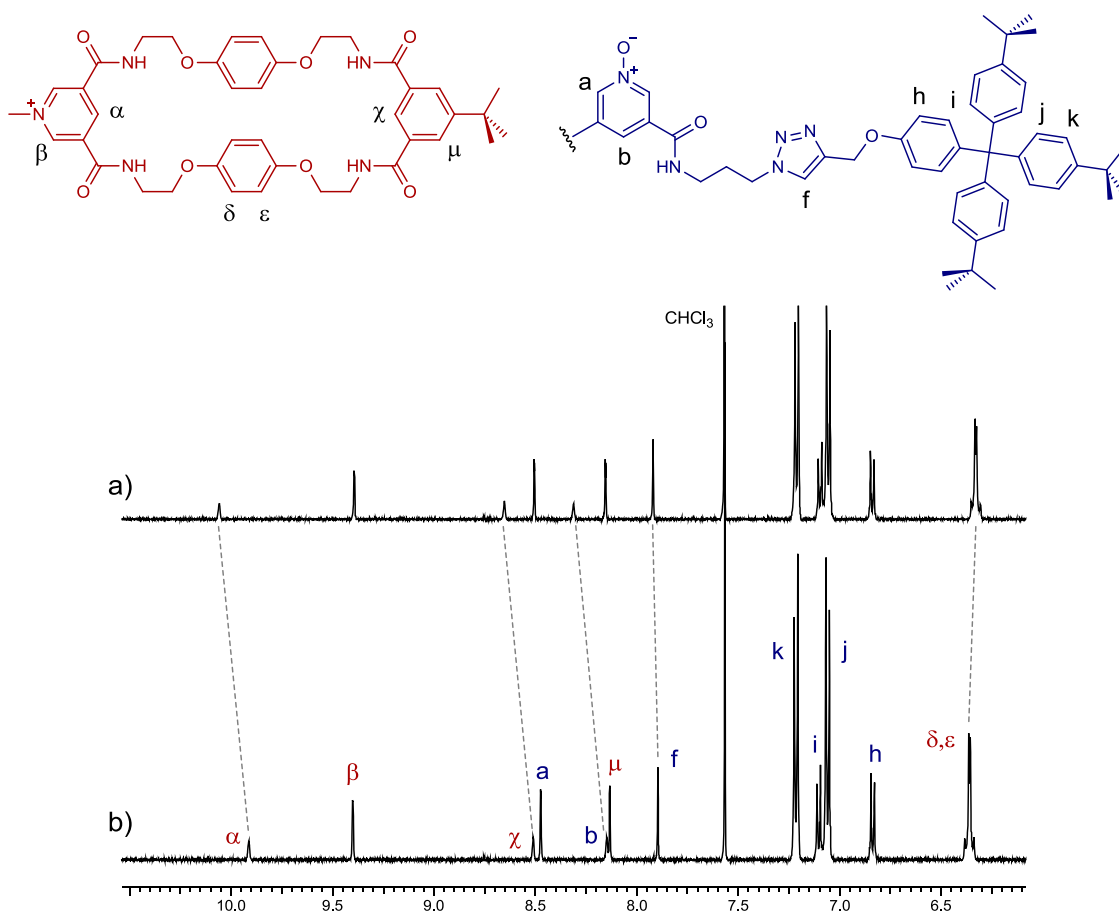


Figure 3.29—Truncated ^1H NMR spectra of a) an equimolar solution of rotaxane **76**· PF_6 and $\text{TBA}\cdot\text{Cl}$ and b) rotaxane **76**· PF_6 (500 MHz, 45:45:10 $\text{CDCl}_3/\text{CD}_3\text{OD}/\text{D}_2\text{O}$, 293 K).

The downfield shifts of axle protons *b* and *f* suggest that the axle wraps around and encapsulates the anion, whereas the observed perturbations of protons *α* and *χ* are indicative of polarising hydrogen bonding interactions between these protons and the anionic guest suggesting that the anion is bound at both sites of the rotaxane in a dynamic manner, as was the case with neutral rotaxane analogues **70–73**. To confirm this, low temperature VT ^1H NMR experiments were again undertaken. As the temperature of an equimolar solution of rotaxane **76**· PF_6 and $\text{TBA}\cdot\text{Cl}$ was lowered, broadening in the aromatic region of the ^1H NMR spectrum was again observed (**Figure 3.30**). This verified that the structure of the rotaxane was dynamic on the NMR timescale and that anion recognition was occurring at both of the rotaxane's recognition sites.

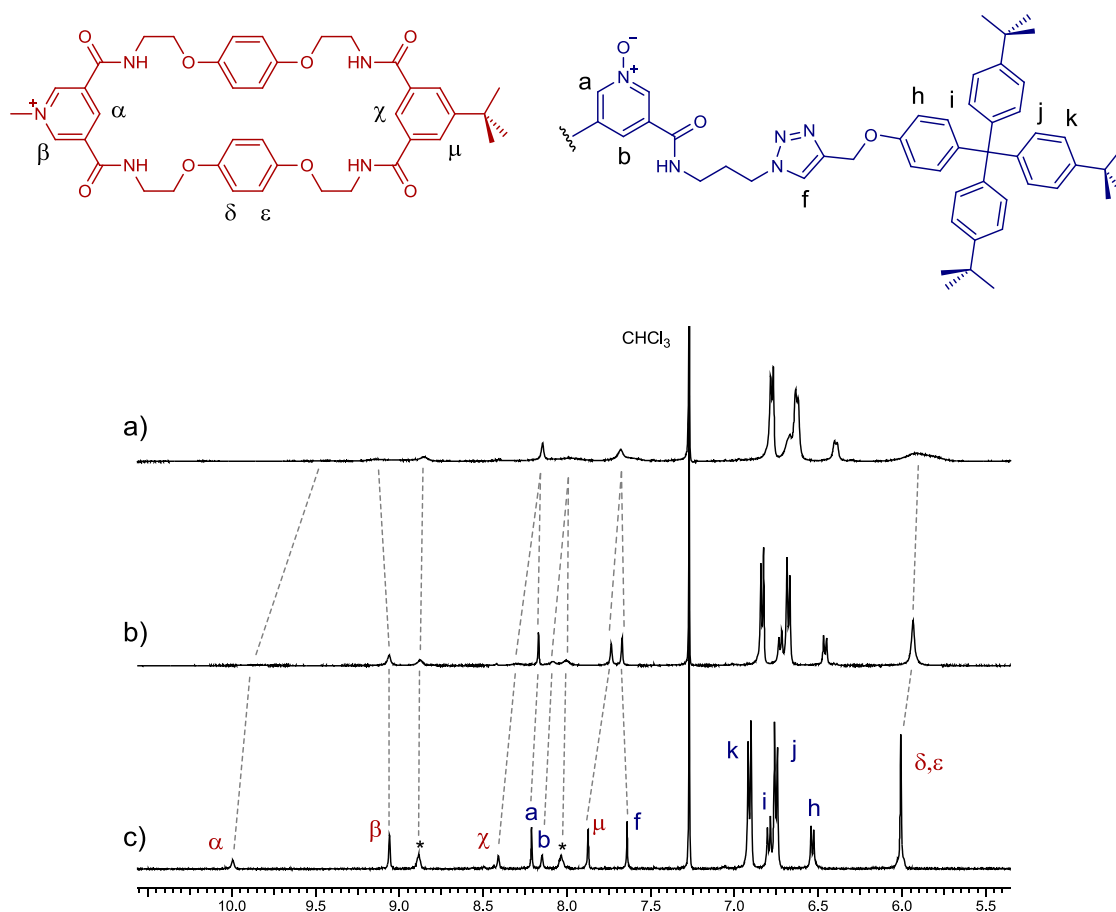


Figure 3.30—Truncated ^1H NMR spectrum of an equimolar solution of rotaxane **76**· PF_6 and TBA·Cl at a) 223 K, b) 248 K and c) 298 K (500 MHz, 1:1 $\text{CDCl}_3/\text{CD}_3\text{OD}$, peaks marked * are unexchanged amide NH protons).

Addition of bromide to a 45:45:10 $\text{CDCl}_3/\text{CD}_3\text{OD}/\text{D}_2\text{O}$ solution of rotaxane **76**· PF_6 at 293 K produced similar ^1H NMR changes as those observed for chloride; however in the case of iodide, acetate and dihydrogen phosphate the magnitudes of the changes in chemical shift ($\Delta\delta_{10 \text{ equiv.}}$) were all less than 0.05 ppm which suggests these anions do not bind to the rotaxane in this competitive aqueous solvent mixture. For chloride and bromide titrations, the downfield shifts of protons α , χ and b were monitored to give titration data (**Figure 3.31**) from which 1:1 stoichiometric association constants were determined using WinEQNMR2¹⁹ (**Table 3.7**). Interestingly, the magnitudes of the anion association constants were found to be dependent upon which proton was monitored, which was not the case with neutral pyridine *N*-oxide axle containing rotaxanes **70–73** (**Section 3.2.2.2**).

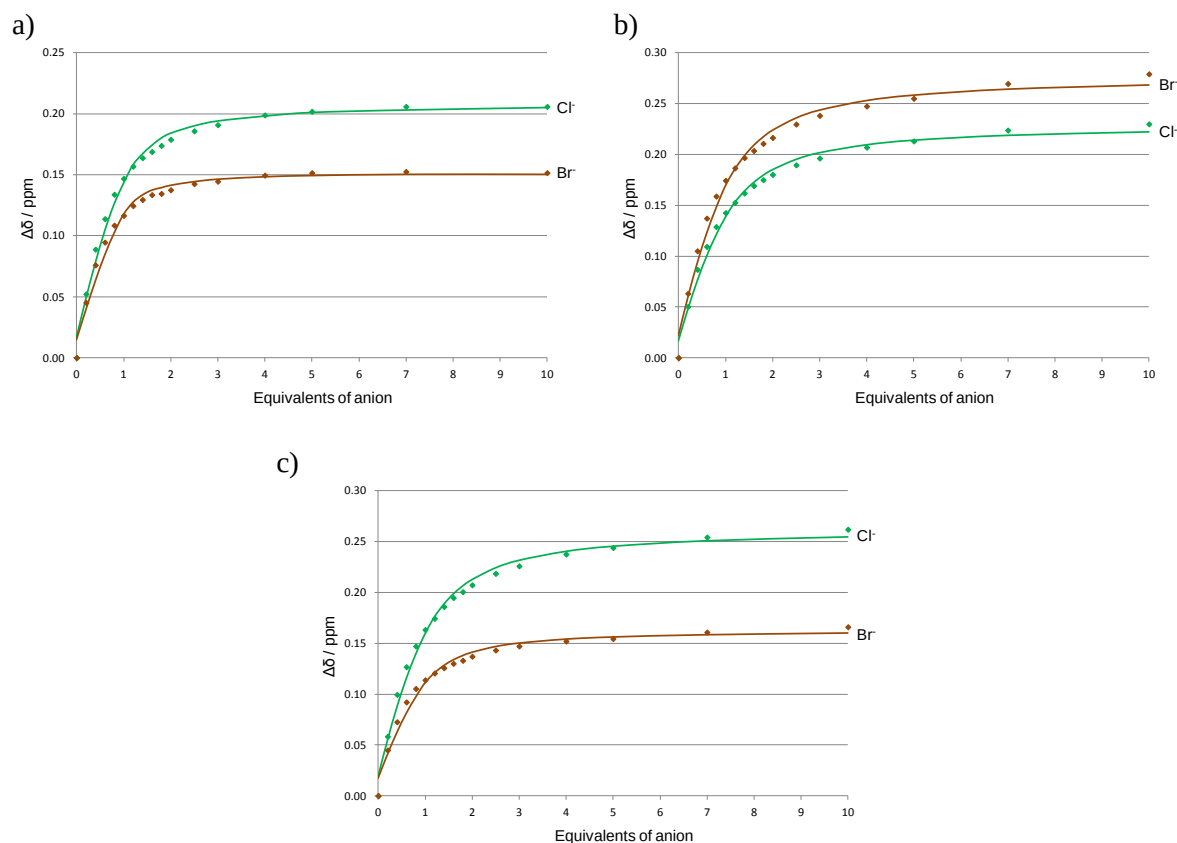


Figure 3.31—Changes in chemical shift, $\Delta\delta$ (ppm), of a) rotaxane proton α , b) rotaxane proton χ and c) rotaxane proton b upon addition of increasing amounts of anion to a solution of rotaxane **76**·PF₆ (500 MHz, 45:45:10 CDCl₃/CD₃OD/D₂O, 293 K, data points represent experimental data, continuous lines represent calculated curves).

Table 3.7—Association constants, K_a (M^{-1}), calculated for anion binding by rotaxane **76**·PF₆ from monitoring the downfield shifts of protons α , χ and b (45:45:10 CDCl₃/CD₃OD/D₂O, 293 K, estimated standard errors in parentheses).

Anion	Proton α	Proton χ	Proton b
Cl [−]	3050(540)	1570(250)	1620(260)
Br [−]	5720(850)	1550(290)	2400(560)
I [−]	NB	NB	NB
OAc [−]	NB	NB	NB
H ₂ PO ₄ [−]	NB	NB	NB

NB indicates no binding of the anion was observed.

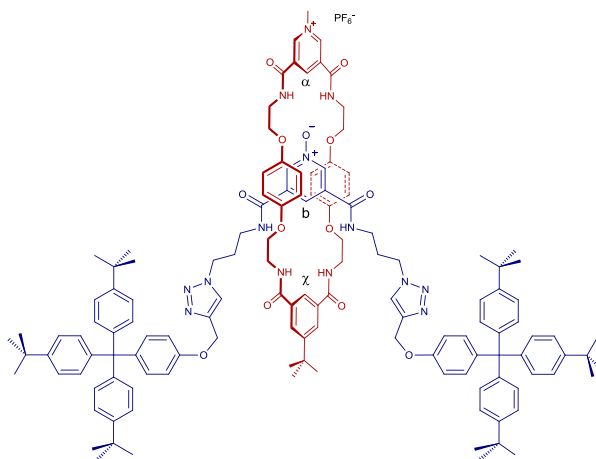
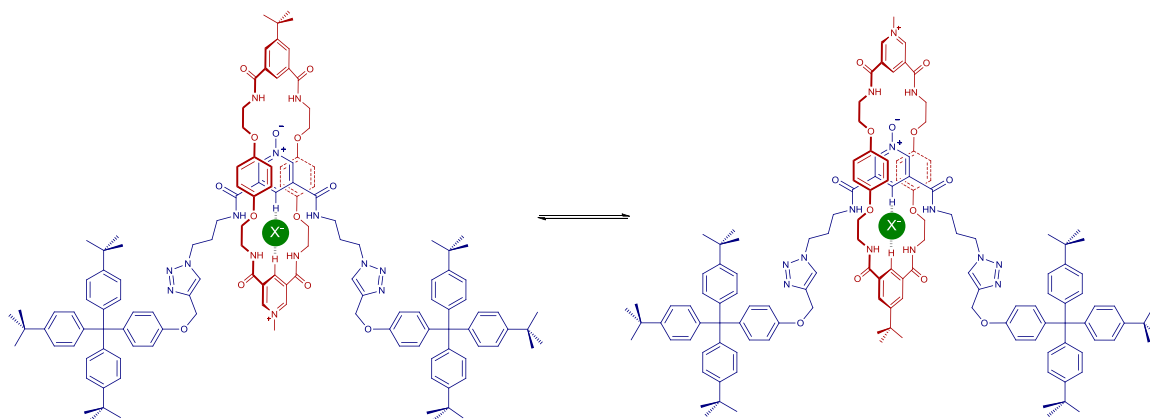


Figure 3.32—Rotaxane **76**·PF₆ with protons α , χ and b labelled.

The largest association constants are obtained from the titration data of macrocyclic pyridinium proton α , suggesting that the halide anion binds most strongly at the pyridinium site of the rotaxane. Binding to the *tert*-butylisophthalamide group of the rotaxane is considerably weaker, which is to be expected given the positive charge of the pyridinium motif. The association constants calculated from the titration data of pyridine *N*-oxide proton b are larger than the respective K_a values for proton χ but smaller than those for proton α . This may be explained by the anion interacting with proton b regardless of whether it is coordinated to the pyridinium or *tert*-butylisophthalamide sites in the rotaxane (**Scheme 3.16**) and so the association constant obtained from monitoring the shift of proton b would be of intermediate magnitude. Rotaxane **76**·PF₆ binds chloride and bromide selectively over acetate, dihydrogen phosphate and iodide. This can be attributed to the rotaxane's interlocked binding domain being of complementary size for the smaller chloride and bromide anions whereas iodide, acetate and dihydrogen phosphate are thought to be too large to penetrate the binding cavity.



Scheme 3.16—Proposed halide anion binding to either the pyridinium or tert-butylisophthalamide sites of rotaxane **76**·PF₆.

Comparison of the halide association constants of rotaxane **76**·PF₆ with those of neutral pyridine *N*-oxide rotaxanes **70–73** in the same solvent mixture (**Table 3.4** and **Table 3.7**) clearly shows that, while all of the systems are selective for chloride and bromide over larger anions, the introduction of a positively charged motif has significantly enhanced the strength of anion binding, as expected.

3.3.4 Summary

A pyridinium functionalised isophthalamide macrocycle was synthesised and its positive charge demonstrated to significantly enhance anion recognition and pseudorotaxane assembly compared to its neutral macrocycle analogues. This facilitated the anion-templated threading-followed-by-stoppering synthesis of a positively charged pyridine *N*-oxide axle containing [2]rotaxane **76**·PF₆, which was isolated in a much improved 39% yield. The rotaxane possesses two potential anion recognition sites and so could have adopted two possible conformations in solution. Low temperature VT ¹H NMR studies suggested the rotaxane was dynamic on the NMR timescale and that both recognition sites were accessible to an anionic guest.

Anion titration experiments showed that the incorporation of a positive charge into the rotaxane structure augments the host's anion recognition properties in 45:45:10 CDCl₃/CD₃OD/D₂O, with superior chloride and bromide anion recognition to its neutral rotaxane analogues being displayed. The rotaxane was found not to bind iodide, acetate or dihydrogen phosphate as a result of its interlocked binding domain being of complementary size for the smaller chloride and bromide anions.

3.4 Conclusions and future work

Four neutral pyridine *N*-oxide axle containing [2]rotaxanes have been synthesised and demonstrated to be the first examples of neutral interlocked host systems to recognise halide anions in aqueous solvent media. These rotaxanes were shown to exhibit selectivity for chloride and bromide over iodide and dihydrogen phosphate, with this observation attributed to their binding domains being of complementary size and shape for the smaller halides. The structure of the rotaxanes was found to be dynamic on the NMR timescale with rapid switching between two possible conformations thought to occur at room temperature, both in the absence and presence of chloride.

An analogous positively charged pyridinium functionalised rotaxane was also prepared and shown to exhibit similar chloride and bromide selectivity. Importantly, the rotaxane bound chloride and bromide significantly more strongly than its neutral rotaxane counterparts, in 45:45:10 CDCl₃/CD₃OD/D₂O, as a result of its positive charge. The structure of the rotaxane was again found to be dynamic on the NMR timescale, with chloride recognition shown to be occurring at both of the rotaxane's recognition sites.

Future work may focus on the construction of analogous rotaxane-based anion sensors. This could be achieved by incorporating reporter groups, such as ferrocene, into the macrocyclic component of the rotaxane structure.

3.5 References and notes for Chapter Three

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CHAPTER FOUR

Chapter Four: β -Cyclodextrin functionalised metal nanoparticles—catalysis and sensing applications

The research outlined in this Chapter was carried out in collaboration with Johnson Matthey. Some experiments were performed by researchers at Johnson Matthey Technology Centre (JMTC) and their assistance is referenced where necessary.

4.1 Introduction

4.1.1 Cyclodextrins

Cyclodextrins are macrocyclic oligosaccharides consisting of 6 (α -cyclodextrin), 7 (β -cyclodextrin), or 8 (γ -cyclodextrin) glucose units. They have been known for more than a century and have many applications including their use in the pharmaceutical industry¹⁻⁵ and as food additives.^{6, 7} Their shape can be thought of as a truncated cone, with secondary and primary alcohols forming the wide and narrow rims respectively (**Figure 4.1**). The differing nucleophilicity and basicity of these sites allows for synthetic discrimination between the two rims.⁸

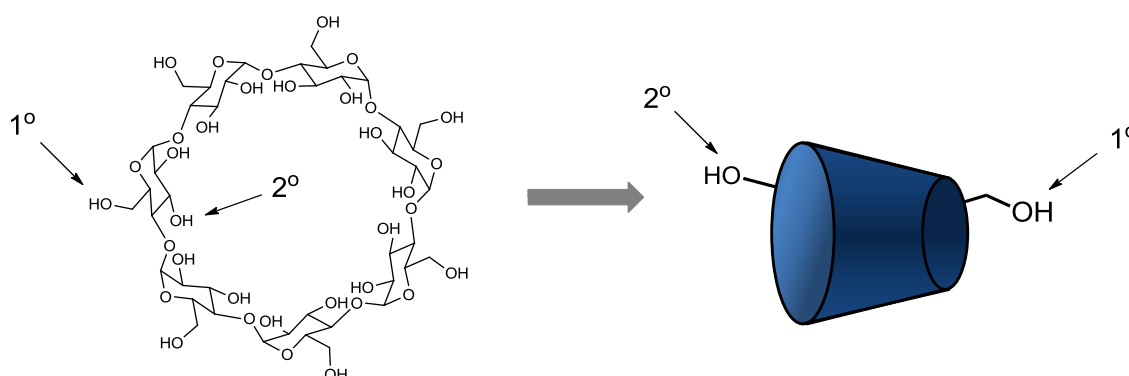


Figure 4.1— β -Cyclodextrin, and its cartoon representation, with secondary and primary alcohols labelled.

The exterior surfaces of cyclodextrin are hydrophilic due to the presence of the hydroxyl groups, whereas the annulus of the cone is hydrophobic because of the surrounding C–H

bonds and ether linkages. This gives rise to cyclodextrins forming inclusion complexes with hydrophobic guests in polar protic solvents, such as water.⁹

Of the three forms, β -cyclodextrin is the most commonly used because of its optimal cavity size for the encapsulation of a vast array of organic molecules through the action of van der Waal's and hydrophobic interactions.⁹ Conversely, the α -form is too small for guest binding, whereas γ -cyclodextrin is larger and more flexible allowing for the inclusion of more than one guest (**Table 4.1**).

Table 4.1— $\log K_a$ values for 1:1 inclusion of various guests by cyclodextrins (H_2O , 298 K).⁹

Guest	α	β	γ
Benzene	1.50	2.23	0.96
2-Naphthalenesulfonate	2.56	5.37	1.58
Anthracene	1.87	3.31	2.35

However, β -cyclodextrin exhibits the poorest water solubility of the three: g per 100 mL = 14.5 (α), 1.85 (β), 23.2 (γ).⁶ This has been shown to be overcome by methylation of its free alcohol groups to form permethylated β -cyclodextrin,¹⁰ with this having the added benefit of rendering it soluble in common organic solvents such as dichloromethane, chloroform and methanol.

4.1.2 Catalytic metal nanoparticles

Owing to their exceptionally high surface area to volume ratio and impressive uniformity of size, the use of metal nanoparticles as new catalysts for a variety of important chemical reactions is unsurprising (Chapter One, **Section 1.5.3.1**).

Metal nanoparticles require a stabilising shell of ligands, polymers, or surfactants, or need to be deposited onto a stabilising matrix to prevent their agglomeration to bulk metal; the functionality of the stabiliser has been shown to affect the surface affinity of a nanocatalyst's

substrate. For example, Dupont and co-workers have demonstrated that ruthenium nanoparticles decorated with nitrile-functionalised ionic liquids (ILs) exclusively hydrogenate nitrile-containing aromatic compounds in the presence of other arenes, such as toluene (**Figure 4.2**).¹¹ The observed selectivity is thought to arise from the aromatic arenes being unable to displace the strongly coordinated nitrile-functionalised IL ligands from the metal surface whereas substrates bearing nitrile functionalities are able to coordinate to the metal surface via ligand exchange.

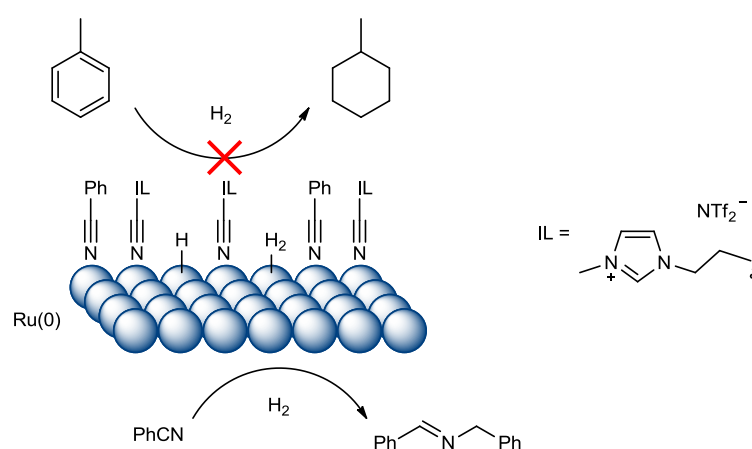


Figure 4.2—Cartoon depicting the selective hydrogenation of nitriles over arenes by ruthenium nanoparticles decorated with nitrile containing ILs. Note that the hydrogenation product of benzonitrile—benzylamine—is rapidly converted to benzylidene benzylamine via aminolysis and coupling.

More recently, Zhu *et al.* have shown that surface modification of Fe₃O₄ metal nanoparticles with EDTA results in catalytic activation of hydrogen peroxide for the removal of organic pollutants, such as pentachlorophenol, from aqueous waste streams (**Figure 4.3**).¹² The strongly coordinated EDTA ligands were shown to bind hydrogen peroxide in close proximity to the nanoparticle surface, through N $\cdots$ H and C(O)O $\cdots$ H hydrogen bonds, allowing for its activation by the metal. Importantly, such catalytic activation by Fe₃O₄ nanoparticles was not observed in the absence of EDTA.

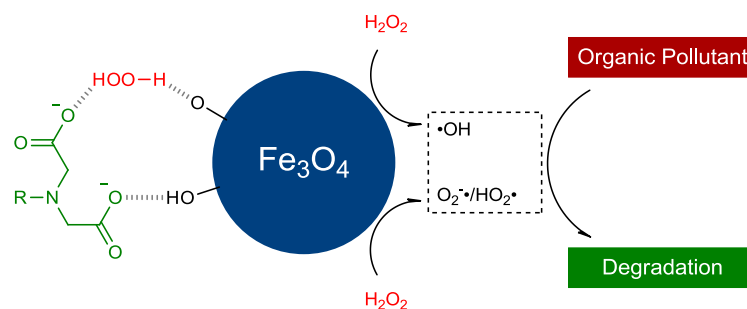


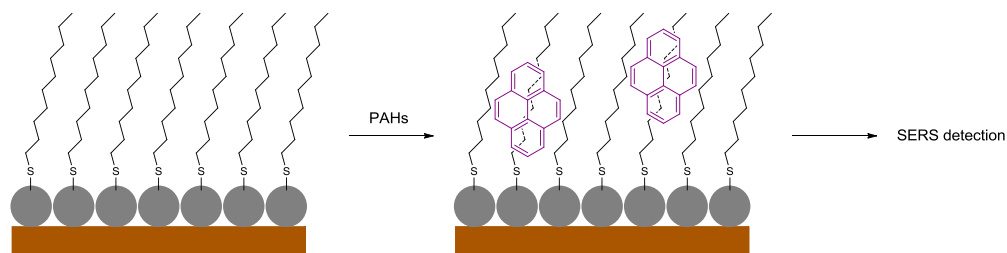
Figure 4.3—Catalytic activation of hydrogen peroxide by EDTA functionalised Fe_3O_4 nanoparticles for the removal of organic pollutants.

4.1.3 Metal nanoparticles and SERS

Ultrasensitive detection of molecular species *via* surface enhanced Raman spectroscopy (SERS) is a growing area of modern research.¹³⁻¹⁵ SERS relies on the molecular species studied being in close contact with a nano-featured metal surface; the excited surface plasmon resonances augment the local electromagnetic field experienced by the molecule resulting in an amplified Raman signal, with enhancements of approximately eight orders of magnitude observed in some cases.¹⁶ With this in mind, it is unsurprising that an array of metal nanoparticle-based SERS sensors have been reported in the literature, as discussed in Chapter One (**Section 1.5.3.2**).

Gold and silver nanoparticles have the most widespread use for SERS applications due to their stability, ease of production and, most importantly, their strong surface plasmon resonance (SPR) in the visible region which is compatible with the laser wavelength of common Raman spectrometers. However, common probe molecules such as alcohols, ethers and non-functionalised aromatics exhibit low affinities for such metals which has resulted in the functionalisation of nanoparticle surfaces with molecular receptors capable of binding the probe species. In this case, host–guest chemistry is exploited to considerably increase exposure of the probe molecule to the local electromagnetic field and give rise to a surface enhanced Raman signal. For example, Haynes and co-workers have used partition layer-

modified silver nanostructured substrates for the SERS detection of polycyclic aromatic hydrocarbons (PAHs), such as anthracene and pyrene, in aqueous solution (**Scheme 4.1**).¹⁷ In their system, the PAHs embed into a mono-layer of 1-decanethiol close enough to the metal surface for a surface enhanced Raman signal to be seen. Importantly, SERS detection was not possible in the absence of the 1-decanethiol partition layer.



Scheme 4.1—SERS detection of PAHs facilitated by partition layer-modified silver substrates.

Gold nanoparticles coated with a thermally responsive poly-(*N*-isopropylacrylamide) microgel (pNIPAM) have been used as similar “molecular traps” for the SERS detection of 1-naphthol.¹⁸ This substrate had previously been unable to be identified *via* SERS due to its low affinity for silver and gold surfaces, however the pNIPAM shell, which can swell or collapse as a function of temperature, was used to trap 1-naphthol sufficiently close to the gold surface to provide a SERS signal.

Finally, the host–guest properties of macrocyclic receptors, such as β -cyclodextrin and calix[4]arene, have also been exploited for SERS detection. For example, Guerrero-Martínez and co-workers have reported SERS chiral recognition and quantification of enantiomers through β -cyclodextrin complexation¹⁹ and Sanchez-Cortes has shown that calix[4]arene functionalised silver nanoparticles are suitable hosts for the SERS detection of pyrene.²⁰

4.1.4 Chapter objectives

This Chapter focuses on exploiting the substrate inclusion properties of β -cyclodextrin in the areas of nanoparticle-based catalysis and SERS sensing. Initially, β -cyclodextrin containing

ligands will be synthesised and used to functionalise the surface of palladium-based catalysts. It is anticipated that this should give rise to interesting selectivities and activities being exhibited by these new catalysts in a number of important chemical reactions. Following this, the potential for β -cyclodextrin appended gold nanoparticles to be used for the SERS detection of a number of chemical species (or *tags*) in aqueous solution will be investigated.

4.2 Catalysis applications

4.2.1 β -Cyclodextrin ligand syntheses and characterisation

A wide range of functional groups have been used to bind ligands to metal nanoparticle surfaces. Thiols²¹⁻²⁴ are the most common due to their inherently strong surface interactions, however ligands containing nitrogen,²⁵⁻²⁸ oxygen²⁹⁻³² and phosphorus³³⁻³⁵ donors have also been reported. With this in mind, two β -cyclodextrin ligands containing amine and dithiolane donors were targeted for palladium metal nanoparticle catalyst synthesis.

Permethylated β -cyclodextrin mono-amine ligand **80** was synthesised *via* an adapted literature procedure (*Scheme 4.2*).³⁶ Commercially available β -cyclodextrin was reacted with tosyl chloride and sodium hydroxide in water kept at 0 °C to form mono-tosylate **77**, which was then refluxed with sodium azide in water overnight to give azide **78**. Methylation of the twenty hydroxyl groups of **78** using iodomethane and sodium hydride in dry DMF afforded the permethylated β -cyclodextrin mono-azide **79**. This was then dissolved in ethanol and stirred with Pd/C (10% by weight) under five atmospheres of hydrogen gas to prepare the target permethylated β -cyclodextrin mono-amine ligand **80** in an overall yield of 10%. Simple EDC coupling of **80** with thioctic acid in dry CH₂Cl₂ afforded mono-dithiolane ligand **81** in 66% yield.

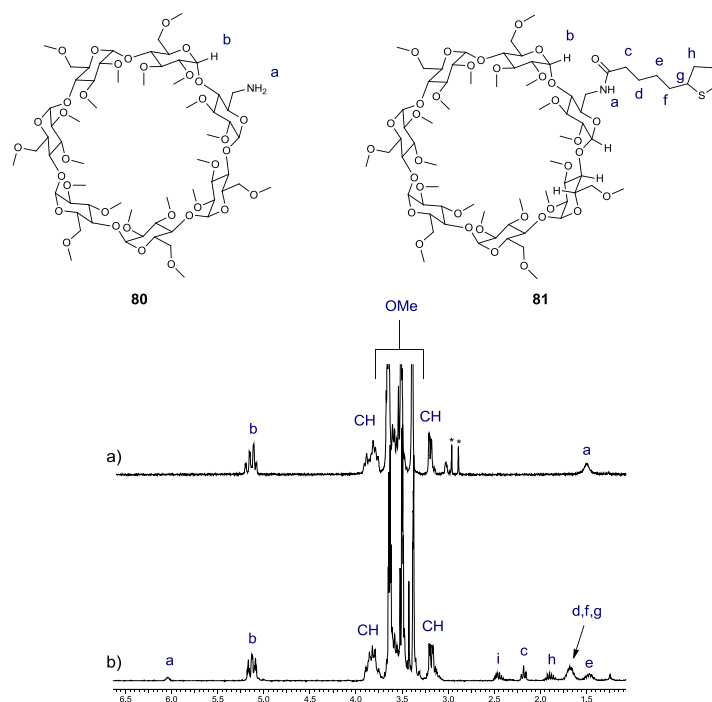


Figure 4.4— ^1H NMR spectra of a) permethylated β -cyclodextrin mono-amine ligand **80** and b) permethylated β -cyclodextrin mono-dithiolane ligand **81** (300 MHz, CDCl_3 , 293 K, peaks marked * correspond to residual DMF solvent).

4.2.2 Catalyst preparation and characterisation

Two industrial samples of support mounted palladium catalysts were provided by Johnson Matthey: palladium on carbon (Pd/C 87L) and palladium on alumina (Pd/ Al_2O_3 Type 324). These catalysts contained naked palladium nanoparticles approximately 2–5 nm in diameter embedded into the support at 5% weight loading and were characterised by X-ray photoelectron spectroscopy (XPS) and transmission electron microscopy (TEM) at JMTC by T. Eralp Erden and Y. Zhao respectively.

XPS is a surface sensitive technique that probes only the outermost atomic layers of a material, giving an overview of their composition, and can be used to determine elemental ratios. The XPS analyses of the Pd/C 87L and Pd/ Al_2O_3 Type 324 catalysts revealed high levels of palladium, as expected, and palladium oxide (**Figure 4.5**). The presence of palladium oxide was unsurprising given the samples had been exposed to air. This will not affect catalytic performance as the reactions to be studied involve the use of hydrogen

(Section 4.2.3) which results in the oxide being reduced *in operando*. High levels of carbon were found in Pd/C 87L, owing to the nature of the support, and trace amounts of chloride, fluoride, sodium, nitrogen and sulfur were observed in both samples.

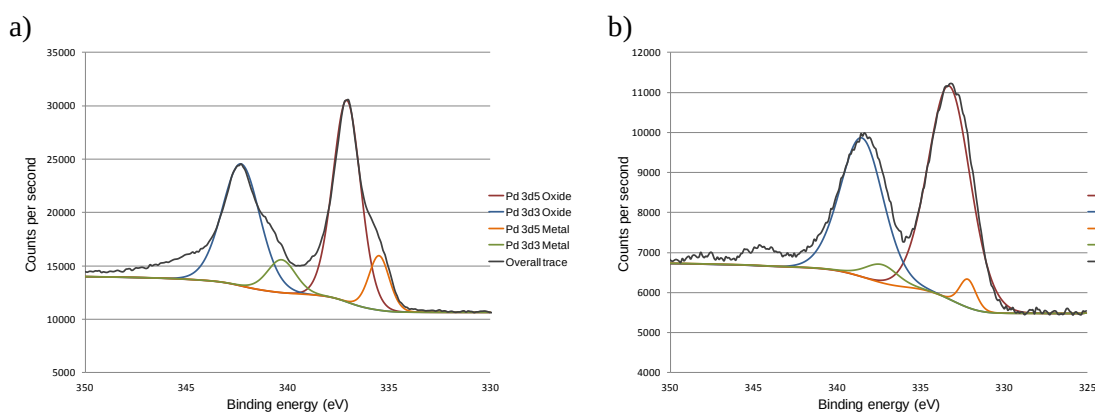


Figure 4.5—Pd and Pd oxide XPS signals for a) 5 wt% Pd/C 87L and b) 5 wt% Pd/Al₂O₃ Type 324 catalysts.

TEM analysis revealed the Pd/Al₂O₃ catalyst to have larger particles: Pd/C 87L mean diameter = 2.31 nm ($\pm$ 0.80, n = 137), Pd/Al₂O₃ Type 324 mean diameter = 4.50 nm ($\pm$ 1.24, n = 49) (where n = number of particles studied). This is likely to be a result of the greater surface area and more porous nature of the carbon support ($\sim$ 2000 m²g⁻¹ (carbon) vs. $\sim$ 140 m²g⁻¹ (alumina)) allowing for the particles to be more highly dispersed. Selected images of both samples are shown below, with an even distribution of the nanoparticles across the supports clearly evident in both cases (**Figure 4.6**).

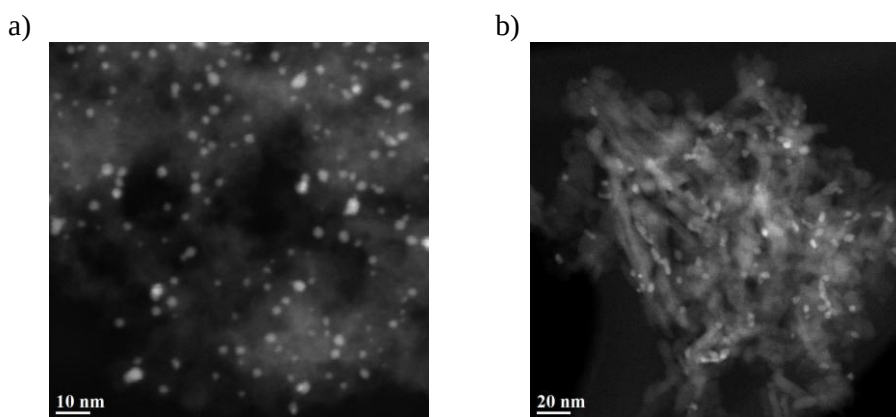


Figure 4.6—TEM images of a) 5 wt% Pd/C 87L and b) 5 wt% Pd/Al₂O₃ Type 324 catalysts. Note different scales.

A series of modified palladium nanoparticle catalysts with differing surface functionalities were then prepared. The general procedure for this involved the addition of the desired standard catalyst (Pd/C 87L or Pd/Al₂O₃ Type 324) to a solution of the stabilising ligand in toluene (1:1 molar ratio of ligand/metal) which was then stirred for two hours to allow the ligand to adsorb onto the metal surface. The newly functionalised catalyst was then collected by filtration and dried under vacuum. Using this method, Pd/C and Pd/Al₂O₃ catalysts functionalised with β -cyclodextrin mono-amine and mono-dithiolane ligands **80** and **81**, and also oleylamine (**Figure 4.7**), were isolated. The oleylamine catalysts were intended to act as control systems to confirm that any interesting catalytic results obtained with the β -cyclodextrin surface modified catalysts arise from the cyclodextrin's substrate inclusion properties and are not a result of more general steric and electronic ligand effects.

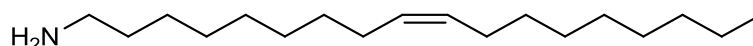


Figure 4.7—Oleylamine ligand for palladium nanoparticle catalyst surface functionalisation.

The samples were all subsequently characterised by XPS and TEM; analyses were run by T. Eralp Erden and Y. Zhao (both JMTC) respectively. The XPS analyses confirmed that surface functionalisation had been successful, with higher levels of sulfur (in the case of ligand **81**) or nitrogen (in the case of oleylamine and ligand **80**) being observed when compared with the unfunctionalised standard catalysts (**Figure 4.8**), as quantified by the ratio of these elements to palladium (**Table 4.2**).

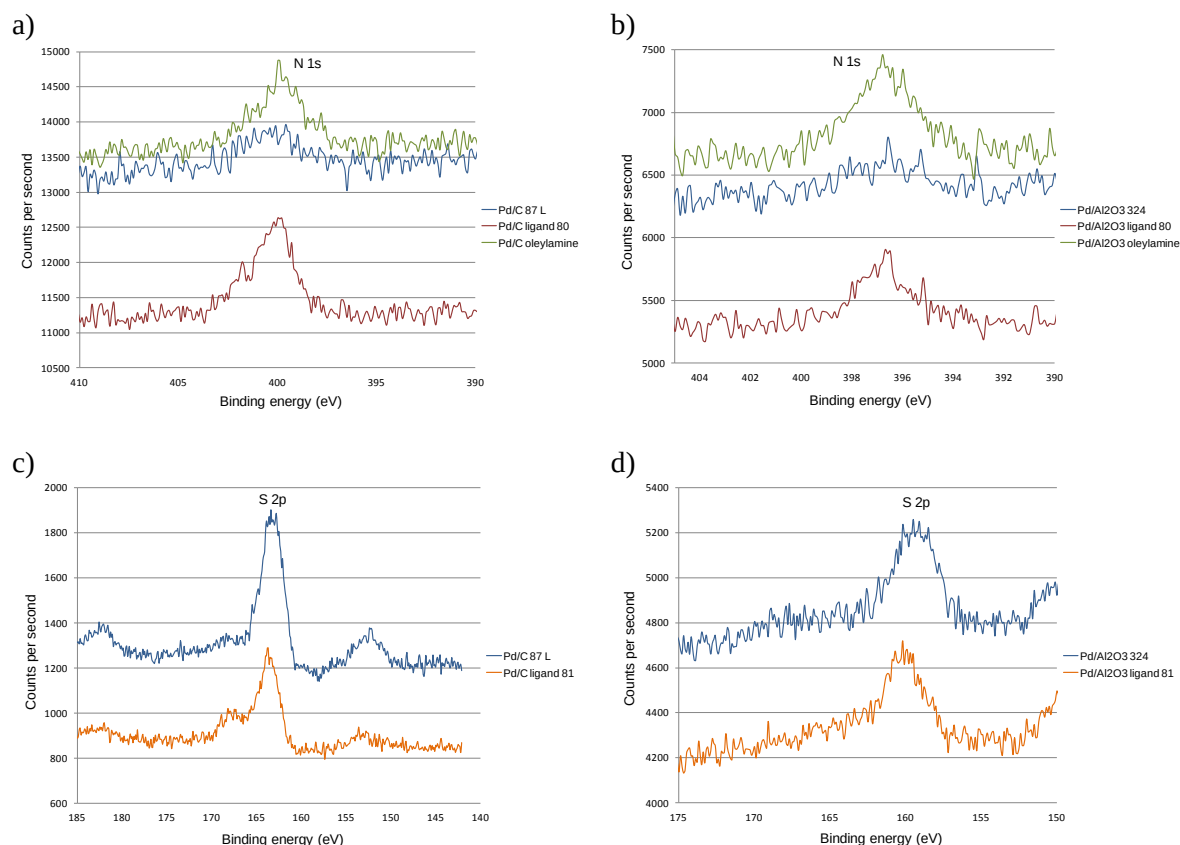


Figure 4.8—N1s and S2p XPS signals for standard and functionalised 5 wt% Pd/C and Pd/Al₂O₃ catalysts.

Table 4.2—Elemental ratios for 5wt% Pd/C and Pd/Al₂O₃ catalysts determined by XPS (Pd(Ox) represents the total palladium content, including Pd oxide).

Catalyst	Pd(Ox):N	Pd(Ox):S
Pd/C 87L	3.23:1	3.72:1
Pd/C ligand 80	0.83:1	—
Pd/C ligand 81	1.51:1	2.20:1
Pd/C oleylamine	1.77:1	3.14:1
Pd/Al ₂ O ₃ Type 324	2.45:1	2.25:1
Pd/Al ₂ O ₃ ligand 80	1.26:1	4.89:1
Pd/Al ₂ O ₃ ligand 81	1.25:1	1.61:1
Pd/Al ₂ O ₃ oleylamine	1.02:1	4.73:1

Studying the TEM images of the new catalysts (**Figure 4.9**) indicated that modifying the surface functionality of the catalysts had, in general, not dramatically altered their size or morphology (**Table 4.3**). A larger mean diameter is observed with the Pd/Al₂O₃ ligand **80**

catalyst, where the particle distribution is more polydisperse, however this is not a significant increase given the small sample size.

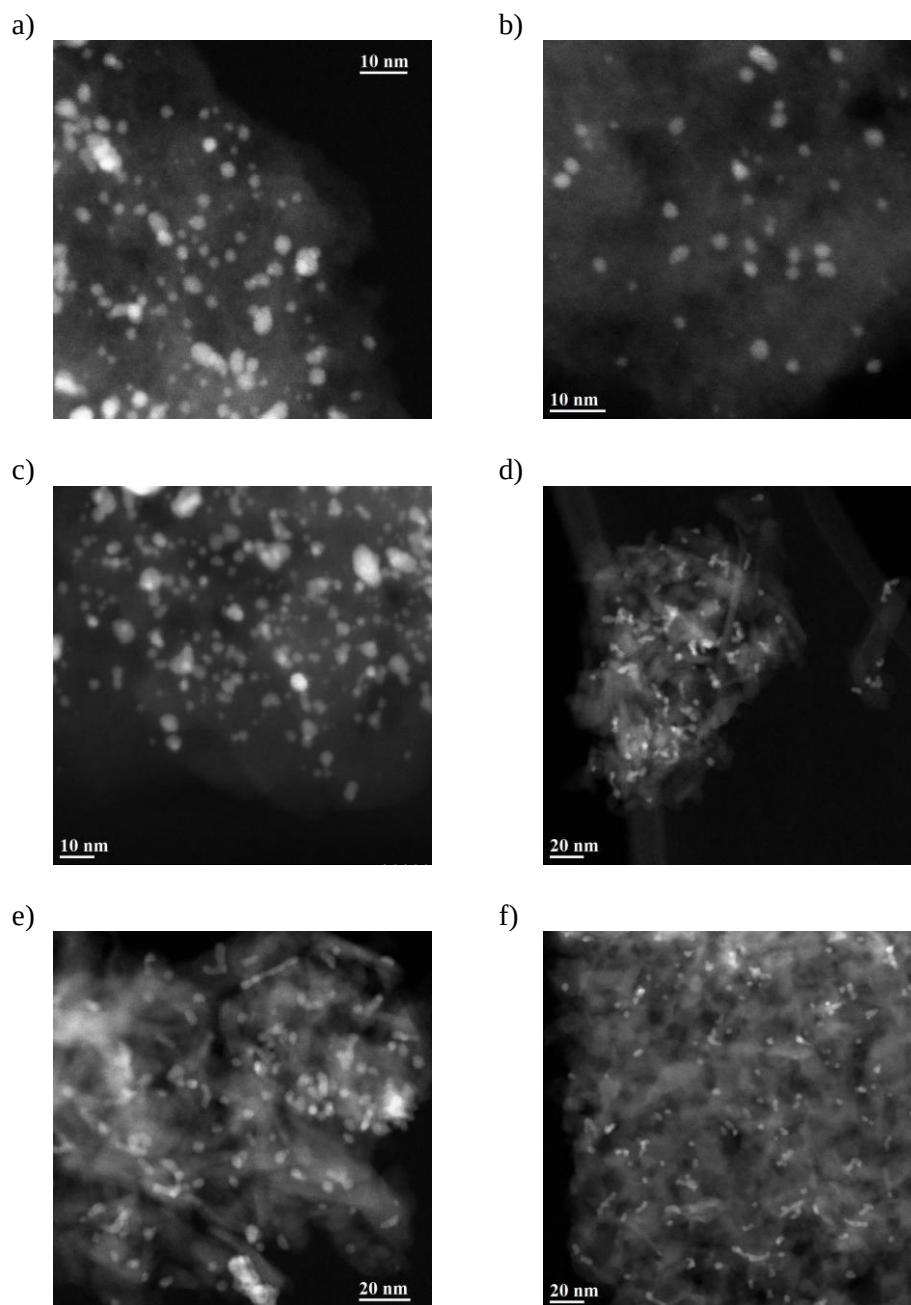


Figure 4.9—TEM images of various 5 wt% Pd catalysts; a) Pd/C ligand **80**, b) Pd/C ligand **81**, c) Pd/C oleylamine, d) Pd/Al₂O₃ ligand **80**, e) Pd/Al₂O₃ ligand **81** and f) Pd/Al₂O₃ oleylamine. Note different scales.

Table 4.3—TEM analyses of 5 wt% Pd/C and Pd/Al₂O₃ catalysts.

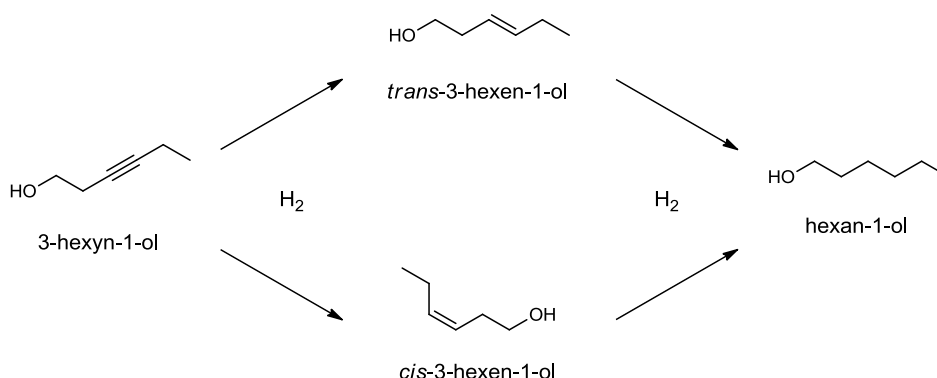
Catalyst	Mean diameter (nm)
Pd/C 87L	2.31 ($\pm$ 0.80, n = 137)
Pd/C ligand 80	2.72 ($\pm$ 1.36, n = 75)
Pd/C ligand 81	2.66 ($\pm$ 0.83, n = 37)
Pd/C oleylamine	3.07 ($\pm$ 1.57, n = 117)
Pd/Al ₂ O ₃ Type 324	4.50 ($\pm$ 1.24, n = 49)
Pd/Al ₂ O ₃ ligand 80	6.02 ($\pm$ 2.68, n = 45)
Pd/Al ₂ O ₃ ligand 81	4.41 ($\pm$ 1.12, n = 65)
Pd/Al ₂ O ₃ oleylamine	4.76 ($\pm$ 2.44, n = 99)

4.2.3 Catalytic testing

All catalytic tests and gas chromatography (GC) analyses reported in this section were performed by C. Brown at JMTC.

4.2.3.1 Hydrogenation of 3-hexyn-1-ol

The hydrogenation of 3-hexyn-1-ol is a common procedure in the fine chemicals industry owing to the partially hydrogenated intermediate *cis*-3-hexen-1-ol, or *leaf alcohol*, having a large global market for its use as a fragrance in perfumes (**Scheme 4.3**).³⁷

**Scheme 4.3**—Hydrogenation pathways of 3-hexyn-1-ol.

The effectiveness of Lindlar's catalyst for selective hydrogenations has been known for some time.³⁸ This mixed-metal Pd-Pb/CaCO₃ system converts alkynes to *cis*-alkenes in high yields

and is the catalyst of choice for the commercial synthesis of leaf alcohol. With this in mind, a commercially available sample of Lindlar's catalyst (Pd-Pb/CaCO₃ A305060-5) was used as a standard for comparison with the surface functionalised catalysts prepared in **Section 4.2.2**.

4.2.3.1.1 Testing in organic solution

Initial catalytic tests were undertaken using 5 mol% of the Pd/C catalysts in 5 mL of ethanol. The reactions were run in a HEL ChemSCAN at 30 °C under 3 bar of H₂ for 200 minutes, after which time the mixture was filtered to remove the catalyst and the resultant solution composition analysed by GC. The reaction progress was monitored by plotting the hydrogen volume uptake as a function of time (**Figure 4.10**).

The maximum hydrogen uptake volume (~120 mL) corresponds to the amount of hydrogen needed to completely convert the 3-hexyn-1-ol starting material to the product alkane, hexan-1-ol. The uptake of half this volume represents the point in the reaction at which 3-hexyn-1-ol has been hydrogenated to *cis*- and/or *trans*-3-hexen-1-ol. Therefore, an uptake curve that follows a straight line to the maximum uptake volume infers that the catalyst has converted 3-hexyn-1-ol to hexan-1-ol, whereas an uptake curve that has a noticeable decrease in gradient at half the maximum uptake volume indicates the catalyst is selective for the intermediate alkene product.

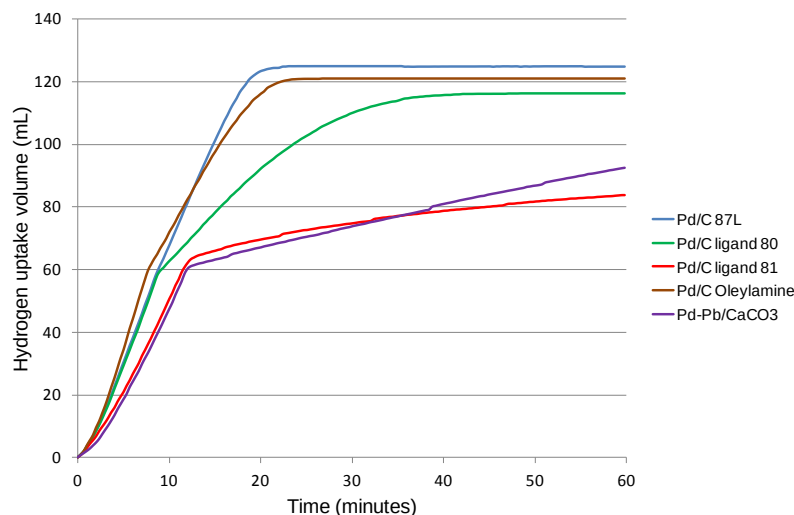


Figure 4.10—Hydrogen uptake curves for the first 60 minutes of the hydrogenation of 3-hexyn-1-ol using Pd/C and Lindlar's catalysts (5 mol% catalyst, 30 °C, EtOH, 3 bar H_2).

For the Pd/C ligand **81** catalyst, it can be seen that the rate of hydrogen uptake once the alkene has been formed is considerably lower than for the other catalysts, suggesting that this system is retarding the formation of 1-hexanol and can be thought of as alkene selective. Importantly, this behaviour is very similar to Lindlar's catalyst (Pd-Pb/CaCO₃), whereas the uptake curves for the other catalysts studied indicate they do not exhibit such selectivity.

The selectivity of a catalyst for the alkene product can be quantified by the value of k_2/k_1 ; k_1 is the initial rate of hydrogen uptake (mL/min) calculated between 2–7 minutes of reaction and k_2 is the rate of hydrogen uptake from when half the maximum uptake volume has been consumed until the maximum uptake volume is reached (**Table 4.4**). A low k_2/k_1 value suggests a preference for the intermediate alkene product and a value ~ 1 indicates that no such selectivity exists.

Table 4.4— k_1 and k_2 values for the hydrogenation of 3-hexyn-1-ol using Pd/C and Lindlar's catalysts (5 mol% catalyst, 30 °C, EtOH, 3 bar H_2).

Catalyst	k_1 (mL/min)	k_2 (mL/min)	k_2/k_1
Pd/C 87L	7.42	6.67	0.90
Pd/C ligand 80	7.23	3.12	0.43
Pd/C ligand 81	5.12	0.72	0.14
Pd/C oleylamine	8.83	5.21	0.59
Pd-Pb/CaCO ₃	5.00	0.68	0.14

Looking at the data for k_1 and k_2 ; it can be seen that the initial rate of hydrogen uptake varies slightly between the Pd/C catalysts but the most dramatic changes are observed for k_2 . In all cases, k_2 was lower for the functionalised systems than for the standard Pd/C 87L catalyst indicating that modifying the surface functionality slows the rate of conversion of the alkene product to hexan-1-ol.

The lowest value of k_2 for these Pd/C systems was obtained with the ligand **81** functionalised catalyst. This, combined with its k_2/k_1 value of 0.14, indicates this catalyst is highly alkene selective and performs almost identically to Lindlar's catalyst as suggested previously by the hydrogen uptake curves (**Figure 4.10**). This implies that the presence of β -cyclodextrin is perhaps hindering the approach of the alkene and retarding the rate of its conversion to hexan-1-ol. However, the catalyst functionalised with β -cyclodextrin mono-amine ligand **80** displayed only modest alkene preference, so perhaps the different donor atoms and chain lengths (from donor atom to β -cyclodextrin) of ligands **80** and **81** are also having an effect on selectivity.

Importantly, the standard Pd/C 87L and oleylamine functionalised catalysts displayed no alkene selectivity, indicating that the results obtained for the Pd/C ligand **80** and ligand **81** catalysts arise solely from the presence of the β -cyclodextrin ligands.

Identical catalytic tests were undertaken with the analogous Pd/Al₂O₃ catalysts. The hydrogen uptake curves and k_2/k_1 values are shown in **Figure 4.11** and **Table 4.5** respectively.

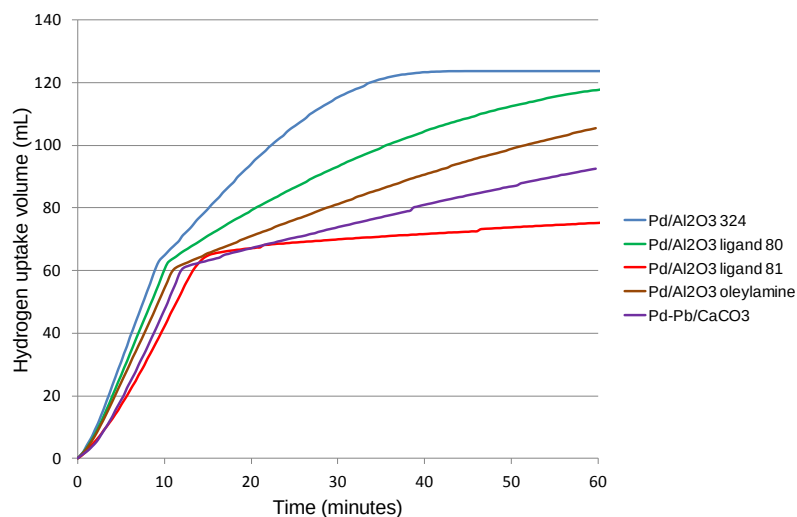


Figure 4.11—Hydrogen uptake curves for the first 60 minutes of the hydrogenation of 3-hexyn-1-ol using Pd/Al₂O₃ and Lindlar's catalysts (5 mol% catalyst, 30 °C, EtOH, 3 bar H₂).

Table 4.5— k_1 and k_2 values for the hydrogenation of 3-hexyn-1-ol using Pd/Al₂O₃ and Lindlar's catalysts (5 mol% catalyst, 30 °C, EtOH, 3 bar H₂).

Catalyst	k_1 (mL/min)	k_2 (mL/min)	k_2/k_1
Pd/Al ₂ O ₃ Type 324	7.33	2.87	0.39
Pd/Al ₂ O ₃ ligand 80	6.45	1.62	0.25
Pd/Al ₂ O ₃ ligand 81	4.21	0.43	0.10
Pd/Al ₂ O ₃ oleylamine	5.75	1.09	0.19
Pd-Pb/CaCO ₃	5.00	0.68	0.14

In contrast to their Pd/C analogues, selectivity for the intermediate product is exhibited by all of the Pd/Al₂O₃ catalysts. This could possibly be due to the lower surface area of the alumina catalysts resulting in a diminished extent of hydrogenation. In addition, the lower porosity of the alumina support may have allowed a greater extent of the metal surface to be functionalised by the ligands, which were previously all shown to lower k_2 (**Table 4.4**). Importantly, the β -cyclodextrin functionalised catalysts display impressive alkene selectivity, especially in the case of the Pd/Al₂O₃ ligand **81** catalyst, which has a k_2/k_1 value lower than

Lindlar's catalyst. Interestingly, the oleylamine catalyst also displays a preference for the alkene, unlike its Pd/C analogue, with this likely due to the surface area argument highlighted previously.

GC analyses of the completed reaction mixtures revealed the major product to be 1-hexanol in all cases. This was expected as the maximum hydrogen uptake volume had been reached, or almost reached, in all of the reactions. Unfortunately, the apparatus used to perform these catalytic tests did not allow for GC measurements to be monitored throughout the reaction and so it was not possible to determine whether the desired *cis*-alkene intermediate product was being formed preferentially during the initial stages of the hydrogenation. This resulted in the catalytic tests with the Pd/C and Pd/Al₂O₃ standard and ligand **81** functionalised samples being repeated with the reaction progress stopped after the uptake of 55 mL of hydrogen. The GC analyses from these reactions are shown below (**Figure 4.12**).

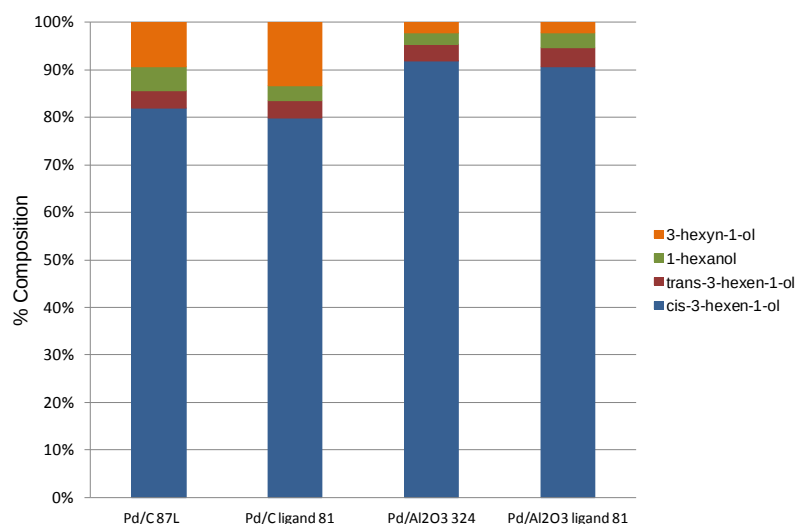


Figure 4.12—Reaction composition analyses for the hydrogenation of 3-hexyn-1-ol using selected Pd/C and Pd/Al₂O₃ catalysts after uptake of 55 mL of H₂ (5 mol% catalyst, 30 °C, EtOH, 3 bar H₂, normalised).

All of the catalysts gave the desired *cis*-alkene as the dominant product with high conversions of 91% (Pd/C 87L), 87% (Pd/C ligand **81**), 98% (Pd/Al₂O₃ 324) and 98% (Pd/Al₂O₃ ligand **81**). Interestingly, the presence of the β -cyclodextrin ligand has next to no influence on the

product distribution at this stage of the reaction, suggesting it has little effect on the conversion of 3-hexyn-1-ol to *cis*-3-hexen-1-ol and confirming the notion that the alkene selectivity observed previously is almost entirely a result of the ligand retarding the conversion of the alkene into hexan-1-ol. It is important to note that whilst these GC results suggest that using the standard Pd/C 87L and Pd/Al₂O₃ catalysts and stopping the reaction early would afford the desired product and render the functionalised catalysts redundant, this would not be practical industrially as this requires careful monitoring of the reaction composition and immediate extraction of the product before it is over-hydrogenated.

In summary, it has been shown that modifying the surface functionality of Pd/C and Pd/Al₂O₃ catalysts alters their selectivity for the catalytic hydrogenation of 3-hexyn-1-ol. Importantly, the systems containing β -cyclodextrin ligands **80** and **81** were found to exhibit a preference for the intermediate alkene, with those functionalised with mono-dithiolane ligand **81** found to be the most alkene selective. This suggests that the presence of the β -cyclodextrin ligands diminishes the rate of conversion of the alkene to the alkane, with the variation between the two ligands possibly due to their different surface attached chain lengths and donor atoms. Comparison of the Pd/C systems with their Pd/Al₂O₃ analogues showed that the alumina supporting catalysts were more alkene biased. This is thought to be due to the relative surface areas of the catalysts; Pd/C is known to have a greater surface area than Pd/Al₂O₃ and so should give rise to a greater extent of hydrogenation and a lesser extent of ligand functionalisation.

4.2.3.1.2 Testing in the presence of water

Cyclodextrins are known to form inclusion complexes with hydrophobic guests in aqueous solution (**Section 4.1.1**). With this in mind, it was anticipated that repeating the hydrogenation of 3-hexyn-1-ol in the presence of water could affect the inclusion properties

of the β -cyclodextrin functionalised catalysts, which in turn would alter their catalytic performance.

Preliminary investigations were undertaken in 10% water/ethanol using 5 mol% catalyst (3 bar H_2 , 30 °C, 200 minutes reaction time). The hydrogen uptake curves and k_2/k_1 values for the Pd/C systems are shown below (**Figure 4.13** and **Table 4.6**); Lindlar's catalyst was again included as a standard.

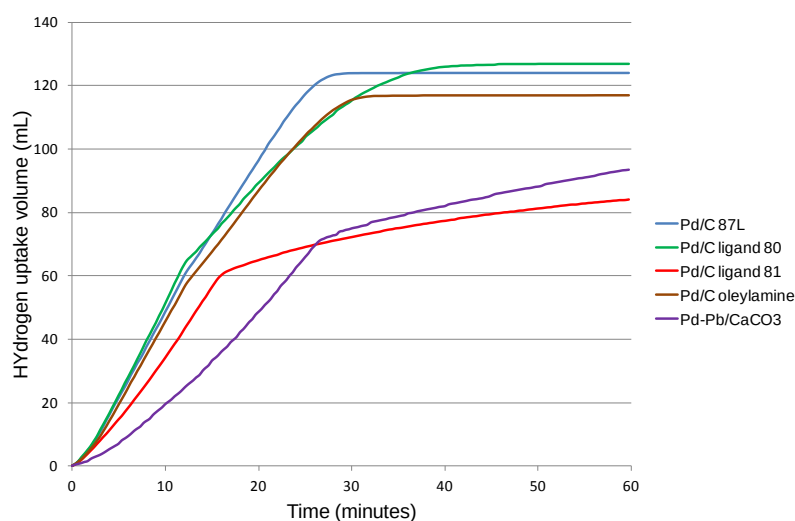


Figure 4.13—Hydrogen uptake curves for the first 60 minutes of the hydrogenation of 3-hexyn-1-ol using Pd/C and Lindlar's catalysts (5 mol% catalyst, 30 °C, 9:1 EtOH/ H_2O , 3 bar H_2).

Table 4.6— k_1 and k_2 values for the hydrogenation of 3-hexyn-1-ol using Pd/C and Lindlar's catalysts (5 mol% catalyst, 30 °C, 9:1 EtOH/ H_2O , 3 bar H_2).

Catalyst	k_1 (mL/min)	k_2 (mL/min)	k_2/k_1
Pd/C 87L	5.27	4.61	0.87
Pd/C ligand 80	5.48	3.27	0.60
Pd/C ligand 81	3.45	0.53	0.15
Pd/C oleylamine	4.90	3.85	0.79
Pd-Pb/ $CaCO_3$	1.91	0.70	0.37

Comparison of the data shown in **Table 4.6** with that obtained in ethanol (**Table 4.4**) clearly shows the addition of water has reduced the initial rate of hydrogen uptake (k_1) in all cases.

This can be accounted for by the reduced solubility of hydrogen in water as compared to ethanol.³⁹ The values for k_2 are also reduced, for the same reason, although to a lesser extent. As with the tests performed in organic solution (**Table 4.4**), the β -cyclodextrin functionalised catalysts displayed selectivity for the alkene product, albeit only slightly in the case of the catalyst functionalised with ligand **80**. The Pd/C 87L and oleylamine containing catalysts were found not to be alkene biased, confirming that the observed selectivities were a direct result of the β -cyclodextrin ligands. Again, the catalyst functionalised with β -cyclodextrin mono-dithiolane ligand **81** was found to be the most alkene selective. Importantly, in the presence of water, this catalyst performed better than Lindlar's catalyst, which had become less alkene selective. This could possibly be a result of the active species from the Lindlar's catalyst leeching into solution in the presence of water. Identical catalytic tests were then performed with the Pd/Al₂O₃ catalysts, the hydrogen uptake curves and quantitative rate data are shown below (**Figure 4.14** and **Table 4.7**).

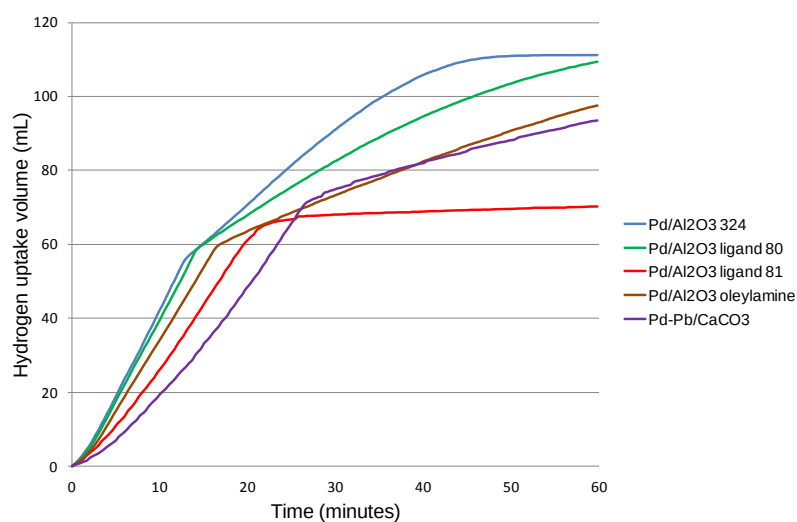


Figure 4.14—Hydrogen uptake curves for the first 60 minutes of the hydrogenation of 3-hexyn-1-ol using Pd/Al₂O₃ and Lindlar's catalysts (5 mol% catalyst, 30 °C, 9:1 EtOH/H₂O, 3 bar H₂).

Table 4.7— k_1 and k_2 values for the hydrogenation of 3-hexyn-1-ol using Pd/Al₂O₃ and Lindlar's catalysts (5 mol% catalyst, 30 °C, 9:1 EtOH/H₂O, 3 bar H₂).

Catalyst	k_1 (mL/min)	k_2 (mL/min)	k_2/k_1
Pd/Al ₂ O ₃ Type 324	4.49	2.14	0.48
Pd/Al ₂ O ₃ ligand 80	4.35	1.47	0.34
Pd/Al ₂ O ₃ ligand 81	2.62	0.05	0.02
Pd/Al ₂ O ₃ oleylamine	3.75	0.90	0.24
Pd-Pb/CaCO ₃	1.91	0.70	0.37

The addition of water has again reduced the rates of hydrogen uptake whilst, in general, having little effect on the selectivities of the Pd/Al₂O₃ systems, as was the case with the Pd/C analogues (**Table 4.5** and **Table 4.7**). However, the Pd/Al₂O₃ ligand **81** catalyst was found to be remarkably more selective for the desired alkene product ($k_2/k_1 = 0.10$ (no water), 0.02 (10% water)) as a result of a dramatic decrease in k_2 from 0.43 (no water) to 0.05 (10% water). This interesting behaviour is difficult to rationalise, given that similar observations were not made with the Pd/C analogue.

GC analysis of the reaction mixtures from the completed catalytic tests showed hexan-1-ol to be the major product for all of the Pd/C and Pd/Al₂O₃ systems. As before, in order to ascertain whether the desired *cis*-alkene was being formed preferentially, catalytic tests with Pd/C 87L, Pd/C ligand **81** and their Pd/Al₂O₃ analogues that ran until the addition of 55 mL of hydrogen were performed. The desired *cis*-alkene was found to be the major product in all cases (**Figure 4.15**).

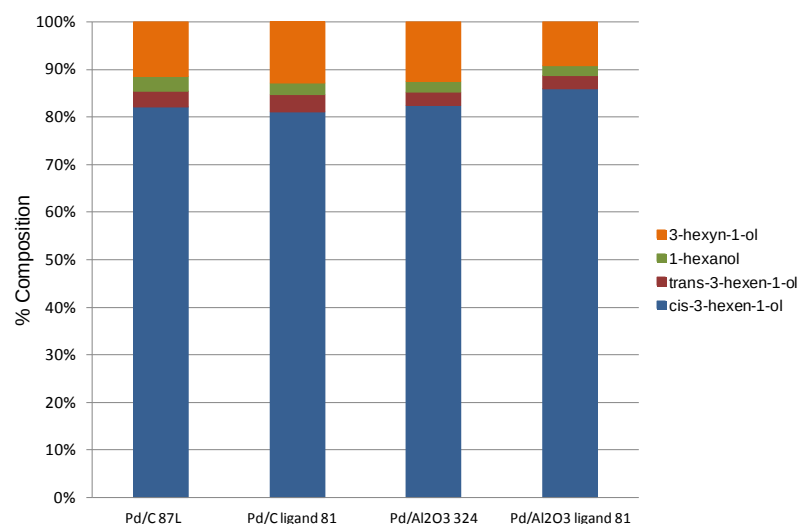


Figure 4.15—Reaction composition analyses for the hydrogenation of 3-hexyn-1-ol using selected Pd/C and Pd/Al₂O₃ catalysts after uptake of 55 mL of H₂ (5 mol% catalyst, 30 °C, 9:1 EtOH/H₂O, 3 bar H₂, normalised).

These preliminary investigations have shown that the performances of the Pd catalysts are influenced by the addition of water to the reaction solvent, with slower rates of hydrogen uptake observed in all cases. This was attributed to the lower solubility of hydrogen in water as compared to ethanol. Interestingly, in the presence of water, the Pd/Al₂O₃ β -cyclodextrin mono-dithiolane ligand **81** functionalised catalyst became more alkene selective whilst Lindlar's catalyst, in contrast, became less selective and the preferences of the remaining catalysts were unaffected. Given these observations, it was decided to further investigate the effects of using an aqueous solvent mixture on the performance of the Pd/Al₂O₃ ligand **81** catalyst for the hydrogenation of 3-hexyn-1-ol. Different proportions of water were added to the reaction solvent in an attempt to find a ratio of water:ethanol that optimised alkene selectivity.

Catalytic tests were undertaken using 5 mol% of the catalyst and a solvent volume of 5 mL (30 °C, 3 bar of H₂, 120 minutes). The reaction progress was monitored by plotting the hydrogen volume uptake as a function of time (**Figure 4.16**) with the corresponding quantitative rate data shown in **Table 4.8**.

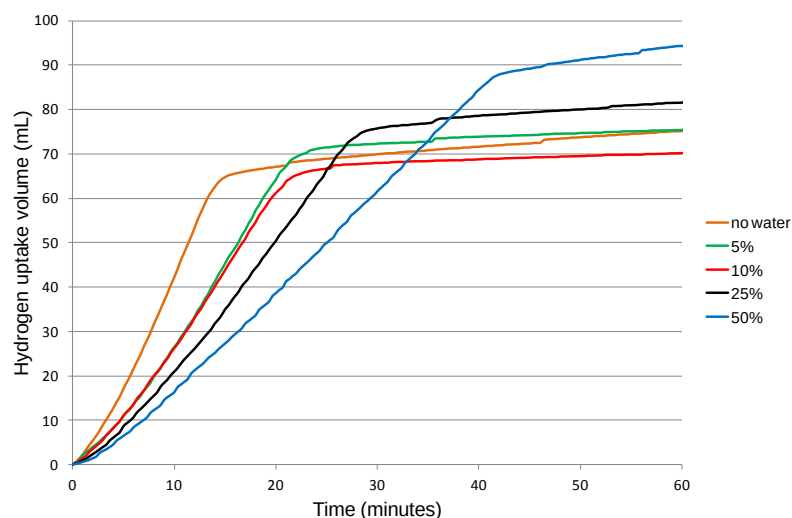


Figure 4.16—Hydrogen uptake curves for the first 60 minutes of the hydrogenation of 3-hexyn-1-ol using β -cyclodextrin ligand **81** functionalised Pd/Al₂O₃ catalyst in a mixed ethanol/water reaction solvent of differing water % (5 mol% catalyst, 30 °C, 3 bar H₂).

Table 4.8— k_1 and k_2 values for hydrogenation of 3-hexyn-1-ol using Pd/Al₂O₃ ligand **81** catalyst in a mixed ethanol/water reaction solvent of differing water % (5 mol% catalyst, 30 °C, 3 bar H₂).

Proportion of water	k_1 (mL/min)	k_2 (mL/min)	k_2/k_1
No water	4.21	0.43	0.10
5%	2.52	0.12	0.05
10%	2.62	0.05	0.02
25%	2.16	0.24	0.11
50%	1.72	0.32	0.19

Importantly, changing the proportion of water in the reaction solvent can be seen to have a clear effect on catalytic performance. For k_1 , increasing the water content decreases the initial rate of hydrogen uptake, whereas its effect on k_2 is more complicated; from 0–10% the conversion of alkene to alkane is retarded but from 10–50% it is enhanced. Due to the interplay of these two factors, the greatest degree of alkene selectivity was observed in 10% water/ethanol.

The former can be easily explained by the decreased solubility of hydrogen in the solvent as the proportion of water increases, whereas the latter is more difficult to rationalise and could perhaps be a result of a combination of hydrogen solubility and substrate inclusion by the

β -cyclodextrin ligand being solvent dependent. It is possible that, as the percentage of water increases, binding of the alkene product by the ligand is enhanced causing a greater extent of hydrogenation. In the future, ^1H NMR titration experiments could be performed to investigate the effect of water content on the substrate inclusion properties of β -cyclodextrin derivative **81**, the results of which might help explain the above observations.

4.2.3.1.3 Summary

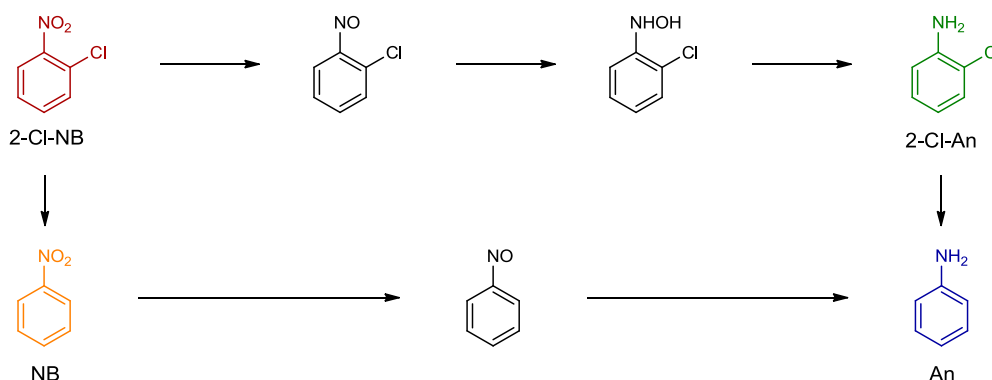
The performance of a series of Pd/C and Pd/Al₂O₃ catalysts for the solution phase hydrogenation of 3-hexyn-1-ol has been investigated. Functionalising the surface of standard catalysts with β -cyclodextrin containing ligands was found to enhance their preference for the desired alkene product, with the Pd/Al₂O₃ β -cyclodextrin mono-dithiolane ligand **81** catalyst exhibiting superior alkene selectivity to the commercially used lead-containing Lindlar's catalyst. The observed selectivities resulted from these catalysts slowing the rate of conversion of the alkene to hexan-1-ol. Importantly, no such selectivity was exhibited by the standard or the oleylamine functionalised control catalysts confirming that these observations arise directly from the presence of the β -cyclodextrin ligands.

Cyclodextrins are known to form inclusion complexes with hydrophobic guests in aqueous media and so investigations into the effect of adding water to the reaction solvent were undertaken. This resulted in the Pd/Al₂O₃ ligand **81** functionalised catalyst displaying increased alkene bias whereas, crucially, the opposite trend was observed with Lindlar's catalyst. Further catalytic investigations confirmed 10% water/ethanol to be the optimal aqueous solvent mixture for the conversion of 3-hexyn-1-ol to leaf alcohol by the Pd/Al₂O₃ ligand **81** functionalised catalyst.

4.2.3.2 Reduction of chloro-nitrobenzene

4.2.3.2.1 2-Chloro-nitrobenzene

The catalytic reduction of chloro-nitrobenzene to chloro-aniline is an important commercial reaction; haloanilines are used in the synthesis of pharmaceuticals, polymers, dyes and agricultural chemicals. However, this reaction is known for its tendency to produce side products through dehalogenation, which is not only wasteful but dangerous due to the highly toxic nature of these substances. A simplified outline of the possible reduction routes of 2-chloro-nitrobenzene (2-Cl-NB) is shown below (**Scheme 4.4**), with substances relevant to this work highlighted. It is clear to see that if the reaction begins with dehalogenation to give nitrobenzene (NB) then the desired 2-chloro-aniline (2-Cl-An) cannot be obtained, instead only aniline (An) can be formed.



Scheme 4.4—Possible reduction pathways of 2-chloro-nitrobenzene.

In the literature, efforts have been focussed on obtaining highly active, selective and low cost catalysts for this reaction. Platinum systems display good selectivity but their increased cost is less desirable.⁴⁰ Palladium catalysts do not perform as well but are more economically viable; as a result attempts to improve performance by altering the support material have been undertaken.⁴⁰⁻⁴³

With this in mind, the abilities of the Pd/C and Pd/Al₂O₃ catalysts synthesised in **Section 4.2.2** to catalyse the reduction of 2-Cl-NB were investigated. As β -cyclodextrin is known to form inclusion complexes with nitro-functionalised aromatic guests,⁹ it was hoped that the catalysts decorated with β -cyclodextrin ligands **80** and **81** would exhibit differing selectivities to the standard and oleylamine catalysts through the action of 2-Cl-NB binding within the cyclodextrin cavities.

Tests were undertaken in a HEL ChemSCAN at 50 °C under 3 bar H₂ in ethanol using 5 mol% of the respective catalyst for 90 minutes. After this time, the hydrogen uptake curves indicated that the reactions had gone to completion, with the exception of the two reactions run in the presence of the ligand **81** functionalised catalysts which appeared to be inactive (**Figure 4.17**). The reaction mixtures were then filtered to remove the catalysts and the solution compositions analysed by gas chromatography (**Figure 4.18** and **Table 4.9**).

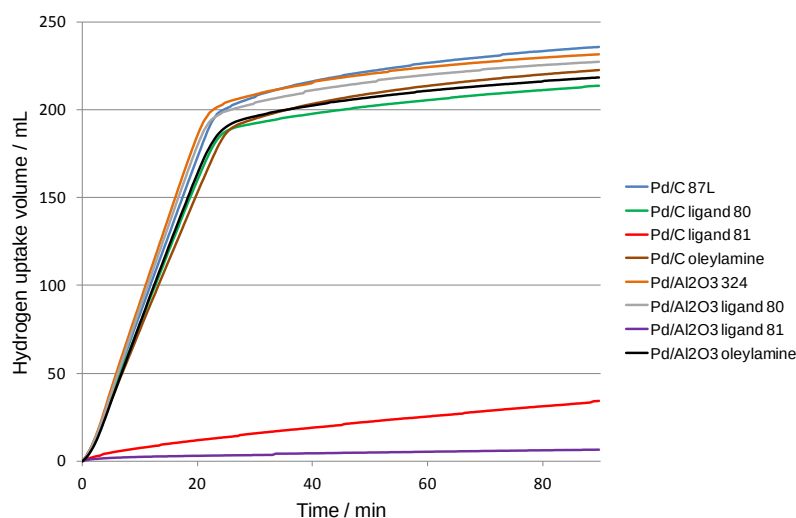


Figure 4.17—Hydrogen uptake curves for the reduction of 2-Cl-NB catalysed by Pd/C and Pd/Al₂O₃ catalysts (5 mol% catalyst, 90 min, 50 °C, EtOH).

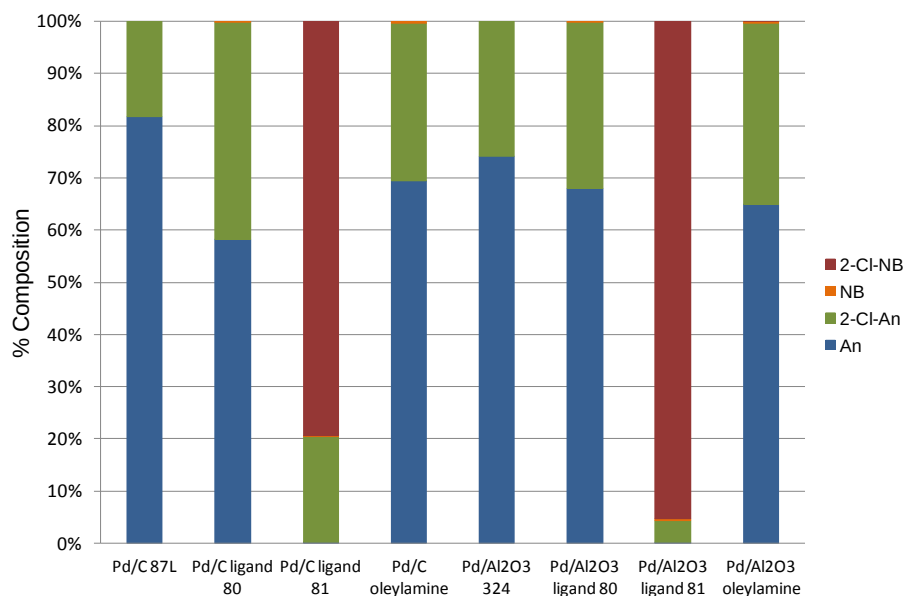


Figure 4.18—Reaction composition analyses for the reduction of 2-Cl-NB catalysed by Pd/C and Pd/Al₂O₃ catalysts (5 mol% catalyst, 3 bar H₂, 90 min, 50 °C, EtOH, normalised).

Table 4.9—Reaction composition (%) and 2-Cl-An:An ratios for the reduction of 2-Cl-NB catalysed by Pd/C and Pd/Al₂O₃ catalysts (5 mol% catalyst, 3 bar H₂, 90 min, 50 °C, EtOH, normalised).

Catalyst	2-Cl-NB	NB	2-Cl-An	An	2-Cl-An:An
Pd/C 87L	—	—	18.2	81.8	1:4.50
Pd/C ligand 80	—	0.2	41.6	58.2	1:1.40
Pd/C ligand 81	79.4	0.2	20.3	0.1	1:0.01
Pd/C oleylamine	—	0.3	30.2	69.5	1:2.30
Pd/Al ₂ O ₃ Type 324	—	—	25.8	74.2	1:2.87
Pd/Al ₂ O ₃ ligand 80	—	0.2	31.8	67.9	1:2.13
Pd/Al ₂ O ₃ ligand 81	95.3	0.3	4.2	0.2	1:0.05
Pd/Al ₂ O ₃ oleylamine	—	0.2	34.8	64.9	1:1.87

As the hydrogen uptake curves indicated, the catalysts functionalised with β -cyclodextrin mono-dithiolane ligand **81** displayed low activities; conversions of 25% and 11% were observed for the Pd/C and Pd/Al₂O₃ catalysts respectively. It is worth noting that what starting material had reacted in these cases was converted to the desired 2-Cl-An product giving favourable high ratios of 2-Cl-An:An, however such low conversions after 90 minutes of reaction severely limits the use of these catalysts.

In all other cases, dehalogenation was pronounced and product mixtures of aniline and 2-Cl-An were obtained, with aniline always found to be the major product. Importantly, the functionalised catalysts gave better 2-Cl-An:An ratios than the commercial standards, particularly in the case of the Pd/C systems, implying that surface modification is favourable. It can be seen that similar reaction compositions are obtained for the oleylamine and ligand **80** functionalised catalysts which suggests that it is not the inclusion properties of the β -cyclodextrin ligand that are affecting selectivity but more general steric or electronic ligand effects.

4.2.3.2.2 3- and 4-Chloro-nitrobenzene

The applicability of the catalysts was further investigated by studying the different isomers of 2-Cl-NB. Identical test conditions to before were used for the reduction of 3- and 4-chloro-nitrobenzene and the GC solution composition analyses are shown below (3-Cl-NB: *Figure 4.19* and *Table 4.10*, 4-Cl-NB: *Figure 4.20* and *Table 4.11*).

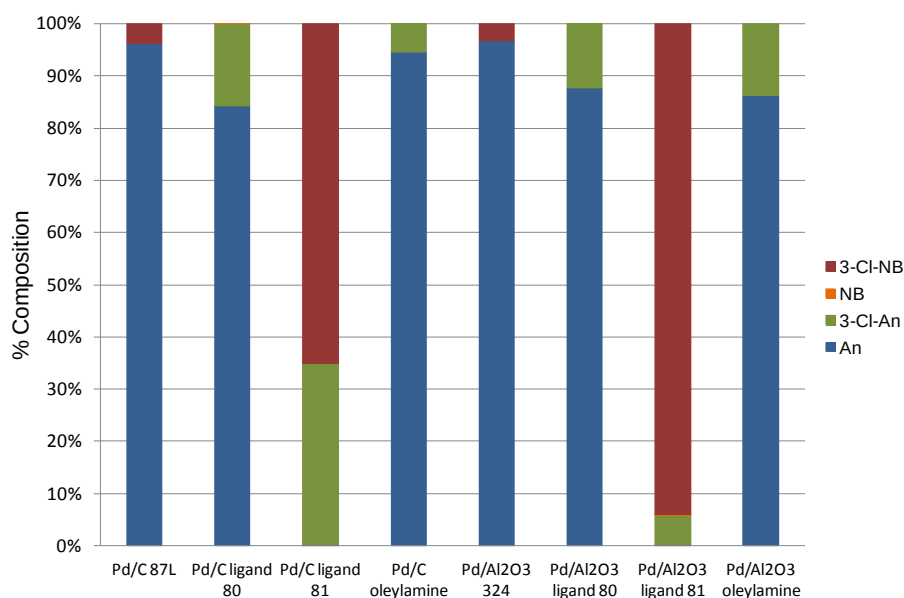


Figure 4.19—Reaction composition analyses for the reduction of 3-Cl-NB catalysed by Pd/C and Pd/Al₂O₃ catalysts (5 mol% catalyst, 3 bar H₂, 90 min, 50 °C, EtOH, normalised).

Table 4.10—Reaction composition (%) and 3-Cl-An:An ratios for the reduction of 3-Cl-NB catalysed by Pd/C and Pd/Al₂O₃ catalysts (5 mol% catalyst, 3 bar H₂, 90 min, 50 °C, EtOH, normalised).

Catalyst	3-Cl-NB	NB	3-Cl-An	An	3-Cl-An:An
Pd/C 87L	3.8	—	—	96.2	—
Pd/C ligand 80	—	—	15.7	84.3	1:5.39
Pd/C ligand 81	65.0	0.1	34.7	0.2	1:0.01
Pd/C oleylamine	—	—	5.4	94.6	1:17.6
Pd/Al ₂ O ₃ Type 324	3.2	—	—	96.8	—
Pd/Al ₂ O ₃ ligand 80	—	—	12.3	87.7	1:7.13
Pd/Al ₂ O ₃ ligand 81	94.1	0.2	5.5	0.3	1:0.05
Pd/Al ₂ O ₃ oleylamine	—	—	13.8	86.2	1:6.26

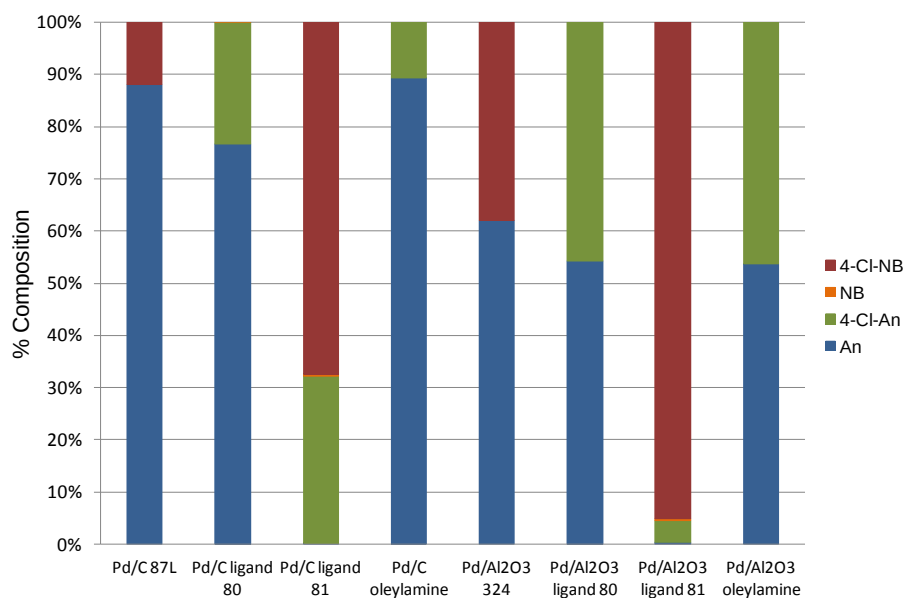
**Figure 4.20**—Reaction composition analyses for the reduction of 4-Cl-NB catalysed by Pd/C and Pd/Al₂O₃ catalysts (5 mol% catalyst, 3 bar H₂, 90 min, 50 °C, EtOH, normalised).

Table 4.11—Reaction composition (%) and 4-Cl-An:An ratios for the reduction of 4-Cl-NB catalysed by Pd/C and Pd/Al₂O₃ catalysts (5 mol% catalyst, 3 bar H₂, 90 min, 50 °C, EtOH, normalised).

Catalyst	4-Cl-NB	NB	4-Cl-An	An	4-Cl-An:An
Pd/C 87L	11.9	—	—	88.1	—
Pd/C ligand 80	—	—	23.3	76.7	1:3.29
Pd/C ligand 81	67.4	0.3	32.1	0.2	1:0.01
Pd/C oleylamine	—	—	10.6	89.4	1:8.43
Pd/Al ₂ O ₃ Type 324	37.9	—	—	62.1	—
Pd/Al ₂ O ₃ ligand 80	—	—	45.7	54.3	1:1.19
Pd/Al ₂ O ₃ ligand 81	95.1	0.3	4.2	0.3	1:0.08
Pd/Al ₂ O ₃ oleylamine	—	—	46.2	53.8	1:1.16

In both cases, the catalysts functionalised with β -cyclodextrin mono-dithiolane ligand **81** again displayed low activities but the small amount of reacted starting material was encouragingly converted to the desired chloro-aniline product.

For the other catalysts, the functionalised systems gave better product distributions than their respective standards, as before, showing that surface functionalisation was favourable. Additionally, the presence of un-reacted starting material when the standard catalysts were used indicates that the functionalised catalysts are more active. As was the case with 2-Cl-An, the similar reaction compositions obtained for the oleylamine and ligand **80** functionalised catalysts imply the substrate inclusion properties of β -cyclodextrin are not affecting selectivity.

4.2.3.2.3 Summary

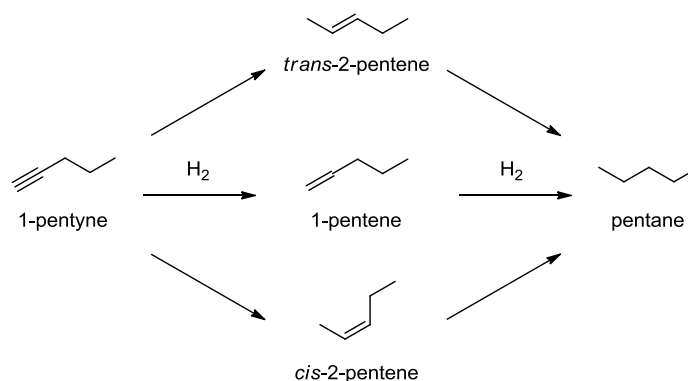
Comparison of the results obtained for the reduction of the three isomers of chloro-nitrobenzene reveals that the surface modified catalysts outperformed their respective standards, with larger ratios of X-Cl-An:An (X = 2, 3, or 4) and higher activities exhibited in all cases. Interestingly, the functionalised Pd/C catalysts were more effective at catalysing the reduction of 2-Cl-NB whereas the Pd/Al₂O₃ catalysts were found to perform best with

4-Cl-NB. Regardless of the substrate, little difference was observed between the oleylamine and ligand **80** functionalised systems implying that the substrate inclusion properties of β -cyclodextrin were having no direct effect on selectivity and that the results obtained arose from more general ligand effects.

Given the high levels of aniline present in all of the reaction mixtures, future work could involve repeating the catalytic tests in the presence of HCl, as this has been shown to significantly reduce dehalogenation.⁴⁴ However, it is worth noting that doing so increases the number of purification steps and can slow the rate of reaction. In addition, given the favourable results obtained in **Section 4.2.3.1.2**, catalytic tests could be performed in the presence of water.

4.2.3.3 Hydrogenation of 1-pentyne

Whilst the substrate inclusion properties of β -cyclodextrin were predominantly intended to affect catalytic performance in solution phase reactions, as discussed in **Sections 4.2.3.1** and **4.2.3.2**, it was also of interest to see if their use would have an effect on vapour phase reactions. As such, the performances of the catalysts synthesised in **Section 4.2.2** for the hydrogenation of 1-pentyne (**Scheme 4.5**) were investigated.



Scheme 4.5—Hydrogenation pathways of 1-pentyne.

The desired product is the partially hydrogenated intermediate, 1-pentene, owing to this type of selective hydrogenation being a vital step in the preparation of polymers in the petrochemical industry.⁴⁵ Other reduction pathways are possible, including migration of the double bond to give either *cis*- or *trans*-2-pentene, as well as over hydrogenation to pentane. Catalytic tests were performed using 5 mol% of the respective catalyst suspended in the centre of a quartz tube through which a mixture of 1-pentyne and 4:6 H₂/He was passed at a flow rate of 200 mL/min. The temperature of the reactive gas stream was gradually increased from 293 K to 523 K and once it had passed over the catalyst bed its composition was analysed by gas chromatography. The product distributions as a function of temperature for the Pd/C and Pd/Al₂O₃ catalysts are shown in **Figure 4.21**.

The standard catalysts (Pd/C 87L and Pd/Al₂O₃ Type 324) display no selectivity for 1-pentene, instead pentane is observed as the major product. At low temperatures the catalysts functionalised with β -cyclodextrin ligands **80** and **81** were found to be selective for the desired 1-pentene product whilst, importantly, the oleylamine analogues were not. This suggests that the observed preference for 1-pentene can be directly attributed to the presence of β -cyclodextrin. The Pd/Al₂O₃ ligand **81** system exhibited unusual behaviour, selectivity for 1-pentene was observed at low (323 K) and high (473 K) temperatures but not at an intermediate temperature (358 K). This action is difficult to rationalise but the results were found to be reproducible. The reaction compositions at low temperature (**Figure 4.22**) and high temperature (**Figure 4.23**) are represented graphically below.

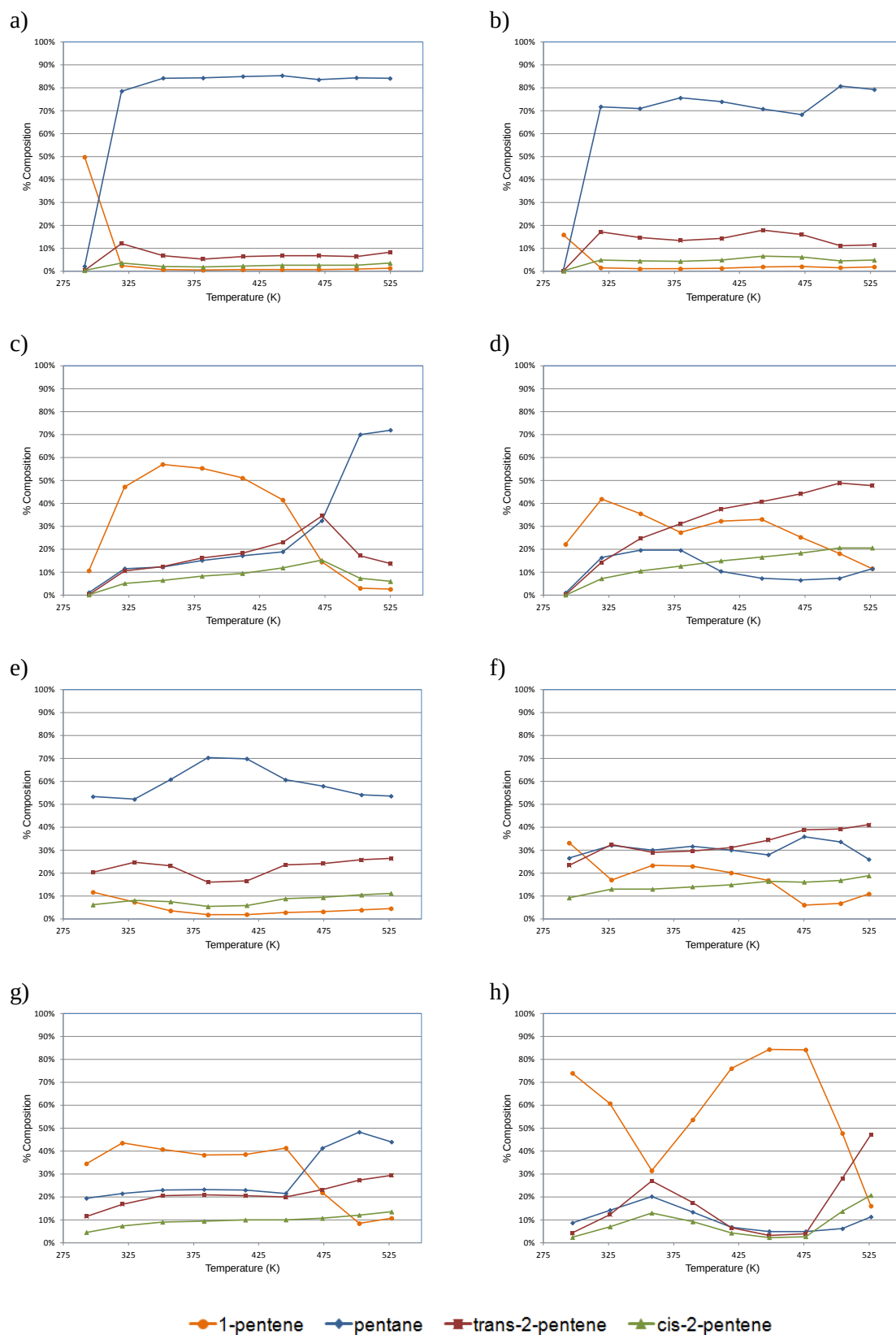


Figure 4.21—Reaction composition analyses for the hydrogenation of 1-pentyne at different reaction temperatures by a) Pd/C 87L, b) Pd/C oleylamine, c) Pd/C ligand **80**, d) Pd/C ligand **81**, e) Pd/Al₂O₃ Type 324, f) Pd/Al₂O₃ oleylamine, g) Pd/Al₂O₃ ligand **80** and h) Pd/Al₂O₃ ligand **81** catalysts (5 mol% catalyst).

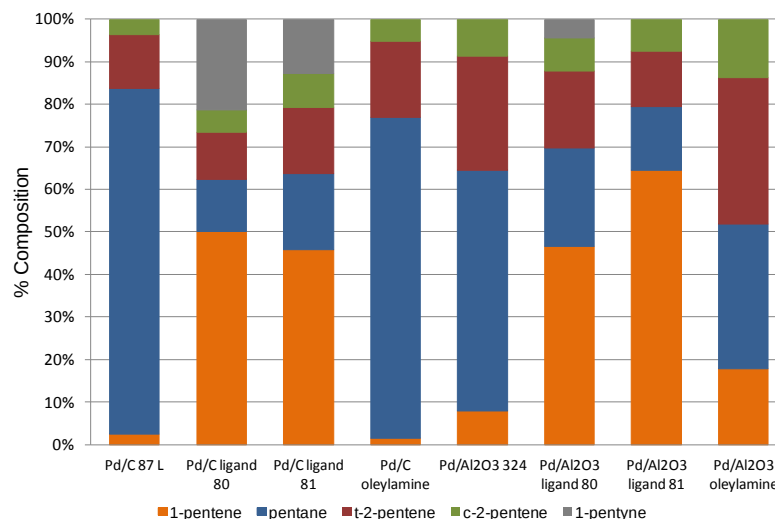


Figure 4.22—Reaction composition analyses for the hydrogenation of 1-pentyne by various Pd catalysts (5 mol% catalyst, 323 K).

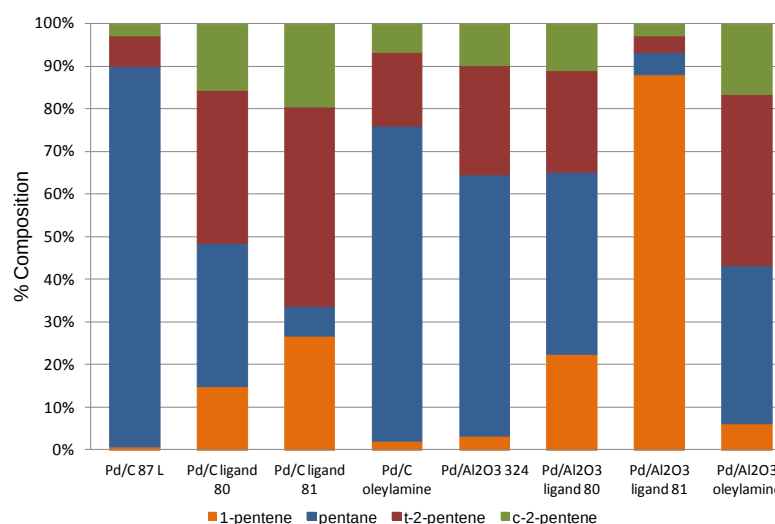


Figure 4.23—Reaction composition analyses for the hydrogenation of 1-pentyne by various Pd catalysts (5 mol% catalyst, 473 K).

At 323 K (**Figure 4.22**), the β -cyclodextrin functionalised catalysts have 45–65% composition of 1-pentene in the product mixture. Whilst these values are not particularly high, it is worth noting that at this lower temperature the 1-pentyne starting material had not been fully consumed. At 473 K (**Figure 4.23**), only the Pd/Al₂O₃ ligand **81** catalyst displayed notable selectivity for 1-pentene, with it making up an impressive 84% of the product distribution. These observations suggest that the presence of β -cyclodextrin enhances the

catalyst's selectivity for 1-pentene, with the cyclodextrin host possibly including the 1-pentyne substrate in such a manner that reduction to 1-pentene is more favourable than the other competing reaction pathways. However, this explanation would not account for the impressive performance of the Pd/Al₂O₃ ligand **81** catalyst at high temperature not being mirrored by its Pd/C or ligand **80** analogues.

4.2.4 Summary

Two β -cyclodextrin containing ligands have been synthesised and used to modify the surface functionality of Pd-based catalysts, resulting in noticeable changes in their ability to catalyse a number of hydrogenation reactions.

The hydrogenation of 3-hexyn-1-ol to the commercially important leaf alcohol (*cis*-3-hexen-1-ol) in ethanol was studied initially; the β -cyclodextrin functionalised catalysts were found to exhibit superior alkene selectivity to their respective unfunctionalised standards and, in the case of the β -cyclodextrin mono-dithiolane ligand **81** containing Pd/Al₂O₃ catalyst, outperform Lindlar's catalyst. Catalytic testing was also performed in the presence of water in the hope of utilising the ability of β -cyclodextrin to include hydrophobic guests. The addition of water was shown to enhance the selectivity of the Pd/Al₂O₃ ligand **81** catalyst for the leaf alcohol product whilst, interestingly, the opposite effect was observed for Lindlar's catalyst. Following this, a systematic study was performed to uncover that 10% water in ethanol was the optimal solvent mixture for the formation of leaf alcohol with the β -cyclodextrin ligand **81** functionalised catalyst.

The effect of using these catalysts for the reduction of the three isomers of chloro-nitrobenzene in ethanol was also studied. The systems functionalised with ligand **81** were found to have very low activities but, encouragingly, the other functionalised catalysts performed better than the commercial standards despite notable dehalogenation. In all cases,

the oleylamine functionalised control catalysts performed similarly to those decorated with β -cyclodextrin ligand **80** implying that the inclusion properties of β -cyclodextrin were having no effect on selectivity and that more general steric or electronic ligand effects were at play.

Finally, the vapour phase hydrogenation of 1-pentyne was studied. It was found that modifying the catalysts' surface functionality again had an effect on performance, with the β -cyclodextrin containing catalysts found to exhibit selectivity for the desired 1-pentene product at low temperatures. The most impressive results were obtained with the Pd/Al₂O₃ ligand **81** catalyst, which was found to be highly selective for 1-pentene at both low and high temperatures.

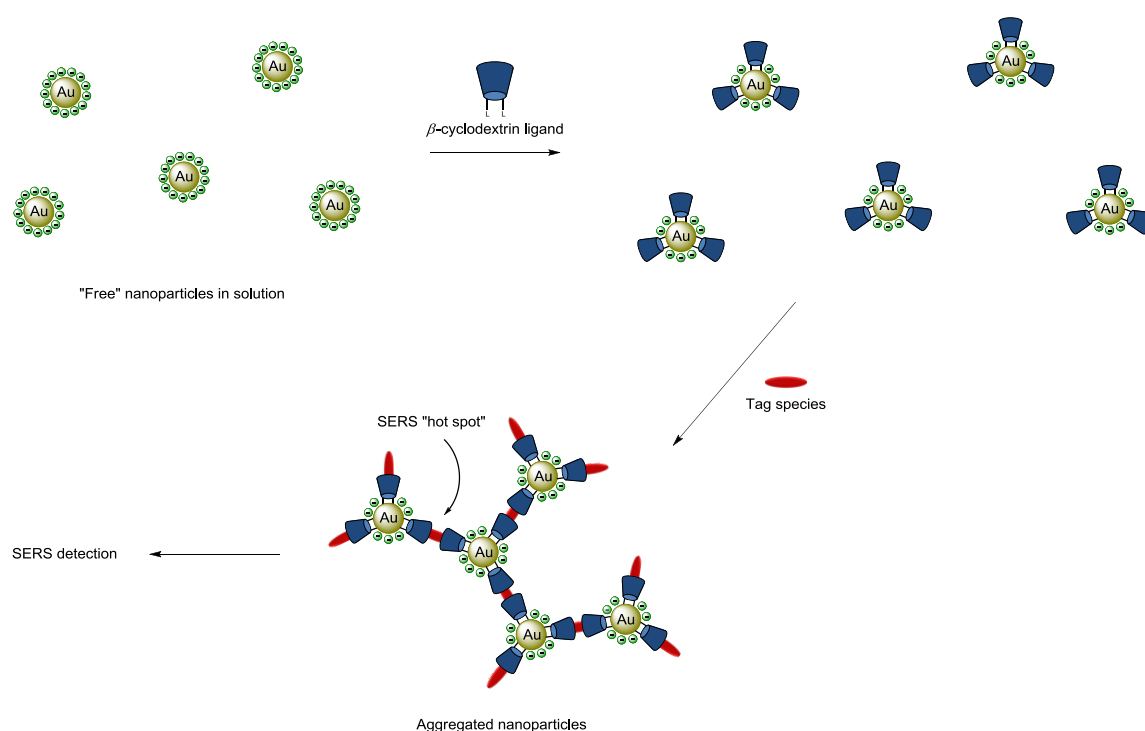
4.3 Sensing applications

4.3.1 Introduction

As outlined in **Section 4.1.3**, the use of metal nanoparticles for the SERS sensing of a wide range of molecular species has gained considerable recent interest. For example, it has been shown that β -cyclodextrin functionalised nanoparticles can exploit the unique inclusion properties of β -cyclodextrin to bind a substrate in close enough proximity to the metal surface to give rise to an enhancement of the substrate's Raman signal.⁴⁶⁻⁴⁹ In such cases, a dispersion of the metal nanoparticles and the SERS substrate is dried onto a glass slide prior to detection, causing the nanoparticles to aggregate. This allows for a greater enhancement of the substrate's Raman signal through the creation of SERS "hotspots," which arise from strong coupling of localised surface plasmon resonances, in the gaps between the aggregated particles.⁵⁰⁻⁵³

At the time of writing, there have been no examples of the use of β -cyclodextrin functionalised metal nanoparticles for SERS sensing in aqueous solvent systems. It is anticipated this could be achieved by exploiting the interaction between a suitably designed

“bi-dentate” tag species and a β -cyclodextrin ligand to give rise to the nanoparticle aggregation necessary for SERS detection (**Scheme 4.6**). Importantly, such aggregation would need to occur in a controlled manner, without precipitation, so as to allow for reproducible results.



Scheme 4.6—Cartoon representation of SERS detection of a tag species via the controlled aggregation of β -cyclodextrin functionalised gold nanoparticles.

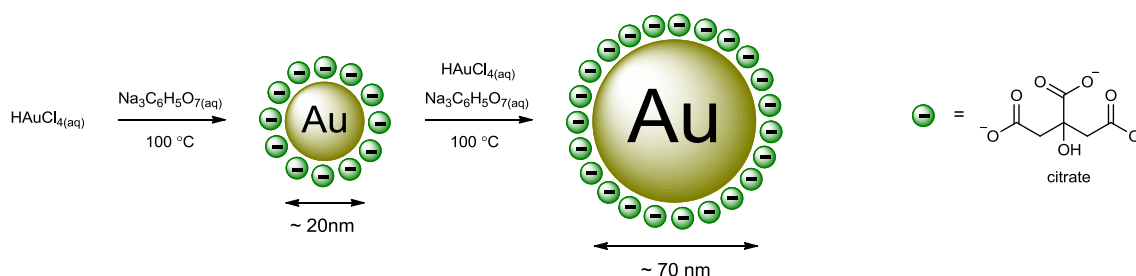
With this in mind, this Section initially examines the ability of a series of tag species to give rise to controlled aggregation of an aqueous dispersion of gold nanoparticles. If successful, attention will then switch to investigating whether such controlled aggregation can be utilised to detect the tag species *via* SERS.

4.3.2 Synthesis of components

Before testing could be undertaken, the necessary components needed to be synthesised: *gold nanoparticles*, a β -cyclodextrin ligand and suitable *tag species*.

4.3.2.1 Gold nanoparticles

Recent work has shown that surface enhancement of the Raman effect is dependent on nanoparticle size, with larger nanoparticles (~50–90 nm) found to give rise to the greatest enhancement.^{54–56} Therefore, an aqueous dispersion of large gold nanoparticles was synthesised via a “seed growth” modified Turkevich procedure (Chapter One, **Section 1.5.2**).^{57, 58}



Scheme 4.7—“Seed growth” synthesis of gold nanoparticles **Au71**.

Initially, a “seed” sample of gold nanoparticles approximately 20 nm in size was prepared by refluxing a 10:1 solution of 1 mM $\text{HAuCl}_{4(\text{aq})}$ and 38.8 mM aqueous sodium citrate until it turned deep red. An aliquot of this seed sample was then added to a refluxing solution of 12 mM $\text{HAuCl}_{4(\text{aq})}$ and heated for a further ten minutes to form the target large gold nanoparticles **Au71** (**Scheme 4.7**). TEM analysis of a sample of this dispersion (performed by S. D. B. Spratt, JMTC) revealed large round and delta-shaped gold nanoparticles (**Figure 4.24a**) with a mean diameter of 70.6 nm (± 1.4 , $n = 36$). UV-visible spectroscopy analysis revealed a PRB centred at 549 nm consistent with the formation of large nanoparticles (**Figure 4.24b**).

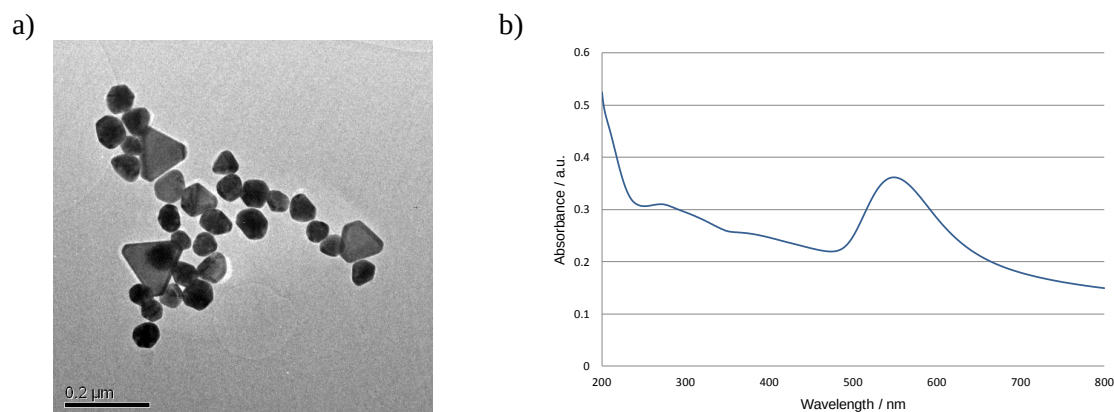
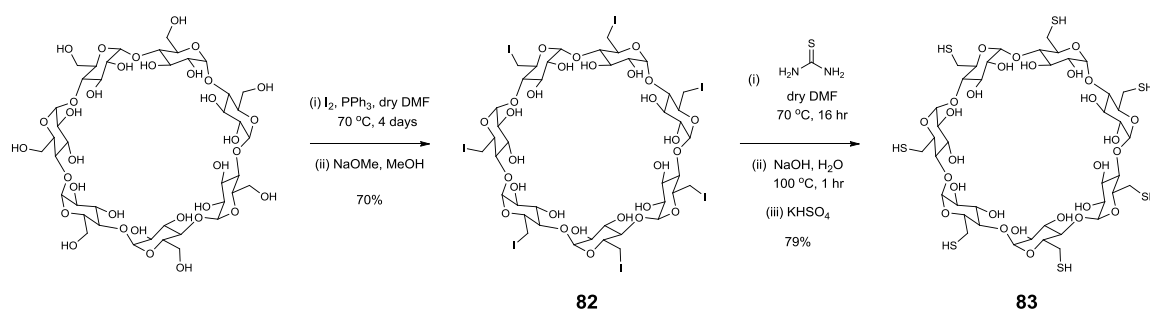


Figure 4.24—a) TEM image and b) UV-visible spectrum (H_2O , 298 K) of a sample of gold nanoparticles **Au71** synthesised by a “seed growth” method.

4.3.2.2 β -Cyclodextrin ligand

As discussed previously (**Section 4.2.1**), thiols are known to bind strongly to gold surfaces and so a β -cyclodextrin ligand bearing seven thiol groups was prepared following a literature procedure (**Scheme 4.8**).⁵⁹

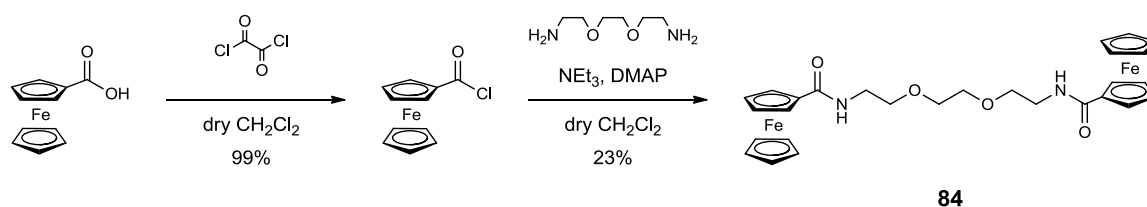


Scheme 4.8—Synthesis of β -cyclodextrin hepta-thiol ligand **83**.

Commercially available β -cyclodextrin was reacted with iodine and triphenylphosphine in dry DMF at 70 °C for four days. The reaction mixture was then basified with NaOMe and the hepta-iodo compound **82** precipitated with methanol in 70% yield. This was then heated at 70 °C with thiourea in dry DMF overnight before the DMF was removed and the crude product refluxed with NaOH in water for one hour. The target β -cyclodextrin hepta-thiol ligand **83** was then precipitated, in 79% yield, using $KHSO_4$.

4.3.2.3 Tags

β -Cyclodextrin is capable of including a vast array of different molecular species, including polycyclic aromatic hydrocarbons (PAHs).^{9, 47, 60} Taking this into account, commercially available anthracene and 1,2-di(4-pyridyl)ethylene (BPE) were chosen as potential SERS tags. These PAHs were both thought to be large enough to bind within two β -cyclodextrin cavities and thus facilitate aggregation. In addition, a larger more flexible bis-ferrocene functionalised tag **84** was synthesised *via* a literature procedure (**Scheme 4.9**)⁶¹ as similar ferrocene derivatives have been reported to bind to multiple β -cyclodextrin hosts.⁶²⁻⁶⁵



Scheme 4.9—Synthesis of bis-ferrocene functionalised tag **84**.

Ferrocenecarboxylic acid was reacted with oxalyl chloride in dry CH_2Cl_2 to form ferrocenoyl chloride in quantitative yield. This was immediately reacted with half an equivalent of 2,2'-(ethane-1,2-diylbis(oxy))diethanamine, in the presence of a catalytic amount of DMAP and triethylamine, to give the target bis-ferrocene tag **84** in 23% yield.

4.3.3 Aggregation experiments

With the desired components successfully prepared, quantitative dynamic light scattering (DLS) aggregation experiments were undertaken. This technique is used to determine the size distribution of a colloidal suspension *via* analysis of the scattering intensity that results when a beam of light is passed through the suspension. DLS measures hydrodynamic diameter (D_H), which is indicative of the apparent size of a *solvated* particle, or cluster of particles, and not just the particle or cluster itself (**Figure 4.25**).

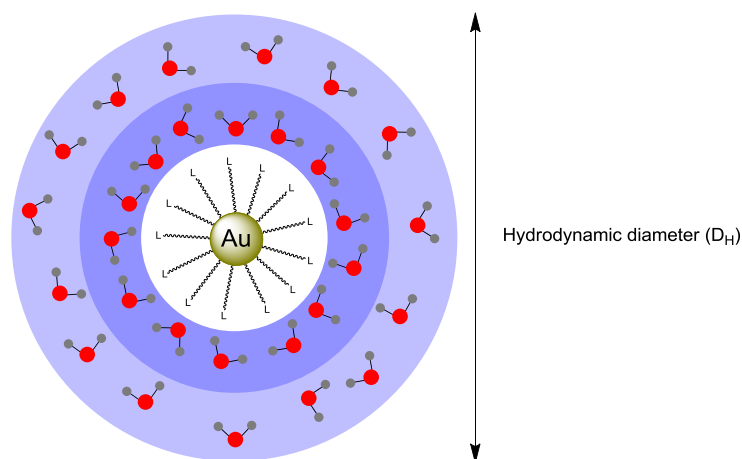


Figure 4.25—Cartoon representation of the hydrodynamic diameter (D_H) of a solvated gold nanoparticle.

All measurements were recorded by C. Malde (JMTC) using a Malvern Zetasizer Nano at a refractive scattering angle of 173° (298 K, dispersant: water, material: gold). Samples were made up by adding the necessary components (β -cyclodextrin hepta-thiol ligand **83** and/or corresponding tag) as DMSO solutions to 2 mL aliquots of **Au71** and left overnight before their size distributions were recorded.⁶⁶ Very small quantities of the various components were used (*e.g.* 1.6×10^{-9} mol of ligand **83**) given the ultra-sensitive nature of the SERS technique that the samples were ultimately intended for. Results are displayed graphically as size distributions by intensity of the particle/cluster diameter (d/nm), with all sizes quoted in the text referring to the Z average diameter of the sample (derived from the intensity weighted mean D_H).

Initially, the effect of adding β -cyclodextrin hepta-thiol ligand **83** to the gold nanoparticles was investigated. Comparison of the size distributions of **Au71** and a mixture of **Au71** and ligand **83** (1:13.5 ratio of Au:**83**) revealed a slight increase in the mean hydrodynamic diameter of the nanoparticles from 54.1 nm to 60.5 nm (**Figure 4.26** and **Table 4.12**). This suggests that the ligand is binding to the surface of the nanoparticles, as expected.

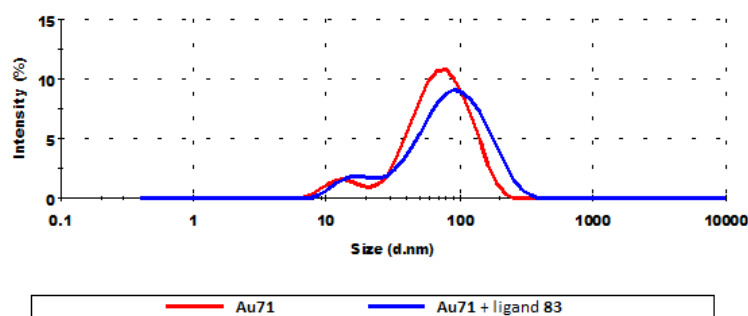
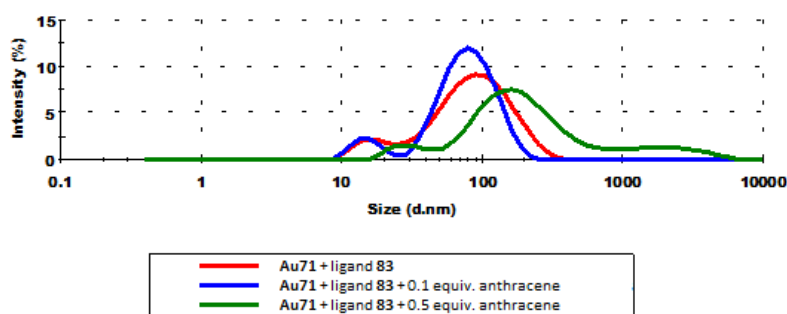


Figure 4.26—Size distribution by intensity of an aliquot of **Au71** before and after the addition of ligand **83**.

With the gold nanoparticles now able to be functionalised with ligand **83**, attempts at inducing controlled aggregation by adding increasing amounts of the three tags to separate aliquots of a mixture of **Au71**/ ligand **83** (1:13.5 Au:**83**) were undertaken.

The addition of 0.1 equivalents (relative to ligand **83**) of anthracene or BPE was found to have very little effect on the hydrodynamic diameter of the nanoparticles but, importantly, the addition of 0.5 equivalents resulted in noticeable increases (**Figure 4.27** and **Table 4.12**). In particular, the addition of 0.5 equivalents of anthracene was found to increase Z average from 60.5 nm to 141.6 nm. These observations indicate that particle/cluster size is directly linked to the amount of tag added and, therefore, aggregation is likely to be arising from the tags binding to the β -cyclodextrin ligands present on the nanoparticle surfaces. Crucially, precipitation of the nanoparticles was not observed and the results were reproducible, suggesting that aggregation was occurring in a controlled manner.

a)



b)

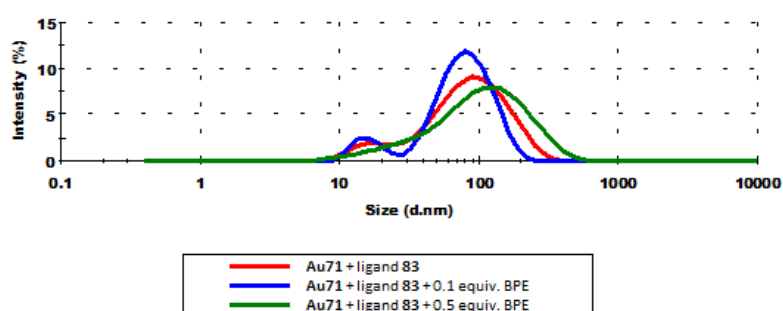


Figure 4.27—Size distribution by intensity of a mixture of **Au71**/ligand **83** after the addition of differing amounts of a) anthracene and b) BPE.

Table 4.12—Size distribution data for the DLS measurements of various samples (PDI is the polydispersity index of Z average).

Sample	Z average (d/nm)	PDI
Au71	54.1	0.278
Au71 + ligand 83	60.5	0.352
Au71 + ligand 83 + 0.1 equiv. anthracene	57.6	0.283
Au71 + ligand 83 + 0.5 equiv. anthracene	141.6	0.460
Au71 + ligand 83 + 0.1 equiv. BPE	57.4	0.279
Au71 + ligand 83 + 0.5 equiv. BPE	76.4	0.398
Au71 + ligand 83 + 0.1 equiv. tag 84	61.0	0.294
Au71 + ligand 83 + 0.5 equiv. tag 84	precipitated	
Au71 + 0.1 equiv. tag 84	59.5	0.341
Au71 + 0.5 equiv. tag 84	63.4	0.342

The addition of 0.1 equivalents of tag **84** had little effect on the hydrodynamic diameter of **Au71**, as was the case with anthracene and BPE, however the addition of 0.5 equivalents of

84 caused the nanoparticles to precipitate and so a size distribution could not be obtained (**Figure 4.28** and **Table 4.12**). This implies that, for the addition of 0.5 equivalents, tag **84** binds to β -cyclodextrin ligand **83** more strongly than anthracene or BPE, giving rise to more dramatic and less controlled aggregation of the nanoparticles.

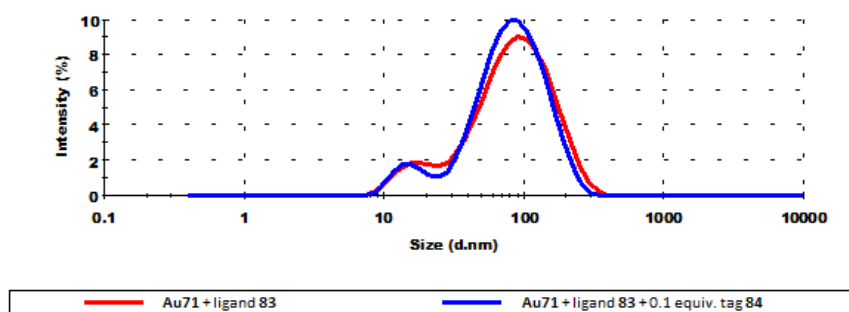


Figure 4.28—Size distribution by intensity of a mixture of **Au71**/ligand **83** before and after the addition of 0.1 equivalents of bis-ferrocene tag **84**.

In order to confirm that the interaction between the tag and β -cyclodextrin ligand was the cause of the observed increases in hydrodynamic diameter, the aggregation experiments with tag **84** were repeated in the absence of β -cyclodextrin ligand **83**. No significant changes in the size distribution of **Au71** were observed upon the addition of either 0.1 or 0.5 equivalents of **84**, highlighting the crucial role ligand **83** plays in the aggregation process (**Figure 4.29** and **Table 4.12**).

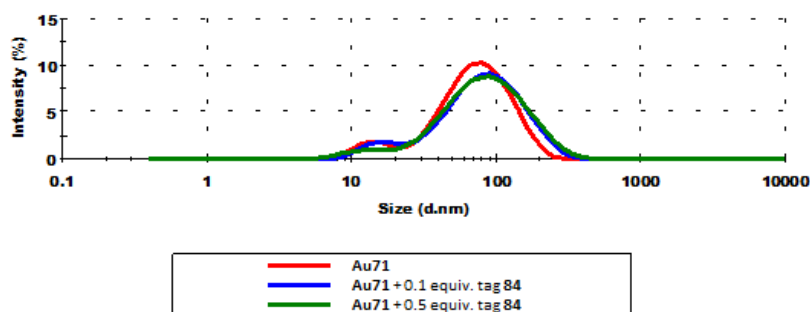


Figure 4.29—Size distribution by intensity of an aliquot of **Au71** before and after the addition of increasing amounts of bis-ferrocene tag **84**.

4.3.4 SERS testing

Having successfully demonstrated the controlled aggregation of an aqueous dispersion of β -cyclodextrin functionalised gold nanoparticles through addition of various tags, the potential for these tag species to be detected *via* SERS was explored.

All SERS measurements were recorded using a Renishaw inVia Raman microscope at Reading University with the help of Dr. O. Khutoryanskaya. Samples were made up following almost identical protocols as used for the DLS aggregation studies; the concentrations of the component solutions remained constant but the volumes added were doubled due to the size of the vials required by the microscope.

Initially, a background spectrum of an aliquot of **Au71** was obtained (**Figure 4.30**). As expected, a broad peak at 3000–3750 cm^{-1} was observed that corresponded to the numerous Raman modes of the water solvent.⁶⁷

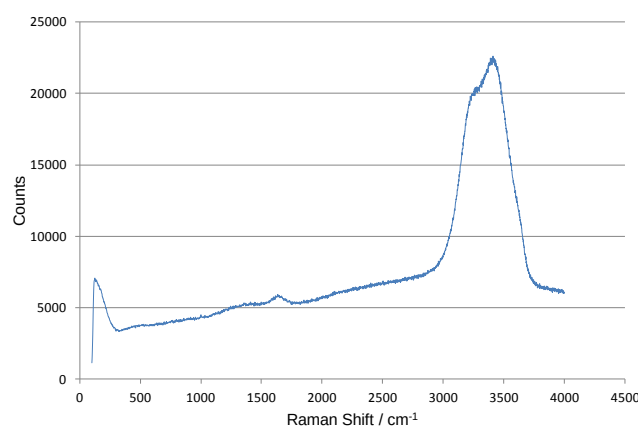


Figure 4.30—Raman spectrum of an aliquot of **Au71** (633 nm laser, 298 K, 4 mL, water).

Ligand **83** was then added to the nanoparticle dispersion (1:13.5 **Au:83**) to provide a second background spectrum. This resulted in the appearance of peaks at 675, 714, 950, 1010, 1418, 2927 and 3011 cm^{-1} in the Raman spectrum (**Figure 4.31**) which corresponded to the CS stretching (675 and 714 cm^{-1}), HCH rocking (950 cm^{-1}), SO stretching (1010 cm^{-1}), HCH

deformation (1418 cm^{-1}) and CH stretching (2927 and 3011 cm^{-1}) modes of the DMSO solvent used to dissolve ligand **83**.⁶⁸

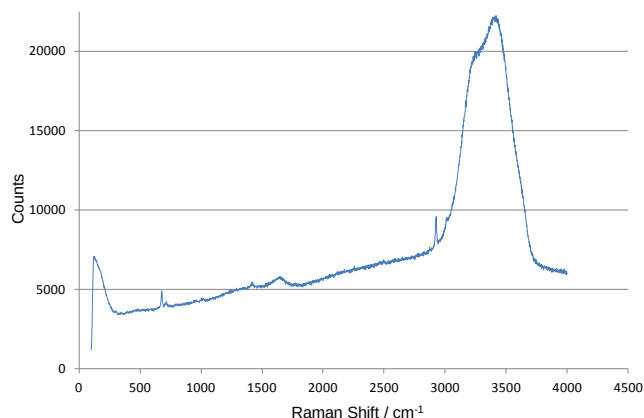


Figure 4.31—Raman spectrum of a mixture of ligand **83**/**Au71** (1:13.5 Au:**83**, 633 nm laser, 298 K, 4 mL, water)

Given that the addition of 0.5 equivalents of anthracene resulted in the largest increase in particle size for the DLS aggregation studies performed **Section 4.3.3**, the possible SERS detection of this tag was studied first. Unfortunately, addition of 0.5 equivalents of anthracene, relative to β -cyclodextrin ligand **83**, only resulted in an increase in the intensity of the previously recorded DMSO peaks (**Figure 4.32**). Three additional DMSO peaks also became apparent: CSC bend (302 cm^{-1}), CSO bend (349 cm^{-1}) and CSO rocking (390 cm^{-1}).⁶⁸

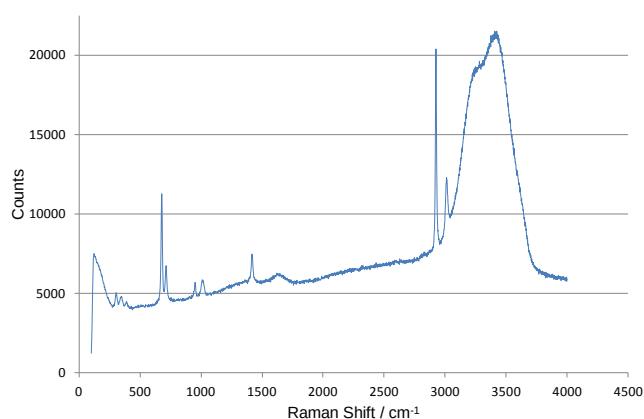


Figure 4.32—Raman spectrum of a mixture of ligand **83**/**Au71** after the addition of 0.5 equivalents of anthracene relative to ligand **83** (1:13.5 Au:**83**, 633 nm laser, 298 K, 4 mL, water).

Identical observations were made when BPE or bis-ferrocene tag **84** were used in place of anthracene, indicating that all three tag species could not be detected despite the previous evidence for aggregation (**Section 4.3.3**). It was thought that the DMSO signals in the Raman spectra could perhaps be masking those of the tags, especially as there is a near seven orders of magnitude molar excess of DMSO relative to the tag species in solution. This problem would be alleviated by dissolving β -cyclodextrin ligand **83** and the three tags in water instead of DMSO, however the poor aqueous solubility of the components, in particular ligand **83**, resulted in further SERS investigations not being possible. Unsuccessful attempts at using other solvents, such as methanol, to aid the dissolution of the components into water before removing the additional solvent prior to measurement were also undertaken.

4.3.5 Summary

The possibility for the substrate inclusion properties of β -cyclodextrin to direct the aggregation of an aqueous solution of gold nanoparticles and allow for the solution phase SERS detection of a series of tag species was investigated. DLS experiments revealed that the addition of anthracene or BPE tags to an aqueous dispersion of gold nanoparticles functionalised with β -cyclodextrin hepta-thiol ligand **83** gave rise to controlled aggregation. SERS tests were then undertaken in the hope that the aggregated nanoparticles would provide sufficient enhancement of the Raman Effect to detect the tag species in aqueous solution. Unfortunately, only DMSO solvent signals were observed in the Raman spectra and subsequent attempts at preventing this by dissolving the components in water were unsuccessful. Exchanging the current components for more water soluble alternatives would be a possible solution; for example, tags such as 2,6-naphthalenedisulfonic acid (**Figure 4.33a**) could be used in conjunction with the methylated form of β -cyclodextrin hepta-thiol ligand **83** (**Figure 4.33b**).

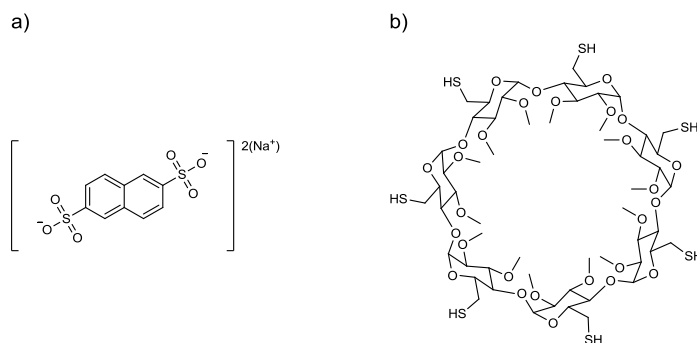


Figure 4.33—a) 2,6-Naphthalenedisulfonic acid disodium salt and b) methylated form of β -cyclodextrin hepta-thiol ligand **83**.

4.4 Conclusions and future work

Initially, a series of β -cyclodextrin functionalised palladium catalysts were prepared and their ability to catalyse a number of important chemical reactions investigated. The presence of a β -cyclodextrin ligand was found to significantly enhance the catalyst's alkene selectivity in the solution phase hydrogenation of 3-hexyn-1-ol, with the observed catalytic performance matching that of the commercial standard, Lindlar's catalyst. This work was then extended by exploring the possibility of utilising the hydrophobic nature of β -cyclodextrin's cavity by introducing water into the reaction mixture. A dramatic increase in alkene selectivity was observed and, notably, the β -cyclodextrin functionalised Pd/Al₂O₃ catalyst displayed superior selectivity to Lindlar's catalyst.

Following this, the reduction of various isomers of chloro-nitrobenzene *via* catalytic hydrogenation reactions was studied. For the reduction of 2- and 3-chloro-nitrobenzene dehalogenation was prevalent and no marked selectivity for the desired chloro-aniline products was observed, however the functionalised catalysts all outperformed the commercial standards. Encouragingly, use of the Pd/Al₂O₃ β -cyclodextrin mono-amine functionalised catalyst for the reduction of 4-chloro-nitrobenzene resulted in a product mixture containing 45% 4-chloro-aniline; a significant decrease in dehalogenation in comparison to the unfunctionalised analogue.

Attention then switched to the vapour phase hydrogenation of 1-pentyne, with the anticipation that even in the absence of solvent the inclusion properties of β -cyclodextrin would affect catalytic performance. This was confirmed by the β -cyclodextrin functionalised catalysts displaying selectivity for the desired 1-pentene product, at low temperature, whereas use of the standard palladium systems resulted in over-hydrogenation to the alkane. Interestingly, the Pd/Al₂O₃ β -cyclodextrin mono-dithiolane catalyst was found to be highly selective for 1-pentene even at high temperature.

Future catalysis work could involve investigating the performance of the β -cyclodextrin functionalised palladium catalysts on other important palladium-catalysed reactions, such as Suzuki and Heck coupling reactions. In addition, the β -cyclodextrin ligands could be used to modify the surface functionality of other precious metal-based catalysts in order to expand the range of reactions that could be studied.

The potential for β -cyclodextrin functionalised gold nanoparticles to be used for the solution phase SERS detection of a series of chemical tags was also explored. It was shown that the substrate inclusion properties of a β -cyclodextrin hepta-thiol ligand could be exploited to aggregate gold nanoparticles in aqueous solution through the addition of various tag species capable of binding within the ligand's cavity. The aggregated nanoparticles were expected to allow for a sufficient enhancement of the Raman Effect to detect the tags species in aqueous solution. Unfortunately, the presence of residual DMSO solvent and the poor water solubilities of the β -cyclodextrin ligand and tags made this problematic and highly challenging. In the future, these issues could potentially be solved by exploring the use of a methylated β -cyclodextrin ligand and tag species with improved water solubility.

4.5 References and notes for Chapter Four

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66. Ligand **83** was added in 40 μ L of DMSO, whilst the tag solutions contained 0.1 equivalents of the tag in 20 μ L of DMSO. These relatively small volumes ensured that the solvent system remained almost entirely aqueous, with the maximum DMSO content being 7% DMSO in water.
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CHAPTER FIVE

Chapter Five: Experimental

5.1 General considerations

5.1.1 Solvents and reagents

Commercially available solvents and reagents were used without further purification unless specified. Dry solvents were obtained by purging with nitrogen and then passing through an MBraun MPSP-800 column. Water was de-ionised and microfiltered using a Milli-Q[®] Millipore machine. NEt₃ was distilled and stored over KOH. All TBA salts, Grubbs' II catalyst, TBTA, Cu(OAc)₂, and Cu(MeCN)₄PF₆ were stored in vacuum desiccators prior to use. Column chromatography was performed on silica gel (particle size: 40–63 µm), preparative TLC was performed on 20 x 20 cm plates with a silica layer thickness of 1 mm.

5.1.2 Instrumental methods

Routine NMR spectra were recorded at 293 K on a Varian Mercury-vx 300 spectrometer (with ¹H NMR operating at 300 MHz, ¹³C at 75 MHz, ¹⁹F at 283 MHz and ³¹P at 122 MHz) or Varian Unity Plus or Bruker Avance III 500 instruments (with ¹H NMR operating at 500 MHz, ¹³C at 126 MHz, ¹⁹F at 471 MHz and ³¹P at 202 MHz). Low resolution mass spectra were obtained using a Micromass LCT Premier XE spectrometer and accurate masses were obtained using a Bruker MicroTOF (ESI-MS), a Waters GCT Classic spectrometer (FI-MS) or a Waters MALDI Micro MX spectrometer (MALDI-MS). Melting points were recorded on a Gallenkamp capillary melting point apparatus and are uncorrected.

UV-vis spectra were recorded on an Agilent Cary Series UV-Vis-Spectrophotometer at 298 K. Samples were prepared in a 3 mL quartz cuvette and concentrations were adjusted to suit the absorption range of the instrument.

XPS analyses were performed using a Thermo V. G. Scientific ESCALAB 250. Powders of the supported nanoparticles were dusted onto carbon tape and thereby mounted on a sample stub. The exciting radiation used in the studies was monochromatised aluminium K α radiation in a 650 μm spot at 200 W power. Charge compensation was activated, provided by the in-lens flood gun at a 2 eV setting and 401 argon ion flood source at a “zero energy” setting.

TEM was conducted using either a Tecnai F20 Transmission Electron Microscope or a Hitachi HD-200 Scanning Transmission Electron Microscope. Samples run on the Tecnai instrument used a voltage of 200 kV and C2 aperture of 30 and 50 μm , whereas those run on the Hitachi instrument used a voltage of 200 kV and an objective aperture of 30 μm in STEM (high angle annular dark field or HAADF) mode. Solid samples were ground between two glass slides and dusted into a holey carbon coated Cu TEM grid, whereas solution samples were dried onto 3 mm Cu grids. Approximately 9 micrographs were recorded for each sample, which can be found in the Digital Appendix.

Solution phase catalytic hydrogenations were performed in a HEL ChemSCAN. Within each reaction cell 5.0 mL of a 0.5 M solution of the substrate in ethanol with 1,4-dioxane (internal standard for GC) was used. Reactions were run at either 30 or 50 $^{\circ}\text{C}$ under 3 bar of H_2 , after which the reaction mixture was filtered to remove the catalyst and the resulting organic phase analysed by gas chromatography using a PerkinElmer Autosystem GC fitted with a 10 m CP-Sil-19 column. Quantification was achieved by comparison to known standard solutions. Vapour phase catalytic hydrogenations were performed using a custom built “in house” apparatus. The catalyst sample (2 mg) was suspended in the centre of a quartz tube, using quartz wool, through which a mixture of the substrate and 4:6 H_2/He was passed at a flow rate of 200 mL/min. The temperature of the reactive gas stream was ramped from 293 to 523 K

and once it had passed over the catalyst bed its composition was analysed by gas chromatography using a Varian CP-3800 GC.

DLS measurements were recorded using a Malvern Zetasizer Nano with a refractive scattering angle of 173° at 298 K. The dispersant and material to be studied were set as water (RI = 1.330, η = 1.003 cP) and gold (RI = 0.200, absorption = 3.300) respectively. Samples were made up in a 3 mL quartz cuvette and allowed to equilibrate at 298 K for 1 minute before measurements were taken. Three measurements were taken and then averaged.

Raman spectra were obtained using a Renishaw inVia Raman microscope at 298 K. Samples (4.0 mL) were made up in 5 mL glass vials and exposed to a 633 nm laser at 50% power for 10 seconds.

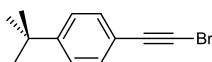
5.1.3 Compound characterisation

The preparation of previously reported compounds was confirmed by ^1H and ^{13}C NMR spectroscopy and low resolution mass spectrometry. Novel compounds were characterised by ^1H and ^{13}C NMR and low and high resolution mass spectrometry. Further characterisation was obtained from, where appropriate, ^{19}F and ^{31}P NMR and melting points. If needed, ^1H NMR assignments were aided by 2D ^1H - ^1H NMR COSY and ROESY spectroscopies.

5.2 Synthetic procedures

5.2.1 Synthetic procedures for Chapter Two

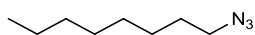
1-(*Tert*-butyl)-4-(bromoethynyl)benzene (5)



4-*Tert*-butylphenylacetylene (350 mg, 2.21 mmol) was dissolved in acetone (5 mL) and then *N*-bromosuccinimide (783 mg, 4.43 mmol) and silver nitrate (44.9 mg, 0.266 mmol) were

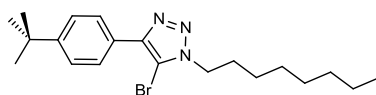
added. The reaction mixture was left to stir at room temperature for 2 hours, in the dark, under nitrogen with the reaction progress monitored *via* TLC. After this time, the reaction mixture was poured onto ice water (10 mL) and the product was extracted with Et₂O (3 x 20 mL), washed with brine (20 mL) and then dried over MgSO₄. The solvent was then removed and the product purified *via* passage through a silica plug (hexane) to give **5** as a pale yellow oil (489 mg, 94%). **MS** (FI-MS) *m/z* 236.0204 ([M]⁺, C₁₂H₁₃Br, calc. 236.0201); **¹H NMR** (300 MHz, CDCl₃) δ 7.55–7.31 (4H, m, ArH), 1.37–1.30 (9H, m, ^tBu); **¹³C NMR** (75 MHz, CDCl₃) δ 152.5, 136.4, 128.4, 125.3, 48.7, 34.8, 31.2, 31.1.

1-Azido-octane (**6**)¹



1-Bromooctane (4.10 g, 21.2 mmol) and sodium azide (2.02 g, 31.1 mmol) were dissolved in DMSO (50 mL). The reaction mixture was stirred at room temperature for 1 day before water (50 mL) was added to quench the reaction. Once the mixture had cooled, the product was extracted into Et₂O (3 x 50 mL), washed with brine (100 mL), dried over MgSO₄ and filtered. The solvent was removed *in vacuo*, without heating, to give the product as a colourless oil (2.98 g, 91%). **¹H NMR** (300 MHz, CDCl₃) δ 3.25 (2H, t, ³*J* = 7.2 Hz, -CH₂N₃), 1.68–1.52 (2H, m, -CH₂), 1.45–1.17 (10H, m, -CH₂), 0.88 (3H, t, ³*J* = 7.2 Hz, -CH₃); **¹³C NMR** (75 MHz, CDCl₃) δ 51.4, 31.7, 29.1, 29.1, 28.8, 26.7, 22.6, 14.0.

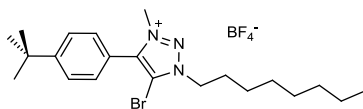
4-(4-*Tert*-butyl)phenyl)-5-bromo-1-octyl-1*H*-1,2,3-triazole (**7**)



Compound **5** (140 mg, 0.590 mmol) and 1-azido-octane **6** (91.6 mg, 0.590 mmol) were dissolved in dry THF (4 mL) before CuBr (84.6 mg, 0.590 mmol) and Cu(OAc)₂ (107.2 mg,

0.590 mmol) were added. The reaction mixture was then left to stir at 50 °C under N₂ for 16 days. The reaction progress was monitored *via* TLC (99:1 CH₂Cl₂/MeOH) and, after it had run to completion, the reaction was quenched with 10% NH₄OH_(aq) (2 mL) before the THF was removed. Water (20 mL) was then added and the crude product extracted with CH₂Cl₂ (3 x 20 mL). The combined organic phase was then washed with water (20 mL) and dried over MgSO₄. The solvent was removed and the product purified *via* silica gel column chromatography (hexane then 95:5 CH₂Cl₂/MeOH) which gave the product as an off-white oily solid (37.8 mg, 16%). **MS** (ESI-MS) *m/z* 392.1684 ([M + H]⁺, C₂₀H₃₁BrN₃, calc. 392.1696); **¹H NMR** (300 MHz, CDCl₃) δ 7.93 (2H, d, ³*J* = 8.8 Hz, Ar*H*), 7.50 (2H, d, ³*J* = 8.3 Hz, Ar*H*), 4.40 (2H, t, ³*J* = 7.3 Hz, -NCH₂), 2.02–1.89 (2H, m, -CH₂), 1.44–1.21 (19H, m, -CH₂ & -^tBu), 0.89 (3H, t, ³*J* = 7.3 Hz, -CH₂CH₃); **¹³C NMR** (75 MHz, CDCl₃) δ 126.4, 125.5, 49.4, 31.7, 31.3, 29.6, 29.1, 29.0, 26.4, 22.6, 14.1.

Bromo-triazolium tetrafluoroborate thread (**8**·BF₄)



Compound **7** (161 mg, 0.409 mmol) was dissolved in dry CH₂Cl₂ (30 mL) and then trimethyloxonium tetrafluoroborate (121 mg, 0.819 mmol) was added. The reaction mixture was left to stir at room temperature under nitrogen for 7 days. After this time, the reaction was quenched with MeOH (5 mL) and the solvent removed *in vacuo*. The crude product was then purified by silica gel column chromatography (98:2 CH₂Cl₂/MeOH to 95:5 CH₂Cl₂/MeOH) to give **8**·BF₄ as an off-white solid (159 mg, 79%). **MS** (ESI-MS) *m/z* 406.1844 ([M - BF₄]⁺, C₂₁H₃₃BrN₃, calc. 406.1852); **¹H NMR** (300 MHz, CDCl₃) δ 7.63–7.52 (4H, m, Ar*H*), 4.56 (2H, t, ³*J* = 7.6 Hz, -NCH₂), 4.20 (3H, s, -N⁺CH₃), 2.14–2.00 (2H, m, -CH₂), 1.46–1.24 (19H, m, -CH₂ & -^tBu), 0.88 (3H, t, ³*J* = 7.1 Hz, -CH₂CH₃); **¹³C NMR**

(75 MHz, CDCl₃) δ 155.6, 142.6, 129.7, 126.6, 118.2, 115.7, 53.3, 39.3, 35.1, 31.6, 31.0, 28.8, 28.1, 26.2, 22.5, 14.0; ¹⁹F NMR (283 MHz, CDCl₃) δ -155.3 (d, *J* = 14.9 Hz).

Anion exchange—general procedure

Bromo-triazolium tetrafluoroborate thread **8**·BF₄ (30.0 mg, 0.0607 mmol) was dissolved in CHCl₃ (5 mL) and washed vigorously with the required 1 M aqueous ammonium halide salt solution (10 x 5 mL). The organic layer was then washed with water (2 x 5 mL), dried over MgSO₄ and filtered. The solvent was removed *in vacuo* to give **8**·Cl and **8**·Br as off-white solids and **8**·I as a yellow solid (76%, 73% and 66% yields respectively). The characterisation data for the products **8**·Cl, **8**·Br and **8**·I are given below.

Bromo-triazolium chloride thread (**8**·Cl)

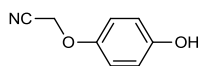
MS (ESI-MS) *m/z* 406.1850 ([M - Cl]⁺, C₂₁H₃₃BrN₃, calc. 406.1852); ¹H NMR (300 MHz, CDCl₃) δ 7.70–7.57 (4H, m, ArH), 4.59 (2H, t, ³*J* = 7.7 Hz, -NCH₂), 4.33 (3H, s, -N⁺CH₃), 2.14–2.01 (2H, m, -CH₂), 1.41–1.23 (19H, m, -CH₂ & -^tBu), 0.89 (3H, t, ³*J* = 6.6 Hz, -CH₂CH₃); ¹³C NMR (75 MHz, CDCl₃) δ 153.2, 142.7, 129.8, 126.7, 116.7, 53.4, 39.8, 35.1, 31.6, 31.0, 28.8, 28.4, 26.2, 22.6, 14.0.

Bromo-triazolium bromide thread (**8**·Br)

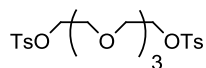
MS (ESI-MS) *m/z* 406.1850 ([M - Br]⁺, C₂₁H₃₃BrN₃, calc. 406.1852); ¹H NMR (300 MHz, CDCl₃) δ 7.74 (2H, d, ³*J* = 8.3 Hz, ArH), 7.60 (2H, d, ³*J* = 8.3 Hz, ArH), 4.58 (2H, t, ³*J* = 7.6 Hz, -NCH₂), 4.37 (3H, s, -N⁺CH₃), 2.15–2.03 (2H, m, -CH₂), 1.39–1.22 (19H, m, -CH₂ & -^tBu), 0.89 (3H, t, ³*J* = 6.7 Hz, -CH₂CH₃); ¹³C NMR (75 MHz, CDCl₃) δ 155.8, 142.4, 130.0, 126.7, 117.2, 53.5, 40.2, 35.1, 31.6, 31.1, 28.8, 28.4, 26.3, 22.6, 14.1.

Bromo-triazolium iodide thread (8·I)

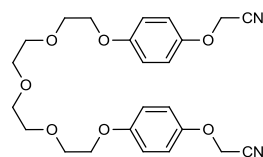
MS (ESI-MS) m/z 406.1842 ($[M - I]^+$, $C_{21}H_{33}BrN_3$, calc. 406.1852); **^1H NMR** (300 MHz, $CDCl_3$) δ 7.73 (2H, d, $^3J = 8.4$ Hz, ArH), 7.60 (2H, d, $^3J = 8.4$ Hz, ArH), 4.60 (2H, t, $^3J = 7.8$ Hz, $-NCH_2$), 4.32 (3H, s, $-N^+CH_3$), 2.20–2.06 (2H, m, $-CH_2$), 1.41–1.22 (19H, m, $-CH_2$ & $-tBu$), 0.89 (3H, t, $^3J = 6.4$ Hz, $-CH_2CH_3$); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 155.8, 149.7, 130.1, 126.7, 117.6, 53.8, 40.4, 35.1, 31.6, 31.0, 28.8, 28.3, 26.4, 22.5, 14.0.

2-(4-Hydroxyphenoxy)acetonitrile (9)²

Hydroquinone (5.00 g, 45.4 mmol) and NaOH (3.63 g, 90.8 mmol) were dissolved in degassed 1:1 1,4-dioxane/water (150 mL). Once the NaOH had completely dissolved, a solution of bromoacetonitrile (5.45 g, 45.4 mmol) in degassed 1,4-dioxane (25 mL) was added. The reaction mixture was then left to stir for 1 hour at room temperature under constant degassing. After this time, the solution was acidified with 1 M $HCl_{(aq)}$ (75 mL) and then extracted with CH_2Cl_2 (3 x 100 mL). The combined organic phases were then dried over $MgSO_4$ and, following filtration, the volatile components were removed by rotary evaporation. The resulting crude orange oil was then purified *via* silica gel column chromatography (99:1 $CH_2Cl_2/MeOH$) to give a pale green oil (5.22 g, 77%). **MS** (ESI-MS) m/z 148.03 ($[M - H]^-$, $C_8H_6NO_2$, calc.148.04); **^1H NMR** (300 MHz, $CDCl_3$) δ 6.94–6.74 (4H, m, ArH), 4.70 (2H, s, $-CH_2CN$), 3.76 (1H, s, $-OH$); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 151.6, 150.5, 116.9, 116.4, 115.4, 55.0.

Bis-tosylate tetraethylene glycol (10)³

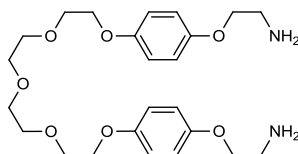
Tetraethylene glycol (5.00 mL, 22.8 mmol) was dissolved in CH₂Cl₂ (50 mL), TsCl (8.73 g, 45.8 mmol) was added and the solution cooled to 0 °C. Powdered KOH (16.8 g, 300 mmol) was then added portionwise to the reaction mixture before it was left to stir at 0 °C for 3 hours. After this time, CH₂Cl₂ (50 mL) was added and the mixture was poured into ice water (150 mL). The aqueous layer was extracted with CH₂Cl₂ (3 x 100 mL) and then the combined organic layers were dried over MgSO₄ and filtered. Following removal of the solvent by rotary evaporation, any remaining TsCl was removed by triturating with Et₂O to give the product as a colourless oil in quantitative yield. **MS** (ESI-MS) *m/z* 525.12 ([M + NH₄]⁺, C₂₂H₃₄NO₉S₂, calc. 525.17); **¹H NMR** (300 MHz, CDCl₃) δ 7.78 (4H, d, ³*J* = 7.9 Hz, *ArH*), 7.33 (4H, d, ³*J* = 7.9 Hz, *ArH*), 4.17–4.09 (4H, m, -CH₂), 3.70–3.61 (4H, m, -CH₂), 3.57–3.49 (8H, m, -CH₂), 2.46–2.35 (6H, m, -CH₃); **¹³C NMR** (75 MHz, CDCl₃) δ 144.8, 132.9, 129.8, 127.9, 70.7, 70.5, 69.2, 68.6, 21.6.

Bis-nitrile 5-oxygen polyether (11)²

2-(4-Hydroxyphenoxy)acetonitrile **9** (0.831 g, 5.60 mmol) and bis-tosylate tetraethylene glycol **10** (1.40 g, 2.80 mmol) were dissolved in dry MeCN (100 mL). K₂CO₃ (0.774 g, 5.60 mmol) was added to the solution, which was then heated at reflux for 48 hours under N₂. After cooling to room temperature, the mixture was filtered to remove the K₂CO₃ and then the solvent was removed *in vacuo*. The resulting sticky brown solid was re-dissolved in CHCl₃

(75 mL) and filtered. Following removal of the solvent, the product was isolated as a white oily solid (1.25 g, 98%). **MS** (ESI-MS) m/z 479.21 ($[M + Na]^+$, $C_{24}H_{28}N_2NaO_7$, calc. 479.18); **^1H NMR** (300 MHz, $CDCl_3$) δ 7.03–6.71 (8H, m, ArH), 4.77–4.59 (4H, m, $-CH_2CN$), 4.17–3.97 (4H, m, $-CH_2$), 3.91–3.79 (4H, m, $-CH_2$), 3.76–3.58 (8H, m, $-CH_2$); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 154.7, 150.7, 116.6, 115.7, 115.6, 70.7, 70.6, 69.7, 67.9, 54.8.

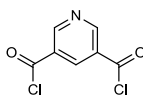
Bis-amine 5-oxygen polyether (**12**)²



Bis-nitrile 5-oxygen polyether **11** (3.38 g, 7.16 mmol) was dissolved in dry THF (100 mL) and added dropwise to 1 M $BH_3 \cdot THF$ (52.3 mL, 52.3 mmol) which had been pre-heated to 70 °C. Once the addition of **11** was complete, the reaction mixture was left to reflux under nitrogen for 4 hours. After this time, the mixture was cooled to room temperature and MeOH was added dropwise to quench the reducing agent until bubbling had ceased. The solvent was reduced by $\frac{3}{4}$ of its volume and then $HCl_{(g)}$ was bubbled through the solution for 30 minutes. The resulting hydrogen chloride salt **12**·2HCl was collected by vacuum filtration and then washed with cold MeOH (50 mL) and hexane (2 x 50 mL) and dried under vacuum (3.65 g, 95%). **12**·2HCl (2.00 g, 3.72 mmol) was then suspended in CH_2Cl_2 (50 mL), 10% $NaOH_{(aq)}$ (50 mL) was added and then the biphasic mixture was stirred vigorously for 30 minutes before the organic phase was washed with water (100 mL) and dried over $MgSO_4$. The solvent was then removed *in vacuo* to yield **12** as an oily white solid (0.857 g, 50%). **MS** (ESI-MS) m/z 465.26 ($[M + H]^+$, $C_{24}H_{37}N_2O_7$, calc. 465.26); **^1H NMR** (300 MHz, $CDCl_3$) δ 6.83–6.73 (8H, m, ArH), 4.02 (4H, t, $^3J = 4.9$ Hz, $-CH_2$), 3.86 (4H, t, $^3J = 5.1$ Hz, $-CH_2$), 3.77 (4H, t, $^3J = 4.9$ Hz, $-CH_2$), 3.70–3.61 (8H, m, $-CH_2$), 3.02–2.89 (4H, m, $-CH_2$),

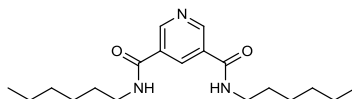
2.02–1.92 (4H, m, $-NH_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.9, 152.8, 115.3, 115.1, 70.5, 70.4, 69.6, 67.8, 41.4.

Pyridine-3,5-dicarbonyl dichloride (**13**)⁴



Pyridine-3,5-dicarboxylic acid (73.2 mg, 0.438 mmol) was suspended in $SOCl_2$ (10 mL) and refluxed overnight under N_2 in the presence of one drop of dry degassed DMF. The excess $SOCl_2$ was then removed by rotary evaporation, using a bump trap, to give a brown solid which was re-dissolved in dry CH_2Cl_2 . The CH_2Cl_2 was then removed *in vacuo* and this process was repeated three times to give **13** a yellow solid in quantitative yield which was used immediately in the next reaction without further purification or characterisation.

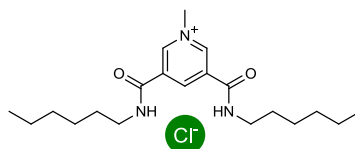
Pyridine thread (**14**)⁵



Compound **13** (1.83 g, 8.98 mmol) was dissolved in dry CH_2Cl_2 (20 mL) and then added dropwise to a solution of hexylamine (1.82 g, 18.0 mmol) and NEt_3 (2.5 mL, 18.0 mmol) in dry CH_2Cl_2 (100 mL) kept at 0 °C. The reaction mixture was stirred for 2 hours before being washed with 10% aqueous citric acid (2 x 100 mL) and water (2 x 100 mL). The organic phase was dried over $MgSO_4$, filtered, and then the solvent removed *in vacuo* to give the product **14** as an off-white solid (2.42 g, 81%). **MS** (ESI-MS) m/z 368.17 ($[M + Cl]^-$, $C_{19}H_{31}ClN_3O_2$, calc. 368.21); ^1H NMR (300 MHz, $CDCl_3$) δ 9.08 (2H, s, *ArH*), 8.51 (1H, s, *ArH*), 7.38 (2H, t, $^3J = 7.5$ Hz, $-NH$), 3.52–3.37 (4H, m, $-NHCH_2$), 1.71–1.56 (4H, m, $-CH_2$),

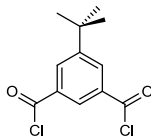
1.43–1.24 (12H, m, $-CH_2$), 0.88 (6H, t, $^3J = 6.8$ Hz, $-CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.8, 150.0, 133.9, 130.3, 40.4, 31.4, 29.4, 26.7, 22.5, 14.0.

Pyridinium chloride thread ($15 \cdot Cl$)⁵



Pyridine thread **14** (1.40 g, 4.20 mmol) and MeI (2 mL, 32.0 mmol) were dissolved in $CHCl_3$ (50 mL) and refluxed under nitrogen for 72 hours. After this time, the reaction mixture was cooled to room temperature and the solvent and excess MeI removed *in vacuo* to give the iodide salt of the pyridinium thread $15 \cdot I$ as an orange solid. This was dissolved in $CHCl_3$ (100 mL) and washed with 1 M $NH_4Cl_{(aq)}$ (8 x 100 mL) and water (2 x 100 mL). The organic phase was then dried over $MgSO_4$, filtered and the solvent removed to give the product $15 \cdot Cl$ as a yellow solid (1.26 g, 78%). **MS** (ESI-MS) m/z 348.23 ($[M - Cl]^+$, $C_{20}H_{34}N_3O_2$, calc. 348.26); ^1H NMR (300 MHz, $CDCl_3$) δ 10.42 (1H, s, ArH), 9.49 (2H, s, ArH), 9.39 (2H, t, $^3J = 3.8$ Hz, $-CONH$), 4.59 (3H, s, $-N^+CH_3$), 3.50–3.39 (4H, m, $-NHCH_2$), 1.78–1.65 (4H, m, $-NHCH_2CH_2$), 1.43–1.22 (12H, m, $-CH_2$), 0.87 (6H, t, $^3J = 6.4$ Hz, $-CH_2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.2, 146.2, 142.1, 134.8, 40.9, 31.4, 29.0, 26.8, 22.5, 14.0.

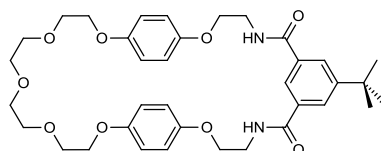
5-(*Tert*-butyl)isophthaloyl dichloride (**16**)⁵



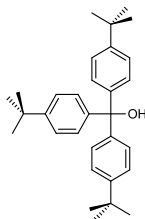
5-(*Tert*-butyl)isophthalic acid (0.444 g, 2.00 mmol) was dissolved in $SOCl_2$ (10 mL) and then heated at reflux under nitrogen for 16 hours, in the presence of one drop of dry degassed

DMF, until the solution became homogeneous. After this time, the excess SOCl_2 was removed *in vacuo* using a bump trap to yield **16** as a cream solid in quantitative yield which was used immediately in the next reaction without further purification or characterisation.

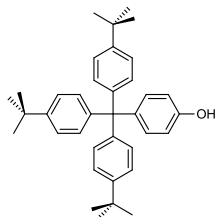
***Tert*-butyl isophthalamide macrocycle (**17**)⁵**



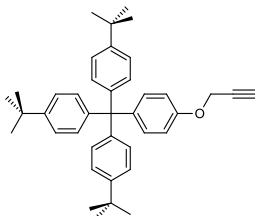
Bis-amine 5-oxygen polyether **12** (0.930 g, 2.00 mmol), pyridinium chloride thread **15**·Cl (0.770 g, 2.00 mmol) and NEt_3 (6 mL, 43.0 mmol) were dissolved in dry CH_2Cl_2 (150 mL) and stirred until the solid had dissolved. A solution of 5-(*tert*-butyl)isophthaloyl dichloride **16** (0.520 g, 2.00 mmol) in dry CH_2Cl_2 (30 mL) was added dropwise to the mixture which was then stirred for 1 hour. After this time, the solution was washed with 10% $\text{HCl}_{(\text{aq})}$ (2 x 100 mL) and water (2 x 100 mL) before the organic phase was dried over MgSO_4 , filtered, and the solvent removed by rotary evaporation. The resulting bright yellow solid was purified *via* silica gel column chromatography (97:3 $\text{CH}_2\text{Cl}_2/\text{MeOH}$) to yield **17** as a pale yellow solid (0.246 g, 20%). **MS** (ESI-MS) m/z 673.33 ($[\text{M} + \text{Na}]^+$, $\text{C}_{36}\text{H}_{46}\text{N}_2\text{NaO}_9$, calc. 673.31); **^1H NMR** (300 MHz, CDCl_3) δ 8.07 (2H, br s, ArH), 7.77 (1H, s, ArH), 6.87–6.79 (2H, m, -NH), 6.79–6.68 (8H, m, ArH), 4.07 (4H, t, $^3J = 4.9$ Hz, $-\text{CH}_2$), 4.02 (4H, t, $^3J = 4.9$ Hz, $-\text{CH}_2$), 3.88–3.78 (8H, m, $-\text{CH}_2$), 3.74–3.66 (8H, m, $-\text{CH}_2$), 1.35 (9H, s, ^tBu); **^{13}C NMR** (75 MHz, CDCl_3) δ 167.2, 153.3, 152.9, 152.5, 134.3, 128.2, 115.6, 115.3, 70.8, 70.7, 69.7, 68.1, 67.2, 39.6, 35.1, 31.1.

Tris(4-*tert*-butyl)phenyl)methanol (18**)⁶**

Magnesium turnings (4.71 g, 0.194 mol) were suspended in dry THF (20 mL) before a few iodine crystals were added. 1-Bromo-4-*tert*-butyl benzene (37.5 g, 0.176 mol) was dissolved in dry THF (100 mL) and then 5 mL of this solution was added to the magnesium suspension, under N₂, to initiate the reaction, with the remainder of the solution then left to add dropwise at a rate to maintain a gentle reflux. Once addition was complete, the reaction mixture was refluxed for 1 hour under N₂. After this time, dry diethyl carbonate (6.24 g, 0.053 mol) dissolved in dry THF (40 mL) was added dropwise to the reaction mixture, which was then refluxed for 1 hour under N₂. The vessel was left to cool to room temperature before being poured into a mixture of ice (~125 g) and conc. H₂SO₄ (20 mL) carefully. The THF was then removed and the resulting solution extracted into CH₂Cl₂ (3 x 100 mL) and washed with 5% NaHCO_{3(aq)} (100 mL) and water (100 mL). The organic phase was then dried (MgSO₄), filtered and the solvent removed to give the crude product, which was purified *via* recrystallisation from boiling cyclohexane (100 mL) to give **18** as an off-white solid (16.7 g, 66%). **MS** (ESI-MS) *m/z* 427.28 ([M - H]⁻, C₃₁H₃₉O, calc. 427.30); **¹H NMR** (300 MHz, CDCl₃) δ 7.36–7.28 (6H, m, ArH), 7.24–7.16 (6H, m, ArH), 2.73 (1H, s, -OH), 1.32 (27H, s, -*t*Bu); **¹³C NMR** (75 MHz, CDCl₃) δ 149.8, 144.2, 127.5, 124.7, 34.4, 31.3.

4-(Tris(4-(*tert*-butyl)phenyl)methyl)phenol (19**)**⁶

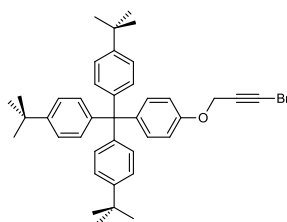
Compound **18** (16.7 g, 39.0 mmol) was dissolved in molten phenol (100 g) by warming in a round bottomed flask over an oil bath. Conc. HCl_(aq) (1 mL) was then added and the mixture refluxed overnight under nitrogen. After this time, the reaction mixture was cooled and KOH_(aq) (120 g in 300 mL de-ionised water) was added before the mixture was filtered to give a pale yellow solid. This was washed with water (500 mL), 20% aqueous acetic acid (500 mL) and water (500 mL) and then re-dissolved in CHCl₃ (1 L), dried (MgSO₄) and filtered. The solvent was removed to give the crude product, which was then suspended in hexane (250 mL) and refluxed for 30 minutes before being filtered to give the pure product as an off-white solid (6.36 g, 32%). **MS** (ESI-MS) *m/z* 527.33 ([M + Na]⁺, C₃₇H₄₄NaO, calc. 527.33); **¹H NMR** (300 MHz, CDCl₃) δ 7.27–7.22 (6H, m, ArH), 7.13–7.03 (8H, m, ArH), 4.62 (1H, s, -OH), 1.31 (27H, s, -^tBu); **¹³C NMR** (75 MHz, CDCl₃) δ 153.2, 148.3, 144.1, 139.8, 132.5, 130.7, 124.0, 113.9, 110.0, 34.3, 31.4.

Terphenyl-stoppered alkyne (20**)**⁷

Compound **19** (300 mg, 0.594 mmol) and propargyl bromide (80% solution in toluene, 0.099 mL, 0.892 mmol) were dissolved in dry DMF (100 mL). K₂CO₃ (411 mg, 2.97 mmol)

was then added to the solution before it was heated at 80 °C for 18 hours under nitrogen. After this time, the reaction mixture was allowed to cool to room temperature, filtered and concentrated. Water (20 mL) was added and the resulting solution extracted with EtOAc (3 x 30 mL). The combined organic fractions were dried over MgSO₄ and filtered before the solvent was removed to give the crude product. This was then purified by silica gel column chromatography (1:1 hexane/CH₂Cl₂) to give **20** as a white solid (270 mg, 84%). **MS** (ESI-MS) *m/z* 565.39 ([M + Na]⁺, C₄₀H₄₆NaO, calc. 565.34); **¹H NMR** (300 MHz, CDCl₃) δ 7.28–7.20 (6H, m, ArH), 7.15–7.05 (8H, m, ArH), 6.89–6.81 (2H, m, ArH), 4.66 (2H, s, -OCH₂), 2.54–2.48 (1H, m, -C≡CH), 1.31 (27H, s, -^tBu); **¹³C NMR** (75 MHz, CDCl₃) δ 148.3, 144.0, 140.5, 132.3, 130.7, 124.0, 113.3, 78.8, 75.4, 63.1, 55.7, 34.3, 31.4.

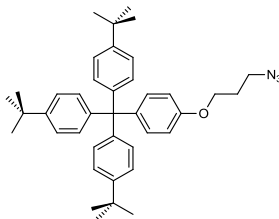
Terphenyl-stoppered bromo-alkyne (**21**)



Terphenyl-stoppered alkyne **20** (470 mg, 0.896 mmol) was dissolved in acetone (40 mL) and then *N*-bromosuccinimide (191 mg, 1.07 mmol) and AgNO₃ (18.3 mg, 0.107 mmol) were added. The reaction mixture was left to stir for 2 hours, in the dark, under nitrogen with the reaction progress being monitored *via* TLC. After this time, the reaction mixture was poured into ice water (50 mL) and then extracted with CH₂Cl₂ (3 x 50 mL). The combined organic phases were washed with brine (50 mL) and then dried over MgSO₄. Following filtration, the solvent was removed *in vacuo* and the resulting crude product was passed through a silica plug (3:1 hexane/EtOAc) to give **21** as an off-white solid (510 mg, 92%). **MS** (ESI-MS) *m/z* 645.2548 ([M + Na]⁺, C₄₀H₄₅BrNaO, calc. 645.2528); **¹H NMR** (300 MHz, CDCl₃) δ 7.26

(6H, d, $^3J = 8.8$ Hz, *ArH*), 7.16–7.06 (8H, m, *ArH*), 6.84 (2H, d, $^3J = 8.8$ Hz, *ArH*), 4.69 (2H, s, $-\text{OCH}_2$), 1.32 (27H, s, $-\text{tBu}$); ^{13}C NMR (75 MHz, CDCl_3) δ 155.4, 148.3, 144.0, 140.5, 132.3, 130.7, 124.0, 113.3, 63.0, 56.7, 47.4, 34.3, 31.4.

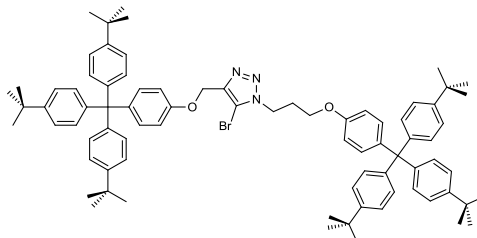
Terphenyl-stoppered propyl azide (**22**)⁷



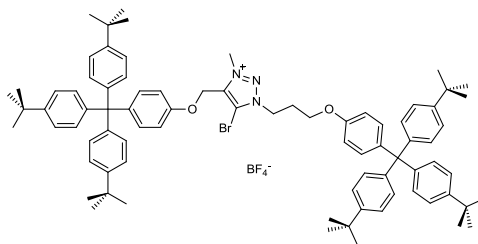
Compound **19** (1.25 g, 2.48 mmol) and 1,3-dibromopropane (0.754 mL, 7.44 mmol) were dissolved in dry MeCN (50 mL). K_2CO_3 (1.03 g, 7.44 mmol) was added to the solution, which was then heated at reflux for 12 hours under N_2 . After this time, the solution was cooled to room temperature, filtered and the solvent was removed. The resultant crude product was dissolved in CH_2Cl_2 (50 mL) and washed with water (3 x 50 mL). The organic phase was then dried (MgSO_4), filtered and the solvent was removed before the residue was purified *via* silica gel column chromatography (2:1 40–60 petroleum ether/ CH_2Cl_2). The resultant white solid was then dissolved in dry DMF (60 mL) and reacted with a three-fold molar excess of NaN_3 at 80 °C overnight. The solvent was removed and the residue was re-dissolved in CH_2Cl_2 (50 mL) and washed with water (3 x 50 mL). The organic phase was then dried over Na_2SO_4 , filtered and the solvent removed to give a white solid, which was purified *via* silica gel column chromatography (2:1 40–60 petroleum ether/ CH_2Cl_2) to give the product as a white solid (0.203 g, 14%). **MS** (ESI-MS) m/z 610.42 ($[\text{M} + \text{Na}]^+$, $\text{C}_{40}\text{H}_{49}\text{N}_3\text{NaO}$, calc. 610.37); ^1H NMR (300 MHz, CDCl_3) δ 7.26–7.21 (6H, m, *ArH*), 7.13–7.06 (8H, m, *ArH*), 6.77 (2H, d, $^3J = 8.8$ Hz, *ArH*), 4.03 (2H, t, $^3J = 5.8$ Hz, $-\text{CH}_2$), 3.53 (2H,

t, $^3J = 6.6$ Hz, $-CH_2$), 2.10–2.00 (2H, m, $-CH_2$), 1.31 (27H, s, $-tBu$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.4, 148.3, 144.1, 139.9, 132.3, 130.7, 124.0, 112.9, 64.3, 63.0, 48.3, 31.4, 28.8.

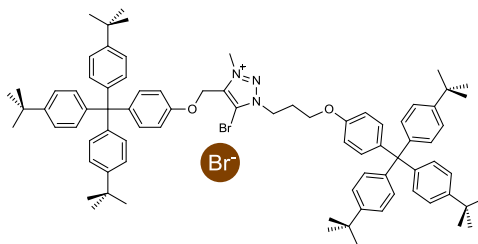
Bromo-triazole axle (23)



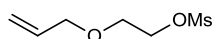
Terphenyl-stoppered bromo-alkyne **21** (216 mg, 0.340 mmol) and terphenyl-stoppered azide **22** (200 mg, 0.340 mmol) were dissolved in dry THF (30 mL). CuBr (48.8 mg, 0.340 mmol) and Cu(OAc)₂ (61.8 mg, 0.340 mmol) were then added and the reaction mixture left to stir at 50 °C under nitrogen for 21 days with the reaction progress monitored *via* TLC. After this time, the reaction was quenched with 10% NH₄OH_(aq) (3 mL) and the THF was removed by rotary evaporation. Water (20 mL) and CH₂Cl₂ (30 mL) were then added to the residue and the organic layer was kept. The aqueous layer was extracted with CH₂Cl₂ (3 x 30 mL) and then the combined organic layers were washed with water (30 mL) and dried over MgSO₄. Following filtration, the solvent was removed *in vacuo* and the crude product was purified by silica gel column chromatography (1:1 CH₂Cl₂/hexane to 9:1 CH₂Cl₂/MeOH) to give **23** as a white solid (326 mg, 79%). **MS** (ESI-MS) m/z 1230.6423 ($[M + Na]^+$, C₈₀H₉₄BrN₃NaO₂, calc. 1230.6422); ^1H NMR (300 MHz, $CDCl_3$) δ 7.31–7.21 (12H, m, ArH), 7.16–7.07 (16H, m, ArH), 6.95–6.87 (2H, m, ArH), 6.80–6.73 (2H, m, ArH), 5.12 (2H, s, $-OCH_2$), 4.60 (2H, t, $^3J = 6.5$ Hz, $-OCH_2CH_2$), 4.02 (2H, t, $^3J = 5.7$ Hz, $-OCH_2CH_2CH_2$), 2.49–2.37 (2H, m, $-OCH_2CH_2$), 1.37–1.28 (54H, m, $-tBu$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.1, 148.3, 144.0, 142.3, 140.2, 140.0, 132.3, 130.7, 124.0, 113.4, 113.0, 63.8, 63.0, 60.7, 46.3, 34.3, 31.4, 29.3.

Bromo-triazolium axle tetrafluoroborate salt ($24 \cdot \text{BF}_4$)

Bromo-triazole axle **23** (108 mg, 0.0893 mmol) was dissolved in dry CH_2Cl_2 (30 mL) and then $(\text{Me}_3\text{O})\text{BF}_4$ (52.8 mg, 0.357 mmol) was added. The reaction mixture was then left to stir at room temperature under N_2 for 2 days. After this time, the reaction was quenched with MeOH (2 mL) and the solvent was removed. The resulting residue was then purified by silica gel column chromatography (98:2 $\text{CH}_2\text{Cl}_2/\text{MeOH}$) to give **24**· BF_4 as a white solid (117 mg, 99%). **MS** (ESI-MS) m/z 1222.6759 ($[\text{M} - \text{BF}_4]^+$, $\text{C}_{81}\text{H}_{97}\text{BrN}_3\text{O}_2$, calc. 1222.6759); **^1H NMR** (300 MHz, CDCl_3) δ 7.27–7.02 (28H, m, *ArH*), 6.84–6.78 (2H, m, *ArH*), 6.73–6.66 (2H, m, *ArH*), 5.30 (2H, br s, $-\text{OCH}_2$), 4.80 (2H, t, $^3J = 6.3$ Hz, $-\text{OCH}_2\text{CH}_2$), 4.32 (3H, s, $-\text{N}^+\text{CH}_3$), 4.11 (2H, t, $^3J = 5.0$ Hz, $-\text{OCH}_2\text{CH}_2\text{CH}_2$), 2.59–2.48 (2H, m, $-\text{OCH}_2\text{CH}_2$), 1.34–1.25 (54H, m, $-\text{tBu}$); **^{13}C NMR** (126 MHz, $\text{DMSO}-d_6$) δ 155.5, 154.8, 147.9, 143.9, 143.8, 140.8, 139.3, 138.2, 131.6, 130.0, 124.4, 119.4, 113.9, 113.2, 64.4, 62.7, 57.3, 54.9, 50.6, 34.1, 31.1, 27.4; **^{19}F NMR** (283 MHz, $\text{DMSO}-d_6$) δ -148.3 (d, $J = 15.9$ Hz).

Bromo-triazolium axle bromide salt (24·Br)

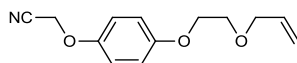
Bromo-triazolium axle tetrafluoroborate salt **24**·BF₄ (100 mg, 0.0763 mmol) was dissolved in CH₂Cl₂ (30 mL) and the resulting solution washed vigorously with 1 M NH₄Br_(aq) (10 x 20 mL) and water (2 x 20 mL). The organic layer was then dried over MgSO₄, filtered and the solvent removed *in vacuo* to give **24**·Br as a white solid in quantitative yield (99.5 mg). **MS** (ESI-MS) *m/z* 1222.6751 ([M - Br]⁺, C₈₁H₉₇BrN₃O₂, calc. 1222.6759); **¹H NMR** (500 MHz, DMSO-*d*⁶) δ 7.32–7.22 (12H, m, ArH), 7.12–6.97 (16H, m, ArH), 6.96–6.90 (2H, m, ArH), 6.73–6.66 (2H, m, ArH), 5.35 (2H, s, -OCH₂), 4.81 (2H, t, ³*J* = 6.1 Hz, -OCH₂CH₂), 4.28 (3H, s, -N⁺CH₃), 4.08 (2H, t, ³*J* = 5.5 Hz, -OCH₂CH₂CH₂), 2.43–2.35 (2H, m, -OCH₂CH₂), 1.28–1.16 (54H, m, -^tBu); **¹³C NMR** (126 MHz, DMSO-*d*⁶) δ 155.5, 154.8, 147.9, 147.8, 143.9, 143.8, 140.8, 139.2, 138.1, 131.6, 130.0, 124.4, 124.3, 119.4, 113.9, 113.2, 64.3, 62.6, 62.5, 57.3, 50.6, 34.1, 31.1, 27.4.

2-(Allyloxy)ethyl methanesulfonate (25)⁸

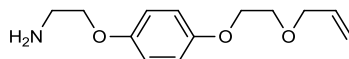
2-Allyloxyethanol (5.24 mL, 49.0 mmol) and NEt₃ (13.0 mL, 93.0 mmol) were dissolved in dry CH₂Cl₂ (100 mL) and stirred under nitrogen in an ice bath. Mesyl chloride (4.17 mL, 53.9 mmol) dissolved in dry CH₂Cl₂ (75 mL) was then added dropwise to the solution. Once the addition was complete, the reaction mixture was allowed to warm to room temperature and was left to stir for 1 hour under nitrogen. After this time, the mixture was washed with

water (2 x 75 mL), 1 M HCl_(aq) (3 x 50 mL) and brine (3 x 75 mL). The organic layer was then dried over MgSO₄, filtered and the solvent removed to give **25** as an orange oil (8.13 g, 92%). **MS** (ESI-MS) *m/z* 203.05 ([M + Na]⁺, C₆H₁₂NaO₄S, calc. 203.04); **¹H NMR** (300 MHz, CDCl₃) δ 5.96–5.80 (1H, m, -CHCH₂), 5.34–5.24 (1H, m, -CHCH₂), 5.24–5.16 (1H, m, -CHCH₂), 4.40–4.33 (2H, m, -OCH₂), 4.06–4.00 (2H, m, -OCH₂), 3.72–3.67 (2H, m, -OCH₂), 3.05 (3H, s, -CH₃); **¹³C NMR** (75 MHz, CDCl₃) δ 133.9, 117.6, 72.1, 69.2, 67.6, 37.6.

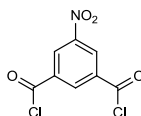
2-(4-(2-(Allyloxy)ethoxy)phenoxy)acetonitrile (**26**)⁹



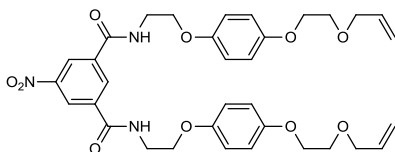
2-(4-Hydroxyphenoxy)acetonitrile **9** (2.48 g, 16.6 mmol) and mesylate **25** (3.00 g, 16.6 mmol) were dissolved in dry MeCN (150 mL). K₂CO₃ (3.22 g, 23.3 mmol) was then added to the solution, which was left to reflux under nitrogen overnight. After this time, the reaction mixture was cooled to room temperature, filtered and the solvent was removed. The residue was then dissolved in CH₂Cl₂ (75 mL) and washed with 1 M HCl_(aq) (2 x 50 mL), water (2 x 50 mL) and brine (2 x 50 mL). The organic phase was then dried over MgSO₄, filtered and the solvent was removed *in vacuo* to give the crude product which was purified *via* silica gel column chromatography (7:3 hexane/EtOAc) to give **26** as a colourless oil (1.93 g, 50%). **MS** (ESI-MS) *m/z* 256.09 ([M + Na]⁺, C₁₃H₁₅NNaO₃, calc. 256.10); **¹H NMR** (300 MHz, CDCl₃) δ 6.92 (4H, d, ³*J* = 3.3 Hz, ArH), 6.03–5.88 (1H, m, -CH=CH₂), 5.37–5.29 (1H, m, -CH=CH₂), 5.23–5.17 (1H, m, -CH=CH₂), 4.71 (2H, s, -CH₂CN), 4.13–4.09 (4H, m, -OCH₂), 3.80 (2H, t, ³*J* = 4.7 Hz, -OCH₂); **¹³C NMR** (75 MHz, CDCl₃) δ 154.8, 150.8, 134.4, 117.4, 116.6, 115.8, 72.4, 68.4, 68.0, 54.8.

2-(4-(2-(Allyloxy)ethoxy)phenoxy)ethanamine (27)⁹

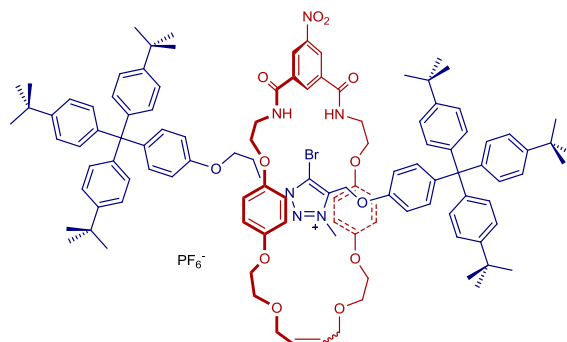
Compound **26** (3.36 g, 14.4 mmol) was dissolved in dry Et₂O (100 mL) and added dropwise to a suspension of LiAlH₄ (0.929 g, 24.5 mmol) in dry Et₂O (100 mL). The reaction mixture was then left to reflux under nitrogen for 3 hours. After this time, the mixture was cooled to room temperature and quenched carefully with water (2 mL), 15% NaOH_(aq) (2 mL) and more water (3 mL). The resulting white precipitate was filtered and washed with Et₂O before the filtrate was dried over MgSO₄ and filtered. The solvent was then removed *in vacuo* to give the product as an orange oil (2.21 g, 65%). **MS** (ESI-MS) *m/z* 238.15 ([M + H]⁺, C₁₃H₂₀NO₃, calc. 238.14); **¹H NMR** (300 MHz, CDCl₃) δ 6.88–6.78 (4H, m, ArH), 6.02–5.85 (1H, m, -CH=CH₂), 5.36–5.24 (1H, m, -CH=CH₂), 5.24–5.14 (1H, m, -CH=CH₂), 4.11–4.05 (4H, m, -OCH₂), 3.92 (2H, t, ³*J* = 4.4 Hz, -OCH₂), 3.77 (2H, t, ³*J* = 4.8 Hz, -OCH₂), 3.04 (2H, t, ³*J* = 5.3 Hz, -CH₂NH₂), 1.96–1.70 (2H, m, -NH₂); **¹³C NMR** (75 MHz, CDCl₃) δ 153.1, 153.0, 134.5, 117.3, 115.5, 115.3, 72.3, 70.6, 68.5, 68.0, 41.5.

5-Nitroisophthaloyl dichloride (28)¹⁰

5-Nitroisophthalic acid (0.989 g, 4.68 mmol) was dissolved in excess SOCl₂ (10 mL) and the resultant mixture was left to reflux under nitrogen overnight in the presence of one drop of dry degassed DMF. Once the solution had become homogeneous, the excess SOCl₂ was removed by rotary evaporation using a bump trap. The resulting product was then used immediately in the next reaction without further purification or characterisation.

Bis-vinyl appended macrocycle precursor (29)¹⁰

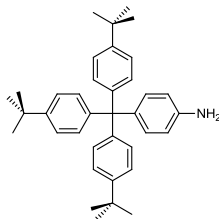
Amine **27** (2.21 g, 9.31 mmol) and NEt_3 (17.7 mL, 126 mmol) were dissolved in dry CH_2Cl_2 (100 mL) and stirred for 10 minutes at 0 °C under nitrogen. 5-Nitroisophthaloyl dichloride **28** (1.16 g, 4.68 mmol) dissolved in dry CH_2Cl_2 (75 mL) was then added dropwise to the solution. The reaction mixture was then left to stir at 0 °C, under nitrogen, for 1 hour. After this time, the solution was warmed to room temperature and washed with 10% $\text{HCl}_{(\text{aq})}$ (3 x 100 mL) and water (3 x 100 mL). The organic layer was dried over MgSO_4 , filtered and the solvent removed *in vacuo* to give the crude product as a dark orange residue. This was purified by silica gel column chromatography (7:3 EtOAc/ CH_2Cl_2) to give **29** as a yellow solid (1.06 g, 35%). **MS** (ESI-MS) m/z 672.30 ($[\text{M} + \text{Na}]^+$, $\text{C}_{34}\text{H}_{39}\text{N}_3\text{NaO}_{10}$, calc. 672.25); **^1H NMR** (300 MHz, CDCl_3) δ 8.66 (2H, br s, ArH), 8.55 (1H, s, ArH), 7.48 (2H, t, $^3J = 5.7$ Hz, -NH), 6.79–6.73 (8H, m, ArH), 6.00–5.84 (2H, m, -CH=CH₂), 5.35–5.24 (2H, m, -CH=CH₂), 5.23–5.15 (2H, m, -CH=CH₂), 4.10–3.99 (12H, m, -CH₂), 3.84–3.73 (8H, m, -CH₂); **^{13}C NMR** (75 MHz, CDCl_3) δ 164.7, 153.1, 152.5, 148.0, 136.1, 134.4, 131.3, 124.6, 117.5, 115.4, 115.2, 72.3, 68.5, 67.8, 66.8, 40.1.

Bromo-triazolium axle containing rotaxane (30·PF₆)

Bis-vinyl appended macrocycle precursor **29** (37.9 mg, 0.0584 mmol) and bromo-triazolium axle bromide salt **24**·Br (114 mg, 0.0875 mmol) were dissolved in dry CH₂Cl₂ (50 mL) and stirred for 30 minutes. After this time, Grubbs' II (3.79 mg, 10% by weight) was added and the reaction mixture left to stir at room temperature, under nitrogen, overnight. The reaction progress was monitored *via* TLC and once all of **29** had reacted the volatile components were removed by rotary evaporation and the crude product was purified *via* preparative TLC (95:5 CH₂Cl₂/MeOH then 1:1 MeCN/CH₂Cl₂). The resulting off-white solid was dissolved in CHCl₃ (20 mL) and washed with 0.1 M NH₄PF_{6(aq)} (10 x 10 mL) and then water (2 x 10 mL). The organic phase was dried over MgSO₄, filtered and the solvent removed *in vacuo* to give **30**·PF₆ as an off-white solid (14.9 mg, 13%). **mp** 146 °C; **MS** (ESI-MS) *m/z* 1843.9143 ([M - PF₆]⁺, C₁₁₃H₁₃₂BrN₆O₁₂, calc. 1843.9081); **¹H NMR** (500 MHz, CDCl₃) δ 8.96 (2H, s, ArH nitro-isophthalamide), 8.46 (1H, s, ArH nitro-isophthalamide), 7.30–7.21 (16H, m, ArH stopper), 7.15–7.06 (14H, m, ArH stopper), 6.88 (2H, d, ³J = 8.7 Hz, ArH stopper), 6.70 (2H, d, ³J = 9.0 Hz, ArH stopper), 6.54–6.47 (4H, m, ArH hydroquinone), 6.43–6.35 (4H, m, ArH hydroquinone), 5.67–5.61 (2H, m, -CH=CH), 4.71 (2H, s, -OCH₂ axle), 4.14–3.98 (9H, m, -CH₂ & -N⁺CH₃), 3.89–3.72 (12H, m, -CH₂), 3.69–3.61 (4H, m, -CH₂), 2.13–1.95 (2H, m, -OCH₂CH₂), 1.33–1.28 (54H, m, -^tBu); **¹³C NMR** (126 MHz, CDCl₃) δ 164.7, 156.7, 154.5, 152.9, 152.3, 149.1, 148.6, 148.4, 144.0, 143.8, 142.4, 140.6, 136.4, 132.6, 132.4, 130.6,

129.7, 126.4, 124.3, 124.1, 115.0, 114.5, 113.2, 112.9, 70.8, 69.3, 67.8, 67.1, 63.2, 63.1, 56.9, 56.8, 50.3, 39.9, 39.8, 34.3, 31.4, 29.7, 27.0, 22.7, 14.1; ^{19}F NMR (283 MHz, CDCl_3) δ -71.2 (d, J = 714.9 Hz); ^{31}P NMR (122 MHz, CDCl_3) δ -144.2 (sept., J = 717.1 Hz).

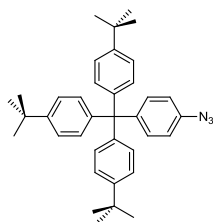
Terphenyl-stoppered amine (**31**)⁶



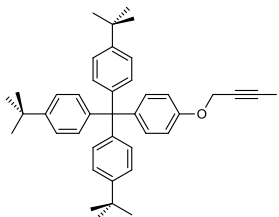
Tris(4-(*tert*-butyl)phenyl)methanol **18** (9.00 g, 21.0 mmol) was suspended in dry benzene (10 mL). Excess acetyl chloride (5 mL) was then added before the mixture was refluxed for 30 minutes under nitrogen. Hexane (50 mL) was then added and the mixture placed in the freezer to precipitate a white powder, which was isolated *via* vacuum filtration and immediately dissolved in aniline (50 mL) before being heated at 130 °C overnight under nitrogen. After cooling to room temperature, the mixture was poured into 10% $\text{HCl}_{(\text{aq})}$ (250 mL) to give a purple precipitate, which was then filtered and washed with 10% $\text{HCl}_{(\text{aq})}$ (2 x 100 mL) and stirred vigorously in saturated $\text{Na}_2\text{CO}_{3(\text{aq})}$ (200 mL). The aqueous suspension was extracted into CH_2Cl_2 (2 x 150 mL), washed with 1 M $\text{K}_2\text{CO}_{3(\text{aq})}$ (100 mL), water (100 mL), dried (MgSO_4), filtered and the solvent removed to give a purple solid. This was then re-dissolved in minimal CH_2Cl_2 and filtered through a short silica pad (eluting with CH_2Cl_2) and the solvent removed to give a pale yellow solid. This was suspended in boiling hexane (300 mL) and hot toluene was added until all the material dissolved (~125 mL). Cooling the solution resulted in the formation of white crystals, which were isolated *via* filtration, washed with hexane (2 x 25 mL) and dried *in vacuo* to give the pure product **31** (5.09 g, 48%). **MS** (ESI-MS) m/z 504.35 ($[\text{M} + \text{H}]^+$, $\text{C}_{37}\text{H}_{46}\text{N}$, calc. 504.36); ^1H NMR

(300 MHz, CDCl₃) δ 7.23 (6H, d, ^3J = 8.9 Hz, ArH), 7.10 (6H, d, ^3J = 8.1 Hz, ArH), 6.97 (2H, d, ^3J = 8.5 Hz, ArH), 6.58 (2H, d, ^3J = 8.5 Hz, ArH), 3.59 (2H, s, -NH₂), 1.31 (27H, s, -^tBu); ¹³C NMR (75 MHz, CDCl₃) δ 148.1, 144.3, 137.6, 130.7, 123.9, 114.0, 34.3, 31.4.

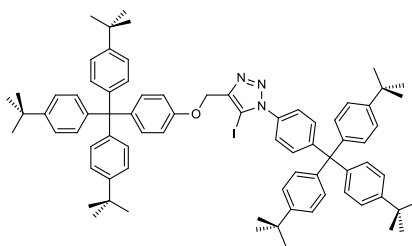
Terphenyl-stoppered azide (**32**)¹¹



Terphenyl-stoppered amine **31** (1.00 g, 1.99 mmol) was suspended in conc. HCl_(aq) (36%, 80 mL) before EtOH (720 mL) was added and the mixture heated to dissolve all of the solid. Once completely dissolved, the reaction mixture was cooled to 0 °C and NaNO₂ (274 mg, 3.97 mmol) and NaN₃ (258 mg, 3.97 mmol) were added. The reaction was stirred under nitrogen for 2 hours with the temperature of the vessel kept below 5 °C at all times. After this time, the reaction mixture was allowed to warm to room temperature overnight. The EtOH was then removed *in vacuo* and water (150 mL) added before the crude product was extracted into Et₂O (3 x 150 mL). This was washed with saturated Na₂CO_{3(aq)} (2 x 150 mL) and brine (150 mL) before being dried (MgSO₄) and filtered. The solvent was then removed to give an off-white powder, which was purified *via* silica gel column chromatography (2:1 40–60 petroleum ether/CH₂Cl₂) to give **32** as an off-white powder (719 mg, 69%). **MS** (ESI-MS) *m/z* 552.32 ([M + Na]⁺, C₃₇H₄₃N₃Na, calc. 552.34); ¹H NMR (300 MHz, CDCl₃) δ 7.25 (6H, d, ^3J = 8.5 Hz, ArH), 7.20 (2H, d, ^3J = 8.8 Hz, ArH), 7.08 (6H, d, ^3J = 9.0 Hz, ArH), 6.91 (2H, d, ^3J = 8.8 Hz, ArH), 1.31 (27H, s, -^tBu); ¹³C NMR (75 MHz, CDCl₃) δ 153.7, 148.5, 143.6, 132.6, 130.6, 124.2, 117.8, 34.9, 31.4.

Terphenyl-stoppered iodo-alkyne (33)¹²

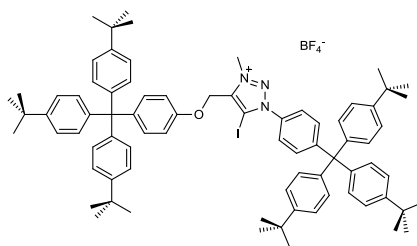
Alkyne **20** (300 mg, 0.552 mmol) was dissolved in acetone (30 mL), *N*-iodosuccinimide (149 mg, 0.663 mmol) and AgNO₃ (11.3 mg, 0.066 mmol) were added and the reaction was left to stir overnight, under N₂, in the dark. After this, the reaction mixture was poured into ice water (50 mL) and extracted with CH₂Cl₂ (3 x 50 mL). The combined organic phase was then washed with brine (50 mL), dried (MgSO₄), filtered and the solvent removed to give the crude product which was purified *via* silica gel column chromatography (2:1 hexane/CH₂Cl₂) to give **33** as an off-white solid (335 mg, 91%). **MS** (ESI-MS) *m/z* 686.27 ([M + NH₄]⁺, C₄₀H₄₉INO, calc. 686.29); **¹H NMR** (300 MHz, CDCl₃) δ 7.24 (6H, d, ³*J* = 8.5 Hz, *ArH*), 7.13–7.06 (8H, m, *ArH*), 6.83 (2H, d, ³*J* = 9.0 Hz, *ArH*), 4.81 (2H, s, -OCH₂), 1.31 (27H, s, -^{*t*}Bu); **¹³C NMR** (75 MHz, CDCl₃) δ 136.8, 132.3, 130.7, 124.0, 113.3, 109.3, 34.9, 31.4.

Shortened iodo-triazole axle (34)

CuI (3.58 mg, 0.019 mmol) and TBTA (10.0 mg, 0.019 mmol) were stirred in dry degassed THF (1 mL) for 20 minutes. After this time, terphenyl-stoppered azide **32** (200 mg, 0.377 mmol) and iodo-alkyne **33** (252 mg, 0.377 mmol), dissolved in dry degassed THF

(5 mL), were added and the reaction mixture left to stir overnight at room temperature under nitrogen. The reaction mixture was then quenched with 10% $\text{NH}_4\text{OH}_{(\text{aq})}$ (5 mL) and the THF removed *in vacuo* before the aqueous phase was extracted into CH_2Cl_2 (3 x 5 mL). The combined organic phase was then dried (MgSO_4), filtered and the solvent removed to give the crude product. This was purified *via* silica gel column chromatography (1:1 CH_2Cl_2 /hexane) to give **34** as a white solid (360 mg, 80%). **MS** (ESI-MS) m/z 1220.5867 ($[\text{M} + \text{Na}]^+$, $\text{C}_{77}\text{H}_{88}\text{IN}_3\text{NaO}$, calc. 1220.5864); **^1H NMR** (300 MHz, CDCl_3) δ 7.17–7.06 (14H, m, ArH), 7.01–6.92 (16H, m, ArH), 6.80 (2H, d, $^3J = 9.1$ Hz, ArH), 5.03 (2H, s, $-\text{OCH}_2$), 1.19–1.14 (54H, m, $-\text{tBu}$); **^{13}C NMR** (75 MHz, CDCl_3) δ 148.8, 148.3, 144.0, 143.2, 140.3, 132.3, 130.7, 124.6, 124.3, 124.0, 113.5, 63.7, 34.3, 31.4.

Shortened iodo-triazolium axle tetrafluoroborate salt (**35**· BF_4)

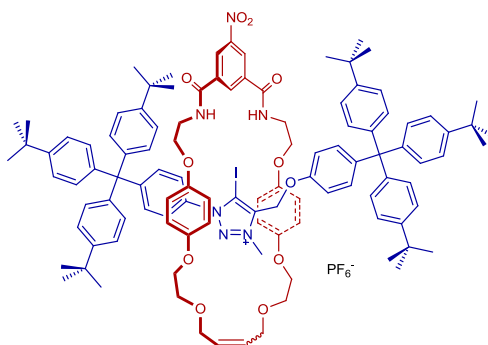


Iodo-triazole **34** (360 mg, 0.301 mmol) was dissolved in dry CH_2Cl_2 (40 mL) and trimethyloxonium tetrafluoroborate (111 mg, 0.751 mmol) was added before the reaction mixture was left to stir at room temperature, under nitrogen, overnight. After this time, the reaction was quenched with MeOH (5 mL) and the solvent removed to give an off-white residue. This was purified *via* silica gel column chromatography (98:2 CH_2Cl_2 /MeOH) to give **35**· BF_4 as a white solid (308 mg, 79%). **MS** (ESI-MS) m/z 1212.6222 ($[\text{M} - \text{BF}_4]^+$, $\text{C}_{78}\text{H}_{91}\text{IN}_3\text{O}$, calc. 1212.6201); **^1H NMR** (300 MHz, CDCl_3) δ 7.54–7.42 (4H, m, ArH), 7.26–7.12 (14H, m, ArH), 7.05 (12H, d, $^3J = 8.5$ Hz, ArH), 6.85 (2H, d, $^3J = 8.5$ Hz, ArH), 5.36 (2H, s, $-\text{OCH}_2$), 4.46 (3H, s, $-\text{N}^+\text{CH}_3$), 1.32–1.25 (54H, m, $-\text{tBu}$); **^{13}C NMR** (75 MHz, CDCl_3)

δ 149.1, 148.5, 143.7, 142.6, 142.1, 132.8, 130.6, 124.9, 124.5, 124.2, 113.4, 63.1, 34.3, 31.4;

^{19}F NMR (283 MHz, CDCl_3) δ -154.8 (d, J = 15.7 Hz).

Shortened iodo-triazolium axle containing rotaxane (**36**· PF_6)

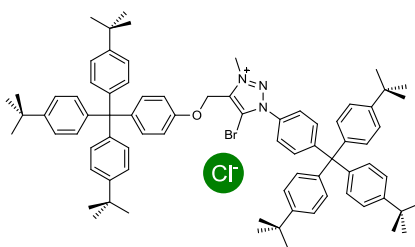


A solution of shortened iodo-triazolium axle tetrafluoroborate salt **35**· BF_4 (165 mg, 0.127 mmol) in CHCl_3 (10 mL) was repeatedly washed with 1 M $\text{NH}_4\text{Cl}_{(\text{aq})}$ (10 x 10 mL) and then washed with water (10 mL). The organic phase was dried over MgSO_4 , filtered and the solvent removed to give **35**·Cl (143 mg, 0.114 mmol) which was then re-dissolved in dry CH_2Cl_2 (30 mL). Bis-vinyl appended macrocycle precursor **29** (112 mg, 0.171 mmol) was then added to the solution, which was stirred for 30 minutes under nitrogen. After this time, Grubbs' II (11.2 mg, 10% by weight) was added and the reaction mixture left to stir at room temperature, under nitrogen, for 2 days. Following this, the volatile components were removed by rotary evaporation and the crude product was initially purified *via* silica gel column chromatography (98:2 $\text{CH}_2\text{Cl}_2/\text{MeOH}$). The resulting off-white solid was dissolved in CHCl_3 (10 mL) and washed with 0.1 M $\text{NH}_4\text{PF}_6_{(\text{aq})}$ (10 x 10 mL) and then water (2 x 10 mL). The organic phase was dried over MgSO_4 , filtered and the solvent removed *in vacuo* to give an off-white solid, which was then further purified *via* preparative TLC (98:2 $\text{CH}_2\text{Cl}_2/\text{MeOH}$) to give the pure product **36**· PF_6 as an off-white solid (26.6 mg, 12%). mp 193 °C (dec.); MS (ESI-MS) m/z 1833.8596 ($[\text{M} - \text{PF}_6]^+$, $\text{C}_{110}\text{H}_{126}\text{IN}_6\text{O}_{11}$,

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extracted into CH₂Cl₂ (3 x 5 mL). The combined organic phase was dried (MgSO₄), filtered and the solvent removed to give the crude product, which was then purified *via* silica gel column chromatography (2:1 CH₂Cl₂/hexane) to give **37** as an off-white solid (138 mg, 52%). **MS** (ESI-MS) m/z 1172.6079 ([M + Na]⁺, C₇₇H₈₈BrN₃NaO, calc. 1172.6003); **¹H NMR** (300 MHz, CDCl₃) δ 7.45–7.37 (4H, m, ArH), 7.25–7.20 (10H, m, ArH), 7.13–7.04 (16H, m, ArH), 6.92 (2H, d, ³*J* = 8.9 Hz, ArH), 5.16 (2H, s, -OCH₂), 1.31–1.28 (54H, m, -^tBu); **¹³C NMR** (75 MHz, CDCl₃) δ 148.8, 148.3, 144.0, 143.2, 140.4, 132.3, 132.2, 130.7, 124.4, 124.1, 123.9, 113.4, 110.0, 63.1, 34.3, 31.4.

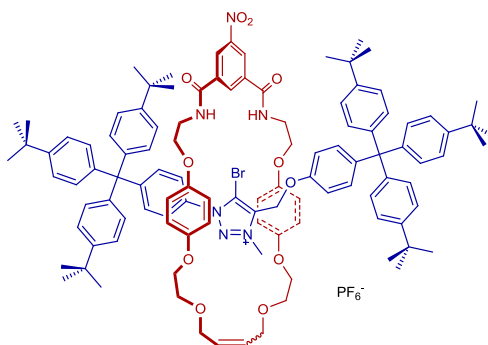
Shortened bromo-triazolium axle chloride salt (**38**·Cl)



Shortened bromo-triazole axle **37** (138 mg, 0.120 mmol) was dissolved in dry CH₂Cl₂ (50 mL). Trimethyloxonium tetrafluoroborate (44.0 mg, 0.300 mmol) was then added to the solution, which was left to stir at room temperature, under nitrogen, overnight. After this time, the reaction was quenched with MeOH (5 mL) and the solvent removed to leave an off-white residue, which was purified *via* silica gel column chromatography (98:2 CH₂Cl₂/MeOH) to give **38**·BF₄ as a white solid. This was then dissolved in CHCl₃ (20 mL) and washed with 1 M NH₄Cl_(aq) (10 x 20 mL) and water (20 mL) before being dried over MgSO₄ and filtered. The solvent was then removed to give **38**·Cl as a white solid (140 mg, 97%). **MS** (ESI-MS) m/z 1164.6341 ([M - Cl]⁺, C₇₈H₉₁BrN₃O, calc. 1164.6340); **¹H NMR** (300 MHz, CDCl₃) δ 7.63–7.49 (4H, m, ArH), 7.32–7.22 (12H, m, ArH), 7.18 (2H, d, ³*J* = 8.8 Hz, ArH), 7.08 (12H, d, ³*J* = 8.4 Hz, ArH), 6.91 (2H, d, ³*J* = 8.8 Hz, ArH), 5.69 (2H, s,

-OCH₂), 4.73 (3H, s, -N⁺CH₃), 1.33–1.29 (54H, m, -^tBu); ¹³C NMR (75 MHz, CDCl₃) δ 149.1, 148.5, 143.7, 132.9, 130.6, 124.5, 124.1, 113.4, 63.1, 34.4, 31.4.

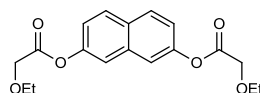
Shortened bromo-triazolium axle containing rotaxane (39·PF₆)



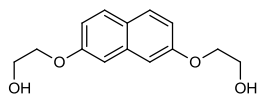
Shortened bromo-triazolium axle chloride salt **38**·Cl (87.0 mg, 0.072 mmol) and bis-vinyl appended macrocycle precursor **29** (70.0 mg, 0.108 mmol) were dissolved in dry CH₂Cl₂ (15 mL) and stirred for 30 minutes under nitrogen. After this time, Grubbs' II (7.00 mg, 10% by weight) was added and the reaction mixture left to stir at room temperature, under nitrogen, for 2 days. Following this, the volatile components were removed by rotary evaporation and the crude product was purified *via* silica gel column chromatography (95:5 CH₂Cl₂/MeOH), followed by preparative TLC (98:2 CH₂Cl₂/MeOH then 1:1 CH₂Cl₂/MeCN). The resulting off-white solid was dissolved in CHCl₃ (10 mL) and washed with 0.1 M NH₄PF_{6(aq)} (10 x 10 mL) and then water (2 x 10 mL). The organic phase was dried over MgSO₄, filtered and the solvent removed *in vacuo* to give an off-white solid, which was then further purified *via* preparative TLC (2:1 CH₂Cl₂/MeCN) to give the pure product **39**·PF₆ as an off-white solid (5.30 mg, 4%). **mp** 153 °C (dec.); **MS** (ESI-MS) *m/z* 1785.8728 ([M - PF₆]⁺, C₁₁₀H₁₂₆BrN₆O₁₁, calc. 1785.8662); ¹H NMR (500 MHz, 1:1 CDCl₃/CD₃OD) δ 8.84–8.80 (2H, m, ArH nitro-isophthalamide), 8.64–8.61 (1H, m, ArH nitro-isophthalamide), 7.47 (2H, d, ³J = 8.8 Hz, ArH stopper), 7.38 (2H, d, ³J = 9.0 Hz, ArH stopper), 7.33 (6H, d,

$^3J = 8.8$ Hz, ArH stopper), 7.27 (6H, d, $^3J = 8.8$ Hz, ArH stopper), 7.20 (2H, d, $^3J = 9.0$ Hz, ArH stopper), 7.10 (6H, d, $^3J = 8.6$ Hz, ArH stopper), 7.05 (6H, d, $^3J = 8.6$ Hz, ArH stopper), 6.73 (2H, d, $^3J = 8.6$ Hz, ArH stopper), 6.47 (4H, d, $^3J = 9.0$ Hz, ArH hydroquinone), 6.38 (4H, d, $^3J = 9.0$ Hz, ArH hydroquinone), 5.70–5.65 (2H, m, $-CH=CH$), 4.65 (2H, s, $-OCH_2$ axle), 4.21 (3H, s, $-N^+CH_3$), 4.02–3.69 (2H, m, $-CH_2$), 3.95–3.89 (2H, m, $-CH_2$), 3.86–3.82 (4H, m, $-CH_2$), 3.82–3.72 (6H, m, $-CH_2$), 3.72–3.65 (2H, m, $-CH_2$), 3.64–3.59 (4H, m, $-CH_2$), 1.30–1.25 (54H, m, $-tBu$); ^{13}C NMR (126 MHz, 1:1 $CDCl_3/CD_3OD$) δ 166.2, 155.4, 153.4, 149.9, 149.3, 144.7, 143.6, 143.0, 139.3, 136.9, 133.4, 131.3, 130.0, 125.9, 125.4, 125.0, 124.4, 115.8, 115.6, 114.1, 71.6, 69.6, 68.6, 67.6, 66.3, 64.6, 40.8, 40.5, 35.0, 34.9, 31.8, 30.4; ^{19}F NMR (283 MHz, 1:1 $CDCl_3/CD_3OD$) δ -74.2 (d, $J = 710.2$ Hz); ^{31}P NMR (122 MHz, 1:1 $CDCl_3/CD_3OD$) δ -144.7 (sept., $J = 712.2$ Hz).

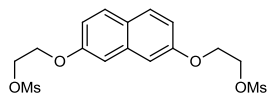
2,7-Bis(ethoxycarbonylmethoxy)naphthalene (**40**)¹³



2,7-Dihydroxynaphthalene (5.00 g, 31.2 mmol) was dissolved in acetone (125 mL). K_2CO_3 (43.1 g, 312 mmol) and ethyl bromoacetate (7.61 mL, 68.6 mmol) were then added before the reaction mixture was left to reflux under nitrogen overnight. After this time, the mixture was cooled to room temperature, filtered and the solvent removed to give an off-white solid which was subsequently recrystallised from EtOH to yield **40** as a white crystalline solid (7.03 g, 68%). **MS** (ESI-MS) m/z 333.12 ($[M + H]^+$, $C_{18}H_{21}O_6$, calc. 333.13); ^1H NMR (300 MHz, $CDCl_3$) δ 7.70 (2H, d, $^3J = 9.0$ Hz, ArH), 7.11 (2H, dd, $^3J = 8.8$ Hz, $^4J = 2.4$ Hz, ArH), 6.99 (2H, d, $^4J = 2.3$ Hz, ArH), 4.73 (4H, s, $-OC(O)CH_2$), 4.31 (4H, q, $^3J = 7.4$ Hz, $-OCH_2CH_3$), 1.32 (6H, t, $^3J = 6.9$ Hz, $-OCH_2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.8, 156.4, 135.3, 129.4, 125.2, 116.4, 106.6, 65.4, 61.4, 14.1.

2,7-Bis(2'-hydroxyethoxy)naphthalene (41)¹³

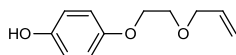
A suspension of LiAlH_4 (2.29 g, 60.3 mmol) in dry THF (100 mL) was cooled to 0 °C before compound **40** (5.00 g, 15.1 mmol) in dry THF (50 mL) was added. The mixture was then refluxed overnight under N_2 . After this time, the reaction mixture was carefully quenched with water (150 mL) before being extracted with EtOAc (3 x 100 mL). The organic layer was then washed with water (2 x 100 mL), dried (MgSO_4) and concentrated to give the product as a white powder (3.13 g, 83%). **MS** (ESI-MS) m/z 249.11 ($[\text{M} + \text{H}]^+$, $\text{C}_{14}\text{H}_{17}\text{O}_4$, calc. 249.11); **^1H NMR** (300 MHz, CDCl_3) δ 7.69 (2H, d, $^3J = 9.3$ Hz, ArH), 7.10–7.01 (4H, m, ArH), 4.21 (4H, t, $^3J = 4.4$ Hz, $-\text{OCH}_2$), 4.04 (4H, t, $^3J = 4.4$ Hz, $-\text{CH}_2\text{OH}$), 1.91–1.66 (2H, m, $-\text{OH}$); **^{13}C NMR** (75 MHz, CD_3OD) δ 159.1, 137.7, 130.2, 126.0, 117.4, 111.6, 107.3, 70.6, 61.9.

2,7-Bis(2'-hydroxyethoxy)naphthalene bis(methanesulfonate)ester (42)¹³

MsCl (3.74 mL, 48.3 mmol) and NEt_3 (6.74 mL, 48.3 mmol) were added to a solution of compound **41** (5.00 g, 20.1 mmol) in dry THF (200 mL). The mixture was left to stir under nitrogen for one hour before being filtered and concentrated. The residue was then dissolved in EtOAc (250 mL), washed with water (4 x 200 mL), dried (MgSO_4), filtered and concentrated to give the crude product as an off-white solid. This was recrystallised from $\text{CH}_2\text{Cl}_2/\text{MeOH}$ to yield the pure product **42** as a white crystalline solid (6.13 g, 75%). **MS** (ESI-MS) m/z 427.04 ($[\text{M} + \text{Na}]^+$, $\text{C}_{16}\text{H}_{20}\text{NaO}_8\text{S}_2$, calc. 427.05); **^1H NMR** (300 MHz, CDCl_3) δ 7.70 (2H, d, $^3J = 8.5$ Hz, ArH), 7.07–7.00 (4H, m, ArH), 4.64 (4H, t, $^3J = 4.3$ Hz,

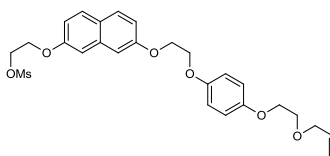
$\text{-CH}_2\text{OMs}$), 4.36 (4H, t, $^3J = 4.5$ Hz, -OCH_2), 3.12 (6H, s, -CH_3); ^{13}C NMR (75 MHz, CDCl_3) δ 156.6, 135.5, 129.5, 124.9, 116.3, 106.4, 67.9, 65.7, 37.8.

4-(2-(Allyloxy)ethoxy)phenol (**43**)⁹



2-(Allyloxy)ethyl methanesulfonate **25** (2.81 g, 15.6 mmol) was added to a solution of hydroquinone (3.26 g, 29.7 mmol) in dry MeCN (125 mL). K_2CO_3 (9.27 g, 67.1 mmol) was then added and the reaction mixture refluxed overnight under nitrogen. The mixture was then cooled, filtered and concentrated to give the crude product which was then suspended in 9:1 $\text{CHCl}_3/\text{EtOH}$ and filtered. The solvent was removed and the resultant residue purified *via* silica gel column chromatography (9:1 $\text{CHCl}_3/\text{EtOH}$) to give **43** as a brown oil (1.82 g, 60%). MS (FI-MS) m/z 194.0951 ($[\text{M}]^+$, $\text{C}_{11}\text{H}_{14}\text{O}_3$, calc. 194.0943); ^1H NMR (300 MHz, CDCl_3) δ 6.79–6.72 (4H, m, ArH), 6.03–5.85 (1H, m, -CH=CH_2), 5.38–5.15 (2H, m, -CH=CH_2), 4.15–4.02 (4H, m, -OCH_2), 3.79 (2H, t, $^3J = 4.7$ Hz, -ArOCH_2); ^{13}C NMR (75 MHz, CDCl_3) δ 152.5, 149.9, 134.2, 117.7, 116.0, 115.7, 72.3, 68.5, 68.0.

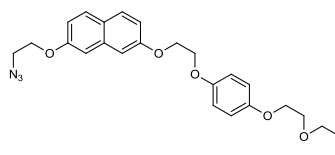
Vinyl-appended mesylate (**44**)



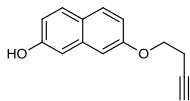
4-(2-(Allyloxy)ethoxy)phenol **43** (480 mg, 2.47 mmol) and K_2CO_3 (1.88 g, 13.6 mmol) were stirred in dry MeCN (100 mL) for 20 minutes. After this time, compound **42** (2.00 g, 4.94 mmol) was added and the reaction mixture refluxed overnight under nitrogen. The mixture was then cooled, filtered and the solvent removed to give the crude product, which was purified *via* silica gel column chromatography (99:1 $\text{CH}_2\text{Cl}_2/\text{MeOH}$) to give **44** as an off-

white solid (0.429 g, 34%). **MS** (ESI-MS) m/z 525.1568 ($[M + Na]^+$, $C_{26}H_{30}NaO_8S$, calc. 525.1554); **^1H NMR** (300 MHz, $CDCl_3$) δ 7.73–7.66 (2H, m, ArH), 7.11–6.98 (4H, m, ArH), 6.94–6.86 (4H, m, ArH), 6.03–5.88 (1H, m, $-CH=CH_2$), 5.37–5.19 (2H, m, $-CH=CH_2$), 4.68–4.62 (2H, m, $-CH_2$), 4.44–4.31 (6H, m, $-CH_2$), 4.13–4.06 (4H, m, $-CH_2$), 3.80 (2H, t, $^3J = 5.0$ Hz, $-CH_2$), 3.13 (3H, s, $-CH_3$); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 134.5, 129.5, 129.2, 124.7, 117.3, 116.8, 115.7, 115.6, 106.3, 72.3, 68.6, 68.0, 67.1, 66.5, 65.7, 37.8.

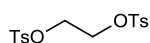
Vinyl-appended azide (45)



Compound **44** (233 mg, 0.464 mmol) was dissolved in dry DMF (50 mL) before NaN_3 (151 mg, 2.32 mmol) was added and the mixture heated at 85 °C overnight. After this time, the reaction mixture was cooled to room temperature and the solvent removed *in vacuo*. The resultant solid was then taken up in Et_2O (50 mL) and washed with water (2 x 40 mL) and brine (2 x 40 mL) before being dried ($MgSO_4$) and filtered. The solvent was then removed to give **45** as an off-white solid (190 mg, 91%). **MS** (ESI-MS) m/z 472.1833 ($[M + Na]^+$, $C_{25}H_{27}N_3NaO_5$, calc. 472.1843); **^1H NMR** (300 MHz, $CDCl_3$) δ 7.74–7.64 (2H, m, ArH), 7.13–7.01 (4H, m, ArH), 6.95–6.85 (4H, m, ArH), 6.05–5.88 (1H, m, $-CH=CH_2$), 5.37–5.18 (2H, m, $-CH=CH_2$), 4.41 (2H, t, $^3J = 5.1$ Hz, $-OCH_2CH_2OPh$), 4.34 (2H, t, $^3J = 5.3$ Hz, $-CH_2OPh$), 4.27 (2H, t, $^3J = 5.1$ Hz, $-CH_2CH_2OCHCH_2$), 4.14–4.06 (4H, m, $-OCH_2CH_2N_3$ & $-OCH_2CHCH_2$), 3.80 (2H, t, $^3J = 4.9$ Hz, $-CH_2OCHCH_2$), 3.67 (2H, t, $^3J = 4.9$ Hz, $-CH_2N_3$); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 135.6, 134.5, 129.3, 129.2, 124.7, 117.4, 116.6, 116.2, 115.7, 106.3, 72.3, 68.6, 68.0, 67.1, 66.8, 66.5, 50.1.

7-(But-3-yn-1-yloxy)naphthalen-2-ol (46)

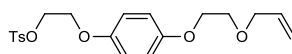
2,7-Dihydroxynaphthalene (500 mg, 3.12 mmol), 3-butyn-1-ol (0.237 mL, 3.12 mmol) and PPh_3 (819 mg, 3.12 mmol) were dissolved in dry THF (100 mL) and the solution cooled to 0 °C. DEAD (0.492 mL, 3.12 mmol) was then added dropwise before the reaction mixture was left to stir overnight under nitrogen. After this time, the solvent was removed and the resulting residue stirred in Et_2O (50 mL) to precipitate the triphenylphosphine oxide side product. This was then removed *via* filtration and the filtrate evaporated to dryness to give an orange oil which was purified by silica gel column chromatography (98:2 $\text{CH}_2\text{Cl}_2/\text{MeOH}$) to yield **46** as a white solid (108 mg, 16%). **MS** (ESI-MS) m/z 211.0763 ($[\text{M} - \text{H}]^-$, $\text{C}_{14}\text{H}_{11}\text{O}_2$, calc. 211.0765); **^1H NMR** (300 MHz, CDCl_3) δ 7.67 (2H, d, $^3J = 8.6$ Hz, ArH), 7.07–6.93 (4H, m, ArH), 4.21 (2H, t, $^3J = 7.1$ Hz, $-\text{OCH}_2$), 2.79–2.72 (2H, m, $-\text{OCH}_2\text{CH}_2$), 2.08 (1H, t, $^4J = 2.6$ Hz, $-\text{C}\equiv\text{CH}$); **^{13}C NMR** (75 MHz, CDCl_3) δ 157.0, 154.2, 135.8, 129.3, 124.4, 116.3, 115.4, 108.7, 105.7, 69.9, 65.9, 19.5, 14.4.

Ethylene glycol bis(toluenesulfonate) (47)¹⁴

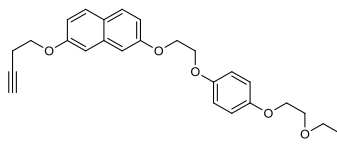
Ethylene glycol (2.00 g, 32.2 mmol) and TsCl (12.3 g, 64.4 mmol) were dissolved in CH_2Cl_2 (100 mL) and cooled to 0 °C. Powdered KOH (23.5 g, 419 mmol) was then added and the reaction mixture stirred for 3 hours at 0 °C. After this time, the reaction mixture was poured onto ice water (150 mL) and the organic layer separated. The aqueous phase was then extracted with CH_2Cl_2 (3 x 100 mL) before the combined organic phase was washed with water (300 mL), dried (MgSO_4) and filtered. The solvent was removed and the residue

trituated with Et₂O, to remove the excess TsCl, before being dried fully to give bis-tosylate **47** as a white solid (7.64 g, 64%). **MS** (ESI-MS) *m/z* 393.02 ([M + Na]⁺, C₁₆H₁₈NaO₆S₂, calc. 393.04); **¹H NMR** (300 MHz, CDCl₃) δ 7.74 (4H, d, ³*J* = 8.2 Hz, Ar*H*), 7.35 (4H, d, ³*J* = 8.2 Hz, Ar*H*), 4.19 (4H, s, -CH₂), 2.47 (6H, s, -CH₃); **¹³C NMR** (75 MHz, CDCl₃) δ 148.2, 132.3, 130.0, 128.0, 66.7, 21.7.

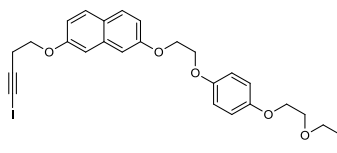
2-(4-(2-(Allyloxy)ethoxy)phenoxy)ethyl 4-methylbenzenesulfonate (**48**)



Compound **43** (1.29 g, 6.62 mmol) was dissolved in dry MeCN (100 mL) and stirred with K₂CO₃ (6.88 g, 49.8 mmol) for 20 minutes under nitrogen. After this time, bis-tosylate **47** (4.92 g, 13.3 mmol) was added and the reaction mixture heated at 85 °C overnight under nitrogen. The mixture was cooled to room temperature and filtered before the solvent was removed *in vacuo*. The resultant solid was then suspended in CHCl₃ and filtered to remove the toluenesulfonic acid side product. The solvent was then removed and the crude product purified *via* silica gel column chromatography (CH₂Cl₂) to give **48** as a pale yellow oil (1.38 g, 53%). **MS** (ESI-MS) *m/z* 415.1188 ([M + Na]⁺, C₂₀H₂₄NaO₆S, calc. 415.1186); **¹H NMR** (300 MHz, CDCl₃) δ 7.82 (2H, d, ³*J* = 8.0 Hz, tosyl Ar*H*), 7.35 (2H, d, ³*J* = 8.0 Hz, tosyl Ar*H*), 6.83 (2H, d, ³*J* = 9.3 Hz, Ar*H*), 6.72 (2H, d, ³*J* = 8.9 Hz, Ar*H*), 6.02–5.87 (1H, m, -CH=CH₂), 5.36–5.18 (2H, m, -CH=CH₂), 4.37–4.31 (2H, m, -CH₂), 4.13–4.05 (8H, m, -CH₂), 3.81–3.76 (2H, m, -CH₂), 2.46 (3H, s, -CH₃); **¹³C NMR** (75 MHz, CDCl₃) δ 152.3, 150.2, 134.3, 129.8, 127.8, 115.9, 115.6, 115.5, 72.2, 68.5, 68.3, 68.0, 66.0, 50.4, 21.5.

2-(2-(4-(2-(Allyloxy)ethoxy)phenoxy)ethoxy)-7-(but-3-yn-1-yloxy)naphthalene (49)

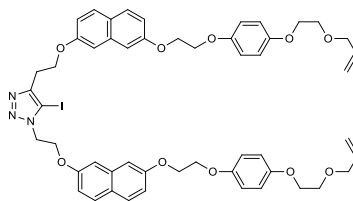
Tosylate **48** (0.700 g, 1.78 mmol) and K_2CO_3 (1.85 g, 13.4 mmol) were stirred for 20 minutes in dry MeCN (150 mL) under nitrogen. Compound **46** (0.379 g, 1.78 mmol) was then added and the reaction mixture heated at 85 °C overnight under nitrogen. After cooling to room temperature, the reaction mixture was filtered and the solvent removed *in vacuo*. The resultant residue was then purified *via* silica gel column chromatography (CH_2Cl_2) to give alkyne **49** as an off-white solid (326 mg, 42%). **MS** (ESI-MS) m/z 455.1819 ($[M + Na]^+$, $C_{27}H_{28}NaO_5$, calc. 455.1829); **^1H NMR** (300 MHz, $CDCl_3$) δ 7.68 (2H, d, $^3J = 9.0$ Hz, ArH), 7.11–7.00 (4H, m, ArH), 6.94–6.87 (4H, m, ArH), 6.03–5.88 (1H, m, $-CH=CH_2$), 5.36–5.19 (2H, m, $-CH=CH_2$), 4.44–4.39 (2H, m, $-CH_2$), 4.38–4.32 (2H, m, $-CH_2$), 4.22 (2H, t, $^3J = 7.1$ Hz, $-CH_2$), 4.13–4.08 (4H, m, $-CH_2$), 3.82–3.77 (2H, m, $-CH_2$), 2.80–2.72 (2H, m, $-CH_2C\equiv CH$), 2.08 (1H, t, $^4J = 2.6$ Hz, $-C\equiv CH$); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 157.1, 156.9, 153.2, 152.8, 135.6, 134.5, 129.1, 124.5, 117.3, 116.4, 116.2, 115.6, 106.3, 106.2, 80.4, 72.3, 69.9, 68.5, 67.9, 67.0, 66.4, 65.8, 19.4.

Vinyl-appended iodo-alkyne (50)

Alkyne **49** (326 mg, 0.753 mmol) and *N*-iodosuccinimide (203 mg, 0.903 mmol) were dissolved in acetone (20 mL) and then $AgNO_3$ (15.3 mg, 0.0903 mmol) was added before the reaction mixture was left to stir overnight, in the dark, under nitrogen. After this time, the

reaction mixture was poured into ice water (50 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic phase was then washed with brine (50 mL), dried (MgSO_4), filtered and the solvent removed to give the crude product. This was then purified *via* silica gel column chromatography (98:2 $\text{CH}_2\text{Cl}_2/\text{MeOH}$) to give **50** as a white solid (336 mg, 80%). **MS** (ESI-MS) m/z 581.0801 ($[\text{M} + \text{Na}]^+$, $\text{C}_{27}\text{H}_{27}\text{INaO}_5$, calc. 581.0795); **^1H NMR** (300 MHz, CDCl_3) δ 7.67 (2H, d, $^3J = 8.9$ Hz, ArH), 7.11–6.98 (4H, m, ArH), 6.94–6.86 (4H, m, ArH), 6.03–5.88 (1H, m, $-\text{CH}=\text{CH}_2$), 5.37–5.19 (2H, m, $-\text{CH}=\text{CH}_2$), 4.44–4.38 (2H, m, $-\text{CH}_2$), 4.38–4.32 (2H, m, $-\text{CH}_2$), 4.20 (2H, t, $^3J = 7.2$ Hz, $-\text{CH}_2$), 4.14–4.07 (4H, m, $-\text{CH}_2$), 3.80 (2H, t, $^3J = 5.0$ Hz, $-\text{CH}_2$), 2.92 (2H, t, $^3J = 7.0$ Hz, $-\text{CH}_2$); **^{13}C NMR** (75 MHz, CDCl_3) δ 157.2, 156.8, 153.3, 152.9, 135.6, 134.5, 129.1, 124.6, 117.3, 116.5, 116.3, 115.7, 106.3, 90.3, 72.3, 68.6, 68.0, 67.1, 66.5, 65.8, 21.7.

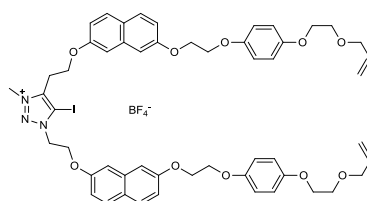
Iodo-triazole containing bis-vinyl appended precursor (**51**)



CuI (2.96 mg, 0.0156 mmol) and TBTA (8.27 mg, 0.0156 mmol) were stirred in dry degassed THF (5 mL) for 20 minutes in the dark under nitrogen. After this time, azide **45** (70.0 mg, 0.156 mmol) and alkyne **50** (87.0 mg, 0.156 mmol), dissolved in dry degassed THF (5 mL), were added to the catalyst solution which was then stirred overnight in the dark under nitrogen. Following this, 10% $\text{NH}_4\text{OH}_{(\text{aq})}$ (10 mL) was added to quench the reaction and the volatile components were removed *in vacuo*. Water (20 mL) was then added to the solution and the product extracted with CH_2Cl_2 (3 x 20 mL). The organic phase was then dried (MgSO_4) and the solvent removed to yield the crude product, which was then purified *via*

silica gel column chromatography (99:1 CH₂Cl₂/MeOH) to give **51** as a white solid (124 mg, 79%). **MS** (ESI-MS) m/z 1030.2751 ([M + Na]⁺, C₅₂H₅₄IN₃NaO₁₀, calc. 1030.2746); **¹H NMR** (300 MHz, CDCl₃) δ 7.65 (2H, d, ³*J* = 6.4 Hz, Ar*H*), 7.62 (2H, d, ³*J* = 5.8 Hz, Ar*H*), 7.08–7.04 (4H, m, Ar*H*), 7.03–6.95 (4H, m, Ar*H*), 6.91–6.88 (8H, m, Ar*H*), 6.03–5.88 (2H, m, -CH=CH₂), 5.37–5.19 (4H, m, -CH=CH₂), 4.84 (2H, t, ³*J* = 5.8 Hz, naphthalene-OCH₂), 4.53 (2H, t, ³*J* = 5.6 Hz, naphthalene-OCH₂), 4.41–4.35 (6H, m, -CH₂), 4.35–4.30 (4H, m, -CH₂), 4.12–4.07 (8H, m, -CH₂), 3.81–3.77 (4H, m, -CH₂), 3.24 (2H, t, ³*J* = 7.0 Hz, triazole-CH₂); **¹³C NMR** (75 MHz, CDCl₃) δ 157.3, 157.2, 156.4, 155.3, 153.3, 152.9, 145.8, 135.7, 134.6, 129.3, 129.1, 117.4, 116.4, 115.6, 106.3, 72.4, 68.6, 68.0, 67.2, 66.5.

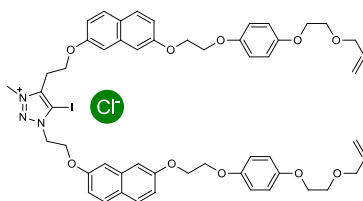
Iodo-triazolium containing bis-vinyl appended precursor tetrafluoroborate salt (52·BF₄)



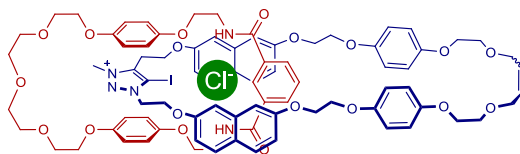
Iodo-triazole containing bis-vinyl appended precursor **51** (114 mg, 0.113 mmol) was dissolved in dry CH₂Cl₂ (30 mL) before (Me₃O)BF₄ (25.1 mg, 0.170 mmol) was added and the reaction mixture left to stir overnight under nitrogen. After this time, MeOH (10 mL) was added to quench the reaction and the solvent was removed to give a pale orange solid. This was purified *via* silica gel column chromatography (95:5 CH₂Cl₂/MeOH) to give **52·BF₄** as an off-white solid (118 mg, 94%). **MS** (ESI-MS) m/z 1022.3099 ([M - BF₄]⁺, C₅₃H₅₇IN₃O₁₀, calc. 1022.3083); **¹H NMR** (300 MHz, CDCl₃) δ 7.58–7.41 (4H, m, Ar*H*), 7.11–7.05 (2H, m, Ar*H*), 7.04–6.94 (4H, m, Ar*H*), 6.83 (8H, s, Ar*H*), 6.81–6.76 (2H, m, Ar*H*), 6.01–5.85 (2H, m, -CH=CH₂), 5.35–5.16 (4H, m, -CH=CH₂), 4.80–4.70 (2H, m, naphthalene-OCH₂), 4.46–4.37 (2H, m, naphthalene-OCH₂), 4.32–4.25 (4H, m, -CH₂), 4.25–4.17 (7H, m, -CH₂ &

-CH₃), 4.16–4.10 (2H, m, -CH₂), 4.10–4.01 (8H, m, -CH₂), 3.75 (4H, t, ³J = 4.7 Hz, -CH₂), 3.24–3.14 (2H, m, triazole-CH₂); ¹³C NMR (75 MHz, CDCl₃) δ 157.3, 156.0, 155.8, 153.2, 152.8, 145.7, 135.5, 134.5, 129.3, 129.1, 124.6, 117.3, 117.0, 115.5, 106.8, 106.5, 106.2, 72.3, 68.5, 68.0, 67.1, 66.6, 38.9; ¹⁹F NMR (283 MHz, CDCl₃) δ -151.9 (d, J = 15.8 Hz).

Iodo-triazolium containing bis-vinyl appended precursor chloride salt (52·Cl)



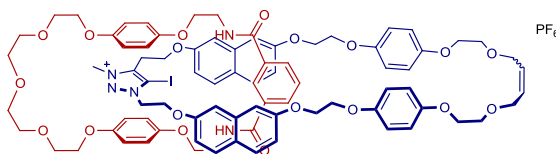
52·BF₄ (70.0 mg, 0.0631 mmol) was dissolved in CHCl₃ (20 mL) and washed with 1 M NH₄Cl_(aq) (10 x 20 mL) and water (20 mL) before being dried (MgSO₄) and filtered. The solvent was then removed to give 52·Cl as an orange solid (61.5 mg, 92%). **MS** (ESI-MS) *m/z* 1022.3099 ([M - Cl]⁺, C₅₃H₅₇IN₃O₁₀, calc. 1022.3083); ¹H NMR (500 MHz, CDCl₃) δ 7.58 (1H, d, ³J = 8.6 Hz, ArH), 7.53 (2H, d, ³J = 8.6 Hz, ArH), 7.47 (1H, d, ³J = 8.6 Hz, ArH), 7.10–7.06 (2H, m, ArH), 7.05–6.98 (3H, m, ArH), 6.96–6.93 (1H, m, ArH), 6.88–6.82 (9H, m, ArH), 6.78–6.74 (1H, m, ArH), 5.98–5.89 (2H, m, -CH=CH₂), 5.34–5.17 (4H, m, -CH=CH₂), 4.91–4.84 (2H, m, -CH₂), 4.53–4.47 (2H, m, -CH₂), 4.38 (3H, s, -CH₃), 4.37–4.32 (4H, m, -CH₂), 4.29–4.24 (4H, m, -CH₂), 4.22–4.16 (2H, m, -CH₂), 4.10–4.04 (8H, m, -CH₂), 3.77 (4H, t, ³J = 4.7 Hz, -CH₂), 3.41–3.35 (2H, m, triazole-CH₂); ¹³C NMR (126 MHz, CDCl₃) δ 157.3, 155.8, 153.3, 152.9, 145.2, 135.5, 134.5, 129.3, 129.1, 124.6, 117.3, 115.6, 106.9, 106.5, 106.2, 103.3, 72.3, 68.6, 68.0, 67.1, 66.7, 65.1, 64.8, 53.6, 38.9.

Hetero-[2]catenane chloride salt (56·Cl)

Isophthalamide macrocycle **55** (33.7 mg, 0.0567 mmol), kindly donated by Dr L. Gilday, and iodo-triazolium containing bis-vinyl appended precursor chloride salt **52·Cl** (40.0 mg, 0.0378 mmol) were dissolved in dry CH₂Cl₂ (10 mL) and stirred for 1 hour under nitrogen. Grubbs' II (4.00 mg, 10% by weight) was then added and the reaction mixture left to stir overnight, in the dark, under nitrogen. After this time, the solvent was removed and the crude product purified *via* preparative TLC (93:7 CH₂Cl₂/MeOH) to give **56·Cl** as an off-white solid (3.52 mg, 6%). **MS** (ESI-MS) *m/z* 1588.5346 ([M - Cl]⁺, C₈₃H₉₁IN₅O₁₉, calc. 1588.5347); **¹H NMR** (500 MHz, CDCl₃) δ 9.40 (1H, s, ArH isophthalamide internal), 8.82–8.74 (2H, m, -NH), 8.52 (2H, d, ³*J* = 7.8 Hz, ArH isophthalamide external), 7.78 (1H, s, ArH naphthalene internal), 7.76–7.69 (2H, m, ArH naphthalene external), 7.64–7.58 (3H, m, ArH naphthalene external & isophthalamide external), 7.39 (1H, s, ArH naphthalene internal), 7.31 (1H, s, ArH naphthalene internal), 7.14 (1H, d, ³*J* = 8.8 Hz, ArH naphthalene external), 7.09 (1H, d, ³*J* = 8.8 Hz, ArH naphthalene external), 7.03 (1H, d, ³*J* = 8.8 Hz, ArH naphthalene external), 6.95–6.88 (4H, m, ArH halogen bonding macrocycle hydroquinone), 6.88–6.81 (4H, m, ArH halogen bonding macrocycle hydroquinone), 6.78 (1H, d, ³*J* = 8.9 Hz, ArH naphthalene external), 6.69 (1H, s, ArH naphthalene internal), 6.35 (4H, d, ³*J* = 8.7 Hz, ArH hydrogen bonding macrocycle hydroquinone), 6.07 (4H, d, ³*J* = 8.7 Hz, ArH hydrogen bonding macrocycle hydroquinone), 5.85–5.82 (2H, m, -CH=CH), 4.76–4.72 (2H, m, -CH₂), 4.64–4.60 (2H, m, -CH₂), 4.60–4.53 (2H, m, -CH₂), 4.50–4.47 (2H, m, -CH₂), 4.43–4.39 (2H, m, -CH₂), 4.35 (3H, s, -CH₃), 4.34–4.27 (2H, m, -CH₂), 4.20–4.16 (2H, m, -CH₂), 4.14–4.00

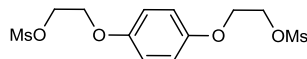
(12H, m, $-CH_2$), 3.81–3.62 (18H, m, $-CH_2$), 3.59–3.51 (4H, m, $-CH_2$), 3.51–3.42 (4H, m, $-CH_2$), 2.80–2.74 (2H, m, $-CH_2$).

Hetero-[2]catenane hexafluorophosphate salt (**56**·PF₆)

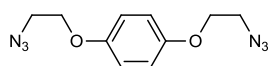


56·Cl (3.52 mg, 0.00217 mmol) was dissolved in CHCl₃ (15 mL) and washed with 0.1 M NH₄PF_{6(aq)} (10 x 10 mL) and water (10 mL) before being dried over MgSO₄ and filtered. The solvent was then removed *in vacuo* to give **56**·PF₆ as an off-white solid (3.16 mg, 84%).
MS (ESI-MS) *m/z* 1588.5346 ([M - PF₆]⁺, C₈₃H₉₁IN₅O₁₉, calc. 1588.5347); **¹H NMR** (500 MHz, CDCl₃) δ 8.47 (2H, br s, $-NH$), 8.30–8.20 (2H, m, *ArH* isophthalamide external), 7.71–7.60 (4H, m, *ArH* naphthalene external), 7.51 (1H, t, ³*J* = 7.8 Hz, *ArH* isophthalamide external), 7.39 (1H, br s, *ArH* isophthalamide internal), 7.23 (1H, s, *ArH* naphthalene internal), 7.15 (1H, s, *ArH* naphthalene internal), 7.11–7.05 (2H, m, *ArH* naphthalene external), 7.00–6.96 (1H, m, *ArH* naphthalene external), 6.94 (1H, s, *ArH* naphthalene internal), 6.90–6.80 (10H, m, *ArH* halogen bonding macrocycle hydroquinone & naphthalene internal & naphthalene external), 6.44 (4H, d, ³*J* = 8.9 Hz, *ArH* hydrogen bonding macrocycle hydroquinone), 6.23 (4H, d, ³*J* = 8.7 Hz, *ArH* hydrogen bonding macrocycle hydroquinone), 5.85–5.81 (2H, m, $-CH=CH$), 4.56–4.51 (2H, m, $-CH_2$), 4.50–4.46 (2H, m, $-CH_2$), 4.43–4.34 (6H, m, $-CH_2$), 4.24 (3H, s, $-CH_3$), 4.14–3.97 (18H, m, $-CH_2$), 3.80–3.59 (20H, m, $-CH_2$), 3.59–3.53 (2H, m, $-CH_2$), 3.19–3.13 (2H, m, $-CH_2$), 2.90–2.85 (2H, m, $-CH_2$); **¹⁹F NMR** (283 MHz, CDCl₃) δ -71.7 (d, *J* = 718.3 Hz); **³¹P NMR** (122 MHz, CDCl₃) δ -144.1 (sept., *J* = 713.7 Hz).

5.2.2 Synthetic procedures for Chapter Three

Hydroquinone bis(2-hydroxyethyl)ether dimesylate (57)¹⁵

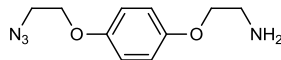
Hydroquinone bis(2-hydroxyethyl)ether (10.0 g, 50.4 mmol) and NEt₃ (18.0 mL, 126 mmol) were dissolved in dry CH₂Cl₂ (250 mL) and the solution cooled to 0 °C. Methanesulfonyl chloride (15.0 mL, 151 mmol) in dry CH₂Cl₂ (100 mL) was then added dropwise over a period of 10 minutes. The resulting mixture was stirred for 15 minutes prior to being washed with 1 M HCl_(aq) (3 x 50 mL), saturated NaHCO_{3(aq)} (3 x 50 mL) and brine (2 x 50 mL). The organic layer was then dried over MgSO₄, filtered and the solvent removed *in vacuo* to give the product as an off-white solid in quantitative yield (19.9 g). **MS** (ESI-MS) *m/z* 377.00 ([M + Na]⁺, C₁₂H₁₈NaO₈S₂, calc. 377.03); **¹H NMR** (300 MHz, CDCl₃) δ 6.85 (4H, s, ArH), 4.55 (4H, t, ³*J* = 4.6 Hz, ArOCH₂), 4.21 (4H, t, ³*J* = 4.5 Hz, -CH₂OSO₂Me), 3.09 (6H, s, -CH₃); **¹³C NMR** (75 MHz, CDCl₃) δ 152.7, 115.8, 110.8, 68.1, 66.5, 37.7.

1,4-Bis(2-azidoethoxy)benzene (58)¹⁵

Bis-mesylate **57** (5.00 g, 14.1 mmol) was dissolved in dry degassed DMF (200 mL), NaN₃ (2.75 g, 42.3 mmol) was added and the reaction mixture then heated at 85 °C overnight under N₂. The mixture was cooled to room temperature, water (300 mL) was added and the product extracted with Et₂O (3 x 100 mL). The organic phase was then washed with brine (3 x 200 mL), dried over MgSO₄, filtered and the solvent removed *in vacuo* to give **58** as an off-white solid (2.91 g, 87%). **MS** (FI-MS) *m/z* 248.1028 ([M]⁺, C₁₀H₁₂N₆O₂, calc. 248.1022); **¹H NMR** (300 MHz, CDCl₃) δ 6.88 (3H, s, ArH), 4.11 (4H, t, ³*J* = 5.0 Hz, -CH₂CH₂N₃), 3.57

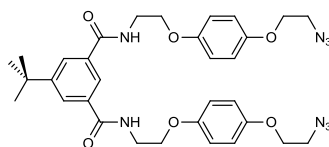
(4H, t, $^3J = 4.7$ Hz, $-\text{CH}_2\text{N}_3$); ^{13}C NMR (75 MHz, CDCl_3) δ 152.8, 115.6, 67.6, 50.1.

2-(4-(2-Azidoethoxy)phenoxy)ethanamine (**59**)¹⁵



PPh_3 (1.53 g, 5.84 mmol), dissolved in 1:1 $\text{Et}_2\text{O}/\text{EtOAc}$ (40 mL), was added dropwise to a vigorously stirred solution of **58** (1.44 g, 5.84 mmol) in 1:1:2 $\text{Et}_2\text{O}/\text{EtOAc}/5\%$ $\text{HCl}_{(\text{aq})}$ (120 mL) at 0 °C. After the addition was complete, the solution was allowed to warm to room temperature before being left to stir overnight. The organic layer was then discarded and the aqueous phase washed with 1:1 $\text{Et}_2\text{O}/\text{EtOAc}$ (3 x 50 mL) before being basified with 10% $\text{NaOH}_{(\text{aq})}$ and the product extracted into CH_2Cl_2 (3 x 80 mL). The organic phase was then dried over MgSO_4 , filtered and the solvent removed *in vacuo* to give the product as an off-white solid (1.30 g, 61%). **MS** (ESI-MS) m/z 223.10 ($[\text{M} + \text{H}]^+$, $\text{C}_{10}\text{H}_{15}\text{N}_4\text{O}_2$, calc. 223.12); ^1H NMR (300 MHz, CDCl_3) δ 6.85 (4H, s, ArH), 4.10 (2H, t, $^3J = 4.9$ Hz, $-\text{OCH}_2\text{CH}_2\text{NH}_2$), 3.94 (2H, t, $^3J = 4.9$ Hz, $-\text{OCH}_2\text{CH}_2\text{N}_3$), 3.56 (2H, t, $^3J = 4.8$ Hz, $-\text{OCH}_2\text{CH}_2\text{NH}_2$), 3.12–3.00 (2H, m, $-\text{OCH}_2\text{CH}_2\text{N}_3$); ^{13}C NMR (75 MHz, CDCl_3) δ 153.5, 152.4, 115.6, 115.5, 70.7, 67.6, 50.2, 41.6.

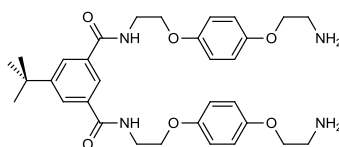
Bis-azide precursor (**60**)



Mono-amine **59** (3.13 g, 14.1 mmol), NEt_3 (3.54 mL, 25.4 mmol) and DMAP (cat.) were dissolved in dry CH_2Cl_2 (100 mL) and then the solution was cooled to 0 °C. 5-*Tert*-butylisophthaloyl dichloride **16** (1.66 g, 6.40 mmol), in dry CH_2Cl_2 (75 mL), was then added

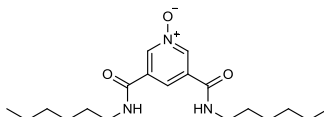
dropwise before the reaction mixture was left to stir at room temperature for two hours under N_2 . After this time, the reaction mixture was washed with 10% $HCl_{(aq)}$ (50 mL) and water (2 x 50 mL), dried over $MgSO_4$, filtered and the solvent removed *in vacuo*. The resulting brown solid was then purified by silica gel column chromatography (6:4 EtOAc/hexane) to give **60** as a white solid (2.77 g, 73%). **MS** (ESI-MS) m/z 635.24 ($[M + Na]^+$, $C_{32}H_{38}N_8NaO_6$, calc. 653.28); **^1H NMR** (300 MHz, $CDCl_3$) δ 7.96 (2H, s, ArH), 7.94 (1H, s, ArH), 6.86 (8H, s, ArH hydroquinone), 6.80–6.72 (2H, m, $-CONHCH_2-$), 4.15–4.07 (8H, m, $-OCH_2-$), 3.90–3.81 (4H, m, $-CONHCH_2-$), 3.57 (4H, t, $^3J = 5.0$ Hz, $-CH_2N_3$), 1.36 (9H, s, $-tBu$); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.3, 165.6, 134.5, 122.3, 115.7, 115.5, 67.6, 67.3, 50.2, 39.7, 35.0, 31.2.

Bis-amine precursor (61)



Bis-azide precursor **60** (276 mg, 0.438 mmol) was dissolved in EtOH (50 mL). 20% by weight Pd/C (55.2 mg) was then added to the solution before it was stirred under 5 atm. of $H_{2(g)}$ overnight. After this time, the reaction mixture was filtered through Celite[®] and the solvent removed *in vacuo* to give the product as a white solid in quantitative yield which was used immediately in the next step without further purification or characterisation.

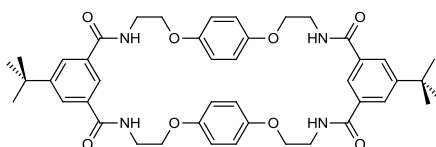
Pyridine *N*-oxide thread (62)¹⁶



Pyridine thread **14** (1.80 g, 5.40 mmol) and $NaHCO_3$ (13.6 g, 162 mmol) were dissolved in 1:1 $H_2O/2$ -butanone (100 mL). A solution of Oxone[®] (9.96 g, 16.2 mmol) in water (50 mL)

was added dropwise and the mixture stirred for 3 hours at room temperature whilst being monitored *via* TLC (95:5 EtOAc/MeOH). Once the reaction had gone to completion, NaCl (35.0 g, 603 mmol) was added and the product was extracted into CHCl₃ (3 x 50 mL) before being dried over MgSO₄ and filtered. The solvent was then removed *in vacuo* to give the product **62** as an off-white solid (1.48 g, 78%). **MS** (ESI-MS) *m/z* 350.25 ([M + H]⁺, C₁₉H₃₂N₃O₃, calc. 350.24); **¹H NMR** (300 MHz, CDCl₃) δ 8.94 (2H, s, ArH), 8.34 (1H, s, ArH), 8.04 (2H, t, ³*J* = 5.5 Hz, -CONH), 3.48–3.36 (4H, m, -CONHCH₂), 1.70–1.56 (4H, m, -CONHCH₂CH₂), 1.43–1.19 (12H, m, -CH₂), 0.88 (6H, t, ³*J* = 6.9 Hz, -CH₃); **¹³C NMR** (75 MHz, CDCl₃) δ 162.2, 140.1, 134.1, 40.7, 31.4, 29.2, 26.7, 22.5, 14.0.

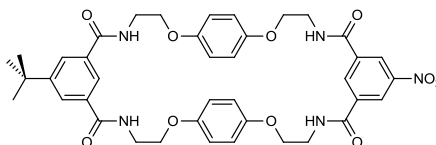
Bis-*tert*-butylisophthalamide macrocycle (**63**)



Bis-amine precursor **61** (254 mg, 0.438 mmol) and NEt₃ (0.130 mL, 0.963 mmol) were dissolved in dry CH₂Cl₂ (20 mL) and loaded into a 20 mL syringe. Acid chloride **16** (113 mg, 0.438 mmol) was then also dissolved in dry CH₂Cl₂ (20 mL) and loaded into a 20 mL syringe. The contents of both syringes were then added dropwise to a stirred flask of dry CH₂Cl₂ (600 mL) under N₂ over 6 hours using a syringe pump. The mixture was then left to stir overnight under N₂. After this, the solvent volume was reduced (~100 mL) and the reaction mixture washed with 1 M HCl_(aq) (2 x 75 mL), H₂O (2 x 75 mL) and brine (2 x 75 mL) before being dried over MgSO₄, filtered and concentrated. The crude product was purified *via* silica gel column chromatography (97:3 CH₂Cl₂/MeOH) to give the product as a white solid (166 mg, 50%). **mp** > 250 °C; **MS** (ESI-MS) *m/z* 787.3649 ([M + Na]⁺, C₄₄H₅₂N₄NaO₈, calc. 787.3677); **¹H NMR** (300 MHz, 1:1 CDCl₃/CD₃OD) δ 8.05 (4H, d, ⁴*J* = 1.8 Hz, ArH *tert*-

butylisophthalamide), 7.99 (2H, t, $^4J = 1.8$ Hz, ArH *tert*-butylisophthalamide), 6.80–6.78 (8H, m, ArH hydroquinone), 4.06 (8H, t, $^3J = 4.9$ Hz, $-\text{OCH}_2$), 3.76 (8H, t, $^3J = 5.0$ Hz, $-\text{CONHCH}_2$), 1.34 (18H, s, $-\text{tBu}$); ^{13}C NMR (75 MHz, 1:1 $\text{CDCl}_3/\text{CD}_3\text{OD}$) δ 168.2, 152.6, 152.1, 133.6, 133.4, 127.6, 121.9, 115.1, 114.9, 114.7, 66.5, 39.4, 34.5, 30.4.

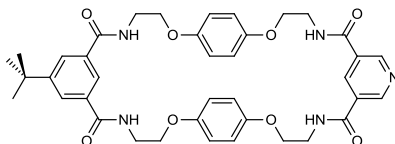
Nitro-isophthalamide macrocycle (**64**)



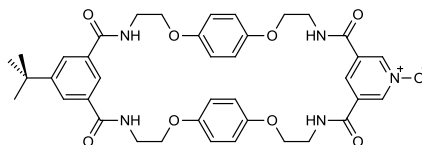
Bis-amine precursor **61** (252 mg, 0.435 mmol) and NEt_3 (0.243 mL, 1.74 mmol) were dissolved in dry CH_2Cl_2 (20 mL) and loaded into a 20 mL syringe. 5-Nitroisophthaloyl dichloride **28** (107 mg, 0.435 mmol) was also dissolved in dry CH_2Cl_2 (20 mL) and loaded into another 20 mL syringe. The contents of both syringes were then added dropwise to a stirred flask of dry CH_2Cl_2 (750 mL) under N_2 over a 6 hour period using a syringe pump. The resulting mixture was then stirred overnight under N_2 . After this time, the solvent volume was reduced *in vacuo* (~150 mL) and the organic phase washed with 10% citric acid_(aq) (3 x 75 mL), water (3 x 75 mL) and brine (3 x 75 mL) before being dried over MgSO_4 and filtered. The solvent was then removed to give a yellow solid which was purified *via* silica gel column chromatography (98:2 $\text{CH}_2\text{Cl}_2/\text{MeOH}$ to 95:5 $\text{CH}_2\text{Cl}_2/\text{MeOH}$) to yield **64** as an off-white solid (76.0 mg, 23%). **mp** 166 °C; **MS** (ESI-MS) m/z 788.2706 ($[\text{M} + \text{Cl}]^-$, $\text{C}_{40}\text{H}_{43}\text{N}_5\text{O}_{10}\text{Cl}$, calc. 788.2704); ^1H NMR (500 MHz, 1:1 $\text{CDCl}_3/\text{CD}_3\text{OD}$) δ 8.80 (2H, s, ArH nitro-isophthalamide), 8.77–8.70 (2H, m, $-\text{CONH}$ nitro-isophthalamide), 8.60 (1H, s, ArH nitro-isophthalamide), 8.37–8.29 (2H, m, $-\text{CONH}$ *tert*-butylisophthalamide), 8.04 (2H, s, ArH *tert*-butylisophthalamide), 8.02 (1H, s, ArH *tert*-butylisophthalamide), 6.76 (8H, s, ArH hydroquinone), 4.10–4.00 (8H, m, $-\text{CONHCH}_2$), 3.81–3.71 (8H, m, $-\text{OCH}_2$), 1.34 (9H, s,

-^tBu); ¹³C NMR (126 MHz, 1:1 CDCl₃/CD₃OD) δ 168.0, 165.1, 152.6, 152.5, 152.0, 148.1, 135.7, 133.5, 130.3, 127.4, 124.7, 121.8, 114.8, 66.5, 66.3, 39.6, 39.3, 34.4, 30.2, 29.1.

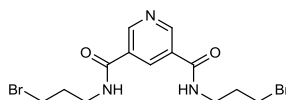
Pyridine macrocycle (65)



Bis-amine precursor **61** (254 mg, 0.438 mmol) and NEt₃ (0.130 mL, 0.963 mmol) were dissolved in dry CH₂Cl₂ (20 mL) and loaded into a 20 mL syringe. Pyridine-3,5-dicarbonyl dichloride **13** (88.9 mg, 0.438 mmol) was then also dissolved in dry CH₂Cl₂ (20 mL) and loaded into another 20 mL syringe. The contents of both syringes were then added dropwise to a stirred flask of dry CH₂Cl₂ (600 mL) under N₂ over 6 hours using a syringe pump. The mixture was then left to stir overnight under N₂. After this time, the solvent volume was reduced (~100 mL) and the reaction mixture washed with 10% citric acid_(aq) (2 x 75 mL), H₂O (2 x 75 mL) and brine (2 x 75 mL) before being dried over MgSO₄, filtered and concentrated. The crude product was purified *via* silica gel column chromatography (98:2 CH₂Cl₂/MeOH to 95:5 CH₂Cl₂/MeOH) to give the product as a white solid (76.3 mg, 25%). **mp** 203 °C (dec.); **MS** (ESI-MS) *m/z* 732.3007 ([M + Na]⁺, C₃₉H₄₃N₅NaO₈, calc. 732.3004); ¹H NMR (300 MHz, 1:1 CDCl₃/CD₃OD) δ 9.10–9.07 (2H, m, ArH pyridine), 8.60 (2H, t, ³J = 5.5 Hz, -CONH pyridine), 8.58–8.55 (1H, m, ArH pyridine), 8.23, (2H, t, ³J = 5.4 Hz, -CONH *tert*-butylisophthalamide), 8.06–8.03 (2H, m, ArH *tert*-butylisophthalamide), 8.01–7.98 (1H, m, ArH *tert*-butylisophthalamide), 6.81–6.75 (8H, m, ArH hydroquinone), 4.10–4.01 (8H, m, -CONHCH₂), 3.80–3.73 (8H, m, -OCH₂), 1.35–1.32 (9H, m, -^tBu); ¹³C NMR (75 MHz, 1:1 CDCl₃/CD₃OD) δ 168.0, 165.4, 152.6, 152.5, 152.0, 150.2, 133.5, 133.2, 129.4, 127.4, 121.8, 114.9, 66.5, 66.3, 39.3, 39.2, 34.4, 30.2, 29.0.

Pyridine *N*-oxide functionalised macrocycle (66)

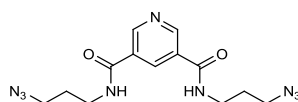
Pyridine macrocycle **65** (50.0 mg, 0.0704 mmol) and NaHCO₃ (177 mg, 2.11 mmol) were dissolved in 1:1 2-butanone/H₂O (20 mL). Oxone[®] (130 mg, 0.423 mmol) was then added and the reaction mixture left to stir at room temperature overnight. After this time, NaCl (408 mg, 7.04 mmol) was added and the product was extracted with EtOAc (6 x 50 mL). The organic phase was then dried over MgSO₄, filtered and the solvent removed to give **66** as an off-white solid (36.4 mg, 71%). **mp** 173 °C (dec.); **MS** (ESI-MS) *m/z* 748.2925 ([M + Na]⁺, C₃₉H₄₃N₅NaO₉, calc. 748.2953); **¹H NMR** (300 MHz, 1:1 CDCl₃/CD₃OD) δ 8.88 (1H, s, ArH pyridine *N*-oxide), 8.72 (2H, s, ArH pyridine *N*-oxide), 8.28 (1H, s, ArH *tert*-butylisophthalamide), 8.05 (2H, s, ArH *tert*-butylisophthalamide), 6.85–6.74 (8H, m, ArH hydroquinone), 4.13–4.00 (4H, m, -OCH₂), 3.80–3.69 (4H, m, -CONHCH₂), 1.37–1.32 (9H, m, -^tBu); **¹³C NMR** (126 MHz, DMSO-*d*⁶) δ 166.5, 162.4, 152.7, 151.1, 139.3, 134.3, 133.3, 126.7, 123.6, 122.5, 115.5, 79.2, 66.6, 66.3, 34.7, 31.0.

N³,N⁵-Bis(3-bromopropyl)pyridine-3,5-dicarboxamide (67)¹⁷

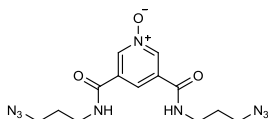
NEt₃ (5.02 mL, 36.0 mmol) was added to a suspension of 3-bromopropylamine hydrobromide (5.25 g, 24.0 mmol) in dry CH₂Cl₂ (100 mL), under nitrogen, which was then cooled to 0 °C. Acid chloride **13** (2.45 g, 12.0 mmol) was dissolved in dry CH₂Cl₂ (50 mL) and added dropwise to the suspension which was kept at 0 °C. After the addition was complete, the

reaction was allowed to warm to room temperature before being stirred overnight under N₂. The reaction mixture was then washed with 10 % HCl_(aq) (2 x 75 mL) to extract the product before the aqueous phase was neutralised with saturated NaHCO_{3(aq)} to give an off-white precipitate. This precipitate was collected *via* vacuum filtration, washed with water (2 x 50 mL) and dried to give **67** as an off-white solid (744 mg, 15%). **MS** (ESI-MS) 449.9663 ([M + HCO₂]⁺, C₁₄H₁₈Br₂N₃O₄, calc. 449.9670); **¹H NMR** (300 MHz, DMSO-*d*⁶) δ 9.10 (2H, d, ⁴*J* = 1.9 Hz, Ar*H*), 8.87 (2H, t, ³*J* = 5.5 Hz, -NH), 8.59 (1H, t, ⁴*J* = 1.9 Hz, Ar*H*), 3.60 (4H, t, ³*J* = 6.7 Hz, -CH₂Br), 3.46–3.37 (4H, m, -NHCH₂), 2.14–2.04 (4H, m, -NHCH₂CH₂); **¹³C NMR** (75 MHz, DMSO-*d*⁶) δ 164.5, 150.4, 134.0, 129.6, 38.0, 32.5, 32.1.

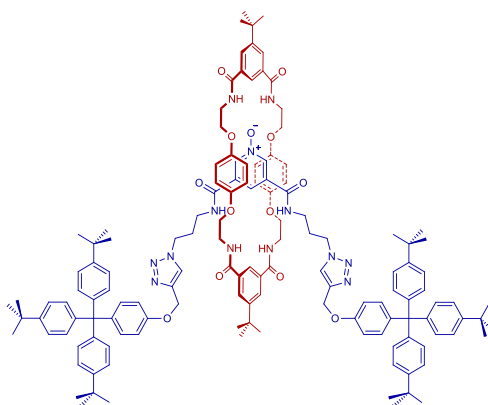
N³,N⁵-Bis(3-azidopropyl)pyridine-3,5-dicarboxamide (68**)**¹⁷



Compound **67** (647 mg, 1.59 mmol) and NaN₃ (310 mg, 4.76 mmol) were dissolved in dry degassed DMF (40 mL) and stirred overnight under N₂ at 85 °C. After this time, the mixture was cooled to room temperature and the solvent removed *in vacuo*. The resultant residue was then dissolved in CH₂Cl₂ (50 mL) and washed with H₂O (50 mL). The organic phase was kept and the aqueous phase extracted with CH₂Cl₂ (2 x 50 mL) before the combined organic phase was washed with brine (3 x 50 mL), dried over MgSO₄ and filtered. The solvent was then removed to give bis-azide **68** as an off-white solid (450 mg, 84%). **MS** (ESI-MS) *m/z* 354.1385 ([M + Na]⁺, C₁₃H₁₇N₉NaO₂, calc. 354.1397); **¹H NMR** (300 MHz, CDCl₃) δ 9.10 (2H, s, Ar*H*), 8.50 (1H, t, ⁴*J* = 2.0 Hz, Ar*H*), 7.33 (2H, t, ³*J* = 5.6 Hz, -CONH), 3.64–3.53 (4H, m, -CONHCH₂), 3.47 (4H, t, ³*J* = 6.4 Hz, -CH₂N₃), 1.99–1.88 (4H, m, -CONHCH₂CH₂); **¹³C NMR** (75 MHz, CDCl₃) δ 165.1, 150.5, 133.6, 49.4, 38.0, 28.6.

Pyridine *N*-oxide axle precursor (69)¹⁷

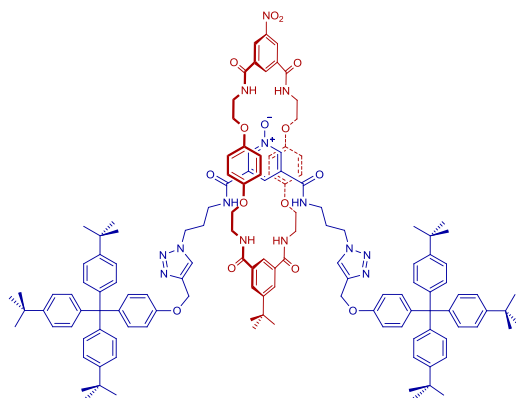
A saturated solution of Oxone[®] (5.02 g, 8.16 mmol) in H₂O (50 mL) was added dropwise to a vigorously stirred mixture of bis-azide **68** (0.450 g, 1.36 mmol) and NaHCO₃ (3.43 g, 40.8 mmol) in 1:1 H₂O/2-butanone (200 mL). After stirring for 2 hours, NaCl (8.98 g, 154 mmol) was added and the product extracted into CHCl₃ (3 x 50 mL). The organic phase was dried over MgSO₄, filtered and the solvent removed to give the product as an off-white solid (0.325 g, 69%). **MS** (ESI-MS) *m/z* 370.1342 ([M + Na]⁺, C₁₃H₁₇N₉NaO₃, calc. 347.1347); **¹H NMR** (300 MHz, CDCl₃) δ 8.98 (2H, s, ArH), 8.37 (1H, s, ArH), 8.15 (2H, t, ³*J* = 5.5 Hz, -NH), 3.62–3.51 (4H, m, -NHCH₂), 3.46 (4H, t, ³*J* = 6.4 Hz, -CH₂N₃), 2.00–1.89 (4H, m, -CH₂CH₂N₃); **¹³C NMR** (75 MHz, CDCl₃) δ 162.4, 140.3, 133.9, 49.1, 38.1, 28.4.

Bis-*tert*-butylisophthalamide rotaxane (70)

Macrocycle **63** (40.6 mg, 0.0531 mmol), pyridine *N*-oxide axle precursor **69** (23.9 mg, 0.0690 mmol), terphenyl-stoppered alkyne **20** (74.9 mg, 0.138 mmol), TBA·Cl (19.2 mg, 0.0690 mmol), TBTA (14.6 mg, 0.0276 mmol) and DIPEA (0.04 mL, 0.207 mmol) were

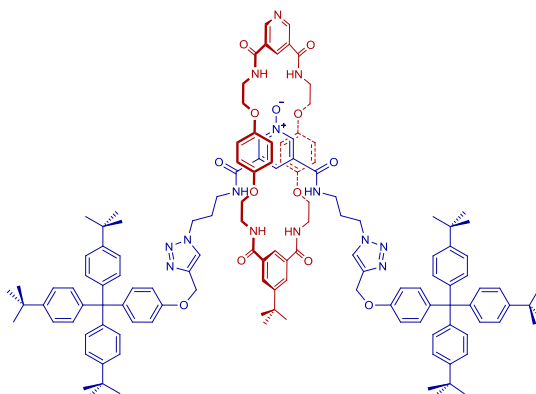
dissolved in CHCl_3 (5 mL). $\text{Cu}(\text{MeCN})_4\text{PF}_6$ (10.3 mg, 0.0276 mmol) was then added and the reaction stirred for 48 hours under nitrogen. After this time, the reaction mixture was washed with H_2O (10 x 10 mL), dried over MgSO_4 and filtered before the solvent was removed *in vacuo*. The resulting solid was then purified by preparative TLC (97:3 $\text{CH}_2\text{Cl}_2/\text{MeOH}$ then 95:5 EtOAc/MeOH) to give rotaxane **70** as an off-white solid (10.7 mg, 9%). **mp** 182 °C; **MS** (ESI-MS) m/z 1121.0921 ($[\text{M} + 2\text{Na}]^{2+}$, $\text{C}_{137}\text{H}_{161}\text{N}_{13}\text{Na}_2\text{O}_{13}$, calc. 1121.1061); **^1H NMR** (500MHz, 1:1 $\text{CDCl}_3/\text{CD}_3\text{OD}$) δ 8.49–8.44 (2H, m, ArH *tert*-butylisophthalamide), 8.43 (2H, s, ArH pyridine *N*-oxide), 8.14 (1H, s, ArH pyridine *N*-oxide), 8.12 (4H, s, ArH *tert*-butylisophthalamide), 7.87 (2H, s, triazole-*H*), 7.19 (12H, d, $^3J = 8.5$ Hz, ArH stopper), 7.07 (4H, d, $^3J = 8.7$ Hz, ArH stopper), 7.03 (12H, d, $^3J = 8.4$ Hz, ArH stopper), 6.81 (4H, d, $^3J = 8.7$ Hz, ArH stopper), 6.36–6.33 (8H, m, ArH hydroquinone), 5.09 (4H, s, $-\text{OCH}_2$ axle), 4.20 (4H, t, $^3J = 7.1$ Hz, $-\text{CH}_2\text{CH}_2$ -triazole), 4.00–3.94 (8H, m, $-\text{CONHCH}_2$ macrocycle), 3.75–3.70 (8H, m, $-\text{CONHCH}_2$ macrocycle), 3.29–3.24 (4H, m, $-\text{CONHCH}_2$ axle), 2.08–1.99 (4H, m, $-\text{CONHCH}_2\text{CH}_2$ axle), 1.34 (9H, s, ^tBu macrocycle), 1.26 (54H, s, ^tBu axle); **^{13}C NMR** (126 MHz, 1:1 $\text{CDCl}_3/\text{CD}_3\text{OD}$) δ 140.2, 133.8, 127.7, 124.3, 124.3 (*sic*), 120.0, 115.8, 112.0, 111.1, 105.6, 103.9, 102.3, 99.9, 95.7, 95.5, 94.3, 88.5, 84.8, 38.2, 34.7, 33.0.

Nitro-isophthalamide functionalised rotaxane (71)

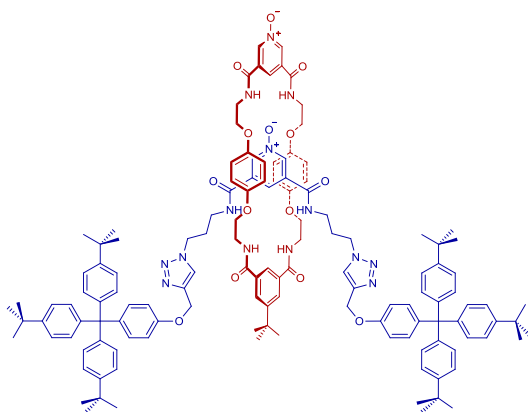


Nitro-isophthalamide macrocycle **64** (30.0 mg, 0.0398 mmol), pyridine *N*-oxide axle

precursor **69** (18.0 mg, 0.0518 mmol), terphenyl-stoppered alkyne **20** (57.0 mg, 0.105 mmol), TBA·Cl (14.4 mg, 0.0518 mmol), TBTA (11.0 mg, 0.0207 mmol) and DIPEA (0.03 mL, 0.155 mmol) were dissolved in CHCl₃ (5 mL). Cu(MeCN)₄PF₆ (7.72 mg, 0.0207 mmol) was then added and the reaction stirred for 48 hours under nitrogen. After this time, the organic phase was washed with H₂O (10 x 15 mL), dried over MgSO₄ and filtered before the solvent was removed *in vacuo*. The resulting solid was then purified by silica gel column chromatography (96:4 CH₂Cl₂/MeOH) followed by preparative TLC (95:5 EtOAc/MeOH then 9:1 EtOAc/MeOH then 3:1 MeCN/CH₂Cl₂) to give the product as an off-white solid (15.0 mg, 17%). **mp** 151 °C; **MS** (MALDI-MS) *m/z* 2209.61 ([M + Na]⁺, C₁₃₃H₁₅₂N₁₄NaO₁₅, calc. 2209.15); **¹H NMR** (500 MHz, 1:1 CDCl₃/CD₃OD) δ 8.99 (1H, s, ArH nitro-isophthalamide), 8.87 (2H, s, ArH nitro-isophthalamide), 8.45 (2H, s, ArH pyridine N-oxide), 8.41 (1H, s, ArH *tert*-butylisophthalamide), 8.10 (2H, s, ArH *tert*-butylisophthalamide), 8.09 (1H, s, ArH pyridine N-oxide), 7.84 (2H, s, triazole-CH), 7.20 (12H, d, ³*J* = 8.4 Hz, ArH stopper), 7.07 (4H, d, ³*J* = 8.8 Hz, ArH stopper), 7.04 (12H, d, ³*J* = 7.9 Hz, ArH stopper), 6.81 (4H, d, ³*J* = 8.8 Hz, ArH stopper), 6.41–6.35 (8H, m, ArH hydroquinone), 5.07 (4H, s, -OCH₂ axle), 4.24 (4H, t, ³*J* = 7.1 Hz, -CH₂CH₂-triazole), 4.01–3.93 (8H, m, -OCH₂ macrocycle), 3.76–3.70 (8H, m, -CONHCH₂ macrocycle), 3.27 (4H, t, ³*J* = 7.1 Hz, -CONHCH₂ axle), 2.10–2.01 (4H, m, -CONHCH₂CH₂ axle), 1.33 (9H, s, ^tBu macrocycle), 1.27 (54H, s, ^tBu axle); **¹³C NMR** (126 MHz, 1:1 CDCl₃/CD₃OD) δ 169.3, 166.6, 162.9, 156.9, 153.6, 153.3, 149.1, 144.9, 141.1, 140.3, 136.9, 134.7, 133.4, 133.0, 131.4, 129.2, 128.6, 128.2, 126.3, 124.8, 116.7, 116.2, 115.8, 115.6, 114.0, 71.5, 67.3, 63.8, 62.2, 37.9, 35.7, 34.9, 31.8, 31.6, 30.3.

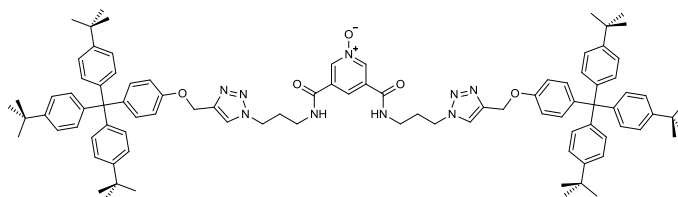
Pyridine functionalised rotaxane (**72**)

Pyridine macrocycle **65** (28.2 mg, 0.0398 mmol), axle precursor **69** (18.0 mg, 0.0518 mmol), alkyne **20** (57.0 mg, 0.105 mmol), TBA·Cl (14.4 mg, 0.0518 mmol), TBTA (11.0 mg, 0.0207 mmol) and DIPEA (0.03 mL, 0.155 mmol) were dissolved in CHCl₃ (5 mL). Cu(MeCN)₄PF₆ (7.72 mg, 0.0207 mmol) was then added and the reaction stirred for 48 hours under nitrogen. After this time, the organic phase was washed with H₂O (10 x 15 mL), dried over MgSO₄ and filtered before the solvent was removed *in vacuo*. The resulting solid was then purified by silica gel column chromatography (95:5 CH₂Cl₂/MeOH) followed by preparative TLC (9:1 EtOAc/MeOH) to yield the product as a white solid (18.0 mg, 16%). **mp** 196 °C; **MS** (ESI-MS) *m/z* 1093.5700 ([M + 2Na]²⁺, C₁₂₃H₁₅₂N₁₄Na₂O₁₃, calc. 1093.5724); **¹H NMR** (500 MHz, 1:1 CDCl₃/CD₃OD) δ 9.19 (2H, s, ArH pyridine), 9.00 (1H, s, ArH pyridine), 8.49 (2H, s, ArH pyridine N-oxide), 8.41 (1H, s, ArH *tert*-butylisophthalamide), 8.13 (2H, s, ArH *tert*-butylisophthalamide), 8.08 (1H, s, ArH pyridine N-oxide), 7.87 (2H, s, triazole-CH), 7.21 (12H, d, ³*J* = 8.3 Hz, ArH stopper), 7.09 (4H, d, ³*J* = 8.7 Hz, ArH stopper), 7.06 (12H, d, ³*J* = 8.3 Hz, ArH stopper), 6.82 (4H, d, ³*J* = 8.7 Hz, ArH stopper), 6.43–6.38 (8H, m, ArH hydroquinone), 5.08 (4H, s, -OCH₂ axle), 4.24 (4H, t, ³*J* = 7.1 Hz, -CH₂CH₂-triazole), 3.99–3.92 (8H, m, -OCH₂ macrocycle), 3.76–3.69 (8H, m, -CONHCH₂ macrocycle), 3.26 (4H, t, ³*J* = 6.3 Hz, -CONHCH₂ axle), 2.08–2.01 (4H, m, -CONHCH₂CH₂ axle), 1.32 (9H, s, ^tBu



tert-butylisophthalamide), 7.93 (2H, s, triazole-CH), 7.19 (12H, d, $^3J = 8.3$ Hz, ArH stopper), 7.07 (4H, d, $^3J = 8.7$ Hz, ArH stopper), 7.03 (12H, d, $^3J = 8.1$ Hz, ArH stopper), 6.82 (4H, d, $^3J = 8.5$ Hz, ArH stopper), 6.38–6.28 (8H, m, ArH hydroquinone), 5.11 (4H, s, -OCH₂ axle), 4.28 (4H, t, $^3J = 7.2$ Hz, -CH₂CH₂-triazole), 4.07–4.03 (4H, m, -CONHCH₂ macrocycle), 3.94–3.90 (4H, m, -CONHCH₂ macrocycle), 3.78–3.69 (8H, m, -OCH₂ macrocycle), 3.35–3.32 (4H, m, -CONHCH₂ axle), 2.12–2.05 (4H, m, -CONHCH₂CH₂ axle), 1.33 (9H, s, ^tBu macrocycle), 1.26 (54H, s, ^tBu stopper); ¹³C NMR (126 MHz, 1:1 CDCl₃/CD₃OD) δ 169.3, 163.9, 162.9, 156.9, 153.7, 153.3, 149.1, 145.0, 141.2, 140.4, 134.7, 133.1, 131.5, 129.1, 124.8, 115.7, 114.0, 67.1, 67.0, 63.9, 62.1, 43.5, 41.3, 41.1, 38.0, 37.2, 35.8.

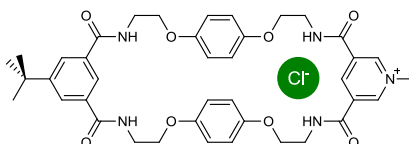
Pyridine *N*-oxide axle (74)



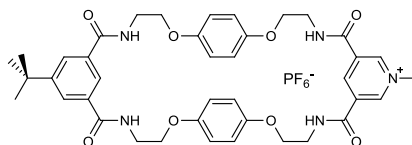
Cu(MeCN)₄PF₆ (26.0 mg, 0.0698 mmol) was added to a solution of axle precursor **69** (30.0 mg, 0.0865 mmol), alkyne **20** (94.0 mg, 0.173 mmol), TBTA (37.0 mg, 0.0698 mmol) and DIPEA (0.06 mL, 0.346 mmol) in CHCl₃ (50 mL). The reaction mixture was then stirred for 48 hours under nitrogen before the solvent was removed *in vacuo* and the resulting solid purified by silica gel column chromatography (96:4 CH₂Cl₂/MeOH) to give **74** as an off-white solid (81.0 mg, 66%). MS (ESI-MS) *m/z* 1454.8396 ([M + Na]⁺, C₉₃H₁₀₉N₉NaO₅, calc. 1454.8444); ¹H NMR (300 MHz, 1:1 CDCl₃/CD₃OD) δ 8.86 (2H, t, $^3J = 5.6$ Hz, -CONH), 8.73 (2H, s, ArH pyridine *N*-oxide), 8.26 (1H, s, ArH pyridine *N*-oxide), 7.92 (2H, s, triazole-CH), 7.20 (12H, d, $^3J = 8.5$ Hz, ArH stopper), 7.09–7.01 (16H, m, ArH stopper), 6.78 (4H, d, $^3J = 8.8$ Hz, ArH stopper), 5.08 (4H, s, -OCH₂), 4.47 (4H, t, $^3J = 6.6$ Hz,

-CH₂triazole), 3.49–3.40 (4H, m, -CONHCH₂), 2.30–2.18 (4H, m, -CONHCH₂CH₂), 1.26 (54H, s, -^tBu); ¹³C NMR (126 MHz, 1:1 CDCl₃/CD₃OD) δ 155.9, 148.4, 144.0, 140.5, 134.0, 132.4, 130.7, 129.2, 129.0, 128.1, 124.1, 113.1, 63.0, 61.4, 54.6, 37.8, 34.3, 31.4, 29.2.

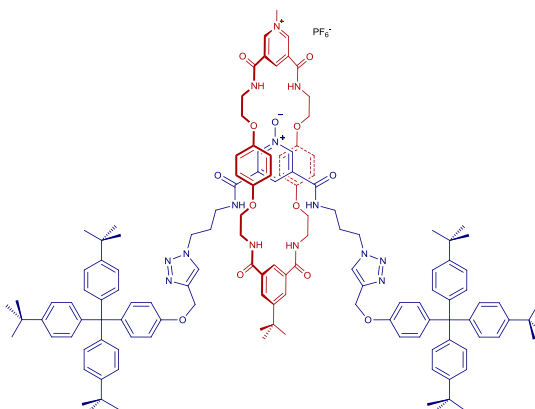
Pyridinium functionalised macrocycle chloride salt (75·Cl)



Pyridine functionalised macrocycle **65** (50.0 mg, 0.0704 mmol) was dissolved in dry DMF (15 mL). MeI (0.035 mL, 0.563 mmol) was then added and the reaction mixture heated at 85 °C for 3 days under nitrogen. After this time, the mixture was cooled to room temperature and the solvent removed. The residue was then re-dissolved in CHCl₃ (50 mL) and washed with 1 M NH₄Cl_(aq) (8 x 50 mL) and water (50 mL) before being dried over MgSO₄ and concentrated to give the product as an orange solid (34.2 mg, 64%). **mp** 188 °C; **MS** (ESI-MS) *m/z* 724.3321 ([M - Cl]⁺, C₄₀H₄₆N₅O₈, calc. 724.3341); ¹H NMR (300 MHz, 1:1 CDCl₃/CD₃OD) δ 9.54 (1H, s, ArH pyridinium), 9.40 (2H, s, ArH pyridinium), 9.26–9.20 (2H, m, -NH pyridinium), 8.05 (1H, s, ArH *tert*-butylisophthalamide), 7.95 (2H, s, ArH *tert*-butylisophthalamide), 6.82–6.74 (8H, m, ArH hydroquinone), 4.49 (3H, s, -N⁺CH₃), 4.14–4.01 (8H, m, -CH₂), 3.86–3.73 (8H, m, -CH₂), 1.39–1.33 (9H, m, -^tBu); ¹³C NMR (75 MHz, 1:1 CDCl₃/CD₃OD) δ 169.3, 162.3, 153.9, 153.7, 153.3, 147.7, 141.8, 134.8, 128.8, 123.2, 116.2, 116.2 (*sic*), 67.7, 67.3, 41.0, 40.6, 37.2, 35.7, 31.5, 30.3.

Pyridinium functionalised macrocycle hexafluorophosphate salt (75·PF₆)

Pyridine functionalised macrocycle **65** (47.6 mg, 0.0670 mmol) was dissolved in dry DMF (15 mL). MeI (0.033 mL, 0.536 mmol) was then added and the reaction mixture heated at 85 °C for 3 days under nitrogen. After this time, the mixture was cooled to room temperature and the solvent removed. The orange residue was then dissolved in 1:1 acetone/water (2 mL) and passed through an Amberlite[®] IRA-400 (Cl) column (1.5 x 7.0 cm) which had been pre-treated with 1 M NaOH_(aq) (250 mL), water (200 mL), 0.1 M NH₄PF_{6(aq)} (250 mL) and then water (200 mL). Following this, the column was washed with 1:1 acetone/water (2 x 10 mL) and then the combined acetone/water solutions were concentrated to give **75·PF₆** as an off-white solid (10.0 mg, 17%). **MS** (ESI-MS) *m/z* 724.3321 ([M - PF₆]⁺, C₄₀H₄₆N₅O₈, calc. 724.3341); **¹H NMR** (300 MHz, 1:1 CDCl₃/CD₃OD) δ 9.68 (1H, s, ArH pyridinium), 9.39 (2H, s, ArH pyridinium), 8.12 (1H, s, ArH *tert*-butylisophthalamide), 8.08 (2H, s, ArH *tert*-butylisophthalamide), 6.77–6.69 (8H, m, ArH hydroquinone), 4.46 (3H, s, -N⁺CH₃), 4.09–4.00 (8H, m, -OCH₂), 3.81–3.71 (8H, m, -CONHCH₂), 1.35 (9H, s, -^tBu); **¹³C NMR** (75 MHz, 1:1 CDCl₃/CD₃OD) δ 169.3, 162.4, 153.8, 153.6, 134.8, 128.8, 116.2, 116.1, 67.7, 35.7, 31.5; **¹⁹F NMR** (283 MHz, 1:1 CDCl₃/CD₃OD) δ -73.5 (d, *J* = 708.8 Hz); **³¹P NMR** (122 MHz, 1:1 CDCl₃/CD₃OD) δ -144.6 (sept., *J* = 717.0 Hz).

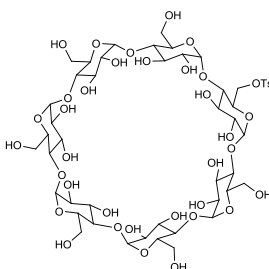
Pyridinium functionalised rotaxane hexafluorophosphate salt (76·PF₆)

Pyridinium functionalised macrocycle chloride salt **75**·Cl (34.2 mg, 0.0450 mmol), axle precursor **69** (20.3 mg, 0.0585 mmol), alkyne **20** (63.5 mg, 0.117 mmol), TBTA (12.4 mg, 0.0234 mmol) and DIPEA (0.03 mL, 0.175 mmol) were dissolved in CHCl₃ (5 mL). Cu(MeCN)₄PF₆ (8.72 mg, 0.0234 mmol) was then added and the reaction stirred for 48 hours under nitrogen. After this time, the solvent was removed *in vacuo* to give an off-white residue which was then purified by preparative TLC (95:5 CH₂Cl₂/MeOH then 96:4 CH₂Cl₂/MeOH) to give rotaxane **76**·Cl. This was then dissolved in CHCl₃ (10 mL) and washed with 0.1 M NH₄PF_{6(aq)} (8 x 10 mL) and water (10 mL) before being dried over MgSO₄ and filtered. The solvent was then removed to give the product rotaxane **76**·PF₆ as an off-white solid (40.7 mg, 39%). **mp** 196 °C; **MS** (ESI-MS) *m/z* 1089.5877 ([M + Na]²⁺, C₁₃₃H₁₅₅N₁₄NaO₁₃, calc. 1089.5892); **¹H NMR** (500 MHz, 1:1 CDCl₃/CD₃OD) δ 10.10 (1H, s, ArH pyridinium), 9.36 (2H, s, ArH pyridinium), 8.61 (1H, s, *tert*-butylisophthalamide), 8.47 (2H, d, ⁴*J* = 1.5 Hz, ArH pyridine *N*-oxide), 8.30 (1H, s, ArH pyridine *N*-oxide), 8.14 (2H, d, ⁴*J* = 1.6 Hz, ArH *tert*-butylisophthalamide), 7.91 (2H, s, triazole-CH), 7.19 (12H, d, ³*J* = 8.7 Hz, ArH stopper), 7.08 (4H, d, ³*J* = 8.9 Hz, ArH stopper), 7.04 (12H, d, ³*J* = 8.4 Hz, ArH stopper), 6.82 (4H, d, ³*J* = 8.7 Hz, ArH stopper), 6.34–6.29 (8H, m, ArH hydroquinone), 5.09 (4H, s, -OCH₂ axle), 4.48 (3H, s, -N⁺CH₃), 4.33 (4H, t, ³*J* = 6.9 Hz, -CH₂CH₂-triazole),

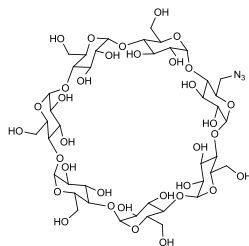
4.03–3.95 (8H, m, $-\text{OCH}_2$ macrocycle), 3.78–3.72 (8H, m, $-\text{CONHCH}_2$ macrocycle), 3.36 (4H, t, $^3J = 6.9$ Hz, $-\text{CONHCH}_2$ axle), 2.17–2.09 (4H, m, $-\text{CONHCH}_2\text{CH}_2$ axle), 1.35 (9H, s, $-\text{tBu}$ macrocycle), 1.26 (54H, s, $-\text{tBu}$ axle); ^{13}C NMR (126 MHz, 1:1 $\text{CDCl}_3/\text{CD}_3\text{OD}$) δ 169.2, 162.7, 162.2, 156.9, 153.7, 153.4, 153.3, 149.1, 148.2, 144.9, 141.2, 140.5, 134.7, 134.4, 133.0, 131.4, 129.3, 124.8, 115.4, 114.0, 66.8, 66.5, 63.8, 62.2, 58.1, 42.0, 41.4, 37.9, 35.8, 34.9, 31.8, 31.6, 30.6; ^{19}F NMR (283 MHz, 1:1 $\text{CDCl}_3/\text{CD}_3\text{OD}$) δ -73.6 (d, $J = 712.9$ Hz); ^{31}P NMR (122 MHz, 1:1 $\text{CDCl}_3/\text{CD}_3\text{OD}$) δ -144.7 (sept., $J = 709.9$ Hz).

5.2.3 Synthetic procedures for Chapter Four

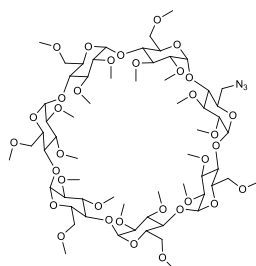
β -Cyclodextrin mono-tosylate (**77**)¹⁸



A solution of β -cyclodextrin (15.0 g, 13.2 mmol) and NaOH (6.34 g, 159 mmol) in water (350 mL) was cooled to 0 °C. TsCl (5.04 g, 26.4 mmol) was then added and the reaction mixture was allowed to stir for 2 hours at 0 °C. After this time, further TsCl (6.30 g, 33.0 mmol) was added and, once a good product distribution was observed by ESI-MS, the reaction was stopped by filtering through Celite[®] with 1 M NaOH_(aq). The filtrate was cooled to 0 °C and neutralised with 10% HCl_(aq) before the solvent volume was reduced (~100 mL). Cooling to 0 °C resulted in the formation of **77** as white precipitate which was collected *via* vacuum filtration and used in the next step without characterisation or further purification.

β -Cyclodextrin mono-azide (78)¹⁸

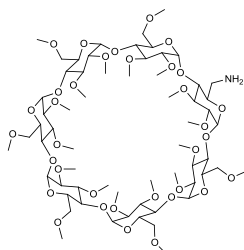
Compound **77** (17.0 g, 13.2 mmol) and NaN₃ (8.58 g, 132 mmol) were dissolved in water (250 mL) and refluxed overnight. After this time, the reaction mixture was cooled to room temperature and the solvent volume reduced (~50 mL) before it was poured into chilled acetone (100 mL) to form **78** as a white precipitate. This was collected *via* vacuum filtration and dried before being used in the next step without further purification or characterisation.

Per-methylated β -cyclodextrin mono-azide (79)¹⁸

Compound **78** (11.3 g, 9.74 mmol) was dissolved in dry DMF (50 mL) and cooled to 0 °C, NaH (60% dispersion in mineral oil, 23.4 g, 584 mmol) was added and the solution stirred for 30 minutes. After this, the solution was cooled to 0 °C and MeI (24.3 mL, 390 mmol) was added dropwise before the reaction mixture was left to stir overnight under N₂. The reaction was then quenched carefully with MeOH (10 mL) before the excess MeI was removed *in vacuo*. The DMF solution was then poured into ice water (200 mL) and extracted with CHCl₃ (4 x 100 mL). Following this, the combined organic phase was dried over MgSO₄ and filtered before the solvent was removed. The resultant residue was then passed through a silica plug

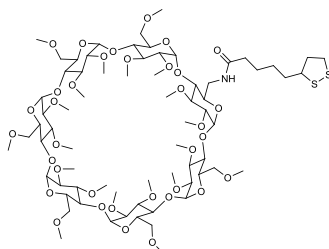
(9:1 $\text{CHCl}_3/\text{MeOH}$) and the solvent removed to give the product **79** as an orange oil, which was used in the next step without characterisation or further purification.

β -Cyclodextrin mono-amine ligand (80**)¹⁸**



Pd/C (867 mg, 10% by weight) was added to a solution of per-methylated β -cyclodextrin mono-azide **79** (8.67 g, 6.02 mmol) in EtOH (50 mL). The reaction mixture was then stirred for 4 days under 5 atm. of $\text{H}_{2(\text{g})}$. After this time, the reaction mixture was filtered through Celite[®] to remove the catalyst and then the solvent was removed *in vacuo*. The crude product was then purified *via* silica gel column chromatography (95:5 $\text{CHCl}_3/\text{MeOH}$) to give the product **80** as a sticky orange solid (820 mg, 10%). **MS** (ESI-MS) m/z 1414.71 ($[\text{M} + \text{H}]^+$, $\text{C}_{62}\text{H}_{112}\text{NO}_{34}$, calc. 1414.71); **$^1\text{H NMR}$** (300 MHz, CDCl_3) δ 5.22–5.06 (7H, m, $\alpha\text{-CH}$), 3.94–3.74 (14H, m, -CH), 3.71–3.44 (63H, m, -CH , of which 3.65 (s) and 3.51 (s) are -OCH_3 groups), 3.39 (18H, br s, -OCH_3), 3.24–3.13 (7H, m, -CH), 1.61–1.41 (2H, m, -NH_2).

β -Cyclodextrin mono-dithiolane ligand (81**)**



β -Cyclodextrin mono-amine ligand **80** (140 mg, 0.0990 mmol) was dissolved in dry CH_2Cl_2 (10 mL). Thiocetic acid (27 mg, 0.129 mmol) and $\text{EDC}\cdot\text{HCl}$ (25 mg, 0.129 mmol) were then

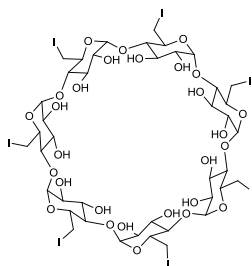
added before the reaction mixture was left to stir overnight under N₂. After this, the solvent was removed and the resultant residue purified by silica gel column chromatography (9:1 CHCl₃/MeOH) to give **81** as an off-white solid (105 mg, 66%). **MS** (ESI-MS) *m/z* 1624.68 ([M + Na]⁺, C₇₀H₁₂₃NNaO₃S₂, calc. 1624.72); **¹H NMR** (300 MHz, CDCl₃) δ 6.09–6.00 (1H, m, -NH), 5.20–5.05 (7H, m, α-CH), 3.92–3.70 (14H, m, -CH), 3.69–3.31 (81H, m, -CH), 3.25–3.10 (7H, m, -CH), 2.52–2.39 (2H, m, -SCH₂), 2.22–2.14 (2H, m, -COCH₂), 1.96–1.82 (2H, m, -SCH₂CH₂), 1.76–1.58 (5H, m, -CH₂ & -SCH), 1.54–1.39 (2H, m, -COCH₂CH₂CH₂).

Functionalised Pd/C and Pd/Al₂O₃ catalyst preparation—general procedure

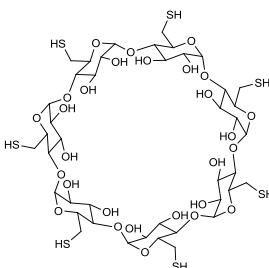
The required standard catalyst, Pd/C 87L or Pd/Al₂O₃ Type 324, (150 mg, 5 wt%) was suspended in toluene (10 mL) before β-cyclodextrin mono-amine ligand **80** (102 mg, 0.0720 mmol), β-cyclodextrin dithiolane ligand **81** (116 mg, 0.0720 mmol), or oleylamine (20 mg, 0.0720 mmol) was added. The suspension was then left to stir for 2 hours at room temperature. After this time, the suspension was filtered to obtain the solid catalyst sample which was then dried thoroughly in a vacuum oven prior to catalytic testing. The TEM data for each of the samples, including the standard Pd/C 87L and Pd/Al₂O₃ Type 324 catalysts, are shown below (**Table 5.1**) whilst full XPS analyses can be found in the Digital Appendix.

Table 5.1—TEM analyses of various 5 wt% Pd/C and Pd/Al₂O₃ catalysts.

Catalyst	Mean diameter (nm)
Pd/C 87L	2.31 (± 0.80, n = 137)
Pd/C ligand 80	2.72 (± 1.36, n = 75)
Pd/C ligand 81	2.66 (± 0.83, n = 37)
Pd/C oleylamine	3.07 (± 1.57, n = 117)
Pd/Al ₂ O ₃ Type 324	4.50 (± 1.24, n = 49)
Pd/Al ₂ O ₃ ligand 80	6.02 (± 2.68, n = 45)
Pd/Al ₂ O ₃ ligand 81	4.41 (± 1.12, n = 65)
Pd/Al ₂ O ₃ oleylamine	4.76 (± 2.44, n = 99)

Hepta-iodo β -cyclodextrin (82**)**¹⁹

PPh₃ (17.3 g, 66.1 mmol) was dissolved in dry DMF (80 mL). I₂ (17.6 g, 69.2 mmol) was then added to the solution over 10 minutes, followed by β -cyclodextrin (5.00 g, 4.41 mmol), before the reaction mixture was heated at 70 °C for 4 days. After this, the mixture was cooled to room temperature and the solvent volume reduced (~50 mL) before NaOMe (25 wt% in MeOH) was added until the solution reached pH 9. This was then left to stir for 30 minutes in an ice bath before being poured into MeOH (400 mL) to precipitate the product as an off-white solid (5.86 g, 70%). **MS** (ESI-MS) m/z 1926.52 ([M + Na]⁺, C₄₂H₆₃I₇NaO₂₈, calc. 1926.67); **¹H NMR** (300 MHz, DMSO-*d*⁶) δ 6.16–5.85 (14H, m, -OH), 5.05–4.93 (7H, m, α -CH), 3.87–3.73 (7H, m, -CH), 3.71–3.52 (14H, m, -CH), 3.49–3.22 (21H, m, -CH).

 β -Cyclodextrin hepta-thiol ligand (83**)**¹⁹

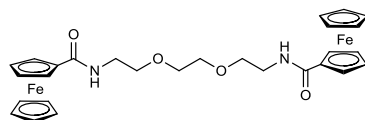
Hepta-iodo β -cyclodextrin **82** (2.00 g, 1.05 mmol) was dissolved in dry DMF (30 mL). Thiourea (639 mg, 8.40 mmol) was added and then the reaction mixture was heated at 70 °C overnight. After this time, the solvent was removed *in vacuo* and the resultant solid re-

dissolved in water (50 mL) before NaOH (273 mg, 6.83 mmol) was added and the solution refluxed for 1 hour. This was then acidified with KHSO₄ to precipitate the product **83** as an off-white solid which was collected *via* vacuum filtration, washed with water (3 x 30 mL) and dried under vacuum (1.03 g, 79%). **MS** (ESI-MS) *m/z* 1269.26 ([M + Na]⁺, C₄₂H₇₀NaO₂₈S₇, calc. 1269.20); **¹H NMR** (300 MHz, DMSO-*d*⁶) δ 5.97–5.92 (7H, m, -OH), 5.85–5.81 (7H, m, -OH), 4.95–4.90 (7H, m, α-CH), 3.73–3.54 (21H, m, -CH), 3.28–3.11 (14H, m, -CH), 2.82–2.69 (7H, m, -CH), 2.14 (7H, t, ³*J* = 8.2 Hz, -SH).

Large gold nanoparticles (Au71)

A 1.0 mM aqueous solution of HAuCl₄ (20 mL) was heated until it began to reflux, at which point, 38.8 mM aqueous sodium citrate (2 mL) was added. The solution was then allowed to reflux until it turned a deep red colour (~10 minutes). After this time, the solution was cooled to room temperature to yield a seed sample of ~20 nm citrate stabilised Au NPs. Aqueous HAuCl₄ (12 mM, 3 mL) was added to water (97 mL) and heated to reflux whilst being stirred vigorously. Once the solution had reached reflux, 1 mL of the previously synthesised seed sample was added and the solution refluxed for a further 10 minutes. After this time, the solution was cooled to room temperature to yield a dispersion of citrate stabilised Au NPs, **Au71**. **UV-vis** (water) PRB = 549 nm; **TEM** mean diameter 70.6 nm (± 1.4, n = 36).

Bis-ferrocene functionalised tag (**84**)²⁰



Ferrocenecarboxylic acid (200 mg, 0.869 mmol) was dissolved in dry CH₂Cl₂ (10 mL) and cooled to 0 °C before oxalyl chloride (0.18 mL, 2.17 mmol) was added dropwise. The reaction mixture was then left to stir overnight under N₂. After this time, the solvent and

excess oxalyl chloride were removed *in vacuo* to give the acid chloride product. This was immediately dissolved in dry CH_2Cl_2 (10 mL) and added dropwise to a solution of 2,2'-(ethane-1,2-diylbis(oxy))diethanamine (51.5 mg, 0.348 mmol), NEt_3 (0.24 mL, 1.74 mmol) and DMAP (cat.) in dry CH_2Cl_2 (10 mL) that had been cooled to 0 °C. The reaction mixture was then stirred overnight under nitrogen before being washed with 1 M $\text{HCl}_{(\text{aq})}$ (3 x 20 mL) and water (3 x 20 mL). The organic phase was then dried over MgSO_4 , filtered and the solvent removed to give the crude product, which was re-dissolved in CH_2Cl_2 and the pure product **84** precipitated with diisopropylether as an orange solid (116 mg, 23%). **MS** (ESI-MS) m/z 595.10 ($[\text{M} + \text{Na}]^+$, $\text{C}_{28}\text{H}_{32}\text{Fe}_2\text{N}_2\text{NaO}_4$, calc. 595.10); **^1H NMR** (300 MHz, CDCl_3) δ 6.34–6.15 (2H, m, -NH), 4.79–4.59 (4H, m, -CO-ferroceneH), 4.39–4.29 (4H, m, -CO-ferroceneH), 4.27–4.15 (10H, m, -ferroceneH), 3.79–3.54 (12H, m, - CH_2).

5.3 ^1H NMR titration protocols

^1H NMR titration spectra were recorded on a Varian Unity Plus or Bruker Avance III 500 spectrometer. A solution of guest (0.05 M) was added to a solution of host (2×10^{-3} M, 0.5 mL) at 293 K. The chemical shift(s) of specific host proton(s) were monitored for seventeen titration points (for 0.0, 0.2, 0.4, 0.6, 0.8, 1.0, 1.2, 1.4, 1.6, 1.8, 2.0, 2.5, 3.0, 5.0, 7.0, and 10.0 equivalents of added guest). The resulting data was analysed using the WinEQNMR2²¹ curve fitting software in experiments where association of guest and host was fast on the NMR timescale.

Binding stoichiometries were investigated by visual analysis of the titration data and by using approximations of Job plots. A graph of $\Delta\delta \cdot \chi_{\text{H}}$ against χ_{H} was plotted, with a 1:1 binding stoichiometry corresponding to a maximum $\Delta\delta \cdot \chi_{\text{H}}$ when χ_{H} was ~ 0.5 (χ_{H} = mole fraction of host, $\Delta\delta$ = change in chemical shift relative to free host).

When using the WinEQNMR2 software, estimates for the association constant and limiting chemical shifts were added to the program's input file. The parameters were refined by non-linear least-squares analysis using WinEQNMR2 to achieve the best fit between observed and calculated chemical shifts. The input parameters for the final chemical shift and association constant were adjusted based on the program output until convergence was reached. Comparison of the calculated and experimental binding isotherms demonstrated that an appropriate model with an appropriate stoichiometry was being used.

WinEQNMR2 provides an estimate of the error (as a standard deviation) of the measurement, which is included with all data in parentheses. It should be noted that these estimated standard errors only account for the fitting of a binding isotherm to the titration data and do not consider systematic errors behind such data, such as an incorrect concentration of the titrant solution.

5.4 Fluorescence titration protocols

Fluorescence emission spectra were recorded on a Horiba Jobin Yvon Fluorlog spectrometer at 293 K. An excitation wavelength of 280 nm was used and the concentration of the host was 1×10^{-5} M. A starting volume of 2.5 mL was used in each titration to which increasing amounts of guest (5×10^{-4} M) were added up to 20 equivalents. The concentration of the host was maintained throughout the titration experiments, with this achieved by making the guest stock solutions using the host stock solution. The changes of intensity of each of the bands were determined by summing the intensity values across the entire band. This gave titration data which were analysed using the DynaFit²² computer program to determine $\log K_a$ values, with the parameters refined using a non-linear least-squares method.

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CHAPTER SIX

Chapter Six: Summary of conclusions

This thesis initially investigated the effects of halogen bonding and increased inter-component preorganisation on the anion recognition properties of a series of halo-triazolium axle containing [2]rotaxanes (Chapter Two). Bromide anion templation was utilised to prepare the first bromo-triazolium containing rotaxane which was subsequently shown to bind bromide and iodide more strongly than its protic rotaxane host analogue. Two novel rotaxanes containing shortened halo-triazolium axles were also prepared and found to exhibit enhanced halide anion recognition as compared to their less preorganised analogues. In particular, the shortened iodo-triazolium axle containing rotaxane exhibited the most impressive anion recognition properties as a result of the greater halogen bond donor ability of iodo-triazolium relative to bromo-triazolium. In addition, a novel fluorescent hetero-[2]catenane containing both halogen and hydrogen bonding macrocycle components was synthesised and demonstrated to bind acetate and dihydrogen phosphate oxoanions strongly in acetonitrile solution.

In Chapter Three, four neutral pyridine *N*-oxide axle containing [2]rotaxanes were synthesised and proved to be the first examples of neutral interlocked host systems capable of halide anion recognition in aqueous solvent media. Moreover, chloride and bromide were bound preferentially over the larger iodide and dihydrogen phosphate anions suggesting the rotaxanes' binding cavities are of complementary size and shape for the smaller halides. An analogous positively charged pyridinium functionalised [2]rotaxane was also shown to bind chloride and bromide selectively, with the strength of anion recognition significantly enhanced as a result of the rotaxane's positive charge. Interestingly, low temperature VT ^1H NMR experiments revealed the structure of the rotaxanes to be dynamic on the NMR

timescale, with rapid switching between two conformations thought to be occurring at room temperature, both in the absence and presence of chloride.

A collaborative project with Johnson Matthey focussing on the synthesis of β -cyclodextrin functionalised metal nanoparticles and their applications as new catalysts and sensors was discussed in Chapter Four. Initially, four β -cyclodextrin functionalised palladium catalysts were prepared and their ability to catalyse a number of industrially relevant chemical reactions investigated. Desirable enhanced alkene selectivity compared to commercial standards was observed when these catalysts were used in the solution phase hydrogenation of 3-hexyn-1-ol and the vapour phase hydrogenation of 1-pentyne. Importantly, alkene selectivity was found to increase when the hydrogenation of 3-hexyn-1-ol was performed in the presence of water. Less marked effects were observed when the β -cyclodextrin functionalised palladium catalysts were used to in the reduction of the 2- and 3-chloro-nitrobenzene. However, the functionalised catalysts were found to give a much greater proportion of the desired 4-chloro-aniline product than the commercial standards when used to catalyse the reduction of 4-chloro-nitrobenzene.

Finally, the application of β -cyclodextrin functionalised gold nanoparticles for the solution phase SERS detection of a series of chemical tags was explored. DLS experiments showed that the inclusion of anthracene and BPE tags by a β -cyclodextrin ligand could be utilised to aggregate an aqueous dispersion of gold nanoparticles in a controlled manner. This was expected to give rise to an enhancement of the tags' Raman signal thus allowing for their detection using SERS; however the presence of residual DMSO solvent and the poor water solubilities of the various components made this highly challenging.

APPENDICES

Appendices

A.1 Crystal structure data

A.1.1 General notes

Crystals suitable for single crystal structure determination were grown by the author, while data acquisition and structure determination were carried out by C. J. Serpell or R. C. Knighton, as stated with each structure.

Data was collected using either graphite monochromated Mo K α radiation ($\lambda = 0.71073$ Å) on a Nonius KappaCCD diffractometer or (for small or weakly diffracting crystals) silicon double crystal monochromated synchrotron radiation ($\lambda = 0.66890$ Å) at Diamond Light Source beamline I19 on a custom built Rigaku diffractometer. Both diffractometers were equipped with a Cryostream N₂ open-flow cooling device¹ and data were collected at 150(2) or 100(2) K.

When using the Nonius machine, a series of ω -scans were typically performed in such a way as to collect every independent reflection to a maximum resolution of 0.77 Å, aiming for 99.5% completeness. Cell parameters and intensity data (including inter-frame scaling) were processed using the DENZO-SMN package.²

When using synchrotron radiation, ω -scans were performed such that a half-sphere of data was collected to a maximum resolution of 0.77 Å. Cell refinement, data reduction and scaling were performed using the CrystalClear package.³

The structures were solved by direct methods using the SIR92 software⁴ or by charge flipping using Superflip.⁵ Structures were refined using full-matrix least-squares on F^2 or F within the CRYSTALS suite.⁶ All non-hydrogen atoms were refined with anisotropic displacement parameters unless specified otherwise. Disordered portions were modelled using refined

partial occupancies. Geometric and vibrational restraints were applied where appropriate to ensure physically reasonable models. Hydrogen atoms were usually located in the difference map, but those attached to carbon atoms were repositioned geometrically. Protic hydrogen atoms that could not be located in the difference map were positioned to satisfy hydrogen bonding requirements. Hydrogen atoms were initially refined with soft restraints on the bond lengths and angles to regularise their geometry, after which the positions were refined with riding constraints.

In some cases, the molecular structure within solvent voids could not be resolved in the difference map and PLATON SQUEEZE^{7, 8} was therefore used to account for the residual electron density in the refinement.

After the construction of a stable, physically reasonable and complete model, the weights were optimised,^{9, 10} analogous reflections were omitted and absent high-angle data (in the case of poorly diffracting samples) were pruned using the Wilson plot. This generally led to convergence of the refinement, giving the final structure.

For the more challenging structures, in which the refinement did not converge immediately, initially half-shifts, then restraints and finally rigid body refinement were used to overcome the problem.

IUCr CheckCIF/PLATON¹¹ was used to validate the structures and warnings were dealt with as appropriate or justified using validation reply forms.

Additional notes and parameters for each structure are given below, whilst the .pdb files containing atomic coordinates are given in the Digital Appendix.

A.1.2 Crystal structure of bromo-triazolium bromide thread (**8**·Br)

Structure determined by C. J. Serpell.

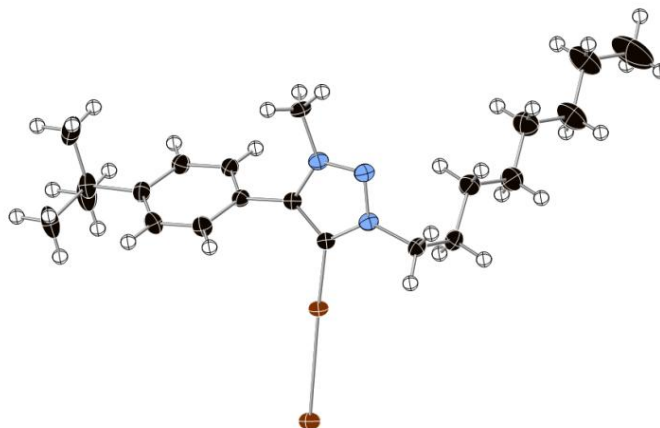


Figure A.1—X-ray crystal structure of bromo-triazolium bromide thread **8**·Br. Thermal ellipsoids displayed at 30% probability.

Table A.1—Crystal structure data for bromo-triazolium bromide thread **8**·Br.

Compound reference	8 ·Br
Chemical formula	C ₂₁ H ₃₃ BrN ₃ ·CHCl ₃ ·Br
Formula Mass	606.70
Crystal system	Monoclinic
<i>a</i> /Å	35.1193(5)
<i>b</i> /Å	11.1440(2)
<i>c</i> /Å	15.5482(2)
<i>α</i> /°	90
<i>β</i> /°	112.2030(7)
<i>γ</i> /°	90
Unit cell volume/Å ³	5633.89(15)
Temperature/K	150
Space group	<i>C</i> 2/ <i>c</i>
No. of formula units per unit cell, <i>Z</i>	8
No. of reflections measured	49519
No. of independent reflections	6411
<i>R</i> _{int}	0.022
Final <i>R</i> _I values (<i>I</i> > 2σ(<i>I</i>))	0.0317
Final <i>wR</i> (<i>F</i> ²) values (<i>I</i> > 2σ(<i>I</i>))	0.0701
Final <i>R</i> _I values (all data)	0.0405
Final <i>wR</i> (<i>F</i> ²) values (all data)	0.0780

A.1.3 Crystal structure of bromo-triazolium iodide thread (8·I)

Structure determined by R. C. Knighton.

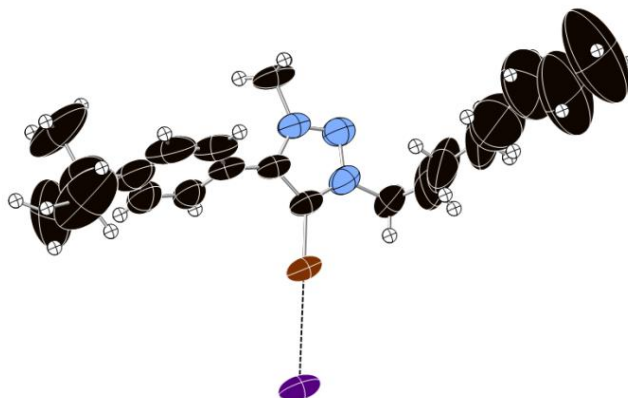


Figure A.2—X-ray crystal structure of bromo-triazolium iodide thread **8·I**. Thermal ellipsoids displayed at 30% probability.

Table A.2—Crystal structure data for bromo-triazolium iodide thread **8·I**.

Compound reference	8·I
Chemical formula	$C_{21}H_{33}BrN_3 \cdot I$
Formula Mass	534.32
Crystal system	Monoclinic
$a/\text{\AA}$	14.4146(7)
$b/\text{\AA}$	10.9553(6)
$c/\text{\AA}$	15.7216(10)
$\alpha/^\circ$	90
$\beta/^\circ$	103.194(2)
$\gamma/^\circ$	90
Unit cell volume/ $\text{\AA}^3$	2417.2(2)
Temperature/K	150
Space group	$P21/a$
No. of formula units per unit cell, Z	4
No. of reflections measured	7986
No. of independent reflections	4188
R_{int}	0.035
Final R_I values ($I > 2\sigma(I)$)	0.0837
Final $wR(F^2)$ values ($I > 2\sigma(I)$)	0.2397
Final R_I values (all data)	0.0935
Final $wR(F^2)$ values (all data)	0.2483
CCDC number	998095

A.1.4 Crystal structure of bromo-triazolium axle containing rotaxane chloride salt (30·Cl)

Structure determined by R. C. Knighton.

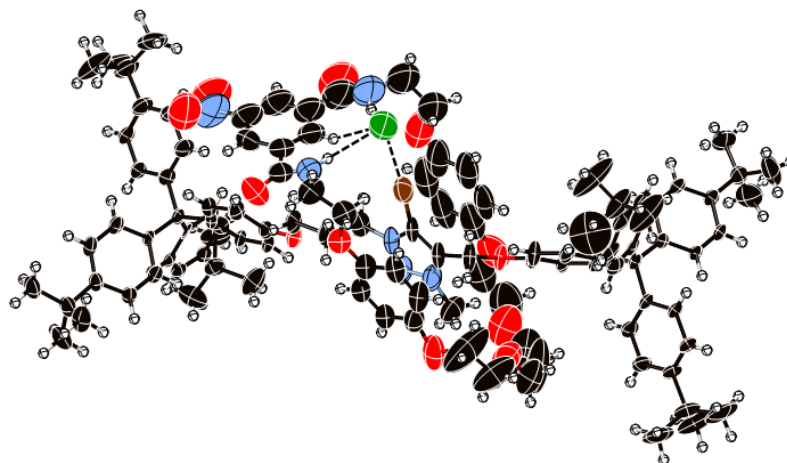


Figure A.3—X-ray crystal structure of bromo-triazolium axle containing rotaxane chloride salt **30·Cl**. Thermal ellipsoids displayed at 30% probability.

Table A.3—Crystal structure data for bromo-triazolium axle containing rotaxane chloride salt **30·Cl**.

Compound reference	30·Cl
Chemical formula	$C_{80}H_{94}BrN_3O_2 \cdot C_{32}H_{35}N_3O_{10} \cdot Cl \cdot CH_3$
Formula Mass	1882.69
Crystal system	Triclinic
$a/\text{\AA}$	15.3366(14)
$b/\text{\AA}$	16.4514(18)
$c/\text{\AA}$	23.944(2)
$\alpha/^\circ$	95.498(8)
$\beta/^\circ$	100.501(8)
$\gamma/^\circ$	108.692(9)
Unit cell volume/ $\text{\AA}^3$	5549.1(10)
Temperature/K	100
Space group	$P\bar{1}$
No. of formula units per unit cell, Z	2
No. of reflections measured	20393
No. of independent reflections	20395
R_{int}	0.165
Final R_I values ($I > 2\sigma(I)$)	0.1281
Final $wR(F^2)$ values ($I > 2\sigma(I)$)	0.3367
Final R_I values (all data)	0.1684
Final $wR(F^2)$ values (all data)	0.4079
CCDC number	998096

A.1.5 Preliminary crystal structure of bromo-triazolium axle containing rotaxane acetate salt (30·OAc)

Structure determined by R. C. Knighton.

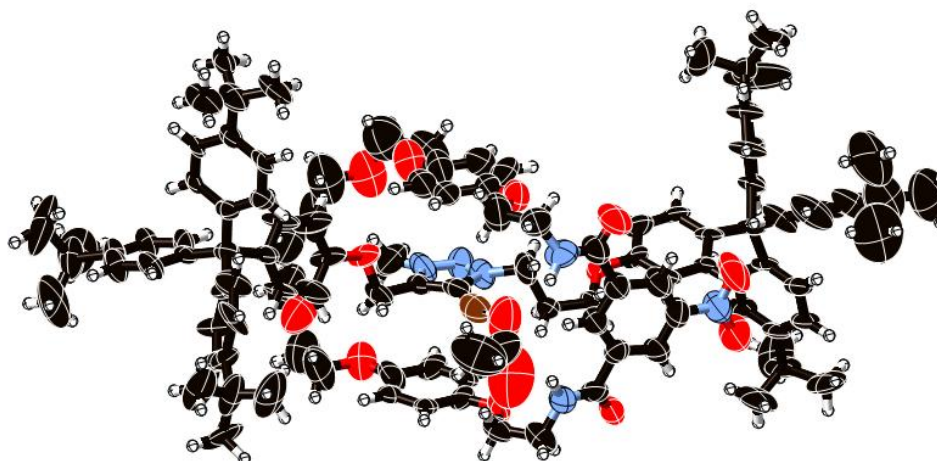


Figure A.4—Preliminary X-ray crystal structure of bromo-triazolium axle containing rotaxane acetate salt 30·OAc. Thermal ellipsoids displayed at 30% probability.

Table A.4—Crystal structure data for bromo-triazolium axle containing rotaxane acetate salt 30·OAc (some data is excluded as this is a preliminary structure showing proof of connectivity only).

Compound reference	30·OAc
Chemical formula	$C_{81}H_{97}BrN_3O_2 \cdot C_{32}H_{35}N_3O_{10} \cdot C_2H_3O_2$
Formula Mass	1905.27
Crystal system	Triclinic
$a/\text{\AA}$	15.480(2)
$b/\text{\AA}$	15.720(2)
$c/\text{\AA}$	27.413(2)
$\alpha/^\circ$	84.533(9)
$\beta/^\circ$	77.486(9)
$\gamma/^\circ$	62.990(14)
Unit cell volume/ $\text{\AA}^3$	5801.8(14)
Temperature/K	150
Space group	$P1$

A.2 Complete characterisation data for rotaxanes 70–73

A.2.1 Bis-*tert*-butylisophthalamide functionalised rotaxane 70

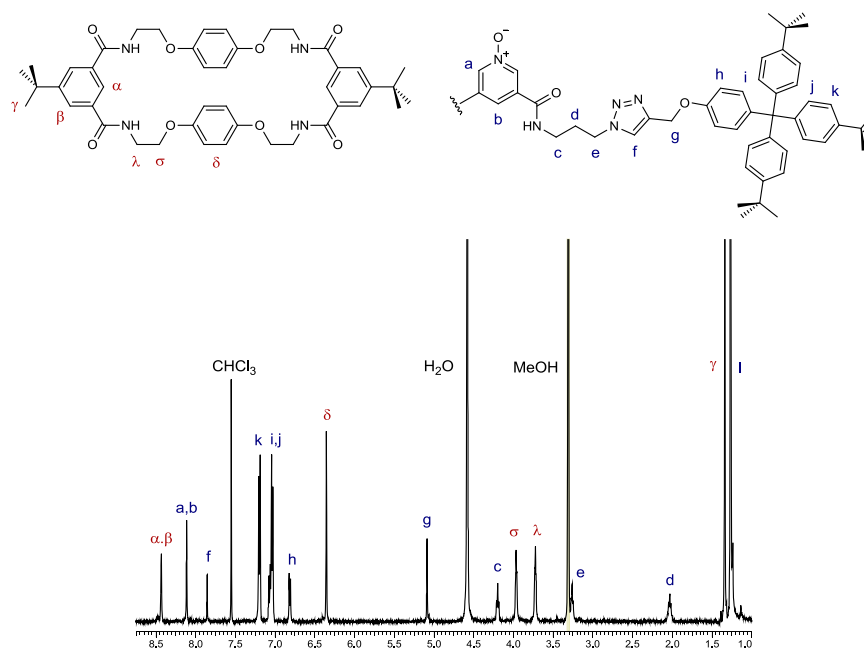


Figure A.5— ^1H NMR spectrum of bis-*tert*-butylisophthalamide functionalised rotaxane 70 (1:1 $\text{CDCl}_3/\text{CD}_3\text{OD}$, 500 MHz, 293 K).

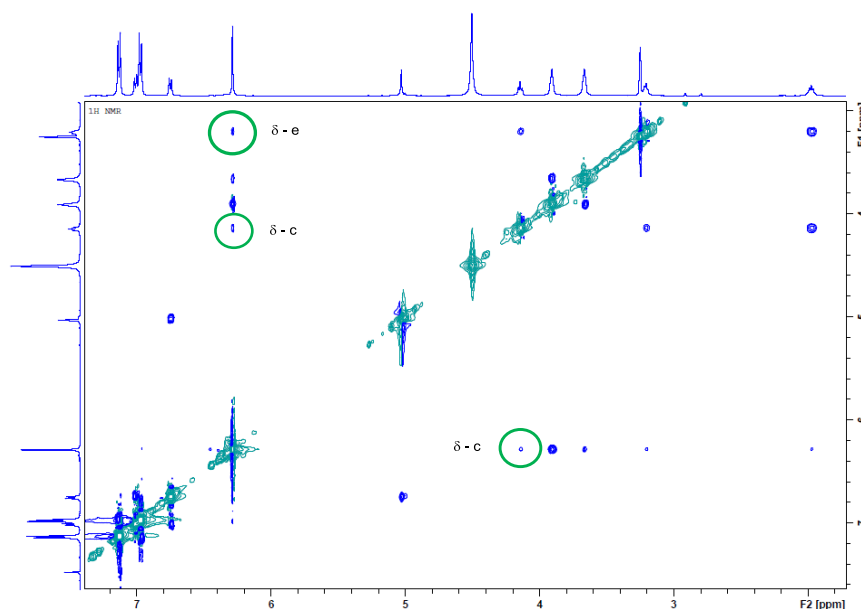


Figure A.6—Truncated 2D ^1H - ^1H ROESY NMR spectrum of bis-*tert*-butylisophthalamide functionalised rotaxane 70 (1:1 $\text{CDCl}_3/\text{CD}_3\text{OD}$, 500 MHz, 293 K).

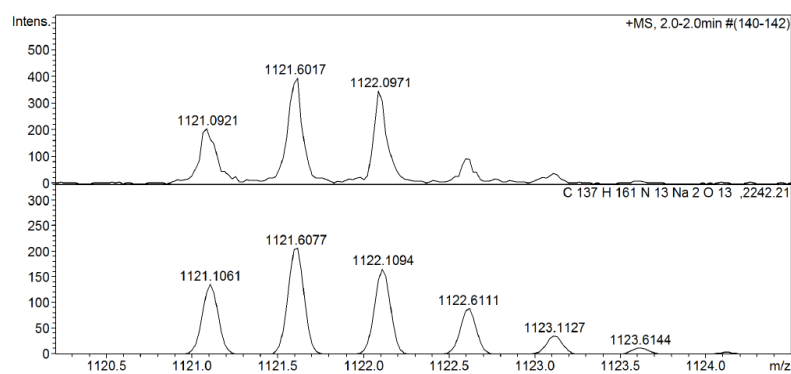


Figure A.7—High resolution ESI-MS spectrum of bis-tert-butylisophthamide functionalised rotaxane **70**.

A.2.2 Nitro-isophthalamide functionalised rotaxane **71**

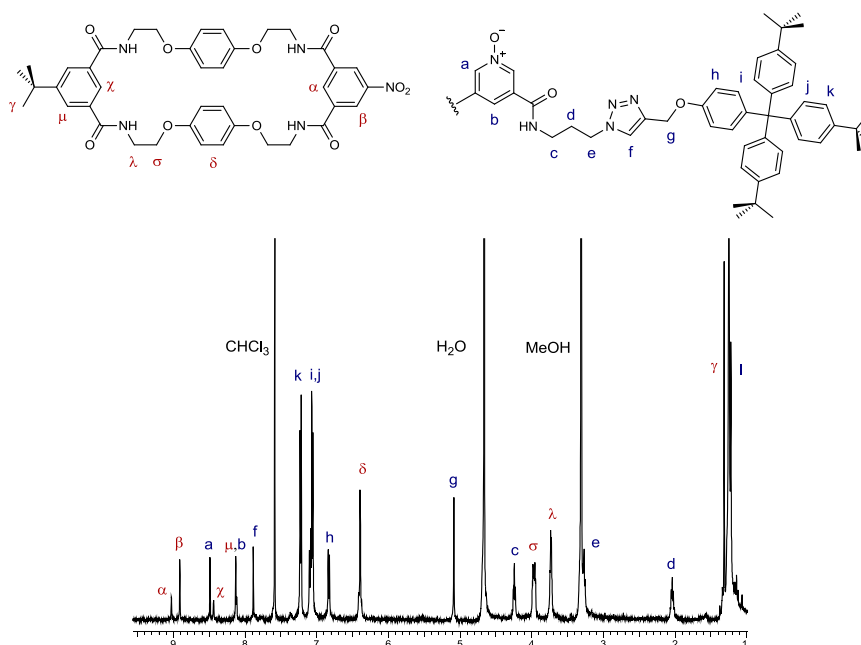


Figure A.8— ^1H NMR spectrum nitro-isophthalamide functionalised rotaxane **71** (1:1 $\text{CDCl}_3/\text{CD}_3\text{OD}$, 500 MHz, 293 K).

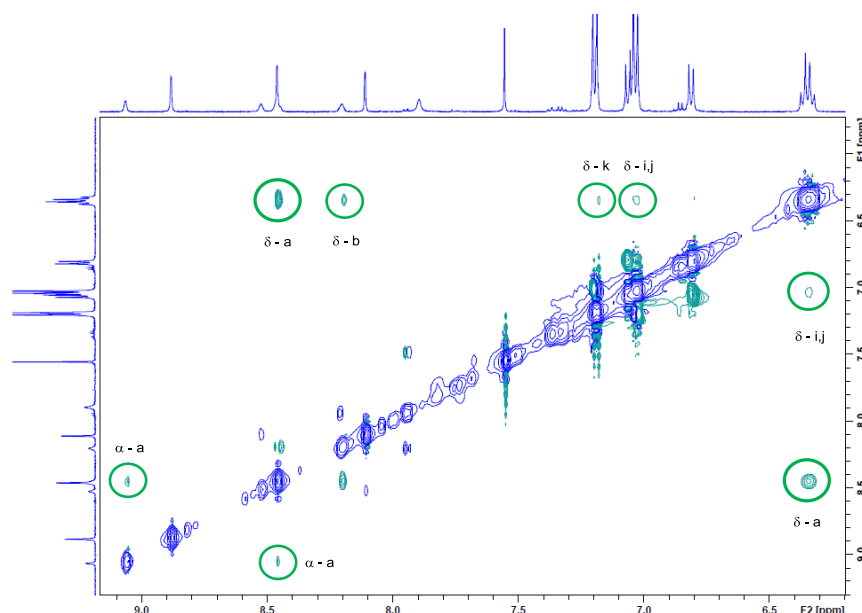


Figure A.9—Truncated 2D ^1H - ^1H ROESY NMR spectrum of nitro-isophthalamide functionalised rotaxane **71** (1:1 $\text{CDCl}_3/\text{CD}_3\text{OD}$, 500 MHz, 293 K).

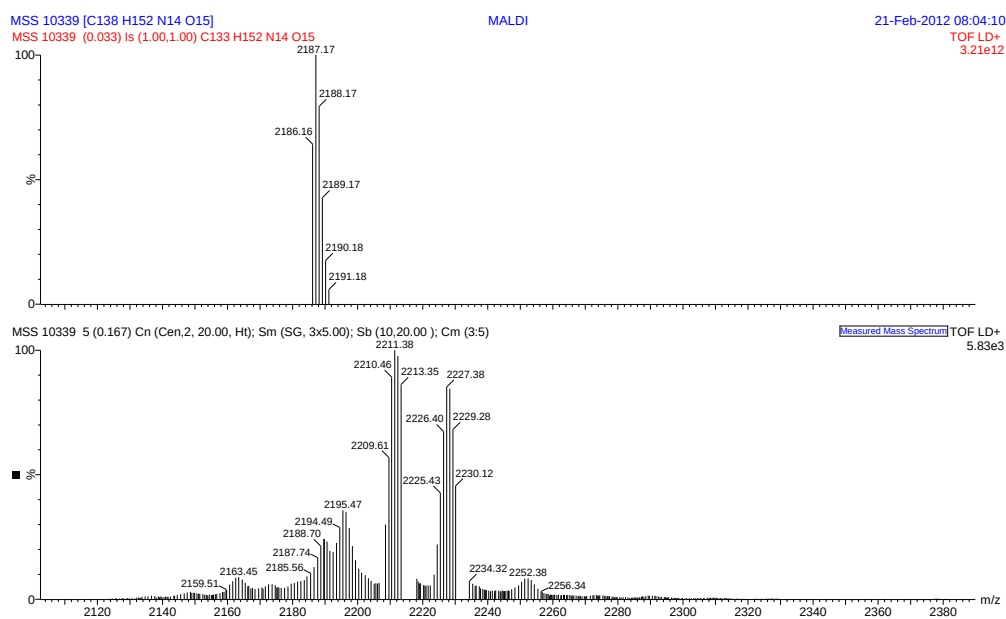


Figure A.10—MALDI-MS spectrum of nitro-isophthalamide functionalised rotaxane **71**.

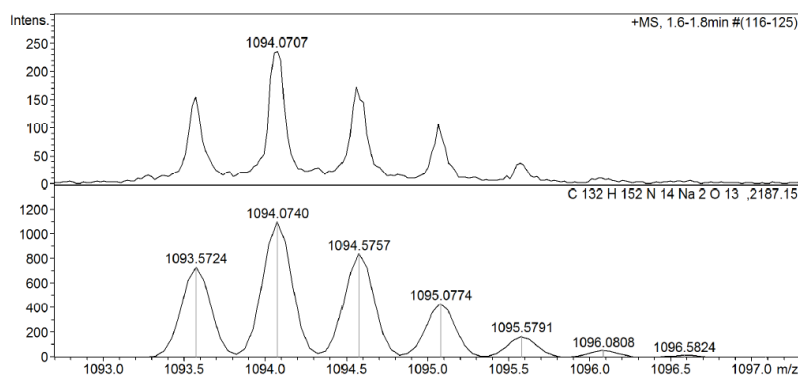


Figure A.13—High resolution ESI-MS spectrum of pyridine functionalised rotaxane **72**.

A.2.4 Pyridine *N*-oxide functionalised rotaxane **73**

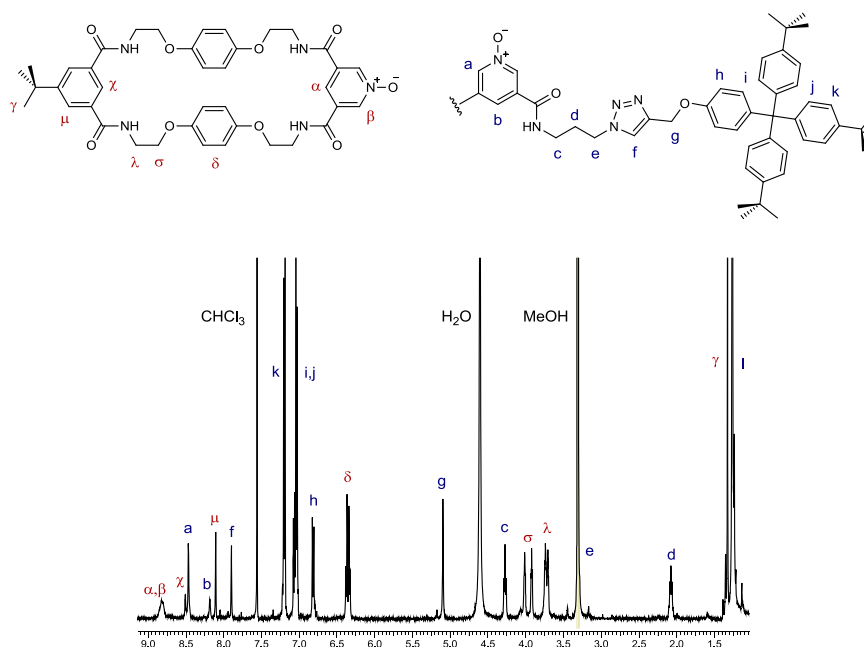


Figure A.14— ^1H NMR spectrum of pyridine *N*-oxide functionalised rotaxane **73** (1:1 $\text{CDCl}_3/\text{CD}_3\text{OD}$, 500 MHz, 293 K).

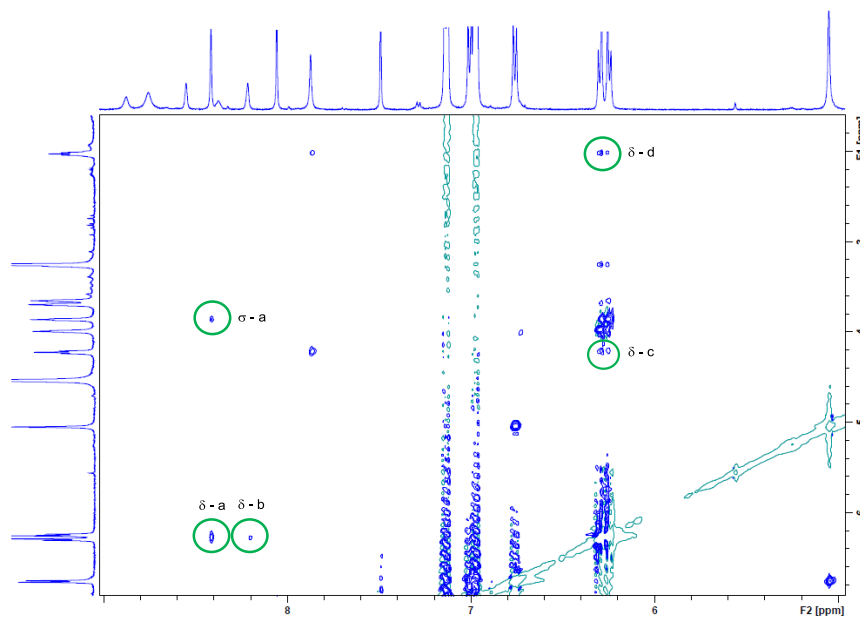


Figure A.15—Truncated 2D ^1H - ^1H ROESY NMR spectrum of pyridine N-oxide functionalised rotaxane **73** (1:1 $\text{CDCl}_3/\text{CD}_3\text{OD}$, 500 MHz, 293 K).

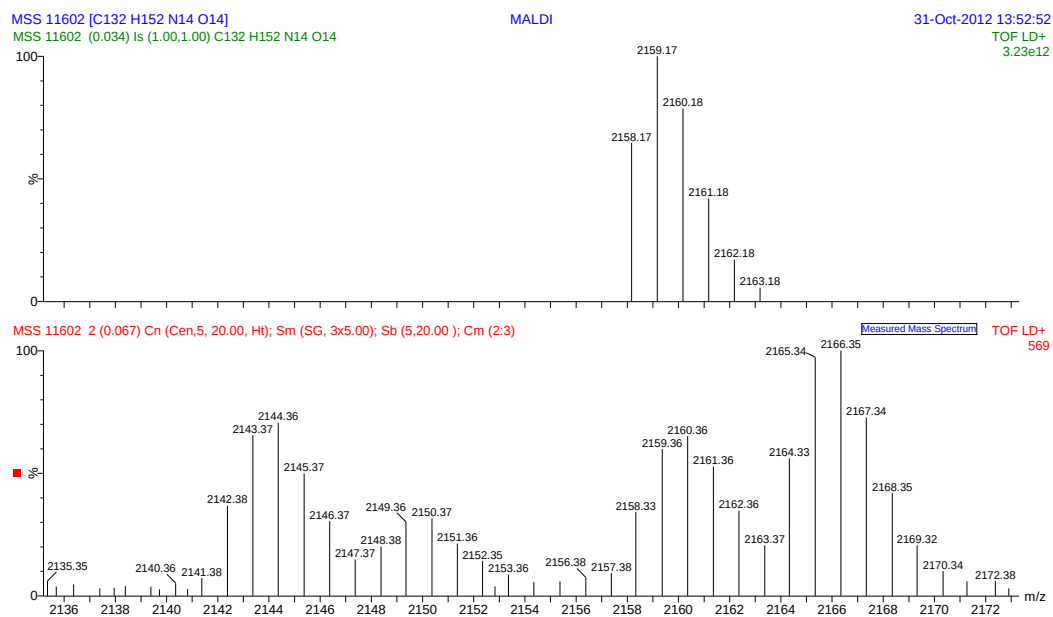


Figure A.16—MALDI-MS spectrum of pyridine N-oxide functionalised rotaxane **73**.

A.3 Contents of the Digital Appendix

The Digital Appendix contains supplementary information regarding the characterisation of the molecules and nanoparticles prepared in this work.

Location	Description
/Crystallographic data/	Atomic coordinates for all crystal structures (.pdb format).
/NP numbering	Translates between thesis nanoparticle numbering scheme and the numbering scheme referred to in the supplementary files (.pdf format).
/TEM data/	Extensive micrographs and size analyses for nanoparticle samples (.pdf format).
/XPS spectra/	XPS spectra for all catalytic nanoparticle samples (.pdf format).

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