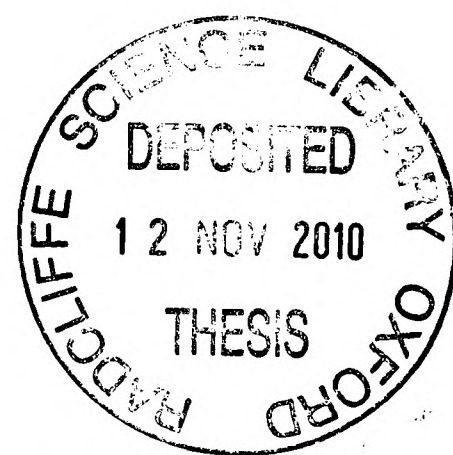
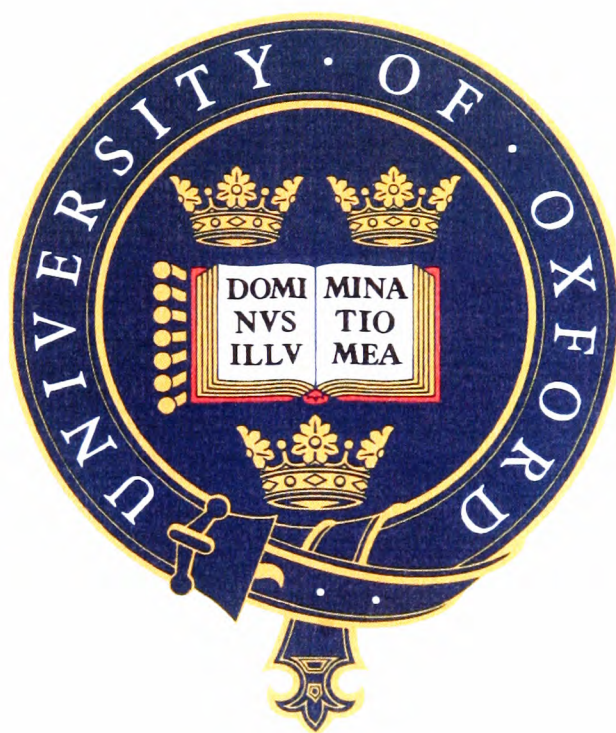


Heteroditopic Calix[4]arene Based Receptors for Ion-Pair Recognition and Mechanical Bond Assembly

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A thesis submitted for the degree of Doctor of Philosophy

Inorganic Chemistry Laboratory

University of Oxford

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Abstract of thesis submitted for the degree of D. Phil.

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This thesis investigates the design, synthesis and binding properties of novel calix[4]arene based heteroditopic receptors and interlocked structures.

Chapter 1 introduces the field of supramolecular chemistry. The areas of host-guest chemistry and self-assembly are introduced, with a particular emphasis on strategies for designing receptors for ions and synthesising interlocked structures.

Chapter 2 details the synthesis and binding properties of calix[4]arene based ion-pair receptors. These receptors show cooperative AND ion-pair recognition, where the receptors show little affinity for the ‘free’ ions but enhanced binding of the ion-pair. The extension of this work to the synthesis of their cryptand analogues is also explored. Finally, efforts towards preparing calix[4]arene based zinc Schiff base anion receptors is reported.

Chapter 3 describes the synthesis of the first calix[4]arene based rotaxane host systems for anions using a new ion-pair templation strategy. NMR spectroscopy and X-ray crystallography demonstrate the successful interlocking of the macrocycle and axle components in the rotaxane structures. Anion binding studies reveal the importance of preorganisation of the host binding cavity on anion binding. The synthesis of rotaxanes using a stoppering approach and catenanes using a ring closing metathesis clipping strategy is also investigated.

Chapter 4 investigates the use of copper catalysed coupling reactions, such as Eglinton coupling and click chemistry, in the preparation of interlocked structures. The synthesis and anion binding properties of a novel catenane are described. Efforts towards the first anion templated synthesis of rotaxanes by slippage and kinetic slippage studies are also reported.

Chapter 5 reports the experimental procedures and characterisation details of the compounds synthesised in this thesis.

Chapter 6 gives supplementary information about titration protocols, kinetic experiments and X-ray crystal structures.

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Glossary of Terms and Abbreviations

Å	Angstrom
β	overall stability constant
δ	chemical shift
ϵ	molar extinction coefficient
λ	wavelength
χ^2	statistical parameter for goodness of fit
ABS	absorbance
AMP	adenosine monophosphate
AND	logic function where both inputs are required for output
Anl	azidonorleucine
Ar	aromatic
ATP	adenosine triphosphate
bipy	bipyridyl
Boc	<i>tert</i> -butyl carbonyl
br	broad
Bu	butyl
C	centigrade
Calcd.	calculated
calix	calixarene
cat.	catalytic
CHEQ	chelation-enhanced fluorescence quenching
CV	cyclic voltammetry or voltammogram
d	doublet
DCC	<i>N,N'</i> -dicyclohexylcarbodiimide
dd	doublet of doublets
dec.	decomposition

DEE	diethyl ether
DIPEA	<i>N,N</i> -diisopropylethylamine
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
EDC.HCl	<i>N</i> -(3-dimethylaminopropyl)- <i>N'</i> -ethylcarbodiimide hydrochloride
EI	electron impact
en	ethylenediamine
ES	electrospray
Et	ethyl
eq	equivalent
FI	field ionisation
g	gram
G	guest
GMP	guanosine monophosphate
GTP	guanosine triphosphate
hr	hour
HOBt	hydroxybenzotriazole
hydroq	hydroquinone
Hz	Hertz
i	iso
INHIBIT	logic gate requiring one input to be absent for output
iso	isophthaloyl
ITC	isothermal calorimetry
k	kilo
K	Kelvin
<i>K</i>	association constant

J	Joules
<i>J</i>	coupling constant
L	ligand, Litre
M	metal, cation, molecular ion, mol L ⁻¹
m	multiplet, milli
<i>m</i>	<i>meta</i>
m/z	mass/charge ratio
Me	methyl
Ms	mesyl
mol	moles
MS	mass spectrometry
n	number
NMR	nuclear magnetic resonance
NOT	logic gate where one input removes the output
NPhth	N-phthalimide
<i>o</i>	<i>ortho</i>
OAc	acetate
p	proton
<i>p</i>	<i>para</i>
PET	photo-induced electron transfer
pH	-log [H ⁺]
Ph	phenyl
phen	phenylene
Phth	phthalimide
ppm	parts per million
Pr	propyl
py	pyridyl, pyridinium
q	quartet

Qu	quinone
quin	quintet
R	universal gas constant, variable substituent, reporter group
RNA	ribonucleic acid
ROESY	rotating-frame nuclear Overhauser effect spectroscopy
s	singlet, second
SWV	square wave voltammetry or voltammogram
t	triplet, time
<i>t</i>	<i>tertiary</i>
TBA	tetrabutylammonium
<i>tert</i>	<i>tertiary</i>
TBTA	<i>tris</i> -(benzyltriazolylmethyl)amine
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin-layer chromatography
tRNA	transfer ribonucleic acid
TTF	tetrathiafulvalene
Ts, tosyl	<i>p</i> -toluene sulfonyl
μ	micro
UV	ultra-violet
μW	microwave irradiation
V	Volt
VT	variable temperature
v	volume
X	halide, anion

Chapter 1

Introduction

1. Introduction

1.1. Supramolecular Chemistry

The award of the Nobel Prize to Pedersen,¹ Lehn² and Cram³ in 1987 signalled the transition of chemistry from the covalent to the non-covalent bond. Supramolecular chemistry has been described as ‘chemistry beyond the molecule’² because, unlike covalent chemistry, supramolecular chemistry exploits reversible weak non-covalent interactions to achieve a wide range of molecular architectures that would not be accessible using conventional covalent chemistry. Supramolecular chemistry can be broadly classified into two areas: host-guest chemistry and self-assembly. Host-guest chemistry investigates the binding of a substrate molecule into a binding site of a receptor, while self-assembly describes the construction of a structure from a number of components using non-covalent interactions (Figure 1.1).

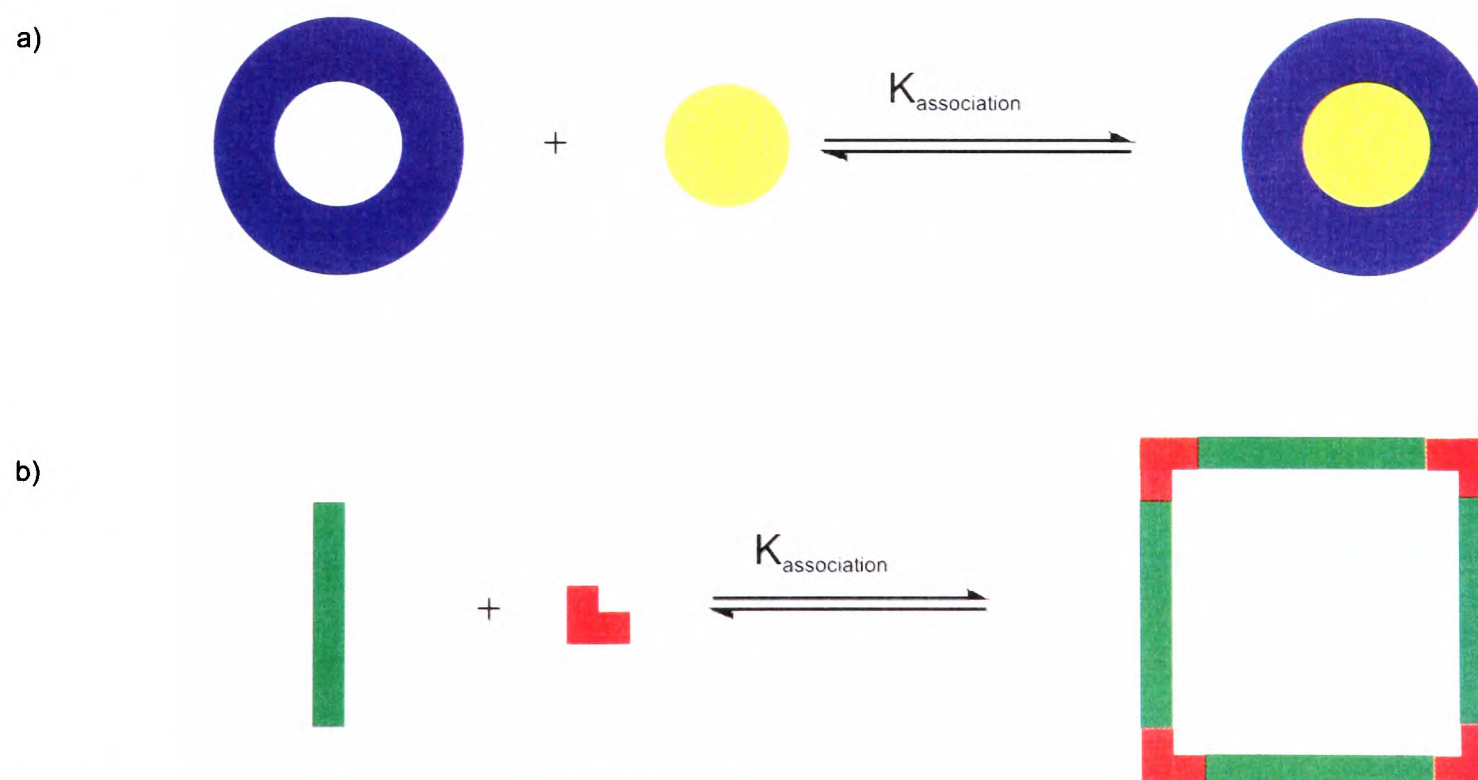


Figure 1.1 a) Host-guest chemistry and b) self-assembly

One of the biggest sources of inspiration for the growth of supramolecular chemistry over the last four decades is Nature. A large number of processes in Nature rely on non-covalent interactions to achieve their function. An example of self-assembly is deoxyribonucleic acid (DNA), one of the most biologically important molecules, which self-assembles into a double

stranded helix driven by hydrogen bonding between complementary base pairs. There are also numerous examples of host-guest chemistry. For example, enzymes exploit molecular recognition to achieve high substrate specificity.

1.1.1. Non-covalent interactions

Both self-assembly and host-guest chemistry utilize non-covalent forces. While individually weaker than covalent bonds ($4\text{--}180\text{ kJ mol}^{-1}$ versus $300\text{--}950\text{ kJ mol}^{-1}$),⁴ strong binding can be achieved by increasing the number of interactions to stabilise the overall structure.

The three main types of electrostatic based interactions are ion-ion, ion-dipole and dipole-dipole interactions (Figure 1.2). The ion-ion interaction is purely electrostatic in nature and the strongest intermolecular force. The strength of the interaction depends on the size and distance between the charges. However, there is no directionality to the force. In contrast, ion-dipole and dipole-dipole interactions are more directional in order to align with the dipole, although they are much weaker compared with ion-ion interactions.

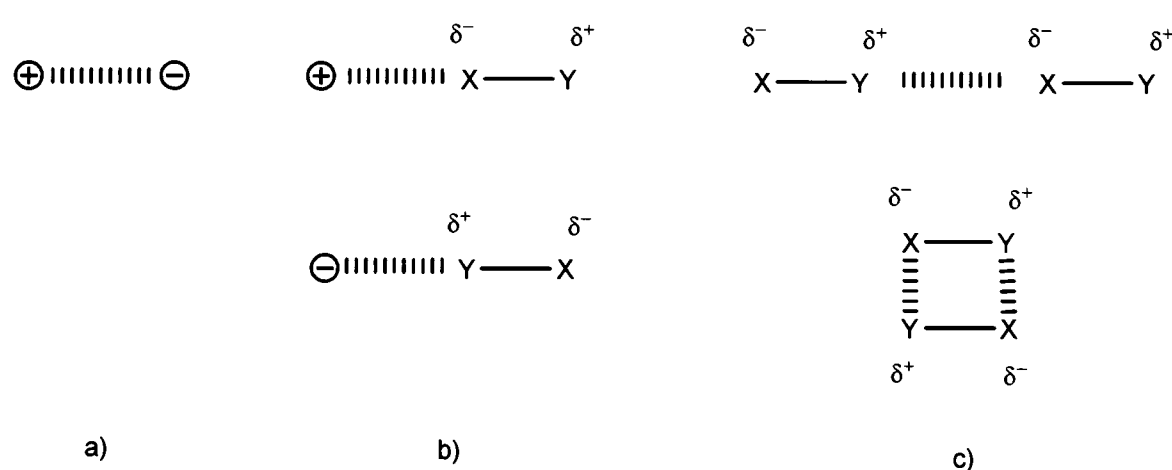


Figure 1.2 Electrostatic based interactions a) ion-ion b) ion-dipole and c) dipole-dipole

Hydrogen bonding is a special case of ion-dipole or dipole-dipole interaction where a hydrogen, bonded to an electronegative atom, is attracted to another electron rich species, for example an anion or another electronegative atom (Figure 1.3). Hydrogen bonds are, as a result, directional with a tendency to be linear and their strength can vary from as little as 4 kJ mol^{-1} to 120 kJ mol^{-1} .⁵ This type of attractive force is exploited in Nature, for example in

the phosphate and sulfate binding proteins, which complex phosphate and sulfate anions respectively by multiple hydrogen bonds.^{6, 7}

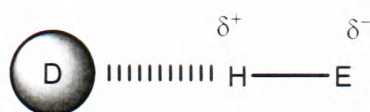


Figure 1.3 Hydrogen bond where D is an electron rich species (eg an anion or electronegative atom) and E is an electronegative atom

Another type of non-covalent interaction gaining more attention recently is the halogen bond (Figure 1.4). Related to the hydrogen bond, except with the hydrogen atom replaced with a halogen atom, this interaction has similar properties to the hydrogen bond. The strength of the halogen bond is comparable to that of the hydrogen bond with a range of strengths from 10 kJ mol⁻¹ to 200 kJ mol⁻¹, and it has been demonstrated that hydrogen bonding can be suppressed in the presence of a halogen bond donor.⁸



Figure 1.4 Halogen bond where D is an electron rich species (eg an anion or electronegative atom), X is a halogen atom and E is an electronegative atom

Van der Waals forces are weak intermolecular forces between a permanent dipole and induced dipole or two instantaneous induced dipoles. These forces are non-directional, highly distance dependent and are usually less than 5 kJ mol⁻¹ in strength. Therefore it is difficult to exploit van der Waals forces in the rational design of supramolecular architectures.

π -stacking interactions play an important role in supramolecular chemistry⁹ and also in Nature, as shown by the π - π stacking interactions between base pairs in DNA. Sanders *et al.* proposed that π - π stacking between two aromatic rings is due to both van der Waals forces between the two π systems and electrostatic interactions between the negatively charged π and positively charged σ frameworks.¹⁰ Figure 1.5 illustrates the two types of π - π stacking: edge-to-face and face-to-face. In the edge-to-face geometry (Figure 1.5a), the π - σ electrostatic interaction is dominant because the two aromatic π systems are no longer

parallel. In the face-to-face mode, repulsion between the two π systems dominates, resulting in an offset geometry, unless one of the π systems is electron deficient. In this case, a stacked geometry is possible if there is enough stabilisation from the π - σ electrostatic interaction (Figure 1.5b). π systems can also interact with ions as demonstrated by the cation- π and anion- π interactions in Figure 1.5c and d respectively. The cation- π interaction is more established¹¹ and it has been studied in the gas phase,¹²⁻¹⁴ solid state¹⁵ and in aqueous solution.¹⁶⁻¹⁸ In contrast, the interaction between an anion and an electron deficient aromatic system is less well-studied, although it is the subject of several recent reviews.^{19, 20} Quinonero and co-workers investigated the existence of such an interaction by theoretical modelling between hexafluorobenzene and anions, and an inspection of the Cambridge Structural Database.²¹ Further crystallographic evidence has been reported by de Hoog *et al.*²² and the existence of the interaction in solution has been investigated for the purpose of making transmembrane anion- π slides.^{23, 24}

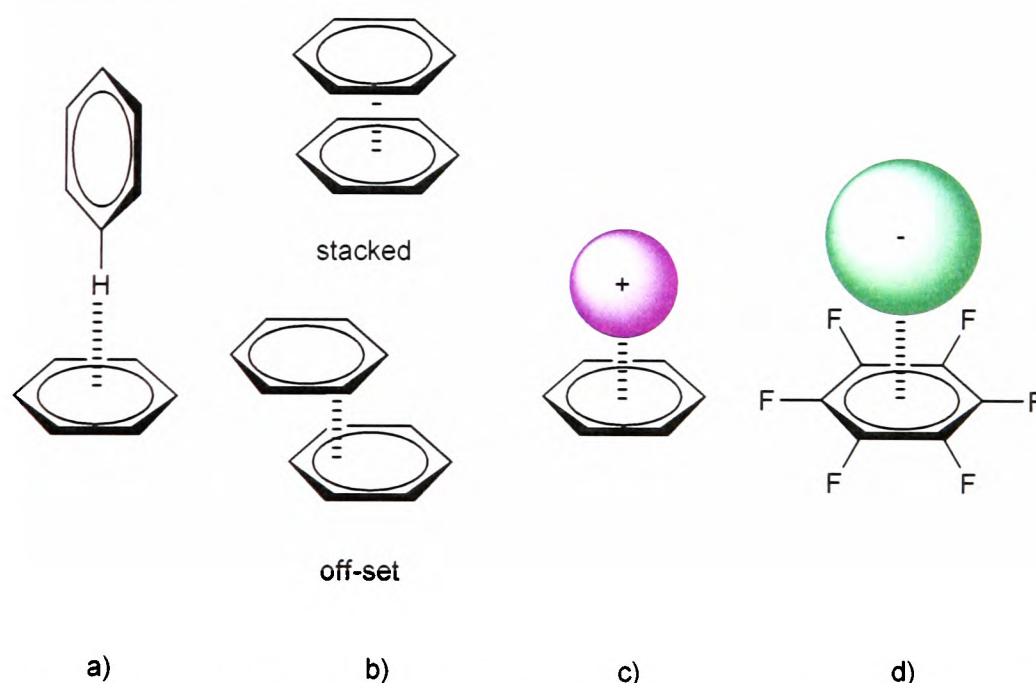


Figure 1.5 π interactions a) edge-to-face b) face-to-face in a stacked and off-set geometry c) cation- π and d) anion- π

1.2. Design Principles for Host-Guest Chemistry

One of the goals of the supramolecular chemist is to design hosts or receptors that will bind a particular guest strongly and selectively. The strength of binding can be quantified by measuring the association constant, K , as defined by the equilibrium in Figure 1.6. A large

association constant indicates strong binding of the guest but not necessarily selectivity for the guest. A receptor is said to be selective for a particular guest when it binds that guest more strongly than others.



$$K = \frac{[\text{Host-Guest}]}{[\text{Host}][\text{Guest}]}$$

Figure 1.6 Host-guest equilibrium and equilibrium constant, K

When designing receptors, a number of principles can be exploited to achieve strong and potentially selective binding, which will be discussed in the following section.

1.2.1. Complementarity

Taking inspiration from enzymes, it has been shown that designing a binding site that is complementary, both in shape and size, to the guest enhances binding. There are two main theories based on work with enzymes: the lock and key model and induced fit model. Emil Fischer proposed the lock and key model in 1894 to explain the specificity of enzymes.²⁵ The enzyme or ‘lock’ has a binding site which will only bind a substrate or ‘key’ which is complementary in size and shape (Figure 1.7a). However, this model is an oversimplification as enzymes are not rigid but rather dynamic and conformationally flexible. The induced fit model proposed by Daniel Koshland²⁶ takes this into account. The enzyme binding site (shown in blue) is not rigid but undergoes a conformational change (red) upon binding the substrate (yellow), much like a hand in a glove (Figure 1.7b). While a small amount of the binding energy is required for the conformation change lowering the stability constant, it is still possible to achieve selective recognition of a substrate.²⁷

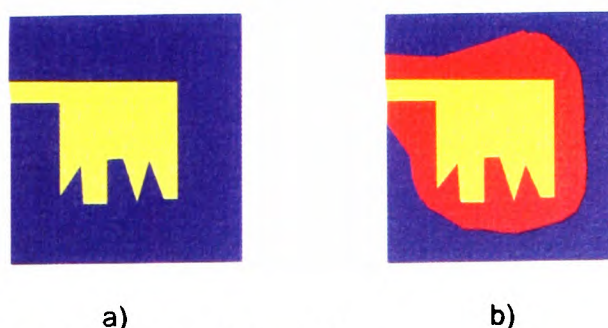


Figure 1.7 a) Lock and key model and b) induced fit model

There are examples of both types of models in Nature and it has been demonstrated that the mechanism of binding can be switched by modification of the binding site.²⁸ Methionyl-tRNA synthetase is an enzyme responsible for catalysing the reaction between methionine and tRNA. Methionine binds to the enzyme in an induced fit mechanism where significant conformational changes of several aromatic amino acids creates a hydrophobic pocket for methionine to bind via the sulfur atom by hydrogen bonding to several amino acid side chains, such as leucine and tryosine.^{29, 30} However, mutation of three amino acid residues in the enzyme active site changes the shape of the binding cavity leading to a loss of several hydrogen bonding interactions with methionine and a change in selectivity from methionine to the methionine analogue azidonorleucine (Anl).²⁸ In addition, there is a switching from an induced fit to a lock and key mechanism since Anl is a better fit for the binding site.

Important lessons for host-guest chemistry can be taken from these examples and others in Nature. Small changes in the binding site can have a dramatic effect on the selectivity and binding strength, and this is also seen in host-guest chemistry. For example, there is a correlation in complex stability of Pedersen's crown ethers with alkali metal cations between the cavity size of the crown ether and cation radius.^{31, 32} The stability constants determined by Frensdorff in MeOH show the increase in cavity size from [18]crown-6 to [21]crown-7 changes the selectivity to caesium from potassium due to complementarity (Figure 1.8).³³

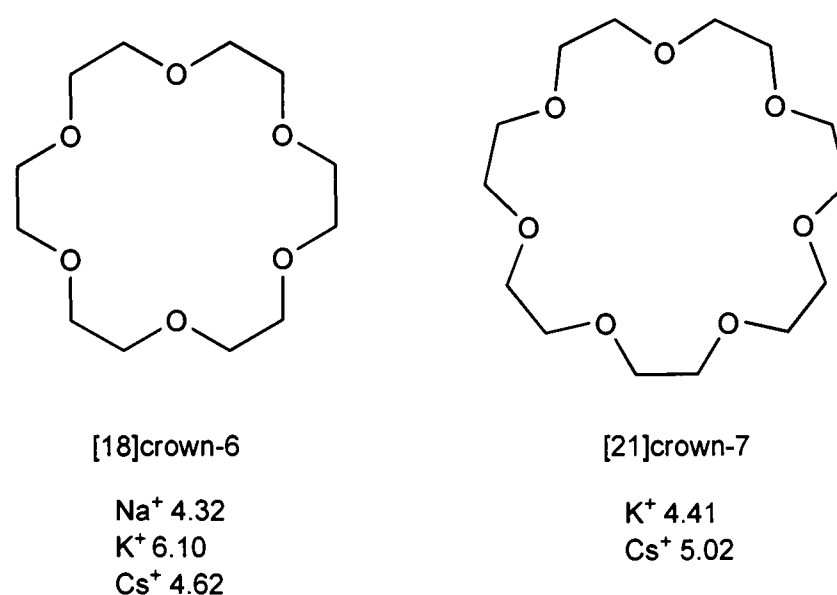


Figure 1.8 Pedersen's crown ethers and stability constants for complexes with alkali metal cations in MeOH

1.2.2. Preorganisation and Cooperativity

In conjunction with complementarity, host-guest binding can also be enhanced by increasing the preorganisation of a system and this can be achieved by exploiting the chelate and macrocyclic effects. In the principle of preorganisation Donald Cram stated ‘the more highly hosts and guests are organised for binding and low solvation prior to their complexation, the more stable will be their complexes.’³ This is evident when comparing the complex stabilities of crown ethers,^{31, 32} cryptands³⁴ and spherands³⁵ with a given alkali metal cation (Figure 1.9). The more preorganised spherand shows strongest binding followed by the cryptand and finally the crown ether. While metal cation complexation is thermodynamically favourable for more preorganised hosts, the rates of complexation and decomplexation are slow.

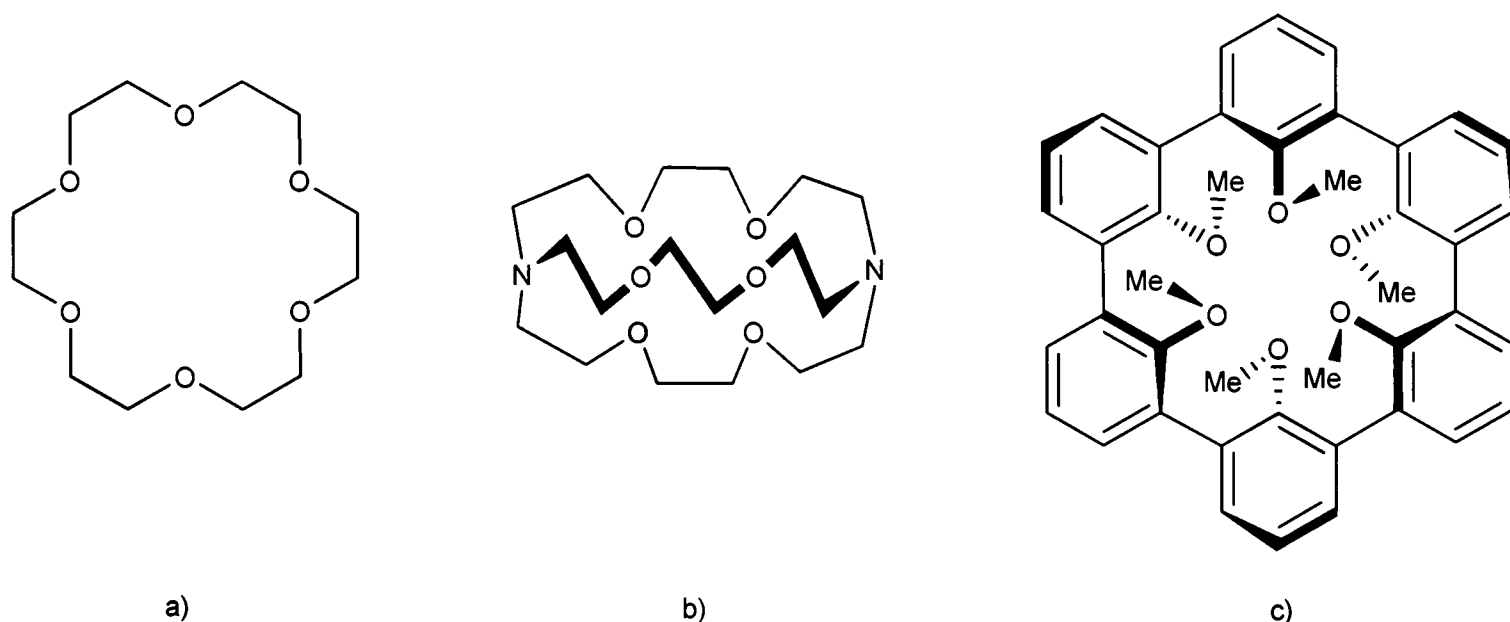


Figure 1.9 a) Crown ether b) cryptand and c) spherand

1.2.2.1. Chelate Effect

The chelate effect describes the enhanced stability of complexes with multidentate ligands compared to the corresponding complex containing monodentate ligands. The nickel complex with the bidentate ethylene diamine ligand is almost ten orders of magnitude more stable than the analogous complex with the monodentate ligand ammonia due to enthalpic and entropic factors (Figure 1.10).³⁶ The size of the chelate ring also affects the stability of the complex with a ring size of 5 or 6 being favourable. A larger chelate ring size reduces the effect due to loss of entropy.

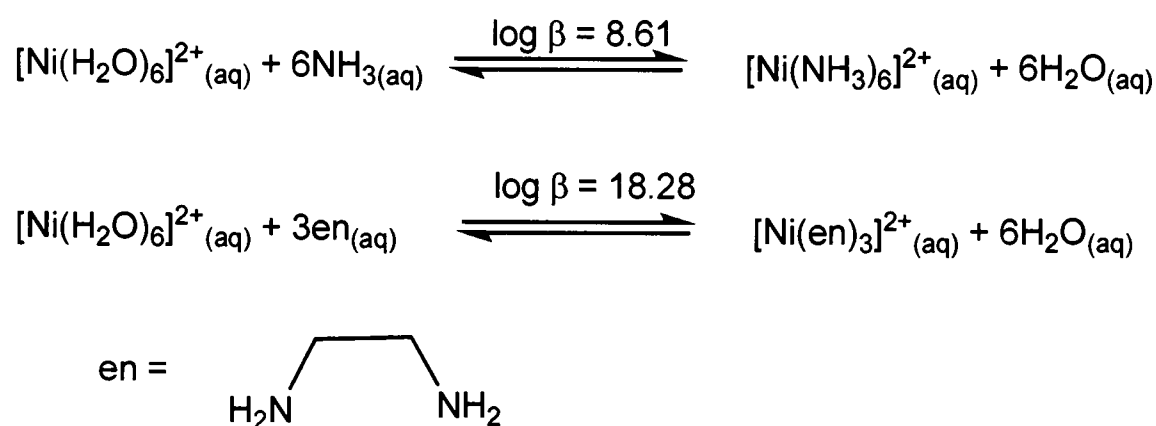


Figure 1.10 The chelate effect demonstrated by stability constants of nickel complexes with monodentate and multidentate ligands

1.2.2.2. Macrocyclic Effect

Related to the chelate effect, the macrocyclic effect refers to the greater stability of complexes with macrocyclic ligands compared with acyclic ligands,³⁷ as demonstrated by the association constants of the zinc complexes with the acyclic ligand L_1 and macrocyclic ligand L_2 (Figure 1.11).³⁸ The effect, like the chelate effect, is driven by enthalpic and entropic factors. Macrocyclic ligands are more preorganised than their acyclic analogues which is entropically more favourable for binding. In addition, macrocycles are less well solvated so the energetic cost for desolvation upon binding is smaller and the repulsion between donor groups is minimised.

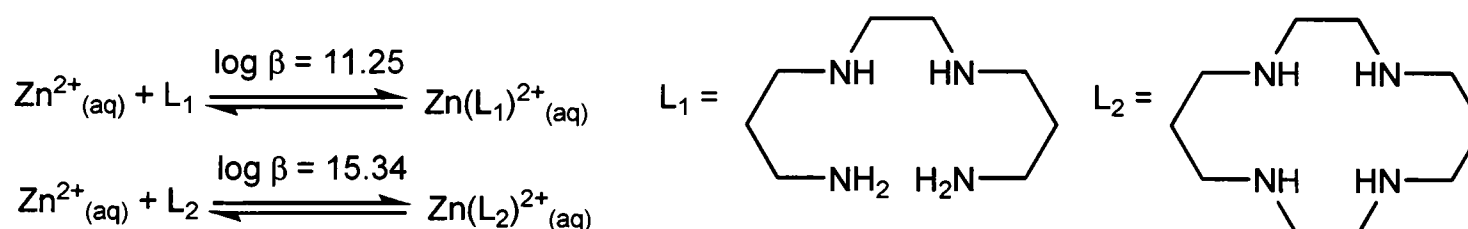


Figure 1.11 The macrocyclic effect demonstrated by the stability constants of zinc complexes with acyclic (L_1) and macrocyclic (L_2) ligands

1.2.3. Solvent Effects

Based on the principles above, it is apparent that a well-designed host needs to have a preorganised binding site complementary to the desired guest. However, the solvent in which the recognition is to take place also needs to be considered since the strength and selectivity of binding is highly dependent on solvent effects. Polar solvents may be able to compete with the guest by interacting with the host via electrostatic interactions and/or hydrogen bonding.

For this reason, guest binding for many synthetic receptors is studied in organic solvents to maximise the strength of the non-covalent interactions.

However, the goal of supramolecular chemists ultimately is to design hosts which will bind guests in water in an effort to better understand and control processes in Nature.³⁹ This presents a difficult challenge due to the competitive nature of water and the required water solubility of the synthetic host. The hydrophobic effect, or the tendency for non-polar molecules to form aggregates in water, can be exploited when designing host systems for binding apolar guests in water (Figure 1.12). The host has a hydrophobic cavity for binding the guest which is filled with ordered water molecules prior to complexation. These ordered water molecules are released upon guest binding which is entropically favourable and the driving force for recognition. Additionally there is a positive enthalpic contribution from the increased hydrogen bonding between water molecules.

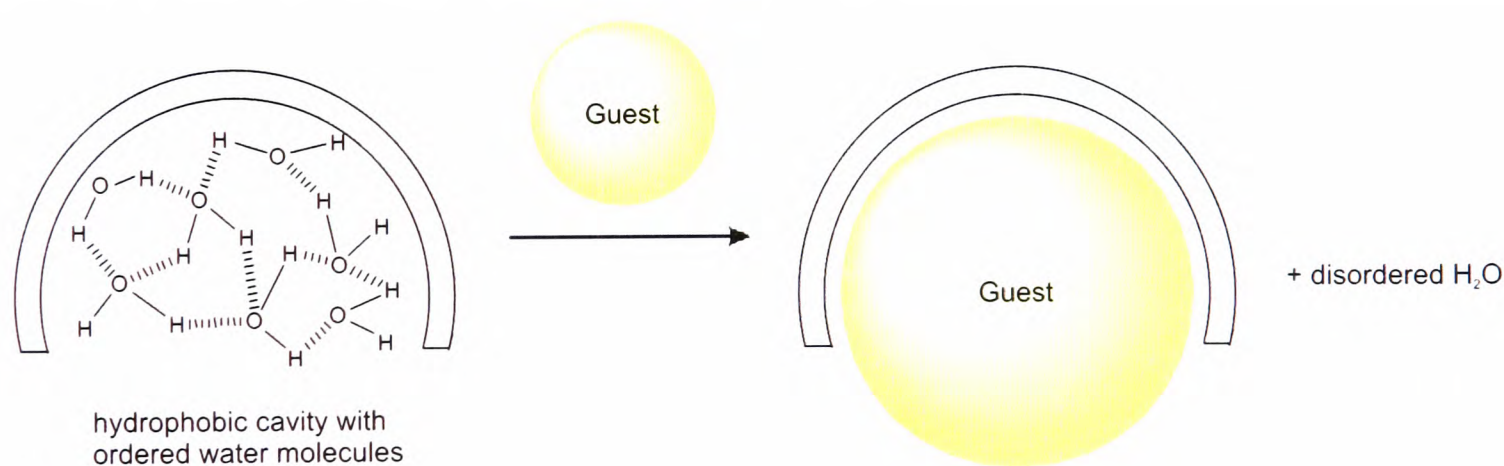


Figure 1.12 The hydrophobic effect

The next sections will review the efforts made towards designing synthetic receptors for the recognition and sensing of charged species.

1.3. Recognition and Sensing of Charged Species

1.3.1. Introduction

Charged species, such as cations and anions, are ubiquitous and the importance of these species in chemical, biological, medical, environmental and industrial processes cannot be underestimated. For example the ClC chloride channel is responsible for controlling the flow

of chloride ions across cell membranes and its misregulation has been linked to muscle and kidney diseases.⁴⁰ As a result, the design and application of synthetic host systems for these species has been of interest for many decades. Applications include the design of ion channel mimics, metal ore extractants, and sensors or extractants for environmental pollutants.

As discussed in Sections 1.1 and 1.2, the recognition of a particular guest can be influenced by the design of the host. In many cases, the detection or ‘sensing’ of a particular guest is also of interest. This requires the incorporation of a reporter group close to the guest binding site into the design of the host. The properties of the reporter group are altered upon guest binding leading to a detectable optical (colorimetric⁴¹ or luminescent⁴²) or electrochemical change.⁴³ Figure 1.13 illustrates three possible strategies for including a reporter group in the host system. In the first, the reporter group (R) is directly part of the guest binding site (Figure 1.13a), while a more common approach is to attach the reporter group to the guest binding site via a linker (Figure 1.13b). The third approach is based on the indicator displacement assay developed by Anslyn and co-workers.⁴⁴ The reporter group is an indicator which will bind in the receptor’s cavity but has a lower affinity for the binding site than the target guest (Figure 1.13c). Upon guest binding, the indicator is displaced from the binding site leading to a change in the indicator’s properties, often a colour change.

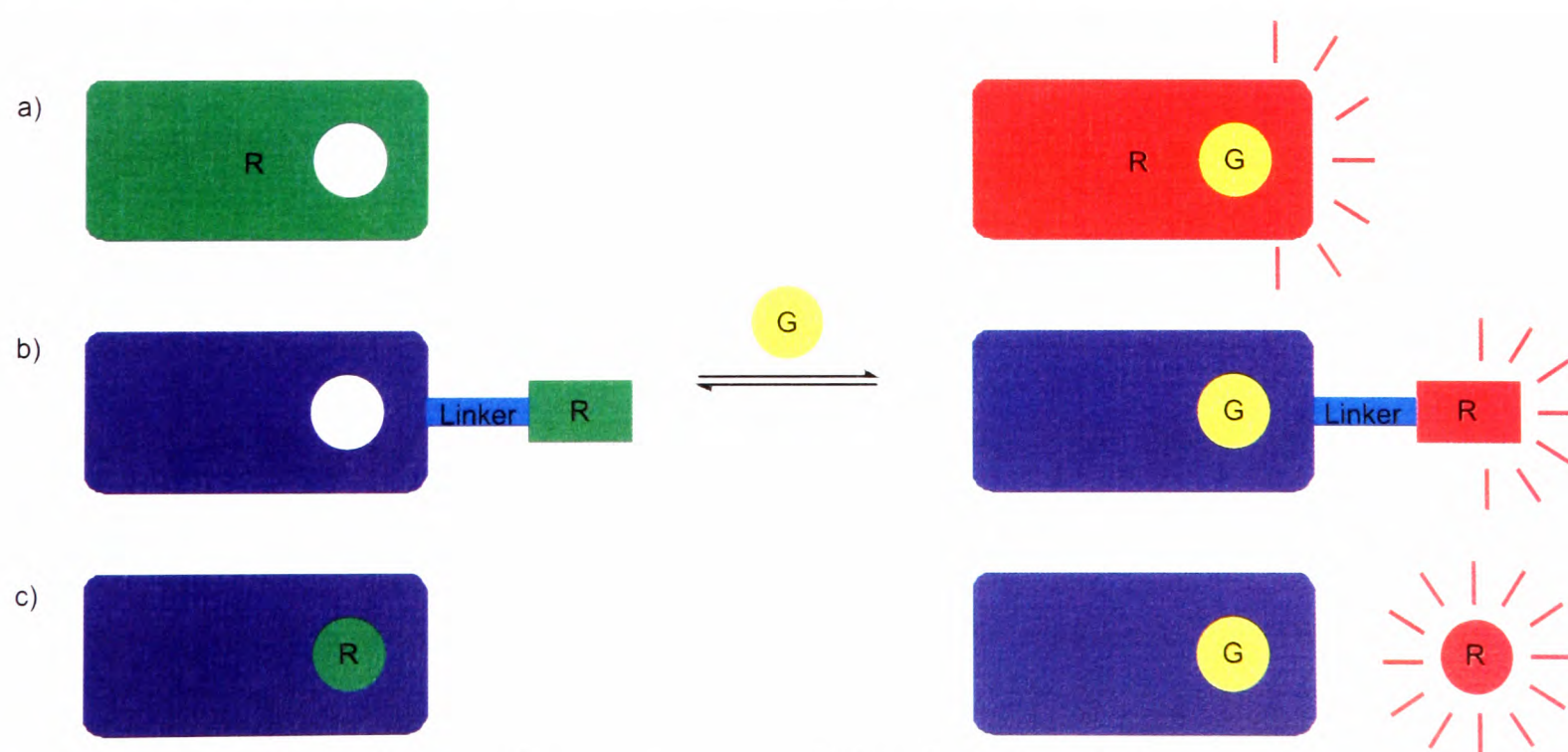


Figure 1.13 Strategies for incorporating reporter groups (R) into the design of a host

The following sections will introduce the design of receptors for cations, anions and ion-pairs for recognition and sensing applications.

1.3.2. Cation Receptors

Cations are involved in many biological, medical and industrial processes. For example many enzymes rely on cationic cofactors for their function like iron in heme proteins. Cation channels are also crucial for maintaining the correct intracellular ion concentrations and in medicine, metals such as gadolinium have important applications for imaging. The extraction of metals from ores and removal of toxic cations are also of industrial and environmental importance.

Numerous examples in Nature provide inspiration for the design of cation receptors such as the macrocycle valinomycin. This molecule selectively binds and transports potassium ions through membranes.⁴⁵ Like Nature, synthetic receptors are often macrocyclic and rely on ion-dipole interactions primarily, but also cation- π interactions to bind cations. The design of cation receptors⁴⁶⁻⁴⁸ has been explored extensively since the pioneering work on crown ethers, cryptands and spherands, as introduced in Section 1.2. This section will focus on the development of the field of cation receptor chemistry from these early receptors.

While Pedersen demonstrated that crown ethers can complex alkali metal cations,^{1, 31, 32} a number of other guests such as alkylammonium,^{49, 50} ammonium⁵¹ and guanidinium⁵⁰ cations will also bind in the cavity. The ability of crown ethers to complex guanidinium cations has been exploited to develop sensors for saxitoxin (Figure 1.14a), a marine toxin which causes paralytic shellfish poisoning. Le Blanc and co-workers have synthesised chemosensors incorporating anthracene⁵² and coumarin⁵³ fluorescent reporter groups for detecting saxitoxin binding in the azacrown (Figure 1.14b). The coumaryl chemosensor was able to detect saxitoxin selectively in H₂O in the presence of potassium and sodium ions by PET

fluorescence enhancement.⁵³ Crown ethers can also complex larger more polarising cations, like mercury, lead and silver, by replacing the hard oxygen donor atoms with soft donor atoms like sulfur. The receptor in Figure 1.14c, combining a squaraine reporter group and crown ethers, was able to selectively detect mercury at nanomolar concentrations in H₂O.⁵⁴

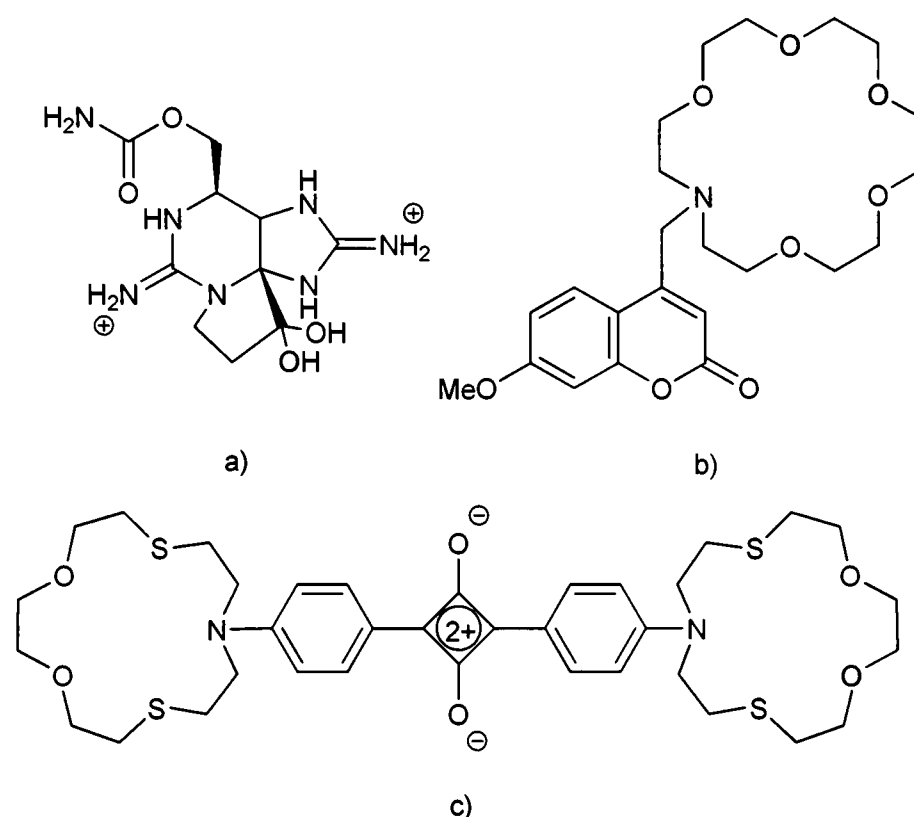
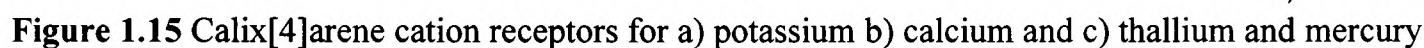
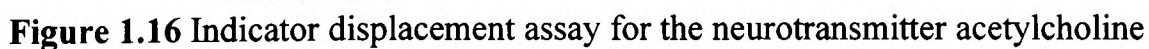


Figure 1.14 a) Marine toxin, saxitoxin b) Le Blanc's chemosensor for saxitoxin and c) squaraine receptor for detecting mercury

The calixarene framework, which will be introduced in more detail in Chapter 2, has also been exploited as a scaffold for many cation receptors. It is preorganised, but yet can exist in different conformations, and has a set of oxygen donor groups which can be further functionalised to enhance cation binding. There are numerous examples of cation receptors combining the calixarene framework with a crown ether to form a calix crown receptor.^{55, 56} The calix[4]arenecrown-5 receptors in the 1,3-alternate conformation were shown to bind potassium selectively over sodium with better K⁺/Na⁺ selectivity than valinomycin in extraction experiments (Figure 1.15a).⁵⁷ Receptors can also be designed to bind larger cations. The receptor in Figure 1.15b incorporates indoaniline groups as optical reporter groups and there is a colour change upon binding of calcium within the ester cavity to the quinone carbonyl oxygens.⁵⁸ Soft metals such as thallium and mercury can also be sensed by the receptor in Figure 1.15c with a dansyl group.⁵⁹ The receptor was able to selectively extract



Calixarene receptors have also been developed for biologically relevant cations such as acetylcholine, a neurotransmitter. Indicator displacement assays have been reported exploiting resorcin[4]arene⁶⁰ and calix[6]arene⁶¹ receptors where a fluorescent molecule binds in the cavity and as a result the fluorescence is quenched. However, addition of acetylcholine displaces this molecule switching on the fluorescence (Figure 1.16).



1.3.3. Anion Receptors

Like cations, anions play fundamental roles in a multitude of processes in Nature, chemistry and industry. For example, the eutrophication of fresh water systems has been linked to the overuse of fertilizers in agriculture, which leads to a buildup of nitrate and phosphate anions.⁶² Fluoride has been shown to prevent tooth decay in low concentrations yet its toxicity is currently being exploited as a means of treating osteoporosis since the body responds to fluoride by increasing bone density.⁶³

Therefore the development of anion receptors is of ever increasing importance and is a subject of intense current interest.^{62, 64-67} However, the field of anion receptor chemistry is relatively underdeveloped compared with cation receptor chemistry. This is because the binding of anions is inherently more difficult than for cations for the following reasons:

- Anions are larger and therefore have lower charge densities than their isoelectronic cations (Table 1.1). As a result, larger binding cavities are required and the strength of binding in systems relying on electrostatic interactions is reduced.

Cation	Ionic radius (Å)	Anion	Ionic radius (Å)
Na ⁺	0.95	F ⁻	1.36
K ⁺	1.33	Cl ⁻	1.81
Rb ⁺	1.48	Br ⁻	1.95
Cs ⁺	1.69	I ⁻	2.16

Table 1.1 The ionic radius of cations and their corresponding isoelectronic anions

- Anions have a variety of geometries including spherical (halide anions), linear (N₃⁻, SCN⁻), tetrahedral (H₂PO₄⁻, SO₄²⁻), trigonal planar (NO₃⁻) and octahedral (PF₆⁻), unlike cations which are mainly spherical. The geometry of the anion needs to be considered when designing a complementary binding site.
- The existence of anions can be highly dependent on pH as many anions, like phosphates, sulfates and carboxylates, can be protonated at low pH and deprotonated

at high pH. For these pH dependent anions, receptors can only be used over a limited pH range.

- Anions are more heavily solvated and the Hofmeister series reflects the relative hydration of anions. Hydrophobic anions, such as iodide, are more strongly bound in hydrophobic binding cavities whereas the hydrophilic anions, like fluoride, have a stronger affinity for binding cavities accessible to polar solvents.

Despite these inherent difficulties, numerous examples of anion receptors exist in Nature and even more impressively, the anion recognition event takes place in aqueous solutions exploiting hydrogen bonding and electrostatic interactions. The sulfate binding⁶ and phosphate binding⁷ proteins are able to selectively bind sulfate and phosphate respectively over other oxoanions via multiple hydrogen bonds. The design of synthetic anion receptors takes inspiration from Nature, often relying on these same non-covalent interactions to bind anions.

1.3.3.1. Positively Charged Receptors

Early examples of anion receptors achieved anion binding primarily through electrostatic interactions between a positively charged receptor and the negatively charged anion. The kapitinand by Park and Simmons was one of the first, and this structure was shown to encapsulate chloride via electrostatic and hydrogen bonding interactions between the protonated amine groups and anion (Figure 1.17a).⁶⁸ It should be noted that this kapatinand is structurally similar to the cryptand cation receptors in Section 1.2 with the exception of the protonated amine groups. Indeed, Lehn synthesised the protonated analogues of the cryptands and discovered they also complexed anions. In some cases, the shape selectivity for spherical ions was maintained like the macrotricyclic receptor, which selectively binds spherical halide anions (Figure 1.17b),⁶⁹ whereas the macrobicyclic receptor in Figure 1.17c is ideal for

binding linear triatomic anions such as azide.⁷⁰

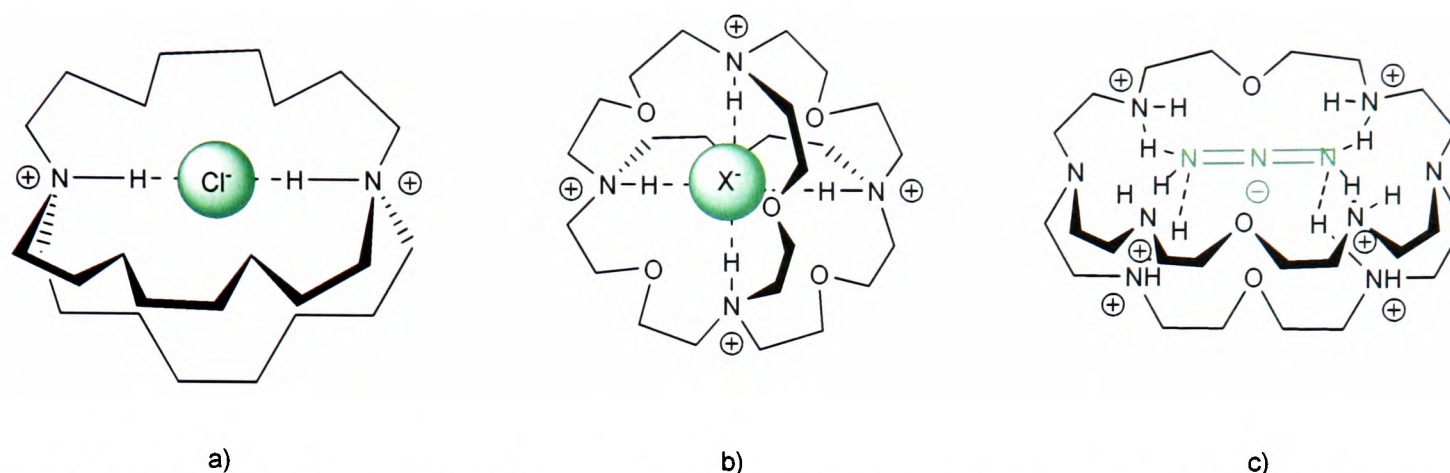
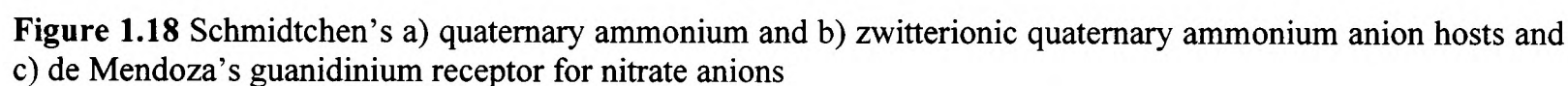


Figure 1.17 a) Park and Simmons' kapitinand and Lehn's b) macrotricyclic and c) macrobicyclic anion receptors

One of the drawbacks of using protonated ammonium groups is the pH dependence of anion binding, particularly in water. For this reason, Schmidtchen developed receptors based on quaternary ammonium groups where the strength of anion binding is determined only by electrostatic interactions (Figure 1.18a). These receptors bind halide anions within the cavity in water and methanolic mixtures, and the selectivity is determined by the alkyl chain length.⁷¹ However, one of the inherent problems with positively charged receptors is the presence of the counteranions which could compete with the anion guest for binding. Large non-coordinating counteranions, such as hexafluorophosphate or tetrafluoroborate in this case, are often used to prevent this. Another approach is to design a zwitterionic host such as the zwitterionic cage in Figure 1.18b. This host was shown to bind the iodide anion more strongly than the other halide ions in D₂O at 327 K.⁷²

The guanidinium motif has also been exploited for many decades as it remains protonated over a wide pH range due to its high pK_a (13.6).^{73, 74} It is able to bind anions via both electrostatic and hydrogen bonding, and has a tendency to bind oxoanions due to the planar Y-shaped arrangement of the donor groups. The nitrate anion is a fairly weak base and as a result it is one of most difficult oxoanions and anions to bind. However, the guanidinium based receptor in Figure 1.18c was shown to bind the nitrate anion very strongly in CH₃CN by isothermal calorimetry (ITC) and X-ray crystallography through hydrogen bonding to the



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over halides and acetate in CDCl_3 (Figure 1.19b).⁷⁸ Interestingly, the cyclic analogue binds dihydrogen phosphate selectively but with a lower affinity than the acyclic receptor despite the increased preorganisation, most likely because the acyclic receptor has the flexibility to adopt a complementary structure to dihydrogen phosphate.

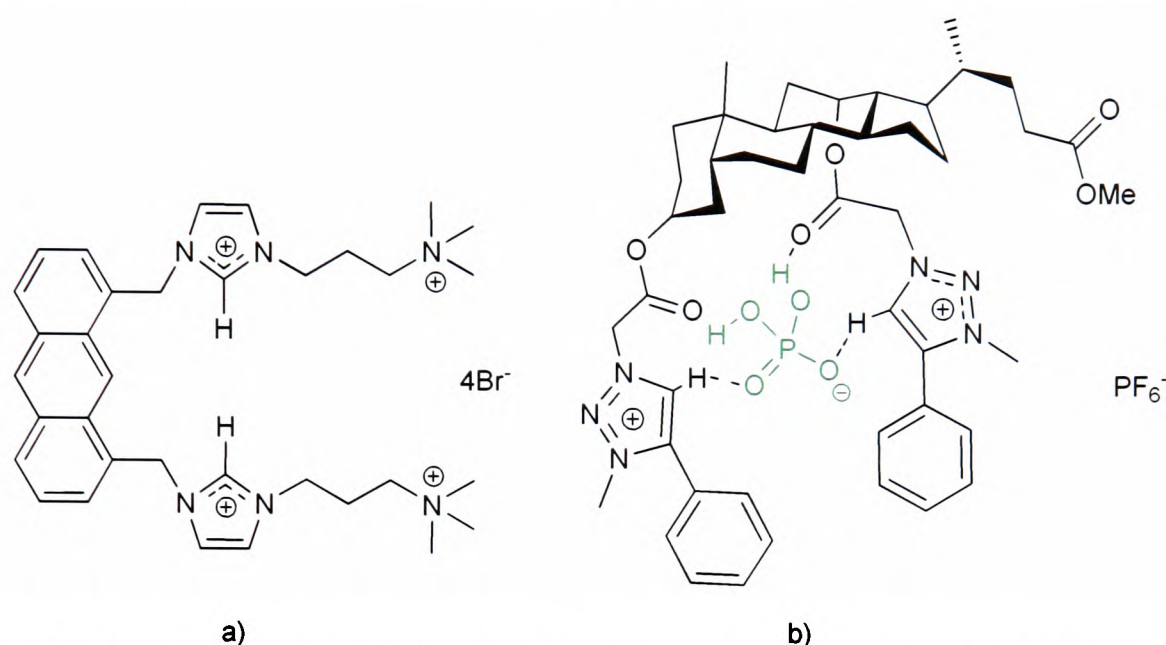
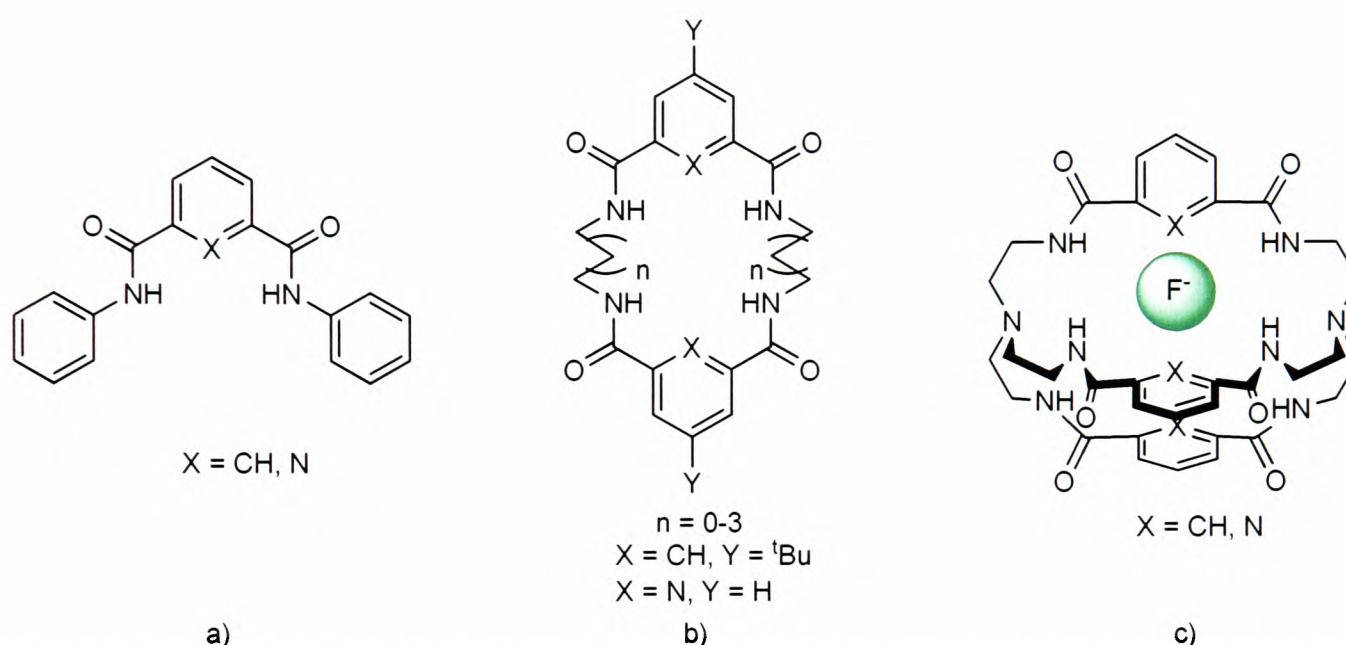


Figure 1.19 a) Yoon's imidazolium receptor for GTP and b) Pandey's triazolium receptor for dihydrogen phosphate

1.3.3.2. Neutral Receptors

The receptors in the previous section primarily relied on electrostatic interactions to achieve binding between the positively charged receptor and anion. However, a number of neutral receptors have been reported which exploit hydrogen bonding motifs such as amides, ureas, thioureas, indoles and pyrroles.^{66, 81} As a consequence of the weaker hydrogen bonding interactions, anion binding is often studied in organic solvent media.

Amide based receptors⁸²⁻⁸⁴ have been studied extensively ever since the first receptor was reported by Pascal in 1986.⁸⁵ The isophthalamide motif, in particular, has been exploited in a number of receptors since it forms strong 1:1 complexes with anions when the amide hydrogen donors are in the syn-syn conformation.⁸⁶ Interestingly, the simple acyclic isophthalamide receptor reported by Crabtree binds anions more strongly than the more preorganised 2,6-pyridine analogue (Figure 1.20a). This was attributed to repulsive interactions between the anion and lone pair on the pyridine. However, the macrocyclic



The urea and thiourea motifs have also been exploited due to their strong hydrogen bonding ability, particularly with oxoanions. Often they show stronger binding than amide groups due to the greater acidity of the urea NH, but this means that the NH can be more susceptible to deprotonation in the presence of anions. Many groups have reported the deprotonation of (thio)urea groups by strongly basic anions such as fluoride,⁹²⁻⁹⁸ maleate⁹⁹ and acetate.^{92, 94, 96, 98, 100} Despite this, there are numerous examples of hydrogen bonding complexes between (thio)urea groups and anions. The tren-based receptor in Figure 1.21a is able to complex anions via three convergent urea groups and solution studies in DMSO-*d*₆ revealed that the receptor binds dihydrogen phosphate more strongly than acetate.¹⁰¹ Interestingly, the X-ray crystal structure showed that the receptor forms a pseudo dimer cage, which encapsulates a dihydrogen phosphate dimer by a number of hydrogen bonding and anion- π interactions.

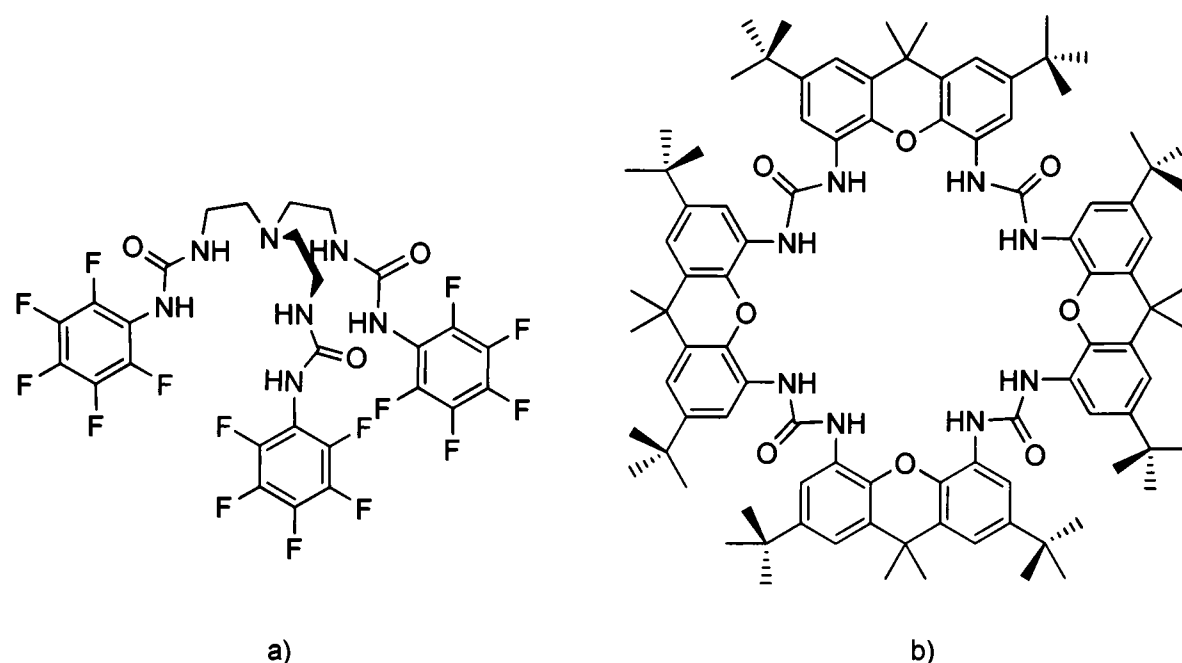


Figure 1.21 a) Tren-based urea receptor and b) Böhmer's tetraurea macrocycle

Böhmer and co-workers have recently reported the anion binding properties of a series of trimeric,¹⁰² tetrameric¹⁰³ and hexameric^{104, 105} macrocycles. The selectivity and stoichiometry of anion binding in 3:1 CH₃CN/THF can be difficult to predict, but many of these macrocycles bind the more basic anions dihydrogen phosphate and acetate with a higher affinity. However, the receptor in Figure 1.21b binds chloride the most strongly in a 1:2 receptor/anion stoichiometry.¹⁰³

Amide and urea groups are often used in conjunction with other anion binding groups such as pyrrole and indole, which each have one hydrogen bonding NH group, to strengthen anion binding. The fluorescent tripodal receptors in Figure 1.22a bind phosphate containing anions, such as dihydrogen phosphate and pyrophosphate, preferentially to halide anions in 95:5 DMSO/H₂O with up to a 200 fold increase in the fluorescence intensity.¹⁰⁶ Arrays of the three receptors in hydrophilic polyurethane matrices were able to detect and distinguish biologically relevant phosphate anions, such as phosphate, pyrophosphate, AMP and ATP, in blood serum. Expanded porphyrin structures such as cyclopyrroles can be synthesised in one step from bipyrrroles by anion templation. Sulfate templates the formation of the cyclo[8]pyrrole in Figure 1.22b and it is isolated as the sulfuric acid salt.¹⁰⁷ This affinity for sulfate results in a high selectivity for sulfate over nitrate in solvent extraction studies and this has important

implications in the extraction of sulfate from nuclear waste, which has a high nitrate concentration.¹⁰⁸

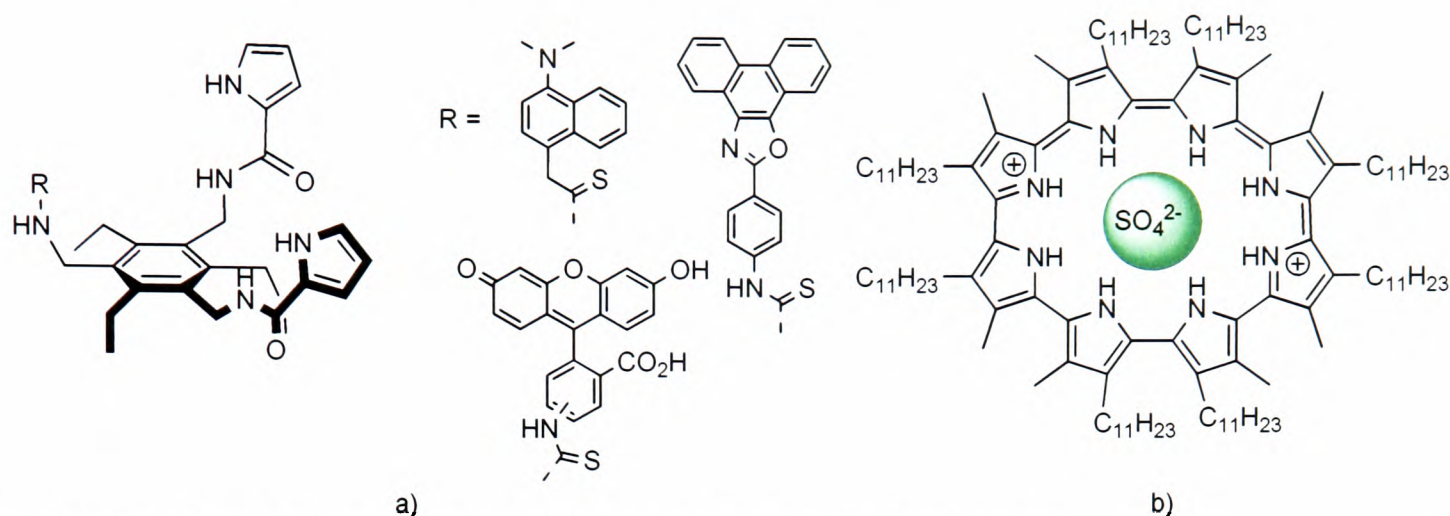


Figure 1.22 Pyrrole containing receptors for a) phosphate anions and b) sulfate

Many indole receptors show selectivity or a high affinity for dihydrogen phosphate,^{95, 109, 110} including the receptor in Figure 1.23a. This receptor is selective for dihydrogen phosphate over fluoride, chloride, benzoate and hydrogen sulfate in CH_2Cl_2 , and binding is detected by a visible colour change.¹¹¹ However, the chiral calix[4]arene receptor functionalised with two indoles on the lower rim showed enantioselective fluorescent recognition of the N-Boc protected alanine anion (Figure 1.23b), and a related receptor could distinguish the enantiomers of the mandelate anion.¹¹² The anion binding ability of indolocarbazoles, such as the simple indolocarbazole in Figure 1.23c, has only recently been reported.¹¹³ This receptor binds benzoate strongly in acetone and sulfate very strongly in CH_3CN .¹¹⁴ Jeong *et al.* have reported the indolocarbazole macrocycle which binds polyatomic anions, such as dihydrogen phosphate, acetate and azide, more strongly than halide anions in 10% MeOH/acetone (Figure 1.23d).¹¹⁵

The hydrogen bonding ability of C-H bonds has only recently been explored. There was early evidence of alkyl C-H hydrogen bonds to anions in the solid state¹¹⁶ and gas phase.¹¹⁷ However, it was not until Hay's theoretical calculations that the importance of C-H hydrogen bonds in anion receptor and supramolecular chemistry was realised.¹¹⁸ Traditionally thought

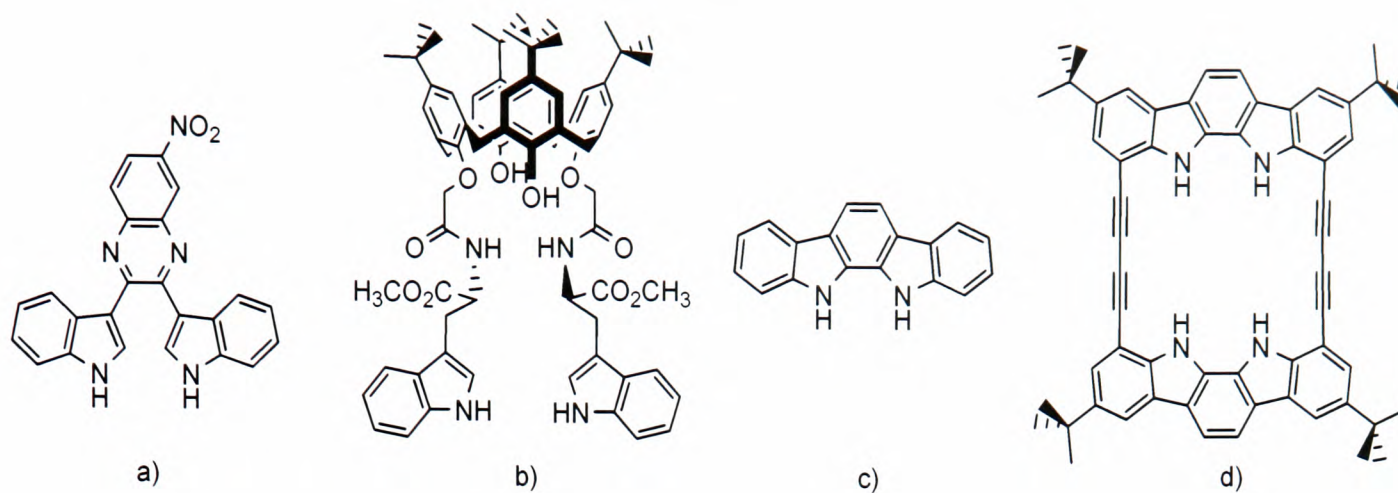


Figure 1.23 Indole containing receptors for a) dihydrogen phosphate and b) the N-Boc protected alanine anion and the indolocarbazole receptors of c) Beer and d) Jeong

to be very weak interactions, the calculations showed that the strength of aryl C-H hydrogen bonds to anions can exceed 50% of the strength of those formed from O-H and N-H groups. The strength of C-H bonds was demonstrated experimentally by Flood and co-workers. The receptor in Figure 1.24a binds chloride with an association constant of $130\,000\text{ M}^{-1}$ in CH_2Cl_2 purely by aromatic C-H hydrogen bonds.¹¹⁹ The receptor consists of three types of aromatic C-H hydrogen bond donors and the relative strengths of these were determined to be triazole > N-linked phenylene > C-linked phenylene.¹²⁰ Craig and co-workers reported a similar oligomer that binds chloride and bromide with similar affinities in acetone by C-H hydrogen bonds (Figure 1.24b).^{121, 122}

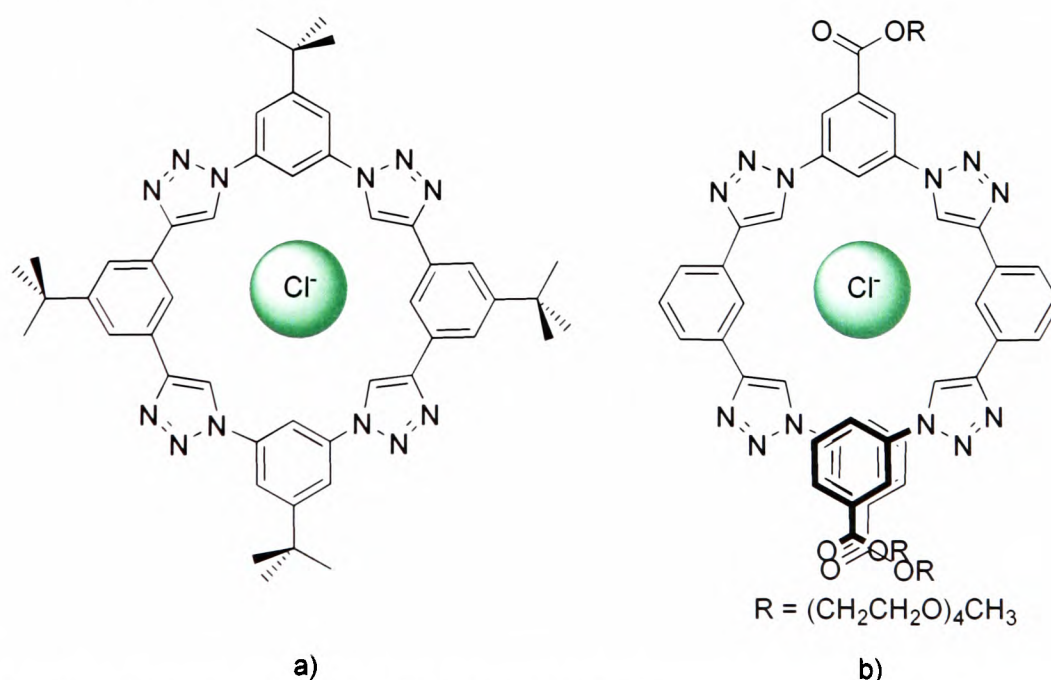


Figure 1.24 The triazole anion receptors of a) Flood and b) Craig

Lewis acid centres can also be exploited for binding anions, in particular Lewis basic ones. Hosts, such as Hawthorne's mercury carborane¹²³ (Figure 1.25a) and Newcomb's tin

containing macrocycles¹²⁴ and cryptands (Figure 1.25b),^{125, 126} have been termed ‘anti-crown’ and ‘anti-cryptand’ hosts since they are charge-reversed analogues of the cation binding crown ethers and cryptands.⁶⁵ The mercury carborane is selective for chloride and this anion templates the formation of the structure, while the tin centres of the cryptand both bind the anion inside the host cavity, which is selective for fluoride. Boron containing receptors have been investigated for a number of years due to their ability to bind fluoride¹²⁷⁻¹³⁰ and cyanide.¹³⁰ Aldridge and co-workers recently reported two receptors in Figure 1.25c, which in the presence of a redox organic dye can act as a Boolean AND/NOT logic gate.¹³¹ The receptor on the left gives a colorimetric response for both fluoride and cyanide, while the one on the right only responds to fluoride in CH₃CN/MeOH.

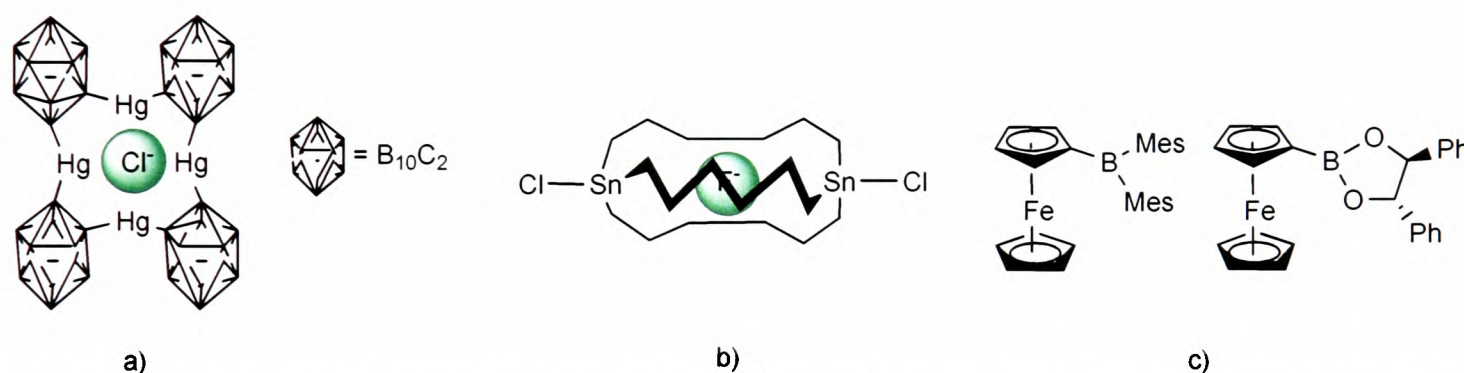


Figure 1.25 a) Hawthorne's mercury carborane b) Newcomb's tin-containing cryptand and c) Aldridge's boron Lewis acidic anion receptors

The Lewis acidic uranyl and zinc cations have also been incorporated into receptor structures as anion binding units. Reinhoudt and co-workers have reported a number of receptors based on the uranyl cation, often appended with additional hydrogen bonding amide groups, which are selective for dihydrogen phosphate (Figure 1.26a).^{132, 133} This family of receptors has been investigated in the development of potentiometric sensors.¹³⁴ Dimetallic zinc dipicolylamine complexes have been investigated as chemosensors since the zinc is not redox active and does not quench the fluorescence of appended dyes.¹³⁵ The anthracene appended dimetallic complex is a fluorescent sensor of dianionic phosphate derivatives, such as phosphorylated tyrosine in aqueous solutions,¹³⁶ and anionic phospholipids on bilayer membranes for the detection of cell apoptosis (Figure 1.26b).¹³⁷

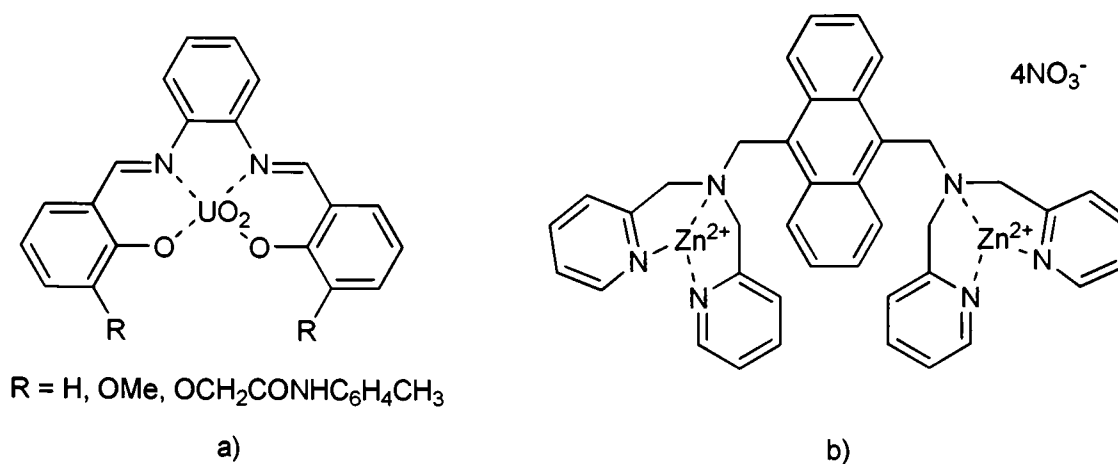


Figure 1.26 a) Reinhoudt's uranyl and b) dimetallic zinc dipicolylamine anion receptors

1.3.4. Ion-pair Receptors

As discussed in earlier sections, the choice of counterion is crucial when designing receptors. For charged receptors it could compete with the desired ionic guest, and for binding studies the counterion could potentially form a strong ion-pair with the desired guest reducing the association constant. For example the anion binding of the urea receptor by Smith *et al.* was inhibited by the presence of alkali cations in CD₃CN due to ion-pairing outside the receptor (Figure 1.27).¹³⁸ The largest effect was seen with sodium ions but this competing ion-pair formation could be reduced by simultaneously binding the cation and anion to the receptor.

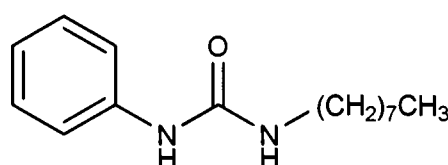


Figure 1.27 Smith's urea receptor

Ion-pair recognition^{139, 140} is an emerging field which takes inspiration from both cation and anion recognition chemistry for the design of ditopic receptors, which are able to simultaneously bind cations and anions. This is important for the development of membrane transport,¹⁴¹ salt extraction¹⁴² and salt solubilisation agents.¹⁴³ There are three common designs of ditopic receptors as illustrated in Figure 1.28. In the first, a cascade complex results from an anionic guest bridging two encapsulated cations (Figure 1.28a). The other two are heteroditopic receptors where the cation and anion are bound individually (Figure 1.28b) or as a zwitterion (Figure 1.28c).

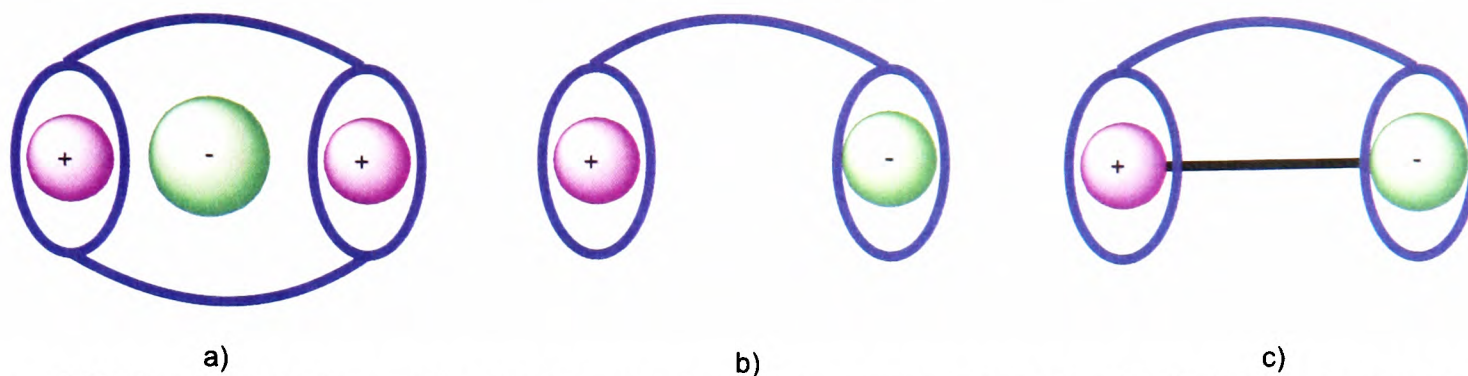


Figure 1.28 Common designs of ditopic receptors a) cascade complex b) heteroditopic ion-pair receptor and c) heteroditopic zwitterion receptor

Ion-pair binding can be achieved by exploiting a cascade complex approach. In most cases, two cationic centres, usually transition metals, bound within a receptor utilise metal-ligand interactions to recognise an ambidentate anion between the two metal centres. Numerous cascade complexes based on macrocyclic and cryptand receptors have been synthesised and demonstrate that selectivity is determined by not only the shape and size of the cavity, but also the bite length between the donor atoms of the anion.^{144, 145} An early example is the macrocycle (Figure 1.29a) which can bind two copper(II) cations and simultaneously bind two azide anions between the metal centres.¹⁴⁶ The related cryptand binds both the isocyanate and azide anions between the two zinc metal centres (Figure 1.29b).¹⁴⁷ However, the incorporation of a fluorescent anthracene groups allows the selective sensing of the azide anion due to fluorescent quenching only in the presence of this anion. A more recent example from Fabbrizzi and co-workers showed selective recognition of GMP over other nucleoside monophosphates in a MeOH/H₂O mixture at pH 7 using a displacement indicator assay with 6-carboxyfluorescein (Figure 1.29c).¹⁴⁸ The dicopper cryptate binds the indicator in a 2:1 receptor/indicator complex and the fluorescence is quenched. Displacement with GMP leads to an increase in the fluorescence and the formation of a 1:1 receptor/GMP complex with metal-ligand bonds with the phosphate group and carbonyl group of guanosine.

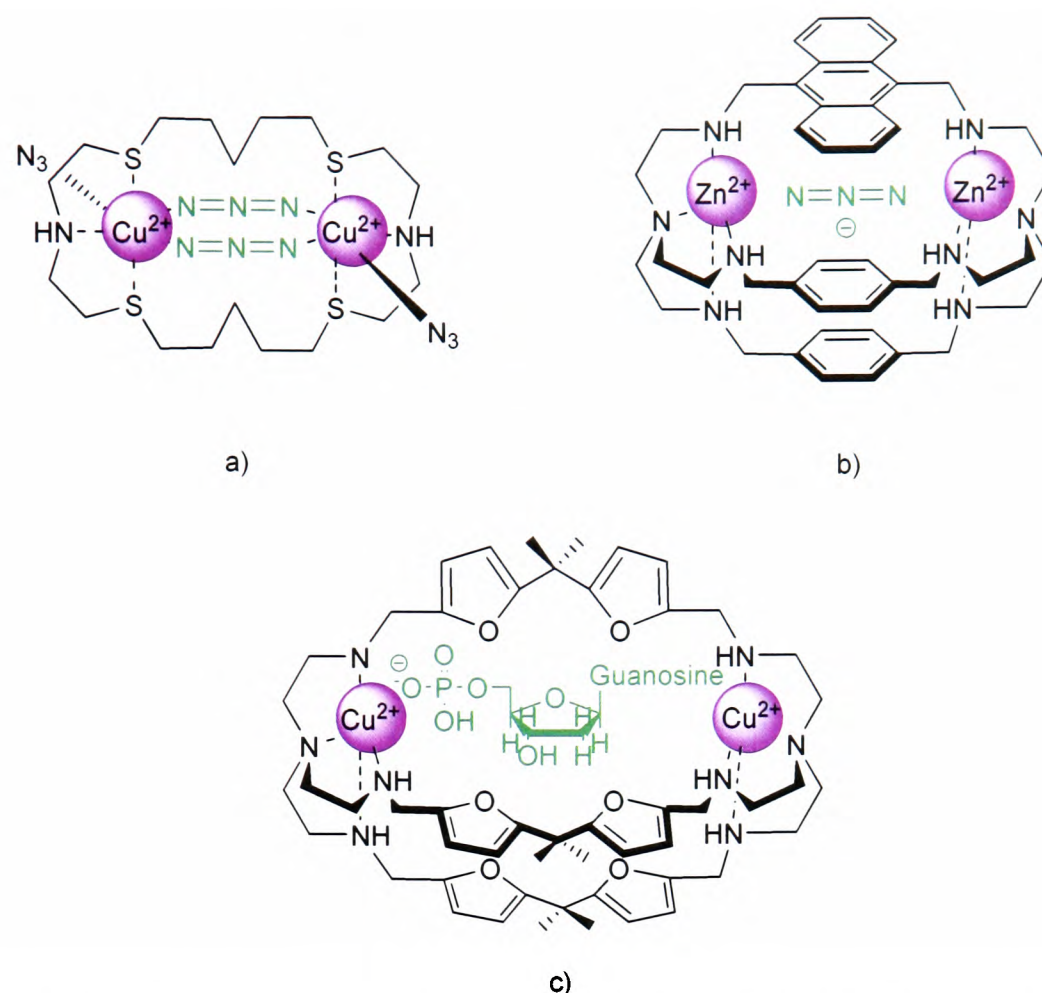


Figure 1.29 Cascade complexes a) macrocycle and b) fluorescent cryptand and c) Fabbri's cryptand derivatives

While there are many examples of cascade complexes with two cations and an anion, the situation with two anions and a cation is much rarer. The first example of an anion based cascade complex was reported by Bowman-James and co-workers (Figure 1.30a).¹⁴⁹ The azacryptand encapsulates two fluorides with a H_2O molecule bridging the two anions. While not an ion-pair cascade complex, it demonstrates the potential synthesis of the anion analogues of the cation based cascade complexes. Fabbri *et al.* reported the heterotritopic receptor which is able to complex two anions and a cation in a cascade-like mechanism (Figure 1.30b).¹⁵⁰ A copper(II) cation binds to the tren unit preorganising the receptor for binding the anions with the first anion binding to the metal centre and the second to the urea groups by hydrogen bonding. It was possible to bind two different anions, chloride and dihydrogen phosphate, by exploiting the different anion binding affinities for the two sites. The chloride anion only binds to the metal centre, while dihydrogen phosphate can bind to both sites. If dihydrogen phosphate binds first to the copper centre, addition of excess chloride anions can translocate it to the urea binding site.

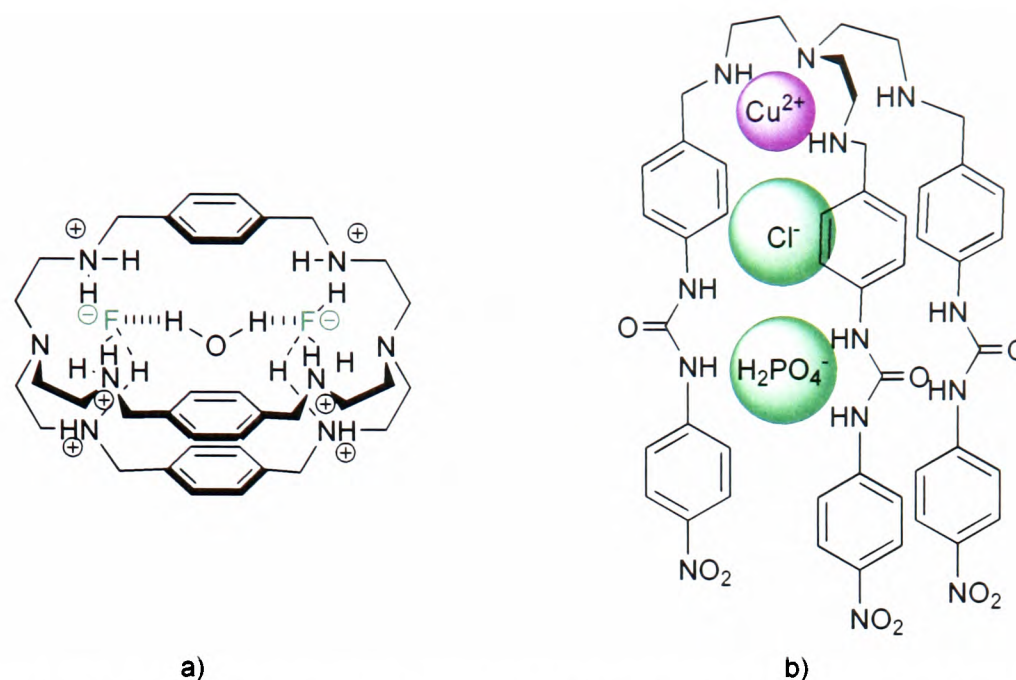


Figure 1.30 a) Bowman-James' anion cascade complex and b) Fabbrizzi's heterotritopic receptor

Ion-pair recognition is much more complicated than the binding of cations and anions individually, often due to cooperative effects. The simplest situation is non-cooperative binding where each ion binds independently of the other. Anticooperative binding occurs when the binding of one ion inhibits the binding of the other, whereas cooperative binding is when the binding of one ion enhances the binding of the other.

Despite the complicated nature of ion-pair binding, there are many examples of receptors which successfully exploit cooperativity through conformational and electrostatic effects. Generally anticooperative binding is an unwanted effect but it has an important application in the development of molecular logic systems. For example the receptors in Figure 1.31 have been proposed as INHIBIT logic devices where the response is controlled by ion-pair binding. The receptor by Tucker is a colorimetric sensor where fluoride binding to the urea group switches the device 'ON', as detected by a colour change from colourless to yellow (Figure 1.31a).¹⁵¹ However, the colorimetric response is turned 'OFF' upon addition of potassium. It is proposed that the complexation of potassium in the crown ether weakens the fluoride binding to the urea group. Kim and co-workers reported the fluorescent calix[4]arene based INHIBIT gate (Figure 1.31b).¹⁵² The complexation of potassium within the crown ether causes a conformational change which maximises π - π stacking interactions between the

pyrene units leading to an enhancement of the excimer emission. However, in the presence of dihydrogen phosphate the excimer emission is switched off due to a PET effect.

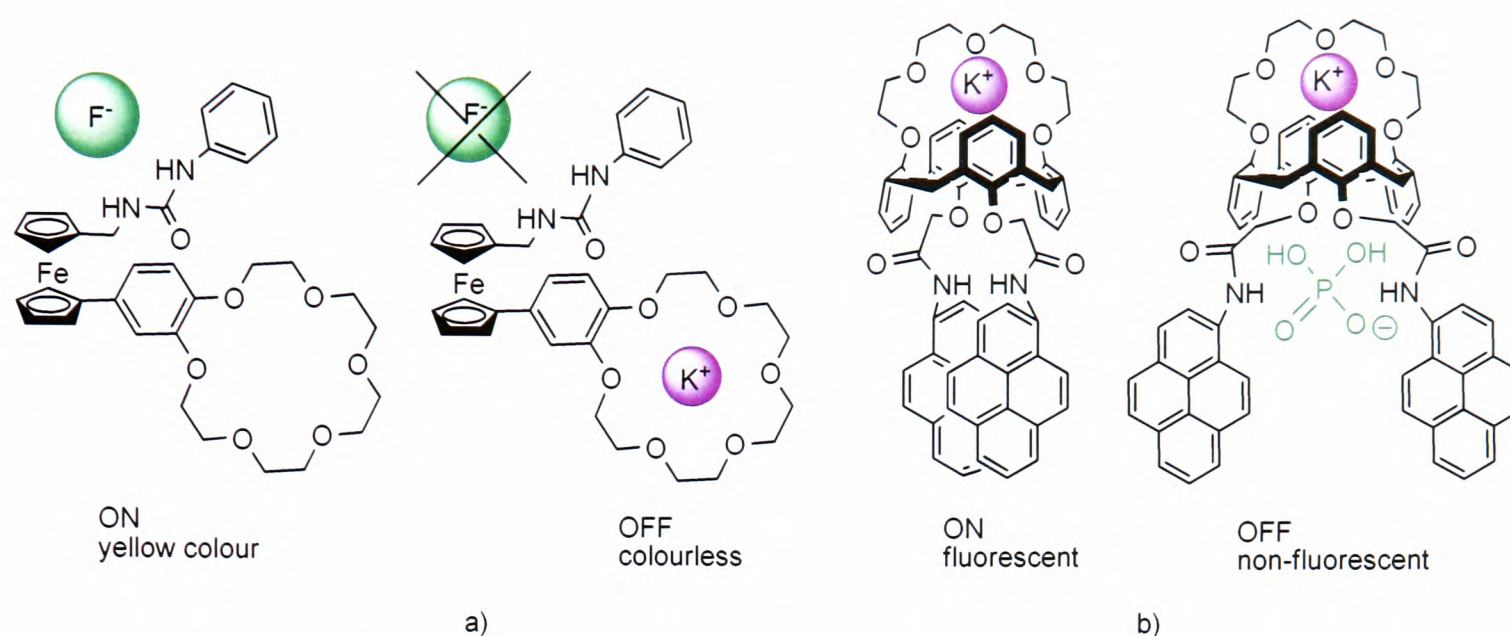


Figure 1.31 Anti-cooperative ion-pair receptors a) Tucker's INHIBIT receptor and b) Kim's calix[4]arene INHIBIT gate

However, it is more common for the design of ion-pair receptors to exploit cooperativity to enhance the binding and selectivity of the ion-pair. An early example is the calix[4]arene based receptor (Figure 1.32a), which solubilised sodium halide ion-pairs in $CDCl_3$.¹⁵³ The sodium cation was essential for binding the anion as cation complexation in the ester cavity preorganises the urea groups for anion binding. Larger cations such as caesium were too large to fit in the cavity and therefore caesium salts did not bind. A more recent example is the calix[4]arene receptor in Figure 1.32b which also relies on cation binding to bind CsF in 9:1 $CDCl_3/CD_3OD$.¹⁵⁴ While the receptor binds fluoride in the calix[4]pyrrole anion binding cavity in $CDCl_3$, there was no evidence of fluoride binding in 9:1 $CDCl_3/CD_3OD$, most likely due to the stronger solvation of fluoride. However, the ion-pair CsF binds to the receptor in this competitive solvent system as evidenced by 1H NMR titration experiments and the solid state structure. Interestingly, the cooperative binding of the solvent separated CsF ion-pair was found to be strongly solvent dependent as the binding of the two ions was non-cooperative in CH_3CN by ITC.

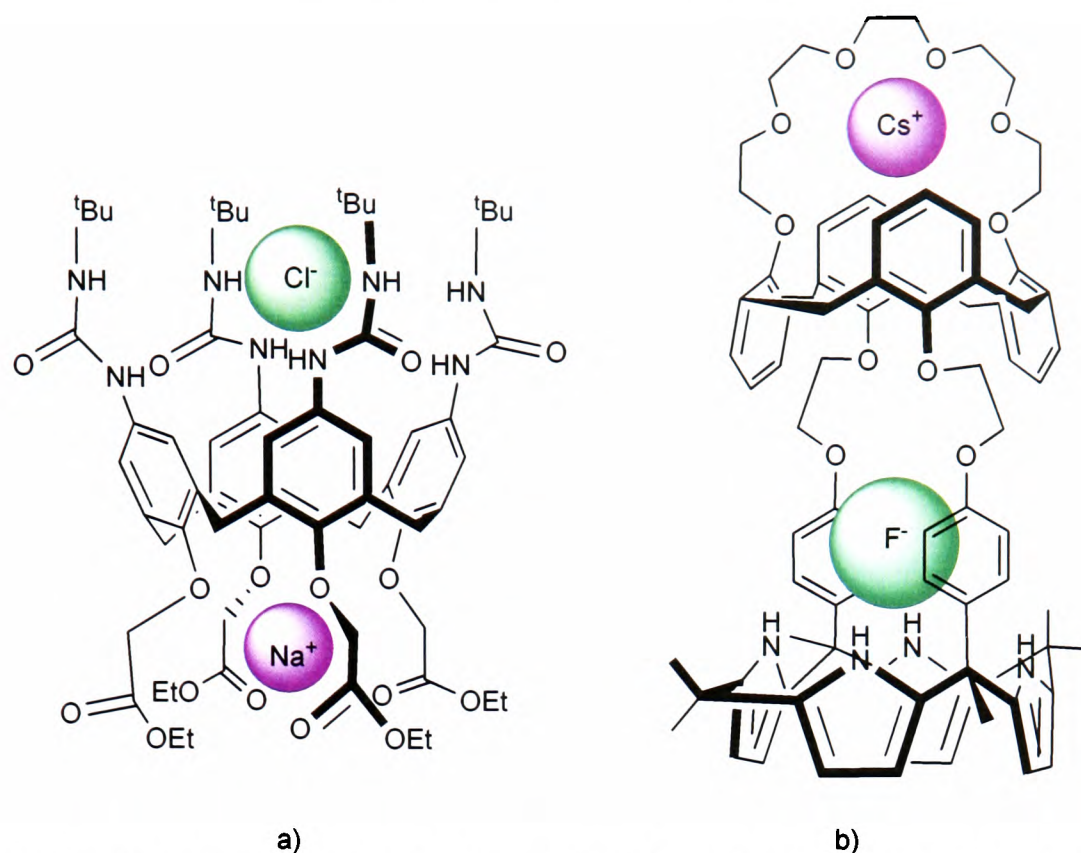


Figure 1.32 Cooperative ion-pair receptors a) for the solubilisation of sodium halide ion-pairs and b) for caesium fluoride

The cation and anion binding sites in the previous examples were disconnected and designed to bind solvent separated ion-pairs. However, when the two sites are closer together, electrostatic in addition to conformational effects can be exploited for cooperative binding. Kubo's ditopic receptor was designed to bind a cation in the crown ether and an anion in the thiourea binding cavity (Figure 1.33a).¹⁵⁵ Binding of diphenylphosphate in CD_3CN was enhanced by a factor of 19 in the presence of potassium due to a conformational change of the crown ether upon binding potassium and an electrostatic interaction. The larger hydrophobic cavity of calix[6]arene has been exploited for the binding of alkylammonium cations but due to the flexibility of the calixarene, anion binding to the urea groups was necessary for inclusion of the cation within the cavity (Figure 1.33b).¹⁵⁶ The nature of the anion was found to be important with greater cation inclusion with bromide than acetate, in contrast to the relative affinities of the anions alone for the receptor. A related more preorganised calix[6]cryptamide receptor also showed cooperative binding of alkylammonium chloride ion-pairs in CDCl_3 where both the cation and anion were necessary for ion-pair recognition.¹⁵⁷

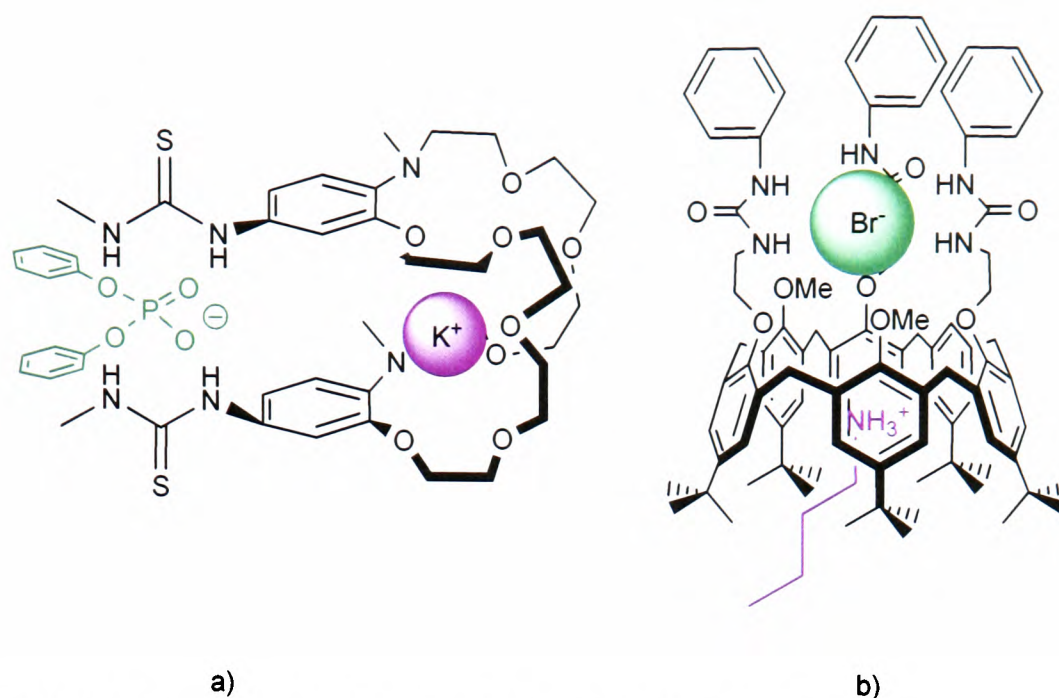


Figure 1.33 a) Kubo's ditopic receptor and b) calix[6]arene ditopic receptor

Ion-pair recognition can be enhanced even further by binding a contact ion-pair. This is more energetically favourable as it minimises unfavourable separation of the two ions upon binding to the receptor.^{158, 159} The macrobicyclic receptor in Figure 1.34a showed cooperative binding of contact ion-pairs KCl and NaCl in DMSO-*d*₆, and in the less competitive solvent system 85:15 CDCl₃/DMSO-*d*₆ there was an impressive 300 fold enhancement of chloride binding in the presence of potassium.¹⁵⁹ The potential of this receptor for membrane transport and salt solubilisation applications has been demonstrated by further studies.^{160, 161} Smith¹³⁹ and a number of other groups have continued to exploit this motif by varying the anion binding group to ferrocene,¹⁶² 2,5-diamidopyrrole¹⁶³ and indolocarbazole¹⁵⁸ (Figure 1.34b). Interestingly, despite having the same cation binding site as Smith's receptor, the indolocarbazole receptor binds NaCl much more strongly than KCl in 9:1 CD₃CN/DMSO-*d*₆. There was a 2000 fold improvement in chloride binding in the presence of sodium compared to approximately 900 fold with potassium. Other motifs have also been exploited for contact ion-pair binding such as uranyl salophen (Figure 1.34c).¹⁶⁴ The ditopic receptor binds ion-pairs such as CsCl by forming a 2:2 receptor/ion-pair complex. The anion binds to the uranyl centre and the cation by an electrostatic interaction with the anion and additional stabilising cation- π interactions with the aromatic side chains.

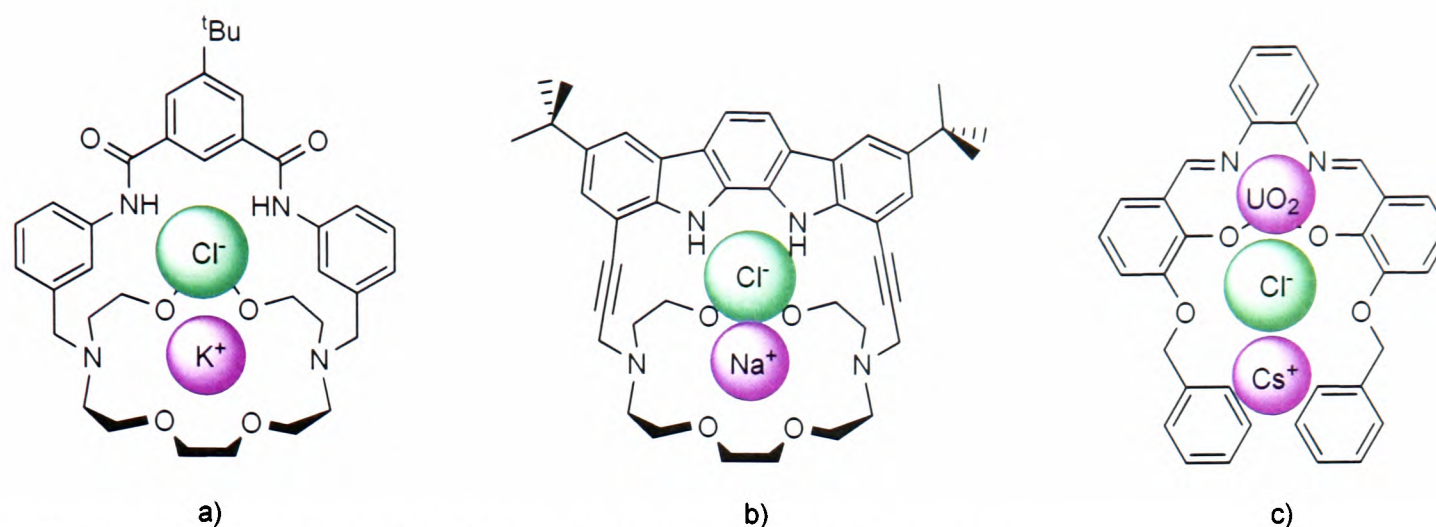


Figure 1.34 Contact ion-pair receptors of a) Smith b) Jeong and c) Rissanen

The binding of zwitterions uses many of the same principles as for binding ion-pairs, but has the added design challenge that the distance between the two binding sites has to be complementary in size and shape to the desired zwitterionic guest. For example the receptor in Figure 1.35a is able to bind zwitterions via the azacrown and polyammonium functionalities.¹⁶⁵ However, the receptor is unable to discriminate between γ -aminobutyric acid and 6-aminohexanoic acid which differ only in the length of the spacer between the anion and cation ($n = 1$ versus $n = 3$) due to the flexibility of the 1,4-dimethylbenzene linker group.

Zwitterionic recognition has biological importance as often the guests of interest are amino acids, which exist as zwitterions at physiological pH. Therefore chiral discrimination may also need to be considered in the receptor design. The receptor in Figure 1.35b was able to enantioselectively and selectively extract the amino acids phenylalanine and tryptophan from aqueous solution into CH_2Cl_2 .¹⁶⁶ Three complementary non-covalent interactions between the receptor and amino acid guest were proposed to be the reason for the selectivity. The carboxylate group can hydrogen bond to the guanidinium unit, the ammonium group binds in the azacrown and there are π - π interactions between the naphthalene of the receptor and the phenyl side chain of the amino acid.

Zwitterion binding can also be sensed by suitable incorporation of a reporter group into the receptor design. The fluorescent zinc macrocycle in Figure 1.35c is able to bind the

ammonium and carboxylate groups of amino acids via the crown ether and coordination to zinc respectively.¹⁶⁷ The zwitterion binding was sensed by fluorescent quenching upon addition of the amino acid, and the receptor showed selectivity for aspartate and cysteine in H₂O/DMF mixtures. It was proposed this selectivity was due to additional coordination of the aspartate and cysteine side chains to the zinc centre.

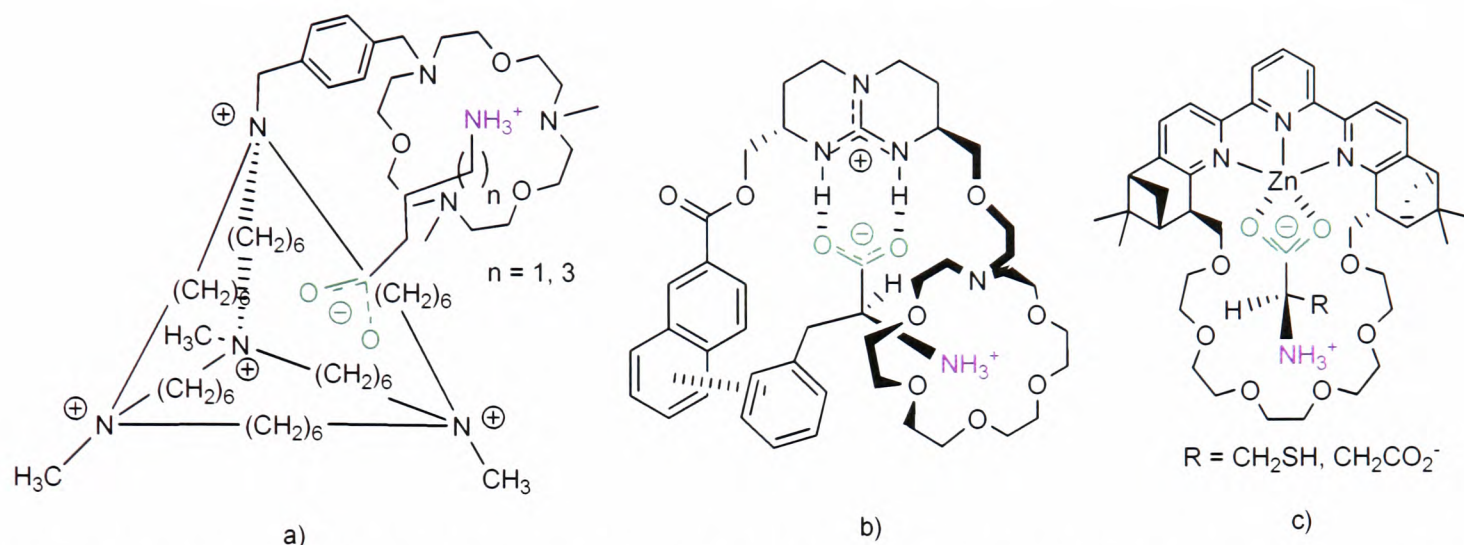


Figure 1.35 Zwitterion receptors based on a) a polyammonium cage b) a guanidinium motif and c) fluorescent zinc macrocycle

1.4. Self-Assembly

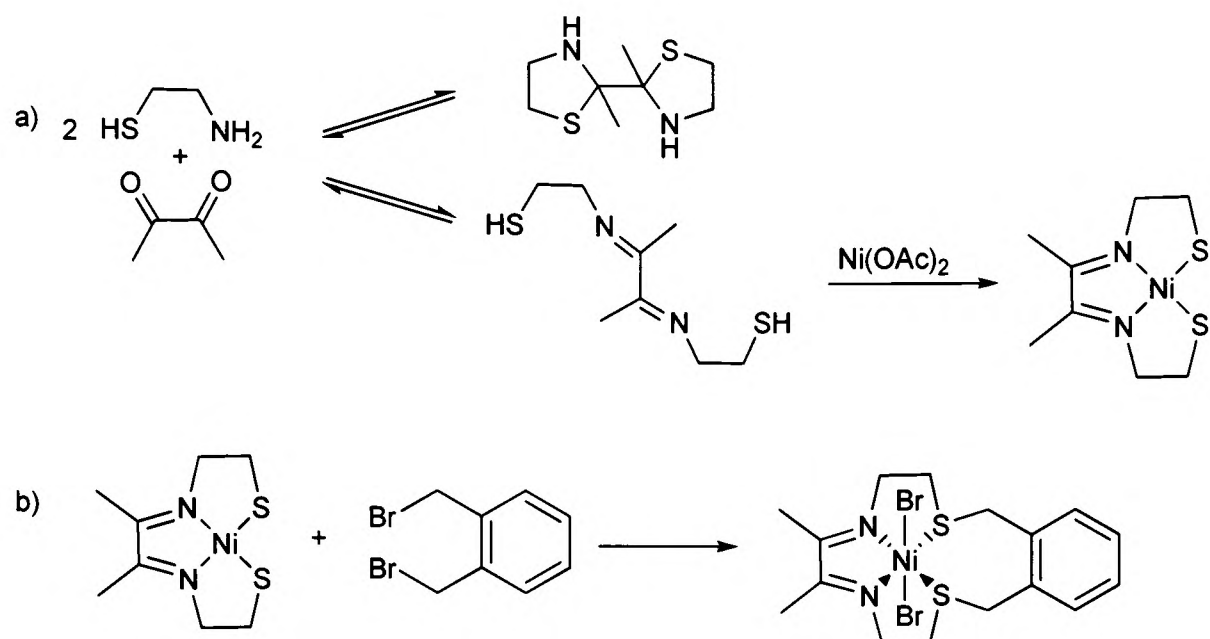
The previous sections have focused on examples of host-guest chemistry, however, self-assembly is another large and active area of supramolecular chemistry. Self-assembly can be exploited to synthesise a wide range of elegant and complicated architectures, which would be either difficult or impossible to synthesise by traditional covalent chemistry. There are numerous examples of self-assembly in Nature for inspiration. For example the tobacco mosaic virus¹⁶⁸ is self-assembled from virus protein subunits and virus nucleic acids, and Fraenkel-Conrat and Williams demonstrated that these inactive components could be re-assembled under suitable conditions to give the infective virus.¹⁶⁹ For the supramolecular chemist, there is a particular interest in the synthesis of interpenetrated and interlocked structures for the synthetic challenge and also for applications in nanotechnology.

Self-assembly can be broadly classified into three areas: equilibrium self-assembly, where thermodynamic factors determine product formation; irreversible self-assembly, where the

kinetic product forms; and directed self-assembly where a template is used to bring together the components for self-assembly. The following section will discuss the use of templates in the assembly of supramolecular architectures. There will be a particular emphasis on examples of interpenetrated and interlocked structures as these are relevant to the theme of this project.

1.4.1. Templated Self-Assembly of Supramolecular Architectures

Templates have been exploited to synthesise a wide range of supramolecular architectures including macrocycles, cages, ladders and helicates.^{62, 170-174} Busch defined a chemical template as a species which “organizes an assembly of atoms, with respect to one or more geometric loci, in order to achieve a particular linking of atoms.”¹⁷¹ A template can influence the assembly of the components thermodynamically or kinetically. A thermodynamic template shifts the equilibrium towards one product which can be isolated in higher yields than in the absence of the template, whereas a kinetic template preorganises the assembly of components into a favourable binding conformation which reacts to form the product quickly and irreversibly.¹⁷⁵ The synthesis of the macrocyclic ligand in Scheme 1.1 uses a nickel(II) cation as both a thermodynamic and kinetic template. As a thermodynamic template, nickel complexation with the biacetyl-bis-mercaptoethyl imine ligand is more favourable than formation of the other possible product, thiazoline (Scheme 1.1a).¹⁷⁶ The preorganisation of this nickel complex also enhances the rate of cyclisation and the macrocyclic ligand forms under a kinetic template effect (Scheme 1.1b).¹⁷⁷



Scheme 1.1 Templated synthesis of a a) chelate ligand using Ni(II) as a thermodynamic template and b) macrocycle ligand using Ni(II) as a kinetic template

Sanders and co-workers have expanded the definition of a template in terms of the topology of the assembled components.¹⁷⁸ A linear template binds the two components so that the reaction can take place (Figure 1.36a). An example of a linear template is the single strand of DNA that templates the formation of the complementary strand during DNA or RNA replication. Cyclisation templates (Figure 1.36b) are often exploited to synthesise macrocycles, such as in Scheme 1.1, but they have also been employed in the synthesis of interlocked structures. However, a more common template for synthesising interlocked structures is the interweaving template (Figure 1.36c) and this will be discussed in more detail in later sections.

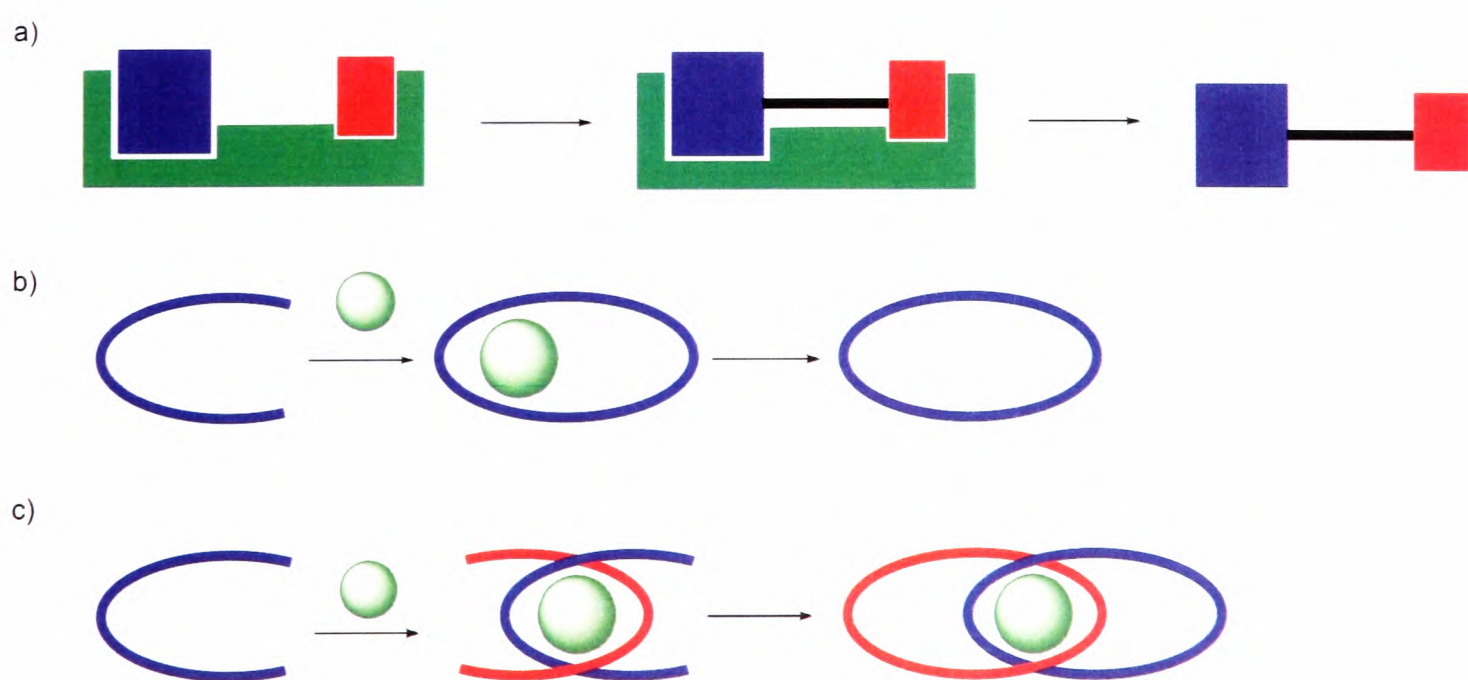


Figure 1.36 Sanders' definition of templates as a) linear b) cyclisation and c) interweaving

1.4.1.1. Cation and Anion Templatation

A number of impressive supramolecular architectures have been formed by cation and anion templated self-assembly. In an example of thermodynamic self-assembly, the tricopper helicate is the only product resulting from a mixture of 3 equivalents of copper(I) tetrafluoroborate, 4 equivalents of 8-aminoquinoline and 2 equivalents of 1,10-phenanthroline-2,9-dicarbaldehyde in CH₃CN (Figure 1.37a).¹⁷⁹ Fujita and co-workers have exploited transition-metal templates to self-assemble a wide range of architectures from molecular squares to nano-sized stacks of aromatic molecules.^{180, 181} The elegant structure in Figure 1.37b consists of two interlocked cages synthesised by the palladium or platinum templated self-assembly of ten components.¹⁸² Stoddart and co-workers reported the impressive near quantitative zinc templated synthesis of the Borromean rings in Figure 1.37c from eighteen components.¹⁸³ The formation of these complex and vastly different architectures from seemingly simple components demonstrates the versatility and utility of templated self-assembly.

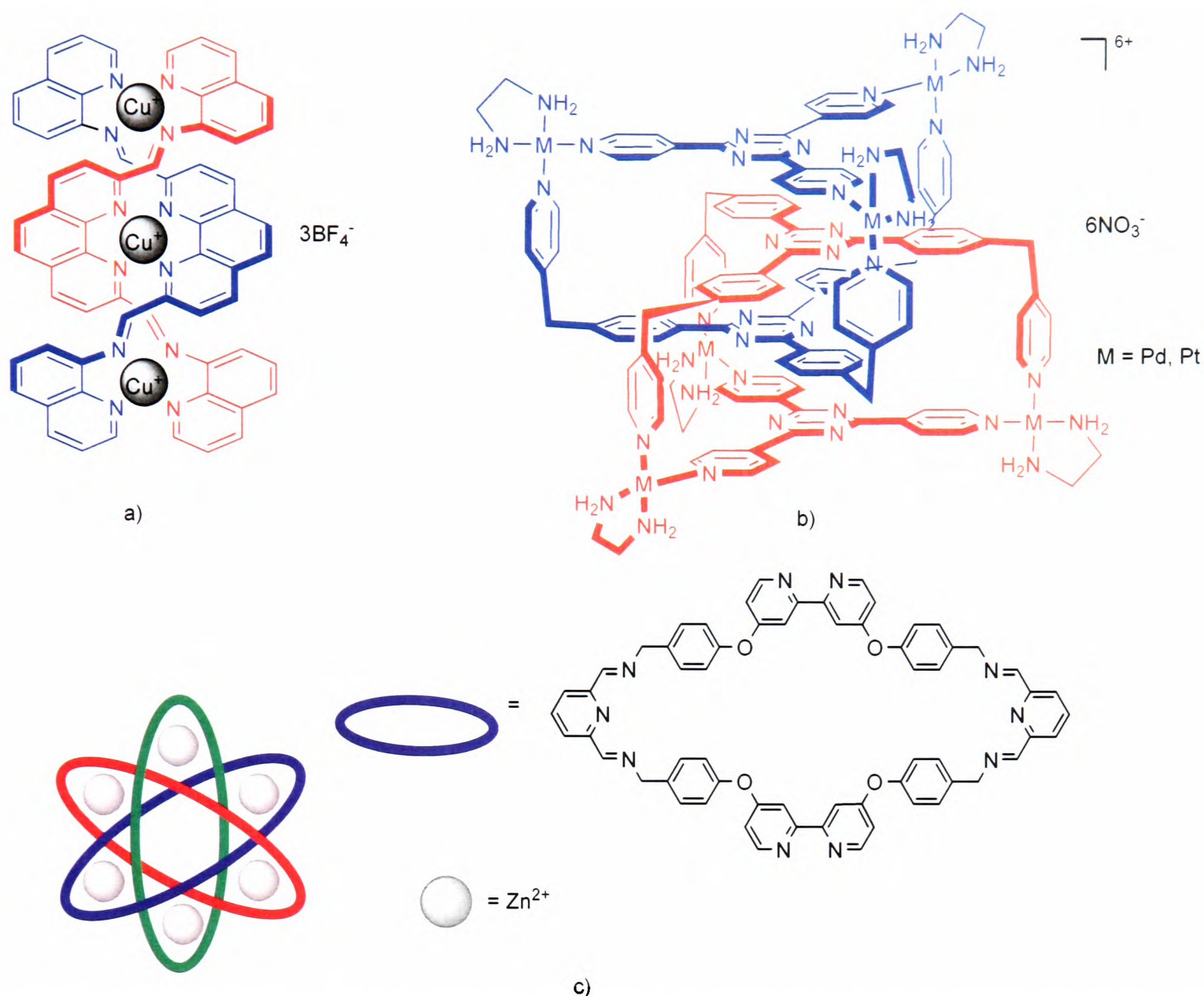


Figure 1.37 Cation templation a) tricopper helicate b) Fujita's two interlocked cages and c) Stoddart's Borromean ring

There are fewer examples of anion templation due to the inherent properties of anions, as discussed in Section 1.3.3. Often the structures formed by anion templation are discovered by accident rather than by rational design. For example, Lehn's serendipitous discovery of the chloride templated assembly of the pentanuclear iron helicate in Figure 1.38 while the formation of a related hexanuclear helicate was templated by sulfate.^{184, 185}

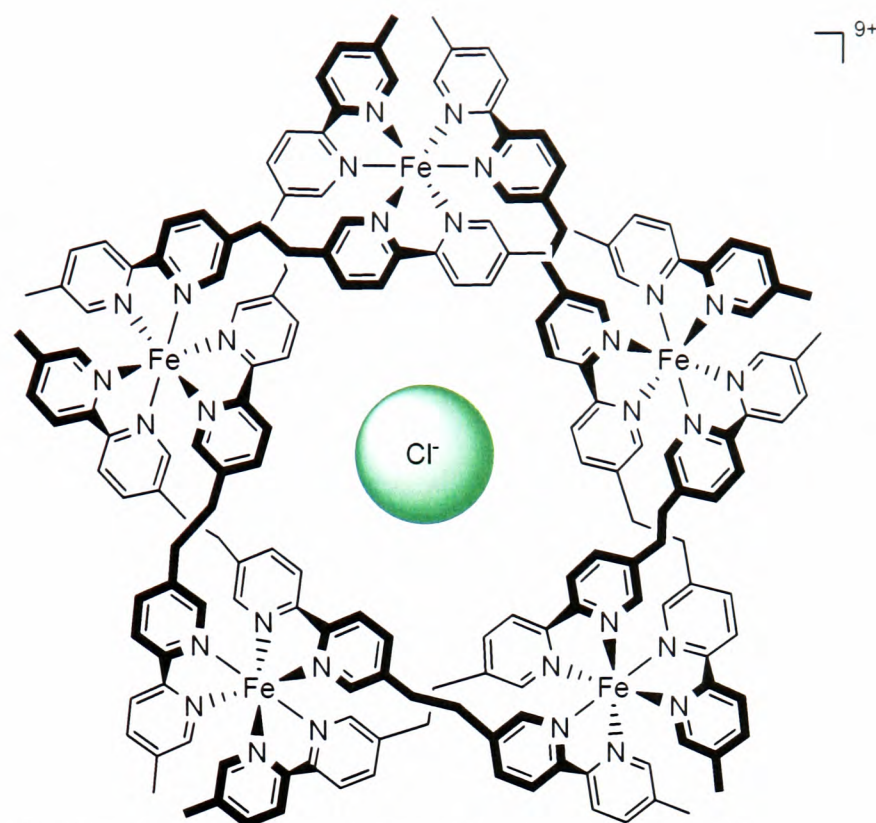


Figure 1.38 Lehn's serendipitous chloride templated pentanuclear iron helicate

Nevertheless, anion templation is a growing field^{170, 186-190} and it has been exploited to synthesise a wide range of architectures including macrocycles,^{191, 192} helicates,¹⁹³ metallacages.^{194, 195} The synthesis of many of the anion receptors discussed in Section 1.3.3 rely on anion templation. For example chloride anions template the formation of Hawthorne's mercury carborane (Figure 1.25a), and sulfate templates the formation of the cyclo[8]pyrrole (Figure 1.22b). Figure 1.39 shows two more recent examples of anion templated macrocycles and metallacages. Luis and co-workers have investigated the use of organic anions to template the formation of pseudopeptidic macrocycles and determined the terephthalate anion to be the best template based on molecular modelling (Figure 1.39a). The macrocycles could be synthesised in yields of greater than 60% using this template, while a complex mixture of oligomers was obtained in the absence of the template.^{196, 197} This shows that strategic anion templation is possible using techniques such as molecular modelling. Weakly coordinating anions such as tetrafluoroborate and hexafluorophosphate can template the formation of unusual metallacages, such as Amouri's cobalt cage in Figure 1.39b.^{198, 199} Different structures are obtained with strongly coordinating anions such as chloride and interestingly, the solid state structure shows encapsulation of the anion between the two metal centres by

weak cobalt-F interactions.

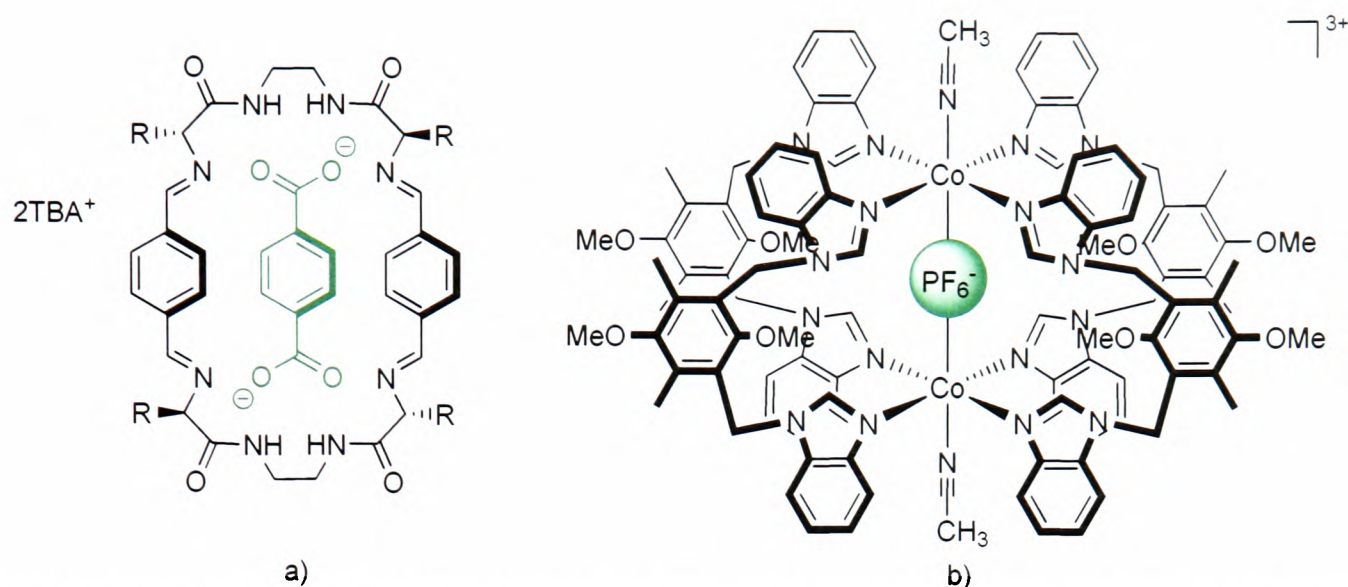


Figure 1.39 a) Luis' terephthalate templated synthesis of pseudopeptidic macrocycles and b) Amouri's hexafluorophosphate templated cobalt cage

1.4.2. Mechanically Interlocked Structures

The synthesis of mechanically interlocked structures is a large and growing area of supramolecular chemistry.^{186, 200-202} Mechanically interlocked structures consist of two or more molecular components interlocked by a mechanical bond so that the components cannot be separated without breaking a covalent bond. Wasserman introduced the concept of topological isomerism²⁰³ in 1961 to describe these structures as topological isomers of the non-interlocked components. Often interlocked structures have different properties to the non-interlocked components due to the different spatial arrangement of the components in the two topological isomers. This has important consequences for applications of mechanically interlocked structures in nanotechnology.

Two of the most common interlocked structures are [n]catenanes (Figure 1.40a) and [n]rotaxanes (Figure 1.40b) where n refers to the number of interlocked components. Catenanes (from the Latin *catena* meaning chain) consist of two or more interlocked rings, whereas rotaxanes (from the Latin *rota* and *axis* meaning wheel and axis respectively) are made up of a macrocycle and stoppered axle. Unlike catenanes, rotaxanes are not topological isomers of their constituent components since rotaxanes can be dissociated into their components, at least in theory, by the macrocycle slipping over the stoppers. Nevertheless,

the components of a rotaxane are mechanically interlocked unlike pseudorotaxanes (Figure 1.40c), which are an important class of interpenetrated structures that are often precursors to catenanes and rotaxanes.

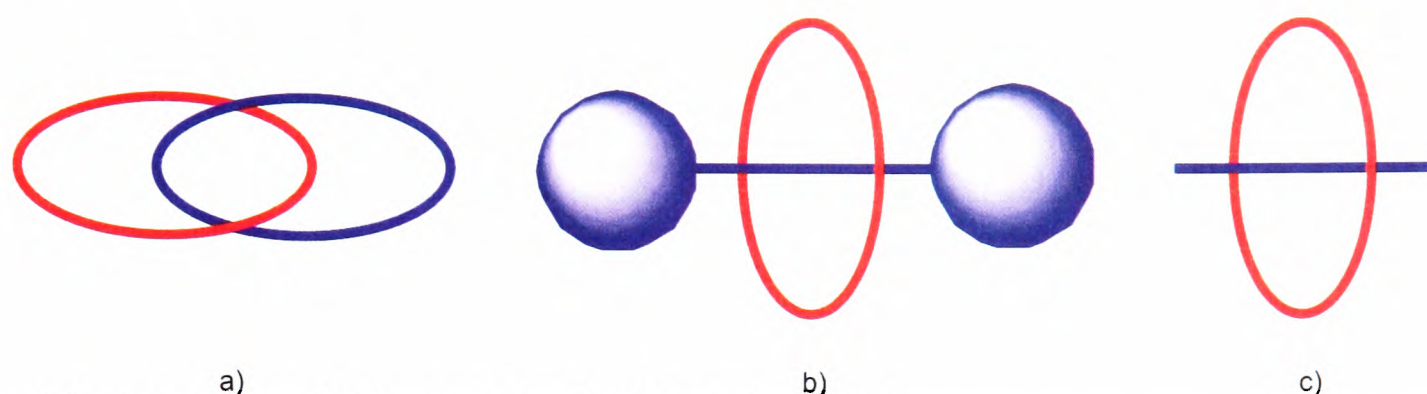
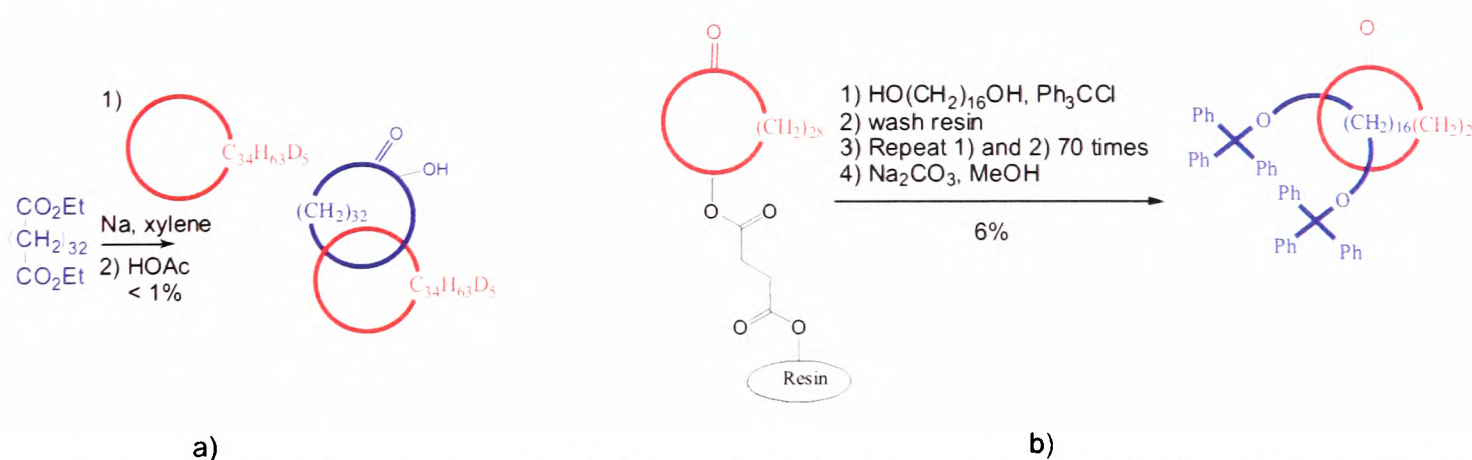


Figure 1.40 a) [2]catenane b) [2] rotaxane and c) [2]pseudorotaxane

Early syntheses of interlocked structures suffered from low yields since they relied on statistical approaches. The first catenane, synthesised by Wasserman in 1960 in less than 1% yield, was formed by the statistical threading of the linear precursor through the macrocycle and subsequent cyclisation (Scheme 1.2a).²⁰⁴ Several years later, Harrison reported the synthesis of the first rotaxane by stoppering a linear precursor threaded through a macrocycle immobilised on a resin (Scheme 1.2b).²⁰⁵ Only trace amounts of the rotaxane could be detected after one cycle but by repeating the cycle 70 times the yield could be improved to 6% following cleavage from the resin.



Scheme 1.2 a) Wasserman's synthesis of the first [2]catenane and b) Harrison's synthesis of the first [2]rotaxane

Given the very low yields associated with the statistical synthesis of rotaxanes and catenanes, it is not surprising that alternative synthetic strategies, such as templation, have been investigated. Following a summary of the approaches for synthesising catenanes and rotaxanes, the following sections will give an overview of the types of interlocked structures

that can be synthesised employing cationic, neutral and anionic templates.

Figure 1.41 summarises the different approaches for the synthesis of catenanes and rotaxanes.

It can be seen that pseudorotaxanes are useful precursors in both the synthesis of catenanes and rotaxanes (Figure 1.41b and d). Interweaving templates are exploited in the synthesis of catenanes either by ‘double clipping’²⁰⁶⁻²⁰⁸ (Figure 1.41a) or ‘clipping’ (Figure 1.41b).²⁰⁹⁻²¹¹

There are a number of different ways for synthesising rotaxanes, although the more common methods are ‘clipping’ a macrocycle precursor around a stoppered axle²¹²⁻²¹⁴ (Figure 1.41c) or ‘stoppering’ a pseudorotaxane (Figure 1.41d).^{215, 216} Rotaxane synthesis by ‘snapping’ involves the formation of a pre-rotaxane where a half-stoppered axle is held in the macrocycle cavity before reacting with another half-stoppered thread to form the rotaxane.^{217, 218} A number of groups have reported the synthesis of rotaxanes via a ‘slippage’ method, where the macrocycle slips over one of the stoppers of the axle usually at elevated temperatures (Figure 1.41f).²¹⁹⁻²²⁴ However, this is only a viable rotaxane synthesis when the barrier to dissociation of the rotaxane into its constituent components cannot be overcome at room temperature, otherwise the species formed is a pseudorotaxane.²²⁵ Somewhat related to slippage is the ‘threading followed by swelling’ strategy recently introduced by Chiu (Figure 1.41g).²²⁶ A pseudorotaxane, formed by the threading of an axle with one stopper group and another group which can become a stopper group, is converted into the rotaxane by a ‘swelling’ reaction.

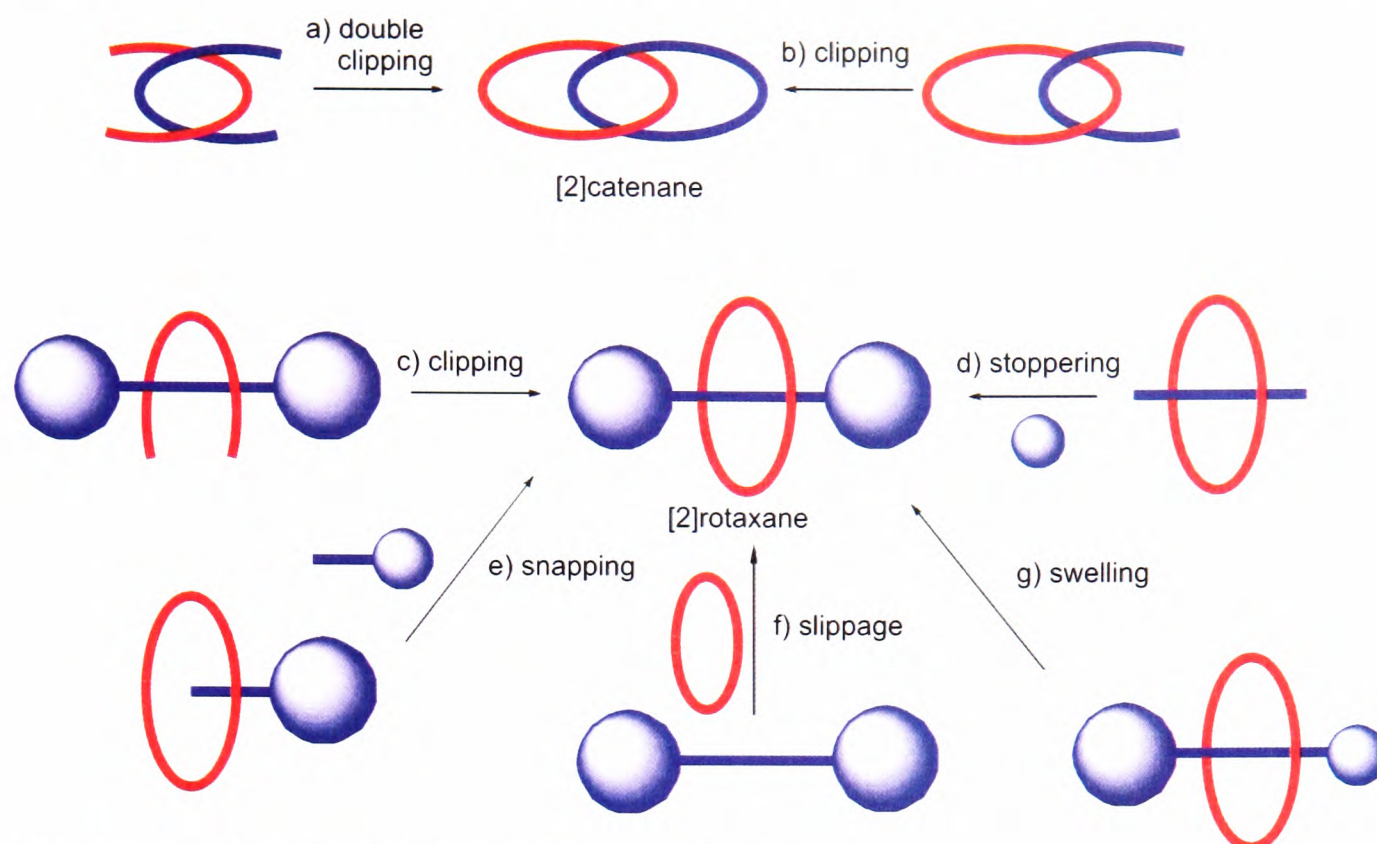


Figure 1.41 Strategies for the synthesis of catenanes and rotaxanes

1.4.2.1. Cation Templatation

Sauvage reported the first cation templated synthesis of a catenane (Figure 1.42a) using copper(I) as an interweaving template. The catenane could be synthesised either in two steps in 42% yield by a clipping strategy around a pre-formed macrocycle or in one step in 27% yield by a double clipping strategy.^{206, 207} The copper template could be removed using potassium cyanide to give the free catenane. More recently, Fujita has exploited the lability of platinum-pyridine bond to synthesise a photoswitchable molecular lock (Figure 1.42b).²²⁷ Upon light irradiation, the platinum-pyridine bonds in a macrocycle are labilised and the [2]catenane forms in quantitative yield driven by the π - π stacking interactions between the electron deficient and rich aromatic rings. Without light irradiation, the catenane is 'locked' in this state even when the interactions between the two rings are removed in non-aqueous solvents. However, light irradiation 'unlocks' the catenane and it dissociates into the two rings in non-aqueous solvents. Leigh and co-workers have recently reported the active template strategy for the synthesis of interlocked structures where the metal acts as both a template and catalyst for the reaction which interlocks the components.^{217, 228} Rotaxanes and catenanes have been synthesised exploiting copper active templates in Cadiot-

Chodkiewicz^{229, 230} and Huisgen-1,3-dipolar cycloaddition ('click')^{217, 230} reactions, and palladium active templates in Heck,²³¹ palladium promoted Michael additions²³² and oxidative alkyne homocoupling.²³³ The hetero[3]rotaxane in Figure 1.42c was synthesised using both copper and palladium active metal templates.²³⁴ Initially a [2]rotaxane was formed with the axle in blue by palladium catalysed alkyne homocoupling and the second axle in green was subsequently threaded through the macrocycle by a copper catalysed 'click' reaction resulting in the hetero[3]rotaxane.

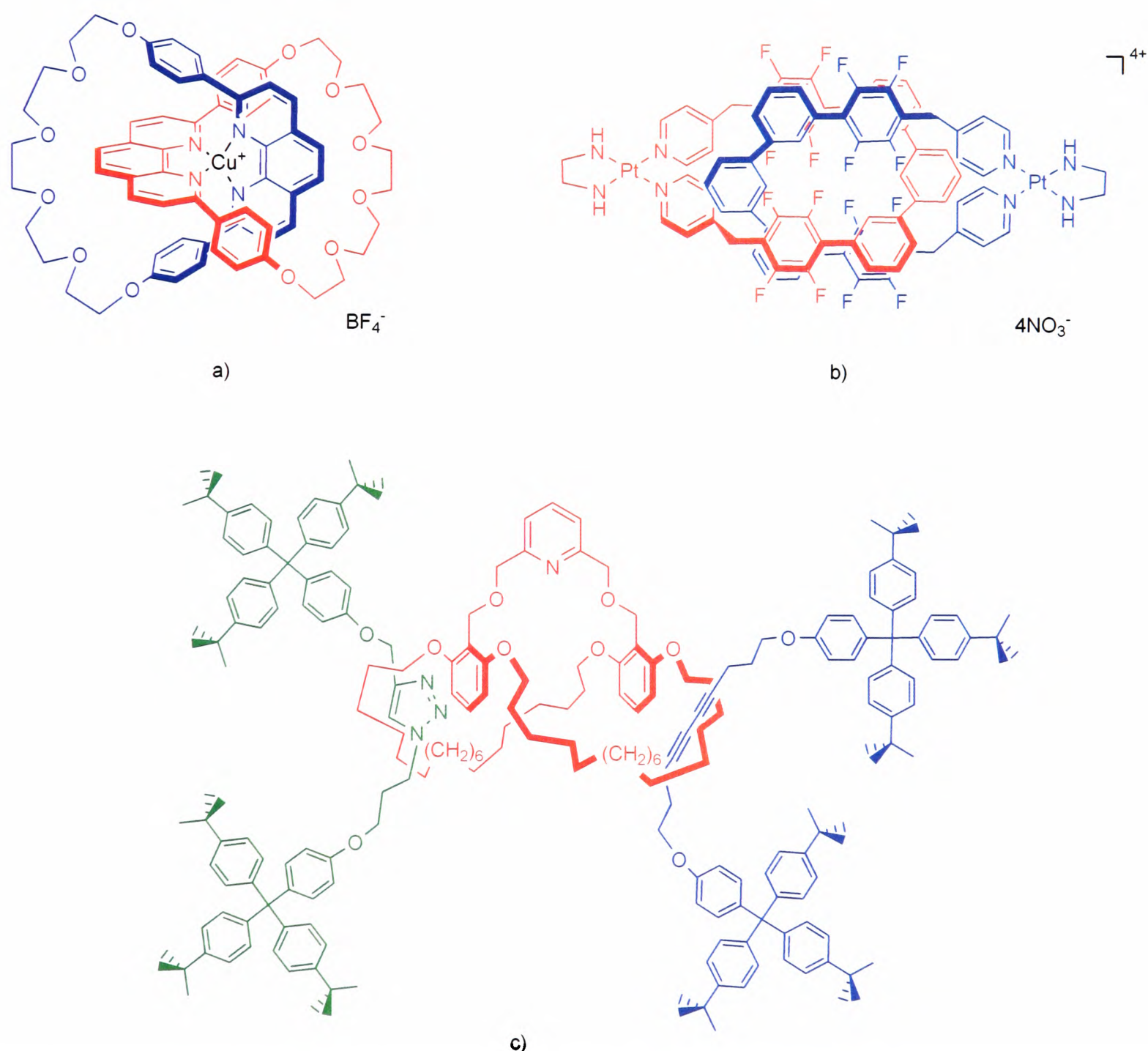


Figure 1.42 a) Sauvage's copper(I) templated [2]catenane b) Fujita's [2]catenane and c) Leigh's active metal templated hetero[3]rotaxane

Organic cationic motifs have also been used as templates in rotaxane and catenane syntheses.

The ability of the ammonium group to thread through crown ether macrocycles has been exploited by Schalley, who recently reported the self-sorting hetero[3]rotaxane

(Figure 1.43a).²³⁵ An equimolar mixture of the four components in CH_2Cl_2 forms a self-sorted hetero[3]pseudorotaxane where only the red macrocycle can thread around the bottom ammonium group since the green macrocycle is too small to slip over the phenyl group. The hetero[3]rotaxane was synthesised in 70% yield from the hetero[3]pseudorotaxane by a stoppering reaction. Chiu and co-workers have also exploited the ammonium group as a template in their solvent-free synthesis of [2]- and [4]rotaxanes.²³⁶ Solvent-free conditions are advantageous when using a threading followed by stoppering approach. This minimises dethreading of the pseudorotaxane during the stoppering reaction potentially improving yields, which is particularly important in the synthesis of higher order interlocked structures. The [4]rotaxane was synthesised in 78% yield following stoppering with 1,8-diaminonaphthalene in solvent-free conditions using solid-state ball-milling (Figure 1.43b).

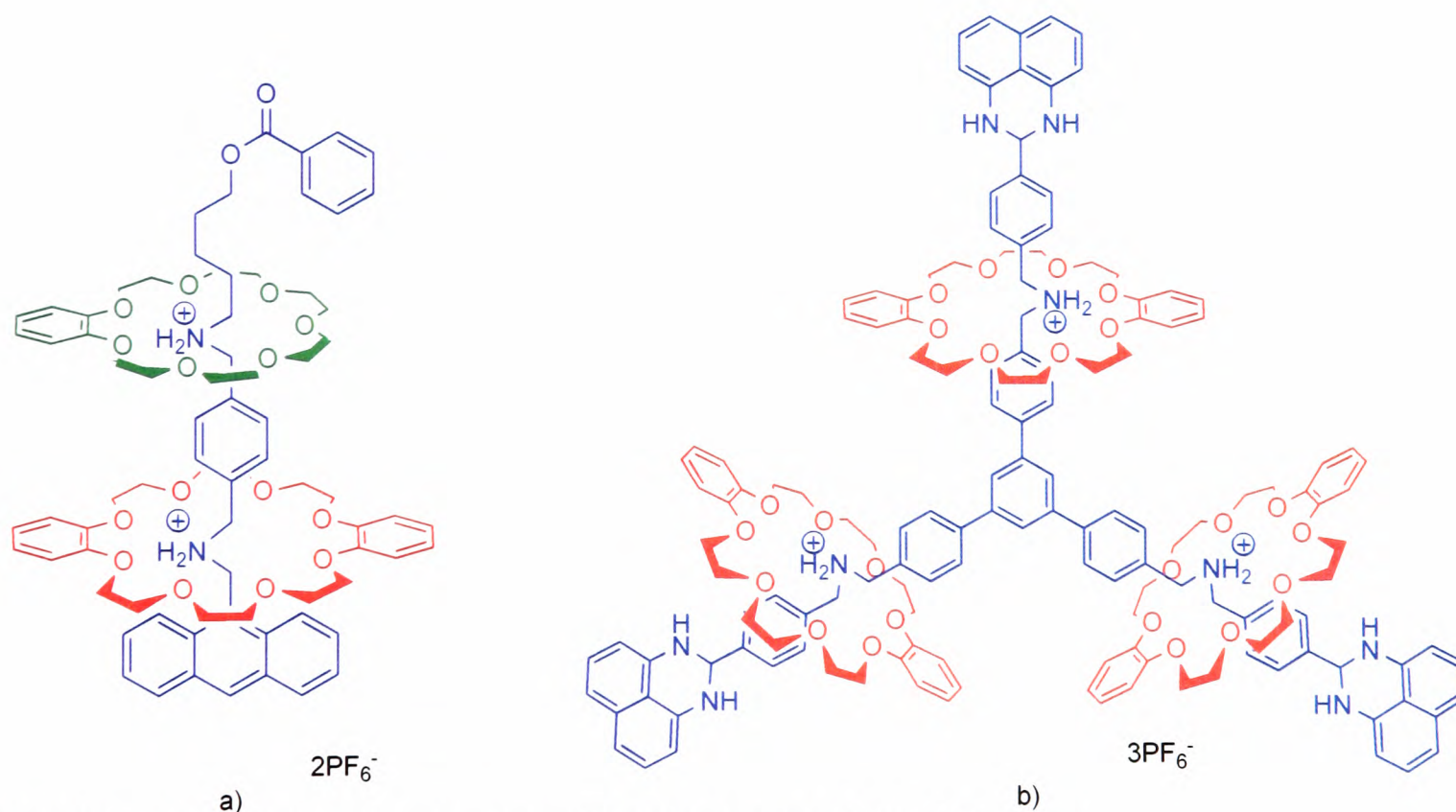


Figure 1.43 a) Schalley's self-sorting hetero[3]rotaxane and b) Chiu's [4]rotaxane

The donor/acceptor based template, pioneered by Stoddart and co-workers using 4,4'-paraquat motifs, exploits π - π stacking interactions between electron deficient and electron rich systems to synthesise rotaxanes and catenanes.^{200, 202, 237-239} The impressive

[5]catenane, named an ‘olympiadane’, was synthesised in 30% yield by templation between the electron rich naphthalene and electron deficient paraquat motifs (Figure 1.44).²⁴⁰

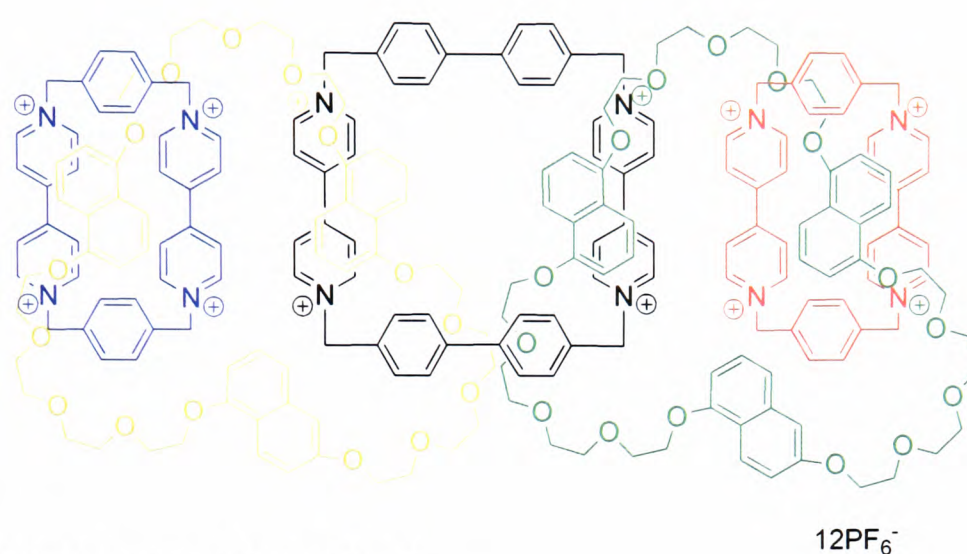


Figure 1.44 Stoddart's [5]catenane, 'olympiadane'

1.4.2.2. Neutral templation

There are an abundance of interlocked structures templated by neutral motifs and these primarily rely on π - π stacking, hydrogen bonding and the hydrophobic effect. A natural extension of the donor/acceptor template work by Stoddart in the previous section is the replacement of the cationic acceptor motif with a neutral electron deficient π -system. Sanders and co-workers have reported the synthesis of a number of catenanes exploiting π - π stacking interactions between electron deficient naphthalenediimide and electron rich naphthalene motifs.^{241, 242} Recent work has demonstrated the presence of the two catenanes in Figure 1.45 in a disulfide dynamic combinatorial library in H₂O.²⁴³ The presence of the catenane in Figure 1.45b is particularly unusual since it consists of three donor motifs but only one acceptor motif. This demonstrates the ability of dynamic combinatorial libraries to generate unexpected structures. While the catenanes were not the major species at equilibrium, the library could be biased under different conditions to amplify each catenane structure.

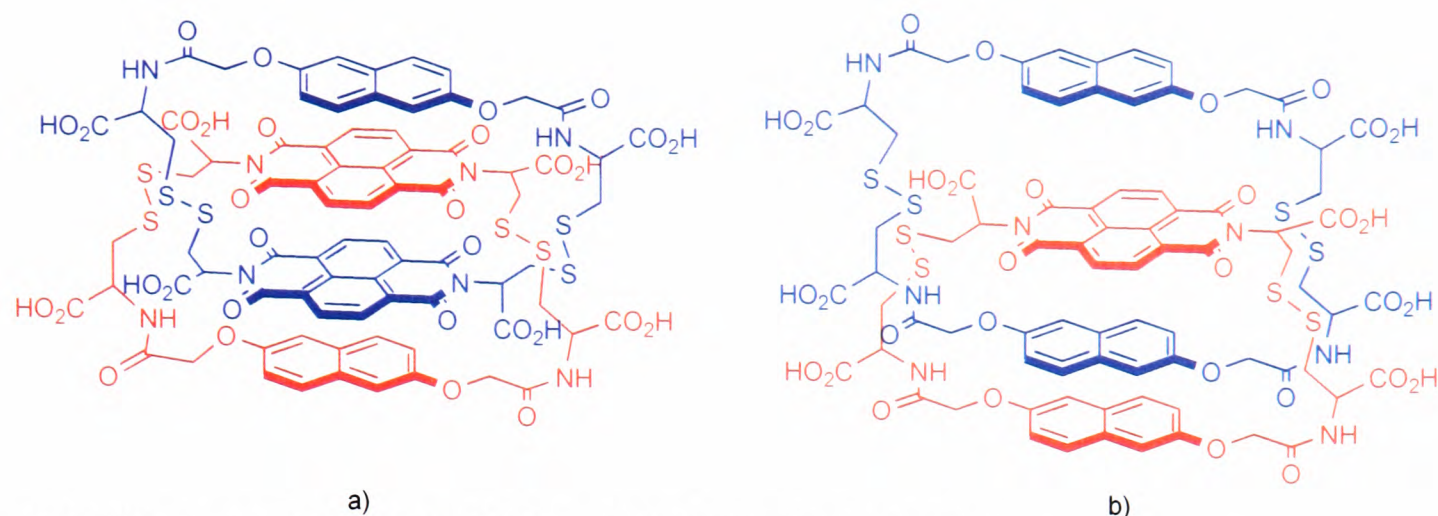


Figure 1.45 [2]catenanes in Sanders' disulfide dynamic combinatorial library

The serendipitous synthesis of a [2]catenane by Hunter in a macrocyclisation reaction with isophthaloyl dichloride (Figure 1.46a) demonstrated that hydrogen bonding interactions can also be exploited to synthesise interlocked structures.²⁰⁸ The formation of this and a number of related catenanes²⁴⁴⁻²⁴⁶ relies on a double clipping strategy, where a number of hydrogen bonding and π - π stacking interactions template the formation of an interweaving assembly of the macrocycle precursors prior to reaction with isophthaloyl dichloride. Böhmer and co-workers have reported the synthesis of fourfold [2]rotaxanes^{214, 247} (Figure 1.46b) and other unusual interlocked topologies²⁴⁸ from hydrogen bonded dimers of tetraurea calix[4]arenes.

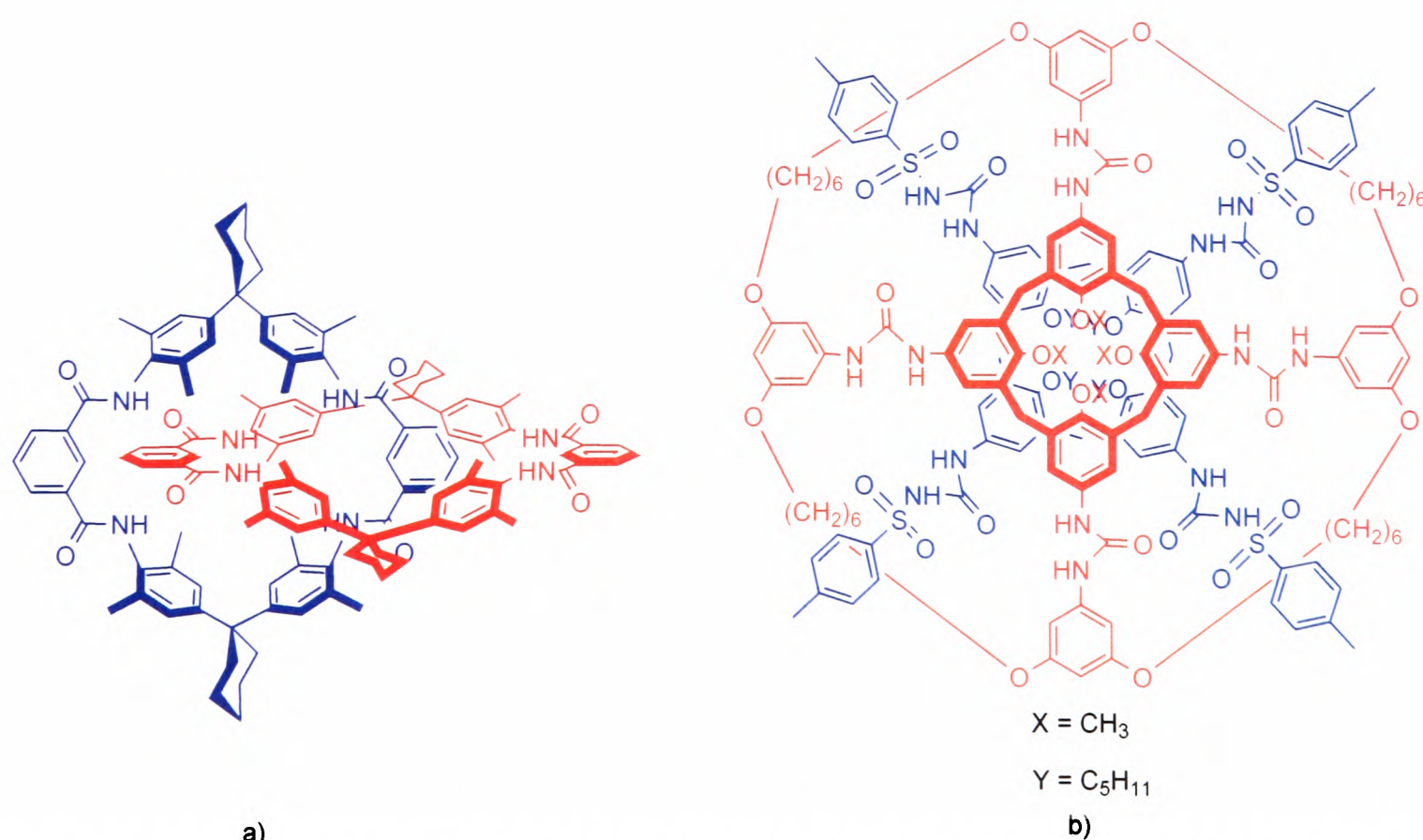


Figure 1.46 Hydrogen bond templated self-assembly a) Hunter's [2]catenane and b) Böhmer's fourfold [2]rotaxane

The hydrophobic cavity of cyclodextrin has been exploited by a number of groups to template the synthesis of rotaxanes in H_2O . The cavity of γ -cyclodextrin is large enough to accommodate two guests and the hetero[3]rotaxane was synthesised by Anderson using Suzuki coupling (Figure 1.47a).²⁴⁹ The rotaxane in Figure 1.47b is one of the first examples of a [1]rotaxane prepared by direct methods. Self-inclusion of the azo-benzene side-arm in 10% DMSO followed by stoppering using Suzuki coupling gave the [1]rotaxane where shuttling of the cyclodextrin ring was possible using photoisomerism.²⁵⁰

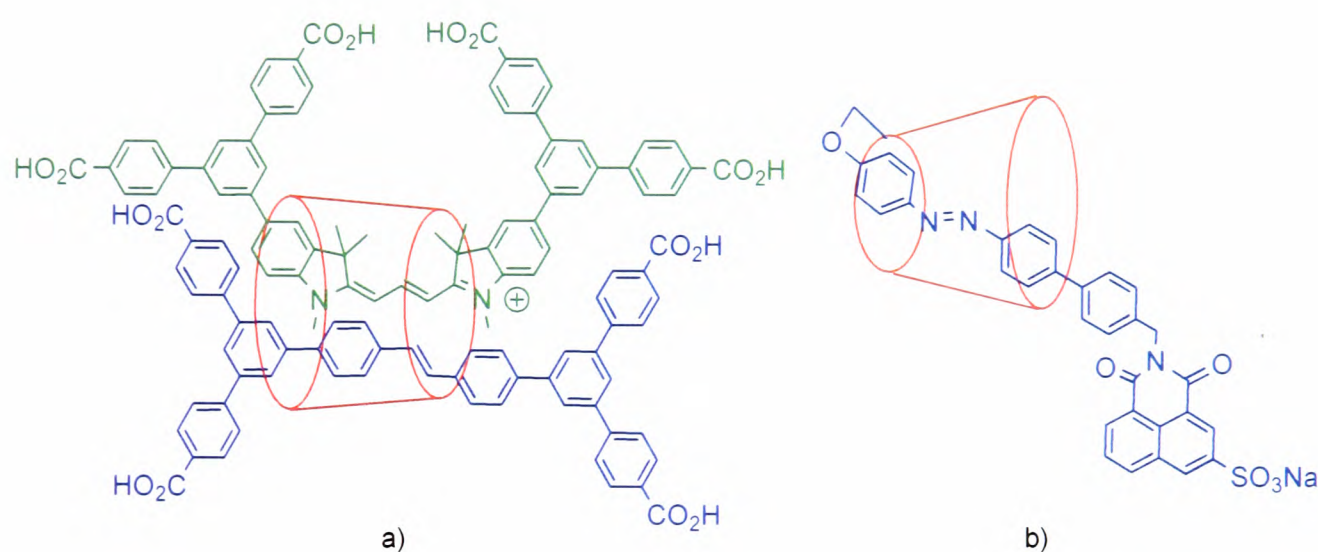


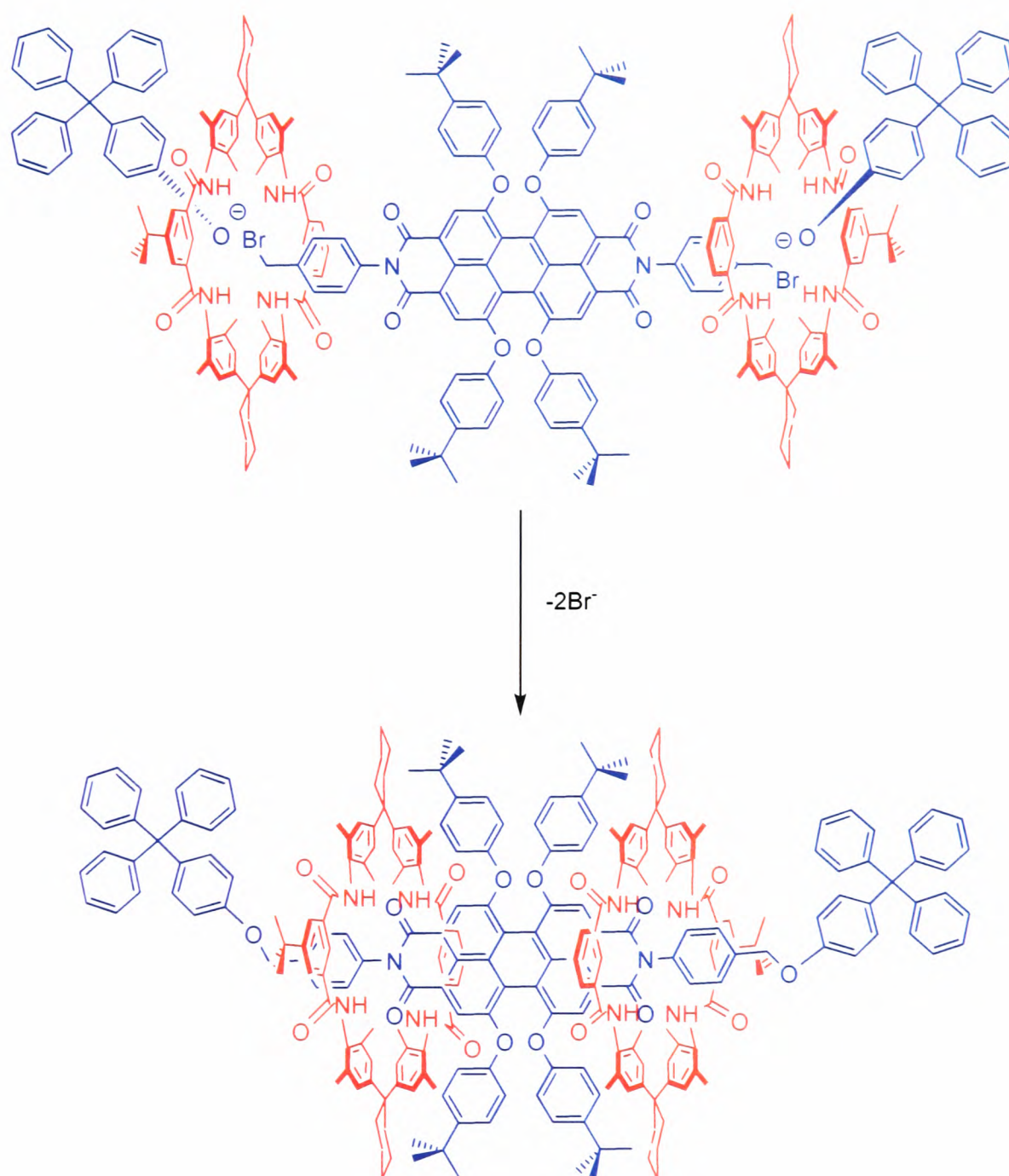
Figure 1.47 Neutral templation exploiting the hydrophobic effect a) Anderson's [3]rotaxane and b) [1]rotaxane

1.4.2.3. Anion Templation

There are numerous examples in the literature of interlocked structures assembled from cation and neutral templates, but there are fewer examples of anion templation for the reasons discussed in Section 1.4.1.1.

A number of anion templated strategies have been developed to synthesise rotaxanes and catenanes. Vögtle and co-workers reported the first example in 1999 using a phenoxide anion template in a snapping strategy²⁵¹ and they have subsequently published the synthesis of a number of rotaxanes including the [3]rotaxane in Scheme 1.3.²⁵² The phenoxide anion template binds in the tetralactam macrocycle forming a 'wheeled supramolecular nucleophile'²⁵³ which reacts with the benzylic bromide to give the [3]rotaxane consuming the

anion template in the process. Hydrogen bonding interactions between the amide groups of the macrocycle and the carbonyl groups of the axle in the rotaxane result in red shifts in the absorbance and fluorescence spectra of the perylene diimide chromophore compared to the free axle.



Scheme 1.3 Vögtle's templated [3]rotaxane synthesis

A number of groups have reported the synthesis of rotaxanes using similar phenoxide templation strategies, except the anion template is retained in the rotaxane structure. Schalley's [3]rotaxane²⁵⁴ (Figure 1.48a) and Smith's squaraine rotaxane²⁵⁵ (Figure 1.48b) both use phenoxide anion templation to thread the axle through the macrocycle and the rotaxane is synthesised by an appropriate stoppering reaction.

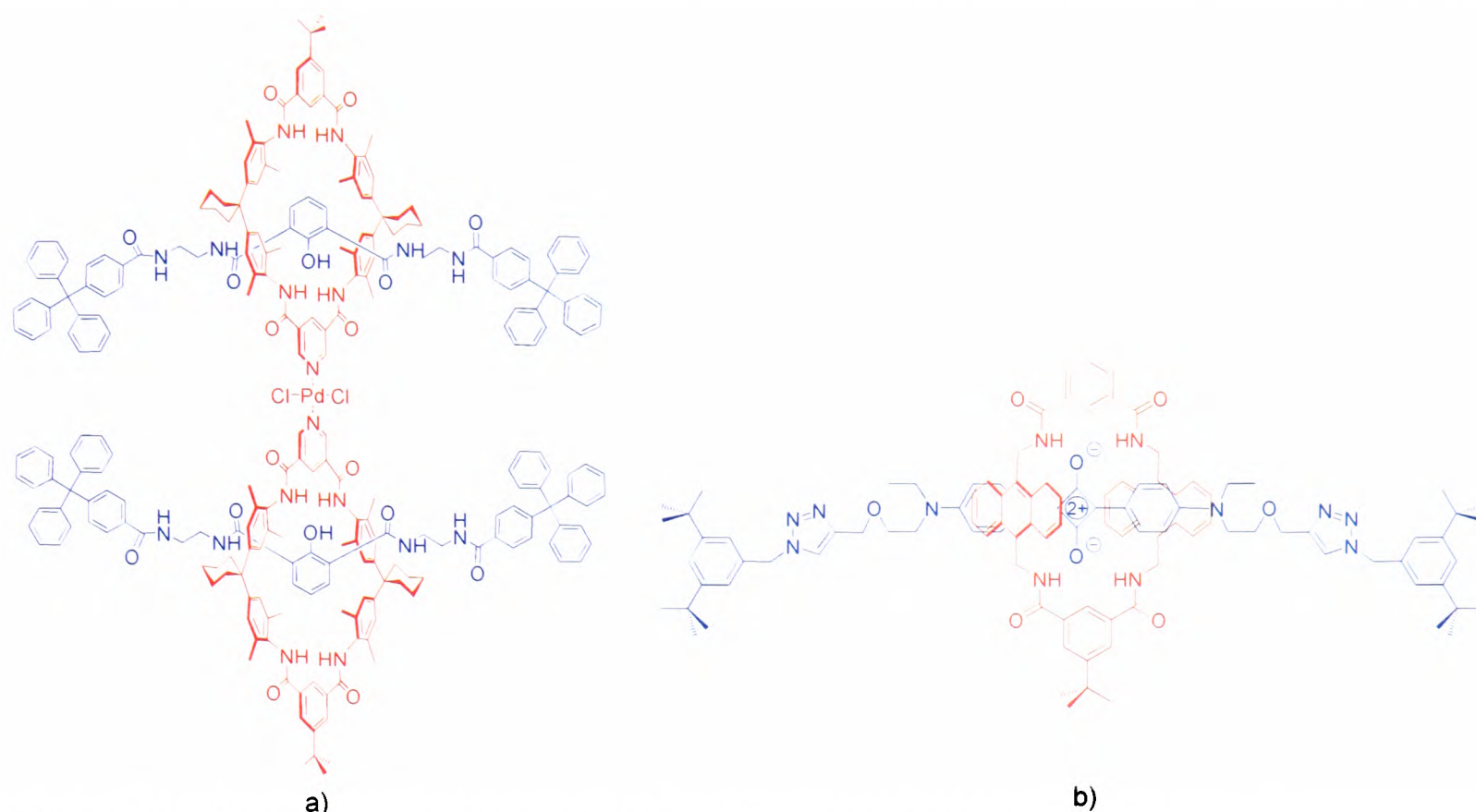


Figure 1.48 a) Schalley's phenoxide templated [3]rotaxane and b) Smith's squaraine rotaxane

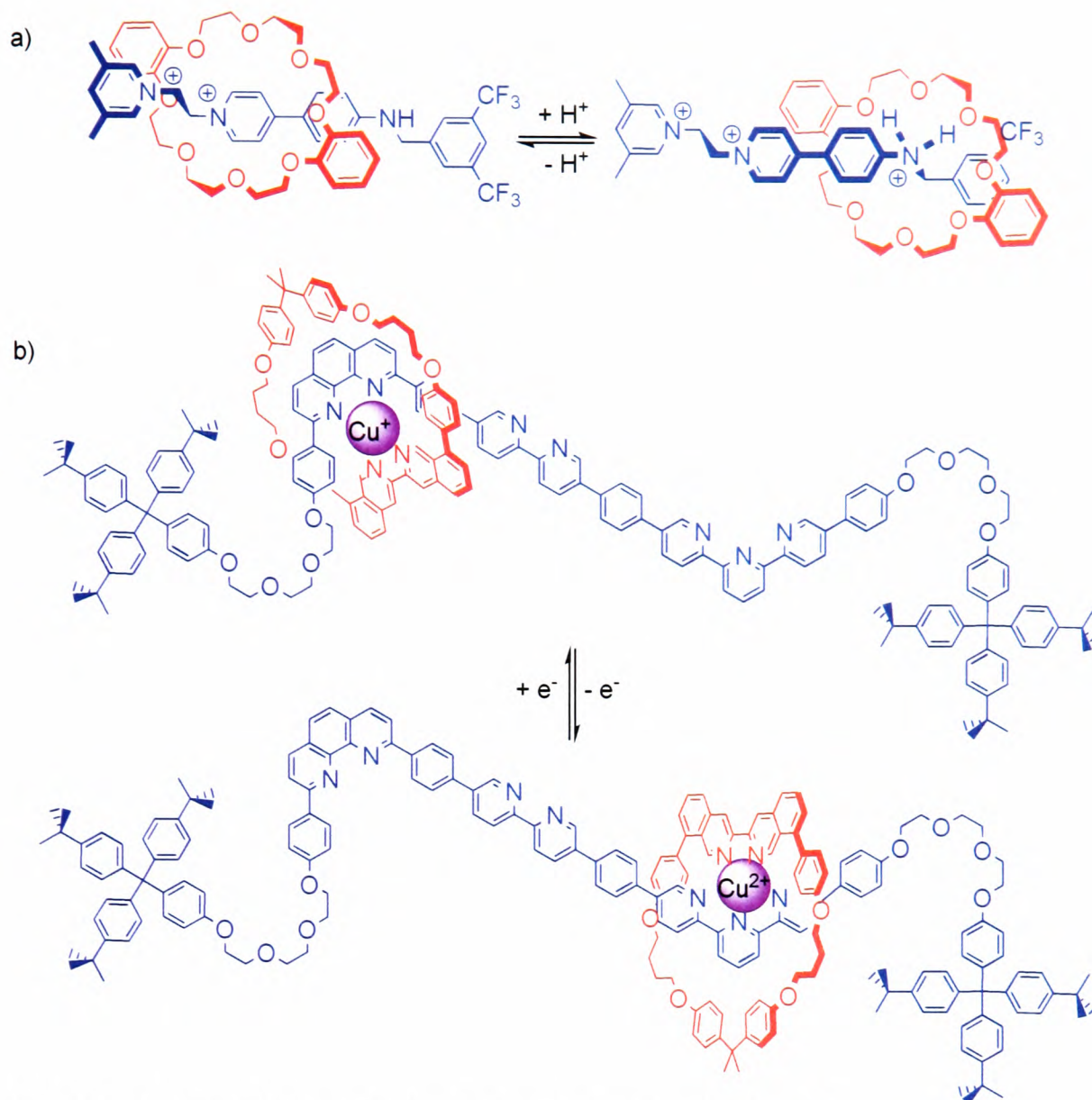
One of the drawbacks of these two anion templation strategies is that the anion template is incorporated into the final rotaxane structure so that it cannot be removed without breaking a mechanical bond. For this reason, Beer and co-workers have developed an anion templation strategy for synthesising pseudorotaxanes, rotaxanes and catenanes where the anion template can be removed.^{188, 210, 256, 257} A three-dimensional topologically unique cavity for anions is created following removal of the anion template leading to potential sensors for anions. This strategy will be discussed in more detail in later chapters.

1.4.2.4. Applications of interlocked structures

The synthesis of interlocked structures is a growing field not only for the synthetic challenge but for use of these structures as molecular machines in nanotechnology. The applications of interlocked structures have been the subject of many reviews^{201, 258-260} and more recent examples will be described to give a brief overview of the main types.

Rotaxanes and catenanes are ideal candidates for the development of molecular machines since translational and rotational motion can be achieved by incorporating more than one station into the design of the interlocked structure. A number of groups have reported the

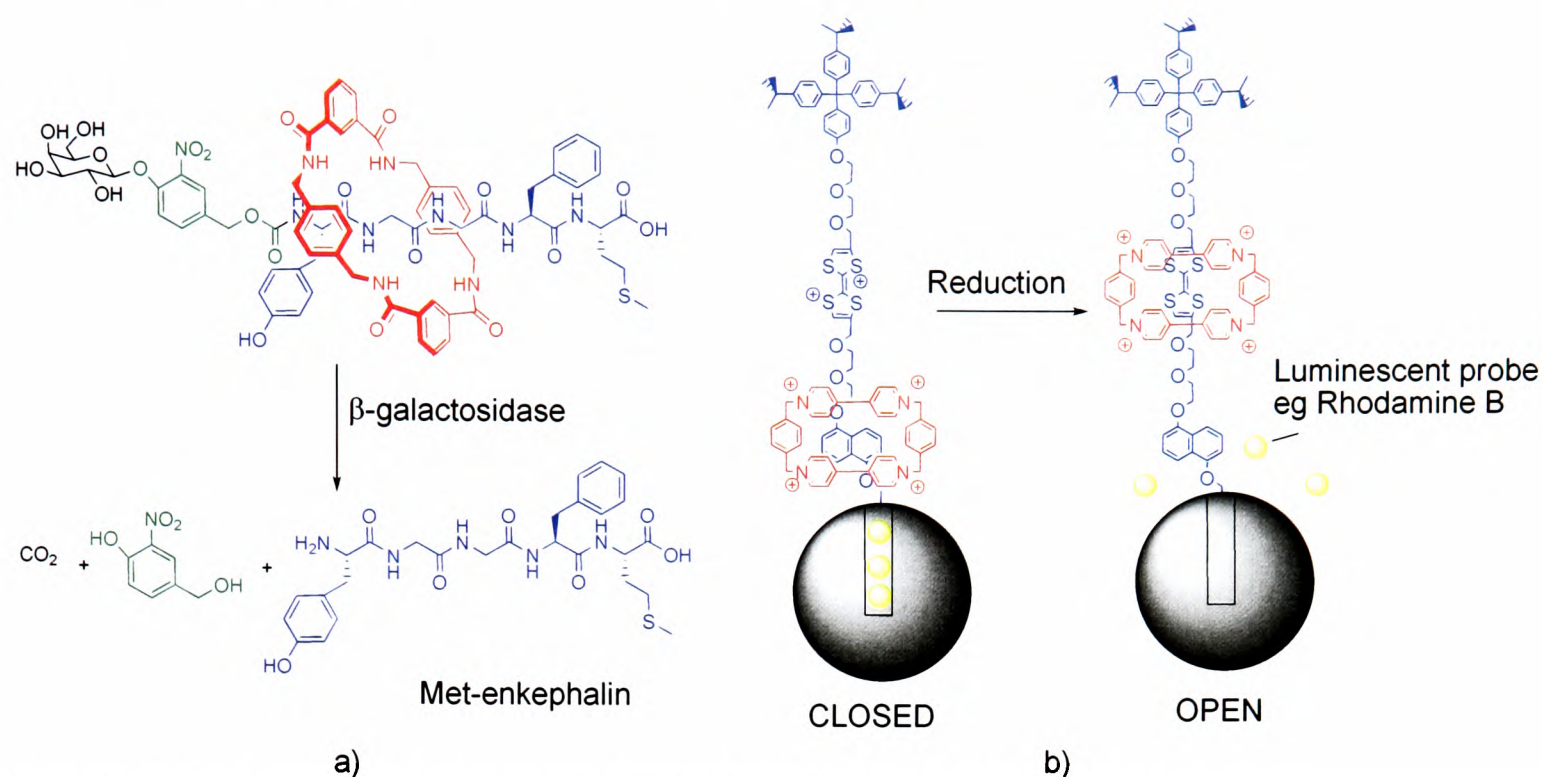
synthesis of molecular shuttles where shuttling between the stations can be triggered by stimuli such as light,²⁶¹ electrochemical^{262, 263} and pH changes. Loeb and co-workers recently reported the molecular shuttle in Scheme 1.4a where shuttling between the 1,2-bis(pyridinium)ethane and benzyl aniline stations is controlled by acid-base chemistry and can be sensed optically.²⁶⁴ The dibenzo-24-crown-8 ether macrocycle resides over the 1,2-bis(pyridinium)ethane station but the macrocycle shuttles to the benzyl aniline station upon protonation of the aniline nitrogen. There is an accompanying colour change from bright orange to colourless, due to elimination of an intramolecular charge transfer between the aniline nitrogen and pyridinium nitrogen in the protonated rotaxane. Sauvage and co-workers have reported a number of electrochemically driven molecular shuttles where shuttling is achieved by exploiting the different coordinational preferences of copper(I) and (II).²⁶⁵⁻²⁶⁷ Scheme 1.4b shows the first example of a molecular shuttle with three stations, based on phenanthroline, terpyridine and bipyridine.²⁶⁸ Upon oxidation from copper(I) to copper(II), the macrocycle shuttles between the phenanthroline and terpyridine stations, a distance of approximately 23 Å. Shuttling over this distance would be expected to be very slow but the chelating bipyridine group between the two stations improves the rate of shuttling so that it is comparable to the rate between the two stations in the absence of the bipyridine group over the much shorter distance of 10 Å.



Scheme 1.4 a) Loeb's pH and b) Sauvage's electrochemical molecular shuttles

A number of interlocked structures are also finding applications as drug delivery agents. The propeptide Met-enkephalin is protected from degradation by peptidases and other enzymes in human plasma by the presence of the macrocycle in Leigh's rotaxane (Scheme 1.5a).²⁶⁹ However, the free pentapeptide can be released by the β -galactosidase catalysed cleavage of the carbohydrate unit of one of the stoppers. Stoddart and co-workers have also described the fabrication of nanovalves based on pseudorotaxanes where release of the cargo in the nanovalve is controlled by light²⁷⁰ and/or pH.²⁷⁰⁻²⁷² The nanovalve based on the bistable [2]rotaxane in Scheme 1.5b is operated by electrochemical signals.²⁷³ The nanovalve is closed when the cyclobis(paraquat-*p*-phenylene) macrocycle encircles the 1,5-dihydroxynaphthalene station but is opened by the macrocycle shuttling to the tetrathiafulvalene (TTF) station upon electrochemical reduction of TTF^{2+} to TTF. The controlled release of the luminescent probe molecules, such as Rhodamine B, loaded in the pores of the mesoporous silica nanoparticles

was monitored by fluorescence spectroscopy.



Scheme 1.5 a) Leigh's propeptide rotaxane and b) Stoddart's molecular nanovalves

The three-dimensional topology of the cavities in interlocked structures has led to interest in developing these structures for sensing applications. Smith's squaraine rotaxane in Figure 1.49a is a reversible optical sensor for chloride anions.²⁷⁴ The chloride anion binds in the tetralactam macrocycle causing the macrocycle to translocate from the squaraine station to the triazole station, inducing an increase of the fluorescence emission of the squaraine dye. This increase is visible to the naked eye and dipsticks containing the rotaxane have been developed to detect the amount of chloride in aqueous solution colorimetrically. Interlocked structures assembled on surfaces have the potential to be used as sensors. Beer and co-workers reported the redox-active rotaxane assembled on a gold surface for sensing anions (Figure 1.49b).²⁷⁵ The electrochemical response of the redox-active groups on both the macrocycle and axle components to anions was measured. The ferrocene group on the axle is too far away from the anion binding site for sensing but the rotaxane selectively detects chloride in the presence of a 100-fold excess of dihydrogen phosphate in CH_3CN by cathodic shifts of the macrocycle ferrocene/ferrocenium redox couple.

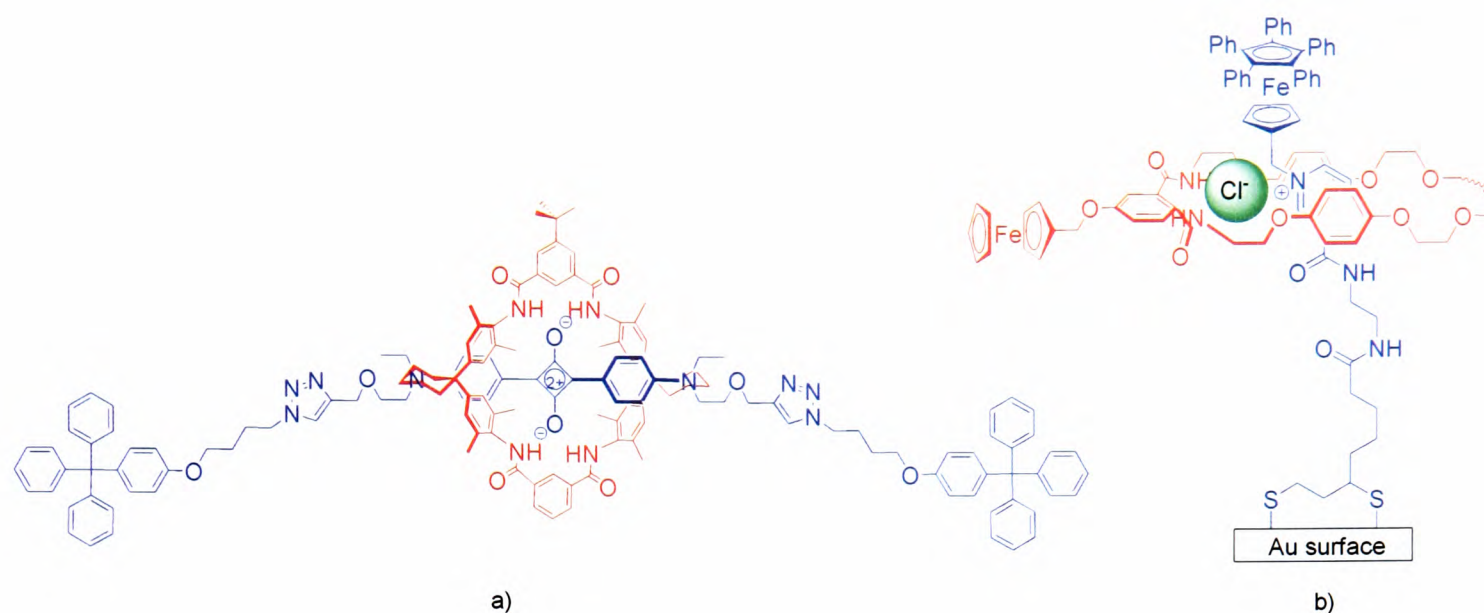


Figure 1.49 a) Smith's reversible optical chloride sensor and b) Beer's redox-active sensory rotaxane

1.5. Aims of the Project

Supramolecular chemistry encompasses a number of areas from host-guest chemistry to self-assembly and the aim of this chapter was to give a general overview of the subject. This research project was primarily concerned with the synthesis of receptors based on the calix[4]arene framework for ion-pair recognition and anion recognition. The versatility of this framework has already been highlighted in examples in this chapter, but this will be explored in greater detail in later chapters.

Chapter 2 details the synthesis and binding properties of calix[4]arene based receptors for ion-pair recognition. The synthesis of macrobicyclic receptors was investigated for binding contact ion-pairs and this work was extended to the synthesis of related cryptand receptors. Finally attempts towards the synthesis of calix[4]arene partial tube structures incorporating Lewis acidic zinc centres as potential anion receptors is presented.

Chapter 3 extends the work of Chapter 2 to the anion templated synthesis of calix[4]arene based interlocked structures by replacing the simple cation of the ion-pair with a cationic thread component. As discussed in Section 1.4.2, there are many strategies for synthesising catenanes and rotaxanes, and a number of these will be explored.

Chapter 4 continues to investigate the synthesis of interlocked structures using copper catalysed coupling reactions.

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Chapter 2

Heteroditopic Receptors for Ion-Pair Recognition

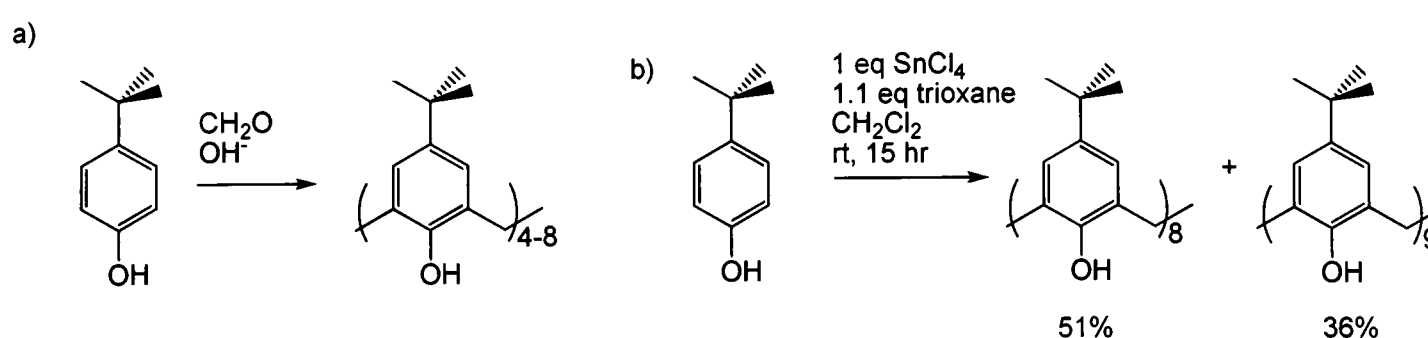
2. Calix[4]arene Based Heteroditopic Receptors for Ion-Pair Recognition

2.1. Introduction

2.1.1. Calixarenes

Calix[n]arenes are a family of cyclophanes consisting of a cyclic array of *n* phenol units. They have been known since the 1940s when Zinke synthesised the tetrameric calix[4]arene,^{1, 2} but it was not until the work of Gutsche in the 1970s that the synthetic accessibility of calixarenes was realised.³

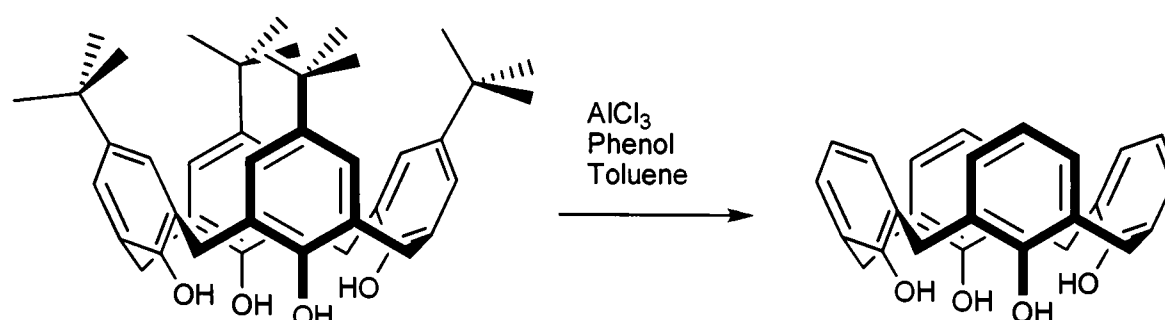
Calixarenes are synthesised from the condensation of *tert*-butyl phenol and formaldehyde in the presence of a base (Scheme 2.1a). The base and solvent has a profound effect on which calixarene predominates in the reaction mixture, and the most common calixarenes, *tert*-butylcalix[4]-, [6]- and [8]-arene, can be isolated in yields of up to 50%, 74% and 64% respectively depending on the conditions used.^{4, 5} Recently, Bew and co-workers have reported the first synthesis of calixarenes using organometallic ferrocenium salts⁶ and the one-pot Lewis acid mediated synthesis of *tert*-butylcalix[9]arene, which has previously been difficult to synthesise in large quantities (Scheme 2.1b).⁷



Scheme 2.1 a) Synthesis of the most common calixarenes and b) Bew's Lewis acid mediated synthesis of calix[9]arene

The remainder of this introduction will focus on calix[4]arenes, as two of these will be used extensively in this thesis. Both *tert*-butylcalix[4]arene and calix[4]arene are now commercially available,⁸ although calix[4]arene is very expensive since it cannot be

synthesised directly from phenol. However, it can be synthesised in multi-gram quantities from *tert*-butylcalix[4]arene by a Friedel-Crafts dealkylation (Scheme 2.2).^{9, 10}



Scheme 2.2 Friedel-Crafts dealkylation of *tert*-butylcalix[4]arene to calix[4]arene

Calix[4]arenes are conformationally flexible due to rotation about the methylene CH₂ groups and they can exist in four extreme conformations from ring inversion through the macrocycle centre (Figure 2.1).¹¹⁻¹³ Interconversion between the four conformations is possible unless the calixarene is functionalised on the lower rim with substituents sterically bulkier than *n*-propyl groups. The different conformations can be distinguished by their characteristic methylene CH₂ chemical shifts in ¹H and ¹³C NMR spectra. For example, the methylene CH₂ in the cone conformation is seen as a doublet of doublets in the ¹H NMR spectrum, whereas it is a singlet in the 1,3-alternate formation.

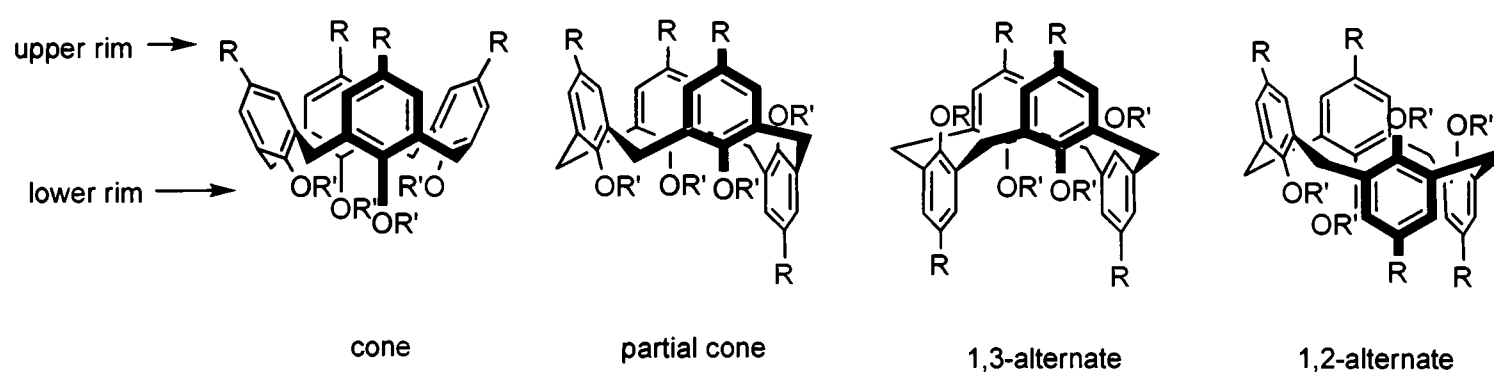
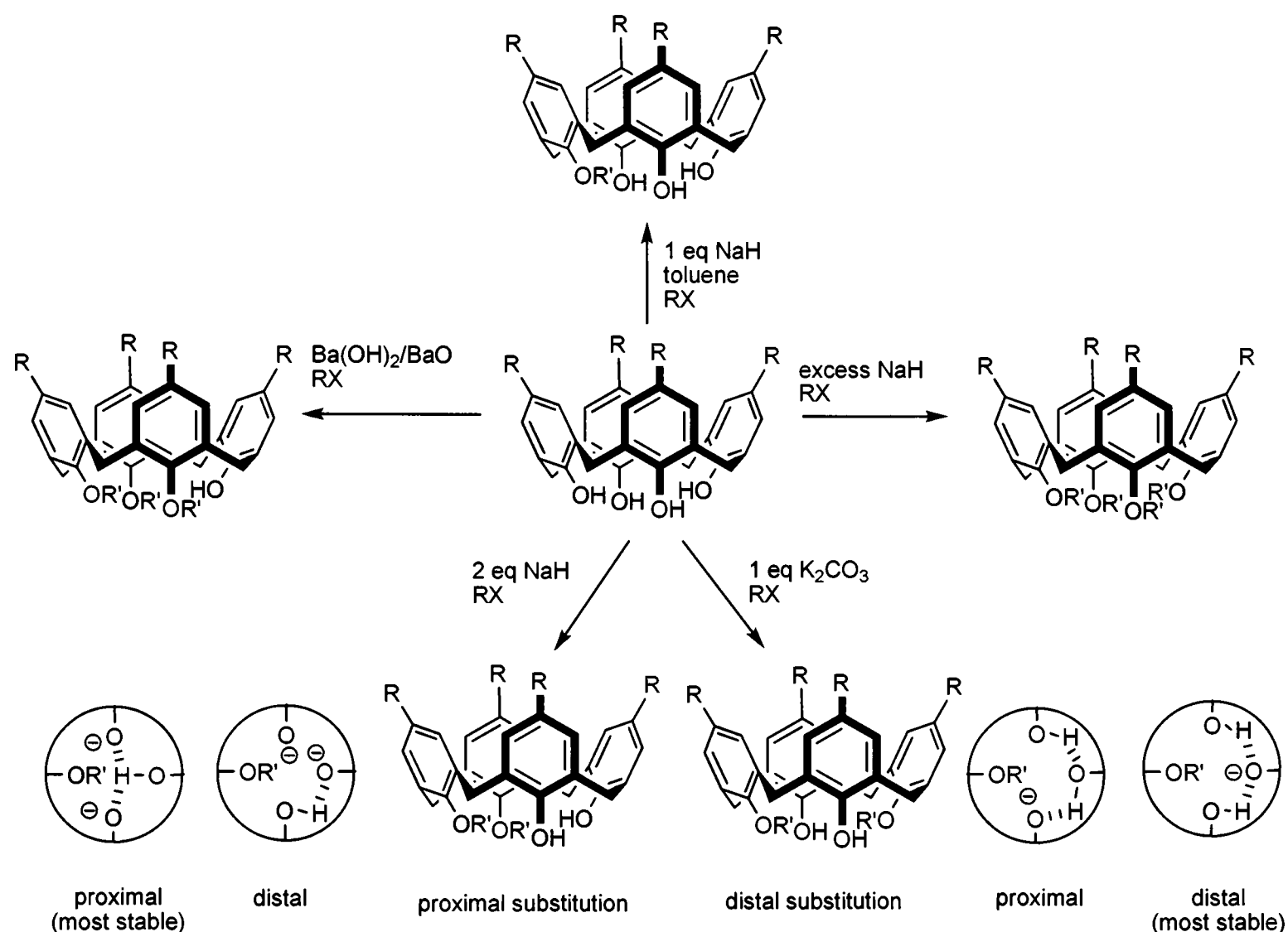


Figure 2.1 Conformations of calix[4]arenes

The widespread use of calixarenes is due to the ease of functionalisation on the upper and/or lower rim. Functionalisation on the lower rim involves the alkylation of the phenoxy groups. The reaction conditions, such as choice of base, determine the conformation and substitution pattern.¹⁴ Scheme 2.3 summarises the conditions used for mono-, di-, tri- or tetra-substitution of the cone conformation (Scheme 2.3). Two regioisomers are possible for disubstitution: 1,3-distal or 1,2-proximal substitution. Strong bases such as NaH favour 1,2-proximal substitution, whereas weak bases such as K₂CO₃ favour 1,3-distal substitution

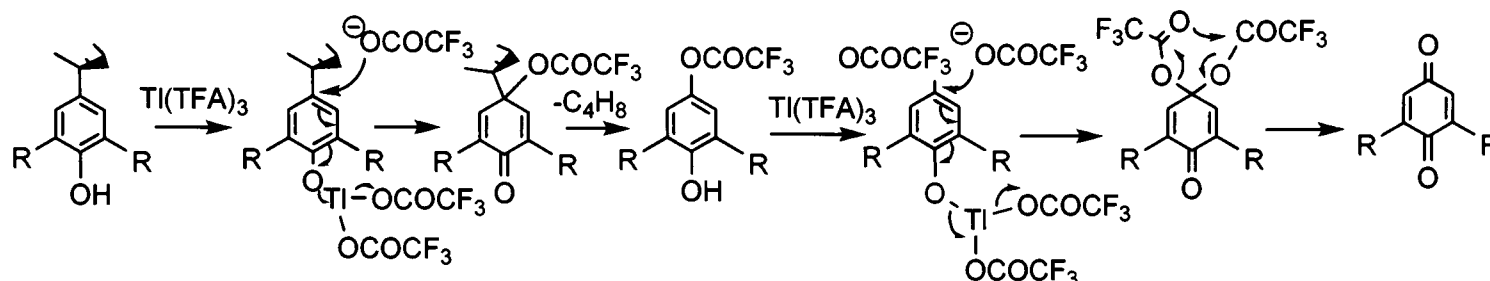
due to stabilisation of the intermediates formed by hydrogen bonding (Scheme 2.3).¹⁵ Upper rim functionalisation can be achieved by electrophilic aromatic substitution of calixarene derivatives and the regioselectivity can be influenced by substituents on the lower rim.



Scheme 2.3 Lower rim functionalisation of calix[4]arenes in the cone conformation

2.1.2. Calixquinones

Calixquinones are a class of calixarenes that can be obtained from oxidation of the phenol units to quinone species. While several multi-step synthetic routes to calixquinones have been developed,^{16, 17} thallium(III) trifluoroacetate is typically used for the oxidation. Scheme 2.4 shows the proposed mechanism for the oxidation, and this method has the advantage that groups *para* to the phenoxy group, such as *tert*-butyl, can be simultaneously removed. A number of calixquinone species derived from *tert*-butylcalix[4]arene have been reported,¹⁸⁻²² and mono-, di-, tri- and tetra-quinone species can be obtained depending on the number of unsubstituted phenol units.²³



Scheme 2.4 Proposed mechanism of thallium trifluoroacetate oxidation of *tert*-butylcalixarene

The toxicity of thallium salts is a concern and the use of alternative oxidants has been explored by a number of groups. Often these are oxidants which are not able to remove *tert*-butyl groups, and therefore only the oxidation of calixarene rather than *tert*-butylcalixarene derivatives is possible. Rosik first reported the chlorine dioxide oxidation of calix[4]arene to calix[4]tetraquinone (Figure 2.2a) in a phosphate buffered solution in 1986.²⁴ Chlorine dioxide has subsequently been used to oxidise calix[4]arene dialkyl ether (Figure 2.2b),^{25, 26} benzoate^{27, 28} and macrocyclic²⁹ derivatives. Several groups have reported the potassium iron(III) hexacyanate oxidation of calix[4]arene derivatives to indoaniline derivatives in the presence of an aniline dye (Figures 1.15b and 2.2c).³⁰⁻³² Other oxidants of calixarene derivatives include sodium perborate tetrahydrate³³ and thallium nitrate.³⁴

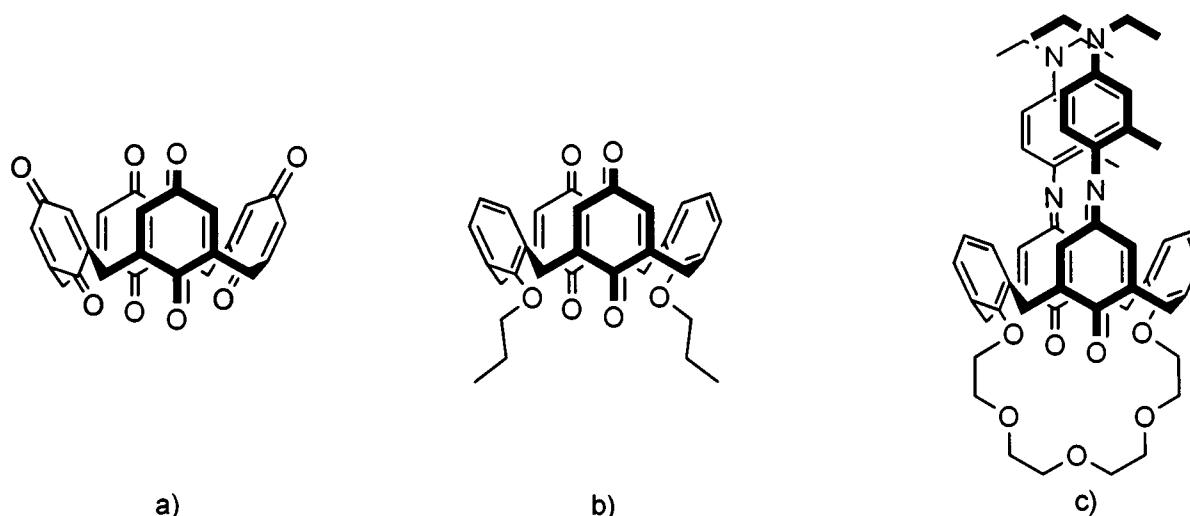


Figure 2.2 a) Calix[4]tetraquinone b) calix[4]diquinone dialkyl ether and c) calix[4]arene indoaniline derivative

2.1.3. Calixarene Based Receptors for Ions

Calixarenes have been exploited as frameworks for many supramolecular hosts due to their ease of functionalisation, and Shinkai has described them as the ‘third generation’ supramolecular host after cyclodextrins and crown ethers.³⁵ Calixarene based cation, anion and ion-pair receptors have been developed and many were introduced in Section 1.3. This

section will focus on examples that are particularly relevant to the projects within this chapter.

The calixarene framework itself has been shown to form inclusion complexes with cations through interaction with the electron rich aromatic rings,³⁶⁻⁴⁰ and there are numerous examples of cation receptors based on the calixarene framework functionalised with suitable cation binding groups.⁴¹⁻⁴³ However, the calixdiquinone motif has also been shown to bind cations, particularly alkali metal cations, through the convergent set of oxygen donor atoms. This motif also acts as an reporter group so that cation binding can be monitored by electrochemical and/or UV/visible spectroscopic methods.^{18, 20, 44} The indoaniline receptor in Figure 2.2c is an off-on-off optical switch where the binding of calcium within the crown ether cavity induces a colour change from blue to green, and this can be switched off by addition of potassium.³¹ Beer's crown ether calix[4]diquinone receptor in Figure 2.3a binds potassium preferentially to sodium and ammonium cations, as determined by UV/visible spectroscopy experiments in MeOH, and the reduction potentials of the calix[4]diquinone motif are shifted anodically in the presence of cations.¹⁸ The related calix[4]diquinone partial tube receptor in Figure 2.3b also electrochemically recognises caesium and rubidium cations in 4:1 CH₂Cl₂/CH₃CN.²⁰ There are also examples of anions perturbing the electrochemistry of the calix[4]diquinone motif.^{45, 46} The reduction potentials of the urea functionalised receptor in Figure 2.3c undergo cathodic shifts of up to 180 mV in the presence of anions such as sulfate in CH₃CN.⁴⁵

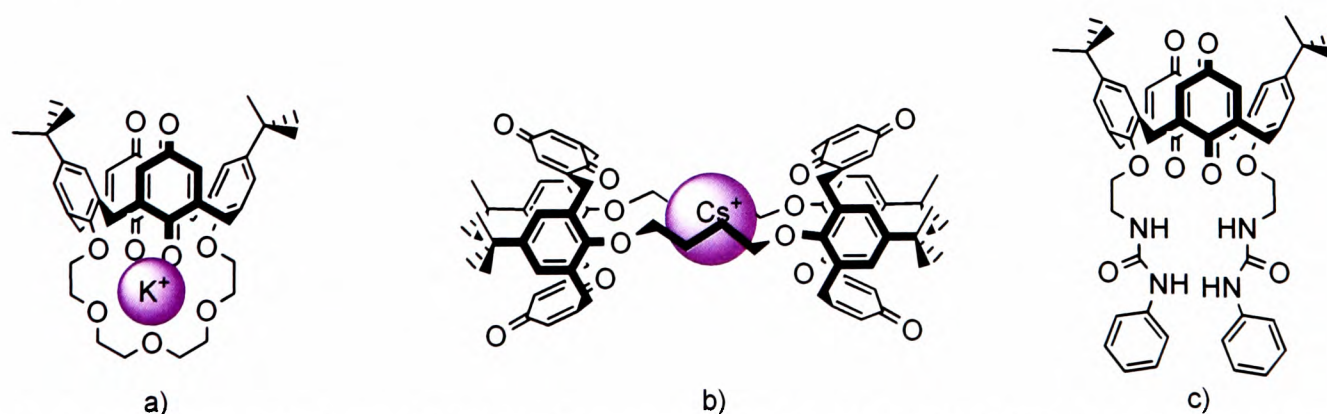


Figure 2.3 a) Potassium selective calix[4]diquinone crown ether b) calix[4]diquinone partial tube receptor for caesium and c) urea functionalised calix[4]diquinone

A number of calixarene based ion-pair receptors were introduced in Section 1.3.4 which exploited cooperativity to bind ion-pairs. Cooperative effects can be difficult to predict when designing ion-pair receptors as a number of equilibria exist in an ion-pair binding system (Figure 2.4). For example, the anion or cation alone may bind as shown by K_1 and K_3 respectively, the ion-pair may bind (K_2) or competing sequestration of the ion-pair from the receptor (K_{ip}) may occur. Ion-pair sequestration is particularly a problem in non-polar solvents.

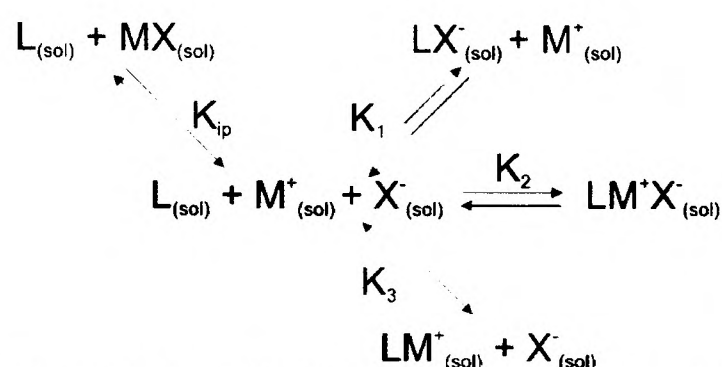


Figure 2.4 Diagram illustrating the various equilibria that can exist in an ion-pair binding system

Recently Venturi *et al.* have discussed the complexity of the equilibria and cooperativity in ion-pair binding systems.⁴⁷ They investigated the binding of the ion-pair tetramethylammonium chloride to the monotopic receptors, designed to bind the cation only (Figure 1.32a) and anion only (Figure 1.32b), and ditopic receptor (Figure 1.32c) in 4:1 CDCl₃/CD₃CN. Comparing the binding ability of the ditopic receptor to the monotopic receptors, cation binding was enhanced by the presence of the anion, but counter-intuitively, anion binding was inhibited by the cation. Therefore ion-pair binding may not always be superior to binding cations or anions individually.

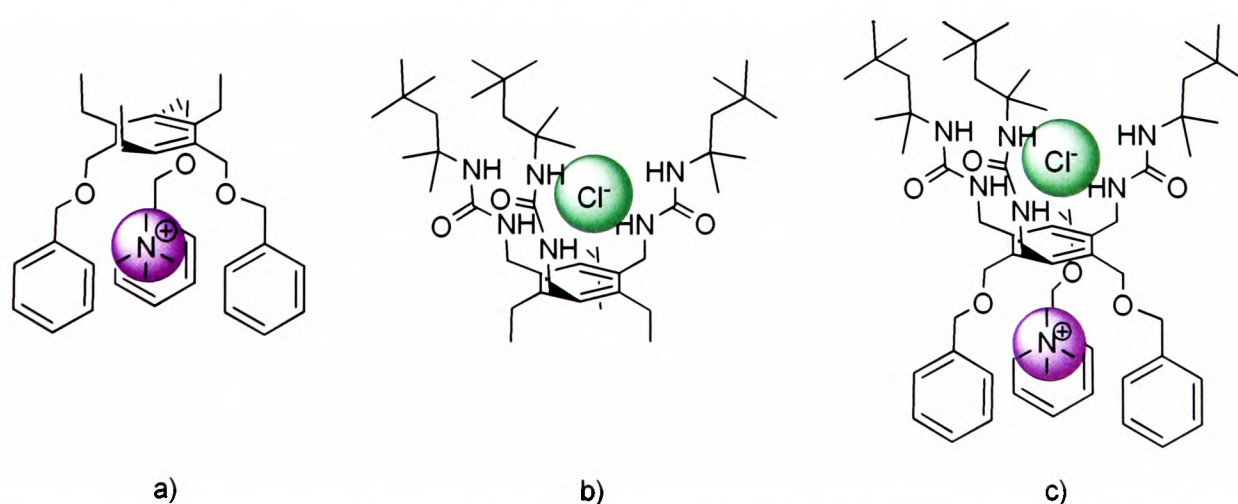


Figure 2.5 Venturi's a) monotopic receptor for cations b) monotopic receptor for anions and c) ditopic receptor for ion-pairs

A number of groups have reported calixarene based ion-pair receptors where the cation and/or anion influence ion-pair recognition. The receptor in Figure 2.6a binds solvent separated ion-pairs such as KCl.⁴⁸ The binding of potassium in the crown ethers causes a conformational change, which preorganises the amide groups for anion binding, and there is an enhanced binding of anions such as chloride, benzoate and acetate. Arduini and co-workers have reported a number of examples of ion-pair recognition controlled by anion allosteric effects, including the receptor in Figure 2.6b.^{49, 50} Coordinating anions, such as tosylate and chloride, hydrogen bond to the OH groups preorganising the cavity for binding a tetramethylammonium cation.

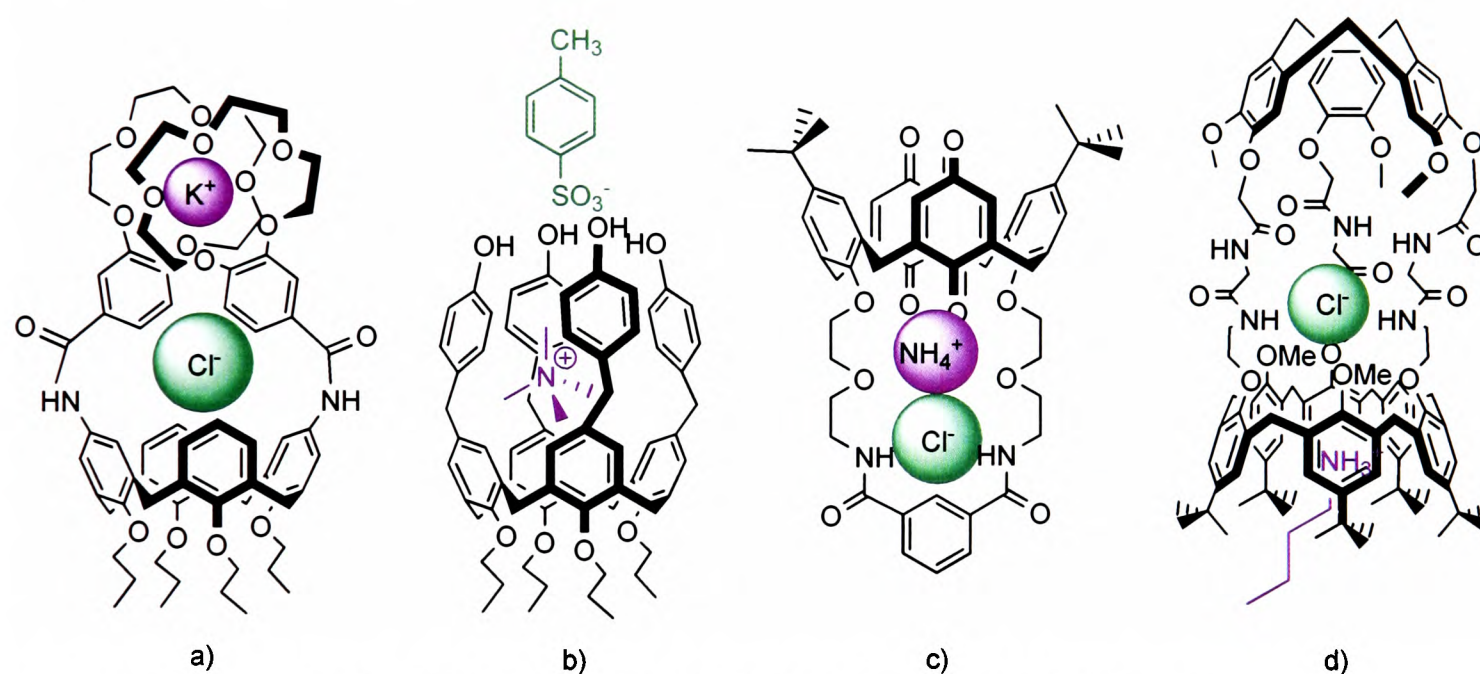


Figure 2.6 Ion-pair recognition controlled by the a) cation b) anion and c) and d) ion-pair

Beer and co-workers reported the first contact ion-pair heteroditopic receptors, which require both the cation and the anion for ion-pair recognition (Figure 2.6c).^{21, 22, 51} These receptors show little affinity for the cation or anion alone but enhanced binding of contact ion-pairs, such as NaCl and NH₄Cl. For this reason they were termed ‘cooperative AND’ ion-pair receptors since the ion-pair recognition follows Boolean AND logic. X-ray crystal structures of the receptor in Figure 2.6c, with and without a bound ion-pair, provided insight into the mechanism behind this unique ion-pair recognition. In the absence of the ion-pair, there is an intramolecular hydrogen bond between one of the quinone oxygens and the amide protons of the isophthalamide anion binding unit, whereas in the presence of NH₄Cl there is a

conformational change with the isophthalamide motif π - π stacking with one of the calix[4]diquinone rings. It was proposed that only ion-pair binding can compensate for the loss of the intramolecular hydrogen bonding interaction in the free receptor, accounting for the low affinity of the receptor for the cation or anion alone. Jabin has subsequently reported the calix[6]cryptamide, which only binds alkylammonium chloride ion-pairs and not the cation or anion alone (Figure 2.6d).⁵²

2.1.4. Aims of this Chapter

The focus of this chapter is the development of new calix[4]arene based ion-pair receptors. The design of the receptors is based on Beer's original cooperative AND ion-pair receptor (Figure 2.6c), where the lower rim of the calix[4]arene is functionalised with a macrocycle incorporating cation and anion binding sites in close proximity for binding contact ion-pairs (Figure 2.7a). In the original receptors, the cation binding site was based on *tert*-butylcalix[4]diquinone and the anion binding sites were isophthalamide derivatives. This work will be extended to investigate the effect of anion binding site variation. One of the ultimate aims is to synthesise a luminescent ion-pair receptor by incorporating a transition metal reporter group into the receptor design (Figure 2.7b). The synthesis and ion-pair binding properties of the calix[4]arene analogues will also be investigated.

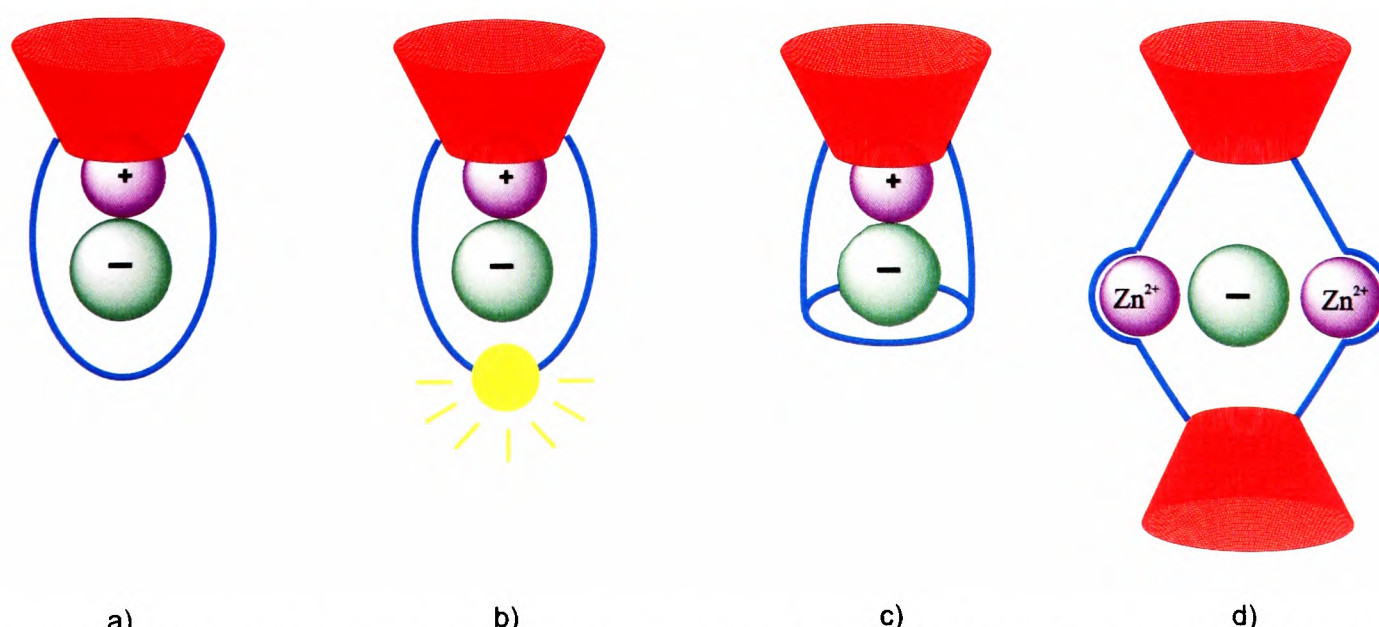


Figure 2.7 General receptor designs a) heteroditopic ion-pair receptor b) luminescent heteroditopic ion-pair sensor c) cryptand heteroditopic ion-pair receptor and d) calix[4]arene based partial tube zinc anion receptor

As an extension of this work, the synthesis of the cryptand analogues of the ion-pair receptors (Figure 2.7c) will be explored. It is hoped that this will enhance ion-pair recognition and discrimination.

The final project of this chapter investigates the synthesis of calix[4]arene structures, which are designed to bind anions via Lewis acidic zinc centres (Figure 2.7d).

2.2. *tert*-Butylcalix[4]diquinone Ion-Pair Receptors

The synthesis of the new *tert*-butylcalix[4]diquinone ion-pair receptors in Figure 2.8, based on Beer's original design, was initially pursued to investigate the effect of varying the nature of the anion binding unit. The *tert*-butyl isophthalamide derivative **1** would be synthesised to investigate whether the *tert*-butyl group prevents the π - π stacking interaction between the anion binding unit and the calix[4]diquinone of the cation binding unit, which appears to be critical to cooperative AND ion-pair recognition. The pyridine derivative **2** would also be prepared to study the effect of preorganisation.

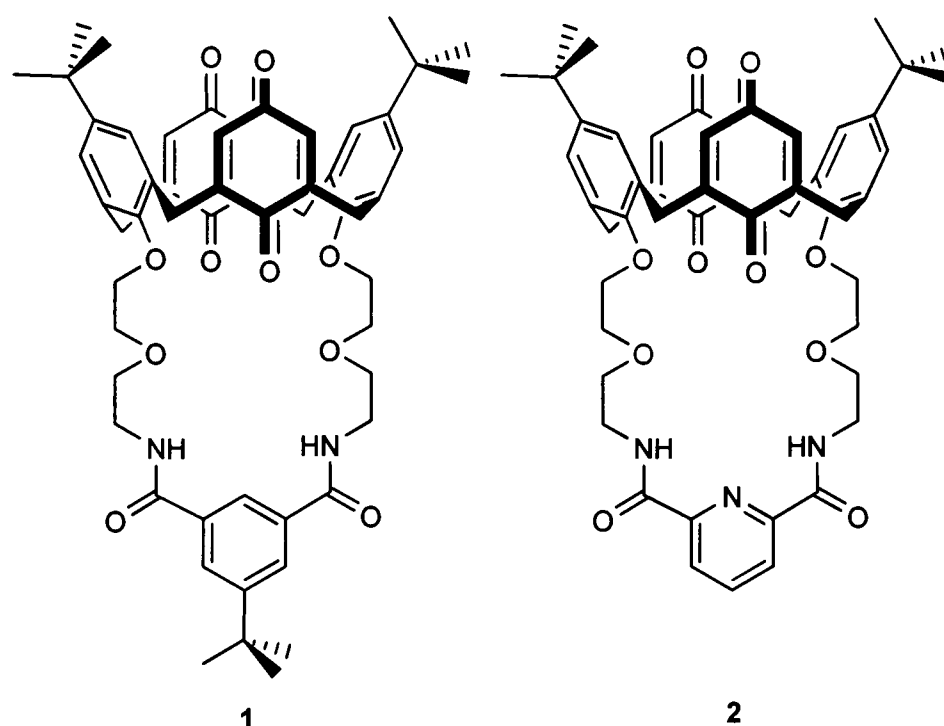
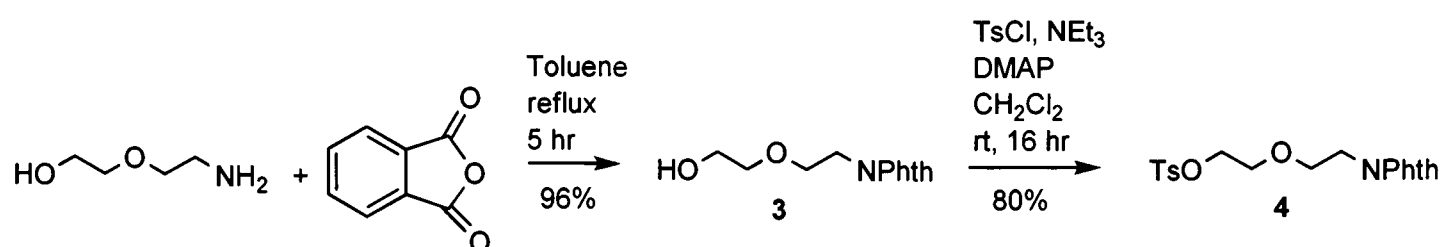


Figure 2.8 Design of target *tert*-butylcalix[4]diquinone ion-pair receptors

2.2.1. Synthesis of Receptors **1** and **2**

In order to synthesise the target receptors, precursor **4** was synthesised for attachment to the lower rim of *tert*-butylcalix[4]arene (Scheme 2.5). 2-(2-Aminoethoxy)ethanol and phthalic

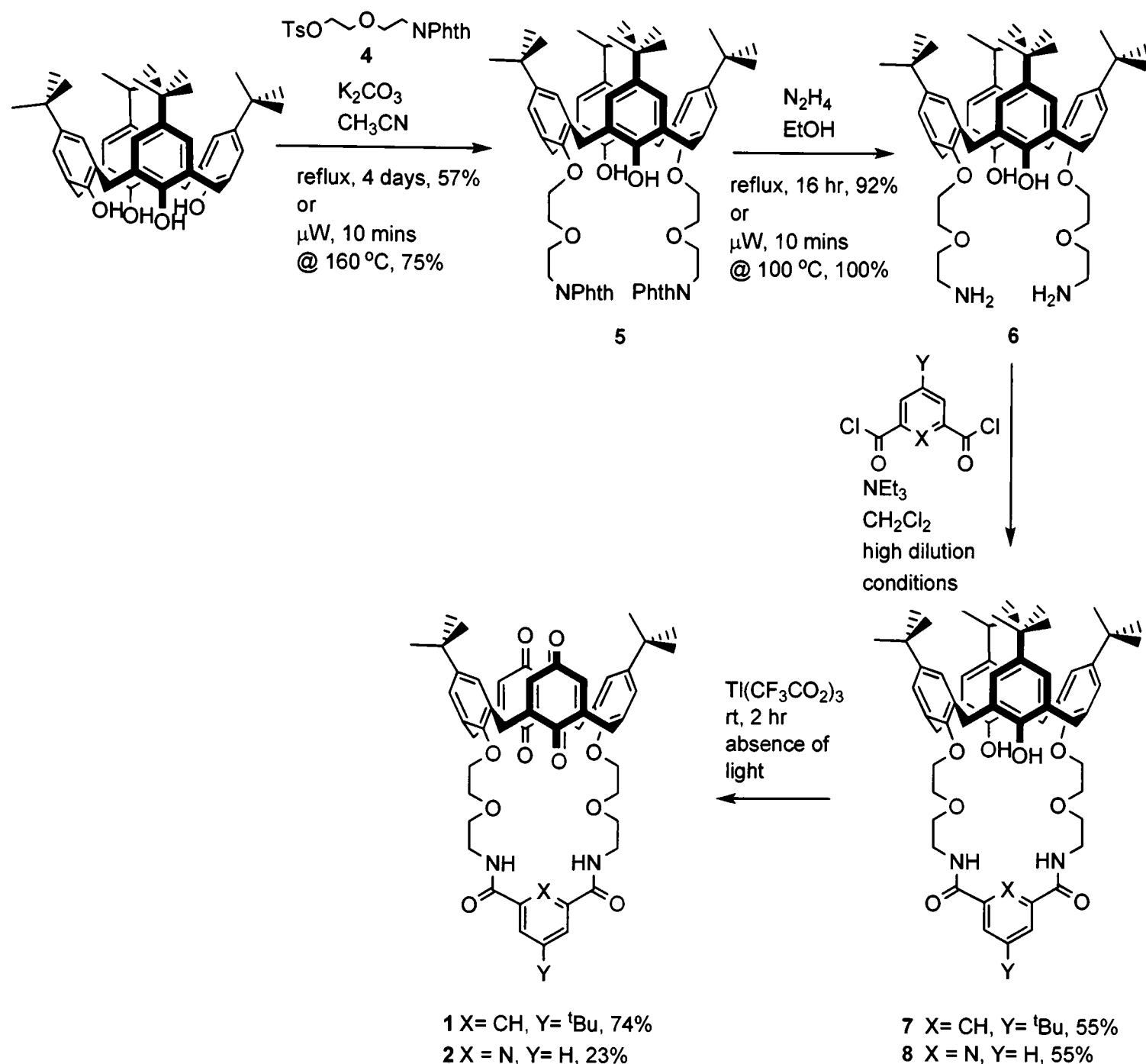
anhydride were heated under reflux for 5 hours in toluene to give precursor **3** in 96% yield.⁵³ Precursor **3** was reacted with tosyl chloride in the presence of triethylamine and a catalytic amount of DMAP in CH₂Cl₂ to give **4** in 80% yield.²²



Scheme 2.5 Synthesis of precursors **3** and **4**

The target *tert*-butylcalix[4]diquinone receptors were synthesised by adapting the established synthetic strategy in Scheme 2.6. The protected amine derivative **5** was synthesised in 57% yield by heating a suspension of *tert*-butylcalix[4]arene, an excess of **4** and two equivalents of K₂CO₃ in CH₃CN under reflux for four days.²² A microwave synthesis of **5** was also developed, where the reactants were heated at 160 °C for 10 minutes under microwave irradiation. In addition to reducing the reaction time, **5** was isolated in the improved yield of 75% following recrystallisation from CH₂Cl₂/EtOH.

The phthalimide protecting groups were removed using hydrazine monohydrate either by heating under reflux for 16 hours or in the microwave for 10 minutes at 100 °C. The resulting bis-amine **6** was reacted with *tert*-butyl isophthaloyl dichloride and 2,6-bis(chlorocarbonyl)pyridine to give the new macrocyclic precursors **7** and **8** respectively in satisfactory yields. The target receptors **1** and **2** were synthesised in 74% and 23% yields respectively by oxidation of **7** and **8** using thallium(III) trifluoroacetate in a TFA solution. Both receptors were characterised by ¹H and ¹³C NMR spectroscopy, electrospray mass spectrometry and melting point analysis.



Scheme 2.6 Preparation of calix[4]diquinone receptors **1** and **2**

Single crystals of receptor **1** were grown by slow evaporation of a CH₂Cl₂ solution and the crystal structure, determined by the University of Oxford X-Ray Crystallography Service, is shown in Figure 2.9.⁵⁴ The calix[4]diquinone is in the 1,3-alternate conformation with the pairs of *tert*-phenyl and quinone rings approximately parallel. The macrocycle is in an extended conformation with some disorder in the *tert*-butyl group of the isophthalamide motif. There are intramolecular hydrogen bonding interactions between the amide protons and one of the quinone carbonyl oxygens with N[⋯]O distances of 3.123 and 3.152 Å.

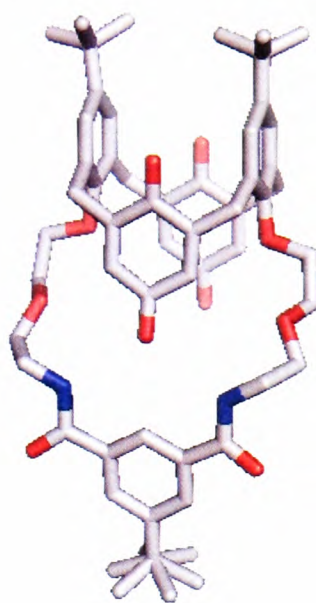


Figure 2.9 Single crystal X-ray structure of receptor 1

2.2.2. Ion-Pair Binding Studies of Receptors 1 and 2

2.2.2.1. Anion Binding Studies

The chloride binding ability of receptor **1** was studied by ^1H NMR spectroscopy in CD_3CN based solvent systems. Titrations were carried out in the presence and absence of coordinating ammonium cations, monitoring the chemical shifts of the anion binding unit protons upon addition of tetrabutylammonium (TBA) chloride. There were very small downfield shifts of the amide protons *c* and isophthaloyl proton *b* upon addition of chloride in the absence of coordinating cations (Table 2.1, Figure 2.10). However, there was no evidence of chloride binding, given the linear relationship between the chemical shift changes and anion concentration. Equally, there were insignificant chemical shift changes upon addition of one equivalent of NH_4PF_6 (Figure 2.10b). However, addition of chloride anions to a 1:1 mixture of the receptor and ammonium cations led to significant downfield shifts of protons *b* and *c* (Figure 2.10a).

Job Plot analysis of the titration data revealed 1:1 binding and it was possible to derive association constants for binding from winEQNMR2⁵⁵ analysis of the titration data, since binding was observed to be fast on the NMR timescale. As expected, there was no evidence of chloride binding in the absence of ammonium cations, and the association constant for receptor **1** in the presence of ammonium cations was calculated to be greater than 10^4 M^{-1} .

in CD₃CN. Therefore, the more competitive solvent system 98:2 CD₃CN/D₂O was used in order to obtain quantitative data and in this solvent system, log K_{Cl⁻} was calculated to be 3.4 from the amide chemical shift data (Table 2.1).

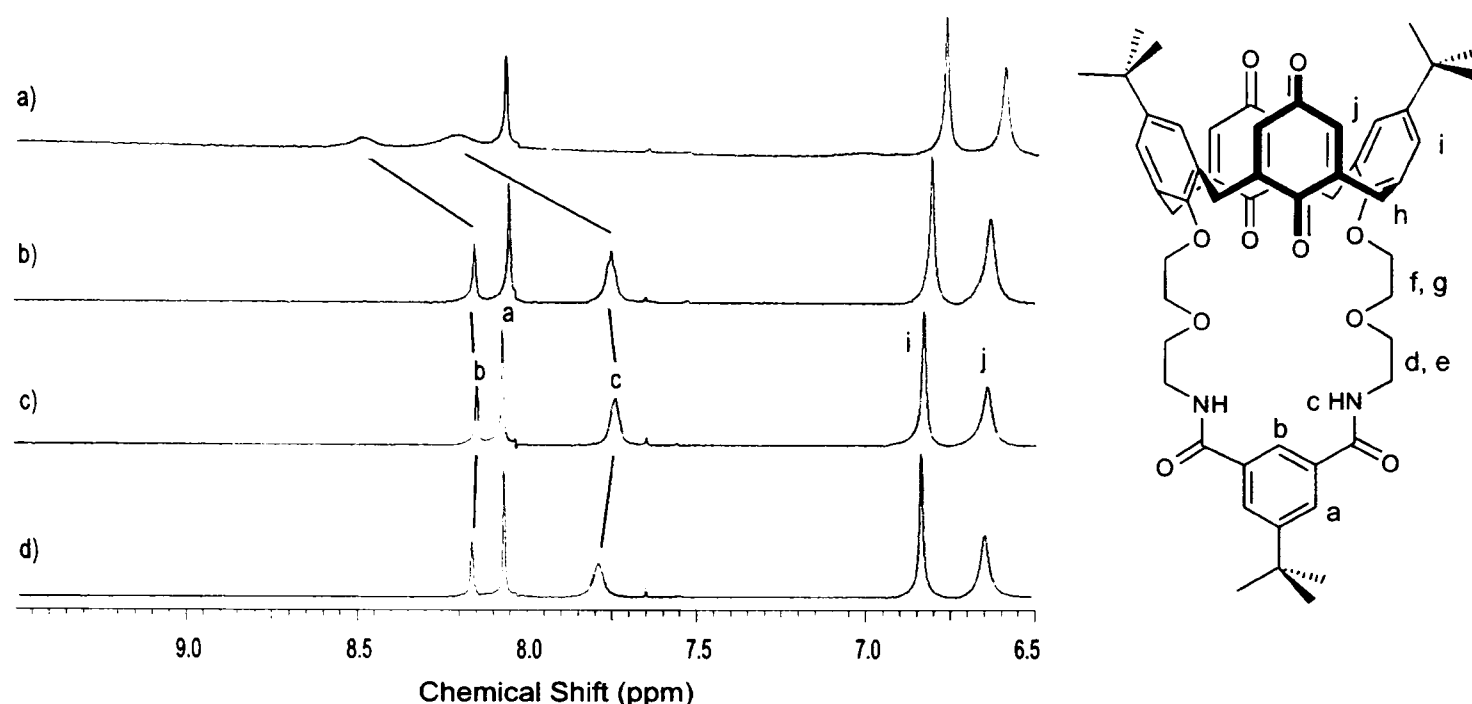


Figure 2.10 Aromatic region of the ¹H NMR spectrum of receptor **1** in the presence of one equivalent of a) NH₄Cl b) NH₄PF₆ c) no guest and d) TBACl in 98:2 CD₃CN/D₂O at 298 K

	$\Delta\delta_{\text{amide}}$ (ppm) ^a	$\Delta\delta_{\text{isoH}}$ (ppm) ^a	log K _{Cl⁻} ^a	$\Delta\delta_{\text{amide}}$ (ppm) ^b	$\Delta\delta_{\text{isoH}}$ (ppm) ^b	log K _{Cl⁻} ^b
1	0.047	0.028	-	0.051	0.017	-
1 .NH ₄ PF ₆	0.947	0.705	> 4	0.478	0.342	3.4
2	nd	nd	nd	0.028	na	-
2 .NH ₄ PF ₆	nd	nd	nd	0.252	na	3.1*

Table 2.1 Chemical shift changes of the amide and isophthaloyl protons upon addition of one equivalent of TBACl in the presence and absence of NH₄PF₆ and association constants derived from the amide chemical shift data in ^a CD₃CN and ^b 98:2 CD₃CN/ D₂O at 298K. - = no evidence of binding. Errors < 10%. * = errors < 15%. nd = not determined. na = not applicable

The aliphatic region of the ¹H NMR titration spectra can provide some information about cation binding, although this will be probed in more detail using UV/visible spectroscopy. Receptor **1** has broad signals particularly for proton *h* in the absence of guest ions, and there is little change upon addition of one equivalent of cations (Figure 2.11b), indicating no cation binding. However, in the presence of the ion-pair NH₄Cl the signals for proton *h* are much sharper and split further apart, suggesting a conformational change of the calix[4]diquinone unit. It is most likely that the calix[4]diquinone is still in the cone conformation due to the presence of two doublets. Additionally the signals for alkyl protons *e-g* are shifted due to

cation binding in the presence of the chloride anion.

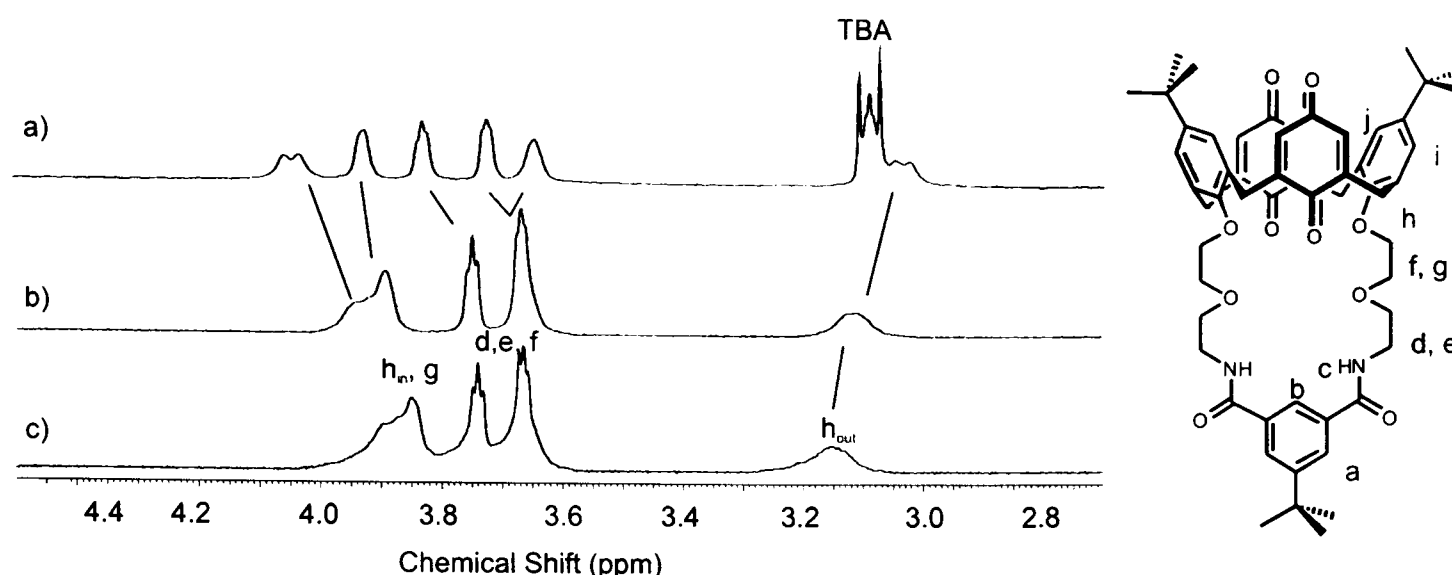


Figure 2.11 Aliphatic region of the ^1H NMR spectrum of receptor **1** in the presence of one equivalent of a) NH_4Cl b) NH_4PF_6 and c) no guest in 98:2 $\text{CD}_3\text{CN}/\text{D}_2\text{O}$ at 298 K

The results from the ^1H NMR titration experiments demonstrate cooperative AND ion-pair recognition, where receptor **1** shows little affinity for either of the ‘free’ ions but enhanced binding of the ion-pair NH_4Cl . This shows that the *tert*-butyl substituent on the isophthalamide unit does not prevent ion-pair recognition.

Analogous titration experiments were carried out for receptor **2** in 98:2 $\text{CD}_3\text{CN}/\text{D}_2\text{O}$, also demonstrating cooperative AND ion-pair recognition of NH_4Cl with an association constant of $\log 3.1$ (Table 2.1). Comparison of the association constants for the two receptors shows that receptor **1** binds NH_4Cl more strongly than receptor **2** unlike Jurczak’s receptors (Figure 1.20b in Section 1.3.2.2), where the pyridine receptor binds anions more strongly than the isophthalamide one due to preorganisation.^{56, 57} Receptors **1** and **2** appear to behave more like the acyclic receptors of Crabtree⁵⁸ (Figure 1.20a), where the reduced affinity of the pyridine based receptor was attributed to the electrostatic repulsion between the lone pair of the pyridine and the negatively charged anion. It is likely that the preorganisation gained from inclusion of the pyridine motif is not as significant as for Jurczak’s receptors, due to the inherent preorganisation of the *tert*-butylcalix[4]arene scaffold.

Previously cooperative AND ion-pair recognition by the receptor has been demonstrated upon addition of the anion to a 1:1 mixture of the cation and receptor, however, binding of the

ion-pair itself has not been investigated. This is more difficult to study since the ion-pairs of interest, such as NH_4Cl , are insoluble in organic solvents and the receptors are insoluble in water. Therefore, the ion-pair was dissolved in a small volume of water, while the receptor was dissolved in a solvent system which included a small percentage of water. This was to prevent precipitation of the ion-pair but ensure that the system was not too competitive for ion-pair binding. The solvent system chosen to study the binding of aqueous NH_4Cl was 0.5% $\text{H}_2\text{O}/\text{CD}_3\text{CN}$ where H_2O was used in favour of D_2O to prevent deuterium exchange of the amide protons in the receptor. For receptor **1**, the isophthaloyl and amide proton peaks both shifted significantly downfield upon the addition of up to two equivalents of NH_4Cl indicating binding of the ion-pair (Figure 2.12). However, these peaks began to shift upfield when more than two equivalents of NH_4Cl were added, and after ten equivalents the isophthaloyl proton peak had returned to its original chemical shift of 8.16 ppm.

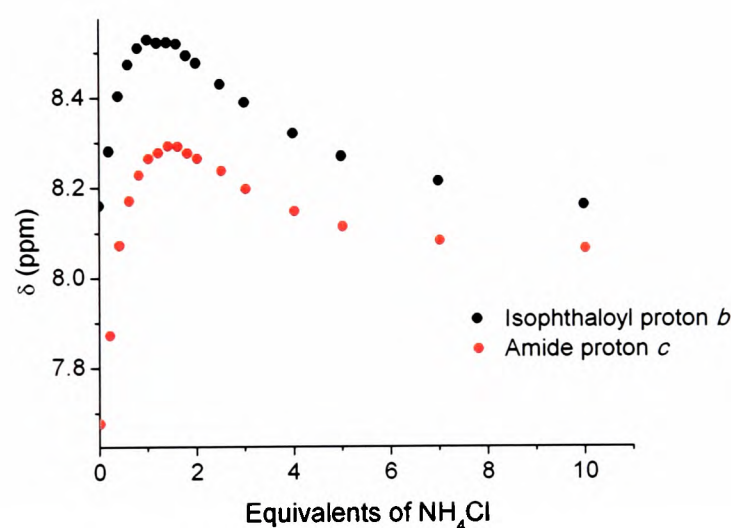


Figure 2.12 Variation in the chemical shift of the amide and isophthaloyl protons upon addition of aqueous NH_4Cl to receptor **1** in 0.5% $\text{H}_2\text{O}/\text{CD}_3\text{CN}$ at 298 K

Consideration of the equilibria involved in ion-pair binding (Figure 2.4) provides an explanation for this behaviour. The experimentally determined association constant is largely dependent on the anion association constant K_1 and ion-pair association constant K_2 , but solvent can also have a significant influence. In the titrations carried out in CD_3CN , the equilibrium constant for ion-pair sequestration, K_{ip} , was not a dominant contributor and the observed anion association constant was larger than K_1 as a result of cooperative binding of

the ion-pair.⁵⁹ However, in the more competitive solvent system 0.5% H₂O/CD₃CN, K_{ip} becomes more significant at increasing concentrations of aqueous NH₄Cl, and sequestration of the ion-pair results in the upfield shift of the amide and isophthaloyl peaks. On account of these results, the ion-pair binding properties of receptor **2** were not investigated. It was hoped that UV/visible spectroscopy would be more suitable to study direct ion-pair binding.

2.2.2.2. Cation Binding Studies

The cation binding ability of the receptors was investigated using UV/visible spectroscopy by monitoring the characteristic calix[4]diquinone $n-\pi^*$ absorption band around 330 nm. Upon addition of sodium and ammonium cations with non-coordinating counterions, there was little change in the absorption spectra indicating no or very weak binding (Figure 2.13a). The addition of potassium ions induced small changes and it was possible to obtain an association constant for 1:1 binding using SPECFIT⁶⁰ (Table 2.2). However, in the presence of one equivalent of chloride, the absorption spectra changed significantly when increasing amounts of the cation solution were added (Figure 2.13b). Job Plot analysis revealed 1:1 binding and the titration spectra were analysed using SPECFIT to obtain association constant values (Table 2.2). It was not possible to obtain an association constant for the binding of sodium ions in the presence of chloride ions due to large errors, despite numerous repetitions of the titration. The addition of TBACl also did not change the absorption spectra.

Both receptors exhibit cooperative AND ion-pair recognition of NaCl and NH₄Cl with a preference for binding NH₄Cl over KCl and NaCl (Table 2.2). These results are consistent with results from the original isophthalamide cooperative AND receptor (Figure 2.6c). The magnitude of the association constants for receptors **1** and **2** are smaller than for the original receptor. For receptor **1** this is not unexpected given the electron donating nature of the *tert*-butyl group on the isophthalamide, which decreases the acidity of the amide protons.

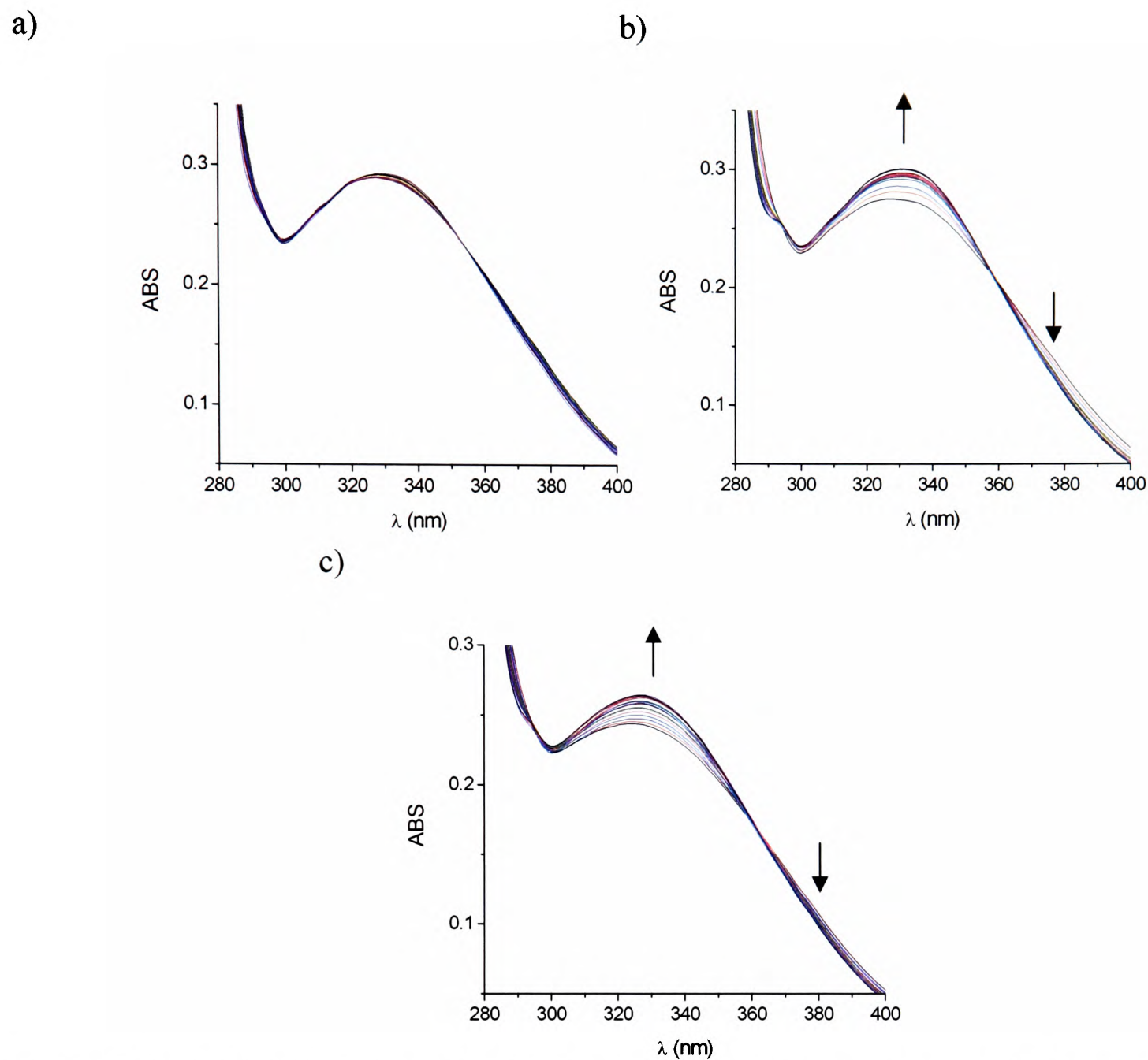


Figure 2.13 Calix[4]diquinone n- π^* absorbance band of receptor **1** upon addition of NH_4PF_6 in the a) absence and b) presence of TBACl in CH_3CN and c) in the presence of aqueous NH_4Cl in 0.5% $\text{H}_2\text{O}/\text{CH}_3\text{CN}$ at 298 K

	log K_{M^+}		
	Na^+	K^+	NH_4^+
1 ^a	-	3.26	-
1 .TBACl ^a	*	3.97	4.60
1 .MCl ^b	3.76	3.84	4.28
2 ^a	-	3.25	-
2 .TBACl ^a	*	3.56	3.90

Table 2.2 Association constants derived from SPECFIT analysis of UV/visible spectroscopic titrations in ^a CH_3CN and ^b 0.5% $\text{H}_2\text{O}/\text{CH}_3\text{CN}$ at 298 K. - = no evidence of binding. Errors < 15%. * = evidence of binding but errors > 15%

However, the lower association constants for receptor **2** are most likely due to the lone pair of the pyridine weakening ion-pair binding as discussed in Section 2.2.2.1.

Direct ion-pair binding was also investigated using UV/visible spectroscopy by titrating small volumes of an aqueous solution of the ion-pair KCl, NH_4Cl or NaCl into a 0.5%

H₂O/CH₃CN solution of the receptor. The change in absorbance indicated binding of the ion-pair to receptor **1** (Figure 2.13c). It was possible to obtain association constants (Table 2.2) as unlike the analogous ¹H NMR titration experiments, the binding curve demonstrates that sequestration of the ion-pair does not appear to be significant over the concentration range investigated (Figure 2.14). This is most likely because the concentration used for the UV/visible titrations was an order of magnitude lower than those for the NMR experiments. The same trend is observed as for indirect ion-pair binding with stronger binding of NH₄Cl followed by KCl and NaCl.

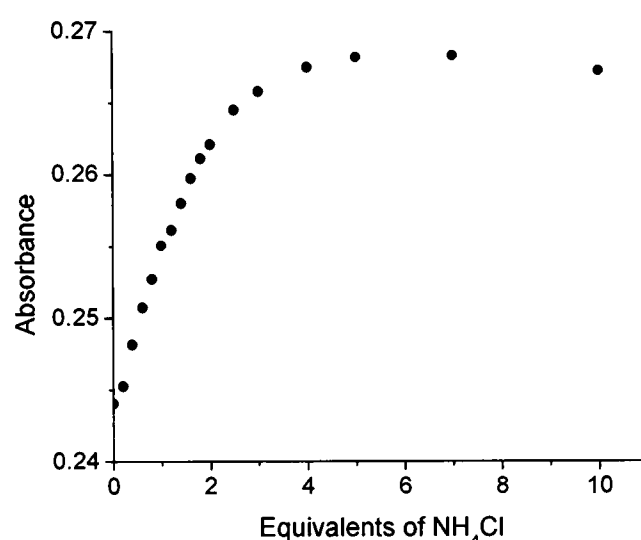


Figure 2.14 Binding curve from the addition of 10 equivalents of aqueous NH₄Cl to receptor **1** in 0.5% H₂O/CH₃CN at 298 K

The ion-pair binding of NH₄Cl to receptor **2** was also investigated in 0.5% H₂O/CH₃CN. A binding curve similar to that in Figure 2.12 was obtained, where the increase of absorbance for up to two equivalents of NH₄Cl indicated ion-pair binding. However, after two equivalents the absorbance began decreasing, most likely due to sequestration of the ion-pair from the receptor at high concentrations of NH₄Cl, and it was not possible to obtain an association constant. Attempts to limit sequestration by dissolving the ion-pair in 10% H₂O/CH₃CN rather than H₂O led to precipitation of the ion-pair during the course of the titration.

Based on the results from both ¹H NMR and UV/visible spectroscopy, the ability to study direct ion-pair binding depends on the receptor, spectroscopic technique and the choice of solvent system. Association constants for receptor **1** were obtained from UV/visible

spectroscopy titrations in 0.5% H₂O/CH₃CN, whereas ion-pair sequestration competed with ion-pair binding in other ¹H NMR and UV/visible titration experiments. Unfortunately reducing the water content of the solvent system led to precipitation problems and therefore, direct ion-pair binding was not investigated any further.

2.2.2.3. Electrochemistry of Receptor 1

In addition to the optical properties of the receptors discussed in Section 2.2.2.2, the calix[4]diquinone unit can theoretically undergo a four electron reduction to the tetraanion (Figure 2.15). Electrochemical studies of receptor 1, in the presence and absence of ions, were carried out in CH₃CN under a N₂ atmosphere using cyclic voltammetric (CV) and square wave voltammetric (SWV) techniques.

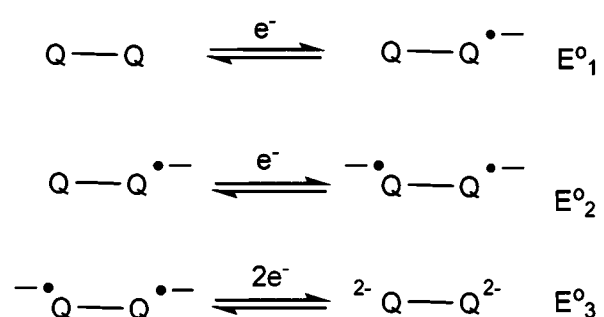


Figure 2.15 Four electron electrochemical reduction of the neutral calix[4]diquinone, Q-Q, to the tetraanion via the neutral radical and radical dianionic species

Figure 2.16 shows the cyclic and square wave voltammograms of receptor 1 at different scan rates in CH₃CN. For ease of discussion, the redox couples have been labelled with a number for the cathodic wave and a number plus a prime for the anodic wave, where present. Redox couples 1/1' and 2/2', at cathodic wave potentials of -0.67 V and -0.85 V respectively referenced to an Ag/AgCl reference electrode, are two quasi-reversible one electron transfers, which can be ascribed to the processes E^o₁ and E^o₂ in Figure 2.15. Additionally there is a broad prewave labelled 4, which has also be observed in related *tert*-butylcalix[4]diquinone systems.^{18, 20} Finally, redox wave 3 at -1.55 V is believed to arise from an irreversible two electron transfer. Casnati and co-workers have suggested that the irreversibility of this wave may be due to the formation of an insoluble hydroquinone species.⁶¹

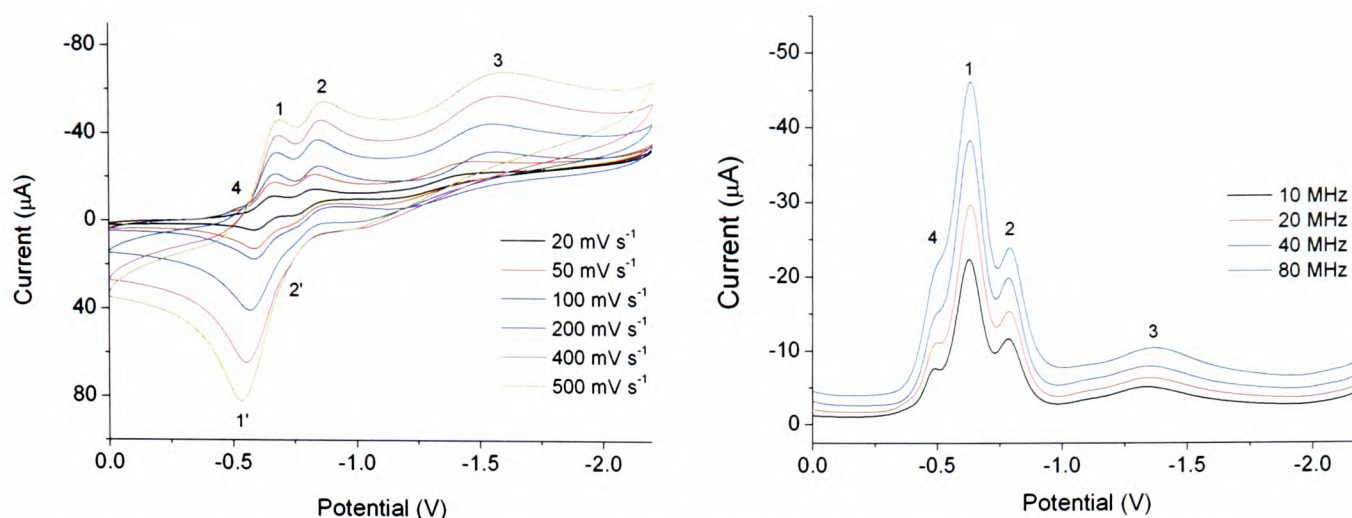


Figure 2.16 Cyclic and square wave voltammograms of receptor **1** at different scan rates in CH_3CN at 298 K. Conditions: 4 mM solution of receptor **1**, 0.1 M TBAPF_6 supporting electrolyte, glassy carbon working electrode, platinum auxiliary electrode, Ag/AgCl reference electrode

The effect of cations, such as potassium and sodium, on the redox waves was then investigated by CV at 100 mV s^{-1} and SWV at 30 Hz. Ammonium cation binding was not explored even though these cations were shown to bind more strongly than potassium by UV/visible spectroscopy. This is because the addition of ammonium cations resulted in EC mechanistic behaviour in a related calix[4]diquinone system, which was attributed to strong interactions between the ammonium cations and the radical anions formed electrochemically.¹⁸ Addition of one equivalent of potassium cations leads to an anodic shift of redox couples 1/1' and 3 and a cathodic shift of redox couple 2/2', although it was not possible to quantify these shifts (Figure 2.17b). However, these new redox waves all disappear upon addition of an excess of potassium cations. Initially it was believed this was due to an insoluble film coating the electrode surface, but cleaning the electrode did not restore the current. Similar results were obtained upon addition of sodium cations and Figure 2.17b shows a comparison of the CVs of receptor **1** in the presence of one equivalent of potassium and sodium.

Having demonstrated the effect of cations on the electrochemistry of receptor **1**, CVs and SWVs were recorded in the presence of chloride anions and ion-pairs. Addition of up to five equivalents of TBACl led to no change in the potential of the redox waves but an increase

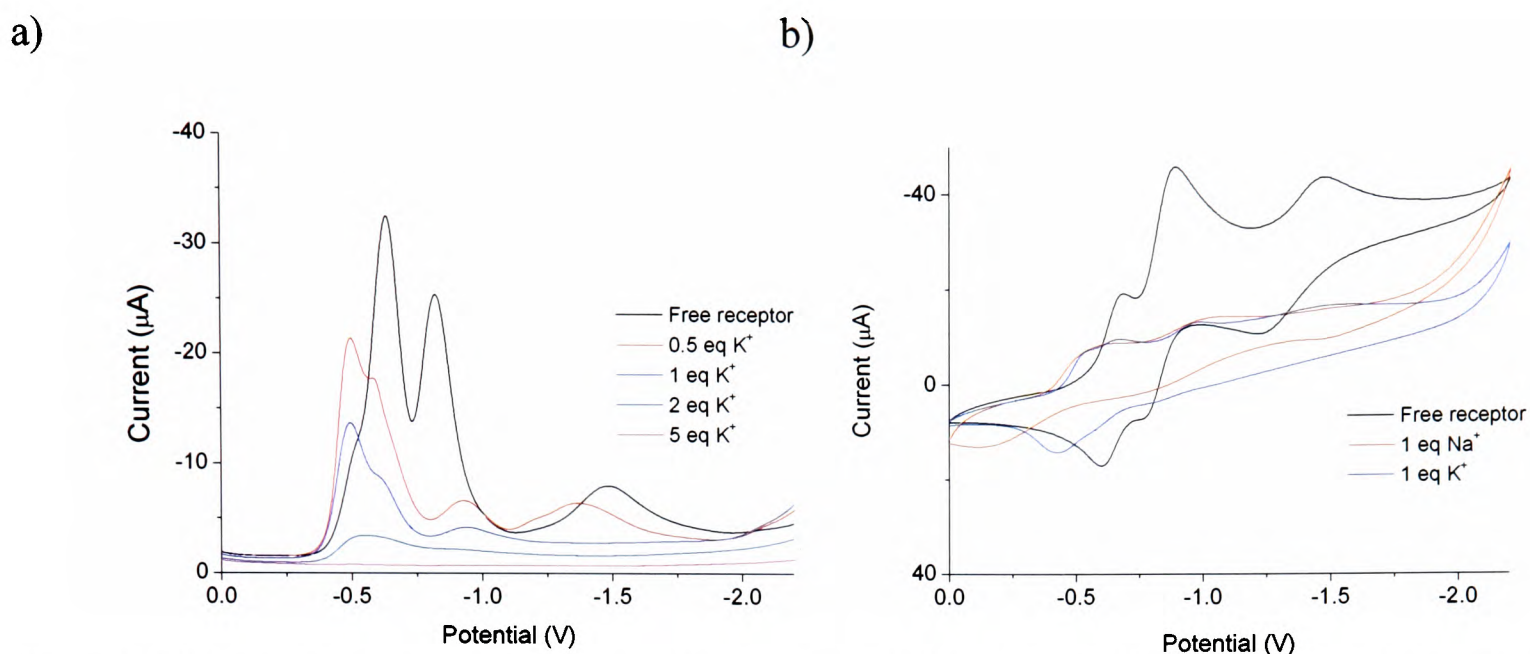


Figure 2.17 a) Square wave voltammograms of receptor **1** at 30 Hz upon addition of up to 5 equivalents of KPF_6 and b) cyclic voltammograms of receptor **1** at 100 mV s^{-1} in the presence of one equivalent of potassium or sodium cations in CH_3CN at 298 K

in the current (Figure 2.18). However, anodic shifts of all three redox waves were observed upon addition of one equivalent of potassium cations to this solution of the receptor and chloride anions. Unfortunately, addition of more than one equivalent of potassium ions led to precipitation of the ion-pair, but there were no further shifts of the redox waves. Figure 2.18 also shows the CV and SWV of the receptor in the presence of one equivalent of potassium cations for comparison, and there appears to be no difference in the redox wave shifts in the presence of the ion-pair.

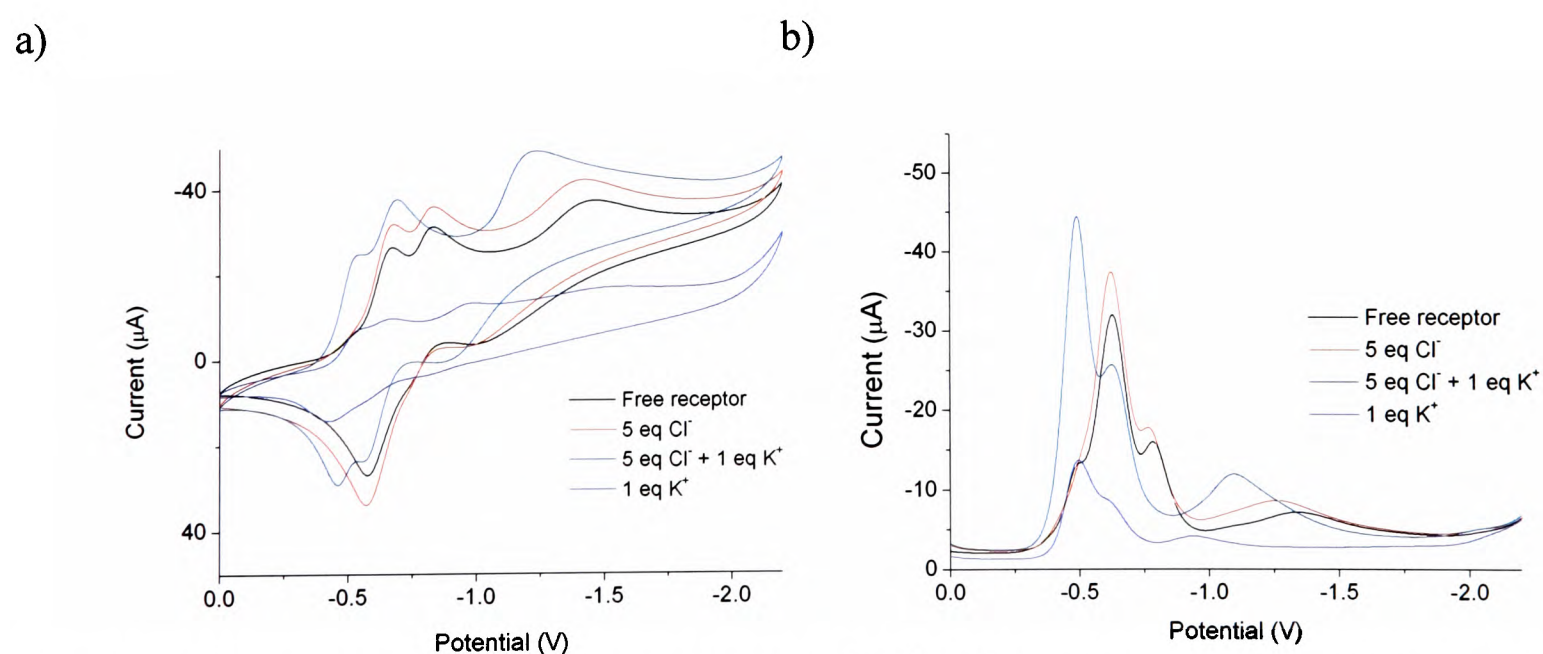


Figure 2.18 a) Cyclic voltammograms recorded at 100 mV s^{-1} and b) square wave voltammograms recorded at 30 MHz of receptor **1** in the presence of various guest ions in CH_3CN at 298 K

The experiment was repeated, but in the presence of only one equivalent of chloride, to prevent precipitation of the ion-pair upon addition of excess cations. Addition of

0.5 equivalents of potassium to a 1:1 mixture of the receptor and chloride anions led to the appearance of a new wave at -0.5 V and an anodic shift of the wave for redox wave 3 (Figure 2.19). The waves for redox couples 1/1' and 2/2' were still present but these disappeared when one equivalent of cations was added. Disappointingly, the addition of excess potassium led to a loss of current. There was no evidence of precipitation and cleaning the electrodes did not restore the current. Similar results were obtained upon addition of sodium cations, although the addition of one equivalent of sodium did not lead to a disappearance of the 1/1' and 2/2' redox waves.

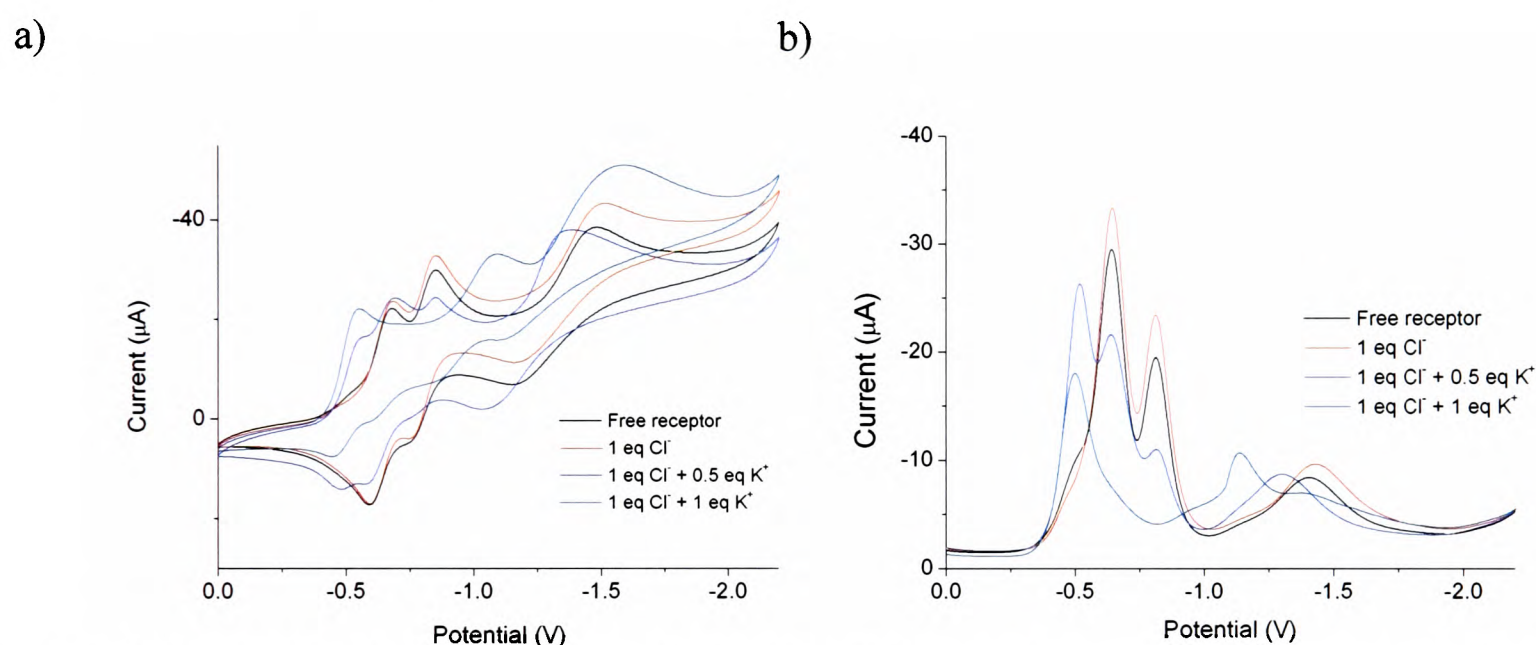


Figure 2.19 a) Cyclic voltammograms recorded at 100 mV s^{-1} and b) square wave voltammograms recorded at 30 MHz of receptor **1** in the presence of various guest ions in CH_3CN at 298 K

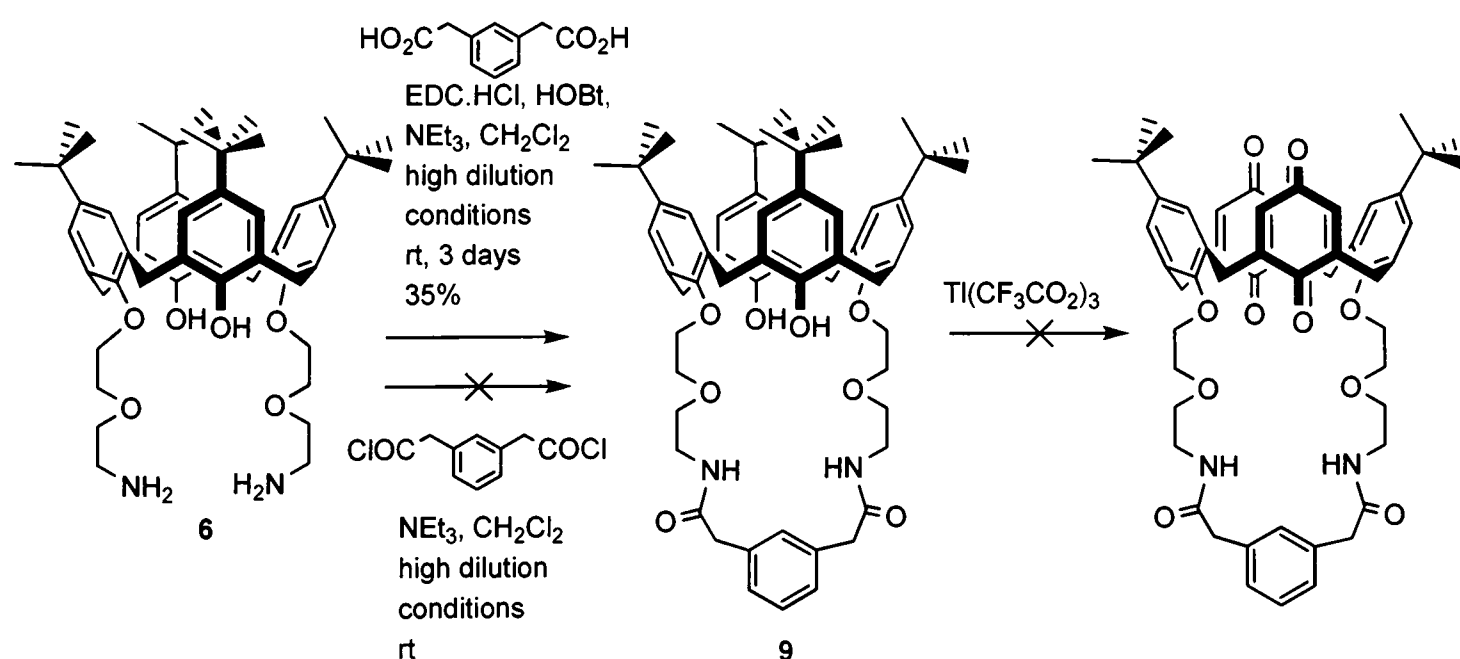
It is difficult to draw definitive conclusions from the electrochemical studies due to conflicting results, both between cations and in the presence of ion-pairs. It would appear that the mechanism for ion-pair binding is complex, as different voltammograms were obtained in the presence of the ion-pair when there was an excess of chloride (Figure 2.18) and equimolar amounts of the anion and cation (Figure 2.19). The results do show that receptor **1** binds both sodium and potassium cations, both in the absence and presence of chloride anions. Therefore the receptor does not exhibit cooperative AND ion-pair recognition electrochemically, most likely because the background electrolyte disrupts the proposed intramolecular hydrogen bond required for cooperative AND ion-pair recognition.

2.2.3. Towards Ditopic Receptors with Anion Binding Site Variation

The synthesis of calix[4]diquinone receptors, with anion binding units based on two isomers of bipyridine and 1,3-phenylenediacetamide, was explored to investigate the effect of anion binding site variation on ion-pair recognition. A similar synthetic strategy to earlier receptors was devised, where the macrocycle precursor would be prepared first from compound **6** before oxidation to the target calix[4]diquinone receptor using thallium trifluoroacetate.

2.2.3.1. Towards a Receptor Containing 1,3-Phenylenediacetamide

Initially the synthesis of the ditopic receptor incorporating the 1,3-phenylenediacetamide group was attempted since 1,3-phenylenediacetic acid is commercially available. The acid chloride was prepared by refluxing the carboxylic acid in thionyl chloride overnight under a N_2 atmosphere and reacted immediately with bis-amine **6** in CH_2Cl_2 under high dilution conditions (Scheme 2.7). However, the preparation of macrocycle **9** proved problematic and this was attributed to problems forming the acid chloride. The isolation of 1,3-phenylenediacetyl chloride prior to macrocyclisation was attempted unsuccessfully using a literature procedure,⁶² and therefore, an alternative synthesis of macrocycle **9** was devised.



Scheme 2.7 Towards the synthesis of the receptor based on 1,3-phenylenediacetamide

This relied on activation of the carboxylic acid for reaction with bis-amine **6** using the

coupling reagent *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (EDC.HCl), which is commonly used in amide bond formation⁶³⁻⁶⁵ in conjunction with reagents such as hydroxybenzotriazole (HOBt). A solution of the activated carboxylic acid was prepared by stirring a suspension of 1,3-phenylenediacetic acid, HOBt and EDC.HCl in dry CH₂Cl₂ until the solid had dissolved. This was reacted with the bis-amine **6** under high dilution conditions and the solution was stirred at room temperature for three days. Following purification by silica gel chromatography, it was possible to isolate macrocycle **9** in 35% yield. The ¹H NMR spectrum of the macrocycle reveals the presence of a single macrocyclic species with the calix[4]arene in the cone conformation, as shown by the pair of doublets for the proton *k* (Figure 2.20). The peak at *m/z* 1003.58 in the electrospray mass spectrum indicates that this is [9 + Na]⁺ rather than the [2+2] macrocycle.

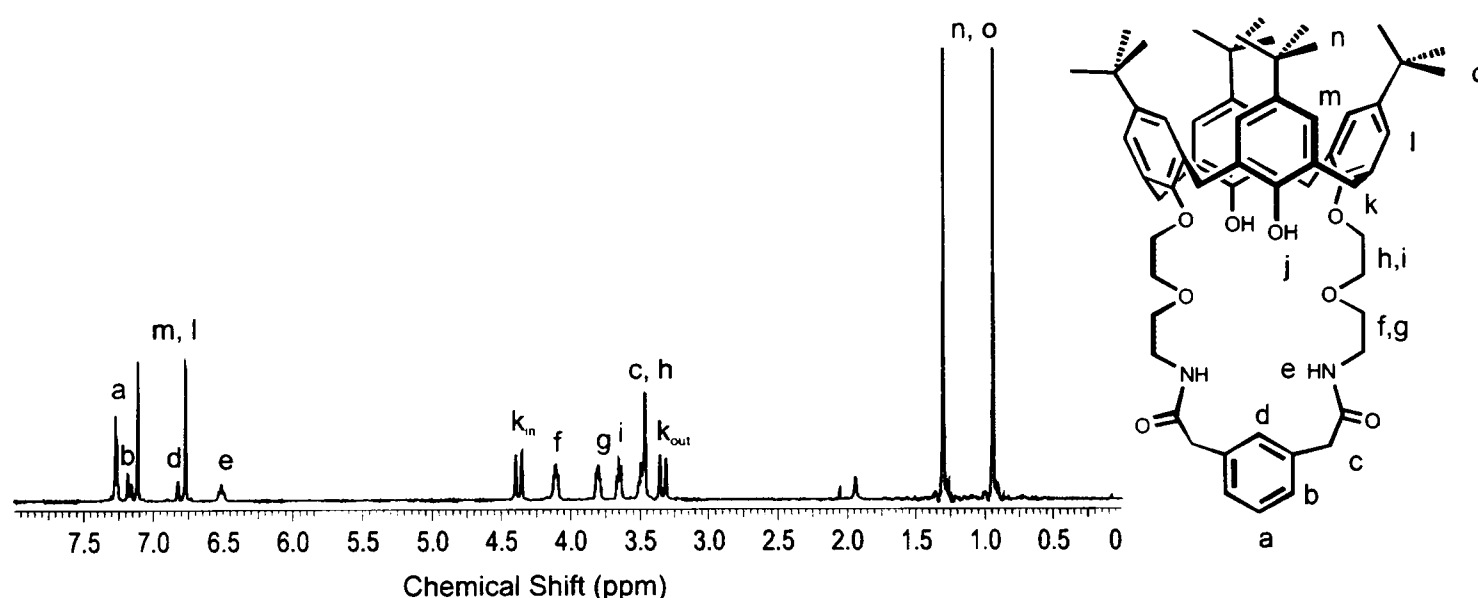


Figure 2.20 ¹H NMR spectrum of macrocycle **9** in CDCl₃ at 298 K

Oxidation to the target calix[4]diquinone receptor was attempted by stirring macrocycle **9** in a solution of thallium trifluoroacetate in the absence of light for 2.5 hours. The yellow solid isolated following recrystallisation from CHCl₃/diethyl ether was a mixture of multiple products, as indicated by the ¹H NMR spectrum. There was evidence of the desired calix[4]diquinone receptor from the peaks at *m/z* 919.44 and 935.41 in the mass spectrum, and further purification was attempted by silica gel chromatography. However, it did not prove possible to isolate the receptor and therefore, attention was turned to the synthesis of ion-pair

receptors with anion binding units based on bipyridine.

2.2.3.2. Towards the Synthesis of a Luminescent Ion-Pair Receptor

The aim of this work is to develop an ion-pair analogue of the luminescent anion receptor reported by Beer (Figure 2.21a), which selectively binds and senses acetate anions.⁶⁶ One possible candidate is the ion-pair receptor in Figure 2.21b, although the synthesis of this receptor and receptor **10** (Figure 2.21c) has previously been attempted within the group.⁶⁷ While thallium trifluoroacetate was successfully used to synthesise the luminescent anion receptor in Figure 2.21a, similar conditions for oxidation of receptor **10** produced an impurity which was attributed to partial oxidation of the bipyridyl group. This work would be repeated to investigate the oxidation step, and extended to the synthesis of the related isomer in Figure 2.21d.

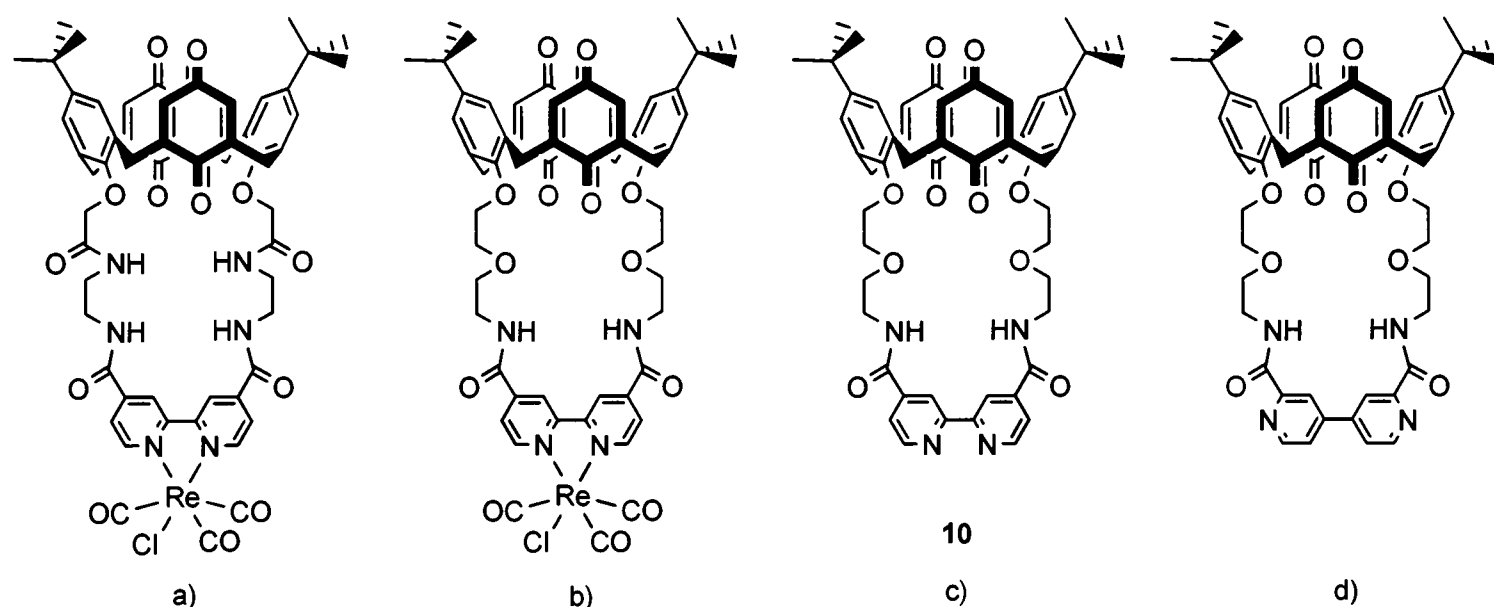
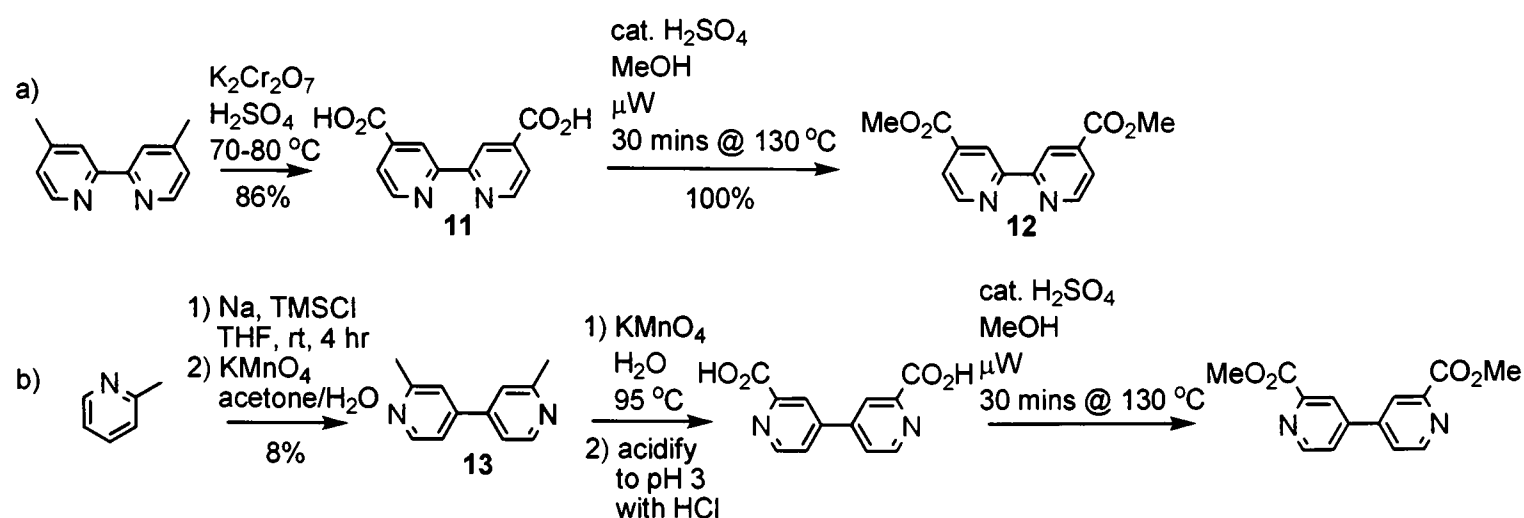


Figure 2.21 a) Beer's luminescent rhenium bipyridyl calix[4]diquinone receptor. Target b) rhenium bipyridyl calix[4]diquinone receptor and c) and d) bipyridyl calix[4]diquinone receptors

First the bipyridine carboxylic acids were synthesised according to Scheme 2.8. 4,4'-Dimethyl-2,2'-bipyridine was oxidised to **11** in 86% yield using potassium dichromate in sulfuric acid.⁶⁸ Compound **11** was converted to the methyl ester **12** for characterisation purposes by heating under microwave irradiation at 130 °C for 30 minutes in the presence of a catalytic amount of H₂SO₄ in MeOH.

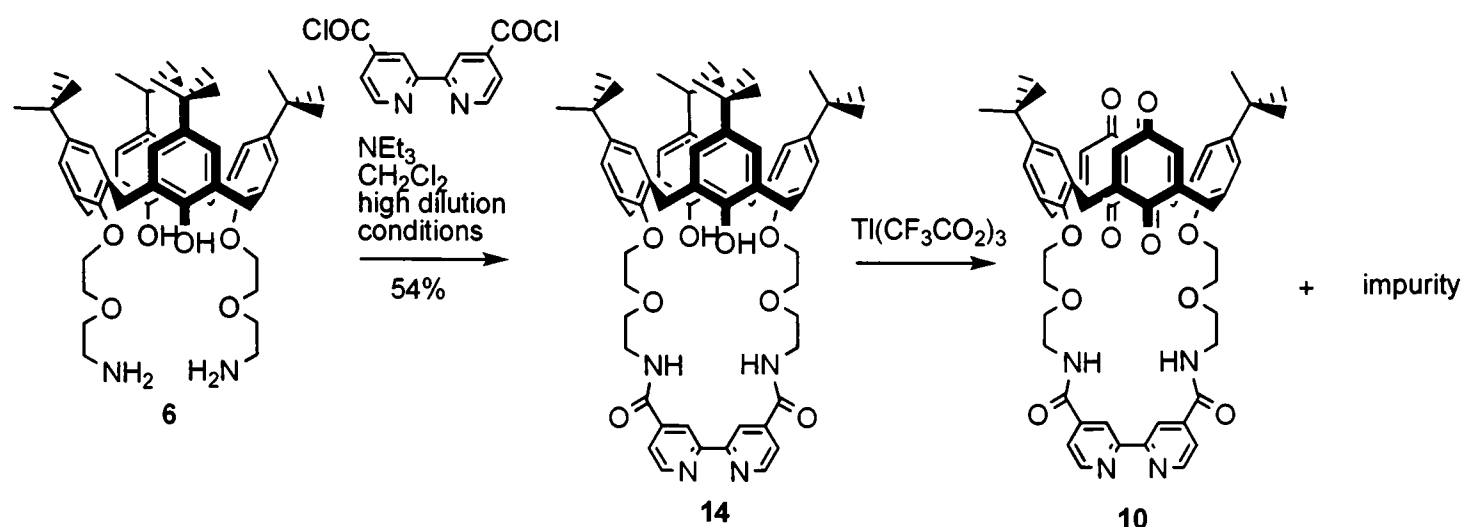


Scheme 2.8 Synthesis of a) 2,2'-bipyridine-4,4'-dicarboxylic acid **11** and b) attempted synthesis of 4,4'-bipyridine-2,2'-dicarboxylic acid

The synthesis of 4,4'-bipyridine-2,2'-dicarboxylic acid exploited the synthetic strategy developed by Rebek and co-workers to synthesise the isomer 4,4'-bipyridine-3,3'-dicarboxylic acid (Scheme 2.8b).⁶⁹ A suspension of 2-picoline, trimethylsilyl chloride and sodium was stirred at room temperature for four hours before addition of potassium permanganate in an acetone/water mixture. The desired product **13** was obtained in 8% yield and this low yield is most likely due to product loss during filtration steps. The oxidation to the dicarboxylic acid was attempted using potassium permanganate and upon acidification with HCl , only a small amount of precipitate was collected. For characterisation this was converted to the methyl ester using the same procedure as for **12**, which revealed an impurity. This impurity may be caused by either incomplete oxidation or decomposition, as it has been reported that the potassium salt of the dicarboxylic acid is prone to decarboxylation in acidic media and decomposition when heated above 80°C .⁷⁰ The intolerance to acidic conditions may also prevent the formation of the acid chloride for macrocyclisation reactions.

It was decided to focus on the bipyridine isomer **11**, since this could be easily prepared, and synthesise macrocycle **14** (Scheme 2.9). If suitable oxidation conditions for the preparation of calix[4]diquinone receptor **10** were found, oxidation of **13** would be investigated further. Compound **11** was converted to the acid chloride by overnight reflux in thionyl chloride and

the reaction with the bis-amine **6** under high dilution conditions produced macrocycle **14** in 54% yield (Scheme 2.9).⁶⁷ Oxidation to receptor **10** was attempted by stirring a thallium trifluoroacetate solution of macrocycle **14** in the absence of light for two hours. As found previously,⁶⁷ the desired product **10** formed but it could not be isolated in satisfactory purity despite repeated recrystallisations.



Scheme 2.9 Synthesis of macrocycle **14** and attempted oxidation to receptor **10**

It was hoped that alternative milder oxidants to thallium trifluoroacetate might be used to oxidise the calixarene unit to the calix[4]diquinone without also oxidising the bipyridine motif. There are several potential candidates for oxidants, including potassium ferricyanide and chlorine dioxide, but these are not suitable for *tert*-butylcalix[4]arene derivatives for the reasons discussed in Section 2.1.2. Therefore the synthesis of bipyridyl receptors based on *tert*-butylcalix[4]arene was not pursued any further, but instead, the synthesis of the calix[4]arene analogues was investigated.

2.3. Calix[4]diquinone Cooperative AND Ion-Pair Receptors

The synthesis of the calix[4]arene analogues of the receptors in Section 2.2 has never been investigated before. Since the design of the target calix[4]diquinone receptors is identical to that of the *tert*-butylcalix[4]diquinone receptors, a similar synthetic strategy would be employed for their synthesis. Initially, receptors **15-17** would be synthesised to establish suitable oxidation conditions and investigate their ion-pair recognition properties before

attempting the preparation of the bipyridyl calix[4]diquinone receptor **18** and its rhenium complex (Figure 2.22).

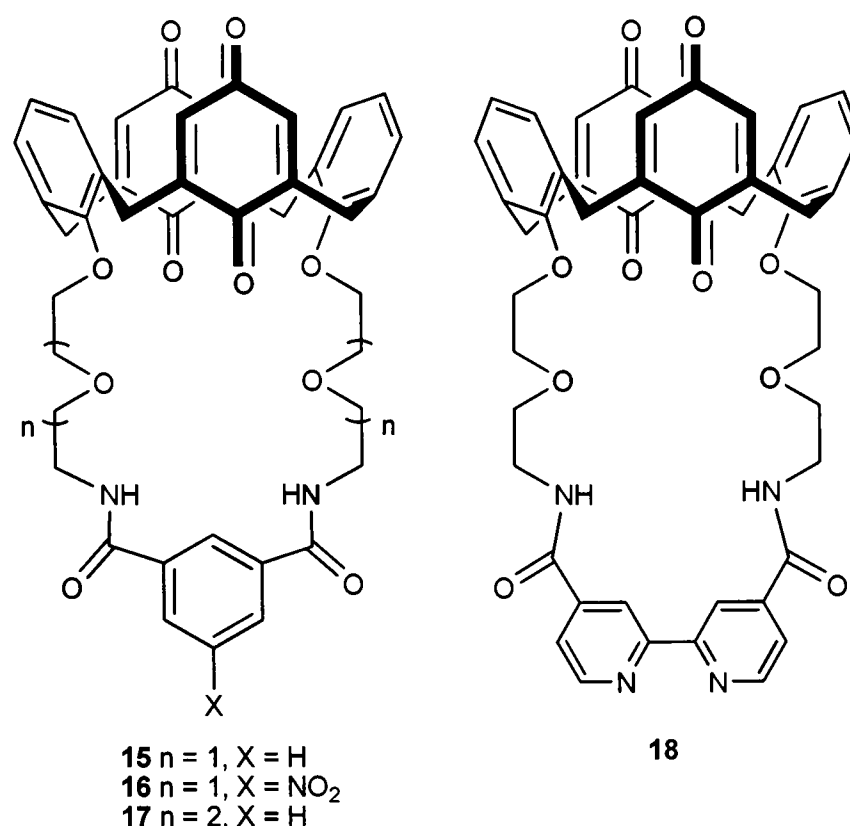
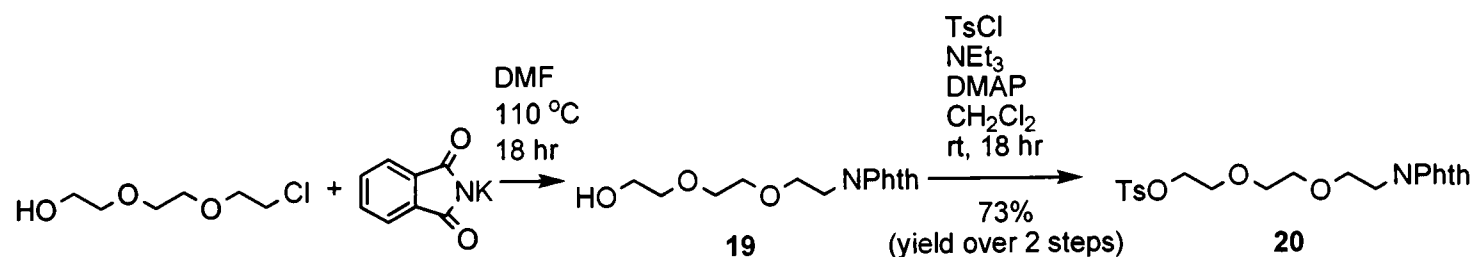


Figure 2.22 Target calix[4]diquinone receptors **15-18**

2.3.1. Synthesis of Receptors **15-17**

2.3.1.1. Synthesis of Macrocyclic Precursors

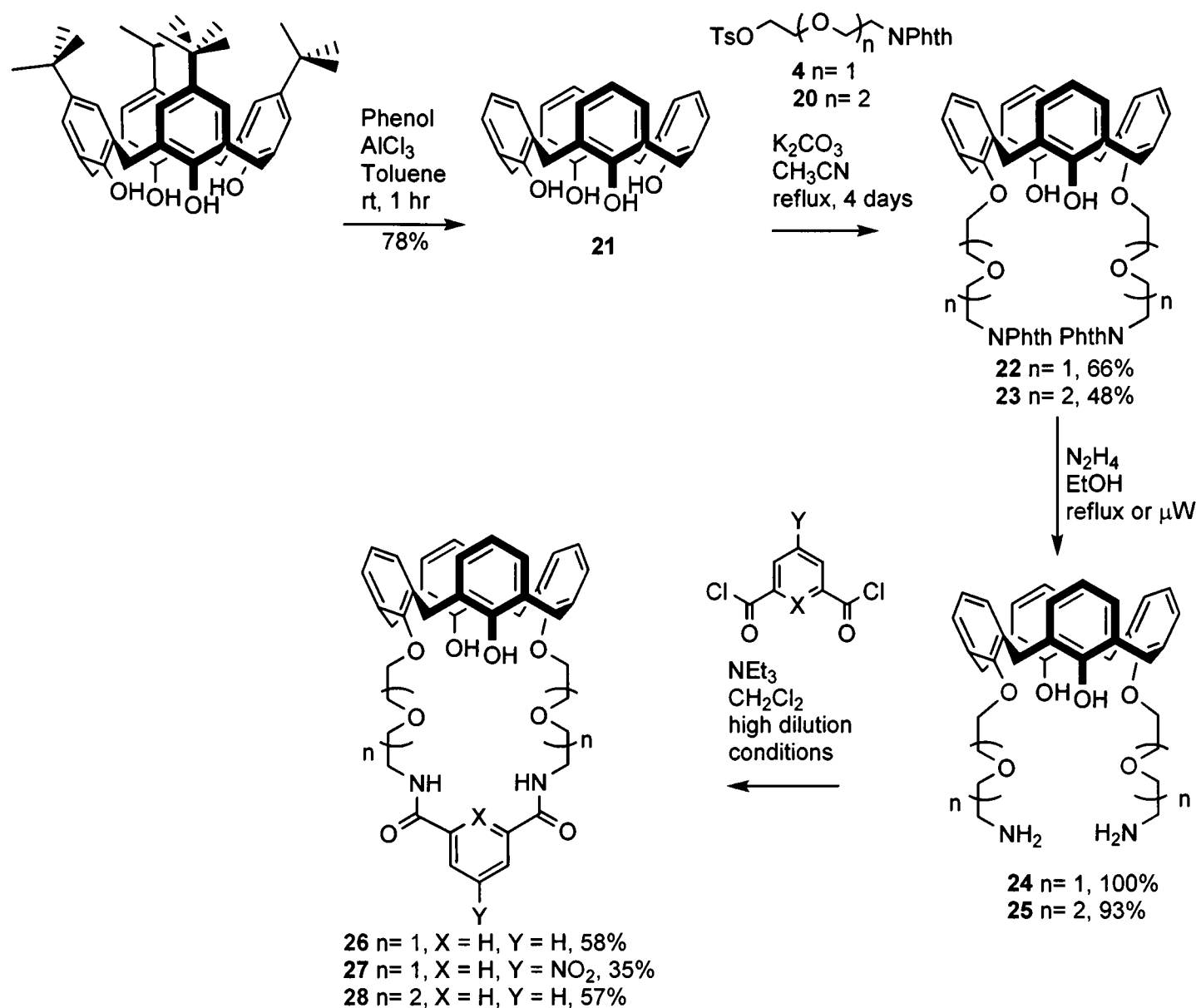
Firstly, it was necessary to prepare precursor **20** according to Scheme 2.10 for the synthesis of receptor **17** with a larger macrocycle cavity. A solution of 2-(2-(2-chloroethoxy)ethoxy)ethanol and potassium phthalimide in DMF was heated for 18 hours at 110°C.^{71, 72} It was not possible to remove all traces of DMF so the resulting oil **19** was tosylated giving compound **20** in 73% overall yield over the two steps.



Scheme 2.10 Synthesis of precursors **19** and **20**

The established *tert*-butylcalix[4]arene synthetic methods were adapted to synthesise the related calix[4]arene based precursors **22-28** (Scheme 2.11). Calix[4]arene **21** was synthesised by the Friedel-Crafts dealkylation of commercially available *tert*-butylcalix[4]arene using

phenol and aluminium trichloride in toluene at room temperature for 1 hour. Calix[4]arene was isolated in 78% yield by recrystallisation from $\text{CHCl}_3/\text{MeOH}$.⁷³



Scheme 2.11 Synthesis of calix[4]arene precursors **22-28**

Compounds **22** and **23** were prepared by heating a suspension of calix[4]arene, 1.1 equivalents of K_2CO_3 and an excess of alkylating agent under reflux in CH_3CN for 4 days. Following purification by silica gel chromatography, compounds **22** and **23** were isolated in 66% and 48% yield respectively. It was also possible to isolate small amounts of the monoalkylated product **29** from the synthesis of **22** (Figure 2.23).

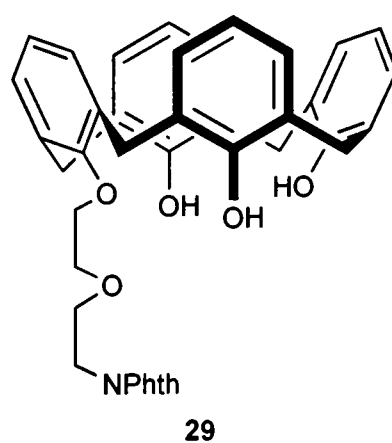


Figure 2.23 Monoalkylated product **29** isolated as a by-product in the synthesis of **22**

Single crystals of **22** suitable for X-ray structure determination were grown by slow evaporation of an EtOAc/hexane mixture.⁵⁴ The calixarene is in the cone conformation and the angle between the best planes of the phenyl ether rings (32.6°) is much shallower than that between the phenol rings (96.6°) (Figure 2.24). One of the phthalimide groups is π -stacking with one of the calixarene rings, and as a result, the local approximate two fold axis of symmetry of the calixarene does not extend to the ether substituents. The two hydroxyl protons form intramolecular hydrogen bonds to the ether oxygens.

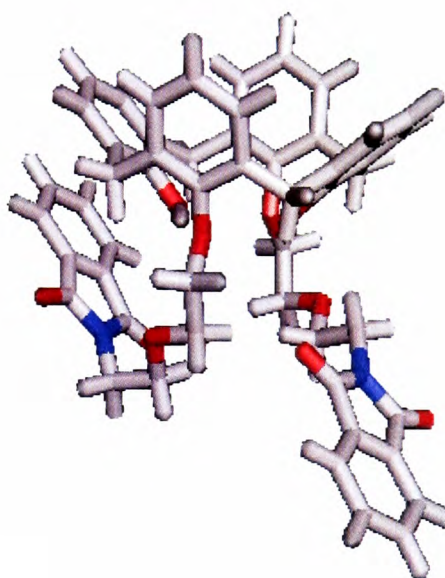


Figure 2.24 X-ray crystal structure of **22**

The phthalimide groups of **22** and **23** were removed using hydrazine monohydrate to give the bis-amine compounds **24** and **25** in almost quantitative yield. Bis-amine **24** was reacted with isophthaloyl dichloride and 5-nitroisophthaloyl dichloride under high dilution conditions to produce the macrocycles **26** and **27** in yields of 58% and 35% respectively, following purification by silica gel chromatography. Macrocyclisation of bis-amine **25** with isophthaloyl dichloride under high dilution conditions gave **28** in 57% yield.

A second product was also isolated from the macrocyclisation with 5-nitroisophthaloyl dichloride. The ^1H NMR spectrum of this product was similar to that of **27**, but they could be distinguished by comparing the aromatic regions of the spectra (Figure 2.25). The similarity of the ^1H NMR spectra suggested that the product was the [2+2] macrocycle **30** and this was confirmed by the peak at m/z 1568.6644 corresponding to $[\mathbf{30} + \text{Na}]^+$ in the mass spectrum.

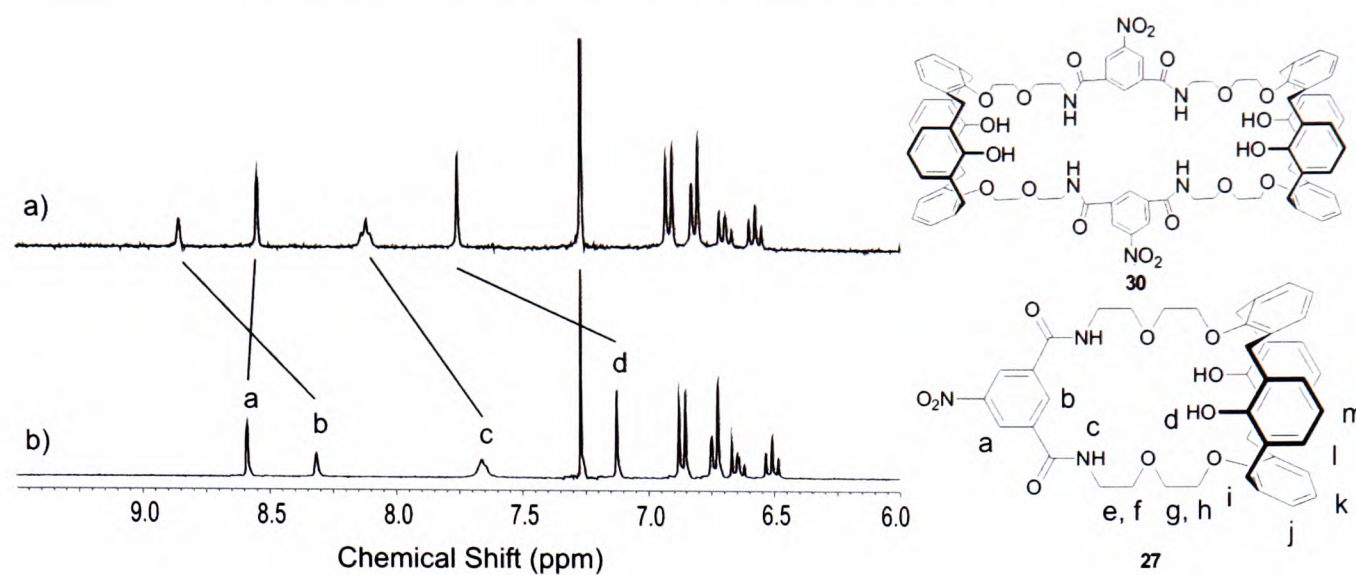


Figure 2.25 Comparison of the aromatic regions of the ^1H NMR spectra of a) **30** and b) **27** in CDCl_3

Single crystals of **27** were grown by slow evaporation of an EtOAc/acetone solution and the X-ray crystal structure is shown in Figure 2.26.⁵⁴ The calix[4]arene is in the cone conformation and the nitro-isophthalamide ring is π - π stacking with one of the calixarene rings. Charge transfer between the electron rich calixarene ring and electron deficient nitro-isophthalamide ring accounts for the green colour of the crystals. There are also intramolecular hydrogen bonds between the phenolic protons and the ether oxygens and a water molecule is bound in the cavity, which has been omitted for clarity.

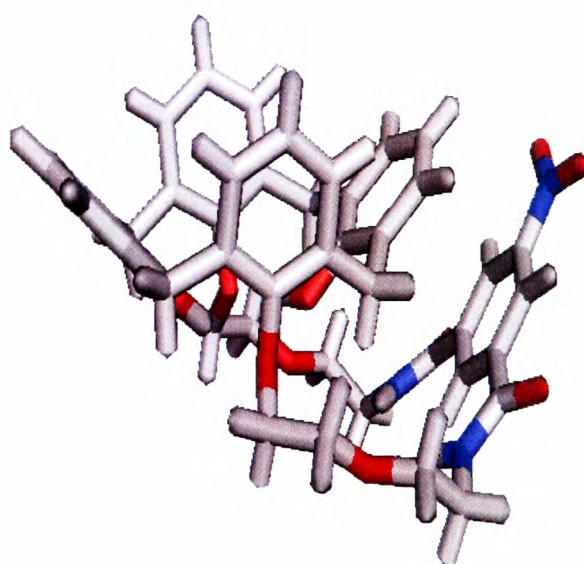
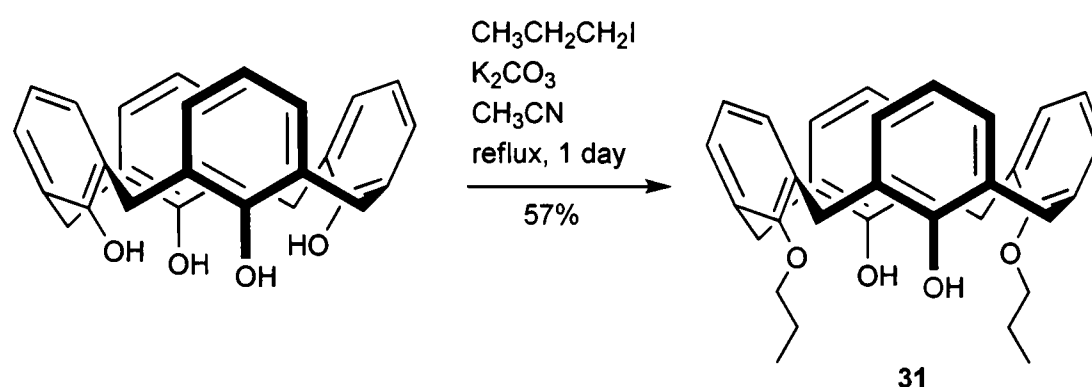


Figure 2.26 X-ray crystal structure of macrocycle **27**

2.3.1.2. Synthesis of Calix[4]diquinone Receptors **15-17**

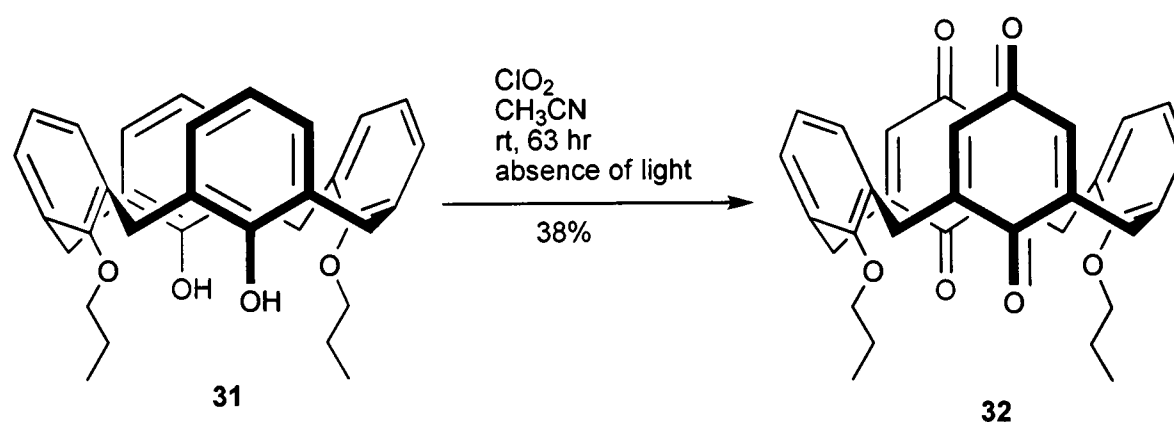
Initially, oxidation of a model system using alternative oxidants to thallium trifluoroacetate was investigated before attempting the synthesis of the target calix[4]diquinone receptors

from macrocycles **26-28**. The model system was chosen to be **31** as the propyl substituents are large enough to lock the calixarene into a cone conformation. Compound **31** was synthesised in 57% yield by heating calix[4]arene with K_2CO_3 and iodopropane in CH_3CN under reflux for 1 day (Scheme 2.12).⁴¹



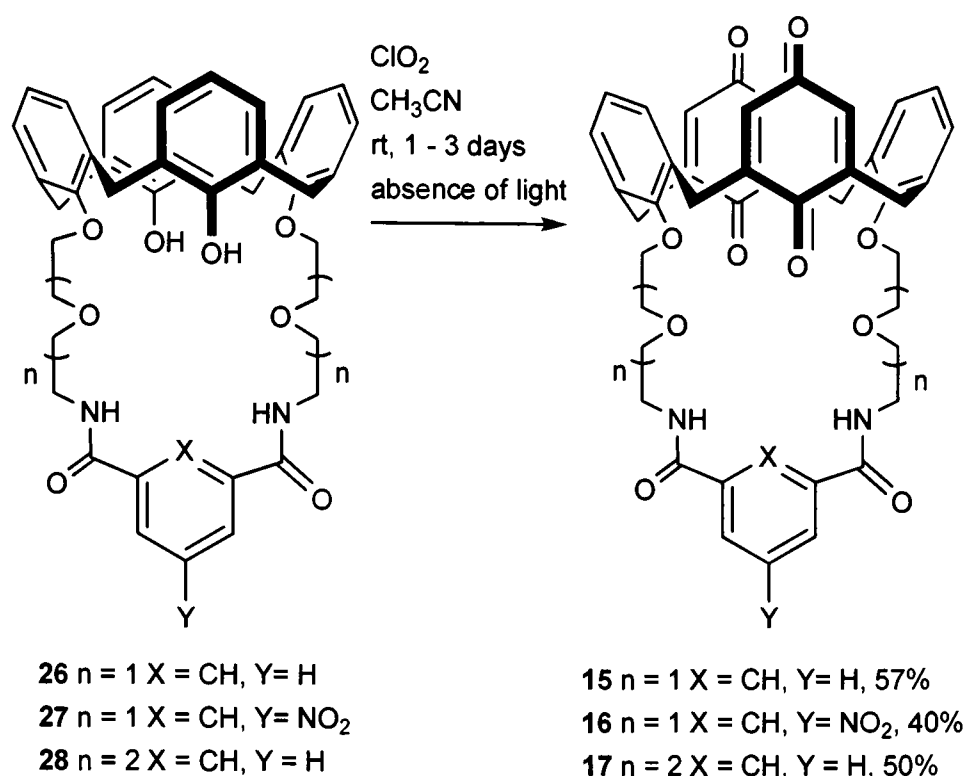
Scheme 2.12 Synthesis of the model system **31**

Chlorine dioxide was initially investigated as an oxidant, as it has been used successfully to oxidise calix[4]arene dialkyl ethers, including **31**, to the corresponding calix[4]diquinone dialkyl ethers.²⁵ The reagent was prepared as an aqueous yellow solution by mixing equal volume solutions of sodium chlorite and sodium persulfate in the absence of light. It was then added to a CH_3CN solution of **31**, and the resulting mixture was stirred for 63 hours in the absence of light (Scheme 2.13). The desired calix[4]diquinone product **32** was isolated as a yellow solid in 38% yield following purification by column chromatography.



Scheme 2.13 Oxidation of the model system by chlorine dioxide

The oxidation of macrocycles **26-28** was then carried out using the same procedure monitoring the reaction progress by TLC, with reaction times varying from 22 hours to 3 days (Scheme 2.14). The calix[4]diquinone receptors **15-17** were isolated in yields of 40-57% following purification by column chromatography.



Scheme 2.14 Oxidation of macrocycles **26-28** to the target calix[4]diquinone receptors **15-17**

The ^1H NMR spectrum of receptor **15** in Figure 2.27 is typical for receptors **15-17** in CDCl_3 , with very broad peaks for all of the protons except those that are part of the anion binding isophthalamide motif. Of particular note for receptor **15** is the chemical shift of the amide protons *d*, which is shifted approximately 1 ppm downfield compared with the *tert*-butylcalix[4]arene analogue. This suggests that there could be stronger intramolecular hydrogen bonding interactions in receptor **15** than in the *tert*-butylcalix[4]arene analogue (Figure 2.6c), possibly due to greater conformational flexibility of the calix[4]diquinone unit without *tert*-butyl groups.

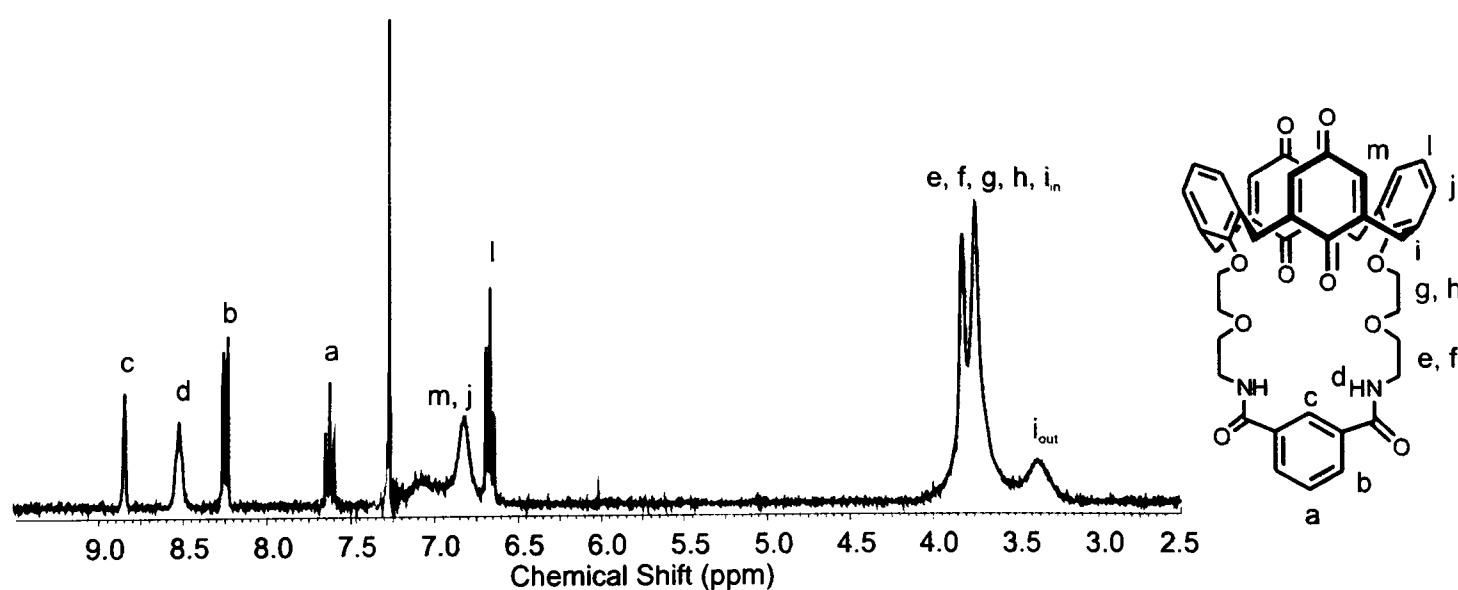


Figure 2.27 ^1H NMR spectrum of receptor **15** in CDCl_3 at 298 K

Single crystals of receptor **15** were grown from slow evaporation of a $\text{CHCl}_3/\text{CH}_3\text{CN}$ solvent mixture. The crystal structure gives solid state evidence for the existence of intramolecular

hydrogen bonds between the amide protons of the isophthalamide anion binding unit and one of the calix[4]diquinone oxygens, with N $\cdots$ O lengths of 3.216 and 3.200 Å (Figure 2.28).⁷⁴ The calix[4]diquinone unit is in the partial cone conformation with the two quinone rings almost perpendicular to one another. In contrast to the X-ray crystal structures of *tert*-butylcalix[4]diquinone receptors (see Figure 2.9 and references 22 and 67), the phenyl rings are no longer parallel but pinched together.

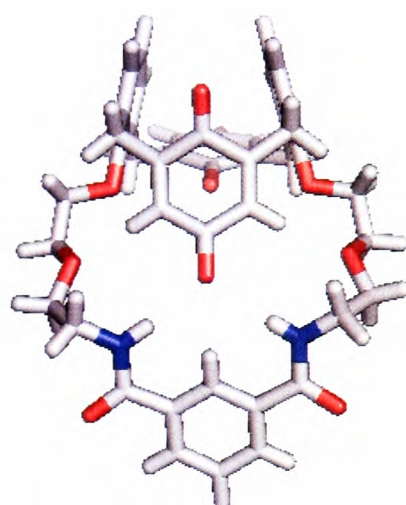


Figure 2.28 X-ray crystal structure of receptor **15**

In order to probe the existence of intramolecular hydrogen bonding in solution, a number of ^1H NMR experiments were carried out. There would be a particular focus on receptor **15** as its amide proton signal showed the most significant downfield shift of the three receptors in CDCl_3 compared with the *tert*-butylcalix[4]arene analogues. Before VT and ROESY experiments were carried out, alternative solvents such as CD_3CN and $\text{DMSO}-d_6$ were investigated since the proton signals of the receptors in CDCl_3 were broad and often overlapping. Unfortunately, the ^1H NMR spectra of all three receptors in $\text{DMSO}-d_6$ were just as broad and there were solubility problems in CD_3CN . Receptors **15** and **16** were completely insoluble and only partially soluble respectively, which might limit the study of their ion-pair recognition properties. Receptor **17**, which contains an additional ethylene glycol unit, was soluble and the ^1H NMR spectrum in CD_3CN showed better resolution of the signals (Figure 2.29a). ROESY analysis revealed correlations between the calix[4]diquinone proton *n* and protons *b-d* of the anion binding unit which suggests there is some conformational

flexibility in solution (Figure 2.29b). This is not surprising since the macrocycle cavity is larger and intramolecular hydrogen bonding interactions are therefore expected to be weaker. Indeed, the chemical shift for the amide protons *d* is virtually unchanged in CD₃CN compared with CDCl₃ (7.14 ppm vs 7.44 ppm) and shifted 1 ppm upfield compared with the smaller analogue **15**, suggesting either very weak or no hydrogen bonding interactions in solution.

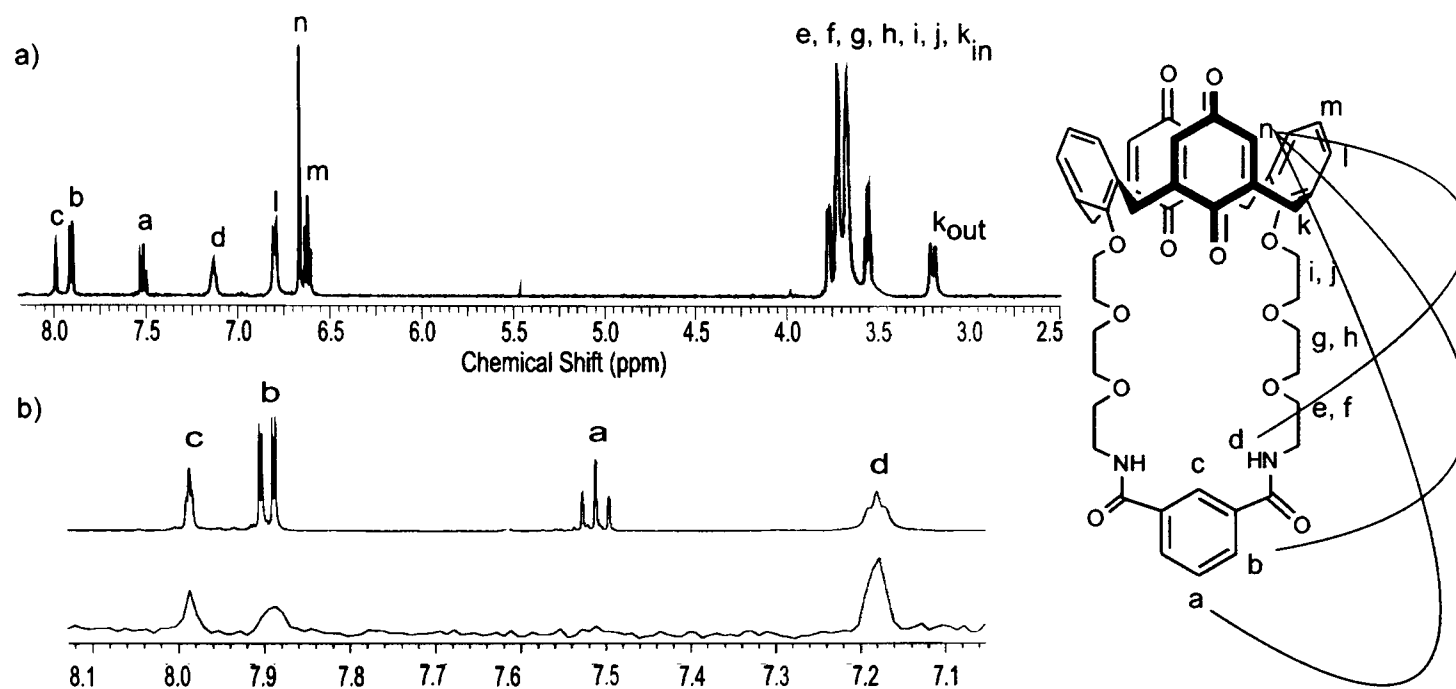


Figure 2.29 a) ¹H NMR spectrum of receptor **17** in CD₃CN at 298 K and b) ROESY analysis showing correlations between proton *n* of the calix[4]diquinone unit and protons *b*-*d* of the anion binding unit

Therefore, attention was focused on receptor **15** and the chemical shift of proton *d* was monitored upon increasing the temperature of the solution in VT ¹H NMR experiments. Initially, the experiment was carried out in CDCl₃ gradually increasing the temperature from 20 °C to 55 °C. This caused the spectra to sharpen and proton *d* shifted upfield by 0.17 ppm. However, when an analogous experiment was carried out in DMSO-*d*₆, it was possible to heat to higher temperatures and more dramatic changes were observed (Figure 2.30). While the proton spectrum was very broad at 20 °C, heating the solution to 100 °C significantly sharpened the signals and there were a number of chemical shift changes. For example the amide proton *d* moved upfield by 0.25 ppm and there was also a small upfield shift of the isophthaloyl proton *c*. In the alkyl region, the methylene proton *i*_{in} moved downfield and there were significant changes for protons *e*-*h*. All of these changes are suggestive of a conformational change of the calix[4]diquinone, possibly due to an intramolecular

hydrogen bond breaking. The upfield shifts of residual solvent signals for H₂O and CHCl₃ are also consistent with this.

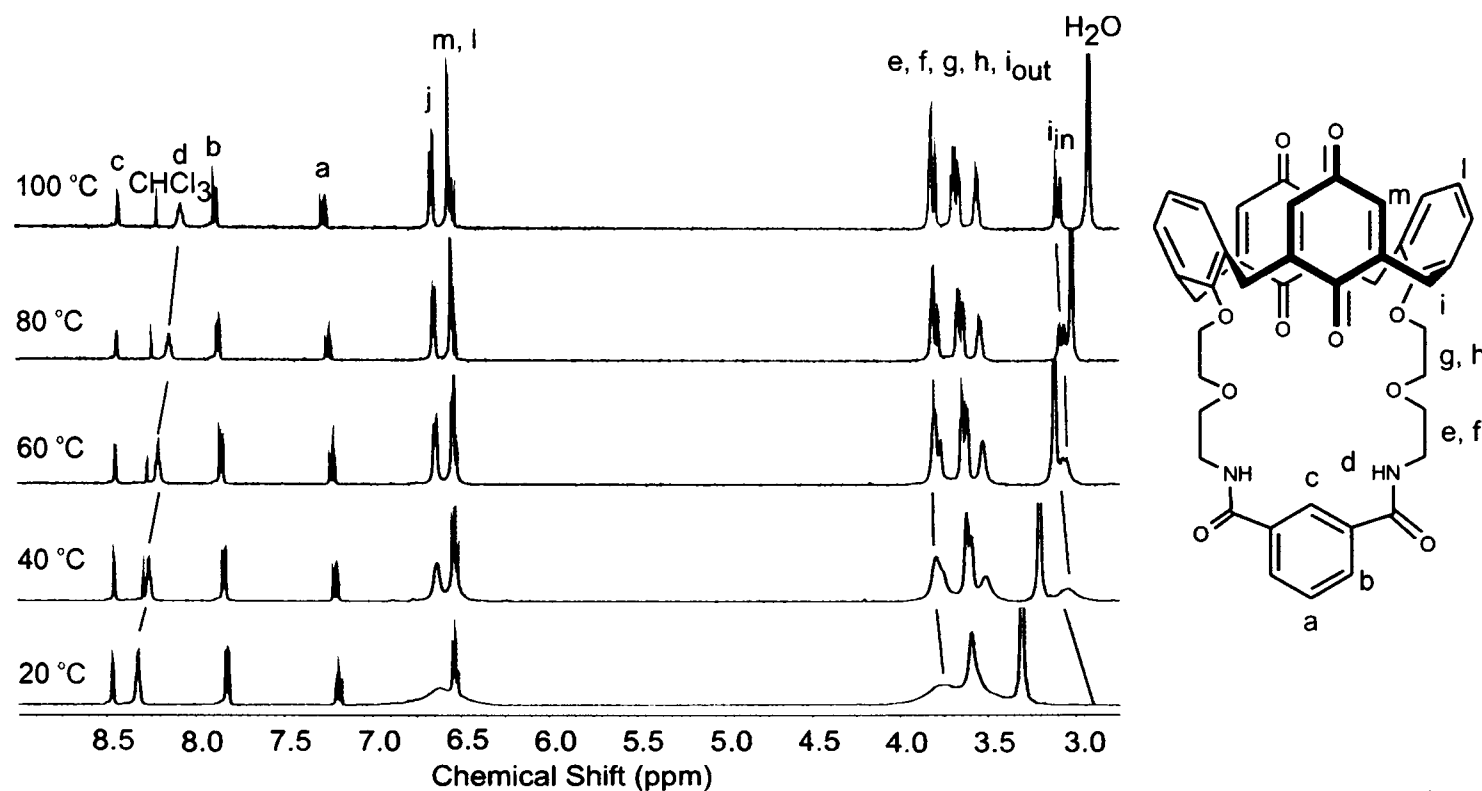


Figure 2.30 Variable temperature experiment showing the effect of increasing temperature on the ¹H NMR spectrum of receptor **15** in DMSO-*d*₆

2.3.2. Ion-Pair Binding Studies

The ion-pair binding properties of receptors **15-17** were investigated by the same protocols used for the analogous *tert*-butylcalix[4]diquinone receptors in Section 2.2.2. However, removal of the *tert*-butyl groups reduces the solubility of the calix[4]diquinone receptors compared with the *tert*-butylcalix[4]diquinone analogues. As a consequence, the scope of the ion-pair binding studies on the calix[4]diquinone receptors **15-17** was limited by the solubility of the receptors at the concentrations required for each technique. It was not possible to study receptor **15** as it was completely insoluble in CH₃CN, even at the low concentrations required for UV/visible spectroscopy experiments.

2.3.2.1. Anion Binding Studies

Receptor **17** showed the greatest solubility in CH₃CN based solvent systems and therefore the initial ¹H NMR titration studies were carried out in CD₃CN using this receptor. Upon addition of ten equivalents of TBACl, there were very small downfield shifts of both the amide proton *d* and isophthaloyl proton *c* signals (Figure 2.31). There was a linear correlation between

the chemical shift of the protons and the chloride concentration, most likely due to the increase in the ionic strength of the solution rather than chloride binding. Addition of one equivalent of chloride anions in the presence of one equivalent of ammonium cations unexpectedly induced very small upfield shifts of protons *c* and *d*. Upon addition of an excess of chloride anions, there were downfield shifts of both protons, but unfortunately, there was no evidence of anion binding from the linear chemical shift change (Figure 2.31). The titration was repeated in the more competitive solvent system 98:2 CD₃CN/D₂O and again, unusual chemical shift changes were observed. However, these were not consistent with the results from the titration in CD₃CN. Similar difficulties obtaining reproducible titration data in CD₃CN based solvent systems were reported for the analogous *tert*-butylcalix[4]diquinone receptor.⁶⁷ For that receptor, more reproducible results were obtained in acetone-*d*₆ but unfortunately further anion binding studies were prevented by the insolubility of receptor **17** in acetone-*d*₆.

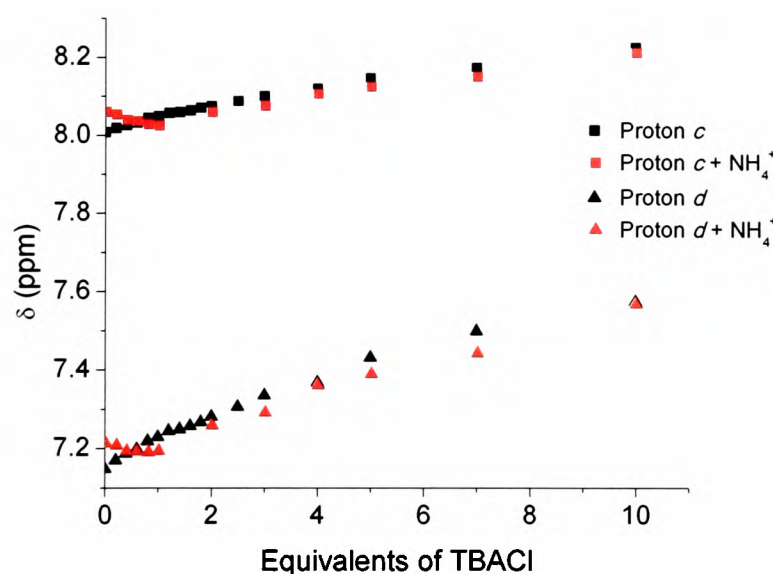


Figure 2.31 Chemical shift changes of the isophthaloyl proton *c* and amide protons *d* of receptor **17** upon addition of TBACl in the absence and presence of one equivalent of NH₄PF₆ in CD₃CN at 298 K. See Figure 2.30 for proton assignments

It was hoped that further insight into the ion-pair binding properties of calix[4]diquinone receptors could be gained from the study of receptor **16**, despite its limited solubility in CH₃CN. Of the three receptors, it was expected to show the strongest binding due to the presence of the electron-withdrawing nitro group which increases the hydrogen bonding

donor ability of the amide protons. For this reason, the studies were attempted in the more competitive solvent system 98:2 CD₃CN/D₂O as it was expected that binding would be too strong in CD₃CN for determination of association constants. It was not possible to carry out the titration in the absence of ammonium cations due to limited solubility in this solvent system. However, it was possible to solubilise the receptor in the presence of an equivalent of ammonium cations and Figure 2.32 shows the chemical shift changes for the isophthaloyl proton *a* upon addition of TBACl. Both the isophthaloyl proton *a* and amide protons broadened into the baseline for up to 0.6 equivalents but the remaining data points clearly demonstrate chloride binding to the receptor. Addition of 1 equivalent of chloride ions induced a downfield shift of 0.59 ppm and Job Plot analysis revealed 1:1 binding. Despite missing a number of data points, it was possible to obtain an association constant of 1080 M⁻¹, with an error of less than 15%.

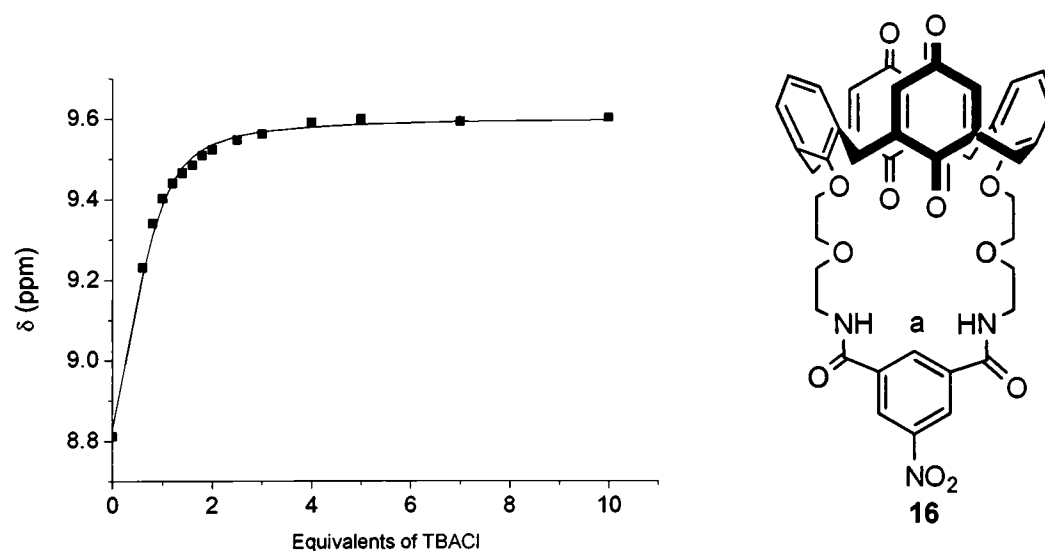


Figure 2.32 Chemical shift changes of the isophthaloyl proton *a* of receptor **16** upon addition of TBACl in the presence of one equivalent of NH₄PF₆ in 98:2 CD₃CN/D₂O at 298 K. Square symbols represent the experimental data points and the line represents the calculated curve

2.3.2.2. Cation Binding Studies

Cation binding studies were undertaken for receptors **16** and **17**, and fortunately receptor **16** was soluble in CH₃CN at the concentration required for titration experiments. There were changes of the calix[4]diquinone n- π^* absorption band upon addition of cations in the absence and presence of one equivalent of chloride (Figure 2.33). Interestingly, there were a number of differences between the absorption spectra of these receptors and the

tert-butylcalix[4]diquinone analogues. Firstly, there was a hypsochromic shift of the absorption band from approximately 330 nm to 310 nm, and the absorbance decreases upon addition of cations.

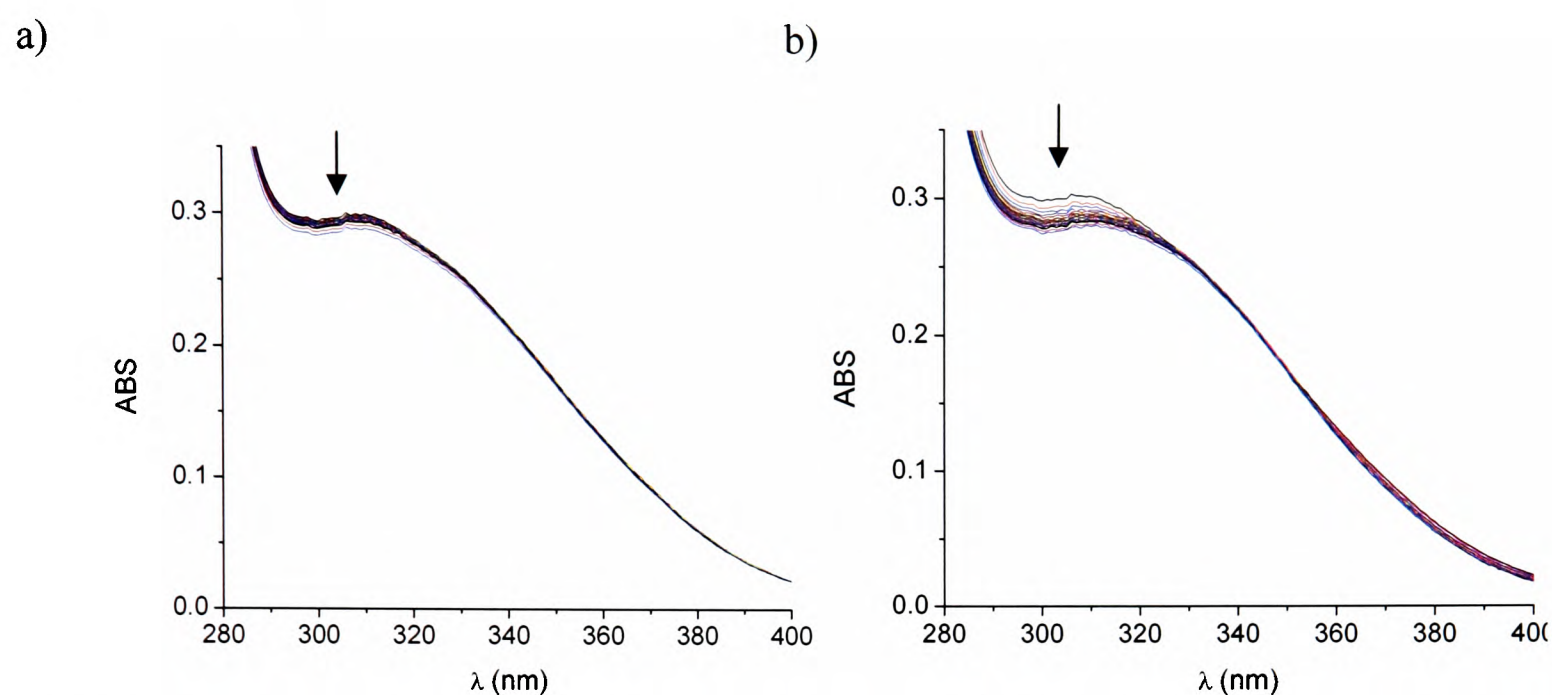


Figure 2.33 Changes in the absorbance of receptor **16** upon addition of NH_4^+ cations in the a) absence and b) presence of one equivalent of chloride ions in CH_3CN at 298 K

	$\log K_{M^+}$		
	Na^+	K^+	NH_4^+
16	-	-	-
16.TBACl	*	4.62	5.03
17	-	-	-
17.TBACl	-	-	-

Table 2.3 Association constants derived from SPECFIT analysis of UV/visible spectroscopy titrations in CH_3CN at 298 K. Errors < 15%. - = no evidence of binding, * = evidence of binding but errors > 15%

The titration data was fitted using SPECFIT and disappointingly, there were insufficient changes to infer cation binding to receptor **17**, even in the presence of chloride (Table 2.3). However, it was possible to obtain association constants for receptor **16** binding NH_4Cl and KCl . While there was evidence of binding NaCl , it was not possible to fit the data to obtain a meaningful association constant with less than 15% error. As expected, the association constants demonstrate that the receptor binds the ion-pairs strongly, binding NH_4Cl more strongly than KCl , with magnitudes that are similar to the *tert*-butylcalix[4]diquinone analogue.⁶⁷ Receptor **16** also demonstrates cooperative AND ion-pair recognition where the receptor shows no affinity for sodium, potassium or ammonium cations unless chloride is

present.

2.3.2.3. Electrospray Mass Spectrometry Competition Experiments

For a number of reasons, including solubility, it was not possible to compare the cation binding properties of receptors **15-17** using a single technique. Therefore, electrospray mass spectrometry (ESMS) competition experiments with sodium, potassium and ammonium cations were undertaken to explore the cation binding preferences of the receptors, rather than obtain quantitative information, using the relative peak heights of the sodium, ammonium and potassium adducts with the receptors.

The peak for the potassium adduct for all three receptors was very small compared to those for the ammonium and sodium adducts (Table 2.4). For receptor **17** the peak height of the ammonium and sodium adducts were very similar, while for receptors **15** and **16** there was a preference for the sodium adduct over ammonium. Disappointingly, these results are not consistent with spectroscopy results.

	Relative peak heights		
	Na ⁺	K ⁺	NH ₄ ⁺
15	1	<0.05	0.67
16	1	0.07	0.55
17	1	<0.05	1.1

Table 2.4 Peak heights of the receptor-cation adducts relative to the receptor-sodium adduct in ESMS competition experiments

2.3.2.4. Extraction Studies

Ion-pair receptors have the potential to be used as membrane transport, salt solubilisation and extraction agents.⁷⁵ Given that solubility problems limited solution based ion-pair binding studies, solid-liquid extraction studies were undertaken to investigate the ability of receptors **15-17** to extract ion-pairs into CDCl₃. Ten equivalents of dried and powdered MCl salts (M = Na, K and NH₄) were added to a 4 mM solution of receptors **15-17**, the resulting suspensions were shaken and ¹H NMR spectra were recorded over a period of a month.

Unfortunately, there was no evidence of salt extraction into CDCl_3 over this time as there was no change in the spectra.

2.3.2.5. Electrochemistry of Receptor 17

The electrochemical properties of receptor **17** were studied using similar techniques to those used in Section 2.2.2.3. Receptor **17** was chosen as a representative example of the calix[4]diquinone receptors since it is the most soluble in CH_3CN . Preliminary studies revealed the electrochemistry of **17** is much more sensitive to oxygen than receptor **1** and therefore all solutions were thoroughly degassed and kept under an atmosphere of N_2 . When these conditions were used, similar CVs to receptor **1** were obtained at different scan rates. These show two quasi-reversible one electron transfers at -0.76 and -0.92 V for redox couples 1/1' and 2/2' respectively and an irreversible two electron transfer at -1.45 V for redox couple 3 (Figure 2.34). Disappointingly, addition of only 0.5 equivalents of potassium and sodium led to an immediate loss of these waves, even after electrode cleaning. Therefore, it was not possible to infer any cation binding.

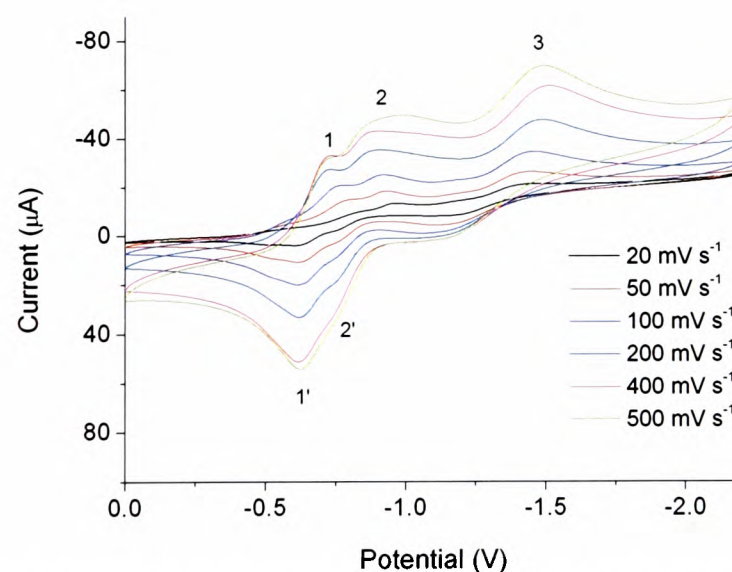


Figure 2.34 CVs of receptor **17** at different scan rates in CH_3CN at 298 K. Conditions: 4 mM solution of receptor **17**, 0.1 M TBAPF_6 supporting electrolyte, glassy carbon working electrode, platinum auxiliary electrode, Ag/AgCl reference electrode

It was hoped that addition of cations in the presence of one equivalent of chloride anions might yield more information than addition of cations alone. As with receptor **1**, there was no change of the redox potentials upon addition of one equivalent of chloride and pleasingly, the

redox waves did not disappear when less than one equivalent of potassium were added (Figure 2.35). The redox waves for 1/1' and 2/2' merged into a single wave that was anodically shifted, as was the wave for 3. Unfortunately addition of more than one equivalent of potassium cations led to precipitation. The experiment was repeated with sodium and addition of 0.5 equivalents of cation led to a complete disappearance of the redox waves. Therefore, further electrochemical studies were not carried out.

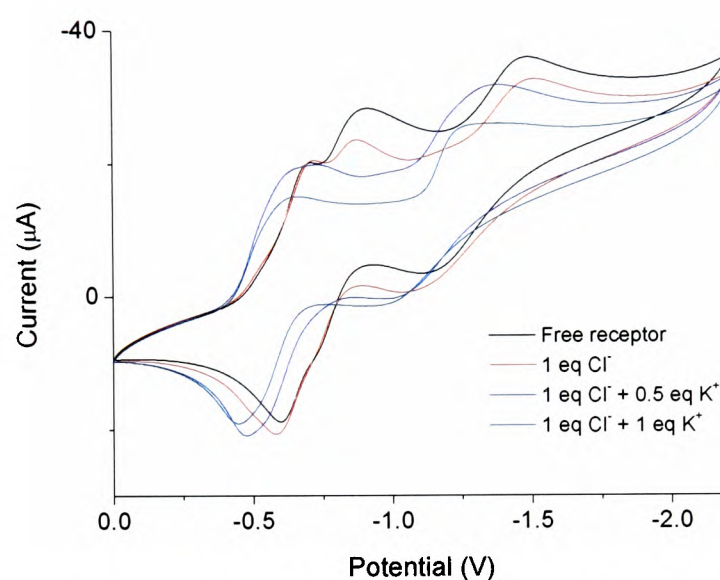


Figure 2.35 Cyclic voltammograms of receptor **17** recorded at 100 mV s^{-1} in the presence of various guest ions in CH_3CN at 298 K

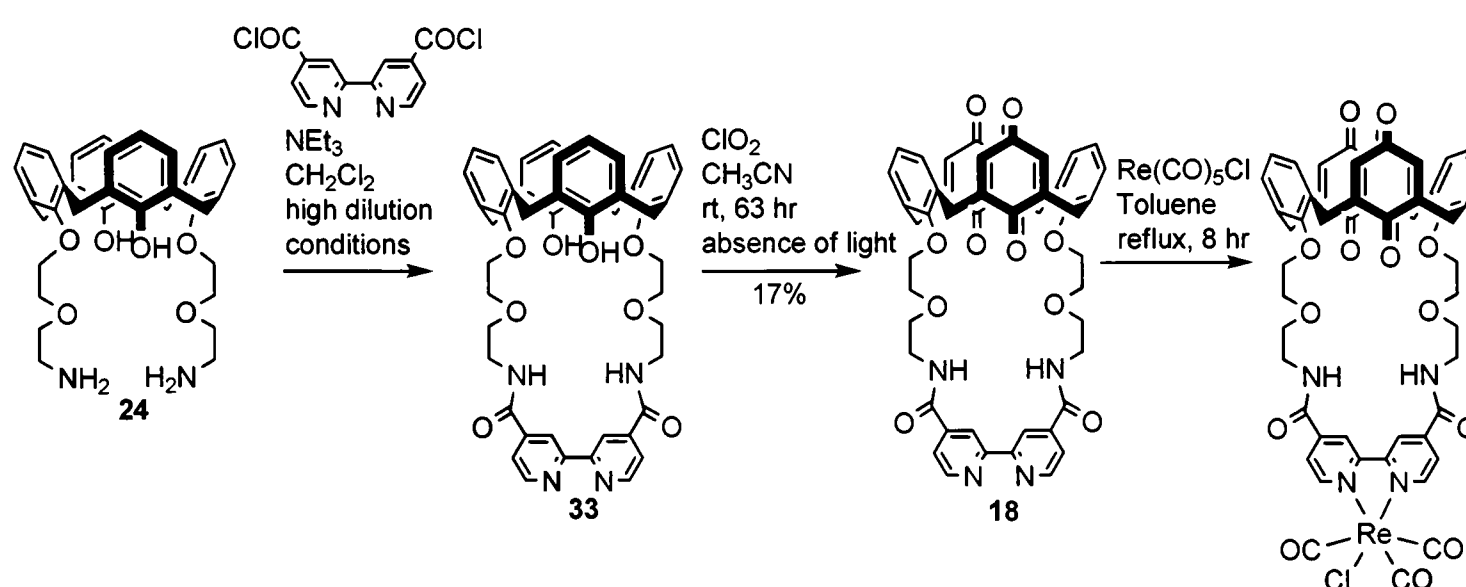
2.3.3. Towards the Synthesis of a Luminescent Heteroditopic Receptor

In Section 2.3.1, calix[4]diquinone receptors were successfully synthesised in good yields by chlorine dioxide oxidation of the macrocycle precursors. This oxidation method offers the potential to synthesise calix[4]diquinone receptors based on bipyridine, which could not be prepared in Section 2.2.3 using thallium trifluoroacetate.

2.3.3.1. Attempted Syntheses of the Receptor

The strategy for synthesising the luminescent receptor is shown in Scheme 2.15. Macrocycle **33** was synthesised by reacting bis-amine **24** with 2,2'-bipyridine-4,4'-dicarbonyl chloride under high dilution conditions. The ^1H NMR spectrum of the macrocycle revealed the desired product and an impurity. It is possible that this was the [2+2] product but it did not prove possible to obtain the macrocycle in satisfactory purity by column chromatography or

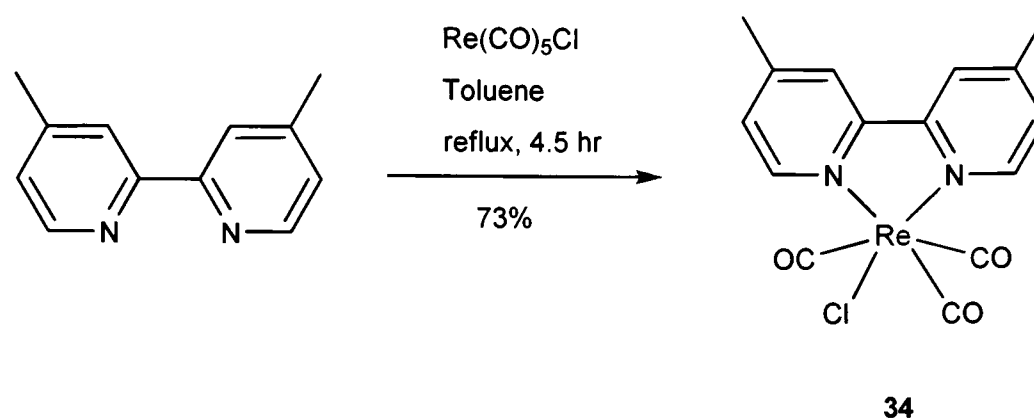
recrystallisation. Therefore it was immediately oxidised to the calix[4]diquinone receptor using chlorine dioxide in the hope that the impurity could be removed at a later stage. A yellow solid was obtained in 17% yield after purification by column chromatography. There was no evidence of partial oxidation of the bipyridine unit using this oxidation method, and the ^1H NMR and mass spectra revealed the yellow solid as the desired product **18**. Initially the complexation of rhenium pentacarbonyl chloride to the bipyridine was attempted in THF using refluxing conditions. While the reaction mixture turned orange, the desired product did not form.



Scheme 2.15 Towards the synthesis of the rhenium bipyridyl calix[4]diquinone receptor

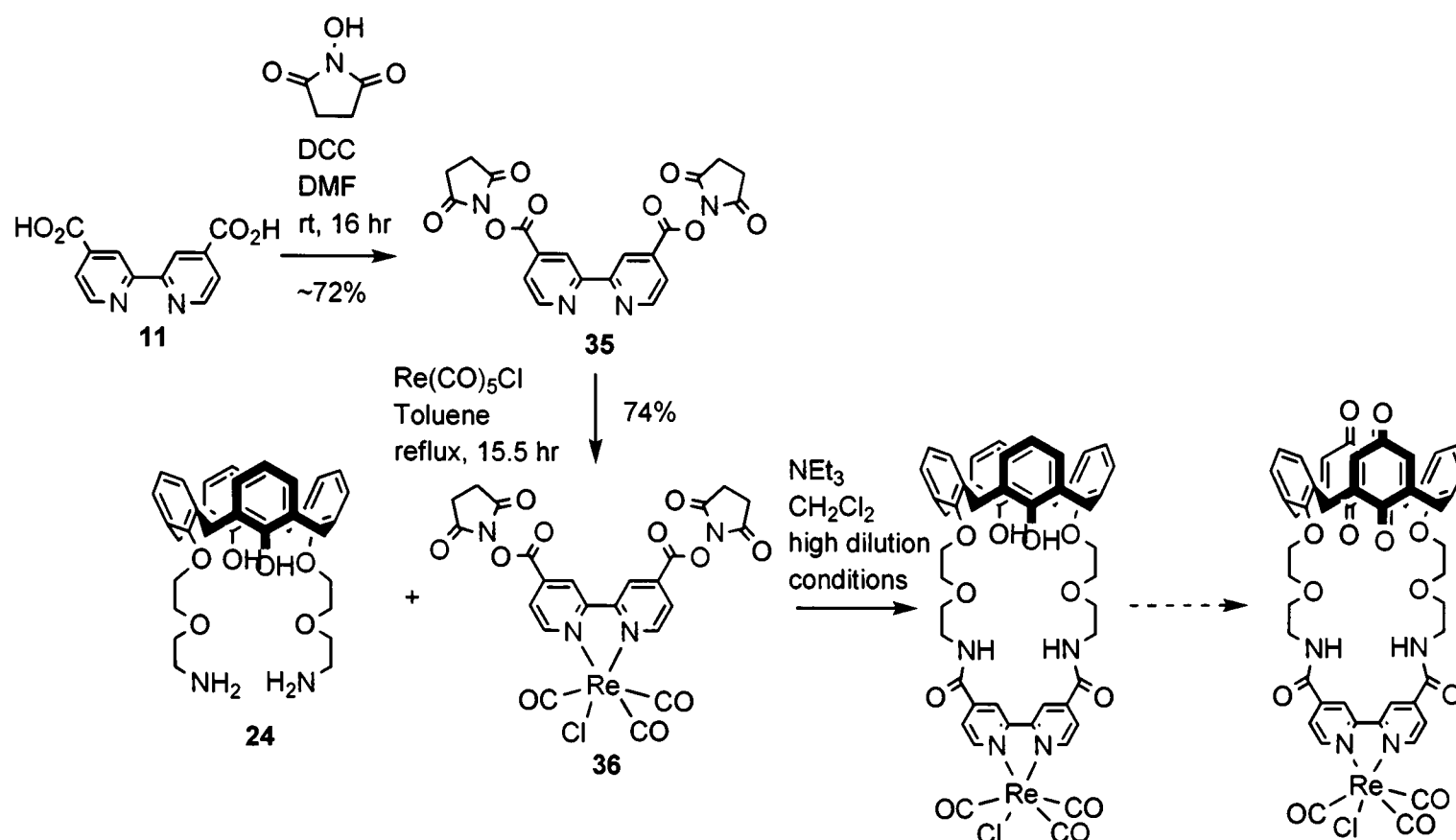
Instead alternative reaction conditions were explored using 4,4'-dimethyl-2,2'-bipyridine as a model system. A mixture of 4,4'-dimethyl-2,2'-bipyridine and rhenium pentacarbonyl chloride was heated under reflux under a N_2 atmosphere for 4.5 hours and the desired rhenium complex **34** precipitated from the reaction mixture as a yellow solid in 73% yield (Scheme 2.16). Therefore, the reaction with **18** was attempted using analogous conditions. Given the low yielding synthesis of receptor **18**, it was only possible to carry out this reaction on a very small scale. Unfortunately the desired product did not precipitate from the reaction mixture, but there was some evidence for its formation. For example, there was a peak at m/z 1199.2 corresponding to [rhenium bipyridyl receptor + MeCN + NH_4] $^+$ in the mass spectrum. However, it was not possible to isolate this given the small scale of the reaction. Since it would be difficult to synthesise receptor **18** in sufficient quantities due to the low

yielding macrocyclisation and oxidation steps, an alternative synthesis of the rhenium bipyridyl receptor was investigated.



Scheme 2.16 Model system testing conditions for complexation of rhenium pentacarbonyl chloride

The new synthetic strategy outlined in Scheme 2.17 avoids the problematic synthesis of macrocycle **33** by preparing the *N*-hydroxysuccinimide activated carboxylic acid **36**. This can be reacted with bis-amine **24** forming the rhenium macrocycle, which can be oxidised to the target receptor. Initially precursor **36** was prepared in two steps from compound **11**. The *N*-hydroxysuccinimide activated carboxylic acid **35** was synthesised in approximately 72% yield by reacting compound **11** with *N*-hydroxysuccinimide in the presence of DCC in DMF.⁷⁶ It was not possible to obtain an accurate yield due to difficulties removing the *N,N'*-dicyclohexylurea by-product, but this could be removed during the next synthetic step. Compound **35** was heated under reflux with rhenium pentacarbonyl chloride in toluene for 15.5 hours, during which time the product **36** precipitated from the reaction mixture. Compound **36** was isolated as an orange solid in 74% yield and this was reacted with bis-amine **24** in the presence of triethylamine under high dilution conditions in CH₂Cl₂. The ¹H NMR spectrum of the crude reaction mixture indicated a number of products had formed, including the macrocycle as shown by the peak at *m/z* 1135.28 in the mass spectrum. Purification of this complex product mixture was attempted by column chromatography and preparative TLC. While a number of yellow bands were isolated, none of these corresponded to the pure rhenium macrocycle. Consequently, the oxidation to the target rhenium bipyridyl calix[4]diquinone receptor was not attempted.



Scheme 2.17 Attempted alternative synthesis of the target rhenium bipyridyl calix[4]diquinone receptor

Thus, it was not possible to isolate the target rhenium bipyridyl receptor, and its synthesis was not investigated any further due to synthetic difficulties.

2.3.3.2. Ion-Pair Binding Studies of Receptor 18

Analogous UV/visible spectroscopy titration experiments to previous studies were carried out to study the cation binding ability of the calix[4]diquinone bipyridyl receptor **18**. It was believed that the larger size of the bipyridine anion binding unit might also influence the size of the cation binding cavity, and therefore the effect of larger cations, such as caesium, and divalent cations, such as barium, was also investigated.

The absorbance spectrum of receptor **18** was similar to that of the related receptors **16-17**, although the calix[4]diquinone $n\text{-}\pi^*$ absorption band is hypsochromically shifted to 295 nm. Similar results to other studies were obtained, with insufficient changes in the absorbance spectra to infer cation binding in the absence of chloride (Figure 2.36a) and enhanced binding of the ion-pairs NH_4Cl and KCl in CH_3CN (Figure 2.36b, Table 2.5). Interestingly, there was no evidence of NaCl binding to the receptor, possibly due to the larger size of the macrocycle cavity, and both KCl and NH_4Cl bind to the receptor with similar affinities.

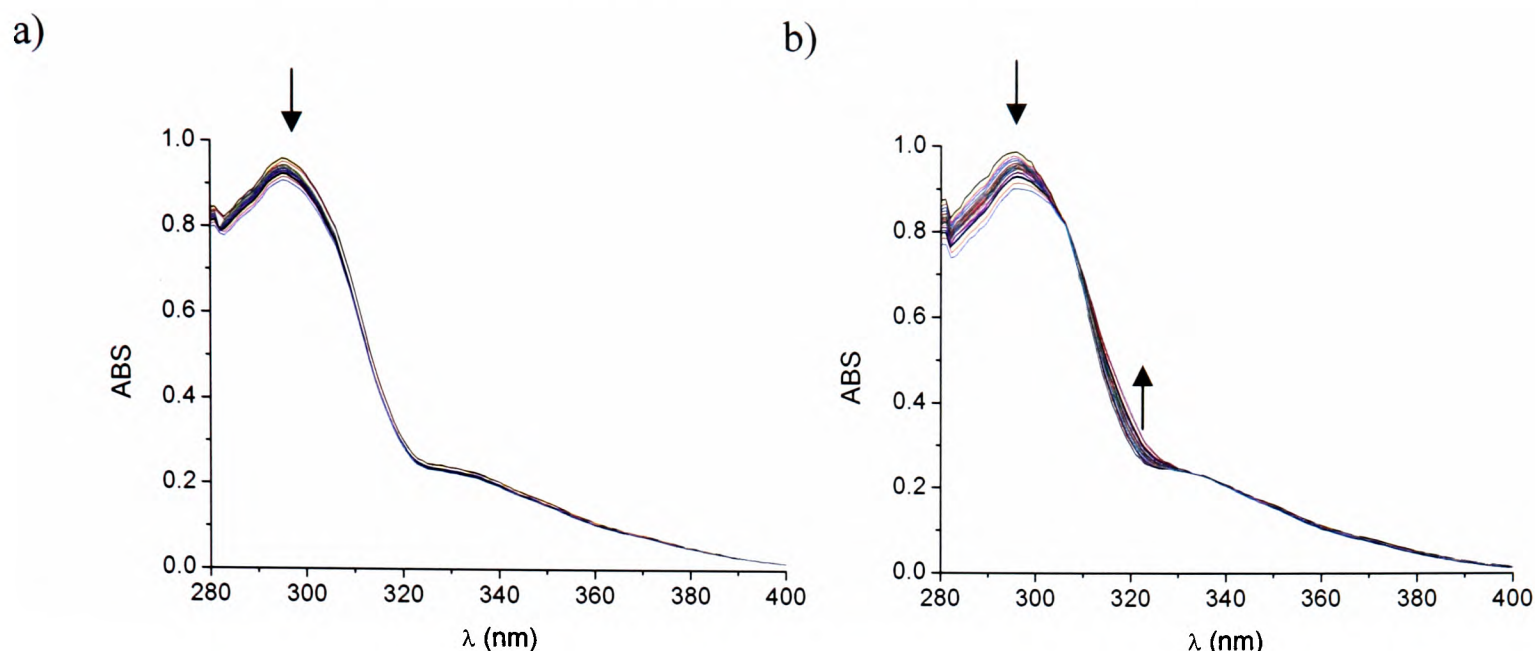


Figure 2.36 Changes in the absorbance of receptor **18** upon addition of ammonium cations in the a) absence and b) presence of one equivalent of TBACl in CH₃CN at 298 K

	log K _M ⁺			
	Na ⁺	K ⁺	NH ₄ ⁺	Ba ²⁺
18	-	-	-	3.68*
18.TBACl	-	3.63 [#]	3.72	3.87

Table 2.5 Association constants derived from SPECFIT analysis of UV/visible spectroscopy titrations in CH₃CN at 298 K. Errors < 15%. - = no evidence of binding, # = association constant derived from addition of 15 equivalents of cation, * = < 22% error

The effect of larger cations was then explored, initially focusing on the addition of caesium cations. Unfortunately, CsClO₄ was only sparingly soluble in CH₃CN at the concentration required for experiments. Preliminary experiments in the presence of one equivalent of chloride anions indicated ion-pair binding, but it was not possible to obtain any quantitative data. Therefore, attention was focused on the effect of the divalent barium cation. Upon addition of barium there were significant changes in the absorbance spectra, with the disappearance of the band at 295 nm and appearance of a new one bathochromically shifted to 306 nm (Figure 2.37a). The absorbance changes were enhanced in the presence of one equivalent of chloride anions (Figure 2.37b). It was possible to obtain 1:1 association constants from the titration data using SPECFIT analysis and these confirm that barium binding is enhanced in the presence of chloride (Table 2.5).

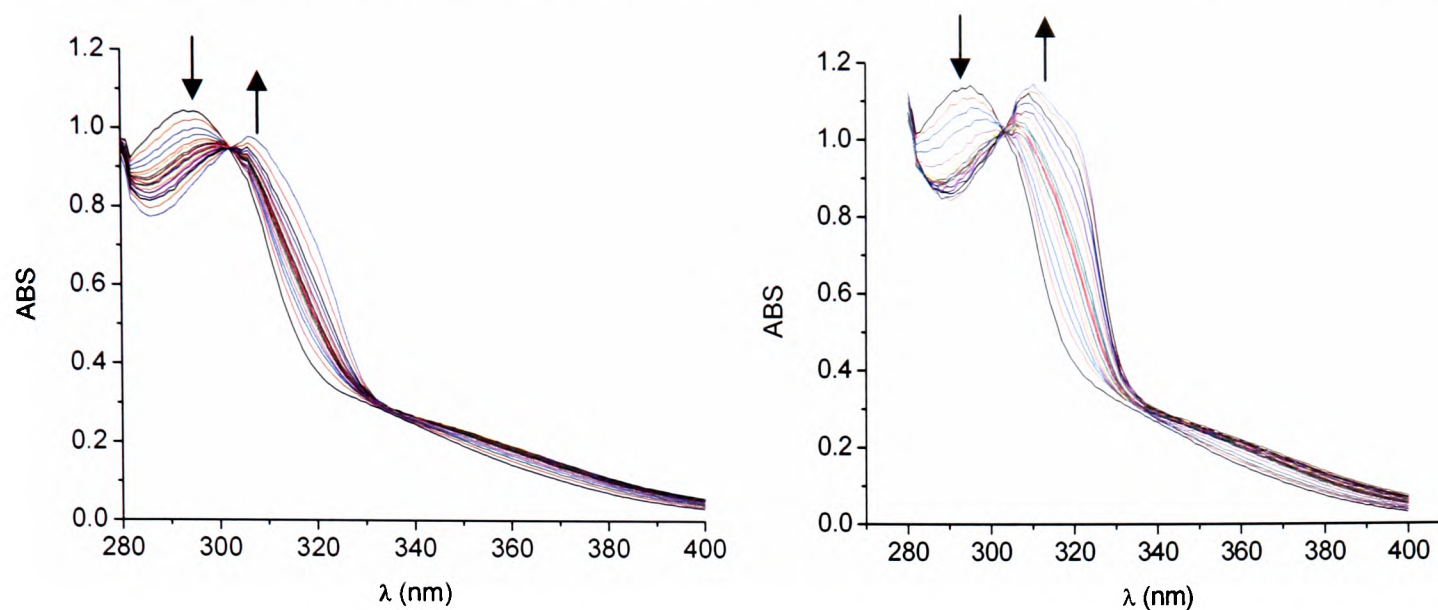


Figure 2.37 Changes in the absorbance of receptor **18** upon addition of barium cations in the a) absence and b) presence of one equivalent of TBACl in CH_3CN at 298 K

It would have been interesting to investigate the effect of the anion on ion-pair binding, both by UV/visible and ^1H NMR spectroscopy titration experiments. Unfortunately, the limited amount of receptor **18** prevented further ion-pair binding studies.

2.4. Cryptand Ion-Pair Receptors

In the previous sections, a number of cooperative AND ion-pair receptors have been synthesised and studied using a number of techniques. Previous work within the group^{22, 67} and many of the X-ray crystal structures in Section 2.3.1 have demonstrated a π -stacking interaction between one of the calixarene rings and the anion binding unit. It has been proposed that this interaction is important for cooperative AND ion-pair recognition. It was envisaged that ion-pair recognition could be enhanced by synthesising cryptand analogues of the receptors in Sections 2.2 and 2.3, since this would increase the number of possible π -stacking interactions between the calix[4]diquinone unit and anion binding unit. The design of the heteroditopic receptors was modified slightly for the cryptand analogues to include a macrocycle on the lower rim of the calixarene as the anion binding unit (Figure 2.38). Initially the calix[4]arene cryptand analogue in Figure 2.38b would be prepared before oxidation to the target calix[4]diquinone receptor using methods developed in previous sections.

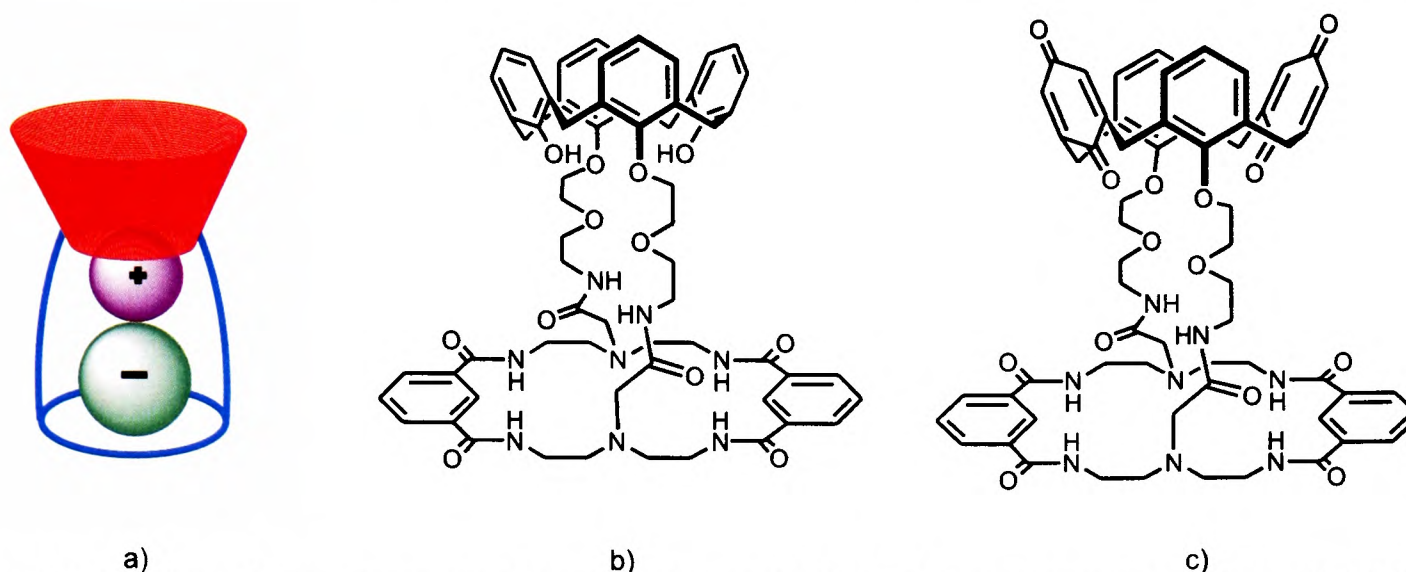


Figure 2.38 Design of target receptors a) general schematic b) calix[4]arene cryptand and c) calix[4]diquinone cryptand ion-pair receptor

2.4.1. Synthesis of Macrocycles

There are several possible strategies for synthesising the target receptors but given the typically low yields associated with macrocyclisation, the synthesis of the macrocycle in Figure 2.39 was investigated first. It could then be attached to the calix[4]arene scaffold before the target receptor was synthesised by oxidation to the calix[4]diquinone.

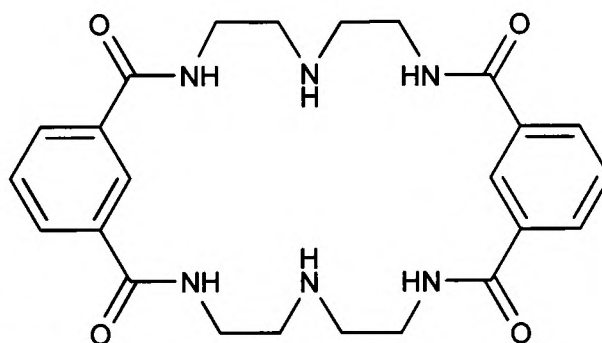
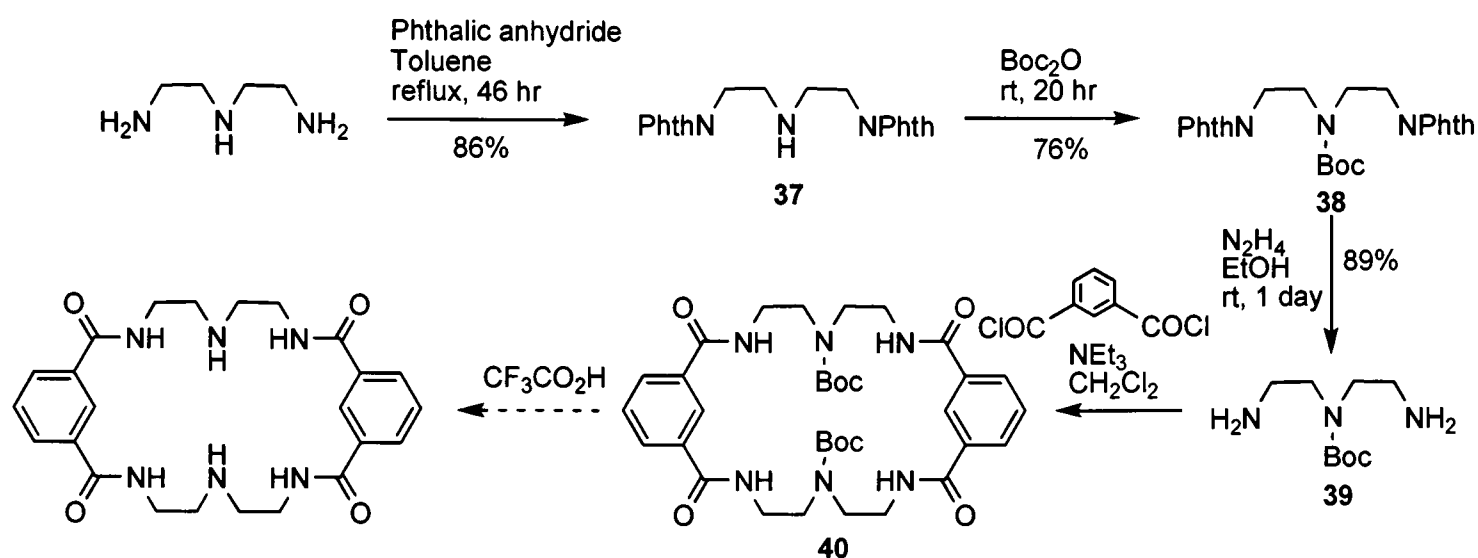


Figure 2.39 Target macrocycle: precursor to the desired receptors

The synthesis of a related pyridine based macrocycle has previously been reported in the literature using a protection/deprotection approach.⁷⁷ The pyridine receptor **2** was an inferior ion-pair receptor to those based on isophthalamide (see Section 2.2.2), and therefore the synthesis of this pyridine based macrocycle was not attempted using this method. Nevertheless, the synthetic route was adapted for the preparation of the isophthalamide based macrocycle (Scheme 2.18). Firstly, the primary amine groups of diethylenetriamine were protected using phthalic anhydride by heating under reflux in toluene for 2 days and compound **37** was isolated as an orange solid in 86% yield. The secondary amine of **37** was then protected by reaction with di-*tert*-butyldicarbonate to give compound **38** in 76% yield.

The phthalimide groups were selectively removed using hydrazine monohydrate to give **39** in 89% yield. The Boc protected macrocycle **40** was formed by reaction of **39** with isophthaloyl dichloride under high dilution conditions. It did not prove possible to isolate **40** in satisfactory purity by silica gel chromatography and the yield was less than 4%.



Scheme 2.18 Attempted synthesis of the isophthalamide macrocycle

The approximate yield of macrocycle **40** from the macrocyclisation step is much lower than the reported 30% yield for the synthesis of the related pyridine macrocycle (Figure 2.40).⁷⁷

The difference could be due to the greater preorganisation of the pyridine macrocycle. Given the number of steps involved in the preparation of these macrocycles, several alternative one-pot syntheses were explored.

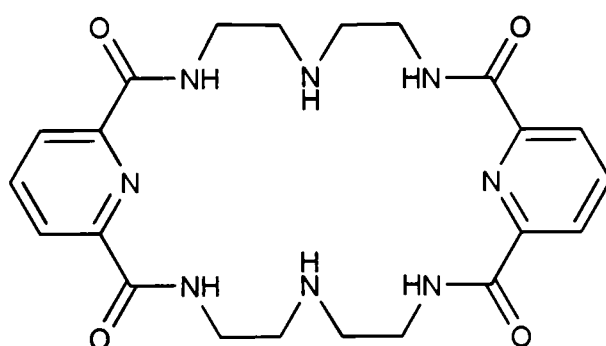


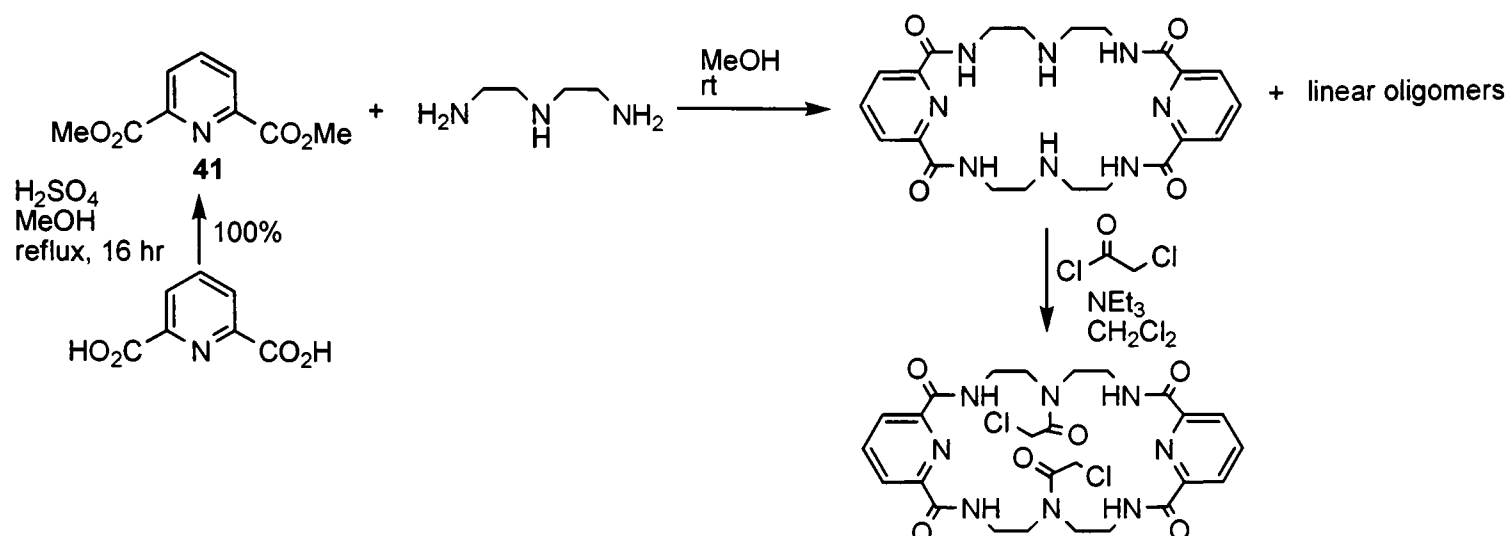
Figure 2.40 Pyridine macrocycle

There are a number of one-pot syntheses of similar pyridine macrocycles in the literature.⁷⁸⁻⁸⁰

For this reason and due to the greater preorganisation in pyridine systems, initial investigations focused on the one-pot synthesis of the pyridine macrocycle in Figure 2.40.

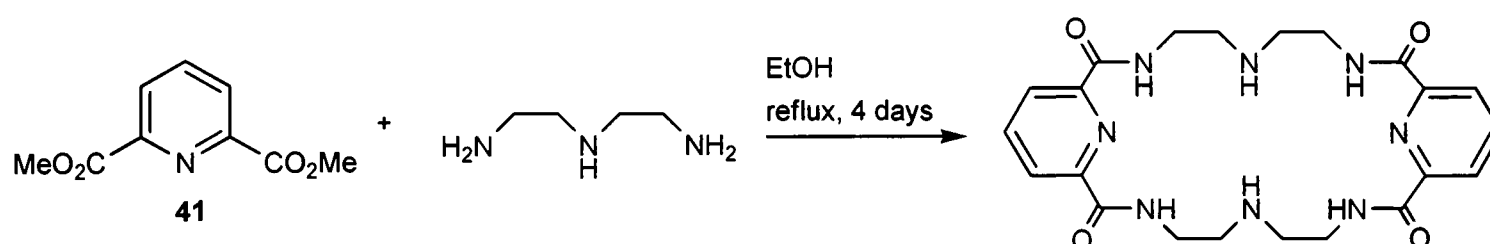
Jurczak's⁷⁸ strategy was employed by reacting compound **41**, prepared from 2,6-pyridinedicarboxylic acid,⁵⁶ and diethylenetriamine in MeOH, both in the presence and

absence of sodium methoxide, at room temperature for several days (Scheme 2.19). While the desired macrocycle formed in both cases, it did not precipitate from the reaction mixture like Jurczak's macrocycles, and unfortunately it could not be separated from the mixture of linear oligomeric by-products by column chromatography. Attempts to improve purification of the macrocycle by functionalisation with chloroacetyl chloride were also unsuccessful.



Scheme 2.19 Attempted one-pot synthesis of the pyridine macrocycle

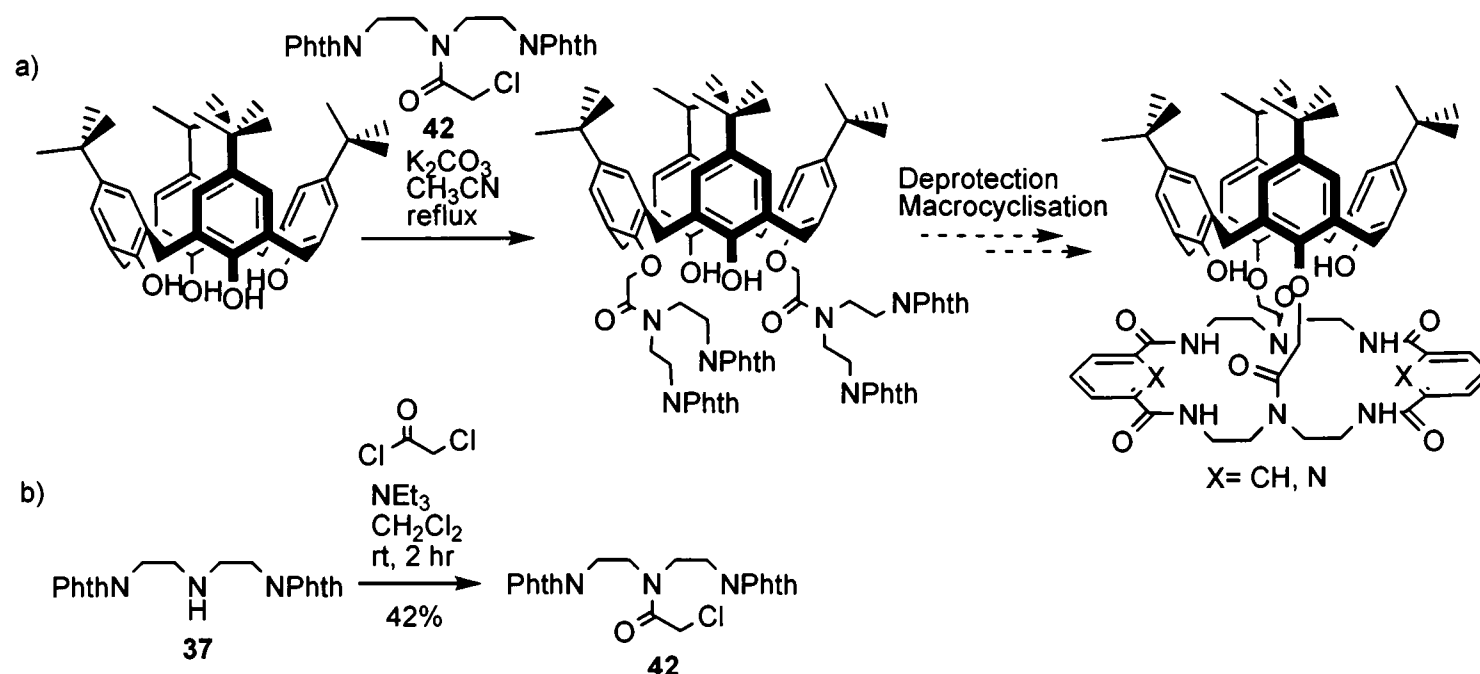
In a final one-pot synthesis attempt, compound **41** and diethylenetriamine were heated under reflux in EtOH for four days,⁷⁹ but it was again not possible to separate the macrocycle from the oligomeric by-products (Scheme 2.20).



Scheme 2.20 Attempted one-pot synthesis of the pyridine macrocycle

2.4.2. Alternative Synthetic Strategy

The synthesis of the target receptors in the previous section was hindered by low yields and purification difficulties. Therefore another strategy was explored where calix[4]arene functionalisation is followed by macrocyclisation (Scheme 2.21a). The feasibility of this approach was investigated using commercially available *tert*-butylcalix[4]arene as a model system.



Scheme 2.21 a) Proposed synthesis of *tert*-butylcalix[4]arene cryptand model system and b) synthesis of precursor **42**

Precursor **42** was successfully synthesised in 42% yield by reacting precursor **37** with chloroacetyl chloride in CH_2Cl_2 (Scheme 2.21b). Alkylation of *tert*-butylcalix[4]arene with **42** was attempted according to Scheme 2.21a. Disappointingly, only the monoalkylated product **43** was isolated in 19% yield from the reaction mixture (Figure 2.41), in addition to unreacted *tert*-butylcalix[4]arene. Since the desired bisalkylated product did not form, this strategy was not explored any further.

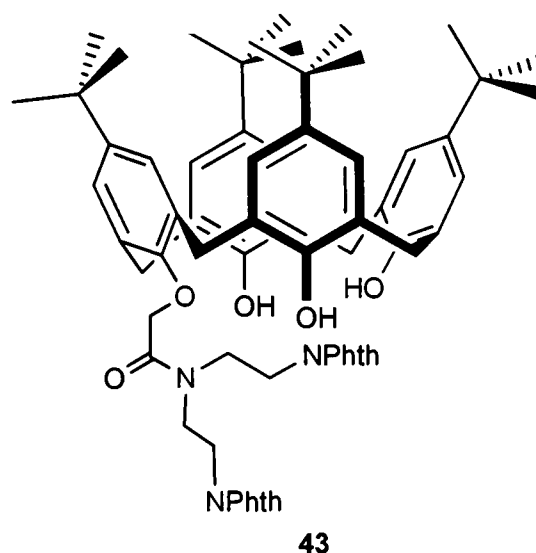


Figure 2.41 Monoalkylated product **43**

2.5. Zinc Schiff Base Calix[4]arene Anion Receptors

Receptors containing Lewis acid centres such as uranyl or zinc have been shown to bind anions (see Section 1.3.3.2). Reinhoudt and co-workers have reported several calixarene based uranyl receptors for anions and neutral molecules, including the receptor in Figure 2.42a.^{81, 82} The aim of this project was to incorporate zinc Schiff base complexes

into a bis-calixarene structure. Figure 2.42b shows the design of the target receptor, where an anion can be complexed between the two zinc centres.

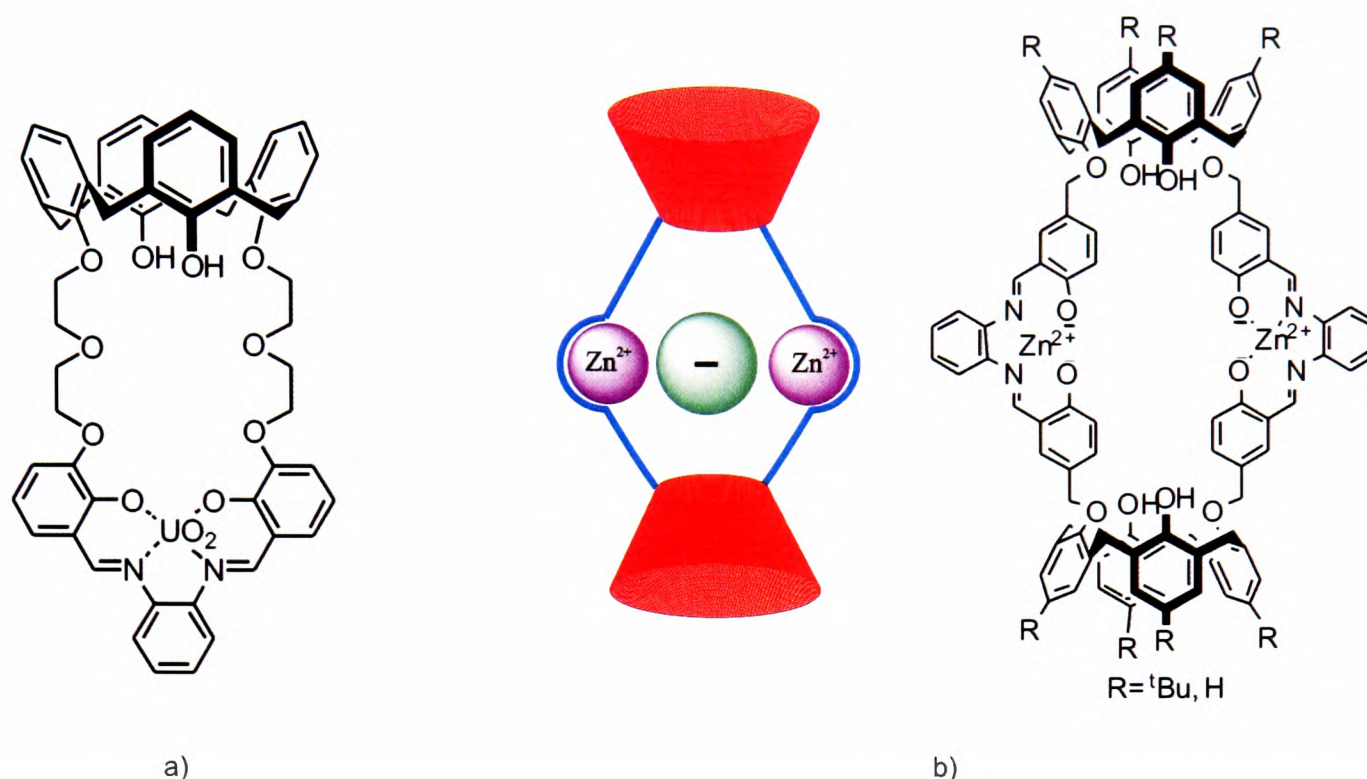
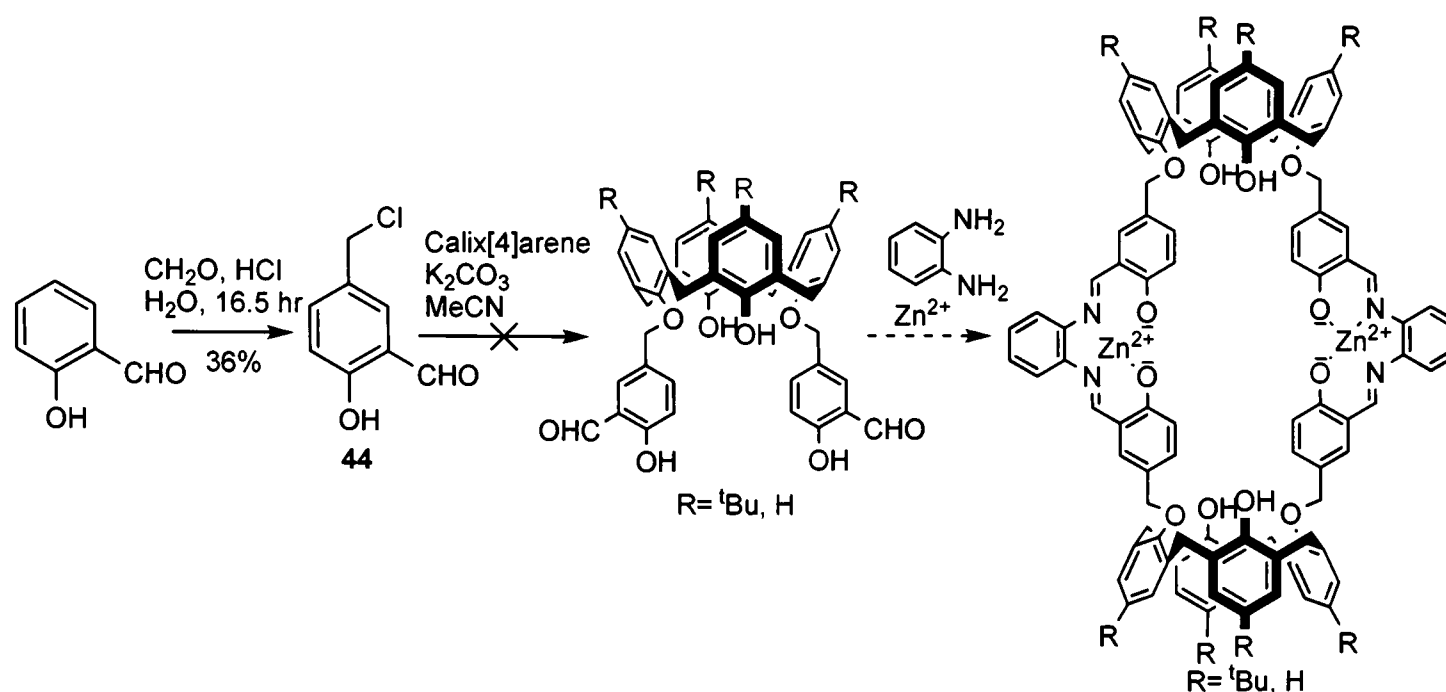


Figure 2.42 a) Reinhoudt's uranyl calix[4]arene receptor for neutral molecules and b) design of the target zinc Schiff base calix[4]arene anion receptor

2.5.1. Initial Synthetic Strategy

Scheme 2.22 outlines the first proposed synthesis of the target receptor. Compound **44** was successfully synthesised in 36% yield according to a literature procedure.⁸³ Subsequent attempts to alkylate *tert*-butylcalix[4]arene with **44** produced an insoluble orange solid, and unreacted *tert*-butylcalix[4]arene was recovered in almost quantitative yield. Despite modifying the reaction conditions, including the use of KI as a catalyst, the desired product was not synthesised.

However, the alkylation of calix[4]arene under similar reaction conditions appeared to be more promising. The mass spectrum of the crude reaction mixture indicated a mixture of unreacted calix[4]arene and mono-, di- and tri- and tetra-alkylated products (Figure 2.43). The complex nature of the ¹H NMR spectrum also confirmed the presence of multiple products, but attempts to purify this mixture by column chromatography and recrystallisation proved unsuccessful.



Scheme 2.22 Proposed synthesis of the zinc Schiff base calix[4]arene anion receptor

The presence of the tri- and tetraalkylated products was unexpected since tri- and tetraalkylation usually require stronger bases than K_2CO_3 , like NaH (see Scheme 2.3). A more likely explanation comes from consideration of the pK_a values for *tert*-butylcalix[4]arene, calix[4]arene and **44**. The phenolic proton of **44**, with a calculated pK_a value of 7.93,⁸⁴ is more likely to be deprotonated than the most acidic proton of calix[4]arene (pK_a 9.38⁸⁴) or *tert*-butylcalix[4]arene (pK_a 9.53⁸⁴) leading to competition between alkylation of the calixarene scaffold and deprotonation of compound **44**. Deprotonation of **44** appears to dominate in the reaction with *tert*-butylcalix[4]arene, while the pK_a of the calix[4]arene is sufficiently low enough for alkylation to compete with deprotonation. The tri- and tetraalkylated products observed in the mass spectrum most likely result from reaction of the mono- and di-alkylated products with further equivalents of compound **44**.

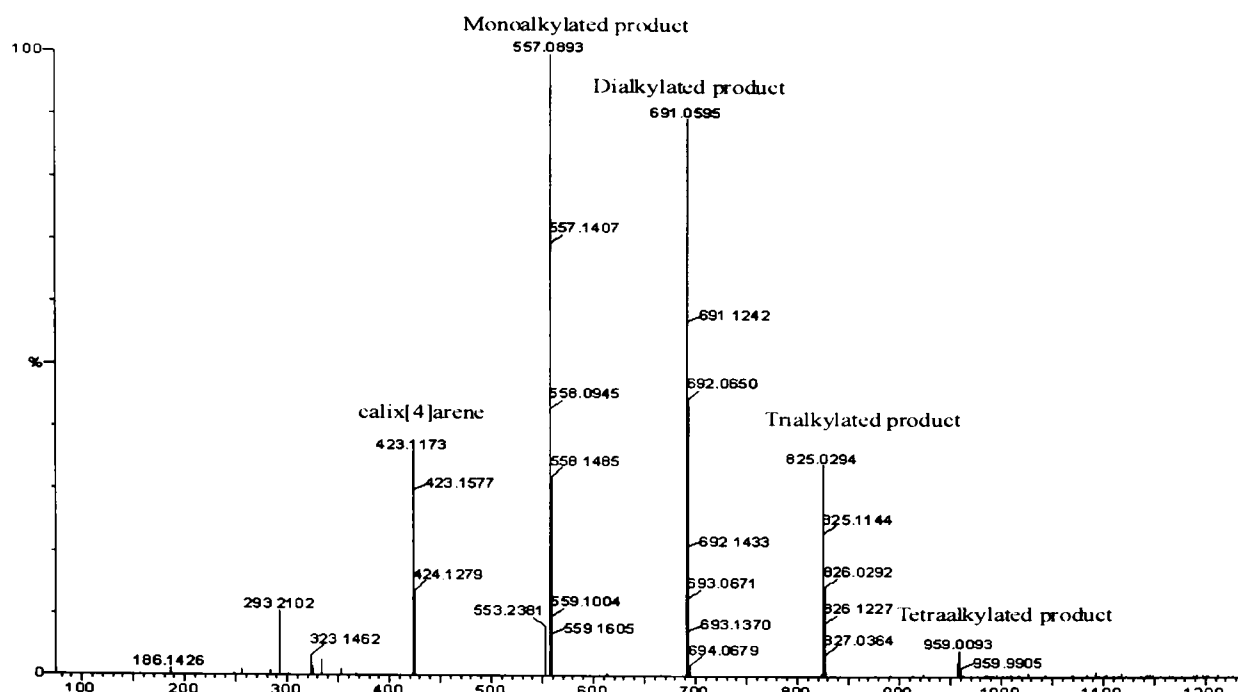
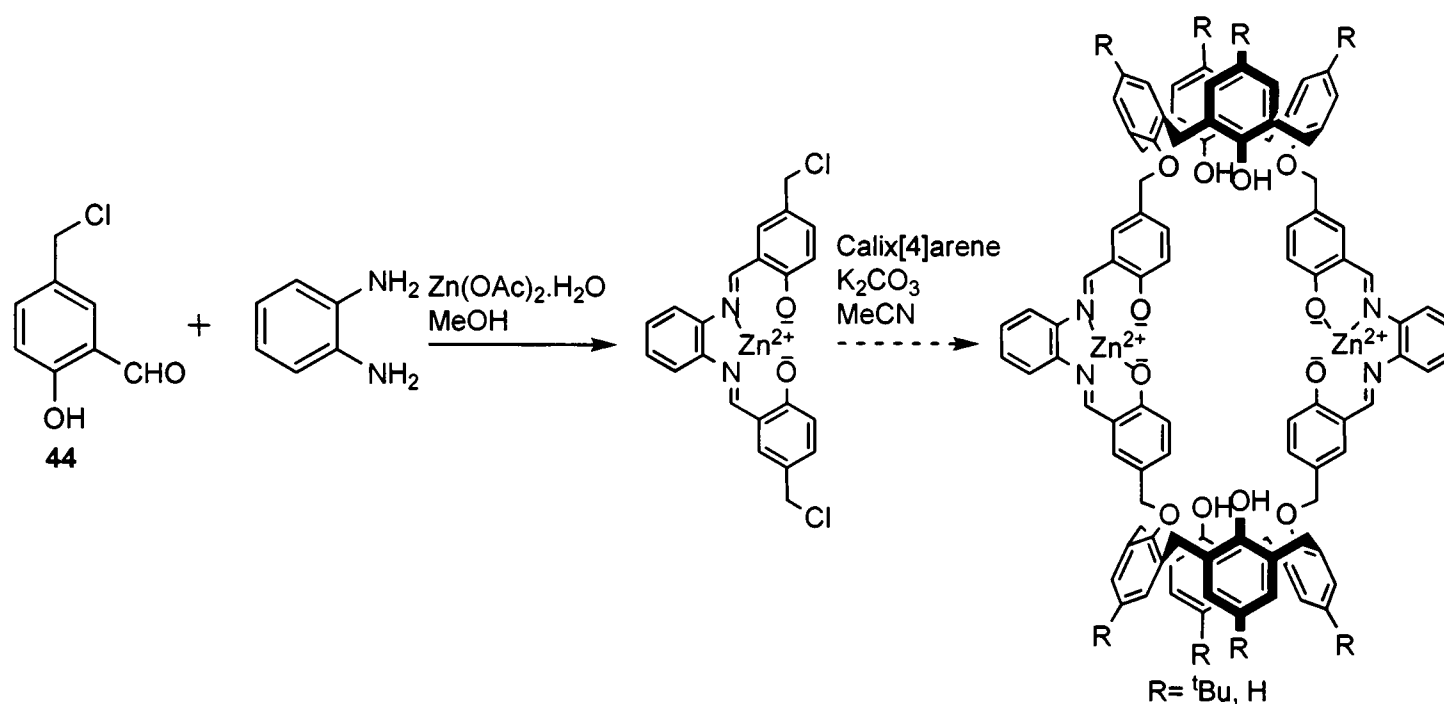


Figure 2.43 Electrospray mass spectrum of the crude reaction mixture from alkylation of calix[4]arene with **44**

2.5.2. Second Strategy: Zinc Schiff Base Complexes Synthesis

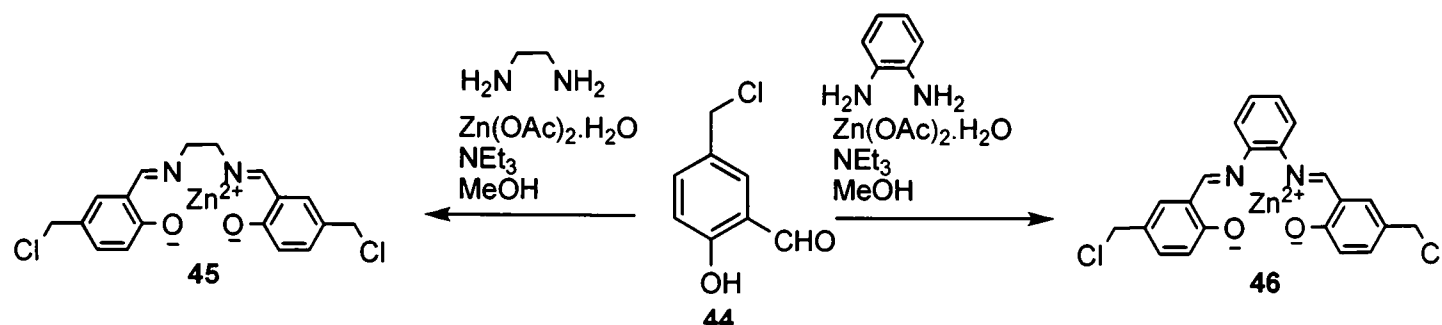
Given the synthetic difficulties detailed above with the reactivity of the hydroxyl group of **44**, a new strategy was developed where the zinc Schiff base complex is synthesised first and then used to bridge two calix[4]arene units (Scheme 2.23).



Scheme 2.23 Proposed modified synthesis of the zinc Schiff base calix[4]arene complex

There are numerous examples of zinc Schiff base complexes in the literature^{83, 85, 86} and the synthesis of complexes **45** and **46** was explored using reaction conditions adapted from some of these preparations (Scheme 2.24). Initially the synthesis of complex **45** was attempted in the absence of triethylamine but this led to multiple products, as evidenced by the complex nature of the ¹H NMR spectrum.⁸⁵ In the presence of triethylamine, impure complexes **45** and

46 precipitated from the reaction mixture as yellow solids.⁸⁶ However, this strategy was not pursued due to the limited solubility of **45** and **46** and purification difficulties.



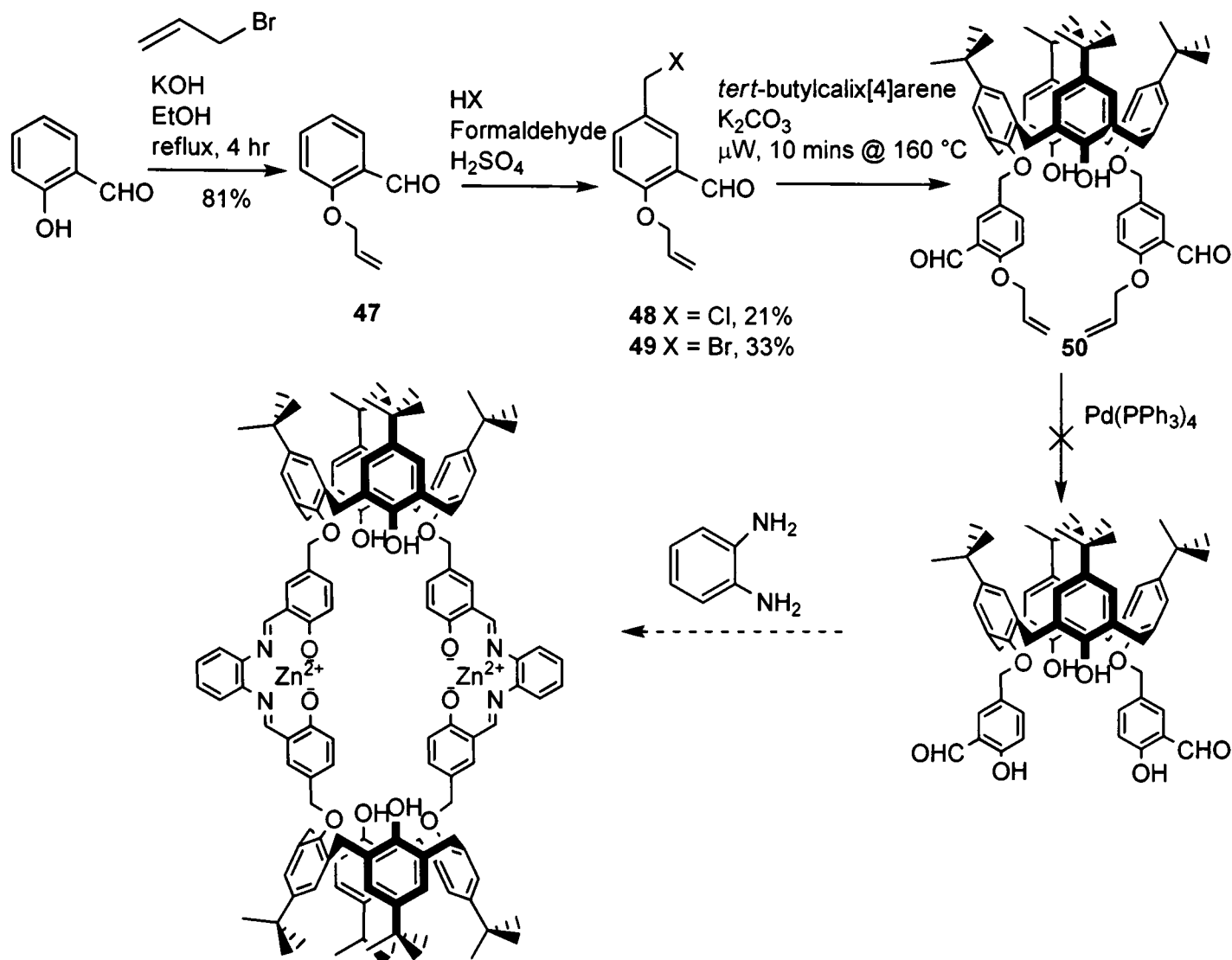
Scheme 2.24 Synthesis of impure complexes **45** and **46**

2.5.3. Third Strategy: Synthesis Employing Protecting Groups

The next synthetic strategy employed the use of protecting groups to mask the reactivity of the hydroxyl group. There are a number of potential protecting groups but the allyl group was chosen because of the literature precedent in Reinhoudt's synthesis of the calix[4]arene uranyl Schiff base complex in Figure 2.42a.⁸¹ The modified synthesis of the target receptor in Scheme 2.25 also employs their protection/deprotection strategy. The hydroxyl group is protected in the first step with an allyl group and a halomethyl group is then introduced, which can be used to attach the protected salicylaldehyde derivative to *tert*-butylcalix[4]arene. The allyl protecting groups are removed by a palladium catalysed reaction and the target compound can be synthesised by zinc templated Schiff base formation.

2.5.3.1. Synthesis of Precursors **48-49**

Compound **47** was successfully prepared according to a literature procedure in 81% yield⁸⁷ before chloromethylation was attempted, using the same conditions as for the preparation of **44**. Unfortunately only a small amount of product formed and varying the reaction conditions, including changing the solvent to acetic acid and using ZnCl_2 as a catalyst, did not improve the yield. While heating the reaction mixture at 70 °C improved the yield, the lability⁸⁸ of the allyl protecting group was a concern as a number of side products also formed. Instead, the reaction was carried out at room temperature in HCl for five days using paraformaldehyde



Scheme 2.25 Modified synthesis using a protection/deprotection approach

rather than aqueous formaldehyde, and a catalytic amount of H_2SO_4 . It was possible to isolate **48** in 21% yield following purification by Kugelrohr distillation. Attempts to improve this yield were unsuccessful. Instead bromomethylation was investigated as it has been found to occur at a faster rate than chloromethylation in similar systems. This has been attributed to the greater acidity of HBr compared with HCl and greater reactivity of the resulting benzyl bromide in nucleophilic displacements.⁸⁹ Indeed, compound **49** was synthesised in an analogous manner to **48**, except using 48% HBr , in the slightly improved yield of 33%.

2.5.3.2. Synthesis of Precursor **50** and Attempted Removal of Allyl Groups

Alkylation of *tert*-butylcalix[4]arene was carried out using both **48** and **49** (Scheme 2.25). While the desired product **50** was the major component of the reaction mixture, it did not prove possible to remove all impurities by column chromatography despite repeated purification attempts. Compound **50** also changes from a white to a brown solid over time, although the ^1H NMR spectrum remains unchanged. The mass spectrum of the mixture

had two peaks at m/z 1019.5 and 1051.5 corresponding to **50** and the related dicarboxylic derivative (Figure 2.44). There was no evidence of the carboxylic acid in the starting materials **48** or **49** by NMR spectroscopy or mass spectrometry, although a different ionisation technique was used. It is not known whether the dicarboxylic derivative is an artefact of the electrospray technique or a genuine impurity from aerial oxidation of the aldehyde. However, the deprotection of the allyl groups was attempted without further purification.

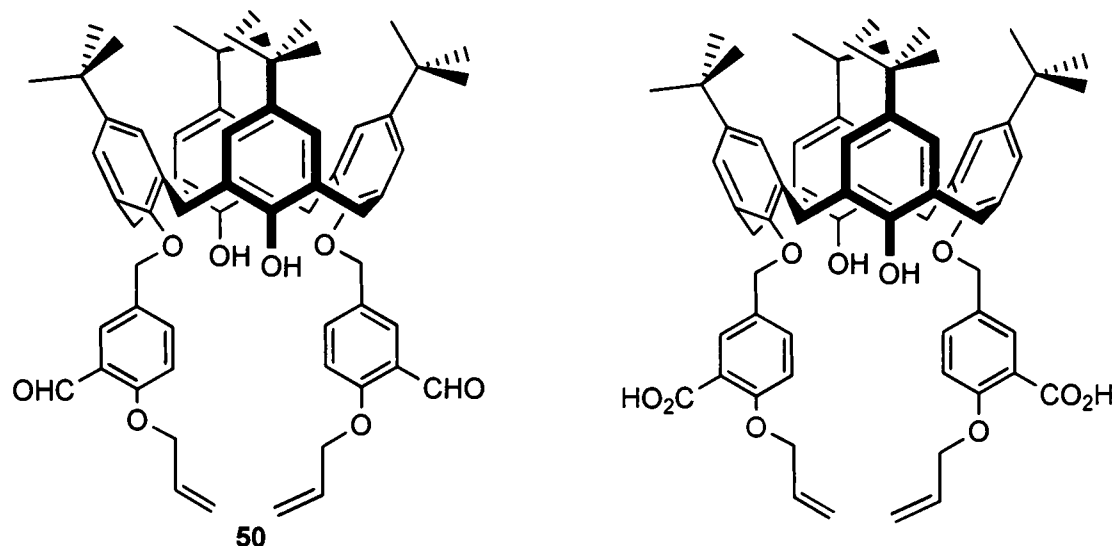
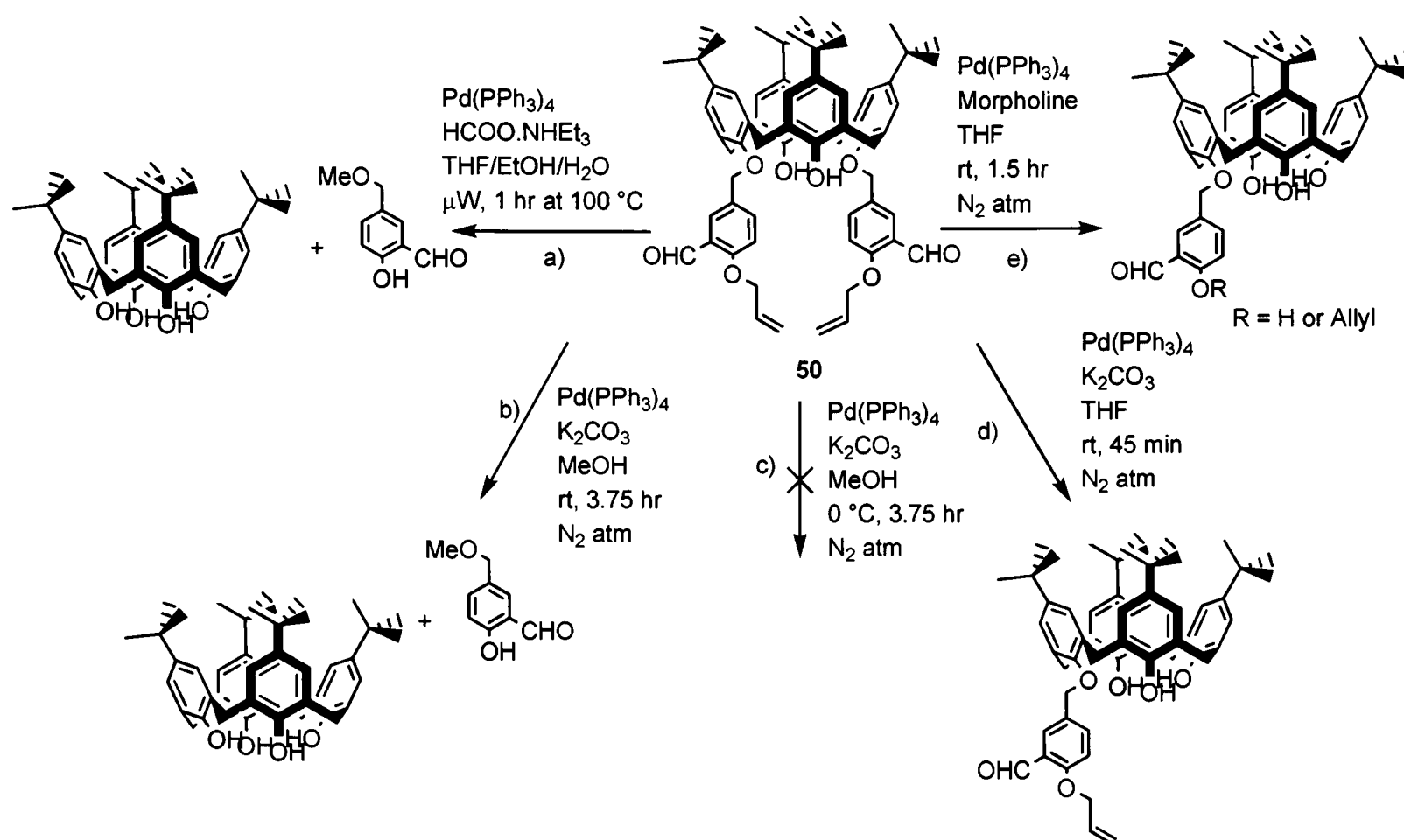


Figure 2.44 Products detected by electrospray mass spectrometry from the alkylation of *tert*-butylcalix[4]arene with **48** or **49**

Removal of the allyl protecting groups was initially attempted using the conditions from Reinhoudt's synthesis (Scheme 2.26a).⁸¹ Disappointingly, this led to cleavage of both the allyl and benzyl ether groups, with over 60% of the starting material recovered as *tert*-butylcalix[4]arene. It was subsequently discovered that triethylammonium formate is commonly used as a hydride source in palladium catalysed transfer hydrogenolysis,⁹⁰⁻⁹² and therefore these deprotection conditions were not suitable for this system.

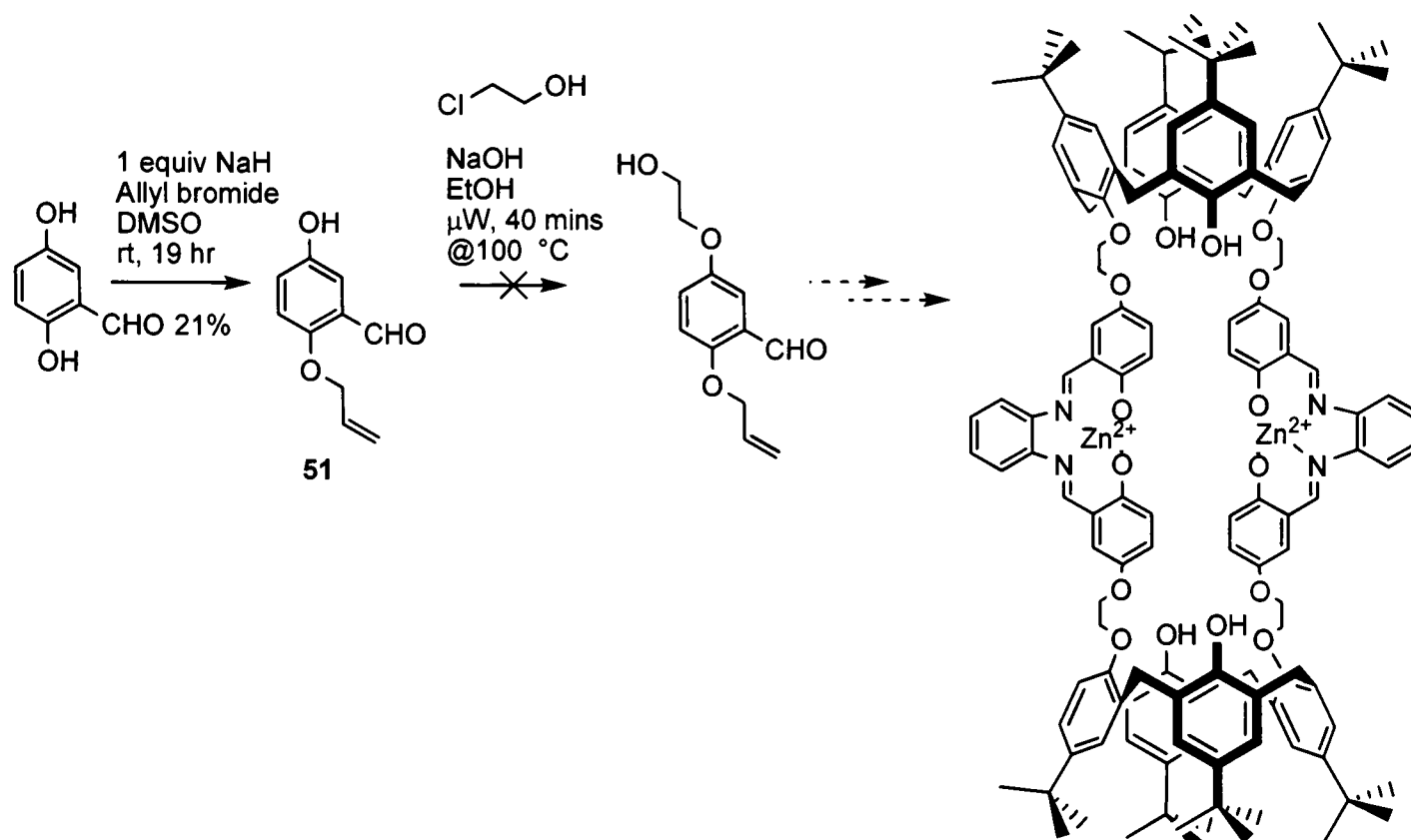
There are several allyl group deprotection strategies in the presence of benzyl ethers,⁹³⁻⁹⁶ but many of these, such as using NaBH_4/I_2 ,⁹³ were unsuitable due to the presence of the aldehyde group. Only methods which reported selective removal of the allyl ether in the presence of benzyl ethers and aldehydes were adapted. Scheme 2.26 summarises the unsuccessful attempts to remove the allyl protecting groups with the proposed products from the reactions, based on the ^1H NMR spectra of the reaction mixtures.^{95, 97}



Scheme 2.26 Attempted selective deprotections of allyl groups

2.5.4. A Final Strategy

Given the difficulties selectively removing the allyl protecting groups it was envisaged that removing the benzyl ether linkages would resolve these problems. Therefore another modified strategy was devised based on 2,5-dihydroxybenzaldehyde (Scheme 2.27). It was possible to selectively monoalkylate this adapting Kessar's strategy⁹⁸ using one equivalent of NaH in DMSO and the desired product **51** was isolated in 21% yield. However, subsequent attempts to improve this yield and react **51** with chloroethanol were unsuccessful, and work on this project was discontinued.



Scheme 2.27 Proposed alternative synthesis of the target compound

2.6. Conclusions and Future Work

The original family of cooperative AND ion-pair receptors has been expanded to include receptors with different anion binding units, macrocycle cavity sizes and calix[4]diquinone scaffolds. Two new *tert*-butylcalix[4]diquinone receptors, **1** and **2**, were successfully synthesised using thallium trifluoroacetate, but unfortunately this oxidant was not suitable for the oxidation of *tert*-butylcalix[4]arene macrocycles containing bipyridine and 1,3-phenylenediacetamide motifs. The use of chlorine dioxide as an alternative oxidant was investigated and for this reason, the synthesis of the novel calix[4]arene precursors and calix[4]diquinone receptors **15-18** was developed. This oxidation method appears to have a wider synthetic application than thallium trifluoroacetate, as it was possible to prepare receptor **18** based on bipyridine. However, the calix[4]diquinone receptors are much less soluble than the related *tert*-butylcalix[4]diquinone receptors, which might limit the utility of this oxidation method. This could be investigated in more detail by attempting the synthesis of receptors with anion binding site variation. Also, the synthesis of receptor **18** could be optimised to make the larger scale synthesis of its luminescent rhenium complex feasible for ion-pair binding studies.

The ion-pair binding properties of the new *tert*-butylcalix[4]diquinone and calix[4]diquinone receptors have been studied using ^1H NMR and UV/visible spectroscopy. These studies reveal that, like the original receptors, they are cooperative AND ion-pair receptors, showing little affinity for free cations and anions, but enhanced binding of ion-pairs such as NH_4Cl . The electrochemistry of receptors **1** and **17** has been studied for the first time. While it was possible to infer cation binding to receptor **1**, both in the absence and presence of an anion by shifts of the redox waves, conclusive results could not be obtained for receptor **17**. Unfortunately it was also not possible to obtain any quantitative information from these studies.

The synthesis of cryptand analogues of the heteroditopic receptors was investigated using a number of strategies, which were ultimately unsuccessful due to difficulties synthesising the necessary macrocyclic precursors. Synthetic challenges also prevented the synthesis of the calix[4]arene based zinc Schiff base anion receptor, despite employing a number of different strategies. Click chemistry could be investigated as a solution to these problems, since it provides an alternative means of attaching a suitable salicylaldehyde derivative to the calix[4]arene scaffold.

The calix[4]arene scaffold has been successfully exploited to synthesise a number of heteroditopic receptors for binding contact ion-pairs. The next chapter will extend this by investigating the synthesis of calix[4]arene based interlocked structures.

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Chapter 3

Calix[4]arene Based Interlocked Structures for Anion Recognition

3. Calix[4]arene Based Interlocked Structures for Anion Recognition

3.1. Introduction

3.1.1. Calixarenes in Interlocked Structures

There has been considerable interest in the synthesis of interlocked structures, such as catenanes and rotaxanes, due to their potential applications as molecular machines, switches and sensors (see Section 1.4.2).¹⁻⁵ As discussed in Chapter 2, the calixarene framework has been exploited for the development of cation, anion and ion-pair receptors. It has also been incorporated into interlocked structures and this chapter will review literature examples before describing efforts towards the synthesis of new calix[4]arene based interlocked structures.

The calixarene is a particularly versatile framework for interlocked structures since it can be used as the macrocycle component in both catenanes and rotaxanes, and as a stopper in the axle components of rotaxanes. The large size and ease of functionalisation make calixarenes attractive as stoppers and there are several examples of rotaxanes with calix[4]arene stoppers,⁶⁻⁸ including Vögtle's rotaxane shown in Figure 3.1a.⁷ The binding properties of larger calixarenes, such as calix[6]arene, can be exploited to thread cationic axle components through the calixarene macrocyclic cavity to form rotaxanes. Arduini and co-workers have reported a number of pseudorotaxane and rotaxane structures, where cation- π and hydrophobic interactions direct interpenetration of viologen based threads through the electron rich macrocyclic cavity.⁹⁻¹³ The rotaxane in Figure 3.1b with an asymmetric axle component was synthesised exploiting unidirectional threading through the calix[6]arene cavity.¹¹

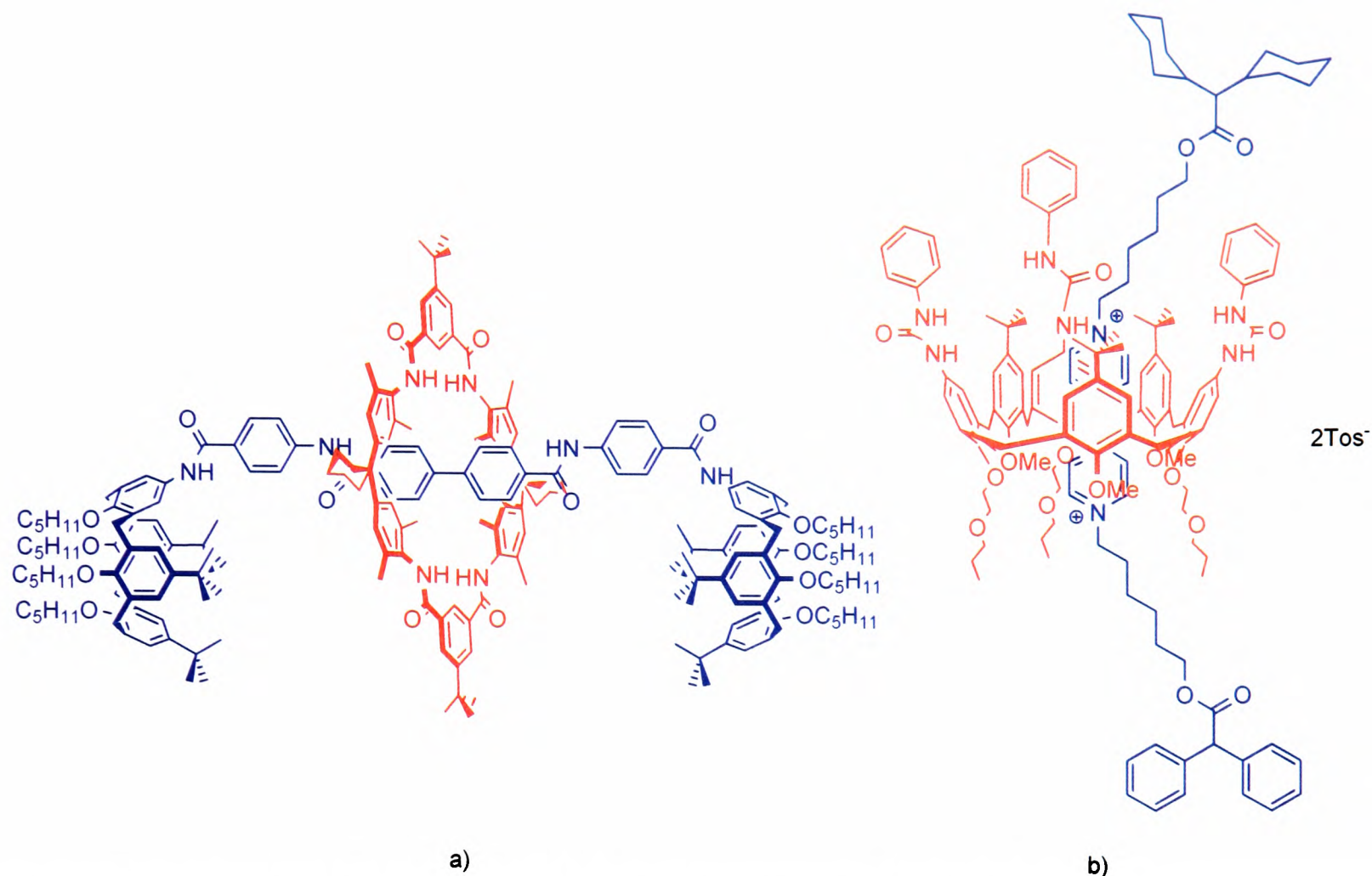


Figure 3.1 Calixarenes as the a) stopper and b) macrocycle components in rotaxanes

The macrocycle cavity of calix[4]arene is not large enough to include thread components, but through functionalisation of the upper and/or lower rim the calix[4]arene framework has been incorporated into a number of catenane and rotaxane structures. The synthesis of these structures often exploits the cationic, neutral and anion templation methods introduced in Section 1.4.2. A number of catenanes have been synthesised using donor/acceptor interactions between hydroquinone and 4,4'-paraquat motifs. Wei and co-workers incorporated the 4,4'-paraquat motif through lower rim functionalisation,¹⁴ whereas Huang's [2]catenane exploits the electron rich nature of the substituted hydroquinone calix[4]arene framework (Figure 3.2a).¹⁵

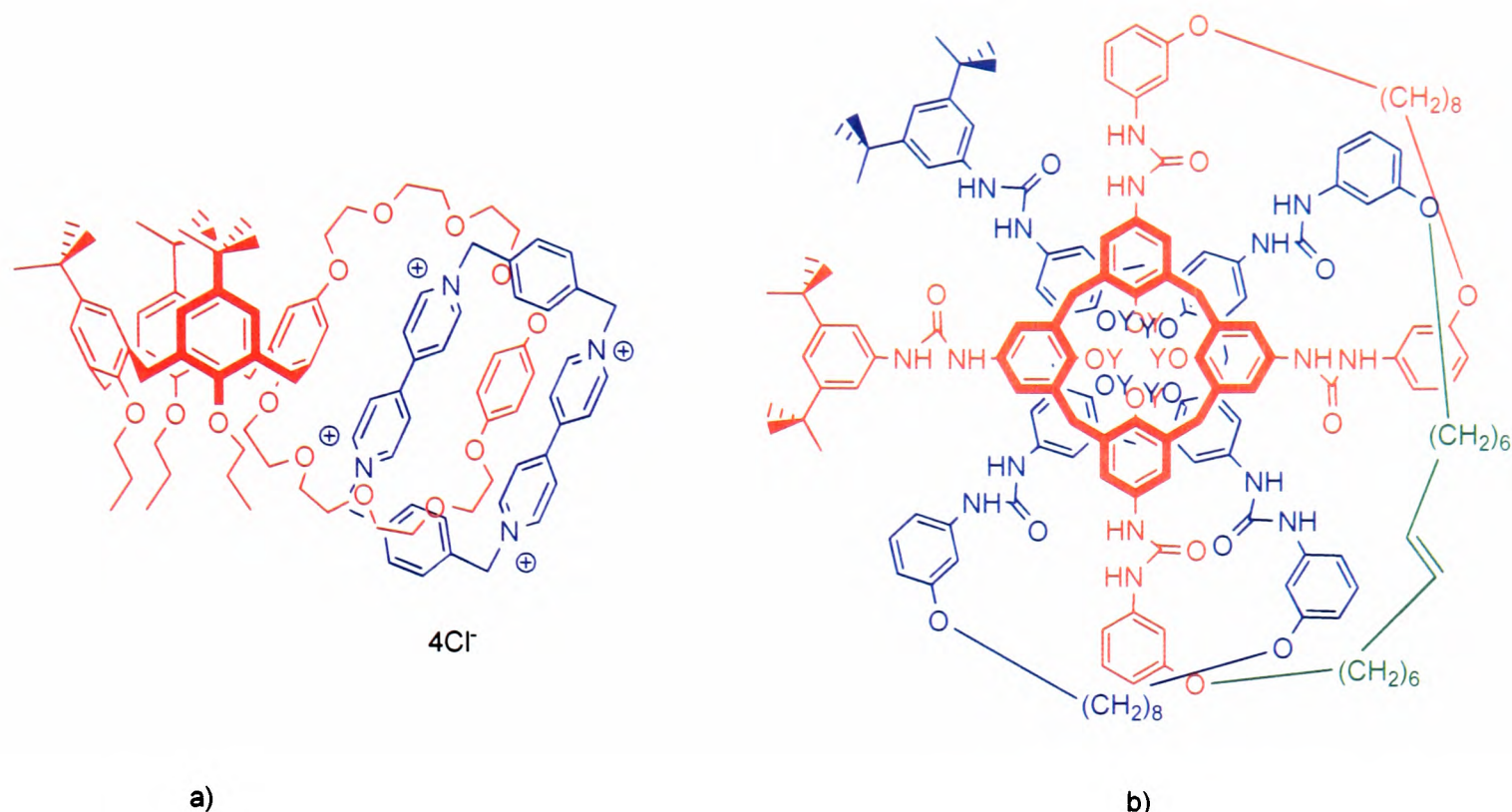


Figure 3.2 Templated assembly of interlocked structures through a) donor/acceptor interactions and b) hydrogen bonding

A number of interlocked structures, including the rotaxane in Figure 3.1a, have been synthesised using neutral templation. Böhmer and co-workers have reported the synthesis of catenanes and rotaxanes, including the fourfold [2]rotaxane in Figure 1.46b, exploiting the hydrogen bonding dimerisation of tetraurea calix[4]arenes.¹⁶⁻¹⁹ More recently, they have extended this approach to prepare interlocked structures with new topologies, such as the structure in Figure 3.2b, which incorporates both catenane and rotaxane structural characteristics.²⁰

Anion templation, although rarer, has also been utilised to synthesise calix[4]arene based interlocked structures. This strategy, which was briefly introduced in Section 1.4.2.3, will be discussed in more detail as the projects in this chapter rely on this approach.

3.1.2. Anion Templated Synthesis of Interlocked Structures

Two strategies for synthesising interlocked structures were discussed in Chapter 1, but these had the disadvantage that the anion template was incorporated permanently into the resulting structure. However, Beer and co-workers have developed an alternative anion templated approach, where the anion template can be removed. This strategy is the anion equivalent

of Sauvage's cation templated systems (see Section 1.4.2.1). The anion, usually chloride, is exploited as an interweaving template to assemble isophthalamide and pyridinium based components in an orthogonal arrangement via hydrogen bonding interactions in non-competitive solvents (Figure 3.3a).²¹ Crucially, the anion template must be a coordinating anion and be coordinatively unsaturated.²² Subsequently, this anion templation strategy was used, in conjunction with a ring closing metathesis clipping reaction, to synthesise a number of [2]rotaxanes and [2]catenanes (Figure 3.3b and c).²³⁻²⁶ The formation of the orthogonal assembly prior to ring closing metathesis was enhanced by additional non-covalent interactions, which were also present in the resulting interlocked structure; there are π - π stacking interactions between the electron rich hydroquinone rings and electron deficient pyridinium unit, and hydrogen bonding C-H $\cdots$ O interactions between the methyl group of the pyridinium unit and polyether part of the macrocycle.

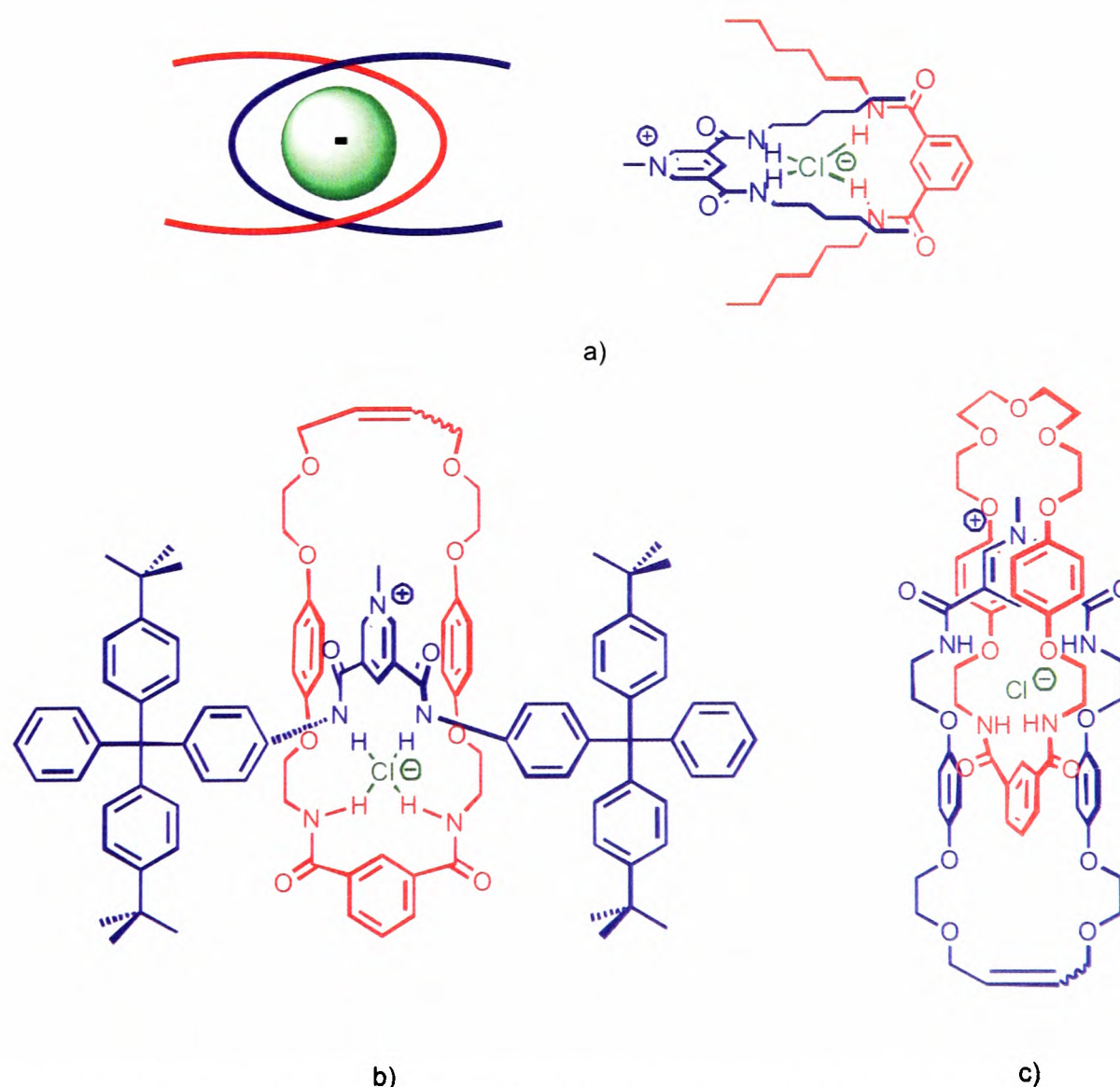


Figure 3.3 Anion templated a) orthogonal assembly b) [2]rotaxane and c) [2]catenane

In this strategy, the anion not only aids the formation of the interlocked structure, but upon removal of the anion, a three-dimensional anion binding cavity is created within the structure that is influenced by the geometry of the templating anion. Therefore, these structures can be used as host systems for anion recognition. Following exchange of the chloride template with the non-coordinating hexafluorophosphate anion, the anion binding properties of the resulting empty anion binding cavity were studied in 1:1 $\text{CDCl}_3/\text{CD}_3\text{OD}$ and found to be selective for the chloride template. This contrasts to the selectivity of the non-interlocked components for oxobasic anions, such as acetate and dihydrogen phosphate.

More recently, the use of alternative anion templates to chloride have been investigated to change the anion selectivity of the resulting interlocked structure. The catenane in Figure 3.4a only formed in the presence of a sulfate template and was selective for this template in 1:1 $\text{CDCl}_3/\text{CD}_3\text{OD}$.²⁷ In the same solvent system, the triazolium containing rotaxane, shown in Figure 3.4b, exhibits unusual selectivity for bromide over chloride, although both chloride and bromide anions template its formation.²⁸

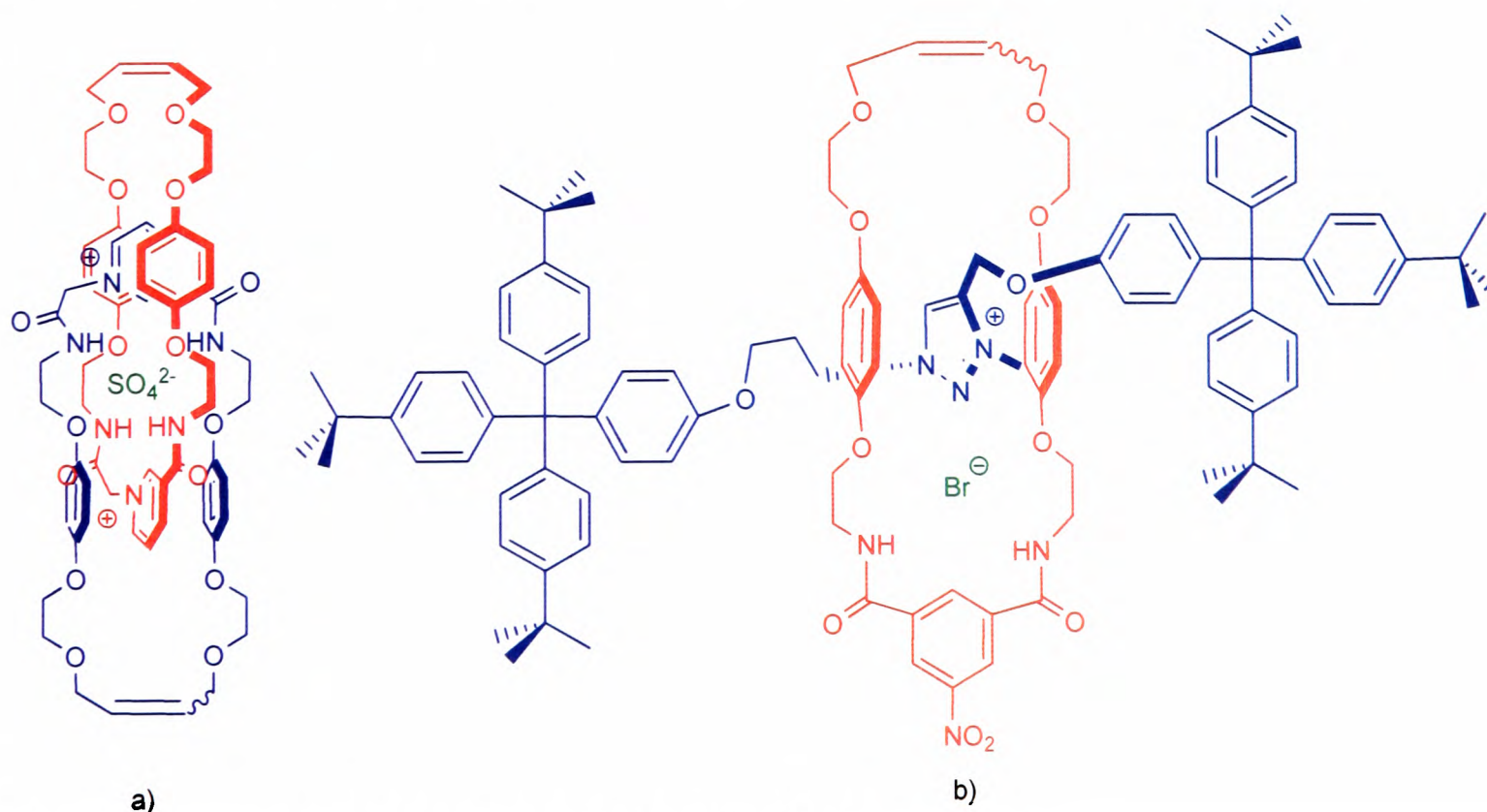
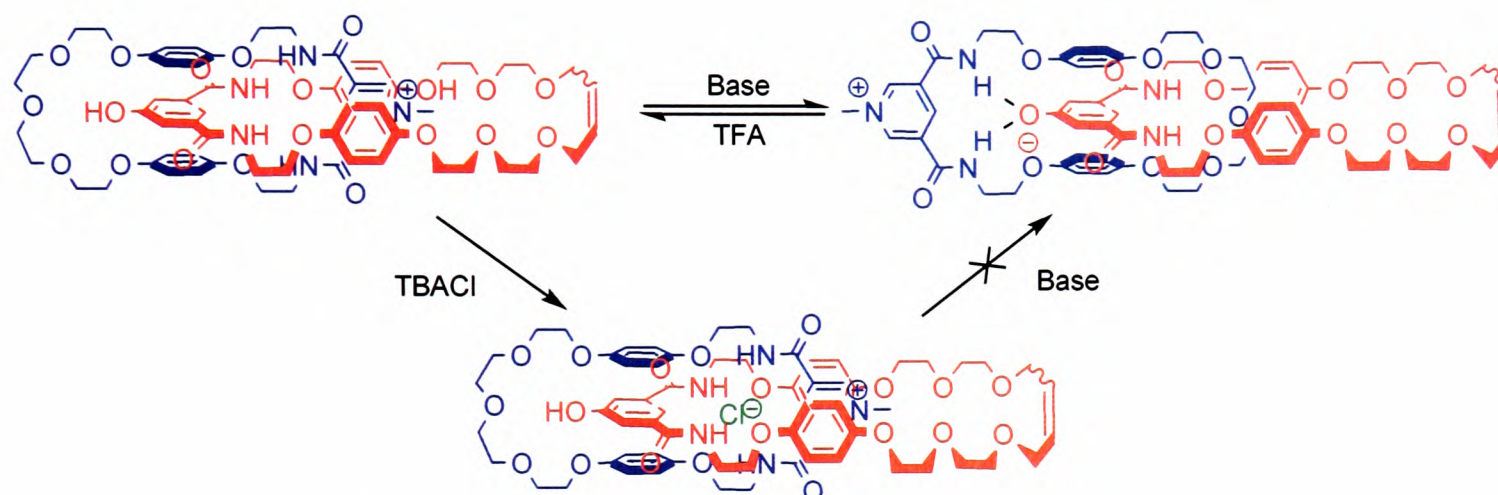


Figure 3.4 a) Sulfate selective catenane and b) bromide selective rotaxane

This anion templation strategy has also been exploited in the development of molecular machines based on interlocked structures. The catenane in Scheme 3.1 was synthesised

using chloride templation and following removal of the template, anion induced and inhibited circumrotation was demonstrated.²⁹ Upon deprotonation of the phenol group, the pyridinium macrocycle undergoes a ring rotation so that the amide protons of the anion binding unit hydrogen bond with the resulting phenolate anion. This process is reversed by TFA and addition of chloride inhibits the ring rotation upon addition of base.



Scheme 3.1 Anion induced and inhibited circumrotation of a [2]catenane

3.1.3. Aims of the Chapter

The catenane shown in Figure 3.5a was the only previously reported example of an anion templated calix[4]arene based interlocked structure.³⁰ The synthesis of new calix[4]arene based catenanes and rotaxanes is the focus of this chapter. As a natural extension of the work in the previous chapter, the design of the target rotaxane and catenane structures resembles that of the ion-pair receptors with replacement of the cation with a suitable cationic thread component (Figure 3.5b).

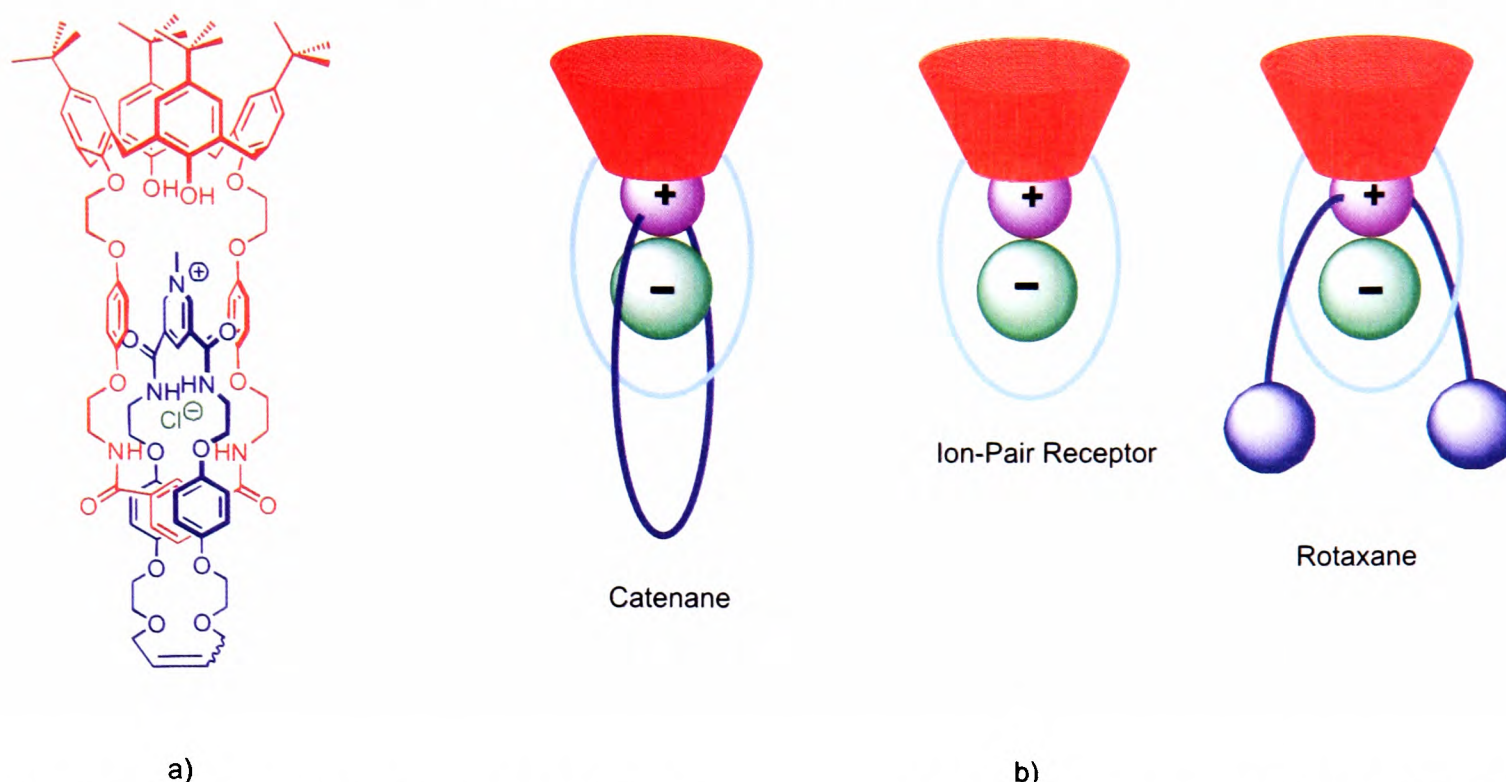
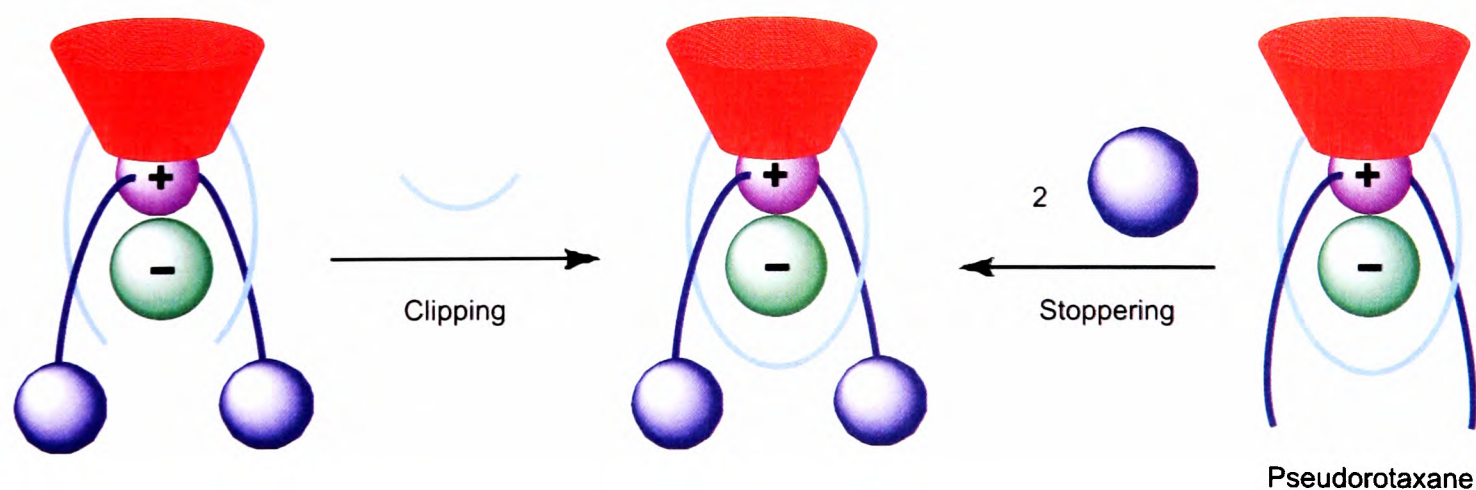


Figure 3.5 a) Anion templated catenane and b) target rotaxane and catenane structures based on modification of the ion-pair receptor design

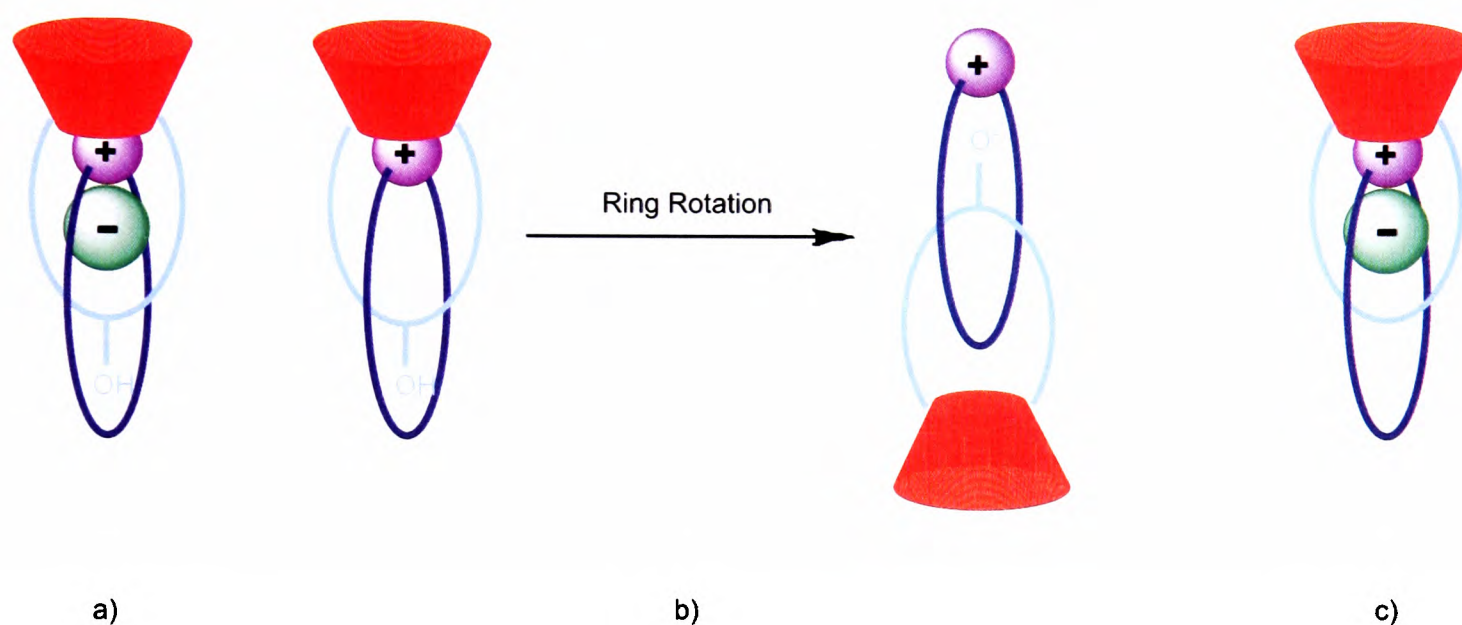
Despite the versatility of the calix[4]arene framework, there are no examples of anion templated calix[4]arene based rotaxanes. A clipping method utilising a ring closing metathesis reaction has been successfully employed to synthesise a number of anion templated rotaxanes, including those in Figures 3.3b and 3.4b.^{6, 23-26} This chapter, however, will investigate the synthesis of calix[4]arene based rotaxanes using an alternative clipping approach exploiting ion-pair templation, and also a stoppering strategy (Scheme 3.2).



Scheme 3.2 The synthesis of calix[4]arene based rotaxanes using clipping and stoppering approaches

The synthesis of calix[4]arene based catenanes will also be explored, initially focusing on the preparation of the *tert*-butylcalix[4]arene analogue of the catenane in Scheme 3.1. The design of the target catenane is shown in Scheme 3.3a, and it is hoped that deprotonation of the hydroxyl group will lead to molecular motion (Scheme 3.3b). The synthesis of the

calix[4]diquinone analogue of the catenane in Figure 3.5a has previously been investigated, but it was discovered that thallium trifluoroacetate oxidation of the macrocycle to the calix[4]diquinone also caused oxidative cleavage of the hydroquinone groups.³¹ Similar oxidation problems with thallium trifluoroacetate were encountered in Chapter 2, and an alternative chlorine dioxide oxidation method was developed. Based on the success of this method, the synthesis of calix[4]diquinone based catenanes will also be investigated (Scheme 3.3c).

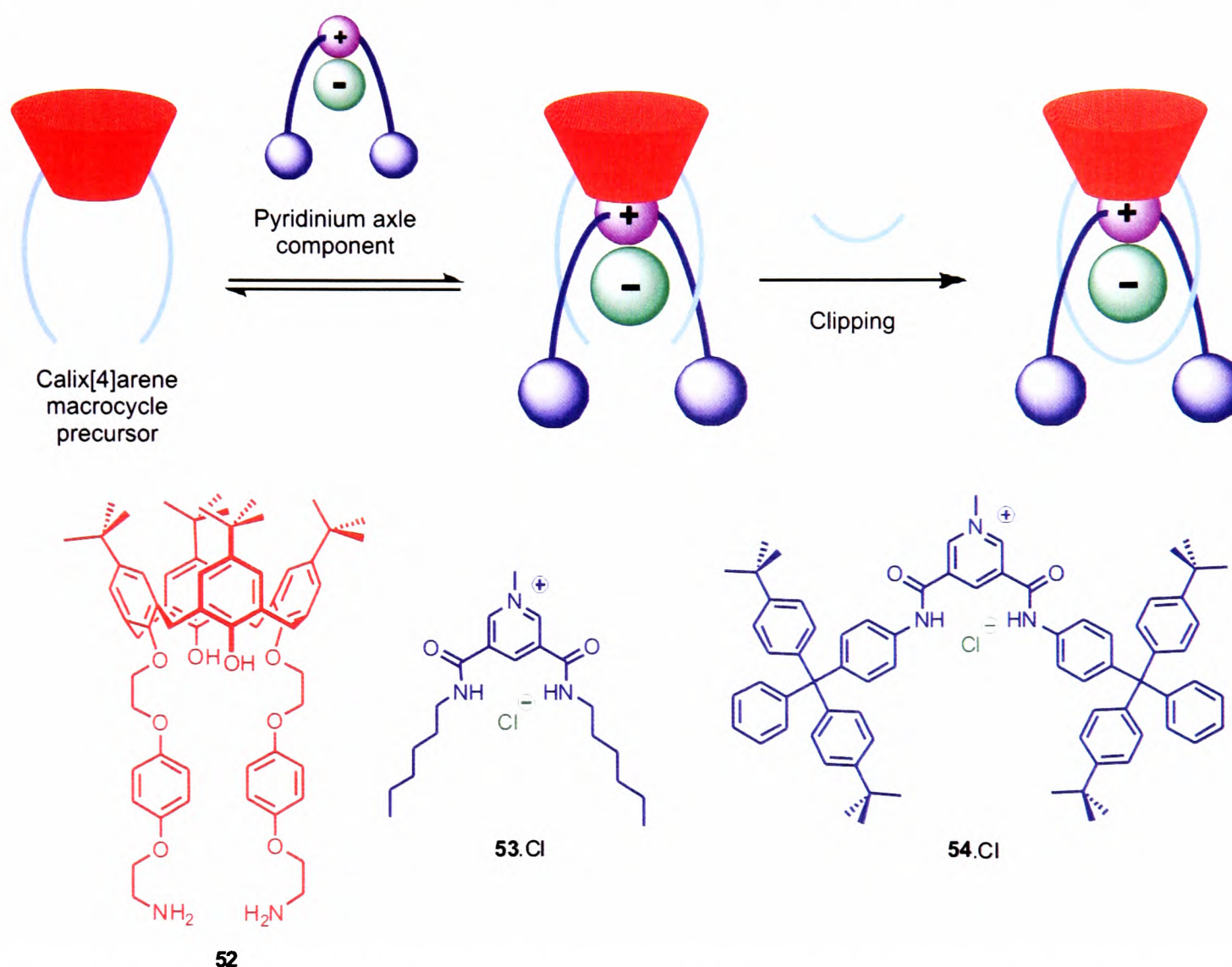


Scheme 3.3 a) Design of catenane for b) proposed anion induced molecular motion and c) design of calix[4]diquinone based catenane

3.2. Ion-Pair Templated Synthesis of *tert*-Butylcalix[4]arene Based Rotaxanes

The new proposed clipping strategy for the synthesis of the target calix[4]arene based [2]rotaxanes is depicted in Scheme 3.4. This approach exploits anion templation and favourable π - π stacking interactions between the calix[4]arene based macrocycle precursor and stoppered pyridinium axle component prior to reaction with a clipping component to form the [2]rotaxane. The calix[4]arene macrocycle precursor **52** incorporates electron rich hydroquinone groups to facilitate π - π stacking interactions with the electron deficient pyridinium axle component. In addition, it is functionalised with terminal amine groups for the clipping condensation reaction with an appropriate bis-acid chloride derivative. Initially the feasibility of this strategy was investigated by the templated synthesis of calix[4]arene

macrocycles using the unstoppered axle **53.Cl**, before attempting the synthesis of the target rotaxane with the stoppered axle **54.Cl**. At the same time as this work was being carried out, the synthesis of rotaxanes using this new strategy was also investigated by Laura Hancock using a flexible polyether hydroquinone bis-amine as the macrocycle precursor component.³²

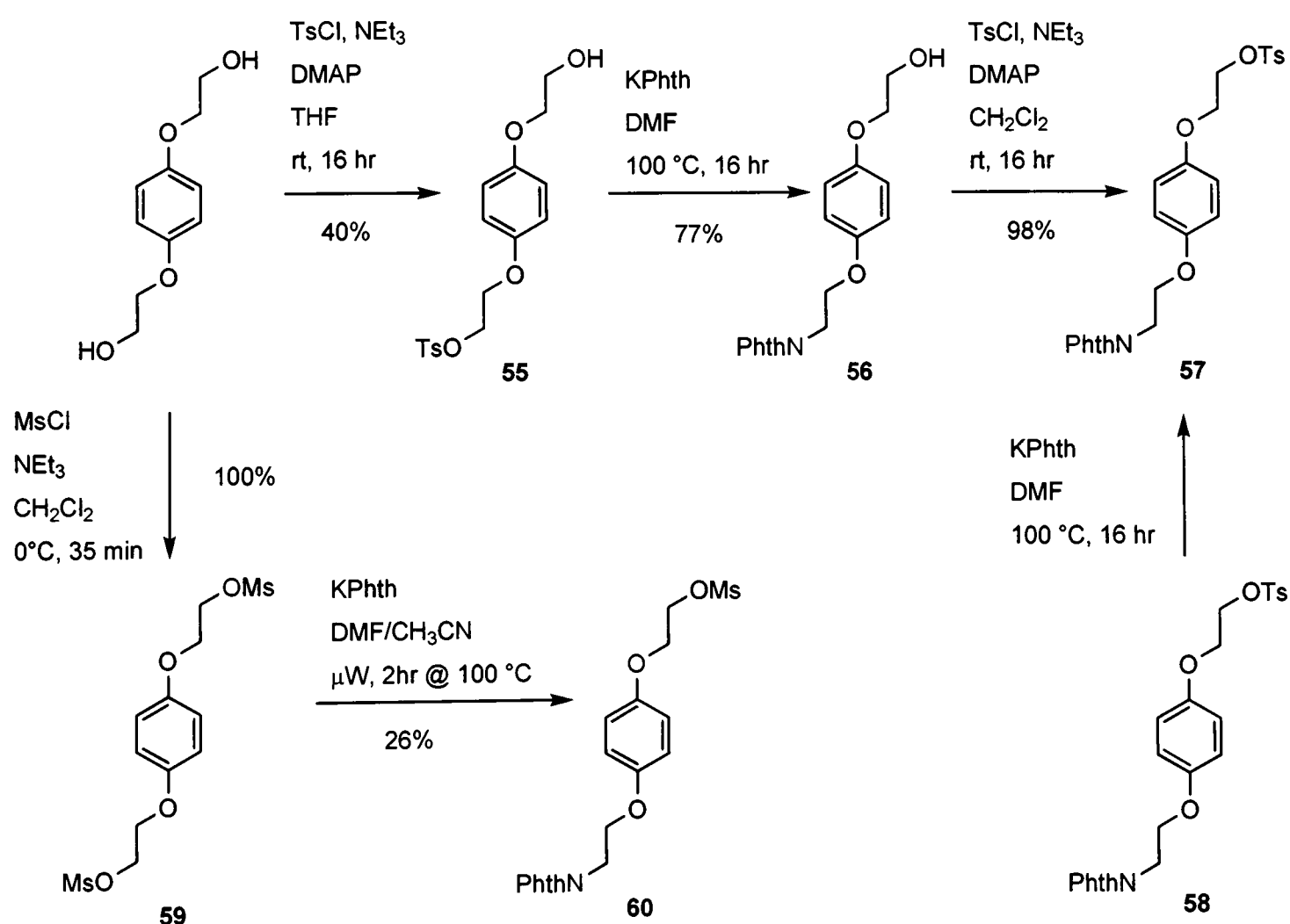


Scheme 3.4 Proposed ion-pair templated synthesis of [2]rotaxanes with target calix[4]arene macrocycle precursor and pyridinium axle components

3.2.1. Synthesis of precursors **52-54.Cl**

The target macrocycle precursor **52** was initially prepared according to established synthetic procedures, which involved the preparation of precursor **57** (Scheme 3.5).³⁰ Hydroquinone bis(2-hydroxyethyl)ether was reacted with tosyl chloride at room temperature in dry THF and the desired monotosylated product **55** was isolated in 40% yield following purification by column chromatography. The phthalimide protected amine **56** was synthesised in 77% yield by reaction with potassium phthalimide in DMF overnight at 100 °C. Tosylation using tosyl chloride, triethylamine and a catalytic amount of DMAP gave **57** in 98% yield. The large

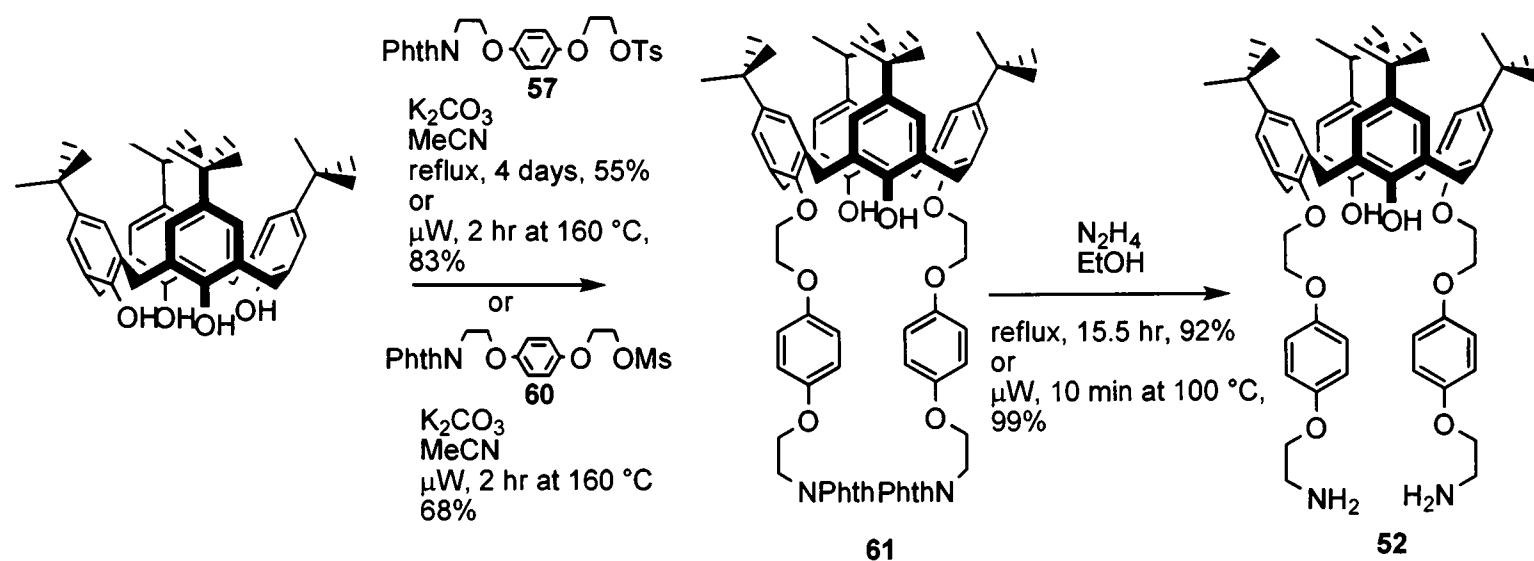
scale synthesis of **57** was made difficult by the low yielding statistical monotosylation at the beginning of the synthesis and the necessary purification of the first two products by column chromatography, even though the last two steps were high yielding. Therefore, alternative syntheses were explored including the preparation of **57** directly from **58**, which was isolated as a by-product from the synthesis of **55**. While **57** did form by heating **58** with potassium phthalimide in DMF at 100 °C, it was not possible to isolate it from the complex mixture of products. Instead, compound **60**, with a mesyl leaving group rather than a tosyl one, was synthesised using the strategy developed by Dr Alexandre Leontiev. Compound **59** was synthesised in quantitative yield from the mesylation of hydroquinone bis(2-hydroxyethyl)ether in CH_2Cl_2 ,³³ and reacted with potassium phthalimide in DMF at 100 °C to give **60** in 26% yield. This method gave the target precursor in similar overall yield to compound **57**, but in one less step and requiring only one chromatographic purification.



Scheme 3.5 Synthesis of precursors **57** and **60**

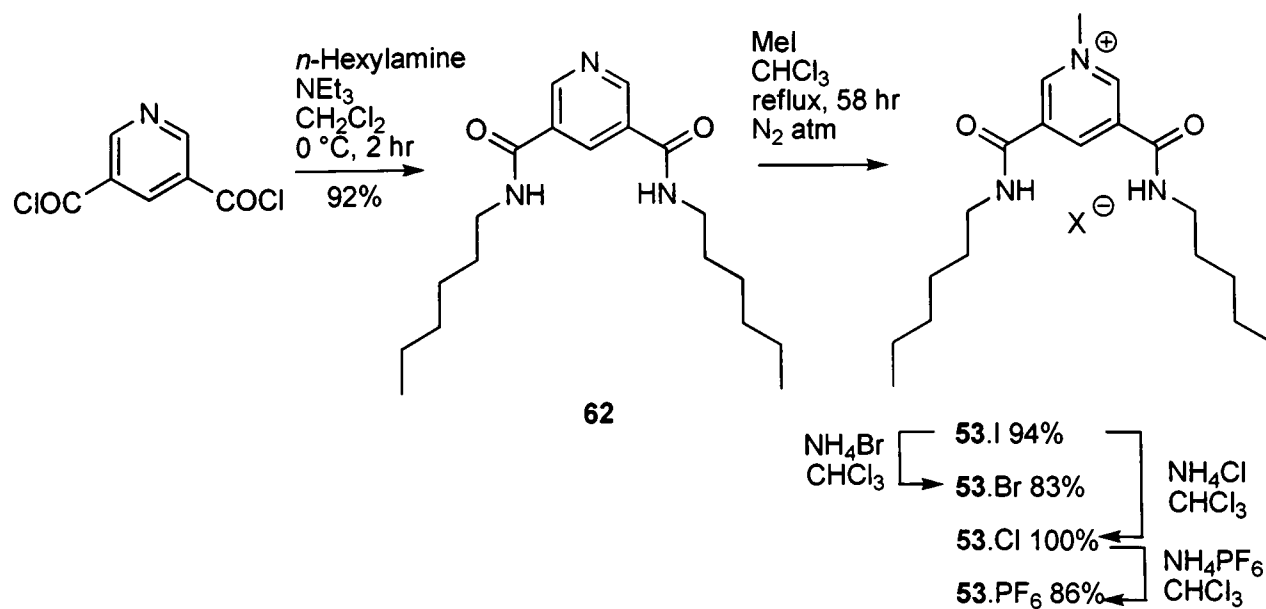
The macrocycle precursor **52** was synthesised in two steps using **57** according to established procedures (Scheme 3.6).³⁰ *tert*-Butylcalix[4]arene, **57** and K_2CO_3 were heated in CH_3CN

under reflux for 4 days and **61** was isolated by column chromatography in 55% yield. This yield could be improved to 83% by heating the reactants under microwave irradiation at 160 °C for 2 hours. An analogous microwave reaction was also developed using **60**, and **61** was isolated in the slightly lower yield of 68%. The macrocycle precursor **52** was isolated in almost quantitative yield following cleavage of the phthalimide groups using hydrazine monohydrate either under reflux or microwave irradiation.



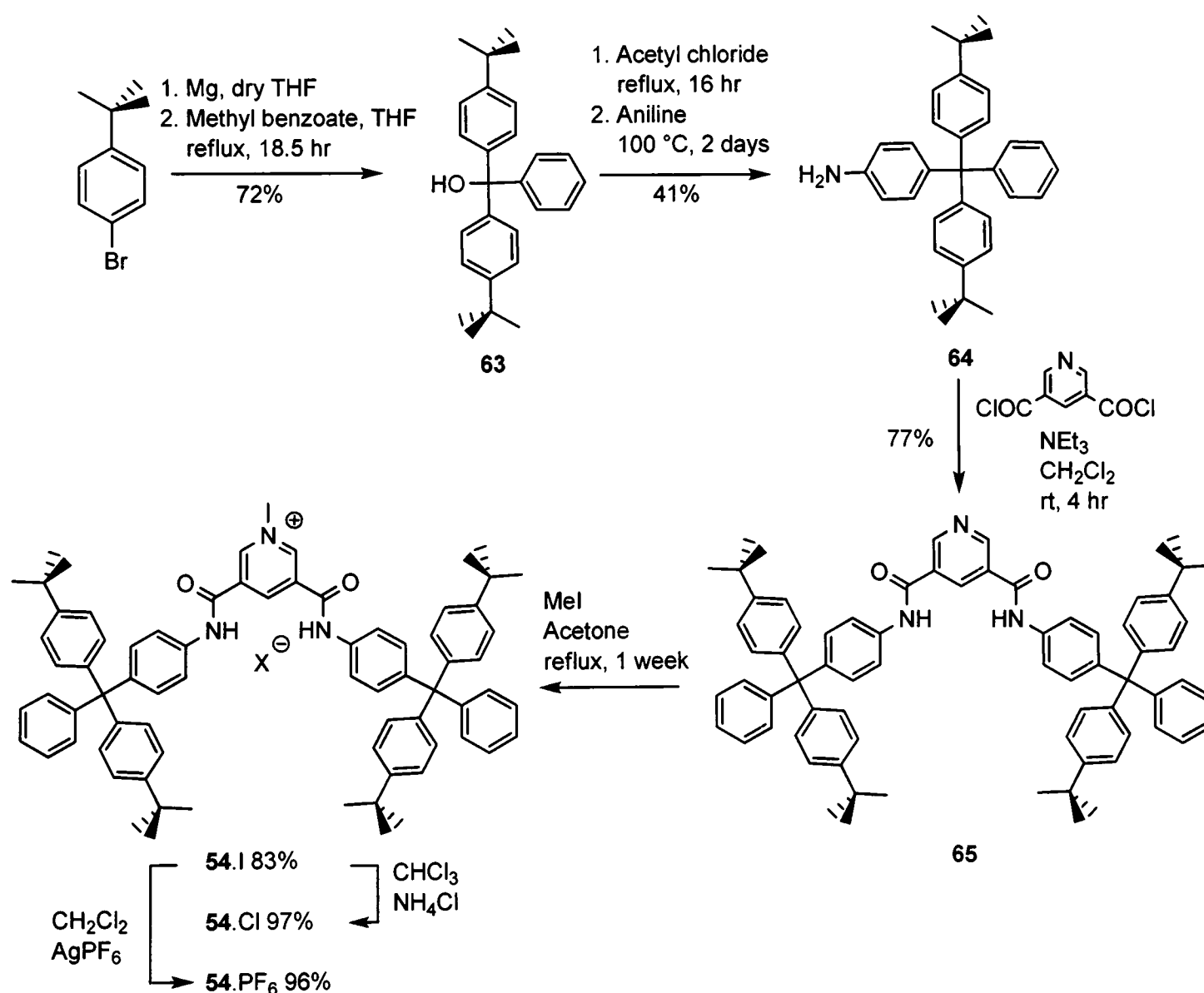
Scheme 3.6 Synthesis of macrocycle precursor **52**

The unstoppered axle component **53.Cl** was prepared according to Scheme 3.7.^{22, 34} *n*-Hexylamine was reacted with 3,5-bis(chlorocarbonyl) pyridine giving **62** in 92% yield. This was heated under reflux with iodomethane in CHCl₃ giving the iodide salt **53.I**, which was subsequently converted to the chloride salt **53.Cl** in quantitative yield using 1 M NH₄Cl and the bromide salt **53.Br** in 83% yield using 1 M NH₄Br. The hexafluorophosphate salt was also prepared in 86% yield by washing a CHCl₃ solution of **53.Cl** with 0.2 M NH₄PF₆.



Scheme 3.7 Synthesis of unstoppered axle component **53.Cl**

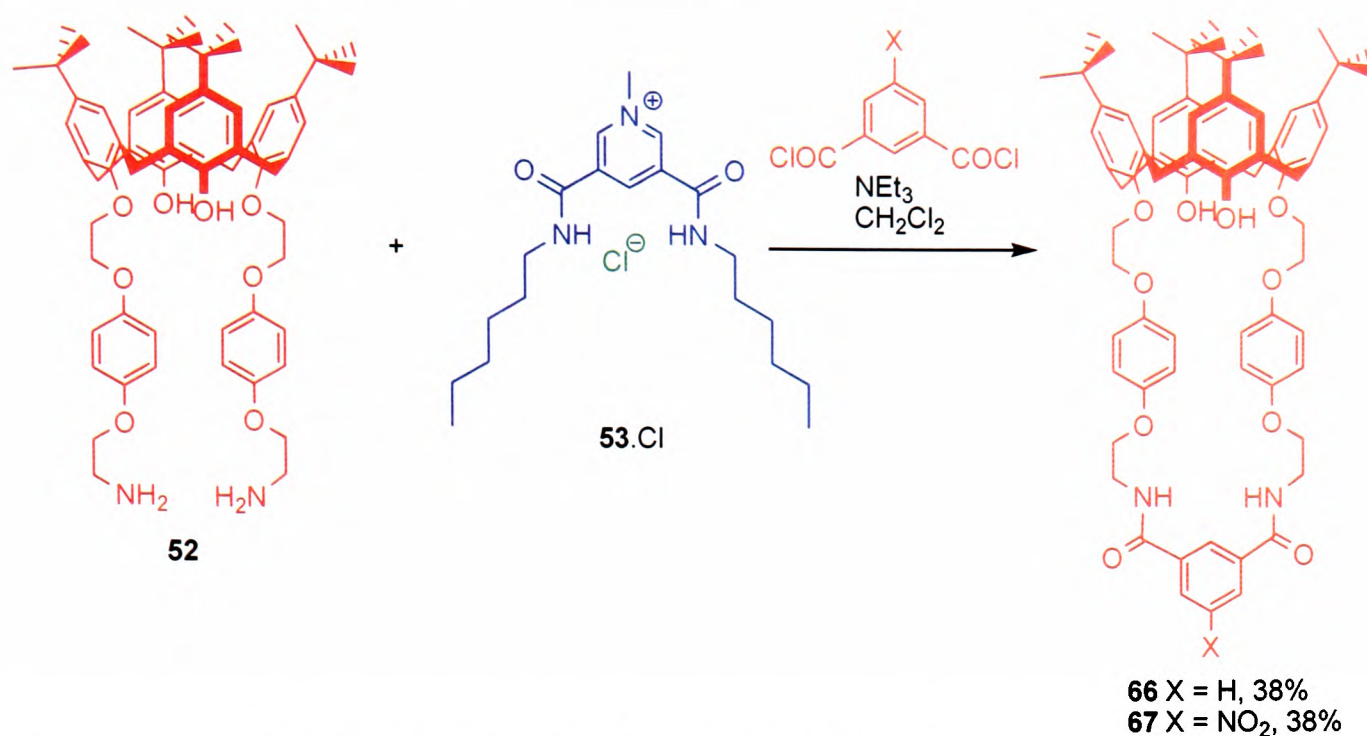
In order to prepare the stoppered axle **54.Cl**, it was necessary to synthesise the stopper derivative **64** (Scheme 3.8).^{26, 35} 1-Bromo-4-*tert*-butylbenzene was converted to the Grignard reagent upon reaction with magnesium turnings in dry THF, and this was reacted with methyl benzoate to give **63** as a white solid in 72% yield. The aniline stopper derivative **64** was synthesised in two steps, firstly by heating under reflux in acetyl chloride for 16 hours and then by heating in aniline at 100 °C for 2 days. Compound **64** was reacted with 3,5-bis(chlorocarbonyl) pyridine in the presence of triethylamine in CH₂Cl₂ to give compound **65**, which was methylated with iodomethane to give the iodide salt **54.I** in 83% yield. Following anion exchange by repeated washing with 1 M NH₄Cl, the chloride salt **54.Cl** was isolated as a yellow solid in 97% yield. The hexafluorophosphate salt was also prepared by stirring a solution of **54.Cl** in CH₂Cl₂ with AgPF₆ in the absence of light.



Scheme 3.8 Synthesis of stoppered axle component **54.Cl**

3.2.2. Ion-Pair Templated Synthesis of Macrocycles

Before the synthesis of rotaxanes was attempted, the ion-pair templated synthesis of calix[4]arene macrocycles was investigated and compared to a number of other macrocyclisation strategies. Whereas the macrocyclisation of bis-amine **52** and isophthaloyl dichloride in the absence of the axle component gave macrocycle **66** in 26% yield, the analogous condensation reaction in the presence of **53.Cl** afforded the macrocycle in an improved yield of 38% (Scheme 3.9). This suggests chloride anion templation in combination with favourable π - π donor-acceptor interactions contribute to the efficacy of macrocycle formation. However, there is no improvement of the yield compared to those obtained by high dilution techniques. Macrocycle **66** was synthesised in 60% yield using a syringe pump or 39% yield using dropping funnels for the addition of the bis-amine and acid chloride. To test the ion-pair templation strategy further, the synthesis of much lower yielding macrocycles by high dilution conditions, such as **67**, was then investigated to see if the yield could be improved (Scheme 3.9). Macrocycle **67**, which has previously been synthesised in 32% yield under high dilution conditions,³⁰ was isolated in the slightly improved yield of 38% yield using **53.Cl** as a template. Based on these results, it was concluded that the ion-pair templation strategy does not significantly improve the yields of macrocyclisation compared with the traditional high dilution synthesis. This is most likely due to the preorganised nature of the calix[4]arene scaffold. However, the template does play an important role in macrocycle formation as demonstrated by the yield decrease in the absence of the template under more concentrated conditions.



Scheme 3.9 Ion-pair templated synthesis of calix[4]arene macrocycles

¹H NMR spectroscopy studies were conducted in order to establish whether association of the bis-amine **52** and template **53.Cl** occurs prior to reaction with the acid chloride. Upon addition of 1 equivalent of **52** to **53.Cl**, very small shifts of the axle protons *c* and *d* were observed (Figure 3.6). Of particular interest are the chemical shift changes and splitting of the macrocycle hydroquinone protons *h* and *i*, as they can be indicative of π – π stacking interactions between the two components. However, there were no significant shifts of any macrocycle precursor signals, and therefore it is difficult to infer any association of the two components. ROESY analysis of the 1:1 mixture of **52** and **53.Cl** also did not reveal any correlations between the two components.

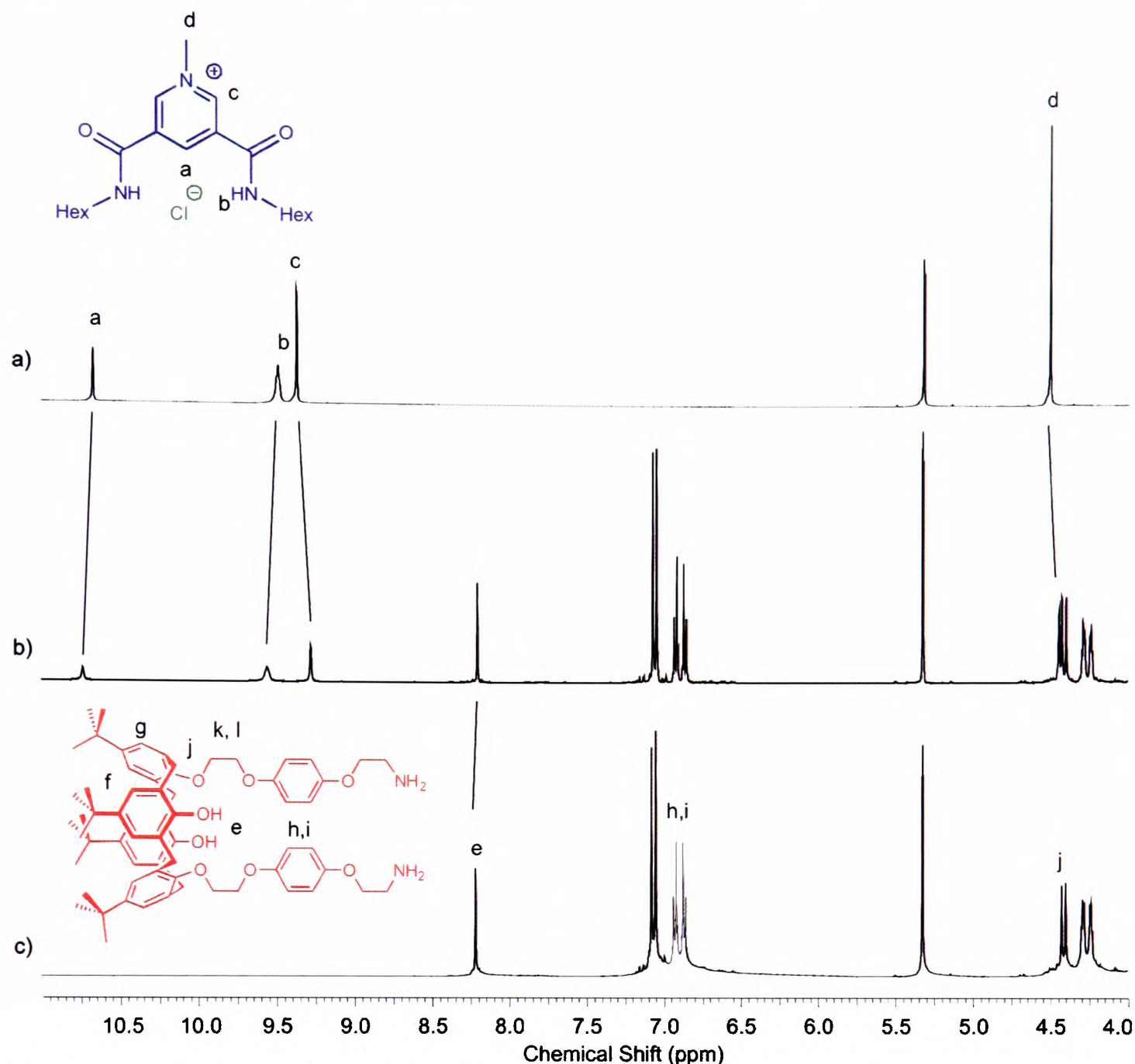


Figure 3.6 ¹H NMR spectrum of a) **53.Cl** b) a 1:1 mixture of **53.Cl** and **52** and c) **52** in CD₂Cl₂ at 298 K

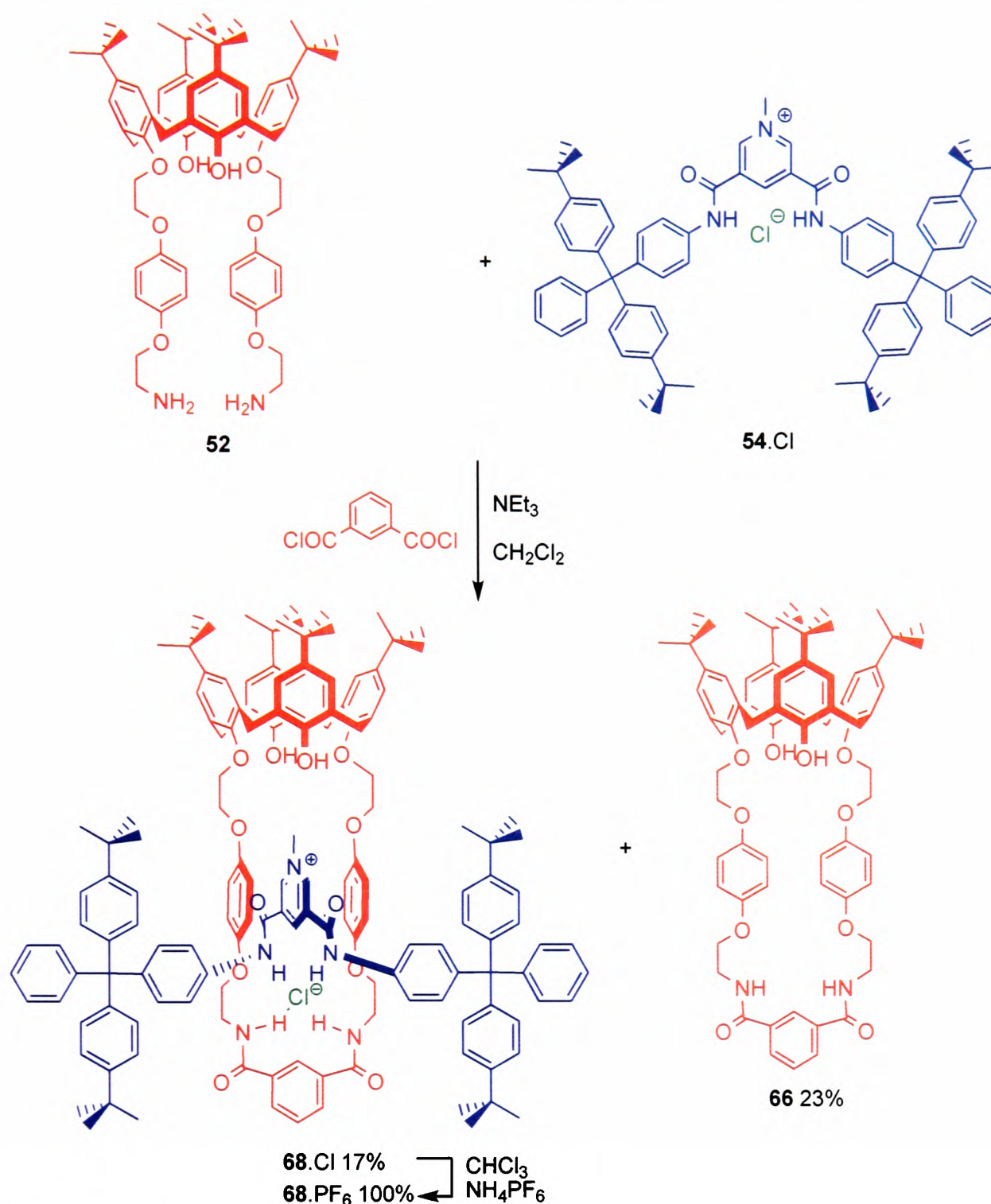
3.2.3. Synthesis of Rotaxane **68.Cl**

While it was difficult to conclusively prove the existence of interactions between the macrocycle precursor **52** and the ion-pair template, calix[4]arene macrocycles were successfully prepared using this ion-pair templation strategy. Therefore attention was turned to the preparation of [2]rotaxane **68.Cl** using the stoppered axle **54.Cl** as the template.

Isophthaloyl dichloride was added to a 1:1 mixture of compounds **52** and **54.Cl** in dry CH₂Cl₂ in the presence of triethylamine (Scheme 3.10). Rotaxane **68.Cl** was isolated in 11% yield following purification by preparative TLC and recrystallisation from CHCl₃/MeOH. In addition, the macrocycle by-product **66** was isolated in 30% yield. The formation of the macrocycle by-product accounts for the lower yield of rotaxane, as compared with a related

rotaxane system where a flexible polyether hydroquinone bis-amine is used as the macrocycle precursor component instead of the relatively more preorganised calix[4]arene bis-amine synthon.³²

In an effort to improve the yield of the rotaxane, a number of the reaction conditions were varied. Compound **54.Cl** has limited solubility in CH₂Cl₂ and therefore this template was replaced by the hexafluorophosphate template **54.PF₆**, which has better organic solvent solubility (Scheme 3.8). The hexafluorophosphate anion was not expected to interfere with any anion templation effects due to the excess of chloride anions produced in the condensation reaction as a consequence of amide formation. Disappointingly, the yield of the rotaxane did not significantly increase using **54.PF₆** as the template. Despite the solubility problems with **54.Cl**, the rotaxane synthesis was repeated in the presence of 1.5 equivalents of **54.Cl** and the rotaxane was isolated in an improved yield of 17%. The macrocycle by-product **66** was also isolated in 23% yield. The rotaxane was characterised by ¹H and ¹³C NMR spectroscopy, high resolution electrospray mass spectrometry, melting point analysis and elemental analysis.



Scheme 3.10 Synthesis of rotaxane 68.Cl

Figure 3.7 shows a comparison of the ¹H NMR spectra of the macrocycle 66, axle 54.Cl and rotaxane 68.Cl in CDCl₃. The downfield shifts of the isophthalamide protons *i* and *j* are indicative of halide anion complexation in the rotaxane's interlocked host binding cavity. In addition, the upfield shifts of the axle proton *d* can be attributed to the competitive binding of chloride in the rotaxane compared with the ion-paired free axle. The upfield shifts and splitting of the hydroquinone protons *m* and *n* result from π - π stacking interactions between the electron deficient pyridinium unit of the axle and electron rich hydroquinone rings of the macrocycle.

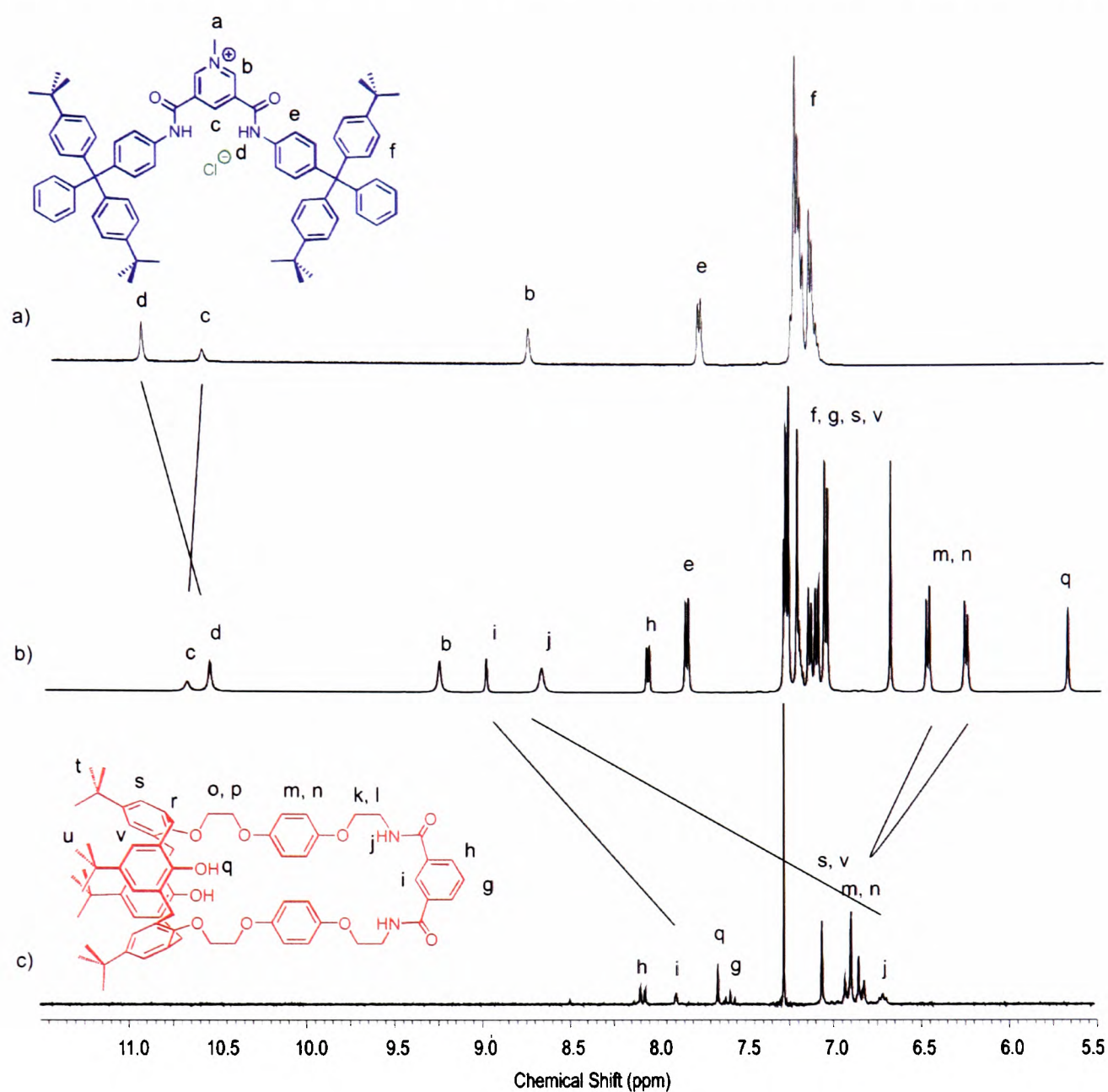


Figure 3.7 ^1H NMR spectra of a) axle **54.Cl** b) rotaxane **68.Cl** and c) macrocycle **66** in CDCl_3 at 298 K

The ROESY spectra of **68.Cl** also reveals a number of through space correlations between the respective macrocycle and axle components as illustrated in Figure 3.8.

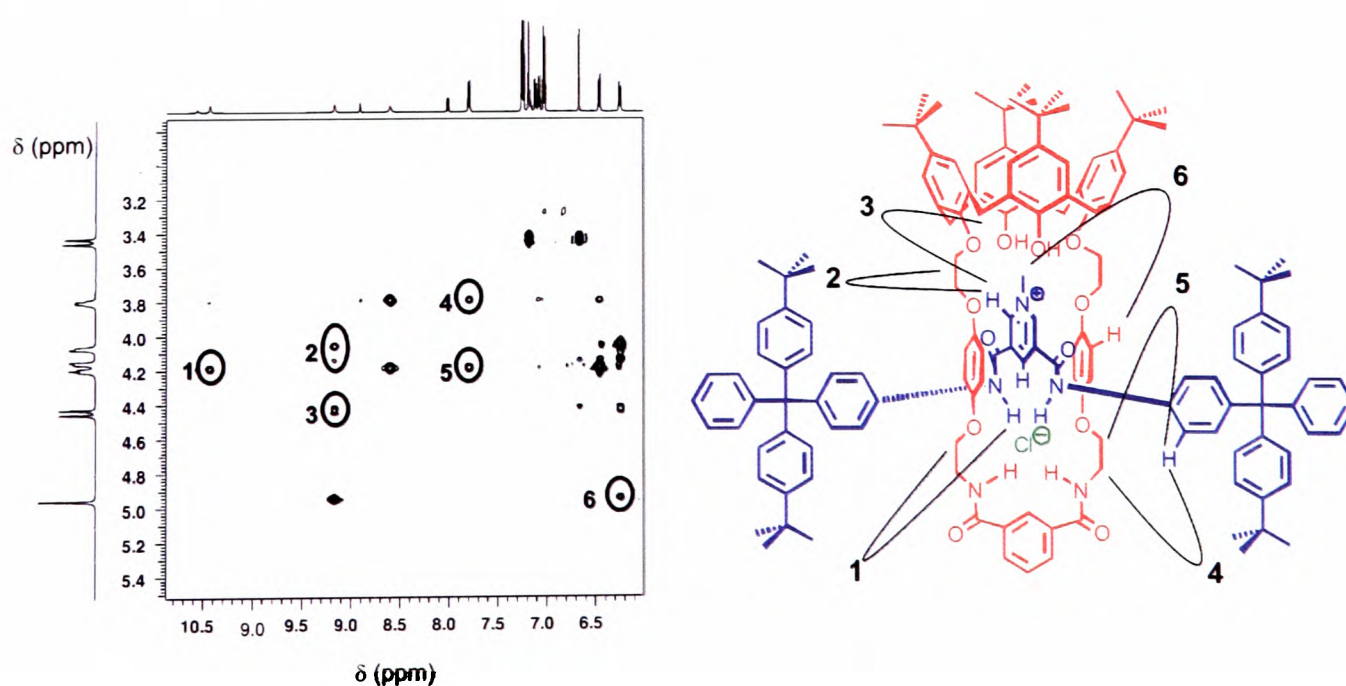


Figure 3.8 Portion of the ROESY spectrum of rotaxane **68.Cl** in CDCl_3 at 298 K illustrating the through space correlations between the calixarene macrocycle and axle components

Single crystals of rotaxane **68.Cl** were obtained by slow evaporation of a solution of the rotaxane in 45:45:10 CDCl₃/CD₃OD/D₂O. Although of a good size, the crystals were found to diffract poorly under standard Mo K α radiation.³⁶ Despite these difficulties, it was possible to collect a useable dataset and the X-ray crystal structure unambiguously confirmed the connectivity and interlocked nature of the structure (Figure 3.9a).

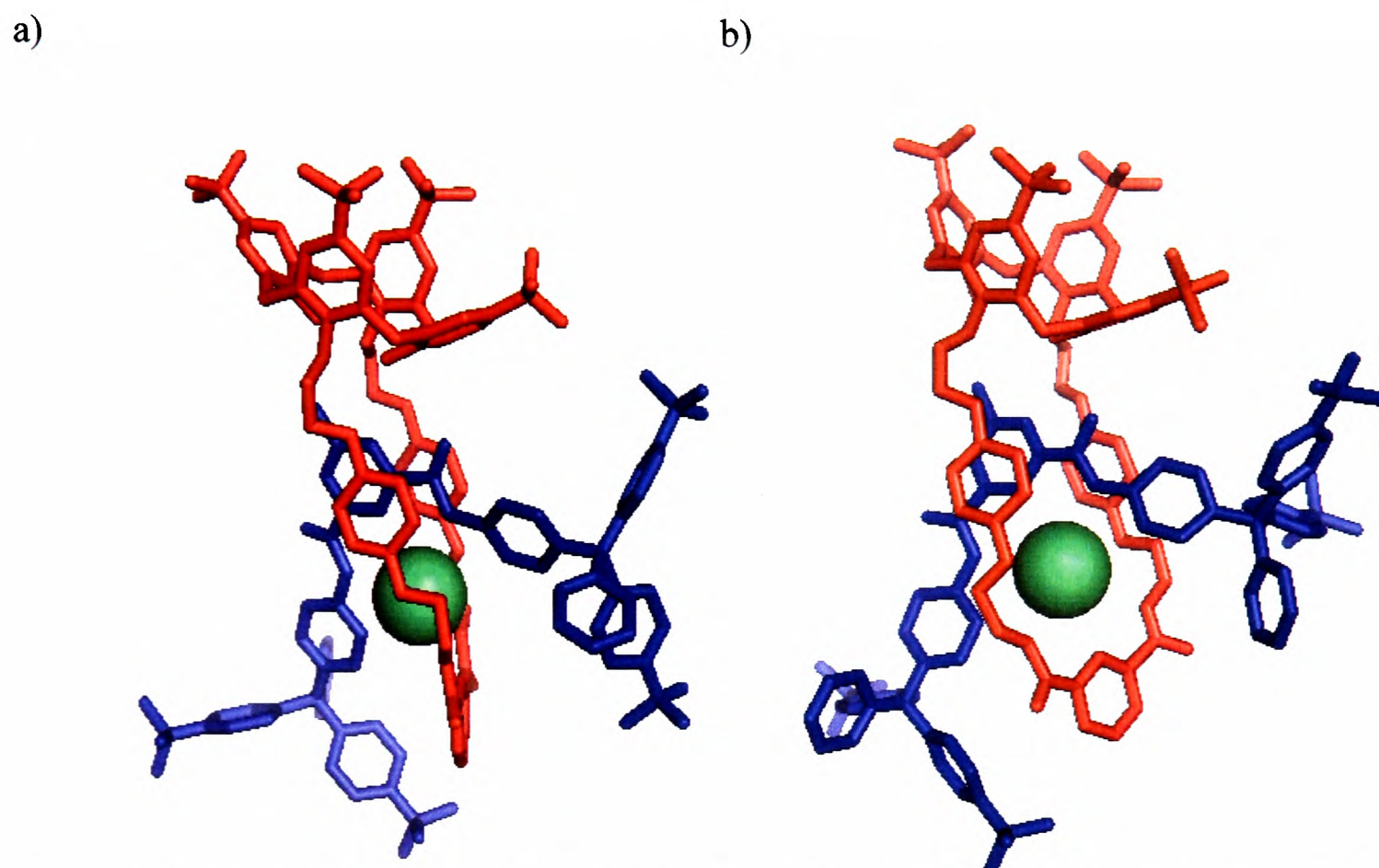


Figure 3.9 X-ray crystal structure of **68.Cl**. Mo K α radiation sample (left) and synchrotron sample (right), displaying anion coordination and differences in stopper conformation. Disorder is omitted for clarity

However, a higher quality dataset was obtained from another crystal from the same sample, and analysed using synchrotron radiation on beamline I19 at Diamond Light Source (Figure 3.4b).³⁷ A number of structural differences were observed from examination of the conformation of the stopper groups, most likely due to solvent loss as evidenced by contraction of one of the cell axes. However, with respect to the supramolecular forces involved, there is little difference between the two samples. The intermolecular forces used to template the rotaxane synthesis in solution are still present in the solid state: hydrogen bonds from both components to the chloride anion; π - π stacking between the electron poor pyridinium unit and the electron rich hydroquinone groups (though with a high degree of

offset); and secondary hydrogen bonding of the pyridinium methyl group to calixarene oxygens (Table 3.1). The chloride anion is tetrahedrally coordinated with respect to the amide protons (a mean N(H)⋯Cl distance of 3.36 Å), but central aryl protons also form close contacts with a mean C(H)⋯Cl distance of 3.32 Å.

N(H) ⋯ Cl distances (Å) ^a	3.222(11), 3.544(37), 3.340(9), ^c 3.246(9), ^c 3.511(12), ^c 3.273(40) ^c
C(H) ⋯ Cl distances (Å) ^a	3.366(14), 3.276(12)
π–π centroid-centroid distances (Å) ^b	4.015(8), 3.749(8)
π–π stacking angle ^b (°)	17.2(7), 8.7(6)
Pyr ⁺ -C(H ₃)-O distances (Å) ^a	3.734(16), 3.428(16), 3.113(13), 3.559(14)

Table 3.1 Selected crystallographic data for rotaxane **68**.Cl^a calculated within CRYSTALS³⁸ using the full variance-covariance matrix^b calculated using PLATON^{39, 40} without inclusion of the covariance and ^c multiplicity of value occurs due to disorder

In order to study the anion binding properties of the rotaxane, the chloride anion template was removed from the respective interlocked host cavity by washing a CHCl₃ solution of **68**.Cl with aqueous NH₄PF₆ (Scheme 3.10). The resulting rotaxane **68**.PF₆ was obtained in 100% yield and was characterised by ¹H, ¹⁹F, ³¹P, ¹³C NMR spectroscopy, electrospray mass spectrometry and melting point analysis. The ROESY NMR spectrum of **68**.PF₆ demonstrates through space correlations between the macrocycle and axle components indicating that anion exchange has preserved the interlocked structure (Figure 3.10).

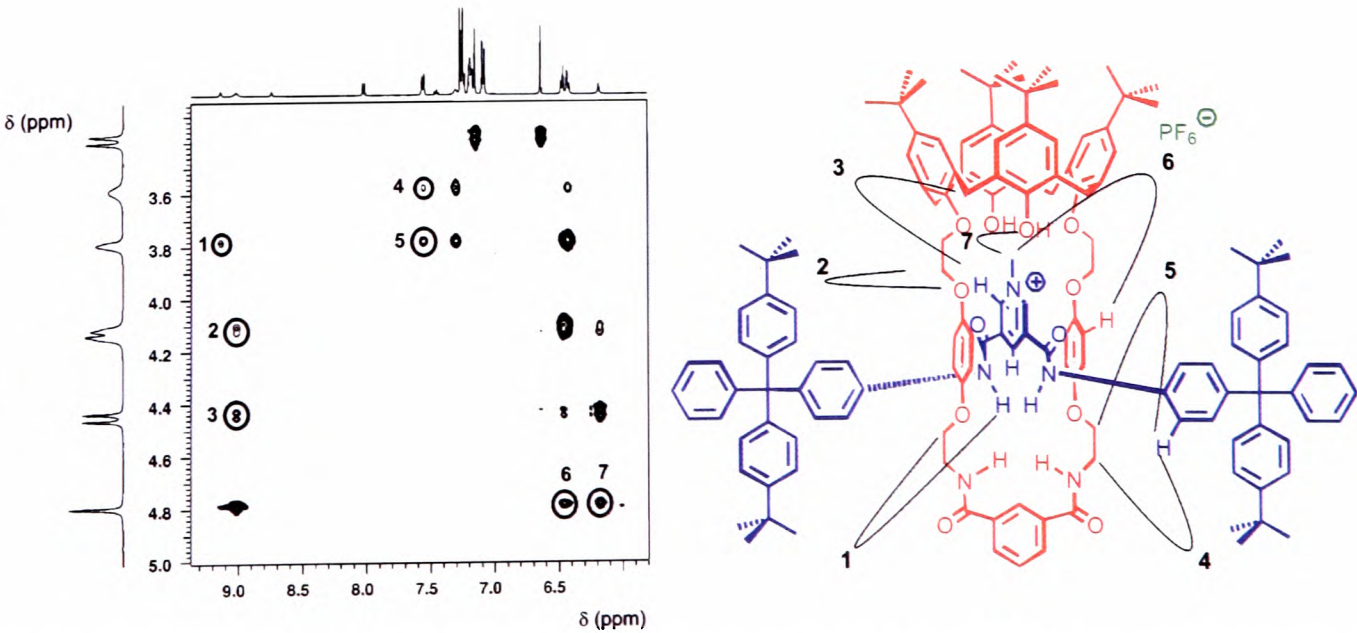


Figure 3.10 Portion of the ROESY spectrum of rotaxane **68**.PF₆ in CDCl₃ at 298 K illustrating the through space correlations between the calixarene macrocycle and axle components

3.2.4. Synthesis of Rotaxane **69.Cl**

In order to discount the possibility that the low yielding synthesis of **68.Cl** was due to the limited solubility of the axle **54.Cl**, the synthesis of rotaxane **69.Cl** based on the new axle component **70.Cl** was investigated (Figure 3.11). It was hoped that the solubility of **70.Cl** would be improved by the presence of the ethylene glycol units and it was expected that this axle would therefore be more conformationally flexible. The effect of preorganisation of the interlocked host's cavity could be investigated by comparing the anion binding properties of rotaxanes **68.Cl** and **69.Cl**.

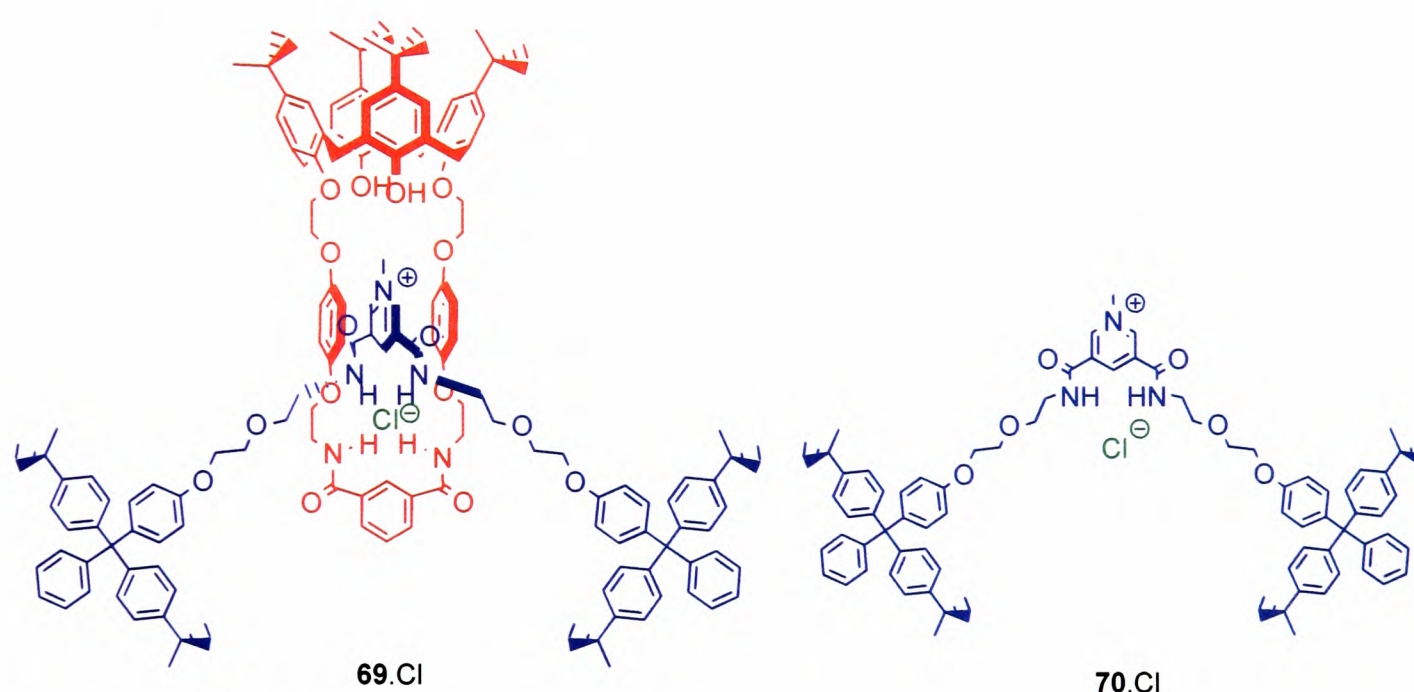
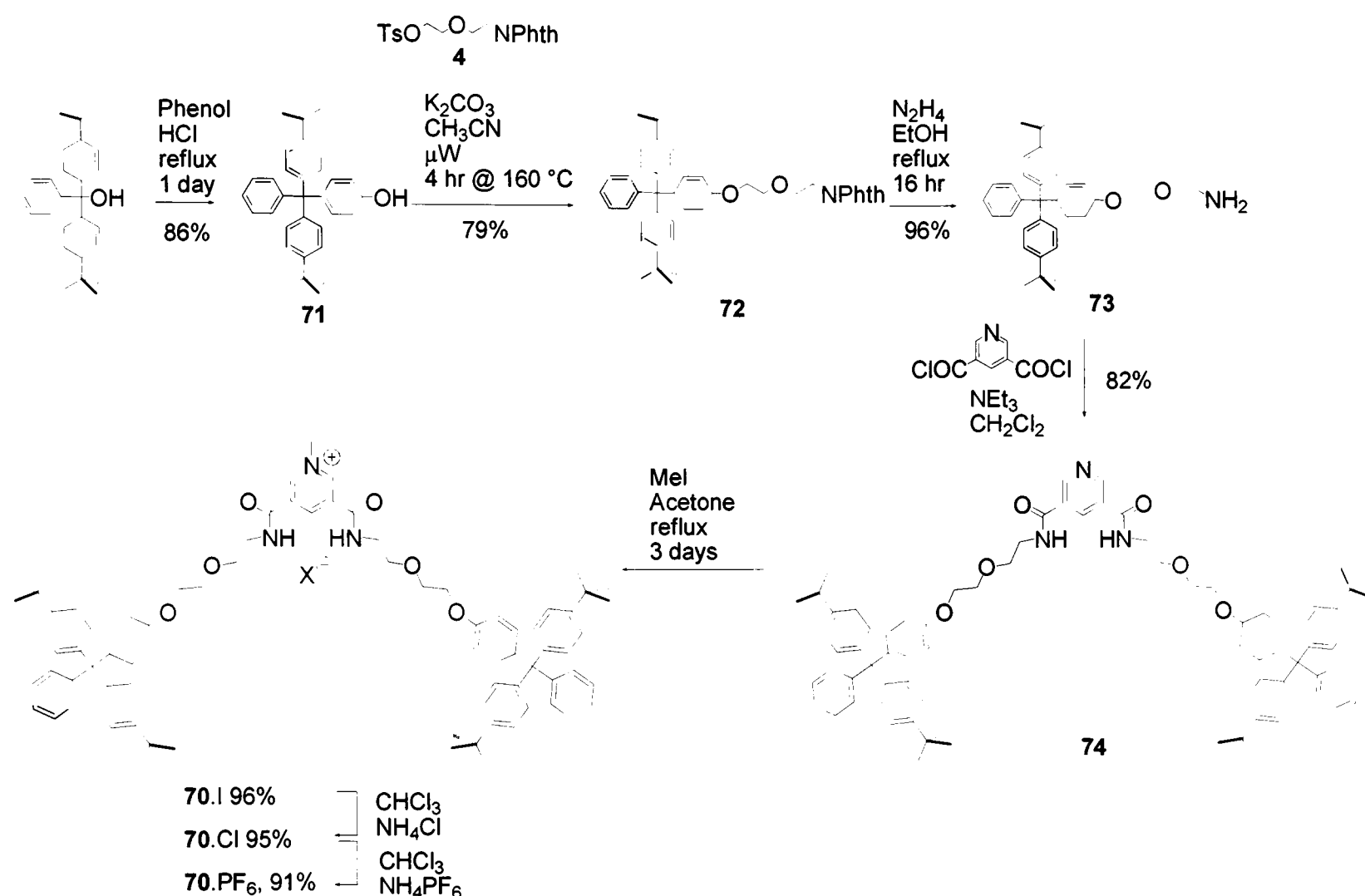


Figure 3.11 Target rotaxane **69.Cl** and novel axle **70.Cl**

The strategy for synthesising the new axle **70.Cl** is outlined in Scheme 3.11. The phenol functionalised stopper **71** was successfully prepared in 86% yield from compound **63** according to a literature procedure.³⁵ Compound **72** was synthesised in 79% yield by heating a suspension of compounds **71** and **4** and K_2CO_3 in CH_3CN in a microwave at 160 °C for 4 hours. The phthalimide protecting groups were removed in 96% yield using hydrazine monohydrate. The resulting amine **73** was reacted with 3,5-bis(chlorocarbonyl) pyridine in CH_2Cl_2 to give **74** in 82% yield. Methylation of **74** with iodomethane afforded **70.I** in 96% yield. The iodide anion was exchanged for chloride by repeated washings with 1 M NH_4Cl to give **70.Cl** in 95% yield. In addition, the non-coordinating hexafluorophosphate salt **70.PF₆**

was prepared for anion binding studies by repeated washing of a solution of **70.Cl** in CHCl_3 with 0.2 M NH_4PF_6 .



Scheme 3.11 Synthesis of axle **70.Cl**

Rotaxane **69.Cl** was synthesised using an analogous synthetic procedure to **68.Cl** and due to the improved solubility of **70.Cl**, it was possible to carry out the reaction at a higher concentration (Scheme 3.12). The rotaxane was isolated in 23% yield following purification by preparative TLC and recrystallisation from CHCl_3 /diisopropyl ether. The macrocycle by-product **66** was also formed, but due to its impure nature it was not possible to obtain an accurate yield.

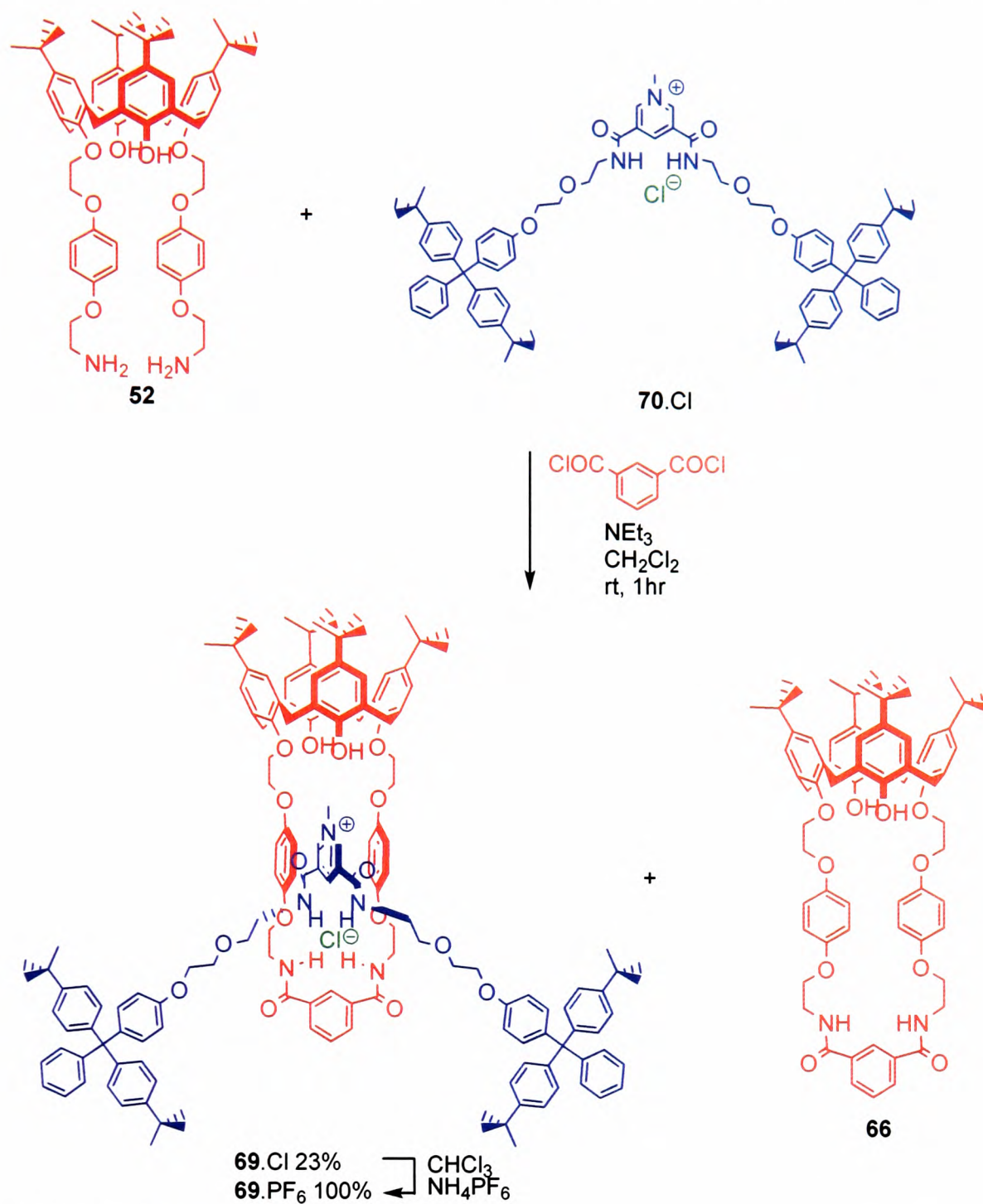
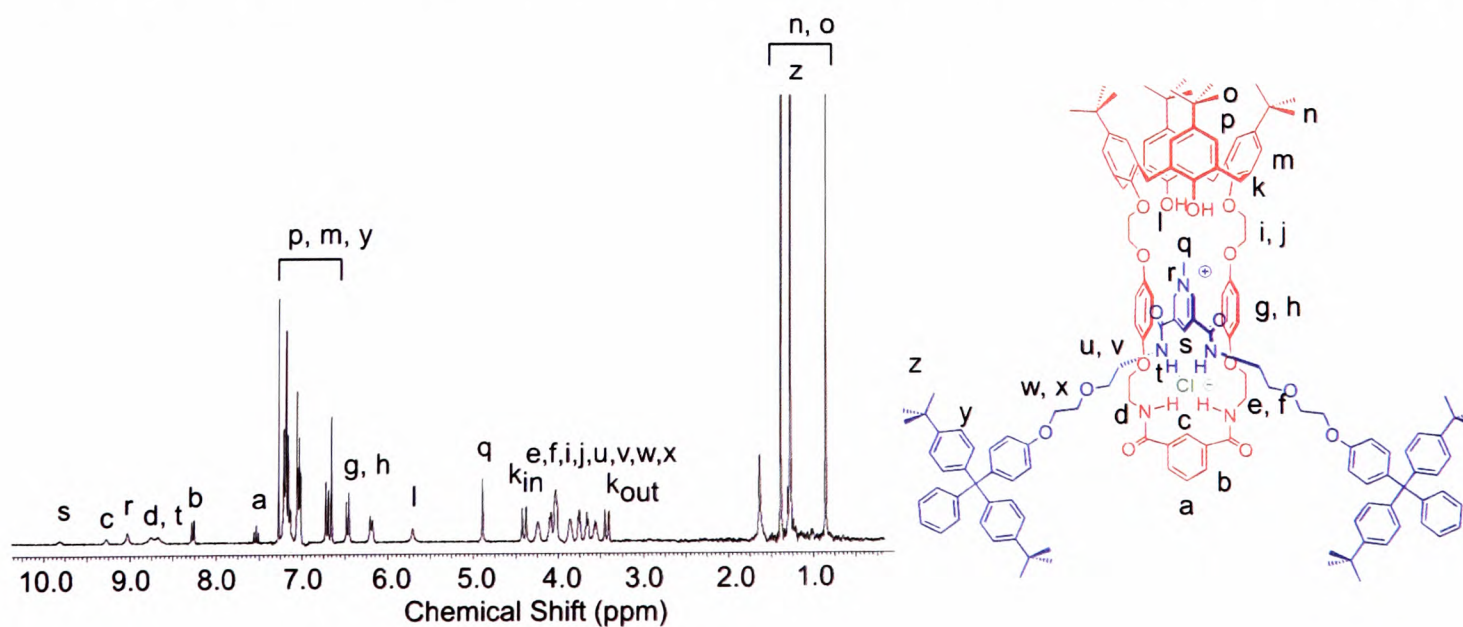
Scheme 3.12 Synthesis of rotaxane **69.Cl**

Figure 3.12 shows the ¹H NMR spectrum of **69.Cl** in CDCl₃ and the interlocked nature of the structure is indicated by the characteristic splitting of the hydroquinone protons *g* and *h*.

Figure 3.12 ¹H NMR spectrum of **69.Cl** in CDCl₃ at 293 K

Additionally the ROESY spectrum of **69.Cl** in CDCl_3 showed the expected correlations between the macrocycle and axle components (Figure 3.13). The rotaxane was also characterised by ^{13}C NMR spectroscopy, high resolution electrospray mass spectrometry and melting point analysis.⁴¹

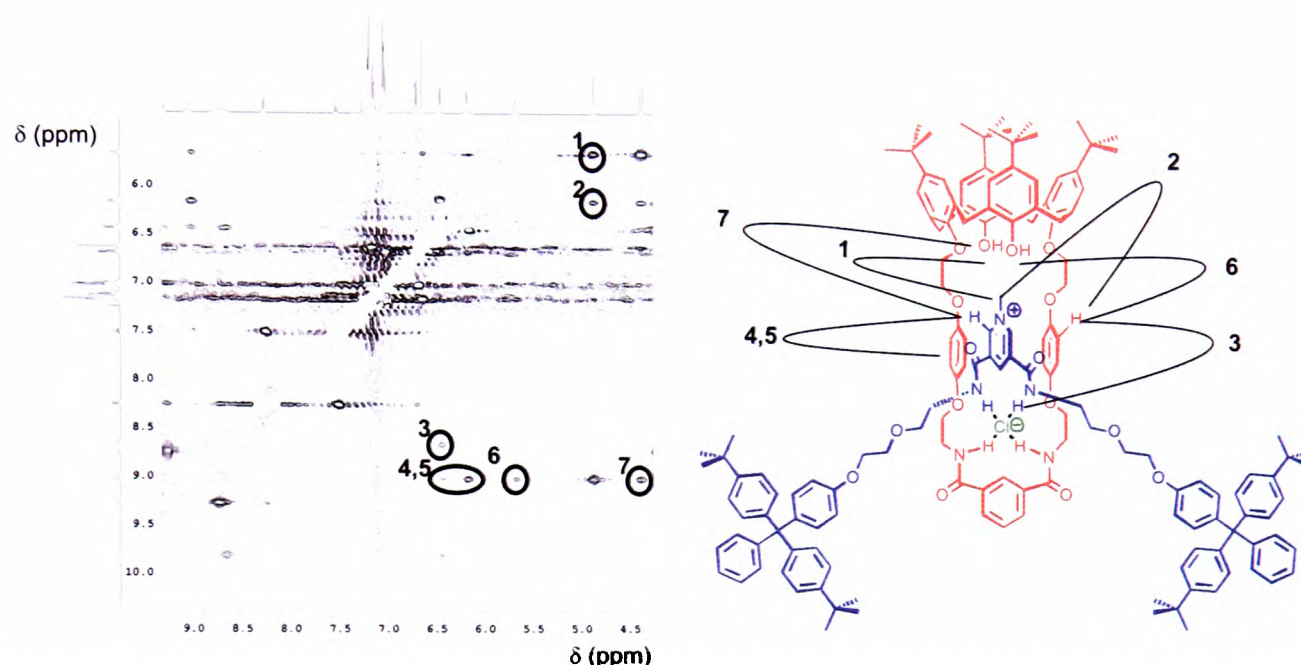


Figure 3.13 Portion of the ROESY spectrum of rotaxane **69.Cl** in CDCl_3 at 298 K illustrating the through space correlations between the calixarene macrocycle and axle components

Rotaxane **69.Cl** was converted to the hexafluorophosphate salt **69.PF₆** in an analogous manner to **68.PF₆** in quantitative yield. The ^1H NMR spectrum of **69.PF₆** was quite broad in CDCl_3 and therefore it was characterised in the more competitive solvent 1:1 $\text{CDCl}_3/\text{CD}_3\text{OD}$, where a sharper spectrum was obtained. This is suggestive of conformational flexibility of the thread component, presumably due to the absence of a coordinating anion directing the pyridinium unit between the macrocycle hydroquinone rings. In order to probe this further a number of ROESY experiments were carried out. The ROESY spectrum in 1:1 $\text{CDCl}_3/\text{CD}_3\text{OD}$ reveals the expected through space correlations between the hydroquinone protons of the macrocycle and the axle pyridinium protons (Figure 3.14). However, there are also correlations between the hydroquinone protons and alkyl protons of both the macrocycle and thread, as indicated by **4** in Figure 3.14. This suggests that the pyridinium unit of the axle is not restricted to residing between the hydroquinone rings of the macrocycle. It was hoped that by cooling the rotaxane in solution, it might be possible to further probe the conformation of the rotaxane.

When a solution of **69**.PF₆ in CDCl₃ was cooled to 243 K, a number of new signals appeared in the ¹H NMR spectrum in addition to those observed at 298 K. It was difficult to interpret the ¹H and ROESY spectra at 243 K, due to the broad and often overlapping signals and therefore this was not investigated any further. However, the appearance of new signals at the lower temperature is indicative of flexibility of the axle component in **69**.PF₆.

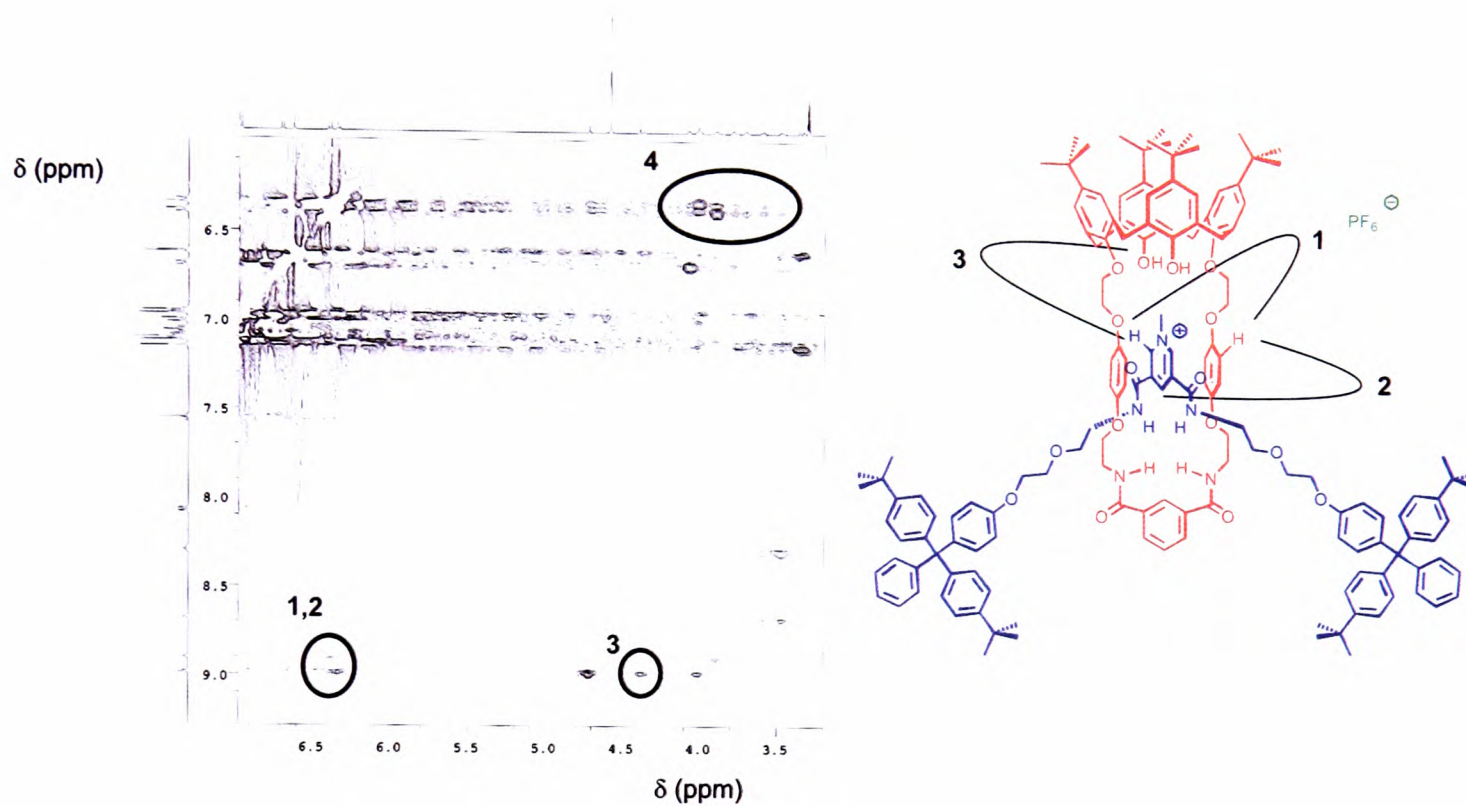


Figure 3.14 Portion of the ROESY spectrum of rotaxane **69**.PF₆ in 1:1 CDCl₃/CD₃OD at 298 K illustrating the through space correlations between the calixarene macrocycle and ion-pair thread components

3.2.5. Anion Binding Properties of Rotaxanes **68**.PF₆ and **69**.PF₆

¹H NMR titration experiments in 1:1 CDCl₃/CD₃OD were undertaken to study the anion binding properties of the rotaxanes **68**.PF₆ and **69**.PF₆ and axle **70**.PF₆. Chemical shift changes were monitored upon addition of a variety of anions, added as their TBA salts. In the presence of anions such as chloride and bromide, downfield shifts of protons *b*, *c* and *i* were observed for both rotaxanes **68**.PF₆ and **69**.PF₆ (Figure 3.15). However, the addition of acetate, dihydrogen phosphate and sulfate induced an upfield shift of proton *c* and downfield shifts of protons *b* and *i*. This is suggestive of a different binding mode for these anions, most likely outside the interlocked cavity due to their large size. In contrast, downfield shifts of protons *b* and *c* were observed upon addition of all anions to the axle **70**.PF₆.

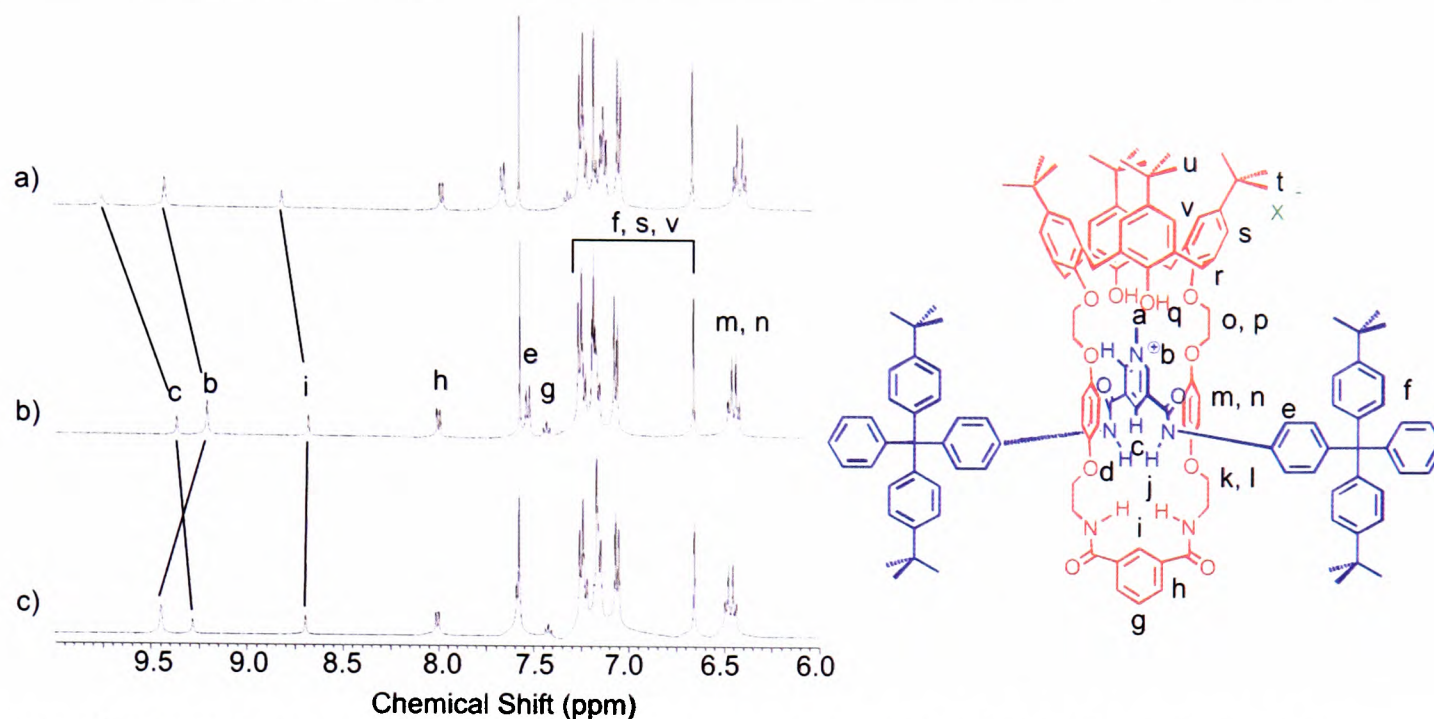


Figure 3.15 ^1H NMR spectra of a) **68.Cl** b) **68.PF₆** and c) **68.H₂PO₄** in 1:1 $\text{CDCl}_3/\text{CD}_3\text{OD}$ at 298 K.

WinEQNMR2⁴² analysis of the titration data (Figures 3.16 and 6.2 in Chapter 6) gave association constant values for rotaxane/anion complexes with a 1:1 stoichiometry (Table 3.2). These association constant values reveal the more preorganised rotaxane **68.PF₆** is the superior anion discriminating and complexing host system. Rotaxane **68.PF₆** is selective for chloride over bromide and the more oxobasic anions acetate and dihydrogen phosphate. This selectivity is due to a complementary size match between the preorganised interlocked binding cavity and the chloride anion, as evidenced in the solid state structure of **68.Cl** (Figure 3.9). Due to the lack of conformational flexibility within the binding cavity, the larger anions bromide, acetate and dihydrogen phosphate cannot be completely encapsulated within the rotaxane cavity. As a result, the magnitude of the association constants for these anions is significantly lower than for chloride. In addition, the large oxoanions most likely associate on the periphery of the cavity in a different binding mode to chloride as evidenced by the upfield shift of proton *c* in Figure 3.8. The rotaxane also binds the divalent sulfate anion very strongly, as expected, with an association constant of greater than 10^4 M^{-1} .

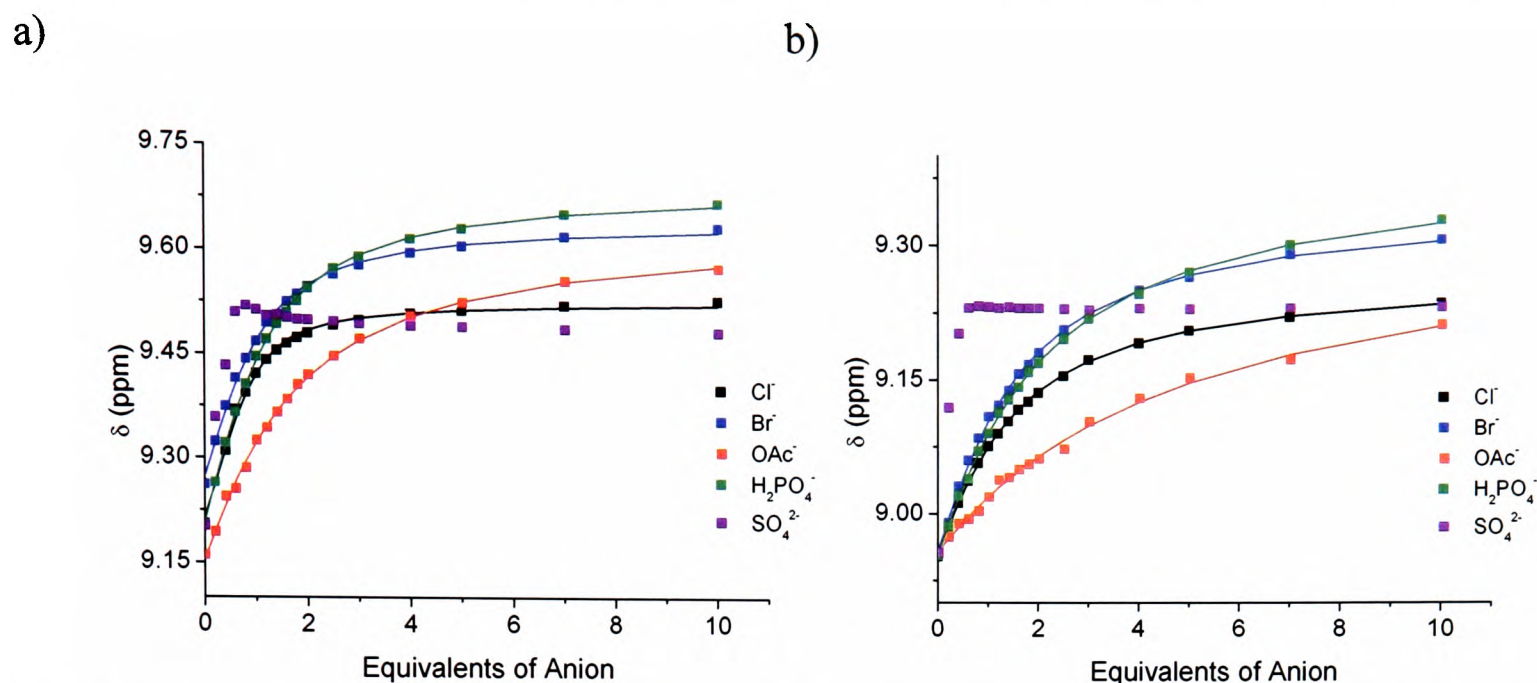


Figure 3.16 Chemical shift change of the *ortho* pyridinium proton *b* upon addition of anions as their TBA salts at 298 K to a solution of a) **68**.PF₆ and b) **69**.PF₆ in 1:1 CDCl₃/CD₃OD. Square symbols represent the experimental data points and the lines represent the calculated curves

X ⁻	68 .PF ₆ ^a	68 .PF ₆ ^b	70 .PF ₆ ^a	69 .PF ₆ ^a
Cl ⁻	3820	620	300	650
Br ⁻	1560	630	440	630
H ₂ PO ₄ ⁻	1140	70*	710	420
OAc ⁻	530	80	160	140*
SO ₄ ²⁻	>10 ⁴	1010	>10 ⁴	>10 ⁴

Table 3.2 Association constants derived from winEQNMR2⁴² analysis of the *ortho* pyridinium proton *b* data from ¹H NMR titration experiments in ^a 1:1 CDCl₃/CD₃OD and ^b 45:45:10 CDCl₃/CD₃OD/D₂O at 298 K. Errors < 10%. * errors < 20%

As rotaxane **68**.PF₆ displays strong binding of chloride and sulfate in 1:1 CDCl₃/CD₃OD, its anion binding properties in aqueous media were also investigated (Table 3.2). In a 45:45:10 CDCl₃/CD₃OD/D₂O solvent mixture the rotaxane binds the halide anions in preference to the monovalent oxoanions and as expected, the association constant values are lower in this more competitive aqueous mixture. It is noteworthy that the rotaxane is no longer selective for chloride over bromide with both anions exhibiting similar binding affinities in the aqueous mixture. This loss of chloride anion selectivity is presumably a consequence of the smaller halide anion's larger hydration energy which effectively competes with the overall anion recognition process.⁴³ An association constant of 1010 M⁻¹ was obtained for sulfate binding, which shows the rotaxane binds sulfate more strongly than chloride in this aqueous mixture due to stronger electrostatic interactions between the host and anion.

The axle **70**.PF₆ and rotaxane **69**.PF₆ exhibit significantly weaker anion binding compared with rotaxane **68**.PF₆ in 1:1 CDCl₃/CD₃OD solutions. Rotaxane **69**.PF₆ has a similar shaped binding cavity to rotaxane **68**.PF₆ and as a result, still binds the halides in preference to the larger oxoanions. However, it cannot discriminate chloride from bromide since the binding cavity is more conformationally flexible and can accommodate the larger bromide in the cavity with a similar affinity to chloride. The axle **70**.PF₆ also cannot significantly discriminate between the halides and as commonly observed for acyclic receptor systems,^{44, 45} it binds the basic dihydrogen phosphate more strongly than the other monovalent anions.

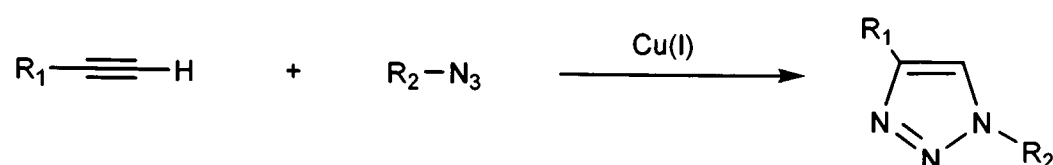
The first calix[4]arene based rotaxane host systems for anions were successfully synthesised using a new clipping strategy that does not rely on a ring closing metathesis reaction. As summarised in Figure 1.41, there are a number of strategies for synthesising rotaxanes, and a stoppering approach was also investigated.

3.3. Towards *tert*-Butylcalix[4]arene Based Rotaxanes by Stoppering

The stoppering approach has been successfully employed by a number of groups to synthesise rotaxanes, exploiting association of the macrocycle and axle components prior to a stoppering reaction. However, there are limitations on the types of stoppering reactions, since the association of the components usually relies on non-covalent interactions. Rotaxanes have been synthesised by stoppering with transition metal complexation,^{46, 47} but the diverse nature and mild conditions of ‘click’ chemistry, introduced by Barry Sharpless in 2001,⁴⁸ has expanded the number of suitable stoppering reactions. A number of rotaxanes have been reported using ‘click’ reactions, including urethane formation,⁴⁹⁻⁵¹ condensation reactions,^{13, 52} Diels-Alder reactions¹⁹ and copper(I) catalysed cycloadditions.^{53, 54}

While ‘click’ chemistry refers to a number of reaction types, only the copper(I) catalysed

alkyne-azide cycloaddition is used in this chapter and for simplicity the term ‘click reaction’ will be used to describe this reaction. It was decided to focus on this copper(I) catalysed reaction between an organic azide and terminal alkyne since it forms the triazole motif, which has been shown to bind anions (Scheme 3.13).⁵⁵⁻⁵⁸



Scheme 3.13 Copper(I) catalysed cycloaddition between a terminal alkyne and azide

Therefore, there is the potential to incorporate a second station into the rotaxane design for molecular motion. The design of the target azide and alkyne synthons are shown in Figure 3.17 with initial efforts focused on their synthesis.

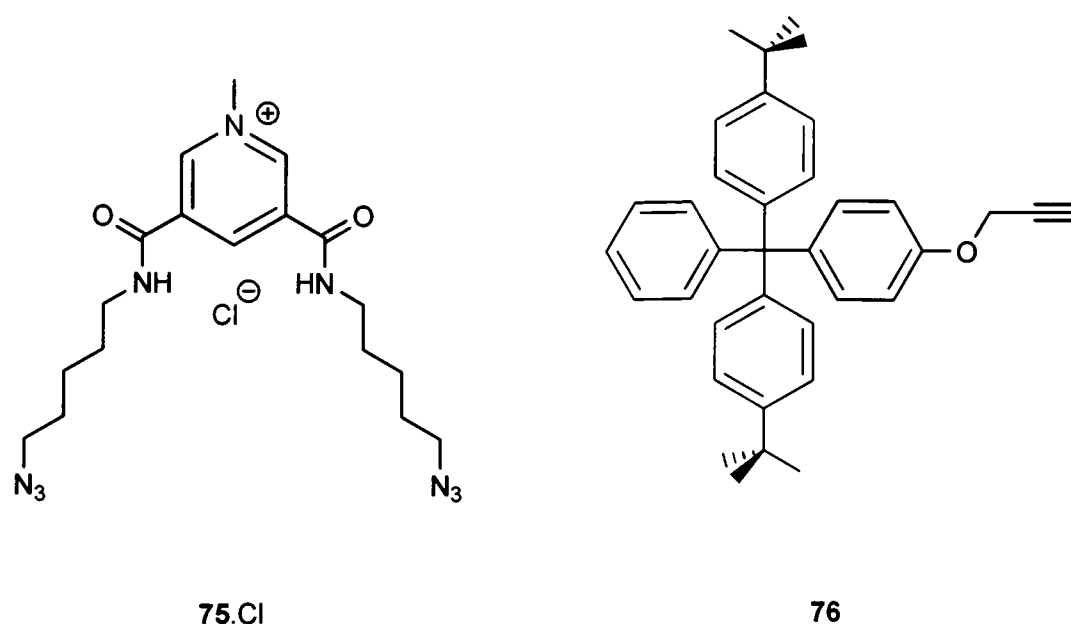
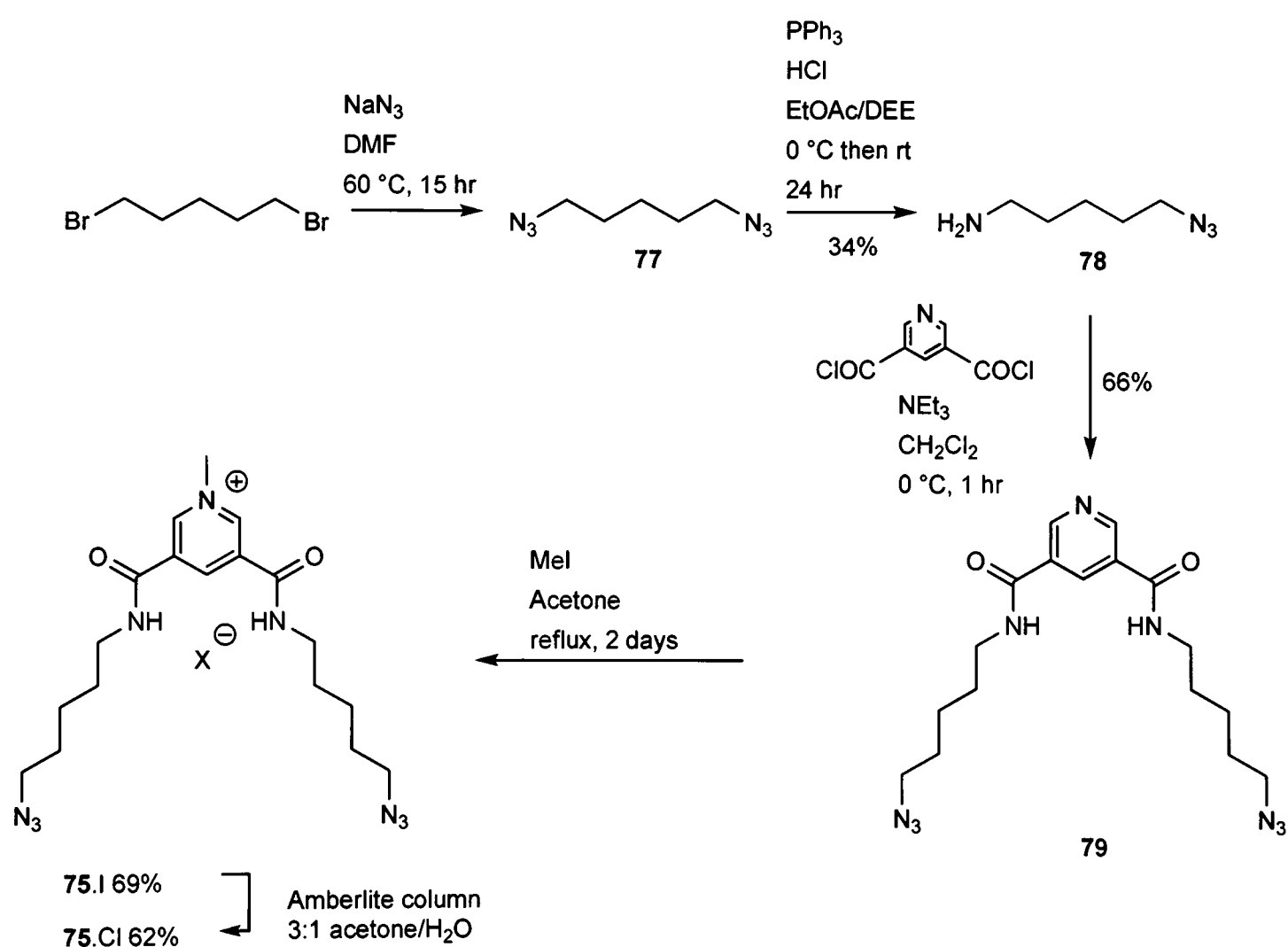


Figure 3.17 Target azide and alkyne synthons

3.3.1. Synthesis of Azide and Alkyne Synthons

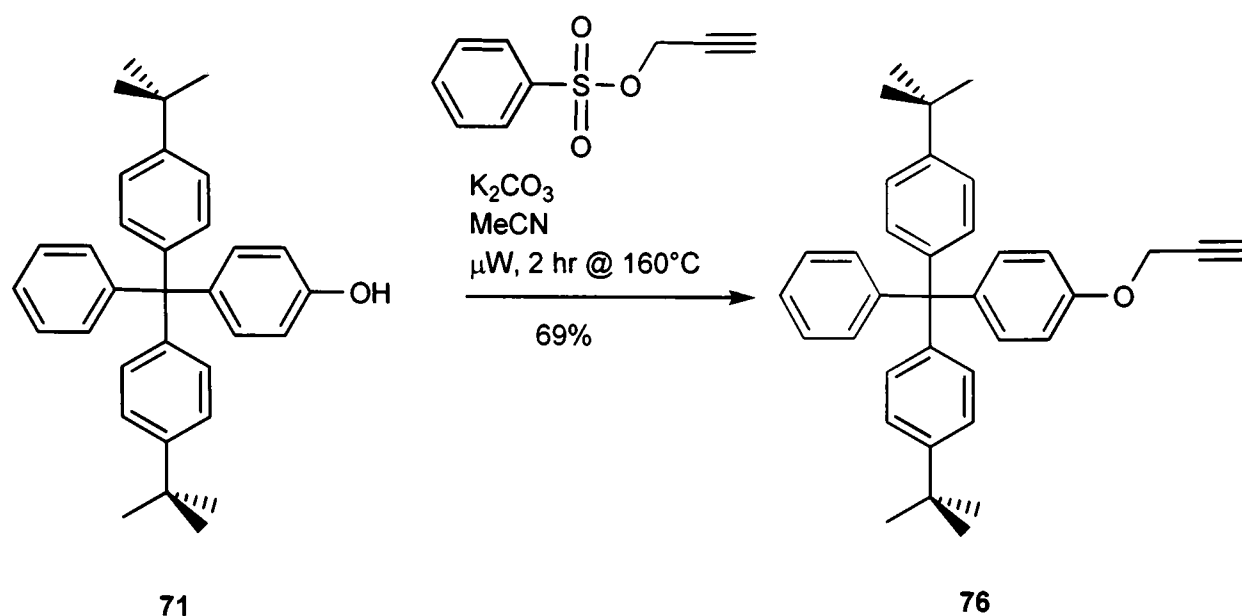
The strategy for synthesising the azide functionalised thread **75.Cl** is outlined in Scheme 3.14. In the first step, 1,5-dibromopentane was reacted with sodium azide to give the bis-azide **77**, which was not isolated but reacted on immediately.⁵⁹ One of the azide groups was selectively reduced using triphenylphosphine in the presence of aqueous HCl in a cooled EtOAc/diethyl ether mixture.⁶⁰ The monoreduced product **78** is extracted into the aqueous layer, which prevents reduction of the second azide group. Upon basifying the aqueous layer with NaOH, the product was extracted into CH₂Cl₂ to give **78** as a colourless oil in 34% yield over two

steps. Precursor **77** was assumed to form in quantitative yield, and the low yield of **78** is most likely due to problems extracting the product from the aqueous layer. Nevertheless, compound **78** was reacted with 3,5-bis(chlorocarbonyl) pyridine in the presence of triethylamine in CH_2Cl_2 to give **79** in 66% yield. Methylation with iodomethane in acetone gave the iodide salt **75.I** in 69% yield, which was converted to the chloride salt **75.Cl**. Initially this was attempted by repeated washing of a CHCl_3 solution of **75.I** with 1 M NH_4Cl , but the product was extracted into the aqueous layer. Following re-extraction into CH_2Cl_2 , the material was redissolved in 3:1 acetone/ H_2O , passed down an Amberlite chloride column and the chloride salt **75.Cl** was isolated as a yellow solid in 62% yield.



Scheme 3.14 Synthesis of azide precursor **75.Cl**

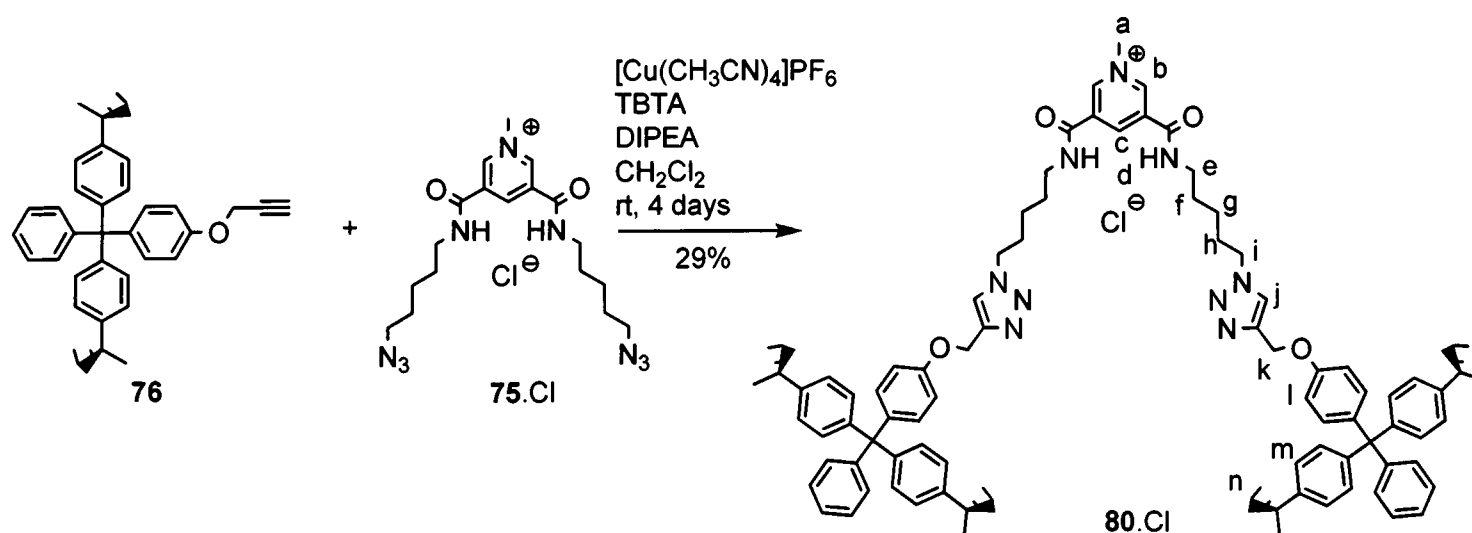
The alkyne functionalised precursor **76** was prepared in one step by heating a suspension of the stopper derivative **71**, propargyl benzenesulfonate and K_2CO_3 in CH_3CN under microwave irradiation (Scheme 3.15). Following purification by silica gel chromatography, **76** was isolated as a white solid in 69% yield.



Scheme 3.15 Microwave synthesis of alkyne precursor **76**

3.3.2. Towards the Synthesis of Rotaxanes by Stoppering

The synthesis of rotaxanes by stoppering was then investigated having prepared the necessary alkyne and azide precursors, in addition to the calix[4]arene macrocycle **66**. Initially, the preparation of the stoppered triazole thread **80.Cl** was explored to establish suitable stoppering reaction conditions (Scheme 3.16). The click reaction has found utility in many areas of chemistry,^{48, 61-63} and as a consequence, there are a number of reaction conditions that could be used. The catalyst $[\text{Cu}(\text{CH}_3\text{CN})_4]\text{PF}_6$ was chosen as it is soluble in non-polar organic solvents, such as CH_2Cl_2 , and the non-coordinating hexafluorophosphate anion would not interfere with any anion templation effects of the chloride anion.



Scheme 3.16 Synthesis of triazole stoppered thread **80.Cl**

A mixture of compounds **76** and **75.Cl** in CH_2Cl_2 in the presence of the base DIPEA and copper catalyst (15% by mol relative to azide component) was stirred at room temperature for 4 days. The desired thread **80.Cl** was isolated in 23% yield, based on the assumption that

the counter-anion is chloride. The chemical shifts of the pyridinium protons *b-d* in the ^1H NMR spectrum are consistent with a chloride anion rather than a hexafluorophosphate anion, with the remaining protons assignments also shown (Figure 3.18). Of particular importance is the triazole peak *j* at 7.70 ppm. While this reaction shows that the stoppering approach is a feasible strategy for synthesising rotaxanes, the low yield was a concern. Attempts were made to improve this, including the use of *tris*-(benzyltriazolylmethyl)amine (TBTA) as an additive, since it has been shown to enhance the catalytic activity of copper(I) salts while simultaneously protecting the catalyst from oxidation and disproportionation.⁶⁴ The yield of **80.Cl** was improved to 29% in the presence of TBTA, but this was not a large enough improvement to consider attempting the rotaxane synthesis. Work within the group has demonstrated that bases such as triethylamine decompose pyridinium based threads, significantly lowering rotaxane yields. In order to discount that the low yields were due to the pyridinium thread decomposing, the reaction was repeated in the absence of the base DIPEA. However, this led to a mixture of starting material, the desired thread **80.Cl** and the half-stoppered thread, as indicated by electrospray mass spectrometry.

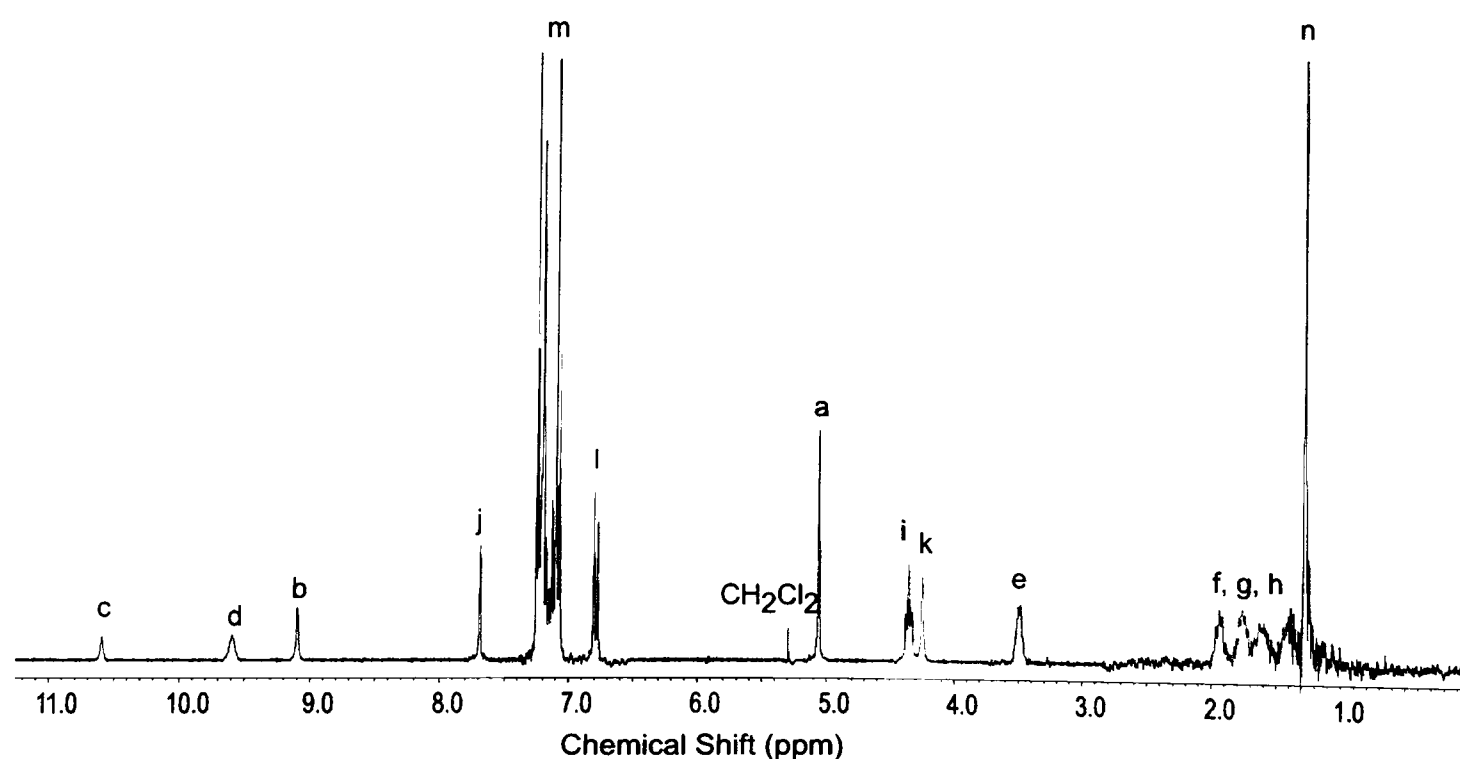
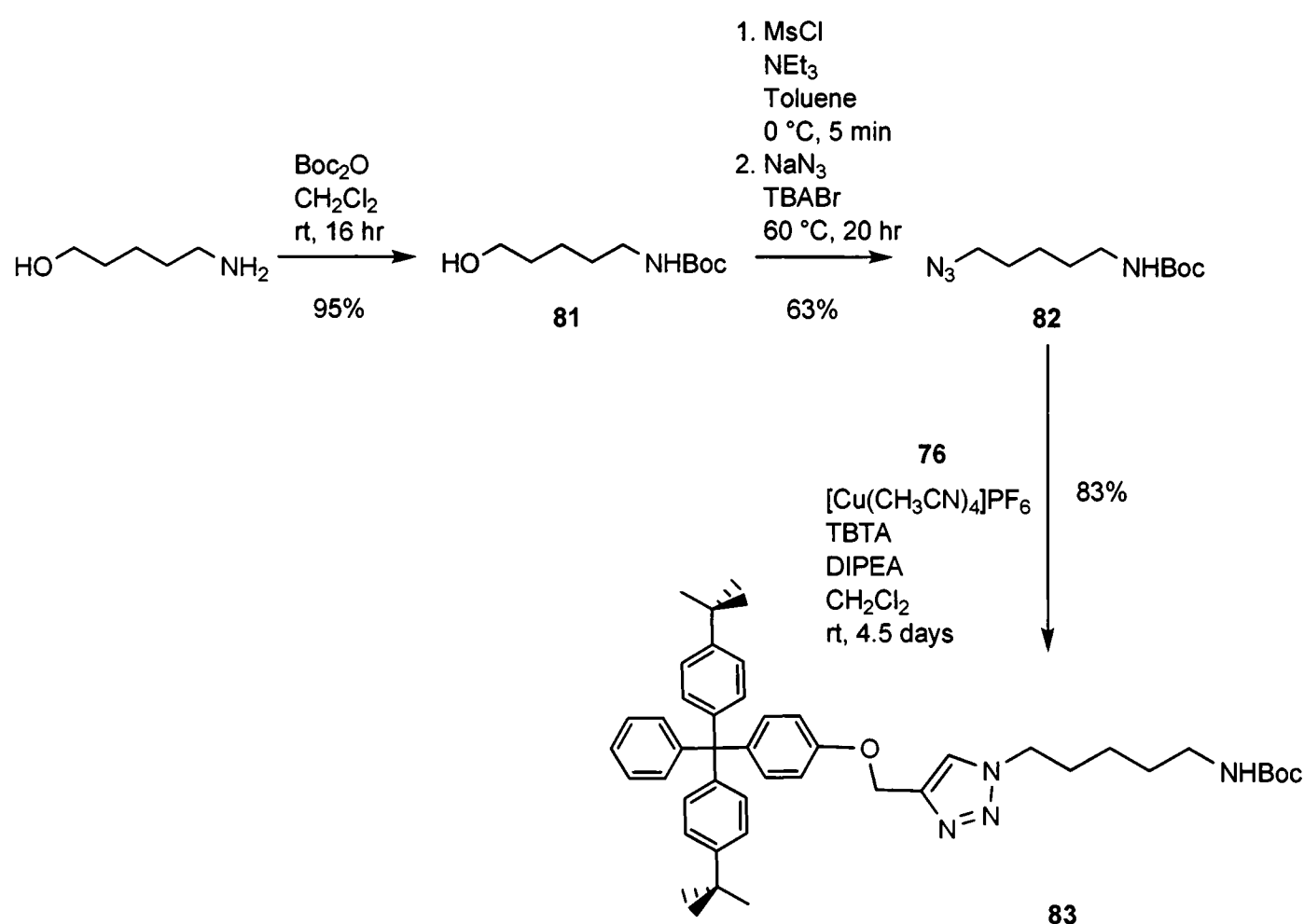


Figure 3.18 ^1H NMR spectrum of **80.Cl** in CDCl_3 at 293 K. See Scheme 3.16 for proton assignments

Unfortunately, it was not possible to significantly improve the yield of the stoppering

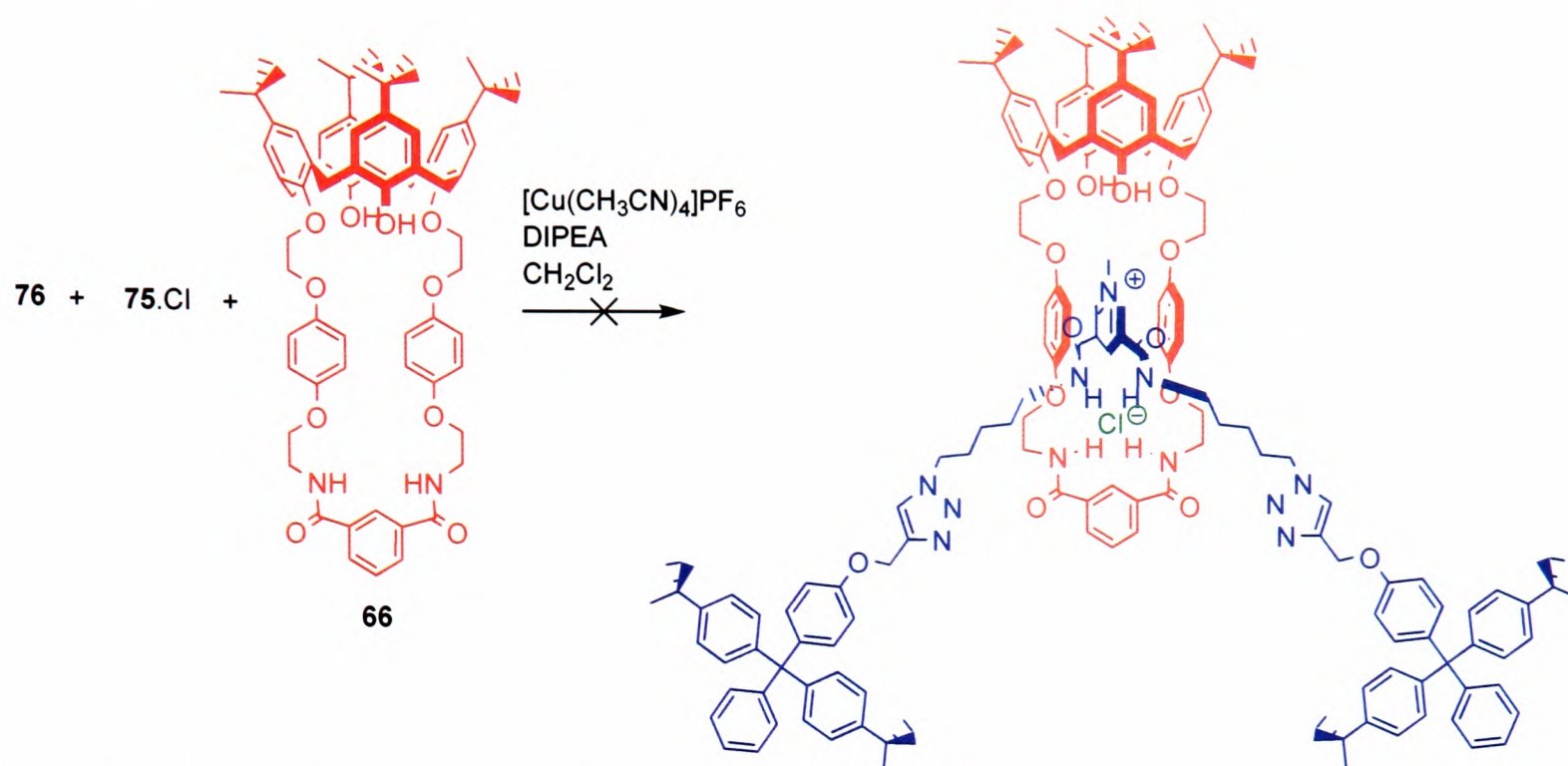
reaction, and instead the click reaction between **76** and **82**, a model for azide precursor **75.Cl**, was investigated to optimise the reaction conditions. Compound **82** was prepared in two steps from commercially available 5-amino-1-pentanol, beginning with the protection of the primary amine using di-*tert*-butyldicarbonate in CH_2Cl_2 to give **81** in 95% yield (Scheme 3.17).⁶⁵ The hydroxyl group was converted to the mesyl leaving group, using methanesulfonyl chloride in the presence of triethylamine at 0 °C in toluene, before reaction with aqueous sodium azide at 60 °C using TBABr as a phase-transfer agent. Compound **82** was isolated as a yellow oil in 63% yield and this was subsequently reacted with **76** in the presence of TBTA stabilised $[\text{Cu}(\text{CH}_3\text{CN})_4]\text{PF}_6$ and DIPEA in CH_2Cl_2 . Pleasingly, the desired product **83** was isolated in 83% yield, which demonstrates the low yield of **80.Cl** is most likely due to the azide component **75.Cl**.



Scheme 3.17 Successful click reaction between **76** and model system **82**

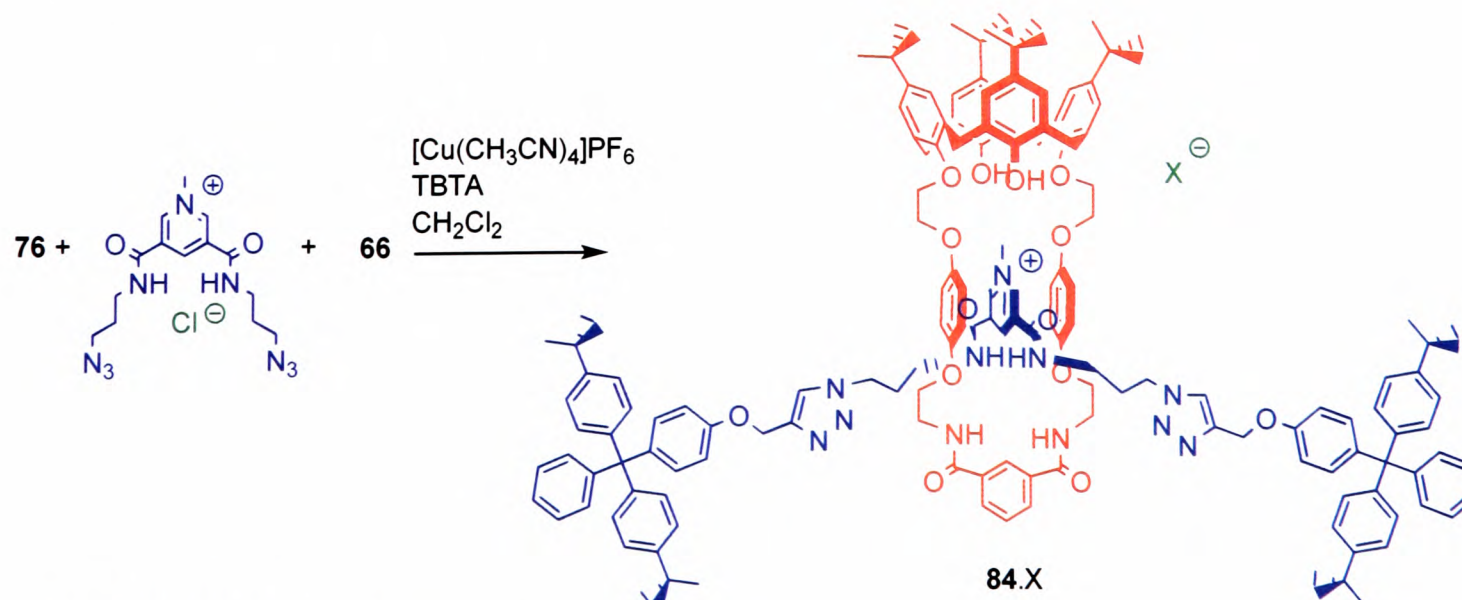
Despite the low yield of **80.Cl**, the click reaction between **75.Cl** and **76** in the presence of the macrocycle **66** was attempted (Scheme 3.18). There was no evidence of rotaxane formation by ^1H NMR spectroscopy, although the stoppered triazole thread **80.Cl** was isolated in 9%

yield.



Scheme 3.18 Attempted rotaxane synthesis by stoppering

The stoppering reaction was then attempted with a different azide thread component, kindly provided by Dr Alexandre Leontiev, which gave evidence of rotaxane formation (Scheme 3.19). It was possible to isolate a small amount of impure rotaxane **84.X**, as indicated by the electrospray mass spectrum in Figure 3.19. However, it was not possible to assign the ^1H NMR spectrum, and the characteristic splitting of the hydroquinone protons was absent. Despite evidence for its formation, the yield of the rotaxane is estimated to be less than 10%, based on the amount isolated and given that over 60% of unreacted **66** was recovered from the reaction mixture.



Scheme 3.19 Synthesis of rotaxane **84.X**

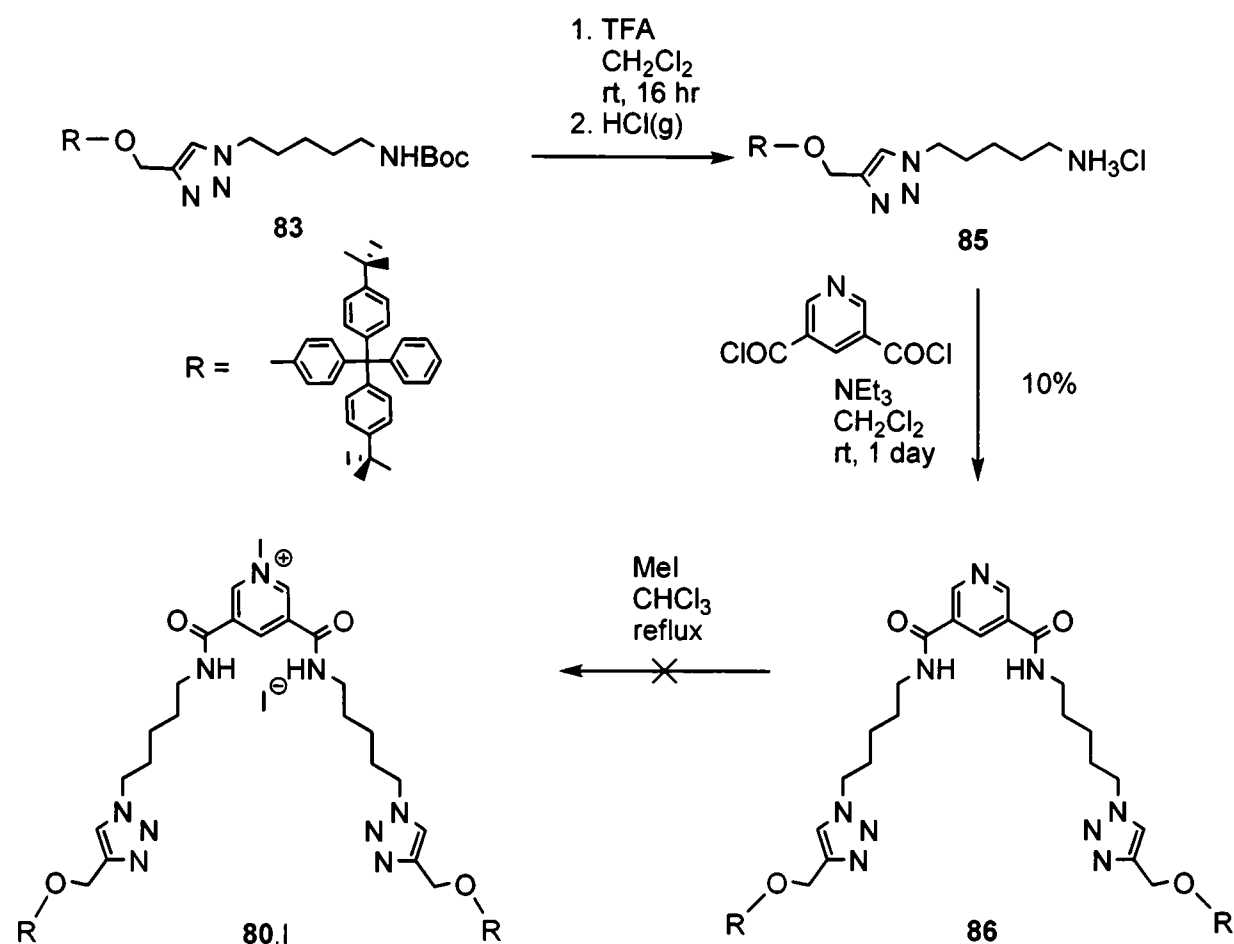
a)

b)



Figure 3.19 a) Electrospray mass spectrum of rotaxane **84.X** and b) theoretical isotope model

The stoppering approach was not investigated any further due to these synthetic difficulties. Instead, an alternative synthesis of the target rotaxanes was investigated exploiting the clipping strategy developed in Section 3.2. This involved the preparation of **80.X** from **83** according to Scheme 3.20. The Boc protecting group was removed using TFA and compound **85** was precipitated as the hydrochloride salt. However, this contained a small amount of an impurity and therefore it was reacted with 3,5-bis(chlorocarbonyl) pyridine without further purification in the presence of triethylamine in CH_2Cl_2 giving **86** in 10% yield over two steps.



Scheme 3.20 Alternative synthesis of 80.X

Methylation of **86** was attempted with iodomethane, as previous work within the group found that this did not alkylate the triazole rings. However, the mass spectrum of the reaction mixture indicated a mixture of products, including **80.I** and most likely the product from alkylation of the triazole rings (Figure 3.20). Attempts to isolate the different products by column chromatography were unsuccessful, due to the small scale of the reaction. Given the low yielding synthesis of **86** and unsuccessful alkylation attempts, this alternative strategy was not pursued.

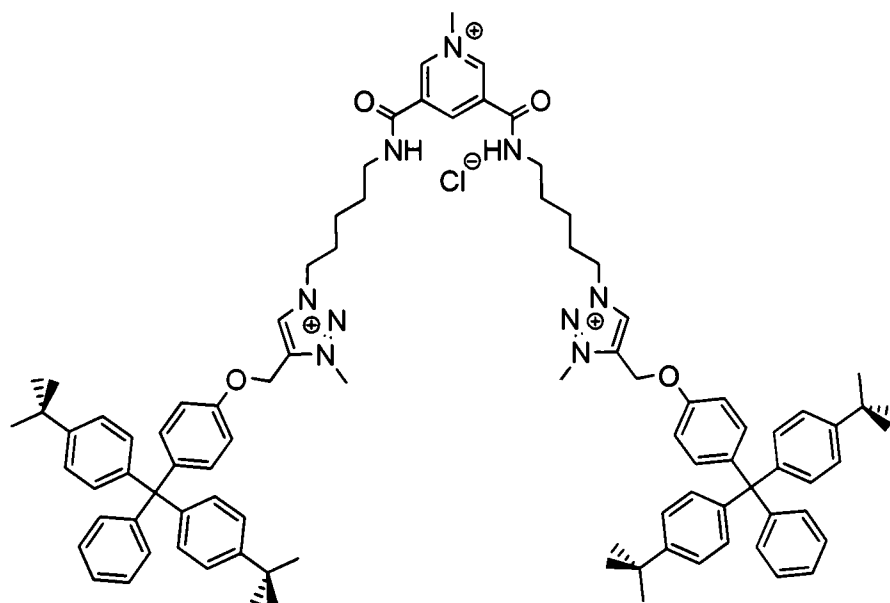
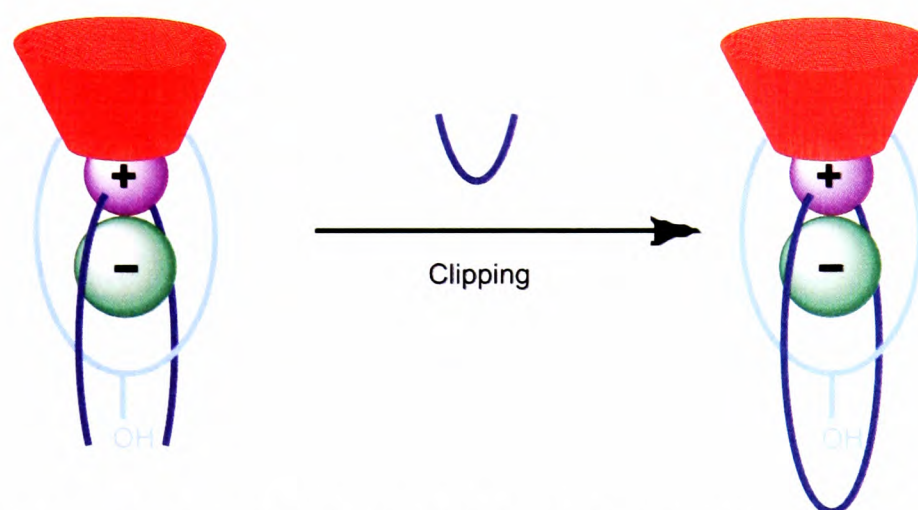


Figure 3.20 One of the proposed products from the reaction of **86** with iodomethane

3.4. *tert*-Butylcalix[4]arene Based Catenanes for Molecular Motion

Attention then turned to the synthesis of calix[4]arene based catenanes, initially focusing on the development of catenanes for molecular motion. The clipping strategy employed for the synthesis of the calix[4]arene based catenane in Figure 3.5a would be employed (Scheme 3.21).



Scheme 3.21 Clipping strategy for the synthesis of calix[4]arene based catenanes

This involves the synthesis of the calix[4]arene macrocycle **87**, which incorporates a hydroxyl group on the anion binding unit, and the macrocycle precursor **88.Cl** appended with terminal alkene groups for the clipping ring closing metathesis reaction (Figure 3.21).

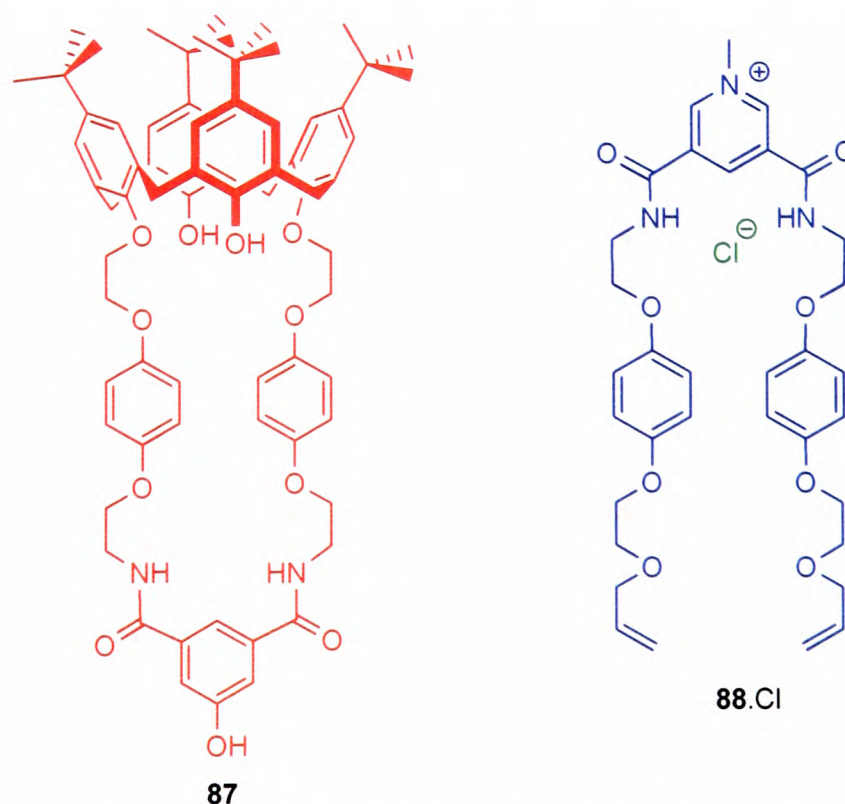
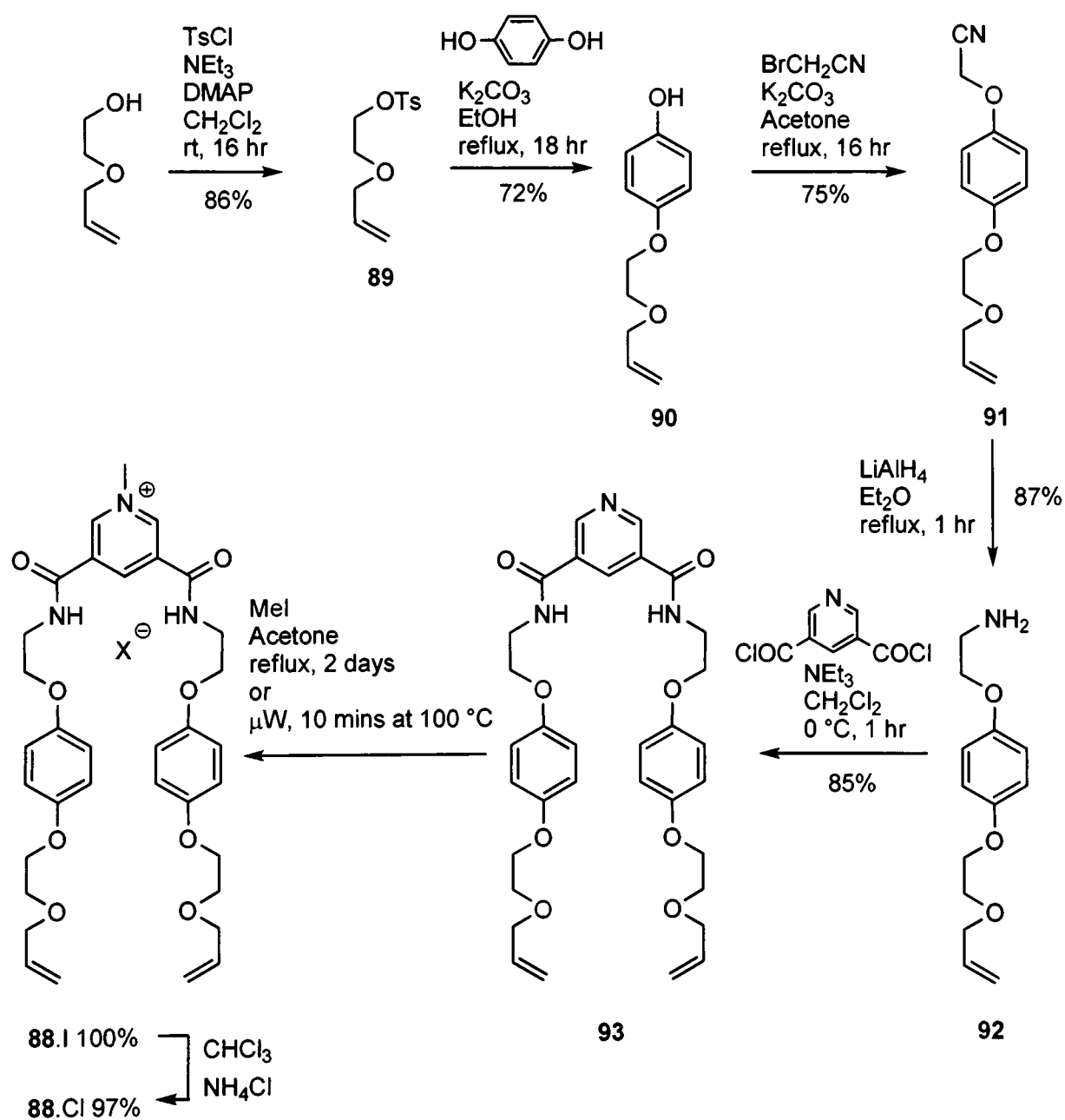


Figure 3.21 Synthesis of calix[4]arene based catenanes using a clipping approach with target macrocycle **87** and macrocycle precursor **88.Cl**

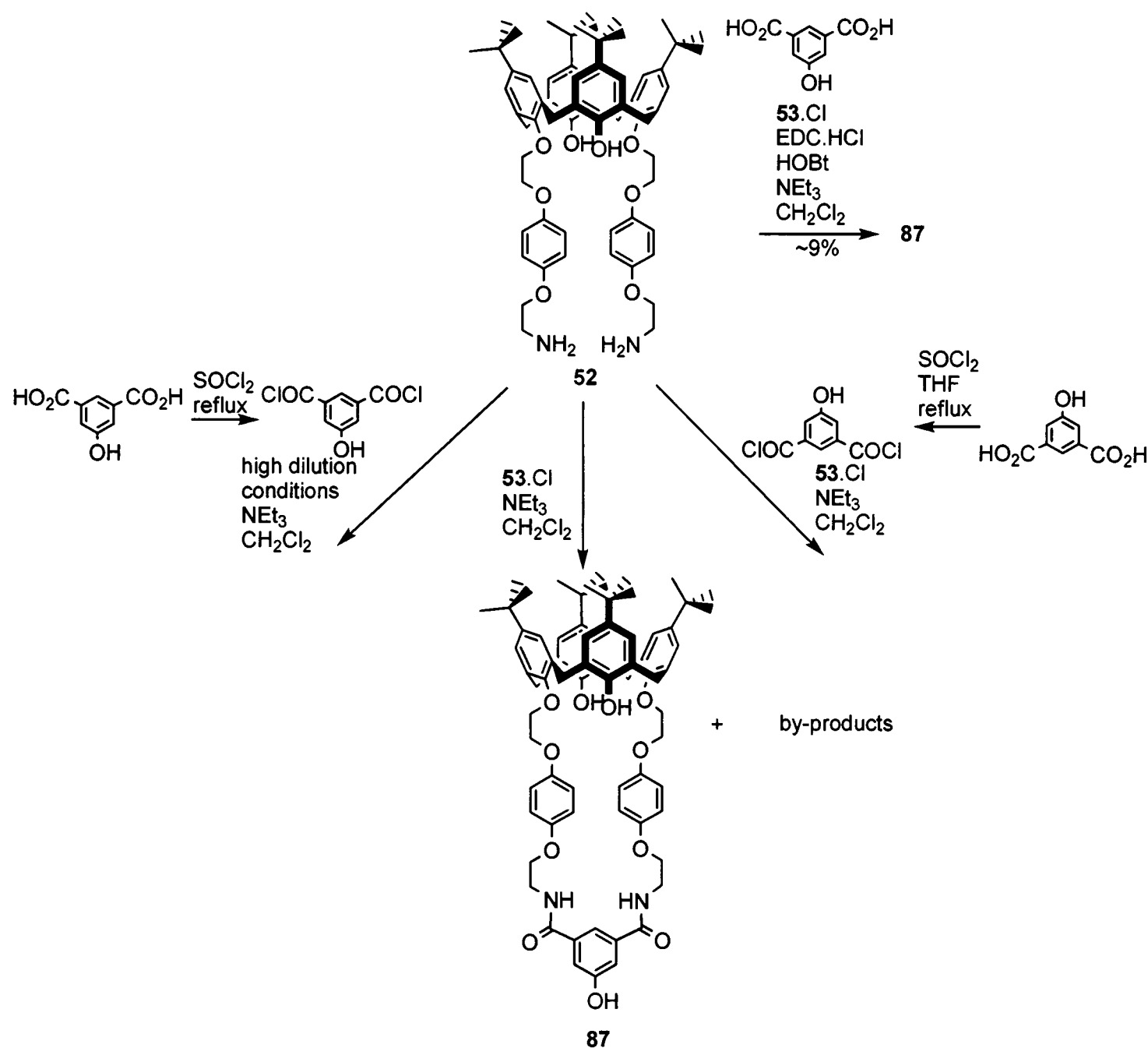
3.4.1. Synthesis of Macrocycle Precursor **88.Cl** and Macrocycle **87**

The macrocycle precursor **88.Cl** was prepared from 2-allyloxyethanol according to Scheme 3.22. Compound **89** was synthesised in 86% yield by tosylation of 2-allyloxyethanol,⁶⁶ and then reacted with an excess of *p*-hydroquinone in the presence of K_2CO_3 to give the monofunctionalised compound **90** in 72% yield.³⁰ This was reacted with bromoacetonitrile in acetone giving nitrile **91**, which was reduced to the amine **92** in 87% yield using $LiAlH_4$.³⁰ The reaction of **92** with 3,5-bis(chlorocarbonyl) pyridine in the presence of triethylamine in CH_2Cl_2 at 0 °C afforded compound **93** in 85% yield.³¹ Methylation with iodomethane and subsequent anion exchange using NH_4Cl gave the desired macrocycle precursor **88.Cl** in good yield.^{23, 31}

Scheme 3.22 Synthesis of precursor **88.Cl**

The synthesis of macrocycle **87** was initially attempted by reacting bis-amine **52** with

5-hydroxyisophthaloyl dichloride, prepared from overnight reflux of the bis-acid in thionyl chloride, in CH_2Cl_2 under high dilution conditions (Scheme 3.23). However, this gave a mixture of products, including **87**, which could not be separated by column chromatography or recrystallisation. A number of the reaction conditions were modified in an attempt to suppress the formation of the by-products, including preparing the acid chloride using a different method⁶⁷ and using **53.Cl** as an ion-pair template, as summarised in Scheme 3.23. However, these strategies also gave an inseparable mixture of products.



Scheme 3.23 Ion-pair templated synthesis of **87** using EDC.HCl coupling

As a final attempt, the macrocyclisation was carried out exploiting both ion-pair templation and EDC.HCl coupling. 5-Hydroxyisophthalic acid was activated in the presence of EDC.HCl and HOBt and added dropwise to a 1:1 mixture of **52** and **53.Cl** in CH_2Cl_2 . It was possible to

isolate a small amount of **87**, which was almost pure by ^1H NMR spectroscopy (Figure 3.22), in less than 9% yield by column chromatography.

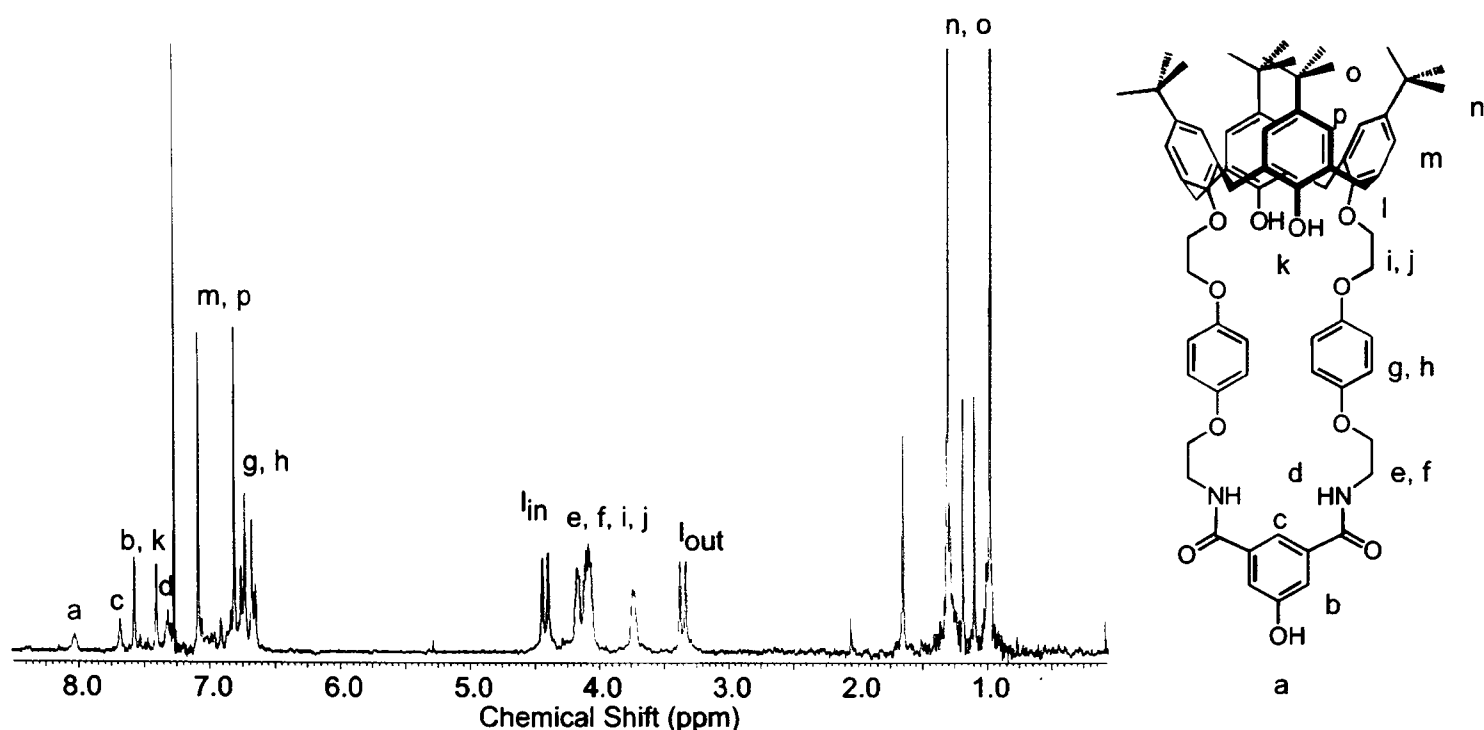
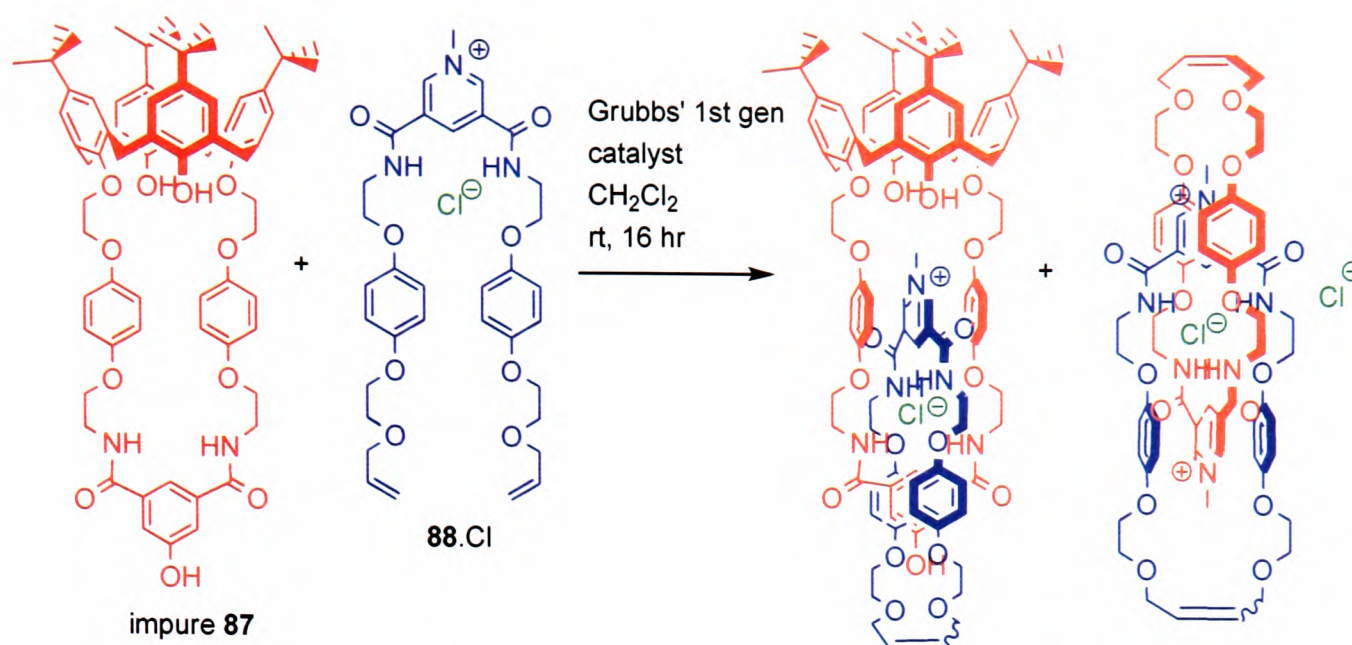


Figure 3.22 ^1H NMR spectrum of impure macrocycle **87**

3.4.2. Towards the Synthesis of the Catenane

Unfortunately, it was not possible to synthesise pure macrocycle **87** in a large enough quantity to attempt the catenane synthesis with **88.Cl**. Instead, the reaction was attempted with the reaction mixture from the unsuccessful macrocyclisation reactions, which was predominantly **87**, in the hope it would be possible to separate the desired catenane product from other by-products. A solution of the macrocycle mixture, **88.Cl** and Grubbs' 1st generation catalyst was stirred at room temperature in CH_2Cl_2 (Scheme 3.24) and the reaction mixture was purified by preparative TLC. It was possible to isolate small quantities of the cyclised thread and the catenane resulting from double cyclisation. There was mass spectrometry evidence for the formation of the desired catenane but it did not prove possible to isolate this product.

Disappointingly, difficulties synthesising the target macrocycle **87** prevented further investigation into the preparation of catenanes for the study of molecular motion. Instead the synthesis of catenanes exploiting another calix[4]arene based macrocycle was explored.



Scheme 3.24 Attempted catenane reaction between impure 87 and 88.Cl

3.5. Calix[4]arene Based Catenanes

The majority of this chapter has focused on the synthesis of interlocked structures based on *tert*-butylcalix[4]arene macrocycles, however, in this section the synthesis of catenanes based on calix[4]diquinone will be explored using a clipping strategy. As discussed in Chapter 2, the calix[4]diquinone motif complexes cations strongly and incorporating this motif into the macrocycle component of the interlocked structure might enhance association of the macrocycle and positively charged macrocycle precursor. Initially synthesis of the calix[4]diquinone macrocycle **94** in Figure 3.23 will be investigated using chlorine dioxide oxidation before attempting the catenane synthesis with macrocycle precursor 88.Cl.

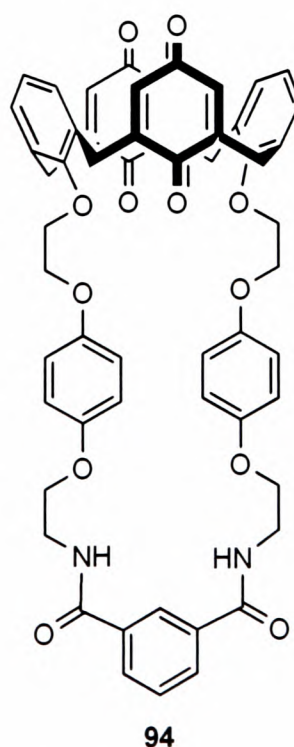
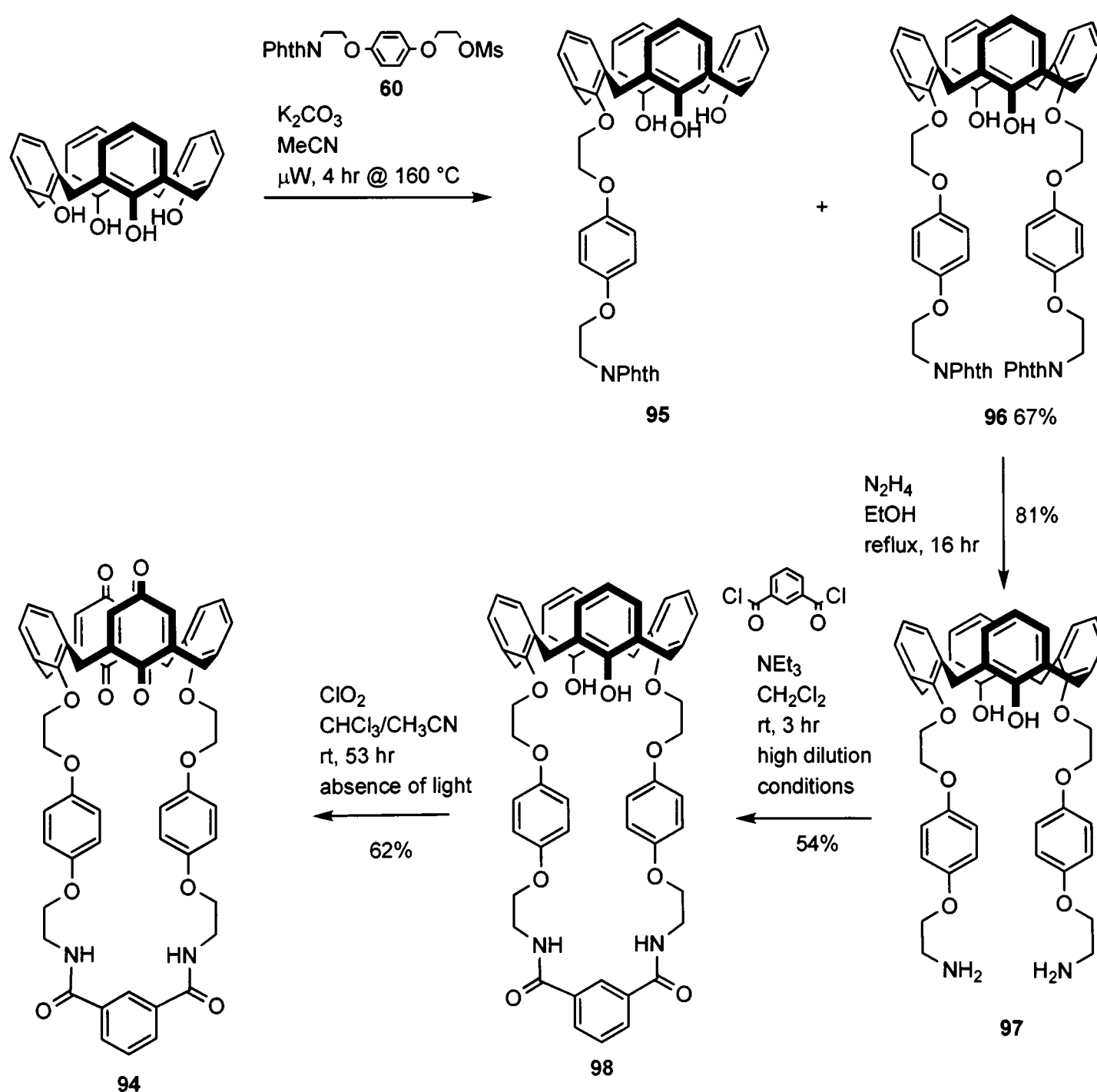


Figure 3.23 Target calix[4]diquinone macrocycle **94**

3.5.1. Calix[4]diquinone Macrocycle Synthesis

The strategy used to synthesise the *tert*-butylcalix[4]arene macrocycle **66** was adapted to prepare the analogous calix[4]arene macrocycle **98** according to Scheme 3.25. Calix[4]arene was alkylated with **60** under microwave irradiation to give the desired product **96** in 67% yield, in addition to small amounts of the monoalkylated product **95**. Removal of the phthalimide protecting groups using hydrazine afforded the bis-amine **97**, which was reacted with isophthaloyl dichloride under high dilution conditions in CH₂Cl₂ to give the macrocycle **98** in 54% yield.



Scheme 3.25 Synthesis of calix[4]diquinone macrocycle **94**

Oxidation of macrocycle **98** to **94** proved problematic, with the limited solubility of **98** in CH₃CN leading to a mixture of unreacted **98** and **94**. When the reaction was repeated in

CHCl_3 for improved solubility, the desired product formed but the oxidative cleavage product (Figure 3.24) was also detected by the peak at m/z 573.2 in the mass spectrum. A number of solvent systems were tested to optimise solubility of the starting material for oxidation but prevent oxidative cleavage of the hydroquinone groups. When the reaction was repeated in 2:1 $\text{CH}_3\text{CN}/\text{CHCl}_3$, oxidative cleavage product was also detected by mass spectrometry. However, it was possible to isolate **94** in 56% yield using 4:1 $\text{CH}_3\text{CN}/\text{CHCl}_3$, with no evidence of the cleavage product, and the yield could be improved to 62% yield in 6:1 $\text{CH}_3\text{CN}/\text{CHCl}_3$.

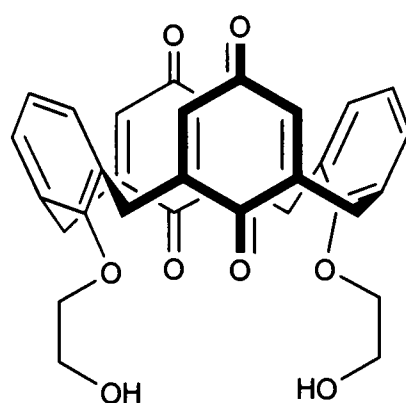
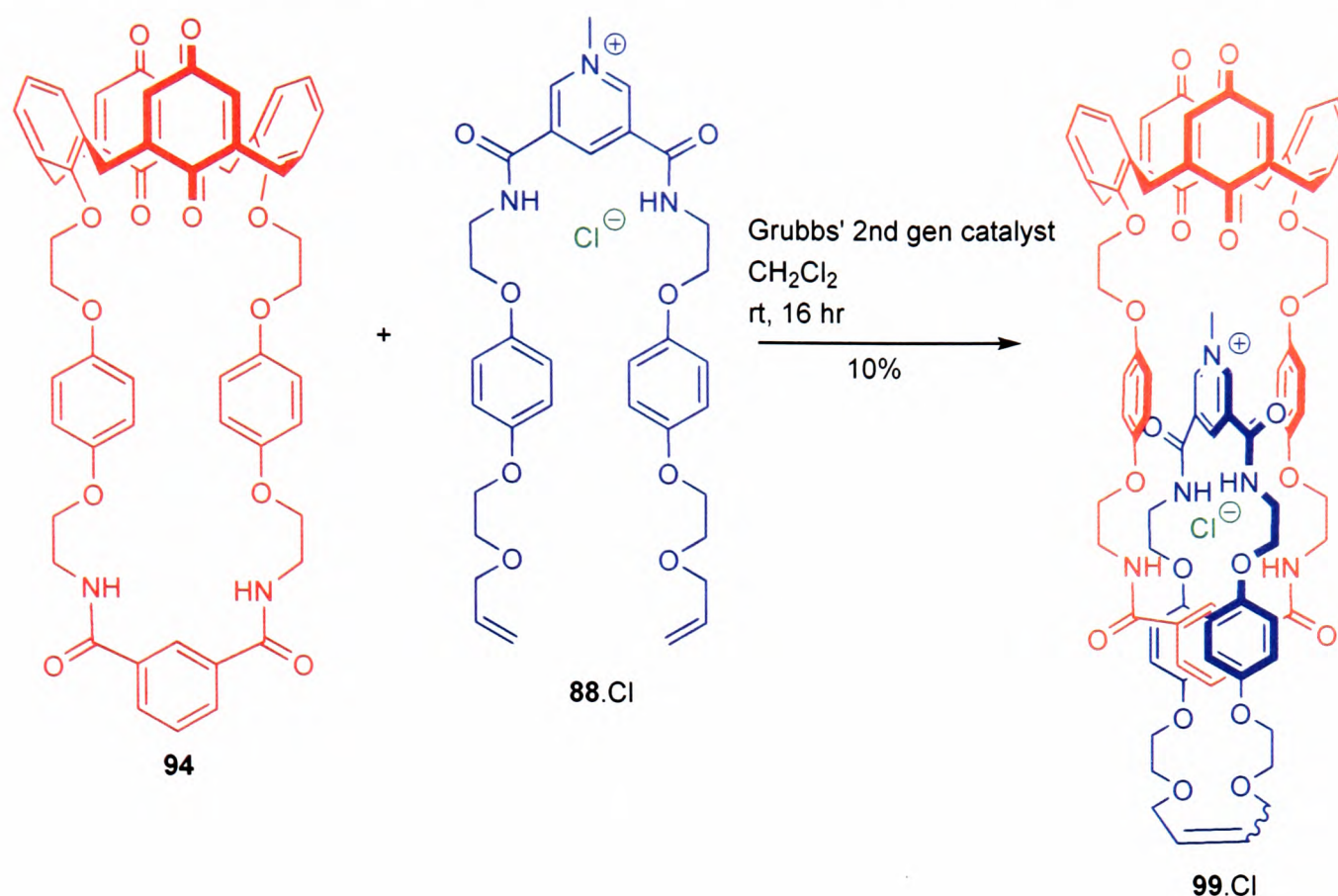


Figure 3.24 Product from oxidative cleavage of the hydroquinone rings

3.5.2. Catenane Synthesis

Catenane **99.Cl** was synthesised by stirring a mixture of **94** and **88.Cl** with Grubbs' 2nd generation catalyst in CH_2Cl_2 for 16 hours (Scheme 3.26) and isolated in 10% yield following purification by preparative TLC.



Scheme 3.26 Synthesis of catenane **99.Cl**

A comparison of the ^1H NMR spectra of the macrocyclic and thread components and the isolated product revealed the successful synthesis of **99.Cl** (Figure 3.25). The disappearance of the multiplets at 5 and 6 ppm and appearance of a singlet for proton *z* in the catenane spectrum indicate that cyclisation of the thread component has occurred. The downfield shifts of the macrocycle protons *c* and *d*, upfield shifts and splitting of the macrocycle hydroquinone protons *g* and *h*, and upfield shifts of the thread protons *p-r* are all consistent with the expected catenane structure.

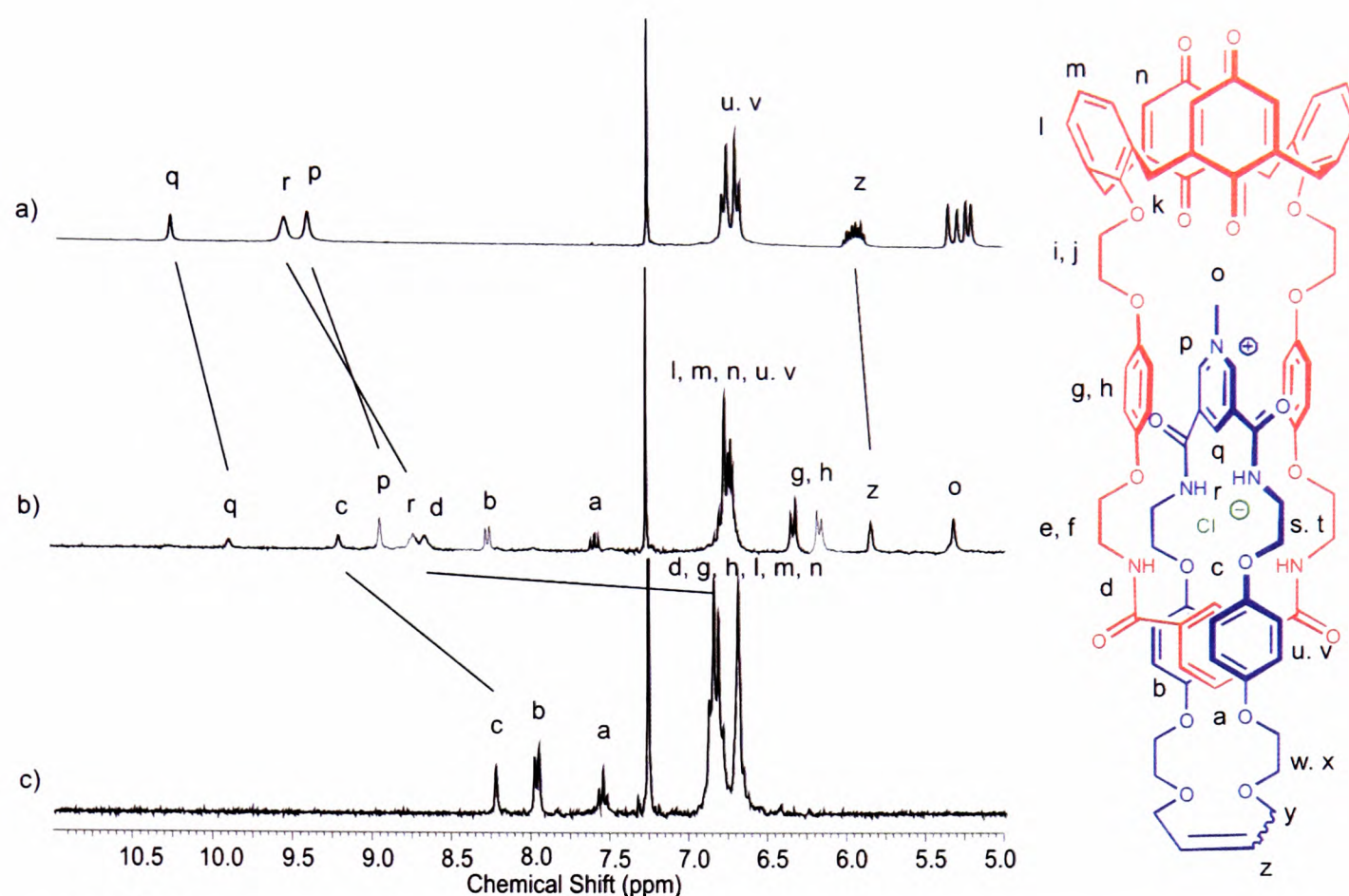


Figure 3.25 ^1H NMR spectra of a) **92.Cl** b) **99.Cl** and c) **94** in CDCl_3 at 293 K

The ROESY spectrum of **99.Cl** also show further evidence for the successful interlocking of the macrocycle and thread components with the expected through space correlations between the two components (Figure 3.26).

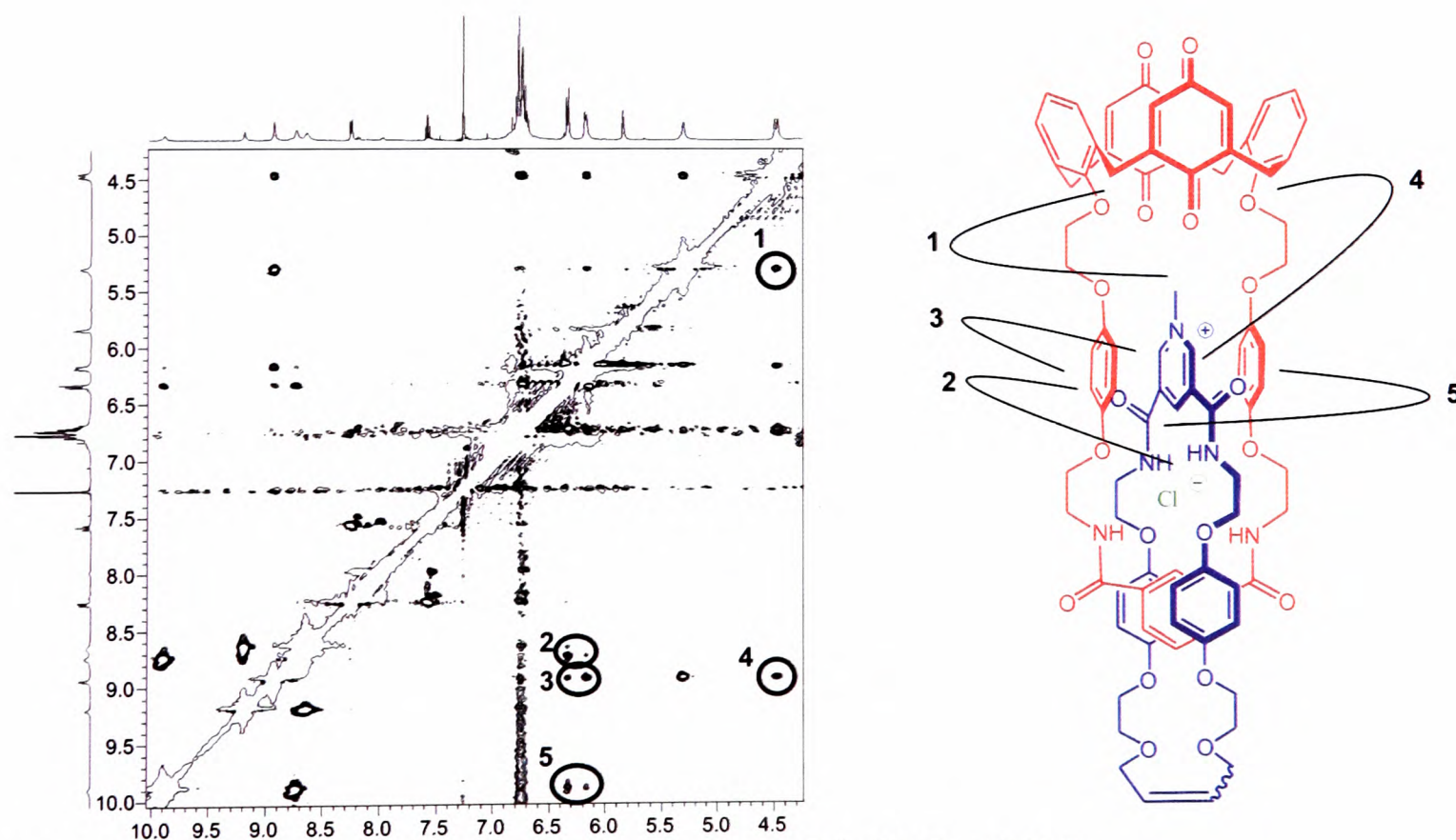


Figure 3.26 Portion of the ROESY spectrum of catenane **99.Cl** in CDCl_3 at 298 K

Unfortunately it was not possible to isolate catenane **99.Cl** in sufficient quantities for anion binding studies, due to difficulties synthesising the calix[4]diquinone macrocycle **94** and the

low yielding synthesis of the catenane.

3.6. Conclusions and Future Work

The first calix[4]arene based [2]rotaxane host systems for anions, **68.Cl** and **69.Cl** incorporating different axle components, have been prepared exploiting a new ion-pair templated clipping strategy. The first X-ray crystal structure of a calix[4]arene based rotaxane anion host system reveals the axle is threaded through the calix[4]arene macrocycle with the chloride anion template complexed within the rotaxane host cavity. Following removal of the chloride anion template, the anion binding properties of the resulting rotaxanes **68.PF₆** and **69.PF₆** were studied by ¹H NMR titration experiments. These reveal that the degree of preorganisation of the host cavity governs the strength and selectivity of anion binding. The more preorganised rotaxane **68.PF₆** is the superior anion host system exhibiting selectivity for chloride in 1:1 CDCl₃/CD₃OD and selectivity for the halide anions in 45:45:10 CDCl₃/CD₃OD/D₂O over the more basic oxoanions. Rotaxane **69.PF₆** having a relatively conformationally flexible binding cavity, however, is a less effective and discriminating anion host system. The rotaxane still binds halide anions in preference to the oxoanions, whilst the axle **70.PF₆** showed preference for oxoanions. The versatility of this new clipping strategy could be investigated further by varying the anion binding unit and axle components.

The synthesis of rotaxanes was also investigated using a stoppering strategy. Disappointingly, the stoppering reaction between **75.Cl** and **76** was low yielding and there was no evidence of rotaxane formation. The click reaction between **76** and an alternative azide axle appeared to be more promising, and it was possible to isolate a small amount of the impure rotaxane. An alternative synthesis of the ion-pair thread **80.Cl** was investigated to synthesise the target rotaxane by the ion-pair templated clipping strategy. Pleasingly, the click reaction was much higher yielding, although competing alkylation of the triazole rings prevented the synthesis of **80.Cl**. This alkylation could be beneficial as it enhances the anion binding ability of the

triazole motif and therefore, the synthesis of rotaxanes using this triazolium containing axle could be investigated further.

The preparation of calix[4]arene based catenanes was investigated using a clipping strategy. Synthetic difficulties prevented the synthesis of catenanes for the study of molecular motion, however, a small amount of catenane **99.Cl**, incorporating a calix[4]diquinone macrocycle, was successfully synthesised. The anion binding properties of this catenane could be investigated in the future following further optimisation of the synthetic strategy.

This chapter has investigated the development of rotaxane syntheses, which do not rely on the use of Grubbs' catalyst. The following chapter will continue to investigate the synthesis of interlocked structures, focusing on a copper catalysed coupling approach.

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Chapter 4

Synthesis of Interlocked Structures using Copper Catalysed Coupling Reactions

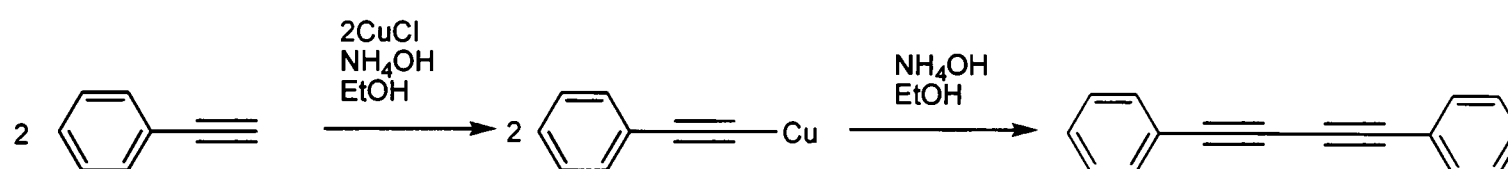
4. Synthesis of Interlocked Structures using Copper Catalysed Coupling Reactions

4.1 Introduction

4.1.1 Synthesis of Interlocked Structures Using Eglinton Coupling

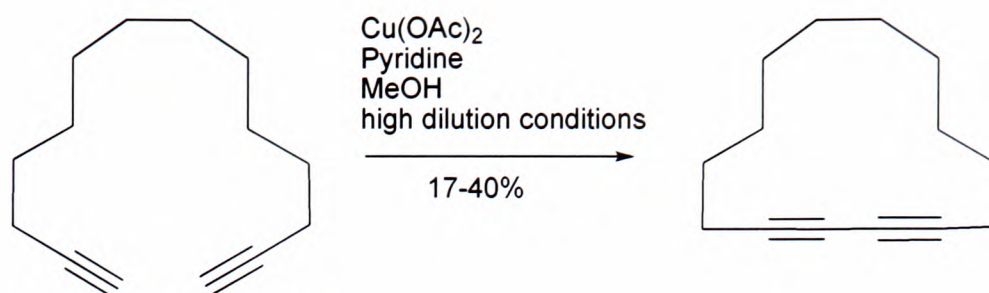
In the previous chapter, the clipping reaction between two terminal alkenes using Grubbs' catalyst was exploited for the synthesis of catenanes. This chapter will explore the synthesis of interlocked structures by copper catalysed clipping reactions between terminal alkynes.

Carl Glaser reported the first oxidative coupling of terminal alkynes using CuCl in 1869 (Scheme 4.1).¹ However, this method involves the isolation of the potentially explosive copper(I) acetylide intermediate, and subsequently a number of variations of Glaser coupling have been developed.² These include Hay coupling using CuCl and *N,N,N',N'*-tetramethylethylenediamine,³ Cadiot-Chodkiewicz coupling between a terminal alkyne and haloalkyne using a copper(I) salt and base,⁴ and Eglinton coupling,⁵ which will be explored as a clipping strategy in this chapter.



Scheme 4.1 Glaser coupling of terminal alkynes

Eglinton coupling between terminal alkynes uses a copper(II) salt, such as copper(II) acetate, and pyridine in MeOH. Eglinton and Galbraith reported the synthesis of a number of macrocycles under high dilution conditions using these reaction conditions (Scheme 4.2).⁵ The copper(II) salt acts as the oxidant, while the pyridine neutralises the acetic acid released in the coupling reaction, in addition to forming a complex with the copper ion.



Scheme 4.2 Eglinton coupling of terminal alkynes

A number of macrocycles have been synthesised using Eglinton coupling, and the coupling reaction has been found to tolerate changes in solvent. For example, Lehn and co-workers reported the synthesis of the macrocycle in Figure 4.1a using CH_2Cl_2 as the solvent.⁶ Pyridine-free Eglinton macrocyclisations have also been developed in DMF and CH_3CN by Staab⁷ and Balzani⁸ respectively (Figure 4.1b and c).

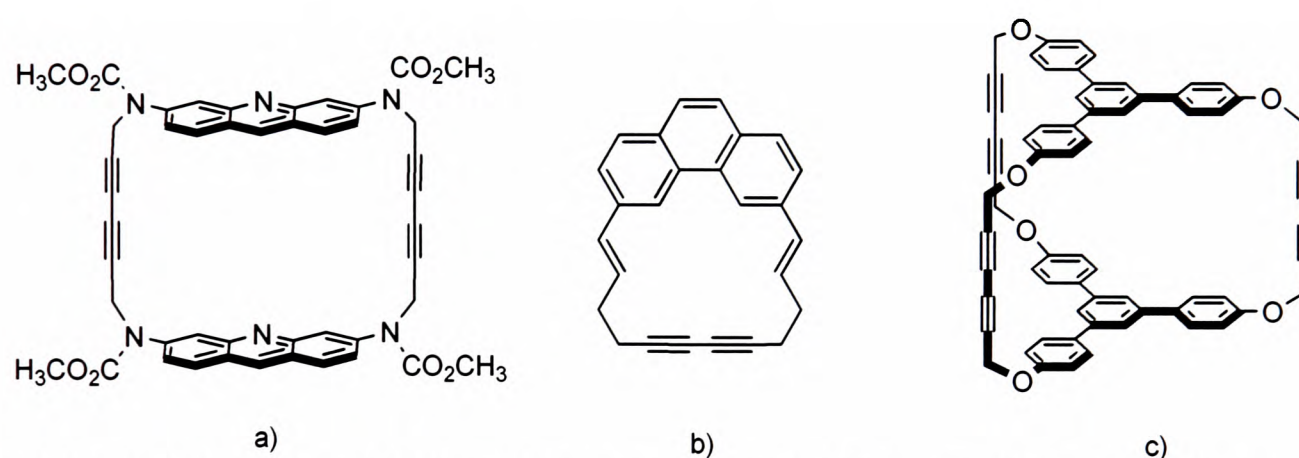


Figure 4.1 a) Lehn's b) Staab's and c) Balzani's macrocycles synthesised using Eglinton coupling

In addition to macrocyclisation, oxidative coupling reactions have been utilised in the preparation of a number of catenanes, including those shown in Figure 4.2. Sauvage and co-workers synthesised the [3]catenane in an impressive 58% yield using two Cu(I) metal ions as interweaving templates and CuCl/CuCl_2 in DMF to achieve the oxidative coupling (Figure 4.2a).^{9, 10} The [2]catenane¹¹ in Figure 4.2b and a number of related catenanes^{11, 12} have been synthesised by Sanders and co-workers using similar reaction conditions.

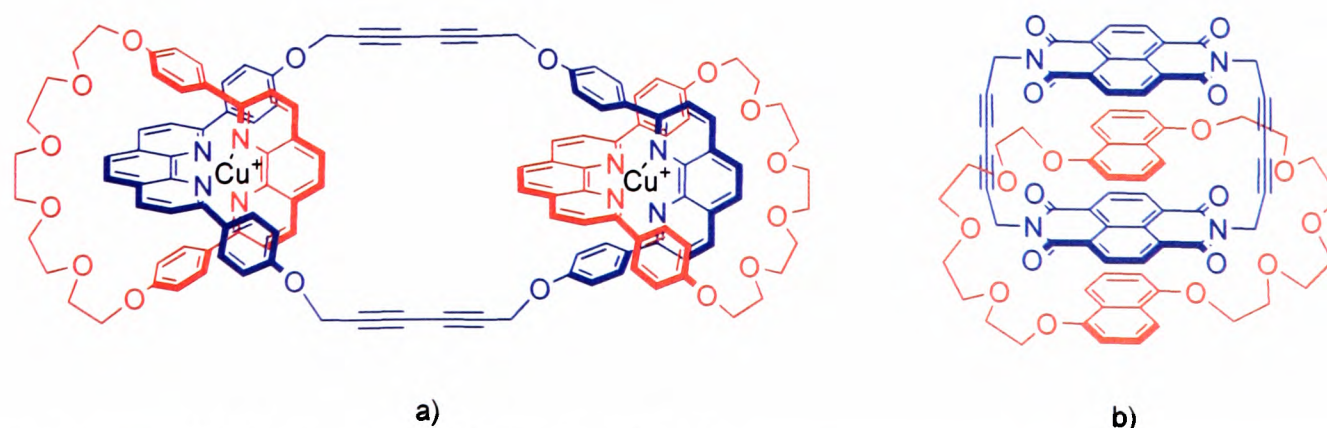


Figure 4.2 a) Sauvage's [3]catenane and b) Sanders' [2]catenane

Eglinton coupling has been exploited by Stoddart and co-workers to synthesise a number of interlocked structures.¹³⁻¹⁶ The oxidative coupling is typically carried out at room temperature in CH_3CN using copper(II) acetate, and the rotaxane in Figure 4.3a was synthesised using a snapping approach.¹⁵ A number of catenanes have also been prepared using a clipping strategy, including the catenane in Figure 4.3b.¹⁶ This catenane acts as a push-button molecular switch where electrochemical or chemical oxidation of the TTF station induces ring rotation of the blue macrocycle, which can be reversed by reduction.

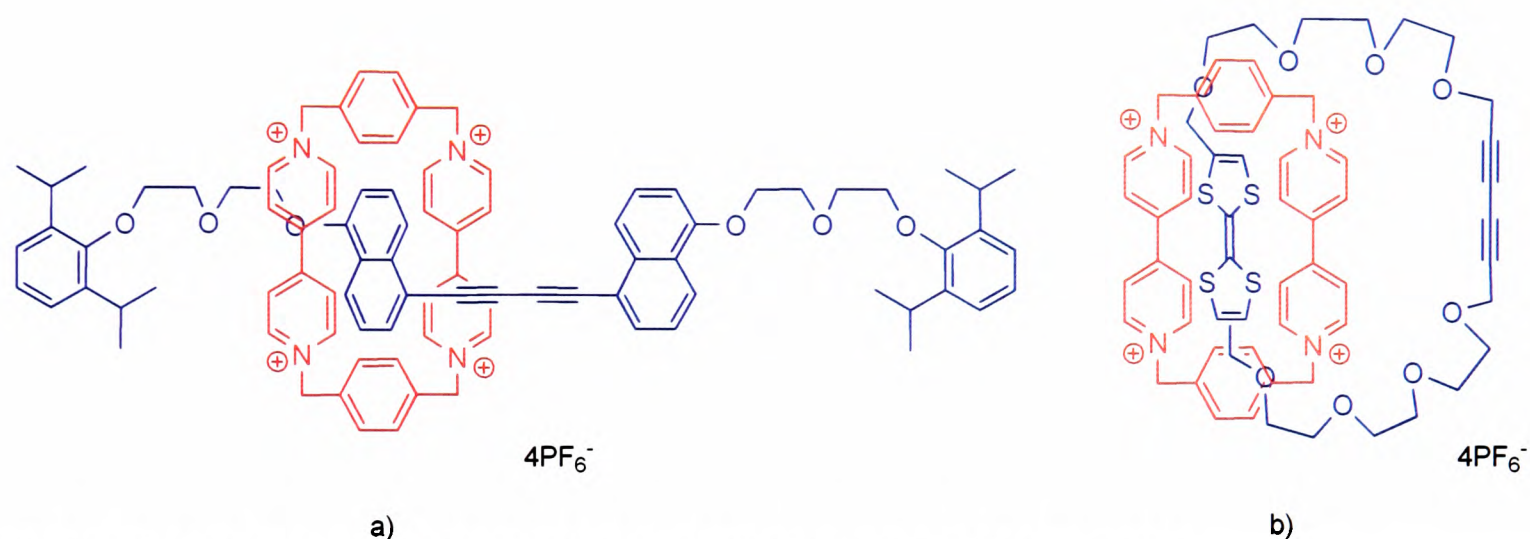
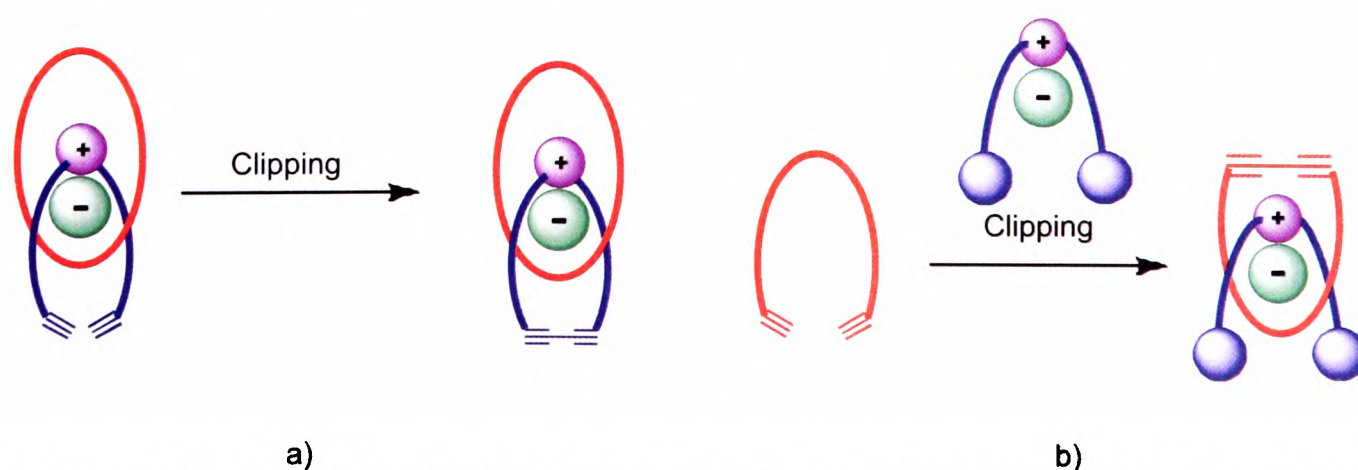


Figure 4.3 Stoddart's a) rotaxane and b) catenane synthesised using Eglinton coupling

4.1.2 Aims of the Chapter

This chapter will investigate the application of Eglinton coupling as a clipping strategy in the anion templated synthesis of interlocked structures (Scheme 4.3). This involves modification of the alkene functionalised macrocycle precursors, used in the Grubbs' ring closing metathesis clipping approach, with terminal alkynes. The compatibility of the Eglinton coupling reaction conditions with the anion templation strategy will also be explored.



Scheme 4.3 The synthesis of a) catenanes and b) rotaxanes using an Eglinton coupling clipping approach

4.2 Synthesis of Catenanes

Initially the synthesis of catenanes using Eglinton coupling was investigated, and Figure 4.4 shows the target macrocycle precursors **100.Cl** and **101.Cl**. Macrocycle precursor **101.Cl** would be synthesised to investigate the effect of the linker length on the Eglinton coupling reaction.

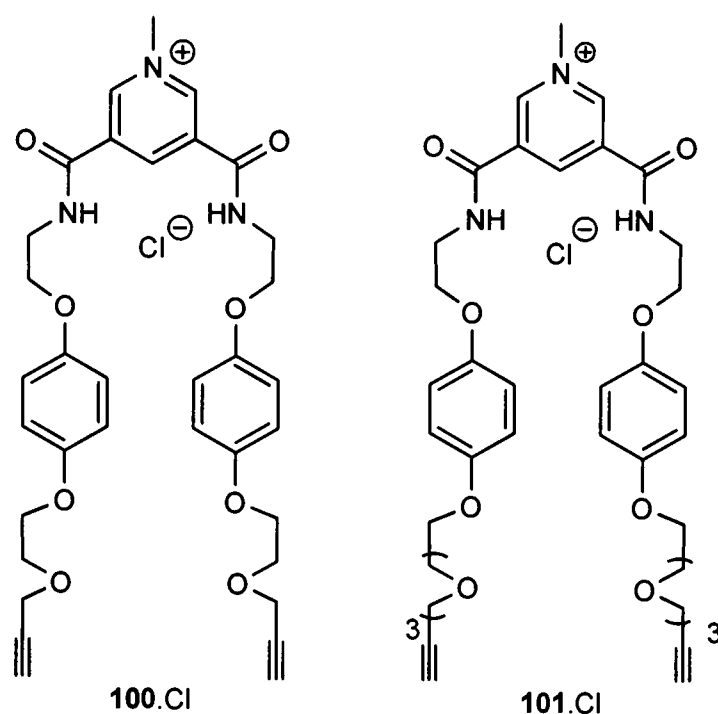
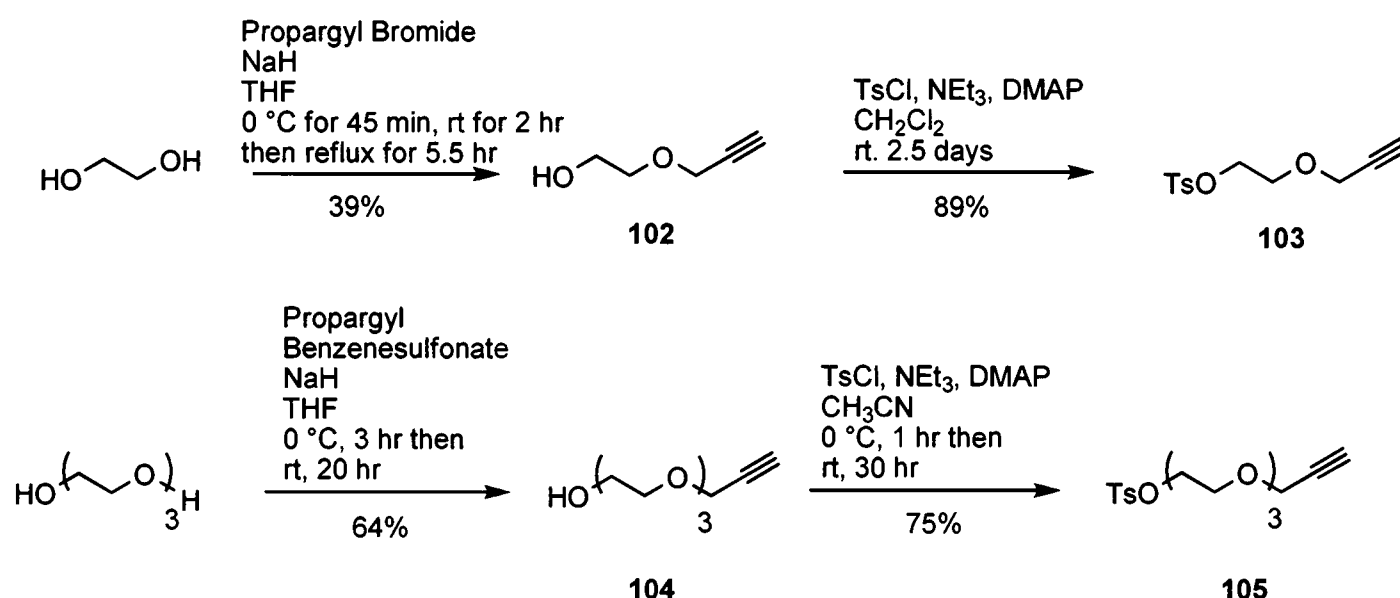


Figure 4.4 Target macrocycle precursors **100.Cl** and **101.Cl**

4.2.1 Synthesis of precursors **103** and **105**

The design of the target macrocycle precursors is based on the alkene analogue **98.X**, synthesised in Section 3.4.1, and therefore a similar synthetic strategy would be employed for their synthesis. Firstly, it was necessary to prepare the alkyne functionalised precursors **103** and **105** using adapted literature procedures. This was achieved by monofunctionalisation of ethylene glycol or triethylene glycol using one equivalent of NaH in THF, followed by tosylation of the remaining hydroxyl group (Scheme 4.4). Precursor **102** was isolated as a colourless oil in 39% yield following reaction with propargyl bromide¹⁷ and purification by silica gel chromatography. A similar yield could also be obtained replacing propargyl bromide with the safer reagent propargyl benzenesulfonate. Reaction of **102** with tosyl chloride in CH₂Cl₂ afforded precursor **103** as a yellow oil in 89% yield. The reaction of triethylene glycol with propargyl benzenesulfonate was much higher yielding than the analogous reaction with

ethylene glycol giving **104** in 64% yield. Precursor **105** was obtained in 75% yield following tosylation in CH₃CN.¹⁸



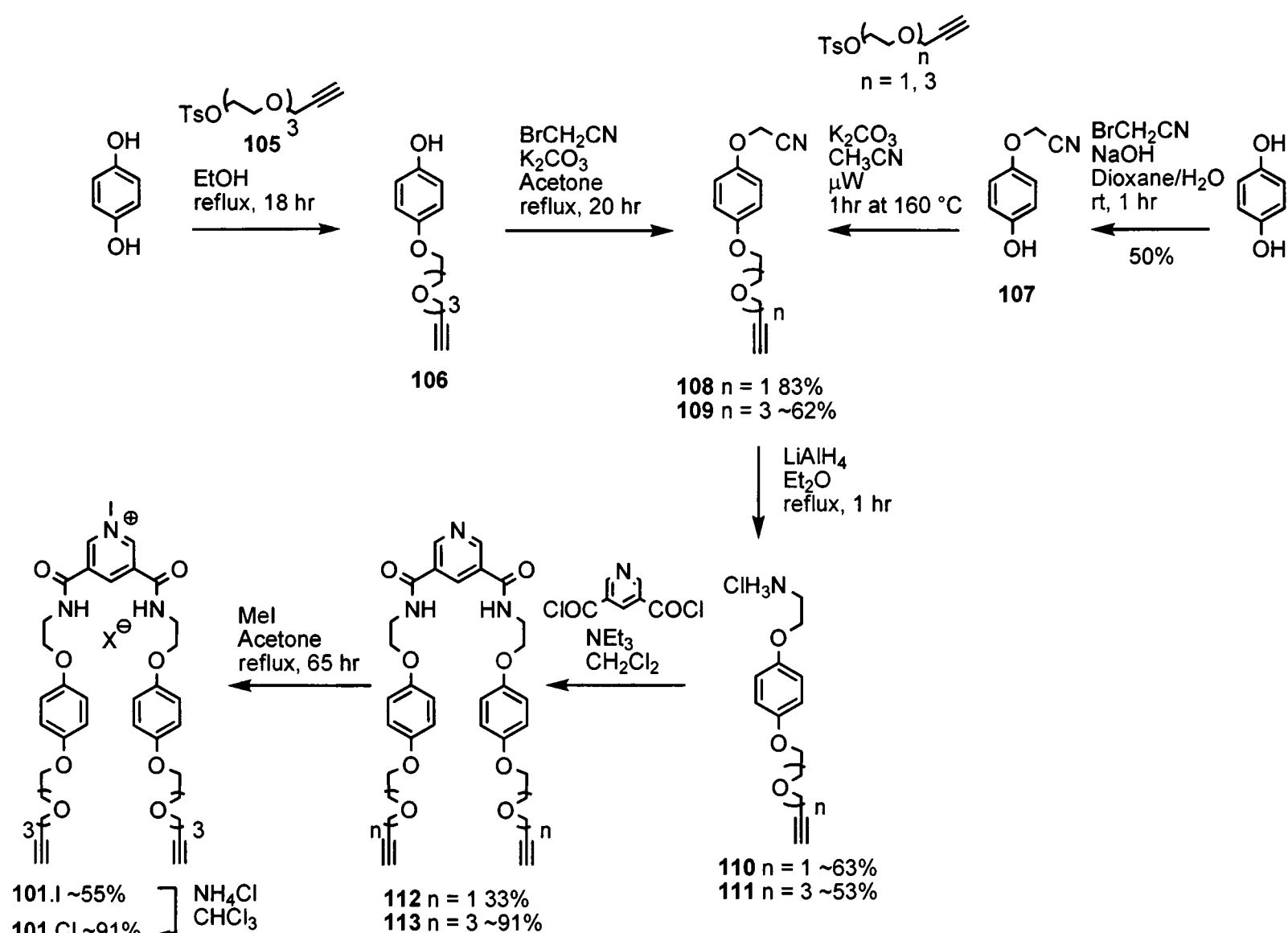
Scheme 4.4 Synthesis of precursors **103** and **105**

4.2.2 Synthesis of Macrocycle Precursors **100.Cl** and **101.Cl**

Monofunctionalisation of hydroquinone was attempted by heating a fourfold excess of *p*-hydroquinone, **105** and K₂CO₃ in EtOH under reflux for 18 hours (Scheme 4.5) and compound **106**, contaminated with excess *p*-hydroquinone, was isolated following purification by silica gel chromatography. In an attempt to improve purification, this mixture was reacted with bromoacetonitrile in the presence of K₂CO₃ in acetone, however, isolation of the desired product **109** by column chromatography was unsuccessful.

Instead, an alternative synthesis of **109** and the shorter analogue **108** was devised (Scheme 4.5). A solution of bromoacetonitrile in dioxane was added to a suspension of *p*-hydroquinone and NaOH in 1:1 dioxane/H₂O and **107** was isolated in 50% yield following purification by silica gel chromatography.¹⁹ Compound **108** was isolated in 83% yield following heating a mixture of **107**, **103** and K₂CO₃ in CH₃CN in a microwave at 160 °C for 1 hour. The synthesis of **109** was carried out using analogous reaction conditions, and isolated in approximately 62% yield contaminated with unreacted **107**. It was not possible to achieve complete separation of these two compounds by column chromatography, despite investigating a number of solvent systems. The reduction of **108** and **109** using LiAlH₄

also proved problematic, with some reduction of the alkyne functionality to the alkene observed, as well as other impurities. It was not possible to isolate pure **110** and **111**, but the purity could be improved by bubbling HCl gas through a CHCl₃ solution of the amine, in order to isolate the amine as the hydrochloride salt.

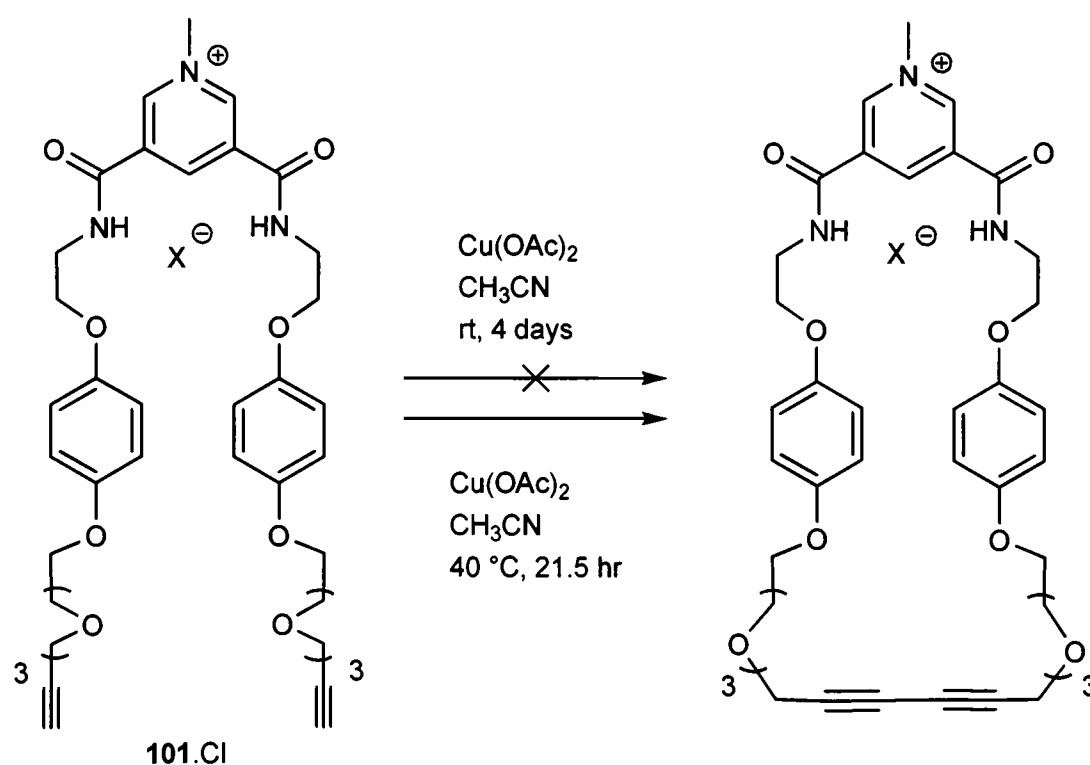


Scheme 4.5 Towards the synthesis of **100.Cl** and **101.Cl**

Despite the purification difficulties, the reactions of **110** and **111** with 3,5-bis(chlorocarbonyl)pyridine were carried out in CH₂Cl₂ giving **112** and **113** respectively. Attempted purification of **112** by column chromatography resulted in a significant loss of material without improving the purity, and therefore purification of **113** was not attempted. Compound **113** was alkylated immediately in the hope of purification at a later stage, and to investigate the feasibility of the Eglinton reaction between the terminal alkynes. Compound **101.I** was isolated in impure form in approximately 55% yield following reaction with iodomethane in acetone and purification by column chromatography. Anion exchange with NH₄Cl afforded impure **101.Cl** in approximately 91% yield.

4.2.3 Attempted Macrocycle Synthesis by Eglinton Coupling

The synthesis of the pyridinium macrocycle by Eglinton coupling (Scheme 4.6) was investigated to establish the feasibility of Eglinton coupling for catenane synthesis using this system. This was initially attempted by stirring **101.Cl** and copper(II) acetate in CH₃CN at room temperature for four days. There was no evidence of reaction, so the reaction was repeated heating at 40 °C for 21.5 hours. This appeared to be more promising as one of the only peaks in the electrospray mass spectrum corresponded to the positively charged macrocycle (m/z 790.3). However, there was limited evidence of the macrocycle in the ¹H NMR spectrum of the crude reaction mixture, and purification by silica gel chromatography was unsuccessful. There are a number of factors which could have prevented the formation and isolation of the macrocycle, including limited solubility, competing oligomerisation and the presence of the acetate anion. It was believed that the mass spectrometry evidence of the macrocycle warranted further investigation into the use of the Eglinton coupling. However, it was decided to focus on a simpler system, with an anion binding cleft based on isophthalamide, and this will be discussed in Section 4.3.



Scheme 4.6 Attempted macrocycle synthesis by Eglinton coupling

4.2.4 Catenane Synthesis by Click Chemistry

While the synthesis of catenanes by Eglinton coupling was not investigated any further, catenanes could be synthesised from a copper(I) catalysed click reaction between macrocycle precursors, such as **100.Cl** or **101.Cl**, and an appropriate bis-azide component, such as **114** (Figure 4.5). Only the synthesis of catenane **115.Cl** from the reaction of **100.Cl** and **114** would be investigated, as it was expected that the flexibility of **101.Cl** might favour inter-molecular rather than intra-molecular click reactions.

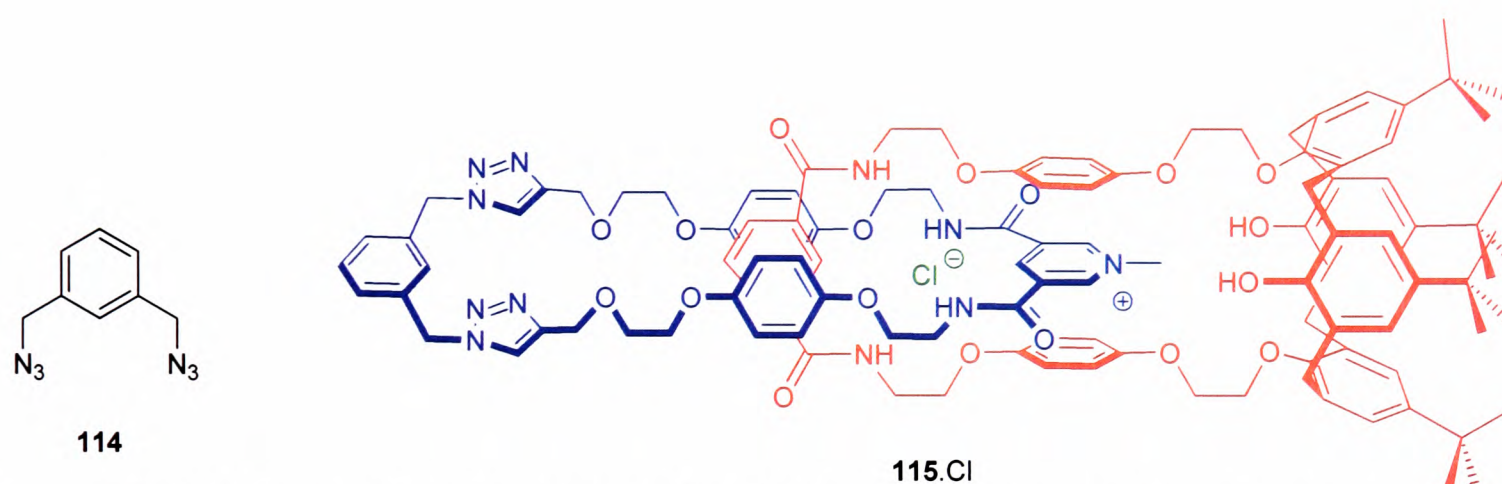
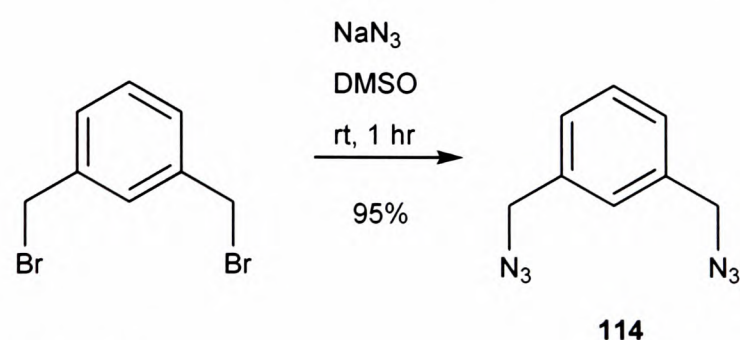


Figure 4.5 Bis-azide **114** and target catenane **115.Cl** synthesised from **100.Cl** and **114** using click chemistry

4.2.4.1 Synthesis of **114** and Alternative Synthesis of **100.Cl**

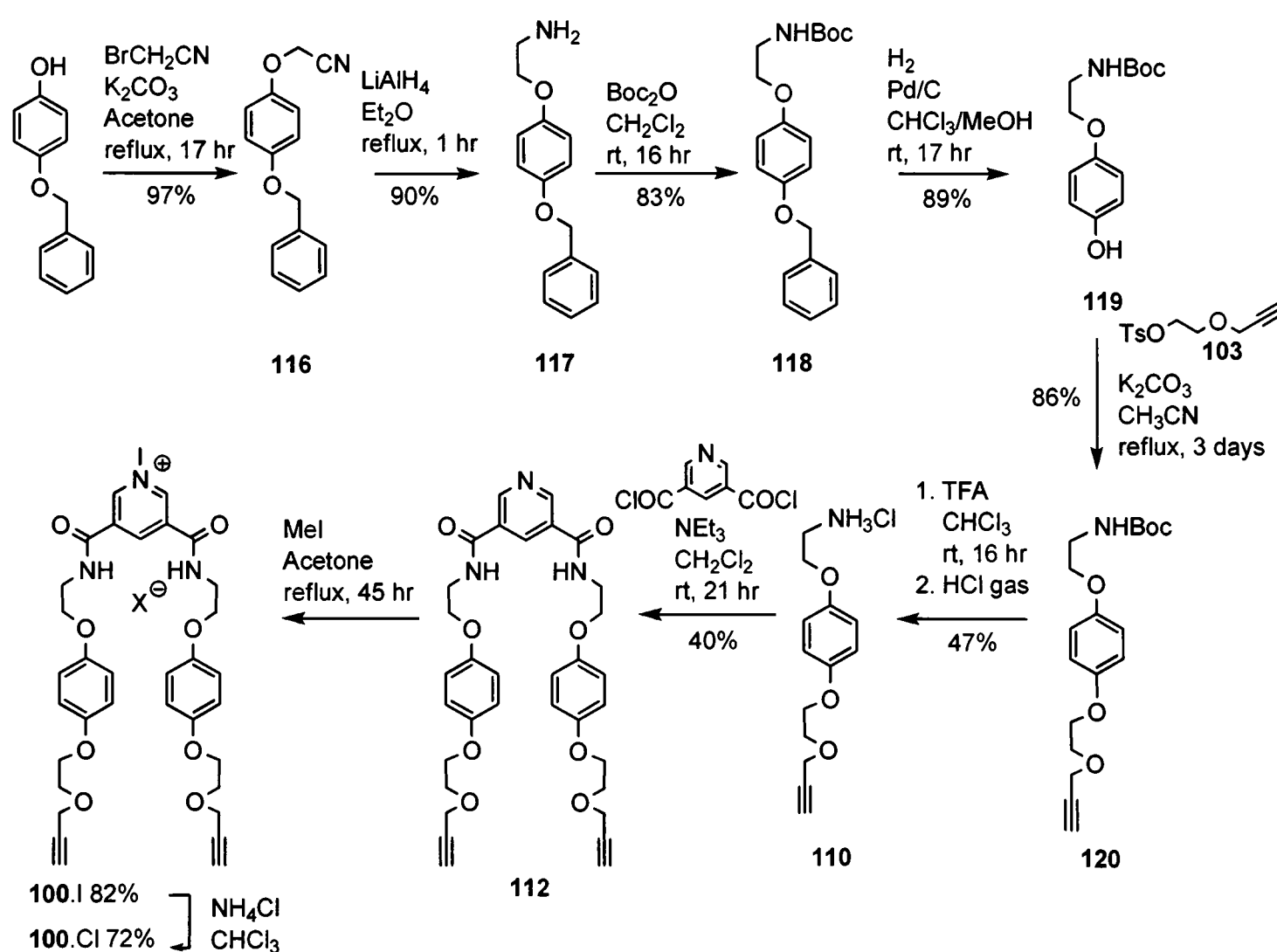
Bis-azide **114** was synthesised in almost quantitative yield from the reaction of commercially available α,α' -dibromo-*m*-xylene with sodium azide in DMSO (Scheme 4.7).²⁰



Scheme 4.7 Synthesis of bis-azide **114**

Before attempting the synthesis of the catenane, it was necessary to develop an alternative synthesis of **100.Cl** to avoid the synthetic problems encountered in Section 4.2.2. Scheme 4.8 outlines the protection/deprotection synthetic strategy employed. 4-(Benzyloxy)phenol was heated under reflux with bromoacetonitrile and K_2CO_3 in acetone to give compound **116**, which was subsequently reduced to amine **117** in 90% using $LiAlH_4$ in diethyl ether.²¹ The

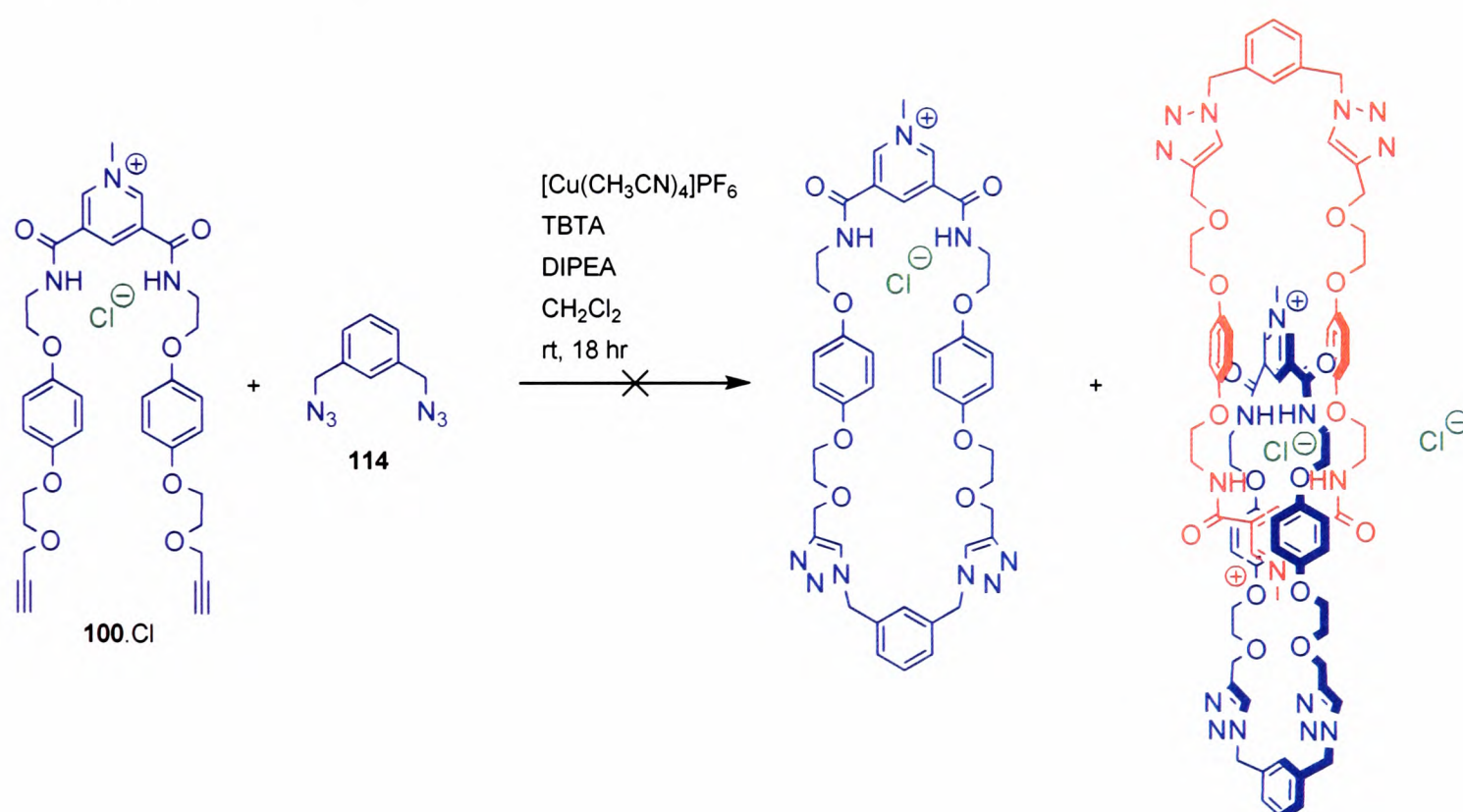
amine group was protected by reaction with di-*tert*-butyldicarbonate in CH₂Cl₂ giving **118** in 83% yield, prior to removal of the benzyl protecting group using H₂ and palladium on carbon.²² Compound **120** was then synthesised in 86% yield by heating a mixture of **119**, **103** and K₂CO₃ under reflux in CH₃CN for 3 days. The Boc protecting group was removed using TFA in CHCl₃ and the amine **110** was isolated as the hydrochloride salt in 47% yield by bubbling HCl gas through the CHCl₃ solution. This was immediately reacted with 3,5-pyridinedicarbonyl in the presence of triethylamine in dry CH₂Cl₂ to give **112** in 40% yield. Methylation with iodomethane in acetone gave **100.I** in 82% yield, and this was converted to **100.Cl** in 73% yield by repeated washing of a CHCl₃ solution with 1 M NH₄Cl.

Scheme 4.8 Alternative synthesis of **100.Cl**

4.2.4.2 Attempted Macrocycle Synthesis

The click reaction between **100.Cl** and **114** using [Cu(CH₃CN)₄]PF₆ in CH₂Cl₂ was investigated before attempting the target catenane synthesis (Scheme 4.9). A yellow solid precipitated almost immediately from the reaction mixture, and the crude reaction mixture was subjected to preparative TLC. While a number of bands were isolated in small

quantities, these were not consistent with the desired macrocycle or catenane from double cyclisation. It is possible that the yellow solid was one of these products, or more likely, linear oligomeric side products. Unfortunately, insolubility prevented characterisation of this solid. The reaction was repeated under similar conditions in a $\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$ biphasic mixture generating the copper catalyst using copper sulfate and sodium ascorbate. However, similar precipitation problems were encountered. Although it was not possible to identify the product of the reaction, the catenane synthesis was then attempted using macrocycle **66** and similar reaction conditions.

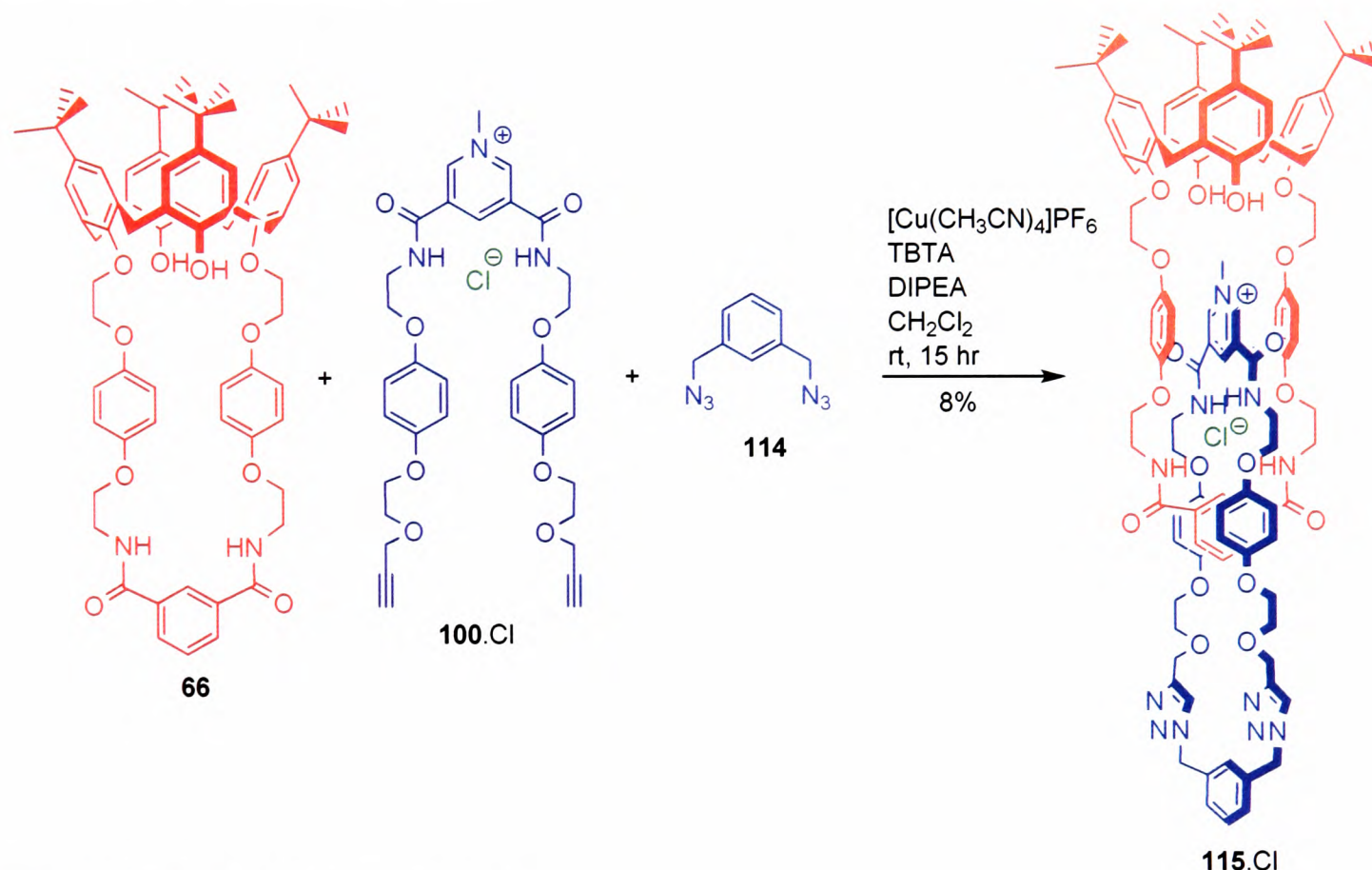


Scheme 4.9 Attempted macrocycle synthesis

4.2.4.3 Catenane Synthesis

A mixture of **66**, **100.Cl** and **114** was stirred in the presence of TBTA stabilised $[\text{Cu}(\text{CH}_3\text{CN})_4]\text{PF}_6$ and DIPEA in CH_2Cl_2 for 15 hours at room temperature (Scheme 4.10). Again, a yellow solid precipitated almost immediately from the reaction mixture, but the desired catenane product **115.Cl** was isolated in 8% yield following purification by preparative TLC. The formation of the unknown by-product accounts for the low yield, although it was possible to recover a significant amount of unreacted **66** and taking the amount of recovered macrocycle into account, the corrected catenane yield is 20%. In an

effort to improve the yield of catenane, a number of reaction conditions were varied. These included concentrating and diluting the reaction mixture, carrying out the reaction under pseudo high dilution conditions and using copper sulfate/sodium ascorbate as the copper(I) source. However, it was not possible to improve the yield, most likely due to the unknown competing side reaction. The properties of this novel catenane were studied using the limited amount of isolated catenane.



Scheme 4.10 Synthesis of catenane **115.Cl**

The catenane was characterised by ^1H and ^{13}C NMR spectroscopy, high resolution mass spectrometry and melting point analysis. The ^1H NMR spectrum of **115.Cl** shows a number of differences to the spectra of macrocycle **66** and macrocycle precursor **100.Cl** (Figure 4.6). The appearance of peaks for protons c_2-f_2 and the triazole proton b_2 confirm the successful copper catalysed clipping reaction between **100.Cl** and **114**. The downfield shifts of macrocycle protons c and d and upfield shifts of protons r , s and t are all consistent with the shown catenane structure. More importantly, π – π stacking interactions between the two macrocyclic components result in the upfield shifts and splitting of the signals for hydroquinone protons g and h , and hydrogen bonding interactions between proton q and the

hydroxyl oxygen of the calix[4]arene macrocycle cause the significant downfield shift of proton *q* and upfield shift of proton *k*.

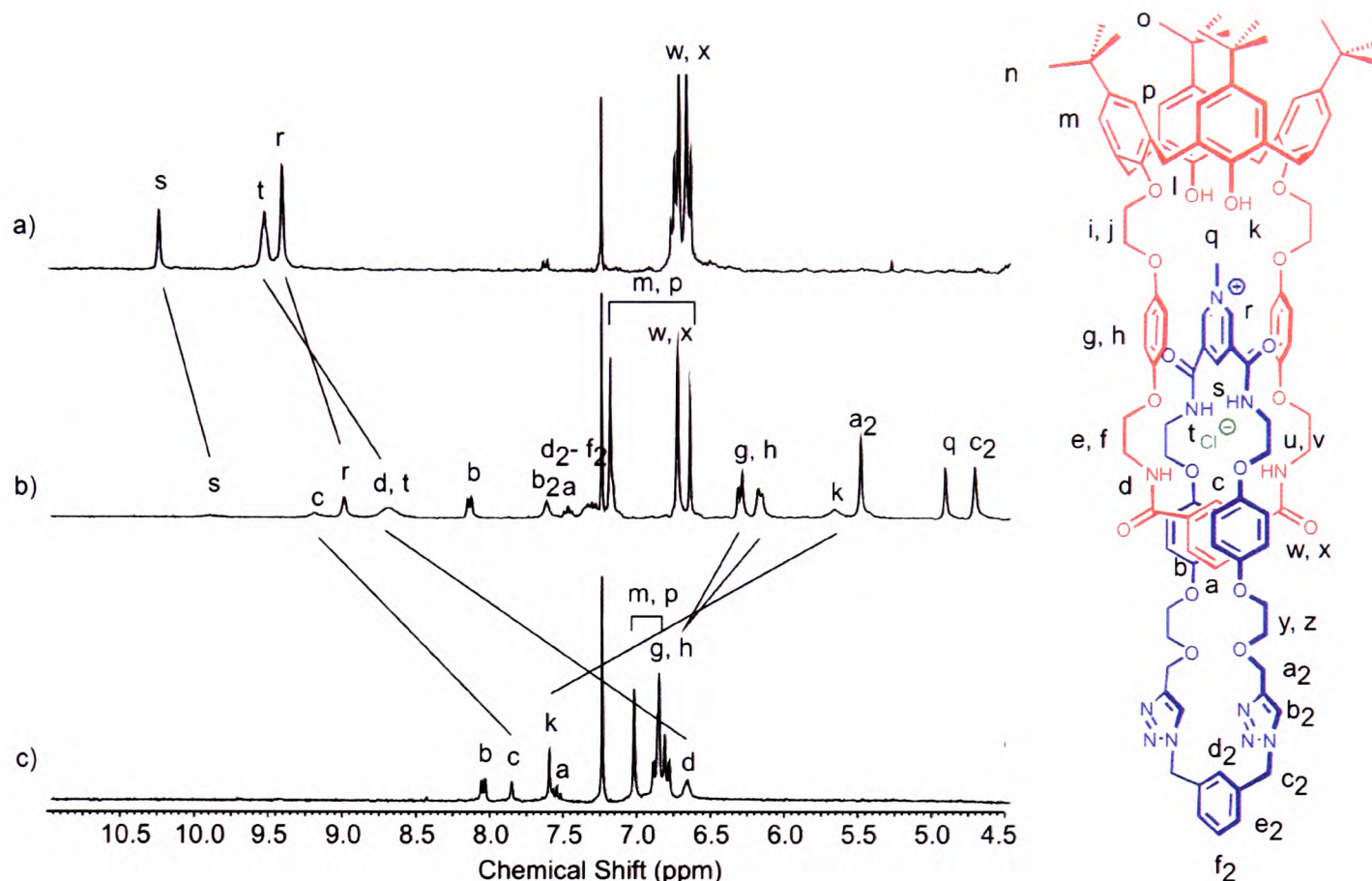


Figure 4.6 ^1H NMR spectra of a) **100.Cl** b) catenane **115.Cl** and c) **66** in CDCl_3 at 293 K

The ROESY spectrum of the catenane also confirmed the successful interlocking of the two macrocycles with through space correlations observed between the macrocyclic components (Figure 4.7).

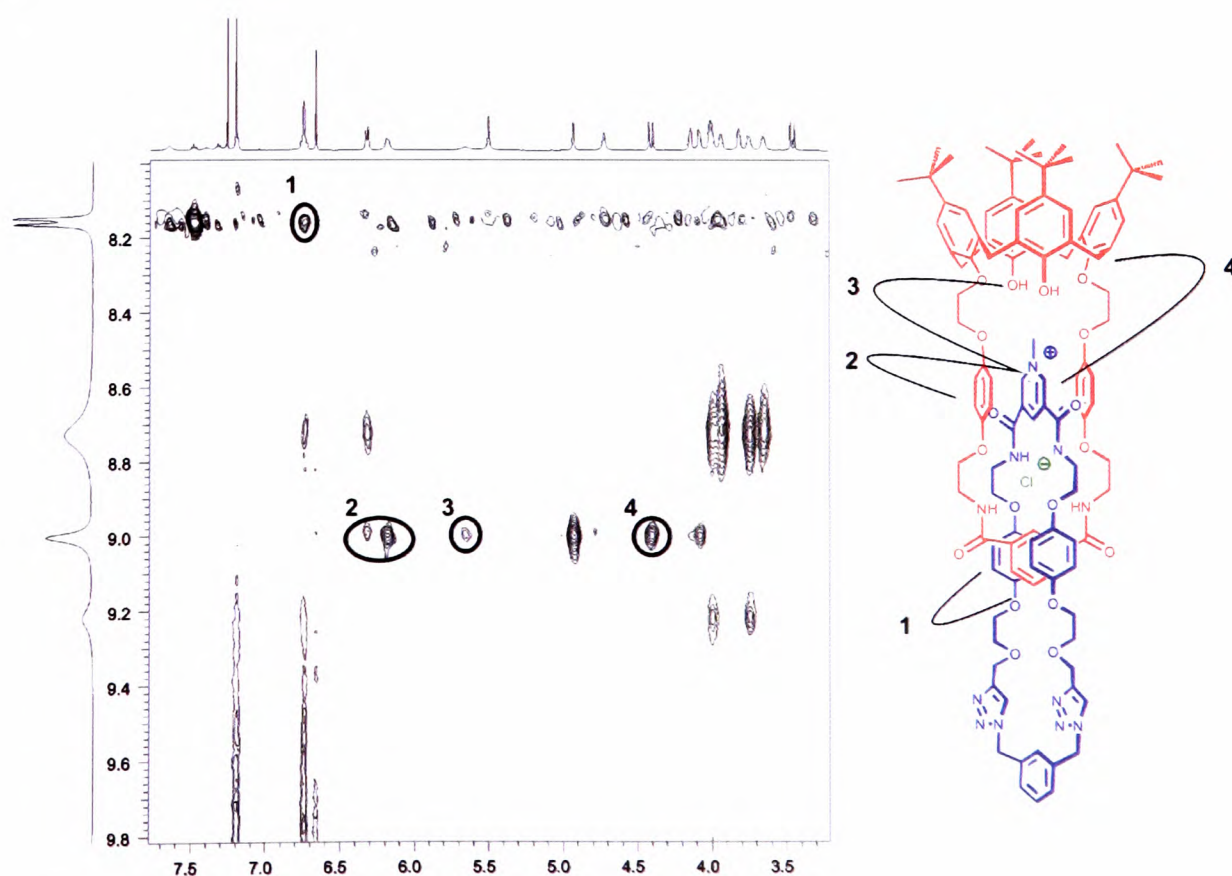


Figure 4.7 ROESY spectrum of catenane **115.Cl** in CDCl_3 at 298 K

4.2.4.4 Anion Binding Studies of **115**.PF₆

In order to study the anion binding properties of the catenane, the chloride template was removed by repeated washing of a CHCl₃ solution of **115**.Cl with 0.2 M NH₄PF₆, and the resulting catenane **115**.PF₆ was isolated in 71% yield. The ¹H NMR spectrum of **115**.PF₆ in CDCl₃ contained broad overlapping signals in the aromatic region and therefore, the catenane was characterised in 1:1 CDCl₃/CD₃OD.

Removal of the chloride template was evident from the upfield shifts of protons *c*, *r* and *s*, and the remaining protons were all assigned except for the signal at approximately 8.5 ppm (Figure 4.9c). In most cases, amide protons are not seen in the ¹H NMR spectrum in protic solvents due to deuterium exchange, but this extra peak has been tentatively assigned as amide proton *t*. Evidence that this signal is an amide is due to the gradual decrease in the signal over time, presumably due to slow deuterium exchange, and the through space correlation **4** to proton *s* in the ROESY spectrum (Figure 4.8).

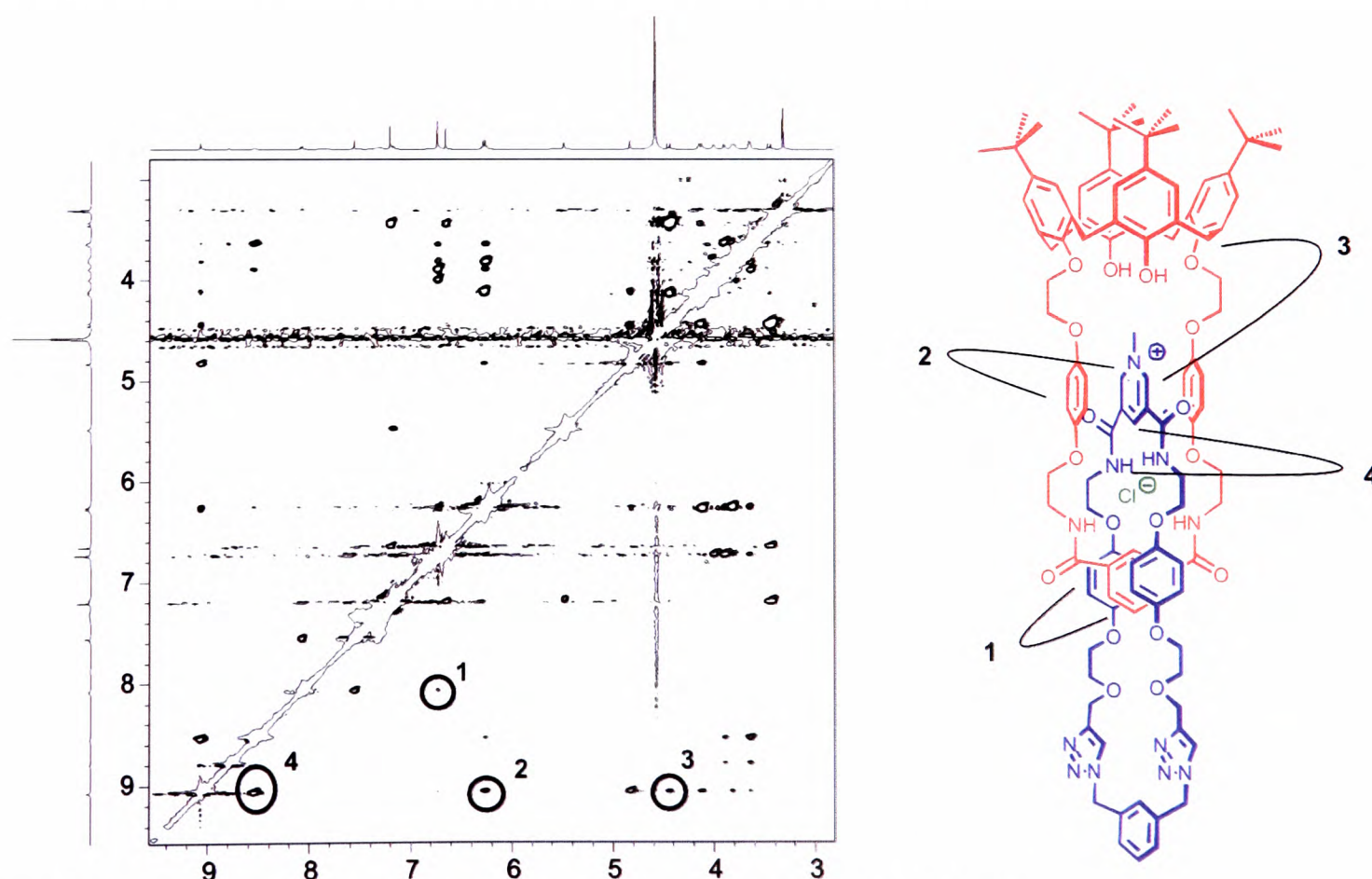


Figure 4.8 ROESY spectrum of **115**.PF₆ showing in 1:1 CDCl₃/CD₃OD at 298 K

Preliminary anion binding studies were carried out in 1:1 CDCl₃/CD₃OD using the limited amount of **115**.PF₆. Upon addition of chloride and bromide anions, there were downfield

shifts of protons *c*, *r* and *s*, indicating anion binding within the anion binding cavity (Figure 4.9a). There was no shift of the triazole proton *b*₂ which indicates that there is no competing anion binding to the triazole groups. It was possible to obtain 1:1 association constants from fitting the titration data for proton *r* using winEQNMR2²³ (Table 4.1), which demonstrate that the catenane binds chloride more strongly than bromide. Addition of dihydrogen phosphate and acetate led to a disappearance of the signal assigned to proton *t*, and an upfield shift of proton *s* and downfield shifts of protons *c* and *r*. These results suggest that the oxoanions bind on the periphery of the anion binding cavity. The titration data did not fit a 1:1 binding model, and despite evidence of a 1:2 host/anion binding stoichiometry from Job Plot analysis, it was not possible to obtain 1:2 association constants. Unfortunately, the limited amount of **115**.PF₆ prevented further anion binding studies, and instead attention turned to the synthesis of rotaxanes using Eglinton coupling.

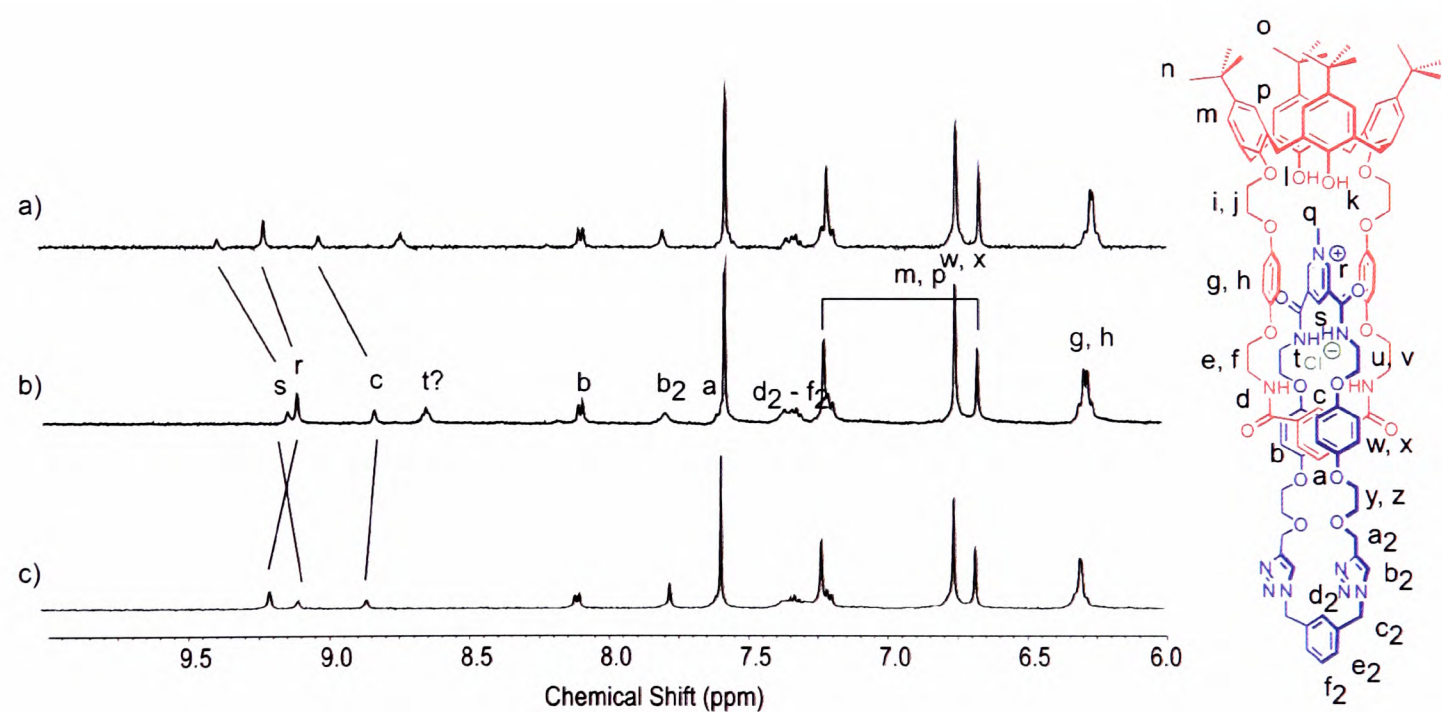


Figure 4.9 ¹H NMR spectra of a) **115**.Cl b) **115**.PF₆ and c) **115**.H₂PO₄ in 1:1 CDCl₃/CD₃OD at 298 K

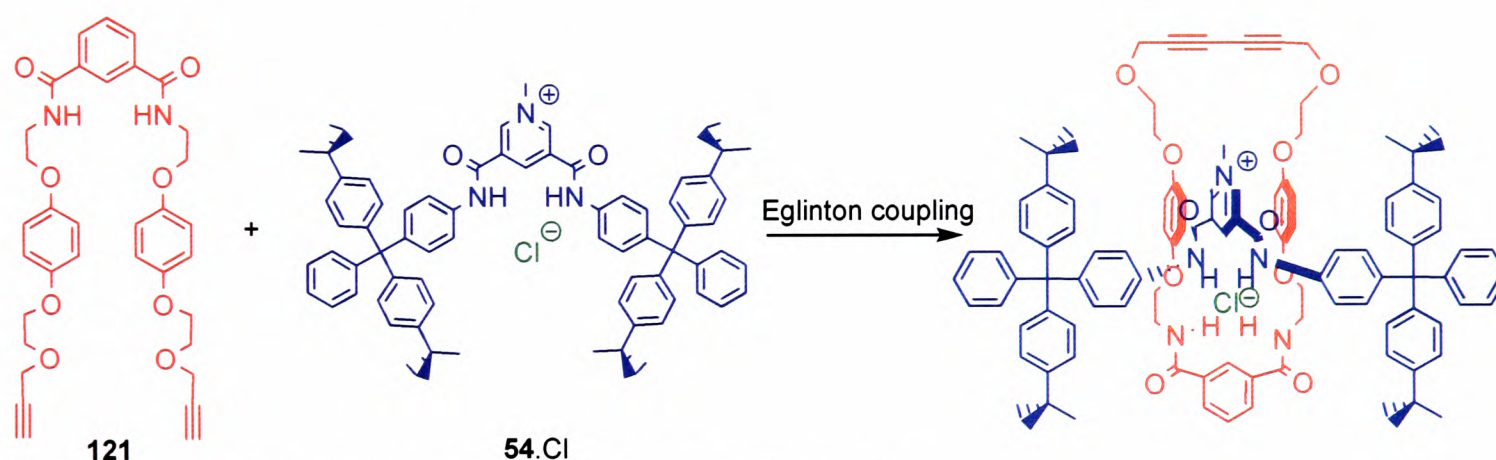
X ⁻	K (M ⁻¹)
Cl ⁻	1790*
Br ⁻	900
OAc ⁻	#
H ₂ PO ₄ ⁻	#

Table 4.1 Association constants derived from winEQNMR2 analysis of proton *s* titration data in 1:1 CDCl₃/CD₃OD at 298 K. Errors < 10%, * errors < 15%. # = evidence of a 1:2 host/anion binding stoichiometry but association constants could not be determined

4.3 Synthesis of Rotaxanes

4.3.1 Towards the Synthesis of Rotaxanes Using Eglinton Coupling

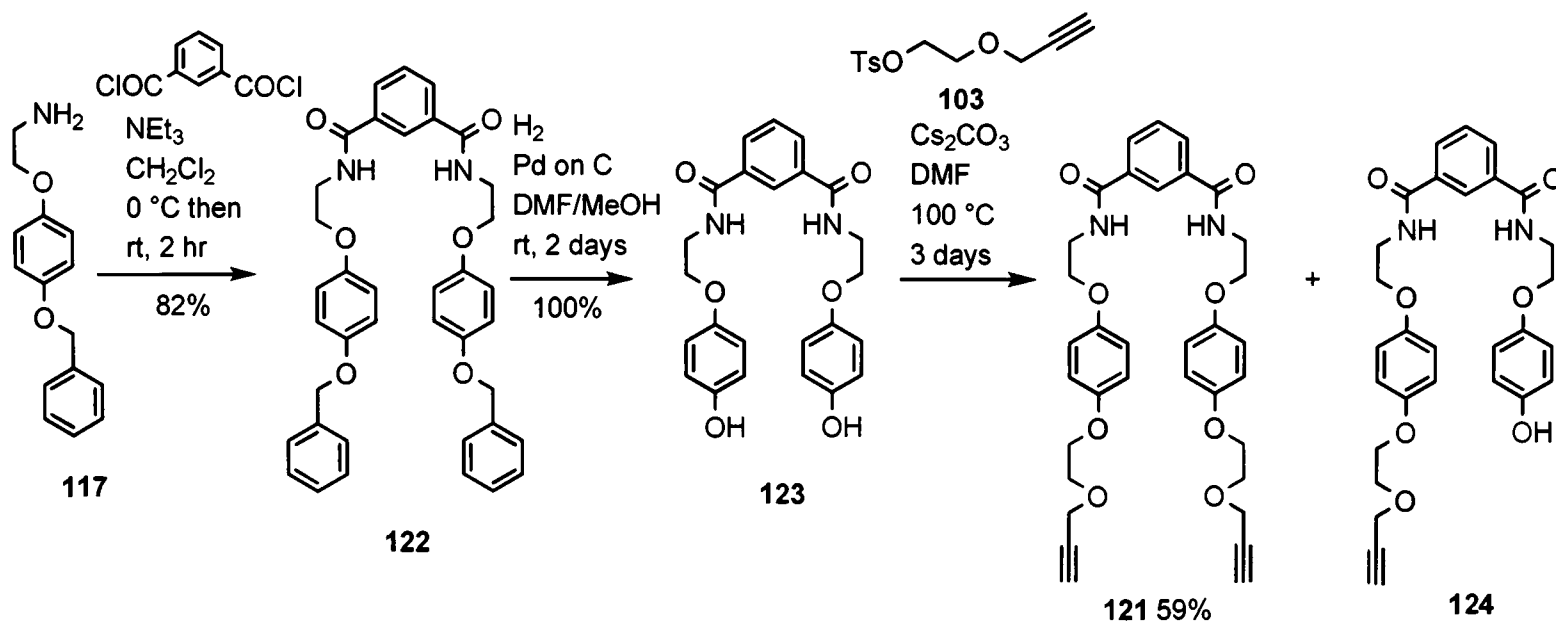
Having experienced difficulties determining the success of the Eglinton coupling reaction with compound **101.Cl**, attention turned to the synthesis of the isophthalamide analogues, as a means of preparing rotaxanes using Eglinton coupling (Scheme 4.11). Efforts focused on the synthesis of **121**, the isophthalamide analogue of **100.Cl**. The macrocycle based on the isophthalamide analogue of **101.Cl** was expected to be too big for the stoppers of axle **54.Cl**, as Bheda and co-workers have reported that the triaryl stoppers can stopper macrocycles with up to 42 carbon, nitrogen, oxygen or sulfur atoms.²⁴



Scheme 4.11 Proposed synthesis of rotaxanes by Eglinton coupling

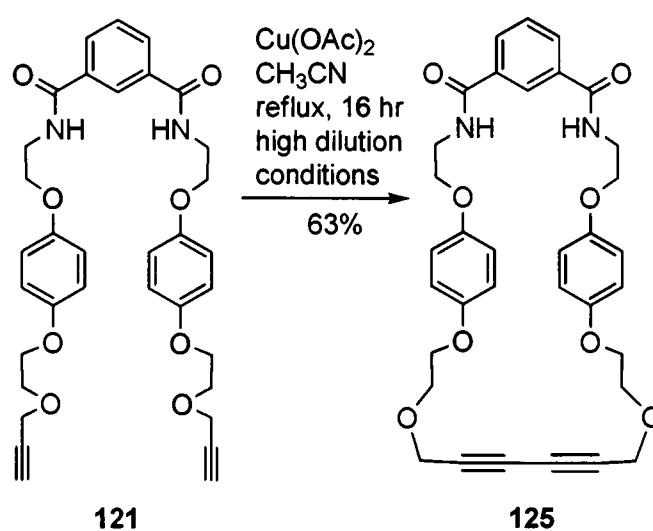
4.3.1.1 Synthesis of Macrocycle Precursor **121**

The synthesis of macrocycle precursor **121** from amine **117** is outlined in Scheme 4.12. Compound **122** was synthesised in 82% yield by reacting amine **117** with isophthaloyl dichloride in the presence of triethylamine in CH_2Cl_2 .²⁵ The benzyl protecting groups were removed by hydrogenation with palladium on carbon in a DMF/MeOH mixture to give **123** in quantitative yield.²⁵ This was reacted with **103** and Cs_2CO_3 in DMF at 100 °C for 3 days affording **121** in 59% yield following purification by column chromatography. During optimisation of the reaction procedure, small amounts of the monoalkylated product **124** were also isolated. This is an interesting compound as there is the potential to develop asymmetric macrocycles, and this will be explored in Section 4.3.3.1.

Scheme 4.12 Synthesis of macrocycle precursor **121**

4.3.1.2 Macrocyclisation Using Eglinton Coupling

The macrocyclisation of precursor **121** by Eglinton coupling of the terminal alkyne groups was then investigated, initially under high dilution conditions (Scheme 4.13). A solution of copper(II) acetate in CH_3CN was added dropwise to a solution of **121** in a large volume of CH_3CN . The reaction mixture was heated under reflux for 16 hours since precursor **121** was sparingly soluble in CH_3CN . The desired macrocycle **125** was obtained in 63% yield following purification by silica gel chromatography, as confirmed by the peak at m/z 621.2203 for $[\mathbf{125} + \text{Na}]^+$ in the high resolution mass spectrum.

Scheme 4.13 Synthesis of macrocycle **125** using Eglinton coupling

The ^1H NMR spectra of **121** and **125** are quite similar, but the successful formation of macrocycle **125** is indicated by the disappearance of the triplet corresponding to proton *l* and replacement of the doublet for proton *k* with a singlet (Figure 4.10).

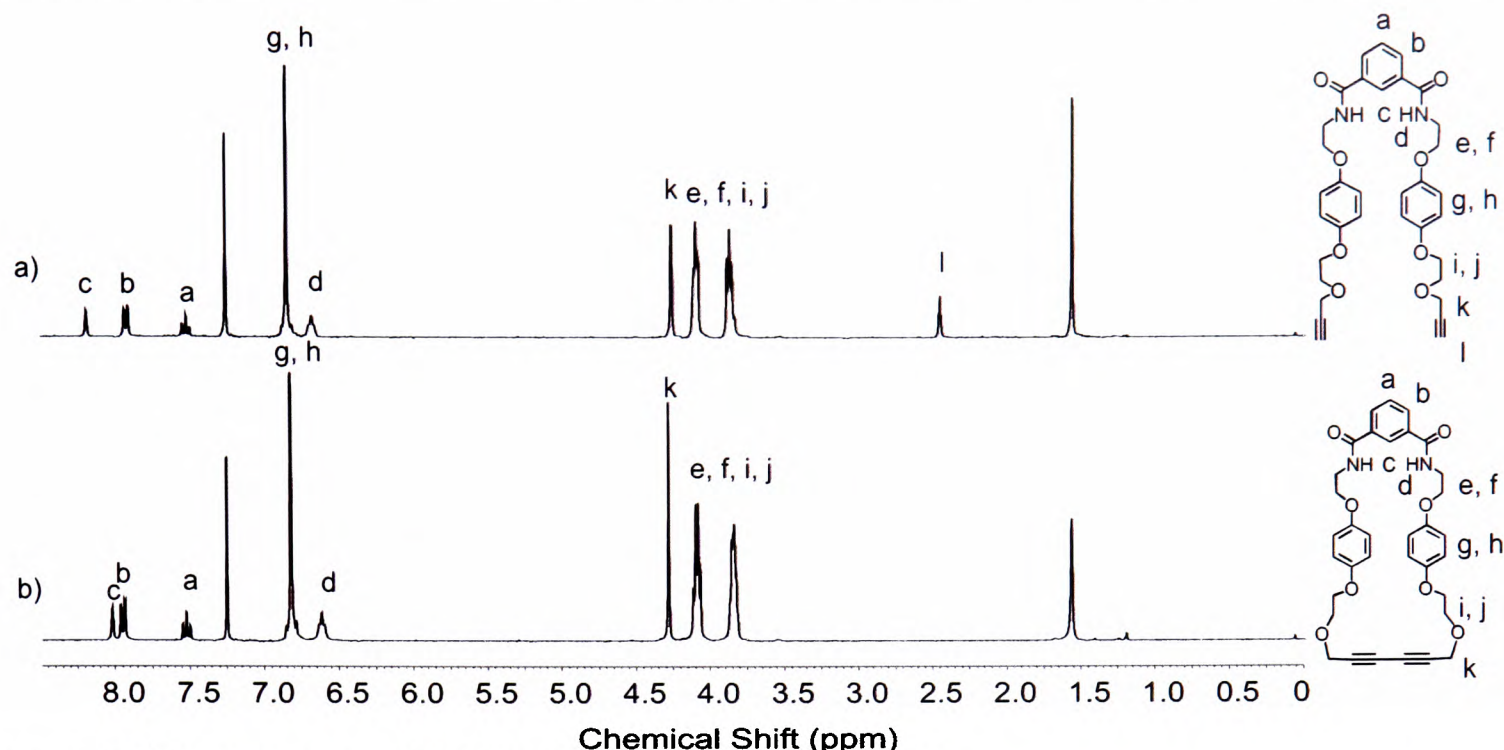


Figure 4.10 ^1H NMR spectra of a) **121** and b) **125** in CDCl_3 at 293 K

Single crystals of **125** were grown from slow evaporation of a solution of **125** and **54**.Cl in $\text{CDCl}_3/\text{CD}_3\text{OD}$ and the X-ray crystal structure clearly shows the planarity of the diyne unit (Figure 4.11).²⁶ The macrocycle is in a chair-like conformation with a disordered methanol solvent molecule (omitted for clarity) bound by weak hydrogen bonds to the isophthalamide amide and *ortho* CH protons.

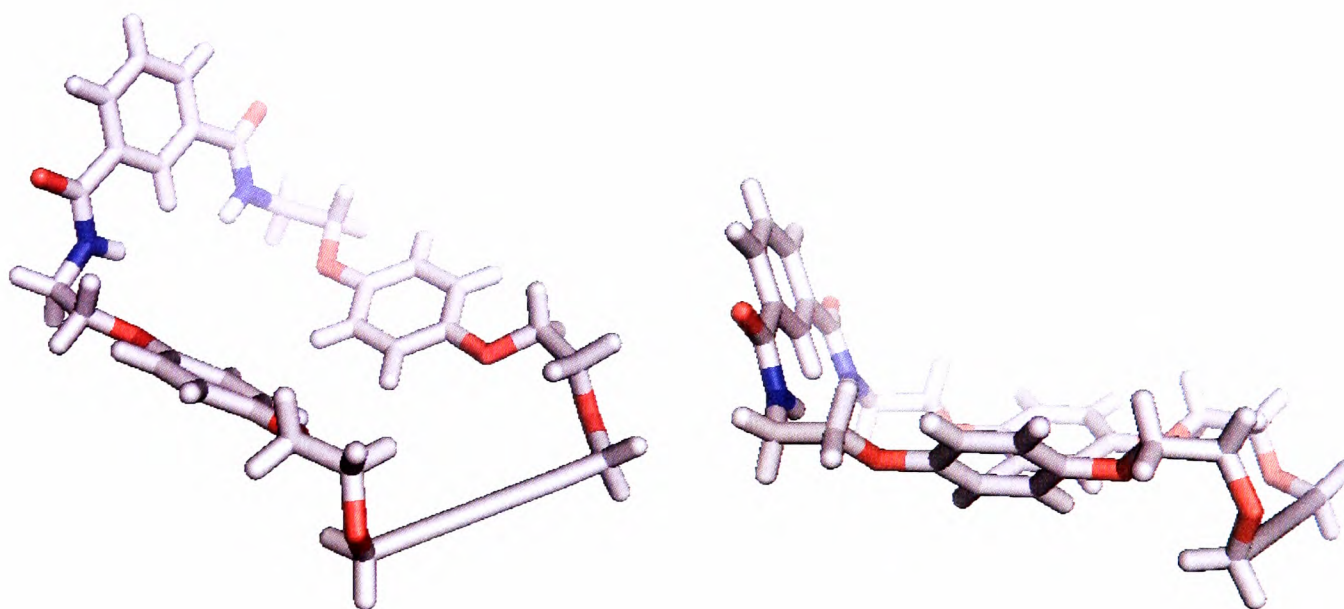


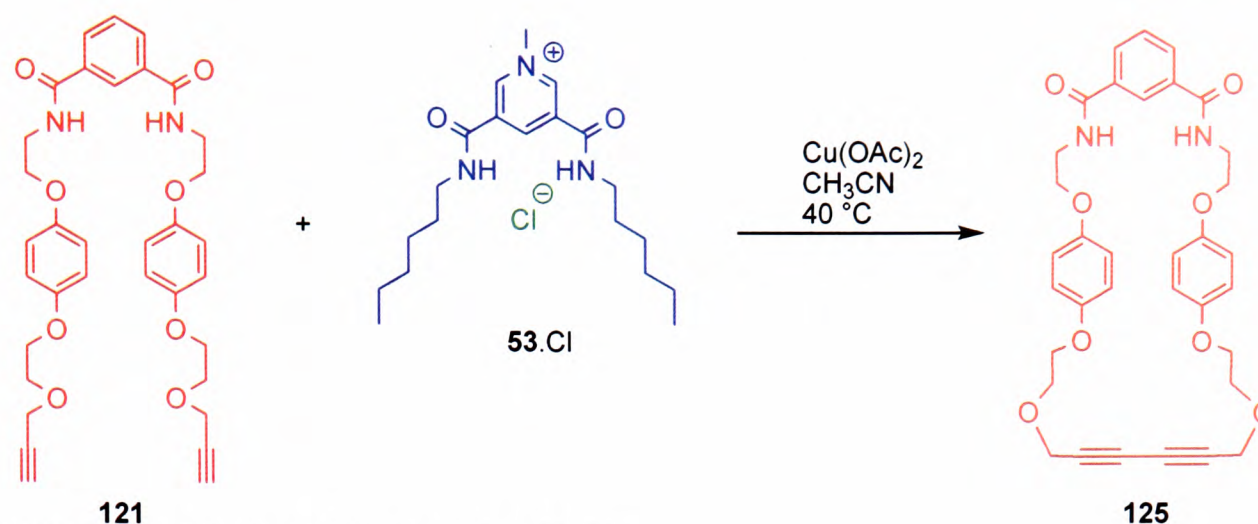
Figure 4.11 X-ray crystal structure of macrocycle **125** from two different views

Having demonstrated that Eglinton coupling can be successfully employed to form macrocycles, attention was turned to extending this clipping strategy to rotaxane synthesis. For rotaxane synthesis to be feasible, the Eglinton reaction needs to be carried out at room temperature in a non-competitive solvent like CH_2Cl_2 to favour association of macrocycle

precursor **121** and axle. Therefore, modification of the macrocyclisation reactions conditions was investigated, as the refluxing conditions in CH₃CN would not be suitable.

Initially, the macrocyclisation was repeated under high dilution conditions carrying out the reaction at 70, 50 and 40 °C. In each case, the desired macrocycle formed but small amounts of starting material were also isolated. In order to improve the solubility of **121** at the lower reaction temperatures, the reaction was carried out in different solvent mixtures. Copper(II) acetate was not soluble in CH₂Cl₂ or CHCl₃ so the reaction was not attempted in these solvents. Instead, a biphasic reaction in CHCl₃/H₂O was carried out at 40 °C but only starting material was recovered, while the reaction in 7:3 CH₃CN/CH₂Cl₂ gave a mixture of **121** and **125**.

The macrocyclisation of **121** using **53.Cl** as a template was then investigated (Scheme 4.14). It was hoped that the **53.Cl** might help solubilise **121** by forming an orthogonal assembly, and it would act as a model system for the rotaxane synthesis using the stoppered axle **54.Cl**. Firstly, a preliminary ¹H NMR titration was carried out to determine whether there was any association of the macrocycle precursor **121** and **53.Cl** at 40 °C in CD₃CN. Upon addition of 10 equivalents of **53.Cl** to **121**, there were very small downfield shifts of the isophthalamide protons *c* and *d*, consistent with chloride binding to **121**. However, there were insufficient upfield shifts and splitting of the macrocycle hydroquinone protons *g* and *h* to infer association of the two components, which is not surprising given the competitive nature of the solvent and raised temperature.



Scheme 4.14 Templated macrocyclisation using **53.Cl**

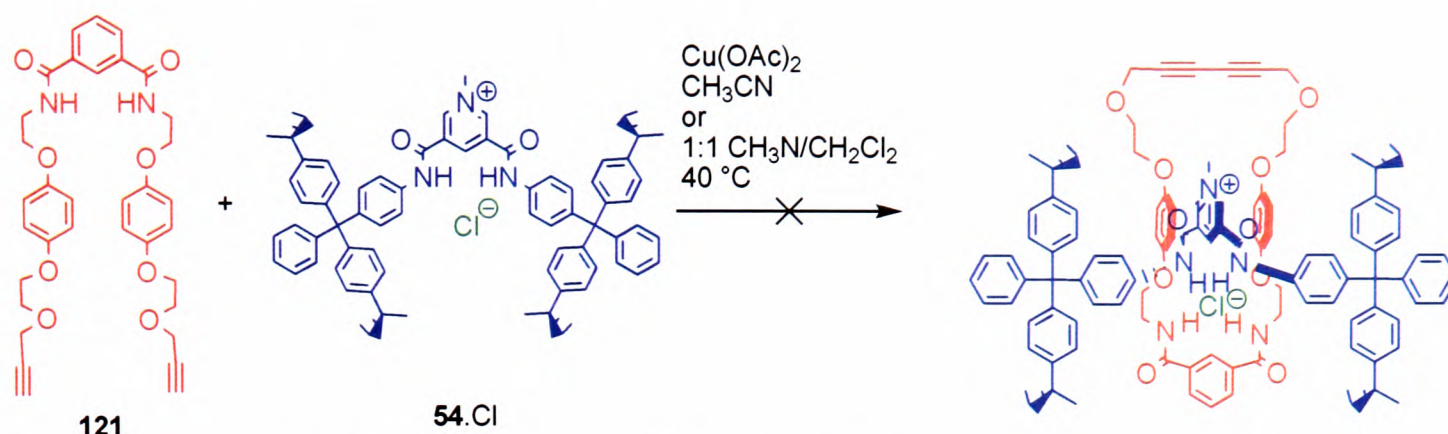
Nevertheless, the templated synthesis of macrocycle **125** was attempted by heating a 1:1 mixture of **121** and **53.Cl** in the presence of copper(II) acetate at 40 °C in CH₃CN for 19 hours. The majority of the crude reaction mixture was a pseudorotaxane of the macrocycle **125** and **53.Cl**, based on the ¹H NMR spectrum and a peak at *m/z* 946.5 in the mass spectrum. Unfortunately, there was also a small amount of starting material and attempts to separate the mixture were unsuccessful. The reaction was repeated at room temperature in a CH₃CN/CH₂Cl₂ mixture but disappointingly, the reaction mixture was mostly unreacted **121** after 9 days.

The use of copper(II) chloride was also investigated as alternative catalyst to copper(II) acetate, to discount that the large excess of acetate anions was interfering with anion templation. Unfortunately, there was no evidence of reaction using high dilution or templation conditions after heating at 40 °C in CH₃CN.

4.3.1.3 Attempted Rotaxane Synthesis by Eglinton Coupling

Attempts to optimise the Eglinton coupling reaction conditions were unsuccessful, nevertheless, the rotaxane synthesis was attempted at 40 °C in CH₃CN using copper(II) acetate (Scheme 4.15). However, there was no evidence of rotaxane or even macrocycle formation. At first this was attributed to the insolubility of **54.Cl** and limited solubility of **121** in CH₃CN. Therefore, the reaction was repeated in a 1:1 mixture of CH₃CN/CH₂Cl₂ but again,

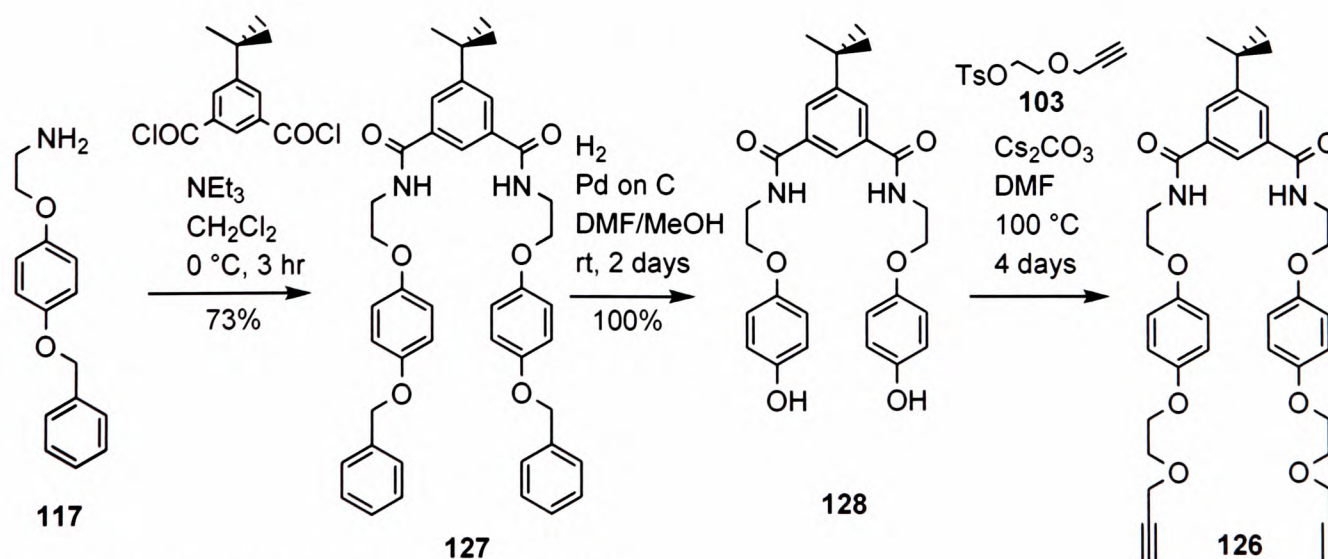
only starting material was recovered.



Scheme 4.15 Attempted synthesis of rotaxane by Eglinton coupling

4.3.1.4 Synthesis of Alternative Macrocycle

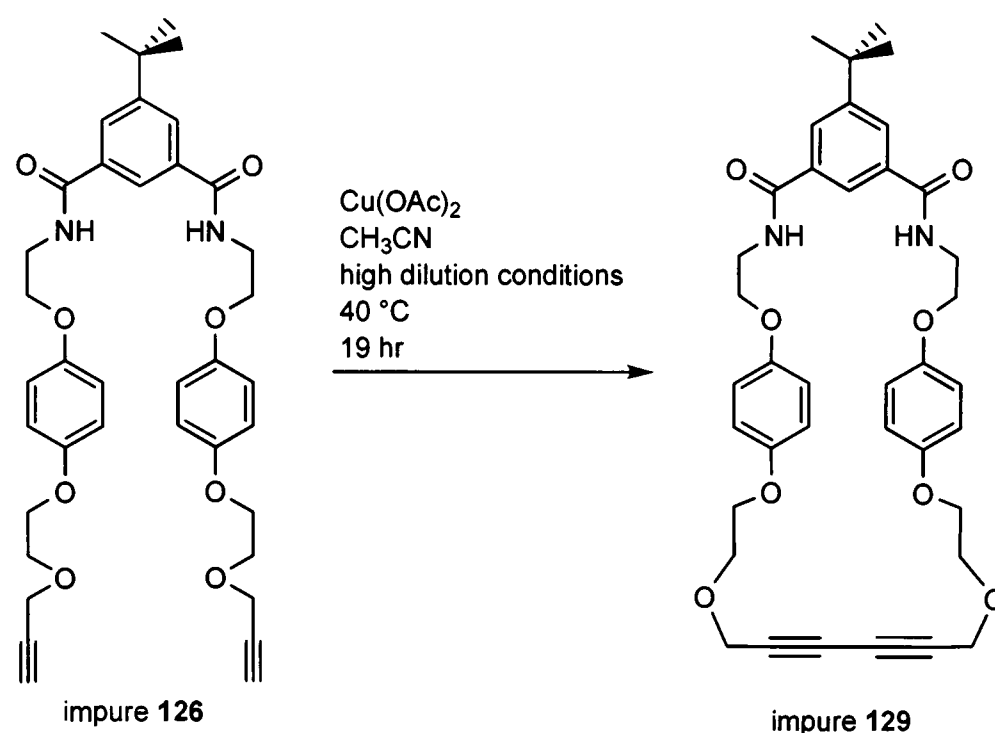
The synthesis of a macrocycle precursor **126** with a *tert*-butyl group was investigated to improve solubility in CH_3CN , in the hope that this would allow the Eglinton reaction to take place at room temperature. An analogous synthetic strategy to the preparation of macrocycle precursor **121** was employed (Scheme 4.16). Amine **117** was reacted with 5-*tert*-butylisophthaloyl dichloride in the presence of triethylamine at 0°C in CH_2Cl_2 to give **127** in 73% yield.²⁷ The benzyl protecting groups were removed using palladium on carbon under a H_2 atmosphere in quantitative yield.²⁷ A suspension of **128**, **103** and Cs_2CO_3 was heated at 100°C for 4 days giving the desired macrocycle precursor **126**. It was not possible to obtain an accurate yield of **126** due to a small amount of contamination from an impurity.



Scheme 4.16 Synthesis of macrocycle precursor **126**

Macrocyclisation by Eglinton coupling was investigated using impure **126**, initially under high dilution conditions at 40°C (Scheme 4.17). Pleasingly, this macrocycle precursor was much more soluble in CH_3CN and the desired macrocycle **129** was isolated. Despite

purification attempts, however, it could not be isolated completely free from impurities. The reaction was repeated at room temperature and there was evidence of macrocycle formation after a week, although the reaction mixture was still approximately 50% unreacted **126**.



Scheme 4.17 Macrocyclisation of **126** using Eglinton coupling

Disappointingly, the Eglinton macrocyclisation reaction does not proceed at room temperature quickly enough for rotaxane synthesis to be feasible, despite improving the solubility of the macrocycle precursor. Instead, attention turned to the synthesis of rotaxanes based on macrocycle **125** exploring different synthetic strategies, including slippage.

4.3.2 Towards Rotaxane Formation via Slippage

4.3.2.1 Introduction

A much less common method for rotaxane synthesis is slippage, which was briefly introduced in Section 1.4.2, where the macrocycle slips over one of the axle stoppers. This usually involves heating the macrocycle and axle components at elevated temperatures to overcome the energy barrier to slippage, $\Delta G^\ddagger_{\text{on}}$, and the resulting rotaxane structure can be kinetically trapped by cooling the equilibrated mixture to room temperature, providing the barrier to slippage_{off} ($\Delta G^\ddagger_{\text{off}}$) cannot be overcome (Figure 4.12). This barrier can be increased by incorporating suitable non-covalent interactions between the macrocycle and axle components, which stabilise the rotaxane compared to the free components.

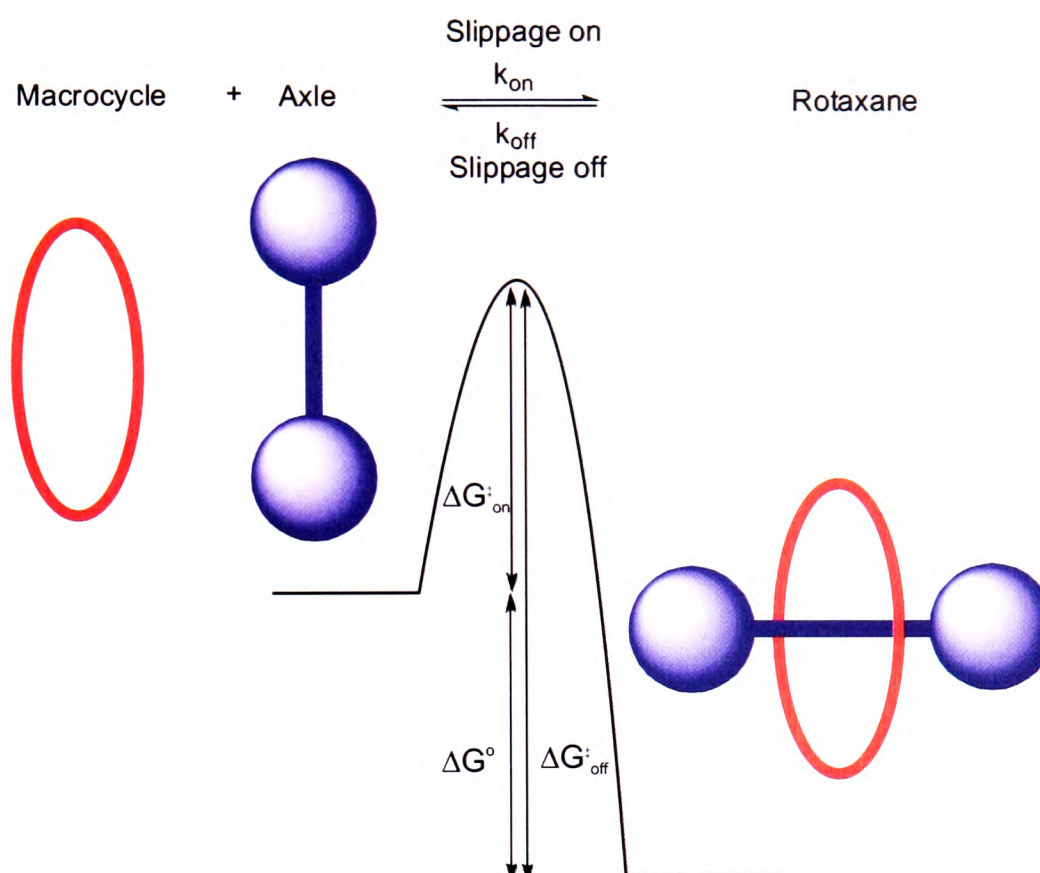


Figure 4.12 Energy level diagram for the formation of rotaxanes by slippage

Stoddart and co-workers reported the first rotaxane synthesis by slippage in 1993.²⁸ The rotaxane in Figure 4.13a was synthesised by heating a mixture of the macrocycle and axle components in CH₃CN at 60 °C, and π – π stacking interactions between the electron rich macrocycle and electron deficient axle stabilised the resulting rotaxane structure. Kinetic studies revealed that the size of both the macrocycle and stoppers of the axle affect the rates of slippage, and no rotaxane formation occurs when the stopper substituent R is an *i*-propyl group.^{28–30} Further investigations also demonstrated the importance of solvent on the stability of the rotaxane. The structure in Figure 4.13b is stable in non-polar solvents, but dissociates into the macrocycle and axle components in polar solvents such as DMSO.³¹ Therefore, the structure is a pseudorotaxane rather than a rotaxane and for this reason, Stoddart and co-workers proposed that pseudorotaxanes lie in the ‘fuzzy’ domain between rotaxanes and the individual components. Species formed by slippage can therefore be classified as either rotaxanes or pseudorotaxanes. Rotaxanes are kinetically stable at room temperature, like the structure in Figure 4.13a, whereas others, like that shown in Figure 4.13b, are pseudorotaxanes that possess some rotaxane character.

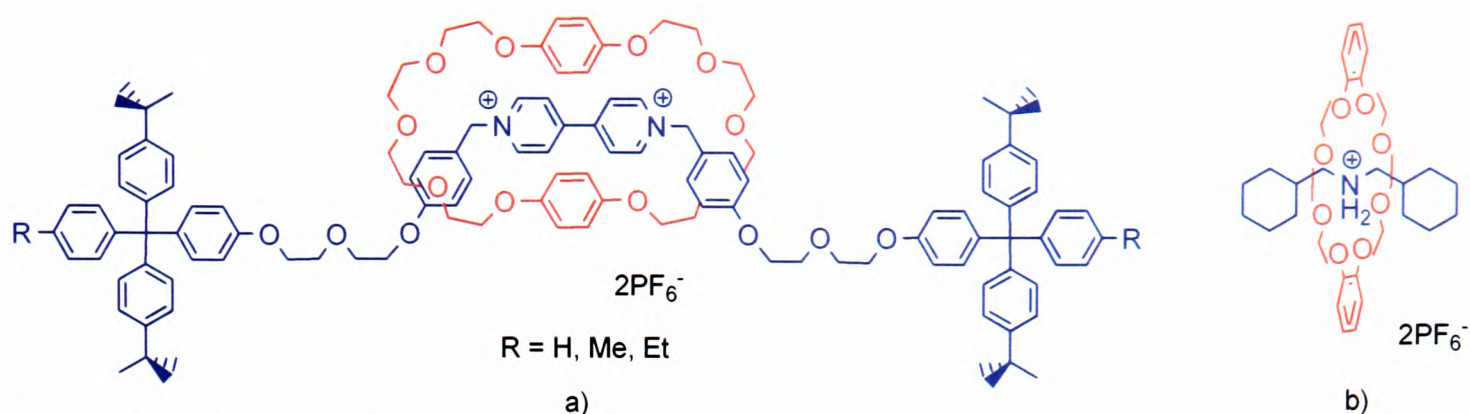
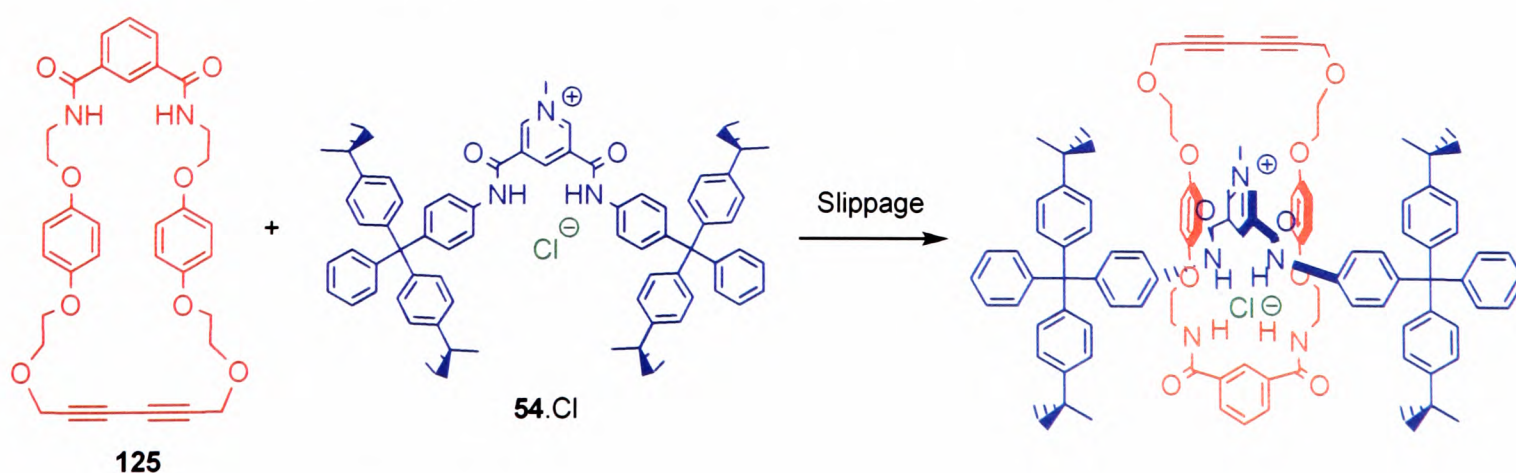


Figure 4.13 Stoddart's slippage rotaxanes

A number of other groups have also reported the synthesis of rotaxanes using slippage, including Loeb³² and Chiu.³³ However, the role of anion templation in the slippage process has not been investigated.

4.3.2.2 Preliminary ¹H NMR spectroscopy experiments

It was questionable whether the stoppers of **54.Cl** are large enough to form rotaxanes with macrocycle **125**, due to the planarity of the diyne unit. Therefore, a number of ¹H NMR experiments were carried out to investigate whether the macrocycle can slip over the stopper groups forming the rotaxane (Scheme 4.18). Initially these were carried out in acetone-*d*₆ but solubility problems limited the scope of the studies. The macrocycle was only partially soluble in acetone-*d*₆, while **54.Cl** was completely insoluble. However, **54.PF₆** was soluble and there was no evidence of slippage of **125** over the stopper groups after 24 hours at room temperature. In order to discount the possibility that the absence of a coordinating anion was preventing slippage of the macrocycle over the stoppers, slippage was investigated in CDCl₃, where solubility of the macrocycle and axle components was not a problem.



Scheme 4.18 Synthesis of rotaxane via slippage

The ^1H NMR spectrum of a 1:1 mixture of **125** and **54.Cl** in CDCl_3 after 8 hours at room temperature showed a new set of signals (shown in green) in addition to signals for the macrocycle (red) and stoppered axle (blue) in Figure 4.14b. These signals correspond to the species formed from slippage of the macrocycle over the stoppers of **54.Cl**. The isophthalamide proton *c* and amide proton *d* of the macrocycle have moved significantly downfield, suggesting a chloride anion is bound within the anion binding cavity. Additionally, the pyridinium cavity protons *o* and *n* have shifted upfield due to the competitive binding of chloride and the hydroquinone protons *g* and *h* have moved upfield and split, which is characteristic of π – π stacking interactions with the pyridinium unit of the axle component.

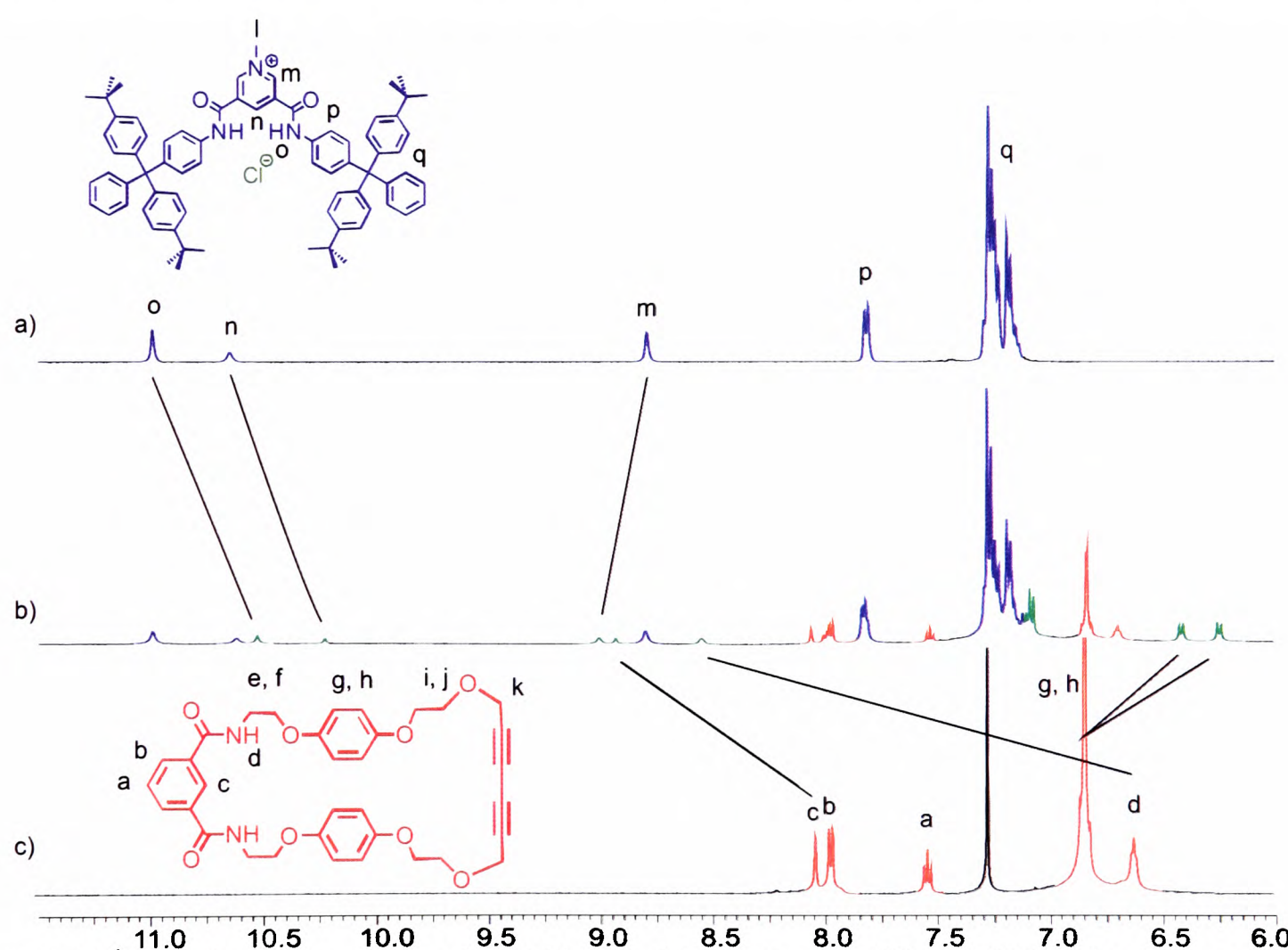


Figure 4.14 ^1H NMR spectra of a) axle **54.Cl** b) a 1:1 mixture of **125** and **54.Cl** after 8 hours at room temperature and c) macrocycle **125** in CDCl_3 at 298 K. The proton signals in green in b) correspond to the slippage species.

Given that the slippage occurs at room temperature, it is unlikely that the species formed by slippage is a rotaxane, but rather a pseudorotaxane. In an effort to confirm this, the NMR sample was diluted in MeOH and submitted for electrospray mass spectroscopy analysis. The mass spectrum showed peaks only for the macrocycle and axle component, which suggests

that the species dissociates into the macrocycle and stoppered axle components in MeOH. Slippage_{off} is promoted since MeOH is a competitive solvent which would disrupt the hydrogen bonding interactions between the macrocycle and axle. Indeed, addition of CD₃OD to an equilibrated mixture of the macrocycle, axle and slippage species led to the disappearance of the signals for slippage species after 18 hours.

These preliminary studies suggest that the species formed by slippage between **125** and **54.Cl** is a pseudorotaxane. It was hoped that preparation of an alternative axle component with sterically bulkier stoppers, such as **130.X** (Figure 4.15), would prevent slippage at room temperature and make it possible to isolate a rotaxane following slippage at an elevated temperature. More detailed kinetic studies of the slippage process would be carried out using the two axles, **54.X** and **130.X**, at two different temperatures. The role of the anion in the slippage process would also be investigated by varying the anion of the axle component. However, it was necessary to first prepare the various anion salts of **54.X** and **130.X**.

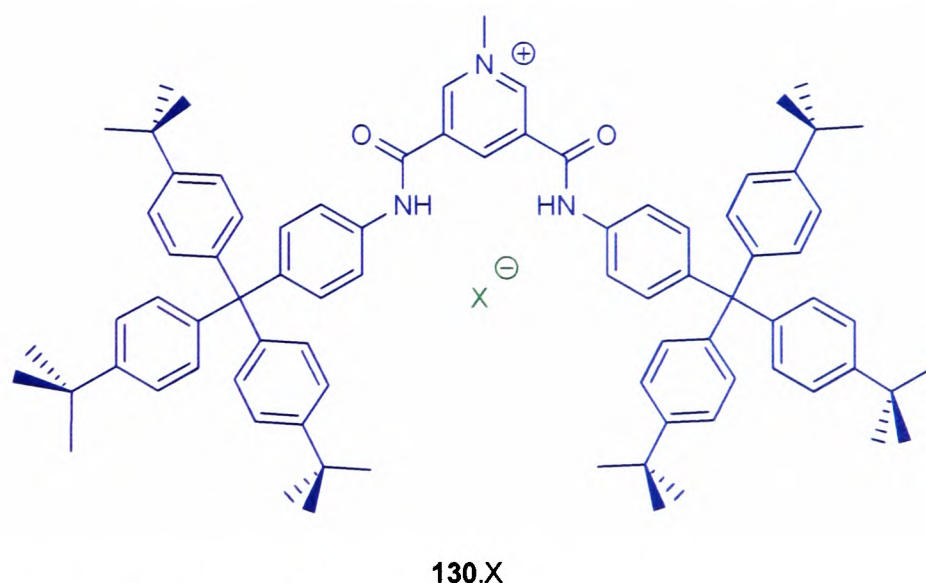
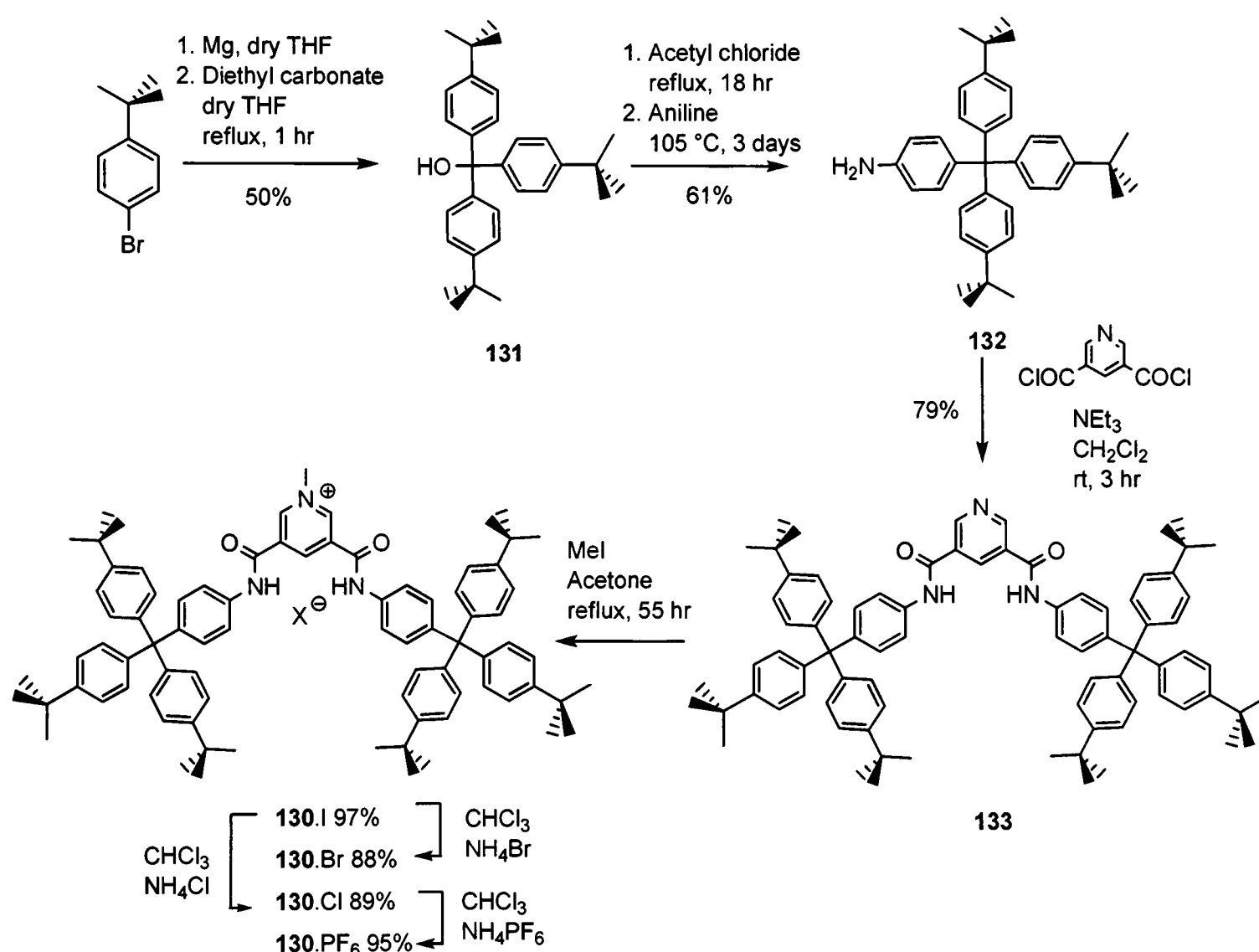


Figure 4.15 Alternative stoppered axle **130.X**

4.3.2.3 Synthesis of **130.X**

The preparation of the chloride, iodide and hexafluorophosphate salts of **54.X** was described in Chapter 3. The bromide salt was also prepared by washing a solution of **54.I** in CHCl₃ repeatedly with 1 M NH₄Br solution. Compounds **130.X** (where X = I, Cl, Br, PF₆) were prepared in a similar manner to **54.X** according to Scheme 4.19.²¹ A Grignard reagent was

prepared by reacting 1-bromo-4-*tert*-butylbenzene with magnesium turnings in dry THF and this was reacted with diethyl carbonate to give **131** in 50% yield. The amine **132** was synthesised in two steps in 61% yield, firstly by heating **131** in acetyl chloride under reflux for 18 hours and then heating in aniline at 105 °C for 3 days. Reaction of **132** with 3,5-bis(chlorocarbonyl) pyridine in CH₂Cl₂ gave **133** in 79% yield, which was methylated with iodomethane to afford **130.I**. Subsequent anion exchange of **130.I** by washing with 1 M NH₄Cl or NH₄Br gave **130.Cl** and **130.Br** respectively in good yields. Repeated washing of a CHCl₃ solution of **130.Cl** with 0.2 M NH₄PF₆ gave **130.PF₆** in 95% yield.

Scheme 4.19 Synthesis of **130.X**

4.3.2.4 Anion Binding and Pseudorotaxane Studies

Anion binding and pseudorotaxane studies for the macrocycle **125** were carried out in order to quantify the strength of anion binding before investigating the role of the anion in the slippage process. The anion binding of the macrocycle precursor **121** was also studied for comparative purposes. Chemical shift changes were observed during ¹H NMR titration experiments in

CDCl₃ upon addition of anions as their TBA salts. Small downfield shifts of the isophthalamide proton *c* and amide proton *d* indicate anion binding occurs within the isophthalamide anion binding cavity (Figure 4.16a) and 1:1 association constants were derived from winEQNMR2 analysis of the isophthalamide proton *c* titration data (Table 4.2). Unsurprisingly, the non-coordinating hexafluorophosphate anion does not bind to either **121** or **125** and the macrocycle precursor **121** binds dihydrogen phosphate preferentially to the other anions, as is commonly observed for acyclic systems. Macrocycle **125** binds the halide anions more strongly than **121** due to the macrocyclic effect. The titration data for acetate could not be fitted to any binding model. While the data for dihydrogen phosphate was consistent with a 1:2 macrocycle/anion binding model, it was not possible to obtain accurate association constants. The magnitudes of all of the association constants were much lower than expected given that CDCl₃ is a non-competitive solvent. It is likely that ion-pairing between the tetrabutylammonium cation and the anion is significant in CDCl₃ and this competes with anion binding lowering the anion binding constant.³⁴ Small downfield shifts of the tetrabutylammonium cation signals were observed over the course of the titration, which is consistent with ion-pairing between tetrabutylammonium cation and the chloride anion. More competitive solvents, such as acetone-*d*₆ and CD₃CN, would reduce the ion-pairing effect, but unfortunately the limited solubility of the macrocycle in these solvents prevented further anion binding studies.

X-	Δδ (ppm) ^a	K (M ⁻¹) ^a	Δδ (ppm) ^b	K (M ⁻¹) ^b
PF ₆ ⁻	-0.002	-	0.001	-
I ⁻	0.026	35	0.036	60
Br ⁻	0.069	55	0.082	60
Cl ⁻	0.13	80	0.139	115
OAc ⁻	0.047	40	0.074	*
H ₂ PO ₄ ⁻	0.245	350	0.084	*

Table 4.2 Chemical shift changes of the isophthalamide proton *c* upon addition of 1 equivalent of anion and 1:1 association constants derived from winEQNMR analysis of the isophthalamide proton titration data for ^amacrocycle precursor **121** and ^b macrocycle **125** in CDCl₃ at 298 K. Errors < 10%. - = no evidence of binding. * = evidence of binding but association constants could not be determined from titration data

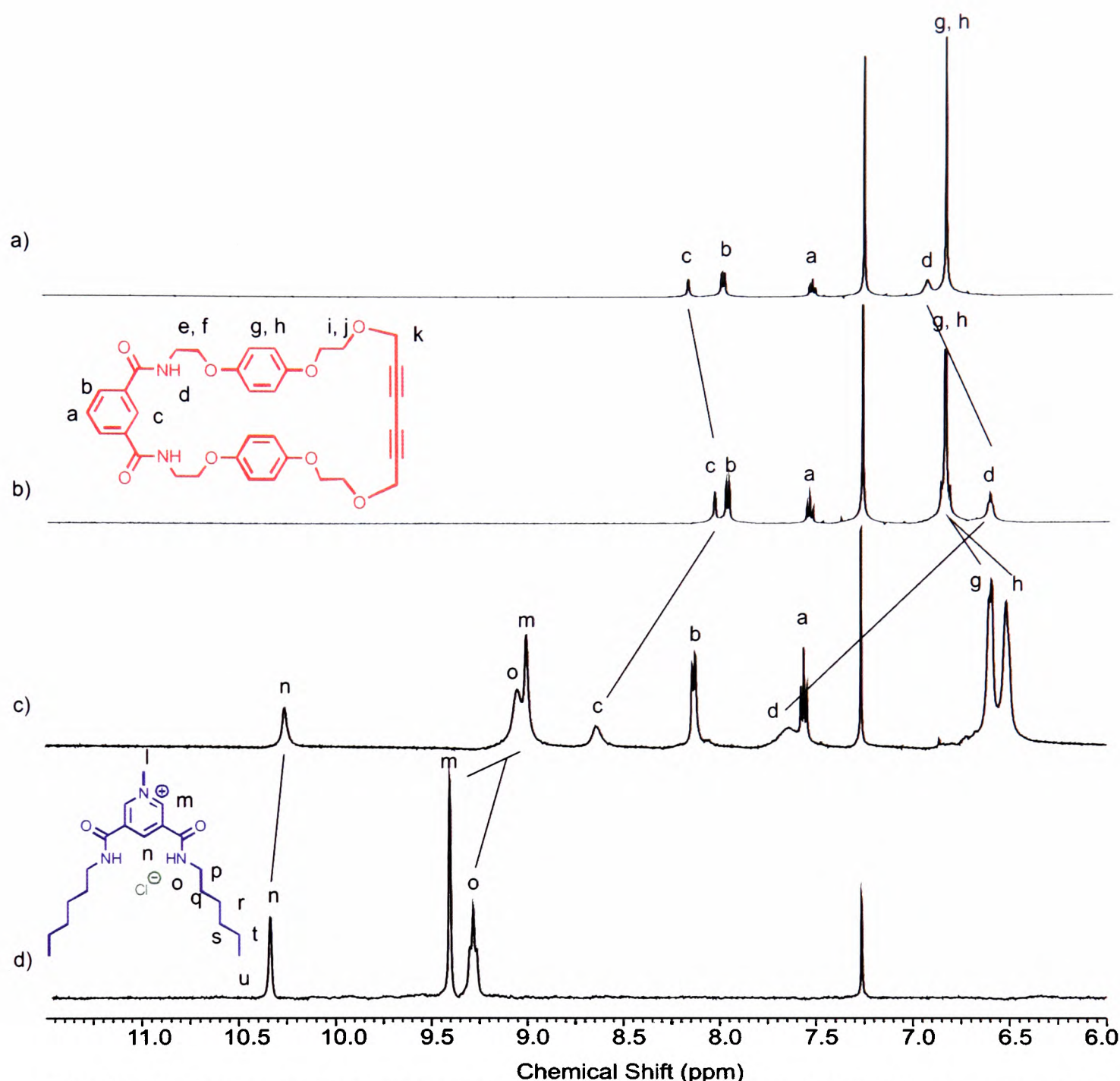


Figure 4.16 ^1H NMR spectra of a) macrocycle **125** and one equivalent of TBACl b) macrocycle **125** c) pseudorotaxane of **125** and **53.Cl** and d) **53.Cl** in CDCl_3 at 298 K

Pseudorotaxane studies with **53.X** were also carried out in CDCl_3 . The downfield shifts of the macrocycle protons *c* and *d* and upfield shifts and splitting of the hydroquinone protons *g* and *h* upon addition of the ion-pair thread were consistent with pseudorotaxane formation (Figure 4.16c). The titration data for hydroquinone proton *g* was analysed using winEQNMR2 to give 1:1 association constants (Table 4.3). The pseudorotaxane association constant is correlated with the strength of the ion-pair with highest affinity for the strongest ion-pair, **53.Cl**. As the strength of the ion-pair decreases from **53.Cl** to **53.I**, the magnitude of the association constant also decreases. Interestingly, **53.PF₆** forms a pseudorotaxane even in the absence of a coordinating anion and with a higher association constant than for **53.I**. This

contrasts to earlier results where slippage did not occur with **54**.PF₆ and previous studies with a related macrocycle where pseudorotaxane formation occurs only in the presence of a coordinating anion.²⁷ In both of these cases, however, the solvent was acetone-*d*₆ which is a more competitive solvent than CDCl₃ reducing the effect of ion-pairing. The decrease in the association constant for **53**.I compared with **53**.PF₆ is most likely due to a poor size fit of the ion-pair in the macrocyclic cavity.

X ⁻	K (M ⁻¹)
PF ₆ ⁻	400
I ⁻	290
Br ⁻	820
Cl ⁻	1350

Table 4.3 Association constants for pseudorotaxane formation derived from winEQNMR2 analysis of titration data for the hydroquinone proton *g* in CDCl₃ at 298 K.

Overall, the association constants for both anion binding and pseudorotaxane formation are relatively low considering that the solvent system is non-competitive and non-polar. It is possible that ion-pairing is competing with the anion binding or threading events, and this could account for the observed pseudorotaxane formation in the absence of a coordinating anion. Unfortunately, solubility problems prevented titration experiments being carried out in more competitive solvents.

4.3.2.5 Slippage Kinetic Studies

The slippage process and the role of the anion were then investigated in more detail by ¹H NMR spectroscopy kinetic experiments. A 1:1 mixture of the macrocycle and stoppered axle (**54**.X or **130**.X), each at a concentration of 5 mM, in CDCl₃ was heated at 298 K or 323 K and ¹H NMR spectra were recorded over a period of time. The signals corresponding to the rotaxane in green increased with time as the signals for the free macrocycle (red) and stoppered thread (blue) decreased (Figure 4.17).

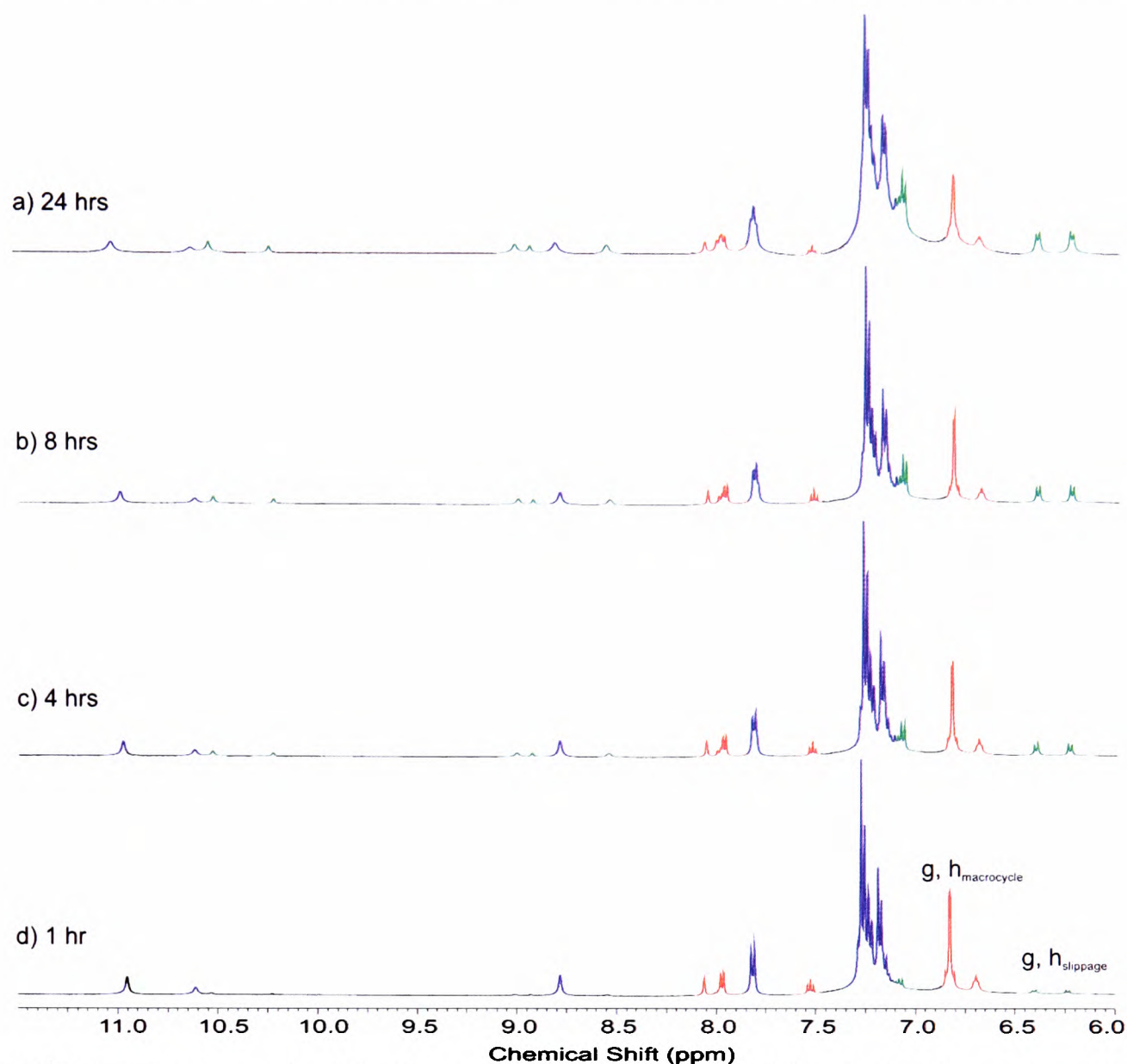


Figure 4.17 ^1H NMR spectra of a 1:1 mixture of **125** (red) and **54.Cl** (blue) showing the appearance of the slippage species (green) over time in CDCl_3 at 298 K

The concentration of the slippage species was obtained by integrating the hydroquinone signals of g, h_{slippage} (in green) relative to the signal of the free macrocycle ($g, h_{\text{macrocycle}}$ in red) and Figure 4.18 shows that the slippage species concentration increases with time until equilibrium is reached.

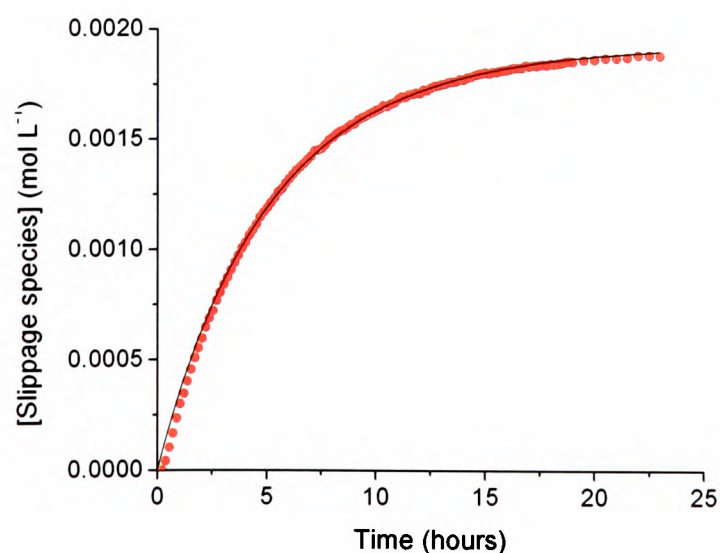
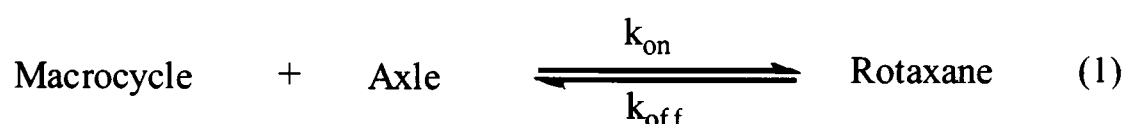


Figure 4.18 Change in concentration of the slippage species formed from **125** and **54.Cl** over time in CDCl_3 at 298 K

It is possible to obtain both kinetic and thermodynamic parameters about the slippage process from this experiment. The slippage process can be described by the equilibrium in equation 1 and the association constant, K_a , can be determined from the rotaxane, macrocycle and thread equilibrium concentrations according to equation 2. In addition, the rate constant for the slippage process, k_{on} , can be determined by fitting the curve to the model described by equation 3 (derived from the integrated rate law^{30, 35}) using a non-linear curve fitting program in Origin.³⁶ The black line in Figure 4.18 shows the fitting of this equation to the experimental data and the statistical parameter χ^2 indicates the quality of the fitting. A value of zero indicates a perfect fit and therefore the smaller the number, the better the fit. The rate constant for slippage_{off}, k_{off} , can also be calculated according to equation 2 using the values calculated for K_a and k_{on} .



$$K_a = \frac{k_{on}}{k_{off}} = \frac{[\text{Rotaxane}]_e}{[\text{Macrocycle}]_e[\text{Axle}]_e} = \frac{R_e}{M_e^2} \quad (2)$$

$$[\text{Rotaxane}]_t = \frac{M_o^2 R_e e^{\left(\frac{k_{on} t (M_o^2 - R_e^2)}{R_e} \right)} - M_o^2 R_e}{M_o^2 e^{\left(\frac{k_{on} t (M_o^2 - R_e^2)}{R_e} \right)} - R_e^2} \quad (3)$$

R_e - equilibrium rotaxane concentration
 M_o - initial macrocycle concentration
 k_{on} - slippage rate constant
 t - time in hours

A comparison of the curves for slippage with the hexafluorophosphate and halide salts of the stoppered axles **54.X** and **130.X** at 298 K and 323 K are shown in Figures 4.19 and 4.20 respectively. The kinetic and thermodynamic parameters for the slippage process in Table 4.4 were calculated from these graphs. It was not possible to study slippage with **54.I** and **54.Br** due to the insolubility and limited solubility of these axles respectively in CDCl_3 . In contrast, the stoppered axles **130.X** were all soluble in CDCl_3 although the rates of slippage were much slower due to the steric hindrance from the extra *tert*-butyl group on the stoppers. It was not possible to obtain accurate data for **130.Cl** at 298 K since preliminary studies showed that

equilibrium was reached after more than 1 week and solvent loss over this time would be significant.

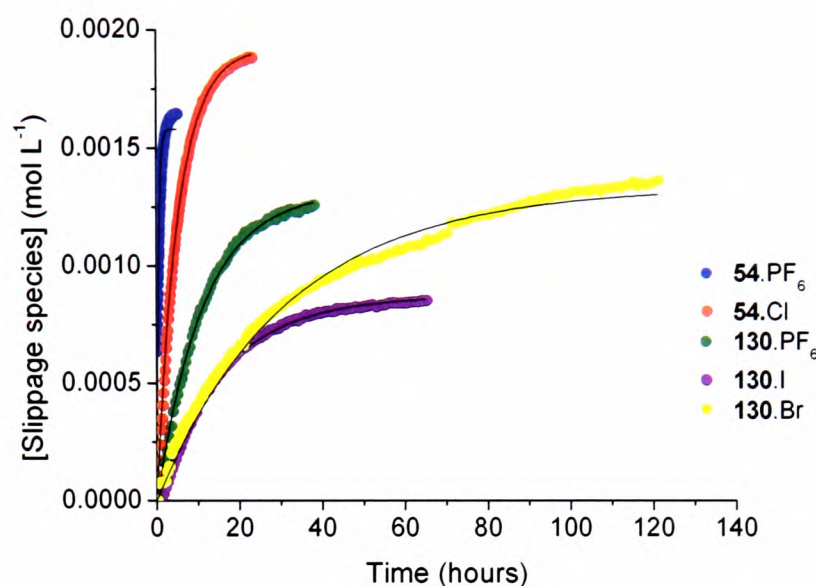


Figure 4.19 Change in the concentration of the slippage species formed from the stoppered axles **54.X** and **130.X** in CDCl_3 at 298 K

The nature of the anion of the stoppered axle does affect both the rate of slippage and the association constant (Figures 4.19 and 4.20, Table 4.4). Slippage was expected to occur for the hexafluorophosphate stoppered axles based on the pseudorotaxane studies, however, unexpectedly, the macrocycle slips over these axles and reaches equilibrium more quickly than for the corresponding axles with coordinating anions. Ion-pairing is significant in CDCl_3 and the rates of slippage are correlated to the strength of the ion-pair, with the slippage rate decreasing as the strength of the ion-pair increases. This suggests that the mechanism of slippage may involve dissociation of the ion-pair prior to slippage, because if the macrocycle slipped over a tight ion-pair, the slippage rates for axles with an iodide anion would be slower than those with chloride anions. It is unlikely that anion binding in the macrocycle isophthalamide cavity occurs prior to slippage as the signals of the free macrocycle and stoppered axle in the ^1H NMR spectra do not shift over time (Figure 4.17). The mechanism for slippage is complicated by a number of competing equilibria, but the results suggest that the dissociation of the ion-pair is the rate-limiting step.

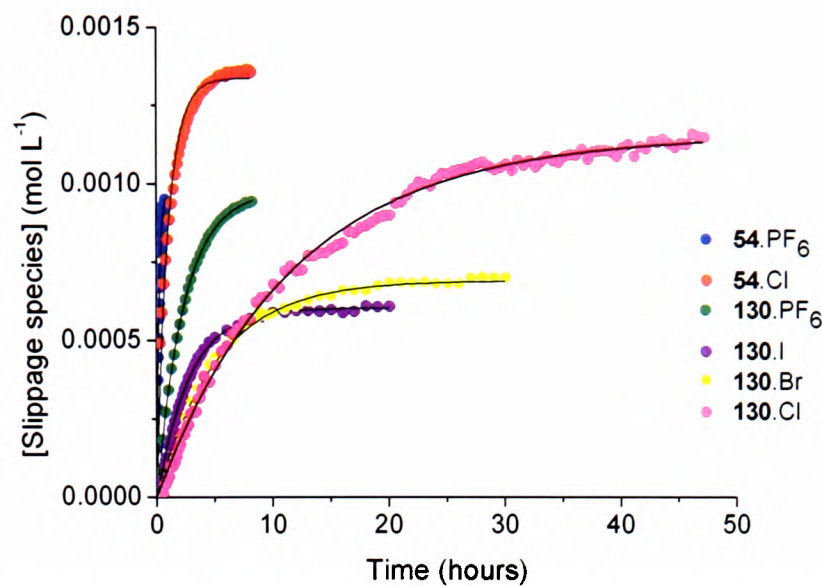


Figure 4.20 Change in the concentration of the slippage species formed from the stoppered axles **54.X** and **130.X** in CDCl₃ at 323 K.

The association constant is also dependent on the ion-pair strength and follows the same trend as in the pseudorotaxane studies, with the highest association constants for the chloride stoppered axles. The association constants for axles with coordinating anions decrease as the ion-pair strength decreases. Interestingly, the association constants for **130.PF₆** at both temperatures are higher than or comparable to those for **130.I** and **130.Br**. This is most likely because of a poor size fit of the ion-pair thread in the macrocycle cavity, which was also observed in the pseudorotaxane studies. The k_{off} rate constants were calculated from the K_a and k_{on} values, and these show that, as expected, coordinating anions stabilise the rotaxane structure slowing the $\text{slippage}_{\text{off}}$ rates.

	298 K					323 K				
	[Rot] _e (mM)	K _a (M ⁻¹)	k _{on} (M ⁻¹ hr ⁻¹)	χ ² (10 ⁻⁹)	k _{off} (hr ⁻¹)	[Rot] _e (mM)	K _a (M ⁻¹)	k _{on} (M ⁻¹ hr ⁻¹)	χ ² (10 ⁻⁹)	k _{off} (hr ⁻¹)
54.PF₆	1.58	135	145.92	7.42	1.08	0.98	61	175.61	0.233	2.90
54.I	a	a	a	a	a	a	a	a	a	a
54.Br	b	b	b	b	b	b	b	b	b	b
54.Cl	1.93	205	15.55	0.378	0.0759	1.34	100	55.52	1.87	0.56
130.PF₆	1.32	97	4.76	0.46	0.0488	0.978	61	16.59	0.019	0.27
130.I	0.872	51	2.21	0.244	0.0431	0.604	31	8.59	0.17	0.28
130.Br	1.34	100	1.72	1.38	0.017	0.691	37	5.37	0.26	0.14
130.Cl	c	c	c	c	c	1.15	78	3.96	0.41	0.051

Table 4.4 Kinetic and thermodynamic parameters for the slippage process obtained from ¹H NMR kinetic experiments in CDCl₃. Parameters for these stoppered axles could not be obtained due to ^a limited solubility ^b insolubility and ^c the slow rate of slippage

Temperature has a predictable effect on the slippage rates and association constants with both of the slippage rates, k_{on} and k_{off} , increasing and the association constant decreasing upon changing the temperature from 298 K to 323 K. The effect of temperature was most significant for slippage with **130**.Cl where the time to reach equilibrium was reduced from over a week to approximately 2 days by heating at 323 K. It was hoped that this could be exploited for rotaxane synthesis, as cooling the equilibrated mixture to room temperature could make the barrier to $\text{slippage}_{\text{off}}$ too high to be overcome at room temperature.

In order to investigate whether the species formed were rotaxanes or pseudorotaxanes, as was suspected with the species formed with **54**.X, CD_3OD was added to an equilibrated mixture of the macrocycle, stoppered thread and slippage species from the experiments at 298 K. The CD_3OD would disrupt stabilising hydrogen bonding and $\pi-\pi$ interactions between the stoppered axle and macrocycle lowering the barrier to $\text{slippage}_{\text{off}}$. A rotaxane species would be stable while a pseudorotaxane species would undergo $\text{slippage}_{\text{off}}$ to the free macrocycle and stoppered axle components. The amount of macrocycle was monitored over time by integrating the hydroquinone signals of the macrocycle relative to the hydroquinone signals of the slippage species at 298 K. Figure 4.21 demonstrates that all of the slippage species are pseudorotaxanes rather than rotaxanes, although the rate of $\text{slippage}_{\text{off}}$ is dependent on the anion and the type of stoppered axle.

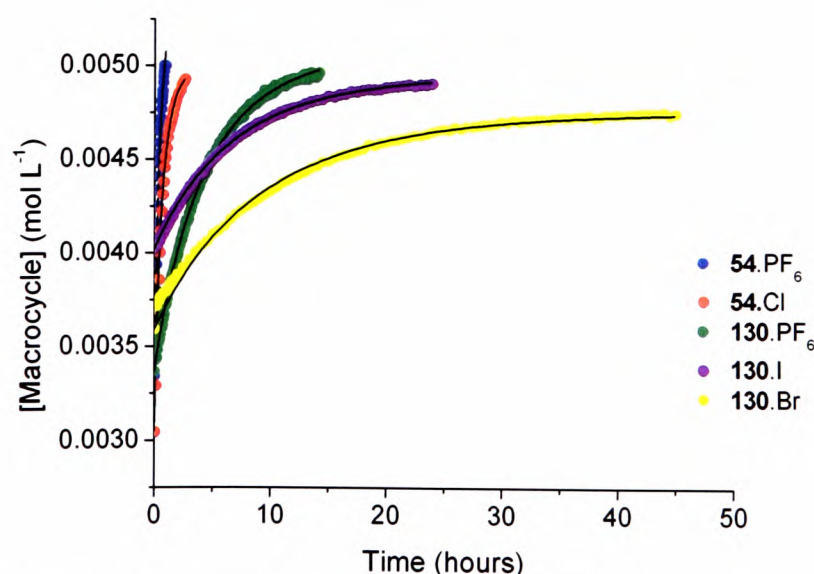


Figure 4.21 Dissociation of the slippage species into the free macrocycle upon addition of 100 μL CD_3OD to an equilibrated mixture of **125**, stoppered axle and slippage species in 500 μL CDCl_3 at 298 K

The rate constants for slippage_{off}, k_{off} , were calculated by fitting the curve to the model described by equation 4 (modified from the rate law) using a non-linear curve fitting program in Origin (Table 4.5). Unsurprisingly, the species formed with **54.X** are completely dissociated within several hours but those formed with **130.X** are more stable, due to the steric bulk of the extra *tert*-butyl group slowing the rate of slippage_{off}. The fastest slippage_{off} rates are achieved with the non-coordinating anion hexafluorophosphate and the rate decreases according to the strength of anion binding.

$$[\text{Macrocycle}]_t = \frac{R_o^2 M_e e^{\left[\frac{k_{\text{off}} t (R_o^2 - M_e^2)}{M_e} \right]} - R_o^2 M_e}{R_o^2 e^{\left[\frac{k_{\text{off}} t (R_o^2 - M_e^2)}{M_e} \right]} - M_e^2} + M_o \quad (4)$$

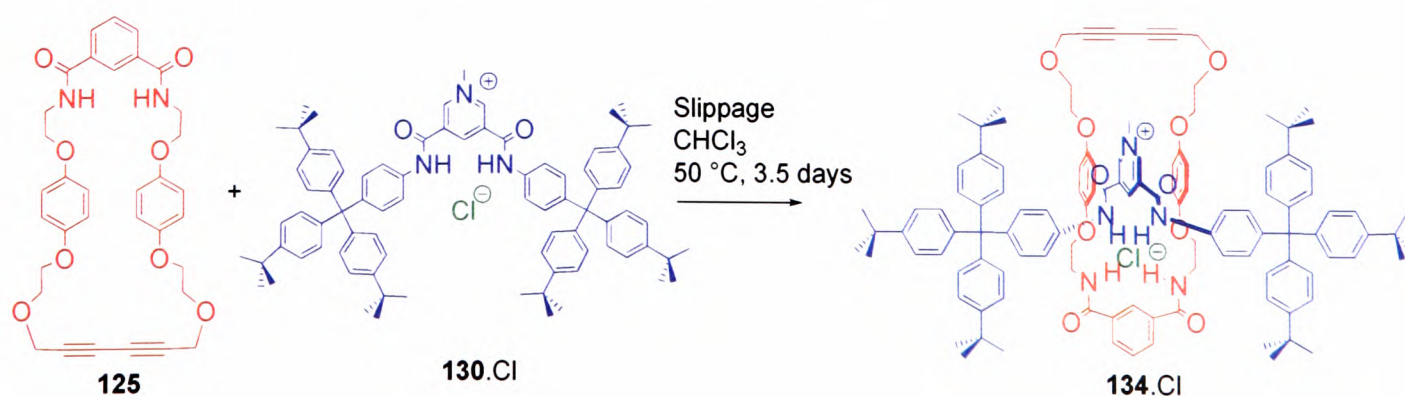
R_o - initial rotaxane concentration
 M_o - initial macrocycle concentration
 M_e - equilibrium macrocycle concentration
 k_{off} - slippage off rate constant
 t - time in hours

	k_{off} (hr ⁻¹)	$\chi^2 (10^{-9})$
54.PF₆	444	2.09
54.Cl	366	0.17
130.PF₆	50.52	0.14
130.I	30.53	0.00305
130.Br	23.26	1

Table 4.5 Slippage_{off} rate constants, k_{off} , upon addition of 100 μL CD_3OD to an equilibrated mixture of **125**, stoppered axle and slippage species in 500 μL CDCl_3 at 298 K

4.3.2.6 Attempted Rotaxane Synthesis

The kinetic slippage studies have proven that the species formed by slippage are not rotaxanes, but the species formed with **130.Br** has more rotaxane character than the other species since it takes more than two days to completely dissociate. It was hoped that the species formed from **130.Cl** would be more stable to slippage_{off} and therefore, the synthesis and isolation of **134.Cl** was attempted (Scheme 4.20).



Scheme 4.20 Attempted synthesis of **134.Cl** by slippage

A mixture of **125** and 3.5 equivalents of **130.Cl** were heated at 50 °C for 3.5 days until equilibrium was reached. The resulting mixture of **125**, **130.Cl** and **134.Cl** was purified by silica gel chromatography but unfortunately a polar solvent system including MeOH was required to achieve chromatographic separation of the components. It was possible to isolate a small amount of **134.Cl** in approximately 17% yield, contaminated with a small amount of the macrocycle and stoppered thread as shown by the ^1H NMR spectrum (Figure 4.22). This was also confirmed by the mass spectrum which showed peaks at m/z 621.27, 1152.83 and 1751.94 corresponding to $[\mathbf{125} + \text{Na}]^+$, $[\mathbf{130.Cl} - \text{Cl}]^+$ and $[\mathbf{134.Cl} - \text{Cl}]^+$ respectively (Figure 4.23). Further purification was not attempted as this could potentially lead to further dissociation of **134.Cl**.

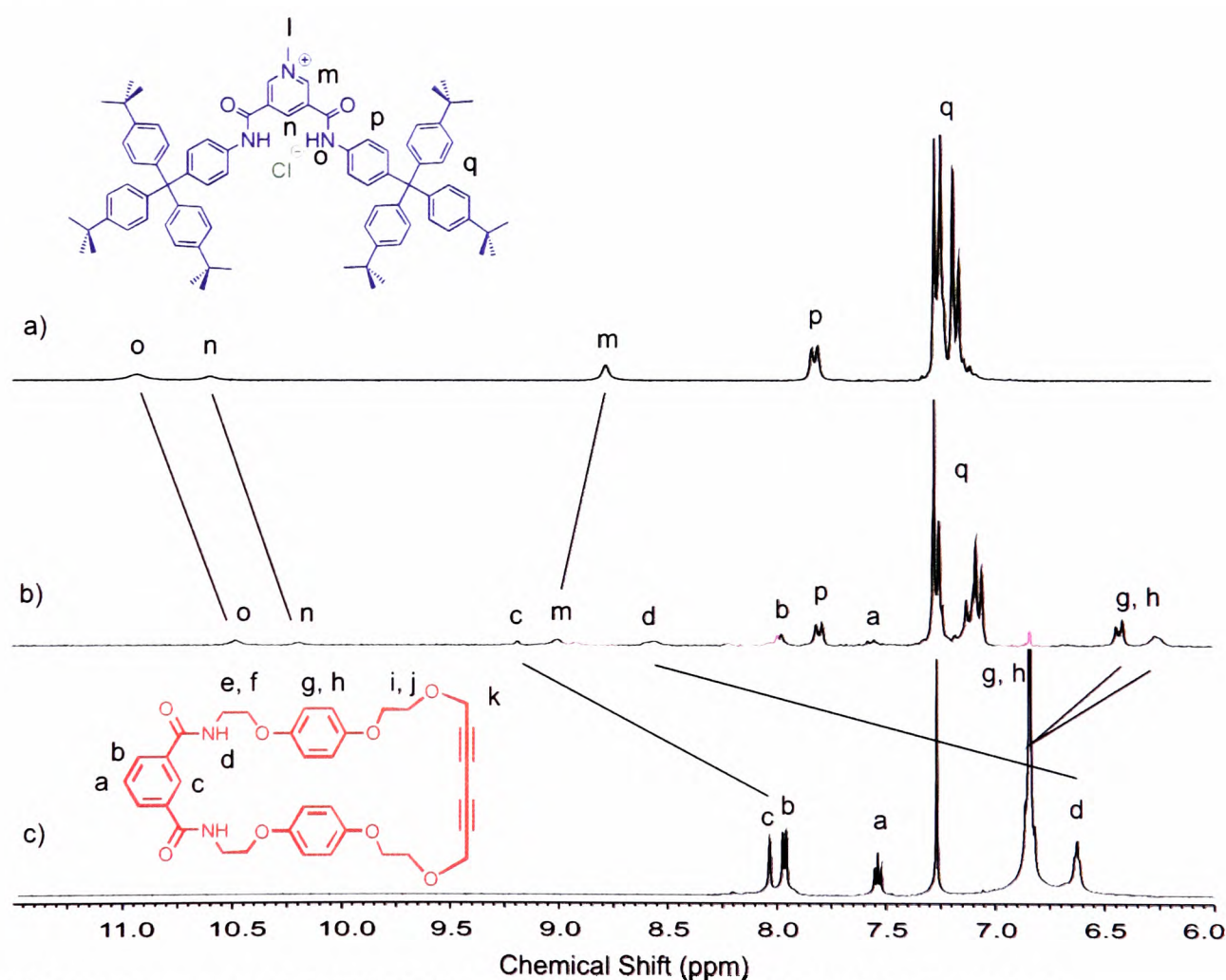


Figure 4.22 ^1H NMR spectra of a) **130.Cl** b) impure **134.Cl** and c) **125** in CDCl_3 at 298 K

$[125 + \text{Na}]^+$
621.27

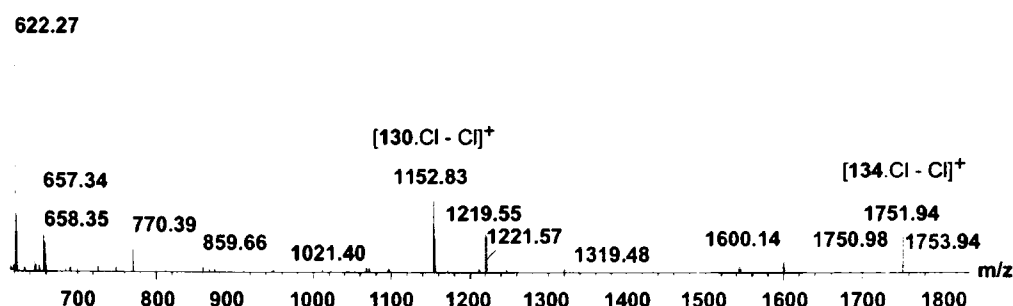


Figure 4.23 Electrospray mass spectrum of the mixture of 125, 130.Cl and 134.Cl

4.3.2.7 Locking Strategies

Disappointingly, it was not possible to isolate any of the slippage species since they were pseudorotaxanes rather than rotaxanes. Instead, strategies for converting the pseudorotaxanes formed by slippage into rotaxanes were explored. The enforced planarity of the diyne unit may force the macrocycle into a conformation where slippage over the stoppers is possible. Removing this planarity after slippage could modify the conformation and size of the macrocycle cavity stabilising the slippage species as a rotaxane where the barrier to $\text{slippage}_{\text{off}}$ is too high to be overcome at room temperature. Hydrogenation of the diyne unit and complexation with cobalt carbonyl after slippage were explored as two strategies for removing the planarity of the diyne unit (Scheme 4.24). The complexation with cobalt carbonyl strategy was investigated first because it has two advantages over the hydrogenation strategy: cobalt carbonyl typically reacts with most alkynes with a half-life of 300s;³⁷ and the reaction can be carried out in chlorinated solvents without the addition of polar solvents like MeOH.

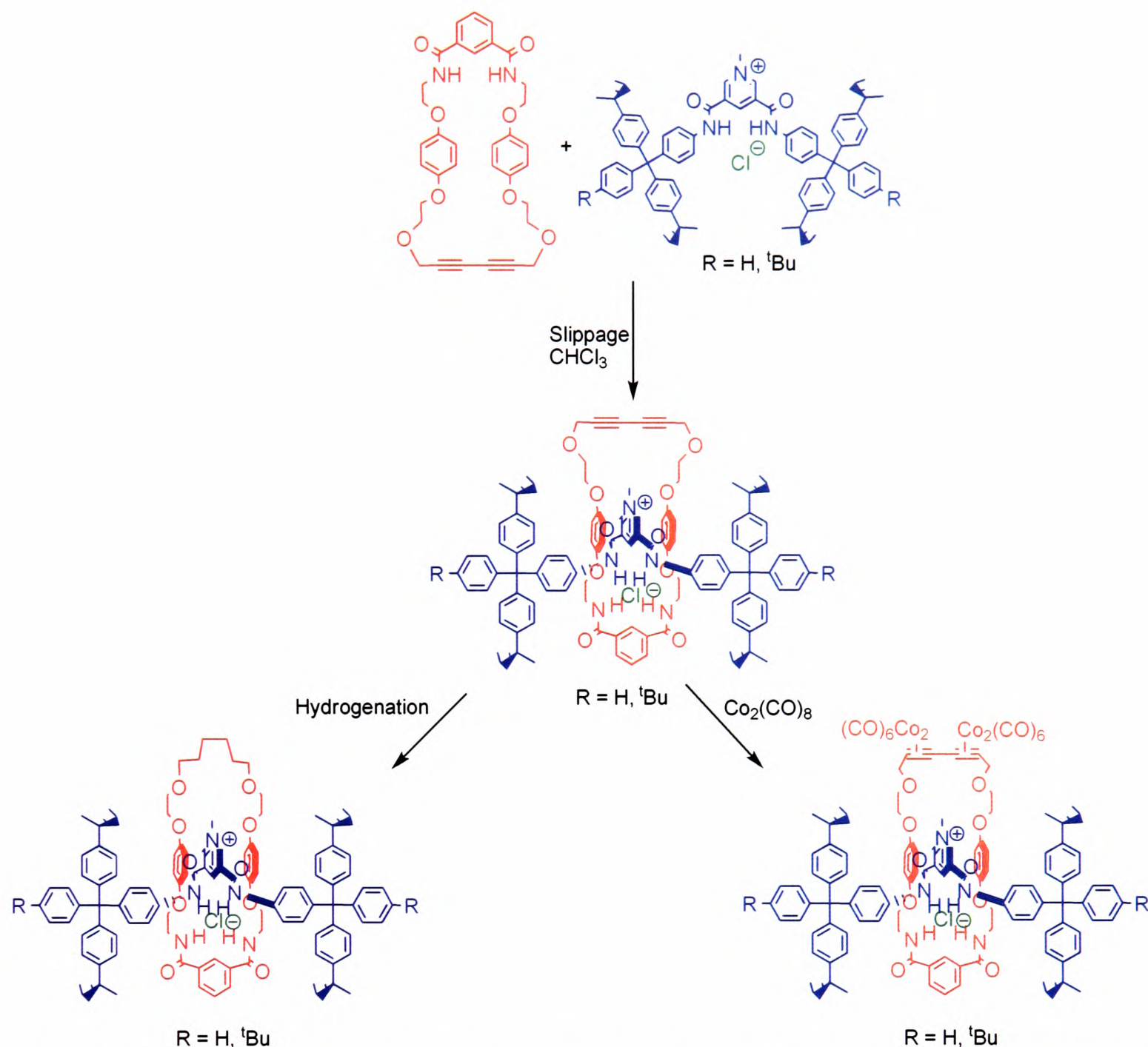
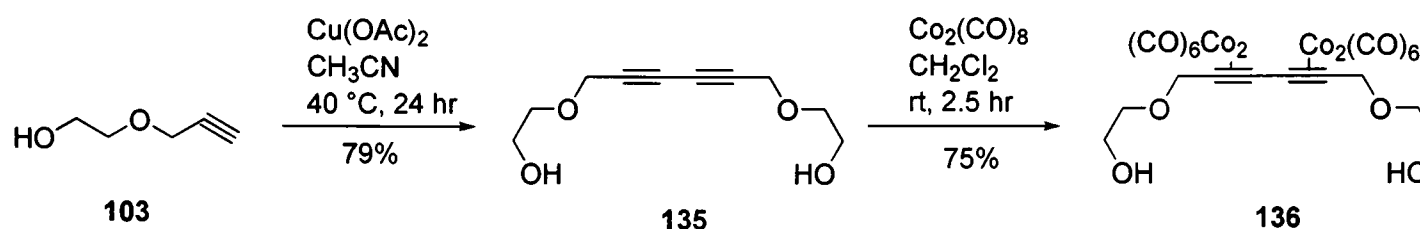


Figure 4.24 Schematic diagram showing the two strategies for converting the pseudorotaxane formed by slippage into a rotaxane

4.3.2.7.1 Complexation with Cobalt Carbonyl

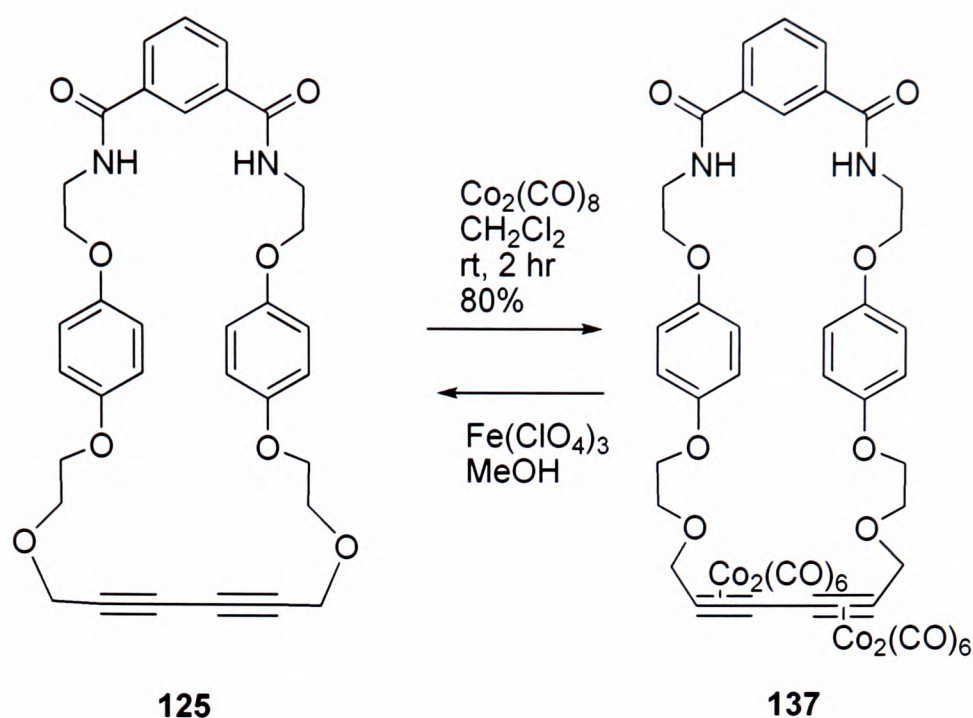
Cobalt carbonyl groups have been used as alkyne protecting groups for many years, but the structural changes upon complexation of the cobalt carbonyl cluster to the alkyne could be exploited to reduce the macrocycle cavity size. The crystal structure of the bis cobalt carbonyl complex of diphenylbutadiyne demonstrated that the C-C-C bond angle decreases from 180° to $139\text{--}145^\circ$ upon complexation with cobalt carbonyl,³⁸ and several groups have exploited this bond angle change to reduce the size of macrocycle cavities.^{39, 40} A similar reduction in the size of the macrocycle cavity of **125** was anticipated upon complexation of the alkynes with cobalt carbonyl groups.

Initially, a model system was prepared to establish suitable conditions for complexing cobalt carbonyl. The model system was chosen to be compound **135**, which was prepared from the Eglinton coupling of two molecules of **103** using copper(II) acetate (Scheme 4.21). The reaction of **135** with excess cobalt carbonyl at room temperature in CH_2Cl_2 gave the desired product **136** in 75% yield following removal of the excess cobalt carbonyl by column chromatography.



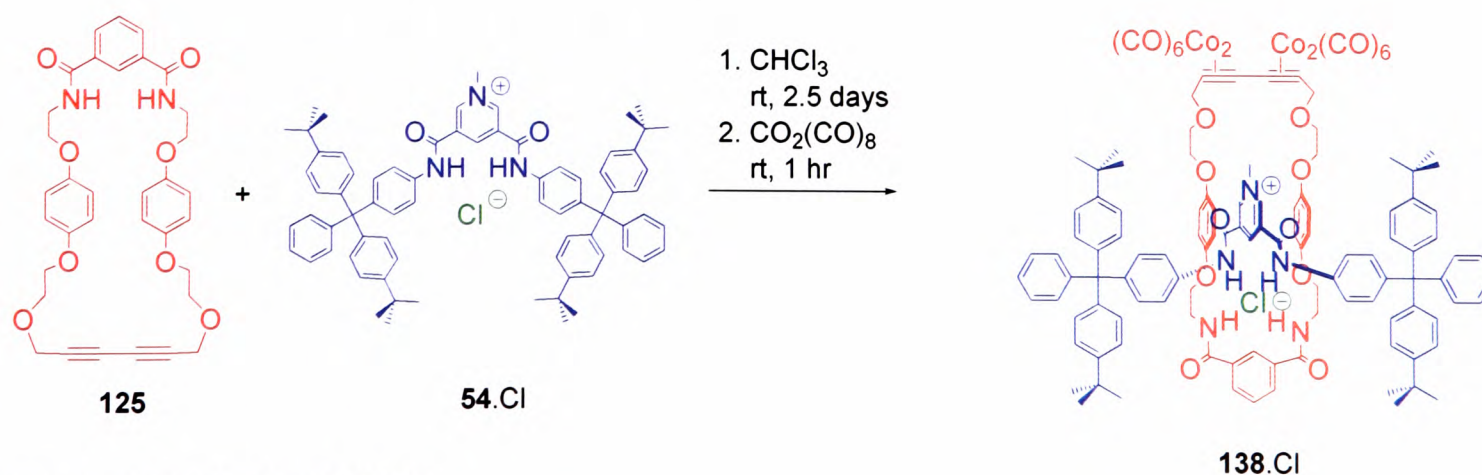
Scheme 4.21 Synthesis of cobalt carbonyl model system **136**

The analogous reaction was carried out using **125** and the cobalt carbonyl protected macrocycle **137** was isolated as a brown solid in 80% yield (Scheme 4.22). Characterisation proved difficult as the ^1H NMR spectrum of the product (Figure 4.25c) was very broad and not dissimilar to that of **125** (Figure 4.25d). The mass spectrum had a peak at m/z 1219.4533 corresponding to $[\mathbf{137} + \text{MeOH} + \text{NH}_4]^+$, although an accurate mass could not be obtained. Further characterisation was prevented by decomposition of the product, either in solution or by air. A brown solid precipitated from solution with time and the ^{13}C NMR spectrum obtained was identical to that of the free macrocycle. Cobalt carbonyl groups are usually removed by oxidation with reagents such as iron(III) perchlorate,⁴¹ and **137** was reacted with an excess of iron(III) perchlorate in MeOH to test the stability of **137** to oxidants (Scheme 4.22). The cobalt carbonyl groups were removed to give the macrocycle **125**.



Scheme 4.22 Synthesis of the cobalt carbonyl protected macrocycle **137** and removal of the cobalt carbonyl groups using iron(III) perchlorate

The synthesis of the cobalt carbonyl protected rotaxane was attempted, despite the decomposition problems with **137**, as it was hoped that the cobalt carbonyl groups might be more stable in the rotaxane structure. A mixture of **125** and 3.5 equivalents of **54.Cl** were stirred at room temperature for 2.5 days until equilibrium had been reached, at which point cobalt carbonyl was added and the reaction was stirred at room temperature (Scheme 4.23). Following purification by preparative TLC, it was possible to isolate a small amount of **138.Cl** contaminated with macrocycle **137**. Unfortunately, decomposition in solution prevented isolation and complete characterisation of **138.Cl**. However, the ^1H NMR spectrum suggested the successful formation of **138.Cl**.



Scheme 4.23 Synthesis of **138.Cl**

Although complete assignment of the ^1H NMR spectrum was made difficult by the broadness of the peaks and contamination with **137** (Figure 4.25b), the upfield shifts and splitting of

the macrocycle hydroquinone protons *g* and *h* and the upfield shift of the axle proton *o* are consistent with an interlocked structure. Additionally, the peak at m/z 2210.04 in the mass spectrum corresponds to $[138.Cl - Cl]^+$ (Figure 4.25e).

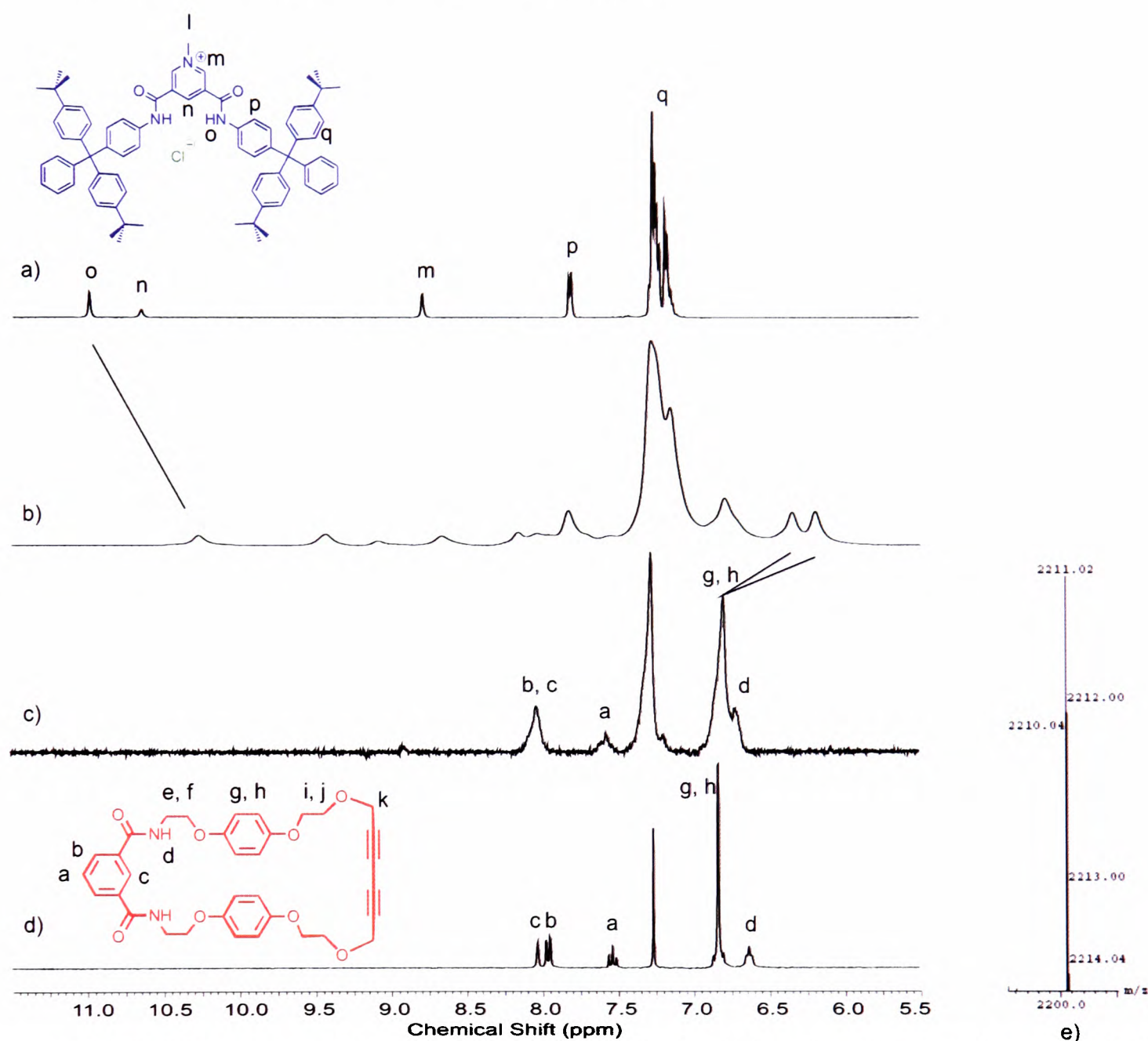


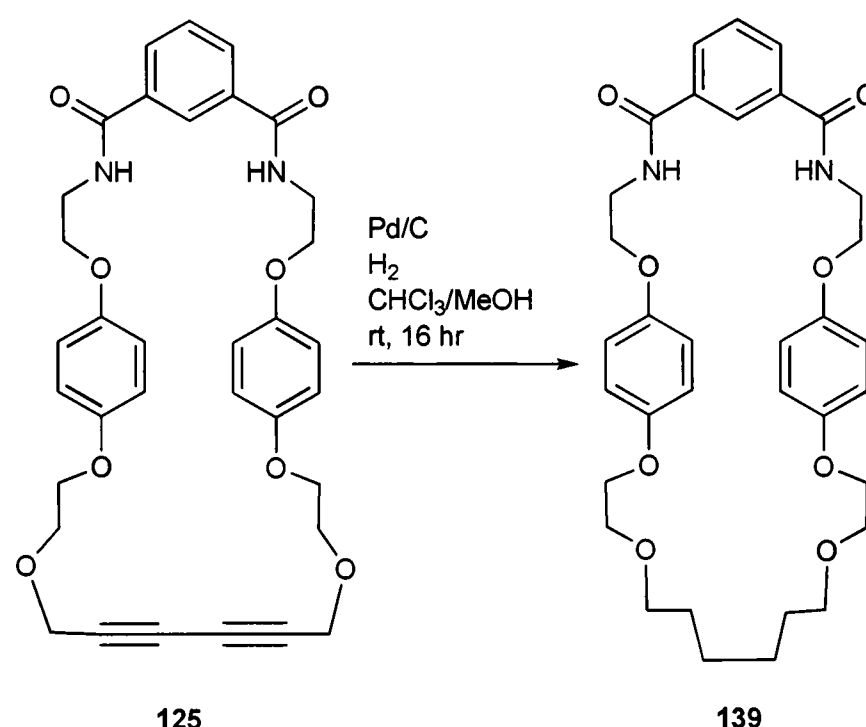
Figure 4.25 1H NMR spectra of a) **54.Cl** b) impure **138.Cl** c) cobalt carbonyl protected macrocycle **137** d) macrocycle **125** in $CDCl_3$ at 298 K and e) electrospray mass spectrum showing the peak for $[138.Cl - Cl]^+$

Disappointingly, the instability of the cobalt carbonyl complexes prevented further investigations into this locking strategy and it was not possible to establish whether **138.Cl** was indeed a rotaxane rather than a pseudorotaxane. Instead, efforts focused on the alternative hydrogenation locking strategy.

4.3.2.7.2 Hydrogenation

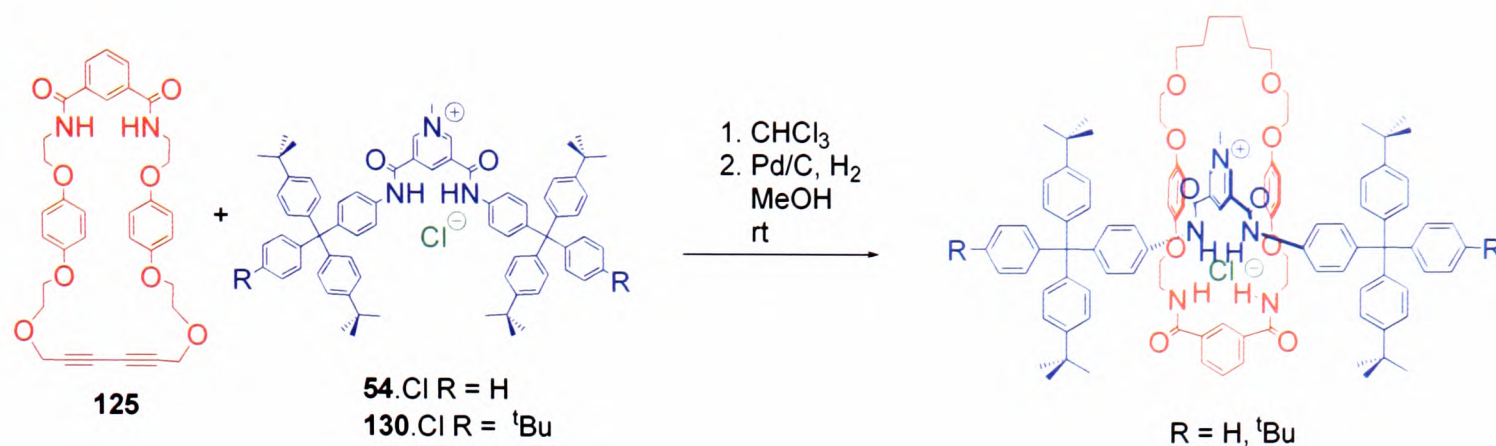
In order to pursue the hydrogenation strategy, hydrogenation conditions compatible with the slippage reaction were investigated. The hydrogenation of the macrocycle was carried out as a

model system using 10% palladium on carbon under a H₂ atmosphere in a CHCl₃/MeOH solvent mixture (Scheme 4.24). Complete conversion of the starting material was achieved, but another product formed, possibly from incomplete hydrogenation, in addition to the desired macrocycle **139**. Despite numerous attempts to prevent the formation of the by-product, it was only possible to isolate a small amount of pure **139** on one occasion (Figure 4.26c). Preliminary slippage studies with **139** and **54**.Cl at 50 °C showed an almost undetectable amount of the rotaxane after 6 hours, which suggests that this strategy may be suitable for synthesising a stable rotaxane.



Scheme 4.24 Hydrogenation of **125**

Therefore, the synthesis of rotaxanes was attempted using this slippage followed by hydrogenation approach. A mixture of **125** and an excess of **54**.Cl were stirred at room temperature in CHCl₃ until equilibrium was reached after 3 days (Scheme 4.25). Palladium on carbon and a small amount of MeOH were added, and the resulting suspension was stirred under a H₂ atmosphere overnight. There was evidence for the successful synthesis from the peak at *m/z* 1645.83 in the electrospray mass spectrum and the upfield shifts and splitting of the hydroquinone protons *g* and *h* in the ¹H NMR spectrum (Figure 4.26).



Scheme 4.25 Synthesis of rotaxanes using a slippage followed by hydrogenation approach

An analogous reaction was carried out using **125** and axle **130.Cl**, except heating at 50 °C for 3 days to reach equilibrium. The peak at m/z 1758.01 in the mass spectrum confirmed the synthesis the hydrogenated slippage species. The isolation of the two proposed rotaxane structures was attempted by silica gel chromatography but this was unsuccessful, most likely because of the small quantities formed, as inferred from the ^1H NMR spectra of the crude reaction mixtures. While the amount of MeOH used in the hydrogenation step was limited to prevent dissociation of the slippage species, it is possible that dissociation became significant over the time required for complete hydrogenation of the alkyne groups.

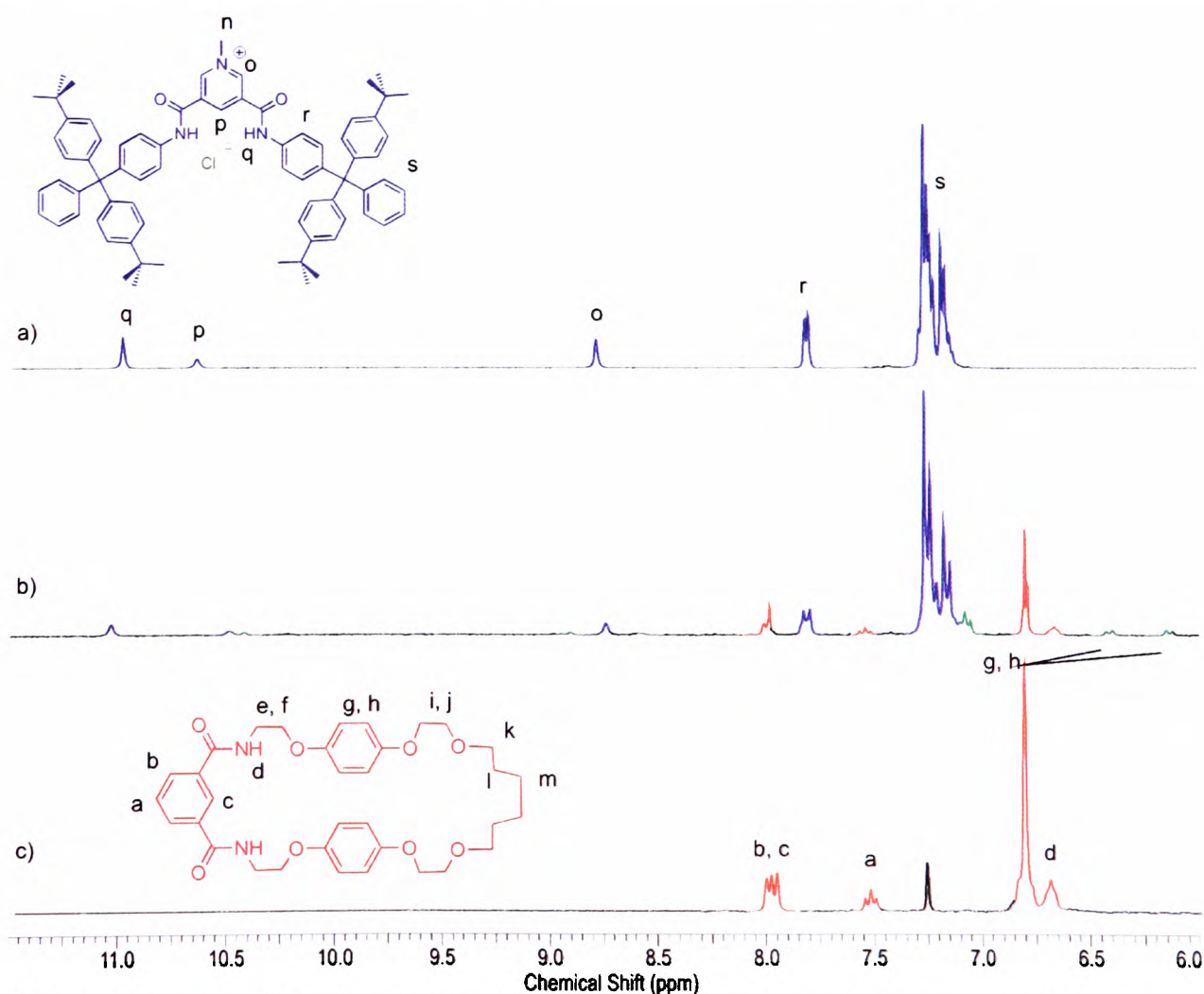
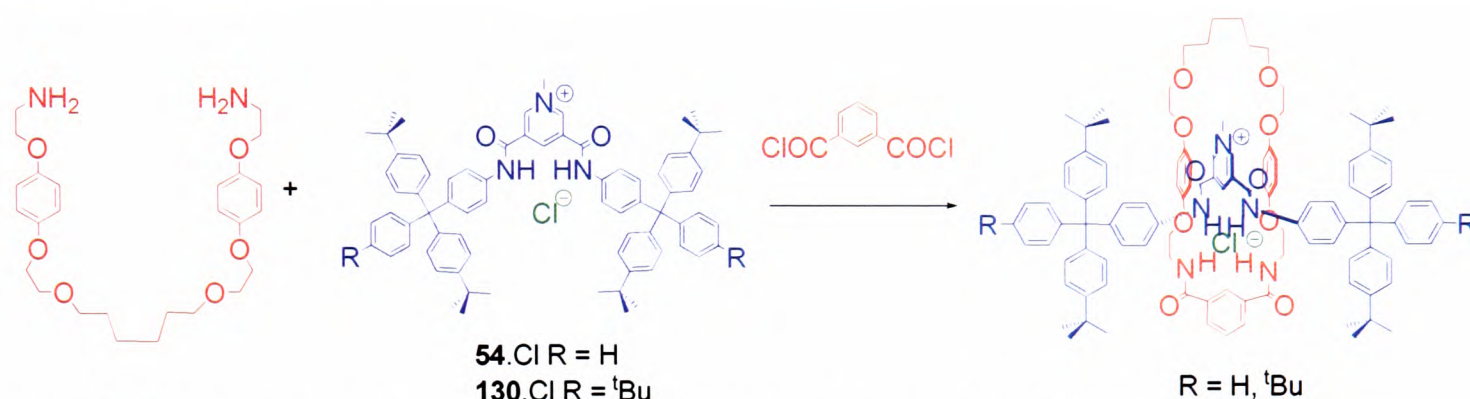


Figure 4.26 ^1H NMR spectra of a) **54.Cl** b) a mixture of **139**, **54.Cl** and the hydrogenated slippage species and c) hydrogenated macrocycle **139** in CDCl_3 at 298 K

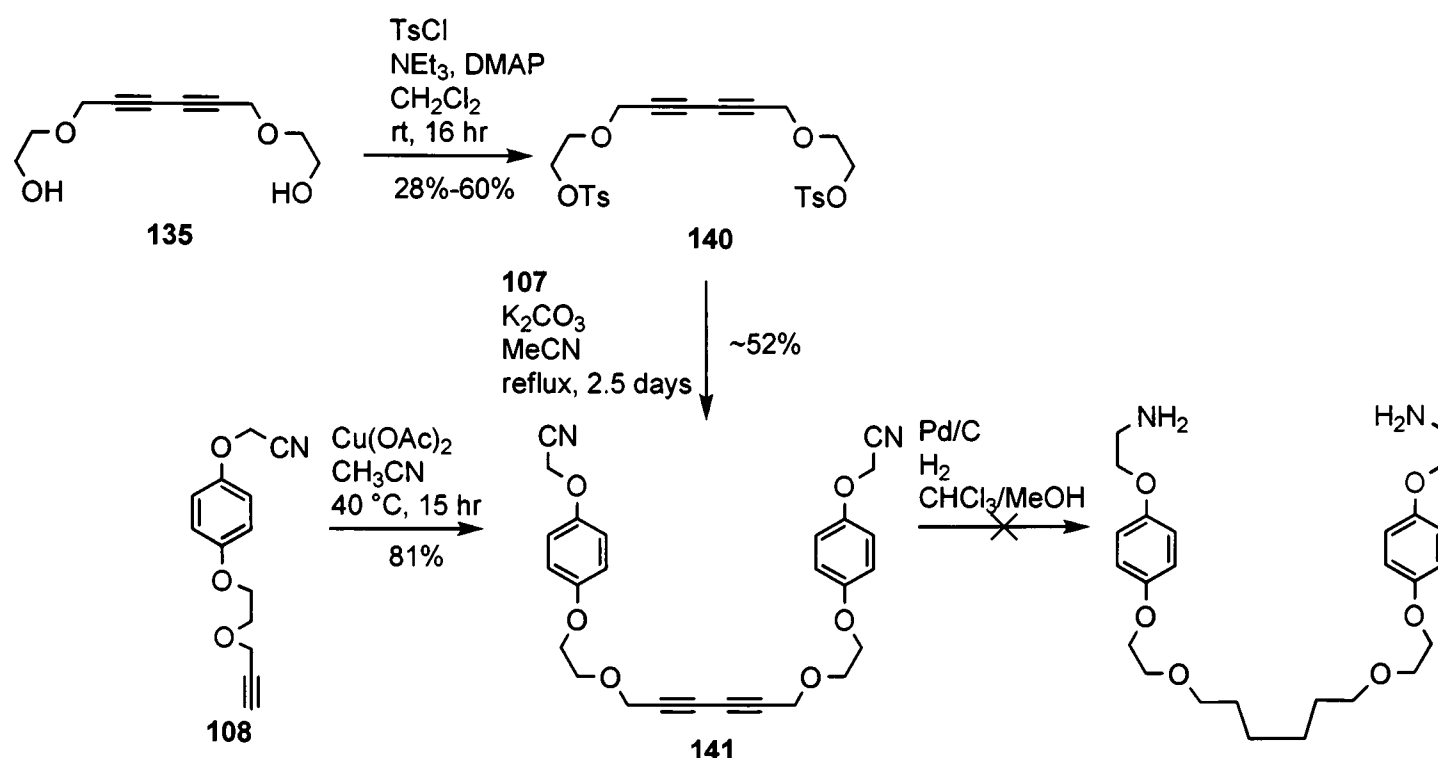
4.3.2.7.3 Alternative Synthesis of the Hydrogenated Macrocycle and Rotaxanes

Synthetic difficulties prevented the isolation of the rotaxanes from the slippage followed by hydrogenation strategy. Instead, the synthesis of rotaxanes based on the hydrogenated macrocycle **139** was investigated exploiting the ion-pair templation strategy developed in Chapter 3 (Scheme 4.26).



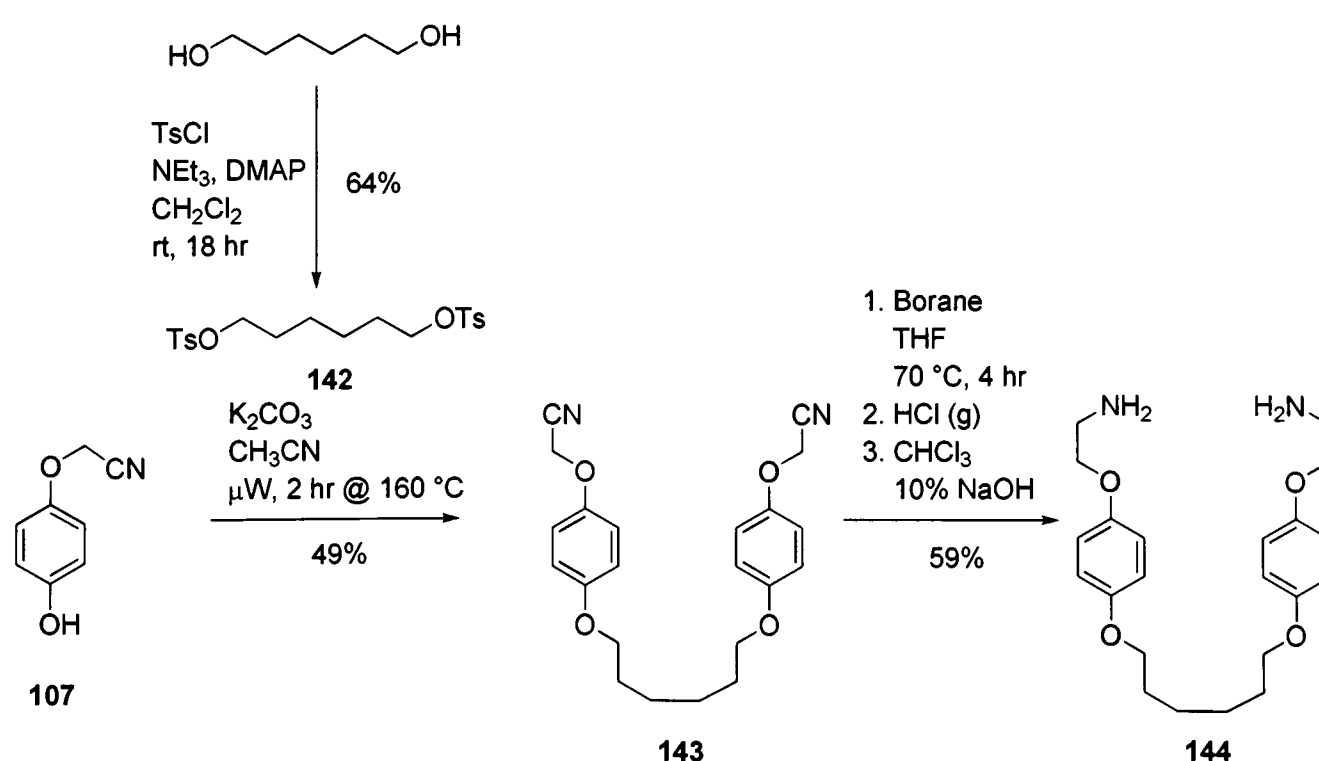
Scheme 4.26 Proposed alternative synthesis of rotaxanes exploiting an ion-pair templation strategy

Initial efforts focused on the preparation of the bis-amine in Scheme 4.27 and this was explored using a number of strategies. In the first strategy, compound **135** was reacted with tosyl chloride in CH₂Cl₂ to give **140**. This reaction was problematic as the yields varied greatly from 28% to 60%, possibly due to decomposition of **135**. Nevertheless, compound **140** was reacted with **107** in the presence of K₂CO₃ in CH₃CN to give **141** in approximately 52% yield. Given the synthetic difficulties, an alternative synthesis from compound **108** was investigated. Eglinton coupling of **108** at 40 °C in CH₃CN gave **141** in the much improved yield of 81%. The simultaneous reduction of the nitrile and alkyne functionalities was attempted using palladium on carbon under a H₂ atmosphere, but there was only evidence of alkyne reduction. A subsequent attempt to reduce the nitrile groups using LiAlH₄ in diethyl ether gave a mixture of products.



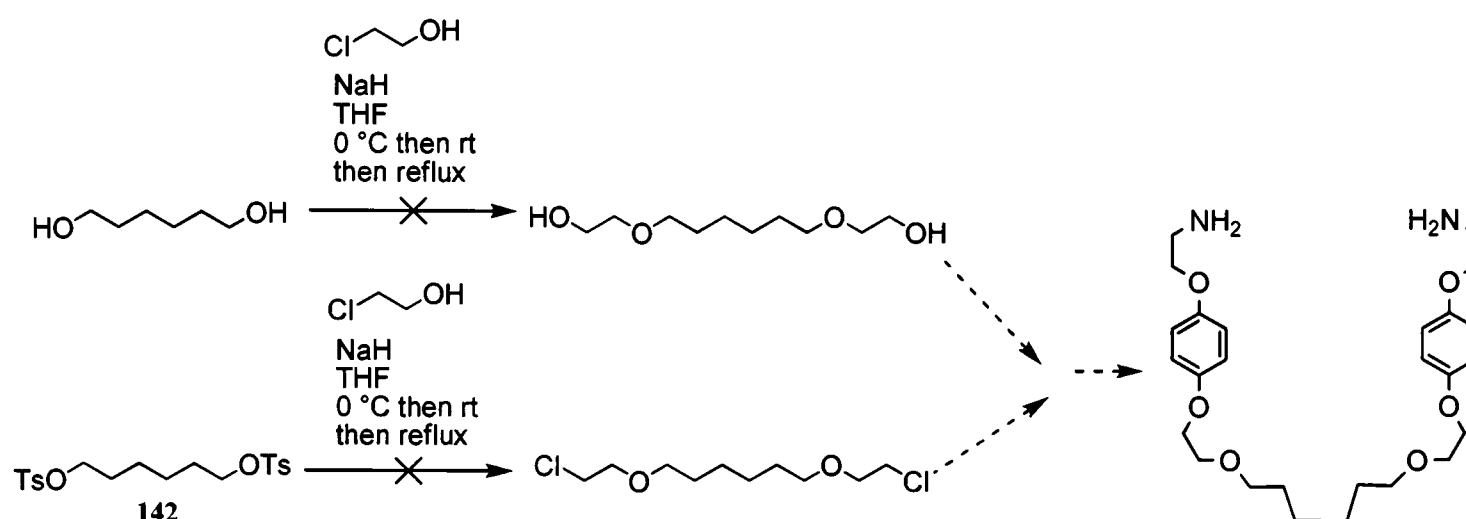
Scheme 4.27 Towards the synthesis of the bis-amine macrocycle precursor

An alternative strategy was devised avoiding the problematic reduction of the alkyne groups using the commercially available 1,6-hexanediol. Initially the feasibility of this synthetic strategy was tested by preparing **144** as a model system (Scheme 4.28). Compound **142** was prepared in 64% yield by tosylation of 1,6-hexanediol in the presence of triethylamine and DMAP in CH₂Cl₂. The reaction of **107** with **142** in the microwave for two hours at 160 °C gave **143** in 49% yield, and subsequent reduction of the nitrile groups using borane in THF gave the bis-amine **144**. Initially this was isolated as the hydrochloride salt, but it was converted back to free amine for characterisation purposes and isolated in 59% yield.



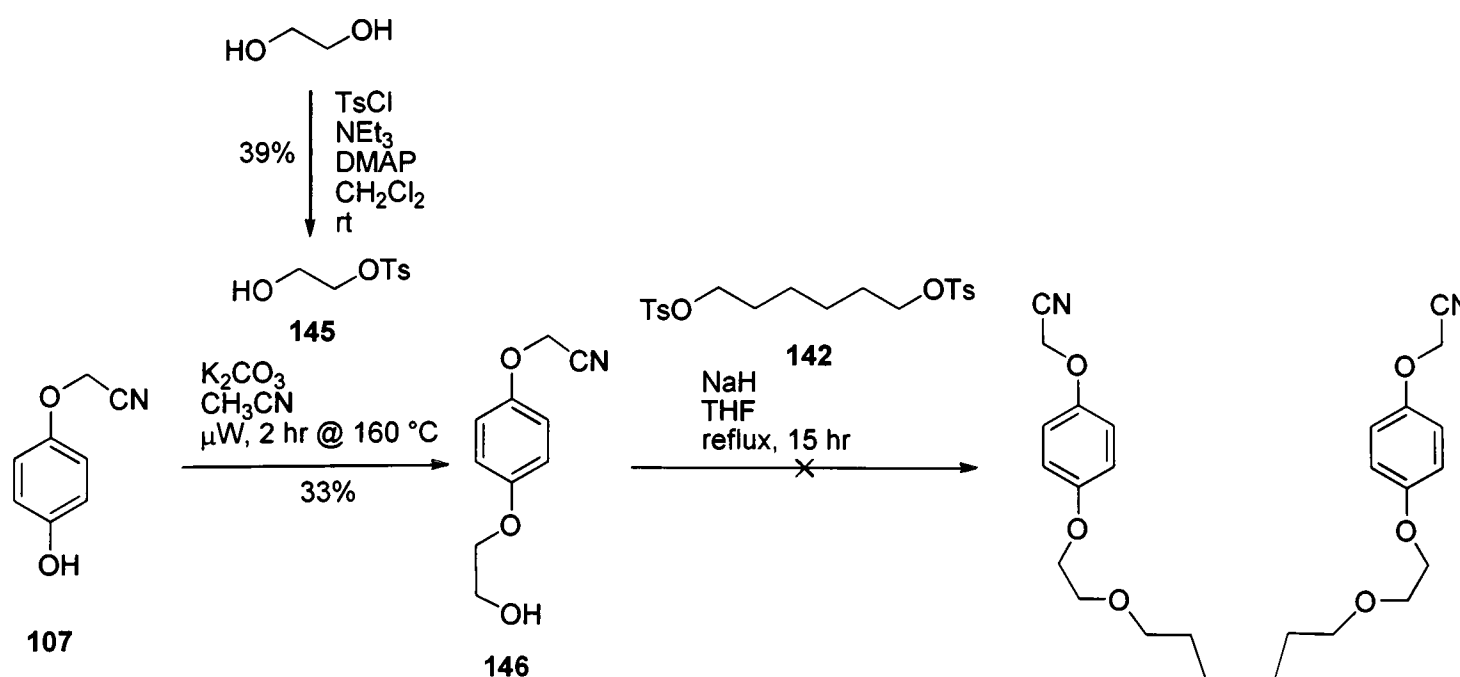
Scheme 4.28 Synthesis of model system

Having successfully prepared the model system, attention then turned to the synthesis of the bis-amine macrocycle precursor in Scheme 4.29 using the same strategy. Disappointingly, attempts to react chloroethanol with 1,6-hexanediol or **142** in the presence of NaH in THF were unsuccessful.



Scheme 4.29 Proposed synthesis of the bis-amine macrocycle precursor

A modified strategy was then investigated according to Scheme 4.30, which involved the synthesis of **145** in 39% yield by monotosylation of ethylene glycol. Compound **146** was prepared in 33% yield by heating a suspension of **107**, **145** and K_2CO_3 in CH_3CN under microwave irradiation. Attempts to improve the yield by varying the reaction conditions were unsuccessful, as was the attempted reaction of **146** with compound **142**.



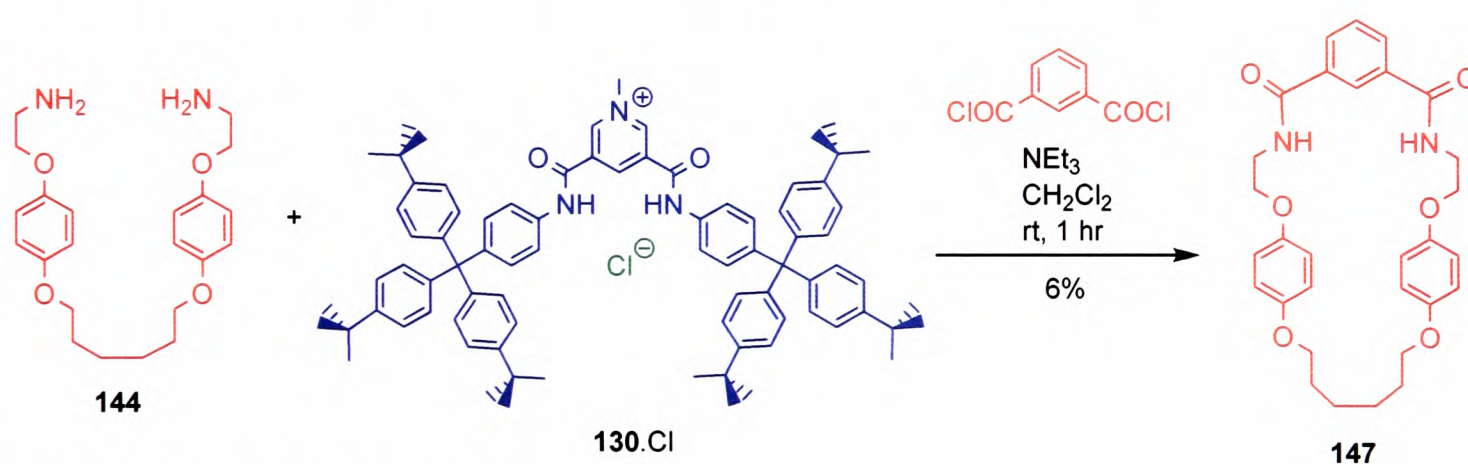
Scheme 4.30 Modified synthesis of the bis-amine macrocycle precursor

Disappointingly, numerous synthetic problems prevented the synthesis of the target bis-amine macrocycle precursor and rotaxanes by the two locking strategies. In the hope of synthesising

rotaxanes by methods other than slippage, the synthesis of smaller macrocycles and axles with larger stoppers was then investigated.

4.3.3 Synthesis of Smaller Macrocycles

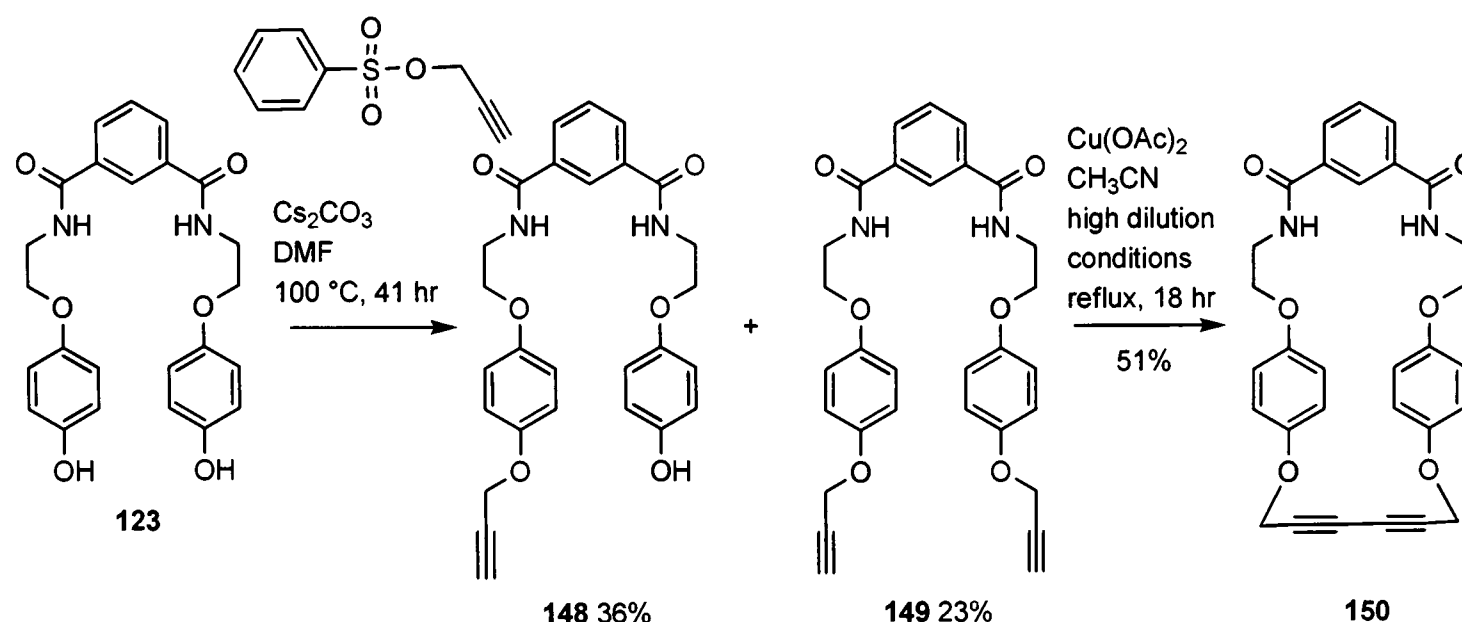
Compound **144**, synthesised in the previous section as a model system, is useful in the development of smaller macrocycles and rotaxane synthesis exploiting the ion-pair templation strategy developed in Chapter 3. The clipping reaction between **144** and isophthaloyl dichloride in the presence of **54.Cl** was attempted in CH_2Cl_2 (Scheme 4.31). There was no evidence of rotaxane formation, and instead a small amount of macrocycle **147** was isolated. This suggests that the macrocycle cavity is too small to thread the axle component **54.Cl** and indeed, there was no evidence of pseudorotaxane formation between **147** and the unstoppered axle **53.Cl** by ^1H NMR spectroscopy or electrospray mass spectrometry.



Scheme 4.31 Attempted rotaxane synthesis

The synthesis of **150** by Eglinton coupling was also carried out to investigate whether the planarity of the alkyne groups increases the macrocycle cavity size to allow pseudorotaxane formation (Scheme 4.32). Propargyl benzenesulfonate was heated with **123** in the presence of Cs_2CO_3 at $100\text{ }^\circ\text{C}$ for 2.5 days in DMF. Following purification by column chromatography, both the monoalkylated product **148** and desired product **149** were isolated in yields of 36% and 23% respectively. The macrocyclisation of **149** by Eglinton coupling was carried out under high dilution conditions in CH_3CN and macrocycle **150** was isolated in 51% yield. Unfortunately, there was no evidence of pseudorotaxane formation with **53.Cl**, and therefore,

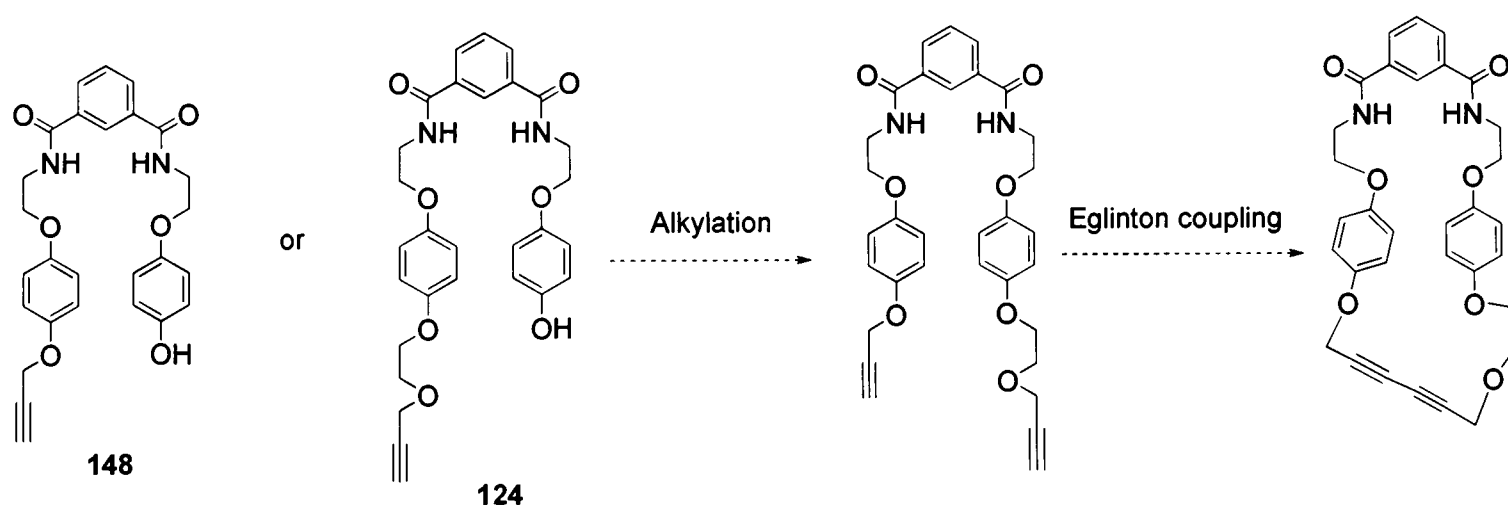
it can be concluded that both **147** and **150** are too small for the synthesis of rotaxanes.



Scheme 4.32 Synthesis of macrocycle **150**

4.3.3.1 Towards Asymmetric Macrocycles

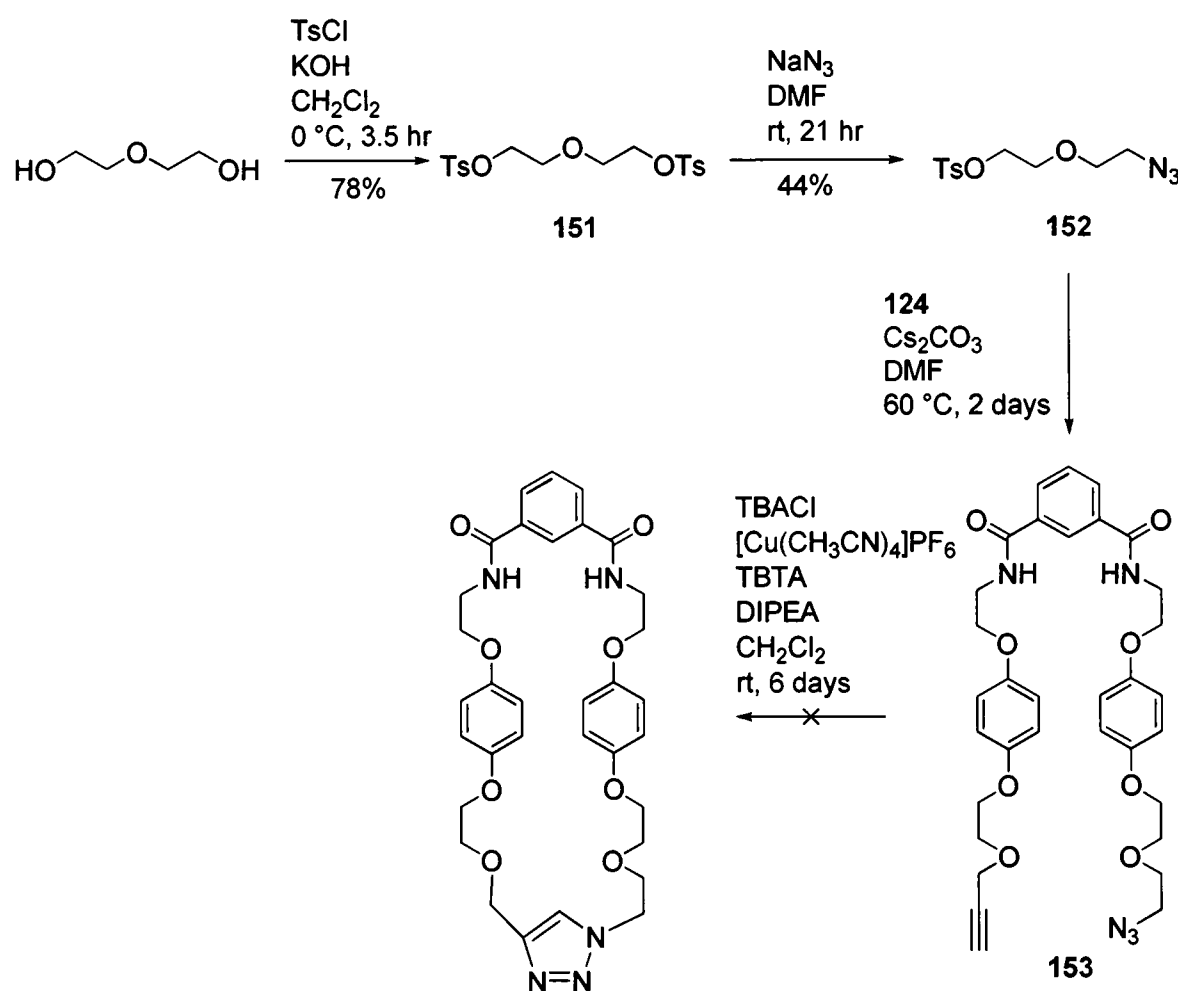
The monoalkylated by-products **124** and **148** are useful synthons in the development of asymmetric macrocycles. Further alkylation of these by-products with a suitable alkyne functionalised precursor followed by Eglinton coupling would give a macrocycle, which is intermediate in size between the small macrocycle **150** and larger macrocycle **125** (Scheme 4.33). Therefore, there is the potential to synthesise rotaxanes using Eglinton coupling, however, this was not investigated as it was not possible to develop suitable reaction conditions for rotaxane synthesis in Section 4.3.1.



Scheme 4.33 Proposed synthesis of asymmetric macrocycles by Eglinton coupling

Instead the synthesis of an asymmetric macrocycle from **124** using click chemistry was investigated according to Scheme 4.34. This involved preparation of the azide functionalised compound **152** from diethylene glycol. Tosylation using KOH in CH_2Cl_2 at $0\text{ }^\circ\text{C}$ gave the

bis-tosylate **151** in 78% yield.⁴² Subsequent reaction of **151** with sodium azide in DMF at room temperature gave a mixture of the bis-azide and mono-azide **152**, which were separated by column chromatography.⁴³ A suspension of **124**, **152** and Cs_2CO_3 in DMF was heated at 60 °C for 2 days and following purification by column chromatography, a small amount of impure **153** was isolated. Unfortunately, **153** was sparingly soluble in chlorinated solvents and therefore, macrocyclisation using click chemistry was investigated before attempting further purification. A suspension of **153**, $[\text{Cu}(\text{CH}_3\text{CN})_4\text{PF}_6]$, TBTA, DIPEA and one equivalent of TBACl, in an effort to improve solubility of **153**, was stirred at room temperature for 6 days in CH_2Cl_2 . During this time there was no evidence of reaction due to the insolubility of **153**, and therefore this synthesis was not investigated any further.



Scheme 4.34 Towards the synthesis of an asymmetric macrocycle by click chemistry

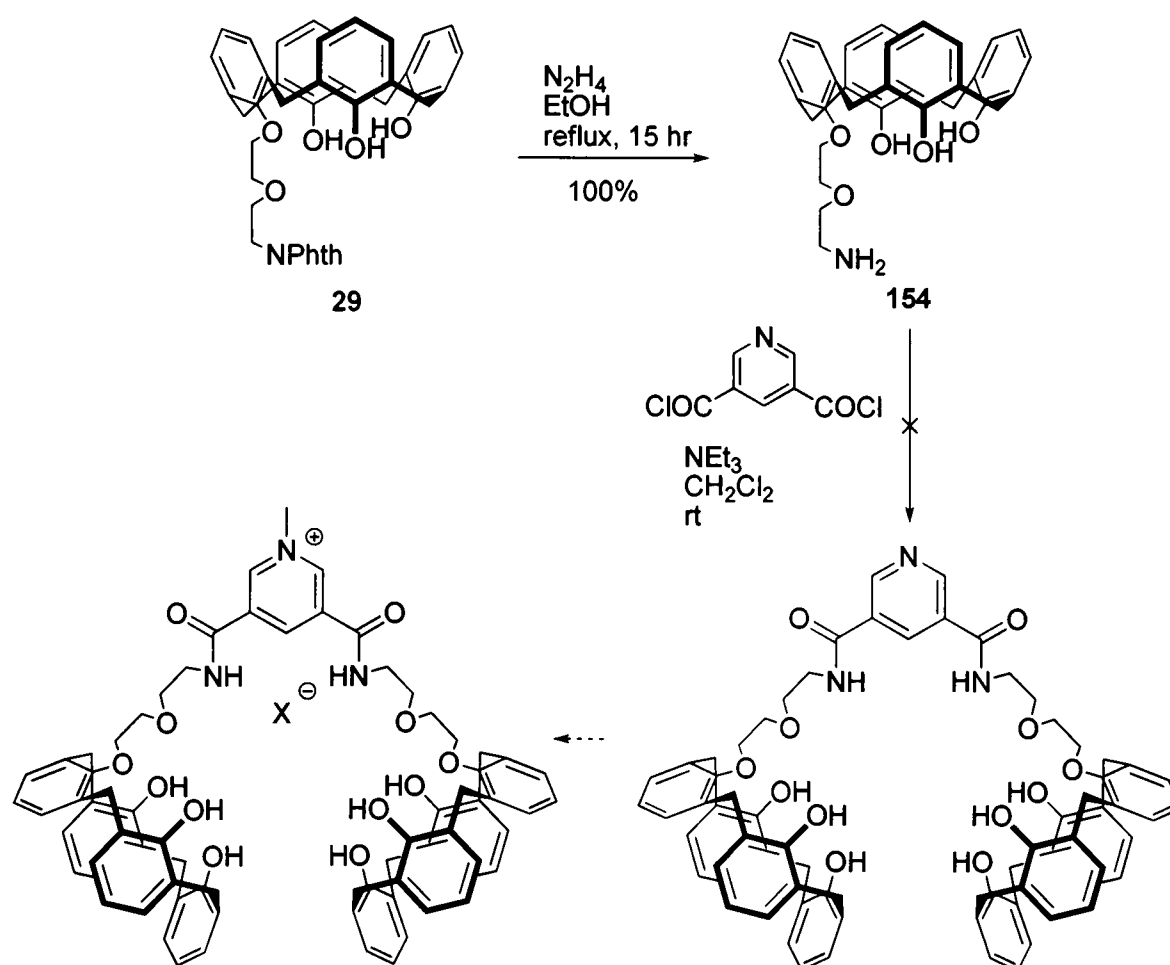
4.3.4 Towards Rotaxanes with Calix[4]arene Stoppered Axle Components

Unfortunately, the macrocycles synthesised in the previous section were not suitable for rotaxane synthesis, and instead the use of larger stopper groups was investigated in the development of rotaxanes based on macrocycle **125**. As discussed in Section 3.1, the use

of calix[4]arenes as stoppers is attractive due to their size and ease of functionalisation. Upper rim functionalised calix[4]arenes have already been exploited as stoppers within the group,⁴⁴ but this section will explore the synthesis of axles with calix[4]arene stoppers functionalised on the lower rim.

4.3.4.1 Axles Based on Compound **29**

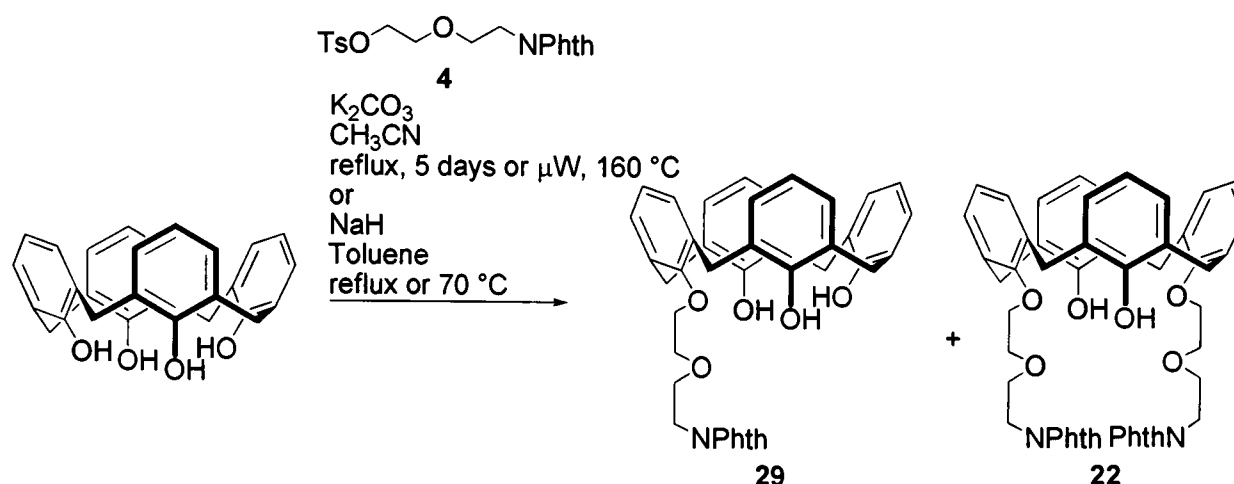
In Section 2.3.1.1, compound **29** was isolated in approximately 20% yield as a by-product in the synthesis of the compound **22**. The synthesis of a stoppered axle component based on **29** was investigated and Scheme 4.35 shows the proposed synthesis. Using the small amount of **29** isolated, the quantitative removal of the phthalimide protecting group was achieved by heating under reflux with hydrazine monohydrate in EtOH. Unfortunately, the reaction of amine **154** with 3,5-bis(chlorocarbonyl) pyridine in CH₂Cl₂ was unsuccessful. Before reattempting this reaction, attention turned to improving the yield of **29** to make the proposed strategy synthetically feasible.



Scheme 4.35 Proposed synthesis of calix[4]arene stoppered axle from compound **29**

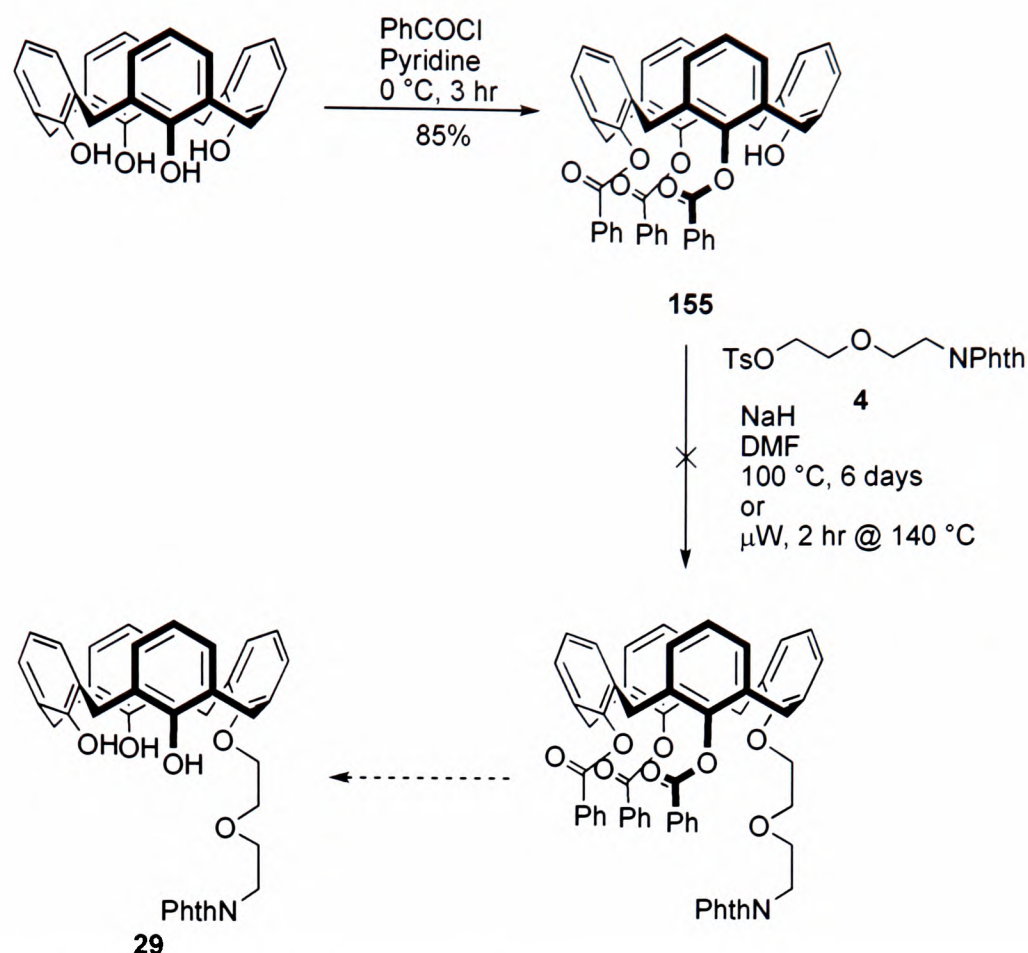
Initial efforts focused on modifying the reaction conditions for synthesising **22** to favour

formation of the monoalkylated product **29** (Scheme 4.36). Varying the amount of K_2CO_3 and **4**, reaction times and temperature did not lead to a significant improvement of the yield of **29** over **22**. Unfortunately, this was also the case when the reaction was repeated in toluene using one equivalent of NaH as the base, heating under reflux or at $70\text{ }^\circ\text{C}$.



Scheme 4.36 Attempts towards optimising the yield of **29** over **22**

An indirect synthesis of **29** was then devised, which involved protection of three hydroxyl groups with benzoyl chloride, alkylation of the remaining hydroxyl group and finally removal of the benzoyl protecting groups by hydrolysis (Scheme 4.37). The tribenzoyl protected calix[4]arene **155** was successfully synthesised in 85% yield by stirring a suspension of calix[4]arene, pyridine and benzoyl chloride in an ice bath for three hours.⁴⁵ The alkylation of the remaining hydroxyl group was attempted by heating a suspension of **155** with an excess of both NaH and compound **4** in DMF at $100\text{ }^\circ\text{C}$ for 6 days or in the microwave for 2 hours at $140\text{ }^\circ\text{C}$. However, only starting material was recovered from both of these reactions.



Scheme 4.37 Attempted synthesis of **29** using protecting groups

Despite numerous attempts, it was not possible to significantly improve the yield of **29** to make the synthesis of the target calix[4]arene stoppered axle feasible.

4.3.4.2 Towards Rotaxanes by Stoppering

Rotaxane synthesis using a stoppering approach was investigated in Section 3.3, and although there was limited success with this method, it was hoped that the stoppering reaction might be more successful by changing the alkyne and macrocycle components. Figure 4.27 shows the alkyne and azide functionalised components, which will be investigated for stoppering reactions with macrocycle **125**.

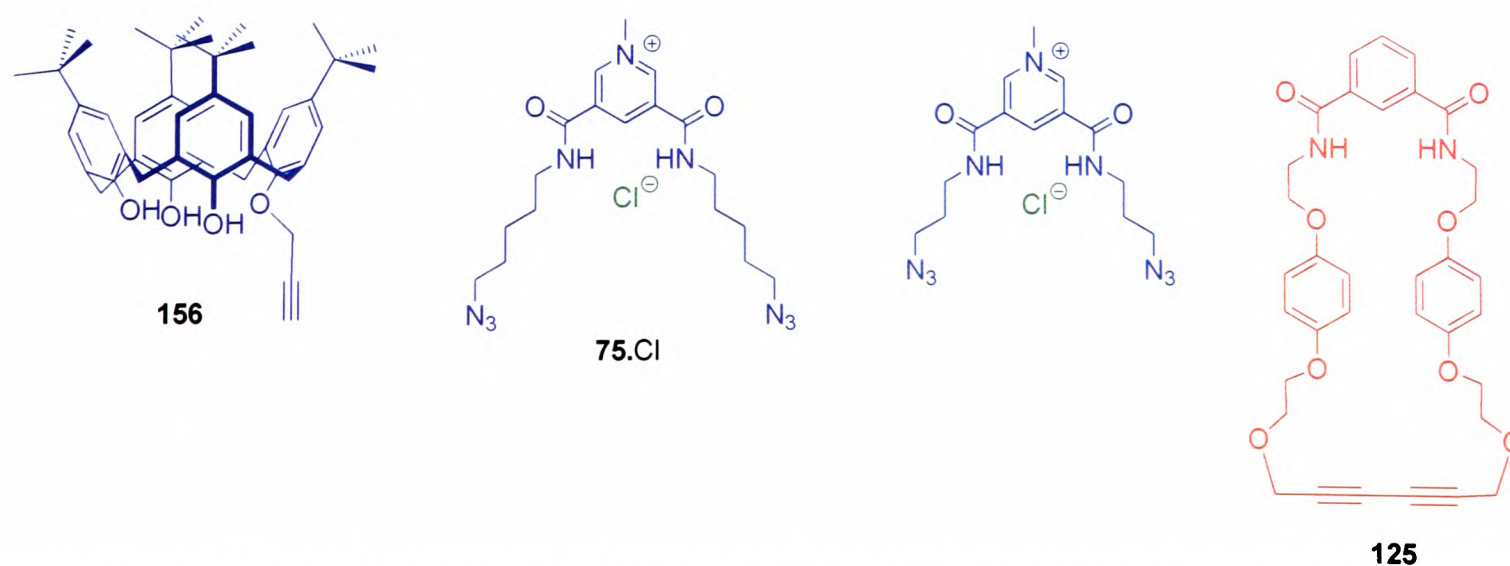
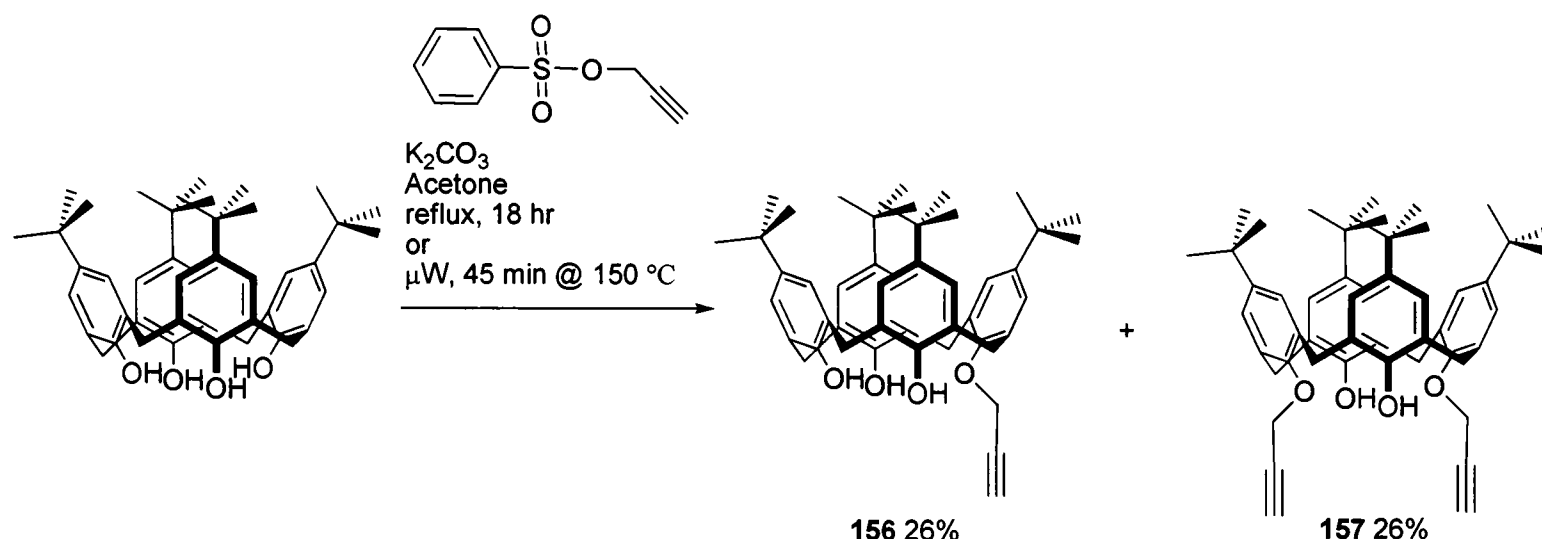


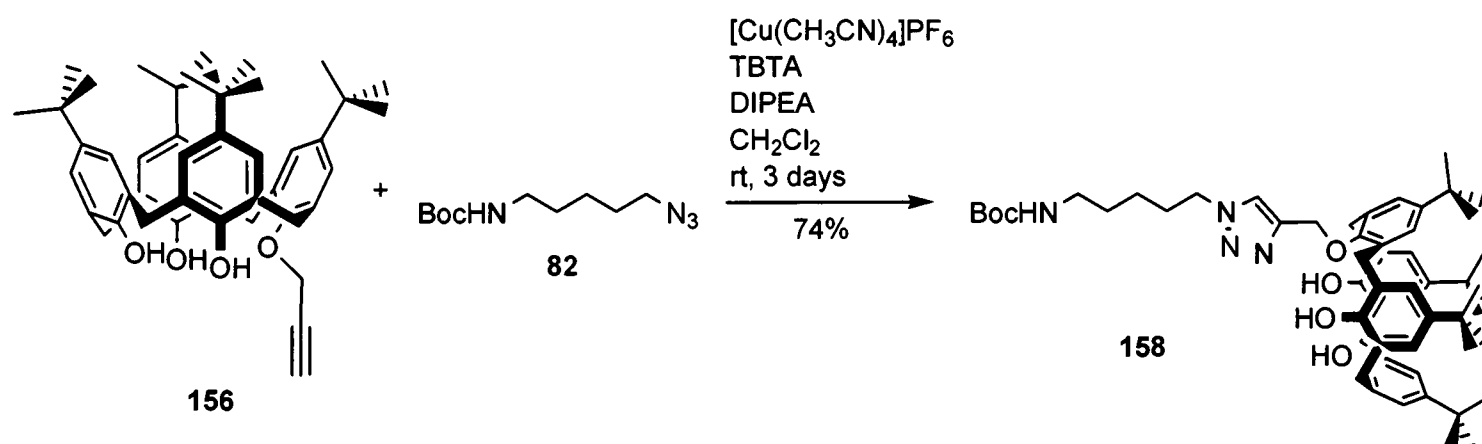
Figure 4.27 Alkyne and azide functionalised components for stoppering reactions with macrocycle **125**

The monofunctionalised alkyne **156** was synthesised in 26% yield by heating a suspension of calix[4]arene, propargyl bromide and K_2CO_3 in acetone under microwave irradiation for 45 minutes at 150 °C (Scheme 4.38).⁴⁶ In addition, the bisalkylated product **157** was also isolated in 26% yield. The analogous reaction, except heating under reflux for 18 hours, gave **156** and **157** in yields of 15 and 40% respectively.



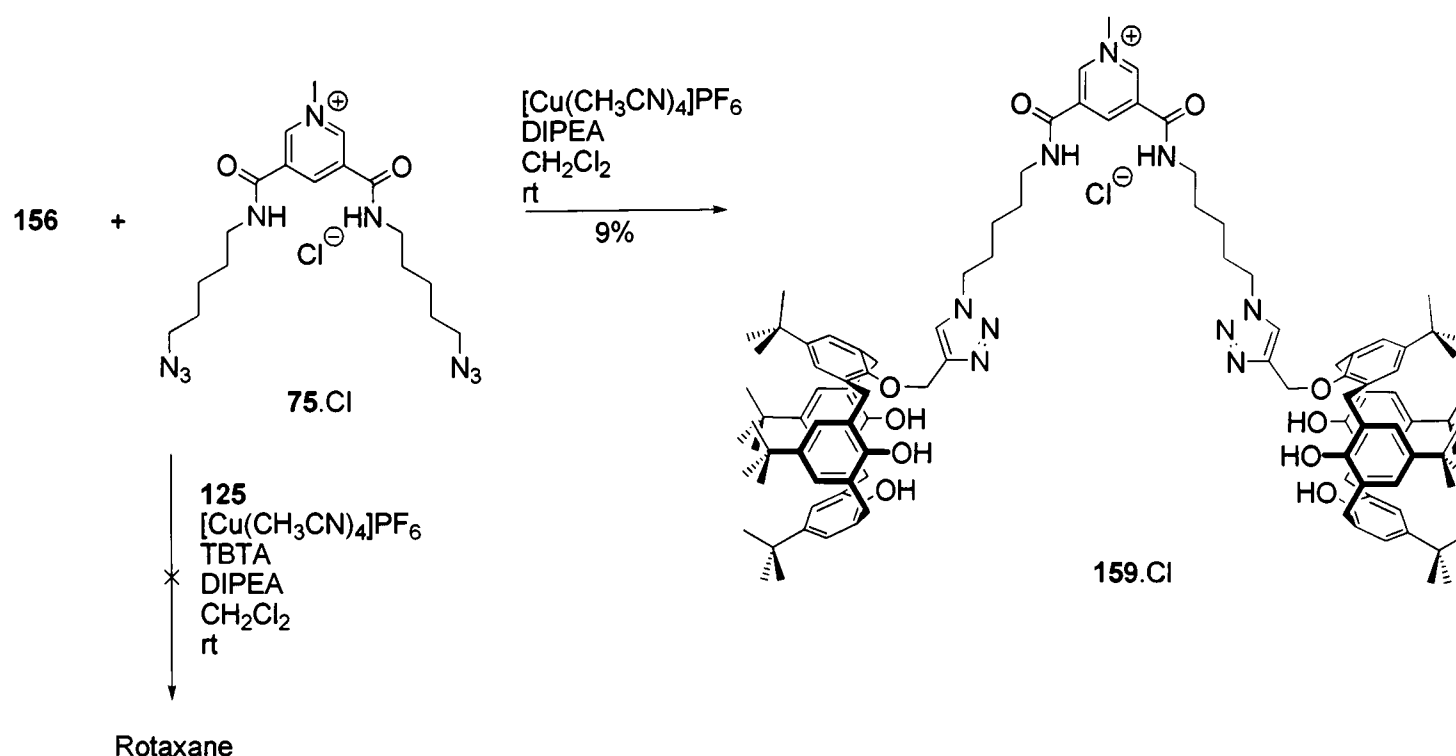
Scheme 4.38 Synthesis of alkyne functionalised calix[4]arene derivatives

The click reaction between **156** and **92** was initially carried out as a model system for the stoppering reaction (Scheme 4.39). Compound **158** was successfully synthesised in 74% yield, and therefore, the stoppering reaction between **85.Cl** and **156** was investigated.



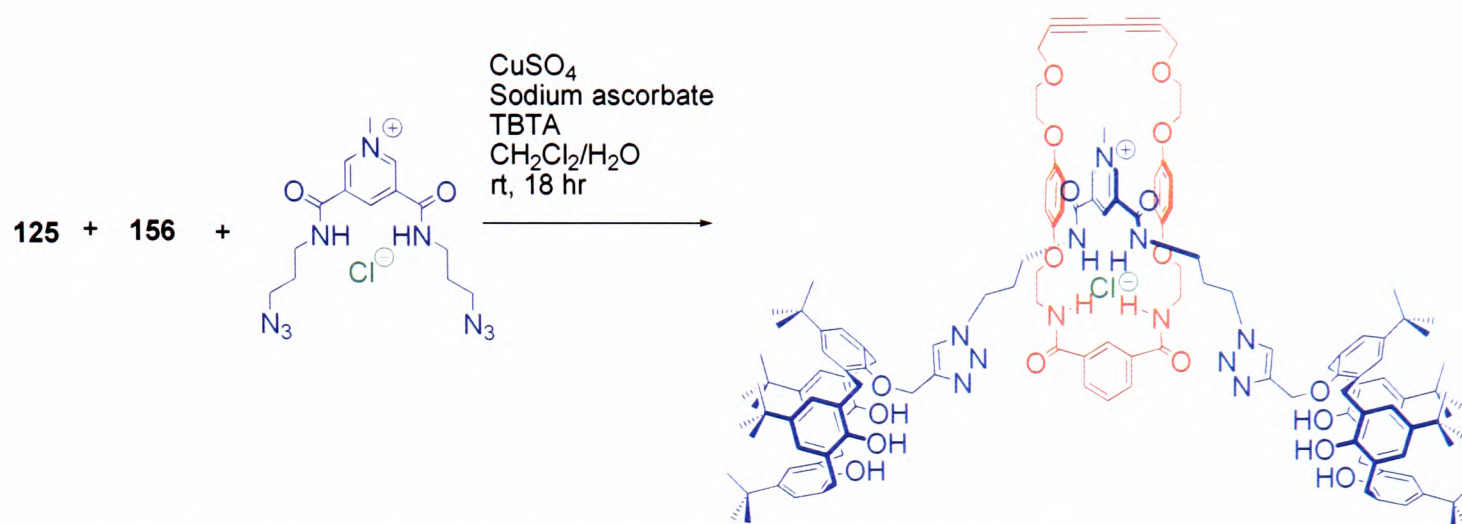
Scheme 4.39 Click reaction for the model system

Firstly, the stoppered axle **159.Cl** was synthesised by reacting **156** and **85.Cl** in the presence of $[Cu(CH_3CN)_4]PF_6$ and DIPEA in CH_2Cl_2 (Scheme 4.40). Disappointingly, this was much lower yielding than the click reaction for the model system.

Scheme 4.40 Synthesis of stoppered axle **157.Cl**

Nevertheless, the stoppering reaction was attempted in the presence of macrocycle **125** using analogous reaction conditions (Scheme 4.40). There was no evidence of rotaxane formation, but the stoppered axle **159.Cl** was detected by electrospray mass spectrometry. It is possible that the copper catalyst coordinates to the alkyne groups of **125** preventing rotaxane formation. However, there was also no evidence of rotaxane formation in Section 3.3 using **85.Cl**.

Therefore, the reaction was repeated with the alternative azide precursor, also used in Section 3.3 with more success, generating the copper catalyst from CuSO_4 and sodium ascorbate in $\text{CH}_2\text{Cl}_2/\text{H}_2\text{O}$ (Scheme 4.41). The ^1H NMR spectrum of the crude reaction mixture did not look promising for rotaxane formation, but purification of the crude reaction mixture by preparative TLC was attempted. However, there was some evidence of rotaxane formation from upfield shifts and splitting of the macrocycle hydroquinone protons in the ^1H NMR spectrum of one isolated band. Unfortunately, this band was contaminated with unreacted **125** and further purification was not attempted since less than 4 mg of impure material was isolated.



Scheme 4.41 Rotaxane synthesis by stoppering using an alternative azide precursor

4.4 Conclusions and Future Work

Eglinton coupling has been investigated as an alternative clipping strategy to ring closing metathesis for synthesising interlocked structures. A number of alkyne functionalised macrocycle precursors were successfully prepared, and initially catenane synthesis using Eglinton coupling was explored. With limited success using this strategy, attention turned to the synthesis of catenane **115.Cl** using click chemistry. This was more successful, although the yield of **115.Cl** was lowered by a competing side-reaction. Nevertheless, preliminary anion binding studies on the catenane following removal of the anion template revealed that the catenane binds chloride more strongly than bromide in 1:1 $\text{CDCl}_3/\text{CD}_3\text{OD}$. This new strategy for synthesising catenanes could be investigated further, by varying the bis-azide component. There is also the potential to incorporate a second station into the catenane design for developing a molecular shuttle. For example, alkylation of the triazole rings would enhance their hydrogen bonding ability and the bis-azide component could contain additional hydrogen bonding motifs.

The synthesis of rotaxanes was also investigated, initially preparing macrocycle **125** in high yield using Eglinton coupling. Unfortunately, the Eglinton coupling reaction conditions were not compatible with the anion templated synthesis of rotaxanes. However, it was discovered that the cavity of macrocycle **125** is large enough to allow slippage over the stoppers of **54.Cl** and **130.Cl** in the first examples of anion templated slippage. Kinetic slippage studies

reveal that the rate of slippage is dependent on the anion with the highest rates achieved with the non-coordinating hexafluorophosphate anion. The strength of the ion-pair determines both the rate of slippage and the association constant with the strongest ion-pairs showing the slowest slippage rates but the highest association constants. The studies also reveal that the species formed are pseudorotaxanes with some rotaxane character, rather than rotaxanes. Two locking strategies were investigated to convert the pseudorotaxanes to rotaxanes following slippage with some success; however, it was not possible to isolate these rotaxanes. Instead, the synthesis of rotaxanes was explored using smaller macrocycles, which were found to be too small, and a stoppering approach with larger calix[4]arene stoppers, which was also unsuccessful.

One solution to these problems is to synthesise a macrocycle that is intermediate in size to **125** and the small macrocycles. The synthesis of asymmetric macrocycles was briefly explored in Section 4.3.3.1 using a monoalkylated by-product, but this was limited by the solubility of the macrocycle precursors. This could be investigated further by incorporating solubilising groups into the design of the asymmetric macrocycle. Alkyne ring closing metathesis catalysts could also be explored, as a means of reducing the macrocycle size by an acetylene group. Recently, Fürstner and co-workers developed the air-stable alkyne metathesis catalyst in Figure 4.28, which is now commercially available.⁴⁷

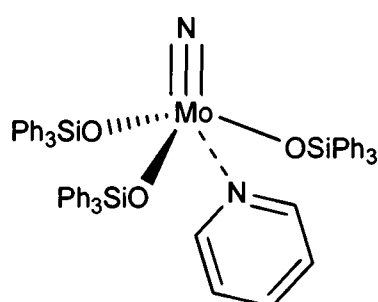


Figure 4.28 Fürstner's molybdenum alkyne ring closing metathesis catalyst

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Chapter 5

Conclusions

5. Conclusions

This thesis has investigated the design, synthesis and binding properties of novel calix[4]arene based heteroditopic receptors for ion-pair recognition and interlocked structures for anion recognition.

A number of novel *tert*-butylcalix[4]diquinone and calix[4]diquinone heteroditopic receptors were successfully prepared in Chapter 1. Ion-pair binding studies using UV/visible and ^1H NMR spectroscopy revealed that these receptors show little affinity for ‘free’ cations or anions, but enhanced binding of the ion-pair. Therefore, these receptors exhibit cooperative AND ion-pair recognition and the family of cooperative AND ion-pair receptors now includes receptors with different anion binding units, macrocycle cavity sizes and calix[4]diquinone scaffolds. The synthesis of a luminescent heteroditopic receptor was also attempted, and this could be investigated further in the future for sensing applications.

The remaining chapters investigated the synthesis of calix[4]arene based interlocked structures for anion recognition as an extension of the work in Chapter 1. A new ion-pair templation strategy was developed to synthesise the first calix[4]arene based rotaxane host systems and anion binding studies revealed that the more preorganised rotaxane is the superior anion host with selectivity for the templating chloride anion in 1:1 $\text{CDCl}_3/\text{CD}_3\text{OD}$. The versatility of this new rotaxane synthetic method could be exploited further by varying the anion binding unit and axle components.

Finally, copper catalysed coupling reactions were utilised to prepare interlocked structures. A novel calix[4]arene based catenane was synthesised using click chemistry and preliminary anion binding studies reveal the catenane is selective for chloride in 1:1 $\text{CDCl}_3/\text{CD}_3\text{OD}$. The first examples of the slippage formation of rotaxane-like structures in the presence of an anion template were also reported between a macrocycle, prepared from Eglinton coupling, and

pyridinium axle components. Kinetic studies revealed that the anion template influences the rate of slippage with the fastest k_{on} rates with the non-coordinating hexafluorophosphate anion and slowest k_{off} rates with coordinating anions, such as chloride. Two strategies were also investigated for converting the rotaxane-like slippage species into rotaxanes.

In conclusion, the target receptors have been synthesised and their ion-pair recognition and anion recognition properties have been investigated.

Chapter 6

Experimental

6. Experimental

6.1. General Procedures

All commercial-grade chemicals and solvents were used without further purification unless otherwise stated. Where dry solvents were used, they were degassed with N₂, dried by passing through an MBraun MPSP-800 column and then used immediately. Triethylamine was distilled over and stored over potassium hydroxide. Thionyl chloride was distilled over triphenyl phosphite. TBA salts, Grubbs' catalyst and AgPF₆ were stored prior to use under vacuum in a desiccator containing phosphorus pentoxide and self-indicating silica gel. Cation salts used in titration experiments were dried on a high vacuum line prior to use. Thallium and silver salts were stored in the absence of light. Deionised water was used in all cases.

¹H, ¹³C, ¹⁹F and ³¹P NMR spectra were recorded on a Varian Mercury 300, a Varian Unity Plus 500 or a Bruker AVII500 with cryoprobe spectrometer at 293 K. Mass spectra were obtained on a Bruker micrOTOF (ESMS), Micromass LCT Premier (ESMS) or a Micromass GCT (EI/FI) spectrometer. Melting points were recorded on a Gallenkamp capillary melting point apparatus and are uncorrected. Elemental analysis was carried out by the services at either London Metropolitan University or the Inorganic Research Laboratory, University of Oxford. Microwave reactions were carried out using a Biotage Initiator 2.0 microwave. Estimated yields are given for impure compounds where there was a trace amount of impurity.

6.2. Synthetic Procedures

6.2.1. General Synthetic Procedures

Thallium trifluoroacetate:¹ A suspension of Tl₂O₃ (4.00 g, 8.76 mmol) in TFA (20 mL) was heated under reflux in the absence of light for 4 days. The reaction mixture was cooled,

filtered and stored in a light protected container. CAUTION: handle with care as thallium derivatives are highly toxic.

General preparation of non-commercially available acid chlorides: A suspension of the carboxylic acid in thionyl chloride was heated under reflux under a N₂ atmosphere until the solid had dissolved. The excess thionyl chloride was removed by distillation *in vacuo*, and the resulting acid chloride was used immediately, assuming to have formed in quantitative yield.

Chlorine dioxide:² Separate solutions of NaClO₂ (0.064 g, 0.71 mmol) and Na₂S₂O₈ (0.082 g, 0.35 mmol) in H₂O (2 mL) were added together in the absence of light to give an aqueous solution of chlorine dioxide (4 mL).

Phosphate buffer: KH₂PO₄ (2 g) was dissolved in H₂O (30 mL) and the pH was adjusted to 5.5 with 1 M NaOH.

6.2.2. Syntheses from Chapter Two

5-*tert*-Butylisophthalamide-diether *tert*-butylcalix[4]diquinone macrobicycle (1):

Compound **7** (0.11 g, 0.11 mmol) was dissolved in a solution of Tl(O₂CCF₃)₃.TFA (4 mL) and stirred in the absence of light for 2 hours. The reaction mixture was concentrated *in vacuo* to approximately one-third of its original volume and poured into 1:1 ice-water (50 mL). The orange suspension was extracted with CHCl₃ (3 x 50 mL) and the organic layer was dried over MgSO₄, filtered and the solution was concentrated *in vacuo*. Purification by silica gel chromatography (98:2 CHCl₃/MeOH) gave **1** as an orange solid (0.075 g, 74%). **m.p.** 180 °C (dec.). ¹H NMR (300 MHz, CDCl₃) δ: 1.13 (18H, s, *t*-Bu), 1.42 (9H, s, *t*-Bu), 3.29 (4H, d, ²*J* = 12.9 Hz, ArCH_{in}H_{out}Qu), 3.74 (20H, m, NCH₂, OCH₂, ArCH_{in}H_{out}Qu), 6.84 (4H, s, calix ArH), 7.08 (4H, br s, calix QuH), 8.26 (2H, s, isoH), 8.46 (2H, br s, NH), 8.61 (1H, s, isoH). ¹³C NMR (125 MHz, CDCl₃) δ: 31.21, 31.38, 32.55, 34.04, 35.11, 41.11, 70.14, 72.03, 74.31, 121.51, 126.59, 128.97, 129.07, 133.32, 133.72, 146.44, 147.31, 152.41, 154.44, 168.03,

185.46, 190.50. **MS (ES⁺)** m/z : 947.4706 [M + Na]⁺. **Elemental Analysis** Calcd. for C₅₆H₆₄N₂O₁₀·2H₂O: C 70.0% H 7.1% N 2.9%. Found: C 69.5% H 6.9% N 2.7%.

2,6-Pyridine-diether *tert*-butylcalix[4]diquinone macrobicycle (2): This was prepared in an analogous manner to **1**, using **8** (0.25 g, 0.26 mmol) and Tl(O₂CCF₃)₃·TFA (4 mL). The crude material was redissolved in CH₂Cl₂ (20 mL), neutralised with triethylamine and filtered through a plug of silica eluting with CH₂Cl₂. The band containing **2** was washed with H₂O (10 mL), dried over MgSO₄, filtered and the solvent was removed *in vacuo* to give an orange solid (0.05 g, 23%). **m.p.** 230 °C (dec.). **¹H NMR** (300 MHz, CDCl₃) δ : 1.12 (18H, s, *t*-Bu), 3.27 (4H, d, ² J = 12.6 Hz, ArCH_{in}CH_{out}Qu), 3.81 (20H, m, ArCH_{in}H_{out}Qu, NCH₂, OCH₂), 6.84 (4H, s, calix ArH), 7.02 (4H, br s, calix QuH), 8.03 (1H, t, ³ J = 7.9 Hz, pyH⁴), 8.40 (2H, d, ³ J = 7.9 Hz, pyH³ and H⁵), 9.59 (2H, t, ³ J = 5.3 Hz, NH). **¹³C NMR** (75.5 MHz, CDCl₃) δ : 31.38, 32.52, 34.03, 40.98, 70.00, 71.13, 73.80, 125.13, 126.65, 129.10, 133.20, 138.56, 146.33, 147.23, 149.21, 154.17, 164.92, 185.49, 190.09. **MS (ES⁺)** m/z : 870.3860 [M + H]⁺, 892.3751 [M + Na]⁺ (Calcd. for C₅₁H₅₅N₃O₁₀Na: 892.3785), 908.3425 [M + K]⁺.

2-(2-Phthalimidoethoxy)ethanol (3):³ 2-(2-Aminoethoxy)ethanol (10.17 g, 0.097 mol) and phthalic anhydride (14.33 g, 0.097 mol) were dissolved in toluene (450 mL) and the resulting solution was heated under reflux using a Dean-Stark apparatus for 5 hours. The reaction mixture was allowed to cool to room temperature, dried over MgSO₄, filtered and the solvent was removed *in vacuo* to give **3** as an off-white solid (21.86 g, 96%). **¹H NMR** (300 MHz, CDCl₃) δ : 3.60 (2H, m, OCH₂), 3.68 (2H, m, CH₂OH), 3.74 (2H, t, ³ J = 5.4 Hz, OCH₂), 3.91 (2H, t, ³ J = 5.4 Hz, NCH₂), 7.72 (2H, dd, ³ J = 5.4 Hz, ⁴ J = 3.0 Hz, PhthH), 7.85 (2H, dd, ³ J = 5.4 Hz, ⁴ J = 3.0 Hz, PhthH). **MS (ES⁺)** m/z : 258.1 [M + Na]⁺.

2-(2-Phthalimidoethoxy)ethanol tosylate (4):⁴ Compound **3** (10.76 g, 0.046 mol) was dissolved in CH₂Cl₂ (100 mL) and triethylamine (10 mL, 0.07 mol), tosyl chloride (8.92 g,

0.046 mol) and DMAP (cat.) were added. The reaction mixture was stirred under a N₂ atmosphere for 16 hours then H₂O (50 mL) was added. The biphasic mixture was stirred vigorously, neutralised by 10% aqueous citric acid and the layers separated. The organic phase was washed with H₂O (2 x 50 mL), dried with MgSO₄, filtered and the solvent removed *in vacuo*. Following overnight trituration in diethyl ether, **4** was isolated as an off-white solid (14.2 g, 80%). ¹H NMR (300 MHz, CDCl₃) δ: 2.44 (3H, s, CH₃), 3.67 (4H, m, OCH₂), 3.84 (2H, t, ³J = 5.7 Hz, NCH₂), 4.11 (2H, m, OCH₂), 7.33 (2H, d, ³J = 7.9 Hz, TosH), 7.74 (4H, m, TosH and PhthH), 7.85 (2H, dd, ³J = 4.4 Hz, ⁴J = 3.2 Hz, PhthH). MS (ES⁺) *m/z*: 412.0999 [M + Na]⁺, 801.2060 [2M + Na]⁺.

5,11,17,23-Tetra-*tert*-butyl-25,27-bis(2-(2-phthalimidoethoxy)ethoxy)-26,28-

dihydroxycalix[4]arene (5):⁴ A suspension of *tert*-butylcalix[4]arene (3.59 g, 5.53 mmol) and K₂CO₃ (1.53 g, 11.07 mmol) in dry CH₃CN (120 mL) was stirred at room temperature under a N₂ atmosphere for 15 minutes. Compound **4** (5.39 g, 13.84 mmol) was added and the resulting mixture was heated under reflux for 4 days, cooled to room temperature and the solvent was removed *in vacuo*. The solid residue was trituated with 1 M HCl (75 mL) then extracted with CH₂Cl₂ (3 x 100 mL). The combined organic layers were washed with H₂O (2 x 100 mL), dried over MgSO₄, filtered and the solvent was removed *in vacuo*. The residue was trituated with EtOH (75 mL) to give **5** as a pale green solid (3.41 g, 57%). **Microwave synthesis:** A suspension of *tert*-butylcalix[4]arene (1 g, 1.54 mmol), **4** (1.50 g, 3.85 mmol) and K₂CO₃ (0.43 g, 3.1 mmol) in dry CH₃CN (15 mL) was stirred for 1 minute before heating under microwave irradiation for 10 minutes at 160 °C. Three identical microwave reactions were carried out and the four reaction mixtures were combined and the solvent was removed *in vacuo*. The combined residues were trituated with 1 M HCl (100 mL) and extracted with CH₂Cl₂ (3 x 100 mL). The combined organic layers were washed with H₂O (2 x 100 mL), dried over MgSO₄, filtered and the solvent was removed *in vacuo*. Recrystallisation from

CH₂Cl₂/EtOH gave **5** (5.00 g, 75%). ¹H NMR (300 MHz, CDCl₃) δ: 1.00 (18H, s, *t*-Bu), 1.23 (18H, s, *t*-Bu), 3.04 (4H, d, ²*J* = 12.9 Hz, ArCH_{in}H_{out}Ar), 4.01 (20H, m, OCH₂, NCH₂, ArCH_{in}H_{out}Ar), 6.78 (4H, s, calix ArH), 6.81 (4H, s, calix ArH), 7.44 (2H, s, OH), 7.48 (4H, m, PhthH), 7.57 (4H, m, PhthH). MS (ES⁺) *m/z*: 1105.6969 [M + Na]⁺.

5,11,17,23-Tetra-*tert*-butyl-25,27-bis(2-(2-aminoethoxy)ethoxy)-26,28-

dihydroxycalix[4]arene (6):⁴ Compound **5** (1.30 g, 1.2 mmol) was suspended in EtOH (30 mL), hydrazine monohydrate (0.6 mL, excess) was added and the resulting suspension was heated under reflux for 16 hours. The reaction mixture was cooled to room temperature and poured into H₂O (50 mL). The white suspension was extracted with CH₂Cl₂ (4 x 40 mL) and the organic extracts were dried over MgSO₄, filtered and the solvent removed *in vacuo* to give the white product **6** (0.91 g, 92%). **Microwave synthesis:** A suspension of **5** (1.30 g, 1.2 mmol) and hydrazine monohydrate (0.57 mL, excess) in EtOH (15 mL) was stirred for 30 seconds and heated under microwave irradiation for 10 minutes at 100 °C. A second microwave reaction was carried out under identical conditions and the combined residues were poured into H₂O (100 mL). The white suspension was extracted with CH₂Cl₂ (4 x 40 mL) and the organic extracts were dried over MgSO₄, filtered and the solvent was removed *in vacuo* to give **6** (2.00 g, 100%). ¹H NMR (300 MHz, CDCl₃) δ: 0.97 (18H, s, *t*-Bu), 1.29 (18H, s, *t*-Bu), 2.95 (4H, t, ³*J* = 4.8 Hz, CH₂NH₂), 3.31 (4H, d, ²*J* = 13.2 Hz, ArCH_{in}H_{out}Ar), 3.70 (4H, m, OCH₂), 3.96 (4H, m, OCH₂), 4.18 (4H, m, OCH₂), 4.37 (4H, d, ²*J* = 13.2 Hz, ArCH_{in}H_{out}Ar), 6.81 (4H, s, calix ArH), 7.05 (4H, s, calix ArH). MS (ES⁺) *m/z*: 412.3049 [M + 2H]²⁺, 823.6214 [M + H]⁺.

5-*tert*-Butylisophthalamide-diether *tert*-butylcalix[4]arene macrobicycle (7): A solution of **6** (0.47 g, 0.57 mmol) in dry CH₂Cl₂ (100 mL) and a solution of 5-*tert*-butylisophthaloyl dichloride (0.57 mmol) in dry CH₂Cl₂ (100 mL) were added dropwise simultaneously to a

stirred solution of triethylamine (0.3 mL, 2.15 mmol) in dry CH₂Cl₂ (250 mL) over 2 hours under a N₂ atmosphere. The reaction mixture was stirred for a further hour once the addition was complete, before it was concentrated *in vacuo* to a volume of 50 mL. This was washed with 1 M HCl (2 x 50 mL), H₂O (50 mL), 1 M NaOH (50 mL) and brine (50 mL). The organic layer was dried over MgSO₄, filtered and the solvent was removed *in vacuo*. The crude material was purified by silica gel chromatography (3:2 EtOAc/petroleum ether) to give **7** as a white solid (0.31 g, 55%). **m.p.** 176-181°C. ¹H NMR (300 MHz, CDCl₃) δ: 0.90 (18H, s, *t*-Bu), 1.31 (18H, s, *t*-Bu), 1.38 (9H, s, *t*-Bu), 3.33 (4H, d, ²*J* = 13.2 Hz, ArCH_{in}H_{out}Ar), 3.79 (8H, m, NCH₂, OCH₂), 3.88 (4H, m, OCH₂), 4.21 (4H, m, OCH₂), 4.34 (4H, d, ²*J* = 13.2 Hz, ArCH_{in}H_{out}Ar), 6.73 (4H, s, calix ArH), 7.04 (2H, s, OH), 7.07 (4H, s, calix ArH), 7.81 (2H, br s, NH), 8.23 (3H, m, isoH). ¹³C NMR (75.5 MHz, CDCl₃) δ: 30.91, 31.21, 31.28, 31.68, 33.84, 33.86, 35.11, 40.11, 69.39, 70.13, 75.15, 121.08, 125.17, 125.61, 127.79, 128.57, 132.31, 133.70, 141.90, 147.11, 149.52, 150.02, 152.52, 166.96. **MS (ES⁺)** *m/z*: 1031.6125 [M + Na]⁺. **Elemental Analysis** Calcd. for C₆₄H₈₄N₂O₈·2H₂O: C: 73.5% H 8.5% N 2.7%. Found: C 73.6% H 8.4% N 2.6%.

2,6-Pyridine-diether *tert*-butylcalix[4]arene macrobicycle (8): This was prepared in an analogous manner to **7**, using 2,6-bis(chlorocarbonyl)pyridine (0.62 mmol), **6** (0.51 g, 0.62 mmol) and triethylamine (0.33 mL, 2.34 mmol). After the addition was complete, the reaction mixture was stirred for a further 2.5 hours at room temperature and then concentrated *in vacuo* to a volume of approximately 100 mL. The organic layer was washed with H₂O (2 x 100 mL), dried over MgSO₄, filtered and the solvent was removed *in vacuo*. Purification by silica gel chromatography (95:5 EtOAc/acetone) gave **8** as a white solid (0.32 g, 55%). **m.p.** 176-178 °C. ¹H NMR (300 MHz, CDCl₃) δ: 0.87 (18H, s, *t*-Bu), 1.27 (18H, s, *t*-Bu), 3.20 (4H, d, ²*J* = 13.2 Hz, ArCH_{in}H_{out}Ar), 3.84 (12H, m, NCH₂, OCH₂), 4.21 (8H, m, ArCH_{in}H_{out}Ar, OCH₂), 6.68 (4H, s, calix ArH), 6.91 (4H, s, calix ArH), 6.99 (2H, s, OH),

7.73 (2H, t, $^3J = 7.6$ Hz, pyH⁴), 8.03 (1H, d, $^3J = 7.6$ Hz, pyH³ and H⁶), 9.19 (2H, br s, NH). ¹³C NMR (75.5 MHz, CDCl₃) δ : 30.88, 30.93, 31.70, 33.75, 33.81, 39.92, 69.43, 69.77, 74.63, 123.94, 124.95, 125.51, 127.59, 132.41, 138.34, 141.43, 146.90, 148.16, 149.01, 149.65, 164.08. MS (ES⁺) m/z : 976.5576 [M + Na]⁺.

1,3-Phenylenediacetamide-diether *tert*-butylcalix[4]arene macrobicycle (9):

1,3-Phenylenediacetic acid (0.073 g, 0.38 mmol) was suspended in dry CH₂Cl₂ (100 mL), and EDC.HCl (0.15 g, 0.81 mmol) and HOBT (0.11 g, 0.79 mmol) were added. This was stirred for 2.5 hours under a N₂ atmosphere, during which time the solid dissolved. Compound 6 (0.31 g, 0.38 mmol) was dissolved in dry CH₂Cl₂ (100 mL). The activated ester and amine solutions were added simultaneously dropwise to a stirred solution of triethylamine (0.13 mL, 0.93 mmol) in dry CH₂Cl₂ (200 mL) over 2 hours and the reaction mixture was stirred for a further 3 days. The solution was concentrated *in vacuo* to approximately 100 mL, washed with 1 M HCl (2 x 100 mL), H₂O (100 mL), 1 M NaOH (100 mL), brine (100 mL), dried over MgSO₄, filtered and the solvent was removed *in vacuo*. The crude material was purified by silica gel chromatography (98:2 CH₂Cl₂/MeOH) to give 9 as a white solid (0.13 g, 35%). m.p. 90-92 °C. ¹H NMR (300 MHz, CDCl₃) δ : 0.92 (18H, s, *t*-Bu), 1.30 (18H, s, *t*-Bu), 3.33 (4H, d, $^2J = 13.1$ Hz, ArCH_{in}H_{out}Ar), 3.49 (8H, m, NCH₂, ArCH₂), 3.65 (4H, t, $^3J = 4.5$ Hz, OCH₂), 3.80 (4H, m, OCH₂), 4.11 (4H, m, OCH₂), 4.38 (4H, d, $^2J = 13.1$ Hz, ArCH_{in}H_{out}Ar), 6.51 (2H, t, $^3J = 5.4$ Hz, NH), 6.77 (4H, s, calix ArH), 6.82 (1H, s, phenH), 7.11 (4H, s, calix ArH), 7.18 (2H, d, $^3J = 7.9$ Hz, phenH), 7.26 (3H, m, phenH, OH). ¹³C NMR (75.5 MHz, CDCl₃) δ : 30.95, 31.38, 31.65, 33.87, 33.90, 39.87, 43.39, 69.36, 69.76, 74.99, 125.33, 125.61, 128.06, 128.17, 129.23, 129.49, 132.37, 135.85, 142.25, 147.12, 149.21, 150.00, 171.32. MS (ES⁺) m/z : 998.6 [M + NH₄]⁺, 1003.6 [M + Na]⁺.

Bipyridyl-diether *tert*-butylcalix[4]diquinone macrobicycle (10):⁵ This was attempted in

an analogous manner to **1**, using **14** (0.12 g, 0.12 mmol) and $\text{Ti}(\text{O}_2\text{CCF}_3)_3 \cdot \text{TFA}$ (1.5 mL). Recrystallisation from $\text{CH}_2\text{Cl}_2/\text{hexane}$ gave impure **10**. ^1H NMR (300 MHz, CDCl_3) δ : 1.10 (18H, br. s, *t*-Bu), 3.26 (4H, m, $\text{ArCH}_{\text{in}}\text{H}_{\text{out}}\text{Qu}$), 3.85 (20H, m, NCH_2 , OCH_2 , $\text{ArCH}_{\text{in}}\text{H}_{\text{out}}\text{Qu}$), 6.84 (8H, m, calix ArH, calix QuH), 8.41 (2H, br s, NH), 8.59 (2H, br s, bipyH), 8.94 (2H, br s, bipyH), 9.52 (2H, br s, bipyH). MS (ES^+) m/z : 947.5 $[\text{M} + \text{H}]^+$, 969.5 $[\text{M} + \text{Na}]^+$.

2,2'-Bipyridine-4,4'-dicarboxylic acid (11):⁶ 4,4'-Dimethyl-2,2'-bipyridine (1.33 g, 7.22 mmol) was added to a stirred solution of 98% sulphuric acid (44 mL). Potassium dichromate (8.52 g, 29 mmol) was added in small portions so that the temperature did not exceed 80 °C, and the solution was stirred until the temperature fell below 40 °C. The green solution was poured into ice water (250 mL), filtered and the solid was washed with H_2O until the filtrate was colourless. The yellow solid was further purified by heating it under reflux in 70% nitric acid (60 mL) for 4 hours. The yellow solution was poured over ice, diluted with H_2O (400 mL) and cooled to precipitate the product. The precipitate was collected by filtration, washed with H_2O (5 x 50 mL), acetone (3 x 20 mL) and dried under suction to give **11** as a white solid (1.51 g, 86%), which was characterised as the dimethyl ester **12**.

Dimethyl 2,2'-bipyridine-4,4'-dicarboxylate (12): A suspension of **11** (0.073 g, 0.3 mmol) with 5 drops of H_2SO_4 in MeOH (3 mL) was stirred for 30 seconds and heated under microwave irradiation for 30 minutes at 130 °C. The solvent was removed *in vacuo*, the residue was redissolved in CH_2Cl_2 (50 mL) and washed with saturated NaHCO_3 (50 mL) and H_2O (3 x 50 mL). The organic layer was dried over MgSO_4 , filtered and the solvent was removed *in vacuo* to give **12** as a white solid (0.11 g, 100%). ^1H NMR (300 MHz, CDCl_3) δ : 4.01 (6H, s, CH_3), 7.92 (2H, d, $^3J = 4.3$ Hz, bipyH), 8.88 (2H, d, $^3J = 4.3$ Hz, bipyH), 8.98 (2H, s, bipyH). MS (ES^+) m/z : 273.0882 $[\text{M} + \text{H}]^+$ (Calcd. for $\text{C}_{14}\text{H}_{13}\text{N}_2\text{O}_4$: 273.0875).

2,2'-Dimethyl-4,4'-bipyridine (13):^{adapted from 7} Sodium (40% by weight in naphthenic oil,

1.30 g, 22.61 mmol) in dry THF (6 mL) was added to a solution of distilled 2-picoline (1.9 mL, 19.24 mmol) and TMSCl (2.44 mL, 19.23 mmol) in dry THF (10 mL). The mixture was stirred at room temperature under a N₂ atmosphere for 4 hours then the solvent was removed *in vacuo*. The residue was redissolved in hot toluene, filtered, the solvent was again removed *in vacuo* and the residue was redissolved in a 75% (v/v) acetone/water mixture. KMnO₄ was added to the stirred solution and the temperature was maintained below 50 °C using an ice bath. The excess MnO₄⁻ was decomposed with EtOH and the suspension was filtered. The filtrate was concentrated *in vacuo* and the resulting aqueous solution was made alkaline with 10% aqueous NaOH and extracted with CHCl₃ (2 x 15 mL). The combined organic layers were dried over MgSO₄, filtered and the solvent was removed *in vacuo*. The crude material was recrystallised from hot hexane to give **13** as a yellow solid (0.27 g, 8%). ¹H NMR (300 MHz, CDCl₃) δ: 2.65 (6H, s, CH₃), 7.33 (2H, d, ³J = 5.1 Hz, bipyH), 7.38 (2H, s, bipyH), 8.60 (2H, d, ³J = 5.1 Hz, bipyH). MS (ES⁺) *m/z*: 185.1088 [M + H]⁺ (Calcd. for C₁₂H₁₃N₂: 185.2179).

Bipyridyl-diether *tert*-butylcalix[4]arene macrobicycle (14):⁵ Separate solutions of the 4,4'-bis(chlorocarbonyl)-2,2'-bipyridine (0.77 mmol) in dry CH₂Cl₂ (100 mL) and **6** (0.64 g, 0.77 mmol) in dry CH₂Cl₂ (100 mL) were added simultaneously dropwise over 2 hours to a solution of triethylamine (0.4 mL, 2.87 mmol) in dry CH₂Cl₂ (400 mL). After the addition was complete, the reaction mixture was stirred for a further hour at room temperature and then concentrated *in vacuo* to a volume of approximately 75 mL. The organic layer was washed with 1 M HCl (2 x 100 mL), H₂O (100 mL), 1 M NaOH (100 mL) and brine (100 mL). The organic layer was dried over MgSO₄, filtered and the solvent removed *in vacuo*. Purification by silica gel chromatography (95:5 THF/MeOH) eluted the product as a pink band to give **14** as a pink solid (0.43 g, 54%). ¹H NMR (300 MHz, CDCl₃) δ: 0.86 (18H, s, *t*-Bu), 1.20 (18H, s, *t*-Bu), 3.13 (4H, d, ²J = 13.2 Hz, ArCH_{in}H_{out}Ar), 3.90 (12H, m, NCH₂, OCH₂), 4.21 (8H, m,

ArCH_{in}H_{out}Ar, OCH₂), 6.65 (4H, s, calix ArH), 6.81 (4 H, s, calix ArH), 7.02 (2H, br s, OH), 7.91 (4H, m, bipyH, NH), 8.21 (2H, br s, bipyH), 8.94 (2H, d, ³J = 4.7 Hz, bipyH). MS (ES⁺) *m/z*: 1031.5663 [M + H]⁺.

Isophthalamide-diether calix[4]diquinone macrobicycle (15): An aqueous solution of ClO₂ (prepared in 4 mL H₂O from 0.064 g NaClO₂ and 0.082 g Na₂S₂O₈) was added to a suspension of **26** (0.096 g, 0.13 mmol) in CH₃CN (5 mL) in the absence of light and the mixture was stirred at room temperature for 70 hours. The organic solvent was removed *in vacuo* and the aqueous layer was extracted with CHCl₃ (3 x 20 mL). The organic layers were washed with H₂O (2 x 20 mL), dried over MgSO₄, filtered and the solvent was removed *in vacuo*. The crude material was purified by silica gel chromatography (95:5 CH₂Cl₂/MeOH) and the product was eluted as the first yellow band to give **15** as a yellow solid (0.057 g, 57%). **m.p.** 200 °C (dec.). ¹H NMR (300 MHz, CDCl₃) δ: 3.36 (4H, br s, ArCH_{in}H_{out}Qu), 3.78 (20H, m, ArCH_{in}H_{out}Qu, OCH₂, NCH₂), 6.66 (2H, m, calix ArH), 6.82 (4H, br s, calix ArH), 7.07 (4H, br s, calix QuH), 7.62 (1H, t, ³J = 7.8 Hz, isoH), 8.25 (2H, dd, ³J = 7.8 Hz, ⁴J = 1.5 Hz, isoH), 8.52 (2H, br s, NH), 8.84 (1H, s, isoH). ¹³C NMR (125 MHz, CDCl₃) δ: 31.13, 41.13, 69.84, 72.28, 73.57, 123.92, 124.08, 129.14, 129.81, 130.20, 132.05, 132.58, 133.99, 147.88, 156.03, 167.61, 185.91. MS (ES⁺) *m/z*: 757.2729 [M + H]⁺ (Calcd. for C₄₄H₄₁N₂O₁₀: 757.2761), 779.2578 [M + Na]⁺.

5-Nitroisophthalamide-diether calix[4]diquinone macrobicycle (16): This was prepared in an analogous manner to **15**, reacting **27** (0.28 g, 0.36 mmol) and an aqueous solution of ClO₂ (prepared in 10 mL H₂O from 0.20 g NaClO₂ and 0.26 g Na₂S₂O₈) in CH₃CN (10 mL) at room temperature for 3 days in the absence of light. The crude yellow solid was purified by silica gel chromatography (96:4 CH₂Cl₂/MeOH) and the product was eluted as the first yellow band giving a yellow solid (0.12 g, 40%). **m.p.** 200 °C (dec.). ¹H NMR (300 MHz, CDCl₃)

δ : 3.39 (4H, br s, $\text{ArCH}_{\text{in}}\text{H}_{\text{out}}\text{Qu}$), 3.83 (20H, m, $\text{ArCH}_{\text{in}}\text{H}_{\text{out}}\text{Qu}$, OCH_2 , NCH_2), 6.67 (2H, t, $^3J = 7.5$ Hz, calix ArH), 6.88 (8H, m, calix ArH , calix QuH), 8.60 (2H, br s, NH), 9.08 (2H, d, $^4J = 1.2$ Hz, isoH), 9.18 (1H, s, isoH). ^{13}C NMR (125 MHz, CDCl_3) δ : 30.91, 41.41, 69.86, 71.88, 73.49, 124.06, 126.72, 129.15, 130.06, 132.46, 136.04, 147.98, 149.06, 156.03, 165.32, 186.21. MS (ES^+) m/z : 819.3 $[\text{M} + \text{NH}_4]^+$, 824.2421 $[\text{M} + \text{Na}]^+$ (Calcd. for $\text{C}_{44}\text{H}_{39}\text{N}_3\text{O}_{12}\text{Na}$: 824.2426), 840.2 $[\text{M} + \text{K}]^+$. **Elemental Analysis** Calcd. for $\text{C}_{44}\text{H}_{39}\text{N}_3\text{O}_{12} \cdot 1.3\text{CHCl}_3$: C 56.9% H 4.2% N 4.4%. Found: C 57.0% H 4.4% N 4.3%.

Isophthalamide-triether calix[4]diquinone macrobicycle (17): This was prepared in an analogous manner to **15**, reacting **28** (0.18 g, 0.23 mmol) and an aqueous solution of ClO_2 (prepared in 6 mL H_2O from 0.11 g NaClO_2 and 0.15 g $\text{Na}_2\text{S}_2\text{O}_8$) in CH_3CN (10 mL) at room temperature for 22 hours in the absence of light. Purification of the crude material by silica gel chromatography (95:5 $\text{CH}_2\text{Cl}_2/\text{MeOH}$) gave the yellow receptor **17** (0.096 g, 50%). **m.p.** 200 °C (dec.). ^1H NMR (500 MHz, CD_3CN) δ : 3.21 (4H, d, $^2J = 13.2$ Hz, $\text{ArCH}_{\text{in}}\text{H}_{\text{out}}\text{Qu}$), 3.56 (4H, m, NCH_2), 3.70 (20H, m, OCH_2), 3.78 (4H, m, $\text{ArCH}_{\text{in}}\text{H}_{\text{out}}\text{Qu}$), 6.63 (2H, t, $^3J = 7.7$ Hz, calix ArH), 6.67 (4H, s, calix QuH), 6.81 (4H, d, $^3J = 7.7$ Hz, calix ArH), 7.14 (2H, br s, NH), 7.52 (1H, t, $^3J = 7.8$ Hz, isoH), 7.91 (2H, dd, $^3J = 7.8$ Hz, $^4J = 2.0$ Hz, isoH), 8.00 (1H, s, isoH). ^{13}C NMR (75.5 MHz, CDCl_3) δ : 31.49, 40.36, 69.84, 70.11, 70.52, 73.75, 123.41, 123.70, 129.10, 129.85, 130.23, 131.39, 132.23, 134.25, 147.97, 156.28, 166.65, 186.30, 189.89. MS (ES^+) m/z : 845.3275 $[\text{M} + \text{H}]^+$ (Calcd. for $\text{C}_{48}\text{H}_{49}\text{N}_2\text{O}_{12}$: 845.3286), 867.3085 $[\text{M} + \text{Na}]^+$, 883.2816 $[\text{M} + \text{K}]^+$. **Elemental Analysis** Calcd. for $\text{C}_{48}\text{H}_{48}\text{N}_2\text{O}_{12} \cdot 2\text{H}_2\text{O}$: C 65.4% H 6.0% N 3.2%. Found: C 65.0% H 5.8% N 3.1%.

Bipyridyl-diether calix[4]diquinone macrobicycle (18): An aqueous solution of ClO_2 (prepared in 4 mL H_2O from 0.12 g NaClO_2 and 0.15 g $\text{Na}_2\text{S}_2\text{O}_8$) was added to a solution of impure **33** (0.15 g, ~ 0.18 mmol) in 1:1 $\text{CHCl}_3/\text{CH}_3\text{CN}$ (10 mL) in the absence of light and the

mixture was stirred at room temperature for 3 days. H₂O (20 mL) was added and the aqueous layer was extracted with CHCl₃ (3 x 20 mL). The combined organic layers were dried over MgSO₄, filtered and the solvent was removed *in vacuo*. Purification by silica gel chromatography (9:1 CHCl₃/MeOH) and recrystallisation from CHCl₃/diethyl ether gave **18** as a yellow solid (0.025 g, 17%). **m.p.** 240 °C (dec.). **¹H NMR** (300 MHz, CDCl₃) δ: 3.37 (4H, m, ArCH_{in}H_{out}Qu), 3.76 (20H, m, ArCH_{in}H_{out}Qu, OCH₂, NCH₂), 6.62 (4H, m, calix ArH), 6.78 (6H, br s, calix QuH), 7.20 (2H, br s, NH), 7.86 (2H, d, ³J = 4.7 Hz, bipyH), 8.23 (2H, s, bipyH), 8.85 (2H, d, ³J = 4.7 Hz, bipyH). **¹³C NMR** (75.5 MHz, CDCl₃) δ: 31.02, 40.60, 69.79, 69.90, 73.25, 118.54, 122.23, 123.87, 130.02, 131.71, 142.70, 147.37 150.13, 150.97, 155.61, 156.42, 165.84, 185.59, 188.68. **MS (ES⁺)** *m/z*: 893.3 [M + CH₃CN + NH₄]⁺, 857.2815 [M + Na]⁺ (Calcd. for C₄₈H₄₂N₄O₁₀Na: 857.2793).

2-(2-(2-Phthalimidoethoxy)ethoxy)ethanol (**19**):^{8,9}

2-(2-(2-Chloroethoxy)ethoxy)ethanol (9.60 g, 57 mmol) was added to a solution of potassium phthalimide (10.54 g, 57 mmol) in DMF (50 mL) and the reaction mixture was heated at 110 °C under a N₂ atmosphere for 18 hours. The reaction mixture was allowed to cool to room temperature, filtered, and the solvent was removed *in vacuo* to give **19** as a yellow oil (~15.20 g). It was not possible to obtain an accurate yield due to difficulty removing all traces of DMF. Therefore the product was reacted on immediately, assuming to have formed in quantitative yield. **¹H NMR** (300 MHz, CDCl₃) δ: 3.54 (2H, m, OCH₂), 3.62 (2H, m, CH₂OH), 3.66 (4H, m, OCH₂), 3.76 (2H, t, ³J = 5.7 Hz, OCH₂), 3.92 (2H, t, ³J = 5.7 Hz, NCH₂), 7.72 (2H, dd, ³J = 5.2 Hz, ⁴J = 3.3 Hz, PhthH), 7.85 (2H, dd, ³J = 5.2 Hz, ⁴J = 3.3 Hz, PhthH). **MS (ES⁺)** *m/z*: 302.1 [M + Na]⁺.

2-(2-(2-Phthalimidoethoxy)ethoxy)ethanol tosylate (20**):** This was prepared in an analogous manner to **4**, reacting **19** (~15.20 g), triethylamine (12 mL, 85 mmol), tosyl

chloride (10.84 g, 57 mmol) and DMAP (cat.) in CH₂Cl₂ (150 mL) for 18 hours. Trituration with diethyl ether gave **20** as a white solid (18.08 g, 73% over 2 steps from 2-(2-(2-chloroethoxy)ethoxy)ethanol). ¹H NMR (300 MHz, CDCl₃) δ: 2.45 (3H, s, CH₃), 3.56 (4H, m, OCH₂), 3.63 (2H, t, ³J = 5.0 Hz, OCH₂), 3.70 (2H, t, ³J = 5.7 Hz, OCH₂), 3.88 (2H, t, ³J = 5.7 Hz, NCH₂), 4.10 (2H, t, ³J = 5.0 Hz, OCH₂), 7.34 (2H, d, ³J = 8.2 Hz, TosH), 7.72 (2H, dd, ³J = 5.5 Hz, ⁴J = 3.2 Hz, PhthH), 7.79 (2H, d, ³J = 8.2 Hz, TosH), 7.85 (2H, dd, ³J = 5.5 Hz, ⁴J = 3.2 Hz, PhthH). MS (ES⁺) *m/z*: 456.0980 [M + Na]⁺, 889.3224 [2M + Na]⁺.

Calix[4]arene (21):¹⁰ A slurry of *tert*-butylcalix[4]arene (14.85 g, 22.9 mmol), phenol (10.10 g, 107 mmol) and anhydrous AlCl₃ (15.65 g, 117 mmol) was stirred in toluene (120 mL) under a N₂ atmosphere for 1 hour. The reaction mixture was poured into 0.2 M HCl (250 mL), the organic layer was separated and concentrated *in vacuo*. Addition of MeOH (40 mL) precipitated the product and **21** was obtained as a white solid following recrystallisation from CHCl₃/MeOH (7.56 g, 78%). ¹H NMR (300 MHz, CDCl₃) δ: 3.54 (2H, br s, ArCH_{in}H_{out}Ar), 4.28 (4H, br s, ArCH_{in}H_{out}Ar), 6.74 (4H, t, ³J = 7.5 Hz, calix ArH), 7.06 (8H, d, ³J = 7.5 Hz, calix ArH), 10.21 (4H, s, OH). MS (ES⁻) *m/z*: 423.1776 [M – H]⁻.

25,27-Bis(2-(2-phthalimidoethoxy)ethoxy)-26,28-dihydroxycalix[4]arene (22): Compound **21** (0.58 g, 1.37 mmol) and K₂CO₃ (0.21 g, 1.52 mmol) were suspended in dry CH₃CN (50 mL) and stirred at room temperature under a N₂ atmosphere for 30 minutes. Compound **4** (1.33 g, 3.42 mmol) was added and the resulting mixture was heated under reflux under a N₂ atmosphere for 4 days. The reaction mixture was cooled to room temperature and the solvent was removed *in vacuo*. The residue was triturated with 1 M HCl (25 mL) and the resulting suspension was extracted with CH₂Cl₂ (3 x 25 mL). The combined organic layers were washed with H₂O (2 x 25 mL), dried over MgSO₄, filtered and the solvent was removed *in vacuo*. The crude white solid was purified by silica gel chromatography (95:5 CHCl₃/acetone)

eluting **22** as the third band to give a white solid (0.78 g, 66%). **m.p.** 190 °C. ^1H NMR (300 MHz, CDCl_3) δ : 3.09 (4H, d, $^2J = 12.9$ Hz, $\text{ArCH}_{\text{in}}\text{H}_{\text{out}}\text{Ar}$), 4.04 (20H, m, $\text{ArCH}_{\text{in}}\text{H}_{\text{out}}\text{Ar}$, OCH_2 , NCH_2), 6.47 (2H, t, $^3J = 7.5$ Hz, calix ArH), 6.67 (2H, t, $^3J = 7.6$ Hz calix ArH), 6.82 (8H, m, calix ArH), 7.49 (4H, m, Phth H), 7.55 (4H, m, Phth H), 7.81 (2H, s, OH). ^{13}C NMR (75.5 MHz, CDCl_3) δ : 30.93, 38.12, 68.54, 70.02, 75.17, 118.82, 122.66, 125.33, 128.01, 128.15, 128.65, 131.78, 133.43, 133.87, 151.35, 152.50, 168.49. **MS** (ES^+) m/z : 881.3537 $[\text{M} + \text{Na}]^+$.

25,27-Bis(2-(2-(2-phthalimidoethoxy)ethoxy)ethoxy)-26,28-dihydroxycalix[4]arene (23):

Compound **21** (0.46 g, 1.08 mmol), K_2CO_3 (0.17 g, 1.2 mmol) and **20** (1.17 g, 2.69 mmol) were suspended in dry CH_3CN (50 mL) and heated under reflux under a N_2 atmosphere for 5 days. The reaction mixture was cooled to room temperature and the solvent was removed *in vacuo*. The residue was triturated with 1 M HCl (25 mL) and extracted with CH_2Cl_2 (3 x 25 mL). The combined organic fractions were washed with H_2O (2 x 25 mL), dried over MgSO_4 , filtered and the solvent removed *in vacuo*. The crude material was purified by silica gel chromatography (95:5 CHCl_3 /acetone) to give **23** as a white solid (0.47 g, 48%). **m.p.** 72-74 °C. ^1H NMR (300 MHz, CDCl_3) δ : 3.33 (4H, d, $^2J = 13.1$ Hz, $\text{ArCH}_{\text{in}}\text{H}_{\text{out}}\text{Ar}$), 3.72 (8H, m, OCH_2 , NCH_2), 3.81 (8H, m, OCH_2), 3.94 (4H, t, $^3J = 4.7$ Hz, OCH_2), 4.11 (4H, m, OCH_2), 4.37 (4H, d, $^2J = 13.1$ Hz, $\text{ArCH}_{\text{in}}\text{H}_{\text{out}}\text{Ar}$), 6.61 (2H, t, $^3J = 7.6$ Hz, calix ArH), 6.71 (2H, t, $^3J = 7.4$ Hz, calix ArH), 6.86 (4H, d, $^3J = 7.6$ Hz, calix ArH), 7.03 (4H, d, $^3J = 7.4$ Hz, calix ArH), 7.68 (4H, dd, $^3J = 5.5$ Hz, $^4J = 3.0$ Hz, Phth H), 7.77 (2H, s, OH), 7.82 (4H, dd, $^3J = 5.5$ Hz, $^4J = 3.0$ Hz, Phth H). ^{13}C NMR (75.5 MHz, CDCl_3) δ : 31.14, 37.19, 67.96, 70.01, 70.19, 71.03, 75.35, 118.79, 123.17, 125.21, 128.06, 128.37, 128.84, 132.11, 133.35, 133.85, 151.82, 153.20, 168.21. **MS** (ES^+) m/z : 969.4337 $[\text{M} + \text{Na}]^+$.

25,27-Bis(2-(2-aminoethoxy)ethoxy)-26,28-dihydroxycalix[4]arene (24): Compound **22**

(2.04 g, 2.38 mmol) was suspended in EtOH (60 mL), hydrazine monohydrate (2 mL, excess) was added and the resulting white suspension was heated under reflux for 16 hours. The reaction mixture cooled to room temperature, poured into H₂O (200 mL) and the suspension was extracted with CH₂Cl₂ (3 x 100 mL). The combined organic layers were dried over MgSO₄, filtered and taken to dryness *in vacuo* to give **24** (1.28 g, 90%). **Microwave synthesis:** A suspension of **22** (0.75 g, 0.87 mmol) and hydrazine monohydrate (0.3 mL, excess) in EtOH (15 mL) was stirred for 30 seconds at room temperature and heated under microwave irradiation for 1.5 hours at 100 °C. The reaction mixture was cooled to room temperature and poured into H₂O (50 mL). The white suspension was extracted with CHCl₃ (3 x 50 mL) and the combined organic extracts were dried over MgSO₄, filtered and the solvent was removed *in vacuo* to give **24** as a white solid (0.53 g, 100%). **m.p.** 122-124 °C. **¹H NMR** (300 MHz, CDCl₃) δ : 2.97 (4H, t, ³*J* = 4.8 Hz, CH₂NH₂), 3.38 (4H, d, ²*J* = 12.9 Hz, ArCH_{in}H_{out}Ar), 3.72 (4H, t, ³*J* = 5.0 Hz, OCH₂), 4.00 (4H, m, OCH₂), 4.21 (4H, m, OCH₂), 4.42 (4H, d, ²*J* = 12.9 Hz, ArCH_{in}H_{out}Ar), 6.66 (2H, t, ³*J* = 7.6 Hz, calix ArH), 6.75 (2H, t, ³*J* = 7.6 Hz, calix ArH), 6.91 (4H, d, ³*J* = 7.6 Hz, calix ArH), 7.06 (4H, d, ³*J* = 7.6 Hz, calix ArH). **¹³C NMR** (75.5 MHz, CDCl₃) δ : 31.15, 41.99, 69.65, 73.43, 75.39, 119.05, 125.40, 128.08, 128.42, 128.93, 133.45, 151.68, 152.99. **MS (ES⁺)** *m/z*: 599.3113 [M + H]⁺ (Calcd. for C₃₆H₄₃N₂O₆: 599.3121).

25,27-Bis(2-(2-(2-aminoethoxy)ethoxy)ethoxy)-26,28-dihydroxycalix[4]arene (25):

Compound **23** (2.19 g, 2.31 mmol) was suspended in EtOH (80 mL) and hydrazine monohydrate (2 mL, excess) was added. The resulting suspension was heated under reflux for 16 hours before the reaction mixture was cooled to room temperature and poured into H₂O (200 mL). The suspension was extracted with EtOAc (3 x 100 mL) and the combined organic layers were dried over MgSO₄, filtered and the solvent was removed *in vacuo* to give **25** (1.48 g, 93%). **m.p.** 136-138 °C. **¹H NMR** (300 MHz, CDCl₃) δ : 2.79 (4H, t, ³*J* = 5.3 Hz,

CH_2NH_2), 3.37 (4H, d, $^2J = 13.1$ Hz, $\text{ArCH}_{\text{in}}\text{H}_{\text{out}}\text{Ar}$), 3.49 (4H, t, $^3J = 5.3$ Hz, OCH_2), 3.71 (4H, m, OCH_2), 3.85 (4H, m, OCH_2), 4.00 (4H, m, OCH_2), 4.20 (4H, m, OCH_2), 4.42 (4H, d, $^2J = 13.1$ Hz, $\text{ArCH}_{\text{in}}\text{H}_{\text{out}}\text{Ar}$), 6.66 (2H, t, $^3J = 7.4$ Hz, calix ArH), 6.72 (2H, d, $^3J = 7.4$ Hz, calix ArH), 6.88 (4H, d, $^3J = 7.4$ Hz, calix ArH), 7.06 (4H, d, $^3J = 7.4$ Hz, calix ArH). ^{13}C NMR (75.5 MHz, CDCl_3) δ : 31.14, 41.75, 70.00, 70.45, 71.03, 73.44, 75.44, 118.93, 125.28, 128.12, 128.43, 128.91, 133.29, 151.83, 153.20. MS (ES^+) m/z : 344.1902 $[\text{M} + 2\text{H}]^{2+}$, 687.3809 $[\text{M} + \text{H}]^+$.

Isophthalamide-diether calix[4]arene macrobicycle (26): A solution of **24** (0.32 g, 0.53 mmol) in dry CH_2Cl_2 (100 mL) and a solution of isophthaloyl dichloride (0.11 g, 0.53 mmol) in dry CH_2Cl_2 (100 mL) were added dropwise simultaneously to a stirred solution of triethylamine (0.3 mL, 2.15 mmol) in dry CH_2Cl_2 (200 mL) over 2 hours under a N_2 atmosphere. The reaction mixture was concentrated *in vacuo* to a volume of 50 mL once the addition was complete and washed with 1 M HCl (2 x 50 mL), H_2O (50 mL), 1 M NaOH (50 mL) and brine (50 mL). The organic layer was dried over MgSO_4 , filtered and the solvent was removed *in vacuo*. The crude material was purified by silica gel chromatography (7:3 EtOAc/acetone) to give **26** as a white solid (0.23 g, 58%). m.p. 285 °C (dec.). ^1H NMR (300 MHz, CDCl_3) δ : 3.29 (4H, d, $^2J = 13.2$ Hz, $\text{ArCH}_{\text{in}}\text{H}_{\text{out}}\text{Ar}$), 3.79 (12H, m, NCH_2 , OCH_2), 4.30 (8H, m, $\text{ArCH}_{\text{in}}\text{H}_{\text{out}}\text{Ar}$, OCH_2), 6.58 (2H, t, $^3J = 7.4$ Hz, calix ArH), 6.68 (2H, t, $^3J = 7.4$ Hz, calix ArH), 6.79 (4H, d, $^3J = 7.4$ Hz, calix ArH), 6.93 (4H, d, $^3J = 7.4$ Hz, calix ArH), 7.32 (2H, s, OH), 7.36 (1H, m, isoH), 7.52 (2H, br s, NH), 7.93 (2H, dd, $^3J = 7.6$ Hz, $^4J = 1.5$ Hz, isoH), 8.10 (1H, s, isoH). ^{13}C NMR (75.5 MHz, CDCl_3) δ : 30.74, 40.03, 68.86, 69.85, 75.28, 119.54, 123.04, 125.40, 127.78, 128.48, 128.98, 129.27, 131.23, 133.04, 133.36, 151.07, 152.08, 166.68. MS (ES^+) m/z : 751.3459 $[\text{M} + \text{Na}]^+$.

5-Nitroisophthalamide-diether calix[4]arene macrobicycle (27): A solution of **24** (0.80 g,

1.34 mmol) in dry CH_2Cl_2 (100 mL) and a solution of 5-nitroisophthaloyl dichloride (1.34 mmol) in dry CH_2Cl_2 (100 mL) were added dropwise simultaneously to a stirred solution of triethylamine (0.72 mL, 5.17 mmol) in dry CH_2Cl_2 (300 mL) over 1.5 hours under a N_2 atmosphere. The reaction mixture was concentrated *in vacuo* to a volume of 50 mL and washed with 1 M HCl (2 x 100 mL), H_2O (100 mL), 1 M NaOH (100 mL) and brine (100 mL). The organic layer was dried over MgSO_4 , filtered and the solvent was removed *in vacuo*. The crude material was purified by silica gel chromatography (7:3 EtOAc/acetone) eluting **27** as the third band to give a green solid (0.37 g, 35%). **m.p.** 290 °C (dec.). ^1H NMR (300 MHz, CDCl_3) δ : 3.24 (4H, d, $^2J = 13.2$ Hz, $\text{ArCH}_{\text{in}}\text{H}_{\text{out}}\text{Ar}$), 3.73 (4H, m, NCH_2), 3.79 (8H, m, OCH_2), 4.20 (4H, d, $^2J = 13.2$ Hz, $\text{ArCH}_{\text{in}}\text{H}_{\text{out}}\text{Ar}$), 4.28 (4H, m, OCH_2), 6.51 (2H, t, $^3J = 7.5$ Hz, calix ArH), 6.64 (2H, t, $^3J = 7.5$ Hz, calix ArH), 6.74 (4H, d, $^3J = 7.5$ Hz, calix ArH), 6.87 (4H, d, $^3J = 7.5$ Hz, calix ArH), 7.13 (2H, s, OH), 7.66 (2H, br s, NH), 8.32 (1H, s, isoH), 8.59 (2H, s, isoH). ^{13}C NMR (75.5 MHz, CDCl_3) δ : 30.52, 40.26, 68.86, 69.50, 75.29, 109.99, 119.62, 125.51, 125.97, 127.79, 128.26, 128.57, 129.05, 132.84, 135.12, 150.71, 151.65, 164.58. **MS** (ES^+) m/z : 796.3348 $[\text{M} + \text{Na}]^+$.

Isophthalamide-triether calix[4]arene macrobicycle (28): Separate solutions of **25** (0.46 g, 0.66 mmol) in dry CH_2Cl_2 (100 mL) and isophthaloyl dichloride (0.13 g, 0.66 mmol) in dry CH_2Cl_2 (100 mL) were added dropwise simultaneously to a stirred solution of triethylamine (0.35 mL, 2.5 mmol) in dry CH_2Cl_2 (250 mL) over 3 hours under a N_2 atmosphere. The reaction mixture was stirred for a further 2 hours before concentrating to approximately 50 mL *in vacuo*. The reaction mixture was washed with 1 M HCl (2 x 100 mL), H_2O (100 mL), 1 M NaOH (100 mL) and brine (100 mL), dried over MgSO_4 , filtered and taken to dryness. Purification by silica gel chromatography (7:3 EtOAc/acetone) gave **28** as a white solid (0.31 g, 57%). **m.p.** 172-174 °C. ^1H NMR (300 MHz, CDCl_3) δ : 3.33 (4H, d, $^2J = 13.2$ Hz, $\text{ArCH}_{\text{in}}\text{H}_{\text{out}}\text{Ar}$), 3.51 (4H, m, NCH_2), 3.67 (4H, t, $^3J = 4.7$ Hz, OCH_2), 3.76

(4H, m, OCH₂), 3.83 (8H, m, OCH₂), 4.02 (4H, m, OCH₂), 4.33 (4H, d, ²J = 13.2 Hz, ArCH_{in}H_{out}Ar), 6.69 (4H, m, calix ArH), 6.84 (4H, d, ³J = 7.3 Hz, calix ArH), 7.06 (4H, d, ³J = 7.3 Hz, calix ArH), 7.53 (4H, m, OH, NH), 7.60 (1H, t, ³J = 7.9 Hz, isoH), 8.11 (2H, dd, ³J = 7.9 Hz, ⁴J = 1.5 Hz, isoH), 8.29 (1H, s, isoH). ¹³C NMR (75.5 MHz, CDCl₃) δ: 31.00, 39.93, 69.35, 69.83, 70.54, 75.07, 119.26, 124.51, 125.32, 128.08, 128.51, 128.96, 129.08, 130.96, 133.11, 134.90, 151.63, 152.84, 167.01. MS (ES⁺) *m/z*: 839.3873 [M + Na]⁺.

25-(2-(2-Phthalimidoethoxy)ethoxy)-26,27,28-trihydroxycalix[4]arene (29): A mixture of calix[4]arene (0.45 g, 1.06 mmol) and K₂CO₃ (0.089 g, 0.64 mmol) in dry CH₃CN (50 mL) was stirred under a N₂ atmosphere at room temperature for 35 minutes. Compound **4** (0.51 g, 1.30 mmol) was added and the reaction mixture was heated at 70 °C for 5 days, cooled to room temperature and the solvent was removed *in vacuo*. The residue was triturated with 1 M HCl (25 mL) and extracted with CH₂Cl₂ (3 x 25 mL). The organic layer was washed with H₂O (2 x 25 mL), dried over MgSO₄, filtered and the solvent was removed *in vacuo*. Purification by silica gel chromatography (95:5 CHCl₃/acetone) eluted the product as the second band. Following titration with EtOAc, **29** was isolated as a white solid (0.15 g, 22%). **m.p.** 222-224 °C. ¹H NMR (300 MHz, CDCl₃) δ: 3.27 (2H, d, ²J = 13.3 Hz, ArCH_{in}H_{out}Ar), 3.37 (2H, d, ²J = 13.3 Hz, ArCH_{in}H_{out}Ar) 4.05 (8H, m, ArCH_{in}H_{out}Ar, NCH₂, OCH₂), 4.29 (2H, m, OCH₂), 4.37 (2H, d, ²J = 13.3 Hz, ArCH_{in}H_{out}Ar), 6.58 (2H, t, ³J = 7.6 Hz, calix ArH), 6.64 (1H, t, ³J = 7.6 Hz, calix ArH), 6.85 (3H, m, calix ArH), 6.95 (4H, d, ³J = 7.6 Hz, calix ArH), 7.05 (2H, d, ³J = 7.6 Hz, calix ArH), 7.53 (2H, m, PhthH), 7.59 (2H, m, PhthH), 9.06 (2H, s, OH), 9.69 (1H, s, OH). ¹³C NMR (75.5 MHz, CDCl₃) δ: 31.07, 31.78, 37.88, 68.69, 69.87, 75.12, 120.95, 121.56, 122.80, 126.04, 128.26, 128.40, 128.57, 128.69, 129.18, 131.73, 133.54, 134.66, 149.54, 150.11, 151.18, 168.33. MS (ES⁺) *m/z*: 642.2835 [M + H]⁺, 664.2295 [M + Na]⁺ (Calcd. for C₄₀H₃₅NO₇Na: 664.2306).

5-Nitroisophthalamide-diether calix[4]arene macrotricycle (30): This product was eluted as the second band during the chromatographic purification of **27** to give **30** as a white solid (0.03 g, 1%). **m.p.** 192-194 °C. $^1\text{H NMR}$ (300 MHz, CDCl_3) δ : 3.26 (8H, d, $^2J = 12.9$ Hz, $\text{ArCH}_{\text{in}}\text{H}_{\text{out}}\text{Ar}$), 3.81 (8H, m, NCH_2), 3.88 (8H, m, OCH_2), 3.97 (8H, m, OCH_2), 4.15 (16H, m, $\text{ArCH}_{\text{in}}\text{H}_{\text{out}}\text{Ar}$, OCH_2), 6.58 (4H, t, $^3J = 7.5$ Hz, calix ArH), 6.70 (4H, t, $^3J = 7.5$ Hz, calix ArH), 6.82 (8H, d, $^3J = 7.5$ Hz, calix ArH), 6.92 (8H, d, $^3J = 7.5$ Hz, calix ArH), 7.76 (4H, s, OH), 8.12 (4H, br s, NH), 8.55 (4H, s, isoH), 8.86 (2H, s, isoH). $^{13}\text{C NMR}$ (75.5 MHz, CDCl_3) δ : 30.95, 40.50, 69.60, 69.74, 75.36, 119.79, 124.71, 125.63, 127.93, 128.50, 129.01, 131.22, 133.04, 136.25, 147.87, 151.24, 152.10, 165.50. **MS** (ES^+) m/z : 1568.6644 $[\text{M} + \text{Na}]^+$.

25,27-Bis(propyl)-26,28-dihydroxycalix[4]arene (31):¹¹ A suspension of calix[4]arene (1.30 g, 3.05 mmol) and K_2CO_3 (1.68 g, 12.18 mmol) in dry CH_3CN (90 mL) was stirred at room temperature for 30 minutes, iodopropane (1.19 mL, 12.2 mmol) was added and the resulting suspension was heated under reflux for 24 hours. The reaction mixture was cooled to room temperature and the solvent removed *in vacuo*. The residue was triturated with 1 M HCl (50 mL) and the suspension was extracted with CH_2Cl_2 (3 x 50 mL). The organic layer was separated, washed with H_2O (2 x 50 mL), dried over MgSO_4 , filtered and then concentrated *in vacuo*. The product was precipitated by addition of MeOH , filtered, washed with MeOH and dried to give **31** as a white solid (0.89 g, 57%). $^1\text{H NMR}$ (300 MHz, CDCl_3) δ : 1.33 (6H, t, $^3J = 7.3$ Hz, CH_3), 2.08 (4H, m, CH_2CH_3), 3.39 (4H, d, $^2J = 13.1$ Hz, $\text{ArCH}_{\text{in}}\text{H}_{\text{out}}\text{Ar}$), 3.99 (4H, t, $^3J = 6.2$ Hz, OCH_2), 4.33 (4H, d, $^2J = 13.1$ Hz, $\text{ArCH}_{\text{in}}\text{H}_{\text{out}}\text{Ar}$), 6.65 (2H, t, $^3J = 7.5$ Hz, calix ArH), 6.76 (2H, d, $^3J = 7.5$ Hz, calix ArH), 6.93 (4H, d, $^3J = 7.5$ Hz, calix ArH), 7.06 (4H, d, $^3J = 7.5$ Hz, calix ArH), 8.33 (2H, s, OH). **MS** (ES^+) m/z : 509.3247 $[\text{M} + \text{H}]^+$, 531.2512 $[\text{M} + \text{Na}]^+$.

25,27-Bis(propyl)-calix[4]diquinone (32):² An aqueous solution of ClO₂ (prepared in 10 mL H₂O from 0.23 g NaClO₂ and 0.3 g Na₂S₂O₈) was added to a suspension of **31** (0.25 g, 0.49 mmol) in CH₃CN (15 mL) in the absence of light and this was stirred at room temperature for 63 hours. The organic solvent was removed *in vacuo* and the aqueous layer was extracted with CHCl₃ (3 x 20 mL). The combined organic layers were washed with H₂O (3 x 20 mL), dried over MgSO₄, filtered and the solvent was removed *in vacuo*. The crude material was purified by silica gel chromatography (92:8 petroleum ether/EtOAc) eluting product **32** as the first yellow band to give a yellow solid (0.10 g, 38%). ¹H NMR (300 MHz, CDCl₃) δ: 1.00 (6H, m, CH₃), 1.81 (4H, m, CH₂CH₃), 3.32 (4H, d, ²J = 12.9 Hz, ArCH_{in}H_{out}Qu), 3.65 (4H, t, ³J = 7.0 Hz, OCH₂), 3.81 (4H, br s, ArCH_{in}H_{out}Qu), 6.63 (6H, m, calix ArH, calix QuH), 6.80 (4H, d, ³J = 7.6 Hz, calix ArH). MS (ES⁺) *m/z*: 559.2082 [M + Na]⁺ (Calcd. for C₃₄H₃₂O₆Na: 559.2091).

Bipyridyl-diether calix[4]arene macrobicycle (33): Separate solutions of 4,4'-bis(chlorocarbonyl)-2,2'-bipyridine (0.44 mmol) in dry CH₂Cl₂ (100 mL) and **24** (0.26 g, 0.44 mmol) in dry CH₂Cl₂ (100 mL) were added simultaneously dropwise over 1.5 hours to a solution of triethylamine (0.18 mL, 1.29 mmol) in dry CH₂Cl₂ (250 mL). After the addition was complete, the reaction mixture was stirred for a further 4 hours at room temperature and then concentrated *in vacuo* to a volume of approximately 100 mL. The organic layer was washed with 1 M HCl (2 x 100 mL), H₂O (100 mL), 1 M NaOH (100 mL) and brine (100 mL). The organic layer was dried over MgSO₄, filtered and the solvent was removed *in vacuo*. Purification by silica gel chromatography (95:5 THF/MeOH) eluted impure **33** as a pink band. Further purification was unsuccessful and therefore the impure material was reacted on. MS (ES⁺) *m/z*: 865.3 [M + CH₃CN + NH₄]⁺.

Tricarbonylchloro(4,4'-dimethyl-2,2'-bipyridine)rhenium (34):^{adapted from 12} A suspension of rhenium pentacarbonyl chloride (30.2 mg, 0.083 mmol) and

4,4'-dimethyl-2,2'-bipyridine (15.6 mg, 0.084 mmol) in dry toluene (7 mL) was heated under reflux under a N₂ atmosphere for 4.5 hours, during which time a yellow solid precipitated from the reaction mixture. This was collected by filtration to give **34** as a yellow solid (29.5 mg, 73%). ¹H NMR (300 MHz, CDCl₃) δ: 2.58 (6H, s, CH₃), 7.34 (2H, d, ³J = 4.8 Hz, bipyH), 7.99 (2H, br s, bipyH), 8.89 (2H, d, ³J = 4.8 Hz, bipyH). MS (ES⁺) *m/z*: 549.1 [M + CH₃CN + NH₄]⁺.

4,4'-Dicarboxysuccinimidyl-2,2'-bipyridine (35):¹³ Compound **11** (0.41 g, 1.67 mmol) and *N*-hydroxysuccinimide (0.38 g, 3.32 mmol) were suspended in dry degassed DMF (15 mL). A solution of DCC (0.69 g, 3.36 mmol) in dry degassed DMF (5 mL) was added dropwise and the reaction was stirred at room temperature under a N₂ atmosphere for 16 hours. The reaction mixture was filtered and the solvent was removed *in vacuo*. The residue was dissolved in CHCl₃, filtered and the solvent was removed *in vacuo*. Trituration with CH₃CN gave **35** contaminated with *N,N'*-dicyclohexylurea (0.52 g, ~72%). ¹H NMR (300 MHz, CDCl₃) δ: 2.96 (8H, br s, CH₂), 8.01 (2H, d, ³J = 5.6 Hz, bipyH), 8.96 (2H, d, ³J = 5.6 Hz, bipyH), 9.14 (2H, s, bipyH). MS (FI⁺) *m/z*: 438.1069.

Tricarbonylchloro(4,4'-dicarboxysuccinimidyl-2,2'-bipyridine)rhenium (36): A suspension of rhenium pentacarbonyl chloride (0.067 g, 0.19 mmol) and **35** (0.098 g, 0.224 mmol) in dry toluene (13 mL) was heated under reflux under a N₂ atmosphere for 15.5 hours, during which time an orange solid precipitated from the reaction mixture. This was collected by filtration and washed with toluene to give **36** (0.10 g, 74%). **m.p.** 280 °C (dec.). ¹H NMR (300 MHz, acetone-*d*₆) δ: 2.89 (8H, m, CH₂), 8.28 (2H, d, ³J = 7.0 Hz, bipyH), 9.36 (4H, m, bipyH). ¹³C NMR (75.5 MHz, DMSO-*d*₆) δ: 25.65, 125.30, 127.36, 134.97, 154.68, 156.22, 159.69, 169.84, 197.24. MS (ES⁺) *m/z*: 764.9766 [M + Na]⁺ (Calcd. for C₂₃H₁₄N₄O₁₁ClReNa: 765.9769).

Bis(2-phthalimidoethyl)amine (37):¹⁴ Phthalic anhydride (5.60 g, 75 mmol), diethylenetriamine (1.94 g, 35 mmol) were dissolved in toluene (200 mL) and the resulting slurry was heated under reflux with a Dean-Stark apparatus for 46 hours. The solution was cooled to room temperature and the solvent was removed *in vacuo*. Trituration of the resulting powder in EtOH (100 mL) for 4.5 hours at room temperature gave the product **37** as an orange solid (5.84 g, 86%). ¹H NMR (300 MHz, CDCl₃) δ: 2.96 (4H, t, ³J = 6.1 Hz, NCH₂) 3.78 (4H, t, ³J = 6.1 Hz, NCH₂) 7.69 (4H, m, PhthH), 7.74 (4H, m, PhthH). MS (ES⁺) *m/z*: 364.1323 [M + H]⁺.

tert-Butyl bis(2-phthalimidoethyl)carbamate (38):¹⁴ Compound **37** (3.34 g, 9.19 mmol), di-*tert*-butyldicarbonate (2.44 g, 11.18 mmol) and K₂CO₃ (3.31 g, 15.17 mmol) were dissolved in 1:1 CH₂Cl₂/CH₃CN (300 mL) and the reaction mixture was stirred at room temperature for 20 hours. The solvent was removed *in vacuo* and the residue was dissolved in CH₂Cl₂ (200 mL), washed with H₂O (2 x 200 mL), dried over MgSO₄, filtered and the solvent was removed *in vacuo*. The resulting yellow oily residue was recrystallised from MeOH/hexane to give **38** as a white solid (3.24 g, 76%). ¹H NMR (300 MHz, CDCl₃) δ: 1.06 (9H, m, *t*-Bu) 3.52 (4H, m, NCH₂) 3.86 (4H, m, NCH₂) 7.67 (2H, dd, ³J = 5.4 Hz, ⁴J = 3.1 Hz, PhthH) 7.72 (2H, dd, ³J = 5.4 Hz, ⁴J = 3.1 Hz, PhthH) 7.83 (4H, m, PhthH). MS (ES⁺) *m/z*: 486.1579 [M + Na]⁺, 949.3177 [2M + Na]⁺.

tert-Butyl bis(2-aminoethyl)carbamate (39):¹⁴ Compound **38** (1.89 g, 4.08 mmol) and hydrazine monohydrate (4 mL, 82 mmol) were stirred in EtOH (200 mL) for 1 day at room temperature, during which time a white precipitate formed. This was removed by filtration and the yellow filtrate was taken to dryness. The residue was extracted with CHCl₃ (5 x 40 mL) and the solvent was removed *in vacuo* to give **39** as a yellow oil (0.74 g, 89%). ¹H NMR (300 MHz, CDCl₃) δ: 1.46 (9H, s, *t*-Bu), 2.86 (4H, t, ³J = 6.5 Hz, NCH₂), 3.29 (4H,

br s, NCH_2). **MS (ES⁺)** m/z : 204.1904 $[\text{M} + \text{H}]^+$.

Isophthalamide macrocycle (40): Separate solutions of **39** (0.71 g, 3.49 mmol) and triethylamine (1.6 mL, 11.38 mmol) in dry CH_2Cl_2 (150 mL), and isophthaloyl dichloride (0.71 g, 3.49 mmol) in dry CH_2Cl_2 (150 mL) were added dropwise over 40 minutes to a 1 L 3 neck flask filled with dry CH_2Cl_2 (350 mL) under a N_2 atmosphere in a dry ice/acetone bath. The reaction mixture was allowed to warm to room temperature and stirred for a further day. The solution was concentrated *in vacuo* to approximately 250 mL, washed with H_2O (2 x 150 mL), dried over MgSO_4 , filtered and the solvent was removed *in vacuo*. The residue was purified by silica gel chromatography eluting the impure product **40** with 1:1 CH_2Cl_2 /acetone. **¹H NMR** (300 MHz, $\text{DMSO}-d_6$) δ : 1.36 (18H, s, *t*-Bu), 3.39 (8H, m, NCH_2), 7.52 (2 H, t, $^3J = 7.5$ Hz, *isoH*), 7.91 (4H, d, $^3J = 7.5$ Hz, *isoH*), 8.27 (2H, m, *isoH*), 8.75 (4H, br s, *NH*). **MS (ES⁺)** m/z : 667.3438 $[\text{M} + \text{H}]^+$ (Calcd. for $\text{C}_{34}\text{H}_{47}\text{N}_6\text{O}_8$: 667.3455), 689.3470 $[\text{M} + \text{Na}]^+$.

Dimethyl 2,6-pyridinedicarboxylate (41):¹⁵ A suspension of 2,6-pyridinedicarboxylic acid (4.08 g, 20 mmol) and H_2SO_4 (0.5 mL) in MeOH (50 mL) was heated under reflux for 16 hours. Upon cooling to room temperature, a white solid precipitated and this was filtered, washed with MeOH and air dried to give **41** (4.00 g, 100%). **¹H NMR** (300 MHz, CDCl_3) δ : 4.04 (6H, s, CH_3), 8.06 (1H, t, $^3J = 7.5$ Hz, pyH^4), 8.33 (2H, d, $^3J = 7.5$ Hz, pyH^3 and H^6). **MS (ES⁺)** m/z : 196.0 $[\text{M} + \text{H}]^+$, 218.0 $[\text{M} + \text{Na}]^+$, 234.0 $[\text{M} + \text{K}]^+$, 413.2 $[2\text{M} + \text{Na}]^+$, 429.1 $[2\text{M} + \text{K}]^+$.

2-Chloro-*N,N*-bis(phthalimidoethyl)acetamide (42): A solution of chloroacetyl chloride (0.1 mL, 1.26 mmol) in CH_2Cl_2 (5 mL) in a dropping funnel was added dropwise to a solution of **37** (0.43 g, 1.17 mmol) in CH_2Cl_2 (10 mL) under a N_2 atmosphere over 30 minutes. The mixture was stirred for a further 2 hours once the addition was complete, then it was washed

with 1 M HCl (2 x 20 mL), H₂O (20 mL) and brine (20 mL). The organic layer was separated, dried over MgSO₄, filtered and the solvent was removed *in vacuo*. The crude solid was triturated in hot MeOH to give **42** as an off-white solid (0.22 g, 42%). **m.p.** 190-192 °C. **¹H NMR** (300 MHz, CDCl₃) δ: 3.67 (2H, m, NCH₂), 3.81 (2H, m, NCH₂), 3.93 (4H, m, NCH₂), 4.05 (2H, s, CH₂Cl), 7.70 (2H, dd, ³*J* = 5.4 Hz, ⁴*J* = 3.1 Hz, Phth*H*), 7.76 (2H, dd, ³*J* = 5.6 Hz, ⁴*J* = 2.9 Hz, Phth*H*), 7.85 (4H, m, Phth*H*). **¹³C NMR** (75.5 MHz, CDCl₃) δ: 35.01, 35.68, 40.43, 43.89, 45.40, 123.32, 123.59, 131.65, 131.94, 133.95, 134.39, 167.49, 167.95, 168.22. **MS (ES⁺)** *m/z*: 440.1718 [M + H]⁺, 462.1595 [M + Na]⁺, 901.3387 [2M + Na]⁺.

5,11,17,23-Tetra-*tert*-butyl-25-*N,N*-bis(phthalimidoethyl)acetamide-26,27,28-

trihydroxycalix[4]arene (43): A suspension of *tert*-butylcalix[4]arene (0.48 g, 0.74 mmol) and K₂CO₃ (0.21 g, 1.5 mmol) in dry CH₃CN (50 mL) was stirred at room temperature under a N₂ atmosphere for 30 minutes before addition of **42** (0.81 g, 1.85 mmol). The resulting mixture was heated at 90 °C under a N₂ atmosphere for 87 hours then cooled to room temperature and the solvent was removed *in vacuo*. The residue was triturated with 1 M HCl (25 mL) and extracted with CH₂Cl₂ (3 x 25 mL). The organic layer was washed with H₂O (2 x 25 mL), dried over MgSO₄, filtered and the solvent was removed *in vacuo*. The crude material was purified by silica gel chromatography (95:5 CHCl₃/acetone) and **43** was isolated as a white solid (0.15 g, 19%). **m.p.** 260 °C (dec.). **¹H NMR** (300 MHz, CDCl₃) δ: 1.19 (27H, s, *t*-Bu), 1.22 (9H, s, *t*-Bu), 3.14 (2H, d, ²*J* = 12.9 Hz, ArCH_{in}H_{out}Ar), 3.31 (2H, d, ²*J* = 13.6 Hz, ArCH_{in}H_{out}Ar), 3.58 (2H, m, NCH₂), 3.96 (6H, m, NCH₂), 4.12 (2H, d, ²*J* = 13.6 Hz, ArCH_{in}H_{out}Ar), 4.26 (2H, d, ²*J* = 12.9 Hz, ArCH_{in}H_{out}Ar), 4.93 (2H, s, ArOCH₂), 6.89 (2H, s, calix Ar*H*), 6.95 (2H, s, calix Ar*H*), 6.99 (4H, s, calix Ar*H*), 7.58 (2H, dd, ³*J* = 5.3 Hz, ⁴*J* = 3.2 Hz, Phth*H*), 7.69 (2H, dd, ³*J* = 5.3 Hz, ⁴*J* = 3.2 Hz, Phth*H*), 7.78 (2H, dd, ³*J* = 4.9 Hz, ⁴*J* = 3.3 Hz, Phth*H*), 7.83 (2H, dd, ³*J* = 4.9 Hz, ⁴*J* = 3.3 Hz, Phth*H*), 9.18 (2H, s, OH), 10.07 (1H, s, OH). **¹³C NMR** (75.5 MHz, CDCl₃) δ: 31.25, 31.45, 31.51, 32.49,

32.96, 33.83, 33.89, 34.11, 35.31, 43.86, 43.99, 71.60, 123.34, 123.66, 125.35, 125.43, 125.66, 126.22, 127.47, 127.83, 128.14, 131.66, 131.92, 133.63, 133.82, 134.26, 142.52, 142.85, 147.52, 148.16, 148.35, 151.05, 168.01, 168.42, 170.23. **MS (ES⁺)** *m/z*: 1074.6283 [M + Na]⁺.

5-(Chloromethyl)-2-hydroxybenzaldehyde (44):¹⁶ Salicylaldehyde (5 mL, 0.047 mol), formaldehyde (35% by weight, 4 mL) and HCl (48 mL) were stirred for 16.5 hours. The brown precipitate was filtered off, redissolved in 80 mL diethyl ether, dried over Na₂SO₄, filtered and the solvent was removed *in vacuo*. The crude material was recrystallised from hot hexane to give **44** as a white solid (2.89 g, 36%). ¹H NMR (300 MHz, CDCl₃) δ: 4.60 (2H, s, CH₂), 7.01 (1H, d, ³J = 8.5 Hz, ArH), 7.58 (2H, m, ArH), 9.91 (1H, s, OH), 11.08 (1H, s, CHO). **MS (EI⁺)** *m/z*: 170.0130 (Calcd. for C₈H₇O₂Cl: 170.0135).

Zinc Schiff base complex (45): Ethylenediamine (0.047 g, 0.78 mmol), **44** (0.28 g, 1.65 mmol), Zn(OAc)₂·2H₂O (0.19 g, 0.86 mmol) and triethylamine (0.3 mL, 2.2 mmol) were dissolved in MeOH (5 mL) and stirred for 1 day at room temperature, during which time a yellow solid precipitated from the reaction mixture. The solid was collected by filtration, washed with MeOH and dried to give impure **45** (0.25 g). ¹H NMR (300 MHz, DMSO-*d*₆) δ: 3.68 (4H, s, CH₂), 4.22 (4H, s, CH₂Cl), 6.59 (2H, d, ³J = 9.1 Hz, ArH), 7.09 (4H, m, ArH), 8.42 (2H, s, imineH).

Zinc Schiff base complex (46): 1,3-Diaminobenzene (0.041 g, 0.38 mmol), **44** (0.14 g, 0.81 mmol), Zn(OAc)₂·2H₂O (0.09 g, 0.42 mmol) and triethylamine (0.15 mL, 1.1 mmol) were dissolved in MeOH (40 mL) and stirred overnight at room temperature, during which time a yellow solid precipitated from the reaction mixture. The solid was collected by filtration, washed with MeOH and dried to give impure **46** (0.11 g). ¹H NMR (300 MHz, DMSO-*d*₆) δ: 4.26 (2H, s, CH₂Cl), 6.67 (2H, m, ArH), 7.20 (2H, m, ArH), 7.37 (4H, s, ArH),

7.90 (2H, m, ArH), 9.01 (2H, s, imineH).

2-Allyloxybenzaldehyde (47):¹⁷ Salicylaldehyde (8 mL, 75 mmol) and KOH (5.90 g, 105 mmol) were suspended in EtOH (25 mL), allyl bromide (9.8 mL, 113 mmol) was added and the mixture was heated under reflux for 4 hours. The suspension was cooled to room temperature and the solvent was removed *in vacuo*. The residue was extracted with CH₂Cl₂ (50 mL) and the organic layer was washed with 10% aqueous KOH solution (50 mL), dried over MgSO₄, filtered and the solvent was removed *in vacuo* to give **47** as a brown oil (9.85 g, 81%). ¹H NMR (300 MHz, CDCl₃) δ: 4.66 (2H, d, ³J = 5.0 Hz, OCH₂), 5.40 (2H, m, CHCH₂), 6.08 (1H, m, CHCH₂), 7.01 (2H, m, ArH), 7.53 (1H, t, ³J = 7.4 Hz, ArH), 7.84 (1H, d, ³J = 7.4 Hz, ArH), 10.54 (1H, s, CHO). MS (FI⁺) *m/z*: 162.0767 (Calcd. for C₁₀H₁₀O₂: 162.0681).

2-(Allyloxy)-5-(chloromethyl)benzaldehyde (48): A solution of **47** (1.00 g, 6.14 mmol), paraformaldehyde (0.28 g, 9.32 mmol), H₂SO₄ (cat.) and HCl (10 mL) were stirred at room temperature for 5 days. The reaction mixture was extracted with CH₂Cl₂ (3 x 20 mL), the solvent was removed *in vacuo* and the residue was purified by Kugelrohr distillation to give **48** as a yellow oil (0.27 g, 21%). ¹H NMR (300 MHz, CDCl₃) δ: 4.57 (2H, s, CH₂Cl), 4.68 (2H, d, ³J = 5.0 Hz, OCH₂), 5.41 (2H, m, CHCH₂), 6.08 (1H, m, CHCH₂), 6.99 (1H, d, ³J = 8.7 Hz, ArH), 7.58 (1H, dd, ³J = 8.7 Hz, ⁴J = 2.2 Hz, ArH), 7.85 (1H, d, ⁴J = 2.2 Hz, ArH), 10.51 (1H, s, CHO). ¹³C NMR (75.5 MHz, CDCl₃) δ: 45.31, 69.34, 113.36, 118.31, 124.87, 128.55, 130.12, 132.07, 136.04, 160.76, 189.15. MS (FI⁺) *m/z*: 210.0457 (Calcd. for C₁₁H₁₁O₂Cl: 210.0448).

2-(Allyloxy)-5-(bromomethyl)benzaldehyde (49): A 48% HBr (40 mL) solution of **47** (3.50 g, 22 mmol), paraformaldehyde (0.96 g, 31.8 mmol) and a couple of drops of H₂SO₄ were stirred at room temperature for 3 days. The aqueous layer was extracted with CH₂Cl₂

(3 x 50 mL) and the organic layer was dried over MgSO_4 , filtered and the solvent was removed *in vacuo*. The crude material was purified by silica gel chromatography (95:5 petroleum ether/EtOAc) and the product was eluted as the third band to give **49** as a white solid (1.67 g, 33%). ^1H NMR (300 MHz, CDCl_3) δ : 4.49 (2H, s, CH_2Cl), 4.69 (2H, dt, $^3J = 5.0$ Hz, $^4J = 1.5$ Hz, OCH_2), 5.41 (2H, m, CHCH_2), 6.08 (1H, m, CHCH_2), 6.98 (1H, d, $^3J = 8.6$ Hz, ArH), 7.59 (1H, dd, $^3J = 8.6$ Hz, $^4J = 2.6$ Hz, ArH), 7.87 (1H, d, $^4J = 2.6$ Hz, ArH), 10.51 (1H, s, CHO). ^{13}C NMR (75.5 MHz, CDCl_3) δ : 32.49, 69.34, 113.41, 118.33, 124.92, 128.84, 130.41, 132.02, 136.44, 160.68, 189.06. MS (FI^+) m/z : 253.9934 (Calcd. for $\text{C}_{11}\text{H}_{11}\text{O}_2\text{Br}$: 253.9942).

5,11,17,23-Tetra-*tert*-butyl-25,27-bis(2-(allyloxy)-5-(phenoxymethyl)benzaldehyde)-

26,28-dihydroxycalix[4]arene (50): Compound **49** (1.04 g, 4.94 mmol), *tert*-butylcalix[4]arene (1.28 g, 1.97 mmol) and K_2CO_3 (0.57 g, 4.16 mmol) were suspended in dry CH_3CN (15 mL), stirred at room temperature for 60 seconds and heated under microwave irradiation for 10 minutes at 160 °C. The solvent was removed *in vacuo* and the resulting yellow residue was triturated with 1 M HCl (50 mL). The suspension was extracted with CH_2Cl_2 (3 x 50 mL) and the organic layer was washed with H_2O (2 x 50 mL), dried over MgSO_4 , filtered and the solvent was removed *in vacuo*. Purification by silica gel chromatography (98:2 CHCl_3 /acetone) eluting impure **50** as the third band gave a white solid (0.74 g). ^1H NMR (300 MHz, CDCl_3) δ : 0.97 (18H, s, *t*-Bu), 1.28 (18H, s, *t*-Bu), 3.25 (4H, d, $^2J = 13.1$ Hz, $\text{ArCH}_{\text{in}}\text{H}_{\text{out}}\text{Ar}$), 4.21 (4H, d, $^2J = 13.1$ Hz, $\text{ArCH}_{\text{in}}\text{H}_{\text{out}}\text{Ar}$), 4.64 (4H, d, $^3J = 5.0$ Hz, OCH_2CH), 5.04 (4H, s, OCH_2), 5.43 (4H, m, CHCH_2), 6.09 (2H, m, CHCH_2), 6.81 (4H, s, calix ArH), 6.93 (2H, d, $^3J = 8.7$ Hz, ArH), 7.04 (4H, s, calix ArH), 7.29 (2H, s, OH), 7.86 (2H, d, $^4J = 2.1$ Hz, ArH), 8.08 (2H, dd, $^3J = 8.7$ Hz, $^4J = 2.1$ Hz, ArH), 10.53 (2H, s, CHO). MS (ES^+) m/z : 1019.5081 $[\text{M} + \text{Na}]^+$.

2-(Allyloxy)-5-hydroxybenzaldehyde (51): 2,5-Dihydroxybenzaldehyde (0.17 g, 1.26 mmol) was dissolved in DMSO (5 mL) and NaH (60% dispersion in mineral oil, 0.052 g, 1.3 mmol) was added. The resulting suspension was stirred at room temperature under a N₂ atmosphere for 1 hour before allyl bromide (0.11 mL, 1.27 mmol) was added. The reaction mixture was stirred at room temperature for 19 hours and then poured into H₂O (20 mL). The brown suspension was extracted with CHCl₃ (3 x 20 mL) and the combined organic layers were washed with H₂O (2 x 20 mL), dried over MgSO₄, filtered and the solvent was removed *in vacuo*. The residue was purified by silica gel chromatography (9:1 petroleum ether/EtOAc) eluting the impure product as the second band. The solvent was removed *in vacuo* and the residue was redissolved in CH₂Cl₂ (20 mL) and washed with saturated NaHCO₃ (3 x 10 mL) and H₂O (5 x 10 mL), and 1 M HCl (10 mL) to remove unreacted starting material. The organic layer was dried over MgSO₄, filtered and the solvent was removed *in vacuo* to give **51** as a yellow oil (0.048 g, 21%). ¹H NMR (300 MHz, CDCl₃) δ: 4.62 (2H, dt, ³J = 5.1 Hz, ⁴J = 1.6 Hz, OCH₂), 5.39 (2H, m, CHCH₂), 6.07 (1H, m, CHCH₂), 6.92 (1H, d, ³J = 8.8 Hz, ArH), 7.08 (1H, m, ArH), 7.31 (1H, m, ArH), 10.48 (1H, s, CHO). ¹³C NMR (75.5 MHz, CDCl₃) δ: 69.86, 113.45, 114.82, 117.99, 124.02, 125.10, 132.52, 150.15, 155.60, 190.70. MS (FT⁺) *m/z*: 178.0638 (Calcd. for C₁₀H₁₀O₃: 178.0630).

6.2.3. Syntheses from Chapter Three

5,11,17,23-Tetra-*tert*-butyl-25,27-bis(4-2-(aminoethoxy)phenoxy)ethoxy)-26,28-dihydroxycalix[4]arene (52):¹⁸ Compound **61** (0.42 g, 0.33 mmol) was suspended in EtOH (20 mL) and hydrazine monohydrate (0.4 mL, excess) was added. The reaction mixture was heated under reflux for 15.5 hours, cooled to room temperature and poured into H₂O (50 mL). Following extraction with EtOAc (3 x 50 mL), the combined organic layers were dried over MgSO₄, filtered and the solvent was removed *in vacuo* to give **52** as a white solid (0.31 g, 92%). **Microwave synthesis:** A suspension of **61** (0.64 g, 0.51 mmol) and hydrazine

monohydrate (0.6 mL, excess) was stirred for 30 seconds at room temperature and heated under microwave irradiation for 10 minutes at 100 °C before being cooled to room temperature. The resulting suspension was poured into H₂O (50 mL) and extracted using EtOAc (3 x 50 mL). The combined organic layers were dried over MgSO₄, filtered and the solvent was removed *in vacuo* to give **52** (0.50 g, 99%). ¹H NMR (300 MHz, CDCl₃) δ: 1.02 (18H, s, *t*-Bu), 1.28 (18H, s, *t*-Bu), 3.06 (4H, t, ³*J* = 4.9 Hz, NCH₂), 3.31 (4H, d, ²*J* = 13.1 Hz, ArCH_{in}H_{out}Ar), 3.93 (4H, t, ³*J* = 4.9 Hz, OCH₂), 4.28 (8H, m, OCH₂), 4.41 (4H, d, ²*J* = 13.1 Hz, ArCH_{in}H_{out}Ar), 6.85 (12H, m, hydroq ArH, calix ArH), 7.04 (4H, s, calix ArH), 7.53 (2H, s, OH). MS (ES⁺) *m/z*: 504.3046 [M + 2H]²⁺, 1007.6145 [M + H]⁺.

3,5-Bis(hexylcarbamoyl)-1-methylpyridinium iodide (53.I):^{19, 20} A solution of **62** (2.74 g, 8.21 mmol) and iodomethane (3 mL, excess) in CHCl₃ (150 mL) was heated under reflux under a N₂ atmosphere for 58 hours. The orange solution was cooled to room temperature, concentrated to approximately half the volume *in vacuo* and poured into diethyl ether (250 mL). The yellow precipitate was filtered off and washed with diethyl ether to give **53.I** (3.68 g, 94%). ¹H NMR (300 MHz, CDCl₃) δ: 0.89 (6H, m, CH₃), 1.36 (12H, m, CH₂), 1.72 (4H, m, CH₂), 3.45 (4H, m, NCH₂), 4.56 (3H, s, N⁺CH₃), 8.68 (2H, t, ³*J* = 5.6 Hz, NH), 9.42 (2H, s, pyH² and H⁶), 9.85 (1H, s, pyH⁴). MS (ES⁺) *m/z*: 348.2 [M – I]⁺, 823.4 [2M – I]⁺.

3,5-Bis(hexylcarbamoyl)-1-methylpyridinium chloride (53.Cl):^{adapted from 19, 20} A biphasic mixture of **53.I** (3.68 g, 7.73 mmol) in CHCl₃ (100 mL) and 1 M NH₄Cl (100 mL) was stirred for 30 minutes. The aqueous layer was separated and washing of the organic layer with NH₄Cl was repeated five times. The organic layer was separated, dried over MgSO₄, filtered and the solvent was removed *in vacuo* to give **53.Cl** as an orange solid (3.23 g, 100%). ¹H NMR (300 MHz, CDCl₃) δ: 0.88 (6H, t, ³*J* = 6.5 Hz, CH₃), 1.35 (12H, m, CH₂), 1.71 (4H, m, NCH₂CH₂), 3.44 (4H, m, NCH₂), 4.57 (3H, s, N⁺CH₃), 9.30 (2H, t, ³*J* = 5.1 Hz, NH), 9.42

(2H, s, pyH² and H⁶), 10.37 (1H, s, pyH⁴). **MS (ES⁺)** *m/z*: 348.2 [M – Cl]⁺, 823.4 [2M – Cl]⁺.

3,5-Bis(hexylcarbamoyl)-1-methylpyridinium bromide (53.Br):²⁰ Compound **53.I** (0.11 g, 0.23 mmol) was dissolved in CHCl₃ (50 mL) and washed with 1 M NH₄Br (8 x 50 mL). The organic layer was dried over MgSO₄, filtered and the solvent was removed *in vacuo* to give **53.Br** (0.082 g, 83%). **¹H NMR** (300 MHz, CDCl₃) δ: 0.89 (6H, m, CH₃), 1.36 (12H, m, CH₂), 1.75 (4H, m, CH₂), 3.48 (4H, m, NCH₂), 4.54 (3H, s, N⁺CH₃), 9.26 (2H, s, pyH² and H⁶), 9.34 (2H, br s, NH), 10.53 (1H, s, pyH⁴). **MS (ES⁺)** *m/z*: 348.3 [M – Br]⁺.

3,5-Bis(hexylcarbamoyl)-1-methylpyridinium hexafluorophosphate (53.PF₆):^{adapted from 20}

A solution of **53.Cl** (0.058 g, 0.15 mmol) in CHCl₃ (50 mL) was washed with 0.2 M NH₄PF₆ (5 x 10 mL) and H₂O (10 mL). The organic layer was dried over MgSO₄, filtered and the solvent was removed *in vacuo* to give **53.PF₆** (0.064 g, 86%). **¹H NMR** (300 MHz, CDCl₃) δ: 0.89 (6H, m, CH₃), 1.35 (12H, m, CH₂), 1.62 (4H, m, CH₂), 3.42 (4H, q, ³*J* = 6.7 Hz, NCH₂), 4.41 (3H, s, N⁺CH₃), 7.41 (2H, t, ³*J* = 5.6 Hz, NH), 9.06 (3H, m, pyH). **¹⁹F NMR** (282.5 MHz, CDCl₃) δ: -71.51 (d, ¹*J* = 713 Hz, PF₆⁻). **³¹P NMR** (121.5 MHz, CDCl₃) δ: -144.67 (septet, ¹*J* = 713 Hz, PF₆⁻). **MS (ES⁺)** *m/z*: 348.3 [M – PF₆]⁺.

3,5-Bis(4-(bis(4-*tert*-butylphenyl)(phenyl)methyl)phenylcarbamoyl)-1-methylpyridinium iodide (54.I):²¹ Compound **65** (0.99 g, 0.97 mmol) was suspended in acetone (50 mL), iodomethane (10 mL, excess) was added and the resulting suspension was heated under reflux for 1 week. The yellow suspension was filtered, and the yellow solid was washed with acetone and dried to give **54.I** (0.94 g, 83%). **¹H NMR** (300 MHz, DMSO-*d*₆) δ: 1.27 (36H, s, *t*-Bu), 4.49 (3H, s, N⁺CH₃), 7.22 (30H, m, ArH), 7.68 (4H, d, ³*J* = 8.8 Hz, ArH), 9.49 (1H, s, pyH⁴), 9.64 (2H, s, pyH² and H⁶), 10.96 (2H, br s, NH). **MS (ES⁺)** *m/z*: 1040.6 [M – I]⁺.

3,5-Bis(4-(bis(4-*tert*-butylphenyl)(phenyl)methyl)phenylcarbamoyl)-1-methylpyridinium

chloride (54.Cl):²¹ A suspension of **54.I** (0.29 g, 0.25 mmol) in CHCl₃ (200 mL) was washed with 1 M NH₄Cl (8 x 200 mL) and H₂O (2 x 200 mL). The organic layer was dried over MgSO₄, filtered and the solvent was removed *in vacuo* to give **54.Cl** as a yellow solid (0.26 g, 97%). ¹H NMR (300 MHz, CDCl₃) δ : 1.28 (36H, m, *t*-Bu), 3.86 (3H, s, N⁺CH₃), 7.21 (30H, m, ArH), 7.80 (4H, d, ³J = 8.5 Hz, ArH), 8.76 (2H, s, pyH² and H⁶), 10.61 (1H, s, pyH⁴), 10.93 (2H, s, NH). MS (ES⁺) *m/z*: 1040.6 [M – Cl]⁺.

3,5-Bis(4-(bis(4-*tert*-butylphenyl)(phenyl)methyl)phenylcarbamoyl)-1-methylpyridinium bromide (54.Br): A suspension of **54.I** (0.10 g, 0.094 mmol) in CHCl₃ (100 mL) was washed with 1 M NH₄Br (6 x 100 mL). The organic layer was dried over MgSO₄, filtered and the solvent was removed *in vacuo* to give **54.Br** (0.10 g, 96%). ¹H NMR (300 MHz, CDCl₃) δ : 1.30 (36H, s, *t*-Bu), 4.14 (3H, s, N⁺CH₃), 7.26 (30H, m, ArH), 7.86 (4H, d, ³J = 8.8 Hz, ArH), 8.93 (2H, s, pyH² and H⁶), 10.47 (1H, s, pyH⁴), 10.95 (2H, br s, NH). MS (ES⁺) *m/z*: 1040.6 [M – Br]⁺.

3,5-Bis(4-(bis(4-*tert*-butylphenyl)(phenyl)methyl)phenylcarbamoyl)-1-methylpyridinium hexafluorophosphate (54.PF₆):²¹ AgPF₆ (0.054 g, 0.21 mmol) was added to a solution of **54.I** (0.15 g, 0.13 mmol) in CH₂Cl₂ (30 mL) and the resulting suspension was stirred for 16 hours at room temperature in the absence of light. The suspension was filtered through Celite and the solvent was removed *in vacuo* to give **54.PF₆** as a yellow solid (0.15 g, 96%). ¹H NMR (300 MHz, CDCl₃) δ : 1.30 (36H, m, *t*-Bu), 3.69 (3H, s, N⁺CH₃), 7.24 (30H, m, ArH), 7.54 (4H, d, ³J = 8.8 Hz, ArH), 8.82 (2H, s, pyH² and H⁶), 9.57 (1H, s, pyH⁴), 10.58 (2H, br s, NH). ¹⁹F NMR (282.5 MHz, CDCl₃) δ : -70.61 (d, ¹J = 715 Hz, PF₆⁻). ³¹P NMR (121.5 MHz, CDCl₃) δ : -144.49 (septet, ¹J = 715 Hz, PF₆⁻). MS (ES⁺) *m/z*: 1040.6 [M – PF₆]⁺.

Hydroquinone bis(2-hydroxyethyl)ether monotosylate (55):¹⁸ Hydroquinone

bis(2-hydroxyethyl)ether (6.34 g, 32 mmol), triethylamine (5.8 mL, 41.6 mmol) and DMAP (cat.) were dissolved in dry THF (150 mL). Tosyl chloride (6.46 g, 33.9 mmol) was added and the resulting mixture was stirred for 16 hours under a N₂ atmosphere. The reaction mixture was filtered, the filtrate taken to dryness and then purified by silica gel chromatography (1:1 petroleum ether/EtOAc). The desired monofunctionalised product **55** was eluted as the third band and isolated as a yellow oil (4.56 g, 40%). ¹H NMR (300 MHz, CDCl₃) δ: 2.46 (3H, s, CH₃), 3.95 (2H, m, OCH₂), 4.03 (2H, m, OCH₂), 4.11 (2H, m, OCH₂), 4.35 (2H, m, OCH₂), 6.78 (4H, m, hydroq ArH), 7.35 (2H, d, ³J = 8.2 Hz, TosH), 7.83 (2H, d, ³J = 8.2 Hz, TosH). MS (ES⁺) *m/z*: 375.0894 [M + Na]⁺.

(2-Hydroxyethoxy)-4-(2-phthalimidoethoxy)benzene (56):¹⁸ Potassium phthalimide (3.20 g, 17 mmol) was added to a solution of **55** (4.06 g, 11 mmol) in DMF (dried over 3 Å molecular sieves, 30 mL) and the resulting suspension was heated at 100 °C under a N₂ atmosphere for 16 hours. The reaction mixture was cooled to room temperature and poured into H₂O (100 mL). The milky suspension was extracted with CH₂Cl₂ (3 x 50 mL) and the combined organic layers were dried over MgSO₄, filtered and the solvent was removed *in vacuo*. The crude material was purified by silica gel chromatography (1:1 petroleum ether/EtOAc) and the product was eluted as the first intense band to give **56** as a white solid (2.78 g, 77%). ¹H NMR (300 MHz, CDCl₃) δ: 2.04 (1H, t, ³J = 5.3 Hz, OH), 3.93 (2H, m, CH₂OH), 4.01 (2H, m, OCH₂), 4.09 (2H, m, NCH₂), 4.19 (2H, m, OCH₂), 6.82 (4H, s, ArH), 7.73 (2H, m, PhthH), 7.87 (2H, m, PhthH). MS (ES⁺) *m/z*: 350.1226 [M + Na]⁺, 677.2554 [2M + Na]⁺.

(2-Tosylethoxy)-4-(2-phthalimidoethoxy)benzene (57):¹⁸ Tosyl chloride (1.78 g, 9.33 mmol), triethylamine (4.55 mL, 32.6 mmol) and DMAP (cat.) were added to a solution of **56** (2.78 g, 8.49 mmol) in dry CH₂Cl₂ (100 mL) and the resulting solution was stirred for

16 hours under a N₂ atmosphere. H₂O (50 mL) was added to the solution and the biphasic mixture was neutralised with 10% aqueous citric acid. The organic layer was washed with H₂O (2 x 50 mL), brine (50 mL), dried over MgSO₄, filtered and the solvent was removed *in vacuo* to give **57** as a white solid (4.00 g, 98%). ¹H NMR (300 MHz, CDCl₃) δ: 2.45 (3H, s, CH₃), 4.07 (4H, m, NCH₂, OCH₂), 4.17 (2H, m, OCH₂), 4.32 (2H, m, OCH₂), 6.68 (2H, m, ArH), 6.78 (2H, m, ArH), 7.34 (2H, d, ³J = 8.2 Hz, TosH), 7.73 (2H, dd, ³J = 5.4 Hz, ⁴J = 3.1 Hz, PhthH), 7.81 (2H, d, ³J = 8.2 Hz, TosH), 7.87 (2H, dd, ³J = 5.4 Hz, ⁴J = 3.1 Hz, PhthH). MS (ES⁺) *m/z*: 504.1015 [M + Na]⁺, 985.2108 [2M + Na]⁺.

Hydroquinone bis(2-hydroxyethyl)ether bistosylate (58): This was eluted as the second band during the chromatographic purification of **55**. ¹H NMR (300 MHz, CDCl₃) δ: 2.46 (6H, s, CH₃), 4.10 (4H, m, NCH₂), 4.34 (4H, m, OCH₂), 6.70 (4H, s, hydroq ArH), 7.35 (4H, d, ³J = 8.1 Hz, TosH), 7.82 (4H, d, ³J = 8.1 Hz, TosH). MS (ES⁺) *m/z*: 524.1 [M + NH₄]⁺, 529.1 [M + Na]⁺.

Hydroquinone bis(2-hydroxyethyl)ether bismesylate (59):²² Hydroquinone bis(2-hydroxyethyl)ether (10.08 g, 51 mmol) and triethylamine (21 mL, 151 mmol) were dissolved in CH₂Cl₂ (200 mL) and cooled to 0 °C. Methanesulfonyl chloride (12 mL, 155 mmol) was added dropwise over 20 minutes and the resulting suspension was stirred at 0 °C for a further 15 minutes. The reaction mixture was washed with cold 10% aqueous HCl (3 x 50 mL), saturated NaHCO₃ (50 mL) and brine (50 mL). The organic layer was dried over MgSO₄, filtered and the solvent was removed *in vacuo* to give **59** as an off-white solid (17.97 g, 100%). ¹H NMR (300 MHz, CDCl₃) δ: 3.10 (6H, s, CH₃), 4.21 (4H, m, OCH₂), 4.56 (4H, m, OCH₂), 6.86 (4H, s, hydroq ArH). MS (ES⁺) *m/z*: 413.1 [M + CH₃CN + NH₄]⁺.

(2-Mesylethoxy)-4-(2-phthalimidoethoxy)benzene (60): A suspension of **59** (2.41 g, 6.8 mmol) and potassium phthalimide (1.26 g, 6.8 mmol) in 1:1 dry degassed DMF/CH₃CN

(15 mL) was stirred at room temperature for 30 seconds then heated at 100 °C for 2 hours under microwave irradiation. An identical reaction was carried out in a second microwave vial and the residues from the two reactions were combined and dissolved in 1 M HCl (80 mL). Following extraction with CH₂Cl₂ (3 x 80 mL), the combined organic layers were dried over MgSO₄, filtered and the solvent was removed *in vacuo*. The residue was purified by silica gel chromatography (1:1 EtOAc/petroleum ether) to give **60** as a white solid (1.45 g, 26%). ¹H NMR (300 MHz, CDCl₃) δ: 3.09 (3H, m, CH₃), 4.10 (2H, m, NCH₂), 4.18 (4H, m, OCH₂), 4.54 (2H, m, OCH₂), 6.82 (4H, m, hydroq ArH), 7.74 (2H, dd, ³J = 5.4 Hz, ⁴J = 3.1 Hz, PhthH), 7.87 (2H, dd, ³J = 5.4 Hz, ⁴J = 3.1 Hz, PhthH). MS (ES⁺) *m/z*: 464.1 [M + CH₃CN + NH₄]⁺.

5,11,17,23-Tetra-*tert*-butyl-25,27-bis(2-(4-(2-phthalimidoethoxy)phenoxy)ethoxy)-26,28-dihydroxycalix[4]arene (61):¹⁸ A suspension of *tert*-butylcalix[4]arene (1.00 g, 1.55 mmol) and K₂CO₃ (0.45 g, 3.26 mmol) in dry CH₃CN (60 mL) was stirred at room temperature under a N₂ atmosphere for 1 hour. Compound **57** (1.87 g, 3.88 mmol) was added and the resulting mixture was heated under reflux for 4 days before cooling to room temperature and removing the solvent. The residue was triturated with 1 M HCl (100 mL) and extracted with CH₂Cl₂ (3 x 100 mL). The combined organic layers were washed with H₂O (2 x 100 mL), dried over MgSO₄ and taken to dryness. Purification by silica gel chromatography (3:2 hexane/EtOAc) eluted the product **61** as the third band to give a white solid (1.08 g, 55%). **Microwave synthesis 1:** A suspension of *tert*-butylcalix[4]arene (0.62 g, 0.96 mmol), **57** (1.10 g, 2.29 mmol) and K₂CO₃ (0.13 g, 0.96 mmol) in dry CH₃CN (15 mL) was stirred for 30 seconds prior to heating under microwave irradiation for 2 hours at 160 °C. The reaction mixture was cooled to room temperature and the solvent was removed *in vacuo*. The residue was redissolved in CHCl₃ (50 mL) and washed with 10% aqueous HCl (3 x 15 mL) and brine (2 x 15 mL). The organic layer was dried over MgSO₄, filtered and the solvent was removed

in vacuo to give the crude material which was recrystallised twice from CH₂Cl₂/MeOH to give **61** (1.00 g, 83%). **Microwave synthesis 2:** An analogous procedure to microwave synthesis 1 was carried out, using *tert*-butylcalix[4]arene (0.47 g, 0.72 mmol), **60** (0.72 g, 1.78 mmol) and K₂CO₃ (0.10 g, 0.73 mmol) in CH₃CN (15 mL). Purification by silica gel chromatography (3:2 petroleum ether/EtOAc) and recrystallisation of the impure fractions from CH₂Cl₂/MeOH, gave **61** (0.62 g, 68%). ¹H NMR (300 MHz, CDCl₃) δ: 1.01 (18H, s, *t*-Bu), 1.27 (18H, s, *t*-Bu), 3.29 (4H, d, ²J = 13.1 Hz, ArCH_{in}H_{out}Ar), 4.08 (4H, m, NCH₂), 4.18 (8H, m, OCH₂), 4.26 (4H, m, OCH₂), 4.38 (4H, d, ²J = 13.1 Hz, ArCH_{in}H_{out}Ar), 6.80 (8H, m, hydroq ArH), 6.85 (4H, s, calix ArH), 7.03 (4H, s, calix ArH), 7.52 (2H, s, OH), 7.71 (4 H, dd, ³J = 5.4 Hz, ⁴J = 3.1 Hz, PhthH), 7.85 (4 H, dd, ³J = 5.4 Hz, ⁴J = 3.1 Hz, PhthH). MS (ES⁺) *m/z*: 1289.5873 [M + Na]⁺.

3,5-Bis(hexylcarbamoyl)pyridine (62):²³ *n*-Hexylamine (2.4 mL, 18.2 mmol) and triethylamine (6 mL, 43.05 mmol) were dissolved in dry CH₂Cl₂ (100 mL) and cooled in an ice bath under a N₂ atmosphere. A solution of 3,5-bis(chlorocarbonyl) pyridine (9 mmol) in dry CH₂Cl₂ (30 mL) was added dropwise slowly and the resulting mixture was stirred for a further 2 hours. The yellow solution was washed with 10% aqueous citric acid (5 x 100 mL), dried over MgSO₄, filtered and the solvent was removed *in vacuo* to give **62** (2.76 g, 92%). ¹H NMR (300 MHz, CDCl₃) δ: 0.89 (6H, m, CH₃), 1.34 (12H, m, CH₂), 1.62 (4H, m, CH₂), 3.47 (4H, m, NCH₂), 7.01 (2H, t, ³J = 5.6 Hz, NH), 8.47 (1H, s, pyH⁴), 9.07 (2H, d, ⁴J = 2.1 Hz, pyH² and H⁶). MS (ES⁺) *m/z*: 334.2 [M + H]⁺, 667.5 [2M + H]⁺.

Bis(4-*tert*-butylphenyl)(phenyl)methanol (63):²⁴ In a 3 neck flask fitted with a condenser, magnesium turnings (1.22 g, 0.05 mol) were heated at 110 °C under a N₂ atmosphere overnight, cooled to 50 °C and dry THF (80 mL) with a catalytic amount of I₂ was added. A solution of 1-bromo-4-*tert*-butylbenzene (8 mL, 0.047 mol) in dry THF (20 mL) was added

dropwise over a period of 30 minutes while heating at 60 °C. The heating was removed once the reaction started and the reaction was stirred at room temperature for a further 2.5 hours. A solution of methylbenzoate (2.8 mL, 0.022 mol) in dry THF (10 mL) was added dropwise over 10 minutes and the mixture was heated under reflux for 18.5 hours. The solution was neutralised with 10% aqueous HCl and extracted with hexane (3 x 50 mL). The combined organic layers were washed with H₂O (3 x 50 mL), dried over MgSO₄, filtered and the solvent was removed *in vacuo*. The yellow oily residue was recrystallised from MeOH to give the white solid **63** (6.02 g, 72%). ¹H NMR (300 MHz, CDCl₃) δ: 1.28 (18H, s, *t*-Bu), 2.76 (1H, s, OH), 7.22 (13H, m, ArH). MS (ES⁺) *m/z*: 355.2 [M - OH]⁺, 762.5 [2M + NH₄]⁺, 1134.7 [3M + NH₄]⁺, 1507.0 [4M + NH₄]⁺.

4-(Bis(4-*tert*-butylphenyl)(phenyl)methyl)aniline (64):²¹ A suspension of **63** (8.24 g, 221 mmol) in acetyl chloride (40 mL) was heated under reflux under a N₂ atmosphere for 16 hours before the solvent was removed by distillation. The yellow solid was redissolved in aniline (40 mL) and heated at 100 °C under a N₂ atmosphere for 2 days, during which time the colour changed from red to purple. The solution was cooled to room temperature and poured slowly into a stirred solution of HCl (20 mL) in H₂O (380 mL). A purple solid was collected and redissolved in CH₂Cl₂ (200 mL). The solution was run down a plug of silica eluting with CH₂Cl₂. Following purification by silica gel chromatography (7:3 petroleum ether/EtOAc), **64** was obtained as a white solid (4.08 g, 41%). ¹H NMR (300 MHz, CDCl₃) δ: 1.36 (18H, s, *t*-Bu), 3.64 (2H, s, NH₂), 6.63 (2H, d, ³*J* = 8.8 Hz, ArH), 7.02 (2H, d, ³*J* = 8.5 Hz, ArH), 7.16 (4H, m, ArH), 7.30 (9H, m, ArH). MS (ES⁺) *m/z*: 448.3 [M + H]⁺, 895.6 [2M + H]⁺, 1343.9 [3M + H]⁺.

3,5-Bis(4-(bis(4-*tert*-butylphenyl)(phenyl)methyl)phenylcarbamoyl)pyridine (65):²¹ A solution of 3,5-bis(chlorocarbonyl) pyridine (2.23 mmol) in dry CH₂Cl₂ (20 mL) was added

dropwise to a solution of **64** (2 g, 4.47 mmol) and triethylamine (0.93 mL, 6.67 mmol) in dry CH₂Cl₂ (80 mL). The reaction mixture was stirred at room temperature under a N₂ atmosphere for 4 hours. The solvent was removed *in vacuo* and the crude solid was heated under reflux in EtOH (100 mL) for 1 hour. The suspension was cooled to room temperature, filtered and the off-white solid was washed with EtOH and dried to give **65** as a white solid (1.76 g, 77%). ¹H NMR (300 MHz, CDCl₃) δ: 1.25 (36H, s, *t*-Bu), 7.18 (30 H, m, ArH), 7.67 (4H, d, ³*J* = 8.8 Hz, ArH), 8.73 (1H, t, ⁴*J* = 2.0 Hz, pyH⁴), 9.22 (2H, d, ⁴*J* = 2.0 Hz, pyH² and H⁶), 10.61 (2H, s, NH). MS (ES⁺) *m/z*: 1026.6 [M + H]⁺.

Isophthalamide-hydroquinone *tert*-butylcalix[4]arene macrobicycle (66):²⁵ Separate solutions of **52** (0.41 g, 0.41 mmol) in dry CH₂Cl₂ (100 mL) and isophthaloyl dichloride (0.08 g, 0.41 mmol) in dry CH₂Cl₂ (100 mL) were added dropwise simultaneously to a stirred solution of triethylamine (0.15 mL, 1.1 mmol) in dry CH₂Cl₂ (310 mL) under a N₂ atmosphere over 8 hours using a syringe pump. The reaction mixture was stirred for a further 16 hours then concentrated *in vacuo* to a volume of 100 mL. The solution was washed with 1 M HCl (2 x 100 mL), H₂O (100 mL), 1 M NaOH (100 mL) and brine (100 mL). The organic layer was dried over MgSO₄, filtered and the solvent was removed *in vacuo*. The crude material was purified by silica gel chromatography (9:1 EtOAc/petroleum ether) to give **66** as a white solid (0.28 g, 60%). **Templated synthesis:** A solution of isophthaloyl dichloride (0.014 g, 0.07 mmol) in dry CH₂Cl₂ (1.5 mL) was added to a solution of **52** (0.068 g, 0.07 mol), **53.Cl** (0.026 g, 0.07 mmol) and triethylamine (0.02 mL, 0.14 mmol) in dry CH₂Cl₂ (3 mL) under a N₂ atmosphere. The reaction mixture was stirred at room temperature for 1 hour, then washed with 1 M HCl (2 x 5 mL) and brine (5 mL). The organic layer was dried over MgSO₄, filtered, the solvent was removed *in vacuo* and the residue was purified by silica gel chromatography (7:3 EtOAc/petroleum ether) to give **66** (0.03 g, 38%). ¹H NMR (300 MHz, CDCl₃) δ: 1.03 (18H, s, *t*-Bu), 1.28 (18H, s, *t*-Bu), 3.34 (4H, d, ²*J* = 13.1 Hz,

ArCH_{in}H_{out}Ar), 3.88 (4H, m, NCH₂), 4.15 (4H, m, OCH₂), 4.29 (4H, m, OCH₂), 4.36 (4H, m, OCH₂), 4.41 (4H, d, ²J = 13.1 Hz, ArCH_{in}H_{out}Ar), 6.71 (2H, t, ³J = 5.4 Hz, NH), 6.87 (12H, m, calix ArH, hydroq ArH), 7.05 (4H, s, calix ArH), 7.58 (1H, t, ³J = 7.7 Hz, ⁴J = 1.6 Hz, isoH), 7.65 (2H, s, OH), 7.89 (1H, s, isoH), 8.08 (2H, dd, ³J = 7.7 Hz, ⁴J = 1.6 Hz, isoH). **MS (ES⁺)** *m/z*: 1154.6 [M + NH₄]⁺, 1159.6 [M + Na]⁺.

5-Nitroisophthalamide-hydroquinone *tert*-butylcalix[4]arene macrobicycle (67):^{adapted}

^{from 18} A solution of 5-nitroisophthaloyl dichloride (0.23 mmol) in dry CH₂Cl₂ (20 mL) was added dropwise to a solution of **52** (0.23 g, 0.23 mmol), **53.Cl** (0.089 g, 0.23 mmol) and triethylamine (0.12 mL, 0.86 mmol) in dry CH₂Cl₂ (20 mL) under a N₂ atmosphere. The reaction mixture was stirred at room temperature for 2.5 hours, then washed with 1 M HCl (2 x 40 mL), H₂O (40 mL), 1 M NaOH (40 mL) and brine (40 mL). The organic layer was dried over MgSO₄, filtered, the solvent was removed *in vacuo* and the residue was purified by preparative TLC (7:3 EtOAc/petroleum ether) to give **67** as a yellow solid (0.10 g, 38%). **¹H NMR** (300 MHz, CDCl₃) δ: 1.01 (18H, s, *t*-Bu), 1.29 (18H, s, *t*-Bu), 3.34 (4H, d, ²J = 13.1 Hz, ArCH_{in}H_{out}Ar), 3.90 (4H, q, ³J = 4.9 Hz, NCH₂), 4.14 (4H, t, ³J = 4.9 Hz, OCH₂), 4.29 (4H, m, OCH₂), 4.34 (4H, m, OCH₂), 4.41 (4H, d, ²J = 13.1 Hz, ArCH_{in}H_{out}Ar), 6.80 (4H, m, calix ArH), 6.88 (8H, m, calix ArH, hydroq ArH), 7.06 (4H, s, calix ArH), 7.45 (2H, s, OH), 8.29 (1H, s, isoH), 8.86 (2H, s, isoH). **MS (ES⁺)** *m/z*: 1204.6 [M + Na]⁺.

Rotaxane (68.Cl): A solution of isophthaloyl dichloride (0.015 g, 0.072 mmol) in dry CH₂Cl₂ (20 mL) was added to a solution of **52** (0.070 g, 0.069 mmol), **54.Cl** (0.11 g, 0.10 mmol) and triethylamine (0.02 mL, 0.14 mmol) in dry CH₂Cl₂ (15 mL). The reaction mixture was stirred at room temperature under a N₂ atmosphere for 1 hour and then washed with 1 M HCl (2 x 10 mL) and brine (10 mL). The organic layer was dried over MgSO₄, filtered and the solvent was removed *in vacuo*. Following purification by preparative TLC (4:1 EtOAc/CHCl₃) and recrystallisation from CHCl₃/MeOH, **68.Cl** was isolated as a yellow

solid (0.021 g, 17%). **m.p.** 250 °C (dec.). **¹H NMR** (300 MHz, CDCl₃) δ: 0.87 (18H, s, *t*-Bu), 1.33 (36H, s, *t*-Bu), 1.39 (18H, s, *t*-Bu), 3.46 (4H, d, ²*J* = 13.6 Hz, ArCH_{in}H_{out}Ar), 3.82 (4H, m, NCH₂), 4.09 (4H, m, OCH₂), 4.19 (8H, m, OCH₂), 4.45 (4H, d, ²*J* = 13.6 Hz, ArCH_{in}H_{out}Ar), 4.97 (3H, s, N⁺CH₃), 5.69 (2H, s, OH), 6.25 (4H, d, ³*J* = 9.1 Hz, hydroq ArH), 6.47 (4H, d, ³*J* = 9.1 Hz, hydroq ArH), 6.67 (4H, s, calix ArH), 7.13 (35H, m, ArH, calix ArH, isoH), 7.81 (4H, d, ³*J* = 8.8 Hz, ArH), 8.02 (2H, d, ³*J* = 7.9 Hz, isoH), 8.62 (2H, br s, NH), 8.92 (1H, s, isoH), 9.16 (2H, s, pyH² and H⁶), 10.44 (2H, br s, NH), 10.59 (1H, br s, pyH⁴). **¹³C NMR** (125 MHz, CDCl₃) δ: 30.90, 31.16, 31.39, 31.75, 33.85, 34.02, 34.30, 41.24, 50.81, 63.77, 65.88, 67.68, 75.19, 114.35, 114.86, 120.85, 124.26, 125.11, 125.52, 125.69, 125.93, 127.33, 128.46, 130.64, 131.09, 131.58, 131.75, 133.21, 134.06, 134.62, 142.78, 143.52, 144.67, 144.99, 146.97, 147.54, 148.32, 149.97, 150.58, 151.70, 154.01, 158.10, 167.11. **MS (ES⁺)** *m/z*: 2177.0742 [M – Cl]⁺. **Elemental Analysis** Calcd. for C₁₄₆H₁₆₂N₅O₁₂Cl: C 79.2% H 7.4% N 3.2%. Found: C 79.0% H 7.3% N 3.2%.

Rotaxane (68.PF₆): A solution of 68.Cl (0.048 g, 0.021 mmol) in CHCl₃ (10 mL) was washed with 0.2 M NH₄PF₆ (5 x 10 mL) and H₂O (10 mL). The combined organic layers were dried over MgSO₄, filtered and the solvent was removed *in vacuo* to give 68.PF₆ as a yellow solid (0.049 g, 100%). **m.p.** 240 °C (dec.). **¹H NMR** (300 MHz, CDCl₃) δ: 0.85 (18H, s, *t*-Bu), 1.32 (36H, s, *t*-Bu), 1.36 (18H, s, *t*-Bu), 3.38 (4H, d, ²*J* = 13.8 Hz, ArCH_{in}H_{out}Ar), 3.58 (4H, m, NCH₂), 3.79 (4H, m, OCH₂), 4.12 (8H, m, OCH₂), 4.44 (4H, d, ²*J* = 13.8 Hz, ArCH_{in}H_{out}Ar), 4.77 (3H, s, N⁺CH₃), 6.18 (2H, s, OH), 6.44 (8H, m, hydroq ArH), 6.64 (4H, s, calix ArH), 7.15 (35 H, m, calix ArH, ArH, NH), 7.45 (2H, t, ³*J* = 7.7 Hz, isoH), 7.56 (4H, d, ³*J* = 8.5 Hz, ArH), 8.02 (2H, dd, ³*J* = 7.7 Hz, ⁴*J* = 1.5 Hz, isoH), 8.73 (1H, s, isoH), 9.00 (2H, br s, pyH² and H⁶), 9.12 (1H, s, pyH⁴), 9.40 (2H, br s, NH). **¹³C NMR** (125 MHz, CDCl₃) δ: 30.91, 31.38, 31.74, 33.82, 33.94, 34.31, 39.86, 50.35, 63.82, 67.16, 67.34, 75.11, 114.65, 115.69, 120.37, 124.32, 125.53, 125.74, 125.84, 125.98, 127.39, 128.33, 128.86, 130.59, 130.85,

131.02, 131.64, 131.86, 133.72, 133.93, 134.12, 141.61, 142.52, 143.40, 144.19, 145.27, 146.82, 147.25, 148.54, 149.91, 150.10, 152.12, 152.92, 158.08, 167.05. ^{19}F NMR (282.5 MHz, CDCl_3) δ : -70.10 (d, $^1J = 715$ Hz, PF_6^-). ^{31}P NMR (202.4 MHz, CDCl_3) δ : -142.71 (septet, $^1J = 715$ Hz, PF_6^-). MS (ES^+) m/z : 2177.1363 $[\text{M} - \text{PF}_6]^+$.

Rotaxane with polyether containing axle (69.Cl): A solution of isophthaloyl dichloride (0.014 g, 0.071 mmol) in dry CH_2Cl_2 (2 mL) was added to a solution of **52** (0.070 g, 0.069 mmol), **70.Cl** (0.13 g, 0.11 mmol) and triethylamine (0.02 mL, 0.14 mmol) in dry CH_2Cl_2 (5 mL). The reaction mixture was stirred at room temperature under a N_2 atmosphere for 1 hour and then washed with 1 M HCl (2 x 5 mL) and brine (5 mL). The organic layer was dried over MgSO_4 , filtered and the solvent was removed *in vacuo*. Following purification by preparative TLC (4:1 EtOAc/ CHCl_3) and recrystallisation by vapour diffusion of diisopropyl ether into a CHCl_3 solution of the rotaxane, **69.Cl** was isolated as a yellow solid (0.039 g, 24%). **m.p.** 200 °C (dec.). ^1H NMR (300 MHz, CDCl_3) δ : 0.86 (18H, s, *t*-Bu), 1.28 (36H, s, *t*-Bu), 1.39 (18H, s, *t*-Bu), 3.43 (4H, d, $^2J = 13.6$ Hz, $\text{ArCH}_{\text{in}}\text{H}_{\text{out}}\text{Ar}$), 3.57 (4H, m, NCH_2), 3.67 (4H, t, $^3J = 4.8$ Hz, OCH_2), 3.76 (4H, t, $^3J = 4.4$ Hz, OCH_2), 3.87 (4H, m, OCH_2), 4.03 (8H, m, OCH_2), 4.10 (4H, m, OCH_2), 4.24 (4H, m, OCH_2), 4.40 (4H, d, $^2J = 13.6$ Hz, $\text{ArCH}_{\text{in}}\text{H}_{\text{out}}\text{Ar}$), 4.89 (3H, s, N^+CH_3), 5.71 (2H, br s, OH), 6.19 (4H, d, $^3J = 8.8$ Hz, hydroq ArH), 6.47 (4H, d, $^3J = 8.8$ Hz, hydroq ArH), 6.65 (4H, s, calix ArH), 6.71 (4H, d, $^3J = 8.8$ Hz, ArH), 7.04 (12H, m, ArH), 7.18 (22H, m, ArH), 7.53 (1H, t, $^3J = 7.9$ Hz, isoH), 8.27 (2H, d, $^3J = 7.9$ Hz, isoH), 8.68 (2H, br s, NH), 8.76 (2H, br s, NH), 9.03 (2H, br s, pyH^2 and H^6), 9.28 (1H, br s, isoH), 9.82 (1H, br s, pyH^4). ^{13}C NMR (125 MHz, CDCl_3) δ : 30.89, 31.08, 31.34, 31.66, 31.74, 33.83, 34.01, 34.25, 39.78, 41.23, 50.61, 63.39, 65.25, 67.16, 67.49, 69.13, 75.21, 113.09, 114.07, 114.74, 124.08, 124.26, 125.51, 125.60, 125.89, 127.17, 128.41, 128.99, 130.63, 130.85, 131.10, 131.51, 131.88, 132.09, 133.53, 133.62, 139.42,

142.75, 143.91, 144.34, 147.36, 147.49, 148.29, 149.97, 150.51, 151.54, 153.78, 156.55, 159.83, 166.83. **MS (ES⁺)** *m/z*: 2353.0742 [M – Cl]⁺.

Rotaxane with polyether containing axle (69.PF₆): A solution of **69.Cl** (0.057 g, 0.024 mmol) in CHCl₃ (20 mL) was washed with 0.2 M NH₄PF₆ (5 x 10 mL) and H₂O (10 mL). The combined organic layers were dried over MgSO₄, filtered and the solvent was removed *in vacuo* to give **69.PF₆** as a yellow solid (0.061 g, 100%). **m.p.** 210 °C (dec.). **¹H NMR** (500 MHz, 1:1 CDCl₃/CD₃OD) δ: 0.81 (18H, s, *t*-Bu), 1.20 (36H, s, *t*-Bu), 1.33 (18H, s, *t*-Bu). 3.35 (4H, d, ²*J* = 13.7 Hz, ArCH_{in}H_{out}Ar), 3.48 (4H, m, NCH₂), 3.60 (4H, t, ³*J* = 4.9 Hz, OCH₂), 3.70 (4H, m, OCH₂), 3.80 (4H, m, OCH₂), 3.86 (4H, t, ³*J* = 4.6 Hz, OCH₂), 4.01 (8H, m, OCH₂), 4.10 (4H, m, OCH₂), 4.37 (4H, d, ²*J* = 13.7 Hz, ArCH_{in}H_{out}Ar), 4.69 (3H, s, N⁺CH₃), 6.38 (8H, m, hydroq ArH), 6.64 (4H, s, calix ArH), 6.72 (4H, d, ³*J* = 8.8 Hz, ArH), 7.07 (34H, m, calix ArH, ArH), 7.60 (1H, t, ³*J* = 7.8 Hz, isoH), 8.09 (2H, d, ³*J* = 7.8 Hz, isoH), 8.64 (1H, s, isoH), 8.88 (1H, s, pyH⁴), 8.95 (2H, s, pyH² and H⁶). **¹³C NMR** (125 MHz, CDCl₃) δ: 30.91, 31.35, 31.75, 33.85, 34.03, 34.26, 39.80, 40.90, 49.95, 63.39, 66.77, 67.15, 67.30, 68.35, 69.39, 75.28, 112.99, 114.49, 115.53, 115.64, 124.11, 125.65, 125.69, 125.82, 127.20, 128.39, 129.20, 130.59, 131.04, 131.43, 131.65, 132.17, 133.08, 134.00, 139.66, 142.21, 143.07, 143.38, 143.84, 147.28, 147.53, 148.35, 149.62, 149.85, 151.53, 152.85, 156.43, 160.34, 167.00. **¹⁹F NMR** (282.5 MHz, CDCl₃) δ: -70.70 (d, ¹*J* = 713 Hz, PF₆⁻). **³¹P NMR** (121.6 MHz, CDCl₃) δ: -143.76 (septet, ¹*J* = 714 Hz, PF₆⁻). **MS (ES⁺)** *m/z*: 2353.1877 [M – PF₆]⁺.

Polyether containing axle (70.I): A solution of **74** (0.27 g, 0.23 mmol) and iodomethane (0.5 mL, excess) in acetone (15 mL) was heated under reflux under a N₂ atmosphere for 3 days. The solvent was removed *in vacuo* to give **70.I** as an orange solid (0.30 g, 96%). **m.p.** 158-160 °C. **¹H NMR** (300 MHz, CDCl₃) δ: 1.29 (36H, s, *t*-Bu), 3.71 (4H, m, NCH₂), 3.85

(8H, m, OCH₂), 4.10 (4H, m, OCH₂), 4.21 (3H, s, N⁺CH₃), 6.73 (4H, d, ³J = 8.8 Hz, ArH), 7.08 (12H, m, ArH), 7.19 (18H, m, ArH), 8.79 (2H, br s, NH), 9.22 (2H, s, pyH² and H⁶), 9.87 (1H, s, pyH⁴). ¹³C NMR (75.5 MHz, CDCl₃) δ: 31.35, 34.27, 40.19, 49.36, 63.41, 67.41, 68.89, 69.40, 113.20, 124.18, 125.66, 127.26, 130.58, 131.01, 132.16, 134.42, 139.79, 141.57, 143.89, 146.26, 147.33, 148.35, 156.34, 160.63. MS (ES⁺) m/z: 1216.7144 [M – I]⁺.

Polyether containing axle (70.Cl): A biphasic mixture of 70.I (0.26 g, 0.20 mmol) in CHCl₃ (100 mL) and 1 M NH₄Cl (100 mL) was stirred vigorously for 30 minutes. The aqueous layer was decanted and the washing procedure was repeated a further four times. The organic layer was dried over MgSO₄, filtered and the solvent was removed *in vacuo*. Compound 70.Cl was obtained as a yellow solid (0.23 g, 95%). m.p. 186-188 °C. ¹H NMR (300 MHz, CDCl₃) δ: 1.29 (36H, s, *t*-Bu), 3.71 (4H, t, ³J = 5.0 Hz, NCH₂), 3.86 (8H, m, OCH₂), 4.11 (4H, m, OCH₂), 4.30 (3H, s, N⁺CH₃), 6.72 (4H, d, ³J = 8.8 Hz, ArH), 7.07 (12H, m, ArH), 7.20 (18H, m, ArH), 9.26 (2H, s, pyH² and H⁶), 9.47 (2H, t, ³J = 4.7 Hz, NH), 10.53 (1H, s, pyH⁴). ¹³C NMR (75.5 MHz, CDCl₃) δ: 31.33, 34.25, 40.38, 49.28, 63.39, 67.30, 69.01, 69.41, 113.09, 124.13, 125.64, 127.22, 130.58, 131.03, 132.16, 133.96, 139.72, 141.37, 143.85, 146.65, 147.30, 148.31, 156.34, 160.39. MS (ES⁺) m/z: 1216.7087 [M – Cl]⁺.

Polyether containing axle (70.PF₆): Compound 70.Cl (0.066 g, 0.053 mmol) was dissolved in CHCl₃ (10 mL) and washed with 0.2 M NH₄PF₆ (5 x 10 mL). The organic layer was separated, dried over MgSO₄, filtered and the solvent was removed *in vacuo* to give 70.PF₆ as a white solid (0.066 g, 91%). m.p. 142-144 °C. ¹H NMR (300 MHz, CDCl₃) δ: 1.29 (36H, s, *t*-Bu), 3.68 (8H, m, NCH₂, OCH₂), 3.78 (4H, m, OCH₂), 4.03 (4H, m, OCH₂), 4.17 (3H, s, N⁺CH₃), 6.70 (4H, d, ³J = 8.8 Hz, ArH), 7.08 (12H, m, ArH), 7.21 (18H, m, ArH), 7.59 (2H, t, ³J = 4.4 Hz, NH), 8.94 (2H, s, pyH² and H⁶), 9.14 (1H, s, pyH⁴). ¹³C NMR (75.5 MHz, CDCl₃) δ: 31.35, 34.27, 40.41, 49.17, 63.43, 67.29, 68.97, 69.42, 113.19, 124.19, 125.68,

127.27, 130.57, 131.02, 132.18, 135.10, 139.95, 141.21, 143.88, 145.78, 147.33, 148.37, 156.17, 160.56. ^{19}F NMR (282.5 MHz, CDCl_3) δ : -72.01 (d, $^1J = 713$ Hz, PF_6^-). ^{31}P NMR (121.6 MHz, CDCl_3) δ : -144.63 (septet, $^1J = 713$ Hz, PF_6^-). MS (ES^+) m/z : 1216.7160 $[\text{M} - \text{PF}_6]^+$.

4-(Bis(4-*tert*-butylphenyl)(phenyl)methyl)phenol (71):²⁴

Bis(4-*tert*-butylphenyl)phenylmethanol (2.90 g, 7.79 mmol) was dissolved in phenol (13.00 g, 138 mmol) upon warming under a N_2 atmosphere, concentrated HCl (0.25 mL) was added and the reaction mixture was heated under reflux for 1 day. The solution was cooled to room temperature and the product was extracted with toluene (3 x 50 mL). The combined organic layers were washed with 1 M NaOH (3 x 100 mL) and H_2O (3 x 100 mL), and dried over MgSO_4 , filtered and the solvent was removed *in vacuo*. The crude material was recrystallised by dissolving it in the minimum amount of hot toluene and hexane (50 mL) was added. The white solid was filtered and washed with hexane to give **71** (2.99 g, 86%). ^1H NMR (300 MHz, CDCl_3) δ : 1.31 (18H, s, *t*-Bu), 4.70 (1H, s, OH), 6.71 (2H, d, $^3J = 9.1$ Hz, ArH), 7.18 (15H, m, ArH). MS (ES^-) m/z : 447.3 $[\text{M} - \text{H}]^-$, 895.5 $[2\text{M} - \text{H}]^-$.

2-(2-(4-(Bis(4-*tert*-butylphenyl)(phenyl)methyl)phenoxy)ethoxy)phthalimide (72): A suspension of **71** (1.27 g, 2.8 mmol), **4** (1.33 g, 3.4 mmol) and K_2CO_3 (0.79 g, 5.7 mmol) in CH_3CN (15 mL) was heated in a microwave for 4 hours at 160 °C. The reaction mixture was cooled to room temperature and the solvent was removed *in vacuo*. The crude material was redissolved in CHCl_3 (50 mL), washed with 1 M HCl (30 mL) and H_2O (2 x 30 mL). The organic layer was dried over MgSO_4 , filtered and the solvent was removed *in vacuo*. Following purification by silica gel chromatography (99:1 $\text{CHCl}_3/\text{MeOH}$), the product **72** was obtained as a white solid (1.43 g, 79%). m.p. 82-84 °C. ^1H NMR (300 MHz, CDCl_3) δ : 1.31 (18H, s, *t*-Bu), 3.83 (4H, m, NCH_2 , OCH_2), 3.93 (2H, m, OCH_2), 4.04 (2H, t, $^3J = 4.8$ Hz,

OCH₂), 6.68 (2H, d, ³J = 8.8 Hz, ArH), 7.06 (6H, m, ArH), 7.21 (9H, m, ArH), 7.66 (2H, dd, ³J = 5.4 Hz, ⁴J = 3.1 Hz, PhthH), 7.81 (2H, dd, ³J = 5.4 Hz, ⁴J = 3.1 Hz, PhthH). ¹³C NMR (75.5 MHz, CDCl₃) δ: 31.34, 34.26, 37.20, 63.40, 67.18, 67.99, 69.06, 113.06, 123.21, 124.09, 125.62, 127.17, 130.64, 131.10, 132.04, 132.07, 133.85, 139.45, 143.92, 147.35, 148.30, 156.43, 168.26. MS (ES⁺) *m/z*: 683.4 [M + NH₄]⁺, 688.3398 [M + Na]⁺ (Calcd. for C₄₅H₄₇NO₄Na: 688.3397), 1348.7 [2M + NH₄]⁺, 1353.6 [2M + Na]⁺.

2-(2-(4-(Bis(4-*tert*-butylphenyl)(phenyl)methyl)phenoxy)ethoxy)ethylamine (73):

Compound **72** (0.32 g, 0.48 mmol) was suspended in EtOH (20 mL), hydrazine monohydrate (0.7 mL, excess) was added and the resulting mixture was heated under reflux for 16 hours. The resulting white suspension was cooled to room temperature, poured in water (50 mL) and then extracted using CH₂Cl₂ (3 x 50 mL). The combined organic layers were dried over MgSO₄, filtered and the solvent was removed *in vacuo* to give **73** as an off-white solid (0.26 g, 96%). *m.p.* 68-70 °C. ¹H NMR (300 MHz, CDCl₃) δ: 1.31 (18H, s, *t*-Bu), 1.83 (2H, br s, NH₂), 2.91 (2H, br s, NCH₂), 3.59 (2H, t, ³J = 5.1 Hz, OCH₂), 3.82 (2H, t, ³J = 4.8 Hz, OCH₂), 4.11 (2H, t, ³J = 4.8 Hz, OCH₂), 6.79 (2H, d, ³J = 9.1 Hz, ArH), 7.10 (6H, m, ArH), 7.24 (9H, m, ArH). ¹³C NMR (75.5 MHz, CDCl₃) δ: 31.35, 34.28, 41.62, 63.43, 67.15, 69.50, 73.11, 113.13, 124.11, 125.65, 127.20, 130.65, 131.11, 132.19, 139.63, 143.92, 147.34, 148.33, 156.50. MS (ES⁺) *m/z*: 536.3539 [M + H]⁺ (Calcd. for C₃₇H₄₆NO₂: 536.3523), 1071.6 [2M + H]⁺.

3,5-Bis(2-(2-(4-(bis(4-*tert*-

butylphenyl)(phenyl)methyl)phenoxy)ethoxy)ethylcarbamoyl)pyridine (74): A solution of 3,5-bis(chlorocarbonyl)pyridine (0.30 mmol) in dry CH₂Cl₂ (15 mL) was added dropwise over 1 hour to a solution of compound **73** (0.32 g, 0.60 mmol) and triethylamine (0.15 mL, 1.1 mmol) in dry CH₂Cl₂ (20 mL) under a N₂ atmosphere. The reaction mixture was left to stir

for 19 hours, then washed with 1 M HCl (2 x 30 mL) and brine (30 mL). The organic layer was dried over MgSO₄, filtered and the solvent was removed *in vacuo* to give **74** as a white solid (0.30 g, 82%). **m.p.** 130-132 °C. **¹H NMR** (300 MHz, CDCl₃) δ: 1.30 (36H, s, *t*-Bu), 3.70 (8H, m, NCH₂, OCH₂), 3.81 (4H, m, OCH₂), 4.06 (4H, m, OCH₂), 6.74 (4H, d, ³*J*=9.1 Hz, Ar*H*), 6.86 (2H, br s, NH), 7.09 (12H, m, Ar*H*), 7.20 (18H, m, Ar*H*), 8.53 (1H, t, ³*J*=2.1 Hz, py*H*⁴), 9.12 (2H, py*H*² and *H*⁶). **¹³C NMR** (75.5 MHz, CDCl₃) δ: 31.35, 34.27, 39.89, 63.43, 67.07, 69.57, 69.76, 113.10, 124.15, 125.67, 127.23, 129.56, 130.61, 131.06, 132.21, 133.31, 139.90, 143.87, 147.30, 148.36, 150.75, 156.16, 164.73. **MS (ES⁺)** *m/z*: 1202.6 [M + H]⁺, 1224.6626 [M + Na]⁺.

3,5-Bis(5-azidopentylcarbamoyl)-1-methylpyridinium iodide (75.I): A solution of **79** (0.45 g, 1.17 mmol) and iodomethane (0.8 mL, excess) in acetone (20 mL) was heated under reflux under a N₂ atmosphere for 2 days. The reaction mixture was cooled to room temperature and poured into diethyl ether (100 mL). The resulting yellow precipitate was collected by filtration, washed with diethyl ether and dried to give **75.I** as a yellow solid (0.43 g, 69%). **¹H NMR** (300 MHz, CDCl₃) δ: 1.48 (4H, m, CH₂), 1.65 (4H, m, CH₂), 1.76 (4H, m, CH₂), 3.30 (4H, t, ³*J*=6.7 Hz, CH₂), 3.48 (4H, m, CH₂), 4.57 (3H, s, N⁺CH₃), 8.73 (2H, t, ³*J*=5.6 Hz, NH), 9.41 (2H, s, py*H*² and *H*⁶), 9.97 (1H, s, py*H*⁴). **¹³C NMR** (75.5 MHz, CDCl₃) δ: 24.14, 28.35, 28.46, 40.29, 49.60, 51.18, 134.53, 141.24, 146.49, 160.27. **MS (ES⁺)** *m/z*: 402.2356 [M – I]⁺ (Calcd. for C₁₈H₂₈N₉O₂: 402.2360), 931.3 [2M – I]⁺.

3,5-Bis(5-azidopentylcarbamoyl)-1-methylpyridinium chloride (75.Cl): A biphasic mixture of **75.I** (0.38 g, 0.72 mmol) in CH₂Cl₂ (100 mL) and 1 M NH₄Cl (100 mL) was stirred vigorously for 30 minutes. The aqueous layer was decanted and the washing process with NH₄Cl was repeated five times. The aqueous layers were concentrated *in vacuo* and extracted with CH₂Cl₂ (3 x 50 mL). The combined organic layers were taken to dryness,

redissolved in 3:1 acetone/H₂O (3 mL) and passed through an Amberlite IRA 400(Cl) ion-exchange column. The eluent was taken to dryness to give **75.Cl** as a yellow solid (0.20 g, 62%). **¹H NMR** (300 MHz, CDCl₃) δ : 1.50 (4H, m, CH₂), 1.66 (4H, m, CH₂), 1.77 (4H, m, CH₂), 3.30 (4H, t, ³*J* = 6.7 Hz, CH₂), 3.49 (4H, m, CH₂), 4.58 (3H, s, N⁺CH₃), 9.30 (2H, s, pyH² and H⁶), 9.59 (2H, t, ³*J* = 5.3 Hz, NH), 10.78 (1H, s, pyH⁴). **¹³C NMR** (75.5 MHz, CDCl₃) δ : 24.18, 28.42, 40.59, 51.25, 135.05, 142.17, 146.04, 160.06. **MS (ES⁺)** *m/z*: 402.2349 [M – Cl]⁺ (Calcd. for C₁₈H₂₈N₉O₂: 402.2360).

4,4'-(Phenyl(4-(prop-2-ynyloxy)phenyl)methylene)bis(*tert*-butylbenzene) (76): A suspension of **71** (0.51 g, 1.14 mmol), propargyl benzenesulfonate (0.27 mL, 1.72 mmol) and K₂CO₃ (0.31 g, 2.26 mmol) in dry CH₃CN (12 mL) was stirred for 30 seconds at room temperature then heated under microwave irradiation for 2 hours at 160 °C. The mixture was cooled to room temperature, the solvent was removed *in vacuo* and the resulting residue was triturated with 1 M HCl (50 mL). Following extraction with CH₂Cl₂ (3 x 50 mL), the combined organic layers were dried over MgSO₄, filtered and the solvent was removed *in vacuo*. The crude material was purified by silica gel chromatography (7:3 petroleum ether/CH₂Cl₂) to give **76** as a white solid (0.38 g, 69%). **m.p.** 68-70 °C. **¹H NMR** (300 MHz, CDCl₃) δ : 1.31 (18H, s, *t*-Bu), 2.53 (1H, t, ⁴*J* = 2.3 Hz, OCH₂CCH), 4.67 (2H, d, ⁴*J* = 2.3 Hz, CH₂CCH), 6.85 (2H, d, ³*J* = 9.1 Hz, ArH), 7.16 (15H, m, ArH). **¹³C NMR** (75.5 MHz, CDCl₃) δ : 31.37, 34.28, 55.73, 63.47, 75.39, 78.74, 113.38, 124.14, 125.70, 127.22, 130.68, 131.13, 132.22, 140.27, 143.84, 147.26, 148.38, 155.47. **MS (FI⁺)** *m/z*: 486.2907 (Calcd. for C₃₆H₃₈O: 486.2923).

1,5-Diazidopentane (77):²⁶ Sodium azide (2.31 g, 35.53 mmol) was added to a solution of 1,5-dibromopentane (1.5 mL, 11.01 mmol) in dry degassed DMF (20 mL) and the mixture was heated at 60 °C under a N₂ atmosphere for 15 hours. The reaction mixture was cooled to

room temperature, H₂O (100 mL) was added and the product was extracted with diethyl ether (4 x 20 mL). The combined organic layers were washed with H₂O (3 x 10 mL) and concentrated *in vacuo* to give **77** as a colourless oil, which was not isolated but reacted onwards immediately. ¹H NMR (300 MHz, CDCl₃) δ: 1.48 (2H, m, CH₂), 1.62 (4H, m, CH₂), 3.31 (4H, t, ³J = 6.7 Hz, CH₂N₃). CAUTION: Low molecular weight azides should be handled carefully, as they are potentially explosive.

1-amino-5-azidopentane (78):²⁷ Intermediate **77** (11.01 mmol) was dissolved in EtOAc (10 mL) and diethyl ether (10 mL), 1 M HCl (30 mL) was added and the solution was cooled to 0 °C. Triphenylphosphine (2.16 g, 8.25 mmol) was added in small portions over 1 hour and the reaction mixture was allowed to warm to room temperature once the addition was complete and stirred at room temperature for 24 hours. The organic layer was discarded and the aqueous layer was washed with CH₂Cl₂ (3 x 10 mL), discarding the organic layers. The aqueous layer was carefully basified to approximately pH 10 with 1 M NaOH and extracted with CH₂Cl₂ (3 x 30 mL). The combined organic layers were dried over MgSO₄, filtered and the solvent was removed *in vacuo* to give **78** as a colourless oil (0.48 g, 34% over two steps from 1,5-dibromopentane). ¹H NMR (300 MHz, CDCl₃) δ: 1.45 (4H, m, CH₂), 1.63 (2H, m, CH₂), 2.72 (2H, m, CH₂), 3.29 (2H, t, ³J = 6.7 Hz, CH₂N₃).

3,5-Bis(5-azidopentylcarbamoyl)pyridine (79): A solution of 3,5-bis(chlorocarbonyl)pyridine (1.87 mmol) in dry CH₂Cl₂ (20 mL) was added dropwise to a solution of **78** (0.48 g, 3.74 mmol) and triethylamine (1 mL, 7.2 mmol) in dry CH₂Cl₂ (30 mL) at 0 °C under a N₂ atmosphere. Once addition was complete, the solution was stirred at 0 °C for a further hour then washed with 1 M HCl (3 x 20 mL) and brine (3 x 20 mL). The organic layer was dried over MgSO₄, filtered and the solvent was removed *in vacuo* to give **79** as an off-white solid (0.48 g, 66%). ¹H NMR (300 MHz, CDCl₃) δ: 1.49 (4H, m, CH₂), 1.68

(8H, m, CH_2), 3.31 (4H, t, $^3J = 6.6$ Hz, CH_2N_3), 3.50 (4H, q, $^3J = 6.7$ Hz, NCH_2), 6.78 (2H, br s, NH), 8.46 (1H, s, pyH^4), 9.09 (2H, s, pyH^2 and H^6). ^{13}C NMR (75.5 MHz, CDCl_3) δ : 24.10, 28.45, 29.02, 40.07, 51.16, 130.13, 133.63, 150.25, 165.05. MS (ES^+) m/z : 388.2202 $[\text{M} + \text{H}]^+$ (Calcd. for $\text{C}_{17}\text{H}_{26}\text{N}_9\text{O}_2$: 388.2204), 410.2 $[\text{M} + \text{Na}]^+$, 775.4, $[2\text{M} + \text{H}]^+$, 797.4 $[2\text{M} + \text{Na}]^+$.

Stoppered triazole axle (80.Cl): A solution of $[\text{Cu}(\text{CH}_3\text{CN})_4]\text{PF}_6$ (2.72 mg, 0.0073 mmol) and TBTA (3.29 mg, 0.0062 mmol) in dry degassed CH_2Cl_2 (1 mL) was added to a solution of **76** (0.068 g, 0.14 mmol), **75.Cl** (0.032 g, 0.073 mmol) and DIPEA (0.024 mL, 0.13 mmol) in dry degassed CH_2Cl_2 (5 mL). The reaction mixture was stirred at room temperature under a N_2 atmosphere for 4 days. The solvent was removed *in vacuo* and the residue was purified by preparative TLC (9:1 $\text{CH}_2\text{Cl}_2/\text{MeOH}$). The band containing **80.Cl** was redissolved in CHCl_3 (15 mL), washed with H_2O (2 x 5 mL) then dried over MgSO_4 , filtered and the solvent was removed *in vacuo* to give an off-white solid (0.030 g, 29%). m.p. 160 °C (dec.). ^1H NMR (300 MHz, CDCl_3) δ : 1.28 (36H, m, *t*-Bu), 1.40 (4H, m, CH_2), 1.77 (4H, m, CH_2), 1.96 (4H, m, CH_2), 3.51 (4H, q, $^3J = 5.6$ Hz, CH_2), 4.27 (2H, s, OCH_2), 4.37 (4H, t, $^3J = 6.7$ Hz, CH_2), 5.08 (3H, s, N^+CH_3), 6.81 (4H, d, $^3J = 9.1$ Hz, ArH), 7.20 (32H, m, ArH), 7.70 (2H, s, CHN_3), 9.11 (2H, s, pyH^2 and H^6), 9.61 (2H, br s, NH), 10.61 (1H, br s, pyH^4). ^{13}C NMR (75.5 MHz, CDCl_3) δ : 23.41, 27.82, 29.46, 31.34, 34.27, 39.98, 50.01, 61.86, 63.44, 113.27, 124.18, 125.56, 127.26, 130.60, 131.06, 132.25, 134.75, 140.09, 143.85, 146.22, 147.29, 148.38, 156.10, 160.38. MS (ES^+) m/z : 1374.8136 $[\text{M} - \text{Cl}]^+$.

***tert*-Butyl 5-hydroxypentylcarbamate (81):**²⁸ A solution of di-*tert*-butyldicarbonate (2.34 g, 10.74 mmol) in CH_2Cl_2 (10 mL) was added dropwise to a solution of 5-amino-1-pentanol (1.00 g, 9.68 mmol) in CH_2Cl_2 (10 mL) under a N_2 atmosphere. The reaction was stirred at room temperature for 16 hours once the addition was complete then diluted with diethyl ether

(20 mL). The solution was washed with phosphate buffer (2 x 10 mL), saturated NaHCO₃ (10 mL) and brine (10 mL). The organic layer was dried over MgSO₄, filtered and the solvent was removed *in vacuo* to give **81** as an oil (1.88 g, 95%). ¹H NMR (300 MHz, CDCl₃) δ: 1.49 (15H, m, CH₂, *t*-Bu), 3.14 (2H, q, ³J = 6.3 Hz, CH₂NHBoc), 3.66 (2H, q, ³J = 6.2 Hz, CH₂OH), 4.54 (1H, br s, NHBoc). MS (ES⁺) *m/z*: 226.1 [M + Na]⁺, 429.2 [2M + Na]⁺.

***tert*-Butyl 5-azidopentylcarbamate (82):**²⁸ Methanesulfonyl chloride (0.34 mL, 4.39 mmol) was added to a solution of **81** (0.88 g, 4.32 mmol) and triethylamine (0.6 mL, 4.3 mmol) in toluene (20 mL) at 0 °C under a N₂ atmosphere. The reaction mixture was stirred for 5 minutes before TBABr (0.14 g, 0.44 mmol) and a solution of sodium azide (2.23 g, 34.3 mmol) in H₂O (10 mL) were added. The resulting biphasic mixture was heated at 60 °C for 20 hours, cooled to room temperature and then diluted with diethyl ether (100 mL). The organic layer was washed with phosphate buffer (20 mL) and brine (20 mL) then dried over MgSO₄, filtered and the solvent was removed *in vacuo* to give **82** as a yellow oil (0.62 g, 63%). ¹H NMR (300 MHz, CDCl₃) δ: 1.51 (15H, m, CH₂, *t*-Bu), 3.13 (2H, q, ³J = 6.3 Hz, CH₂NHBoc), 3.28 (2H, t, ³J = 6.7 Hz, CH₂N₃), 4.52 (1H, br s, NHBoc). MS (ES⁺) *m/z*: 479.3 [2M + Na]⁺.

***tert*-Butyl 5-(1-((4-(bis(4-*tert*-butylphenyl)(phenyl)methyl)phenoxy)methyl)-1*H*-1,2,3-triazol-4-yl)pentylcarbamate (83):** [Cu(CH₃CN)₄]PF₆ (15.13 mg, 0.041 mmol) and TBTA (23.86 mg, 0.045 mmol) were added to a solution of **76** (0.20 g, 0.4 mmol), **82** (0.10 g, 0.44 mmol) and DIPEA (0.11 mL, 0.63 mmol) in dry degassed CH₂Cl₂ (20 mL). The solution was stirred under a N₂ atmosphere in the absence of light for 4.5 days. The organic layer was washed with H₂O (2 x 20 mL), dried over MgSO₄, filtered and the solvent was removed *in vacuo*. The residue was purified by silica gel chromatography (99:1 CH₂Cl₂/MeOH) eluting **83** as the second band to give a white solid (0.24 g, 83%). **m.p.** 74-76 °C. ¹H NMR

(300 MHz, CDCl₃) δ : 1.39 (31H, m, CH₂, *t*-Bu), 1.95 (2H, quin, ³*J* = 7.1 Hz, CH₂), 3.11 (2H, q, ³*J* = 6.2 Hz, CH₂NHBoc), 4.37 (2H, t, ³*J* = 7.1 Hz, CH₂N₃), 4.51 (1H, br s, NHBoc), 5.19 (2H, br s, OCH₂), 6.87 (2H, d, ³*J* = 8.8 Hz, ArH), 7.20 (15H, m, ArH), 7.63 (1H, br s, CHN₃). ¹³C NMR (75.5 MHz, CDCl₃) δ : 23.69, 28.38, 29.49, 29.77, 31.33, 34.26, 40.11, 63.43, 79.20, 113.29, 124.11, 125.67, 127.20, 130.64, 131.10, 132.25, 139.96, 143.83, 147.27, 148.38, 155.94, 156.09. MS (ES⁺) *m/z*: 737.4388 [M + Na]⁺ (Calcd. for C₄₆H₅₈N₄O₃Na: 737.4401).

Stoppered rotaxane (84.X): [Cu(CH₃CN)₄]PF₆ (2.23 mg, 0.006 mmol) was added to a solution of **66** (0.034 g, 0.03 mmol), **76** (0.033 g, 0.068 mmol), 3,5-bis(5-azidopropylcarbamoyl)-1-methylpyridinium chloride (0.014 g, 0.035 mmol) and TBTA (5.14 mg, 0.0097 mmol) in dry degassed CH₂Cl₂ (2 mL). The solution was stirred under a N₂ atmosphere for 17 hours before the solvent was removed *in vacuo* and the residue was purified by preparative TLC (1:1 hexane/acetone). There was electrospray mass spectrometry evidence of rotaxane **84.X** in the third band isolated from the TLC plate. MS (ES⁺) *m/z*: 2455.3583 [M – X]⁺.

5-(1-((4-(Bis(4-*tert*-butylphenyl)(phenyl)methyl)phenoxy)methyl)-1*H*-1,2,3-triazol-4-yl)pentan-1-amine (85): A solution of **83** (0.18 g, 0.26 mmol) and TFA (1 mL, excess) in CH₂Cl₂ (5 mL) was stirred at room temperature for 16 hours, then washed with 1 M NaOH (2 x 5 mL) and brine (5 mL). The organic layer was dried over MgSO₄, filtered and the solvent was removed *in vacuo*. The residue was redissolved in CHCl₃, HCl gas was bubbled through the solution and the product was precipitated as the hydrochloride salt upon addition of hexane. This was collected by filtration, washed with hexane and dried to give impure **85**, which was immediately reacted on.

3,5-Bis(-1-((4-(Bis(4-*tert*-butylphenyl)(phenyl)methyl)phenoxy)methyl)-1*H*-1,2,3-triazol-

4-yl)pentylcarbamoyl)pyridine (86): A solution of 3,5-bis(chlorocarbonyl)pyridine (0.077 mmol) in dry CH₂Cl₂ (2 mL) was added to a solution of impure **85** and triethylamine (0.07 mL, 0.5 mmol) in dry CH₂Cl₂ (15 mL) under a N₂ atmosphere. The reaction mixture was stirred at room temperature for 1 day before washing with 1 M HCl (2 x 15 mL) and brine (15 mL). The organic layer was dried over MgSO₄, filtered and the solvent was removed *in vacuo*. The residue was purified by silica gel chromatography, eluting the first band with 98:2 CH₂Cl₂/MeOH and the second band with 95:5 CH₂Cl₂/MeOH. The second band was taken to dryness to give **86** as a white solid (0.037 g, 10% over two steps from **83**). **m.p.** 142-144 °C. ¹H NMR (300 MHz, CDCl₃) δ: 1.33 (36H, s, *t*-Bu), 1.67 (4H, m, CH₂), 1.91 (8H, m, CH₂), 3.48 (4H, m, CH₂), 4.39 (4H, m, CH₂), 5.02 (4H, br s, OCH₂), 6.77 (4H, d, ³*J* = 8.8 Hz, ArH), 7.17 (30H, m, ArH), 7.56 (2H, br s, CHN₃), 7.83 (2H, br s, NH), 8.58 (2 H, br s, pyH² and H⁶), 9.24 (1 H, br s, pyH⁴). ¹³C NMR (75.5 MHz, CDCl₃) δ: 22.75, 27.80, 29.21, 31.33, 34.27, 39.30, 49.70, 61.49, 63.42, 75.90, 76.36, 113.13, 124.14, 125.70, 127.23, 130.61, 131.06, 132.29, 140.17, 143.78, 147.21, 148.41, 155.91, 165.32. **MS (ES⁺)** *m/z*: 1382.7902 [M + Na]⁺ (Calcd. for C₈₉H₁₀₁N₉O₄Na: 1382.7869).

5-Hydroxyisophthalamide-hydroquinone *tert*-butylcalix[4]arene macrobicycle (87): 5-Hydroxyisophthalic acid (0.059 g, 0.32 mmol) was suspended in dry CH₂Cl₂ (50 mL) and HOBt (0.093 g, 0.69 mmol), EDC.HCl (0.13 g, 0.68 mmol) were added. The suspension was stirred at room temperature under a N₂ atmosphere for 3.5 hours, then this was added dropwise to a solution of **52** (0.33 g, 0.32 mmol), **53.Cl** (0.12 g, 0.32 mmol) and triethylamine (0.1 mL, 0.72 mmol) in dry CH₂Cl₂ (80 mL). Once addition was complete, the stirring was continued for a further 2 days, before washing with 1 M HCl (2 x 100 mL), H₂O (100 mL) and brine (100 mL). The organic layer was dried over MgSO₄, filtered and the solvent was removed *in vacuo*. The crude material was purified by silica gel chromatography (8:2 EtOAc/petroleum ether) to give impure **87** as a white solid (0.034 g, ~9%). ¹H NMR

(300 MHz, CDCl₃) δ : 0.98 (18H, s, *t*-Bu), 1.30 (18H, s, *t*-Bu), 3.35 (4H, d, $^2J = 13.2$ Hz, ArCH_{in}H_{out}Ar), 3.74 (4H, m, NCH₂), 4.13 (12H, m, OCH₂), 4.42 (4H, d, $^2J = 13.2$ Hz, ArCH_{in}H_{out}Ar), 6.72 (8H, m, hydroq ArH), 6.83 (4H, m, calix ArH), 7.08 (4H, m, calix ArH), 7.32 (2H, br s, NH), 7.42 (2H, m, OH), 7.60 (2H, m, isoH), 7.68 (1H, s, isoH), 8.03 (1H, br s, OH). **MS (ES⁺)** m/z : 1170.6 [M + NH₄]⁺, 1175.6157 [M + Na]⁺ (Calcd. for C₇₂H₈₄N₂O₁₁Na: 1175.5967).

3,5-Bis(2-(4-(2-(allyloxy)ethoxy)phenoxy)ethylcarbamoyl)-1-methylpyridinium iodide

(88.I):²⁹ A solution of **93** (0.088 g, 0.14 mmol) and iodomethane (0.5 mL, excess) in acetone (20 mL) was heated under reflux under a N₂ atmosphere for 42 hours. The solvent was removed *in vacuo* to give **88.I** as an orange oily residue (0.11 g, 100%). **Microwave synthesis:** A suspension of **93** (0.10 g, 0.167 mmol) and iodomethane (0.17 mL, 2.73 mmol) was stirred for 30 seconds at room temperature then heated for 10 minutes at 100 °C under microwave irradiation. The solvent and excess iodomethane were removed *in vacuo* to give **88.I** (0.13 g, 100%). **¹H NMR** (300 MHz, CDCl₃) δ : 3.77 (4H, m, NCH₂), 3.86 (4H, m, OCH₂), 4.03 (4H, m, OCH₂), 4.10 (4H, m, OCH₂CHCH₂), 4.18 (4H, m, OCH₂), 4.47 (3H, s, N⁺CH₃), 5.28 (4H, m, CHCH₂), 5.96 (2H, m, CHCH₂), 6.75 (8H, m, hydroq ArH), 8.94 (2H, t, $^3J = 5.6$ Hz, NH), 9.31 (2H, s, pyH² and H⁶), 9.91 (1H, s, pyH⁴). **MS (ES⁺)** m/z : 620.2883 [M – I]⁺.

3,5-Bis(2-(4-(2-(allyloxy)ethoxy)phenoxy)ethylcarbamoyl)-1-methylpyridinium chloride

(88.Cl):^{5, 29} Compound **88.I** (0.94 g, 1.26 mmol) was dissolved in CHCl₃ (150 mL) and stirred for 30 minutes with 1 M NH₄Cl (150 mL). The aqueous layer was decanted and the washing procedure was repeated a further five times. The organic layer was dried over MgSO₄, filtered and the solvent was removed *in vacuo* to give **88.Cl** as a brown solid (0.80 g, 97%). **¹H NMR** (300 MHz, CDCl₃) δ : 3.77 (8H, m, NCH₂, OCH₂), 4.03 (4H, t, $^3J = 4.6$ Hz, OCH₂), 4.11 (8H,

m, OCH_2 , $\text{OCH}_2\text{CHCH}_2$), 4.44 (3H, br s, N^+CH_3), 5.27 (4H, m, CHCH_2), 5.94 (2H, m, CHCH_2), 6.74 (8H, m, hydroq ArH), 9.42 (2H, s, pyH^2 and H^6), 9.57 (2H, br s, NH), 10.29 (1H, s, pyH^4). MS (ES^+) m/z : 620.2960 $[\text{M} - \text{Cl}]^+$ (Calcd. for $\text{C}_{34}\text{H}_{42}\text{N}_3\text{O}_8$: 629.2972).

2-(Allyloxy)ethanol tosylate (89):³⁰ A solution of 2-allyloxyethanol (3.6 mL, 33.7 mmol), tosyl chloride (6.41 g, 33.6 mmol), triethylamine (7 mL, 50.2 mmol) and DMAP (cat.) in CH_2Cl_2 (100 mL) was stirred at room temperature under a N_2 atmosphere for 16 hours. H_2O (50 mL) was added and the biphasic mixture was acidified with 10% aqueous citric acid. The layers were separated and the organic layer was washed with H_2O (2 x 100 mL) and brine (100 mL), dried over MgSO_4 , filtered and the solvent was removed *in vacuo* to give **89** as a colourless oil (7.41 g, 86%). ^1H NMR (300 MHz, CDCl_3) δ : 2.45 (3H, s, CH_3), 3.63 (2H, t, $^3J = 4.6$ Hz, $\text{OCH}_2\text{CHCH}_2$), 3.95 (2H, d, $^3J = 5.6$ Hz, OCH_2), 4.18 (2H, t, $^3J = 4.6$ Hz, OCH_2), 5.20 (2H, m, CHCH_2), 5.81 (1H, m, CHCH_2), 7.35 (2H, d, $^3J = 8.2$ Hz, TosH), 7.81 (2H, d, $^3J = 8.2$ Hz, TosH). MS (ES^+) m/z : 279.0596 $[\text{M} + \text{Na}]^+$.

4-(2-(Allyloxy)ethoxy)phenol (90):¹⁸ A suspension of **89** (7.23 g, 28.2 mmol), *p*-hydroquinone (12.46 g, 113 mmol) and K_2CO_3 (4.29 g, 31 mmol) in EtOH (200 mL) was heated under reflux for 18 hours under a N_2 atmosphere. The resulting suspension was cooled to room temperature, filtered and the filtrate was taken to dryness. The residue was redissolved in H_2O (50 mL), acidified to pH 2.5 with 1 M HCl and extracted with CHCl_3 (3 x 50 mL). The combined organic layers were dried over MgSO_4 , filtered and the solvent was removed *in vacuo*. The crude material was purified by silica gel chromatography (3:2 hexane/EtOAc) and the product **90** was eluted as the second band giving a yellow oil (3.93 g, 72%). ^1H NMR (300 MHz, CDCl_3) δ : 3.79 (2H, m, OCH_2), 4.09 (4H, m, OCH_2 , $\text{OCH}_2\text{CHCH}_2$), 5.27 (3H, m, OH, CHCH_2), 5.94 (1H, m, CHCH_2), 6.77 (4H, m, hydroq ArH). MS (FI^+) m/z : 194.0941 (Calcd. for $\text{C}_{11}\text{H}_{14}\text{O}_3$: 194.0943).

2-(4-(2-(Allyloxy)ethoxy)phenoxy)acetonitrile (91):¹⁸ Bromoacetonitrile (1.53 mL, 22 mmol) was added to a solution of **90** (3.90 g, 20 mmol) and K₂CO₃ (3.07 g, 22.2 mmol) in acetone (100 mL). The resulting suspension was heated under reflux under a N₂ atmosphere for 16 hours before being cooled to room temperature and filtered. The solvent was removed *in vacuo* to give a brown oil, which was redissolved in CHCl₃ and filtered through a plug of silica to give **91** as a yellow oil (3.59 g, 75%). ¹H NMR (300 MHz, CDCl₃) δ: 3.80 (2H, t, ³J = 4.8 Hz, OCH₂), 4.11 (4H, m, OCH₂, OCH₂CHCH₂), 4.72 (2H, s, CH₂CN), 5.29 (2H, m, CHCH₂), 5.95 (1H, m, CHCH₂), 6.93 (4H, m, hydroq ArH). MS (ES⁺) *m/z*: 256.0829 [M + Na]⁺.

2-(4-(2-(Allyloxy)ethoxy)phenoxy)ethylamine (92):¹⁸ A solution of **91** (3.19 g, 13.68 mmol) in dry diethyl ether (50 mL) was added dropwise to a stirred suspension of LiAlH₄ (0.79 g, 20.87 mmol) in dry diethyl ether (200 mL) under a N₂ atmosphere. Once addition was complete, the resulting mixture was heated under reflux under a N₂ atmosphere for 1 hour, cooled to room temperature and the unreacted LiAlH₄ was neutralised with 10% aqueous NaOH. H₂O (100 mL) was added and the ether layer was decanted and the aqueous layer was extracted with diethyl ether (8 x 100 mL). The combined organic layers were dried over MgSO₄, filtered and the solvent was removed *in vacuo* to give **92** as a yellow oil (2.28 g, 87%). ¹H NMR (300 MHz, CDCl₃) δ: 1.60 (2H, br s, NH₂), 3.06 (2H, t, ³J = 5.1 Hz, CH₂NH₂), 3.79 (2H, m, OCH₂), 3.94 (2H, t, ³J = 5.1 Hz, OCH₂), 4.09 (4H, m, OCH₂, OCH₂CHCH₂), 5.26 (2H, m, CHCH₂), 5.94 (1H, m, CHCH₂), 6.84 (4H, m, hydroq ArH). MS (ES⁺) *m/z*: 238.1395 [M + H]⁺.

3,5-Bis(2-(4-(2-(allyloxy)ethoxy)phenoxy)ethylcarbamoyl)pyridine (93):⁵ A stirred solution of **92** (2.82 g, 11.89 mmol) and triethylamine (4.6 mL, 33 mmol) in dry CH₂Cl₂ (200 mL) was cooled to 0 °C under a N₂ atmosphere. A solution of

3,5-bis(chlorocarbonyl)pyridine (5.96 mmol) was added dropwise over 40 minutes and the reaction mixture was stirred for a further hour at 0 °C. The yellow solution was washed with 1 M HCl (3 x 150 mL), brine (3 x 150 mL), dried over MgSO₄, filtered and the solvent was removed *in vacuo* to give **93** as a brown solid (3.09 g, 85%). ¹H NMR (300 MHz, CDCl₃) δ: 3.79 (4H, m, NCH₂), 3.89 (4H, m, OCH₂), 4.11 (12H, m, OCH₂, OCH₂CHCH₂), 5.27 (4 H, m, CHCH₂), 5.94 (2H, m, CHCH₂), 6.87 (8H, m, hydroq ArH), 8.57 (1H, s, pyH⁴), 9.14 (2H, s, pyH² and H⁶). MS (ES⁺) *m/z*: 606.2839 [M + H]⁺ (Calcd. for C₃₃H₄₀N₃O₈: 606.2815), 628.2525 [M + Na]⁺, 644.2274 [M + K]⁺.

Isophthalamide-hydroquinone calix[4]diquinone macrobicycle (94): An aqueous solution of ClO₂ (prepared in 3 mL H₂O from 0.052 g NaClO₂ and 0.069 g Na₂S₂O₈) was added to a solution of **98** (0.073 g, 0.08 mmol) in 6:1 CH₃CN/CHCl₃ (7 mL) in the absence of light and the mixture was stirred at room temperature for 53 hours. The organic solvent was removed *in vacuo* and the aqueous layer was extracted with CHCl₃ (3 x 20 mL). The organic layers were dried over MgSO₄, filtered and the solvent was removed *in vacuo*. The crude yellow solid was purified by silica gel chromatography (97:3 CH₂Cl₂/MeOH) and the product **94** was eluted as the first yellow band giving a yellow solid (0.046 g, 62%). m.p. 200 °C (dec.). ¹H NMR (300 MHz, CDCl₃) δ: 3.38 (4H, d, ²*J* = 11.7 Hz, ArCH_{in}H_{out}Qu), 3.90 (12H, m, NCH₂, OCH₂), 4.07 (4H, m, OCH₂), 4.15 (4H, br s, ArCH_{in}H_{out}Qu), 6.76 (20H, m, calix ArH, hydroq ArH, NH), 7.54 (1H, t, ³*J* = 7.7 Hz, isoH), 7.98 (2H, d, ³*J* = 7.7 Hz, isoH), 8.24 (1H, s, isoH). ¹³C NMR (75.5 MHz, CDCl₃) δ: 31.37, 39.68, 67.01, 67.18, 72.58, 115.03, 115.20, 123.84, 125.78, 128.91, 129.90, 130.12, 130.22, 132.44, 134.98, 147.30, 152.50, 152.79, 155.76, 167.15, 188.33. MS (ES⁺) *m/z*: 958.3 [M + NH₄]⁺, 963.3081 [M + Na]⁺ (Calcd. for C₅₆H₄₈N₂O₁₂Na: 963.3099).

25-(4-2-(Phthalimidoethoxy)phenoxy)ethoxy)-26,27,28-trihydroxycalix[4]arene (95): A

suspension of calix[4]arene (0.40 g, 0.93 mmol), **60** (0.91 g, 2.23 mmol) and K_2CO_3 (0.14 g, 1.03 mmol) in acetone (15 mL) was stirred for 30 seconds and heated under microwave irradiation for 2 hours at 140 °C. The resulting suspension was cooled to room temperature and the solvent was removed *in vacuo*. The residue was redissolved in $CHCl_3$ (50 mL) and washed with 10% aqueous HCl (2 x 20 mL) and brine (20 mL). The organic layer was dried over $MgSO_4$, filtered and the solvent was removed *in vacuo*. Purification by silica gel chromatography (9:1 $CHCl_3$ /EtOAc) eluted the monoalkylated product **95** as the second band to give a white solid (0.16 g, 23%). **m.p.** 108-110 °C. 1H NMR (300 MHz, $CDCl_3$) δ : 3.43 (2H, d, $^2J = 14.1$ Hz, $ArCH_{in}H_{out}Ar$), 3.47 (2H, d, $^2J = 12.9$ Hz, $ArCH_{in}H_{out}Ar$), 4.11 (2H, m, NCH_2), 4.21 (4H, m, OCH_2 , $ArCH_{in}H_{out}Ar$), 4.50 (6H, m, OCH_2 , $ArCH_{in}H_{out}Ar$), 6.66 (3H, t, $^3J = 7.6$ Hz, calix ArH), 6.90 (3H, m, calix ArH), 6.99 (6H, m, hydroq ArH , calix ArH), 7.05 (2H, d, $^3J = 7.6$ Hz, calix ArH), 7.11 (2H, d, $^3J = 7.1$ Hz, calix ArH), 7.72 (2H, dd, $^3J = 5.3$ Hz, $^4J = 2.9$ Hz, Phth H), 7.87 (2H, dd, $^3J = 5.3$ Hz, $^4J = 2.9$ Hz, Phth H), 9.23 (2H, s, OH), 9.72 (1H, s, OH). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ : 31.23, 31.82, 37.38, 65.34, 67.08, 74.50, 77.20, 115.64, 115.73, 120.89, 121.68, 123.26, 126.17, 128.36, 128.42, 128.61, 128.73, 129.33, 131.92, 133.93, 134.37, 149.34, 150.53, 151.26, 152.74, 152.98, 168.15. **MS (ES $^+$)** m/z : 756.2562 $[M + Na]^+$ (Calcd. for $C_{46}H_{39}NO_8Na$: 756.2568).

25,27-Bis(4-2-(phthalimidoethoxy)phenoxy)ethoxy)-26,28-dihydroxycalix[4]arene (96):

A suspension of calix[4]arene (0.28 g, 0.65 mmol), **60** (0.65 g, 1.61 mmol), K_2CO_3 (0.099 g, 0.72 mmol) in CH_3CN (15 mL) was stirred for 30 seconds then heated under microwave irradiation for 4 hours at 160 °C. The resulting suspension was cooled to room temperature and the solvent was removed *in vacuo*. The residue was redissolved in $CHCl_3$ (50 mL) and washed with 10% aqueous HCl (2 x 50 mL) and brine (50 mL). The organic layer was dried over $MgSO_4$, filtered and the solvent was removed *in vacuo*. Purification by silica gel chromatography (9:1 $CHCl_3$ /EtOAc) eluted the product as the third band to give **96** as a white

solid (0.45 g, 67%). **m.p.** 170-172 °C. **¹H NMR** (300 MHz, CDCl₃) δ: 3.36 (4H, d, ²J = 12.9 Hz, ArCH_{in}H_{out}Ar), 4.09 (4H, m, NCH₂), 4.18 (8H, m, OCH₂), 4.26 (4H, m, OCH₂), 4.41 (4H, d, ²J = 12.9 Hz, ArCH_{in}H_{out}Ar), 6.63 (2H, t, ³J = 7.3 Hz, calix ArH), 6.75 (2H, m, calix ArH), 6.81 (8H, s, hydroq ArH), 6.93 (4H, d, ³J = 7.3 Hz, calix ArH), 7.04 (4H, d, ³J = 7.3 Hz, calix ArH), 7.70 (4H, dd, ³J = 5.2 Hz, ⁴J = 3.0 Hz, PhthH), 7.85 (4H, dd, ³J = 5.2 Hz, ⁴J = 3.0 Hz, PhthH), 8.02 (2H, s, OH). **¹³C NMR** (75.5 MHz, CDCl₃) δ: 31.22, 37.39, 65.32, 67.17, 74.13, 115.50, 115.87, 118.86, 123.27, 125.38, 128.08, 128.34, 128.91, 131.94, 133.60, 133.97, 151.61, 152.70, 153.01, 153.17, 168.16. **MS (ES⁺)** *m/z*: 1060.4 [M + NH₄]⁺, 1065.35399 [M + Na]⁺ (Calcd. for C₆₄H₅₄N₂O₁₂Na: 1065.35690).

25,27-Bis(4-2-(aminoethoxy)phenoxy)ethoxy)-26,28-dihydroxycalix[4]arene (97): A suspension of **96** (0.71 g, 0.68 mmol) and hydrazine monohydrate (1 mL, excess) in EtOH (50 mL) was heated under reflux for 16 hours, cooled to room temperature and poured into H₂O (50 mL). The white suspension was extracted with EtOAc (4 x 50 mL) and the combined organic layers were dried over MgSO₄, filtered and the solvent removed *in vacuo* to give **97** as a white solid (0.43 g, 81%). **m.p.** 84-86 °C. **¹H NMR** (300 MHz, CDCl₃) δ: 3.07 (4H, t, ³J = 5.1 Hz, CH₂NH₂), 3.38 (4H, d, ²J = 13.2 Hz, ArCH_{in}H_{out}Ar), 3.94 (4H, t, ³J = 5.1 Hz, OCH₂), 4.26 (4H, m, OCH₂), 4.30 (4H, m, OCH₂), 4.44 (4H, d, ²J = 13.2 Hz, ArCH_{in}H_{out}Ar), 6.65 (2H, t, ³J = 7.5 Hz, calix ArH), 6.77 (2H, m, calix ArH), 6.87 (8H, m, hydroq ArH), 6.95 (4H, d, ³J = 7.5 Hz, calix ArH), 7.06 (4H, d, ³J = 7.5 Hz, calix ArH), 8.02 (2H, br s, OH). **¹³C NMR** (75.5 MHz, CDCl₃) δ: 31.22, 41.25, 67.14, 69.87, 74.15, 115.35, 115.89, 118.92, 125.44, 128.11, 128.36, 128.93, 13.56, 151.64, 152.85, 153.14. **MS (ES⁺)** *m/z*: 392.2 [M + 2H]²⁺, 783.3624 [M + H]⁺ (Calcd. for C₄₈H₅₁N₂O₈: 783.3640).

Isophthalamide-hydroquinone calix[4]arene macrobicycle (98): Separate solutions of **97** (0.20 g, 0.26 mmol) in dry CH₂Cl₂ (100 mL) and isophthaloyl dichloride (0.054 g, 0.26 mmol)

in dry CH_2Cl_2 (100 mL) were added dropwise simultaneously to a stirred solution of triethylamine (0.1 mL, 0.72 mmol) in dry CH_2Cl_2 (200 mL) over 1 hour under a N_2 atmosphere. The reaction mixture was stirred for a further 3 hours, concentrated *in vacuo* to a volume of 100 mL and washed with 1 M HCl (2 x 100 mL), H_2O (100 mL), 1 M NaOH (100 mL) and brine (100 mL). The organic layer was dried over MgSO_4 , filtered and the solvent removed *in vacuo*. The crude material was purified by silica gel chromatography (97:3 $\text{CH}_2\text{Cl}_2/\text{MeOH}$) giving **98** as a white solid (0.13 g, 54%). **m.p.** 178-180 °C. ^1H NMR (300 MHz, CDCl_3) δ : 3.40 (4H, d, $^2J = 12.9$ Hz, $\text{ArCH}_{\text{in}}\text{H}_{\text{out}}\text{Ar}$), 3.87 (4H, q, $^3J = 4.8$ Hz, NCH_2), 4.15 (4H, t, $^3J = 4.8$ Hz, OCH_2), 4.33 (8H, m, OCH_2), 4.43 (4H, d, $^2J = 12.9$ Hz, $\text{ArCH}_{\text{in}}\text{H}_{\text{out}}\text{Ar}$), 6.67 (2H, t, $^3J = 7.4$ Hz, calix ArH), 6.82 (12H, m, calix ArH , hydroq ArH , NH), 6.95 (4H, d, $^3J = 7.4$ Hz, calix ArH), 7.07 (4H, d, $^3J = 7.4$ Hz, calix ArH), 7.57 (1H, t, $^3J = 7.7$ Hz, isoH), 7.89 (2H, s, isoH), 8.05 (1H, s, OH), 8.05 (2H, d, $^3J = 7.7$ Hz, isoH). ^{13}C NMR (75.5 MHz, CDCl_3) δ : 31.27, 39.67, 67.35, 67.53, 74.26, 115.74, 116.15, 119.06, 123.25, 125.55, 128.18, 128.41, 129.02, 129.53, 131.21, 133.52, 134.53, 151.74, 152.90, 153.13, 153.30, 166.82. **MS** (ES^+) m/z : 930.4 $[\text{M} + \text{NH}_4]^+$, 935.3513 $[\text{M} + \text{Na}]^+$ (Calcd. for $\text{C}_{56}\text{H}_{52}\text{N}_2\text{O}_{10}\text{Na}$: 935.3514), 951.3 $[\text{M} + \text{K}]^+$.

Catenane (99.Cl): Grubbs' second generation catalyst (4 mg, 10% by weight) was added to a solution of **94** (0.044 g, 0.047 mmol) and **88.Cl** (0.039 g, 0.059 mmol) in dry degassed CH_2Cl_2 (10 mL) under a N_2 atmosphere. The reaction mixture was stirred at room temperature for 16 hours, the solvent was removed *in vacuo* and the residue was purified by preparative TLC (96:4 $\text{CH}_2\text{Cl}_2/\text{MeOH}$). Catenane **99.Cl** was isolated as a yellow solid (7.2 mg, 10%). ^1H NMR (300 MHz, CDCl_3) δ : 3.17 (4H, $^2J = 12.9$ Hz, $\text{ArCH}_{\text{in}}\text{H}_{\text{out}}\text{Ar}$), 3.56 (4H, m, NCH_2), 3.72 (4H, m, OCH_2), 3.77 (4H, m, OCH_2), 3.87 (4H, m, OCH_2), 4.10 (20H, m, OCH_2), 4.48 (4H, d, $^2J = 12.9$ Hz, $\text{ArCH}_{\text{in}}\text{H}_{\text{out}}\text{Ar}$), 5.32 (3H, s, N^+CH_3), 5.85 (2H, s, CHCH), 6.17 (4H, d, $^3J = 8.8$ Hz, hydroq ArH), 6.34 (4H, d, $^3J = 8.8$ Hz, hydroq ArH), 6.76 (18H, m, calix

ArH, hydroq ArH), 7.59 (1H, t, $^3J = 7.8$ Hz, isoH), 8.27 (2H, d, $^3J = 7.8$ Hz, isoH), 8.65 (2H, br s, NH), 8.74 (2H, br s, NH), 8.95 (2H, s, pyH² and H⁶), 9.20 (1H, s, isoH), 9.89 (1H, s, pyH⁴). ¹³C NMR (125 MHz, CDCl₃) δ: 29.77, 39.90, 41.31, 65.36, 66.42, 67.33, 68.37, 68.68, 71.23, 73.28, 113.46, 114.75, 114.96, 115.99, 123.95, 128.53, 129.03, 129.44, 130.48, 131.92, 132.45, 133.30, 133.50, 144.52, 148.89, 151.70, 152.64, 152.88, 153.73, 154.35, 159.91, 166.73, 186.07, 187.99. MS (ES⁺) *m/z*: 1532.5871 [M – Cl]⁺ (Calcd. for C₈₈H₈₆N₅O₂₀: 1532.5861).

6.2.4. Syntheses from Chapter Four

3,5-Bis(2-(4-(2-(prop-2-ynyloxy)ethoxy)phenoxy)ethylcarbamoyl)-1-methylpyridinium

iodide (100.I): A solution of **112** (0.25 g, 0.42 mmol) and iodomethane (0.5 mL, excess) in acetone (30 mL) was heated under reflux under a N₂ atmosphere for 45 hours. The reaction mixture was cooled to room temperature, the solvent was removed *in vacuo* and the residue was purified by silica gel chromatography (9:1 CH₂Cl₂/MeOH) giving **100.I** as an orange solid (0.25 g, 82%). ¹H NMR (300 MHz, CDCl₃) δ: 2.51 (2H, t, $^4J = 2.2$ Hz, OCH₂CCH), 3.83 (8H, m, NCH₂, OCH₂), 4.03 (4H, m, OCH₂), 4.17 (4H, m, OCH₂), 4.28 (4H, d, $^4J = 2.2$ Hz, OCH₂CCH), 4.49 (3H, s, N⁺CH₃), 6.72 (8H, m, hydroq ArH), 8.86 (2H, t, $^3J = 4.7$ Hz, NH), 9.37 (2H, s, pyH² and H⁶), 9.86 (1H, s, pyH⁴). ¹³C NMR (75.5 MHz, CDCl₃) δ: 40.05, 49.39, 58.49, 66.34, 67.63, 68.38, 75.05, 79.36, 115.32, 115.61, 133.40, 141.15, 146.22, 152.61, 152.70, 160.71. MS (ES⁺) *m/z*: 616.2655 [M – I]⁺ (Calcd. for C₃₄H₃₈N₃O₈: 616.2653).

3,5-Bis(2-(4-(2-(prop-2-ynyloxy)ethoxy)phenoxy)ethylcarbamoyl)-1-methylpyridinium

chloride (100.Cl): Compound **100.I** (0.15 g, 0.2 mmol) was dissolved in CHCl₃ (50 mL) and washed with 1 M NH₄Cl (8 x 50 mL). The organic layer was dried over MgSO₄, filtered and the solvent was removed *in vacuo*. The residue was purified by silica gel chromatography (9:1

CHCl₃/MeOH) to give **100.Cl** as an orange solid (0.09 g, 72%). ¹H NMR (300 MHz, CDCl₃) δ: 2.50 (2H, t, ⁴J = 2.3 Hz, OCH₂CCH), 3.78 (4H, m, NCH₂), 3.85 (4H, m, OCH₂), 4.04 (4H, m, OCH₂), 4.12 (4H, m, OCH₂), 4.27 (4H, d, ⁴J = 2.3 Hz, OCH₂CCH), 4.46 (3H, s, N⁺CH₃), 6.75 (8H, m, hydroq ArH), 9.43 (2H, s, pyH² and H⁶), 9.55 (2H, br s, NH), 10.26 (1H, s, pyH⁴). ¹³C NMR (75.5 MHz, CDCl₃) δ: 40.17, 48.96, 58.36, 66.15, 67.55, 68.29, 75.00, 79.31, 115.17, 115.41, 133.37, 141.25, 146.21, 152.65, 160.60. MS (ES⁺) m/z: 616.2660 [M – Cl]⁺ (Calcd. for C₃₄H₃₈N₃O₈: 616.2653).

3,5-Bis(2-(4-(2-(2-(2-(prop-2-ynyloxy)ethoxy)ethoxy)ethoxy)phenoxy)ethylcarbamoyl)-1-methylpyridinium iodide (101.I): A solution of **113** (0.32 g, 0.45 mmol) and iodomethane (0.5 mL, excess) in acetone (20 mL) was heated under reflux under a N₂ atmosphere for 65 hours. The reaction mixture was cooled to room temperature and the solvent was removed *in vacuo*. The residue was redissolved in CHCl₃ (50 mL), washed with H₂O (2 x 20 mL), dried over MgSO₄, filtered and the solvent was removed *in vacuo*. Purification by silica gel chromatography (9:1 CH₂Cl₂/MeOH) gave impure **101.I** as an orange oily solid (0.23 g, ~55%). ¹H NMR (300 MHz, CDCl₃) δ: 2.41 (2H, t, ⁴J = 2.4 Hz, OCH₂CCH), 3.73 (20H, m, NCH₂, OCH₂), 3.88 (8H, m, OCH₂), 4.07 (4H, d, ⁴J = 2.4 Hz, OCH₂CCH), 4.26 (4H, t, ³J = 5.0 Hz, OCH₂), 4.51 (3H, s, N⁺CH₃), 6.64 (4H, d, ³J = 9.1 Hz, hydroq ArH), 6.86 (4H, d, ³J = 9.1 Hz, hydroq ArH), 8.82 (2H, t, ³J = 5.4 Hz, NH), 9.43 (2H, s, pyH² and H⁶), 9.70 (1H, s, pyH⁴). MS (ES⁺) m/z: 792.3683 [M – I]⁺ (Calcd. for C₄₂H₅₄N₃O₁₂: 792.3702).

3,5-Bis(2-(4-(2-(2-(2-(prop-2-ynyloxy)ethoxy)ethoxy)ethoxy)phenoxy)ethylcarbamoyl)-1-methylpyridinium chloride (101.Cl): A biphasic mixture of impure **101.I** (0.22 g, 0.24 mmol) in CHCl₃ (100 mL) and 1 M NH₄Cl (100 mL) was stirred vigorously for 30 minutes. The aqueous layer was decanted and the washing procedure was repeated a further four times. The organic layer was dried over MgSO₄, filtered and the solvent was

removed *in vacuo* to give impure **101.Cl** as an orange solid (0.18 g, ~91%). ¹H NMR (300 MHz, CDCl₃) δ: 2.41 (2H, t, ⁴J = 2.4 Hz, OCH₂CCH), 3.70 (16H, m, NCH₂, OCH₂), 3.81 (8H, m, OCH₂), 3.92 (4H, m, OCH₂), 4.09 (4H, d, ⁴J = 2.4 Hz, OCH₂CCH), 4.22 (4H, m, OCH₂), 4.49 (3H, s, N⁺CH₃), 6.64 (4H, d, ³J = 9.0 Hz, hydroq ArH), 6.84 (4H, d, ³J = 9.0 Hz, hydroq ArH), 9.45 (2H, s, pyH² and H⁶), 9.59 (2H, br s, NH), 10.16 (1H, s, pyH⁴). MS (ES⁺) *m/z*: 792.3699 [M – Cl]⁺ (Calcd. for C₄₂H₅₄N₃O₁₂: 792.3702).

2-(Prop-2-ynyloxy)ethanol (102):³¹ Anhydrous ethylene glycol (15 mL, 269 mmol) was dissolved in dry THF (130 mL) and added dropwise to a suspension of NaH (60% dispersion in mineral oil, 3.02 g, 75.4 mmol) in dry THF (120 mL) at 0 °C under a N₂ atmosphere over 45 minutes. The reaction mixture was stirred for 2 hours at room temperature, propargyl bromide (80% in toluene, 7.6 mL, 68.2 mmol) was added and the suspension was heated for 5.5 hours under reflux. After cooling to room temperature, the reaction mixture was diluted with H₂O (120 mL) and the organic solvent was removed *in vacuo*. The aqueous solution was extracted with EtOAc (4 x 50 mL) and the combined organic layers were washed with brine (50 mL), dried over MgSO₄, filtered and the solvent was removed *in vacuo*. The resulting oil was purified by silica gel chromatography (3:2 petroleum ether/EtOAc) eluting the product **102** as the third band giving a colourless oil (2.69 g, 39%). ¹H NMR (300 MHz, CDCl₃) δ: 2.47 (1H, t, ⁴J = 2.4 Hz, OCH₂CCH), 3.67 (2H, m, OCH₂), 3.77 (2H, m, OCH₂), 4.22 (2H, d, ⁴J = 2.4 Hz, OCH₂CCH). MS (FI⁺) *m/z*: 99.0449 (Calcd. for C₅H₇O₂ 99.0446).

2-(Prop-2-ynyloxy)ethanol tosylate (103): Tosyl chloride (4.19 g, 21.98 mmol), triethylamine (6 mL, 43.05 mmol) and DMAP (cat.) were added to a solution of **102** (2.19 g, 21.87 mmol) in CH₂Cl₂ (150 mL). The resulting mixture was stirred at room temperature under a N₂ atmosphere for 2.5 days before H₂O (50 mL) was added and the biphasic mixture was neutralized with 10% aqueous citric acid. The organic layer was washed with H₂O

(2 x 50 mL), dried over MgSO_4 , filtered and the solvent was removed *in vacuo* to give **103** as a yellow oil (4.92 g, 89%). ^1H NMR (300 MHz, CDCl_3) δ : 2.43 (1H, t, $^4J = 2.4$ Hz, OCH_2CCH), 2.46 (3H, s, CH_3), 3.74 (2H, m, CH_2OH), 4.13 (2H, d, $^4J = 2.4$ Hz, OCH_2CCH), 4.20 (2H, m, OCH_2), 7.35 (2H, d, $^3J = 8.1$ Hz, TosH), 7.82 (2H, d, $^3J = 8.1$ Hz, TosH). MS (ES^+) m/z : 277.1 $[\text{M} + \text{Na}]^+$, 318.1 $[\text{M} + \text{CH}_3\text{CN} + \text{Na}]^+$, 531.1 $[2\text{M} + \text{Na}]^+$.

2-(2-(2-(Prop-2-ynyloxy)ethoxy)ethoxy)ethanol (104):^{adapted from 32} To a stirred solution of triethylene glycol (9.26 g, 61.6 mmol) in dry THF (50 mL) at 0 °C under a N_2 atmosphere was added NaH (60% dispersion in mineral oil, 1.60 g, 40.09 mmol) The resulting suspension was stirred for 30 minutes, propargyl benzenesulfonate (4.8 mL, 30.65 mmol) was added and stirring was continued for a further 2.5 hours at 0 °C then 20 hours at room temperature. The suspension was poured into H_2O (50 mL), and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried over MgSO_4 , filtered and the solvent was removed *in vacuo*. Compound **104** was isolated as a yellow oil following purification by silica gel chromatography (3:2 EtOAc/petroleum ether then EtOAc) eluting the product as the third band (3.72 g, 64%). ^1H NMR (300 MHz, CDCl_3) δ : 2.44 (1H, t, $^4J = 2.1$ Hz, OCH_2CCH), 3.62 (2H, m, CH_2OH), 3.71 (10H, m, OCH_2), 4.22 (2H, d, $^4J = 2.1$ Hz, OCH_2CCH). MS (ES^+) m/z : 211.2 $[\text{M} + \text{Na}]^+$.

2-(2-(2-(Prop-2-ynyloxy)ethoxy)ethoxy)ethanol tosylate (105):^{adapted from 32} Tosyl chloride (7.50 g, 39.34 mmol) was slowly added to a stirred solution of **104** (3.72 g, 19.76 mmol), triethylamine (7 mL, 50.22 mmol) and DMAP (cat.) in CH_3CN (50 mL) at 0 °C. The suspension was stirred at 0 °C for 1 hour and 30 hours at room temperature then poured into H_2O (50 mL). Following extraction with EtOAc (3 x 50 mL), the combined organic layers were dried over MgSO_4 , filtered and the solvent was removed *in vacuo*. The resulting oil was purified by silica gel chromatography (3:1 petroleum ether/EtOAc then 1:1 petroleum

ether/EtOAc) to give **105** as an orange oil (5.50 g, 75%). $^1\text{H NMR}$ (300 MHz, CDCl_3) δ : 2.44 (1H, t, $^4J = 2.4$ Hz, OCH_2CCH), 2.46 (3H, s, CH_3), 3.60 (4H, s, OCH_2), 3.66 (6H, m, OCH_2), 4.17 (2H, m, OCH_2), 4.20 (2H, d, $^4J = 2.4$ Hz, OCH_2CCH), 7.35 (2H, d, $^3J = 8.2$ Hz, TosH), 7.81 (2H, d, $^3J = 8.2$ Hz, TosH). **MS** (ES^+) m/z : 360.2 $[\text{M} + \text{NH}_4]^+$, 365.1 $[\text{M} + \text{Na}]^+$, 702.2 $[2\text{M} + \text{NH}_4]^+$, 707.2 $[2\text{M} + \text{Na}]^+$.

4-(2-(2-(2-(Prop-2-ynyloxy)ethoxy)ethoxy)ethoxy)phenol (106): A suspension of *p*-hydroquinone (0.63 g, 5.73 mmol), **105** (0.49 g, 1.43 mmol) and K_2CO_3 (0.22 g, 1.56 mmol) in EtOH (30 mL) was heated under reflux under a N_2 atmosphere for 18 hours. The reaction mixture was cooled to room temperature, filtered and the solvent of the filtrate was removed *in vacuo*. The brown residue was redissolved in H_2O (20 mL), acidified to pH 2 with 1 M HCl and extracted with CHCl_3 (4 x 30 mL). The combined organic layers were dried over MgSO_4 , filtered and the solvent was removed *in vacuo*. Purification by silica gel chromatography (1:1 petroleum ether/EtOAc) gave impure **106** (0.28 g, ~63%). $^1\text{H NMR}$ (300 MHz, CDCl_3) δ : 2.43 (1H, t, $^4J = 2.4$ Hz, OCH_2CCH), 3.73 (8H, m, OCH_2), 3.84 (2H, m, OCH_2), 4.06 (2H, m, OCH_2), 4.20 (2H, d, $^4J = 2.4$ Hz, OCH_2CCH), 4.84 (1H, br s, OH), 6.75 (4H, m, hydroq ArH).

2-(4-Hydroxyphenoxy)acetonitrile (107):³³ Bromoacetonitrile (4.2 mL, 61 mmol) was added dropwise to a degassed solution of 1:1 dioxane/ H_2O (120 mL) containing NaOH (4.88 g, 122 mmol) and *p*-hydroquinone (6.72 g, 61 mmol) under a N_2 atmosphere at room temperature. The reaction mixture was stirred for one hour and acidified to pH 1 with 10% aqueous HCl (40 mL). The product was extracted with CH_2Cl_2 (4 x 50 mL), the solvent was removed *in vacuo* and the crude material was purified by silica gel chromatography (98:2 $\text{CH}_2\text{Cl}_2/\text{MeOH}$) to give **107** as a yellow oil (4.57 g, 50%). $^1\text{H NMR}$ (300 MHz, CDCl_3) δ : 4.72 (2H, s, CH_2CN), 6.82 (2H, m, hydroq ArH), 6.91 (2H, m, hydroq ArH). **MS** (ES^-) m/z :

148.1 [M – H][–].

2-(4-(2-(Prop-2-ynyloxy)ethoxy)phenoxy)acetonitrile (108): A suspension of **107** (0.68 g, 4.53 mmol), **103** (0.99 g, 3.87 mmol) and K₂CO₃ (0.59 g, 4.27 mmol) in CH₃CN (15 mL) was stirred for 30 seconds and heated under microwave irradiation at 160 °C for 1 hour. The resulting suspension was cooled to room temperature, filtered and the solvent was removed *in vacuo*. The residue was purified by silica gel chromatography (99:1 CH₂Cl₂/MeOH) eluting the product **108** as the first band giving a yellow oil (0.75 g, 83%). ¹H NMR (300 MHz, CDCl₃) δ: 2.48 (1H, t, ⁴J = 2.4 Hz, OCH₂CCH), 3.90 (2H, t, ³J = 4.7 Hz, OCH₂), 4.13 (2H, t, ³J = 4.7 Hz, OCH₂), 4.28 (2H, d, ⁴J = 2.4 Hz, OCH₂CCH), 4.72 (2H, s, CH₂CN), 6.93 (4H, m, hydroq ArH). ¹³C NMR (75.5 MHz, CDCl₃) δ: 54.76, 58.49, 67.68, 68.14, 74.81, 79.33, 115.35, 115.74, 116.56, 150.81, 154.60. MS (ES⁺) *m/z*: 249.2 [M + NH₄]⁺, 254.0786 [M + Na]⁺ (Calcd. for C₁₃H₁₃NO₃Na: 254.0788).

2-(4-(2-(2-(2-(Prop-2-ynyloxy)ethoxy)ethoxy)ethoxy)phenoxy)acetonitrile (109): A suspension of **107** (0.31 g, 2.05 mmol), **105** (0.71 g, 2.07 mmol) and K₂CO₃ (0.31 g, 2.25 mmol) in CH₃CN (50 mL) was heated reflux under a N₂ atmosphere for 24 hours. The reaction mixture was cooled to room temperature, filtered and the solvent was removed *in vacuo*. Purification by silica gel chromatography (99:1 CH₂Cl₂/MeOH) gave the impure product **109** contaminated with **107** (0.40 g, ~62%). **Microwave synthesis:** A suspension of **107** (1.09 g, 7.3 mmol), **105** (2.13 g, 6.22 mmol) and K₂CO₃ (0.96 g, 6.93 mmol) in CH₃CN (15 mL) was stirred for 30 seconds then heated under microwave irradiation for 2 hours at 160 °C. The reaction mixture was cooled to room temperature, filtered and the solvent was removed *in vacuo*. Purification by silica gel chromatography (98:2 CH₂Cl₂/MeOH) gave the impure product **109**, contaminated with **107** (1.22 g, ~62%). ¹H NMR (300 MHz, CDCl₃) δ: 2.43 (1H, t, ⁴J = 2.4 Hz, OCH₂CCH), 3.73 (8H, m, OCH₂), 3.86 (2H, m, OCH₂), 4.11 (2H, m,

OCH₂), 4.22 (2H, d, ⁴J = 2.4 Hz, OCH₂CCH), 4.72 (2H, s, CH₂CN), 6.92 (4H, m, hydroq ArH). ¹³C NMR (75.5 MHz, CDCl₃) δ: 54.77, 58.31, 58.35, 67.88, 69.01, 69.65, 70.35, 70.55, 70.70, 74.49, 79.57, 115.33, 115.69, 116.52, 150.71, 154.70. MS (ES⁺) m/z: 337.2 [M + NH₄]⁺, 342.1302 [M + Na]⁺ (Calcd. for C₁₇H₂₁NO₅Na: 342.1312), 656.3 [2M + NH₄]⁺, 661.3 [2M + Na]⁺.

2-(4-(2-(Prop-2-ynyloxy)ethoxy)phenoxy)ethylamine hydrochloride (110): A solution of **108** (0.58 g, 2.53 mmol) in dry diethyl ether (20 mL) was added dropwise to a suspension of LiAlH₄ (0.17 g, 4.50 mmol) in dry diethyl ether (90 mL) under a N₂ atmosphere over 15 minutes. The suspension was heated under reflux for 1 hour, cooled to room temperature and the excess LiAlH₄ was quenched with 10% aqueous NaOH (4 mL). H₂O (30 mL) was added and the organic layer was decanted. The aqueous layer was extracted with diethyl ether (5 x 30 mL) and the combined organic layers were dried over MgSO₄, filtered and concentrated *in vacuo*. The product was precipitated as a brown solid by bubbling HCl gas through the solution to give impure **110** (0.43 g, ~63%). **Improved synthesis:** Compound **120** (0.82 g, 2.44 mmol) and TFA (3 mL, excess) were dissolved in CHCl₃ (50 mL) and the reaction was stirred at room temperature for 16 hours. The solution was washed with 1 M NaOH (2 x 50 mL), and the combined aqueous layers were extracted with CHCl₃ (2 x 20 mL). The combined organic layers were dried over MgSO₄, filtered and concentrated *in vacuo*. HCl gas was bubbled through the CHCl₃ solution of the amine to precipitate **110** as the hydrochloride salt (0.31 g, 47%). ¹H NMR (300 MHz, 1:1 CDCl₃/CD₃OD) δ: 2.69 (1H, t, ⁴J = 2.4 Hz, OCH₂CCH), 3.31 (2H, m, CH₂NH₃Cl), 3.87 (2H, m, OCH₂), 4.09 (2H, m, OCH₂), 4.15 (2H, m, OCH₂), 4.24 (2H, d, ⁴J = 2.4 Hz, OCH₂CCH), 6.89 (4H, s, hydroq ArH). ¹³C NMR (75.5 MHz, 1:1 CDCl₃/CD₃OD) δ: 40.08, 59.11, 65.32, 68.61, 69.09, 75.89, 79.89, 116.38, 116.49, 153.17, 154.50. MS (ES⁺) m/z: 236.1281 [M – Cl]⁺ (Calcd. for C₁₁H₁₈NO₃: 236.1281).

2-(4-(2-(2-(2-(Prop-2-ynyloxy)ethoxy)ethoxy)ethoxy)phenoxy)ethylamine hydrochloride (111): A solution of **109** (0.75 g, 2.34 mmol) in dry diethyl ether (20 mL) was added dropwise to a suspension of LiAlH_4 (0.16 g, 4.19 mmol) in dry diethyl ether (65 mL) under a N_2 atmosphere. The resulting suspension was heated under reflux for 1 hour, cooled to room temperature and the excess LiAlH_4 was neutralised with 10% aqueous NaOH (6 mL) and H_2O (15 mL). The aqueous layer was extracted with diethyl ether (5 x 20 mL) and the combined organic layers were dried over MgSO_4 , filtered and the solution was concentrated *in vacuo* to approximately 20 mL. HCl gas was bubbled through the solution to precipitate the impure product **111** as the hydrochloride salt (0.29 g, ~53%). ^1H NMR (300 MHz, CD_3OD) δ : 2.85 (1H, t, $^4J = 2.4$ Hz, OCH_2CCH), 3.34 (2H, t, $\text{CH}_2\text{NH}_3\text{Cl}$), 3.69 (8H, m, OCH_2), 3.82 (2H, m, OCH_2), 4.08 (2H, m, OCH_2), 4.17 (4H, m, OCH_2 , OCH_2CCH), 6.93 (4H, m, hydroq ArH). ^{13}C NMR (75.5 MHz, CD_3OD) δ : 40.58, 59.16, 65.99, 69.30, 70.22, 71.05, 71.49, 71.67, 71.82, 76.10, 80.72, 116.83, 116.87, 153.85, 155.28. MS (ES^+) m/z : 324.1804 $[\text{M} - \text{Cl}]^+$ (Calcd. for $\text{C}_{17}\text{H}_{26}\text{NO}_5$: 324.1805).

3,5-Bis(2-(4-(2-(prop-2-ynyloxy)ethoxy)phenoxy)ethylcarbamoyl)pyridine (112): A solution of 3,5-bis(chlorocarbonyl)pyridine (0.58 mmol) in dry CH_2Cl_2 (20 mL) was added dropwise to a solution of **110** (0.31 g, 1.15 mmol) and triethylamine (0.25 mL, 1.8 mmol) in dry CH_2Cl_2 (30 mL) under a N_2 atmosphere. The mixture was stirred at room temperature for a further 21 hours then washed with 1 M HCl (2 x 30 mL) and brine (30 mL). The organic layer was dried over MgSO_4 , filtered and the solvent was removed *in vacuo* to give **112** as a white solid (0.14 g, 40%). ^1H NMR (300 MHz, CDCl_3) δ : 2.47 (2H, t, $^4J = 2.4$ Hz, OCH_2CCH), 3.89 (8H, m, NCH_2 , OCH_2), 4.12 (8H, m, OCH_2), 4.28 (4H, d, $^4J = 2.4$ Hz, OCH_2CCH), 6.85 (8H, m, hydroq ArH), 7.00 (2H, br s, NH), 8.47 (1H, t, $^4J = 2.1$ Hz, pyH^4), 9.13 (2H, d, $^4J = 2.1$ Hz, pyH^2 and H^6). ^{13}C NMR (75.5 MHz, $\text{DMSO}-d_6$) δ : 39.14, 57.59, 66.36, 67.20, 67.80, 77.34, 80.23, 115.35, 115.44, 129.50, 134.05, 150.45, 152.48, 152.57,

164.61. **MS (ES⁺)** *m/z*: 602.2507 [M + H]⁺ (Calcd. for C₃₃H₃₆N₃O₈: 602.2497), 624.2 [M + Na]⁺.

3,5-Bis(2-(4-(2-(2-(2-(prop-2-

ynyloxy)ethoxy)ethoxy)ethoxy)phenoxy)ethylcarbamoyl)pyridine (113): A solution of 3,5-bis(chlorocarbonyl)pyridine (0.5 mmol) in dry CH₂Cl₂ (10 mL) was added dropwise to a solution of **111** (0.36 g, 1.00 mmol) and triethylamine (0.5 mL, 3.6 mmol) in dry CH₂Cl₂ (20 mL) under a N₂ atmosphere. The mixture was stirred at room temperature for a further 4.5 hours then washed with 1 M HCl (3 x 20 mL) and brine (20 mL). The organic layer was dried over MgSO₄, filtered and the solvent was removed *in vacuo* to give impure **113** as a brown oily residue (0.33 g, ~91%). **¹H NMR** (300 MHz, CDCl₃) δ: 2.43 (2H, t, ⁴*J* = 2.4 Hz, OCH₂CCH), 3.72 (16H, m, NCH₂, OCH₂), 3.82 (8H, m, OCH₂), 4.01 (4H, m, OCH₂), 4.11 (4H, m, OCH₂), 4.18 (4H, d, ⁴*J* = 2.4 Hz, OCH₂CCH), 6.75 (8H, m, hydroq ArH), 7.70 (2H, br s, NH), 8.94 (1H, s, pyH⁴), 9.15 (2H, s, pyH² and H⁶). **¹³C NMR** (75.5 MHz, CDCl₃) δ: 40.03, 58.33, 66.66, 67.76, 68.96, 69.04, 69.80, 70.38, 70.58, 70.62, 75.67, 79.46, 115.29, 115.38, 129.94, 149.24, 152.64, 152.95, 164.18. **MS (ES⁺)** *m/z*: 778.3569 [M + H]⁺ (Calcd. for C₄₁H₅₂N₃O₁₂: 778.3546), 800.3 [M + Na]⁺.

1,3-Bis(azidomethyl)benzene (114):^{adapted from 34} A solution of α,α'-dibromo-*m*-xylene (0.25 g, 0.94 mmol) and sodium azide (0.17 g, 2.61 mmol) in DMSO (15 mL) was stirred at room temperature for 1 hour, before the reaction was quenched at 0 °C with H₂O (30 mL). The mixture was extracted with diethyl ether (3 x 30 mL) and the combined organic layers were washed with H₂O (3 x 25 mL), dried over MgSO₄, filtered and the solvent was removed *in vacuo* to give **114** as a colourless oil (0.17 g, 95%). **¹H NMR** (300 MHz, CDCl₃) δ: 4.38 (4H, s, CH₂), 7.31 (3H, m, ArH), 7.41 (1H, m, ArH).

Catenane (115.Cl): [Cu(CH₃CN)₄]PF₆ (6.16 mg, 0.017 mmol) was added to a solution of **66**

(0.092 g, 0.081 mmol), **100.Cl** (0.071 g, 0.11 mmol), **114** (0.02 g, 0.11 mmol), DIPEA (0.04 mL, 0.23 mmol) and TBTA (8.73 mg, 0.016 mmol) in degassed CH₂Cl₂ (10 mL). The reaction mixture was stirred under a N₂ atmosphere for 15 hours at room temperature, during which time a yellow precipitate formed. The precipitate was filtered off, and the filtrate was taken to dryness. The residue from the filtrate was purified by preparative TLC (96:4 CH₂Cl₂/MeOH). The catenane **115.Cl** was isolated as a yellow solid (0.0126 g, 8%) and unreacted **66** (0.057 g, 62%) was recovered. **m.p.** 220 °C (dec.). ¹H NMR (300 MHz, CDCl₃) δ: 0.87 (18H, s, *t*-Bu), 1.40 (18H, s, *t*-Bu), 3.47 (4H, d, ²*J* = 13.8 Hz, ArCH_{in}H_{out}Ar), 3.67 (4H, m, NCH₂), 3.76 (4H, m, NCH₂), 3.83 (4H, m, OCH₂), 3.95 (4H, m, OCH₂), 4.01 (8H, m, OCH₂), 4.10 (4H, m, OCH₂), 4.15 (4H, m, OCH₂), 4.42 (4H, d, ²*J* = 13.8 Hz, ArCH_{in}H_{out}Ar), 4.74 (4H, s, CH₂), 4.94 (3H, s, N⁺CH₃), 5.52 (4H, s, OCH₂N₃), 5.69 (2H, br s, OH), 6.20 (4H, d, ³*J* = 7.9 Hz, hydroq ArH), 6.33 (4H, d, ³*J* = 7.9 Hz, hydroq ArH), 6.67 (4H, s, calix ArH), 6.76 (8H, s, hydroq ArH), 7.21 (4H, s, calix ArH), 7.35 (4H, m, phenH), 7.50 (1H, t, ³*J* = 7.6 Hz, isoH), 7.65 (2H, br s, CHN₃), 8.17 (2H, d, ³*J* = 7.6 Hz, isoH), 8.73 (4H, br s, NH), 9.02 (2H, s, pyH² and H⁶), 9.24 (1H, s, isoH), 9.88 (1H, s, pyH⁴). ¹³C NMR (125 MHz, CDCl₃) δ: 31.75, 33.85, 34.04, 39.99, 41.20, 50.82, 53.66, 64.96, 66.31, 67.60, 68.03, 69.00, 75.24, 114.04, 114.57, 115.06, 115.55, 123.11, 124.07, 125.56, 125.93, 127.31, 128.16, 128.44, 128.97, 129.95, 131.51, 131.82, 133.53, 135.72, 142.84, 144.36, 147.56, 149.98, 150.48, 151.60, 152.73, 152.97, 153.76, 159.80, 166.83. **MS (ES⁺)** *m/z*: 1940.9638 [M – Cl]⁺ (Calcd. for C₁₁₄H₁₃₀N₁₁O₁₈: 1940.9590).

Catenane (115.PF₆): A solution of **115.Cl** (0.023 g, 0.012 mmol) in CHCl₃ (10 mL) was washed with 0.2 M NH₄PF₆ (5 x 10 mL). The organic layer was dried over MgSO₄, filtered and the solvent was removed *in vacuo* to give **115.PF₆** as a yellow solid (0.018 g, 71%). ¹H NMR (300 MHz, 1:1 CDCl₃/CD₃OD) δ: 0.84 (18H, s, *t*-Bu), 1.37 (18H, s, *t*-Bu), 3.44 (4H, d, ²*J* = 13.5 Hz, ArCH_{in}H_{out}Ar), 3.64 (8H, m, NCH₂), 3.81 (8H, m, OCH₂), 3.89 (4H, m,

OCH₂), 4.00 (4H, m, OCH₂), 4.12 (8H, m, OCH₂), 4.44 (4H, d, ²*J* = 13.5 Hz, ArCH_{in}H_{out}Ar), 4.63 (4H, s, CH₂), 4.83 (3H, s, N⁺CH₃), 5.48 (4H, s, OCH₂N₃), 6.27 (8H, m, hydroq ArH), 6.65 (4H, s, calix ArH), 6.73 (8H, s, hydroq ArH), 7.18 (4H, m, calix ArH), 7.30 (4H, m, phenH), 7.57 (1H, t, ³*J* = 7.9 Hz, isoH), 7.87 (2H, br s, CHN₃), 8.07 (2H, d, ³*J* = 7.9 Hz, isoH), 8.54 (2H, br s, NH), 8.79 (1H, s, isoH), 9.06 (3H, s, pyH). ¹³C NMR (125 MHz, CDCl₃) δ: 29.67, 30.89, 31.73, 33.83, 34.01, 40.52, 50.22, 53.61, 64.82, 66.01, 67.24, 67.99, 69.02, 75.20, 114.22, 115.20, 115.55, 122.91, 125.62, 125.84, 127.31, 128.18, 128.40, 129.08, 129.89, 131.47, 133.41, 133.95, 135.64, 142.87, 143.77, 147.46, 149.84, 150.19, 151.67, 152.60, 153.00, 160.27, 167.03. ¹⁹F NMR (282.5 MHz, CDCl₃) δ: -72.14 (d, ¹*J* = 700 Hz, PF₆⁻). ³¹P NMR (121.5 MHz, CDCl₃) δ: -141.85 (septet, ¹*J* = 720 Hz, PF₆⁻). MS (ES⁺) *m/z*: 1940.9608 [M – PF₆]⁺ (Calcd. for C₁₁₄H₁₃₀N₁₁O₁₈: 1940.9590).

2-(4-(Benzyloxy)phenoxy)acetonitrile (116):²³ A suspension of 4-benzyloxyphenol (8.02 g, 40.05 mmol), bromoacetonitrile (3.1 mL, 44.5 mmol) and K₂CO₃ (6.11 g, 44.2 mmol) in acetone (120 mL) was heated under reflux under a N₂ atmosphere for 17 hours. The reaction was cooled to room temperature, filtered and the solvent was removed *in vacuo* to give a brown residue. This was redissolved in CHCl₃ and filtered through a plug of silica gel. The eluent was taken to dryness to give **116** as a white solid (9.27 g, 97%). ¹H NMR (300 MHz, CDCl₃) δ: 4.72 (2H, s, CH₂CN), 5.05 (2H, s, OCH₂Ph), 6.96 (4H, s, hydroq ArH), 7.41 (5H, m, ArH). MS (ES⁺) *m/z*: 262.08 [M + Na]⁺.

2-(4-(Benzyloxy)phenoxy)ethylamine (117):²³ A solution of **116** (3.58 g, 14.95 mmol) in dry diethyl ether (150 mL) was added dropwise to a suspension of LiAlH₄ (1.13 g, 29.78 mmol) in dry diethyl ether (200 mL) over 1 hour under a N₂ atmosphere. The reaction mixture was heated under reflux for 1 hour, cooled to room temperature then quenched with H₂O (1.1 mL), 10% aqueous NaOH (1.1 mL) and H₂O (3.3 mL). The suspension was filtered and the filtrate

was dried over MgSO_4 , filtered and the solvent was removed *in vacuo* to give **117** as an off-white solid (3.26 g, 90%). ^1H NMR (300 MHz, CDCl_3) δ : 3.07 (2H, t, $^3J = 5.1$ Hz, CH_2NH_2), 3.95 (2H, t, $^3J = 5.13$ Hz, OCH_2), 5.03 (2H, s, OCH_2Ph), 6.88 (4H, m, hydroq ArH), 7.41 (5H, m, ArH). MS (ES^+) m/z : 244.2 $[\text{M} + \text{H}]^+$.

tert-Butyl 2-(4-(benzyloxy)phenoxy)ethylcarbamate (118):²⁹ A solution of **117** (1.26 g, 5.18 mmol) and di-*tert*-butyldicarbonate (1.28 g, 5.86 mmol) in dry CH_2Cl_2 (50 mL) was stirred at room temperature under a N_2 atmosphere for 16 hours. The solvent and excess di-*tert*-butyldicarbonate were removed *in vacuo* and the residue was redissolved in CH_2Cl_2 and filtered through a plug of silica gel. The solvent was removed *in vacuo* and the residue was triturated with hexane. The white solid was collected by filtration, washed with hexane and dried to give **118** (1.48 g, 83%). ^1H NMR (300 MHz, CDCl_3) δ : 1.46 (3H, s, *t*-Bu), 3.52 (2H, m, NCH_2), 3.98 (2H, t, $^3J = 5.13$ Hz, OCH_2), 5.03 (3H, s, OCH_2Ph , NHBoc), 6.83 (2H, m, hydroq ArH), 6.92 (2H, m, hydroq ArH), 7.38 (5H, m, OCH_2ArH). MS (ES^+) m/z : 366.2 $[\text{M} + \text{Na}]^+$, 709.3 $[2\text{M} + \text{Na}]^+$.

tert-Butyl 2-(4-(hydroxy)phenoxy)ethylcarbamate (119):²⁹ Compound **118** (1.15 g, 3.34 mmol) was dissolved in 3:2 $\text{CHCl}_3/\text{MeOH}$ (50 mL) and palladium on carbon (0.11 g, 10% by mass) was added. The resulting suspension was stirred at room temperature under a H_2 atmosphere for 17 hours, then filtered through Celite and the filtrate was taken to dryness. The residue was redissolved in CHCl_3 (50 mL), filtered and the solvent was removed *in vacuo* to give **119** as a white solid (0.75 g, 89%). ^1H NMR (300 MHz, CDCl_3) δ : 1.53 (9H, s, *t*-Bu), 3.50 (2H, m, NCH_2), 3.94 (2H, t, $^3J = 4.8$ Hz, OCH_2), 5.04 (1H, br s, OH), 6.76 (4H, s, hydroq ArH). MS (ES^+) m/z : 276.1 $[\text{M} + \text{Na}]^+$, 529.2 $[2\text{M} + \text{Na}]^+$.

tert-Butyl 2-(4-(2-(prop-2-ynyloxy)ethoxy)phenoxy)ethylcarbamate (120): A suspension of **119** (0.74 g, 2.92 mmol), **103** (1.09 g, 4.29 mmol) and K_2CO_3 (0.62 g, 4.45 mmol) in

CH₃CN (40 mL) was heated under reflux for 3 days. The reaction mixture was cooled to room temperature and the solvent was removed *in vacuo*. The residue was redissolved in CHCl₃ (50 mL) and washed with 1 M HCl (2 x 20 mL) and H₂O (20 mL). The organic layer was dried over MgSO₄, filtered and the solvent was removed *in vacuo*. Following purification by silica gel chromatography (CH₂Cl₂ to remove the first band then 99:1 CH₂Cl₂/MeOH) eluting **120** as the second band to give a yellow oil, which solidifies upon standing (0.84 g, 86%). ¹H NMR (300 MHz, CDCl₃) δ: 1.46 (9H, m, *t*-Bu), 2.47 (1H, t, ⁴*J* = 2.4 Hz, OCH₂CCH), 3.50 (2H, m, NCH₂), 3.89 (2H, m, OCH₂), 3.97 (2H, m, OCH₂), 4.11 (2H, m, OCH₂), 4.28 (2H, d, ⁴*J* = 2.4 Hz, OCH₂CCH), 4.99 (1H, br s, NHBoc), 6.85 (4H, m, hydroq ArH). ¹³C NMR (75.5 MHz, CDCl₃) δ: 28.36, 40.15, 58.53, 67.67, 67.82, 68.28, 74.74, 79.41, 115.28, 115.65, 152.86, 153.06, 155.85. MS (ES⁺) *m/z*: 358.1632 [M + Na]⁺ (Calcd. for C₁₈H₂₅NO₅Na: 358.1625).

Bis(2-(4-(2-(prop-2-ynyloxy)ethoxy)phenoxy)ethyl)isophthalamide (121): A suspension of **123** (0.97 g, 2.22 mmol), **103** (1.42 g, 5.58 mmol) and Cs₂CO₃ (1.61 g, 4.93 mmol) in dry degassed DMF (45 mL) was heated at 100 °C under a N₂ atmosphere for 3 days. The reaction mixture was cooled to room temperature, filtered and the solvent was removed *in vacuo*. Purification by silica gel chromatography (98:2 CH₂Cl₂/MeOH) gave **121** as a white solid (0.79 g, 59%). ¹H NMR (300 MHz, CDCl₃) δ: 2.47 (2H, t, ⁴*J* = 2.4 Hz, OCH₂CCH), 3.88 (8H, m, NCH₂, OCH₂), 4.11 (8H, m, OCH₂), 4.27 (4H, d, ⁴*J* = 2.4 Hz, OCH₂CCH), 6.72 (2H, t, ³*J* = 5.3 Hz, NH), 6.86 (8H, m, hydroq ArH), 7.53 (1H, t, ³*J* = 7.7 Hz, isoH), 7.93 (2H, dd, ³*J* = 7.7 Hz, ⁴*J* = 1.8 Hz, isoH), 8.21 (1H, s, isoH). ¹³C NMR (75.5 MHz, CDCl₃) δ: 39.75, 58.54, 67.20, 67.82, 68.29, 74.77, 115.40, 115.71, 125.49, 129.01, 130.05, 134.68, 152.74, 153.23, 166.69. MS (ES⁺) *m/z*: 601.3 [M + H]⁺, 618.3 [M + NH₄]⁺, 623.2 [M + Na]⁺, 659.3107 [M + CH₃CN + NH₄]⁺ (Calcd. for C₃₆H₄₃N₄O₈: 659.3075).

Bis(2-(4-(benzyloxy)ethoxy)phenoxy)ethyl)isophthalamide (122):¹⁹ A solution of isophthaloyl dichloride (0.76 g, 3.75 mmol) in dry CH₂Cl₂ (20 mL) was added dropwise over 15 minutes to a solution of **117** (1.82 g, 7.48 mmol) and triethylamine (1.3 mL, 9.33 mmol) in dry CH₂Cl₂ (40 mL) at 0 °C under a N₂ atmosphere. The reaction mixture was allowed to warm to room temperature and the stirring was continued for a further 2 hours, during which time a white solid precipitated from the reaction mixture. This was collected by filtration and washed with CH₂Cl₂ (2 x 20 mL) and MeOH (2 x 20 mL) to give **122** as a white solid (1.89 g, 82%). ¹H NMR (300 MHz, DMSO-*d*₆) δ: 3.63 (4H, m, NCH₂), 4.06 (4H, t, ³*J* = 5.6 Hz, OCH₂), 5.03 (4H, s, CH₂Ph), 6.92 (8H, m, hydroq ArH), 7.37 (10H, m, CH₂ArH), 7.56 (1H, t, ³*J* = 7.6 Hz, isoH), 7.99 (2H, d, ³*J* = 7.6 Hz, isoH), 8.35 (1H, s, isoH), 8.81 (2H, t, ³*J* = 5.1 Hz, NH). MS (ES⁻) *m/z*: 615.24991 [M – H]⁻ (Calcd. for C₃₈H₃₅N₂O₆: 615.25006).

Bis(2-(4-hydroxyphenoxy)ethyl)isophthalamide (123):¹⁹ Compound **122** (3.24 g, 5.25 mmol) was suspended in a mixture of DMF (120 mL) and MeOH (30 mL). Palladium on carbon (0.32 g, 10% by mass) was added and the suspension was stirred under a H₂ atmosphere at room temperature for 2 days. The reaction mixture was filtered through Celite and the solvent was removed *in vacuo* to give **123** as an off-white solid (2.41 g, 100%). ¹H NMR (300 MHz, DMSO-*d*₆) δ: 3.61 (4H, m, NCH₂), 4.01 (4H, t, ³*J* = 5.7 Hz, OCH₂), 6.66 (4H, d, ³*J* = 8.8 Hz, hydroq ArH), 6.78 (4H, d, ³*J* = 8.8 Hz, hydroq ArH), 7.56 (1H, t, ³*J* = 7.7 Hz, isoH), 7.99 (2H, d, ³*J* = 7.7 Hz, isoH), 8.35 (1H, s, isoH), 8.80 (2H, t, ³*J* = 5.0 Hz, NH), 8.92 (2H, s, OH). MS (ES⁺) *m/z*: 495.2 [M + CH₃CN + NH₄]⁺.

N¹-(2-(4-Hydroxyphenoxy)ethyl)-N³-(2-(4-(2-(prop-2-ynyloxy)ethoxy)phenoxy)ethyl)isophthalamide (124): A suspension of **123** (0.43 g, 0.99 mmol), **103** (0.62 g, 2.44 mmol) and K₂CO₃ (0.35 g, 2.51 mmol) in dry degassed DMF (15 mL) was stirred for 30 seconds then heated under microwave irradiation for 2 hours at

100 °C. The reaction mixture was cooled to room temperature, filtered and the solvent was removed *in vacuo*. Purification by silica gel chromatography (98:2 CH₂Cl₂/MeOH) gave **124** as a white solid (0.21 g, 41%). ¹H NMR (300 MHz, DMSO-*d*₆) δ: 3.45 (1H, t, ⁴*J* = 2.3 Hz, OCH₂CCH), 3.59 (4H, m, NCH₂), 3.72 (2H, m, OCH₂), 4.01 (6H, m, OCH₂), 4.18 (2H, d, ⁴*J* = 2.3 Hz, OCH₂CCH), 6.64 (2H, d, ³*J* = 8.8 Hz, hydroq ArH), 6.76 (2H, d, ³*J* = 8.8 Hz, hydroq ArH), 6.86 (4H, m, hydroq ArH), 7.54 (1H, t, ³*J* = 7.7 Hz, isoH), 7.97 (2H, dd, ³*J* = 7.7 Hz, ⁴*J* = 1.3 Hz, isoH), 8.33 (1H, s, isoH), 8.78 (2H, m, NH), 8.90 (1H, s, OH). ¹³C NMR (75.5 MHz, DMSO-*d*₆) δ: 39.06, 39.12, 57.59, 66.41, 66.47, 67.19, 67.79, 77.35, 80.23, 115.34, 115.41, 115.48, 115.72, 126.33, 128.39, 129.82, 134.46, 151.20, 151.30, 152.50, 152.53, 166.06, 166.09. MS (ES⁺) *m/z*: 541.1941 [M + Na]⁺ (Calcd. for C₂₉H₃₀N₂O₇Na: 541.1945), 577.3 [M + CH₃CN + NH₄]⁺.

Isophthalamide macrocycle with diyne linker (125): A solution of Cu(OAc)₂ (0.13 g, 0.65 mmol) in CH₃CN (50 mL) was added dropwise to a solution of **121** (0.14 g, 0.23 mmol) in CH₃CN (100 mL), and the mixture was heated under reflux for 16 hours, cooled to room temperature and the solvent was removed *in vacuo*. The residue was redissolved in H₂O (30 mL) and extracted with CH₂Cl₂ (5 x 30 mL). The combined organic layers were dried over MgSO₄, filtered and the solvent was removed *in vacuo*. Following purification by silica gel chromatography (98:2 CHCl₃/MeOH), **125** was isolated as a white solid (0.086 g, 63%). ¹H NMR (300 MHz, CDCl₃) δ: 3.85 (8H, m, NCH₂, OCH₂), 4.09 (8H, m, OCH₂), 4.30 (4H, s, OCH₂CCH), 6.74 (2H, t, ³*J* = 5.6 Hz, NH), 6.82 (8H, m, hydroq ArH), 7.51 (1H, t, ³*J* = 7.8 Hz, isoH), 7.96 (2H, dd, ³*J* = 7.8 Hz, ⁴*J* = 1.6 Hz, isoH), 8.05 (1H, s, isoH). ¹³C NMR (75.5 MHz, CDCl₃) δ: 39.78, 59.05, 67.14, 67.84, 68.47, 70.62, 75.36, 115.40, 115.81, 124.76, 129.06, 130.37, 134.59, 152.78, 153.04, 166.85. MS (ES⁺) *m/z*: 621.2203 [M + Na]⁺ (Calcd. for C₃₄H₃₄N₂O₈Na: 621.2207).

Bis(2-(4-(2-(prop-2-ynyloxy)ethoxy)phenoxy)ethyl)-5-*tert*-butylisophthalamide (126): A suspension of **128** (0.33 g, 0.67 mmol) and Cs₂CO₃ (0.49 g, 1.49 mmol) in dry degassed DMF (40 mL) was heated at 100 °C for 30 minutes under a N₂ atmosphere. Compound **103** (0.52 g, 2.05 mmol) was added, and heating was continued for a further 4 days. The reaction mixture was cooled to room temperature, filtered and the solvent was removed *in vacuo*. Purification by silica gel chromatography (98:2 CH₂Cl₂/MeOH) gave impure **126** (0.38 g). ¹H NMR (300 MHz, CDCl₃) δ: 1.33 (9H, s, *t*-Bu), 2.45 (2H, t, ⁴*J* = 2.4 Hz, OCH₂CCH), 3.85 (8H, m, NCH₂, OCH₂), 4.08 (8H, m, OCH₂), 4.25 (4H, d, ⁴*J* = 2.4 Hz, OCH₂CCH), 6.68 (2H, t, ³*J* = 5.3 Hz, NH), 6.80 (8H, m, hydroq ArH), 7.93 (2H, s, isoH), 7.95 (2H, s, isoH). MS (ES⁺) *m/z*: 679.2991 [M + Na]⁺ (Calcd. for C₃₈H₄₄N₂O₈Na: 679.2990).

Bis(2-(4-(benzyloxy)ethoxy)phenoxy)ethyl)-5-*tert*-butylisophthalamide (127):²⁰ A solution of **117** (2.47 g, 10.15 mmol) and triethylamine (1.8 mL, 12.91 mmol) in dry CH₂Cl₂ (80 mL) under a N₂ atmosphere was cooled to 0 °C, and a solution of 5-*tert*-butylisophthaloyl dichloride (5.08 mmol) in dry CH₂Cl₂ (40 mL) was added dropwise over 30 minutes. The reaction mixture was allowed to warm to room temperature, stirred for a further 2.5 hours then washed with 10% aqueous HCl (2 x 100 mL) and brine (100 mL). The organic layer was dried over MgSO₄, filtered and the solvent was removed *in vacuo*. Recrystallisation of the residue from hot MeOH gave **127** as a white solid (2.50 g, 73%). ¹H NMR (300 MHz, CDCl₃) δ: 1.37 (9H, s, *t*-Bu), 3.87 (4H, q, ³*J* = 5.3 Hz, NCH₂), 4.12 (4H, t, ³*J* = 5.0 Hz, OCH₂), 5.02 (4H, s, CH₂Ph), 6.69 (2H, t, ³*J* = 5.3 Hz, NH), 6.88 (8H, m, hydroq ArH), 7.37 (10H, m, CH₂ArH), 7.92 (1H, s, isoH), 7.96 (2H, s, isoH). MS (ES⁺) *m/z*: 695.3 [M + Na]⁺.

Bis(2-(4-hydroxyphenoxy)ethyl)-5-*tert*-butylisophthalamide (128):²⁰ A suspension of **127** (1.68 g, 2.5 mmol) and palladium on carbon (0.17 g, 10% by mass) in EtOH (100 mL) and CHCl₃ (30 mL) was stirred at room temperature under a H₂ atmosphere for 17 hours. The

reaction mixture was filtered through Celite and the solvent was removed *in vacuo* to give **128** as an off-white solid (1.27 g, 100%). $^1\text{H NMR}$ (300 MHz, acetone- d_6) δ : 1.35 (10H, s, *t*-Bu), 3.75 (4H, q, $^3J = 5.9$ Hz, NCH_2), 4.09 (4H, t, $^3J = 5.9$ Hz, OCH_2), 6.77 (8H, m, hydroq ArH), 8.11 (2H, s, isoH), 8.20 (2H, t, $^3J = 5.9$ Hz, NH), 8.25 (1H, s, isoH). **MS (ES $^+$)** m/z : 515.2 $[\text{M} + \text{Na}]^+$, 1007.5 $[2\text{M} + \text{Na}]^+$.

5-*tert*-Butylisophthalamide macrocycle with diyne linker (129): A solution of $\text{Cu}(\text{OAc})_2$ (0.062 g, 0.31 mmol) in CH_3CN (40 mL) was added dropwise to a solution of **126** (0.037 g, ~ 0.056 mmol) in CH_3CN (60 mL), and the mixture was heated under reflux for 19 hours, cooled to room temperature and the solvent was removed *in vacuo*. The residue was redissolved in H_2O (20 mL) and extracted with CH_2Cl_2 (4 x 20 mL). The combined organic layers were dried over MgSO_4 , filtered and the solvent was removed *in vacuo*. Following purification by silica gel chromatography (98:2 $\text{CH}_2\text{Cl}_2/\text{MeOH}$), impure **129** was isolated (0.029 g). $^1\text{H NMR}$ (300 MHz, CDCl_3) δ : 1.36 (9H, s, *t*-Bu), 3.85 (8H, m, NCH_2 , OCH_2), 4.10 (8H, m, OCH_2), 4.30 (4H, s, OCH_2CCH), 6.64 (2H, br s, NH), 6.85 (8H, m, hydroq ArH), 7.78 (1H, s, isoH), 8.00 (2H, s, isoH). **MS (ES $^+$)** m/z : 677.2836 $[\text{M} + \text{Na}]^+$ (Calcd. for $\text{C}_{38}\text{H}_{42}\text{N}_2\text{O}_8\text{Na}$: 677.2833).

3,5-Bis(4-(tris(4-*tert*-butylphenyl)methyl)phenylcarbamoyl)-1-methylpyridinium iodide (130.I):²³ A suspension of **133** (0.69 g, 0.61 mmol) and iodomethane (5 mL, excess) in acetone (20 mL) was heated under reflux under a N_2 atmosphere for 55 hours. The reaction mixture was cooled to room temperature and poured into diethyl ether (100 mL) to precipitate the product. The solid was collected by filtration, washed with diethyl ether to give **130.I** as a yellow solid (0.76 g, 97%). $^1\text{H NMR}$ (300 MHz, CDCl_3) δ : 1.29 (54H, s, *t*-Bu), 4.06 (3H, br s, N^+CH_3), 7.13 (12H, m, ArH), 7.24 (16H, m, ArH), 7.76 (4H, d, $^3J = 8.2$ Hz, ArH), 8.86 (2H, s, pyH^2 and H^6), 10.12 (1H, s, pyH^4), 10.56 (2H, br s, NH). **MS (ES $^+$)** m/z : 1152.8

$[M - I]^+$.

3,5-Bis(4-(tris(4-*tert*-butylphenyl)methyl)phenylcarbamoyl)-1-methylpyridinium

chloride (130.Cl):²³ A solution of **130.I** (0.50 g, 0.39 mmol) in CHCl_3 (70 mL) was washed with 1 M NH_4Cl (8 x 70 mL). The organic layer was dried over MgSO_4 , filtered and the solvent was removed *in vacuo*. Purification by silica gel chromatography (95:5 $\text{CHCl}_3/\text{MeOH}$) gave **130.Cl** as a yellow solid (0.41 g, 89%). ^1H NMR (300 MHz, CDCl_3) δ : 1.30 (54H, s, *t*-Bu), 3.85 (3H, s, N^+CH_3), 7.15 (12H, m, *ArH*), 7.26 (16H, m, *ArH*), 7.82 (4H, d, $^3J = 8.2$ Hz, *ArH*), 8.78 (2H, s, pyH^2 and H^6), 10.59 (1H, s, pyH^4), 10.94 (2H, br s, NH). MS (ES^+) m/z : 1152.8 $[M - \text{Cl}]^+$.

3,5-Bis(4-(tris(4-*tert*-butylphenyl)methyl)phenylcarbamoyl)-1-methylpyridinium

bromide (130.Br):²³ A solution of **130.I** (0.087 g, 0.068 mmol) in CHCl_3 (30 mL) was washed with 1 M NH_4Br (8 x 30 mL). The organic layer was dried over MgSO_4 , filtered and the solvent was removed *in vacuo* to give **130.Br** as a yellow solid (0.073 g, 88%). ^1H NMR (300 MHz, CDCl_3) δ : 1.30 (54H, s, *t*-Bu), 4.07 (3H, s, N^+CH_3), 7.16 (12H, d, $^3J = 7.1$ Hz, *ArH*), 7.27 (16H, s, *ArH*), 7.85 (4H, d, $^3J = 8.2$ Hz, *ArH*), 8.91 (2H, s, pyH^2 and H^6), 10.51 (1H, s, pyH^4), 10.96 (2H, br s, NH). MS (ES^+) m/z : 1152.8 $[M - \text{Br}]^+$.

3,5-Bis(4-(tris(4-*tert*-butylphenyl)methyl)phenylcarbamoyl)-1-methylpyridinium

hexafluorophosphate (130.PF₆):^{adapted from 23} A solution of **130.Cl** (0.029 g, 0.024 mmol) in CHCl_3 (10 mL) was washed with 0.2 M NH_4PF_6 (5 x 5 mL) and H_2O (5 mL). The organic layer was dried over MgSO_4 , filtered and the solvent was removed *in vacuo* to give **130.PF₆** as a yellow solid (0.031 g, 95%). ^1H NMR (300 MHz, CDCl_3) δ : 1.29 (54H, s, *t*-Bu), 4.09 (3H, s, N^+CH_3), 7.12 (12H, d, $^3J = 8.2$ Hz, *ArH*), 7.25 (16H, m, *ArH*), 7.59 (4H, d, $^3J = 8.2$ Hz, *ArH*), 8.80 (2H, s, pyH^2 and H^6), 9.42 (3H, m, pyH^4 and NH). ^{19}F NMR (282.5 MHz, CDCl_3) δ : -70.54 (d, $^1J = 715$ Hz, PF_6^-). ^{31}P NMR (121.5 MHz, CDCl_3) δ :

-144.48 (septet, $^1J = 715$ Hz, PF_6^-). **MS (ES $^+$)** m/z : 1152.8 $[\text{M} - \text{PF}_6]^+$.

4-(Tris(4-*tert*-butylphenyl)methanol (131): In a 3 neck flask fitted with a condenser, magnesium turnings (3.69 g, 0.15 mol) were heated at 110 °C under a N_2 atmosphere overnight, cooled to 50 °C and dry THF (10 mL) with a catalytic amount of I_2 was added. A solution of 1-bromo-4-*tert*-butylbenzene (25 mL, 0.14 mol) in dry THF (70 mL) was added dropwise at a rate to maintain a gentle reflux. The reaction mixture was heated under reflux for 1 hour then a solution of diethyl carbonate (6 mL, 0.05 mol) in dry THF (70 mL) was added dropwise while heating under reflux. Once addition was complete, heating under reflux continued for a further hour. The reaction mixture was cautiously quenched with an ice (~150 g) and H_2SO_4 (12 mL) mixture. The aqueous mixture was extracted with CH_2Cl_2 (3 x 100 mL) and the combined organic layers were washed with 5% Na_2CO_3 (100 mL) and H_2O (4 x 100 mL) then dried over MgSO_4 , filtered and the solvent was removed *in vacuo*. The residue was triturated in hot hexane to give the white solid **131** (10.62 g, 50%). ^1H NMR (300 MHz, CDCl_3) δ : 1.25 (27H, s, *t*-Bu), 2.99 (1H, s, OH), 7.20 (12H, m, ArH). **MS (ES $^-$)** m/z : 427.3 $[\text{M} - \text{H}]^-$.

4-(Tris(4-*tert*-butylphenyl)methyl)aniline (132):²³ A suspension of **131** (4.84 g, 113 mmol) in acetyl chloride (30 mL) was heated under reflux under a N_2 atmosphere for 18 hours and the solvent was removed by distillation. The residue was redissolved in aniline (25 mL) and heated at 105 °C under a N_2 atmosphere for 3 days, during which time the colour changed from red to purple. The solution was cooled to room temperature and poured slowly into a stirred solution of 1 M HCl (300 mL). The precipitate was collected by filtration, washed with 1 M K_2CO_3 , redissolved in CH_2Cl_2 and filtered through a plug of silica gel. The solvent was removed *in vacuo*, the residue was triturated with hexane and the solid collected was purified by silica gel chromatography (1:2 petroleum ether/ CH_2Cl_2). Compound **132** was obtained as a

white solid (3.48 g, 61%). $^1\text{H NMR}$ (500 MHz, CDCl_3) δ : 1.27 (27H, s, *t*-Bu), 6.68 (2H, d, $^3J = 8.5$ Hz, ArH), 7.01 (2H, d, $^3J = 8.5$ Hz, ArH), 7.09 (6H, d, $^3J = 8.8$ Hz, ArH), 7.23 (6H, d, $^3J = 8.8$ Hz, ArH). **MS (ES⁺)** m/z : 504.4 $[\text{M} + \text{H}]^+$, 526.3 $[\text{M} + \text{Na}]^+$.

3,5-Bis(4-(tris(4-*tert*-butylphenyl)methyl)phenylcarbamoyl)pyridine (133):²³ A solution of 3,5-bis(chlorocarbonyl) pyridine (1.74 mmol) in dry CH_2Cl_2 (30 mL) was added dropwise to a solution of **132** (1.76 g, 3.49 mmol) and triethylamine (0.61 mL, 4.38 mmol) in dry CH_2Cl_2 (100 mL) over 3 hours. The reaction mixture was washed with 1 M HCl (3 x 100 mL) and H_2O (3 x 100 mL), and the organic layer was dried over MgSO_4 , filtered and the solvent was removed *in vacuo*. The residue was triturated in hot hexane, the solid was collected and washed with cold hexane to give **133** as a white solid (1.57 g, 79%). $^1\text{H NMR}$ (300 MHz, CDCl_3) δ : 1.31 (54H, s, *t*-Bu), 7.11 (12H, d, $^3J = 8.2$ Hz, ArH), 7.25 (16H, d, $^3J = 9.4$ Hz, ArH), 7.53 (4H, d, $^3J = 8.2$ Hz, ArH), 8.06 (2H, br s, NH), 8.65 (1H, s, pyH^4), 9.23 (2H, s, pyH^2 and H^6). **MS (ES⁺)** m/z : 1160.8 $[\text{M} + \text{Na}]^+$.

Slippage ‘rotaxane’ (134.Cl): A solution of **125** (14.7 mg, 0.025 mmol) and **130.Cl** (0.10 g, 0.085 mmol) in CHCl_3 (20 mL) was heated at 50 °C for 3.5 days. The reaction mixture was filtered to remove precipitated **130.Cl** and the solvent was removed *in vacuo*. The residue was purified by silica gel chromatography (initially eluting with 99:1 $\text{CH}_2\text{Cl}_2/\text{MeOH}$ then 98:2 $\text{CH}_2\text{Cl}_2/\text{MeOH}$) eluting impure **134.Cl** as the third band to give a yellow solid (18.9 mg). Further purification was not attempted to prevent further dissociation of **134.Cl** into its axle and macrocycle components. **MS (ES⁺)** m/z : 1751.9 $[\text{M} - \text{Cl}]^+$.

2,2'-(Hexa-2,4-diyne-1,6-dylbis(oxy))diethanol (135): A solution of **103** (0.57 g, 5.73 mmol) and $\text{Cu}(\text{OAc})_2$ (1.94 g, 10.19 mmol) in CH_3CN (30 mL) was heated at 40 °C for 24 hours. H_2O (20 mL) was added and the organic solvent was removed *in vacuo*. The aqueous mixture was extracted with CH_2Cl_2 (5 x 30 mL), and the combined organic layers

were dried over MgSO_4 , filtered and the solvent was removed *in vacuo* to give **135** as a yellow oil, which solidified upon standing (0.45 g, 79%). $^1\text{H NMR}$ (300 MHz, CDCl_3) δ : 2.00 (2H, br s, OH), 3.66 (4H, m, OCH_2), 3.77 (4H, m, OCH_2), 4.29 (4H, s, OCH_2CC). $^{13}\text{C NMR}$ (75.5 MHz, CDCl_3) δ : 58.80, 61.46, 70.38, 71.40, 75.21. **MS** (ES^+) m/z : 221.0791 $[\text{M} + \text{Na}]^+$ (Calcd. for $\text{C}_{10}\text{H}_{14}\text{O}_4\text{Na}$: 221.0784).

Cobalt carbonyl protected 2,2'-(hexa-2,4-diyne-1,6-dylbis(oxy))diethanol (136):

Compound **135** (0.075 g, 0.38 mmol) was dissolved in dry degassed CH_2Cl_2 (5 mL) and a solution of cobalt carbonyl (0.6 g, excess) in dry degassed CH_2Cl_2 (10 mL) was added. The reaction mixture was stirred at room temperature under a N_2 atmosphere for 2.5 hours, filtered and the solvent was removed *in vacuo*. The brown residue was purified by silica gel chromatography (CHCl_3), eluting **136** as the second band to give a brown solid (0.22 g, 75%). $^1\text{H NMR}$ (300 MHz, CDCl_3) δ : 2.01 (2H, br s, OH), 3.81 (8H, br s, OCH_2), 4.75 (4H, br s, OCH_2CC). $^{13}\text{C NMR}$ (75.5 MHz, CDCl_3) δ : 40.10, 53.06, 62.00, 71.63, 72.51, 200.49. **MS** (ES^+) m/z : 792.7515 $[\text{M} + \text{Na}]^+$ (Calcd. for $\text{C}_{22}\text{H}_{14}\text{Co}_4\text{O}_{16}\text{Na}$: 792.7502).

Cobalt carbonyl protected isophthalamide macrocycle (137): Compound **125** (0.021 g, 0.035 mmol) was dissolved in dry degassed CH_2Cl_2 (10 mL) and a solution of cobalt carbonyl (0.07 g, excess) in dry degassed CH_2Cl_2 (3 mL) was added. The reaction mixture was stirred at room temperature under a N_2 atmosphere for 2 hours, filtered and the solvent was removed *in vacuo*. The brown residue was purified by silica gel chromatography, eluting with CHCl_3 to remove unreacted cobalt carbonyl then 98:2 $\text{CHCl}_3/\text{MeOH}$ to elute the product **137** as the second band to give a brown solid (0.033 g, 75%). $^1\text{H NMR}$ (300 MHz, CDCl_3) δ : 4.03 (16H, m, NCH_2 , OCH_2), 4.79 (4H, br s, OCH_2CC), 6.76 (10H, m, hydroq ArH, NH), 7.59 (1H, m, isoH), 8.03 (3H, br s, isoH). **MS** (ES^+) m/z : 1192.8931 $[\text{M} + \text{Na}]^+$. Decomposition of **137** prevented further characterisation.

Cobalt carbonyl protected ‘rotaxane’ (138.Cl): Compound **125** (0.029 g, 0.049 mmol) and **54.Cl** (0.18 g, 0.17 mmol) were dissolved in CHCl_3 (15 mL) and stirred at room temperature for 2.5 days until equilibrium was reached. The reaction mixture was degassed, cobalt carbonyl was added (0.072 g, excess) and stirring was continued for a further hour before the solvent was removed *in vacuo*. The residue was purified by preparative TLC to give impure **138.Cl** as the lower brown band (0.012 g). **MS (ES⁺)** m/z : 2111.0 $[\text{M} - \text{Cl}]^+$.

Isophthalamide macrocycle with alkyl linker (139): A suspension of **125** (0.049 g, 0.082 mmol) and palladium on carbon (5 mg, 10% by mass) in a mixture of CHCl_3 (5 mL) and MeOH (0.05 mL) was stirred under a H_2 atmosphere for 16 hours. The reaction mixture was filtered through Celite, the solvent was removed *in vacuo* and the residue was purified by silica gel chromatography (98:2 $\text{CH}_2\text{Cl}_2/\text{MeOH}$). On one occasion it was possible to isolate a small amount of pure **139** as a white solid. **¹H NMR** (300 MHz, CDCl_3) δ : 1.38 (4H, m, CH_2), 1.58 (4H, m, CH_2), 3.51 (4H, t, $^3J = 6.2$ Hz, OCH_2), 3.73 (4H, m, NCH_2), 3.85 (4H, m, OCH_2), 4.04 (4H, m, OCH_2), 4.10 (4H, m, OCH_2), 6.70 (2H, br s, NH), 6.82 (8H, s, hydroq ArH), 7.54 (1H, t, $^3J = 7.8$ Hz, isoH), 7.99 (2H, d, $^3J = 7.8$ Hz, isoH), 8.02 (1H, s, isoH). **¹³C NMR** (75.5 MHz, CDCl_3) δ : 25.80, 29.49, 39.75, 67.19, 68.25, 69.08, 71.21, 115.36, 115.79, 124.53, 129.15, 130.51, 134.58, 152.61, 153.34, 166.83. **MS (ES⁺)** m/z : 629.2831 $[\text{M} + \text{Na}]^+$ (Calcd. for $\text{C}_{34}\text{H}_{42}\text{N}_2\text{O}_8\text{Na}$: 629.2833).

2,2’-(Hexa-2,4-diyne-1,6-dylbis(oxy))diethanol bistosylate (140): Compound **135** (0.27 g, 1.34 mmol) was dissolved in CH_2Cl_2 (20 mL) and triethylamine (0.4 mL, 2.87 mmol), tosyl chloride (0.54 g, 2.83 mmol) and DMAP (cat.) were added. The reaction mixture was stirred under a N_2 atmosphere for 16 hours then H_2O (20 mL) was added. The biphasic mixture was stirred vigorously, neutralised by 10% aqueous citric acid and the layers separated. The organic phase was washed with H_2O (2 x 20 mL), brine (20 mL), dried with MgSO_4 , filtered

and the solvent removed *in vacuo*. Purification by silica gel chromatography (1:1 petroleum ether/EtOAc) gave **140** as a yellow oil (0.41 g, 60%). ^1H NMR (300 MHz, CDCl_3) δ : 2.46 (6H, s, CH_3), 3.72 (4H, m, OCH_2), 4.19 (8H, m, OCH_2), 7.36 (4H, d, $^3J = 8.2$ Hz, TosH), 7.81 (4H, d, $^3J = 8.2$ Hz, TosH). ^{13}C NMR (75.5 MHz, CDCl_3) δ : 21.63, 58.81, 67.35, 68.76, 70.68, 74.80, 127.93, 129.83, 132.74, 144.91. MS (ES^+) m/z : 529.0971 $[\text{M} + \text{Na}]^+$ (Calcd. for $\text{C}_{24}\text{H}_{26}\text{O}_6\text{S}_2\text{Na}$: 529.0961), 565.2 $[\text{M} + \text{CH}_3\text{CN} + \text{NH}_4]^+$.

2,2'-(4,4'-(2,2'-(Hexa-2,4-diyne-1,6-diylbis(oxy))bis(ethane-2,1-diyl))bis(oxy))bis(4,1-phenylene))bis(oxy)diacetonitrile (141): A suspension of **140** (0.27 g, 0.52 mmol), **107** (0.20 g, 1.33 mmol) and K_2CO_3 (0.17 g, 1.22 mmol) in dry CH_3CN (30 mL) was heated under reflux for 2.5 days under a N_2 atmosphere. The reaction mixture was cooled to room temperature, filtered and the solvent was removed *in vacuo*. Purification by silica gel chromatography (99:1 $\text{CH}_2\text{Cl}_2/\text{MeOH}$) gave impure **141** (0.13 g, ~52%). **Improved synthesis**: A suspension of **108** (0.20 g, 0.85 mmol) and $\text{Cu}(\text{OAc})_2$ (0.30 g, 1.57 mmol) in CH_3CN (20 mL) was heated at 40 °C for 15 hours. H_2O (10 mL) was added and the organic solvent was removed *in vacuo*. The aqueous mixture was extracted with CH_2Cl_2 (4 x 10 mL), and the combined organic layers were dried over MgSO_4 , filtered and the solvent was removed *in vacuo* to give **141** as an off-white solid (0.16 g, 81%). ^1H NMR (300 MHz, CDCl_3) δ : 3.90 (4H, m, OCH_2), 4.12 (4H, m, OCH_2), 4.36 (4H, s, OCH_2CC), 4.72 (4H, s, CH_2CN), 6.93 (8H, m, hydroq ArH). ^{13}C NMR (75.5 MHz, CDCl_3) δ : 54.78, 59.04, 67.10, 67.69, 68.43, 70.62, 75.20, 115.78, 116.60, 150.87, 154.57. MS (ES^+) m/z : 478.2 $[\text{M} + \text{NH}_4]^+$, 483.1519 $[\text{M} + \text{Na}]^+$ (Calcd. for $\text{C}_{26}\text{H}_{24}\text{N}_2\text{O}_6\text{Na}$: 483.1527).

1,6-Hexanediol bistosylate (142): 1,6-Hexanediol (6.06 g, 51.28 mmol) was dissolved in CH_2Cl_2 (150 mL) and triethylamine (18 mL, 129 mmol), tosyl chloride (20.58 g, 100 mmol) and DMAP (cat.) were added. The reaction mixture was stirred under a N_2 atmosphere for

18 hours then H₂O (50 mL) was added. The biphasic mixture was stirred vigorously, neutralised by 10% aqueous citric acid and the layers separated. The organic phase was washed with H₂O (2 x 50 mL), dried over MgSO₄, filtered and the solvent removed *in vacuo*. Following trituration in diethyl ether, **142** was isolated as a white solid (14.10 g, 64%). ¹H NMR (300 MHz, CDCl₃) δ: 1.27 (4H, m, CH₂), 1.60 (4H, m, CH₂), 2.46 (6H, s, CH₃), 3.99 (4H, t, ³J = 6.5 Hz, OCH₂), 7.36 (4H, d, ³J = 8.2 Hz, TosH), 7.78 (4H, d, ³J = 8.2 Hz, TosH). MS (ES⁺) *m/z*: 444.2 [M + NH₄]⁺, 449.1 [M + Na]⁺.

2,2'-(4,4'-(Hexa-1,6-diylbis(oxy))bis(4,1-phenylene))bis(oxy)diacetonitrile (143): A suspension of **108** (0.21 g, 1.43 mmol), **142** (0.27 g, 0.64 mmol) and K₂CO₃ (0.20 g, 1.41 mmol) in CH₃CN (8 mL) was stirred for 30 seconds before heating under microwave irradiation for 2 hours at 160 °C. The reaction mixture was cooled to room temperature, filtered and the solvent was removed *in vacuo*. The residue was filtered through a plug of silica gel to give **143** as a white solid (0.12 g, 49%). m.p. 92-94 °C. ¹H NMR (300 MHz, CDCl₃) δ: 1.56 (4H, m, CH₂), 1.81 (4H, m, CH₂), 3.94 (4H, t, ³J = 6.5 Hz, OCH₂), 4.72 (4H, s, CH₂CN), 6.91 (8H, m, hydroq ArH). ¹³C NMR (75.5 MHz, CDCl₃) δ: 25.81, 29.19, 54.95, 68.31, 115.54, 116.70, 150.54, 155.12. MS (ES⁺) *m/z*: 403.1622 [M + Na]⁺ (Calcd. for C₂₂H₂₄N₂O₄Na: 403.1628), 783.4 [2M + Na]⁺.

2,2'-(4,4'-(Hexa-1,6-diylbis(oxy))bis(4,1-phenylene))bis(oxy)diethylamine (144): A solution of 1 M borane in THF (5 mL) was heated at 70 °C under a N₂ atmosphere and a solution of **143** (0.16 g, 0.41 mmol) in dry THF (30 mL) was added dropwise over 45 minutes. Once addition was complete, the reaction mixture was heated under reflux for 4 hours, before being cooled to room temperature and quenching the excess borane with MeOH. The product was precipitated as the hydrochloride salt following addition of a couple of drops of HCl. The solid was collected by filtration, washed with cold MeOH then

resuspended in CHCl_3 (20 mL). 10% aqueous NaOH (20 mL) was added and the biphasic mixture was stirred vigorously until the solid dissolved. The organic layer was washed with H_2O (20 mL), dried over MgSO_4 , filtered and the solvent was removed *in vacuo* to give **144** as an off-white solid (0.094 g, 59%). **m.p.** 132-134 °C. ^1H NMR (300 MHz, CDCl_3) δ : 1.53 (8H, m, NH_2 , CH_2), 1.82 (4H, m, CH_2), 3.06 (4H, t, $^3J = 5.3$ Hz, NCH_2), 3.93 (8H, m, OCH_2), 6.84 (8H, m, hydroq ArH). ^{13}C NMR (75.5 MHz, CDCl_3) δ : 25.88, 29.31, 41.69, 68.41, 70.82, 115.40, 152.94, 153.34. **MS** (ES^+) m/z : 411.2250 $[\text{M} + \text{Na}]^+$ (Calcd. for $\text{C}_{22}\text{H}_{32}\text{N}_2\text{O}_4\text{Na}$: 411.2254).

Ethylene glycol monotosylate (145): Ethylene glycol (10 mL, 179 mmol) was dissolved in CH_2Cl_2 (100 mL) and tosyl chloride (3.44 g, 18.04 mmol), triethylamine (2.5 mL, 17.94 mmol) and DMAP (cat.) were added. The reaction was stirred at room temperature under a N_2 atmosphere overnight and H_2O (50 mL) was added. The biphasic mixture was neutralised with 10% aqueous citric acid, and the organic layer was washed with H_2O (50 mL), dried over MgSO_4 , filtered and the solvent was removed *in vacuo*. The residue was purified by silica gel chromatography (98:2 $\text{CH}_2\text{Cl}_2/\text{MeOH}$) eluting the product **145** as the third band to give **145** as a colourless oil (1.50 g, 39%). ^1H NMR (300 MHz, CDCl_3) δ : 1.92 (1H, br s, OH), 2.47 (3H, s, CH_3), 3.83 (2H, m, OCH_2), 4.16 (2H, m, OCH_2), 7.37 (2H, d, $^3J = 8.2$ Hz, TosH), 7.82 (2H, d, $^3J = 8.2$ Hz, TosH). **MS** (ES^+) m/z : 239.0 $[\text{M} + \text{Na}]^+$, 455.1 $[2\text{M} + \text{Na}]^+$.

2-(4-(2-Hydroxyethoxy)phenoxy)acetonitrile (146): A suspension of **107** (0.26 g, 1.77 mmol), **145** (0.42 g, 1.94 mmol) and K_2CO_3 (0.27 g, 1.95 mmol) in CH_3CN (10 mL) was stirred for 30 seconds before heating under microwave irradiation for 2 hours at 160 °C. The reaction mixture was cooled to room temperature and the solvent was removed *in vacuo*. The residue was redissolved in CHCl_3 (50 mL) and washed with 1 M HCl (2 x 50 mL) and brine

(50 mL). The organic layer was dried over MgSO_4 , filtered and the solvent was removed *in vacuo*. The residue was filtered through a plug of silica gel eluting with 98:2 $\text{CH}_2\text{Cl}_2/\text{MeOH}$ to give **146** as a colourless oil (0.11 g, 33%). $^1\text{H NMR}$ (300 MHz, CDCl_3) δ : 2.06 (1H, br s, OH), 3.96 (2H, m, OCH_2), 4.06 (2H, m, OCH_2), 4.73 (2H, s, CH_2CN), 6.93 (4H, m, hydroq ArH). $^{13}\text{C NMR}$ (75.5 MHz, CDCl_3) δ : 54.82, 61.46, 69.71, 115.28, 115.69, 116.72, 150.94, 154.62. **MS** (ES^+) m/z : 216.0631 $[\text{M} + \text{Na}]^+$ (Calcd. for $\text{C}_{10}\text{H}_{11}\text{NO}_3\text{Na}$: 216.0631).

Small isophthalamide macrocycle with alkyl linker (147): A solution of isophthaloyl dichloride (0.028 g, 0.14 mmol) in dry CH_2Cl_2 (2 mL) was added to a suspension of **144** (0.052 g, 0.13 mmol), **130.Cl** (0.16 g, 0.13 mmol) and triethylamine (0.04 mL, 0.29 mmol) in dry CH_2Cl_2 (25 mL) under a N_2 atmosphere. The reaction mixture was stirred for 1 hour then washed with 1 M HCl (2 x 25 mL) and H_2O (25 mL). The organic layer was dried over MgSO_4 , filtered and the solvent was removed *in vacuo*. The residue was purified by silica gel chromatography (98:2 $\text{CH}_2\text{Cl}_2/\text{MeOH}$) eluting a mixture of **147** and **130.Cl** as the third band. Purification of this band by preparative TLC (4:1 EtOAc/ CHCl_3) gave **147** as a white solid (4 mg, 6%). $^1\text{H NMR}$ (300 MHz, CDCl_3) δ : 1.49 (4H, m, CH_2), 1.71 (4H, m, CH_2), 3.86 (4H, q, $^3J = 5.0$ Hz, NCH_2), 3.95 (4H, t, $^3J = 6.2$ Hz, OCH_2), 4.10 (4H, t, $^3J = 5.0$ Hz, OCH_2), 6.67 (2H, br s, NH), 6.75 (8H, m, hydroq ArH), 7.55 (1H, t, $^3J = 7.8$ Hz, isoH), 7.94 (1H, s, isoH), 8.02 (2H, dd, $^3J = 7.8$ Hz, $^4J = 1.2$ Hz, isoH). $^{13}\text{C NMR}$ (75.5 MHz, CDCl_3) δ : 24.66, 28.27, 39.65, 67.27, 68.17, 115.39, 116.12, 123.87, 129.37, 130.84, 134.70, 152.44, 153.53, 166.80. **MS** (ES^+) m/z : 541.2307 $[\text{M} + \text{Na}]^+$ (Calcd. for $\text{C}_{30}\text{H}_{34}\text{N}_2\text{O}_6\text{Na}$: 541.2309).

N^1 -(2-(4-Hydroxyphenoxy)ethyl)- N^3 -(2-(4-(prop-2-

ynyloxy)phenoxy)ethyl)isophthalamide (148): A suspension of **123** (0.36 g, 0.82 mmol), propargyl benzenesulfonate (0.5 mL, 3.19 mmol) and Cs_2CO_3 (0.8 g, 2.46 mmol) in dry degassed DMF (60 mL) was heated under a N_2 atmosphere for 41 hours at 100 °C. The

reaction mixture was cooled to room temperature, filtered and the solvent was removed *in vacuo*. The brown residue was purified by silica gel chromatography (98:2 CH₂Cl₂/MeOH) eluting the second band to give the monoalkylated product **148** as an off-white solid (0.14 g, 36%). **m.p.** 148-150 °C. ¹H NMR (300 MHz, DMSO-*d*₆) δ: 3.53 (1H, t, ⁴*J* = 1.9 Hz, OCH₂CCH), 3.61 (4H, quin, ³*J* = 5.8 Hz, NCH₂), 4.01 (2H, t, ³*J* = 5.8 Hz, OCH₂), 4.07 (2H, t, ³*J* = 5.8 Hz, OCH₂), 4.71 (2H, d, ⁴*J* = 1.9 Hz, OCH₂CCH), 6.66 (2H, d, ³*J* = 8.8 Hz, hydroq ArH), 6.78 (2H, d, ³*J* = 8.8 Hz, hydroq ArH), 6.91 (4H, s, hydroq ArH), 7.56 (1H, t, ³*J* = 7.8 Hz, isoH), 7.99 (2H, d, ³*J* = 7.8 Hz, isoH), 8.35 (1H, s, isoH), 8.80 (2H, q, ³*J* = 4.7 Hz, NH), 8.92 (1H, s, OH). ¹³C NMR (75.5 MHz, DMSO-*d*₆) δ: 55.88, 66.41, 66.49, 78.04, 79.56, 115.34, 115.51, 115.75, 115.95, 126.37, 128.43, 129.85, 134.48, 151.23, 151.32, 152.98, 166.10, 166.13. MS (ES⁺) *m/z*: 497.1684 [M + Na]⁺ (Calcd. for C₂₇H₂₆N₂O₆Na: 497.1683).

***N*¹,*N*³-Bis(2-(4-(prop-2-ynyloxy)phenoxy)ethyl)isophthalamide (149):** This was eluted as the first band during the chromatographic purification of **148** to give the bisalkylated product **149** as a white solid (0.094 g, 23%). **m.p.** 136-138 °C. ¹H NMR (300 MHz, CDCl₃) δ: 2.45 (1H, t, ⁴*J* = 2.4 Hz, OCH₂CCH), 3.82 (4H, q, ³*J* = 5.3 Hz, NCH₂), 4.06 (4H, m, OCH₂), 4.59 (4H, d, ⁴*J* = 2.4 Hz, OCH₂CCH), 6.65 (2H, br s, NH), 6.83 (8H, m, hydroq ArH), 7.47 (1H, m, ³*J* = 7.8 Hz, isoH), 7.88 (2H, d, ³*J* = 7.8 Hz, isoH), 8.14 (1H, s, isoH). ¹³C NMR (75.5 MHz, CDCl₃) δ: 39.71, 56.49, 67.15, 75.38, 78.71, 115.34, 116.15, 125.44, 129.01, 130.05, 134.65, 152.01, 153.18, 166.68. MS (ES⁺) *m/z*: 535.1841 [M + Na]⁺ (Calcd. for C₃₀H₂₈N₂O₆Na: 535.1840).

Small isophthalamide macrocycle with diyne linker (150): A solution of Cu(OAc)₂ (0.11 g, 0.56 mmol) in CH₃CN (50 mL) was added dropwise to a solution of **149** (0.062 g, 0.12 mmol) in CH₃CN (100 mL), and the mixture was heated under reflux for 18 hours, cooled to room

temperature and the solvent was removed *in vacuo*. The residue was redissolved in H₂O (30 mL) and extracted with CHCl₃ (3 x 30 mL). The combined organic layers were dried over MgSO₄, filtered and the solvent was removed *in vacuo*. Following purification by silica gel chromatography (98:2 CHCl₃/MeOH) and recrystallisation from hot CHCl₃/MeOH, **150** was isolated as a white solid (0.031 g, 51%). **m.p.** 220 °C (dec.). **¹H NMR** (300 MHz, CDCl₃) δ : 3.87 (4H, q, $^3J = 5.3$ Hz, NCH₂), 4.10 (4H, t, $^3J = 5.1$ Hz, OCH₂), 4.73 (4H, s, OCH₂CC), 6.67 (2H, t, $^3J = 5.3$ Hz, NH), 6.85 (8H, m, hydroq ArH), 7.54 (1H, t, $^3J = 7.6$ Hz, isoH), 7.97 (2H, d, $^3J = 7.6$ Hz, isoH), 8.04 (1H, s, isoH). **¹³C NMR** (75.5 MHz, CDCl₃) δ : 36.69, 56.21, 66.89, 70.75, 74.59, 115.11, 116.17, 130.26, 134.82, 151.26, 153.23, 167.03. **MS (ES⁺)** m/z : 533.1682 [M + Na]⁺ (Calcd. for C₃₀H₂₆N₂O₆Na: 533.1683).

Diethylene glycol bistosylate (151):³⁵ Diethylene glycol (4.96 g, 46.7 mmol) and tosyl chloride (18.11 g, 95 mmol) were dissolved in CH₂Cl₂ (50 mL) and the solution was cooled to 0 °C. Powdered KOH (20.90 g, 572 mmol) was slowly added and the reaction mixture was stirred at 0 °C for 3.5 hours. Ice water (100 mL) was added, the organic layer was separated and the aqueous layer was extracted with CH₂Cl₂ (3 x 50 mL). The combined organic layers were washed with H₂O (50 mL), dried over MgSO₄, filtered and the solvent was removed *in vacuo* to give **151** as a white solid (15.17 g, 78%). **¹H NMR** (300 MHz, CDCl₃) δ : 2.46 (6H, s, CH₃), 3.61 (4H, m, OCH₂), 4.10 (4H, m, OCH₂), 7.37 (4H, d, $^3J = 8.2$ Hz, TosH), 7.79 (4H, d, $^3J = 8.2$ Hz, TosH). **MS (ES⁺)** m/z : 473.1 [M + CH₃CN + NH₄]⁺.

2-(Azidoethoxy)ethyl monotosylate (152):³⁵ A suspension of **151** (1.00 g, 2.47 mmol) and sodium azide (0.18 g, 2.71 mmol) in dry degassed DMF (10 mL) was stirred at room temperature under a N₂ atmosphere for 21 hours. CH₂Cl₂ (10 mL) was added to precipitate the salts and the filtrate concentrated *in vacuo* and purified by silica gel chromatography (3:2 petroleum ether/EtOAc), eluting the product **152** as the first band (0.31 g, 44%). **¹H NMR**

(300 MHz, CDCl₃) δ : 2.46 (3H, s, CH₃), 3.33 (2H, t, $^3J = 4.7$ Hz, OCH₂), 3.62 (2H, t, $^3J = 4.7$ Hz, CH₂N₃), 3.71 (2H, t, $^3J = 4.7$ Hz, OCH₂), 4.18 (2H, t, $^3J = 4.7$ Hz, OCH₂), 7.36 (2H, d, $^3J = 7.9$ Hz, TosH), 7.82 (2H, d, $^3J = 7.9$ Hz, TosH). MS (ES⁺) m/z : 286.1 [M + H]⁺, 303.1 [M + NH₄]⁺, 344.1 [M + CH₃CN + NH₄]⁺.

***N*¹-(2-(4-(2-(2-Azidoethoxy)ethoxy)phenoxy)ethyl)-*N*³-(2-(4-(2-(prop-2-ynyloxy)ethoxy)phenoxy)ethyl)isophthalamide (153)**: A suspension of **124** (0.19 g, 0.37 mmol), **152** (0.17 g, 0.61 mmol) and Cs₂CO₃ (0.15 g, 0.46 mmol) in dry degassed DMF (17 mL) was heated at 60 °C under a N₂ atmosphere for 2 days. The reaction mixture was cooled to room temperature, filtered and the solvent was removed *in vacuo*. Purification by silica gel chromatography (98:2 CH₂Cl₂/MeOH) eluted impure **153** as the second band (0.11 g). MS (ES⁺) m/z : 654.28 [M + Na]⁺.

25-(2-(2-Aminoethoxy)ethoxy)-26,27,28-trihydroxycalix[4]arene (154): Compound **29** (0.22 g, 0.35 mmol) and hydrazine monohydrate (0.1 mL, excess) were suspended in EtOH (15 mL) and heated under reflux for 15 hours during which time the solid dissolved. The reaction mixture was cooled to room temperature, poured into H₂O (20 mL) and extracted with CH₂Cl₂ (4 x 20 mL). The combined organic fractions were dried over MgSO₄, filtered and the solvent was removed *in vacuo* to give **154** as a white solid (0.19 g, 100%). **m.p.** 140 °C (dec.). ¹H NMR (300 MHz, CDCl₃) δ : 3.06 (2H, t, $^3J = 5.0$ Hz, CH₂NH₂), 3.46 (4H, d, $^2J = 13.2$ Hz, ArCH_{in}H_{out}Ar), 3.77 (2H, t, $^3J = 5.0$ Hz, OCH₂), 4.12 (2H, m, OCH₂), 4.27 (2H, d, $^2J = 13.2$ Hz, ArCH_{in}H_{out}Ar), 4.34 (2H, m, OCH₂), 4.47 (2H, d, $^2J = 13.2$ Hz, ArCH_{in}H_{out}Ar), 6.68 (3H, m, calix ArH), 6.89 (1H, t, $^3J = 7.6$ Hz, calix ArH), 7.06 (8H, m, calix ArH). ¹³C NMR (75.5 MHz, CDCl₃) δ : 31.24, 32.00, 41.82, 69.62, 73.34, 75.31, 120.90, 121.53, 126.05, 128.38, 128.54, 128.63, 128.68, 128.74, 128.82, 128.92, 129.25, 134.39, 149.81, 150.61, 151.54. MS (ES⁺) m/z : 512.2417 [M + H]⁺ (Calcd. for C₃₂H₃₄NO₅:

512.2431), 1023.5 [2M + H]⁺.

25,26,27-Tribenzyloxy-28-hydroxycalix[4]arene (155):³⁶ A solution of calix[4]arene (0.67 g, 1.57 mmol) in pyridine (8 mL) was cooled to 0 °C and benzoyl chloride (1.6 mL, 13.78 mmol) was added. The resulting suspension was stirred for a further 3 hours and poured into H₂O (100 mL). The precipitate was filtered, washed with H₂O and recrystallised from CHCl₃/MeOH to give **155** as a white solid (0.98 g, 85%). ¹H NMR (300 MHz, CDCl₃) δ: 3.50 (2H, d, ²J = 14.1 Hz, ArCH_{in}H_{out}Ar), 3.81 (6H, m, ArCH_{in}H_{out}Ar, ArCH_{in}H_{out}Ar), 5.45 (1H, s, OH), 6.58 (4H, m, calix ArH), 6.72 (2H, m, calix ArH), 6.89 (2H, m, calix ArH), 7.02 (4H, m, calix ArH), 7.24 (5H, m, calix ArH), 7.51 (4H, m, calix ArH), 7.74 (2H, calix ArH), 8.08 (4H, m, calix ArH). MS (ES⁺) *m/z*: 759.2 [M + Na]⁺.

5,11,17,23-Tetra-*tert*-butyl-25-prop-2-ynyloxy-26,27,28-trihydroxycalix[4]arene (156):³⁷ A suspension of *tert*-butylcalix[4]arene (3.10 g, 4.78 mmol) and K₂CO₃ (0.57 g, 4.15 mmol) in acetone (50 mL) was heated under reflux for 1 hour. Propargyl benzenesulfonate (1 mL, 6.39 mmol) was added and heating under reflux was continued for a further 18 hours. The reaction mixture was cooled to room temperature, the solvent was removed *in vacuo* and the residue was redissolved in CH₂Cl₂ (100 mL). This was washed with 10% aqueous HCl (50 mL), dried over MgSO₄, filtered and the solvent was removed *in vacuo*. Purification by silica gel chromatography (1:1 CH₂Cl₂/cyclohexane) eluted the impure monoalkylated product **156** as the second band. Following recrystallisation from CHCl₃/MeOH, **156** was isolated as a white solid (0.49 g, 15%). The bisalkylated product **157** was eluted as the third band to give a white solid (1.37 g, 40%). **Microwave synthesis:** Propargyl benzenesulfonate (0.3 mL, 1.92 mmol), *tert*-butylcalix[4]arene (1.04 g, 1.6 mmol) and K₂CO₃ (0.19 g, 1.35 mmol) were suspended in acetone (15 mL), stirred at room temperature for 30 seconds and heated under microwave irradiation for 45 minutes at 150 °C. The solvent was removed *in vacuo* and the resulting yellow residue was redissolved in CH₂Cl₂ (50 mL). This was

washed with 1 M HCl (25 mL), dried over MgSO₄, filtered and the solvent was removed *in vacuo*. Purification by silica gel chromatography (3:2 CH₂Cl₂/petroleum ether) eluted **156** as the third band (0.30 g, 26%) and **157** as the fourth band (0.30 g, 26%). ¹H NMR (300 MHz, CDCl₃) δ: 1.21 (36H, m, *t*-Bu), 2.74 (1H, br s, OCH₂CCH), 3.45 (4H, d, ²*J* = 13.5 Hz, ArCH_{in}H_{out}Ar), 4.29 (2H, d, ²*J* = 13.5 Hz, ArCH_{in}H_{out}Ar), 4.47 (2H, d, ²*J* = 13.5 Hz, ArCH_{in}H_{out}Ar), 4.94 (2H, s, OCH₂CCH), 7.00 (2H, s, calix ArH), 7.06 (4H, s, calix ArH), 7.10 (2H, s, calix ArH), 9.27 (2H, s, OH), 10.12 (1H, s, OH). MS (ES⁺) *m/z*: 745.5 [M + CH₃CN + NH₄]⁺.

5,11,17,23-Tetra-*tert*-butyl-25,27-bis(prop-2-ynyloxy)-26,28-dihydroxycalix[4]arene

(157):³⁷ This was isolated as a white solid as a by-product in the synthesis of **156**. ¹H NMR (500 MHz, CDCl₃) δ: 0.87 (18H, s, *t*-Bu), 1.28 (18H, s, *t*-Bu), 2.52 (2H, t, ⁴*J* = 2.4 Hz, OCH₂CCH), 3.32 (4H, d, ²*J* = 13.7 Hz, ArCH_{in}H_{out}Ar), 4.37 (4H, d, ²*J* = 13.7 Hz, ArCH_{in}H_{out}Ar), 4.74 (4H, d, ⁴*J* = 2.4 Hz, OCH₂CCH), 6.51 (2H, s, OH), 6.73 (4H, s, calix ArH), 7.08 (4H, s, calix ArH). MS (ES⁺) *m/z*: 783.5 [M + CH₃CN + NH₄]⁺.

5,11,17,23-Tetra-*tert*-butyl-25-(*tert*-butyl-5-(1*H*-1,2,3-triazol-4-yl)pentylcarbamate-

26,27,28-trihydroxycalix[4]arene (158): A solution of [Cu(CH₃CN)₄]PF₆ (15.13 mg, 0.041 mmol) and TBTA (21.35 mg, 0.04 mmol) in dry degassed CH₂Cl₂ (2 mL) was added to a solution of **156** (0.25 g, 0.37 mmol), **82** (0.088 g, 0.39 mmol) and DIPEA (0.07 mL, 0.4 mmol) in dry degassed CH₂Cl₂ (30 mL). The solution was stirred under a N₂ atmosphere in the absence of light for 3 days. The organic layer was washed with H₂O (2 x 20 mL), dried over MgSO₄, filtered and the solvent was removed *in vacuo*. The residue was purified by silica gel chromatography (3:2 petroleum ether/EtOAc) to give **158** as a white solid (0.25 g, 74%). **m.p.** 102-104 °C. ¹H NMR (300 MHz, CDCl₃) δ: 1.20 (36H, m, *t*-Bu), 1.43 (9H, s, *t*-Bu), 1.58 (2H, m, CH₂), 2.06 (2H, m, CH₂), 3.10 (2H, m, CH₂), 3.44 (4H, t, ²*J* = 13.3 Hz,

ArCH_{in}H_{out}Ar), 4.19 (2H, d, $^2J = 13.3$ Hz, ArCH_{in}H_{out}Ar), 4.40 (2H, d, $^2J = 13.3$ Hz, ArCH_{in}H_{out}Ar), 4.53 (4H, m, NCH₂), 5.34 (2H, s, OCH₂), 7.05 (8H, m, calix ArH), 8.29 (1H, s, CHN₃). ^{13}C NMR (75.5 MHz, CDCl₃) δ : 23.59, 28.38, 29.49, 29.97, 31.20, 31.44, 32.23, 32.94, 33.89, 33.97, 34.26, 40.20, 50.41, 69.89, 79.09, 123.90, 125.71, 126.54, 127.47, 127.96, 128.17, 133.52, 143.29, 143.73, 147.50, 148.13, 148.62, 148.89, 155.94. MS (ES⁺) m/z : 937.5816 [M + Na]⁺ (Calcd. for C₅₇H₇₈N₄O₆Na: 937.5814).

Stoppered triazole axle (159.Cl): A solution of [Cu(CH₃CN)₄]PF₆ (10.02 mg, 0.027 mmol) in dry degassed CH₂Cl₂ (5 mL) was added to a solution of **156** (0.18 g, 0.26 mmol), **75.Cl** (0.055 g, 0.13 mmol) and DIPEA (0.04 mL, 0.23 mmol) in dry degassed CH₂Cl₂ (10 mL). The solution was stirred under a N₂ atmosphere in the absence of light for 63 hours. The organic layer was washed with H₂O (2 x 20 mL), dried over MgSO₄, filtered and the solvent was removed *in vacuo*. The residue was purified by silica gel chromatography (95:5 CH₂Cl₂/MeOH) to give **159.Cl** as an orange solid (21.1 mg, 9%). ^1H NMR (300 MHz, CDCl₃) δ : 1.12 (72H, m, *t*-Bu), 1.50 (4H, m, CH₂), 1.81 (4H, m, CH₂), 2.12 (4H, m, CH₂), 3.43 (12H, m, ArCH_{in}H_{out}Ar, CH₂), 4.13 (4H, m, ArCH_{in}H_{out}Ar), 4.36 (7H, m, ArCH_{in}H_{out}Ar, N⁺CH₃), 4.53 (4H, m, CH₂N₃), 5.27 (4H, s, OCH₂), 7.06 (16H, m, calix ArH), 8.23 (2H, br s, CHN₃), 9.29 (6H, m, OH, pyH² and H⁴), 9.57 (2H, br s, NH), 9.99 (2H, br s, OH), 10.50 (1H, s, pyH⁴). ^{13}C NMR (125 MHz, CDCl₃) δ : 23.37, 27.84, 29.68, 31.21, 31.45, 32.31, 32.90, 33.89, 33.95, 34.26, 40.12, 50.31, 69.31, 125.71, 126.54, 127.57, 128.00, 128.09, 133.56, 134.98, 143.27, 143.63, 146.06, 146.64, 147.58, 148.12, 148.60, 148.90, 160.62. MS (ES⁺) m/z : 1775.1009 [M – Cl]⁺ (Calcd. for C₁₁₂H₁₄₄N₉O₁₀: 1775.1031).

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Chapter 7

Supplementary Information

7. Supplementary Information

7.1. Titration Protocols

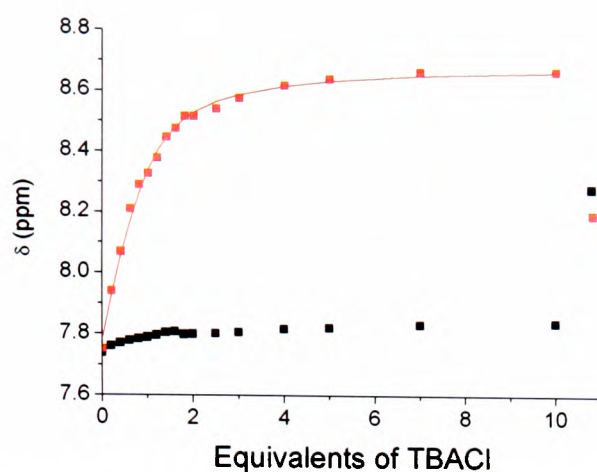
7.1.1. ^1H NMR Titrations

^1H NMR spectra were recorded on a Varian Unity Plus 500 spectrometer at 298 K. Anion binding titration studies were carried out by titrating a solution of the guest anion as its tetrabutylammonium salt (TBAX) into a solution of the host species. Where necessary, a 1:1 mixture of the host and NH_4PF_6 was also prepared. The initial sample volume was 500 μL , the starting concentration of the host species was 1.5 mM and the concentration of the anion solution was 0.075 M. Seventeen aliquots of the anion solution were added until a total of 10 equivalents of anion had been added. The following volumes of anion were added: 10 x 2 μL , 2 x 5 μL , 2 x 10 μL , 1 x 20 μL , 1 x 30 μL . After each addition the solution was thoroughly shaken and the ^1H NMR spectrum was recorded monitoring the chemical shift changes of the relevant protons of the host.

The resulting titration data were analysed using the winEQNMR2¹ computer program. The observed chemical shift data, host and guest concentrations at each titration point and estimates for the binding constant, limiting chemical shifts and complex stoichiometry were added to the input file. The parameters were refined by non-linear least-squares analysis to achieve the best fit between the observed and calculated chemical shifts. The parameters were varied until values for the association constant converged. There was good agreement between the experimental and calculated binding curves which demonstrated that the model was appropriate.

7.1.1.1. Binding curves

a)



b)

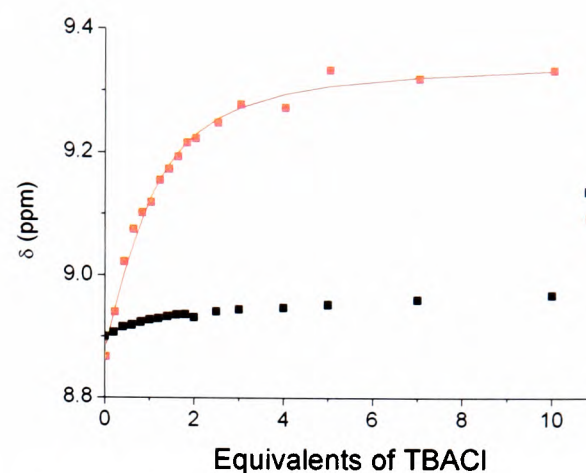
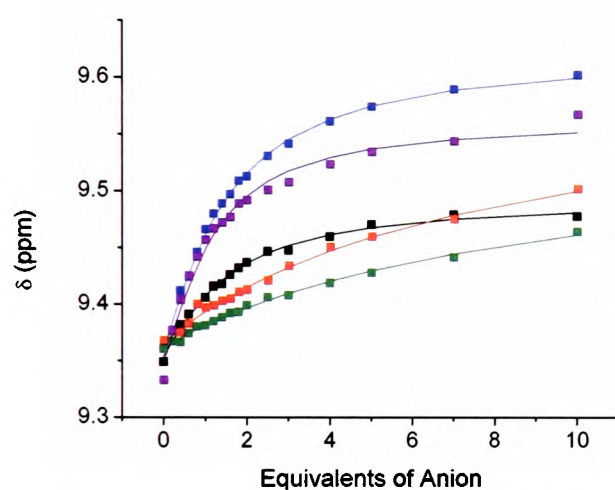


Figure 7.1 Chemical shift change of the amide proton upon addition of TBACl in the presence and absence of coordinating ammonium cations to a solution of a) receptor **1** and b) receptor **2** at 298 K in 98:2 CD₃CN/D₂O. Square symbols represent the experimental data points and the lines represent the calculated curves

a)



b)

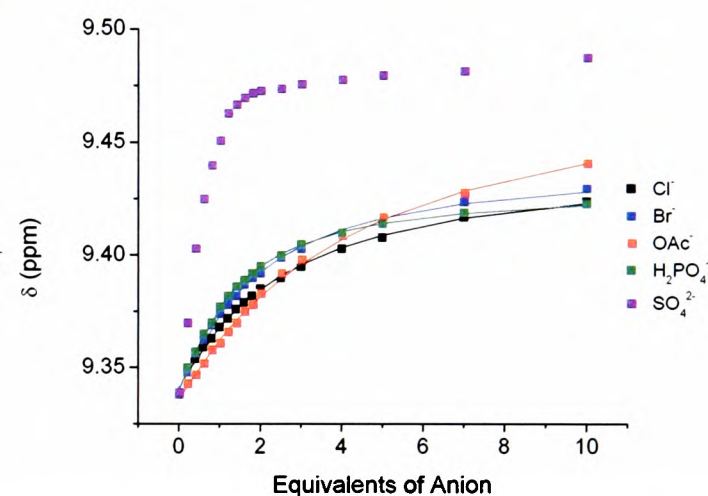


Figure 7.2 Chemical shift change of the *ortho* pyridinium proton upon addition of anions as their TBA salts at 298 K to a solution of a) **68**.PF₆ in 45:45:10 CDCl₃/CD₃OD/D₂O and b) **70**.PF₆ in 1:1 CDCl₃/CD₃OD. Square symbols represent the experimental data points and the lines represent the calculated curves

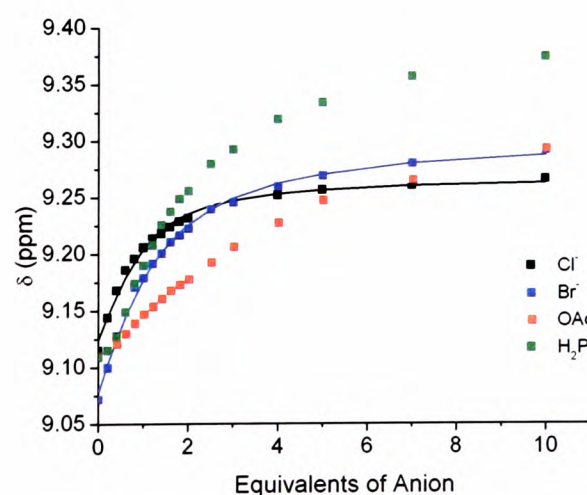
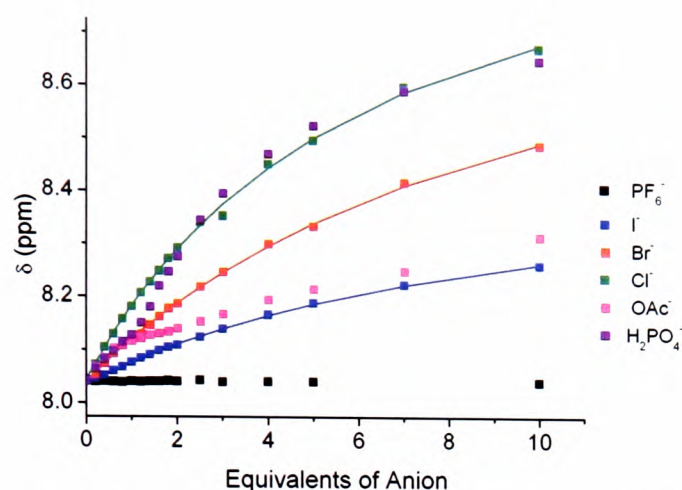


Figure 7.3 Chemical shift change of the *ortho* pyridinium proton upon addition of anions as their TBA salts at 298 K to a solution of catenane **115**.PF₆ in 1:1 CDCl₃/CD₃OD. Square symbols represent the experimental data points and the lines represent the calculated curves

a)



b)

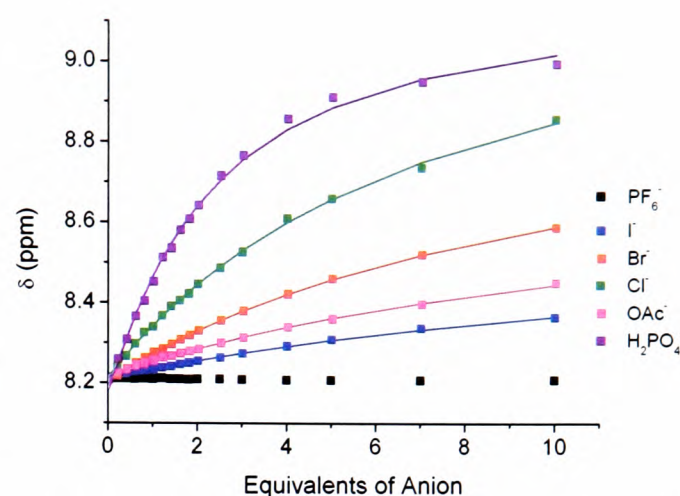


Figure 7.4 Chemical shift change of the isophthalamide cavity proton upon addition of anions as their TBA salts at 298 K to a solution of a) macrocycle **125** and b) macrocycle precursor **121** in CDCl_3 . Square symbols represent the experimental data points and the lines represent the calculated curves

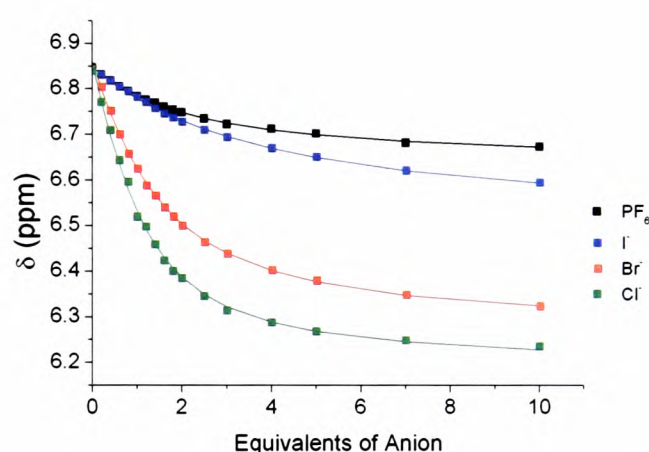


Figure 7.5 Chemical shift change of the hydroquinone proton of macrocycle **125** upon addition of **53.X** at 298 K in CDCl_3 . Square symbols represent the experimental data points and the lines represent the calculated curves

7.1.2. UV/visible Spectroscopy Titrations

UV/visible spectra were recorded on a Perkin-Elmer Lambda 19 spectrometer or a Shimadzu UV-2401PC spectrometer at 298 K. Cation binding titration studies were carried out by titrating a solution of the guest cation as its hexafluorophosphate or perchlorate salt into a solution of the host species. Where necessary, a 1:1 mixture of the host and TBACl was also prepared. The initial sample volume was 3 mL, the starting concentration of the host species was 0.1 mM and the concentration of the cation solution was 0.03 M. Seventeen aliquots of the cation solution were added until a total of 10 equivalents of cation had been added. The following volumes of cation were added: 10 x 2 μL , 2 x 5 μL , 2 x 10 μL , 1 x 20 μL , 1 x 30 μL . After each addition, the UV/visible spectrum was recorded monitoring changes of the calix[4]diquinone $n\text{-}\pi^*$ absorption band.

The resulting titration data were analysed using the SPECFIT² computer program. The spectra, host and guest concentrations at each titration point, complex stoichiometry and whether the component species were coloured were included in the input file. The parameters were refined by global analysis using singular value decomposition and non-linear modelling by the Levenberg-Marquardt method. The parameters were varied until values for the association constant converged. There was good agreement between the experimental and calculated binding curves, calculated concentration profiles and calculated spectra of the complexes, demonstrating that the model was appropriate.

7.1.3. Electrochemistry Titrations

Electrochemical studies on selected calix[4]diquinone receptors were carried out using square wave and cyclic voltammetric techniques. Voltammograms were recorded under a N₂ atmosphere at 298 K using a glassy carbon working electrode, platinum auxiliary electrode and Ag/AgCl reference electrode connected to a Potentiostat (Autolab PGSTAT12 using GPES software). Square wave voltammograms were recorded at 30 MHz and cyclic voltammograms were recorded at 100 mV s⁻¹, unless specified otherwise. The starting concentration of the host species was 4 mM in dry degassed CH₃CN, with 0.1 M TBAPF₆ as the supporting electrolyte, and the initial sample volume was 2.5 mL. Titrations were carried out by titrating a 0.25 M solution of the guest species (NaClO₄, KPF₆ or TBACl) into a solution of the host species. Four aliquots of the guest species were added until a total of 5 equivalents of guest had been added. The following volumes of guest were added: 2 x 5 µL, 2 x 10 µL, 1 x 20 µL. In some cases, four aliquots of another guest species were added to investigate ion-pair recognition. After each addition, the square wave and cyclic voltammograms were recorded monitoring potential changes of the calix[4]diquinone redox waves.

7.2. Job Plots

The stoichiometry of host-guest complexes could be determined from Job Plot analysis of the titration data. This involves plotting the mole fraction of one component against the difference in the parameter being monitored. The mole fraction was calculated by dividing the number moles of the receptor present by the total number of moles in the system. For ^1H NMR titrations the chemical shift change, $\Delta\delta$, relative to the starting chemical shift was calculated for each point and multiplied by the mole fraction. The Job plot was produced by plotting the product of $\Delta\delta$ and mole fraction versus the mole fraction. Figure 7.6a shows one example indicating a 1:1 binding stoichiometry from the maximum at mole fraction 0.5. For UV/visible titrations the maximum absorbance at each point was taken and corrected for dilution by multiplication by (volume of solution/3 mL). The difference in corrected absorbance, ΔABS , was calculated for each data point and multiplied by the mole fraction. This was plotted versus mole fraction to give the Job Plots, like that in Figure 7.6b.

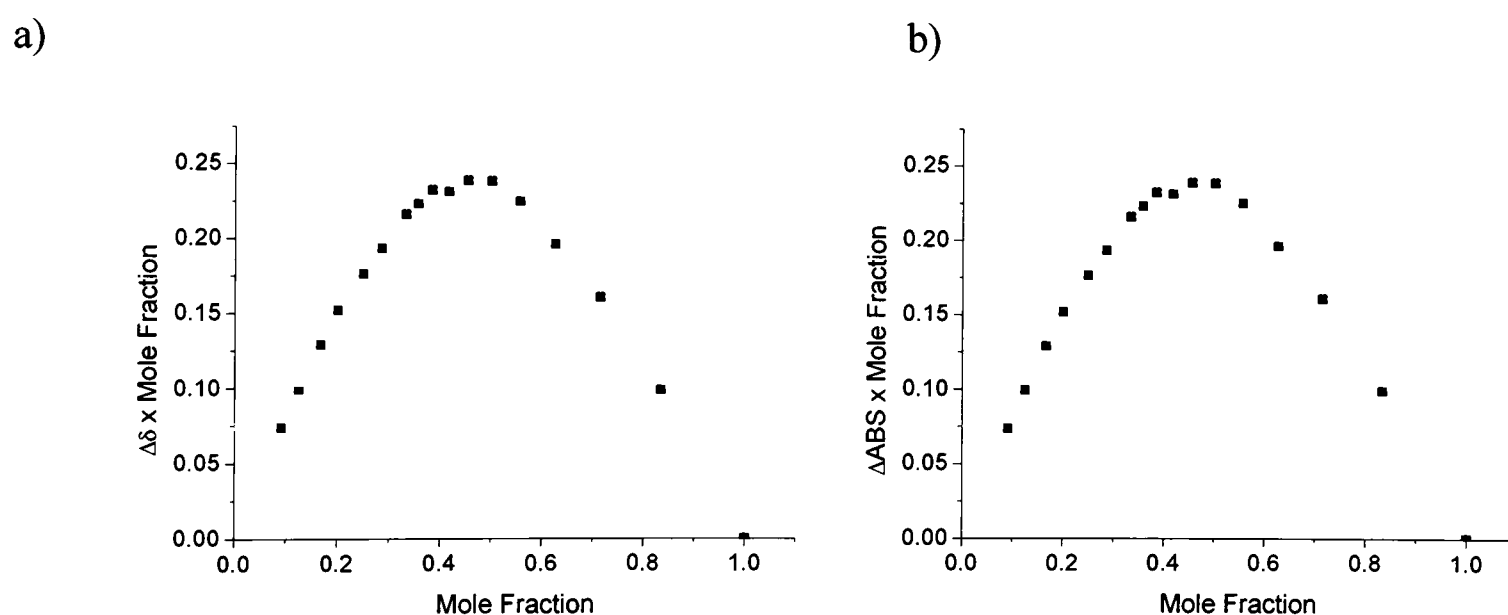


Figure 7.6 Job Plots of a) the ^1H NMR titration data of 1. NH_4PF_6 with TBACl and b) the UV/visible titration data of 1.TBACl with NH_4PF_6 showing a maximum at mole fraction 0.5 corresponding to a 1:1 stoichiometry

7.3. Slippage Kinetic Studies

7.3.1. Slippage

The strategy employed by Stoddart and co-workers to study the kinetics of rotaxane formation by slippage was adapted for these studies.^{3, 4} An equimolar mixture of macrocycle **125** and the

stoppered ion-pair axle (**54.X** or **130.X** where X = Cl, Br, I, PF₆) was prepared in 500 μ L CDCl₃, so that the concentration of each component was 5 mM. The slippage experiments were carried out on a Varian Unity Plus 500 NMR spectrometer, maintaining the temperature at either 298 K or 323 K using the variable temperature probe. The progress of the slippage reaction was monitored by recording ¹H NMR spectra at regular intervals, controlled by a kinetic array, over a period of time. The concentration of the slippage species was determined according to equation (1) by integrating the hydroquinone signals of the slippage species and the hydroquinone signals of the free macrocycle. ¹H NMR spectra were recorded until equilibrium was reached.

$$\frac{\int \text{Hydroquinone}_{\text{slippage}}}{\int (\text{Hydroquinone}_{\text{macrocycle}} + \text{Hydroquinone}_{\text{slippage}})} \times 0.005 = [\text{Slippage}] \quad (1)$$

The concentration of the slippage species was plotted versus time and a number of thermodynamic and kinetic parameters were obtained from the curves. The association constant was determined according to equation (2) from the equilibrium concentrations.

$$K_a = \frac{k_{on}}{k_{off}} = \frac{[\text{Rotaxane}]_e}{[\text{Macrocycle}]_e[\text{Axle}]_e} = \frac{R_e}{M_e^2} = \frac{R_e}{(0.005 - R_e)^2} \quad (2)$$

The rate constant for the slippage process, k_{on} , was determined by fitting the experimental data to the model described by equation (3)⁵ using the non-linear fitting program in Origin.⁶ The initial macrocycle concentration, M_0 , was fixed at 0.005 M and estimated values for the equilibrium concentration, R_e , and rate constant, k_{on} , were inputted into the model. The parameters were varied until the values for R_e and k_{on} converged. The statistical parameter χ^2 was also determined for the fitting process, and this indicated that there was good agreement between the model and experimental data.

$$[Rotaxane]_t = \frac{M_o^2 R_e e^{\left(\frac{k_{on}t(M_o^2 - R_e^2)}{R_e}\right)} - M_o^2 R_e}{M_o^2 e^{\left(\frac{k_{on}t(M_o^2 - R_e^2)}{R_e}\right)} - R_e^2} \quad (3)$$

R_e - equilibrium rotaxane concentration
 M_o - initial macrocycle concentration
 k_{on} - slippage rate constant
 t - time in hours

7.3.2. Slippage_{off}

The rate of slippage_{off} at 298 K was studied using similar methods. 100 μ L CD₃OD was added to an equilibrated mixture of the macrocycle, stoppered ion-pair axle and slippage species in 500 μ L CDCl₃, and ¹H NMR spectra were recorded at regular intervals over a period of time. The amount of free macrocycle was determined by integrating the hydroquinone signals of the free macrocycle and the hydroquinone signals of the slippage species, and spectra were recorded until equilibrium was reached. The rate constant for the slippage_{off} process, k_{off} , was determined by fitting the experimental data to the model described by equation (4), which was modified from equation (3), using the non-linear fitting program in Origin.⁶ The initial macrocycle concentration, M_o , was fixed at the concentration determined prior to addition of CD₃OD and the equilibrium macrocycle concentration, M_e , was fixed at 0.005 M. The value of the initial concentration, R_o , was estimated from the equilibrium concentration of the slippage species in the slippage on experiment above. This parameter and the estimated rate constant, k_{off} , were varied until the values for R_o and k_{off} converged. The statistical parameter χ^2 was also determined for the fitting process, and this indicated that there was good agreement between the model and experimental data.

$$[Macrocycle]_t = \frac{R_o^2 M_e e^{\left[\frac{k_{off}t(R_o^2 - M_e^2)}{M_e}\right]} - R_o^2 M_e}{R_o^2 e^{\left[\frac{k_{off}t(R_o^2 - M_e^2)}{M_e}\right]} - M_e^2} + M_o \quad (4)$$

R_o - initial rotaxane concentration
 M_o - initial macrocycle concentration
 M_e - equilibrium macrocycle concentration
 k_{off} - slippage off rate constant
 t - time in hours

7.4. X-ray Crystal Structures

The data files for X-ray crystal structures in this thesis are attached on a CD. Relevant refinement data are given in the tables below with ORTEP thermal ellipsoid plots.

7.4.1. X-Ray Crystal Structure of Receptor 1

Crystal identification	5503
Chemical formula	C ₅₆ H ₆₄ N ₂ O ₁₀
Formula weight	925.09
Temperature (K)	150
Wavelength (Å)	0.71073
Crystal system	Triclinic
Space group	P-1
<i>a</i> (Å)	13.4651(3)
<i>b</i> (Å)	13.4770(3)
<i>c</i> (Å)	13.6637(4)
α (°)	98.499(1)
β (°)	93.210(1)
γ (°)	98.034(1)
Cell volume (Å ³)	2420.79(10)
Z	2
Calculated density (Mg/m ³)	1.269
Absorption coefficient (mm ⁻¹)	0.087
F ₀₀₀	988
Crystal size (mm)	0.12 x 0.10 x 0.09
Description of crystal	Clear intense yellow block
Absorption correction	Semi-empirical from equivalents
Transmission coefficients (min, max)	0.992, 0.923
θ range for data collection (°)	5.10 ≤ θ ≤ 27.42
Index ranges	-17 ≤ <i>h</i> ≤ 17, -17 ≤ <i>k</i> ≤ 17, -17 ≤ <i>l</i> ≤ 17
Reflections measured	17257
Unique reflections	10797
R _{int}	0.0669
Observed reflections (<i>I</i> > 2σ(<i>I</i>))	5572
Refinement method	Full-matrix least-squares on F ²
Parameters refined	632
Weighting scheme	Modified Sheldrick
Goodness of fit	1.014
R	0.0794

wR	0.205
Residual electron density (min, max) (eÅ ⁻³)	-0.293, 0.436

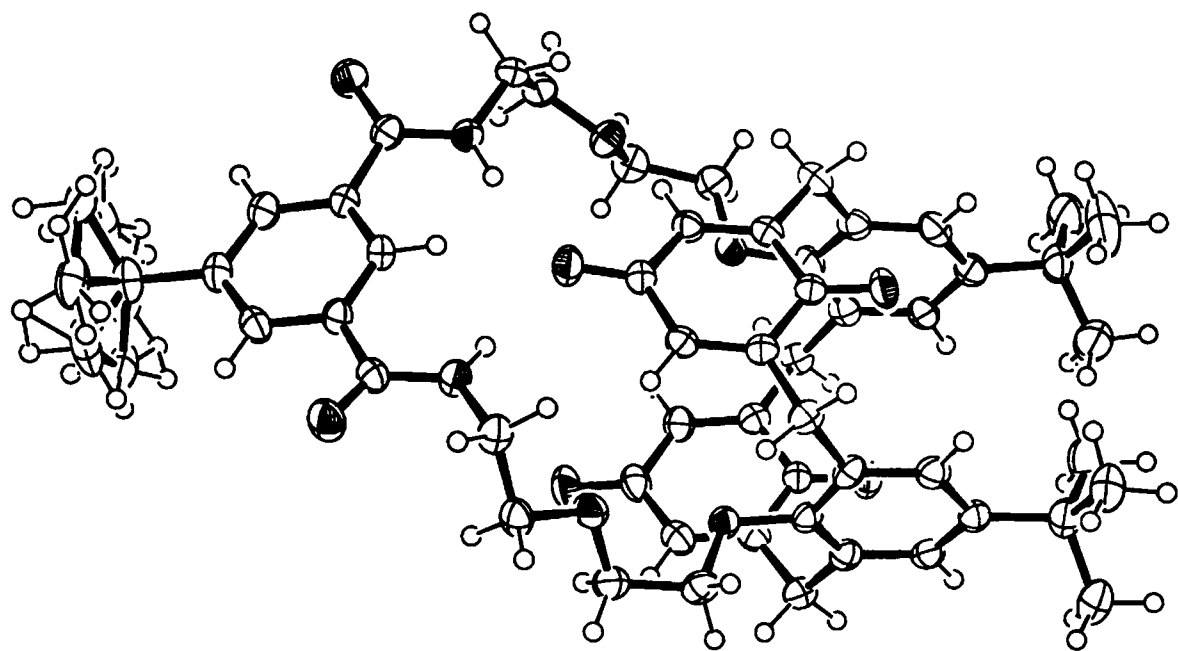


Figure 7.7 ORTEP thermal ellipsoid plot of the single crystal structure of receptor 1 at 50% probability. Solvent has been omitted for clarity

7.4.2. X-Ray Crystal Structure of Receptor 15

Crystal identification	014CJS09
Chemical formula	C ₄₄ H ₄₀ N ₂ O ₁₀ ·0.96(CHCl ₃)·0.54(C ₂ H ₃ N)
Formula weight	893.34
Temperature (K)	150
Wavelength (Å)	0.71073
Crystal system	Triclinic
Space group	P-1
<i>a</i> (Å)	11.5030 (3)
<i>b</i> (Å)	13.4039 (4)
<i>c</i> (Å)	14.5562 (5)
α (°)	76.3517 (14)
β (°)	82.0783 (15)
γ (°)	81.4218 (14)
Cell volume (Å ³)	2144.24 (11)
<i>Z</i>	2
Calculated density (Mg/m ³)	1.384
Absorption coefficient (mm ⁻¹)	0.27
<i>F</i> ₀₀₀	930.900
Crystal size (mm)	0.24 × 0.12 × 0.10
Description of crystal	Yellow block
Absorption correction	Multi-scan DENZO/SCALEPACK ⁷
Transmission coefficients (min, max)	0.85, 0.97
θ range for data collection (°)	5.2 ≤ θ ≤ 27.5

Index ranges	$-13 \leq h \leq 14, -17 \leq k \leq 17, -18 \leq l \leq 16$
Reflections measured	30051
Unique reflections	9701
R_{int}	0.075
Observed reflections ($I > 2\sigma(I)$)	6290
Refinement method	Full-matrix least-squares on F^2
Parameters refined	604
Weighting scheme	Modified Sheldrick
Goodness of fit	1.0
R	0.066
wR	0.175
Residual electron density (min, max) ($\text{e}\text{\AA}^{-3}$)	-0.6, 0.6

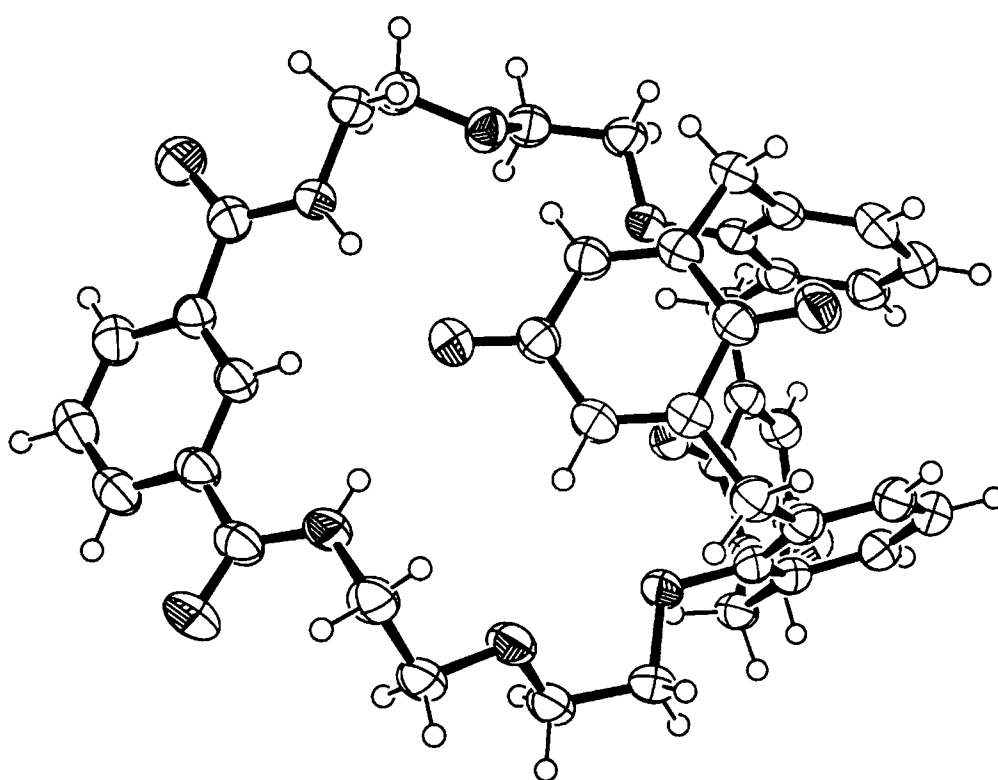


Figure 7.8 ORTEP thermal ellipsoid plot of the single crystal structure of receptor **15** at 50% probability. Solvent has been omitted for clarity

7.4.3. X-Ray Crystal Structure of Precursor **22**

Crystal identification	5378
Chemical formula	$\text{C}_{52}\text{H}_{46}\text{N}_2\text{O}_{10}$
Formula weight	858.94
Temperature (K)	150
Wavelength ($\text{\AA}$)	0.71073
Crystal system	Monoclinic
Space group	$P 2_1/c$
a ($\text{\AA}$)	12.5858(2)
b ($\text{\AA}$)	20.2654(2)
c ($\text{\AA}$)	17.1345(2)

α (°)	90
β (°)	99.8495(5)
γ (°)	90
Cell volume (Å ³)	4305.85(10)
Z	4
Calculated density (Mg/m ³)	1.325
Absorption coefficient (mm ⁻¹)	0.092
F_{000}	1808
Crystal size (mm)	0.28 x 0.34 x 0.42
Description of crystal	Colourless block
Absorption correction	Semi-empirical from equivalent reflections
Transmission coefficients (min, max)	0.96, 0.97
θ range for data collection (°)	$5.0 \leq \theta \leq 27.5$
Index ranges	$-16 \leq h \leq 16, 0 \leq k \leq 26, 0 \leq l \leq 22$
Reflections measured	49220
Unique reflections	10052
R_{int}	0.045
Observed reflections ($I > 3\sigma(I)$)	5775
Refinement method	Full-matrix least-squares on F
Parameters refined	585
Weighting scheme	Chebyshev 3-term polynomial
Goodness of fit	1.1083
R	0.0350
wR	0.0393
Residual electron density (min, max) (eÅ ⁻³)	-0.17, 0.20

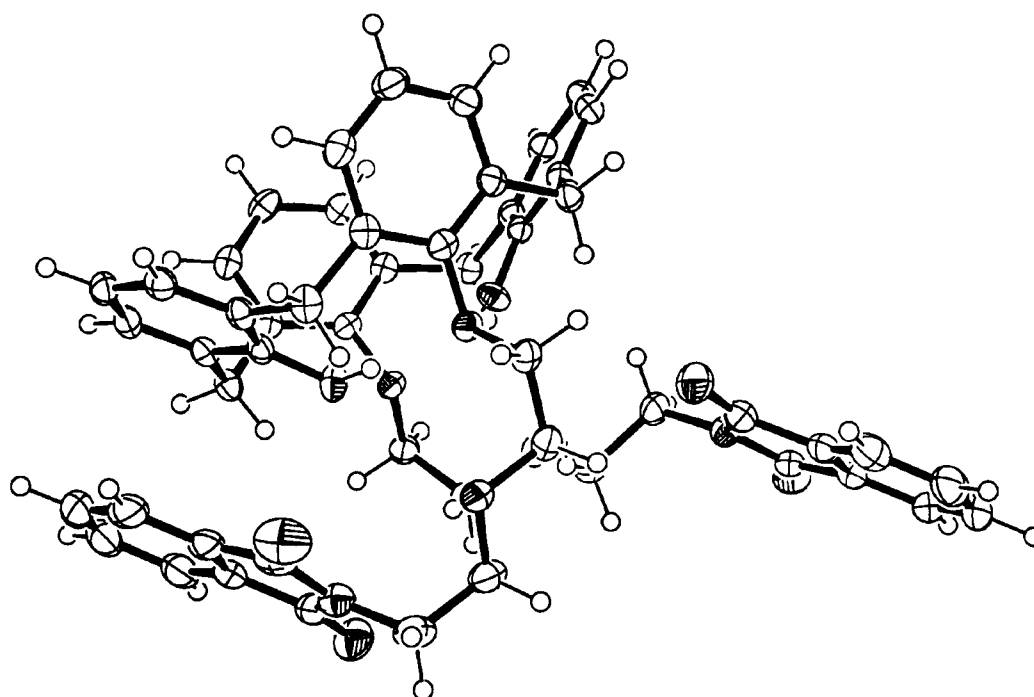


Figure 7.9 ORTEP thermal ellipsoid plot of the single crystal structure of precursor **22** at 50% probability. Solvent has been omitted for clarity

7.4.4. X-Ray Crystal Structure of Macrocycle 27

Crystal identification	5386
Chemical formula	C ₄₄ H ₄₃ N ₃ O ₁₀ ·H ₂ O·0.5(C ₅ H ₁₀ O ₂)
Formula weight	842.92
Temperature (K)	150
Wavelength (Å)	0.71073
Crystal system	Monoclinic
Space group	P21/a
<i>a</i> (Å)	13.3790 (1)
<i>b</i> (Å)	15.0967 (2)
<i>c</i> (Å)	20.7767 (3)
α (°)	90
β (°)	103.7671 (5)
γ (°)	90
Cell volume (Å ³)	4075.89 (9)
Z	4
Calculated density (Mg/m ³)	1.374
Absorption coefficient (mm ⁻¹)	0.10
F ₀₀₀	1784
Crystal size (mm)	0.44 × 0.32 × 0.20
Description of crystal	Colourless plate
Absorption correction	Multi-scan DENZO/SCALEPACK ⁷
Transmission coefficients (min, max)	0.82, 0.98
θ range for data collection (°)	5.0 ≤ θ ≤ 29
Index ranges	-18 ≤ <i>h</i> ≤ 18, -20 ≤ <i>k</i> ≤ 20, -28 ≤ <i>l</i> ≤ 28
Reflections measured	87793
Unique reflections	10734
R _{int}	0.069
Observed reflections (<i>I</i> > 2σ(<i>I</i>))	6235
Refinement method	Full-matrix least-squares on F
Parameters refined	559
Weighting scheme	Modified Sheldrick
Goodness of fit	1.08
R	0.052
wR	0.06
Residual electron density (min, max) (eÅ ⁻³)	-0.58, 0.39

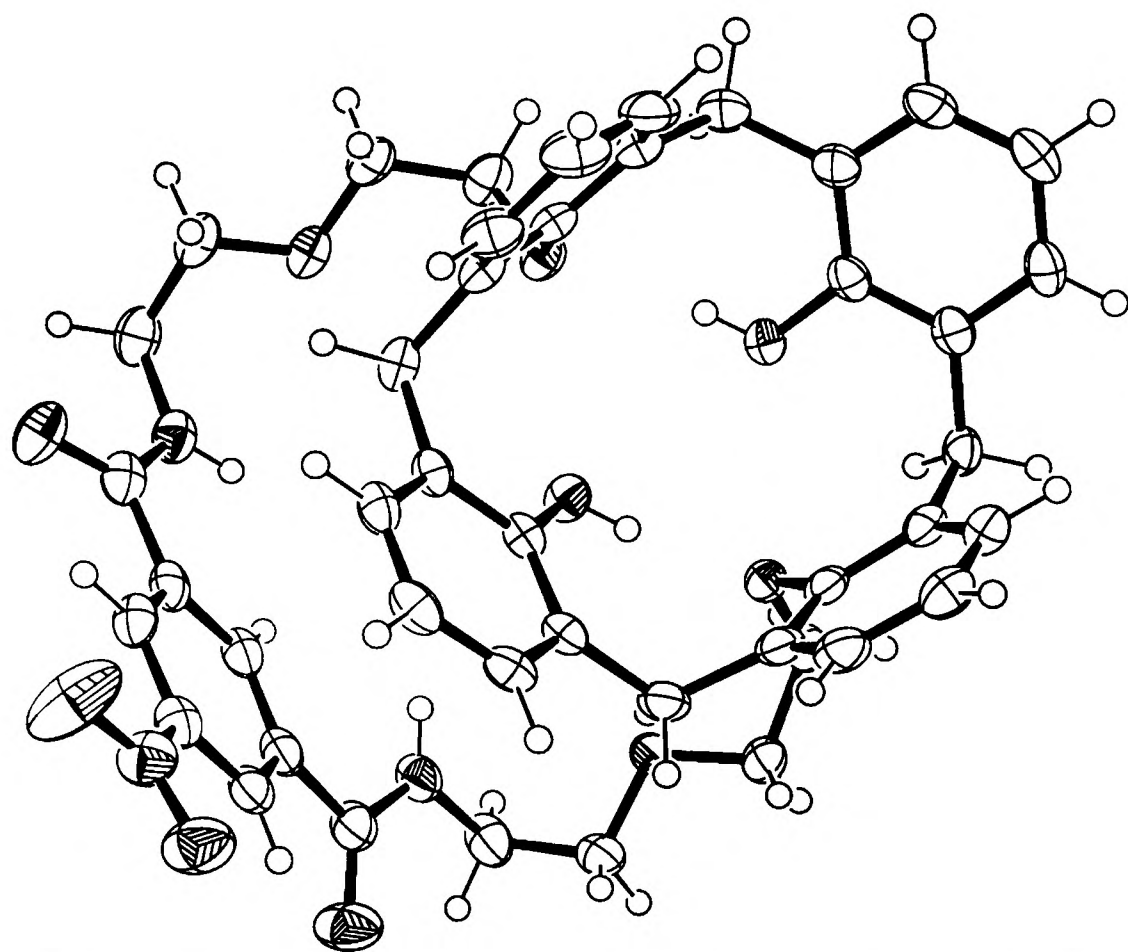


Figure 7.10 ORTEP thermal ellipsoid plot of the single crystal structure of macrocycle **27** at 50% probability. Solvent has been omitted for clarity

7.4.5. X-Ray Crystal Structures of **68.Cl**

CCDC-748852 & 748853 contain the supplementary crystallographic data for these crystal structures. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

	Mo radiation sample	Synchrotron sample
Chemical formula	C ₇₂ H ₈₄ N ₂ O ₁₀ , C ₇₄ H ₇₈ N ₃ O ₂ Cl, 4.58 (CHCl ₃), 3.20 (CH ₃ OH), 1.00 (H ₂ O)	C ₇₂ H ₈₄ N ₂ O ₁₀ , C ₇₄ H ₇₈ N ₃ O ₂ Cl
Formula weight	2881.42	2214.37
Temperature (K)	150(2) K	150(2) K
Wavelength (Å)	0.71073	0.68890
Crystal system	Triclinic	Triclinic
Space group	<i>P</i> -1	<i>P</i> -1
<i>a</i> (Å)	17.8690(2)	17.718(4)
<i>b</i> (Å)	22.3890(3)	22.426(5)
<i>c</i> (Å)	24.6480(4)	22.537(5)
α (°)	113.9572(7)	61.60(3)
β (°)	109.2993(6)	74.13(3)

$\gamma(^{\circ})$	92.5668(6)	85.80(3)
Cell volume ($\text{\AA}^3$)	8319.8(2)	7560(4)
Z	2	2
Calculated density (Mg/m^3)	1.150	0.973
Absorption coefficient (mm^{-1})	0.30	0.08
F_{000}	3038.256	2371.999
Crystal size (mm)	$0.43 \times 0.40 \times 0.31$	$0.50 \times 0.50 \times 0.30$
Description of crystal	Yellow block	Yellow block
Absorption correction	Multi-scan DENZO/SCALEPACK ⁷	Multi-scan DENZO/SCALEPACK ⁷
Transmission coefficients (min, max)	0.76, 0.91	0.62, 0.98
θ range for data collection ($^{\circ}$)	$5.1 \leq \theta \leq 25$	$2.0 \leq \theta \leq 30.1$
Index ranges	$-21 \leq h \leq 21, -26 \leq k \leq 25, -29 \leq l \leq 29$	$-15 \leq h \leq 15, -17 \leq k \leq 20, 0 \leq l \leq 20$
Reflections measured	77523	19176
Unique reflections	27968	11218
R_{int}	0.06	0
Observed reflections ($I > 2\sigma(I)$)	18290	6882
Refinement method	Full-matrix least-squares on F	Full-matrix least-squares on F^2
Parameters refined	2305	1504
Weighting scheme	Chebyshev 3-term polynomial	Chebyshev 3-term polynomial
Goodness of fit	1.81	1.16
R	0.175	0.143
wR	0.187	0.278
Residual electron density (min, max) ($\text{e}\text{\AA}^{-3}$)	-1.23, 1.41	-0.51, 0.88

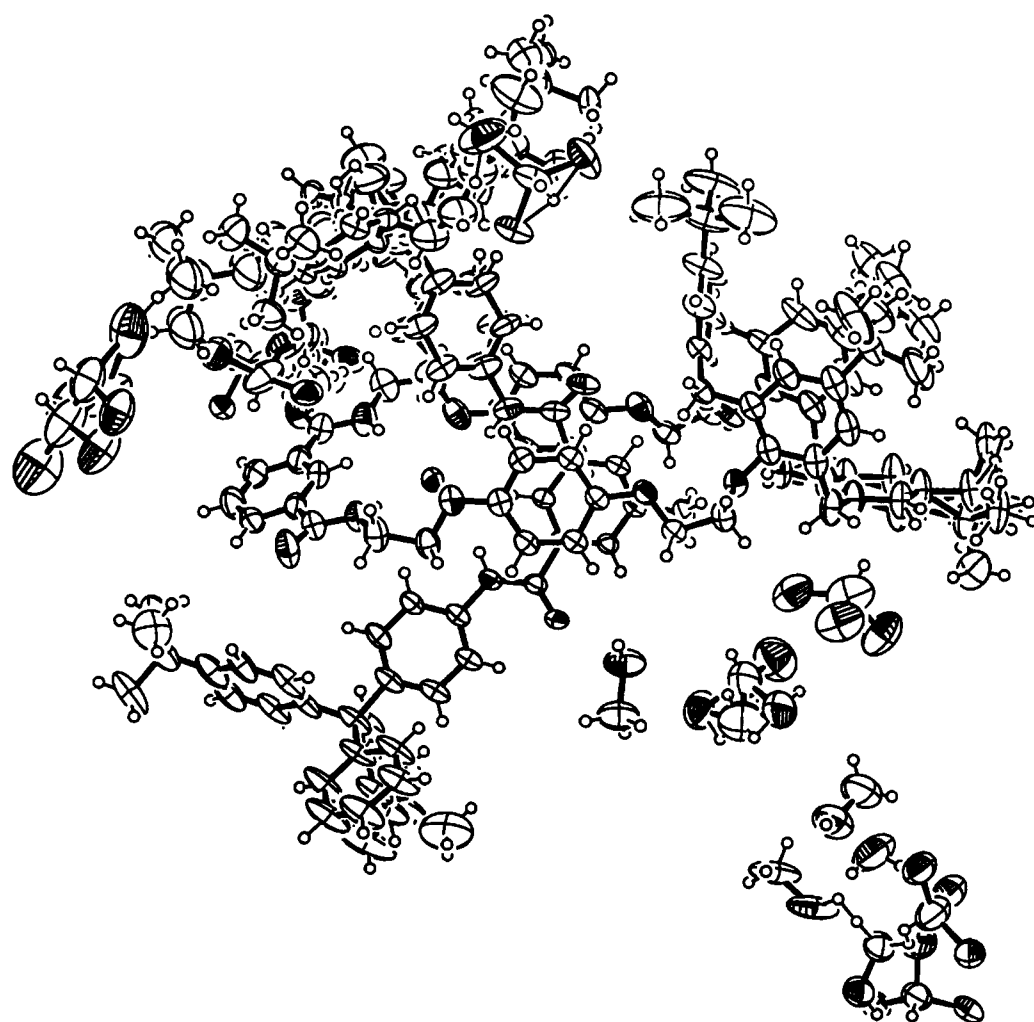


Figure 7.11 ORTEP thermal ellipsoid plot of the Mo radiation single crystal structure of rotaxane 68.Cl at 50% probability.

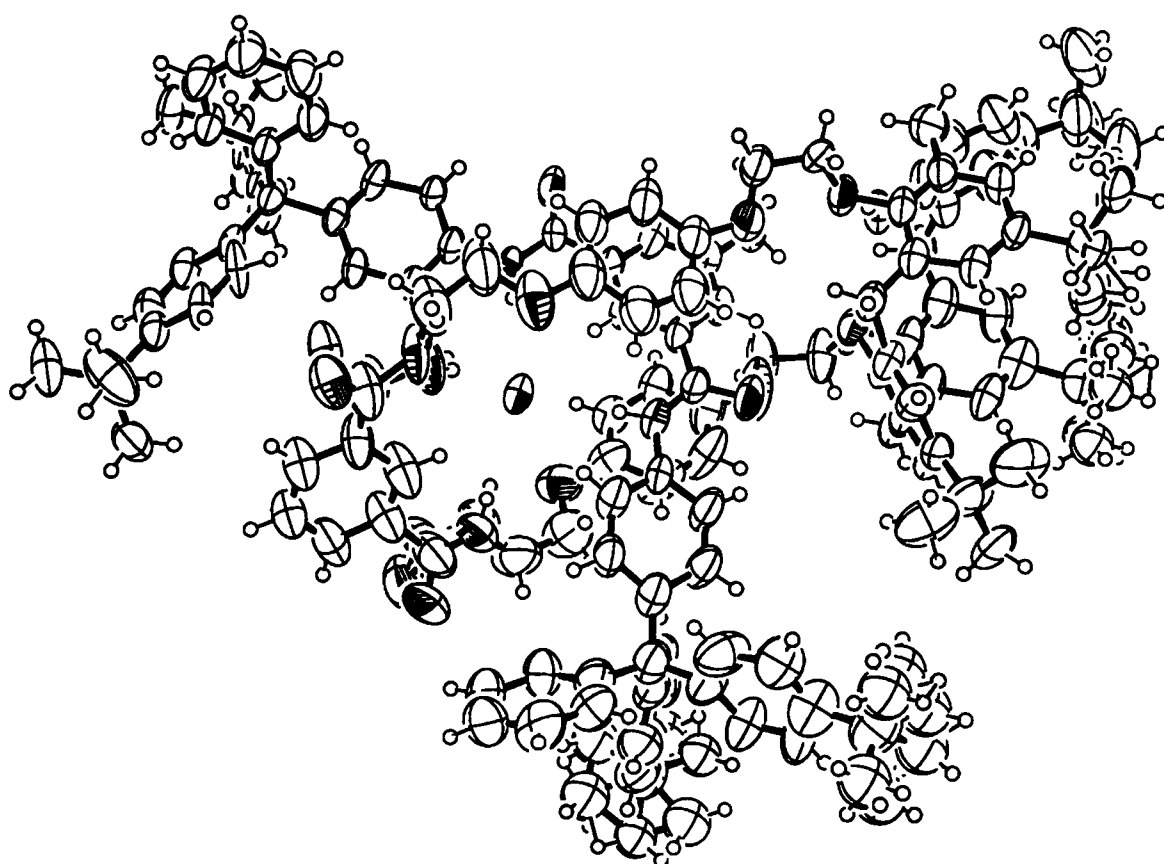


Figure 7.12 ORTEP thermal ellipsoid plot of the synchrotron radiation single crystal structure of rotaxane 68.Cl at 50% probability.

7.4.6. X-Ray Crystal Structure of Macrocycle **125**

Crystal identification	003NGW09
Chemical formula	$\text{C}_{34}\text{H}_{34}\text{N}_2\text{O}_8 \cdot \text{CH}_4\text{O}$
Formula weight	630.69
Temperature (K)	150
Wavelength (Å)	0.71073
Crystal system	Triclinic
Space group	P-1
a (Å)	7.5682 (3)
b (Å)	11.9550 (3)
c (Å)	18.9583 (6)
α (°)	74.9264 (11)
β (°)	83.7027 (13)
γ (°)	80.0389 (14)
Cell volume (Å ³)	1627.54 (9)
Z	2
Calculated density (Mg/m ³)	1.287
Absorption coefficient (mm ⁻¹)	0.09
F_{000}	668
Crystal size (mm)	0.30 × 0.16 × 0.16
Description of crystal	Colourless block
Absorption correction	Multi-scan DENZO/SCALEPACK ⁷
Transmission coefficients (min, max)	0.90, 0.99
θ range for data collection (°)	$1.1 \leq \theta \leq 27.5$
Index ranges	$-9 \leq h \leq 8, -15 \leq k \leq 15, -24 \leq l \leq 23$
Reflections measured	25258
Unique reflections	7373
R_{int}	0.034
Observed reflections ($I > 2\sigma(I)$)	4446
Refinement method	Full-matrix least-squares on F^2
Parameters refined	434
Weighting scheme	Chebyshev 3-term polynomial
Goodness of fit	0.98
R	0.074
wR	0.195
Residual electron density (min, max) (eÅ ⁻³)	-0.41, 0.53

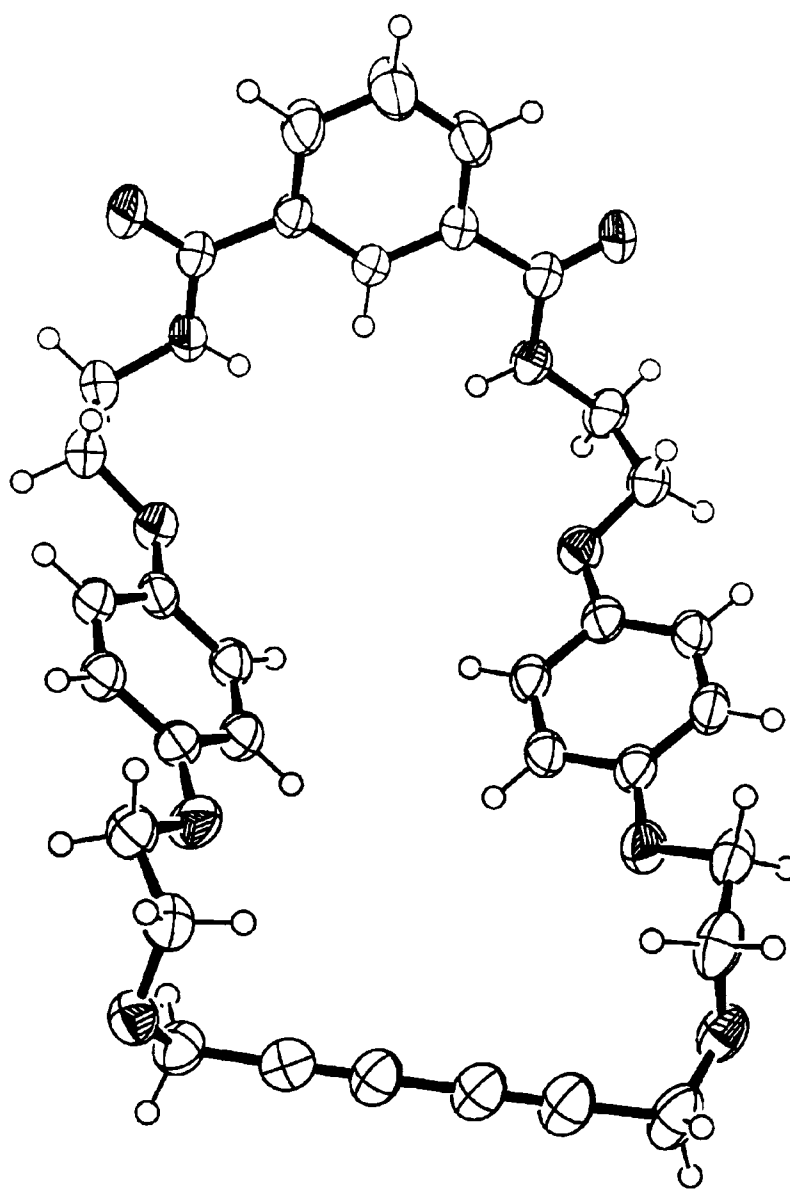


Figure 7.13 ORTEP thermal ellipsoid plot of the single crystal structure of macrocycle **125** at 50% probability. Solvent has been omitted for clarity

7.5. References

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