

Ion-Pair and Anion Recognition by Macrocycles and Interpenetrative Assemblies

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A thesis submitted for the degree of Doctor of Philosophy

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This thesis investigates the design and synthesis of macrocycles and examines their ion-pair recognition, anion recognition and interpenetrative assembly capabilities.

Chapter One introduces the field of supramolecular chemistry. Key concepts in host–guest complexation and self-assembly are outlined, with particular emphasis on the design of host systems for anion and ion-pair recognition.

Chapter Two details the synthesis and binding properties of a heteroditopic 1,2,3-triazole-containing macrocycle that exhibits cooperative ion-pair recognition. Solution and solid-state evidence shows that the triazole motif simultaneously binds anions and cations. The extension of this work towards the formation of interlocked structures containing an expanded heteroditopic macrocycle and threading components is explored.

Chapter Three discusses the design and syntheses of series of electron-deficient macrocycles based on imidazolium, pyridinium and triazole. These are investigated for anion binding ability and assembly of interpenetrative assemblies with electron-rich threading components.

Chapter Four describes research into the formation of interpenetrative assemblies using neutral components. Their design is based around aromatic donor–acceptor interactions and halogen bonding.

Chapter Five presents some conclusions from the research undertaken.

Chapter Six provides titration protocols, Job plot approximations, experimental procedures and characterisation of the compounds described in this thesis.

Appendix details additional X-ray crystallographic data. Data files for X-ray crystallographic structures are enclosed on a CD.

Dedication

TO MY FAMILY, FOR THEIR LOVE ♡

Acknowledgements

Firstly, I would like to thank Professor Paul Beer. The opportunity to do my DPhil in such an excellent laboratory was enhanced by Paul's encouragement and guidance, insight and experience. I would like to thank Henry Fraser for being fun to supervise and his contribution over the course of his Part II project. For funding, thanks to the ICL, EPSRC and St Edmund Hall.

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Simon Picot

List of Abbreviations

Å	Angstrom	A	anion, acceptor
Abs	absorbance	ADP	adenosine diphosphate
AMP	adenosine monophosphate	Ar	aromatic
ATP	adenosine triphosphate	β	overall stability constant
bipy	bipyridine	Boc	<i>tert</i> -butyl carbonyl
br	broad	Bu	butyl
C	centigrade	calc.	calculated
calix	calixarene	cat.	catalytic
CV	cyclic voltammetry/voltammogram	d	doublet
δ	chemical shift	D	donor, dimensional
Δ	change	DABCO	1,4-diazabicyclo[2.2.2]octane
DCE	dichloroethane	DCM	dichloromethane
<i>dec.</i>	decomposition	DIPEA	<i>N,N</i> -diisopropylethylamine
DMF	dimethylformamide	DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid	EDTA	ethylenediamine tetracarboxylic acid
EI	electron impact	en	1,2-ethylenediamine
ESI-MS	electrospray ionisation mass spec- trometry	Et	ethyl
eq	equivalent	FI-MS	field ionisation mass spectrometry
g	gram	Hq	hydroquinone

hr	hour	HR-MS	high resolution (ESI) mass spectrometry
Hz	Hertz	i	iso
Imid	imidazole	Iso	isophthaloyl
ITC	IsoThermal Calorimetry	k	kilo
K	Kelvin	K_a	association constant
J	Joules	J	coupling constant
L	ligand	M	metal, cation, molecular ion, mol dm ⁻³
m	multiplet, milli, meta	m/z	mass/charge ratio
Me	methyl	Ms	mesyl
mol	moles	MRI	magnetic resonance imaging
MS	mass spectrometry	μw	microwave irradiation
n	number	NDI	naphthalene diimide
NMR	nuclear magnetic resonance	o	ortho
OAc	acetate	p	para
pH	-log [H ⁺]	Ph	phenyl
P _i	inorganic phosphate	PP _i	inorganic pyrophosphate
ppm	parts per million	Pr	propyl
Pyr	pyridyl, pyridinium	q	quartet
qn	quintet	Qu	quinone
R	gas constant, variable substituent	ROESY	rotating Nuclear Overhauser Effect
s	singlet, second, secondary	SAM	self-assembled monolayer
STM	Scanning Tunnelling Microscope	t	triplet, time, tertiary
TBA	tetra ⁿ butylammonium	tert	tertiary
TBTA	tris-(benzyltriazolylmethyl)amine	TFA	trifluoroacetic acid
THF	tetrahydrofuran	TLC	thin-layer chromatography
Ts	tosyl, ^p toluene sulfonyl	μ	micro
UV	ultra-violet	v	volume
V	Volt	X	halide, anion

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Chapter 1

Introduction

1.1 Supramolecular chemistry

In 1987, the field of supramolecular chemistry was thrust into the limelight. The Nobel Prize in Chemistry was awarded to Cram,¹ Lehn² and Pedersen³ for “their development and use of molecules with structure-specific interactions of high selectivity.”⁴ These pioneers in the field of “chemistry beyond the molecule” made key advances around concepts such as preorganisation, complementary recognition and selectivity.^{1–3} Over the past three and a half billion years,^{5–7} life has evolved highly advanced systems, inspiring research in many fields. Enzymes catalyse reactions with an efficiency that organic chemists strive to match, such as diffusion-limited triose-phosphate isomerase (Figure 1.1a);^{8–10} supramolecular chemists attempt to emulate functions such as active transmembrane biological pumps,^{11,12} and highly selective ion capture in differentiated sulfate and phosphate binding (Figure 1.11).^{13–17}

(a) *Picture removed*

(b) *Picture removed*

Figure 1.1 Complex organisation and structure in biology: (a) secondary and tertiary enzyme structure of the globule of triose-phosphate isomerase¹⁸ and (b) a DNA zip.¹⁹

Research into supramolecular chemistry can broadly be divided in two: *a*) host–guest complexes, formed between a convergently interacting host and a divergently interacting guest and *b*) self-assembly, where reversible interactions between multiple components result in a thermodynamically favoured structure. Self-assembly is notably used by biological systems to replicate DNA, which then coils and folds into higher order structures (Figure 1.1b).¹⁹ The correct matching of DNA base pairs is essential for efficient replication — an error rate of only 1 in 10^8 is observed in *E.Coli*.²⁰

This introductory chapter will first explore the tools available to supramolecular chemists, followed by key supramolecular concepts. Having established a basis of intermolecular interactions, a brief overview of research using these methods in ion binding and forming interlocked structures will then be presented. Particularly relevant to the research work in this thesis are the topics of anion and ion-pair recognition, and design strategies for the template-directed assembly of mechanically interlocked molecules. Finally, the objectives of this thesis will be discussed.

1.2 Non-covalent interactions

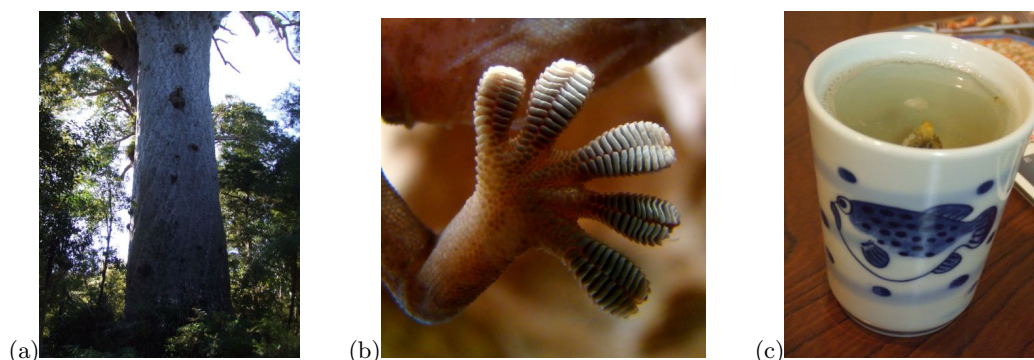


Figure 1.2 Large scale supramolecular forces: (a) Tane Mahuta kauri tree lifting water 50 m by capillary action,^{21,22} (b) geckos stick to walls by London dispersion forces from their feet,²³ and (c) *Fugu* (pufferfish) tetrodotoxin targets the sodium channels causing muscle paralysis

Whilst traditional synthetic organic chemistry prepares molecules by forming covalent bonds, the construction of supermolecules is achieved by supramolecular chemists using non-covalent bonding interactions. This typically encompasses a range of reversible intermolecular interactions of differing strengths that in combination result in a thermodynamically stable association of two or more components. Despite generally being weaker than covalent bonds, multiple non-covalent interactions can achieve remarkable effects (examples in Figure 1.2), drawing variously on reversibility, directionality and solvent effects, as will be described later. Table 1.1 shows some typical strengths of binding for various non-covalent interactions.²⁴

Interaction	Bond strength /kJ mol ⁻¹	Directionality
Ion-ion	100–350	None
Ion-dipole	50–200	Moderate
Dipole-dipole	5–50	Strong
Hydrogen bond	4–60 ^[a]	Variable
Halogen bond	5–50 ^[b]	Very Strong
London dispersion force	<5	None

Table 1.1 Typical bond strengths and directionality for non-covalent interactions. Outlying examples exist as [a] $\text{F}-\text{H}\cdots\text{F}^-$ can reach 120 kJ mol⁻¹ and [b] $\text{I}-\text{I}\cdots\text{I}^-$ is ~ 200 kJ mol⁻¹

1.2.1 Electrostatics

All chemical bonds are electrostatic interactions — a shared electron cloud between two nuclei describing a covalent bond — but the term “electrostatics” is typically used to describe interactions between permanently localised charges. These coulombic attractions comprise, in decreasing strength, ion-counterion, ion-dipole and dipole-dipole interactions.

CATION-ANION

The strength of ionic bonding between formally charged species (Figure 1.3a) is comparable to that of a single covalent bond (150–350 kJ mol⁻¹). Coulomb’s Law of attraction varies inversely with the square of distance and is proportional to charge.

ION-DIPOLE

All heteronuclear covalent bonds contain a directional permanent dipole, as the differing nuclei attract the electron cloud asymmetrically (Figure 1.3b). Comparison of Pauling electronegativities allows the direction of polarisation to be gauged, for example with the integral bonds of organic structures $^{\delta-}\text{C}-\text{H}^{\delta+}$ and $^{\delta+}\text{C}-\text{O}^{\delta-}$.

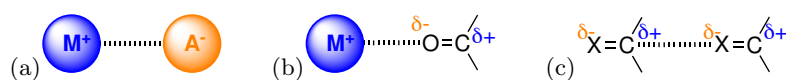


Figure 1.3 Electrostatic attractions: (a) ion-ion, (b) ion-dipole and (c) dipole-dipole

PERMANENT DIPOLE–DIPOLE

Combining two directional permanent dipole components results in a milder strength of interaction, but with more directional organisation (Figure 1.3c).

VAN DER WAALS INDUCED DIPOLE (London dispersion force)

Van der Waals attraction is generated by random fluctuations in the electron cloud resulting in a temporary dipole. This polarises nearby species, creating a weak temporary attraction. The strength of van der Waals attraction increases with molecule size and a correspondingly larger and more polarisable electron cloud, illustrated in the increasing boiling points of linear alkanes with increasing size and number of electrons (Table 1.2).

	Methane	Ethane	Propane	Butane	Pentane	Hexane
Carbons	1	2	3	4	5	6
Electrons	10	18	26	34	42	50
Boiling point	−162°C	−89°C	−42°C	0°C	36°C	69°C

Table 1.2 Increasing boiling points with increasing size of linear alkane illustrate London dispersion forces at work^{25,26}

1.2.2 Three-atom bonding, special dipole interactions

HYDROGEN BONDING

A covalent bond between a hydrogen atom and an electronegative element ($D = N, O, Cl, F$) or system (such as pyridine, pyrimidine, trifluoromethane) exhibits a permanent dipole. The hydrogen terminus is relatively positive and attracts other electronegative species (see Figure 1.4a), acting akin to a proton donated to an electron-rich acceptor (A). Hydrogen bonds exhibit a wide range of bond strengths and directionality, with $A \cdots H-D$ angles ranging from 90° in weak interactions to near 180° in strong interactions. Deoxyribonucleic acid base pairs are held together by hydrogen bonds, such as the glycine–cytosine pair (ADD–DAA) shown in Figure 1.4b.

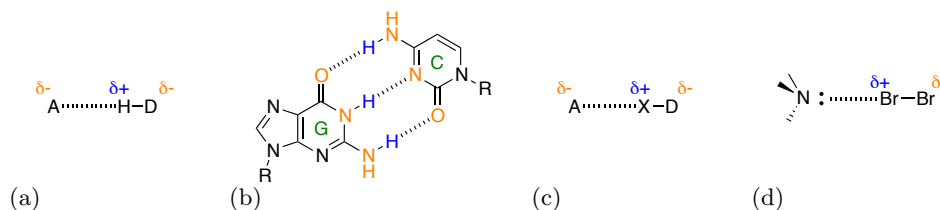


Figure 1.4 3-atom attractions: (a) generic hydrogen bonding and (b) G–C nucleoside hydrogen bonding in DNA. (c) Generic halogen bonding and (d) the first example, $\text{Me}_3\text{N} \cdot \text{Br}_2$

HALOGEN BONDING

Analogous to hydrogen bonding, halogen bonding is described by $\text{A} \cdots \text{X}-\text{D}$, where X = halogen (Figure 1.4c). As part of the $\text{X}-\text{D}$ covalent bond, a relatively positively charged area at the halogen atom terminus is created by the σ^* orbital, termed the σ -hole. Descending the Periodic Table, halogen bonds are progressively stronger as the halogens become more polarisable and less electronegative, with relatively more positive σ -holes. Halogen bonds are similar in strength to hydrogen bonds, but $\text{A} \cdots \text{X}-\text{D}$ angles are always close to linearity, $160\text{--}180^\circ$, due to positioning of the halogen δ^+ .²⁷ The classic $\text{Me}_3\text{N} \cdot \text{Br}_2$ complex has existed for over a century (Figure 1.4d), yet halogen bonding remains an underdeveloped tool in the armoury of the supramolecular chemist.^{28,29}

1.2.3 π -system interactions

For over two decades, the nature of interactions between π -systems was explained using electrostatics, whereby the π - σ attraction overcomes the π - π repulsion in either edge-to-face or offset stacking modes (Figures 1.5a and b, respectively).^{30,31} More recently, literature reports are suggesting that solvation effects and interactions between substituents on the aromatic ring are also significant.^{32,33} The π - π stacking interaction between aromatic systems is now thought to only exist between extended aromatic species, and is overused as an imprecise term for small-scale aromatic interactions.^{34,35} The special case of classic supramolecular face-to-face stacks between alternating electron-rich and electron-poor aromatic components appears to be the exception rather than the norm (Figure 1.5c). In

solvation terms, a study by Iverson and co-workers into complexation between electron-rich 1,5-dialkoxynaphthalene and electron-poor 1,4,5,8-naphthalene diimide found that association was stronger in more polar solvents due to solvation effects. Where electrostatics dominate then the non-polar solvents would be expected to afford the stronger associations.³³

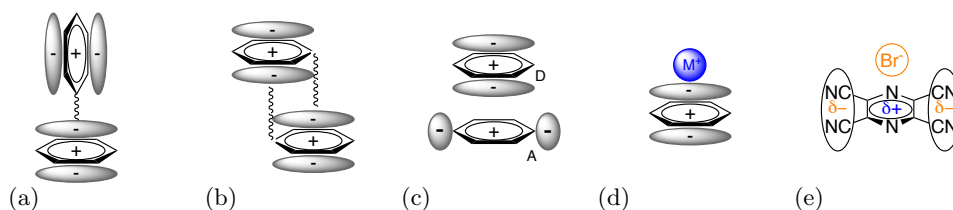


Figure 1.5 π - π stacking interactions in (a) edge-to-face and (b) face-to-face offset modes, and donor-acceptor (c) face-to-face superimposed, as well as (d) cation- π and (e) bromide-tetracyanopyrazine anion- π attractions

CATION- π

Cations are attracted to electron-rich π -orbitals (Figure 1.5d), with bonding enhanced by electron-donating aromatic substituents or greater charge density on the cation, with $\text{Li}^+ > \text{Na}^+ > \text{K}^+$ for gaseous benzene binding.³⁶ Cation- π interactions are thought to provide a key role in protein structure,³⁷ cation transportation channels (e.g. K^+)³⁸ and neurotransmission (*via* acetylcholine).³⁹

ANION- π

Despite repulsion by the π electron cloud, an anion may be more strongly attracted to the proton-rich nuclei when lying above an atomic centre. Aromatic systems that have many electron-withdrawing substituents exhibit a relatively electron-poor π -cloud, inverting the quadrupole. Research by Kochi and co-workers on electron-deficient aromatic centres identified charge-transfer complexes formed upon addition of anions. A new absorption band appeared at 400 nm upon bromide addition to tetracyanopyrazine (Figure 1.5e).⁴⁰

1.2.4 Coordinate bonding

Coordinate bonding between a Lewis acid and base is not strictly a non-covalent interaction but has been exploited extensively in supramolecular chemistry, especially in the fields of anion binding (see Section 1.4) and self-assembly (Section 1.6).

SOLVATION

Solvation effects play a key role in determining the strength of intermolecular association. For electrostatic interactions between a host and guest, both the solvent polarity (dielectric constant) and hydrogen bond donor–acceptor ability play major roles in dictating binding strength. An investigation by Schmidtchen, Sessler and Gale into the chloride affinity of *meso*-octamethylcalix[4]pyrrole found significant solvent-dependent variation, see Table 1.3 for data.⁴¹ The selection of countercation also affected binding strength.

Solvent	TEACl, K_a / M^{-1}	TBACl, K_a / M^{-1}
DMSO	2.3×10^3	2.2×10^5
Acetonitrile	2.2×10^5	2.5×10^5
Nitromethane	1.9×10^4	2.4×10^4
1,2-DCE	4.2×10^4	1.5×10^4
DCM	3.6×10^4	4.3×10^2

Table 1.3 *meso*-Octamethylcalix[4]pyrrole binding strength to chloride is highly solvent dependent with K_a determined by ^1H NMR spectroscopic titrations at 295 K

HYDROPHOBIC EFFECT

The “universal solvent”, water, acts as a particularly competitive solvent, both as an excellent hydrogen bond donor and acceptor.^{42,43} The “hydrophobic effect” arises due to the polarity of the water molecule and its two hydrogen bond donors matched to two acceptors, creating strong solvent–solvent interactions. Upon encapsulation in a hydrophobic (lipophilic) host cavity, water D–A interactions are constrained to a very ordered pattern to optimise the number of enthalpically favourable hydrogen bonds.⁴⁴ The inclusion of a hydrophobic guest displaces water molecules into the free aqueous media, gaining significant entropy and increasing solvent–solvent interactions, thus favourably influencing the overall

host–guest complex formation. Examples can be noted in proteins,^{45,46} surfactants,^{47–49} and encapsulation by cyclodextrins and cyclophanes.^{50,51}

1.2.5 Concepts

From the fundamental building blocks of supramolecular chemistry, there are also some key concepts that expand our understanding of how biological systems have harnessed the power of intermolecular interactions.

Through work on enzymes,^{52,53} Emil Fischer developed a first explanation, “Schlüssel-Schloss-Prinzip” (Figure 1.6a),⁵⁴ for their selectivity. In essence, the enzyme must match the geometrical structure of the substrate like a lock and key.⁵³

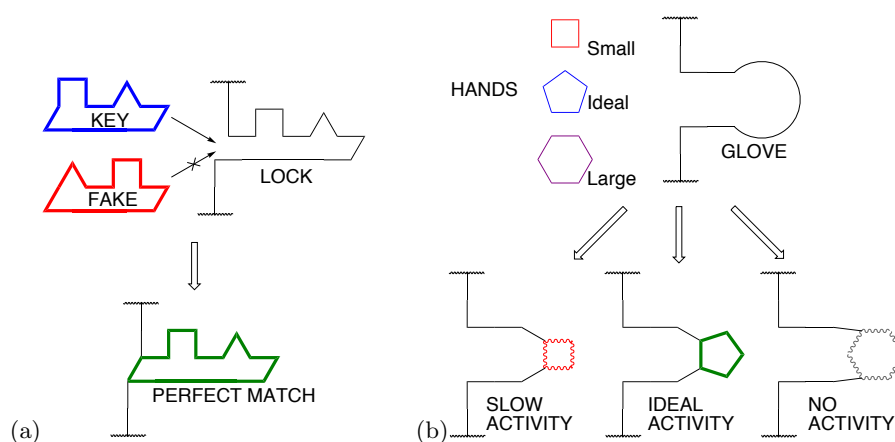


Figure 1.6 Host–Guest interactions in (a) Lock-and-Key and (b) Induced Fit models

Later, however, smaller-than-ideal substrates were found to react, albeit more slowly,⁵⁵ leading to Koshland’s “Induced Fit” or “Hand-in-Glove” principle (Figure 1.6b).^{56,57} The approach of a guest induces a change in a partially flexible host molecule, rearranging itself in order to create the best match to the guest entity. Sub-optimal substrates are bound, but with reduced enzyme functionality.

COMPLEMENTARITY

The successful association between a host and a guest relies on complementary mutual recognition.^{1,58,59} Complementarity also ensures selectivity, where the host preferentially binds the matched guest over sub-optimal alternatives. Enzymes display exceptional selectivity, but an example of complementarity is shown in the artificially matched DDAA–AADD hydrogen bonding association in Figure 1.7a.^{60,61}

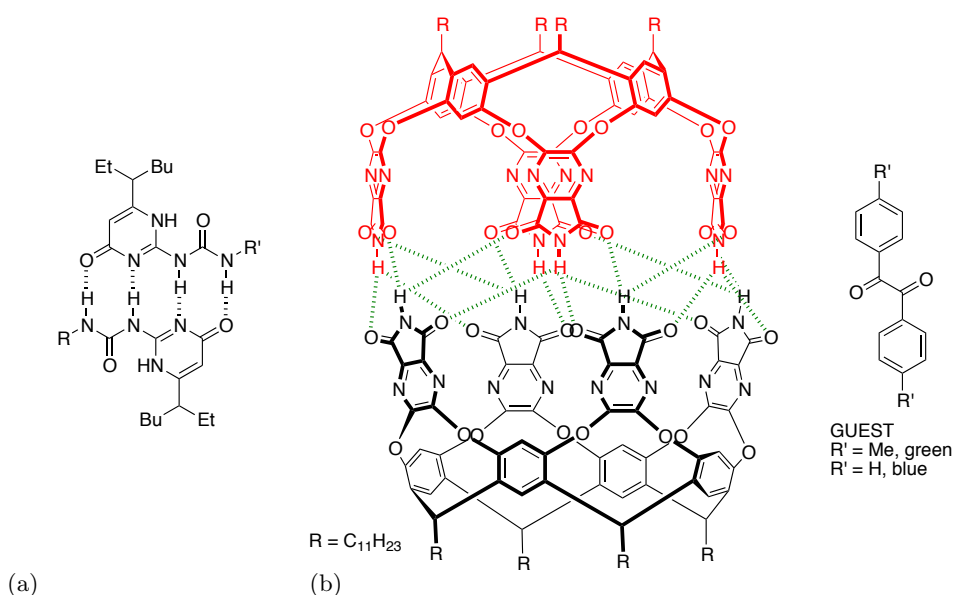


Figure 1.7 Complementarity results in (a) four hydrogen bonds DDAA–AADD and (b) a capsule for “Goldilocks” chromophore sensing of guests

Despite the idealised scenario of a perfect, tight fit, Rebek has instead proposed that for fully-encapsulated guests, an occupation of 55% ($\pm 9\%$) of the host cavity space is optimal.⁶² This was demonstrated in capsules that sense by colour change according to the packing of the guest substrate in the 1,3,5-trimethylbenzene (mesitylene) solvent.⁶³ Excited at 320 nm, the fluorescence of the benzil derivative guests shown in Figure 1.7b are quenched by molecular oxygen, however, in the presence of the capsule, fluorescence is observed. For $R' = \text{Me}$ the *cis*-conformation is enforced giving a green colour, whilst the smaller $R' = \text{H}$ is blue in the *trans*-conformation. In addition, the longer hydrogen bonds formed between the two capsule halves are observed by ^1H NMR spectroscopy as the capsule imide signal is at δ 9.99 ppm and 9.81 ppm for the shorter ($R' = \text{H}$) and longer ($R' = \text{Me}$) guests, respectively.

CHELATE EFFECT

Chelation occurs where more than one point of interaction (denticity) exists between two components. The equilibria in Figure 1.8 demonstrate the increased thermodynamic stability of Cu(II) and Ni(II) complexes with the bidentate *en* ligand over the corresponding complexes with the monodentate NH₃ ligand (Figure 1.8).^{64,65} Both enthalpic and entropic contributions favour the chelated complexes.

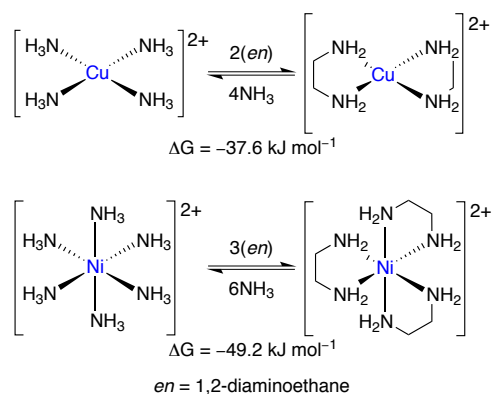


Figure 1.8 The chelate effect is demonstrated with Cu^{II} (*top*) and Ni^{II} (*bottom*) preferentially coordinated by bidentate 1,2-diaminoethane (*en*) ligands over monodentate ammonia ligands^{24,65,66}

MACROCYCLIC EFFECT

Complexes containing macrocyclic ligands are more stable than their acyclic analogues both in thermodynamic and kinetic respects. The thermodynamic stability derives from enthalpic and entropic contributions. Macrocycles are less well-solvated than an oligomeric acyclic analogue (podand¹), with correspondingly fewer molecule–solvent bonds to break during complexation. Entropically, a macrocyclic host has a preorganised guest cavity and therefore loses fewer degrees of freedom upon complexation than a corresponding acyclic ligand. Macrocyclic complexes are kinetically inert due to the rate of dissociation being slow. The first macrocyclic effect was reported by Cabbiness, as shown in Figure 1.9a.⁶⁷ Aqueous Cu(II) was bound by a tetra-aza macrocycle four orders of magnitude more strongly than the comparable acyclic ligand.

PREORGANISATION

According to Cram, the principle of preorganisation suggests that “the more highly hosts

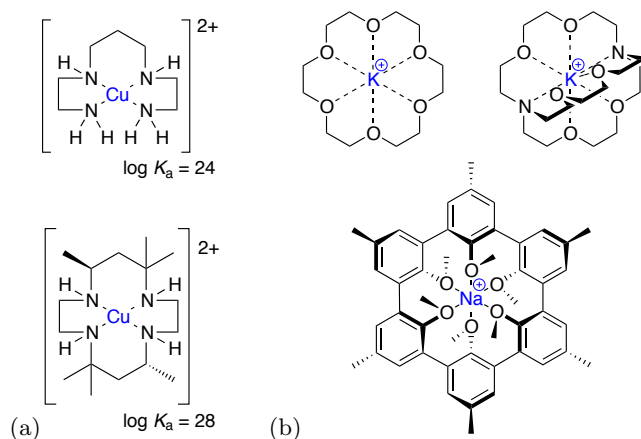


Figure 1.9 (a) The first macrocyclic effect discovered by Cabbiness using Cu^{II} ligands and (b) clockwise, increasingly preorganised hosts: Pedersen's 18-crown-6, Lehn's 2,2,2-cryptand and Cram's spherand for alkali metal binding

and guests are organized [sic] for binding and low solvation prior to their complexation, the more stable will be their complexes.”^{1,68} Therefore in the complexation event, no adjustment of the ligand is required and no thermodynamic penalties are incurred. The concept was demonstrated by a sequence of investigations into increasingly preorganised hosts for cations.^{69,70} Initial developments were by Pedersen into crown ethers that were selective for alkali metals,^{71,72} followed by Lehn's macrobicycle or cryptand that were more preorganised and efficient hosts.^{73,74} Cram's spherands displayed further preorganisation, denticity and restriction on bond rotation (Figure 1.9b)^{75–77} and were so cyclic and preorganised that cation binding relieved the strain of so many proximate lone pairs.^{59,78}

1.3 Importance of cations and anions

Ions pervade the world we live in. For life to have developed from Titan's apolar liquid hydrocarbon lakes,^{79–83} confirmed by the Hubble telescope^{84,85} and *Cassini-Huygens* probe,^{86,87} its use of ions would have to had to overcome the enthalpic challenge of breaking down massive crystal lattices. However, our aqueous environment exists with a wide variety of hydrated ions.^{42,43,88–94} Current research into the recognition of charged species can be

broadly broken down into two approaches: *a)* emulating enzyme functions in Nature, such as transmembrane transportation and selective ion recognition, and *b)* modern-day applications, such as toxic waste clean-up.

1.3.1 Importance of cation recognition and sensing

Cations are essential biologically, as a central component of porphyrin-containing enzymes providing the basis for both photosynthesis in plants and oxygen transportation in red-blooded vertebrates.^{95,96} Magnesium (II)-containing chlorophylls are key visible light-absorbing chemicals in photosynthesis, with the full structure of *chlorophyll a* elucidated by Fleming⁹⁷ in Figure 1.10a.

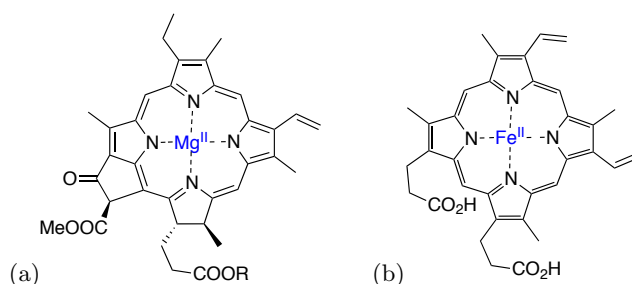


Figure 1.10 Porphyrins in biology: (a) Mg(II) in *chlorophyll a* and (b) Fe(II) in a *haeme b* subunit. Iron(II)-containing haemoglobin's quaternary structure comprises four haeme units — a *haeme b* subunit is shown in Figure 1.10b. Haemoglobin demonstrates positive cooperativity when binding oxygen, as each successive oxygen molecule bound facilitates subsequent binding until all four available *haeme* sites are oxygenated.^{98,99} Metals are also present in other biological enzymes such as in vitamin B₁₂ (cobalt),^{100,101} cytochrome P450 (iron),¹⁰² bacterial iron-sulfur proteins,¹⁰³ and electron-transfer agent plastocyanin (copper).^{104,105}

Another key set of biological processes focuses around concentrations of Na⁺, K⁺ and Ca²⁺ ions, with a concentration gradient across mammalian cellular membranes.^{24,106} These metal ions are key in nerve signal conduction and muscle contraction, with highly

selective transmembrane transportation channels present *in vivo*.¹⁰⁷ The potassium-based regulation of heartbeat generates particular interest,^{108–110} with selective transport of K^+ over Na^+ mandatory to achieve the critical potential gradient for muscle excitation and contraction.^{111,112}

Cation sensing is also important in artificial fields of research. Medically, lanthanide-based contrast agents are used in Magnetic Resonance Imaging (MRI)¹¹³ to help visualise organs.^{114–117} Industrial applications include selective metal extraction from complex ores,¹¹⁸ cleaning up nuclear waste by-products such as $^{90}Sr^{2+}$ and $^{137}Cs^+$,^{119,120} and removing toxic mercury impurities from drinking water.¹²¹

1.3.2 Importance of anion recognition and sensing

The biological inspiration for anion recognition is also significant. 70% of enzymes and substrates, such as the multiply anionic adenosine tri-/di-phosphate (ATP/ADP) system for transporting chemical energy, are negatively charged *in vivo*.^{122–124} As medical understanding has progressed anions have been revealed as key factors, with impaired function of chloride and bicarbonate cross-membrane transportation potentially causing cystic fibrosis,^{125–127} and fluoride used as a drinking water additive for prevention of dental caries¹²⁸ and as a treatment for osteoporosis.¹²⁹ Interestingly, recent research has discovered that dietary inorganic nitrate may form a critical alternative pathway for metabolism and improve mitochondrial efficiency *in vivo*.¹³⁰

Biological applications for the tetrahedral sulfate and phosphate anions are distinct, leading to differentiated proteins that select for each one based on nuances in hydrogen bonding geometry.¹³¹ The *Salmonella typhimurium* sulfate binding protein (Figure 1.11a) acts as a transport receptor for sulfate anions. Sulfate is bound by seven hydrogen bonds, with no cations assisting in complexation.^{14,16,17} As is normal in protein host–guest interactions, the

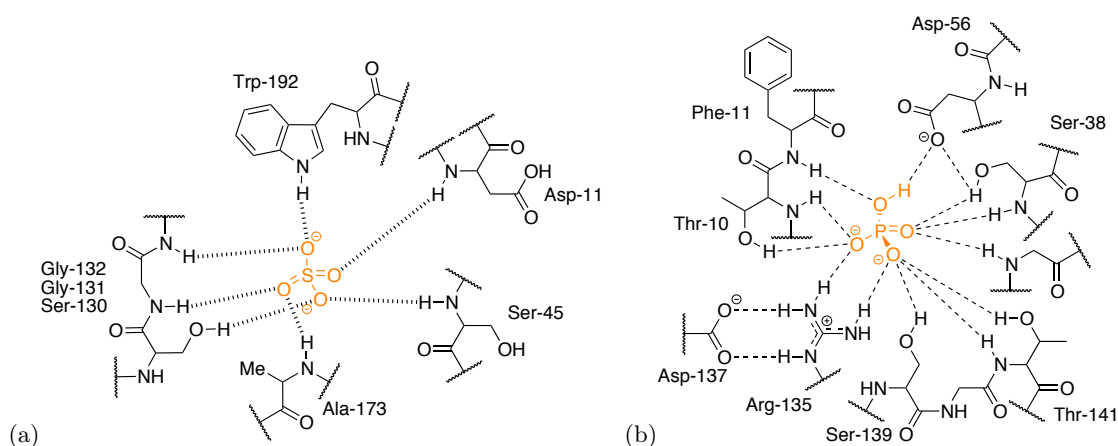


Figure 1.11 Selective anion capture in biology by (a) *Salmonella* sulfate binding protein and (b) *E. coli* phosphate binding protein

hydrogen bonding residues and sulfate anion are contained within the fold of two globular domains, shielded from any competition by water molecules. Aside from its function in ATP/ADP, phosphate is involved in a range of biological functions, including cell membrane formation, bone structure, signalling and concentration gradient maintenance.¹³² Interestingly, the *E. coli* phosphate binding protein in Figure 1.11b contains a cationic residue and a hydrogen-bond acceptor carboxylate, for H_2PO_4^- recognition.^{13,15}

Our ever-increasing population and industrialisation is also generating anions as pollutants. Modern intensive crop farming requires equally intensive fertilisation. Overaddition of nitrates and phosphates results in soil water run-off into local water networks leading to eutrophication.^{133,134} Perchlorates are used as rocket fuel, but also affect the function of the thyroid gland.¹³⁵ Nuclear fission as a power source delivers anionic radioactive pertechnetate ($^{99}\text{TcO}_4^-$), which contaminates groundwater as a β -emitter.¹³⁶ The disaster at the Fukushima nuclear plant also released copious amounts of radioactive β -emitter $^{131}\text{I}^-$ into the environment.¹³⁷ Detecting toxic anions such as cyanide is also required as these anions inhibit *cytochrome c* oxidase function, impairing effective respiration.¹³⁸ Nerve agents such as Sarin may be detected by the fluoride anion that results from hydrolysis.¹³⁹

1.4 Anion coordination chemistry

Whilst Pedersen and Lehn were developing crown ethers and cryptands for cation binding in the late 1960s, initial forays into synthetic anion receptor design were made. The first anion binding macrocycle described by Park and Simmons was shown to bind halides in aqueous solvent media (Figure 1.12a),¹⁴⁰ whereas Lehn produced a bis-tren polyammonium azide-selective receptor (b).¹⁴¹ Despite this early progress, anion coordination chemistry was slow to develop;¹⁴² although progress in the past two decades may be inferred by the explosion in reviews of anion binding.^{142–160}

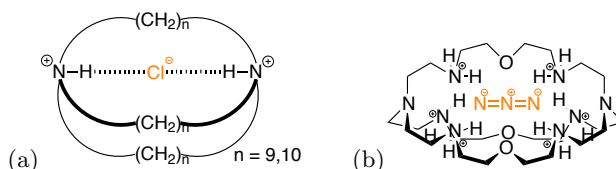


Figure 1.12 Early developments in anion recognition with (a) Park and Simmons' halide-binding macrocycle and (b) Lehn's azide-binding macrobicyclic receptor

1.4.1 Challenges in the recognition of anions

In comparison with cation recognition, anion recognition is considerably more challenging due to a number of factors, including size, geometry, pH dependence and hydration characteristics.

Electrons	Anion	Ionic Radius / Å	Cation	Ionic Radius / Å
10	F ⁻	1.33	Na ⁺	1.02
18	Cl ⁻	1.81	K ⁺	1.38
36	Br ⁻	1.96	Rb ⁺	1.52
54	I ⁻	2.20	Cs ⁺	1.67
10	O ²⁻	1.40	Mg ²⁺	0.72
18	S ²⁻	1.84	Ca ²⁺	1.00

Table 1.4 Ionic radii for isoelectronic elemental cations and anions demonstrate the relatively greater anion size and lower charge density, with all values given for 6-coordinate environments

Table 1.4 illustrates that anions are larger than isoelectronic cations and thus have a lower charge-to-size ratio.¹⁶¹ The wide variety of anion geometries (Figure 1.13) necessitates

tailoring host cavity shapes to match the charge localisation and dipole directionality in a complementary fashion.

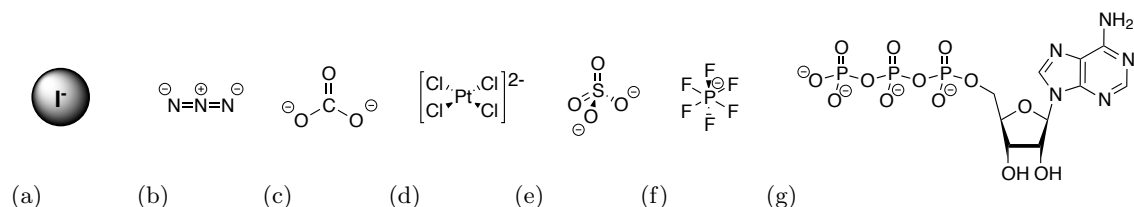


Figure 1.13 Anions exist in a wide variety of geometries: (a) spherical, (b) linear, (c) trigonal planar, (d) square planar, (e) tetrahedral, (f) octahedral and (g) complex

Some anions, such as carboxylate, are also prone to protonation at low pH, potentially resulting in neutral species in the functional window of the desired host (e.g. polyammonium receptors). At physiological pH, phosphate exists predominantly in an equilibrium between the monoanionic H_2PO_4^- and the dianionic species HPO_4^{2-} .

Anions are strongly solvated by protic solvents, especially water; receptors must therefore bind anionic guests sufficiently strongly in order to compete with favourable solvent–anion hydrogen bonding interactions. Under aqueous conditions, the Hofmeister series usefully orders anions from hydrophilicity (highly solvated by water) to hydrophobicity: F^- , OH^- , H_2PO_4^- , SO_4^{2-} > AcO^- , Cl^- , NO_3^- > N_3^- , Br^- > I^- , ClO_4^- , SCN^- .¹⁶² Hydrophobic anions will naturally be bound more strongly in the solvent-excluding cavity of a receptor in aqueous media.

1.4.2 Synthetic anion receptors

The plethora of synthetic anion receptors described in the literature may conveniently be divided into positively charged and neutral receptor systems.

1.4.2.1 Positively charged anion receptors

In order to bind negatively charged species, positively charged receptors were the natural first approach. As in Section 1.2, although electrostatic interactions are non-directional, in combination with hydrogen bonding, a degree of directionality and selectivity can be imparted into the binding motifs. Classic examples from Nature are ammonium and guanidinium in amino acid components.

Lehn's tetraprotonated cage mediated the electrostatic approach through four convergent N–H hydrogen-bond donors (Figure 1.14a). This receptor for spherical anions was size-matched to chloride and bound with higher affinity than the larger bromide anion by at least three orders of magnitude, with iodide only weakly complexed.¹⁴¹ Schmidtchen's elegant cage of quaternary ammonium motifs avoided the pitfalls of the pH-dependence of polyammonium receptors (Figure 1.14b).^{163,164} The hexyl-chain variant proved size selective for bromide, whilst the larger octyl-chain receptor binds iodide selectively in aqueous media. A zwitterionic analogue was developed that showed significantly enhanced halide recognition in water due to the absence of receptor counteranion competition.¹⁶⁵

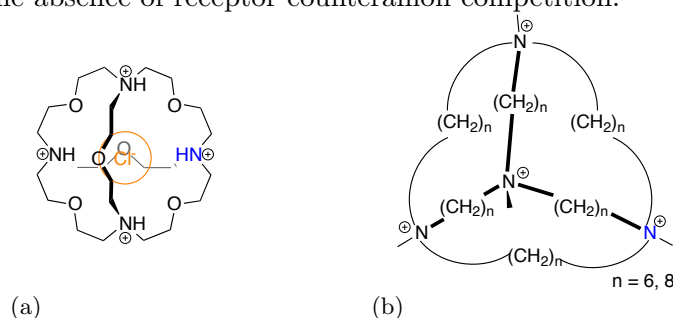


Figure 1.14 Polyammonium binding anions: (a) Lehn's tetraprotonated ammonium cage for chloride, (b) Schmidtchen's quaternary ammonium cage for bromide/iodide

Guanidinium is incorporated into the arginine amino acid and exists as a protonated cationic residue over a wide pH range due to its high pK_a .^{166,167} The guanidinium motif has long been known to be an excellent oxoanion binding motif, with Anslyn's early work on bis-guanidinium systems mimicking the staphylococcal nuclease phosphate binding site.¹⁶⁸ This was succeeded by Schmidtchen's further use of orthogonal guanidiniums in an acyclic receptor for the tetrahedral dihydrogen phosphate, shown in Figure 1.15a.¹⁶⁹

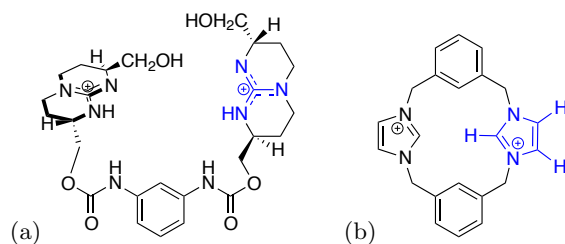


Figure 1.15 Further cationic motifs for binding anions: (a) Schmidtchen's guanidinium host for phosphate and (b) Alcalde's imidazolium cyclophane for phosphate

The five-member heterocycle imidazolium has been integrated into a range of acyclic and macrocyclic receptor structural frameworks that bind anions *via* favourable charge-assisted C–H hydrogen bonding. For example the bis-imidazolium cyclic hosts described by Alcalde exhibit the selectivity trend $\text{H}_2\text{PO}_4^- > \text{F}^- > \text{CH}_3\text{CO}_2^-$ in $\text{DMSO}-d_6$ (Figure 1.15b).^{170,171} Other configurations of multiple imidazoliums exhibit differing selectivities; Sato's tris-imidazolium tripod was found to be chloride-selective over the other halides in CD_3CN , with an association constant of 75000 M^{-1} .¹⁷² Replacing single imidazolium spacers with double imidazolium motifs yielded a tetra-imidazolium cyclophane that was found to selectively bind fluoride over other monovalent anions in $\text{DMSO}-d_6$, with a surprising 1:1 binding stoichiometry given its tetracationic nature.¹⁷³

1.4.2.2 Neutral hydrogen-bond donor anion receptors

The amide backbone of a peptide chain contains excellent hydrogen bond donors and acceptors. Multiple amides were used in tandem in Pascal's early macrobicycle, shown in Figure 1.16a.¹⁷⁴ The isophthalamide motif was first reported by Hamilton when investigating nucleotide recognition,¹⁷⁵ followed by Still when working on peptides.¹⁷⁶ Crabtree's work on its halide binding properties ascertained its *syn-anti* position for dipole minimisation and the conformational change to *syn-syn* for anion binding.¹⁷⁷ The simple acyclic model in Figure 1.16b was found to be chloride-selective over the other halides and the basic acetate anion as well, with strong chloride binding in dichloromethane of 60000 M^{-1} .^{178,179}

Jurczak's 2,6-bis-amide pyridine system shown in Figure 1.16c exhibited the macrocyclic effect, with enhanced and selective binding of acetate by the macrocycle with an association constant of 2640 M^{-1} , against only 45 M^{-1} in DMSO for the acyclic system.^{180–182}

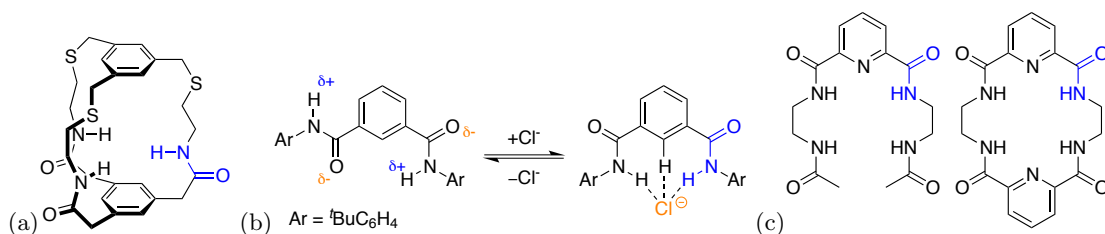


Figure 1.16 Amide-containing hydrogen-bond donor receptors: (a) Pascal's macrobicyclic, (b) Crabtree's chelating isophthalamide and (c) Jurczak's pair of isophthalamide-like systems that exhibit the macrocyclic effect

Building on previous work on polypeptides, where a 2:1 sandwich complex around sulfate was formed,¹⁸³ Kubik recently introduced a bis-cyclic triply-linked polypeptide cage, shown in Figure 1.17a. This complexes sulfate in up to 65% $\text{H}_2\text{O}/\text{CH}_3\text{OH}$, an order of magnitude more efficiently than a mono-linked variant.¹⁸⁴

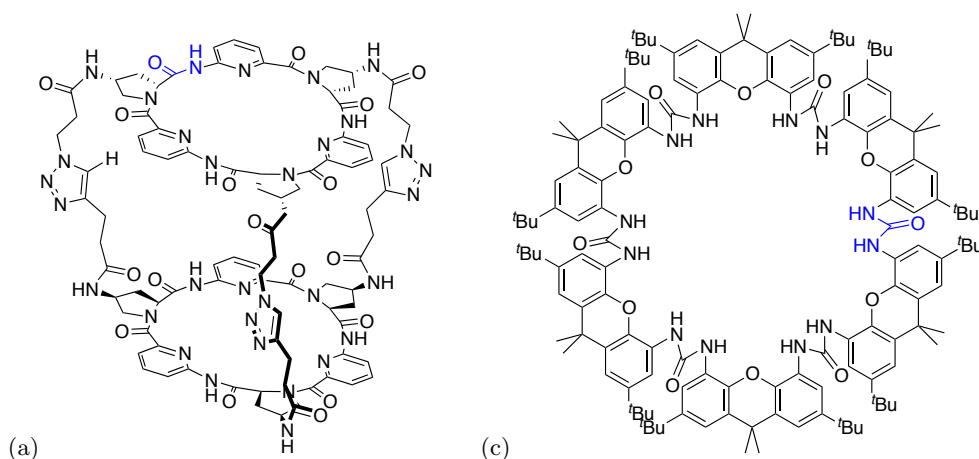


Figure 1.17 Large macrocycles based on neutral hydrogen-bond donor interactions: (a) Kubik's double-decker triazole-linked cyclopeptide sandwiches sulfate and (b) Böhmer's urea-based macrocycle

The urea motif is perfectly set up for Y-shaped oxoanion binding. Böhmer and co-workers have prepared a series of cyclic oligomers containing three,¹⁸⁵ four,¹⁸⁶ six and eight¹⁸⁷ urea groups, with the hexamer featured in Figure 1.17b exhibiting acetate selectivity with two oxoanions bound per macrocycle in 1:3 $\text{THF}/\text{CH}_3\text{CN}$.¹⁸⁸

The pyrrole heterocycle is perfectly set up for anion binding by its aromatic N–H donor motif. Extensive exploration in the area of calix[4]pyrroles has been carried out by Sessler and Gale as these receptors enable four convergent N–H bonds to complex the anion.^{41,189–193} Ease of attaching solubilising groups to the calixpyrrole structural framework has opened up applications in ion-pair cross-membrane transportation, covered in Section 1.5. The strapped calix[4]pyrrole reported by Lee and co-workers shown in Figure 1.18a selectively binds chloride in DMSO-*d*₆ at $\sim 10^5$ M^{−1},¹⁹⁴ around 100-fold greater than the unstrapped analogue.

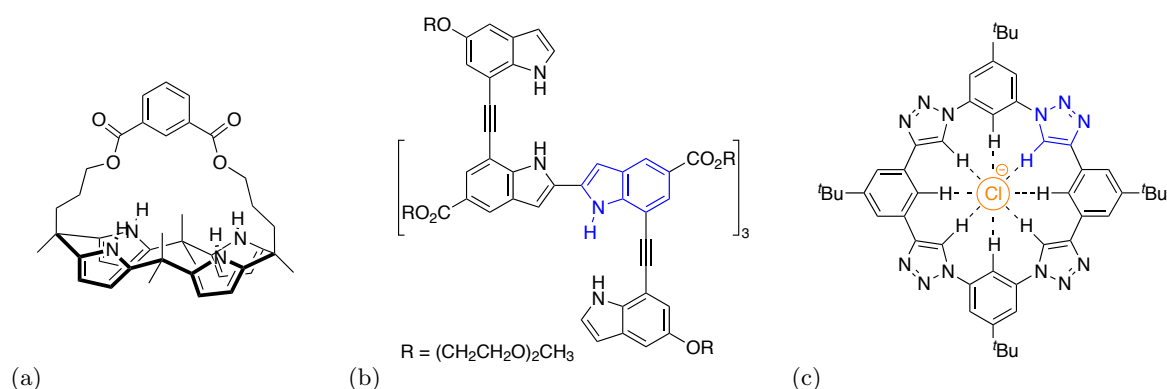


Figure 1.18 Further neutral hydrogen-bond donors: (a) Lee's strapped calix[4]pyrrole for small halides, (b) Jeong's indole oligomer wraps around acetate (c) Flood's preorganised C–H hydrogen bonding triazolophane

Indole is an anion binding motif also used in Nature, included in the tryptophan side chain. Jeong has incorporated the indole motif into oligomers and macrocycles and reported comparative investigations of anion binding.^{195–198} The foldamer shown in Figure 1.18b was found to wrap around the chloride anion in 10% H₂O/CH₃CN, with a binding constant determined by UV-vis spectroscopy of 2.3×10^4 M^{−1}.¹⁹⁵

The use of C–H hydrogen bonding as a sole mode for anion binding has its foundations in the theoretical work and study of crystallographic databases by Hay on alkyl and arene C–H hydrogen bonding.¹⁹⁹ The 1,2,3-triazole motif has been demonstrated to be a potent C–H hydrogen bond donor as has the cationic triazolium analogue. Seminal work by Flood

and Craig^{200,201} developed a series of acyclic and macrocyclic triazole-based receptors for binding spherical anions.^{202,203} The triazolophane shown in Figure 1.18c selectively binds chloride with an association constant of 10^7 M^{-1} in CD_2Cl_2 , an enhancement of six orders of magnitude over the acyclic oligomer.^{203,204}

HALOGEN-BOND DONORS

The halogen bond has been known for a while, but pioneering work by Resnati and Metrangolo was required to highlight its significant appearances in crystal structures.²⁰⁵ With little solution-state evidence, Taylor's progress on tripodal halogen-bonding anion receptors proved key, also demonstrating the selectivity of halogen bonding for halides, even over more basic oxoanions (Figure 1.19). Monitoring of the ^{19}F NMR spectra determined the affinity for chloride to be 10^4 M^{-1} in acetone.²⁰⁶ A subsequent mixed hydrogen- and halogen-binding host was also halide selective.²⁰⁷

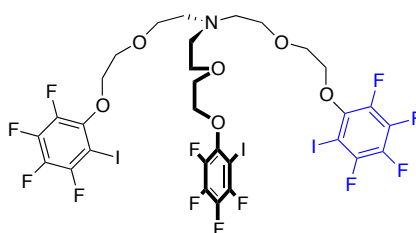


Figure 1.19 Halogen-bond donors in solution: Taylor's tripod halogen bonds to chloride

1.4.2.3 Lewis acidic motifs

Lewis acidic hosts tend to be selective for small, hard anions, with excellent lone pair donating ability, such as F^- , CN^- , OH^- and H^- . As well as metals such as mercury and tin,²⁰⁸ other suitable Lewis acids are located in the Periodic Table as metalloids: boron, silicon,²⁰⁹ and germanium, with such behaviour exploited in semiconductor development.^{210–214}

Boron-based anion receptors began with Shriver's early chelating receptor for methoxide in toluene, as shown in Figure 1.20a. Recent receptors for both fluoride and cyanide demonstrate

increased Lewis acidity by conjugation to cationic substituents: Kawashima's cation-assisted azaborine functions in DMSO/H₂O and Jäkle's thiophene-boron fluorescent sensor in THF (Figure 1.20b and c).^{215,216} Armand's series of functional borates (Figure 1.20d) are notable for their versatility and tunability in usefully binding anions from battery salts such as LiF, Li₂O and Li₂O₂ in DMF.²¹⁷

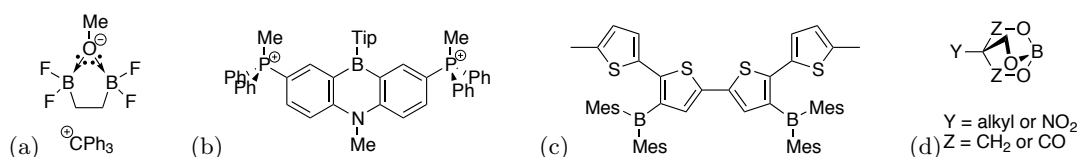


Figure 1.20 Boron-containing Lewis acids: (a) Shriver's chelator, (b) Kawashima's azaborine, (c) Jäkle's fluorescent boron-thiophene and (d) Armand's borates for carrying battery anions

Early examples of metal-based Lewis acid receptors include the mercuraboranes produced by Hawthorne that showed, in the solid state, the mercury centres coordinating to chloride in the plane of the cyclic receptor (Figure 1.21a) and the larger iodide perching peripherally.^{218,219} Further examples of cyclic receptors containing three and five mercury centres were then developed by Shur,^{220,221} as well as Jäkle's mercury-ferrocene receptor that senses anions electrochemically (Figure 1.21b).²²²

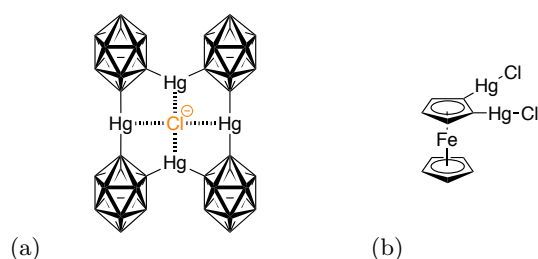


Figure 1.21 Metal-containing Lewis acids: (a) Hawthorne's mercuraborane and (b) Jäkle's chelating mercury-ferrocene receptor

1.4.2.4 Selectivity for particular anions

The following section highlights receptors that exhibit notable selectivity for target anions of varying geometry.

FLUORIDE

Although the most charge-dense halide, binding fluoride can prove difficult: *a*) fluoride is heavily solvated by water and *b*) fluoride's hardness and basicity is sufficient to deprotonate hydrogen bond donors.¹⁵³

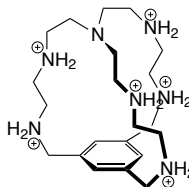


Figure 1.22 Hard anion selection by Steed's fluoride receptor

Inspired by Lehn's small octaaza cryptand, which in the hexaprotonated form selectively binds fluoride,^{223,224} Steed incorporated a phenyl ring at one end for increased preorganisation (Figure 1.22). This cage selectively bound fluoride over chloride by five orders of magnitude in water.²²⁵ The crystal structure of the fluoride cryptate reveals fluoride bound by three ammonium hydrogen bonds and three C–H hydrogen bonds, suggesting that preorganisation and an exact size match for fluoride were the dominant factors.

BROMIDE

Recent work by Kubik explored the triazole group as an amide mimic, replacing half the amides in a cyclic six-component peptide with triazoles to give a C_3 symmetric variant (Figure 1.23b).²²⁶ This receptor bound less strongly than the iodide-selective hexa-amide original, but was found to be bromide-selective in methanol as evidenced by the results of IsoThermal Calorimetry (ITC). The trade-off amongst the halides between solvation by the protic solvent *versus* charge density was influenced by a receptor size-matched to bromide.

IODIDE

As the largest and most diffuse common halide, iodide can either be bound by size-matching the receptor cavity to the large anion or by exploiting protic solvents that competitively solvate harder anions creating an enthalpic barrier to binding. With respect to the former

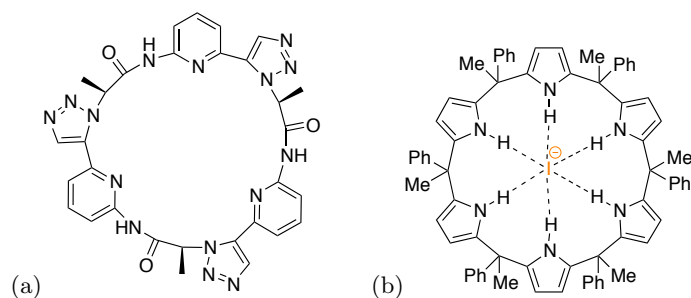


Figure 1.23 Halide-selective receptors: (a) Kubik's bromide-selective triazole analogue of polypeptides and (b) Calix[6]pyrrole — sized for iodide

approach, calix[6]pyrrole (Figure 1.23c) exhibited iodide selectivity, with an association constant of 6600 M^{-1} in aprotic acetonitrile-doped chloroform.²²⁷

AZIDE

To bind nitrogen-containing linear anions, use of azaphilic metal centres is relatively common, but selectivity is challenging to achieve. Li and Li developed a bis-porphyrin-containing cage that used triazole linkers to provide additional C–H hydrogen bonding interactions in acetone, where the cavity size was tailored to ensure optimal Zn–Zn distances for azide (Figure 1.24a).²²⁸

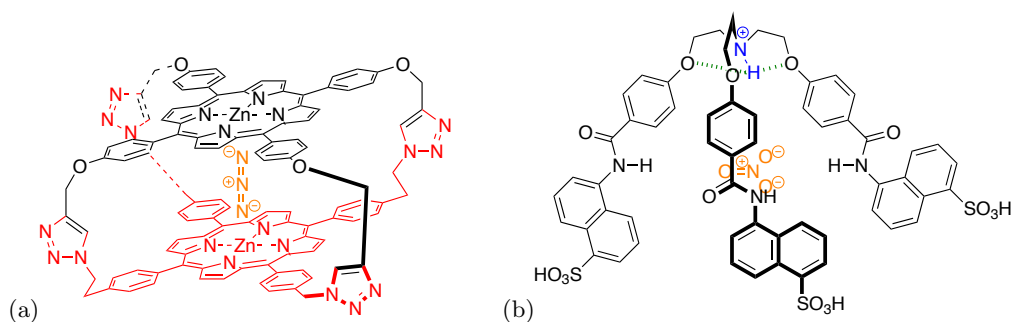


Figure 1.24 Receptors for 1-D and 2-D anions: (a) Li and Li's porphyrin-triazole cage for linear azide and (b) Sun's trisamide tripod with solvent-reversible nitrate encapsulation

NITRATE

Recent work by Sun has designed a tripodal host that incorporates the amide motif and is nitrate-selective in aqueous solvent media (Figure 1.24b).^{229,230} Addition of nitric acid to the sulfonated receptor system protonates the capping nitrogen atom, attracting the nearby

oxygen atoms and preorganising the host for anion binding. The nitrate adduct formed with an association constant of 430 M^{-1} in 20% $\text{D}_2\text{O}/\text{DMSO}-d_6$.

SULFATE

Sulfate recognition was the subject of a recent review, which emphasised its importance with involvement in water hardness and nuclear waste, and biological involvement with sulfate binding proteins (Figure 1.11a).¹⁵⁸ Sulfate has been calculated as theoretically accepting up to twelve hydrogen bond donors from its first solvation sphere (see also Kubik's sandwich, Figure 1.18c), but can also exist in solution as the monovalent hydrogen sulfate.²³¹

Wu and Yang have incorporated the urea motif into acyclic receptors for sulfate.^{232,233} Interestingly, the tris-urea binds sulfate more strongly in DMSO than the tetra-urea oligomer, shown in Figure 1.25a, due to better conformational complementarity. In aqueous mixtures, however, the tetra-urea receptors bind more strongly due to the greater chelate and hydrophobic effects. The sulfate anion was bound in 1:1 stoichiometry with an association constant of $1.27 \times 10^5 \text{ M}^{-1}$ in 10% $\text{DMSO}-d_6/\text{D}_2\text{O}$.

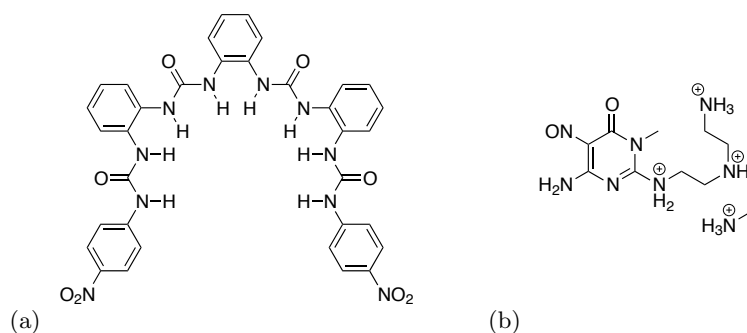


Figure 1.25 Receptors for oxoanions: (a) tetraurea for sulfate and (b) Bianchi and Garzon's polyammonium ADP host

PHOSPHATE SPECIES DISCRIMINATION

Early work on detecting AMP, ADP and ATP was undertaken by Lehn using polyammonium macrocycles through electrostatic attraction and hydrogen bonding, where the dominant electrostatics provided charge-based selectivity with affinities in the order $\text{ATP} > \text{ADP} >$

AMP.²³⁴ Successful recognition of ADP over ATP under aqueous conditions has recently been achieved by Bianchi and Garzon using the receptor shown in Figure 1.25b.^{235,236} This host exploits the combination of electrostatics for capturing the phosphorylated region and complementary pyrimidine hydrogen bonding to ensure selectivity in binding the nucleosides over inorganic phosphate derivatives (P_i , PP_i and PPP_i).

1.4.3 Anion sensing

The integration of reporter groups into anion receptor design enables the anion recognition event to be signalled *via* a macroscopic response. A variety of electrochemical and fluorescent anion sensors have been described in the literature. A recent example of an electrochemical sensor is the tris-ferrocene-urea receptor shown in (Figure 1.26a), which exhibited cathodic shifts in the ferrocene/ferrocenium redox couple of up to $\Delta E_p -190$ mV in the presence of SO_4^{2-} in $CHCl_3$.²³⁷

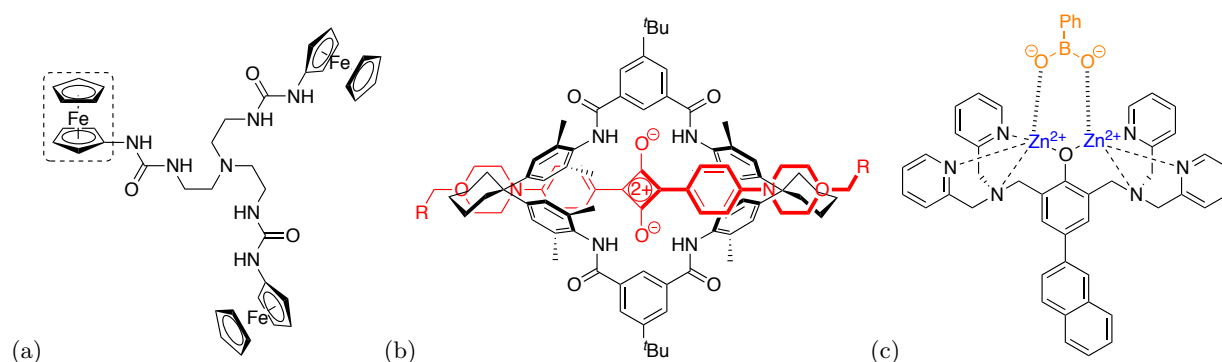


Figure 1.26 Anion sensing by: (a) electrochemistry using a metal centre, (b) a shuttling optical sensor and (c) displacement-induced fluorescence

By incorporating a squaraine dye into a [2]rotaxane, Smith achieved optical sensing of chloride (Figure 1.26c).²³⁸ Chloride addition to the [2]rotaxane in $CDCl_3$ induces shuttling of the squaraine away from the macrocycle, unveiling the dye. Adsorption of the [2]rotaxane onto dipsticks yielded a fully-reversible, quantitative, optical chloride sensor in aqueous media.

Hong's recent diphosphate receptor is based around a dinuclear zinc(II) complex (Figure 1.26b) and displays very unusual selectivity in assays displacing the coordinated boronic acid. This gives a strong fluorescent response with enhanced emission at 440 nm in binding pyrophosphate (PP_i), yet has no effect upon addition of ATP or any other triphosphate nucleobases.²³⁹ A similar pyrophosphate-induced displacement sensor has also been developed in collaboration with Sessler.^{240,241}

1.5 Ion-pair recognition

1.5.1 Two ions, two binding motifs

The progression from monotopic receptors designed for only anion or only cation binding to ditopic ion-pair binding is beneficial due to a reduction in the energy penalty otherwise incurred by separating ions from their counterions.^{118,242,243} Ion-pair recognition is an emerging field in supramolecular chemistry with applications in salt solubilisation and extraction, and through-membrane transport (see Section 1.5.5).^{243–245} Electron-rich cation-binding motifs and electron-deficient anion-binding sites are incorporated into the host design structural framework to produce a heteroditopic receptor.

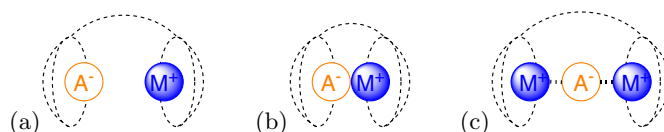


Figure 1.27 Heteroditopic ion-pair receptors with (a) separated ions, (b) a contact ion-pair and (c) a cascade complex

Heteroditopic ion-pair receptors can broadly be broken down into three separate design categories: *a*) receptors for separated ion-pairs (Figure 1.27a), *b*) receptors for contact ion-pairs (Figure 1.27b) and *c*) cascade complexes (Figure 1.27c). Separated ion-pair hosts bind the cation and anion at some distance apart. Contact ion-pair hosts are theoretically more favourable as the heteroditopic binding sites allow close approach of the ions, eliminating the

enthalpic penalty of separation. The third type, a cascade complex, is formed by an anion sandwiched between two cations binding in the cavity.

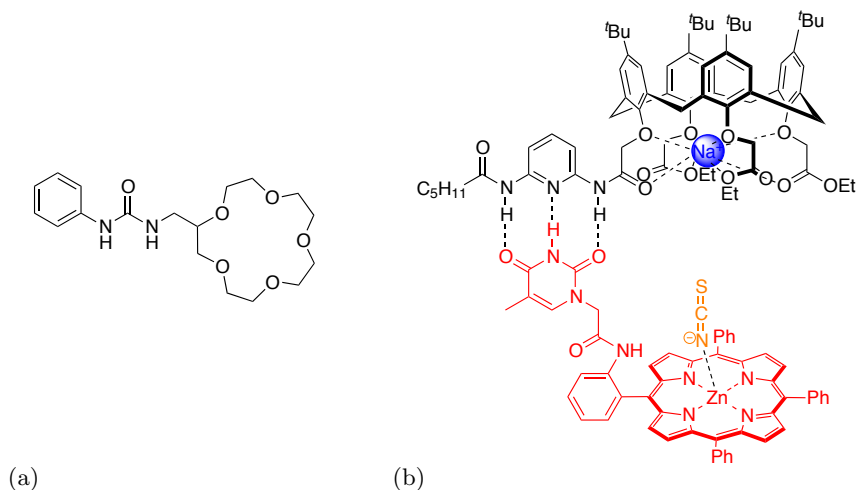
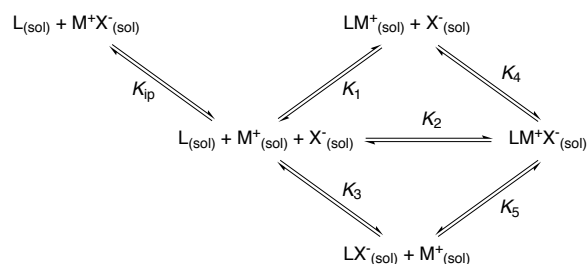


Figure 1.28 Cooperativity in ion-pair binding: (a) between Smith’s crown and urea motifs and (b) cation complexation breaks intramolecular bonding in Reinhoudt’s hydrogen bonding system

Smith and co-workers studied the anion and ion-pair binding affinities of a series of urea and crown-urea receptors. The host system shown in Figure 1.28a was found to display cooperative ion-pair binding in CD_3CN . In the presence of Na^+ , K^+ and Cs^+ , binding of NO_3^- was up to eight-fold stronger than in their absence.²⁴⁶ In general, cooperativity in this system was found to improve with decreasing charge/size ratio of the cation and with decreasing anion basicity.

In Rudkevich and Reinhoudt’s receptor (Figure 1.28b), sodium binding to the multiple calixarene ester groups breaks the intramolecular hydrogen bonds, allowing the two components to associate with hydrogen bond formation DDD–AAA.²⁴⁷ The combined receptor shows enhanced affinity for the SCN^- anion in toluene with K_a of 25000 M^{-1} *versus* only 10 M^{-1} for the anion receptor only (*red*).

The complexity of ion-pair binding is illustrated by the simplified set of equilibria in Scheme 1.1. The formation of the ion-pair complex between the host and cation and anion guests (K_2) has to compete with host–cation complexation (K_1), host–anion complexation



Scheme 1.1 Some competitive ion-pair binding equilibria^{243,248}

(K_3), and ion-pair sequestration (K_{ip}). Ion-pair sequestration is particularly significant in less polar solvents leading to precipitation. If the anion and cation binding events are independent, i.e. non-cooperative, then $K_1 = K_5$ and $K_3 = K_4$, with the overall ion-pair formation (K_2) governed by each event. Where positive cooperativity is observed, ion-pair binding (K_2) is mutually enhanced by the presence of both cation and anion over the sum of K_1 and K_3 , whilst anti-cooperative behaviour results in K_2 being less than their sum.

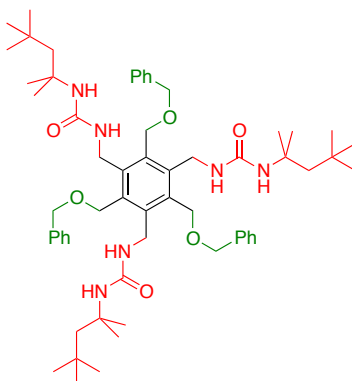


Figure 1.29 An heteroditopic receptor that exhibits anti-cooperative ion-pair binding behaviour

Interestingly, whilst Smith's crown-urea (Figure 1.28a) exhibited enhancement of anion binding for NO_3^- in the presence of cations, a reduction in association constant was observed for the AcO^- anion in the presence of either Na^+ or Cs^+ . Work by Roelens has revealed that binding both parts of the ion-pair may not necessarily be superior to binding just one individual anion.^{249–251} An anti-cooperative receptor is shown in Figure 1.29, where the anion-binding host (without the green components) attracts anions more strongly than the receptor shown and *vice-versa* for the cation-binding host (no red components).

1.5.2 Separated ion-pair receptors

The theme of using initial binding of an ion to preorganise the receptor for the counterion binding event is commonly used. Chung has used a calix[4]arene scaffold to provide initial preorganisation for a lower-rim bis-substituted host selective for copper binding ($K_a = 17200 \text{ M}^{-1}$ in CH_3CN).²⁵² In the absence of Cu(II) , the receptor does not bind anions at all, due to intramolecular hydrogen bonding. Cu(II) coordination preorganises the amine motifs and also renders them more acidic (Figure 1.30a). This results in successful binding of fluoride or acetate [$K_a(\text{AcO}^-) = 159000 \text{ M}^{-1}$ in CH_3CN].

The calix[4]arene structure may be orthogonally functionalised on the upper- and lower-rims. In Wang’s separated ion-pair receptor, the oxacalix[2]arene[2]triazine adopts the 1,3-alternate configuration.²⁵³ The triazine heterocycle provides π -anion binding, combined with a classic azacrown for cation binding. In addition, the $[\text{Host} \cdot \text{Zn}^{2+}]$ complex (Figure 1.30b) binds Cl^- , Br^- and NO_3^- in CH_3CN , none of which were previously recognised in the absence of Zn^{2+} .

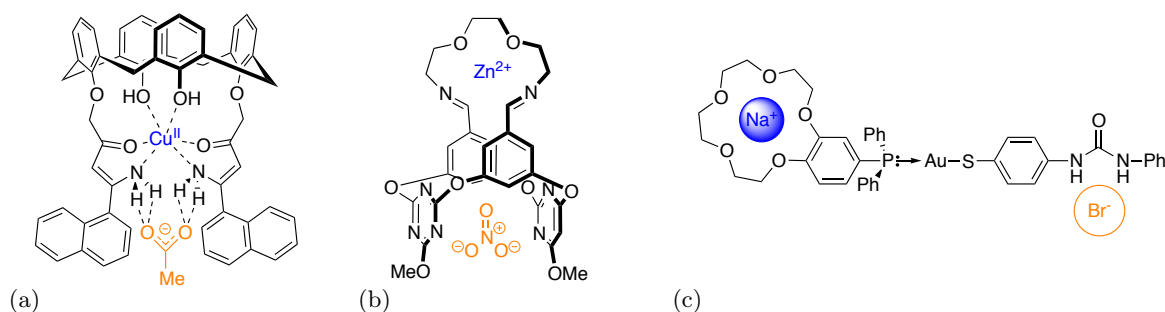


Figure 1.30 Separated ion-pair binding with (a) Chung’s CuX host, (b) Wang’s anion- π system and (c) Yam’s crown-urea system, which exhibits cooperative and anti-cooperative behaviour

An interesting study in cooperativity was carried out on the crown-urea host designed by Yam containing a linear Au(I) spacer (Figure 1.30c).²⁵⁴ The addition of one equivalent of NaClO_4 to the receptor enhanced the binding affinity of the receptor for I^- from 16 to 34 M^{-1} in a $\text{CH}_3\text{CN}/\text{DMSO}$ mixture. However, anti-cooperativity was observed for Cl^- , with diminished binding from 600 to 150 M^{-1} in the same solvent. The tendency for increased cooperativity between larger anions and cations has been studied by Smith.^{242,246,255,256} Smaller, more

basic anions have an increased tendency towards ion-pairing and are sequestered with the cation in crown-type cavities, away from anion-binding motifs.

1.5.3 Contact ion-pair receptors

Smith's contact ion-pair crown-urea receptor (Figure 1.28a) is an example of the host system adopting a pincer position to bring the cation and anion together. Preorganisation, due to initial ion binding, for subsequent enhanced counterion binding has been displayed in a tripodal ion-pair receptor modelled on tren tris-urea systems.²⁵⁷ The capping phosphine oxide faces endohedrally, presenting oxygen lone pairs for metal coordination. Addition of one equivalent of Li^+ cations to the host (Figure 1.31a) wraps the tripod arms for anion chelation, resulting in an eight-fold enhancement in Br^- binding, from 50 to 400 M^{-1} in CD_3CN . In contrast, addition of Na^+ cations has minimal effect on subsequent anion binding.

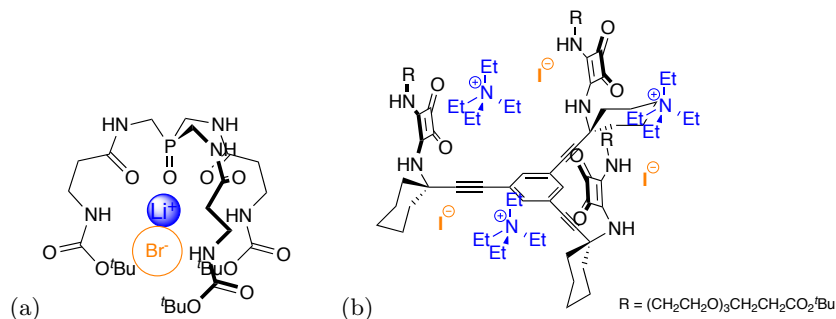


Figure 1.31 Ion-pair binding to (a) Haley and Johnson's phosphine oxide tripod and (b) Costa's tripodal receptor forms a triple contact ion-pair complex

Costa has recently developed a squaramide-based tripod for ion-pair recognition, which is highly unusual in hosting three sets of contact ion-pairs.²⁵⁸ On each arm the squaramide N–H hydrogen bond donors are convergently orientated for anion complexation; on the reverse face lone-pair rich C=O can chelate cations. This results in a C_3 symmetric binding mode with each arm binding a separated ion-pair of NR_4^+I^- , but the host as a complete entity exists with contact ion-pairs in 2.5% $\text{DMSO}-d_6/\text{CDCl}_3$ (Figure 1.31b). Of further interest is the order of binding affinities, $K_{\text{ip},2\text{nd}} > K_{\text{ip},1\text{st}} > K_{\text{ip},3\text{rd}}$, with the implication that the first

ion-pair binding is cooperative for the second ion-pair to bind. But steric effects may hinder complexation in the third ion-pair binding due to the bulk of the guests.

1.5.4 Cascade complexes

Transition metals are often incorporated into supramolecular frameworks to enhance hydrogen bond donation and assist in assembly. In cascade complexes the metals are directly linked to the coordinated central anion inside a host cavity designed to accommodate all three species.²⁵⁹ Early work by Fabbrizzi focused on Cu(II) ions bound by the tren capping motifs (Figure 1.32a), where the bipyramidal Cu(II) ions retained an unsaturated axial binding position and formed the bromide adduct with an association constant of 1000 M^{-1} in aqueous media.^{260,261}

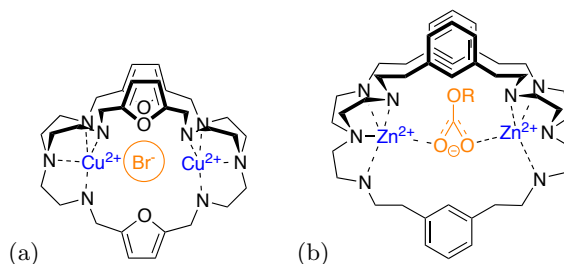


Figure 1.32 Cascade complexes with (a) Cu(II) ions around bromide and (b) Zn(II) ions sandwiching RCO_3^- in a cryptate

The more recent zinc cryptate featured in Figure 1.32b was reported by Lu and is able to fixate atmospheric CO_2 .^{262,263} This cryptate can bind bicarbonates sandwiched by two zinc centres inside the host cavity. Under alcoholic conditions a solvent molecule complexes the zinc on the internal position, but is then available for nucleophilic attack on CO_2 , with subsequent conversion *in situ* to bicarbonate, then the alcoholic ester.

1.5.5 Applications of ion-pair receptors

Applications for ion-pair receptors have centred on their key roles in salt solubilisation and extraction as a means of improving industrial ore extraction and technology to clean-up environmental pollutants and radioactive ions (Section 1.3). In biological mimics, ion-pair receptors are increasingly being developed to emulate transportation across cell membranes by symport and antiport mechanisms.

SALT EXTRACTION/ SOLUBILISATION

It is rare for heteroditopic receptors to display ion-pair binding behaviour in both separated and contact modes, Sessler's calix[4]arene strapped calix[4]pyrrole being one such example.²⁶⁴ This concept was further developed into a receptor that possessed three binding cavities, one for anion binding, one for moderately good caesium cation binding and one for excellent potassium binding.²⁶⁵ This host was shown to bind CsNO_3 in a contact ion-pair manner (Figure 1.33a), but binding of KCl , albeit as a separated ion-pair, was preferred (Figure 1.33b).

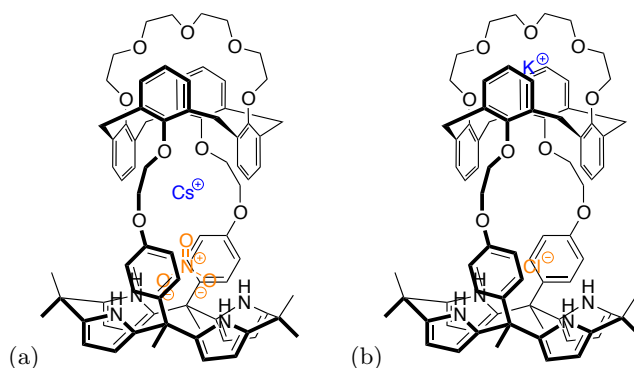


Figure 1.33 Ion-pair extraction of CsNO_3 by (a) contact ion-pair binding, then displacement to form (b) a separated KCl ion-pair

This was then used in a successful liquid–liquid extraction of CsNO_3 from nitrobenzene into water. A nitrobenzene layer of $[\text{Host} \cdot \text{CsNO}_3]$ was placed in contact with an aqueous layer of $\text{KClO}_4(\text{aq})$. The CsNO_3 was transferred into the aqueous layer, whilst the resultant $[\text{Host} \cdot \text{KClO}_4]$ complex was extracted into the nitrobenzene layer. Washing this $[\text{Host} \cdot \text{KClO}_4]/\text{nitrobenzene}$ solution with CHCl_3 and H_2O removed KClO_4 to afford a recyclable host for selective ion-pair extraction.

MEMBRANE TRANSPORTATION

Sessler and Gale have exploited ditopic calix[4]pyrrole-based receptors for membrane ion-pair transportation.^{266–268} Ion-pair co-transportation is advantageous in maintaining the charge gradient across cellular membranes, rather than creating an increasingly unfavourable differential. In the kidneys a Na^+Cl^- symporter acts to reabsorb Na^+ and Cl^- prior to the fluid exiting the body as urine.²⁶⁹ Gale and Sessler's recent collaboration with Lee produced the polyether-strapped calix[4]pyrrole shown in Figure 1.34.²⁷⁰ Two possible cation binding modes exist, either: *a*) a small alkali cation (Li^+ to K^+) bound by the crown, or *b*) a large alkali cation (Rb^+ and Cs^+) bound in the calixpyrrole. These display contact and separated ion-pair binding behaviour respectively. The host was found to co-transport alkali metals with chloride across a membrane and was also able to antiport nitrate ions.

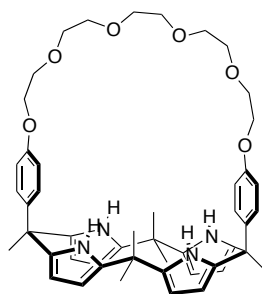


Figure 1.34 Transmembrane ion-pair transportation by a strapped calixpyrrole

1.6 Templated assembly

As defined by Busch “a chemical template organizes [sic] an assembly of atoms, with respect to one or more geometric loci, in order to achieve a particular linking of atoms.”²⁷¹ Templatation is therefore key in directing the assembly of complex structures. Of particular relevance to this thesis, the usage of anionic and cationic templates for formation of macrocycles and interlocked structures will be explored. As an example of a low-yielding untemplated approach, the first [2]catenane was reported by Wasserman in 1960.²⁷² Using a purely statistical approach to cyclise a diester through a large cycloalkane produced a [2]catenane in a mere 1% yield (Figure 1.35a).

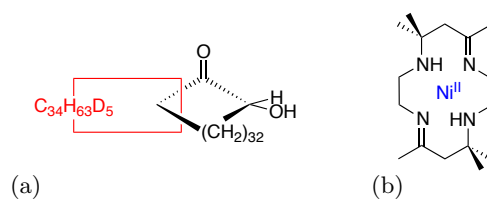
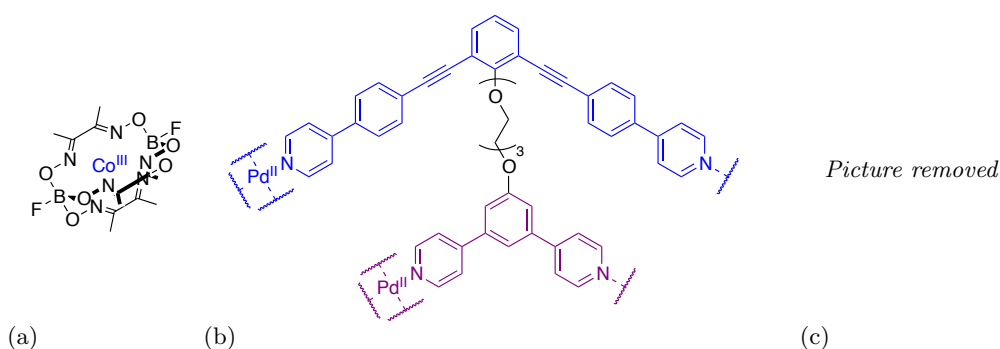


Figure 1.35 An easy choice: (a) an untemplated [2]catenane and (b) a templated macrocycle

An early example of templation that exploits transition metal coordination geometry is shown in Figure 1.35b.²⁷³ Curtis used a central coordinating Ni(II) cation to preorganise 1,2-diaminoethane ligands around the square planar centre. Schiff-base formation with acetone formed a macrocycle despite decomposition of the individual components.^{274,275}

1.6.1 Cation-templated assembly

Cation templation is well-established and has been used to create a range of supramolecular structures, such as macrocycles, cages, helicates and interlocked structures. An early example of metal-templated assembly and synthesis was demonstrated by Rose.²⁷⁶ Three bis-oxime ligands self-arrange octahedrally around a Co(III) centre and upon addition of two equivalents of BF_3 the encapsulation is completed by a double capping reaction to form the macrobicyclic complex shown in Figure 1.36a.



Picture removed

Figure 1.36 Cation-templated structures by (a) Rose using cobalt, and (b) Fujita's $[\text{ML}_2]_n$ Pd(II)-templated cage-within-a-cage, monomer subunit and (c) crystal of the sphere-in-sphere structure²⁷⁷

Some of the most impressive metal-templated superstructures have been developed by Fujita and co-workers. From isolating a Pd(II) square complex,²⁷⁸ rather than a continuous lattice,

research has expanded into development of [2]catenanes,²⁷⁹ a water-soluble octahedral cage,²⁸⁰ a molecular reaction flask that generates unusual reaction selectivities,^{281,282} and spherical molecular cages from 8 Pd(II) centres to 24 and upwards, including a recent stellated polyhedron.²⁸³ Just one of many impressive cages reported is the sphere-within-a-sphere coordination structure. Two ligands that previously have formed $M_{12}L_{24}$ complexes were linked together and in combination with the Pd(II) centres, did so again in an orthogonal manner, with one spherical molecular cage constructed inside another, as illustrated in Figure 1.36b and c.²⁷⁷

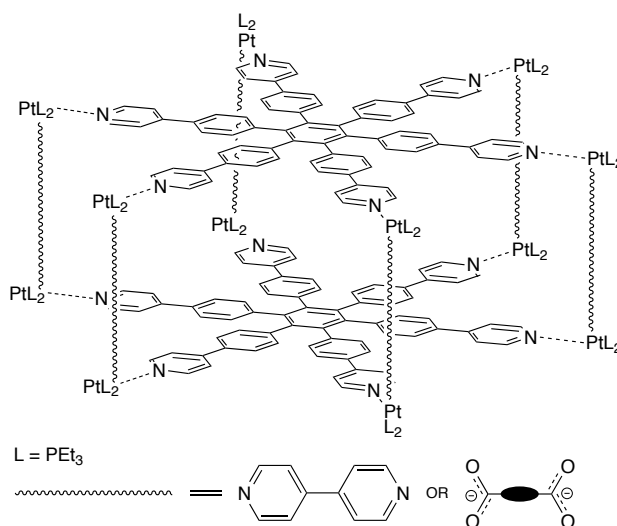


Figure 1.37 Cation-templated formation of a hexagonal prism by Stang

Stang has been developing prisms of increasing complexity and variety, with particular use of the square planar coordination geometry of platinum to rationally design architectures. A combination of a Pt(II) and a NO_3^- template were reported to generate a D_{3h} symmetric nanocage with three linking arms.²⁸⁴ Recently reported was the D_{6h} hexagonal prism shown in Figure 1.37.²⁸⁵ Self-assembly of this 3-D cage around the key Pt(II) centres has been identified with an interplanar spacer of either 4,4'-bipy or one of a variety of rigid dicarboxylate bidentate ligands.

Increasingly advanced architectures are also being constructed from metal-containing multiple-porphyrin systems. Particular emphasis on this area has been made in research by

Anderson with an annulene sandwich,²⁸⁶ a molecular wheel with radial spokes,²⁸⁷ and a figure-of-eight nanoring.²⁸⁸

1.6.2 Anion-templated assembly

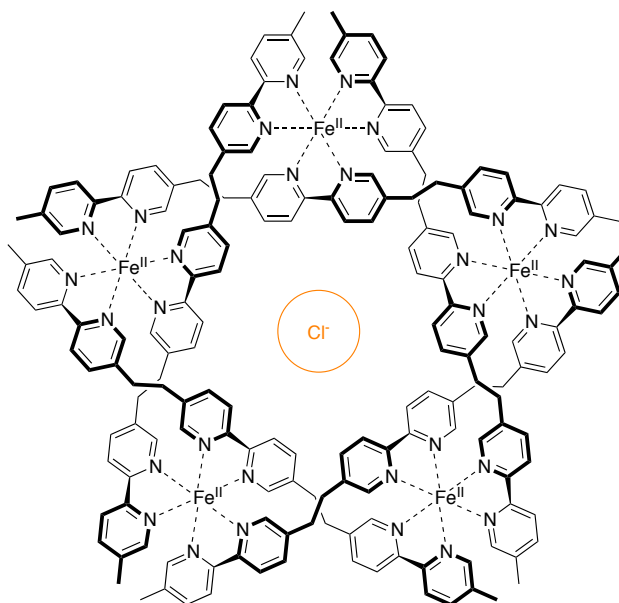


Figure 1.38 An unexpected templation, with Lehn's formation of a pentameric double helicate of ligated Fe(II) ions around a central chloride template

As with anion recognition, the field of anion templation developed more slowly than its cation counterpart — anions lack the ligand field coordination geometries of transition metals, and have small charge-to-radius ratios and high solvation enthalpies.^{142,144,150,151} Despite these hindrances, anions have successfully been used as templates for formation of superstructures. An unusual result in anion-templated synthesis was reported by Lehn in 1996.²⁸⁹ Mixing of iron(II) chloride and a tris-bipy ligand spontaneously assembled into the double helicate structure depicted in Figure 1.38 in quantitative yield. Serendipitous leads in chemistry typically unlock new areas of research; Leigh has recently reported a pentafoil knot based on the templation system uncovered by Lehn.²⁹⁰

Ballester has recently reported pseudorotaxane formation that is templated by linear anions, using a macrocycle with highly rigidified diyne spacers.²⁹¹ In chloroform solution, a heterodi-

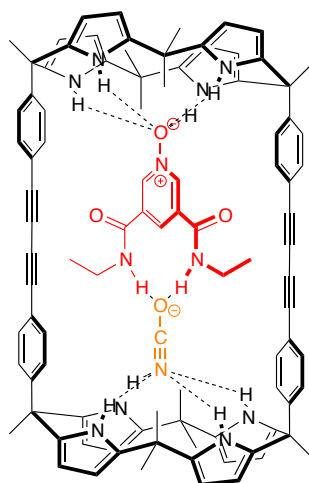


Figure 1.39 Early anion-templated structures: Ballester's pseudorotaxane templated by linear anions

topic pyridine *N*-oxide axle penetrated the macrocycle cavity in the presence of the linear anions: $\text{N}=\text{N}=\text{N}^-$, $\text{S}=\text{C}=\text{N}^-$ and $\text{O}=\text{C}=\text{N}^-$, as shown in Figure 1.39. Anion addition also slowed the pirouetting motion of the thread inside the cavity, with desymmetrisation observable on a ^1H NMR timescale at room temperature.

1.7 Interlocked structures

Significant research efforts have focused on the construction and application of interlocked structures, producing systems that are both aesthetically appealing and functional. Mechanically interlocked structures are inseparable by any component motion, inspiring the potential dynamic functions in molecular switching and machine-like nanotechnological applications, due to the ability of the components to independently slip, slide and rotate.

Biological inspiration has also been a driving force behind the use of interlocked structures in host-guest systems. A brief glance back at the sulfate and phosphate binding proteins of Figure 1.11 shows seven and twelve host-guest hydrogen bonds respectively. Furthermore, the guest species is fully encapsulated by the host and solvent is excluded. Whilst

three-dimensional encapsulation is achievable with a single host component, increasing pre-organisation in the sequence macrocycle $\Rightarrow$ cryptand $\Rightarrow$ spherand demonstrates increasingly strong host–guest association, but also increasingly slow complex formation. By providing separate components to encompass the guest, the kinetic lability is upheld whilst retaining a three-dimensional solvophobic binding cavity.

1.7.1 Pseudorotaxanes, rotaxanes and catenanes

In order to describe the nature of interlocked structures, some definitions and standard nomenclature is required. Pseudorotaxanes, as depicted in Figure 1.40a, are precursors in many routes to forming interlocked structures. Two-component singly-interlocked structures are possible as either [2]rotaxanes or [2]catenanes (Figure 1.40b and c, respectively).

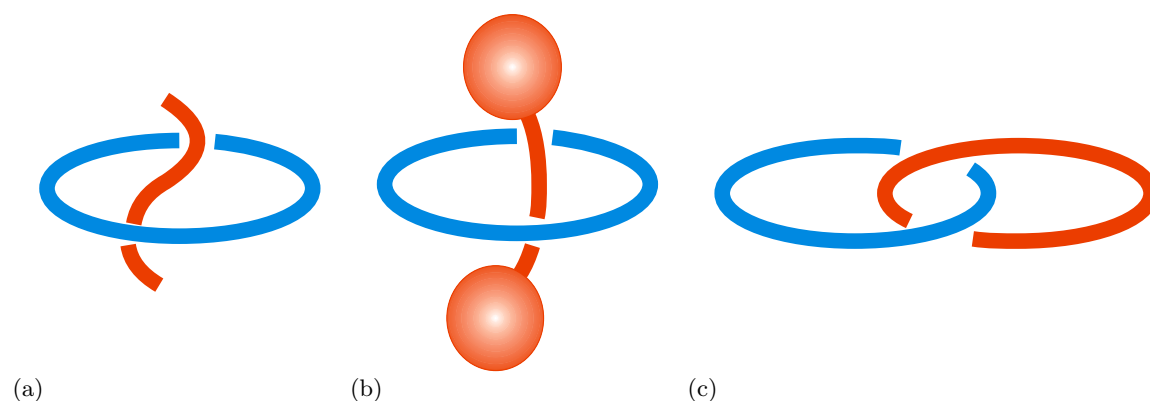
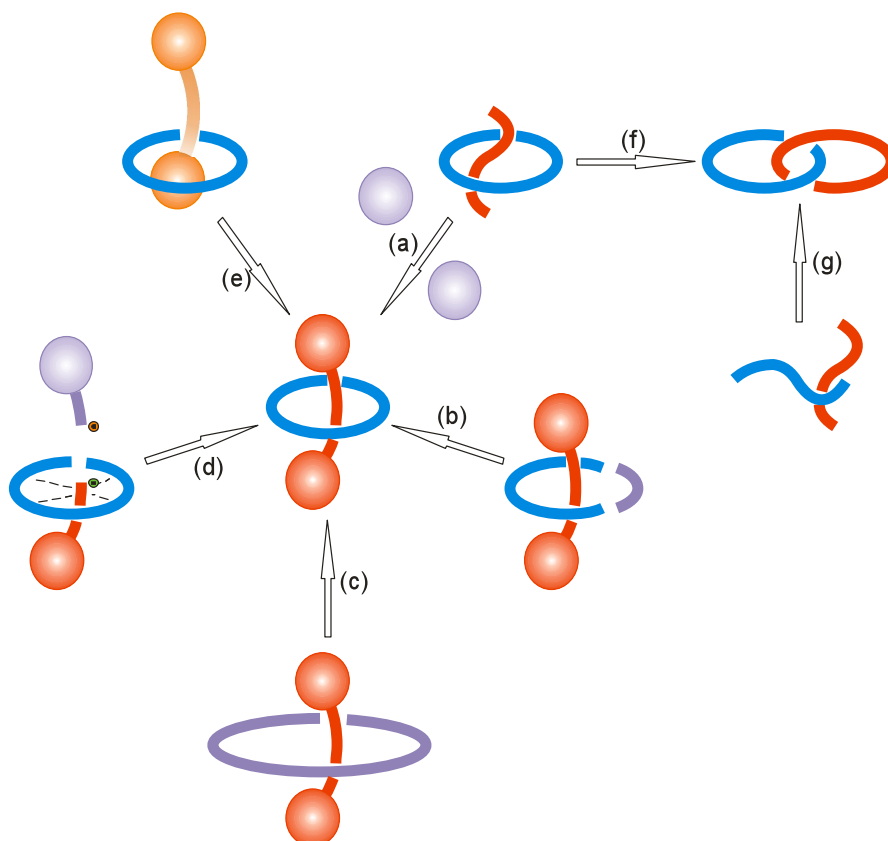


Figure 1.40 Two-component singly-interlocked structures *vis*: (a) a precursor pseudorotaxane, (b) a rotaxane and (c) a catenane

[2]Rotaxanes consist of a macrocycle with an axle threaded through the topological hole in the ring, requiring sufficiently bulky stoppering end-groups on the axle such that the macrocycle is unable to slip off. [2]Catenanes consist of two macrocycles that are mutually threaded through the cavities of each other — interpenetrated and interlocked. For n interlocked components, $[n]$ rotaxanes and $[n]$ catenanes are also possible.

Topologically, a catenane is two *tori* (rings) joined in an interlocked manner such that

they cannot be unjoined by continuous deformation. On the other hand, a rotaxane is topologically two separate components. This topological difference means that numerous synthetic approaches are available to form rotaxanes, contrasted with a mere two methods of catenane formation, as illustrated in Scheme 1.2.



Scheme 1.2 Scheme illustrating methods of forming rotaxanes by (a) stoppering, (b) clipping, (c) slip-and-shrink, (d) trapping and (e) slippage, and catenanes by (f) cyclisation and (g) double cyclisation

Synthetic approaches to rotaxane formation:

- a)* stoppering — from an initial pseudorotaxane, bulky stopper end-groups are tacked onto the ends of the axle to prevent the axle slipping off the macrocycle (Scheme 1.2a);
- b)* clipping — with an acyclic chain (clip) wrapped around a pre-stoppered axle, the chain ends are joined to complete the macrocycle and form the rotaxane (Scheme 1.2b);
- c)* “slip-and-shrink/swell” — the initial pseudorotaxane is between a macrocycle and an axle with insufficiently bulky stopper groups. The macrocycle is then tweaked to shrink in size

until unable to pass over the stopper end-groups (Scheme 1.2c);

- d)* trapping²⁹² — a semiaxle is partially threaded through the macrocycle cavity, followed by fusing another (hetero-)semiaxle component from the other side (Scheme 1.2d);
- e)* slippage — under certain conditions, usually elevated temperature, a carefully sized, stoppered axle may overcome the kinetic energy barrier to thread the macrocycle; reverting to ambient conditions significantly reduces the rate of slippage, isolating the rotaxane. This approach is cautiously placed in the rotaxane-forming category, as de-slippage is possible, but may not be observable over appreciable timescales (Scheme 1.2e).

Synthetic approaches to catenane formation:

- f)* cyclisation — from an initial pseudorotaxane, the ends of the acyclic component are linked around the opposite side of the macrocycle (typically hetero-catenation, Scheme 1.2f);
- g)* double cyclisation — from two acyclic components, both must be cyclised whilst remaining in a nestled position; a template is required (typically homo-catenation, Scheme 1.2g).

1.7.2 Templated formation of interlocked structures

As Wasserman discovered (see Figure 1.35a), attempting the synthesis of interlocked structures using a statistical method is very low yielding.²⁷² Cations and anions have been essential templates to preorganise the components for interlocked structure synthesis.

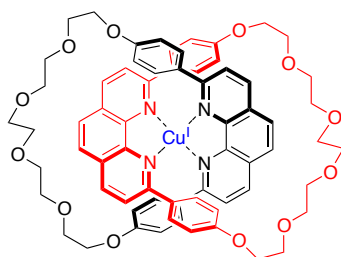


Figure 1.41 Sauvage produced the first catenane using a Cu(I) metal template

The coordination geometry of transition metals was well-suited to early approaches to interlocked structure formation. Sauvage has produced many notable systems centred on the

Cu(I/II) 4/5-coordination axis. The [2]catenane shown in Figure 1.41 was the first catenane to be synthesised using a metal template.²⁹³ Two phenanthroline-containing ligands are preorganised tetrahedrally around the Cu(I) centre, followed by double cyclisation of the long polyether chains to complete the homocatenane interlocked structure. The mechanism of action in forming the catenane was likened to that of DNA gyrase, which wraps DNA and cuts/restitches it to release coiling tension.

The nucleophilicity of anions has been exploited by Vögtle in the “trapping” method of interlocked structure synthesis.^{292,294} Coordination of a phenoxide semiaxle threaded through the macrocycle cavity presents the nucleophile on the opposite side from the bulky mono-stopper. Approach of a suitable electrophile, shown in Figure 1.42, allows the labile benzylic bromide to be displaced by π -assisted S_N2 to form a [2]rotaxane.

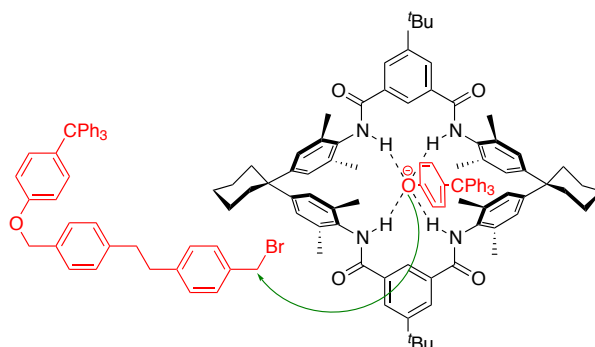


Figure 1.42 Vögtle “traps” the phenoxide nucleophile in the cavity before rotaxane formation

Beer has produced significant work on anion-templated interlocked structures, from the first chloride-templated pseudorotaxane,²⁹⁵ to the [2]rotaxane shown in Figure 1.43a²⁹⁶ and a [2]catenane.²⁹⁷ The pyridinium thread forms a tight ion-pair with the anionic template, mediated by hydrogen bonding, with further complexation of the otherwise coordinatively unsaturated chloride anion by the macrocycle isophthalamide hydrogen bond donors. Additional intermolecular interactions within the [2]rotaxane are C–H $\cdots$ O hydrogen bonds between the *N*-methyl pyridinium and the macrocycle polyether chain, and aromatic donor–acceptor interactions between the electron-rich macrocycle hydroquinones and the electron-poor pyridinium thread.

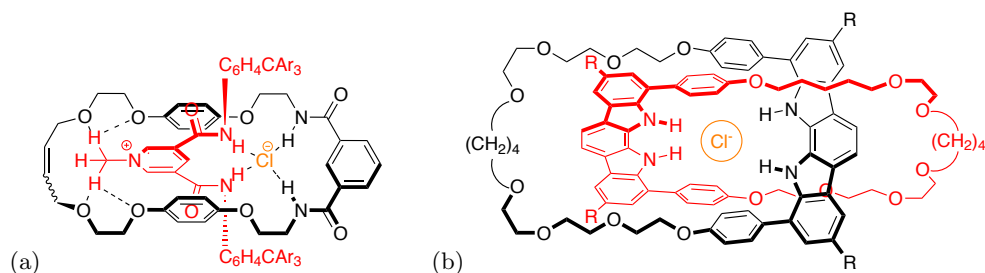


Figure 1.43 Anion-templated structures: (a) Beer's interlocked chloride-templated [2]rotaxane is formed by stoppering and (b) Jeong's chloride-templated indolocarbazole [2]catenane is formed by double cyclisation

Jeong has successfully integrated indoles and indolocarbazoles into anion sensing receptors, as discussed in Section 1.4, and has also extended into research on secondary structures either in wrapping or interlocked architectures. Chloride and sulfate were used as directing species for foldamers based upon the oligoindole and oligoindolocarbazole recognition motifs respectively.^{197,198} Both sets of oligomers wrapped into a helix around the central templating anion, exhibiting fluorescence changes. Chloride has further been demonstrated as an anion template in formation of an indolocarbazole-based homo[2]catenane by double cyclisation, as shown in Figure 1.43b.²⁹⁸

1.7.3 Higher-order interlocked structures

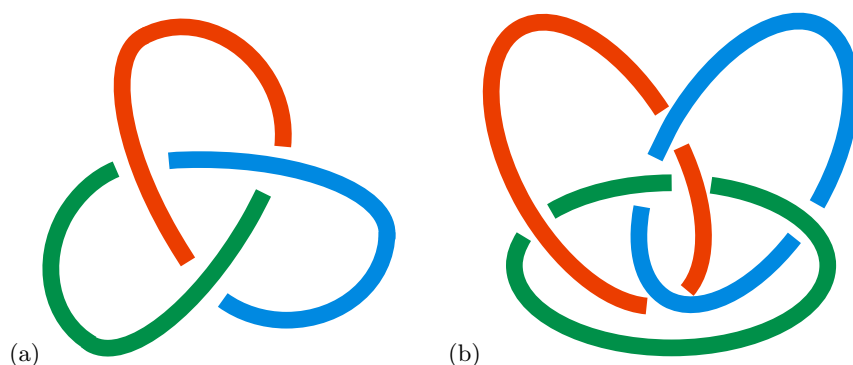


Figure 1.44 Higher-order interlocking: (a) model trefoil knot and (b) model Borromean rings

Once singly interlocked structures had been successfully constructed, researchers sought greater complexity in structures that are multiply interlocked, such as the multiply-

interlocked trefoil knot and Borromean rings shown in Figure 1.44a and b. The boundaries of interlocking complexity are ever-expanding, with $[n]$ rotaxanes and $[n]$ catenanes being constructed with a greater number of components, and a recent report on synthesis of the first double trefoil knot.²⁹⁹

Leigh's trefoil knot pictured in Figure 1.45a was formed by "active-metal templation". Cu(I) is bound by the two bipy motifs in the acyclic precursor, bringing the two chain ends into proximity. Further Cu(I) coordination by the pyridine induces azide-alkyne cycloaddition through the cavity to form the desired trefoil knot.

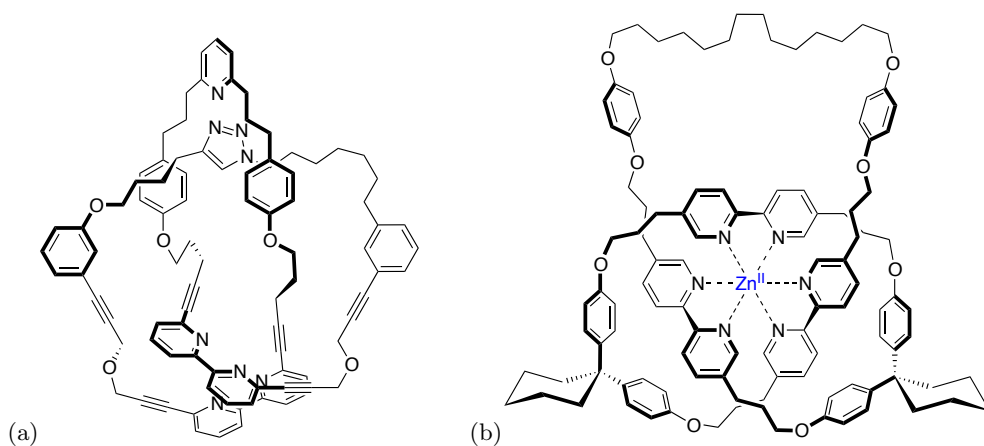


Figure 1.45 Forming higher-order interlocked structures by templated synthesis: (a) Leigh's small trefoil knot formed by Cu(I) active metal templation,³⁰⁰ and (b) Hunter's trefoil knot formed around a central Zn^{2+}

The Zn(II) template was utilised by Hunter for its octahedral coordination geometry in forming a trefoil knot (Figure 1.37b).³⁰¹ The flexible acyclic tris 2,2'-bipy-containing ligand wrapped around the centre metal template to form an open knot, with Grubbs' Ring Closing Metathesis (RCM) and subsequent alkene hydrogenation sealing the knot.

With the 2012 Olympics in London, the five interlocked rings of the Olympic movement are fresh in the mind (Figure 1.46a). This inspired the Royal Society of Chemistry to seek a molecular level five-fold ring system, culminating in olympicene (the radical form as imaged

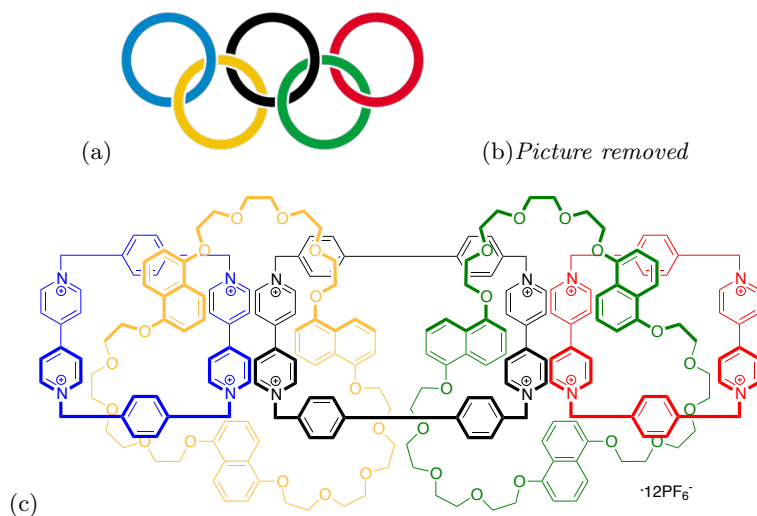


Figure 1.46 Olympic inspiration: (a) the Olympic rings, (b) olympicene radical and (c) interlocked olympiadane

by atomic force microscopy is shown in Figure 1.46a),³⁰² whilst Stoddart has previously described a five-ring interlocked system, olympiadane (Figure 1.46c).³⁰³

1.7.4 Molecular machines

Much of the biological inspiration in supramolecular chemistry centres on functional systems — transporters and assemblers, pumps and catalysts. While this thesis is primarily focused on the use of mechanically interlocked molecules as host systems, a more commonly exploited application is in the area of molecular machines. Highlighted below are interlocked structures in action as molecular machines to do work or provide useful functions.

Sauvage has developed a three-station fast-moving molecular shuttle based on copper-containing [2]rotaxanes (Figure 1.47).³⁰⁴ This system was used to investigate the effect of spacer groups between two different possible sites for copper-coordination on the axle (depicted as A and C). The distance of 23 Å between sites A and C had shown prohibitively slow shuttling between the sites, however, the introduction of intermediate site B assists in

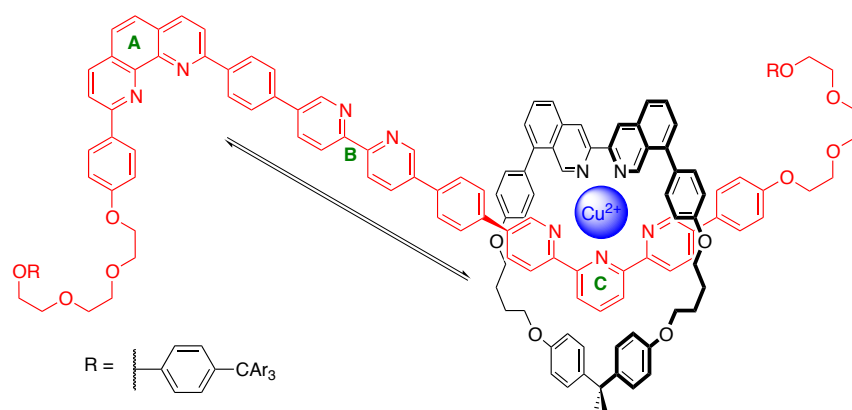


Figure 1.47 Molecular machines 1: Sauvage's [2]rotaxane fast molecular shuttle

stabilising the copper ion in transit, accelerating the shuttle function. From a 4-coordinate (2 axle and 2 macrocycle) Cu(I) complex at site A, it was possible to oxidise the copper and translate to 5-coordinate (3 axle and 2 macrocycle) site C for Cu(II) with a rate constant of 0.4 s^{-1} , with the reverse process proceeding at a speedy 50 s^{-1} . This intermediate station concept may allow rapid translations over lengthy conjugated molecular wires.

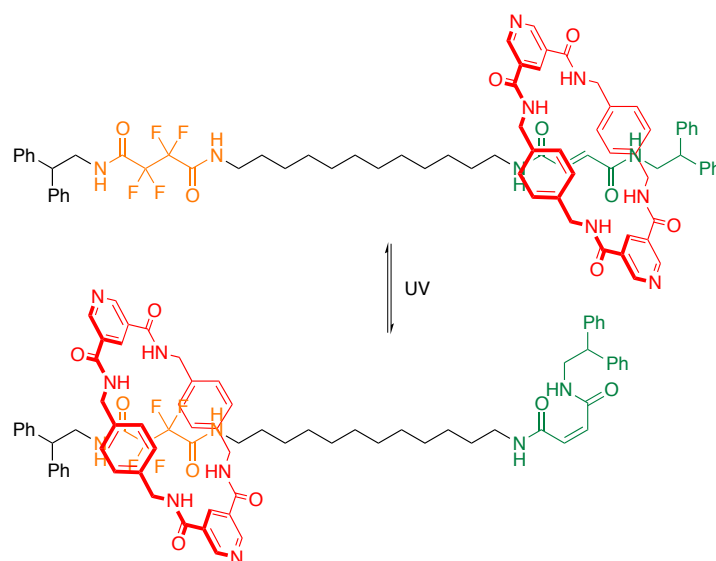


Figure 1.48 Molecular machines 2: Leigh's [2]rotaxanes on a SAM for moving water

Whereas Sauvage's machine currently exhibits only nanoscale motion, Leigh has published a striking example of a macro-scale effect created by tweaking intermolecular forces.³⁰⁵ The [2]rotaxane shown in Figure 1.48 was physisorbed onto the surface of a $-\text{CO}_2\text{H}$ -terminated gold self-assembled monolayer. The initially preferred state (top) is hydrophobic, causing a

water droplet on the surface to form with a large contact angle, minimising solvent–surface interactions. Shining UV light on the surface isomerises the alkene double bond from E to Z, forcing the macrocycle to move along the [2]rotaxane to cover the hydrophobic fluorine-rich area. The newly-exposed hydrophilic amide section allows the water to spread out. Suitable movement of a UV lamp over the surface of the material forces a water droplet to move along it; motion up a 12° incline was reported.

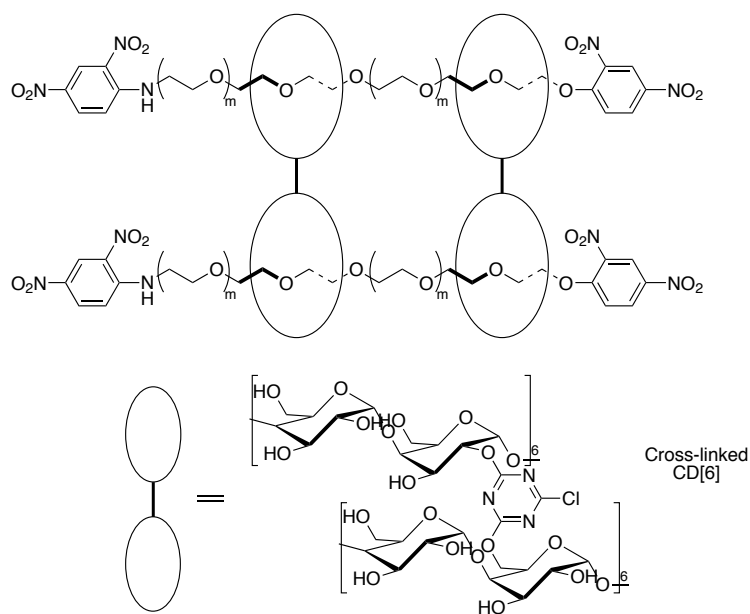


Figure 1.49 Ito’s cross-linked multiple polyrotaxane gel is used for scratch-resistant coatings on mobile phone screens

Highlighting versatility in the translation and rotational abilities of interlocked structures, Ito has developed a series of polyrotaxane gels, fibres and films.³⁰⁶ The initial composition is of polyrotaxanes with multiple α -cyclodextrins wrapped around polyglycol axles. Cross-linking of cyclodextrins between polyrotaxanes creates a gel that is transparent with good tensility and low viscosity. In addition, the ability of the cyclodextrin–cyclodextrin linkers to rotate and translate along the long polyether axles generates significant elasticity — even significant deformation merely displaces the cyclodextrins further along the axle, which can then return upon release of tension. This concept has already been applied to scratch-resistant top-coating on mobile phones currently on sale. The structure of one of these “sliding-ring gel” polyrotaxanes is shown in Figure 1.49.³⁰⁷

1.8 Objectives

This thesis focuses on developing novel host systems for ion pairs and anions through heteroditopic receptors and interlocked structures.

Chapter 2 is concerned with research into ion-pair recognition through the synthesis of heteroditopic receptors. The chapter covers the design, synthesis and characterisation of a novel heteroditopic macrocycle. Anion and cation binding studies are undertaken by both ^1H NMR and UV-vis spectroscopy, followed by identification of suitable ion-pair binding. A macrocyclic precursor to the heteroditopic receptor is investigated for use in anion binding and interlocked structures. Expansion of the heteroditopic macrocycle extended investigations to incorporate a heteroditopic thread, targeting an interlocked structure for ion-pair binding.

Chapter 3 focuses on anion recognition using cationic macrocycles and attempts at constructing interlocked host systems. A variety of cationic motifs are explored for integration into macrocycles for preorganised anion recognition and suitable donor–acceptor interactions with electron-rich threads. The chapter covers the design, synthesis and characterisation of a number of suitable cationic macrocycles. Anion binding studies are undertaken and selectivity trends established. Work towards interlocked structures for anion binding is also explored, identifying electron-rich threads containing anion-binding motifs.

Chapter 4 describes research conducted into the formation of interlocked structures containing neutral macrocyclic components. The first part of the chapter discusses work towards an anion-binding interlocked structure, with particular focus on the aromatic donor–acceptor interactions between electron-poor macrocycles and an electron-rich thread. The second part covers the design of interpenetrative systems which exploit halogen bonding interactions between macrocycle and thread.

Chapter 2

Ion-Pair Receptors

2.1 Introduction

There has been significant focus recently on developing heteroditopic ion-pair receptors.^{118,243–245} Whilst monotopic cation- and anion-recognition have been well-developed, the effect of the counterion on the respective binding processes can be considerable.^{41,308} As outlined in the introductory chapter (Section 1.5), the integration of a second binding motif to capture the counterion can be designed to favour cooperative binding of both ions through mutually attractive electrostatic interactions and preorganisation effects.^{118,242} The field of ion-pair recognition also has applications in salt solubilisation and extraction, and transmembrane transportation.^{309–311}

This chapter is separated into three parts, all of which are based around receptors containing 1,2,3-triazole motifs. Importantly, this heterocycle is a versatile ion-recognising unit for both cations and anions. The research undertaken in this chapter focuses on three sections:

- (i) the development of a novel calixdiquinone macrocycle, which is designed to cooperatively bind ion-pairs;
- (ii) attempts at forming anion-binding interlocked structures that contain derivatives of the macrocycle developed in the previous section;
- (iii) the assembly of interlocked structures using an expanded heteroditopic macrocycle capable of binding both cations and anions.

2.2 Ion-pair recognition by triazole-containing macrocycles

2.2.1 Introduction to key motifs

CALIX[4]ARENE AND CALIX[4]DIQUINONE

The versatile calix[4]arene is part of a family of macrocycles that include larger calix[*n*]arenes,³¹² resorcinarenes,^{313–315} calixpyrroles^{193,241,266} and pyrogallolarenes.³¹⁶ *t*-Butylcalix[4]arene was the first such structure synthesised by condensation of *t*-butyl-phenol and formaldehyde,^{317–319} with the larger cyclic oligomer 6- and 8-mer systems being isolated as by-products.^{320,321}

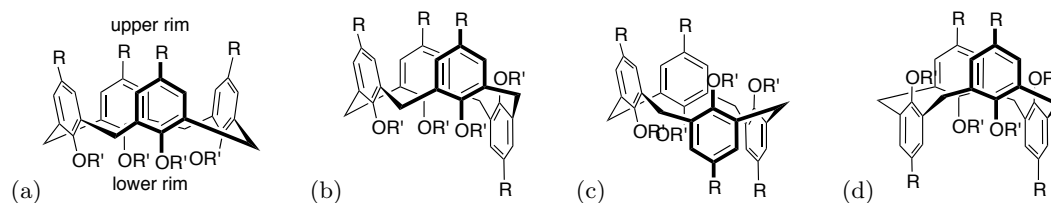
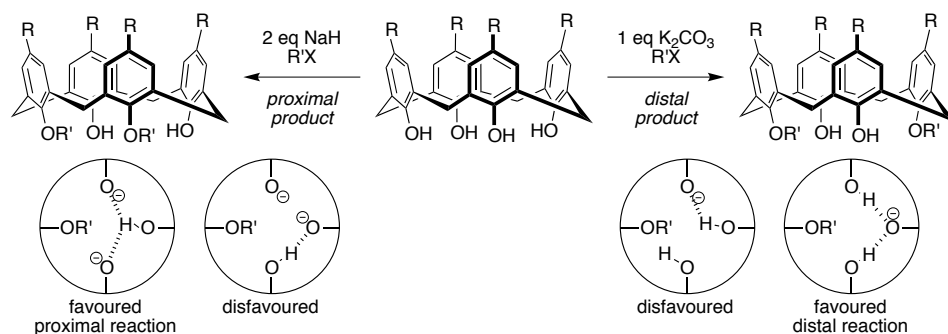


Figure 2.1 Calix[4]arene displays a variety of conformers: (a) cone, (b) partial cone, (c) 1,2-alternate and (d) 1,3-alternate

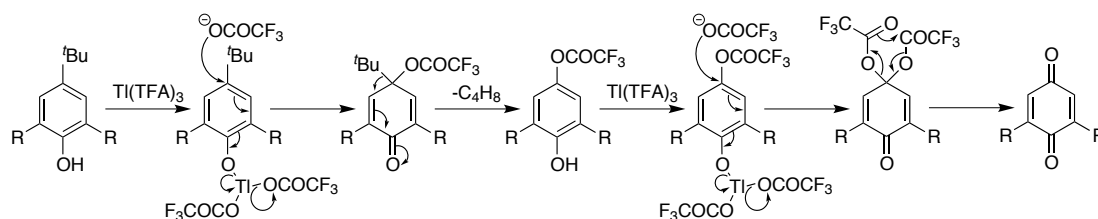
Calix[4]arenes are able to rotate about their linker methylene $-CH_2-$ groups, leading to the array of conformers displayed in Figure 2.1.^{322,323} Switching between these conformers is unrestricted until the lower rim R' substituents exceed the steric bulk of *n*-propyl groups.

These versatile macrocycles can be functionalised on either the upper rim (R groups in Figure 2.1a) or lower rim. *t*-Butylcalix[4]arene is commercially available and was chosen for the work in this thesis due to its dual functions as a relatively rigid scaffold and lipophilic solubilising group. Use of the sterically bulky *t*-butyl groups on the upper rim favours the cone and partial cone conformations, maximising the *t*-butyl group separation whilst retaining the potential for intramolecular hydrogen bonding through lower-rim unfunctionalised O–H groups.



Scheme 2.1 Careful control of basic reaction conditions in calixarene lower rim substitution yields either the 1,2- (*proximal*) or 1,3-substituted (*distal*) product as required

Lower rim functionalisation through the calix[4]arene O–H groups proceeds by a S_N2 mechanism and requires a suitable base and electrophile. Addition of one equivalent of strong base gives a monofunctionalised product and excess strong base yields the tetrafunctionalised product, whilst control using a $Ba(OH)_2/BaO$ mixture affords the trisubstituted derivative. Bis-substitution may result in two regioisomers: 1,2-substitution (*proximal*) and 1,3-substitution (*distal*). Scheme 2.1 shows the hydrogen bonding from deprotonation using strong (*proximal* product) or weak bases (*distal* product). Once mono-substitution has occurred, double-deprotonation by a strong base favours an O–H group between the two O^- atoms for maximal hydrogen bonding; mono-deprotonation by a weak base favours an O^- atom between two O–Hs.



Scheme 2.2 Reaction of thallium(III) trifluoroacetate with *t*-butylcalixarene phenols both oxidises the phenol to quinone and cleaves the *para*-positioned *t*-butyl group

Oxidation of the phenol components within the calixarene structure yields calixquinones. Described by McKillop, thallium(III) trifluoroacetate is the oxidant of choice, despite being acutely toxic, see safety warning, Section 6.5.^{324,325} The suggested mechanism of oxidation in Scheme 2.2 shows that the phenol oxidises to quinone and that cleavage of the *t*-butyl group occurs at the *para*-position.

Particularly relevant to the research undertaken in this section is the use of calixarenes and calixquinones as cation binding motifs due to the convergent electron-rich oxygen atoms in the cone conformation. Some examples have been outlined in the introduction (Section 1.5) with oxygen-rich calixarenes binding sodium (Figure 1.28b)²⁴⁷ or copper (Figure 1.30a),²⁵² a nitrogen- and oxygen-substituted calixarene binding zinc (Figure 1.30b),²⁵³ as well as an ion-pair extractor (Figure 1.33).^{264,265}

“CLICK” REACTIONS AND 1,2,3-TRIAZOLE

The concept of “click” chemistry was proposed by Sharpless as a synthetic ideal to mimic the prevalence in Nature of heteroatomic links between key carbon frameworks (C–X–C).³²⁶ As highlighted by Huisgen, 1,3-dipolar cycloadditions are useful to synthesise five-member heterocycles.³²⁷ In the absence of a catalyst this process required elevated temperatures and exhibited poor regioselectivity in forming 1,2,3-triazoles from azides and di-substituted acetylenes.³²⁸

Developed by Sharpless and Meldal,^{329,330} the copper(I)-catalysed azide–alkyne cycloaddition (CuAAC) variant of the Huisgen reaction can be carried out under “click” reaction conditions. This method demonstrates regioselectivity and has been utilised for effective late-stage coupling of sizeable precursors to supramolecular architectures (e.g. Figure 1.17a).^{184,331} The benefits of using the CuAAC reaction include *a*) very mild reaction conditions using weak bases at room temperature, *b*) readily-prepared terminal azide and alkyne starting reagents, *c*) the resulting 1,2,3-triazole has an electron-poor π -system, which can be enhanced by alkylation at a nitrogen atom and *d*) the resulting 1,2,3-triazole also contains a polarised C–H proton suitable for anion binding.^{202,204}

The anion-binding ability of 1,2,3-triazoles was highlighted in the introduction through Flood’s work on triazolophanes (Figure 1.18c).^{203,204} Another example from Craig’s work on

triazole-containing oligomers is shown in Figure 2.2a, with the acyclic host wrapping around the central chloride anion.^{200,201}

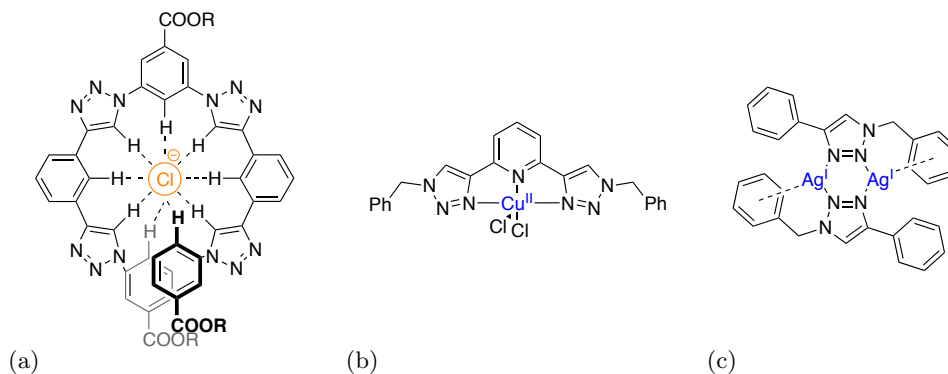


Figure 2.2 Triazole versatility: (a) Craig's oligomer wraps around the chloride anion; Crowley's triazole-based ligands coordinate transition metal cations through the (b) 3-position and (c) both 2- and 3-positions

The cation-binding ability of 1,2,3-triazoles has been investigated in work by Bronisz,³³² Gebbink,³³³ Astruc,³³⁴ and Crowley.^{335–338} Recognition by the Lewis basic electron-rich triazole nitrogens typically occurs through the 3-position as shown in Figure 2.2b.³³⁹ However, metal coordination *via* the 2-position is also known (shown in Figure 2.2c³⁴⁰) and solid-state crystal structures provide evidence of metal cation binding configurations with both sites coordinating. However, thus far only two examples of triazole-containing ditopic receptors have been reported.^{341,342}

2.2.2 Macrocyclic design

Previous work by Beer and co-workers has described a series of heteroditopic calix[4]diquinone isophthalamide receptors.^{248,343} In particular, the first example of a heteroditopic receptor that bound a contact ion-pair with AND cooperativity was reported (Figure 2.3).^{248,344,345} In 2% water/acetonitrile, the presence of either just a halide anion (with TBA⁺ countercation) or an alkali metal (with PF₆⁻, ClO₄⁻ counteranion) failed to disrupt the internal hydrogen bonding structure of the receptor between the isophthalamide N–H and the calix[4]diquinone C=O groups. However, the addition of both cation and anion, such as NaCl, was sufficient

to overcome the enthalpic penalty of breaking these intramolecular hydrogen bonding interactions.

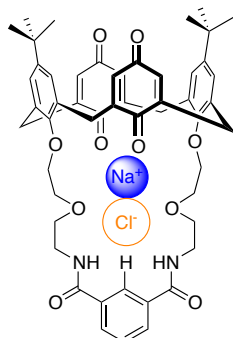


Figure 2.3 Beer's heteroditopic receptor with AND cooperativity in ion-pair binding

Inserting the 1,2,3-triazole group into the macrocycle, in place of the polyether linkers, will afford a novel macrocycle (**1**) with a more rigid spacer group between the anion- and cation-binding motifs. In addition, Figure 2.4 illustrates the potential use of the triazole unit in its cation- (a) and anion-binding (b) capacities. In the former, the triazole nitrogens act as Lewis bases to coordinate the cation; in the latter, the triazole C–H is a hydrogen bond donor to the anion. The heteroditopic receptor **1** also has the potential to bind ion-pairs through triazole-group participation.

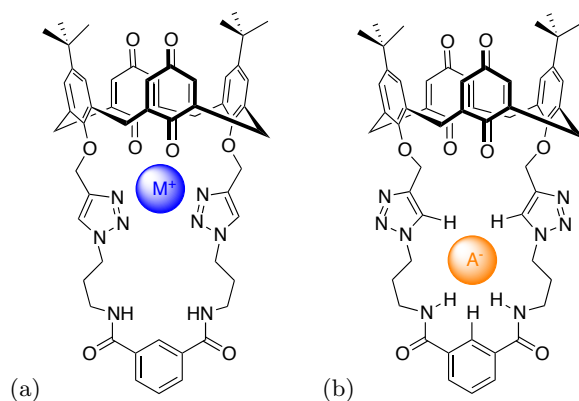
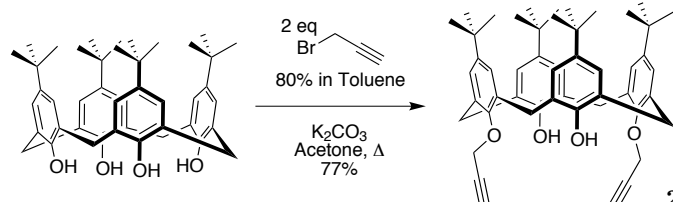


Figure 2.4 Target macrocycle **1** contains the cation-binding calixdiquinone motif and the anion-binding isophthalamide motif. 1,2,3-Triazole may (a) coordinate to cations through the Lewis basic nitrogens or (b) bind to anions through C–H hydrogen bonding

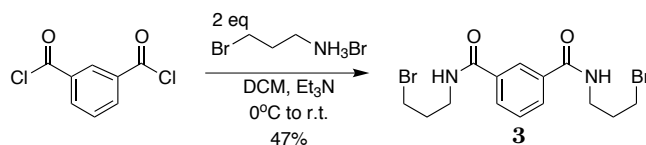
2.2.3 Macrocycle synthesis

t-Butylcalix[4]arene was lower-rim 1,3-functionalised according to a literature procedure to form the doubly propargyl-substituted synthon, **2**, as shown in Scheme 2.3.^{346,347}



Scheme 2.3 Synthetic route to propargyl-functionalised calix[4]arene derivative **2**

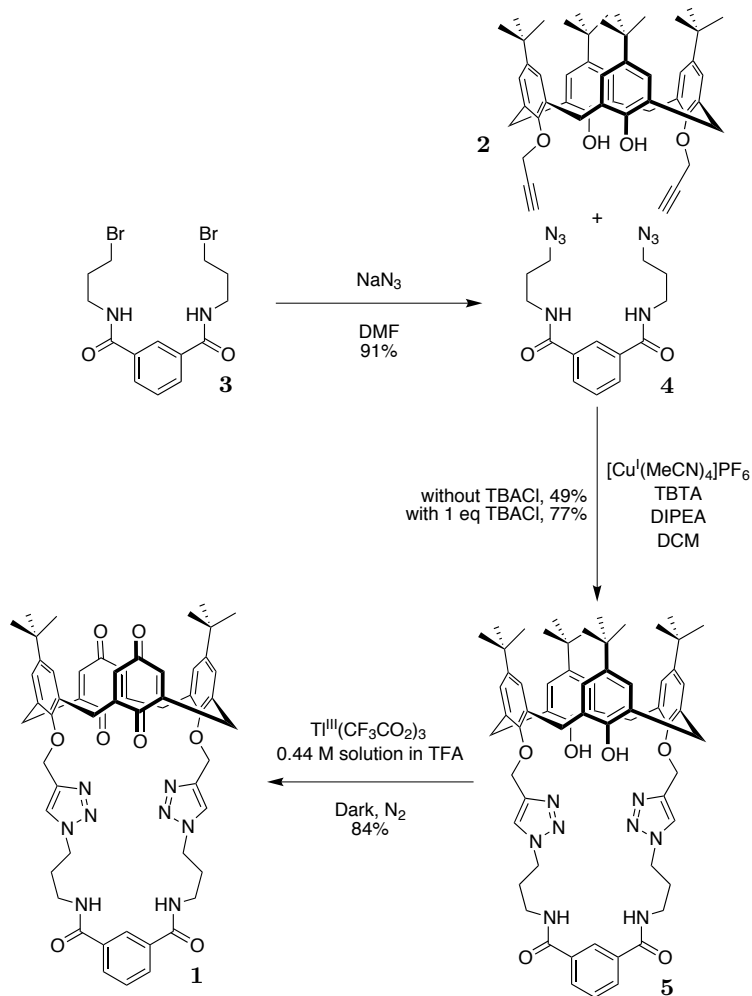
Following a literature procedure, commercially available isophthaloyl dichloride was condensed with two equivalents of 3-bromopropylamine hydrobromide in the presence of triethylamine to form isophthalamide derivative **3**, as shown in Scheme 2.4.³⁴⁸



Scheme 2.4 Synthesis of bromide-containing isophthalamide derivative **3**

The synthesis of target heteroditopic receptor **1** is shown in Scheme 2.5. Excess sodium azide was reacted with bromo-appended isophthalamide **3** to afford the required bis-azide derivative, **4**. A double copper(I)-catalysed azide-alkyne cycloaddition (CuAAC) reaction between calix[4]arene derivative **2** and bis-azide **4** afforded the bis-triazole-containing macrocycle **5** in 49% yield. It is noteworthy that when the cyclisation reaction was carried out in the presence of one equivalent of tetrabutylammonium chloride, the yield increased significantly to 77%. This observation indicates that the chloride anion is acting as a template, *via* coordination to the isophthalamide motif of **4**, preorganising the azide groups in a *syn-syn* conformation as described in Figure 1.16b, thus favouring the cyclisation process. A fresh solution of thallium(III) trifluoroacetate in TFA was carefully prepared^{324,325} (see safety warning, Section 6.5) and then used to oxidise macrocycle **5** to produce the target calix[4]diquinone triazole receptor **1** in good yield, 84%. The efficiency of this reaction was found to be heavily dependent on the quality of the acutely toxic thallium oxidant, which is highly light-sensitive,

either proceeding very well or producing toxic, intractable mixtures of partially oxidised side-products.



Scheme 2.5 Synthetic route to macrocycle **1**

2.2.4 Macrocycle characterisation

Precursor macrocycle **5** is a white solid, with the assigned ^1H NMR spectrum shown in Figure 2.5. Despite the large number of aromatic peaks, the symmetry of the molecule and the widely differing chemical environments allow each peak to be distinguished. The ditopic receptor was also characterised by ^{13}C NMR spectroscopy and high resolution ESI-MS.

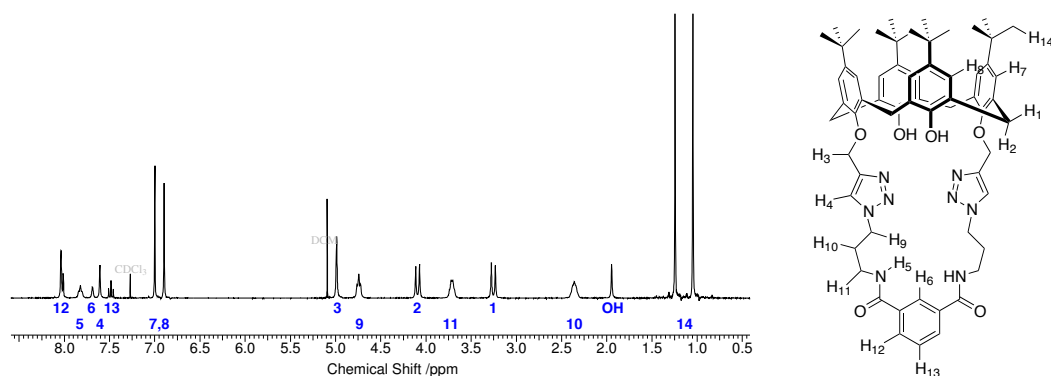


Figure 2.5 Fully assigned ^1H NMR spectrum (300 MHz, CDCl_3 , 298 K) of macrocycle **5**

Heteroditopic receptor **1** is a pale yellow solid, with the assigned ^1H NMR spectrum shown in Figure 2.6. The electron-withdrawing oxygens reduce the ring current of the calixdiquinone aromatic system, resulting in a more upfield chemical shift at δ 6.39 ppm compared with the phenolic signal at 6.89 ppm in the calix[4]arene. Increased intramolecular hydrogen bonding in **1** compared with **5** may explain the downfield shift of the isophthalamide internal proton to δ 8.44 ppm from 7.69 ppm and triazole C–H singlet to 7.95 ppm from 7.61 ppm, whilst the broad isophthalamide N–H is relatively upfield at 7.58 ppm compared with 7.82 ppm in the precursor. The ditopic receptor was also characterised by ^{13}C NMR spectroscopy and high resolution ESI-MS.

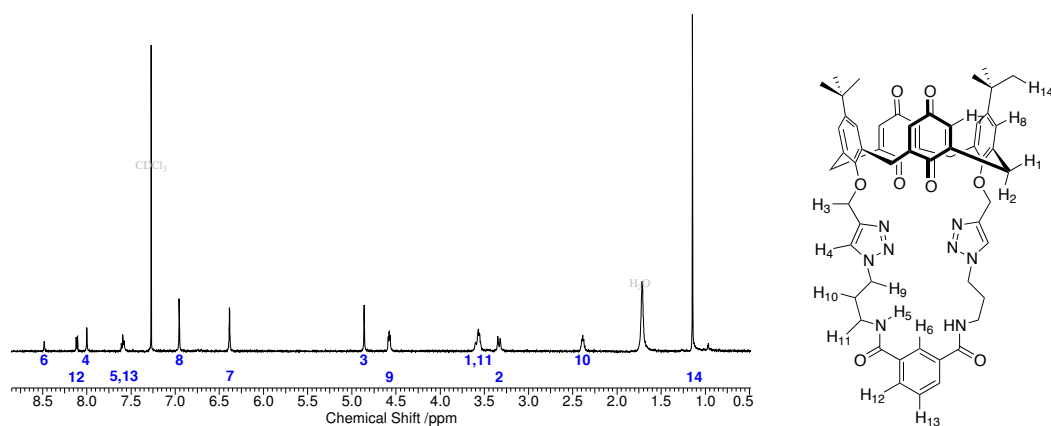


Figure 2.6 Fully assigned ^1H NMR spectrum (300 MHz, CDCl_3 , 298 K) of macrocycle **1**

Slow evaporation of a solution of **1** in CD_3CN produced crystals of sufficient quality for structure determination by single crystal X-ray diffraction. The structure (Figure 2.7) shows

the calix[4]diquinone unit in the partial cone conformation, with the two *t*butylphenyl rings almost parallel (14°); the quinone rings are antiparallel but converge on the cavity, with an interplanar angle of 40°. The rest of the macrocycle lies in a nearly planar conformation and in the absence of coordinating anions the isophthalamide and triazoles adopt dipole-minimising *syn-anti* conformations.

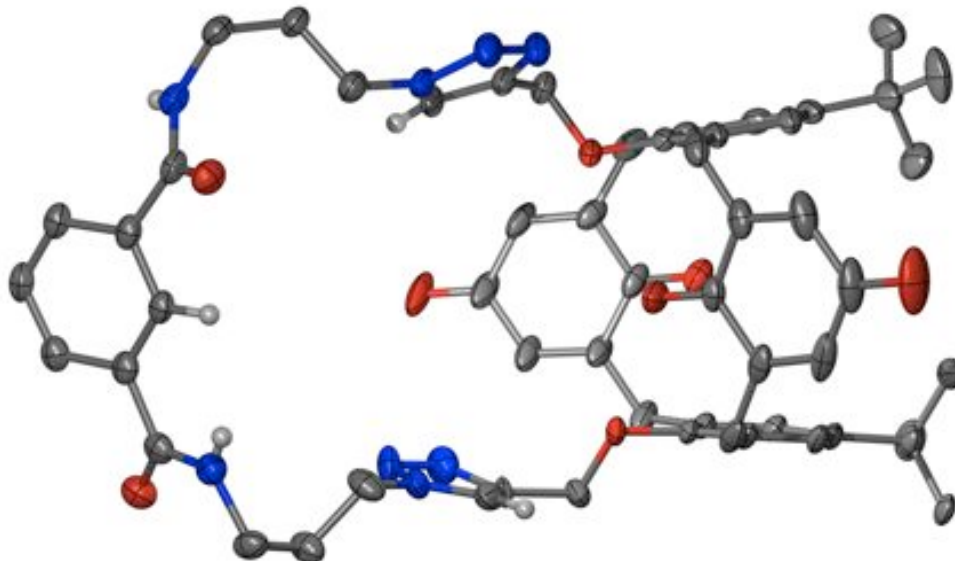


Figure 2.7 Single crystal structure of **1** grown from CD₃CN. Non-donating hydrogen atoms and solvent molecules are omitted for clarity. Thermal ellipsoids displayed at 30% probability

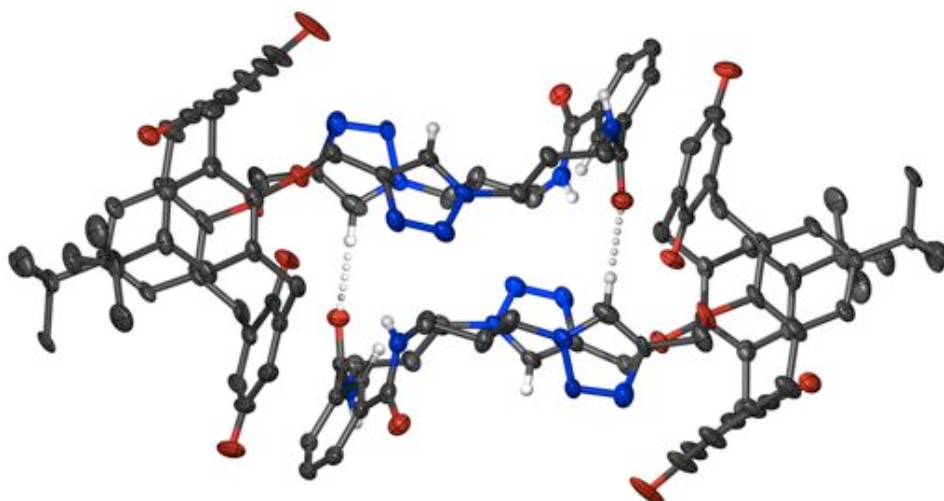


Figure 2.8 Dimerisation of **1** grown from CD₃CN is exhibited in the solid state. Non-donating hydrogen atoms and solvent molecules are omitted for clarity. Thermal ellipsoids displayed at 30% probability

The solid-state packing dimerisation of the macrocycle is shown in Figure 2.8. There are intermolecular hydrogen bonds between the triazoles and isophthalamides [$\text{C}-\text{H} \cdots \text{O}$ 3.11(2) and 3.17(1) Å] that induce a mean distortion in the isophthalamide system of 31.6(5)°. The quinone and isophthalamide interact in a parallel offset manner with a distance between the isophthalamide phenyl centroid and quinone hydrogen of 3.296 Å.

2.2.5 Cation-and anion-binding studies

The cation- and anion-binding properties of **1** were investigated by ^1H NMR and UV-vis spectroscopic analysis.

CATION BINDING

Monovalent cations were used to ascertain the cation-binding affinity and selectivity of receptor **1**. These were added as MPF_6 salts ($\text{M} = \text{K}^+$, Na^+ and NH_4^+) to ^1H NMR solutions of **1** in 2% $\text{D}_2\text{O}/\text{CD}_3\text{CN}$, with PF_6^- chosen as a non-coordinating counteranion. In these qualitative studies, downfield shifts were induced in the triazole protons (H_4): with the potassium cation $\Delta\delta +0.08$ ppm (Figure 2.9) and sodium cation $\Delta\delta +0.09$ ppm, causing larger perturbations compared with the ammonium cation $\Delta\delta +0.04$ ppm.

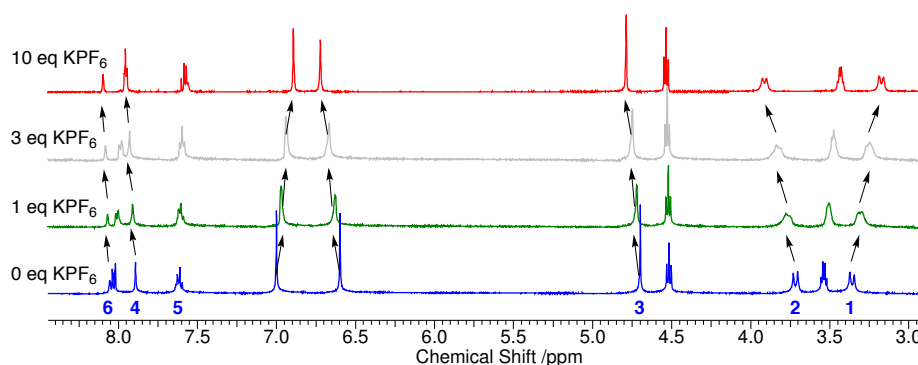


Figure 2.9 ^1H NMR spectra of receptor **1** upon addition of equivalents of KPF_6 . 500 MHz; solvent, 2% $\text{D}_2\text{O}/\text{CD}_3\text{CN}$; temperature, 293 K; $[\mathbf{1}]_i = 1.5 \times 10^{-3} \text{ mol dm}^{-3}$; titrant $[\text{KPF}_6] = 0.075 \text{ mol dm}^{-3}$. For ^1H NMR assignments see Figure 2.6

Notably, the $-CH_2-$ protons (H_3) between the triazole and calix[4]diquinone motifs are also shifted downfield upon cation addition, whilst the aromatic protons of the calix[4]diquinone (H_7 , H_8) converge and the AB quartet of the calix $-CH_2-$ protons (H_1 , H_2) diverge. These shifts suggest that cation addition induces a conformational change in the calix[4]diquinone in order for the lower rim oxygen and triazole nitrogen donors to complex the cation as depicted in Figure 2.4a.

The chemical shift of the triazole proton was monitored by ^1H NMR spectroscopy as it shifted upfield upon addition of equivalents of cation (Figure 2.10). Job plot approximations indicated a 1:1 binding stoichiometry (see Chapter 6).

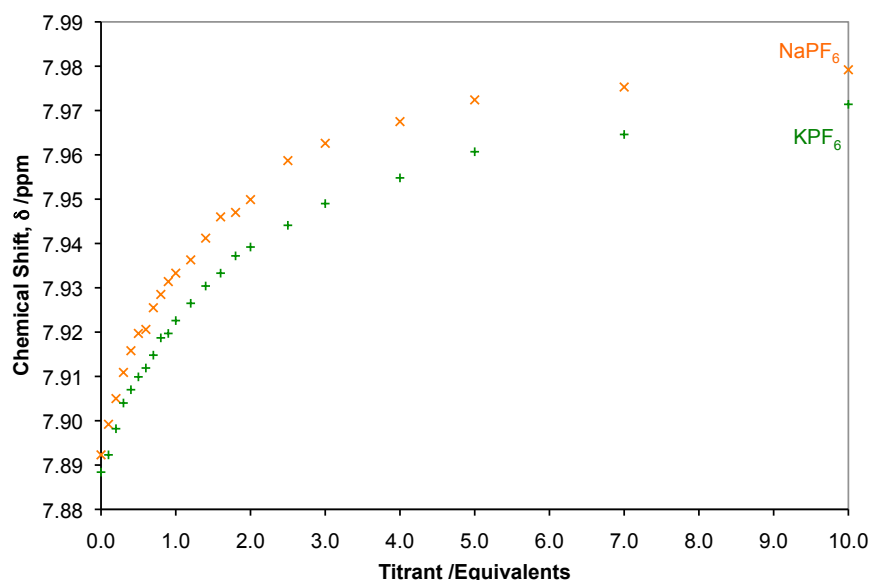


Figure 2.10 Monitoring the chemical shift of the triazole proton of **1** by ^1H NMR spectroscopy (500 MHz, 2% D_2O/CD_3CN , 293 K) upon addition of KPF_6 (+) or $NaPF_6$ (x)

UV-vis spectroscopic titrations were undertaken in 2% H_2O/CH_3CN , monitoring the $n-\pi^*$ quinone absorption of **1** around 330 nm upon addition of cations.³⁴⁹ Significant enhancement of the $n-\pi^*$ quinone absorption was observed upon Na^+ and K^+ addition (Figure 2.11a and b, respectively). Addition of NH_4^+ (Figure 2.11c), however, caused little effect, suggesting very weak binding.

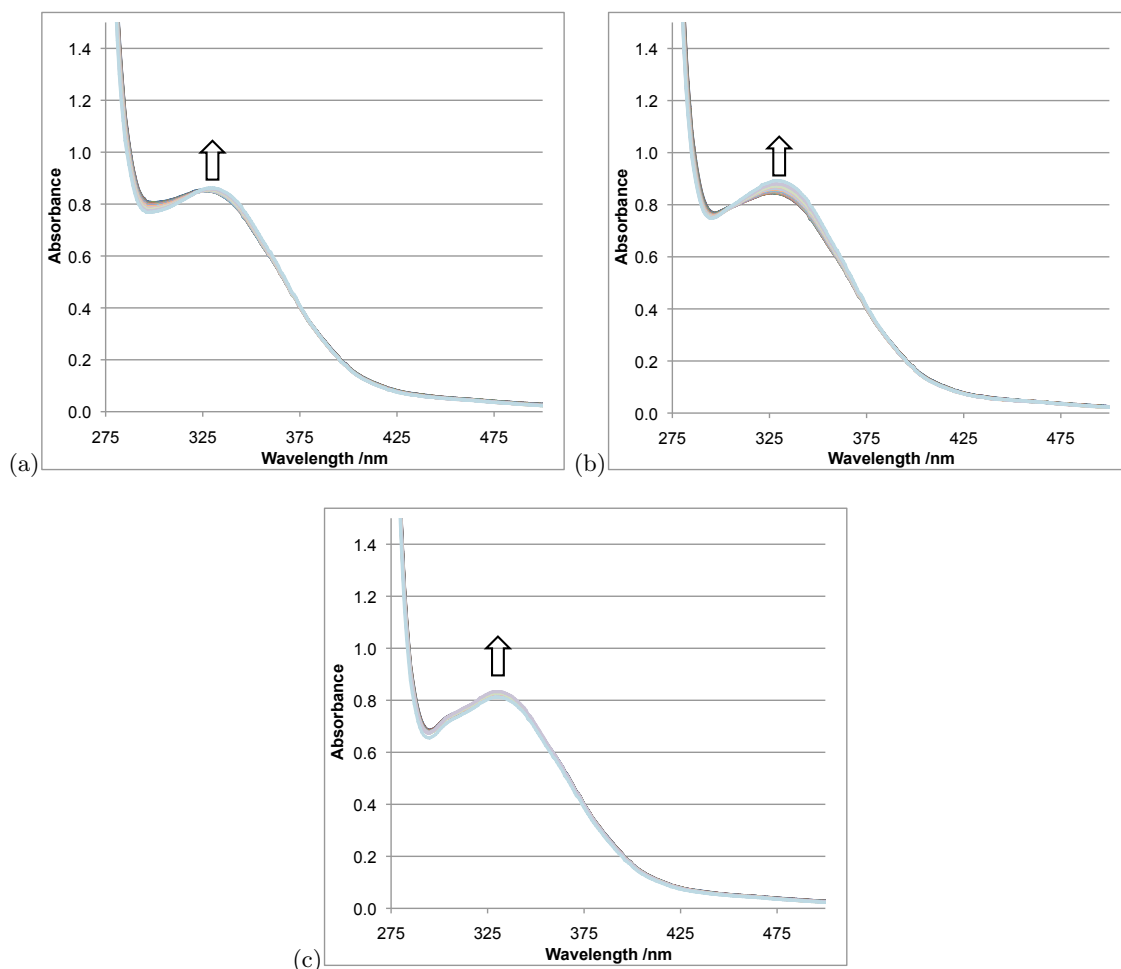


Figure 2.11 Enhancement of the $n-\pi^*$ quinone absorbance of **1** in response to addition of (a) NaPF_6 , (b) KPF_6 or (c) NH_4PF_6 . Solvent, 2% $\text{H}_2\text{O}/\text{CH}_3\text{CN}$; temperature, 298 K; $[\mathbf{1}]_i = 3 \times 10^{-4} \text{ mol dm}^{-3}$; titrant $[\text{KPF}_6] = 0.09 \text{ mol dm}^{-3}$

Specfit[®]³⁵⁰ analysis of the UV-vis titration data gave 1:1 stoichiometric association constants (Table 2.1) which reveal that Na^+ forms the strongest cation complex, followed by K^+ , whilst NH_4^+ is only bound very weakly.

Cation	Association K_{11} / M^{-1} [a]
K^+	155
Na^+	460
NH_4^+ [b]	–[c]

Table 2.1 UV-vis K_{11} values for interactions of **1** with various cations. Solvent, 2% $\text{H}_2\text{O}/\text{CH}_3\text{CN}$; temperature, 298 K; $[\mathbf{1}]_i = 3 \times 10^{-4} \text{ mol dm}^{-3}$; titrant $[\text{MPF}_6] = 0.09 \text{ mol dm}^{-3}$. [a] Errors <10%, [b] titrant as 5% $\text{H}_2\text{O}/\text{CH}_3\text{CN}$ solution for solubility, [c] binding too weak to be determined

ANION BINDING

^1H NMR spectroscopy was used to examine the anion binding affinities and selectivity of the macrocycle. Particular focus was placed on the hydrogen bond donating triazole C–H protons and the isophthalamide motif, with its two N–H and internal C–H protons. Anions were added as their TBAX salts ($\text{X} = \text{Cl}^-$, Br^- and I^-), where tetraⁿbutylammonium (TBA^+) is a bulky and relatively non-coordinating cation. Upon addition of each halide anion, the isophthalamide (H_5), internal phenyl protons (H_6) and triazole protons (H_4) were all found to shift downfield (Figure 2.12).

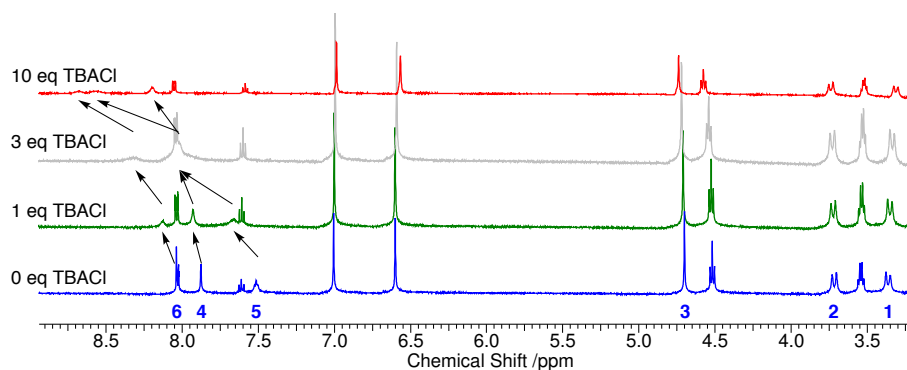


Figure 2.12 Cavity triazole (H_4), isophthalamide (H_5) and internal C–H (H_6) protons shift downfield in response to addition of TBACl. 500 MHz; solvent, 2% $\text{D}_2\text{O}/\text{CD}_3\text{CN}$; temperature, 293 K; $[\mathbf{1}]_i = 1.5 \times 10^{-3} \text{ mol dm}^{-3}$; titrant $[\text{TBACl}] = 0.075 \text{ mol dm}^{-3}$. For ^1H NMR assignments see Figure 2.6

The isophthalamide internal phenyl proton, H_6 , was monitored as it is central to the anion-chelating motif and the resonance did not broaden, in contrast to the amide N–H proton signal. For this proton (H_6), halide addition induced shifts $\Delta\delta$ that were largest for chloride (+0.64 ppm), followed by bromide (+0.14 ppm), with iodide causing only a modest perturbation (+0.06 ppm). The significant downfield shifts of these key protons indicate that the halide anion is bound in the receptor cavity by cooperative hydrogen bonding from the triazole and isophthalamide groups as suggested in Figure 2.4b.

Upon TBAX addition to **1**, the chemical shift of isophthalamide phenyl proton (H_6) was monitored by ^1H NMR spectroscopy, as shown in Figure 2.13, and Job plot analysis

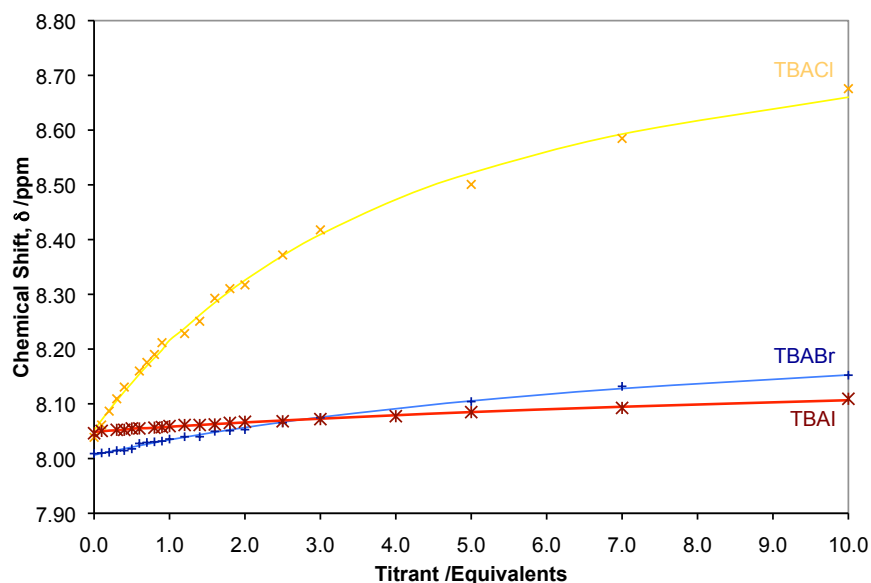


Figure 2.13 Monitoring the chemical shift by ^1H NMR spectroscopy (500 MHz, 2% $\text{D}_2\text{O}/\text{CD}_3\text{CN}$, 293 K) of the isophthalamide internal proton upon addition of TBACl ($\times$), TBABr ($+$) or TBAI ($*$)

indicated a 1:1 binding mode for each halide. Association constants were determined using WinEQNMR2 analysis of the ^1H NMR titration data monitoring the isophthalamide internal proton (H_6).³⁵¹ Table 2.2 reveals that receptor **1** exhibits a preference for the smaller, more charge dense chloride anion.^{178,179}

Anion	Association K_{11} / M^{-1}
Cl^-	178(16)
Br^-	67(5)
I^-	31(3)

Table 2.2 ^1H NMR K_{11} values for interactions of **1** with various anions. 500 MHz; solvent, 2% $\text{D}_2\text{O}/\text{CD}_3\text{CN}$; temperature, 293 K; $[\mathbf{1}]_i = 1.5 \times 10^{-3} \text{ mol dm}^{-3}$; titrant $[\text{TBAX}] = 0.075 \text{ mol dm}^{-3}$

Slow evaporation of a solution of **1** in 2% $\text{D}_2\text{O}/\text{CD}_3\text{CN}$ containing excess TBACl gave crystals of the $[\mathbf{1} \cdot 2\text{TBACl} \cdot \text{H}_2\text{O}]$ complex suitable for structural analysis by single crystal X-ray diffraction. The structure (Figure 2.14) shows a chloride anion bound in the isophthalamide cavity. A second chloride anion is bound in an intermolecular manner between triazoles from different macrocycles, triazole $\text{C}-\text{H} \cdots \text{Cl}$ 3.486(9) Å, supporting the ^1H NMR spectroscopy solution-state evidence for triazole $\text{C}-\text{H} \cdots$ anion interactions.

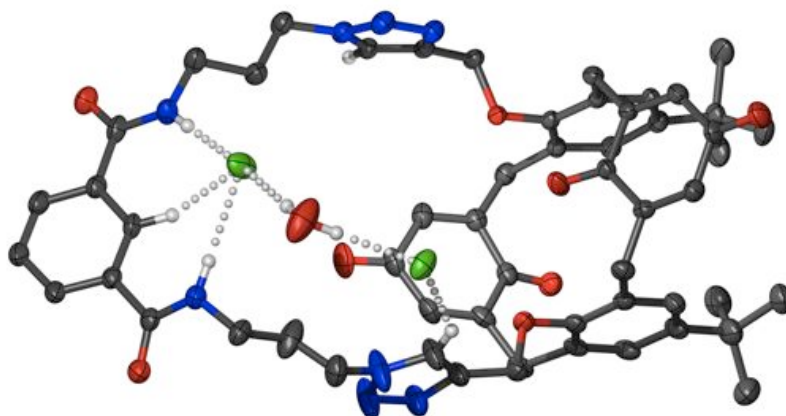


Figure 2.14 Single crystal structure of $[1 \cdot 2\text{TBA} \cdot \text{Cl} \cdot \text{H}_2\text{O}]$, note the chloride bound intermolecularly by the triazole H_4 . Hydrogen atoms not involved in hydrogen bonding and non-coordinating solvents and tetrabutylammonium cations are omitted for clarity. Thermal ellipsoids displayed at 30% probability

In this instance, the calix[4]diquinone unit is again found to adopt the partial cone conformation, with the two *t*-butylphenyl rings almost parallel, and convergent quinone rings having an interplanar angle of 48° . A second chloride anion is bound within the macrocycle cavity by hydrogen bonding to the chelating isophthalamide motif through its amide and phenyl protons [$\text{N}-\text{H} \cdots \text{Cl}$ 3.286(6) and 3.238(6) Å, and internal $\text{C}-\text{H} \cdots \text{Cl}$ 3.415(6) Å] and inducing a mean distortion of $18.8(7)^\circ$. A water solvent molecule bridges between the two chloride anions with hydrogen bond distances for $\text{O}-\text{H} \cdots \text{Cl}$ 3.22(1) and 3.082(9) Å. The bulky TBA resides outside the macrocycle cavity and remains proximate to its chloride counteranion, but is not shown for clarity. The solid-state structure of the $[1 \cdot 2\text{TBA} \cdot \text{Cl} \cdot \text{H}_2\text{O}]$ complex highlights the *intermolecular* triazole–halide and amide–halide anion interactions in a 2:1 stoichiometry; ^1H NMR solution-state anion-binding investigations indicated cooperative triazole and amide hydrogen bond–halide recognition with 1:1 binding stoichiometry. Later evidence in the solid-state indicates the presence of an *intramolecular* binding cavity formed by the isophthalamide and triazoles (see structure, Figure 2.23).

2.2.6 Ion-pair binding studies

NMR SPECTROSCOPY

^1H NMR spectroscopy was used to monitor titration of halide anions (as TBAX salts) into 2% $\text{D}_2\text{O}/\text{CD}_3\text{CN}$ solutions of macrocycle **1** containing one equivalent of cation (MPF_6).

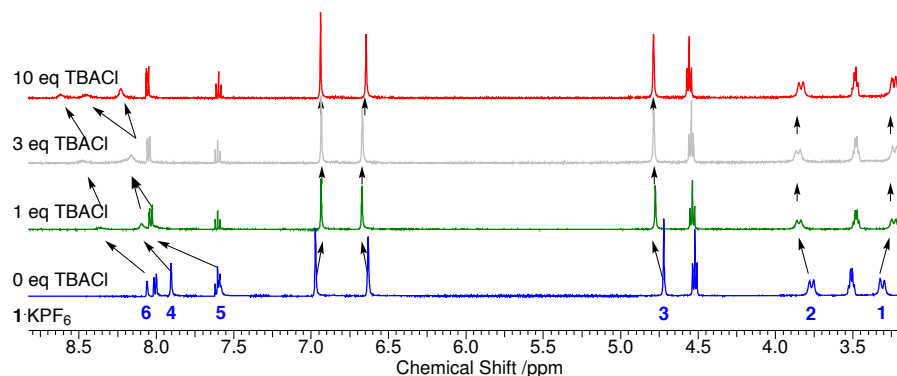


Figure 2.15 ^1H NMR spectra of receptor **1**· KPF_6 upon addition of equivalents of TBACl with corresponding KCl ion-pair formation in the cavity. 500 MHz; solvent, 2% $\text{D}_2\text{O}/\text{CD}_3\text{CN}$; temperature, 293 K; $[\mathbf{1}\cdot\text{KPF}_6]_{\text{i}} = 1.5 \times 10^{-3} \text{ mol dm}^{-3}$; titrant $[\text{TBACl}] = 0.075 \text{ mol dm}^{-3}$. For ^1H NMR assignments see Figure 2.6; for reference to the KPF_6 titration, see Figure 2.9

As observed with the free macrocycle, the triazole and isophthalamide proton resonances of the $[\mathbf{1}\cdot\text{KPF}_6]$ complex were shifted significantly downfield upon chloride addition (see Figure 2.15). Triazole proton (H_4) exhibited a larger magnitude of perturbation $\Delta\delta +0.19 \text{ ppm}$ for $\mathbf{1}\cdot\text{KPF}_6$ *versus* $\Delta\delta +0.09 \text{ ppm}$ for **1**. In the isophthalamide motif the N–H (H_5) and internal C–H (H_6) proton resonances also experienced greater downfield shifts by at least 0.1 ppm for $\mathbf{1}\cdot\text{KPF}_6$, compared with the shifts observed upon addition of chloride to **1**.

Chloride binding to $\mathbf{1}\cdot\text{KPF}_6$ also concomitantly caused the resonances of the calix[4]diquinone aryl protons (H_7 , H_8) to converge, the calix $-\text{CH}_2-$ protons (H_1 , H_2) to diverge and the $-\text{OCH}_2-$ adjacent to the triazole (H_3) to shift downfield. Once one equivalent of chloride had been added, further addition induced no further perturbations in these receptor proton signals, indicating strong chloride binding in the cavity and no further cooperativity once an ion-pair has been formed. In contrast, further chloride addition resulted in the isophthalamide protons shifting progressively downfield.

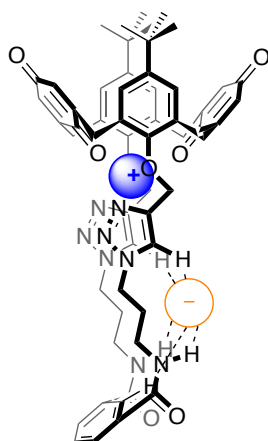


Figure 2.16 Possible solution-state ion-pair binding by heteroditopic receptor **1**

The S-shaped conformation in Figure 2.16 suggests a possible K^+Cl^- ion-pair binding mode, in which the triazole motifs function simultaneously in Lewis base mode with nitrogens coordinating the cation, as well as C–H hydrogen-bond donors to bind the halide anion.

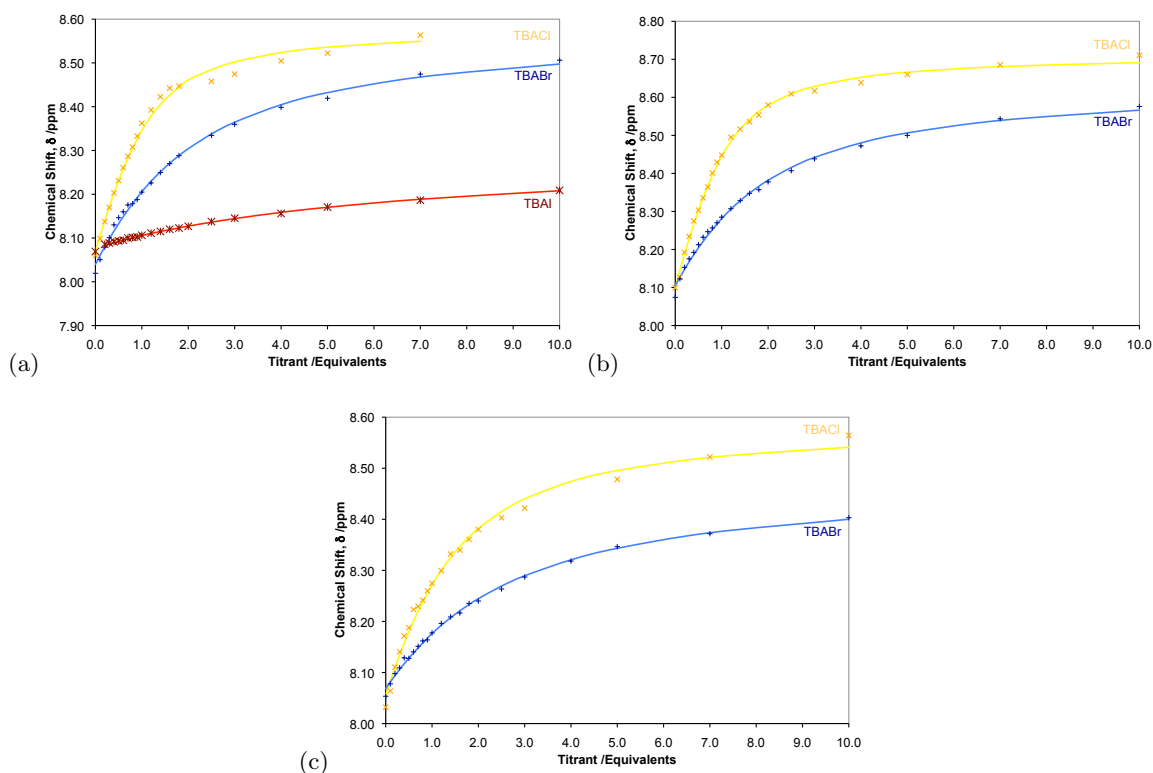


Figure 2.17 Monitoring the chemical shift (500 MHz, 2% D₂O/CD₃CN, 293 K) of the isophthalamide internal proton (H₆) upon addition of equivalents of TBACl (×), TBABr (+) or TBAI (*) salts to (a) [1·KPF₆], (b) [1·NaPF₆] and (c) [1·NH₄PF₆]

The distinct peak for the isophthalamide phenyl proton (H_6) was monitored upon addition of equivalents of anion to $[1 \cdot \text{MPF}_6]$ complexes, as shown in Figure 2.17. Analysis of the titration data by WinEQNMR2³⁵¹ gave the association constants, shown in Table 2.3.

Anion titrated	Cation solute	Association $K_{\text{obs}} / \text{M}^{-1}$	Cooperativity ^[a]
Cl^-	None	178(16)	n/a
Cl^-	KPF_6	1711(65)	9.6
Cl^-	NaPF_6	1950(129)	10.9
Cl^-	NH_4PF_6	747(28)	4.2
Br^-	None	67(5)	n/a
Br^-	KPF_6	414(36)	6.2
Br^-	NaPF_6	479(42)	7.2
Br^-	NH_4PF_6	307(22)	4.6
I^-	None	31(3)	n/a
I^-	KPF_6	96(5)	3.1

Table 2.3 ^1H NMR K_{obs} values for interactions of **1** with various ion-pair combinations. 500 MHz; solvent, 2% $\text{D}_2\text{O}/\text{CD}_3\text{CN}$; temperature, 293 K; $[1 \cdot \text{MPF}_6]_{\text{i}} = 1.5 \times 10^{-3} \text{ mol dm}^{-3}$; titrant $[\text{TBAX}] = 0.075 \text{ mol dm}^{-3}$. [a] Cooperativity factor is calculated by $K_{\text{obs}}(\text{anion, ion-pair})/K_{\text{obs}}(\text{anion, free})$

In all cases it was found that halide anion binding was enhanced significantly in the presence of coordinating cations. The degree of cooperativity in ion-pair binding was calculated by the ratio of affinity in the presence of a coordinating ion-pair over that with a non-coordinating counteranion, $K_{\text{obs}}(\text{cation, ion-pair})/K_{\text{obs}}(\text{cation, free})$. Overall, K_{obs} for halide binding to $1 \cdot \text{MPF}_6$ was typically 3 to 11 times greater than the halide association constants determined for receptor **1** alone.

Approximations of Job plot experiments indicated a 1:1 binding stoichiometry for the monovalent cation-halide anion ion-pairs, where the halide is the chloride or bromide (see Chapter 6). Iodide binding was too weak to ensure reliable stoichiometry determination.

The chloride anion is preferred by the isophthalamide and triazole cavity, forming the optimal ion-pair with Na^+Cl^- . Despite recent literature indicating increased cooperativity for larger anions (see Section 1.5),^{246,249–251} relatively weaker cooperative ion-pair associations are observed with the larger halides bromide and iodide, emphasising the excellent match of the Na^+Cl^- pair to the macrocycle cavity.

UV-VIS SPECTROSCOPY

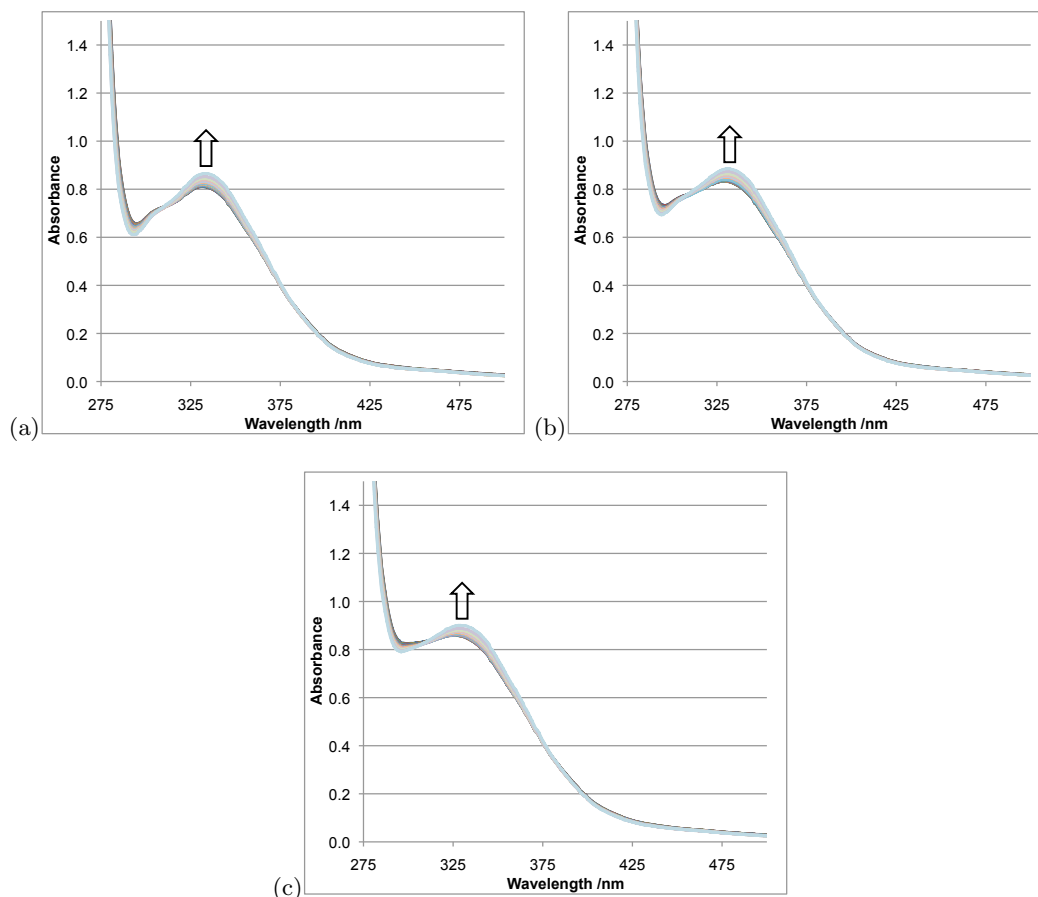


Figure 2.18 Enhancement of the $n\text{-}\pi^*$ quinone absorbance in response to addition of KPF_6 to a complex of (a) $[\mathbf{1}\cdot\text{TBACl}]$, (b) $[\mathbf{1}\cdot\text{TBABr}]$ and (c) $[\mathbf{1}\cdot\text{TBAI}]$. Solvent, 2% $\text{H}_2\text{O}/\text{CH}_3\text{CN}$; temperature, 298 K; $[\mathbf{1}]_i = 3\times 10^{-4} \text{ mol dm}^{-3}$; titrant $[\text{KPF}_6] = 0.09 \text{ mol dm}^{-3}$

UV-vis spectroscopic analysis was used to monitor changes upon addition of cations in the absorption of a solution of receptor **1** with one equivalent of halide anion in 2% $\text{H}_2\text{O}/\text{CH}_3\text{CN}$. The results upon addition of KPF_6 , NaPF_6 and NH_4PF_6 are shown in Figures 2.18, 2.19 and 2.20, respectively.

The $n\text{-}\pi^*$ quinone absorption was monitored and in all cases showed enhancement of the band centred at 325 nm, with some ion-pair combinations shifting the absorption maximum towards 330 nm. SpecFit[®] analysis of the absorbance curves determined that

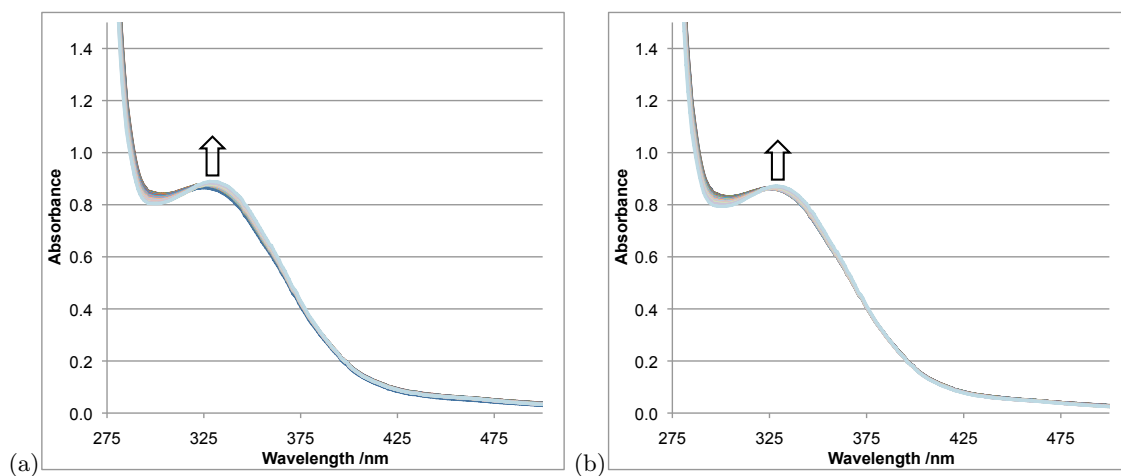


Figure 2.19 Enhancement of the $n-\pi^*$ quinone absorbance in response to addition of NaPF_6 to a complex of (a) $[1\cdot\text{TBACl}]$ and (b) $[1\cdot\text{TBABr}]$. Solvent, 2% $\text{H}_2\text{O}/\text{CH}_3\text{CN}$; temperature, 298 K; $[1]_i = 3 \times 10^{-4} \text{ mol dm}^{-3}$; titrant $[\text{NaPF}_6] = 0.09 \text{ mol dm}^{-3}$

for all three of the cations studied, the macrocycle–halide complex was superior to the free macrocycle in binding the cation (Table 2.4). Optimal ion-pair cooperativity was established by addition of NaPF_6 to the $[1\cdot\text{TBACl}]$ complex in agreement with NMR titration results. Despite the very weak affinity of free macrocycle **1** for the ammonium cation, the presence of either chloride or bromide anions with the macrocycle effectively “switches on” this binding. Further evidence for ion-pair binding was sought in the solid state.

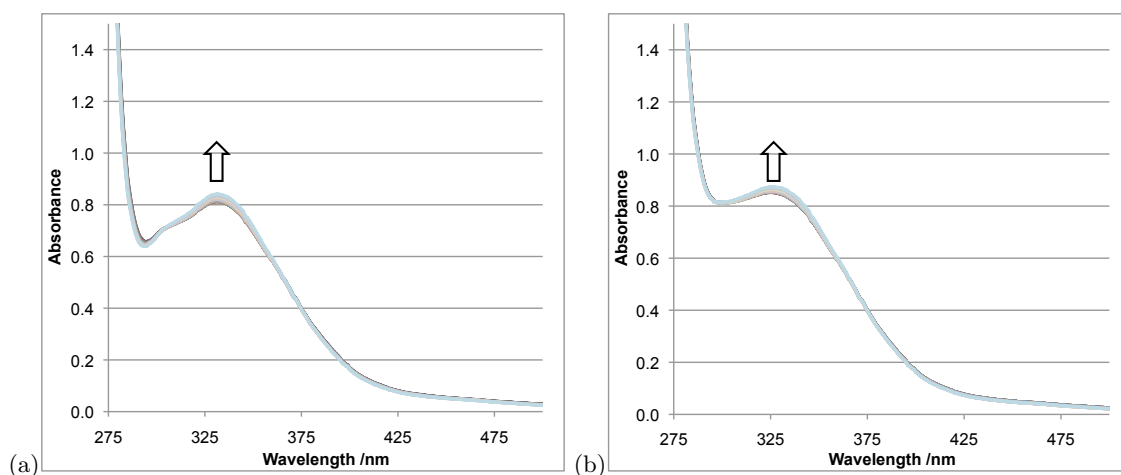


Figure 2.20 Enhancement of the $n-\pi^*$ quinone absorbance in response to addition of NH_4PF_6 to a complex of (a) $[1\cdot\text{TBACl}]$ and (b) $[1\cdot\text{TBABr}]$. Solvent, 2% $\text{H}_2\text{O}/\text{CH}_3\text{CN}$; temperature, 298 K; $[1]_i = 3 \times 10^{-4} \text{ mol dm}^{-3}$; titrant $[\text{NH}_4\text{PF}_6] = 0.09 \text{ mol dm}^{-3}$

Cation titrated	Anion solute	Association $K_{\text{obs}} / \text{M}^{-1}$ ^[a]	Cooperativity ^[b]
K ⁺	None	155	n/a
K ⁺	Cl ⁻	330	2.1
K ⁺	Br ⁻	250	1.6
K ⁺	I ⁻	220	1.4
Na ⁺	None	460	n/a
Na ⁺	Cl ⁻	1000	2.2
Na ⁺	Br ⁻	640	1.4
NH ₄ ⁺ ^[c]	None	- ^[d]	n/a
NH ₄ ⁺ ^[c]	Cl ⁻	370	n/a
NH ₄ ⁺ ^[c]	Br ⁻	300	n/a

Table 2.4 UV-vis K_{obs} values for interactions of **1** with various ion-pair combinations. Solvent, 2% H₂O/CH₃CN; temperature, 298 K; [**1**·TBACl]_i = 3×10⁻⁴ mol dm⁻³; titrant [MPF₆] = 0.09 mol dm⁻³. [a] Errors <10%, [b] cooperativity factor is calculated by $K_{\text{obs (cation, ion-pair)}}/K_{\text{obs (cation, free)}}$, [c] titrant as 5% H₂O/CH₃CN solvent for solubility, [d] binding too weak to be determined

2.2.7 Ion-pair binding in the solid state

Single crystals of macrocycle **1** with various ion pairs were grown by slow evaporation of a solution of [**1**·MPF₆] (where M is the desired coordinating cation) in 2% D₂O/CD₃CN in the presence of excess TBAX (where X is the desired coordinating anion). The structures were determined using synchrotron radiation at Diamond Beamline I19 by Ben Mullaney.³⁵² In all these structures neither TBA⁺ nor PF₆⁻ were present. When coordinating cations were bound in the cavity, the calix[4]diquinone unit was observed to adopt a pinched cone conformation; the two ^tbutylphenyl rings almost parallel and the quinone rings orientated convergently, with an interplanar angle of 68°, facilitating oxygen coordination to the cation.

[**1**·KCl·2.1(H₂O)]: The K⁺ and Cl⁻ ions are bound in the crystal structure in an unusual intermolecular contact ion-pair manner. Importantly, the triazole motif acts as a Lewis basic metal cation host and as a C–H···halide anion hydrogen-bond donor (Figure 2.21), corroborating the evidence from solution-state ¹H NMR ion-pair binding studies. One triazole motif acts in Lewis basic mode with nitrogen binding to the potassium, N···K 3.102(5) Å; the other triazole in the macrocycle C–H hydrogen bonds intermolecularly to the chloride anion of an adjacent macrocycle complex, C–H···Cl 3.546(6) Å.

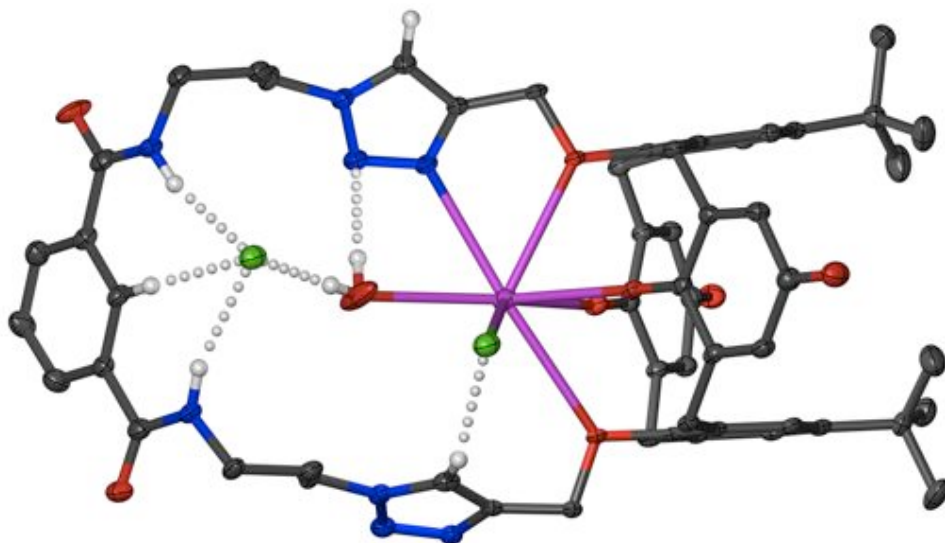


Figure 2.21 Single crystal structure of $[1 \cdot \text{KCl} \cdot 2.1(\text{H}_2\text{O})]$, with the intermolecular KCl contact ion-pair shown. Additionally the triazole lone pair is shown to interact with K^+ and the triazole C—H is shown to bind to Cl^- . Only hydrogen atoms involved in hydrogen bonding are shown for clarity. Thermal ellipsoids displayed at 30% probability

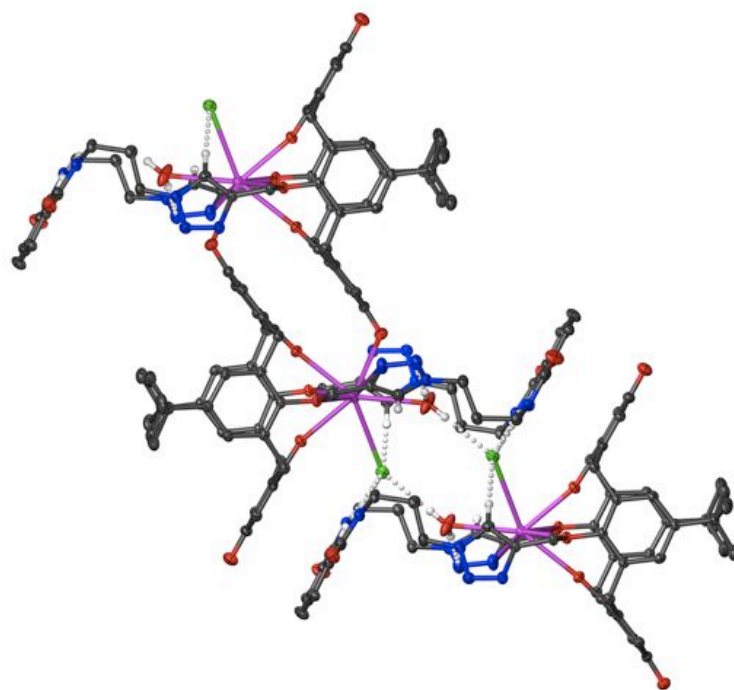


Figure 2.22 Single crystal structure of $[1 \cdot \text{KCl} \cdot 2.1(\text{H}_2\text{O})]_n$, demonstrating intermolecular packing and the key KCl contact ion-pair. Only hydrogen atoms involved in hydrogen bonding are shown for clarity. Thermal ellipsoids displayed at 30% probability

Oxygen interactions with the potassium cation [quinone $\text{O} \cdots \text{K}$ 2.643(4), 2.798(4) Å and phenyl $\text{O} \cdots \text{K}$ 2.949(3), 3.085(3) Å, and an intermolecular quinone $\text{O} \cdots \text{K}$ 2.747(4) Å]

are supplemented by triazole nitrogen lone pair–potassium coordination and also a contact ion-pair between the K^+ of one molecule and Cl^- [cation–anion distance 3.304(2) Å] of that of an adjacent complex in a pseudo-dimer configuration (Figure 2.22). The solid-state structure of the $NH_4^+Cl^-$ complex of a calix[4]diquinone polyether isophthalamide receptor was also observed to be dimeric in the AND contact ion-pair receptor previously reported by Beer and co-workers.³⁴⁵ A bridging water molecule within the macrocycle cavity hydrogen bonds to chloride [$O-H \cdots Cl$ 3.269(8) Å] and a lone pair interacts with potassium [$O \cdots K$ 2.857(8) Å]. Chloride is bound intramolecularly by the isophthalamide motif [amide $N-H \cdots Cl$ 3.291(5) and 3.296(5) Å, and internal $C-H \cdots Cl$ 3.512(6) Å] and induces a mean distortion of 4.6(6)°.

[1·NaCl·1.0(H_2O)]: The Na^+ and Cl^- ions are separated by a water molecule in the macrocycle cavity (Figure 2.23). A triazole $C-H$ forms an intramolecular hydrogen-bonding cavity for chloride [triazole $C-H \cdots Cl$ 3.585(6) Å] together with the isophthalamide motif. It is particularly noteworthy that this solid-state structure exhibits amide $N-H$ s and triazole $C-H$ in an intramolecular cooperative binding mode to the same anion within the macrocycle cavity.

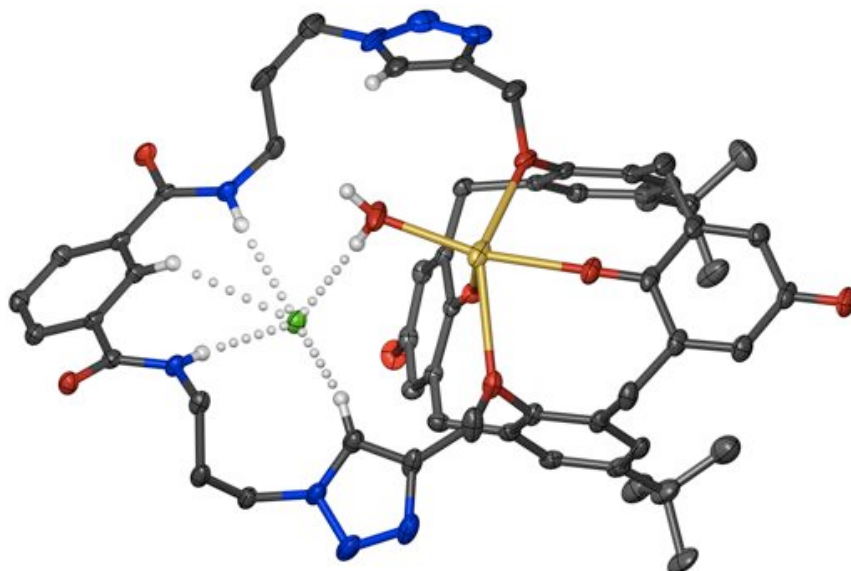


Figure 2.23 Single crystal structure of [1·NaCl·1.0(H_2O)], with a water molecule separating the ion-pair in the cavity. Cl^- is bound by an array of intramolecular hydrogen bonds from the triazole and isophthalamide. Only hydrogen atoms involved in hydrogen bonding are shown for clarity. Thermal ellipsoids displayed at 30% probability

Calix[4]diquinone oxygens interact with the sodium cation, quinone $\text{O} \cdots \text{Na}$ 2.357(5), 2.292(4) Å and phenyl $\text{O} \cdots \text{Na}$ 2.740(5), 2.530(5) Å. In addition, the sodium is coordinated by a water molecule, $\text{Na} \cdots \text{O}$ 2.297(5) Å, which also hydrogen bonds to the chloride in the cavity, $\text{O}-\text{H} \cdots \text{Cl}$ 3.131(5) Å. The chloride anion is bound intramolecularly by the isophthalamide motif [amide $\text{N}-\text{H} \cdots \text{Cl}$ 3.310(5) and 3.419(5) Å, and internal $\text{C}-\text{H} \cdots \text{Cl}$ 3.515(6) Å], inducing a mean distortion of $22.6(5)^\circ$, and also by the triazole hydrogen bond.

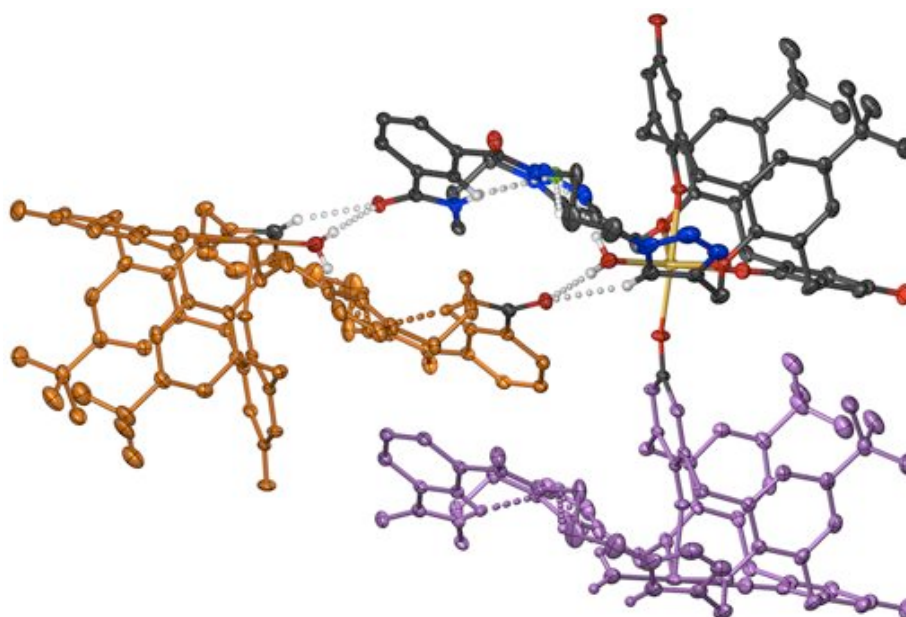


Figure 2.24 Single crystal structure of $[1 \cdot \text{NaCl} \cdot 1.0(\text{H}_2\text{O})]$, demonstrating intermolecular packing. Only hydrogen atoms involved in hydrogen bonding are shown for clarity. Thermal ellipsoids displayed at 30% probability

The solid-state packing trimerisation of the macrocycle is shown in Figure 2.24. The water molecule binding the ion-pair in the cavity of one macrocycle acts as a bridge to the amide motif of another molecule, with $\text{O}-\text{H} \cdots \text{O}$ 2.893(6) Å. A triazole–amide intermolecular interaction is also found with $\text{C}-\text{H} \cdots \text{O}$ 3.542(7) Å.

$[1 \cdot \text{NH}_4\text{Cl} \cdot 4.0(\text{H}_2\text{O})]$: The NH_4^+ and Cl^- ions are separated in the cavity by >6 Å. Two water molecules are displayed in the crystal structure and represent a disordered water molecule of total occupancy 0.7 that may mediate the interactions between the two ions (Figure 2.25). One position (occupancy 0.4) has a short ammonium contact [$\text{NH}_4 \cdots \text{OH}_2$ 2.56(3) Å and

HO–H $\cdots$ Cl 3.97(3) Å]; the other (occupancy 0.3) has a short chloride contact [NH₄ $\cdots$ OH₂ 3.12(4) Å and HO–H $\cdots$ Cl 3.44(4) Å]. The disorder may be due to competing ion–ion and quinone–ion interactions. Also, the triazole motif binds chloride in an intermolecular fashion by C–H $\cdots$ Cl.

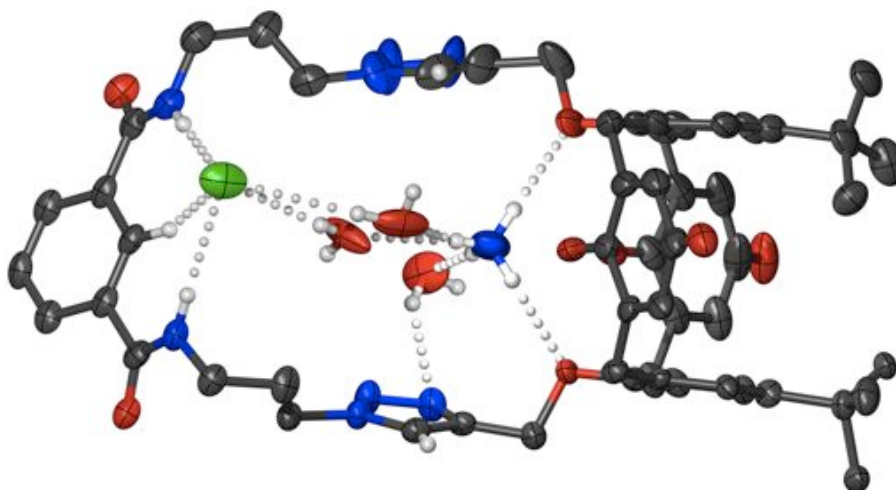


Figure 2.25 Single crystal structure of [1·NH₄Cl·4.0(H₂O)], with the guest ions widely separated in the cavity. The triazole forms hydrogen bonds to Cl[−] in an intermolecular fashion. Only hydrogen atoms involved in hydrogen bonding are shown for clarity. Thermal ellipsoids displayed at 30% probability

The data was of insufficient quality to precisely determine the calixdiquinone oxygen interactions [quinone O $\cdots$ NH₄ 2.701(17), 2.758(16) Å and phenyl O $\cdots$ NH₄ 2.930(14), 3.074(14) Å] with the ammonium cation, therefore the protons were directed to hydrogen bond to the hosted solvent molecules. The chloride anion is bound intramolecularly by the isophthalamide motif [amide N–H $\cdots$ Cl 3.453(10) and 3.364(10) Å, and internal C–H $\cdots$ Cl 3.628(12) Å], inducing a mean distortion of 23.1(9) Å, and also by the intermolecular triazole hydrogen bond.

[1·KBr·2.5(H₂O)]: The K⁺ and Br[−] are separated within the cavity by >6 Å. The quality of crystals obtained by evaporation was inferior to the previous examples, however, the position of the ion guests within the host cavity (Figure 2.26) is similar to that found in the other crystal structures. In this case, the solvent molecule bound to the potassium cation [K $\cdots$ O 2.72(3) Å] may be too far away from the bromide to infer a hydrogen bonding interaction to bridge the ion-pair .

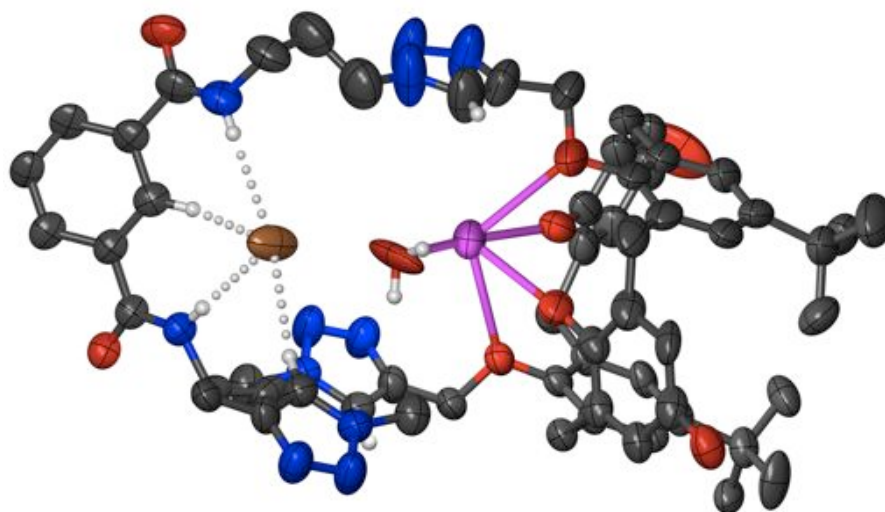


Figure 2.26 Single crystal structure of $[1 \cdot \text{KBr} \cdot 2.5(\text{H}_2\text{O})]$, note the dimerisation in a similar manner to that observed in the $[1 \cdot \text{KCl} \cdot 2.1(\text{H}_2\text{O})]$ structure (Figure 2.22). Hydrogen atoms not involved in hydrogen bonding are omitted for clarity. Thermal ellipsoids displayed at 30% probability

A comparison of the position of the bromide anion in the cavity with the position of chloride in the $[1 \cdot \text{KCl} \cdot 2.1(\text{H}_2\text{O})]$ (Figure 2.22) suggests that bromide is slightly perched rather than wholly in the isophthalamide plane as with chloride. The amides of the isophthalamide motif are also distorted out of the plane by a mean angle of $27(6)^\circ$. This indicates that the cavity is size-matched for chloride over bromide, as well as favouring chloride's greater charge density.

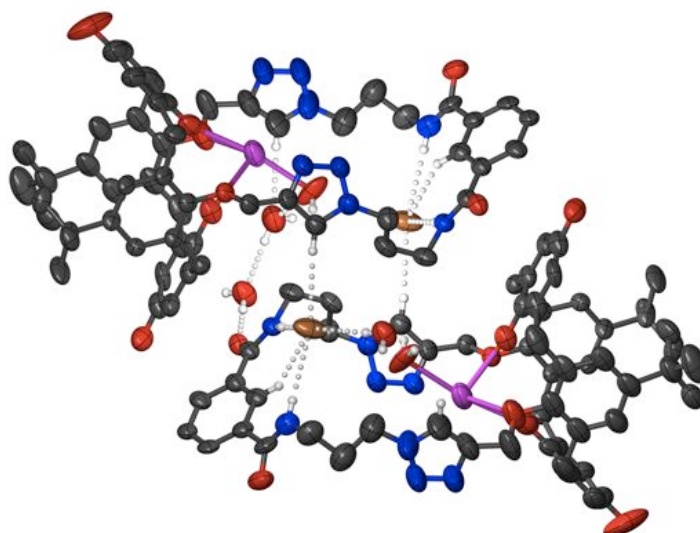


Figure 2.27 Single crystal structure of $[1 \cdot \text{KBr} \cdot 2.5(\text{H}_2\text{O})]$, demonstrating intermolecular packing. Only hydrogen atoms involved in hydrogen bonding are shown for clarity. Thermal ellipsoids displayed at 30% probability

The dimer solid-state packing arrangement in Figure 2.27 shows the triazole group binding intermolecularly to bromide with $\text{C}-\text{H}\cdots\text{Br}$. Some solvent-mediated interaction may also hold the macrocycles in position.

COMPARISON OF CRYSTAL STRUCTURES

Van der Waals radii values were used from articles by Bondi,³⁵³ and Rowland and Taylor.³⁵⁴ In Table 2.5, the solid state data from the isophthalamide motif are compared across the crystals obtained. The distances between the isophthalamide motif and the bound anion, and the distortion of the amides out of the plane are shown. Amongst the ion-pair structures, stronger solution-state ion-pair binding (see NMR and UV-vis data) corresponds to shorter solid-state hydrogen bonds, however, the shortest length is for the TBACl structure in the absence of a competing cation that draws the anion to it. The structures of the free macrocycle and in the presence of KBr exhibited the greatest isophthalamide distortions. The bromide anion is perched above the isophthalamide motif, whilst the free macrocycle is distorted by dimer-like packing in the solid state.

Crystal of 1 in the presence of	Free	TBACl	KCl	NaCl	NH₄Cl	KBr
C–H $\cdots$ X length, $\Sigma\text{VdW}\%$	n/a	3.415(6) Å 75.2%	3.512(6) Å 77.4%	3.515(6) Å 77.4%	3.628(12) Å 79.9%	3.661(12) Å 78.9%
Mean N–H $\cdots$ X length, $\Sigma\text{VdW}\%$	n/a	3.262(6) Å 74.3%	3.294(5) Å 75.0%	3.365(5) Å 76.7%	3.409(10) Å 77.7%	3.476(17) Å 77.4%
Isophthalamide distortion $\angle$	31.6(5)°	18.8(7)°	4.6(6)°	22.6(5)°	23.1(9)°	27(1)°

Table 2.5 Comparison between the solid state structures of **1** shows significant variation in hydrogen bond length between macrocycle and anion and in the induced distortion of the isophthalamide motif

In Table 2.6, the solid state data from the calixdiquinone motif are compared across the crystals obtained. The oxygen–cation distances, angle between the planes of the quinone rings and the conformation of the calixdiquinone in the solid state are shown. In agreement with the solution-state investigations, the $\text{C}=\text{O}\cdots\text{H}-\text{N}$ bond is slightly weaker than those for the sodium and potassium cations. In the solid state, there is not a significant preference between the sodium and potassium cations by the calixdiquinone oxygens. In the absence

of coordinating cations, the calixdiquinone is found in a partial cone conformation, with the quinone rings at an angle of 40–50°. There is remarkable similarity between the ion-pair structures, in which the coordinating cation induces the cone structure for optimal chelation and with an angle between the quinone rings of ~68°.

Crystal of 1 in the presence of	Free	TBACl	KCl	NaCl	NH₄Cl	KBr
Mean C=O...M length, Σ VdW%	n/a	n/a	3.017(3) Å 70.7%	2.635(5) Å 69.5%	3.002(14) Å 72.2%	2.977(16) Å 69.7%
Angle between quinone rings	40°	48°	68°	68°	68°	69°
Conformation of calixdiquinone	Partial	Partial	Cone	Cone	Cone	Cone

Table 2.6 Comparison between the solid state structures of **1** shows a switch to the cone conformer in the presence of coordinating cations

Data table summaries of the crystallographic information from the crystal structures presented above may be found in the Appendix. Full CIF files of the crystal structures are enclosed on the CD attached.

2.2.8 Conclusions

Two novel macrocycles, calix[4]arene **5** and calix[4]diquinone **1**, have been synthesised and fully characterised. The calix[4]diquinone is a heteroditopic receptor, with recognition sites for both cations and anions. The key 1,2,3-triazole motif is incorporated into both macrocycles and possesses both cation- and anion-binding ability *via* its Lewis basic nitrogens and C–H hydrogen-bond donors.

¹H NMR and UV-visible spectroscopic titrations investigated the cation- and anion-binding properties of receptor **1**. Carried out in a polar solvent mixture of 2% water/acetonitrile, ion-pair combinations of halides with monovalent cations were found to bind cooperatively. UV-vis spectroscopy established that cation binding occurs at the calix[4]diquinone oxygens,

whilst ^1H NMR spectroscopy established that the triazole nitrogen Lewis basic groups also coordinate to cations. ^1H NMR spectroscopy determined that anion binding was effected by a combination of the isophthalamide convergent C–H and N–Hs with the triazole C–H hydrogen-bond donors.

Cation coordination by the electron-rich calix[4]diquinone oxygens and triazole nitrogens enhances the strength of halide complexation at the isophthalamide site of the receptor. In the case of the optimal Na^+Cl^- ion-pair, cooperativity resulted in an 11-fold increase in binding strength. Halide anion binding at the receptor’s isophthalamide motif also enhances cation complexation.

A number of receptor–ion-pair adduct solid-state structures have been determined by X-ray crystallography. These structures further corroborate the ^1H NMR solution-state ion-binding results that the triazole motifs are capable of coordinating simultaneously to both cation and anion guest species (Figure 2.16).

2.2.9 Publication

This work has recently been published in *Chemistry — A European Journal* (featured article).³⁵⁵

2.3 Electron-deficient macrocycles for pseudorotaxane investigations

2.3.1 Macrocycle design

The original purpose for macrocycle **5** was as a potential precursor component in an anion binding [2]rotaxane. The 1,2,3-triazoles would offer a possible surface for π - π interactions with an electron-rich thread. Alkylation to form the 1,2,3-triazolium motif would provide an even more electron-poor π -surface and create a stronger C-H hydrogen-bond donor. This could be achieved by methylating either macrocycle **5** or **1**, with the advantage of the latter being the potential of quinones for UV-vis sensing of the anion binding event. These target macrocycles are shown in Figure 2.28a (**6**) and b (**7**).

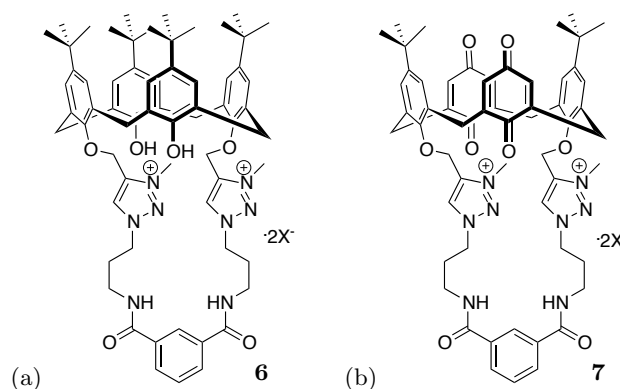


Figure 2.28 1,2,3-triazolium provides an electron-poor π -surface in macrocycles (a) **6** and (b) **7**

The objectives in this section were to prepare **6** and **7** and investigate pseudorotaxane formation with electron-rich threads containing core motifs such as indolocarbazole and dihydroxy naphthalene in the absence and presence of chloride.

2.3.2 Introduction to key motifs

INDOLOCARBAZOLE

The indolocarbazole motif, introduced by Beer to anion sensing, contains a planar core with

two N–H hydrogen bond donors in a chelating fashion and also provides an electron-rich surface for π – π interactions. The core motif (blue in Figure 2.29a) was selective for benzoate over the halides and other oxoanions in acetonitrile.³⁵⁶ The extensive conjugated π -system is also UV-vis active and can be used as a sensor for either anion binding events or the formation of interlocked structures. This has been developed by Beer and others for use in interlocked structures^{348,357,358} and also by Jeong in comparative investigations of oligomer against macrocycle anion binding.^{197,198} The oligomer shown in Figure 2.29a was acetate selective, with a binding constant $>10^6 \text{ M}^{-1}$ in a 10% DMSO/acetonitrile mixture.¹⁹⁶

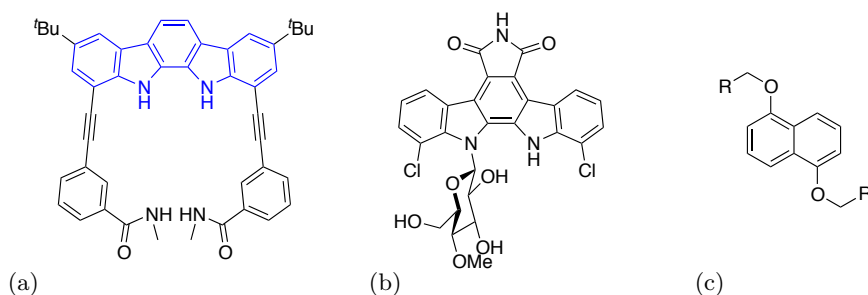


Figure 2.29 Electron-rich threads: indolocarbazole (a) Jeong's oligomer wraps around acetate with its chelating N–Hs and (b) incorporated into antitumour agent Rebeccamycin; and (c) 1,5-dihydroxy naphthalene ether

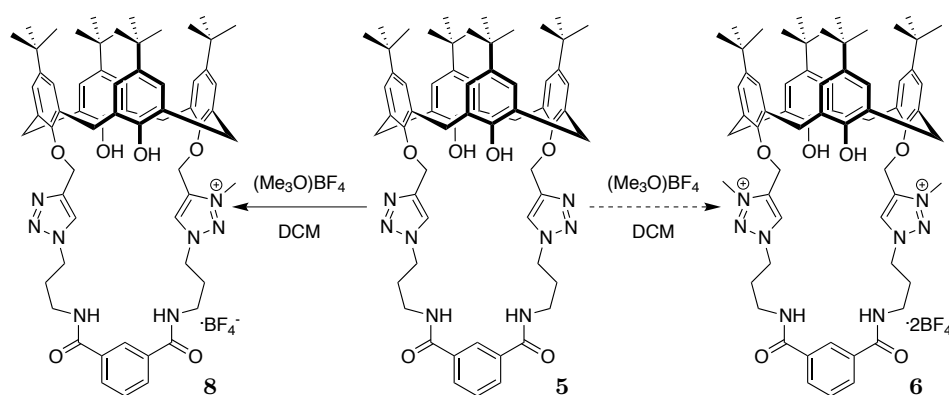
Indolocarbazole derivatives based on Rebeccamycin (Figure 2.29b), have been designed as antibiotics and antitumour agents.³⁵⁹ Studies on indolocarbazole derivatives indicate that they can intercalate DNA, particularly in proximity to the electron-deficient aromatic system of the thymine (T) base.³⁶⁰

DIHYDROXY NAPHTHALENE ETHER

Naphthalene diols have often been used in supramolecular chemistry in the context of exploiting their aromatic electron-rich character, for assembling interlocked structures *via* favourable aromatic donor–acceptor interactions (see Section 1.7, Figure 2.29c and Figure 3.1a).^{303,361–365}

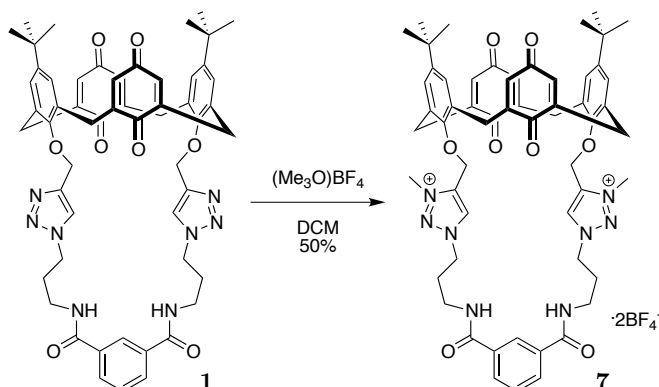
2.3.3 Macrocycle synthesis

Double methylation of the triazoles required a suitably powerful alkylating reagent, therefore Me_3OBF_4 was selected over MeI. The dialkylated macrocycle **6** was formed in very low yield (Scheme 2.6), with the impure product identifiable by ^1H NMR spectroscopy and ESI-MS. However, the monotriazolium intermediate, **8**, could successfully be identified and isolated. The attempted two-stage synthesis of the bis-triazolium receptor, **6**, by further alkylation of the monotriazolium derivative was unsuccessful.



Scheme 2.6 Synthetic route to macrocycle **6** and side-product **8**

An analogous attempt at forming the alkylated calixdiquinone macrocycle, **7**, was carried out on a test scale (Scheme 2.7). A small amount of the desired product was identified, however, further reactions to produce more material were thwarted by the limited availability of precursor **1**, due to the variable yield of the thallium(III) oxidation process.



Scheme 2.7 Synthetic route to macrocycle **7**

2.3.4 Macrocycle characterisation

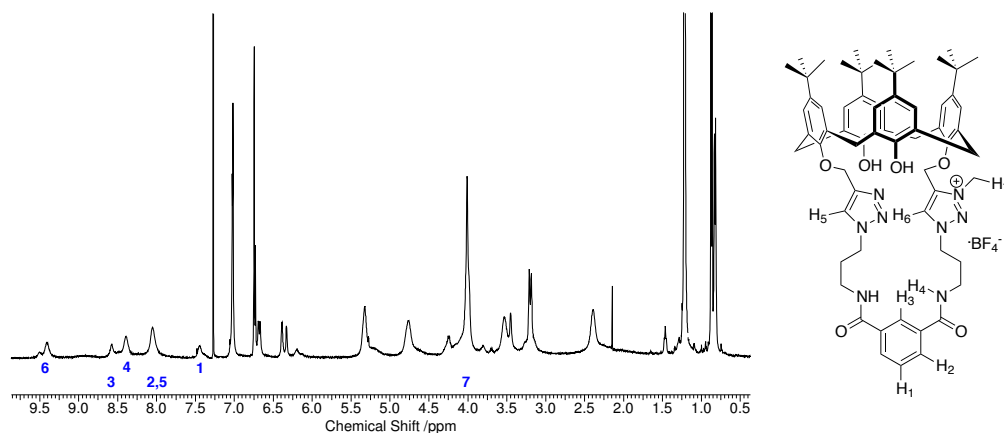


Figure 2.30 Partially assigned ^1H NMR spectrum (500 MHz, CDCl_3 , 293 K) of macrocycle **8**

The ^1H NMR spectrum for monotriazolium macrocycle **8** is shown in Figure 2.30. The broad peaks (at 500 MHz resolution) are caused by the presence of the triazolium, with the asymmetry of the molecule causing peak broadening and splitting. The triazolium proton was found to be very deshielded at δ 9.51 ppm and the triazolium methyl peak was observed at 4.01 ppm. Downfield shifts compared with macrocycle **5** were also induced in the other aromatic peaks. The macrocycle was also characterised by ^{13}C NMR spectroscopy and high resolution ESI-MS.

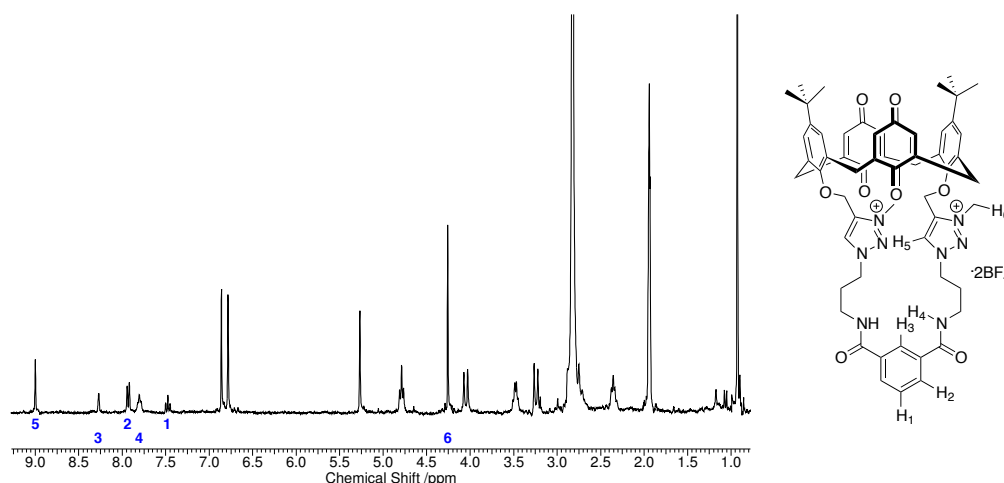
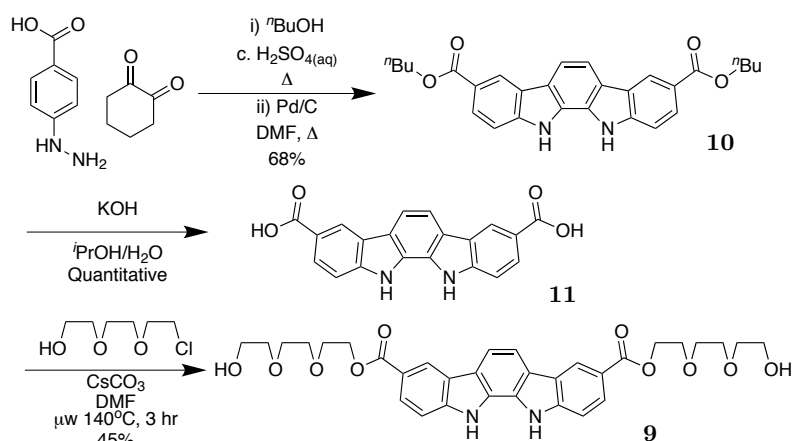


Figure 2.31 Partially assigned ^1H NMR spectrum (300 MHz, CD_3CN , 298 K) of macrocycle **7**

The peaks of the bis-alkylated calixdiquinone **7** were identified from the ^1H NMR spectrum shown in Figure 2.31. The triazolium methyl group is found as the expected singlet at δ 4.27 ppm. The macrocycle was also identified by high resolution ESI-MS.

2.3.5 Thread design and synthesis

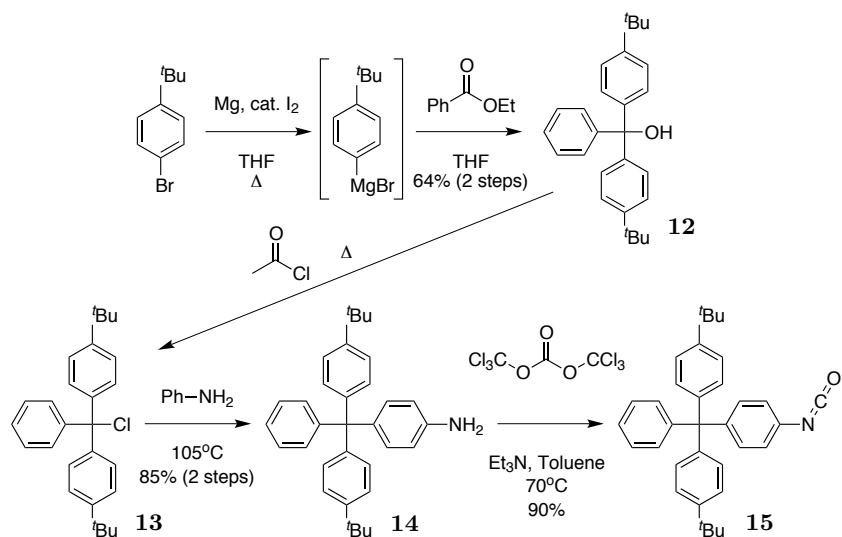
A suitable electron-rich indolocarbazole axle component had previously been designed and synthesised by Beer and co-workers.^{348,366} The lengthy polyether arms on axle **9** are essential for solubilising the extensive aromatic indolocarbazole core, but also provide an increased barrier to dethreading of the axle in pseudorotaxane formation.³⁶⁷ Synthesis of the unstoppered axle was carried out according to the literature procedure (Scheme 2.8) and the intermediate diester, **10**, and diacid, **11**, were soluble only in hot DMF.



Scheme 2.8 Synthetic route to axle **9**

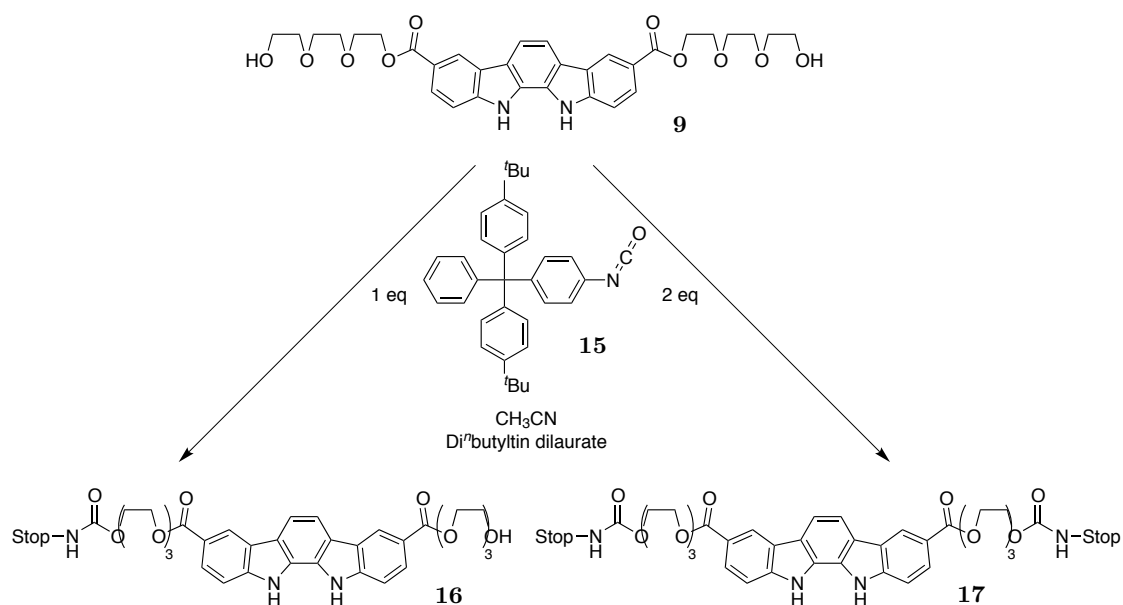
As the calixarene-based macrocycles were predominantly soluble in chlorinated solvents, the axles for pseudorotaxane formation studies would also require such solubility. Unstoppered axle **9** was soluble in highly polar solvents, but mono-stoppering with bulky, lipophilic t butyl-containing groups should ensure chloroform solubility.³⁴⁸

The triaryl foundation for the stopper groups was synthesised according to an established literature procedure (Scheme 2.9).³⁶⁸ A Grignard reaction formed tertiary alcohol **12**, which was then chlorinated (**13**) and reacted on to form the aniline-appended stopper (**14**). The desired stoppering precursor (**15**) was formed as the reactive isocyanate, which was immediately reacted on.



Scheme 2.9 Synthetic route to stopper **15**

Under mild reaction conditions, isocyanate stopper **15** was combined with indolocarbazole axle **9** to form a mixture of the mono- and di-stoppered threads, **16** and **17** respectively (Scheme 2.10).³⁴⁸ Both derivatives proved to be soluble in chloroform and dichloromethane, with the mono-stoppered compound suitable for pseudorotaxane formation studies.



Scheme 2.10 Synthetic route to the soluble mono- (**16**) and side-product di-stoppered axles (**17**)

The stoppers and threads synthesised were characterised by ^1H and ^{13}C NMR spectroscopy

and ESI-MS and agreed with literature data.^{348,368} For reference the key aromatic core protons are assigned in the ^1H spectrum of mono-stoppered thread **16** as displayed in Figure 2.32.

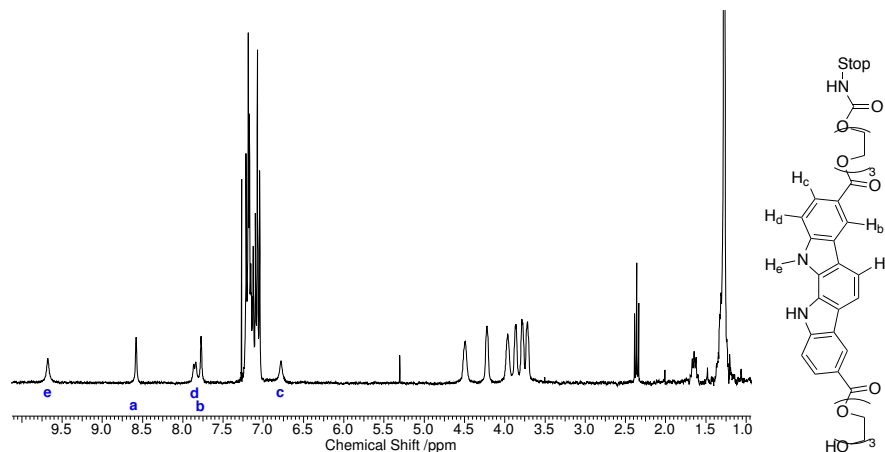
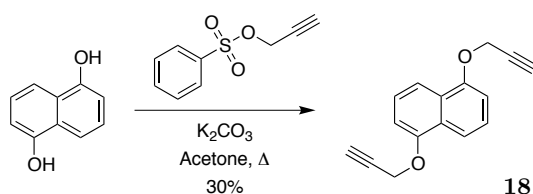


Figure 2.32 Partially assigned ^1H NMR spectrum (300 MHz, CDCl_3 , 298 K) of thread **16**

Whilst the indolocarbazole threads could be stoppered in a mild urethane-forming reaction, dihydroxy naphthalenes are more easily functionalised and compound **18** was considered as a potential threading component. 1,2,3-Triazole formation from an azide and an alkyne proceeds cleanly at room temperature, which is favourable for rotaxane formation *via* stoppering whilst retaining an axle inside the macrocycle cavity. The synthesis of dialkyne thread **18** is shown in Scheme 2.11 and follows a one-step literature procedure.³⁶⁹ Purification by column chromatography yielded the desired product as a grey-brown solid in 30% yield.



Scheme 2.11 Synthetic route to axle **18**

As this thread will be used in pseudorotaxane studies, its ^1H NMR spectrum was fully assigned and these protons are highlighted in Figure 2.33.

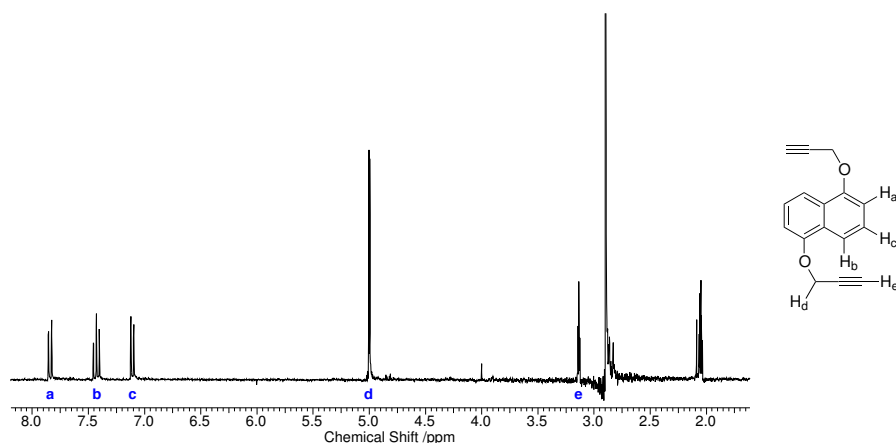


Figure 2.33 Fully assigned ^1H NMR spectrum (300 MHz, acetone- d_6 , 298 K) of thread **18**

2.3.6 Pseudorotaxane studies

Due to the lack of sufficient amounts of alkylated macrocycles **7** or **8**, pseudorotaxane studies were instead carried out between macrocycles **5** and **1**, and monostoppered indolocarbazole thread **16** in CDCl_3 (Figure 2.34).

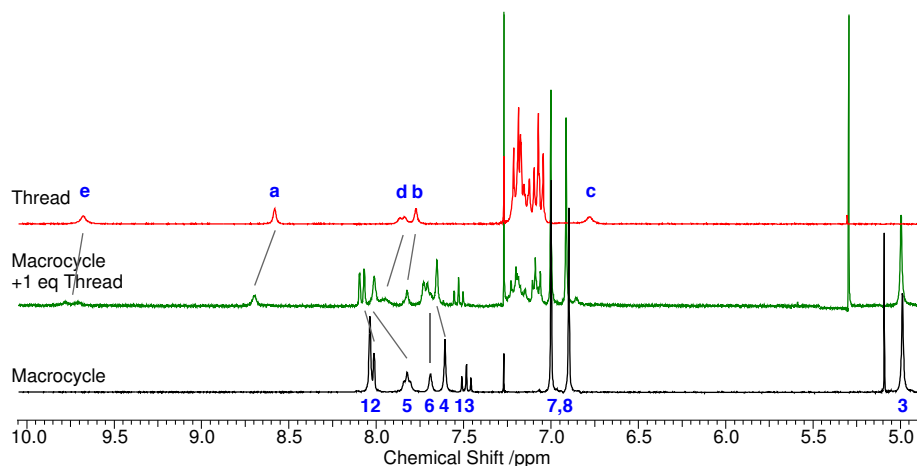


Figure 2.34 Pseudorotaxane formation study of macrocycle **5** with one equivalent of indolocarbazole thread **16** by ^1H NMR spectroscopy (500 MHz, CDCl_3 , 293 K). For ^1H NMR assignments see Figures 2.5 and 2.32

The addition of one equivalent of **16** to macrocycle **5** in CDCl_3 was monitored by ^1H NMR spectroscopy (Figure 2.34). Promisingly, some macrocycle–thread interactions were observed, with the macrocycle amide N–H protons (H_5) being deshielded $\Delta\delta +0.19$ ppm, while other modest upfield macrocycle chemical shifts of $+0.05$ ppm were noted. The thread N–H protons (H_e) and indolocarbazole C–Hs were also deshielded by 0.13–0.20 ppm.

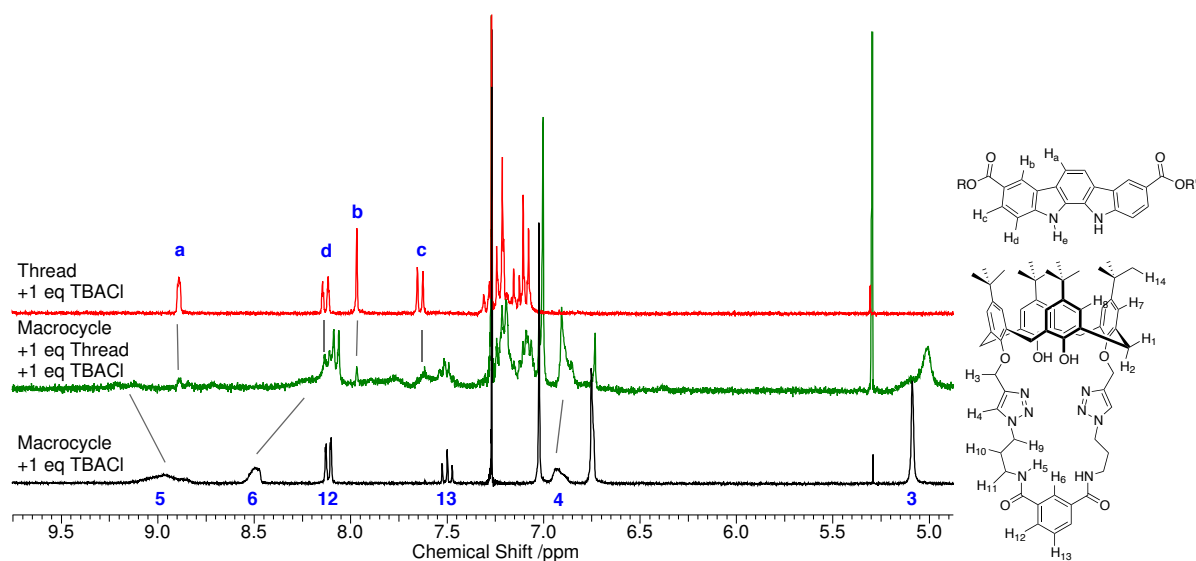


Figure 2.35 Anion-templated pseudorotaxane formation study of macrocycle **5** with one equivalent of indolocarbazole thread **16** in the presence of one equivalent of TBACl by ^1H NMR spectroscopy (500 MHz, CDCl_3 , 293 K). For ^1H NMR assignments see Figures 2.5 and 2.32

Chloride anion-templated threading was monitored in a 1:1:1 mixture of macrocycle/thread/anion in CDCl_3 , with strong interactions observed between the anion and indolocarbazole motif (Figure 2.35). The chemical shifts of the macrocycle in the 1:1:1 mixture were compared with the peaks seen in the $[\mathbf{5}\cdot\text{Cl}]$ complex. The triazole proton displays the same resonance at 6.92 ppm for both the 1:1:1 pseudorotaxane study mixture and the $[\mathbf{5}\cdot\text{Cl}]$ complex, indicating no change upon addition of the thread. The amide N–H protons also show little difference between the two studies, indicating triazole–anion and amide–anion hydrogen bonding in the 1:1:1 mixture. Surprisingly, despite the amide resonances indicating anion binding, the isophthalamide phenyl proton (H_6) at δ 7.78 ppm in the 1:1:1 mixture is more comparable with the free macrocycle signal at δ 7.68 ppm, than at 8.50 ppm for the $[\mathbf{5}\cdot\text{Cl}]$ complex. The isophthalamide phenyl protons do not appear to be not involved in anion binding in the 1:1:1 mixture.

A previous indolocarbazole-based [2]-rotaxane showed protons H_a and H_b of the indolocarbazole deshielded by 0.5 ppm due to interaction with the chloride inside the macrocycle cavity, which is not seen here.³⁴⁸ This suggests that the indolocarbazole thread, and the

macrocycle amide and triazole moieties bind to the chloride outside of the macrocycle cavity. Figure 2.36 illustrates the thread position outside of the macrocycle cavity, with the triazole and amide motifs binding the chloride. The key observation that the internal isophthalamide proton is not involved in anion binding in the 1:1:1 mixture behaviour suggests the chloride outside of the cavity and that the macrocycle cavity may be too small to accommodate both thread and anion.

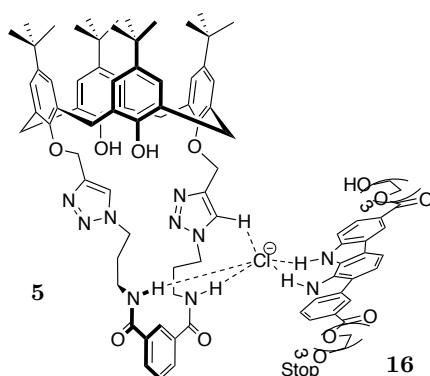


Figure 2.36 Depiction of suspected interaction between macrocycle **5** and thread **16** outside the cavity

A similar anion-templated threading attempt between macrocycle **1** and thread **16** in the presence of one equivalent of TBACl was carried out (Figure 2.37). The indolocarbazole thread again showed no differences upon addition of macrocycle to the [**16** · Cl] complex. Significant shifts were only induced in the macrocycle isophthalamide protons, whilst the triazole C–H intramolecular hydrogen bonding to the calixdiquinone C=O groups remains unperturbed.

Pseudorotaxane formation studies were also carried out between macrocycle **5** and naphthaquinone thread **18** in CDCl₃. No evidence of interactions between the triazole macrocycle and electron-rich thread was observed. Subsequent anion addition only affected the chemical shift of the macrocycle N–H₅, whilst the thread reproduced the chemical shifts seen in anion complexation.

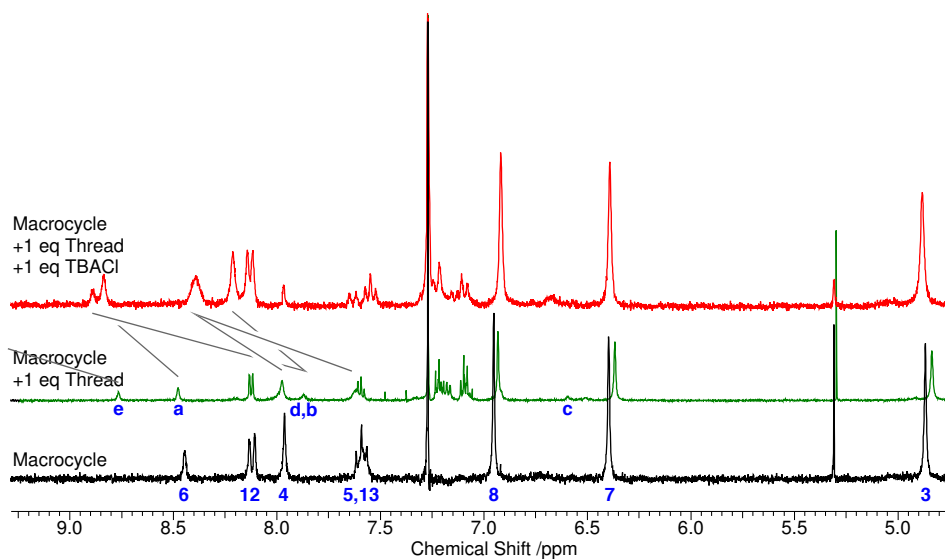


Figure 2.37 Anion-templated pseudorotaxane formation study of macrocycle **1** with one equivalent of indolocarbazole thread **16** in the presence of one equivalent of TBACl by ^1H NMR spectroscopy (500 MHz, CDCl_3 , 293 K). For ^1H NMR assignments see Figures 2.6 and 2.32

It may be that for both macrocycle **5** and **1** the cavity is too small to allow electron-rich threads to penetrate or that the donor–acceptor triazole–indolocarbazole interactions are insufficient to favour pseudorotaxane assembly. The formation of intramolecular hydrogen bonds between the triazole C–Hs, calixarene O–Hs and calixdiquinone C=Os may further constrict the cavity.

2.3.7 Conclusions

Novel macrocycles containing 1,2,3-triazolium have been synthesised and identified as monoalkylated calix[4]arene, **8**, and dialkylated calixdiquinone, **7**, variants, with some evidence also found for the bis-triazolium calix[4]arene macrocycle, **6**. Unfortunately, it proved prohibitively difficult to synthesise and isolate sufficient quantities of these triazolium-based macrocycles for undertaking anion binding and pseudorotaxane investigations.

Macrocycles **1** and **5** have been investigated for their potential in forming pseudorotaxanes with electron-rich threads. No direct evidence was observed that the threads studied (indolo-

carbazole **16** and dihydroxy naphthalene ether **18**) intercalated within the macrocycle cavity even in the presence of a chloride anion template. The macrocycle cavity is thought to be too small to allow these threads to interpenetrate, especially as intramolecular hydrogen bonding between the triazole C–Hs, calixarene O–Hs and calixdiquinone C=Os will further constrict the cavity.

2.4 Towards ion-pair binding by interlocked structures

The successful ion-pair binding macrocycle, **1**, described earlier in this chapter provided the basis for progress towards an interlocked structure for ion-pair binding. The ion recognition versatility of 1,2,3-triazole was established, with its Lewis basic nitrogens and C–H hydrogen-bond donor capable of simultaneously binding cations and anions, respectively, in solution. Incorporated into a macrocycle component, the integration of the triazole motif into the axle covalent structural framework would also provide anion- and cation-binding ability in a putative interlocked structure. The classic aromatic donor–acceptor combination of electron-rich hydroquinone and electron-deficient pyridinium and pyridine *N*-oxide derivatives was identified as a suitable method for threading the axle component through the macrocycle.

2.4.1 Introduction to key motifs

PYRIDINIUM

N-Alkylated pyridinium has long been used for its electron-deficient π -surface as a constituent of cyclobis(paraquat-*p*-phenylene), covered in more detail in Chapter 3.^{370,371} More recently, *N*-methylated pyridinium has been incorporated into the core of electron-deficient axles, providing a means of threading the axle between two parallel electron-rich π -systems in the macrocycle. An example of *N*-methyl pyridinium in an anion-templated interlocked structure was mentioned in the introduction (Figure 1.43a).^{295–297} In addition to its cationic nature, 3,5-bis-substituted pyridinium possesses potent C–H hydrogen-bond donors at the *ortho*- and *para*-positions.

PYRIDINE *N*-OXIDE

Oxidation of the pyridine nitrogen forms the pyridine *N*-oxide. This core is less electron-deficient than the *N*-methyl pyridinium, resulting in diminished anion-binding and π -interaction ability. However, the key to this motif is its retention of an electronegative

atom at one end for cation binding, whilst improving the hydrogen-bond donor ability at the *para*-position.

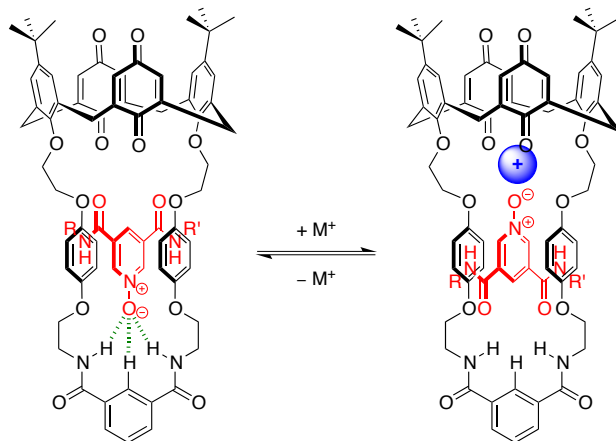


Figure 2.38 The pyridine *N*-oxide axle is bound by the macrocycle isophthalamide as shown and pirouettes in the cavity upon cation coordination at the calixdiquinone

Recent research by Beer and co-workers has utilised the pyridine *N*-oxide core integrated into the axle as part of a [2]rotaxane formed by cation templation (Figure 2.38).³⁷² The electronegative oxygen atom of the pyridine *N*-oxide motif is bound by the macrocycle isophthalamide motif. However, upon coordination of either Na^+ or Ba^{2+} by the calixdiquinone motif in 5:1 $\text{CDCl}_3/\text{CD}_3\text{CN}$, the axle pirouettes to provide additional coordination through the oxygen centre. Ballester has reported a pyridine *N*-oxide core in a heteroditopic axle as part of an anion-templated pseudorotaxane in chloroform; this was highlighted in the introductory chapter (Figure 1.39).²⁹¹

HYDROQUINONE

Hydroquinone is an electron-rich aromatic system designed for aromatic donor–acceptor interactions with similarly-sized electron deficient systems.^{363,373–375} Hydroquinone has previously been used to assist intercalation of pyridinium axles (see introduction, Section 1.7).^{295–297}

2.4.2 Macrocycle design

As macrocycle **5** was thought to be too small for threading components to penetrate, the cavity size required expansion. Incorporation of the electron-rich hydroquinone motif increases macrocycle size with a rigid linker and provides a π -surface to attract potential electron-deficient axle core motifs. The cation-binding calix[4]diquinone and anion-binding isophthalamide are retained, together with the amphiphilic 1,2,3-triazole. This expanded target macrocycle **19** is shown in Figure 2.39 with expected positions for cation binding, axle threading and anion binding illustrated.

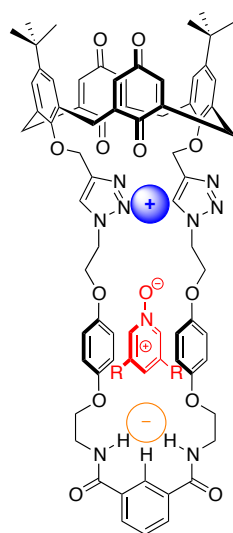
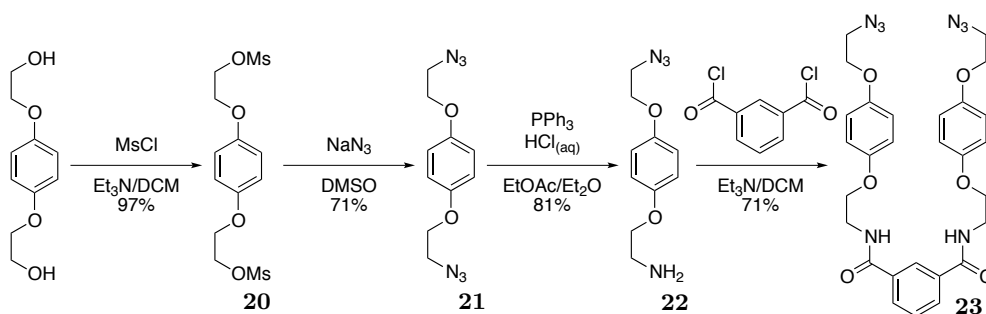


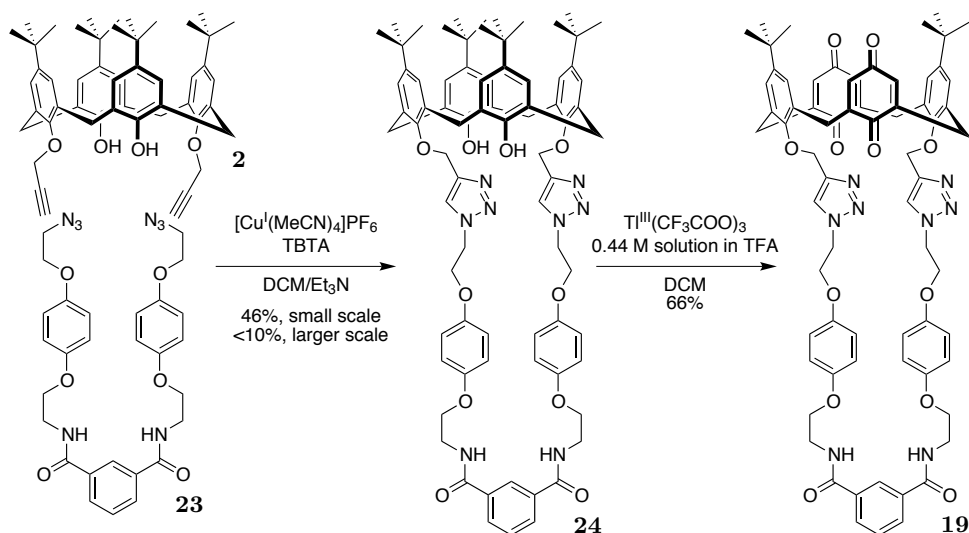
Figure 2.39 The large target macrocycle **19** contains the cation-binding calix[4]diquinone cavity with triazoles, the anion-binding isophthalamide pocket and the electron-rich hydroquinone linker for π - π interactions with the electron-deficient pyridine *N*-oxide thread

2.4.3 Macrocycle synthesis



Scheme 2.12 Synthetic route to azide-appended precursor **23**

The synthesis of the mixed amine/azide-appended linker **22** proceeded according to literature precedent.^{376,377} Mesylation of commercially available hydroquinone dialcohol gave **20**, which was reacted with sodium azide to form diazide **21**. Mono-reduction by triphenylphosphine afforded the mixed amine/azide, **22**. Two equivalents of **22** were then condensed with isophthaloyl dichloride to form the azide-appended “click” reaction precursor **23** (Scheme 2.12).



Scheme 2.13 Synthetic route to heteroditopic macrocycle **19**

The synthesis of dialkyne **2** has already been described in Scheme 2.3. This dialkyne was reacted on a small scale with diazide **23** under high dilution conditions in a double CuAAC reaction to form the expanded calix[4]arene macrocycle, **24**. Due to the lengthy arms attached to the isophthalamide motif, attempted templation with one equivalent of TBACl had no effect on the reaction yield. Purification of macrocycle **24** was undertaken by both column chromatography and preparative TLC, as isolating the desired macrocycle from TBTA was extremely difficult. This problem was compounded when attempting this macrocyclisation on a larger scale, even when reducing the stoichiometry of copper(I)-stabilising TBTA in the reaction.³⁷⁸ An impure sample of **24** was oxidised with fresh thallium(III) trifluoroacetate reagent in TFA,^{324,325} to afford a small quantity of relatively pure target macrocycle **19** (Scheme 2.13, see also the safety warning in Section 6.5).

2.4.4 Macrocycle characterisation

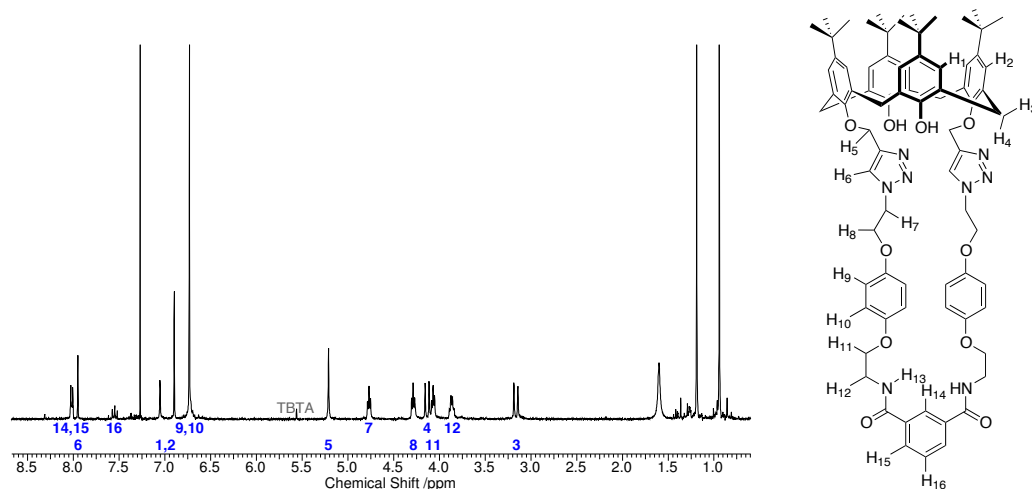


Figure 2.40 Partially assigned ¹H NMR spectrum (300 MHz, CD₃CN, 298 K) of macrocycle **24**

Precursor macrocycle **24** is a white solid, with the partially assigned ¹H NMR spectrum shown in Figure 2.40. The macrocycle was also characterised by ¹³C NMR spectroscopy and high resolution ESI-MS.

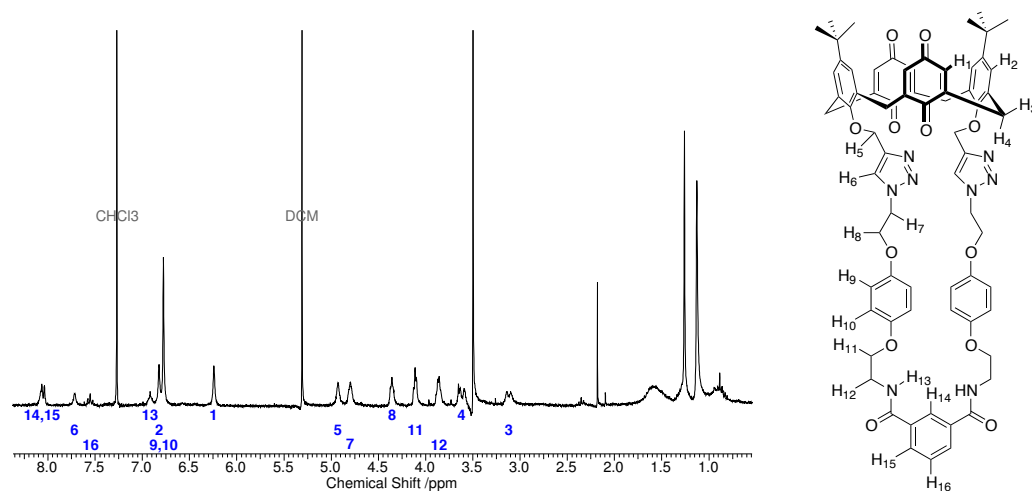


Figure 2.41 Partially assigned ¹H NMR spectrum (300 MHz, CDCl₃, 298 K) of macrocycle **19**

Heteroditopic receptor **19** is a yellow-orange solid, but was difficult to completely purify, with the partially assigned ¹H NMR spectrum shown in Figure 2.41. The electron-withdrawing oxygens reduce the ring current of the calixdiquinone aromatic system, resulting in a more upfield chemical shift at δ 6.24 ppm, compared with the phenolic signal at 6.90 ppm in the calix[4]arene. The other proton signals in the aromatic region occur at similar chemical shifts

in macrocycle **24** and macrocycle **19**. Minor impurities in macrocycle **19** may contribute to the peak broadening in the alkyl region. The heteroditopic receptor was also further characterised by high resolution ESI-MS, but was not purified in sufficient quantity to obtain a ^{13}C NMR spectrum.

2.4.5 Preliminary cation binding studies

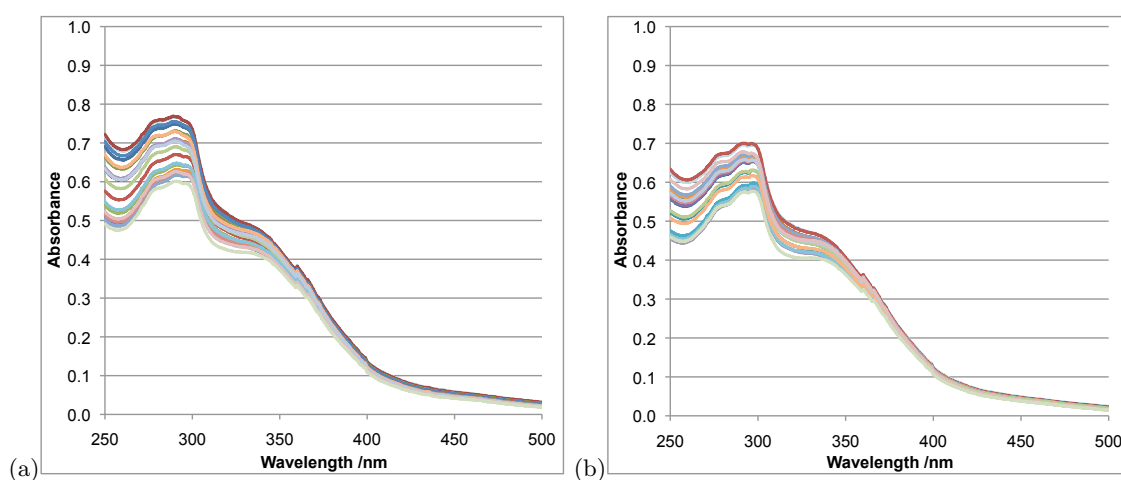


Figure 2.42 Variation in the absorbance of macrocycle **19** in response to addition of (a) KPF_6 and (b) NaPF_6 , respectively. Solvent, 2% $\text{H}_2\text{O}/\text{CH}_3\text{CN}$; temperature, 298 K; $[\mathbf{19}]_i = 3 \times 10^{-4} \text{ mol dm}^{-3}$; titrant $[\text{MPF}_6] = 0.09 \text{ mol dm}^{-3}$

The monovalent cations K^+ and Na^+ were used to ascertain the cation-binding affinity of the expanded heteroditopic macrocycle **19**. Added as their MPF_6 salts, these resulted in the UV-vis absorbances shown in Figures 2.42a and b, for KPF_6 and NaPF_6 addition, respectively. At first glance, there appears to be cation-induced enhancement of the absorbance around the local maximum at 290 nm. However, odd results were found by monitoring the absorbance at 290 nm as there was no smooth change in absorbance, but cation-independent fluctuations. These strange absorbances remain unexplained, perhaps traces of TBTA polluting the sample of **19** might be responsible.

2.4.6 Thread design

To ensure binding capability for both cations and anions, two 1,2,3-triazole groups were to be incorporated into the target axle structure.

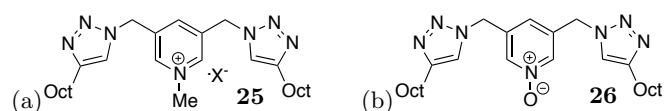


Figure 2.43 Model thread components (a) **25** and (b) **26** both contain electron-deficient aromatic cores for π -interactions, with hydrogen-bond donating C–Hs and amphiphilic 1,2,3-triazole linkers

Model thread components **25** and **26** (Figures 2.43a and b, respectively) were proposed as being synthetically accessible and suitable for investigating cation- and anion-binding properties, as well as pseudorotaxane formation with macrocycle **19**.

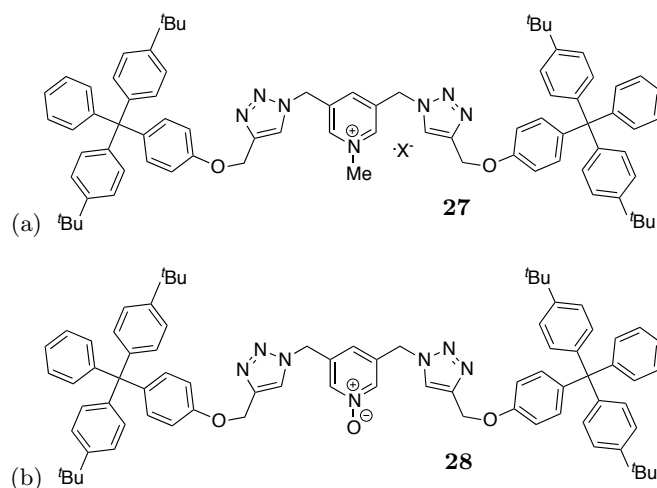
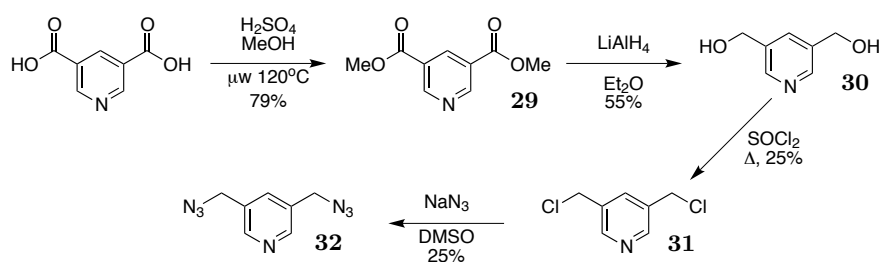


Figure 2.44 Stoppered axles (a) **27** and (b) **28** were targeted to study the required stopper bulk to prevent slippage

Whilst macrocycle **5** has an internal ring of 32 atoms, the expanded macrocycle **19** is significantly larger, with a ring of 46 atoms. Therefore, stoppered axle variants **27** and **28** were also targeted to investigate whether the tetraaryl stoppers would be sufficiently bulky to prevent slippage of the macrocycle off the axle (Figures 2.44a and b, respectively). If sufficient, then appropriate bis-azide functionalised pyridinium or pyridine *N*-oxide derivatives could interpenetrate the macrocycle cavity using anion and/or cation templation, prior to stoppering by click reaction.

2.4.7 Thread synthesis

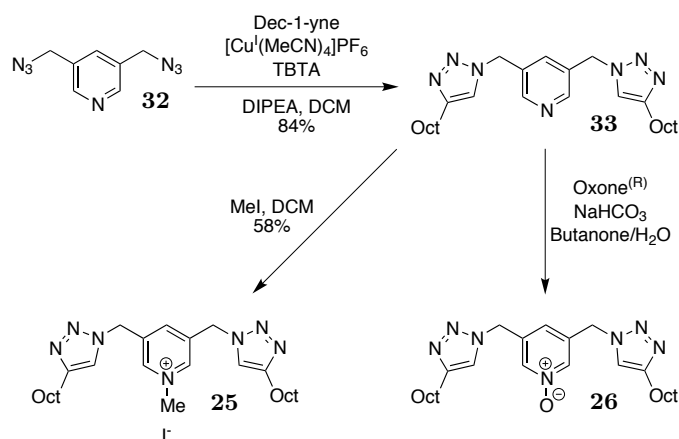
The 3,5-disubstituted pyridine core was synthesised according to a modified procedure with the first three steps based on literature precedent (Scheme 2.14).³⁷⁹ Commercially available 3,5-pyridinedicarboxylic acid was converted to the methyl ester (**29**). This was then carefully reduced to dialcohol **30** using only a small excess of fresh LiAlH_4 , as overaddition of LiAlH_4 resulted in reduction of the pyridine group. In addition, successful isolation of dialcohol **30** was problematic as this precursor is known to decompose under ambient conditions by absorbing $\text{CO}_{2(\text{g})}$. Immediately reacting the dialcohol with thionyl chloride afforded reactive dichloride intermediate **31**, which was swiftly reacted on with excess sodium azide in DMSO to afford the novel 3,5-bis-azide methylene pyridine derivative required (**32**) in only 3% yield over four steps.



Scheme 2.14 Synthetic route to key 3,5-substituted pyridyl core **32**

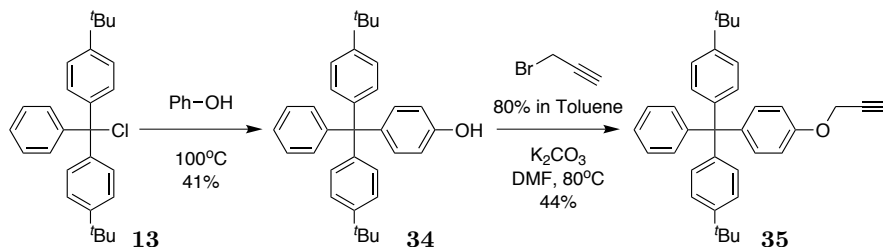
The fickle nature of the ester reduction and subsequent chlorination reaction, combined with the instability of the intermediates formed results in the low-yielding later steps. Diazide **32** was stored in the freezer to delay decomposition.

Final synthetic steps to octyl-appended model axles **25** and **26** are shown in Scheme 2.15. The double click reaction with dec-1-yne proceeded smoothly to form bis-triazole compound **33**. Methylation required a large excess of methyl iodide in DCM and proceeded almost exclusively at the more nucleophilic pyridine nitrogen, rather than at any triazole nitrogens. However, conversion from the iodide salt to the non-coordinating hexafluorophosphate



Scheme 2.15 Synthesis of model octyl-chain threads containing *N*-methyl pyridinium, **25**, and pyridine *N*-oxide, **26**

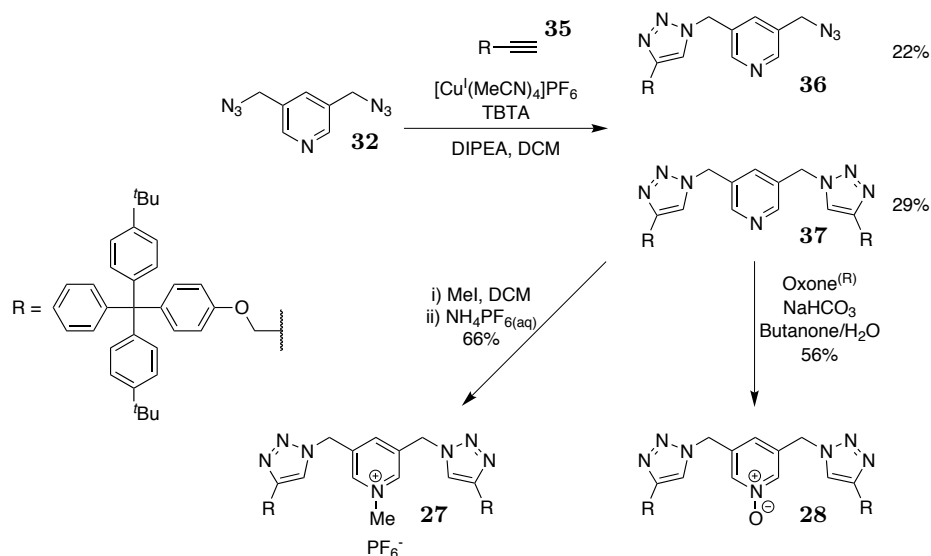
anion proved problematic and unsuccessful either *via* washing with $\text{NH}_4\text{PF}_6(\text{aq})$ or using ion-exchange resin. Oxidation to form the *N*-oxide was partially successful, as the reaction with Oxone[®] reagent afforded a sample of **26**. Unfortunately, this could not be separated from starting material **33**. The estimated yield based on integration in the ^1H NMR spectrum is 72%.



Scheme 2.16 Synthetic route to alkyne-appended stopper **35**

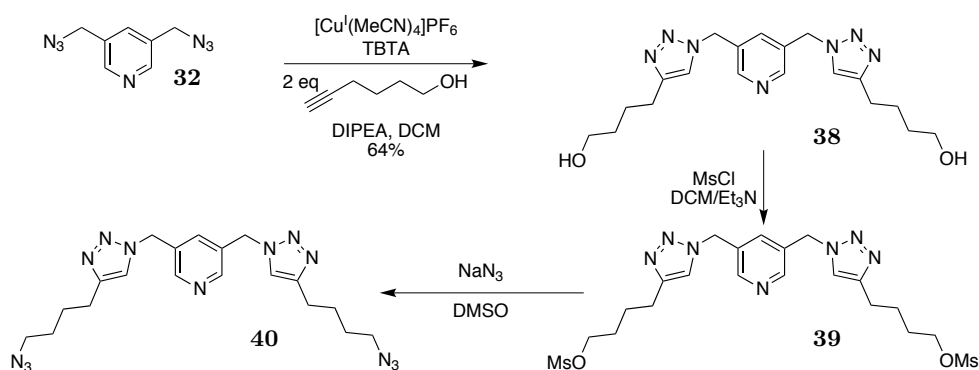
Alkyne-appended bulky *t*butyl-containing stopper groups, required in the synthesis of axles **27** and **28**, were synthesised according to literature procedures as shown in Scheme 2.16. The synthesis of triaryl component, **13**, has already been described (Scheme 2.9) and further reaction with phenol afforded the phenol-appended stopper, **34**.³⁶⁸ This was reacted with propargyl bromide to deliver the required stopper with a terminal alkyne, **35**.^{377,380}

This alkyne-appended stopper, **35**, was initially reacted in a 1:1 stoichiometry with bis-azide pyridine **32**, with the CuAAC reaction forming a mixture of mono- (**36**, 22%) and bis-reacted



Scheme 2.17 Synthesis of stoppered threads containing *N*-methyl pyridinium, **27**, and pyridine *N*-oxide, **28**

products (**37**, 29%). The mono-stoppered product was intended for use as a semiaxle in rotaxane formation, however, swift decomposition at the α -azide was identified, requiring it to be reacted with further stopper **35** to afford the stable bis-stoppered axle, **37**. From pyridyl axle **37**, the methylation and subsequent ion-exchange to form hexafluorophosphate salt **27** proceeded smoothly, as did oxidation with Oxone[®] to form pyridine *N*-oxide **28** as shown in Scheme 2.17.



Scheme 2.18 Synthesis of the thread precursor, **40**, to [2]catenane formation

The synthetic route towards bis-azide-appended threads is shown in Scheme 2.18. Two equivalents of commercially available hex-5-yn-1-ol were coupled to **32** *via* copper(I)-catalysed click reaction to form the dialcohol, **38**. Although successful on a small scale, this substrate

was extremely hygroscopic and could not be extracted from the aqueous layer in larger scale reactions. Attempts at removing all solvents formed an aqueous gel, even under high vacuum. With only a small quantity of dialcohol **38** in hand, it was reacted on to ascertain the feasibility of the subsequent synthetic steps. The dialcohol was reacted with methanesulfonyl chloride to form dimesylate **39**. This was immediately reacted on with sodium azide to afford a sample of diazide, **40**, sufficient for characterisation, but no further reactions.

2.4.8 Thread characterisation

Alkylated pyridinium octyl thread **25** was a water-soluble mixed I^-/PF_6^- salt after the attempted ion-exchange and could not be separated from the salty aqueous mixture for any characterisation or further use.

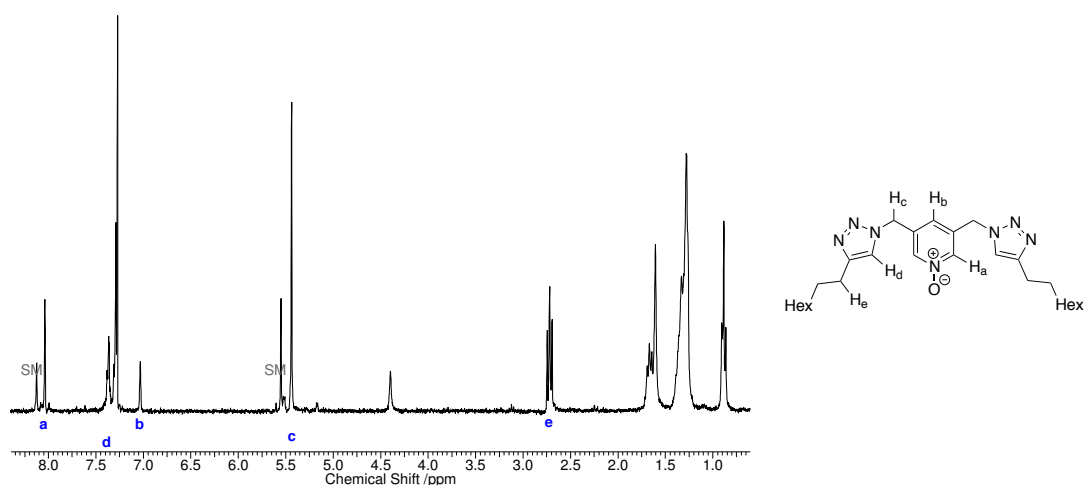


Figure 2.45 Partially assigned ^1H NMR spectrum (300 MHz, CDCl_3 , 298 K) of octyl-chain thread **26**, SM = starting material **33**

Octyl pyridine *N*-oxide thread **26** was identified by ESI-MS in its inseparable mixture with the pyridine precursor **33**. By comparison with the starting material ^1H NMR spectrum the signals for the *N*-oxide derivative were identified, as shown in Figure 2.45. The pyridinium *ortho*- and *para*-protons are at δ 8.04 and 7.03 ppm, respectively, with the triazole C–H at 7.37 ppm.

The two stoppered threads were successfully synthesised and purified as white solids and could be characterised fully by ^1H and ^{13}C NMR spectroscopy and high resolution ESI-MS. The ^1H NMR spectrum of **27** is shown in Figure 2.46 and contains the characteristic pyridinium methyl singlet at δ 4.15 ppm. The pyridinium *ortho*- and *para*-protons are downfield at δ 8.51 and 8.20 ppm, respectively, with the triazole C–H at 7.81 ppm.

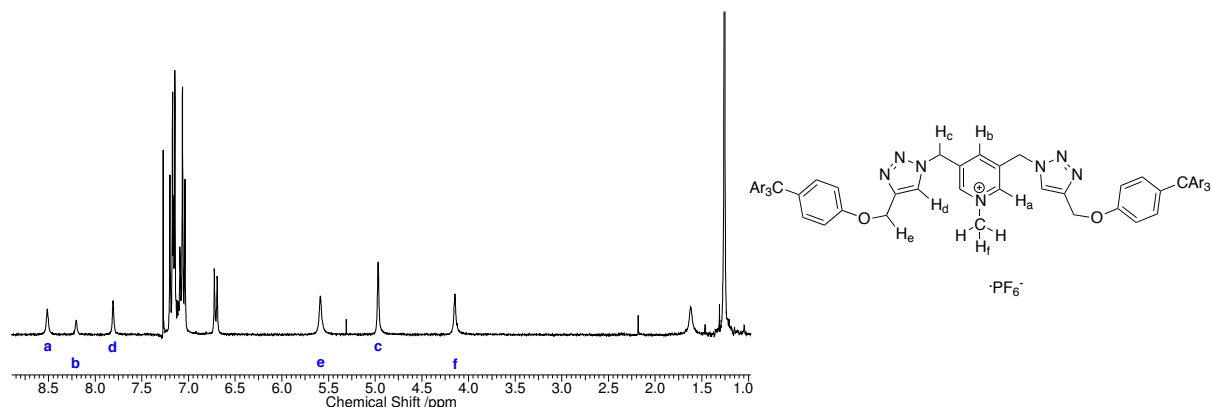


Figure 2.46 Partially assigned ^1H NMR spectrum (300 MHz, CDCl_3 , 298 K) of stoppered thread **27**

The ^1H NMR spectrum of **28** is shown in Figure 2.47. The aromatic protons of this neutral compound are upfield relative to the cationic methyl pyridinium derivative, with signals for the pyridine *ortho*-proton at δ 8.10 and the triazole C–H at 7.67 ppm.

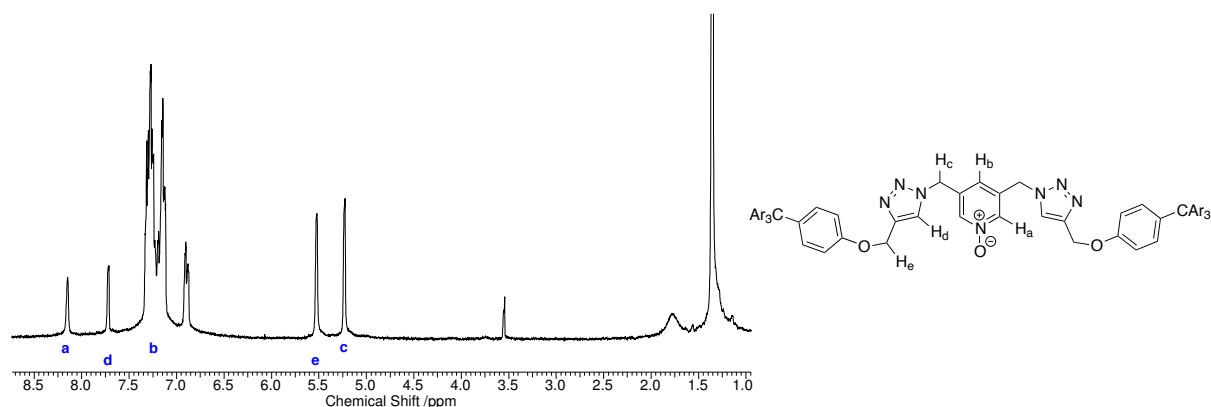


Figure 2.47 Partially assigned ^1H NMR spectrum (300 MHz, CDCl_3 , 298 K) of stoppered thread **28**

2.4.9 Preliminary anion binding studies

^1H NMR spectroscopy was used to examine the preliminary anion-binding affinities of compounds **26**, **27** and **28**. This was investigated in acetone- d_6 , with monovalent anions

added as their TBAX salts ($X = \text{Cl}, \text{Br}, \text{I}$). Changes in the chemical shifts of the pyridine *ortho*- and *para*-protons were most significant, with shifts in the pyridinium *N*-methyl protons also observed. Unfortunately, the triazole proton was typically overlaid by the aryl protons of the terphenyl substituents, so could not be followed. In the case of **26** the solubility problems prevented association constant determination.

Compound	Anion	Association K_{11} / M^{-1}
N^+Me , 27	Cl^-	$>10^4$
N^+Me , 27	Br^-	6430 (673)
N^+Me , 27	I^-	1360 (95)
N^+O^- , 28	Cl^-	47 (7)
N^+O^- , 28	Br^-	19 (1)
N^+O^- , 28	I^-	12 (1)

Table 2.7 ^1H NMR K_{11} values for interactions of compounds **27** and **28** with various anions. 500 MHz; solvent, acetone- d_6 ; temperature, 293 K; $[\text{Thread}]_i = 1.5 \times 10^{-3} \text{ mol dm}^{-3}$; titrant $[\text{TBACl}] = 0.075 \text{ mol dm}^{-3}$

Association constants (Table 2.7) were determined by monitoring the *para*-pyridyl proton (Figure 2.48) using WinEQNMR2 analysis.³⁵¹ Table 2.7 shows, as expected, that the cationic pyridinium derivative, **27**, binds halide anions far more strongly than the neutral pyridine *N*-oxide counterpart, **28**.

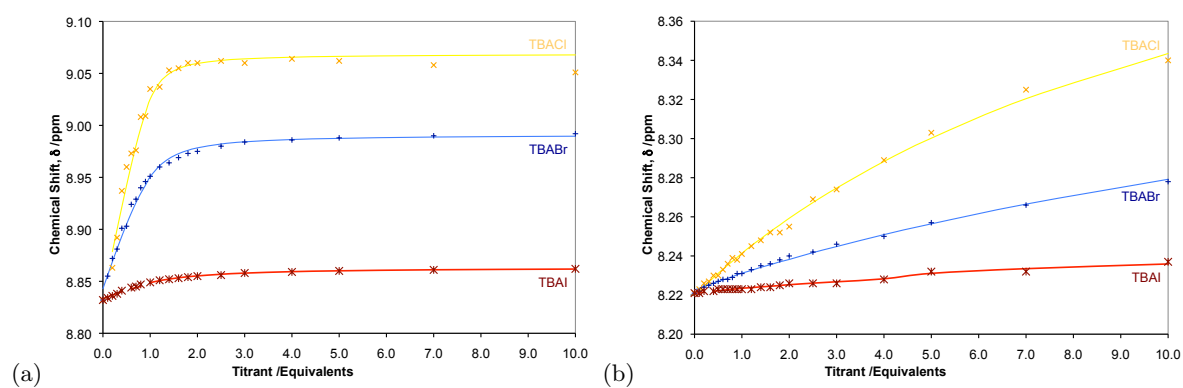


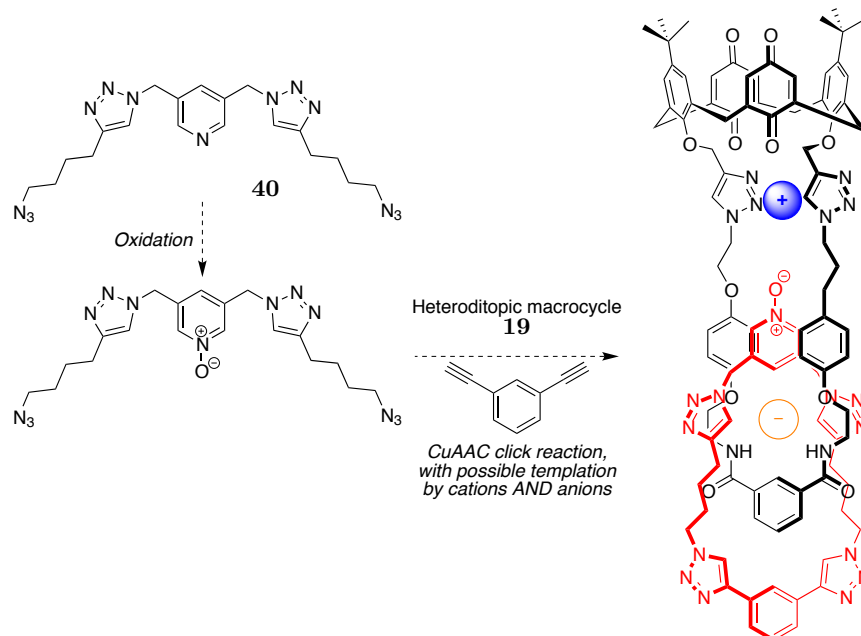
Figure 2.48 Monitoring the chemical shift (500 MHz, acetone- d_6 , 293 K) of the *para*-proton upon addition of equivalents of TBACl ($\times$), TBABr ($+$) or TBAI ($*$) to compounds (a) **27** and (b) **28**

The affinity of thread **27** for the halides is strong, especially for Cl^- and Br^- , and approximations of Job plot experiments for threads **27** and **28** clearly indicated a 1:1 binding stoichiometry (see Chapter 6).

2.4.10 Conclusions and future work

Two novel large heteroditopic macrocycles **19** and **24** have been synthesised. Unfortunately, difficulties were encountered in purification when attempting to prepare samples of the macrocycles on a larger scale, with yields reducing significantly. The limited supply of material curtailed any in-depth cation and anion binding studies from being undertaken.

A new series of potential threads containing 1,2,3-triazole has been synthesised and characterised, despite a torturous synthetic route with many decomposable intermediates. Both *N*-methyl pyridinium and pyridine *N*-oxide cores have been utilised in anticipation of anion templated interpenetration within an electron-rich macrocycle. Anion titrations by ^1H NMR spectroscopy have determined that the cationic *N*-methyl pyridinium motif binds halide anions more strongly than the neutral pyridine *N*-oxide derivative, with both exhibiting a preference for chloride. The discovery that bis-azide precursor **32** decomposes has prevented [2]rotaxane formation with macrocycle **19** based on a stoppering method being explored.



Scheme 2.19 Suggested synthetic route towards an ion-pair sensing [2]catenane, formed by an ion-pair templated CuAAC click reaction

Progress has been made towards a versatile azide-appended axle precursor that is stable for application in interlocked structure synthesis. Once the synthesis of this bis-azide is optimised, only a few steps remain for the formation of an ion-pair binding [2]catenane, the suggested synthetic route for which is shown in Scheme 2.19. Formation of the interlocked structure between two heteroditopic components may be possible under ion-pair templation conditions.

Chapter 3

Cationic Macrocycles and Electron-Rich Threads

3.1 Introduction

This chapter will focus on the formation of interpenetrative structures containing cationic macrocycles and electron-rich threads for anion recognition. The chapter is separated into three parts, each characterised by the nature of the cyclic cationic motif used for anion binding and pseudorotaxane assembly studies with electron-rich threads, as follows:

- (i) imidazolium-based cationic macrocycles;
- (ii) cationic macrocycles containing the pyridinium motif;
- (iii) triazole-based macrocycles.

3.1.1 The cationic macrocycle “box”

The 4,4'-bipyridinium moiety (viologen) has been used for over two decades^{370,371} as an electron-deficient motif for attracting anions and, when integrated into a cyclic framework, for assembling interpenetrative structures with electron-rich threads.^{362,363,365,374,375,381,382} In particular, incorporation into a tetracationic macrocycle has typically been in the form of cyclobis(paraquat-*p*-phenylene) — a rigid macrocyclic box with significantly electron-deficient π -surfaces for interactions with electron-rich species.

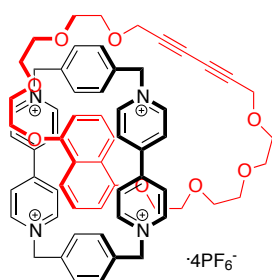


Figure 3.1 The 4,4'-bipyridinium macrocycle box in Stoddart's [2]catenane with naphthalene diol. One such recent example is the water-soluble [2]catenane reported by Stoddart (Figure 3.1).³⁶¹ This combines the traditional elements of the viologen and naphthalene diol motifs, but with sufficient glycol solubilising spacers to allow synthesis of the [2]catenane under mild Glaser coupling in aqueous media.

Work by Brown *et al.* modified the 4,4'-bipyridinium-based macrocycle with incorporation of the isophthalamide motif (covered in Section 1.4), creating a macrocycle with improved anion-binding properties.³⁴⁸ In conjunction with an indolocarbazole axle (also covered in Chapter 2), the macrocycle was incorporated into a [2]rotaxane using the stoppering method without requiring a templating anion, Figure 3.2.

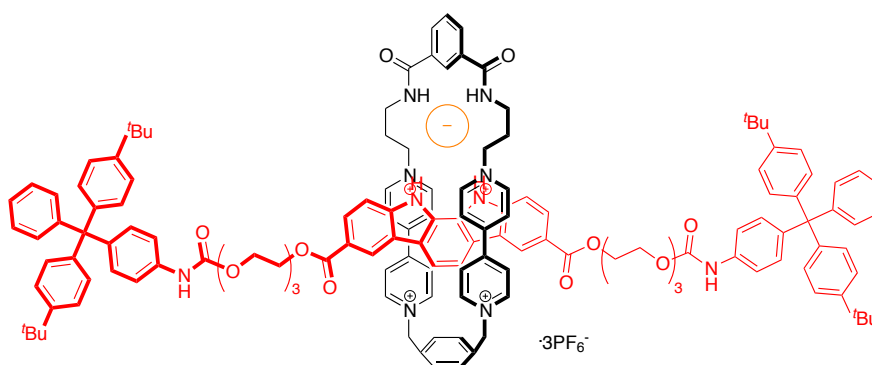


Figure 3.2 Beer's anion-sensing [2]rotaxane with indolocarbazole and a bipyridinium-containing macrocycle box

A major drawback in the use of cyclic 4,4'-bipyridinium receptors for anion sensing is their propensity to decompose upon addition of anions such as F^- and SO_4^{2-} ,³⁴⁸ by either attacking the electrophilic ArCH_2Pyr linker or by electron transfer to the viologen moiety.^{383,384}

The body of research in this chapter will seek an optimal balance between cationic macrocycles suitable both for donor-acceptor π - π stacking with electron-rich threads and for efficient anion binding, whilst retaining some elements of the facile synthesis seen in the previous examples.

3.2 Imidazolium-based macrocycles

3.2.1 System design

Research by Beer and co-workers investigated the direct replacement of the 4,4'-pyridinium motif of a cyclic structure with imidazolium as the cationic component instead. The viologen is a linear linking moiety and to achieve a comparable effect, two imidazoles were separated by a phenyl linker to form a rigid spacer and produce macrocycle **41** (Figure 3.3a).³⁸⁵ Importantly, no signs of decomposition were seen upon anion addition, with deprotonation only occurring with F^- .

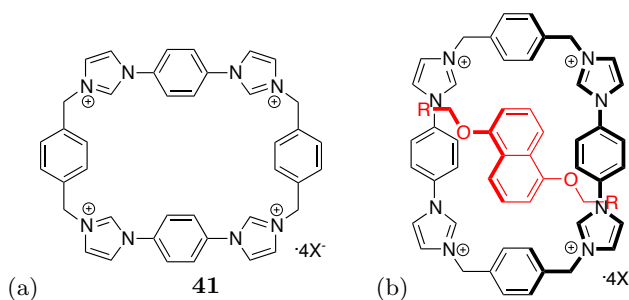


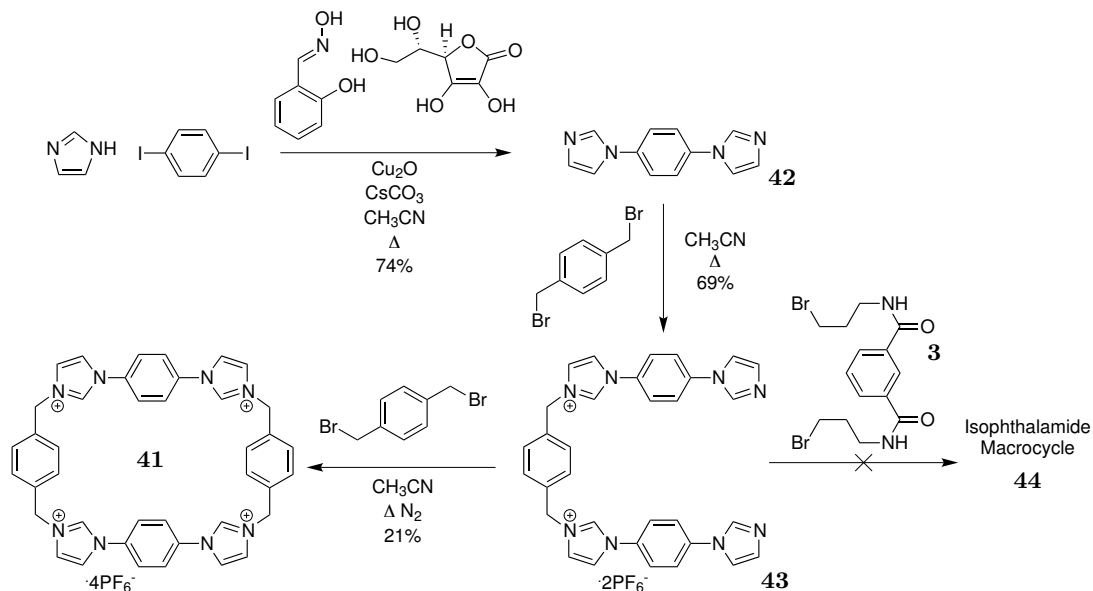
Figure 3.3 Cationic box analogue (a) tetraimidazolium macrocycle **41** and (b) a target [2]rotaxane using a dihydroxy naphthalene ether derivative

Although there was some evidence for pseudorotaxane formation between **41** and 1,5-disubstituted naphthalene diol derivatives, preliminary attempts at forming [2]rotaxanes were unsuccessful.³⁸⁶ The initial aim of this chapter was therefore to focus on attempts at constructing new [2]rotaxanes, such as in Figure 3.3b, containing macrocycle **41** as the ring component.

3.2.2 Macrocycle synthesis and characterisation

The synthesis of macrocycle **41** was carried out according to the recently published procedure (Scheme 3.1).³⁸⁵ A double Ullman coupling forms bis-imidazole **42**, followed by reaction

with α,α' -dibromoxylene to produce precursor **43**. Cyclisation with a further equivalent of α,α' -dibromoxylene, followed by anion exchange, affords desired macrocycle **41**.



Scheme 3.1 Synthetic route to macrocycle **41**

The attempted synthesis of the related isophthalamide-containing macrocycle was also undertaken by reaction of compound **43** with compound **3**. However, in spite of numerous purification attempts, the product macrocycle **44** proved inseparable from the dicationic precursor, **43**.

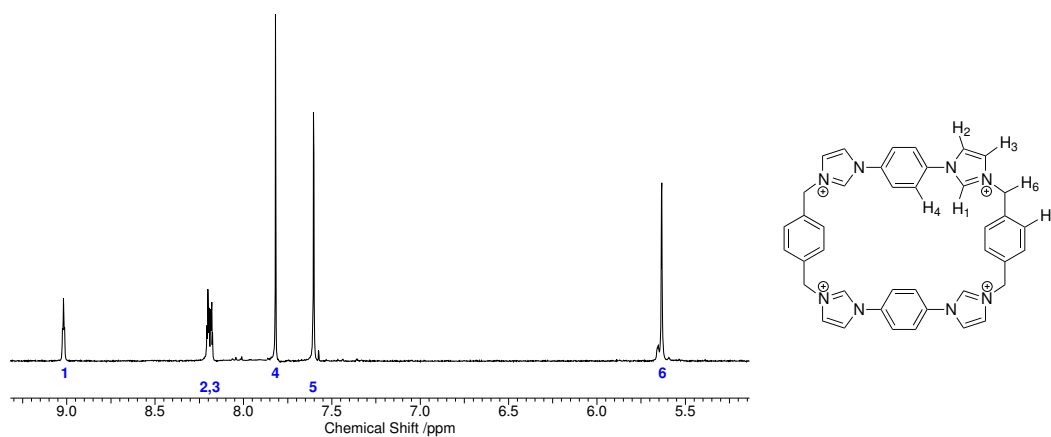


Figure 3.4 Fully assigned ^1H NMR spectrum (300 MHz, CD_3CN , 298 K) for macrocycle **41**

The successful synthesis of macrocycle **41**, a white solid, was confirmed by comparison of ^1H and ^{13}C NMR spectra and EI-MS data with those reported. As this macrocycle will be

used in pseudorotaxane studies, the key protons from its ^1H NMR spectrum are assigned, as highlighted in Figure 3.4.

This symmetrical macrocycle has few complications in assignation. The most deshielded proton is H_1 at δ 9.03 ppm, residing next to two nitrogens on the imidazolium. The other imidazolium protons H_2 and H_3 are very close together at ~ 8.2 ppm. Phenyl protons H_4 and H_5 follow according to through-bond proximity to electron-withdrawing groups and the only non-aromatic protons are $\text{ArCH}_2\text{Ar}'$ at 5.64 ppm.

3.2.3 Thread design

Previous work in the group had identified 1,5-dihydroxy naphthalene ethers as suitable intercalators of macrocycle **41**. The threads chosen were composed of varying chain lengths, because once an axle precursor has intercalated the cavity of the macrocycle, longer chain “arms” can result in a greater energy barrier to dethreading, leading to a better chance of a successful rotaxation reaction.³⁶⁷ These threads are shown in Figure 3.5 and contain propargyl (**18**, a), glycol (**45**, b) and tetraglycol (**46**, c) substituents respectively.

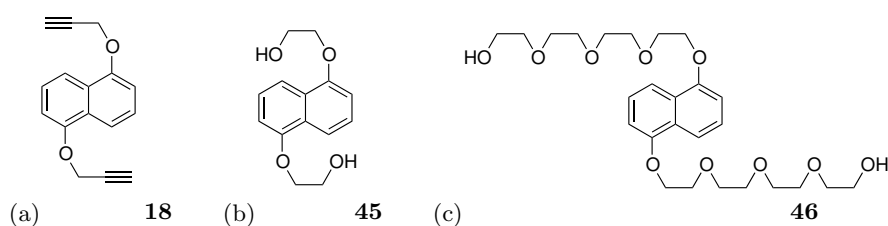


Figure 3.5 Suitable 1,5-dihydroxy naphthalene ether derivatives for intercalating macrocycle **41**, with (a) propargyl (**18**), (b) glycol (**45**) and (c) tetraglycol (**46**) chains

The favoured approach to [2]rotaxane synthesis was using a stoppering method under mild reaction conditions. Two appropriate reactions are the “click” reaction to form 1,2,3-triazole by azide–alkyne cycloaddition and carbamate formation from primary alcohols and highly reactive isocyanates ($\text{RN}=\text{C}=\text{O}$). Both of these sets of reactions proceed at room temperature and are inherently clean, i.e. with few undesired side-products. Also, the triazole and

carbamate covalent linkers incorporated into the resulting axle structure provide additional anion binding motifs for the desired [2]rotaxane, as shown in Figure 3.6a and b, respectively.

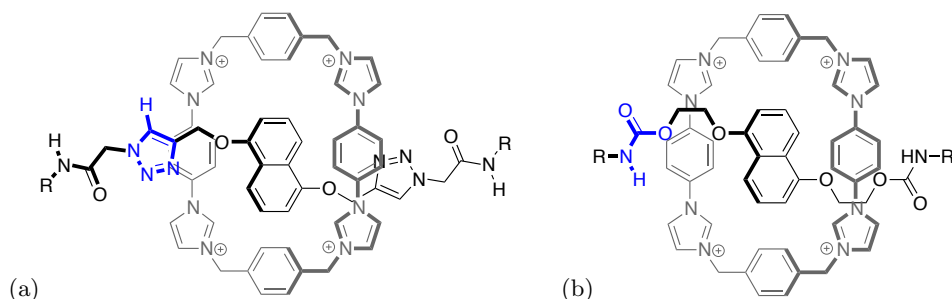
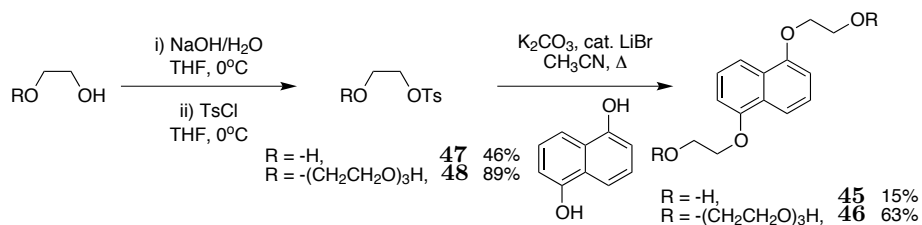


Figure 3.6 The stoppering methods introduce anion binding motifs to the dihydroxy naphthalene ethers: (a) amide and triazole onto the propargyl-functionalised precursor and (b) carbamate onto the glycol-functionalised precursors

3.2.4 Thread synthesis

All three threads were prepared from commercially available 1,5-naphthalene diol. The synthesis of propargyl-substituted axle **18** was previously described in Scheme 2.11.³⁶⁹



Scheme 3.2 Synthetic route to polyether axles **45** and **46**

Both of the glycol derivatised threads were prepared in a two-stage process, *via* a tosylate intermediate. The standard literature procedure of reacting a basic solution of either excess ethylene or tetraethylene glycol with *p*-toluenesulfonyl chloride was used to form the monotosylated species, glycol **47** or tetraglycol **48**, respectively.^{387–389} This was then followed by reaction with 1,5-naphthalene diol in the presence of base and catalytic LiBr to assist the electrophilicity of the substrate in the S_N2 reaction. The glycol- (**45**) and tetraglycol-substituted (**46**) threads were obtained as a brown solid and red oil, respectively, following purification by column chromatography.³⁹⁰

3.2.5 Thread characterisation

The glycol (**45**) and tetraglycol (**46**) threads were characterised by ^1H and ^{13}C NMR spectroscopy and ESI-MS, with data agreeing well with published results.^{389,390} Unsurprisingly, these two axles exhibited little difference between their ^1H NMR spectra in the aromatic region — key for monitoring during (pseudo)rotaxanation studies. The aromatic protons from the more soluble tetraglycol thread **46** are assigned in Figure 3.7.

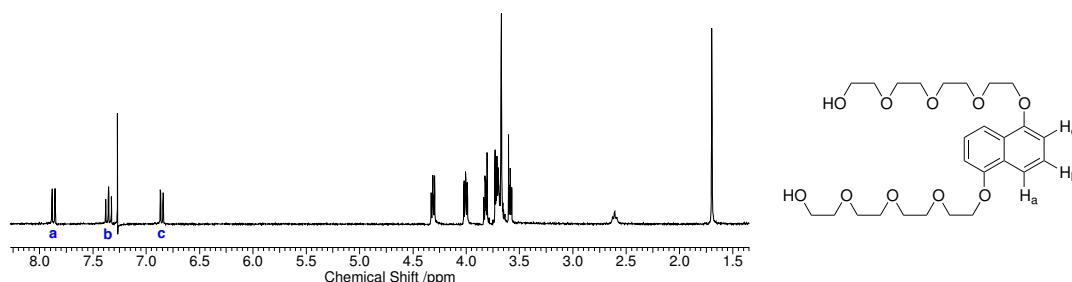


Figure 3.7 ^1H NMR spectrum (300 MHz, CDCl_3 , 298 K) assigning the aromatic resonances of axle component **46**

3.2.6 Pseudorotaxane studies

Studies were carried out by ^1H NMR spectroscopy to investigate whether pseudorotaxanes were formed between electron-poor macrocycle **41** and the electron-rich threads. A straightforward approach was undertaken initially with a qualitative comparison monitoring the chemical shifts of macrocycle and thread with a 1:1 equimolar combination of the two components in CD_3CN solution.

The addition of one equivalent of propargyl-appended axle **18** to macrocycle **41** was monitored by ^1H NMR spectroscopy, as shown in Figure 3.8. Despite the very short (three-atom) linkers from the 1,5-naphthalene diol, thread intercalation of the macrocycle induces small changes in the chemical shifts of both components. The macrocycle phenyl and xylenic protons resonances (H_4 and H_5) converge, with the phenyl resonances (H_4) shifting upfield by 0.03 ppm, whilst xylene (H_5) shifts downfield by 0.01 ppm. The axle aromatic proton

resonances display a greater effect, with all the aromatics shifting upfield. H_a moves by -0.05 ppm, H_b $\Delta\delta$ -0.05 ppm and H_c by -0.03 ppm.

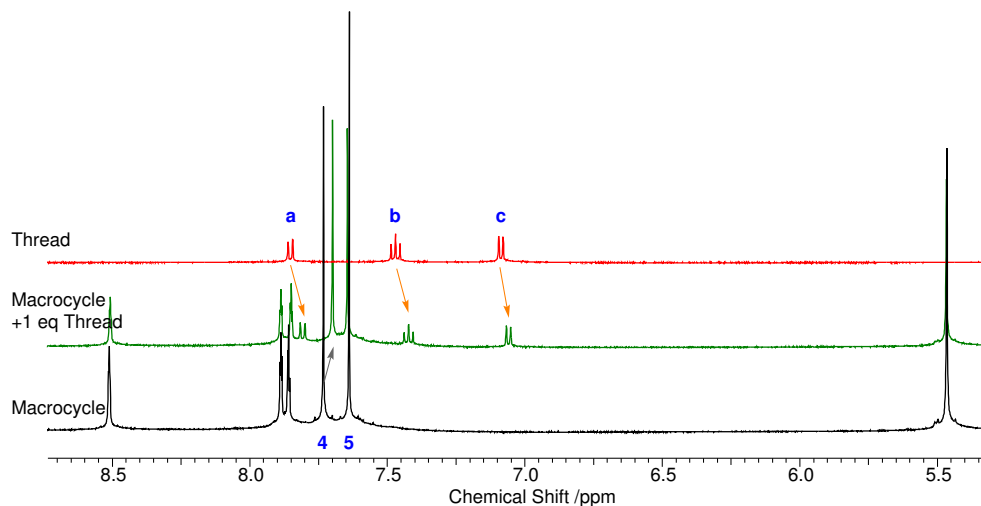


Figure 3.8 Investigating pseudorotaxane formation between macrocycle **41** and one equivalent of propargyl-appended thread **18** by ^1H NMR spectroscopy (300 MHz, CD_3CN , 298 K). For ^1H NMR assignments see Figure 3.4

The effect of an extended polyether chain on the aromatic π - π donor-acceptor stacking interaction was anticipated to be minimal, with a far greater effect expected from the long arms, increasing the energy barrier to slippage dethreading and increasing the effective intercalation of the naphthalene axle inside the macrocycle. The addition of one equivalent of polyether-appended axle **46** to macrocycle **41** is shown in Figure 3.9.

A far greater effect is induced in the chemical shifts of both components, suggesting that the equilibrium lies further towards pseudorotaxane formation compared with the short-chain propargyl study. All the macrocycle proton resonances exhibit noticeable changes, with the greatest being experienced by H_1 (downfield 0.04 ppm), H_3 (upfield 0.08 ppm) and H_5 (upfield 0.24 ppm). The axle aromatic proton resonances also display a far greater change, with all the aromatics shifted significantly upfield. H_a moves by $\Delta\delta$ -0.53 ppm, H_b by -0.46 ppm and H_c by -0.29 ppm. Whilst the macrocycle protons' shifts are complex with both upfield and downfield adjustments, the axle component upfield shifts are more straightforward to explain. The donation of π -electron density from the electron-rich dihydroxy naphthalene

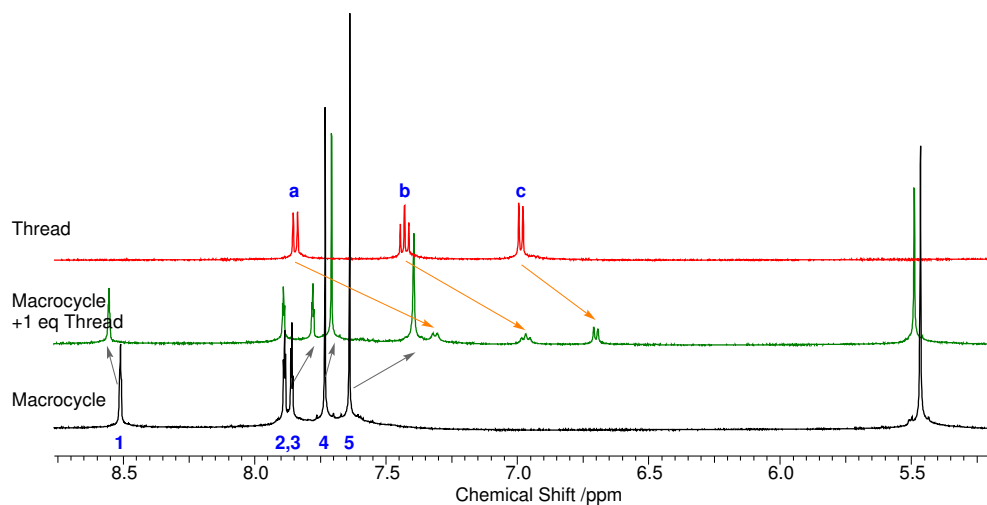


Figure 3.9 Investigating pseudorotaxane formation between macrocycle **41** and one equivalent of tetraglycol-appended thread **46** by ^1H NMR spectroscopy (300 MHz, CD_3CN , 298 K). For ^1H NMR assignments see Figures 3.4 and 3.7

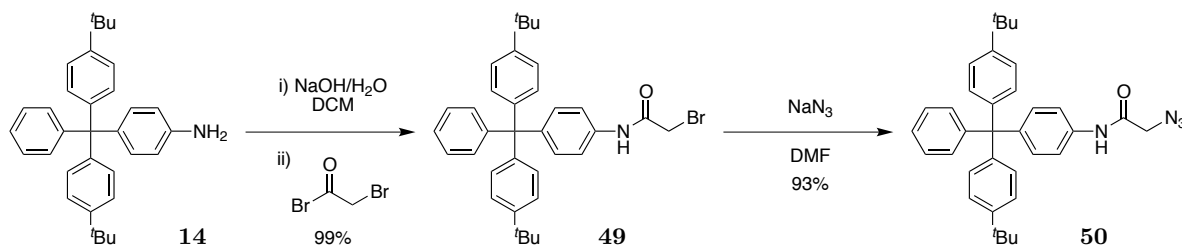
ether axle to the cationic macrocycle reduces the electron density on the dihydroxy naphthalene. This in turn results in a diminished ring current around the naphthalene, reducing the effective magnetic field exerted on the aromatic protons, with a corresponding upfield shift.

The analogous equimolar 1:1 pseudorotaxane ^1H NMR study between macrocycle **41** and the short chain glycol-appended thread **45** displayed some changes in chemical shift, however, these were noticeably more modest than observed for the longer thread **46**. As expected, the thread aromatic resonances all exhibited small upfield shifts. In the macrocycle, one resonance, H_1 , exhibited a small downfield shift, with the other macrocycle resonances unaffected. Therefore work on the glycol-appended thread **45** was discontinued in favour of the longer-chain analogue **46**.

3.2.7 Rotaxation attempts

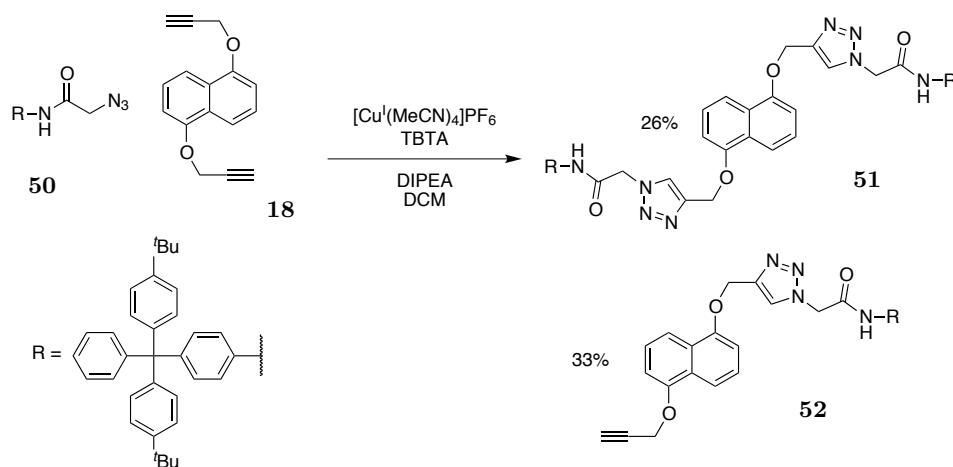
With evidence for pseudorotaxane formation by ^1H NMR spectroscopy, suitable stoppers were required for [2]rotaxane formation. Aniline stopper precursor **14** has been described in the previous chapter and was deemed a good starting point for the synthesis of an

azide-appended bulky stopper. In the two-step synthesis shown in Scheme 3.3, the aniline precursor was first reacted with bromoacetyl bromide to form bromide-appended **49** in near-quantitative yield. Subsequent reaction with sodium azide also proceeded smoothly to afford the desired azide-appended stopper, **50**.



Scheme 3.3 Synthetic route to a bulky stoppering group for [2]rotaxane formation by click reaction — azide-appended **50**

Stoppering to form the carbamate linker by reaction between a primary alcohol and an isocyanate has been described in the previous chapter (Chapter 2). The same isocyanate-based stopper, **15**, was therefore also used in this instance.



Scheme 3.4 Synthesis of mono- (**51**) and di-stoppered (**52**) triazole-containing electron-rich axle components *via* “click” reaction

The stoppering reactions for axle formation were first tested to obtain reference samples to assist in determining whether subsequent [2]rotaxanation reactions were viable. The reaction scheme for CuAAC stoppering of **18** with one equivalent of **50** was carried out as shown in Scheme 3.4. Purification by column chromatography isolated both the mono- (**51**) and di-stoppered (**52**) threads in yields of 33% and 26%, respectively.

3.2.8 Designing alternative macrocycles

As a tetracationic macrocycle, **41** was found to bind a range of anions that varied in their shape, charge and basicity. However, the cyclic receptor did not display clear selectivity for any one anion. The incorporation of an isophthalamide group into the macrocycle, instead of the standard xylene spacer, would provide a more focused and selective anion-binding recognition site of the macrocycle, whilst retaining the tetracationic system set up for aromatic donor–acceptor interactions. Also, the integration of the larger isophthalamide linker group expands the cavity, providing sufficient space between the macrocycle and an axle to bind anions and introduce the possibility of [2]rotaxane formation by anion templation. An alternative target macrocycle containing isophthalamide is shown in Figure 3.10a.

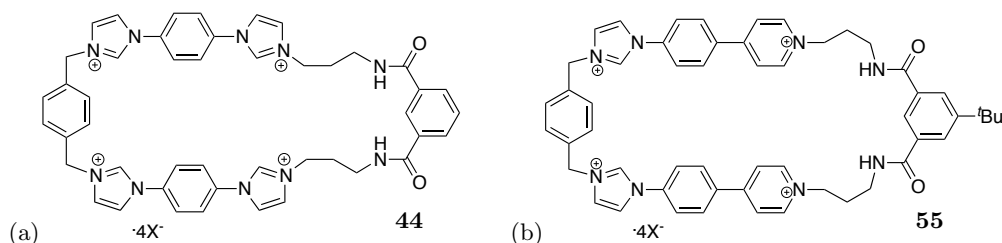
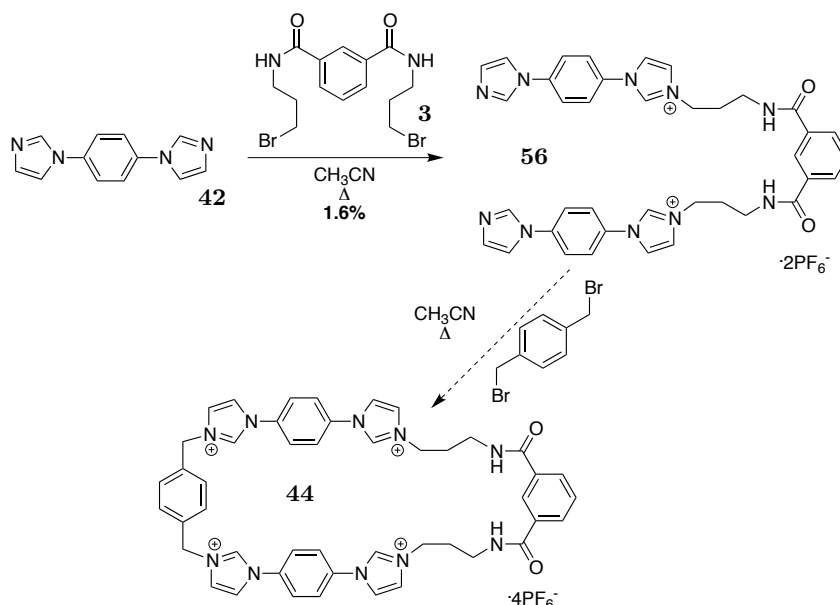


Figure 3.10 Alternative target macrocycles with additional anion binding motifs: (a) tetraimidazolium-isophthalamide macrocycle **44** and (b) a mixed imidazolium-pyridinium system, **55**

The drawback to this approach is that alkylation reactions at primary (1°) centres are significantly more difficult by S_N2 than at benzylic centres, which also have π -stabilisation assistance. Concerns over the viability of the S_N2 reaction required to make the isophthalamide macrocycle variant were addressed with synthetic attempts being undertaken towards a third macrocycle, **55**. This mixed imidazolium-pyridinium macrocycle (Figure 3.10b) utilises the enhanced nucleophilic pyridine precursor for the challenging S_N2 macrocyclisation.

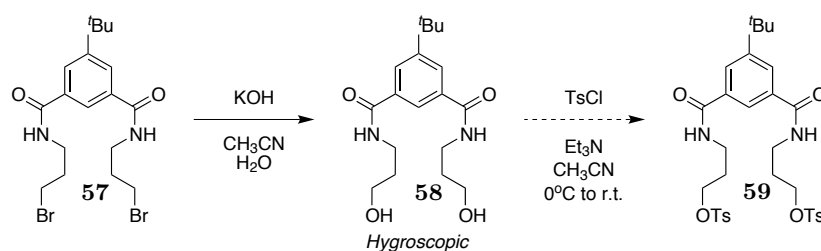
3.2.9 Alternative macrocycle synthesis

It was hoped that an alternative reaction route (Scheme 3.6), by first combining the bis-imidazole **42** with isophthalamide derivative **3**, would afford a more soluble precursor.



Scheme 3.6 Attempted synthetic route to macrocycle **44**

Instead, the desired dicationic precursor **56** could only be isolated in a prohibitively small 1.6% yield. Modification of this reaction step by addition of NaI to enhance the substrate electrophilicity and/or reaction by microwave irradiation at 165°C proved fruitless as well. It is thought that the available nitrogen lone pair on the imidazole is too poor a nucleophile to effectively perform the S_N2 reaction with the bromo-propyl substituent of compound **3**.

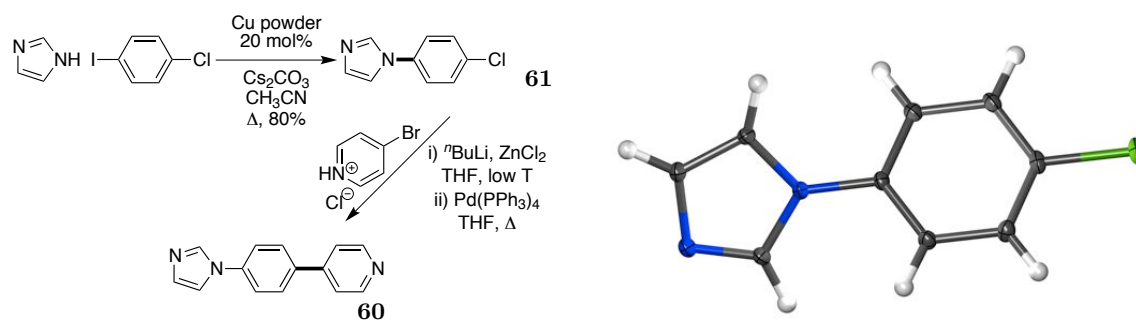


Scheme 3.7 Attempted synthesis of tosyl-appended isophthalamide derivative, **59**

Primary tosylates were thought to be superior electrophiles to alkyl bromides and thus improve the yield of the macrocyclisation reaction. Attempts to produce a more electrophilic isophthalamide derivative proved synthetically challenging due to the hygroscopicity of the 1° alcohol intermediate, formed in progress towards the tosylate-appended variant (Scheme 3.7). Bis-bromo compound **57** was synthesised and basic hydroxylation formed the hygroscopic bis-alcohol, **58**. A test reaction to form the ditosylate **59** resulted in an inseparable mixture.

This approach was therefore abandoned in pursuit of macrocycle **55**.

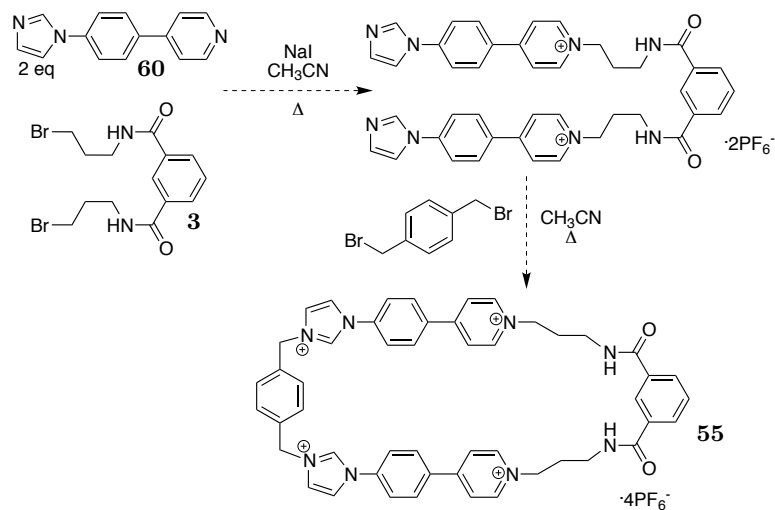
The required imidazole-pyridine precursor, **60** was synthesised as shown in Scheme 3.8. Using 4-iodo-1-chlorobenzene as the central precursor allowed selective orthogonal functionalisation by metal-catalysed coupling reactions. Ullmann coupling does not proceed at aryl chloride centres, so could be carried out without forming any side-products. The initial Ullmann coupling of imidazole with 4-iodo-1-chlorobenzene was adapted from the literature procedure laid out by Hu's group.³⁹¹ This reaction is reliable and can be scaled up to synthesise multi-gram quantities of **61** in excellent yields, typically >70%.



Scheme 3.8 Synthetic route to imidazole-pyridine **60**, precursor to macrocycle **55**, with a crystal structure of intermediate **61**. Thermal ellipsoids displayed at 30% probability

Single crystals of intermediate **61** were obtained and the solid-state structure was elucidated using X-ray crystallography by Nicholas White, confirming the proposed structure (Scheme 3.8, *right*). The chlorine atom present in the structure provides solid-state evidence for coupling occurring cleanly at the I–Ar position, validating the orthogonal functionalisation approach. The following Negishi cross-coupling procedure was loosely based on that used by Stanetty in synthesis of compounds containing joined pyridines and pyrimidines.³⁹² This reaction was attempted on several occasions, but was only successful on one small-scale run — this produced the desired product with minor impurities after column chromatography in an estimated yield of 60%. Subsequent attempts at larger scales were unsuccessful, whilst reactions at the same scale did not generate useful quantities of synthon **60**. It is suspected that significant homo–homo coupling is occurring in the reaction mixture, producing polyaromatic impurities that are difficult to extract. The intended synthetic route

would again have utilised orthogonal reactivity by reacting pyridine with 1° bromides in the presence of imidazole, then reacting the imidazole termini with α,α' -dibromo^pxylylene, to yield macrocycle **55** (Scheme 3.9).



Scheme 3.9 Intended synthetic route towards macrocycle **55** could not be carried out

3.2.10 Conclusions and future work

If a reliable and high-yielding synthesis of imidazole-pyridyl synthon **60** could be developed, then synthetic progress towards macrocycle **55** might be completed, with subsequent anion binding and anion-templated pseudorotaxane investigations undertaken.

A qualitative comparison between the effect of a lengthy polyether chain *versus* a short glycol chain on the naphthalene threading component established that the longer chain appeared to interact more significantly with macrocycle **41**, an effect which has previously been noted in other systems.³⁶⁷ Further research may be carried out investigating the failed [2]rotaxanation reactions using macrocycle **41**. As shown in Scheme 3.5, it is possible to isolate mono-stoppered thread **54**, which could be used as a possible superior axle precursor for initial pseudorotaxane formation. A more detailed discussion of the problems encountered in forming rotaxanes is outlined in conclusions of the next section.

3.3 Pyridinium-based macrocycles

The imidazolium-based macrocycles described in the previous section proved synthetically challenging, mainly due to the poor nucleophilicity of the imidazole nitrogen centre and solubility problems. These issues were addressed by the twin approach of forming the cationic motif at a later stage in the synthesis and using pyridinium-based macrocycles, as the pyridine nitrogen atom is more nucleophilic than that of imidazole.

3.3.1 Macrocycle design

The generalised structure of the series of target macrocycles is shown in Figure 3.11.

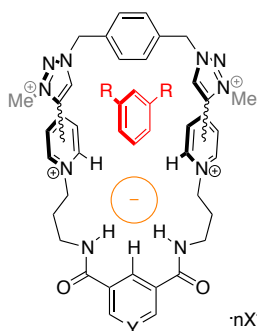


Figure 3.11 The generalised macrocycle shown is the basis for a series of similar macrocycles for investigating anion binding and rotaxane formation

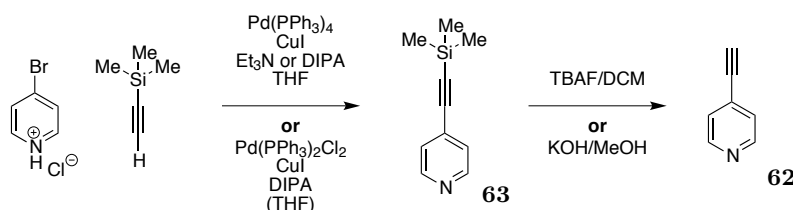
The key features of all these macrocycles are: *a)* the cationic pyridinium motif, *b)* an isophthalamide group, to convergently hydrogen bond to anions, *c)* 1,2,3-triazole covalent linkages with the potential for alkylation to triazolium and *d)* the xylenic linker to ensure rigidity and allow space for an axle to thread.

3.3.2 Macrocycle synthesis

DICATIONIC BIS-PYRIDINIUM TRIAZOLE MACROCYCLES

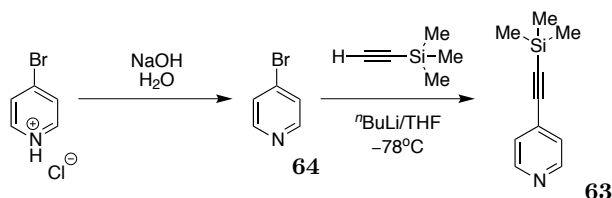
The 3-isomer of ethynylpyridine was used initially because of its commercial availability.

In contrast, as 4-ethynylpyridine is available at a prohibitive price and decomposes rapidly under ambient conditions, synthesis of fresh material was undertaken. An initial approach to macrocycle formation was validated using 3-ethynylpyridine, and then repeated with the 4-ethynylpyridine isomer, **62**.



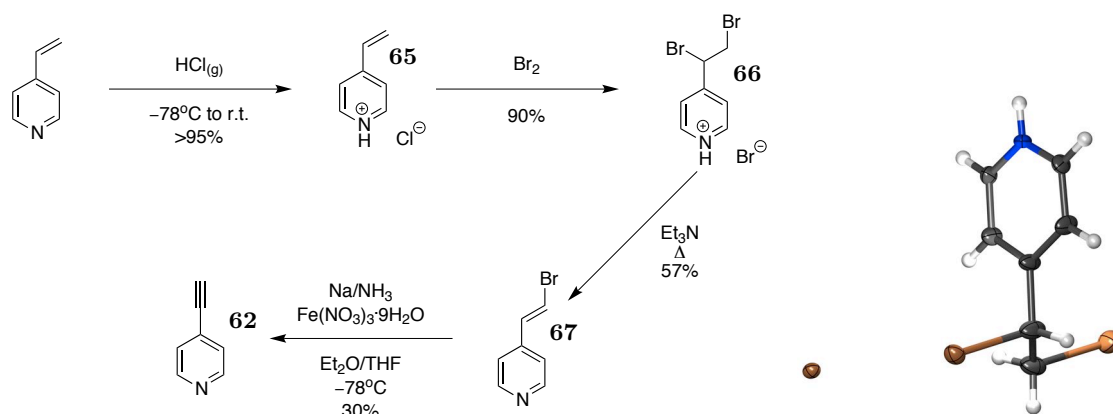
Scheme 3.10 Failed synthesis of 4-ethynylpyridine (**62**) by metal-catalysed coupling reaction

The literature suggested that a Sonogashira coupling reaction would be the optimal approach, forming 4-ethynylpyridine *via* the trimethylsilyl protected intermediate, **63**.^{393–398} Starting with 4-bromopyridine hydrochloride, several different variations in using this palladium-catalysed synthetic route were attempted, as shown in Scheme 3.10. In almost all cases, the reaction proved unsuccessful. An alternative method of coupling the TMS-alkyne to bromopyridine (**64**) was undertaken (Scheme 3.11). However, these efforts were also unsuccessful, indicating that the common intermediate product, **63** was unstable.



Scheme 3.11 Failed synthetic attempts towards 4-ethynylpyridine (**62**) by lithiation

Successful synthesis of 4-ethynylpyridine **62** was undertaken through alternative intermediates, as shown in Scheme 3.12.^{399,400} 4-Vinylpyridine is commercially available as a cheap starting material and was reacted as the hydrochloride salt (**65**). Bromination forms the lachrymatory dibromide **66**, with crystals suitable for solid-state structure determination providing evidence for halide ion exchange to the bromide salt (*right*, Scheme 3.12). The first HBr elimination from crystalline **66** proceeded straightforwardly by refluxing in triethylamine to form bromovinyl species **67**, whilst also deprotonating the pyridinium.

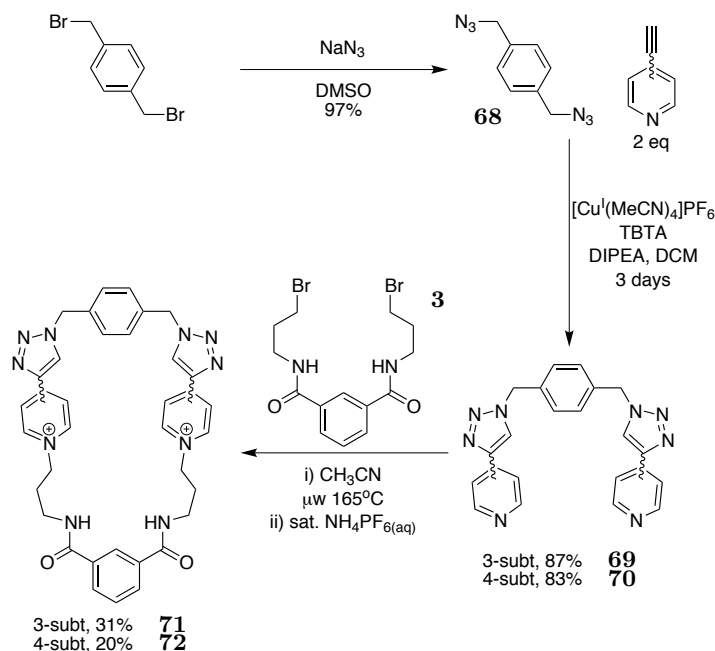


Scheme 3.12 Successful four-step synthesis of 4-ethynylpyridine, **62**, with a crystal structure of intermediate **66**. Thermal ellipsoids shown at 30% probability

The final elimination to form the desired product, 4-ethynylpyridine, had to be carried out using $\text{NH}_3(\text{l})$, with catalytic $\text{Fe}(\text{NO}_3)_3$ added to activate the solution. Extraction, then sublimation yielded pure **62** as a white crystalline sublimate in a yield optimised at 30%. 4-Ethynylpyridine **62** was found to be unstable at room temperature and even storage at -32°C failed to prevent some decomposition. Therefore, once synthesised, **62** was used immediately and reacted on with bis-azido-xylene (**68**) to form the stable bis-triazole, **70**, as shown in Scheme 3.13.

The synthesis of the 3- and 4-isomers of dicationic triazole pyridinium macrocycles is outlined in Scheme 3.13. Commercial α,α' -dibromoxylene was reacted with NaN_3 in DMSO to produce a suitable xylenic linker with terminal azides **68**.⁴⁰¹ In a double CuAAC reaction, bis-azido-xylene **68** was then reacted with either the commercial 3- or fresh 4-ethynylpyridine (**62**), to form the respective intermediates **69** and **70**. This coupling click reaction used the typical reagents, $[\text{Cu}^{\text{I}}(\text{MeCN})_4]\text{PF}_6$ and TBTA, with optimisation of the reaction improving yields from $\sim 35\%$ to $>80\%$. Care was taken to remove all copper impurities by washing with a 0.1 M $\text{EDTA}_{(\text{aq})}$ solution and the resultant yields for the reactions of the 3- and 4-isomer were very similar. Once formed, the 4-isomer (**70**) appeared to be fairly resistant to decomposition, in contrast to the 4-ethynyl pyridine precursor, **62**.

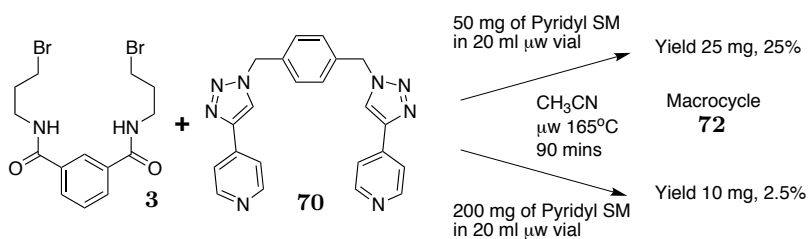
A double S_N2 reaction with bis-bromo-isophthalamide compound **3** afforded dicationic macrocycles **71** and **72**. Under conventional conditions, both with and without addition of NaI to enhance the electrophilicity of **3**, this macrocyclisation was not found to proceed ideally, with most of the starting material oligomerising and only minimal amounts of macrocycle being detected in or extracted from the precipitated mixture.



Scheme 3.13 Successful synthesis from ethynylpyr of macrocycles **71** and **72**

Instead, a microwave-assisted synthetic procedure was used, with irradiation at 165°C , followed by dropwise addition of sat. $\text{NH}_4\text{PF}_6(\text{aq})$, which induced precipitation of the crude cyclic product (Scheme 3.14). This was then purified by preparative TLC (1% sat. $\text{NH}_4\text{PF}_6(\text{aq})/\text{acetone}$) to give the desired macrocycles **71** and **72** as white solids. Interestingly the 3-isomer reaction proceeded more smoothly in 31% yield, compared with only 20% for the 4-isomer macrocyclisation step.

These microwave reactions required careful optimisation, with Scheme 3.14 demonstrating an absolute limit to yields and diminishing returns from more concentrated microwave reactions.



Scheme 3.14 Optimisation of macrocyclisation

There was a delicate balance for the S_N2 reaction between the mild pyridine nucleophile and weakly electrophilic primary bromo substituent. Higher concentrations and faster reaction rates increased oligomerisation, whilst macrocyclisation required sufficient reactivity. Addition of NaI was found to favour oligomer formation, whilst addition of a Cl⁻ template had no effect, presumably due to *in situ* generation of displaced Br⁻ anions for auto-templation. Incorporating a more electrophilic group, such as tosylate, onto the propyl chain had been thwarted previously due to the hygroscopic nature of the bis-alcohol intermediate (see Scheme 3.7).

Single crystals of precursor derivative **70** were grown from acetonitrile solution. A crystal structure could be determined by X-ray diffraction, however, the quality of the data was only of sufficient quality to display the molecule in a ball-and-stick representation. Interestingly, the solid-state structure of **70** (Figure 3.12) exists with the two pyridyl groups widely separated.

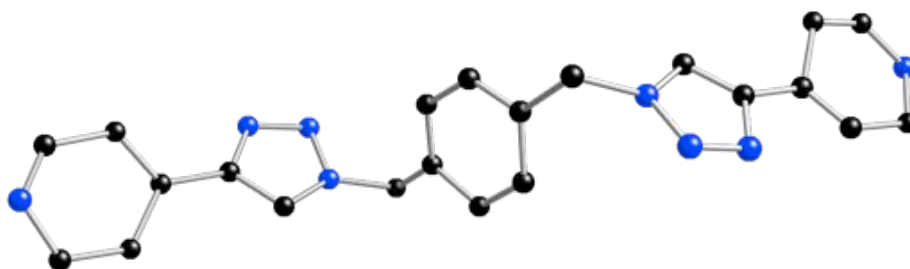
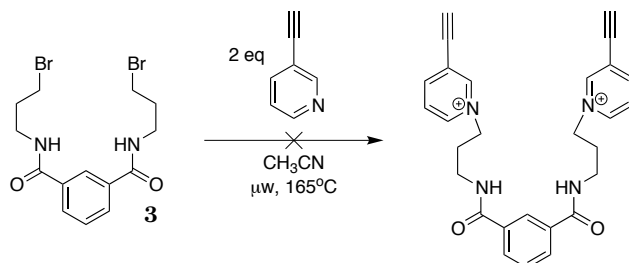


Figure 3.12 Ball-and-stick crystal structure of bis-pyridine clip **70**

An alternative synthetic route was also attempted by first alkylating 3-ethynylpyridine with **3** (Scheme 3.15), as *N*-substituents also appear to stabilise the pyridyl group against

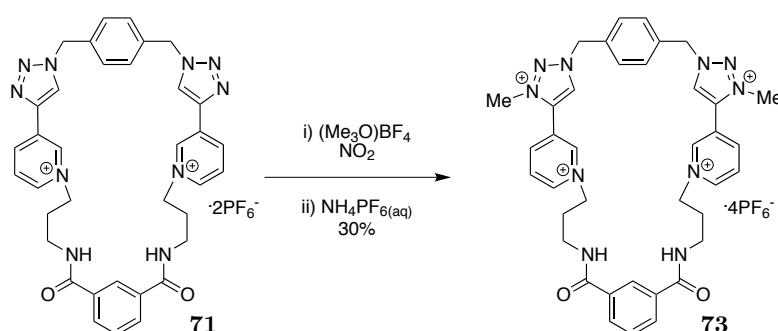
decomposition. Under microwave irradiation, this reaction failed due to decomposition of the 3-ethynylpyridine starting material.



Scheme 3.15 Alternative synthetic route by first alkylating the pyridyl with **3**

TETRACATIONIC BIS-PYRIDINIUM TRIAZOLIUM MACROCYCLE SYNTHESIS

Only limited quantities of 4-isomer macrocycle **72** were able to be isolated due to the difficulties in synthesising fresh 4-ethynylpyridine and the low-yielding macrocyclisation step. Therefore, attention focused on alkylating the dicationic 3-isomer macrocycle to afford tetracationic macrocycle **73** (Scheme 3.16). Methylation proceeded well with six equivalents of $(\text{Me}_3\text{O})\text{BF}_4$, with column chromatography purification requiring a highly polar eluant (5:3:2 MeCN/ H_2O /sat. $\text{KNO}_3(\text{aq})$), followed by anion exchange to afford the desired tetracationic macrocycle, **73**, in 30% yield.

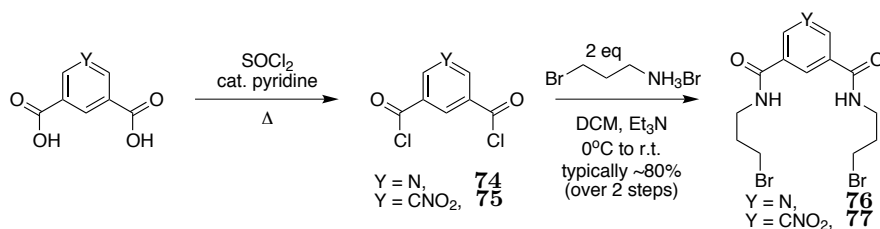


Scheme 3.16 Successful synthesis of tetracationic 3-isomer macrocycle, **73**

ISOPHTHALAMIDE VARIATION

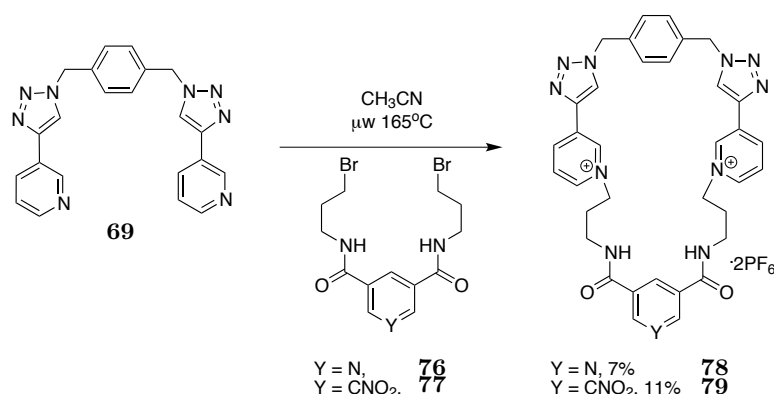
In order to investigate the effect of the substituents at the 5-position on isophthalamide, analogues containing electron-withdrawing pyridyl and nitro groups were synthesised. The generalised synthesis of bis-bromo-appended isophthalamide analogues is shown in

Scheme 3.17. The dicarboxylic acids required are commercially available and chlorination under refluxing SOCl_2 affords reactive acid chlorides **74** (pyridyl) and **75** (5-nitro). Subsequent amide formation with two equivalents of 3-bromopropylamine hydrobromide yields the desired 5-functionalised isophthalamide derivatives **76** and **77**, respectively.



Scheme 3.17 Generalised synthesis of isophthalamide derivatives with terminal bromides, to form pyridyl- **76** and nitro-substituted **77**

Disappointingly, analogous cyclisation reactions between nucleophile **69** and electrophiles **76** and **77** proceeded in low yields of 7% and 11%, for macrocycles **78** and **79** respectively (Scheme 3.18). Sufficient material was only isolated for characterisation of each macrocycle.



Scheme 3.18 Generalised synthesis of macrocycles with variation at the 5-position on isophthalamide, *vis* pyridyl- **78** and nitro-substituted **79** analogues

3.3.3 Macrocycle characterisation

The ^1H NMR spectrum of dicationic 4-isomer macrocycle **72** is shown in Figure 3.13. The key protons in the aromatic region are assigned, with the broad amide (H_4) visible in the acetonitrile solvent. The *meta*-pyridinium protons (H_6) and internal isophthalamide proton (H_3) were found to overlap slightly around δ 8.3 ppm.

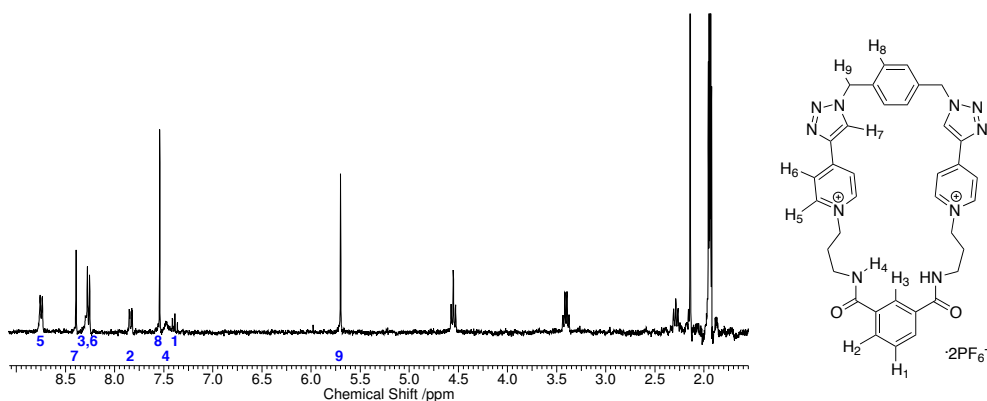


Figure 3.13 Partially assigned ^1H NMR spectrum (300 MHz, CD_3CN , 298 K) of macrocycle **72**

Slow evaporation of a solution of **72** in acetone in the presence of PF_6^- counteranions gave single crystals of the macrocycle as the NaPF_6 adduct, suitable for X-ray single crystal structural analysis. The structure was determined by Ben Mullaney and shows that the macrocycle adopts a planar conformation (Figure 3.14). In the solid state, pseudodimerisation is observed, with the isophthalamides of the two macrocycles demonstrating parallel offset aromatic stacking interactions — the distance from the centroid of one ring to the overlaying carbon of the other is 3.532 Å. In addition, a bridging sodium links the two macrocycles through their amides, with $\text{C}=\text{O} \cdots \text{Na}$ 2.755(5) Å.

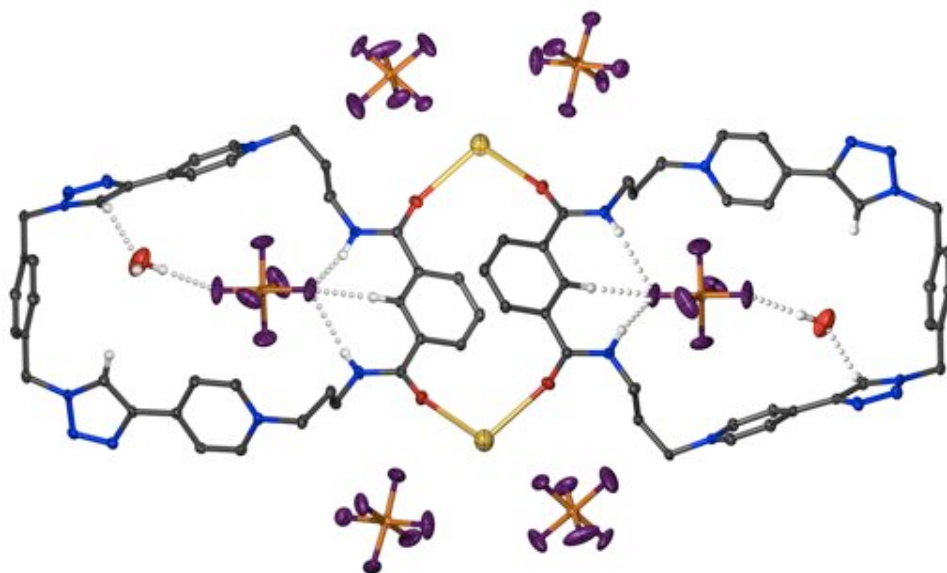


Figure 3.14 Structure determined by single crystal X-ray diffraction of macrocycle **72** grown from acetone solvent in the presence of PF_6^- counteranions; some residual NaPF_6 is also present. Thermal ellipsoids displayed at 30% probability

Despite the relatively non-coordinating nature of the PF_6^- anion, in this solid-state structure one of the PF_6^- anions resides within the cavity formed by the convergent isophthalamide and pyridinium hydrogen-bond donors. Whilst the pyridinium motifs appear to be too far away to interact with the PF_6^- anion, the following distances between the isophthalamide components and the nearest fluorine atom in the cavity suggest hydrogen bonding: amide $\text{N}-\text{H} \cdots \text{F}$ 3.502(7) and 3.125(7) Å, and internal phenyl $\text{C}-\text{H} \cdots \text{F}$ 3.297(7) Å. The amides of the isophthalamide also distorted out of the plane by a mean angle of 21.5(5)°.

The ^1H NMR spectrum of dicationic 3-isomer macrocycle **71** is shown in Figure 3.15. The key protons in the aromatic region are more complex to assign, with the *meta*-pyridinium protons (H_7) and internal isophthalamide proton (H_3) again overlapping. The *para*-pyridinium proton (H_8) may form intramolecular hydrogen bonds to triazole nitrogens and is assigned downfield from the *ortho*-proton, H_6 .

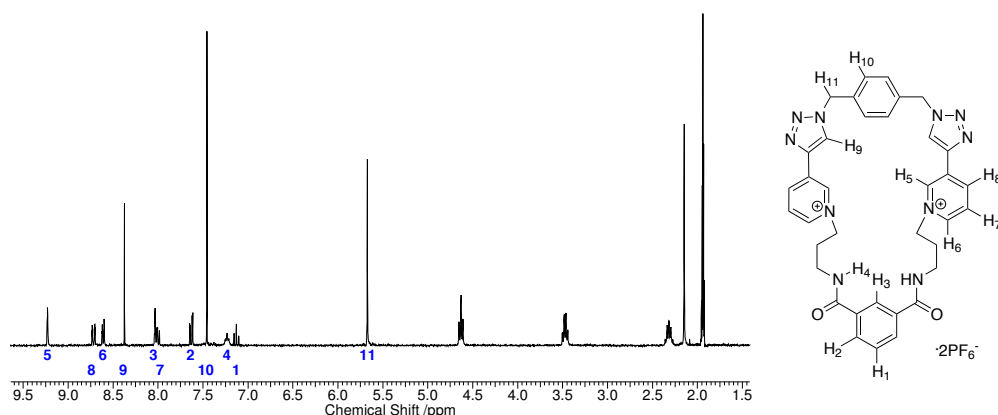


Figure 3.15 Partially assigned ^1H NMR spectrum (300 MHz, CD_3CN , 298 K) of macrocycle **71**

The ^1H NMR spectrum of tetracationic macrocycle **73** is shown in Figure 3.16. The 1,2,3-triazolium proton (H_9) is further downfield at δ 8.73 ppm compared with 8.38 ppm for the triazole analogue. The triazolium methyl singlet (H_{12}) is found at δ 4.22 ppm.

Due to the increased overall positive charge the pyridinium *ortho*- (H_6) and *meta*-protons (H_7) are shifted relatively downfield compared with macrocycle **71**, $\Delta\delta \sim 0.3$ ppm. Inter-

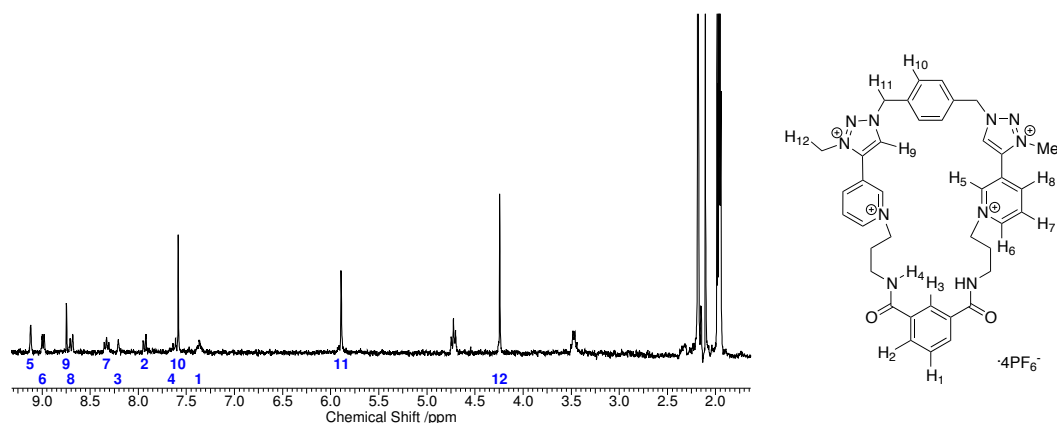


Figure 3.16 Partially assigned ^1H NMR spectrum (300 MHz, CD_3CN , 298 K) of macrocycle **73**

estingly, the *para*- (H_8) and other *ortho*-protons (H_5) do not shift downfield, as the loss of intramolecular hydrogen bonding to the triazole counteracts this effect.

For completeness, the partially assigned ^1H NMR spectra of macrocycles **78**, see Figure 3.17, and **79**, see Figure 3.18, in acetone- d_6 are shown. The synthesis of macrocycle **78** was particularly low-yielding and it proved difficult to isolate a sample of macrocycle that appeared completely pure by NMR spectroscopy.

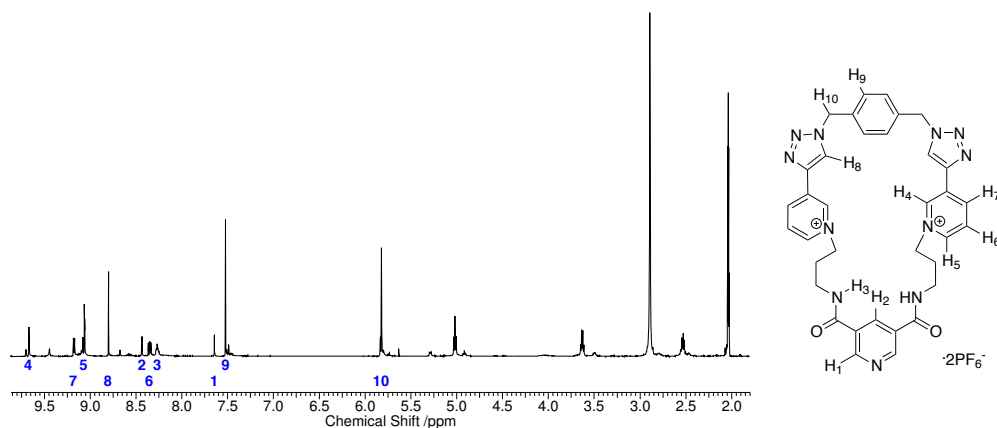


Figure 3.17 Partially assigned ^1H NMR spectrum (300 MHz, acetone- d_6 , 298 K) of macrocycle **78**

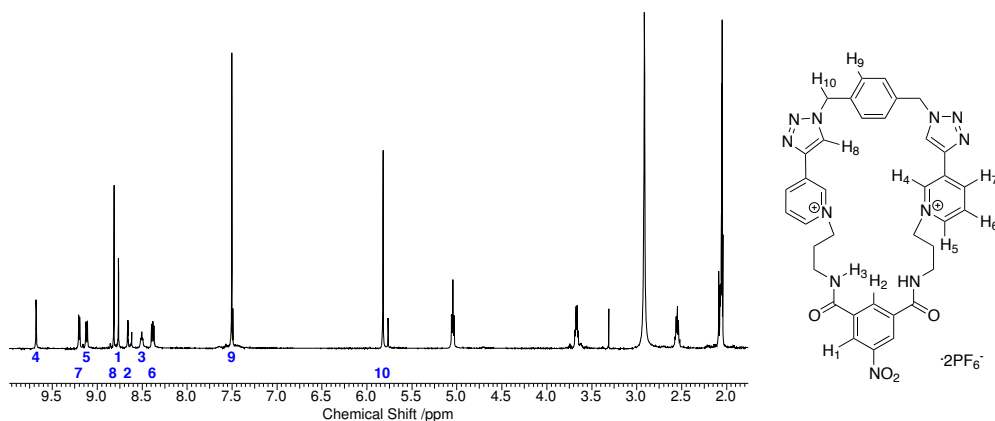


Figure 3.18 Partially assigned ^1H NMR spectrum (300 MHz, acetone- d_6 , 298 K) of macrocycle **79**

3.3.4 Anion binding

The anion-binding affinities and selectivity of dicationic macrocycles **71** and **72**, and tetracationic macrocycle **73** were examined by ^1H NMR spectroscopy. Monovalent anions were added as their TBA^+ salts. Solubility problems necessitated using $\text{DMSO-}d_6$ as a suitably competitive solvent for these titrations.

The 4-isomer pyridinium dicationic macrocycle **72** was investigated initially for anion binding ability by titrations with Cl^- , Br^- and H_2PO_4^- anions. In each of these cases, significant downfield perturbations of the chemical shifts of the *ortho*-pyridinium (H_5) and isophthalamide phenyl (H_3) and amide (H_4) protons were observed. Analogous titration experiments with the 3-isomer dicationic macrocycle **71** and F^- , Cl^- , Br^- , H_2PO_4^- , HSO_4^- , BF_4^- and AcO^- anions also typically revealed significant downfield shifts of the macrocycle's triazole, pyridinium and isophthalamide phenyl and amide protons.

Selected spectra from the titration of TBACl into a $\text{DMSO-}d_6$ solution of macrocycle **72** are shown in Figure 3.19. The magnitude of these shifts was greater for chloride than for bromide, which might suggest a stronger binding event for the smaller halide. Addition of one equivalent of chloride induced downfield shifts +0.17 ppm in the *ortho*-pyridinium and +0.42 ppm in the isophthalamide phenyl protons, whilst the triazole resonance shifted upfield

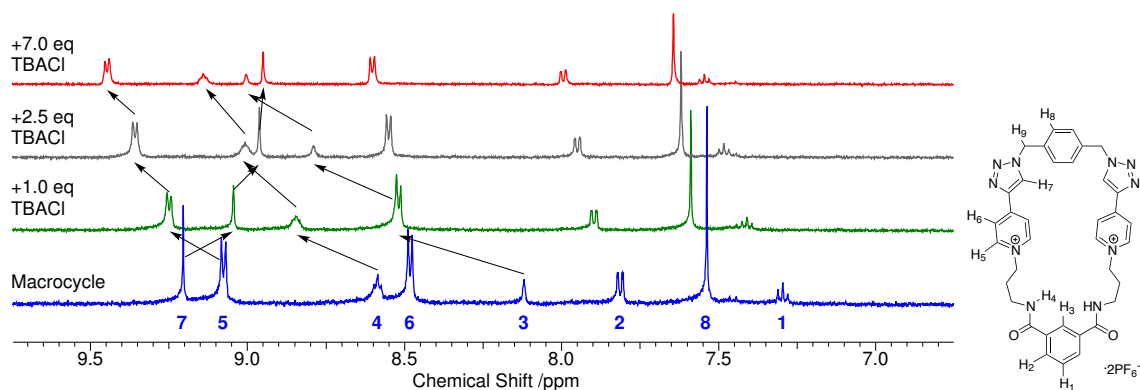


Figure 3.19 Aromatic region of the ^1H NMR spectra of receptor **72** upon addition of equivalents of TBACl. 500 MHz; solvent, $\text{DMSO-}d_6$; temperature, 293 K; $[\mathbf{72}]_i = 1.5 \times 10^{-3} \text{ mol dm}^{-3}$; titrant $[\text{TBACl}] = 0.075 \text{ mol dm}^{-3}$. For ^1H NMR assignments, see Figure 3.13

by 0.16 ppm. Bromide addition induced smaller shifts of $\Delta\delta +0.04$ ppm and $+0.12$ ppm, respectively, with the triazole again shifting upfield $\Delta\delta -0.03$ ppm. WinEQNMR2 analysis of the titration data monitoring the H_3 proton (Figure 3.19) determined 1:1 stoichiometry association constants for Cl^- and Br^- of 670 M^{-1} and 300 M^{-1} respectively, which confirms that Cl^- is bound more strongly.

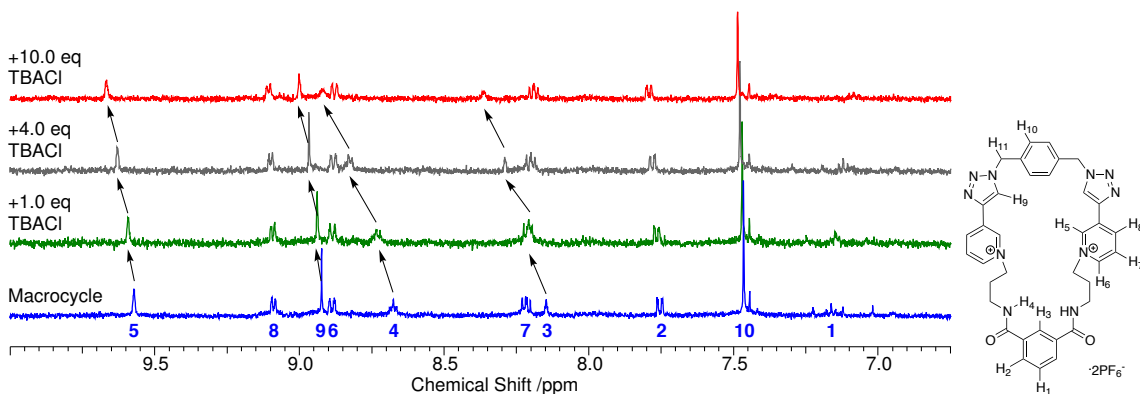


Figure 3.20 Aromatic region of the ^1H NMR spectra of receptor **71** upon addition of equivalents of TBACl. 500 MHz; solvent, $\text{DMSO-}d_6$; temperature, 293 K; $[\mathbf{71}]_i = 1.5 \times 10^{-3} \text{ mol dm}^{-3}$; titrant $[\text{TBACl}] = 0.075 \text{ mol dm}^{-3}$. For ^1H NMR assignments, see Figure 3.15

In comparison, chloride addition did induce downfield shifts of the proton signals of **71** (Figure 3.20), but of a smaller magnitude than observed with the macrocyclic isomer, **72**. Addition of one equivalent of chloride induced downfield shifts $\Delta\delta +0.02$ ppm in the *ortho*-pyridinium (H_5) and $+0.06$ ppm in the isophthalamide phenyl (H_3) protons.

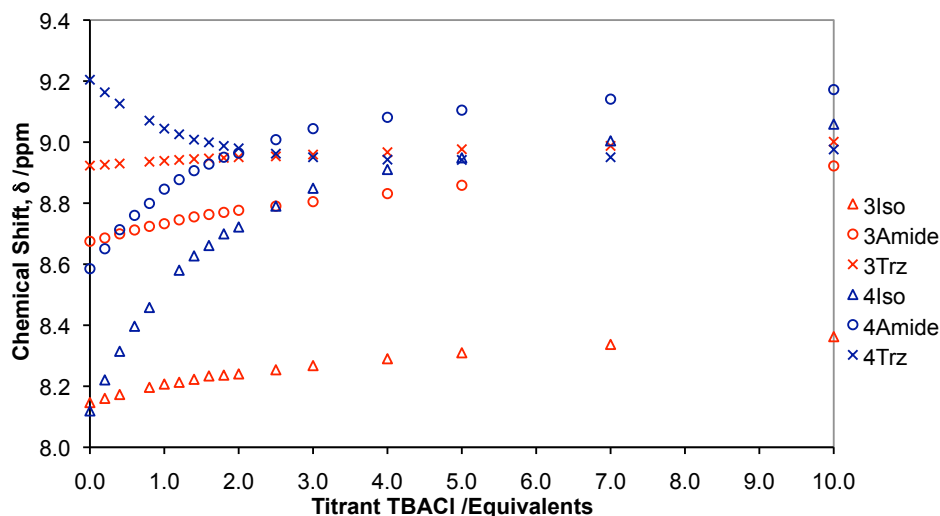


Figure 3.21 The triazole ($\times$) and isophthalamide phenyl (Δ) and amide ($\circ$) proton signals shift in the ^1H NMR spectra upon TBACl addition to receptors **71** (red) and **72** (blue). 500 MHz; solvent, $\text{DMSO-}d_6$; temperature, 293 K; $[\text{Macrocycle}]_i = 1.5 \times 10^{-3} \text{ mol dm}^{-3}$; titrant $[\text{TBACl}] = 0.075 \text{ mol dm}^{-3}$

The various proton resonances of macrocycles **71** (red) and **72** (blue) were monitored by ^1H NMR spectroscopy, with all but one of the triazole and isophthalamide protons shifting downfield upon addition of TBACl (Figure 3.21). The key difference between the binding of the 3-isomer and 4-isomer macrocycles is in the behaviour of the triazole protons during titrations. Upon anion addition, the 3-isomer triazole proton (H_9) shifts downfield, suggesting a macrocycle conformation that allows triazole $\text{C-H} \cdots$ anion coordination. In contrast, the 4-isomer spacer separates the triazole from the anion-binding site and thus C-H proton (H_7) shifts upfield upon anion addition instead. The 4-pyridinium–anion coordination may draw electron density through the conjugated system, reducing the ring current from the triazole aromatic system, inducing the upfield shift seen. These shifts suggest that the anion-binding cavity comprises the isophthalamide motif and *ortho*-pyridinium C-Hs , with only minor assistance from triazole C-H hydrogen bonding in macrocycle **72**.

Addition of TBAH_2PO_4 to macrocycle **72** also resulted in downfield shifts of the pyridinium and isophthalamide protons (Figure 3.22). Between 0 and 10 equivalents of H_2PO_4^- addition, the amide was shifted significantly downfield $\Delta\delta +1.67 \text{ ppm}$, with smaller shifts induced in the *ortho*-pyridinium ($+0.29 \text{ ppm}$) and isophthalamide phenyl protons ($+0.87 \text{ ppm}$).

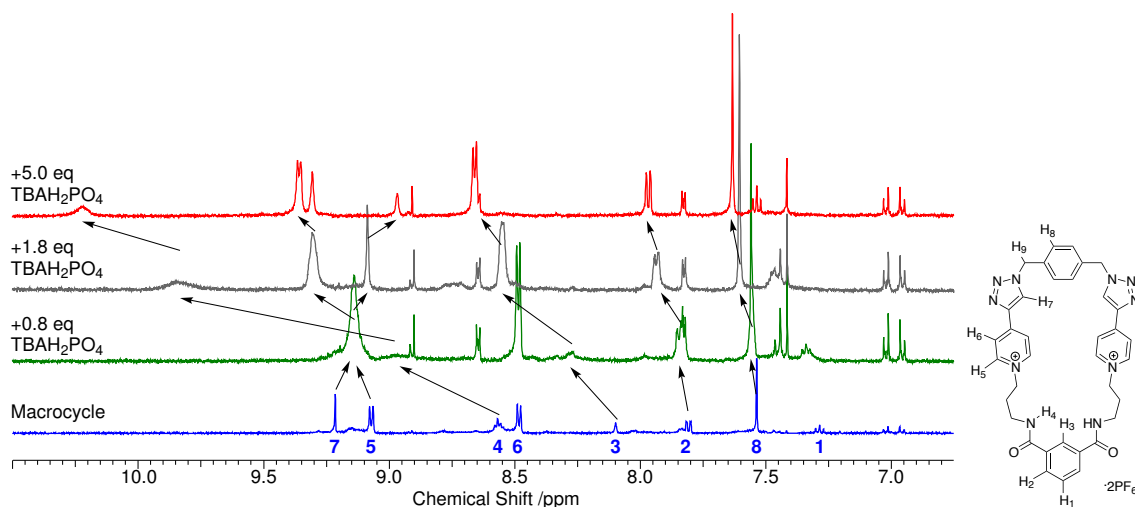


Figure 3.22 Aromatic region of the ^1H NMR spectra of receptor **72** upon addition of equivalents of TBAH_2PO_4 . 500 MHz; solvent, $\text{DMSO}-d_6$; temperature, 293 K; $[\mathbf{72}]_i = 1.5 \times 10^{-3} \text{ mol dm}^{-3}$; titrant $[\text{TBAH}_2\text{PO}_4] = 0.075 \text{ mol dm}^{-3}$. For ^1H NMR assignments, see Figure 3.13

However, in contrast to the 1:1 halide binding stoichiometry observed previously, addition of these anions induced sigmoidal movements and splitting in the macrocycle proton signals, which could not be fitted to a binding stoichiometry using WinEQNMR2 analysis.³⁵¹

Addition of each of TBAOAc and TBAH_2PO_4 to macrocycle **71** resulted in downfield shifts of the protons involved in anion binding. Again, sigmoidal titration curves resulted from monitoring the macrocycle internal isophthalamide C–H proton (Figure 3.23a and b).

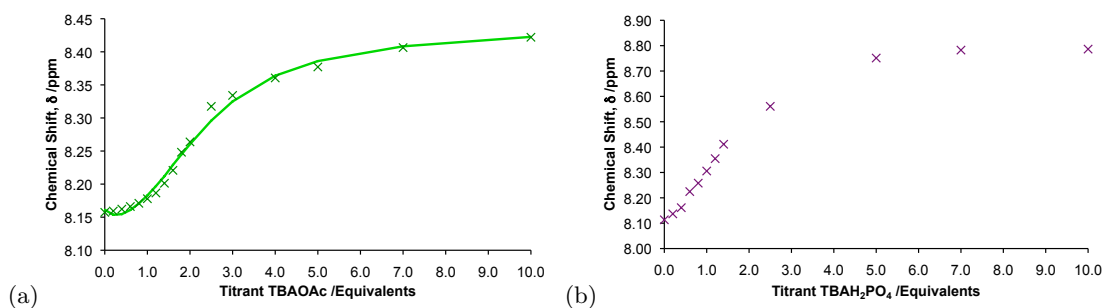


Figure 3.23 The sigmoidal chemical shift changes are observed by ^1H NMR spectroscopy (500 MHz, $\text{DMSO}-d_6$, 293 K) for **71** internal isophthalamide proton (H_3) upon addition of either (a) TBAOAc ($\times$) or (b) TBAH_2PO_4 ($\times$)

Job plot approximations for these anion titrations suggested a 2:1 anion–macrocycle binding mode (see Chapter 6). Unfortunately, in the case of H_2PO_4^- , association constants could not be determined by WinEQNMR2 analysis.³⁵¹ Upon coordination by the macrocycle the H_2PO_4^- anion and conjugate dianion are stabilised by the anion binding motif. This may induce a shift in the equilibrium from the monoanion, H_2PO_4^- , to the dianion, HPO_4^{2-} , resulting in complex anion binding behaviour.

For the AcO^- titration, however, WinEQNMR2 analysis determined association constants for the 2:1 binding stoichiometry as shown in Table 3.1.³⁵¹ Surprisingly, there appear to be no cooperativity effects with minimal difference between the K_{11} and K_{12} binding values, when the trend $K_{11} > K_{12}$ is expected on statistical grounds and due to mutual electrostatic repulsion. The K_{11} binding strength of AcO^- is stronger than those determined for the halides, which may be attributed to the oxoanion’s greater basicity (see Table 3.1). Table 3.1 shows the chloride and bromide anion binding affinities of 3-isomer macrocycle **71** are significantly weaker than those of 4-isomer macrocycle **72**.

Anion	[72] ²⁺ , K_{11} / M^{-1} [a]	[71] ²⁺ , K_{11} / M^{-1} [a]
Cl^-	670(17)	160(7)
Br^-	300(33)	–[a]
AcO^- [b]	K_{11} , 1209(29) K_{12} , 1270[c]	n/a

Table 3.1 ^1H NMR K_{11} values for interactions of macrocycles **72** and **71** with various anions. 500 MHz; solvent, $\text{DMSO}-d_6$; temperature, 293 K; $[\text{Macrocycle}]_i = 1.5 \times 10^{-3} \text{ mol dm}^{-3}$; titrant $[\text{TBAX}] = 0.075 \text{ mol dm}^{-3}$. [a] Binding too weak to be determined, [b] AcO^- anions were bound in a 2:1 stoichiometry, therefore K_{11} is defined for the equilibrium $[\text{M}] + [\text{L}] \rightleftharpoons [\text{ML}]$ and K_{12} for the equilibrium $[\text{ML}] + [\text{L}] \rightleftharpoons [\text{ML}_2]$, [c] derived from the calculated overall association constant β_{12} / K_{11}

An improvement over the viologen-based macrocycles was noted, as upon addition of basic anions to 3-isomer macrocycle **71**, no evidence of decomposition was observed. Fluoride addition resulted in deprotonation of the amide N–H protons, with corresponding formation of HF_2^- anions and the diagnostic appearance of the characteristic triplet resonance in the ^1H NMR spectrum at 16 ppm.^{402,403} Titrations with monovalent anions HSO_4^- and BF_4^- induced no observable changes in the macrocycle proton resonances, suggesting that macrocycle **71** does not interact significantly with these anions.

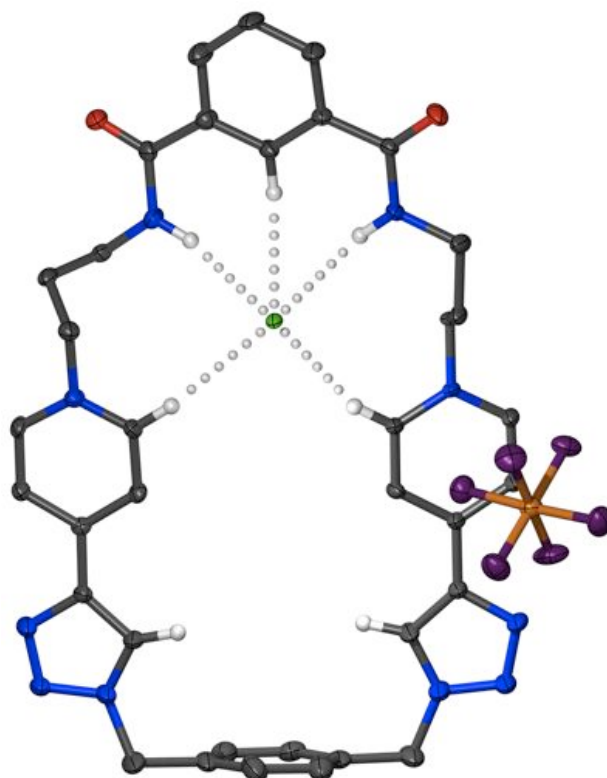


Figure 3.24 Structure determined by single crystal X-ray diffraction of receptor **72** in the presence of excess TBACl grown from CD_3CN solvent. Thermal ellipsoids displayed at 30% probability

Slow evaporation of a solution of **72** in acetonitrile containing excess TBACl gave single crystals of the macrocycle–chloride complex suitable for X-ray single crystal structural analysis. The structure was determined by Dr Nathan Kilah (Figure 3.24) and shows the macrocycle adopting a relatively planar conformation. A chloride anion is bound in the macrocycle in an intramolecular manner between the convergent hydrogen-bond donors of the isophthalamide group [internal phenyl $\text{C}-\text{H} \cdots \text{Cl}$ 3.529(8) Å and amide $\text{N}-\text{H} \cdots \text{Cl}$ 3.446(6) and 3.229(7) Å] and the pyridinium *ortho*-protons [$\text{C}-\text{H} \cdots \text{Cl}$ 3.550(8) and 3.478(8) Å]. This corroborates the solution-state evidence for the mode of anion binding in the cavity by convergent isophthalamide and pyridinium $\text{N}-\text{H}$ and $\text{C}-\text{H} \cdots$ anion interactions.

Due to the paucity of tetracationic macrocycle **73** available, an anion binding titration was only carried out with TBACl. As anticipated, chloride addition induced large downfield shifts in the proton signals of **73**, with one equivalent of chloride inducing shifts of $\Delta\delta$ +0.20 ppm

in the *ortho*-pyridinium (H_5) and +0.19 ppm in the isophthalamide phenyl (H_3) protons. Figure 3.25 shows selected spectra from the addition of Cl^- to macrocycle **73** to illustrate the shifts induced. WinEQNMR2 analysis of the titration data determined a 1:1 association constant of 1290(240) M^{-1} .

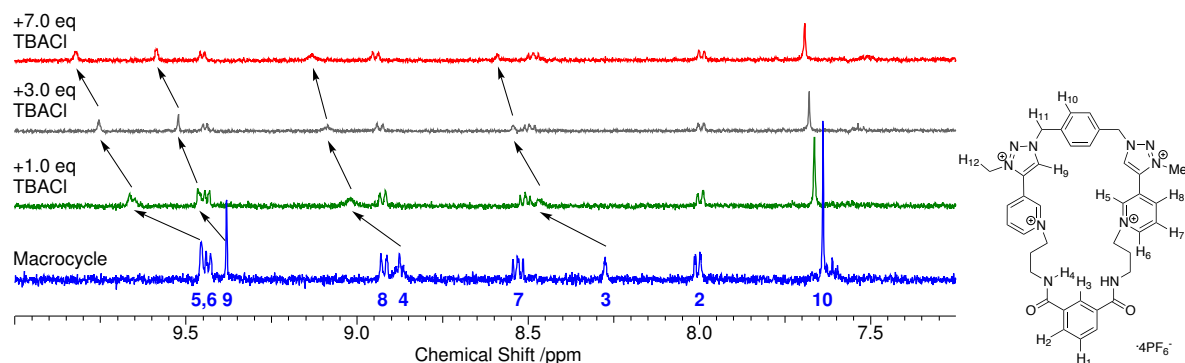


Figure 3.25 Aromatic region of the ^1H NMR spectra of receptor **73** upon addition of equivalents of TBACl. 500 MHz; solvent, $DMSO-d_6$; temperature, 293 K; $[73]_i = 1.5 \times 10^{-3} \text{ mol dm}^{-3}$; titrant $[TBACl] = 0.075 \text{ mol dm}^{-3}$. For ^1H NMR assignments, see Figure 3.16

Comparing the macrocycles' chloride-binding ability, the 4-isomer **72** exhibits stronger association than the 3-isomer **71**. From both solution-state and solid-state data, the availability of the pyridinium *ortho*-protons for hydrogen bonding from the planar 4-isomer may contribute to its advantage over the bent 3-isomer. Unsurprisingly, tetracationic **73** displayed superior chloride binding compared with the dicationic macrocycles, binding eight times more strongly than its dicationic precursor **71**.

3.3.5 Pseudorotaxane studies

Studies were carried out using ^1H NMR spectroscopy to investigate whether pseudorotaxanes were formed between the cationic pyridinium macrocycles and the electron-rich indolocarbazole thread, **9** (Figure 3.26).

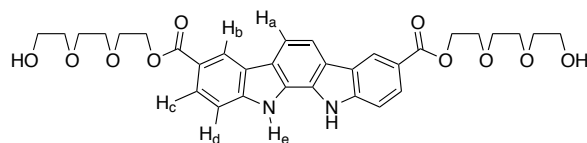


Figure 3.26 The key aromatic protons of indolocarbazole thread **9** labelled for ease of reference

A qualitative comparison of ^1H NMR spectra of the chemical shifts of macrocycle and thread with an equimolar combination of the two, followed by addition of one equivalent of TBACl to check for anion templation effects were undertaken in CD_3CN solution.

DICATIONIC 4-ISOMER MACROCYCLE **72**

A ^1H NMR spectrum of an equimolar 1:1 mixture of dicationic macrocycle **72** and indolocarbazole thread **9** is shown in Figure 3.27. Comparison with spectra of the free components indicated changes in chemical shift for all of the proton signals in the diagnostic aromatic region. Particularly significant are the shifts of the aromatic protons H_a , $\Delta\delta$ -0.12 ppm, and H_b , -0.35 ppm, of the indolocarbazole core, that were expected to shift upfield when interacting with the macrocycle. In turn the xylenic protons (H_8) were shifted downfield $\Delta\delta$, $+0.11$ ppm. The macrocycle pyridinium peaks were broadened and shifted upfield, with $\Delta\delta$ -0.14 ppm and -0.22 ppm for (H_5) and (H_6), respectively, indicating interaction between the macrocycle and thread π -systems.

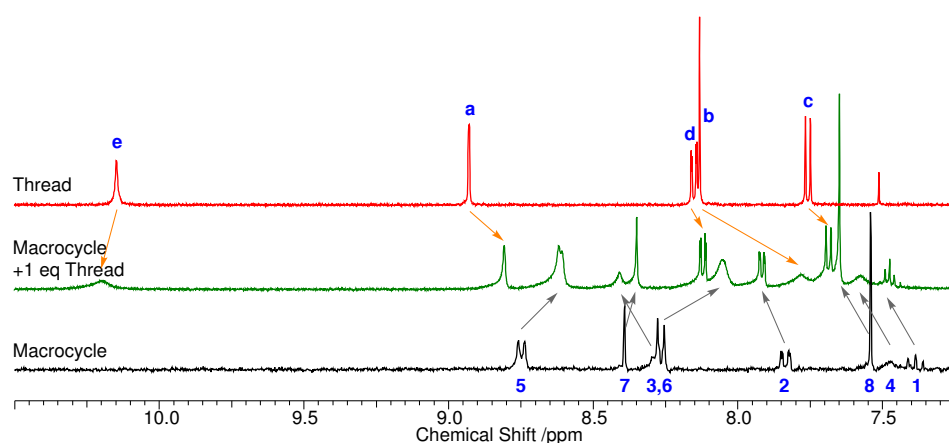


Figure 3.27 Pseudorotaxane formation study of macrocycle **72** with one equivalent of indolocarbazole thread **9** by ^1H NMR spectroscopy (500 MHz, CD_3CN , 293 K). For ^1H NMR assignments, see Figures 3.13 and 3.26

As both macrocycle and thread bind chloride strongly, addition of TBACl to the mixture was monitored by ^1H NMR spectroscopy to determine whether pseudorotaxane formation was enhanced or inhibited. As shown in Figure 3.28, addition of one equivalent of chloride anions broadens the proton signals and appears to shift the equilibrium towards pseudorotaxane formation. The isophthalamide phenyl proton (H_3) and indolocarbazole ($\text{N}-\text{H}_e$) participate in the anion binding event, $\Delta\delta$ +0.87 ppm and +0.54 ppm respectively, whilst the diagnostic indolocarbazole H_a proton shifts further upfield, with $\Delta\delta$ -0.14 ppm, due to interaction with the macrocycle. This suggests that the pseudorotaxane assembly is stabilised in the presence of a templating chloride anion.

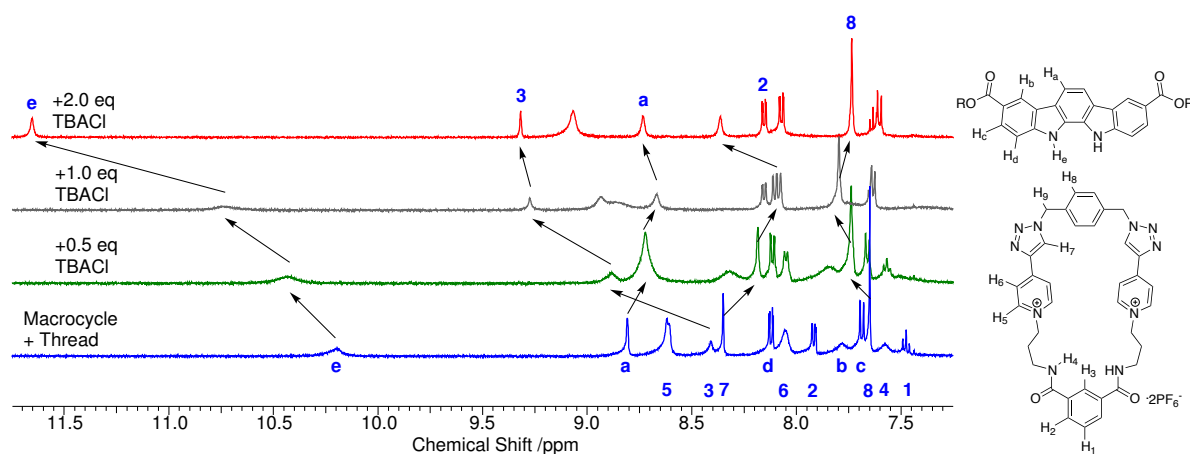


Figure 3.28 Anion-templated pseudorotaxane formation study by addition of TBACl to a 1:1 mixture of macrocycle **72** with indolocarbazole thread **9** by ^1H NMR spectroscopy (500 MHz, CD_3CN , 293 K). For ^1H NMR assignments, see Figure 3.13 and 3.26

Addition of the second equivalent of TBACl then favours dethreading as excess chloride anions continue to be bound by the indolocarbazole $\text{N}-\text{H}_s$ and macrocycle isophthalamide binding motifs. Evidence for dethreading is provided by the reversal in the shifts induced for the thread H_a and macrocycle triazole and xylene (H_7 and H_8) resonances.

To garner further evidence for pseudorotaxane formation, 2D-ROESY NMR spectroscopy was carried out on the 1:1 mixture of macrocycle/thread. No intermolecular cross peaks were observed however, which may be due to the insufficient solubility of the macrocycle and thread components in CD_3CN for detecting interactions by ROESY.

DICATIONIC 3-ISOMER MACROCYCLE **71**

In contrast, an analogous titration experiment with an equimolar 1:1 mixture of dicationic macrocycle **71** and indolocarbazole thread **9** showed minimal changes in the ^1H NMR spectrum from the individual components (Figure 3.29). This may be due to the relatively less accessible macrocycle cavity preventing thread intercalation. The more open planar configuration of 4-isomer macrocycle **72**, as deduced in the solid-state (Figures 3.14 and 3.24), appears to be more preorganised for thread intercalation and exhibits pseudorotaxane formation both with and without a templating chloride anion.

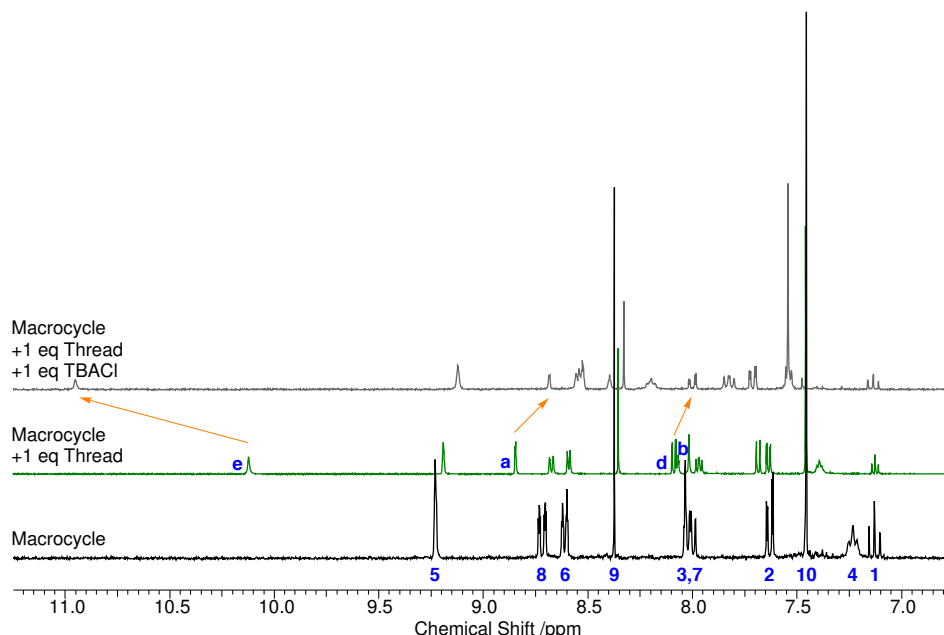


Figure 3.29 Anion-templated pseudorotaxane formation study of macrocycle **71** with one equivalent of indolocarbazole thread **9** in the presence of one equivalent of TBACl by ^1H NMR spectroscopy (500 MHz, CD_3CN , 293 K). For ^1H NMR assignments, see Figure 3.15 and 3.26

However, subsequent addition of one equivalent of TBACl as a potential template to the equimolar mixture of **71** and **9** induced observable changes in the ^1H NMR spectrum. Particularly significant are the upfield shifts of many peaks, rather than the downfield shifts observed upon addition of TBACl to free macrocycle **71**, see Figure 3.20. The indolocarbazole N–Hs bind to the anion, with a downfield shift, $\Delta\delta +0.83$ ppm, whilst proton H_a is notably

shifted upfield, $\Delta\delta$ -0.16 ppm, which is indicative of interactions between the thread and the macrocycle.

A 2D-ROESY NMR spectroscopy experiment was also carried out on the 1:1:1 mixture of macrocycle/thread/TBACl. Unfortunately, no intermolecular cross-peaks were observed, giving no indication of the through-space proximity of the indolocarbazole thread to the macrocycle. This again might be attributed to insufficient solubility of the indolocarbazole thread component in CD_3CN for detection of interactions by ROESY.

These 1-D ^1H NMR spectroscopic studies suggest that macrocycle **71** is less favourably preorganised for intercalation by electron-rich thread **9** than the cyclic 4-isomer **72**. Addition of a templating chloride anion seems to further stabilise the pseudorotaxane assembly between **72** and indolocarbazole thread.

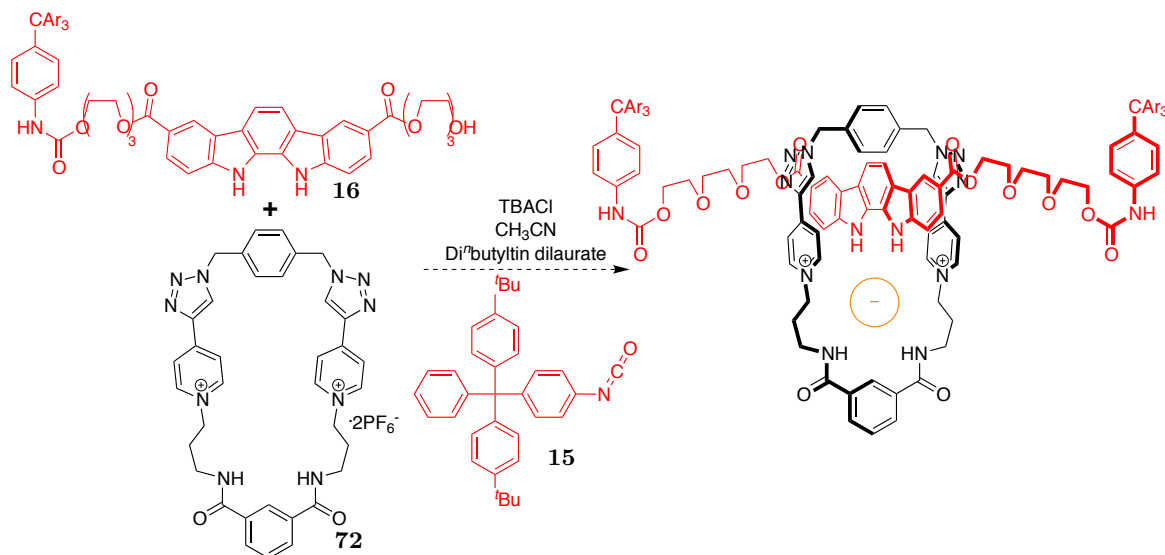
TETRACATIONIC MACROCYCLE **73**

Analogous equimolar ^1H NMR titration studies between tetracationic macrocycle **73** and indolocarbazole thread **9** revealed insignificant changes from the respective ^1H NMR spectra of the free components. Addition of one equivalent of templating TBACl induced precipitation. It is thought that despite the enhanced electrostatic attractions between the tetracationic macrocycle and indolocarbazole electron-rich thread, the cavity of the 3-isomer macrocycle may not be suitable for intercalation.

3.3.6 Rotaxanation attempts

Based on the promising pseudorotaxane assembly experiments between macrocycle **72** and indolocarbazole thread **9**, the synthesis of a [2]rotaxane was attempted. The mono-stoppered thread **16** was deemed the most suitable indolocarbazole component for rotaxanation

attempts; its synthesis using tetraaryl stopper **15** to form the urethane linker is described in Scheme 2.10.



Scheme 3.19 Anion-templated synthesis of target [2]rotaxane anion host system containing macrocycle **72** and an indolocarbazole thread

Several attempts at [2]rotaxation formation were made both in the absence and presence of a TBACl template in CH_3CN solution (Scheme 3.19). Disappointingly, no evidence of [2]rotaxation was observed in any of these reactions, neither by ESI-MS nor by ^1H NMR spectroscopy of the crude reaction mixture. However, ESI-MS did ascertain the presence of the bis-urethane stoppered indolocarbazole axle product, suggesting that the stoppering reaction was proceeding, but outside of the macrocycle cavity.

3.3.7 Conclusions

A series of five novel cationic macrocycles have been successfully prepared and characterised. Each of these macrocycles contains two electron-poor pyridinium motifs. These provide π -interactions with electron-rich threads and anion binding ability *via* electrostatics and C–H hydrogen bonding. Derivatives of the convergent isophthalamide motif were also integrated into the anion-binding cavity of each macrocycle.

Despite synthetic challenges, dicationic 3- (**71**) and 4-isomer (**72**) macrocycles were successfully prepared. During anion titration studies, these macrocycles were found to be stable to the addition of basic oxoanions, unlike previous 4,4'-pyridinium-based macrocycles.^{348,383,384}

Both macrocycles bound halides in a 1:1 stoichiometry in the polar solvent, DMSO-*d*₆, with **72** binding chloride and bromide more strongly than **71**. Titrations with oxoanions AcO[−] and H₂PO₄[−] suggested that 2:1 binding stoichiometries were likely. Solid-state structures of macrocycle **72** in its free (Figure 3.14) and chloride-complexed (Figure 3.24) modes were obtained. Both of these structures showed a planar macrocycle conformation, with chloride bound by convergent hydrogen bond donation from the isophthalamide and pyridinium motifs.

Methylation of **71** formed the 1,2,3-triazolium motif within tetracationic macrocycle **73**. As expected on electrostatic grounds, the tetracationic analogue was found to bind chloride more strongly than the dicationic macrocycles.

The synthesis of cyclic analogues of **71** with pyridyl (**78**) and 5-nitro (**79**) substitution at the isophthalamide position was achieved, however, isolated yields were very low, preventing further study.

Pseudorotaxane studies by ¹H NMR spectroscopy with indolocarbazole thread **9** indicated a relatively more stable interpenetrative assembly resulting from planar macrocycle **72** compared with **71**. Disappointingly, attempts at forming the target [2]rotaxane by a mild anion-templated stoppering of the pseudorotaxane were not successful.

DIFFICULTIES IN FORMING ROTAXANES

In the past two sections, evidence from ¹H NMR spectroscopic studies has strongly suggested that pseudorotaxane formation occurs when the electron-deficient macrocycle and electron-

rich thread under study were mixed in solution. Despite this, attempts at rotaxane formation did not prove successful. Isolation of the free doubly-stoppered axle confirms that the stoppering reaction is proceeding outside of the macrocycle cavity. Possible causes of this external reaction are additional thread–macrocycle interactions and steric clash due to the bulk of the stopper. Where threads were tested that have short arms, the close approach of the bulky stopper groups for reaction is disfavoured in the complex by steric clash with the macrocycle. Alternatively, the threads with longer polyether attachments may be interacting further with the electron-deficient macrocycle, with the oxygens on the arms wrapping close to the macrocycle. This phenomenon has also previously been suggested in research by Stoddart.³⁶⁷ With the arms wrapped around the macrocycle, approach of the bulky stoppering groups is again disfavoured. Considering the equilibrium between the free macrocycle and free thread *versus* the complex, removal of the free thread by stoppering would remove this component from the threading equilibrium. This would consequently shift the equilibrium to form further free thread and macrocycle. Therefore, relatively faster stoppering outside the macrocycle cavity would result in predominant production of the free stoppered axle and little rotaxane formation.

3.4 Triazole-based macrocycles

3.4.1 Macrocycle design and synthesis

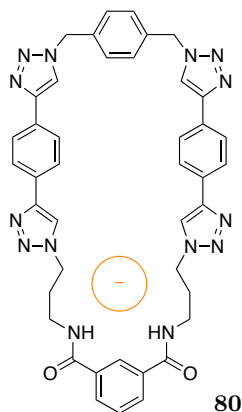
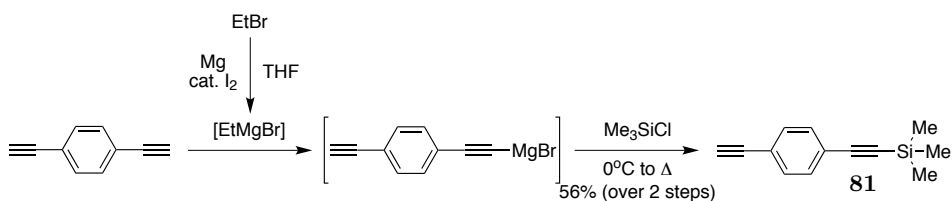


Figure 3.30 1,2,3-triazole-containing macrocycle **80** for anion coordination and with the potential for alkylation to 1,2,3-triazolium motifs

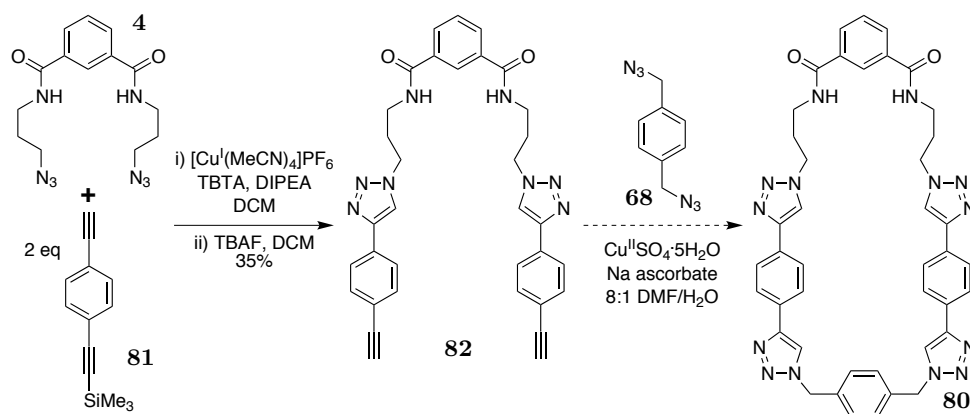
Attempts were also made to synthesise a macrocyclic tetratriazole analogue, **80**, shown in Figure 3.30. This neutral macrocycle also has the potential for alkylation to generate the corresponding cationic tetratriazolium cyclic congener, which would be expected to exhibit enhanced anion recognition and pseudorotaxane assembly properties with suitable electron-rich axle components.



Scheme 3.20 Synthesis of mono-protected dialkynyl phenyl core **81**

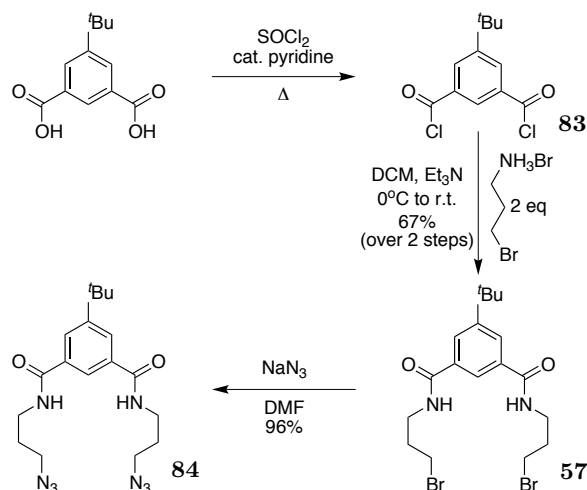
The synthesis of a mono-protected precursor, **81**, was carried out by Grignard reaction with TMSCl according to a literature procedure (Scheme 3.20).⁴⁰⁴ Recrystallisation and sublimation successfully isolated the mono-protected compound.

The synthetic route attempted towards the tetratriazole macrocycle is shown in Scheme 3.21. Terminal alkyne **81** was coupled with bis-azide **4**, followed by addition of TBAF to deprotect the TMS groups. Upon aqueous work-up, the white precipitate isolated proved to be the



Scheme 3.21 Synthetic attempt towards macrocycle **80**

deprotected product, **82**. Aqueous copper(I)-catalysed azide–alkyne cycloaddition between **82** and bis-azide **68** was carried out under high dilution macrocyclisation conditions in an 8:1 DMF/H₂O solvent mixture required to dissolve poorly soluble compound **82**. The desired tetratriazole macrocycle **80** was detected by ESI-MS, but could not be isolated from the reaction mixture. A similar reaction in the presence of a chloride anion template was also unable to be purified.

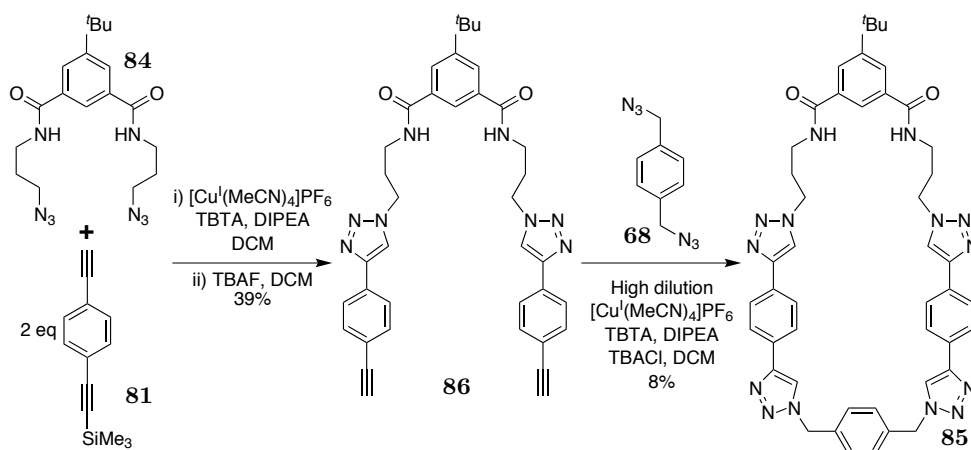


Scheme 3.22 Synthesis of solubilising *t*-butyl-functionalised precursor **84**

In an effort to improve solubility, the synthesis of a *t*-butyl-substituted analogue of compound **82** was attempted (Scheme 3.22). Bis-acid dichloride **83** was immediately condensed with two equivalents of 3-bromopropylamine hydrobromide in the presence of triethylamine to

produce bromo-propyl derivative **57**. Reaction of **57** with sodium azide afforded the required precursor with terminal azides, **84**, in an excellent 64% yield over three steps.

As was hoped, the *t*butyl-isophthalamide derivative, **84**, and subsequent compounds exhibited improved but limited solubility and were used in the synthesis of target macrocycle **85** (Scheme 3.23). Copper(I)-catalysed click reaction of bis-azide **84** with mono-protected **81** proceeded in 39% yield. Deprotection gave the *t*butyl-containing free bis-alkyne **86**. Copper(I)-catalysed azide-alkyne cycloaddition between **86** and **68** was carried out in DCM, with the limited solubility of bis-alkyne **86** ensuring high dilution conditions.



Scheme 3.23 Synthetic route towards target macrocycle **85**, using additional *t*butyl solubilisation

A precipitate occurred during the macrocyclisation reaction and this was isolated and washed with DCM. This white solid was only sparingly soluble in hot DMSO, allowing the presence of macrocycle to be confirmed by ESI-MS. This reaction was repeated in the presence of a chloride anion template. A precipitate was again observed in the reaction mixture, collected and triturated with hot DMSO-*d*₆ enabling the macrocycle, **85**, to be characterised by ¹H NMR (Figure 3.31). Further repeated DMSO triturations failed to obtain the macrocycle in any significant quantity, suggesting that insoluble oligomeric side-products dominate.

The assigned ^1H NMR spectrum of the isolated macrocycle is shown in Figure 3.31 and the high-resolution ESI-MS shows the $[\text{M}+\text{Na}]^+$ ion (Figure 3.32). The difficulties of low yield and extraction by DMSO prevented further study of this macrocycle.

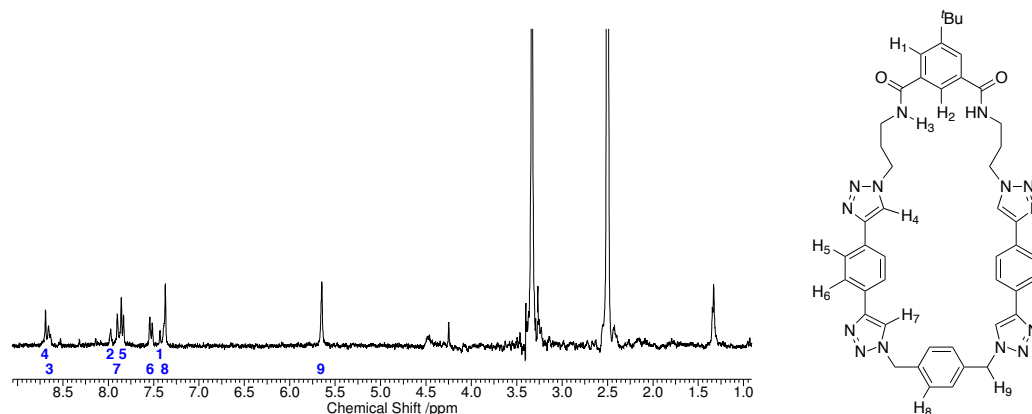


Figure 3.31 Key protons are assigned in the ^1H NMR spectrum (300 MHz, $\text{DMSO}-d_6$, 298 K) of macrocycle **85**, with slight impurities

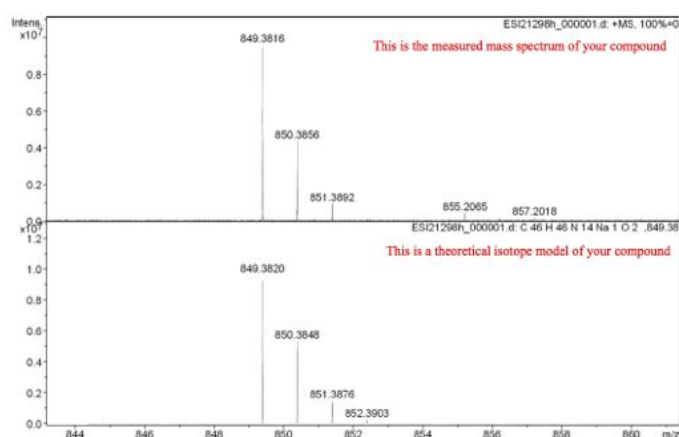
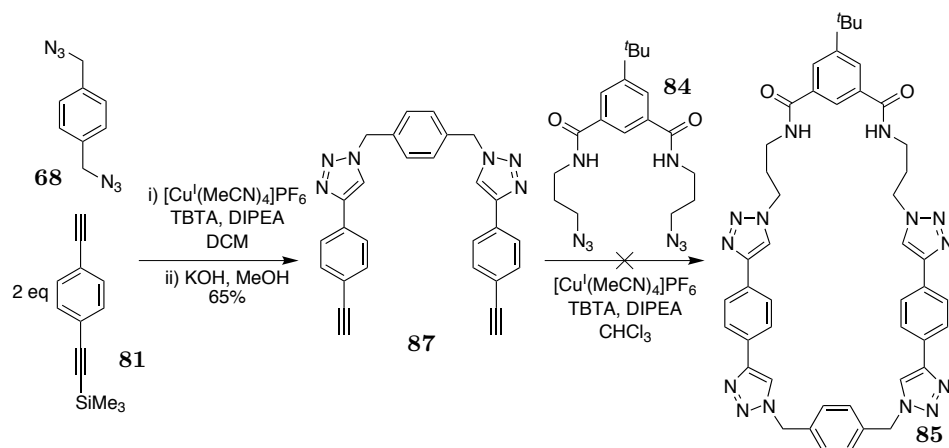


Figure 3.32 High-resolution ESI-MS of macrocycle **85**, flying as the $[\text{M}+\text{Na}]^+$ species

A final attempt at obtaining macrocycle **85** in reasonable quantity was carried out *via* the synthetic route shown in Scheme 3.24. The CuAAC reaction between bis-azide **68** and alkyne **81** and subsequent deprotection proceeded smoothly to afford the alternative bis-alkyne precursor **87** in 65% yield.

Despite the bis-alkyne's favourable solubility in chloroform solution, when reacted with bis-azide **84**, ESI-MS analysis of isolated products provided no evidence for the formation of macrocycle **85**.



Scheme 3.24 Alternative synthetic route towards target macrocycle **85**, initially *via* xylenic substitution

3.4.2 Conclusions

Various synthetic routes were explored for the preparation of target neutral tetratriazole macrocycles **80** and **85**. Progress was hindered each time at the macrocyclisation stage by formation of oligomeric by-products and difficulties in solubility, despite the incorporation of a lipophilic *t*butyl group into macrocycle **85**. Unfortunately, only very small amounts of **85** were isolated for characterisation by ESI-MS and ^1H NMR spectroscopy.

Chapter 4

Neutral Systems

4.1 Introduction

This chapter will focus on the attempted formation of interlocked structures using neutral macrocycles and threads. The chapter contains two distinct parts, each identified by the intermolecular interaction upon which interlocked structure assembly is based:

- (i) research targeting a [2]rotaxane host system for anions, with focus on a donor–acceptor interaction between the electron-poor macrocycle π -system and the electron-rich thread π -system, as well as exploring the possibility of a [2]rotaxane formed by anion templation;
- (ii) work towards interlocked structures with the association of macrocycle and threading component driven by halogen bonding interactions.

4.2 A π donor–acceptor system

4.2.1 Introduction to key motifs

NAPHTHALENE DIIMIDE (NDI)

1,4,5,8-Naphthalene diimide (NDI) and the related larger system, perylene diimide (PDI), are both shown in Figure 4.1a, top and bottom respectively. These are large, planar aromatic groups with electron-poor π -systems, due to the electron-withdrawing effects of the oxygen substituents. One major drawback for the incorporation of NDI into the components of interlocked structures is that the motif can dramatically decrease the compound solubility, displaying π – π stacking in the solid-state, whilst aggregation is observed in solution.^{405–408} Research into NDI and PDI systems has uncovered methods for improving solubility, even to the point of being water-soluble,⁴⁰⁹ but such methods are synthetically challenging, with solubilising substituents attached directly to the NDI core,^{410–412} or using bulky lipophilic dendrimers.^{413,414} Substitution of the NDI core is non-trivial and involves multiple reaction steps. Incorporation of *p*-*tert*-butylcalix[4]arene was the preferred alternative method for mitigating any adverse effects on solubility.

In terms of functionality, NDI is particularly prized for three further aspects: *a*) it can be used as an *n*-type organic semiconductor, *b*) its compact π -system often makes it a candidate for intercalation and *c*) the conjugated aromatic core is redox- and photo-active, allowing for use as an electrochemical and fluorescent sensor.

Organic semiconductors are sought after for their flexibility and low cost, and their synthesis under mild reaction conditions allows film deposition without chemically or thermally damaging the underlying substrates.⁴¹⁵ However, suitable organic *n*-type semiconductors for use as electron carriers are relatively rare.^{416,417} TetraNDI-monomers have previously demonstrated *n*-type semiconductor behaviour, quenching *p*-type polymer films,⁴¹⁸ with recent developments leading to the conjugated polymer system shown in Figure 4.1b.^{414,419}

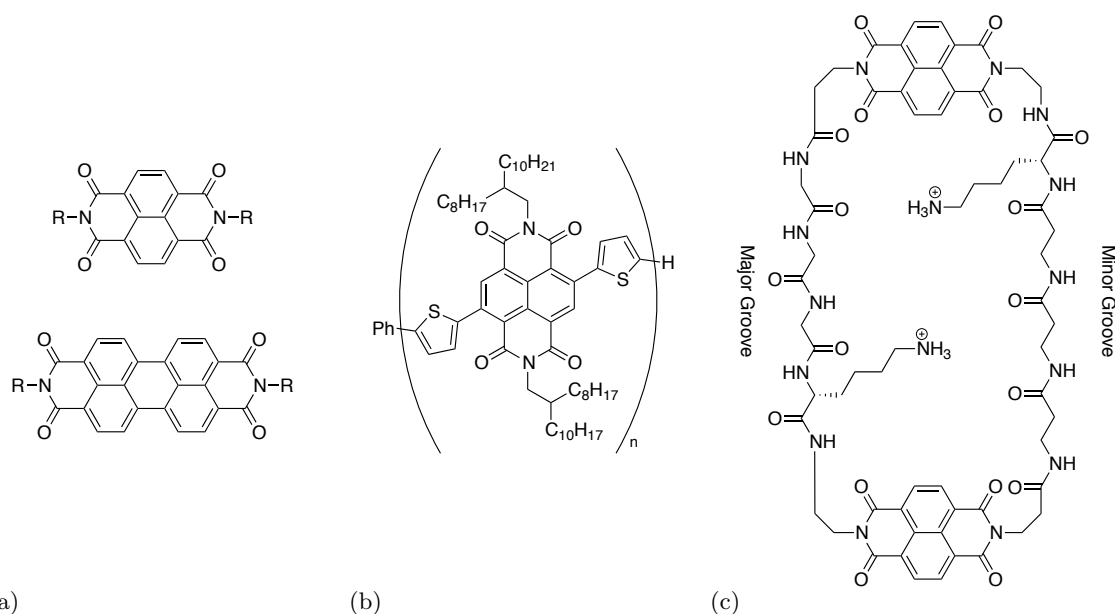


Figure 4.1 The naphthalene diimide motif in action: (a) 1,4,5,8-naphthalene diimide, NDI, and the larger PDI, (b) incorporated into an *n*-type semiconductor and (c) an NDI-based DNA intercalator

NDI has been particularly noted for its ability to intercalate DNA. The NDI-containing macrocycle developed by Iverson was found to form a pseudocatenane with DNA strands.⁴¹³ One side-linker of the macrocycle was shown to be suited to major groove binding; the other side-linker to minor groove binding, as shown in Figure 4.1c. The mechanism of intercalation exploits the “breathing” modes of the DNA double strand, whereby the hydrogen bonding ladders between base pairs occasionally relax, allowing the macrocycle to slip in and form a postulated pseudocatenane. Freccero has reported an NDI-based guest that selectively binds to G-quadruplex strands in preference to DNA, with ensuing stabilisation of the quadruplex structure. Terminal functional groups on the guest could also be activated for alkylation of the quadruplex strands.⁴²⁰

The redox properties of NDI, PDI and a variety of related diimides were described over twenty years ago and it was found that one- and two-electron reductions were reversible and dependent on the amine substituent group.⁴²¹ The first and second potentials for the NDI analogue ($R = {}^n\text{Bu}$) (Figure 4.1a) were reported as -0.50 and -1.03 V respectively, against the standard calomel electrotrode in 0.1 M $(\text{Bu}_4\text{N})_3\text{BF}_4/\text{CH}_3\text{CN}$. Further work

on core-substituted NDI with a variety of aromatic additions found a range of reduction potentials against a ferrocene reference from -0.68 to -1.15 V for the first reduction and -0.83 to -1.55 V for the second.⁴¹²

NDI has been used in self-assembling supramolecular systems by Sanders and Pantoş to form a variety of superstructures, including [2]catenanes,⁴²² [3]catenanes⁴²³ and, in particular, helical self-assembly to form nanotubes.^{424–426} Interestingly, in the latest of these examples, self-assembly of the amino acid-containing monomer, shown in Figure 4.2a, was directed into nanotubes by the introduction of templating C_{60} (Figure 4.2b).⁴²⁶

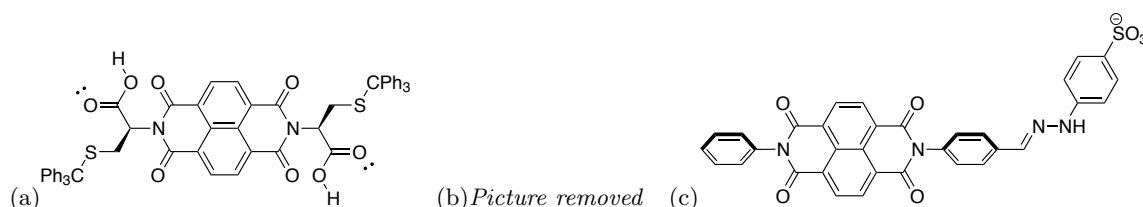


Figure 4.2 NDI cores for binding neutral molecules (a) templated by C_{60} to form nanotubes, with (b) a space-filling model.⁴²⁶ For binding anions (c) transports chloride across an egg yolk membrane

Matile has also investigated applications of NDI, using both core-substituted^{427,428} and amine-functionalised approaches. Of particular note is a report on the anion-binding properties of a series of NDI monomers with variable substitution at the amine R-position.⁴²⁹ These were examined particularly for their anion- π interactions due to the large and relatively electron-poor π -system of the NDI core. As well as theoretical and electrochemical determinations, an anion transportation system was tested across an egg yolk vesicle membrane. From the series tested, the compound shown in Figure 4.2c was the most effective, being solely halide-selective and generating a 9:1 ratio of extracellular Cl^- to I^- . In terms of relevance to this project, the important effect of substituents on the anion-binding affinity of the NDI core is highlighted.

4.2.2 Macrocycle design

Previous work by Beer and co-workers has described a pseudorotaxane assembly incorporating an isophthalamide-containing macrocycle and an NDI-containing thread.⁴³⁰ The pseudorotaxane shown in Figure 4.3a also acted as a displacement assay for anion sensing. The NDI threaded through the macrocycle and was stabilised by aromatic donor–acceptor interactions, however upon chloride anion addition the NDI thread was displaced from the macrocycle cavity with isophthalamide N–H $\cdots$ A[−] hydrogen bonding preferred. This principle was then extended to a [2]rotaxane system whereby an NDI- and amide-containing axle might shuttle upon anion addition. A similar system using redox shuttling has also been described by Leigh.⁴³¹

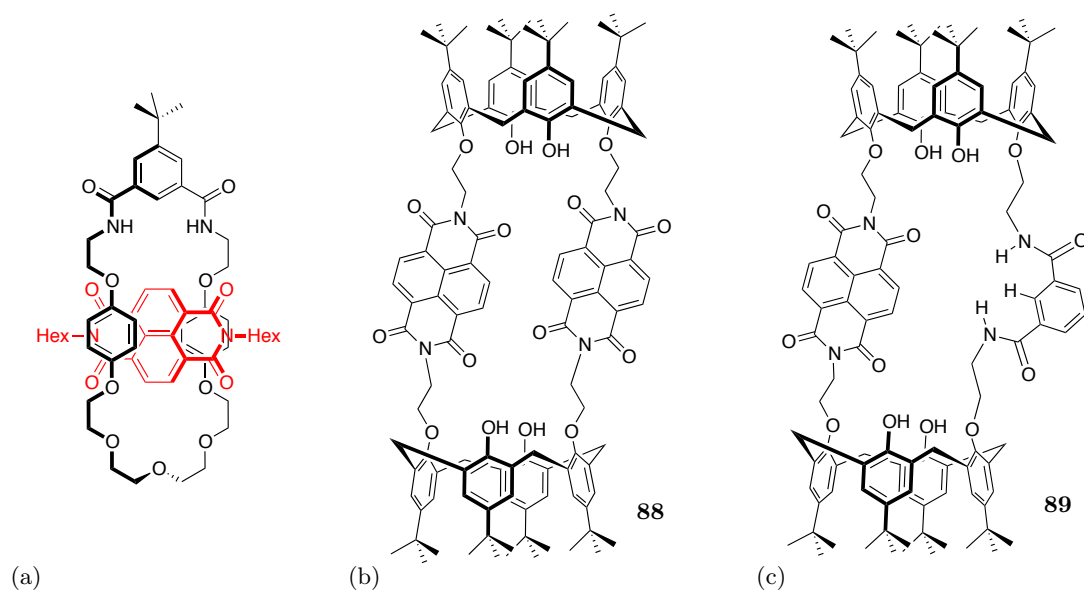


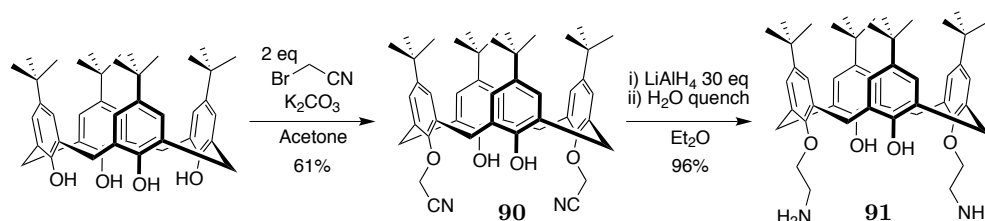
Figure 4.3 NDI-containing axle (a) previously reported in a pseudorotaxane and macrocycles: (b) initial D_{2h} symmetric target, **88**, and (c) secondary target, **89**, with isophthalamide for assisted anion binding

In the work described herein, the NDI motif was instead integrated into a bis-calix[4]arene macrocyclic structural framework, as shown in Figure 4.3b. Macrocycle **88** was identified as an initial synthetic target — its key advantages included the sole use of the NDI at its core, with the expectation that the calix[4]arene motifs would aid solubility in organic solvents. The two electron-deficient NDI groups of **88** would favour pseudorotaxane formation with

potential electron-rich threading components, which could be monitored by ^1H NMR and UV-vis spectroscopy.

Secondary synthetic target macrocycle **89** shown in Figure 4.3c was designed to recognise anions *via* possible anion- π interactions with the NDI motif and isophthalamide group hydrogen bonding.

4.2.3 Macrocycle synthesis

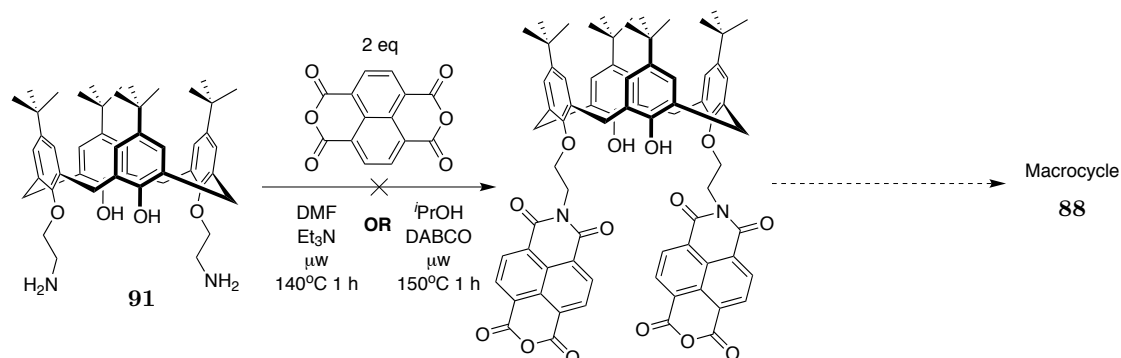


Scheme 4.1 Synthesis of the key capping calix[4]arene precursor

The synthesis of target macrocycle precursors is shown in Schemes 4.1 and 4.3. Following a procedure previously developed in the group,⁴³² commercially available 4-*t*-butylcalix[4]arene was reacted with bromoacetonitrile to form the lower-rim 1,3-substituted bis-nitrile, **90**. Reduction using a small excess of LiAlH_4 occasionally gave only the mono-reduced product, so a large excess of LiAlH_4 was used, followed by careful quenching with H_2O , which afforded the bis-amine, **91**, in 59% yield over two steps (Scheme 4.1).

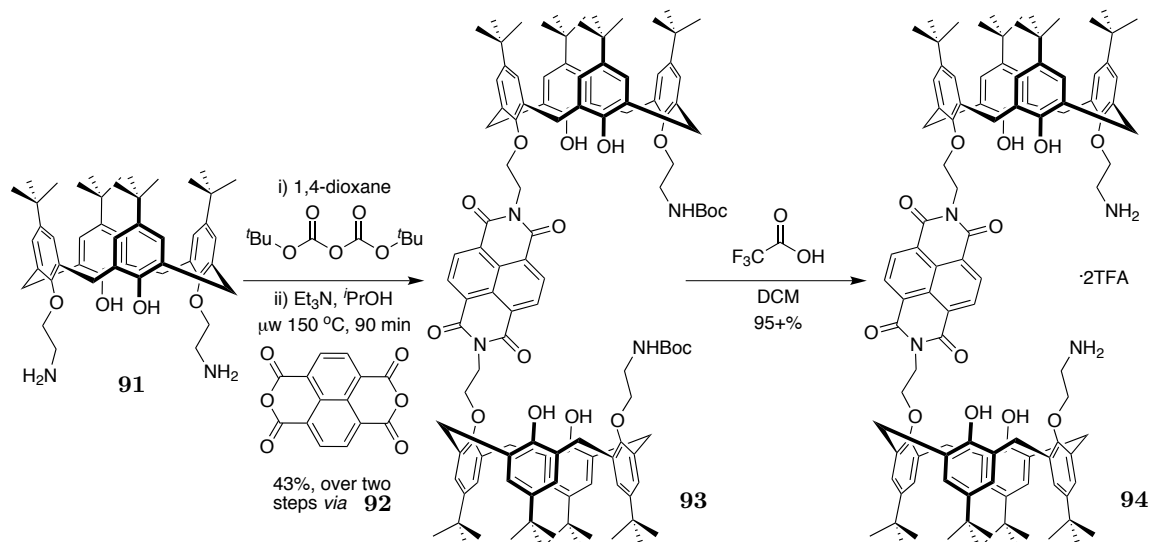
With bis-amine **91** in hand, trial reactions were attempted either to immediately attach two NDI components or directly make the desired macrocycle (**88**). Test reactions in DMF and Et_3N with two equivalents of the NDI precursor, 1,4,5,8-naphthalene tetracarboxylic dianhydride, were undertaken to yield a 1,3-disubstituted calix[4]arene with pendant anhydrides. These would then be suitable for reaction with a further equivalent of bis-amine **91** to form macrocycle **88**, as outlined in Scheme 4.2. These reactions in DMF and Et_3N showed a mixture of products by TLC, but no sign of the 1,3-dianhydride intermediate by ^1H NMR

spectroscopy or MALDI-MS. Further attempts were made using microwave irradiation in both DMF/Et₃N and *iso*-propanol/DABCO reaction conditions, but no evidence for the desired product was observed.



Scheme 4.2 The most direct routes to synthesising macrocycle **88** were unsuccessful

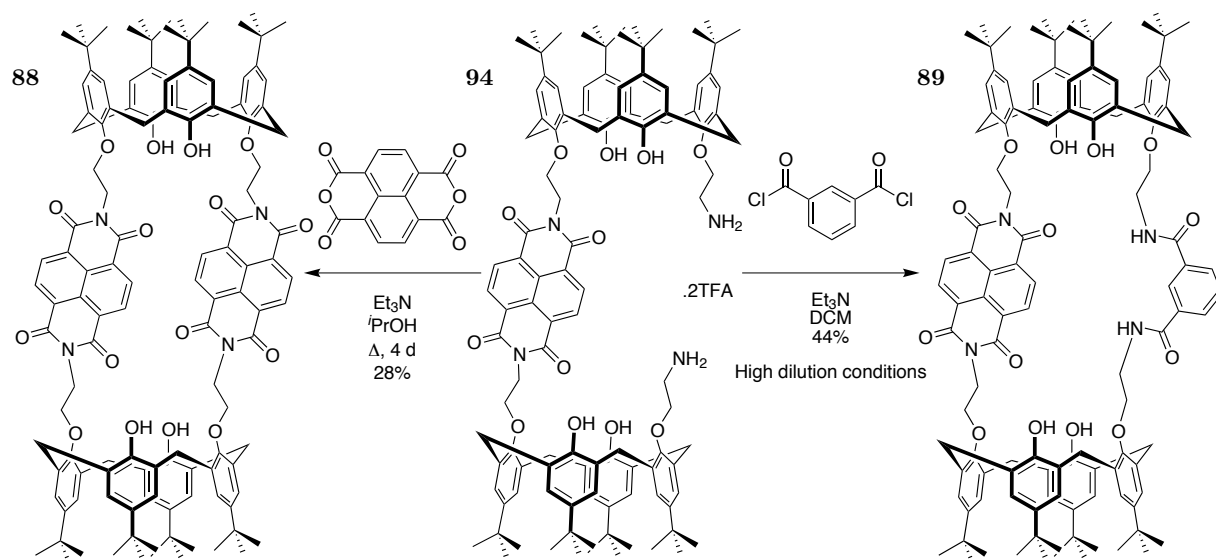
Attempting the more ambitious approach to direct macrocyclisation by reaction of one equivalent of the dianhydride precursor with one equivalent of the bis-amine **91** in *iso*-propanol with DABCO gave no evidence of the macrocycle or any of the desired intermediate products by MALDI-MS.



Scheme 4.3 Synthetic route towards the NDI-containing precursor

Hence, an alternative protection-monofunctionalisation-deprotection synthetic route, shown in Scheme 4.3, was undertaken. Monoprotection of bis-amine **91** with di-*tert*-butyl carbonate in 1,4-dioxane proceeded smoothly in 65% yield. The resultant mono-protected species (**92**)

was then reacted on in a 2:1 ratio with the dianhydride, yielding NDI-containing compound **93**. The Boc protecting groups were then removed by reaction with trifluoroacetic acid to afford bis-amine compound **94**, which was ready for macrocyclisation.



Scheme 4.4 In the macrocyclisation step each of the two desired macrocycles could be formed

Macrocyclisation could be employed from compound **94** to form either of the two target macrocycles. Clipping the loop with a further equivalent of NDI precursor was successfully carried out under high-dilution macrocyclisation conditions in an *iso*-propanol/ Et_3N solvent mixture at reflux to form macrocycle **88** in a reasonable yield of 28%. A high-dilution method was employed for the more facile macrocyclisation with isophthaloyl dichloride. This afforded target macrocycle **89** in an improved yield of 44% (Scheme 4.4).

4.2.4 Macrocycle characterisation

Macrocycle **88** was a pale pink/orange solid and was found to have the simple ^1H NMR spectrum in CDCl_3 , shown in Figure 4.4, expected of such a symmetric molecule. All eight equivalent NDI aromatic protons appeared at δ 8.85 ppm and the phenyl groups of the calix[4]arene produced two distinct signals at 7.05 and 6.61 ppm. Also visible are the calix[4]arene alkyl linking axial and equatorial protons at δ 4.24 and 3.27 ppm (AB

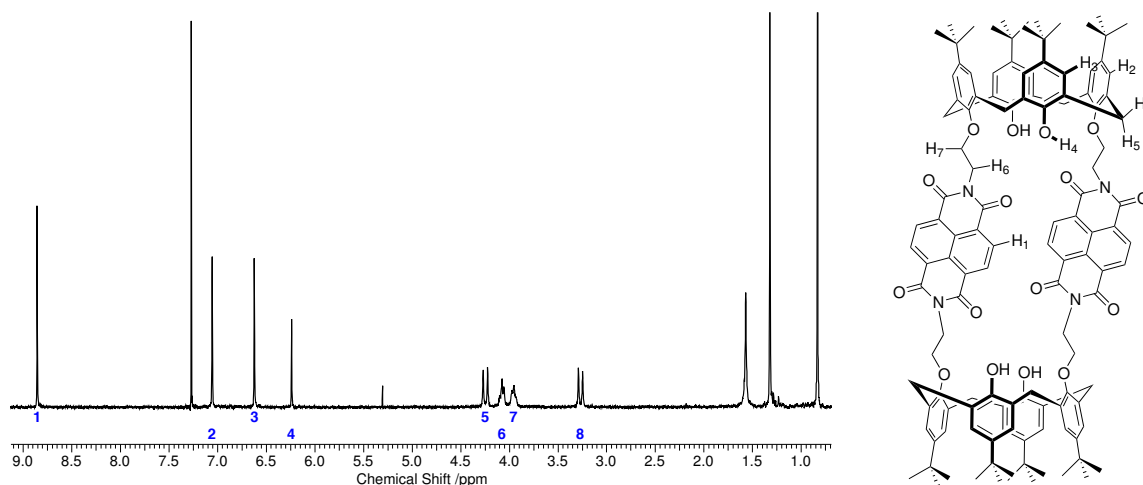


Figure 4.4 Fully assigned ^1H NMR spectrum (300 MHz, CDCl_3 , 298 K) of macrocycle **88**

quartet). Surprisingly the macrocycle proved to be more soluble in room temperature CDCl_3 than hot $\text{DMSO}-d_6$; solubility in CDCl_3 is estimated at $<1 \text{ mg ml}^{-1}$. In spite of the *p*-*tert*-butylcalix[4]arene groups, the macrocycle's solubility was limited. A sample was submitted to a 500 MHz cryoprobe NMR spectrometer to obtain a ^{13}C NMR spectrum. The macrocycle was also characterised by MALDI-MS and melting point analysis. Cyclic voltammetry in DCM revealed quasi-reversible one-electron reduction of **88** at -1.25 V *versus* ferrocene using an Ag/Ag^+ reference, compared with a typical value of -1.10 V *versus* ferrocene for NDI (see Chapter 6).⁴⁰⁸

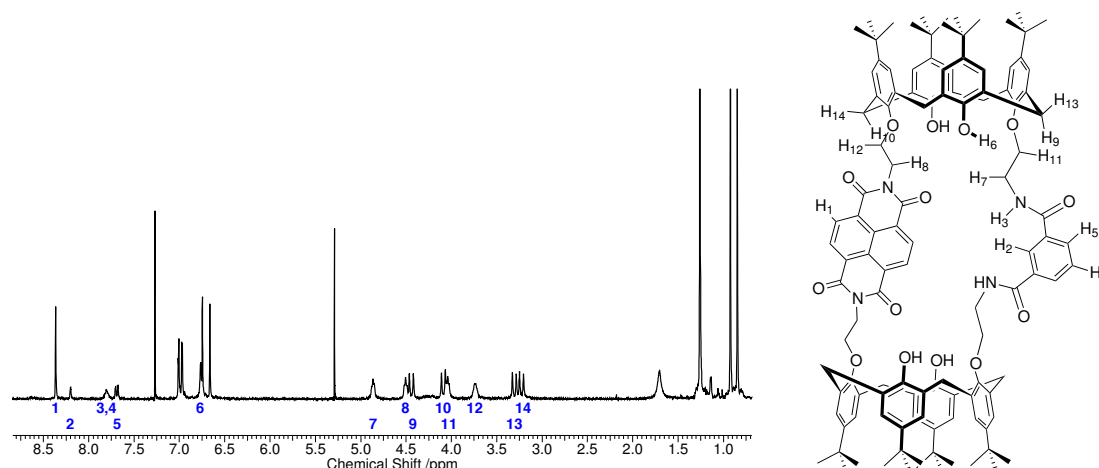


Figure 4.5 Partially assigned ^1H NMR spectrum (300 MHz, CDCl_3 , 298 K) of macrocycle **89**

Orange, isophthaloyl-containing macrocycle **89** was found to be significantly more soluble. The ^1H NMR spectrum of **89** in CDCl_3 (Figure 4.5) revealed NDI protons at δ 8.37 ppm, the isophthalamide N–Hs were at 8.20 ppm and the internal C–H proton at 7.81 ppm. The alkyl region also showed split methylene resonances compared with the symmetrical cyclic counterpart, **88**, with the calix[4]arene signals split into two AB quartets. The macrocycle was also characterised by ^{13}C NMR spectroscopy, high resolution ESI-MS and melting point analysis.

4.2.5 Anion binding studies with NDI-containing macrocycles

The anion binding properties of macrocycle **88** were probed by ^1H NMR spectroscopy (500 MHz, CDCl_3 , 293 K) by addition of stoichiometric amounts of tetrabutylammonium(TBA)-anion salts. Anion recognition might occur *via* anion– π and possible hydrogen bonding interactions with the calix[4]arene O–H groups. The addition of each of Cl^- , Br^- or I^- produced no significant shift in the ^1H NMR spectrum of **88**. In chloroform solution, ion-pairing between TBA^+ and X^- may be too strong for the macrocycle to compete with. Unfortunately, the poor solubility of **88** in acetone and acetonitrile prevented further titration experiments being undertaken.

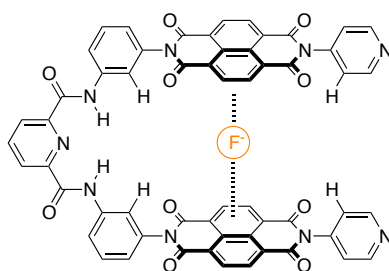


Figure 4.6 Saha's aryl-substituted NDI proved suitable for binding TBAF in DMSO

Macrocycle **89** was also titrated with one equivalent of TBACl in CDCl_3 , but surprisingly showed no change in its ^1H NMR spectrum. A recent report by Saha revealed an acyclic bis-NDI-containing receptor linked by an 2,6-bis-amide pyridine that can selectively detect fluoride anions in $\text{DMSO}-d_6$ solution.⁴³³ In light of this, a ^1H NMR titration with

TBAF · H₂O in DMSO-*d*₆ was undertaken, however, the poor solubility of these macrocycles interfered again, with precipitation of the macrocycle observed. A further titration in CDCl₃ was then carried out, with addition of up to 10 equivalents of TBAF · H₂O failing to cause any significant perturbations — even deprotonation of the amide protons was not observed.

4.2.6 Pseudorotaxane assembly studies

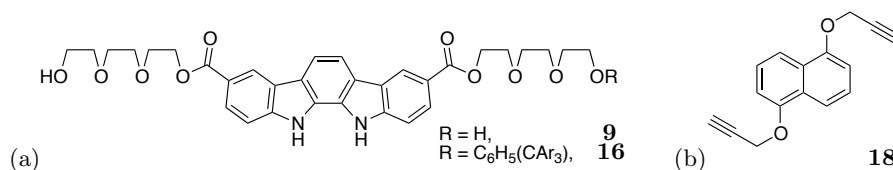


Figure 4.7 Pseudorotaxane formation studies used thread derivatives based on: (a) indolocarbazole and (b) dihydroxy naphthalene ether

The disappointing anion-binding properties of macrocycles **88** and **89** might be enhanced by addition of a suitable anion-binding axle component to form a [2]rotaxane. The electron-rich indolocarbazole threads (**9** and **16**) and 1,5-naphthalene diol derivative (**18**, of which a sample was kindly donated by Dr Chris Serpell) were chosen for this purpose (Figure 4.7).

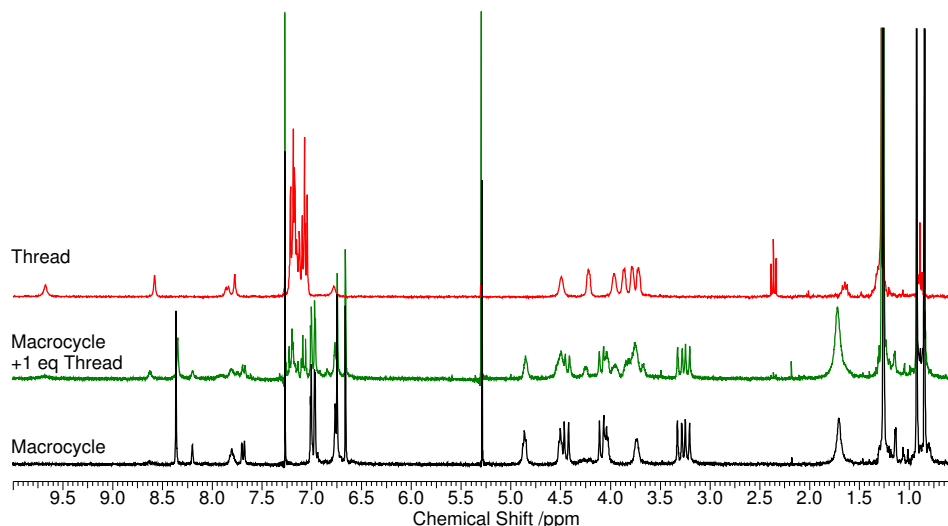


Figure 4.8 Pseudorotaxane formation study of macrocycle **89** with one equivalent of indolocarbazole thread **9** by ¹H NMR spectroscopy (300 MHz, CDCl₃, 298 K)

For macrocycle **88**, initial pseudorotaxane formation with an indolocarbazole derivative **9** was attempted. Mutual solubility problems required the use of a 1:1 CDCl₃/acetone-*d*₆ mixture

for the titration experiment. Disappointingly, no evidence of chemical shift perturbations in the equimolar 1:1 macrocycle/thread ^1H NMR spectrum was observed, suggesting that pseudorotaxane formation is not favourable. Furthermore, even in the presence of one equivalent of Cl^- , no shifts of macrocycle protons were observed.

Analogous titration experiments with macrocycle **89** and one equivalent of **16** also failed to provide any evidence for interpenetrative assembly (Figure 4.8). For the 1:1:1 mixture of macrocycle/indolocarbazole thread/TBACl a colour change from orange to pink was observed, however, again ^1H NMR spectroscopy showed minimal change. No change was observed for attempted stoichiometric pseudorotaxane formation with the simple electron-rich naphthalene thread **18**.

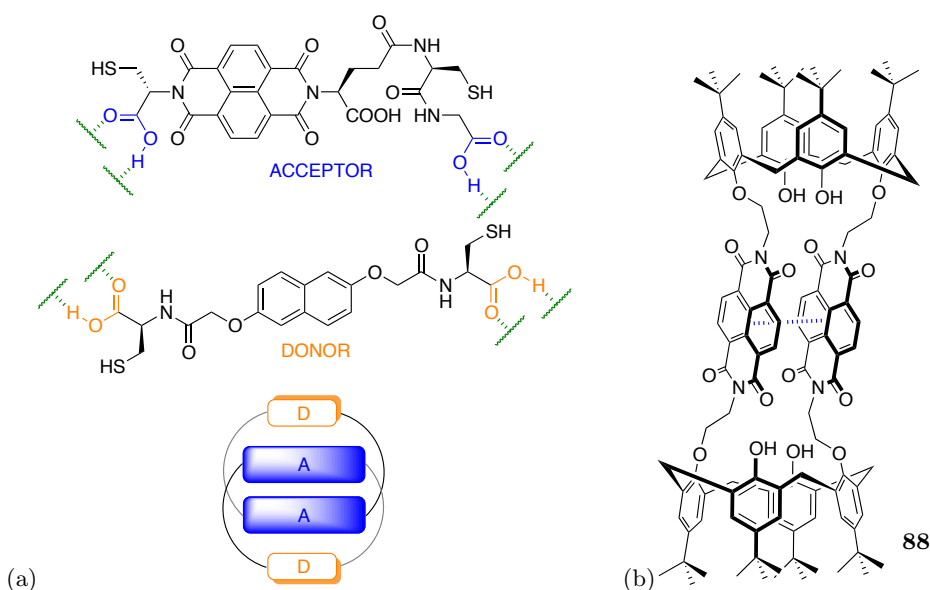


Figure 4.9 NDI self-stacking (a) observed by Sanders in unusually stacked [2]catenanes and (b) suspected in macrocycle **88**

Recent work by Sanders has identified that 2,8- and 1,5-naphthalene diol derivatives will form aromatic stacks with NDI, as evidenced by the synthesis of a [2]catenane.^{422,434} Their investigation used a dynamic combinatorial library with both π -donor and π -acceptor assembly components possessing terminal carboxylic acids for hydrogen-bond linking. One such combination is shown in Figure 4.9a, where the expected stacking mode for [2]catenane

formation under thermodynamic conditions would be of an alternating DADA nature to maximise donor–acceptor interactions. The unusual DAAD [2]catenane stack was observed in significant proportion, with the two NDI components closely approaching each other. Two possible reasons for this were postulated: *a*) the NDI π -systems were so severely contracted that the two aromatic moieties could approach with less repulsion than expected and *b*) the aqueous medium in which the library was assembled produced a hydrophobic effect, with the large solvatophobic NDI π -system nestling away from solvent molecules inside the [2]catenane cavity. In comparison, both the contracted π -systems and solvatophobic effects may have conspired to give a preferential closely-stacked conformer of macrocycle **88**, as shown in Figure 4.9b, with little room for electron-rich threads to penetrate the cavity.

4.2.7 Conclusions

The 1,4,5,8-naphthalene diimide group was explored as a suitable π -acceptor motif in donor–acceptor interactions and interpenetrative assembly. To this end, two novel NDI- and bis-calix[4]arene-containing macrocycles have been synthesised and characterised. Both macrocycles were formed through a six-step synthetic procedure, including the use of protecting groups where required.

In spite of the calix[4]arene groups, the first macrocycle, **88**, exhibited limited solubility in dichloromethane or chloroform solutions. Anion-binding studies in CDCl_3 revealed no evidence of complexation taking place, suggesting that strong TBAX ion-pairing may be responsible. In pseudorotaxane formation studies with π electron-rich threads, no threading was seen and the NDI cores were suspected of stacking closely together.

Replacing one NDI core for isophthalamide afforded the second macrocycle, **89**. This exhibited better solubility, but was still unable to bind anions in CDCl_3 . Attempts at forming pseudorotaxanes were again unsuccessful.

Use of the NDI motif in future supramolecular systems must be carefully considered. The choice of *N*-substituent is key in directing the compound for solubility and effective use. The potential for aggregation and close π - π stacking of multiple NDI cores should not be underestimated.

4.3 Assembling interpenetrative structures *via* halogen bonding

4.3.1 Introduction to key principles

HALOGEN BONDING

The principles of halogen bonding and its similarity to hydrogen bonding were briefly outlined in the introduction, Section 1.2. Key criteria in designing halogen bonding-based receptors are to ensure that the halogen donor atom is both sufficiently polarisable, the larger and more diffuse the better, and also has electron-withdrawing substituent groups, to form a more positive σ -hole to receive electron density. The stringent linearity of the halogen bond also needs to be considered in receptor design.

(a)*Picture removed* (b)*Picture removed*

Figure 4.10 Modelled electrostatic potential surfaces illustrating (a) the positive σ -hole of CF_3I available for donating a halogen bond and (b) no corresponding σ -hole on CF_4 ⁴³⁵

Seminal theoretical work by Clark *et al.* predicted the order of halogen bond donor strength as $\text{I} > \text{Br} > \text{Cl} > \text{F}$.^{435,436} Electrostatic potential modelling of CF_3I (Figure 4.10a) and CF_4 (Figure 4.10b) demonstrate the positive terminus on the polarised iodine atom of CF_3I , whereas the terminus of the fluorine atom in CF_4 is still negative.

The corresponding halogen-bond acceptor, the source of electron density, can be any neutral or negatively charged Lewis base.⁴³⁷ Motifs that are commonly used for their lone pair availability tend to be tertiary amines, pyridines, carbonyls and *N*-oxides ($\text{R}_3\text{N}^+-\text{O}^-$).

4.3.2 System design

The Beer group has lately been investigating the role of halogen bonding in interpenetrative assembly and has reported the first anion-templated halogen bonding pseudorotaxane (Figure 4.11a⁴³⁸) and subsequently constructed a [2]catenane (Figure 4.11b).⁴³⁹

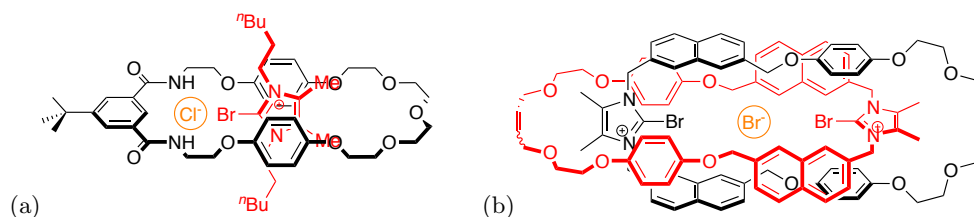


Figure 4.11 Work by Beer on interlocked halogen bonding structures with (a) the first anion-templated halogen bonding pseudorotaxane and (b) the first halogen bonding [2]catenane

By incorporating a neutral Lewis base halogen-bond acceptor, such as pyridine, into a cyclic framework (**95**), exclusive use of halogen bonding may be exploited for pseudorotaxane assembly. A symmetric target halogen bonding [2]rotaxane is pictured in Figure 4.12. Note that the centres of all the halogen bond donors and acceptors are designed to align in a linear fashion to provide maximal halogen bonding.

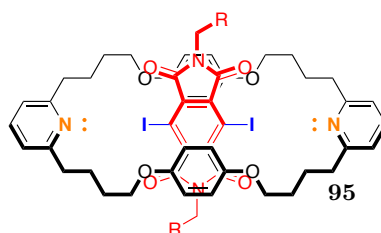


Figure 4.12 Target [2]rotaxane with an axle threaded through target macrocycle **95** by halogen bonding

The thread's electron-deficient π -conjugated core is designed to enhance polarisation of the C–I bond, thereby generating a stronger halogen-bond donor, enhancing aromatic donor–acceptor interactions and contributing to the stability of the interpenetrated assembly. Other possible pyridyl-containing cyclic variants (**96** and **97**) were also considered, as shown in Figure 4.13.

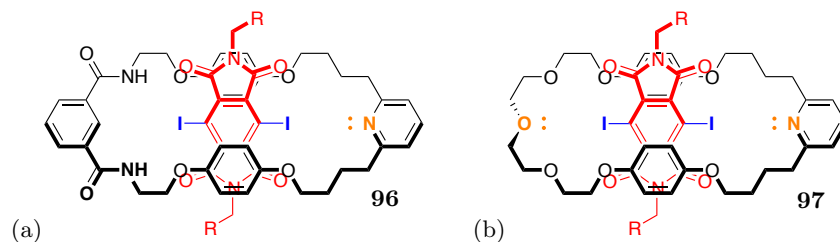


Figure 4.13 Further [2]rotaxanes held by (a) fewer halogen bonds, with macrocycle **96**, or (b) lesser halogen bonds, with macrocycle **97**

4.3.3 Attempted synthesis of pyridyl-based halogen-bond acceptor macrocycles

The three macrocycles described above share similar structures and thus syntheses were devised towards key synthons: **98**, **99**, **3** and **100** (Figure 4.14).

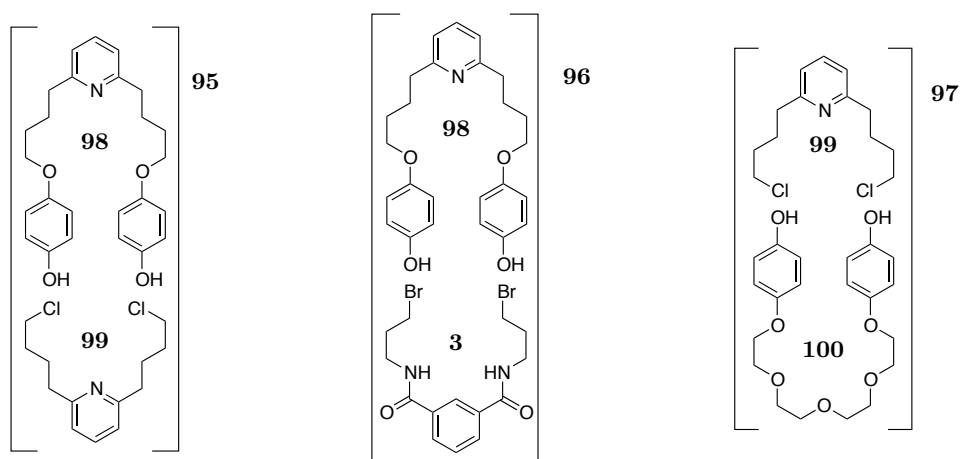
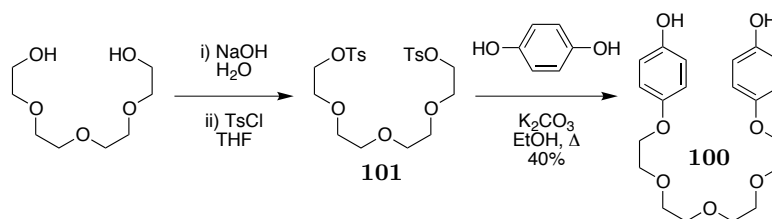


Figure 4.14 Partial disconnections displayed for each of the three macrocycles

SYNTHON **100**

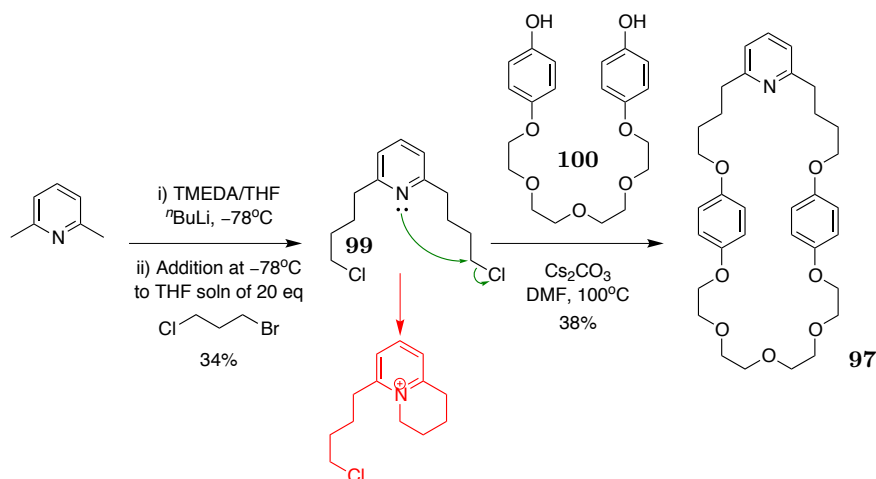
Polyether intermediate **100** was synthesised in a two-step process according to a literature procedure (Scheme 4.5).³⁷³ First, the polyether was doubly tosylated in a basified mixture (**101**) and was then reacted with a large excess of 1,4-hydroquinone to afford intermediate **100** in a 40% yield.



Scheme 4.5 Synthesis of hydroquinone intermediate, **100**, precursor to macrocycle **97**

SYNTHON **99**

Initial attempts at forming bis-chloro-functionalised pyridine intermediate **99** from 2,6-lutidine and 1-bromo-3-chloropropane were unsuccessful, although significant amounts of the mono-functionalised product were detected. Distillation of the TMEDA and 2,6-lutidine, azeotroping the 1-bromo-3-chloropropane and using fresh n BuLi were sufficient to remove (mainly aqueous) impurities and resulted in a successful reaction, depicted in Scheme 4.6. If left under ambient conditions the yellow oily product was found to partition into a biphasic system of orange/yellow oils, with ^1H NMR spectroscopy confirming decomposition, a likely mechanism is intermolecular nucleophilic attack (6-*exo-tet*) by the pyridine nitrogen on C–Cl. The product was stable in the freezer for up to 2 weeks.



Scheme 4.6 Synthesis of key dichloride intermediate, **99** and continuation to macrocycle **97**

Attempted macrocyclisation reactions to form polyether macrocycle variant **97** were carried out on a small scale and found evidence of success in the crude mixture by ESI-MS (m/z : $[\text{M}+\text{H}]^+$ 566.33 and $[\text{M}+\text{Na}]^+$ 588.31). The $[\text{M}+\text{Na}]^+$ peak was particularly prominent, no doubt due to the polyether chain cation-binding site. Successful purification by column

chromatography afforded a slightly impure sample of the desired macrocycle in 38% yield (Scheme 4.6).

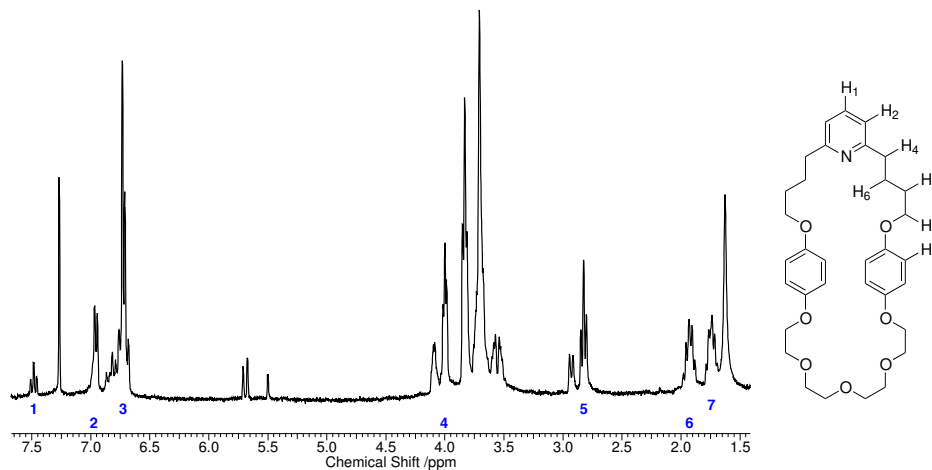
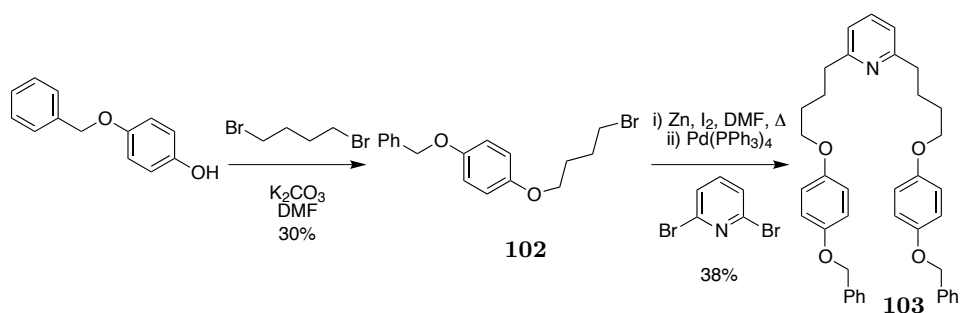


Figure 4.15 ^1H NMR spectrum (300 MHz, CDCl_3 , 298 K) with assignation indicating the key protons of macrocycle **97**

Macrocycle **97** was isolated as an impure off-white solid. Key proton resonances in its ^1H NMR spectrum are shown in Figure 4.15. The chemical shifts from each component of the macrocycle are segregated into separate regions, with the pyridyl protons in the region δ 7.5 to 6.9 ppm, hydroquinone protons δ 6.7 to 6.6 ppm, polyglycol protons δ 3.5 to 4.1 ppm and alkyl linker protons δ 3.0 to 1.5 ppm. The macrocycle was also characterised by ^{13}C NMR spectroscopy and high resolution ESI-MS.

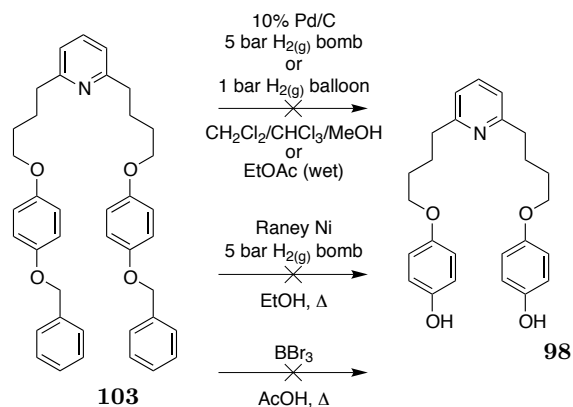
SYNTHON **98**

The synthetic approach to key hydroquinone intermediate **98** was a three-step process. To avoid reaction on both sides of the hydroquinone, a benzyl-protected precursor was proposed, with deprotection to be carried out at the final stage. Initial bromo-precursor **102** was synthesised according to a literature procedure,⁴⁴⁰ with particular care taken to remove any residual 1,4-dibromobutane before the subsequent Negishi reaction step. The double Negishi reaction was carried out using 2,6-dibromopyridine and was successful in forming benzyl-protected hydroquinone-appended pyridine **103** in a reasonable yield (Scheme 4.7).



Scheme 4.7 Synthetic progress to protected precursor, **103**

Removal of a benzyl group to deprotect the corresponding alcohol was presumed facile, however, unfortunately the deprotection step proved to be unusually problematic. The presence of a pyridine in the substrate had been found to interfere with hydrogenation in similar systems in the group, possibly binding to the palladium catalyst, and slowing the reaction significantly. Initial deprotection attempts were carried out using 10% *wt.* Pd/C using a bomb apparatus under a 5 bar atmosphere of hydrogen. A 1:1 mixture of chloroform/methanol was used to solubilise the starting material. This reaction worked once on a small scale over 5 days; most frustratingly this was not reproducible at any subsequent attempt, despite extending the reaction time to over 2 weeks.



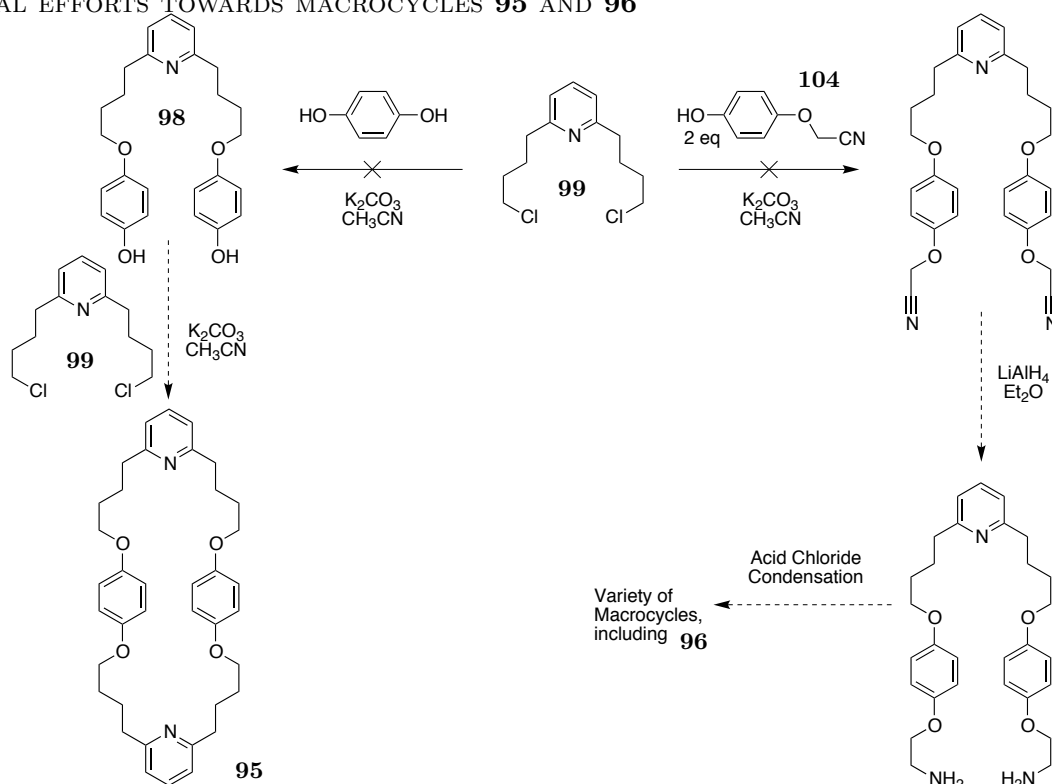
Scheme 4.8 Attempted formation of key hydroquinone intermediate, **98**

Multiple attempts were made at hydrogenations, using either the bomb conditions or a periodically-refilled hydrogen balloon. Attempts with a variety of solvents were made including chloroform, dichloromethane, 1:1 chloroform/methanol, 1:1 dichloromethane/methanol and neat methanol, as well as wet ethyl acetate. No indication of the product was found

by either ^1H NMR spectroscopy or ESI-MS. Several different pots of 10% *wt.* Pd/C were also used, to no avail. After over 20 unsuccessful hydrogenation attempts, this method was abandoned.

Further attempts at hydrogenation were made using Raney Nickel. This was both used when freshly activated over refluxing EtOH and also from an entirely fresh supply. Reactions were carried out in the 5 bar hydrogenation bomb and were unsuccessful. ^1H NMR spectra in CD_3OD indicated possible reduction of the pyridine component. A final attempt at selective removal of the benzyl group was carried out using boron tribromide and acetic acid reaction conditions, however this also was fruitless, with no change observed (Scheme 4.8).

FINAL EFFORTS TOWARDS MACROCYCLES **95** AND **96**



Scheme 4.9 Final attempts at progress towards macrocycles **95** and **96**

In the absence of any sample of **98**, direct reaction of bis-chloro-pyridyl compound **99** with hydroquinones were attempted (Scheme 4.9). The reaction between **99** and 1,4-hydroquinone

in a 1:1 stoichiometry in basic acetonitrile solution was attempted to form macrocycle **95**, however, no desired products were detected by either ^1H NMR spectroscopy or ESI-MS. A similar effort was made towards macrocycle **96** by reaction of **99** with monofunctionalised hydroquinone **104**, which was prepared by a standard group procedure.⁴⁴¹ This also proved to be unsuccessful.

4.3.4 Alternative halogen bond acceptor macrocycles

An alternative set of pyridine-containing macrocycles were targeted (Figure 4.16), with the polyether linkages enabling new synthetic routes to be explored. Of particular importance was the possibility of using tosylates instead of chloro substituents in $\text{S}_{\text{N}}2$ reactions.

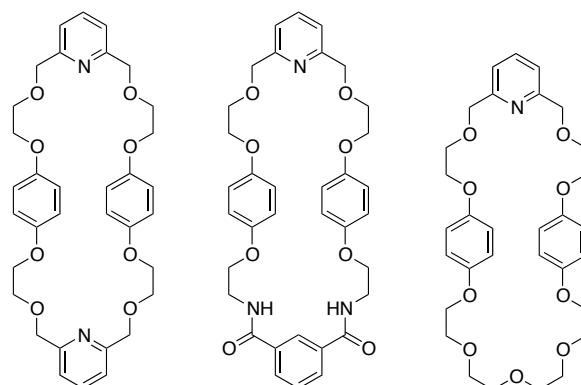
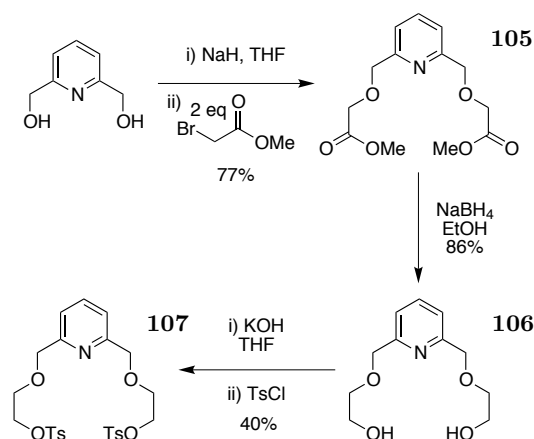


Figure 4.16 Alternative target macrocycles with glycol, rather than alkyl, linkers

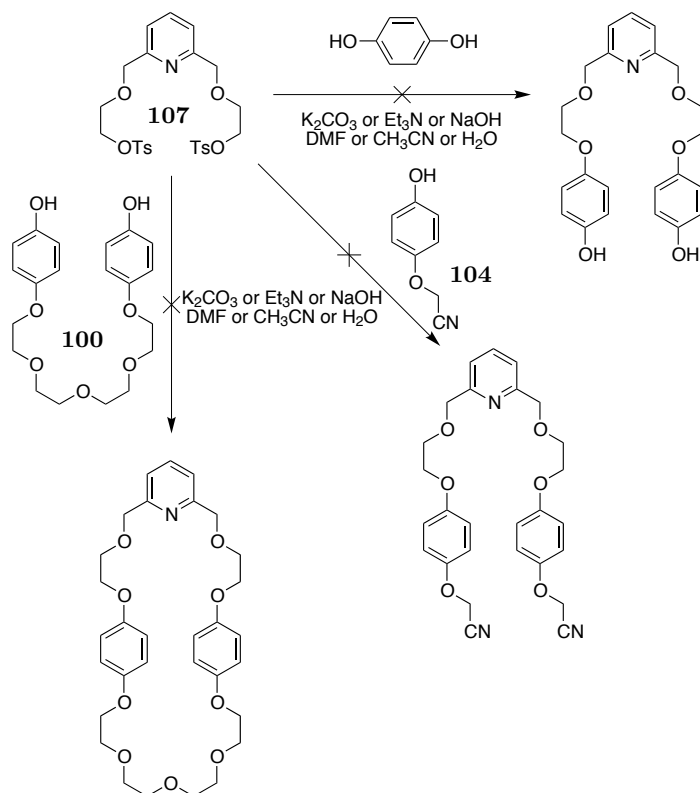
4.3.4.1 Syntheses of pyridyl precursors

Initial progress was made by synthesising a ditosylate precursor, **107** (Scheme 4.10). From 2,6-dimethanol-pyridine, the glycol chain was extended using an α -haloester. Ester **105** was reduced using NaBH_4 to form alcohol **106**, following literature precedent.^{442,443} Ditosylate **107** is reported to decompose rapidly under ambient conditions, therefore it was prepared *in situ* and immediately used in follow-up reactions.^{443,444}



Scheme 4.10 Formation of an electrophilic ditosylate precursor, **107**

Unfortunately, all subsequent reactions of **107** with various phenolate derivatives in basic solutions were unsuccessful (Scheme 4.11). These reactions were carried out without success in each of the following sets of reaction conditions: *a*) DMF with K_2CO_3 , *b*) DMF with Et_3N , *c*) refluxing acetonitrile with K_2CO_3 , *d*) refluxing acetonitrile with Et_3N and *e*) water with NaOH.



Scheme 4.11 Next stage reactions from ditosylate **107** were unsuccessful

4.3.5 Conclusions and future work

Synthetic progress towards target pyridyl-containing macrocycles designed for accepting halogen bonds with appropriate halogen-bond donor threads was problematic. In all but one case, synthetic difficulties thwarted the cyclic products being isolated.

Future work could focus on a larger scale synthesis of macrocycle **97** for halogen bond directed pseudorotaxane investigations.

Chapter 5

Conclusions

This thesis focused on developing novel host systems for ion pairs and anions through heteroditopic receptors and interlocked structures. Some motifs for binding anions were outlined in the introduction with those utilised in the work in this thesis including: cationic imidazolium, pyridinium and triazolium, and neutral isophthalamide and naphthalene diimide. Calixarenes and calixdiquinones were consistently used throughout this work as solubilising scaffolds and, in the latter case, as a cation binding motif. The key triazole group was identified as containing functionality for binding cations through its Lewis basic nitrogen and for binding anions through C–H hydrogen bonding.

5.1 Macrocyclic receptors

During this body of research several novel macrocycles were successfully synthesised. These host macrocycles typically contained two of the electron-deficient motifs described above for anion binding, creating multiple interactions in the binding pocket. In most cases, significant synthetic problems were overcome in order to achieve the target compounds, either by investigating alternative synthetic routes or precise modification of reaction procedures. In particular, despite a challenging macrocyclisation step, a series of pyridinium-based cationic macrocycles was developed for comparison in anion binding studies.

The copper(I)-catalysed azide–alkyne cycloaddition was carried out in many of the synthetic routes, forming triazole linkers. This efficient “click”-type reaction proceeded in mild conditions and proved to be insensitive to a variety of functional groups. Careful adjustment of the double reaction to form macrocycle **5** (Scheme 2.5) resulted in a notable improvement. Here, the addition of one equivalent of a templating chloride anion in the macrocyclisation step significantly increased the yield from 49% to 77%.

Investigations into the ion binding properties of these novel receptors were carried out in competitive, polar solvents, typically DMSO or a mixture of 2% H₂O/MeCN.

5.2 Ion-pair binding

The ion-pair binding ability of novel heteroditopic receptor **1** was investigated in the solution state by ¹H NMR and UV/vis spectroscopy. Both of these techniques ascertained that for combinations of monovalent anions and cations the binding was mutually cooperative, with anion binding enhanced by the presence of the cation and *vice-versa*. Titrations monitored by ¹H NMR spectroscopy found that once one equivalent of chloride anions had been added to [**1**·KPF₆] in solution, the cation was bound strongly in the cavity, with further addition inducing no further perturbations in the diagnostic receptor proton signals (Figure 2.15). Both techniques identified some selectivity for the Na⁺Cl⁻ ion pair, with up to an 11-fold enhancement in binding strength over the individual ions (Tables 2.3 and 2.4).

Numerous crystal structures were determined of ion-pair adducts to macrocycle **1**, as slow evaporation yielded crystals of suitable quality for structural determination by X-ray diffraction. In a few cases, macrocycles packed in the crystal structure in pseudo-dimer or -trimer configurations (such as in Figure 2.24), using peripheral hydrogen bonding and aromatic donor–acceptor interactions. Notable structures include that of the NaCl adduct (Figure 2.23), where an intramolecular anion binding pocket is formed by the isophthalamide and triazole hydrogen bond donors, as desired; in the KCl adduct (Figure 2.22), an intermolecular contact ion-pair occurs in the solid-state. Water molecules were also found to bridge between the two ions of the pair in several structures (Figures 2.23, 2.25 and 2.27).

Triazole had previously been established as a group for binding either anions or cations (examples in Figure 2.2), however, the triazole motifs in the crystal structure KCl adduct

(Figure 2.21) bind both the anion and the cation. In addition, solution-state investigations suggest simultaneous binding of the anion and cation by the triazole motif (as illustrated in Figure 2.16), which had not previously been reported.³⁵⁵

5.3 Anion binding

Novel macrocycles containing electron-deficient moieties were investigated for their anion binding affinities by ^1H NMR spectroscopy. In general, chloride was favoured from amongst the monovalent anions, due to its charge density and the size match it has for the isophthalamide motif (Figure 3.24). In contrast, bromide typically perches out of the plane of the isophthalamide motif and distorts the orientation of the amide groups.

For the series of pyridinium macrocycles developed in Section 3.3, tetracationic macrocycle **73** exhibited a greater anion binding affinity in solution over the dicationic congeners. A direct comparison between the dicationic *meta*- (**71**) and *para*-functionalised (**72**) isomers was undertaken, as described in Table 3.1. The more symmetrical *para*-functionalised macrocycle bound monovalent anions more strongly, having two available pyridinium *ortho*-protons unrestricted by steric clashes for hydrogen bonding.

X-ray diffraction on crystals of the *para*-functionalised dicationic **72** determined structures with a planar conformation for the macrocycle in the solid state. Interestingly, in the presence of NaPF_6 the crystal structure determined suggests hydrogen bonding from the isophthalamide motif to the relatively non-coordinating PF_6^- anion (Figure 3.14). The macrocycles also pack in a dimer-like fashion, mediated by sodium bridging two amide oxygens ($\text{O} \cdots \text{Na} \cdots \text{O}$) and close approach of the isophthalamide phenyl rings. In the presence of chloride anions, the chloride is found to bind in the intramolecular pocket formed by the isophthalamide and pyridinium *ortho*-protons (Figure 3.24).

Whilst investigating neutral macrocycles as anion receptors, incorporating solubilising calixarene scaffolds into the macrocycle design enabled successful generation of a soluble macrocycle containing two naphthalene diimide moieties. Unfortunately anions were not found to bind to this macrocycle, nor to a similar macrocycle containing both isophthalamide and naphthalene diimide electron-deficient motifs.

5.4 Towards interlocked structures

Having successfully achieved synthesis of novel electron-deficient macrocycles and established that they bound anions in polar solvents, attention was directed towards interlocked structures. Despite being unsuccessful in numerous attempts at forming an interlocked structure, this research uncovered some interesting interactions.

The macrocyclic precursor, compound **5**, to the heteroditopic ion-pair receptor was investigated for pseudorotaxane formation with an indolocarbazole-based thread. Addition of a chloride template induced proton resonances in the thread that indicated chloride binding, whilst only the macrocycle triazoles and amides were binding to chloride. The lack of isophthalamide phenyl proton binding to the anion and ring current effects on the indolocarbazole thread lead to the conclusion that the thread tends to reside outside the macrocycle cavity (depicted in Figure 2.36). Some progress towards a rotaxane to be formed by ion-pair templation was made, by expanding the macrocycle and initiating synthesis of a new pyridinium-based thread series.

Cationic imidazolium- and pyridinium-based macrocycles (Sections 3.2 and 3.3, respectively) were developed with the potential for complexing an electron-rich axle component in the cavity. Pseudorotaxane investigations by ^1H NMR spectroscopy appeared promising and indicated superior association where threads had longer chains (Figure 3.9). This effect has

also previously been reported by Stoddart.³⁶⁷ Rotaxanation reactions were attempted under mild reaction conditions via either a urethane-forming stoppering or a copper(I)-catalysed azide–alkyne cycloaddition. In all cases, no evidence of the desired rotaxane was found, although some free doubly-stoppered thread was isolated after each reaction. Disappointingly, it appears that a combination of macrocycle/stopper steric clashing and thread arm coordination to the macrocycle results in the complexed thread being less readily available for reaction. Faster stoppering of the free thread removes this component from the threading equilibrium, shifting the equilibrium to form further free thread and macrocycle. This stoppering outside the macrocycle cavity would result in predominant production of the free stoppered axle and little rotaxane formation.

Macrocycle **88** contains two electron-deficient naphthalene diimide groups positioned for aromatic donor–acceptor interactions with an electron-rich axle component. However, pseudorotaxane formation studies did not provide any evidence for macrocycle–thread association. Axle components may be hindered from threading the cavity as the contracted naphthalene diimide cores approach each other. Research by Sanders has identified this unusual stacking of two large aromatic acceptor groups in NDI-containing [2]catenanes.^{422,434}

5.5 Summary

The successful syntheses of several novel series of macrocycles that contain electron-deficient components have been described in this thesis. Anion and ion-pair binding studies were carried out and established that binding occurs in polar solvents, with evidence from both the solution- and solid-state. Pseudorotaxane formation studies then provided evidence for threading of electron-deficient macrocycles by electron-rich axle components. The key 1,2,3-triazole linker formed by copper(I)-catalysed azide–alkyne cycloaddition was shown to bind anions and cations simultaneously for the first time.

Chapter 6

Experimental

6.1 General information

All commercial-grade reagents were used as provided and without further purification unless otherwise noted. Dry solvents were obtained by purging with nitrogen and then passing through a MBraun MPSP-800 column. Water was de-ionised and microfiltered using a Milli-Q Millipore[®] machine. The TBTA reagent for CuAAC reactions was prepared according to a literature procedure.⁴⁴⁵

All tetraⁿbutylammonium (TBA) salts were stored in a vacuum desiccator containing phosphorus pentoxide and self-indicating silica gel prior to use. Et₃N was distilled over KOH, then stored over KOH under N₂. 2,6-Lutidine was distilled over KOH, then stored over KOH under N₂. Tetramethylethylenediamine was distilled over KOH, then stored over KOH under N₂. Isophthaloyl dichloride was purified by redissolving in dry DCM and filtering. Thallium salts were stored in the fridge in the absence of light. 1-Bromo-3-chloropropane was dried by azeotroping off any H₂O with repeated sequential addition of dry THF and evaporation under high vacuum with a CO_{2(s)}/acetone trap.

Column chromatography was performed on silica gel (160–200 mesh), and thin-layer chromatography (TLC) was performed on preparative silica gel GF plates with UV254 (1000 microns, Analtech, USA). Melting points were recorded on a Gallenkamp capillary melting point apparatus and are uncorrected; where novel compounds were low M_W and contained organic azides or 1,2,3-triazole, melting points were not determined for safety reasons. ¹H, ¹³C, ¹⁹F and ³¹P NMR spectra were recorded on a Varian Mercury VX300 or Bruker DPX200 spectrometer at 293 K, or a Varian Unity Plus 500 at 298 K, or a Bruker AVII 500 with cryoprobe. ¹H NMR titrations were performed using the Varian Unity Plus 500 spectrometer. ¹H ROESY NMR spectra were recorded using the maximum possible concentration using the Varian Unity Plus 500 spectrometer. Mass spectra were performed on a Micromass LCT Premier (ESI), Bruker microTOF (ESI), Micromass GCT (EI/FI) spectrometer or a Waters Micromass MALDI micro MX (MALDI-TOF) mass spectrometer.

Where multiple ions corresponding to the desired product were found in the low resolution ESI-MS, these are all listed. Reactions by microwave irradiation were carried out using a Biotage Initiator 2.0 microwave. UV-vis spectra were recorded on a PG Instruments T60U spectrometer. Samples were prepared in a 1 or 3 ml quartz cuvette and concentrations were adjusted to suit the absorption range of the instrument.

6.2 Titration protocols

6.2.1 ^1H NMR spectroscopy

^1H NMR titrations were carried out using a Varian Unity Plus 500 spectrometer at 293 K. Anion binding titrations added a solution of the guest anion as its tetraⁿbutylammonium salt (TBAX) into a solution of the host species. Cation binding titrations added a solution of the guest cation as its hexafluorophosphate salt (MPF_6) into a solution of the host species. For ion-pair titrations, an equimolar solution of the host with one equivalent of the anion or cation salt was prepared. The initial sample volume was 500 μl , with an initial concentration of the host species of 1.5 mM. The initial concentration of the ion solution to be titrated was 0.075 M. Aliquots of the ion solution were added sequentially to achieve NMR spectra recordings of the following molar ratios of titrated ion to host species: 0 eq, 0.1 eq, 0.2 eq, 0.3 eq, 0.4 eq, 0.5 eq, 0.6 eq, 0.7 eq, 0.8 eq, 0.9 eq, 1.0 eq, 1.2 eq, 1.4 eq, 1.6 eq, 1.8 eq, 2.0 eq, 2.5 eq, 3.0 eq, 4.0 eq, 5.0 eq, 7.0 eq and 10.0 eq. For instances of weak binding all of these data points were required for analysis, but where strong binding occurred, the data points at 0.1, 0.3, 0.5, 0.7 and 0.9 equivalents were not carried out. The resulting titration data, including chemical shifts, host and guest concentrations and binding constant estimates were analysed using the WinEQNMR2³⁵¹ computer program. The parameters were refined by non-linear least-squares analysis to achieve the best fit between the observed and calculated chemical shifts and checked for

agreement between the experimental data and modelled binding curve. Iterations were performed using varying estimates to achieve convergence on the most accurate binding constant.

6.2.2 UV/vis spectroscopy

UV/vis titrations were carried out using a PG Instruments T60U spectrometer at 298 K. Cation binding titrations added a solution of the guest cation as its hexafluorophosphate salt (MPF_6) to a 3 ml solution of the host species in a quartz cuvette. For ion-pair titrations, an equimolar solution of the host with one equivalent of the anion salt was prepared. The initial concentration of the host species of 0.1 mM and the initial concentration of the cation solution to be titrated was 0.03 M. Aliquots of the cation solution were added sequentially to achieve NMR spectra recordings of the following molar ratios of titrated ion to host species: 0 eq, 0.1 eq, 0.2 eq, 0.3 eq, 0.4 eq, 0.5 eq, 0.6 eq, 0.7 eq, 0.8 eq, 0.9 eq, 1.0 eq, 1.2 eq, 1.4 eq, 1.6 eq, 1.8 eq, 2.0 eq, 2.5 eq, 3.0 eq, 4.0 eq, 5.0 eq, 7.0 eq and 10.0 eq for a total of 22 data points. The resulting titration data monitored changes in the calix[4]diquinone $n-\pi^*$ absorption band; this was analysed with host and guest concentrations, expected stoichiometry and colour of species using the SpecFit[®] computer program.³⁵⁰ The parameters were refined by refined by global analysis using least squares data fitting by the Levenberg-Marquardt method. The observed and calculated spectra were checked for agreement between the experimental data and modelled binding curves.

6.3 Job plot approximations

Titration data from the ^1H NMR spectra was analysed in approximations of Job plots to determine the binding stoichiometry of the complex.⁴⁴⁶ In these titrations, the concentration of the host decreases gradually throughout the titration, whilst true Job plots require constant concentrations. The product between the molar ratio of the host and the change in

chemical shift from pure host ($\chi_H \times \Delta\delta$) is plotted against the molar ratio of the host (χ_H). The position of the maximum indicates the point at which the change in the gradient of chemical shift change is greatest and can be used to infer the stoichiometry of complexation. A maximum at molar ratio (χ_H) 0.5 indicates a 1:1 host:guest binding stoichiometry.

6.3.1 Chapter 2

The Job plot approximation shown in Figure 6.1 indicates a 1:1 binding stoichiometry upon addition of alkali metal cation salts to macrocyclic receptor **1** as monitored by ^1H NMR spectroscopy.

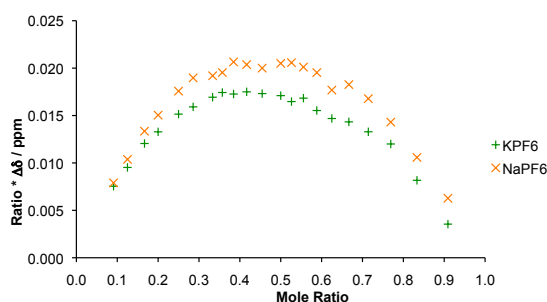


Figure 6.1 Job plot approximations to determine binding stoichiometries upon addition of KPF_6 (+) or NaPF_6 (x) to **1**, monitoring the triazole proton by ^1H NMR spectroscopy (500 MHz, 2% $\text{D}_2\text{O}/\text{CD}_3\text{CN}$, 293 K)

The Job plot approximations shown in Figure 6.2 indicate a 1:1 binding stoichiometry upon addition of halide anion salts to $[\mathbf{1} \cdot \text{MPF}_6]$ complexes as monitored by ^1H NMR spectroscopy.

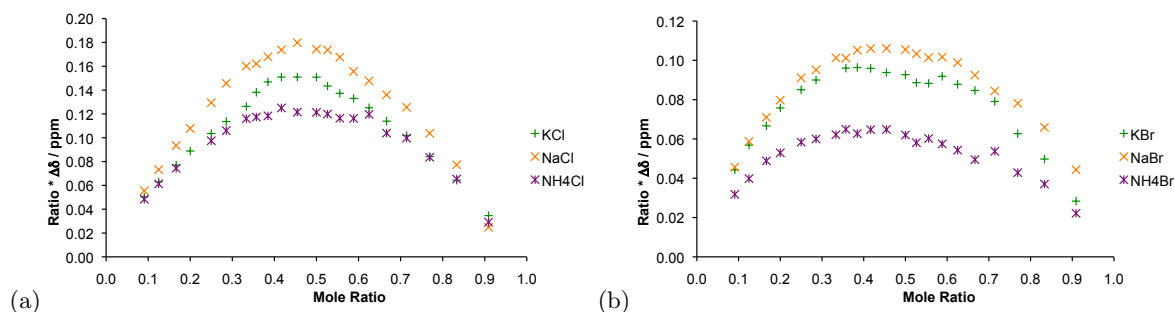


Figure 6.2 Approximations of Job plot experiments indicate 1:1 binding stoichiometry upon addition of (a) chloride and (b) bromide to $[\mathbf{1} \cdot \text{MPF}_6]$ complexes, monitoring the isophthalamide phenyl proton by ^1H NMR spectroscopy (500 MHz, 2% $\text{D}_2\text{O}/\text{CD}_3\text{CN}$, 293 K)

The Job plot approximations in Figure 6.3 display the addition of halide anion salts to compounds **27** and **28**, monitoring the *para*-pyridinium proton by ^1H NMR spectroscopy and indicating a 1:1 binding stoichiometry with **27**.

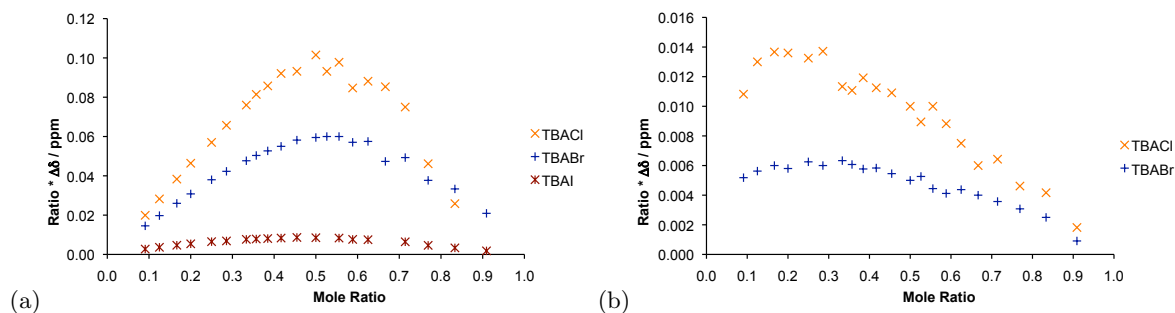


Figure 6.3 Approximations of Job plot experiments upon addition of TBACl ($\times$), TBABr ($+$) or TBAI ($*$) to threads (a) **27** and (b) **28**, monitoring the *para*-pyridyl proton by ^1H NMR spectroscopy (500 MHz, acetone- d_6 , 293 K)

6.3.2 Chapter 3

The Job plot approximation shown in Figure 6.4 indicates a 1:1 binding stoichiometry upon addition of chloride anion salts to macrocyclic receptor **71** as monitored by ^1H NMR spectroscopy. Sigmoidal shapes for oxoanion addition may indicate 2:1 binding stoichiometry.

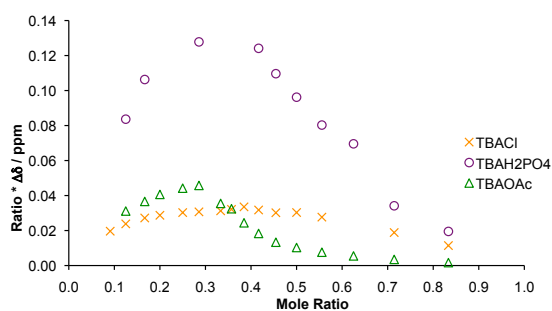


Figure 6.4 Job plot approximations to determine binding stoichiometries upon addition of TBACl ($\times$), TBAH_2PO_4 ($\circ$) or TBAOAc ($\triangle$) to **71**, monitoring the isophthalamide phenyl proton by ^1H NMR spectroscopy (500 MHz, DMSO- d_6 , 293 K)

6.4 Electrochemistry

The electrochemistry of macrocycle **88** was investigated to determine the reversibility of the redox behaviour of its NDI motifs. Electrochemistry was limited to chlorinated solvents due to the poor solubility of **88**. Square wave voltammetry forward and back scans in dichloromethane showed good reversibility.

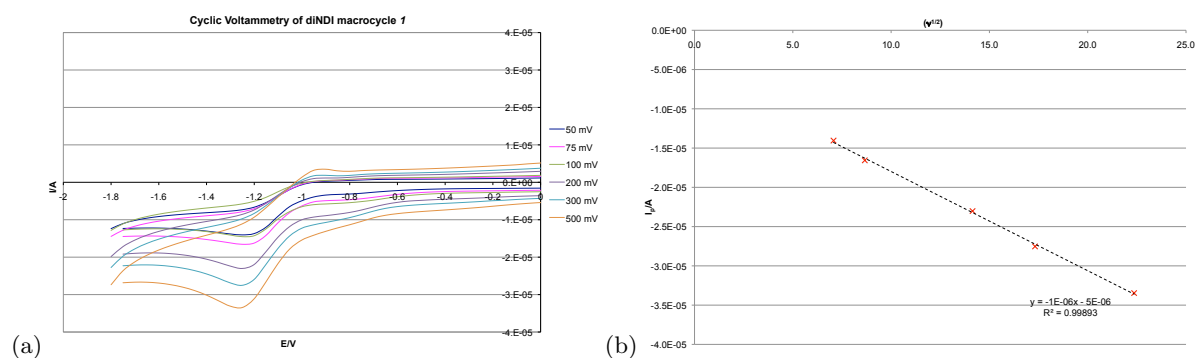


Figure 6.5 Voltammograms of macrocycle **88** in DCM using a 0.1 M TBAPF₆(MeCN) supporting electrolyte with an Ag/AgNO₃ reference electrode at 298 K, with (a) the cyclic scans and (b) plot of Intensity against $\sqrt{\text{scanrate}}$

Cyclic voltammetry ascertained the one-electron reduction potential of macrocycle **88** in DCM at -1.25 V *versus* ferrocene using an Ag/Ag⁺ reference, compared with a value of typically -1.10 V *versus* ferrocene for NDI.⁴⁰⁸ Quasi-reversible behaviour was established by satisfying the criterion of I_p proportional to the $\sqrt{\text{scanrate}}$, $\nu^{1/2}$, with no indication of decomposition over repeat cycles (Figure 6.5b).

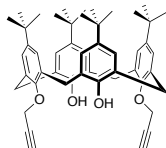
6.5 Synthetic procedures

SAFETY WARNING

Thallium(III) compounds are used as oxidants in the synthetic procedures to form calixdiquinones in the following compounds: $\text{Ti}^{\text{III}}(\text{CF}_3\text{CO}_2)_3$, **1** and **19**. Thallium is a heavy metal that is identified as being potentially fatal by inhalation (H300) or oral uptake (H330) and accumulates with repeated exposure (H373).¹ Longer term adverse effects may be caused in aquatic environments (H411). Handle with care.

6.5.1 Chapter 2

The following procedures are from Chapter 2.



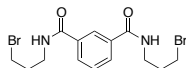
Calix[4]arene 1,3-dialkyne, **2**³⁴⁶

4-*t*-Butylcalix[4]arene (930 mg, 1.44 mmol), K_2CO_3 (475 mg, 2.4 eq) and propargyl bromide [80% in toluene] (581 mg, 3.4 eq) were added to dry acetone (20 ml). The reaction mixture was refluxed under N_2 overnight. The cooled reaction mixture was then filtered and the solvent removed from the filtrate *in vacuo*. The solid residue was triturated with MeOH twice to wash away the impurities, leaving the desired product as a white crystalline solid (800 mg, 1.10 mmol, 77%).

TLC: 1:1 DCM/*cyclo*-hexane, R_f 0.20; ^1H NMR (300 MHz, CDCl_3 , 298 K): δ 7.08 (4H, s, ArH), 6.73 (4H, s, ArH), 6.51 (2H, s, ArOH), 4.76 (4H, d, $^4J = 2.4$ Hz, OCH_2CC), 4.38 (4H, d, $^2J = 13.2$ Hz AB, ArCH_2Ar), 3.34 (4H, d, $^2J = 13.2$ Hz AB, ArCH_2Ar), 2.55 (2H, t, $^4J = 2.4$ Hz, $\text{C}\equiv\text{CH}$), 1.32 (18H, s, *t*Bu), 0.91 (18H, s, *t*Bu); ^{13}C NMR (75 MHz, CDCl_3 , 298 K):

¹Sigma Aldrich® material safety data sheets

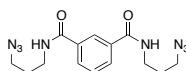
δ 150.3, 149.4, 147.3, 141.6, 132.6, 127.9, 125.5, 125.0, 78.7, 76.3, 63.3, 33.8, 32.1, 31.7, 31.0; ESI-MS: +ve [M+Na] 747.4; -ve [M-H] 723.4; the characterisation data correspond well with those published.^{346,347}



Isophthalamide bis-bromide derivative, **3**³⁴⁸

3-Bromopropylamine hydrobromide (8.0 g, 2 eq) was added to dry DCM (200 ml) and dry Et₃N (15 ml) and the suspension was then cooled in an ice bath, stirring under N₂. Isophthaloyl dichloride (3.7 g, 18 mmol) was added and the mixture stirred at 0°C under N₂ for 20 minutes. The reaction mixture was then allowed to warm to room temperature and was stirred for a further hour. DCM (400 ml) was added to the reaction mixture and this was then washed successively with 10% HCl_(aq) (3 × 150 ml), sat. NaHCO_{3(aq)} (2 × 150 ml) and H₂O (2 × 150 ml). The organic components were dried over MgSO₄, then the solvent removed *in vacuo* to afford the desired product as a white solid (6.4 g, 16 mmol, 86%).

m.p.: 104°C; ¹H NMR (300 MHz, CDCl₃, 298 K): δ 8.19 (1H, t, ⁴*J* = 1.5 Hz, IsoH), 7.92 (2H, dd, ³*J* = 7.5 & ⁴*J* = 1.8 Hz, IsoH), 7.53 (1H, t, ³*J* = 7.5 Hz, IsoH), 6.54 (2H, br, CONH), 3.64 (2H, q, ³*J* = 6.3 Hz, NHCH₂R), 3.49 (2H, t, ³*J* = 6.6 Hz, BrCH₂R), 2.21 (2H, tt, ³*J* = 6.6 Hz & 6.3 Hz, RCH₂R'); ¹³C NMR (75 MHz, CDCl₃, 298 K): δ 166.8, 134.7, 129.9, 129.1, 125.3, 38.8, 32.0, 30.9; ESI-MS: -ve [M-H] 405.0, [M-Cl] 441.0; the characterisation data correspond well with those published.³⁴⁸

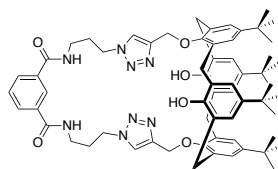


Isophthalamide bis-azide derivative, **4**

Dibromide **3** (2.00 g, 4.92 mmol) was dissolved in dry, degassed DMF (50 ml) and sodium azide (3.20 g, 10 eq) was then added. The reaction mixture was stirred under N₂ at room temperature overnight and then added to H₂O (250 ml). A white precipitate formed and this was extracted from the aqueous layer with DCM (6 × 100 ml). The combined organic

fractions were dried over MgSO_4 and the solvents carefully removed *in vacuo* with no heating to afford the desired product as a white solid (1.47 g, 4.45 mmol, 91%).

m.p.: 75–77°C; ^1H NMR (300 MHz, CDCl_3 , 298 K): δ 8.17 (1H, t, $^4J = 1.8$ Hz, IsoH), 7.90 (2H, dd, $^3J = 7.8$ & $^4J = 1.8$ Hz, IsoH), 7.49 (1H, t, $^3J = 7.8$ Hz, IsoH), 6.74 (2H, br, CONH), 3.54 (2H, dt, $^3J = 6.6$ Hz & 6.0 Hz, NHCH_2R), 3.43 (2H, t, $^3J = 6.3$ Hz, $\text{N}_3\text{CH}_2\text{R}$), 1.90 (2H, q, $^3J = 6.6$ Hz, $\text{RCH}_2\text{R}'$); ^{13}C NMR (75 MHz, CDCl_3 , 298 K): δ 167.2, 134.7, 130.0, 128.8, 125.3, 49.3, 37.7, 28.7; ESI-MS: +ve $[\text{M}+\text{Na}]$ 353.14; –ve $[\text{M}-\text{H}]$ 329.13, $[\text{M}+\text{Cl}]$ 365.11; HR-MS: +ve $[\text{M}+\text{Na}]$ 353.1445, expected $[\text{C}_{14}\text{H}_{18}\text{N}_8\text{NaO}_2]^+$ 353.1445

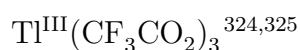


Calix[4]arene triazole macrocycle, **5**

Diazide **4** (100 mg, 0.303 mmol) and dialkyne **2** (220 mg, 0.303 mmol) were dissolved in dry DCM (100 ml). To this was added tetrabutylammonium chloride (84 mg, 1 eq), TBTA (2 mg, 1 mol%), $[\text{Cu}^{\text{I}}(\text{CH}_3\text{CN})_4]\text{PF}_6$ (57 mg, 0.5 eq) and DIPEA (158 μl , 3 eq). The reaction mixture was stirred at room temperature under N_2 for 3 days. The reaction mixture was then washed with 1 M $\text{HCl}_{(\text{aq})}$ (100 ml), sat. $\text{NaHCO}_{3(\text{aq})}$ (100 ml), then H_2O (100 ml). The organic component was dried over MgSO_4 and the solvent removed *in vacuo* to produce a pale yellow solid. This was then purified by column chromatography, removing a fast-running yellow fraction (0–10% EtOH/DCM), to isolate the pure macrocycle as a white glassy solid (247 mg, 0.234 mmol, 77%). In the absence of one equivalent of TBACl this reaction proceeded in 49% yield.

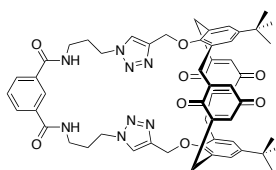
TLC: 4% EtOH/DCM, R_f 0.34; m.p.: *dec.* 200°C; ^1H NMR (300 MHz, CDCl_3 , 298 K): δ 8.03 (2H, d, $^3J = 6.6$ Hz, IsoH), 7.82 (2H, br, $^3J = 5.4$ Hz, CONH), 7.69 (1H, s, IsoH), 7.61 (2H, s, TrzH), 7.48 (1H, t, $^3J = 7.5$ Hz, IsoH), 6.99 (4H, s, ArH), 6.89 (4H, s, ArH), 4.98 (4H, s, OCH_2Trz), 4.74 (4H, t, $^3J = 6.0$ Hz, TrzCH_2R), 4.09 (4H, d, $^2J = 12.9$ Hz AB, calix CH_2 calix), 3.74–3.68 (4H, m, NHCH_2R), 3.25 (4H, d, $^2J = 12.9$ Hz AB, calix CH_2 calix),

2.35 (4H, br, RCH₂R'), 1.93 (2H, s, OH), 1.23 (18H, s, ^tBu), 1.04 (18H, s, ^tBu); ¹³C NMR (75 MHz, CDCl₃, 298 K): δ 166.6, 150.2, 149.3, 147.7, 144.3, 141.9, 133.9, 132.8, 131.4, 129.5, 127.4, 125.8, 125.2, 124.4, 123.2, 69.1, 58.7, 49.2, 37.6, 34.1, 33.8, 32.1, 31.6, 31.0; ESI-MS: +ve [M+H] 1055.5, [M+Na] 1077.5; [M-H] 1053.6, [M+Cl] 1089.5; HR-MS: +ve [M+Na] 1077.5914, expected [C₆₄H₇₈N₈NaO₆]⁺ 1077.5937



See safety warning, Section 6.5.

In the dark, thallium(III) oxide (5.0 g, 11 mmol) was added to trifluoroacetic acid (2 ml). The reaction mixture was stirred at reflux under N₂ in the dark for 4 days. Further trifluoroacetic acid (to make up 25 ml) was added to redissolve the white suspension. The reaction mixture was then carefully filtered through cotton wool and the resulting solution was stored in brown glass in a dark fridge as Tl^{III}(CF₃CO₂)₃ [0.88 M solution in TFA].



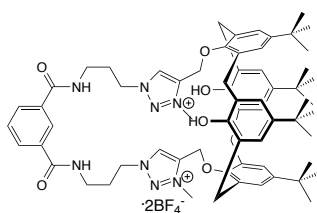
Calix[4]diquinone triazole macrocycle, **1** adapted from 324,325,344,345,349

See safety warning, Section 6.5.

In the dark, macrocycle **5** (500 mg, 0.474 mmol) was added to Tl^{III}(CF₃CO₂)₃ [0.88 M solution in TFA] (6.45 ml, 12 eq). The reaction mixture was stirred under N₂ in the dark at room temperature for 2 days. To the orange reaction mixture was added DCM (15 ml), this was then washed with H₂O (3 × 15 ml), dried over MgSO₄, filtered and the solvent removed *in vacuo* to produce the crude product as a yellow solid (485 mg). This was then purified by recrystallising from DCM/Et₂O and the desired product was collected and dried *in vacuo* to afford a yellow solid (385 mg, 0.397 mmol, 84%).

TLC: 4% MeOH/DCM, R_f 0.46; m.p.: *dec.* 175°C; ¹H NMR (300 MHz, CDCl₃, 298 K): δ 8.44 (1H, s, IsoH), 8.11 (2H, d, ³J = 7.8 Hz, IsoH), 7.95 (2H, s, TrzH), 7.58 (2H, br,

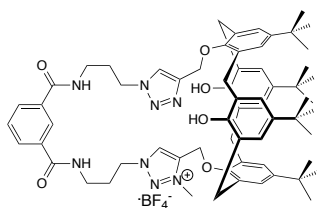
CONH), 7.58 (1H, t, $^3J = 7.8$ Hz, IsoH), 6.94 (4H, s, calixH), 6.39 (4H, s, QuH), 4.86 (4H, s, OCH₂Trz), 4.58 (4H, t, $^3J = 6.0$ Hz, TrzCH₂R), 3.60–3.54 (8H, m, QuCH₂calix & NHCH₂R), 3.36 (4H, d, $^2J = 13.2$ Hz AB, QuCH₂calix), 2.41–2.36 (4H, m, RCH₂R'), 1.17 (18H, s, *t*Bu); ¹³C NMR (75 MHz, CD₃CN, 298 K): δ 188.9, 185.6, 167.1, 154.3, 147.5, 146.7, 144.1, 134.2, 132.5, 130.8, 129.1, 128.9, 127.6, 124.6, 123.9, 66.9, 47.8, 36.9, 34.1, 33.7, 31.4, 29.8; ESI-MS: +ve [M+Na] 993.43; –ve [M+Cl] 1005.43; HR-MS: +ve [M+Na] 993.4269, expected [C₅₆H₅₈N₈NaO₈]⁺ 993.4270



Calix[4]arene bis-triazolium macrocycle, **6**

Macrocycle **5** (50 mg, 0.047 mmol) was dissolved in freshly dried CHCl₃ (50 ml). To this was added trimethyloxonium tetrafluoroborate (42 mg, 6 eq) and the reaction was refluxed under N₂ for 2 days. Further methylating agent (12 eq) was added portionwise over the next 5 days under reflux. Solvents were removed *in vacuo* to afford a light brown oil. Not isolated.

ESI-MS: +ve [M²⁺] 542.32; HR-MS: +ve [M²⁺] 542.3250, expected [C₆₆H₈₄N₈O₆]²⁺ 542.3251

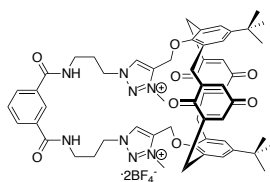


Calix[4]arene monotriazolium macrocycle, **8**

Macrocycle **5** (80 mg, 0.076 mmol) was dissolved in dry DCM (30 ml). To this was added trimethyloxonium tetrafluoroborate (5.5 mg, 0.5 eq) and the reaction was stirred at room temperature under N₂ for 24 hours. More methylating agent (0.5 eq) was added and the reaction stirred at room temperature under N₂ for another 2 days. The reaction mixture was

then added to DCM (50 ml) and washed with H₂O (3 × 50 ml), dried over MgSO₄ and the solvent removed *in vacuo*. The product was purified by column chromatography (0–30% EtOH/DCM) to yield the desired product as a white solid (39 mg, 0.034 mmol, 44%).

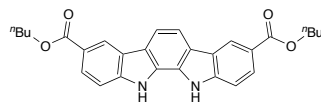
TLC: 6% MeOH/DCM, R_f 0.90; ¹H NMR (500 MHz, CDCl₃, 293 K): δ 8.06 (2H, s, TrzH), 8.02 (2H, d, ³J = 7.8 Hz, IsoH), 7.88 (2H, br, CONH), 7.70 (1H, s, IsoH), 7.48 (1H, t, ³J = 7.5 Hz, IsoH), 7.00 (4H, s, ArH), 6.89 (4H, s, ArH), 4.99 (4H, s, OCH₂R), 4.74 (4H, br, ³J = 6.0 Hz, TrzCH₂R), 4.09 (4H, d, ²J = 12.9 Hz AB, calixCH₂calix), 3.74–3.66 (4H, m, NHCH₂R), 3.25 (4H, d, ²J = 12.9 Hz AB, calixCH₂calix), 2.36 (4H, br, RCH₂R'), 1.25 (18H, s, ^tBu), 1.04 (18H, s, ^tBu); ¹³C NMR (75 MHz, CDCl₃, 298 K): δ 166.8, 150.2, 149.3, 147.7, 144.2, 141.9, 133.9, 132.8, 131.3, 129.4, 127.4, 125.8, 125.2, 124.5, 123.4, 69.0, 49.3, 37.6, 34.1, 33.8, 32.1, 31.6, 31.0, 29.8; ESI-MS: +ve [M⁺] 1069.65



Calix[4]diquinone bis-triazolium macrocycle, **7**

Diquinone macrocycle **1** (50 mg, 0.052 mmol) was dissolved in dry DCM (20 ml). To this was added trimethyloxonium tetrafluoroborate (31 mg, 4 eq) and the reaction was stirred at room temperature under N₂ overnight. The solvent was then removed *in vacuo* and the crude mixture analysed by TLC (10% MeOH/DCM) to find three spots. The product was then purified by column chromatography (10–50% MeOH/DCM) to yield the desired product as a pale yellow solid (30 mg, 0.026 mmol, 50%).

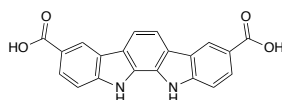
TLC: 20% MeOH/DCM, R_f 0.46; ¹H NMR (300 MHz, acetone-*d*₆, 298 K): δ 9.12 (2H, s, TrzH), 8.39 (1H, s, IsoH), 8.05 (2H, d, ³J = 7.8 Hz, IsoH), 7.92 (2H, t, ³J = 6.6 Hz, CONH), 7.59 (1H, t, ³J = 7.8 Hz, IsoH), 6.98 (4H, s, calixH), 6.90 (4H, s, QuH), 5.39 (4H, s, OCH₂Trz), 4.91 (4H, t, ³J = 6.6 Hz, TrzCH₂R), 4.37 (6H, s, TrzCH₃), 4.17 (4H, d, ²J = 13.2 Hz AB, QuCH₂calix), 3.60 (4H, br, NHCH₂R), 3.36 (4H, d, ²J = 13.2 Hz AB, QuCH₂calix), 2.49–2.45 (4H, m, RCH₂R'), 1.00 (18H, s, ^tBu); ESI-MS: +ve [M²⁺] 500.29



Indolocarbazole diester, **10**^{348,366}

cyclo-Hexane-1,2-dione (560 mg, 5 mmol) and 4-hydrazinylbenzoic acid (1.7 g, 2.2 eq) were suspended in *n*butanol (100 ml). Conc. H₂SO₄ (1 ml) was added dropwise by syringe and the reaction mixture then heated to reflux for 3 days. The reaction mixture was cooled to room temperature for 24 hours, then filtered and washed with MeOH (3 × 5 ml), H₂O (5 × 40 ml) and MeOH again (2 × 20 ml). The precipitate was collected as a yellow solid (1.8 g). The solid was then dissolved in DMF (30 ml) and Pd/C [10% by wt.] (160 mg) was added. The mixture was heated to reflux under N₂ for 24 hours, then filtered whilst hot to remove the Pd/C and washed with hot DMF (3 × 10 ml). The combined filtrate and DMF washings were concentrated *in vacuo* to a volume of 20 ml. To this was added H₂O (100 ml) and the precipitate collected by filtration, washed with H₂O (2 × 20 ml), then MeOH (5 ml) and dried under high vacuum to afford the desired product as a grey solid (1.5 g, 3.4 mmol, 68%).

m.p.: *dec.* >300°C; ¹H NMR (300 MHz, DMSO-*d*₆, 298 K): δ 11.57 (2H, s, NH), 8.84 (2H, s, ArH), 8.11 (2H, s, ArH), 8.03 (2H, d, ³*J* = 8.7 Hz, ArH), 7.80 (2H, d, ³*J* = 8.7 Hz, ArH), 4.32 (2H, t, ³*J* = 6.6 Hz, OCH₂R), 1.75 (2H, qn, ³*J* = 6.9 Hz, OCH₂CH₂R), 1.49 (2H, q, ³*J* = 7.5 Hz, RCH₂Me), 0.97 (3H, t, ³*J* = 7.5 Hz, RCH₃); ¹³C NMR (75 MHz, DMSO-*d*₆, 298 K): δ 166.9, 142.2, 126.5, 126.2, 124.3, 123.7, 122.3, 121.0, 113.1, 111.9, 64.3, 30.8, 19.2, 14.0; ESI-MS: –ve [M–H] 455.2, [2M–H] 911.3; the characterisation data correspond well with those published.³⁴⁸

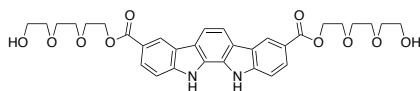


Indolocarbazole diacid, **11**^{348,366}

Di^{*n*}butyl ester **10** (1.50 g, 2.26 mmol) was suspended in *iso*-propanol (21.5 ml). To this was added a solution of KOH (12.3 g, 100 eq) in H₂O (43 ml). This was then heated under reflux

until the substrate had dissolved and the reaction mixture had formed a clear yellow biphasic solution (2 days). The cooled reaction mixture was filtered and 1 M HCl_(aq) was carefully added to the filtrate until neutral. The resulting precipitate was collected by filtration, washed with H₂O (5 × 20 ml), then MeOH (2 × 10 ml) and dried under high vacuum to afford the desired product as a grey solid (1.12g, 3.26 mmol, 99%).

m.p.: *dec.* >300°C; ¹H NMR (300 MHz, DMSO-*d*₆, 298 K): δ 12.62 (2H, s, OH), 11.52 (2H, s, NH), 8.83 (2H, s, ArH), 8.09 (2H, s, ArH), 8.03 (2H, d, ³*J* = 8.7 Hz, ArH), 7.78 (2H, d, ³*J* = 8.7 Hz, ArH); ¹³C NMR (75 MHz, DMSO-*d*₆, 298 K): δ 168.1, 141.7, 126.2, 123.9, 123.3, 122.2, 121.5, 120.8, 112.7, 111.4; ESI-MS: –ve [M–H] 343.1, [2M–H] 687.1; the characterisation data correspond well with those published.³⁴⁸

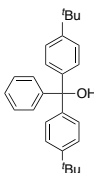


Indolocarbazole polyether, **9**³⁴⁸

Diacid **11** (300 mg, 0.872 mmol) was dissolved in dry, degassed DMF (15 ml) in a 20 ml microwave vial. To this was added Cs₂CO₃ (567 mg, 2 eq) and the reaction mixture was purged with N₂ for 20 minutes. 2-(2-(2-chloroethoxy)ethoxy)ethanol (630 µl, 5 eq) was then added *via* syringe and the reaction heated in a microwave at 140°C for 3 hours. This reaction was repeated twice and the mixtures combined. The solvent was then removed *in vacuo* to produce a yellow/brown oil (446 mg). This was then purified by flash column chromatography (0–20% MeOH/EtOAc) and the solvent then removed *in vacuo* to produce a white solid. This was further purified by dissolving in 1:1 CHCl₃/hexane and precipitation induced by leaving at –32°C for 2 weeks. The residue was filtered off and washed with cold 1:1 CHCl₃/hexane and the desired product collected as a white solid (375 mg, 0.617 mmol, 71%).

TLC: 5% MeOH/DCM, R_f 0.14; m.p.: 158°C; ¹H NMR (300 MHz, CD₃CN, 298 K): δ 10.09 (2H, s, NH), 8.88 (2H, d, ⁴*J* = 1.8 Hz, ArH), 8.11 (2H, dd, ³*J* = 8.7 Hz & ⁴*J* = 1.8 Hz, ArH), 8.09 (2H, s, ArH), 7.72 (2H, d, ³*J* = 8.7 Hz, ArH), 5.45 (2H, s, ROH), 4.51–4.48 (2H, m, RCO₂CH₂R'), 3.89–3.85 (2H, m, polyglycol), 3.72–3.49 (8H, m, polyglycol); ¹³C NMR

(75 MHz, CD₃CN, 298 K): 168.0, 143.7, 127.3, 124.5, 123.5, 123.1, 122.3, 113.8, 112.4, 110.1, 73.4, 71.4, 71.1, 70.0, 64.9, 62.0; ESI-MS: +ve [M+Na] 631.26, [2M+Na] 1239.54; –ve [M–H] 607.20, [2M–H] 1212.51; the characterisation data correspond well with those published.³⁴⁸



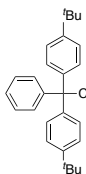
Trisaryl alcohol, **12**³⁶⁸

Magnesium turnings (2.00 g, 2 eq) were heated in a three-necked round-bottomed flask at 100°C under N₂ overnight, then allowed to cool. Dry THF (12 ml) was added to cover the magnesium and iodine (5 mg, *cat.*) was also added. A solution of 1-bromo-4-*t*-butylbenzene (14.03 g, 2 eq) in dry THF (30 ml) was prepared, 5 ml was added to the reaction mixture and decolourisation was observed. The reaction mixture was heated to reflux under N₂, the remaining 1-bromo-4-*t*-butylbenzene solution was added over 20 minutes and effervescence was observed. The reaction mixture was then allowed to cool to room temperature and was stirred under N₂ for a further 2 hours.

Ethyl benzoate (4.94 g, 32.9 mmol) was dissolved in dry THF (4 ml) and then added over 20 minutes to the fresh solution of Grignard reagent and a red/brown colour was observed. The reaction mixture was stirred at room temperature under N₂ overnight. The reaction mixture was then carefully neutralised with 10% HCl_(aq) until no further effervescence was observed and a clear biphasic system had formed. To this was added H₂O (80 ml) and this was then extracted with DCM (2 × 100 ml). The combined organic fractions were washed with H₂O (3 × 200 ml), dried over MgSO₄ and the solvent removed *in vacuo* to give a fluorescent yellow oil. The desired product was recrystallised from hot MeOH to afford the desired product as solid white crystals (10.7 g, 28.6 mmol, 87%).

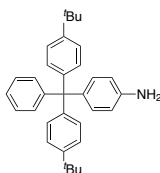
¹H NMR (300 MHz, CDCl₃, 298 K): δ 7.49–7.47 (4H, m, ArH), 7.36–7.24 (9H, m, ArH), 1.31 (18H, *t*Bu); ¹³C NMR (75 MHz, CDCl₃, 298 K): δ 149.7, 144.2, 141.0, 128.8, 128.7, 127.2, 126.7, 124.8, 87.0, 34.6, 31.6; ESI-MS: +ve [M+Na] 395.25, [2M+Na] 767.46; –ve [M–H]

371.24, [2M–H] 743.50; the characterisation data correspond well with those published.³⁶⁸



Trisaryl chloride, **13**³⁶⁸

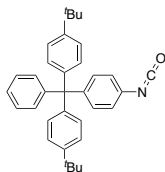
Alcohol **12** (8.33 g, 22.3 mmol) was added to acetyl chloride (30 ml), immediately giving an orange colour. The reaction mixture was stirred at reflux under N₂ overnight. The excess solvent was then removed *in vacuo* to afford a white/yellow solid product which was immediately reacted on with no analysis (assumed quantitative yield).



Aniline stopper, **14**³⁶⁸

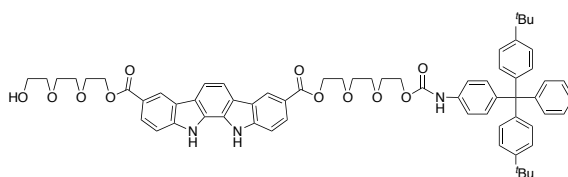
Chloride **13** (8.15 g, 20.9 mmol) was added to aniline (30 ml). The reaction mixture was stirred under N₂ at 105°C for 2 days, with a colour change from orange to purple observed. The mixture was allowed to cool and then added to 10% HCl_(aq) (300 ml) and stirred for 20 minutes. The resulting purple precipitate was collected by filtration and the solid then washed with sat. K₂CO_{3(aq)} (50 ml) and H₂O (2 × 50 ml). The solid was dissolved in DCM (200 ml), dried over MgSO₄ and filtered through silica to produce an orange solution. The solvent was removed from the filtrate *in vacuo* to produce an orange semi-solid. The solid was dissolved in hot toluene and cooled to afford the recrystallised product as an off-white solid (8.05 g, 18.0 mmol, 86%).

¹H NMR (300 MHz, CDCl₃, 298 K): δ 7.32–7.23 (9H, m, ArH), 7.15 (4H, d, ³*J* = 14.4 Hz, ArH), 7.03 (2H, d, ³*J* = 14.4 Hz, ArH), 6.65 (2H, d, ³*J* = 14.4 Hz, ArH), 1.35 (18H, s, ^{*t*}Bu); ESI-MS: +ve [M+H] 448.31, [2M+H] 895.62; the characterisation data correspond well with those published.³⁶⁸



Aniline isocyanate stopper, **15**³⁴⁸

Aniline **14** (500 mg, 1.12 mmol), dry Et₃N (170 μ l, 1.1 eq) and triphosgene (166 mg, 0.5 eq [effectively 1.5 eq]) were added to dry toluene (160 ml). The reaction mixture was stirred at 70°C under N₂ overnight. The cooled reaction mixture was filtered to remove Et₃N · HCl and the solvent then removed from the filtrate *in vacuo*. The residue was dried under high vacuum to afford the desired product as an off-white foamy solid (478 mg, 1.01 mmol, 90%). This was then immediately reacted on with no analysis (assumed quantitative yield).

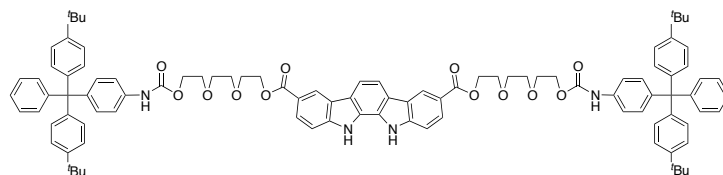


Monostoppered indolocarbazole polyether, **16**

A sample of this compound was kindly donated by Dr Asha Brown, with further quantities synthesised according to the literature procedure.³⁴⁸

Indolocarbazole thread **9** (200 mg, 0.328 mmol) was dissolved in dry CH₃CN (90 ml) by vigorous heating under N₂. Isocyanate stopper **15** (157 mg, 1 eq) was dissolved in dry CH₃CN (30 ml) and half of this was then added to the cooled thread solution. Diⁿbutyltin dilaurate (5 drops, *cat.*) was added to the solution and the reaction mixture stirred at room temperature under N₂ for 3 days. The other half of the isocyanate stopper solution was then added and the reaction mixture stirred for a further 2 days. The solvent was then removed *in vacuo*. The crude product was purified by flash column chromatography (0–5% MeOH/CHCl₃) and the solvent removed *in vacuo* to afford the desired product as a white solid (160 mg, 0.147 mmol, 45%).

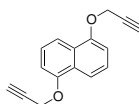
TLC: 5% MeOH/DCM, R_f 0.24; ^1H NMR (300 MHz, $\text{DMSO-}d_6$, 298 K): δ 10.09 (2H, s, NH), 8.89 (2H, d, $^4J = 1.5$ Hz, ArH), 8.13 (2H, d, $^4J = 1.8$ Hz, ArH), 8.11–8.06 (6H, m, ArH), 7.74 (2H, d, $^3J = 9.0$ Hz, ArH), 7.61 (H, s, ArH), 5.47 (2H, s, OH), 4.53–4.49 (2H, m, $\text{RCO}_2\text{CH}_2\text{R}$), 3.89–3.85 (2H, m, polyglycol), 3.74–3.52 (H, m, polyglycol); ^{13}C NMR (75 MHz, $\text{DMSO-}d_6$, 298 K): δ 176.0, 160.2, 157.4, 151.0, 147.9, 143.8, 142.0, 134.4, 130.7, 130.4, 130.0, 127.7, 126.3, 124.5, 123.4, 120.9, 112.8, 111.7, 109.6, 104.7, 72.6, 72.4, 70.0, 69.8, 69.8, 68.7, 63.2, 60.3, 34.1, 31.1; ESI-MS: not observed; the characterisation data correspond well with those published.³⁴⁸



Distoppered indolocarbazole polyether, **17**³⁴⁸

This di-reacted product was also identified from the same experiment used to synthesise **16**.

^1H NMR (300 MHz, CDCl_3 , 298 K): δ 9.68 (2H, s, NH), 8.58 (2H, s, ArH), 7.85 (2H, d, $^3J = 7.5$ Hz, ArH), 7.77 (2H, s, ArH), 7.05–7.22 (34H, m, ArH), 6.78 (2H, s, ArH), 4.49 (4H, s, $\text{RCO}_2\text{CH}_2\text{R}$), 4.22 (4H, s, polyglycol), 3.97–3.72 (16H, m, polyglycol), 1.27 (36H, s, ^tBu); ESI-MS: +ve $[\text{M}+\text{Na}]$ 1578.75; –ve $[\text{M}+\text{Cl}]$ 1590.75; the characterisation data correspond well with those published.³⁴⁸

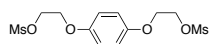


Dihydroxy naphthalene propargyl ether, **18**³⁶⁹

1,5-Dihydroxynaphthalene (1.00 g, 6.25 mmol), propargyl benzenesulfonate (2.44 ml, 2.5 eq) and K_2CO_3 (2.16 g, 2.5 eq) were added to acetone (100 ml). The reaction mixture was then stirred at reflux under N_2 overnight, with a colour change from purple, through green and yellow, to orange. The solid was filtered off and washed with further acetone (20 ml) and the

solvents were removed *in vacuo*. The product was purified by column chromatography (0–10% EtOAc/60–80°C petrol) to yield the pure product as a grey-brown solid (449 mg, 1.89 mmol, 30%).

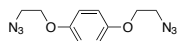
TLC: 10% EtOAc/60–80°C petrol, R_f 0.56; ^1H NMR (300 MHz, acetone- d_6 , 298 K): δ 7.84 (2H, d, $^3J = 8.7$ Hz, ArH), 7.43 (2H, t, $^3J = 8.1$ Hz, ArH), 7.11 (2H, d, $^3J = 7.5$ Hz, ArH), 5.00 (2H, d, $^4J = 2.4$ Hz, OCH_2R), 3.13 (1H, t, $^4J = 2.4$ Hz, $\text{C}\equiv\text{CH}$); ^{13}C NMR (75 MHz, acetone- d_6 , 298 K): δ 154.1, 127.7, 126.2, 115.6, 107.4, 79.7, 72.3, 56.9; ESI-MS: +ve $[\text{M}+\text{H}]$ 237.10; the characterisation data correspond well with those published.³⁶⁹



Hydroquinone dimesylate, **20**^{376,377}

A solution of hydroquinone bis(2-hydroxyethyl) ether (10.0 g, 50.5 mmol) was dissolved in dry DCM (200 ml) and dry Et_3N (21 ml, 5 eq) at 0°C. To this was added dropwise methanesulfonyl chloride (12 ml, 3 eq) and the reaction mixture was then stirred at 0°C under N_2 for 1 hour, then allowed to warm to room temperature over 3 hours. The reaction mixture was washed with 10% $\text{HCl}_{(\text{aq})}$ (3×50 ml), sat. $\text{NaHCO}_{3(\text{aq})}$ (3×50 ml) and brine (50 ml), dried over MgSO_4 and the solvent removed *in vacuo*. The desired product was afforded as a pale orange solid (17.3 g, 48.8 mmol, 97%), which was stored in the freezer.

^1H NMR (300 MHz, CDCl_3 , 298 K): δ 6.86 (4H, s, ArH), 4.56 (4H, t, $^3J = 4.5$ Hz, RCH_2OMs), 4.21 (4H, t, $^3J = 4.5$ Hz, OCH_2R), 3.10 (6H, s, SO_2CH_3); ^{13}C NMR (75 MHz, CDCl_3 , 298 K): δ 152.7, 115.8, 68.1, 66.5, 37.8; ESI-MS: +ve $[\text{M}+\text{Na}]$ 377.01; –ve $[\text{M}+\text{Cl}]$ 389.02; the characterisation data correspond well with those published.^{376,377}

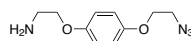


Hydroquinone diazide, **21**^{376,377}

To a solution of sodium azide (1.50 g, 3 eq) in DMSO (20 ml) was added dimesylate **20** (2.72 g, 7.7 mmol). The reaction mixture was then stirred at room temperature under N_2 for 5 days. This was quenched by addition of H_2O (30 ml) and then extracted with Et_2O ($3 \times$

75 ml). The combined organics were washed with H₂O (50 ml), dried over MgSO₄ and the solvent carefully removed *in vacuo* to afford the desired product as a yellow oil, when left to stand this crystallised into a colourless solid (1.55 g, 6.25 mmol, 81%).

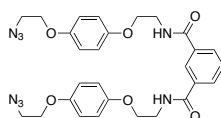
¹H NMR (300 MHz, CDCl₃, 298 K): δ 6.88 (4H, s, ArH), 4.12 (4H, t, ³*J* = 5.1 Hz, OCH₂R), 3.58 (4H, t, ³*J* = 5.1 Hz, RCH₂N₃); ¹³C NMR (75 MHz, CDCl₃, 298 K): δ 152.8, 115.7, 67.6, 50.2; ESI-MS: –ve [M+Cl] 283.27; the characterisation data correspond well with those published.^{376,377}



Hydroquinone azide-amine, **22**^{376,377}

A solution of diazide **21** (1.00 g, 4 mmol) in 1:1:2 EtOAc/Et₂O/5% HCl_(aq) (40 ml) was stirred at 0°C under N₂. To this was added dropwise over 1 hour a solution of triphenylphosphine (1.06 g, 4 mmol) in the same solvent system (20 ml). The reaction mixture was allowed to warm to room temperature and was stirred under N₂ for 3 days. To this was added further 5% HCl_(aq) (15 ml), the whole was shaken and the organics discarded. The aqueous fraction was carefully basified with 10% NaOH_(aq), then extracted with DCM (3 × 30 ml). The combined organics were dried over MgSO₄ and solvent removed *in vacuo* to afford the desired product as a colourless oil (570 mg, 2.57 mmol, 81%).

¹H NMR (300 MHz, CDCl₃, 298 K): δ 6.87 (4H, s, ArH), 4.12 (2H, t, ³*J* = 5.1 Hz, OCH₂R), 3.96 (2H, t, ³*J* = 5.1 Hz, OCH₂R), 3.58 (2H, t, ³*J* = 5.1 Hz, RCH₂N₃), 3.08 (2H, t, ³*J* = 5.1 Hz, RCH₂NH₂); ¹³C NMR (75 MHz, CDCl₃, 298 K): δ 153.6, 152.4, 115.6, 115.4, 70.8, 67.6, 50.2, 41.6; ESI-MS: +ve [M+H] 223.10; the characterisation data correspond well with those published.^{376,377}

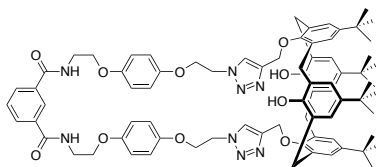


Expanded isophthalamide bis-azide derivative, **23**

Amine **22** (550 mg, 2.2 eq) was dissolved in dry DCM (150 ml) and dry Et₃N (15 ml)

at 0°C. Isophthaloyl dichloride (229 mg, 1.13 mmol) was carefully added portionwise and the reaction mixture stirred at 0°C under N₂ for 2 hours, then allowed to warm to room temperature overnight. DCM (100 ml) was added and the whole was then washed with 10% HCl_(aq) (3 × 100 ml), sat. NaHCO_{3(aq)} (2 × 100 ml) and H₂O (2 × 100 ml), dried over MgSO₄ and the solvent removed *in vacuo*. The crude residue was purified by column chromatography (0–3% EtOH/CHCl₃), isolating the desired product as a white solid (461 mg, 0.803 mmol, 71%).

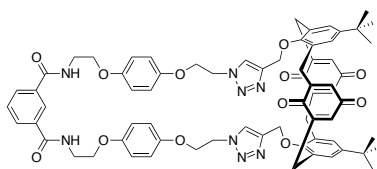
TLC: 3% MeOH/DCM, R_f 0.55; m.p.: 131–133°C; ¹H NMR (300 MHz, CDCl₃, 298 K): δ 8.23 (1H, t, ⁴J = 1.8 Hz, ArH), 7.96 (2H, dd, ³J = 7.5 Hz, ⁴J = 1.8 Hz, ArH), 7.55 (1H, d, ³J = 7.5 Hz, ArH), 6.88 (8H, s, ArH), 6.70 (2H, br, CONH), 4.15–4.11 (8H, m, OCH₂R), 3.89 (4H, q, ³J = 5.1 Hz, CONHCH₂), 3.59 (4H, t, ³J = 5.1 Hz, RCH₂N₃); ¹³C NMR (75 MHz, CDCl₃, 298 K): δ 166.7, 153.0, 152.7, 134.7, 130.0, 129.0, 115.7, 115.5, 67.6, 67.2, 50.19, 39.7; ESI-MS: +ve [M+Na] 597.21; –ve [M–H] 573.21, [M+Cl] 609.17; HR-MS: +ve [M+Na] 597.2167, expected [C₂₈H₃₀N₈NaO₆]⁺ 597.2181



Expanded calix[4]arene triazole macrocycle, **24**

Diazide **23** (30 mg, 0.052 mmol) and dialkyne **2** (38 mg, 0.052 mmol) were dissolved in dry DCM (50 ml). To this was added [Cu^I(CH₃CN)₄]PF₆ (6 mg, 0.1 eq), TBTA (3 mg, 0.1 eq) and then DIPEA (27 µl, 3 eq). The reaction mixture was stirred at room temperature under N₂ for 9 days. This was then washed with 1 M HCl_(aq) (30 ml), sat. NaHCO_{3(aq)} (30 ml), H₂O and brine (30 ml) and the organics dried over MgSO₄. The solvent was removed *in vacuo* and the crude residue was purified by preparative thin layer chromatography (5% MeOH/DCM). This afforded a yellow solid containing traces of TBTA and the desired macrocycle (31 mg, 0.024 mmol, 46%).

TLC: 5% MeOH/DCM, R_f 0.26; ^1H NMR (300 MHz, CDCl_3 , 298 K): δ 8.03–8.01 (3H, m, IsoH), 7.95 (2H, s, TrzH), 7.55 (1H, t, $^3J = 6.3$ Hz, IsoH), 7.05 (4H, s, ArH), 6.90 (4H, s, ArH), 6.73 (8H, s, HqH), 5.21 (4H, s, OCH_2Trz), 4.77 (4H, t, $^3J = 5.1$ Hz, TrzCH_2R), 4.29 (4H, t, $^3J = 5.1$ Hz, OCH_2R), 4.13 (4H, d, $^3J = 12.9$ Hz, calix CH_2 calix), 4.07 (4H, t, $^3J = 5.1$ Hz, OCH_2R), 3.89–3.84 (4H, m, NHCH_2R), 3.16 (4H, d, $^3J = 12.9$ Hz, calix CH_2 calix), 1.19 (18H, s, $t\text{Bu}$), 0.94 (18H, s, $t\text{Bu}$); ^{13}C NMR (75 MHz, CDCl_3 , 298 K): δ 166.9, 162.2, 153.4, 152.6, 150.6, 149.7, 147.3, 144.2, 141.7, 134.6, 132.7, 127.9, 125.9, 125.8, 125.2, 124.7, 116.0, 115.7, 67.5, 67.4, 50.0, 39.9, 34.1, 33.9, 31.9, 31.8, 31.2, 29.9; ESI-MS: +ve $[\text{M}+\text{H}]$ 1299.72, $[\text{M}+\text{Na}]$ 1321.70; -ve $[\text{M}-\text{H}]$ 1297.63, $[\text{M}+\text{Cl}]$ 1333.64; HR-MS: +ve $[\text{M}+\text{Na}]$ 1321.6699, expected $[\text{C}_{78}\text{H}_{90}\text{N}_8\text{NaO}_{10}]^+$ 1321.6672



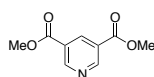
Expanded calix[4]diquinone triazole macrocycle, **19**

See safety warning, Section 6.5.

In the dark, thallium(III) trifluoroacetate, $\text{Tl}^{\text{III}}(\text{CF}_3\text{COO})_3$, (84 mg, 10 eq) was dissolved in dry DCM (600 μl) and stirred at -1°C . To this was added trifluoroacetic acid (170 μl), followed by dropwise addition of a solution of macrocycle **24** (20 mg, 0.015 mmol) in dry DCM (600 μl). The reaction mixture was stirred at -1°C under N_2 in the dark for 60 minutes (carefully monitoring by ESI-MS), before quenching with H_2O (2 ml). The reaction mixture was partitioned between 1:1 DCM/ H_2O (50 ml), which was then separated. The organics were then washed with H_2O (2×20 ml), dried over MgSO_4 and the solvent removed *in vacuo*. The crude residue was then purified by preparative thin layer chromatography (10% MeOH/DCM). The desired product was isolated as a yellow solid (12 mg, 0.010 mmol, 66%).

TLC: 10% MeOH/DCM, R_f 0.60; ^1H NMR (300 MHz, CDCl_3 , 298 K): δ 8.07 (1H, s, IsoH), 8.05 (2H, d, $^3J = 7.5$ Hz, IsoH), 7.72 (2H, s, TrzH), 7.55 (1H, t, $^3J = 7.5$ Hz, IsoH), 6.92 (2H, br, CONH), 6.82 (4H, s, calixH), 6.78 (4H, s, HqH), 6.24 (4H, s, QuH) 4.93

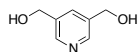
(4H, br, OCH₂Trz), 4.80 (4H, br, TrzCH₂R), 4.36 (4H, br, OCH₂R), 4.11 (4H, t, ³*J* = 5.4 Hz, OCH₂R), 3.89–3.84 (4H, m, NHCH₂R), 3.65–3.58 (4H, m, calixCH₂Qu), 3.12 (4H, d, ³*J* = 12.6 Hz, calixCH₂Qu), 1.26 (9H, s, ^{*t*}Bu), 1.13 (9H, s, ^{*t*}Bu); ¹³C NMR (75 MHz, CDCl₃, 298 K): δ 190.5, 188.8, 187.9, 167.1, 153.5, 153.3, 152.7, 152.6, 147.7, 134.7, 132.5, 131.2, 129.6, 129.4, 127.3, 127.2, 124.4, 115.8, 115.7, 67.5, 67.2, 50.1, 39.9, 34.3, 32.1, 31.5, 29.9; ESI-MS: +ve [M+Na] 1237.54, [M+K] 1253.51; –ve [M–H] 1213.44, [M+Cl] 1249.48; HR-MS: +ve [M+Na] 1237.5052, expected [C₇₀H₇₀N₈NaO₁₂]⁺ 1237.5005



Pyridine diester, **29**³⁷⁹

3,5-Pyridinedicarboxylic acid (2.5 g, 15 mmol) was suspended in MeOH (9 ml) in a 20 ml microwave vial. To this was carefully added conc. H₂SO₄ (8.5 ml) and the resulting reaction solution was heated in a microwave at 120°C for 20 minutes. The reaction mixture was then added to ice and basified with 25% NH₄OH_(aq) (20 ml). The resulting suspension was extracted with Et₂O (3 × 150 ml). The combined organics were dried over MgSO₄ and the solvent removed *in vacuo* to afford the desired product as a white solid (2.3 g, 12 mmol, 80%).

TLC: 5% MeOH/DCM, R_f 0.80; ¹H NMR (300 MHz, CD₃OD, 298 K): δ 9.29 (2H, d, ⁴*J* = 2.1 Hz, PyrH), 8.83 (1H, t, ⁴*J* = 2.1 Hz, PyrH), 3.99 (6H, s, COOCH₃); ESI-MS: +ve [M+H] 196.07; the characterisation data correspond well with those published.³⁷⁹

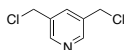


Pyridine dialcohol, **30** adapted from 379

A slurry of lithium aluminium hydride (940 mg, 3.2 eq) in dry Et₂O (100 ml) was stirred vigorously over ice and under N₂. To this was carefully added diester **29** (1.5 g, 7.7 mmol) and the reaction mixture was allowed to warm to room temperature overnight. H₂O (1 ml) was added to quench the reaction and the mixture was stirred for a further hour. The solids were

filtered, washed with Et₂O (100 ml) and the washings retained. The residue was sonicated and triturated with hot MeOH (50 ml) and filtered whilst hot. The two sets of filtrates were combined and the solvents removed *in vacuo* to afford the desired product as a pungent yellow solid (590 mg, 4.2 mmol, 55%). The product is known to decompose under ambient conditions by absorbing CO₂, so was reacted on as soon as possible.

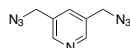
¹H NMR (300 MHz, CD₃OD, 298 K): δ 8.39 (2H, br, PyrH), 7.79 (1H, br, PyrH), 4.64 (4H, s, PyrCH₂OH); ¹³C NMR (75 MHz, CD₃OD, 298 K): δ 147.6, 139.3, 135.7, 62.7; the characterisation data correspond well with those published.³⁷⁹



Pyridine dichloride, **31** adapted from 379

Dialcohol **30** (152 mg, 1.09 mmol) was suspended in thionyl chloride (20 ml), then the reaction mixture was refluxed under N₂ overnight. The solvent was removed *in vacuo* using a CO_{2(s)}/acetone trap at -78°C. The residue was sonicated with CH₃CN, then filtered. Solvent was removed from the filtrate *in vacuo*, then the residue was partitioned between 1:1 DCM/sat. Na₂CO_{3(aq)} (100 ml) and extracted further with DCM (2 × 50 ml). The combined organics were dried over MgSO₄ and the solvent removed *in vacuo* to afford the desired product as a yellow oil (48 mg, 0.27 mmol, 25%). This was reacted on immediately.

¹H NMR (300 MHz, DMSO-*d*₆, 298 K): δ 8.61 (2H, d, ⁴*J* = 1.8 Hz, PyrH), 7.95 (1H, t, ⁴*J* = 1.8 Hz, PyrH), 4.85 (4H, s, PyrCH₂Cl); ¹³C NMR (75 MHz, DMSO-*d*₆, 298 K): δ 149.5, 136.8, 133.7, 42.9; ESI-MS: not observed; the characterisation data correspond well with those published.³⁷⁹

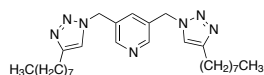


Pyridine diazide, **32**

Dichloride **31** (1.6 g, 9.1 mmol) was dissolved in DMSO (80 ml). To this was added sodium azide (1.8 g, 3 eq) and the reaction mixture was stirred at room temperature under N₂ for

3 days. H₂O (200 ml) was added to quench the reaction, which was then extracted with Et₂O (4 × 200 ml). The combined organics were washed with H₂O (300 ml) and brine (300 ml), dried over MgSO₄ and the solvent removed *in vacuo*. The desired product was afforded as a pungent orange oil (430 mg, 2.3 mmol, 25%).

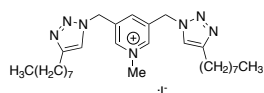
¹H NMR (300 MHz, CDCl₃, 298 K): δ 8.57 (2H, s, PyrH), 7.66 (1H, s, PyrH), 4.45 (4H, s, PyrCH₂N₃); ¹³C NMR (75 MHz, CDCl₃, 298 K): δ 149.1, 135.2, 131.4, 51.9; ESI-MS: +ve [M+H] 190.08; HR-MS: not observed.



Pyridine ditriazole octyl chain, **33**

Diazide **32** (33 mg, 0.17 mmol), dec-1-yne (63 mg, 2 eq), TBTA (47 mg, 0.5 eq) and [Cu^I(CH₃CN)₄]PF₆ (33 mg, 0.5 eq) were dissolved in dry DCM (30 ml). To this was added DIPEA (183 μl, 6 eq) and the reaction mixture was stirred at room temperature under N₂ for 5 days. DCM (40 ml) was added and the reaction mixture was then washed with 1 M HCl_(aq) (40 ml), sat. Na₂CO_{3(aq)} (40 ml), H₂O (40 ml) and brine (40 ml), dried over MgSO₄ and the solvent removed *in vacuo*. The residue was purified by column chromatography (0–5% EtOH/DCM) isolating the desired product as a white solid (68 mg, 0.15 mmol, 84%).

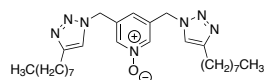
TLC: 5% MeOH/DCM, R_f 0.25; ¹H NMR (300 MHz, CDCl₃, 298 K): δ 8.54 (2H, d, ⁴J = 1.8 Hz, PyrH), 7.71 (2H, s, TrzH), 7.50 (1H, t, ⁴J = 1.8 Hz, PyrH), 5.51 (4H, s, PyrCH₂Trz), 2.70 (4H, t, ³J = 7.2 Hz, TrzCH₂R), 1.67–1.60 (4H, m, RCH₂R'), 1.37–1.27 (20H, m, RCH₂R'), 0.90–0.85 (6H, m, RCH₃); ¹³C NMR (75 MHz, CDCl₃, 298 K): δ 149.7, 129.3, 129.0, 128.3, 120.8, 51.2, 32.0, 29.6, 29.5, 29.4, 25.9, 22.8, 14.3; ESI-MS: +ve [M+H] 466.36, [M+Na] 488.33; [M–H] 464.34, [M+Cl] 500.31; HR-MS: +ve [M+Na] 488.3476, expected [C₂₇H₄₃N₇Na]⁺ 488.3472



Methyl pyridinium ditriazole octyl chain, **25**

Dioctyl compound **33** (150 mg, 0.323 mmol) was dissolved in dry DCM (7 ml) in a 10 ml vial. To this was added methyl iodide (402 μ l, 20 eq) and the vial was carefully stoppered and sealed with parafilm. The reaction mixture was stirred at room temperature under N₂ for 8 days, then the solvents removed *in vacuo*. The residue was triturated with DCM, leaving a slightly impure residue. This was purified by silica plug, to remove the iodine and fast-running yellow impurity (0–25% MeOH/DCM), isolating the iodide salt as a yellow solid (58 mg, 0.096 mmol, 30%). Attempted ion exchange to the PF₆[−] salt either by washing with NH₄PF_{6(aq)} or using ion-exchange resin resulted in an intractable mixture.

TLC: Iodide salt, 25% MeOH/DCM, R_f 0.41; ESI-MS: +ve [M] 480.37; HR-MS: +ve [M] 480.3804, expected [C₂₈H₄₆N₇]⁺ 480.3809

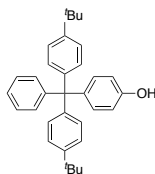


Pyridine *N*-oxide ditriazole octyl chain, **26** ^{adapted from 377}

Dioctyl compound **33** (50 mg, 0.11 mmol) and NaHCO₃ (277 mg, 30 eq) were dissolved in 1:1 H₂O/butanone (20 ml). A saturated solution of Oxone[®] (202 mg, 3 eq) in H₂O (1.5 ml) was added dropwise and the reaction mixture was stirred at room temperature under N₂ overnight. Sodium chloride (1 g) was added and the mixture extracted with CHCl₃ (3 × 20 ml), dried over MgSO₄ and the solvent removed *in vacuo*. The residue was purified by column chromatography (0–7.5% MeOH/DCM), isolating a white solid contaminated by starting material. The estimated yield by ¹H NMR spectroscopy was 72%.

TLC: 5% MeOH/DCM, R_f 0.16; ¹H NMR (300 MHz, CDCl₃, 298 K): δ 8.04 (2H, s, PyrH), 7.37 (1H, br, PyrH), 7.29 (2H, br, TrzH), 5.44 (4H, s, PyrCH₂Trz), 2.72 (4H, t, ³J = 7.8 Hz, TrzCH₂R), 1.67 (4H, t, ³J = 7.5 Hz, alkyl), 1.40–1.25 (20H, m, alkyl), 0.88 (6H, t, ³J = 6.6 Hz, RCH₃); ESI-MS: +ve [M+Na] 504.34; −ve [M−H] 480.34, [M+Cl] 516.31; HR-MS:

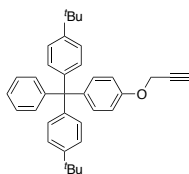
+ve [M+Na] 504.3416, expected [C₂₇H₄₃N₇NaO]⁺ 504.3421



Phenol stopper, **34**³⁶⁸

Chloride **13** (8.72 g, 22.3 mmol) was added to phenol (25 g). The reaction mixture was stirred under N₂ at 100°C overnight, with a colour change from blood red to dark yellow observed. The mixture was allowed to cool and was then added to H₂O (100 ml), followed by extraction with toluene (3 × 100 ml). The combined organics were washed with 10% NaOH_(aq) (3 × 200 ml), then H₂O (3 × 200 ml) and dried over Na₂SO₄. The yellow solution was decolourised with activated charcoal and filtered, then the solvent removed *in vacuo*. Trituration by stirring in hot hexane for 30 minutes, then collecting the white solid, afforded the desired pure product (4.10 g, 9.15 mmol, 41%).

¹H NMR (300 MHz, CDCl₃, 298 K): δ 7.38–7.08 (15H, m, ArH), 6.68 (2H, d, ³J = 9.0 Hz, ArH), 1.31 (18H, s, ^tBu); ¹³C NMR (75 MHz, CDCl₃): δ 153.4, 143.9, 139.4, 132.4, 130.6, 129.4, 127.3, 125.8, 124.2, 121.5, 120.1, 114.0, 63.4, 34.3, 31.3; ESI-MS: –ve [M–H] 447.26, [M+Cl] 483.22, [2M–H] 895.46; the characterisation data correspond well with those published.³⁶⁸

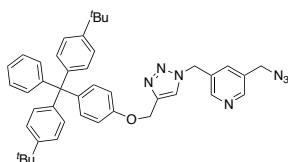


Phenol alkyne stopper, **35**³⁷⁷

Phenol stopper **34** (2.0 g, 4.57 mmol) and K₂CO₃ (3.16 g, 5 eq) were added to dry, degassed DMF (50 ml). To this was added propargyl bromide [80% in toluene] (764 µl, 1.5 eq) and the reaction mixture was heated to 80°C under N₂ overnight. The reaction mixture was allowed to cool and then concentrated *in vacuo*. To this was added H₂O (150 ml) and this was extracted

with EtOAc (3×150 ml). The combined organics were washed with brine (150 ml), dried over MgSO_4 and the solvent removed *in vacuo*. The crude product was then purified by column chromatography (20–40% DCM/60–80°C petrol) to yield the desired product as a white foamy solid (980 mg, 2.0 mmol, 44%).

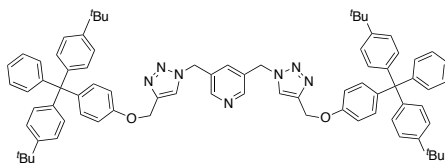
TLC: 20% DCM/60–80°C petrol, R_f 0.30; ^1H NMR (300 MHz, CDCl_3 , 298 K): δ 7.40–7.26 (15H, m, ArH), 7.01 (2H, d, $^3J = 9.0$ Hz, ArH), 4.80 (2H, s, $\text{RCH}_2\text{R}'$), 2.65 (1H, s, $\text{C}\equiv\text{CH}$) 1.31 (18H, s, ^tBu); ^{13}C NMR (75 MHz, CDCl_3): δ 155.5, 148.4, 147.3, 143.8, 140.3, 132.2, 131.1, 130.7, 127.2, 125.7, 124.1, 113.4, 78.7, 75.4, 63.5, 55.7, 34.3, 31.4; ESI-MS: +ve $[\text{M}+\text{Na}]$ 509.27, $[\text{2M}+\text{Na}]$ 995.58; –ve $[\text{M}+\text{Cl}]$ 521.24; the characterisation data correspond well with those published.³⁷⁷



Pyridine triazole monostoppered, **36**

This mono-reacted product (115 mg, 0.170 mmol, 22%) was also isolated from the same experiment used to synthesise **37**, as a white solid.

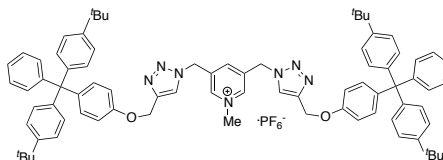
TLC: 3% MeOH/DCM, R_f 0.30; ^1H NMR (300 MHz, CDCl_3 , 298 K): δ 7.75 (2H, s, TrzH), 7.72 (2H, br, PyrH), 7.40–7.21 (18H, m, ArH & PyrH), 5.72 (2H, s, PyrCH_2Trz), 5.31 (2H, s, OCH_2Trz), 4.54 (2H, s, PyrCH_2N_3), 1.44 (18H, s, ^tBu); ^{13}C NMR (75 MHz, CDCl_3 , 298 K): δ 156.0, 148.4, 147.2, 143.8, 140.1, 132.3, 131.1, 130.6, 127.2, 125.7, 124.1, 122.6, 113.2, 77.2, 63.4, 61.9, 51.7, 34.3, 31.3; ESI-MS: +ve $[\text{M}+\text{H}]$ 676.37, $[\text{M}+\text{Na}]$ 698.36; –ve $[\text{M}+\text{Cl}]$ 710.33; HR-MS: +ve $[\text{M}+\text{Na}]$ 698.3559, expected $[\text{C}_{43}\text{H}_{45}\text{N}_7\text{NaO}]^+$ 698.3578



Pyridine ditriazole distoppered, **37**

Diazide **32** (150 mg, 0.794 mmol), propargyl stopper **35** (384 mg, 0.79 mmol), TBTA (127 mg, 0.3 eq) and $[\text{Cu}^{\text{I}}(\text{CH}_3\text{CN})_4]\text{PF}_6$ (90 mg, 0.3 eq) were dissolved in dry DCM (150 ml). To this was added DIPEA (414 μl , 3 eq) and the reaction mixture was stirred at room temperature under N_2 for 7 days. The mixture was washed with 1 M $\text{HCl}_{(\text{aq})}$ (150 ml), sat. $\text{Na}_2\text{CO}_{3(\text{aq})}$ (150 ml), H_2O (150 ml) and brine (150 ml), dried over MgSO_4 and the solvent removed *in vacuo*. The residue was purified by column chromatography (0–4% $\text{EtOH}/\text{CHCl}_3$), isolating the di-reacted product as a yellow, foamy solid (265 mg, 0.228 mmol, 29%).

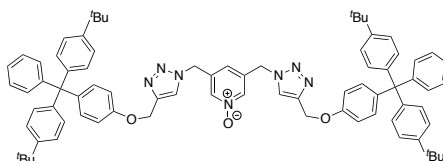
TLC: 3% MeOH/DCM , R_f 0.26; ^1H NMR (300 MHz, CDCl_3 , 298 K): δ 7.72–7.60 (4H, m, PyrH & TrzH), 7.25–7.06 (33H, m, ArH & PyrH), 6.84 (2H, d, $^3J = 8.7$ Hz, ArH), 5.66 (4H, br, PyrCH_2Trz), 5.17 (4H, s, COCH_2Trz), 1.30 (36H, s, ^tBu); ^{13}C NMR (75 MHz, CDCl_3 , 298 K): δ 148.5, 148.4, 143.8, 131.1, 130.7, 127.2, 124.2, 113.2, 111.0, 110.0, 108.1, 77.2, 53.5, 34.3, 31.4; ESI-MS: +ve $[\text{M}+\text{H}]$ 1162.70, $[\text{M}+\text{NH}_4]$ 1179.72, $[\text{M}+\text{Na}]$ 1184.68; $[\text{M}+\text{Cl}]$ 1196.60; HR-MS: +ve $[\text{M}+\text{Na}]$ 1184.6456, expected $[\text{C}_{79}\text{H}_{83}\text{N}_7\text{NaO}_2]^+$ 1184.6500



Methyl pyridinium ditriazole stoppered, **27**

Distoppered compound **27** (50 mg, 0.043 mmol) was dissolved in dry DCM (0.5 ml). To this was added methyl iodide (54 μl , 20 eq) and the vial was carefully sealed. The reaction mixture was stirred at room temperature under N_2 for 4 days, then the solvents removed *in vacuo*. The residue was purified by column chromatography (0–15% MeOH/DCM), isolating the pure product iodide salt as a yellow solid. This was then redissolved in DCM (50 ml) and stirred vigorously with 0.1 M $\text{NH}_4\text{PF}_6_{(\text{aq})}$ (50 ml) for 2 hours. This was then separated and the organics further washed with 0.1 M $\text{NH}_4\text{PF}_6_{(\text{aq})}$ (5×25 ml), H_2O (2×25 ml), dried over MgSO_4 and the solvent removed *in vacuo*. The pure product hexafluorophosphate salt was afforded as a white solid (34 mg, 0.029 mmol, 66%).

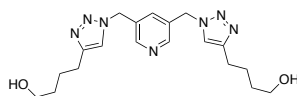
TLC: 10% MeOH/DCM, R_f 0.45; ^1H NMR (300 MHz, CDCl_3 , 298 K): PF_6^- salt δ 8.51 (2H, s, PyrH), 8.20 (1H, s, PyrH), 7.81 (2H, s, TrzH), 7.20–7.04 (H, m, ArH), 6.71 (2H, d, $^3J = 8.7$ Hz, ArH), 5.59 (2H, s, COCH_2Trz), 4.97 (4H, s, PyrCH_2Trz), 4.15 (3H, s, PyrCH_3), 1.26 (36H, s, ^tBu); ^{13}C NMR (75 MHz, CDCl_3 , 298 K): PF_6^- salt δ 155.9, 148.4, 147.3, 143.8, 140.3, 132.3, 131.0, 130.6, 127.3, 124.2, 113.3, 77.2, 63.4, 34.3, 31.4; ESI-MS: +ve $[\text{M}]$ 1176.70; HR-MS: +ve $[\text{M}]$ 1176.6849, expected $[\text{C}_{80}\text{H}_{86}\text{N}_7\text{O}_2]^+$ 1176.6838



Pyridine *N*-oxide ditriazole stoppered, **28** adapted from 377

Distoppered compound **37** (100 mg, 0.086 mmol) and NaHCO_3 (144 mg, 20 eq) were dissolved in 1:1 H_2O /butanone (20 ml). A saturated solution of Oxone[®] (106 mg, 2 eq) in H_2O (0.8 ml) was added dropwise and the reaction mixture was stirred at room temperature under N_2 for 4 days. Sodium chloride (1 g) was added and the mixture extracted with CHCl_3 (3×25 ml), dried over MgSO_4 and the solvent removed *in vacuo*. The residue was purified by column chromatography (0–4% MeOH/DCM), isolating an impure product. This was further purified by preparative thin layer chromatography (7% MeOH/DCM), affording the desired product as a white glassy solid (56 mg, 0.048 mmol, 56%).

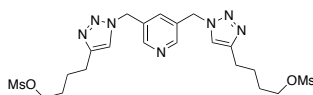
TLC: 5% MeOH/DCM, R_f 0.36; ^1H NMR (300 MHz, CDCl_3 , 298 K): δ 8.10 (2H, br, PyrH), 7.67 (2H, br, TrzH), 7.28–7.06 (31H, m, ArH & PyrH), 6.87–6.83 (4H, m, ArH), 5.48 (2H, s, COCH_2Trz), 5.12 (2H, s, PyrCH_2Trz), 1.26 (36H, s, ^tBu); ^{13}C NMR (75 MHz, CDCl_3 , 298 K): δ 155.9, 148.4, 147.2, 145.6, 143.8, 140.2, 138.2, 134.8, 132.3, 131.1, 130.7, 127.2, 125.7, 124.2, 122.9, 113.2, 63.5, 61.8, 50.3, 34.3, 31.4; ESI-MS: +ve $[\text{M}+\text{K}]$ 1216.64; –ve $[\text{M}+\text{Cl}]$ 1212.59; HR-MS: +ve $[\text{M}+\text{Na}]$ 1200.6421, expected $[\text{C}_{79}\text{H}_{83}\text{N}_7\text{NaO}_3]^+$ 1200.6450



Pyridine ditriazole alcohol derivative, **38**

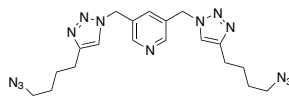
Diazide **32** (68 mg, 0.36 mmol), 5-hexyn-1-ol (84 μ l, 2.1 eq), TBTA (38 mg, 0.2 eq) and $[\text{Cu}^{\text{I}}(\text{CH}_3\text{CN})_4]\text{PF}_6$ (67 mg, 0.5 eq) were dissolved in dry DCM (30 ml). To this was added DIPEA (376 μ l, 3 eq) and the reaction mixture was stirred at room temperature under N_2 for 10 days. DCM (50 ml) was added and the mixture was then washed with 1 M $\text{HCl}_{(\text{aq})}$ (150 ml), sat. $\text{Na}_2\text{CO}_{3(\text{aq})}$ (150 ml), H_2O (150 ml) and brine (150 ml). The combined aqueous fractions were basified by addition of NaOH pellets and the H_2O removed *in vacuo*. The residue was triturated with DCM and then MeOH and the solids discarded. The filtrate was purified by column chromatography (0–20% MeOH/DCM, then 2% $\text{NH}_4\text{OH}_{(\text{aq})}$ /20% MeOH/DCM), affording the desired product as an off-white solid (54 mg, 0.14 mmol, 39%).

TLC: 10% MeOH/DCM, R_f 0.11; ^1H NMR (300 MHz, CD_3OD , 298 K): δ 8.54 (2H, d, $^4J = 1.8$ Hz, PyrH), 7.81 (2H, s, TrzH), 7.68 (1H, t, $^4J = 1.8$ Hz, PyrH), 5.64 (4H, s, PyrCH_2Trz), 3.57 (4H, t, $^3J = 6.3$ Hz, RCH_2OH), 2.71 (4H, t, $^3J = 7.5$ Hz, TrzCH_2R), 1.77–1.51 (8H, m, alkyl); ^{13}C NMR (75 MHz, CD_3OD , 298 K): δ 149.9, 137.4, 134.0, 123.6, 62.7, 51.9, 33.2, 27.0, 26.2; ESI-MS: +ve $[\text{M}+\text{H}]$ 386.23, $[\text{M}+\text{Na}]$ 408.20, $[\text{M}+\text{K}]$ 424.19; –ve $[\text{M}-\text{H}]$ 384.22, $[\text{M}+\text{Cl}]$ 420.19; HR-MS: +ve $[\text{M}+\text{Na}]$ 408.2111, expected $[\text{C}_{19}\text{H}_{27}\text{N}_7\text{NaO}_2]^+$ 408.2118



Pyridine ditriazole mesylate derivative, **39**

Dialcohol **38** (50 mg, 0.13 mmol) was dissolved in dry, degassed DMF (10 ml) and dry Et_3N (72 μ l, 4 eq) at 0°C under N_2 . To this was added dropwise a solution of methanesulfonyl chloride (22 μ l, 2.2 eq) in dry, degassed DMF (5 ml). The reaction mixture was stirred at 0°C under N_2 for 90 minutes, then the solvent removed *in vacuo*. The crude product was afforded as an off-white solid and was reacted on without further analysis (assumed quantitative yield).



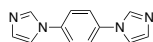
Pyridine ditriazole azide derivative, **40**

Sodium azide (19 mg, 2.3 eq) was dissolved in DMSO (10 ml). To this was added dimesylate **39** (70 mg, 0.13 mmol) and the reaction mixture was stirred at room temperature under N₂ overnight. Further sodium azide (30 mg, 3 eq) was added and the reaction stirred overnight. The reaction was quenched with H₂O (10 ml) and stirred for 1 hour, then extracted with Et₂O (3 × 25 ml). The combined organics were washed with H₂O (20 ml), dried over MgSO₄ and the solvent removed carefully *in vacuo* to afford the desired product as a white solid (5 mg, 0.011 mmol, 9%).

TLC: 10% MeOH/DCM, R_f 0.69; ¹H NMR (300 MHz, CDCl₃, 298 K): δ 8.61 (2H, s, PyrH), 7.59 (1H, s, PyrH), 7.33 (2H, s, TrzH), 5.54 (4H, s, PyrCH₂Trz), 3.31 (4H, t, ³J = 6.3 Hz, RCH₂N₃), 2.75 (4H, t, ³J = 7.2 Hz, TrzCH₂R), 1.84–1.66 (8H, m, alkyl); ¹³C NMR (75 MHz, CDCl₃, 298 K): δ 148.5, 135.9, 131.2, 125.5, 120.9, 51.1, 50.9, 28.3, 26.4, 25.1; ESI-MS: +ve [M+H] 436.25, [M+Na] 458.20, [M+K] 474.21; –ve [M+Cl] 470.20; HR-MS: +ve [M+Na] 458.2248, expected [C₁₉H₂₅N₁₃Na]⁺ 458.2248

6.5.2 Chapter 3

The following procedures are from Chapter 3.

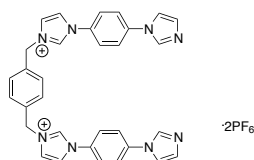


Bis-imidazole linker, **42**³⁸⁵

Imidazole (3.40 g, 2.5 eq), 1,4-diiodobenzene (6.60 g, 20.0 mmol), Cs₂CO₃ (19.6 g, 3 eq) and L-ascorbic acid (1.06 g, 0.3 eq) were added to dry CH₃CN (500 ml) under N₂ in a three-necked round-bottom flask. Salicylaldoxime (1.10 g, 0.4 eq) and copper(I) oxide (572 mg, 0.2 eq) were added whilst stirring under N₂. The reaction mixture was stirred at reflux under N₂ for 3 days. To this was then added DCM (100 ml) and the suspension was filtered through celite, washing with DCM (50 ml). The solvents were removed from the filtrate *in vacuo*. The residue was then triturated with Et₂O (3 × 80 ml), redissolved in DCM and the solvent then

removed *in vacuo*. The fast-running impurities were removed from the residue by silica plug wash (0–80% EtOAc/Et₂O). The product remained adsorbed onto the silica and was eluted with 25% MeOH/CHCl₃. The solvent was removed *in vacuo* to yield the desired product as a yellow solid (3.10 g, 14.8 mmol, 74%).

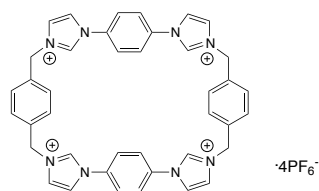
¹H NMR (300 MHz, CDCl₃, 298 K): δ 7.90 (2H, t, ⁴*J* = 1.2 Hz, ImidH), 7.54 (4H, s, ArH), 7.32 (2H, t, ⁴*J* = 1.2 Hz, ImidH), 7.26 (2H, t, ⁴*J* = 1.2 Hz, ImidH); ¹³C NMR (75 MHz, CDCl₃, 298 K): δ 136.4, 135.5, 130.9, 122.9, 118.2; ESI-MS: +ve [M+H] 211.11; the characterisation data correspond well with those published.³⁸⁵



Bis-imidazole xylene precursor, **43**³⁸⁵

Bis-imidazole **42** (1.5 g, 5 eq) was dissolved in dry CH₃CN (40 ml) and was refluxed under N₂. To this was added dropwise a solution of α,α' -dibromoxylene (377 mg, 1.43 mmol) in dry CH₃CN (80 ml) over 1 hour. The reaction mixture was refluxed under N₂ for 2 hours, then allowed to cool to room temperature. The precipitate was filtered off and washed with CH₃CN (50 ml). The residue was redissolved in near-boiling H₂O (75 ml) and sat. NH₄PF_{6(aq)} was added dropwise until no further precipitation was observed. This was cooled in a fridge overnight. The precipitate was filtered and dried under high vacuum to afford the desired product as a white solid (803 mg, 0.986 mmol, 69%).

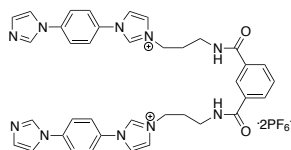
¹H NMR (300 MHz, CD₃CN, 298 K): δ 9.74–9.71 (2H, m, ImidH), 8.24–8.21 (2H, m, ImidH), 8.14 (2H, s, ImidH), 8.06 (4H, s, ImidH), 7.95–7.93 (2H, m, ArH), 7.90–7.88 (4H, m, ArH), 7.65–7.62 (6H, m, ArH), 7.08 (2H, br, ImidH), 5.70–5.68 (4H, m, ArCH₂Imid); ¹³C NMR (75 MHz, acetone-*d*₆, 298 K): δ 137.1, 136.5, 130.7, 126.0, 125.9, 125.4, 125.2, 124.5, 122.9, 111.0, 50.4; MALDI-MS: +ve [M · PF₆] 668.98, expected [C₃₂H₂₈N₈PF₆]⁺ 669.21; the characterisation data correspond well with those published.³⁸⁵



Tetrakis-imidazolium macrocycle, **41**³⁸⁵

Bis-imidazole compound **43** (1.0 g, 1.23 mmol) was dissolved in dry CH₃CN (200 ml) and was refluxed under N₂. To this was added dropwise a solution of α,α' -dibromoxylene (325 mg, 1.23 mmol) in dry CH₃CN (300 ml) over 3 hours. The reaction mixture was refluxed under N₂ for 2 days, then allowed to cool to room temperature. The mixture was filtered and the filtrate retained. The solvent was removed *in vacuo* from the filtrate, then the residue was triturated with acetone (200 ml) and the residue retained. The residue was redissolved in hot H₂O (50 ml) and sat. NH₄PF_{6(aq)} was added dropwise until no further precipitation was observed. This was cooled in a fridge overnight. The precipitate was filtered off to afford the desired macrocycle as a white solid (315 mg, 0.261 mmol, 21%).

¹H NMR (300 MHz, CD₃CN, 298 K): δ 9.03 (4H, s, ImidH), 8.22–8.19 (8H, m, ImidH), 7.83 (8H, s, ArH), 7.62 (8H, s, ArH), 5.64 (8H, s, ImidCH₂Ar); ¹³C NMR (75 MHz, acetone-*d*₆, 298 K): δ 136.9, 135.8, 131.6, 126.0, 125.3, 122.8, 54.7; MALDI-MS: +ve [M · 3 PF₆] 1063.09, expected [C₄₀H₃₆N₈P₄F₂₄]⁺ 1063.20; the characterisation data correspond well with those published.³⁸⁵



Bis-imidazole isophthalamide precursor, **56**

A suspension of bis-imidazole **42** (1.50 g, 5 eq) in dry CH₃CN (150 ml) was refluxed under N₂ until fully dissolved. To this was added dropwise a solution of dibromide **3** (580 mg, 1.43 mmol) and sodium iodide (429 mg, 2 eq) in dry CH₃CN (150 ml) over 2 hours. The reaction mixture was then stirred at reflux under N₂ for a further 4 hours, then left to stand

for 7 days. The suspension was filtered and the solvent removed from the filtrate *in vacuo* to yield a yellow residue, which was retained. This was then triturated with H₂O (2 × 60 ml). The aqueous washings were combined and to this was added sat. NH₄PF_{6(aq)} (2.33 g, 10 eq). The white microprecipitate was partially collected. This was added to the original yellow residue and these were triturated with hot H₂O and recrystallised by slow cooling (600 mg). The precipitate was dissolved in CH₃CN/EtOH and purified by silica plug (20–40% MeOH/DCM, then CH₃CN, then 14:2:1 CH₃CN/H₂O/sat. NH₄PF_{6(aq)}). The solvents were removed from the product fractions *in vacuo*, then the mixture cooled in a fridge for 2 hours. The precipitate was filtered off and dried to afford the pure white solid (22 mg, 0.023 mmol, 1.6%).

TLC: baseline in 30% MeOH/DCM; m.p.: 196–198°C; ¹H NMR (300 MHz, CD₃CN, 298 K): δ 9.14 (2H, t, ⁴J = 1.5 Hz, ImidH), 8.31 (1H, t, ⁴J = 1.5 Hz, IsoH), 7.97 (2H, dd, ³J = 7.8 Hz & ⁴J = 1.8 Hz, IsoH), 7.75 (2H, t, ⁴J = 2.1 Hz, ImidH), 7.68 (2H, t, ⁴J = 1.8 Hz, ImidH), 7.66–7.54 (15H, m, ImidH & ArH & IsoH), 4.34 (4H, t, ³J = 6.9 Hz, ImidCH₂R), 3.49 (4H, q, ³J = 6.0 Hz, NHCH₂), 2.25–2.20 (4H, m, RCH₂R'); ¹³C NMR (75 MHz, CD₃CN, 298 K): δ 168.1, 136.9, 136.7, 136.0, 135.0, 131.6, 131.4, 130.1, 127.1, 125.5, 124.7, 123.1, 49.1, 37.2, 30.9; ESI-MS: +ve [M²⁺] 333.18, [M · PF₆] 811.34; not observed by HR-MS; MALDI-MS: [M · PF₆] 811.30, expected [C₃₈N₃₈H₁₀O₂P₂F₁₂⁺] 811.28



Ethylene glycol monotosylate, **47**³⁸⁷

NaOH (320 mg, 1.6 eq) was dissolved in H₂O (2 ml). This was then added carefully to a solution of ethylene glycol (2.78 ml, 10 eq) in THF (10 ml) cooled over ice. A solution of *p*-toluenesulfonyl chloride (955 mg, 5 mmol) in THF (10 ml) was then added dropwise to the basic reaction mixture over ice. This was stirred and allowed to warm to room temperature overnight. The reaction mixture was then added to ice-water (50 ml) and extracted with DCM (3 × 50 ml). The combined organics were washed with H₂O (70 ml), dried over MgSO₄ and the solvent removed *in vacuo*. After drying under high vacuum, the desired product was isolated as a red oil (495 mg, 2.28 mmol, 46%).

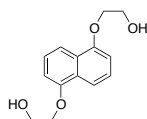
^1H NMR (300 MHz, CDCl_3 , 298 K): δ 7.74 (2H, dt, $^3J = 8.4$ Hz & $^4J = 2.1$ Hz, ArH), 7.39–7.32 (2H, m, ArH), 4.15 (2H, t, $^3J = 4.5$ Hz, OCH_2R), 3.82 (2H, t, $^3J = 4.5$ Hz, OCH_2R), 2.46 (3H, s, ArCH_3), 1.88–1.83 (1H, m, OH); ^{13}C NMR (75 MHz, CDCl_3 , 298 K): δ 145.3, 132.3, 129.9, 127.9, 71.6, 66.7, 21.7; ESI-MS: +ve $[\text{M}+\text{Na}]$ 239.04, $[2\text{M}+\text{Na}]$ 455.12; the characterisation data correspond well with those published.³⁸⁷



Tetraethylene glycol monotosylate, **48**³⁸⁹

NaOH (335 mg, 1.6 eq) was dissolved in H_2O (2 ml). This was added to a solution of tetraethylene glycol (9.04 ml, 10 eq) in THF (5 ml) over ice. Once the temperature had stabilised, a solution of *p*-toluenesulfonyl chloride (1.00 g, 5.24 mmol) in THF (5 ml) was added over 1 hour under stirring. The reaction mixture was then stirred at room temperature for a further hour over ice, then left in the freezer overnight. The reaction mixture was stirred at room temperature for a further hour, then added to ice-water (50 ml) and was extracted with DCM (3×50 ml). The combined organic fractions were then washed with H_2O (2×20 ml), dried over MgSO_4 and the solvent removed *in vacuo*. The desired product was afforded as a clear, colourless oil (1.62 g, 4.66 mmol, 89%).

^1H NMR (300 MHz, CDCl_3 , 298 K): δ 7.78 (2H, d, $^3J = 8.1$ Hz, ArH), 7.33 (2H, d, $^3J = 8.1$ Hz, ArH), 4.14 (2H, t, $^3J = 4.8$ Hz, OCH_2R), 3.70–3.54 (14H, m, polyglycol), 2.71 (1H, br, OH), 2.43 (3H, s, ArCH_3); ^{13}C NMR (75 MHz, CDCl_3 , 298 K): δ 144.8, 132.8, 129.7, 127.9, 72.4, 70.6, 70.5, 70.4, 70.3, 70.2, 69.2, 68.6, 21.5; ESI-MS: +ve $[\text{M}+\text{H}]$ 349.15, $[\text{M}+\text{Na}]$ 371.13, $[\text{M}+\text{K}]$ 387.10; the characterisation data correspond well with those published.³⁸⁸

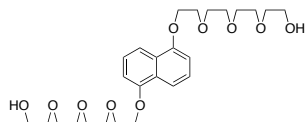


Dihydroxy naphthalene glycol ether, **45**

1,5-Dihydroxynaphthalene (170 mg, 1.06 mmol), 2-*p*-toluenesulfonylethanol **47** (460 μl , 2 eq),

lithium bromide (9 mg, 0.1 eq) and K_2CO_3 (585 mg, 4 eq) were added to dry CH_3CN (70 ml). The reaction mixture was stirred at reflux under N_2 for 4 days, then the solvent was removed *in vacuo* from the cooled reaction mixture. The residue was redissolved in H_2O (80 ml) at 65°C , then allowed to cool in a fridge overnight. The black/purple precipitate was collected, with the yellow filtrate discarded. The residue was triturated with MeOH (200 ml) and the solvent removed *in vacuo* from the red solution to yield the desired product as a brown solid (39 mg, 0.160 mmol, 15%).

^1H NMR (300 MHz, $\text{DMSO}-d_6$, 298 K): δ 7.80 (2H, d, $^3J = 8.1$ Hz, ArH), 7.37 (2H, t, $^3J = 8.1$ Hz, ArH), 6.98 (2H, d, $^3J = 8.1$ Hz, ArH), 4.14 (4H, t, $^3J = 5.1$ Hz, ArOCH_2R), 3.85 (4H, t, $^3J = 4.5$ Hz, RCH_2OH); ESI-MS: +ve $[\text{M}+\text{Na}]$ 271.10; –ve $[\text{M}+\text{Cl}]$ 283.27; the characterisation data correspond well with those published.³⁹⁰

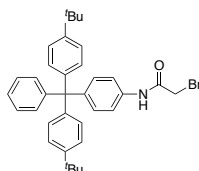


Dihydroxy naphthalene polyether, **46**³⁸⁹

Monotosylate **48** (1.50 g, 2 eq), K_2CO_3 (1.19 g, 4 eq) and lithium bromide (10 mg, *cat.*) were added to dry CH_3CN (100 ml), followed by purging with N_2 for 1 hour. To this was then added 1,5-dihydroxynaphthalene (345 mg, 2.16 mmol) and the reaction was stirred at reflux under N_2 for 2 days. The cooled reaction mixture was filtered and the residue dissolved in hot H_2O (150 ml), then extracted with DCM (3×50 ml). The combined filtrate and organic fractions were concentrated *in vacuo* to produce a dark red oil. This was then dissolved in DCM (100 ml) and carefully washed with 3:1 brine/10% $\text{NaOH}_{(\text{aq})}$ (3×50 ml), dried over MgSO_4 and the solvent removed *in vacuo* to yield an impure brown oil. Further purification by column chromatography (4–25% EtOH/ CHCl_3) isolated the desired product as a red oil (696 mg, 1.36 mmol, 63%).

TLC: 4% EtOH/ CHCl_3 , R_f 0.38; ^1H NMR (300 MHz, CDCl_3 , 298 K): δ 7.87 (2H, d, $^3J = 8.7$ Hz, ArH), 7.36 (2H, t, $^3J = 7.8$ Hz, ArH), 6.86 (2H, d, $^3J = 7.5$ Hz, ArH), 4.31 (4H, t, $^3J = 4.8$ Hz, ArOCH_2R), 4.01 (4H, t, $^3J = 4.8$ Hz, $\text{ArOCH}_2\text{CH}_2\text{O}$), 3.82–3.58 (24H,

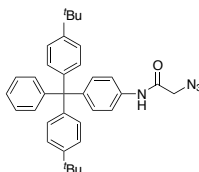
m, polyglycol), 2.61 (2H, t, $^3J = 6.0$ Hz, ROH); ^{13}C NMR (75 MHz, CDCl_3 , 298 K): δ 154.3, 126.7, 125.1, 114.6, 105.7, 72.5, 71.0, 70.6, 70.3, 69.8, 68.3, 67.9, 61.7; ESI-MS: +ve $[\text{M}+\text{Na}]$ 535.22; $[\text{M}+\text{K}]$ 551.26; -ve $[\text{M}-\text{H}]$ 511.29, $[\text{M}+\text{Cl}]$ 547.27; the characterisation data correspond well with those published.³⁸⁹



Aniline bromide stopper, **49**

Aniline stopper **14** (2.24 g, 5.00 mmol) was dissolved in DCM (35 ml). To this was added 1.25 M $\text{NaOH}_{(\text{aq})}$ (4 ml, 1 eq) and the reaction mixture was stirred vigorously at room temperature for 15 minutes. A solution of bromoacetyl bromide (567 μl , 1.3 eq) in DCM (30 ml) was then added dropwise and the reaction mixture allowed to stir at room temperature for 4 days. To this was then added H_2O (15 ml) and the mixture separated. The organics were washed with H_2O (2×15 ml), dried over MgSO_4 and the solvent removed *in vacuo*. Drying under high vacuum afforded the desired product as an off-white solid (2.83 g, 4.97 mmol, 99%).

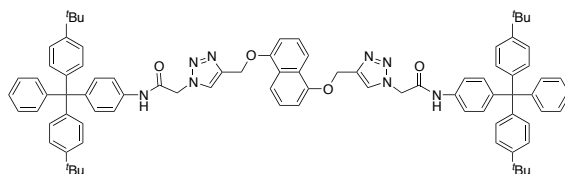
m.p.: *dec.* 82°C; ^1H NMR (300 MHz, CDCl_3 , 298 K): δ 8.15 (1H, br, CONH), 7.45 (2H, d, $^3J = 9.0$ Hz, ArH), 7.31–7.23 (11H, m, ArH), 7.15 (4H, d, $^3J = 9.0$ Hz, ArH), 4.05 (2H, s, RCH_2Br), 1.35 (18H, s, $t\text{Bu}$); ^{13}C NMR (75 MHz, CDCl_3): δ 163.2, 148.5, 146.9, 144.3, 143.5, 134.4, 131.8, 131.1, 130.6, 127.3, 125.8, 124.3, 118.9, 63.8, 34.3, 31.4, 29.5; ESI-MS: +ve $[\text{M}+\text{Na}]$ 590.20 & 592.20; -ve $[\text{M}-\text{H}]$ 566.20 & 568.20; HR-MS: +ve $[\text{M}+\text{Na}]$ 590.2014 & 592.1999, expected $[\text{C}_{35}\text{H}_{38}\text{BrNNaO}]^+$ 590.2029 & 592.2011



Aniline azide stopper, **50**

Bromide-appended stopper **49** (1.50 g, 2.64 mmol) was dissolved in dry, degassed DMF (70 ml). To this was added sodium azide (858 mg, 5 eq) and the reaction mixture was stirred at room temperature under N₂ overnight. The reaction mixture was then carefully concentrated *in vacuo*. The crude mixture was partitioned between Et₂O (100 ml) and H₂O (50 ml) and then further washed with H₂O (2 × 50 ml), dried over MgSO₄ and the solvent removed *in vacuo*. The desired product was afforded as an off-white foamy solid (1.30 g, 2.45 mmol, 93%).

m.p.: *dec.* 84°C; ¹H NMR (300 MHz, CDCl₃, 298 K): δ 7.96 (1H, br, CONH), 7.42 (2H, d, ³J = 9.0 Hz, ArH), 7.26–7.18 (11H, m, ArH), 7.09 (4H, d, ³J = 9.0 Hz, ArH), 4.15 (2H, s, RCH₂N₃), 1.31 (18H, s, ^tBu); ¹³C NMR (75 MHz, CDCl₃): δ 196.3, 131.8, 131.1, 130.6, 127.3, 125.8, 124.3, 124.2, 118.9, 53.0, 34.3, 31.3; ESI-MS: +ve [M+H] 531.32, [M+NH₄] 548.34, [M+Na] 553.29; –ve [M–H] 529.30, [M+Cl] 565.28; HR-MS: +ve [M+Na] 553.2928, expected [C₃₅H₃₈N₄NaO]⁺ 553.2938



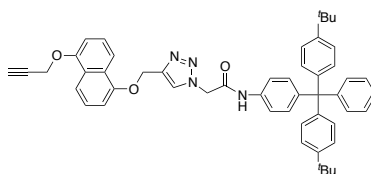
Dihydroxy naphthalene ether ditriazole distoppered, **52**

Azide stopper **50** (569 mg, 1.00 mmol), dialkyne **18** (238 mg, 1.00 mmol), TBTA (106 mg, 0.2 eq) and [Cu^I(CH₃CN)₄]⁺PF₆[–] (75 mg, 0.2 eq) were dissolved in dry DCM (300 ml). To this was added DIPEA (514 μl, 3 eq) and the yellow reaction mixture was stirred at room temperature under N₂ for 3 days. The reaction mixture was washed with 10% HCl_(aq) (2 × 250 ml), sat. NaHCO_{3(aq)} (2 × 250 ml) and H₂O (2 × 200 ml), dried over MgSO₄, then the solvent removed *in vacuo*, to produce the crude product as a yellow-brown solid (1 g). This was purified by column chromatography (0–3% MeOH/CHCl₃) to produce a mixture of the mono- and di-reacted products. These were separated by further column chromatography (Et₂O, then 50–80% EtOAc/60–80°C petrol) to afford the desired di-reacted product as a

glassy yellow solid (318 mg, 0.245 mmol, 25%).

TLC: 3% MeOH/DCM, R_f 0.14

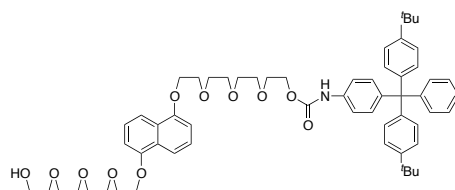
^1H NMR (300 MHz, $\text{DMSO}-d_6$, 298 K): δ 7.86 (4H, t, $^3J = 7.8$ Hz, ArH), 7.35 (4H, t, $^3J = 8.1$ Hz, ArH), 7.24–7.17 (26H, m, ArH), 7.08 (4H, d, $^3J = 8.7$ Hz, ArH), 6.98 (4H, d, $^3J = 7.2$ Hz, TrzH), 5.41 (4H, s, COCH_2Trz), 5.18 (4H, s, OCH_2Trz), 3.50 (2H, s, CONH), 1.30 (36H, s, ^tBu); ^{13}C NMR (75 MHz, 1:1 $\text{CD}_3\text{CN}/\text{CDCl}_3$, 298 K): δ 164.7, 155.0, 152.8, 149.3, 148.1, 144.9, 136.0, 132.0, 131.4, 131.1, 128.4, 126.6, 126.2, 125.4, 119.7, 110.8, 110.5, 107.2, 106.3, 86.1, 64.6, 62.9, 34.9, 31.6; ESI-MS: +ve $[\text{M}+\text{Na}]$ 1319.72, $[\text{M}+\text{K}]$ 1335.70; –ve $[\text{M}-\text{H}]$ 1295.68, $[\text{M}+\text{Cl}]$ 1331.66; HR-MS: +ve $[\text{M}+\text{Na}]$ 1319.6807, expected $[\text{C}_{86}\text{H}_{88}\text{N}_8\text{NaO}_4]^+$ 1319.6821



Dihydroxy naphthalene ether triazole monostoppered, **51**

This mono-reacted product (250 mg, 0.326 mmol, 33%) was also isolated from the same experiment used to synthesise **52**.

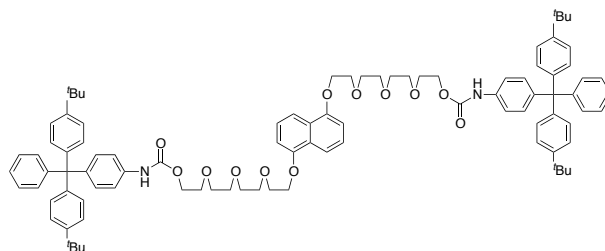
TLC: 3% MeOH/DCM, R_f 0.30; ^1H NMR (300 MHz, CD_3CN , 298 K): δ 8.68 (1H, s, CONH), 8.03 (1H, s, TrzH), 7.80 (2H, d, $^3J = 8.1$ Hz, ArH), 7.47–7.15 (20H, m, ArH), 7.03 (2H, d, $^3J = 7.5$ Hz, ArH), 5.38 (2H, s, COCH_2Trz), 5.23 (2H, s, OCH_2R), 4.93 (1H, d, $^4J = 2.4$ Hz, $\text{OC}\equiv\text{CH}$), 1.29 (18H, s, ^tBu); ^{13}C NMR (75 MHz, CDCl_3 , 298 K): δ 162.9, 153.5, 153.0, 148.4, 146.9, 143.5, 131.7, 131.0, 130.6, 127.3, 126.7, 126.6, 125.7, 125.2, 125.1, 124.2, 119.0, 115.1, 106.3, 106.1, 78.5, 75.6, 63.7, 62.0, 60.4, 56.1, 34.3, 31.3, 21.1, 14.2; ESI-MS: +ve $[\text{M}+\text{H}]$ 767.46, $[\text{M}+\text{Na}]$ 789.45, $[\text{M}+\text{K}]$ 805.42; –ve $[\text{M}-\text{H}]$ 765.41, $[\text{M}+\text{Cl}]$ 801.39; HR-MS: –ve $[\text{M}-\text{H}]$ 765.3840, expected $[\text{C}_{51}\text{H}_{49}\text{N}_4\text{O}_3]^+$ 765.3810



Dihydroxy naphthalene polyether monostoppered, **54**

Tetraglycol thread **46** (510 mg, 10 eq) was dissolved in dry CH_3CN (10 ml). To this was added diⁿbutyltin dilaurate (3 drops, *cat.*), followed by a solution of isocyanate stopper **15** (47 mg, 0.10 mmol) in dry CH_3CN (20 ml). The reaction mixture was stirred at room temperature under N_2 for 2 days. The solvent was removed *in vacuo* and the residue purified by column chromatography (0–5% MeOH/DCM) to isolate an impure product (63 mg). This was then further purified by preparative thin layer chromatography (2% MeOH/DCM) to isolate the desired product as a white solid (33 mg, 0.034 mmol, 34%).

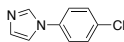
TLC: 3% MeOH/DCM, R_f 0.25; ^1H NMR (300 MHz, CDCl_3 , 298 K): δ 7.83 (2H, d, $^3J = 8.4$ Hz, ArH), 7.30 (2H, t, $^3J = 8.4$ Hz, ArH), 7.24–7.05 (17H, m, ArH), 6.94 (1H, br, CONH), 6.82 (2H, t, $^3J = 7.2$ Hz, ArH), 4.30–4.24 (4H, m, OCH_2R), 3.99–3.95 (4H, m, OCH_2R), 3.81–3.76 (4H, m, OCH_2R), 3.70–3.54 (20H, m, OCH_2R), 2.33 (1H, br, OH), 1.27 (18H, s, ^tBu); ^{13}C NMR (75 MHz, CDCl_3 , 298 K): δ 155.4, 154.5, 153.6, 148.6, 147.3, 143.9, 142.4, 135.7, 131.9, 131.3, 130.8, 127.5, 126.9, 125.3, 124.4, 117.7, 114.8, 114.6, 114.5, 105.9, 104.7, 72.7, 71.2, 71.1, 70.9, 70.8, 70.7, 70.5, 70.0, 69.6, 68.1, 64.3, 63.8, 61.9, 55.7, 34.5, 31.5; ESI-MS: +ve $[\text{M}+\text{H}]$ 986.58, $[\text{M}+\text{Na}]$ 1008.51, $[2\text{M}+\text{H}]$ 1972.90; –ve $[\text{M}+\text{Cl}]$ 1030.54; HR-MS: +ve $[\text{M}+\text{Na}]$ 1008.5222, expected $[\text{C}_{60}\text{H}_{75}\text{NNaO}_{11}]^+$ 1008.5232



Dihydroxy naphthalene polyether distoppered, **53**

This product was also found by ESI-MS during the same experiment as **54**.

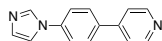
ESI-MS: +ve [M+K] 1498.81



Bis-imidazole linker, **61** adapted from 391

Imidazole (2.86 g, 2 eq) and 4-iodo-1-chlorobenzene (5.00 g, 21 mmol) were dissolved in dry CH₃CN (250 ml). Cs₂CO₃ (13.8 g, 2 eq) and copper powder (1.34 g, 1 eq) were then added and the reaction mixture refluxed under N₂ for 4 days. Reaction monitoring by TLC (DCM) could not be done, as the copper salts remained on the baseline. The reaction mixture was allowed to cool and the blue, white and red solids were then filtered off under very light suction. The solvent was then removed *in vacuo* and the residue then redissolved in CH₃CN (15 ml). After stirring for 2 hours at 60°C in 0.02 M EDTA_(aq)/ 1 M NH₄OH_(aq) (85 ml) to remove all the copper, the CH₃CN was carefully removed *in vacuo*. DCM (50 ml) was added to the brown oil and aqueous fractions and the mixture extracted with DCM (2 × 30 ml). The combined organics were washed with H₂O (100 ml) and brine (100 ml), then dried over MgSO₄. The solvent was removed *in vacuo* to afford a brown oil, which cooled to form an off-white solid (2.66 g, 15.0 mmol, 71%).

¹H NMR (300 MHz, CDCl₃, 298 K): δ 7.93 (1H, s, ImidH), 7.52 (4H, s, ArH), 7.44 (1H, ImidH), 7.12 (1H, s, ImidH); ¹³C NMR (75 MHz, CD₃CN, 298 K): δ 137.5, 137.0, 133.4, 131.5, 131.1, 123.9, 119.5; ESI-MS: +ve [M+H] 179.03; –ve [M+Cl] 204.99; the characterisation data correspond well with those published.⁴⁴⁷



Imidazole pyridine linker, **60** adapted from 392

Aryl chloride **61** (500 mg, 2.81 mmol) was added to dry THF (20 ml) under N₂ and cooled over a CO₂(s)/acetone bath. To this was carefully added ⁿBuLi [1.6 M in hexanes] (2.02 ml, 1.15 eq) and the reaction mixture was stirred at –78°C for a further hour. A solution of dry ZnCl₂ (439 mg, 1.15 eq) in dry THF (10 ml) was then carefully added and the reaction mixture

allowed to warm to room temperature under N₂, with a colour change to orange-red.

4-Bromopyridine hydrochloride (545 mg, 2.81 mmol) was dissolved in H₂O (5 ml) and 10% NaOH_(aq) (approx. 2 ml) was added until pH > 7. This was then extracted with Et₂O (4 × 15 ml), dried over MgSO₄ and the solvent removed *in vacuo* to yield a pale yellow oil of free 4-bromopyridine, **64**.

Pd(PPh₃)₄ (162 mg, 5 mol%) was added to the reaction mixture, followed by a solution of 4-bromopyridine, **64**, in dry THF (15 ml). The reaction mixture was then stirred at reflux under N₂ overnight. To the cooled reaction mixture was then added H₂O (30 ml) and the mixture neutralised with 10% NaOH_(aq) (<5 ml). This was then extracted with Et₂O (3 × 60 ml), the combined organics dried with brine (50 ml) and then over MgSO₄. The solvent was removed *in vacuo* to produce a brown oil (830 mg), which was purified by column chromatography (0–6% MeOH/DCM). The middle fractions afforded an impure yellow solid (292 mg, 1.32 mmol, 47%).

¹H NMR (300 MHz, CDCl₃, 298 K): δ 8.62 (1H, d, ³J = 6.3 Hz, ImidH), 8.36 (2H, s, H), 7.66 (1H, d, ³J = 6.3 Hz, ImidH), 7.53 (4H, dt, ³J = 9.0 Hz & ⁴J = 2.1 Hz, ArH), 7.41–7.39 (4H, m, ArH), 7.36 (4H, dt, ³J = 6.3 Hz & ⁴J = 1.5 Hz, ArH); ESI-MS: –ve [2M–H] 441.21



4-Bromopyridine, **64**⁴⁴⁸

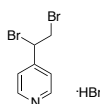
4-Bromopyridine hydrochloride (1.00 g, 5.15 mmol) was dissolved in H₂O (20 ml) and cooled in an ice bath. To this was added 10% NaOH_(aq) until pH > 7, with an orange colour observed, followed by stirring at room temperature for 30 minutes. The reaction mixture was extracted with DCM (30 ml), then Et₂O (30 ml), then DCM (30 ml). The combined organics were dried over MgSO₄ and the solvents removed *in vacuo* to form the free 4-bromopyridine as a yellow oil. This was immediately reacted on with no analysis (assumed quantitative yield).



4-Vinylpyridine salt, **65**³⁹⁹

4-Vinylpyridine (50 ml, 460 mmol) was dissolved in dry Et₂O (300 ml) under N₂ over ice. Formed by slow addition of conc. H₂SO₄ (270 ml, 11 eq) to sodium chloride (269 g, 10 eq), HCl_(g) was bubbled through the reagent. The reaction mixture was left to warm to room temperature overnight in air. The white precipitate was collected and washed carefully with Et₂O (6 × 50 ml) to remove all pink starting material. The HCl salt was isolated as a white solid (51 g, 360 mmol, 78%).

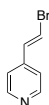
ESI-MS: +ve [M · H] 106.05, [2 M · H] 211.12



Pyridine dibromide salt, **66**³⁹⁹

Pyridine salt **65** (50.0 g, 357 mmol) was suspended in dry CHCl₃ (500 ml) and stirred over ice. To this was added dropwise bromine (36.6 ml, 2 eq), with an immediate colour change from yellow to orange observed. The reaction mixture was stirred over ice for 1 hour, then for a further hour at room temperature. To this was then added Et₂O (400 ml) and mixed vigorously. The resulting red solution was poured off the red semi-solid. This semi-solid was further washed with Et₂O (5 × 100 ml). Acetone (250 ml) was added to initiate a bromoform reaction to remove any excess bromine, with a concomittant colour change from red to yellow under vigorous stirring. The solid product was filtered off as the yellow (lachrymatory) hydrobromide salt (74.2 g, 214 mmol, 60%).

¹H NMR (300 MHz, DMSO-*d*₆, 298 K): δ 9.00–8.97 (2H, m, ArH), 8.22–8.19 (2H, m, ArH), 5.83–5.72 (1H, m, ArCHBrR), 4.60–4.32 (2H, m, RCH₂Br); ESI-MS: +ve [M · H] 265.90; the characterisation data correspond well with those published.³⁹⁹



Vinylpyridine bromide, **67**⁴⁰⁰

Pyridine salt **66** (65.7 g, 190 mmol) was added in portions to dry Et₃N (450 ml). The suspension was stirred at room temperature under N₂ for 3 days. The reaction mixture was heated to 90°C for 4 hours, then allowed to cool. The grey precipitate was filtered off and washed with Et₂O (4 × 100 ml). The combined filtrates were concentrated *in vacuo* and dried under high vacuum to afford the product as an orange-brown oil (28.7 g, 158 mmol, 78%).

¹H NMR (300 MHz, CDCl₃, 298 K): δ 8.62 (2H, dd, ³*J* = 7.5 Hz & ⁴*J* = 1.8 Hz, ArH), 7.48 (2H, dd, ³*J* = 7.5 Hz & ⁴*J* = 1.8 Hz, ArH), 6.37 (1H, d, ³*J* = 2.4 Hz, ArCH=CHBr), 5.98 (1H, d, ³*J* = 2.4 Hz, ArCH=CHBr); ¹³C NMR (75 MHz, CDCl₃, 298 K): δ 150.2, 145.5, 128.3, 121.4, 121.0; ESI-MS: not observed; the characterisation data correspond well with those published.⁴⁰⁰



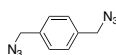
4-Ethynylpyridine, **62**⁴⁰⁰

Liquid ammonia (200 ml) was condensed into a 1 litre 3-necked round-bottomed flask and cooled to −78°C with a CO_{2(s)}/acetone condenser under N₂. A small amount of sodium was added and the mixture stirred until the blue colour permeated the solution. Ferric nitrate (60 mg, *cat.*) was added, with the reaction mixture turning a tan colour. The rest of the sodium (3.15 g, 2.5 eq) was then very carefully added piecewise, resulting in a blue-tan suspension, which was stirred for 1 hour at −78°C under N₂. A solution of **67** (10.0 g, 54.3 mmol) in 1:1 dry Et₂O/THF (60 ml) was added dropwise over 4 hours, taking care not to build up frozen reagent on the inside of the flask. The reaction mixture was allowed to warm to −30°C and was stirred under reflux for 1 hour. The liquid ammonia was then allowed to evaporate whilst stirring under N₂ overnight.

Et₂O (250 ml) was added to the residue, then H₂O (200 ml) and the mixture was extracted with Et₂O (2 × 100 ml). The combined organics were then washed with H₂O (2 × 130 ml), dried over MgSO₄ and the solvent carefully removed *in vacuo*. The resulting light brown

residue was then purified by sublimation (80°C, cold water condenser, N₂ atm.). The pure product was sublimed as a white crystalline solid (1.70 g, 16.5 mmol, 30%). The product decomposes rapidly under ambient conditions and was reacted on as soon as possible.

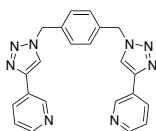
¹H NMR (300 MHz, CDCl₃, 298 K): δ 8.60 (2H, dd, ³*J* = 7.5 Hz & ⁴*J* = 1.5 Hz, ArH), 7.35 (2H, dd, ³*J* = 7.5 Hz & ⁴*J* = 1.5 Hz, ArH), 3.30 (1H, s, C≡CH); ¹³C NMR (75 MHz, CDCl₃, 298 K): δ 149.8, 130.3, 126.0, 81.9, 80.9; the characterisation data correspond well with those published.⁴⁰⁰



α,α' -Diazidoxylene, **68**

Sodium azide (2.22 g, 3 eq) was suspended in DMSO (100 ml). To this was added α,α' -dibromoxylene (3.00 g, 11.4 mmol). The reaction mixture was stirred at room temperature under N₂ overnight. H₂O (100 ml) was added and the product was extracted with Et₂O (4 $\times$ 80 ml). The combined organics were washed with H₂O (4 $\times$ 80 ml) and brine (100 ml), then dried over MgSO₄ and the solvent carefully removed *in vacuo*. The product was isolated as a yellow oil that solidified upon cooling (2.09 g, 11.1 mmol, 97%).

m.p.: 31°C; ¹H NMR (300 MHz, CDCl₃, 298 K): δ 7.23 (4H, s, ArH), 4.21 (4H, s, ArCH₂N₃); ¹³C NMR (75 MHz, CDCl₃, 298 K): δ 135.1, 128.0, 53.7; ESI-MS: –ve [M+Cl] 223.04; the characterisation data correspond well with literature precedent.^{401,449}

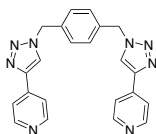


3-Pyridyl xylene precursor, **69**

Diazide **68** (227 mg, 1.21 mmol) and 3-ethynylpyridine (250 mg, 2 eq) were dissolved in dry DCM (300 ml). [Cu^I(CH₃CN)₄]PF₆ (187 mg, 0.5 eq), TBTA (308 mg, 0.5 eq) and DIPEA (2.0 ml, 9 eq) were then added and the solution was left to stir under N₂ for 2 days. DCM (100 ml) was removed from the reaction mixture *in vacuo* and 1 M HCl_(aq) (2 $\times$ 50 ml) was

added to form a white precipitate in the aqueous layer, which was then separated and filtered. The precipitate was then stirred for 2 hours in sat. $\text{Na}_2\text{CO}_{3(\text{aq})}$ (100 ml), then filtered off and retained. This was then dissolved in hot CH_3CN (100 ml) and stirred in 0.02 M $\text{EDTA}_{(\text{aq})}$ / 1 M $\text{NH}_4\text{OH}_{(\text{aq})}$ (40 ml) for 4 hours before removing the solvent *in vacuo*. The crude product was washed with H_2O (4×20 ml) and then dried under high vacuum to afford the desired product as a pale yellow crystalline solid (404 mg, 1.03 mmol, 84%).

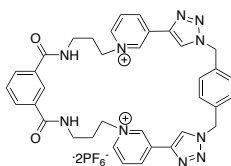
m.p.: *dec.* 190°C; ^1H NMR (500 MHz, $\text{DMSO}-d_6$, 293 K): δ 9.04 (2H, d, $^4J = 1.8$ Hz, PyrH), 8.76 (2H, s, TrzH), 8.53 (2H, dd, $^3J = 5.2$ Hz & $^4J = 1.8$ Hz, PyrH), 8.21 (2H, d, $^3J = 7.8$ Hz, PyrH), 7.47 (2H, dd, $^3J = 7.8$ Hz & 5.2 Hz, PyrH), 7.39 (4H, s, ArH), 5.68 (4H, s, ArCH_2Trz); ^{13}C NMR (75 MHz, $\text{DMSO}-d_6$, 298 K): δ 148.8, 146.2, 143.8, 135.9, 132.6, 128.5, 126.6, 124.1, 122.3, 52.7; ESI-MS: +ve [M+H] 395.18, [M+Na] 417.16, [2M+Na] 811.34; –ve [M+Cl] 429.16; HR-MS: +ve [M+H] 395.1731, expected $[\text{C}_{22}\text{H}_{19}\text{N}_8]^+$ 395.1733



4-Pyridyl xylene precursor, **70**

Diazide **68** (274 mg, 1.46 mmol) and 4-ethynylpyridine **62** (300 mg, 2 eq) were dissolved in dry DCM (300 ml). $[\text{Cu}^{\text{I}}(\text{CH}_3\text{CN})_4]\text{PF}_6$ (272 mg, 0.5 eq), TBTA (388 mg, 0.5 eq) and DIPEA (761 μl , 3 eq) were then added, resulting in a cloudy yellow mixture. The reaction was left to stir at room temperature under N_2 for 2 days. 1 M $\text{HCl}_{(\text{aq})}$ (2×300 ml) was then added to form a white precipitate in the aqueous layer which was then separated and filtered. The precipitate was then stirred for 2 hours in sat. $\text{Na}_2\text{CO}_{3(\text{aq})}$ (100 ml), then filtered off. This was then dissolved in hot CH_3CN (100 ml) and stirred in 0.02 M $\text{EDTA}_{(\text{aq})}$ / 1 M $\text{NH}_4\text{OH}_{(\text{aq})}$ (40 ml) for 4 hours before removing the solvent *in vacuo*. The crude product was washed with H_2O (4×20 ml) and then dried under high vacuum to afford the desired product as a white solid (504 mg, 1.28 mmol, 88%).

m.p.: *dec.* >250°C; ^1H NMR (500 MHz, DMSO- d_6 , 293 K): δ 8.86 (2H, s, TrzH), 8.61 (4H, d, $^3J = 7.8$ Hz, PyrH), 7.80 (4H, d, $^3J = 7.8$ Hz, PyrH), 7.39 (4H, s, ArH), 5.68 (4H, s, ArCH₂Trz); ^{13}C NMR (75 MHz, DMSO- d_6 , 298 K): δ 150.3, 144.4, 137.7, 135.8, 128.5, 123.6, 119.5, 52.8; ESI-MS: +ve [M+H] 395.17, [M+Na] 417.15, [2M+Na] 811.33; –ve [M–H] 393.17, [M+Cl] 429.14, [2M+Cl] 823.30; HR-MS: +ve [M+H] 395.1726, expected [C₂₂H₁₉N₈]⁺ 395.1727

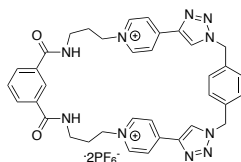


3-Pyridinium dicationic macrocycle, **71**

3-Pyridine triazole **69** (54 mg, 0.137 mmol) and dibromide **3** (55.6 mg, 0.137 mmol) were suspended in dry CH₃CN (20 ml). This was heated in a microwave at 165°C for 90 minutes, then the solvent was removed *in vacuo*. The residue was triturated with H₂O (15 ml) to form a suspension, after which the solid was removed and the filtrate washed with DCM (15 ml). To the aqueous fraction, sat. NH₄PF₆(aq) solution was added dropwise to afford a white precipitate, until no further precipitation was observed. This was filtered and the residue dried under vacuum to yield the desired product as a white solid (40 mg, 0.043 mmol, 31%).

m.p.: *dec.* 230°C; ^1H NMR (500 MHz, acetone- d_6 , 293 K): δ 9.70 (2H, s, PyrH), 9.16 (2H, d, $^3J = 6.4$ Hz, PyrH), 9.01 (2H, d, $^3J = 8.3$ Hz, PyrH), 8.80 (2H, s, TrzH), 8.32 (2H, dd, $^3J = 8.3$ Hz & 6.4 Hz, PyrH), 8.14 (1H, s, IsoH), 8.11 (2H, br, NH), 7.80 (2H, dd, $^3J = 7.8$ Hz & $^4J = 2.1$ Hz, IsoH), 7.56 (4H, s, ArH), 7.19 (1H, t, $^3J = 7.8$ Hz, IsoH), 5.83 (4H, s, ArCH₂Trz), 5.02 (4H, t, $^3J = 6.8$ Hz, PyrCH₂R), 3.64–3.58 (4H, m, NHCH₂R), 2.57–2.28 (4H, m, RCH₂R'); ^{13}C NMR (75 MHz, acetone- d_6 , 298 K): δ 167.1, 144.0, 142.5, 141.7, 141.4, 136.7, 135.1, 132.6, 130.5, 129.7, 129.5, 128.9, 126.4, 124.5, 61.1, 54.2, 37.1, 31.4; ^{19}F NMR (282 MHz, CD₃CN, 298 K): δ –71.3 (d, $^1J = 710$ Hz, PF₆[–]); ^{31}P NMR (122 MHz, CD₃CN, 298 K): δ –144.7 (septet, $^1J = 710$ Hz, PF₆[–]); ESI-MS: +ve [M²⁺] 320.15, [M · Cl] 675.28,

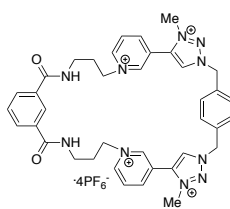
$[M \cdot PF_6]$ 785.29; HR-MS: +ve $[M \cdot PF_6]$ 785.2652, expected $[C_{36}H_{36}F_6N_{10}O_2P]^+$ 785.2659



4-Pyridinium dicationic macrocycle, **72**

4-Pyridine triazole **70** (54 mg, 0.137 mmol) and dibromide **3** (55.6 mg, 0.137 mmol) were suspended in dry CH_3CN (20 ml). This was heated in a microwave at $165^\circ C$ for 90 minutes, then the solvent was removed *in vacuo*. The residue was triturated with H_2O (15 ml) to form a suspension, after which the solid was removed and the filtrate washed with DCM (15 ml). To the aqueous fraction, sat. $NH_4PF_6(aq)$ solution was added dropwise to afford a white precipitate, until no further precipitation was observed. The residue was isolated and purified by preparative thin layer chromatography (acetone/1% sat. $NH_4PF_6(aq)$), yielding the desired product as a white solid (25 mg, 0.027 mmol, 20%).

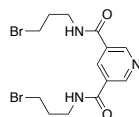
m.p.: *dec.* $215^\circ C$; ^1H NMR (500 MHz, CD_3CN , 293 K): δ 8.80 (4H, d, $^3J = 6.9$ Hz, PyrH), 8.43 (2H, s, TrzH), 8.34 (1H, s, IsoH), 8.31 (4H, d, $^3J = 6.9$ Hz, PyrH), 7.88 (2H, dd, $^3J = 7.8$ Hz & $^4J = 2.0$ Hz, IsoH), 7.58 (4H, s, ArH), 7.53 (2H, br, NH), 7.42 (1H, t, $^3J = 7.8$ Hz, IsoH), 5.72 (4H, s, $ArCH_2Trz$), 4.57 (4H, t, $^3J = 6.8$ Hz, $PyrCH_2R$), 3.42 (4H, q, $^3J = 6.4$ Hz, $NHCH_2R$), 2.29 (4H, qn, $^3J = 6.8$ Hz, RCH_2R'); ^{13}C NMR (75 MHz, acetone- d_6 , 298 K): δ 167.3, 147.6, 146.3, 136.7, 135.8, 135.5, 134.0, 130.7, 130.0, 129.5, 127.2, 127.1, 123.8, 59.4, 54.7, 36.6, 31.4; ^{19}F NMR (282 MHz, CD_3CN , 298 K): δ -71.6 (d, $^1J = 710$ Hz, PF_6^-); ^{31}P NMR (122 MHz, CD_3CN , 298 K): δ -144.9 (septet, $^1J = 710$ Hz, PF_6^-); ESI-MS: +ve $[M]^{2+}$ 320.19, $[M \cdot PF_6]$ 785.34; HR-MS: +ve $[M \cdot PF_6]$ 785.2653, expected $[C_{36}H_{36}F_6N_{10}O_2P]^+$ 785.2659



3-Pyridinium bis-triazolium tetracationic macrocycle, **73**

Macrocycle **71** (60 mg, 0.065 mmol) was dissolved in dry nitromethane (20 ml) and trimethylloxonium tetrafluoroborate (29 mg, 3 eq) was added. The reaction mixture was stirred at room temperature under N₂ for 24 hours, then more methylating agent (3 × 3 eq) was added over 3 days. The reaction mixture was concentrated *in vacuo* before being purified by column chromatography (5:3:2 CH₃CN/H₂O/sat. KNO_{3(aq)}). The solvents were removed *in vacuo* and the remaining solid washed with sat. NH₄PF_{6(aq)} (2 ml) in H₂O (20 ml), then with H₂O (10 ml). The residue was dried under high vacuum to afford the desired product as a white solid (24 mg, 0.019 mmol, 30%).

¹H NMR (500 MHz, CD₃CN, 293 K): δ 9.10 (2H, s, PyrH), 8.97 (2H, d, ³*J* = 5.9 Hz, PyrH), 8.73 (2H, s, TrzH), 8.70 (2H, d, ³*J* = 8.3 Hz, PyrH), 8.31 (2H, dd, ³*J* = 5.9 & 8.3 Hz, PyrH), 8.19 (1H, s, IsoH), 7.91 (2H, dd, ³*J* = 8.0 Hz & ⁴*J* = 2.0 Hz, IsoH), 7.59 (1H, t, ³*J* = 8.0 Hz, IsoH), 7.56 (4H, s, ArH), 7.35 (2H, br, NH), 5.87 (4H, s, ArCH₂Trz), 4.70 (4H, t, ³*J* = 7.0 Hz, PyrCH₂R), 4.22 (6H, s, TrzCH₃), 3.50–3.42 (4H, m, NHCH₂R), 2.35–2.26 (4H, m, RCH₂R'); ¹⁹F NMR (282 MHz, CD₃CN, 298 K): δ –72.9 (d, ¹*J* = 710 Hz, PF₆[–]); ³¹P NMR (122 MHz, CD₃CN, 298 K): δ –145.0 (septet, ¹*J* = 710 Hz, PF₆[–]); HR-MS: +ve [M · 3 PF₆] 1105.2374, expected [C₃₈H₄₂F₁₈N₁₀O₂P₃]⁺ 1105.2418

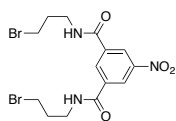


Pyridyl 3,5-amide bis-bromide derivative, **76**

Pyridine-3,5-dicarboxylic acid (2.0 g, 12 mmol) was added to thionyl chloride (20 ml) and refluxed under N₂ for 24 hours. The excess thionyl chloride was removed *in vacuo* to afford reactive bis-acid chloride **74** as an off-white solid, which was dried under high vacuum. 3-Bromopropylamine hydrobromide (4.94 g, 2 eq) and bis-acid chloride **74** (2.3 g, 11 mmol) were suspended in dry DCM (100 ml) and the mixture was cooled to 0°C. Dry Et₃N (9.4 ml, 60 mmol) was then added to the suspension, and allowed to stir at room temperature under N₂ for 2 hours. The solution was then washed with 10% HCl_(aq) (2 × 100 ml), followed by

neutralisation with sat. $\text{Na}_2\text{CO}_{3(\text{aq})}$. The resultant precipitate was filtered and washed with H_2O (5×20 ml), then dried under high vacuum to yield the desired product as a pale yellow solid (2.9 g, 7.2 mmol, 81%).

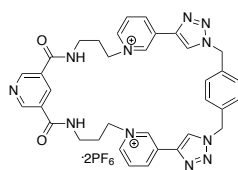
^1H NMR (500 MHz, CDCl_3 , 293 K): δ 9.14 (2H, d, $^4J = 2.4$ Hz, IsoH), 8.49 (1H, t, $^4J = 2.4$ Hz, IsoH), 6.63 (2H, br, NH), 3.66 (4H, q, $^3J = 6.4$ Hz, NHCH_2R), 3.50 (4H, t, $^3J = 6.4$ Hz, BrCH_2R), 2.22 (4H, qn, $^3J = 6.4$ Hz, $\text{RCH}_2\text{R}'$); ^{13}C NMR (75 MHz, $\text{DMSO}-d_6$, 298 K): δ 164.2, 150.3, 134.0, 129.6, 37.9, 32.4, 32.1; FI-MS: +ve [M] 406.95



5-Nitro isophthalamide bis-bromide derivative, **77**

5-Nitroisophthalic acid (3.0 g, 14 mmol) was added to thionyl chloride (20 ml) and refluxed under N_2 for 24 hours. The excess solvent was removed *in vacuo* followed by DCM (2×30 ml) washes. This was then dried under high vacuum to afford bis-acid chloride **75** as an off-white solid. 3-Bromopropylamine hydrobromide (6.02 g, 2 eq) and bis-acid chloride **75** (3.41 g, 13.8 mmol) were suspended in dry DCM (100 ml) at 0°C , followed by addition of dry Et_3N (10 ml). The reaction mixture was allowed to warm to room temperature over 2 hours under N_2 before being washed with 10% $\text{HCl}_{(\text{aq})}$ (2×100 ml), sat. $\text{NaHCO}_{3(\text{aq})}$ (2×100 ml) and H_2O (2×100 ml). The precipitate in the organic layer was filtered off and dried under high vacuum. The organic layer was dried over MgSO_4 and solvent removed *in vacuo* to produce a yellow solid. This was then recrystallised from 1:1 hot CHCl_3 /hexane (100 ml). Filtering and combining with the original precipitate afforded the desired product as a white solid (4.80 g, 10.6 mmol, 80%).

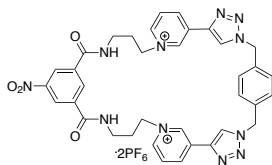
^1H NMR (500 MHz, CDCl_3 , 293 K): δ 8.76 (2H, d, $^4J = 2.0$ Hz, IsoH), 8.55 (1H, t, $^4J = 2.0$ Hz, IsoH), 6.63 (2H, br, NH), 3.70 (4H, q, $^3J = 6.4$ Hz, NHCH_2R), 3.52 (4H, t, $^3J = 6.4$ Hz, BrCH_2R), 2.26 (4H, qn, $^3J = 6.4$ Hz, $\text{RCH}_2\text{R}'$); ^{13}C NMR (75 MHz, acetone- d_6 , 298 K): δ 165.1, 149.2, 137.6, 132.8, 125.0, 39.5, 33.5, 32.1; FI-MS: +ve [M] 450.97



3-Pyridinium dicationic pyridyl macrocycle, **78**

Compound **76** (41 mg, 0.10 mmol) and 3-pyridine triazole **69** (39 mg, 0.10 mmol) were suspended in dry CH₃CN (20 ml) in a microwave vial. The reaction was heated in a microwave at 165°C for 90 minutes. The solvent was then removed *in vacuo* and the residue was triturated with H₂O (10 ml). The resulting suspension was filtered. The filtrate was washed with DCM (20 ml), then sat. NH₄PF₆(aq) was added dropwise to yield a precipitate from the aqueous fractions. This was filtered and dried under high vacuum to yield the desired product as an off-white solid (10 mg, 0.011 mmol, 11%).

¹H NMR (500 MHz, acetone-*d*₆, 293 K): δ 9.68 (2H, s, PyrH), 9.19 (2H, d, ³*J* = 6.0 Hz, PyrH), 9.09 (2H, d, ³*J* = 8.3 Hz, PyrH), 9.07 (2H, d, ⁴*J* = 1.8 Hz, IsoH), 8.82 (2H, s, TrzH), 8.45 (1H, t, ⁴*J* = 1.8 Hz, IsoH), 8.37 (2H, dd, ³*J* = 6.0 & 8.3 Hz, PyrH), 8.28 (2H, br, NH), 7.54 (4H, s, ArH), 5.84 (4H, s, ArCH₂Trz), 5.04 (4H, t, ³*J* = 6.8 Hz, PyrCH₂R), 3.65 (4H, q, ³*J* = 6.8 Hz, NHCH₂R), 2.55 (4H, qn, ³*J* = 6.8 Hz, RCH₂R'); ¹³C NMR (75 MHz, acetone-*d*₆, 298 K): δ 165.8, 151.2, 144.1, 142.6, 141.7, 141.6, 139.4, 136.6, 132.7, 130.2, 129.6, 124.5, 60.9, 54.2, 36.9, 31.6; ¹⁹F NMR (282 MHz, acetone-*d*₆, 298 K): δ -73.3 (d, ¹*J* = 710 Hz, PF₆⁻); ³¹P NMR (122 MHz, acetone-*d*₆, 298 K): δ -144.1 (septet, ¹*J* = 710 Hz, PF₆⁻); HR-MS: +ve [M · PF₆] 786.2591, expected [C₃₅H₃₅F₆N₁₁O₂P]⁺ 786.2612

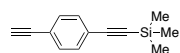


3-Pyridinium dicationic nitro macrocycle, **79**

Compound **77** (69 mg, 0.15 mmol) and 3-pyridine triazole **69** (60 mg, 0.15 mmol) were suspended in dry, degassed DMF (20 ml) in a microwave vial. The reaction was heated in a microwave at 165°C for 90 minutes. The solvent was then removed *in vacuo* and the residue

was triturated with H₂O (10 ml). The resulting suspension was filtered. The filtrate was washed with DCM (20 ml), then sat. NH₄PF_{6(aq)} was added dropwise to yield a precipitate from the aqueous fractions. This was filtered and dried under high vacuum to yield the desired product as an off-white solid (11 mg, 0.011 mmol, 7%).

¹H NMR (500 MHz, acetone-*d*₆, 293 K): δ 9.68 (2H, s, PyH), 9.20 (2H, d, ³*J* = 6.4 Hz, PyrH), 9.12 (2H, d, ³*J* = 8.3 Hz, PyrH), 8.81 (2H, s, TrzH), 8.76 (2H, d, ⁴*J* = 1.5 Hz, IsoH), 8.66 (1H, t, ⁴*J* = 1.5 Hz, IsoH), 8.51 (2H, br, NH), 8.17 (2H, dd, ³*J* = 6.4 & 8.3 Hz, PyrH), 7.28 (4H, s, ArH), 5.60 (4H, s, ArCH₂Trz), 4.82 (4H, t, ³*J* = 7.4 Hz, PyrCH₂R), 3.45 (4H, q, ³*J* = 5.9 Hz, NHCH₂R), 2.33 (4H, qn, ³*J* = 6.8 Hz, RCH₂R'); ¹³C NMR (75 MHz, acetone-*d*₆, 298 K): δ 164.6, 143.4, 141.7, 141.6, 136.4, 135.9, 135.9, 132.1, 131.8, 128.9, 128.7, 124.3, 123.8, 53.4, 36.5, 31.0, 27.9; ¹⁹F NMR (282 MHz, acetone-*d*₆, 298 K): δ -72.4 (d, ¹*J* = 710 Hz, PF₆⁻); ³¹P NMR (122 MHz, acetone-*d*₆, 298 K): δ -144.7 (septet, ¹*J* = 710 Hz, PF₆⁻); HR-MS: +ve [M · PF₆] 830.2507, expected [C₃₆H₃₅F₆N₁₁O₄P]⁺ 830.2515

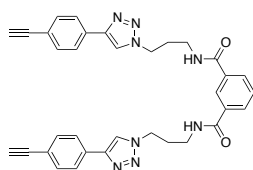


Monoprotected dialkyne linker, **81**⁴⁰⁴

Magnesium turnings (209 mg, 1.2 eq) were heated under N₂ in a round-bottomed flask to remove H₂O then allowed to cool before adding bromoethane (0.59 ml, 7.94 mmol), iodine (5 mg, *cat.*) and dry THF (8 ml). This was then heated to effervescence and stirred for 3 hours at room temperature under N₂. The whole was cooled to -78°C and a solution of 1,4-diethynylbenzene (1.00 g, 7.94 mmol) in dry THF (10 ml) was carefully added whilst stirring. The Grignard mixture was stirred for 2 hours under N₂ then allowed to warm to 0°C, after which a solution of trimethylsilyl chloride (1.01 ml, 7.94 mmol) in dry THF (10 ml) was added dropwise. The reaction mixture was then stirred for 2 days at room temperature under N₂ before being neutralised with 10% HCl_(aq). H₂O (30 ml) was then added and the product was extracted into DCM (3 × 50 ml), dried over MgSO₄ and the solvent removed *in vacuo* to afford a pale yellow solid. This was sublimed (50°C, N_{2(l)} condenser, *in vacuo*) to remove the starting material, then recrystallised with hot EtOH (2 ml) and 1 drop of 1 M HCl_(aq) to

yield the desired product as a yellow solid (880 mg, 4.44 mmol, 56%).

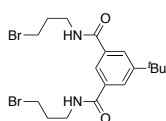
^1H NMR (300 MHz, CDCl_3 , 298 K): δ 7.45 (4H, s, ArH), 3.18 (1H, s, $\text{C}\equiv\text{CH}$), 0.08 (9H, s, SiCH_3); ^{13}C NMR (75 MHz, CDCl_3 , 298 K): δ 132.1, 132.0, 123.8, 122.3, 104.5, 96.7, 83.4, 79.2, 1.0; FI-MS: $[\text{M}^+]$ 198.10; the characterisation data correspond well with those published.⁴⁰⁴



Isophthalamide ditriazole alkyne derivative, **82**

Diazide **4** (140 mg, 0.424 mmol) and mono-protected dialkyne **81** (168 mg, 2 eq) were dissolved in dry DCM (100 ml). $[\text{Cu}^{\text{I}}(\text{CH}_3\text{CN})_4]\text{PF}_6$ (15 mg, 0.1 eq), TBTA (21 mg, 0.1 eq) and DIPEA (220 μl , 3 eq) were added and the reaction mixture was stirred for 3 days at room temperature under N_2 . The reaction mixture was then washed with 1 M $\text{HCl}_{(\text{aq})}$ (100 ml), sat. $\text{NaHCO}_{3(\text{aq})}$ (150 ml) and H_2O (100 ml), dried over MgSO_4 , and the solvent removed *in vacuo* to produce the trimethylsilyl-protected intermediate as a pale yellow solid (204 mg, 0.281 mmol, 66%). This was then dissolved in DCM (40 ml) and TBAF [1 M solution in THF] (826 μl , 3 eq) was added. The reaction mixture was stirred for 20 minutes under N_2 , then washed with H_2O (3×50 ml). The white precipitate was filtered and dried under high vacuum to afford the desired product as a white solid (130 mg, 0.223 mmol, 53% overall).

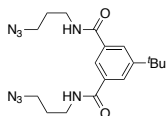
^1H NMR (300 MHz, $\text{DMSO}-d_6$, 298 K): δ 8.70 (2H, br, NH), 8.68 (2H, s, TrzH), 8.31 (1H, t, $^4J = 1.8$ Hz, IsoH), 7.96 (2H, dd, $^3J = 7.6$ Hz, $^4J = 1.8$ Hz, IsoH), 7.85 (4H, d, $^3J = 8.2$ Hz, ArH), 7.55 (4H, d, $^3J = 8.2$ Hz, ArH), 7.54 (1H, t, $^3J = 7.6$ Hz, IsoH), 4.49 (4H, t, $^3J = 7.0$ Hz, ArCH_2Trz), 4.25 (2H, s, $\text{C}\equiv\text{CH}$), 3.39–3.31 (4H, m, NHCH_2R), 2.24–2.20 (4H, m, $^3J = 6.4$ Hz, $\text{RCH}_2\text{R}'$); HR-MS: +ve $[\text{M}+\text{Na}]$ 605.2372, expected $[\text{C}_{34}\text{H}_{30}\text{N}_8\text{NaO}_2]^+$ 605.2389



5-*t*Butyl isophthalamide bis-bromide derivative, **57**

5-*t*Butylisophthalic acid (2.00 g, 9.01 mmol) was added to thionyl chloride (20 ml) and pyridine (1 drop, *cat.*) and refluxed under N₂ for 24 hours. Excess thionyl chloride was removed *in vacuo*, followed by drying the residue under high vacuum to afford reactive bis-acid chloride **83** as an off-white solid. 3-Bromopropylamine hydrobromide (3.65 g, 2 eq) and bis-acid chloride **74** (2.10 g, 8.11 mmol) were suspended in dry DCM (100 ml) at 0°C. Dry Et₃N (5.7 ml, 5 eq) was added and the reaction mixture stirred for 30 minutes at room temperature under N₂. The solution was washed with 1 M HCl_(aq) (2 × 50 ml), sat. NaHCO_{3(aq)} (2 × 50 ml) and H₂O (2 × 50 ml), then dried over MgSO₄ before removing the solvent *in vacuo* to afford the desired product as a pale yellow crystalline solid (2.52 g, 5.45 mmol, 67%).

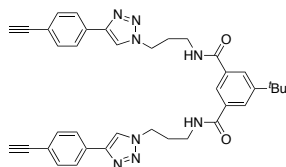
¹H NMR (300 MHz, CDCl₃, 298 K): δ 7.95 (3H, br, IsoH), 6.63 (2H, br, NH), 3.62 (4H, q, ³J = 6.4 Hz, NHCH₂R), 3.50 (4H, t, ³J = 6.4 Hz, BrCH₂R), 2.22 (4H, qn, ³J = 6.4 Hz, RCH₂R'), 1.35 (9H, s, *t*Bu); ¹³C NMR (75, CDCl₃, 298 K): δ 168.4, 153.5, 135.0, 127.7, 124.1, 38.6, 35.1, 34.9, 32.2, 30.9; ESI-MS: +ve [M+Na] 485.04



5-*t*Butyl isophthalamide bis-azide derivative, **84**

Dibromide **57** (1.0 g, 2.2 mmol) was dissolved in dry, degassed DMF (70 ml) and sodium azide (421 mg, 3 eq) was added. The reaction was heated to 90°C under N₂ overnight, then the solvent removed *in vacuo*. The oily residue was washed with H₂O (20 ml) before extracting the product into DCM (3 × 20 ml). The organic phase was dried over MgSO₄, filtered and the solvent removed *in vacuo* with no heating to afford the desired product as a pale yellow solid (810 mg, 2.1 mmol, 95%).

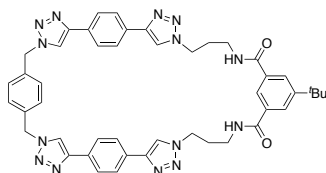
¹H NMR (300 MHz, CDCl₃, 298 K): δ 7.97 (3H, br, IsoH), 6.69 (2H, br, NH), 3.61–3.53 (4H, m, NHCH₂R), 3.46 (4H, t, ³J = 6.8 Hz, RCH₂N₃), 1.93 (4H, qn, ³J = 6.8 Hz, RCH₂R'), 1.37 (9H, s, *t*Bu); ¹³C NMR (75 MHz, CDCl₃, 298 K): δ 167.4, 152.5, 134.4, 127.3, 124.0, 49.4, 37.8, 35.0, 31.1, 28.7; ESI-MS: +ve [M+Na] 409.19



5-*t*-Butyl isophthalamide ditriazole alkyne derivative, **86**

t-Butyl diazide **84** (400 mg, 1.04 mmol) and mono-protected dialkyne **81** (412 mg, 2 eq) were dissolved in dry DCM (70 ml). $[\text{Cu}^{\text{I}}(\text{CH}_3\text{CN})_4]\text{PF}_6$ (37 mg, 0.1 eq), TBTA (53 mg, 0.1 eq) and DIPEA (540 μl , 3 eq) were then added and the reaction mixture stirred for 3 days at room temperature under N_2 . This was then washed with 1 M $\text{HCl}_{(\text{aq})}$ (100 ml), sat. $\text{NaHCO}_{3(\text{aq})}$ (150 ml) and H_2O (100 ml), dried over MgSO_4 , and the solvent removed *in vacuo*. The resulting pale yellow solid was purified by column chromatography (7% MeOH/DCM) to form the trimethylsilyl-protected intermediate (305 mg, 0.39 mmol). A solution of KOH pellets (203 mg, 3.8 mmol) in MeOH (10 ml) was added to a solution of this trimethylsilyl-protected intermediate in DCM (30 ml). The reaction mixture was stirred under N_2 overnight and then washed with H_2O (2×50 ml). The organic layer was dried over MgSO_4 and the solvent removed *in vacuo* to afford the desired product as a pale yellow solid (258 mg, 0.406 mmol, 39%).

^1H NMR (500 MHz, CDCl_3 , 293 K): δ 7.98 (2H, d, $^4J = 1.8$ Hz, IsoH), 7.90 (2H, s, TrzH), 7.59 (4H, d, $^3J = 8.0$ Hz, ArH), 7.52 (1H, t, $^4J = 1.8$ Hz, IsoH), 7.47 (4H, d, $^3J = 8.0$ Hz, ArH), 4.62 (4H, t, $^3J = 6.8$ Hz, ArCH_2Trz), 3.73–3.65 (4H, m, NHCH_2R), 3.13 (2H, s, $\text{C}\equiv\text{CH}$), 2.39–2.35 (4H, m, $\text{RCH}_2\text{R}'$), 1.32 (9H, s, *t*Bu); HR-MS: +ve $[\text{M}+\text{Na}]$ 661.3012, expected $[\text{C}_{38}\text{H}_{38}\text{N}_8\text{NaO}_2]^+$ 661.3015

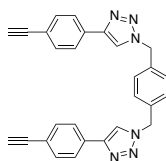


Tetratriazole *t*butyl-isophthalamide macrocycle, **85**

Dialkyne **86** (130 mg, 0.204 mmol), $[\text{Cu}^{\text{I}}(\text{CH}_3\text{CN})_4]\text{PF}_6$ (22.4 mg, 0.3 eq), TBTA (32 mg,

0.3 eq) and TBACl (54 mg, 0.204 mmol) were dissolved in dry DCM (200 ml) and DIPEA (106 μ l, 3 eq) was added. Diazide **68** (38.3 mg, 0.204 mmol) was dissolved in dry DCM (100 ml) and added to the reaction mixture dropwise over 2 hours. This was stirred for 5 days under N₂, forming a precipitate. This was then filtered off and washed with DCM (2 $\times$ 20 ml), before drying under high vacuum to afford the desired product as a pale yellow solid (13.4 mg, 0.016 mmol, 8%).

¹H NMR (300 MHz, DMSO-*d*₆): δ 8.65 (2H, br, NH), 8.63 (2H, s, TrzH), 8.53 (2H, s, TrzH), 7.98 (1H, t, ⁴*J* = 1.8 Hz, IsoH), 7.89 (2H, d, ⁴*J* = 1.8 Hz, IsoH), 7.85 (8H, s, ArH), 7.43 (4H, s, ArH), 5.66 (4H, s, ArCH₂Trz), 4.46 (4H, t, ³*J* = 7.0 Hz, TrzCH₂R), 3.49–3.41 (4H, m, NHCH₂R), 2.14–2.08 (4H, m, RCH₂R'), 1.34 (9H, s, ^{*t*}Bu); ¹³C NMR (75 MHz, DMSO-*d*₆): δ 166.3, 151.1, 145.5, 134.4, 132.3, 131.2, 127.7, 126.6, 125.2, 123.8, 122.1, 120.9, 83.4, 81.4, 47.7, 36.7, 34.8, 31.0, 29.8; ESI-MS: +ve [M+H] 827.44; –ve [M+Cl] 871.39; HR-MS: +ve [M+Na] 849.3816, expected [C₄₆H₄₆N₁₄NaO₂]⁺ 849.3826



Xylene ditriazole alkyne derivative, **87**

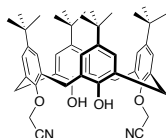
Diazide **68** (128 mg, 0.68 mmol) and mono-protected dialkyne **81** (270 mg, 2 eq) were dissolved in dry DCM and [Cu^I(CH₃CN)₄]PF₆ (51 mg, 0.1 eq), TBTA (72 mg, 0.1 eq) and DIPEA (365 μ l, 3 eq) were added. The reaction mixture was stirred for 3 days at room temperature under N₂ and was washed with 1 M HCl_(aq) (3 $\times$ 50 ml), sat. NaHCO_{3(aq)} (3 $\times$ 50 ml) and H₂O (3 $\times$ 50 ml). The organic phase was dried over MgSO₄ and the solvent removed *in vacuo*. The yellow solid was purified by column chromatography (2% MeOH/DCM) to afford the trimethylsilyl-protected intermediate as a pale yellow solid (258 mg, 0.441 mmol, 65%). A solution of KOH (302 mg, 15 eq) in MeOH (10 ml) was added to a solution of this trimethylsilyl intermediate (210 mg, 0.359 mmol) in DCM (25 ml). The reaction mixture was stirred under N₂ for 4 hours, forming a precipitate. This was filtered off, washed with H₂O (2

× 20 ml) and dried under high vacuum to afford the desired product as a white solid (112 mg, 0.329 mmol, 86%).

^1H NMR (300 MHz, CDCl_3 , 298 K): δ 7.77 (4H, d, $^3J = 8.8$ Hz, ArH), 7.70 (2H, s, TrzH), 7.53 (4H, d, $^3J = 8.8$ Hz, ArH), 7.35 (4H, s, ArH), 5.60 (4H, s, ArCH_2Trz), 4.25 (2H, s, $\text{C}\equiv\text{CH}$); ^{13}C NMR (75 MHz, $\text{DMSO}-d_6$): δ 145.9, 135.9, 132.3, 131.0, 128.4, 125.3, 122.2, 121.0, 83.4, 81.5, 52.7; ESI-MS: +ve $[\text{M}+\text{H}]$ 441.20; HR-MS: +ve $[\text{M}+\text{Na}]$ 363.1656, expected $[\text{C}_{28}\text{H}_{20}\text{N}_6\text{Na}]^+$ 363.1647

6.5.3 Chapter 4

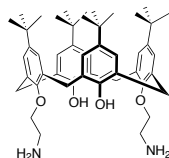
The following procedures are from Chapter 4.



Calix[4]arene 1,3-dinitrile, **90**⁴³²

To a solution of 4-*t*butylcalix[4]arene (4.00 g, 6.17 mmol) in dry acetone (200 ml) was added K_2CO_3 (1.87 g, 2.2 eq). The mixture was stirred at room temperature under N_2 for 4 hours. Bromoacetonitrile (1.85 g, 2 eq) was then added and the reaction mixture stirred under N_2 for a further 4 days. TLC showed some mononitrile impurity, so further bromoacetonitrile (0.5 eq) was added and the reaction mixture stirred under N_2 for 24 hours. The reaction mixture was then filtered and the solvent removed from the filtrate *in vacuo*. This residue was dissolved in DCM (250 ml), washed with dilute $\text{HCl}_{(\text{aq})}$ (250 ml) and H_2O (2×100 ml), dried over MgSO_4 and the solvent removed *in vacuo*. The residue was purified by column chromatography (0–2% MeOH/DCM) and the solvent removed *in vacuo* to produce a white solid (3.29 g). This was then recrystallised from $\text{CHCl}_3/\text{MeOH}$ and the pure product was filtered off as a white crystalline solid (2.75 g, 3.79 mmol, 61%).

TLC: 1% MeOH/DCM, R_f 0.16; 30% EtOAc/Hex, R_f 0.57; m.p.: *dec.* 235°C; ^1H NMR (300 MHz, CDCl_3 , 298 K): δ 7.13 (4H, s, ArH), 6.74 (4H, s, ArH), 5.58 (2H, s, OH), 4.82 (4H, s, OCH_2CN), 4.24 (4H, d, $^2J = 13.5$ Hz AB, calix CH_2 calix), 3.46 (4H, d, $^2J = 13.5$ Hz AB, calix CH_2 calix), 1.34 (18H, s, ^tBu), 0.89 (18H, s, ^tBu); ^{13}C NMR (75 MHz, CDCl_3 , 298 K): δ 150.0, 148.8, 148.7, 142.6, 131.9, 127.9, 126.3, 125.4, 115.2, 60.5, 34.1, 31.8, 31.7, 31.0; ESI-MS: +ve $[\text{M}+\text{Na}]$ 749.45; –ve $[\text{M}-\text{H}]$ 725.44, $[\text{M}+\text{Cl}]$ 761.41; HR-MS: +ve $[\text{M}+\text{Na}]$ 749.4280, expected $[\text{C}_{48}\text{H}_{58}\text{N}_2\text{NaO}_4]^+$ 749.4289; the characterisation data correspond well with those previously established.⁴³²

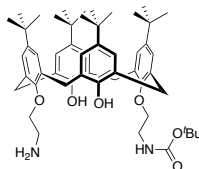


Calix[4]arene 1,3-diamine, **91** adapted from 432

A slurry of lithium aluminium hydride (940 mg, 30 eq) in dry Et_2O (150 ml) was stirred vigorously in an ice bath for 1 hour. To this was added **90** (600 mg, 0.826 mmol) and the reaction mixture was then refluxed under N_2 for 6 hours. The reaction mixture was cooled in an ice bath and $\text{Na}_2\text{SO}_4 \cdot 10 \text{H}_2\text{O}$ (12 g, 4 eq *versus* lithium aluminium hydride) was carefully added to quench excess lithium aluminium hydride. After stirring at room temperature for 1 hour a thick white precipitate had formed, which was then filtered off. The solvent was carefully removed *in vacuo* from the filtrate to afford the desired product as an off-white foamy solid (585 mg, 0.797 mmol, 96%).

m.p.: *dec.* 122°C; ^1H NMR (300 MHz, CDCl_3 , 298 K): δ 7.05 (4H, s, ArH), 6.99 (4H, s, ArH), 4.34 (4H, d, $^2J = 12.9$ Hz AB, calix CH_2 calix), 4.09 (4H, t, $^3J = 4.8$ Hz, OCH_2R), 3.38 (4H, d, $^2J = 12.9$ Hz AB, calix CH_2 calix), 3.32 (4H, t, $^3J = 4.8$ Hz, RCH_2NH_2), 1.26 (18H, s, ^tBu), 1.12 (18H, s, ^tBu); ^{13}C NMR (75 MHz, CDCl_3 , 298 K): δ 150.3, 149.1, 147.5, 142.0, 133.2, 127.6, 125.8, 125.4, 78.7, 42.7, 34.1, 33.8, 32.2, 31.6, 31.5, 31.1; ESI-MS: +ve $[\text{M}+\text{H}]$ 735.5, $[\text{M}+\text{Na}]$ 757.5; –ve $[\text{M}-\text{H}]$ 733.5; HR-MS: +ve $[\text{M}+\text{H}]$ 735.5071, expected

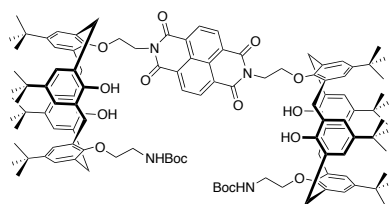
$[\text{C}_{48}\text{H}_{67}\text{N}_2\text{O}_4]^+$ 735.5095; the characterisation data correspond well with those previously established.⁴³²



Calix[4]arene amine boc-protected, **92**

To a solution of diamine **91** (400 mg, 0.545 mmol) in dry 1,4-dioxane (80 ml) was added a solution of di-*t*butyl dicarbonate (48.0 mg, 0.4 eq) in dry 1,4-dioxane (20 ml). The reaction mixture was stirred at room temperature under N_2 overnight. The solvent was removed *in vacuo* and the residue dissolved in DCM (100 ml). To this was added H_2O (100 ml) and the product was further extracted into the organic layer using DCM (4×100 ml). The combined organics were dried over MgSO_4 and the solvent removed *in vacuo* to produce a sticky colourless solid (360 mg). The residue was purified by column chromatography (0–5% MeOH/DCM). The solvent was then removed *in vacuo* to afford the desired mono-protected product as an off-white foamy solid (233 mg, 0.279 mmol, 63%).

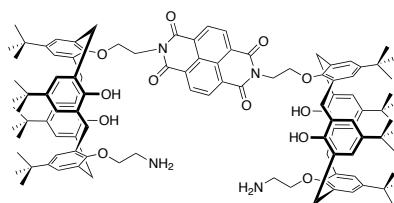
TLC: 5% MeOH/DCM, R_f 0.30; m.p.: 109–112°C; ^1H NMR (300 MHz, CDCl_3 , 298 K): δ 7.06–7.04 (8H, m, ArH), 4.37–4.24 (4H, m, calix CH_2 calix), 4.12 (4H, t, $^3J = 4.5$ Hz, OCH_2R), 3.79 (2H, br, $\text{RCH}_2\text{NHR}'$), 3.72 (2H, s, OH), 3.43 (2H, br, $\text{RCH}_2\text{NHR}'$) 3.39–3.36 (4H, m, calix CH_2 calix), 1.49 (9H, s, *t*Bu), 1.26 (18H, s, *t*Bu), 1.17 (9H, s, *t*Bu), 1.16 (9H, s, *t*Bu); ^{13}C NMR (75 MHz, CDCl_3 , 298 K): δ 150.2, 148.9, 148.8, 147.9, 147.7, 142.2, 133.4, 133.1, 127.5, 127.4, 126.1, 126.0, 125.5, 125.4, 78.5, 75.4, 67.1, 53.2, 42.4, 34.2, 33.8, 32.3, 31.6, 31.5, 31.2, 28.5; ESI-MS: +ve $[\text{M}+\text{H}]$ 835.52, $[\text{M}+\text{Na}]$ 857.53; –ve $[\text{M}-\text{H}]$ 833.56; HR-MS: +ve $[\text{M}+\text{H}]$ 835.5598, expected $[\text{C}_{53}\text{H}_{75}\text{N}_2\text{O}_6]^+$ 835.5620



NDI dicalix[4]arene boc-protected, **93**

Mono-protected **92** (178 mg, 2.2 eq) and 1,4,5,8-naphthalenetetracarboxylic dianhydride (26 mg, 0.097 mmol) were suspended in 10:1 *iso*-propanol/Et₃N (11 ml) in a 20 ml microwave vial. The reaction was heated in a microwave at 150°C for 90 minutes, then the solvent was removed *in vacuo*. The residue was purified by column chromatography (0–30% EtOAc/hexane). The solvent was removed from the orange band *in vacuo* to afford the product as an orange-red solid (82 mg, 0.043 mmol, 44%).

¹H NMR (300 MHz, CDCl₃, 298 K): δ 8.79 (4H, s, NDI-H), 7.51 (4H, br, OH), 7.02–6.81 (16H, m, ArH), 4.91 (4H, br, OCH₂R), 4.33–4.21 (12H, m, calixCH₂calix & OCH₂R), 4.13 (4H, br, RCH₂NHR'), 3.85 (4H, br, RCH₂NHR'), 3.37–3.22 (8H, m, calixCH₂calix), 1.40 (18H, s, ^tBu), 1.24 (36H, s, ^tBu), 1.00 (18H, s, ^tBu), 0.96 (18H, s, ^tBu); ¹³C NMR (75 MHz, CDCl₃, 298 K): δ 162.9, 150.5, 149.5, 149.2, 147.4, 147.3, 141.7, 132.8, 132.6, 131.2, 127.8, 127.6, 126.8, 126.6, 125.8, 125.3, 125.1, 79.2, 75.7, 34.1, 34.0, 33.8, 32.0, 31.8, 31.2, 31.1, 28.5; ESI-MS: +ve [M+Na] 1924.9; -ve [M–H] 1900.9; HR-MS: +ve [M+Na] 1925.0102, expected [C₁₂₀H₁₄₈N₄NaO₁₆]⁺ 1925.0816

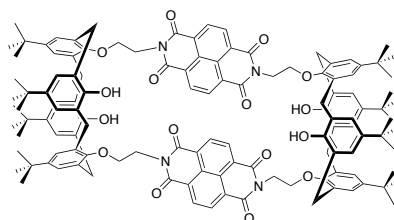


NDI dicalix[4]arene amine, **94**

Trifluoroacetic acid (5 ml) was carefully added to a solution of protected **93** (97 mg, 0.052 mmol) in dry DCM. The reaction mixture was stirred at room temperature under N₂ for 6 hours. The solvents were then carefully removed *in vacuo* to afford the ditrifluoroacetic

acid salt of the desired product as a red solid (100 mg, 0.052 mmol, 100%).

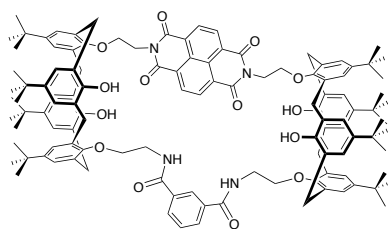
m.p.: *dec.* 212°C; ^1H NMR (300 MHz, CDCl_3 , 298 K): δ 8.84 (4H, s, NDI-H), 8.41 (6H, br, NH_3^+), 8.08 (4H, br, OH), 7.04–6.89 (16H, m, ArH), 4.87 (4H, br, $\text{RCH}_2\text{NH}_3^+$), 4.49–4.42 (4H, m, OCH_2R), 4.10 (8H, d, $^2J = 12.9$ Hz, calix CH_2 calix), 3.48 (4H, d, $^2J = 13.5$ Hz, OCH_2R), 3.30 (4H, d, $^2J = 12.9$ Hz, RCH_2NDI), 2.92 (8H, d, $^2J = 13.5$ Hz AB, calix CH_2 calix), 1.22 (36H, s, ^tBu), 1.07 (18H, s, ^tBu), 1.02 (18H, s, ^tBu); ^{13}C NMR (75 MHz, CDCl_3 , 298 K): δ 163.5, 149.5, 149.4, 148.7, 148.0, 147.8, 143.0, 132.7, 132.4, 131.6, 127.8, 127.2, 126.9, 126.5, 126.3, 126.1, 125.7, 125.5, 53.5, 34.3, 34.2, 34.0, 32.3, 31.7, 31.1; ESI-MS: +ve $[\text{M}+2\text{H}]^{2+}$ 851.8, $[\text{M}+\text{H}]$ 1702.8; HR-MS: +ve $[\text{M}+\text{H}]$ 1702.9277, expected $[\text{C}_{110}\text{H}_{133}\text{N}_4\text{O}_{12}]^+$ 1702.9948



Bis-NDI dicalix[4]arene macrocycle, **88**

Diamine **94** (340 mg, 0.176 mmol) and 1,4,5,8-naphthalenetetracarboxylic dianhydride (47.2 mg, 1 eq) were suspended in *iso*-propanol (750 ml) and Et_3N (17 ml). The reaction mixture was refluxed under N_2 for 4 days, with the orange colour deepening after 24 hours. The solvent was then removed *in vacuo* and the product purified by recrystallisation from $\text{CHCl}_3/\text{MeOH}$ at -32°C over 3 days. The desired product was then filtered off as a pale pink/orange solid (95 mg, 0.049 mmol, 28%).

m.p.: *dec.* 190°C; ^1H NMR (300 MHz, CDCl_3 , 298 K): δ 8.85 (8H, s, NDI-H), 7.05 (8H, s, ArH), 6.61 (8H, s, ArH), 6.23 (4H, s, OH), 4.25 (8H, d, $^2J = 12.9$ Hz AB, calix CH_2 calix), 4.07 (8H, br, NCH_2R), 3.95 (8H, br, OCH_2R), 3.27 (8H, d, $^2J = 12.9$ Hz, calix CH_2 calix), 1.31 (36H, s, ^tBu), 0.82 (36H, s, ^tBu); ^{13}C NMR (125 MHz, CDCl_3 , cryoprobe): δ 162.8, 150.8, 150.1, 147.0, 141.5, 132.0, 131.8, 128.0, 126.6, 125.6, 125.2, 70.9, 39.2, 34.0, 32.0, 31.5, 31.1, 29.9; MALDI-MS: +ve $[\text{M}]$ 1933.97, $[\text{M}+\text{Na}]$ 1956.52



NDI isophthalamide dicalix[4]arene macrocycle, **89**

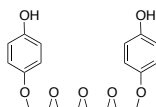
Diamine **94** (100 mg, 0.052 mmol) was dissolved in DCM (50 ml) and isophthaloyl dichloride (10.5 mg, 0.052 mmol) was separately dissolved in DCM (50 ml). Under N₂, these two solutions were added dropwise over 1 hour to a solution of Et₃N (0.5 ml) in DCM (100 ml) over an ice bath. The reaction mixture was then allowed to warm to room temperature and was stirred under N₂ overnight. The solvent was removed *in vacuo*, followed by column chromatography (0–4% MeOH/DCM), but this failed to purify the product. The mixture was purified by preparative thin layer chromatography (5% MeOH/DCM) and the major orange band was collected, affording the desired macrocycle product as an orange solid (42 mg, 0.023 mmol, 44%).

m.p.: *dec.* 220°C; ¹H NMR (300 MHz, CDCl₃, 298 K): δ 8.36 (4H, s, NDI-H), 8.19 (1H, d, ⁴*J* = 1.5 Hz, IsoH), 7.80 (2H, br, CONH), 7.69 (2H, dd, ³*J* = 8.1 Hz & ⁴*J* = 1.5 Hz, IsoH), 7.01–6.97 (9H, m, ArH & IsoH), 6.76 (4H, s, OH), 6.74 (4H, s, ArH), 6.65 (4H, s, ArH), 4.86 (4H, t, ³*J* = 7.8 Hz, NCH₂R), 4.50 (4H, t, ³*J* = 7.8 Hz, NCH₂R), 4.44 (4H, d, ²*J* = 12.9 Hz AB, calixCH₂calix), 4.09 (4H, d, ²*J* = 13.2 Hz AB, calixCH₂calix), 4.04 (4H, br, OCH₂R), 3.76–3.70 (4H, m, OCH₂R), 3.31 (4H, d, ²*J* = 13.2 Hz AB, calixCH₂calix), 3.23 (4H, d, ²*J* = 12.9 Hz AB, calixCH₂calix), 1.25 (36H, s, ^{*t*}Bu), 0.92 (18H, s, ^{*t*}Bu), 0.84 (18H, s, ^{*t*}Bu); ¹³C NMR (75 MHz, CDCl₃, 298 K): δ 165.7, 163.6, 150.9, 150.3, 148.7, 147.6, 146.9, 142.0, 133.4, 132.6, 132.2, 130.5, 129.7, 128.8, 127.8, 126.5, 125.9, 125.7, 125.2, 77.4, 75.0, 73.8, 58.6, 41.3, 40.4, 34.1, 34.0, 31.9, 31.6, 31.2, 31.1; ESI-MS: –ve [M–H] 1830.9; HR-MS: –ve [M–H] 1830.9489, expected [C₁₁₈H₁₃₃N₄O₁₄][–] 1830.9857



Polyether ditosylate, **101**

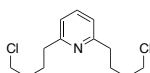
Kindly donated by Dr Alex Leontiev.



Hydroquinone glycol, **100**

1,4-Hydroquinone (11.0 g, 10 eq), ditosylate **101** (5.02 g, 10.0 mmol) and K_2CO_3 (3.04 g, 2.2 eq) were dissolved in EtOH (200 ml). The reaction mixture was refluxed under N_2 overnight. The solvent was removed *in vacuo*, then the residue dissolved in H_2O (250 ml) and acidified with 10% $\text{HCl}_{(\text{aq})}$ (100 ml). This was then extracted with CHCl_3 (2×400 ml), with the combined organics dried over MgSO_4 , then the solvents removed *in vacuo*. The crude residue was purified by column chromatography (2:1 DCM/ Et_2O) to afford the desired product as a yellow oil (1.51 g, 4.00 mmol, 40%).

TLC: 2:1 DCM/ Et_2O , R_f 0.38; ESI-MS: +ve $[\text{M}+\text{Na}]$ 401.18; –ve $[\text{M}-\text{H}]$ 377.18, $[\text{M}+\text{Cl}]$ 413.16; the characterisation data correspond well with those previously established.⁴⁵⁰



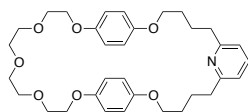
Pyridine dichloride derivative, **99**

Freshly dried 2,6-lutidine (1.0 ml, 8.60 mmol) and tetramethylethylenediamine (3.1 ml, 2.4 eq) were added to dry THF (10 ml) under N_2 and cooled over a $\text{CO}_2(\text{s})$ /acetone bath. To this was carefully added $n\text{BuLi}$ [1.6 M in hexanes] (20 ml, 3.6 eq) and the deep orange mixture was gradually allowed to warm to room temperature under N_2 .

1-Bromo-3-chloropropane (17 ml, 20 eq) was added to dry THF (30 ml) under N_2 and cooled over a $\text{CO}_2(\text{s})$ /acetone bath. To this was carefully added the lithiated solution through a cannula by positive N_2 pressure. The reaction mixture was allowed to warm to room temperature, then stirred for 3 days under N_2 .

H₂O (50 ml) was carefully added to quench the reaction mixture. The THF was then removed *in vacuo* and the crude product extracted from the aqueous component with hexanes (3 × 200 ml). The combined organics were dried over MgSO₄, then the solvent removed *in vacuo*. The resultant crude orange oil was first purified by silica plug to remove any excess 1-bromo-3-chloropropane (60–80°C petrol). The silica was then extracted with acetone to elute the product, which was further purified by column chromatography (0–50% EtOAc/60–80°C petrol, then acetone). The solvents were removed *in vacuo* to afford the pure product as a yellow oil (760 mg, 2.92 mmol, 34%).

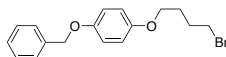
TLC: 10% EtOAc/hexane, R_f 0.18; ^1H NMR (300 MHz, CDCl_3 , 298 K): δ 7.51 (1H, t, $^3J = 7.8$ Hz, PyrH), 6.97 (2H, d, $^3J = 7.8$ Hz, PyrH), 3.57 (4H, t, $^3J = 6.0$ Hz, RCH_2Cl), 2.79 (4H, t, $^3J = 7.2$ Hz, PyrCH_2R), 1.93–1.78 (8H, m, $\text{RCH}_2\text{R}'$); ^{13}C NMR (75 MHz, CDCl_3 , 298 K): δ 161.0, 136.6, 119.9, 44.9, 37.5, 32.2, 27.2; ESI-MS: +ve $[\text{M}+\text{H}]$ 260.13

Pyridine hydroquinone polyether macrocycle, **97**

100 (50 mg, 0.13 mmol) was dissolved in dry, degassed DMF (70 ml). To this was added Cs₂CO₃ (86 mg, 2 eq), then a solution of dichloride **99** (34 mg, 0.13 mmol) in dry DMF (5 ml). The resulting suspension was stirred at 100°C under N₂ for 3 days. The reaction mixture was allowed to cool to room temperature with solvent then removed *in vacuo*. The residue was redissolved in CHCl₃ (200 ml), then washed with H₂O (3 × 100 ml) and brine (100 ml). The combined organics were dried over MgSO₄ and the solvent removed *in vacuo*. The crude residue was purified by column chromatography (0–8% MeOH/DCM) to isolate an impure macrocycle as an off-white solid (28 mg, 0.050 mmol, 38%).

TLC: 5% MeOH/DCM, R_f 0.54; ^1H NMR (300 MHz, CDCl_3 , 298 K): δ 7.49 (1H, t, $^3J = 7.8$ Hz, PyrH), 6.96 (2H, d, $^3J = 7.8$ Hz, PyrH), 6.82–6.68 (8H, m, HqH), 4.12–4.08 (4H, m, OCH_2R), 4.02–3.98 (4H, m, PyrCH_2R), 3.83–3.54 (12H, m, polyglycol), 2.83 (4H, t, $^3J = 6.9$ Hz, $\text{RCH}_2\text{R}'$), 1.93 (4H, qn, $^3J = 7.8$ Hz, $\text{RCH}_2\text{R}'$), 1.74 (4H, qn, $^3J = 7.8$ Hz, $\text{RCH}_2\text{R}'$);

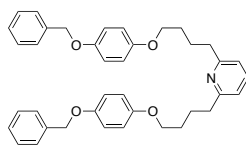
^{13}C NMR (75 MHz, CD_3OD , 298 K): δ 153.7, 152.6, 116.9, 71.8, 71.7, 71.1, 69.5; ESI-MS: +ve $[\text{M}+\text{H}]$ 566.33, $[\text{M}+\text{Na}]$ 588.31, $[\text{M}+\text{K}]$ 604.33; –ve $[\text{M}-\text{H}]$ 564.33, $[\text{M}+\text{Cl}]$ 600.31; HR-MS: +ve $[\text{M}+\text{H}]$ 566.3094, expected $[\text{C}_{33}\text{H}_{44}\text{NO}_7]^+$ 566.3112



Benzyl hydroquinone bromide derivative, **102** adapted from 440

1,4-Dibromobutane (12 ml, 2 eq) and K_2CO_3 (10.4 g, 1.4 eq) were added to dry DMF (50 ml) at room temperature. A solution of 4-benzyloxyphenol (10.0 g, 50.0 mmol) in dry DMF (20 ml) was added dropwise. The resulting suspension was stirred under N_2 at room temperature for 2 hours, then at 75°C for a further 2 hours. The reaction mixture was allowed to cool to room temperature, then was filtered and washed with EtOAc (2×50 ml). The combined organics were washed with H_2O (4×300 ml), with NaCl added to improve separation. The organics were then dried over MgSO_4 and the solvents removed *in vacuo*. The crude product was purified by column chromatography (DCM), with the first few fractions being the desired product. The solvents were removed *in vacuo*, with heating required to remove excess 1,4-dibromobutane. The resulting yellow oil was dried under high vacuum, sonicated with hexane for 30 minutes, then triturated 3 times with hexane to wash away the remaining 1,4-dibromobutane. The pure product was isolated as a crystalline white solid (5.06 g, 15.1 mmol, 30%).

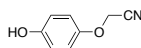
TLC: DCM, R_f 0.85; m.p.: $69-70^\circ\text{C}$; ^1H NMR (300 MHz, CDCl_3 , 298 K): δ 7.46–7.33 (5H, m, ArH), 6.91 (2H, d, $^3J = 9.3$ Hz, HqH), 6.83 (2H, d, $^3J = 9.3$ Hz, HqH), 5.02 (2H, s, OCH_2Ph), 3.95 (2H, t, $^3J = 6.0$ Hz, OCH_2R), 3.50 (2H, t, $^3J = 6.6$ Hz, RCH_2Br), 2.12–2.03 (2H, m, $\text{RCH}_2\text{R}'$), 1.97–1.88 (2H, m, $\text{RCH}_2\text{R}'$); ^{13}C NMR (75 MHz, CDCl_3 , 298 K): δ 153.2, 153.0, 137.2, 128.5, 127.9, 127.5, 115.8, 115.3, 110.0, 70.7, 67.4, 33.5, 29.5, 28.0; ESI-MS: +ve $[\text{M}+\text{Na}]$ 357.08 & 359.08



Pyridine hydroquinone benzyl derivative, **103**

Zinc dust (429 mg, 3.3 eq) and iodine (56 mg, 0.11 eq) were stirred in dry, degassed DMF (10 ml) under N₂ until the solution had decolourised. Bromide **102** (1.47 g, 2.2 eq) was added and the mixture stirred at 80°C overnight under N₂. After cooling to room temperature, to this was added 2,6-dibromopyridine (474 mg, 2.00 mmol) and Pd(PPh₃)₄ (46 mg, 2 mol%) under N₂. The reaction mixture was then stirred at room temperature under N₂ for 7 days. 25% NH₄OH_(aq) (100 ml) and EtOAc (100 ml) were added and the mixture stirred vigorously for 2 hours. This was then separated and the combined organics washed with H₂O (100 ml) and brine (100 ml), then dried over MgSO₄. The solvents were removed *in vacuo* to afford a yellow oil that solidified at room temperature. The crude product was purified by column chromatography (0–2% MeOH/DCM), the solvent was removed *in vacuo* and recrystallisation from ⁱPr₂O afforded the pure product as a white solid (448 mg, 0.763 mmol, 38%).

TLC: 2% MeOH/DCM, R_f 0.95; m.p.: 71–73°C; ¹H NMR (300 MHz, CDCl₃, 298 K): δ 7.48–7.36 (13H, m, ArH & PyrH), 6.97–6.86 (8H, m, HqH), 5.05 (4H, s, OCH₂Ph), 3.95 (4H, t, ³J = 6.6 Hz, OCH₂R), 1.84–1.74 (4H, m, RCH₂R'), 1.62–1.47 (4H, m, RCH₂R'), 1.02 (4H, t, ³J = 7.5 Hz, PyrCH₂R'); ¹³C NMR (75 MHz, CDCl₃, 298 K): δ 153.5, 152.8, 137.3, 128.5, 127.8, 127.4, 116.9, 115.7, 115.5, 115.3, 70.6, 68.2, 67.8, 33.7, 31.4; ESI-MS: +ve [M+Na] 610.32; –ve [M+Cl] 622.29; HR-MS: +ve [M+H] 588.3109, expected [C₃₉H₄₂NO₄]⁺ 588.3108

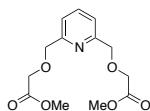


Hydroquinone nitrile, **104**⁴⁴¹

A 1:1 solution of 1,4-dioxane/H₂O (300 ml) was purged with N₂ for 1 hour. To this was added NaOH (3.2 g, 2 eq) and hydroquinone (4.40 g, 40.0 mmol). This was purged for a further hour. Bromoacetonitrile (2.79 ml, 40 mmol) was then added and the reaction mixture stirred at room temperature under N₂ for 1 hour. 10% HCl_(aq) (25 ml) was added to neutralise the

reaction mixture, which was then extracted with DCM (3×250 ml). The combined organics were dried over MgSO_4 and the solvent removed *in vacuo* to produce a yellow oil (7.43 g). This was purified by column chromatography (1–2% MeOH/DCM), then dried under high vacuum to afford the desired mono-reacted product as an off-white solid (2.69 g, 18.1 mmol, 45%).

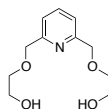
TLC: 2% MeOH/DCM, R_f 0.37; ^1H NMR (300 MHz, $\text{DMSO}-d_6$, 298 K): δ 6.91 (2H, d, $^3J = 9.3$ Hz, ArH), 6.82 (2H, d, $^3J = 9.3$ Hz, ArH), 4.78 (1H, s, ArOH), 4.72 (2H, s, ArCH_2CN); ^{13}C NMR (75 MHz, CDCl_3 , 298 K): δ 165.6, 151.5, 150.7, 117.0, 116.4, 55.0; ESI-MS: –ve $[\text{M}-\text{H}]$ 148.04; the characterisation data correspond well with those published.⁴⁴¹



Pyridine glycol ester, **105** adapted from 443,451

2,6-Dimethanolpyridine (4.17 g, 30.0 mmol) was suspended in dry THF (150 ml) at 0°C . To this was carefully added NaH [60% dispersion in mineral oil] (4.80 g, 4 eq) and the grey suspension was stirred at room temperature under N_2 for 1 hour. A solution of methyl bromoacetate (11.2 ml, 4 eq) in dry THF (50 ml) was added dropwise and the reaction mixture was then stirred at room temperature under N_2 overnight. The reaction was cooled to 0°C and quenched with H_2O (25 ml). The THF was removed *in vacuo* and the aqueous fraction then extracted with EtOAc (4×70 ml). The combined organics were dried over MgSO_4 and the solvent removed *in vacuo*. The residue was purified by column chromatography (5–20% acetone/ CHCl_3) to afford the desired product as an off-white solid (6.54 g, 23.1 mmol, 77%).

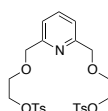
^1H NMR (300 MHz, $\text{DMSO}-d_6$, 298 K): δ 7.75 (1H, t, $^3J = 7.8$ Hz, PyrH), 7.42 (2H, d, $^3J = 7.8$ Hz, PyrH), 4.74 (4H, s, $\text{OCH}_2\text{CO}_2\text{R}$), 4.23 (4H, s, PyrCH_2O), 3.78 (6H, s, RCO_2CH_3); ^{13}C NMR (75 MHz, CDCl_3 , 298 K): δ 170.5, 156.9, 137.5, 120.6, 74.1, 67.9, 51.9; ESI-MS: +ve $[\text{M}+\text{H}]$ 284.09, $[\text{M}+\text{Na}]$ 306.09; the characterisation data correspond well with those published.⁴⁵¹



Pyridine glycol, **106** adapted from 443,451

Diester **105** (6.54 g, 23.1 mmol) was dissolved in fresh EtOH (200 ml) at 0°C under N₂. To this was carefully added NaBH₄ (3.51 g, 4 eq) and the reaction mixture was stirred at room temperature under N₂ overnight. H₂O (150 ml) was carefully added to quench the reaction, then stirred for 1 hour. The THF and EtOH were carefully removed *in vacuo*, then the aqueous fraction concentrated to a volume of 80 ml. Hot extraction at 55°C with CHCl₃ (2 × 200 ml) retrieved the product from the aqueous layer. The combined organics were then dried over MgSO₄ and the solvent removed *in vacuo* to afford the desired product as a yellow oil (4.51 g, 19.9 mmol, 86%).

¹H NMR (300 MHz, CDCl₃, 298 K): δ 7.69 (1H, t, ³*J* = 7.8 Hz, PyrH), 7.19 (2H, d, ³*J* = 7.8 Hz, PyrH), 5.12 (2H, s, ROH), 4.72 (4H, s, PyrCH₂O), 3.84–3.75 (8H, m, OCH₂R & RCH₂OH); ¹³C NMR (75 MHz, CDCl₃, 298 K): δ 157.8, 137.6, 120.5, 73.6, 72.9, 61.7; ESI-MS: +ve [M+H] 228.14, [M+Na] 250.11; the characterisation data correspond well with those published.⁴⁵¹



Pyridine glycol tosylate, **107** adapted from 443,444

Dialcohol **106** (650 mg, 2.86 mmol) was dissolved in dry THF (10 ml). Pulverised KOH (481 mg, 3 eq) was added, followed by stirring the mixture at 0°C for 1 hour. To this was added a solution of *p*-toluenesulfonyl chloride (1.37 g, 2.5 eq). The reaction mixture was stirred at 0°C under N₂ for 5 hours, then allowed to warm to room temperature overnight, turning from orange to blue. This was filtered and the residue washed with further THF (25 ml). The filtrate was retained and the solvent removed *in vacuo*, immediately followed by purification by column chromatography (0–80% EtOAc/60–80°C petrol, then CHCl₃) to afford the desired

product as a yellow oil (613 mg, 1.15 mmol, 40%). The product decomposes rapidly, so was stored in the freezer and reacted on as soon as possible.

TLC: 80% EtOAc/60–80°C petrol, R_f 0.50; ^1H NMR (300 MHz, CDCl_3 , 298 K): δ 8.02 (1H, t, $^3J = 8.1$ Hz, PyrH), 7.47 (4H, d, $^3J = 7.8$ Hz, ArH), 7.26 (4H, d, $^3J = 7.8$ Hz, ArH), 7.12 (2H, d, $^3J = 8.1$ Hz, PyrH), 4.83 (4H, s, PyrCH₂O), 4.48 (4H, s, OCH₂R), 3.92–3.86 (4H, m, RCH₂OTs), 2.12 (6H, s, ArCH₃); ESI-MS: +ve [M+H] 536.15, [M+Na] 558.11, [M+K] 574.14; –ve [M+Cl] 570.12; the characterisation data correspond well with those published.⁴⁴⁴

Appendix: Crystallographic Data

Introduction

Single crystal X-ray structures were collected and analysis was carried out by Ben Mullaney, Nicholas White and Dr Nathan Kilah. Crystallographic data (excluding structure factors) for the published structures relating to heteroditopic macrocycle **1** and its adducts have been deposited with the Cambridge Crystallographic Data Centre; their numbers are provided at the bottom of the respective data tables.

Single crystal X-ray diffraction data were collected for **1** and [**1**·TBACl] using graphite monochromated Cu K α radiation ($\lambda = 1.5418$ Å) on an Oxford Diffraction/Agilent Technologies SuperNova diffractometer. The **66**, **61** and **72** data were collected using a graphite monochromated Mo K α radiation ($\lambda = 0.71073$ Å) on a Nonius κ CCD diffractometer. For [**1**·KCl·2.1H₂O], [**1**·NaCl·1.0(H₂O)], [**1**·NH₄Cl·4.0(H₂O)], [**1**·KBr·2.5(H₂O)] and [**72**·Cl·PF₆], data were collected using silicon double crystal monochromated synchrotron radiation ($\lambda = 0.68890$ Å) at Diamond Light Source beamline I19 on a custom built Rigaku diffractometer.³⁵² Both diffractometers were equipped with a Cryostream N₂ open-flow cooling device,⁴⁵² and the data were collected at 150(2) K or 100(2) K.

Series of ω -scans were performed to a maximum resolution of 0.77 Å. Cell refinement, data reduction, and scaling were performed using either CrysAlisPro,⁴⁵³ DENZO/SCALEPACK⁴⁵⁴ or the CrystalClear package.⁴⁵⁵ The structures were solved by direct methods using the SIR92 software,⁴⁵⁶ or by charge flipping using Superflip.⁴⁵⁷ The structures were refined using full-matrix least-squares on F² within the CRYSTALS suite.⁴⁵⁸

All non-hydrogen atoms were refined with anisotropic displacement parameters. Disordered portions were modelled using refined partial occupancies. Geometric and vibrational restraints were applied where appropriate to ensure physically reasonable models. The H atoms were usually located in the difference map, but those attached to carbon atoms were

repositioned geometrically. H atoms that could not be located in the difference map were positioned to satisfy hydrogen-bonding requirements. The H atoms were initially refined with soft restraints on the bond lengths and angles, after which the positions were refined with riding constraints. For **1**, [**1**·NaCl·1.0(H₂O)] and [**72**·Cl·PF₆] the structures contained voids, which contained diffuse electron density that could not be resolved in the difference map, and PLATON SQUEEZE^{459,460} was used to include this residual electron density in the refinement.

After the construction of a stable, chemically reasonable, and complete model, the weights were optimised,^{461–463} outlying reflections were omitted, and, in the case of poorly diffracting samples, data beyond the diffraction limit were removed using the Wilson plot as a guide. Molecular graphics were produced using X-Seed,⁴⁶⁴ and POV-RAY.⁴⁶⁵

Many of the crystals described in this thesis were small and very poorly diffracting, and often required synchrotron radiation to get diffraction to an appropriate resolution to determine the crystal structure. Synchrotron radiation or long exposure times using Cu K_α radiation were often necessary. In such cases the crystals still demonstrated weak diffraction, and the use of high-intensity radiation led to degradation of the crystal integrity, and often resulted in incomplete datasets. Significant numbers of restraints and/or PLATON SQUEEZE were often necessary for a sensible refinement. Bond distances should not be treated as absolute, but the structures still provide a good guide to the molecular architecture.

Complete data, including particular refinement details where appropriate, are presented in CIF format on the accompanying CD.

Data tables

The following data tables provide selected crystallographic data for solid-state crystal structures for the following:

- (i) heteroditopic receptor **1** and its complexes with various salts;
- (ii) imidazole-benzyl-chloride **61**;
- (iii) the HBr salt of dibromoethyl pyridine (**66**);
- (iv) 4-isomer dicationic macrocycle **72** as the NaPF_6 adduct and its PF_6Cl salt.

The following data tables are from Chapter 2.

Compound	1	[1·2TBACl]
Moiety Formula	C ₅₆ H ₅₈ N ₈ O ₈ , C ₂ H ₃ N	C ₅₆ H ₅₈ N ₈ O ₈ , 2(C ₁₆ H ₃₆ N), 2(Cl), H ₂ O
F_w	1012.15	1544.94
Crystal size /mm ³	0.13 × 0.07 × 0.03	0.12 × 0.08 × 0.04
Crystal system	Triclinic	Triclinic
Space group	$P\bar{1}$	$P\bar{1}$
a /Å	11.1540(4)	11.6490(7)
b /Å	11.4113(5)	11.7443(15)
c /Å	22.3139(11)	34.272(2)
α /°	82.085(4)	93.318(8)
β /°	80.852(4)	93.295(6)
γ /°	80.783(3)	106.527(9)
V /Å ³	2749.4(2)	4474.1(7)
Z	2	2
T /K	150(2)	150(2)
Radiation type	Cu K $_{\alpha}$	Cu K $_{\alpha}$
λ /Å	1.5418	1.5418
μ /mm ⁻¹	0.672	1.115
$F(000)$	1072	1672
θ /°	3.94 to 76.59	3.89 to 78.13
Index ranges	-13 ≤ h ≤ 14 -14 ≤ k ≤ 14 -27 ≤ l ≤ 28	-14 ≤ h ≤ 14 -14 ≤ k ≤ 14 -42 ≤ l ≤ 43
Reflections collected	27850	46284
Independent reflections (R_{int})	11390 (0.040)	18572 (0.055)
Data/restraints/parameters	7902/78/784	11766/286/1054
GOF on F^2	0.9747	1.0551
R_1 ($I > 2\sigma(I)$) ^[a]	0.0798	0.1050
wR_2 ($I > 2\sigma(I)$) ^[b]	0.2121	0.2786
R_1 (all data)	0.0951	0.1250
wR_2 (all data)	0.2252	0.3002
CCDC number	863826	863827

Table 1 Data tables for crystals of **[1]** and **[1·2TBACl]**. [a] $R_1 = \Sigma ||F_o| - |F_c|| / \Sigma |F_o|$. [b] $wR_2 = [\Sigma w(F_o^2 - F_c^2)^2 / \Sigma w(F_o^2)^2]^{1/2}$

Compound	[1·KCl]	[1·NaCl]
Moiety Formula	C ₅₆ H ₅₈ N ₈ O ₈ , 0.9(C ₂ H ₃ N), Cl, K, 2.1(H ₂ O)	C ₅₆ H ₅₈ N ₈ O ₈ , Cl, Na, H ₂ O
F_w	1120.45	1047.58
Crystal size /mm ³	0.12 × 0.09 × 0.04	0.11 × 0.08 × 0.05
Crystal system	Triclinic	Triclinic
Space group	$P\bar{1}$	$P\bar{1}$
a /Å	10.9706(9)	9.8189(7)
b /Å	16.6835(12)	11.2637(8)
c /Å	17.2797(14)	28.516(2)
α /°	75.623(7)	93.974(6)
β /°	76.566(7)	99.267(6)
γ /°	80.903(6)	112.061(7)
V /Å ³	2962.8(4)	2855.6(4)
Z	2	2
T /K	100(2)	100(2)
Radiation type	Synchrotron	Synchrotron
λ /Å	0.6889	0.6889
μ /mm ⁻¹	0.198	0.135
$F(000)$	1181	1104
θ /°	1.86 to 32.19	2.74 to 31.8
Index ranges	−16 ≤ h ≤ 16 −25 ≤ k ≤ 21 −25 ≤ l ≤ 25	−14 ≤ h ≤ 14 −16 ≤ k ≤ 16 −41 ≤ l ≤ 42
Reflections collected	38271	34807
Independent reflections (R_{int})	18510 (0.123)	17071 (0.150)
Data/restraints/parameters	8326/0/721	8142/65/730
GOF on F^2	0.9786	0.9639
R_1 ($I > 2\sigma(I)$) ^[a]	0.0745	0.0860
wR_2 ($I > 2\sigma(I)$) ^[b]	0.1696	0.2025
R_1 (all data)	0.1085	0.1289
wR_2 (all data)	0.2160	0.2427
CCDC number	863828	863829

Table 2 Data tables for crystals of [1·KCl] and [1·NaCl]. [a] $R_1 = \Sigma ||F_o| - |F_c|| / \Sigma |F_o|$. [b] $wR_2 = [\Sigma w(F_o^2 - F_c^2)^2 / \Sigma w(F_o^2)^2]^{1/2}$

Compound	[1·NH ₄ Cl]	[1·KBr]
Moiety Formula	C ₅₆ H ₅₈ N ₈ O ₈ , H ₄ N, 4(H ₂ O), Cl	C ₅₆ H ₅₈ N ₈ O ₈ , K, Br, 2.5H ₂ O
F_w	1096.68	1134.56
Crystal size /mm ³	0.09 × 0.08 × 0.05	0.10 × 0.06 × 0.03
Crystal system	Monoclinic	Monoclinic
Space group	$P2_1/c$	$P2_1/c$
a /Å	10.7718(11)	10.647(10)
b /Å	19.4091(17)	18.819(16)
c /Å	29.808(3)	29.61(3)
α /°	90	90
β /°	99.140(10)	99.415(8)
γ /°	90	90
V /Å ³	6152.9(10)	5853(9)
Z	4	4
T /K	100(2)	100(2)
Radiation type	Synchrotron	Synchrotron
λ /Å	0.6889	0.6889
μ /mm ⁻¹	0.126	0.836
$F(000)$	2328	2372
θ /°	1.68 to 31.85	1.35 to 32.25
Index ranges	−16 ≤ h ≤ 15 −29 ≤ k ≤ 28 −44 ≤ l ≤ 43	−16 ≤ h ≤ 15 −27 ≤ k ≤ 21 −42 ≤ l ≤ 41
Reflections collected	86625	46321
Independent reflections (R_{int})	20848 (0.346)	19530 (0.284)
Data/restraints/parameters	6422/395/793	5324/819/694
GOF on F^2	0.9969	0.9906
R_1 ($I > 2\sigma(I)$) ^[a]	0.1418	0.1996
wR_2 ($I > 2\sigma(I)$) ^[b]	0.2524	0.3188
R_1 (all data)	0.1955	0.2350
wR_2 (all data)	0.2897	0.3331
CCDC number	863830	863831

Table 3 Data tables for crystals of [1·NH₄Cl] and [1·KBr]. [a] $R_1 = \Sigma ||F_o| - |F_c|| / \Sigma |F_o|$. [b] $wR_2 = [\Sigma w(F_o^2 - F_c^2)^2 / \Sigma w(F_o^2)^2]^{1/2}$

The following data tables are from Chapter 3.

Compound	61
Moiety Formula	C ₉ H ₇ ClN ₂
F_w	178.62
Crystal size /mm ³	0.7 × 0.4 × 0.3
Crystal system	Monoclinic
Space group	$P2_1/c$
a /Å	7.9602(3)
b /Å	11.2584(4)
c /Å	9.1566(2)
α /°	90
β /°	98.2739(19)
γ /°	90
V /Å ³	812.07(5)
Z	4
T /K	150(2)
Radiation type	Mo
λ /Å	0.71073
μ /mm ⁻¹	0.406
$F(000)$	368
θ /°	5.153 to 27.459
Index ranges	−10 ≤ h ≤ 10 −14 ≤ k ≤ 14 −11 ≤ l ≤ 11
Reflections collected	3247
Independent reflections (R_{int})	1851 (0.020)
Data/restraints/parameters	1657/0/109
GOF on F^2	0.9353
R_1 ($I > 2\sigma(I)$) ^[a]	0.0327
wR_2 ($I > 2\sigma(I)$) ^[b]	0.0718
R_1 (all data)	0.0428
wR_2 (all data)	0.0812
CCDC number	—

Table 4 Data tables for crystals of **61**. [a] $R_1 = \Sigma ||F_o| - |F_c|| / \Sigma |F_o|$. [b] $wR_2 = [\Sigma w(F_o^2 - F_c^2)^2 / \Sigma w(F_o^2)^2]^{1/2}$

Compound	66
Moiety Formula	C ₇ H ₈ Br ₂ N, Br
F_w	345.86
Crystal size /mm ³	0.42 × 0.18 × 0.14
Crystal system	Monoclinic
Space group	$C2/c$
a /Å	11.7750(5)
b /Å	12.7134(6)
c /Å	14.6654(7)
α /°	90
β /°	102.849(2)
γ /°	90
V /Å ³	2143.47(17)
Z	8
T /K	150(2)
Radiation type	Mo
λ /Å	0.71073
μ /mm ⁻¹	11.236
$F(000)$	1296
θ /°	5.12 to 27.49
Index ranges	−15 ≤ h ≤ 15 −15 ≤ k ≤ 16 −19 ≤ l ≤ 19
Reflections collected	9370
Independent reflections (R_{int})	2444 (0.053)
Data/restraints/parameters	2444/0/100
GOF on F^2	0.9446
R_1 (I>2σ(I)) ^[a]	0.0551
wR_2 (I>2σ(I)) ^[b]	0.1170
R_1 (all data)	0.0795
wR_2 (all data)	0.1412
CCDC number	—

Table 5 Data tables for crystals of **66**. [a] $R_1 = \Sigma ||F_o| - |F_c|| / \Sigma |F_o|$. [b] $wR_2 = [\Sigma w(F_o^2 - F_c^2)^2 / \Sigma w(F_o^2)^2]^{1/2}$

Compound	[72 ·NaPF ₆]	[72 ·Cl·PF ₆]
Moiety Formula	C ₃₆ H ₃₆ N ₁₀ O ₂ , C ₃ H ₆ O, 3 (F ₆ P), H ₂ O, Na	C ₃₆ H ₃₆ N ₁₀ O ₂ , Cl, F ₆ P, C ₂ H ₃ N
F_w	1174.72	862.21
Crystal size /mm ³	0.26 × 0.16 × 0.06	0.10 × 0.10 × 0.02
Crystal system	Monoclinic	Monoclinic
Space group	$P2_1/n$	$P2_1/c$
a /Å	12.30760(10)	19.300(12)
b /Å	24.8161(2)	7.641(5)
c /Å	16.1088(2)	56.63(3)
α /°	90	90
β /°	99.5597(3)	94.865(9)
γ /°	90	90
V /Å ³	4851.73(8)	8322(9)
Z	4	8
T /K	150(2)	150(2)
Radiation type	Mo	Synchrotron
λ /Å	0.71073	0.6889
μ /mm ⁻¹	0.254	0.206
$F(000)$	2392	3568
θ /°	5.11 to 27.48	1.06 to 32.99
Index ranges	−15 ≤ h ≤ 15 −32 ≤ k ≤ 32 −20 ≤ l ≤ 20	−29 ≤ h ≤ 29 −11 ≤ k ≤ 11 −83 ≤ l ≤ 83
Reflections collected	88072	80160
Independent reflections (R_{int})	11023 (0.030)	28990 (0.214)
Data/restraints/parameters	6921/0/676	11654/1146/1126
GOF on F^2	0.9146	0.8915
R_1 ($I > 2\sigma(I)$) ^[a]	0.0891	0.1501
wR_2 ($I > 2\sigma(I)$) ^[b]	0.2106	0.3327
R_1 (all data)	0.1227	0.1789
wR_2 (all data)	0.2351	0.3667
CCDC number	—	—

Table 6 Data tables for crystals of [**72**·NaPF₆] and [**72**·Cl·PF₆]. [a] $R_1 = \Sigma ||F_o| - |F_c|| / \Sigma |F_o|$.
[b] $wR_2 = [\Sigma w(F_o^2 - F_c^2)^2 / \Sigma w(F_o^2)^2]^{1/2}$

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