Metal-Based Function in [2]Rotaxanes: from Molecular-Level Motion to Dipolar Interactions

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To my Family, Friends and Partner
Chapter One: Rotaxanes: from Synthetic Challenge to Smart Materials

1.1 Introduction .................................................................................................... 2
1.2 Synthetic Approaches to Rotaxanes ............................................................... 4
  1.2.1 Hydrophobic Interactions ...................................................................... 5
  1.2.2 π-π Interactions ..................................................................................... 6
  1.2.3 Hydrogen Bonding Interactions ............................................................ 7
    1.2.3.1 Ammonium-Crown-Ether-Based Rotaxanes .................................... 7
    1.2.3.2 Amide-Based Rotaxanes .............................................................. 8
    1.2.3.3 Anion-Based Rotaxanes .............................................................. 9
  1.2.4 Transition Metal-Based Rotaxanes ....................................................... 10
    1.2.4.1 Passive Metal Templates ............................................................. 10
    1.2.4.2 Active Metal Templates .............................................................. 12
    1.2.4.3 Metal as Structural Features ........................................................ 13
1.3 Molecular Shuttles ........................................................................................ 15
  1.3.1 Degenerate Molecular Shuttles ............................................................. 16
  1.3.2 Stimuli-Responsive Molecular Shuttles ............................................... 19
    1.3.2.1 Shuttling through pH Changes ..................................................... 20
    1.3.2.2 Shuttling through Redox Processes ............................................. 21
    1.3.2.3 Shuttling through Addition or Removal of Metal Ions ................. 24
    1.3.2.4 Shuttling through Photochemical and Thermal Stimuli ............... 25
    1.3.2.5 Shuttling through Covalent Bond Formation .............................. 26
1.4 Exploiting Shuttling Motion to Trigger Physical Property Changes .............. 27
1.5 Conclusions and Perspectives ..................................................................... 32
Chapter Two: Complexation-Induced Translational Isomerism: Shuttling through Stepwise Competitive Binding

Synopsis

2.1 Introduction

2.2 Results and Discussion

2.3 Conclusion

2.4 Experimental Section

2.5 References and Notes

Chapter Three: An AllostERICALLY Regulated Molecular Shuttle

Synopsis

3.1 Introduction

3.2 Results and Discussion

3.3 Conclusion

3.4 Experimental Section

3.5 References and Notes

Chapter Four: A Metal-Complex-Tolerant CuAAC “Click” Protocol Exemplified through the Preparation of Homo- and Mixed-Metal-Coordinated Rotaxanes

Synopsis

4.1 Introduction

4.2 Results and Discussion

4.3 Conclusion

4.4 Experimental Section

4.5 References and Notes
Abstract

This Thesis explores the utilisation of transition metal ions in functional interlocked architectures to provoke large-amplitude changes and to prepare model systems for the investigation of dipolar interactions.

Two novel mechanisms for inducing shuttling in hydrogen-bond assembled architectures have been developed. In the first example, a metal chelating group is attached to the preferred binding site for a benzylic amide macrocycle via a methylene spacer within a two-station rotaxane. Metal ion complexation followed by deprotonation of the carboxamide nitrogen nearest the chelate group results in simultaneous binding of the metal ion both to the stopper and, crucially, to the high affinity station, thus inducing translocation of the macrocycle to the second binding site through competitive binding effects. In the second example, the same metal chelating group is directly attached to the high affinity station. In this architecture, simple metal complexation (Cu$^{II}$ or Cd$^{II}$) to the stopper greatly attenuates the affinity of the adjacent binding site for the macrocycle due to sterics. This allosteric effect causes the macrocycle to move to a second station, distant from metal-binding site. In both molecular shuttles, this large-amplitude motion can be reversed by removal of the metal ion. In addition, a novel strategy for the assembly of hydrogen-bonded rotaxanes containing paramagnetic species in the macrocycle and the thread using the Cu$^I$-catalysed terminal alkyne-azide cycloaddition reaction is demonstrated. As a result, a range of unique homo- and mixed- metal-coordinated rotaxanes were prepared in very good yields. These systems were then utilised to establish and investigate dipolar interactions between the two paramagnetic metal centres using continuous wave electron paramagnetic resonance. Mechanically interlocked architectures are particularly well suited to investigate this type of interactions as the two components are not covalently bound and are held together at a fixed distance. This yields structures with dipolar coupling pathways that are not dominated by the normally predominant through-bond interactions. The new synthetic strategy was then extended to synthesise rotaxanes with octamethylferrocene stoppers and metal-containing macrocycles. These systems were used to investigate and quantify the effects of dipolar interactions on the redox behaviour of the octamethylferrocene unit via cyclic and square-wave voltammetry measurements.
Declaration

The scientific work described in this thesis was carried out in the School of Chemistry at the University of Edinburgh between September 2004 and September 2007. Unless otherwise stated, it is the work of the author and has not been submitted in whole or in support of an application for another degree or qualification of this or any other University or institute of learning.

Signed ................................

Date ..........AUGUST 2008.............
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### List of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tr>
<td>Å</td>
<td>Angstrom</td>
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<tr>
<td>A</td>
<td>Hyperfine constant</td>
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<td>aq</td>
<td>Aqueous</td>
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<tr>
<td>δ</td>
<td>Chemical shift</td>
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<tr>
<td>Boc</td>
<td>tert-Butyloxycarbonyl</td>
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<tr>
<td>BPA</td>
<td>Bis(2-picoly)amine</td>
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<tr>
<td>br</td>
<td>Broad</td>
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<td>Cald</td>
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<td>cat.</td>
<td>Catalytic amount</td>
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<td>CV</td>
<td>Cyclic voltammetry</td>
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<td>CuAAC</td>
<td>Cu¹-catalysed terminal alkyne-azide cycloaddition</td>
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<td>d</td>
<td>Doublet</td>
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<tr>
<td>decomp.</td>
<td>Decomposes</td>
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<tr>
<td>DIPEA</td>
<td>N,N-Disopropylethylamine</td>
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<tr>
<td>DMAP</td>
<td>4-(Dimethylamino)pyridine</td>
</tr>
<tr>
<td>DMF</td>
<td>N,N-Dimethylformamide</td>
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<tr>
<td>DMSO</td>
<td>Dimethyl sulfoxide</td>
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<tr>
<td>E</td>
<td>Trans isomer</td>
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<tr>
<td>EDCI·HCl</td>
<td>1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride</td>
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<td>EDTA</td>
<td>Ethylenediamine tetraacetic acid</td>
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<tr>
<td>EI</td>
<td>Electron impact</td>
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<tr>
<td>EPR</td>
<td>Electron paramagnetic resonance</td>
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<td>equiv.</td>
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<tr>
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<td>Et₃N</td>
<td>Triethylamine</td>
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<td>FAB</td>
<td>Fast atom bombardment</td>
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<td>Ferrocene</td>
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<tr>
<td>HRMS</td>
<td>High resolution mass spectrometry</td>
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</table>
IR  Infrared
J   Coupling constant
LRMS Low resolution mass spectrometry
m   Multiplet
mac Macrocycle
Me  Methyl
mg  Milligram
MHz Mega hertz
min Minutes
mL  Millilitres
mmol Millimoles
mp  Melting point
MS  Mass spectrometry
m/z Mass-to-charge ratio
NMR Nuclear magnetic resonance
3-NOBA 3-Nitrobenzyl alcohol
Ph Phenyl
ppm Parts per million
q   Quartet
quant. Quantitative
quint. Quintet
RT Room temperature
s   Singlet
SWV Square-wave voltammetry
TEMPO 2,2,6,6-Tetramethylpiperidine-1-oxyl
THF Tetrahydrofuran
TFA Trifluoroacetic acid
TLC Thin layer chromatography
TM  Transition metal
VT  Variable temperature
Z   Cis isomer
ZFS Zero-field splitting
General Comments on Experimental Data

Prior to use, isophthaloyl dichloride was purified by recrystallisation from hexane; p-xylylenediamine was purified by distillation under reduced pressure; triethylamine was dried by distillation from calcium hydride, then stored over 4 Å molecular sieves. Chloroform (CHCl₃) and tetrahydrofuran (THF) solvents were analytical grade, without stabilizer; dry acetonitrile, chloroform, dichloromethane, N,N-dimethylformamide (DMF), methanol, tetrahydrofuran and toluene were obtained by passing these solvents through activated alumina columns on a PureSolv™ solvent purification system (Innovative Technologies, Inc., MA). Unless stated otherwise, all other reagents were purchased from commercial sources and used without further purification. Column chromatography was carried out using Kiesegel C60 (Fisher Scientific) as the stationary phase. Preparative thin-layer chromatography (TLC) was performed on glass-backed plates pre-coated with silica 60 F254 adsorbent (20 cm × 20 cm, with concentration zone, 0.25 mm thick, Fluka) and analytical TLC was performed on aluminium-backed sheets pre-coated with silica 60 F254 adsorbent (0.25 mm thick, Merek, Germany) and visualized under UV light. Size exclusion chromatography was performed using Toyopearl HW-405 (Tosoh, Japan) with methanol/chloroform in a 1:1 v/v ratio as the eluent. Routine ¹H and ¹³C NMR spectra were recorded at 400 MHz on a Bruker AV 400 instrument. Spectra were recorded at ambient temperature, unless otherwise stated. Chemical shifts (δ) are reported in parts per million from low to high field and referenced to residual solvent. Standard abbreviations indicating multiplicity are used as follows: br s = broad, d = doublet, m = multiplet, q = quartet, quint. = quintet, s = singlet, t = triplet. In many cases [D₇]DMF was used as a solvent and the ¹H was referenced to 2.935 ppm for the downfield methyl signal. ¹³C was reference to the amide carbon triplet at 163.15. Fast atom bombardment (FAB) and electron impact (EI) mass spectrometry was carried out by the services at the University of Edinburgh.
CHAPTER ONE

Rotaxanes: from Synthetic Challenge to Smart Materials

By three methods we might learn wisdom:
first, by reflection, which is noblest;
second, by imitation, which is easiest,
and third, by experience, which is the bitterest.

K’ung Fu-tzu, Chinese philosopher (551-479 BCE)
1.1 Introduction

A molecular-level machine can be defined as a kinetically stable assembly of distinct number of components designed to perform mechanical movement as a result of an appropriate external stimulus.\textsuperscript{[1]} Examples of the utility of such machines are found in our body which, itself, can be viewed as a complex collection of molecular-level devices that power our motion, repair damage and coordinate our senses, emotions and thoughts.\textsuperscript{[2]}

Research into understanding the operational mechanisms of biological machines is exceedingly challenging and progress has been limited due to the complexity of such systems. However, the development of sophisticated techniques such as optical tweezers, probe microscopies and high resolution protein crystallography has helped to shed light on the mechanisms by which these complicated but extraordinary devices function.\textsuperscript{[3,4]} Among these examples are F\textsubscript{1}F\textsubscript{0}-ATPase, DNA and RNA polymerases and ribosomes.\textsuperscript{[2]} Using rotational motion powered by the flow of protons through the channels of the membrane-spanning F\textsubscript{0} domain, F\textsubscript{1}F\textsubscript{0}-ATPase assembles ATP from ADP and inorganic phosphate – the primary process for generating the cell’s main energy currency.\textsuperscript{[5]} Meanwhile, during protein translation, the motion of the small ribosomal subunits around the larger ribosome is utilised to assemble strands of mRNA and the compact tRNA globules.\textsuperscript{[4]}

Learning how to mimic limited aspects of biological systems such as performing work, selective catalysis, information storage, molecular recognition, large-amplitude movement and self-assembly has been a goal for many synthetic chemists, physicists and engineers worldwide, and represents an important fundamental challenge.\textsuperscript{[1]}

The challenge arises because the principals governing molecular machines are different to those working in the macroscopic world, where inertial forces dominate. This means that objects move when enough energy is given to the system and they stop when that energy is dissipated. At the molecular level, inertia is negligible.\textsuperscript{[11]}

The motion of molecular devices is governed by forces acting on the objects at a particular moment. Among these forces Brownian motion\textsuperscript{[6]} – the constant and random movement of molecules at temperatures above 0 K – dominates. Therefore, even trying to generate controlled large-amplitude motion becomes a hard task.
In 1959, at the annual meeting of the American Physical Society at the California Institute of Technology, Richard P. Feynman first proposed the concept of synthetic molecular-level machines.\(^{[7]}\) He later suggested — in his celebrated discussion of a miniature ratchet and pawl\(^{[8]}\) — a plausible mechanism to power molecular motors, where the random thermal fluctuations are rectified by imposing physical barriers.\(^{[1]}\)

Since Feynman’s proposal, two distinct strategies have been developed to synthesise tiny machines: a top-down approach and a bottom-up strategy. While physicists and engineers are tackling the problem using the former, which essentially becomes harder as devices are scaled down, chemists are better equipped for the bottom-up approach, which involves synthesising molecular components that assemble into larger functional systems.\(^{[1]}\) However, building the components of the molecular machine is only half the battle. Perhaps more challenging is making them responsive to stimuli in a controlled and useful way to ultimately create molecular-level devices.

In this field, the unique properties of mechanically-interlocked architectures make them promising precursors for the development of synthetic molecular-level machines. Figure 1.1 shows cartoon representations of different mechanically-interlocked structures. A rotaxane is a molecule in which a macrocycle is threaded onto a dumbbell-shaped molecule. Both ends of the acyclic thread have bulky groups or stoppers to prevent dissociation of the components (Figure 1.1a). A similar concept is used in catenanes, the difference being that two cyclic units are interlocked with one another (Figure 1.1b). Borromean rings consist of three rings linked to one another so that the cleavage of any one results in the disassembly of the interlocked structure (Figure 1.1c) — no two rings in the assembly are interlocked as in a catenane. Finally, a trefoil knot is the simplest prime knot with 3 crossings (Figure 1.1d).\(^{[9]}\) All these interlocked architectures are molecules and not supramolecular complexes, because to separate their components a covalent bond must be broken.\(^{[9]}\)

![Figure 1.1](image-url) Mechanically-interlocked architectures: a) rotaxane, b) catenane, c) Borromean rings, d) trefoil knot.
The mechanical bond in rotaxanes and catenanes reduces the degrees of freedom of their constituents so that the motion only needs to be controlled in a few directions in which often an extraordinary large-amplitude submolecular motion is allowed. This aspect is similar to that observed in many biological systems where motion of one unit is restricted by a track or a pore\textsuperscript{[1]} and is the main reason that these interlocked architectures are ideal precursors for the development of molecular machinery.

This thesis will focus on exploiting the unique properties of rotaxane architectures in order to explore how metal coordination in such structures may be used to affect both mechanical and metal-based properties. The remainder of this Chapter will briefly survey templating-strategies to rotaxane structures, and shuttling mechanisms promoted by different external stimuli. In addition, the use of controlled mechanical motion to induce physical property changes in solution, and at surfaces and interfaces will also be examined.

1.2 Synthetic Approaches to Rotaxanes

Early attempts at synthesising rotaxanes involved a statistical approach where the threading of the macrocycle around the axle was based purely on chance.\textsuperscript{[10]} In this way, in 1967 Harrison and Harrison reported the synthesis of the first rotaxane. In their preparation, a macrocyclic lactone was attached to a solid support (Scheme 1.1, 1) and was repeatedly treated with a solution containing decane-1,10-diol (Scheme 1.1, 2) and triphenylmethyl chloride. A total number of 70 iterations were needed to achieve a 6\% yield of rotaxane 3 (Scheme 1.1). The low yields are attributed to the entropically unfavourable threading step.\textsuperscript{[11]}

![Scheme 1.1 Harrison and Harrison's first rotaxane.\textsuperscript{[11]}](image_url)
For a long time the synthesis of rotaxanes was based on statistical approaches. However, following the advent and application of aspects of supramolecular and coordination chemistry, more efficient strategies for the synthesis of a wide variety of mechanically-interlocked molecular species were developed.\cite{1,9,12}

Noncovalent interactions can be employed to guide the assembly of the molecular components prior to or during formation of covalent bonds so that interlocked structures are generated in high yields.\cite{1,9,12} Several different approaches to efficiently template the formation of rotaxanes have been reported (Figure 1.2).

![Figure 1.2 Template methods for the synthesis of rotaxanes: a) threading followed by capping; b) threading followed by swelling; c) clipping.](image)

In the threading method (Figure 1.2a), a linear molecule is inserted through the cavity of a preformed macrocycle directed by noncovalent interactions forming a pseudorotaxane. By endcapping the thread with bulky groups, the pseudorotaxane is stoppered and a kinetically stable rotaxane is formed. Recently, a method related to threading and capping has been reported (Figure 1.2b).\cite{13} In this case a pseudorotaxane can be stoppered by rearrangement of one terminal group to enlarge its size and form a rotaxane. In the clipping method (Figure 1.2c), on the other hand, a region in a preformed dumbbell-shaped molecule is employed as a template for the formation of a macrocycle.\cite{1,9,12}

Remarkable examples using different types of noncovalent interactions for the preparation of rotaxanes will be discussed below.

### 1.2.1 Hydrophobic Interactions

In 1981, Ogino synthesised the first cyclodextrin-containing rotaxane (Scheme 1.2, 4) using hydrophobic interactions. A cyclodextrin (Scheme 1.2, 5) is a cyclic
oligosaccharide consisting of six or more α-1,4-linked D-glucopyranose units that give a rigid, well-defined cavity with a conical shape. Due to its conformation, the interior of the cavity is less hydrophilic than both ends. This aspect was utilised by Ogino to form an inclusion complex of α- and β-cyclodextrin with diamine 6, which resulted in a compound that was then stoppered with [CoCl₂en₂]Cl (en = ethylenediamine) to afford rotaxane 4 in good yields.¹⁴

Scheme 1.2 Ogino's cyclodextrin-containing rotaxane.¹⁴

From then on, Harada¹⁵ and Anderson¹⁶, in particular, have widely used hydrophobic interactions to synthesise a variety of interesting cyclodextrin-containing rotaxanes.

1.2.2 π-π Interactions

The discovery in 1987 that bisparaphenylenene-34-crown-10 was able to act as a host for paraquat provided the starting point for a wide range of template directed strategies for the synthesis of mechanically-interlocked architectures.¹⁷ The first rotaxane based on π-π stacking interactions was prepared in 1991 (Scheme 1.3).¹⁸ Treatment of an acetonitrile solution containing equimolar amounts of π-electron deficient paraquat derivative 7 and dibromide 8 with excess of π-electron donating thread 9 and AgPF₆ at room temperature for 7 days resulted in the formation of rotaxane 1₀⁴⁺ in 10% yield.¹⁸ Since then, Stoddart and co-workers have extensively used this type of π-electron donor-acceptor interaction to prepare catenanes¹⁹ and rotaxanes making them one of the most recognisable rotaxane-forming motifs in the literature.¹⁶,²⁰,²¹
1.2.3 Hydrogen Bonding Interactions

The hydrogen bond is defined as an attractive interaction between a hydrogen donor, A-H, and a hydrogen acceptor, B, where A and B are usually the highly electronegative elements N, O or F. Although the strength of these electrostatic interactions depends on the overlap and therefore proximity of the atomic orbitals of the two species, they are considered to be one of the strongest of all intermolecular forces. Hydrogen bonds also have a defined direction and tend to produce multicentric linkages – features that make these interactions very important for template-directed strategies for the synthesis of interlocked architectures.\[20\]

1.2.3.1 Ammonium-Crown-Ether-Based Rotaxanes

In 1995, Busch showed that [24]crown-8 (Scheme 1.4, 11) forms a stable hydrogen-bonded complex with alkylammonium salt 12.\[21\] The resulting compound can then be stoppered with acylating agent 13 to form rotaxane 14. Due to the solubility of 13 in neat CHCl₃ and/or H₂O, rotaxane 14 can be obtained in homogeneous (CHCl₃) or heterogeneous (CHCl₃/H₂O) solutions (Scheme 1.4). Interestingly, the yield of rotaxane 14 is two times higher in a heterogeneous solution as a consequence of the enhanced formation of the hydrogen-bonded pseudorotaxane.\[21\]
Chapter One  
Rotaxanes: from Synthetic Challenge to Smart Materials

Scheme 1.4 Busch’s ammonium-crown ether-based rotaxane.[21]

Subsequently, Stoddart and co-workers have adopted this strategy to synthesise a wide range of rotaxanes based on the interaction between threads containing ammonium salts and crown ether macrocycles.[1b,d,f]

1.2.3.2 Amide-Based Rotaxanes

The first amide-based interlocked architecture (a catenane) was reported by Hunter in 1992.[22] A few years later, Leigh and co-workers synthesised the first amide-based rotaxane (Scheme 1.5). Rotaxane 15 was prepared as a means to obtain macrocycle 16, which could not be accessed by simpler approaches. Cooperative multipoint hydrogen bonding between the macrocycle precursor and thread 17 templated the formation of the benzilic amide macrocycle to furnish rotaxane 15, which was subsequently disassembled via transesterification of the bulky stoppers to afford 16.[23]

Scheme 1.5 Leigh’s hydrogen-bond-based rotaxane.[23]

Leigh and co-workers later demonstrated that preorganisation of the peptide template increases the yield of rotaxane formation. The precise and complementary
positioning between the hydrogen-bond donor groups in the macrocycle and the hydrogen-bond acceptors in fumaramide thread 18 enhances the formation of species in which the precursors are held in the correct conformation for cyclisation and rotaxane formation to occur. The benzylic amide macrocycle fumaramide-based rotaxane (Scheme 1.6, 19) is obtained in > 95% yield, making this synthetic pathway one of the most effective routes of all known rotaxane-templated strategies.\textsuperscript{[24]}

Scheme 1.6 Fumaramide-based rotaxane.\textsuperscript{[24]}

### 1.2.3.3 Anion-Based Rotaxanes

The first rotaxane based on the template assistance of an anion was described by Vögtle and co-workers in 1999. Multiple hydrogen bonds between phenolate anion 20 and lactam macrocycle 21 directed the synthesis of rotaxane 22 in an impressive 95% yield (Scheme 1.7).\textsuperscript{[25]}

Scheme 1.7 Vögtle’s anion-based rotaxane.\textsuperscript{[25]}

The assembly of a rotaxane based on chloride-pyridinium interactions was later demonstrated by Beer. In this case, the chloride anion orientates the macrocycle and the thread in an orthogonal arrangement to form the rotaxane via clipping method using ring-closing metathesis.\textsuperscript{[26]}
1.2.4 Transition Metal-Based Rotaxanes

Metal coordination is perhaps the strongest kind of interaction utilised in the preparation of interlocked molecular structures. Like hydrogen bonds, directionally conferred by the preferred coordination geometry of the metal ions templates the formation of interlocked architectures in very high yields. Metal-containing rotaxanes can be divided into three different categories depending on the role of the metal ion.

1.2.4.1 Passive Metal Templates

In a passive metal template strategy, the coordination geometry of the metal ion brings the reactive fragments into the right spatial orientation to furnish mechanically-interlocked architectures in good yields. In 1983, Sauvage and co-workers demonstrated the ability of Cu\(^{1+}\) to direct the formation of a mechanically-interlocked architecture.\[^{[27]}\] By adopting the same strategy, Gibson synthesised the first rotaxane using such approach (Scheme 1.8, 23).\[^{[28]}\] Treatment of a phenanthroline-containing macrocycle and phenanthroline-based bisphenol with Cu\(^{1+}\) afforded complex 24, in which the two ligands are arranged in a mutually orthogonal orientation that direct stoppering with 1-(1,1-bis(4-tert-butylphenyl)-4-iodobutyl)benzene. Rotaxane 23 was then obtained by removing the metal ion with amberlite-CN resin (Scheme 1.8).\[^{[28]}\]

![Scheme 1.8 Gibson's metal-templated synthesis of rotaxane 23.][28]

Subsequently, Sauvage reported the synthesis of a rotaxane stoppered by two rigid porphyrins using the same transition metal template-directed strategy (Scheme 1.9, 25). Condensation of complex 26 with compounds 27 and 28, followed by addition of chloranil furnished 25 in a modest 25% yield.\[^{[29]}\] This system was prepared
to investigate the electron transfer between the two porphyrin units as it mimics certain features of the reaction centre of bacterial photosynthetic complexes.\[30\] Thereafter, a rotaxane containing a third porphyrin ring on the macrocycle was prepared.\[31\] The electron transfer in this rotaxane was enhanced by coordinating the phenanthroline units in the macrocycle and the thread by either Ag\[^{+}\] or Cu\[^{+}\].\[32\] 

![Scheme 1.9 Sauvage's porphyrin stoppered rotaxane.\[29\]](image)

In 2004, Leigh and co-workers utilised metal-ligand interactions to template the synthesis of rotaxanes 30 and 31 based on the octahedral\[33\] and square planar\[34\] geometries of divalent metal ions such as Zn\[^{II}\] and Pd\[^{II}\], respectively (Scheme 1.10).

![Scheme 1.10 Leigh's octahedral\[33\] and square planar\[34\] rotaxanes.]

1.2.4.2 Active Metal Templates

In the active-metal template-directed strategy developed by Leigh and co-workers, the metal ion has two functions: to work as a template to hold the constituents of the interlocked architecture in a specific geometric arrangement and to catalyse a reaction that leads to the preparation of the mechanically-interlocked architecture in very good yields.\[35\]
Scheme 1.11 shows the active-metal template synthesis of rotaxane 32 via a CuI-catalysed terminal alkyne-azide cycloaddition (CuAAC) reaction. This procedure may be carried out in either stoichiometric or catalytic mode (Scheme 1.11, a and b, respectively). Addition of one equivalent of Cu(CH3CN)4PF6 to a solution of macrocycle 33, azide 34 and alkyne 35 in CH2Cl2 yields rotaxane 32 in 94% after demetalation with KCN. Subsequently, 32 could also be obtained using substoichiometric amounts of CuI. This is possible by adding pyridine to liberate CuI from the multidentate rotaxane product so that it can reassume its catalytic role.\[35]\n
Recently, this active-template rotaxane-forming strategy has been extended to palladium catalysed transformations such as homocoupling of terminal alkynes\[36]\ and oxidative Heck cross-couplings.\[37]\n
Scheme 1.11 Leigh's active-metal template CuAAC synthesis of rotaxanes: a) stoichiometric amount of Cu$^+$; b) catalytic amount of Cu$^+$.

$L = \text{CH}_3\text{CN}, \text{H}_2\text{O}, \text{pyridine}, \text{solvent or a donor atom from another rotaxane, macrocycle or thread.}^{[33]}

1.2.4.3 Metals as Structural Features

In 1981 Ogino used bulky Co$^{\text{III}}$ complexes to stopper an inclusion compound of 1,12-diaminododecane and a $\alpha$- or $\beta$-cyclodextrin (Scheme 1.2).$^{[14]}$ From then on, a
range of rotaxanes in which metals form part of the linear or cyclic backbone structures have been reported.\cite{38}

Ferrocene units have also been shown to act as stoppers in rotaxanes. The first example was presented by Kaifer in 1991\cite{39} and since then a range of ferrocene-containing rotaxanes have been prepared.\cite{40} Latterly, an ammonium-crown ether-based [3]rotaxane capped by two ferrocene units via a cross-metathesis reaction has been published.\cite{41}

Loeb and co-workers realised that pseudorotaxane $36^{2+}$ could be utilised to obtain a range of metal-containing rotaxanes.\cite{42} Interestingly, changing the pseudorotaxane to transition metal ratio gave rise to a variety of 1D and 2D metal-organic rotaxane frameworks (MORFs) (Scheme 1.12).\cite{43} Even 3D MORFs were obtained on substituting $36^{2+}$ with a bis($N$-oxide) pseudorotaxane analogue and adding metal ions with larger coordination spheres ($\text{Ln}^{III}$).\cite{44}

![Scheme 1.12 Loeb's 1D and 2D MORFs.\cite{43}](image)

Instead of using metal ions as stoppers, Jeong and co-workers utilised Os$^{\text{VI}}$ to bridge the constituents of a macrocycle to form rotaxane 37. The kinetically labile nature of this coordination bond allows the peptide thread 38 to penetrate the cavity of macrocycle 39 via a reversible clipping process to furnish the mechanically-interlocked architecture 37 in good yields (Scheme 1.13).\cite{45}
In 1991, Bickelhaupt and co-workers reported the synthesis of a Mg" containing rotaxane. Addition of MgPh₂ to a solution containing macrocycle 40 in toluene furnished rotaxane 41 as evidenced by NMR spectroscopy. However, rotaxane 41 could not be isolated because it exists in rapid equilibrium with complex 42 (Scheme 1.14).[46]

1.3 Molecular Shuttles

The thread in rotaxanes imposes rotational and translational restrictions on the dynamic motion of the macrocycle. This can be combined with noncovalent interactions between the macrocycle and areas of the thread to allow the precise control over the relative position of the two components.[47] This is the reason why interlocked architectures are important precursors for the development of prototypical structural units for device applications.[1,9]
There are two large-amplitude motions with respect to the thread that macrocycles can display in rotaxanes: translation along the axle, formally called shuttling (Figure 1.3a) and rotation around the thread, known as pirouetting (Figure 1.3b).

![Figure 1.3 Cartoon representing the two types of large-amplitude motion in rotaxanes: a) shuttling and b) pirouetting.](image)

### 1.3.1 Degenerate Molecular Shuttles

A molecular shuttle is a rotaxane in which the thread bears two binding sites (or stations) so that the macrocycle can move between the stations with rates that are determined both by the strength of the binding interaction and a distance-dependant diffusional factor.

The first such molecular shuttle was reported by Stoddart and co-workers in 1991 (Figure 1.4a). Shuttle 43 consists of a tetracationic cyclophane macrocycle and a linear thread bearing two identical hydroquinol stations separated by a polyether spacer (Figure 1.4a). At room temperature in solution, the thermal energy is sufficient to allow the cyclophane macrocycle to move back and forth between the two degenerate stations at a rate of 1100 times per second. Energetically, this is represented as a double-minimum potential energy surface (Figure 1.4b). If the solution is cooled down to 223 K, the macrocycle no longer has enough energy to overcome the activation energy barrier and the shuttling motion stops.
Another way to stop shuttling would be to make the kinetic barrier considerably larger than the available thermal energy. This was successfully achieved by Leigh and co-workers. At room temperature, the benzilic amide macrocycle in rotaxane 44 shuttles rapidly between the two chemically identical peptide stations (Scheme 1.15, 44). Then, by simply introducing a bulky N-tosyl group, the motion of the macrocycle is stopped (Scheme 1.15, 45). The system can be returned to its original state upon removal of the tosylimino group.\[49\]

Scheme 1.15 Disruption of shuttling through covalent bond formation.\[49\]
In 44 the rate at which the benzylic amide macrocycle shuttles between the stations can be accelerated by increasing the polarity of solvent. Polar solvents reduce the strength of the hydrogen bond interactions between macrocycle and binding site which decreases the free energy barrier and, therefore, increases the rate of the shuttling process.[49]

Apart from chemically modifying the molecular shuttle, the motion of the macrocycle can be stopped by means of coordination chemistry. At room temperature, the crown ether macrocycle in rotaxane 46 shuttles back and forth between the two degenerate bipyridinium stations (dark blue) (Scheme 1.16). However, addition of Cu\(^{1}\) affords the kinetically stable dimeric complex [Cu(46)\(^{2}\)]\(^{9+}\) in which the translational motion of the macrocycles is blocked (Scheme 1.16). Removal of Cu\(^{1}\) by ion-exchange resin restores the shuttling motion.[50]

Scheme 1.16 Disruption of shuttling through metal ion coordination.[50]
1.3.2 Stimuli-Responsive Molecular Shuttles

In rotaxanes containing two different well-separated stations, the position of the macrocycle is determined both by the difference in binding affinity of the ring for each of the stations and the available thermal energy. The macrocycle is preferentially located at the station with the highest binding affinity. This situation opens up the possibility of using an appropriate external stimulus to alter the relative order of binding affinities; either increasing the affinity of the weaker station or decreasing the affinity of the stronger site and thereby causing a change in the preferred position of the macrocycle. The system can then be returned to its original state if the initial binding affinities are restored by an additional stimulus.\(^1\)

It is important to keep in mind that the external stimulus does not induce directional motion of the macrocycle – it only alters the equilibrium between the two co-conformations,\(^5\) so that the background thermal energy, in the form of Brownian motion, allows the change in the position of the macrocycle.\(^1\)

In 1994, Stoddart, Kaifer and co-workers reported the first stimuli-responsive molecular shuttle (Figure 1.5).\(^5\) At room temperature, the tetracationic cyclophane macrocycle shuttles rapidly between the two \(\pi\)-electron donor benzidine (light blue) and biphenol stations (red). When the solution is cooled to 229 K, the shuttling motion slows down and the two positional isomers of \(47^{4+}\) can be observed by NMR (in a ratio 21:4) and UV/Vis absorption spectroscopies. Addition of \(\text{CF}_3\text{CO}_2\text{D}\) destabilises the initially preferred station (blue) so that the cyclophane macrocycle moves over the biphenol station (red) (Figure 1.5 [47-2D]\(^{6+}\)).\(^5\)

The original co-conformation can be restored by neutralisation of the protonated benzidine binding site by \([\text{D}_5]\)pyridine. The position of the macrocycle can also be switched by electrochemical oxidation of the benzidine residue through a similar mechanism.\(^5\)
The types of external stimulus that can be used to control large-amplitude movement in molecular shuttles depend on the nature of the noncovalent interactions that hold the macrocycle at a particular station. Stimuli-responsive molecular shuttles based on pH changes, redox processes, photochemical reactions, metal ion coordination and covalent bond formation have all been synthesised. Some of the most interesting examples will appear in the following sections.

1.3.2.1 Shuttling through pH Changes

Although $47^+$ was the first pH-switchable molecular shuttle, its relatively poor positional discrimination compromised its utility for the preparation of more sophisticated synthetic molecular devices. More recently, Stoddart and co-workers have developed a variety of systems based on the complexation of secondary alkylammonium stations by crown ether macrocycles. Among many important examples based on this system, the “molecular elevator” $[48\cdot3H]^+$ is probably one of the most remarkable (Scheme 1.17).
As shown in Scheme 1.17, the molecular elevator \([48\cdot3H]\)^{9+}\) consists of three crown ether macrocycles attached together by a triphenylene core and three fused thread-like components bearing a secondary alkylammonium unit (pink) and a bipyridinium station (dark blue). Initially the tris-crown ether macrocycle resides mainly over the secondary alkylammonium recognition centre. However, treatment of \([48\cdot3H]\)^{9+}\) with more than three equivalents of phosphazene \(P_1\cdot tBu\) base results in deprotonation of the alkylammonium binding site. Destabilising the noncovalent intercomponent interaction between macrocycle and the initially preferred station induces its translocation to the bipyridinium station (Scheme 1.17, \(48^{6+}\)). Addition of more than three equivalents of trifluoroacetic acid returns the system to its original state.\(^{54}\)

Recently, Leigh and co-workers have reported the synthesis of two pH-switchable molecular shuttles. In the first example,\(^{55}\) a benzylic amide macrocycle translocates away from a peptide station to bind a phenolate anion site. In the second example,\(^{56}\) the position of a palladium-complexed macrocycle is switched by selective protonation of one of the two pyridine-based stations followed by heating. The additional external stimulus is required due to the kinetic stability of the palladium bond between thread and macrocycle.\(^{56}\)

1.3.2.2 Shuttling through Redox Processes

In order to achieve a redox-switched molecular shuttle with greater positional integrity to that observed in \(47^{4+}\), Stoddart and co-workers synthesised bistable rotaxane \(49^{4+}\). Molecular shuttle \(49^{4+}\) consists of a thread bearing a tetraethiafulvalene
station (green) and a dioxynaphthalene (orange) binding site, and a cyclophane macrocycle. At room temperature, the $^1$H NMR and absorption spectra of $49^{\text{++}}$ shows that the macrocycle spends most of its time on the tetrathiafulvalene station. Upon oxidation of the initially preferred station, either by chemical or electrochemical means, the macrocycle moves to the second site, as confirmed by NMR and UV/Vis spectroscopies.$^{[57]}$

![Scheme 1.18 Redox-controlled molecular shuttle.$^{[57]}$](image)

After Stoddart's initial example (Figure 1.5, $47^{\text{++}}$), a variety of redox-controlled shuttles incorporating these two $\pi$-electron-donating species and their derivatives have been reported.$^{[58]}$

In 2001, Leigh and co-workers synthesised a redox-active molecular shuttle with a remarkable positional discrimination.$^{[59]}$ Hydrogen-bonded rotaxane 50 consists of a benzylic amide macrocycle locked onto a thread bearing a succinamide unit (orange) and a naphthalimide (dark blue) binding site (Scheme 1.19, 50). The two sets of bifurcated hydrogen bond interactions between the benzylic amide macrocycle and the succinamide unit not only template the formation of the rotaxane in good yields but also determine the preferred position of the macrocycle at room temperature (Scheme 1.19, 50). Translocation of the macrocycle to the second site takes place following one-electron reduction of the naphthalimide (Scheme 1.19, $50^-$). Reducing the radical anion makes this unit a better hydrogen bond acceptor than the succinamide moiety, changing the equilibrium between the two binding sites and,
therefore, the position of the macrocycle (Scheme 1.19, 50\textsuperscript{−}). The system can be returned to its original state by reoxidation of the naphthalimide unit (Scheme 1.19).\textsuperscript{59} Because the formation of the radical can be achieved by photochemical or electrochemical means, the shuttling motion can be investigated via transient absorption spectroscopy or cyclic voltammetry experiments, respectively.\textsuperscript{59}

In 1999, Sauvage and co-workers reported the first electrochemically switched transition metal-based molecular shuttle.\textsuperscript{60} This system utilises the preferred coordination number displayed by different oxidation states of copper to bring about large-amplitude motions. Molecular shuttle Cu\textsuperscript{I}(51) consists of a bidentate 2,9-diphenyl-1,10-phenanthroline containing macrocycle and a thread incorporating two recognition sites, namely, a tridentate terpyridine (orange) and a bidentate phenanthroline (light blue). Cu\textsuperscript{I} has a strong tendency to form four-coordinated complexes so that the macrocycle resides exclusively over the phenanthroline station. However, electrochemical oxidation of Cu\textsuperscript{I} to Cu\textsuperscript{II} switches the position of the macrocycle, due to the fact that Cu\textsuperscript{II} preferentially forms higher coordination complexes – a situation that is only possible at the a tridentate terpyridine station (Scheme 1.20, Cu\textsuperscript{II}(51)). Upon reduction, the system is returned to the original co-conformation.\textsuperscript{60}
1.3.2.3 Shuttling through Addition or Removal of Metal Ions

Instead of changing the oxidation state of the metal ion to induce a large positional change, the position of the crown ether macrocycle in molecular shuttle 52 can be simply switched by addition of two equivalents of LiClO$_4$. The coordination of two lithium cations between the crown ether macrocycle and the carbonyl groups of pyromellitic diimide unit (green) translocates the macrocycle to this newly preferred station (Scheme 1.21, [Li$_2$(52)]$^{2+}$). Addition of a large excess of [18]crown-6 to sequester the metal ions returns the system to its original state.\[^{[61]}\]
1.3.2.4 Shuttling through Photochemical and Thermal Stimuli

The position of the benzylic amide macrocycle in hydrogen-bonded molecular shuttle (E)-53 can be changed by photochemical means. This is possible because photo-isomerisation of the fumaramide unit (green) into its cis olefin isomer (maleamide) reduces the number of hydrogen bond interactions between the macrocycle and the station so that the ring translocates to the newly preferred succinamide station (orange) (Scheme 1.22, (Z)-53). The position of the macrocycle can be reversed by thermal conversion of the maleamide back into the fumaramide.\textsuperscript{[62]}
Additionally, a tristable molecular shuttle based on a similar structure was reported in 2003.\textsuperscript{[63]} In this system the benzylic amide macrocycle can be located in three different sites through of combination of photochemical and thermal stimuli.\textsuperscript{[63]}

1.3.2.5 Shuttling through Covalent Bond Formation

Alternatively, the position of the benzylic amide macrocycle in molecular shuttle (E)-53 can be switched by the formation of covalent bonds. Treatment of rotaxane (E)-53 with cyclopentadiene results in the formation of a cyclo-adduct which alters the hydrogen bonding geometry of the amide bonds and reduces the affinity of the macrocycle. Therefore, the macrocycle translocates to the now preferred succinic amide-ester via biased Brownian motion (Scheme 1.23, 54). Due to the reversibility of the Diels-Alder reaction, the system can be returned to its original preferred co-conformation by breaking the C-C bond. This process is carried out under reduced pressure in a flash vacuum pyrolysis (FVP) apparatus.\textsuperscript{[64]}
1.4 Exploiting Shuttling Motion to Trigger Physical Property Changes

As shown above, the position of the macrocycle in molecular shuttles can be precisely controlled by an external stimulus. This large-amplitude positional change can then be exploited to produce a physical response. A few examples of such stimuli-responsive molecular shuttles are given below.

In 2003, Leigh and co-workers reported one of the first examples in which the controlled large-amplitude positional change in molecular shuttles is exploited to produce a useful response. In rotaxane (E)-55 the macrocycle resides exclusively over the fumaramide station far away from the chiral centre of the glycyl-L-leucine station (orange). However, when the position of the macrocycle is switched by photoisomerisation of the olefin unit (Scheme 1.24, (Z)-55), a strong induced circular dichroism (ICD) response is detected because the aromatic rings in the macrocycle are now held in a chiral arrangement (Scheme 1.24, b). The system can be returned to its original co-conformer by applying a second stimulus.
Scheme 1.24 Chiroptical bistable molecular shuttle: a) reversible switching of the molecular shuttle; b) circular dichroism spectra (0.1mM in CHCl₃) at 298 K of (E)-55 (purple) and (Z)-55 (blue).\textsuperscript{65}

Utilising a similar chemical structure, Leigh and co-workers later reported a molecular shuttle that can switch fluorescence on and off. In this case, an anthracene fluorophore, which also acts as a stopper, is directly attached to a glycyglycine station (orange) (Scheme 1.25, a). In order to quench the fluorescence by electron transfer, a benzylic amide macrocycle bearing two pyridinium units was used. The initially preferred co-conformer in which the macrocycle is held far from the anthracene unit fluoresces strongly (Scheme 1.25, b (E)-56) but once the position of the macrocycle is reversed by photoisomerisation of the olefinic unit, fluorescence is almost completely quenched (Scheme 1.25, b (Z)-56). The intensity difference between the \textit{trans} and the \textit{cis} isomers in CH₂Cl₂ is 200:1. This difference is greatly reduced in polar solvents due to erosion of the macrocycle positional integrity.\textsuperscript{66}
Tian and co-workers demonstrated that photochemical conversion of a trans-stilbene to its cis-isomer induces translocation of the macrocycle towards the fluorophore stopper in a cyclodextrin-based rotaxane. This motion is accompanied by an enhancement in the fluorescence intensity of the terminal group.\textsuperscript{67} Since then, more complex fluorescent molecular switches have been reported by the same group.\textsuperscript{68}

For many potential applications, molecular switches may have to operate in an organised and cooperative manner. Thus, arrangement of such molecules on surfaces or at interfaces is an important challenge. One of the most remarkable steps towards this goal was reported by Stoddart and co-workers in 2005.\textsuperscript{69} [3]Rotaxane 57\textsuperscript{8+} consists of two sets of redox-active tetrathiafulvalene and naphthalene units separated by a rigid spacer and two tetracationic cyclophane macrocycles incorporating a disulfide tether. This “molecular muscle” was deposited onto a silicon microcantilever beam coated with a thin layer of gold which was then inserted into a fluid cell.
Addition of aqueous Fe(C1O4)3 caused the macrocycle of the approximately six billion molecular shuttles to collectively move to the naphthalene station (Scheme 1.26, $57^{12+}$). This process shortens the distance between the two macrocycles and, as a consequence the microcantilever beams bend upwards. Treatment with ascorbic acid returns the system to its original state. Although these two processes could be repeated up to 25 times the beam deflection of the microcantilever decreased considerably each time.[69]

![Scheme 1.26 Chemical structure of Stoddart’s molecular muscle and schematic representation of the bending process of a beam as a consequence of the translocation of the macrocycles.][69]

Utilising an analogous stimuli-responsive molecular shuttle (Scheme 1.27, a) Stoddart and co-workers showed that the passage of luminescent molecules in and out the pores of spherical silica particles could be controlled by switching the position of the macrocycle. When mesoporous silica particles functionalised with rotaxanes are immersed in solution, the luminescent solutes diffuse into the cavities (Scheme 1.27, b). This is possible because the valve is opened – the macrocycle sits over the green station far from the silica surface. However, addition of Fe(C1O4)3 to a dry solution of the silica particles switches the position of the macrocycle to the naphthalene station,
blocking the entrance to the pores and trapping the solute inside the cavity. The luminescent guest can then be released by returning the system to its original state by treating molecular valve $58^{4+}$ with ascorbic acid.\[^{70}\]

![Scheme 1.27](image)

**Scheme 1.27** a) Chemical structure of molecular shuttle $58^{4+}$; b) the confinement and release operation of a molecular valve. Light blue circles represent luminescent molecules.\[^{70}\]

In the same year, Leigh and co-workers showed the directional transport of a microlitre droplet of diiodomethane over a uniform monolayer of molecular shuttles on a surface (Scheme 1.28, b). Photoisomerisation of the double bond in rotaxane $(E)$-$59\cdot2H^+$ controls the position of the benzylic amide macrocycle so that it is held distant from the fluoroalkane region in $(E)$-$59\cdot2H^+$ and covers this region in $(Z)$-$59\cdot2H^+$. This photo-trigger shuttling motion is maintained when the rotaxanes are attached to a monolayer of 11-mercaptoundecanoic acid supported on gold, giving a surface that can be switched between hydrophobic (Scheme 1.28, c (left)) to hydrophilic states (Scheme 1.28, c (right)). Placing a droplet of diiodomethane on the $(E)$-$59\cdot2H^+$ surface and irradiating only one side creates a gradient in surface free energy. The
result is motion of the droplet to the irradiated region so as to maximise surface free energy. Remarkably, the diiodomethane droplet was also transported up a 12° incline.\cite{71}

Scheme 1.28  a) Light-switchable molecular shuttle containing a fluoroalkane unit; b) schematic representation of rotaxanes 59 grafted onto a monolayer of 11-mercaptoundecanoic acid on Au(111) over a glass or mica surface, before (left) and after (right) irradiation; c) lateral photographs of the directional transport of a drop of diiodomethane over such a surface.\cite{71}

1.5 Conclusions and Perspectives

Thanks to the advent and application of aspects of supramolecular and coordination chemistry, the days where the preparation of mechanically-interlocked architectures proceeded in dreadful yields are past. High yielding template strategies for the synthesis of rotaxanes have allowed synthetic chemists to focus all their efforts on the fabrication of functional molecular devices that exploit these novel molecular
architectures. Molecular shuttles are ideal precursors for the construction of synthetic molecular motors and machines because large-amplitude motion can be precisely controlled and exploited to trigger physical property changes such as conductivity, expression of chirality and fluorescence. However, an important step in harnessing these property changes and converting molecular-level devices into macroscopic technologies will be transferring molecular switches from bulk solution to interfaces or onto surfaces.

Over the last five years a few remarkable examples of switchable and detectable physical property changes occurring on surfaces have been reported. It is, therefore, not surprising that many efforts in the field of molecular machines are going in this direction.

Nevertheless, novel mechanisms for switching the position of the macrocycle in molecular shuttles and the investigation of other distance dependent physical properties in stimuli-responsive switches are also vital to expanding this remarkable field into new frontiers.

1.6 Thesis Layout

This thesis describes the synthesis of hydrogen-bond assembled rotaxanes containing metal ions at specific positions on the thread and the macrocycle. Chapters Two and Three describe two novel shuttling mechanisms in which the complexation of a metal ion causes destabilisation of the initially preferred station resulting in the translocation of the macrocycle to the unaffected binding site. Chapter Four describes a novel strategy for the assembly of multiple (homo- and mixed-) metal-containing hydrogen-bonded rotaxanes using the Huisgen-Meldal-Fokin Cu¹-catalysed terminal alkyne-azide cycloaddition reaction. Chapter Five describes the investigation of through-space interactions in simple mechanically-interlocked systems containing paramagnetic species in macrocycle and thread by means of electron paramagnetic resonance. Finally, Chapter Six describes the effect of dipolar interactions on the redox process at an electroactive centre in a series of models based on hydrogen-bonded ferrocene-containing rotaxanes.

Chapters Two to Four are presented in the form of articles that have already been published in peer-reviewed journals. No attempt has been made to rewrite the work
out of content. In order to maintain consistency through the thesis Chapters Five and Six, which have yet to be published, have been written in a similar manner. A brief synopsis has been attached in order to put the research into perspective.

1.7 References and Notes


[6] This movement was observed in 1827 by the Scottish botanist Robert Brown when investigating small particles within pollen grains suspended in water.


[10] The first interlocked architecture (a catenane) was achieved by Wasserman in 1960; E. Wasserman, J. Am. Chem. Soc. 1960, 82, 4433-4434.


[47] The thread generally being the larger of the two constituents in rotaxanes is normally considered stationary when describing relative motions of the two components.


[51] Co-conformers refer to the relative positions of the mechanically-interlocked components with respect to each other.


CHAPTER TWO

Complexation-Induced Translational Isomerism:
Shuttling through Stepwise Competitive Binding

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Synopsis

In order to use molecular shuttles for the construction of synthetic molecular motors and machines, precise control over the relative position of the interlocked components is required. To date, this has been achieved in only a handful of "stimuli-responsive molecular shuttles" that demonstrate high positional integrity. In this Chapter, a novel metal-mediated mechanism for inducing shuttling in a hydrogen-bond assembled architecture is reported.

Coordination of Cd$^{II}$ (or Cu$^{II}$) ions to the bis(2-picolyl)amino(BPA)-derivatised glycylglycine unit, followed by deprotonation of the adjacent amide group with one equivalent of an appropriate base, progressively wraps the metal ion around the peptide unit. This process destabilises the originally preferred station so that the macrocycle translocates to the weaker binding site (succinic amide ester) via biased Brownian motion. Removal of the metal ion and reprotonation of the amide group returns the system to its original state.

In this system the macrocycle is held either in close proximity or far away from the metal chelating group. This feature could be used to prepare a pH-switchable molecular shuttle where the distance between the two metal ions – one on the macrocycle and other on the thread – can be controlled.
2.1 Introduction

Although many carefully designed rotaxane-forming reactions have been developed in recent years,[1] new strategies[2] for switching the position of the macrocycle on the thread in response to an external trigger[3,4] — a key requirement for developing mechanical molecular devices based on such architectures[4] — remain rare. Competitive substrate binding is often used to bring about conformational changes that elicit function in biological “machines”[5] and has been successfully utilised in artificial host-guest systems,[6] chemical sensing[7] and molecular Boolean logic operations.[8] However, as the macrocycle-thread interactions in a rotaxane are normally chosen so as to maximize the efficiency of the template mechanism, it is difficult to find competitive binders that can effectively disrupt these threaded and inherently self-organised complementary networks.[9,10] One elegant solution[11] to this problem is to utilise the preferred binding geometries of different metal d-orbital configurations (e.g. tetrahedral Cu$^{I}$ → five-coordinate Cu$^{II}$ or Zn$^{II}$) in transition-metal-based molecular shuttles.[12,13] Here we report on an alternative solution, which does not involve a change in metal ion or oxidation state but uses the binding of a transition metal to move a macrocycle in a hydrogen-bonded molecular shuttle. Coordination of Cu$^{II}$ or Cd$^{II}$ to a bis(2-picolyl)amino (BPA)-derivatised glycine “station”, followed by deprotonation of the adjacent amide group, progressively wraps up the peptide station, which leads to displacement of the macrocycle to an intrinsically weaker hydrogen-bonding site. In the case of Cu$^{II}$, the change in binding mode perturbs sensitive transitions within the d-orbitals and the change in position of the shuttle is consequently accompanied by a colour change.

2.2 Results and Discussion

The new shuttling strategy evolved out of the chance observation of an unusual controlled stepwise binding sequence of Cu$^{II}$ to a multidentate ligand. Whilst attempting to develop methodology for the attachment of paramagnetic metal ions to macrocycles in rotaxanes (see Chapters 4, 5 and 6), we prepared ligand 1,[14,15] which features a glycine residue substituted with two picoline units at its $N$ terminus. Addition of CuCl$_2$·2H$_2$O to 1 in CH$_3$CN led to the formation of 2, light blue crystals
of which separated from the saturated liquors and gave the X-ray crystal structure shown in Figure 2.1.\textsuperscript{[16]} Cooling the solution of 2 to -20 °C in the presence of an additional half-equivalent of CuCl\textsubscript{2}·2H\textsubscript{2}O resulted in the deposition of large emerald-green crystals\textsuperscript{[17]} of 3 on the walls of the flask, which yielded the crystal structure shown in Figure 2.1. Addition of one equivalent of NaH to solutions of either 2 or 3 in DMF led to a third type of BPA-Cu\textsuperscript{II} complex as lime-green crystals of 4 (Figure 2.1). The binding of the Cu\textsuperscript{II} ion – from the initial tridentate chelation of CuCl\textsubscript{2} to the BPA moiety in 2, to loss of a Cl\textsuperscript{-} ligand and coordination to the carbonyl oxygen of the amide group in 3, and finally exchange of the carbonyl for the nitrogen atom upon deprotonation of the amide group in 4 – results in progressive wrapping of the peptide unit around the metal (Figure 2.1).\textsuperscript{[18]} We reasoned that integration of this stepwise changing coordination motif into a macrocycle-binding site in a peptide-based molecular shuttle might permit the complexation-controlled translocation of the macrocycle from one station to another.

\textbf{Figure 2.1} X-ray crystal structures\textsuperscript{[16]} of 2 (initial), 3 (upon cooling)\textsuperscript{[17]} and 4 (after addition of NaH) showing the change in binding mode of Cu\textsuperscript{II} to the multidentate ligand. C grey, Cl yellow, N blue, O red; all hydrogen atoms except the amide proton have been omitted for clarity. Reagents and conditions: a) 0.5 equiv. CuCl\textsubscript{2}·2H\textsubscript{2}O, -20 °C, 100%; b) NaH or phosphazene P\textsubscript{1}-tBu base, 91%. The insets show photographs of the corresponding powdered, crystalline solids (from the left) 2, 3 and 4. Selected bond lengths [Å]: a) Cu1-N1 2.080, Cu1-N17 2.018, Cu1-N24 1.995, Cu1-C11- 2.240, Cu1-Cl2 2.569; b) Cu1-N1 2.036, Cu1-N17 1.972, Cu1-N24 2.015, Cu1-C11- 2.231, Cu1-O3 2.373; c) Cu1-N1 2.031, Cu1-N17 2.099, Cu1-N24 2.124, Cu1-C11- 2.250, Cu1-N4 2.055.
To study the chemistry of the BPA-modified peptide station in a simple model system, we first prepared thread 5 and rotaxane 6 (Scheme 2.1). Formation of 6 proceeded in 44% yield from 5 (Scheme 2.1, a), which suggests that the affinity of the benzylic amide macrocycle for the BPA-glycylglycine station should be similar to that of other peptide-based stations, namely, intermediate between a strongly binding preorganised fumaramide group and a more weakly binding succinic amide ester moiety.\[^{[9a]}\] The X-ray crystal structure of rotaxane 6 shows that both carbonyl groups and both amide protons of the thread are involved in intercomponent hydrogen bonding to the macrocycle in the solid state (Figure 2.2 b).\[^{[19]}\]

**Scheme 2.1** Synthesis of rotaxane 6 from the BPA-glycylglycine thread 5 and their respective complexes with CuCl\(_2\) and Cd(NO\(_3\))\(_2\) (\(\equiv MX_2\)) (atom-lettering scheme corresponds to \(^1\)H NMR assignments in Figure 2.3). Reagents and conditions: a) \(p\)-xylylene diamine, isophthaloyl dichloride, Et\(_3\)N, CHCl\(_3\), 44%; b) CuCl\(_2\)-2H\(_2\)O or Cd(NO\(_3\))\(_2\)-4H\(_2\)O, (7CuCl\(_2\)) 90%, (8CuCl\(_2\)) 90%, (7Cd(NO\(_3\))\(_2\)) 85%, (8Cd(NO\(_3\))\(_2\)) 92%; c) NaH or phosphazene P\(_x\)-tBu base, (9CuCl) 77%, (9CdNO\(_3\)) 82%. The coordination bond indicated by a dashed line in 9MX is only observed in the cadmium complex.
The chelation geometries adopted by the BPA-glycylglycine station were studied by binding 5 and 6 to \( \text{Cu}^{II} \) as well as \( \text{Cd}^{II} \) — a diamagnetic metal that generally adopts ligand coordination geometries that are similar to those of \( \text{Cu}^{II} \) — with nitrogen-containing ligands, and attempted subsequent deprotonation of one of the amide groups (Scheme 2.1).\(^{[20]}\) The X-ray crystal structures of several of the resulting complexes are shown in Figure 2.2, and the \(^1\)H NMR spectra ([D\(_6\)]acetone,\(^{[21]}\) 298 K) of the free ligands 5 and 6 and their complexes with \( \text{Cd(NO}_3\text{)}_2 \) are shown in Figure 2.3. The changes in the signals for the BPA protons (H\(_a\)–j) upon complexation of cadmium ions and the shielding of protons of the peptide (H\(_h\), H\(_f\) and H\(_k\)) by the macrocycle in the rotaxanes compared to those of the thread confirm that the structures in solution are closely related to those in the solid state. Correlation spectroscopy (COSY) assisted in the full assignment of peaks of all \(^1\)H NMR spectra. This technique gives detailed information about neighbouring protons and interactions between protons in different parts of the molecule. For example, Figure 2.4 shows the \(^1\)H-\(^1\)H COSY spectrum of thread 5, where cross peaks at \( \Delta \delta = 7.1-8.3 \) ppm allowed the identification of the pyridine protons.

First, addition of \( \text{CuCl}_2 \cdot 2\text{H}_2\text{O} \) or \( \text{Cd(NO}_3\text{)}_2 \cdot 4\text{H}_2\text{O} \) to both the thread and rotaxane smoothly generated complexes of the type 7\( \text{M(X)}_2 \) and 8\( \text{M(X)}_2 \), respectively (\( \text{M} = \text{Cu, Cd} \); Scheme 2.1, b). The solid-state structure of 8\( \text{Cd(NO}_3\text{)}_2 \) (Figure 2.2d) shows a coordination geometry similar to that of the intermediate complex 3 (Figure 2.1b), that is, featuring metal coordination to the carboxamide carbonyl oxygen.

Second, addition of one equivalent of a suitable base\(^{[22]}\) (Scheme 2.1, c) to the thread intermediate complexes 7\( \text{CuCl}_2 \) and 7\( \text{Cd(NO}_3\text{)}_2 \) yielded 9\( \text{CuCl} \) and 9\( \text{CdNO}_3 \), respectively. The X-ray crystal structure of 9\( \text{CuCl} \) (Figure 2.2a) displays a \( \text{Cu}^{II} \) coordination sphere similar to that of 4 (Figure 2.1c), as well as an additional (albeit long at 3.188 Å) directional hydrogen bond between the proton (N7H) of the second amide group and the formal nitrogen anion (N4) of the coordinating carboxamido functionality. The X-ray crystal structure of 9\( \text{CdNO}_3 \) (Figure 2.2c) is closely related, but with the metal ion additionally coordinated to the carbonyl oxygen of the second carboxamide group. The binding of \( \text{Cd}^{II} \) (or \( \text{Cu}^{II} \)) ion to the BPA-glycine carbonyl oxygen presumably lowers the pK\(_a\) value of the adjacent NH proton in complexes of the type 7\( \text{M(X)}_2 \) and 8\( \text{M(X)}_2 \), which allows selective deprotonation at this site. However, neither of the metal coordination geometries shown in Figure 2.2a or c
would leave room on the peptide unit for a benzylic amide macrocycle to occupy, or sufficient hydrogen-bonding partners for it to bind to, in a rotaxane or molecular shuttle. Indeed, treatment of $8\text{CuCl}_2$ or $8\text{Cd(NO}_3)_2$ with strong bases$^{[22]}$ led to complicated reaction mixtures and significant degradation of the rotaxane structures, seemingly as a consequence of the macrocycle sterically preventing deprotonation of the coordination-activated carboxamide or adoption of the wrapped-up metal-ligand coordination architecture.
Chapter Two

Complexation-Induced Translational Isomerism: Shuffling through Stepwise Competitive Binding

Figure 2.2 X-ray crystal structures \(^{[16]}\) of a) 9CuCl; b) 6; c) 9CdNO\(_3\), and d) 8Cd(NO\(_3\))\(_2\). C (thread) yellow, C (macrocycle) blue, metal atoms Cu\(^{II}\) and Cd\(^{II}\) grey, N blue, O red; all hydrogen atoms except for the amide protons have been omitted for clarity. Selected bond lengths [Å]: a) Cu1-N1 2.052, Cu1-N4 1.968, Cu1-N24 2.176, Cu1-N31 2.079, Cu1-C11 2.238, N7H-N4 3.188; b) N2H-O40 1.877, N42H-O10 2.201, N39H-O21 1.944, N29H-O43 1.961; c) Cd1-N1 2.443, Cd1-N4 2.205, Cd1-O6 2.476, Cd1-N24 2.304, Cd1-N31 2.416, Cd1-O41 2.407, Cd1-O42 2.509; d) Cd1-N37 2.443, Cd1-N60 2.364, Cd1-N67 2.323, Cd1-O39 2.331, Cd1-O72 2.335, Cd1-O73 2.463, Cd1-O77 2.794, Cd1-O75 2.400, N43H-O21 1.863, N40H-O10 1.861, N2H-O42 2.017.

The model compounds confirm the generic basis of the stepwise binding chemistry and provide \(^1\)H NMR spectroscopic fingerprints (Figure 2.3) of the various
coordination modes, both with and without the macrocycle occupying the station. These spectra could be used to determine the position of the macrocycle in a more elaborated molecular shuttle, in particular distinguishing between whether Cd$^{II}$ is bound to a carbonyl oxygen or carboxamido nitrogen atom and whether the macrocycle still occupies the BPA-glycylglycine station.

![Diagram of complexes](image)

**Figure 2.3** Partial $^1$H NMR spectra (400 MHz, [D$_6$]acetone, 298 K) of a) 5; b) 6; c) 7Cd(NO$_3$)$_2$; d) 8Cd(NO$_3$)$_2$, and e) 9CdNO$_3$. Resonances are coloured and labelled as in Scheme 2.1. Peaks shown in light grey in part e) originate from the phosphazene P$_{1-tBu}$ base.
Accordingly, we prepared the two-station thread 11 and rotaxane 12 which feature BPA-derivatised glycyglicine (green) and succinic amide ester (orange) stations for the macrocycle (Scheme 2.2). The rationale behind the design was that although the ring would be expected to predominantly occupy the BPA-glycylglycine binding site in metal-complexed 13, the ring would still spend some time away from the peptide station on the weaker binding succinic amide ester moiety. Whilst it is on the succinic amide ester station, the ring should not sterically hinder the coordination-activated peptide (as it does so effectively in 8Cd(NO₃)₂, Scheme 2.1), so this minor translational isomer can then be selectively deprotonated at the carboxamide adjacent to the BPA unit. In accord with Le Chatelier’s principle, 14 is formed. If the cadmium ion wraps itself up in the deprotonated glycylglycine residue in the manner seen with the model systems, this will switch off the peptide station and result in the macrocycle of 14 predominantly occupying the succinic amide ester station (Scheme 2.2).
Scheme 2.2 Conversion of thread 11 to rotaxane 12 and the reversible complexation of rotaxane 12 with Cd(NO$_3$)$_2$·4H$_2$O (atom-lettering scheme corresponds to $^1$H NMR assignments in Figure 2.4). Reagents and conditions: a) $p$-xylylene diamine, isophthaloyl dichloride, Et$_3$N, CHCl$_3$, 22%; b) Cd(NO$_3$)$_2$·4H$_2$O; c) phosphazene $P$_r-$t$Bu base; d) NaCN, NH$_4$Cl. Yields for conversions b–d were quantitative by $^1$H NMR spectroscopic analysis.

Pleasingly, the $^1$H NMR spectra of rotaxanes and threads (Figure 2.5) were fully consistent with the predicted behaviour. The relative shielding of the peptide protons in the $^1$H NMR spectrum of 12 compared to 11 (Figure 2.5a and b, respectively) confirms that the occupancy of the stations is approximately 90:10 in favour of the glycylglycine station in [D$_6$]acetonitrile at 298 K.$^{[21]}$ Addition of one equivalent of Cd(NO$_3$)$_2$·4H$_2$O to 11 and 12 to form the Cd(NO$_3$)$_2$-thread complex and 13, respectively (Scheme 2.2, b), resulted in little change (except for the BPA protons) in the $^1$H NMR spectra in [D$_6$]acetone at room temperature (compare Figures 2.5c and d with Figures 2.5a and b, respectively), indicating that the preferred position of the
macrocycle remains unchanged despite chelation of the terminal peptide carbonyl group to a metal. The shifts experienced by the protons around the metal-binding region – for example H_f and H_h – are similar to those in 8Cd(NO_3)_2 (Figure 2.3d). However, subsequent deprotonation of the amide proton H_g of 13 with one equivalent of phosphazene P_1-tBu^{[22]} base (Scheme 2.2, c) causes major changes (Figure 2.5e). The upfield shifts of H_m, H_o and H_p – δ = 3.2, 2.5 and 2.4 ppm in the Cd(NO_3)_2-thread complex (Figure 2.5c) to δ = 2.4, 1.7 and 1.5 ppm, respectively – are clear evidence for the translocation of the macrocycle to the succinic amide ester station (orange). Similarly, the downfield shift of H_f (δ = 3.2 ppm in 13 (Figure 2.5d) to δ = 4.0 ppm) and the restoration of H_f to its position δ = 3.2 ppm in the thread (Figure 2.5c) show that the peptide station (green) is no longer occupied by the benzylic amide macrocycle. The small upfield movement in H_h is consistent with the shift brought about by coordination of the deprotonated amide group to the metal, as seen with 9CdNO_3 (Figure 2.3e).

The transition-metal-binding-induced translocation of the macrocycle in the hydrogen-bonded shuttle is fully reversible (Scheme 2.2, d). Removal of the Cd^{II} ion from 14 with excess NaCN and reprotonation of the amide nitrogen atom with NH_4Cl quantitatively regenerates 12.
Finally, indirect evidence for a similar shuttling mechanism using Cu$^{II}$ binding is provided by the change in absorption of weak (likely d-d) transitions in the low-energy region of the UV/Vis spectrum of 15 upon addition of P$_{1}$-tBu (Figure 2.6). The colour change that occurs during a single-spot-to-single-spot transformation, as revealed by thin layer chromatographic analysis, is almost indistinguishable to that observed during the conversion of 3 to 4 (Figure 2.1). As the base-promoted transformation (8CuCl$_2$ → 10CuCl) does not occur for the short rotaxane (Scheme 2.1, c), yet does take place 15 → 16 (Figure 2.6), it seems reasonable to conclude that the colour change is accompanied by the same change in the position of macrocycle that occurs in the cadmium-coordinated molecular shuttle (Scheme 2.2, c).
2.3 Conclusion

We have described a mechanism through which a large-amplitude mechanical movement can be induced within a hydrogen-bonded molecular shuttle by the stepwise competitive binding of transition-metal ions. The peptide station is progressively wrapped up by the metal which disrupts hydrogen-bonding interactions between the station and the macrocycle and causes its displacement to the second station. The control over shuttling while the metal is bound to the thread provides two well-defined states in which the macrocycle is held either close to or distant from a single metal atom. This feature could be used to construct rotaxanes that display the intriguing property of being able to switch the distance between two metal centres —
which are not connected by chemical bonds – by an externally triggered mechanical motion.

2.4 Experimental Section

General

(Bis(2-pyridylmethyl)amino)acetic acid,[24] 4-(2,2-diphenylethoxy)-4-oxobutanoic acid[25] and 2,2-diphenylethyl 4-(12-aminododecylamino)-4-oxobutanoate[25] were prepared according to published protocols. All other reagents were purchased from commercial sources and used without further purification.

2-Amino-N-(2,2-diphenylethyl)-acetamide

EDCI (4.78 g, 25.0 mmol) was added in small batches to a solution of N-boc-glycine (1.89 g, 10.8 mmol) and DMAP (3.06 g, 25.0 mmol) in dichloromethane (200 mL) at room temperature. The reaction mixture was stirred for 10 min, at which time 2,2-diphenylethylamine (2.00 g, 10.1 mmol) was added in one portion. The reaction mixture was allowed to stir at room temperature for an additional 14 h. Then it was washed with 1 M aqueous HCl (3 x 20 mL), saturated aqueous sodium hydrogen carbonate (3 x 20 mL) and saturated aqueous sodium chloride (2 x 20 mL), dried (MgSO₄) and concentrated under reduced pressure to give a colourless solid. The residue was taken up in dichloromethane (30 mL), to this was added trifluoroacetic acid (2 mL) at 0 °C, and the mixture was allowed to warm to room temperature and was stirred for 6 h. The reaction mixture was concentrated under reduced pressure. The remaining residue was taken up in chloroform (100 mL), washed with 1 M NaOH (1 x 20 mL) and saturated sodium chloride (2 x 20 mL), dried (MgSO₄) and concentrated under reduced pressure to give 2-amino-N-(2,2-diphenylethyl)-acetamide as a colourless solid (2.14 g, 83%); mp > 212 °C (decomp); ¹H NMR (400 MHz, [D₆]DMSO): δ = 8.47 (t, J = 5.0 Hz, H_a), 8.00 (br s, 2H, H_d), 7.32–7.20 (m, 1OH, H_ph), 4.19 (t, J = 7.8 Hz, 1H, H_e), 3.81–3.77 (m, 2H, H_d), 3.44 (s, 2H, H_b); ¹³C
NMR (100 MHz, CDCl₃): δ = 166.5, 143.0, 128.8, 128.0, 126.8, 50.4, 43.6; HRMS (FAB, 3-NOBA matrix): m/z = 255.1494 [(M+H)⁺] (anal. calcd for C₁₆H₁₉N₂O₅⁺: m/z = 255.1497).

**Dimethyl 5-(2-(bis(pyridine-2-ylmethyl)amino)acetamido)isophthalate (1)**

EDCI (0.56 g, 2.9 mmol) was added in small batches to a solution of (bis(2-pyridylmethyl)amino)acetic acid (0.50 g, 1.9 mmol) and DMAP (0.36 g, 2.9 mmol) in dichloromethane (100 mL) at room temperature. The reaction mixture was stirred for 10 min, at which time dimethyl 5-aminoisophthalate (0.41 g, 1.9 mmol) was added in one portion, and the mixture was stirred for an additional 14 h. The reaction mixture was then washed with saturated aqueous sodium hydrogen carbonate (3 x 20 mL), saturated aqueous sodium chloride (2 x 20 mL), dried (MgSO₄) and concentrated under reduced pressure to give a colourless solid. The residue was recrystallised from acetone (20 mL) to furnish 1 as a white solid (0.62 g, 71%); mp 138-140 °C; ¹H NMR (400 MHz, CDCl₃): δ = 11.51 (br s, 1H, Hg), 8.70 (d, J = 1.5 Hz, 2H, Hₐ), 8.65 (d, J = 4.8 Hz, 2H, Hₐ), 8.36 (t, J = 1.5 Hz, 1H, H₃), 7.57 (t, J = 9.1 Hz, 2H, H₅), 7.20 (d, J = 7.8 Hz, 2H, H₆), 7.16 (t, J = 7.7 Hz, 2H, H₆), 3.90 (s, 10H, Hₑ & Hₛ), 3.49 (s, 2H, H₇); ¹³C NMR (100 MHz, CDCl₃): δ = 184.0, 166.3, 157.9, 131.1, 125.7, 124.7, 123.4, 122.8, 60.1, 58.8, 52.4; HRMS (FAB, 3-NOBA matrix): m/z = 449.1827 [(M+H)⁺] (anal. calcd for C₂₄H₂₅N₄O₅⁺: m/z = 449.1825).
Dimethyl 5-(2-(bis(pyridine-2-ylmethyl)amino)acetamido)isophthalate copper (II) dichloride (2)

To a solution of 1 (0.50 g, 1.1 mmol) in acetonitrile (10 mL), a saturated solution of CuCl₂·2H₂O (0.21 g, 1.2 mmol) in acetonitrile (1 mL) was added. The reaction mixture was stirred for 1 h, during which time a crystalline solid precipitated. The reaction mixture was filtered and the solid was washed with acetonitrile to furnish 2 as a light blue solid (0.6 g, 91%); mp 190-192 °C; HRMS (FAB, 3-NOBA matrix): m/z = 546.0748 [(M-C₁)⁺] (anal. calcd for C₂₄H₂₄C₁uN₄O₅⁺: m/z = 546.0731).

Dimethyl 5-(2-(bis(pyridine-2-ylmethyl)amino)acetamido)isophthalate copper (II) dichloride (4)

To a solution of 2 (100 mg, 0.23 mmol) in DMF (10 mL) was added NaH (10 mg, 0.25 mmol). The mixture was stirred for 1 h. The solution was concentrated under reduced pressure. The crude material was dissolved in acetonitrile, and immediately an emerald-green crystalline solid precipitated (110 mg, 91%); mp 184-185 °C; HRMS (FAB, 3-NOBA matrix): m/z = 546.0730 [(M-C₁)⁺] (anal. calcd for C₂₄H₂₃CuN₄O₅⁺: m/z = 546.0687).
2-(Bis-pyridin-2-ylmethyl-amino)-N-[(2,2-diphenylethylcarbamoyl)-methyl]-acetamide (5)

EDCI (4.78 g, 25.0 mmol) was added in small batches to a solution of (bis(2-pyridylmethyl)amino)acetic acid (2.86 g, 11.1 mmol) and DMAP (3.06 g, 25.0 mmol) in dichloromethane (300 mL). The reaction mixture was stirred for 10 min, after which time 2-amino-N-(2,2-diphenylethyl)-acetamide (2.59 g, 10.2 mmol) was added in one portion, then the mixture was stirred for an additional 14 h at room temperature. The solution was washed with saturated aqueous sodium hydrogen carbonate (3 x 50 mL), saturated aqueous sodium chloride (2 x 50 mL), dried (MgSO₄) and concentrated under reduced pressure to give a colourless solid (3.63 g, 72%). The residue was taken up in a minimum amount of toluene and upon cooling to -20 °C crystalline 5 separated from solution; mp 120-124 °C; ¹H NMR (400 MHz, [D₆]acetone): δ = 8.72 (t, J = 5.8 Hz, 1H, H₉), 8.56 (d, J = 4.8 Hz, 2H, Hₐ), 7.77 (dt, J = 7.6 Hz and J = 1.8 Hz, 2H, Hₘ), 7.56 (br s, 1H, Hₗ), 7.49 (d, J = 7.8 Hz, 2H, Hₜ), 7.27-7.19 (m, 12H, Hₘ & Hₚ), 4.22 (t, J = 7.8 Hz, 1H, Hₗ), 3.86 (dd, J = 7.8 Hz and J = 2.0 Hz, 2H, Hₗ), 3.82 (d, J = 6.1 Hz, 2H, Hₖ), 3.76 (s, 4H, Hₜ), 3.22 (s, 2H, Hₗ); ¹³C NMR (100 MHz, CDCl₃): δ = 171.8, 169.7, 158.0, 149.3, 141.8, 136.7, 128.3, 127.7, 126.6, 123.3, 122.5, 60.1, 58.1, 50.3, 43.7, 43.2; HRMS (FAB, 3-NOBA matrix): m/z = 494.2554 [(M+H)⁺] (anal. calcd for C₃₀H₃₂N₅O₂⁺: m/z = 494.2556).
2-(Bis-pyridin-2-y1methyl-amino)-N-[(2,2-diphenylethylcarbamoyl)-methyl]-acetamide copper (II) dichloride (7CuCl₂)

To a solution of 5 (1.0 g, 2.0 mmol) in acetonitrile (25 mL), a saturated solution of CuCl₂·2H₂O (0.36 g, 2.1 mmol) in acetonitrile (1 mL) was added. The reaction mixture was stirred for 1 h, during which time a solid precipitated. The reaction mixture was filtered and the solid was washed with acetonitrile to furnish 7CuCl₂ as a blue solid (1.3 g, 90%); mp > 166 °C (decomp); HRMS (FAB, 3-NOBA matrix): m/z = 591.1469 [(M-Cl)⁺] (anal. calcd for C₃₀H₃₁ClCuN₅O₂: m/z = 591.1462).

2-(Bis-pyridin-2-ylmethyl-amino)-N-[(2,2-diphenylethylcarbamoyl)-methyl]-acetamide cadmium (II) dinitrate (7Cd(NO₃)₂)

To a solution of 5 (0.50 g, 1.0 mmol) in acetonitrile (15 mL), a saturated solution of Cd(NO₃)₂·4H₂O (0.34 g, 1.1 mmol) in acetonitrile (1 mL) was added. The reaction mixture was stirred for 1 h, during which time a solid precipitated. The reaction mixture was filtered and the solid was washed with acetonitrile to furnish 7Cd(NO₃)₂ as a white solid (0.62 g, 85%); ¹H NMR (400 MHz, [D₆]acetone): δ = 8.66 (d, J = 4.7 Hz, 2H, Hₐ), 8.42 (t, J = 5.8 Hz, 1H, Hₗ), 8.00 (dt, J = 7.7 Hz and J = 1.6 Hz, 2H, Hₜ), 7.56-7.50 (m, 5H, Hₕ, Hₘ, Hₖ, & Hₜ), 7.26-7.13 (m, 10H, Hₘ), 4.30 (s, 4H, Hₚ), 4.19 (t, J = 7.9 Hz, 1H, Hₜ), 3.77 (dd, J = 7.8 Hz and J = 5.8 Hz, 2H, Hₗ), 3.65 (t, J = 4.8, 2H, Hₚ), 3.57-3.56 (m, 2H, Hₗ); ¹³C NMR (100 MHz, [D₇]DMF): δ = 173.5, 168.9, 158.9, 155.9, 150.8, 144.1, 141.1, 129.6, 129.1, 127.5, 126.2, 125.7, 58.7, 57.0, 51.7, 44.8, 43.8.
Chapter Two  
Complexation-Induced Translational Isomerism: Shuttling through Stepwise competitive binding

2-(Bis-pyridin-2-ylmethyl-amino)-N-[(2,2-diphenylethylcarbamoyl)-methyl]-acetamide cadmium (II) dinitrate (9CdNO₃)

To a solution of (7Cd(NO₃)₂) (0.01 g, 0.02 mmol) in DMF (1 mL) was added phosphazene P₁-tBu (4 mg, 0.02 mmol). The mixture was stirred for 1 h. The reaction mixture was concentrated under reduced pressure to furnish 9CdNO₃ as a white solid (7 mg, 77%); ¹H NMR (400 MHz, [D₆]acetone): δ = 8.78 (d, J = 3.6 Hz, 2H, Hₐ), 8.22-8.21 (br s, 1H, Hᵦ), 8.02 (t, J = 7.3 Hz, 2H, Hₑ), 7.60-7.58 (m, 4H, Hᵦ & Hᵦ), 7.31-7.10 (m, 10H, Hᵦ), 4.39 (t, J = 7.8 Hz, 2H, Hᵦ), 3.94 (dd, J = 23.4 Hz and J = 15 Hz, 4H, Hₑ), 3.82-3.80 (m, 2H, Hᵦ), 3.75 (t, J = 9.2, 2H, Hᵦ), 2.99 (s, 2H, Hᵦ).

([2](1,7,14,20-Tetraaza-2,6,15,19-tetraoxo-3,5,9,12,16,18,22,25-tetrabenzocyclohexacosane)-(2-(bis-pyridin-2-ylmethyl-amino)-N-[(2,2-diphenylethylcarbamoyl)-methyl]-acetamide) rotaxane (6)

A flask containing 5 (1.0 g, 2.0 mmol) and triethylamine (5.8 mL, 41 mmol) in chloroform (250 mL) was fitted with a rubber septum and a large magnetic stir bar and stirred vigorously. To this were simultaneously added solutions of p-xylylene diamine (2.8 g, 20 mmol) in chloroform (50 mL) and isophthaloyl dichloride (4.1 g, 20 mmol) in chloroform (50 mL) at equal rates via motor-driven syringe pumps over a period of 6 h. The resulting suspension was filtered over celite and concentrated under reduced pressure. To the residue was added acetone (100 mL) and the resulting
suspension was filtered, then the filtrate was collected and concentrated under reduced volume. The remaining residue was subjected to column chromatography on silica gel using dichloromethane/methanol/NH₄OH (aq) in a 9.2:0.8:0.005 v/v ratio as eluent to yield, in order of elution, the unconsumed thread and rotaxane (0.89 g, 44%); mp = 139-141 °C; ¹H NMR (400 MHz, [D₆]acetone): δ = 8.52 (d, J = 4.8 Hz, 2H, Hₐ), 8.43 (t, J = 4.8 Hz, 4H, H₈), 8.34 (s, 2H, H₆), 8.10 (dd, J = 7.7 Hz and J = 1.6 Hz, 4H, H₈), 7.85 (br s, 1H, Hₗ), 7.79 (br s, 1H, Hₖ), 7.64 (t, J = 7.8 Hz, 2H, H₇), 7.56 (t, J = 7.8 Hz, 2H, Hₖ), 7.22-6.96 (m, 14H, Hₐ, H₉ & Hₚₗₚ), 6.84 (s, 8H, H₉), 4.35 (m, 8H, H₈), 3.86 (t, J = 7.9 Hz, 1H, Hₗ), 3.76 (s, 4H, Hₖ), 3.54 (dd, J = 7.9 Hz and J = 5.6 Hz, 2H, Hₗ), 2.20 (d, J = 5.8 Hz, 2H, Hₗ); ¹³C NMR (100 MHz, CD₂Cl₂): δ = 167.1, 158.3, 149.7, 142.2, 137.5, 137.0, 134.7, 131.1, 129.3, 129.0, 128.0, 127.2, 126.0, 123.5, 122.9, 58.2, 44.8; HRMS (FAB, 3-NOBA matrix): m/z = 1026.4658 [(M+H)⁺] (anal. calcd for C₆₂H₆₀N₉O₆⁺: m/z = 1026.4667).

(1,7,14,20-Tetraaza-2,6,15,19-tetraoxo-3,5,9,12,16,18,22,25-tetrabenzocyclohexacosane)-(2-(bis-pyridin-2-ylmethyl-amino)-N-[2,2-diphenylethylcarbamoyl]-methyl-acetamide) cadmium (II) dinitrate rotaxane (8Cd(NO₃)₂)

To a solution of 6 (100 mg, 0.10 mmol) in acetonitrile (15 mL), a saturated solution of Cd(NO₃)₂·4H₂O (30 mg, 0.10 mmol) in acetonitrile (1 mL) was added. The reaction mixture was stirred for 1 h, during which time a solid precipitated. The reaction mixture was filtered and the solid was washed with acetonitrile to furnish 8Cd(NO₃)₂ as a white solid (113 mg, 92%); ¹H NMR (400 MHz, [D₆]acetone): δ = 8.78 (t, J = 5.3 Hz, 4H, Hₖ), 8.53 (d, J = 4.5 Hz, 2H, Hₐ), 8.41 (s, 2H, Hₖ), 8.18 (dd, J = 7.8 Hz and J = 1.6 Hz, 4H, Hₖ), 8.13 (dt, J = 7.7 Hz and J = 1.5 Hz, 2H, Hₖ), 7.90 (t,
Chapter Two

Complexation-Induced Translational Isomerism: Shuttling through Stepwise Competitive Binding

$J = 4.8 \text{ Hz}, 1H, H_\text{g}$, 7.72 (t, $J = 7.8 \text{ Hz}, 2H, H_\text{d}$), 7.65 (t, $J = 6.3 \text{ Hz}, 2H, H_\text{b}$), 7.52 (d, $J = 7.8 \text{ Hz}, 2H, H_\text{d}$), 7.26-7.14 (m, 1H, H_\text{i} & H_\text{Ph}), 6.87 (s, 8H, H_F), 4.40-4.28 (m, 8H, H_E), 3.98 (t, $J = 8.0 \text{ Hz}, 1H, H_\text{k}$), 3.65 (dd, $J = 29.7 \text{ Hz}$ and $J = 16.0 \text{ Hz}, 4H, H_e$), 3.55 (dd, $J = 7.8 \text{ Hz}$ and $J = 5.9 \text{ Hz}, 2H, H_j$), 2.20 (d, $J = 5.2 \text{ Hz}, 2H, H_a$) 2.42 (br s, 2H, H_j); $^{13}$C NMR (100 MHz, [D_7]DMF): $\delta = 168.4, 167.5, 158.9, 150.6, 143.6, 141.6, 141.3, 138.7, 135.9, 131.4, 130.0, 129.6, 129.4, 128.6, 127.7, 127.5, 126.3, 125.9, 59.3, 44.7, 43.8, 42.4.

2,2-Diphenylethyl 4-(12-(2-aminoacetamido)dodecylamino)-4-oxobutanoate

EDCI (2.70 g, 14.1 mmol) was added in small batches to a solution of Boc-glycine (1.00 g, 5.71 mmol) and DMAP (1.72 g, 14.1 mmol) in dichloromethane (200 mL) at room temperature. The reaction mixture was stirred for 10 min, at which time 2,2-diphenylethyl 4-(12-aminododecylamino)-4-oxobutanoate (2.74 g, 5.71 mmol) was added in one portion. The reaction mixture was allowed to stir at room temperature for an additional 14 h. The solution was washed with 1 M aqueous HCl (3 x 20 mL), saturated aqueous sodium hydrogen carbonate (3 x 20 mL) and saturated aqueous sodium chloride (2 x 20 mL), dried (MgSO_4) and concentrated under reduced pressure to give a colourless solid. The residue was taken up in dichloromethane (30 mL), to this was added trifluoroacetic acid (2 mL) at 0 °C and the mixture was allowed to warm to room temperature and stirred for an additional 6 h. The reaction mixture was concentrated under reduced pressure. The remaining residue was taken up in chloroform (100 mL) and washed with 1 M NaOH (1 x 30 mL) and saturated sodium chloride (2 x 30 mL), dried (MgSO_4) and concentrated under reduced pressure to give 2,2-diphenylethyl 4-(12-(2-aminoacetamido)dodecylamino)-4-oxobutanoate as a colourless solid (2.18 g, 71%); mp 76-80 °C; $^1$H NMR (400 MHz, CDCl_3): $\delta = 7.23$-$7.14$ (m, 10H, H_\text{Ph}), 5.44 (br s, 1H, H_k), 4.56 (d, $J = 7.9 \text{ Hz}, 2H, H_d$), 4.28 (t, $J = 7.3 \text{ Hz}, 1H, H_i$), 3.27 (s, 2H, H_b), 3.20 (q, $J = 6.5 \text{ Hz}, 2H, H_g$), 3.11 (q, $J = 7.3 \text{ Hz}, 2H, H_d$), 2.52 (t, $J = 7.0 \text{ Hz}, 2H, H_j$), 2.26 (t, $J = 6.8 \text{ Hz}, 2H, H_j$), 1.51-1.44 (m, 4H, H_F & H_e), 1.18 (br s, 16H, alkyl CH_2); $^{13}$C NMR (100 MHz, CDCl_3): $\delta = 183.8, 172.9,
157.9, 141.0, 128.6, 128.2, 126.8, 66.9, 49.8, 42.2, 39.6, 31.1, 29.7, 29.6, 29.5, 29.2, 26.9; HRMS (FAB, 3-NOBA matrix): \( m/z = 538.3647 \) [(M+H)\(^+\)] (anal. calcd for \( \text{C}_{32}\text{H}_{48}\text{N}_{3}\text{O}_{4} \): \( m/z = 538.3645 \)).

2,2-Diphenylethyl 4-[(12-[(2-(bis(pyridine-2-ylmethyl)amino)acetamido)acetamido)dodecylamino]-4-oxobutanoate (11)

EDCI (1.6 g, 8.1 mmol) was added in small batches to a solution of \( \text{(bis(2-pyridylmethyl)amino)acetic acid (0.82 g, 3.2 mmol) and DMAP (1.0 g, 8.1 mmol) in} \) dichloromethane (200 mL). The reaction mixture was stirred for 10 min, at which time 2,2-diphenylethyl 4-[(12-(2-aminoacetamido)dodecylamino)-4-oxobutanoate (1.7 g, 3.2 mmol) was added in one portion, and the solution was stirred for an additional 14 h at room temperature. The reaction mixture was then washed with saturated aqueous sodium hydrogen carbonate (3 x 50 mL), saturated aqueous sodium chloride (2 x 50 mL), dried (MgSO\(_4\)) and concentrated under reduced pressure to give a colourless solid. The remaining residue was subjected to column chromatography on silica gel using dichloromethane/methanol/N\(_2\)OH (aq) in a 9.6:0.4:0.0025 v/v ratio as eluent to furnish 11 as a white solid (2.0 g, 83%) mp 86-88 \(^\circ\)C; \(^1\)H NMR (400 MHz, [D\(_6\)]acetone): \( \delta = 8.97 \) (br s, 1H, H\(_g\)), 8.62 (d, \( J = 4.8 \) Hz, 2H, H\(_a\)), 7.90 (t, \( J = 7.1 \) Hz, 2H, H\(_c\)), 7.70 (d, \( J = 7.5 \) Hz, 2H, H\(_d\)), 7.52 (br s, 1H, H\(_n\)), 7.42, (t, \( J = 5.8 \) Hz, 2H, H\(_b\)), 7.36-7.24 (m, 10H, H\(_{Ph}\)), 7.07 (br s, 1H, H\(_i\)), 4.66 (d, \( J = 7.6 \) Hz, 2H, H\(_q\)), 4.42 (t, \( J = 7.8 \) Hz, 1H, H\(_r\)), 4.05 (s, 4H, H\(_c\)), 3.90 (d, \( J = 4.3 \) Hz, 2H, H\(_h\)), 3.40 (s, 2H, H\(_j\)), 3.19-3.07 (m, 4H, H\(_j\) & H\(_m\)), 2.50 (t, \( J = 7.1 \) Hz, 2H, H\(_o\)), 2.39 (t, \( J = 7.1 \) Hz, 2H, H\(_p\)), 1.46-1.41 (m, 4H, H\(_k\) & H\(_l\)), 1.26 (br s, 16H, alkyl CH\(_2\)); \(^{13}\)C NMR (100 MHz, [D\(_6\)]acetone): \( \delta = 175.2, 173.1, 159.5, 158.8, 150.0, 142.6, 137.4, 129.3, 129.0, 127.5, 124.3, 123.2, 67.1, 60.8, 58.7, 50.7, 43.0, 39.6, 30.9, 27.5; HRMS (FAB, 3-NOBA matrix): \( m/z = 777.4703 \) [(M+H)\(^+\)] (anal. calcd for \( \text{C}_{46}\text{H}_{61}\text{N}_{6}\text{O}_{5}^{+} \): \( m/z = 777.4703 \)).
2,2-Diphenylethyl 4-(12-(2-(bis(pyridine-2-ylmethyl)amino)acetamido)dodecylamino-4-oxobutanoate cadmium (II) dinitrate (11 Cd(NO₃)₂)

To a solution of 11 (0.01 g, 0.02 mmol) in [D₆]acetone (1 mL), Cd(NO₃)₂·4H₂O (6 mg, 0.02 mmol) was added. The reaction mixture was stirred for 1 h. Yield (>97%); ^1^H NMR (400 MHz, [D₆]acetone): δ = 8.67 (d, J = 4.1 Hz, 2H, H₉), 8.10 (br s, 1H, H₆), 8.00 (dt, J = 7.7 Hz and J = 1.3 Hz, 2H, H₂), 7.56 (d, J = 7.7 Hz, 2H, H₃), 7.32-7.19 (m, 13H, H₉, H₆ & H₈), 7.03 (br s, 1H, H₁), 4.62 (d, J = 7.6 Hz, 2H, H₄), 4.39 (t, J = 7.6 Hz, 1H, H₆), 4.34 (s, 4H, H₃), 3.74 (t, J = 7.6 Hz, 2H, H₂), 3.68-3.67 (m, 2H, H₃), 3.16-3.07 (m, 4H, H₁ & H₃), 2.46 (t, J = 7.1 Hz, 2H, H₁), 2.35 (t, J = 7.1 Hz, 2H, H₃), 1.46-1.38 (m, 4H, H₃ & H₄), 1.25 (br s, 16H, alkyl CH₂); ^1^C NMR (100 MHz, [D₇]DMF): δ = 171.5, 168.5, 158.9, 155.9, 150.5, 143.0, 141.1, 129.6, 129.3, 127.8, 126.1, 125.6, 67.5, 59.6, 51.0, 49.9, 44.0, 40.1 (x2), 27.9, 27.8.

([12](1,7,14,20-Tetraaza-2,6,15,19-tetraoxo-3,5,9,12,16,18,22,25-tetrabenzocyclohexacosane)-(2,2-diphenylethyl 4-(12-(2-(bis(pyridine-2-ylmethyl)amino)acetamido)dodecylamino-4-oxobutanoate) rotaxane (12)

Synthesis of 12 was similar to that described for 6, except that thread 11 (0.70 g, 0.9 mmol) was used in place of 5. The quantities of the other components were: p-xylylene diamine (2.04 g, 15.0 mmol), isophthaloyl dichloride (3.05 g, 15.0 mmol)
and triethylamine (4.22 mL, 30.0 mmol). The residue was separated by column chromatography on silica gel using dichloromethane/methanol/NH$_4$OH (aq) in a 9.6:0.4:0.0025 v/v ratio as eluent to furnish 12 as a white solid (0.268 g, 22%) mp 58-60 °C; $^1$H NMR (400 MHz, [D$_6$]acetone): $\delta$ = 8.58 (d, $J$ = 4.5, 2H, $H_a$), 8.43 (s, 2H, $H_c$), 8.29 (br s, 5H, $H_D$ & $H_g$), 8.13 (d, $J$ = 7.8 Hz, 4H, $H_b$), 7.68-7.59 (m, 4H, $H_d$ & $H_e$), 7.49 (br s, 1H, $H_i$), 7.34-7.22 (m, 14H, $H_{Ph}$, $H_d$ & $H_b$), 7.19 (s, 8H, $H_F$), 7.13 (br s, 1H, $H_m$), 4.63-4.58 (m, 6H, $H_E$ & $H_q$), 4.40-4.31 (m, 5H, $H_E$ & $H_r$), 3.87 (s, 4H, $H_e$), 3.31 (s, 2H, $H_f$), 3.08 (q, $J$ = 6.6 Hz, 2H, $H_m$), 3.00 (d, $J$ = 5.3 Hz, 2H, $H_b$), 2.76 (q, $J$ = 6.0 Hz, 2H, $H_j$), 2.29 (t, $J$ = 7.1 Hz, 2H, $H_o$), 2.16 (t, $J$ = 6.9 Hz, 2H, $H_p$) 1.41 (br s, 2H, $H_1$), 1.25-0.98 (m, 18H, alkyl CH$_2$ & $H_k$); $^{13}$C NMR (100 MHz, [D$_6$]acetone): $\delta$ = 173.4, 166.9, 159.4, 149.9, 142.6, 138.8, 137.6, 135.6, 131.4, 129.8, 129.4, 129.3, 129.0, 127.5, 126.7, 124.1, 123.3, 67.2, 60.8, 58.7, 50.6, 44.7, 42.6, 40.0, 39.9, 30.9, 27.5; HRMS (FAB, 3-NOBA matrix): m/z = 1309.6819 [(M+H)$^+$] (anal. calcd for C$_{78}$H$_{89}$N$_{10}$O$_9$): m/z = 1309.6814.

(12)[(1,7,14,20-Tetraaza-2,6,15,19-tetraoxo-3,5,9,12,16,18,22,25-tetarbenezocyclohexacosane)-(2,2-diphenylethyl 4-(12-(2-(2-(1bis(pyridine-2-ylmethyl)amino)acetamido)acetamido)dodecylamino)acetamido)acetamido)dodecylamino-4-oxobutanoate) copper (II) dichloride rotaxane (15)

To a solution of 12 (50 mg, 0.035 mmol) in acetonitrile (5 mL), a saturated solution of CuCl$_2$·2H$_2$O (12 mg, 0.038 mmol) in acetonitrile (1 mL) was added. The reaction mixture was stirred for 1 h, during which time a solid precipitated. The reaction mixture was filtered and the solid was washed with acetonitrile to furnish 15 as a light blue solid (50 mg, 90%); mp > 132 °C (decomp); HRMS (FAB, 3-NOBA matrix): m/z = 1406.5723 [(M-Cl)$^+$] (anal. calcd for C$_{78}$H$_{88}$ClCuN$_{10}$O$_9$: m/z = 1406.5720).
Chapter Two

Complexation-Induced Translational Isomerism: Shuttling through Stepwise Competitive Binding

([2](1,7,14,20-Tetraaza-2,6,15,19-tetraoxo-3,5,9,12,16,18,22,25-tetrabenzocyclohexacosane)-(2,2-diphenylethyl 4-(12-(2-(2-(bis(pyridine-2-ylmethyl)amino)acetamido)acetamido)dodecylamino-4-oxobutanoate) cadmium (II) dinitrate rotaxane (13)

![Chemical Structure Diagram]

To a solution of 12 (0.01 g, 0.01 mmol) in [D\textsubscript{6}]acetone (1 mL), Cd(NO\textsubscript{3})\textsubscript{2}·4H\textsubscript{2}O (2 mg, 0.01 mmol) was added. The reaction mixture was stirred for 1 h. Yield (>97%); \textsuperscript{1}H NMR (400 MHz, [D\textsubscript{6}]acetone): \(\delta = 8.59-8.57\) (m, 6H, \(H_D\) & \(H_d\)), 8.41 (s, 2H, \(H_c\)), 8.32 (t, \(J = 5.5\) Hz, 1H, \(H_g\)), 8.13-8.06 (m, 6H, \(H_B\) & \(H_e\)), 7.66-7.60 (m, 4H, \(H_A\) & \(H_b\)), 7.52 (d, \(J = 7.9\) Hz, 2H, \(H_d\)), 7.32-7.18 (m, 12H, \(H_{Ph}, H_i\) & \(H_n\)), 7.08 (s, 8H, \(H_f\)), 4.54 (d, \(J = 7.6\) Hz, 2H, \(H_q\)), 4.47-4.30 (m, 9H, \(H_E\) & \(H_r\)), 3.88 (s, 4H, \(H_e\)), 3.38-3.37 (m, 2H, \(H_h\)), 3.02 (s, 2H, \(H_g\)), 2.95-2.93 (m, 2H, \(H_m\)), 2.78 (br s, 2H, \(H_j\)), 2.27 (t, \(J = 7.0\) Hz, 2H, \(H_o\)), 2.17 (t, \(J = 6.7\) Hz, 2H, \(H_p\)) 1.40-1.32 (m, 2H, \(H_l\)), 1.18-1.04 (m, 16H, alkyl CH\textsubscript{2}) 1.00-0.93 (m, 2H, \(H_k\)).
To a solution of 12 (0.01 g, 0.01 mmol) in [D$_7$]DMF (1 mL) was added phosphazene P$_{1-t}$Bu (2 mg, 0.01 mmol). The mixture was stirred for 1 h. Yield (> 97%); $^1$H NMR (400 MHz, [D$_6$]acetone): $\delta = 8.68$-$8.62$ (m, 2H, $H_a$), 8.46 (s, 2H, $H_c$), 8.23 (br s, 5H, $H_D$ & $H_g$), 8.12-$8.09$ (m, 4H, $H_B$), 8.04-$7.97$ (q, $J = 7.3$ Hz, 2H, $H_e$), 7.60-$7.54$ (m, 6H, $H_a$, $H_b$ & $H_d$), 7.30-$7.10$ (m, 20H, $H_{Ph}$, $H_i$, $H_m$ & $H_F$), 4.63-$4.17$ (m, 15H, $H_E$, $H_r$, $H_e$ & $H_q$), 3.93 (s, 2H, $H_j$), 3.11 (br s, 2H, $H_i$), 3.04 (s, 2H, $H_h$), 2.34 (br s, 2H, $H_m$), 1.67-$1.65$ (m, 2H, $H_o$), 1.50-$1.48$ (m, 2H, $H_p$), 1.25 (br s, 2H, $H_k$), 1.13-$1.10$ (m, 16H, alkyl CH$_2$), 0.80 (br s, 2H, $H_1$).

2.5 References and Notes

Chapter Two

Complexation-Induced Translational Isomerism: Shuttling through Stepwise Competitive Binding


[8] For example, see: R. Ballardini, V. Balzani, A. Credi, M. T. Gandolfi, S. J. Langford, S. Menzer, L. Prodi, J. F. Stoddart, M. Venturi, D. J. Williams,


[15] \[1 = 5-\{2-(\text{bis-pyridin-2-ylmethyl-}a\text{mino})-\text{acetyl-lamino}\}-\text{isophthalic acid dimethyl ester}; \]
\[5 = 2-(\text{bis-pyridin-2-ylmethyl-}a\text{mino})-N-\{2,2-\text{diphenyl-}
\text{ethylcarbamoyl}\}-\text{methyl}-\text{acetamide}; \]
\[8 = \{\{2\}(1,7,14,20-\text{Tetraaaza-2,6,15,19-tetraoxo-3,5,9,12,16,18,22,25-tetraenzenzyenolhexacosane})-(2-(\text{bis-pyridin-2-}
\text{ylmethyl-}a\text{mino})-N-\{2,2-\text{diphenyl-ethylcarbamoyl}\}-\text{methyl}-\text{acetamide}\} \]
\[\text{rotaxane}; \]
\[11 = 2,2-\text{Diphenylethyl 4-(12-(2-(\text{bis-pyridin-2-ylmethyl-}a\text{mino})-}\text{acetamido}) \text{acetamido}) dodecylamino-4-oxobutanoate}; \]
\[12 = \{\{2\}(1,7,14,20-\text{Tetraaaza-2,6,15-19-tetraoxo-3,5,9,12,16,18,22,25-
\text{tetraenzenzyenolhexacosane})-(2,2-\text{diphenylethyl 4-(12-(2-(\text{bis-pyridin-2-}
\text{ylmethyl-}a\text{mino})-}\text{acetamido}) \text{acetamido}) dodecylamino-4-oxobutanoate}\} \]
\[\text{rotaxane}. \]

[16] X-ray crystal structural data for \[2, 3, 6, 9\text{CdNO}_3\] and \[8\text{Cd(NO}_3)_2\] were collected at 93 K using a Rigaku Saturn (MM007 high flux RA/MoKa radiation, confocal optic), while \[4\] and \[9\text{CuCl}\] were collected at 93 K using a Mercury (MM007 high flux RA/MoKa radiation, confocal optic). All data collections employed narrow frames (0.3-1.0°) to obtain at least a full hemisphere of data. Intensities were corrected for Lorentz polarization and absorption effects (multiple equivalent reflections). Structures were solved by direct methods, non-hydrogen atoms were refined anisotropically with C-H protons being refined in riding geometries (SHELXTL) against \[F^2\]. In most cases, amide protons were refined isotropically subject to a distant constraint.
The protons on solvate molecules were not allowed for in the refinement. Data for 2-0.5CH₃CN-0.055H₂O: C₂₅H₂₅61Cl₆CuN₄.5O₅.06, M = 604.44, crystal size 0.1 x 0.05 x 0.01 mm³, trigonal, P-3, a = 40.804(2), c = 8.4772(4) Å, Z = 18, \( \rho_{\text{calcld}} = 1.478 \text{ Mg m}^{-3} \); \( \mu = 1.044 \text{ mm}^{-1} \), 91570 collected, 14360 unique (\( R_{\text{int}} = 0.0825 \)) giving \( R = 0.1258 \) for 12778 observed data \([F_o > 4\sigma(F_o)]\), \( S = 1.189 \) for 1037 parameters. Residual electron density extremes were 1.500 and -1.250 eÅ⁻³.

For 3-0.5H₂O: C₄₈H₄₉O₆Cu₃N₈O₁₀₅, M = 1309.27, crystal size 0.1 x 0.05 x 0.03 mm³, monoclinic, \( P2(1)/n \), a = 8.1667(16), \( b = 30.257(5) \), \( c = 23.377(4) \) Å, \( Z = 4 \), \( \rho_{\text{calcld}} = 1.506 \text{ Mg m}^{-3} \); \( \mu = 1.433 \text{ mm}^{-1} \), 51258 collected, 11852 unique (\( R_{\text{int}} = 0.0484 \)) giving \( R = 0.1234 \) for 9492 observed data \([F_o > 4\sigma(F_o)]\), \( S = 1.540 \) for 691 parameters. Residual electron density extremes were 2.381 and -1.117 eÅ⁻³.

Data for 4: C₂₄H₂₃ClCuN₄O₅, M = 546.45, crystal size 0.2 x 0.1 x 0.1 mm³, monoclinic, \( C2/c \), a = 14.026(3), \( b = 11.390(3) \), \( c = 30.259(6) \) Å, \( Z = 8 \), \( \rho_{\text{calcld}} = 1.513 \text{ Mg m}^{-3} \); \( \mu = 1.940 \text{ mm}^{-1} \), 9975 collected, 3728 unique (\( R_{\text{int}} = 0.0333 \)) giving \( R = 0.0456 \) for 3104 observed data \([F_o > 4\sigma(F_o)]\), \( S = 1.024 \) for 329 parameters. Residual electron density extremes were 0.472 and -0.383 eÅ⁻³.

Data for 9CuCl: C₃₀H₃₀Cu₅N₅O₂, M = 591.58, crystal size 0.2 x 0.1 x 0.1 mm³, monoclinic, \( P2(1)/n \), a = 16.089(3), \( b = 9.9833(18) \), \( c = 16.968(3) \) Å, \( Z = 4 \), \( \rho_{\text{calcld}} = 1.446 \text{ Mg m}^{-3} \); \( \mu = 0.940 \text{ mm}^{-1} \), 15979 collected, 4822 unique (\( R_{\text{int}} = 0.0333 \)) giving \( R = 0.0486 \) for 4460 observed data \([F_o > 4\sigma(F_o)]\), \( S = 1.053 \) for 357 parameters. Residual electron density extremes were 2.384 and -0.553 eÅ⁻³.

For 9CdNO₃: C₃₀H₃₀CdN₆O₅, M = 667.00, crystal size 0.15 x 0.15 x 0.05 mm³, monoclinic, \( P2(1)/c \), a = 9.8549(14), \( b = 17.620(3) \), \( c = 16.444(3) \) Å, \( Z = 4 \), \( \rho_{\text{calcld}} = 1.553 \text{ Mg m}^{-3} \); \( \mu = 0.817 \text{ mm}^{-1} \), 4953 unique (\( R_{\text{int}} = 0.0301 \)) giving \( R = 0.0285 \) for 4357 observed data \([F_o > 4\sigma(F_o)]\), \( S = 1.085 \) for 384 parameters. Residual electron density extremes were 1.387 and -0.435 eÅ⁻³.

For 8Cd(NO₃)₂: C₆₂H₅₉CdN₁₁O₁₂, M = 1262.6, crystal size 0.1 x 0.1 x 0.03 mm³, monoclinic, \( C2/c \), a = 28.252(13), \( b = 10.588(5) \), \( c = 42.457(19) \) Å, \( Z = 8 \), \( \rho_{\text{calcld}} = 1.439 \text{ Mg m}^{-3} \); \( \mu = 0.426 \text{ mm}^{-1} \), 27366 collected, 9652 unique (\( R_{\text{int}} = 0.0925 \)) giving \( R = 0.0814 \) for 5850 observed data \([F_o > 4\sigma(F_o)]\), \( S = 1.076 \) for 857 parameters. Residual electron density extremes were 0.976 and -0.640 eÅ⁻³. The protons on solvate molecules were not allowed for in the refinement. CCDC 269894-269900 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/data_request/cif.

[17] Some of the emerald-green colour of 3 can be attributed to the [CuCl₄]⁻ counterion.

[18] Wrapped up metal-peptide complexes are widely seen in biological contexts, for example, with copper and various tripeptide ligands; see: a) H. Sigel, R. B. Martin, Chem. Rev. 1982, 82, 385-426; b) P. Deschamps, P. P. Kulkarni, M. Gautam-Basak, B. Sarkar, Coord. Chem. Rev. 2005, 249, 895-909. However,
the use of a designed auxiliary ligand attached to the peptide that facilitates stepwise control over the binding modes is, to the best of our knowledge, unknown.


[21] The molecular shuttle rotaxane and thread cadmium complexes were insufficiently soluble in CDCl$_3$ or CD$_2$Cl$_2$ for $^1$H NMR studies, so [D$_6$]acetone was used throughout.


[23] Without this discrimination, the more-complicated molecular shuttle system containing multiple amide groups would not be able to function.


CHAPTER THREE

An Allosterically Regulated Molecular Shuttle

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Synopsis

Chapter Two demonstrated that the motion of a benzylic amide macrocycle can be induced by coordination of a metal ion to a bis(2-picolyl)amino(BPA)-derivatised glycyglycine unit, followed by deprotonation of the carboxamide nitrogen nearest to the chelate group in a “competitive binding” mechanism. In this Chapter, a second metal-mediated shuttling method utilising a similar architecture is shown, but this time, rather than competing for the same donor atoms, the metal ion and macrocycle compete for the same 3D space.

Initially, the macrocycle resides overwhelmingly on the succinamide station that is directly attached to the BPA unit. However, addition of one equivalent of Cd(NO$_3$)$_2$ results in chelation of the three nitrogen atoms of the BPA ligand to the metal ion, demanding a change in the orientation of the carboxamide carbonyl with respect to the other carbonyl groups in the peptide station. This results in a significantly decreased affinity of the macrocycle for the binding site and leads to its translocation to the intrinsically weaker hydrogen bonding succinic amide ester station. The motion is completely reversible on removal of the metal ion.

This controlled large-amplitude motion, therefore, offers the possibility to use metal-binding events as an external stimulus to trigger physical property changes.
3.1 Introduction

One of nature's most effective ways of influencing chemical function from afar is through allosteric control.[1] This occurs - most typically in proteins - when activity at a substrate-binding site is modulated by the complexation of an effector molecule or ion at a second site. The binding sites are frequently several nanometers apart, and communication between them is achieved through a variety of mechanisms, the details of which are not well understood but often involve multiple substrate-binding sites and cooperative complexation events that are accompanied by large-amplitude movements of polypeptide chains and other molecular subunits.[2] However, to achieve any kind of distant control in response to binding in synthetic systems is far from trivial. Most of the artificial allosteric receptors developed to date feature one or more substrate-interaction sites directly conformationally coupled to an effector binding site.[3] Herein, we report on a mechanically linked substrate/host ensemble (a rotaxane) which contains two spatially and chemically distinct "substrate" hydrogen-bonding sites, only one of which is influenced by the coordination of a metal ion (the "effector") to an adjacent tridentate ligand fragment. The result is a stimuli-responsive molecular shuttle[4] that undergoes a large-amplitude internal motion (change in the position of the macrocycle), allosterically regulated through a small, but highly significant, conformational change brought about by complexation of a transition metal at the effector site.

3.2 Results and Discussion

The molecular shuttle allosteric control mechanism has its origins in anomalous behaviour observed for some simple hydrogen-bonded rotaxanes that bear metal-chelating stoppers containing a bis(2-picoly)amine (BPA)[5] moiety (Scheme 3.1). Rotaxanes 1 and 2, in which the BPA unit is connected to the hydrogen-bonding groups of the thread by an ethylene spacer, react readily with various transition-metal salts including CuCl₂·2H₂O, which yields complexes 3 and 4, respectively (Scheme 3.1, a and b). The X-ray crystal structures of 3 and 4 (Figure 3.1a and b) show the typical four intercomponent hydrogen bonds between the benzylic amide groups of the macrocycle and the amide groups of the thread,[6] together with the predicted...
coordination of the BPA ligands to each metal ion in a tridentate fashion. However, to our surprise, rotaxanes 5 and 6, in which the ethylene spacer is absent and the BPA unit is attached directly to the hydrogen-bonding station of the thread, were found not to react\(^7\) with CuCl\(_2\)·2H\(_2\)O or similar transition-metal salts even under forcing conditions (Scheme 3.1, c and d). This behaviour is in marked contrast to that of their parent threads which react like rotaxanes 1 and 2 to give the expected coordination complexes, indicating that the reduced electron density on the nitrogen atom caused by the adjacent carbonyl group is not the reason for the lack of reaction of 5 and 6.\(^5\)
Scheme 3.1 Rotaxanes 1, 2, 5 and 6 and their attempted complexation reactions with one (a, c) or two (b, d) equivalents of CuCl$_2$·2H$_2$O in DMF at room temperature (RT). Complexes 3 and 4 are formed in near-quantitative yield and were purified by recrystallisation from acetonitrile/DMF.$^{[1]}$ 7 and 8 could not be detected even upon heating at 80 °C for 12 h.$^{[7]}$ The free threads of 1, 2, 5 and 6 each react readily with CuCl$_2$·2H$_2$O in DMF at RT to form coordination complexes that are analogous to 3 and 4.

The X-ray crystal structures of 5 and 6 (Figure 3.1c-f) reveal the reason for their lack of reactivity. Although the macrocycles in 5 and 6 form hydrogen bonds to the thread through the four intercomponent hydrogen bonds – shown in the stick representation, Figures 3.1c and d – analogous to rotaxanes 1 and 2, the pyridine arms of the BPA groups are forced close-to-parallel with the isophthalamide groups of the macrocycle – concomitantly forming favourable π-π stacking interactions – to accommodate the ring on the hydrogen bonding site. To chelate to a metal ion by
using all three nitrogen atoms of the BPA group, the pyridine arms must twist orthogonally, causing them to enter space that is already occupied by the benzylic amide macrocycle. However, the macrocycle physically has nowhere else to move to in either 5 or 6 – see the space-filling representations, Figure 3.1e and f – and so the conformational change required for the BPA group to chelate to a transition metal cannot take place in these short congested rotaxane structures.

Figure 3.1 X-ray crystal structures[81] of a) 3; b) 4; c) 5 and d) 6 in stick representation, and e) 5 and f) 6 in space-filling van der Waals radius form. C (thread) yellow, C (macrocycle) blue, O red, N dark blue, CuII grey, Cl green, H white. In the stick representations, all hydrogen atoms except for the amide and olefin protons have been omitted for clarity. Selected bond distances [Å]: 3; N12-Cu2 2.075, N42-Cu2 1.987, N112-Cu2 1.987, Cl3-Cu2 2.235, Cl4-Cu2 2.563, N264H-O222 2.236, N354H-O222 2.353, N174H-O192 2.260, N84H-O192 2.290; 4; N11-Cu1 2.076, N41-Cu1 2.001, N111-Cu1 2.027, Cu1-C11 2.497, Cu1-C11 2.322, N172H-O191 2.140, N82H-O191 2.260; 5; N20H-O42 2.239, N29H-O42 2.136, N2H-O45 2.687, N11H-O45 1.957; 6; N172H-O161 1.985, N82H-O161 2.212.
The prospect of a situation where, despite binding at different sites, metal- and macrocycle-binding modes compete for the same 3D space led us to consider whether translocation of the macrocycle to a second hydrogen-bonding site on a thread could be induced by a metal-binding interaction. As a model we designed rotaxane 9 (Scheme 3.2), which contains three carbonyl hydrogen-bond acceptors on the thread in what can be viewed as an elongated hydrogen-bonding station — for clarity in interpreting the $^1$H NMR spectra (Figure 3.2), one half of this unit is coloured in green and the other in orange. With this extended station, the macrocycle in 9 has space to occupy (and hydrogen-bonding partners) when a metal binds to, and rearranges the conformation of, the BPA-containing stopper. The solid-state structure of 9 (Scheme 3.2, b) reveals that the macrocycle is bound to the central carbonyl group (O41) of the thread through hydrogen bonds between the carboxamide hydrogen donors (N20H and N29H) and the amide carbonyl group adjacent to the diphenylacetyl stopper (O44). However, the carbonyl group (O38) adjacent to the BPA station is also in the plane of the other two carbonyl groups (O41 and O44) on the thread, and in solution one would expect an equilibrium to exist between the hydrogen bonding of N11H and O44 and a similar interaction between O38 and N2H (Scheme 3.2, a). Indeed, the $^1$H NMR spectrum of rotaxane 9 in CD$_3$CN (Figure 3.2b) reveals that this is the case, with the chemical shifts of both internal methylene groups H$_f$ and H$_h$ (green and orange, respectively) shifted upfield ($\Delta \delta H_f = 0.6$ ppm; $\Delta \delta H_h = 1.0$ ppm) relative to the free thread (Figure 3.2a) as a result of shielding from the macrocycle.
**Scheme 3.2** Rotaxane 9 with an extended hydrogen-bonding site and its subsequent complexation to generate $9M(X)\_2$ ($M(X)\_2 = \text{CuCl}_2$ or $\text{Cd(NO}_3\text{)}\_2$): a) the solution positional equilibrium of the macrocycle in 9 (atom-lettering scheme corresponds to $^1\text{H NMR assignments in Figure 3.2})$ The complexes $9M(X)\_2$ were prepared by addition of a solution of the appropriate metal salt in acetonitrile to solution of 9 in acetonitrile at RT and purified by crystallization. b, c) X-ray crystal structures of 9 and $9\text{CuCl}_2$, respectively. C (thread) yellow, C (macrocycle) blue, O red, N dark blue, $\text{Cu}^{\text{II}}$ grey, Cl green, H white; all hydrogen atoms except for the amide protons have been omitted for clarity. Selected bond distances [Å]: 9; N20H-O41 2.026, N29H-O41 2.192, N11H-O44 1.888; $9\text{CuCl}_2$; N37-Cu1 2.432, N60-Cu1 1.976, N67-Cu1 1.987, Cl1-Cu1 2.256, Cl2-Cu1 2.227, N2H-O41 2.190, N11H-O41 2.153, N29H-O44 1.885. The red circles highlight the enforced change in conformation of the BPA ligand and adjacent peptide unit upon coordination to a metal ion.

Addition of CuCl$_2$·2H$_2$O to 9 results in formation of complex 9CuCl$_2$, the X-ray crystal structure of which is shown in Scheme 3.2, c. The most striking characteristic of this solid-state structure is the chelation of all three BPA nitrogen atoms – including the carboxamide nitrogen, N37 – to the Cu$^{\text{II}}$ ion, together with the out-of-plane tilting of carbonyl oxygen O38 relative to the plane in which the other two
carbonyl oxygen atoms (O41 and O44) of the thread lie. As Cd$^{II}$ is a diamagnetic metal with similar binding properties to Cu$^{II}$, treatment of 9 with Cd(NO$_3$)$_2$$\cdot$4H$_2$O allowed us to study the solution behaviour of metal chelation to 9 using $^1$H NMR spectroscopy (compare Figure 3.2c with 3.2b and d). As expected, the binding of a metal ion to the BPA stopper alters the equilibrium of hydrogen bonding between the three carbonyl hydrogen-bond acceptors in 9, causing a shift of the signal for $H_h$ (orange) further upfield and a slight downfield shift of the resonance for $H_f$ (green) in 9Cd(NO$_3$)$_2$ relative to those in the free rotaxane. Comparison of the $^1$H NMR spectra of 9Cd(NO$_3$)$_2$ with the Cd(NO$_3$)$_2$-thread complex revealed a similar trend, that is, a large upfield shift of the signal for $H_h$ and a much smaller shift for that of $H_f$. The changes indicate that the macrocycle no longer shuttles back and forth along the thread in 9Cd(NO$_3$)$_2$ but is restricted mainly to a position over the $H_h$ methylene group between carbonyl oxygens O41 and O44.

Encouraged by the results from this model system we prepared a two-station rotaxane, 10, with hydrogen-bonding sites of substantially differing affinities$^{[9]}$ for the macrocycle, separated by a C$_{12}$ alkyl chain. The station of known$^{[9]}$ higher binding affinity (succinamide, shown in green) is directly attached to the metal-binding BPA
unit, while the station of inherent lower affinity\(^9\) (succinic amide ester, shown in orange) is attached to a nonchelating diphenylacetyl stopper (Scheme 3.3). In 10, the macrocycle occupies the position over the green station more than 95% of the time at 273K in CD\(_3\)CN, as revealed by the large (\(\Delta\delta = 1.5\) ppm) upfield shift of the signals for the protons H\(_f\) and H\(_g\) (compare Figure 3.3b and a). In comparison, the signals for protons H\(_a\) and H\(_o\) (orange station) appear at similar chemical shifts in rotaxane 10 (Figure 3.3b) and the parent thread (Figure 3.3a).

![Scheme 3.3 An allosterically regulated molecular shuttle. Rotaxane 10 consists of a BPA metal-chelating site (the "effector" binding site), two hydrogen-bonding stations of different intrinsic affinities (substrate-binding sites), and a benzylic amide macrocycle substrate. Metal complexation of 10 occurs quantitatively at RT with Cd(NO\(_3\))\(_2\)·4H\(_2\)O in CD\(_3\)CN. The reverse transformation is accomplished by treatment with excess NaCN (5 equiv.).](image)

The addition of one equivalent of Cd(NO\(_3\))\(_2\)·4H\(_2\)O to 10 in CD\(_3\)CN results in a dramatic change in the \(^1\)H NMR spectrum (Figure 3.3c). The major differences in the spectra of 10 and 11 are the large (\(\Delta\delta = 1.1\) ppm) downfield shift of protons H\(_f\) and H\(_g\) (green station) and the upfield shift (\(\Delta\delta = 0.7\) ppm) of the peaks for H\(_a\) and H\(_o\) (orange station) in the metal-coordinated rotaxane. In addition, protons H\(_n\), H\(_p\) and H\(_q\) at the periphery of the orange station are also shielded by the macrocycle (\(\Delta\delta = 0.3\) ppm). Collectively, these data indicate that the macrocycle has moved from residing predominantly over the green station to being positioned mainly over the orange...
station. The difference in the chemical shifts of 11 relative to those of the parent thread bound to Cd(NO₃)₂ (Figure 3.3d) confirms the change in position of the macrocycle. The coordination reaction, and change in position of the macrocycle, is reversed by treatment with NaCN (Scheme 3.3).

![Figure 3.3 Partial ¹H NMR spectra (400 MHz, CD₂CN, 273 K) of a) the parent thread of 10, b) 10, c) 11 and d) the complex of the parent thread of 10 with Cd(NO₃)₂. Resonances are coloured and labelled as shown in Scheme 3.3. Peaks shown in light grey arise from residual nondeuterated solvent and water.](image)

3.3 Conclusion

The stimuli-induced shuttling between 10 and 11 (Scheme 3.3) corresponds to a negative heterotropic allosteric binding event\(^{[10]}\) – inhibition of hydrogen bonding of the macrocycle at the succinamide unit through the conformational change induced by metal chelation at the BPA site – that leads to translocation of the macrocycle to the inherently weaker hydrogen-bonding succinic amide ester site, which lies 1.5 nm away. Similarly, large movements in rotaxanes have been used to bring about changes in conductivity,\(^{[4d,11]}\) circular dichroism,\(^{[12]}\) fluorescence,\(^{[13]}\) porosity,\(^{[14]}\) surface energy\(^{[15]}\) and to carry out mechanical work,\(^{[15,16]}\) largely as a result of chemical
(redox, acid-base and photochemical) reactions on the covalent structure of the rotaxane. An allosteric shuttling mechanism offers the possibility of using metal binding events as the energy source or operating stimulus for functional synthetic molecular machines.

3.4 Experimental Section

General

Bis-(2-picoly)amine (BPA),[17] (2-aminoethyl)bis(2-pyridylmethyl)amine,[18] N-(2,2-diphenylethyl)-fumaric acid,[9] 2-(2-(2,2-diphenylethanamido)acetamido)acetic acid[19] and 2,2-diphenylethyl-4-(12-aminododecylamo)-4-oxobutanoate[9] were prepared according to published procedures. All other reagents were purchased from commercial sources and used without further purification.

\[ N^{1}-(2-(\text{pyridine-2-ylmethyl)amino})\text{ethyl})-N^{4}-(2,2\text{-diphenylethyl})\text{fumaramide} \]

Oxalyl chloride (8.10 mL, 16.2 mmol) was added to \(N\)-(2,2-diphenylethyl)-fumaric acid (3.25 g, 11.0 mmol) in dichloromethane (20 mL) at room temperature. The reaction mixture was warmed to 40 °C and stirred for 3 h, at which point all the material had dissolved to form a yellow solution. All volatiles were removed under vacuum and the residue was triturated with chloroform (3 x 5 mL). The yellow residue was taken up in chloroform (30 mL) and added to a solution of (2-aminoethyl)bis(2-pyridylmethyl)amine (2.61 g, 11.0 mmol) and triethylamine (3.09 mL, 22.0 mmol) in chloroform (200 mL) at 0 °C. The reaction mixture was slowly allowed to warm to room temperature and stirred for an additional 14 h. The reaction mixture was then washed with saturated aqueous 1M NaOH (3 x 20 mL), saturated aqueous sodium chloride (2 x 20 mL) and water (2 x 30 mL), dried (MgSO\(_4\)) and concentrated under reduced pressure to give a colourless solid (5.09 g, 89%); mp 170-172 °C; \(^1\)H NMR (400 MHz, CD\(_2\)Cl\(_2\)): \(\delta = 8.46 (d, J = 4.9 \text{ Hz}, 3\text{H, } H_a \& H_h), 7.54 (t, \text{ etc.}) \}

83
$J = 7.6 \text{ Hz}, 2H, H_c), 7.25-7.12 \text{ (m, 12H, } H_{Ph} \text{ & } H_d), 7.08 \text{ (t, } J = 4.8 \text{ Hz, 2H, } H_i), 6.91 \text{ (d, } J = 15.2 \text{ Hz, 1H, } H_j), 6.63 \text{ (d, } J = 15.2 \text{ Hz, 1H, } H_k), 6.09 \text{ (br s, 1H, } H_l), 4.16 \text{ (t, } J = 8.0 \text{ Hz, 1H, } H_m), 3.90 \text{ (dd, } J = 7.9 \text{ Hz and } J = 2.0 \text{ Hz, 2H, } H_n), 3.78 \text{ (s, 4H, } H_e), 3.26 \text{ (dd, } J = 10.8 \text{ Hz and } J = 5.9 \text{ Hz, 2H, } H_g), 2.69 \text{ (t, } J = 5.8 \text{ Hz, 2H, } H_h); ^{13}\text{C NMR (100 MHz, } CD_2Cl_2): \delta = 193.0, 174.1, 164.1, 159.7, 157.9, 157.8, 149.5, 142.3, 136.8, 134.2, 132.0, 128.3, 127.2, 123.4, 122.5, 60.1, 50.9, 44.3, 38.3; \text{ HRMS (FAB, 3-NOBA matrix): } m/z = 520.2719 \text{ [(M+H)] (anal. calcd for C}_{32}\text{H}_{34}\text{N}_{5}\text{O}_{2}: m/z = 520.2713).}$

$$\text{[(2)(1,7,14,20-Tetraaza-2,6,15,19-tetraoxo-3,5,9,12,16,18,22,25-tetrabenzocyclohexacos ane)-(N^1-(2-(bis(pyridine-2-ylmethyl)amino)ethyl)-N^4-(2,2-diphenylethyl)fumaramide) rotaxane (1)}}$$

A flask containing $N^1$-(2-(bis(pyridine-2-ylmethyl)amino)ethyl)$-N^4$-(2,2-diphenylethyl)fumaramide (2.0 g, 3.8 mmol) in chloroform (250 mL) was fitted with a rubber septum and a large magnetic stir bar and stirred vigorously. To this were simultaneously added a mixture of $p$-xylylene diamine (4.2 g, 31 mmol) and triethylamine (6.2 g, 62 mmol) in chloroform (50 mL) and isophthaloyl dichloride (6.2 g, 31 mmol) in chloroform (50 mL) at equal rates via motor-driven syringe pumps over a period of 6 h. The resulting suspension was filtered over celite and concentrated under reduced pressure. To the residue was added acetone (100 mL) and the resulting suspension was filtered, the filtrate collected and concentrated under reduced pressure. The remaining residue was subjected to column chromatography on silica gel using dichloromethane/methanol/NH$_4$OH (aq) in a 9.2:0.8:0.005 v/v ratio as eluent to yield, in order of elution, the unconsumed thread and rotaxane 1 (3.69 g, 91%); mp > 205 °C (decomp); $^1\text{H NMR (400 MHz, } CD_2Cl_2): \delta = 9.39 \text{ (br s, 1H, } H_h),
8.63 (s, 2H, H₁C), 8.48 (d, J = 4.8 Hz, 2H, H₂), 8.00 (dd, J = 7.7 Hz and J = 1.3 Hz, 4H, H₃), 8.09 (br s, 4H, H₄), 7.69 (dt, J = 7.7 Hz and J = 1.7 Hz, 2H, H₅), 7.61 (t, J = 7.8 Hz, 2H, H₆), 7.46 (br s, 1H, H₇), 7.31-7.19 (m, 14H, H₈, H₉ & H₁₀), 6.86 (s, 8H, H₁₁), 6.04 (d, J = 14.9 Hz, 1H, H₁₂), 5.72 (d, J = 14.9 Hz, 1H, H₁₃), 4.50-4.32 (m, 8H, H₁₄), 3.93 (dd, J = 7.8 Hz and J = 2.0 Hz, 2H, H₁₅), 3.73 (s, 4H, H₁₆), 3.25-3.24 (m, 2H, H₁₇), 2.66 (t, J = 5.3 Hz, 2H, H₁₈); ³¹C NMR (100 MHz, CD₂Cl₂): δ = 167.0, 166.0, 165.8, 158.3, 158.1, 149.6, 142.3, 137.6, 137.2, 134.4, 131.6, 130.8, 129.7, 129.5, 129.2, 128.2, 127.4, 125.3, 124.5, 123.3, 52.1, 50.9, 44.7, 44.5, 37.9; HRMS (FAB, 3-NOBA matrix): m/z = 1052.4825 [(M+H)⁺] (anal. calcd for C₆₄H₆₂N₉O₆⁺: m/z = 1052.4823).

[(2)[1,7,14,20-Tetraaza-2,6,15,19-tetraoxo-3,5,9,12,16,18,22,25-tetrabenzocyclohexacos ane)-(N₁-(2-(bis(pyridine-2-ylmethyl)amino)ethyl)-N₄-(2,2-diphenylethyl)fumaramide) copper (II) dichloride rotaxane (3)]

To a solution of 1 (0.50 g, 0.48 mmol) in DMF (25 mL), a saturated solution of CuCl₂·2H₂O (0.90 g, 0.53 mmol) in DMF (1 mL) was added. The reaction mixture was stirred for 1 h. The solution was then concentrated under reduced pressure and the solid was purified by recrystallisation from acetonitrile/DMF to furnish 3 as a light blue solid (0.57 g, 100%); mp > 216 °C (decomp); HRMS (FAB, 3-NOBA matrix): m/z = 1149.3734 [(M-Cl)⁺] (anal. calcd for C₆₄H₆₁ClCuN₉O₆⁺: m/z = 1149.3729).
To a mixture of (2-aminoethyl)bis(2-pyridylmethyl)amine (3.39 g, 14.0 mmol) and triethylamine (2.40 mL, 17.1 mmol) in chloroform (200 mL) at 0 °C was slowly added a solution of fumaryl chloride (1.00 g, 6.81 mmol) in chloroform (50 mL). After the addition it was allowed to warm to room temperature and stirred overnight. The mixture was then washed with 1M NaOH (2 x 50 mL) and water (2 x 50 mL) and the volatiles were removed under reduced pressure. The residue was recrystallised from acetone (20 mL) to furnish \( N^1, N^4 \)-bis(2-(bis(pyridin-2-ylmethyl)amino)ethyl)fumaramide as a pale yellow solid (3.53 g, 92%); mp 146-148 °C; \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta = 8.65 \) (br s, 2H, \( H_b \)), 8.54 (d, \( J = 4.8 \) Hz, 4H, \( H_a \)), 7.54 (t, \( J = 7.6 \) Hz, 4H, \( H_c \)), 7.24 (d, \( J = 7.8 \) Hz, 4H, \( H_d \)), 7.09 (t, \( J = 7.8 \) Hz, 4H, \( H_b \)), 7.04 (s, 2H, \( H_i \)), 3.84 (s, 8H, \( H_e \)), 3.42 (dd, \( J = 10.7 \) Hz and \( J = 5.8 \) Hz, 4H, \( H_g \)), 2.77 (t, \( J = 5.5 \) Hz, 4H, \( H_j \)); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \( \delta = 164.5, 158.9, 149.2, 136.7, 132.9, 123.1, 122.3, 59.8, 52.4, 38.0 \); HRMS (FAB, 3-NOBA matrix): \( m/z = 565.3046 \) [(M+H)\(^+\)] (anal. calcd for C\(_{32}\)H\(_{37}\)N\(_8\)O\(_2\)\(^+\): \( m/z = 565.3039 \)).
Chapter Three

An Allosteric Regulated Molecular Shuttle

[(2)1,7,14,20-Tetraaza-2,6,15,19-tetraoxo-3,5,9,12,16,18,22,25-tetrabenzocyclohexacos ane)-(N¹,N⁴-bis(2-(bis(pyridin-2-ylmethyl)amino)ethyl)fumaramide) rotaxane (2)

Synthesis of rotaxane 2 was similar to that described for 1, except that thread N¹,N⁴-bis(2-(bis(pyridin-2-ylmethyl)amino)ethyl)fumaramide (0.60 g, 1.0 mmol) was used. The quantities of the other components were: p-xylylene diamine (1.1 g, 8.0 mmol), isophthaloyl dichloride (1.6 g, 8.0 mmol) and triethylamine (2.5 mL, 18 mmol). The residue was separated by column chromatography on silica gel using dichloromethane/methanol/NH₄OH (aq) in a 9.6:0.4:0.0025 v/v ratio as eluent to furnish 2 as a white solid (0.82 g, 75%); mp > 200 °C (decomp); ^1H NMR (400 MHz, CDCl₃): δ = 9.49 (br s, 2H, Hₘ), 8.91 (s, 2H, Hₐ), 8.34 (d, J = 5.1 Hz, 4H, Hₐ), 8.21 (d, J = 6.5 Hz, 4H, Hₐ), 8.11 (t, J = 4.8 Hz, 4H, Hₐ), 7.58-7.49 (m, 6H, Hₐ & Hₐ), 7.15 (d, J = 7.6 Hz, 4H, Hₐ), 6.99-6.96 (m, 4H, Hₐ), 6.85 (s, 8H, Hₐ), 5.89 (s, 2H, Hₐ), 4.36 (br s, 8H, Hₐ), 3.80 (s, 8H, Hₐ), 3.32-3.30 (m, 4H, Hₐ), 2.75 (t, J = 5.6 Hz, 4H, Hₐ); ^13C NMR (100 MHz, CDCl₃): δ = 191.4, 166.5, 158.1, 149.1, 137.0, 137.0, 134.0, 131.7, 129.7, 129.2, 124.5, 123.4, 122.7, 59.3, 44.1, 38.7; HRMS (FAB, 3-NOBA matrix): m/z = 1097.5153 [(M+H)⁺] (anal. calcd for C₆₄H₆₅N₁₂O₆⁺: m/z = 1097.5150).
Chapter Three  
An Allosteric Regulated Molecular Shuttle

([2](1,7,14,20-Tetraaza-2,6,15,19-tetraoxo-3,5,9,12,16,18,22,25-tetrabenzocyclohexacos ane)-(N$^1$,N$^4$-bis(2-(bis(pyridin-2-ylmethyl)amino)ethyl)fumaramide) copper (II) dichloride rotaxane (4)

To a solution of 2 (0.50 g, 0.48 mmol) in DMF (25 mL), a saturated solution of CuCl$_2$·2H$_2$O (0.16 g, 0.96 mmol) in DMF (1 mL) was added. The reaction mixture was stirred for 1 h. The solution was then concentrated under reduced pressure and the solid was purified by recrystallisation from acetonitrile/DMF to furnish 4 as a blue solid (0.66 g, 100%); mp > 245 °C (decomp); HRMS (FAB, 3-NOBA matrix): m/z = 1327.2733 [(M-Cl)$^+$] (anal. calcd for C$_{64}$H$_{64}$Cl$_3$Cu$_2$N$_2$O$_6$: m/z = 1327.2729).

N$^1$-(2,2-Diphenylethyl)-N$^4$-bis(pyridine-2-ylmethyl)fumaramide

EDCI (4.05 g, 21.2 mmol) was added in small batches to a solution of N-(2,2-diphenylethyl)-fumaric acid (2.50 g, 8.47 mmol) and DMAP (2.59 g, 21.2 mmol) in dichloromethane (200 mL) at room temperature. The reaction mixture was stirred for 10 min, after which time bis(2-picoly)amine (1.99 g, 10.0 mmol) was added in one portion. The solution was then allowed to stir at room temperature for an additional 14 h. The reaction mixture was washed with saturated aqueous 1M NaOH (3 x 20 mL), saturated aqueous sodium chloride (2 x 20 mL) and water (2 x 30 mL), dried (MgSO$_4$) and concentrated under reduced pressure to give a colourless solid. The residue was recrystallised from acetone to furnish N$^1$-(2,2-diphenylethyl)-N$^4$,N$^4$-...
bis(pyridine-2-ylmethyl)fumaramide as a colourless solid (3.51 g, 87%); mp 54-56 °C; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 8.48 (d, $J$ = 4.8 Hz, 1H, $H_a$), 8.42 (d, $J$ = 4.8 Hz, 1H, $H_a$), 7.59-7.53 (m, 2H, $H_c$), 7.35 (d, $J$ = 14.6 Hz, 1H, $H_f$), 7.24-7.07 (m, 14H, $H_{PH}$, $H_b$ & $H_d$), 6.75 (d, $J$ = 14.6 Hz, 1H, $H_g$), 5.85 (br s, 1H, $H_h$), 4.73 (s, 4H, $H_e$), 4.13 (t, $J$ = 7.8 Hz, 1H, $H_j$), 3.88 (t, $J$ = 5.8 Hz, 2H, $H_i$); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ = 166.1, 164.0, 156.7, 155.9, 149.9, 142.3, 141.4, 135.0, 130.2, 128.5, 128.1, 128.0, 127.0, 126.6, 126.5, 122.6, 121.1, 77.2, 52.9, 51.6, 50.4, 44.1; HRMS (FAB, 3-NOBA matrix): $m/z$ = 477.2291 [(M+H)$^+$] (anal. calcd for C$_{30}$H$_{79}$N$_4$O$_7$: $m/z$ = 477.2291).

Synthesis of rotaxane 5 was similar to that described for 1, except that thread $N^1$-(2,2-diphenylethyl)-$N^4,N^4$-bis(pyridine-2-ylmethyl)fumaramide (1.5 g, 3.1 mmol) was used. The quantities of the other components were: $p$-xylylene diamine (3.4 g, 25.2 mmol), isophthaloyl dichloride (5.1 g, 25 mmol) and triethylamine (7.2 g, 51 mmol). The residue was separated by column chromatography on silica gel using dichloromethane/methanol/NH$_4$OH (aq) in a 9.6:0.4:0.0025 v/v ratio as eluent to furnish 5 as a white solid (3.0 g, 96%); mp > 200 °C (decomp); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ = 8.51 (d, $J$ = 4.8 Hz, 1H, $H_a$), 8.28 (br s, 3H, $H_a$ & $H_c$), 8.04 (d, $J$ = 7.8 Hz, 4H, $H_b$), 7.88 (br s, 1H, $H_b$), 7.50-7.48 (m, 6H, $H_A$ & $H_D$), 7.40 (dt, $J$ = 7.7 Hz and $J$ = 1.7 Hz, 1H, $H_c$), 7.25-7.11 (m, 12H, $H_{PH}$, $H_C$ & $H_b$), 7.02 (dd, $J$ = 7.2 Hz and $J$ = 1.9 Hz, 1H, $H_b$), 6.78 (d, $J$ = 7.6 Hz, 1H, $H_d$), 6.72 (s, 8H, $H_f$), 6.61 (d, $J$ = 7.6 Hz, 1H, $H_d$), 6.04 (d, $J$ = 14.7 Hz, 1H, $H_j$), 5.68 (d, $J$ = 14.7 Hz, 1H, $H_g$), 4.52 (s, 2H, $H_i$), 4.46 (s, 2H, $H_j$), 4.29-4.18 (m, 9H, $H_E$ & $H_j$), 3.84 (t, $J$ = 5.8 Hz, 2H, $H_i$); $^{13}$C NMR
(100 MHz, CDCl$_3$): $\delta = 166.0, 157.5, 156.1, 154.6, 149.8, 149.3, 141.6, 141.5, 136.8, 133.5, 132.6, 131.5, 130.2, 129.0, 128.8, 128.5, 127.9, 127.2, 127.0, 126.5, 123.7, 123.0, 121.2, 77.0, 53.3, 53.0, 52.5, 50.4, 45.8, 44.9, 43.9; HRMS (FAB, 3-NOBA matrix): $m/z = 1009.4403 [(M+H)^+]$ (anal. calcd for C$_{62}$H$_{57}$N$_8$O$_6$: $m/z = 1009.4401$).

$N^1,N^1,N^4,N^4$-Tetrakis(pyridin-2-ylmethyl)fumaramide

![Structural formula](image)

To a mixture of bis(2-picolyl)amine (2.0 g, 10 mmol) and triethylamine (1.7 mL, 12 mmol) in chloroform (200 mL) at 0 °C was slowly added a solution of fumaryl chloride (0.8 g, 5.2 mmol) in chloroform (50 mL). After the addition it was allowed to warm to room temperature and stirred overnight. The mixture was then washed with 1M NaOH (2 x 50 mL), water (2 x 50 mL) and the volatiles where removed under reduced pressure. The residue was purified by column chromatography 1:10 methanol/chloroform to give $N^1,N^1,N^4,N^4$-tetrakis(pyridin-2-ylmethyl)fumaramide as a white solid (2.2 g, 92%); mp 128-130 °C; $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 8.47$ (d, $J = 2.1$ Hz, 2H, $H_a$), 8.43 (d, $J = 2.1$ Hz, 2H, $H_d$), 7.56 (t, $J = 7.8$ Hz, 4H, $H_c$), 7.50 (s, 1H, $H_f$), 7.25 (d, $J = 7.9$ Hz, 2H, $H_d$), 7.20 (s, 1H, $H_f$), 7.12-7.09 (m, 6H, $H_b$ & $H_d$), 4.78 (s, 4H, $H_e$), 4.74 (s, 4H, $H_e$); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 157.9, 149.9, 137.0, 132.2, 122.6, 121.2, 53.1, 51.4, 45.8; HRMS (FAB, 3-NOBA matrix): $m/z = 479.2201 [(M+H)^+]$ (anal. calcd for C$_{28}$H$_{27}$N$_6$O$_2^+$: $m/z = 479.2195$).
The synthesis of rotaxane 6 was similar to that described for 1, except that thread $N^1,N^4,N^4$-tetrakis(pyridin-2-ylmethyl)fumaramide (1.0 g, 2.1 mmol) was used. The quantities of the other components were: $p$-xylylene diamine (2.3 g, 17 mmol), isophthaloyl dichloride (3.4 g, 17 mmol) and triethylamine (4.8 mL, 34 mmol). The residue was separated by column chromatography on silica gel using dichloromethane/methanol/NH$_4$OH (aq) in a 9.6:0.4:0.0025 v/v ratio as eluent to furnish 6 as a white solid (2.0 g, 95%); mp $>$ 200°C (decomp); $^1$H NMR (400 MHz, CDCl$_3$): $\delta = 8.55$ (d, $J = 4.5$ Hz, 2H, H$_a$), 8.46 (s, 2H, H$_c$), 8.28 (d, $J = 4.5$ Hz, 2H, H$_a$), 8.17 (d, $J = 7.8$ Hz, 4H, H$_b$), 7.51 (t, $J = 7.8$ Hz, 2H, H$_d$), 7.47 (br s, 4H, H$_D$), 7.24-7.19 (m, 14H, H$_F$ & H$_b$), 7.09 (d, $J = 7.8$ Hz, 2H, H$_d$), 7.03 (t, $J = 7.8$ Hz, 2H, H$_b$), 6.64 (d, $J = 7.8$ Hz, 2H, H$_d$), 6.12 (s, 2H, H$_j$), 4.85 (br s, 4H, H$_E$), 4.64 (s, 4H, H$_e$), 4.54 (s, 4H, H$_e$), 3.45 (br s, 4H, H$_E$); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta = 166.1$, 165.6, 157.9, 154.7, 149.7, 137.3, 136.8, 133.5, 131.9, 129.6, 129.2, 129.0, 124.1, 123.2, 123.0, 53.4, 52.8; HRMS (FAB, 3-NOBA matrix): $m/z = 1011.4309 [(M+H)^+]$ (anal. calcd for C$_{60}$H$_{55}$N$_{10}$O$_5$: $m/z = 1011.4306$).
**N-(2-(2-(Bis(pyridine-2-ylmethyl)amino)-2-oxoethylamino)-2-oxoethyl)-2,2-diphenylethanamide**

EDCI (2.2 g, 12 mmol) was added in small batches to a solution of 2-(2-(2,2-diphenylethanamido)acetamido)acetic acid (1.5 g, 4.6 mmol) and DMAP (1.4 g, 12 mmol) in dichloromethane (200 mL). The reaction mixture was stirred for 10 min, after which time bis(2-picoly)amine (0.92 g, 4.6 mol) was added in one portion, and the mixture was stirred for an additional 14 h at room temperature. The solution was then washed with saturated aqueous sodium hydrogen carbonate (3 x 50 mL), saturated aqueous sodium chloride (2 x 50 mL), dried (MgSO₄) and concentrated under reduced pressure to give a colourless solid. The remaining residue was subjected to column chromatography on silica gel using dichloromethane/methanol/NH₄OH (aq) in a 9.6:0.4:0.0025 v/v ratio as eluent to furnish **N-(2-(2-(bis(pyridine-2-ylmethyl)amino)-2-oxoethylamino)-2-oxoethyl)-2,2-diphenylethanamide** as a white solid (2.1 g, 88%); mp 152-154 °C; ¹H NMR (400 MHz, CD₃CN): δ = 8.47 (d, J = 4.8 Hz, 1H, Hₐ), 8.44 (d, J = 4.8 Hz, 1H, Hₐ), 7.67-7.60 (m, 2H, Hₑ), 7.29-7.13 (m, 14H, Hₑ, Hₑ & Hₑ), 6.91 (br s, 2H, Hᵢ & Hᵢ), 4.95 (s, 1H, Hᵢ), 4.58 (s, 4H, Hₑ), 4.15 (d, J = 4.8 Hz, 2H, Hₑ), 3.77 (d, J = 5.5 Hz, 2H, Hᵢ); ¹³C NMR (100 MHz, CD₃CN): δ = 202.1, 157.5, 149.3, 148.8, 139.7, 136.6, 136.3, 128.5, 128.1, 126.6, 122.4, 121.9, 121.7, 121.4, 51.64, 51.05, 40.8; HRMS (FAB, 3-NOBA matrix): m/z = 508.2352 [(M+H)⁺] (anal. calcd for C₃₀H₃₀N₅O₃⁺: m/z = 508.2349).
Chapter Three  

An Allosteric Regulated Molecular Shuttle

\[ N-(2-(2-(\text{Bis(pyridine-2-ylmethyl)amino})-2-oxoethylamino)-2-oxoethyl)-2,2-diphenylethanamide \text{cadmium (II) dinitrate} \]

To a solution of \( N-(2-(2-(\text{Bis(pyridine-2-ylmethyl)amino})-2-oxoethylamino)-2-oxoethyl)-2,2\)-diphenylethanamide (0.01 mg, 0.02 mmol) in CD\(_3\)CN (1 mL), Cd(NO\(_3\))\(_2\)·4H\(_2\)O (6 mg, 0.02 mmol) was added. The reaction mixture was stirred for 1 h. Yield (>97%); \(^1\)H NMR (400 MHz, CD\(_3\)CN): \( \delta = 8.63 \text{ (d, } J = 5.1 \text{ Hz, } 2\text{H, } H_a), \)
\( 7.97 \text{ (t, } J = 7.7 \text{ Hz, } 2\text{H, } H_c), \)
\( 7.52-7.48 \text{ (m, } 4\text{H, } H_d \text{ & } H_b), \)
\( 7.31-7.23 \text{ (m, } 10\text{H, } H_{Ph}), \)
\( 6.96-6.91 \text{ (m, } 2\text{H, } H_g \text{ & } H_i), \)
\( 4.98 \text{ (s, } 1\text{H, } H_j), \)
\( 4.67 \text{ (br s, } 4\text{H, } H_e), \)
\( 3.99 \text{ (d, } J = 5.0 \text{ Hz, } 2\text{H, } H_h), \)
\( 3.75 \text{ (d, } J = 5.8 \text{ Hz, } 2\text{H, } H_f); \)
\(^{13}\)C NMR (100 MHz, CD\(_3\)CN): \( \delta = 184.4, \)
\( 173.1, \)
\( 170.3, \)
\( 158.7, \)
\( 150.3, \)
\( 145.8, \)
\( 140.9, \)
\( 140.8, \)
\( 129.7, \)
\( 129.4, \)
\( 127.8, \)
\( 125.3, \)
\( 125.0, \)
\( 118.2, \)
\( 54.2, \)
\( 43.5, \)
\( 42.9. \)

\( \left(1\right)\left(1,7,14,20\text{-Tetraaza-2,6,15,19-tetraoxo-3,5,9,12,16,18,22,25-tetrabenzocyclohexacos ane)-(N-(2-(2-(\text{Bis(pyridine-2-ylmethyl)amino})-2-oxoethylamino)-2-oxoethylamino)-2-oxoethyl)-2,2-diphenylethanamide\right) \text{rotaxane (9)} \]

The synthesis of rotaxane 9 was similar to that described for 1, except that thread \( N-(2-(2-(\text{Bis(pyridine-2-ylmethyl)amino})-2-oxoethylamino)-2-oxoethylamino)-2,2\)-diphenylethanamide (1.0 g, 2.0 mmol) was used. The quantities of the other components were: \text{p-xylylene diamine (2.1 g, 16 mmol)}, \text{isophthaloyl dichloride (3.2}
g, 16 mmol) and triethylamine (4.4 mL, 32 mmol). The residue was separated by column chromatography on silica gel using dichloromethane/methanol/NH₄OH (aq) in a 9.6:0.4:0.0025 v/v ratio as eluent to furnish 9 as a white solid (1.1 g, 53%); mp > 210 °C (decomp); ¹H NMR (400 MHz, CD₃CN): δ = 8.48 (s, 2H, Hc), 8.35 (d, J = 5.3 Hz, 1H, Hₐ), 8.24 (d, J = 5.3 Hz, 1H, Hₐ), 8.02 (dd, J = 7.7 Hz and J = 1.6 Hz, 4H, H₈), 7.55-7.51 (m, 6H, H₄ & H₆), 7.40 (tt, J = 7.7 Hz and J = 1.8 Hz, 2H, H₉), 7.25-7.03 (m, 12H, H₈ & H₉), 6.99 (s, 8H, HF), 6.80 (d, J = 8.1 Hz, 1H, H₉), 6.74 (d, J = 7.8 Hz, 2H, H₈ & H₉), 6.64 (br s, 1H, Hₙ), 4.86 (s, 1H, Hₙ), 4.44-4.14 (m, 12H, H₉ & H₈), 3.22 (d, J = 5.3 Hz 2H, H firestore); 13C NMR (100 MHz, CD₃CN): δ = 165.5, 157.2, 137.1, 133.9, 130.6, 128.7, 128.6, 128.3, 128.1, 126.7, 124.4, 43.2; HRMS (FAB, 3-NOBA matrix): m/z = 1040.4463 [(M+H)⁺] (anal. calcd for C₆₂H₅₈N₉O₇⁺: m/z = 1040.4459).

([2](1,7,14,20-Tetraaza-2,6,15,19-tetraoxo-3,5,9,12,16,18,22,25-tetrabenzo cyclohexacosen) - (N-(2-(2-(bis(pyridine-2-ylmethyl)amino)-2-oxoethylamino)-2-oxoethylamino)-2-oxoethyl)-2,2-diphenylethanamide) copper (II) dichloride rotaxane (9CuCl₂)

To a solution of 9 (0.50 g, 0.48 mmol) in DMF (25 mL), a saturated solution of CuCl₂·2H₂O (0.90 g, 0.53 mmol) in DMF (1 mL) was added. The reaction mixture was stirred for 1 h. The solution was concentrated under reduced pressure and the solid was purified by recrystallisation from acetonitrile/DMF to furnish 9CuCl₂ as a light blue solid (0.56 g, 100%); mp > 230 °C (decomp); HRMS (FAB, 3-NOBA matrix): m/z = 1137.3373 [(M-Cl)⁺] (anal. calcd for C₆₂H₅₇ClCuN₉O₇⁺: m/z = 1137.3365).
Chapter Three  
An Allosteric Regulated Molecular Shuttle

\[(\{2\}(1,7,14,20-\text{Tetraaza-2,6,15,19-tetraoxo-3,5,9,12,16,18,22,25-tetrabenzocyclohexacene})-(N-(2-(2-(\text{bis(pyridine-2-ylmethyl)amino)}-2-oxoethylamino)}-2-oxoethyl)-2,2-diphenylethanamide) \text{ cadmium (II) dinitrate rotaxane} (9\text{Cd(NO}_3\text{)}_2)\]

![Diagram of the rotaxane structure]

To a solution of 9 (0.01 g, 0.01 mmol) in CD$_3$CN (1 mL), Cd(NO$_3$)$_2$·4H$_2$O (3 mg, 0.01 mmol) was added. The reaction mixture was stirred for 1 h. Yield (> 97%); $^1$H NMR (400 MHz, CD$_3$CN): $\delta = 8.41$ (br s, 2H, $H_a$), 8.06 (dd, $J = 7.8$ Hz and $J = 1.4$ Hz, 4H, $H_b$), 7.99-7.95 (m, 4H, $H_C$ & $H_D$), 7.40 (br s, 4H, $H_D$), 7.63 (t, $J = 7.8$ Hz, 2H, $H_A$), 7.42-7.41 (m, 4H, $H_d$ & $H_b$), 7.23-7.09 (m, 10H, $H_{Ph}$) 6.96 (s, 8H, $H_F$), 6.40 (br s, 1H, $H_g$), 6.04 (br s, 1H, $H_g$), 4.73 (s, 1H, $H_j$), 4.41-4.21 (m, 12H, $H_E$ & $H_e$), 3.28 (d, $J = 5.3$ Hz 2H, $H_h$), 2.79 (d, $J = 4.8$ Hz, 2H, $H_h$).

\[2,2-\text{Diphenylethyl} \text{-}4-\text{(12-(4-(\text{bis(pyridine-2-ylmethyl)amino })-4-oxobutanamido} )\text{dodecyl amino}-4-\text{oxobutanoate}}\]

![Diagram of the amino acid structure]

To a solution of 2,2-diphenylethyl-4-(12-aminododecylamino)-4-oxobutanoate (1.0 g, 2.1 mmol) in tetrahydrofuran (200 mL) was added succinic anhydride (0.21 g, 2.1 mmol) and the reaction mixture was warmed to 60 °C for 1 h. The reaction mixture was then allowed to stir for an additional 4 h at room temperature, at which point all volatiles were removed under reduced pressure. The residue was taken up in
dichloromethane (200 mL) and to this was added DMAP (0.64 g, 5.2 mmol) and EDCI (1.0 g, 5.2 mmol) in small batches at room temperature. The reaction mixture was stirred for 10 min, after which time bis(2-picoly)amine (0.42 g, 2.1 mmol) was added in one portion. The reaction mixture was allowed to stir at room temperature for an additional 14 h. The solution was then washed with saturated aqueous 1M NaOH (3 x 20 mL), saturated aqueous sodium chloride (2 x 20 mL) and water (2 x 30 mL), dried (MgSO₄) and concentrated under reduced pressure to give a colourless solid (1.3 g, 78%); mp 88-90 °C; ¹H NMR (400 MHz, CD₃CN): δ = 8.55 (d, J = 4.8 Hz, 1H, Hₐ), 8.47 (d, J = 4.8 Hz, 1H, Hₐ), 7.73-7.67 (m, 2H, Hₐ), 7.35-7.22 (m, 14H, Hₚₐ, Hₖ & Hₜ), 6.49 (br s, 1H, Hₐ), 6.30 (br s, 1H, Hₘ), 4.73 (s, 2H, Hₑ), 4.65 (s, 2H, Hₑ), 4.61 (d, J = 7.6 Hz, 2H, Hₚₙ), 4.36 (t, J = 7.6 Hz, 1H, Hₚₙ), 3.11-3.10 (m, 4H, Hₗ & H₁), 2.74 (t, J = 6.6 Hz, 2H, Hₗ), 2.44-2.42 (m, 4H, Hₕ & Hₘ), 2.30 (t, J = 7.0 Hz, 2H, Hₖ), 1.41 (br s, 4H, Hₚ & Hₖ), 1.27 (br s, 16H, alkyl CH₂); ¹³C NMR (100 MHz, CD₃CN): δ = 157.6, 157.1, 149.2, 148.7, 136.5, 136.2, 128.2, 127.7, 126.4, 122.2, 121.7, 121.3, 121.2, 65.9, 52.5, 50.9, 49.4, 38.5, 30.5, 29.7, 29.0, 28.9, 28.8, 28.7, 28.0, 26.2; HRMS (FAB, 3-NOBA matrix): m/z = 762.4600 [(M+H)⁺] (anal. calcd for C₄₆H₆₀N₅O₅⁺: m/z = 762.4594).

2,2-Diphenylethyl 4-(12-(4-(bis(pyridine-2-ylmethyl)amino)-4-oxobutanamido)dodecyl amino)-4-oxobutanoate cadmium (II) dinitrate

To a solution of 2,2-diphenylethyl 4-(12-(4-(bis(pyridine-2-ylmethyl)amino)-4-oxobutanamido)dodecyl amino)-4-oxobutanoate (0.01 mg, 0.01 mmol) in CD₃CN (1 mL), Cd(NO₃)₂·4H₂O (4 mg, 0.01 mmol) was added. The reaction mixture was stirred for 1 h. Yield (> 97%); ¹H NMR (400 MHz, CD₃CN): δ = 8.64 (br s, 2H, Hₐ), 7.97 (t, J = 7.3 Hz, 2H, Hₚₐ), 7.51-7.49 (m, 4H, H₂b & H₂d), 7.33-7.20 (m, 10H, Hₚₙ), 6.87 (br s, 1H, Hₚₙ), 6.29 (br s, 1H, Hₚₙ), 4.70 (br s, 4H, Hₑ), 4.60 (d, J = 7.6 Hz, 2H, Hₚₙ), 4.33 (t, J = 7.5 Hz, 1H, Hₚₙ), 3.11-3.04 (m, 4H, H₁ & Hₚₙ), 2.54-2.43 (m, 4H, H₂ & Hₚₙ), 2.40 (t,
Chapter Three

An Allosteric Regulated Molecular Shuttle

\[ J = 6.6 \text{ Hz}, 2H, H_n \], 2.27 (t, \( J = 6.7 \text{ Hz}, 2H, H_0 \)), 1.40 (t, \( J = 6.5 \text{ Hz}, 2H, H_j \)), 1.33 (t, \( J = 6.7 \text{ Hz}, 2H, H_0 \)), 1.27-1.23 (m, 16H, alkyl CH2); \(^1^3^C\) NMR (100 MHz, CD\(_3\)CN): \( \delta = 158.4, 142.6, 141.0, 129.5, 129.0, 127.6, 124.9, 118.2, 54.7, 50.6, 40.3, 39.8, 31.6, 31.0, 30.2 \) (x2), 30.1, 30.0, 29.9 \) (x2), 29.8, 29.1, 27.5, 27.3.

(\([2](1,7,14,20\)-Tetraaza-2,6,15,19-tetraoxo-3,5,9,12,16,18,22,25-tetrabenzocyclohexacosenes)-(2,2-diphenylethyl 4-(12-(4-(bis(pyridine-2-ylmethyl)anilino)-4-oxobutanamido)dodecylamino)-4-oxobutanoate) rotaxane (10)

The synthesis of rotaxane 10 was similar to that described for 1, except that thread 2,2-diphenylethyl 4-(12-(4-(bis(pyridine-2-ylmethyl)amino)-4-oxobutamidododecylamino)-4-oxobutanoate (1.0 g, 1.2 mmol) was used in this case. The quantities of the other components were: p-xylene diamine (1.7 g, 12 mmol), isophthaloyl dichloride (2.5 g, 12 mmol) and triethylamine (2.5 g, 24 mmol). The residue was separated by column chromatography on silica gel using dichloromethane/methanol/NH\(_4\)OH (aq) in a 9.6:0.4:0.0025 v/v ratio as eluent to furnish 10 as a white solid (0.65 g, 42%); mp 62-64 °C; \(^1^H\) NMR (400 MHz, CD\(_3\)CN): \( \delta = 8.57 \) (s, 2H, Hc), 8.30 (d, \( J = 4.0 \text{ Hz}, 1H, H_d \)), 8.13 (d, \( J = 9.4 \text{ Hz}, 5H, H_B \) & H_a), 7.67 (br s, 4H, Hb), 7.60 (t, \( J = 7.9 \text{ Hz}, 2H, H_d \)), 7.43 (dt, \( J = 7.7 \text{ Hz and } J = 1.8 \text{ Hz}, 2H, H_c \)), 7.34-7.21 (m, 12H, Hp, H_b & H_d), 7.10 (br s, 9H, H_p & H_f), 6.81 (d, \( J = 7.8 \text{ Hz}, 1H, H_d \)), 6.68 (br s, 1H, H_b), 6.40 (br s, 1H, H_m), 4.62-4.59 (m, 4H, H_p & H_o), 4.45-4.33 (m, 10H, HE & H_e) 4.33 (t, \( J = 7.7 \text{ Hz},1H, H_q \)), 3.06-3.04 (m, 4H, H_i & H_j), 2.38 (t, \( J = 6.7 \text{ Hz}, 2H, H_a \)), 2.26 (t, \( J = 6.8 \text{ Hz}, 2H, H_d \)), 1.41-1.37 (m, 4H, H_j & H_k), 1.25-1.20 (m, 18H, alkyl CH\(_2\) & H_j) 1.03-1.00 (m, 2H, H_g); \(^1^3^C\) NMR (100 MHz, CD\(_3\)CN): \( \delta = 173.2, 165.3, 157.3, 157.2, 155.6, 149.3, 149.2, 141.6, 138.0, \)
Chapter Three

An Allosteric Regulated Molecular Shuttle

136.5, 134.0, 128.9, 128.5, 127.9, 126.6, 122.8, 122.4, 121.0, 66.1, 53.1, 52.2, 49.6, 42.9, 39.0, 38.8, 29.9, 29.3, 29.1, 29.0, 28.8, 28.7, 27.5, 26.4, 26.3; HRMS (FAB, 3-NOBA matrix): \( m/z = 1294.6707 \). (anal. calcd for \( \text{C}_{78}\text{H}_{88}\text{N}_9\text{O}_9^+ \): \( m/z = 1294.6705 \)).

\[ [(2)(1,7,14,20-Tetraaza-2,6,15,19-tetraoxo-3,5,9,12,16,18,22,25-tetrabenzocyclohexac ane)-(2,2-diphenylethyl 4-(12-(4-(bis(pyridine-2-ylmethyl)amino)-4-oxobutanamido)de cylamino)-4-oxobutanoate) cadmium (II) dinitrate rotaxane (11) \]

To a solution of 10 (0.01 g, 0.01 mmol) in CD\(_3\)CN (1 mL), Cd(NO\(_3\))\(_2\)-4H\(_2\)O (2 mg, 0.01 mmol) was added. The reaction mixture was stirred for 1h. Yield (> 97%); \(^1\)H NMR (400 MHz, CD\(_3\)CN): \( \delta = 8.55 \) (d, \( J = 4.3 \) Hz, 2H, Ha), 8.30 (s, 2H, Hc), 8.07 (dd, \( J = 7.8 \) Hz and \( J = 1.7 \) Hz, 4H, Hb), 7.84 (t, \( J = 7.3 \) Hz, 2H, Hc), 7.67 (br s, 4H, Hg), 7.58 (t, \( J = 7.3 \) Hz, 2H, Hf), 7.39 (t, \( J = 6.3 \) Hz, 2H, Hb), 7.34 (d, \( J = 7.5 \) Hz, 2H, Hg) 7.30-7.18 (m, 10H, H_{ph}), 7.08 (s, 8H, Hr), 6.89 (br s, 1H, Hb), 6.52 (br s, 1H, H_{m}), 4.61 (br s, 4H, Hz), 4.44-4.40 (m, 10H, H_E & H_p), 4.20 (t, \( J = 7.6 \) Hz, 1H, H_q), 2.99 (t, \( J = 7.0 \) Hz, 2H, H_i), 2.80 (t, \( J = 7.2 \) Hz, 2H, H_i), 2.12 (br s, 2H, H_j), 2.03 (br s, 2H, H_j), 1.84 (br s, 2H, H_k), 1.65 (br s, 2H, H_k), 1.28-1.18 (m, 4H, H_j & H_k), 1.25-1.20 (br s, 16H, alkyl CH\(_2\)), \(^{13}\)C NMR (100 MHz, CD\(_3\)CN): \( \delta = 166.7, 158.3, 142.5, 138.9, 135.3, 131.7, 129.9, 129.8, 128.9, 127.7, 125.5, 124.5, 118.2, 67.4, 54.4, 50.5, 40.2, 40.0, 30.0, 29.8, 29.7 (x2), 29.6, 27.4, 27.3.

3.5 References and Notes


[7] There was no indication of reaction by colour change, mass spectrometry or thin-layer chromatography.
Crystals of 3 and 4 of suitable quality for X-ray diffraction studies were obtained by carefully layering a solution of the appropriate complex in N,N-dimethylformamide with CH₃CN (approximately 1:10 v/v). Single crystals of 5, 6, 9 and 9CuCl₂ were grown from slow evaporation of saturated solutions in CH₃CN, CHCl₃, CH₂Cl₂ and CH₂Cl₂/DMF (5:1 v/v), respectively. Data for 3, 4, 5, 6 and 9CuCl₂ were collected on a Bruker SMART CCD diffractometer, whereas data for 9 were collected on a Rigaku Saturn (MM007 high flux RA/MoKα radiation, confocal optic). Data were collected at 150 K for 3, 4 and 6, 125 K for 5 and 9CuCl₂, and 93 K for 9. All data collections employed narrow frames (0.3-1.0°) to obtain at least a full hemisphere of data. Intensities were corrected for Lorentz polarization and absorption effects (multiple equivalent reflections). Structures were solved by direct methods, non-hydrogens atoms were refined anisotropically with CH protons being refined in riding geometries (SHELXTL) against F.

In most cases amide protons were refined isotropically subject to a distant constraint. 33.75DMF: C₇₀H₇₈Cl₁Cu₁N₁₄O₈, M= 1512.34, crystal size 0.19 x 0.18 x 0.08 mm³, monoclinic, P21/c, a = 12.7343(5), b = 19.0061(8), c = 15.7470(7) Å, Z = 2, ρcalcld = 1.438 Mg m⁻³; μ = 0.828 mm⁻¹, 20841 collected, 7515 unique (Rint = 0.0450) giving R = 0.0791 for 5367 observed data [F₀ > 4σ(F₀)], 5 was 0.112 for 444 parameters. Residual electron density extremes were 0.663 and -0.851 eÅ⁻³. 5: C₆₂H₅₆N₈O₆, M = 1009.15, crystal size 0.21 x 0.1 x 0.1 mm³, monoclinic, C2/c, a = 31.107(10), b = 18.677(6), c = 21.001(7) Å, Z = 8, ρcalcld = 1.318 Mg m⁻³; μ = 0.086 mm⁻¹, 31645 collected, 9198 unique (Rint = 0.5301) giving R = 0.1611 for 2791 observed data [F₀ > 4σ(F₀)], 5 was 0.994 for 707 parameters. Residual electron density extremes were 0.833 and -0.380 eÅ⁻³.

6(CHCl₃)₃: C₆₄H₅₈Cl₁₂N₁₀O₆, M = 1488.66, crystal size 0.59 x 0.46 x 0.41 mm³, triclinic, P -1, a = 11.8069(7), b = 12.2006(7) Å, Z = 4, ρcalcld = 1.485 Mg m⁻³; μ = 0.559 mm⁻¹, 16004 collected, 7684 unique (Rint = 0.04) giving R = 0.0526 for 6362 observed data [F₀ > 4σ(F₀)], 5 was 0.9917 for 415 parameters. Residual electron density extremes were 0.44 and -0.36 eÅ⁻³. 9: C₆₂H₅₉N₉O₈, M = 1058.18, crystal size 0.1 x 0.03 x 0.03 mm³, triclinic, P -1, a = 10.9491(5), b = 14.8382(2), c = 18.5719(8) Å, Z = 2, ρcalcld = 1.311 Mg m⁻³; μ = 0.716 mm⁻¹, 32650 collected, 7414 unique (Rint = 0.0782) giving R = 0.0806 for 5270 observed data [F₀ > 4σ(F₀)], 5 was 1.051 for 746 parameters. Residual electron density extremes were 0.288 and -0.313 eÅ⁻³. 9CuCl₂·3DMF·2H₂O: C₆₈.₇₅H₇₅.₇₅Cl₂CuN₁₁.₂₅O₁₀.₇₅, M = 1366.1, crystal size 0.16 x 0.1 x 0.1 mm³, monoclinic, P2(1)/n, a = 25.279(6), b = 10.970(3), c = 25.649(6) Å, Z = 4, ρcalcld = 1.288 Mg m⁻³; μ = 0.451 mm⁻¹, 44451 collected, 12876 unique (Rint = 0.4536) giving R = 0.1614 for 4795 observed data [F₀ > 4σ(F₀)], 5 was 1.038 for 856 parameters. Residual electron density extremes were 1.180 and -0.718 eÅ⁻³. The protons on solvate molecules were not allowed for in the refinement. CCDC 281563-281568 (3, 4, 5, 6, 9 and 9CuCl₂, respectively) contain the supplementary crystallographic data for this Chapter. These data can be
obtained free of charge from The Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif.


A Metal-Complex-Tolerant CuAAC “Click” Protocol Exemplified through the Preparation of Homo- and Mixed-Metal-Coordinated Rotaxanes

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Synopsis

Chapters Two and Three discussed two novel mechanisms for inducing shuttling in hydrogen-bond assembled architectures. These two shuttling strategies evolved from attempts to develop methodology for the synthesis of rotaxanes containing metal ions on the thread and the macrocycle.

In this Chapter, the preparation of such complexes is demonstrated using Cu$^+$-catalysed terminal alkyne-azide cycloaddition (CuAAC "click" reaction). The reaction of a copper-complexed azide rotaxane and a simple alkyne-functionalised tridentate ligand bound to either CuCl$_2$ or CrCl$_3$ resulted in the formation of homo- and mixed metal-containing hydrogen-bond assembled architectures in very good yields.

Interestingly, it was possible to effectively remove Cu$^{II}$ and selectively coordinate other metal ions at the vacant BPA site(s) to access a range of bimetallic structures.
4.1 Introduction

Since its discovery,[1] the Huisgen-Meldal-Fokin Cu²⁺-catalysed terminal alkyne-azide cycloaddition (the CuAAC “click”[2] reaction) has attracted great interest[3] because of its utility in chemically bonding functional molecular fragments in a precise, predictable and efficient fashion under a myriad of conditions and situations.[4] Despite its exceptional versatility, however, to date there have been few reports on performing the CuAAC reaction in the presence of other redox-active metal ions or substrates containing multidentate binding sites capable of sequestering the copper catalyst.[5-7] The few examples of metal-coordinated alkyne or azides that have been successfully employed in the CuAAC reaction thus far include ethynylferrocene,[8-10] an organometallic iridium complex,[11] metalloporphyrins,[12,13] a lanthanide-bound cyclen derivative,[14] and a ruthenium dimer functionalised with an alkyne[15] and Cu⁺-coordinated rotaxanes.[16] While some of these examples offer methods for attaching specific metals to particular molecular structures, most of the complexes are kinetically inert and none allow for the ready variation of the metal.

Here we present a strategy for the assembly of multiple (homo- and mixed-) metal-containing products using the CuAAC reaction by employing a simple alkyne functionalised tridentate ligand, 1, capable of coordinating to a variety of transition metal ions (Scheme 4.1). Through this synthon, a series of homo- and mixed-metal-chelated rotaxanes has been prepared (Scheme 4.2 and 4.3).

4.2 Results and Discussion

When attempting the CuAAC reaction in the presence of potentially ligating groups, the temptation is to use the Cu⁺⁺ salt in excess quantities to compensate for copper being sequestered by the ligand. The situation is further complicated if other transition metal ions are present as they may be displaced, either directly by the Cu⁺⁺ or labilised by electron transfer to or from the redox-sensitive Cu⁺⁺. However, during studies to derivatise rotaxanes with metal-chelating groups,[17] we found that an alkyne-derivatised bis-pyridin-2-ylmethyl-amine (BPA) tridentate ligand 1 bound to either CuCl₂, [1CuCl₂], or the kinetically inert CrCl₃, [1CrCl₃], could be effectively employed in the CuACC reaction using a catalytic amount (10 mol%) of Cu⁺⁺ to
generate the metal-containing triazoles [2CuCl₂] and [2CrCl₃] in 80% and 82% yields, respectively (Scheme 4.1).

![Scheme 4.1 Attempted CuAAC-mediated couplings of various mono-metallated alkyne substrates (1MCl₆), with benzyl azide. Reagents and conditions: a) propargyl bromide, Et₃N, toluene, reflux, 12 h, 60%; b) MCl₆, CH₃OH, RT, 1 h; c) benzyl azide, 0.1 equiv. Cu(CH₃CN)₄PF₆, 1.1 equiv. N,N-diisopropylethylamine (DIPEA), CHCl₃/CH₃OH (9:1), RT, 12 h.

Attempts to extend this protocol to produce other first row transition metal complexes of 2, including [2ZnCl₂], [2MnCl₂], [2FeCl₃] and [2CoCl₂], were unsuccessful, however. Although in some cases increasing the amount of the Cu⁺ catalyst used to > 1 equivalent enabled the CuAAC reaction to proceed, this also resulted in displacement of the original metal from the BPA unit by Cu²⁺. In contrast, Cr³⁺ was not displaced during the formation or isolation of [2CrCl₃], nor did it participate in any electron transfer reactions. In fact, forcing conditions (1.5 equiv. of KCN, CH₃OH, reflux, 12 h, 80%) were necessary to liberate it from the derivatised BPA ligand.

These results led us to develop a method for coupling homo- and mixed-metal chelated fragments with the CuAAC reaction, exemplified through a series of rotaxanes (Schemes 4.2 and 4.3). A functionalised rotaxane, 3, bearing two BPA chelating sites – one attached to the rotaxane macrocycle, one to the rotaxane thread – was synthesised using a hydrogen bond-templated clipping strategy (Scheme 4.2).¹⁸ To a solution of thread 4¹⁹ and 5 (obtained from deprotection of 6, Scheme 4.2, a) in CHCl₃, was added 5-azidoisophthaloyl dicloride,¹⁹ to yield azido-rotaxane 7 (52%, Scheme 4.2, b). Prior to reacting the azido-rotaxane with alkynes [1CuCl₂] and [1CrCl₃], the BPA tridentate binding site of the thread was protected by coordination to Cu²⁺, generating [7(thread-CuCl₂)] (Scheme 4.2, c). Complexes [3(mac-
CuCl₂(thread-CuCl₂) and 3(mac-CrCl₃)(thread-CuCl₂) were then obtained in good yields using the standard CuAAC conditions (Scheme 4.2, d).

The lability of the Cu²⁺ allowed us to remove it and selectively coordinate other metal ions at the vacant BPA site(s). Compound 3(mac-CuCl₂)(thread-CuCl₂) was fully demetallated by simple washing with a saturated solution of Na₂EDTA (tetrosodium ethylenediamine tetraacetate) to give the metal-free rotaxane 3 (Scheme 4.3, a). Addition of ZnCl₂ then afforded the bis-Zn²⁺-metallated complex 3(mac-ZnCl₂)(thread-ZnCl₂) (Scheme 4.3, b). Alternatively, mixed-metal-chelated rotaxanes could be prepared. Selective removal of Cu²⁺ from 3(mac-CrCl₃)(thread-CuCl₂) afforded the kinetically stable mono-metallated rotaxane 3(mac-CrCl₃) (Scheme 4.3, c). 3(mac-CrCl₃) was then complexed with ZnCl₂ to produce the mixed-bis-metallated complex 3(mac-CrCl₃)(thread-ZnCl₂) (Scheme 4.3, d). To the best of our knowledge, this is only the second example of a mixed-metal coordinated rotaxane. The protection of the BPA ligand with Cu²⁺ or Cr³⁺ – which could
subsequently be reduced to labile Cr\(^{II}\) if it needed to be removed – makes it compatible with the CuAAC reaction and provides a general means of incorporating metal atoms or binding sites into organic structures via “click” chemistry.

![Scheme 4.3 Preparation of homo- and mixed-metallated rotaxanes. Reagents and conditions: a) Na\(_4\)EDTA (aq saturated), RT, 100%; b) ZnCl\(_2\), CH\(_3\)OH, RT, 1 h, 98%; c) Na\(_4\)EDTA (aq saturated), RT, 100%; d) ZnCl\(_2\), CH\(_3\)OH, RT, 1 h, 97%.]

The diamagnetic complex [3(mac-ZnCl\(_2\))(thread-ZnCl\(_2\))] was amenable to structural investigation by \(^1\)H NMR spectroscopy. The partial 400 MHz \(^1\)H NMR spectra of thread 4, demetallated rotaxane 3, and [3(mac-ZnCl\(_2\))(thread-ZnCl\(_2\))] in [D\(_7\)]DMF are shown in Figure 4.2. The upfield shifts of the coincident fumaramide olefin protons (H\(_f\) and H\(_i\)) in the rotaxane relative to those of the free thread 4 are typical of benzylic amide macrocycle-based rotaxanes, resulting from shielding of the xylylene rings. In addition to the appearance of resonances from the second BPA binding site (H\(_{M..R}\)), the distinctive triazole proton (H\(_L\)) signal is evident (Figure 4.1b and 4.1c). In the spectrum of compound [3(mac-ZnCl\(_2\))(thread-ZnCl\(_2\))] (Figure 4.1c), the BPA aromatic protons are shifted downfield relative to those in 3 (Figure 4.1b) due to metal coordination. Although the fumaramide olefin signals become separated as their inequivalence is emphasised by the zinc coordination to one end of the thread (Figure 4.1c), the metal complexation does not appear to significantly change the conformation or co-conformation adopted by the mechanically-interlocked fragments.
Chapter Four  
A Metal-Complex-Tolerant CuAAC “Click” Protocol Exemplified through the Preparation of Homo- and Mixed-Metal-Coordinated Rotaxanes

4.3 Conclusion

We have outlined a transition metal tolerant CuAAC protocol for the synthesis of mono- and bis-metallated rotaxanes using a simple alkyne-functionalised tridentate ligand and its metal complexes. Indeed, the methodology should prove a useful general way of appending a metal ion or complex to an organic scaffold, even when it contains redox-active or kinetically labile metals or vacant ligand sites. The ability to generate homo- and hetero-metallated rotaxanes should allow for the exploration of noncovalent distance-dependent properties — for example electronic, magnetic and photochemical — between metal centres.

4.4 Experimental Section

General

Unless stated otherwise, all reagents and anhydrous solvents were purchased from Aldrich Chemicals and used without further purification. bis(2-picolyl)amine was prepared according to literature procedure. The synthesis and spectroscopic data for 4 have been previously reported.
Chapter Four  
A Metal-Complex-Tolerant CuAAC “Click” Protocol Exemplified through the Preparation of Homo- and Mixed-Metal-Coordinated Rotaxanes

N,N-Bis(pyridin-2-ylmethyl)prop-2-yn-1-amine (1)

To a stirred solution of bis(2-picoly)amine (BPA) (3.00 g, 15.1 mmol) in toluene (150 mL), propargyl bromide (80% in toluene) (2.02 mL, 15.1 mmol) and triethylamine (2.12 mL, 15.1 mmol) were added. The reaction was heated to reflux for 24 h, during which time a solid precipitated. The reaction mixture was filtered and the filtrate was separated by column chromatography on silica gel using dichloromethane/acetonitrile/NH₄OH (aq) in a 5:5:0.1 v/v ratio as eluent to furnish 1 as a brown oil (2.62 g, 73%); ¹H NMR (400 MHz, CDCl₃): δ = 8.52 (d, J = 4.8 Hz, 2H, H₁₅), 7.62 (dt, J = 7.7 Hz and J = 1.8 Hz, 2H, H₁₄), 7.47 (d, J = 7.8 Hz, 2H, H₁₂), 7.12 (ddd, J = 7.3 Hz, J = 5.0 Hz and J = 1.0 Hz, 2H, H₁₁), 3.88 (s, 4H, H₁₆), 3.38 (d, J = 2.3 Hz, 2H, H₁₇), 2.27 (t, J = 2.4 Hz, 1H, H₁₈); ¹³C NMR (100 MHz, CDCl₃): δ = 158.7, 149.2, 136.6, 123.2, 122.2, 78.3, 73.7, 59.4, 42.6; HRMS (FAB, 3-NOBA matrix): m/z = 238.1348 [(M+H)⁺] (anal. calcd for C₁₅H₁₆N₃⁺: m/z = 238.1339).

General Procedure for the formation of [1MXₙ]

To a solution of 1 (1.0 g, 4.2 mmol) in methanol (10 mL) was added a saturated solution of the metal chloride salt (1.1 equiv.) in methanol. The solution was stirred for 1 h, during which time a solid precipitated. The reaction mixture was filtered and washed with methanol (5 mL).
N,N-Bis(pyridin-2-ylmethyl)prop-2-yn-1-amine copper (II) dichloride [1CuCl2]

CuCl2·2H2O, green-blue solid (1.5 g, 95%); mp > 143 °C (decomp); FT-IR (KBr): 3249 (m, C-H alkyl), 2106 (m, C-C alkyl), cm⁻¹; λmax (DCM:MeOH [1:1]) (ε(M¹ cm⁻¹)): 707 nm (1.65×10²); HRMS (FAB, 3-NOBA matrix): m/z = 335.0248 [(M-Cl)⁺ (anal. calcd for C15H15ClCuN3: m/z = 335.0251)].

N,N-Bis(pyridin-2-ylmethyl)prop-2-yn-1-amine chromium (III) trichloride [1CrCl3]

CrCl3(THF)3, green solid (1.6 g, 95%); mp > 255 °C (decomp); FT-IR (KBr): 3272 (m, C-H alkyl), 2119 (m, C-C alkyl), cm⁻¹; λmax (DCM:MeOH [1:1]) (ε(M¹ cm⁻¹)): 454 nm (1.90×10²), 622 nm (1.25×10²); HRMS (FAB, 3-NOBA matrix): m/z = 393.9859 [M⁺] (anal. calcd for C15H15Cl3CrN3: m/z = 393.9737).

N,N-Bis(pyridin-2-ylmethyl)prop-2-yn-1-amine zinc (II) dichloride [1ZnCl2]

ZnCl2·Et2O, cream white solid (1.4 g, 88%); mp > 210 °C (decomp); ¹H NMR (400 MHz, [D7]DMF): δ = 9.16 (d, J = 4.2 Hz, 2H, Hₐ), 8.20 (t, J = 7.4 Hz, 2H, Hₜ).
7.78 (d, J = 8 Hz, 2H, H₀), 7.75 (t, 2H, H₂), 4.32 (br s, 4H, H₅), 3.54 (s, 2H, H₄), 3.50 (s, 1H, H₃); °C NMR (100 MHz, [D₇]DMF): δ = 155.5, 150.1, 141.8, 125.7, 125.6, 78.6, 77.2, 56.6, 43.1; HRMS (FAB, 3-NOBA matrix): m/z = 336.0244 [(M-Cl⁺)] (anal. calcd for C₁₅H₁₅ClZnN₃⁺; m/z = 336.0246).

\[ \text{N,N-Bis(pyridin-2-ylmethyl)prop-2-yn-1-amine manganese (II) dichloride [1MnCl₂]} \]

MnCl₂·4H₂O, white solid (1.3 g, 83%); mp > 251 °C (decomp); FT-IR (KBr): 3242 (m, C-H alkyne), 2110 (m, C-C alkyne), cm−1; λ_max (DCM:MeOH [1:1]) (ε(M⁻¹cm⁻¹)): 454 nm (1.90×10²), 622 nm (1.25×10²); no absorptions in the visible spectrum; HRMS (FAB, 3-NOBA matrix): m/z = 327.0302 [(M-Cl⁺)] (anal. calcd for C₁₅H₁₅ClMnN₃⁺; m/z = 327.0335).

\[ \text{N,N-Bis(pyridin-2-ylmethyl)prop-2-yn-1-amine iron (III) trichloride [1FeCl₃]} \]

FeCl₃·6H₂O, yellow solid (1.5 g, 91%); mp > 162 °C (decomp); FT-IR (KBr): 3270 (m, C-H alkyne), 2117 (m, C-C alkyne), cm⁻¹; λ_max (DCM:MeOH [1:1]) (ε(M⁻¹cm⁻¹)): 384 nm (8.40×10²); HRMS (FAB, 3-NOBA matrix): m/z = 363.000 [(M-Cl⁺)] (anal. calcd for C₁₅H₁₅Cl₂FeN₃⁺; m/z = 362.9992).
N,N-Bis(pyridin-2-ylmethyl)prop-2-yn-1-amine iron (III) trichloride [1CoCl₂]

![Chemical Structure]

CoCl₂·6H₂O, white solid (1.4 g, 86%); mp > 216 °C (decomp); FT-IR (KBr): 3240 (m, C-H alkyne), 2113 (m, C-C alkyne), cm⁻¹; λmax (DCM:MeOH [1:1]) (ε(M⁻¹cm⁻¹)): 584 nm (1.40×10²), 628 nm (1.00×10²); HRMS (FAB, 3-NOBA matrix): m/z = 331.0292 [(M-Cl)⁺] (anal. calcd for C₁₅H₁₅ClCoN₃: m/z = 331.0287).

N-((1-Benzyl-1H-1,2,3-triazol-4-yl)methyl)(pyridin-2-yl)-N-(pyridin-2-ylmethyl) methanamine copper (II) dichloride [2CuCl₂]

![Chemical Structure]

To a solution of benzyl azide (50 mg, 0.38 mmol), [1CuCl₂] (154 mg, 0.41 mmol) and N,N-disopropylethylamine (0.066 mL, 0.38 mmol) in dichloromethane/methanol in a 9:1 v/v ratio (10 mL) was added Cu(CH₃CN)₄PF₆ (14 mg, 0.038 mmol). The resulting mixture was stirred for 12 h. The solution was concentrated under reduced pressure. To the residue was added acetone (5 mL) and the resulting suspension was filtered. The solid was washed with acetone (5 mL) to furnish [2CuCl₂] as a blue solid (171 mg, 90%); mp > 133 °C (decomp); FT-IR (KBr): 3112 (m), 1611 (s); λmax (DCM:MeOH [1:1]) (ε(M⁻¹cm⁻¹)): 713 nm (1.70×10⁵); HRMS (FAB, 3-NOBA matrix): m/z = 468.0894 [(M-Cl)⁺] (anal. calcd for C₂₂H₂₂ClCuN₆⁺: m/z = 468.0890).
Chapter Four  A Metal-Complex-Tolerant CuAAC “Click” Protocol Exemplified through the Preparation of Homo- and Mixed-Metal-Coordinated Rotaxanes

\[ N-(1\text{-}Benzyl\text{-}1\text{-}H\text{-}1,2,3\text{-}triazol\text{-}4\text{-}yl)\text{methyl}(pyridin\text{-}2\text{-}yl)\text{\textminus}N\text{-(pyridin\text{-}2\text{-}ylmethyl)}\text{methanamine chromium (III) trichloride} \ [2\text{CrCl}_3] \]

The synthesis of \([2\text{CrCl}_3]\) was similar to that described for \([2\text{CuCl}_2]\), except that \([1\text{CrCl}_3] \) (0.21 g, 0.41 mmol) was used. The reaction mixture was concentrated under reduced pressure. To the residue was added acetone (5 mL) and the resulting suspension was filtered. The solid was washed with acetone (5 mL) to furnish \([2\text{CrCl}_3]\) as a green solid (0.19 g, 95%); mp > 211 °C (decomp); FT-IR (KBr): 3114 (m, \( C=\text{triazole} \)), 1610 (s, \( \text{C=C} \text{triazole} \)), cm\(^{-1}\); \( \lambda_{\text{max}} \) (DCM:MeOH [1:1]) (\( \epsilon(M^{-1}\text{cm}^{-1}) \)): 451 nm (1.85\( \times \)10\(^2\)), 620 nm (1.20\( \times \)10\(^2\)); HRMS (FAB, 3-NOBA matrix): \( m/z = 492.0683 \) [(M-Cl)+] (anal. calcd for \( C_{22}H_{22}Cl_2CrN_6^+ \): \( m/z = 492.0688 \)).

\[ N-(1\text{-}Benzyl\text{-}1\text{-}H\text{-}1,2,3\text{-}triazol\text{-}4\text{-}yl)\text{methyl}(pyridin\text{-}2\text{-}yl)\text{\textminus}N\text{-(pyridin\text{-}2\text{-}ylmethyl)}\text{methanamine} \ (2) \]

A solution of \([2\text{CuCl}_2]\) (100 mg, 0.20 mmol) in CHCl\(_3\)/isopropanol in a 3:1 v/v ratio (25mL) was washed with saturated aqueous, basic EDTA (3 x 10 mL) and saturated aqueous sodium chloride (2 x 10 mL), dried (MgSO\(_4\)) and concentrated under reduced pressure to furnish 2 as a yellow oil (64 mg, 87%). \(^1\text{H NMR} \) (400 MHz, CDCl\(_3\)): \( \delta = 8.50 \) (d, \( J = 4.1 \) Hz, 2H, \( H_R \)), 7.62 (dt, \( J = 7.7 \) Hz and \( J = 1.8 \) Hz, 2H, \( H_P \)), 7.52 (d, \( J = 7.8 \) Hz, 2H, \( H_D \)), 7.50 (s, 1H, \( H_L \)), 7.37-7.21 (m, 5H, \( H_{ph} \)), 7.12 (ddd, \( J = 7.3 \) Hz and \( J = 5.0 \) Hz and \( J = 1.0 \) Hz, 2H, \( H_D \)), 3.85 (s, 2H, \( H_M \)), 3.82
(s, 4H, H₅); $^{13}$C NMR (100 MHz, CDCl₃): δ = 159.2, 149.0, 144.7, 136.4, 134.8, 129.0, 128.6, 127.9, 123.2, 122.9, 122.2, 59.6, 54.0, 48.6; HRMS (FAB, 3-NOBA matrix): $m/z = 371.1984 [(M+H)^+]$ (anal. calcd for C$_{22}$H$_{33}$N$_6$: $m/z = 371.1984$).

$N^1,N^3$-Bis(4-(aminomethyl)benzyl)isophthalamide (5)

![Chemical Structure of $N^1,N^3$-Bis(4-(aminomethyl)benzyl)isophthalamide (5)](image)

To a suspension of 6 (4.20 g, 6.94 mmol) in chloroform (150 mL) was added trifluoroacetic acid (5.15 mL, 69.4 mmol). The pale yellow solution was stirred vigorously for 12 h. The reaction mixture was concentrated under pressure to give a pale yellow solid. The resulting powder was stirred with Amberlyst A-21 resin in a dichloromethane/methanol 1:1 v/v ratio (150 mL) for 1 h. The solvent was removed under pressure to yield a hygroscopic powder (2.79 g, 100%); $^1$H NMR (400 MHz, [D$_6$]DMSO): δ = 9.31 (t, $J = 6.8$ Hz, 2H, H$_D$), 8.44 (s, 1H, H$_C$), 8.06 (dd, $J = 7.8$ Hz and $J = 1.4$ Hz, 2H, H$_B$), 7.58 (t, $J = 7.7$ Hz, 1H, H$_A$), 7.40 (d, $J = 8.0$ Hz, 4H, H$_F$), 7.36 (d, $J = 8.0$ Hz, 4H, H$_E$), 5.40 (br s, 4H, H$_I$), 4.50 (d, $J = 5.1$ Hz, 4H, H$_E$), 3.95 (s, 4H, H$_B$); $^{13}$C NMR (100 MHz, [D$_6$]DMSO): δ = 167.0, 141.2, 135.7, 133.7, 130.9, 129.9, 128.6, 127.2, 43.7, 43.6; HRMS (FAB, 3-NOBA matrix): $m/z = 403.2127 [(M+H)^+]$ (anal. calcd for C$_{24}$H$_{27}$N$_4$O$_2$: $m/z = 403.2134$).
Chapter Four  A Metal-Complex-Tolerant CuAAC "Click" Protocol Exemplified through the Preparation of Homo- and Mixed-Metal-Coordinated Rotaxanes

[4-({3-[4-(tert-Butoxycarbonylamino-methyl)-benzylcarbamoyl]-benzoylamino-methyl}-benzyl]-carbamic acid tert-butyl ester (6)

\[
\begin{align*}
\text{O} & \quad \text{A} \\
\text{NH} & \quad \text{B} \\
\text{C} & \quad \text{NH} \\
\text{D} & \quad \text{G} \\
\text{E} & \quad \text{F} \\
\text{H} & \quad \text{Boc} \\
\text{Boc} & \quad \text{Boc}
\end{align*}
\]

1-(N-Boc-aminomethyl)-4-(aminomethyl)benzene (5.00 g, 21.2 mmol) and triethylamine (7.46 mL, 53.1 mmol) in CH₃Cl (150 mL) were cooled to 0 °C. Isophthaloyl dichloride (2.15 g, 10.6 mmol) was dissolved in CH₃Cl (75mL) and added dropwise over 1 h. The reaction mixture was allowed to warm to room temperature and was stirred for a further 12 h, during which time a solid precipitated. The reaction mixture was filtered and the solid was washed with diethyl ether to furnish a light brown solid (5.30 g, 81%); mp 188-190 °C; ¹H NMR (400 MHz, [D₆]DMSO): δ = 9.17 (t, J = 6.0 Hz, 2H, H₆), 8.42 (s, 1H, H₅), 8.03 (dd, J = 7.7 Hz and J = 1.7 Hz, 2H, H₈), 7.57 (t, J = 7.7 Hz, 1H, H₄), 7.38 (t, J = 6.0 Hz, 2H, H₇), 7.28 (d, J = 8.1 Hz, 4H, H₉), 7.19 (d, J = 8.1 Hz, 4H, H₈), 4.47 (d, J = 6.0 Hz, 4H, H₇), 4.10 (d, J = 6.0 Hz, 4H, H₆), 1.39 (s, 18H, H₉); ¹³C NMR (100 MHz, [D₆]DMSO): δ = 165.8, 155.8, 137.9, 134.6, 129.9, 128.4, 127.2, 126.9, 126.3, 77.7, 43.1, 42.5, 28.2; HRMS (FAB, 3-NOBA matrix): m/z = 603.3183 [(M+H)+] (anal. calcd for C₃₄H₄₃N₄O₆+: m/z = 603.3183).
Chapter Four  A Metal-Complex-Tolerant CuAAC “Click” Protocol Exemplified through the Preparation of Homo- and Mixed-Metal-Coordinated Rotaxanes

\[ \text{([2](Azido-1,7,14,20-tetraaza-2,6,15,19-tetraoxo-3,5,9,12,16,18,22,25-tetrabenzocyclohexacosane)-(N^1-(2-(bis(pyridine_2-y1methy1)amjo)ethy1).v} \]

\[ \text{4}(2,2-diphenylethyl)fumaramide) \text{ rotaxane (7)} \]

To a suspension of 4 (0.300 g, 0.577 mmol), 5 (2.78 g, 6.93 mmol) and triethylamine (2.43 mL, 17.3 mmol) in chloroform (200 mL) was added a solution of 5-azidoisophthaloyl dichloride (1.69 g, 6.93 mmol) in chloroform (50 mL) via motor-driven syringe pump over a period of 6 h. The reaction mixture was stirred for a further 12 h. The resulting precipitate was filtered over celite and the solution was washed with saturated aqueous sodium hydrogen carbonate (3 x 20 mL), saturated aqueous sodium chloride (2 x 20 mL), dried (MgSO}_4 and concentrated under reduced pressure. The remaining residue was subjected to column chromatography on silica gel using dichloromethane/methanol/NH\text{aq} (aq) in a 9.6:0.4:0.01 v/v ratio as eluent to yield rotaxane (0.335 g, 52%); mp > 196 °C (decomp); \text{^1H NMR (400 MHz, [D7]DMF): \delta = 8.95 (t, J = 5.5 Hz, 1H, Hk), 8.79 (t, J = 5.5 Hz, 1H, Hh), 8.77 (s, 1H, Hc), 8.59 (s, 1H, Hj), 8.49 (d, J = 5.8 Hz, 2H, Ha), 8.18 (dd, J = 7.7 Hz and J = 1.5 Hz, 2H, Hb), 8.12 (t, J = 5.5 Hz, 2H, Hi), 8.07 (t, J = 5.0 Hz, 2H, HD), 7.80 (d, J = 1.2 Hz, 2H, He), 7.74 (t, J = 7.7 Hz, 1H, Hj), 7.72 (dt, J = 7.7 Hz and J = 1.8 Hz, 2H, Hc), 7.52 (d, J = 7.8 Hz, 2H, Hg), 7.37-7.31 (m, 10H, H Ph), 7.26-7.20 (m, 2H, Hb), 7.02 (s, 8H, HF & HG), 5.94 (s, 2H, Hf & Hg), 4.47-4.37 (m, 8H, HE & HH), 4.26 (t, J = 7.8 Hz, 1H, Hm), 3.93 (dd, J = 7.8 Hz and J = 2.3 Hz, 2H, Hh), 3.82 (s, 4H, Hg), 3.37 (dd, J = 14.0 Hz and J = 6.0 Hz, 2H, Ha), 2.69 (t, J = 7.7 Hz, 2H, Hb); \text{^13C NMR (100 MHz, [D7]DMF): \delta = 167.1, 166.8, 166.7, 165.7, 150.0, 143.9, 142.2, 138.4, 138.0, 137.5, 137.4, 135.5, 132.0, 131.1, 131.0, 130.1, 129.7, 129.2, 129.1, 127.7, 125.8, 124.0, 123.2, 122.4, 122.1, 60.8, 53.5, 51.5, 45.1, 44.6, 44.5, 38.8; HRMS (FAB, 3-}
NOBA matrix): $m/z = 1093.4814 \ [(M+H)^+]$ (anal. calcd for $C_{64}H_{61}N_{12}O_{6}^+: m/z = 1093.4837$).

$[(2)(\text{Azido-1,7,14,20-tetraaza-2,6,15,19-tetraoxo-3,5,9,12,16,18,22,25-tetrabenzocyclohexacosane})-(N^1-\text{(2-(bis(pyridine-2-ylmethyl)amino)ethyl)-N}^1-\text{(2,2-diphenylethyl)fumaramide}) \text{ copper (II) dichloride rotaxane [7(thread-CuCl}_2\)])$

To a solution of rotaxane 7 (200 mg, 0.18 mmol) in methanol (20 mL) was added a saturated solution of CuCl$_2$·2H$_2$O (34 mg, 0.20 mmol) in methanol (1 mL). The reaction mixture was stirred for 1 h, during which time a solid precipitated. The reaction mixture was filtered and the solid was washed with methanol to furnish [7(thread-CuCl$_2$)] as a light blue solid (213 mg, 95%); mp > 213 °C (decomp); FT-IR (KBr): 3443 (br s, $N$-H amide), 3307 (br s, $N$-H amide), 2115 (s, $N=N$ azide) cm$^{-1}$; $\lambda_{\text{max}}$ (DCM:MeOH [1:1]) ($\varepsilon$(M$^{-1}$cm$^{-1}$)): 708 nm (1.60×10$^2$); HRMS (FAB, 3-NOBA matrix): $m/z = 1190.3710 \ [(M-Cl)^+]$ (anal. calcd for $C_{64}H_{60}ClCuN_{12}O_{6}^+: m/z = 1190.3743$).
Chapter Four  
A Metal-Complex-Tolerant CuAAC "Click" Protocol Exemplified through the Preparation of Homo- and Mixed-Metal-Coordinated Rotaxanes

([2]({1H-1,2,3-Triazol-4-yl-N,N-bis(pyridine-2-yl methyl)methanamine copper (II) dichloride}-1,7,14,20-tetraaza-2,6,15,19-tetraoxo-3,5,9,12,16,18,22,25-tetrabenzocyclohexacosane)-(N'-(2-(bis(pyridine-2-ylmethyl)amino)ethyl)-N^4-(2,2-diphenylethyl)fumaramide) copper (II) dichloride rotaxane [3(mac-CuCl_2)(thread-CuCl_2)]

To a solution of [7(thread-CuCl_2)] (0.1 g, 0.08 mmol), [1CuCl_2] (0.04 g, 0.1 mmol) and N,N-disopropylethylamine (0.01 mL, 0.08 mmol) in dichloromethane/methanol in a 9:1 v/v ratio (10 mL) was added Cu(CH_3CN)_4PF_6 (0.005 g, 0.01 mmol). The solution was stirred for 12 h. The reaction mixture was concentrated under reduced pressure. To the residue was added acetone (10 mL) and the resulting suspension was filtered. The solid was washed with acetone (5 mL) to furnish [3(mac-CuCl_2)(thread-CuCl_2)] as a light blue solid (0.1 g, 80%); mp > 210 °C (decomp); FT-IR (KBr): 3290 (br s, N-H amide) cm^{-1}; \lambda_{max} (DCM:MeOH [1:1]) (\epsilon(M^{-1}cm^{-1})): 713 nm (3.50\times10^2); HRMS (FAB, 3-NOBA matrix): m/z = 1560.1284 [(M-CI)\textsuperscript{+}] (anal. calcd for C_{79}H_{75}Cl_3Cu_2N_{15}O_6\textsuperscript{+}: m/z = 1560.3682).
Chapter Four  
A Metal-Complex-Tolerant CuAAC “Click” Protocol Exemplified through the  
Preparation of Homo- and Mixed-Metal-Coordinated Rotaxanes

(\([2]([1H-1,2,3-Triazol-4-yl-N,N-bis(pyridine-2-yl-methyl)methanamine \chiromium (III) trichloride]-1,7,14,20-tetraaza-2,6,15,19-tetraoxo-3,5,9,12,16,18,22,25-tetramethylenocyclohexacosane)-(N1-(2-(bis(pyridine-2-ylmethyl)amino)ethyl)-N4-(2,2-diphenylethyl)fumaramide) copper (II) dichloride rotaxane [3(mac-CrCl3)(thread-CuCl2)]

To a solution of [7(thread-CuCl2)] (0.1 g, 0.08 mmol), [1CrCl3] (0.04 g, 0.1 mmol) and N,N-disopropylethylamine (0.01 mL, 0.08 mmol) in dichloromethane/methanol in a 9:1 v/v ratio (10 mL) was added Cu(CH3CN)4PF6 (0.005 g, 0.01 mmol). The solution was stirred for 12 h. The reaction mixture was concentrated under reduced pressure. To the residue was added acetone (10 mL), the resulting suspension was filtered and the solid was washed with acetone (5 mL) to furnish [3(mac-CrCl3)(thread-CuCl2)] as a light green solid (0.1 g, 82%); mp > 220 °C (decomp); FT-IR (KBr): 3272 (br s, N-H amide), 2115 (s, N=N azide) cm⁻¹; λmax (DCM:MeOH [1:1]) (ε(M⁻¹cm⁻¹)): 449 nm (2.20×10⁵), 625 nm (1.25×10⁵), 724 nm (1.70×10⁵); HRMS (FAB, 3-NOBA matrix): m/z = 1584.8869 [(M-Cl)⁺] (anal. calcd for C₇₉H₇₅Cl₄CrCuN₁₅O₆⁺: m/z = 1584.3480).
Chapter Four  A Metal-Complex-Tolerant CuAAC “Click” Protocol Exemplified through the Preparation of Homo- and Mixed-Metal-Coordinated Rotaxanes

\[(\{1H-1,2,3-Triazol-4-yl-N,N-bis(pyridine-2-yl-methyl)methanamine \}-1,7,14,20-tetraaza-2,6,15,19-tetraoxo-3,5,9,12,16,18,22,25-tetrabenzocyclohexacosane)-(N’-(2-(bis(pyridine-2-ylmethyl)amino)ethyl)-N^4-(2,2-diphenylethyl)fumaramide)rotaxane (3)\]

A solution of \([3(mac-CrCl_3)(thread-CuCl_2)]\) (0.1 g, 0.08 mmol) in chloroform/isopropanol in a 3:1 v/v ratio (15 mL) was washed with saturated aqueous, basic EDTA (3 x 10 mL) and saturated aqueous sodium chloride (2 x 10 mL), dried (MgSO_4) and concentrated under reduced pressure to give a yellow oil. The remaining residue was subjected to column chromatography on silica gel using dichloromethane/acetonitrile/\(\text{NH}_4\text{OH}\) (aq) in a 5:5:0.2 v/v ratio as eluent to furnish 3 as a light yellow oil (0.08 g, 72%).

\(^1\text{H NMR (400 MHz, [D}_7\text{]DMF):} \delta = 9.25 (s, 1H, H_L), 8.95 (t, J = 5.2 Hz, 1H, H_k), 8.86 (s, 1H, H_j), 8.79 (t, J = 5.5 Hz, 1H, H_h), 8.78 (s, 1H, H_c), 8.71 (s, 2H, H_k), 8.58 (d, J = 4.7 Hz, 2H, H_R), 8.48 (d, J = 4.1 Hz, 2H, H_a), 8.22 (s, 2H, H_i), 8.19 (dd, J = 7.7 Hz and J = 1.4 Hz, 2H, H_B), 8.08 (s, 2H, H_D), 7.87-7.80 (m, 2H, H_O & H_P), 7.75 (t, J = 7.7 Hz, 1H, H_A), 7.71 (dt, J = 7.7 Hz and J = 1.8 Hz, 2H, H_c), 7.51 (d, J = 7.7 Hz, 2H, H_d), 7.37-7.29 (m, 10H, H_Q & H_Ph), 7.23-7.19 (m, 4H, H_b & H_Pb), 7.05 (d, J = 9.0 Hz, 4H, H_C), 7.03 (d, J = 9.0 Hz, 4H, H_F), 5.97 (s, 2H, H_j & H_h), 4.52-4.40 (m, 8H, H_E & H_H), 4.26 (t, J = 7.8 Hz, 1H, H_m), 4.03 (s, 2H, H_M), 3.97 (s, 4H, H_N), 3.94 (t, J = 7.5 Hz, 2H, H_i), 3.83 (s, 4H, H_g), 3.40-3.37 (m, 2H, H_E), 2.71 (t, J = 6.7 Hz, 2H, H_j); \(^{13}\text{C NMR (100 MHz, [D}_7\text{]DMF):} \delta = 167.1, 166.9, 166.7, 165.6, 160.7, 160.4, 150.1, 150.0, 147.1, 143.9, 139.1, 138.4, 138.0, 137.6,
Chapter Four  A Metal-Complex-Tolerant CuAAC “Click” Protocol Exemplified through the Preparation of Homo- and Mixed-Metal-Coordinated Rotaxanes

137.4 (x2), 135.5, 132.0, 131.1, 131.0, 130.1 (x2), 129.6 (x2), 129.2, 129.0, 127.7, 125.8, 125.4, 123.9 (x2), 123.2, 123.0, 60.8, 60.6, 53.5, 51.5, 49.8, 45.1, 44.7, 44.5, 38.8; HRMS (FAB, 3-NOBA matrix): \( m/z = 1330.6064 \) [(M+H)⁺] (anal. calcd for \( \text{C}_{79}\text{H}_{76}\text{N}_{15}\text{O}_6^+ \): \( m/z = 1330.6103 \)).

\([\{\text{IH}-1,2,3-\text{Triazol}-4-\text{yl-N,N-bis(pyridine-2-yl-methyl)methanamine-zinc (II) dichloride}\}-1,7,14,20-\text{tetraaza-2,6,15,19-tetraoxo-3,5,9,12,16,18,22,25-tetrabenzocyclohexacosane)-(N'(2-(bis(pyridine-2-ylmethyl)amino)ethyl)-N'(2,2-diphenylethyl)fumaramide) zinc (II) dichloride rotaxane}[3(\text{mac-ZnCl}_2)(\text{thread-ZnCl}_2)]\)

To a solution of rotaxane 3 (0.05 g, 0.04 mmol) in methanol (5 mL) was added a saturated solution of \( \text{ZnCl}_2 \) (0.01 g, 0.08 mmol) in methanol (1mL). The reaction was stirred for 1 h, during which time a solid precipitated. The solid was filtered and washed with methanol (5 mL) to furnish \( \text{[3(mac-ZnCl}_2)(\text{thread-ZnCl}_2)]} \) as a white solid (0.06 g, 98%); mp > 235 °C (decomp); \( ^1\text{H} \) NMR (400 MHz, [\( \text{D}_7 \)]DMF): \( \delta = 9.25 \) (s, 1H, \( \text{H}_d \)), 9.19 (d, \( J = 4.8 \) Hz, 2H, \( \text{H}_b \)), 9.05 (d, \( J = 4.1 \) Hz, 2H, \( \text{H}_a \)), 8.92 (t, \( J = 5.2 \) Hz, 1H, \( \text{H}_e \)), 8.62 (t, \( J = 5.0 \) Hz, 1H, \( \text{H}_b \)), 8.78 (s, 1H, \( \text{H}_j \)), 8.68 (s, 2H, \( \text{H}_k \)), 8.65 (s, 1H, \( \text{H}_c \)), 8.23 (dt, \( J = 7.6 \) Hz and \( J = 1.4 \) Hz, 2H, \( \text{H}_f \)), 8.21 (dd, \( J = 7.7 \) Hz and \( J = 1.4 \) Hz, 2H, \( \text{H}_p \)), 8.06 (s, 2H, \( \text{H}_p \)), 7.92 (dt, \( J = 7.6 \) Hz and \( J = 1.4 \) Hz, 2H, \( \text{H}_o \)), 7.90 (t, \( J = 7.5 \) Hz, 2H, \( \text{H}_e \)), 7.81-7.75 (m, 5H, \( \text{H}_4, \text{H}_O \) and \( \text{H}_q \)), 7.61 (t, \( J = 6.3 \) Hz, 2H, \( \text{H}_b \)), 7.52 (d, \( J = 7.7 \) Hz, 2H, \( \text{H}_d \)), 7.38-7.26 (m, 8H, \( \text{H}_p \)), 7.24-7.18 (m, 2H, \( \text{H}_p \)), 7.00 (d, \( J = 9.0 \) Hz, 4H, \( \text{H}_b \)), 6.98 (d, \( J = 9.0 \) Hz, 4H, \( \text{H}_f \)), 5.91 (d, \( J = 15.1 \) Hz, 1H, \( \text{H}_j \)), 5.79 (d, \( J = 9.0 \) Hz, 4H, \( \text{H}_o \)), 5.48 (d, \( J = 9.0 \) Hz, 4H, \( \text{H}_f \)), 5.15 (s, 2H, \( \text{H}_q \)), 4.10 (s, 2H, \( \text{H}_q \)), 3.90 (s, 2H, \( \text{H}_o \)), 3.75 (s, 2H, \( \text{H}_r \)), 3.65 (s, 2H, \( \text{H}_r \)), 3.55 (s, 2H, \( \text{H}_r \)), 3.45 (s, 2H, \( \text{H}_r \)), 3.35 (s, 2H, \( \text{H}_r \)), 3.25 (s, 2H, \( \text{H}_r \)), 3.15 (s, 2H, \( \text{H}_r \)).
To a solution of rotaxane \([3(mac-CrCl_3)]\) (0.07 g, 0.04 mmol) in methanol (5 mL) was added a saturated solution of ZnCl\(_2\) (0.007 g, 0.05 mmol) in methanol (1 mL). The reaction was stirred for 1 h, during which time a solid precipitated. The solid was filtered and washed with methanol (5 mL) to furnish \([3(mac-CrCl_3)(thread-ZnCl_2)]\) as a light green solid (0.06 g, 90%); mp > 246 °C (decomp); FT-IR (KBr): 3257 (br s, N-H<sub>amide</sub>) cm<sup>-1</sup>; λ<sub>max</sub> (DCM:MeOH [1:1]) (ε(M<sup>-1</sup>cm<sup>-1</sup>)): 448 nm (1.90×10<sup>2</sup>), 622 nm (1.25×10<sup>2</sup>); HRMS (FAB, 3-NOBA matrix): m/z = 1585.0926 [(M+H)<sup>+</sup>] (anal. calcd for C<sub>79</sub>H<sub>75</sub>C<sub>14</sub>CrN<sub>15</sub>O<sub>6</sub>Zn<sup>2+</sup>; m/z = 1585.3475).
Chapter Four  
A Metal-Complex-Tolerant CuAAC “Click” Protocol Exemplified through the Preparation of Homo- and Mixed-Metal-Coordinated Rotaxanes

\[([\{1H-1,2,3-Triazol-4-yl-N,N-bis(pyridine-2-yl-methyl) methanamine-chromium (III) trichloride\}]_{3}, 17,14,20-tetraaza-2,6,15,19-tetraoxo-3,5,9,12,16,18,22,25-tetrazenobicyclohexacosane)-(N\textsuperscript{1}-(2-(bis(pyridine-2-ylmethyl)amino)ethyl)-N\textsuperscript{4}-(2,2-diphenylethyl)fumaramide) rotaxane [3(mac-CrCl\textsubscript{3})]

A solution of \([3(mac-CrCl\textsubscript{3})(thread-CuCl\textsubscript{2})]\) (0.1 g, 0.06 mmol) in CHCl\textsubscript{3}/isopropanol in a 3:1 v/v ratio (15 mL) was washed with saturated aqueous, basic EDTA (3 x 10 mL) and saturated aqueous sodium chloride (2 x 10 mL), dried (MgSO\textsubscript{4}) and concentrated under reduced pressure to give a green solid. The product was subjected to column chromatography on silica gel using dichloromethane/acetonitrile/NH\textsubscript{4}OH (aq) in a 5:5:0.1 v/v ratio as eluent to furnish \([3(mac-CrCl\textsubscript{3})]\) as a light green solid (0.07 g, 71%); mp > 211 °C (decomp); FT-IR (KBr): 3261 (br s, N-H amide) cm\textsuperscript{-1}; \(\lambda_{\text{max}}\) (DCM:MeOH [1:1]) (ε(M\textsuperscript{-1}cm\textsuperscript{-1})): 449 nm (2.10×10\textsuperscript{3}), 625 nm (1.35×10\textsuperscript{3}); HRMS (FAB, 3-NOBA matrix): \(m/z = 1487.4586\) [(M+H\textsuperscript{+})] (anal. calcd for C\textsubscript{79}H\textsubscript{76}Cl\textsubscript{3}CrN\textsubscript{15}O\textsubscript{6}): \(m/z = 1487.4574\).

4.5 References and Notes


CHAPTER FIVE

Towards Magnetic Dipolar Interactions in Rotaxanes

Acknowledgment

All practical work reported in this Chapter was shared equally with Dr. Bryan D. Koivisto. EPR experiments were carried out by Daniel Sells and Joanna Wolowska under the supervision of Prof. Eric McInnes at the University of Manchester. These people are gratefully acknowledged for their contribution.
Synopsis

The controlled large-amplitude motion achievable in stimuli-responsive molecular shuttles such as those described in Chapters Two and Three can be used as a generic basis for creating molecular-level switches if combined with a distance-dependent chemical or physical property. In this Chapter, we utilise the unique nature of interlocked architectures to study one such property – dipolar interactions between paramagnetic species.

Using the novel synthetic methodology developed in Chapter Four, a range of simple mechanically-interlocked models containing paramagnetic species on macrocycle and thread are prepared. The macrocycle and the thread in rotaxanes are not covalently bound resulting in structures with dipolar coupling pathways that are not dominated by the normally predominant through-bond interactions. Dipolar interactions between paramagnetic centres cause splitting of line shapes in EPR spectra for the two species with unpaired of electrons. This splitting is then used to quantify these weak magnetic interactions.

Unfortunately, dipolar interactions were not observed in any of the systems investigated by CW-EPR. This is likely a consequence of the linewidths of the spectra which sets an upper limit on the magnitude of the magnetic interaction that can be detected.
5.1 Introduction

Synthetic chemists have cleverly designed and synthesised rotaxane-based bistable interlocked architectures (molecular shuttles) as means to control mechanical motion at the molecular level.\textsuperscript{[1]} Although most of their efforts have been focused on using different external stimuli to translocate the macrocycle from an original preferred binding site to a second one, exploiting such a movement to trigger property changes is becoming an important challenge. Biological systems extensively utilise controlled sub-molecular positional changes to perform essential tasks.\textsuperscript{[2]} Allosteric enzymes, for example, utilise the conformational change promoted by the complexation of an effector molecule to a specific site to regulate enzyme activity.\textsuperscript{[3]} The double ring architecture of chaperonin can be opened to allow a non-native protein to bind inside the cavity where folding to produce a reactive structure takes place.\textsuperscript{[4]} More complex again, in terms of both structure and function, are the motor proteins such as kinesis and myosin which are responsible for large-scale motion within and outwith the cell.\textsuperscript{[2]}

Rotaxane-based molecular shuttles present a generic basis for the construction of molecular-level mechanical switches for controlling properties that depend on the spatial separation of the constituents.\textsuperscript{[5a]} Therefore, it seems rather unusual that only a few molecular shuttles capable of altering physical properties have been synthesised to date.\textsuperscript{[5]} Among many distance-dependent physical properties that could be altered using this controlled large-amplitude movement, magnetism is one of the most interesting due to its high technological importance, for example in relation to the construction of single-molecule magnets.\textsuperscript{[6]} Single-molecule magnets are species that display spontaneous magnetisation below a critical temperature and may lead to magnetic materials with a variety of unique properties such as high processability, low density and a combination of magnetic, optical and/or electronic properties.\textsuperscript{[6,7]}

The magnetic properties of a system are mainly determined by the orientation and strength of spin-spin interactions between fragments containing unpaired electrons. In principal, these interactions are governed by two mechanisms: an isotropic exchange contribution (through-bond interactions) and an anisotropic dipolar contribution (through-space interactions).\textsuperscript{[8,9]}
Spin-spin interactions can be studied using continuous wave electron paramagnetic resonance (CW-EPR), as this technique is a powerful tool for measuring and quantifying the magnetic interactions of systems containing unpaired electrons. The spectrum is normally recorded as the first derivative of the net absorption of radiation by a sample whose electronic energy levels have been separated by an applied magnetic field, $H_0$ (Figure 5.1).

Figure 5.1 Splitting of the electronic energy levels by a magnetic field, $H$.

Two types of information can be obtained: the “g factor”, which corresponds to the chemical shifts of different species; and the hyperfine constant, $A$, which arises from the interaction between unpaired electrons and paramagnetic centres in close proximity. If the spectrum is well-resolved, the values of $g$ and $A$ can be obtained via direct analysis of lineshapes of the EPR spectrum and/or computer simulation and fitting techniques.

Spin-spin interactions between paramagnetic centres are strongly distance dependent and, if the centres are close enough, may cause splitting of line shapes in EPR spectra for the two unpaired of electrons. This splitting, which is similar to that observed in NMR spectra, can be interpreted to obtain the $g$ and $A$ values. These values are then utilised to determine the isotropic exchange and anisotropic dipolar contributions of the spin-spin interaction.

Although through-bond interactions have been extensively studied, investigation of systems whose spins interact predominantly through-space remains limited. This is because molecular systems where the two paramagnets could be held together at a fixed distance in the absence of the normally dominant exchange-coupling contributions are extremely difficult to design.
Mechanically-interlocked architectures are particularly well suited to investigate these interactions, as they consist of two or more components that are not covalently bound. Placing paramagnetic species in the macrocycle and the thread components of a rotaxane should yield structures with dipolar coupling pathways that are not dominated by the normally predominant exchange-coupling pathways.

Figure 5.2 illustrates molecular arrangements of two paramagnetic species which would be expected to result in largely through-bond (Figure 5.2a) or through-space (Figure 5.2b) interactions.

![Figure 5.2](image)

**Figure 5.2** Electron-electron spin-spin interactions with a) isotropic exchange; b) anisotropic dipolar as major contributors.

Simple models of the class represented by Figure 5.2b will set the basis for understanding and quantifying the dipolar contribution in systems where spin-spin interactions occur largely by spatial proximity of orbitals on atoms that are not covalently bound – or which are linked by a long covalent tether. Furthermore, it is essential to comprehend the effect that through-space interactions generate on the EPR spectrum lineshape before more complex mechanically-controlled magnetic switches are synthesised. Such systems may contribute to the development of spectroscopic and theoretical methods for studying such subtle magnetic interactions as they relate to biological systems. Dipolar interactions have been widely investigated in proteins containing clusters of paramagnetic centres and/or organic free radicals because insight into metric and dynamic features can be achieved. Unfortunately, as a consequence of their complexity, this is not always possible.

Herein, simple mechanically-interlocked systems (rotaxanes) containing paramagnetic species in macrocycle and thread are synthesised to establish and investigate dipolar interactions. The metal centres in the macrocycle are varied in order to study any effect on the magnitude of spin-spin interaction. CW-EPR in frozen solution was employed to study the magnetic properties and magnetic-coupling strengths of these simple models.
5.2 Results and Discussion

5.2.1 Spin $\frac{1}{2}$ - Spin $\frac{1}{2}$ Systems


![Scheme 5.1 Preparation of rotaxane [2(mac-CuCl$_2$)(thread-CuCl$_2$)] via a CuAAC reaction.[13] Reagents and conditions: a) [3CuCl$_2$], 0.1 equiv. Cu(CH$_3$CN)$_4$PF$_6$, DIPEA, CH$_2$Cl$_2$/CH$_3$OH (9:1), RT, 12 h, 80%.

This unique and unprecedented rotaxane provides the opportunity to investigate spin $\frac{1}{2}$ - spin $\frac{1}{2}$ systems. However, it is essential to establish and differentiate the spectroscopic signatures of the magnetically isolated systems, [1(thread-CuCl$_2$)] and [3CuCl$_2$], as a means to recognise any changes in the spectrum of [2(mac-CuCl$_2$)(thread-CuCl$_2$)]. The frozen-solution[16] X-band and Q-band EPR spectra of [1(thread-CuCl$_2$)] in CH$_2$Cl$_2$/CH$_3$OH is shown in Figure 5.3. It can be observed that the number of lines in the low-field hyperfine pattern exceeds that expected for an S = $\frac{1}{2}$ species interacting with a Cu$^+$ nucleus. In fact, the better resolved Q-band spectrum (Figure 5.1b) shows eight lines which imply that one unpaired electron is actually interacting with two equivalent copper nuclei. Therefore, the observed anisotropic spectrum is that of an S = 1 species where the zero-field splitting (ZFS) is of the same order of magnitude as the Cu$^{+}$ hyperfine interaction – very small.
This unresolved spectrum can then be simulated with $S = 1$, $|D| = 80$ G, $g_z = 2.18$, $g_x = 2.018$, $g_y = 2.06$, $A_z = 80$ G suggesting that $[\text{1}(\text{thread-CuC}_2^2)]$ is in fact an alkoxide-bridged Cu dimer where coppers belonging to different molecules bind head to head (Scheme 5.2).

The paramagnetic centre of complex $[3\text{CuCl}_2]$ has a similar local coordination sphere to that of $[\text{1}(\text{thread-CuC}_2^2)]$, and therefore displays nearly identical EPR spectra (not shown).

As mentioned above, through-space interactions between paramagnetic centres may cause splitting of line shapes in EPR spectra for the two unpaired of electrons.\[11\] Unfortunately, in the X-band and the better resolved Q-band EPR (Figure 5.4) spectra of $[2(\text{mac-CuCl}_2)(\text{thread-CuC}_2^2)]$, line splitting caused by spin-spin interaction is not observed. The four parallel features in the low field correspond to the unpaired electron interacting with a Cu$^{II}$ nucleus. Therefore, these spectra are characteristic of monomeric or, rather, non-interacting Cu$^{II}$ nuclei.
Simulation of the Q-band spectrum gives $g_x = 2.018$, $g_y = 2.043$, $g_z = 2.212$, $A_x = 172$ G, which are typical value patterns for a Cu$^{II}$ complex with geometries derived from octahedral structure — square pyramidal or intermediate geometries.

![Diagram of Cu](image)

**Figure 5.4** a) X-band and b) Q-band EPR spectra of $[2(mac-CuC_1_2)(thread-CuC_1_2)]$ in DMF/toluene at 120 K (frozen solution).

In addition, the observed hyperfine value for $[2(mac-CuC_1_2)(thread-CuC_1_2)]$ is double that observed for the isolated system $[1(thread-CuC_1_2)]$, which is consistent with dimerisation of the latter. This value is obtained because the unpaired electrons are exchange-coupled between two copper nuclei and hence they only experience half the strength of the interaction with either Cu nucleus.

It is important to notice that the two Cu$^{II}$ ions in $[2(mac-CuC_1_2)(thread-CuC_1_2)]$ must have identical EPR spectra (i.e. spin-Hamiltonian parameters) because only one distinct Cu monomer is detected. This is, of course, consistent with the same local coordination spheres that the two Cu ions experience (Scheme 5.1).

**5.2.2 Spin $\frac{1}{2}$ - Spin $\frac{3}{2}$ Systems**

Although it has been suggested that the magnitude of the electron-electron interaction decreases as the number of unpaired electrons increases, increasing this number may affect other parameters that modify the interaction itself.$^{[11]}$ Therefore, $[2(mac-CrC_1_3)(thread-CuC_1_2)]$ was designed to investigate the effect of increasing the spin on the macrocycle on the magnitude of the dipolar interaction (Scheme 5.3).
Chapter Five  
Towards Magnetic Dipolar Interactions in Rotaxanes

The \( [2(\text{mac-CrCl}_3)(\text{thread-CuCl}_2)] \) rotaxane synthesis was carried out according to Scheme 5.3. Addition of Cu\(^1\) catalyst to a solution of \([1(\text{thread-CuCl}_2)], [3\text{CrCl}_3]\) and DIPEA in CH\(_2\)Cl\(_2\)/CH\(_3\)OH smoothly generated \([2(\text{mac-CrCl}_3)(\text{thread-CuCl}_2)]\) in a 82% yield.

![Scheme 5.3 Preparation of \([2(\text{mac-CrCl}_3)(\text{thread-CuCl}_2)]\) via a CuAAC reaction. Reagents and conditions: a) \([3\text{CrCl}_3], 0.1 \text{ equiv. Cu(CH}_3\text{CN)}_4\text{PF}_6, \text{DIPEA, CH}_2\text{Cl}_2/\text{CH}_3\text{OH (9:1), RT, 12 h, 82%}.\]

Fine-structure resolved spectra of the magnetically-isolated component \([3\text{CrCl}_3]\) were observed in DMF/toluene frozen solution (Figure 5.5). The weak features designated with arrows in the X-band spectrum (Figure 5.5a) are due to the ZFS of the \( S = \frac{3}{2} \text{Cr}^{III} \) ion as a consequence of electron-electron interactions.

![Figure 5.5 a) X-band and b) Q-band EPR spectra of \([3\text{CrCl}_3]\) in DMF/toluene at 120 K (frozen solution). Arrows indicate weak features due to ZFS in \( \text{Cr}^{III} \).]
Although in the higher resolution Q-band spectrum these weak features are not observed, the spectrum can be simulated with $S = \frac{3}{2}$, an isotropic $g$-value of 1.97 (consistent with a $d^3$ configuration), and $|D| = 0.12$ cm$^{-1}$. Electron-electron interactions are defined by two parameters, $D$ and $E$, and they measure the symmetry of the metal centre. Although their values can be varied arbitrarily, in practice they are governed by the rhombicity parameter ($\lambda = E/D$) and can only take fixed values from 0 (axial symmetry) to $\frac{1}{3}$ (maximum rhombic splitting). The rhombicity parameter of $[3\text{CrCl}_3]$ is equal to $\frac{1}{3}$, which suggests that the local coordination at Cr$^{\text{III}}$ is highly distorted.[7-10]

The X and Q-band spectra of $[2(\text{mac-CrCl}_3)(\text{thread-CuCl}_2)]$ in CH$_3$OH/CH$_2$Cl$_2$ in frozen-solution are shown in Figure 5.6.

Once again no line splitting for the two paramagnetic centres is observed. The X-band spectrum in Figure 5.6a appears to be merely the superposition of the isolated model systems $[3\text{CrCl}_3]$ and $[2(\text{mac-CuCl}_2)(\text{thread-CuCl}_2)]$.

Figure 5.7 shows the overlaid spectra of $[3\text{CrCl}_3]$ in red, $[2(\text{mac-CuCl}_2)(\text{thread-CuCl}_2)]$ in green, and $[2(\text{mac-CuCl}_2)(\text{thread-CrCl}_3)]$ in black. Similar to the model compounds (Figure 5.5), the weak features (black spectrum indicated by arrows) arise as a consequence of ZFS in Cr$^{\text{III}}$. Additionally, the four parallel features in the low field are a consequence of the unpaired electron interacting with Cu and Cr nuclei.
Figure 5.7 X-band EPR spectra of [2(mac-CrCl₃)(thread-CuCl₂)] (black) compared against analogous spectra of [3CrCl₃] (red) and [2(mac-CuCl₂)(thread-CuCl₂)] (green). Arrows indicate weak features due to ZFS in Cr³⁺.

Unfortunately, any interaction between the paramagnetic centres on macrocycle and thread of complexes [2(mac-CuCl₂)(thread-CuCl₂)] and [2(mac-CrCl₃)(thread-CuCl₂)] are not detected in CW-EPR.

5.2.3 Spin \( \frac{1}{2} \) - Spin \( \frac{7}{2} \) Systems

To further investigate the effect of increasing the spin number on the spin-spin interaction, complex [2(mac-Gd)(thread-CuCl₂)] was designed (Scheme 5.4). Lanthanides have a high coordination number, therefore, it was necessary to introduce a different alkyne-funtionalised ligand. Ligand 4,\(^{[17]}\) which has been shown to coordinate to a number of lanthanides, was synthesised according to Scheme 5.4.
Scheme 5.4 Synthesis of [2(mac-Gd)(thread-CuCl$_2$)] from complexes [4Gd] and [1(mac-CuCl$_2$)].

Reagents and conditions: a) GdBr$_3$, KOH, H$_2$O, RT, 1 h, quantitative; b) [1(mac-CuCl$_2$)], 1.5 equiv. Cu(CH$_3$CN)$_4$PF$_6$, DIPEA, CH$_3$Cl/CH$_3$OH/H$_2$O (8:1.5:0.5), RT, 12 h, 86%.

Treatment of 4 with GdBr$_3$ in H$_2$O at pH 6.0 efficiently generated complex [4Gd]. Lamentably, the standard CuAAC protocol conditions proved to be insufficient for the synthesis of [2(mac-Gd)(thread-CuCl$_2$)], which required more than 1 equivalent of the Cu$^1$ catalyst.

The X-band spectrum of [2(mac-Gd)(thread-CuCl$_2$)] in DMF/H$_2$O frozen solution is shown in Figure 5.8.

Figure 5.8 X-band EPR spectrum of [2(mac-Gd)(thread-CuCl$_2$)] in DMF/H$_2$O at 110 K (frozen solution).
Unfortunately, no line splitting was observed. The spectrum shown in Figure 5.8 is simply a superposition of the spectra of isolated systems [4Gd] (not shown) and [2(mac-CuCl_2)(thread-CuCl_2)] (Figure 5.4). The relatively intense resonance signal at $g = 1.99$ and peaks at lower field are due to Gd^{III} and Cu^{II}, respectively. Moreover, the value of the hyperfine coupling of Cu^{II} (170 G) is characteristic of monomeric Cu^{II}.

The experimental linewidth sets an upper limit on the magnitude of the magnetic interaction detectable which decreases the sensitivity of the EPR experiment. The linewidth in all the EPR spectra shown is relatively high ($< 10^{-3}$ cm$^{-1}$) due to the presence of metal ions. Therefore, through-space interactions between the paramagnetic centres must be significantly smaller than this set value.

5.2.4 Diradical Spin $\frac{1}{2}$ - Spin $\frac{1}{2}$ Systems

Organic radicals are ideal building blocks for the synthesis of new magnetic materials as a consequence of their unpaired electrons and rich chemistry. Introduction of organic radicals to specific positions on the macrocycle and thread would allow the investigation of dipolar interactions in rotaxanes in a similar manner to that studied above for paramagnetic metal centres. Radicals typically display EPR spectra with narrower linewidths than metal ions, which may increase the resolution of this technique by decreasing the limit set by the experimental linewidths. This fact may improve the possibility of observing splitting of the lineshapes due to through-space interactions.

Verdazyl and nitroxide families of organic radicals are two of the most well-studied. They have been frequently explored for use in molecular magnets and they are relatively easy to synthesise. Therefore, these organic radicals are excellent building blocks for our desired diradical rotaxane.

Such a diradical rotaxane, 5, is shown in Scheme 5.5 and consists of a TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl) radical – which is sufficiently large to act as a stopper – bound to the peptide station and a verdazyl radical attached to the macrocycle by means of a triazole linkage.
Studies towards accessing rotaxane 5 are ongoing, however, synthesis of isolated systems 6 and 7 has been successfully achieved. Thread 6 was synthesised by peptide coupling of commercially available 4-amino TEMPO and \(N\)-(2,2-diphenylethyl)-fumaric acid.\(^{[11]}\)

Compound 7, which was synthesised to mimic the environment of the verdazyl radical in rotaxane 5, was prepared according to Scheme 5.6. Compound 8 was obtained from condensation of aldehyde 9 with bis(1-methylhydrazide) in CH\(_3\)OH, followed by deprotection of the TMS group. Radical 10 was then prepared by oxidation of 8 by benzoquinone. Compound 7 was synthesised from compound 11 using our standard CuAAC protocol conditions\(^{[13]}\) in a 79% yield.

Scheme 5.6 Preparation of compound 7. Reagents and conditions: a) carbonic acid bis(1-methylhydrazide), CH\(_3\)OH, reflux, 16 h, 39%; b) KF, CH\(_3\)OH, RT, 16 h, 89%; c) 1.5 equiv. benzoquinone, CH\(_2\)Cl\(_2\), RT, 12 h, 90%; d) 11, 0.1 equiv. Cu(CH\(_3\)CN)\(_4\)PF\(_6\), DIPEA, CH\(_2\)Cl\(_2\)/CH\(_3\)OH 9:1, RT, 12 h, 79%.
5.3 Conclusion

Although a range of hydrogen-bond based rotaxanes containing paramagnetic species in the macrocycle and thread has been successfully synthesised, through-space interactions between the paramagnetic centres have not been observed in CW-EPR. This is likely a consequence of the large linewidths that the spectra displayed due to the presence of metal ions. Observed linewidths of \(< 10^{-3} \text{ cm}^{-1}\) are much larger than the expected magnitudes of dipolar interactions.\(^{[8,11]}\)

Using radicals as the paramagnetic species may avoid such problems, and to this end synthetic efforts towards rotaxanes of the type 5 are now ongoing.

5.4 Experimental Section

General

Unless stated otherwise, all reagents and anhydrous solvents were purchased from Aldrich Chemicals and used without further purification. The synthesis and spectroscopic data of \([1\text{thread-CuC12}], [2\text{(mac-CuC12)(thread-CuC12)}], [2\text{(mac-CrCl3)(thread-CuC12)}], [3\text{CuCl2}], [3\text{CrCl3}]\) have been previously reported.\(^{[15,17]}\) \(N\)-\((2,2\text{-diphenylethyl})\)-fumaric acid\(^{[11]}\) and carbonic acid bis(1-methylhydrazide)\(^{[19]}\) and were prepared according to literature procedures.

\{4,10-Bis-carboxymethyl-7-[(2-propynylcarbamoyl)-methyl]-1,4,7,10-tetraaza-cyclododec-1-yl\}-acetate gadolinium (III) (4Gd)

\[
\text{Gd} \quad \text{O} \quad \text{O} \quad \text{N} \\
\text{O} \quad \text{N} \quad \text{N} \quad \text{O} \\
\text{O} \quad \text{N} \quad \text{N} \quad \text{O} \\
\text{N} \quad \text{N} \quad \text{N} \quad \text{N}
\]

To a solution of \(N\)-propargyl amide tri-acetic acid (150 mg, 0.34 mmol) in water (10 mL), gadolinium tribromide (160 mg, 0.40 mmol) in water (5 mL) was added at pH 6 which was adjusted by addition of KOH (0.2 M aq.). The resulting mixture was
stirred for 2 h at room temperature, and the pH readjusted by further addition KOH (0.2 M aq.). The reaction mixture was concentrated under reduced pressure. To the residue was added ethanol (10 mL) and the resulting suspension was filtered. The solid was washed with ethanol (5 mL) to furnish 4Gd as a pale yellow solid (195 mg, 100%); mp > 347 °C (decomp); HRMS (FAB, 3-NOBA matrix): m/z = 597.1309 [(M+H)\(^+\)] (anal. calcd for C\(_{19}\)H\(_{29}\)GdN\(_5\)O\(_7\): m/z = 597.1308).

\( [2]([1H-1,2,3-Triazol-4-yl-N,N-(4,10-bis-carboxymethyl-7-(2-propynylcarbamoyl)-methyl]-1,4,7,10-tetraaza-cyclododec-1-yl)-acetate gadolinium methanamine]-1,7,14,20-tetraaza-2,6,15,19-tetraoxo-3,5,9,12,16,18,22,25-tetrabenzocyclohexacosane)-(N\(^{\text{I}}\)-(2-(bis(pyridine-2-ylmethyl)amino)ethyl)-N\(^{\text{IV}}\)-(2,2-diphenylethyl)fumaramide) copper (II) dichloride rotaxane [2(mac-Gd)(thread-CuCl\(_2\))] \)

To a solution of \([1(thread-CuCl\(_2\)])\) (89 mg, 0.073 mmol) in dichloromethane/methanol in a 5:5 v/v ratio (10 mL), a solution of 4Gd (109 mg, 0.18 mmol) in H\(_2\)O was added. After 5 min, \(N,N\)-disopropylethylamine (0.03 mL, 0.14 mmol) and Cu(CH\(_3\)CN)\(_4\)PF\(_6\) (27 mg, 0.073 mmol) were added. The resulting mixture was stirred for 12 h. The solution was concentrated under reduced pressure. To the residue was added acetone (10 mL) and the resulting suspension was filtered. The solid was washed with acetone (5 mL) to furnish the desired compound [2(mac-
Gd(thread-CuCl₂) as a pale blue solid (113 mg, 86%); mp > 246 °C (decomp);
HRMS (FAB, 3-NOBA matrix): m/z = 875.7745 [(M-2Cl)₂⁺]/2 (anal. calcd for
C₈₃H₈₈CuN₁₇O₁₃²⁺: m/z = 875.7645).

N¹-(2,2-Diphenylethyl)-N⁴-(1-oxyl-2,2,6,6-tetramethylpiperidin-4-yl)fumaramide
(6)

EDCI (489 mg, 2.34 mmol) was added in small batches to a solution of N-(2,2-
diphenylethyl)-fumaric acid (378 mg, 1.28 mmol) and triethylamine (0.360 mL, 2.34
mmol) in dichloromethane (40 mL) at room temperature. The reaction mixture was
stirred for 10 min, after which time 4-amino-2,2,6,6-tetramethylpiperidine-1-oxyl
(200 mg, 1.28 mmol) was added in one portion. The reaction mixture was allowed to
stir at room temperature for an additional 14 h. The reaction mixture was washed with
saturated aqueous sodium chloride (2 x 5 mL), water (2 x 10 mL), dried (MgSO₄) and
concentrated under reduced pressure to give a light red solid. The remaining residue
was subjected to column chromatography on silica gel using
dichloromethane/methanol in a 9.8:0.2 v/v ratio as eluent to furnish compound 6 as a
light red solid (453 mg, 79%); mp 146-148 °C; HRMS (FAB, 3-NOBA matrix): m/z =
449.2682 [(M+H)⁺] (anal. calcd for C₇₇H₃₅N₃O₃⁺: m/z =449.2678).
Chapter Five
Towards Magnetic Dipolar Interactions in Rotaxanes

$N^1,N^3$-Dibenzyl-5-(4-(1,5-dimethyl-6-oxo-1,2,4,5-tetrazinan-3-yl)phenyl-1H-1,2,3-triazol-1-yl)isophthalamide (7)

To a solution of 11 (120 mg, 0.31 mmol), radical 8 (84 mg, 0.37 mmol) and $N,N$-disopropylethylamine (0.054 mL, 0.31 mmol) in dichloromethane/methanol in a 9:1 v/v ratio (10 mL), was added Cu(CH$_3$CN)$_4$PF$_6$ (12 mg, 0.031 mmol). The resulting mixture was stirred for 12 h. The solution was concentrated under reduced pressure and the crude recrystallised from ethyl acetate to yield radical 7 as a dark red solid (150 mg, 79%); mp > 194 °C (decomp); HRMS (FAB, 3-N0BA matrix): $m/z$ = 612.2440 [M$^+$] (anal. calcd for C$_{34}$H$_{30}$N$_9$O$_3$:$m/z$ = 612.2472).

6-(4-Ethynylphenyl)-2,4-dimethyl-1,2,4,5-tetrazinan-3-one (8)

To a solution of 10 (345 mg, 1.5 mmol) in dichloromethane (15 mL) was added cyclohexa-2,5-diene-1,4-dione (195 mg, 1.8 mmol). The resulting mixture was stirred for 12 h. The solution was concentrated under reduced pressure and the residue subjected to column chromatography on silica gel using dichloromethane/methanol in a 9.8:0.2 v/v ratio as eluent to furnish radical 8 as a dark red solid (300 mg, 90%); mp 143...
136-138 °C; HRMS (FAB, 3-NOBA matrix): $m/z = 227.0927 \ [M^+]$ (anal. calcd for C$_{12}$H$_{11}$N$_{4}$O$: m/z = 227.0933$).

**Dimethyl-6-(4-2-(trimethylsilyl)ethynyl)phenyl)-1,2,4,5-tetrazinan-3-one (9)**

To a gentle refluxing solution of carbonic acid bis(1-methylhydrazine) (1.0 g, 8.5 mmol) in methanol (10 mL) was added a solution of 4-((trimethylsilyl)ethynyl)benzaldehyde (1.5 g, 7.6 mmol) in methanol (100 mL) via motor-driven syringe pump over a period of 3 h. The solution was then refluxed for a further 16 h. The reaction mixture was concentrated under reduced pressure and the crude recrystallised from ethyl acetate to furnish 9 as a white solid (0.78 g, 39%); mp 160-162 °C; $^1$H NMR (400 MHz, [D$_6$]DMSO): $\delta = 7.52$ (d, $J = 8.2$ Hz, 2H, H$_N$), 7.46 (d, $J = 8.4$ Hz, 2H, H$_M$), 5.75 (d, $J = 7.4$ Hz, 2H, H$_P$), 4.94 (t, $J = 7.3$ Hz, 1H, H$_O$), 2.93 (s, 6H, H$_Q$), 0.23 (s, 9H, H$_L$); $^{13}$C NMR (100 MHz, [D$_6$]DMSO): $\delta = 154.3$, 137.8, 131.4, 127.4, 121.5, 104.9, 94.3, 68.1, 37.6, -0.2; HRMS (FAB, 3-NOBA matrix): $m/z = 303.1645 \ [(M+H)^+]$ (anal. calcd for C$_{15}$H$_{23}$N$_{4}$OSi$: m/z = 303.1641$).

**6-(4-Ethynylphenyl)-2,4-dimethyl-1,2,4,5-tetrazinan-3-one (10)**

To a solution of 9 (0.800 g, 2.65 mmol) in methanol (30 mL), excess potassium fluoride (1.88 g, 32.3 mmol) was added. The reaction mixture was stirred at room temperature for 16 h. The crude was concentrated under reduced pressure and
Chapter Five Towards Magnetic Dipolar Interactions in Rotaxanes

dissolved in dichloromethane (50 mL). The solution was washed with saturated aqueous sodium chloride (3 x 15 mL), dried (MgSO₄) and concentrated under reduced pressure. The crude was recrystallised from hot ethyl acetate to furnish a white solid (0.6 g, 89%); mp 168-170 °C; ¹H NMR (400 MHz, [D₆]DMSO): δ = 7.54 (d, J = 8.2 Hz, 2H, H₅), 7.48 (d, J = 8.3 Hz, 2H, H₆), 5.75 (d, J = 7.2 Hz, 2H, H₇), 4.95 (t, J = 7.2 Hz, 1H, H₈), 4.19 (s, 1H, H₉), 3.32 (s, 6H, H₁₀); ¹³C NMR (100 MHz, [D₆]DMSO): δ = 154.3, 137.7, 131.5, 127.4, 121.1, 83.2, 68.4, 37.6; HRMS (FAB, 3-NOBA matrix): m/z = 230.1162 [M⁺] (anal. calcd for C₁₂H₁₄N₄O₂⁺: m/z = 230.1168).

5-Azido-N₁,N₃-dibenzyloisophthalamide (11)

Phenylmethanamine (5.00 g, 21.2 mmol) and triethylamine (7.46 mL, 53.1 mmol) in CH₂Cl₂ (150 mL) were cooled to 0 °C. 5-azidoisophthaloyl dichloride (2.59 g, 10.6 mmol) was dissolved in CH₂Cl₂ (75 mL) and added dropwise over 1 h. The reaction mixture was allowed to warm to room temperature and was stirred for a further 12 h which time a solid precipitated. The solid was filtered to furnish compound 11 as a white solid (3.35 g, 82%); mp 162-164 °C; ¹H NMR (400 MHz, [D₆]DMSO): δ = 9.28 (t, J = 5.9 Hz, 2H, H₁), 8.25 (s, 1H, H₂), 7.76 (d, J = 1.4 Hz, 2H, H₃), 7.36-7.22 (m, 10H, H₄ & H₅), 4.50 (d, J = 5.9 Hz, 4H, H₆); ¹³C NMR (100 MHz, [D₆]DMSO): δ = 164.7, 140.1, 139.3, 136.1, 128.3, 127.3, 126.8, 123.2, 120.3, 42.7; HRMS (FAB, 3-NOBA matrix): m/z = 386.1577 [(M+H)⁺] (anal. calcd for C₂₂H₂₀N₅O₂⁺: m/z = 386.1617).

5.5 References and Notes

Chapter Five
Towards Magnetic Dipolar Interactions in Rotaxanes


[16] The EPR spectra were obtained in dried purified solvents in frozen-solution to avoid elimination of anisotropic dipolar contribution through fast tumbling of molecules.


CHAPTER SIX

Investigating the Effect of Dipolar Interactions in Redox-Active Rotaxanes

Acknowledgment

All practical work reported in this Chapter was shared equally with Dr. Bryan D. Koivisto, whose contribution is very gratefully acknowledged.
Synopsis

Chapter Four demonstrated a strategy to introduce paramagnetic centres to the macrocycle for the preparation of bimetallic rotaxanes. In Chapter Five, dipolar interactions between the paramagnetic species in such system were then investigated by electron paramagnetic resonance.

In Chapter Six, a series hydrogen-bonded rotaxanes with an octamethylferrocene unit in the thread and a macrocycle bearing different metal ions is prepared. Such systems are utilised to investigate and quantify the effects of dipolar interactions on the redox behaviour of the octamethylferrocene moiety by cyclic voltammetry and square-wave voltammetry techniques.

Dipolar interactions with metal ions bearing unpaired electrons should stabilise the cationic form of the octamethylferrocene, making it harder to reduce. Such a trend is indeed observed in the prepared series of model systems. The shifts detected, however, are rather small to be reliably quantified by these two voltammetry techniques.
6.1 Introduction

Synthetic chemists have been inspired to design and synthesise molecular devices by the desire to both mimic and understand fundamental aspects of natural systems.\(^1\) Chief among these are the myriad enzymes – proteins with long linear chains of amino acids ranging from 65 to 2,500 units that fold to produce three-dimensional (3D) structures.\(^2\) These rather flexible 3D structures catalyse specific biochemical transformations by reducing the activation energy of a reaction so that substrates are converted into specific products at accelerated rates.\(^3\) However, some enzymes need the assistance of cofactors to carry out their function. Cofactors are nonpeptidic molecules that bind to the active site by means of hydrogen bonding, π-stacking and other electrostatic interactions.\(^1-4\) The vast majority of such cofactors are redox-active units for which the noncovalent interactions at the active site serve to regulate the redox potential. Unfortunately, in such complex systems it is extremely difficult to differentiate and quantify the effects of each individual interaction on the redox behaviour of the cofactor.

Synthetic models that mimic the effects of molecular recognition on redox processes at electroactive centres may shed light on such systems.\(^5\) Rotello and co-workers, for example, have been able to individually quantify the effect of hydrogen bonding and π-stacking interactions on the redox behaviour of flavin units. They have demonstrated that the hydrogen-bond interactions between flavins and diacyl diaminopyridines greatly stabilise the flavin anion, whereas π-stacking between flavin and xanthene-based molecules stabilises the neutral state. Both these types of interaction are present in natural flavoenzymes, and by balancing their effects a wide range of reduction potentials is achieved for the cofactor.\(^5\) More recently, Kaifer and co-workers have investigated the electronic communication within stable hydrogen-bonded dimers containing identical ferrocene centres by means of electrochemical techniques. They observed that the reduction potential of one of the ferrocene units changes dramatically due to the communication that both species experience via hydrogen bonds. This interaction was detected even though the ferrocene centres were separated by more than 10 Å.\(^6\)

The majority of noncovalent interactions are electrostatic in nature. Changes in the oxidation state of redox-active molecules, therefore, significantly vary the charge
density and/or electronic distribution of any interacting species. Thus, the opportunity arises both to use redox chemistry to affect molecular recognition properties and/or to use electrochemical techniques as a probe of noncovalent interactions, as they may modify the electrochemical behaviour of the redox-active species.$^{[7,8]}$

Electrochemical methods have been extensively used as means to investigate redox reactions,$^{[9]}$ reaction intermediates$^{[10]}$ and to acquire information about the stability of a product.$^{[11]}$ In particular, cyclic voltammetry (CV) demonstrates high sensitivity, accuracy and an easy operational procedure.$^{[12]}$ A typical electrochemical cell contains three electrodes: a reference, a working and a counter electrode. The applied potential ($E$), measured between the working and the reference electrode, is varied linearly from an initial potential ($E_i$) to a pre-defined value ($E_{t,1}$) where the scan is reversed and run in opposite direction. The current response ($i$) obtained throughout this process is measured between the working and counter electrode and is typically plotted versus applied potential as shown in Figure 6.1.$^{[13]}$

![Figure 6.1](image_url)

**Figure 6.1** Cyclic voltammogram at 298 K of octamethylferrocene. Experiment carried out on 1 mmol L$^{-1}$ solution of octamethylferrocene in anhydrous DMF with Bu$_4$NBF$_4$ (0.1 mol L$^{-1}$) as electrolyte and ferrocene as internal standard. Scan rate: 0.10 V s$^{-1}$; Working electrode: Pt. Arrows indicate direction of the potential scan.

The most important parameters that can be obtained from a cyclic voltammogram are the peak currents ($i_{pc}$, $i_{pa}$) and peak potential ($E_{pc}$, $E_{pa}$) of the cathodic and anodic peaks, respectively (Figure 6.1). However, the half-wave potential which is the average value of the peak potentials is normally reported for reversible redox couples.$^{[13]}$
Herein, we report a series of hydrogen-bonded rotaxanes which have been prepared to explore the effect of dipolar interactions on the redox process at an electroactive centre. Rotaxanes\textsuperscript{[14]} with a redox-active unit in the thread and metal-containing macrocycle are ideal synthetic models to study this type of interaction because the two components are not covalently bound. This results in systems where communication between the two centres is largely dipolar in nature.

Such systems have never been realised before and will allow the observation and quantification of through-space interactions between the redox-active moiety and the metallic unit by CV and square-wave voltammetry (SWV). Investigation of such subtle magnetic interactions is important to explain certain effects detected in biological systems and may also lead to novel molecular electronic devices.

6.2 Results and Discussion

Rotaxane \([1(mac\text{-}Fc)]\) (Scheme 6.1) bears two key features: an octamethylferrocenyl redox-active stopper\textsuperscript{[15]} and a ferrocene-containing\textsuperscript{[16]} macrocycle. The later is prepared by means of a Cu\textsuperscript{1}-catalysed terminal alkyne-azide cycloaddition (the CuAAC\textsuperscript{[17]} “click”\textsuperscript{[18]} reaction) on rotaxane 2. This procedure is a powerful tool used to append functional molecular fragments in a precise, predictable and efficient manner.\textsuperscript{[19]}
Chapter Six  Investigating the Effect of Dipolar Interactions in Redox-Active Rotaxanes

Scheme 6.1 Assembly of rotaxane [1(mac-Fc)] via a CuAAC reaction (atom-lettering and colour scheme corresponds to $^1$H NMR assignments in Figure 6.1). Reagents and conditions: a) NH$_2$OH, CH$_3$OH, 78 °C, 3 h, 75%; b) LiAlH$_4$, THF, 0 °C to 70 °C, 16 h, 95%; c) N-(2,2-diphenylethyl)-fumaric acid, 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDCI-HCl), triethylamine (Et$_3$N), 0 °C to RT, 12 h, 62%; d) 5-azidoisophthaloyl dichloride, CHCl$_3$, Et$_3$N, RT, 12 h, 52%; e) ethynylferrocene, 0.1 equiv. Cu(CH$_3$CN)$_4$PF$_6$, DIPEA, CH$_2$Cl$_2$/CH$_3$OH (9:1), RT, 12 h, 87%.

The octamethylferrocene stopper was synthesised according to Scheme 6.1 from octamethylferrocenyl aldehyde, 3.$^{[20]}$ Condensation of the aldehyde 3 with NH$_2$OH in CH$_3$OH afforded oxime 4 which was then reduced with LiAlH$_4$ to obtain amine 5. Thread 6 was then prepared by peptide coupling of 5 and N-(2,2-diphenylethyl)-fumaric acid$^{[21]}$ in a 62% yield. Treatment of 6 with 12 equivalents of $N,N$-bis(4-(aminomethyl)benzyl)isophthalamide and 5-azidoisophthaloyl dichloride afforded azido-rotaxane 2 in 52% yield. Complex [1(mac-Fc)] was then prepared in high yield using the standard CuAAC reaction conditions with the commercially available ethynylferrocene (Scheme 6.1).

The partial 400 MHz $^1$H NMR spectra of thread 6, azido-rotaxane 2 and [1(mac-Fc)] in [D$_6$]DMSO at 360 K are shown in Figure 6.2. The upfield shifts of the coincident fumaramide olefin protons (H$_h$ and H$_i$) in the rotaxane relative to those of the free thread 6 are typical of benzylic amide macrocycle-based rotaxanes, resulting from shielding by the xylylene rings in the macrocycle. In addition, the appearance of resonances from the Fc macrocycle unit (H$_{M,0}$) and the distinctive triazole (H$_L$) proton signal confirms the presence of [1(mac-Fc)] (Figure 6.2c).
To investigate the electronic communication between the octamethylferrocene and the ferrocene moieties, cyclic and square-wave voltammograms were recorded.

In the voltammetric experiments a one-compartment electrochemical cell was used. The working and counter electrodes were isolated platinum wires. The reference electrode was a non-aqueous Ag/Ag⁺ electrode with a fill solution of anhydrous DMF with Bu₄NBF₄. The experiments were carried out on 1 mmol L⁻¹ solutions in anhydrous DMF with Bu₄NBF₄ (0.1 mol L⁻¹) as a supporting electrolyte. Ferrocene was employed as internal standard in studying thread 6 and rotaxane 2, whereas in the case of ferrocene-containing rotaxane [1(mac-Fc)], nitroquinoline was used to avoid obscuring the signal from the molecule under study.

The cyclic voltammogram in anhydrous DMF of rotaxane 2 (Figure 6.3a) exhibits a reversible, one-electron process typical of octamethylferrocynyl units. In contrast, [1(mac-Fc)] shows two reversible redox processes, corresponding to oxidation of first the octamethylferrocene and then the ferrocene moieties (Figure 6.3b).
Chapter Six  Investigating the Effect of Dipolar Interactions in Redox-Active Rotaxanes

The reduction potentials for 6, 2 and [1(mac-Fc)] were then obtained using SWV, an electrochemical technique with excellent accuracy. In this technique the potential is scanned with a series of square-wave pulses superimposed on a slowly changing potential. This process decreases the acquisition time and rejects any background currents.\textsuperscript{12,13} The results obtained by SWV are summarised in Table 1.

Table 1 Reduction potentials for octamethylferrocene derivatives obtained from SWV.

<table>
<thead>
<tr>
<th>Octamethylferrocene Derivative</th>
<th>( E_{1/2} ) (mV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>-357(^*)</td>
</tr>
<tr>
<td>2</td>
<td>-332(^*)†</td>
</tr>
<tr>
<td>[1(mac-Fc)]</td>
<td>-332(^\dagger)</td>
</tr>
</tbody>
</table>

\(^*\) Versus ferrocene/ferrocinium.
\(^\dagger\) Versus nitroquinoline/nitroquinolinium.

A +25 mV shift in the oxidation potential of the redox-active unit in rotaxane 2 compared to parent thread 6 was observed (Table 1), resulting from stabilisation of the octamethylferrocene moiety. This is due to the presence of the benzylic amide

Figure 6.3 Cyclic voltammograms at 298 K of 2 and [1(mac-Fc)]. Experiment carried out on 1 mmol L\(^{-1}\) solution of 2 or [1(mac-Fc)] in anhydrous DMF with Bu\(_4\)NBF\(_4\) (0.1 mol L\(^{-1}\)) as electrolyte and ferrocene (a) and nitroquinoline (b) as internal standards, respectively. Scan rate: 0.10 Vs\(^{-1}\); Working electrode: Pt.
macrocycle which removes electron density around the redox-active unit through hydrogen bonding to the thread, making it harder to oxidise compared to 6.

Unfortunately, no further shift in the potential was observed when $[1(mac-Fc)]$ was investigated indicating that the electronic communication between the octamethylferrocene and the ferrocene units does not significantly affect the reduction potential of the former.

Concurrently, it was reasoned that the introduction ions to the macrocycle of a bis-pyridin-2-ylmethylamine (BPA) tridentate ligand \(^{[22]}\) bearing different metal by means of a triazole linkage would allow us to investigate and quantify the effects of dipolar interactions on the redox behaviour of octamethylferrocene moiety on the thread. Dipolar interaction between metal ions with unpaired electrons and the octamethylferrocene should shift the reduction potential of the later to more negative values, a consequence of stabilisation of the octamethylferrocinium cation.

For this purpose we designed rotaxanes $[7(mac-CuCl_2)]$ and $[7(mac-CrCl_3)]$, which were prepared according to Scheme 6.2 from $[8CuCl_2]$ or $[8CrCl_3]$, respectively, using the standard CuAAC conditions.\(^{[22]}\)

![Scheme 6.2 Assembly of $[7(mac-CuCl_2)]$ and $[7(mac-CrCl_3)]$ complexes via a CuAAC reaction. Reagents and conditions: $[8CuCl_2]$ or $[8CrCl_3]$, 0.1 equiv. Cu(CH$_3$CN)$_4$PF$_6$, DIPEA, CH$_2$Cl$_2$/CH$_3$OH 9:1, RT, 12 h.](image)

In order to prepare $[7(mac-ZnCl_2)]$ – a metal complex containing a diamagnetic species with similar geometry to Cu$^{II}$ – $[7(mac-CuCl_2)]$ was demetallated by washing with a saturated aqueous solution of Na$_4$EDTA. Addition of ZnCl$_2$ to 7, afforded $[7(mac-ZnCl_2)]$ in a 95% yield (Scheme 6.3).
The CV response of thread 6, rotaxane 2 and compound 7 are shown in Figure 6.4. All cyclic voltammograms display a reversible redox process corresponding to the octamethylferrocenium cation. The values of the reduction potentials for these compounds as well as for complexes of 7 with Zn^{II}, Cu^{II} and Cr^{III}, as measured by SWV, are displayed in Table 2.
Figure 6.4 Cyclic voltammograms at 298 K of thread 6, rotaxane 2 and 7. Experiments carried out on 1 mmol L⁻¹ solutions in anhydrous DMF with Bu₄NBF₄ (0.1 mol L⁻¹) as electrolyte and ferrocene as internal standard. Scan rate: 0.10 V/s; Working electrode: Pt.

Table 2 Reduction potentials for octamethylferrocene derivatives obtained from SWV.

<table>
<thead>
<tr>
<th>Octamethylferrocene Derivative</th>
<th>E₁/₂ (mV)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>-357</td>
</tr>
<tr>
<td>2</td>
<td>-332</td>
</tr>
<tr>
<td>7</td>
<td>-325</td>
</tr>
<tr>
<td>[7(mac-ZnCl₂)]</td>
<td>-326</td>
</tr>
<tr>
<td>[7(mac-CuCl₂)]</td>
<td>-330</td>
</tr>
<tr>
<td>[7(mac-CrCl₃)]</td>
<td>-330</td>
</tr>
</tbody>
</table>

*Versus ferrocene/ferrocenium.
As discussed above, a +25 mV shift in the oxidation potential of the octamethylferrocene unit of rotaxane 2 was observed compared to thread 6. The reduction potential of 7, which contains the BPA ligand attached to the macrocycle via a triazole unit, results in an additional +7 mV shift of the reduction potential as a consequence of further stabilization of the octamethylferrocene.

Unfortunately, the presence of metal ions with different numbers of unpaired electrons did not cause large changes in the redox potential of the octamethyl ferrocene/octamethyl ferrocenium couple. Complexes [7(mac-ZnCl₂)] and [7(mac-CuCl₂)] – compounds that have similar structures – show only a 4 mV difference in reduction potential of the octamethylferrocene unit. Although small, this difference was consistently observed over a series of three repetitions for all the complexes. Furthermore, a shift in reduction potential to more negative values on introduction of metal complexes with unpaired electrons is consistent with dipolar stabilisation of the cation. Lamentably, no effect on changing the number of unpaired electrons was observed.

In addition, complexes [9(mac-Fc)(thread-CuCl₂)], [9(mac-Fc)(thread-ZnCl₂)] and [9(mac-Fc)(thread-CrCl₃)] were investigated by CV and SWV. As shown in Schemes 6.4 and 6.5, the metal chelating sites are now bound to the peptide station and the ferrocene units are attached to the macrocycle by a triazole moiety.

Addition of CuCl₂·2H₂O or CrCl₃·(THF)₃ to 9 in CH₃OH afforded complexes [9(thread-CuCl₂)] and [9(thread-CrCl₃)], respectively, in very good yields (Scheme 6.4). [9(mac-Fc)(thread-CuCl₂)] and [9(mac-Fc)(thread-CrCl₃)] were then prepared by means of CuAAC from the commercially available ethynylferrocene (Scheme 6.4).
Investigating the Effect of Dipolar Interactions in Redox-Active Rotaxanes

Chapter Six

N3

\[ \text{Scheme 6.4 Assembly of ferrocene-containing rotaxanes via CuAAC reactions. Reagents and conditions: a) } \text{MCl₂, CH₃OH, RT, 1 h; b) ethynylferrocene, 0.1 equiv. Cu(CH₃CN)₄PF₆, DIPEA, CH₂Cl₂/CH₃OH 9:1, RT, 12 h.} \]

\[ \text{[9(mac-Fc)(thread-ZnCl₂)] was then obtained by demetallation of [9(mac-Fc)(thread-CuCl₂)] followed by addition of ZnCl₂ (Scheme 6.5).} \]

\[ \text{[9(mac-Fc)(thread-CuCl₂)] \quad [9(mac-Fc)(thread-CrCl₃)] \quad [9(mac-Fc)(thread-CrCl₃)] \quad [9(mac-Fc)(thread-CuCl₂)] \quad [9(mac-Fc)(thread-ZnCl₂)] \]

\[ \text{Scheme 6.5 Preparation of [9(mac-Fc)(thread-ZnCl₂)]. Reagents and conditions: a) Na₄EDTA (aq saturated), RT, 71%; b) ZnCl₂, CH₃OH, RT, 1 h, 93%.} \]

The reduction potentials of these ferrocene-containing molecules as measured by SWV are shown in Table 3.

\[ \text{Table 3 Reduction potentials for ferrocene derivatives obtained from SWV.} \]

<table>
<thead>
<tr>
<th>Ferrocene Derivative</th>
<th>( E_{1/2} ) (mV) *</th>
</tr>
</thead>
<tbody>
<tr>
<td>[9(mac-Fc)(thread-ZnCl₂)]</td>
<td>+458</td>
</tr>
<tr>
<td>[9(mac-Fc)(thread-CuCl₂)]</td>
<td>+456</td>
</tr>
<tr>
<td>[9(mac-Fc)(thread-CrCl₃)]</td>
<td>+453</td>
</tr>
</tbody>
</table>

* Versus octamethyl ferrocene/octamethyl ferrocenium.
Once again, it can be seen that the effect of changing the metal complexes is to shift the redox potential to more negative values, suggesting dipolar stabilisation of the ferrocene cation. Furthermore, in this case a greater shift is observed in the presence of the Cr$^{III}$. It must be noted, however, that although the shifts observed from rotaxane complexes 7 and 9 are reproducible and consistent with theory, their very small values make any quantification of this effect by the techniques employed here very difficult.

6.3 Conclusion

Even though the interplay between molecular recognition and redox processes is a common theme in biological systems, the isolation and quantification of each individual contribution is extremely difficult and becomes even harder when the interactions under study are subtle. Rotaxanes are ideal substrates with which to study dipolar interaction between a redox-active unit and a metal ion bound to different interlocked components. In this study a valuable series of model compounds has been prepared and evidence for dipolar interactions demonstrated. At present, however, the magnitude of this effect is at the very limit of detection of the CV and CWV techniques. In order to build on this study, it will be necessary to employ more sensitive probes of dipolar interactions and/or design interlocked systems in which the interacting components are held in closer proximity and with perhaps less conformational freedom. Finally, it should ultimately be possible to introduce switching mechanisms into such systems in order to control the magnitude of dipolar interaction in a distance-dependent fashion.

6.4 Experimental Section

General

Unless stated otherwise, all reagents and anhydrous solvents were purchased from Aldrich Chemicals and used without further purification. Octamethyl ferrocene carboxaldehyde$^{[20]}$, $N,N$-bis(pyridin-2-ylmethyl)prop-2-yn-1-amine, 9 and $[9$(thread-CuCl$_2$)]$^{[22]}$ were prepared according to literature procedure.
Chapter Six

Investigating the Effect of Dipolar Interactions in Redox-Active Rotaxanes

\[ ([1H-1,2,3-Triazol-4-yl-ferroceny]-1,7,14,20-tetraaza-2,6,15,19-tetraoxo-3,5,9,12,16,18,22,25-tetrabenzocyclohexacosane)-(N^1-(2,2-diphenylethyl)-N^4-((octamethylferrocenyl)methyl)fumaramide rotaxane [1(mac-Fc)]) \]

To a solution of rotaxane 2 (50 mg, 0.04 mmol), ethynylferrocene (11 mg, 0.05 mmol) and \(N, N\)-disopropylethylamine (0.01 mL, 0.04 mmol) in dichloromethane/methanol in a 9:1 v/v ratio (10 mL) was added Cu(CH\(_3\)CN\(_4\))PF\(_6\) (2 mg, 0.01 mmol). The resulting mixture was stirred for 12 h. The solution was concentrated under reduced pressure. To the residue was added acetone (10 mL), the resulting suspension was filtered, and the solid was washed with acetone (5 mL) to furnish \( [1(\text{mac-Fc})] \) as an orange solid (51 mg, 87%); mp > 220 °C (decomp); \(^1\text{H} \) NMR (400 MHz, \([\text{D}_6]\)DMSO): \( \delta = 9.02 \) (s, 1H, \( H_L \)), 8.75 (s, 1H, \( H_O \)), 8.69 (s, 1H, \( H_J \)), 8.61 (d, \( J = 1.2 \) Hz, 2H, \( H_k \)), 8.28 (br s, 1H, \( H_I \)), 8.11-8.02 (m, 5H, \( H_B, H_D, H_G \)), 7.93-7.91 (m, 2H, \( H_I \)), 7.67 (t, \( J = 7.7 \) Hz, 1H, \( H_d \)), 7.26-7.16 (m, 10H, \( H_{Ph} \)), 6.88 (s, 8H, \( H_F & H_G \)), 5.79 (s, 2H, \( H_h & H_i \)), 4.88 (t, \( J = 1.8 \) Hz, 2H, \( H_M \)), 4.40-4.23 (m, 1OH, \( H_N, H_E & H_H \)), 4.18 (t, \( J = 7.7 \) Hz, 1H, \( H_d \)), 4.13 (s, 5H, \( H_k \)), 3.38 (br s, 2H, \( H_J \)), 3.72-3.69 (m, 2H, \( H_k \)), 3.19 (s, 1H, \( H_c \)), 1.74-1.55 (m, 24H, \( H_a, H_b, H_d & H_e \)); \(^{13}\text{C} \) NMR (100 MHz, \([\text{D}_6]\)DMSO): \( \delta = 165.7, 164.7, 142.5, 136.0, 134.1, 130.7, 129.6, 128.6, 127.7, 126.5, 125.2, 124.7, 121.1, 118.6, 75.0, 69.3, 68.6, 66.5, 43.6, 43.5, 43.3, 9.6, 9.5, 9.3, 9.0; HRMS (FAB, 3-NOBA matrix): \( m/z = 1388.5105 \) [(M+H)\(^+\)] (anal. calcd for \( \text{C}_{81}\text{H}_{82}\text{Fe}_2\text{N}_9\text{O}_5^+ \): \( m/z = 1388.5072 \)).
Chapter Six  
Investigating the Effect of Dipolar Interactions in Redox-Active Rotaxanes

\((2)\)(Azido-1,7,14,20-tetraaza-2,6,15,19-tetraoxo-3,5,9,12,16,18,22,25-tetrabenzocyclohexacosane)-(N\(^1\)-(2,2-diphenylethyl)-N\(^4\)-
(octamethylferrocenyl)methyl)fumaramide rotaxane (2)

To a suspension of thread 6 (300 mg, 0.496 mmol), \(N,N\)-bis-(4-aminomethyl-benzyl)-isophthalamide (2.40 g, 5.95 mmol) and triethylamine (2.03 mL, 14.9 mmol) in chloroform (200 mL) was added a solution of 5-azidoisophthaloyl dichloride (1.45 g, 5.95 mmol) in chloroform (50 mL) via motor-driven syringe over a period of 6 h. The reaction mixture was stirred for a further 12 h. The resulting precipitate was filtered over celite and the solution washed with saturated aqueous sodium hydrogen carbonate (3 x 20 mL), saturated aqueous sodium chloride (2 x 20 mL), dried (\(\text{MgSO}_4\)) and concentrated under reduced pressure. The remaining residue was subjected to column chromatography on silica gel using dichloromethane/methanol in a 9.6:0.4 v/v ratio as eluent to yield rotaxane 2 as a yellow solid (303 mg, 52%); mp > 205 °C (decomp); \(^1\)H NMR (400 MHz, \([\text{D}_7\]DMF): \(\delta = 8.95\) (t, \(J = 5.4\) Hz, 1H, \(H_j\)), 8.81 (s, 1H, \(H_c\)), 8.77 (t, \(J = 5.0\) Hz, 1H, \(H_g\)), 8.63 (s, 1H, \(H_d\)), 8.18 (dd, \(J = 7.7\) Hz and \(J = 1.4\) Hz, 2H, \(H_b\)), 8.13 (t, \(J = 4.9\) Hz, 2H, \(H_i\)), 8.07 (t, \(J = 4.9\) Hz, 2H, \(H_D\)), 7.97 (d, \(J = 0.9\) Hz, 2H, \(H_k\)), 7.75 (t, \(J = 7.7\) Hz, 1H, \(H_d\)), 7.36-7.21 (m, 1OH, \(H_{ph}\)), 7.00 (s, 8H, \(H_F\) & \(H_G\)), 5.94 (d, \(J = 15.1\) Hz, 1H, \(H_h\)), 5.89 (d, \(J = 15.1\) Hz, 1H, \(H_i\)), 4.47-4.33 (m, 8H, \(H_E\) & \(H_G\)), 4.25 (t, \(J = 7.9\) Hz, 1H, \(H_j\)), 4.01-4.00 (m, 2H, \(H_H\)), 3.92 (dd, \(J = 7.6\) Hz and \(J = 1.9\) Hz, 2H, \(H_k\)), 3.27 (s, 1H, \(H_c\)), 1.78-1.62 (s, 24H, \(H_a, H_b, H_d\) & \(H_e\)); \(^{13}\)C NMR (100 MHz, \([\text{D}_7\]DMF): \(\delta = 167.2, 166.7, 166.2, 165.7, 144.0, 142.1, 138.3, 138.0, 137.4, 135.7, 135.4, 132.0, 131.2, 130.6, 130.1, 130.0, 129.1, 127.7, 126.0, 122.7, 122.0, 51.5, 45.1, 44.6, 44.5, 12.5, 11.8, 10.6, 10.2, 9.9; HRMS
Chapter Six  Investigating the Effect of Dipolar Interactions in Redox-Active Rotaxanes

(FAB, 3-NOBA matrix): $m/z = 1177.4847 \ [M^+]$ (anal. calcd for C$_{69}$H$_{71}$FeN$_9$O$_6^+$: $m/z = 1177.4877$).

(Octamethylferrocenyl)carboxaldehyde oxime (4)

A mixture of aldehyde 3 (5.10 g, 15.6 mmol), sodium hydroxide (3.75 g, 93.8) and hydroxylamine chlorohydrate (2.17 g, 31.3 mmol) in ethanol (350 mL) was refluxed for 3 h. After cooling, the mixture was hydrolysed and extracted by dichloromethane (3 x 150 mL). The organic layer was dried (MgSO$_4$) and the solvent removed under reduced pressure to give complex 4 as a dark yellow solid (4.00 g, 75%); mp $> 146$ °C (decomp); $^1$H NMR (400 MHz, [D$_7$]DMF): 10.59 (s, 1H, H$_g$), 7.93 (s, 1H, H$_f$), 3.43 (s, 1H, H$_e$), 1.85-1.60 (m, 26H, H$_a$, H$_b$, H$_d$ & H$_e$); $^{13}$C NMR (100 MHz, [D$_7$]DMF): $\delta = 149.8$, 83.5, 82.2 (x 2), 81.0, 73.6, 72.7, 11.8, 11.2, 10.2, 9.9; HRMS (FAB, 3-NOBA matrix): $m/z = 341.1429 \ [M^+]$ (anal. calcd for C$_{19}$H$_{27}$FeNO: $m/z = 341.1442$).

(Octamethylferrocenyl)methanamine (5)

Compound 4 (1.0 g, 3.0 mmol) was added dropwise to a suspension of lithium aluminium hydride (0.31 g, 9.1 mmol) in tetrahydrofuran (55 mL). The solution was heated to reflux for 12 h. The reaction mixture was allowed to cool to room temperature, hydrolysed, neutralised and extracted with diethyl ether. The solution was dried (MgSO$_4$) and concentrated under reduced pressure to furnish 5 as yellow solid (2.9 g, 95%); mp $> 154$ °C (decomp); $^1$H NMR (400 MHz, [D$_7$]DMF): 3.46 (s, 2H, H$_f$), 3.25 (s, 1H, H$_c$), 1.81-1.67 (m, 26H, H$_a$, H$_b$, H$_d$, H$_e$ & H$_g$); $^{13}$C NMR (100
MHz, [D$_7$]DMF): $\delta = 85.1, 80.6, 80.5, 80.2, 79.5, 71.5, 38.9, 12.1, 10.5, 10.2, 10.1$; HRMS (FAB, 3-NOBA matrix): $m/z = 327.1653$ [M$^+$] (anal. calcd for C$_{19}$H$_{29}$FeN: $m/z = 327.1649$).

**N$^1$-(2,2-Diphenylethyl)-N$^4$-((octamethylferroceny)methyl)fumaramide (6)**

![Diagram of N$^1$-(2,2-Diphenylethyl)-N$^4$-((octamethylferroceny)methyl)fumaramide (6)](image)

EDCI (1.2 g, 6.1 mmol) was added in small batches to a solution of $N$-(2,2-diphenylethyl)-fumaric acid (0.92 g, 3.1 mmol) and triethylamine (0.83 mL, 6.1 mmol) in dichloromethane (100 mL) at room temperature. The reaction mixture was stirred for 10 min after which time amine 5 (1.0 g, 3.1 mmol) was added in one portion. The solution was allowed to stir at room temperature for an additional 14 h. The reaction mixture was washed with aqueous 1M NaOH (3 x 20 mL), saturated aqueous sodium chloride (2 x 20 mL), water (2 x 30 mL), dried (MgSO$_4$) and concentrated under reduced pressure to give a yellow solid. The crude was recrystallised from acetone to furnish thread 6 as a yellow solid (1.1 g, 62%); mp $> 225$ °C (decomp); $^1$H NMR (400 MHz, [D$_7$]DMF): $\delta = 8.54$ (t, $J = 5.6$ Hz, 1H, $H_j$), 8.28 (t, $J = 4.9$ Hz, 1H, $H_g$), 7.38-7.21 (m, 10H, $H_{Ph}$), 6.97 (d, $J = 15.1$ Hz, 1H, $H_h$), 6.93 (d, $J = 15.1$ Hz, 1H, $H_i$), 4.34 (t, $J = 7.9$ Hz, 1H, $H_j$), 4.16 (d, $J = 5.1$ Hz, 2H, $H_f$), 3.95 (dd, $J = 7.8$ Hz and $J = 2.0$ Hz, 2H, $H_k$), 3.31 (s, 1H, $H_e$), 1.78-1.68 (s, 24H, $H_{a, b, d, e}$); $^{13}$C NMR (100 MHz, [D$_7$]DMF): $\delta = 164.2, 162.3, 144.2, 134.2, 133.8, 129.6, 129.1, 127.5, 51.6, 44.9, 11.9, 10.4, 10.3$; HRMS (FAB, 3-NOBA matrix): $m/z = 604.2760$ [M$^+$] (anal. calcd for C$_{37}$H$_{44}$FeN$_2$O$_2^+$: $m/z = 604.2752$).
Chapter Six  Investigating the Effect of Dipolar Interactions in Redox-Active Rotaxanes

([2]({1H1,2,3-Triazo1-4-y1-N,N-bis(pyridine-2-yl methyl)methanamine copper (II) dichloride}-1,7,14,20-tetraaza-2,6,15,19-tetraoxo-3,5,9,12,16,18,22,25-tetrabenzocyclohexacosane)-(N1-(2,2-diphenylethyl)-N4-
((octamethylferrocenyl)methyl)fumaramide rotaxane [7(mac-CuCl2)])

To a solution of rotaxane 2 (50 mg, 0.042 mmol), [8CuCl2] (19 mg, 0.051 mmol) and N,N-disopropylethylamine (0.0073 mL, 0.042 mmol) in dichloromethane/methanol in a 9:1 v/v ratio (10 mL) was added Cu(CH3CN)4PF6 (1.6 mg, 0.0042 mmol). The resulting mixture was stirred for 12 h. The solution was concentrated under reduced pressure. To the residue was added acetone (10 mL), the resulting suspension was filtered, and the solid washed with acetone (5 mL) to furnish [7(mac-CuCl2)] as a pale blue solid (51 mg, 79%); mp > 230 °C (decomp); HRMS (FAB, 3-NOBA matrix): m/z = 1513.5253 [(M-Cl)+] (anal. calcd for C84H87ClFeN12O6+: m/z = 1513.5205).
Chapter Six  Investigating the Effect of Dipolar Interactions in Redox-Active Rotaxanes

\[(\{1H-1,2,3-Triazol-4-yl-N\textsubscript{2}bis(pyridine-2-yl methyl)methanamine\} - 1,7,14,20-tetraaza-2,6,15,19-tetraoxo-3,5,9,12,16,18,22,25-tetrabenzocyclohexacosane)-(N\textsuperscript{1}-\text{-}(2,2-diphényl ethyl)-N\textsuperscript{4}-((octamethylferrocenyl)methyl)fumaramide rotaxane (7)\]

A solution of \[\{7(mac-CuCl\textsubscript{2})\}\] (50 mg, 0.035 mmol) in chloroform/isopropanol in a 3:1 v/v ratio (15 mL) was washed with saturated aqueous, basic EDTA (3 x 10 mL), saturated aqueous sodium chloride (2 x 10 mL), dried (MgSO\textsubscript{4}) and concentrated under reduced pressure to give a dark yellow oil. The remaining residue was subjected to column chromatography on silica gel using dichloromethane/acetonitrile/NH\textsubscript{4}OH (aq) in a 5:5:0.2 v/v ratio as eluent to furnish complex 7 as a dark yellow oil (32 mg, 70\%). \^\textsuperscript{1}H NMR (400 MHz, [D\textsubscript{6}]DMSO): \(\delta = 8.80\) (s, 1H, \(H_I\)), 8.76 (s, 1H, \(H_C\)), 8.70 (s, 1H, \(H_J\)), 8.54 (s, 2H, \(H_K\)), 8.51 (d, \(J = 3.6\) Hz, 2H, \(H_R\)), 8.29 (br s, 1H, \(H_i\)), 8.11-8.06 (m, 5H, \(H_B, H_D, H_G\)), 7.96-7.92 (m, 2H, \(H_I\)), 7.73 (t, \(J = 6.9\) Hz, 2H, \(H_P\)), 7.66 (t, \(J = 7.7\) Hz, 1H, \(H_A\)), 7.59 (d, \(J = 7.5\) Hz, 2H, \(H_O\)), 7.26-7.15 (m, 12H, \(H_Q, H_R\)), 6.88 (s, 8H, \(H_F, H_G\)), 5.79 (s, 2H, \(H_h\)), 4.40-4.16 (m, 8H, \(H_E, H_H\)), 4.18 (t, \(J = 7.0\) Hz, 1H, \(H_I\)), 4.00 (s, 2H, \(H_M\)), 3.94 (s, 4H, \(H_N\)), 3.82 (br s, 2H, \(H_j\)), 3.73-3.69 (m, 2H, \(H_k\)), 3.20 (s, 1H, \(H_e\)), 1.75-1.53 (m, 24H, \(H_a, H_b, H_d, H_e\)); \^\textsuperscript{13}C NMR (100 MHz, [D\textsubscript{6}]DMSO): \(\delta = 166.7, 165.2, 164.7, 159.0, 148.9, 145.3, 142.5, 137.4, 136.5, 136.1, 136.0, 134.1, 130.8, 129.7, 129.3, 129.0, 128.6, 128.4, 127.7, 126.5, 125.2, 124.8, 122.5, 122.4, 122.1, 121.5, 59.0, 49.9, 48.4, 43.6, 43.5, 43.3, 11.1, 11.0, 9.5,
9.2, 9.1, 9.0; HRMS (FAB, 3-NOBA matrix): \( m/z = 1414.6173 \) [\( M^+ \)] (anal. calcd for \( C_{84}H_{86}FeN_{12}O_6^+ \): \( m/z = 1414.6143 \)).

\[ \text{[(2)\{1H-1,2,3-Triazol-4-yl-N,N-bis(pyridine-2-yl methyl) methanamine zinc (II) dichloride\}-1,7,14,20-tetraaza-2,6,15,19-tetraoxo-3,5,9,12,16,18,22,25-tetrabenzo cyclohexacosane\}-(N^1-(2,2-diphenylethyl)-N^4-((octamethylferrocenyl)methyl)fumaramide rotaxane [7(mac-ZnCl_2)]]} \]

To a solution of 7 (50 mg, 0.035 mmol) in methanol (5 mL) was added a saturated solution of ZnCl_2 (5.3 mg, 0.039 mmol) in methanol (1mL). The reaction was stirred for 1h during which time a solid precipitated. The solid was filtered and washed with methanol (5 mL) to furnish [7(mac-ZnCl_2)] as a pale yellow solid (48 mg, 95%); mp > 240 °C (decomp); HRMS (FAB, 3-NOBA matrix): \( m/z = 1514.5293 \) [(M-Cl)^+] (anal. calcd for \( C_{84}H_{87}ClFeN_{12}O_6Zn^+ \): \( m/z = 1514.5201 \)).
Chapter Six  Investigating the Effect of Dipolar Interactions in Redox-Active Rotaxanes

([2]([1H-1,2,3-Triazol-4-yl-N,N-bis(pyridine-2-yl methyl)methanamine chromium (II) trichloride]-1,7,14,20-tetraaza-2,6,15,19-tetraoxo-3,5,9,12,16,18,22,25-tetrabenzocyclohexacosane)-(N^1-(2,2-diphenylethyl)-N^4-((octamethylferrocenyl)methyl)fumaramide rotaxane [7(mac-CrCl_3)])

To a solution of 2 (20 mg, 0.017 mmol), [8CrCl_3] (8.1 mg, 0.020 mmol) and N,N-disopropylethylamine (0.0030 mL, 0.017 mmol) in dichloromethane/methanol in a 9:1 v/v ratio (10 mL) was added Cu(CH_3CN)_4PF_6 (0.63 mg, 0.0017 mmol). The resulting mixture was stirred for 12 h. The solution was concentrated under reduced pressure. To the residue was added acetone (10 mL), the resulting suspension was filtered and was washed with acetone (5 mL) to furnish [7(mac-CrCl_3)] as a pale green solid (22 mg, 83%); mp > 255 °C (decomp); HRMS (FAB, 3-NOBA matrix): m/z = 1536.4921 [(M-Cl)^+] (anal. calcd for C_84H_86Cl_2CrFeNi_2O_6^+: m/z = 1536.4925).
To a solution of ([2](azido-1,7,14,20-tetraaza-2,6,15,19-tetraoxo-3,5,9,12,16,18,22,25-tetrabenzocyclohexacosane)-(N\(^1\)-2-(bis(pyridine-2-ylmethyl)amino)ethyl)-N\(^4\)-(2,2-diphenylethyl)fumaramide) chromium (II) trichloride rotaxane [9(thread-CrCl\(_3\))] in tetrahydrofuran (20 mL) was added a saturated solution of CuCl\(_3\)·(THF)\(_3\) (69 mg, 0.18 mmol) in tetrahydrofuran (1 mL). The reaction mixture was stirred for 1 h during which time a solid precipitated. The reaction mixture was filtered, and the solid washed with methanol to furnish as a green solid (219 mg, 97%); mp > 298 °C (decomp); HRMS (FAB, 3-NOBA matrix): \(m/z = 1214.3514\) [(M-Cl)+] (anal. calcd for C\(_{64}\)H\(_{60}\)Cl\(_2\)CrN\(_{12}\)O\(_6\)\(^+\): \(m/z = 1214.3541\)).
To a solution of [9(thread-CrCl₃)] (100 mg, 0.080 mmol), ethynylferrocene (20 mg, 0.10 mmol) and N,N-disopropylethylamine (0.014 mL, 0.080 mmol) in dichloromethane/methanol in a 9:1 v/v ratio (10 mL) was added Cu(CH₃CN)₄PF₆ (3.0 mg, 0.0080 mmol). The resulting mixture was stirred for 12 h. The solution was concentrated under reduced pressure. To the residue was added acetone (10 mL), the resulting suspension was filtered and washed with acetone (5 mL) to furnish [9(mac-Fc)(thread-CrCl₃)] as a pale green solid (96 mg, 82%); mp > 235 °C (decomp); HRMS (FAB, 3-NOBA matrix): m/z = 1424.3674 [(M-Cl)⁺] (anal. calcd for C₇₆H₇₀Cl₂CrFeN₁₂O₆⁺: m/z = 1424.3673).
Chapter Six: Investigating the Effect of Dipolar Interactions in Redox-Active Rotaxanes

\[(\{1H-1,2,3-Triazol-4-yl-ferrocenyl\}_1,7,14,20-tetraaza-2,6,15,19-tetraoxo-3,5,9,12,16,18,22,25-tetraabenzocyclohexacosane)-(N^1-(2-(bis(pyridine-2-ylmethyl)amino)ethyl)-N^4-(2,2-diphenylethyl)furaramide)\) copper (II) dichloride rotaxane \([9(mac-Fc)(thread-CuCl_2)]\)

To a solution \([9(thread-CrCl_3)]\) (100 mg, 0.080 mmol), ethynylferrocene (20 mg, 0.096 mmol) and \(N,N\)-disopropylethylamine (0.014 mL, 0.080 mmol) in dichloromethane/methanol in a 9:1 v/v ratio (10 mL) was added \(\text{Cu(CH}_3\text{CN)}_4\text{PF}_6\) (3.0 mg, 0.0080 mmol). The resulting mixture was stirred for 12 h. The solution was concentrated under reduced pressure. To the residue was added acetone (10 mL), the resulting suspension was filtered and washed with acetone (5 mL) to furnish \([9(mac-Fc)(thread-CuCl_2)]\) as a solid pale green solid (94 mg, 81%); mp > 200 °C (decomp); HRMS (FAB, 3-NOBA matrix): \(m/z = 1400.3884 \ [\text{(M-Cl)}^+]\) (anal. calcd for \(C_{76}H_{70}ClCuFeN_{12}O_6^+: m/z = 1400.3875\)).
A solution of \([9(\text{mac-Fe})(\text{thread-CuCl}_2)]\) (100 mg, 0.070 mmol) in chloroform/isopropanol in a 3:1 v/v ratio (15 mL) was washed with saturated aqueous, basic EDTA (3 x 10 mL) and saturated aqueous sodium chloride (2 x 10 mL), dried (MgSO\(_4\)) and concentrated under reduced pressure to give a dark orange oil. The remaining residue was subjected to column chromatography on silica gel using dichloromethane/acetonitrile/NH\(_4\)OH (aq) in a 5:5:0.2 v/v ratio as eluent to furnish 9 as a dark brown oil (63 mg, 71%); \(^1\)H NMR (400 MHz, [D\(_7\)]DMF): \(\delta = 9.35\) (s, 1H, \(H_d\)), 8.95 (t, \(J = 5.3\) Hz, 1H, \(H_a\)), 8.86 (s, 1H, \(H_d\)), 8.80-8.78 (m, 2H, \(H_b\) & \(H_c\)), 8.74 (d, \(J = 0.9\) Hz, 2H, \(H_B\)), 8.49 (d, \(J = 4.5\) Hz, 2H, \(H_a\)), 8.20 (dd, \(J = 7.6\) Hz and \(J = 1.3\) Hz, 4H, \(H_B\) & \(H_I\)), 8.08-8.05 (m, 2H, \(H_B\)), 7.76 (t, \(J = 7.7\) Hz, 1H, \(H_d\)), 7.72 (dt, \(J = 7.7\) Hz and \(J = 1.8\) Hz, 2H, \(H_c\)), 7.53 (d, \(J = 7.8\) Hz, 2H, \(H_d\)), 7.37-7.30 (m, 8H, \(H_p\)), 7.24-7.21 (m, 4H, \(H_b\) & \(H_p\)), 7.05 (s, 8H, \(H_G\) & \(H_F\)), 5.97 (s, 2H, \(H_J\) & \(H_I\)), 4.99 (t, \(J = 1.8\) Hz, 2H, \(H_m\)), 4.54-4.38 (m, 10H, \(H_E\), \(H_H\) & \(H_I\)), 4.26 (t, \(J = 7.9\) Hz, 1H, \(H_m\)), 4.18 (s, 5H, \(H_D\)), 3.95 (dd, \(J = 7.6\) Hz and \(J = 1.9\) Hz, 2H, \(H_l\)), 3.85 (s, 4H, \(H_e\)), 3.39-3.41 (m, 2H, \(H_g\)), 2.73-2.71 (m, 2H, \(H_J\)); \(^{13}\)C NMR (100 MHz, [D\(_7\)]DMF): \(\delta = 167.2, 166.9, 166.7, 165.7, 150.0, 143.9, 139.0, 138.4, 138.0, 137.5, 137.4, 135.5, 132.0, 131.1, 131.0, 130.1, 129.7, 129.1, 127.7, 125.8, 125.2, 124.0, 123.3, 122.5, 119.8, 76.7, 70.6, 69.8, 67.9, 60.8, 53.6, 51.7, 45.1, 44.7, 44.5, 38.9; HRMS (FAB, 3-
Chapter Six

Investigating the Effect of Dipolar Interactions in Redox-Active Rotaxanes


\[ \text{([2]}(1H-1,2,3-Triazol-4-yl-ferrocenyl)-1,7,14,20-tetraaza-2,6,15,19-tetraoxo-3,5,9,12,16,18,22,25-tetramethylcyclohexacose)-(N\text{'}-(2-(bis(pyridine-2-ylmethyl)amino)ethyl)-N\text{'}-(2,2-diphenylethyl)fumaramide) zinc (II) dichloride rotaxane [9(mac-Fc)(thread-ZnCl2)]\]

To a solution of 9 (50 mg, 0.038 mmol) in methanol (5 mL) was added a saturated solution of ZnCl2 (5.7 mg, 0.042 mmol) in methanol (1 mL). The reaction was stirred for 1h during which time a solid precipitated. The solid was filtered and washed with methanol (5 mL) to furnish [9(mac-Fc)(thread-ZnCl2)] as a orange solid (53 mg, 93%); mp > 220 °C (decomp); 1H NMR (400 MHz, [D7]DMF): \( \delta = 9.37 \) (s, 1H, H_L), 9.01 (d, J = 4.6 Hz, 2H, H_a), 8.93 (t, J = 5.3 Hz, 1H, H_b), 8.75 (s, 3H, H_f & H_k), 8.66-8.63 (m, 2H, H_b & H_l), 8.21 (dd, J = 7.7 Hz and J = 1.0 Hz, 2H, H_g), 8.10-8.01 (m, 2H, H_D), 7.96 (t, J = 7.7 Hz, 2H, H_c), 7.91 (t, J = 4.9 Hz, 2H, H_j), 7.76 (t, J = 7.8 Hz, 1H, H_d), 7.78 (t, J = 7.8 Hz, 2H, H_b), 7.54 (d, J = 7.8 Hz, 2H, H_d), 7.35-7.28 (m, 8H, H_ph), 7.23-7.19 (m, 2H, H_ph), 7.00 (s, 8H, H_G & H_F), 5.92 (d, J = 15.0 Hz, 1H, H_i), 5.80 (d, J = 15.0 Hz, 1H, H_j), 4.99 (t, J = 1.7 Hz, 1H, H_M), 4.58-4.29 (m, 14H, H_N, H_E, H_H, & H_l), 4.24 (t, J = 7.9 Hz, 1H, H_m), 4.18 (s, 5H, H_O), 3.94 (dd, J = 7.6 Hz and J = 1.9 Hz, 2H, H_i), 3.47-3.45 (m, 2H, H_g), 2.85-2.82 (m, 2H, H_j); 13C NMR (100 MHz, [D7]DMF): \( \delta = 167.1, 166.9, 166.6, 165.5, 155.9, 149.7, 143.9, 143.7, 141.7, 139.0, 138.5, 138.1, 137.5, 132.0, 131.6, 130.4, 130.2, 130.0, 129.7, 129.0, 127.7, 125.7, 125.6, 125.2, 125.0, 122.6, 76.7, 70.6, 69.8, 67.8, 57.1, 51.5, 45.1, 44.5, 44.4; HRMS
Chapter Six  
Investigating the Effect of Dipolar Interactions in Redox-Active Rotaxanes

(FAB, 3-NOBA matrix): $m/z = 1402.3921 \ [\text{(M-Cl)}^+]$ (anal. calcd for C$_{76}$H$_{70}$ClFeN$_{12}$O$_6$Zn$^+$: $m/z = 1402.3904$).

6.5 References and Notes


Initially a ferrocene-containing thread was successfully synthesised. Although formation of a macrocycle around this thread proceeded in good yields, de-threading of the mechanically-interlocked components occurred in polar solvents. This suggested that the ferrocene unit was not large enough to act as a stopper for typical benzylic amide macrocycle and so the octamethyl-substituted analogue was employed.


Appendix

Published Papers


Complexation-Induced Translational Isomerism: Shuttling through Stepwise Competitive Binding

**

Dana S. Marlin, Diego Gonzalez Cabrera, David A. Leigh,* and Alexandra M. Z. Slawin

Although many carefully designed rotaxane-forming reactions have been developed in recent years,[11] new strategies[12] for switching the position of the macrocycle on the thread in response to an external trigger[3,4]—a key requirement for developing mechanical molecular devices based on such architectures[4]—remain rare. Competitive substrate binding is often used to bring about conformational changes that elicit function in biological "machines"[10] and has been successfully utilized in artificial host–guest systems,[6] chemical sensing,[7] and molecular Boolean logic operations.[8] However, as the macrocycle-thread interactions in a rotaxane are normally chosen so as to maximize the efficiency of the template mechanism, it is difficult to find competitive binders that can effectively disrupt these threaded and inherently self-organized complementary networks.[5,6] One elegant solution[11] to this problem is to utilize the preferred binding geometries of different metal d-orbital configurations (e.g. tetrahedral Cu²⁺—five-coordinate Cu²⁺ or Zn²⁺) in transition-metal-based molecular shuttles.[10,13] Here we report an alternative solution, which does not involve a change in metal ion or oxidation state but uses the binding of a transition metal to move a macrocycle in a hydrogen-bonded molecular shuttle. Coordination of Cu²⁺ or Cd²⁺ ions to a bis(2-picolyl)amino (BPA)-derivatized glycine "station", followed by deprotonation of the adjacent amide group progressively wraps up the peptide station which leads to displacement of the macrocycle to an intrinsically weaker hydrogen-bonding site. In the case of Cu²⁺, the change in binding mode perturbs sensitive transitions within the d orbitals and the change in position of the shuttle is consequently accompanied by a color change.

The new shuttling strategy evolved out of the chance observation of an unusual controlled stepwise binding sequence of Cu²⁺ ions to a multidentate ligand. Whilst attempting to develop methodology for the attachment of paramagnetic metal ions to macrocycles in rotaxanes, we prepared ligand H₁,[14,15] which features a glycine residue substituted with two picoline units at its N terminus. Addition of CuCl₂·2H₂O to H₁ in CH₃CN led to the formation of H₁CuCl₂, light blue crystals of which separated from the saturated liquors and gave the X-ray crystal structure shown in Figure 1a.[16] Cooling the solution of H₁CuCl₂ to −20°C in the presence of an additional half-equivalent of CuCl₂·2H₂O resulted in the deposition of large emerald-green crystals[14,15] of [H₁CuCl₂][CuCl₄] on the walls of the flask which yielded the crystal structure shown in Figure 1b. Addition of one equivalent of Na₂S to solutions of either H₁CuCl₂ or H₁-(CuCl)[CuCl₄] in NN-dimethylformamide led to a third type of BPA–Cu²⁺ complex as lime-green crystals of 1CuCl (Figure 1c). The binding of the Cu²⁺ ion—from the initial tridentate chelation of CuCl₂ to the BPA moiety in H₁CuCl₂, to loss of a Cl⁻ ligand and coordination to the carbonyl oxygen of the amide group in [H₁CuCl⁺], and finally exchange of the carbonyl group for the nitrogen atom upon deprotonation of the amide group in 1CuCl—results in progressive wrapping of the peptide unit around the metal (Figure 1).[18] We reasoned that integration of this stepwise changing coordination motif into a macrocycle-binding site in a peptide-based molecular shuttle might permit the complexation-controlled translocation of the macrocycle from one station to another.

To study the chemistry of the BPA-modified peptide station in a simple model system, we first prepared thread H₂...
and rotaxane H23 (Scheme 1). Formation of H23 proceeded in 44% yield from H22 (Scheme 1, a) which suggests that the affinity of the benzylic amide macrocycle for the BPA-glycylglycine station should be similar to that of other peptide-based stations, namely, intermediate between a strongly binding preorganized fumaramide group and a more weakly binding succinic amide ester moiety. The X-ray crystal structure of rotaxane H23 shows that both carbonyl groups and both amide protons in the thread are involved in intercomponent hydrogen bonding to the macrocycle in the solid state (Figure 2b).

The chelation geometries adopted by the BPA-glycylglycine station were studied by binding H22 and H23 to CuII as well as CdII, a diamagnetic metal that generally adopts ligand-coordination geometries that are similar to those of CuII with nitrogen-containing ligands, and attempted subsequent deprotonation of one of the amide groups (Scheme 1, c). The X-ray crystal structures of several of the resulting complexes are shown in Figure 2, and the 1H NMR spectra ([D6]acetone, 298 K) of the free ligands H22 and H23 and their complexes with Cd(NO3)2 are shown in Figure 3. The changes in the signals for the BPA protons (H24) upon complexation of cadmium ions and the shielding of the protons of the peptide (H24, H25, and H26) by the macrocycle in the rotaxanes compared to those of the thread confirm that the structures in solution are closely related to those in the solid state.

First, addition of CuCl2·2H2O or Cd(NO3)2·4H2O to both the thread and rotaxane smoothly generated complexes of the type H22MX2 and H3MX3, respectively (M = Cu, Cd; Scheme 1, b). The solid-state structure of H3Cd(NO3)2 (Figure 2b) shows a coordination geometry which is similar to that of the intermediate [H1CuCl]+ complex (Figure 1 b), that is, featuring metal coordination to the carboxamide carbonyl oxygen.

Second, addition of one equivalent of a suitable base (Scheme 1, c) to the thread intermediate complexes H22CuCl2 and H22Cd(NO3)2 yielded H2CuCl and H2CdNO3, respectively. The X-ray crystal structure of H2CuCl (Figure 2a) displays a CuII coordination sphere that is similar to that of lCuCl (Figure 1 c) as well as an additional (albeit long at 3.188 Å) directional hydrogen bond between the proton (N7H) of the second amide group and the formal nitrogen anion (N4) of the coordinating carboxamido functionality. The X-ray crystal structure of H2CdNO3 (Figure 2c) is closely related, but with the metal ion additionally coordinated to the carbonyl oxygen of the second carboxamide group. The binding of CdIII (or CuII) ion to the BPA-glycine carbonyl oxygen presumably lowers the pK® value of the adjacent NH proton in complexes of the type H2Mx2 and H,2Mx3 which
allows selective deprotonation at this site. However, neither of the metal coordination geometries shown in Figure 2a or c would leave room on the peptide unit for a benzyl amide macrocycle to occupy, or sufficient hydrogen-bonding partners for it to bind to, in a rotaxane or molecular shuttle. Indeed, treatment of H$_2$3CuCl$_2$ or H$_2$3Cd(NO$_3$)$_2$ with strong bases led to complicated reaction mixtures and significant degradation of the rotaxane structures, seemingly as a consequence of the macrocycle sterically preventing deprotonation of the coordination-activated carboxamide or adoption of the wrapped-up metal-ligand coordination architecture.

The model compounds confirm the generic basis of the stepwise binding chemistry and provide $^1$H NMR spectroscopic fingerprints (Figure 3) of the various coordination modes, both with and without the macrocycle occupying the station. These spectra could be used to determine the position of the macrocycle in a more elaborate molecular shuttle, in particularly distinguishing between whether Cd$^{II}$ is bound to a carbonyl oxygen or a carboxamido nitrogen atom and whether the macrocycle still occupies the BPA-glycylglycine station.

Accordingly, we prepared the two-station thread H$_2$4 and rotaxane H$_2$5 which feature BPA-derivatized glycylglycine (green) and succinic amide ester (orange) stations for the macrocycle (Scheme 2). The rationale behind the design was that although the ring would be expected to predominantly occupy the BPA-glycylglycine binding site in H$_2$5Cd(NO$_3$)$_2$, the ring would still spend some time away from the peptide station on the weaker binding succinic amide ester moiety. Whilst it is on the succinic amide ester station, the ring should
not sterically hinder the coordination-activated peptide (as it does so effectively in $\text{H}_2\text{Cd(NO}_3\text{)}_2$, Scheme 1), so this minor translational isomer can then be selectively deprotonated at the carboxamide adjacent to the BPA unit. In accord with Le Chatelier's principle, $\text{H}_5\text{Cd(NO}_3\text{)}_3$ is formed. If the cadmium ion wraps itself up in the deprotonated glycyiglycine residue in the manner seen with the model systems, this will switch off the peptide station and result in the macrocycle of $\text{H}_5\text{Cd(NO}_3\text{)}_3$ predominately occupying the succinic amide ester station (Scheme 2).

Pleasingly, the $^1$H NMR spectra of the rotaxanes and threads (shown in Figure 4) were fully consistent with the predicted behavior. The relative shielding of the peptide protons in the $^1$H NMR spectrum of $\text{H}_5$ compared to $\text{H}_4$ (Figure 4a and b, respectively) confirms that the occupancy of the macrocycle is approximately 90:10 in favor of the glycyiglycine station in [D$_6$]acetone at 298 K. Addition of one equivalent of Cd(NO$_3$)$_2$·4H$_2$O to $\text{H}_4$ and $\text{H}_5$ to form $\text{H}_4\text{Cd(NO}_3\text{)}_2$ and $\text{H}_5\text{Cd(NO}_3\text{)}_2$, respectively (Scheme 2b), resulted in little change (except for the BPA protons) in the $^1$H NMR spectra in [D$_6$]acetone at room temperature (compare Figures 4c and d with Figures 4a and b, respectively), indicating that the preferred position of the macrocycle remains unchanged despite chelation of the terminal peptide carbonyl group to a metal — the shifts experienced by the protons around the metal-binding region, for example, $\text{H}_a$ and $\text{H}_b$, are similar to those in $\text{H}_3\text{Cd(NO}_3\text{)}_2$ (Figure 3d). However, subsequent deprotonation of the amide proton $\text{H}_g$ of $\text{H}_5\text{Cd(NO}_3\text{)}_2$ with one equivalent of phosphazene base P$_{1-}$tBu$^{[25]}$ (Scheme 2c) causes major changes (Figure 4e). The upfield shifts of $\text{H}_m$ ($\delta=3.2$ ppm in $\text{H}_4\text{Cd(NO}_3\text{)}_2$, Figure 4c) to $\delta=2.4$, 1.7, and 1.5 ppm, respectively) are clear evidence for the translocation of the macrocycle to the succinic amide ester station (marked in orange). Similarly, the downfield shift of $\text{H}_f$ ($\delta=4.0$ ppm in $\text{H}_5\text{Cd(NO}_3\text{)}_2$, Figure 4d) to $\delta=4.0$ ppm and the restoration of $\text{H}_j$ to its position at $\delta=3.2$ ppm in the thread (Figure 4c) show that the peptide station (marked in green) is no longer occupied by the benzylic amide macrocycle. The small upfield movement in $\text{H}_a$ is consistent with the shift brought about by coordination of the deprotonated amide group to the metal, as seen with H2CdNO3 (Figure 3e).

The transition-metal-binding-induced translocation of the macrocycle in the hydrogen-bonded shuttle is fully reversible (Scheme 2d). Removal of the Cd$^{II}$ ion from H5CdNO3 with
excess CN⁻ and reprotonation of the amide nitrogen atom with NH₂Cl quantitatively regenerates H₅Cu₂.

Finally, indirect evidence for a similar shuttling mechanism using Cu⁴⁺ binding is provided by the change in absorption of weak (likely d-d) transitions in the low-energy region of the UV/Vis spectrum of H₅CuCl₂ upon addition of P₁-tBu (Figure 5). The color change that occurs during a single-spot-to-single-spot transformation, as revealed by thin layer chromatographic analysis, is almost indistinguishable to that observed during the conversion of [H₁CuCl]⁺ to 1CuCl (Figure 1). As the base-promoted transformation (H₃CuCl₂ → H₅CuCl) does not occur for the short rotaxane (Scheme 1, c), yet does take place for H₅CuCl₂ → H₅CuCl (Figure 5), it seems reasonable to conclude that the color change is accompanied by the same change in the position of macrocycle that occurs in the cadmium-coordinated molecular shuttle (Scheme 2, c).

In conclusion, we have described a mechanism through which a large amplitude mechanical movement can be induced within a hydrogen-bonded molecular shuttle by the stepwise competitive binding of transition-metal ions. The peptide station is progressively wrapped up by the metal which disrupts hydrogen-bonding interactions between the station and macrocycle and causes displacement of the macrocycle to a second station. The control over shuttling while the metal is bound to the thread provides two well-defined states in which the macrocycle is held either close to or distant from a single metal atom. This feature could be used to construct rotaxanes that display the intriguing property of being able to switch the distance between two metal centers, which are not connected by chemical bonds, by an externally triggered mechanical motion.

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[1] For some recent examples of new rotaxane syntheses, see:


Communications

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A novel strategy for the synthesis of DNA-functionalized tetrahedra has been developed. The tetrahedron is composed of four identical DNA strands and four non-DNA molecules, which are connected in a tetrahedral arrangement.

The tetrahedron can be used as a building block for the assembly of larger, more complex molecular architectures. The DNA strands provide a template for the arrangement of the non-DNA molecules, allowing for precise control over the geometry and orientation of the final structure.

This approach offers several advantages over traditional methods for the synthesis of complex molecular structures. It allows for the facile introduction of functional groups and the modulation of the properties of the resulting architectures. The use of DNA as a template also provides a framework for the incorporation of biological molecules and the design of materials with specific functionalities.

The tetrahedron could have applications in various fields, including nanotechnology, materials science, and biology. It may enable the development of new materials with unique properties and the creation of complex structures for the manipulation of biomolecules.
could be used to deprotonate BPA at its terminal amide group.


[23] Without this discrimination, the more-complicated molecular shuttle system containing multiple amide groups would not be able to function.
One of Nature's most effective ways of influencing function from afar is through allosteric control.\[1\] This occurs—most typically in proteins—when activity at a substrate-binding site is modulated by the complexation of an effector molecule or...
ion at a second site. The binding sites are frequently several nanometers apart, and communication between them is achieved through a variety of mechanisms, the details of which are not well understood but often involve multiple substrate-binding sites and cooperative complexation events that are accompanied by large amplitude movements of polypeptide chains and other molecular subunits. However, to achieve any kind of distant control in response to binding in synthetic systems is far from trivial. Most of the artificial allosteric receptors developed to date feature one or more substrate-interaction sites directly conformationally coupled to an effector-binding site. Herein, we report on a mechanically linked substrate/host ensemble (a [2]rotaxane), which contains two spatially and chemically distinct "substrate" hydrogen-bonding sites, only one of which is influenced by the coordination of a metal ion (the "effector") to an adjacent tridentate ligand fragment. The result is a stimuli-responsive molecular shuttle that undergoes a large amplitude internal motion (change in the position and binding strength of the macrocycle), allosterically regulated through a small, but highly significant, conformational change brought about by complexation of a transition metal at the effector site.

The molecular shuttle allosteric control mechanism has its origins in anomalous behavior observed for some simple hydrogen-bonded rotaxanes that bear metal-chelating stoppers containing a bis-(2-picolyl)amine (BPA) moiety (Scheme 1). Rotaxanes 1 and 2, in which the BPA unit is connected to the hydrogen-bonding groups of the thread by an ethylene spacer, react readily with various transition-metal salts including CuCl₂, which yields complexes 1CuCl₂ and 2(CuCl₂)₂, respectively (Scheme 1 a and b). The X-ray crystal structures of 1CuCl₂ and 2(CuCl₂)₂ (Figure 1 a and b) show the typical four intercomponent hydrogen bonds between the benzylamide groups of the macrocycle and the amide groups of the thread, together with the predicted coordination of the BPA ligands to each metal ion in a tridentate fashion. However, to our surprise, rotaxanes 3 and 4, in which the ethylene spacer is absent and the BPA unit is attached directly to the hydrogen-bonding station of the thread, were found not to react with CuCl₂ or similar transition-metal salts even under forcing conditions (Scheme 1 c and d). This behavior is in marked contrast to that of their parent threads, which react like rotaxanes 1 and 2 to give the expected coordination complexes of a transition metal at the effector site.

The prospect of a situation where, despite binding at different sites, metal- and macrocycle-binding modes compete for the same 3D space led us to consider whether translocation of the macrocycle to a second hydrogen-bonding site on a thread could be induced by a metal-binding interaction. As a model we designed rotaxane 5 (Scheme 2), which contains three carbonyl hydrogen-bond acceptors on the thread in what can be viewed as an elongated hydrogen-bonding station (for clarity in interpreting the ¹H NMR spectra (Figure 2), one half of this unit is colored in green and the other in orange). With this extended station the macrocycle in 5 has space to occupy (and hydrogen-bonding partners) when a metal binds to, and rearranges the conformation of, the BPA-containing stopper. The solid-state structure of 5 (Scheme 2b) reveals that the macrocycle is bound to the central carbonyl group (O41) of the thread through hydrogen bonds between the carboxamide hydrogen donors (N20H and N29H) and the amide carbonyl group adjacent to the diphenylacetyl stopper (O44). However, the carbonyl group (O38) adjacent to the BPA station is also in the plane of the other two carbonyl groups (O41 and O44) on the thread, and in solution one
would expect an equilibrium to exist between the hydrogen bonding of N11H and O44 and a similar interaction between O38 and N2H (Scheme 2a). Indeed, the $^1$H NMR spectrum of rotaxane S in CD$_3$CN (Figure 2b) reveals that this is the case, with the chemical shifts of both internal methylene groups H$_1$ and H$_h$ (green and orange, respectively) shifted upfield ($\Delta$H$_1$ = 0.7 ppm; $\Delta$H$_h$ = 1.0 ppm) relative to those of the free thread (Figure 2a), as a result of shielding from the macrocycle.

Addition of CuCl$_2$ to S results in formation of complex 5CuCl$_2$, the X-ray crystal structure of which is shown in Scheme 2c. The most striking characteristics of this solid-state structure are the chelation of all three BPA nitrogen atoms (including the carboxamide nitrogen, N71) to the Cu$^{II}$ ion, together with the out-of-plane tilting of carbonyl oxygen O38 relative to the plane in which the other two carbonyl oxygen atoms (O41 and O43) of the thread lie. As cadmium is a diamagnetic metal with similar binding properties to Cu$^{II}$, treatment of S with Cd(NO$_3$)$_2$ allowed us to study the solution behavior of metal chelation to S using $^1$H NMR spectroscopy (compare Figure 2c with Figure 2b and d). As expected, the binding of a metal ion to the BPA stopper alters the equilibrium of hydrogen bonding between the three carbonyl hydrogen-bond acceptors in S, causing a shift of the signal for H$_h$ (orange) further upfield and a slight downfield shift of the resonance for H$_1$ (green) in 5Cd(NO$_3$)$_2$, relative to those in the free rotaxane. Comparison of the $^1$H NMR spectra of 5Cd(NO$_3$)$_2$ with the Cd(NO$_3$)$_2$–thread complex revealed a similar trend, that is, a large upfield shift of the signal for H$_h$ and a much smaller shift for that of H$_1$.

The red circles highlight the enforced change in conformation of the BPA ligand and adjacent peptide unit upon coordination to a metal ion.

**Scheme 2.** Synthesis of [2]rotaxane S with an extended hydrogen-bonding site and its subsequent complexation to generate 5MX$_2$ (MX$_2$ = CuCl$_2$ or Cd(NO$_3$)$_2$): a) the solution positional equilibrium of the macrocycle in S (atom-lettering scheme corresponds to $^1$H NMR assignments in Figure 2). The complexes 5MX$_2$ were prepared by addition of a solution of the appropriate metal salt in acetonitrile to a solution of S in acetonitrile at room temperature and purified by crystallization. b, c) X-ray crystal structures of S and 5CuCl$_2$, respectively. C (thread) yellow, C (macrocycle) turquoise, O red, N dark blue, Cu gray, Cl green, H white; all hydrogen atoms except for the amide protons have been omitted for clarity. Selected bond lengths [\(\text{Å}\)]:

- In S: N20H–O41 2.026, N29H–O42 2.192, N11H–O44 1.885;

The changes indicate that the
macrocyle no longer shuttles back and forth along the thread in 5Cd(NO₃)₂, but is restricted mainly to a position over the H₆ methylene group between carbonyl oxygen atoms O41 and O43.

Encouraged by the results from this model system we prepared a two-station [2]rotaxane, 6, with hydrogen-bonding sites of substantially differing affinities for the macrocycle separated by a C₁₂ alkyl chain. The station of known higher binding affinity (succinamide, shown in green) is directly attached to the metal-binding BPA unit, while the station of inherent lower affinity (succinic amide ester, shown in orange) is attached to a nonchelating diphenylacetyl stopper (Scheme 3). In 6, the macrocycle occupies the position over the green station more than 95% of the time at 273 K in CD₃CN, as revealed by the large (Δδ = 1.1 ppm) downfield shift of the signals for protons H₂ and H₃ (compare Figure 3b and a). In comparison, the signals for protons H₄ and H₅ (orange station) appear at similar chemical shifts in rotaxane 6 (Figure 3a) and the parent thread (Figure 3a).

The addition of one equivalent of Cd(NO₃)₂ to 6 in CD₃CN results in a dramatic change in the ¹H NMR spectrum (Figure 3c). The major differences in the spectra of 6 and 6Cd(NO₃)₂ are the large (Δδ = 1.1 ppm) downfield shift of the signals for protons H₂ and H₃ (green station) and the upfield shift (Δδ = 0.7 ppm) of the peaks for H₄ and H₅ (orange station) in the metal-coordinated rotaxane. In addition, protons H₆, H₇, and H₈ at the periphery of the orange station are also shielded by the macrocycle (Δδ ≈ 0.3 ppm). Collectively these data indicate that the macrocycle has moved from residing predominantly over the green station to being positioned mainly over the orange station. The difference in the chemical shifts of 6Cd(NO₃)₂ relative to those of the parent thread bound to Cd(NO₃)₂ (Figure 3d) confirms the change in position of the macrocycle. The coordination reaction, and change in position of the macrocycle, is reversed by treatment with NaCN (Scheme 3).

The stimuli-induced shuttling between 6 and 6Cd(NO₃)₂ (Scheme 3) corresponds to a negative heterotropic allosteric...
energy, 1151 and to carry out mechanical work, 1152 dichroism, 1121 fluorescence, 1131 porosity, [141 and surface been used to bring about changes in conductivity, 11  circular 1.5 nm away. Similarly large movements in rotaxanes have

[5] For examples of Cu1 1 and Cd1 1 bound to BPA tertiary amide

[4] 1 1

[3] For reviews on synthetic allosteric receptor systems, see: a) T.


[1] For recent reviews on allosterie in biological systems, see: a) J.-P.

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Communications

3, 4, 5, and 5CuCl₂, respectively) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.


A series of mono- and bis-metallated [2]rotaxanes has been prepared using a CuAAC ‘click’ protocol that is compatible with metal-coordinated building blocks and ligands; the methodology provides a general means for appending a metal ion or complex to an organic scaffold via Cu(1)-catalysed ‘click’ chemistry, even when the molecule contains redox-active or kinetically labile metals or vacant ligand sites.

Since its discovery, the Huisgen–Meldal–Fokin Cu(1)-catalysed terminal alkyne–azide cycloaddition (the CuAAC2 ‘click’ reaction) has attracted great interest because of its utility in chemically bonding functional molecular fragments in a precise, predictable and efficient fashion under a myriad of conditions and situations. Despite its exceptional versatility, however, to date there have been few reports on performing the CuAAC reaction in the presence of other redox-active metal ions or substrates containing multidentate bonding sites capable of sequestering the copper catalyst. The few examples of metal-coordinated alkenes or azides to have been successfully employed in the CuAAC reaction thus far include ethynylferrocene, an organometallic iridium complex, metalloporphyrins, a lanthanide-bound cyclen derivative, a ruthenium dimer functionalised with an alkyne and Cu(1)-coordinated rotaxanes. While some of these examples offer methods for attaching specific metals to particular molecular structures, most of the complexes are kinetically inert and none allow for the ready variation of the metal.

Here we present a strategy for the assembly of multiple (homo- and mixed-) metal-containing products using the CuAAC reaction by employing a simple alkyne functionalised tridentate ligand, 1, capable of coordinating to a variety of transition metal ions (Scheme 1). Through this synthon, a series of [2]rotaxanes (Schemes 2 and 3). A functionalised [2]rotaxane, 3, bearing two BPA chelating sites (one attached to the rotaxane macrocycle, one to the rotaxane thread) was synthesised using a hydrogen bond-templated clipping strategy (Scheme 2). To a solution of thread 4 and 5 (obtained from deprotection of 6, Scheme 2, step a) in CHCI3, was added 5-azidoisophthaloyl dichloride 4 to yield aido[2]rotaxane 3, bearing two BPA chelating sites (one attached to the rotaxane macrocycle, one to the rotaxane thread) was synthesised using a hydrogen bond-templated clipping strategy (Scheme 2). To a solution of thread 4 and 5 (obtained from deprotection of 6, Scheme 2, step a) in CHCl3, was added 5-azidoisophthaloyl dichloride to yield azido[2]rotaxane 7 (52% yield, Scheme 2, step b). Prior to reacting the azido[2]rotaxane with alkenes [1CuCl2] and [1CrCl3], the BPA tridentate binding site of the thread was protected by coordination to Cu(1), generating [7(thread-CuCl2)] (Scheme 2, step c). Complexes CuCl2, [1CuCl2], or the kinetically inert CrCl3, [1CrCl3], could be effectively employed in the CuAAC reaction using a catalytic amount (10 mol%) of Cu(1) to generate the metal-containing triazoles [2CuCl2] and [2CrCl3] in 80% and 82% yields, respectively (Scheme 1).

Attempts to extend this protocol to other first row transition metal complexes of 2, including [2ZnCl2], [2MnCl2], [2FeCl3] and [2CoCl3], were unsuccessful, however. Although in some cases increasing the amount of the Cu(1) catalyst used to 1 equivalent enabled the CuAAC reaction to proceed, this also resulted in displacement of the original metal from the BPA unit by oxidised Cu(II). In contrast, Cr(III) was not displaced during the formation or isolation of [2CrCl3], nor did it participate in any electron transfer reactions. In fact, forcing conditions (1.5 equiv. of KCN, CH3OH, reflux, 12 h, 80%) were necessary to liberate it from the derivatised BPA ligand.

These results led us to develop a method for coupling homo- and mixed-metal chelated fragments with the CuAAC reaction, exemplified through a series of [2]rotaxanes (Schemes 2 and 3). A functionalised [2]rotaxane, 3, bearing two BPA chelating sites (one attached to the rotaxane macrocycle, one to the rotaxane thread) was synthesised using a hydrogen bond-templated clipping strategy (Scheme 2). To a solution of thread 4 and 5 (obtained from deprotection of 6, Scheme 2, step a) in CHCl3, was added 5-azidoisophthaloyl dichloride to yield azido[2]rotaxane 7 (52% yield, Scheme 2, step b). Prior to reacting the azido[2]rotaxane with alkenes [1CuCl2] and [1CrCl3], the BPA tridentate binding site of the thread was protected by coordination to Cu(1), generating [7(thread-CuCl2)] (Scheme 2, step c). Complexes

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† Electronic supplementary information (ESI) available: Synthesis and characterization of all compounds. See DOI: 10.1039/b713501g

Scheme 1 Attempted CuAAC-mediated couplings of various monometallated alkyne substrates, [1MCl], with benzyl azide. a) Propargyl bromide, Et3N, toluene, reflux, 12 h, 60%; b) MCl, CH3OH, RT, 1 h; c) benzyl azide, 0.1 equiv. Cu(CH3CN)2PF6, 1.1 equiv. N,N-diisopropylethylamine (DIPEA), CH3Cl2-CH3OH (9:1), RT, 12 h.
The difference in lability of the metal ions allowed us to remove the Cu(ii) and selectively coordinate other metal ions at the vacant BPA site(s). Compound [3(mac-CrCl3(thread-ZnCl2)]) was then prepared. Selective removal of the Cu(ii) from [3(mac-CrCl3(thread-CuCl2)]) afforded the kinetically stable mono-metallated rotaxane [3(mac-CrCl3)] (Scheme 3, step c). [3(mac-CrCl3)] was then complexed with ZnCl2 to produce the mixed-bis-metallated rotaxane complex [3(mac-CrCl3)(thread-ZnCl2)] (Scheme 3, step d). To the best of our knowledge, this is only the second example of a mixed-metal coordinated rotaxane.15 The protection of the BPA ligand with Cu(ii) or Cr(iii) (which could subsequently be reduced to labile Cu(ii) if it needed to be removed) makes it compatible with the CuAAC reaction and provides a general means of incorporating metal atoms or binding sites into organic structures via 'click' chemistry.

The diamagnetic complex [3(mac-ZnCl3)(thread-ZnCl2)] was amenable to structural investigation by 1H NMR spectroscopy. The partial 400 MHz 1H NMR spectra of the thread (4), demetallated rotaxane (3), and [3(mac-ZnCl3)(thread-ZnCl2)] in [D2]-DMF are shown in Fig. 1. The upfield shifts of the coincident fumaramide olefin protons (Hd and He) in the rotaxane relative to those of the free thread 4 are typical of benzylic amide macrocycle-based rotaxanes,13 resulting from shielding of the xylene rings. In addition to the appearance of resonances from the second BPA binding site (Hf, 8.7ppm), the distinctive triazole proton (H L ) signal is evident (Fig. 1b and 1c). In the spectrum of compound [3(mac-ZnCl3)(thread-ZnCl2)] (Fig. 1c) the BPA aromatic protons are shifted downfield relative to those in 3 (Fig. 1b) due to metal coordination. Although the fumaramide olefin signals become separated as their inequivalence is emphasised by the zinc coordination to one end of the thread (Fig. 1c), the metal complexation does not appear to significantly change the conformation or co-conformation adopted by the mechanically interlocked fragments.

In conclusion, we have outlined a transition metal tolerant CuAAC protocol for the synthesis of mono- and bis-metallated [2]rotaxanes using a simple alkyne-functionalised tridentate ligand and its metal complexes. Indeed the methodology should prove a useful general way of appending a metal ion or complex to an organic scaffold, even when it contains redox-active or kinetically labile metals or vacant ligand sites. The ability to generate homo- and hetero-metallated [2]rotaxanes should allow for the exploration of non-covalent distance-dependent properties (e.g. electronic, magnetic and photochemical) between metal centres.
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Notes and references


3 For a list of publications featuring 'click chemistry', the vast majority employing the CuAAC reaction, see: http://www.scripps.edu/chem/sharpless/click.html.


