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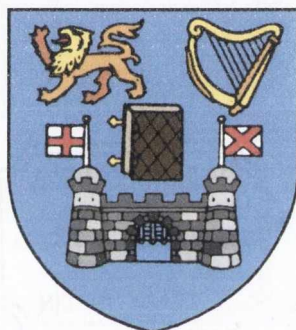
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Thio(Urea) Derivatives – From Anion Sensing and Recognition Towards Supramolecular Assemblies

Elaine M. Boyle

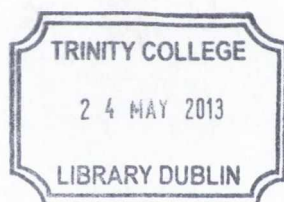
October 2012



**University of Dublin
Trinity College**

**Based on research carried out under the direction of
Prof. Thorfinnur Gunnlaugsson**

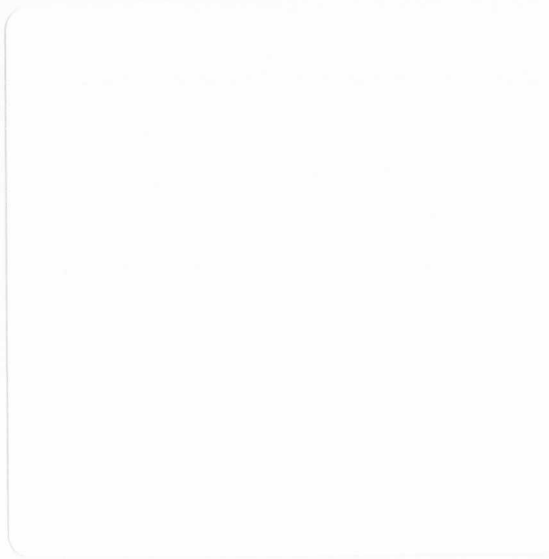
*A thesis submitted to the School of Chemistry,
University of Dublin, Trinity College for the degree of
Doctor of Philosophy*



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Elaine M. Hoyle

For My Family

“Nothing that’s worthwhile is ever easy...”

Nicholas Sparks

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Abstract

This thesis entitled “(Thio)Urea Derivatives – From Anion Sensing and Recognition to Supramolecular Assemblies consists of seven chapters.

Chapter 1 provides an introduction to the field of anion sensing using various organic scaffolds incorporating the thio(urea) moiety. The importance of anion sensing and the challenges associated with the development of receptors for the recognition of anions are detailed. An overview of the recent developments in the field is also given. The second half of the introduction focuses on the development of interlocked assemblies with a particular emphasis on rotaxanes. Finally, a summary of the work described in this thesis is outlined.

Chapter 2 describes the synthesis and characterisation of three novel thiourea-based anion receptors with an acetamide functionality for comparison with their urea counterparts, previously investigated in our group. The three receptors differ only in the position of the amide functionality relative to the hydrogen bonding urea moiety (being *para*, *meta*, and *ortho*). Their anion binding ability is examined using UV-Vis absorption and ^1H NMR spectroscopy. This simple modification has a significant effect on the anion recognition ability, the strength of the recognition process, and the stoichiometry for these sensors.

Chapter 3 outlines the ability of two thiourea functionalised Tröger's base derivatives, previously synthesised in the group, in the recognition of various anions. The binding affinities of these compounds are investigated by UV-Vis absorption and ^1H NMR titrations in $\text{DMSO-}d_6$. The two receptors, appended with CF_3 and NO_2 groups, bind various anions *via* different binding modes with the CF_3 derivative not showing any modulation of the UV-Vis absorption spectrum upon titration with H_2PO_4^- and SO_4^{2-} . In comparison, the NO_2 analogue displays large changes upon titration with these anions. A combination of H-bonding interactions and deprotonation occurs.

Chapter 4 outlines the synthesis of a series of novel tripodal receptors, possessing highly organised urea binding sites. Each receptor consists of three urea moieties, connected to a central C_{3v} symmetrical phenyl platform *via* amide linkage. The anion binding capabilities of the receptors were evaluated by ^1H NMR spectroscopy in $\text{DMSO-}d_6$. The binding interactions are all best fit to a 1:1 stoichiometry and, in some cases, mass spectrometry confirmed the presence of a 1:1 host:guest complex between the receptors and anions such as H_2PO_4^- and AcO^- . The synthesis of a second generation of these tripodal urea-based receptors containing a tertiary amide group is also described and the anion binding abilities examined by ^1H NMR spectroscopy and X-ray crystallography. The

formation of a highly organised cavity is confirmed by X-ray crystallography whereby anions such as SO_4^{2-} are encapsulated between two host molecules.

In Chapter 5, a series of Ru(II) complexes incorporating a urea binding site are described. The synthesis of each derivative is discussed, in addition to their photophysical properties. The spectroscopic effects of the Ru(II) excited state upon anion binding is detailed. It was found that the position of the urea moiety (*para* vs. *meta*) played a very important role in the binding of anions such as F^- and SO_4^{2-} .

Chapter 6 discusses the attempted synthesis of urea-based rotaxane, whereby an anionic thread was designed to H-bond to a urea functionalised macrocycle. A small library of molecules with terminal olefin groups were synthesised and characterised. Ring closing metathesis (RCM) using Grubbs' catalyst afforded the macrocyclic analogues and the anion binding ability of both acyclic and cyclic derivatives evaluated by ^1H NMR spectroscopy. The synthesis of a thread containing a benzoate moiety, suitable for H-bonding to the urea component was then undertaken and attempted formation of interlocked molecules such as catenanes *via* anion templation and a rotaxane attempted.

Finally, Chapter 7 outlines the experimental parameters used, and presents the synthesis and characterisation of the compounds discussed within this Thesis. Subsequently, literature references are provided, followed by the Appendices, which provides spectroscopic and titration data to support work described in the main text.

Abbreviations

Å	ångström (1×10^{-10} m)
Abs	absorbance
ADP	adenosine diphosphate
AMP	adenosine monophosphate
ATP	adenosine triphosphate
a.u.	arbitrary units
AuNP	gold nanoparticles
br	broad
<i>bpy</i>	bipyridine
conc.	concentrated
cyclen	1,4,7,10-tetraazacyclododecane
δ	chemical shift
d	doublet
dd	doublet of doublets
dt	doublet of triplets
DCM	dichloromethane
DMF	<i>N,N</i> -dimethylformamide
DMAP	4(<i>N,N</i> -dimethylamino)pyridine
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
ϵ	molar extinction coefficient
equiv.	equivalents
EDC·HCl	1-ethyl-3-(3-diemthylaminopropyl)carbodiimide
ES	electrospray
ESMS	electrospray mass spectrometry
EtOAc	ethyl Acetate
EtOH	ethanol
G	unspecified guest
H	unspecified host
hr	hours
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
h ν	energy

Hz	Hertz
IC	internal conversion
ICT	internal charge transfer
IR	infra red
ISC	intersystem crossing
<i>J</i>	coupling constant (expressed in Hz)
λ	wavelength
L	unspecified ligand
LMWG	low molecular weight gelator
Ln	lanthanide
m	multiplet
MALDI-ToF	matrix assisted laser desorption ionisation - time of flight
MeCN	acetonitrile
MeOH	methanol
mins	minute
MLCT	metal to ligand charge transfer
m.p.	melting point
<i>m/z</i>	mass to charge ratio
nm	nanometre
naph	naphthalimide ring
NMR	nuclear magnetic resonance
Pd/C	palladium on carbon catalyst
PET	photoinduced electron transfer
pH	$-\log[\text{H}_3\text{O}^+]$
<i>phen</i>	1,10-phenanthroline
$\text{p}K_a$	$-\log[K_a]$ where K_a is the acidity constant
ppm	parts per million
qt	quaternary
q	quartet
RF	radio frequency
room temp.	room temperature
s	singlet
t	triplet
TBA	tetra <i>n</i> -butylammonium
TLC	thin layer chromatography

TMS	tetramethylsilane
UV-Vis	ultra violet-visible
ν	frequency

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Chapter 1

Introduction

1. Introduction

Anions play an important role in a range of chemical, biological and environmental processes. Consequently the recognition of anions and the design and synthesis of different receptors for the detection of various anions has attracted much interest in the field of supramolecular chemistry.^{1,2} Supramolecular chemistry refers to the area of chemistry that focuses on the non-covalent bonding interactions of molecules, such as H-bonds, π - π -stacking interactions, electrostatic and van der Waals forces, hydrophobic effects or even metal–ligand bonds.^{3,4} Since its beginnings, over four decades ago, this field has evolved into an exceptionally dynamic and interdisciplinary area and has fuelled major advances at the frontiers of chemistry with areas such as the natural sciences, physics, materials science and engineering. Applications include molecular recognition, development of receptors and sensors, interlocked assemblies, *i.e.* rotaxanes and catenanes and their potential to act as sophisticated nanoscale electronic and mechanical devices and materials.⁵ This thesis will focus on the development of thio(urea)-based anion sensors utilising H-bonding interactions and the use of this interaction in the design and synthesis towards interlocked assemblies such as rotaxanes and catenanes. A number of approaches have been employed to enhance both anion binding ability and selectivity, mainly involving the use of various organic scaffolds and functional groups. This chapter will look to introduce the various topics discussed in this thesis, beginning with a brief discussion of sensing and the challenges of anion recognition. This will be followed by a description of the different types of anion receptor, along with a discussion of relevant examples from the literature.

1.1 Sensors

Sensors, in general, are devices that signal the presence of either matter or energy; reversibly and in real time.⁶ In supramolecular chemistry, a sensor is defined as a receptor that interacts with an analyte producing a detectable change in a signal.⁷ Receptors specifically designed for sensing purposes are generally called *chemosensors*.⁸ Chemosensors should have non-invasive and non-destructive properties and offer a method of obtaining real-time, on-line information.

1.1.1 Chemosensors

Generally, the principles behind chemical sensing have involved the design of small simple molecules that specifically identify a single ion or a molecular species in a competitive

media in a reversible manner in a given concentration range (for continuous monitoring the need for reversibility is a necessity, however in the case of once-off measurements, *e.g.* analysis of blood, such reversibility is not essential).⁹ Typically there are three main groups of analyte for which these sensors are designed to detect:

- cationic (*e.g.* metal ions such as Na^+ and K^+)
- anionic (*e.g.* halide ions, AcO^-)
- zwitterions, *i.e.* an overall net charge of zero (*e.g.* amino acids)

Information at the molecular level is then amplified to a macroscopic level and consequently can open the door to the determination (qualitative or quantitative) of certain guests, which naturally depends on the method of detection (*e.g.* electrochemical techniques, luminescence techniques).⁸ Consequently chemosensors are usually categorised by their target and their mechanism of signal transduction. The development of chemosensors is particularly important for use in:

- (i) industry (for monitoring chemical processes, pollution *etc.*)
- (ii) diagnostic and therapeutic medicine (critical care analysis, electrolyte analysis) and biotechnology
- (iii) environmental monitoring.¹⁰

1.2 Anion Sensing

Anion coordination chemistry has attracted growing attention in supramolecular chemistry due to the essential roles that anions play in biology, medicine, catalysis, and environmental science. The topic has its roots in work carried out in the late 1960s, when Park and Simmons reported the first bicyclic diammonium ion-derived synthetic organic ligands capable of halide complexation.¹¹ Although the field made little progress over the next few decades, in comparison to that of cation recognition, nowadays extensive research efforts are dedicated to the design and development of simple and sensitive chemosensors for anions.¹²

1.2.1 The Importance of Anion Sensing

Anions are ubiquitous throughout biological systems. They are carriers of genetic information (DNA is a polyanion) and the majority of biological structures such as neurotransmitters, enzymes substrates and co-factors and nucleic acids are anionic.¹³

Many other biological processes depend on the presence or transport of anions, *e.g.* blood pressure regulation, metabolism maintenance and the acid base balance within the body are all dependant on chloride.¹⁵ Iodine is necessary for the synthesis of thyroid hormones and thyroid gland functions¹⁶, while phosphate is involved in bone formation¹⁷. Molecular recognition of phosphate anions is crucial to a myriad of other biological processes involving gene regulation, metabolism, antibiotic resistance, signal transduction, *etc.*¹⁸ Pyrophosphate is a biologically important target because it is the product of ATP hydrolysis under cellular conditions, and the detection of pyrophosphate is being investigated as a real-time DNA sequencing method.¹⁹ Fluoride has received a lot of attention because of its importance in dental care and osteoporosis. Conversely an excess of fluoride can compromise the immune system and it is also the product formed upon hydrolysis of the nerve agent sarin gas.²⁰ Sulfate is involved in activation and detoxification of a variety of endogenous and exogenous substances such as steroids, neurotransmitters, and bile acids, while sulfate conjugation is essential for the biosynthesis of a large number of structural proteins.²¹

Anions are also increasingly important for many industrial processes, as well as in agriculture. Thus, the detrimental affects of anions are also a matter of environmental concern. The overuse of phosphate in agricultural fertilisers has led to the eutrophication of rivers and waterways, while excess nitrates from fertilisers are also toxic to many aquatic species.²² Pertechnetate production during reprocessing of nuclear fuel and its subsequent discharge into the seas and oceans is another example.²³ Therefore, there is a critical need to develop anion sensors for complex media such as in blood or serum, cells, soil, freshwater, *etc.* However, the complex nature of anions (in comparison to many cations) must be accounted for when designing anion-selective and sensitive luminescent or colorimetric probes.

1.2.2 Challenges in Anion Sensing

The design and synthesis of anion receptors is, on the whole quite challenging and a number of factors are attributed to this. By definition all anions, except AlH_4^- , B^- and *closo*- $\text{B}_{12}\text{H}_{12}^{2-}$, have lone pairs of electrons. They possess high Lewis basicity, an important feature that may add directionality to the system and thus render it sensitive to the spatial arrangement and orientation of binding groups. Anions are larger than isoelectronic cations and therefore have a lower charge-to-radius ratio (Table 1.1), resulting in less effective electrostatic binding compared to the smaller cation.²⁴

Table 1.1: Difference in the radii of typical isoelectric anions and cations in octahedral environments.

Cations	r (Å)	Anions	r (Å)	Δr (Å)
Na ⁺	1.16	F ⁻	1.19	0.03
K ⁺	1.52	Cl ⁻	1.67	0.15
Rb ⁺	1.66	Br ⁻	1.82	0.16
Cs ⁺	1.81	I ⁻	2.06	0.25

Anions also exhibit a wide range of geometries, illustrated in Figure 1.1. Consequently superior designs are required to make receptors complementary to their anionic guest, although this can also offer a useful property in controlling the selectivity of the receptor. Furthermore anions may be pH sensitive (becoming protonated at low pH and so losing their negative charge) so receptors must function within the pH window of their target anion. Finally solvent effects are also a key feature in controlling anion binding strength and selectivity.²⁵

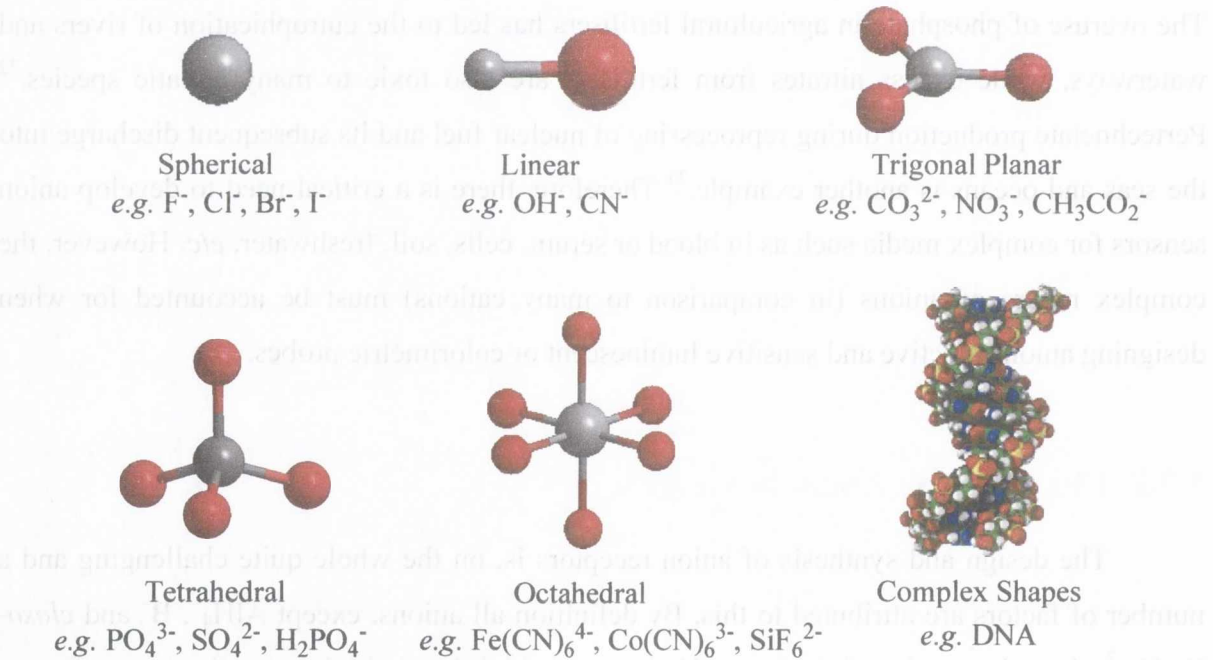


Figure 1.1: The structural variety of anions.

A potential anion receptor must effectively compete with the solvent environment in which the anion-recognition event occurs. In organic solvents, it is not so difficult to capture and detect anions because the solvation energy is relatively small and electrostatic interactions operate effectively. However, in aqueous solvents, which are relevant to biological applications, it is very difficult to recognise anions because of the strong hydration.²⁶ For

example, aprotic solvents would be the media of choice for a charge neutral receptor with ion-dipole interactions but if the receptor is positively charged then it is possible to use protic solvents.

1.3 Methods of Observing Host-Anion Interactions

Once the chemosensor has recognised the target anion, the anion binding process can then be studied using a range of techniques. These include various types of spectroscopy, *i.e.* UV-Vis absorption spectroscopy, luminescence, ^1H Nuclear Magnetic Resonance (NMR) spectroscopy, electrochemical responses or optical sensing, *i.e.* colorimetric or “naked eye” sensors. Each of these methods examines a separate part of the binding process and/or overall equilibrium, whilst operating over different sensitivity ranges, for example 10^{-5} M for UV-Vis or as low as 10^{-12} M for fluorescence spectroscopy and 10^{-3} M for NMR. Even though it is not as sensitive as luminescence techniques, ^1H NMR can still provide valuable information about the changing environment of various acidic protons, thus offering information about the interaction of receptor and guest. However, in terms of supramolecular devices, fluorescence detection offers distinct advantages, *i.e.* high selectivity and sensitivity, in the design of molecular sensors and has been exploited in numerous examples of chemical and analytical applications.²⁷

1.4 Types of Anion Receptors

Two strategies of anion recognition have been mostly developed to date, one based on cationic ligands such as polyammonium, guanidinium, quaternary ammonium and Lewis acids as the anion binding site.²⁸ More recently, metal-based receptors have been established as a class of anion receptors that provide some important advantages over purely organic hosts by combining the structural and functional properties of metal centres with the recognition capabilities of organic ligands.²⁹

A second type of receptor based on charge neutral ligands such as amides, ureas, thioureas, calix[4]pyrroles and related ligands have also been the focus of many design strategies.¹² The latter have been shown to have high affinities and selectivities for anionic guests.³⁰ The classification of anion receptors on the basis of the nature of the interaction is summarised in Figure 1.2.

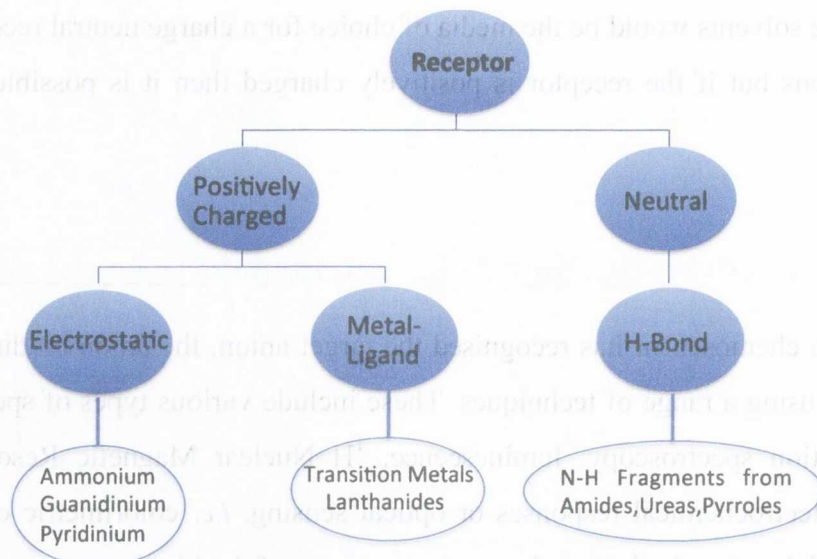


Figure 1.2: Electrical state of anion receptors and the nature of the anion receptor interaction.

1.4.1 Positively-charged Anion Receptors

Anion recognition has largely been achieved by using charged host molecules – the earliest synthetic anion receptor systems were comprised of ammonium-based cryptand-like receptors capable of encapsulating halide anions¹¹. Other metal free receptors include guanidinium-based³¹, ammonium-based³² and pyridinium-based receptors³³, however positively charged receptors can also be metal-coordinated receptors.³⁴ If robust inert metal centres are employed, the resulting complex can be investigated as an anion receptor without the need to take into account any competition for metal coordination between the ligands and the target anion.

1.4.2 Charge-Neutral Anion Receptors

Currently, the focus has been on the development of electro-neutral receptors that bind *via* weaker H-bonding. Specifically, the receptor must act as an H-bond donor and the anion as an H-bond acceptor. The first synthesised neutral anion receptor had a cage structure with the N–H groups directed into the centre of the cavity, in which the small spherical fluoride anion could be included.³⁵ Among neutral H-bond donor groups used to bind anions are amides, pyrroles, indoles, ureas, thioureas and carbamides.³⁶ The focus of this thesis, however, will only be on (thio)urea based receptors with the following sections firstly giving an overview of the (thio)urea functionality and thereafter detailing receptors of this type.

1.4.3 Urea and Thiourea

In 1828, Friedrich Wöhler synthesised urea, demolishing the generally accepted “vitalistic” belief that only living organisms could produce organic substances.³⁷ Subsequently, urea and its derivatives have played important roles in science and life. Since the pioneering work of Wilcox³⁸ and Hamilton³⁹ that showed urea moieties can act as appropriate binding sites for anions, in particular oxoanions such as AcO^- , a variety of receptors containing a (thio)urea subunit have been developed and applied for anion complexation and sensing over the past two decades. The main characteristic of these derivatives, and a property that makes them quite multifunctional, is the acidity of their N-H protons. The anions form H-bonds with these protons and since the H-bond is directional, it allows the urea and thiourea to be more selective in its binding. Thiourea, however, is generally a much stronger acid than urea ($\text{p}K_{\text{A}} = 21.1$ and 26.9 , respectively in DMSO), thus it is expected that thiourea containing receptors establish stronger H-bond interactions and form more stable complexes with anions than their urea containing counterparts,⁴⁰ although this has not always been found to be the case.⁴¹ Urea and thioureas are known to form directed hydrogen bonds with spherical ions (*e.g.* halide ions), tetrahedral-shaped phosphate, and form particularly strong complexes with planar carboxylate anions.⁴²

1.4.4 Design Principles of (Thio)Urea Anion Receptors

When building an artificial receptor, as with the design of any supramolecular host system, consideration should be given to the specifics of the targeted anion. As such there have been many structural modifications to (thio)urea-containing receptors that have been attempted:

- (i) to increase the acidity of the (thio)ureido N-H protons by introducing electron-withdrawing substituent(s), *e.g.* $-\text{NO}_2$, $-\text{CF}_3$, *via* the mediation of a π -system such as a phenyl ring
- (ii) to include other interactions such as additional hydrogen bonding, through the introduction of N-H, O-H, pyrrole or indole groups, and electrostatic interactions, and/or
- (iii) to form a preorganised binding cleft/cavity using a rigid (*e.g.* calixarene) or flexible structural skeleton that leads to a binding environment with size/shape complementary for a given anion.

One of the most popular approaches in the design of receptor molecules involves covalently introducing binding sites and signalling subunits to the chemosensors. The photoinduced electron transfer (PET) system using the “fluorophore-spacer-receptor” format (Figure 1.3), developed for cations by de Silva *et al.*,⁴³ is one of the most common methods in the design of fluorescent sensors and switches. In general, a PET sensor comprises a receptor responsible for guest binding and a fluorophore moiety, which is the site of both the excitation and emission of light connected *via* a short spacer. Consequently, the sensitivity is directly related to the strength of the emission signal produced after complexation of the guest molecule by the receptor. The spacer should prevent $n \rightarrow \pi$ or $\pi \rightarrow \pi$ ground state interactions between the two components and so the only communication pathway should be in the form of electron transfer, *e.g.* in the excited state. Such chemosensors should show ideal PET behaviour upon ion recognition, *i.e.* only the quantum yield, intensity (Φ_F) and the fluorescence lifetimes are affected upon ion recognition.^{44,45}

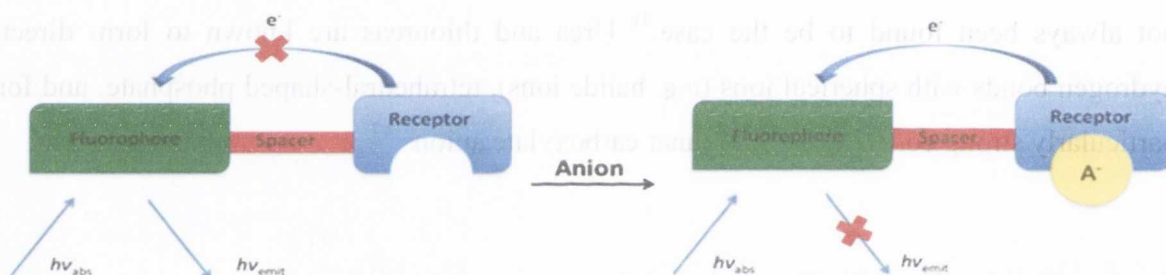


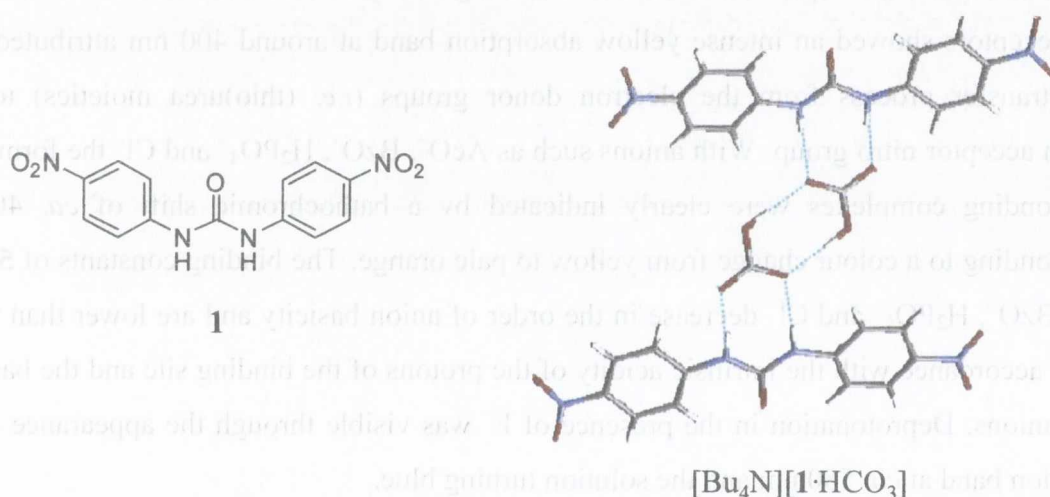
Figure 1.3: The fluorophore-spacer-receptor model of PET sensors based on the design of de Silva *et al.*, originally achieved with cations.⁴⁶

1.4.5 Urea and Thiourea as Anion Receptors

The seminal papers by Wilcox and Hamilton and the synthetic accessibility of urea and thioureas has allowed their inclusion in a wide variety of anion receptors of varying sophistication, with much effort still devoted to the synthesis and study of these effective anion receptors.⁴⁷

An initial example of a simple urea-based receptor and its interaction with various anions, studied by Fabbrizzi and co-workers, is receptor **1**.⁴⁸ In CH_3CN solution, the addition of oxoanions resulted in the formation of a new band at *ca.* 370 nm appearing in the UV-Vis spectrum with a concomitant decrease of the band at 345 nm, resulting in a bright yellow colour change of the solution. In the case of AcO^- , this well defined red-shift of the charge-transfer band is ascribed to the fact that, on interaction with the acetate ion, electron density is

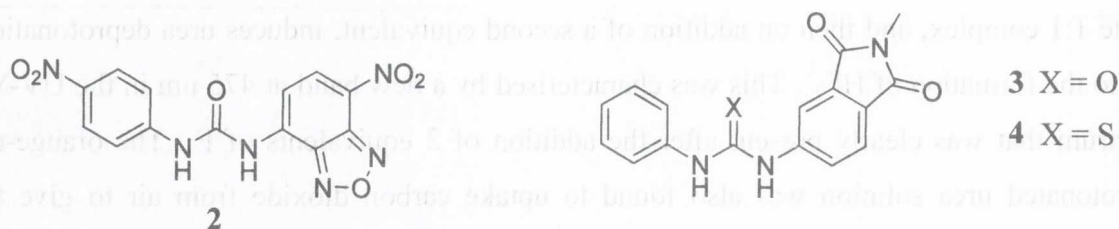
transferred on the urea moiety, which makes the intensity of the dipole increase and shifts the charge-transfer band to a longer wavelength. Monitoring these spectral changes allowed the association constants to be determined quantitatively, whose stability decreases with the decreasing basicity of the anion ($\text{AcO}^- > \text{BzO}^- > \text{H}_2\text{PO}_4^- > \text{NO}_2^- > \text{HSO}_4^- > \text{NO}_3^-$). On the other hand, the F^- ion first establishes a hydrogen-bonding interaction with **1** to give the most stable 1:1 complex, and then on addition of a second equivalent, induces urea deprotonation, due to the formation of HF_2^- . This was characterised by a new band at 475 nm in the UV-Vis spectrum that was clearly present after the addition of 2 equivalents of F^- . The orange-red deprotonated urea solution was also found to uptake carbon dioxide from air to give the tetrabutylammonium (TBA) salt of the hydrogencarbonate H-bond complex, $[\text{Bu}_4\text{N}][\text{1}\cdot\text{HCO}_3^-]$ whose crystal and molecular structures were determined.



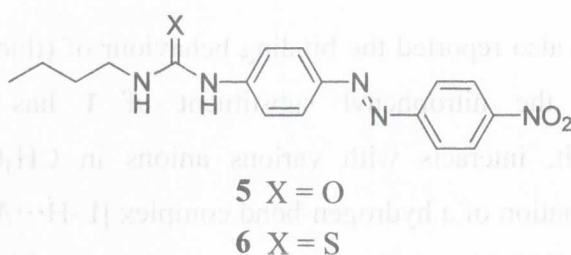
The same group have also reported the binding behaviour of (thio)urea receptors **2-4**.^{40,49} Receptor **2**, in which the nitrophenyl substituent of **1** has been replaced by a nitrobenzofurazan subunit, interacts with various anions in CH_3CN , according to two consecutive steps: 1) formation of a hydrogen-bond complex $[\text{L}\cdot\text{H}\cdots\text{A}]^-$ and 2) deprotonation of $\text{L}\cdot\text{H}$ to give L^- and $[\text{HA}_2]^-$, as shown by spectrophotometric and ^1H NMR titration experiments. The second step arises with more basic anions, such as F^- and H_2PO_4^- .

Receptors **3** and **4** contain a phthalimide substituent, a classical chromophore, appended at one nitrogen atom of the (thio)urea subunit, in order to provide an optical signal for reporting on the receptor–anion interaction. In line with the previous two receptors, **1** and **2**, both derivatives **3** and **4** formed H-bond complexes with various oxoanions. However, it was found that the stability of the 1:1 H-bonding complex strictly relates to the acidity of the $-\text{NH}$ protons in the receptor and the basicity of the anions. Again, deprotonation of the

(thio)ureido–NHs occurs in the presence of an excess amount of highly basic anions, typically F^- , which is characterised by the appearance of a new and substantially red-shifted absorption band and a drastic solution colour change. It was also found that the more acidic thiourea derivative **4** was much more readily deprotonated than the less acidic urea analogue **3**.

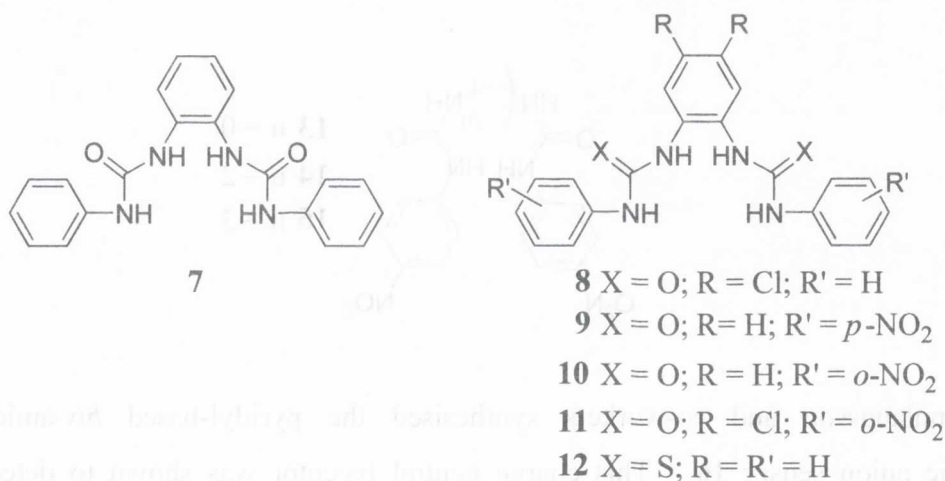


Receptors **5** and **6**, reported by Marínez-Máñez and co-workers in collaboration with Rurack, also allow a comparison of the anion binding ability of urea and thiourea.⁵⁰ Both azo-based receptors showed an intense yellow absorption band at around 400 nm attributed to a charge-transfer process from the electron donor groups (*i.e.* (thio)urea moieties) to the electron acceptor nitro group. With anions such as AcO^- , BzO^- , $H_2PO_4^-$ and Cl^- the formation of H-bonding complexes were clearly indicated by a bathochromic shift of *ca.* 40 nm corresponding to a colour change from yellow to pale orange. The binding constants of **5** with AcO^- , BzO^- , $H_2PO_4^-$ and Cl^- decrease in the order of anion basicity and are lower than those of **6**, in accordance with the intrinsic acidity of the protons of the binding site and the basicity of the anions. Deprotonation in the presence of F^- was visible through the appearance of an absorption band at *ca.* 580 nm and the solution turning blue.



The thiourea derivative, **6**, was also determined to be a sensor of carbon dioxide. The blue colour change of the solution, occurring upon deprotonation of the thiourea unit by F^- , could be maintained if the solution was kept under argon. However, if left open to the air the mixture turned yellow due to dissolution of carbon dioxide in the solution. The authors conclude, through 1H NMR studies that the thiourea moiety is hydrogen-bonding to HCO_3^- , formed through a reaction between traces of water and carbon dioxide in the presence of basic fluoride.

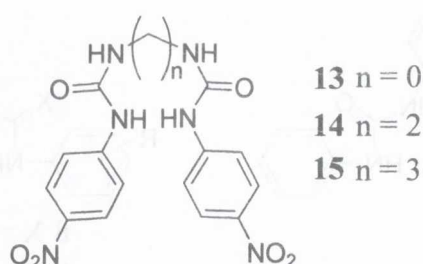
Gale and co-workers have developed a series of anion receptors based upon an *ortho*-phenylenediamine core, **7-12**.^{51,52} Receptor **7** was found to show selectivity for carboxylates. In the solid state, an X-ray crystal structure revealed that the receptor forms four hydrogen bonds to a bound benzoate anion. By attaching electron-withdrawing groups to the central and pendant aryl groups of the bis-urea skeleton the work was extended to increase the affinity for anions in DMSO-*d*₆/0.5% water solution. Receptor **8**, bearing a dichloro-functionalised central aryl group, displayed significantly enhanced anion affinities relative to compound **7**, with the largest relative change in association constant observed for H₂PO₄[−], which increased by a factor of 6.4 compared to AcO[−] which increased by a factor of 2.5. The anion stability constant values obtained for compounds **9** and **10**, where the electron withdrawing nitro group was appended *para*- and *ortho*- to the pendant phenyl rings, however were only slightly higher than those observed for compound **7** in the case of **9** and actually lower in the case of **10**. The relative reduction in the affinities for the observed anions remained fairly constant, indicating that the presence of the nitro groups was not altering the selectivity of the bis-urea skeleton. Following ¹H NMR investigations, the authors suggest that an increase in acidity on the central ring in compound **8** leads to higher stability constants, possibly due to a higher degree of preorganisation occurring in this system as compared to compounds **7** and **9**.



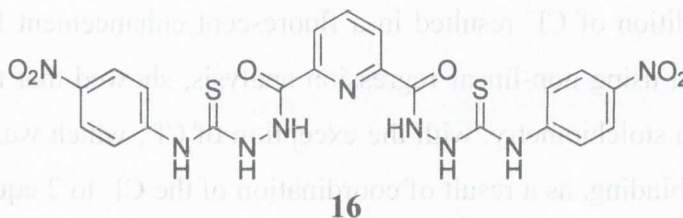
In order to increase the observed association constants further, both the *ortho*-positioned nitro group on the pendant aryl rings and the 4,5-dichloro functionalised central ring were combined to afford compound **11**. This led to an increase in stability constants, especially with H₂PO₄[−]. However in the case of AcO[−], the acidity of the urea protons was increased to such a degree that the behaviour may be indicative of deprotonation as was observed in the ¹H NMR titration, a process that was accompanied by a colour change from yellow to red. A bis-thiourea receptor, **12** was also investigated as to whether it would exhibit

similar behaviour to that displayed by the bis-urea, **7**. Unexpectedly, receptor **12** showed lower binding constants with carboxylates, by almost one order of magnitude, than those seen for receptor **7**. The larger sulfur atom in **12** that distorts the shape of the binding site was assumed to be responsible.

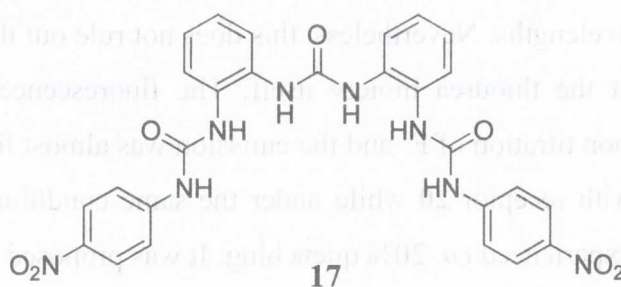
Lin and co-workers found the distance between two urea fragments significantly impacted the anion binding abilities of a series of receptors.⁵³ Studies using UV-Vis absorption and ¹H NMR spectroscopies found that **13** was an excellent sensor of F⁻ while **14** was sensitive to H₂PO₄⁻. Furthermore, the recognition process was also accompanied by distinct colour changes, allowing the receptors to function as colorimetric sensors. Receptor **15**, however, could not distinguish any of the anions investigated. The authors conclude the steric configuration of **13** is suited to the small spherical halide while **14** geometrically matches that of the tetrahedral H₂PO₄⁻. The longer chain of receptor **15** results in the two urea fragments being too far away to have selectivity for the anions investigated. When two or more urea moieties are attached to an organic scaffold, their relative positions are, to a large extent, constrained in space. Steric recognition of a targeted anion will be achieved only when the urea groups are constrained such that they have a strong interaction with the targeted anion and weakened interactions with competing anions.⁵⁴



Gunnlaugsson and co-workers synthesised the pyridyl-based *bis*-amidithiourea colorimetric anion sensor **16**.⁵⁵ This charge neutral receptor was shown to detect various anions in both DMSO and 4:1 DMSO-H₂O solutions where the anion recognition was visible to the naked eye. Significantly, **16** was able to clearly distinguish between AMP over ADP or ATP in water, with the solution going from colourless to yellow (even at low concentrations). Using UV-Vis absorption and NMR spectroscopy, the nature of the anion receptor interaction was determined and it was demonstrated that these colorimetric changes were due to the formation of either H-bonding complexes or deprotonation between the anions and **16**, or a combination of both. Sensor **16** is the first example of such a charge neutral colorimetric anion sensor that detects phosphate anions in (mixed) aqueous media.

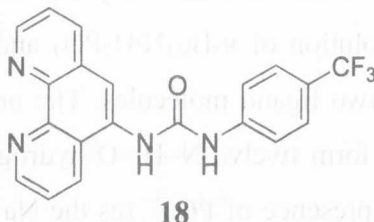


Tris-urea receptor, **17**, has recently been reported by Wu and co-workers for the complexation of tetrahedral oxoanions such as H_2PO_4^- and SO_4^{2-} .⁵⁶ Single crystals, obtained from a DMSO/25% water solution of $n\text{-Bu}_4\text{N}\cdot\text{H}_2\text{PO}_4$ and **17**, revealed deprotonation of the anion when coordinated by two ligand molecules. The urea groups chelate the anion on the edge of the tetrahedron and form twelve $\text{N-H}\cdots\text{O}$ hydrogen bonds. The ^1H NMR studies in $\text{DMSO-}d_6$ /25% water in the presence of PO_4^{3-} (as the Na^+ salt) and Et_3N show the same 2:1 (host:guest) stoichiometry in solution. The addition of H_3PO_4 or HClO_4 results in proton transfer to the coordinated anion and, subsequently, complex dissociation was observed. Extended NMR studies show that this process was reversible upon addition of Et_3N . The same reversible binding of the deprotonated anion was observed for SO_4^{2-} , whilst HSO_4^- was not coordinated. Stability constants of the formed complexes were determined using UV-Vis titration experiments in DMSO/25% water. Fitting of the titration curve to a 2:1 (host:guest) model results in $\log K_{1:1} = 5.0$ and $\log K_{2:1} = 12.0$ for PO_4^{3-} (as the Na^+ salt). Job plot experiments reveal a 1:1 binding mode of SO_4^{2-} (as the TBA salt) under comparable experimental conditions with the binding constant in this case calculated to be $\log K_a = 4.72$.



The high sensitivity of fluorescence detection has also resulted in (thio)urea groups being incorporated into a variety of fluorescent sensors for anions. The 1,10-phenanthroline (*phen*)-based urea ligand **18**, reported by dos Santos *et al.*⁵⁷, was synthesised and the effect that anion coordination had on the photophysical properties of the *phen* moiety was investigated. The absorption spectrum of **18** showed only minor changes upon anion recognition, however, upon addition of AcO^- , H_2PO_4^- and F^- to a CH_3CN solution of **18**, the fluorescence emission was considerably quenched (98%, 94% and 93% respectively).

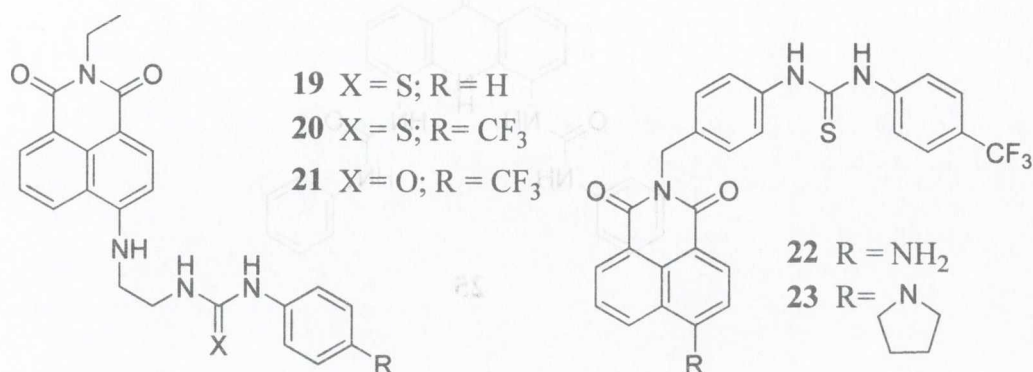
Interestingly, the addition of Cl^- resulted in a fluorescent enhancement for **18**. Fitting these fluorescence changes, using non-linear regression analysis, showed that these anions bind to **18** in 1:1 (host:guest) stoichiometry, with the exception of Cl^- , which was shown to give rise to 1:1 as well as 1:2 binding, as a result of coordination of the Cl^- to 2 equivalents of **18**. This was the first example of a simple charge neutral fluorescent sensor, which showed good selectivity for Cl^- .



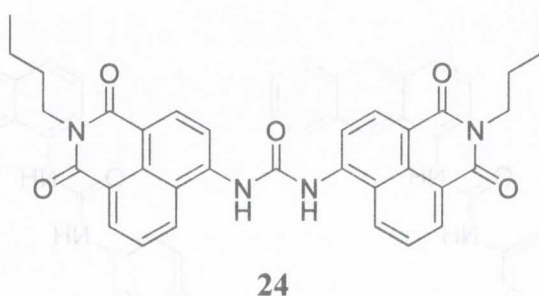
The (thio)urea series of receptors **19–21** developed by Gunnlaugsson and co-workers bearing a naphthalimide fluorophore represent good examples of PET fluorescent sensors.⁵⁸ Absorption and fluorescence titrations were carried out in DMSO with AcO^- , H_2PO_4^- , F^- , Cl^- and Br^- . Only minor changes in the absorption spectra were observed upon titration with the various anions, except in the case of F^- . In the case of receptor **19** and F^- significant changes were observed in the UV-Vis spectrum, where the absorption was shifted to longer wavelength with the formation of a clear isosbestic point at 452 nm and some changes also observed at shorter wavelengths. These changes, however, do not support deprotonation of the 4-amino moiety, within this concentration range, as this would give rise to a shift of the ICT band towards longer wavelengths. Nevertheless, this does not rule out the possibility that such deprotonation occurs at the thiourea moiety itself. The fluorescence emission of **19** was dramatically affected upon titration of F^- and the emission was almost fully quenched. Similar results were obtained with receptor **20** while under the same conditions the fluorescence of urea analogue **21** only experienced *ca.* 20% quenching. It was proposed that the F^- recognition initially occurs by hydrogen bonding of the anion to the (thio)urea moiety of the receptor, followed by deprotonation which makes the receptor highly electron rich and enhances the PET quenching of the naphthalimide excited state.

Receptors **22** and **23**, also developed by Gunnlaugsson and co-workers, differ from **19–21** in the position at which the *N*-arylthiourea moiety is linked to the fluorophore.⁵⁹ An enhanced PET-type fluorescence quenching was also observed upon anion binding to its thiourea moiety. Both H_2PO_4^- and F^- also gave rise to quenching of fluorescence in **22** and **23**, where for **22** the emission was quenched by *ca.* 60% and 95% for H_2PO_4^- and F^- ,

respectively. These results demonstrate that the emission can be quenched from either ‘end’ of the naphthalimide moiety; a phenomenon not normally seen for naphthalimide-based sensors for cations.

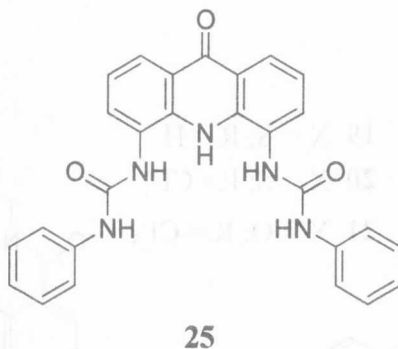


Fabrizzi and co-workers have also utilised the naphthalimide chromophore for the chromogenic detection of anions.⁶⁰ Attachment of two naphthalimide units *via* a urea linker yielded chemosensor **24**, which proved effective for the detection of carboxylic acids as determined through colorimetric and fluorescent experiments. Anion-triggered deprotonation was also observed. In DMSO anions such as AcO[−] and H₂PO₄[−] were found to induce a single deprotonation of the receptor, whilst more basic anions such as F[−] and OH[−] induced double deprotonation. Owing to its charge transfer transition, naphthalimide is a yellow colour. The deprotonated species were shown to be red (LH[−]) and blue (L^{2−}) respectively.

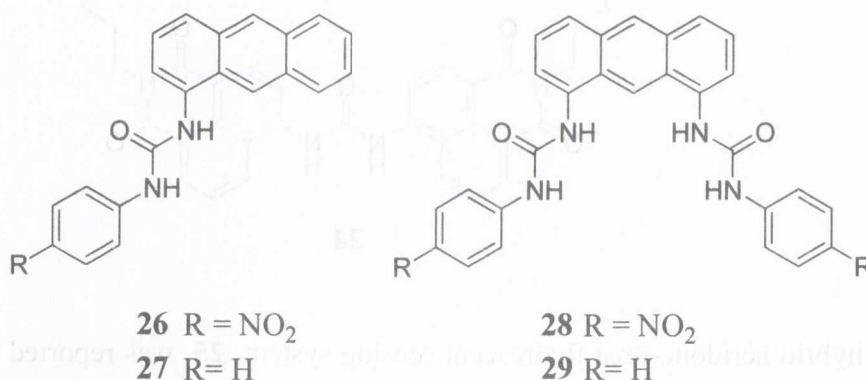


A hybrid acridone-urea fluorescent sensing system, **25**, was reported by Gale and co-workers where dramatic quenching of the receptor emission was observed upon the addition of H₂PO₄[−] (as the TBA salt) in an CH₃CN-DMSO solution (94:6).⁶¹ Addition of Cl[−] led to a much smaller decrease in emission intensity, while the addition of AcO[−] and BzO[−] produced a slight increase in intensity. The emission enhancement observed with the latter anions was attributed to deprotonation of the receptor. The binding of H₂PO₄[−] was probed by ¹H NMR

spectroscopy in DMSO-*d*₆/0.5% water. Interestingly, a combination of supramolecular complexation, deprotonation, and receptor tautomerization was concluded from these studies.

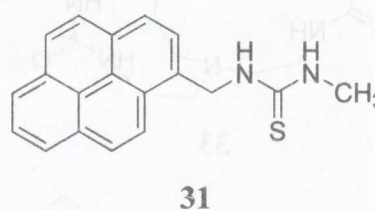
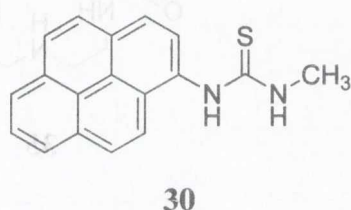


Yoon, Kim, and co-workers studied the anion binding of phenylurea-anthracene receptors **26-29**.⁶² These receptors were found to be highly selective for F⁻ and HP₂O₇³⁻ over H₂PO₄⁻, Cl⁻, Br⁻, I⁻, HSO₄⁻, and AcO⁻ in DMSO. The nitro derivative receptors **26** and **28** and the interactions with TBA anion salts were followed using UV-Vis absorption spectroscopy, whereas the binding behaviour of receptors **27** and **29** were followed through fluorescence spectroscopy. Using the latter method, binding constants of $2.6 \times 10^3 \text{ M}^{-1}$ and $6.0 \times 10^3 \text{ M}^{-1}$ were determined for the interaction of HP₂O₇³⁻ with receptors **27** and **29**, respectively. Interestingly, the ¹H NMR spectroscopic studies of receptors **26** and **28** in DMSO-*d*₆ led to the conclusion that, in addition to the urea units, the 9-H atom of anthracene played a role in mediating the anion-binding process.

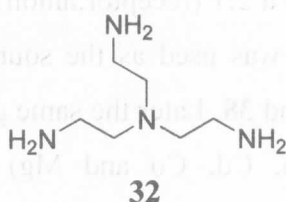


Fluorescent pyrene receptors have also been found to be effective for anion recognition. Receptor **30**, with the pyrene unit directly conjugated to the thiourea moiety displayed a significant emission increase upon the addition of AcO⁻ and H₂PO₄⁻ (as TBA salts) in CH₃CN.⁶³ A binding constant of $8.70 \times 10^2 \text{ M}^{-1}$ was determined for the H₂PO₄⁻ complex, but a strong preference for AcO⁻ was also reported. Receptor **31** was designed to

include a spacer between the recognition and the reporter subunits.⁶⁴ This sensor displayed a quenching of the pyrene monomer emission followed by intramolecular exciplex formation between the thiourea and the pyrene in the presence of anions. The quenching was attributed to the increased electron-donating ability of the thiourea when complexed to an anion. On the basis of the magnitude of this effect, it was concluded that receptor **31** binds AcO^- more effectively than either H_2PO_4^- or Cl^- . A binding constant of $5.2 \times 10^3 \text{ M}^{-1}$ was reported for the H_2PO_4^- complex in acetone. However, the use of different solvents in these studies prevents a direct comparison between the receptors.

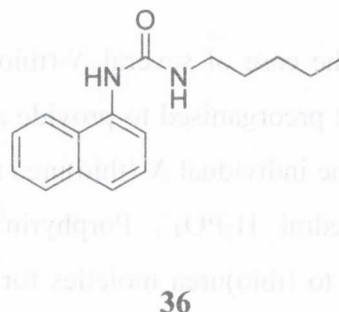
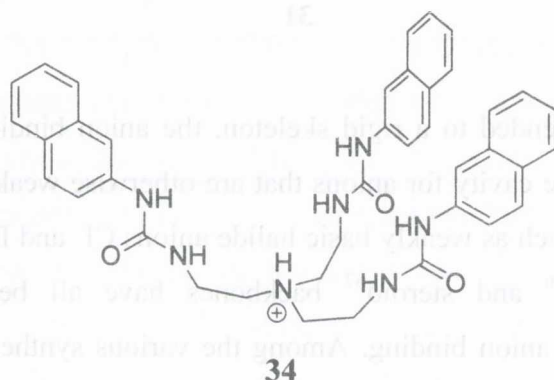
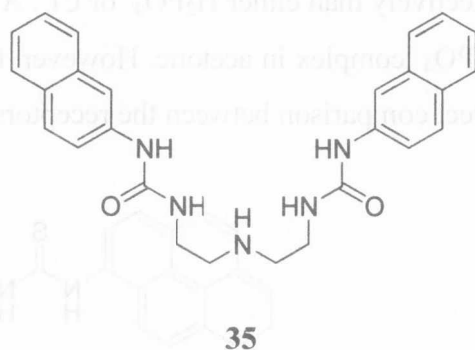
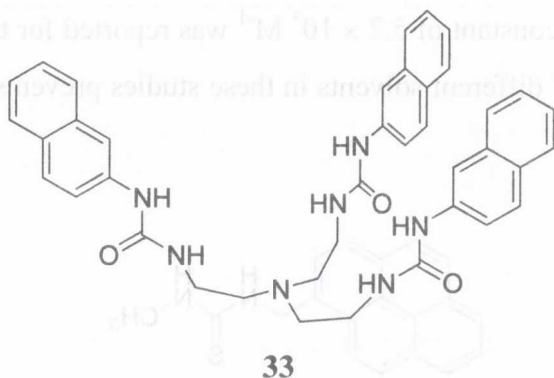


In the case of several *N*-(thio)ureas appended to a rigid skeleton, the anion binding sites can be preorganised to provide a favourable cavity for anions that are otherwise weakly bound by the individual *N*-(thio)urea receptor, such as weakly basic halide anions Cl^- and Br^- and tetrahedral H_2PO_4^- . Porphyrin⁶⁵, cyclen⁶⁶ and steroid⁶⁷ backbones have all been conjugated to (thio)urea moieties for improved anion binding. Among the various synthetic hosts, trigonal receptors based on the prototype of tri(2-aminoethyl)amine (*tren*), **32**, have been of special interest for their preorganised C_3 -symmetry anion binding geometry.⁶⁸



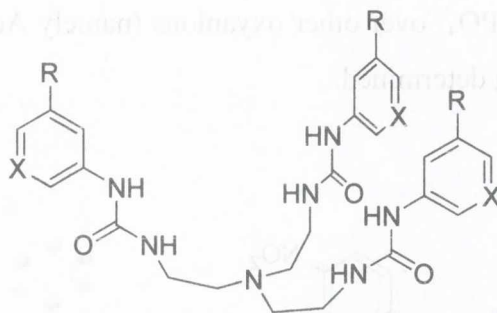
A number of acyclic anion receptors of this type have been designed by attaching various functional groups, and some have indeed shown very good binding ability. An early example of this type of receptor are the tripodal hosts, **33** and **34** containing naphthylurea groups developed by Wu and co-workers.⁶⁹ The anion coordination and fluorescence properties of **33** and **34** were compared with the model compounds **35** and **36**. A significant enhancement in the fluorescence intensity was observed upon the addition of TBA anion salts in DMF, with the derived association constant for H_2PO_4^- determined to be $1.1 \times 10^4 \text{ M}^{-1}$. It was also found that for HSO_4^- the binding was significantly weaker, and halide anions such as Br^- or I^-

displayed no spectral changes. On the basis of control studies, the authors suggested that the spectral response and the strong binding affinity resulted from protonation of the central tertiary amine, an event that would lead to a reduction in the PET quenching and a strong charge-charge association within the resultant complex ($33 \cdot \text{H}_2\text{PO}_4^-$).



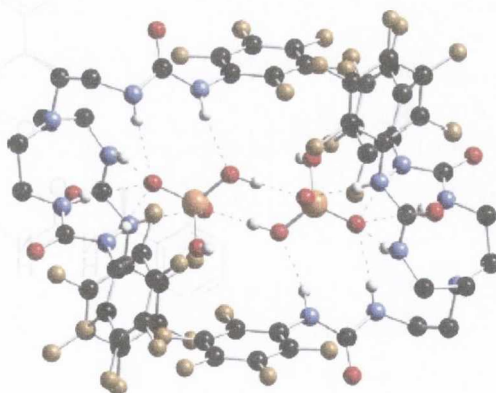
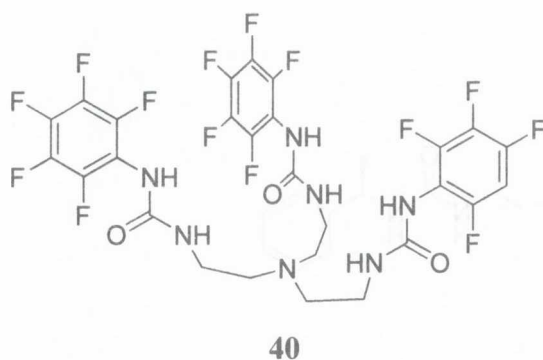
Costelcan *et al.*⁷⁰ showed that *tren*-based receptors **37** and **38** could coordinatively saturate SO_4^{2-} binding the anions in a 2:1 (receptor:anion) stoichiometry *via* twelve hydrogen bonds. In this work, silver sulfate was used as the source of the anion resulting in a 1-D coordination polymer with compound **38**. Later the same group crystallised receptor **39** with a variety of MSO_4 salts ($\text{M} = \text{Zn}, \text{Cd}, \text{Co}$ and Mg) from 1:1 $\text{H}_2\text{O}/\text{MeOH}$ solution.⁷¹ Interestingly, this compound could be used to selectively crystallise SO_4^{2-} from highly competitive mixtures of aqueous solutions.

Wu, Janiak Yang and co-workers also studied receptor **38** and reported that the receptor assembles with metal sulfate salts MSO_4 ($\text{M} = \text{Mn}, \text{Zn}$) to afford supramolecular cages $[\text{SO}_4 \subset \text{L}_2]$ that encapsulates the SO_4^{2-} ion *via* multiple hydrogen bonds in a three-dimensional structure held by second-sphere coordination.⁷² Both ^1H NMR spectroscopy and negative-ion mode ESI-MS spectrometry revealed significantly strong SO_4^{2-} binding in solution.



- 37** R = H; X = CH
38 R = CN; X = CH
39 R = H; X = N

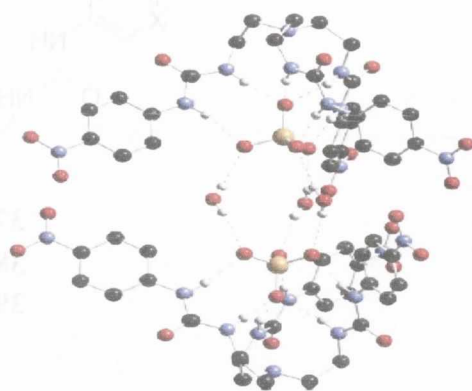
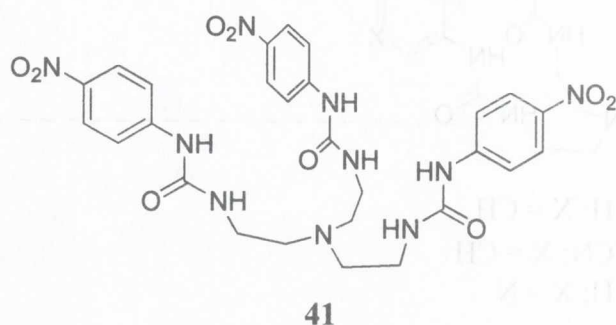
Ghosh and co-workers synthesised the pentafluorophenyl-substituted receptor **40**, which was designed to achieve high anion binding affinities through the inclusion of electron-withdrawing groups on the phenyl rings.⁷³ In fact, **40** was found to form a dimer complex with H_2PO_4^- where the dimer is encapsulated within the C_{3v} symmetrical cavity of the receptor, as determined by single crystal X-ray diffraction analysis. The $[\mathbf{40} \cdot \text{H}_2\text{PO}_4^-]$ dimer, shown below, is held in place by a combination of seven hydrogen bonds and two additional intermolecular anion- π interactions. The solution state binding properties of **40** and other oxyanions such as AcO^- , NO_3^- and perchlorate were investigated by ^1H NMR titrations in $\text{DMSO}-d_6$. It was found that H_2PO_4^- and AcO^- bind to **40** forming 1:1 complexes with $\log K = 5.52$ and 4.45, respectively.



$2[\mathbf{40} \cdot \text{H}_2\text{PO}_4^-]$

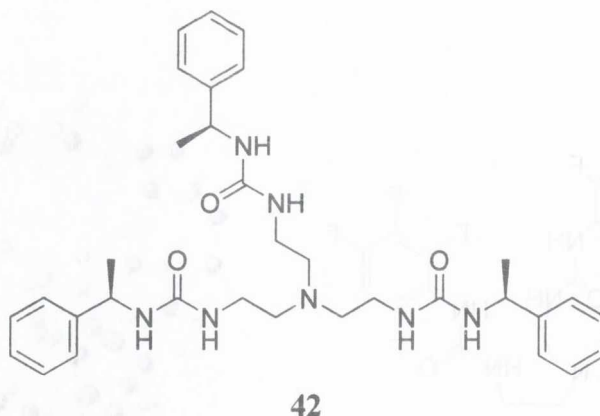
Tren-based tris-ureas containing electron-withdrawing groups have also been investigated by Das and Ganguly.⁷⁴ In this case receptor **41**, containing nitrophenyl chromophoric subunits, was shown to encapsulate a rugby ball-shaped $\text{SO}_4^{2-}\text{-H}_2\text{O-SO}_4^{2-}$ cluster in $\text{CH}_3\text{CN-H}_2\text{O}$ mixture (95:5 v/v), with the X-ray crystal structure shown below. In solution, UV-Vis titrations in $\text{CH}_3\text{CN-H}_2\text{O}$ (95:5 v/v) showed that receptor **41** interacted

strongly with tetrahedral H_2PO_4^- over other oxyanions (namely AcO^- , NO_3^- and perchlorate) with $\log K_a = 4.26 \text{ M}^{-1}$ being determined.



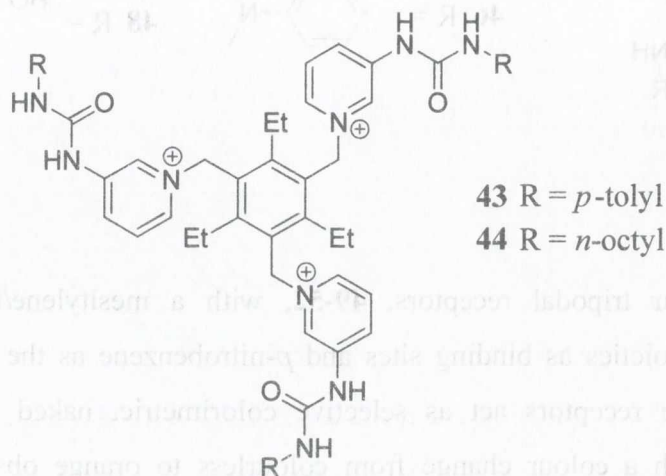
[41· SO_4^{2-} · H_2O · SO_4^{2-} ·41]

Steed and co-workers have done extensive work using tripodal receptor platforms.³³ One such example developed by this group is an enantiomerically pure tris-urea, **42**, which in addition to binding Cl^- anions, is able to act as a low molecular weight gelator (LMWG).⁷⁵ The self-association and anion interactions are in competition with the formation of the helical gel fibres partially inhibited by addition of Cl^- anions (a process which triggers full crystallisation of **42**).

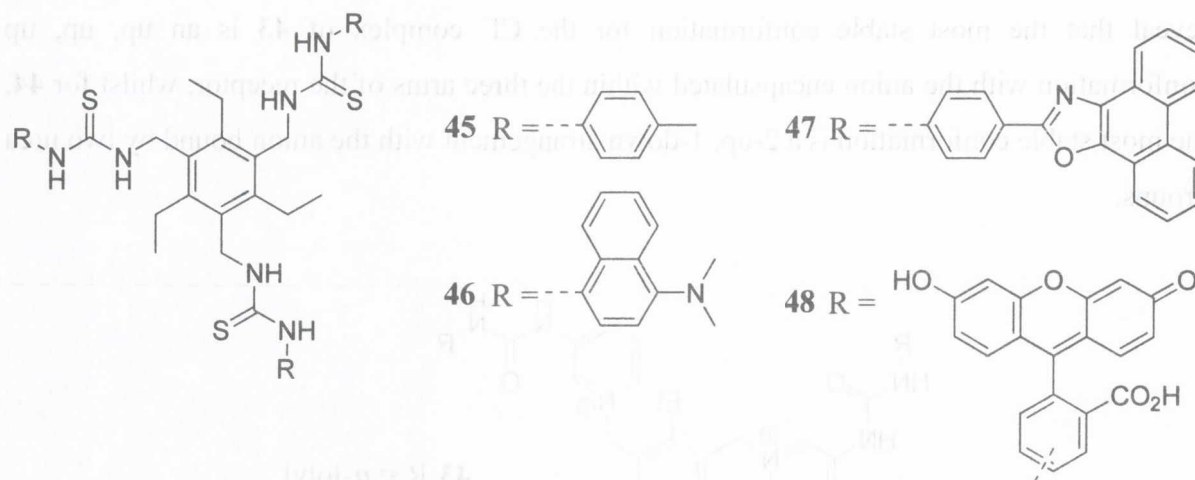


A more rigid and preorganised scaffold used in the design of tripodal anion receptors is the 1,3,5-substituted benzene subunit, the binding moieties of which in the 1,3,5-positions are directed to one face of the ring. Continuing their work on tripodal receptors for anions, Steed and co-workers reported a very elegant example of two tripodal tris-urea pyridinium-containing receptors **43** and **44** with *para*-tolyl or octyl substituents, respectively.⁷⁶ The association behaviour with anionic guests was studied using several methods including solid-state, ^1H NMR spectroscopic titrations (in $\text{DMSO}-d_6$) and computational studies. The studies

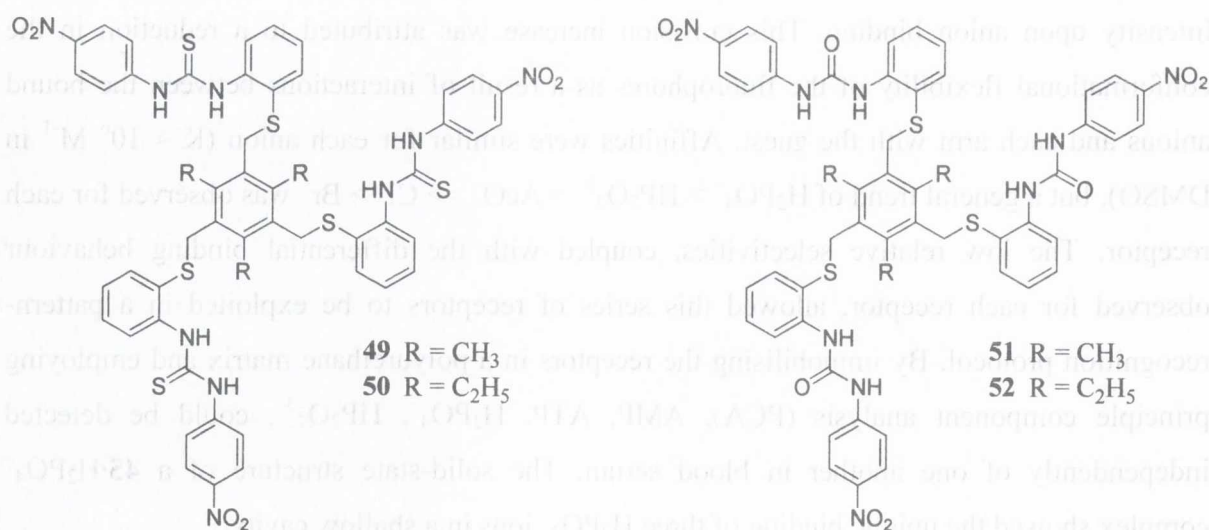
reveal that the most stable conformation for the Cl^- complex of **43** is an up, up, up conformation with the anion encapsulated within the three arms of the receptor, whilst for **44**, the most stable conformation is a 2-up, 1-down arrangement with the anion bound by two urea groups.



Anzenbacher and co-workers have synthesised a series of fluorophore tagged thiourea-based anion receptors, **45-48** and studied for the sensing of phosphates in blood serum.⁷⁷ All of the receptors in this series formed 1:1 complexes with anions (as TBA salts) according to ^1H NMR spectroscopic studies with **46-48** displaying an increase in the observed fluorescence intensity upon anion binding. This emission increase was attributed to a reduction in the conformational flexibility of the fluorophores as a result of interactions between the bound anions and each arm with the guest. Affinities were similar for each anion ($K \approx 10^6 \text{ M}^{-1}$ in DMSO), but a general trend of $\text{H}_2\text{PO}_4^- > \text{HP}_2\text{O}_7^{3-} > \text{AcO}^- \gg \text{Cl}^- > \text{Br}^-$ was observed for each receptor. The low relative selectivities, coupled with the differential binding behaviour observed for each receptor, allowed this series of receptors to be exploited in a pattern-recognition protocol. By immobilising the receptors in a polyurethane matrix and employing principle component analysis (PCA), AMP, ATP, H_2PO_4^- , $\text{HP}_2\text{O}_7^{3-}$, could be detected independently of one another in blood serum. The solid-state structure of a **45**· H_2PO_4^- complex showed the unique binding of three H_2PO_4^- ions in a shallow cavity.

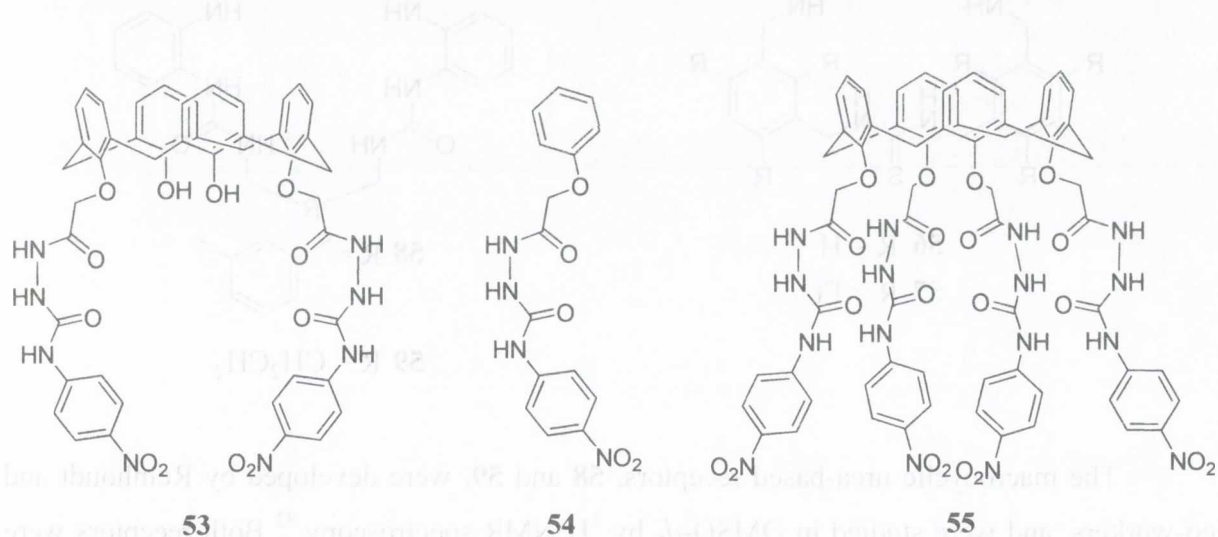


Recently, four tripodal receptors, **49-52**, with a mesitylene/triethylbenzene core bearing (thio)urea moieties as binding sites and *p*-nitrobenzene as the signalling unit have been reported.⁷⁸ The receptors act as selective colorimetric, naked eye sensors for the spherical F^- ion with a colour change from colourless to orange observed. The thiourea derivatives, **49** and **50** form stable 1:1 H-bonded complexes with F^- and to some extent with $H_2PO_4^-$, while the urea analogues **51** and **52** do not show any interaction at lower concentrations of F^- but at higher concentrations undergo completely reversible deprotonation, concomitant with a colorimetric change with the production of stable HF_2^- .



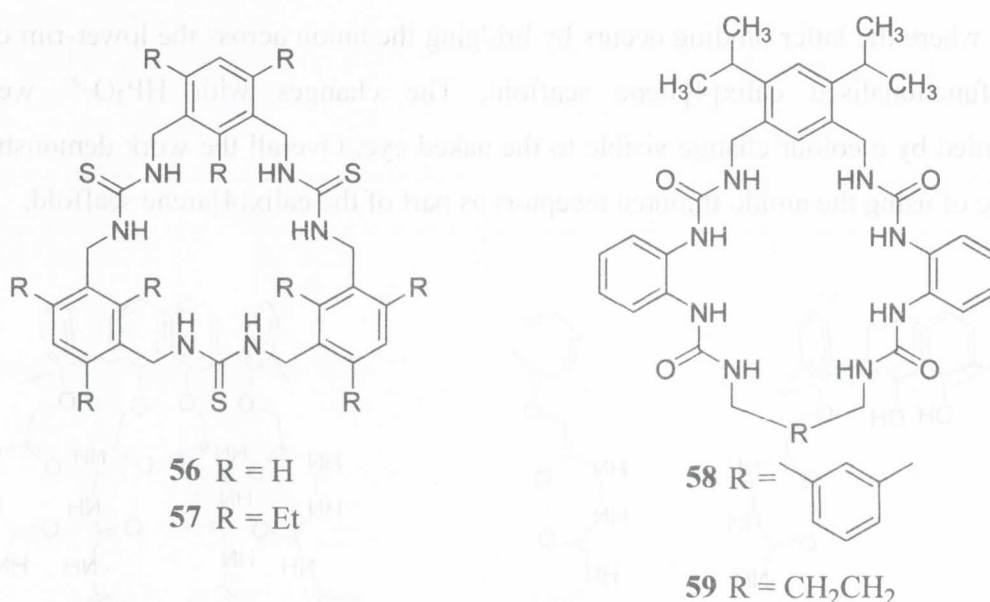
Macrocyclic anion receptors with multidentate (thio)urea units provide another kind of preorganisation of the anion binding sites into a cavity shape.⁴⁷ There are two classes of receptor in this category, namely (thio)ureas appended to macrocycles and macrocycles composed of (thio)urea moieties. In the former group calix[*n*]arenes are the most employed macrocycles since both the size and conformation can be varied.

Quinlan *et al.*⁷⁹ attached two amido-thiourea nitrobenzene moieties to the rim of a 1,3-disubstituted calix[4]arene scaffold, which afforded receptor **53**. A model compound, **54**, consisting of only the amido-thiourea nitrobenzene unit was also synthesised for comparison and the anion binding properties of both compounds were evaluated through absorption spectroscopy. Whilst both sensors gave rise to red shifts in their absorption spectra in the presence of anions such as AcO^- , the authors demonstrate that **53** can bind F^- in a 1:1 stoichiometry with concomitant colorimetric changes from yellow to purple, where the binding occurs through hydrogen bonding initially and deprotonation at higher F^- concentrations. It was also shown that a strong 1:1 binding is observed for H_2PO_4^- and $\text{HP}_2\text{O}_7^{3-}$, where the latter binding occurs by bridging the anion across the lower-rim cavity of the 1,3-functionalised calix[4]arene scaffold. The changes with $\text{HP}_2\text{O}_7^{3-}$ were also accompanied by a colour change visible to the naked eye. Overall the work demonstrates the advantage of using the amido thiourea receptors as part of the calix[4]arene scaffold.



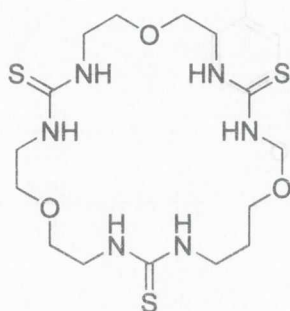
The work was later extended to incorporate four amido-thiourea nitrophenyl moieties in the calix[4]arene framework making receptor **55** symmetrical with a preorganised H-bonding cavity.⁸⁰ Sensor **55** shows highly selective and efficient binding with $\text{HP}_2\text{O}_7^{3-}$ and Br^- in a 1:1 stoichiometry. In the case of F^- and AcO^- , however, 2:1 complexes were formed and the preorganisation effect also lead to efficient binding of Cl^- . Sensor **55** was principally developed as a colorimetric naked-eye sensor for anions. This was indeed found to be the case for anions such as F^- and $\text{HP}_2\text{O}_7^{3-}$ where the colour changed from colourless to red, while for AcO^- the solution turned from colourless to light yellow, enabling the distinction of this anion. These changes were assigned to the disturbance in the ICT nature of the anion receptor, which gives rise to red shifts in the absorption spectra.

The tris-thiourea macrocyclic receptors **56** and **57** were investigated by Lee and Hong.⁸¹ Receptor **56** was reported to be selective for H_2PO_4^- over AcO^- and Cl^- (as the TBA salts), determined from ^1H NMR spectroscopic experiments carried out in $\text{DMSO}-d_6$. In contrast, receptor **57** was found to bind anions in order of basicity (*i.e.*, $\text{AcO}^- > \text{H}_2\text{PO}_4^- > \text{Cl}^-$). In the case of receptor **57**, binding constants were determined to be 2-fold higher for H_2PO_4^- and 15-fold higher for AcO^- than those reported with receptor **56**. This increase in binding affinity was attributed to increased preorganisation of the macrocyclic core in the case of the ethyl substituents.



The macrocyclic urea-based receptors, **58** and **59**, were developed by Reinhoudt and co-workers, and were studied in $\text{DMSO}-d_6$ by ^1H NMR spectroscopy.⁸² Both receptors were found to form 1:1 complexes with H_2PO_4^- via H-bonding interactions. Receptor **59**, with higher structural flexibility, demonstrated enhanced selectivity for H_2PO_4^- (binding constant of $4.0 \times 10^3 \text{ M}^{-1}$) over Cl^- (100-fold) compared to that of **58** (5-fold). On the basis of NMR experiments, the relatively low affinity for Cl^- displayed by these receptors was rationalised as being due to the fact that only the outside urea moieties can participate in chloride binding, whereas all four urea moieties can participate in H_2PO_4^- binding. The analogous cleft-like bis-urea receptors without the R bridge were also examined and showed differing binding stoichiometries for H_2PO_4^- and Cl^- . It was therefore determined that the size of the preorganised cavity in the macrocyclic derivatives **58** and **59** dictated the preference for the bound anions.

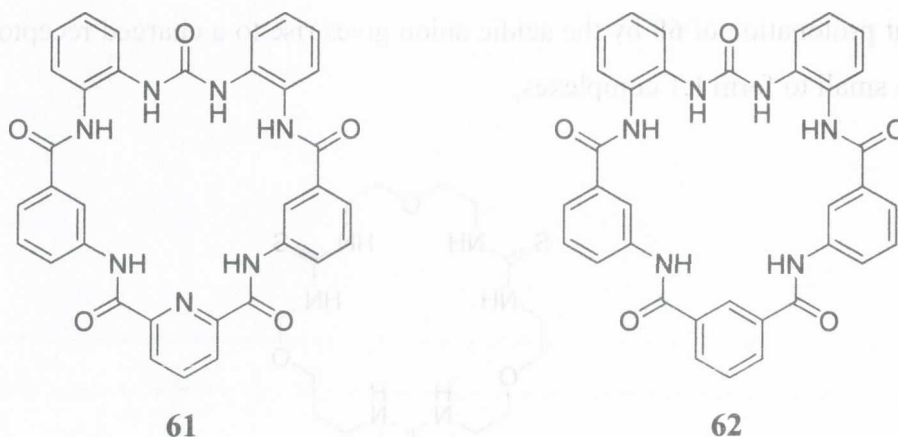
Herges, König, and co-workers later reported the anion binding properties of a thiourea macrocycle containing ether linkages, **60**.⁸³ ^1H NMR studies carried out in $\text{DMSO-}d_6$ led to the suggestion that this macrocycle bound a number of anions (added as the TBA salts) with varying stoichiometries. Complexes of 1:1 (receptor:anion) stoichiometry were indicated for NO_3^- , AcO^- , CN^- , Br^- , I^- and HSO_4^- , whereas 2:3, 2:1 and 1:2 complexes were found for SO_4^{2-} , H_2PO_4^- and Cl^- , respectively. The authors reason that in the case of HSO_4^- it is most likely that protonation of **60** by the acidic anion gives rise to a charged receptor, $\text{60}\cdot\text{H}^+$, while Cl^- is too small to form 1:1 complexes.

**60**

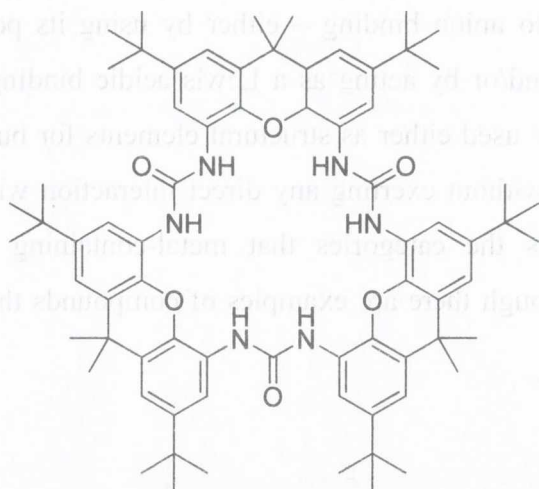
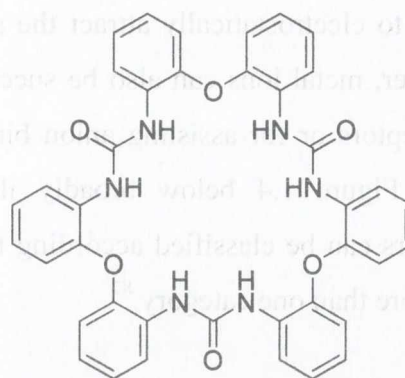
Gale and co-workers reported macrocyclic receptor **61**, which contains a 2,6-dicarboxamidopyridine group and a *N,N'*-diphenylurea moiety linked by two phenylamides, providing a convergent set of H-bond donors for anion complexation.⁸⁴ This compound showed high selectivity for carboxylate anions over H_2PO_4^- and Cl^- , binding AcO^- approximately 100 times more strongly than H_2PO_4^- both in $\text{DMSO-}d_6/0.5\%$ water and in $\text{DMSO-}d_6/5\%$ water solution. The binding mode proposed was that one oxygen atom of the carboxylate bound to the two ureido-NHs while the other oxygen atom bound to the 2,6-dicarboxamidopyridine-NHs. However, the analogous receptor without the phenylenediamine linker displayed a 1:2 host:guest binding stoichiometry with H_2PO_4^- and a high binding constant of $1.85 \times 10^5 \text{ M}^{-2}$ determined. Interestingly, crystals of **61** were grown by slow evaporation of a solution of the receptor in DMSO in the presence of TBAF. Rather than a fluoride complex, a mixed carbonate-fluoride complex was obtained with carbonate (presumably arising from CO_2 fixation by the fluoride solution) bound within the macrocyclic cavity and hydrated fluoride bound outside the macrocyclic cavity.

The isophthalamide containing receptor **62** was also investigated but was found to be unstable in solution and underwent hydrolysis after 1 hour in $\text{DMSO-}d_6$.⁸⁵ Additionally the receptor did not display the high carboxylate selectivity as exhibited by receptor **61**. In the presence of AcO^- smaller shifts of the amide group ^1H NMR resonances were observed than

in **61**, suggesting that the amides are not predisposed to form a convergent H-bonding array. The authors attribute this instability to the macrocycle adopting a twisted conformation that is prone to hydrolysis. Receptor **61** in contrast possesses a pyridine nitrogen atom that can accept H-bonds from the adjacent amide groups forcing the macrocycle to adopt a more planar conformation.



Böhmer *et al.*⁸⁶ have recently synthesised a class of macrocycles in which three urea subunits are linked by xanthene and/or diphenyl ether spacers. It was anticipated that the xanthene containing macrocycle **63** would be quite rigid, while macrocycle **64** should exhibit a higher degree of flexibility. The binding tendencies of these tris-urea macrocycles towards anions were investigated in CH₃CN through spectrophotometric titrations. Interestingly, this study revealed the existence of a significant counter-cation effect on the receptor–anion equilibria. In particular, Cl[−] was added both as a TBA salt and as [Na(2.2.2-crypt)]⁺ salt. The most relevant difference was observed for the formation of the 1:1 complex of **64** with Cl[−] when using the TBA salt, where $\log K = 6.0 \pm 0.1$, whereas, in the presence of the sodium cryptate cation, $\log K = 5.1 \pm 0.2$.

**63****64**

The crystal structure of the $[\text{Bu}_4\text{N}][\mathbf{64}\cdot\text{Cl}^-]$ salt complex was also determined and is shown below. It can be seen that Cl^- receives six H-bonds from the three urea subunits. Equilibrium studies showed that the flexible macrocycle **64** forms a 1:1 complex with Cl^- , which is 25-fold more stable than the rigid macrocycle **63** ($\log K = 6.0 \pm 0.1$ and 4.6 ± 0.2 , respectively, as TBA salts). This may reflect the ability of the flexible receptor **64** to place its N–H fragments in the most favourable positions for establishing H-bonds with Cl^- . Moreover, it was observed that upon addition of an excess of Cl^- the 1:2 complex $[\text{Cl}^-\cdots\text{L}\cdots\text{Cl}^-]^{2-}$ forms, when $\text{L} = \mathbf{64}$ ($\log K_2 = 5.5 \pm 0.3$), but not when $\text{L} = \mathbf{63}$. The different behaviour was ascribed to different degrees of flexibility of the two receptors; in particular **64** can spatially rearrange its urea subunits in order to interact with two Cl^- 's.

 $[\text{Bu}_4\text{N}][\mathbf{64}\cdot\text{Cl}^-]$

1.4.6 Metal-based Anion Receptors

Metal complexes play an important role in anion receptor chemistry.²⁹ The presence of a metal ion can introduce a range of advantageous physicochemical properties to this class of

receptor. The metal can contribute directly to anion binding – either by using its positive charge to electrostatically attract the anion and/or by acting as a Lewis acidic binding site. However, metal ions can also be successfully used either as structural elements for building up receptors or for assisting anion binding, without exerting any direct interaction with the anion. Figure 1.4 below broadly illustrates the categories that metal-containing anion receptors can be classified according to, although there are examples of compounds that fall into more than one category.⁸⁷

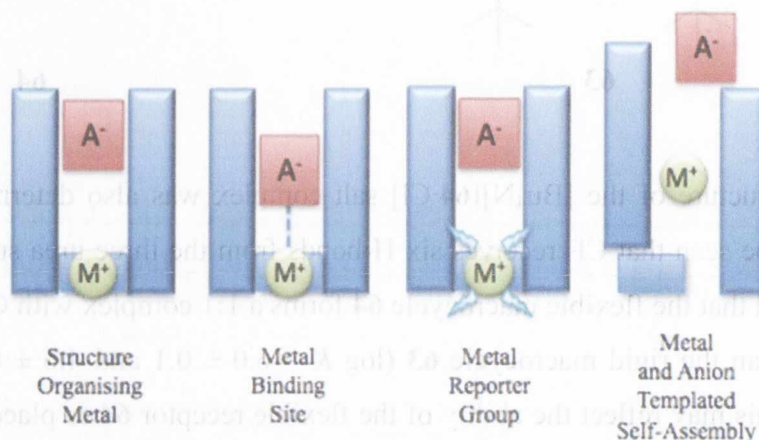
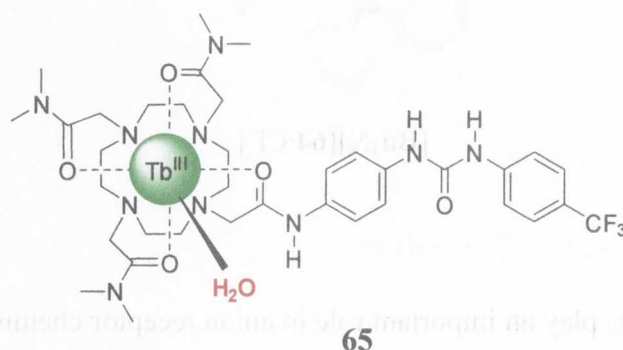
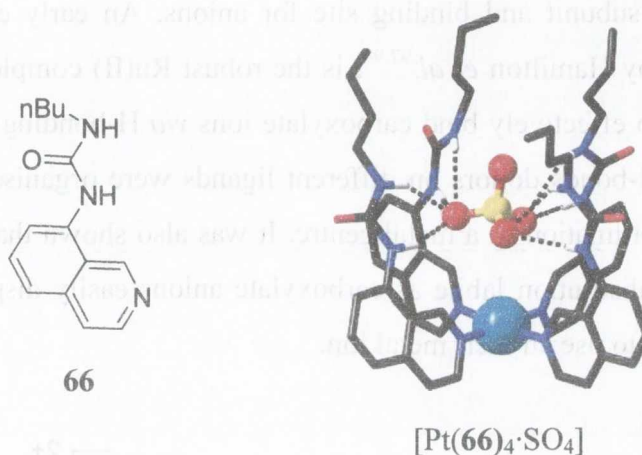


Figure 1.4: Classes of anion-binding metal complexes.

Metal ions, in the appropriate geometrical circumstances, can also improve the affinity of (thio)urea-based receptors toward anions.⁸⁸ By employing lanthanide metal coordination, Gunnlaugsson and co-workers developed a Tb^{3+} /diaryl-urea complex, **65**, that exhibited high anion affinity.⁸⁹ It was found that **65** displayed high selectivity for H_2PO_4^- in CH_3CN , however absorption titrations indicated that the anion binding was more complicated than a 1:1 stoichiometry. The high anion affinity was attributed to the neighbouring lanthanide ion, which acts as a strong Lewis acid to enhance the H-bonding tendency of the ureido $-\text{NH}$ protons.



The simple monodentate ligand **66** is based on an isoquinoline ring system and by coordinating four of these ligands to an inert Pt(II) centre, Loeb and Gale *et al.*⁹⁰ were able to arrange four urea functionalities into a single binding site. Strong 1:1 interactions were observed in solution for halides and symmetrical oxyanions, *e.g.* SO_4^{2-} , which likely involved surrounding the anion in a “cone” conformation. This was shown categorically by X-ray crystallography for the SO_4^{2-} ion, which demonstrated all eight N-H donors from the four urea moieties were organised so that they are directed to the anion which is nestled into the binding pocket.



Among metal-based luminescent systems ruthenium (Ru(II)) complexes are well known. No other metallic compounds, with the possible exception of ferrocene, show similar stability and flexibility. In particular, Ru(II) polypyridyl complexes have been investigated in perhaps greater detail than any other class of luminescent complexes.⁹¹ The following sections will, therefore, focus on the chemical and luminescent properties these complexes have to offer and their role in anion recognition and sensing.

1.4.7 Ru(II) Polypyridyl Complexes

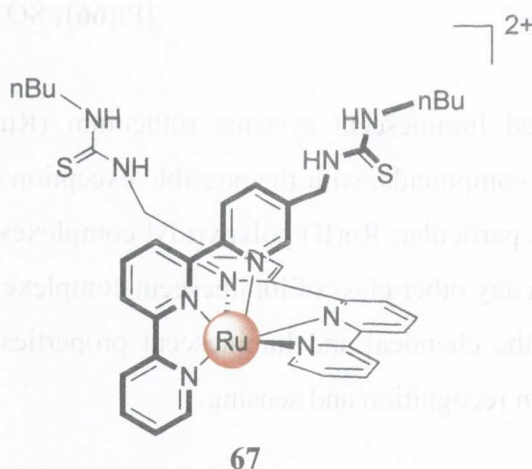
Ru(II) polypyridyl systems have been one of the most extensively investigated complexes due to their chemical stability, redox properties, excited state reactivity, and luminescent emission.⁹² The popularity of these compounds continues to be driven by the wide range of applications that Ru(II) polypyridyl systems find use in. They have long been employed as both spectroscopic probes and photoreactive reagents for DNA,⁹³ while also been used extensively in materials science, solar cells⁹⁴ and more recently in anion recognition.⁹⁵

When Ru(II) polypyridyl complexes are functionalised with H-bonding moieties (*e.g.* amides, ureas), an increase in the emission of the MLCT band is generally observed in the presence of anions. It has been proposed that the observed increase in emission is a consequence of the

bound anion serving to rigidify the receptor and thus inhibiting vibrational and rotational modes of non-radiative decay.⁹⁶ The binding affinities can be tuned quite dramatically through an appropriate choice of the spacer/bridging moieties.

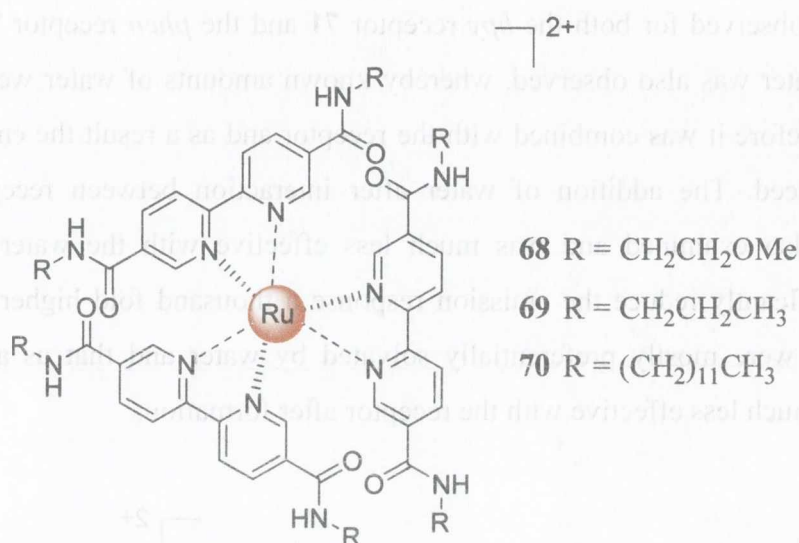
1.4.7.1 Luminescent Sensing of Anions by Ru(II) Polypyridyl-based Receptor Systems

The combination of a Ru(II) polypyridyl moiety and an appropriate ligand can provide an ideal signalling subunit and binding site for anions. An early example of this type of receptor, designed by Hamilton *et al.*^{97,98}, is the robust Ru(II) complex (as the PF₆⁻ salt) **67**, which was shown to effectively bind carboxylate ions *via* H-bonding to the thiourea protons. Thus, two sets of H-bonds donors on different ligands were organised into a single binding site due to their coordination to a metal centre. It was also shown that the Fe(II) analogue of this receptor was substitution labile as carboxylate anions easily displaced the *terpy* ligands reinforcing the need to use an inert metal ion.

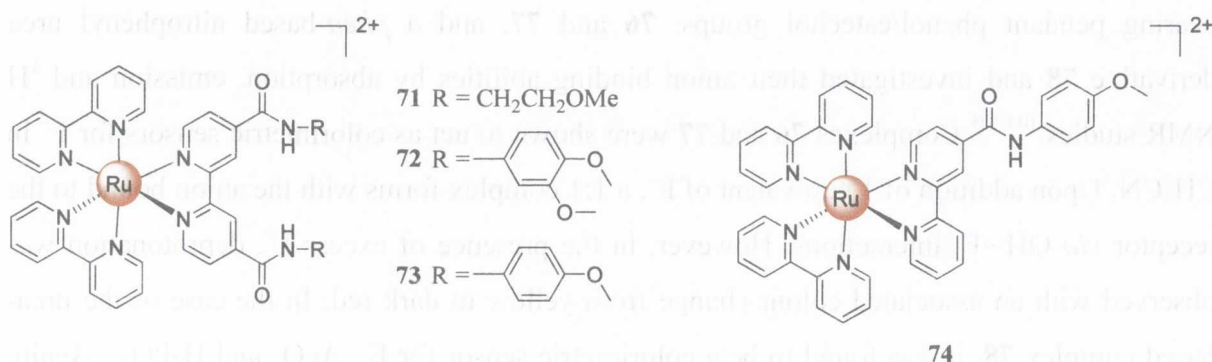


Tris(2,2'-bipyridyl)ruthenium(II), Ru(II)-(bpy)₃, is highly emissive and, when one of the *bpy* ligands is substituted by a chemical receptor, the fluorescence of the complex changes in the presence of specific analytes. Beer and co-workers have reported extensive studies on the anion binding properties of substituted Ru(II)-(bpy)₃ complexes through its incorporation into acyclic⁹⁹, macrocyclic¹⁰⁰ and calix[4]arene structural frameworks.¹⁰¹ Complexes **68-70**, where the *bpy* core is functionalised with amide groups provide two convergent anion binding sites.⁹⁹ The six amide moieties form two binding sites, as determined from the X-ray crystal structure of receptor **68** and Cl⁻. Association constants determined by UV-Vis absorption titrations reveal that log K_{1:1} = 7.47 and log K_{1:2} = 12.9 for Cl⁻ binding by **68** in 9:1 CH₂Cl₂-

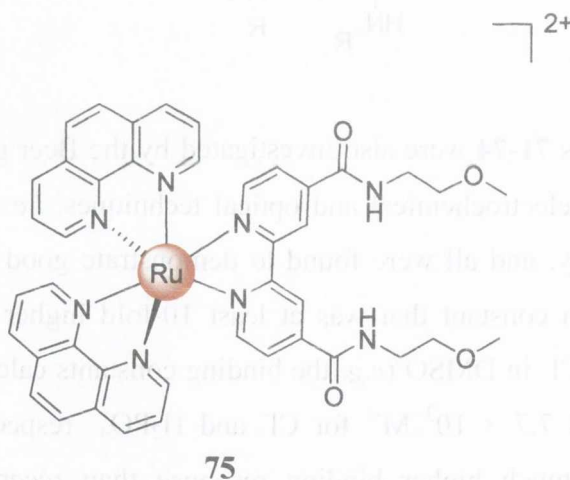
MeOH. The binding constants were all found to decrease as the MeOH fraction increased; however the selectivities were found to change. For example, in both 9:1 and 7:3 CH₂Cl₂-MeOH, the selectivity of complex **68** was found to follow the sequence Cl⁻ > NO₃⁻ > AcO⁻ while receptor **70** was found to follow a different pattern when the CH₂Cl₂-MeOH ratio was 1:1, namely NO₃⁻ > Cl⁻ > AcO⁻. This difference was rationalised in terms of solvation effects.



The response of receptors **71-74** were also investigated by the Beer group through the use of ¹H NMR spectroscopic, electrochemical and optical techniques, *i.e.* UV-Vis absorption and fluorescence spectroscopy, and all were found to demonstrate good selectivities for H₂PO₄⁻, displaying an association constant that was at least 10-fold higher than the corresponding association constant for Cl⁻ in DMSO (*e.g.* the binding constants calculated for compound **73** were $4.8 \times 10^2 \text{ M}^{-1}$ and $7.7 \times 10^3 \text{ M}^{-1}$ for Cl⁻ and H₂PO₄⁻ respectively).¹⁰² Interestingly, receptor **73** showed a much higher binding response than receptor **74**, illustrating the importance of multiple amide H-bonding interactions.

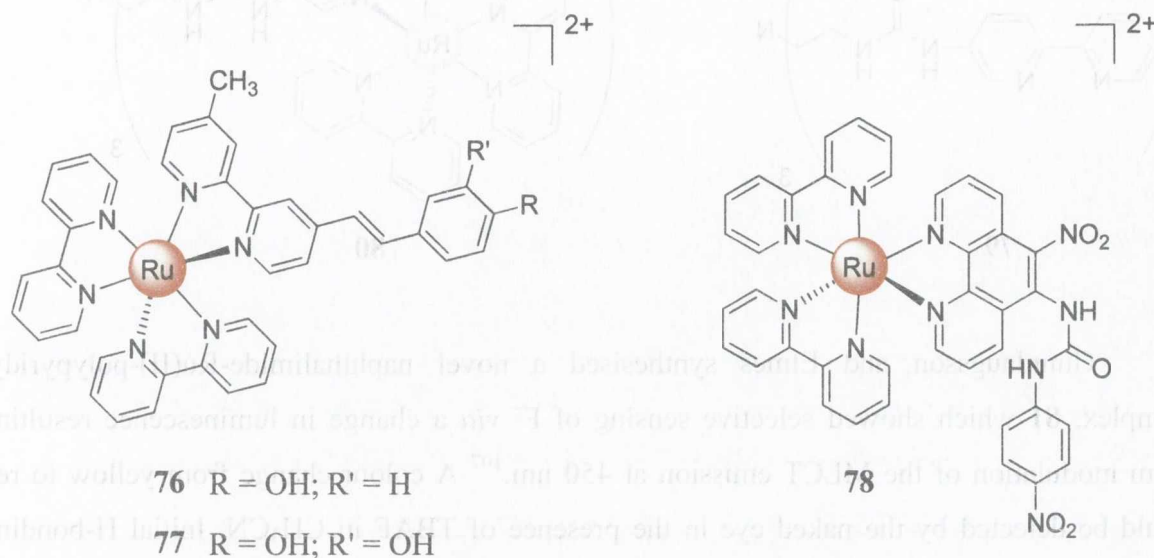


Receptors **68**, **71** and the *phen*-based complex **75** were also investigated by Vos and co-workers.¹⁰³ A comparison of the emission behaviour of receptors **68**, **71**, and **75** in the presence of H_2PO_4^- (as the TBA salt) in CH_3CN was studied. Emission intensity and lifetime increases were observed for all three receptors up to the point where 2.5 equivalents of H_2PO_4^- had been added. When greater quantities of anion were added, receptor **68** displayed an unexpected decrease in the emission intensity. Similar binding was, to a first approximation, observed for both the *bpy* receptor **71** and the *phen* receptor **75**. An extreme sensitivity to water was also observed, whereby known amounts of water were added to the anion solution before it was combined with the receptor and as a result the emission increase was much reduced. The addition of water after interaction between receptor and anion occurred was also examined and was much less effective with the water concentrations needed to significantly reduce the emission response a thousand fold higher. This indicates that the anions were mostly preferentially solvated by water and that as a result H-bond formation was much less effective with the receptor after formation.

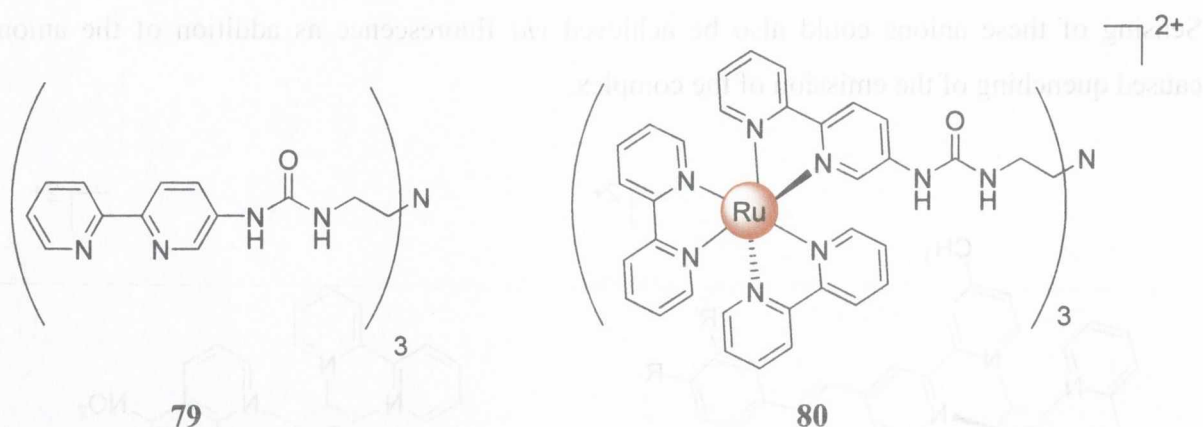


Das and co-workers have reported Ru(II) polypyridyl complexes (as the Cl^- salts) bearing pendant phenol/catechol groups, **76** and **77**, and a *phen*-based nitrophenyl urea derivative **78** and investigated their anion binding abilities by absorption, emission and ^1H NMR studies.^{104,105} Complexes **76** and **77** were shown to act as colorimetric sensors for F^- in CH_3CN . Upon addition of 1 equivalent of F^- , a 1:1 complex forms with the anion bound to the receptor *via* $\text{OH}\cdots\text{F}^-$ interactions. However, in the presence of excess F^- , deprotonation was observed with an associated colour change from yellow to dark red. In the case of the urea-based complex **78**, it was found to be a colorimetric sensor for F^- , AcO^- and H_2PO_4^- . Again, at low concentration of anions a 1:1 hydrogen-bonded adduct was observed in CH_3CN , however, at higher concentrations, classic Brønsted acid–base-type reactions prevailed.

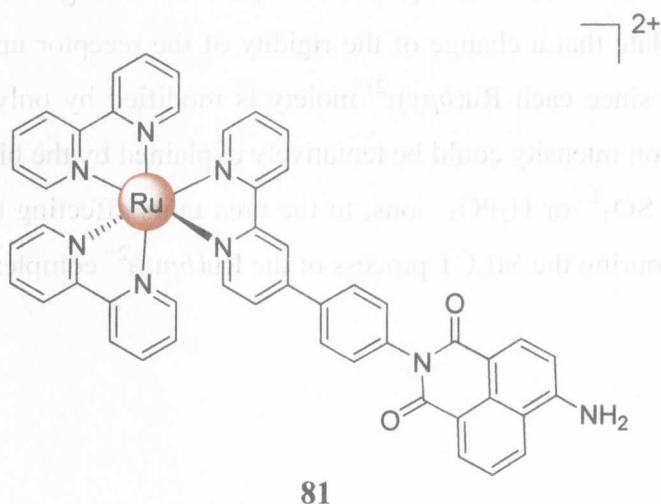
Sensing of these anions could also be achieved *via* fluorescence as addition of the anion caused quenching of the emission of the complex.



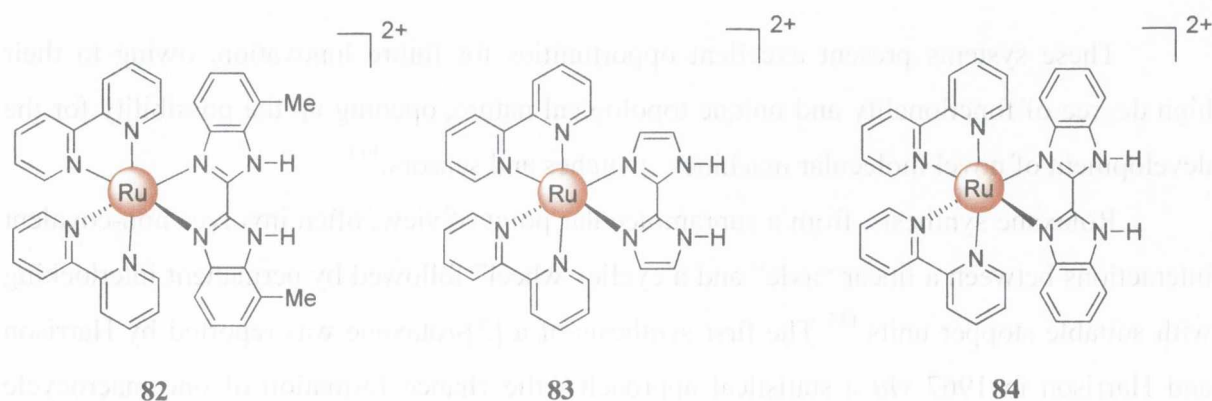
The tripodal tris(urea) ligand with *bpy* substituents, **79** and the corresponding Ru(II) complex, **80**, (as the PF_6^- salt) were both investigated for their anion binding abilities using ^1H NMR spectroscopy, fluorescence, and UV-Vis spectroscopy (for **79**).¹⁰⁶ Both compounds displayed large downfield shifts of the urea NH groups upon addition of 1 equivalent of SO_4^{2-} or H_2PO_4^- , as observed by ^1H NMR studies in $\text{DMSO}-d_6$, with binding constants determined to be larger than 10^4 M^{-1} for **79**. Other anions (HSO_4^- , Cl^- , Br^- , I^- , NO_3^- and ClO_4^-) resulted in only slight or no changes. Upon excitation at 447 nm complex **80** displayed the characteristic MLCT emission at 600 nm and upon addition of 1 equivalent of SO_4^{2-} or H_2PO_4^- a decrease of the emission intensity with a slight red shift (*ca.* 5 nm) was observed, while the other anions mentioned above induced slight or no significant changes of the emission intensity. The authors postulate that a change of the rigidity of the receptor upon anion binding might not be significant since each $\text{Ru}(\text{bpy})_3^{2+}$ moiety is modified by only one urea arm, and the decrease of emission intensity could be tentatively explained by the binding interactions of the anions, especially SO_4^{2-} or H_2PO_4^- ions, to the urea units affecting the excited states of *bpy* ligands and disfavours the MLCT process of the $\text{Ru}(\text{bpy})_3^{2+}$ complex.



Gunnlaugsson and Elmes synthesised a novel naphthalimide-Ru(II)-polypyridyl complex, **81** which showed selective sensing of F^- via a change in luminescence resulting from modulation of the MLCT emission at 450 nm.¹⁰⁷ A colour change from yellow to red could be detected by the naked eye in the presence of TBAF in CH_3CN . Initial H-bonding interactions of the anion with **81**, using the amine residue as the H-bond donor, followed by deprotonation results in the observed spectral changes. However, only minor changes were observed in the absorption spectra in the presence of AcO^- , Cl^- and HSO_4^- . Fluorescence studies ($\lambda_{ex} = 435$ nm) in CH_3CN show a quenching of the emission at 615 nm upon the addition of F^- ($\log K_{1:1} = 4.20$, $\log K_{1:2} = 3.7$). Similar fluorescence quenching was also observed with AcO^- ($\log K_{1:1} = 4.25$, $\log K_{1:2} = 3.11$), Cl^- ($\log K_{1:1} = 2.90$) and $H_2PO_4^-$ ($\log K_{1:1} = 4.52$), where the addition of (TBA) HSO_4^- did not result in any significant spectral changes. Competitive experiments show further quenching of the MLCT emission if F^- is added to a solution of **81** in the presence of an excess of $H_2PO_4^-$, whereas the other studied anions do not result in any spectral changes.



Another Ru(II)-(*bpy*)₂-based anion receptor, reported by Ye and co-workers is the biimidazole-like complex **82**.¹⁰⁸ The photophysical, electrochemical and anion sensing properties of **82** were compared with the two previously investigated systems, **83** and **84**.^{109,110} The high acidity of the N-H protons in these complexes make them likely to be deprotonated in the presence of strongly basic anions such as F[−] and AcO[−], while forming H-bonds with weakly basic anions such as Cl[−], Br[−], I[−], NO₃[−] and HSO₄[−]. Complexes **83** and **84** displayed distinct behaviours toward various anions and this was attributed to the different p*K*_a values of the complexes, *i.e.* the p*K*_a of **83** is 7.2 and **84** is 5.7. Complex **83** was found to H-bond to Cl[−], Br[−], I[−], NO₃[−] and HSO₄[−], while AcO[−] was also found to H-bond but then mono-proton transfer occurs and a colour change from yellow to orange-brown. Complex **84** underwent a stepwise deprotonation with AcO[−]: firstly the formation of the mono-deprotonated species at lower concentrations of the anion and then the bi-deprotonated complex at higher concentrations. It was found that the addition of 10 equivalents of F[−] and AcO[−] to a solution of **82** in CH₃CN induced a significant red shift of the MLCT band from 462 nm to 548 nm, while the other anions listed above only induced minor changes in the absorption spectra. However, the emission spectra of **82**, **83** and **84** were completely quenched upon addition of 1 equivalent of F[−] and AcO[−]. This was attributed to mono-deprotonation processes of the complexes. Complex **82** also underwent a two-step colour change, from yellow to orange and then to violet upon addition of F[−] and AcO[−]. The authors conclude that the anion binding ability of these complexes can be tuned by their p*K*_a values. A moderate p*K*_a value of 6.21 for **82** in CH₃CN-H₂O (2:3 v/v) media gives it stronger H-bonding affinity to the five anions, with 4 to 5 fold increase of the binding constants compared to complex **83** (p*K*_a is 7.2). On the other hand, the additional methyl groups at the 7 and 7' positions of **82** may also play an important role in the enhancement of binding strength.



The anion recognition and sensing field has grown over the past few decades to the extent that the field is now an established and important area of supramolecular chemistry. The progressive understanding of and subsequent ability to control the intermolecular forces between host and guest, has enabled the design of superior supramolecular architectures ranging from molecular cage-like assemblies and helicates to mechanically interlocked supramolecules, such as rotaxanes, catenanes, and knots.¹¹¹ Therefore, the main focus of the next section will be on systems of the latter type, with a specific emphasis on rotaxanes.

1.5 Interlocked Assemblies

During the last two decades, the construction of interlocked molecules such as rotaxanes and catenanes has received much attention owing to their unique structures and properties.¹¹² The threading of one component through another in a reversible manner leads to a pseudorotaxane, and where this threading is irreversible (capped by suitable bulky end groups) a rotaxane is formed. The permanent interlocking of two ring components produces a catenane.¹¹³ The basic motifs of these assemblies are illustrated below in Figure 1.5.

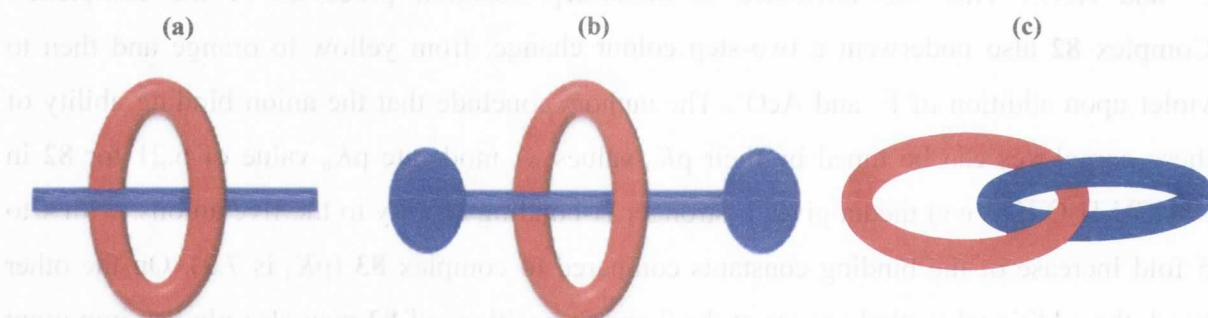
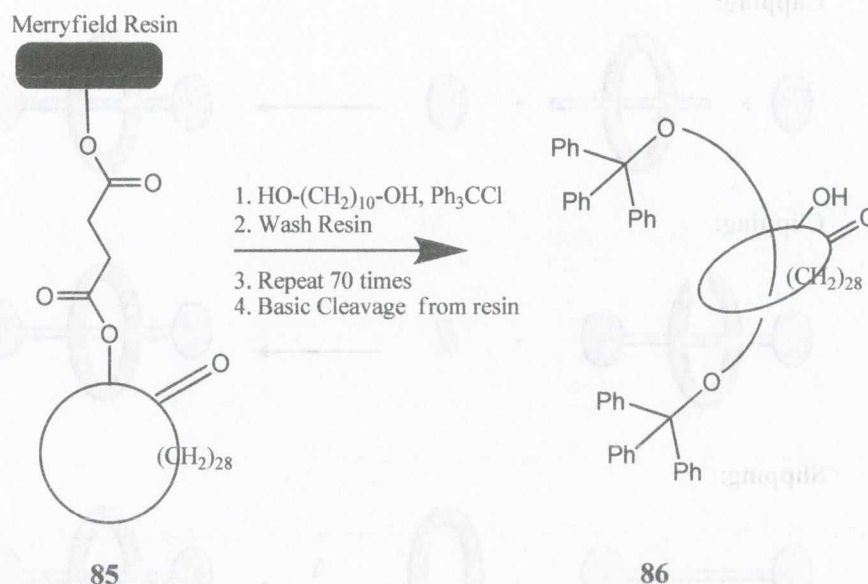


Figure 1.5: (a) [2]-pseudorotaxane, (b) [2]-rotaxane, and (c) [2]-catenane. The number in square brackets corresponds to the number of interpenetrated components.

These systems present excellent opportunities for future innovation, owing to their high degree of functionality and unique topological nature, opening up the possibility for the development of novel molecular machines, switches and sensors.¹¹⁴

Rotaxane synthesis, from a supramolecular point of view, often involves non-covalent interactions between a linear “axle” and a cyclic “wheel” followed by permanent interlocking with suitable stopper units.¹¹⁵ The first synthesis of a [2]-rotaxane was reported by Harrison and Harrison in 1967 via a statistical approach - the chance formation of one macrocycle being threaded through another.¹¹⁶ They called it a “hooplane”. A cyclic ketone with a pendant carboxylic acid function, coupled to a Merrifield resin (**85**) was continually treated on a

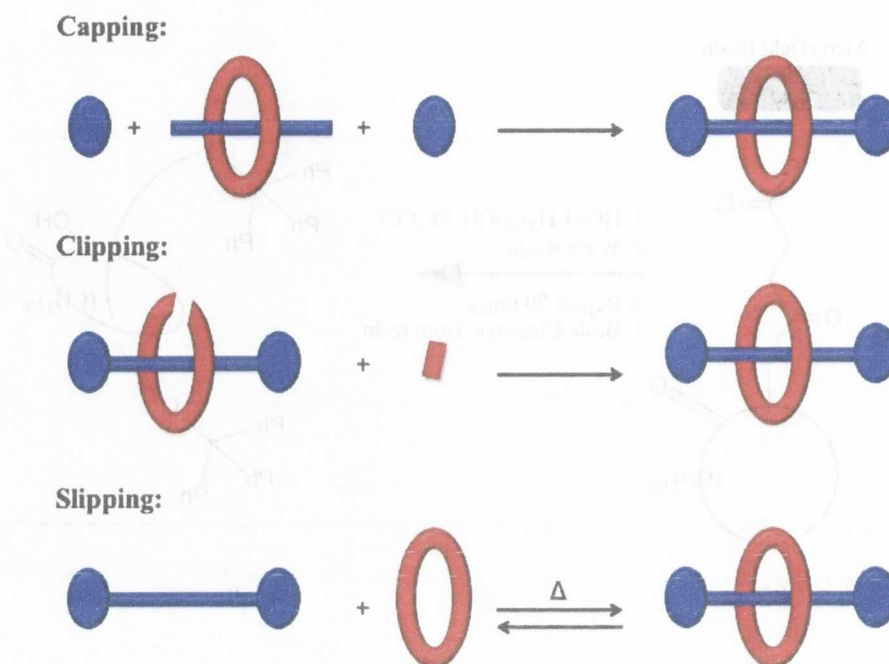
column with decane-1,10-diol and triphenylmethyl chloride. Following cleavage of the rings from the resin and purification, the [2]-rotaxane, **86**, was obtained in 6% yield.



Although the statistical approach was subsequently improved, it was not until the 1980's and the introduction of Cu(I)-template strategies by Sauvage and colleagues that marked the first practical synthetic routes to interlocked assemblies.¹¹⁷ This seminal approach employs the tetrahedral coordination geometry of a Cu(I) ion to hold a pair of bidentate ligands in a mutually orthogonal orientation forming a crossover point that directs subsequent macrocyclisation or “stoppering” reactions toward threaded architectures. Other template syntheses followed based on electrostatic interactions,¹¹⁸ metal-ligand coordination,¹¹⁹ H-bonding¹²⁰ and π - π interactions¹²¹ *etc.*, all leading to the wide variety of synthetic methods available today.

The three most common strategies for rotaxane synthesis are “capping”, “clipping”, and “slipping” (Scheme 1.1), although others do exist. Synthesis *via* the capping method relies strongly upon a thermodynamically driven template effect; that is the thread is held within the macrocycle by non-covalent interactions. This dynamic complex, or pseudorotaxane, is then converted to the desired rotaxane by covalently attaching the ends of the threaded guest with large groups preventing disassociation of the self assembly. The clipping method is similar to the capping reaction, except the macrocycle component assembles around a preformed thread molecule. The macrocycle then undergoes a ring closing reaction yielding the rotaxane. The method of slipping is one that exploits the kinetic stability of the rotaxane. If the end groups of the axle are of an appropriate size it will be able to reversibly thread through the macrocycle

at higher temperatures. By cooling the dynamic complex it becomes kinetically trapped as a rotaxane at the lower temperature.¹²²



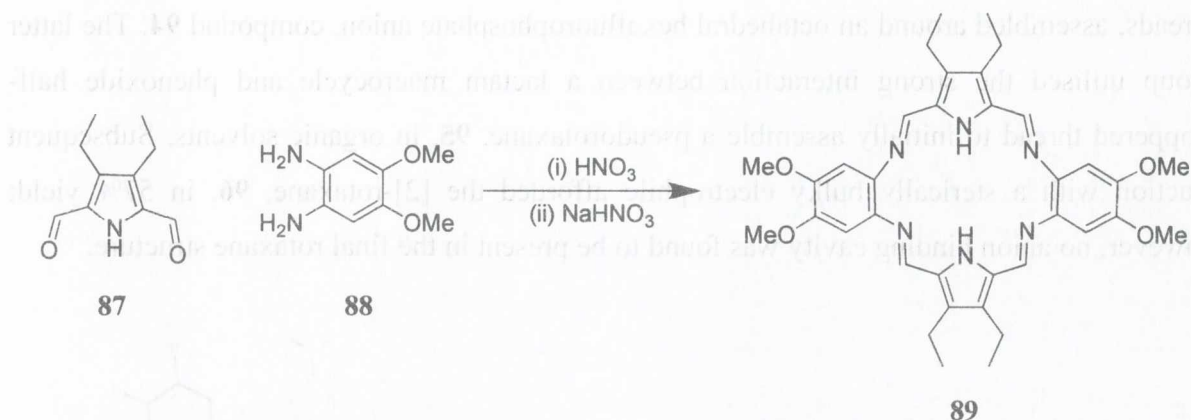
Scheme 1.1: Common non-covalent bond directed strategies for rotaxane synthesis.

1.5.1 Anion-Templated Assembly of Interlocked Structures

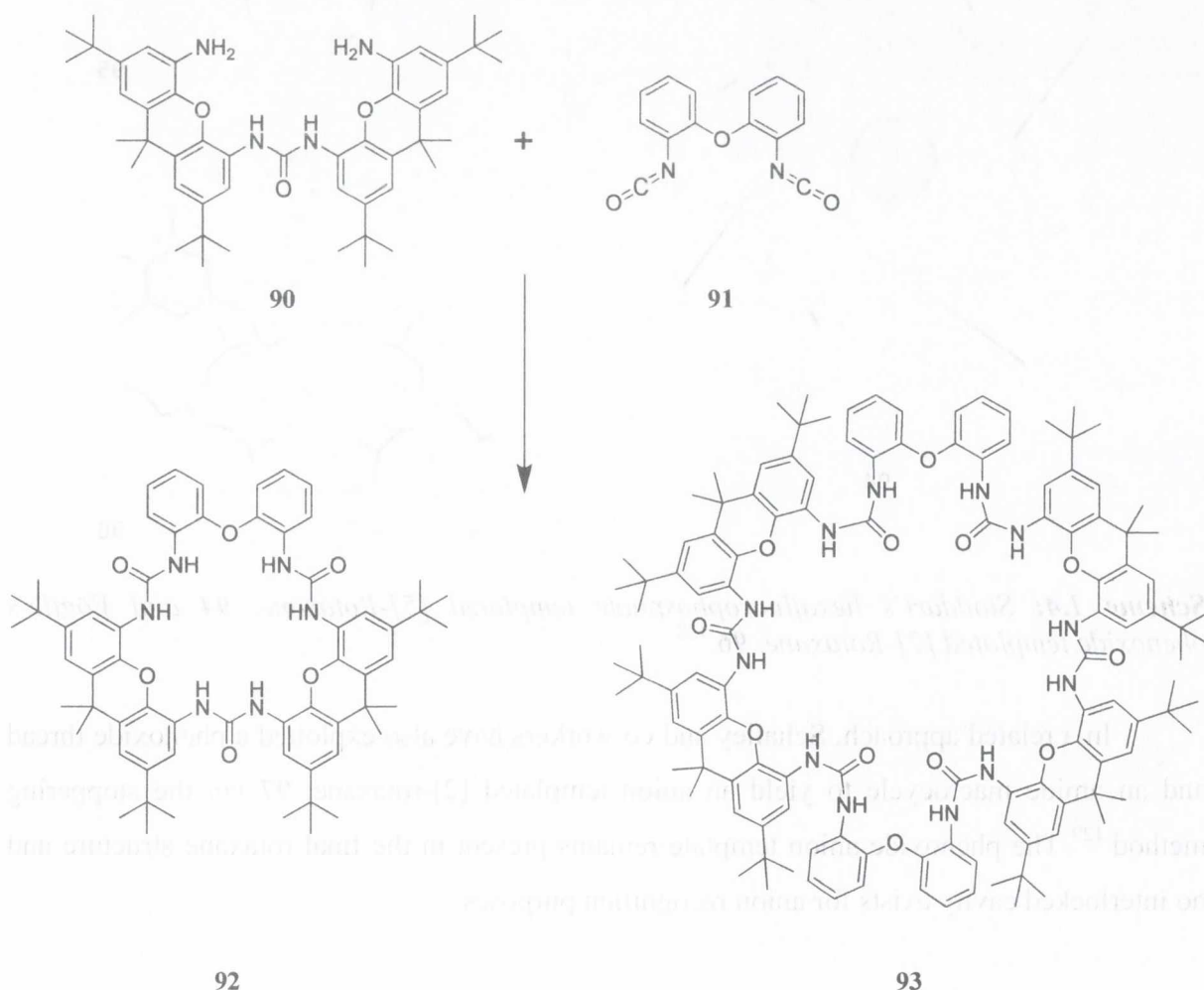
Manipulating anions to direct supramolecular assembly of the nature discussed above has seldom been reported in the literature and the area remains largely unexploited. Although various serendipitous cases where anions have templated the formation of interpenetrated compounds exist¹²³, rarely are strategically templated examples reported within the field of catenane and rotaxane synthesis. One of the first examples of the deliberate use of anions for templation purposes was reported by Sessler and co-workers in 1992.¹²⁴ It was shown that the Schiff base condensation reaction between 3,4-diethylpyrrole-2,5-dicarbaldehyde (**87**) and 4,5-diamino-1,2-dimethoxybenzene (**88**) afforded macrocycle **89** in quantitative yields when nitric acid was used as the reaction catalyst, Scheme 1.2. In contrast, when HCl was used to catalyse the reaction no macrocycle was formed, indicating that the nitrate anion played a crucial templating role in the synthesis of **89**.

Building on previous work, Böhmer and co-workers have also used inorganic anions in the templated synthesis of cyclic hexaurea macrocycles such as **92** and **93**, which contain xanthene or diphenyl spacer groups.¹²⁵ In the absence of any anionic template, reaction of diamine **90** with the diisocyanate **91** predominantly affords cyclic triurea **92**. However, in the

presence of Cl^- the larger [2 + 2] macrocycle **93** is the major product, Scheme 1.3. X-ray crystallography and ^1H NMR studies of **93** revealed that two Cl^- ions are simultaneously bound within the hexaurea macrocycle.

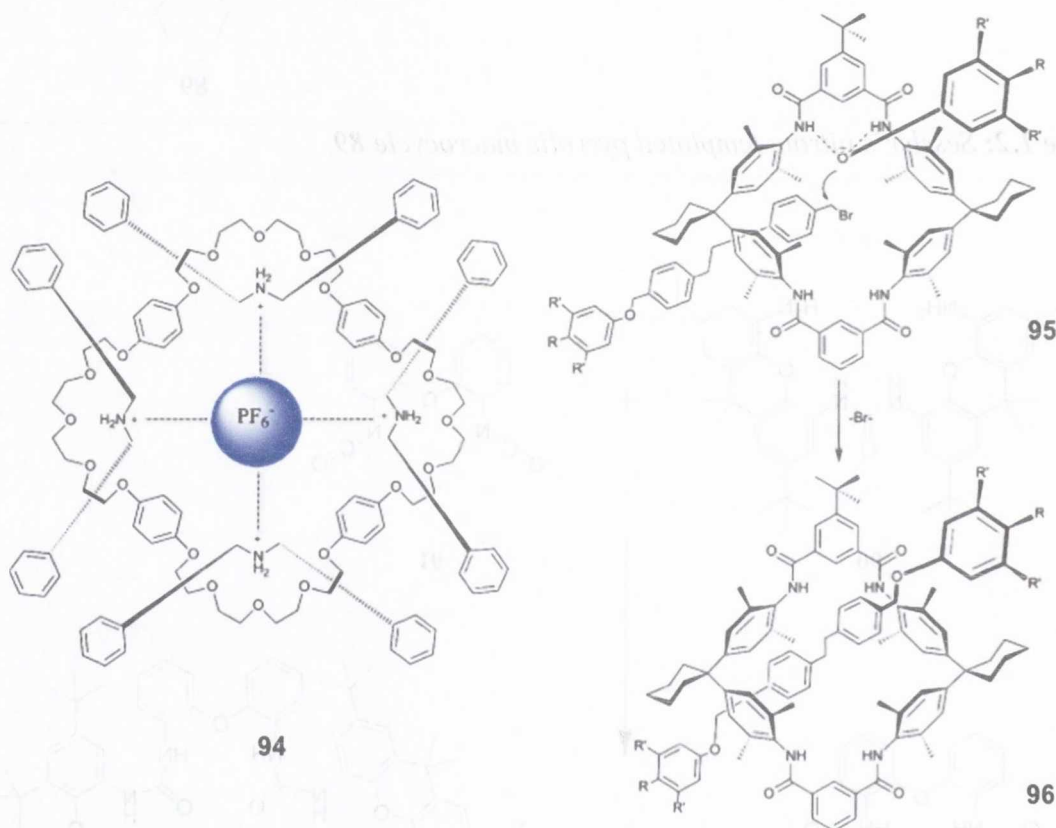


Scheme 1.2: Sessler's nitrate templated pyrrolic macrocycle **89**.



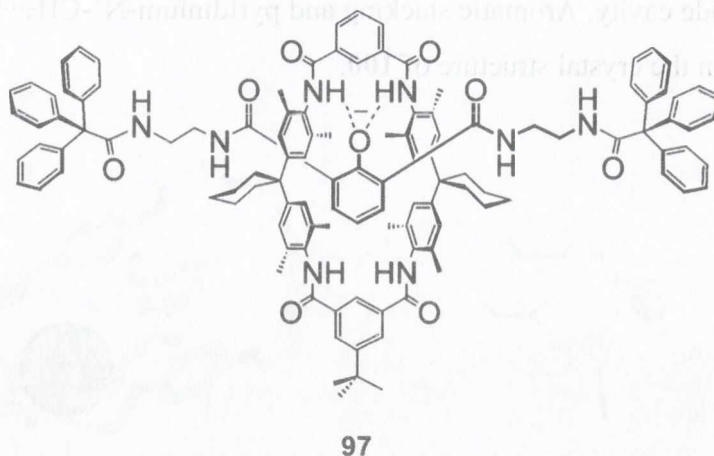
Scheme 1.3: Böhmer and co-workers triurea (**92**) and hexaurea (**93**) macrocycles, the latter templated by two Cl^- anions.

The first examples of interlocked species synthesised by anion-templated approaches were the pseudorotaxanes and rotaxanes reported in the late 1990's by Stoddart and co-workers and Vögtle and co-workers, shown in Scheme 1.4.^{126,127} Stoddart's design of [5]- and [6]-pseudorotaxane structures, incorporating polyether macrocycles and dibenzylammonium threads, assembled around an octahedral hexafluorophosphate anion, compound **94**. The latter group utilised the strong interaction between a lactam macrocycle and phenoxide half-stoppered thread to initially assemble a pseudorotaxane, **95**, in organic solvents. Subsequent reaction with a sterically bulky electrophile afforded the [2]-rotaxane, **96**, in 57% yield; however, no anion binding cavity was found to be present in the final rotaxane structure.

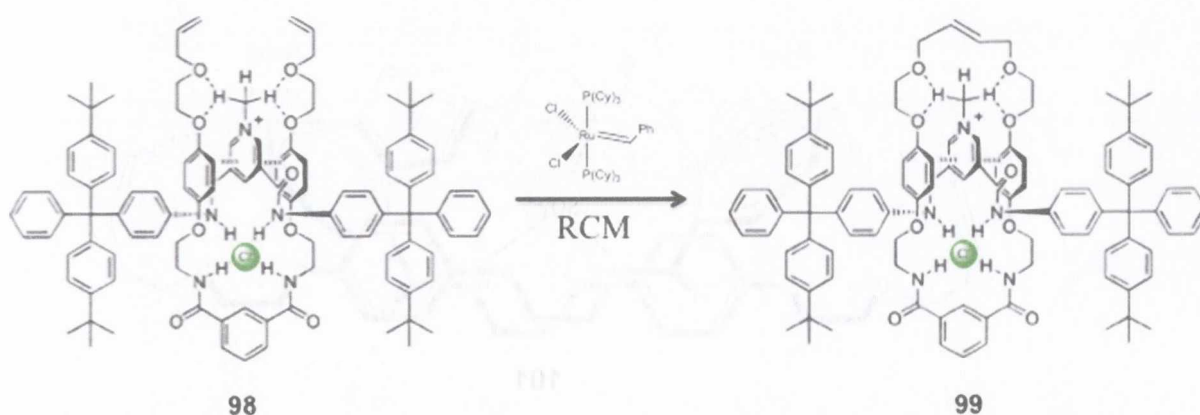


Scheme 1.4: Stoddart's hexafluorophosphate templated [5]-Rotaxane, **94** and Vögtle's phenoxide templated [2]-Rotaxane, **96**.¹²⁸

In a related approach, Schalley and co-workers have also exploited a phenoxide thread and an amide macrocycle to yield an anion templated [2]-rotaxane, **97** via the stoppering method.¹²⁹ The phenoxide anion template remains present in the final rotaxane structure and no interlocked cavity exists for anion recognition purposes.



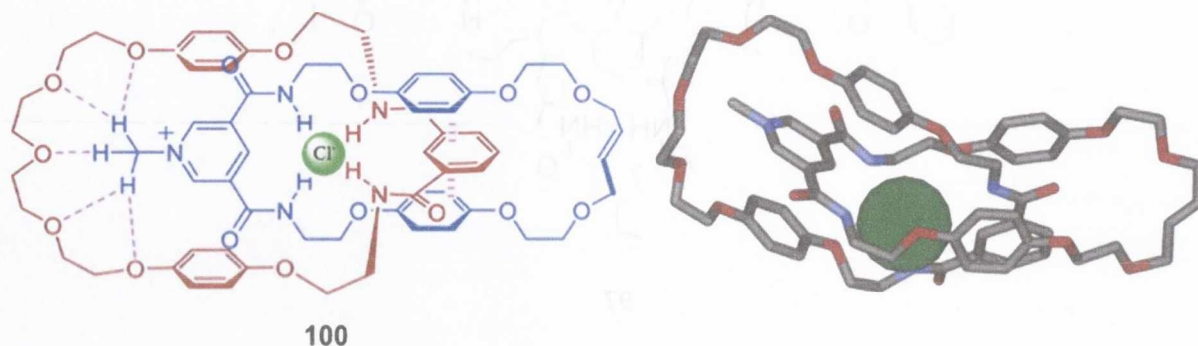
Beer and co-workers have done extensive work using anion templation in the synthesis of interlocked assemblies.¹³⁰ Indeed, a general method of using anions to template the formation of a range of pseudorotaxanes, rotaxanes and catenanes have been described by them. A very elegant example developed by this group is the use of anion templation in the synthesis of a [2]-rotaxane such as **99**.¹³¹ Using Cl^- to associate a pyridinium chloride thread, stoppered with tetra-phenyl groups and a macrocycle containing an isophthalamide binding cleft functionalised with two hydroquinone containing side chains **98**, the [2]-rotaxane **99** was obtained in 47% yield following a ring closing metathesis (RCM) reaction using Grubbs' catalyst, shown in Scheme 1.5. No rotaxane formation was detected with analogous Br^- , I^- or PF_6^- pyridinium salts, indicating the critical role of Cl^- .



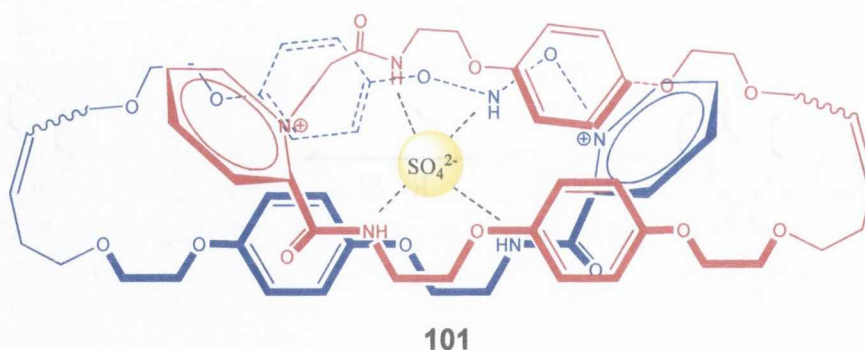
Scheme 1.5: Cl^- templated synthesis of a [2]-Rotaxane, **99** via clipping strategy.¹²⁸

Later, the same group reported the first example of using anion templation to synthesise catenanes where again Cl^- templates the initial formation of a [2]-pseudorotaxane and subsequent clipping affords the catenane **100**.¹³² The crystal structure is also shown below and confirms the interlocked nature of the two macrocyclic rings and the location of the Cl^-

anion within the amide cavity. Aromatic stacking and pyridinium- $\text{N}^+-\text{CH}_3\cdots$ polyether H-bonds were also observed in the crystal structure of **100**.



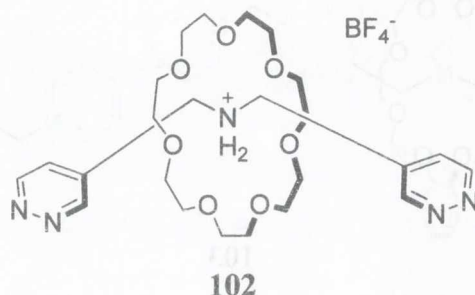
More recently, the use of SO_4^{2-} to template the synthesis of a pyridinium nicotinamide [2]-catenane, **101** in excellent yields has been reported by Beer and co-workers, as shown below.¹³³ In an analogous fashion to the Cl^- templated double clipping strategy discussed above, the SO_4^{2-} ion was shown to template the orthogonal assembly of two mono-cationic threads. Double RCM of the acyclic *bis*-vinyl pyridinium nicotinamide sulfate salt afforded **101** in 80% yield. Analogous RCM cyclisation reactions using Cl^- , Br^- or PF_6^- salts of the pyridinium nicotinamide thread failed to produce the desired catenane. As expected, subsequent anion binding studies performed on the PF_6^- salt of **101** revealed selectivity for the templating SO_4^{2-} over Cl^- , Br^- and AcO^- , which is contrary to the anion selectivity properties of the acyclic thread, which has a binding preference for AcO^- .



The examples highlighted in this section clearly demonstrate the real potential of anions in templating the assembly of complex supramolecular architectures which by appropriate future design may have practical sensing, switching and molecular machine applications.

1.6 Potential Applications

Even today the synthetic challenge of rotaxane formation remains a strong driving-force for some research groups. In 2008, Sheng-Hsien Chiu and co-workers created the smallest rotaxane reported to date, **102**, made from just 76 atoms with a molecular mass of $510 \text{ g}\cdot\text{mol}^{-1}$.¹³⁴ The axle is a dialkylammonium ion that threads through a crown ether ring. After grinding the mixture with a tetrazine, the axle is then capped with pyridazine stoppers to make the rotaxane in 81% yield.

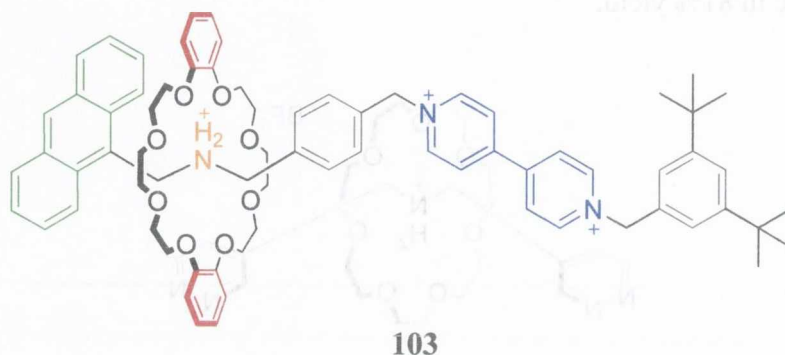


However, the main source of interest for research on interlocked molecules is the interesting properties and potential applications of the molecules themselves. Interlocked molecules regularly display strikingly different properties to their non-interlocked analogues, *e.g.* differences in spectroscopic responses, chemical reactivity or mechanical properties. These differences are a direct result of the interlocked architecture, yet perhaps the most exciting consequence of the mechanical bond, is the unique way in which different parts of the molecule can move with respect to the rest of the system. Rotaxanes are appealing systems for the construction of “molecular machines”, as these systems are termed, because two molecular motions in particular can be exploited, namely translation, *i.e.* shuttling of the ring along the thread, and rotation of the ring around the axle on which it is threaded.^{112,135}

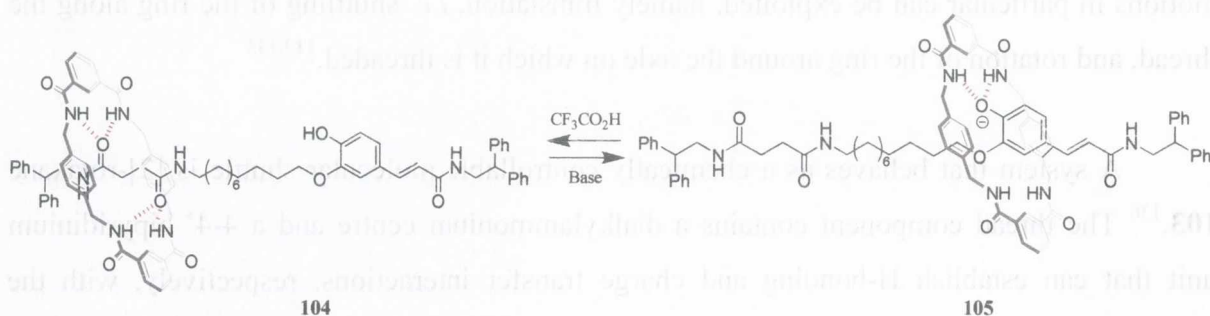
A system that behaves as a chemically controllable molecular shuttle is [2]-rotaxane **103**.¹³⁶ The thread component contains a dialkylammonium centre and a 4-4'-bipyridinium unit that can establish H-bonding and charge transfer interactions, respectively, with the dibenzo-24-crown-8 (DB24C8) ring component, a crown ether with electron donor properties. An anthracene moiety is used as a stopper due to its useful absorption; luminescence and redox properties in monitoring the dynamics of the system.

Since the $\text{N}^+\text{-H}\cdots\text{O}$ H-bonding interactions between the macrocycle and the ammonium centre are much stronger than the charge transfer interactions of the ring with the bipyridinium ring, the rotaxane exists as only one of the two possible translational isomers.

Deprotonation of the ammonium centre, however, causes 100% displacement of the macrocycle to the bipyridinium unit. Deprotonation of the ammonium centre with a base weakens the H-bonding interactions and causes quantitative displacement of the *DB24C8* ring by Brownian motion to the bipyridinium unit, while reprotonation with an acid directs the ring back to the ammonium centre. This switching process was investigated in solution by ^1H NMR spectroscopy, electrochemical and photophysical measurements.



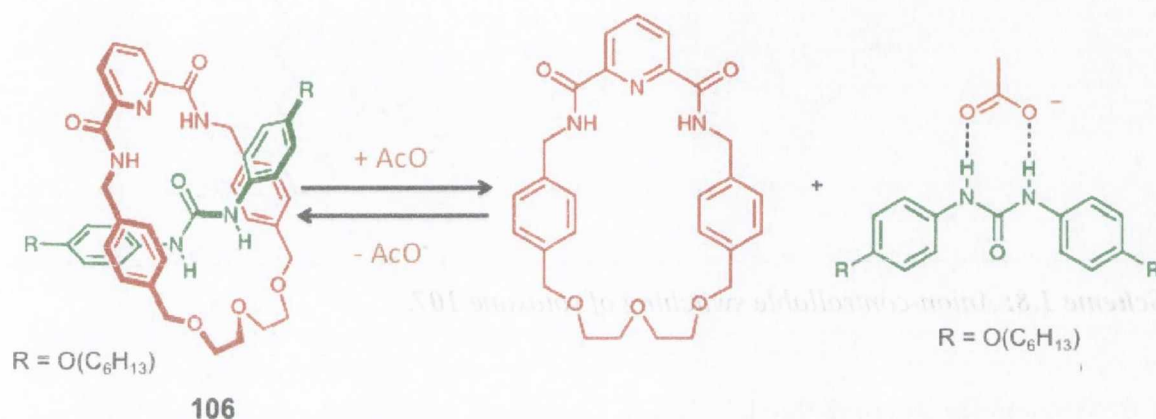
The first pH-switchable shuttle to exploit anion H-bonding interactions was reported in 2004 by Leigh and co-workers.¹³⁷ The formation of the benzylic amide macrocycle is templated by a succinamide station in the thread, shown in Scheme 1.6. However, the thread also includes a cinnamate derivative. As the phenol is a poor H-bonding group, the macrocycle resides on the succinamide station >95% of the time in the neutral form, **104**. Deprotonation in $\text{DMF-}d_7$ results in the macrocycle changing position to bind to the strongly basic phenolate anion, **105**. Reprotonation returns the system to its original state and the macrocycle to its initial position, **104**.



Scheme 1.6: pH-switched anion-induced shuttling in a H-bonded [2]-rotaxane in $\text{DMF-}d_7$ at room temperature.

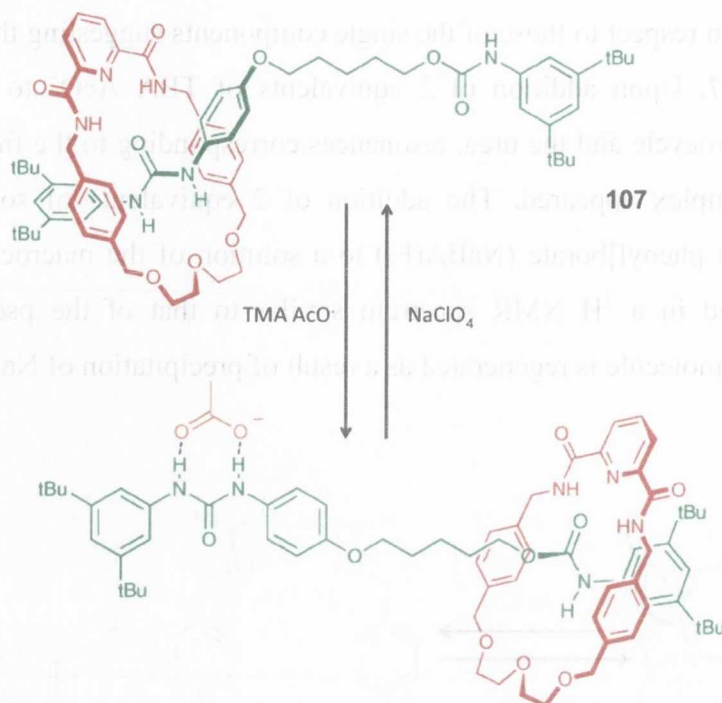
Chiu and co-workers have reported the synthesis of pseudorotaxane **106** and rotaxane **107**, which are AcO^- -controlled molecular switches (Scheme 1.7 and Scheme 1.8).¹³⁸ The ^1H NMR spectrum of an equimolecular mixture of the macrocycle and the diphenyl urea in

CDCl_3 is different in respect to those of the single components suggesting the formation of the pseudorotaxane **107**. Upon addition of 2 equivalents of TBA AcO^- to an equimolecular mixture of the macrocycle and the urea, resonances corresponding to the free macrocycle and the urea- AcO^- complex appeared. The addition of 2 equivalents of sodium tetrakis[3,5-bis(trifluoromethyl) phenyl]borate (NaBARF_4) to a solution of the macrocycle, urea and the TBA AcO^- resulted in a ^1H NMR spectrum similar to that of the pseudorotaxane **106**, suggesting that the molecule is regenerated as a result of precipitation of NaAcO .



Scheme 1.7: AcO^- -controllable threading and unthreading of pseudorotaxane **106**.

In the case of rotaxane **107**, ^1H NMR demonstrated that in $\text{CDCl}_3\text{-CD}_3\text{CN}$ (1:1 v/v) the macrocycle resided on the urea station. The addition of 5 equivalents of tetramethylammonium (TMA) AcO^- to **107** induced significant changes in the spectrum suggesting that the macrocycle had moved from the urea station toward the carbamate station (Scheme 1.8). Subsequent addition of 5 equivalents of NaClO_4 to this solution resulted in a spectrum similar to the one of the pure rotaxane, indicating the shift of the macrocycle back to the urea station.



Scheme 1.8: Anion-controllable switching of rotaxane **107**.

1.7 Work Described Within This Thesis

The overall aim of this research project was the development of novel (thio)urea based receptors for the recognition and sensing of anions. By incorporating the advantageous H-bonding properties of the (thio)urea moiety into structurally simple sensors to more complex supramolecular assemblies, it is possible to tailor the selectivity and sensitivity of the receptor to various anions.

Chapter 2 details the synthesis, photophysical properties and anion binding abilities of a new series of thiourea-based anion receptors and compares their anion binding ability with their urea counterparts previously synthesised within our research group. The synthesis and anion binding studies of these receptors were undertaken to gain a better understanding of the strength and type of interaction occurring between thiourea and various anions and compare this with our recent work in this area.

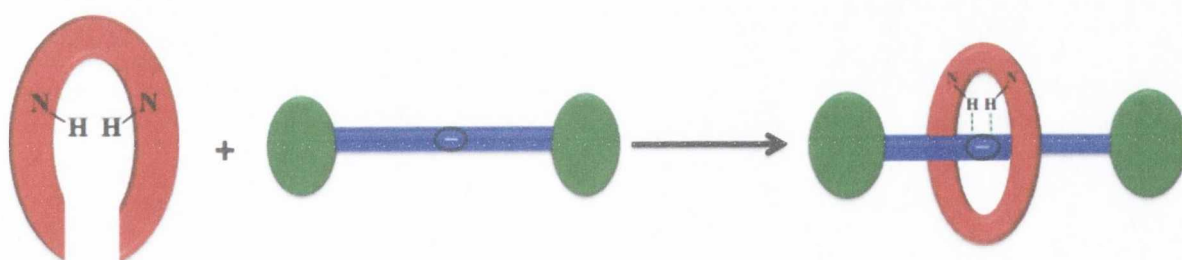
Chapter 3 discusses results from investigations into the anion binding ability of two thiourea functionalised Tröger's base derivatives previously synthesised in the Gunnlaugsson group.¹³⁹ It was anticipated that the unique structural features of these compounds, coupled with two thiourea binding sites, would provide an ideal receptor structure for the recognition of anions; and to the best of our knowledge has not been used for this purpose to date.

Chapter 4 continues in developing extended geometries for molecular recognition and describes the synthesis of a series of novel tripodal receptors and their anion binding abilities, investigated by ¹H NMR spectroscopy. The receptors contain three urea binding sites and it

was anticipated that the central platform of the receptors would enable cooperative binding of anions by all three moieties. The work was extended with an additional three tripodal receptors synthesised, differing to the original receptors in that they contained a tertiary amide group, eliminating any cooperative binding interactions between the amide and urea functionalities. These second generation receptors were also investigated by ^1H NMR spectroscopy and several structures elucidated by X-ray crystallography, including the receptors bound to various anions.

In Chapter 5, a series of Ru(II) polypyridyl complexes functionalised with a urea binding site as novel fluorescent anion sensors are described. The synthesis of each complex is discussed and crystals of three of the complexes were obtained that were suitable for X-ray structural determinations. The spectroscopic effects of the Ru(II) ground and excited state as well as NMR binding data is detailed.

Chapter 6 details the attempted development of superior supramolecular assemblies, *i.e.* interlocked structures such as rotaxanes and catenanes. The design of these structures was based upon the H-bonding interactions that urea and its derivatives can establish with anionic species. This anion templation approach can hold two components together *via* H-bonding and allows for the completion of the synthesis of the interlocked molecule, illustrated below in Scheme 1.9. A small library of acyclic and cyclic urea based compounds were synthesised for use as the macrocycle component in the construction of a rotaxane. The anion binding properties of these compounds were also investigated by ^1H NMR spectroscopy and a comparison of acyclic and cyclic derivatives investigated.



Scheme 1.9: Schematic representation of the [2]-rotaxane target based on H-bonding interactions between NH moieties and an anionic thread. The roles of the interlocked components can also be reversed, *i.e.* a urea-based thread and an anionic macrocycle are also possible.

Finally, in Chapter 7, general experimental procedures are provided and the synthesis of each of the compounds discussed is given.

Chapter 2

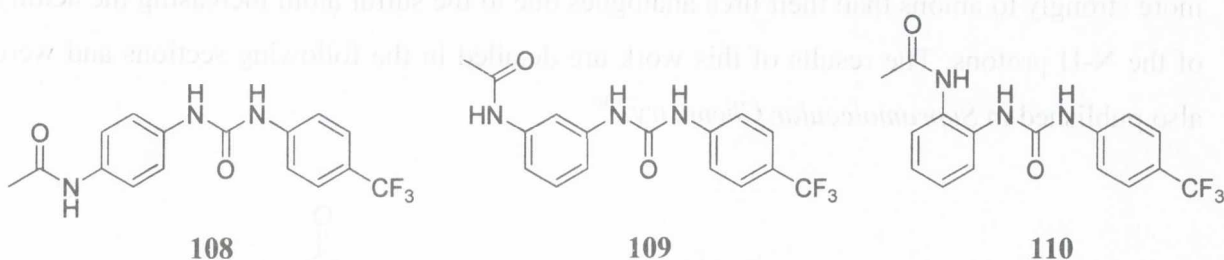
Diaryl Thiourea-Based Anion Receptors

2. Introduction

The recognition and sensing of anions in both organic and aqueous solutions has become an active field of research within supramolecular chemistry.^{9,140} Much effort has been devoted to the detection of anions due to the important roles they play in physiology, industry and in the environment.¹ Using luminescent and colorimetric methods, and in particular, charge neutral receptors such as ureas and thioureas (as they are excellent H-bond donors) are of particular interest.¹⁴¹ The anions usually form strong directional H-bonding complexes with the N-H protons, which are better H-bond donors than simple amides; allowing the urea and thiourea moiety to be more selective in its binding.

The combination of either ureas or thioureas in conjunction with amides as H-bonding receptors within the same structure has only recently been explored,^{142,143} and it has been shown that the combination of two H-bond donor groups has given rise to significant enhancements in anion binding affinity. This has recently been explored by Jiang and co-workers, who have demonstrated the use of additional functional groups to enhance the H-bonding ability of anion receptors by developing *N*-(*o*-methoxybenzamido)-based thioureas, where the anion binding at the urea moiety was greatly enhanced by the introduction of the methoxy substituent.¹⁴⁴

Another example of such a combination of H-bond donors are the acetamide functionalised diaryl urea-based receptors **108-110**, previously synthesised within our research group,¹⁴⁵ where for the first time, it was demonstrated that the recognition and sensing of anions could occur through “positive allosteric effects” in addition to the synergetic action of more than one H-bonding donor.



In the case of **108** and **109**, the binding of the anions at the urea moiety was shown to enhance or activate the recognition ability of the amide moiety (*i.e.* an allosteric effect), illustrated in Figure 2.1. This enabled these receptors to bind anions in a 1:1 as well as a 1:2 binding stoichiometry, the latter occurring *via* the amide functional group. However, this second anion binding interaction (*i.e.* at the amide site) only occurred after this primary

recognition at the urea site took place. The third receptor, **110**, with the amide functionality *ortho* to the urea moiety, only gave rise to a 1:1 binding stoichiometry, where the amide moiety cooperatively participated in the initial anion binding event at the urea site. The receptors **108-110** were found to interact strongly with anions such as AcO^- , H_2PO_4^- , $\text{HP}_2\text{O}_7^{3-}$ and F^- in CH_3CN as determined by changes in their respective absorption spectra.

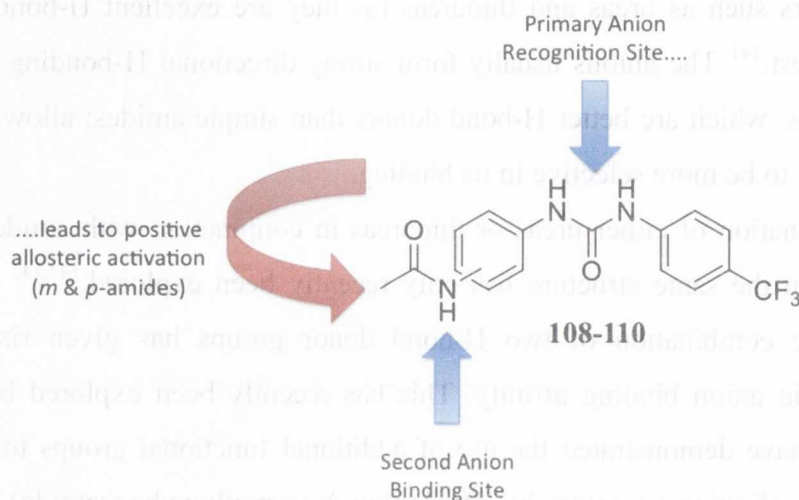
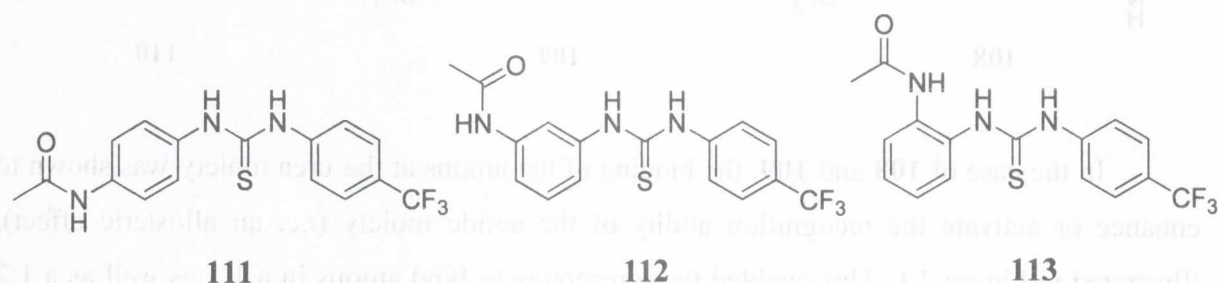


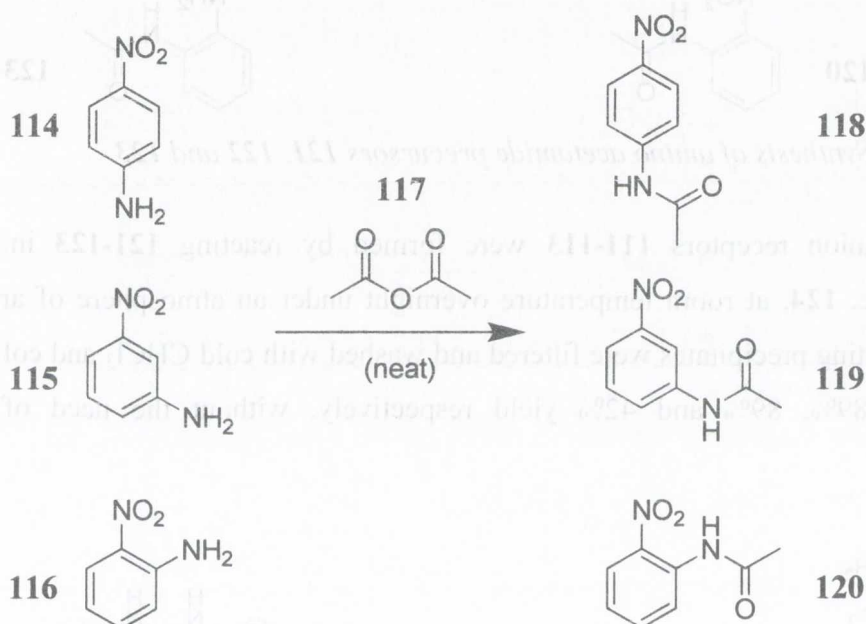
Figure 2.1: Mode of anion binding of receptors **108-110**.¹⁴⁵

Generally, thioureas are considered to form more stable complexes with anions than their urea counterparts due to their enhanced N-H acidity⁴⁰ and, as the allosteric mode of action had not, to the best of our knowledge, previously been explored using thiourea-based anion receptors, the aim of the work presented in this Chapter was the syntheses and photophysical analysis of three diaryl thiourea-based anion receptors for comparison with their urea counterparts, **108-110**. As already stated, thioureas are generally thought to bind more strongly to anions than their urea analogues due to the sulfur atom increasing the acidity of the N-H protons. The results of this work are detailed in the following sections and were also published in *Supramolecular Chemistry*.¹⁴⁶



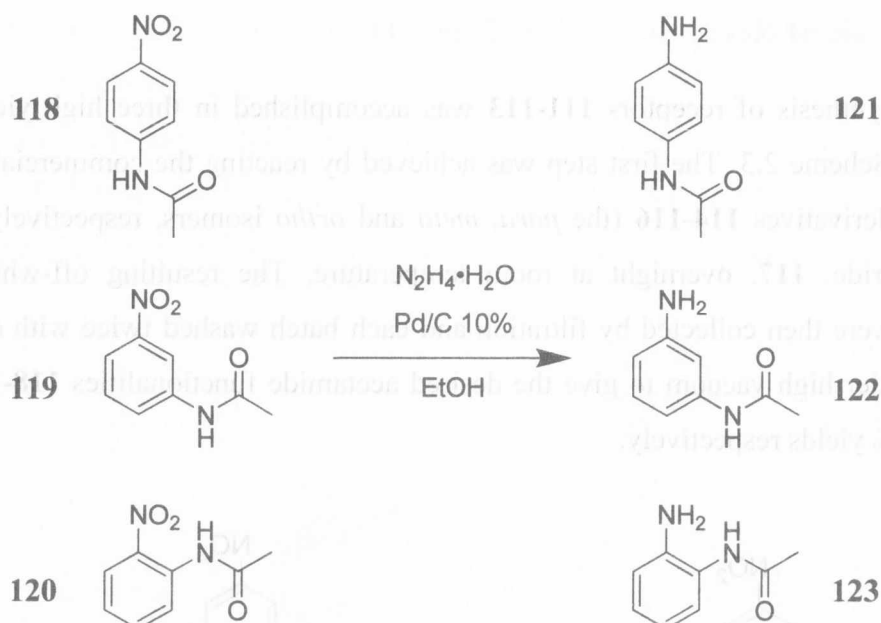
2.1 Synthesis of Receptors 111, 112 and 113

The synthesis of receptors **111-113** was accomplished in three high yielding steps, Scheme 2.1-Scheme 2.3. The first step was achieved by reacting the commercially available nitroaniline derivatives **114-116** (the *para*, *meta* and *ortho* isomers, respectively) with neat acetic anhydride, **117**, overnight at room temperature. The resulting off-white coloured precipitates were then collected by filtration and each batch washed twice with diethyl ether and dried under high vacuum to give the desired acetamide functionalities **118-120** in 67%, 57% and 71% yields respectively.



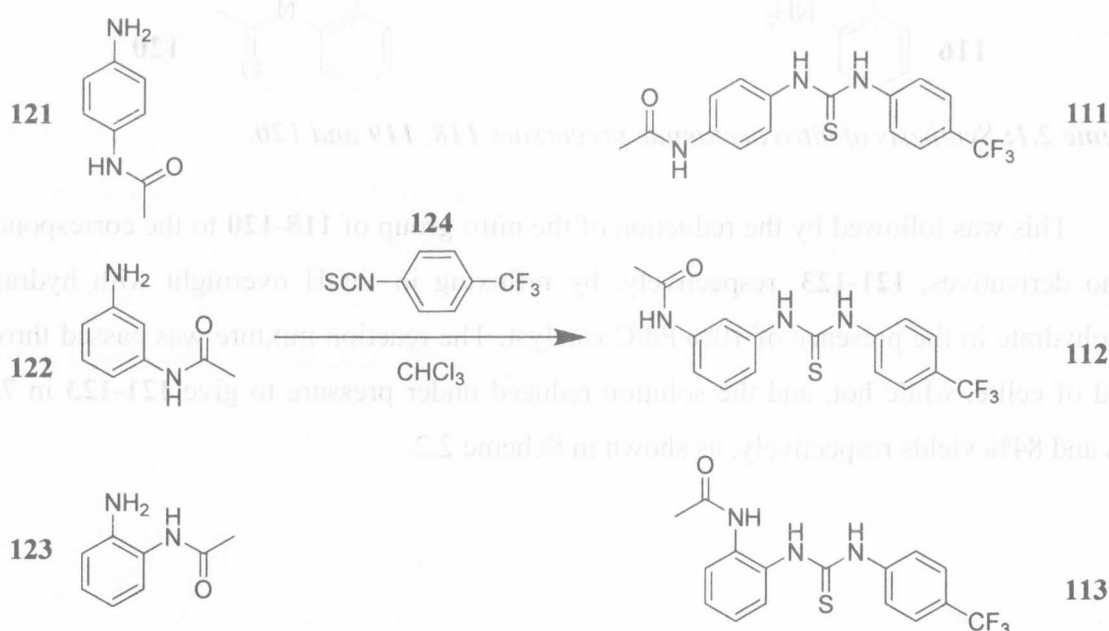
Scheme 2.1: Synthesis of nitro acetamide precursors **118**, **119** and **120**.

This was followed by the reduction of the nitro group of **118-120** to the corresponding amino derivatives, **121-123**, respectively, by refluxing in EtOH overnight with hydrazine monohydrate in the presence of 10% Pd/C catalyst. The reaction mixture was passed through a pad of celite, while hot, and the solution reduced under pressure to give **121-123** in 73%, 80% and 84% yields respectively, as shown in Scheme 2.2.



Scheme 2.2: Synthesis of amino acetamide precursors **121**, **122** and **123**.

The anion receptors **111-113** were formed by reacting **121-123** in CHCl_3 with isothiocyanate, **124**, at room temperature overnight under an atmosphere of argon, Scheme 2.3. The resulting precipitates were filtered and washed with cold CHCl_3 and collected to give **111-113** in 89%, 89% and 42% yield respectively, without the need of any further purification.



Scheme 2.3: Synthesis of receptors **111**, **112** and **113**.

2.2 Characterisation of Receptors **111**, **112** and **113**.

The three receptors were fully characterised using ^1H NMR, ^{13}C and ^{19}F NMR, mass spectrometry and elemental analysis. The ^1H NMR spectrum (400 MHz, $\text{DMSO-}d_6$) of **111** showed the presence of a broad peak at 9.98 ppm corresponding to the two thiourea protons and the amide proton, shown in Figure 2.2. The symmetrical nature of the receptor can be seen in the aromatic region with four doublets present, each integrating to two protons. The phenyl protons located next to the p - CF_3 group are the most downfield aromatic protons at 7.76 ppm, while the protons adjacent to the acetamide resonated at 7.69 ppm. The protons neighbouring the thiourea moiety appeared at 7.56 ppm for the p - CF_3 phenyl ring and at 7.36 ppm for the acetamide ring. The methyl peak was observed at 2.05 ppm. The ^{13}C showed two resonances at 179.5 ppm and 168.0 ppm corresponding to the two quaternary carbonyl groups. The presence of the CF_3 group was determined by the occurrence of a signal at -60.84 ppm in the ^{19}F spectrum. ES-MS analysis showed the presence of a single peak at 352.0731 corresponding to the $[\text{M} - \text{H}]^-$ species of **111**.

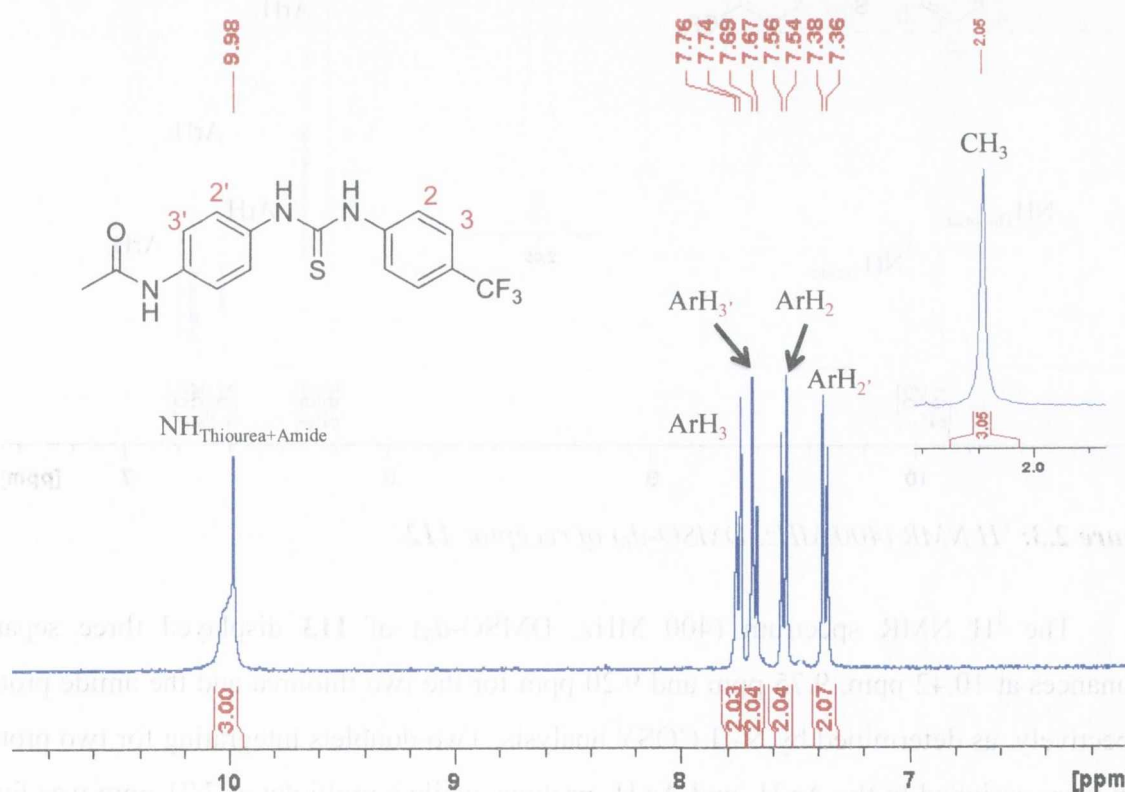


Figure 2.2: ^1H NMR (400 MHz, $\text{DMSO-}d_6$) of receptor **111**.

In the case of receptor **112** the resonance for the thiourea protons appeared at 10.06 ppm and the amide proton as a separate resonance at 9.97 ppm in the ^1H NMR spectrum (400 MHz, $\text{DMSO-}d_6$), Figure 2.3. As the acetamide moiety is in the *meta* position, the aromatic

region contains five sets of signals. Again, the most downfield signal corresponded to the protons adjacent to the p -CF₃ group along with the proton situated between the acetamide and thiourea functionalities (Ar-H₂). Other defining features were the triplet at 7.26 ppm assigned to the Ar-H₅ and the two doublets at 7.37 ppm and 7.21 ppm, each integrating for one proton assigned to the Ar-H₄ and Ar-H₆, respectively. The methyl peak was also observed at 2.04 ppm for **112**. The presence of two signals occurring at 179.4 ppm and 168.3 ppm in the ¹³C NMR were indicative of the two quaternary carbonyl groups. The CF₃ group was also present in the ¹⁹F spectrum at -60.84 ppm. ES-MS analysis showed the presence of a single peak at 376.0731 corresponding to the [M + Na]⁺ species of **112**.

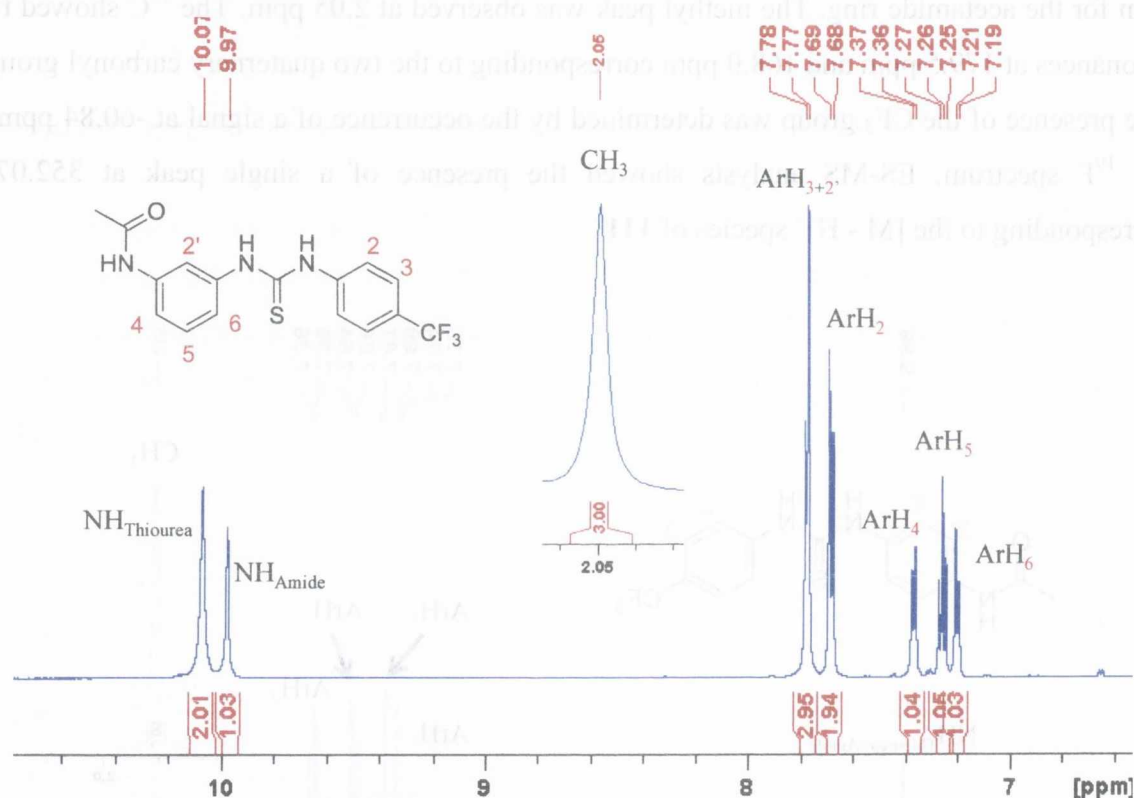


Figure 2.3: ¹H NMR (400 MHz, DMSO-*d*₆) of receptor **112**.

The ¹H NMR spectrum (400 MHz, DMSO-*d*₆) of **113** displayed three separate resonances at 10.42 ppm, 9.75 ppm and 9.20 ppm for the two thiourea and the amide protons respectively, as determined by N-H COSY analysis. Two doublets integrating for two protons each were assigned to the Ar-H₃ and Ar-H₂ protons, while a multiplet at 7.21 ppm was found to correspond to the Ar-H₄₊₅ protons, Figure 2.4. The methyl protons were observed at 2.08 ppm. The ¹³C NMR showed the presence of two resonances at 180.1 ppm and 169.1 ppm corresponding to the two quaternary carbonyl groups. The CF₃ group was present in the ¹⁹F spectrum at -60.86 ppm. ES-MS analysis showed the presence of a single peak at 376.0700 corresponding to the [M + Na]⁺ species of **113**.

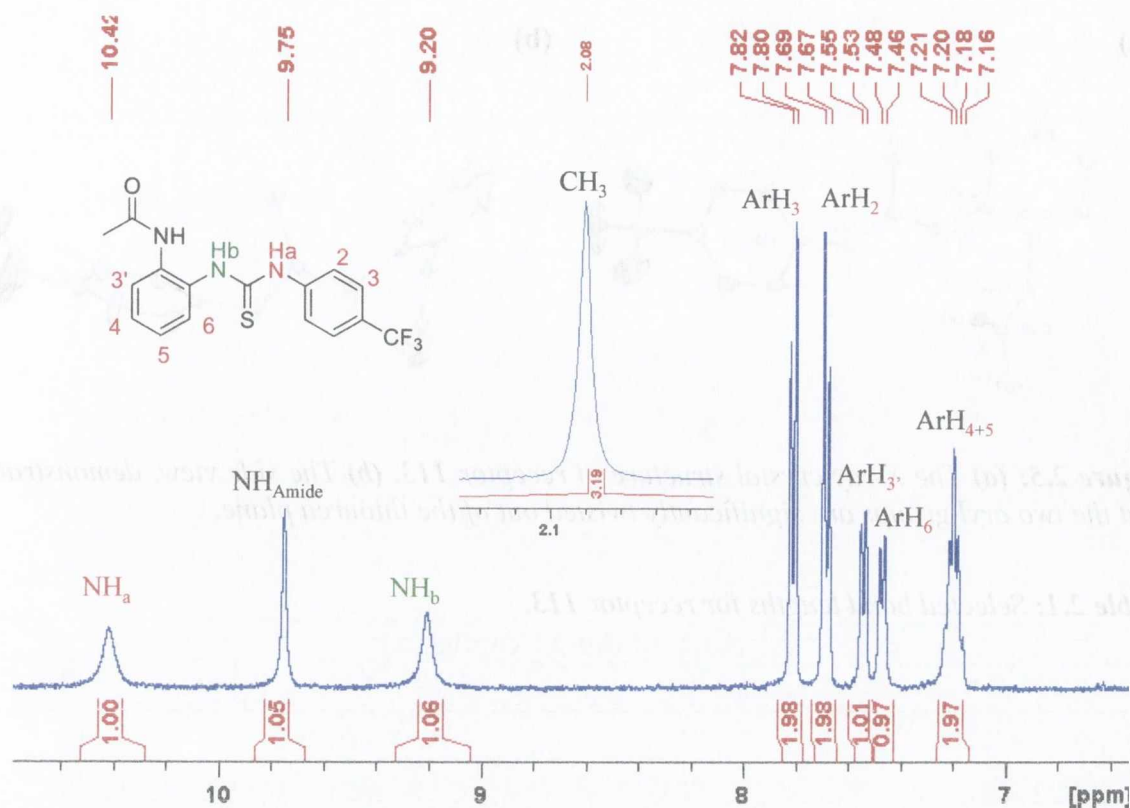


Figure 2.4: ^1H NMR (400 MHz, $\text{DMSO}-d_6$) of receptor **113**.

It was found that all the receptors formed crystalline materials, however only in the case of receptor **113** were crystals suitable for X-ray crystallographic analysis obtained. Colourless crystals were formed from a mixture of CHCl_3 and MeOH at room temperature and the resulting X-ray crystal structure was solved by Dr. Thomas McCabe, School of Chemistry TCD. Details of the analysis will be discussed in the following section.

2.3 Crystal Structure Analysis of Receptor **113**

The crystal structure of receptor **113** is shown in Figure 2.5 (a), with selected bond lengths detailed in Table 2.1. It can be seen from Figure 2.5 (a) that the N-H protons of the thiourea moiety are in the *syn* conformation making the receptor suitable for directional H-bonding. It can also be seen from Figure 2.5 (b) that the two aryl groups are significantly twisted out of the plane of the thiourea moiety.

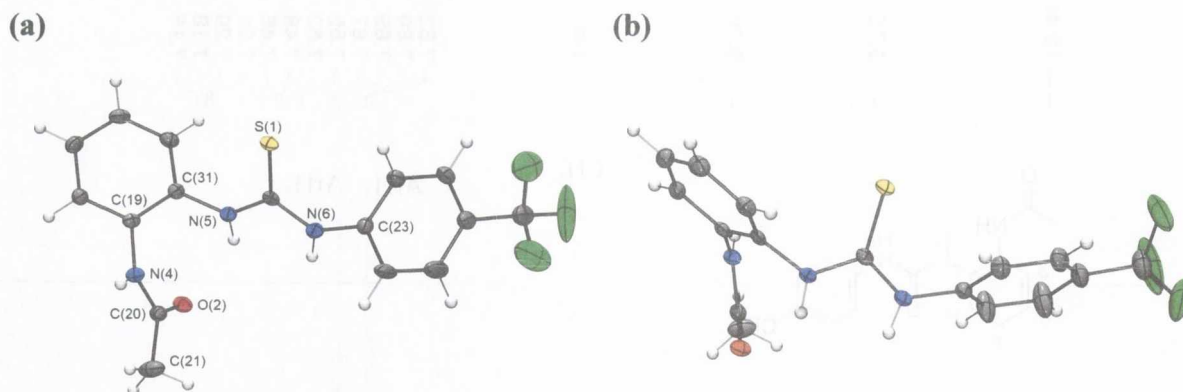


Figure 2.5: (a) The X-ray crystal structure of receptor **113**. (b) The side view, demonstrating that the two aryl groups are significantly twisted out of the thiourea plane.

Table 2.1: Selected bond lengths for receptor **113**.

Selected Bond Lengths (Å)			
C23 – N6	1.419	C19 – N4	1.425
N6 – C22	1.349	N4 – C20	1.340
C22 – S1	1.683	C20 – O2	1.240
C22 – N5	1.361	C20 – C21	1.503
N5 – C31	1.424		

In receptor **113** two types of H-bonding interaction were observed, as shown in Figure 2.6. The first interaction was an intermolecular interaction between N6 $\cdots$ O2 with a distance of 1.965 Å. The second intramolecular interaction exists between N5 $\cdots$ O2 with a distance of 2.766 Å. These values are similar to those obtained for urea **110**, *i.e.* 2.18 Å and 2.94 Å.

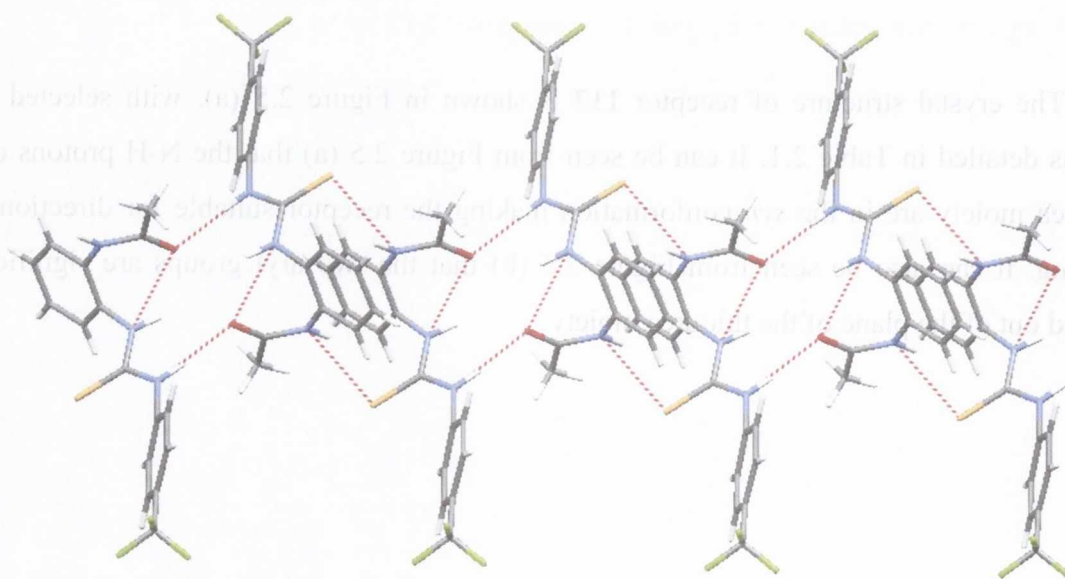


Figure 2.6: The H-bonding interactions in receptor **113**.

The packing diagram of **113**, viewed down the crystallographic *a*-axis is shown in Figure 2.7, illustrating an extensive intermolecular H-bonding network that exists between the amide protons and one of the N-H protons of the thiourea moiety; while no π - π stacking was observed for the aromatic moieties, most likely prevented by the CF₃ groups. The overall packing diagram was quite similar to that observed for the urea receptor **110**.¹⁴⁵

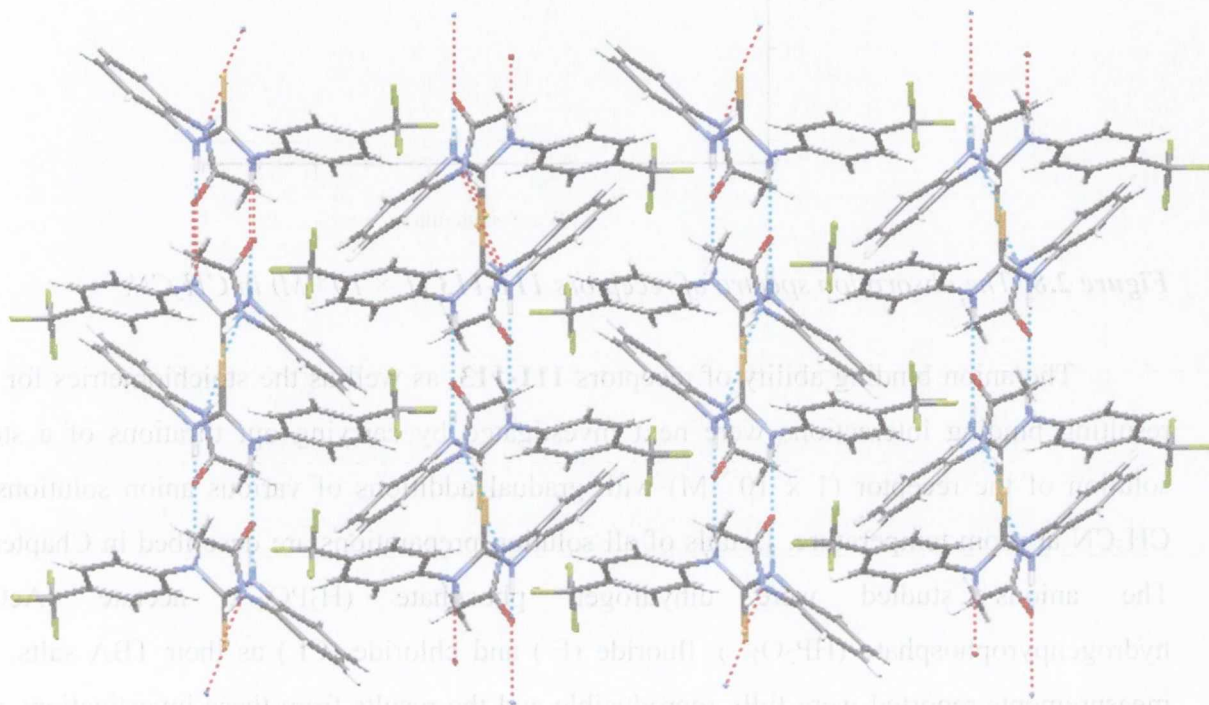


Figure 2.7: Packing diagram of **113** viewed down the crystallographic *a*-axis.

2.4 Photophysical Evaluation of Receptors **111-113**

The absorption spectra of sensors **111-113** are shown in Figure 2.8 when recorded at room temperature in CH₃CN. All three receptors showed similar characteristic absorption bands centred at *ca.* 280 – 283 nm with $\epsilon_{283} = 28220 \text{ M}^{-1} \text{ cm}^{-1}$, $\epsilon_{282} = 19220 \text{ M}^{-1} \text{ cm}^{-1}$ and $\epsilon_{280} = 19260 \text{ M}^{-1} \text{ cm}^{-1}$ for **111**, **112** and **113** respectively, assigned to their π - π^* transitions. A second band was observed at *ca.* 248 nm for **112** and as a shoulder at *ca.* 235 nm for **113**. Upon excitation at the λ_{max} , the receptors only gave rise to weak fluorescence emission.

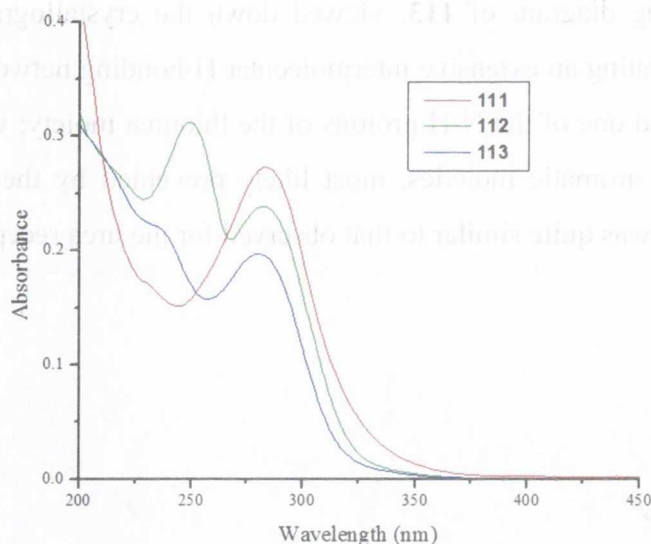


Figure 2.8: The absorption spectra of receptors **111-113** (1×10^{-5} M) in CH_3CN .

The anion binding ability of receptors **111-113**, as well as the stoichiometries for the resulting binding interactions were next investigated by carrying out titrations of a stock solution of the receptor (1×10^{-5} M) with gradual additions of various anion solutions in CH_3CN at room temperature. Details of all solution preparations are described in Chapter 7. The anions studied were dihydrogen phosphate (H_2PO_4^-), acetate (AcO^-), hydrogenpyrophosphate ($\text{HP}_2\text{O}_7^{3-}$), fluoride (F^-) and chloride (Cl^-) as their TBA salts. All measurements reported were fully reproducible and the results from these investigations will be discussed in the following sections.

2.4.1 Anion Binding Ability of Receptor **111**

The changes observed in the absorption spectrum of **111** upon titration with the various anions showed a bathochromic shift of the band centred at 282 nm to *ca.* 300 nm. The titration of **111** with AcO^- is shown in Figure 2.9 (a), and clearly shows that the absorption spectrum is significantly affected upon interaction with the anion.

Figure 2.9 (a) shows the band centred at *ca.* 283 nm was shifted to *ca.* 294 nm with the formation of an isosbestic point at *ca.* 282 nm. It can also be seen from Figure 2.9 (b) that the number of equivalents of anion required to reach a plateau is *ca.* 2 equivalents, with only minor changes occurring thereafter. These changes indicate that the interaction between receptor **111** and AcO^- is H-bonding.

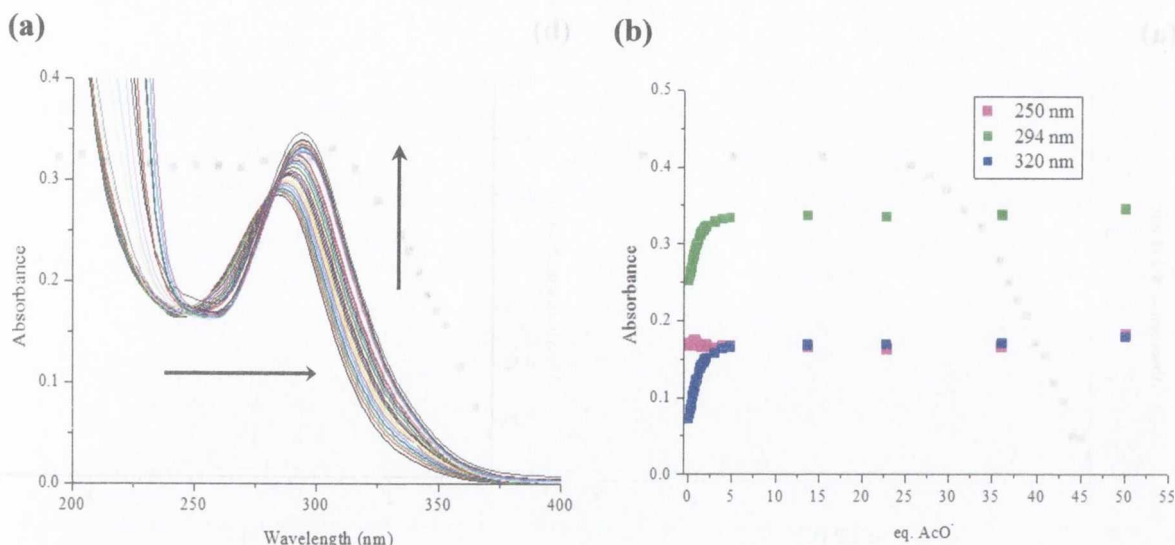


Figure 2.9: (a) Changes observed in the absorption spectrum of receptor **111** (1.1×10^{-5} M) upon titration with AcO⁻ (0 → 4.6 mM) in CH₃CN. (b) The changes in the absorbance at 250 nm, 294 nm and 320 nm as a function of equivalents of AcO⁻.

The same behaviour was observed for HP₂O₇³⁻ and F⁻, Figure 2.10 (a) and (b) respectively, indicating the rapid formation of a very stable host-guest species in solution, however it was found that the number of equivalents of anion required to reach a plateau was also *ca.* 2 equivalents for HP₂O₇³⁻ whereas it was *ca.* 4 equivalents in the case of F⁻, Figure 2.11 (a) and (b), respectively.

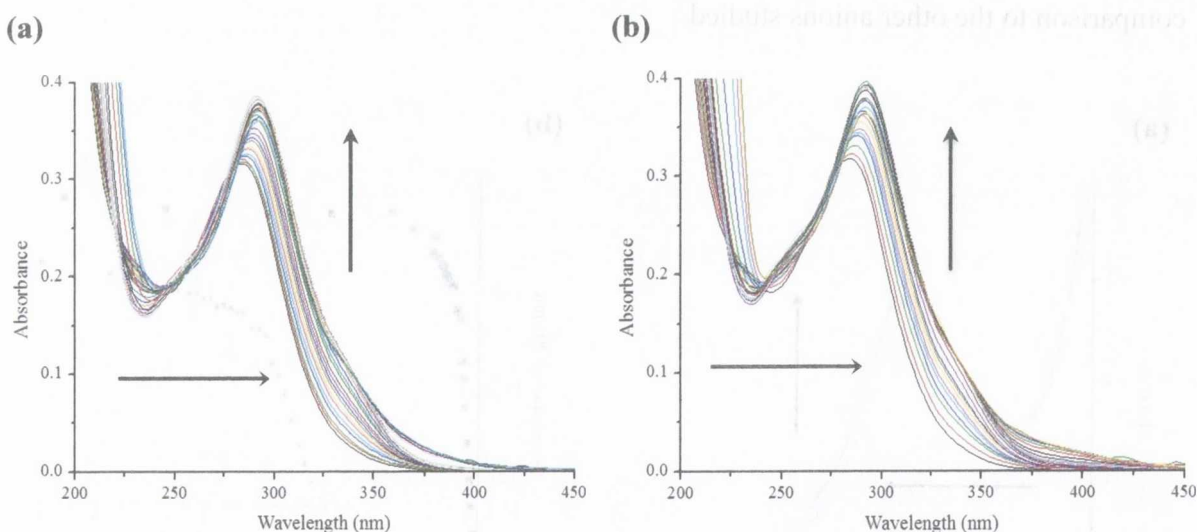


Figure 2.10: (a) Changes observed in the absorption spectrum of receptor **111** (1.05×10^{-5} M) upon titration with HP₂O₇³⁻ (0 → 5.1 mM) in CH₃CN. (b) Changes observed in the absorption spectrum of receptor **111** (1.05×10^{-5} M) upon titration with F⁻ (0 → 4.2 mM) in CH₃CN.

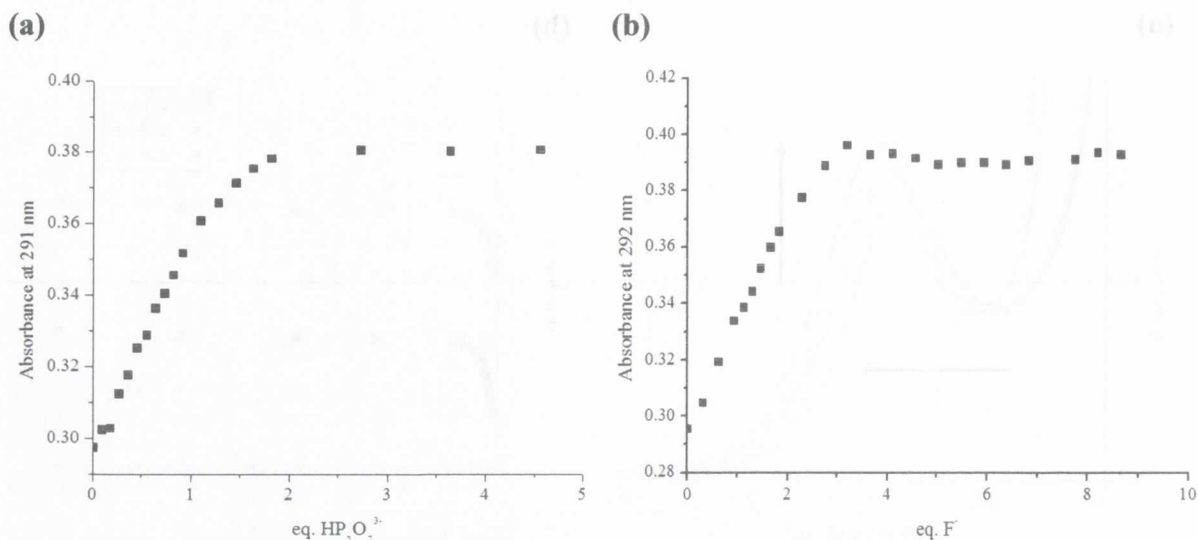


Figure 2.11: (a) The changes in the absorbance of **111** ($1.05 \times 10^{-5} \text{ M}$) at 291 nm as a function of equivalents of $\text{HP}_2\text{O}_7^{3-}$. (b) The changes in the absorbance of **111** ($1.04 \times 10^{-5} \text{ M}$) at 292 nm as a function of equivalents of F^- .

In the case of H_2PO_4^- the band centred at *ca.* 283 nm exhibited a slightly smaller red shift to *ca.* 291 nm, Figure 2.12 (a), with a plateau being reached upon *ca.* 15 equivalents of anion, Figure 2.12 (b). The spectral changes observed for Cl^- were, however, less significant during initial additions of anion ($0 \rightarrow 2$ equivalents) and only matched the changes of anions such as AcO^- and H_2PO_4^- at much higher concentrations of the anion (Appendix, Figure A2.2). This is an indication of a weaker binding interaction between the receptor and Cl^- , in comparison to the other anions studied.

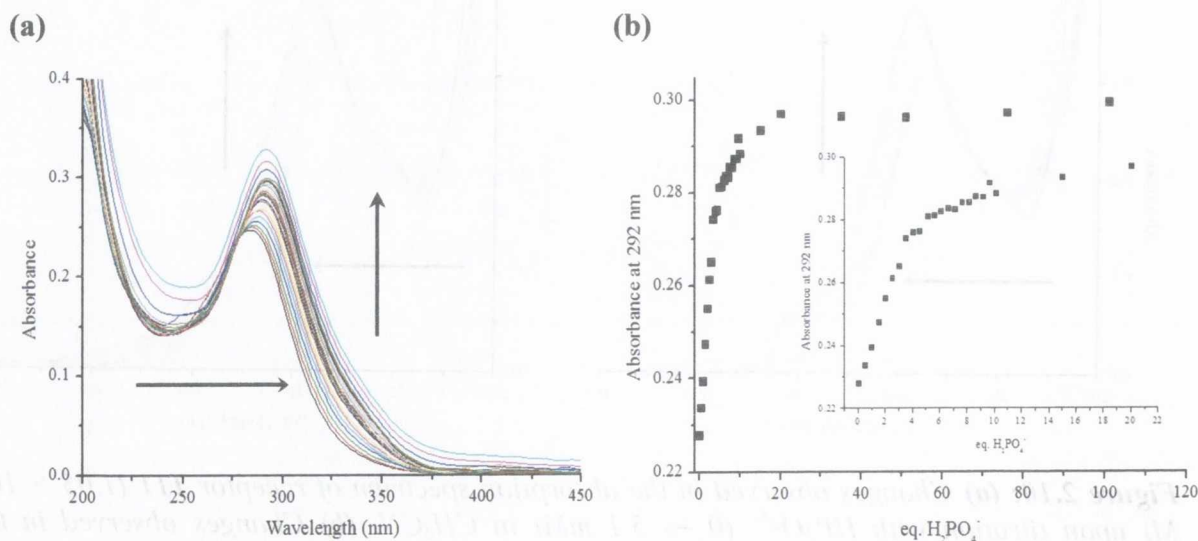
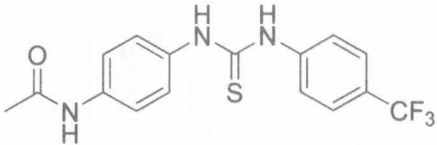


Figure 2.12: (a) Changes observed in the absorption spectrum of receptor **111** ($1.1 \times 10^{-5} \text{ M}$) upon titration with H_2PO_4^- ($0 \rightarrow 5.2 \text{ mM}$) in CH_3CN . (b) The changes in the absorbance at 292 nm as a function of equivalents of H_2PO_4^- . The inset shows the changes observed between 0 and 22 equivalents of H_2PO_4^- .

From the changes observed in the absorption spectra of **111** upon titration with the different anions, binding constants ($\log K$) for complex formation between the anions (G) and **111** (L) were determined by fitting the absorption data using the non-linear least squares regression program SPECFIT™. In each case, the data was successfully fitted with good convergence factors and the obtained stoichiometries and corresponding $\log K$ values are listed in Table 2.2. It was found that all of the anions were best fit to 1:1 and 2:1 (guest:host) stoichiometries with receptor **111**.

The changes observed for the titration of **111** with AcO^- at 294 nm and the corresponding fit obtained from SPECFIT™ are shown in Figure 2.13 (a). It can be seen that the best fit was obtained by fitting the data to a 1:1 and 2:1 species (guest:host). The speciation distribution diagram, shown in Figure 2.13 (b), is depicted from 0 $\rightarrow$ 55 equivalents and shows that the formation of the 1:1 species is very rapid while the 2:1 (guest:host) species becomes the most dominant in solution, occurring after *ca.* 4 equivalents of anion. However 95% formation of the 2:1 species is not reached until *ca.* 20 equivalents. The binding constant determined for the 1:1 species between receptor **111** and AcO^- was also the highest of the anions investigated, by almost one order of magnitude ($\log K_{1:1} = 6.3 \pm 0.2$).

Table 2.2: Binding constants and binding modes between anions and receptor **111**.

Receptor (L)	Anion (G)	Binding Mode	log	Std.
		$G_n:L_m$	$K_{n:m}$	Deviation ($\pm$)
 111	AcO^-	G:L	6.3	0.2
		$G_2:L$	5.1	0.4
	F^-	G:L	4.8	0.1
		$G_2:L$	4.3	0.3
	H_2PO_4^-	G:L	5.3	0.2
		$G_2:L$	4.7	0.5
	$\text{HP}_2\text{O}_7^{3-}$	G:L	5.76	0.01
		$G_2:L$	1.5	0.1
	Cl^-	G:L	4.1	0.1
		$G_2:L$	3.3	0.3

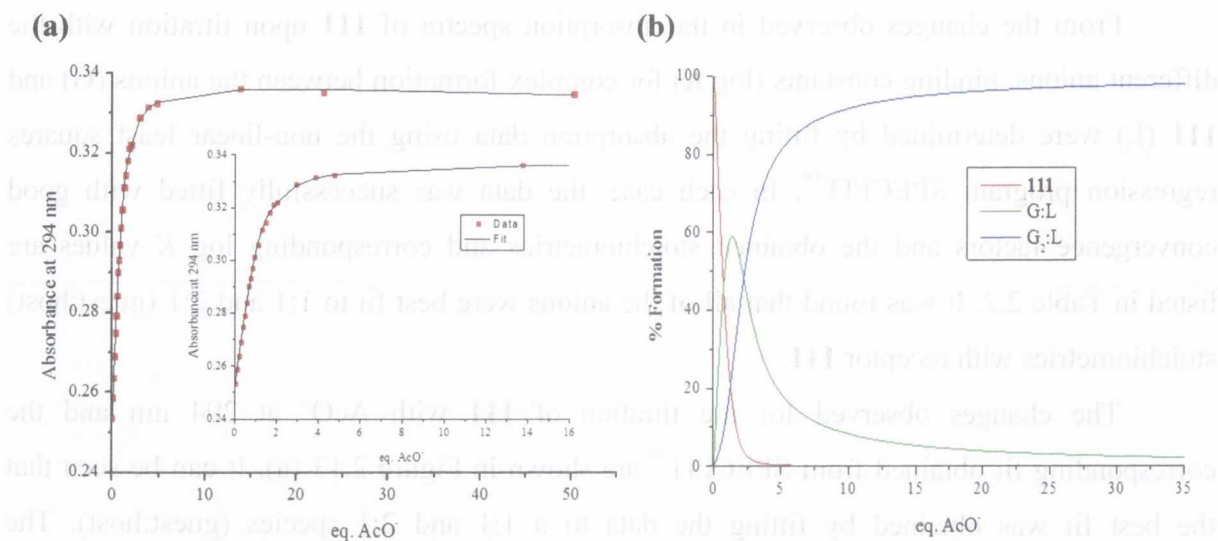


Figure 2.13: (a) Experimental binding isotherm for the titration of **111** and AcO⁻ and the corresponding fit from SPECFIT[™]. The inset shows the fit between 0 and 16 equivalents of AcO⁻. (b) Speciation distribution diagram for the absorption titration of **111** (L) with AcO⁻.

In comparison, the titration between receptor **111** and H₂PO₄⁻ displayed a slightly different binding profile but was also best fit to 1:1 and 2:1 (guest:host) stoichiometries. The binding isotherm and the corresponding fit are shown in Figure 2.14 (a). Again from the speciation distribution diagram, Figure 2.14 (b), it can be seen that the 1:1 species was formed very rapidly but the 2:1 species became the most dominant after *ca.* 10 equivalents of H₂PO₄⁻ with over 80% formation at this point. Excellent fits were also obtained for the other anions investigated (Appendix, Figure A2.3-A2.4).

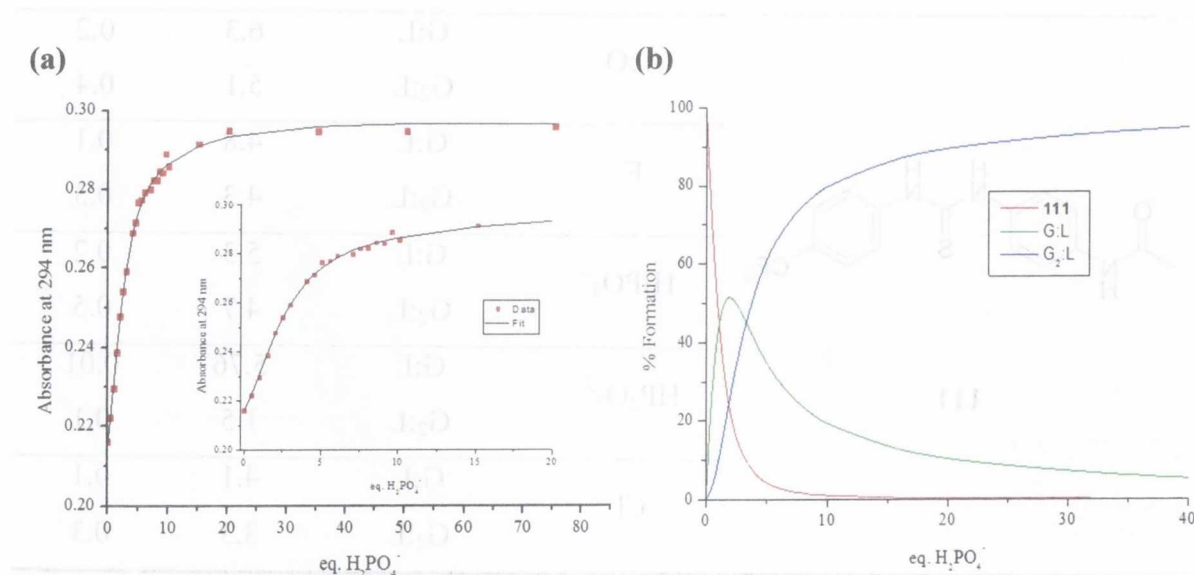


Figure 2.14: (a) Experimental binding isotherm for the titration of **111** and H₂PO₄⁻ and the corresponding fit from SPECFIT[™]. The inset shows the fit between 0 and 20 equivalents of H₂PO₄⁻. (b) Speciation distribution diagram for the absorption titration of **111** (L) with H₂PO₄⁻.

It can be seen from Table 2.2 that Cl^- exhibited the weakest interaction with receptor **111**, with a binding constant of $\log K_{1:1} = 4.1 (\pm 0.1)$ and $\log K_{2:1} = 3.3 (\pm 0.3)$ while the binding constants determined for F^- were the second lowest, $\log K_{1:1} = 4.8 (\pm 0.1)$ and $\log K_{2:1} = 4.3 (\pm 0.3)$. In comparison, AcO^- , $\text{HP}_2\text{O}_7^{3-}$ and H_2PO_4^- had the strongest interactions, indicating a preference of **111** for oxy-anions over spherical halides.

From these results, the first binding mode, *i.e.* the 1:1 species, can be ascribed to the interaction between the anions and the thiourea moiety of **111** through H-bonding. Upon further addition of anion, a second binding interaction was observed and this interaction was attributed to the anion binding to the amide functionality *para* to the urea moiety.

In comparison to the corresponding urea receptor **108**, it was found that the binding affinity of **111** with the various anions was generally stronger, which was the anticipated trend. For example, AcO^- and H_2PO_4^- gave rise to binding constants of $\log K_{1:1} = 6.3 \pm 0.2$ and $\log K_{1:1} = 5.3 \pm 0.2$ respectively for receptor **111**, while the binding constants for the urea analogue **108** were determined to be $\log K_{1:1} = 5.29 \pm 0.03$ and $\log K_{1:1} = 4.93 \pm 0.05$. The lower affinity of the urea analogues, **108-110**, towards the various anions is perhaps due to the presence of the less electron withdrawing oxygen atom of the urea receptors, resulting in the N-H protons being less efficient H-bond donors. It is also worth noting that the presence of two guest:host complexes, namely the 1:1 and 2:1 species between **111** and Cl^- were found to exist while the urea receptor **108** only formed the 1:1 complex. This is most likely due to the enhanced acidity of the thiourea receptor in comparison to the urea analogue.

2.4.2 Anion Binding Ability of Receptor 112

Having established the anion binding ability of **111**, the structural isomer **112** was next investigated. Besides the characteristic absorption band $\lambda_{\text{max}} = 282 \text{ nm}$, receptor **112** also had a band centred at *ca.* 252 nm. The largest spectral changes observed were those between **112** and $\text{HP}_2\text{O}_7^{3-}$, illustrated in Figure 2.15 (a). It can be seen from Figure 2.15 (a) that the absorption spectrum of **112** was red-shifted from *ca.* 282 nm to *ca.* 287 nm with the concomitant loss of the band centred at *ca.* 252 nm at higher concentrations of the anion. Interestingly the band at 282 nm becomes blue shifted at higher concentrations of anion. Figure 2.15 (b) indicates a plateau was reached before the addition of 5 equivalents of the anion. The same trend was also followed when plotting the changes in absorbance at different wavelengths.

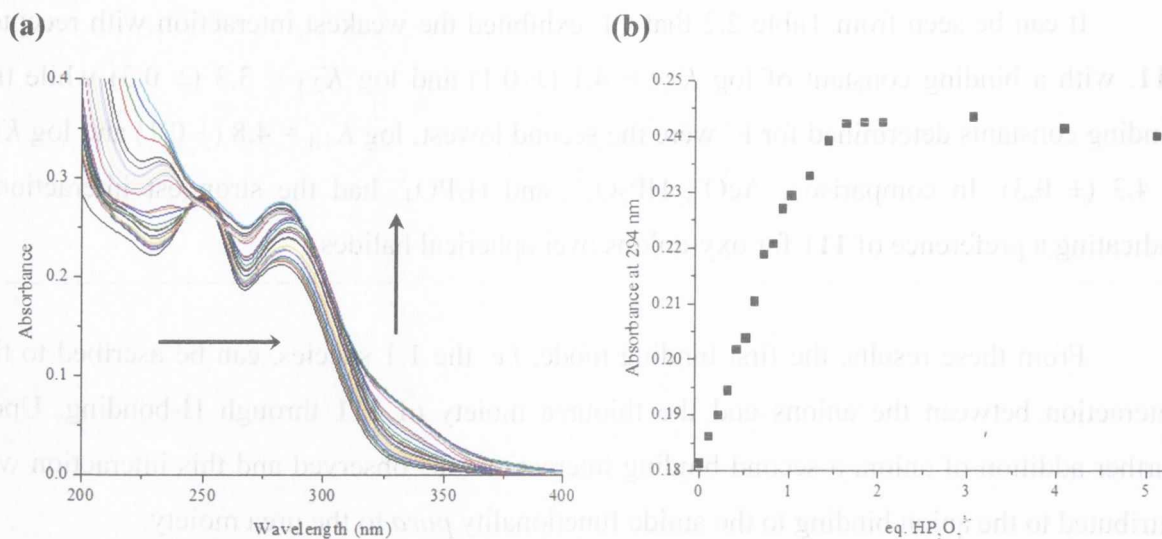


Figure 2.15: (a) Changes in the absorption spectrum of receptor **112** (1.1×10^{-5} M) upon titration with $\text{HP}_2\text{O}_7^{3-}$ ($0 \rightarrow 4.6$ mM) in CH_3CN . (b) The changes in the absorbance at 294 nm as a function of equivalents of $\text{HP}_2\text{O}_7^{3-}$.

In the case of H_2PO_4^- and AcO^- similar behaviour was also observed, with a bathochromic shift of the λ_{max} to longer wavelengths upon increasing anion concentration, Figure 2.16 (a) and (b). However no blue shift occurred during later additions as had been observed in the titration with $\text{HP}_2\text{O}_7^{3-}$. No clear isosbestic points were observed in these titrations, however, a ‘pseudo isosbestic point’ at *ca.* 240 nm was present in the titration with AcO^- , which indicates the presence of at least two species in solution. A plot of the changes at 282 nm as a function of anion equivalents reveal a plateau was reached at 4 equivalents in the case of H_2PO_4^- , but at 2 equivalents for AcO^- (Appendix, Figure A2.5).

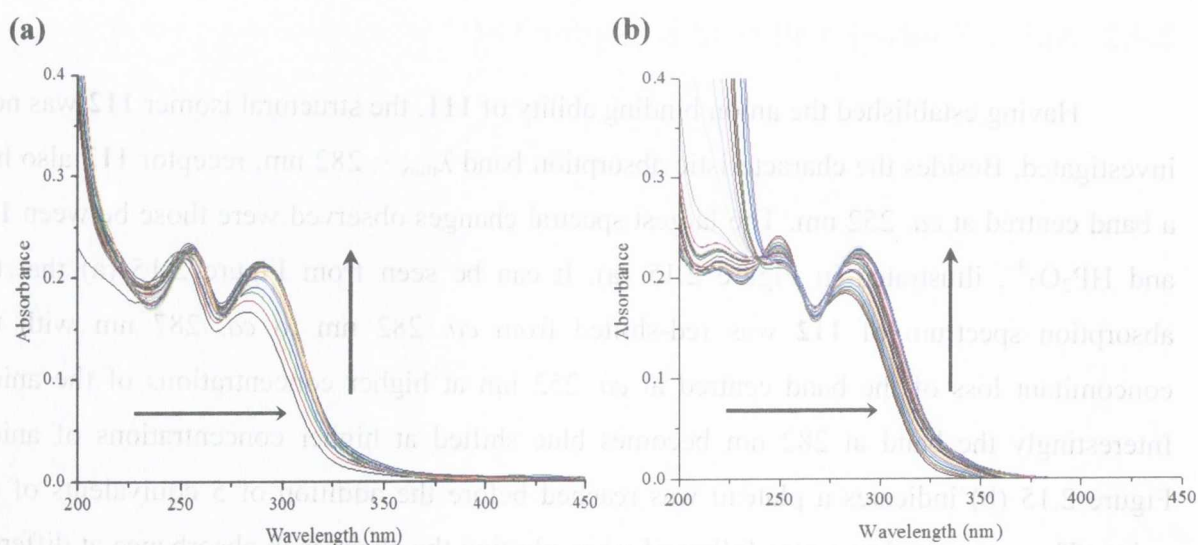


Figure 2.16: (a) Changes observed in the absorption spectrum of receptor **112** (1.1×10^{-5} M) upon titration with H_2PO_4^- ($0 \rightarrow 4.6$ mM) in CH_3CN . (b) Changes observed in the absorption spectrum of receptor **112** (1.08×10^{-5} M) upon titration with AcO^- ($0 \rightarrow 4.55$ mM) in CH_3CN .

The changes in the absorption spectrum upon titration with F^- , shown in Figure 2.17 (a), show a slight red shift of the band centred at *ca.* 282 nm. However, it was much less pronounced than that seen for $HP_2O_7^{3-}$. Moreover, the loss of the band at *ca.* 252 nm occurs at higher concentrations of F^- , with the concomitant formation of a shoulder at *ca.* 330 nm. From Figure 2.17 (b) it can be seen that a plateau is reached at *ca.* 5 equivalents of the anion.

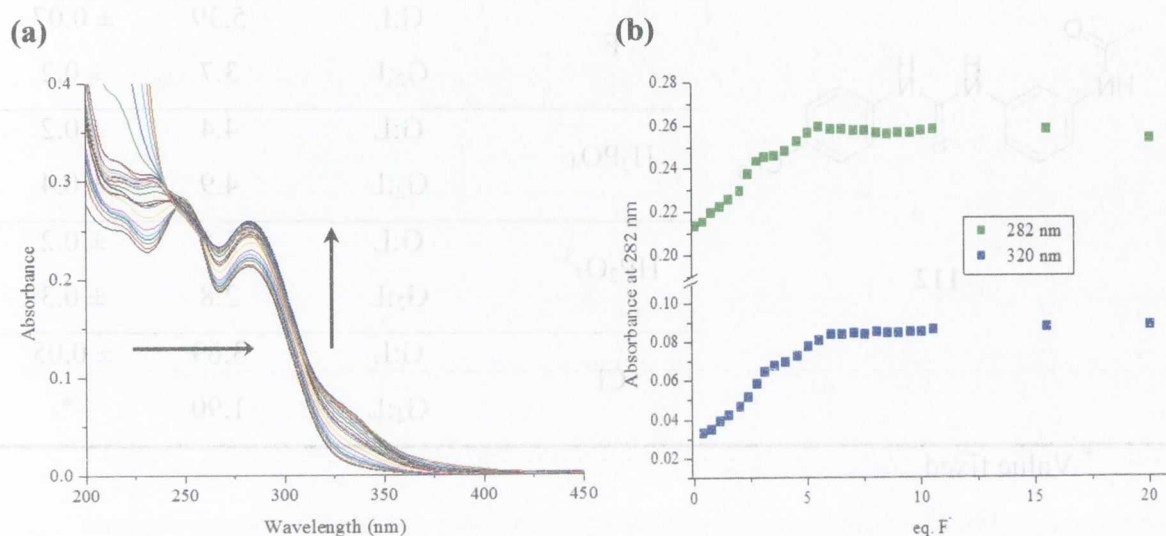


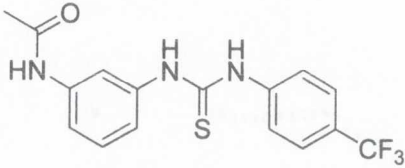
Figure 2.17: (a) Changes in the absorption spectrum of receptor **112** (1.1×10^{-5} M) upon titration with F^- ($0 \rightarrow 4.2$ mM) in CH_3CN . (b) The changes in the absorbance at 282 nm and 320 nm as a function of equivalents of F^- .

The spectral changes observed for Cl^- again occurred only at higher concentrations of the anion, and the bathochromic shift caused by the interaction with Cl^- was the smallest among the anions studied (Appendix, Figure. A2.6). No other significant changes in the shape or position of the λ_{max} of the spectra were observed.

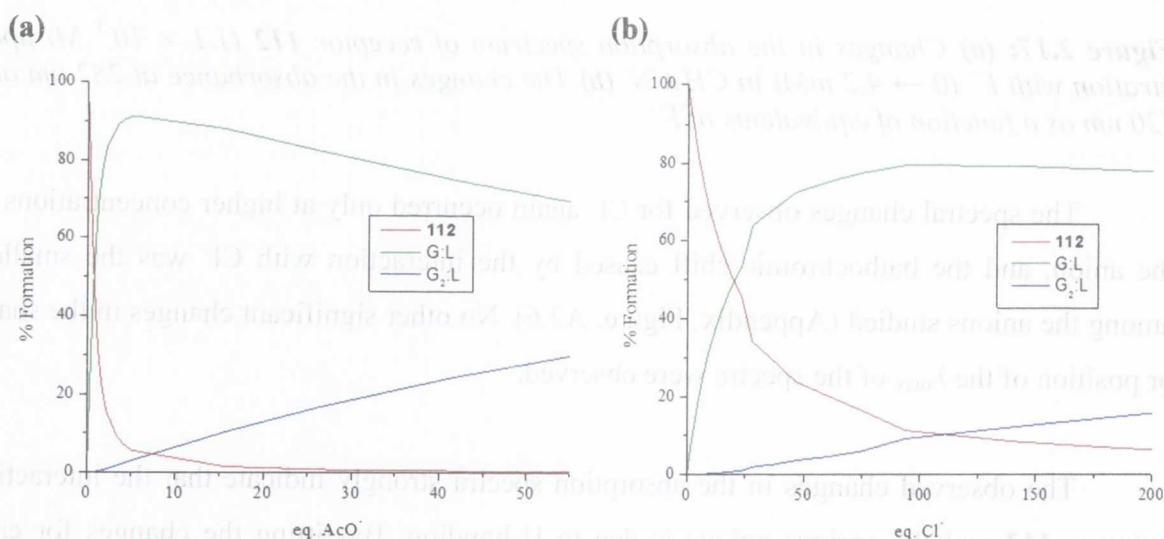
The observed changes in the absorption spectra strongly indicate that the interaction between **112** and the various anions is due to H-bonding. By fitting the changes for each titration, the binding constants for these anions and **112** were determined using SPECFITTM, the results of which are shown in Table 2.3. Again, all the anions were found to bind to the receptor *via* multiple binding modes.

It was found that the data for each anion was best fit to 1:1 and 2:1 (guest:host) stoichiometries. It appears that the formation of the 1:1 species was the most dominant species in solution for AcO^- and Cl^- , with a much smaller contribution from the 2:1 stoichiometry at higher equivalents of the anion, as shown in Figure 2.18 (a) and (b) respectively.

Table 2.3: Binding constants and binding modes between anions and receptor 112.

Receptor (L)	Anion (G)	Binding Mode $G_n:L_m$	$\log K_{n:m}$	Std. Deviation ($\pm$)
 112	AcO^-	G:L	5.6	± 0.1
		$G_2:L$	2.9	± 0.2
	F^-	G:L	5.39	± 0.07
		$G_2:L$	3.7	± 0.2
	H_2PO_4^-	G:L	4.4	± 0.2
		$G_2:L$	4.9	± 0.4
	$\text{HP}_2\text{O}_7^{3-}$	G:L	5.5	± 0.2
		$G_2:L$	2.8	± 0.3
	Cl^-	G:L	3.69	± 0.05
		$G_2:L$	1.90	—*

* Value fixed

**Figure 2.18: (a) Speciation distribution diagram for the absorption titration of 112 (L) with AcO^- . (b) Speciation distribution diagram for the absorption titration of 112 (L) with Cl^- .**

The changes in the absorption spectrum of 112 upon titration with H_2PO_4^- and the resultant fit obtained from SPECFITTM are depicted in Figure 2.19 (a). In contrast to AcO^- and Cl^- , the most dominant species in solution was found to be a 2:1 (guest:host) stoichiometry with only a very minor contribution from the 1:1 species, Figure 2.19 (b).

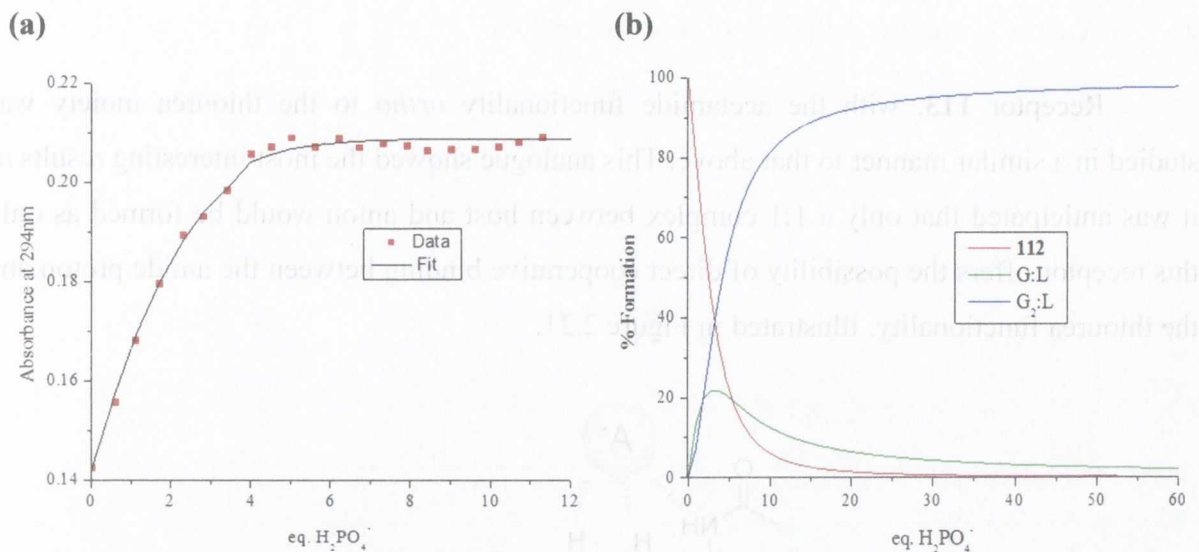


Figure 2.19: (a) Experimental binding isotherm for the titration of **112** and H_2PO_4^- and the corresponding fit from SPECFIT™. (b) Speciation distribution diagram for the absorption titration of **112** (L) with H_2PO_4^- .

In summary, the results obtained for **112** were significantly different to those observed for its urea counterpart, **109**. The binding constants determined for **109** with anions such as F^- , H_2PO_4^- and $\text{HP}_2\text{O}_7^{3-}$ were all best fitted to 1:1, 1:2 and 2:1 stoichiometries with the anion becoming “sandwiched” between the urea moieties of two ligands, illustrated in Figure 2.20, before the activation of the acetamide functionality lead to the formation of the 2:1 species. This behaviour was not observed between **112** and any of the anions studied herein. It was also noted that while AcO^- gave rise to slightly higher 1:1 binding to **112** in comparison to **109**, $\log K_{1:1} = 5.6 \pm 0.1$ and $\log K_{1:1} = 5.41 \pm 0.02$, respectively, Cl^- gave a lower binding constant $\log K_{1:1} = 3.69 \pm 0.05$ and $\log K_{1:1} = 4.86 \pm 0.09$ for **112** and **109**, respectively.

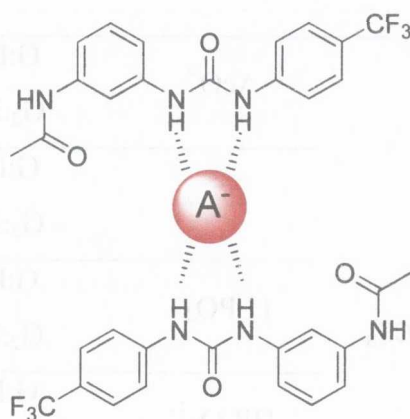


Figure 2.20: The proposed binding interaction between urea receptor **109** with anions.

2.4.3 Anion Binding Ability of Receptor 113

Receptor **113**, with the acetamide functionality *ortho* to the thiourea moiety was studied in a similar manner to that above. This analogue showed the most interesting results as it was anticipated that only a 1:1 complex between host and anion would be formed as only this receptor offers the possibility of direct cooperative binding between the amide proton and the thiourea functionality, illustrated in Figure 2.21.

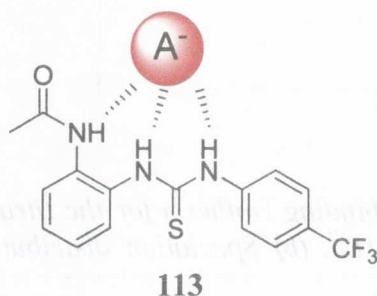
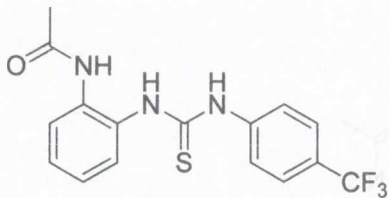


Figure 2.21: Predicted cooperative binding motif between the amide and thiourea moieties of receptor **113** with anions.

These were the results previously observed with the urea analogue. However, analysis of the data obtained, as shown in Table 2.4, indicates that this is not the case. Indeed the changes observed for all of the anions were best fitted to both 1:1 and 2:1 (guest:host) stoichiometries.

Table 2.4: Binding constants and binding modes between anions and receptor **113**.

Receptor (L)	Anion (G)	Binding Mode $G_n:L_m$	log $K_{n:m}$	Std. Deviation ($\pm$)
 113	AcO^-	G:L	5.46	± 0.05
		$G_2:L$	3.4	± 0.3
	F^-	G:L	5.30	± 0.05
		$G_2:L$	3.5	± 0.2
	H_2PO_4^-	G:L	4.81	± 0.01
		$G_2:L$	4.6	± 0.1
	$\text{HP}_2\text{O}_7^{3-}$	G:L	6.33	± 0.06
		$G_2:L$	2.1	± 0.2
	Cl^-	G:L	3.20	± 0.07
		$G_2:L$	2.0	± 0.01

The titration of **113** with H_2PO_4^- is shown in Figure 2.22 (a). It was found that the band centred at *ca.* 280 nm was red shifted to *ca.* 290 nm with the concomitant formation of an isosbestic point at *ca.* 235 nm. By plotting the changes in the absorbance at 250 nm, 280 nm and 320 nm, it was determined that a plateau was reached at *ca.* 5 equivalents of anion (Appendix, Figure A2.7). As can be seen from Figure 2.22 (b), an excellent fit was obtained for the changes observed in Figure 2.22 (a).

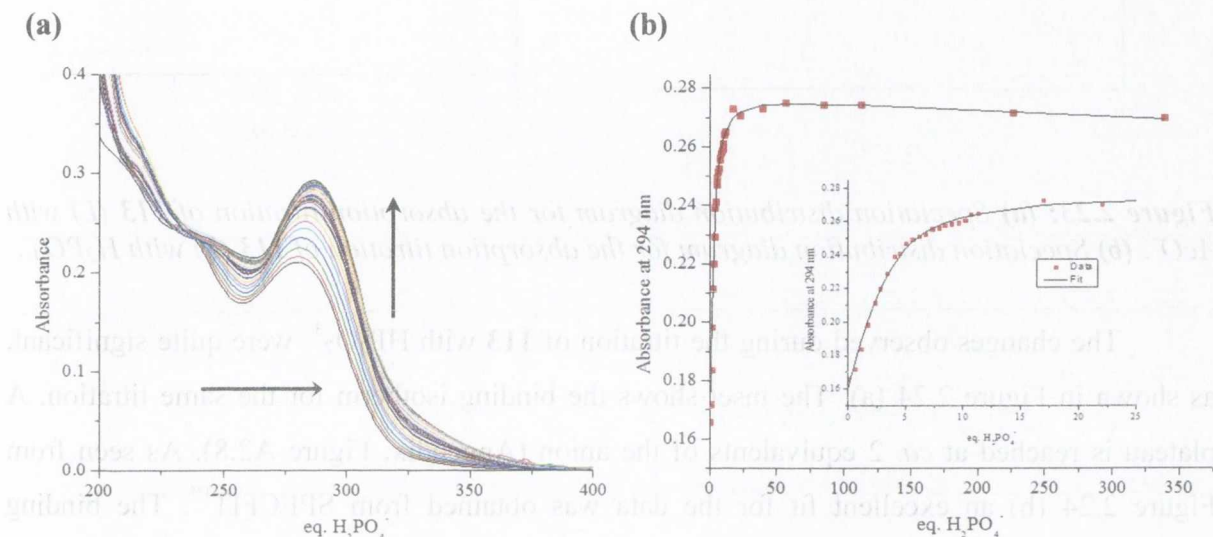


Figure 2.22: (a) Changes in the absorption spectrum of **113** (1.09×10^{-5} M) upon titration with H_2PO_4^- (0 → 4.72 mM) in CH_3CN . (b) Fit to the experimental binding isotherm obtained using SPECFIT™. The inset shows the fit between 0 and 25 equivalents of H_2PO_4^- .

Upon analysis of the titration data, two binding constants were determined in which the 1:1 stoichiometry resulted in a $\log K_{1:1} = 4.81 \pm 0.01$ and a second strong binding interaction with a $\log K_{2:1} = 4.6 \pm 0.1$ for **113** with H_2PO_4^- was also determined. Both AcO^- and F^- exhibited a strong 1:1 binding interaction with **113**, with $\log K_{1:1} = 5.46 \pm 0.05$ and $\log K_{1:1} = 5.30 \pm 0.05$ determined, respectively. However, the binding interaction for the 2:1 species for these anions was not as strong as that seen for H_2PO_4^- , as illustrated in Figure 2.23. The 1:1 species reaches 80% yield by *ca.* 5 equivalents of AcO^- , while the 1:1 complex of **113** and H_2PO_4^- only reached 40% formation by approximately the same number of equivalents. The reverse was observed with the 2:1 species, *i.e.* 50% formation by *ca.* 60 equivalents for AcO^- vs. 80% formation by *ca.* 20 equivalents for H_2PO_4^- .

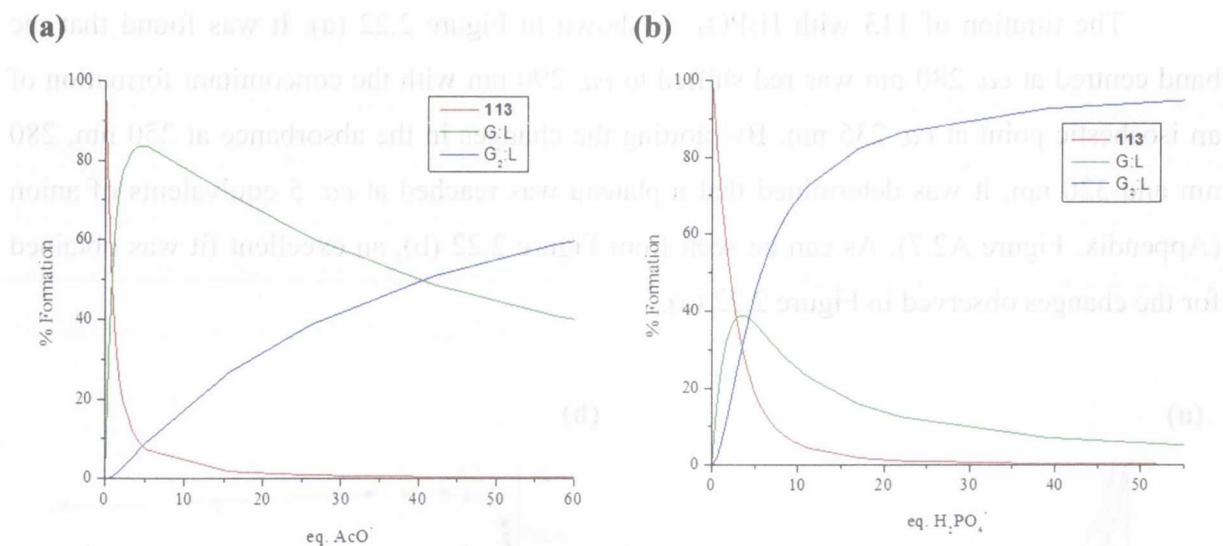


Figure 2.23: (a) Speciation distribution diagram for the absorption titration of **113** (L) with AcO^- . (b) Speciation distribution diagram for the absorption titration of **113** (L) with H_2PO_4^- .

The changes observed during the titration of **113** with $\text{HP}_2\text{O}_7^{3-}$ were quite significant, as shown in Figure 2.24 (a). The inset shows the binding isotherm for the same titration. A plateau is reached at *ca.* 2 equivalents of the anion (Appendix, Figure A2.8). As seen from Figure 2.24 (b) an excellent fit for the data was obtained from SPECFITTM. The binding constant for the 1:1 species was determined to be the highest of all the anions studied with $\log K_{1:1} = 6.33 \pm 0.06$. However the 2:1 (guest:host) complex was much less significant with $\log K_{2:1} = 2.1 \pm 0.2$ being determined.

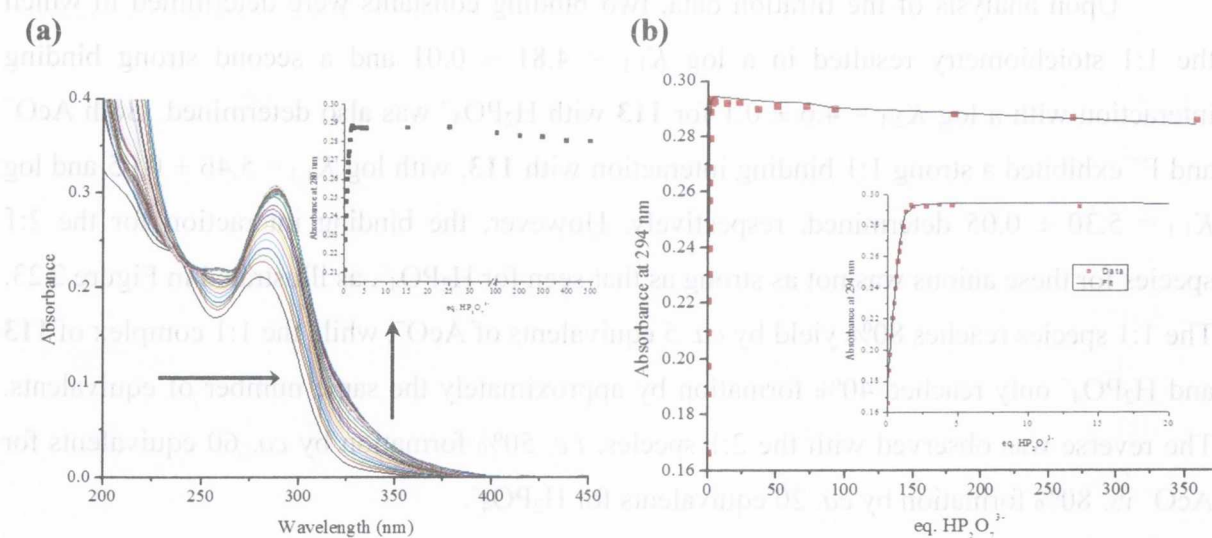


Figure 2.24: (a) Changes in the absorption spectrum of **113** (1×10^{-5} M) upon titration with $\text{HP}_2\text{O}_7^{3-}$ (0 → 4.6 mM) in CH_3CN . The inset shows the changes in the absorbance at 280 nm as a function of equivalents of $\text{HP}_2\text{O}_7^{3-}$. (b) Fit to the experimental binding isotherm obtained using SPECFITTM.

Once again the smallest spectral changes observed were for Cl^- , where the band at *ca.* 280 nm was red shifted to *ca.* 285 nm, Figure 2.25 (a). The formation of an isosbestic point was present at shorter wavelengths, at *ca.* 235 nm and the changes continued to occur even at very high concentrations of the anion, up to *ca.* 200 equivalents of the anion. The fit obtained for the titration is shown in Figure 2.25 (b), however the binding constants obtained for both the 1:1 and 2:1 (guest:host) stoichiometries were the lowest obtained for all the anions studied with $\log K_{1:1} = 3.20 \pm 0.07$ and $\log K_{2:1} = 2.0 \pm 0.01$, respectively.

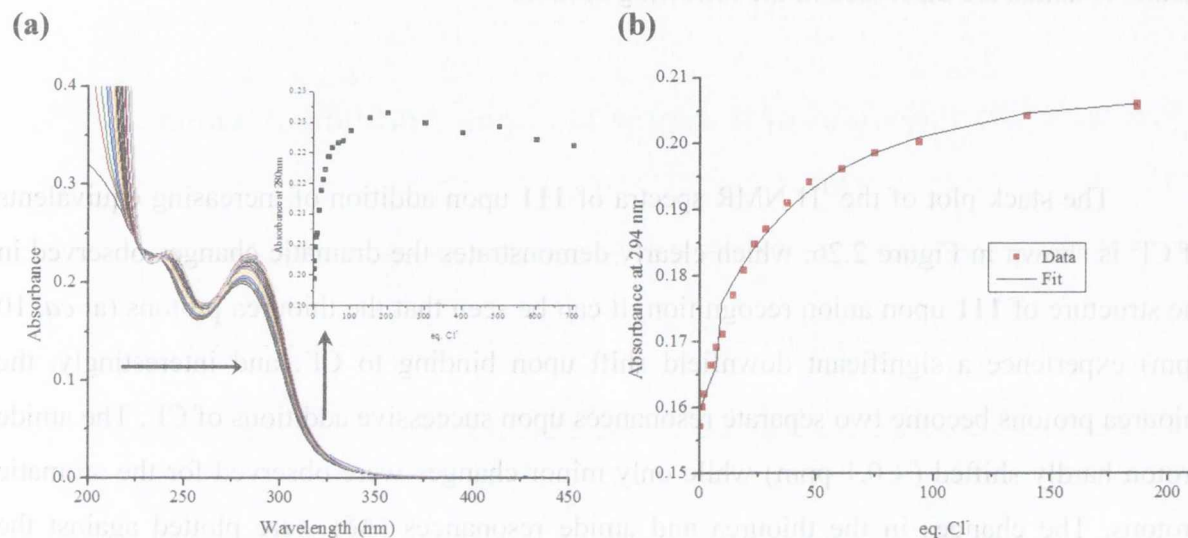


Figure 2.25: (a) Changes in the absorption spectrum of **113** (1×10^{-5} M) upon titration with Cl^- ($0 \rightarrow 5.6$ mM) in CH_3CN . The inset shows the changes in the absorbance at 280 nm as a function of equivalents of Cl^- . (b) Fit to the experimental binding isotherm obtained using SPECFITTM.

When these results were compared to that of the urea analogue **110** it was also found that there were some similarities. The binding constants obtained for AcO^- were almost identical with $\log K_{1:1} = 5.45 \pm 0.02$ and $\log K_{1:1} = 5.46 \pm 0.02$ for **113** and **110** respectively. Furthermore, the results for Cl^- were also comparable with $\log K_{1:1} = 3.60 \pm 0.05$ and $\log K_{1:1} = 3.20 \pm 0.07$ for **113** and **110** respectively. This pattern is repeated with the other anions studied. However, the main anomaly is the 2:1 stoichiometries obtained for **113** with all of the anions investigated. This is in stark contrast with the results obtained for the urea analogue **110** as it appeared that the amide functionality of receptor **113** is orientated such that a 2:1 species is possible.

In order to gain a better understanding of these interactions, ¹H NMR studies of **111-113** and the various anions were carried out and the results of these investigations will be discussed in the following sections.

2.5 ^1H NMR Titrations of Receptors **111-113** with Anions

^1H NMR spectroscopy is a useful technique to directly observe the effect of anion complexation on the N-H protons of receptors such as **111-113**. Therefore, ^1H NMR titrations were also carried out in order to further understand the binding affinities of these receptors towards the various anions studied photophysically. The ^1H NMR titrations of **111-113** were all carried out in $\text{DMSO}-d_6$, which enabled us to clearly follow the changes in the chemical environment of all of the N-H protons in these structures upon binding to the anions. The results obtained are discussed in the following section.

2.5.1 ^1H NMR Titrations of Receptor **111** upon Addition of Anions

The stack plot of the ^1H NMR spectra of **111** upon addition of increasing equivalents of Cl^- is shown in Figure 2.26, which clearly demonstrates the dramatic changes observed in the structure of **111** upon anion recognition. It can be seen that the thiourea protons (at *ca.* 10 ppm) experience a significant downfield shift upon binding to Cl^- , and interestingly, the thiourea protons become two separate resonances upon successive additions of Cl^- . The amide proton hardly shifted (< 0.1 ppm) while only minor changes were observed for the aromatic protons. The changes in the thiourea and amide resonances ($\Delta\delta$) were plotted against the equivalents of anion added, shown in Figure 2.27 (a) and (b) respectively, to give binding isotherms for the titration. The thiourea protons (N-Ha and N-Hb) were shifted downfield, with changes still occurring even at higher concentrations of Cl^- , indicative of strong H-bonding to the receptor moiety. The amide proton (N-Hc) was also immediately shifted downfield with the more significant changes occurring after *ca.* 2 equivalents. These results confirm the results previously observed from the absorption studies.

The results observed between **111** and AcO^- , depicted by the binding isotherm in Figure 2.28, show that the binding of the anion had a major effect on the N-H protons, which in the case of the thiourea N-H protons occurred within the addition of 0 to 1.5 equivalents of AcO^- , Figure 2.28 (a). It can be seen from Figure 2.28 (b) that the amide proton was shifted upfield initially. However, beyond 1.5 equivalents it was shifted downfield as a function of increased AcO^- concentration. This phenomenon was also observed for the urea analogues **108-110**, and was attributed to the anion initially binding at the urea moiety *via* H-bonding, with the amide functionality becoming activated at higher concentrations of the anion. These results also correlate with the absorption studies carried out with **111** and the various anions discussed previously.

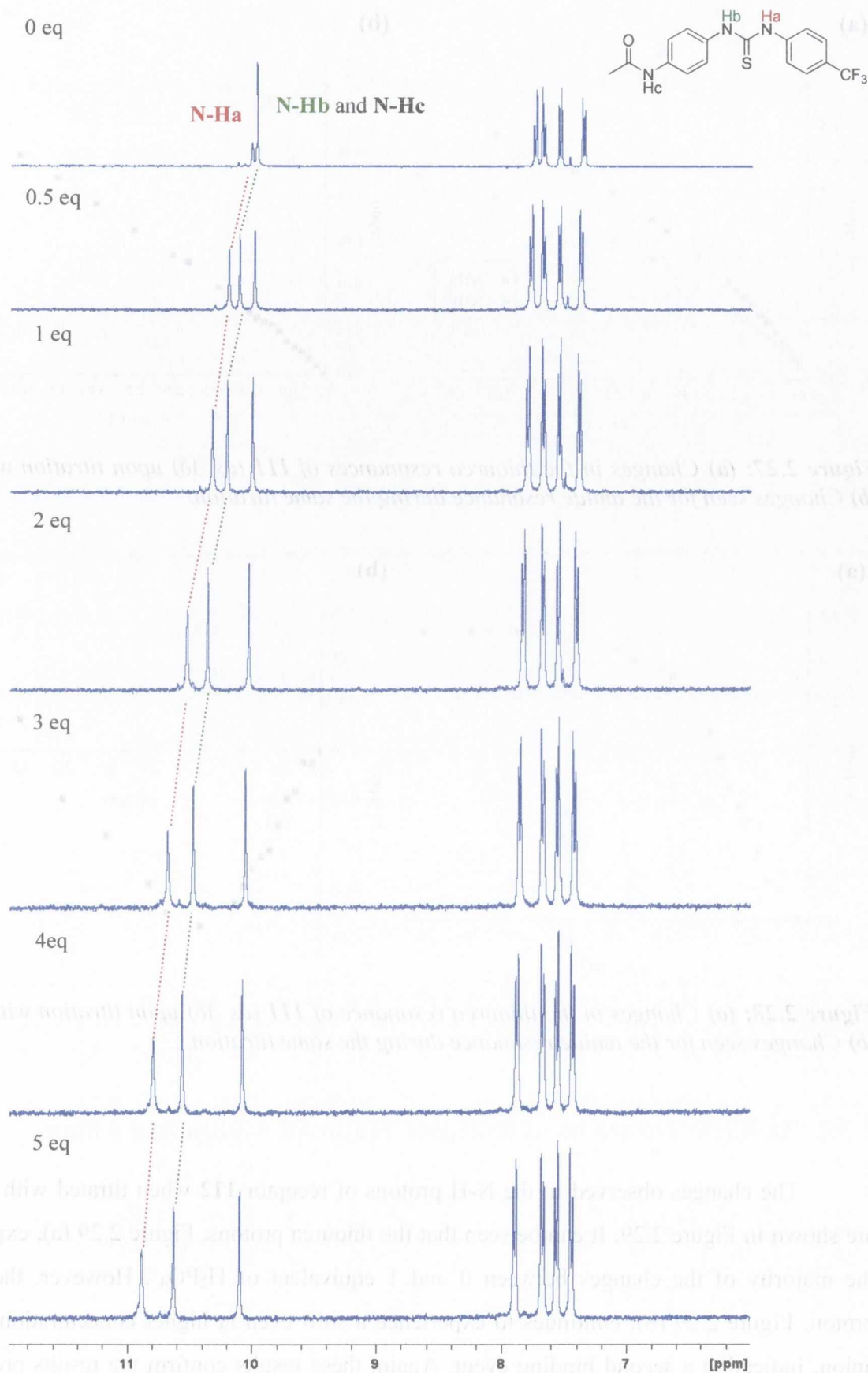


Figure 2.26: Stack plot of the ^1H NMR (400 MHz, $\text{DMSO}-d_6$) spectra of **111** (7×10^{-3} M) upon addition of 0.5, 1, 2, 3, 4 and 5 equivalents of CT. **N-Ha** and **N-Hb** are the thiourea protons, while **N-Hc** is the amide proton.

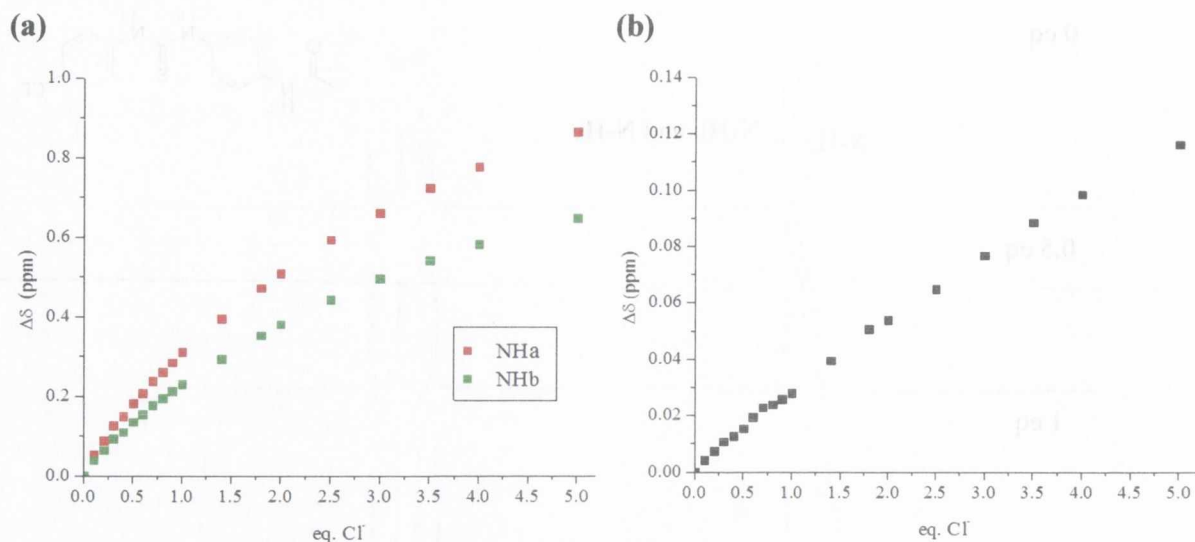


Figure 2.27: (a) Changes in the thiourea resonances of **111** (as $\Delta\delta$) upon titration with Cl^- . (b) Changes seen for the amide resonance during the same titration.

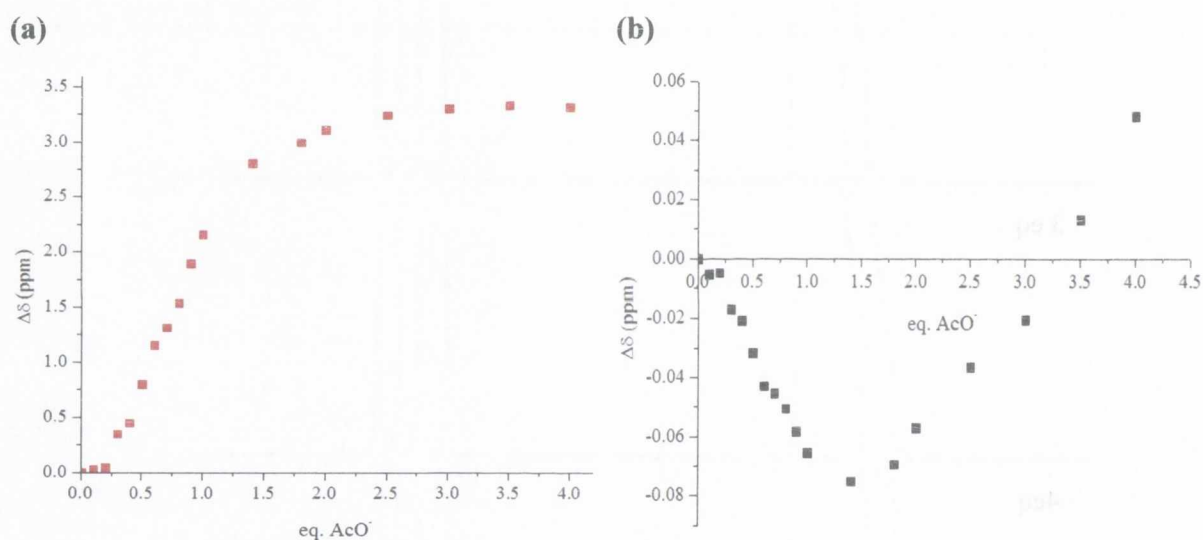


Figure 2.28: (a) Changes in the thiourea resonance of **111** (as $\Delta\delta$) upon titration with AcO^- . (b) Changes seen for the amide resonance during the same titration.

2.5.2 ^1H NMR Titrations of Receptor **112** upon Addition of Anions

The changes observed in the N-H protons of receptor **112** when titrated with H_2PO_4^- are shown in Figure 2.29. It can be seen that the thiourea protons, Figure 2.29 (a), experience the majority of the changes between 0 and 1 equivalent of H_2PO_4^- . However, the amide proton, Figure 2.29 (b), continues to experience a shift even at higher concentrations of the anion, indicating a second binding event. Again, these results confirm the results previously determined from the absorption studies. Similar results were seen for the titration between **112** and AcO^- , with the majority of the changes occurring between 0 and 1.5 equivalents for the

thiourea protons, Figure 2.30 (a). The amide proton was again initially shifted upfield but at higher concentrations of the anion it experienced a downfield shift, Figure 2.30 (b).

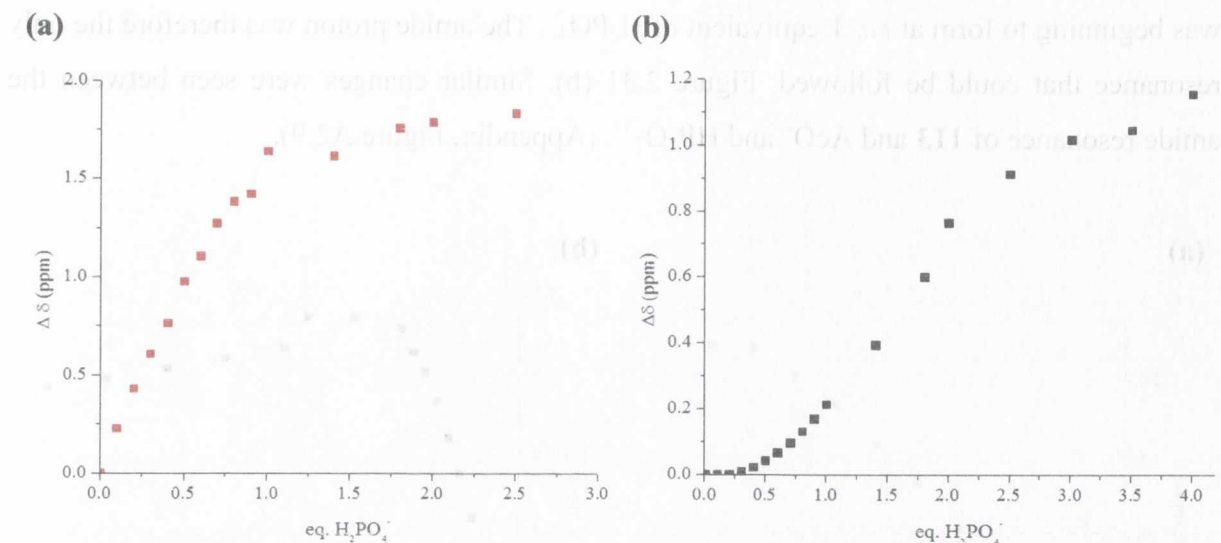


Figure 2.29: (a) Changes in the thiourea resonance of **112** (as $\Delta\delta$) upon titration with H_2PO_4^- . (b) Changes seen for the amide resonance during the same titration.

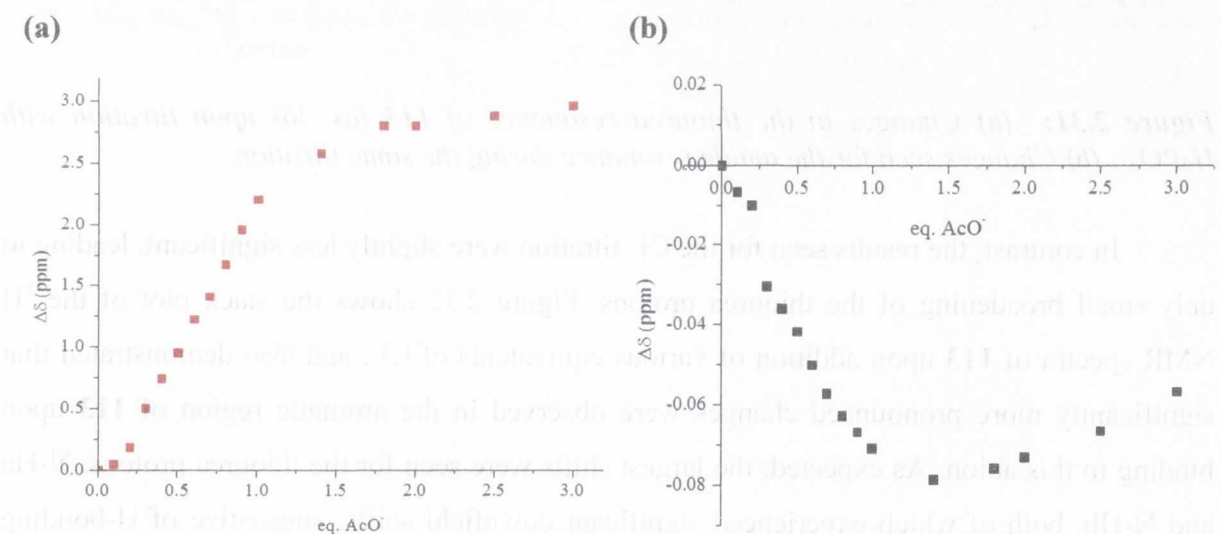


Figure 2.30: (a) Changes in the thiourea resonance of **112** (as $\Delta\delta$) upon titration with AcO^- . (b) Changes seen for the amide resonance during the same titration.

2.5.3 ^1H NMR Titrations of Receptor **113** upon Addition of Anions

The third receptor **113**, which demonstrated the most unusual results in the absorption studies out of the three receptors, was also investigated by ^1H NMR spectroscopy. The interaction with this receptor and the various anions was indeed quite strong, as determined by the magnitude of the shift of the thiourea and amide protons. In general, the thiourea protons experienced a large downfield shift with a concomitant broadening of the two resonances. For

example, Figure 2.31 (a) shows the plot of the changes in the thiourea resonance ($\Delta\delta$) against the equivalents of added H_2PO_4^- . Even at lower concentrations of the anion, the protons were so broadly shifted that the resonances were not visible. However, it appeared that a plateau was beginning to form at *ca.* 1 equivalent of H_2PO_4^- . The amide proton was therefore the only resonance that could be followed, Figure 2.31 (b). Similar changes were seen between the amide resonance of **113** and AcO^- and $\text{HP}_2\text{O}_7^{3-}$, (Appendix, Figure A2.9).

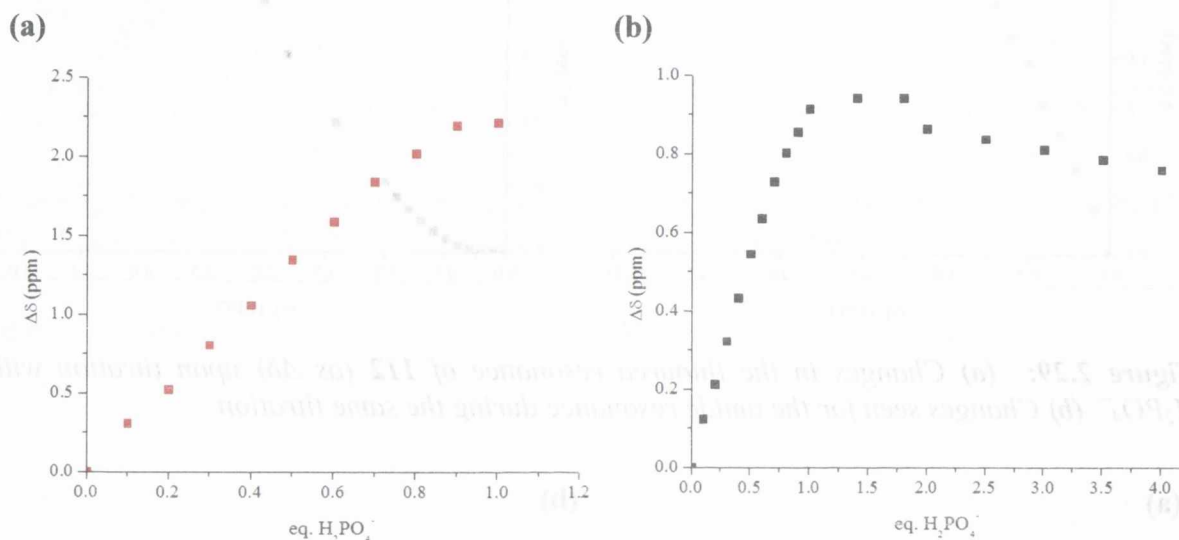


Figure 2.31: (a) Changes in the thiourea resonance of **113** (as $\Delta\delta$) upon titration with H_2PO_4^- . (b) Changes seen for the amide resonance during the same titration.

In contrast, the results seen for the Cl^- titration were slightly less significant, leading to only small broadening of the thiourea protons. Figure 2.32 shows the stack plot of the ^1H NMR spectra of **113** upon addition of various equivalents of Cl^- , and also demonstrated that significantly more pronounced changes were observed in the aromatic region of **113** upon binding to this anion. As expected, the largest shifts were seen for the thiourea protons, N-Ha and N-Hb, both of which experienced significant downfield shifts, suggestive of H-bonding between **113** and Cl^- . However, the amide proton, N-Hc did not appear to be shifted and it was therefore concluded that the amide proton was not involved in the binding to any great extent.

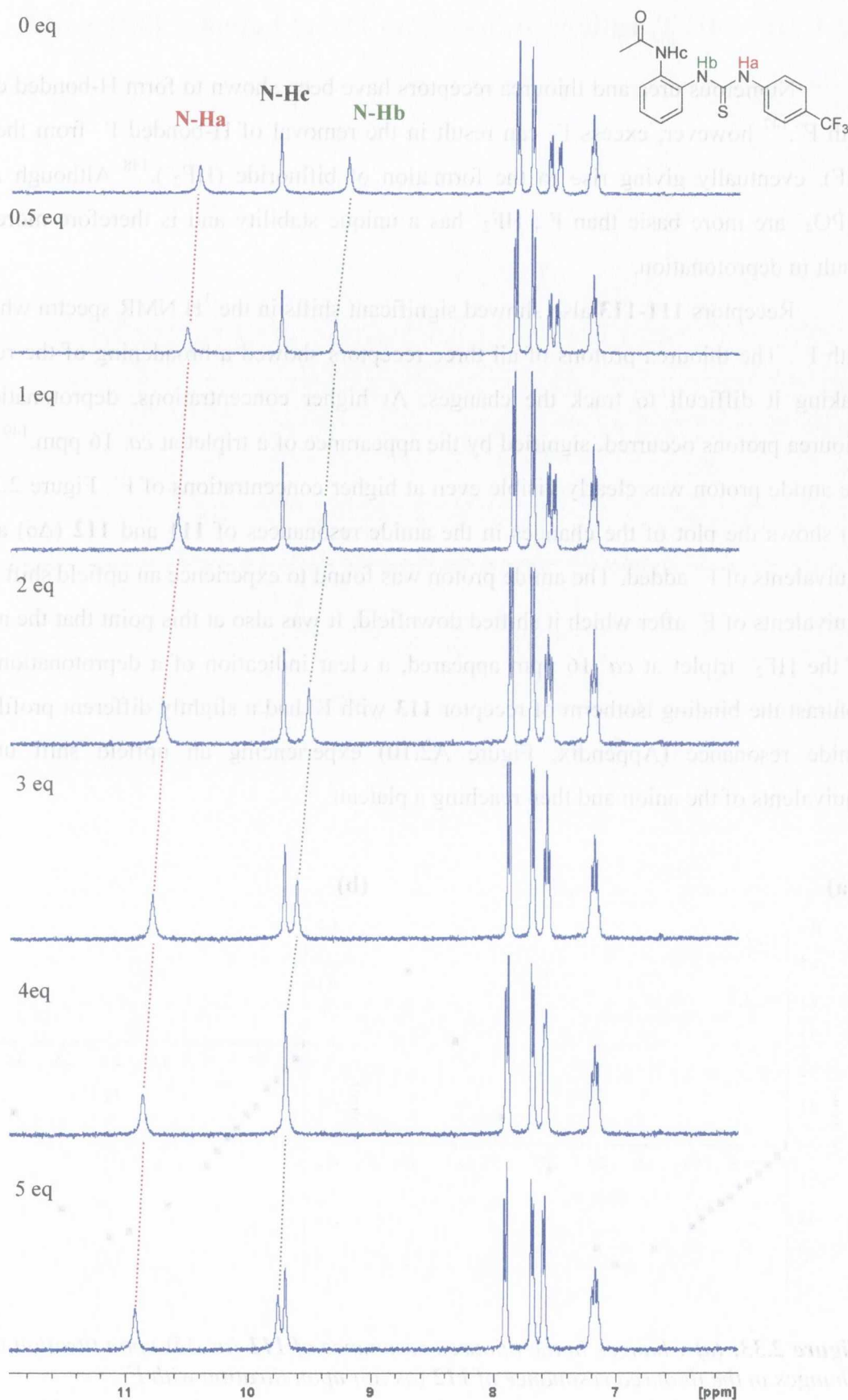


Figure 2.32: Stack plot of the ^1H NMR (400 MHz, $\text{DMSO}-d_6$) spectra of **113** (7×10^{-3} M) upon addition of 0.5, 1, 2, 3, 4, and 5 equivalents of CT. **N-Ha** and **N-Hb** are the thiourea protons, while **N-Hc** is the amide proton.

2.5.4 ^1H NMR Titrations of Receptors **111**-**113** upon Addition of F^-

Numerous urea and thiourea receptors have been shown to form H-bonded complexes with F^- ,¹⁴⁷ however, excess F^- can result in the removal of H-bonded F^- from the complex (HF), eventually giving rise to the formation of bifluoride (HF_2^-).¹⁴⁸ Although AcO^- and H_2PO_4^- are more basic than F^- , HF_2^- has a unique stability and is therefore more likely to result in deprotonation.

Receptors **111**-**113** also showed significant shifts in the ^1H NMR spectra when titrated with F^- . The thiourea protons of all three receptors showed a broadening of the resonances, making it difficult to track the changes. At higher concentrations, deprotonation of the thiourea protons occurred, signified by the appearance of a triplet at *ca.* 16 ppm.¹⁴⁹ However, the amide proton was clearly visible even at higher concentrations of F^- . Figure 2.33 (a) and (b) shows the plot of the changes in the amide resonances of **111** and **112** ($\Delta\delta$) against the equivalents of F^- added. The amide proton was found to experience an upfield shift until *ca.* 2 equivalents of F^- after which it shifted downfield. It was also at this point that the appearance of the HF_2^- triplet at *ca.* 16 ppm appeared, a clear indication of a deprotonation event. In contrast the binding isotherm of receptor **113** with F^- had a slightly different profile with the amide resonance (Appendix, Figure A2.10) experiencing an upfield shift until *ca.* 2 equivalents of the anion and then reaching a plateau.

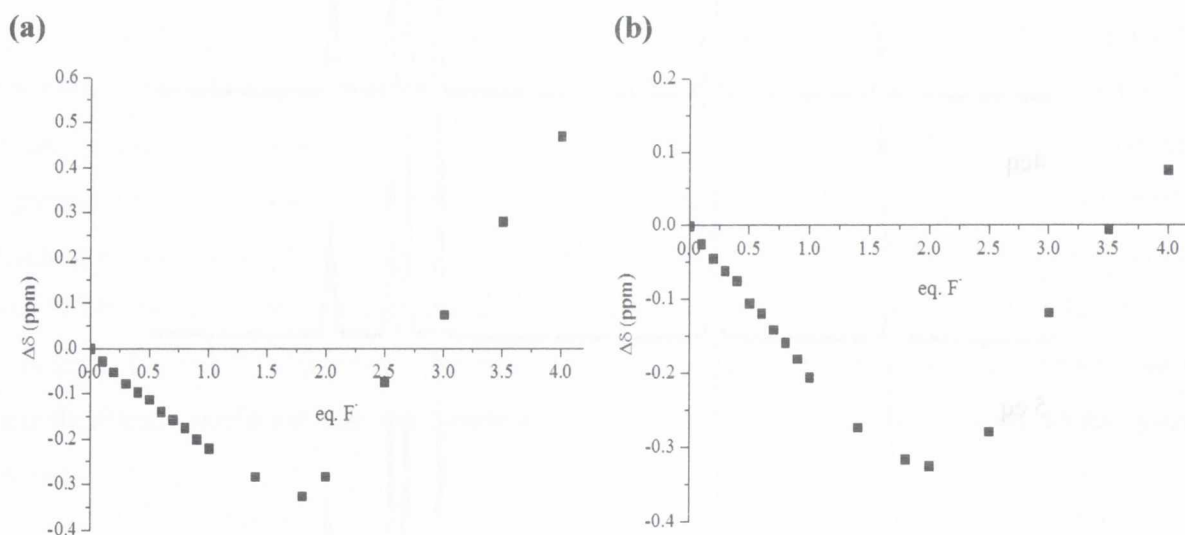


Figure 2.33: (a) Changes in the thiourea resonance of **111** (as $\Delta\delta$) upon titration with F^- . (b) Changes in the thiourea resonance of **112** (as $\Delta\delta$) upon titration with F^- .

These ^1H NMR studies are in agreement with the data obtained from the UV-Vis absorption titrations. It was found that the position of the acetamide functionality on the ring greatly influenced the anion binding affinity of receptors **111**-**113**, especially for receptor **113**

where it is available as a second binding site for the various anions but is unavailable to bind them in the urea analogue **110**. This second binding event is a direct consequence of the thiourea moiety present in receptor **113**.

2.6 Conclusion

In conclusion, three anion receptors **111-113** have been synthesised, and fully characterised, and their various spectroscopic properties analysed in the presence of several biologically important anions. Crystals suitable for X-ray crystal structure analysis were obtained for receptor **113**. All of the receptors were found to interact *via* H-bonding with various anions such as AcO^- , F^- , H_2PO_4^- , $\text{HP}_2\text{O}_7^{3-}$ and Cl^- as determined by the changes in their respective absorption spectra. A possible conformation for the H-bonding complex formed between **111-113** and AcO^- is illustrated in Figure 2.34.

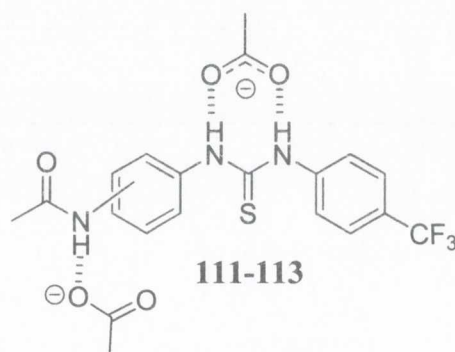


Figure 2.34: Possible H-bonding complex between **111-113** and AcO^- .

When compared to their urea counterparts, **108-110**, many of the anticipated trends were not observed. For example, it was expected that the thiourea receptors would show increased binding affinity to the various anions compared to the urea analogues, however in some instances this was not found to be the case. Also receptor **113** was only expected to bind in a 1:1 stoichiometry due to cooperative binding between the amide and thiourea functionalities, but all of the anions formed a 2:1 species with this receptor. It has been suggested that thioureas are conformationally more flexible than their urea analogues, leading to the possibility that any conformational changes within the thiourea receptors may affect, to a certain extent, their anion binding properties.^{150,151} We have also compared the binding affinity of **111** and **112**, particularly with that of **108** and **109**, respectively. These demonstrate that the thiourea receptors are, in general, stronger anion binders. The ratio between $\log K_{1:1}$ and $\log K_{2:1}$ (as $\log K_{2:1}/\log K_{1:1}$) for these receptors can also be compared. These results show that for **111**, the binding of AcO^- , F^- , H_2PO_4^- , $\text{HP}_2\text{O}_7^{3-}$ and Cl^- gave $\log K_{1:1}/\log K_{2:1}$ values of

0.71, 0.83, 0.87 and 0.79 for these anions, respectively, while for the urea analogue **108**, this ratio was 0.66, 0.51, 0.62 and 0.58. Similar trends were also seen for **112** upon comparison with **109**. This seems to suggest that the ‘allosteric effect’ might be stronger in the thiourea systems.

In conclusion, these anion receptors **111–113** have been synthesised and fully characterised, and their various spectroscopic properties measured in the presence of several biologically important anions. Of note, suitable for X-ray crystal structure analysis were obtained for receptor **112**. All of the receptors were found to interact via H-bonding with various anions such as AcO^- , F^- , H_2PO_4^- , HPO_4^{2-} , $\text{H}_2\text{O}_4^{2-}$ and Cl^- as determined by the changes in their respective absorption spectra. A possible conformation for the H-bonding complex formed between **111–113** and AcO^- is illustrated in Figure 2.34.



Figure 2.34: Possible H-bonding complex between **111–113** and AcO^- .

When compared to their urea counterparts, **108–110**, many of the anticipated trends were not observed. For example, it was expected that the thiourea receptors would show increased binding affinity to the various anions compared to the urea analogues, however in some instances this was not found to be the case. Also, receptor **112** was only expected to bind in a 1:1 stoichiometry due to cooperative binding between the amide and thiourea functionalities, but all of the anions formed a 2:1 species with this receptor. It has been suggested that thioureas are conformationally more flexible than their urea analogues, leading to the possibility that any conformational changes within the thiourea receptors may affect to a certain extent their anion binding properties.¹⁰⁰ We have also compared the binding affinity of **111** and **112** (predominantly with that of **108** and **109**, respectively). These demonstrate that the thiourea receptors are, in general, stronger anion binders. The ratio between $\log K_1$ and $\log K_2$ (as $\log K_2/\log K_1$) for these receptors can also be compared. These results show that for **111**, the binding of AcO^- , F^- , H_2PO_4^- , HPO_4^{2-} and Cl^- give $\log K_2/\log K_1$ values of

Chapter 3

Thiourea Functionalised Tröger's Base Anion Receptors

Chapter 3

Introduction to the Chapter

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3. Introduction

As described in previous Chapters, the recognition of anions *via* non-covalent interactions is of major interest in host-guest chemistry. In particular, the use of molecular clefts have attracted significant attention in supramolecular chemistry due to their ability to allow functional groups to be orientated in defined geometries.^{152,153} Specific geometries can also be exploited by arranging the H-bond donors around the acceptors in three-dimensional space.¹⁵⁴ If the host's preorganised binding cavity complements the guest's geometry, then high selectivity can be achieved.¹⁵⁵

Tröger's base (**125**) is a structural motif, first described by Julius Tröger in 1887,¹⁵⁶ which has become a core building block in supramolecular chemistry due to its chirality and relatively rigid geometry, illustrated in Figure 3.1.¹⁵⁷ Specifically, Tröger's base is a chiral diamine bearing two stereogenic bridge-head nitrogen atoms. The two aromatic rings fused to the central bicyclic framework are almost perpendicular to each other, creating a rigid, V-shaped C₂-symmetrical molecular scaffold.¹⁵⁸ It was originally prepared from *p*-toluidine in a condensation reaction with formaldehyde, however it was not until 1935 that its structure was correctly elucidated by Spielman¹⁵⁹ and in 1944 the two enantiomers first separated by Prelog.¹⁶⁰ In 1986, the structure was unambiguously confirmed with the aid of single-crystal X-ray diffraction analysis, Figure 3.1 (b).¹⁶¹

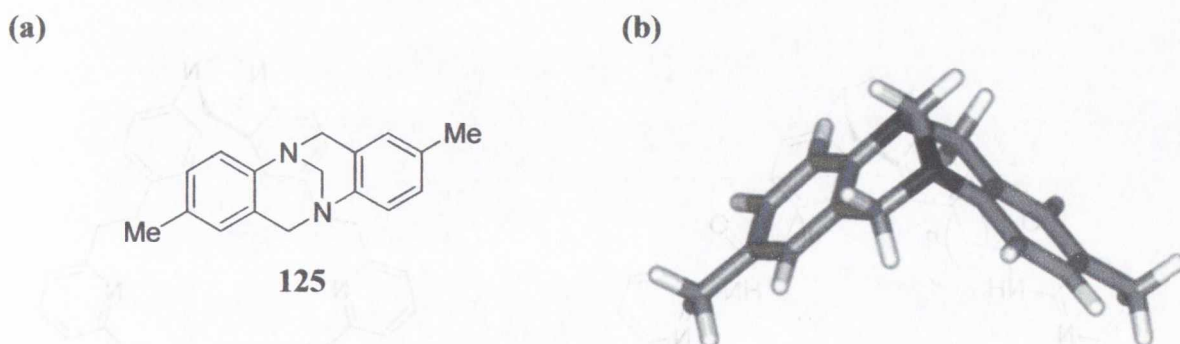


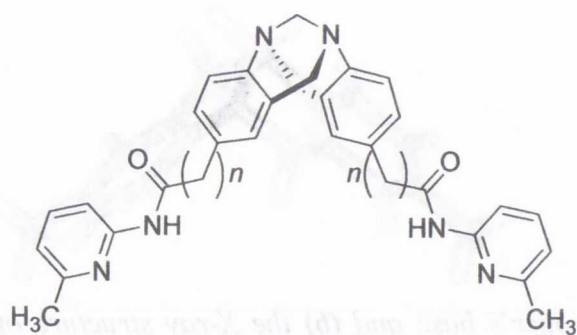
Figure 3.1: (a) The structural formula of Tröger's base and (b) the X-ray structure of the optimised geometry of the (S,S)-enantiomer.¹⁵⁹

The unique shape and chirality of **125** has played a considerable role in the field of supramolecular chemistry and the following section will give an overview of some of the examples that have incorporated **125** derivatives into various supramolecular systems. However, considering these attractive features, it would be expected that significant interest in analogues of **125** in the area of anion recognition would exist. Surprisingly, such applications remain completely unexplored.

3.1 Applications of Tröger's Base Derivatives

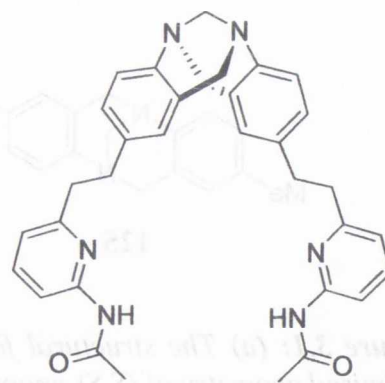
Since the 1980's, following the initial studies of Wilcox and co-workers who did extensive work with Tröger's base derivatives,¹⁶² a revival in the interest of its chemistry ensued.¹⁶³ The extensive use of **125** now plays an important role in supramolecular chemistry, specifically in the area of molecular recognition, as well as in the development of torsion balances,¹⁶⁴ water-soluble cyclophanes,¹⁶⁵ chiral solvating agents¹⁶⁶ and in the formation of various hydrogen- and metal-ligand bonding receptors.^{167,168}

The design and synthesis of amidopyridine Tröger's base receptors **126-128**, with different chain lengths to facilitate the recognition of dicarboxylic acids, were reported by Goswami and Ghosh.¹⁶⁹ ¹H NMR spectroscopic titrations carried out in 98:2% CDCl₃-DMSO-*d*₆ solution, with a series of dicarboxylic acids showed that the cavity of **126** was selective for suberic acid. Strong complexation of **126** with suberic acid was also observed by fluorescence spectroscopy, with a binding constant of $K_a = 2.5 \times 10^4 \text{ M}^{-1}$ calculated and found to concur with the value observed in the ¹H NMR titration experiments. The more flexible receptors **127** and **128** exhibited weaker binding to the same dicarboxylic acids. A marginal increase in K_a was observed for suberic and sebacic acids. However, the stoichiometry of these complexes, determined from the breaks in the titration curve ($\Delta\delta$ vs. $C_{\text{guest}}/C_{\text{host}}$), was 1:2 (guest:host) rather than 1:1.



126; $n = 0$

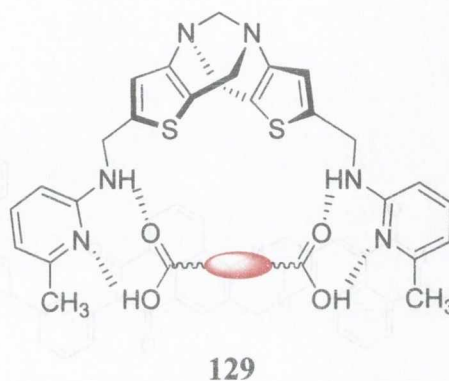
127; $n = 1$



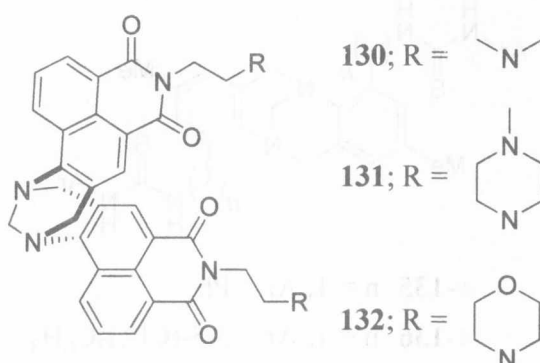
128

In a related study, Kobayashi and Moriwaki reported the thiophene Tröger's base derivative **129** bearing two pyridylamino groups for targeting both aliphatic and aromatic dicarboxylic acids.¹⁷⁰ The complexation properties of **129** were studied by ¹H NMR spectroscopic titrations in 99.5:0.5% CDCl₃-DMSO-*d*₆ solution. The stoichiometry and

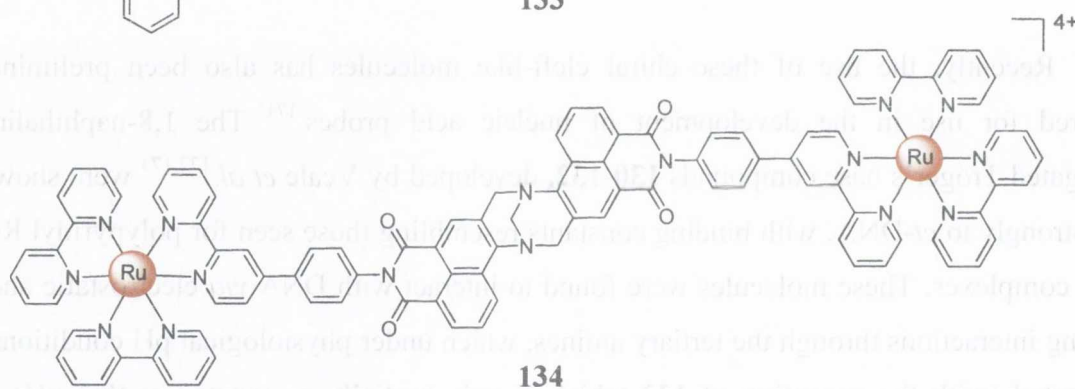
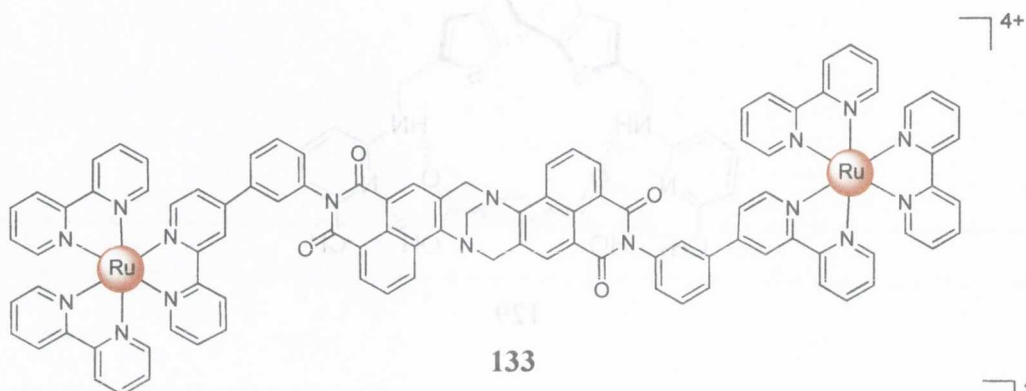
chemical shift of the 3'-H of the pyridine ring. All dicarboxylic acids studied, except for malonic acid and phthalic acid, were proposed to form complexes with **129** in a 1:1 stoichiometry, binding the dicarboxylic acids non-selectively with a binding affinity in the range of approximately 10^3 – 10^4 M⁻¹. In contrast, significantly higher selectivity was determined for malonic ($K_a = 1.9 \times 10^5$ M⁻²) and phthalic ($K_a = 7.0 \times 10^4$ M⁻²) acids, which was found to bind to receptor **129** with a 1:2 (guest:host) stoichiometry.



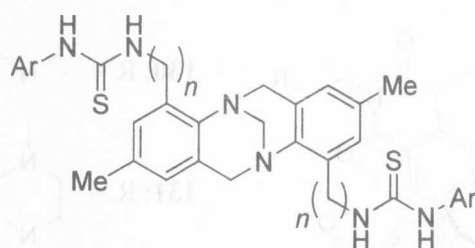
Recently, the use of these chiral cleft-like molecules has also been preliminarily explored for use in the development of nucleic acid probes.¹⁷¹ The 1,8-naphthalimide conjugated Tröger's base compounds **130–132**, developed by Veale *et al.*^{172,173} were shown to bind strongly to *ct*-DNA, with binding constants resembling those seen for polypyridyl Ru(II) metal complexes. These molecules were found to interact with DNA *via* electrostatic and H-bonding interactions through the tertiary amines, which under physiological pH conditions are protonated (with the exception of **132** which is only partially protonated at that pH). The compounds were also shown to have the ability to bind to DNA *via* intercalation; and interestingly, could also function as dual imaging–therapeutic agents as biological imaging studies showed that the structures accumulated within the nucleus and gave rise to cellular death in drug-resistant K562 leukaemia cell lines.



The use of Tröger's base in conjunction with metal ion complexes has also been demonstrated to be an effective way of enhancing the binding of such structures to DNA.¹⁷⁴ Molecules **133** and **134**, which are appended to both a 1,8-naphthalimide chromophore and a Ru(II)-polypyridyl centre, are such an example recently reported by Gunnlaugsson and co-workers.¹⁷⁵ These compounds were found to stabilise double stranded DNA and also undergo rapid cellular uptake, displaying good luminescence without affecting cell viability even after 24 hours of incubation.



To the best of our knowledge, the only example of thiourea functionalised Tröger's base are compounds **135-137** however, they were studied for their catalytic activity in Michael addition reactions of malonate derivatives to *trans*- β -nitrostyrene.¹⁷⁶



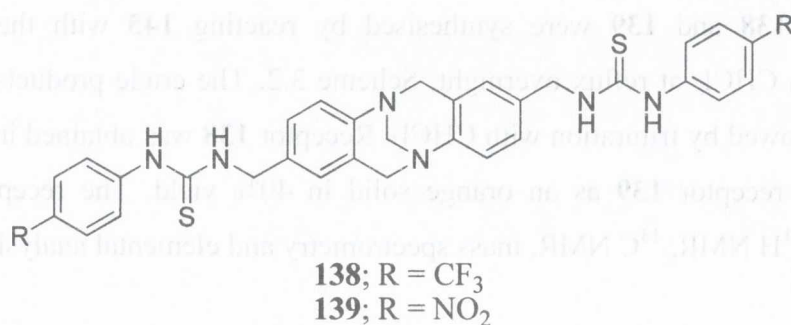
$\pm$ -**135** $n = 1$, Ar = Ph

$\pm$ -**136** $n = 1$, Ar = 3,5-(CF₃)₂C₆H₃

$\pm$ -**137** $n = 0$, Ar = 3,5-(CF₃)₂C₆H₃

As outlined at the beginning of this section, functionalisation of the aromatic rings of **125** allowed the development of a range of receptors for the recognition of carboxylic and nucleic acids. Examples also exist for the recognition of barbiturates and amino acids.¹⁷⁷ However, the focus still continues to lie with synthetic approaches to Tröger's base derivatives and enantiomer separation.¹⁵⁷ Moreover, the area of anion recognition using Tröger's base derivatives is completely unexploited. To date, no examples of this unique structural framework incorporated into a receptor for the detection of anions have been reported. As the diazocine bridge orients two aryl rings in a tweezer-like structure, the shape (and chirality) of **125** offers the opportunity to design a V-shaped structure, which *via* attachment of H-bond donor groups such as thiourea provide an ideal receptor structure for the recognition of anions.

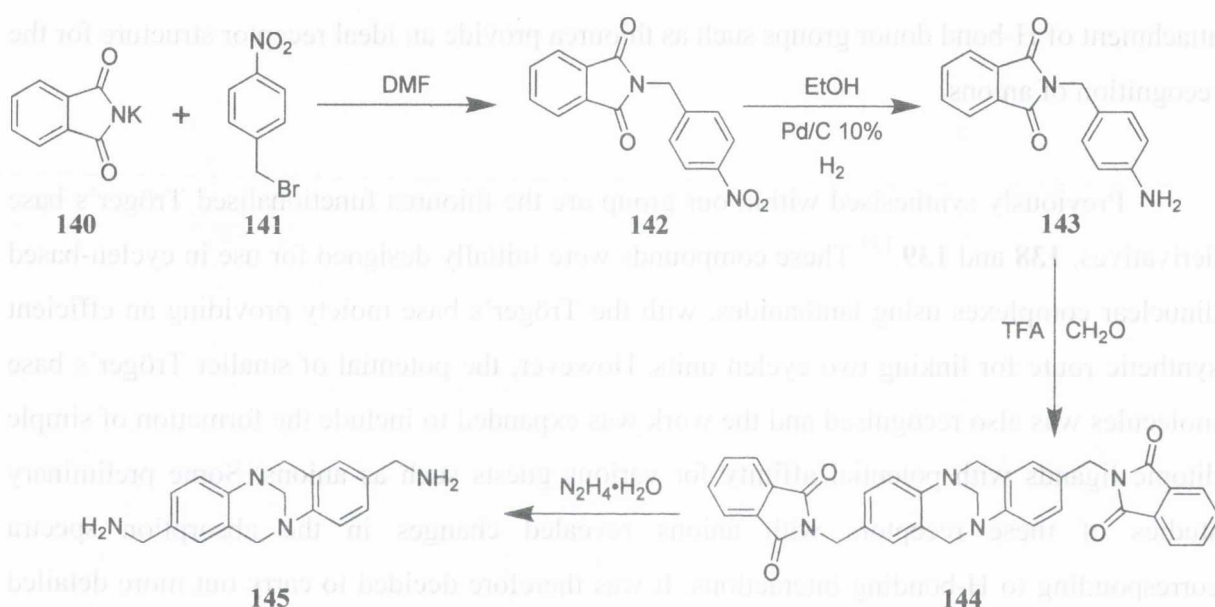
Previously synthesised within our group are the thiourea functionalised Tröger's base derivatives, **138** and **139**.¹³⁹ These compounds were initially designed for use in cyclen-based dinuclear complexes using lanthanides, with the Tröger's base moiety providing an efficient synthetic route for linking two cyclen units. However, the potential of smaller Tröger's base molecules was also recognised and the work was expanded to include the formation of simple ditopic ligands with potential affinity for various guests such as anions. Some preliminary studies of these receptors with anions revealed changes in the absorption spectra corresponding to H-bonding interactions. It was therefore decided to carry out more detailed studies and investigate the interaction of these receptors with various anions



3.2 Synthesis and Characterisation of Receptors **138** and **139**

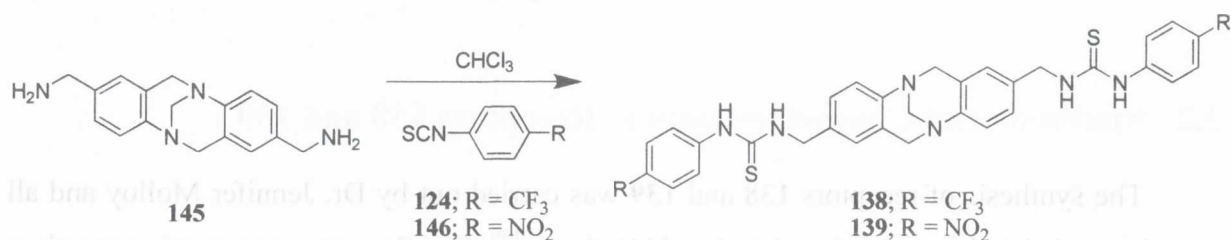
The synthesis of receptors **138** and **139** was carried out by Dr. Jennifer Molloy and all experimental details can be found in her PhD thesis.¹³⁹ The first step was to stir potassium phthalimide, **140**, with 4-nitrobenzylbromide, **141**, in DMF overnight, Scheme 3.1. Dissolution of the crude product in H₂O and extraction into a EtOAc/Toluene (2:1) mixture

followed by washing with H₂O gave **142** as white crystals in 64% yield. Reduction of the nitro group of **142** by hydrogenation at 3 atm in the presence of 10% Pd/C yielded **143** as yellow crystals in quantitative yield. Formation of the Tröger's base, **144**, was achieved by stirring **143** with 3 equivalents of formaldehyde and trifluoroacetic acid (TFA) under an atmosphere of argon. The solvent was removed under reduced pressure and subsequent extraction of the residue into CHCl₃ and washing with H₂O gave **144** as a brown oil in 30% yield. Deprotection of the phthalimide group was achieved by stirring with neat hydrazine at 80°C overnight. Extraction into CHCl₃ and washing with H₂O gave **145** as a yellow oil in 61% yield.



Scheme 3.1: Synthesis of Tröger's base amine intermediate **145**.

Receptors **138** and **139** were synthesised by reacting **145** with the corresponding isothiocyanate in CHCl₃ at reflux overnight, Scheme 3.2. The crude products were collected by filtration, followed by trituration with CHCl₃. Receptor **138** was obtained in 43% yield as a white solid and receptor **139** as an orange solid in 40% yield. The receptors were fully characterised by ¹H NMR, ¹³C NMR, mass spectrometry and elemental analysis.



Scheme 3.2: Synthesis of receptors **138** and **139** from the Tröger's base **145**.

The ^1H NMR (400 MHz, $\text{DMSO}-d_6$) spectrum of **138** is shown in Figure 3.2, which demonstrated the presence of the thiourea protons at 9.84 ppm (NH_a) and 8.35 ppm (NH_b) as broad singlets. The methylene protons of the diazocine ring are identified by the presence of well-separated doublet of doublets between 4.07 – 4.64 ppm. The methylene spacer between the thiourea and aromatic Tröger's unit also appears in this region. The aromatic region consists of two doublets at 7.71 ppm and 7.63 ppm, assigned to the CF_3 -phenyl protons while the resonances of the aromatic protons corresponding to the phenyl groups attached to the Tröger's base were further upfield at 7.12 ppm and 6.91 ppm. ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) demonstrated the presence of the quaternary carbon of the thiourea group at 180 ppm and the quaternary carbon of the CF_3 group at 127 ppm. The CF_3 group was also detected in the ^{19}F spectrum at -60.8 ppm.

The ^1H NMR spectrum of receptor **139** (Figure A3.1, Appendix) demonstrated similar features with presence of the thiourea protons at 10.15 ppm and 8.58 ppm and the aromatic protons of the nitrophenyl groups as two doublets at 8.18 ppm and 7.84 ppm. The distinctive diazocine bridge of the Tröger's base was observed between 4.07 ppm and 4.64 ppm. ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) demonstrated the presence of the $\text{C}-\text{NO}_2$ group at 146 ppm, while the carbonyl group of the thiourea moiety resonated at 180 ppm.

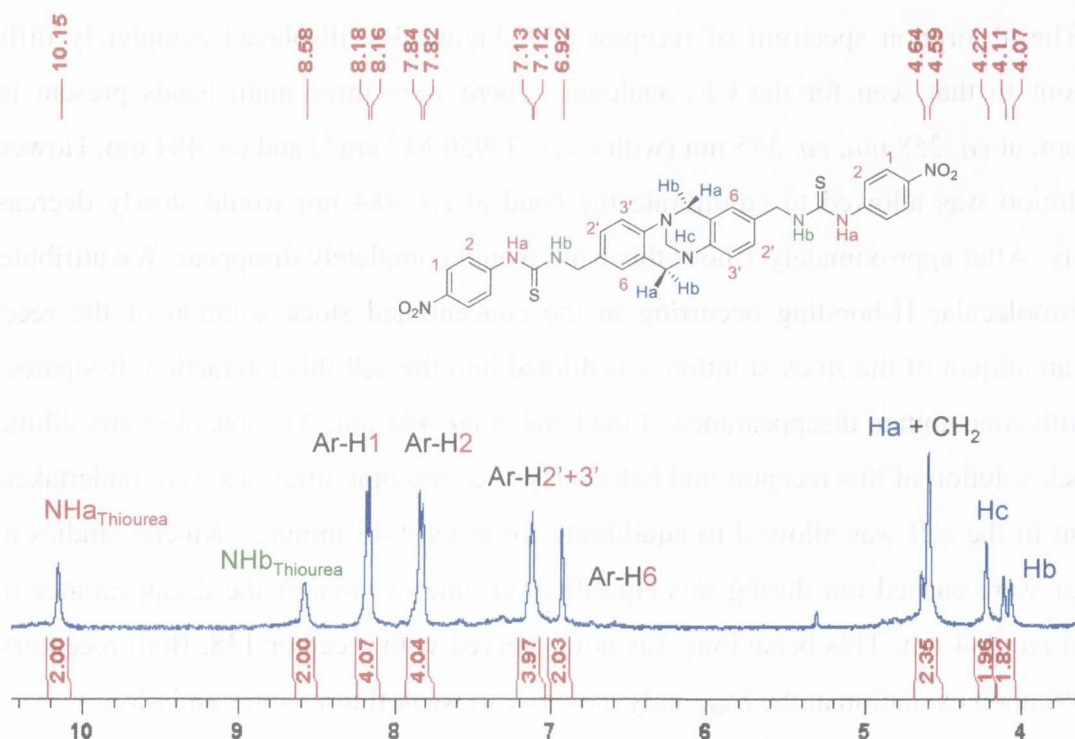


Figure 3.2: ^1H NMR spectrum (400 MHz, $\text{DMSO}-d_6$) of **138**.

3.3 Photophysical Evaluation of Receptors 138 and 139

The absorption spectrum of receptor **138** is shown in Figure 3.3 when recorded at room temperature in DMSO solution. There are two main absorption bands centred at *ca.* 260 nm and a shoulder at *ca.* 284 nm with $\epsilon_{284} = 33750 \text{ M}^{-1} \text{ cm}^{-1}$. Upon excitation at the λ_{max} the receptor only gave rise to weak fluorescence emission.

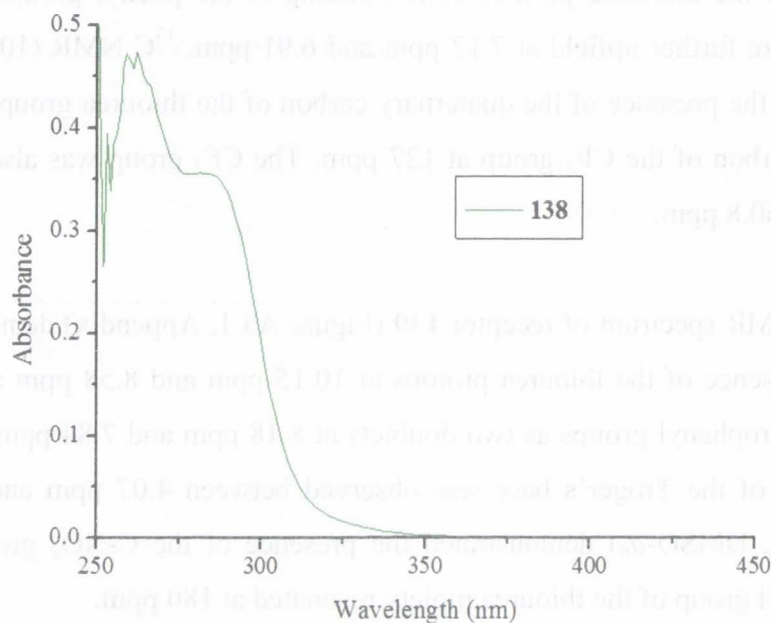


Figure 3.3: The absorption spectrum of receptor **138** (*ca.* $1 \times 10^{-5} \text{ M}$) in DMSO.

The absorption spectrum of receptor **139**, Figure 3.4, displayed completely different behaviour to that seen for the CF_3 analogue. There were three main bands present in the spectrum, at *ca.* 258 nm, *ca.* 355 nm (with $\epsilon_{355} = 32950 \text{ M}^{-1} \text{ cm}^{-1}$) and *ca.* 484 nm. However if the solution was allowed to equilibrate the band at *ca.* 484 nm would slowly decrease in intensity. After approximately 1 hour this band would completely disappear. We attribute this to intermolecular H-bonding occurring in the concentrated stock solution of the receptor. When an aliquot of the stock solution was diluted into the cell this interaction dissipates over time with concomitant disappearance of the band at *ca.* 484 nm. As such, after any dilution of the stock solution of this receptor and before any spectroscopic titrations were undertaken, the solution in the cell was allowed to equilibrate for at least 45 minutes. Kinetic studies of the receptor were carried out during this equilibration time to monitor the disappearance of the band at *ca.* 484 nm. This behaviour was not observed with receptor **138**. Both receptors **138** and **139**, upon excitation at the λ_{max} , only gave rise to weak fluorescence emission.

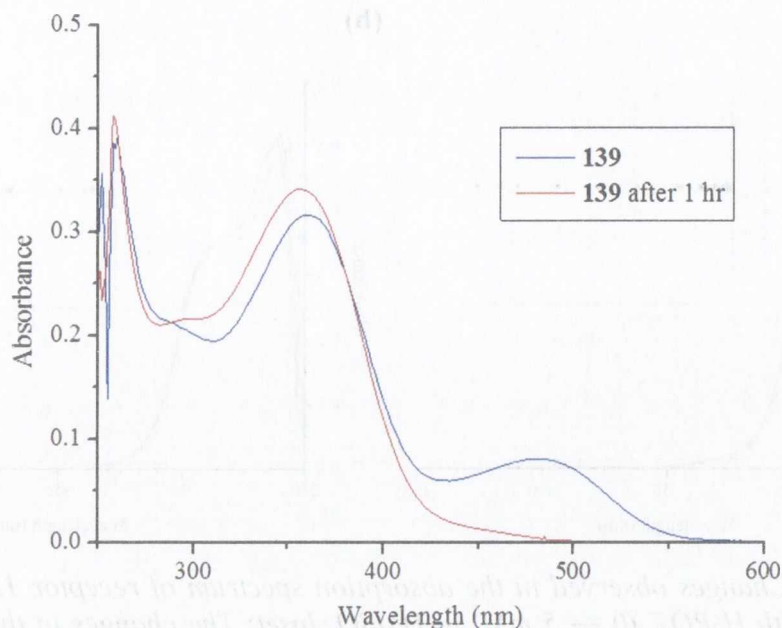


Figure 3.4: The absorption spectrum of receptor **139** (1×10^{-5} M) in DMSO at $t = 0$ hr (-) and after $t = 1$ hr (-).

Spectroscopic anion titrations were next carried out using UV-Vis absorption spectroscopy. Solutions of H_2PO_4^- , AcO^- , F^- , $\text{HP}_2\text{O}_7^{3-}$ and SO_4^{2-} as their TBA salts in DMSO were added to a solution of either **138** or **139** (ca. 1×10^{-5} M) in DMSO. The changes observed were measured and quantified and all titrations were repeated to ensure reproducibility and to minimise error. The results from these investigations will be discussed in the following sections.

3.3.1 Anion Binding Ability of Receptor **138**

Detailed UV-Vis absorption titrations were firstly carried out with **138** and H_2PO_4^- and the family of spectra obtained shown in Figure 3.5 (a). It can be seen that the changes were very minor and were not suitable for analysis of the binding stoichiometry using SPECFIT™. In an analogous manner, the binding of AcO^- to receptor **138** was investigated, Figure 3.5 (b). Again the absorption spectrum of **138** was unaffected upon titration with AcO^- . These results were quite unexpected as the strong electron withdrawing ability of the $p\text{-CF}_3$ moiety should enhance the acidity of the N-H protons and hence become better H-bond donors. The cleft-like structure of the receptor should also be advantageous, from a structural point of view, in the anion binding ability of **138**.

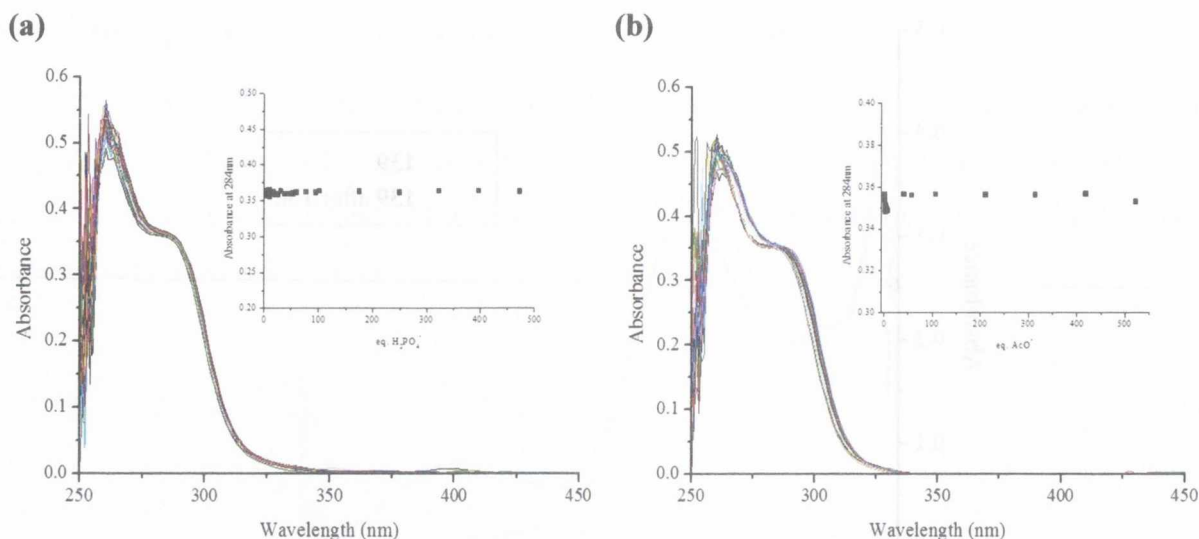


Figure 3.5: (a) Changes observed in the absorption spectrum of receptor **138** (1×10^{-5} M) upon titration with H_2PO_4^- (0 $\rightarrow$ 5 mM) in DMSO. Inset: The changes in the absorbance at 284 nm as a function of equivalents of H_2PO_4^- . (b) Changes observed in the absorption spectrum of receptor **138** (1×10^{-5} M) upon titration with AcO^- (0 $\rightarrow$ 5 mM) in DMSO. Inset: The changes in the absorbance at 284 nm as a function of equivalents of AcO^- .

A similar trend was again observed upon titration with SO_4^{2-} with no major modulation of the absorption spectrum occurring, even at high concentrations of the anion, Figure 3.6. Again these results are unusual as SO_4^{2-} is an attractive anion to study due to its orthogonal tetrahedral coordination preference and strong binding capability as a consequence of its di-negative charge. Furthermore, SO_4^{2-} has been shown to have a high coordination number preference with examples in the literature of between four and twelve H-bonds interacting with a single SO_4^{2-} anion at any one time.¹⁷⁸

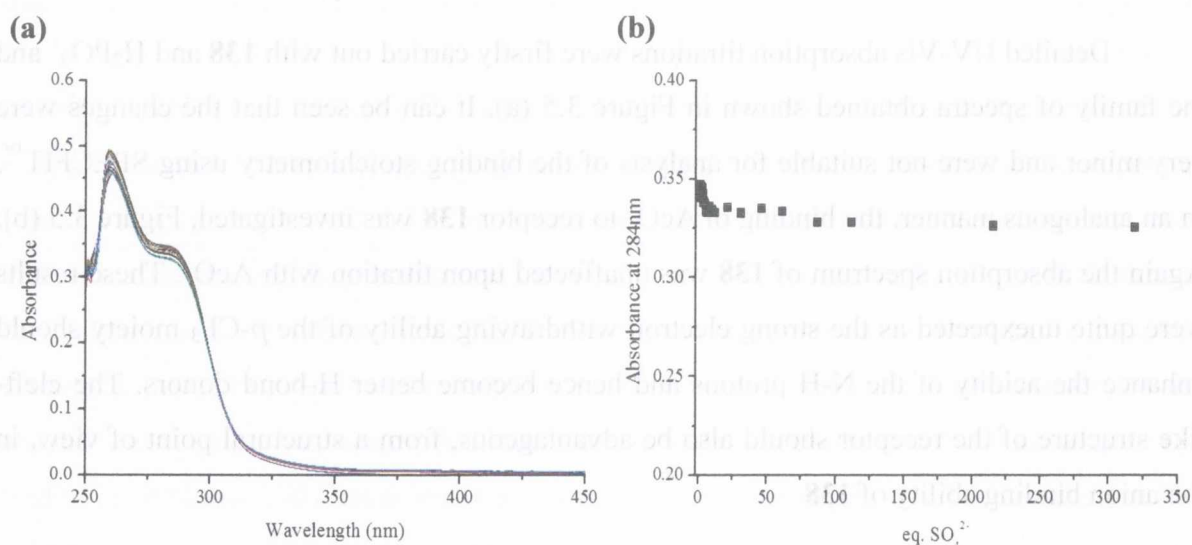


Figure 3.6: (a) Changes observed in the absorption spectrum of receptor **138** (1×10^{-5} M) upon titration with SO_4^{2-} (0 $\rightarrow$ 3.71 mM) in DMSO. (b) The changes in the absorbance at 284 nm as a function of equivalents of SO_4^{2-} .

The next anion investigated was $\text{HP}_2\text{O}_7^{3-}$ and in contrast to the results seen for the previous anions studied, the results obtained in these studies were inconsistent and not reproducible. The changes observed in a titration with $\text{HP}_2\text{O}_7^{3-}$ are shown in Figure 3.7 (a). It can be seen that initially the changes are quite minor at low concentrations of the anion, however at *ca.* 15 equivalents of the anion, Figure 3.7 (b), formation of a band at *ca.* 332 nm occurs. This is then followed by a much sharper increase in the same band upon further addition of the anion and a simultaneous decrease in the band at 284 nm.

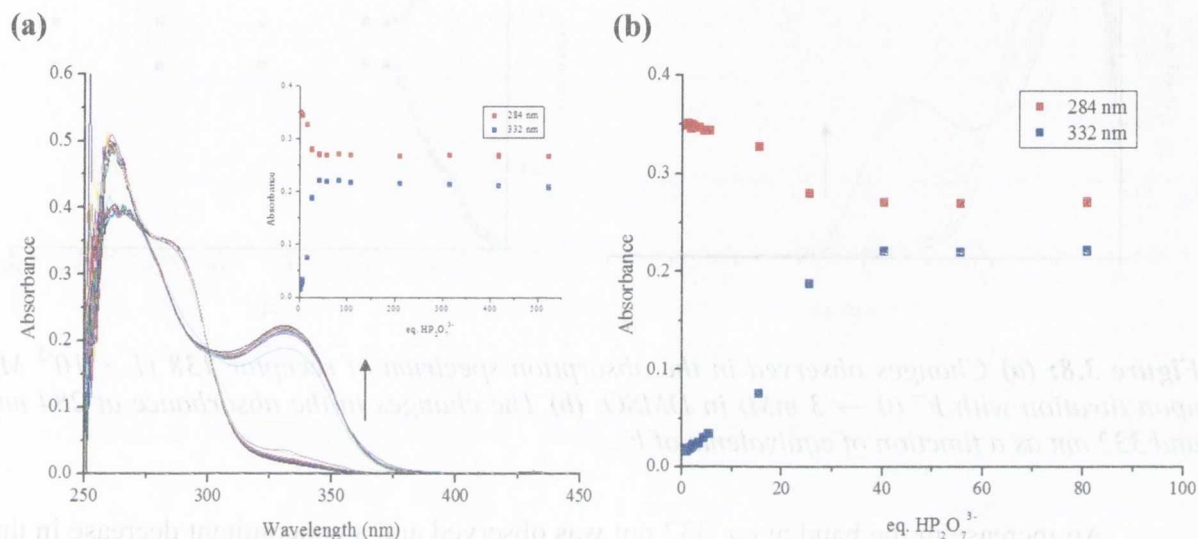


Figure 3.7: (a) Changes observed in the absorption spectrum of receptor **138** ($1 \times 10^{-5} \text{ M}$) upon titration with $\text{HP}_2\text{O}_7^{3-}$ ($0 \rightarrow 3.6 \text{ mM}$) in DMSO. Inset: The changes in the absorbance at 284 nm and 332 nm as a function of equivalents of $\text{HP}_2\text{O}_7^{3-}$. (b) The changes in the absorbance at 284 nm and 332 nm as a function of equivalents of $\text{HP}_2\text{O}_7^{3-}$ shown between 0 and 100 equivalents.

It is possible that initially there is a weak H-bonding interaction between the anion and the thiourea moiety occurring, corresponding to the minor changes seen in the spectrum. After the addition of 15 equivalents the sharp increase in the band at *ca.* 332 nm could signify deprotonation. These changes could not be fit using SPECFITTM, which is likely due to the occurrence of multiple binding and deprotonation processes occurring in solution. It should also be mentioned that this titration was repeated multiple times and, even though the behaviour was the same each time (*i.e.* minor changes occurring initially followed by a sharp increase at *ca.* 332 nm) the number of equivalents at which the increase occurred varied with each titration.

The last anion to be studied was F^- , which, as stated in Chapter 2, can form H-bonded complexes with receptors such as **138** but can also result in deprotonation of acidic protons

and the concomitant formation of HF_2^- . As shown in Figure 3.8 (a), significant changes were seen in the absorption spectrum of **138** upon addition of F^- and compared to the titration with $\text{HP}_2\text{O}_7^{3-}$ the changes seen for F^- were consistent and fully reproducible.

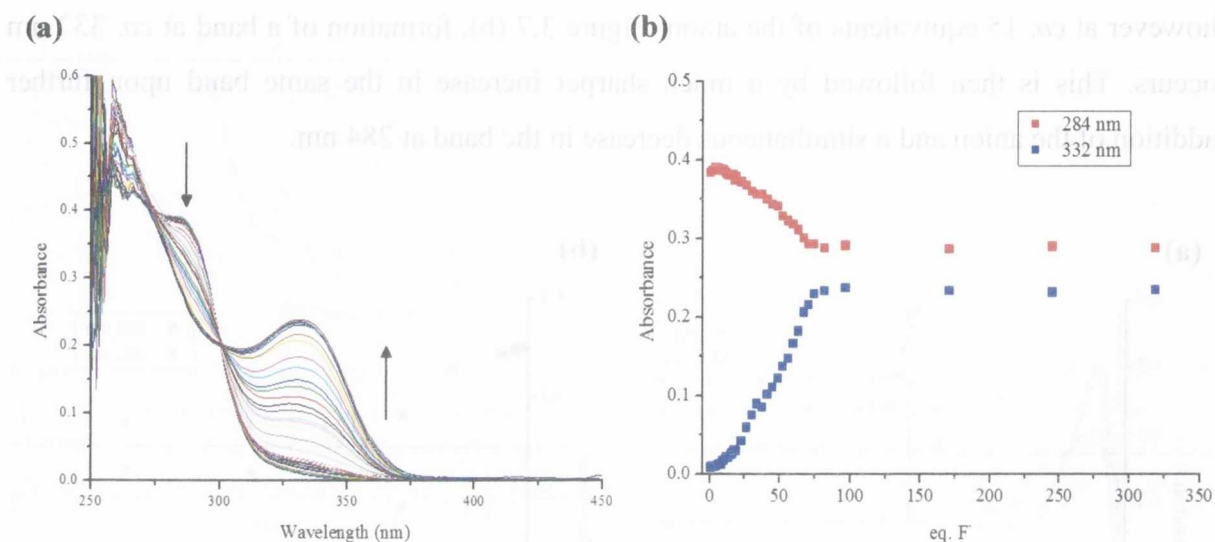
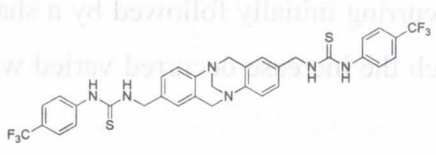


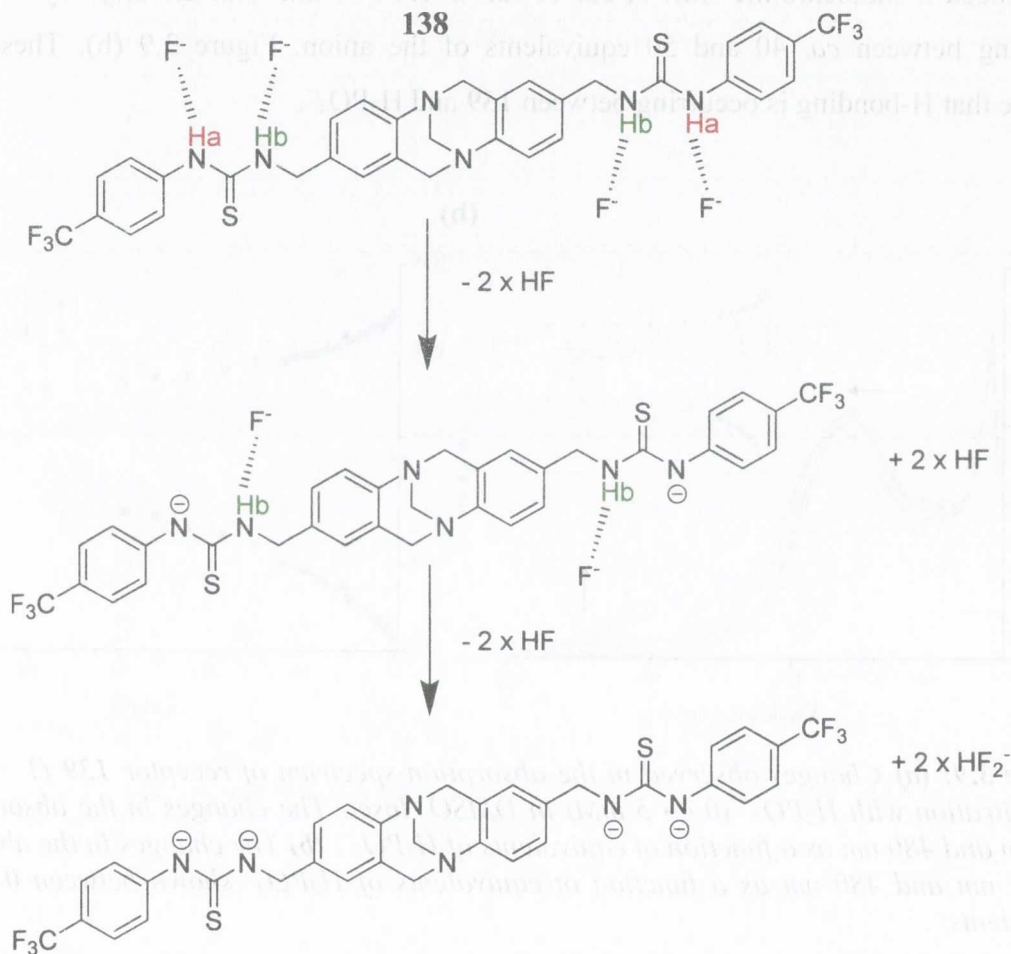
Figure 3.8: (a) Changes observed in the absorption spectrum of receptor **138** (1×10^{-5} M) upon titration with F^- ($0 \rightarrow 3$ mM) in DMSO. (b) The changes in the absorbance at 284 nm and 332 nm as a function of equivalents of F^- .

An increase in the band at *ca.* 332 nm was observed and a concomitant decrease in the band at *ca.* 284 nm with the formation of an isosbestic point at *ca.* 300 nm. By plotting the changes in the absorption spectrum at 284 nm and 332 nm as a function of F^- , Figure 3.8 (b), the changes appeared to reach a plateau at *ca.* 80 equivalents of the anion. It was possible to fit this data using SPECFITTM and the resulting binding constants are shown in Table 3.1.

Table 3.1: Binding constants and binding modes between F^- and receptor **138**.

Receptor (L)	Anion (G)	Binding Mode $G_n:L_m$	$\log K_{n:m}$	Std. Deviation ($\pm$)
 138	F^-	$G_4:L$	6.61	0.18

These changes can almost certainly be attributed to initial H-bonding followed by deprotonation. Initially, there are four H-bonded F^- anions to **138**, i.e. $G_4:L$ species, Scheme 3.3. However as the N-Ha of **138** is directly conjugated to the highly electron withdrawing p - CF_3 group making it highly acidic and it can easily be deprotonated to form HF, leaving both the deprotonated and 2:1 (guest:host) species in solution. Following this initial deprotonation the second H-bonded F^- to N-Hb of **138** is removed leaving a doubly deprotonated thiourea moiety. It is at this point the plateau occurs.



Scheme 3.3: Proposed order of deprotonation of the thiourea protons of **138**.

The studies carried out with this receptor provided some interesting results with no interaction seen between the receptor and any of the smaller oxanions studied. In contrast, the results between **138** and $HP_2O_7^{3-}$ and F^- were the largest spectroscopic responses observed. The final species in solution after titration of **138** with F^- is most likely the doubly deprotonated receptor.

3.3.2 Anion Binding Ability of Receptor 139

Receptor **139** was investigated in an identical manner to that of **138**. However, as mentioned earlier, intermolecular H-bonding was found to occur between the thiourea moieties of **139** and as a result the solution of **139** was allowed to equilibrate before any spectroscopic titrations were carried out. The absorption spectrum of **139** exhibited a λ_{max} at *ca.* 355 nm, which upon titration with H_2PO_4^- gave rise to a new absorption band centred at *ca.* 480 nm, similar to that seen before equilibration. The band centred at *ca.* 355 nm experienced a bathochromic shift of *ca.* 15 nm to *ca.* 370 nm with the majority of changes occurring between *ca.* 40 and 50 equivalents of the anion, Figure 3.9 (b). These results indicate that H-bonding is occurring between **139** and H_2PO_4^- .

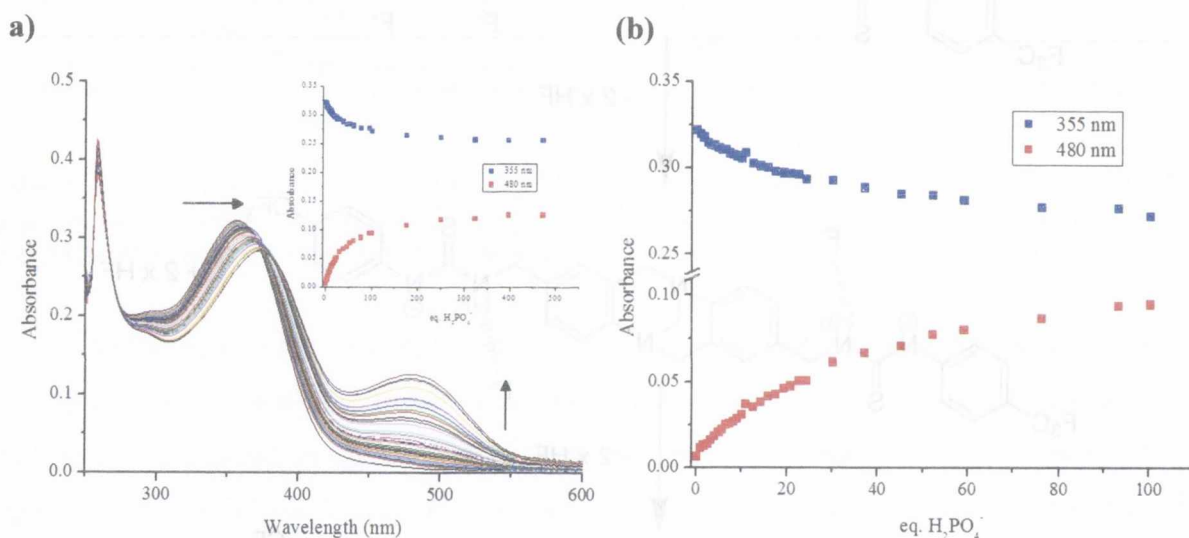


Figure 3.9: (a) Changes observed in the absorption spectrum of receptor **139** (1×10^{-5} M) upon titration with H_2PO_4^- (0 $\rightarrow$ 5 mM) in DMSO. Inset: The changes in the absorbance at 355 nm and 480 nm as a function of equivalents of H_2PO_4^- . (b) The changes in the absorbance at 355 nm and 480 nm as a function of equivalents of H_2PO_4^- shown between 0 and 100 equivalents.

Figure 3.10 (a) shows the family of spectra obtained upon titration with AcO^- . Again the new band at *ca.* 480 nm appears during the course of the titration and the band at *ca.* 355 nm also experiences a similar hypochromic and bathochromic shift to that seen for H_2PO_4^- . There was no clear isosbestic point observed in this titration but a ‘pseudo’ isosbestic point at *ca.* 377 nm could be seen. In comparison to the titration with H_2PO_4^- , a plateau was reached much earlier, at *ca.* 20 equivalents of the anion, Figure 3.10 (b). It can also be seen that at higher concentrations of AcO^- , from *ca.* 200 equivalents, absorbance of the bands at *ca.* 355 nm and *ca.* 480 nm undergo a slight increase and decrease respectively, indicating that the changes are bi-phasic.

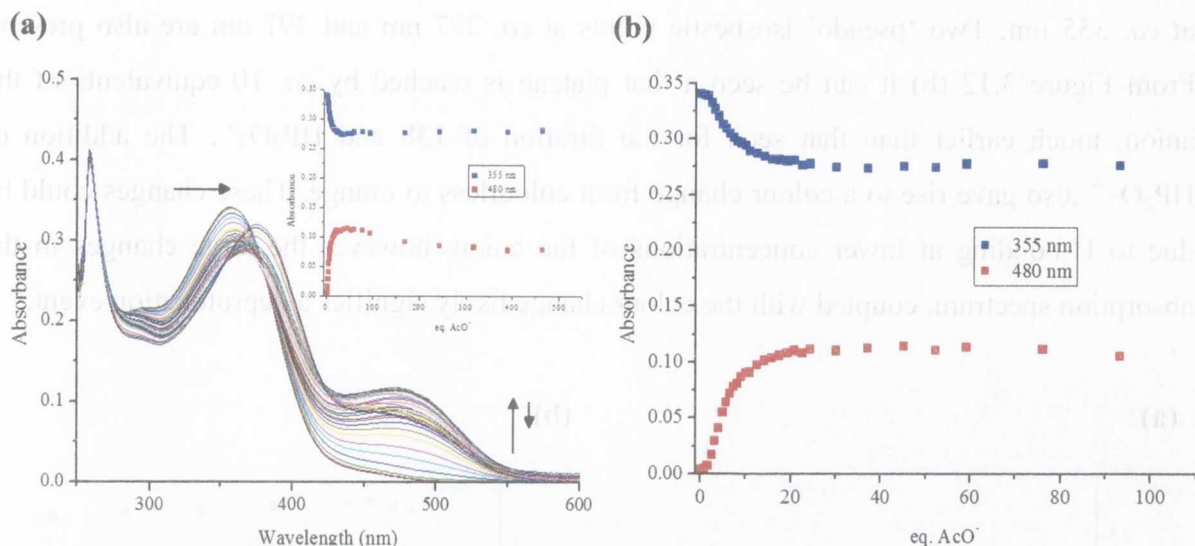


Figure 3.10: (a) Changes observed in the absorption spectrum of receptor **139** (1×10^{-5} M) upon titration with AcO^- ($0 \rightarrow 5$ mM) in DMSO. Inset: The changes in the absorbance at 355 nm and 480 nm as a function of equivalents of AcO^- . (b) The changes in the absorbance at 355 nm and 480 nm as a function of equivalents of AcO^- shown between 0 and 100 equivalents.

In contrast to the results obtained for H_2PO_4^- and AcO^- , SO_4^{2-} did not result in significant change of the absorption spectrum of receptor **139**, even at high concentrations (> 400 equivalents) of the anion, as shown in Figure 3.11.

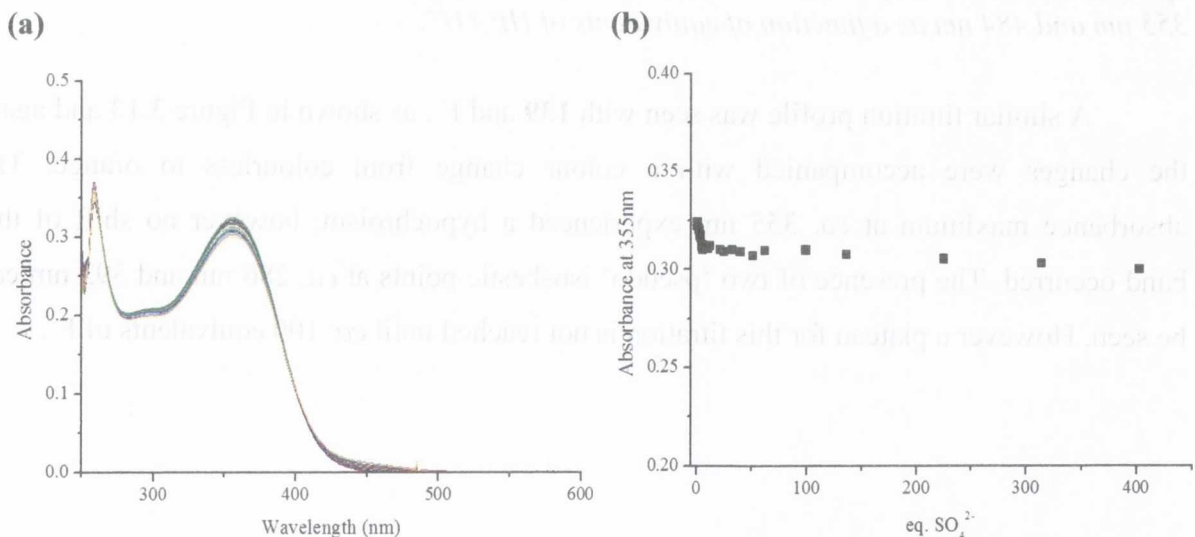


Figure 3.11: (a) Changes observed in the absorption spectrum of receptor **139** (1×10^{-5} M) upon titration with SO_4^{2-} ($0 \rightarrow 3.6$ mM) in DMSO. (b) The changes in the absorbance at 355 nm as a function of equivalents of SO_4^{2-} .

The changes observed in the absorption spectrum of **139** upon titration with $\text{HP}_2\text{O}_7^{3-}$ are shown in Figure 3.12. It can be seen from Figure 3.12 (a) that the band at *ca.* 484 nm increases upon increasing concentration of $\text{HP}_2\text{O}_7^{3-}$ with a concomitant decrease of the band

at *ca.* 355 nm. Two 'pseudo' isosbestic points at *ca.* 297 nm and 397 nm are also present. From Figure 3.12 (b) it can be seen a that plateau is reached by *ca.* 10 equivalents of the anion, much earlier than that seen for the titration of **138** and $\text{HP}_2\text{O}_7^{3-}$. The addition of $\text{HP}_2\text{O}_7^{3-}$ also gave rise to a colour change from colourless to orange. These changes could be due to H-bonding at lower concentrations of the anion, however the large changes in the absorption spectrum, coupled with the colour change likely signifies a deprotonation event.

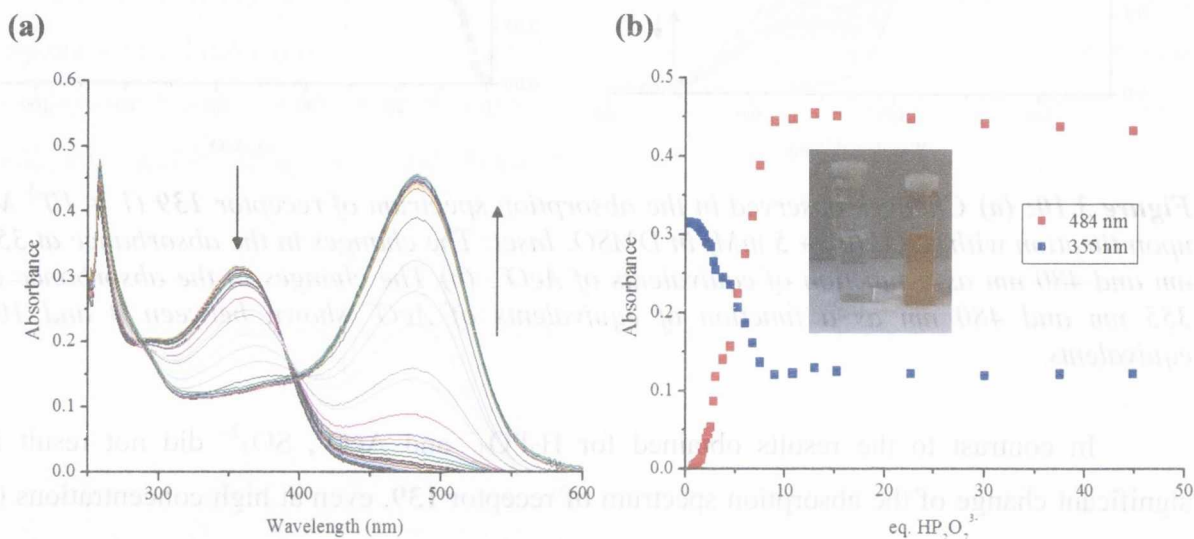


Figure 3.12: (a) Changes observed in the absorption spectrum of receptor **139** (1×10^{-5} M) upon titration with $\text{HP}_2\text{O}_7^{3-}$ (0 → 0.28 mM) in DMSO. (b) The changes in the absorbance at 355 nm and 484 nm as a function of equivalents of $\text{HP}_2\text{O}_7^{3-}$.

A similar titration profile was seen with **139** and F^- , as shown in Figure 3.13 and again the changes were accompanied with a colour change from colourless to orange. The absorbance maximum at *ca.* 355 nm experienced a hypochroism, however no shift of this band occurred. The presence of two 'pseudo' isosbestic points at *ca.* 286 nm and 392 nm can be seen. However a plateau for this titration is not reached until *ca.* 100 equivalents of F^- .

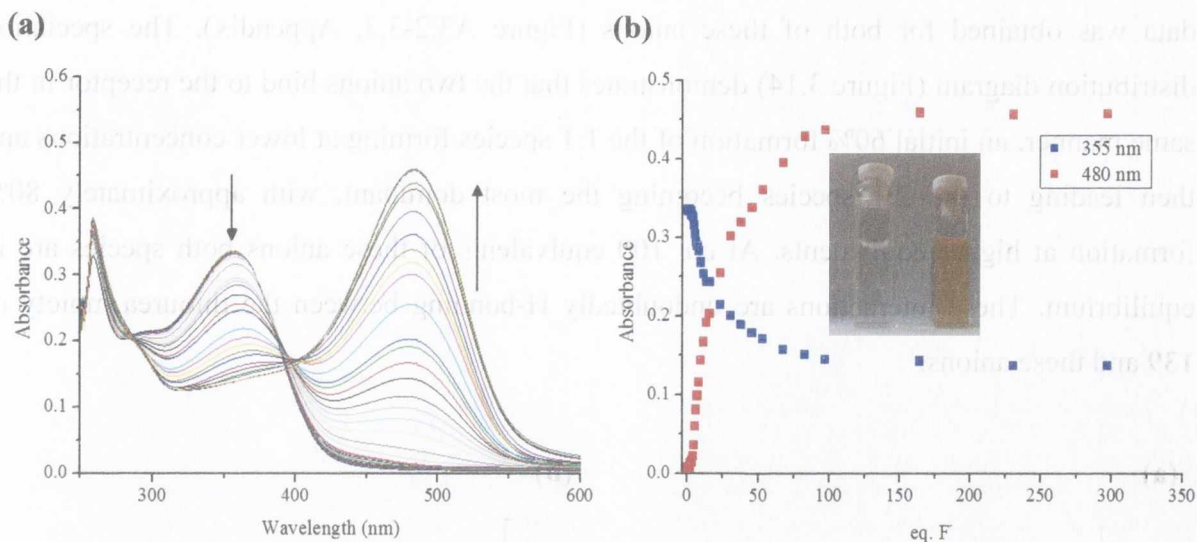
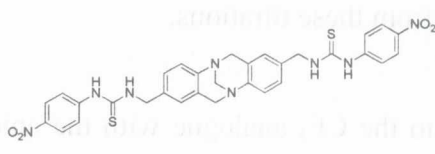


Figure 3.13:(a) Changes observed in the absorption spectrum of receptor **139** (1×10^{-5} M) upon titration with F^- ($0 \rightarrow 2.7$ mM) in DMSO. (b) The changes in the absorbance at 355 nm and 480 nm as a function of equivalents of F^- .

From the observed changes in the UV-Vis spectroscopic studies the binding affinities for each anion were determined using SPECFITTM. The binding constants obtained are summarised in Table 2.3. The two oxyanions showed identical binding modes and very similar binding constants, while the results for the spherical halide F^- show a different interaction.

Table 3.2: Binding constants and binding modes between anions and receptor **139**.

Receptor (L)	Anion (G)	Binding Mode $G_n:L_m$	log $K_{n:m}$	Std. Deviation ($\pm$)
 139	AcO^-	G:L	4.13	0.03
		$G_2:L$	3.10	0.05
	$H_2PO_4^-$	G:L	4.25	0.05
		$G_2:L$	3.15	0.07
	F^-	$G_2:L$	8.19	0.04
		$G_4:L$	6.69	0.12
	$HP_2O_7^{3-}$	-	-	-
	SO_4^{2-}	-	-	-

The data for the titration of AcO^- and $H_2PO_4^-$ were both best fitted to a 1:1 and 2:1 (guest:host) stoichiometry, giving very similar binding constants for both anions with the values for $H_2PO_4^-$ only marginally higher than that obtained for AcO^- . An excellent fit of the

data was obtained for both of these anions (Figure A3.2-3.3, Appendix). The speciation distribution diagram (Figure 3.14) demonstrates that the two anions bind to the receptor in the same manner, an initial 60% formation of the 1:1 species forming at lower concentrations and then leading to the 2:1 species becoming the most dominant, with approximately 80% formation at higher equivalents. At *ca.* 100 equivalents of these anions both species are in equilibrium. These interactions are undoubtedly H-bonding between the thiourea moiety of **139** and these anions.

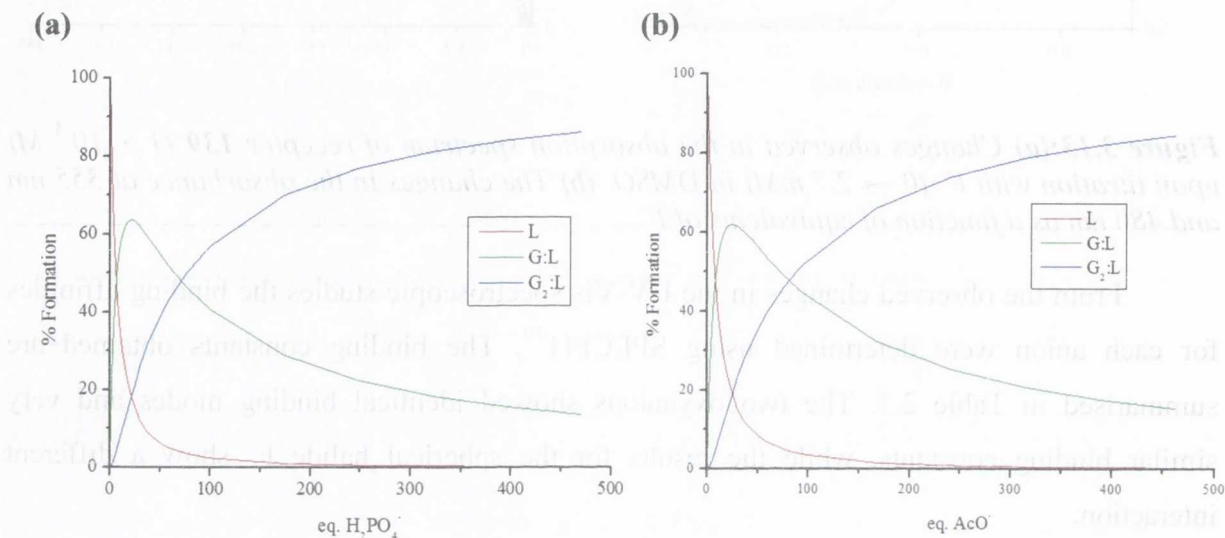


Figure 3.14: (a) Speciation distribution diagram for the absorption titration of **139** (L) and H_2PO_4^- . (b) Speciation distribution diagram for the absorption titration of **139** (L) and AcO^- .

Although some of the largest spectral responses were again seen upon titration with $\text{HP}_2\text{O}_7^{3-}$, analysis of the changes using SPECFIT™ did not result in a fit within the acceptable error limits, most likely due to the complex nature of the changes. The results obtained for F^- are very similar to that seen for **138** and are most likely due H-bonding initially but deprotonation is the main outcome that can be concluded from these titrations.

The varying response of this receptor compared to the CF_3 analogue with the anions studied has provided some very interesting results. Receptor **139** does indeed show H-bonding interactions with AcO^- and H_2PO_4^- with relatively strong binding constants determined for both the 1:1 species ($\log K_{1:1} = 4.13 \pm 0.03$ and 4.25 ± 0.05 , respectively) and the 2:1 complex ($\log K_{2:1} = 3.10 \pm 0.05$ and 3.15 ± 0.07 , respectively), while receptor **138** showed no interaction with these anions at all. Interestingly neither receptor showed any binding interaction with SO_4^{2-} . The most significant changes occurred between both receptors with $\text{HP}_2\text{O}_7^{3-}$ and F^- . In addition, colorimetric changes have been observed for **139** upon addition

of $\text{HP}_2\text{O}_7^{3-}$ and F^- , while such changes were not observed for the other anions studied. Due to the presence of the nitro groups, which are more electron withdrawing than the CF_3 groups of **138**, the N-H protons are highly acidic and more readily deprotonated.

3.4 ^1H NMR Titrations of Receptors **138** and **139** with Anions

This section investigates the interactions of **138** and **139** with various anions using ^1H NMR spectroscopy. The changes in the ^1H NMR spectra of $\text{DMSO}-d_6$ solutions were monitored upon the addition of AcO^- and H_2PO_4^- as their TBA salts, as these were the two anions that showed the most significant spectral differences between the two receptors. A titration with TBA SO_4^{2-} was also carried out to see if any interaction between this anion and the receptors occurred at higher concentrations.

3.4.1 ^1H NMR Titrations of Receptor **138** upon Addition of Anions

Although no significant changes were observed in the absorption spectrum of **138** upon titration of H_2PO_4^- , changes were observed in the ^1H NMR spectrum upon addition of H_2PO_4^- , depicted by the binding isotherm in Figure 3.15 (a). (The stack plot for the titration can be found in the Appendix, Figure A3.4.) It can be seen that the anion did interact with the receptor with a final chemical shift of *ca.* 2.2 ppm for the NHa being observed and a smaller shift of *ca.* 1.7 ppm for the NHb. The doublet assigned to the protons of the phenyl ring *ortho* to the CF_3 group also experienced a small downfield shift. A plateau was observed at *ca.* 2 equivalents of the anion. These changes, indicative of H-bonding, were only observed in the higher concentration range that the NMR studies were evaluated in, as the absorption spectrum of **138** was not perturbed at all upon addition of H_2PO_4^- .

The data obtained for the titration of **138** with AcO^- (Appendix, A3.5), again plotted as the cumulative changes in chemical shift ($\Delta\delta$) against the equivalents of anion added, Figure 3.15 (b), showed a similar trend. It appears that the binding of AcO^- was slightly stronger than that seen for H_2PO_4^- as both NHa and NHb experienced larger downfield shifts of *ca.* 3 ppm and 3.2 ppm, respectively. The doublet assigned to the protons of the phenyl ring *ortho* to the CF_3 group also experienced a small downfield shift. This binding interaction, most likely due to H-bonding, was also not seen during the UV-Vis titration of receptor **138** with AcO^- .

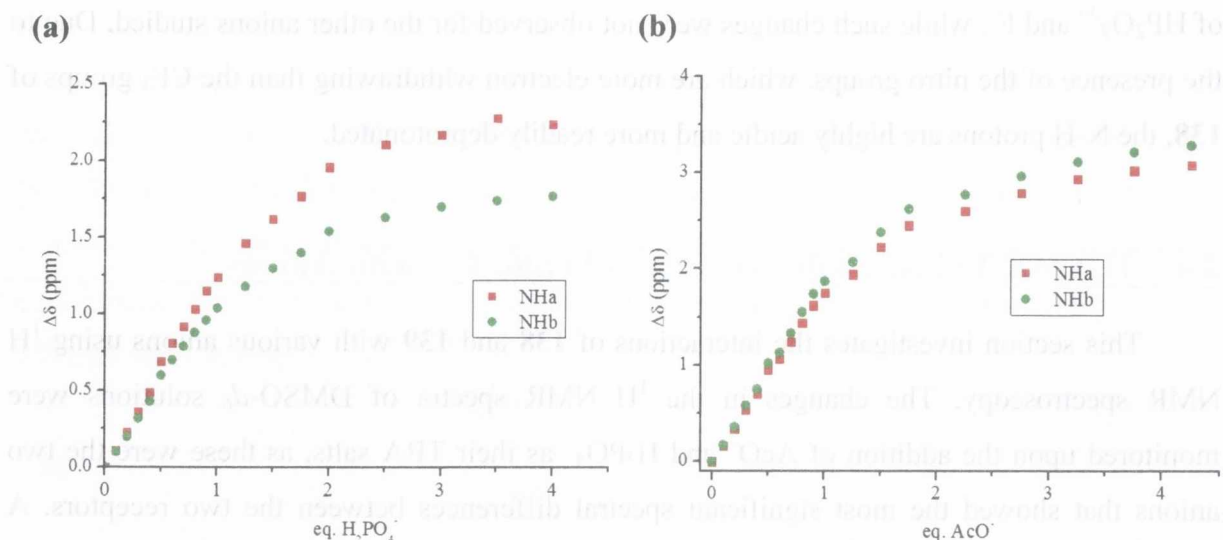


Figure 3.15: Changes in the thiourea resonances of **138** (as $\Delta\delta$) upon titration with (a) H_2PO_4^- and (b) AcO^- .

In direct contrast the titration of **138** with SO_4^{2-} did not show any perturbation of the thiourea protons or any other resonance in the spectrum (Appendix, Figure A3.6-7), correlating with the results obtained from the UV-Vis absorption titration.

3.4.2 ^1H NMR Titrations of Receptor **139** upon Addition of Anions

The successive addition of H_2PO_4^- to **139** resulted in significant changes in the chemical shifts of the thiourea protons (Appendix, Figure A3.8). In the case of NHa the resonance became considerably broadened after the addition of *ca.* 0.5 equivalents and completely disappeared after *ca.* 1 equivalent of H_2PO_4^- , the NHb proton was therefore the only proton that could be followed throughout the course of the titration, Figure 3.16 (a). In contrast to the results seen for receptor **138**, the phenyl protons *ortho* to the thiourea shifted downfield while the protons *ortho* to the NO_2 group shifted upfield; also becoming quite broadened. Additionally, the aromatic protons adjacent to the Tröger's base moiety and their multiplicities were clearly resolved after *ca.* 1 equivalent of the anion before then also becoming broadened. A more definite plateau was also observed in the binding isotherm compared to the same titration with **138**, indicating that a more stable complex was formed. A colour change from pale yellow to deep orange was observed after the addition of *ca.* 0.5 equivalents of H_2PO_4^- .

The titration of **139** and AcO^- , a plot of $\Delta\delta$ versus equivalents of AcO^- is shown in Figure 3.16 (b), was slightly different to that seen for H_2PO_4^- . The two thiourea resonances were clearly visible throughout the titration, showing almost identical changes in chemical shifts, over *ca.* 3 ppm, a larger shift than that seen for H_2PO_4^- . The phenyl protons adjacent to

the thiourea moiety merged to become one singlet at *ca.* 2 equivalents of the anion, while the other aromatic resonances became more resolved (Appendix, Figure A3.9). The binding profile indicates a plateau was reached at *ca.* 2 equivalents of the anion. Again a drastic colour change from pale yellow to deep orange was also observed almost immediately, after the addition of 0.2 equivalents of AcO^- .

Titration of **139** with SO_4^{2-} resulted in no modulation of the ^1H NMR spectrum (Appendix, Figure A3.10-11), as was seen with **138**. No colour change was observed, as had occurred with H_2PO_4^- and AcO^- , even at higher equivalents of the anion.

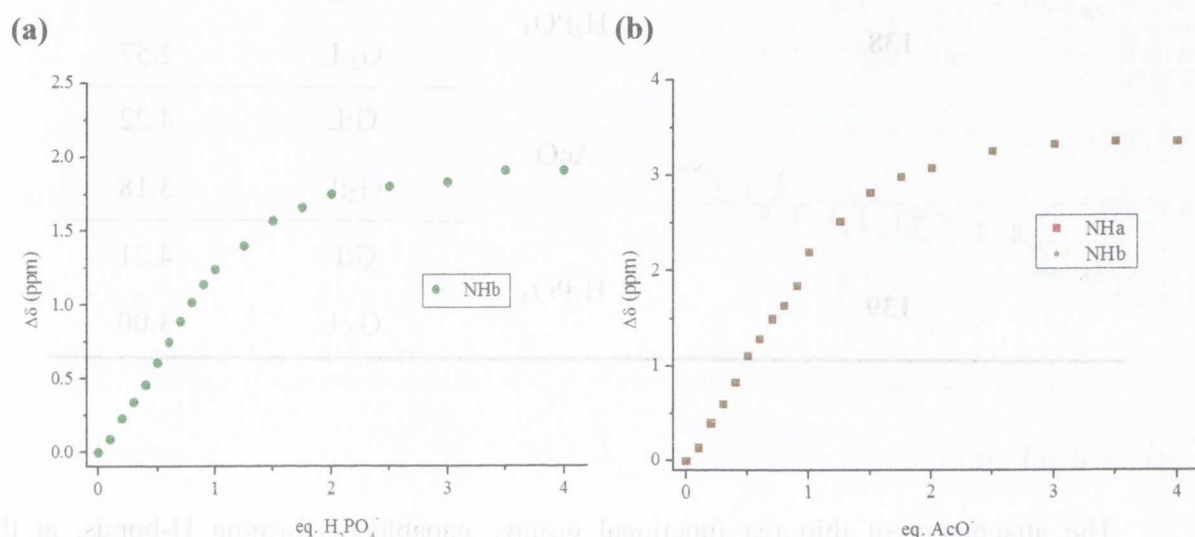


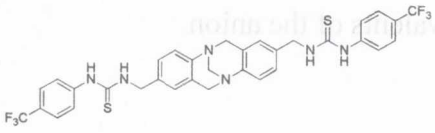
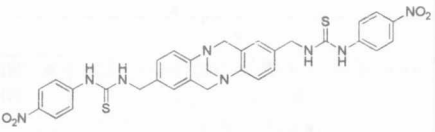
Figure 3.16: Changes in the thiourea resonances of **139** (as $\Delta\delta$) upon titration with (a) H_2PO_4^- and (b) AcO^- .

Binding constants were determined for both receptors **138** and **139** with AcO^- and H_2PO_4^- , as their N-H protons underwent large chemical shifts. The ^1H NMR data was fitted using *NMRTit HGG*, which fits to 1:1 and 2:1 (guest:host) binding isotherms, respectively by an iterative procedure (Appendix A3.12-3.15). The results are summarised in Table 3.3 and it can be seen that the binding constant values for receptor **139** are in good agreement with those observed from the UV-Vis absorption titrations. The binding constants obtained for **138** are, as expected from the absence of changes in the UV-Vis absorption titrations, lower than those determined for **139**.

The ^1H NMR titrations of receptors **138** and **139** gave some interesting results. It was expected that **138** would not show any interaction with H_2PO_4^- and AcO^- however, contrary to the absorption studies, it can be concluded that these anions do in fact form H-bonded complexes with the receptor. The results for receptor **139** were found to be in agreement with the UV-Vis spectroscopic titrations as the formation of H-bonded complexes with H_2PO_4^- and

AcO^- were confirmed. Colour changes were also observed upon addition of these anions to **139**. Interestingly, neither receptor was found to interact in any way with SO_4^{2-} .

Table 3.3: Binding constants and binding modes between anions and receptor **139.**

Receptor (L)	Anion (G)	Binding Mode $G_n:L_m$	$\log K_{n:m}$
 138	AcO^-	G:L	3.18
		$G_2:L$	3.07
	H_2PO_4^-	G:L	3.42
		$G_2:L$	2.57
	AcO^-	G:L	4.22
		$G_2:L$	3.18
 139	H_2PO_4^-	G:L	4.21
		$G_2:L$	3.00

3.5 Conclusion

The attachment of thiourea functional groups, capable of forming H-bonds, at the extremities of the Tröger's base skeleton to create synthetic receptors for the recognition of anions has been investigated. The two receptors were synthesised and fully characterised and photophysical properties have been described. The anion recognition abilities of both receptors were investigated by UV-Vis absorption and ^1H NMR spectroscopy.

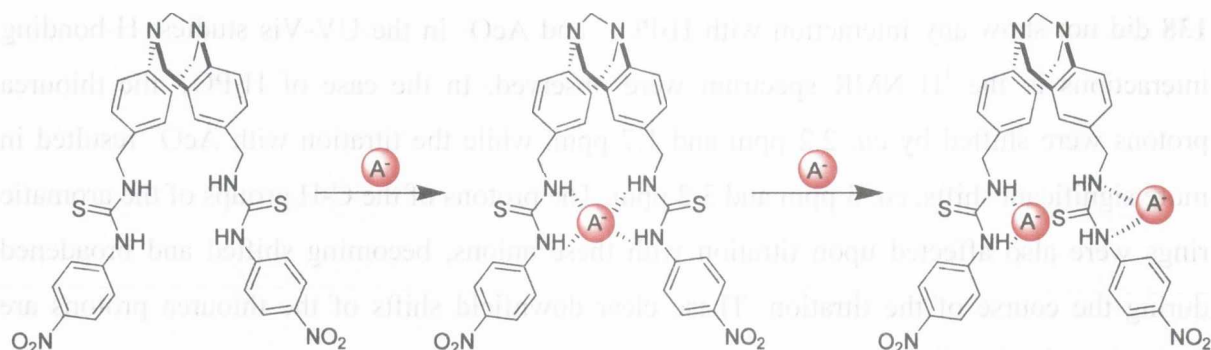
It was found from the UV-Vis studies that the CF_3 analogue **138** did not interact with H_2PO_4^- , AcO^- or SO_4^{2-} , but the absorption spectrum did show modulation upon titration with $\text{HP}_2\text{O}_7^{3-}$ and F^- , most likely due to deprotonation. In contrast, the NO_2 derivative **139** did show H-bonding interactions with H_2PO_4^- and AcO^- , but also did not interact with SO_4^{2-} . Furthermore **139** exhibited a colour change from colourless to orange upon addition of $\text{HP}_2\text{O}_7^{3-}$ and F^- , behaviour not observed for the other anions. In addition, fitting of the titration data using SPECFITTM, the binding affinity of **139** for H_2PO_4^- and AcO^- was calculated. In both cases, the anions were found to form a 1:1 and 2:1 (guest:host) complex in solution with **139**. The binding constants were only marginally different for both anions and the speciation distribution diagram also showed a near identical trend.

In order to further evaluate these interactions with the two receptors, ^1H NMR spectroscopic titrations were also carried out with **138** and **139**. It was found that even though

138 did not show any interaction with H_2PO_4^- and AcO^- in the UV-Vis studies, H-bonding interactions in the ^1H NMR spectrum were observed. In the case of H_2PO_4^- the thiourea protons were shifted by *ca.* 2.2 ppm and 1.7 ppm, while the titration with AcO^- resulted in more significant shifts, *ca.* 3 ppm and 3.2 ppm. The protons of the C-H groups of the aromatic rings were also affected upon titration with these anions, becoming shifted and broadened during the course of the titration. These clear downfield shifts of the thiourea protons are indicative of H-bonding interactions.

In the case of **139**, where significant modulation of the absorption spectrum was observed upon titration with H_2PO_4^- and AcO^- , the thiourea protons also experienced shifts of a similar magnitude to **138**. However, the NHa proton of **139** was significantly broadened and disappeared after the addition of *ca.* 1 equivalent of H_2PO_4^- , while both resonances were clearly visible throughout the course of the titration with AcO^- with a plateau reached at *ca.* 2 equivalents of each anion. Furthermore colour changes from pale yellow to deep orange were also observed upon addition of these anions, allowing them to function as colorimetric sensors. Even at the higher concentration of the ^1H NMR experiments no interaction was observed for either receptor with SO_4^{2-} .

It can be concluded that receptor **138** does show some H-bonding interactions with H_2PO_4^- and AcO^- , however these are only evident through ^1H NMR spectroscopy. In contrast the titrations with $\text{HP}_2\text{O}_7^{3-}$ and F^- clearly showed that a different process was occurring in solution with the main species after titration with these anions most likely to be the deprotonated receptor. In the case of **139**, the results obtained from the ^1H NMR investigations correlated well with the UV-Vis spectroscopic studies, where significant changes were exhibited in both the absorption spectrum and in the chemical shifts of both thiourea protons of **139** upon addition of H_2PO_4^- and AcO^- . An excellent fit of the absorption data and binding constants for these anions were also determined. Initially a 1:1 species is present; a schematic of this binding process is shown in Scheme 3.4, with the anion bound *via* both thiourea moieties and the receptor acting as a molecular tweezers. At higher concentrations one anion is bound to each thiourea group, giving the 2:1 (guest:host) complex.



Scheme 3.4: Proposed binding modes between receptor **139** and anions.

Attaching H-bond donor units to a suitable molecular scaffold is a common method for achieving preorganisation of the binding cavity and the use of conformationally preorganised receptors have been shown to bind anions very efficiently.¹⁷⁹ The two thiourea functionalised Tröger's base receptors detailed in this chapter are the first example of this unique structural framework being incorporated into synthetic receptors for anions. The results highlight the fact that exceptionally strong complexation can be achieved through the active cooperation of multiple, prepositioned H-bonds in a preorganised binding cavity.

It can be concluded that receptor **139** does show some H-bonding interactions with HPO_4^{2-} and AsO_4^{3-} however there are only evident through ^1H NMR spectroscopy. In contrast the titrations with HPO_4^{2-} and I^- clearly showed that a different process was occurring in solution with the main species after titration with these anions most likely to be the deprotonated receptor in the case of **139**, the results obtained from the ^1H NMR investigations correlated well with the UV-Vis spectroscopic studies when significant changes were exhibited in both the absorption spectrum and in the chemical shifts of both thiourea protons of **139** upon addition of HPO_4^{2-} and AsO_4^{3-} . An excellent fit of the absorption data and binding constants for these anions were also determined. Initially a 1:1 species is present a schematic of this binding process is shown in Scheme 3.4 with the anion bound via both thiourea moieties and the receptor acting as a molecular tweezers. At higher concentrations one anion is bound to each thiourea group, giving the 2:1 (guest:host) complex.

Chapter 4

Tripodal Urea-Based Anion Receptors

4. Introduction

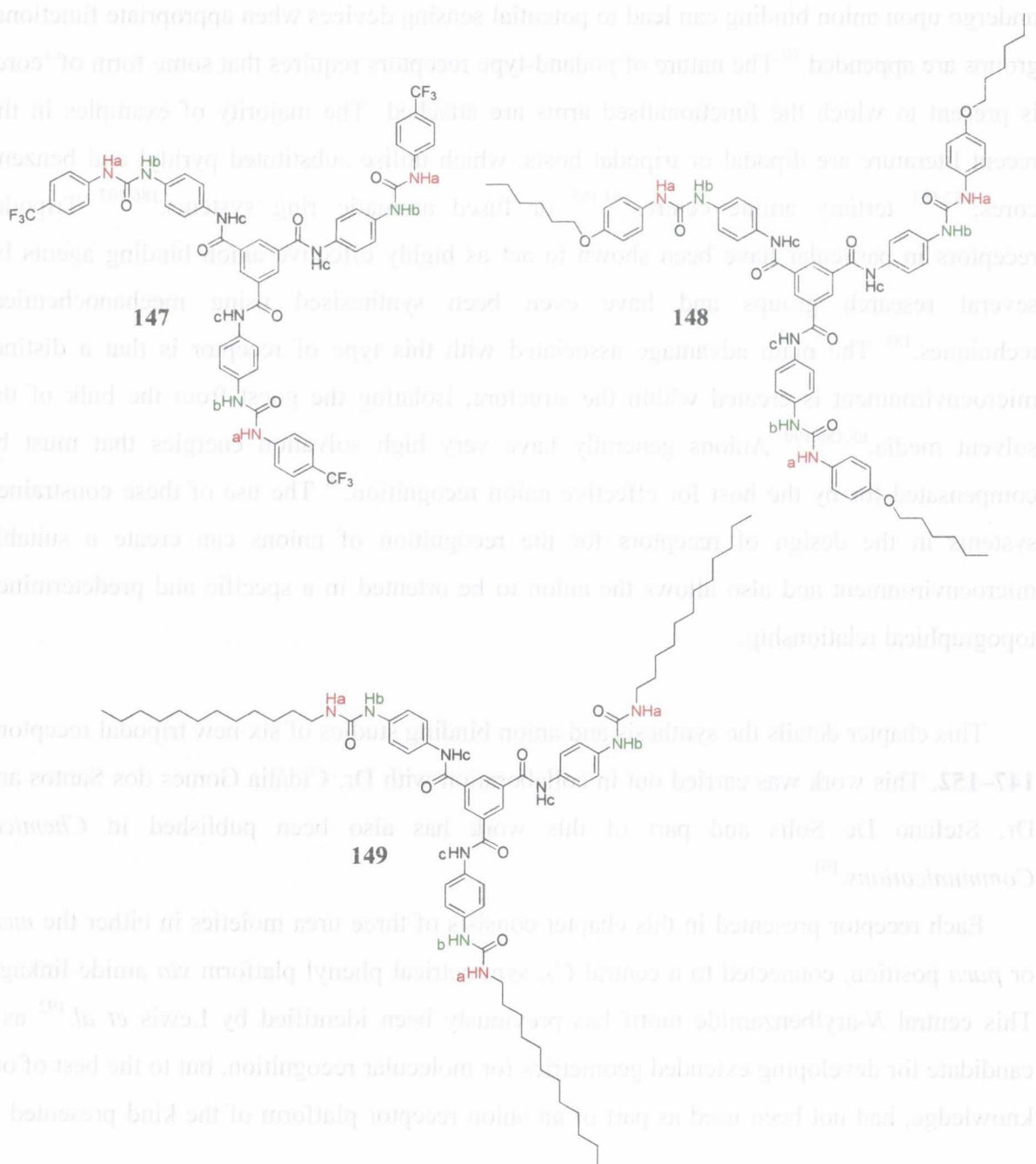
A variety of organic scaffolds and functional groups containing H-bond donors have been utilised for anion recognition, and as detailed in previous chapters.^{67,180,181} Success, however, depends on the structural nature of scaffolds that can preorganise the binding cavity and are complimentary to the prospective guest, whilst also maintaining the right physical properties (*e.g.* solubility) to operate in the desired solvent.

The topology of podand-type receptors provides a unique recognition platform for the detection of anions while also possessing highly desirable properties such as accessibility, tuneability, strong binding and selectivity. The rapid rates of complexation and decomplexation within podand systems and the conformational changes that they are able to undergo upon anion binding can lead to potential sensing devices when appropriate functional groups are appended.⁷⁶ The nature of podand-type receptors requires that some form of ‘core’ is present to which the functionalised arms are attached. The majority of examples in the recent literature are dipodal or tripodal hosts, which utilise substituted pyridyl and benzene cores;^{182,183} tertiary amine centres^{184,185} or fused aromatic ring systems.^{186,187} Tripodal receptors in particular have been shown to act as highly effective anion binding agents by several research groups and have even been synthesised using mechanochemical techniques.¹⁸⁸ The main advantage associated with this type of receptor is that a distinct microenvironment is created within the structure, isolating the guest from the bulk of the solvent media.^{68,189,190} Anions generally have very high solvation energies that must be compensated for by the host for effective anion recognition.⁶⁸ The use of these constrained systems in the design of receptors for the recognition of anions can create a suitable microenvironment and also allows the anion to be oriented in a specific and predetermined topographical relationship.

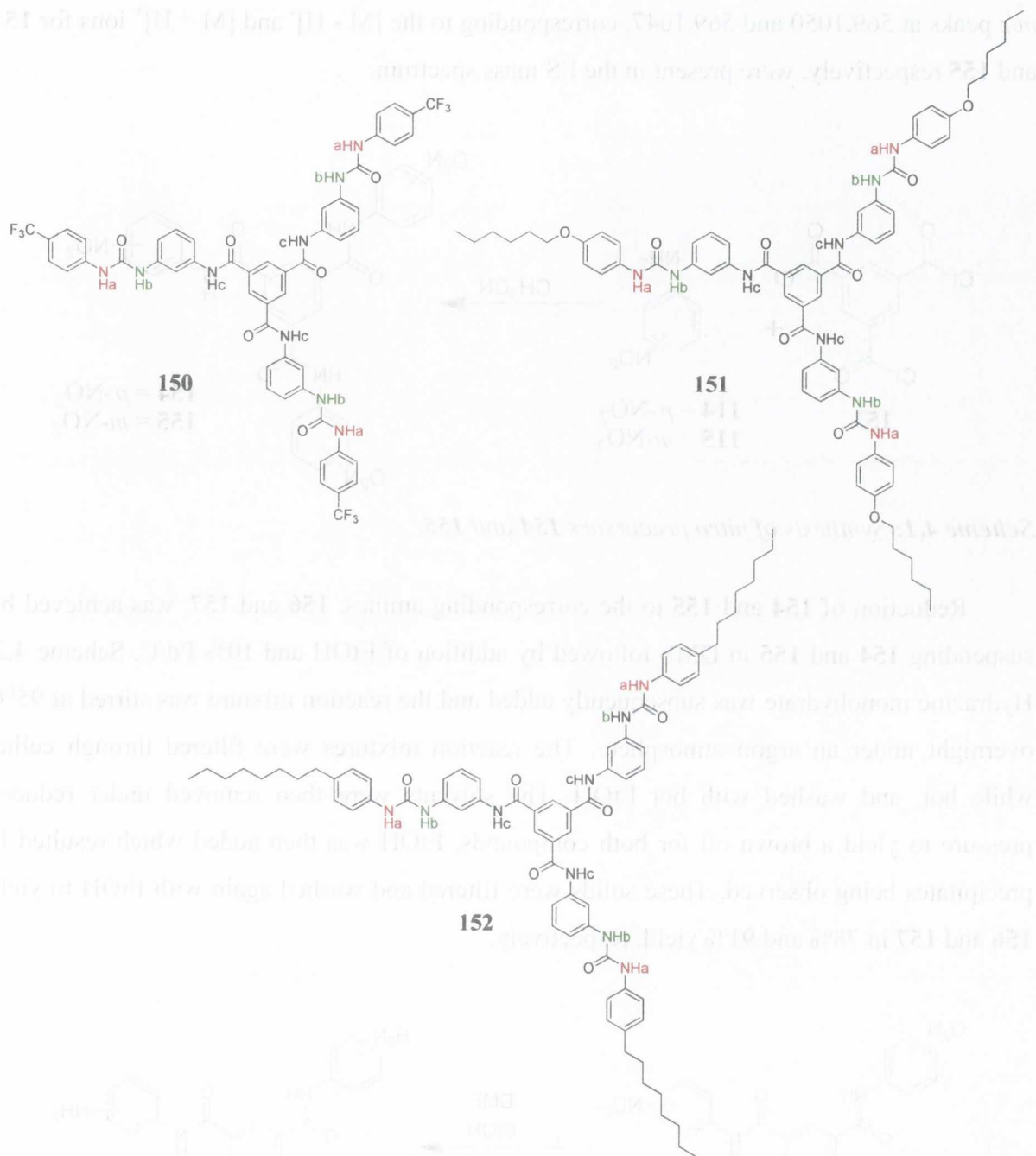
This chapter details the synthesis and anion binding studies of six new tripodal receptors, **147–152**. This work was carried out in collaboration with Dr. Cidália Gomes dos Santos and Dr. Stefano De Solis and part of this work has also been published in *Chemical Communications*.¹⁹¹

Each receptor presented in this chapter consists of three urea moieties in either the *meta* or *para* position, connected to a central C_{3v} symmetrical phenyl platform *via* amide linkage. This central *N*-arylbenzamide motif has previously been identified by Lewis *et al.*¹⁹² as a candidate for developing extended geometries for molecular recognition, but to the best of our knowledge, had not been used as part of an anion receptor platform of the kind presented in

this thesis. Having previously demonstrated that simple urea¹⁴⁵ and thiourea¹⁴⁶ receptors with acetamide functionalities (Chapter 2) could participate in positive cooperative binding, we anticipated that for **147-152**, this central platform would enable cooperative or synergetic binding of anions by all of the three urea sites. We also envisaged that this binding would affect the chemical shifts of the amide protons in the ¹H NMR due to the conformational changes that these structures would undergo upon anion binding. The three *para* derivatives **147-149** are shown below and while **147** has an electron-withdrawing CF₃ group, **148** and **149** have long alkyl chains which could facilitate the use of these structures as potential membrane transporters.^{193,194} In the case of **148**, the alkyl chain is conjugated to a phenyl ring *via* an ether linkage while **149** has the alkyl chain directly attached to the urea moiety.



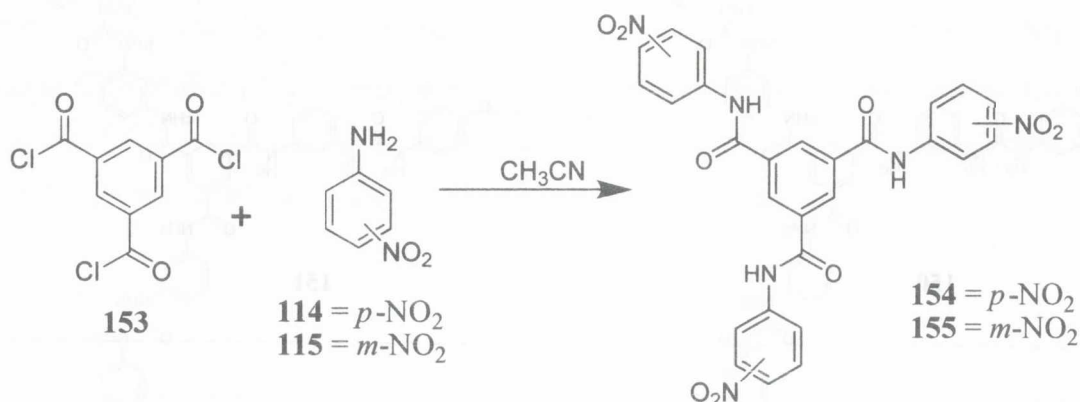
The *meta* derivatives also include one electron-withdrawing analogue, **150**, in the series and two with alkyl chains of different lengths **151** and **152**. Both alkyl chains are connected to a phenyl ring, however **151** also has an ether linkage while **152** does not.



4.1 Synthesis of Receptors 147-152

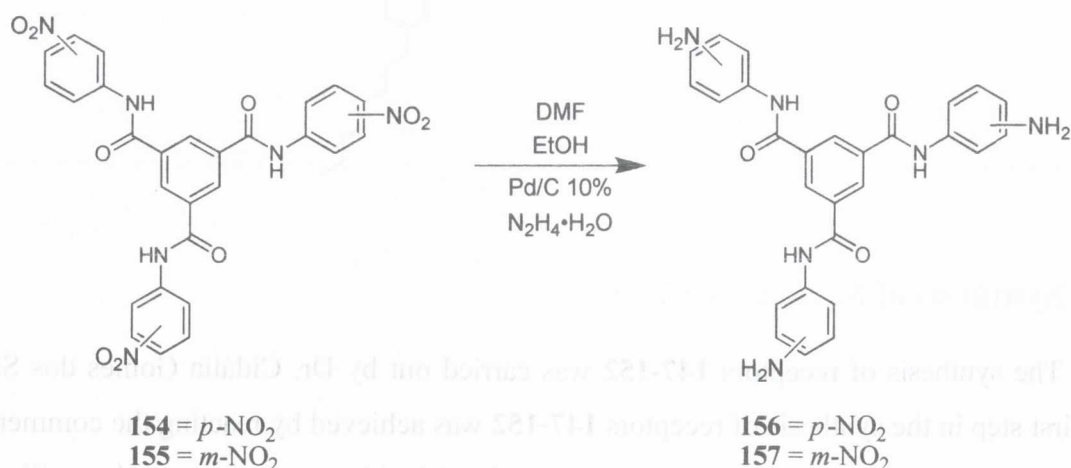
The synthesis of receptors **147-152** was carried out by Dr. Cidália Gomes dos Santos. The first step in the synthesis of receptors **147-152** was achieved by reacting the commercially available 1,3,5-benzenetricarbonyl trichloride, **153**, with either *para* or *meta* nitroaniline, **114** and **115** respectively, in CH₃CN at reflux overnight, Scheme 4.1. The resulting precipitate was then filtered and washed with cold CH₃CN to give **154** and **155** in 84% and 91% yield

respectively. The ^1H NMR spectrum (400 MHz, $\text{DMSO}-d_6$) of **154** and **155** showed the amido N-H at 11.18 ppm and 11.10 ppm, respectively. Addition of D_2O resulted in the disappearance of these exchangeable protons and was also confirmed by N-H COSY analysis. The expected m/z peaks at 569.1050 and 569.1047, corresponding to the $[\text{M} - \text{H}]^-$ and $[\text{M} + \text{H}]^+$ ions for **154** and **155** respectively, were present in the ES mass spectrum.



Scheme 4.1: Synthesis of nitro precursors **154** and **155**.

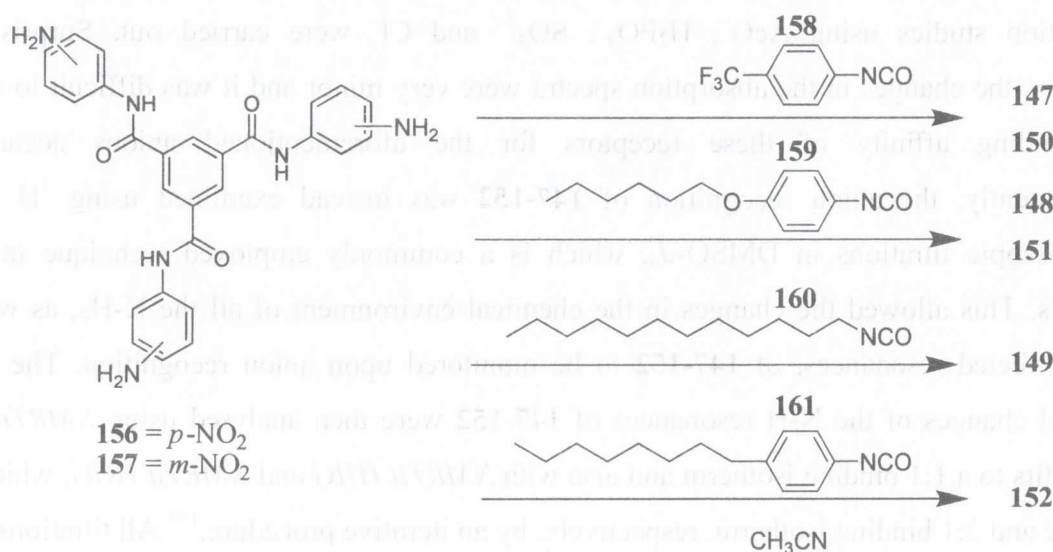
Reduction of **154** and **155** to the corresponding amines, **156** and **157**, was achieved by suspending **154** and **155** in DMF followed by addition of EtOH and 10% Pd/C, Scheme 4.2. Hydrazine monohydrate was subsequently added and the reaction mixture was stirred at 95°C overnight under an argon atmosphere. The reaction mixtures were filtered through celite, while hot, and washed with hot EtOH. The solvents were then removed under reduced pressure to yield a brown oil for both compounds. EtOH was then added which resulted in precipitates being observed. These solids were filtered and washed again with EtOH to yield **156** and **157** in 78% and 91% yield, respectively.



Scheme 4.2: Synthesis of amino precursors **156** and **157**.

Successful formation of the reduced products was confirmed by ^1H NMR analysis (400 MHz, $\text{DMSO}-d_6$) with the N-H proton corresponding to the amide functionality shifted downfield to 10.17 ppm and 10.26 ppm for **156** and **157**, respectively. The NH_2 group resonated at 5.04 ppm and 5.17 ppm, again identified by exchange with D_2O and N-H COSY analysis, for **156** and **157**, respectively. ES-MS analysis showed the presence of a peak at 481.1986 and 481.1981, for **156** and **157** respectively, corresponding to the $[\text{M} + \text{H}]^+$ species.

The final receptors **147-152** were then formed by suspending **156** or **157** into hot CH_3CN followed by the addition of the appropriate isocyanates, **158-161**, and heating the resulting mixtures at reflux overnight under an inert atmosphere, Scheme 4.3. This resulted in the formation of precipitates, which were filtered and washed with cold CH_3CN giving **147-152** in 85%, 95%, 67%, 91%, 89% and 91% yields, respectively. Receptors **147-152** were characterised by ^1H NMR (Appendix, Figure A4.1-4.5), ^{13}C NMR, mass spectrometry and infrared spectroscopy. The ^1H NMR spectrum (400 MHz, $\text{DMSO}-d_6$) of **147** is shown in Figure 4.1 and shows the most downfield proton at 10.55 ppm corresponds to that of the amido linker. The resonance at 9.12 ppm is the urea proton attached to the CF_3 phenyl ring while the other urea N-H resonates at 8.83 ppm. The central aryl proton, CH1, appears at 8.69 ppm. Further characterisation by ^{13}C NMR analysis showed two resonances at 164.2 ppm and 152.3 ppm corresponding to the two quaternary carbonyl groups. The presence of the CF_3 group was determined by the occurrence of a signal at -60.52 ppm in the ^{19}F spectrum. The expected peak at $m/z = 1041.2686$ for the $[\text{M} + \text{H}]^+$ species was observed in the MALDI-ToF spectrum.



Scheme 4.3: Synthesis of receptors **147-152**.

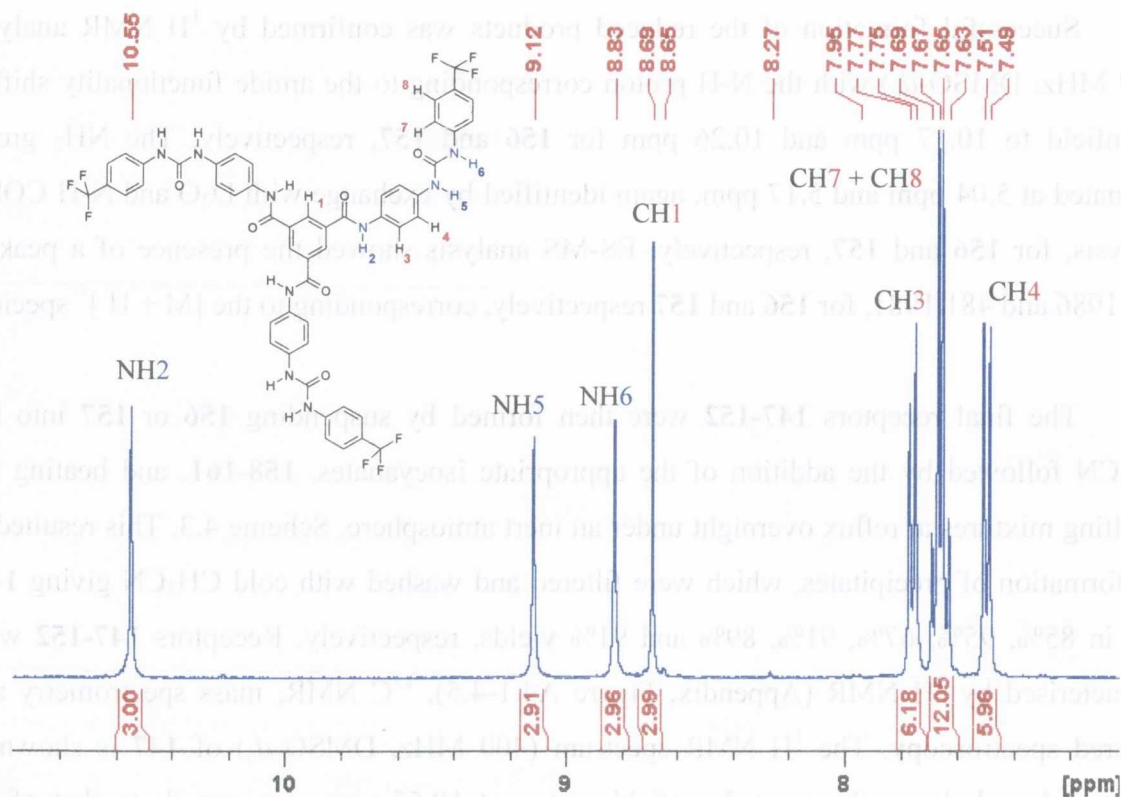


Figure 4.1: ^1H NMR spectrum (400 MHz, $\text{DMSO}-d_6$) of receptor **147**.

Having synthesised and characterised these sensors, detailed spectroscopic titrations were carried out with several anions and will be discussed in the following sections. All titrations were repeated multiple times to ensure reproducibility.

4.2 Anion Binding Studies of Receptors 147-152

In order to evaluate the binding affinity of **147-152** for various anions, UV-Vis absorption studies using AcO^- , H_2PO_4^- , SO_4^{2-} and Cl^- were carried out. Surprisingly, however, the changes in the absorption spectra were very minor and it was difficult to assess the binding affinity of these receptors for the aforementioned anions accurately. Consequently, the anion recognition of **147-152** was instead examined using ^1H NMR spectroscopic titrations in $\text{DMSO}-d_6$, which is a commonly employed technique in such analysis. This allowed the changes in the chemical environment of all the N-Hs, as well as other affected resonances, of **147-152** to be monitored upon anion recognition. The anion induced changes of the N-H resonances of **147-152** were then analysed using *NMRTit HG*, which fits to a 1:1 binding isotherm and also with *NMRTit HHG* and *NMRTit HGG*, which fits to a 1:2 and 2:1 binding isotherm, respectively, by an iterative procedure.¹⁹⁵ All titrations were repeated a number of times to ensure reproducibility.

4.2.1 ^1H NMR Titrations of *Para* Derivatives 147-149

The first receptor to be investigated was the *para* CF_3 derivative **147**. The successive addition of AcO^- to **147** resulted in significant changes in the chemical shifts of several protons, Figure 4.2. As expected the largest shifts were seen for the two urea protons, N-Ha and N-Hb, both of which experienced significant downfield shifts of *ca.* 3.3 ppm and 3.4 ppm respectively, indicative of strong H-bonding between the receptor moieties and AcO^- . The amide proton, N-Hc, however only experienced a small shift and it is possible that this shift is conformationally induced, signifying the binding of AcO^- to the urea moieties and is not due to direct binding of the anion to the amides. The aromatic resonances also became highly resolved during the course of the titration. A detailed stack plot of the changes occurring between 1 and 2 equivalents of AcO^- is displayed in the Appendix (Appendix, Figure A4.6).

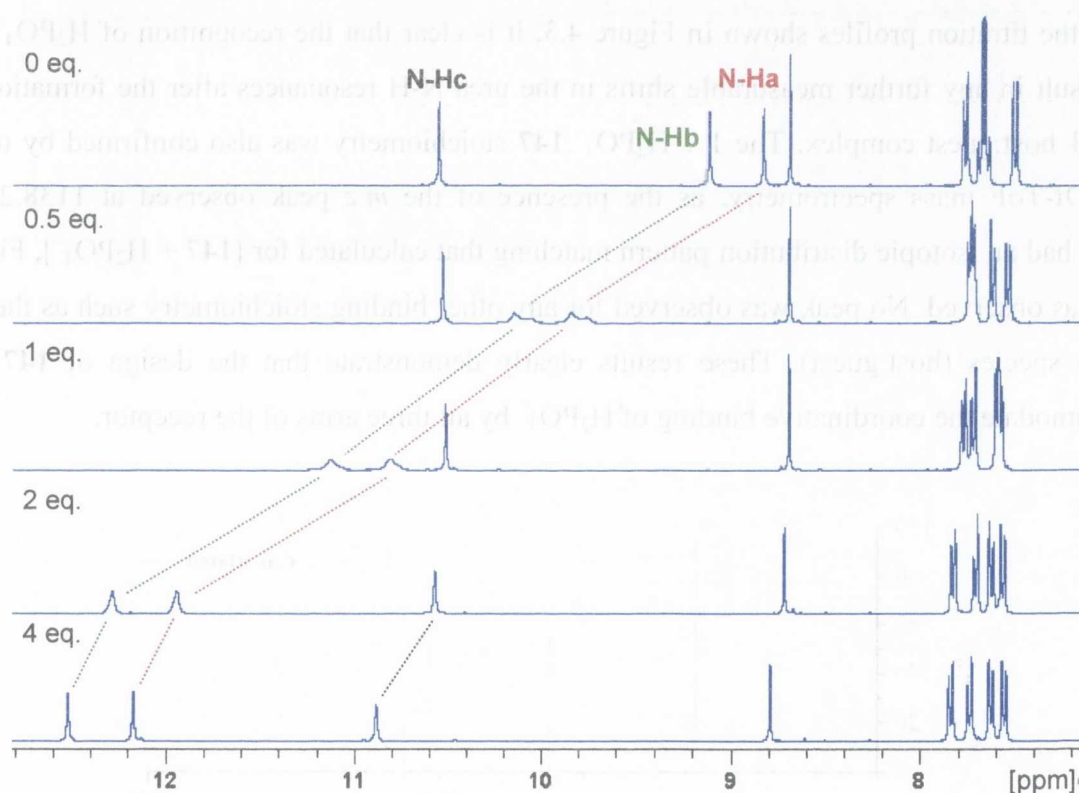


Figure 4.2: Stack plot of ^1H NMR spectra (400 MHz, DMSO-d_6) of **147** (7×10^{-3} M) upon addition of 0.5, 1, 2 and 4 equivalents of AcO^- . N-Ha and N-Hb are the urea protons, while N-Hc is the amide proton.

The successive addition of H_2PO_4^- to **147** also resulted in significant changes in the chemical shifts of several protons. Large shifts of similar magnitude to AcO^- , *ca.* 2.2 ppm were observed for both of the urea protons. By plotting the $\Delta\delta\text{H}$ for the urea protons against the equivalents of H_2PO_4^- , binding isotherms were obtained and are shown in Figure 4.3.

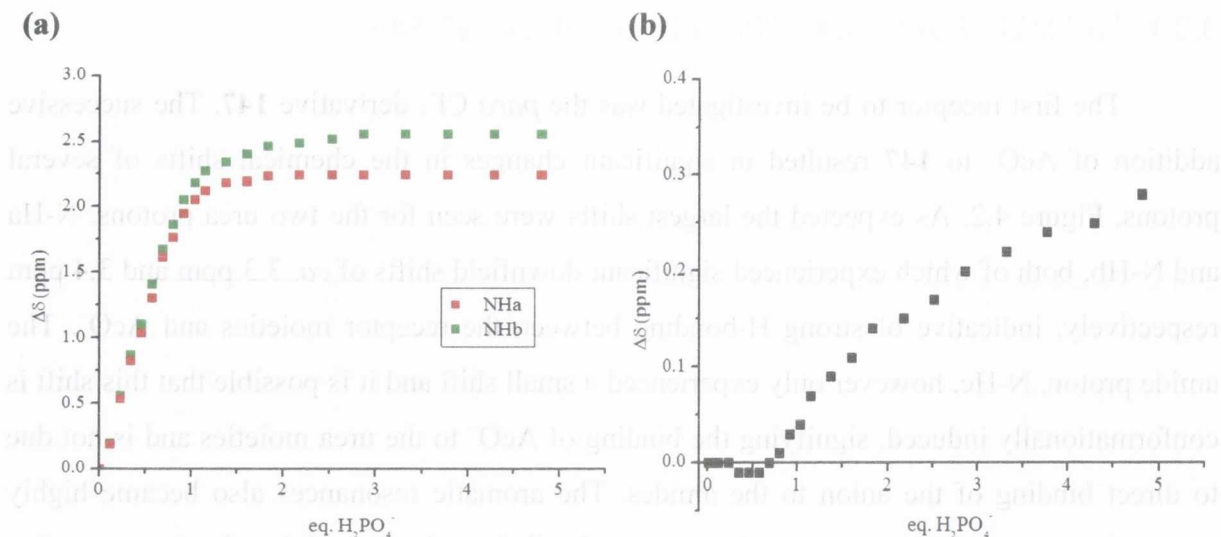


Figure 4.3: Changes in the (a) urea and (b) amide resonances of **147** (as $\Delta\delta$) upon titration with H_2PO_4^- .

From the titration profiles shown in Figure 4.3, it is clear that the recognition of H_2PO_4^- did not result in any further measurable shifts in the urea N-H resonances after the formation of the 1:1 host:guest complex. The 1:1 H_2PO_4^- :**147** stoichiometry was also confirmed by using MALDI-ToF mass spectrometry, as the presence of the m/z peak observed at 1138.2332, which had an isotopic distribution pattern matching that calculated for [**147** + H_2PO_4^-], Figure 4.4, was observed. No peak was observed for any other binding stoichiometry such as the 1:2 or 1:3 species (host:guest). These results clearly demonstrate that the design of **147** can accommodate the coordinative binding of H_2PO_4^- by all three arms of the receptor.

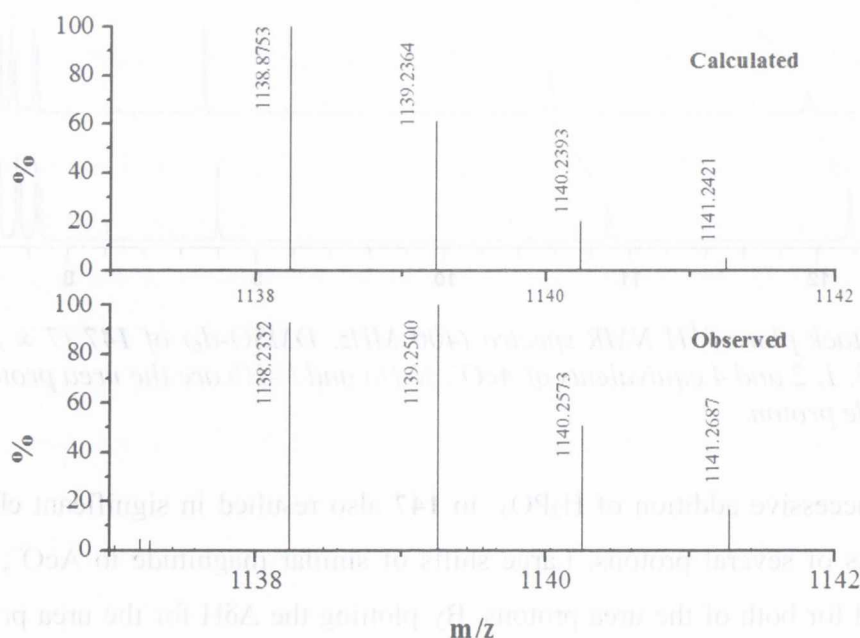


Figure 4.4: The calculated (top) and observed (bottom) isotopic distribution pattern (MALDI-ToF MS) for [**147** + H_2PO_4^-].

Similar behaviour was observed for SO_4^{2-} , where the largest changes in the ^1H NMR spectrum were observed upon the addition of one equivalent. However the chemical shift of the amide proton, *meta* to the urea, was less significant being shifted slightly upfield by *ca.* 0.2 ppm and no changes occurring after the addition of one equivalent. The binding isotherms for this titration are shown in Figure 4.5 and the changes for the urea protons indicate a 1:1 host:guest stoichiometric interaction in solution.

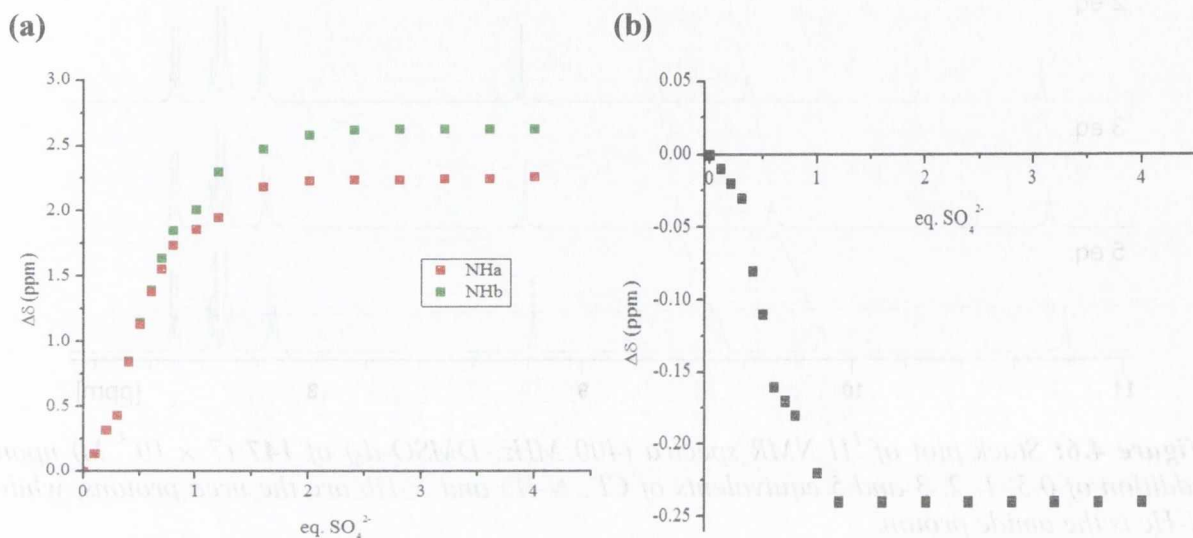


Figure 4.5: Changes in the (a) urea and (b) amide resonances of **147** (as $\Delta\delta$) upon titration with SO_4^{2-} .

The last anion to be investigated was Cl^- , and from the stack plot shown in Figure 4.6, it can be seen that although the urea protons undergo a small shift it was less significant. The amide proton was shifted by only *ca.* 0.1 ppm within the addition of one equivalent of Cl^- and so it can be concluded that there is no substantial contribution from the amide proton in the sensing mechanism of **147**. The aromatic protons retain their multiplicity throughout the titration.

The binding affinity of **147** with the anions studied was further assessed by fitting the changes of the N-H resonances of the urea protons to 1:1 and 1:2 (host:guest) stoichiometries (Appendix, Figure A4.7-8). The results are summarised in Table 4.1 and on all occasions the best fit was obtained using a 1:1 binding model. It can be seen that receptor **147** showed the highest affinity for H_2PO_4^- with a $\log K_{1:1} = 4.2 \pm 0.1$. However, the interaction between **147** and SO_4^{2-} was also strong ($\log K_{1:1} = 3.7 \pm 0.2$). The receptor showed the lowest affinity for Cl^- ($\log K_{1:1} = 2.10 \pm 0.07$), which is not unexpected as the changes in the chemical shifts of the urea protons upon titration with Cl^- were the least shifted.

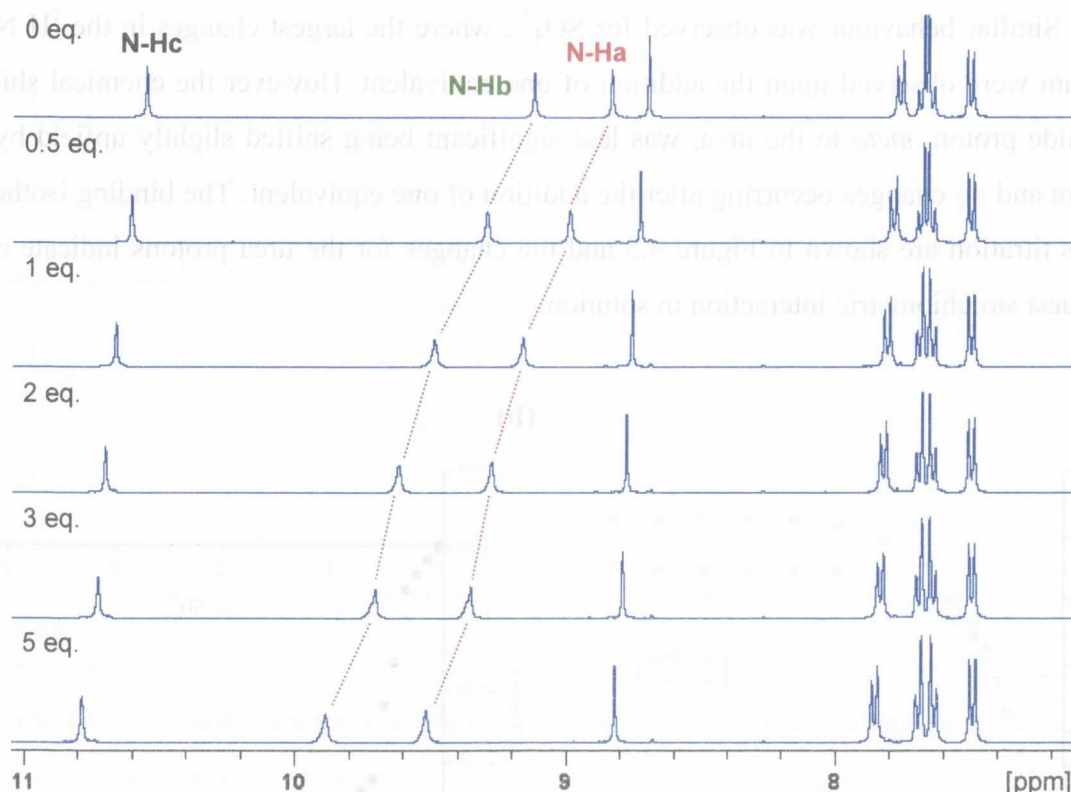


Figure 4.6: Stack plot of ^1H NMR spectra (400 MHz, DMSO-d_6) of **147** (7×10^{-3} M) upon addition of 0.5, 1, 2, 3 and 5 equivalents of Cl^- . **N-Ha** and **N-Hb** are the urea protons, while **N-Hc** is the amide proton.

Table 4.1: Binding constants determined for **147** from ^1H NMR titrations in DMSO-d_6 .

Receptor (L)	Anion (G)	Binding Mode $\text{G}_n:\text{L}_m$	log $K_{n:m}$	Std. Deviation ($\pm$)
147	AcO^-	1:1	2.79	0.07
	H_2PO_4^-	1:1	4.2	0.1
	SO_4^{2-}	1:1	3.7	0.2
	Cl^-	1:1	2.10	0.07

Molecular modelling using MM2 of the binding of receptor **147** to these anions showed the formation of a closely associated host-guest complex, where the amide protons are directed away from the anion binding site (*i.e.* receptor pocket), Figure 4.7. All molecular modelling calculations were carried out by Prof. Paul E Kruger, University of Canterbury, Christchurch, New Zealand.

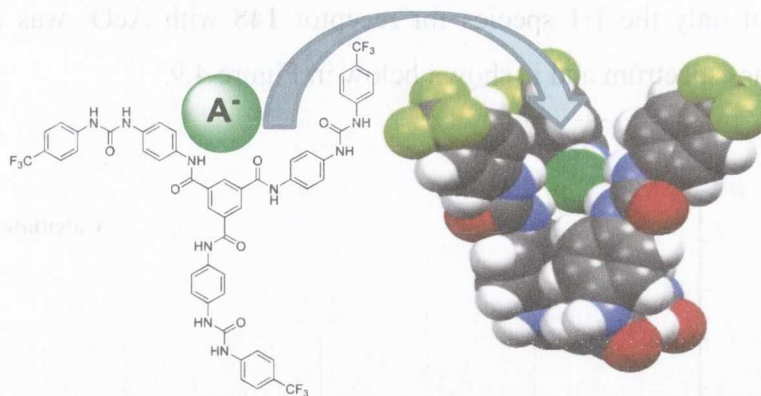


Figure 4.7: MM2 modelling of receptor **147** with anions.

The next receptor to be investigated was **148**, which contains a hexyl chain connected to the phenyl ring *via* an ether functionality. The ^1H NMR spectra of receptor **148** upon addition of AcO^- showed fast exchange processes and significant downfield shifts of the urea protons, *ca.* 3.1 ppm for both protons, strongly indicating that all six N-H protons were cooperatively involved in H-bonding to AcO^- in solution. The binding isotherm for the titration, obtained by plotting the changes in the chemical shifts of the urea protons against the equivalents of AcO^- added, Figure 4.8 (a), indicates that a plateau is reached at *ca.* 1 equivalent of the anion. The titration profile of the amide proton is also shown and although the magnitude of the downfield shift was not as significant, it was followed by an upfield shift after the addition of *ca.* 1 equivalent of AcO^- . This indicates the amide is not contributing to the binding process as small changes in the chemical shift of the amide protons are considered to be a result of conformational changes of the scaffolds.

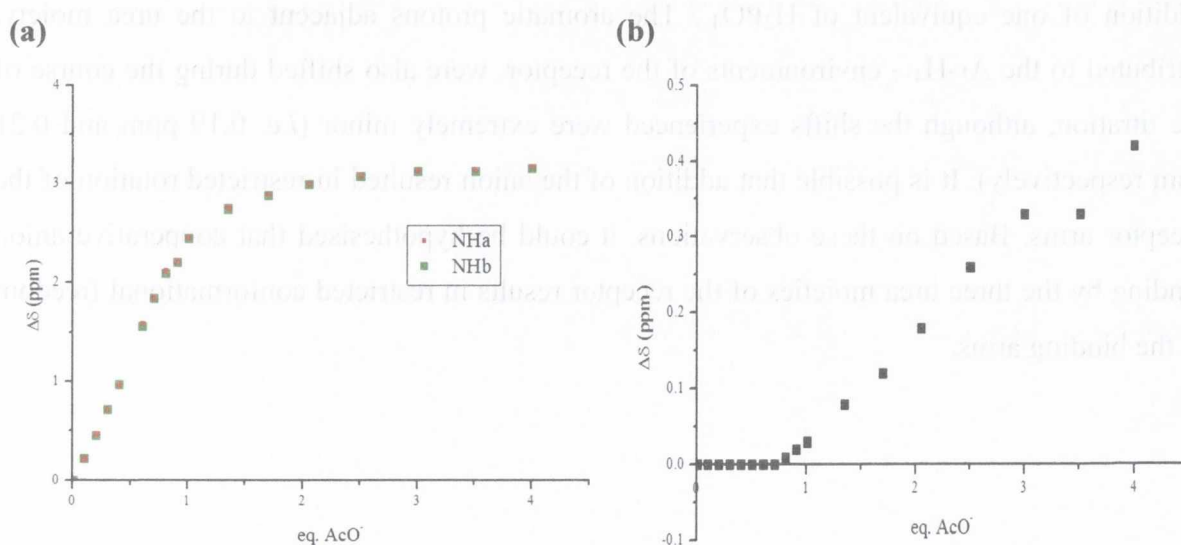


Figure 4.8: Changes in the (a) urea and (b) amide resonances of **148** (as $\Delta\delta$) upon titration with AcO^- .

The formation of only the 1:1 species for receptor **148** with AcO^- was also evident in the MALDI-ToF mass spectrum and is shown below in Figure 4.9.

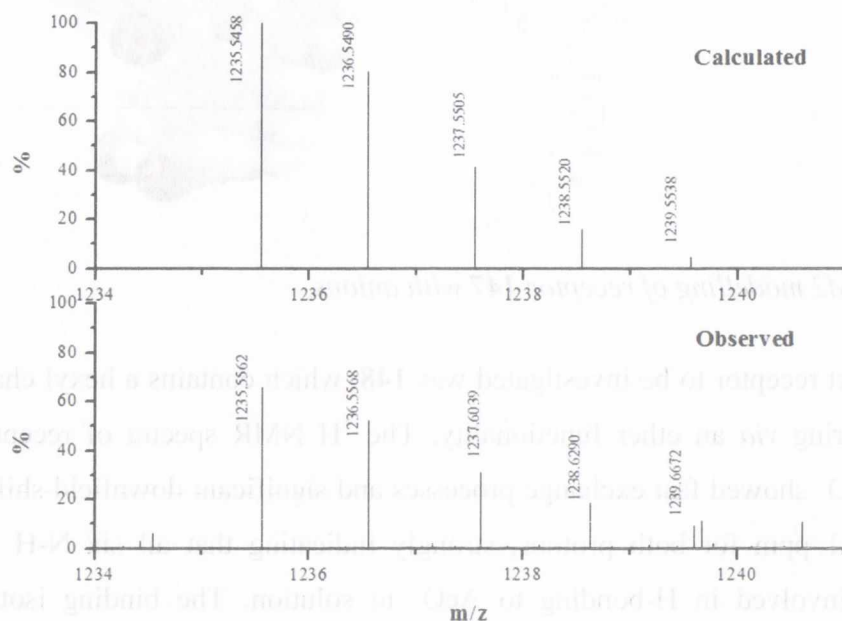


Figure 4.9: The calculated (top) and observed (bottom) isotopic distribution pattern (MALDI-ToF MS) for $[[\mathbf{148} - \text{H}]^- + \text{AcO}^- + \text{K}^+]$.

The titration of **148** with H_2PO_4^- resulted in similar behaviour indicative of fast exchange on the NMR timescale. The urea protons were shifted significantly downfield from their original positions, as shown in the stack plot in Figure 4.10; and this was attributed to the formation of a new host-guest complex in solution. It can also be seen that the amide proton experiences a very minor shift, however the N-H β resonance is masked by this signal after the addition of one equivalent of H_2PO_4^- . The aromatic protons adjacent to the urea moiety, attributed to the Ar-H $_{4+7}$ environments of the receptor, were also shifted during the course of the titration, although the shifts experienced were extremely minor (*i.e.* 0.19 ppm and 0.21 ppm respectively). It is possible that addition of the anion resulted in restricted rotation of the receptor arms. Based on these observations, it could be hypothesised that cooperative anion binding by the three urea moieties of the receptor results in restricted conformational freedom of the binding arms.

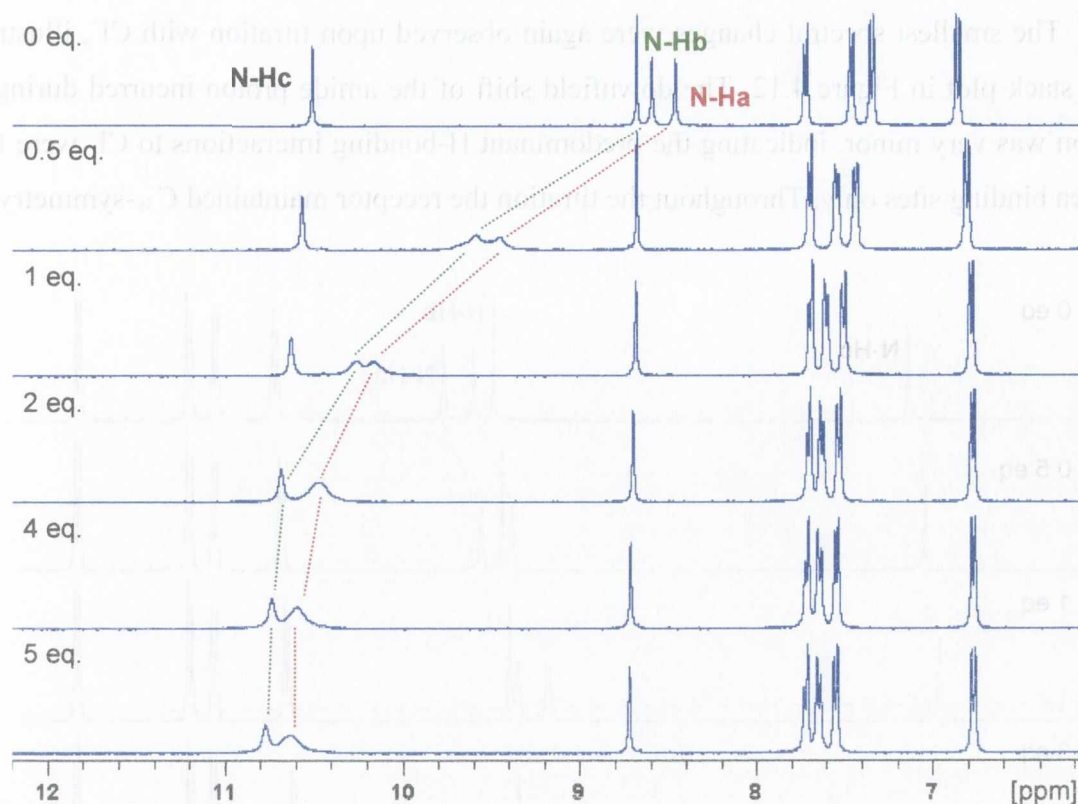


Figure 4.10: Stack plot of ^1H NMR spectra (400 MHz, $\text{DMSO}-d_6$) of **148** (7×10^{-3} M) upon addition of 0.5, 1, 2, 4 and 5 equivalents of H_2PO_4^- . *N-Ha* and *N-Hb* are the urea protons, while *N-Hc* is the amide proton.

In contrast to the results seen for **148** with AcO^- and H_2PO_4^- , beyond the addition of 0.5 equivalents of SO_4^{2-} the urea protons broadened to such an extent that they could no longer be observed (Appendix, A4.9) while the amide proton underwent a gradual upfield shift after the addition of *ca.* 1 equivalent of anion before then reaching a plateau, shown in Figure 4.11. These observations suggest that **148** initially forms a 1:1 complex at lower concentrations of SO_4^{2-} , however again the amide proton does not appear to contribute to the binding process.

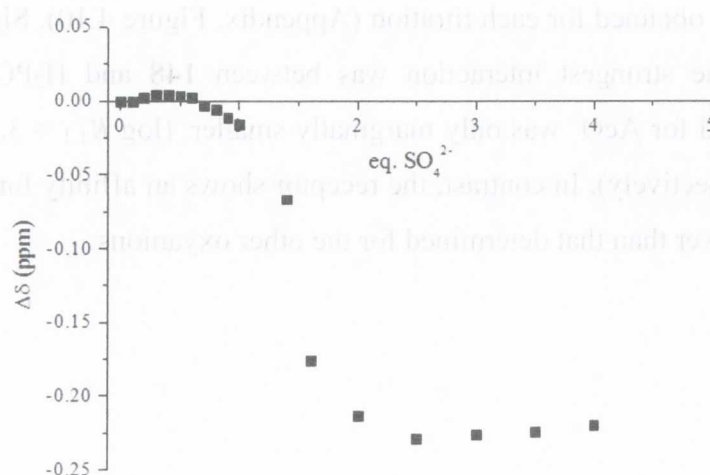


Figure 4.11: The changes in the amide resonances of **148** (as $\Delta\delta$) upon titration with SO_4^{2-} .

The smallest spectral changes were again observed upon titration with Cl^- , illustrated in the stack plot in Figure 4.12. The downfield shift of the amide proton incurred during the titration was very minor, indicating the predominant H-bonding interactions to Cl^- were from the urea binding sites only. Throughout the titration the receptor maintained C_{3v} -symmetry.

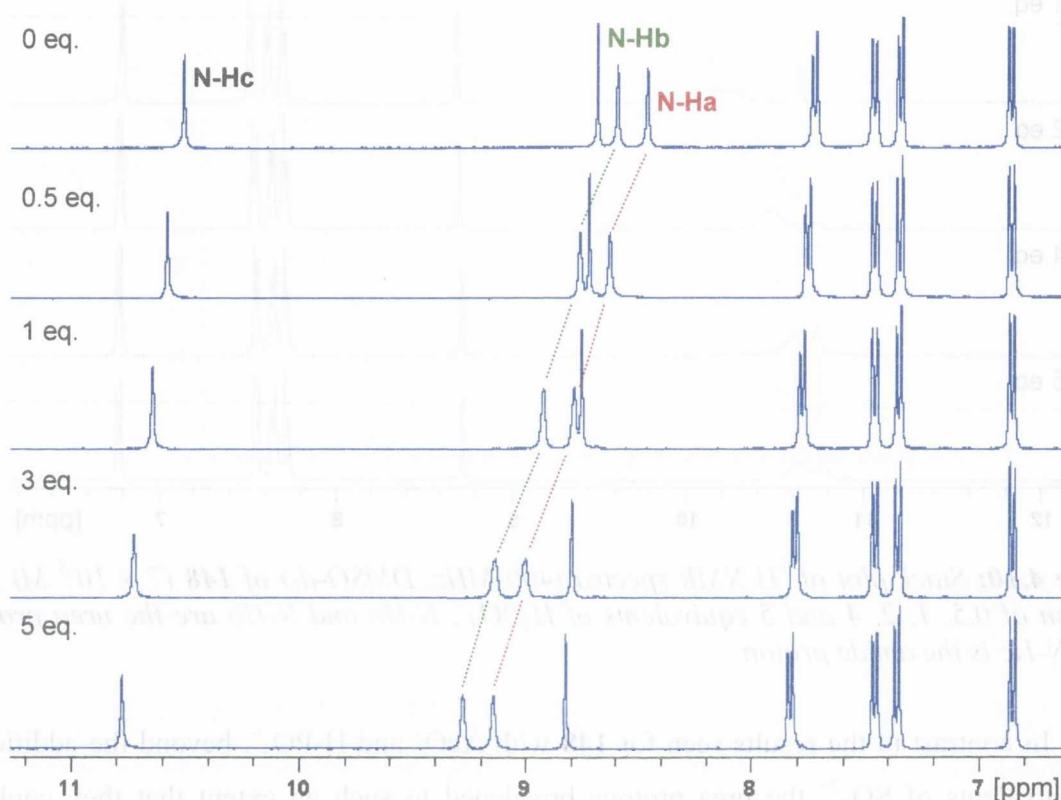


Figure 4.12: Stack plot of ^1H NMR spectra (400 MHz, DMSO-d_6) of **148** (7×10^{-3} M) upon addition of 0.5, 1, 3 and 5 equivalents of Cl^- . *N-Ha* and *N-Hb* are the urea protons, while *N-Hc* is the amide proton.

The binding constants calculated for receptor **148** with the anions studied are presented in Table 4.2. In all instances the data confirms the presence of a 1:1 binding interaction and an excellent fit was obtained for each titration (Appendix, Figure 4.10). Similar to that seen with receptor **147**, the strongest interaction was between **148** and H_2PO_4^- while the binding constant obtained for AcO^- was only marginally smaller, ($\log K_{1:1} = 3.5 \pm 0.1$ and $\log K_{1:1} = 3.25 \pm 0.04$, respectively). In contrast, the receptor shows an affinity for SO_4^{2-} that is an order of magnitude lower than that determined for the other oxyanions.

Table 4.2: Binding constants determined for **148** from ^1H NMR titrations in $\text{DMSO}-d_6$.

Receptor (L)	Anion (G)	Binding Mode $G_n:L_m$	log $K_{n:m}$	Std. Deviation ($\pm$)
148	AcO^-	1:1	3.25	0.04
	H_2PO_4^-	1:1	3.5	0.1
	SO_4^{2-}	1:1	2.1	0.1
	Cl^-	1:1	2.81	0.07

The final receptor in the *para* series to be investigated was compound **149**, which has a long electron donating 12-carbon chain directly functionalised to the urea moiety.

Interestingly, upon titration with AcO^- this receptor behaved in a different manner to that seen for **147** and **148**. A steady downfield shift in the urea protons was observed during the course of the titration. However, even upon addition of excess AcO^- (> 4 equivalents) did not result in a full plateau being reached, making accurate assessments of the binding interaction very difficult. As a consequence of the flexible nature of the long alkyl chain appended to the receptor moiety, **149** is not as conformationally preorganised and restrained when compared to the other derivatives studied. The stack plot of part of the titration of **149** and AcO^- is shown in Figure 4.13 and it can be seen that although the urea protons are continuously shifted, the amide proton does not appear to experience any interaction with the anion. The aromatic protons of the central benzene core also retain their multiplicities and do not display any kind of shift.

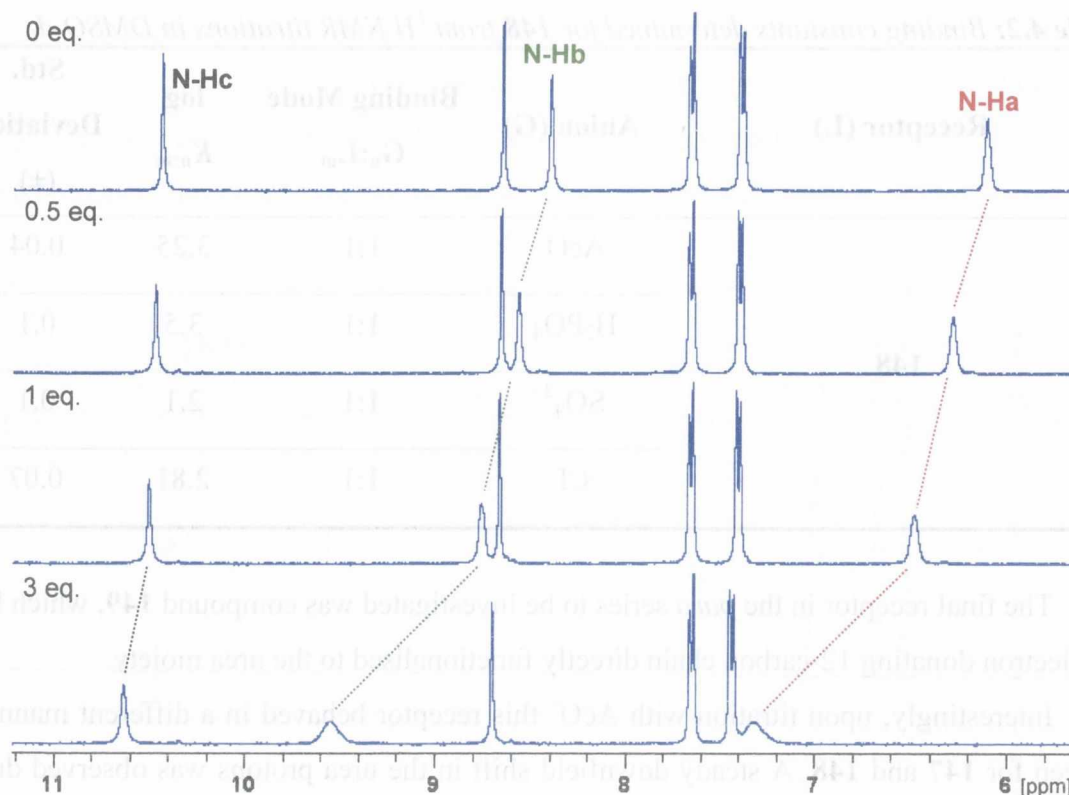


Figure 4.13: Stack plot of ^1H NMR spectra (400 MHz, $\text{DMSO}-d_6$) of **149** (7×10^{-3} M) upon addition of 0.5, 1 and 3 equivalents of AcO^- . *N-Ha* and *N-Hb* are the urea protons, while *N-Hc* is the amide proton.

The family of spectra obtained from the ^1H NMR titration of receptor **149** with H_2PO_4^- is shown in Figure 4.14. The urea protons were shifted downfield, as had been observed for **147** and **148**, throughout the titration. However, this shift was much less significant to that that seen previously with receptors **147** and **148**, *ca.* 1 ppm. It can be seen that the magnitude of the downfield shift of the amide proton was slightly larger than that observed for previous anions and it could be possible that in this instance the anion is interacting, albeit weakly, to the amide proton. The aromatic protons also underwent a very slight shift, although compared to that experienced by the N-H protons, this shift was negligible.

Addition of 0.2 equivalents of SO_4^{2-} caused both urea proton signals to broaden significantly into the baseline of the spectra so they were hardly observed. The amide proton also became significantly broadened and difficult to follow, even before the addition of 0.5 equivalents of SO_4^{2-} . It was therefore very challenging to make any assessment of the binding interaction of receptor **149** with SO_4^{2-} .

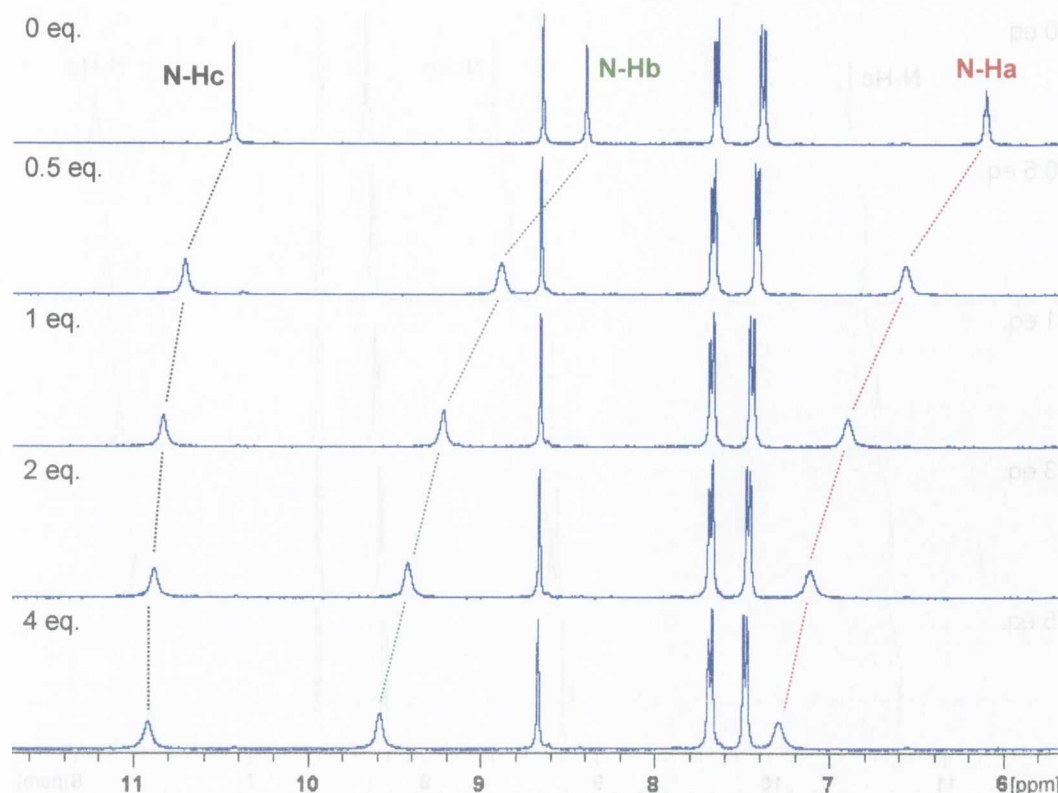


Figure 4.14: Stack plot of ^1H NMR spectra (400 MHz, $\text{DMSO-}d_6$) of **149** (7×10^{-3} M) upon addition of 0.5, 1, 2 and 4 equivalents of H_2PO_4^- . *N-Ha* and *N-Hb* are the urea protons, while *N-Hc* is the amide proton.

The titration of **149** with Cl^- did not result in any significant changes in the ^1H NMR spectrum, with the *N-Ha* and *N-Hb* experiencing shifts of *ca.* 0.33 ppm and 0.47 ppm respectively, while the amide proton also experienced a downfield shift of *ca.* 0.31 ppm, Figure 4.15. The aromatic protons also did not undergo any major changes.

Due to the combination of H-bonding and conformational effects, the chemical shift data for the titration of **149** with AcO^- and SO_4^{2-} could not be fit to an appropriate model, preventing the determination of stability constants using these protons. Indeed, the titration profiles observed differed drastically from those seen for the other *para* analogues. However, binding constants for the other anions were determined and an excellent fit obtained in all instances for the 1:1 species; these results are shown in Table 4.3.

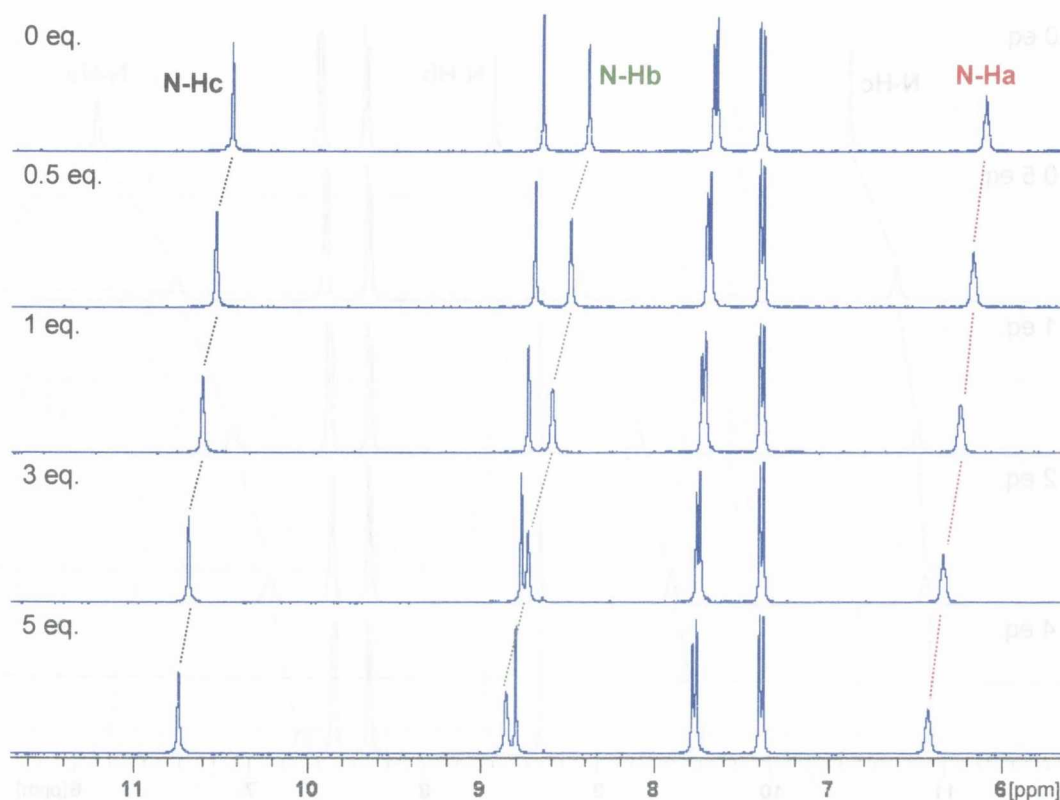


Figure 4.15: Stack plot of ^1H NMR spectra (400 MHz, DMSO-d_6) of **149** ($7 \times 10^{-3} \text{ M}$) upon addition of 0.5, 1, 3 and 5 equivalents of Cl^- . *N-Ha* and *N-Hb* are the urea protons, while *N-Hc* is the amide proton.

Table 4.3: Binding constants determined for **149** from ^1H NMR titrations in DMSO-d_6 .

Receptor (L)	Anion (G)	Binding Mode $G_n:L_m$	$\log K_{n:m}$	Std. Deviation ($\pm$)
149	AcO^-		-*	
	H_2PO_4^-	1:1	2.84	0.07
	SO_4^{2-}		-*	
	Cl^-	1:1	2.05	0.04

* Isotherm could not be fitted to a 1:1 or 2:1 binding model.

In general, the values of the binding constants obtained for receptor **149** with H_2PO_4^- and Cl^- are reasonably modest. It is possible that the highly polar nature of the solvent is having some effect on the interaction of this very flexible receptor with these anions. The lack of the second aryl group also means the N-H protons of the urea are probably the least acidic in this series, thus reducing their H-bonding ability of the receptor.

4.2.2 ^1H NMR Titrations of *Meta* Derivatives 150-152

The first *meta* receptor to be investigated was **150**, which has the electron withdrawing CF_3 group and is the structural isomer of receptor **147**.

The changes observed for the urea resonances upon binding of AcO^- were quite significant, *ca.* 2 ppm, with the majority of the changes occurring between 0 $\rightarrow$ 1 equivalent (Appendix, A4.11 for a more detailed stack plot) of the anion, shown in Figure 4.16. Thereafter the signals for these protons become very sharp but no other shift occurs. In contrast to these significant changes, the amide proton did not experience any notable change in chemical shift, but splitting of the aromatic resonances was observed. The experimental data obtained from the titration of AcO^- and **150** suggest strong binding and formation of a 1:1 H-bonded complex.

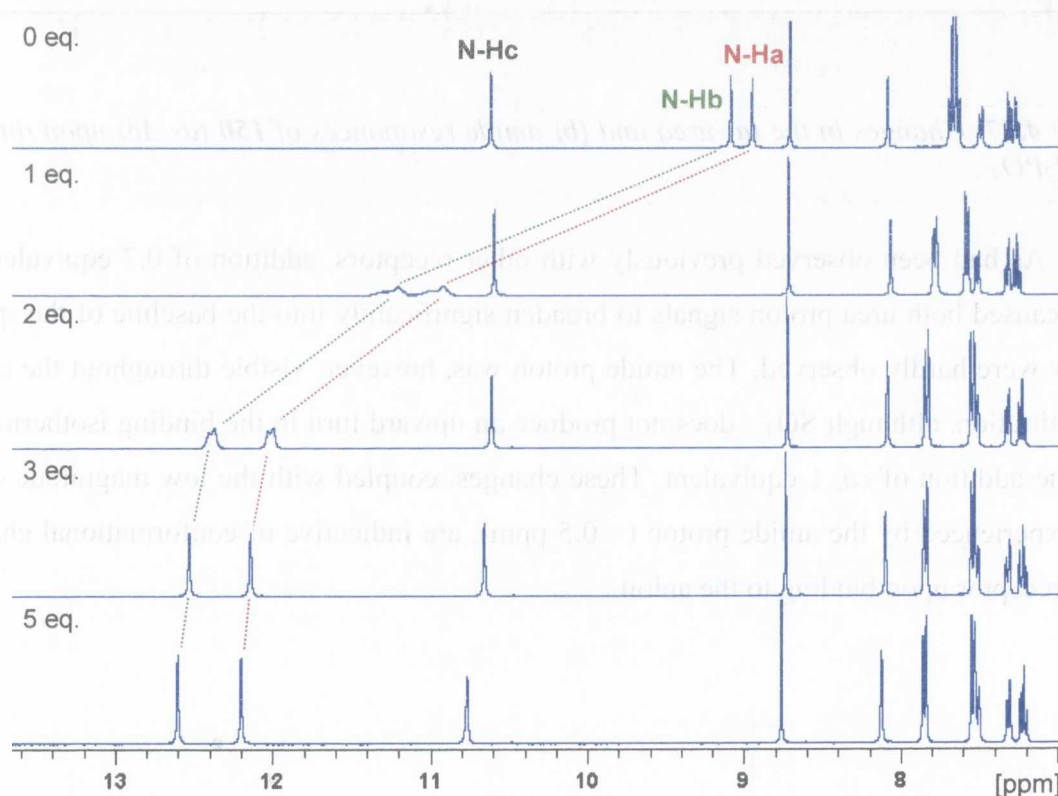


Figure 4.16: Stack plot of ^1H NMR spectra (400 MHz, $\text{DMSO}-d_6$) of **150** (7×10^{-3} M) upon addition of 1, 2, 3 and 5 equivalents of AcO^- . *N-Ha* and *N-Hb* are the urea protons, while *N-Hc* is the amide proton.

The chemical shifts observed for the urea protons of **150** upon titration with H_2PO_4^- anion is shown in Figure 4.17. Addition of 0.5 equivalents of anion caused both the urea protons to broaden significantly, however, the change in chemical shift could still be monitored. The most significant changes occurred up to the addition of *ca.* 1 equivalent of H_2PO_4^- , however a more considerable downfield shift of the N-Hb occurred than that of the

N-Ha. This suggests that **150** initially forms 1:1 complexes at lower concentrations of H_2PO_4^- while at higher concentrations of anion more complex equilibria may exist. The shift experienced by the amide proton underwent the majority of changes by *ca.* 1 equivalent.

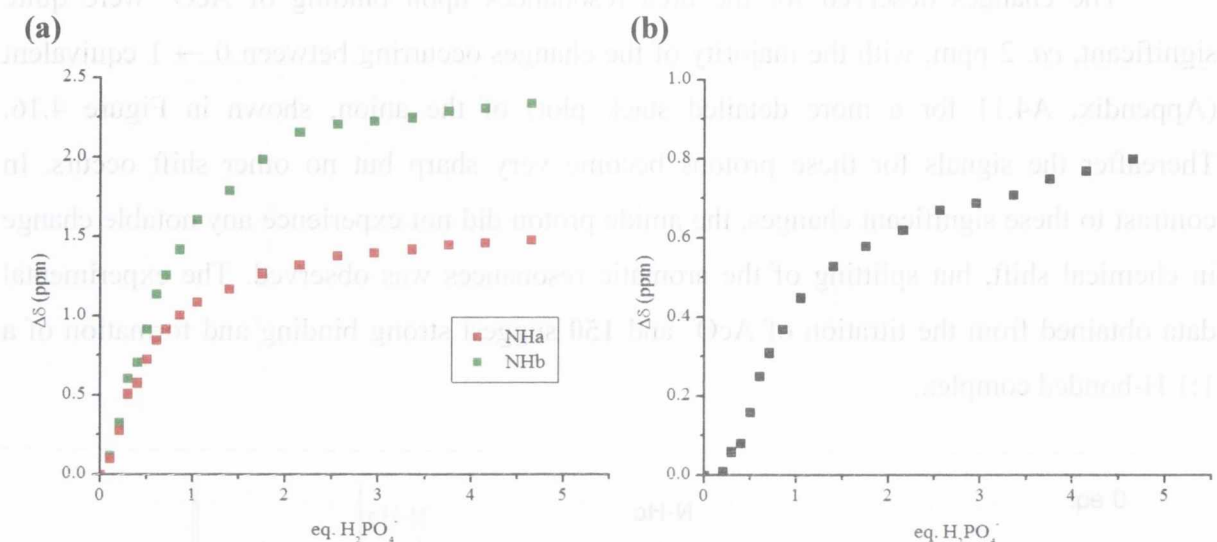


Figure 4.17: Changes in the (a) urea and (b) amide resonances of **150** (as $\Delta\delta$) upon titration with H_2PO_4^- .

As had been observed previously with other receptors, addition of 0.7 equivalents of SO_4^{2-} caused both urea proton signals to broaden significantly into the baseline of the spectra so they were hardly observed. The amide proton was, however, visible throughout the course of the titration, although SO_4^{2-} does not produce an upward turn in the binding isotherm until after the addition of *ca.* 1 equivalent. These changes, coupled with the low magnitude of the shift experienced by the amide proton (< 0.5 ppm), are indicative of conformational changes in the receptor upon binding to the anion.

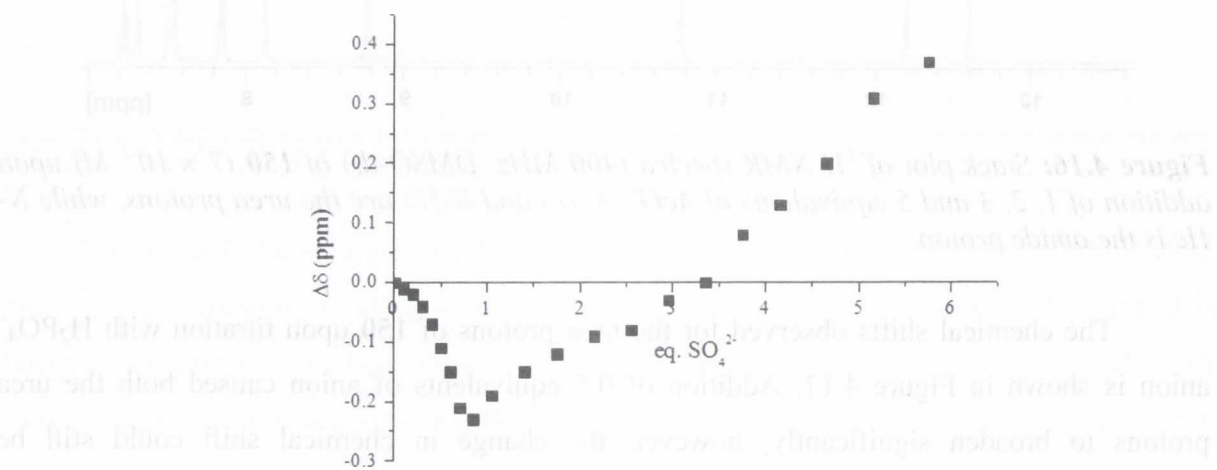


Figure 4.18: Changes in the amide resonance of **150** (as $\Delta\delta$) upon titration with SO_4^{2-} .

There were some considerable changes in the chemical shift of the urea protons upon addition of Cl^- , up to the addition of *ca.* 1 equivalent, suggesting the formation of a stable 1:1 complex, Figure 4.19. The amide proton also shifted up to the addition of *ca.* 1 equivalent, but thereafter no further shifts were observed. It can also be seen that the aromatic region experienced some changes during the course of the titration with the signals splitting and becoming slightly more resolved upon addition of the anion.

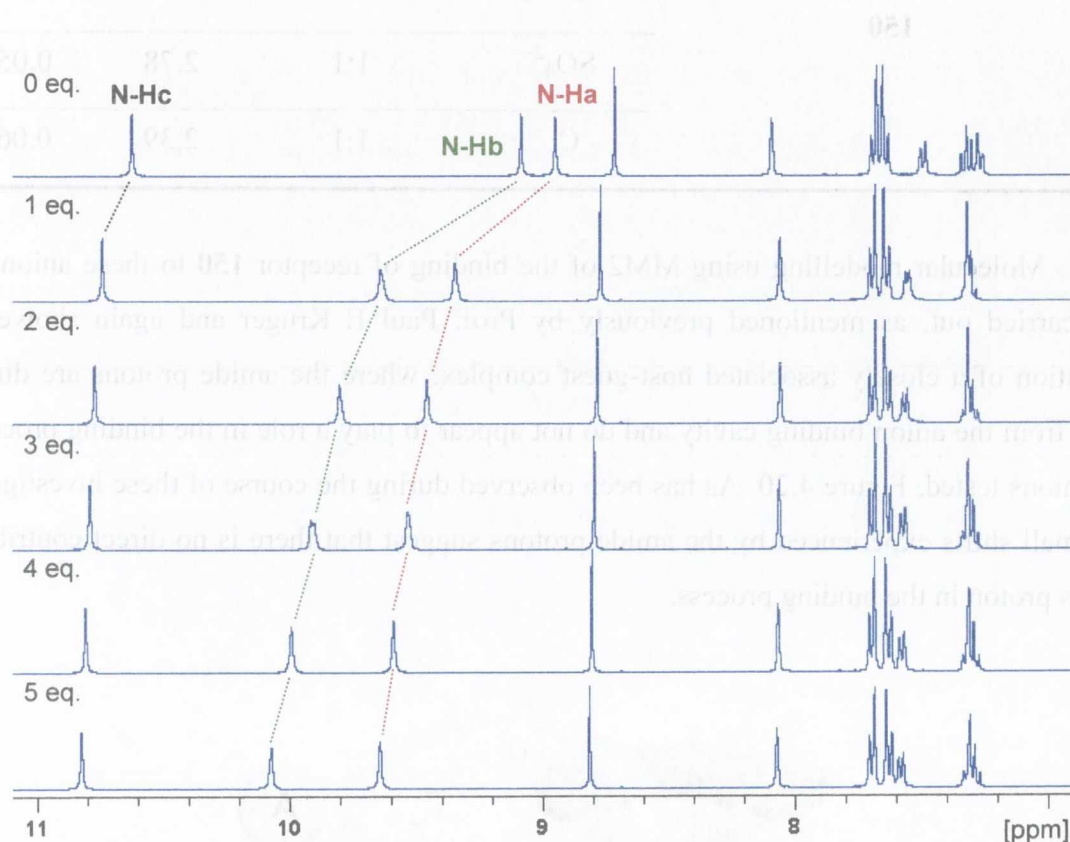


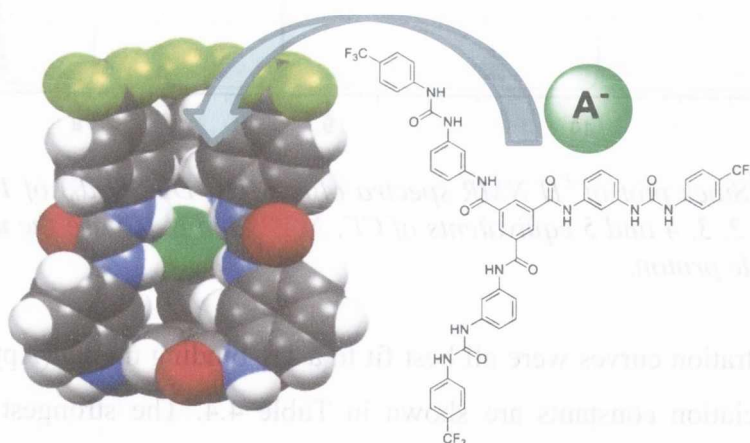
Figure 4.19: Stack plot of ^1H NMR spectra (400 MHz, DMSO-d_6) of **150** (7×10^{-3} M) upon addition of 1, 2, 3, 4 and 5 equivalents of Cl^- . *N-Ha* and *N-Hb* are the urea protons, while *N-Hc* is the amide proton.

The titration curves were all best fit to a 1:1 binding model (Appendix, Figure A4.12) and the association constants are shown in Table 4.4. The strongest interaction was seen between **150** and H_2PO_4^- while the value for Cl^- was almost an order of magnitude lower. It appears that the interaction of receptor **150** with this anion is, energetically, the least favourable and can perhaps be attributed to the large anionic radius (1.81 Å) of the spherical Cl^- ion. The constants obtained for AcO^- and SO_4^{2-} were very similar, *i.e.* $\log K = 2.81 \pm 0.07$ and $\log K = 2.78 \pm 0.05$, respectively. This could be attributed to **150** providing a preferential binding environment for tetrahedral oxyanions.

Table 4.4: Binding constants determined for **150** from ^1H NMR titrations in $\text{DMSO}-d_6$.

Receptor (L)	Anion (G)	Binding Mode $G_n:L_m$	$\log K_{n:m}$	Std. Deviation ($\pm$)
150	AcO^-	1:1	2.81	0.07
	H_2PO_4^-	1:1	3.1	0.1
	SO_4^{2-}	1:1	2.78	0.05
	Cl^-	1:1	2.39	0.06

Molecular modelling using MM2 of the binding of receptor **150** to these anions was also carried out, as mentioned previously by Prof. Paul E Kruger and again showed the formation of a closely associated host-guest complex, where the amide protons are directed away from the anion binding cavity and do not appear to play a role in the binding process of the anions tested, Figure 4.20. As has been observed during the course of these investigations the small shifts experienced by the amide protons suggest that there is no direct contribution of this proton in the binding process.

**Figure 4.20:** MM2 modelling of receptor **150** with anions.

The next receptor to be evaluated was **151**, possessing a short alkyl chain linked to the phenyl ring *via* an oxygen atom and is structurally comparable to receptor **148**.

A considerable downfield shift, *ca.* 3 ppm, of the urea protons of **151** was observed when this receptor was titrated with AcO^- , levelling off after the addition of *ca.* 1 equivalent with no shift in signal position being observed thereafter, Figure 4.21 (a). Moreover, the amide proton also shifted slightly downfield, *ca.* 0.3 ppm, but only after the addition of *ca.* 1

equivalent of AcO^- , Figure 4.21 (b). These results suggest that the changes in the chemical shifts of the amide proton were due to the binding event between the urea moieties of the receptor and the anion.

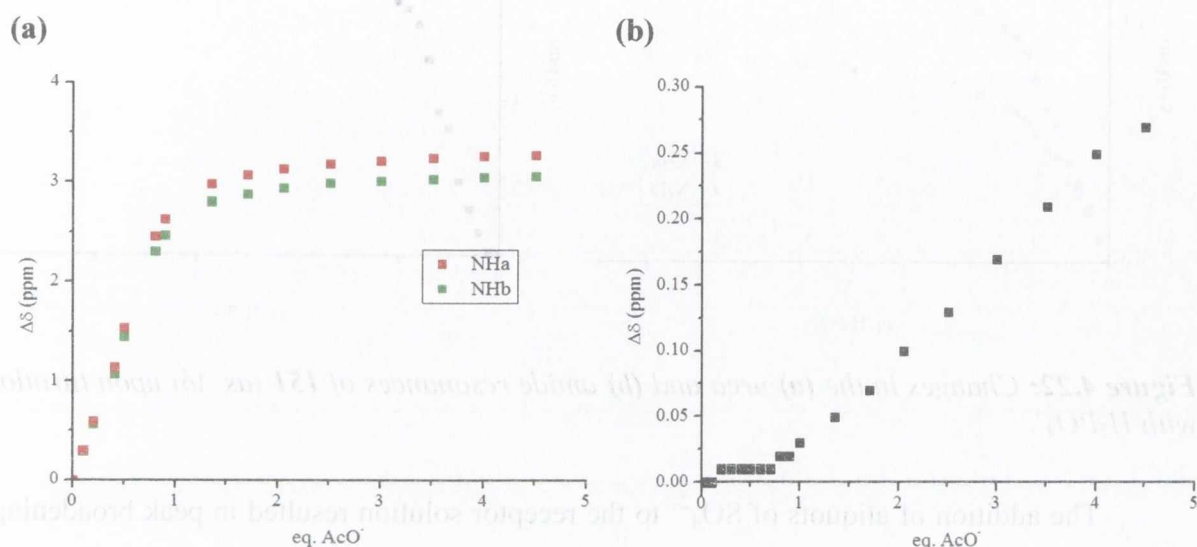


Figure 4.21: Changes in the (a) urea and (b) amide resonances of **151** (as $\Delta\delta$) upon titration with AcO^- .

The ^1H NMR spectrum of **151** also showed notable shifts of the urea resonances with increasing addition of H_2PO_4^- , Figure 4.22 (a), and although the protons did not experience a shift of the same magnitude as that seen for AcO^- (*ca.* 2 vs. 3 ppm for N-Ha), the net effect upon titration of receptor **151** with H_2PO_4^- points to the formation of a stable 1:1 species. The small shift (< 0.8 ppm) experienced by the amide proton was most likely induced by conformational effects. Additionally, the aromatic protons all experienced a minor shift and their multiplicities became more resolved throughout the titration.

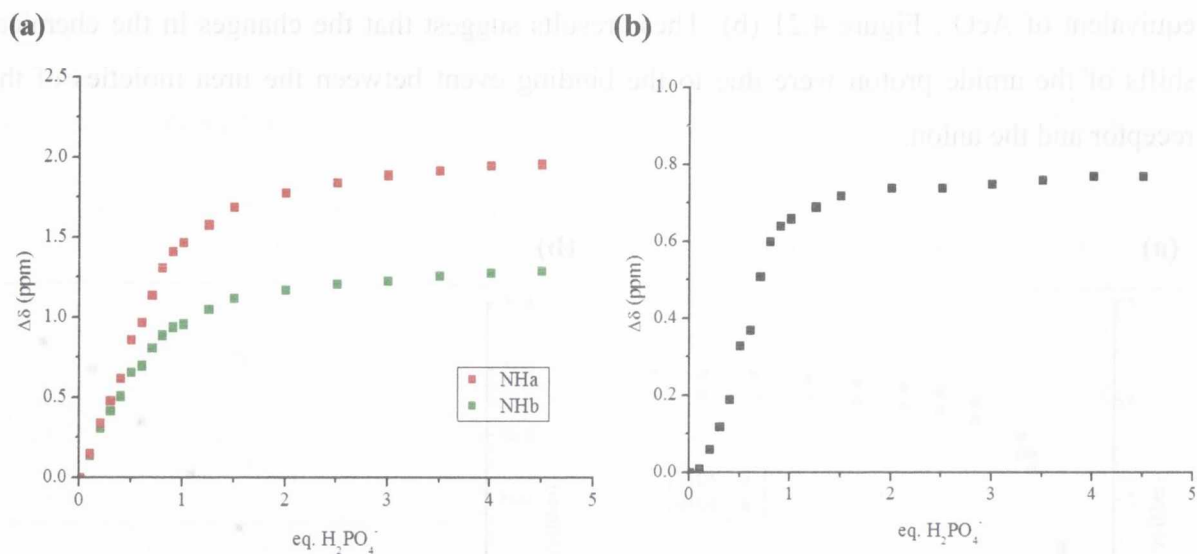


Figure 4.22: Changes in the (a) urea and (b) amide resonances of **151** (as $\Delta\delta$) upon titration with H_2PO_4^- .

The addition of aliquots of SO_4^{2-} to the receptor solution resulted in peak broadening, making accurate determination of the binding interaction difficult. These protons also did not reach a full plateau even at higher concentrations of the anion, while the amide proton experienced a very minor upfield shift of *ca.* 0.15 ppm, before gradually shifting upfield to almost its original position, Figure 4.23 (b). The aromatic protons were also significantly affected upon addition of the anion, converging to become one broad signal.

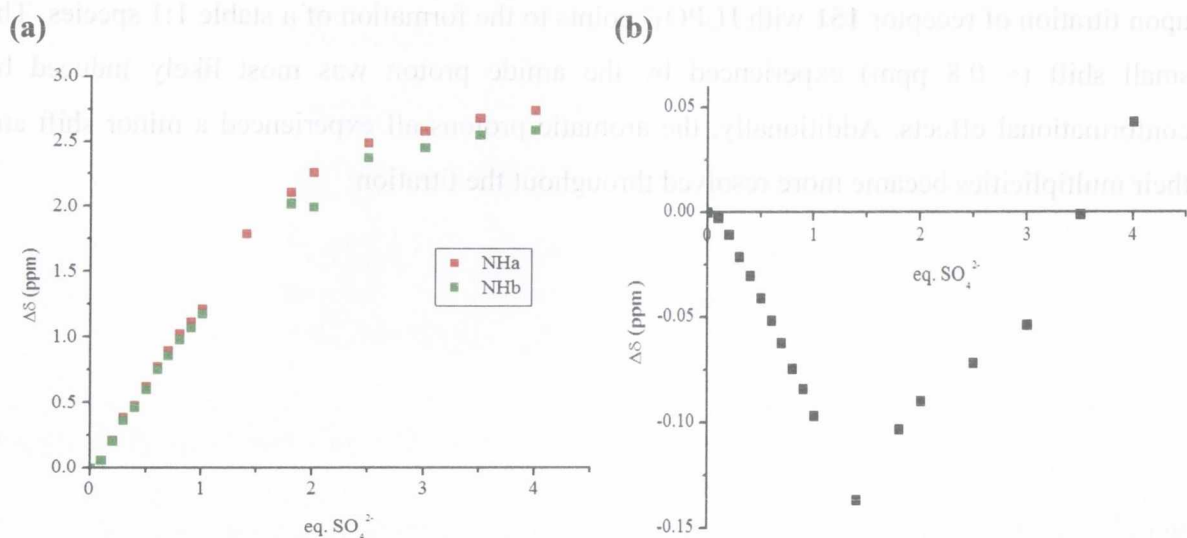


Figure 4.23: Changes in the (a) urea and (b) amide resonances of **151** (as $\Delta\delta$) upon titration with SO_4^{2-} .

The addition of Cl^- did not show any significant change in chemical shift of the urea protons, only *ca.* 0.6 ppm, indicating a very weak interaction. The stack plot of the titration is presented in Figure 4.24. The amide proton did not experience any kind of shift nor did the aromatic protons show any shift or resolution of multiplicities.

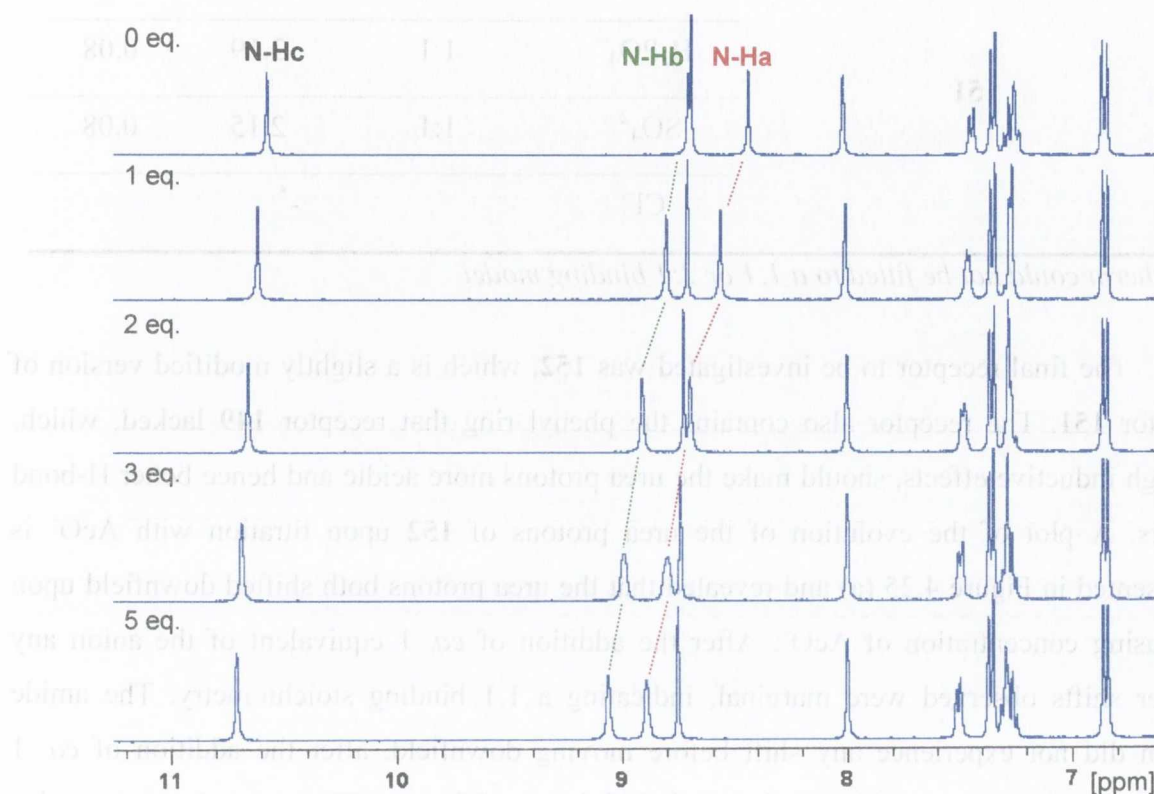


Figure 4.24: Stack plot of ^1H NMR spectra (400 MHz, DMSO-d_6) of **151** (7×10^{-3} M) upon addition of 1, 2, 3, and 5 equivalents of Cl^- . *N-Ha* and *N-Hb* are the urea protons, while *N-Hc* is the amide proton.

Analysis of the binding isotherms all gave excellent fits for a 1:1 binding stoichiometry (Appendix, Figure A4.13), except in the case of Cl^- as the experimental data obtained from the titration suggests very weak binding and as a result the data did not fit to a suitable binding model. The results are summarised in Table 4.5. The smaller changes to the amide protons observed in the titrations suggest no binding association, presumably adopting an orientation in which the proton points outwards rather than into the binding cavity. For this receptor AcO^- gave the largest binding constant, followed by H_2PO_4^- with a slightly lower value.

Table 4.5: Binding constants determined for **151** from ^1H NMR titrations in $\text{DMSO}-d_6$.

Receptor (L)	Anion (G)	Binding Mode $G_n:L_m$	$\log K_{n:m}$	Std. Deviation ($\pm$)
151	AcO^-	1:1	3.7	0.1
	H_2PO_4^-	1:1	3.19	0.08
	SO_4^{2-}	1:1	2.15	0.08
	Cl^-		-*	

* Isotherm could not be fitted to a 1:1 or 2:1 binding model.

The final receptor to be investigated was **152**, which is a slightly modified version of receptor **151**. The receptor also contains the phenyl ring that receptor **149** lacked, which, through inductive effects, should make the urea protons more acidic and hence better H-bond donors. A plot of the evolution of the urea protons of **152** upon titration with AcO^- is represented in Figure 4.25 (a) and revealed that the urea protons both shifted downfield upon increasing concentration of AcO^- . After the addition of *ca.* 1 equivalent of the anion any further shifts observed were marginal, indicating a 1:1 binding stoichiometry. The amide proton did not experience any shift before moving downfield, after the addition of *ca.* 1 equivalent of AcO^- , to a higher chemical shift by *ca.* 0.2 ppm. The aromatic protons also became more resolved during the course of the titration.

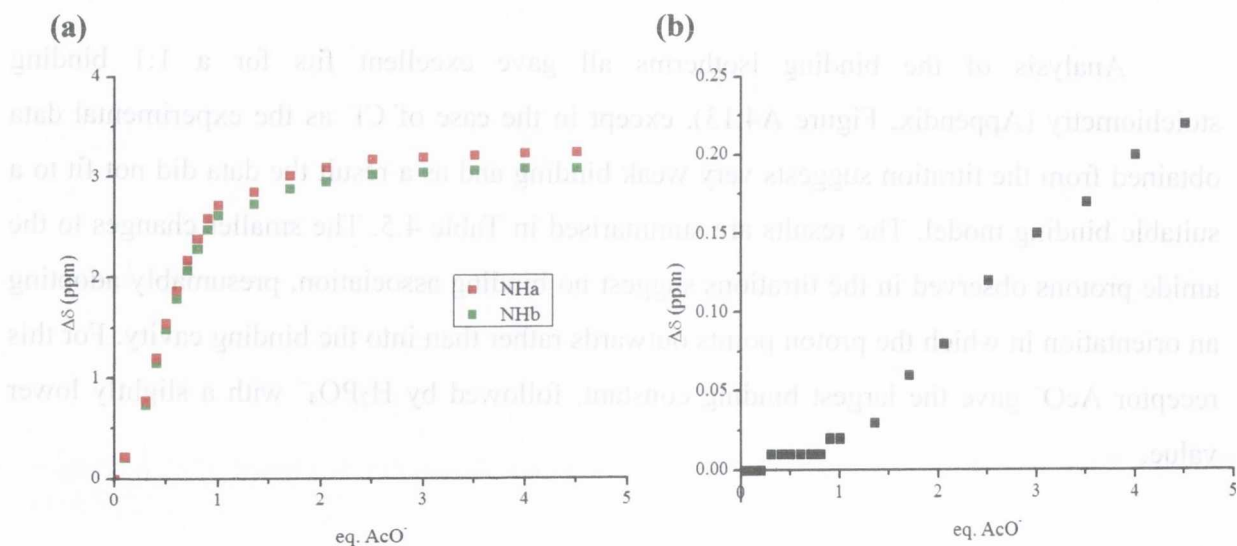


Figure 4.25: Changes in the (a) urea and (b) amide resonances of **152** (as $\Delta\delta$) upon titration with AcO^- .

The titration with H_2PO_4^- displayed similar behaviour to that of AcO^- , however in general, all the signals in the ^1H NMR spectrum broadened at the initial stages of the titration; but sharpened as the titration progressed, a consequence of the displacement of the equilibrium towards the more stable H-bonded complex. The N-Hb proton was visible throughout the titration, while the N-Ha became too broadly shifted to be accurately followed at all stages and so it was not included in the plot in Figure 4.26 (a). In contrast to the other receptors, the amide proton of **152** gradually shifted downfield by *ca.* 0.7 ppm until the addition of *ca.* 1 equivalent of H_2PO_4^- and then reached a full plateau. This behaviour indicates, in this case, that the amide proton is playing a role in the binding process and cooperatively binding the anion in association with the urea moiety.

Conversely, the titration profile of receptor **152** with SO_4^{2-} did not show such a plateau at *ca.* 1 equivalent, but instead gradually increased further. The amide proton experienced a very minor upfield shift and then, at *ca.* 1.5 equivalents, returned downfield although the changes were only in the region of *ca.* 0.15 ppm.

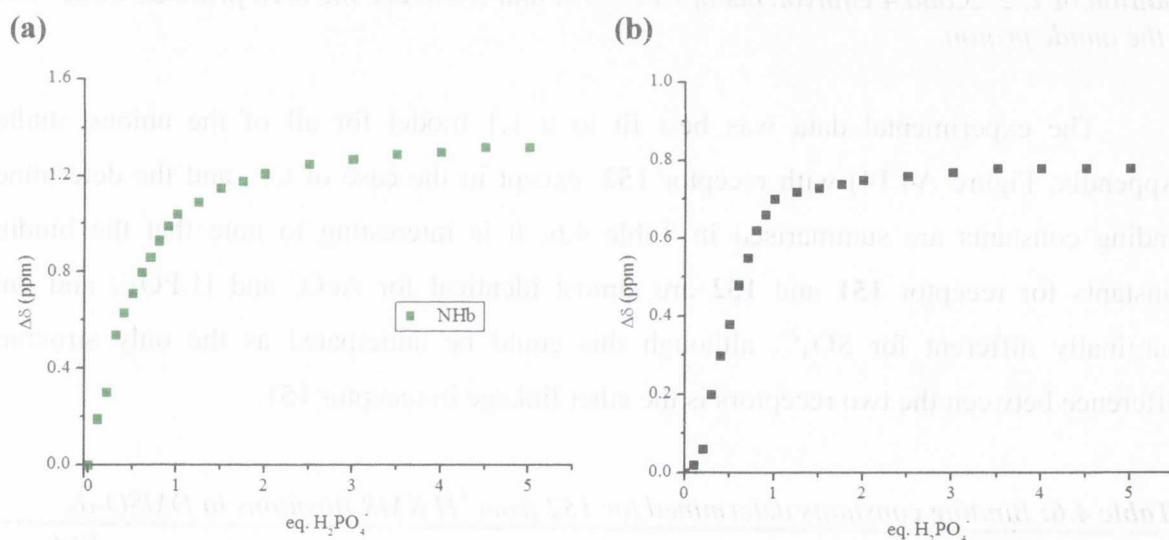


Figure 4.26: Changes in the (a) urea and (b) amide resonances of **152** (as $\Delta\delta$) upon titration with H_2PO_4^- .

The final anion to be studied was Cl^- and, as seen with most of these receptors, did not result in significant changes upon increasing addition of the anion; with the urea protons being shifted by *ca.* 0.5 ppm and did not have any impact on the amide proton, Figure 4.27.

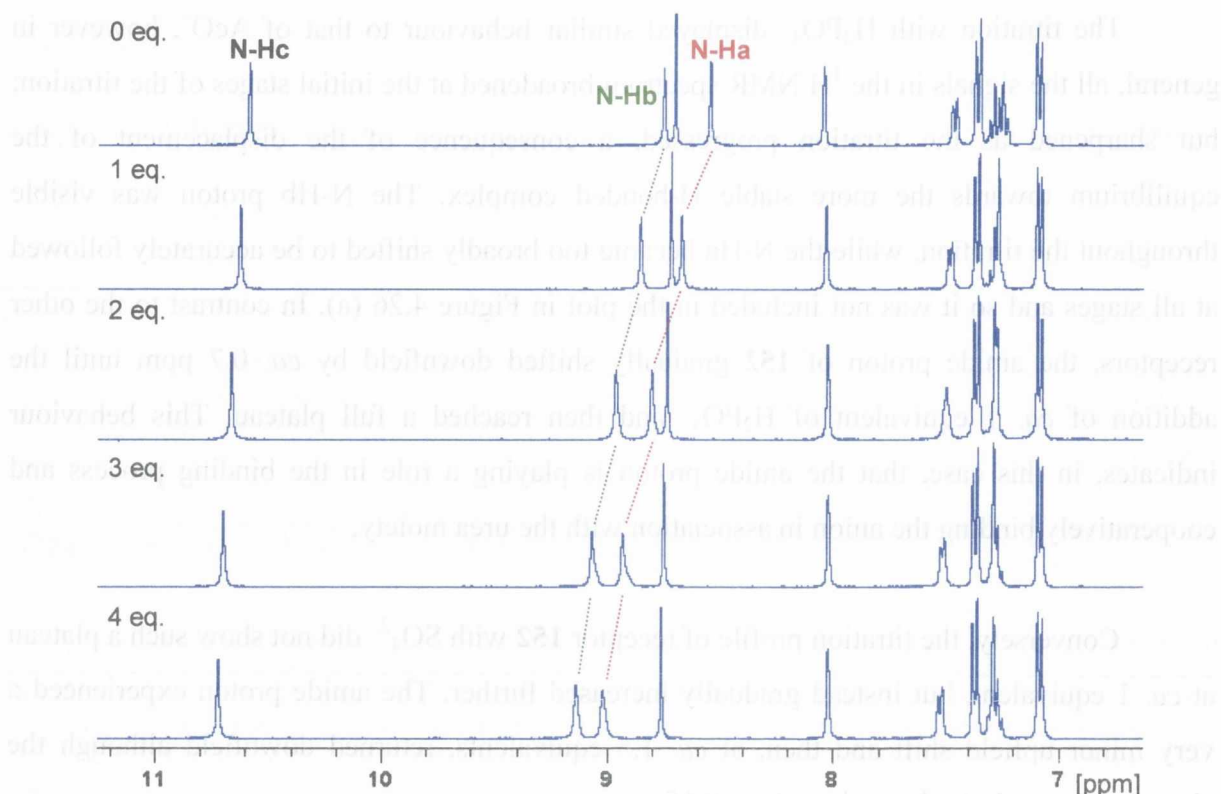


Figure 4.27: Stack plot of ^1H NMR spectra (400 MHz, DMSO-d_6) of **152** (7×10^{-3} M) upon addition of 1, 2, 3 and 4 equivalents of Cl^- . *N-Ha* and *N-Hb* are the urea protons, while *N-Hc* is the amide proton.

The experimental data was best fit to a 1:1 model for all of the anions studied (Appendix, Figure A4.14) with receptor **152**, except in the case of Cl^- , and the determined binding constants are summarised in Table 4.6. It is interesting to note that the binding constants for receptor **151** and **152** are almost identical for AcO^- and H_2PO_4^- , and only marginally different for SO_4^{2-} , although this could be anticipated as the only structural difference between the two receptors is the ether linkage in receptor **151**.

Table 4.6: Binding constants determined for **152** from ^1H NMR titrations in DMSO-d_6 .

Receptor (L)	Anion (G)	Binding Mode $G_n:L_m$	log $K_{n:m}$	Std. Deviation ($\pm$)
152	AcO^-	1:1	3.7	0.1
	H_2PO_4^-	1:1	3.2	0.1
	SO_4^{2-}	1:1	2.06	0.09
	Cl^-		-*	

* Isotherm could not be fitted to a 1:1 or 2:1 binding model.

4.2.3 Comparison of *Para* (147-149) and *Meta* Receptors (150-152)

The changes observed for the urea N-H resonances of **147** and **150** upon binding to H_2PO_4^- and SO_4^{2-} clearly indicates that both structures bind these anions in a 1:1 stoichiometry, where the N-H protons were shifted by *ca.* 1.5-2.5 ppm upon H-bonding to the anions. Similar behaviour was observed for Cl^- and AcO^- for both receptors, where the largest changes in the ^1H NMR were observed upon the addition of one equivalent of these anions. As we had observed in our previous work,^{145,146} the amide proton (*meta* to the urea) of **150** also experienced a significant downfield shift upon titration with H_2PO_4^- and Cl^- , being shifted by *ca.* 0.6 ppm within the addition of one equivalent of these anions. In contrast, these chemical shifts were less significant upon titration with SO_4^{2-} and AcO^- , being shifted by *ca.* 0.1 ppm. Moreover, for the structural *para* isomer **147**, only Cl^- gave rise to such shifts, *ca.* 0.15 ppm, after the addition of one equivalent.

It is also clear that the recognition of H_2PO_4^- did not result in any further measurable shifts in the urea N-H resonance after the formation of the 1:1 host:guest complex, as determined by the titration profiles. Confirmation of this 1:1 stoichiometry between **147** and H_2PO_4^- was also obtained using MALDI-TOF mass spectrometry. On all occasions the binding affinity of **147** and **150** to the aforementioned anions was best fit to a 1:1 stoichiometry, displaying high affinity for these receptors as evaluated by the binding constants of anions such as H_2PO_4^- . Excluding Cl^- , **147** gave rise to higher binding affinity for these ions than **150**, which in the case of H_2PO_4^- resulted in a $\log K_{1:1} = 4.2 \pm 0.1$, for **147**, while an order of magnitude lower binding constant of $\log K_{1:1} = 3.1 \pm 0.1$, was observed for **150**. The importance of the substitution pattern of the diaryl urea core (*e.g.* *meta* vs. *para*) of these receptors was also clearly highlighted. As the highest binding constant values were found to be for H_2PO_4^- out of all the anions tested for both receptors it is clear that **147** and **150** have high affinity for tetrahedral anions. The interaction between **147** and SO_4^{2-} was also relatively strong with $\log K_{1:1} = 3.7 \pm 0.2$, again being an order of magnitude larger than that seen for **150**.

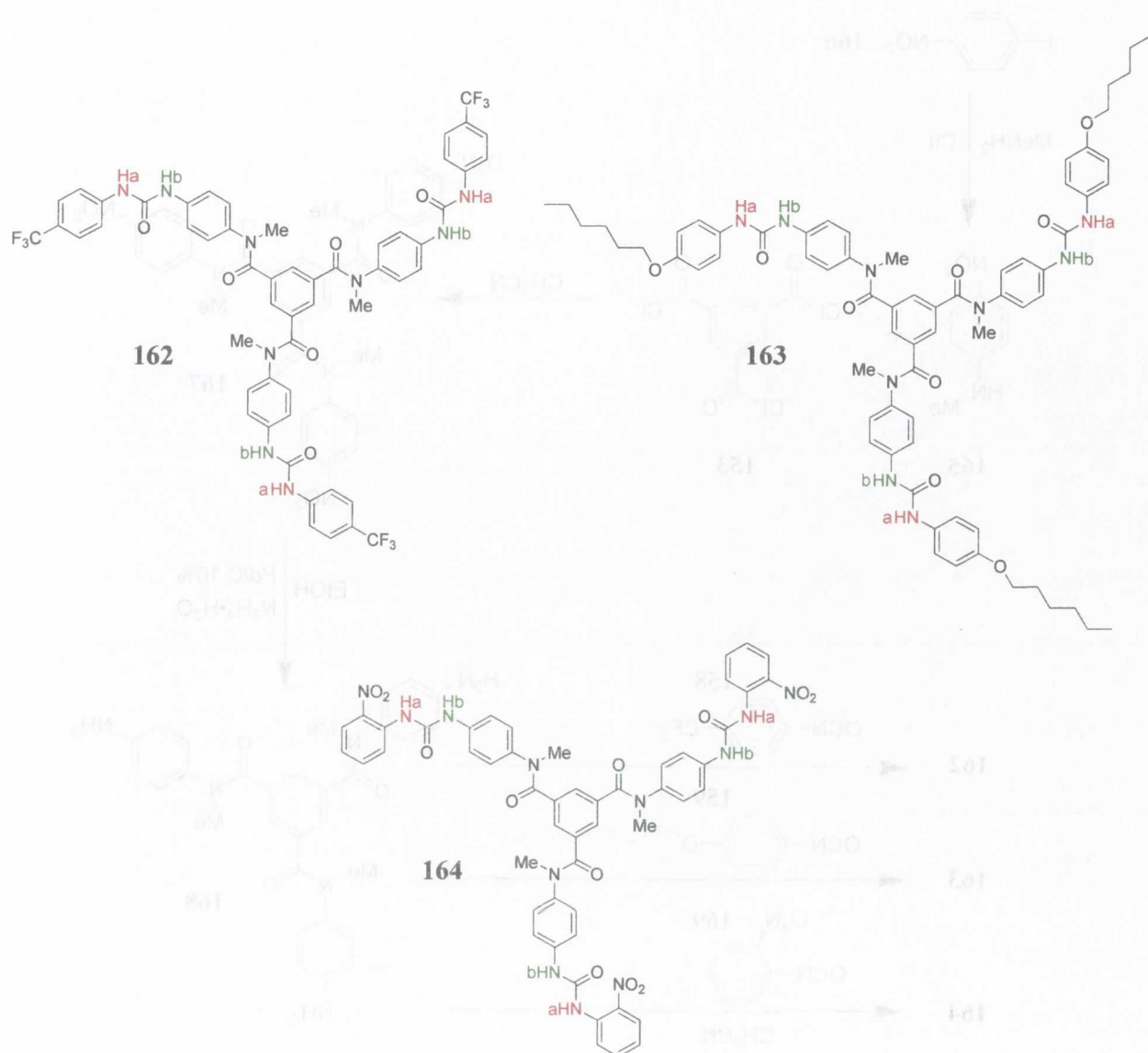
Next the electron donating receptors *m*- and *p*-urea-phenylalkoxy chain derivatives, **148** and **151**, were investigated. The interaction with AcO^- and SO_4^{2-} displayed very similar results with the urea protons experiencing a large downfield shift of *ca.* 2.5-3 ppm before reaching a plateau. In contrast, the amide proton of both receptors experienced a significantly smaller shift to that seen for **147** and **150**. The formation of the 1:1 species for receptor **148** with AcO^- was also evident in the MALDI-ToF mass spectrum. Similar shifts were seen for H_2PO_4^- while the smallest spectral changes were observed upon titration with Cl^- . The results

from these NMR titrations were also best fit to 1:1 binding, from which $\log K_{1:1}$ was determined. Here, receptor **148** showed a slightly higher affinity for these anions than **151**; albeit the difference in $\log K_{1:1}$ was to a lesser extent than that seen for **147** and **150**. Interestingly, the binding of AcO^- was significantly higher for both of these receptors compared to **147** and **150**. In both cases, the smallest $\log K_{1:1}$ was observed for SO_4^{2-} .

The *m*-urea-phenyl-alkyl chain and the *p*-urea-alkyl chain based receptors **149** and **152** were also analysed in an analogous manner. Here, **152**, a slightly modified version of **151**, was determined to have higher affinity for the anions than **149**, which is to be expected as **149** lacks the second aryl group which, through inductive effects makes the protons in **152** more acidic and hence, better H-bond donors. In fact, comparison of **151** and **152** showed that both display similar affinity for these anions. Analysis of the binding of AcO^- and SO_4^{2-} to **149** did not result in a full plateau being reached after the addition of excess anions, making accurate determination of $\log K_{1:1}$ difficult. From the analysis of **152**, slightly higher affinity was seen for AcO^- over H_2PO_4^- , the latter being of similar magnitude, to that seen for **150** and **151**. In contrast the binding of SO_4^{2-} was significantly weaker for **152** than seen for **150** but of similar magnitude to that seen for **151**. Receptor **149** also showed a significant interaction with H_2PO_4^- and Cl^- , but in contrast to that seen for the other receptors, it was the lowest in the series.

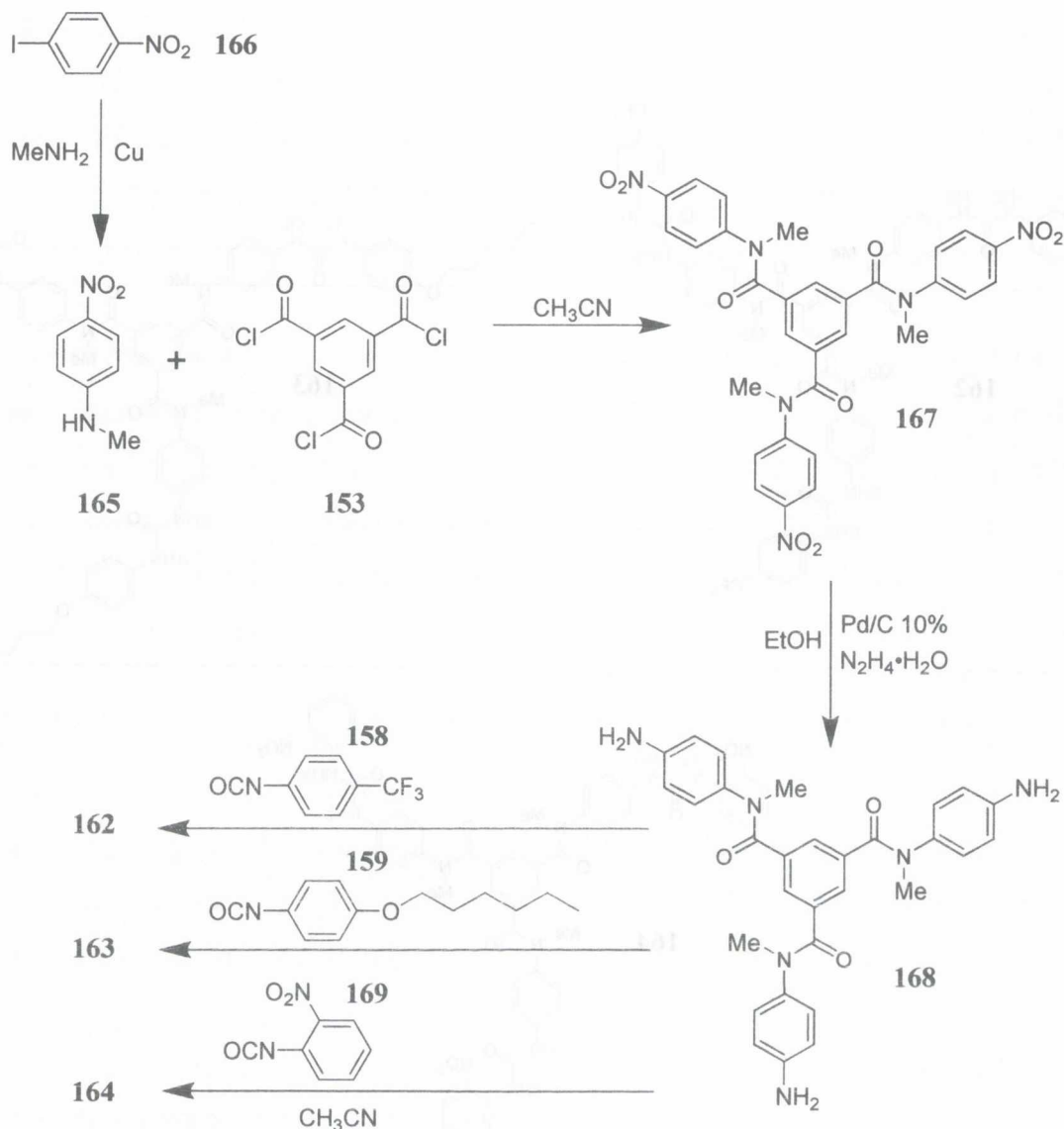
In summary six novel tripodal receptors were developed, **147-152**, possessing highly organised urea binding sites, and their binding properties determined with various anions using ^1H NMR titrations. These showed high binding affinities for H_2PO_4^- and AcO^- . Moreover, **147** also showed high affinity for SO_4^{2-} . The results clearly show that our simple design principle facilitates the development of novel anion receptors possessing tuneable cooperative binding.

To further develop these anion binding motives, a second generation of tripodal receptors, **162-164**, were synthesised and their anion binding properties evaluated. As the amide proton of **147-152** did not play an active role in the binding process, these receptors contain tertiary amides. This work was done in collaboration with Dr. Komala Pandurangan, who carried out the synthesis and obtained all crystals that are discussed in the following sections.



4.3 Synthesis of Second Generation Tripodal Receptors 162-164

The second generation receptors **162-164** were synthesised in a four step synthesis by Dr. Komala Pandurangan from 1,3,5-benzenetricarbonyl trichloride, **153**, and *N*-methyl 4-nitroaniline, **165** (Scheme 4.4). Formation of compound **165** was achieved by heating 1-iodo-4-nitrobenzene, **166**, in excess aqueous methyl amine with copper catalyst at reflux in a pressure tube overnight. Extraction into EtOAc, followed by column chromatography eluting CHCl_3 and EtOAc (85:15%) gave **165** in 60% yield. Reaction of **153** and **165** in CH_3CN at reflux overnight and precipitation from acetone gave tri-nitro compound **167** in 40% yield. Reduction to the corresponding tri-amine **168** was achieved by microwave irradiation of **167** in EtOH at 80°C with hydrazine mono-hydrate and 10% Pd/C for 40 minutes. Filtration through a pad of celite, followed by washing with a hot EtOH/ CH_3CN mixture gave the desired product in 30-60% yield.



Scheme 4.4: Synthesis of second generation receptors **162-164**.

The final stage in the synthesis was reaction of **168** with the corresponding isocyanate (**158**, **159** or **169**) at 95°C in CH₃CN for 48 hours. Multiple recrystallisations with hot CH₃CN/MeOH gave receptors **162** and **164** in 70% and 60% yields respectively, while receptor **163** required column chromatography eluting CHCl₃:MeOH (90:10) to give the desired product in 60% yield. The receptors were characterised by conventional methods such as ¹H NMR (Appendix, Figure A4.15-4.16), ¹³C NMR, IR spectroscopy, mass spectrometry and elemental analysis. The ¹H NMR spectrum (400 MHz, DMSO-*d*₆) obtained for receptor **162** is shown in Figure 4.28 where it can be seen that the urea protons are the most downfield with the N-Ha, appended to the CF₃ phenyl ring, appearing at 9.10 ppm. The broad singlets at 7.01 ppm and 6.79 ppm correspond to the central phenyl core and the aryl protons adjacent to the tertiary amide group, respectively. The methyl protons resonated at 3.24 ppm. The

presence of the $[M - H]^-$ species at $m/z = 1082.302$ in the MALDI-ToF spectrum also indicated successful formation of **162**.

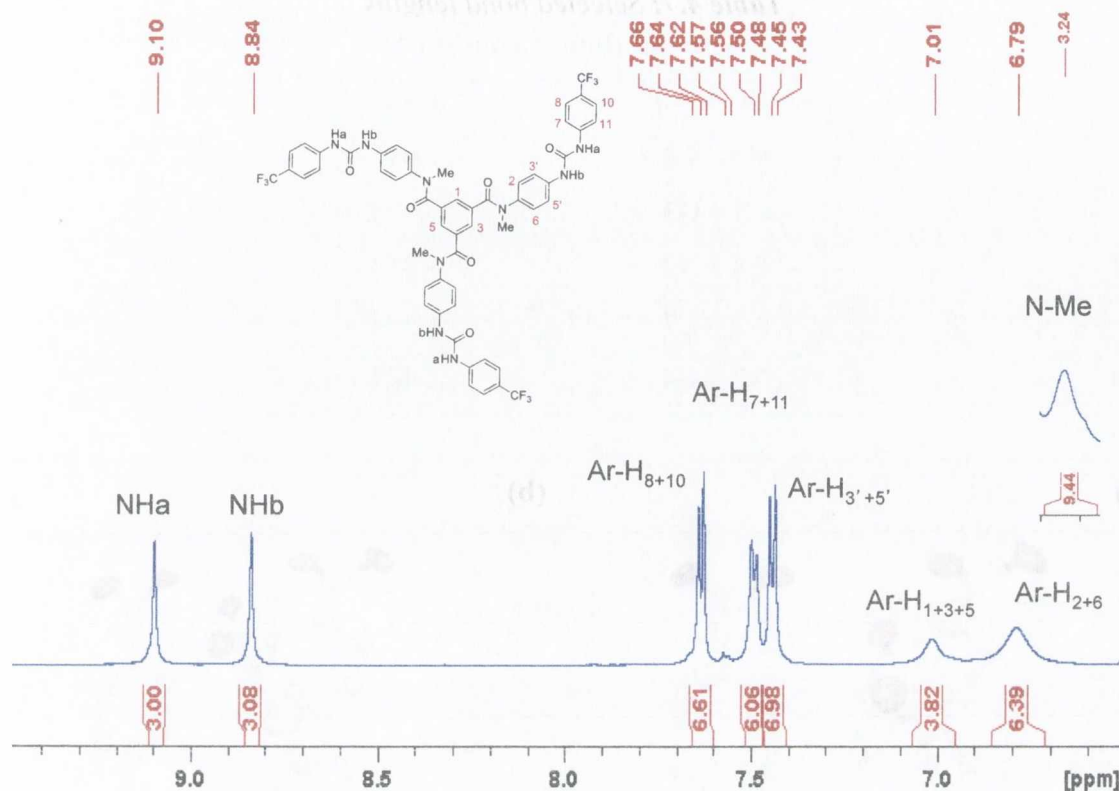


Figure 4.28: ^1H NMR spectrum (400 MHz, $\text{DMSO}-d_6$) of receptor **162**.

Crystals of tri-nitro building block **167** suitable for X-ray crystallographic analysis were grown *via* liquid/vapour crystallisation in DMSO and methanol. The resulting X-ray crystal structure was solved by Dr. Jonathan Kitchen, School of Chemistry, TCD and details of the analysis will be discussed in the following section.

4.3.1 Crystal Structure of Precursor **167**

The crystal structure of tri-nitro compound **167** is shown in Figure 4.29, with selected bond lengths detailed in Table 4.7. As this compound is the framework from which the anion receptor will be constructed, it was important to ensure this platform would give the receptor the desired shape; with the arms facing upwards creating a cavity allowing an ideal binding pocket for anions. Indeed, it can be seen that the desired conformation required for a tripodal receptor is present and the molecule has C_{3v} symmetry. Both the carbonyl oxygens and the methyl group of the tertiary amide point outside the cavity of the tripodal structure, as predicted in the design of these structures. It can also be seen from Figure 4.29 (b) that there is

H-bonding present between the amido-oxygens of the compound with methanol solvent molecules.

Table 4.7: Selected bond lengths

Selected Bond Lengths (Å)	
C9 – C10	1.383
C9 – C8	1.496
C8 – O3	1.228
C8 – N2	1.354
N2 – C7	1.474
N2 – C4	1.427

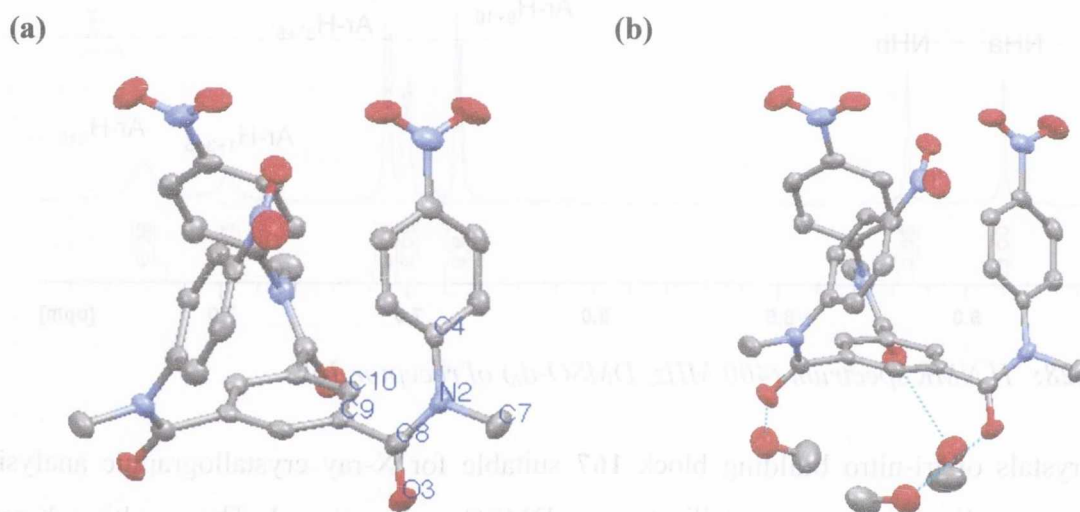
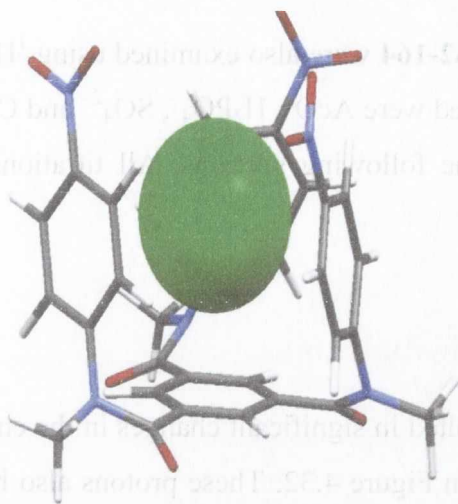


Figure 4.29: (a) The X-ray crystal structure of compound 167. (b) H-bonding interactions between the oxygens of the CH_3 of the tertiary amide with methanol molecules.

Molecular modelling was also carried out by Prof. Paul E Kruger and suggested that Cl^- would be an ideal fit for the cavity of the tripodal structure, Figure 4.30. It appears there are strong π -anion interactions. Recent studies have shown that aromatic C-Hs can form H-bonds with anions when present in a receptor, as determined by crystallography, ^1H NMR and theoretical structures.¹⁹⁶ It has also been demonstrated that C-H hydrogen bonding interactions with benzene can form complexes that are 58-61% as stable as the corresponding H_2O complex.

(a)



(b)

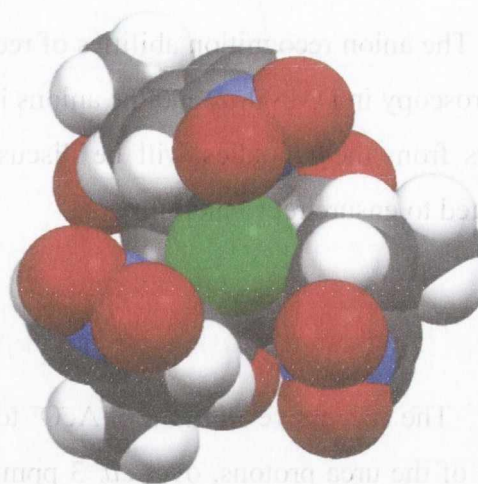


Figure 4.30: Molecular modelling of compound **167** with Cl^- (a) stick format and (b) space fill.

4.3.2 Crystal Structure of Receptor **163**

Crystals with the composition **163**·(DMSO)₂ were obtained from slow evaporation of DMSO-*d*₆ by Dr. Komala Pandurangan and the crystal structure, solved by Dr. Jonathan Kitchen, is shown in Figure 4.31. The asymmetric unit contains one independent molecule and it can be seen that the desired shape of the receptor with upward facing arms is maintained. Such an arrangement gives rise to a pseudo-cone geometry, forming a central cavity in which an ideal anion binding pocket exists. One of the urea moieties is facing inwards towards the cavity while the other two urea “arms” face away from the cavity and interact with two DMSO molecules *via* H-bonding (omitted for clarity), one to each arm.

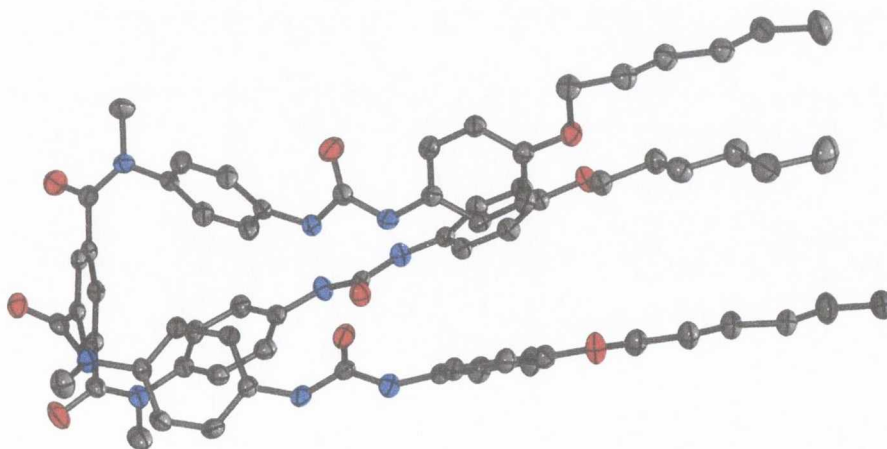


Figure 4.31: The X-ray crystal structure of receptor **163**. (Receptor **163** was H-bonded to two DMSO molecules but have been omitted for clarity).

4.4 Anion Binding Studies of Second Generation Receptors 162-164

The anion recognition abilities of receptors **162-164** were also examined using ^1H NMR spectroscopy in $\text{DMSO}-d_6$ and the anions investigated were AcO^- , H_2PO_4^- , SO_4^{2-} and Cl^- . The results from these studies will be discussed in the following sections. All titrations were repeated to ensure reproducibility.

4.4.1 ^1H NMR Titrations of Receptor 162 with Anions

The successive addition of AcO^- to **162** resulted in significant changes in the chemical shifts of the urea protons, over *ca.* 3 ppm, shown in Figure 4.32. These protons also became quite broadened and towards the end of the titration were difficult to follow. The aromatic protons became more resolved during the initial stages of the titration but during later additions merged together. Interpretation of these results was difficult but could lead to the conclusion that co-existence of multiple complexes, *e.g.* 1:1, 2:1 3:1 guest:host stoichiometries, are present.

Nevertheless, the disappearance of the urea resonances at higher equivalents did not allow a reliable binding isotherm to be obtained and prevented any possibility of calculating a binding constant. The fact that a mixture of species can be detected; along with the apparent strength of the anion binding, makes elucidation of this system difficult. A plot of the evolution of the urea protons upon titration with AcO^- is presented in the Appendix (Appendix, Figure A4. 19).



Figure 4.31: The 2D crystal structure of receptor 162. Receptor 162 was H-bonded to two DMSO molecules but have been omitted for clarity.

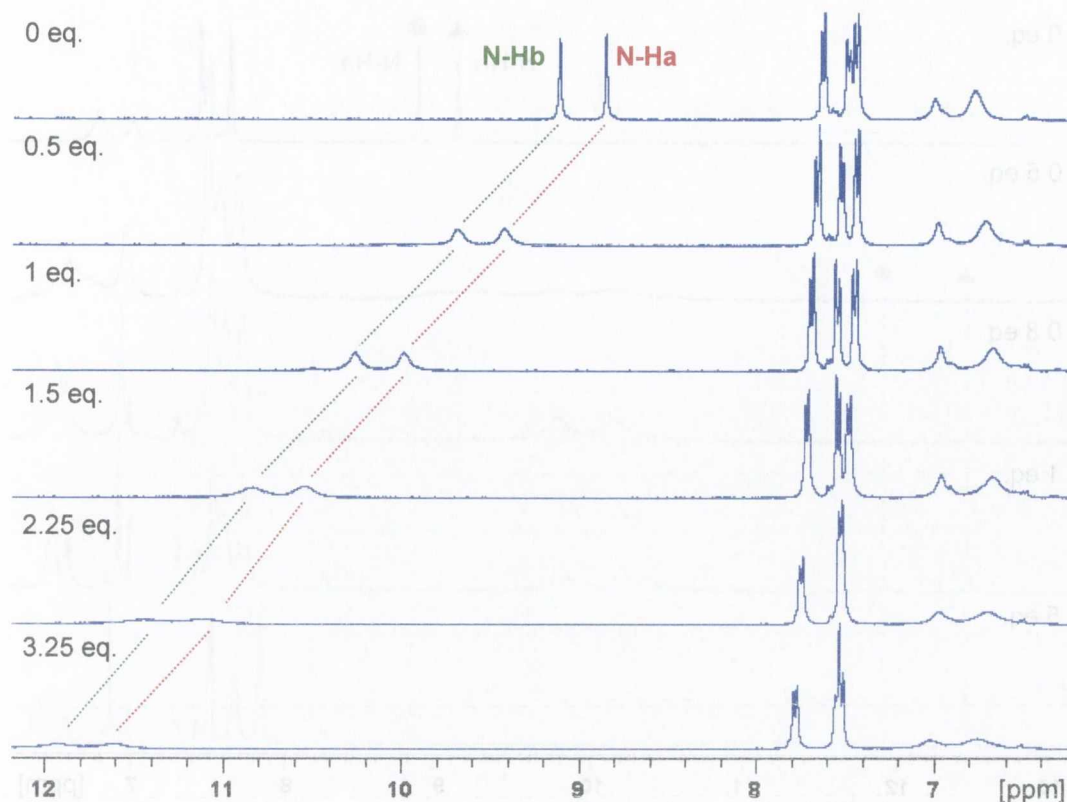


Figure 4.32: Stack plot of ^1H NMR spectra (400 MHz, $\text{DMSO}-d_6$) of **162** (7×10^{-3} M) upon addition of 0.5, 1, 1.5, 2.25 and 3.25 equivalents of AcO^- . *N-Ha* and *N-Hb* are the urea protons.

The titration of **162** with H_2PO_4^- displayed dissimilar behaviour, indicative of slow exchange on the NMR timescale. New signals for each proton environment appeared significantly downfield from the original positions observed for the urea protons upon the addition of anion; attributed to the formation of a new host-guest complex in solution, Figure 4.33. A steady increase in the population of the new signals was observed as the titration progressed, until after one equivalent of anion had been added, the original urea protons could no longer be observed indicating very strong 1:1 binding. As both sets of signals were visible until after the addition of 1 equivalent of the anion it is likely there were multiple species in solution until the more dominant new host:guest complex became fully formed in solution. It is possible the larger size of the H_2PO_4^- anion, compared to AcO^- , causes the involvement of all the available H-bond donor functions in the structure of **162**.¹⁹⁷ Recently Young and Joliffe reported a similar finding with (thio)urea-based tripodal receptors.¹⁹⁸ The aromatic signals also showed broadening and the appearance of new signals.

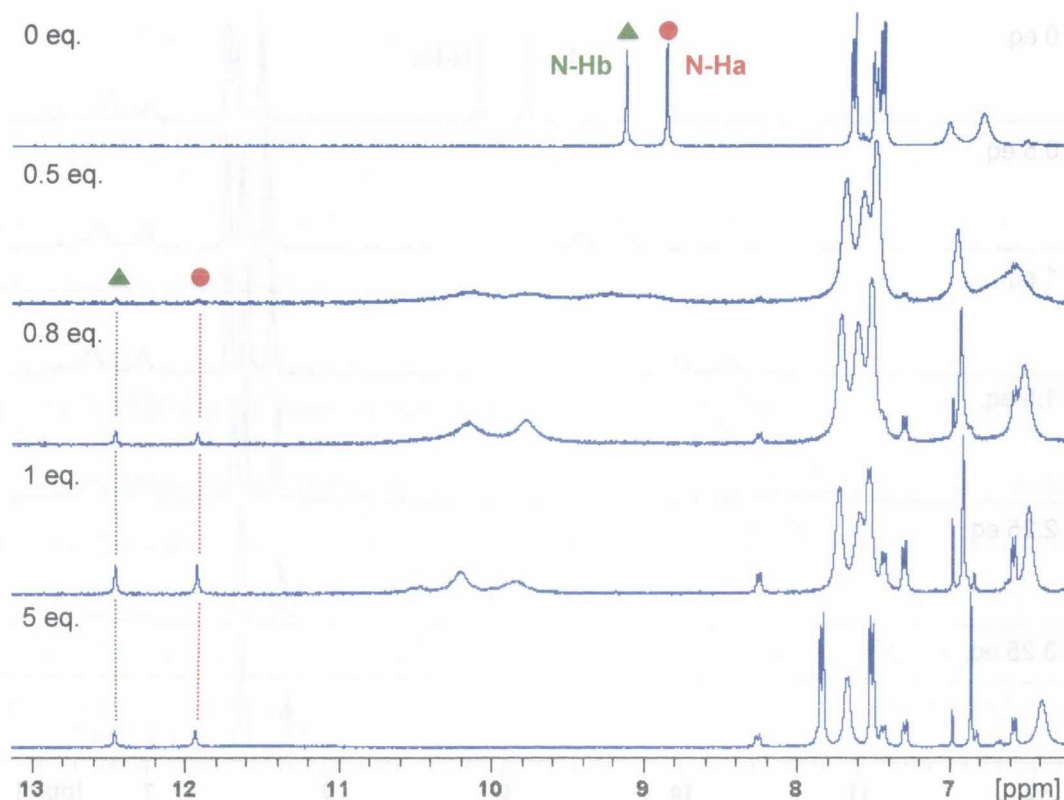


Figure 4.33: Stack plot of ^1H NMR spectra (400 MHz, $\text{DMSO-}d_6$) of **162** (7×10^{-3} M) upon addition of 0.5, 0.8, 1, and 5 equivalents of H_2PO_4^- . *N-Ha* and *N-Hb* are the urea protons.

The titration of **162** and SO_4^{2-} displayed a different binding interaction than previously seen with the previous two oxyanions. The evolution of the ^1H NMR spectra revealed that the urea protons shifted downfield by 0.9 ppm for *N-Ha* and over 1 ppm for *N-Hb*, Figure 4.34 and Figure 4.35, attributed to H-bonding to the anionic guest. This behaviour, compared to any of the results obtained for receptors **147-152**, was selective for SO_4^{2-} and could be attributed to both the nearly ideal complementarity of the binding site for SO_4^{2-} and the rigidity of its H-bonding environment. First, the complementarity provides for shape and size recognition through the urea functional groups in **162**. In direct contrast, the AcO^- and H_2PO_4^- ions, with their different shapes, perhaps do not fit as well as the tetrahedral SO_4^{2-} ion within this H-bonding cavity as they require a different geometric arrangement of the urea groups for optimal binding. The aromatic protons also experienced a small upfield shift as the titration progressed.

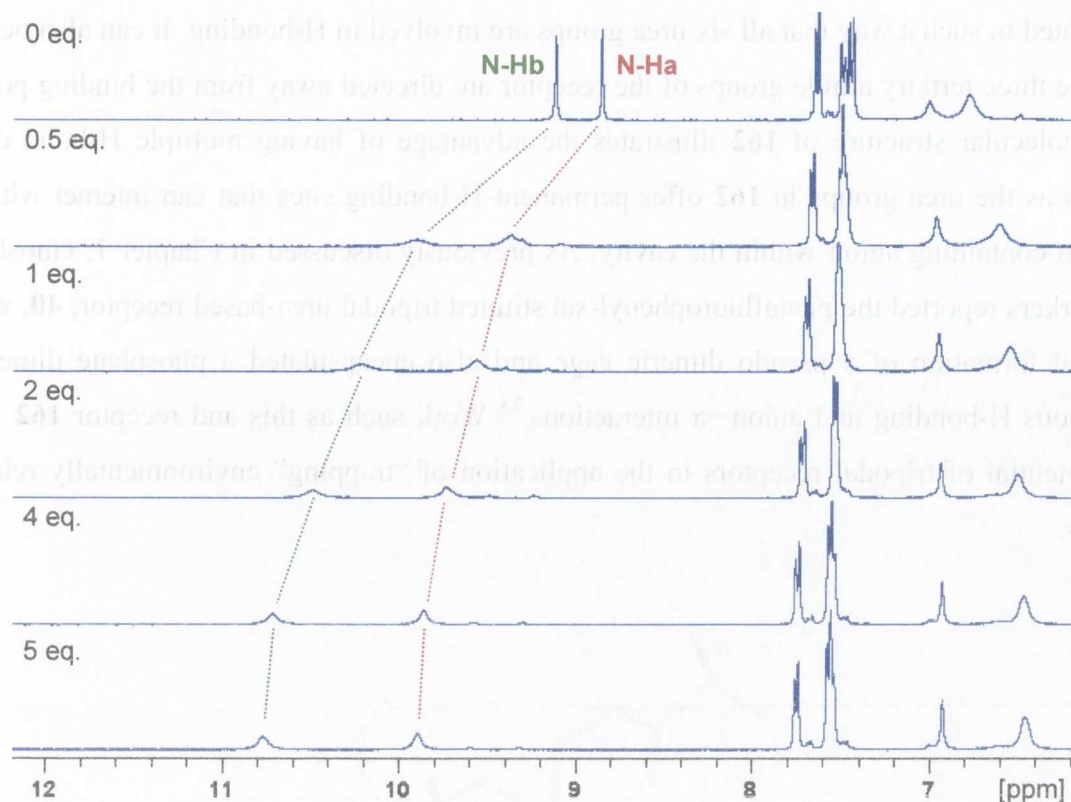


Figure 4.34: Stack plot of ^1H NMR spectra (400 MHz, $\text{DMSO}-d_6$) of **162** (7×10^{-3} M) upon addition of 0.5, 1, 2, 4 and 5 equivalents of SO_4^{2-} . N-Ha and N-Hb are the urea protons.

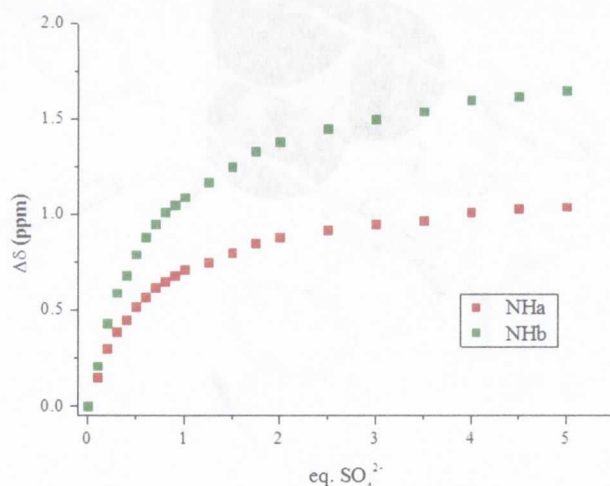


Figure 4.35: Changes in the urea resonances of **162** (as $\Delta\delta$) upon titration with SO_4^{2-} .

The evidence from the ^1H NMR titration that receptor **162** provided a binding pocket with ideal complementarity for SO_4^{2-} was confirmed by X-ray crystallography. Crystals with the composition $(\mathbf{162})_2 \cdot \text{SO}_4^{2-}$ were grown by slow evaporation from MeCN and isolated as hexagonal shaped crystals by Dr. Komala Pandurangan. The data, collected by Dr. Jonathan Kitchen and discussed here is preliminary and as such the quality is insufficient for detailed interactions to be examined. It can be seen from Figure 4.36 that two molecules of **162** encapsulate the anion *via* H-bonding to the urea moieties. The encapsulated SO_4^{2-} is

orientated in such a way that all six urea groups are involved in H-bonding. It can also be seen that the three tertiary amide groups of the receptor are directed away from the binding pocket. The molecular structure of **162** illustrates the advantage of having multiple H-bond donor groups as the urea groups in **162** offer permanent H-bonding sites that can interact with the oxygen-containing anion within the cavity. As previously discussed in Chapter 1, Ghosh and co-workers reported the pentafluorophenyl-substituted tripodal urea-based receptor, **40**, which showed formation of a pseudo dimeric cage and also encapsulated a phosphate dimer *via* numerous H-bonding and anion $\cdots\pi$ interactions.⁷³ Work such as this and receptor **162** show the potential of tripodal receptors in the application of “trapping” environmentally relevant anions.

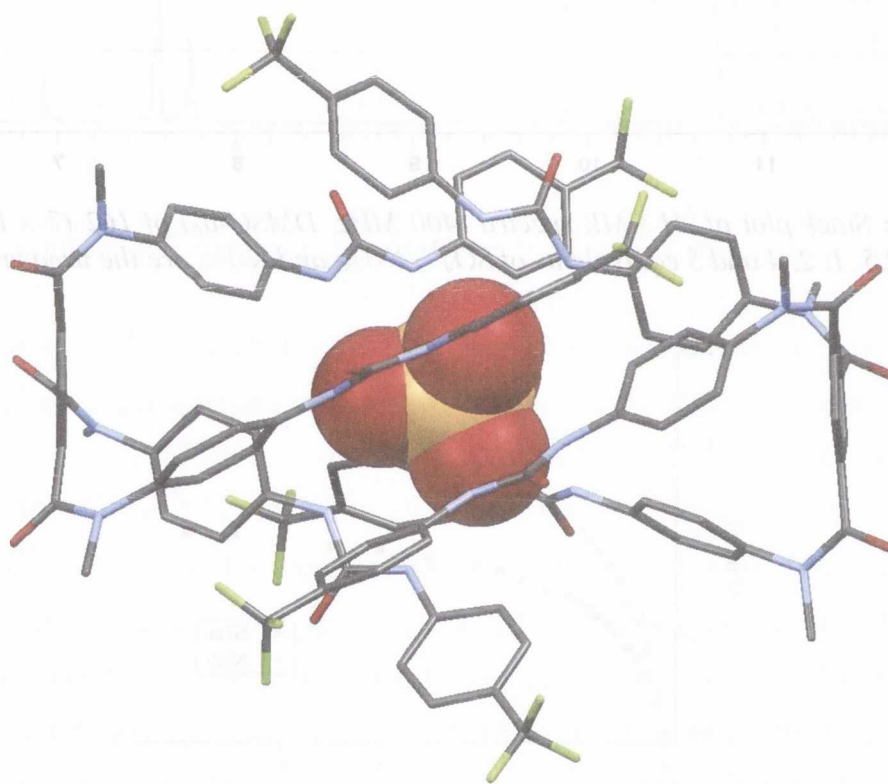


Figure 4.36: Crystal structure of receptor **162** with encapsulated SO_4^{2-} in a 2:1 (host:guest) binding stoichiometry.

Fitting of the ^1H NMR data to a $\text{H}_2:\text{G}$ model using *NMRTit HHG* determined binding constants of $\log K_{1:1} = 1.78$ and $\log K_{2:1} = 3.01$, with the fit obtained shown in Figure 4.37. The low binding constant obtained for the 1:1 species is not unexpected as clearly the more favourable interaction is two host molecules encapsulating the SO_4^{2-} ion.

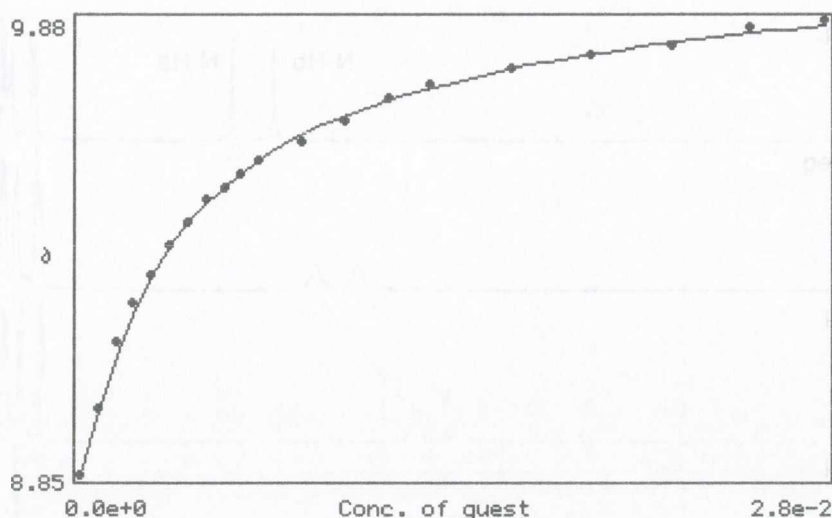


Figure 4.37: The binding isotherm and fit obtained for **162** upon fitting the changes in the chemical shift of the urea protons to a 2:1 (host:guest) complexation model upon titration of SO_4^{2-} .

The final anion to be investigated with this receptor was Cl^- and, again, in direct contrast to the results seen for the first generation analogue **147**, resulted in significant downfield shifts of the urea protons by *ca.* 3.1 ppm, Figure 4.38. The aromatic protons also became resolved up to the addition of 1 equivalent but subsequent additions of the anion resulted in these protons becoming broadened and shifted together, Figure 4.39. Due to the continuous downfield shifts of these protons, the data was unsuitable for fitting to an appropriate model preventing the determination of stability constants using these protons.

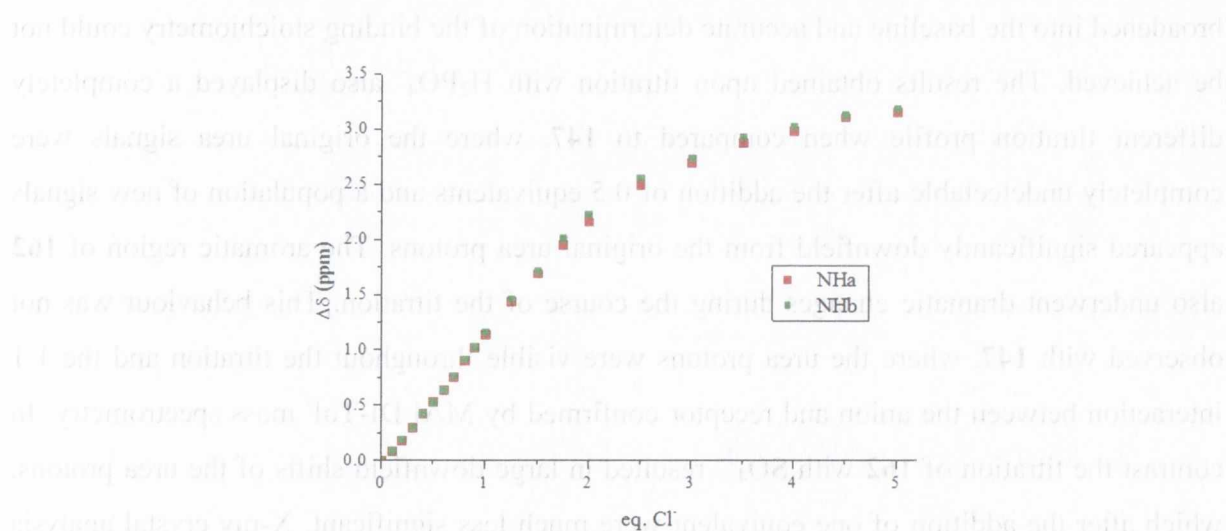


Figure 4.38: Changes in the urea resonances of **162** upon titration with Cl^- .

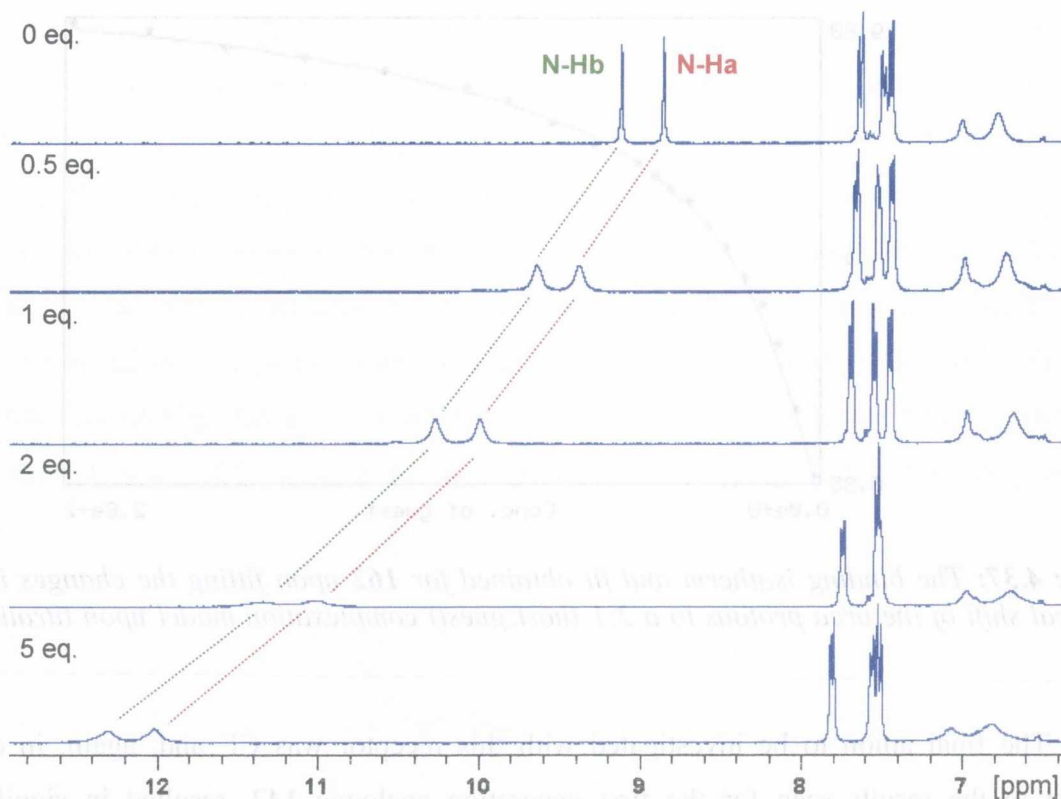


Figure 4.39: Stack plot of ^1H NMR spectra (400 MHz, $\text{DMSO-}d_6$) of **162** (7×10^{-3} M) upon addition of 0.5, 1, 2 and 5 equivalents of Cl^- . *N-Ha* and *N-Hb* are the urea protons.

Receptor **162** displayed very different behaviour with the various anions than that seen with its first generation counterpart **147**. Although the urea protons of both receptors displayed large shifts upon titration with AcO^- , the urea protons of **162** became significantly broadened into the baseline and accurate determination of the binding stoichiometry could not be achieved. The results obtained upon titration with H_2PO_4^- also displayed a completely different titration profile when compared to **147**, where the original urea signals were completely undetectable after the addition of 0.5 equivalents and a population of new signals appeared significantly downfield from the original urea protons. The aromatic region of **162** also underwent dramatic changes during the course of the titration. This behaviour was not observed with **147**, where the urea protons were visible throughout the titration and the 1:1 interaction between the anion and receptor confirmed by MALDI-ToF mass spectrometry. In contrast the titration of **162** with SO_4^{2-} resulted in large downfield shifts of the urea protons, which after the addition of one equivalent were much less significant. X-ray crystal analysis revealed two host molecules encapsulating one SO_4^{2-} ion, with $\log K_{1:1} = 1.78$ and $\log K_{2:1} = 3.01$ determined. The last anion to be investigated was Cl^- and again, in contrast to **147** where only very minor changes in the spectrum were observed, shifted significantly downfield upon addition of the anion.

Although the only difference between the first and second generation receptors are the substituents of the amido group, it appears this modification has a major impact on the anion binding properties of these receptors. It was determined that the amido proton did not play an active role in the anion binding of **147**, however it is possible it may have some function in how the cavity is preorganised or the effect of the slightly more electron donating N-H group compared to the tertiary amide of **162** may also play a role in how the receptor binds the anion.

4.4.2 ^1H NMR Titrations of Receptor **163** with Anions

Significant changes in the chemical shifts of both urea protons, up to *ca.* 2.5 ppm were found in the ^1H NMR spectrum of **163** upon addition of AcO^- , shown in Figure 4.40. After the addition of one equivalent both protons became broadened and appeared as one signal, Figure 4.41. The aromatic region underwent minor changes. Fitting of the ^1H NMR data resulting in binding constants of $\log K_{1:1} = 2.30$ and $\log K_{2:1} = 3.35$ being determined using *NMRTit HHG* (Appendix, Figure A4.21). Similarly to **162** and SO_4^{2-} and also in contrast to **148**, the most favourable interaction is the 2:1 (host:guest) species with the binding constant for the second species being over an order of magnitude higher.

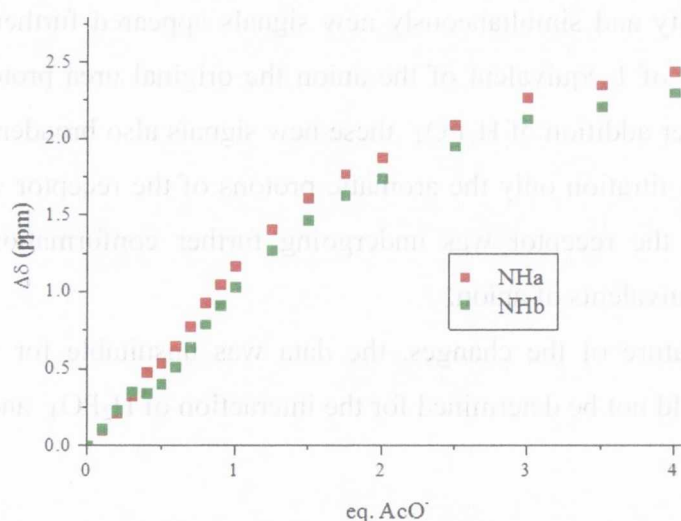


Figure 4.40: Changes in the urea resonances of **163** (as $\Delta\delta$) upon titration with AcO^- .

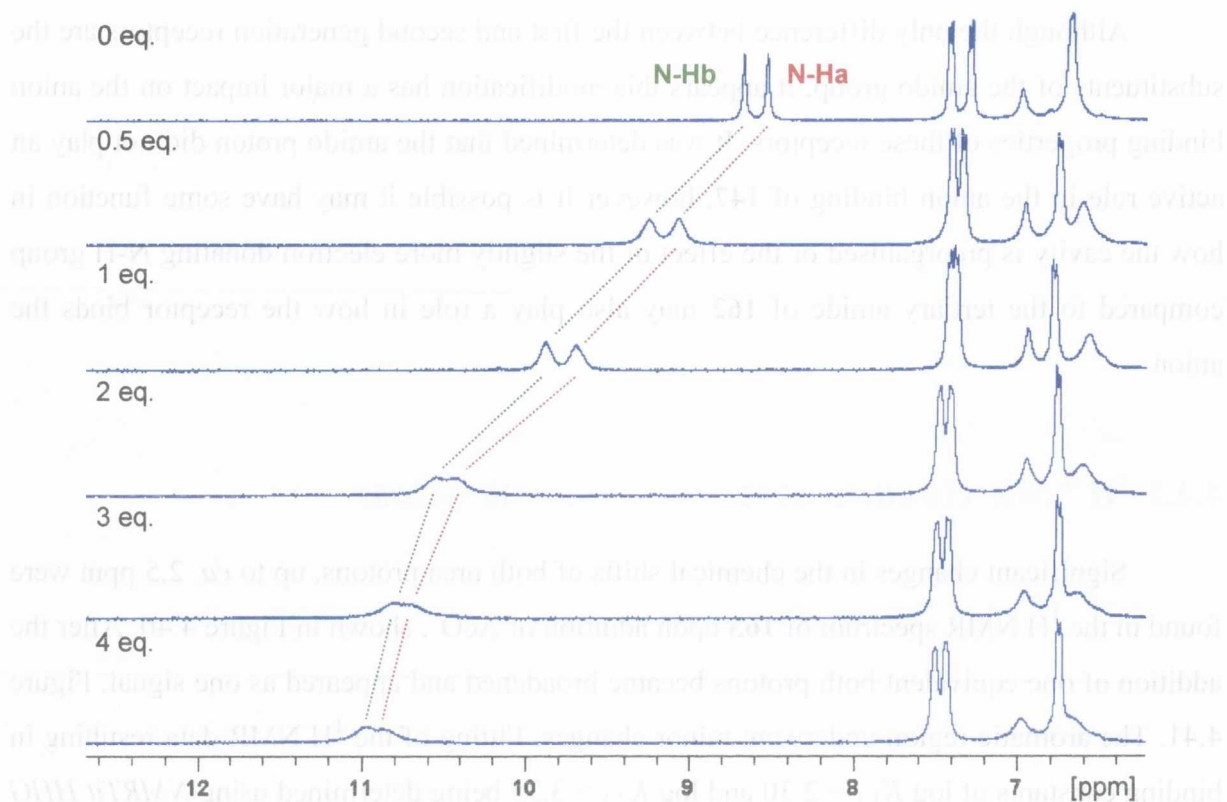


Figure 4.41: Stack plot of ^1H NMR spectra (400 MHz, $\text{DMSO}-d_6$) of **163** (7×10^{-3} M) upon addition of 0.5, 1, 2, 3 and 4 equivalents of AcO^- . *N-Ha* and *N-Hb* are the urea protons.

In the case of H_2PO_4^- the spectrum underwent dramatic changes with significant broadening and shifting of all signals of receptor **163**. Immediately the urea protons appeared to decrease in intensity and simultaneously new signals appeared further downfield, Figure 4.42. By the addition of 1 equivalent of the anion the original urea protons were no longer observed. Upon further addition of H_2PO_4^- these new signals also broadened and disappeared and by the end of the titration only the aromatic protons of the receptor were visible, Figure 4.43, indicating that the receptor was undergoing further conformational changes in the presence of higher equivalents of anion.

Due to the nature of the changes, the data was unsuitable for fitting and as such binding constants could not be determined for the interaction of H_2PO_4^- and **163**.

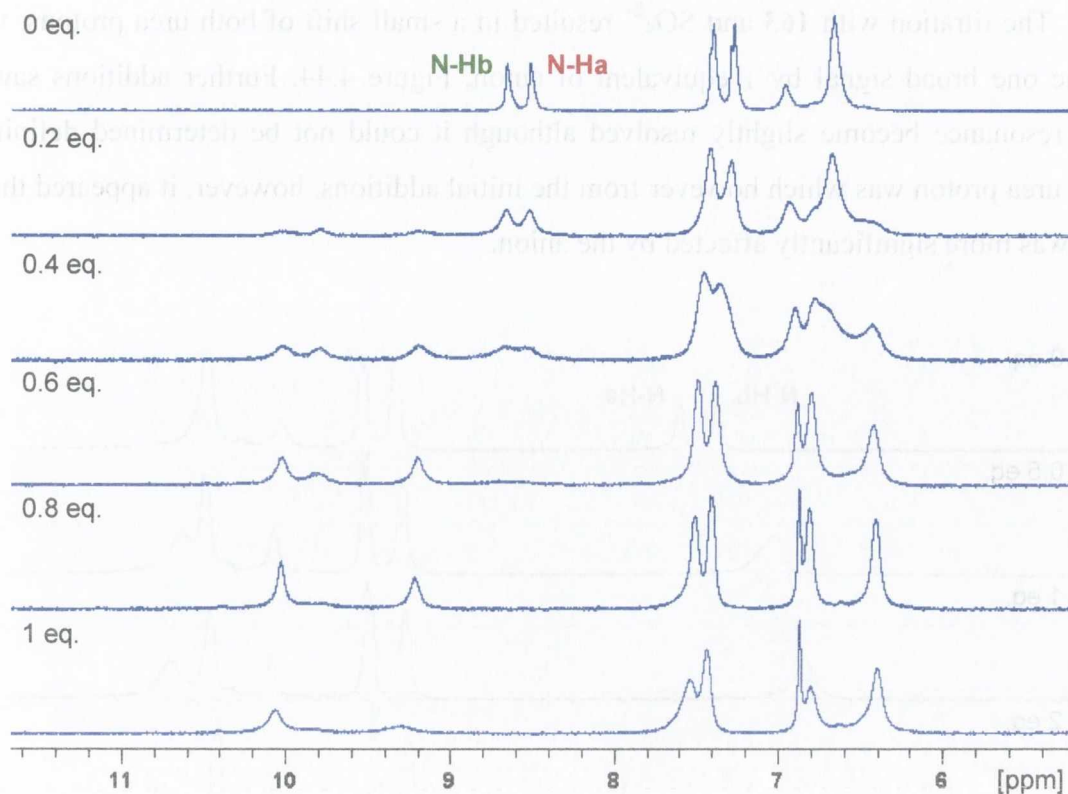


Figure 4.42: Stack plot of ^1H NMR spectra (400 MHz, $\text{DMSO}-d_6$) of **163** ($7 \times 10^{-3} \text{ M}$) upon addition of 0.2, 0.4, 0.6, 0.8 and 1 equivalents of H_2PO_4^- . N-Ha and N-Hb are the urea protons.

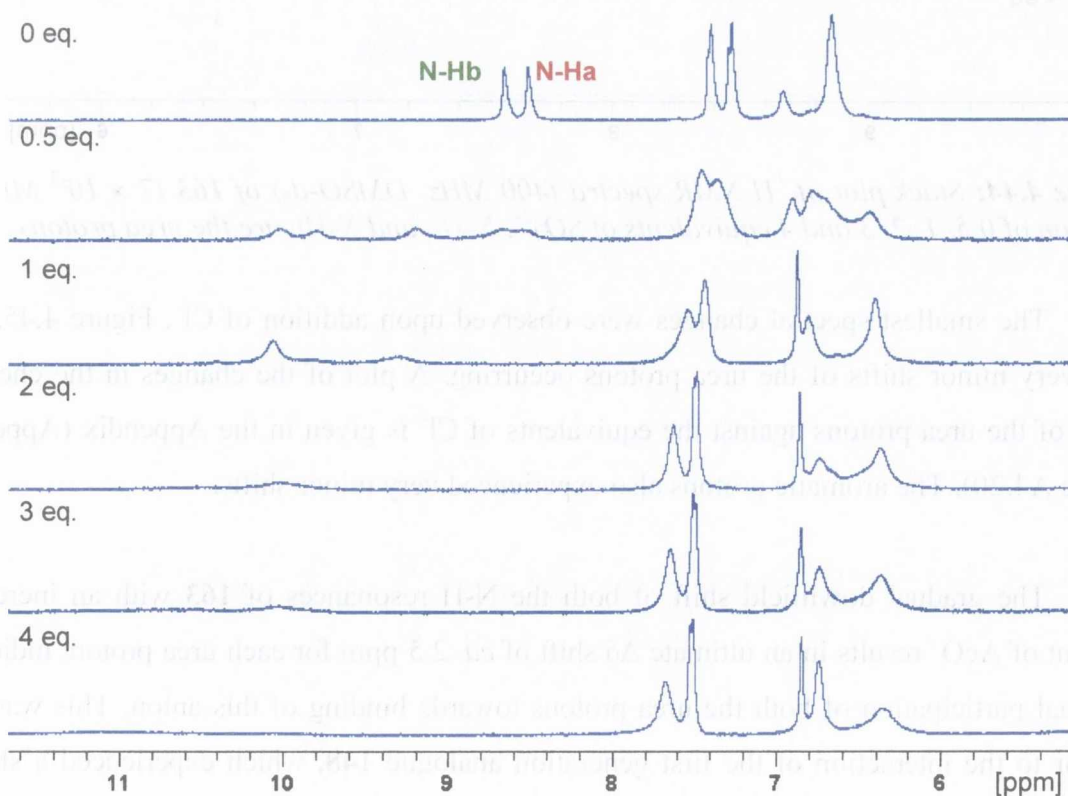


Figure 4.43: Stack plot of ^1H NMR spectra (400 MHz, $\text{DMSO}-d_6$) of **163** ($7 \times 10^{-3} \text{ M}$) upon addition of 0.5, 1, 2, 3 and 4 equivalents of H_2PO_4^- . N-Ha and N-Hb are the urea protons.

The titration with **163** and SO_4^{2-} resulted in a small shift of both urea protons, which became one broad signal by 1 equivalent of anion, Figure 4.44. Further additions saw this broad resonance become slightly resolved although it could not be determined definitively which urea proton was which however from the initial additions, however, it appeared that the N-Ha was more significantly affected by the anion.

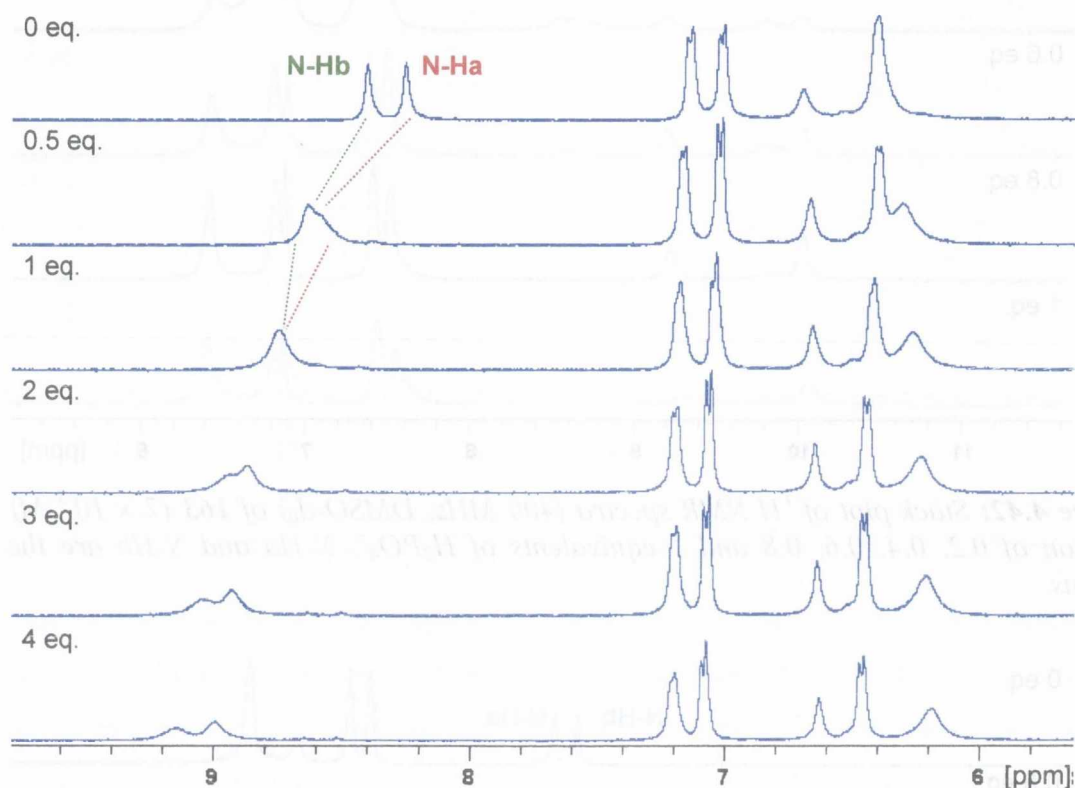


Figure 4.44: Stack plot of ^1H NMR spectra (400 MHz, DMSO-d_6) of **163** (7×10^{-3} M) upon addition of 0.5, 1, 2, 3 and 4 equivalents of SO_4^{2-} . N-Ha and N-Hb are the urea protons.

The smallest spectral changes were observed upon addition of Cl^- , Figure 4.45, with only very minor shifts of the urea protons occurring. A plot of the changes in the chemical shifts of the urea protons against the equivalents of Cl^- is given in the Appendix (Appendix, Figure A4.20). The aromatic protons also experienced very minor shifts.

The gradual downfield shift of both the N-H resonances of **163** with an increasing amount of AcO^- results in an ultimate $\Delta\delta$ shift of *ca.* 2.5 ppm for each urea proton, indicative of equal participation of both the urea protons towards binding of this anion. This was very similar to the interaction of the first generation analogue **148**, which experienced a shift of comparable magnitude while the 1:1 binding stoichiometry of **148** and AcO^- was also determined by MALDI-ToF mass spectrometry. However, upon fitting the data **163** and AcO^- the best fit obtained was for a 1:1 and 2:1 (host:guest) stoichiometry (Appendix, Figure

A6.21). When the values were compared, the 1:1 species of **148** with AcO^- is an order of magnitude higher, *i.e.* $\log K_{1:1} = 3.25$ and $\log K_{1:1} = 2.30$ for **148** and **163**, respectively, however the overall stability of the second generation receptor **163** and AcO^- is more stable due to the formation of a multi-host assembly.

The titration with **163** and H_2PO_4^- displayed dissimilar behaviour to that seen for **148**. The broadening of the urea protons and the eventual disappearance of these signals after the addition of 1 equivalent of H_2PO_4^- made analysis of the binding interaction very difficult to establish. In the case of SO_4^{2-} the urea protons became broadened and shifted but were visible throughout the course of the titration, contrary to what occurred with **148** where after the addition of 0.5 equivalents only the amide proton could be followed for analysis as the urea protons had broadened into the baseline of the spectrum. Both receptors showed minimal response to Cl^- with only very minor changes occurring upon addition of the anion, which as previously described is indicative of an energetically unfavourable interaction.

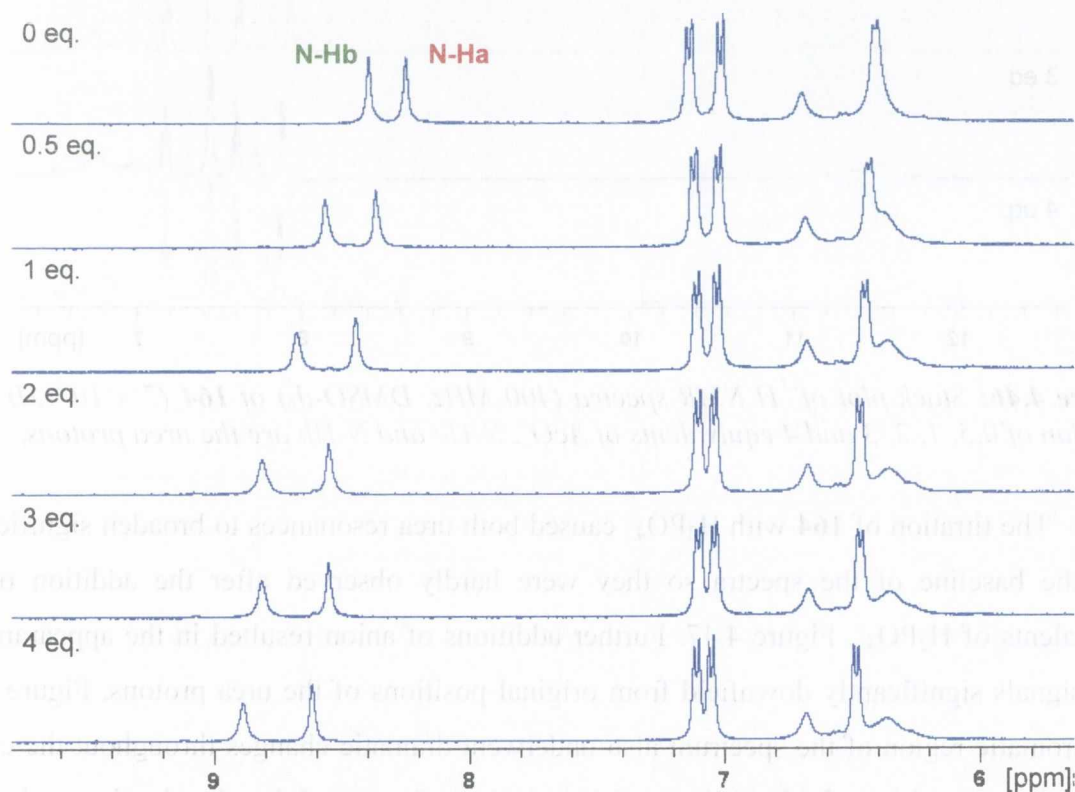


Figure 4.45: Stack plot of ^1H NMR spectra (400 MHz, DMSO-d_6) of **163** (7×10^{-3} M) upon addition of 0.5, 1, 2, 3 and 4 equivalents of Cl^- . *N-Ha* and *N-Hb* are the urea protons.

4.4.3 ^1H NMR Titrations of Receptor **164** with Anions

The stack plot of **164** upon titration with AcO^- is shown in Figure 4.46 and it can be seen that the urea protons undergo a gradual downfield shift upon increasing AcO^-

concentration, eventually becoming significantly broadened with both protons merging to become one broad signal by the end of the titration. The binding isotherm for the titration can be found in the Appendix (Appendix, Figure A4.22). The aromatic protons also underwent a gradual upfield shift throughout the titration, possibly due to either desolvation effects as DMSO is displaced from the cavity by the anion or conformational changes in the receptor.⁸⁴

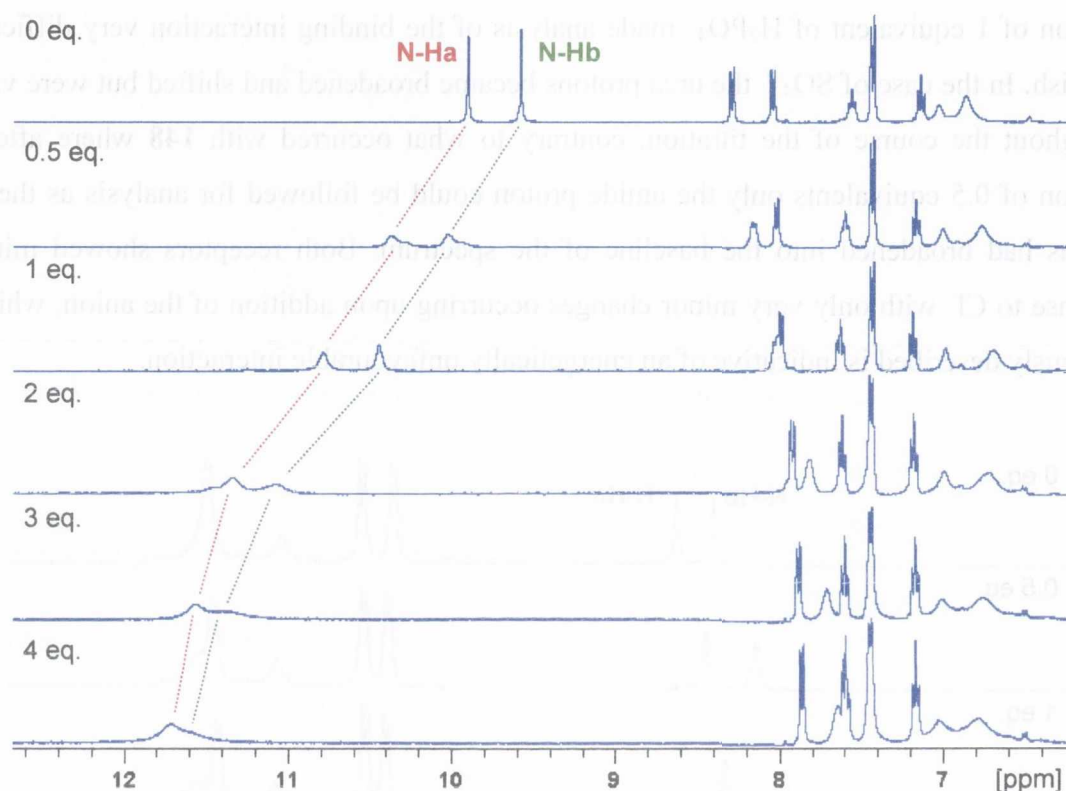


Figure 4.46: Stack plot of ^1H NMR spectra (400 MHz, $\text{DMSO}-d_6$) of **164** (7×10^{-3} M) upon addition of 0.5, 1, 2, 3 and 4 equivalents of AcO^- . *N-Ha* and *N-Hb* are the urea protons.

The titration of **164** with H_2PO_4^- caused both urea resonances to broaden significantly into the baseline of the spectra so they were hardly observed after the addition of 0.4 equivalents of H_2PO_4^- , Figure 4.47. Further additions of anion resulted in the appearance of new signals significantly downfield from original positions of the urea protons, Figure 4.48. The aromatic region of the spectrum also underwent dramatic changes throughout the course of the titration with upfield shifting and broadening of most of the signals observed, again possibly due to desolvation or conformational effects upon the receptor binding to the anion. In this case, calculation of binding constants was also impossible due to the nature of the changes occurring.

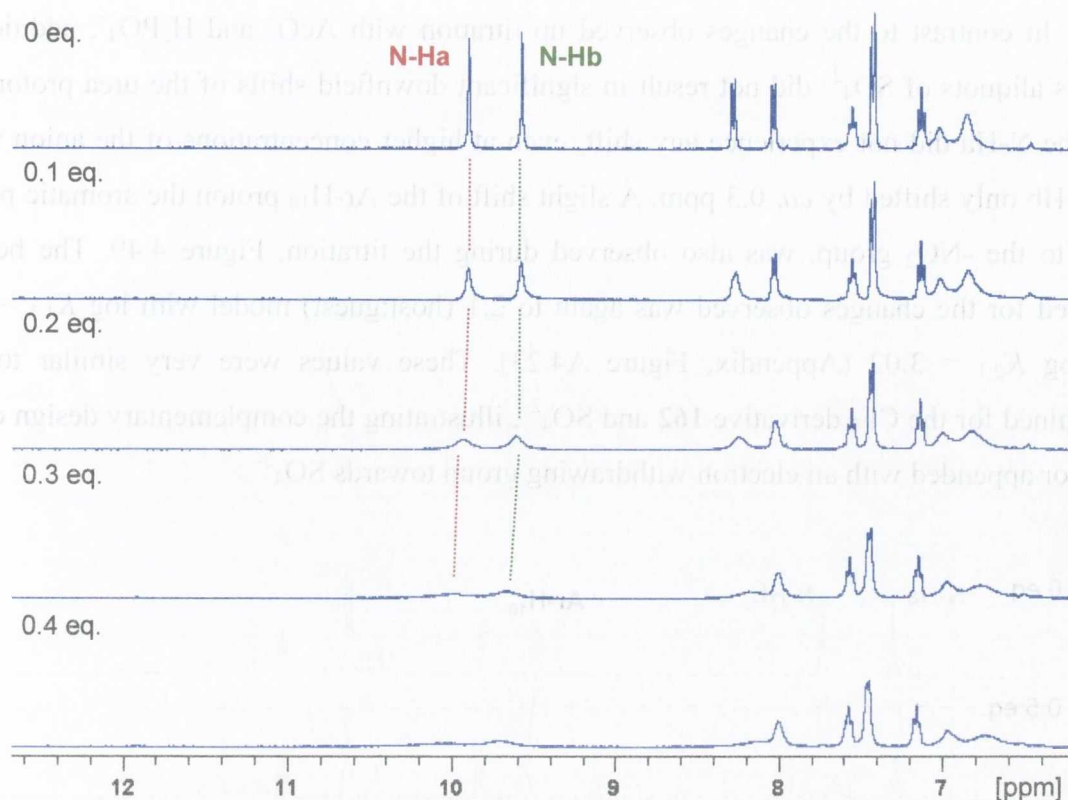


Figure 4.47: Stack plot of ^1H NMR spectra (400 MHz, DMSO-d_6) of **164** ($7 \times 10^{-3} \text{ M}$) upon addition of 0.1, 0.2, 0.3 and 0.4 equivalents of H_2PO_4^- . N-Ha and N-Hb are the urea protons.

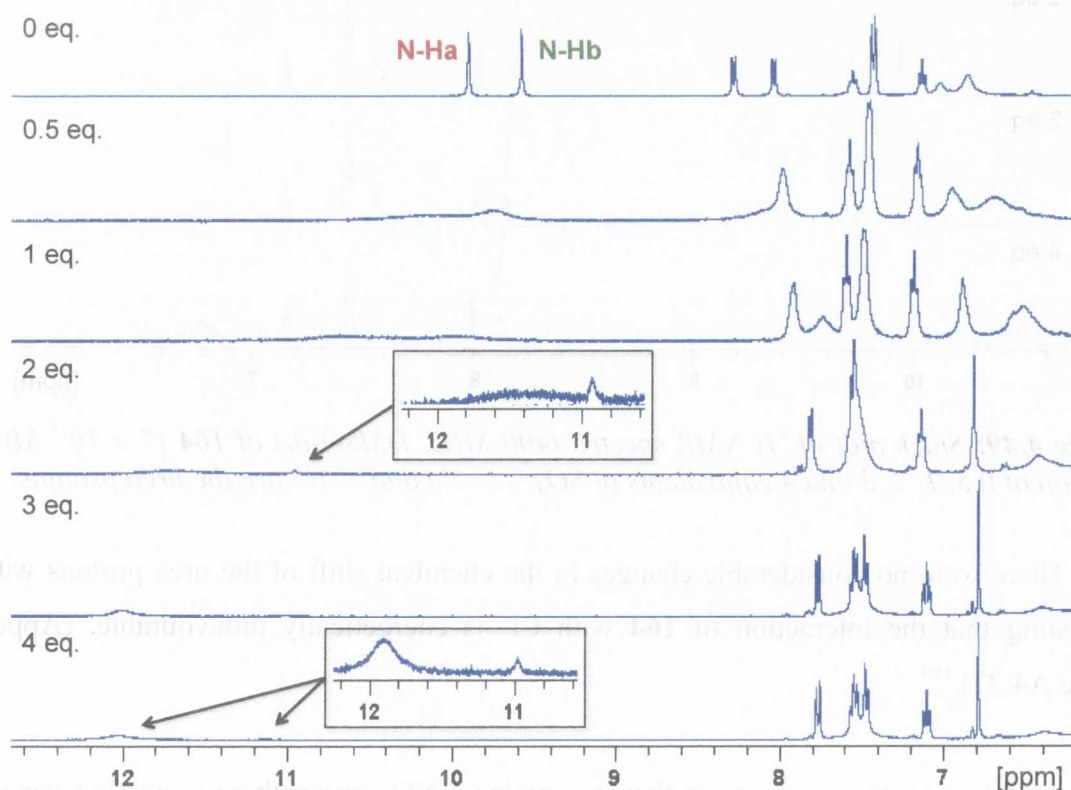


Figure 4.48: Stack plot of ^1H NMR spectra (400 MHz, DMSO-d_6) of **164** ($7 \times 10^{-3} \text{ M}$) upon addition of 0.5, 1, 2, 3 and 4 equivalents of H_2PO_4^- . N-Ha and N-Hb are the urea protons.

In contrast to the changes observed upon titration with AcO^- and H_2PO_4^- , addition of various aliquots of SO_4^{2-} did not result in significant downfield shifts of the urea protons. In fact, the N-Ha did not experience any shift, even at higher concentrations of the anion while the N-Hb only shifted by *ca.* 0.3 ppm. A slight shift of the Ar-H₁₀ proton the aromatic proton *ortho* to the $-\text{NO}_2$ group, was also observed during the titration, Figure 4.49. The best fit obtained for the changes observed was again to 2:1 (host:guest) model with $\log K_{1:1} = 1.96$ and $\log K_{2:1} = 3.02$ (Appendix, Figure A4.23). These values were very similar to that determined for the CF_3 derivative **162** and SO_4^{2-} , illustrating the complementary design of the receptor appended with an electron withdrawing group towards SO_4^{2-} .

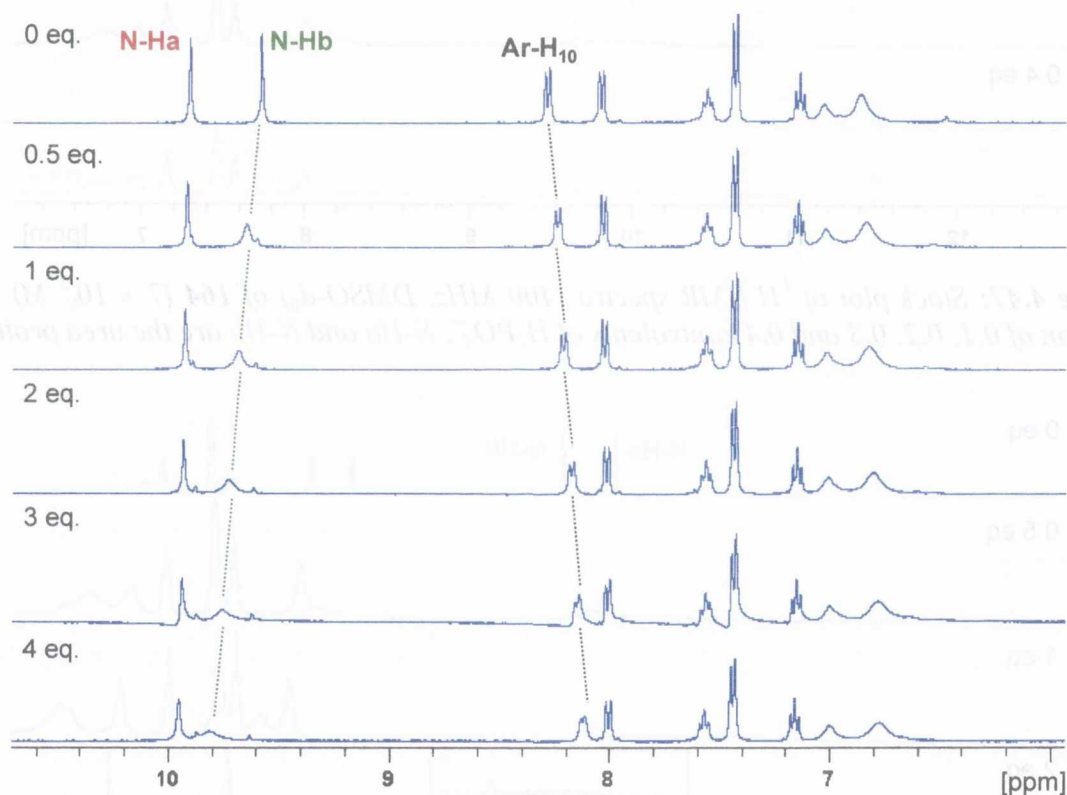


Figure 4.49: Stack plot of ^1H NMR spectra (400 MHz, $\text{DMSO}-d_6$) of **164** (7×10^{-3} M) upon addition of 0.5, 1, 2, 3 and 4 equivalents of SO_4^{2-} . N-Ha and N-Hb are the urea protons.

There were no considerable changes in the chemical shift of the urea protons with Cl^- suggesting that the interaction of **164** with Cl^- is energetically unfavourable, (Appendix, Figure A4.22).¹⁹⁹

As this receptor is unique in that it contains a NO_2 group there is no first generation derivative to compare to. However, it appears in the case of AcO^- the downfield shift of the urea protons is indicative of H-bonding as seen previously with the other receptors. In contrast, H_2PO_4^- displayed a different binding profile whereby the urea protons were no

longer visible after the addition of 0.4 equivalents of anion. Only after the addition of *ca.* 2 equivalents of H_2PO_4^- were new signals detected at *ca.* 11 ppm and 12 ppm, respectively.

Unusually, the interaction of **164** and SO_4^{2-} did not appear to involve both protons as only the N-Hb became broadened and experienced a very small shift of *ca.* 0.3 ppm while the N-Ha did not experience any kind of shift. The *ortho* position of the NO_2 functionality could H-bond to the urea N-H that it is directly adjacent to, as illustrated in Figure 4.50, and could impact the anion binding ability of this receptor. It is possible that this receptor only has one N-H bond donor available to bind the anion.

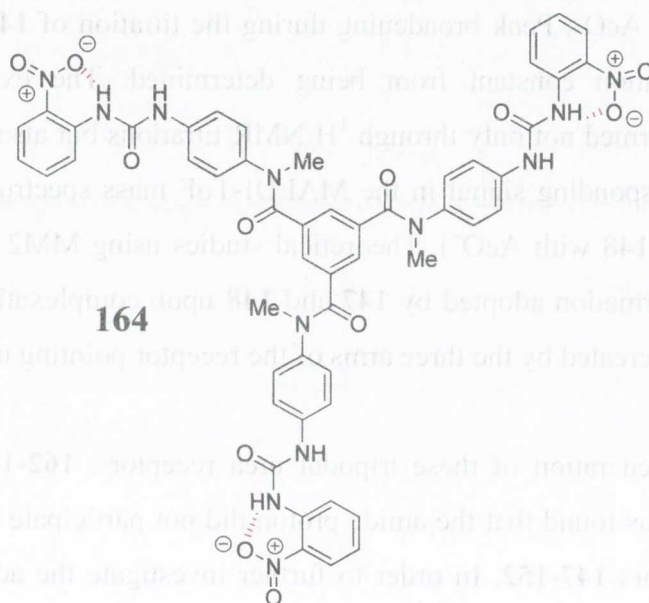


Figure 4.50: H-bonding interaction between the urea N-Ha and the NO_2 group of **164**.

4.5 Conclusion

The strategy for the design of the tripodal receptors described in this Chapter was based upon two concepts:

- N-H bonds in the receptor aligned in parallel to effectively complex an anion;
- the flexibility of the receptors would allow encapsulation of anions such as H_2PO_4^- and SO_4^{2-} .

This binding motif defines a cavity where three different types of hydrogen bonding can be established from urea N-Hs, an amide N-H function and an aromatic CH. The lower part of the host cavity was expected to be an attractive anion-binding pocket by virtue of its proximity to all three urea binding sites. In general, the results support the suggestion that, although these tripodal receptors are conformationally flexible with a large degree of freedom, encapsulation of the anions studied takes place by generation of a preorganised cavity *via*

multiple H-bonding interactions in solution. Interestingly, the amide proton of receptors **147-152** was not found to play any active role in the anion binding process.

Receptor **147** showed the highest affinity for H_2PO_4^- out of all the receptors studied with a notable $\log K_{1:1} = 4.2 \pm 0.1$ determined, while the structurally similar receptors **151** and **152** showed a preference for AcO^- with $\log K_{1:1} = 3.7 \pm 0.1$ calculated for both receptors. The interaction with these anions and Cl^- was the least preferential of the anions studied with the highest binding constant determined to be $\log K_{1:1} = 2.81 \pm 0.07$ between receptor **148** and this anion. It is also worth noting that the only receptor that showed a relatively strong interaction with SO_4^{2-} was receptor **147** with $\log K_{1:1} = 3.7 \pm 0.2$, a similar affinity to that seen for **151** and **152** with AcO^- . Peak broadening during the titration of **149** with SO_4^{2-} actually prevented an association constant from being determined. The existence of these 1:1 complexes were confirmed not only through ^1H NMR titrations but also in some cases by the presence of the corresponding signal in the MALDI-ToF mass spectrum (receptor **147** with H_2PO_4^- and receptor **148** with AcO^-). Theoretical studies using MM2 have also shown that the most likely conformation adopted by **147** and **148** upon complexation contains the anion in the binding pocket created by the three arms of the receptor pointing upward.

The second generation of these tripodal urea receptors, **162-164**, contained tertiary amide groups, as it was found that the amide proton did not participate in the binding process in the case of receptors **147-152**. In order to further investigate the advantage of having an additional H-bond donor and to determine does it have any impact on the anion binding ability, receptors **162-164** were synthesised with a methyl functionalised amide. The crystal structure of **167** confirmed the upward facing arms of the core structure, providing an ideal cavity for anion recognition. This core structure was found to behave in the same manner when functionalised with pendant arms as determined from the X-ray crystal structure of **163**.

The titrations of **162** and various anions resulted in dissimilar behaviour to that observed for its first generation counterpart **147**, illustrating that one small modification to the structure can have a major effect on the anion binding properties of the receptor. Upon titration with AcO^- the urea protons became too broadened to make any accurate assessments of the binding interaction but most likely multiple binding stoichiometries were present in solution. Addition of H_2PO_4^- resulted in a new set of ^1H NMR signals besides those of the ligand, which can be attributed to the anion complex that appeared at the expense of the free ligand as a consequence of slow exchange of N-H protons on the NMR time scale.²⁰⁰ The intensity of the new signals increased gradually with the addition of H_2PO_4^- , while the signals

corresponding to the ligand decreased and disappeared completely after 1 equivalent of the anion was added. The N-H signals of the complex appeared as sharp singlet signals and the saturated changes were observed after adding one equivalent of the anion. There were no further changes when more anion was added. The titration of **162** and SO_4^{2-} showed a gradual downfield shift of the urea protons, indicative of H-bonding. X-ray crystallography indeed confirmed the formation of a highly organised cavity in which the SO_4^{2-} anion was encapsulated between two receptor molecules. Fitting of the ^1H NMR data determined two different binding interactions with $\log K_{1:1} = 1.76$ and $\log K_{2:1} = 3.01$. The strength of this binding interaction makes this receptor an ideal candidate for membrane transporters. In contrast, addition of Cl^- did not result in any kind of plateau being reached with changes still occurring at higher equivalents of the anion. This might be due to multiple equilibria in the system, deprotonation events and mixed stoichiometries being the most likely processes to occur.

The hexyloxy derivative **163** also displayed different titration profiles to that of its first generation analogue **148**. Upon addition of AcO^- a significant downfield shift of the urea protons was observed, with the signals becoming much less sharp after the addition of 1 equivalent. Similar problems were encountered during NMR titrations with **163** and H_2PO_4^- . Up to the addition of 0.4 equivalents of H_2PO_4^- a downfield shift of the N-H groups was observed, while the addition of more aliquots of anion resulted in the appearance of new peaks further downfield. This behaviour has been observed previously for receptors that bind anions through multiple hydrogen bonds and has been explained by the deprotonation of bound H_2PO_4^- and the subsequent formation of a monohydrogen phosphate (HPO_4^{2-}) complex.¹⁹⁴

The final receptor to be investigated was the NO_2 functionalised derivative **164**. In this case the electron-withdrawing effect of the NO_2 substituent not only increases binding to anions, but would also increase the binding to other H-bond acceptors such as the DMSO solvent. Data analysis of the NMR titrations of **164** with AcO^- and H_2PO_4^- was greatly hindered by peak broadening, which can be indicative of a proton transfer from the ligand to the anion or from bound anion to free anion in solution. Interestingly, the titration of **164** with SO_4^{2-} only displayed a very minor shift of the N-Hb upon addition of the anion, while the N-Ha did not experience any shift. Nonetheless fitting of the changes of the chemical shift of the N-Hb resulted in two species being identified in solution with $\log K_{1:1} = 1.96$ and $\log K_{2:1} = 3.02$, which were very similar to the values obtained for **162** and SO_4^{2-} . The titration of **164** with Cl^- did not result in any major shifts of the urea protons. This could be due to a number

of reasons, including lack of complementarity between the anion and the binding site or simply an energetically unfavourable interaction.

By employing crystalline host environments functionalised with urea anion-coordinating groups as a means to obtain maximal three-dimensional complementarity and rigidity, the contribution from several H-bonding groups and the impact of geometric requirements on the binding ability of benzene-based tripodal receptors towards various anions has been investigated. The results presented in this Chapter demonstrate that a judicious choice of correct geometry and appropriate functional groups is critical to achieve the complementary H-bonding interactions required for effective anion recognition.

The hexyl derivative **103** also displayed different titration profiles to that of its first generation analogue **100**. Upon addition of $\Delta\delta$, a significant downfield shift of the urea protons was observed, with the signals becoming much less sharp after the addition of 1 equivalent. Similar problems were encountered during NMR titrations with **103** and H_2PO_4^- . Up to the addition of 0.4 equivalents of H_2PO_4^- , a downfield shift of the N-H groups was observed, while the addition of more aliquots of anion resulted in the appearance of new peaks further downfield. This behaviour has been observed previously for receptors that bind anions through multiple hydrogen bonds and has been explained by the deprotonation of bound H_2PO_4^- and the subsequent formation of a monohydrogen phosphate (HPO_4^{2-}) complex.¹⁰⁴

The final receptor to be investigated was the NO₂ functionalised derivative **104**. In this case the electron-withdrawing effect of the NO₂ substituent not only increases binding to anions, but would also increase the binding to other H-bond receptors such as the DMF-50 solvent. Data analysis of the NMR titrations of **104** with AcO⁻ and H_2PO_4^- was greatly hindered by peak broadening, which can be indicative of a proton transfer from the ligand to the anion or from bound water to the anion. Interestingly, the titration of **104** with SO_4^{2-} only displayed a very minor shift of the N-Hs upon addition of the anion, while the N-Hs did not experience any shift. Nevertheless, noting of the changes of the chemical shift of the N-Hs resulted in two species being identified in solution with $\log K_{11} = 1.96$ and $\log K_{21} = 3.03$, which were very similar to the values obtained for **103** and SO_4^{2-} . The titration of **104** with CT did not result in any major shifts of the urea protons. This could be due to a number

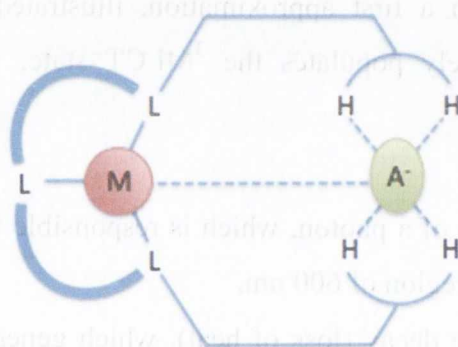
Chapter 5

Ru(II) Polypyridyl Urea-Based Anion Receptors

5. Introduction

A large number of synthetic anion receptors have been designed to date based on purely organic frameworks.^{201,202} Conversely, the use of metal containing receptors for the recognition of anions has received limited attention. Coordination of a metal cation, however, offers an effective means of enhancing the H-bond donor tendencies of (thio)ureas.²⁹ Transition metal complexes can be used as structural elements in the design of anion receptors or for assisting with anion binding and have played an important role in anion receptor chemistry with a diverse range of metals and anion-binding groups studied to date.^{203,204} The best metal-based anion receptors combine both the electrostatic attraction of the metal centre and the directional binding effects of appended H-donor functional groups on the ligands, illustrated in Figure 5.1.¹²³ Furthermore, careful consideration of the metal centre can confer useful spectroscopic properties to the receptor.

The metal centre preorganises the H-bonding groups and can also interact directly with the anion



The metallo-host binds the anionic guest by H-bonding and metal-ligand interactions

Figure 5.1: Schematic representation of a metallo-host containing H-bonding groups for anion recognition.

Complexes incorporating Ru(II) metal centres and, in particular, Ru(II) polypyridyl complexes have been shown to be excellent receptors for the recognition of anions.^{205,206} Ru(II) is a unique metal due to its ability to form complexes that cover the widest range of oxidation states theoretically allowed for a transition metal, *e.g.* from +8 in $[\text{RuO}_4]$ to -2 in $[\text{Ru}(\text{CO})_4]^{2-}$. However the most common are the Ru(II) and Ru(III) oxidation states.²⁰⁷ Ru(II) polypyridyl complexes have been investigated in possibly greater detail than any other class of luminescent metal complexes and have found wide ranging applications in solar cells,²⁰⁸ oxygen sensors²⁰⁹ and DNA probes²¹⁰ *etc.*

In order to understand how Ru(II) polypyridyl complexes interact, an explanation of their photophysics is necessary. The most studied complex in this series is $[\text{Ru(II)}-(bpy)_3]^{2+}$, ($bpy = 2,2\text{-bipyridine}$), due to its high stability, strong and long-lived luminescence and ability to undergo redox reactions; and as such the photophysical mechanisms of this complex will be described in the following section.

5.1 Photophysical Properties of Ru(II) Polypyridyl Complexes

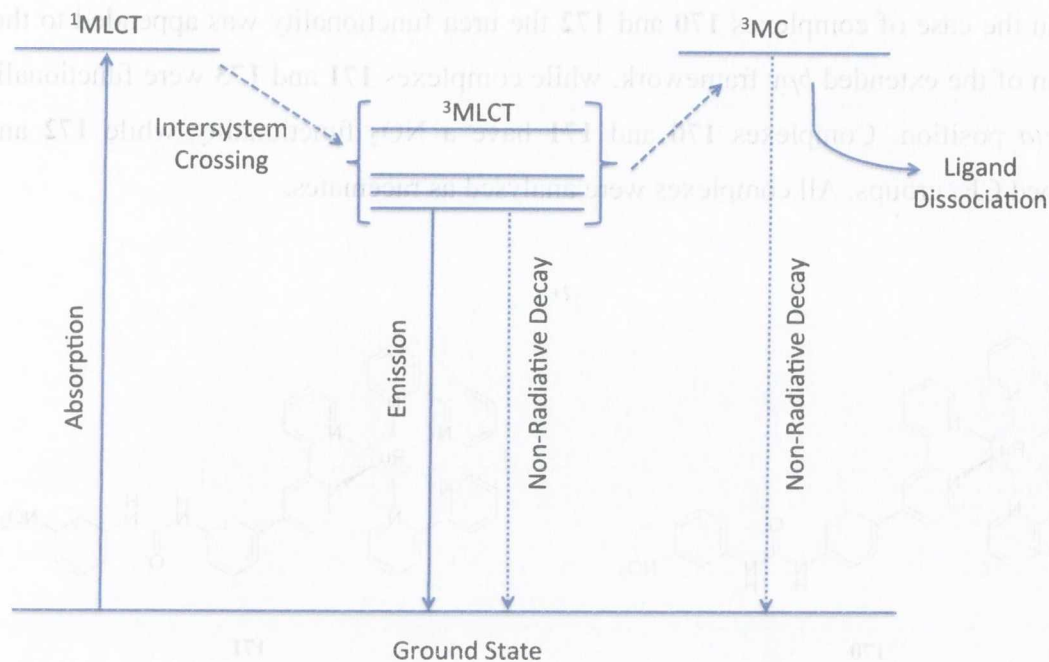
Polypyridyl complexes of Ru(II) have a d^6 electronic configuration and a preferred octahedral geometry. Surrounding the metal ion, polypyridyl ligands interact with Ru through σ -donor orbitals located on the nitrogen atoms and π -donor and π^* -acceptor molecular orbitals delocalised on the aromatic rings.²¹¹

The prototypical compound $[\text{Ru(II)}-(bpy)_3]^{2+}$ absorbs energy in the visible region of the electromagnetic spectrum populating a metal-to-ligand charge transfer ($^1\text{MLCT}$) state that corresponds to the formal transfer of one electron from the metal-centred HOMO to the ligand-centred LUMO, in a first approximation, illustrated in Scheme 5.1.⁹¹ Intersystem crossing then quantitatively populates the $^3\text{MLCT}$ state, which is generally deactivated through:

- the emission of a photon, which is responsible for the observed emission in the wavelength region of 600 nm,
- non-radiative decay (loss of heat), which generally controls the lifetime of the $^3\text{MLCT}$ in many Ru(II) polypyridyl complexes; or
- through the population of the ^3MC state, which itself is non-emissive and can give rise to ligand loss.

For Ru(II) polypyridyl complexes, the relatively small energy difference between the $^3\text{MLCT}$ and ^3MC states allows, under certain experimental conditions, population of the latter from the former. Compared to its group VIII counterparts, Ru(II) offers a good compromise between:

- (i) kinetic lability and low metal-centred $d-d$ excited states (Fe(II)), and
- (ii) kinetic inertness and low ligand-centred $\pi-\pi^*$ excited states (Os(II)).



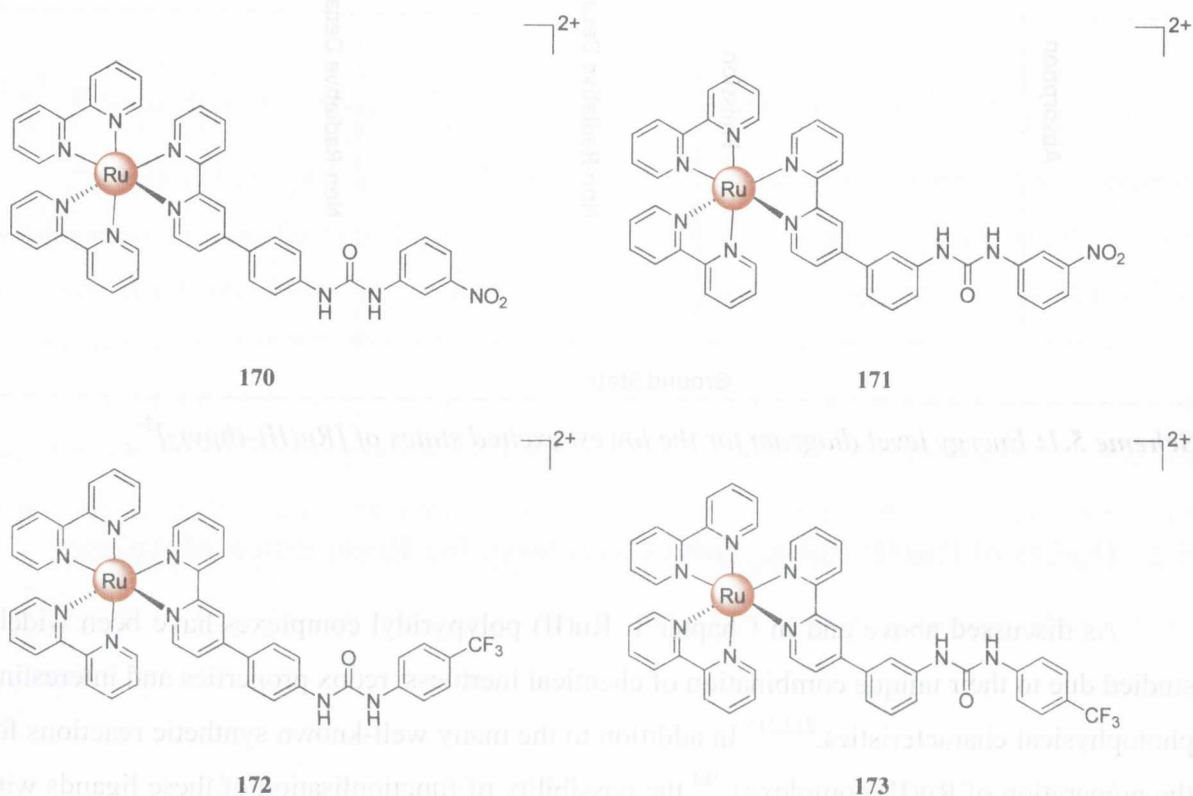
Scheme 5.1: Energy level diagram for the lowest excited states of $[Ru(II)-(bpy)_3]^{2+}$.

5.2 Design of Ru(II) Polypyridyl Complexes for Recognition of Anions

As discussed above and in Chapter 1, Ru(II) polypyridyl complexes have been widely studied due to their unique combination of chemical inertness, redox properties and interesting photophysical characteristics.^{212,213} In addition to the many well-known synthetic reactions for the preparation of Ru(II) complexes,²¹⁴ the possibility of functionalisation of these ligands with appropriate H-bond donor groups makes these complexes attractive for use in anion recognition.²⁰³

With these considerations in mind, we^{107,175,215} and others^{216,217} have exploited the incorporation of the $Ru(II)-(bpy)_3$ moiety as a signalling subunit and also extensively exploited urea-based ligands as a binding site in the synthesis of anion receptors.^{218,219} However, these have not been utilised in tandem. In this work, four highly luminescent $Ru(II)-(bpy)_3$ -based complexes containing a urea moiety, **170-173**, were designed and synthesised. As stated above, for anion recognition the latter has some advantages over organic molecules as the positive charge on the metal ion results in electrostatic interactions with negatively charged species leading to strong host-guest interactions. By combining electrostatic and H-bonding interactions, it was envisaged that these complexes would be highly effective anion sensors. This work was carried out in collaboration with Dr. Jonathan Kitchen and the preliminary results communicated in a special issue of *Inorganica Chimica Acta*.²²⁰

In the case of complexes **170** and **172** the urea functionality was appended to the *para* position of the extended *bpy* framework, while complexes **171** and **173** were functionalised in the *meta* position. Complexes **170** and **171** have a NO₂ functionality while **172** and **173** contained CF₃ groups. All complexes were analysed as racemates.



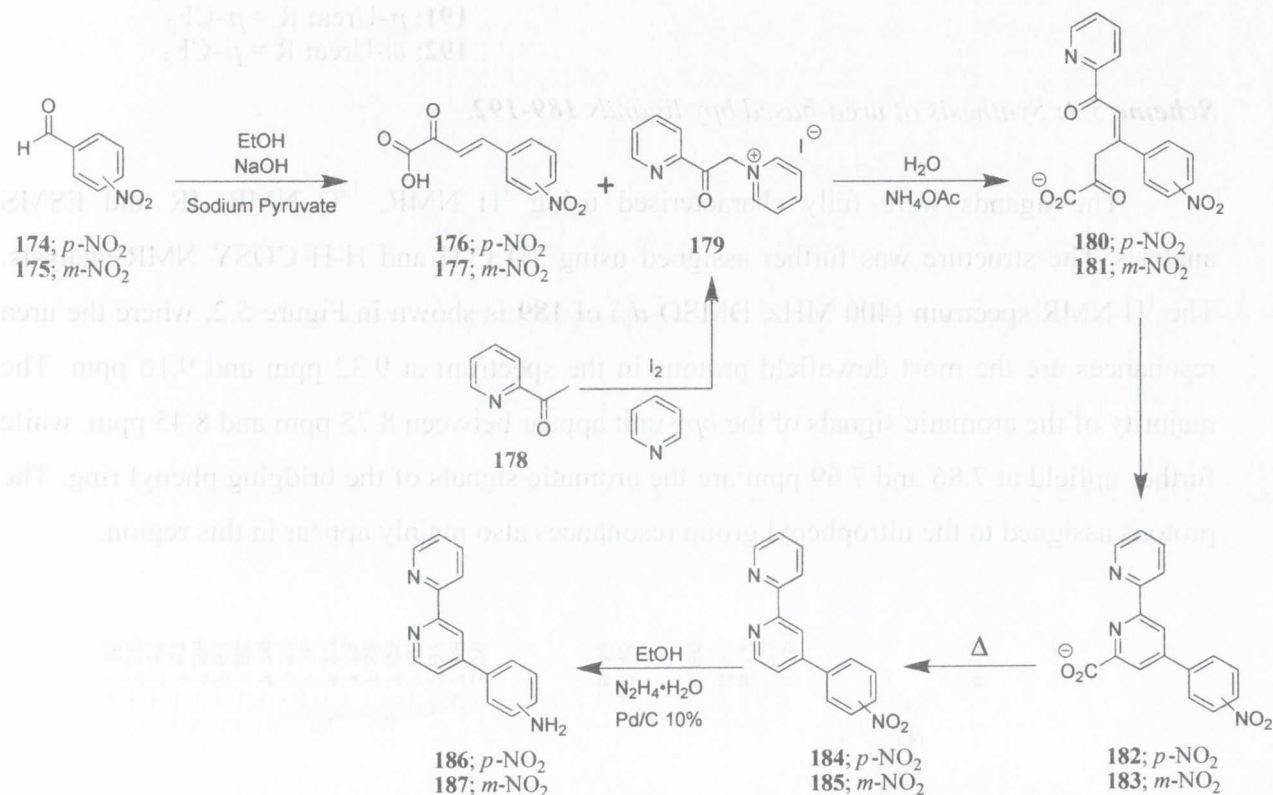
5.3 Synthesis

The target compounds **170-173** were prepared from commercially available starting materials. The same procedure was applied to the synthesis of all analogues and full experimental details are provided in Chapter 7.

5.3.1 Synthesis and Characterisation of Urea-based *Bpy* Ligands 189-192

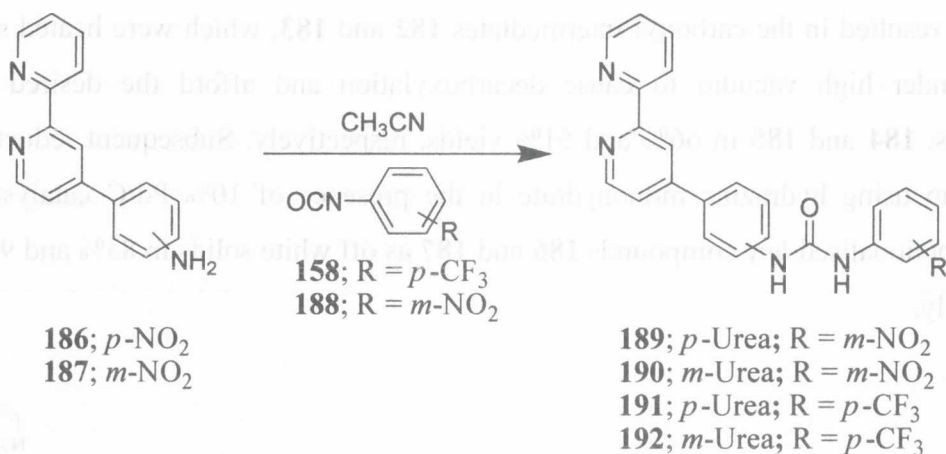
The first step of the synthesis of **170-173** involved the condensation of either **174** or **175** with sodium pyruvate under basic conditions at 0°C, shown in Scheme 5.2. Acidification of the reaction mixture with 0.1 M HCl yielded chalcones **176** and **177** as yellow solids in 66% and 54% yields, respectively. Pyridacyl pyridinium iodide, **179**, was refluxed in water with **176** or **177** to give intermediates **180** and **181**, incorporating the first pyridine moiety. Ammonium acetate, which was also present in the reaction mixture, subsequently reacted at the two carbonyl groups to initiate the second ring closure and installed the second pyridine

ring. This resulted in the carboxyl intermediates **182** and **183**, which were heated strongly ($> 150^{\circ}\text{C}$) under high vacuum to cause decarboxylation and afford the desired nitro *bpy* derivatives, **184** and **185** in 66% and 51% yields, respectively. Subsequent reduction of the nitro group using hydrazine monohydrate in the presence of 10% Pd/C catalyst gave the aniline functionalised *bpy* compounds **186** and **187** as off white solids in 83% and 94% yields, respectively.



Scheme 5.2: Synthesis of aniline functionalised *bpy* derivatives **186** and **187**.

The final stage in the synthesis of the ligands was to react the aniline functionalised *bpy* compounds **186** and **187** with the relevant isocyanate, **158** or **188** to give the urea-based *bpy* ligands **189-192**, Scheme 5.3. This was achieved *via* microwave assisted synthesis in CH₃CN at 100°C for 40 minutes. Following this, a pale solid formed which was isolated by suction filtration affording **189-192** in 70%, 76%, 76% and 81% yields, respectively.



Scheme 5.3: Synthesis of urea-based *bpy* ligands **189-192**.

The ligands were fully characterised using ¹H NMR, ¹³C NMR, IR and ESMS analysis. The structure was further assigned using 2D C-H and H-H COSY NMR analysis. The ¹H NMR spectrum (400 MHz, DMSO-*d*₆) of **189** is shown in Figure 5.2, where the urea resonances are the most downfield protons in the spectrum at 9.32 ppm and 9.16 ppm. The majority of the aromatic signals of the *bpy* unit appear between 8.75 ppm and 8.45 ppm, while further upfield at 7.86 and 7.69 ppm are the aromatic signals of the bridging phenyl ring. The protons assigned to the nitrophenyl group resonances also mainly appear in this region.

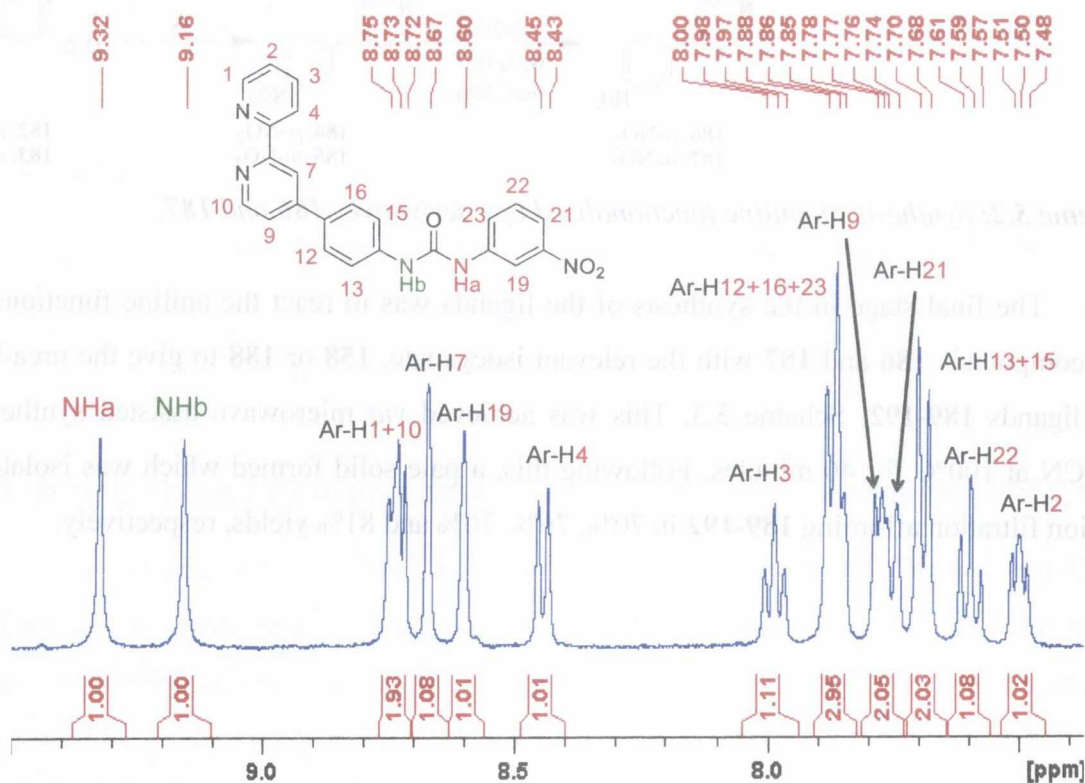


Figure 5.2: ¹H NMR (400 MHz, DMSO-*d*₆) spectrum of **189**.

The ^{13}C NMR spectrum (150 MHz, $\text{DMSO-}d_6$) showed the carbonyl resonance of the urea moiety at 152.3 ppm, while the quaternary carbons of the *bpy* unit appeared at 155.9 ppm and 155.2 ppm. Successful formation of **189** was also confirmed by the presence of the $[\text{M} + \text{H}]^+$ ion at 412.1411 in the ES mass spectrum.

The ^1H NMR spectrum (400 MHz, $\text{DMSO-}d_6$) of **190** showed a similar set of signals (Appendix, Figure A5.1) to that of **189**. The urea protons resonated at 9.33 ppm and 9.14 ppm, while the *bpy* protons mainly appeared at 8.79 ppm and 8.46 ppm. The expected m/z peak at 412.1410, corresponding to the $[\text{M} + \text{H}]^+$ ion, was present in the ES mass spectrum.

In the case of ligand **191**, the slightly less electron withdrawing CF_3 group resulted in the urea protons appearing at 9.17 ppm and 9.07 ppm in the ^1H NMR spectrum (600 MHz, $\text{DMSO-}d_6$), Figure 5.3. The signals corresponding to the *bpy* unit appeared between 8.74 ppm and 7.98 ppm, while the aromatic protons associated with the CF_3 phenyl ring all resonated between 7.71 ppm and 7.66 ppm. The ^{13}C NMR spectrum (150 MHz, $\text{DMSO-}d_6$) of **191** showed the quaternary carbons associated with the *bpy* component at 155.8 ppm and 155.2 ppm, while the carbonyl group of the urea moiety appeared at 152.1 ppm.

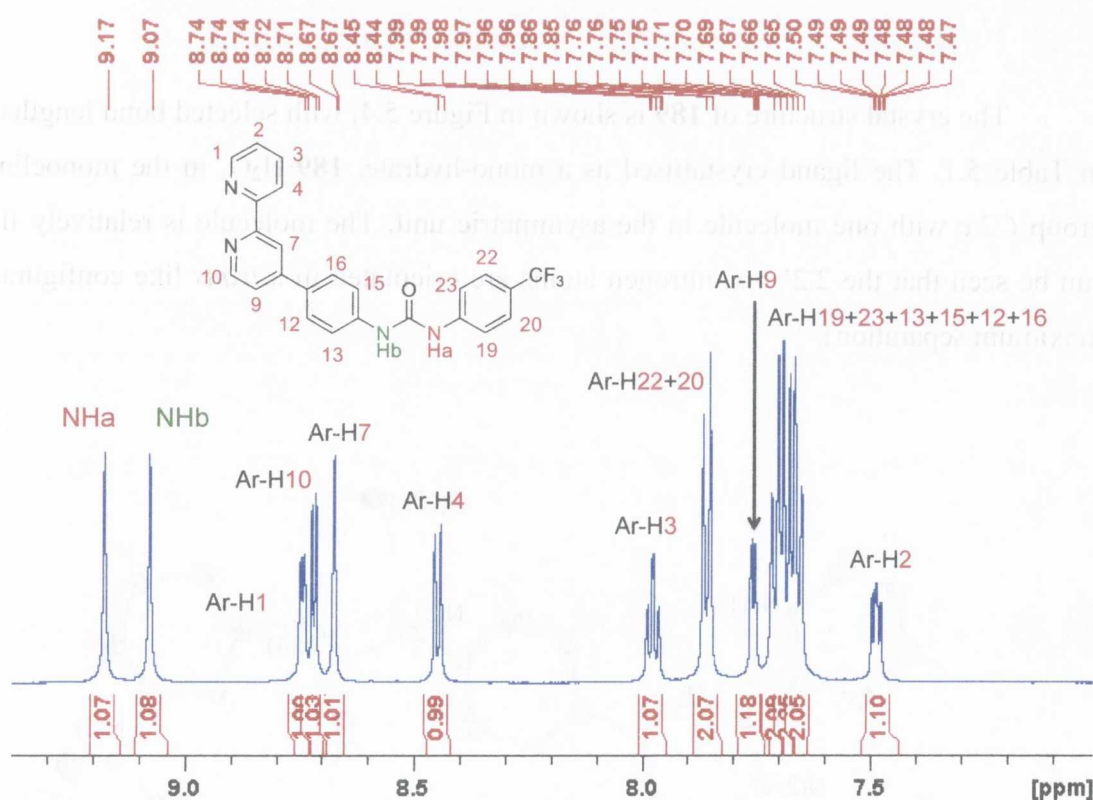


Figure 5.3: ^1H NMR (600 MHz, $\text{DMSO-}d_6$) spectrum of **191**.

The carbon of the CF_3 group resonated at 124.5 ppm, which could also be detected in the ^{19}F spectrum with a signal at -60.57 ppm. ESMS showed the presence of a single peak at 435.1442 corresponding to the $[\text{M} + \text{H}]^+$ species of **191**.

The ^1H NMR spectrum (600 MHz, $\text{DMSO-}d_6$) of ligand **192** was also very similar to that seen for the previous ligands (Appendix, Figure A5.2). The urea protons resonated at 9.17 ppm and 9.07 ppm. The ^{19}F spectrum showed the presence of a single resonance at -60.55 ppm. Successful formation of this compound was also evident from accurate mass spectrometry, where **192** displayed a peak at 435.1435, corresponding to $[\text{M} + \text{H}]^+$ ion.

The molecular structures of **189**, **191** and **192** were further established by X-ray crystallography. Poor quality pale yellow irregular plates of **189**· H_2O , thin colourless plate-like crystals of **191**· H_2O and colourless rod shaped crystals of **192** were grown from slow evaporation of EtOH and the low temperature (108 K) X-ray structure was determined by Dr. Jonathan Kitchen, School of Chemistry TCD. Details of the analyses of **189** and **192** will be discussed in the following section, while the structure and associated data of **191** can be found in the Appendix (Appendix, Figure A5.4).

5.3.2 Crystal Structure Analysis of Ligands **189** and **192**

The crystal structure of **189** is shown in Figure 5.4, with selected bond lengths detailed in Table 5.1. The ligand crystallised as a mono-hydrate, **189**· H_2O , in the monoclinic space group $C2/c$ with one molecule in the asymmetric unit. The molecule is relatively flat and it can be seen that the 2,2'-*bpy* nitrogen atoms are orientated in a *trans* like configuration (*i.e.* maximum separation).

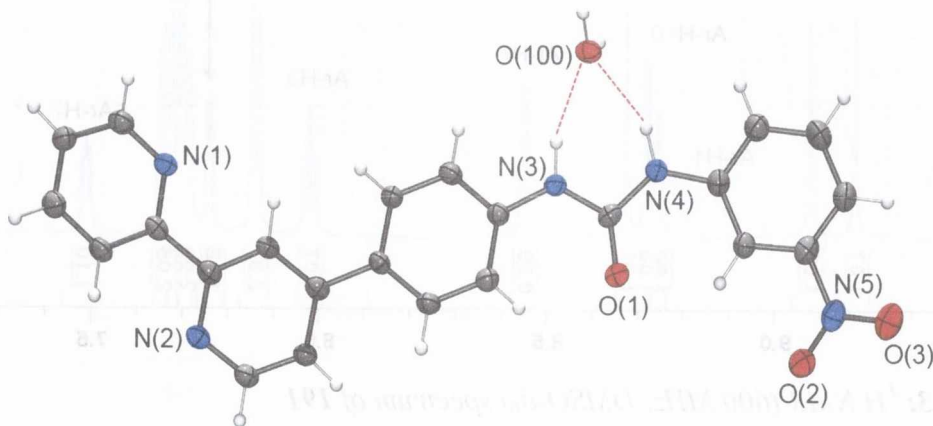


Figure 5.4: The X-ray crystal structure of ligand **189**· H_2O .

Packing interactions in $189 \cdot \text{H}_2\text{O}$, shown in Figure 5.5, involve the urea nitrogen atoms acting as H-bond donors to the interstitial water molecule. In addition, the water molecule is H-bonded to the pyridyl nitrogen atoms on two symmetry generated adjacent molecules. Selected bond lengths are detailed in Table 5.1.

Table 5.1: Selected bond lengths for 189.

Selected Bond Lengths (Å)	
N3 – C17	1.387
C17 – O1	1.240
C17 – N4	1.402
N5 – O2	1.248
N5 – O3	1.258

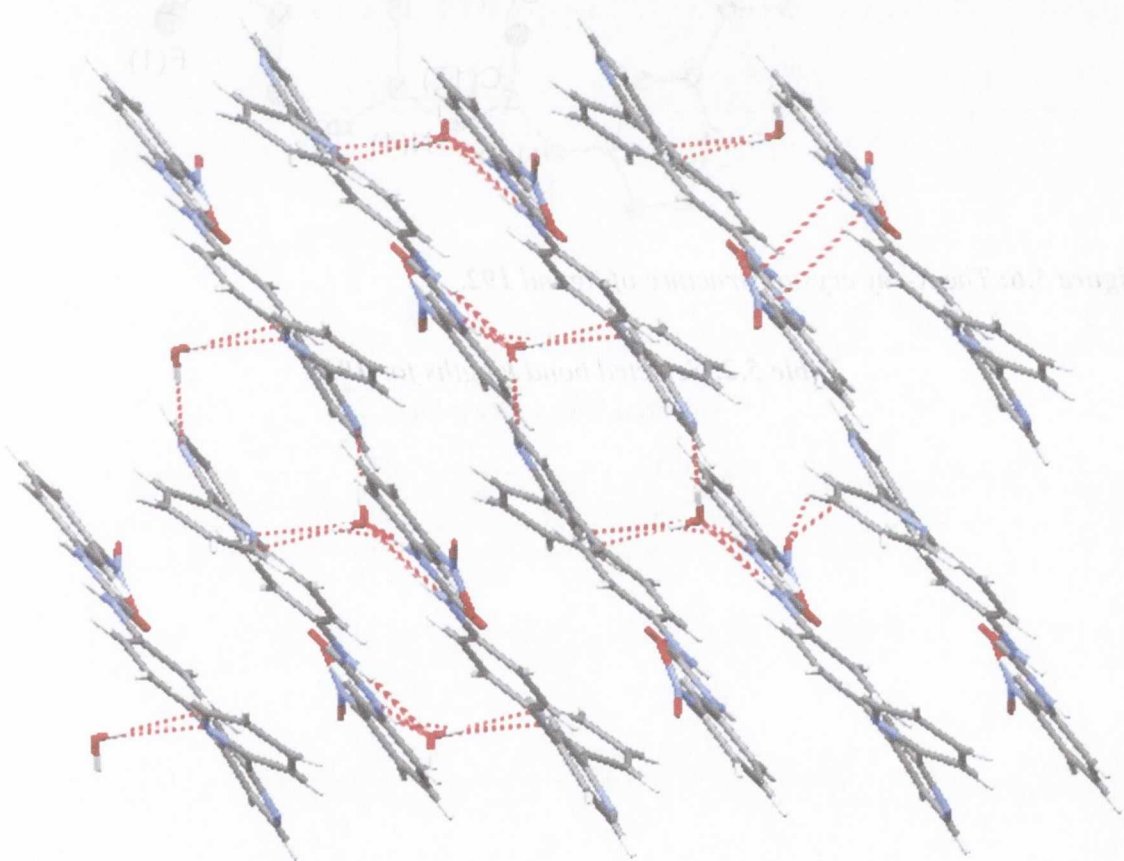


Figure 5.5: Packing diagram in $189 \cdot \text{H}_2\text{O}$ viewed down the crystallographic b -axis. The dashed red line denotes H-bonding interactions.

The crystal structure of ligand **192** is shown in Figure 5.6 and similarly to **189**·H₂O revealed a relatively planar molecule. In contrast to the structure of **189**·H₂O (and **191**, Appendix Figure A5.4) was the configuration of the *bpy* nitrogen atoms. In **192** they are orientated in a *cis* like arrangement, which results in quite different packing interactions. The urea protons are in the *syn* conformation, ideal for H-bonding. Selected bond lengths are presented in Table 5.2. Packing interactions for this ligand are governed by both hydrogen bonding and π - π stacking interactions, shown in Figure 5.7, and interestingly the urea protons are H-bonding to the neighbouring 2,2'-*bpy* nitrogen atoms. This results in a H-bonded 'crisscross' type network rather than the sheet-like configuration of **189**·H₂O.

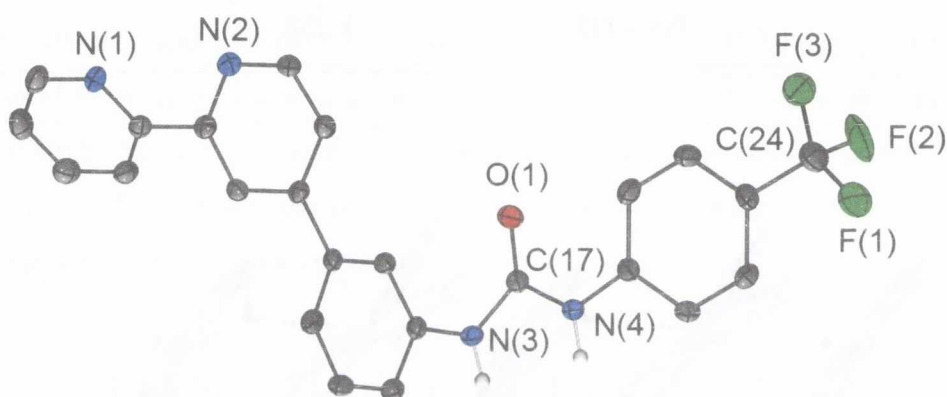


Figure 5.6: The X-ray crystal structure of ligand **192**.

Table 5.2: Selected bond lengths for **192**.

Selected Bond Lengths (Å)	
N3 – C17	1.381
C17 – O1	1.220
C17 – N4	1.376
C24 – F1	1.324
C24 – F2	1.365
C24 – F3	1.333

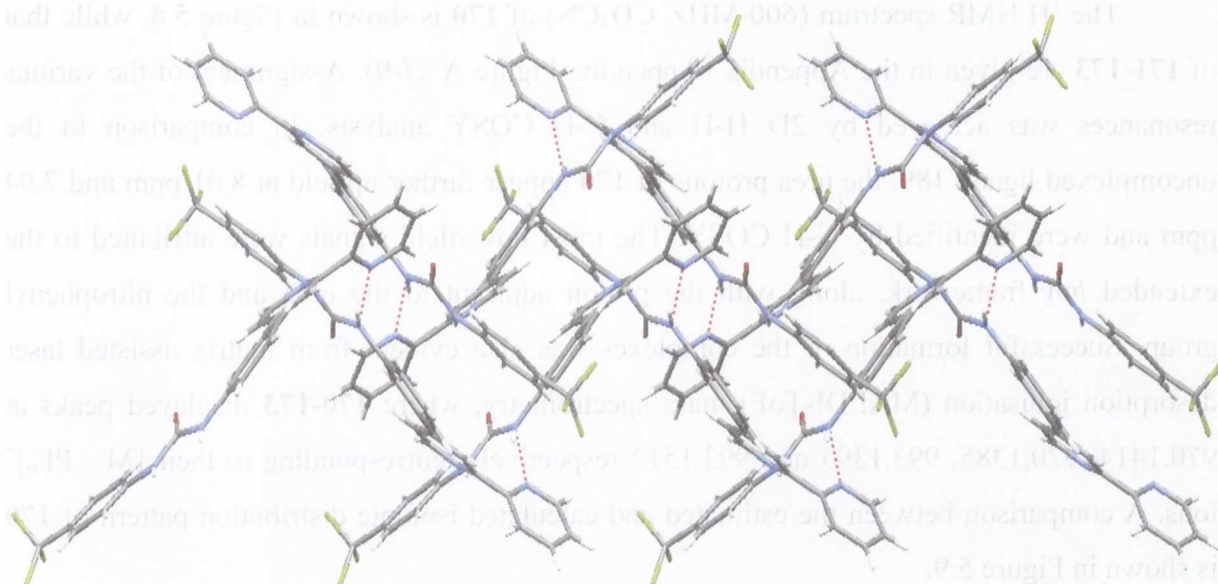
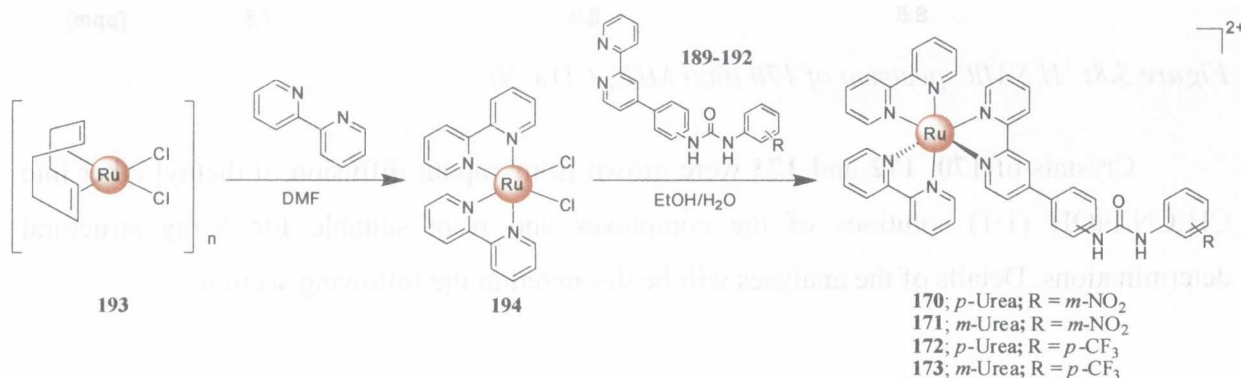


Figure 5.7: Packing diagram in **192** viewed down the crystallographic *b*-axis.

5.3.3 Complexation

The microwave-assisted synthesis of *cis-bis*-(bpy)Ru(II), **194**, was achieved by reaction with Ru(cod)Cl₂, **193**, in DMF, Scheme 5.4. Ligands **189-192** were subsequently complexed with the *cis-bis*-(bpy)Ru(II) precursor **194** in a 1:1 solvent mixture of EtOH and H₂O at 120°C for 45 minutes. The resulting red/orange solution was added to an aqueous solution of excess ammonium hexafluorophosphate yielding a bright orange precipitate, which was collected by suction filtration. The complexes were purified by flash column chromatography on silica (eluting with 40:4:1 CH₃CN:H₂O:NaNO₃(sat. aq.)) to give **170-173** in 20%, 27%, 29% and 21% yields respectively. Subsequent precipitation of the tris complexes as their PF₆ salts was achieved by addition of a concentrated ethanolic solution of NH₄PF₆. These novel complexes were characterised by ¹H NMR, ¹³C NMR, IR spectroscopy, HRMS, elemental analysis and, where possible, by single crystal X-ray crystallography.



Scheme 5.4: Complexation of **189-192** with *cis-bis*-(bpy)Ru(II) **194**.

The ^1H NMR spectrum (600 MHz, CD_3CN) of **170** is shown in Figure 5.8, while that of **171-173** are given in the Appendix (Appendix, Figure A5.7-9). Assignment of the various resonances was achieved by 2D H-H and C-H COSY analysis. In comparison to the uncomplexed ligand **189**, the urea protons of **170** appear further upfield at 8.01 ppm and 7.94 ppm and were identified by N-H COSY. The most downfield signals were attributed to the extended *bpy* framework; along with the proton adjacent to the urea and the nitrophenyl group. Successful formation of the complexes was also evident from matrix assisted laser desorption ionisation (MALDI-ToF) mass spectrometry, where **170-173** displayed peaks at 970.1414, 970.1385, 993.1393 and 993.1512 respectively, corresponding to their $[\text{M} - \text{PF}_6]^+$ ions. A comparison between the estimated and calculated isotopic distribution pattern of **170** is shown in Figure 5.9.

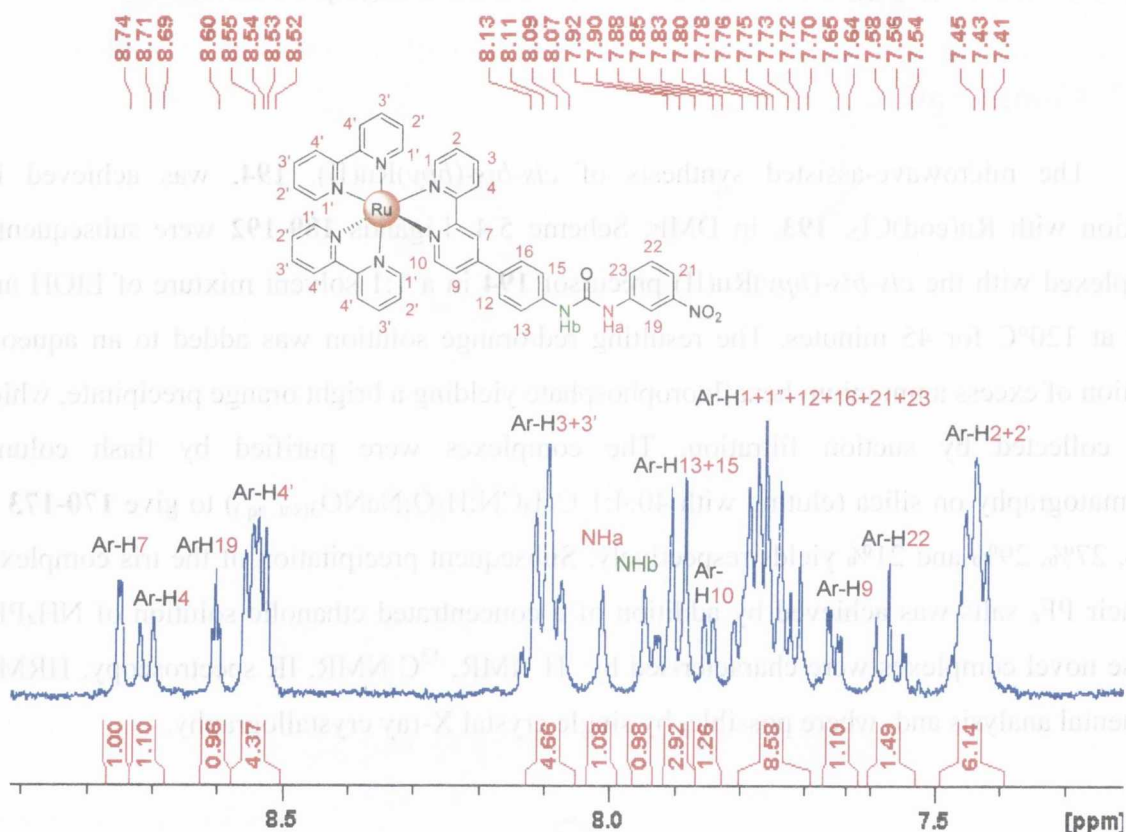


Figure 5.8: ^1H NMR spectrum of **170** (600 MHz, CD_3CN).

Crystals of **170**, **172** and **173** were grown from vapour diffusion of diethyl ether into $\text{CH}_3\text{CN}/\text{EtOH}$ (1:1) solutions of the complexes and were suitable for X-ray structural determinations. Details of the analyses will be discussed in the following section.

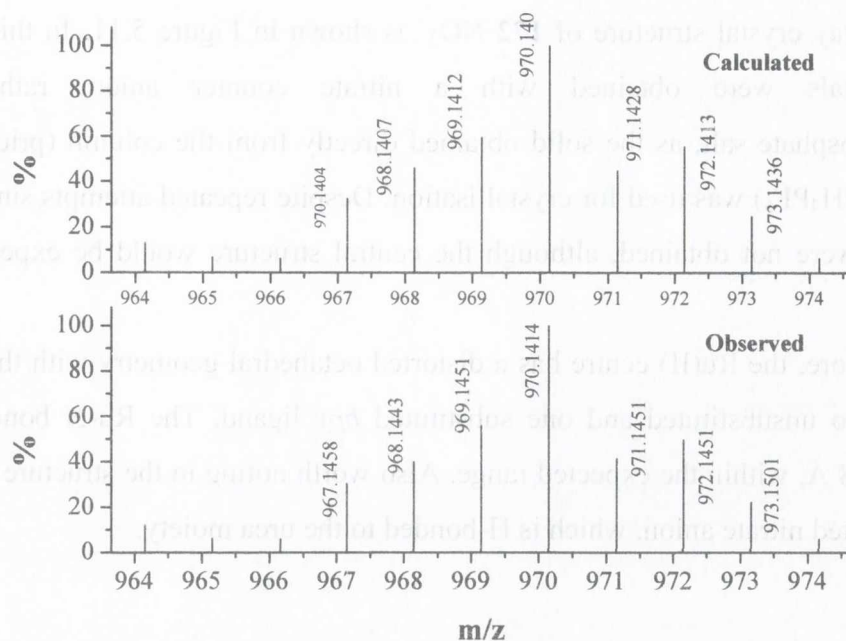


Figure 5.9: The calculated (top) and observed (bottom) isotopic distribution pattern (MALDI-ToF MS) for $[170 + \text{PF}_6]^+$.

5.3.4 Crystal Structure Analysis of Complexes 170, 172 and 173

Small, poor quality, red rod shaped crystals of complex **170** were obtained from slow diffusion of ether into a solution of MeCN and the low temperature (108 K) crystal structure determined, shown in Figure 5.10. Unfortunately the data set was only of sufficient quality to allow the connectivity to be established and as a result packing, *etc* will not be discussed.

The metal centre is six-coordinate, bonding to six nitrogen atoms ($1.999\text{--}2.084 \text{ \AA} \pm 0.001 \text{ \AA}$) from three bidentate ligands. There is no difference in the bond distances to the two types of *bpy* ligand and the coordination geometry is distorted octahedral. The Ru-N distances are in the expected range for complexes of this type.

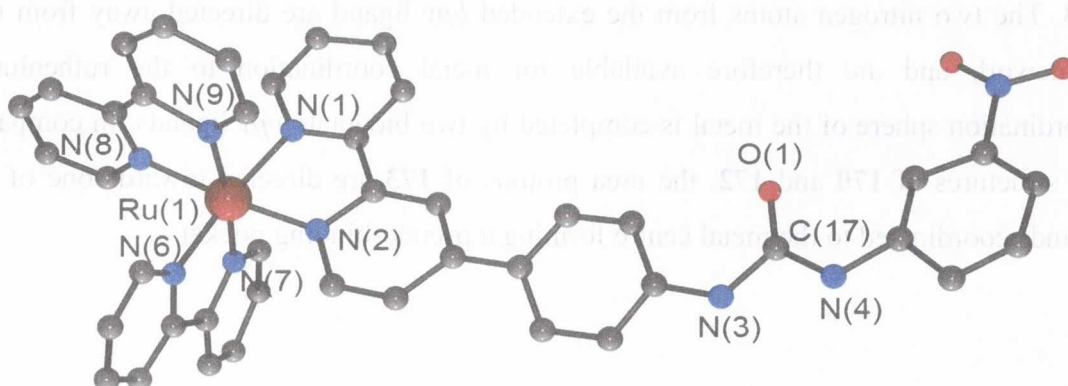


Figure 5.10: The X-ray crystal structure of **170** from ether and MeCN.

The X-ray crystal structure of **172**·NO₃[−] is shown in Figure 5.11. In this case red rod shaped crystals were obtained with a nitrate counter anion, rather than the hexafluorophosphate salt, as the solid obtained directly from the column (prior to treatment with excess NH₄PF₆) was used for crystallisation. Despite repeated attempts single crystals of the PF₆ salt were not obtained, although the central structure would be expected to be the same.

Once more, the Ru(II) centre has a distorted octahedral geometry with the metal centre bonded to two unsubstituted and one substituted *bpy* ligand. The Ru-N bonds range from 2.052 to 2.068 Å, within the expected range. Also worth noting in the structure is the position of the associated nitrate anion, which is H-bonded to the urea moiety.

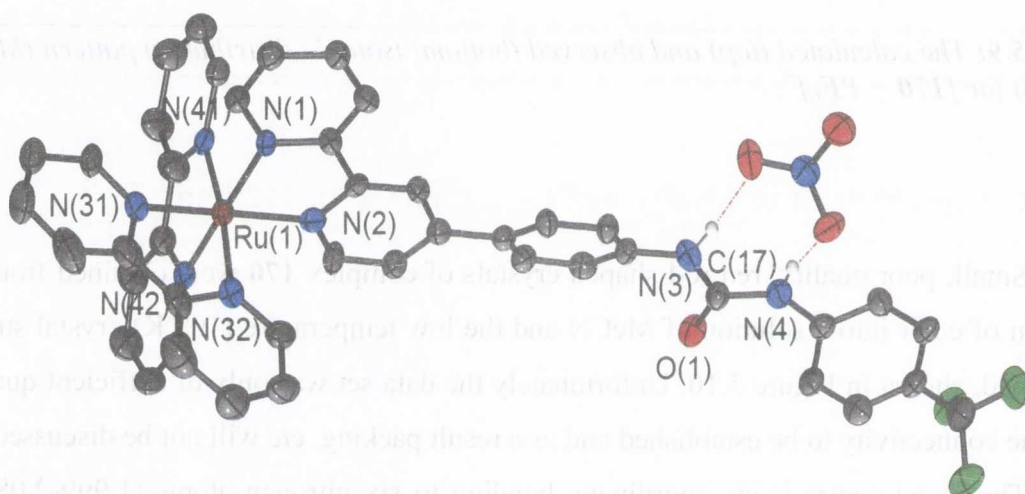


Figure 5.11: The X-ray crystal structure of **172** obtained from CH₃CN:H₂O:NaNO₃(sat. aq.) after silica column.

The crystal structure of **173** contains a [Ru(II)-(bpy)₂**192**]²⁺ cation shown in Figure 5.12; and was again obtained from slow diffusion of ether into a solution of MeCN containing **173**. The two nitrogen atoms from the extended *bpy* ligand are directed away from the urea framework and are therefore available for metal coordination to the ruthenium. The coordination sphere of the metal is completed by two bidentate *bpy* ligands. In comparison to the structures of **170** and **172**, the urea protons of **173** are directed towards one of the *bpy* ligands coordinated to the metal centre forming a pseudo-binding pocket.

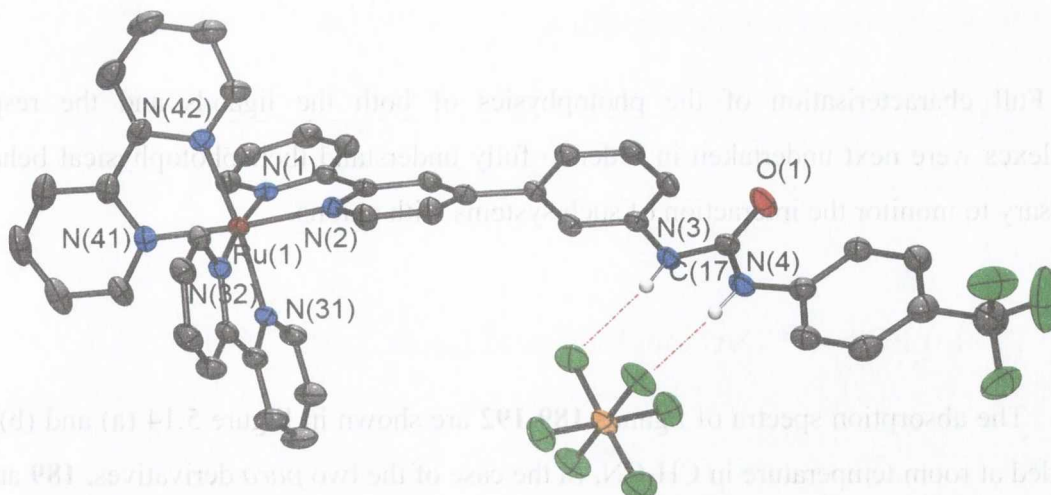


Figure 5.12: The X-ray crystal structure of **173**.

The packing of complex **173** is shown in Figure 5.13, and it can be seen that it packs in a dimeric manner. Weak π - π stacking interactions occur between the bridging phenyl rings of the extended *bpy* frameworks of the complexes with a centroid $\cdots$ centroid distance of 3.832 Å calculated for the interaction. An important feature to note is the H-bonding interactions of both the urea moiety and the *bpy* protons to the PF_6^- counteranion, again highlighting the ability of the H-bond donor group incorporated into the Ru(II) receptor. The carbonyl group of the urea functionality also shows H-bonding interactions to adjacent *bpy* protons.

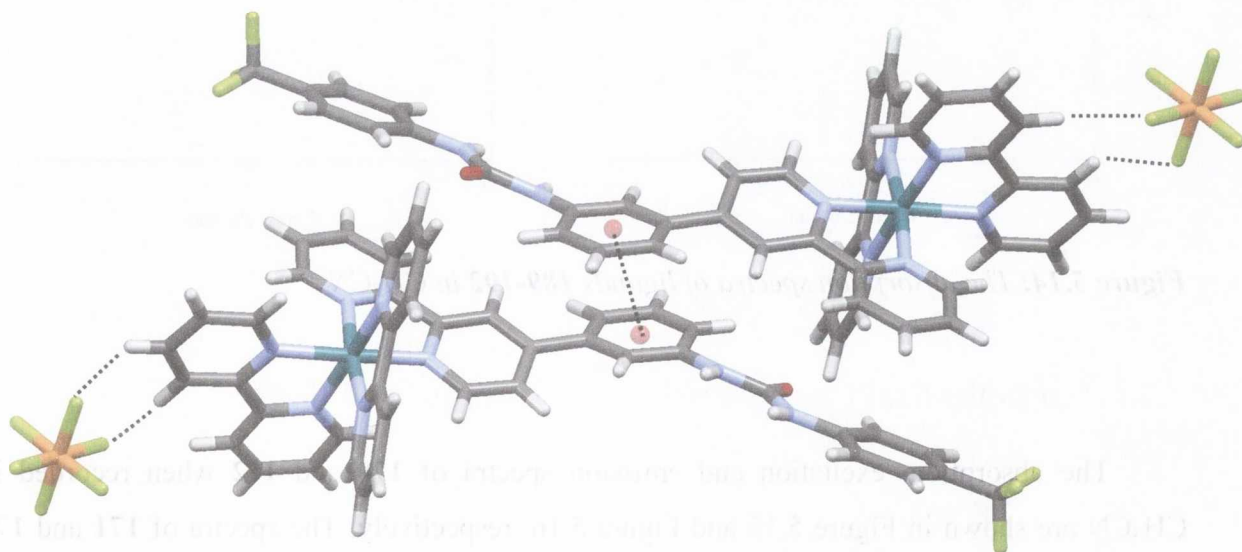


Figure 5.13: Packing interactions in **173**.

5.4 Photophysical Characterisation

Full characterisation of the photophysics of both the ligands and the respective complexes were next undertaken in order to fully understand their photophysical behaviour; necessary to monitor the interaction of such systems with anions.

5.4.1 Photophysical Characterisation of Ligands 189-192

The absorption spectra of ligands **189-192** are shown in Figure 5.14 (a) and (b), when recorded at room temperature in CH₃CN. In the case of the two *para* derivatives, **189** and **191**, both ligands displayed a similar characteristic absorption band centred at *ca.* 288 nm, while *meta* derivatives **190** and **192** show absorption maxima centred at 250 nm and 263 nm, respectively. A shoulder was also observed at *ca.* 243 nm for **189** and at *ca.* 260 nm for **191**. Upon excitation at the λ_{max} the ligands only gave rise to weak fluorescence emission.

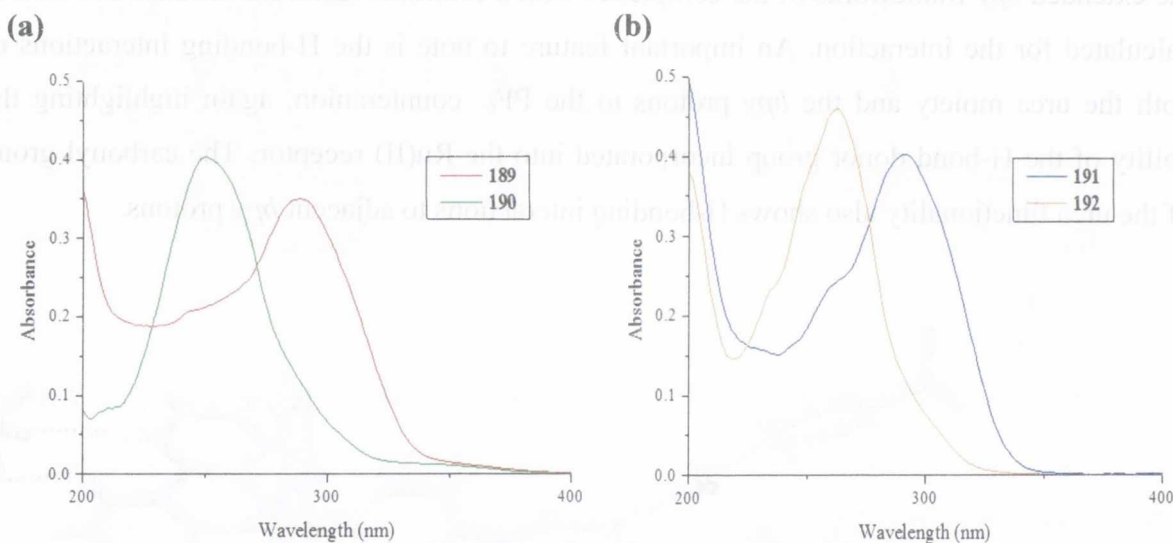


Figure 5.14: The absorption spectra of ligands **189-192** in CH₃CN.

5.4.2 Photophysical Characterisation of Complexes 170-173

The absorption, excitation and emission spectra of **170** and **172** when recorded in CH₃CN are shown in Figure 5.15 and Figure 5.16, respectively. The spectra of **171** and **173** are given in the Appendix (Appendix, Figure A5.12 (a) and (b), respectively).

The UV-Vis absorption spectrum of both **170** and **172** in CH₃CN gave rise to a broad MLCT band centred at *ca.* 450 nm and three bands at shorter wavelengths of 245 nm, 288 nm and 334 nm, respectively. The band at 288 nm was characteristic of π - π^* intra-ligand transitions of the ancillary *bpy* ligands. A summary of the absorption properties of **170-173** as

well as their respective molar absorptivities is given in Table 5.3. The fluorescence emission spectrum of **170** and **172** showed a broad emission band at 615 nm upon excitation into the MLCT absorption band at 450 nm, while the fluorescence emission spectrum of both complexes ($\lambda_{\text{em}} = 615 \text{ nm}$) structurally matched that of their respective absorption spectra.

Table 5.3: Absorption properties of **170-173** in CH_3CN .

Complex	λ_{max} (nm) [ϵ ($\text{M}^{-1} \text{cm}^{-1}$)] in CH_3CN	
	π - π^* (IL)	MLCT
170	288 [86000]	450 [16300]
171	288 [84200]	450 [16100]
172	288 [92100]	450 [20100]
173	288 [129000]	450 [16600]

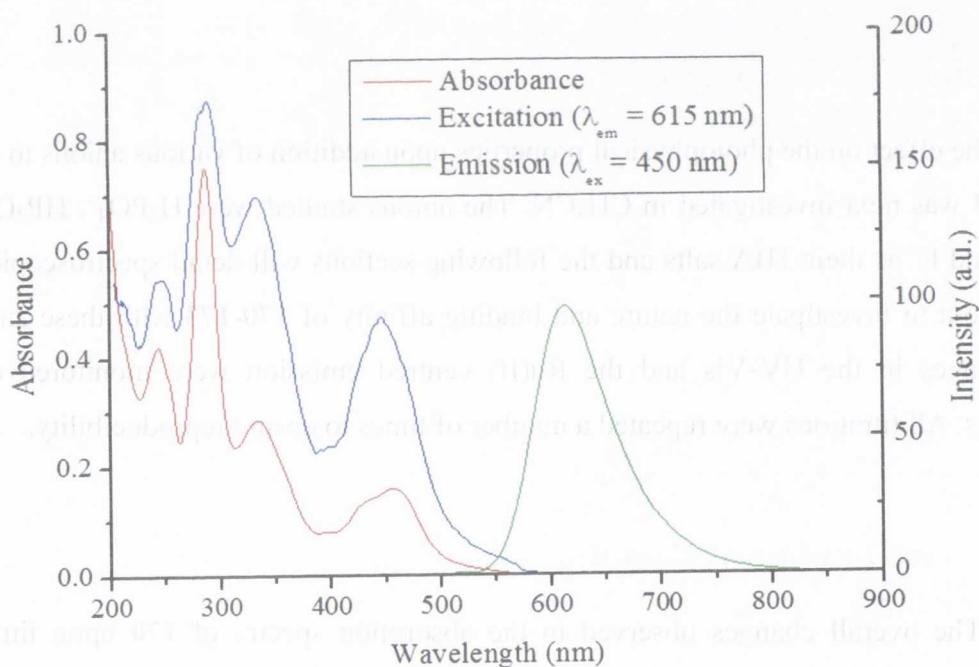


Figure 5.15: The UV-Vis, excitation and emission spectra of **170** in CH_3CN .

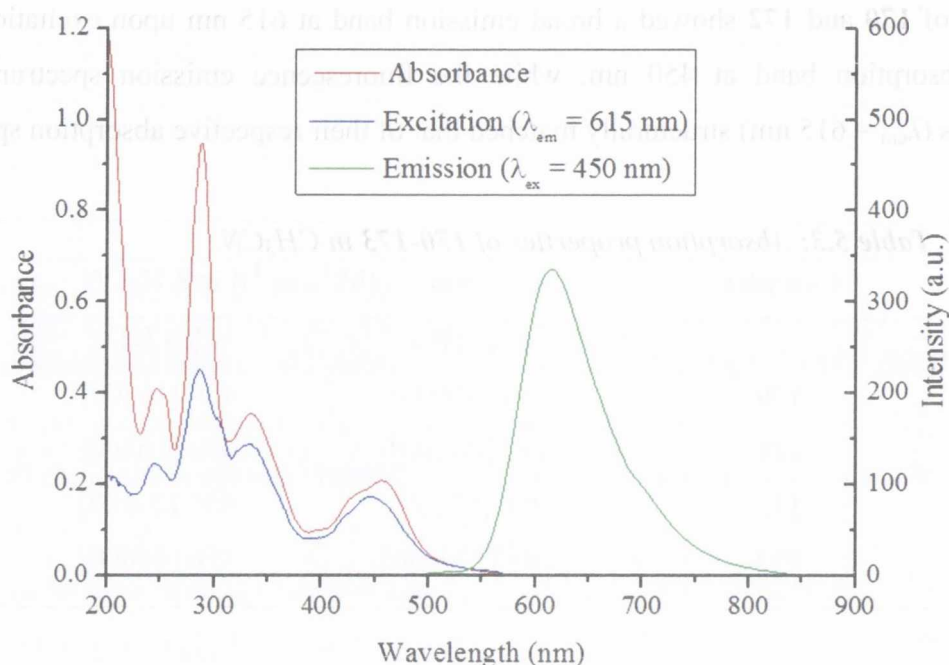


Figure 5.16: The UV-Vis, excitation and emission spectra of **172** in CH_3CN .

5.5 Anion Binding Studies

The effect on the photophysical properties upon addition of various anions to complexes **170-173** was next investigated in CH_3CN . The anions studied were H_2PO_4^- , $\text{HP}_2\text{O}_7^{3-}$, AcO^- , SO_4^{2-} and F^- as their TBA salts and the following sections will detail spectroscopic titrations carried out to investigate the nature and binding affinity of **170-173** with these anions. Both the changes in the UV-Vis and the Ru(II) centred emission were monitored during the titrations. All titrations were repeated a number of times to ensure reproducibility.

5.5.1 Anion Binding of Complex 170

The overall changes observed in the absorption spectra of **170** upon titration with AcO^- are shown in Figure 5.17 (a) and show a slight decrease in all absorption bands with a significant red shift of *ca.* 22 nm for the 334 nm transition. Only a slight decrease in the MLCT band at 450 nm was observed with no noticeable shift in the λ_{max} . The changes in the excited state character of **170** are shown in Figure 5.17 (b) and it can be seen that the binding of AcO^- gave rise to moderate changes in the emission spectrum of **170** with a 34% decrease in emission intensity of the MLCT band at 615 nm. The spectroscopic changes observed for this titration were consistent with association of complex **170** with the anion.

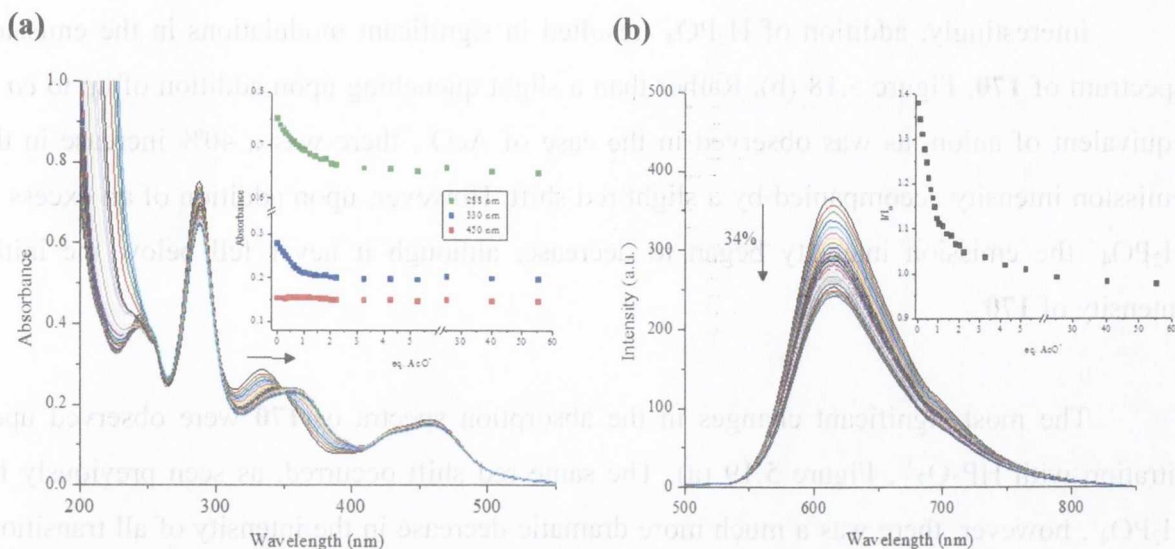


Figure 5.17: The changes observed in the (a) absorption and (b) emission spectra of **170** in CH₃CN upon titration with AcO⁻. Inset (a) The changes in the absorbance at 288 nm, 330 nm and 450 nm (b) relative changes in the emission intensity of **170** as a function of equivalents of AcO⁻.

The titration of **170** with H₂PO₄⁻ displayed larger modulations to the absorption spectrum than that seen for AcO⁻, with all the transitions red shifted to a greater extent, Figure 5.18 (a). A decrease in the band at *ca.* 288 nm with a concomitant bathochromic shift in the transition at 334 nm was observed. Formation of two isosbestic points at *ca.* 355 nm and 412 nm can also be seen. The appearance of two simultaneous isosbestic points signifies the presence of two different absorbing species that exist in equilibrium.²²¹ The MLCT band also experienced a slight hypochroism of 17% with a minor red shift of 4 nm.

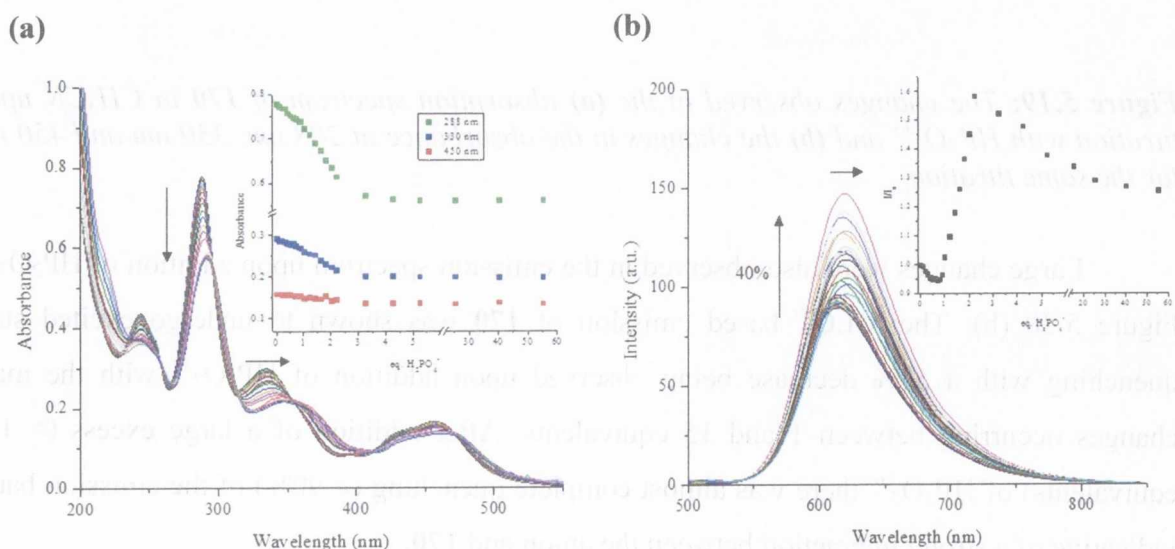


Figure 5.18: The changes observed in the (a) absorption and (b) emission spectra of **170** in CH₃CN upon titration with H₂PO₄⁻. Inset (a) The changes in the absorbance at 288 nm, 330 nm and 450 nm (b) relative changes in the emission intensity of **170** as a function of equivalents of H₂PO₄⁻.

Interestingly, addition of H_2PO_4^- resulted in significant modulations in the emission spectrum of **170**, Figure 5.18 (b). Rather than a slight quenching upon addition of up to *ca.* 1 equivalent of anion, as was observed in the case of AcO^- , there was a 40% increase in the emission intensity accompanied by a slight red shift. However, upon addition of an excess of H_2PO_4^- the emission intensity began to decrease, although it never fell below the initial intensity of **170**.

The most significant changes in the absorption spectra of **170** were observed upon titration with $\text{HP}_2\text{O}_7^{3-}$, Figure 5.19 (a). The same red shift occurred, as seen previously for H_2PO_4^- , however, there was a much more dramatic decrease in the intensity of all transitions upon addition of excess $\text{HP}_2\text{O}_7^{3-}$. The band centred at *ca.* 334 nm experienced a bathochromic shift of *ca.* 33 nm while the MLCT transition was red shifted by *ca.* 13 nm.

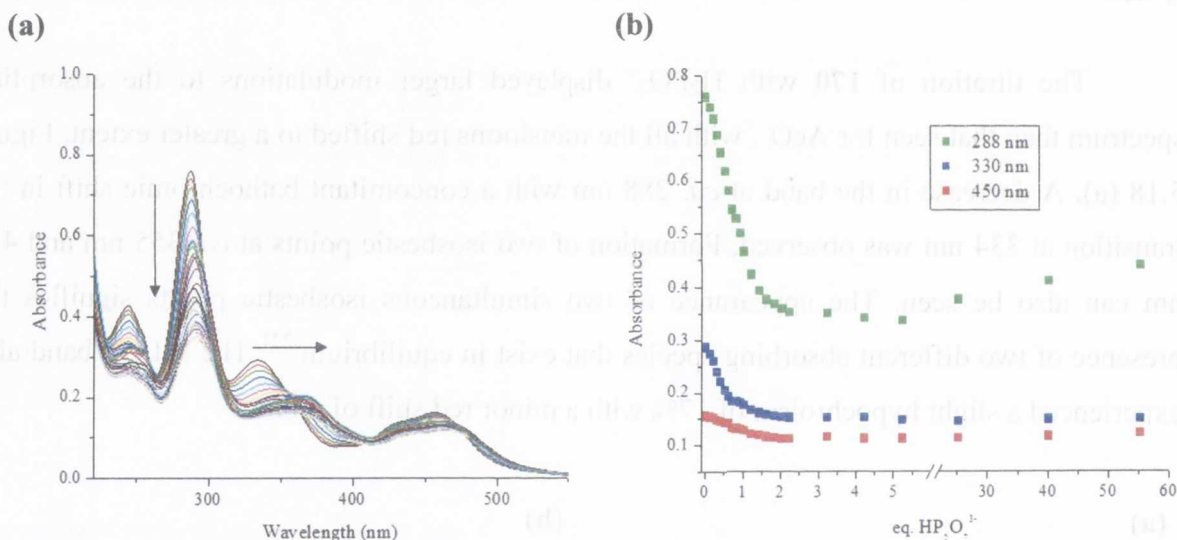


Figure 5.19: The changes observed in the (a) absorption spectrum of **170** in CH_3CN upon titration with $\text{HP}_2\text{O}_7^{3-}$ and (b) the changes in the absorbance at 288 nm, 330 nm and 450 nm for the same titration.

Large changes were also observed in the emission spectrum upon addition of $\text{HP}_2\text{O}_7^{3-}$, Figure 5.20 (b). The MLCT based emission of **170** was shown to undergo excited state quenching with a 53% decrease being observed upon addition of $\text{HP}_2\text{O}_7^{3-}$ with the main changes occurring between 1 and 15 equivalents. After addition of a large excess (> 100 equivalents) of $\text{HP}_2\text{O}_7^{3-}$ there was almost complete quenching ($> 90\%$) of the emission band, indicative of a strong interaction between the anion and **170**.

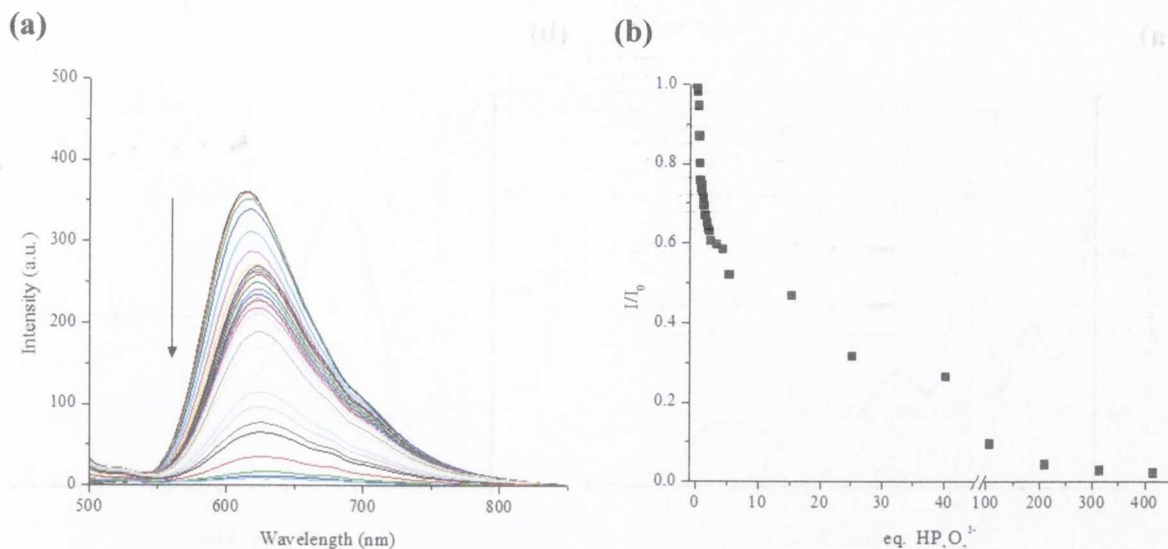


Figure 5.20: The changes observed in the (a) emission spectra of **170** in CH_3CN upon titration with $\text{HP}_2\text{O}_7^{3-}$ and (b) relative changes in the emission intensity of **170** as a function of equivalents of $\text{HP}_2\text{O}_7^{3-}$.

Titration of **170** with SO_4^{2-} were also carried out, however precipitation of the complex unfortunately occurred in the early stages of the titration and we were unable to obtain any reliable results or data suitable for fitting (Appendix, Figure A5.13). This process is most likely an anion exchange phenomenon.

The final anion to be investigated was F^- and some very surprising results were obtained as no change in either the absorption or the emission spectra occurred, Figure 5.21, even upon addition of up to *ca.* 400 equivalents of anion, despite the fact that this anion can function as a base and deprotonate the urea receptor in CH_3CN , as seen previously in this Thesis. This result was quite unexpected, and in contrast to many other anion sensors developed in which F^- often results in dramatic changes to the absorbance or emission spectra through deprotonation of N-H protons and subsequent modulation in the various photophysical properties of the sensors.

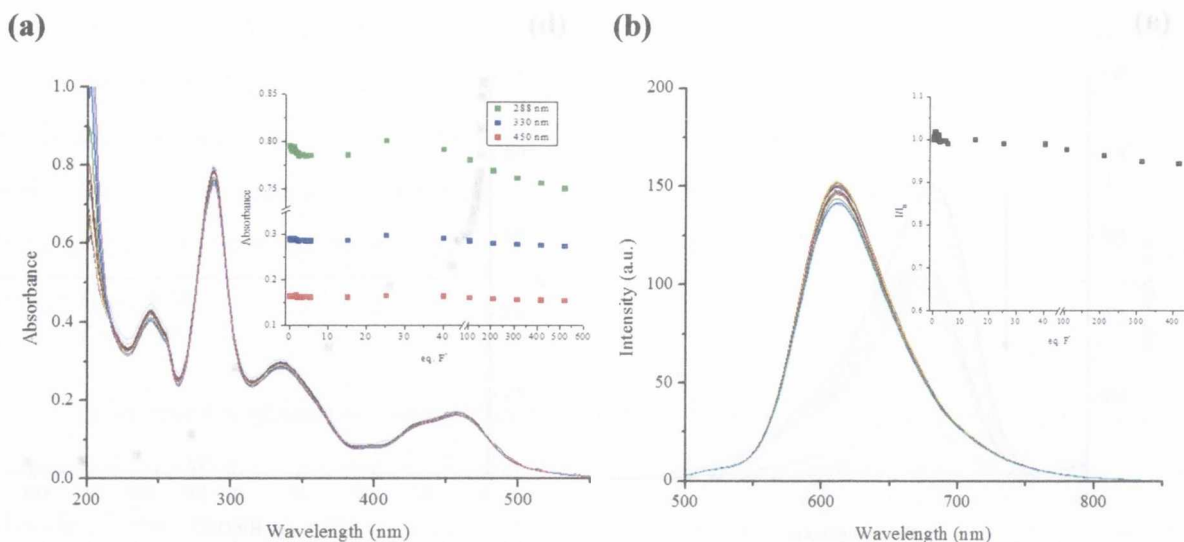


Figure 5.21: The changes observed in the (a) absorption and (b) emission spectra of **170** in CH_3CN upon titration with F^- . Inset (a) The changes in the absorbance at 288 nm, 330 nm and 450 nm (b) relative changes in the emission intensity of **170** as a function of equivalents of F^- .

In order to gain information on the host:guest stoichiometries of **170** with the various anions, the changes in both the absorbance and fluorescence spectra were fit using the non linear regression analysis program SPECFITTM. Table 5.4 summarises the binding constants obtained.

Table 5.4: Binding constants and binding modes between anions and **170**.

Complex (H)	Anion (G)	Binding Mode $G_n:H_m$	Absorption		Fluorescence	
			$\log K_{n:m}$	Std.	$\log K_{n:m}$	Std.
				Deviation ($\pm$)		Deviation ($\pm$)
170	AcO^-	1:1	7.72	0.26	6.86	0.19
		2:1	6.06	0.63	4.41	0.51
		3:1	2.16	0.78	2.65	0.99
	H_2PO_4^-	1:1	6.55	0.20	6.85	0.12
		2:1	5.48	0.37	5.85	0.24
		3:1	4.18	0.41	4.14	0.35
	$\text{HP}_2\text{O}_7^{3-}$	1:1	5.63	0.09	6.52	0.19
		2:1	3.12	0.18	3.48	0.39
	SO_4^{2-}		-*		-*	
	F^-		-*		-*	

*Data unsuitable for non-linear regression analysis.

Analysis of the results shows that **170** demonstrated a high affinity for AcO^- , with a binding constant of $\log K_{1:1} = 7.72 (\pm 0.26)$ determined for the 1:1 species. Higher order stoichiometries with $\log K_{2:1} = 6.06 (\pm 0.63)$ and $\log K_{3:1} = 2.16 (\pm 0.78)$ were also observed. From Figure 5.22 (a), it can be seen that an excellent fit of the data was obtained. This clearly demonstrates the role of the ruthenium Lewis acid centre in **170**, which makes the urea moiety a very effective H-bond donor. Analogous fitting of the emission changes gave similar binding constants to that of the absorbance data. The origin of this binding we attribute to the interaction of the anion with the urea moiety, which takes place through H-bonding. Indeed, analysis of the binding event, by constructing a speciation distribution diagram demonstrated that within the addition of one equivalent of the anion *ca.* 90% of the sensor was complexed to the anion, Figure 5.22 (b).

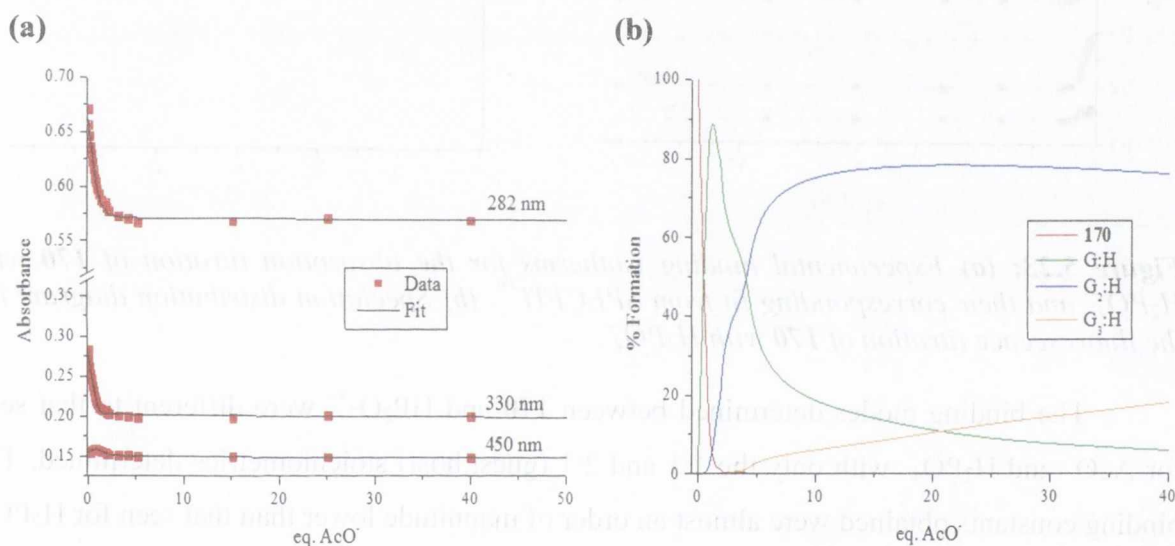


Figure 5.22: (a) Experimental binding isotherms for the absorption titration of **170** with AcO^- and their corresponding fit from SPECFIT™. (b) Speciation distribution diagram for the fluorescence titration of **170** with AcO^- .

In competition to this binding, however, was the 2:1 species, which can either be due to a weaker interaction with the urea moiety, or more likely, through electrostatic interactions with the metal complex itself. This latter phenomenon is more likely, as at higher anion concentrations the 3:1 stoichiometry becomes the dominant one; a species most likely to be that of electrostatic interactions and charge balancing.

In the case of H_2PO_4^- the changes were also best fit to 1:1, 2:1 and 3:1 binding stoichiometries, with $\log K_{1:1} = 6.55 (\pm 0.20)$, $\log K_{2:1} = 5.48 (\pm 0.37)$ and $\log K_{3:1} = 4.18 (\pm 0.41)$ being determined with an excellent fit obtained from SPECFIT™, Figure 5.23 (a). The 1:1 binding was lower than that found for AcO^- , and the G:H-bonded complex was formed in

a slightly lower yield, *ca.* 60% as seen in the speciation distribution diagram in Figure 5.23 (b). Fitting of the fluorescence data gave similar binding profiles and constants. The most interesting feature of this titration, however, was the increase in the emission spectrum upon addition of H_2PO_4^- , a phenomenon not seen with this complex and the other anions studied, making **170** a selective ‘switch on’ sensor for H_2PO_4^- .

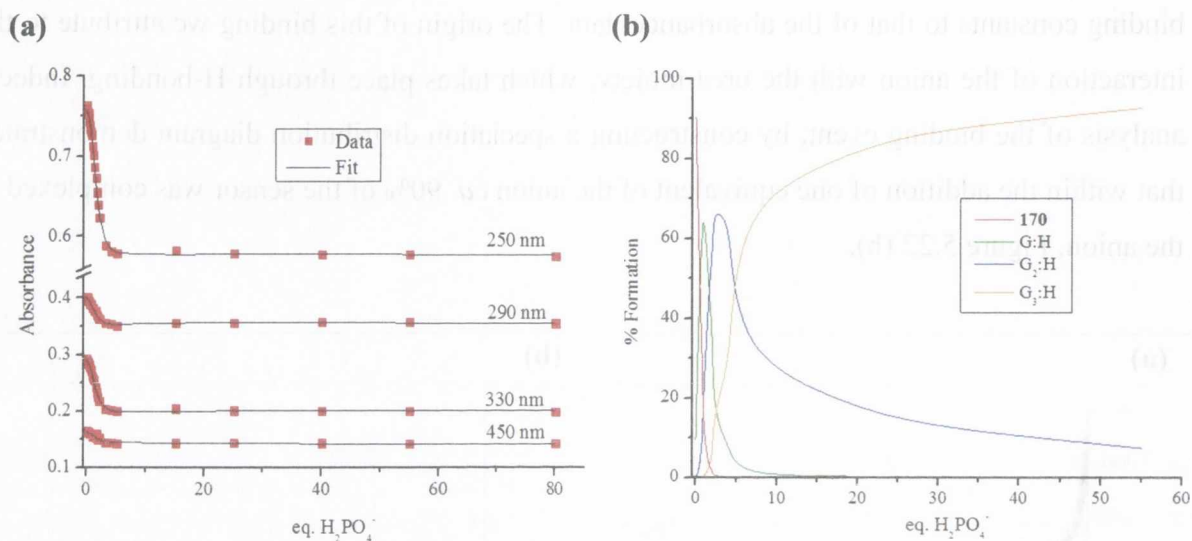


Figure 5.23: (a) Experimental binding isotherms for the absorption titration of **170** with H_2PO_4^- and their corresponding fit from SPECFIT™. (b) Speciation distribution diagram for the fluorescence titration of **170** with H_2PO_4^- .

The binding modes determined between **170** and $\text{HP}_2\text{O}_7^{3-}$ were different to that seen for AcO^- and H_2PO_4^- with only the 1:1 and 2:1 (guest:host) stoichiometries determined. The binding constants obtained were almost an order of magnitude lower than that seen for H_2PO_4^- with $\log K_{1:1} = 5.63 (\pm 0.09)$ and over two orders of magnitude lower in the case of the 2:1 species with $\log K_{2:1} = 3.12 (\pm 0.18)$. Fitting of the fluorescence data gave the same speciation as observed for the absorption data. The most dominant species in solution was the 1:1 complex at over 90% formation but at higher concentrations of the anion the 2:1 (guest:host) species was the major species in solution.

To confirm that the spectral changes were solely due to the H-bonded adduct formed between these anions and the urea functionality, similar experiments were repeated with $[\text{Ru}(\text{II})-(\text{bpy})_3]^{2+}$ as this system would function as a model compound, lacking the urea receptor moiety.

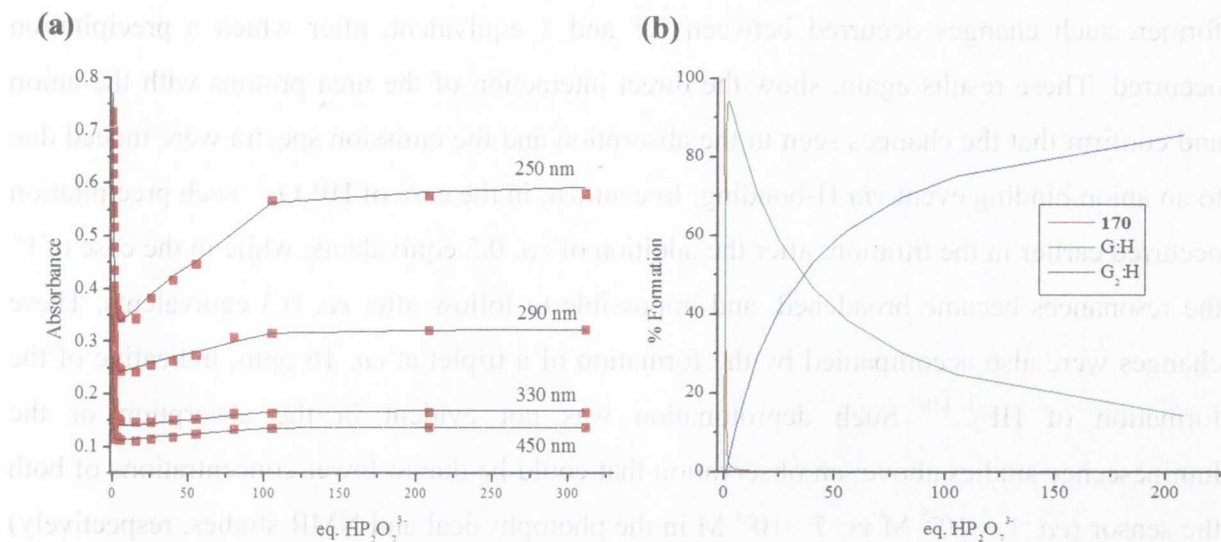


Figure 5.24: (a) Experimental binding isotherms for the absorption titration of **170** with $\text{HP}_2\text{O}_7^{3-}$ and their corresponding fit from SPECFIT™. (b) Speciation distribution diagram for the fluorescence titration of **170** with $\text{HP}_2\text{O}_7^{3-}$.

5.5.1.1 Spectroscopic Titrations with Model Compound $[\text{Ru}(\text{II})-(\text{bpy})_3]^{2+}$

To further explore the nature of the anion binding interactions seen above for **170**, the changes in the luminescence of $[\text{Ru}(\text{II})-(\text{bpy})_3]^{2+}$ (as the PF_6^- salt) upon addition of these same anions in CH_3CN were also investigated. These titrations showed that in the case of AcO^- and F^- no significant changes occurred in either the absorption or the emission spectra upon addition of 400 equivalents of these anions. In the case of H_2PO_4^- , $\text{HP}_2\text{O}_7^{3-}$, and SO_4^{2-} no spectral changes occurred either; but after the addition of 28 equivalents of H_2PO_4^- , 5 equivalents of $\text{HP}_2\text{O}_7^{3-}$, and 3 equivalents of SO_4^{2-} a precipitation occurred, which could suggest some anion exchange interactions with $[\text{Ru}(\text{II})-(\text{bpy})_3]^{2+}$. These results clearly support the findings above that the modulation in the Ru(II) centred MLCT emission was most likely due to the binding of these anions to the urea moiety in **170**.

5.5.2 ^1H NMR Titrations of Complex **170**

Further studies to elucidate the nature of the binding interaction between complex **170** and the anions studied in the above photophysical titrations were conducted. ^1H NMR titrations of **170** with H_2PO_4^- , $\text{HP}_2\text{O}_7^{3-}$ and F^- in $\text{DMSO}-d_6$ were carried out and the evolution of the urea N-H protons monitored, as well as other changes in the spectrum such as changes in the aromatic region.

In the case of H_2PO_4^- and $\text{HP}_2\text{O}_7^{3-}$, the urea protons were all in fast exchange, and became broadened and shifted downfield upon H-bonding to H_2PO_4^- and $\text{HP}_2\text{O}_7^{3-}$. For the

former, such changes occurred between 0.1 and 1 equivalent, after which a precipitation occurred. These results again, show the direct interaction of the urea protons with the anion and confirm that the changes seen in the absorption and the emission spectra were indeed due to an anion binding event *via* H-bonding. In contrast, in the case of $\text{HP}_2\text{O}_7^{3-}$ such precipitation occurred earlier in the titration, after the addition of *ca.* 0.5 equivalents, while in the case of F^- the resonances became broadened, and impossible to follow after *ca.* 0.3 equivalents. These changes were also accompanied by the formation of a triplet at *ca.* 16 ppm, indicative of the formation of HF_2^- .¹⁴⁸ Such deprotonation was not evident in the absorption or the luminescence studies above; an observation that could be due to lower concentrations of both the sensor (*ca.* 1×10^{-5} M vs. 7×10^{-3} M in the photophysical and NMR studies, respectively) and the anions (1×10^{-3} M $\rightarrow$ 0.1 M vs. 0.28 M in the photophysical and NMR studies, respectively) in CH_3CN .

5.5.3 Anion Binding of Complex 171

The next complex to be investigated was the structural isomer **171**, with the urea in the *meta* position. The absorption spectrum of **171** has slightly different features to that of the *para* derivative **170**. Although the bands centred at *ca.* 255 nm and 288 nm were visible, there was no transition at *ca.* 334 nm. The MLCT transition was unchanged at *ca.* 450 nm.

As shown in Figure 5.25 (a), the absorption spectrum was largely unaffected with increasing AcO^- concentration. This was in direct contrast with the *para* complex **170**, which saw moderate changes in all transitions upon addition of AcO^- . The band centred at *ca.* 255 nm experienced a slight hypochroism, while there was no change in the MLCT band at 450 nm. Upon addition of AcO^- the MLCT-based emission band centred at 615 nm was seen to decrease by *ca.* 20%, which was to a lesser extent compared to the quenching experienced by **170**, Figure 5.25 (b).

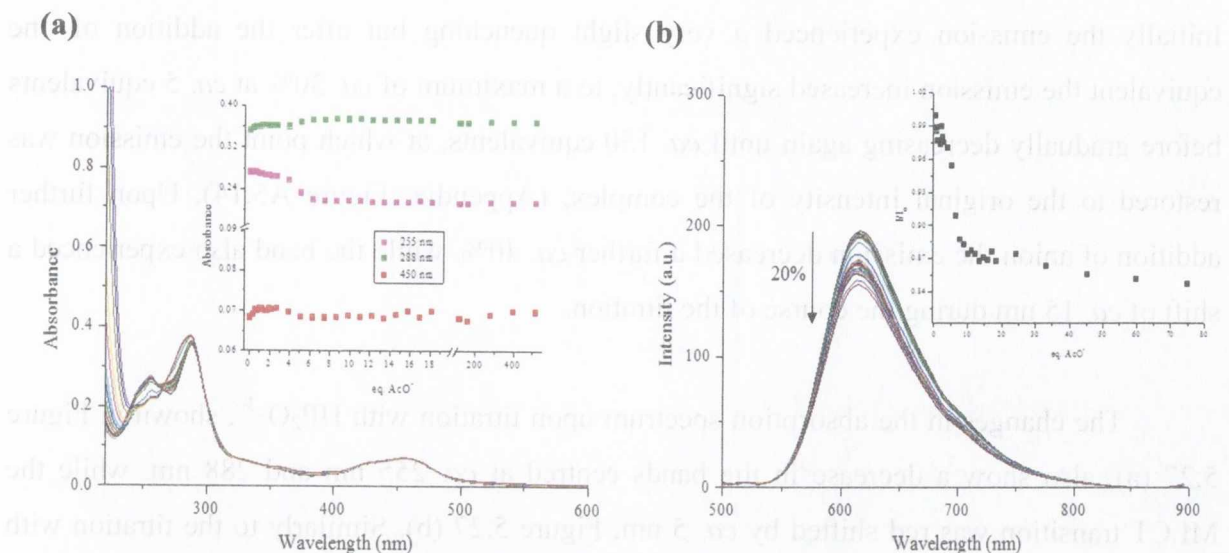


Figure 5.25: The changes observed in the (a) absorption and (b) emission spectra of **171** in CH_3CN upon titration with AcO^- . Inset (a) The changes in the absorbance at 255 nm, 330 nm and 450 nm and (b) relative changes in the emission intensity of **171** as a function of equivalents of AcO^- .

The changes in the absorption spectrum of **171** upon titration with H_2PO_4^- were more pronounced than that seen for AcO^- , but were not as significant as those experienced by **170**, Figure 5.26 (a). The bands centred at 255 nm and 288 nm decreased in absorbance throughout the course of the titration; while there was very little change in the MLCT absorption band. The titration profile for the MLCT-based emission, however, was very interesting, illustrated in Figure 5.26 (b).

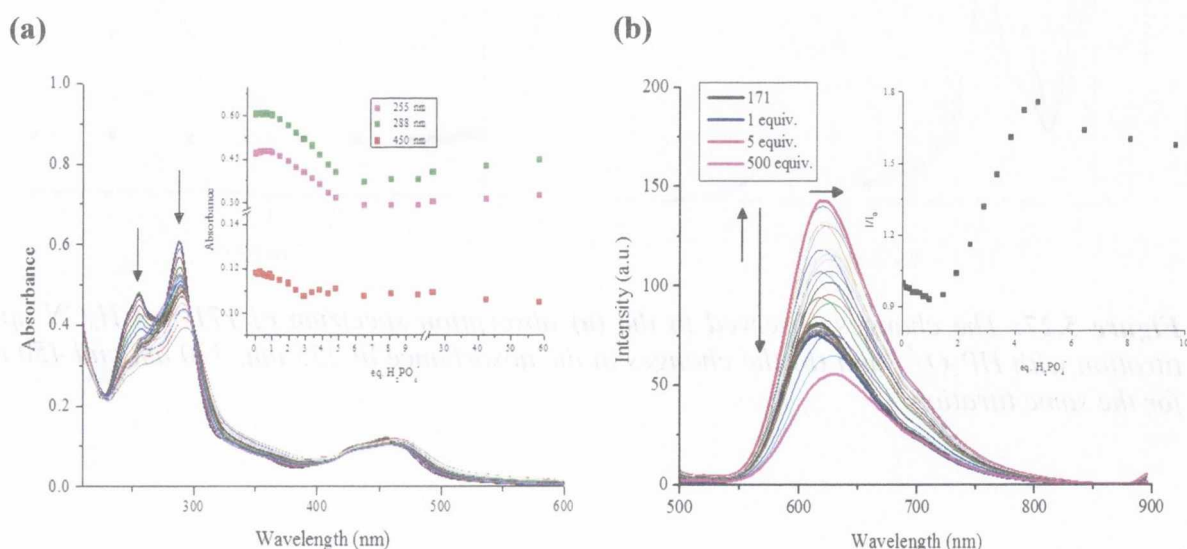


Figure 5.26: The changes observed in the (a) absorption and (b) emission spectra of **171** in CH_3CN upon titration with H_2PO_4^- . Inset (a) The changes in the absorbance at 255 nm, 330 nm and 450 nm and (b) relative changes in the emission intensity of **171** as a function of equivalents of H_2PO_4^- .

Initially the emission experienced a very slight quenching but after the addition of one equivalent the emission increased significantly, to a maximum of *ca.* 30% at *ca.* 5 equivalents before gradually decreasing again until *ca.* 150 equivalents, at which point the emission was restored to the original intensity of the complex, (Appendix, Figure A5.14). Upon further addition of anion the emission decreased a further *ca.* 40%, while the band also experienced a shift of *ca.* 15 nm during the course of the titration.

The changes in the absorption spectrum upon titration with $\text{HP}_2\text{O}_7^{3-}$, shown in Figure 5.27 (a), also show a decrease in the bands centred at *ca.* 255 nm and 288 nm, while the MLCT transition was red shifted by *ca.* 5 nm, Figure 5.27 (b). Similarly to the titration with H_2PO_4^- , **171** displayed marked changes in its fluorescence spectrum upon binding to $\text{HP}_2\text{O}_7^{3-}$ as the initial additions of $\text{HP}_2\text{O}_7^{3-}$ resulted in an immediate fluorescence enhancement up to the addition of one equivalent, with further additions of the anion resulting in the emission decreasing to a plateau around *ca.* 80 equivalents of $\text{HP}_2\text{O}_7^{3-}$, suggesting a biphasic interaction of the complex with $\text{HP}_2\text{O}_7^{3-}$, Figure 5.28 (a) and (b).

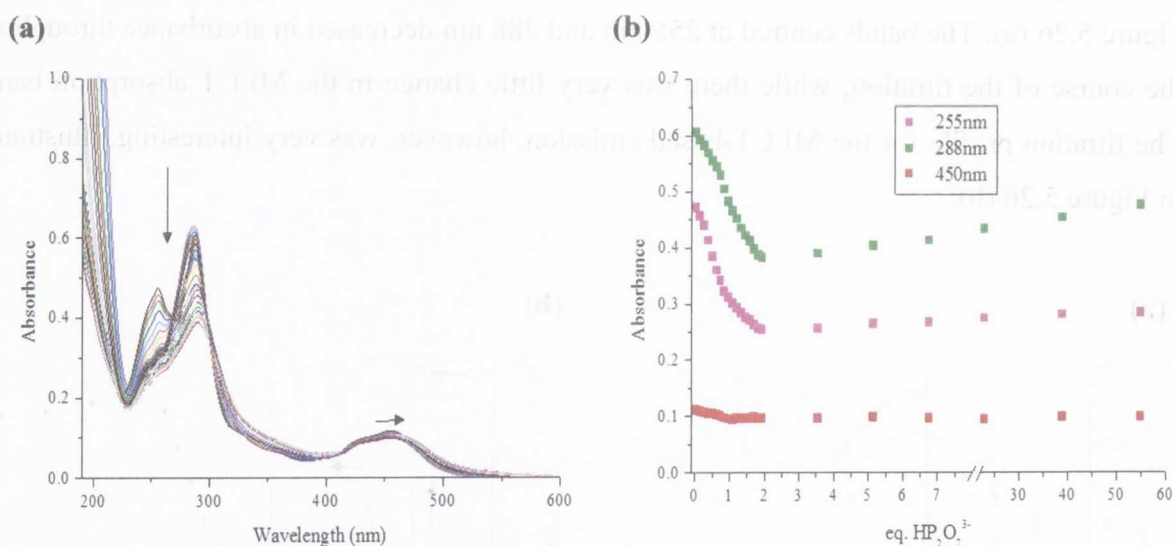


Figure 5.27: The changes observed in the (a) absorption spectrum of **171** in CH_3CN upon titration with $\text{HP}_2\text{O}_7^{3-}$ and (b) the changes in the absorbance at 255 nm, 330 nm and 450 nm for the same titration.

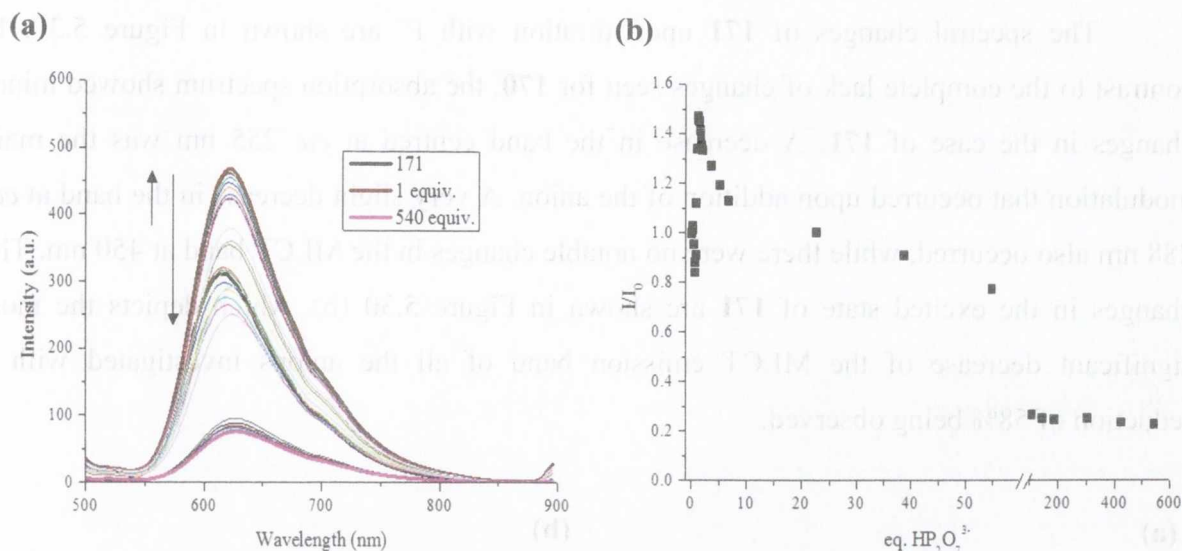


Figure 5.28: The changes observed in the (a) emission spectra of **171** in CH_3CN upon titration with $\text{HP}_2\text{O}_7^{3-}$ and (b) relative changes in the emission intensity of **171** as a function of equivalents of $\text{HP}_2\text{O}_7^{3-}$.

In contrast to the results obtained for the titration of **170** with SO_4^{2-} , where a precipitate crashed out of solution during the early stages of the titration, the results for **171** show an initial decrease in the intensity of the transitions at 255 nm and 288 nm, followed by a slight increase and blue shift at higher concentrations of the anion. The MLCT transition remained unaffected by SO_4^{2-} throughout. The MLCT based emission, however, was shown to have its excited state effectively quenched by 37% upon addition of SO_4^{2-} , with the main changes occurring between $0 \rightarrow 10$ equivalents.

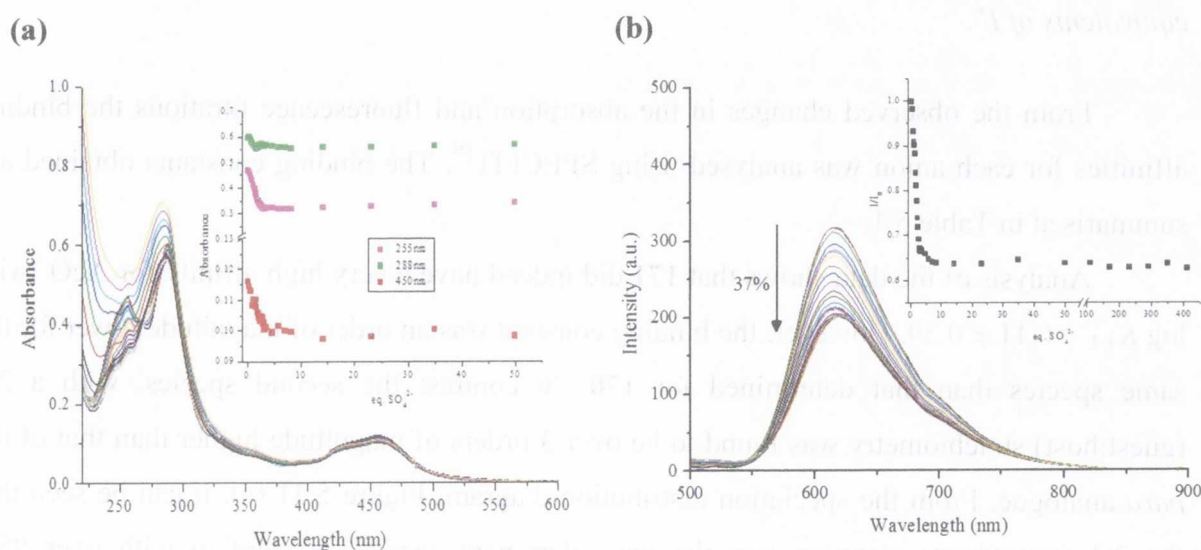


Figure 5.29: The changes observed in the (a) absorption and (b) emission spectra of **171** in CH_3CN upon titration with SO_4^{2-} . Inset (a) The changes in the absorbance at 255 nm, 288 nm and 450 nm and (b) relative changes in the emission intensity of **171** as a function of equivalents of SO_4^{2-} .

The spectral changes of **171** upon titration with F^- are shown in Figure 5.30. In contrast to the complete lack of changes seen for **170**, the absorption spectrum showed minor changes in the case of **171**. A decrease in the band centred at *ca.* 255 nm was the main modulation that occurred upon addition of the anion. A very slight decrease in the band at *ca.* 288 nm also occurred, while there were no notable changes in the MLCT band at 450 nm. The changes in the excited state of **171** are shown in Figure 5.30 (b), which depicts the most significant decrease of the MLCT emission band of all the anions investigated with a reduction of 58% being observed.

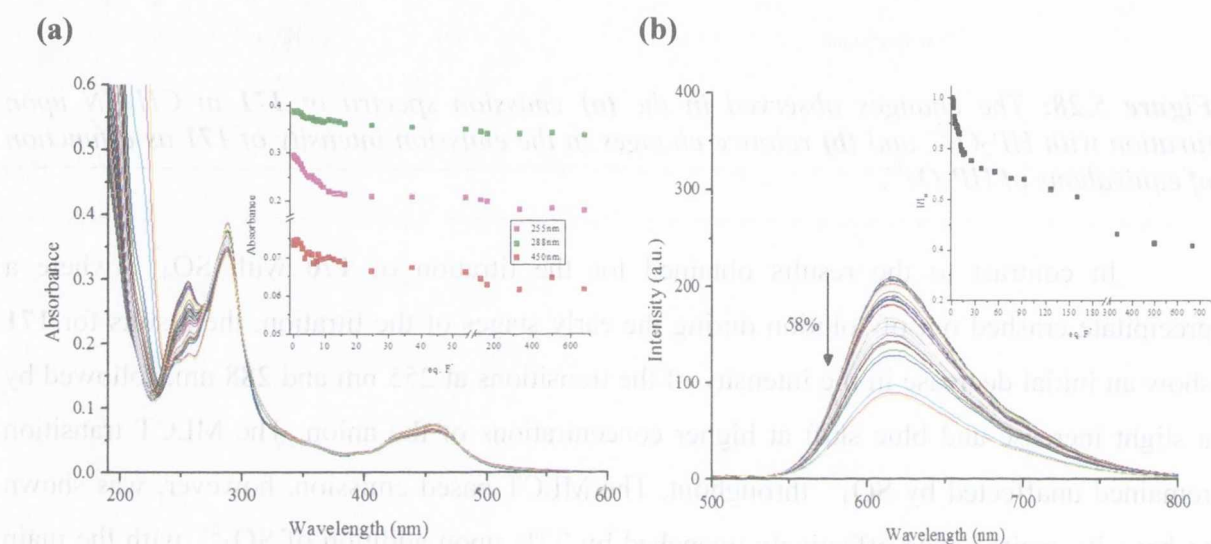


Figure 5.30: The changes observed in the (a) absorption and (b) emission spectra of **171** in CH_3CN upon titration with F^- . Inset (a) The changes in the absorbance at 255 nm, 330 nm and 450 nm and (b) relative changes in the emission intensity of **171** as a function of equivalents of F^- .

From the observed changes in the absorption and fluorescence titrations the binding affinities for each anion was analysed using SPECFITTM. The binding constants obtained are summarised in Table 5.1.

Analysis of the data shows that **171** did indeed have a very high affinity for AcO^- with $\log K_{1:1} = 6.11 \pm 0.39$. However, the binding constant was an order of magnitude lower for the same species than that determined for **170**. In contrast the second species, with a 2:1 (guest:host) stoichiometry was found to be over 3 orders of magnitude higher than that of the *para* analogue. From the speciation distribution diagram, Figure 5.31 (a), it can be seen that the 2:1 (guest:host) complex was the most dominant species in solution with over 95% formation by *ca.* 10 equivalents. These results were also reflected in the binding constants obtained from the fluorescence data.

Due to the complex nature of the changes that occurred upon titration with H_2PO_4^- and $\text{HP}_2\text{O}_7^{3-}$, it was not possible to fit the data and obtain reliable binding constants.

Table 5.5: Binding constants and binding modes between anions and 171.

Complex (H)	Anion (G)	Absorption			Fluorescence	
		Binding Mode $G_n:H_m$	$\log K_{n:m}$	Std. Deviation ($\pm$)	$\log K_{n:m}$	Std. Deviation ($\pm$)
171	AcO^-	1:1	6.11	0.39	5.34	0.53
		3:1	9.83	0.77	9.68	0.99
	H_2PO_4^-		- *		- *	
	$\text{HP}_2\text{O}_7^{3-}$		- *		- *	
	SO_4^{2-}	1:1	5.59	0.06	5.17	0.14
		2:1	6.97	0.38	7.0	0.7
		3:1	- **		2.73	0.87
	F^-	1:1	4.31	0.11	4.49	0.08
		2:1	4.17	0.26	2.7	0.2

* Data unsuitable for non-linear regression analysis.

** Species not found

In the case of SO_4^{2-} , an excellent fit of the absorbance data was obtained for the 1:1 and 2:1 (guest:host) stoichiometries, Figure 5.31 (b). However upon analysis of the fluorescence data a third species was also identified, *i.e.* a 3:1 (guest:host) species. As the binding constants determined for the 1:1 and 2:1 species from the absorbance and fluorescence data are almost identical; and as the value for the 3:1 stoichiometry is relatively small, $\log K_{3:1} = 2.73 \pm 0.87$ and only observed upon analysis of the fluorescence data, it is possible that this binding interaction can only be determined by analysis of excited state processes.

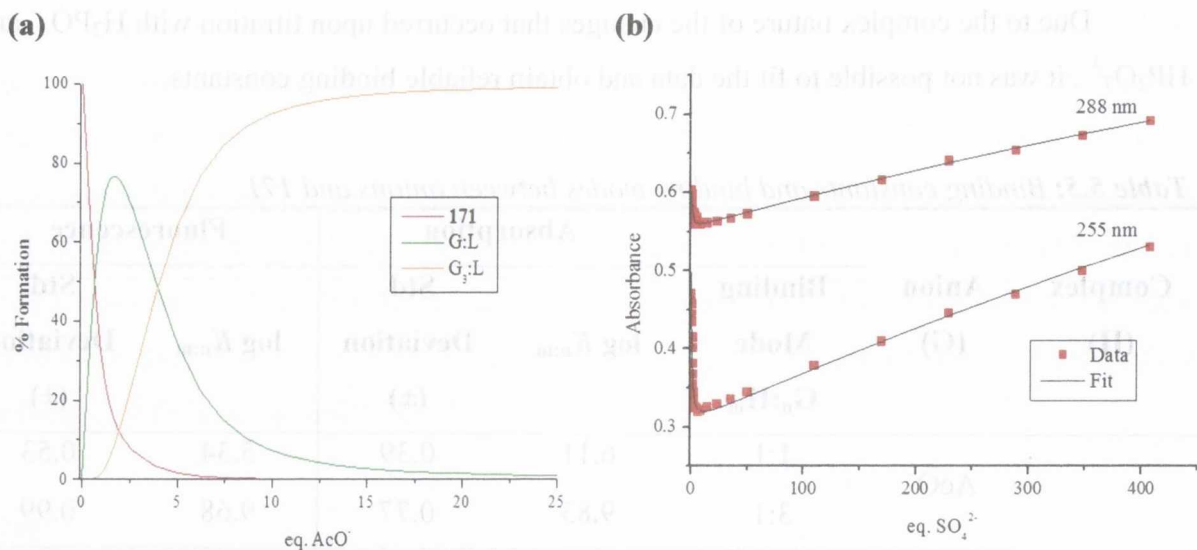


Figure 5.31: (a) Speciation distribution diagram for the absorption titration of **171** with AcO^- . (b) Experimental binding isotherms for the absorption titration of **171** with SO_4^{2-} and their corresponding fit from SPECFITTM.

The changes in the absorption spectrum of **171** with F^- were analysed in a similar manner and a three component system provided the best fit of the data, namely the complex, a 1:1 and 2:1 (guest:host) binding stoichiometry, Figure 5.32. The predominant species was the 2:1 complex with almost 80% formation at higher equivalents of F^- .

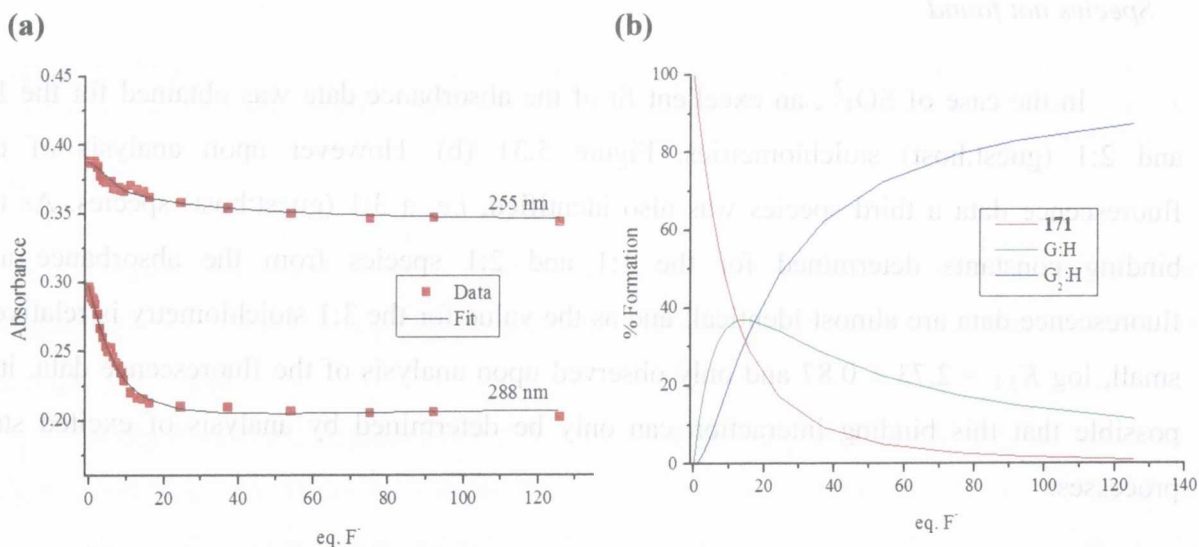


Figure 5.32: (a) Experimental binding isotherms for the absorption titration of **171** with F^- and their corresponding fit from SPECFITTM. (b) Speciation distribution diagram for the same titration.

The titrations of the various anions with this complex provided some interesting results. Undoubtedly, the substitution pattern of the urea moiety (*i.e.* *para* vs. *meta*) plays an important role in the interaction of the complex with the various anions. In the case of SO_4^{2-} ,

the *para* analogue **170** resulted in precipitation occurring upon titration with the anion while in contrast the *meta* derivative, **171**, showed changes in the absorption spectrum and, more significantly, a 37% decrease in the MLCT-based emission. The binding constants determined for the titration also indicated quite a strong interaction with $\log K_{1:1} = 5.59 \pm 0.06$ and $\log K_{2:1} = 6.97 \pm 0.38$, while the presence of third binding interaction was also detected in the excited state with $\log K_{3:1} = 2.73 \pm 0.87$.

The other major difference seen between the two complexes was the interaction with F^- . The *para* complex **170** showed no changes in either the absorption or emission spectrum, even at very high concentrations of the anion while the *meta* derivative **171** saw a decrease in the band centred at *ca.* 255 nm in the UV-Vis titration, while the emission was reduced by 58% in the presence of the anion, the second most significant decrease seen for either complex with the anions studied. The binding constants determined from the absorption studies reveal a relatively strong interaction between the complex and the anion with two species determined to be present in solution, $\log K_{1:1} = 4.31 \pm 0.11$ and $\log K_{2:1} = 4.17 \pm 0.26$.

The interaction of $H_2PO_4^-$ and $HP_2O_7^{3-}$ with **171** was more complex than that determined for **170**. In the case of $H_2PO_4^-$, the changes that occurred in the absorption spectrum were less significant than that seen for **170**, however still resulted in decreases of the two main transitions in the spectrum. The MLCT-based emission did undergo dramatic changes upon titration with the anion. A very slight decrease of the emission occurred up to the addition of *ca.* 1 equivalent followed by an increase of 30% up to the addition of *ca.* 5 equivalents. Thereafter, the emission decreased to the original intensity of the complex, after which a further reduction of 40% was observed. Also noteworthy was a red shift of the emission band, by *ca.* 15 nm, by the end of the titration. Conversely, **170** showed a significant increase in the emission band upon addition of $H_2PO_4^-$, the only anion to cause such a 'switch on' effect. The results obtained for the titration of $HP_2O_7^{3-}$ were also quite complicated, with the reverse of the $H_2PO_4^-$ induced changes occurring in the emission spectrum. The initial additions of the anion resulted in a significant increase in the emission intensity, up to *ca.* 1 equivalent. Thereafter, however the complex was shown to have its excited state effectively quenched with a plateau reached at *ca.* 80 equivalents. In comparison to **170**, this initial fluorescence enhancement was not observed with the anion completely 'switching off' the emission upon addition of excess $HP_2O_7^{3-}$.

The only anion to show similar behaviour for both complexes was AcO^- , although the interaction with **170** was determined to be stronger than that of **171**, with $\log K_{1:1} = 7.72 \pm 0.26$ and $\log K_{1:1} = 6.11 \pm 0.39$, respectively. The changes in both the absorption and emission

spectra of **170** displayed a higher degree of modulation than that of **171** with the emission, for example, being decreased by 34% and 20% respectively.

Having investigated the two NO₂ functionalised complexes, the next two complexes to be analysed were the slightly less electron withdrawing CF₃ derivatives **172** and **173**. As the substitution pattern of **170** and **171** played a major role in selectivity of anions such as SO₄²⁻ and F⁻, it was anticipated that the CF₃ complexes might also exhibit selectivity for certain anions.

5.5.4 Anion Binding of Complex **172**

The interaction of AcO⁻ with **172** was firstly examined using UV-Vis spectroscopy and the changes observed are shown in Figure 5.33 (a). As had been seen previously, the bands centred at 288 nm and 330 nm decreased, while the 330 nm transition also shifted quite significantly, by *ca.* 23 nm. The MLCT band at 450 nm underwent a slight decrease. The complex was shown to have its MLCT-based emission quenched by 23%, a lesser degree than that observed for **170** but marginally higher than that seen for **171**.

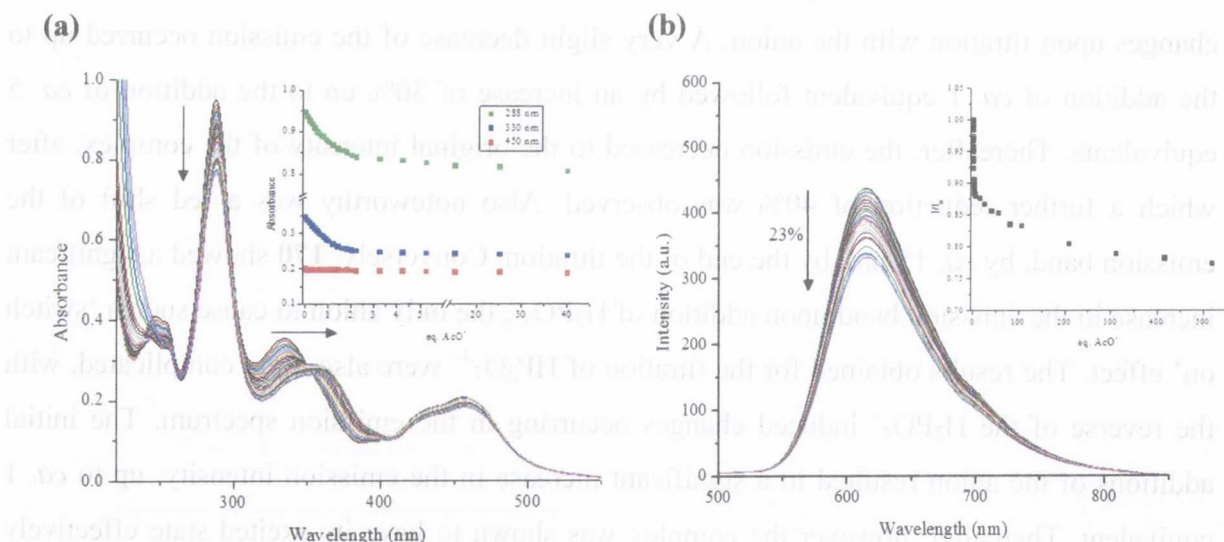


Figure 5.33: The changes observed in the (a) absorption and (b) emission spectra of **172** in CH₃CN upon titration with AcO⁻. Inset (a) The changes in the absorbance at 288 nm, 330 nm and 450 nm and (b) relative changes in the emission intensity of **172** as a function of equivalents of AcO⁻.

The changes in the absorption spectrum of **172** upon titration with H₂PO₄⁻ are shown in Figure 5.34 (a). All transitions experience a decrease while concomitantly the MLCT band red shifts by *ca.* 16 nm. The formation of an isosbestic point at 355 nm also indicates the

presence of more than one species in solution. As had been observed previously with **170**, an increase in the emission of **172** occurred upon increasing concentration of H_2PO_4^- , with the majority of changes occurring between 0 $\rightarrow$ 5 equivalents, Figure 5.34 (b). This fluorescence enhancement was quite significant and increased by a maximum of 60%, which was 20% higher than that observed for **170**.

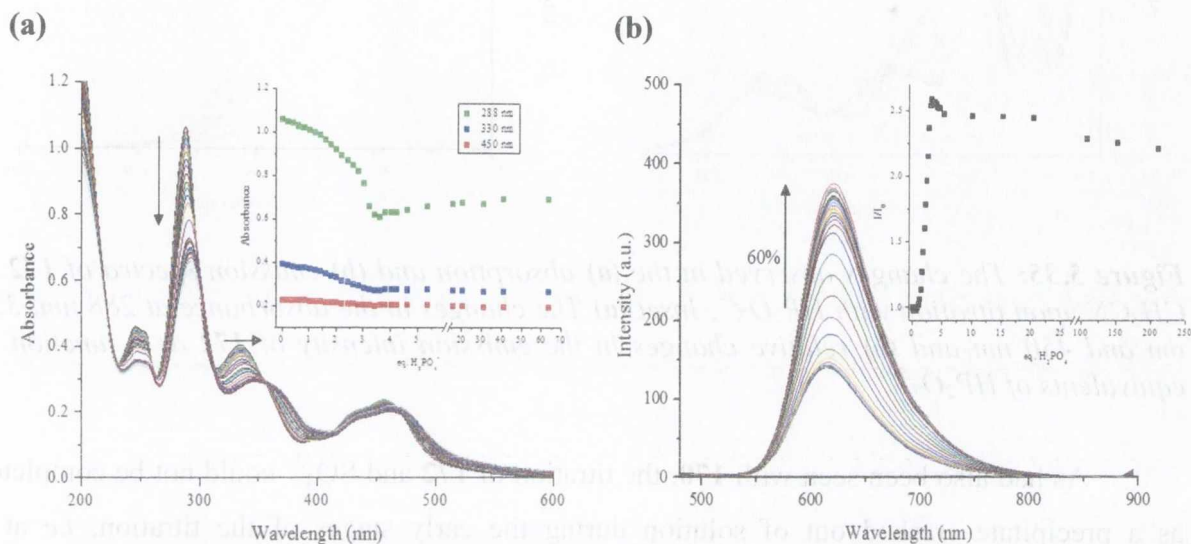


Figure 5.34: The changes observed in the (a) absorption and (b) emission spectra of **172** in CH_3CN upon titration with H_2PO_4^- . Inset (a) The changes in the absorbance at 288 nm, 330 nm and 450 nm and (b) relative changes in the emission intensity of **172** as a function of equivalents of H_2PO_4^- .

As shown in Figure 5.35 (a), the absorption spectrum of **172** changes remarkably with increasing $\text{HP}_2\text{O}_7^{3-}$ concentration. The bands centred at 288 and 334 nm decreased, as did the MLCT band at 450 nm. Furthermore, the transition at 330 nm underwent a large shift of *ca.* 32 nm. The MLCT-based emission of **172** also underwent dramatic changes upon titration with $\text{HP}_2\text{O}_7^{3-}$. An initial fluorescence enhancement was observed up to the addition of *ca.* 1.5 equivalents. However, thereafter significant quenching of the emission band occurred, accompanied by a red shifting of the emission maximum to *ca.* 635 nm.

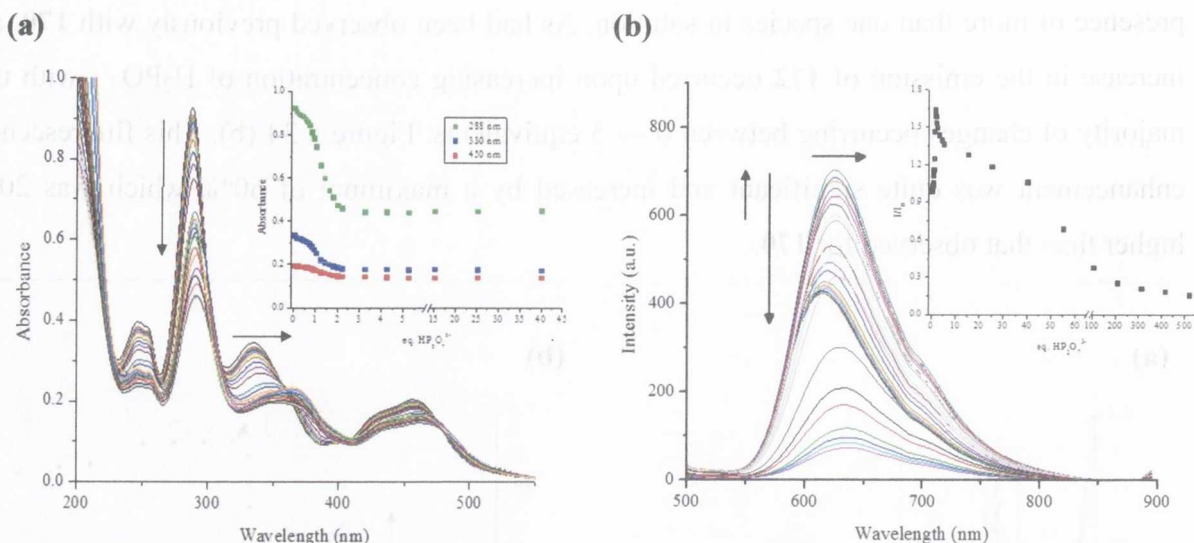


Figure 5.35: The changes observed in the (a) absorption and (b) emission spectra of **172** in CH_3CN upon titration with $\text{HP}_2\text{O}_7^{3-}$. Inset (a) The changes in the absorbance at 288 nm, 330 nm and 450 nm and (b) relative changes in the emission intensity of **172** as a function of equivalents of $\text{HP}_2\text{O}_7^{3-}$.

As had also been seen with **170**, the titration of **172** and SO_4^{2-} could not be completed as a precipitate crashed out of solution during the early stages of the titration, *i.e.* at 2 equivalents of anion. One possibility for this is that the *para* analogues form a very strong binding interaction with this anion, resulting in a highly insoluble system, which precipitates out of solution. From the crystal structures it can be seen the urea moieties of **170** and **172** are freely available for binding, but in the case of the *meta* derivative **171** the N-H's are directed towards the *bpy* groups and the Ru(II) centre, as such the geometric arrangement of the binding site is not as freely available to the anion as that of the *para* derivatives.

As can be seen from Figure 5.36 (a), addition of F^- caused modest changes to the absorption spectrum of **172**, with the majority occurring up to the addition of *ca.* 5 equivalents. A shift of *ca.* 15 nm was observed for the MLCT band. No further change in the spectral pattern was observed. Similarly, the effects on the luminescence intensity were quite moderate upon addition of F^- with a decrease of 26% of the MLCT-based emission observed. In comparison to **170**, where no changes occurred and **171** where an extreme 58% decrease was observed, these changes are quite modest and perhaps reflect the effect of substitution and appended functional groups.

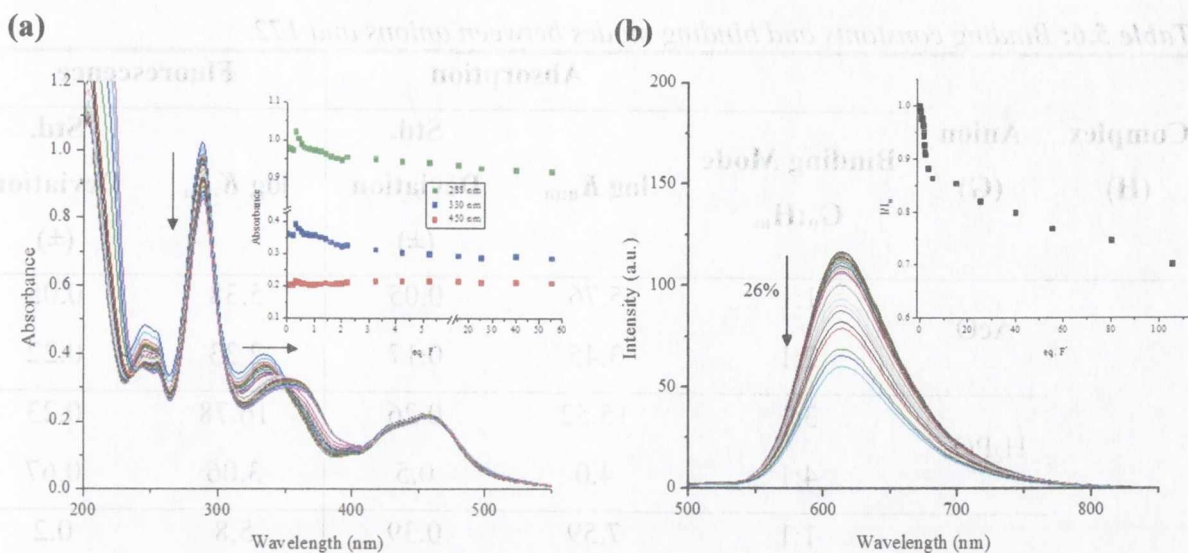


Figure 5.36: The changes observed in the (a) absorption and (b) emission spectra of **172** in CH₃CN upon titration with F⁻. Inset (a) The changes in the absorbance at 288 nm, 330 nm and 450 nm and (b) relative changes in the emission intensity of **172** as a function of equivalents of F⁻.

The data from the absorbance and fluorescence titrations were analysed using SPECFITTM and the binding constants and binding modes are presented in Table 5.6.

The binding constant for the 1:1 species of **172** and AcO⁻ was at least an order of magnitude lower than those determined previously for **170** and **171**. In this instance, a 2:1 species was also observed, however the interaction did not appear to be very strong with $\log K_{2:1} = 3.45 \pm 0.17$, although it did become the dominant species in solution at higher concentrations of the anion, Figure 5.37. Fitting of the changes observed in the fluorescence titration also gave a similar binding profile with comparable binding constants.

Analysis of the spectroscopic data for **172** and H₂PO₄⁻ could only be fit to a 3:1 and 4:1 (guest:host) species, as shown in Table 5.6, however the values of the binding constants are too large for the formation of these species *via* H-bonding interactions. Moreover, it was difficult to understand the nature of the formation of these species, and further evaluation of this interaction could not be investigated using ¹H NMR as the spectrum became too broadened to accurately follow the binding event. The urea N-H's of the complex do, however, undergo immediate shifting and broadening upon addition of the anion, < 0.5 equivalents of anion, which was indicative of the formation of a very rapid and stable host:guest complex in solution.

Table 5.6: Binding constants and binding modes between anions and 172.

Complex (H)	Anion (G)	Binding Mode $G_n:H_m$	Absorption		Fluorescence	
			$\log K_{n:m}$	Std. Deviation ($\pm$)	$\log K_{n:m}$	Std. Deviation ($\pm$)
172	AcO^-	1:1	5.76	0.05	5.38	0.05
		2:1	3.45	0.17	2.33	0.22
	H_2PO_4^-	3:1	15.52	0.26	16.78	0.23
		4:1	4.0	0.5	3.06	0.67
	$\text{HP}_2\text{O}_7^{3-}$	1:1	7.59	0.39	5.8	0.2
		2:1	6.51	0.77	2.13	0.82
		3:1	2.87	0.76	4.19	0.99
	SO_4^{2-}		-*		-*	
	F^-	1:1	5.7	0.3	6.59	0.56
		2:1	5.66	0.51	5.32	0.99
		3:1	3.13	0.43	2.83	0.99

*Data unsuitable for non-linear regression analysis.

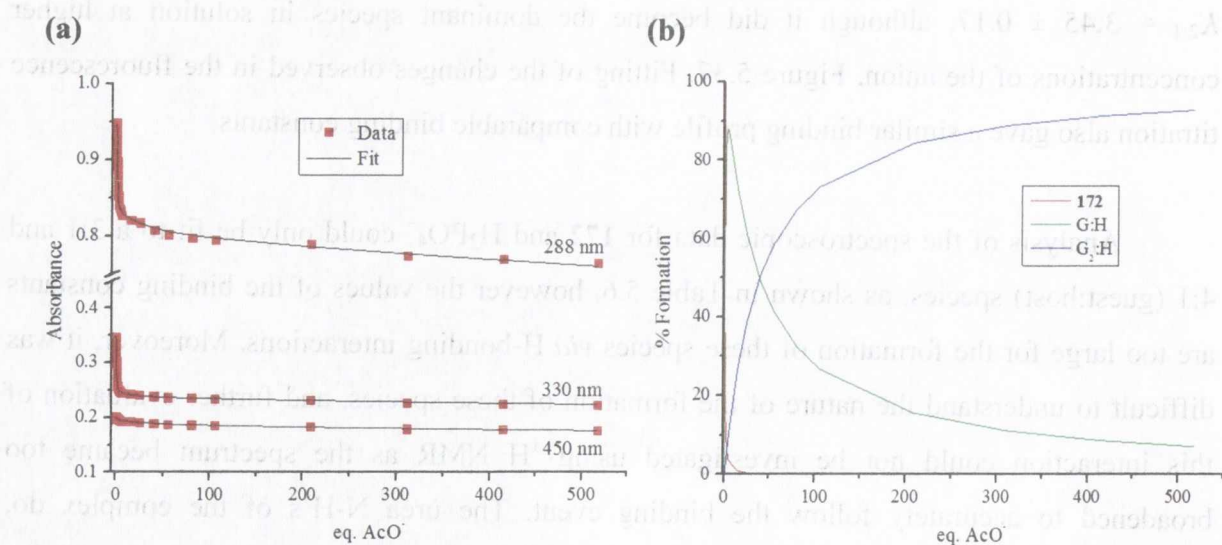


Figure 5.37: (a) Experimental binding isotherms for the absorption titration of 172 with AcO^- and their corresponding fit from SPECFIT™. **(b)** Speciation distribution diagram for the same titration.

The titration with $\text{HP}_2\text{O}_7^{3-}$ also displayed complex interactions with 172. However, binding constants for a 1:1, 2:1 and 3:1 (guest:host) species were determined with $\log K_{1:1} = 7.59 \pm 0.39$, $\log K_{2:1} = 6.51 \pm 0.77$, $\log K_{3:1} = 2.87 \pm 0.76$, respectively and a reasonable fit of

the data obtained, Figure 5.38 (a). From the speciation diagram, Figure 5.38 (b) the 1:1 species was formed quite rapidly to a maximum of 60%, however the 2:1 becomes the most dominant with over 95% formation at *ca.* 5 equivalents of $\text{HP}_2\text{O}_7^{3-}$. At the expense of this interaction, the 3:1 species begins to form after the addition of *ca.* 5 equivalents.

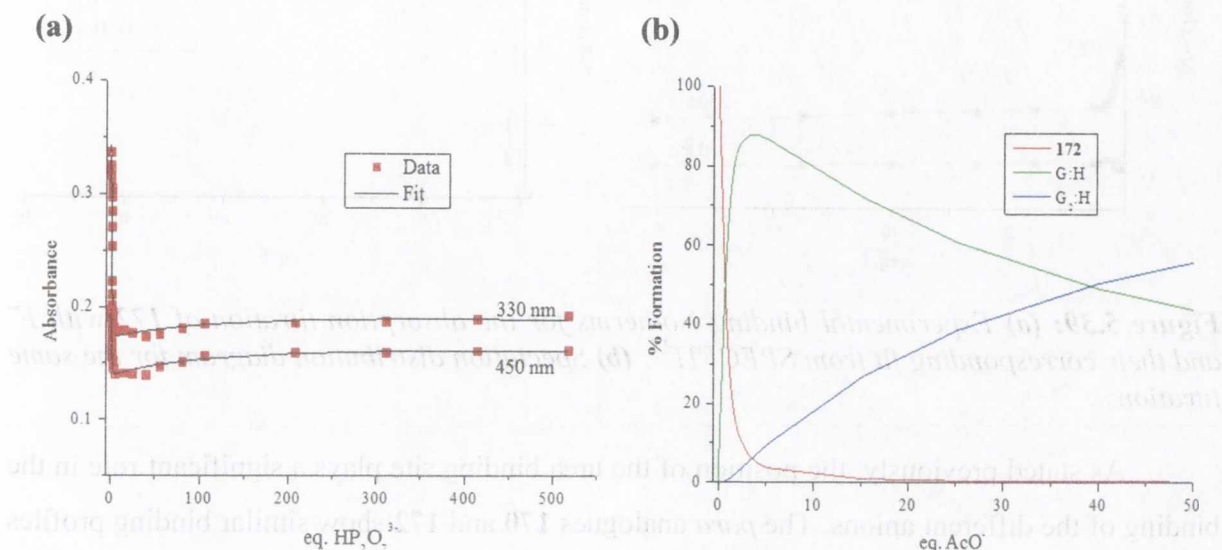


Figure 5.38: (a) Experimental binding isotherms for the absorption titration of 172 with $\text{HP}_2\text{O}_7^{3-}$ and their corresponding fit from SPECFITTM. (b) Speciation distribution diagram for the same titration.

In the case of F^- , the changes were also best fit to a four component system with a 1:1, 2:1 and 3:1 (guest:host) binding interaction observed. The binding constants determined for the first two species were relatively strong and of similar magnitude with $\log K_{1:1} = 5.7 \pm 0.3$ and $\log K_{2:1} = 5.66 \pm 0.51$, respectively. However the value for the third species, $\log K_{3:1} = 3.13 \pm 0.43$ was over two orders of magnitude lower. Additionally, the speciation distribution plot shows that the 1:1 species forms initially, however after *ca.* 1 equivalent the formation of the 2:1 species reaches a maximum of almost 90% before the 3:1 interaction contributes to a maximum of *ca.* 20%. Again, the fit of the fluorescence data was in agreement with absorption titrations.

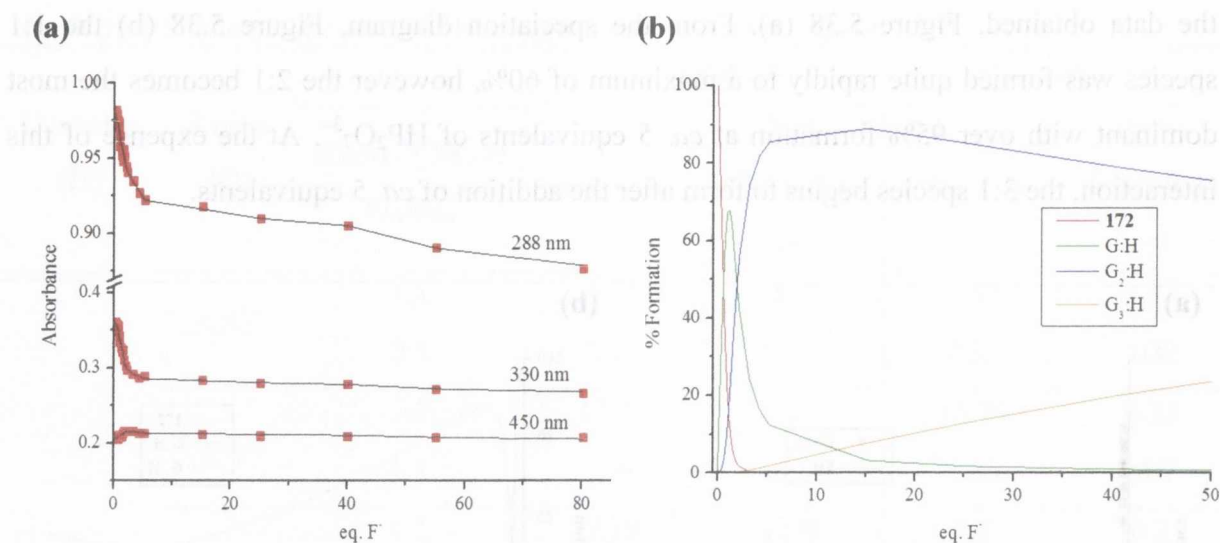


Figure 5.39: (a) Experimental binding isotherms for the absorption titration of **172** with F^- and their corresponding fit from SPECFIT™. (b) Speciation distribution diagram for the same titration.

As stated previously, the position of the urea binding site plays a significant role in the binding of the different anions. The *para* analogues **170** and **172** show similar binding profiles for $H_2PO_4^-$ and $HP_2O_7^{3-}$, with a ‘switch on’ and ‘switch off’ effect of the MLCT-based emission observed for these anions respectively. As had been seen with **170**, titration of SO_4^{2-} resulted in precipitation of the complex, which perhaps could be due to the geometrical arrangement of the binding site of the *para* analogues as this phenomenon had not been seen with the *meta* derivative **171**. In the case of AcO^- different binding modes for both *para* complexes were observed, with **170** best fit to a 1:1, 2:1 and 3:1 (guest:host) stoichiometry while the third species was not observed between **172** and the anion. Finally, F^- showed completely different behaviour with **172** as no changes in either the absorption or emission spectrum was observed for **170** while modest changes in the absorption spectrum occurred and a 26% reduction in the emission spectrum observed.

5.5.5 Anion Binding of Complex 173

The final complex to be studied was the CF_3 -functionalised *meta* urea analogue, **173**. The changes observed upon titration with AcO^- are shown in Figure 5.40 and it can be seen that the anion had very little effect on the absorption spectrum; a slight increase in the band at 288 nm was observed. No other spectral changes of interest were observed. The MLCT-based emission experienced minor quenching, to a maximum decrease of 17% at *ca.* 20 equivalents, upon increasing AcO^- concentration.

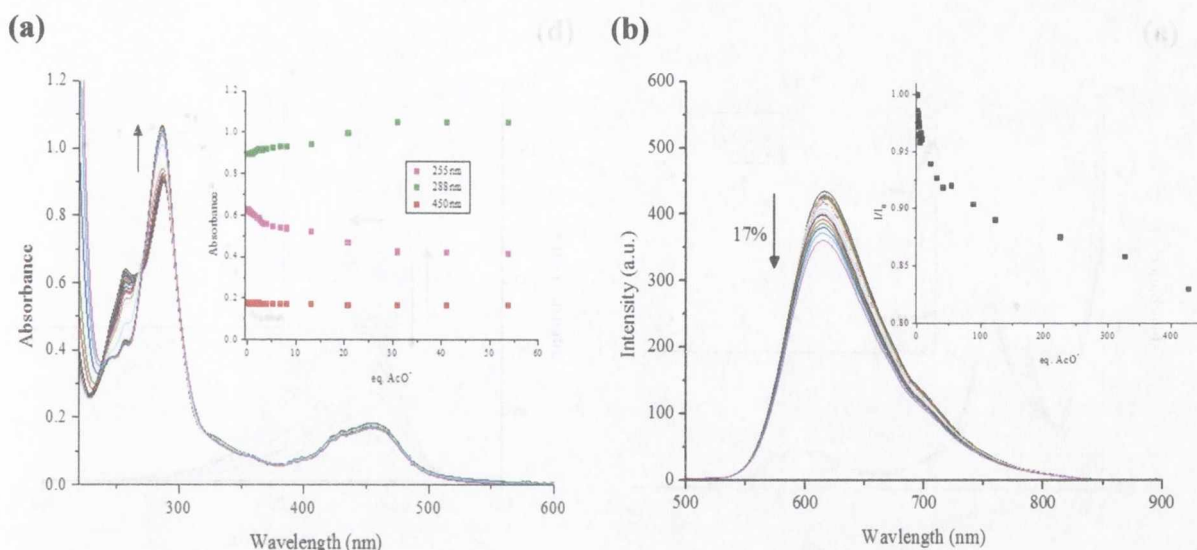


Figure 5.40: The changes observed in the (a) absorption and (b) emission spectra of **173** in CH₃CN upon titration with AcO⁻. Inset (a) The changes in the absorbance at 255 nm, 288 nm and 450 nm and (b) relative changes in the emission intensity of **173** as a function of equivalents of AcO⁻.

In the case of H₂PO₄⁻ a decrease in all the main transitions of the absorption spectrum was observed, Figure 5.41 (a). However, it was the emission spectrum that displayed the most interesting features; with an initial increase in the fluorescence intensity observed, however this only occurred after the addition of 1 equivalent of the anion (Inset, Figure 5.41 (b)). The maximum increase was seen at *ca.* 3.5 equivalents of the anion and following this further addition of H₂PO₄⁻ induced quenching of the emission, where a plateau was reached at very high concentrations of the anion (Appendix, Figure A5.15). Overall, a 47% reduction in the emission was observed by the end of the titration. Similar behaviour with an analogous sigmoidal type binding profile was seen for complex **171** and H₂PO₄⁻.

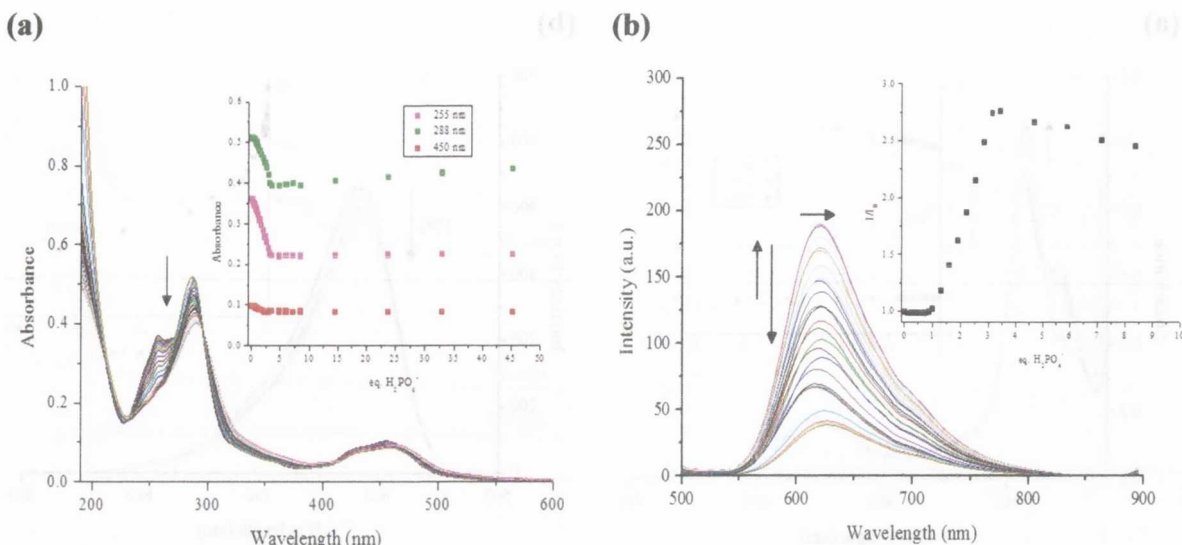


Figure 5.41: The changes observed in the (a) absorption and (b) emission spectra of **173** in CH_3CN upon titration with H_2PO_4^- . Inset (a) The changes in the absorbance at 255 nm, 288 nm and 450 nm and (b) relative changes in the emission intensity of **173** as a function of equivalents of H_2PO_4^- .

The absorption spectrum of **173** upon increasing concentration of $\text{HP}_2\text{O}_7^{3-}$ showed similar behaviour to that seen with H_2PO_4^- . A decrease in the transitions at 255 nm and 288 nm was observed with no major changes being observed in the MLCT band at 450 nm, Figure 5.42 (a). Again the emission spectrum displayed significant changes upon addition of the anion, Figure 5.42 (b). A shift of *ca.* 10 nm in the MLCT-based emission centred at 615 nm occurred during the initial stages of the titration. After the addition of *ca.* 2 equivalents of $\text{HP}_2\text{O}_7^{3-}$ significant quenching of the emission followed, *ca.* 60%, until a plateau was reached at very high equivalents of the anion, *ca.* 150 equivalents.

The titration with SO_4^{2-} showed decreases in the main transitions, however at higher concentrations the bands increased again, eventually resulting in the loss of the band at 255 nm, Figure 5.43 (a). As there was no precipitation of the complex during the course of the titration, it can be further reasoned that the position of the urea moiety has a major impact on the binding of SO_4^{2-} . Additionally, the emission spectrum was considerably affected by the addition of SO_4^{2-} , as shown in Figure 5.43 (b). Here, the emission was quenched by 36% upon addition of *ca.* 5 equivalents of the anion, with no noticeable changes in the position of the λ_{max} .

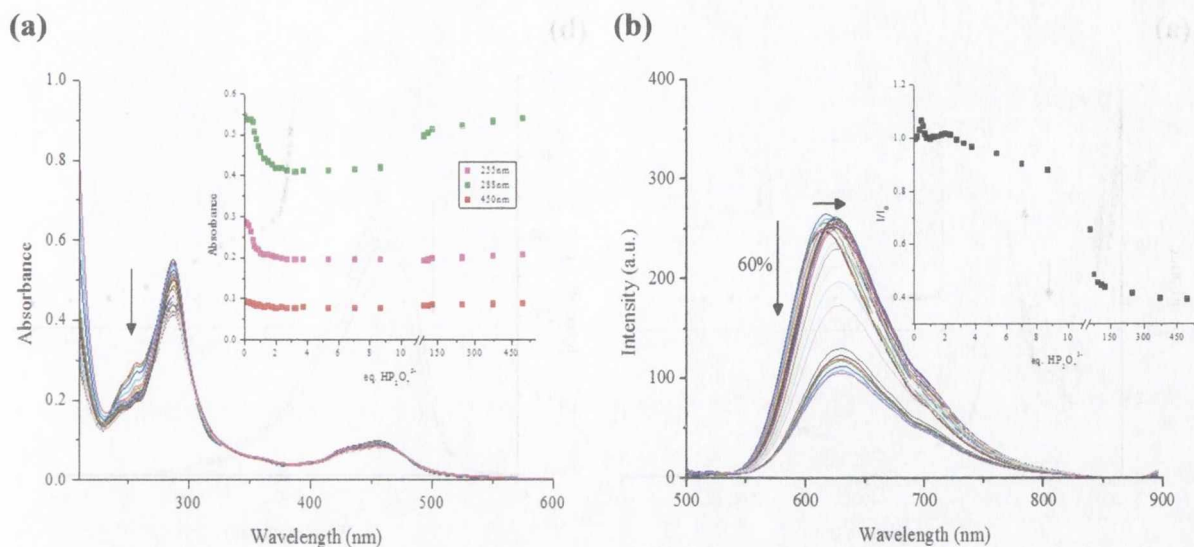


Figure 5.42: The changes observed in the (a) absorption and (b) emission spectra of **173** in CH_3CN upon titration with $\text{HP}_2\text{O}_7^{3-}$. Inset (a) The changes in the absorbance at 255 nm, 288 nm and 450 nm and (b) relative changes in the emission intensity of **173** as a function of equivalents of $\text{HP}_2\text{O}_7^{3-}$.

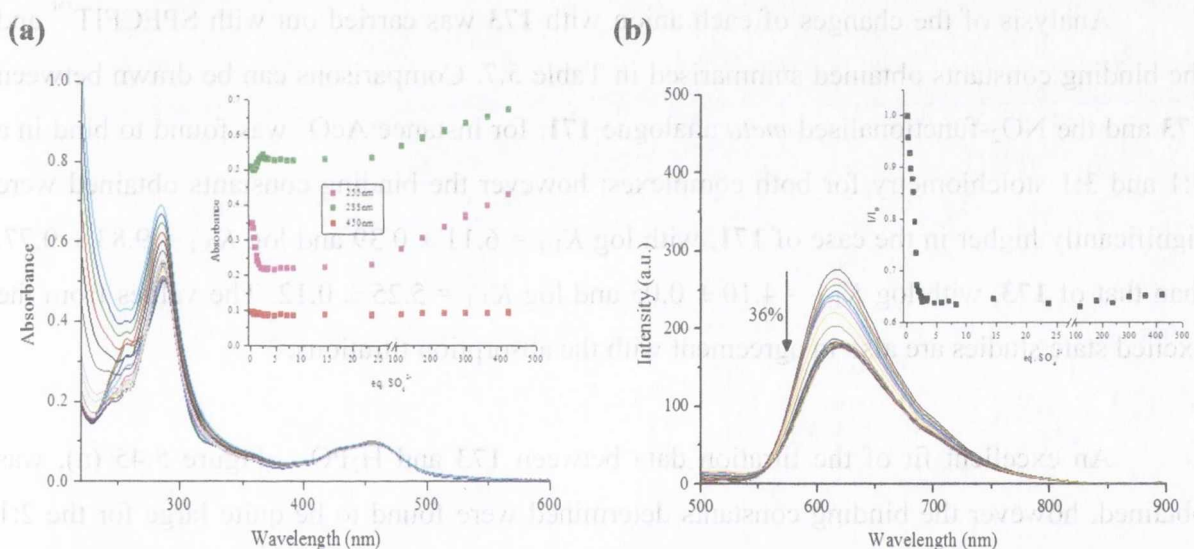


Figure 5.43: The changes observed in the (a) absorption and (b) emission spectra of **173** in CH_3CN upon titration with SO_4^{2-} . Inset (a) The changes in the absorbance at 255 nm, 288 nm and 450 nm and (b) relative changes in the emission intensity of **173** as a function of equivalents of SO_4^{2-} .

The changes in the absorption spectrum of **173** upon titration with F^- were slightly different to that seen previously with this anion. As before, a decrease in the band centred at 255 nm was observed, however the transition at 288 nm actually showed a small increase, Figure 5.44 (a). The MLCT band at 450 nm remained unchanged throughout the titration. The changes in the emission were also monitored and titration with F^- induced a 44% quenching of the MLCT-based emission, with a reduction still occurring at high equivalents of F^- before eventually reaching a plateau.

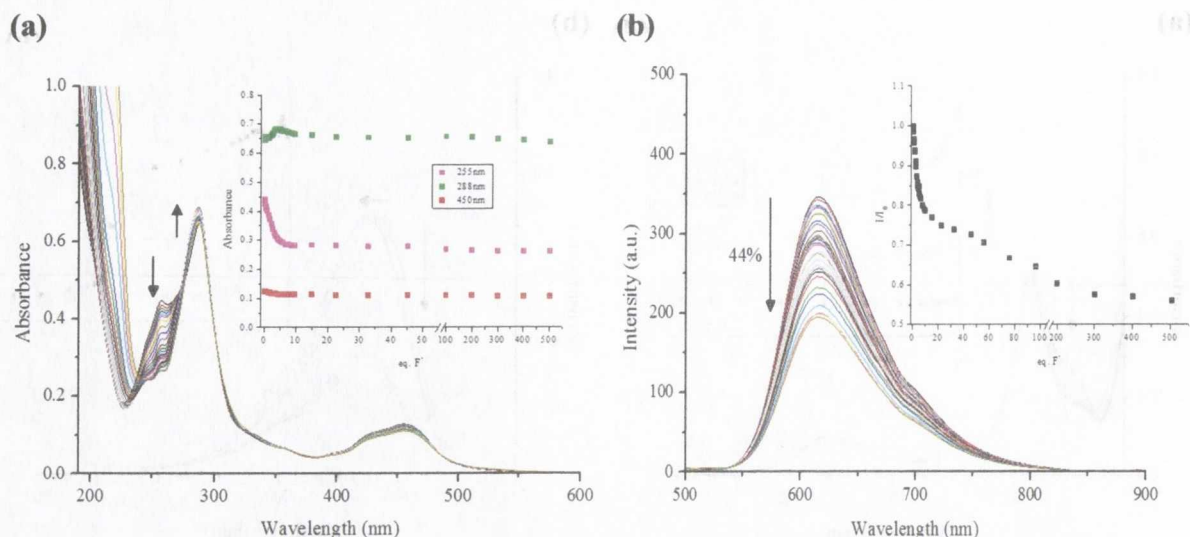


Figure 5.44: The changes observed in the (a) absorption and (b) emission spectra of **173** in CH_3CN upon titration with F^- . Inset (a) The changes in the absorbance at 255 nm, 288 nm and 450 nm and (b) relative changes in the emission intensity of **173** as a function of equivalents of F^- .

Analysis of the changes of each anion with **173** was carried out with SPECFITTM and the binding constants obtained summarised in Table 5.7. Comparisons can be drawn between **173** and the NO_2 -functionalised *meta* analogue **171**, for instance AcO^- was found to bind in a 1:1 and 3:1 stoichiometry for both complexes; however the binding constants obtained were significantly higher in the case of **171**, with $\log K_{1:1} = 6.11 \pm 0.39$ and $\log K_{3:1} = 9.83 \pm 0.77$, than that of **173**, with $\log K_{1:1} = 4.10 \pm 0.05$ and $\log K_{3:1} = 5.25 \pm 0.12$. The values from the excited state studies are also in agreement with the absorption titrations.

An excellent fit of the titration data between **173** and H_2PO_4^- , Figure 5.45 (a), was obtained, however the binding constants determined were found to be quite large for the 2:1 (guest:host) interaction with $\log K_{2:1} = 10.49 \pm 0.0$, while a much smaller contribution from the 3:1 species was observed with $\log K_{3:1} = 3.30 \pm 0.19$. The speciation distribution plot, shown in Figure 5.45 (b), clearly illustrates that the initial additions of H_2PO_4^- gives rise to the 2:1 (guest:host) complex with *ca.* 90% formation by *ca.* 10 equivalents of anion. However, the 3:1 stoichiometry begins to dominate at higher concentrations of the anion before reaching a maximum of *ca.* 80% formation. Analysis of the fluorescence titration data further confirmed these results.

Table 5.7: Binding constants and binding modes between anions and 173.

Complex (H)	Anion (G)	Binding Mode $G_n:H_m$	Absorption		Fluorescence	
			$\log K_{n:m}$	Std. Deviation ($\pm$)	$\log K_{n:m}$	Std. Deviation ($\pm$)
173	AcO^-	1:1	4.10	0.05	4.06	0.20
		3:1	5.25	0.12	7.66	0.33
	H_2PO_4^-	2:1	10.49	0.09	10.56	0.10
		3:1	3.30	0.19	3.41	0.19
	$\text{HP}_2\text{O}_7^{3-}$	1:1	6.21	0.09	6.18	0.18
		3:1	6.77	0.20	7.14	0.35
	SO_4^{2-}	1:1	6.13	0.09	5.55	0.09
		2:1	2.00	0.28	4.11	0.25
	F^-	1:1	4.61	0.14	4.78	0.07
		2:1	4.68	0.28	3.08	0.20

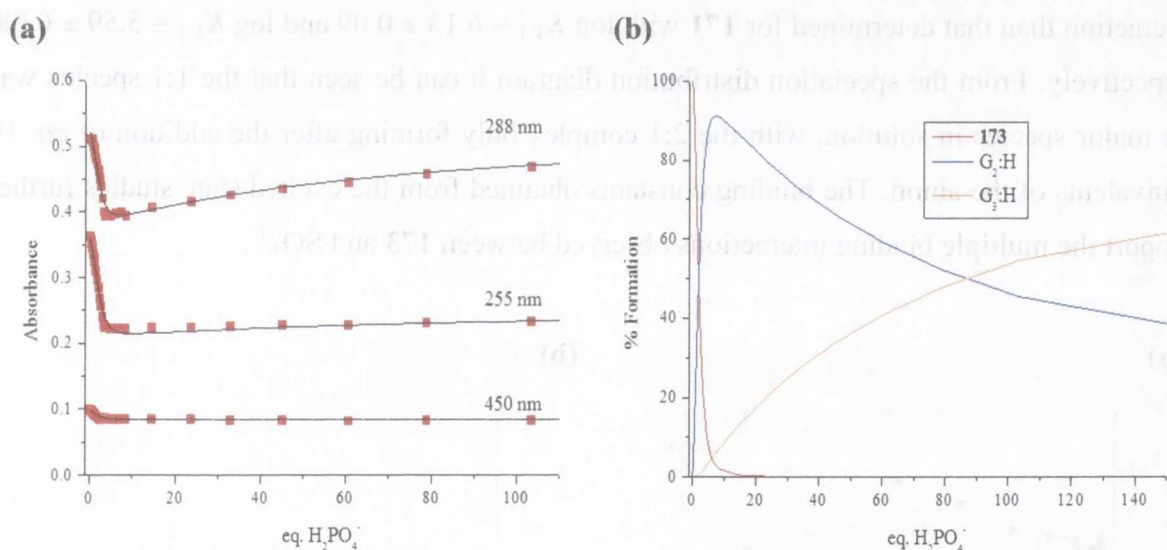


Figure 5.45: (a) Experimental binding isotherms for the absorption titration of 173 with H_2PO_4^- and their corresponding fit from SPECFITTM. **(b)** Speciation distribution diagram for the same titration.

In the case of $\text{HP}_2\text{O}_7^{3-}$ the best fit to the experimental data was obtained for 1:1 and 3:1 binding interactions. Interestingly, the values are of very similar magnitude and the speciation distribution plot shows that the 1:1 species almost reaches 100% formation at *ca.* 5 equivalents of $\text{HP}_2\text{O}_7^{3-}$, while the 3:1 interaction becomes the most dominant at higher equivalents of $\text{HP}_2\text{O}_7^{3-}$, Figure 5.46 (b).

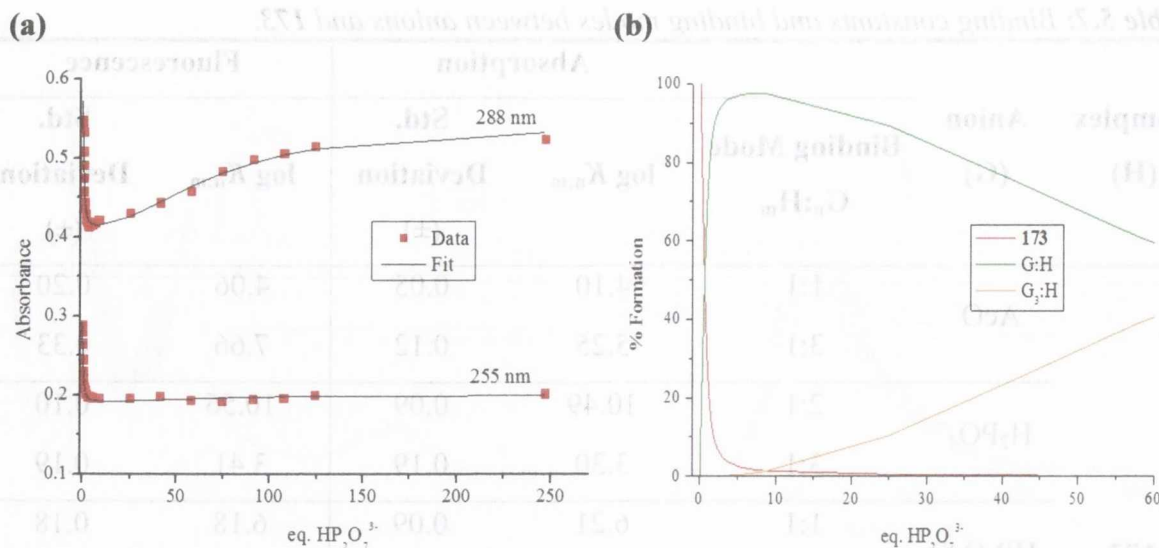


Figure 5.46: (a) Experimental binding isotherms for the absorption titration of **173** with $\text{HP}_2\text{O}_7^{3-}$ and their corresponding fit from SPECFIT™. (b) Speciation distribution diagram for the same titration.

The excellent fit to the experimental data for the titration of **173** and SO_4^{2-} is shown in Figure 5.47 (a). The results for **171** and **173** are again comparable in this case as a 1:1 and 2:1 species were determined for both complexes. The value for **173** was slightly higher for the 1:1 interaction than that determined for **171** with $\log K_{1:1} = 6.13 \pm 0.09$ and $\log K_{1:1} = 5.59 \pm 0.08$, respectively. From the speciation distribution diagram it can be seen that the 1:1 species was the major species in solution, with the 2:1 complex only forming after the addition of *ca.* 10 equivalents of the anion. The binding constants obtained from the excited state studies further support the multiple binding interactions observed between **173** and SO_4^{2-} .

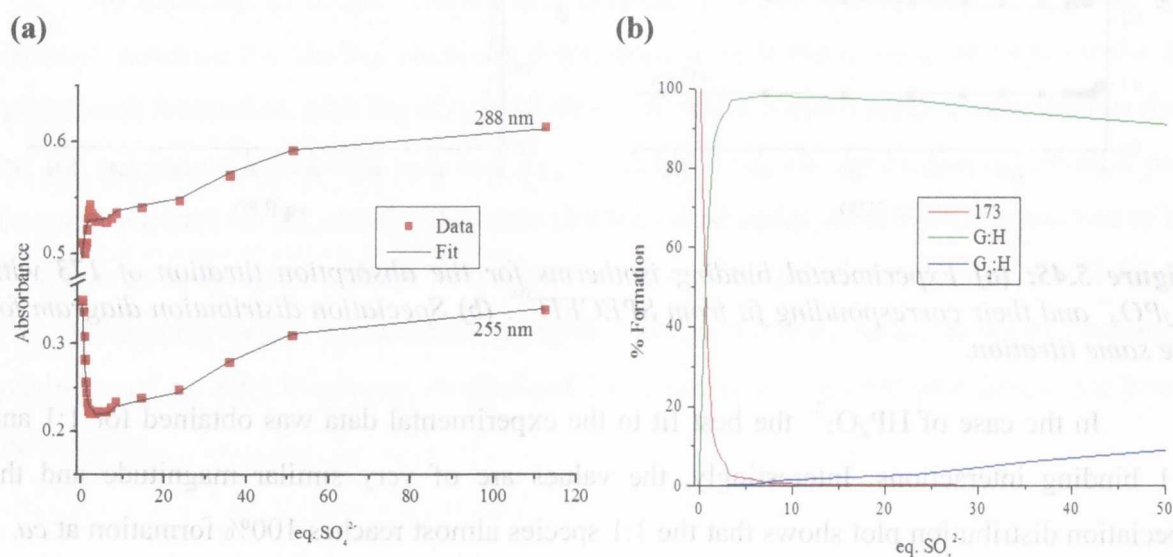


Figure 5.47: (a) Experimental binding isotherms for the absorption titration of **173** with SO_4^{2-} and their corresponding fit from SPECFIT™. (b) Speciation distribution diagram for the same titration.

The fit to the experimental data for binding interactions between **173** and F^- is shown in Figure 5.48 (a) and supports multi-step binding modes. Analysis of the speciation distribution diagram shows that the predominant species was the 2:1 (guest:host) interaction with a relatively strong binding constant of $\log K_{2:1} = 4.68 \pm 0.28$. The 1:1 interaction was also present in solution, however it only accounts for *ca.* 30% yield at *ca.* 5 equivalents of F^- . Similarly to the results obtained from the absorption titrations, the fluorescence titrations with F^- also showed distinct binding interactions.

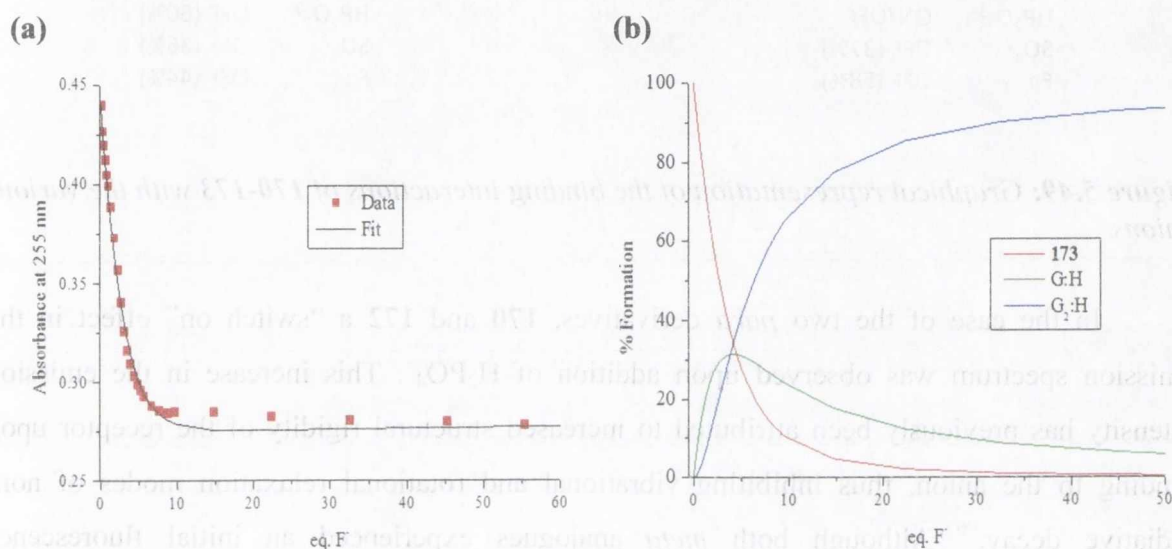


Figure 5.48: (a) Experimental binding isotherms for the absorption titration of **173** with F^- and their corresponding fit from SPECFIT™. (b) Speciation distribution diagram for the same titration.

5.6 Conclusion and Future Work

In summary, four complexes incorporating the $[Ru(II)-(bpy)_3]$ core as a luminescent unit and a pendant urea functionality as a binding site have been synthesised and their binding interaction with various anions investigated. Luminescence and UV-Vis studies suggest strong complexation with the anions studied, the positive charge of the fluorogenic unit enhancing the binding interaction as a result of strong electrostatic interactions. Furthermore, control experiments with $[Ru(II)-(bpy)_3]^{2+}$ and the anions did not show any spectral change in the absorption or emission spectrum, confirming that the urea moiety of the complexes was involved in H-bonding. Moreover, the position of the urea binding site was found to play a significant role in the binding interactions of the four complexes, depicted in Figure 5.49.

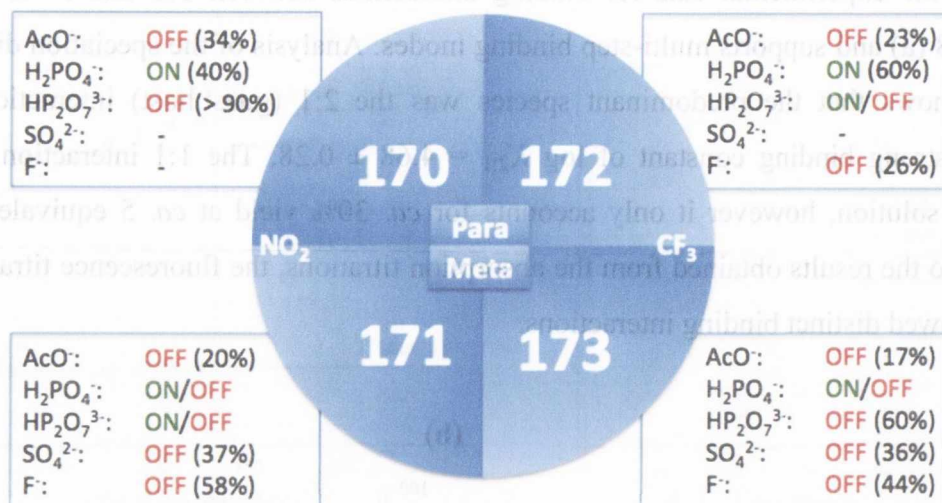


Figure 5.49: Graphical representation of the binding interactions of **170-173** with the various anions.

In the case of the two *para* derivatives, **170** and **172** a “switch on” effect in the emission spectrum was observed upon addition of H_2PO_4^- . This increase in the emission intensity has previously been attributed to increased structural rigidity of the receptor upon binding to the anion, thus inhibiting vibrational and rotational relaxation modes of non-radiative decay.⁹⁶ Although both *meta* analogues experienced an initial fluorescence enhancement after the addition of *ca.* 1 equivalent of H_2PO_4^- , this was followed by a large decrease in the emission intensity.

Another interesting trend observed for the *para* complexes was precipitation of the receptors upon addition of SO_4^{2-} . This could be ascribed to the geometrical arrangement of the *para* complexes, which have a freely available binding site, as seen from the crystal structures and can form highly stable but insoluble adducts with SO_4^{2-} . Conversely, **171** and **173** both experienced the same magnitude of fluorescence quenching upon titration with SO_4^{2-} , making the *meta* derivatives selective for the recognition of SO_4^{2-} via spectroscopic monitoring. It is possible that the strong basicity of SO_4^{2-} enhanced electron density on the urea protons, which subsequently propagates to the metal bound *bpy* ring, causing an increase of the intramolecular quenching in emission intensity.²⁰⁶

Interestingly, the titration of **170** with F^- did not result in any changes in the absorption or emission spectrum while in the case of **172** a decrease of *ca.* 26% was observed in the excited state studies. However, in comparison to the *meta* complexes, which underwent significant quenching (58% and 44% for **171** and **173**, respectively) upon titration with F^- , this was the smallest decrease observed. Titration of **170-173** with AcO^- resulted in fluorescence quenching in all cases in the order **170** > **172** > **171** > **173**, again illustrating the effect of the

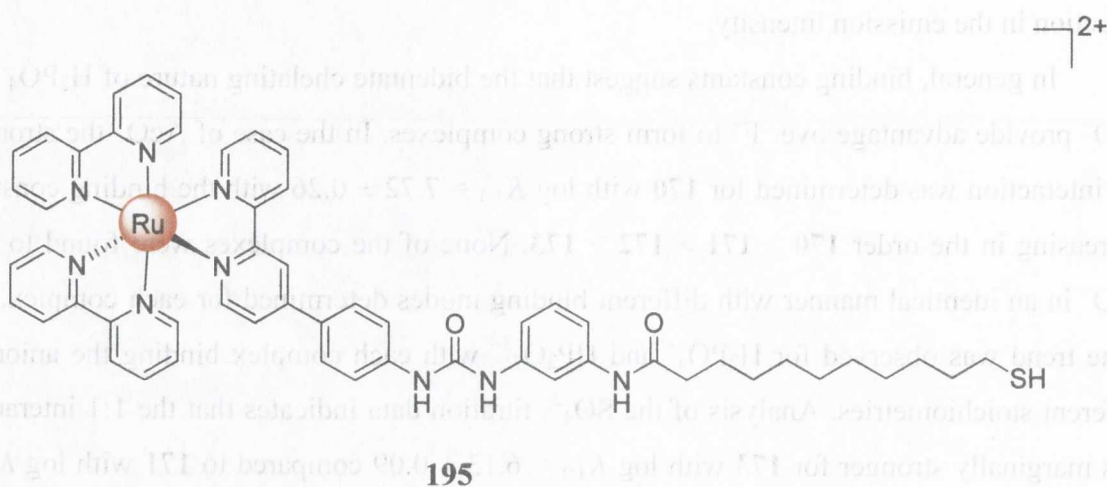
position of the urea binding site. The fluorescence emission of **170-173** was also considerably affected upon titration with $\text{HP}_2\text{O}_7^{3-}$. The trend in this instance was **170** and **173** both experienced large degrees of quenching while **171** and **172** saw initial increases followed by a reduction in the emission intensity.

In general, binding constants suggest that the bidentate chelating nature of H_2PO_4^- and AcO^- provide advantage over F^- to form strong complexes. In the case of AcO^- the strongest 1:1 interaction was determined for **170** with $\log K_{1:1} = 7.72 \pm 0.26$ with the binding constants decreasing in the order **170** > **171** > **172** > **173**. None of the complexes were found to bind AcO^- in an identical manner with different binding modes determined for each complex. The same trend was observed for H_2PO_4^- and $\text{HP}_2\text{O}_7^{3-}$ with each complex binding the anions in different stoichiometries. Analysis of the SO_4^{2-} titration data indicates that the 1:1 interaction was marginally stronger for **173** with $\log K_{1:1} = 6.13 \pm 0.09$ compared to **171** with $\log K_{1:1} = 5.59 \pm 0.08$. However, the 2:1 (guest:host) binding constant was dramatically higher for **171** with $\log K_{2:1} = 6.97 \pm 0.08$ than that of **173** with $\log K_{2:1} = 2.00 \pm 0.28$. It is also worth noting that a third species between **171** and SO_4^{2-} was observed upon analysis of the fluorescence data with $\log K_{3:1} = 2.73 \pm 0.87$ that was not identified in the analysis of the absorbance data. The results obtained for *meta* complexes **171** and **173** with F^- are comparable with identical binding modes and similar binding constants determined for both complexes, although the interaction with **173** was found to be slightly stronger.

^1H NMR studies of **170** also indicated involvement of the urea N-Hs in binding anions such as H_2PO_4^- , $\text{HP}_2\text{O}_7^{3-}$ and F^- . However, due to the broadening and shifting of the urea protons that occurred upon anion binding, followed by a precipitation, presumably due to an anion exchange event, it was impossible to obtain detailed information on the binding events of these anions. It was also for these reasons that ^1H NMR titrations were not undertaken with complexes **171-173**.

In conclusion, the results presented in this Chapter have demonstrated that Ru(II)–polypyridyl complexes **170-173** possess a unique set of photophysical properties that has allowed the nature of their interaction with various anions to be probed by ground and excited state titrations. Future perspectives of this work will look to further evaluate the anion binding ability of **170-173** in aqueous solution, as conversion to the chloride salt would allow water solubility of the complexes. Complexes **170-173** could also have the potential to act as DNA binding agents as the literature contains many examples of Ru(II) complexes such as those described here which have therapeutic properties.²²²⁻²²⁴ Reduction of the nitro group in **170**

and **171** would also allow attachment of various chains such as the thiol terminated chain in **195**, which would allow further functionalisation of the complexes to gold nanoparticles.



Chapter 6

Towards Interlocked Assemblies

6. Introduction

The concept of preorganisation, proposed by Cram²²⁵, has played an important role in supramolecular and host:guest chemistry; while the significance of preorganisation of binding sites in host-guest complexation processes has been discussed in previous Chapters in this Thesis. Preorganised host molecules decrease the loss of conformational entropy upon binding with complementary guest species; and as a result of this minimisation of entropy loss, preorganised hosts show strong binding abilities.²²⁶ This concept is also applicable to the development of interlocked assemblies.

During the past few decades, interest in mechanically interlocked molecules (MIMs), such as rotaxanes and catenanes (as there are others), has grown to an unparalleled level of activity due to their intriguing physical and chemical properties, applications in molecular electronics, potential as smart materials with adjustable surface properties²²⁷ and as components of molecular machinery.²²⁸ The synthesis of these molecules, in which the components are connected mechanically²²⁹ rather than covalently, has become a challenging and interesting task, particularly for chemists and materials scientists. In the late 1980s and the early 1990s, with the evolution of supramolecular chemistry and a better understanding of the processes of host-guest molecular recognition it became possible to take advantage of non-covalent intermolecular forces.²³⁰ Initially the synthesis of the interlocked structures was accomplished using a statistical threading approach, in which the statistical probability of threading a linear molecule through the annulus of a macrocycle to form an interpenetrated rotaxane was very low.¹¹⁶ To overcome the low yields obtained by this technique, a variety of methodologies were developed, in particular the application of templation strategies has led to a great improvement in the yields of rotaxane synthesis.²³¹ Classically, there are two main strategies for the template-directed synthesis of rotaxanes, as described in Chapter 1:

- the ‘clipping’ strategy proceeds *via* a preformed thread coordinated to a ‘u-shape’ which is closed, or ‘clipped’ around the thread. The macrocycle may also be assembled about the thread from multiple fragments in this strategy.
- In the ‘stoppering’ approach, the axle is threaded through the macrocycle, followed by attachment of the stoppers.

It should be noted that a third approach to pseudorotaxane assembly, ‘slippage’, also exists, whereby a system is heated so that the ring may slip over the stoppers, where it is kinetically trapped upon cooling. However this is not template-directed and the molecules produced are not, according to the IUPAC definition, rotaxanes.

The mostly widely used non-covalent templates include metal-ligand,^{232,233} donor-acceptor,²³⁴ H-bonding,²³⁵ anion¹²⁸ and hydrophobic templation.²³⁶ Metal-ligand templation was first introduced by the Sauvage group in 1983¹¹⁷ where, as illustrated in Figure 6.1 (a), the tetrahedral geometry of Cu(I) was exploited to hold two *phen* containing moieties orthogonally and generate the necessary cross-over points for mechanical bond formation. The metal can act as a multifunctional centre that not only holds the organic building blocks together, but also keeps them in an appropriate orientation to fit the geometrical shape for the generation of the new mechanical bond between the ligands. A 6-coordinate metal template allowed the use of tridentate *terpy* ligands, which were coordinated to Ru(II), shown in Figure 6.1 (b).

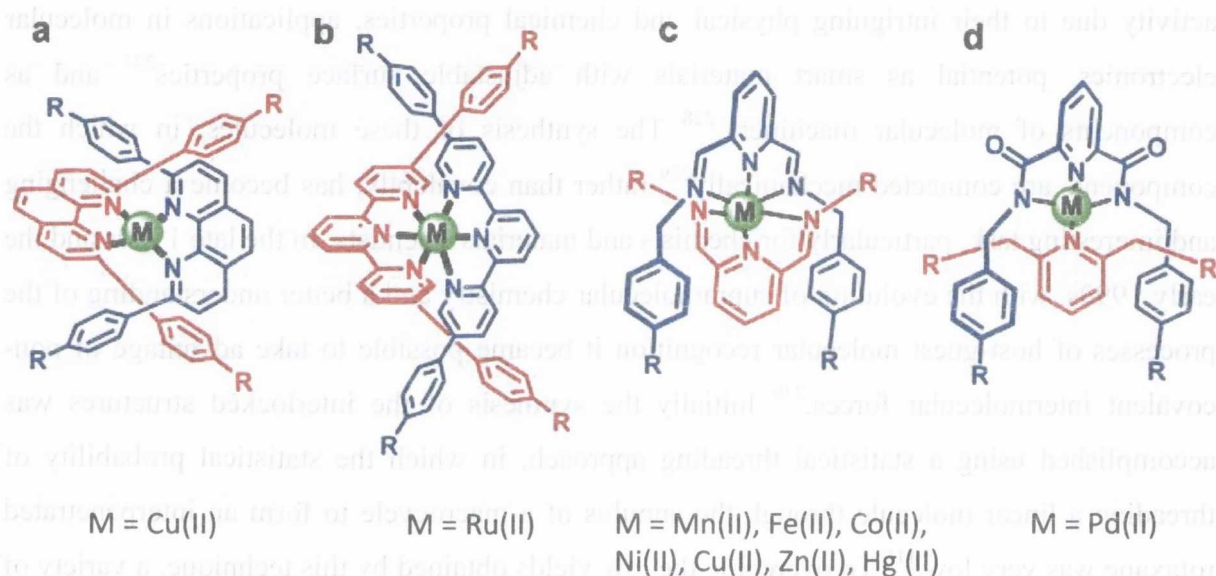


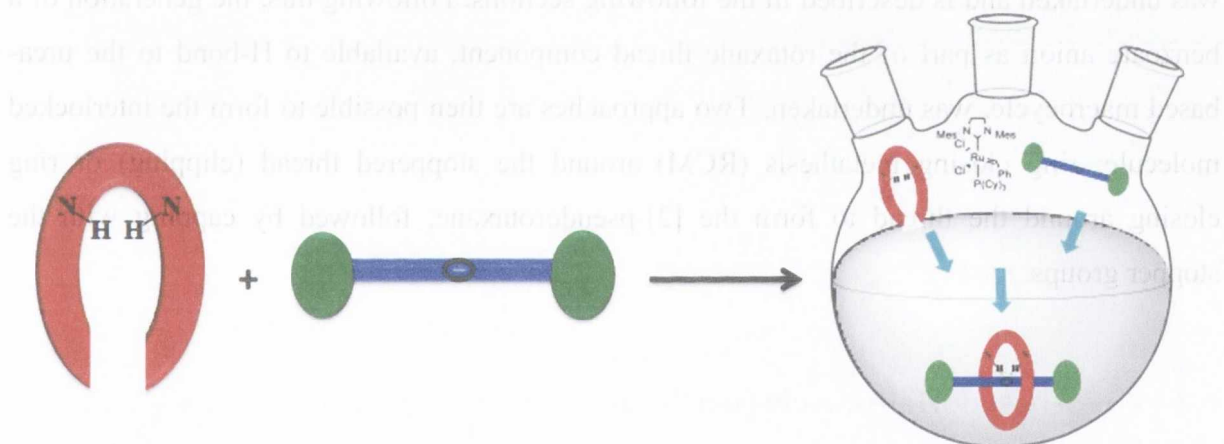
Figure 6.1: Widely used metal-ligand templates in the construction of rotaxanes and catenanes.²³⁰

Leigh and co-workers extended the concept of Sauvage's tetrahedral Cu(I) template and developed a series of octahedral complexes between metal ions and two *bis*(2,6-diiminopyridine)-derived ligands for the subsequent formation of catenanes (Figure 6.1 (c)), while another system based on palladium complexes having 2,6-pyridinedicarboxamide-containing tridentate macrocyclic ligands was also developed, Figure 6.1 (d).^{237,238}

The group of Stoddart has led the way in the use of donor-acceptor π - π interactions in the assembly of mechanically interlocked architectures.²³⁹ The donor-acceptor template employs aromatic stacking forces as the main supramolecular interaction that holds the components together in a certain spatial arrangement while Beer and co-workers have been pioneers in the area of anion templated self-assembly of rotaxanes and catenanes.

Despite the introduction of several non-covalent templates pioneered by Sauvage, Stoddart and others, which has made the preparation of MIMs much more feasible and efficient than before, it still remains necessary and challenging to develop novel and efficient templates for the construction of such topologically intriguing molecules.²³⁰

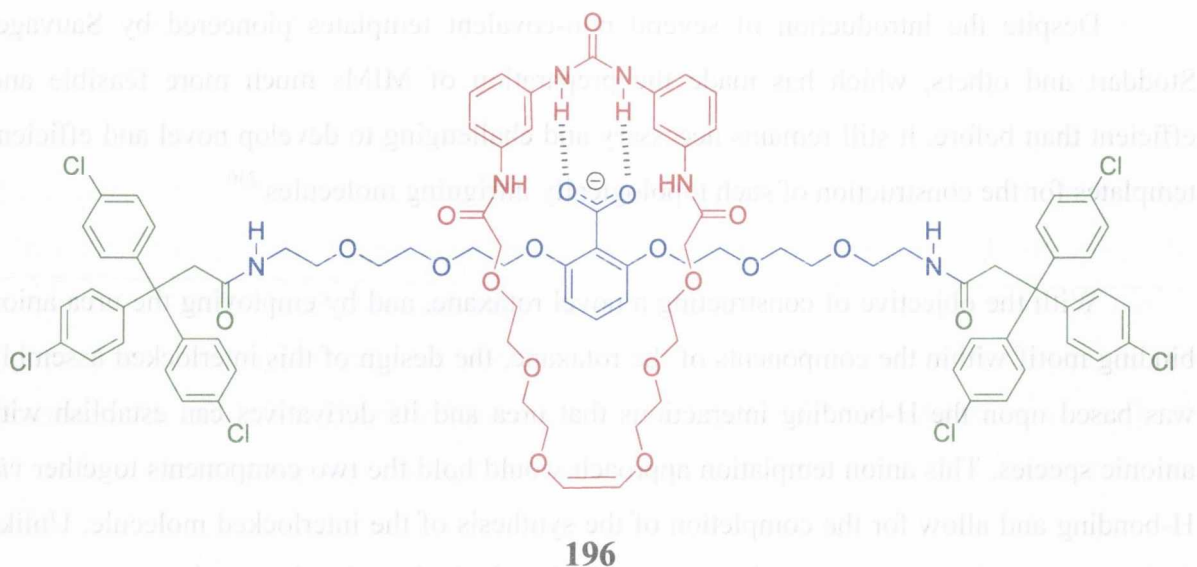
With the objective of constructing a novel rotaxane, and by employing the urea anion binding motif within the components of the rotaxane, the design of this interlocked assembly was based upon the H-bonding interactions that urea and its derivatives can establish with anionic species. This anion templation approach would hold the two components together *via* H-bonding and allow for the completion of the synthesis of the interlocked molecule. Unlike their macro-scale counterparts, however, this interlocked molecule requires no external interference; all the pieces can be combined together and the rotaxane can self assemble in a one pot synthesis, Scheme 6.1. The challenge is how to engineer a synthetic route in which the assembly happens on demand.



Scheme 6.1: Schematic of a one pot synthesis of a urea-based rotaxane.

6.1 Design Strategy

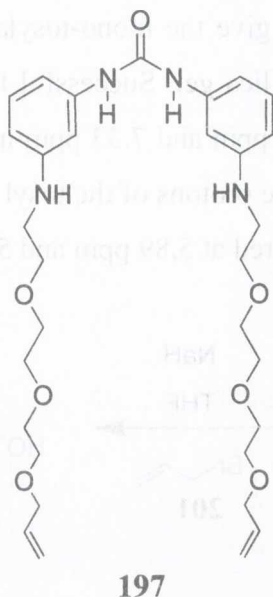
The target rotaxane molecule, **196**, is shown below and as previously mentioned, the formation of the rotaxane will be based upon H-bonding interactions between a diaryl urea moiety and an anionic species. H-bonding is one of the most important and attractive supramolecular interactions due to its strength, selectivity and directionality; ideal features that can be exploited in the construction of a rotaxane.



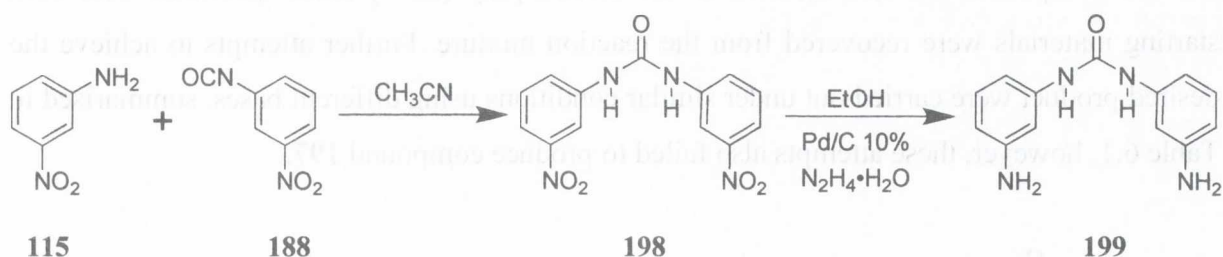
As shown above, the target [2]-rotaxane molecule **196** is achieved by passing an anionic thread through the cavity of a urea macrocycle, which should be a suitable system due to the urea's affinity for anion recognition. Firstly, the synthesis of the urea-based macrocycle was undertaken and is described in the following sections. Following this, the generation of a benzoate anion as part of the rotaxane thread component, available to H-bond to the urea-based macrocycle, was undertaken. Two approaches are then possible to form the interlocked molecule: ring closing metathesis (RCM) around the stoppered thread (clipping) or ring closing around the thread to form the [2]-pseudorotaxane, followed by capping with the stopper groups.

6.2 Urea-based Macrocycle Synthesis

The target urea molecule before ring closing, **197**, is shown below. In order to synthesise compound **197**, the precursors **198** and **199** were initially synthesised, as illustrated in Scheme 6.2.



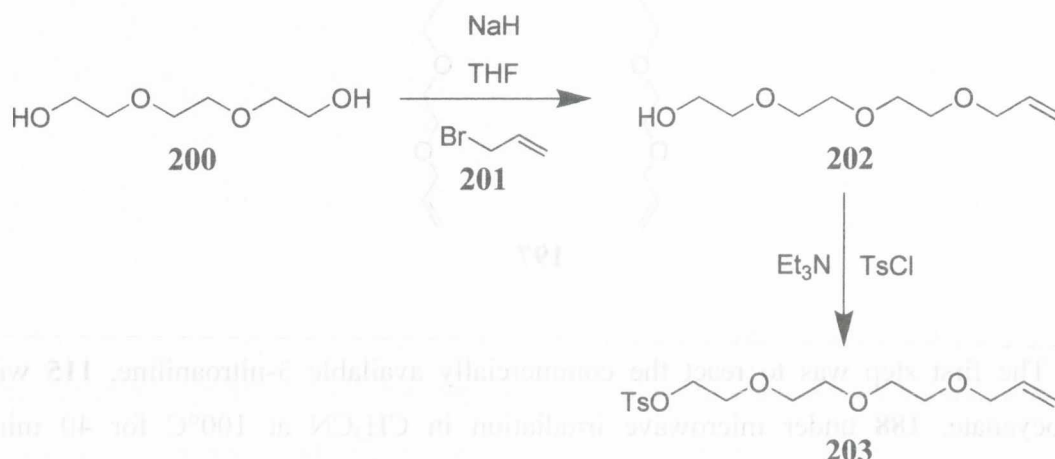
The first step was to react the commercially available 3-nitroaniline, **115** with 3-nitroisocyanate, **188** under microwave irradiation in CH_3CN at 100°C for 40 minutes. Compound **198** was obtained, in 85% yield, by triturating the crude product with CHCl_3 . The nitro groups of compound **198** were then reduced by dissolving the compound in EtOH, followed by the addition of 10% Pd/C and hydrazine monohydrate and heating at 80°C under microwave irradiation for 40 minutes. After filtration through a celite plug, **199** was obtained in 44% yield. The ^1H NMR spectrum (400 MHz, $\text{DMSO}-d_6$) of **198** showed the urea N-H protons at 9.45 ppm. The distinguishing features of the reduced product, **199**, were the shift of the urea protons upfield to 8.23 ppm, along with the presence of a singlet at 4.98 ppm assigned to the amine protons.



Scheme 6.2: Synthesis of precursors **198** and **199**.

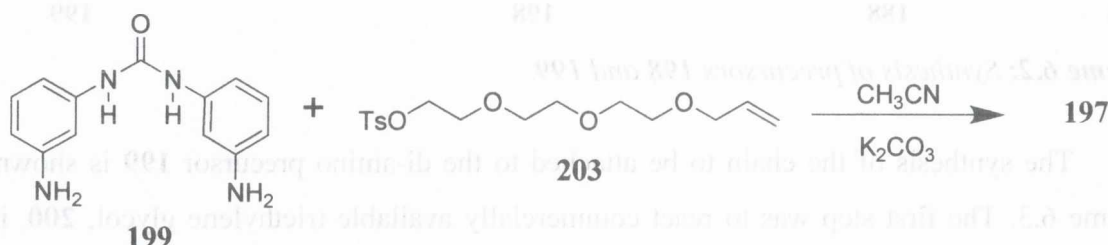
The synthesis of the chain to be attached to the di-amino precursor **199** is shown in Scheme 6.3. The first step was to react commercially available triethylene glycol, **200**, in a solution of THF with sodium hydride and allyl bromide, **201**.²⁴⁰ The crude product was purified by column chromatography (gradient eluent 70:30 hexane:EtOAc) with compound **202** obtained in 29% yield. The mono-allyl compound **202** was then reacted with tosyl

chloride in the presence of Et_3N to give the mono-tosylated species **203** in 45% yield after chromatographic purification over silica gel. Successful formation of **203** was confirmed by the presence of two doublets at 7.79 ppm and 7.33 ppm in the ^1H NMR spectrum (400 MHz, CDCl_3) corresponding to the aromatic protons of the tosyl groups while the protons associated with the terminal alkene group appeared at 5.89 ppm and 5.28 ppm.



Scheme 6.3: Synthesis of chain **203**.

In order to obtain the acyclic compound **197**, compound **199** was dissolved in CH_3CN and stirred with K_2CO_3 for 15 minutes, Scheme 6.4. Following this compound **203** was added dropwise and the reaction stirred overnight at reflux. After overnight stirring, solvent was removed under reduced pressure, the crude product re-dissolved in CH_2Cl_2 and the K_2CO_3 removed by suction filtration. The solvent was again removed under reduced pressure and a dark orange oil obtained. ^1H NMR analysis, however, did not show formation of the product and the compound was not detected in the electrospray ($\text{ES}^{+/-}$) mass spectrum, with both starting materials were recovered from the reaction mixture. Further attempts to achieve the desired product were carried out under similar conditions using different bases, summarised in Table 6.1, however, these attempts also failed to produce compound **197**.

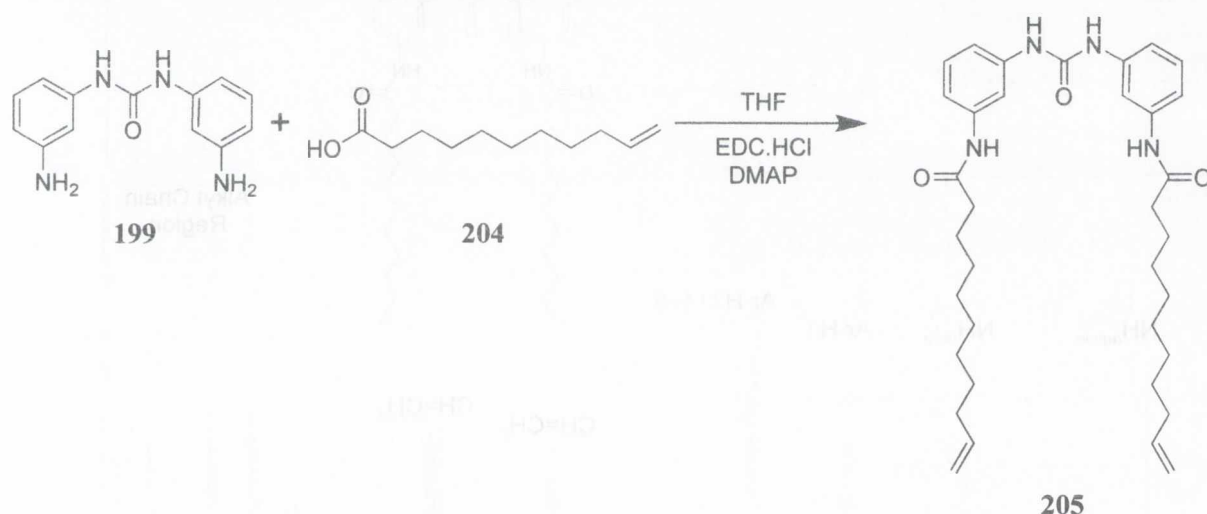


Scheme 6.4: Synthesis of acyclic compound **197**.

Table 6.1: Methods attempted for formation of **197**.

Attempt	Base	Result
1	K ₂ CO ₃	Starting material recovered
2	K ₂ CO ₃ /KI	Starting material recovered
3	Cs ₂ CO ₃	Starting material recovered
4	Et ₃ N	Starting material recovered
5	DIPEA	Starting material recovered

Following the unsuccessful attempts to synthesise **197** a new approach was required to obtain a suitable macrocycle component. The commercially available chain **204** in Scheme 6.5 was a potential alternative to the tosylated chain **203** and could be coupled to the amide functionalities of **199** via a peptide coupling reaction.

**Scheme 6.5:** Synthesis of alternative acyclic compound **205**.

Therefore, this approach was initially attempted by dissolving **199** in dry THF and the solution cooled to 0°C. Compound **204** was added to the reaction mixture followed by 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC·HCl) and DMAP and stirred at 0°C for 1 hour and then at ambient temperature overnight. After overnight stirring a light yellow solution was present. The solvent was removed under reduced pressure, the crude product **205** re-dissolved in CH₂Cl₂ and extracted with water (6 × 50 mL). A yellow oil was obtained after drying the CH₂Cl₂ solution over MgSO₄ and removing the solvent under reduced pressure. The ¹H NMR spectrum, (400 MHz, DMSO-*d*₆), of **205** showed product formation however there were multiple impurities present. An excellent solvent for peptide coupling reactions is CH₂Cl₂, therefore the reaction was repeated using this solvent under the exact same conditions to see if any side reactions could be minimised and improve the overall

efficiency of the reaction. Following overnight stirring a cloudy white solution was present and the reaction mixture directly diluted with water (50 mL) and extracted (5 × 50 mL). It was noted that a third phase between the aqueous and organic layers was present, which was subsequently separated by centrifugation and collected by filtration to give an off white solid in 79% yield. The ^1H NMR spectrum (400 MHz, $\text{DMSO-}d_6$), Figure 6.2, showed the pure product present with successful formation of **205** indicated by the presence of the amide proton at 7.18 ppm and the terminal alkene protons at 5.80 ppm and 4.94 ppm. The $[\text{M} + \text{Na}]^+$ species ($m/z = 597.3770$) was observed in the ES-MS.

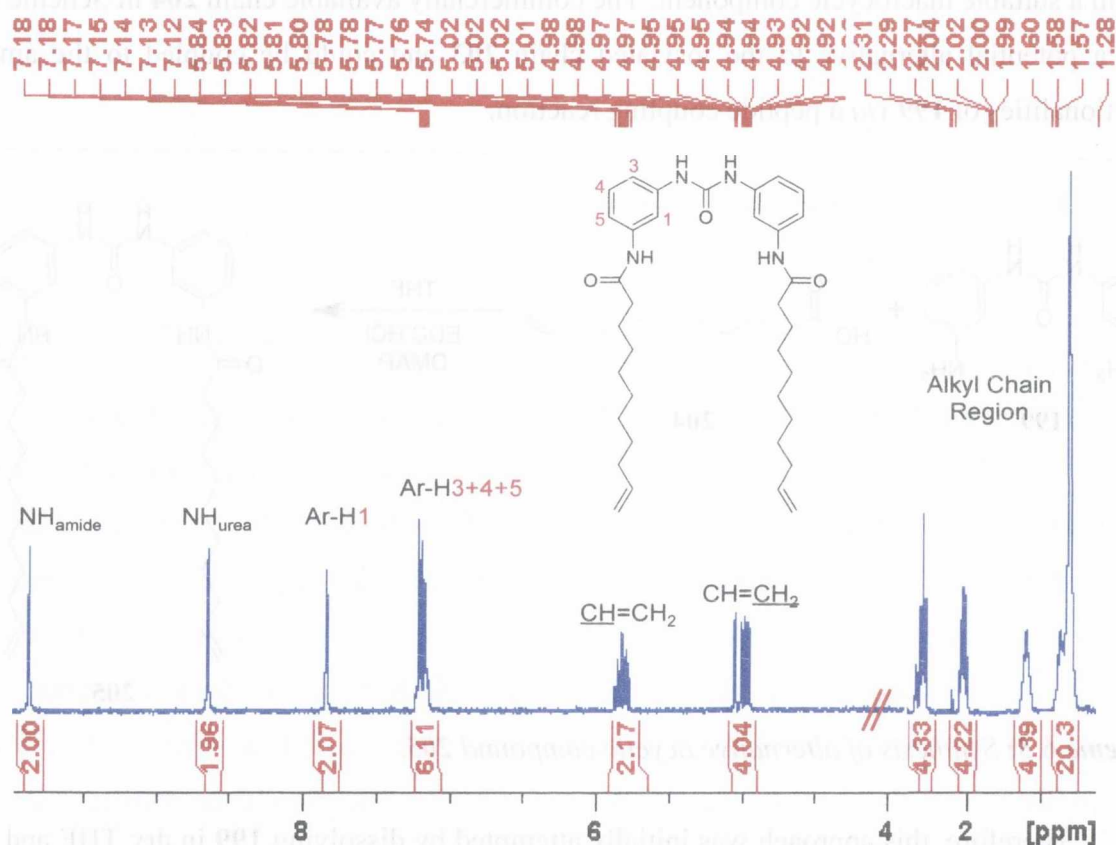
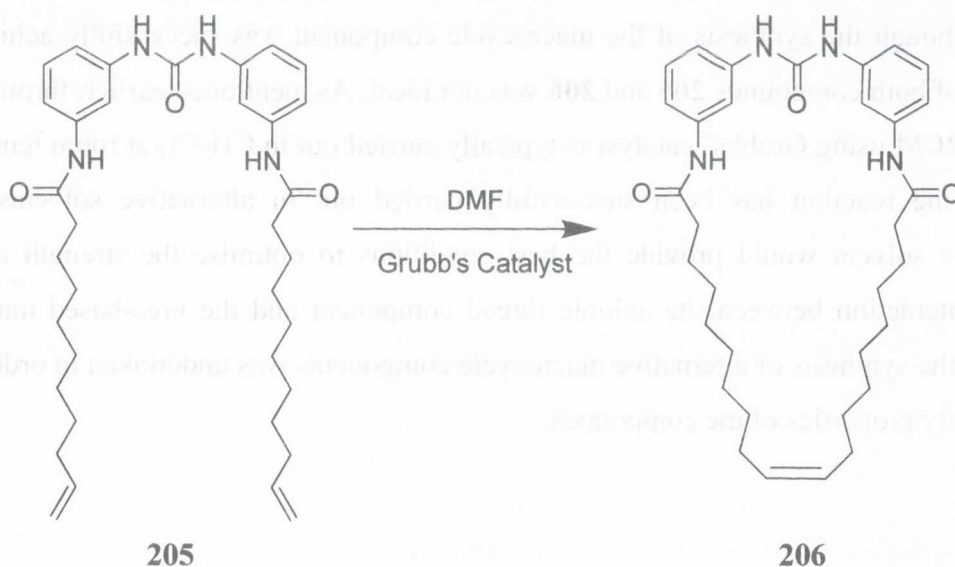


Figure 6.2: ^1H NMR spectrum (400 MHz, $\text{DMSO-}d_6$) of **205**.

Following successful synthesis of **205** the next stage was to establish the reaction conditions for successful formation of the macrocycle, **206**. As compound **205** contains terminal olefin groups the most common approach to macrocyclisation is ring closing metathesis (RCM) using Grubbs' catalyst. Olefin metathesis is a unique carbon skeleton redistribution in which unsaturated carbon-carbon bonds are rearranged in the presence of metal carbene complexes.²⁴¹ The reaction is most commonly carried out in CH_2Cl_2 as the non-competing solvent maximises the strength of the inter-component H-bonding. However, as compound **205** was insoluble in CH_2Cl_2 it was unlikely to result in successful

macrocyclisation. Nonetheless, the reaction was attempted in this solvent using Grubbs' second generation catalyst, as it was possible that reactive intermediates or possibly the product could result in solubilisation.

As predicted, however only starting material was recovered, even after attempting the reaction at room temperature, at reflux and also in a pressurised microwave vial at 100°C, consequently it was necessary to find an alternative solvent. The only two solvents that compound **205** could be solubilised in were either DMF or DMSO, therefore the reaction was attempted in DMF and microwave irradiated at 160°C for 10 minutes, Scheme 6.6. Following this, the solvent was removed under reduced pressure and the dark solid obtained triturated with CH₂Cl₂ to remove any catalyst. The ¹H NMR spectrum (400 MHz, DMSO-*d*₆) showed the presence of a singlet at 5.39 ppm indicative of successful macrocyclisation, as shown in Figure 6.3. The multiplets at 5.80 ppm and 4.94 ppm associated with the terminal alkene groups had also disappeared indicating the reaction had gone to completion with compound **206** formed in 95% yield. The remainder of the spectrum contained almost identical features to that of **205**.



Scheme 6.6: RCM reaction of **205** to give macrocycle **206**.

The reaction was also attempted with Grubbs' first generation and Hoveyda-Grubbs catalyst to ensure that the reaction could not be completed at room temperature in CH₂Cl₂. Unfortunately, irrespective of the catalyst the optimum conditions remained using DMF as the solvent and microwave irradiation at 160°C.

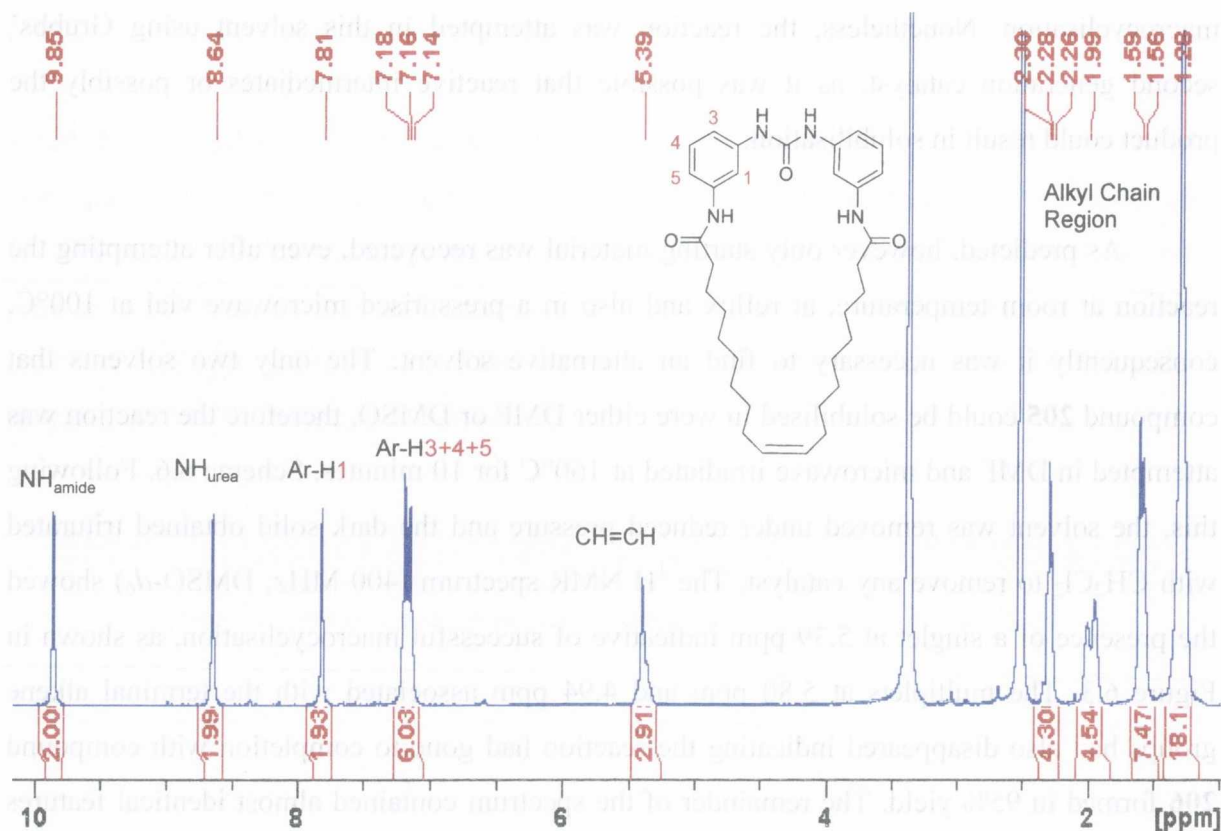
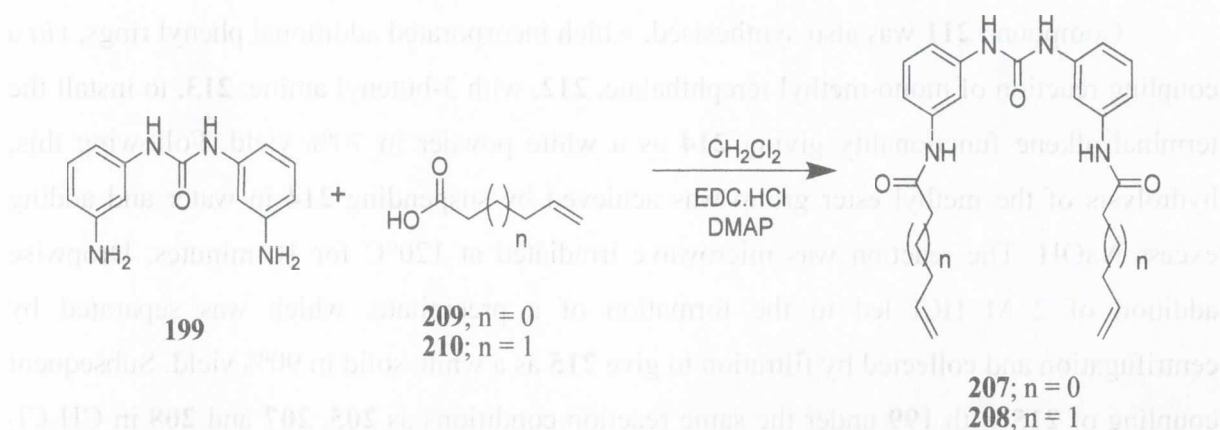


Figure 6.3: ^1H NMR spectrum of macrocycle **206**.

Although the synthesis of the macrocycle component was successfully achieved, the solubility of both compounds **205** and **206** was not ideal. As mentioned earlier, throughout the literature RCM using Grubbs' catalyst is typically carried out in CH_2Cl_2 at room temperature. Although the reaction has been successfully carried out in alternative solvents, a non-competitive solvent would provide the best conditions to optimise the strength of the H-bonding interaction between the anionic thread component and the urea-based macrocycle. Therefore the synthesis of alternative macrocycle components was undertaken in order to vary the solubility properties of the compounds.

6.2.1 Synthesis of Macrocycles **207**, **208** and **211**

It was envisaged that shortening the length of the alkyl chain of **205** could help to improve solubility. Therefore compounds **207** and **208**, with 6 and 7 carbon chain lengths respectively, were synthesised in an identical manner to that of **205** using di-amino precursor **199** and chains **209** and **210** respectively, Scheme 6.7. On both occasions the reactions led to the formation of a third phase upon dilution with water and CH_2Cl_2 , subsequently separated by centrifugation and collected by filtration to give off white solids in 74% and 80% yields, respectively.



Scheme 6.7: Synthesis of acyclic compounds **207** and **208**.

The ^1H NMR spectrum (400 MHz, $\text{DMSO}-d_6$) of **207** is shown in Figure 6.4 while that of **208** can be found in the Appendix (Appendix, Figure A6.1). The features are largely similar to that of **205** with the N-H resonances of the urea and amide groups present at 8.62 ppm and 9.86 ppm, respectively, while the aromatic protons all resonated between 7.81 ppm and 7.14 ppm. The terminal alkene protons resonated at 5.85 ppm and 5.02 ppm. The ^{13}C NMR spectrum (100 MHz, $\text{DMSO}-d_6$) of **207-208** showed the expected number of peaks and the $[\text{M} + \text{Na}]^+$ ions ($m/z = 457.2231$ and 485.2546) for both compounds observed using MALDI-ToF.

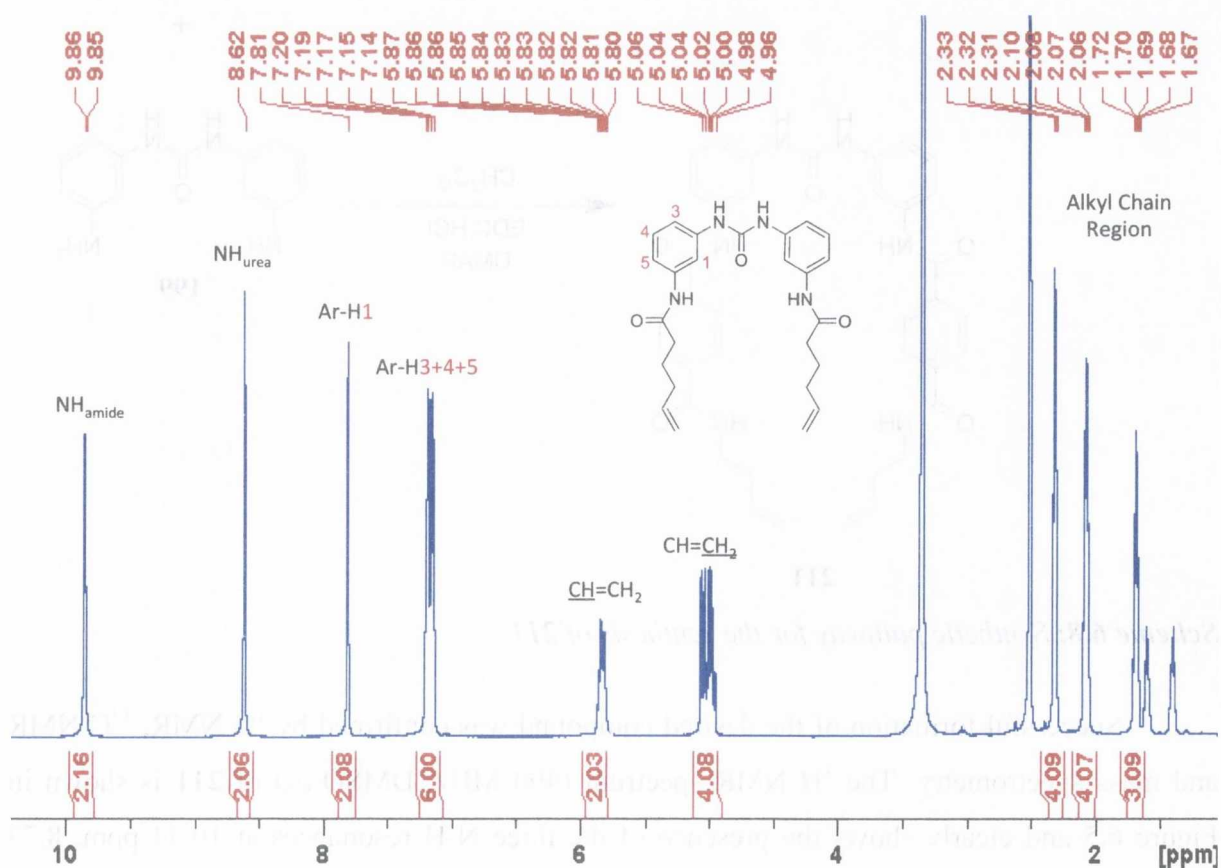
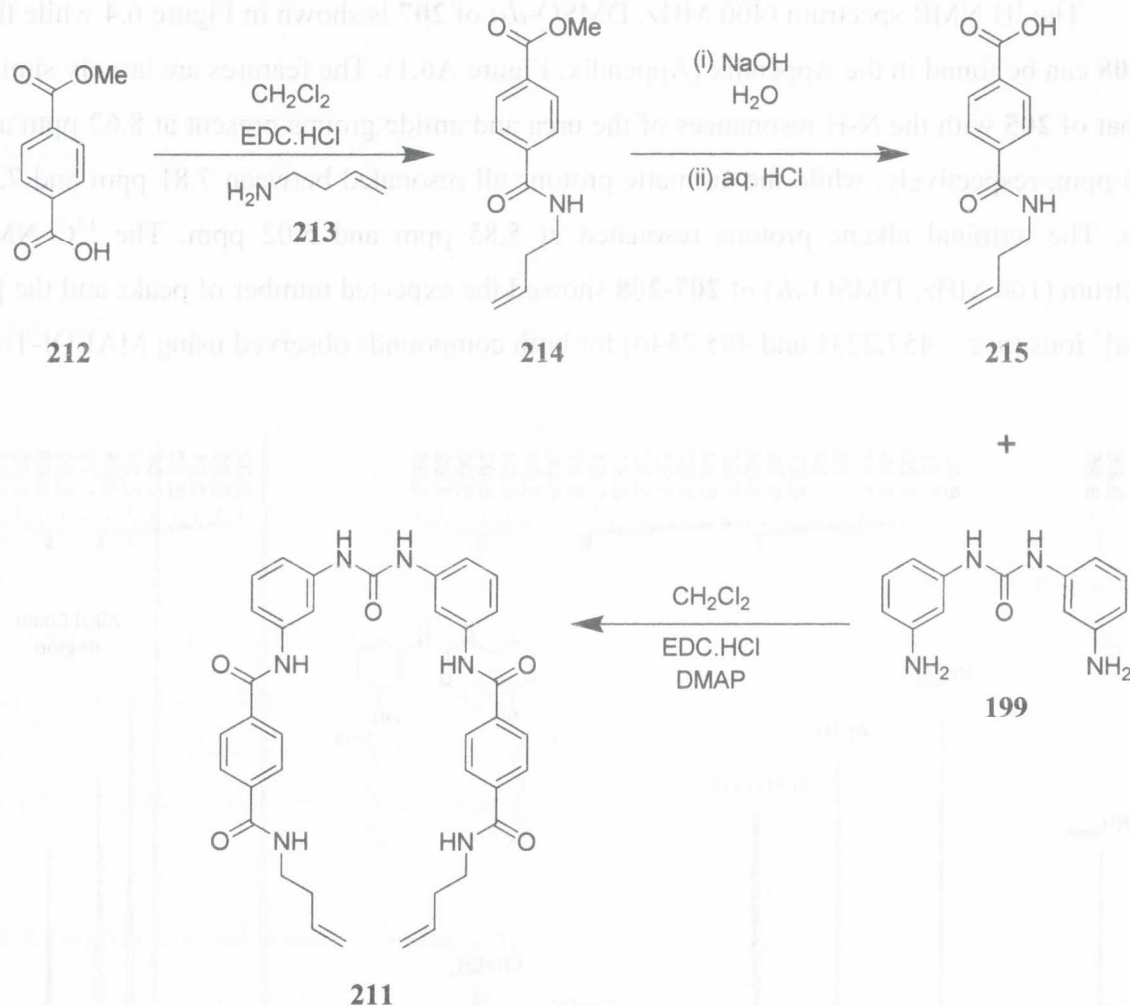


Figure 6.4: ^1H NMR spectrum of compound **207**.

Compound **211** was also synthesised, which incorporated additional phenyl rings, *via* a coupling reaction of mono-methyl terephthalate, **212**, with 3-butenyl amine, **213**, to install the terminal alkene functionality giving **214** as a white powder in 70% yield. Following this, hydrolysis of the methyl ester group was achieved by suspending **214** in water and adding excess NaOH. The reaction was microwave irradiated at 120°C for 10 minutes. Dropwise addition of 2 M HCl led to the formation of a precipitate, which was separated by centrifugation and collected by filtration to give **215** as a white solid in 90% yield. Subsequent coupling of **215** with **199** under the same reaction conditions as **205**, **207** and **208** in CH₂Cl₂ with EDC·HCl and DMAP gave compound **211** as an off white solid in 65% yield.



Scheme 6.8: Synthetic pathway for the synthesis of **211**.

Successful formation of the desired compound was confirmed by ¹H NMR, ¹³C NMR and mass spectrometry. The ¹H NMR spectrum (400 MHz, DMSO-*d*₆) of **211** is shown in Figure 6.5 and clearly shows the presence of the three N-H resonances at 10.34 ppm, 8.73 ppm and 8.65 ppm. The signal at 8.73 ppm, N-H_{urea}, is that of the urea proton located next to the phenylene moiety, as determined by selective NOE. These exchangeable N-H protons

were easily identifiable by the addition of D₂O to the ¹H NMR sample. The ¹³C NMR spectrum of **211** contained the expected number of resonances with the urea quaternary carbon found at 152 ppm and the amido carbon at 164 ppm. The ES⁺ mass spectrum of **211** confirmed the presence of the [M + Na]⁺ ion giving *m/z* = 667.2651.

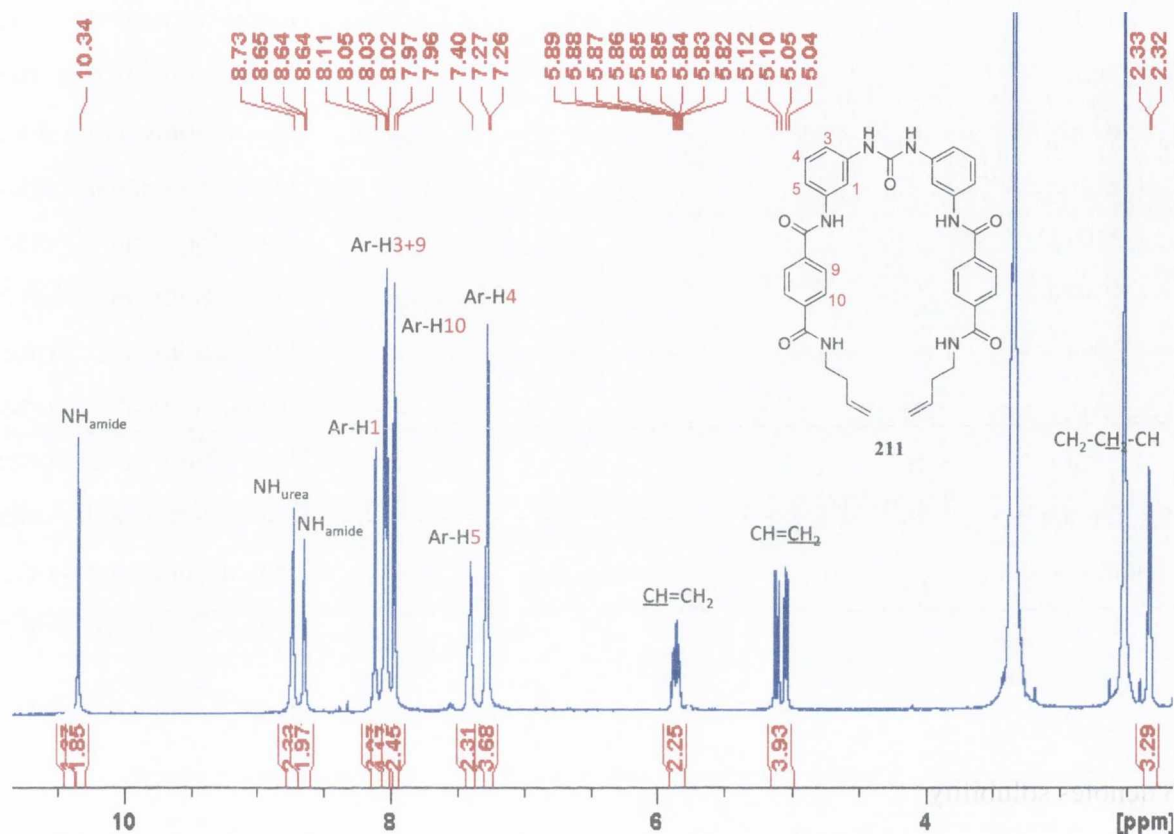


Figure 6.5: ¹H NMR spectrum (400 MHz, DMSO-*d*₆) of compound **211**.

The successful synthesis of a urea-based compound functionalised with terminal olefin groups suitable for RCM was initially hindered by the lack of solubility of **205** in solvents optimal for the RCM reaction, especially for the attempted synthesis of an interlocked molecule as high temperatures and competitive solvents would be detrimental to H-bond formation between the components of the rotaxane. The subsequent development of three other derivatives **207**, **208** and **211** were then investigated for different solubility properties and are summarised in Table 6.2 below. Unfortunately despite all attempts to solubilise compounds **205-208** and **211** the compounds only remained in solution in DMF and DMSO. Nevertheless, RCM of the open analogues **207**, **208** and **211** was investigated and will be discussed in the following section.

Table 6.2: Solubility properties of 205-208 and 211.

Solvent	Solubility					Additional Information
	205	206	207	208	211	
CH ₂ Cl ₂	-	-	-	-	-	Heated/Sonicated/Vortex
MeOH	-	-	-	-	-	Heated/Sonicated/Vortex
EtOH	-	-	-	-	-	Heated/Sonicated/Vortex
Acetone	-	-	-	-	-	Heated/Sonicated/Vortex
EtOAc	-	-	-	-	-	Heated/Sonicated/Vortex
Hexane	-	-	-	-	-	Heated/Sonicated/Vortex
CHCl ₃	-	-	-	-	-	Heated/Sonicated/Vortex
CH ₃ CN	-	-	-	-	-	Heated/Sonicated/Vortex
Ether	-	-	-	-	-	Heated/Sonicated/Vortex
DMF	S	S	S	S	S	Heated/Sonicated/Vortex
DMSO	S	S	S	S	S	Heated/Sonicated/Vortex
1,4-Dioxane	-	-	-	-	-	Heated/Sonicated/Vortex
Toluene	-	-	-	-	-	Heated/Sonicated/Vortex
THF	-	-	-	-	-	Heated/Sonicated/Vortex
DMF/CH ₃ CN (4:1)	-	-	-	-	-	Heated/Sonicated/Vortex

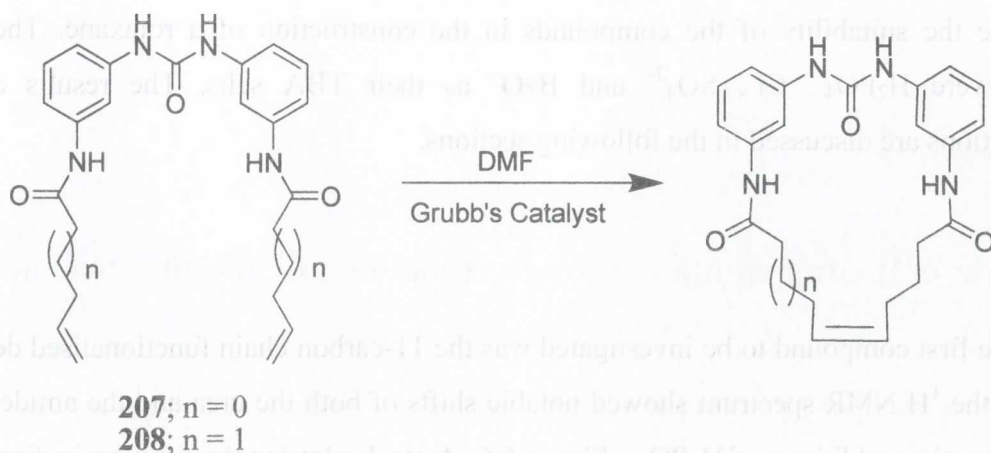
* S denotes solubility

6.2.2 RCM of 207, 208 and 211

Following successful synthesis of various urea-based acyclic derivatives the next stage was to attempt RCM on these structures. Having established that the solubility of the compounds had not been altered to allow dissolution in non-polar, non-competitive solvents such as CH₂Cl₂ the RCM reaction of **207**, **208** (Scheme 6.9) and **211** was attempted using the same methodology as **205** in DMF using Grubbs' catalyst.

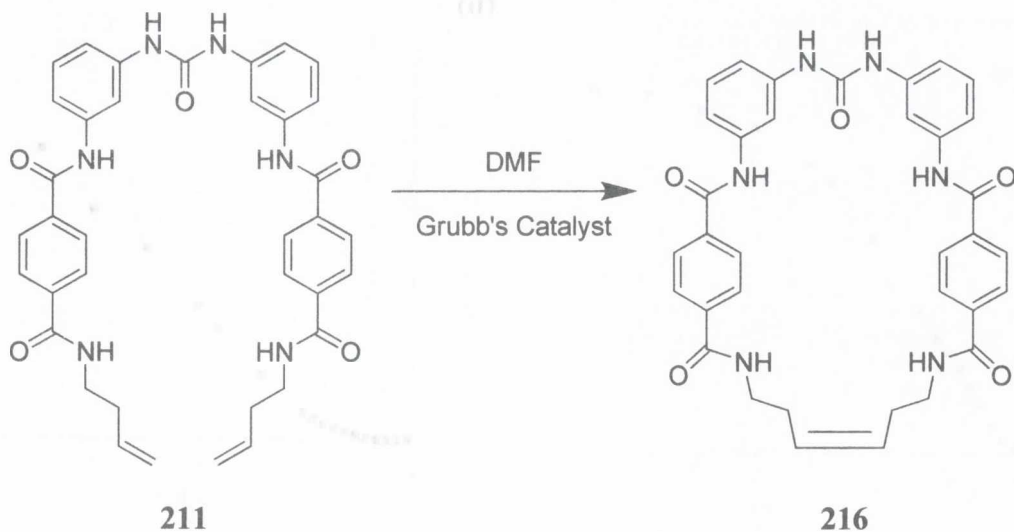
Unfortunately, the RCM of **207** and **208** did not go to completion, despite multiple attempts and only ever resulted in a mixture of both open and closed analogues. Due to the lack of solubility in any solvent other than DMF and DMSO, coupled with no difference in the polarity of these compounds, attempts at separating the acyclic starting material **207** from the desired macrocycle product repeatedly failed. Recrystallisation from DMF and DMSO was also attempted; however in every instance a powder crashed out of solution and upon analysis a mixture of compounds was still present. Compared to **206**, the size of the

macrocycle is much smaller and a possible explanation for the reaction not going to completion is the closed conformation of **207** or **208** is too strained and therefore unfavourable.



Scheme 6.9: RCM of **207** and **208**.

In contrast, the RCM of **211**, shown in Scheme 6.10, was successful and the macrocyclic compound **216** was obtained following microwave irradiation in DMF in the presence of Grubbs' catalyst in moderate yield (50%). The ^1H NMR (400 MHz, $\text{DMSO}-d_6$) of **216** confirmed macrocyclisation by the presence of the singlet at 5.41 ppm, similar to that seen for **206**. The remaining features of the spectrum were the same as those described for **211**. In addition to the ^1H NMR analysis of **216**, the compound was also characterised by ^{13}C NMR (100 MHz, $\text{DMSO}-d_6$) and the $[\text{M} + \text{Na}]^+$ ion observed using MALDI-ToF.



Scheme 6.10: RCM of **211**.

Although RCM of **207** and **208** failed, a small library of novel urea-based acyclic (**205**, **207**, **208** and **211**) and macrocyclic (**206** and **216**) compounds were successfully synthesised. Therefore, the anion binding capabilities of these compounds were next investigated by ^1H NMR spectroscopy in $\text{DMSO}-d_6$ for comparison of acyclic vs. macrocycle and also to determine the suitability of the compounds in the construction of a rotaxane. The anions studied were H_2PO_4^- , Cl^- , SO_4^{2-} and BzO^- as their TBA salts. The results of these investigations are discussed in the following sections.

6.2.3 Anion Binding Studies of Acyclic Compounds **205**, **207**, **208** and **211**

The first compound to be investigated was the 11-carbon chain functionalised derivative **205** and the ^1H NMR spectrum showed notable shifts of both the urea and the amide protons upon increasing additions of H_2PO_4^- , Figure 6.6. A stack plot for the titration is displayed in the Appendix (Appendix, Figure A6.2). It can be seen that the urea protons experience a downfield shift of *ca.* 1.5 ppm until the addition of 2 equivalents of anion, after which a plateau forms, Figure 6.6 (a). In contrast, the amide protons only began to shift significantly downfield after the addition of 1 equivalent, Figure 6.6 (b). This is indicative of a second binding interaction occurring after binding at the urea site has taken place. This positive allosteric effect was also seen with the simple (thio)urea-based receptors **108-113** in Chapter 2. The ^1H NMR data was best fit to a 1:2 (host:guest) stoichiometry as predicted with $\log K_{1:1} = 2.32$ and $\log K_{1:2} = 3.75$ obtained from *NMRTit HGG* (Appendix, Figure A6.3).

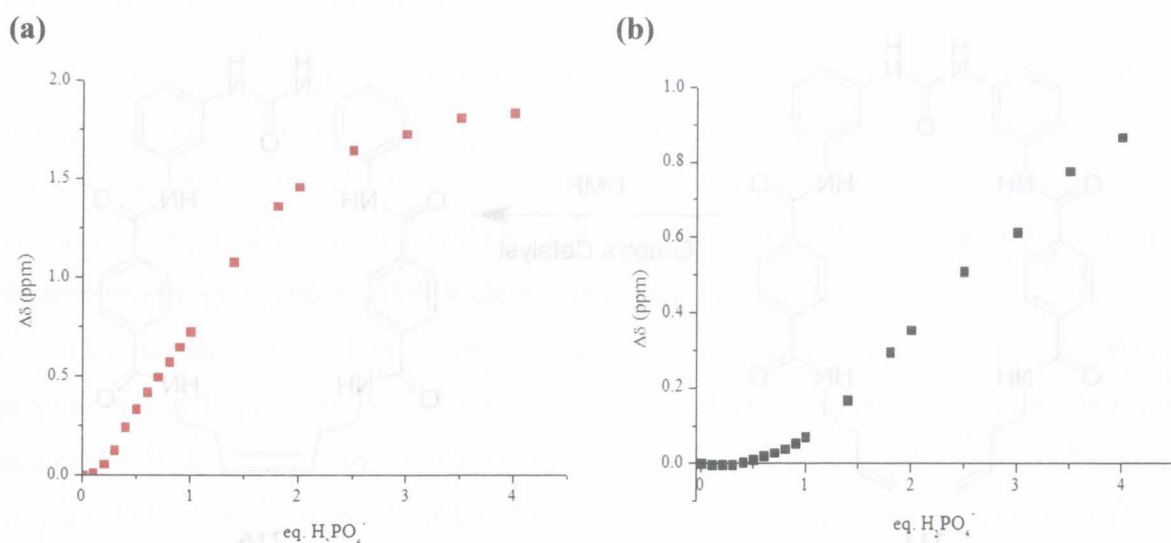


Figure 6.6: Changes in the (a) urea and (b) amide resonances of **205** (as $\Delta\delta$) upon titration with H_2PO_4^- .

The next anion to be studied with **205** was SO_4^{2-} and a different binding profile to that of H_2PO_4^- was observed (Appendix A6.4). The chemical shift difference experienced by the urea protons was *ca.* 3 ppm and a plateau was reached by 1 equivalent of the anion. In addition, the amide protons experienced a very minor upfield shift (< 0.1 ppm), which gradually shifted back downfield after the addition of 1 equivalent. The binding of SO_4^{2-} was analysed using *NMRTit HG*. The changes in the chemical shifts of the urea N-H proton fitted well to a 1:1 stoichiometric interaction with $\log K_{1:1} = 3.90$ calculated (Appendix, Figure A6.5). In comparison to H_2PO_4^- , where a 1:2 (host:guest) interaction was observed, with the second binding interaction occurring at the amide site, clearly shows the receptor interacts with both anions in a different manner.

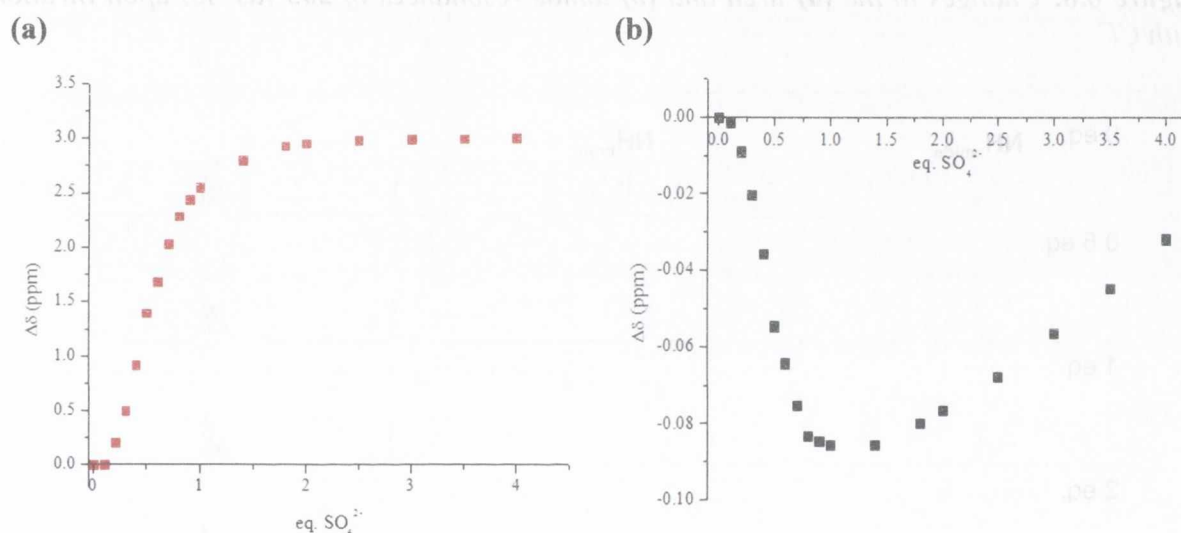


Figure 6.7: Changes in the (a) urea and (b) amide resonances of **205** (as $\Delta\delta$) upon titration with SO_4^{2-} .

The addition of Cl^- resulted in a small (< 0.5 ppm), continuous downfield shift of the urea protons, however a plateau was never reached, even at higher equivalents of Cl^- , while the amide protons only experienced a very minor shift (< 0.1 ppm), Figure 6.8 and Figure 6.9. This behaviour is characteristic of a very weak binding interaction and is most likely energetically unfavourable, as has been observed with other urea-based receptor in this Thesis. Due to the minor shifts experienced by **205** upon titration with Cl^- , a binding constant could not be obtained from the data set.

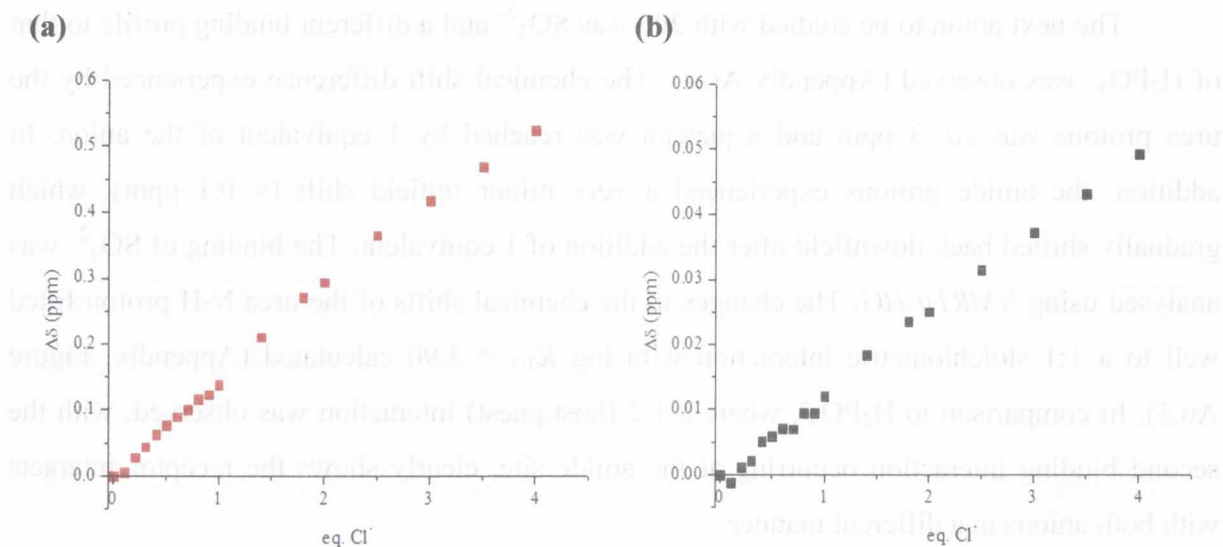


Figure 6.8: Changes in the (a) urea and (b) amide resonances of **205** (as $\Delta\delta$) upon titration with Cl^- .

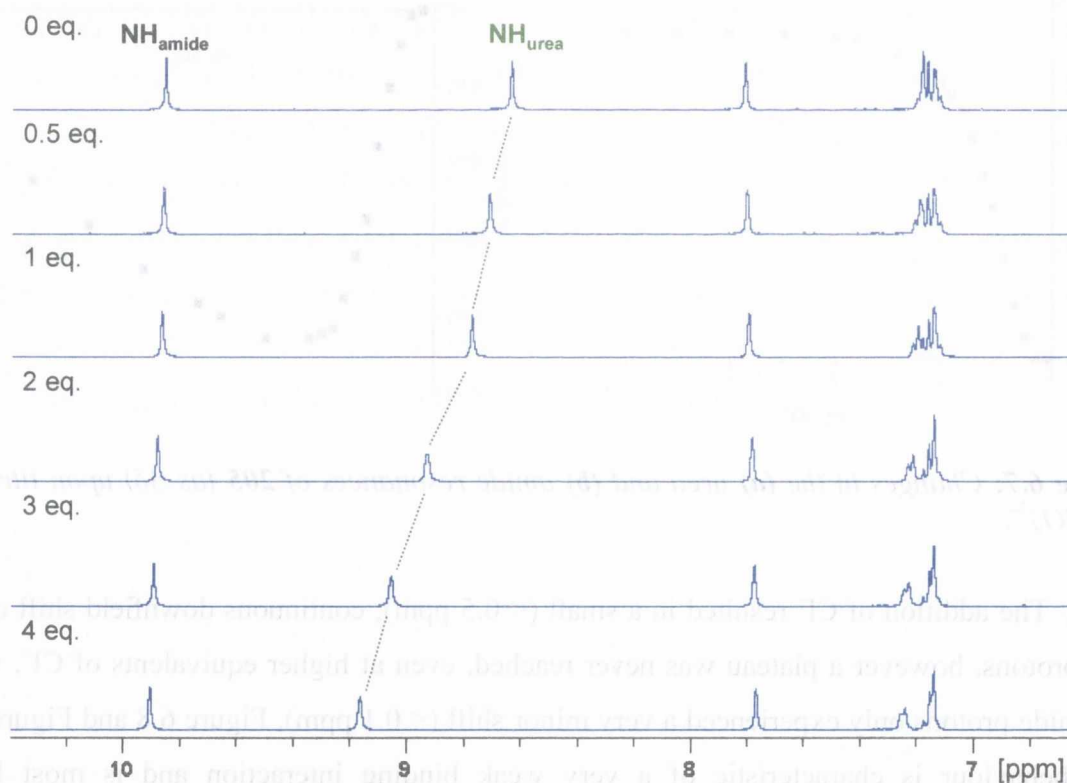


Figure 6.9: Stack plot of ^1H NMR spectra (400 MHz, DMSO-d_6) of **205** ($7 \times 10^{-3} \text{ M}$) upon addition of 0, 0.5, 1, 2, 3, and 4 equivalents of Cl^- .

The addition of benzoate resulted in the urea protons displaying a similar binding profile to that seen for H_2PO_4^- while the amide protons behaved in an opposing manner, shifting upfield, albeit by a very small shift ($< 0.02 \text{ ppm}$) until the addition of 2 equivalents before returning to their original position, Figure 6.10. The stack plot for the titration is displayed in the Appendix (Appendix, Figure A6.6) The ^1H NMR data was best fit to a 1:2 (host:guest) stoichiometry with $\log K_{1:1} = 2.39$ and $\log K_{1:2} = 3.70$ obtained from *NMRTit HGG*

(Appendix, Figure A6.7). The values obtained are very similar to that of H_2PO_4^- , not surprising as both titrations followed the same profile.

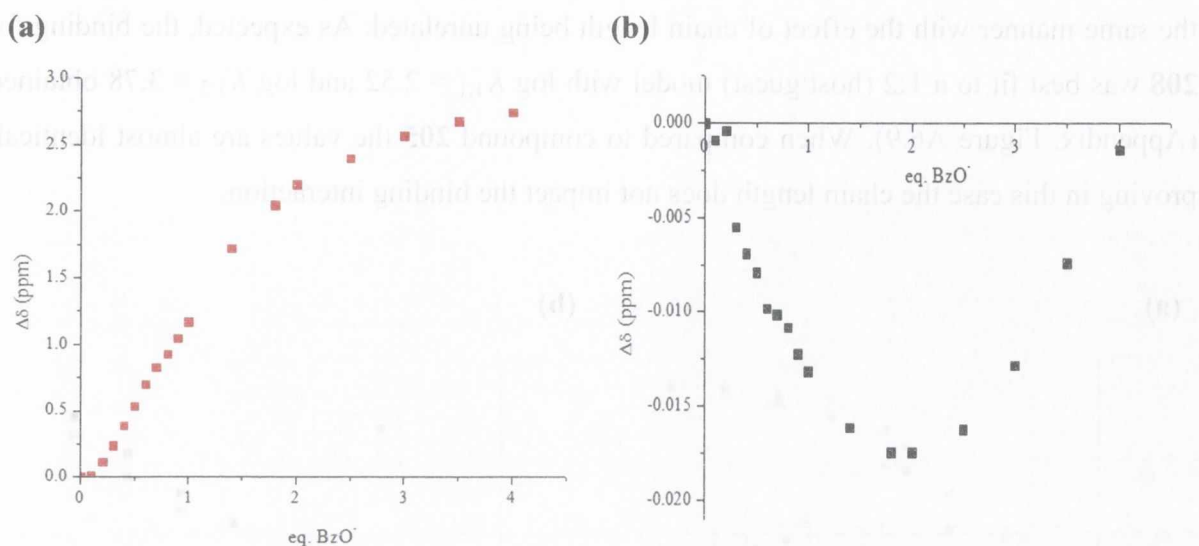


Figure 6.10: Changes in the (a) urea and (b) amide resonances of **205** (as $\Delta\delta$) upon titration with BzO^- .

During the binding process the host undergoes conformational readjustment in order to arrange its binding sites in the manner most complementary to the guest and at the same time minimising unfavourable interactions between one binding site and another on the host.²⁴² In the case of compound **205**, each anion resulted in a different binding profile and perhaps this phenomenon can be correlated to the size and shape of each anion. The titration with SO_4^{2-} was the only anion to give in a 1:1 stoichiometry from the binding isotherm with $\log K_{1:1} = 3.90$. For H_2PO_4^- and benzoate the plateau appeared to begin to form at 2 equivalents of these anions. Both titrations also resulted in almost identical binding constants for the 1:1 and 1:2 (host:guest) interactions, *i.e.* $\log K_{1:1} = 2.32$ and 2.39 , for H_2PO_4^- and benzoate, respectively. Also, only in the case of H_2PO_4^- the amide proton did appear to be strongly involved in the binding process as in all other instances the changes observed for the amide proton were extremely minor, attributed to conformational changes upon binding of the anion to the urea moiety.

The shorter chain derivatives, **207** and **208** were next investigated and a large degree of similarity between both compounds themselves and also between the 11-carbon chain analogue **205** was observed. In the case of H_2PO_4^- , there were very minor differences in the binding profile of the urea protons of **207** and **208**, Figure 6.11 (a) with a plateau approaching at 2 equivalents of H_2PO_4^- . The stack plot for the titration of **207** and H_2PO_4^- is shown in Figure 6.12, while that of **208** is given in the Appendix (Appendix, Figure A6.8). After the

addition of 1 equivalent of the anion, an upward turn of the binding curve was also observed for the amide protons of both compounds, Figure 6.11 (b). This behaviour was also seen for compound **205** and consequently reveals that compounds **205**, **207** and **208** bind this anion in the same manner with the effect of chain length being unrelated. As expected, the binding for **208** was best fit to a 1:2 (host:guest) model with $\log K_{1:1} = 2.52$ and $\log K_{1:2} = 3.78$ obtained (Appendix, Figure A6.9). When compared to compound **205** the values are almost identical, proving in this case the chain length does not impact the binding interaction.

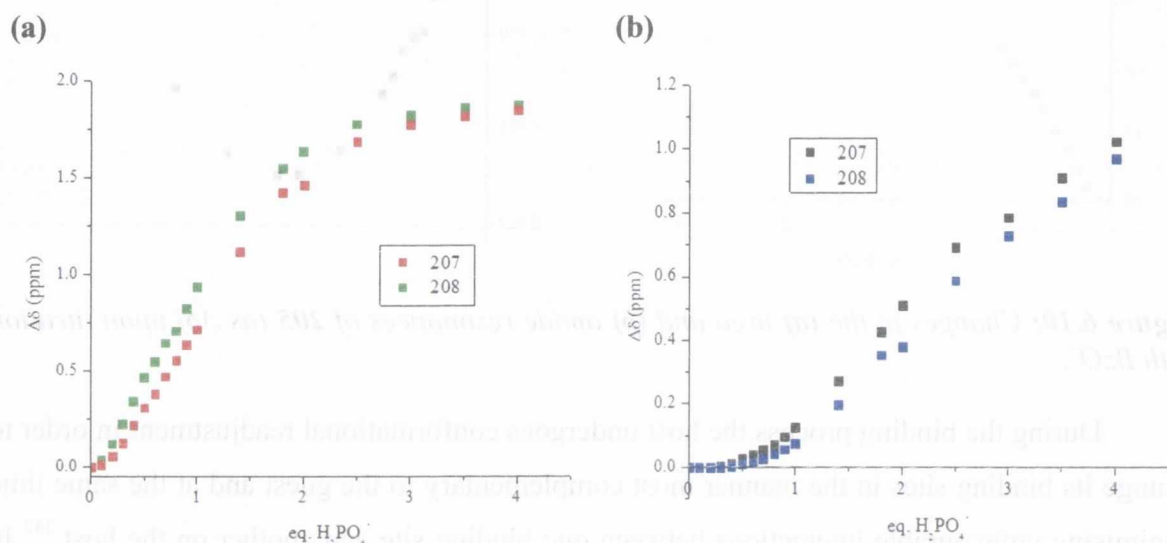


Figure 6.11: Changes in the (a) urea and (b) amide resonances of **207** and **208** (as $\Delta\delta$) upon titration with H_2PO_4^- .

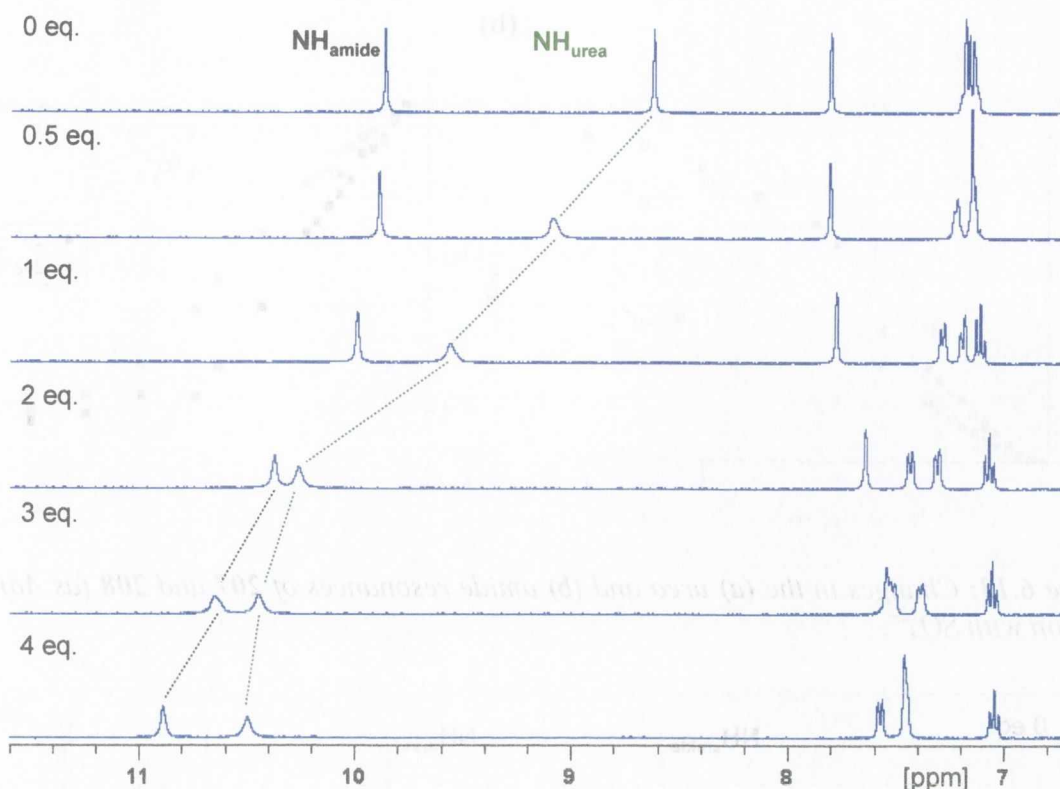


Figure 6.12: Stack plot of ^1H NMR spectra (400 MHz, DMSO-d_6) of **207** (7×10^{-3} M) upon addition of 0, 0.5, 1, 2, 3, and 4 equivalents of H_2PO_4^- .

In contrast to **205**, the binding profile observed for **207** and **208** upon addition of SO_4^{2-} did not reach a plateau at 1 equivalent but instead the urea protons continued to shift downfield and only changed slope at *ca.* 2 equivalents, as shown in the stack plot for the titration of **208** in Figure 6.14 and in the Appendix for **207** (Appendix, Figure A6.10). The titration profile for the amide proton mirrored this result with a small upfield shift observed until 2 equivalents of anion before reaching a plateau. In a similar manner to H_2PO_4^- , the titration was best to fit to a 1:2 (host:guest) stoichiometry with $\log K_{1:1} = 2.57$ and $\log K_{1:2} = 3.25$ for **207** and $\log K_{1:1} = 2.15$ and $\log K_{1:2} = 2.42$ for **208** (Appendix, Figure A6.11-12). In this case, the chain length does appear to have a significant effect on the binding interaction with SO_4^{2-} .

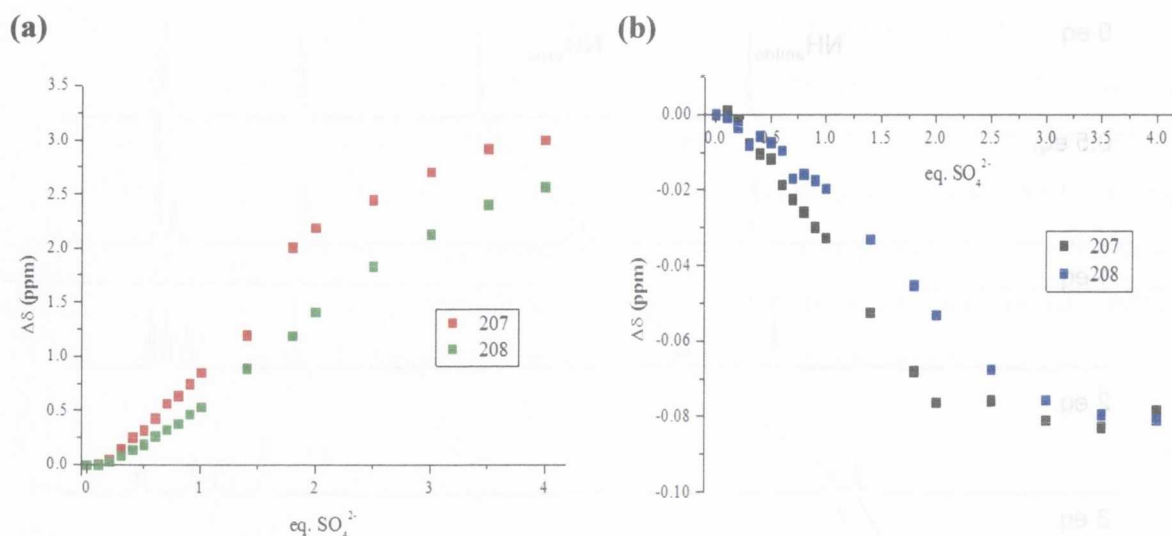


Figure 6.13: Changes in the (a) urea and (b) amide resonances of **207** and **208** (as $\Delta\delta$) upon titration with SO_4^{2-} .

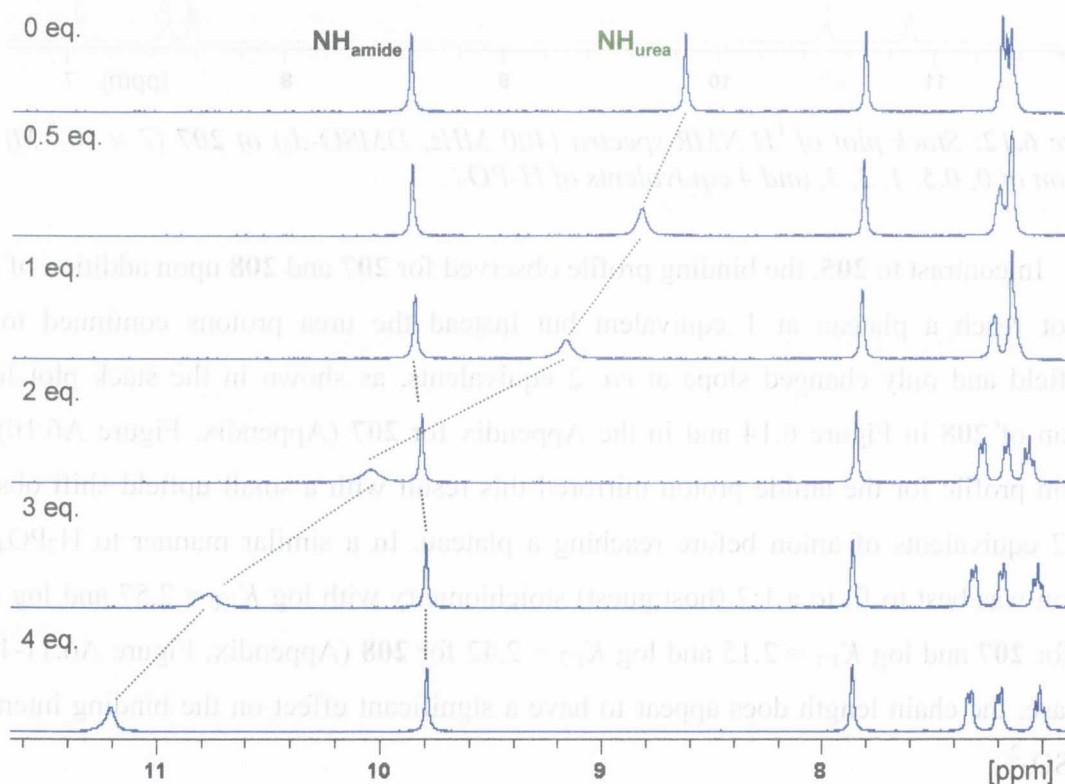


Figure 6.14: Stack plot of ^1H NMR spectra (400 MHz, DMSO-d_6) of **208** ($7 \times 10^{-3} \text{ M}$) upon addition of 0, 0.5, 1, 2, 3, and 4 equivalents of SO_4^{2-} .

The interaction with **207** and **208** and the Cl^- anion also displayed a linear binding profile for the urea protons, Figure 6.15 (a), identical to that seen for **205** and again can be attributed to the unfavourable interaction between the two receptors and this anion. The amide proton also did not contribute to the binding process, Figure 6.15 (b). The data was unsuitable for fitting and binding constants could not be obtained for this titration.

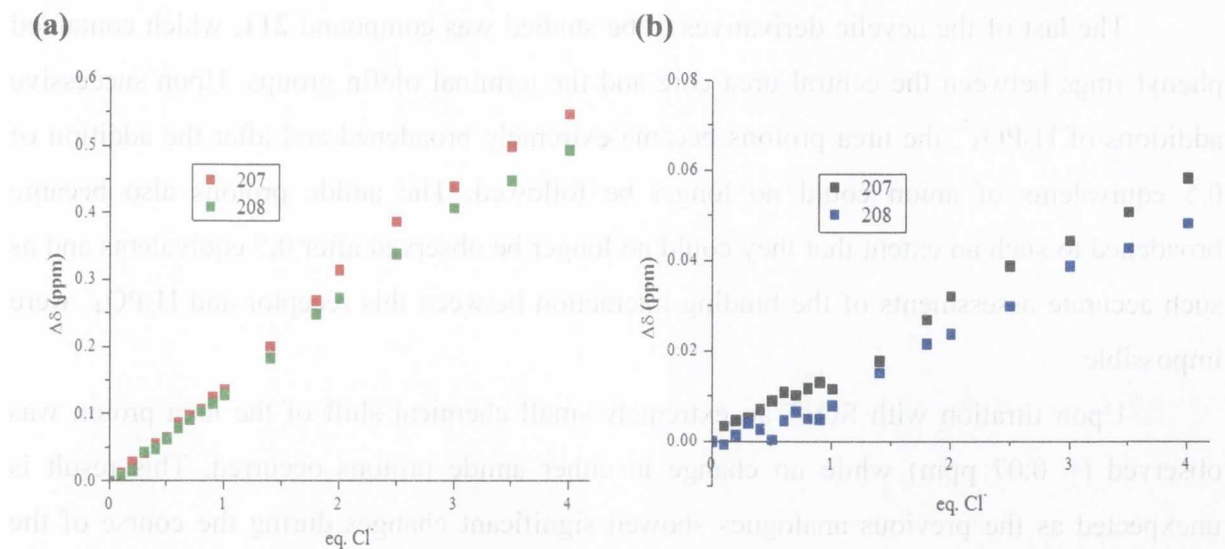


Figure 6.15: Changes in the (a) urea and (b) amide resonances of **207** (as $\Delta\delta$) upon titration with Cl^- .

The final anion to be investigated with these receptors was benzoate and like H_2PO_4^- and Cl^- showed a very similar trend to that seen for **205**. After the addition of 2 equivalents, a plateau began to form while the amide protons of both receptors barely exhibited any shift during the course of the titration (< 0.02 ppm), Figure 6.16. The stack plots for the changes observed during the course of the titrations are given in the Appendix (Appendix, Figure A6.13-14). Comparable binding constants of $\log K_{1:1} = 2.32$ and $\log K_{1:2} = 3.31$ for **207** and $\log K_{1:1} = 2.47$ and $\log K_{1:2} = 3.62$ for **208** were obtained from *NMRTit HGG* (Appendix, A6.15-16). These values are also very similar to that obtained for receptor **205**, indicating the three compounds bind benzoate in the same manner.

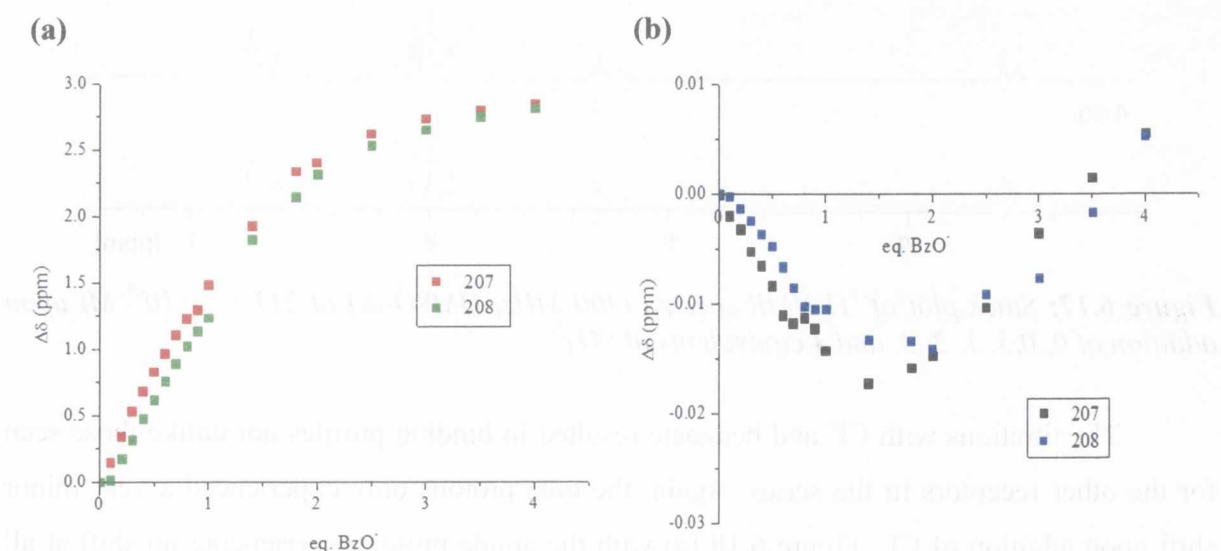


Figure 6.16: Changes in the (a) urea and (b) amide resonances of **207** and **208** (as $\Delta\delta$) upon titration with BzO^- .

The last of the acyclic derivatives to be studied was compound **211**, which contained phenyl rings between the central urea core and the terminal olefin groups. Upon successive additions of H_2PO_4^- , the urea protons became extremely broadened and after the addition of 0.5 equivalents of anion could no longer be followed. The amide protons also became broadened to such an extent that they could no longer be observed after 0.5 equivalents and as such accurate assessments of the binding interaction between this receptor and H_2PO_4^- were impossible.

Upon titration with SO_4^{2-} an extremely small chemical shift of the urea proton was observed (< 0.07 ppm) while no change in either amide protons occurred. This result is unexpected as the previous analogues showed significant changes during the course of the titrations with the various anions and would require more detailed investigations. The stack plot for the titration is shown in Figure 6.17.

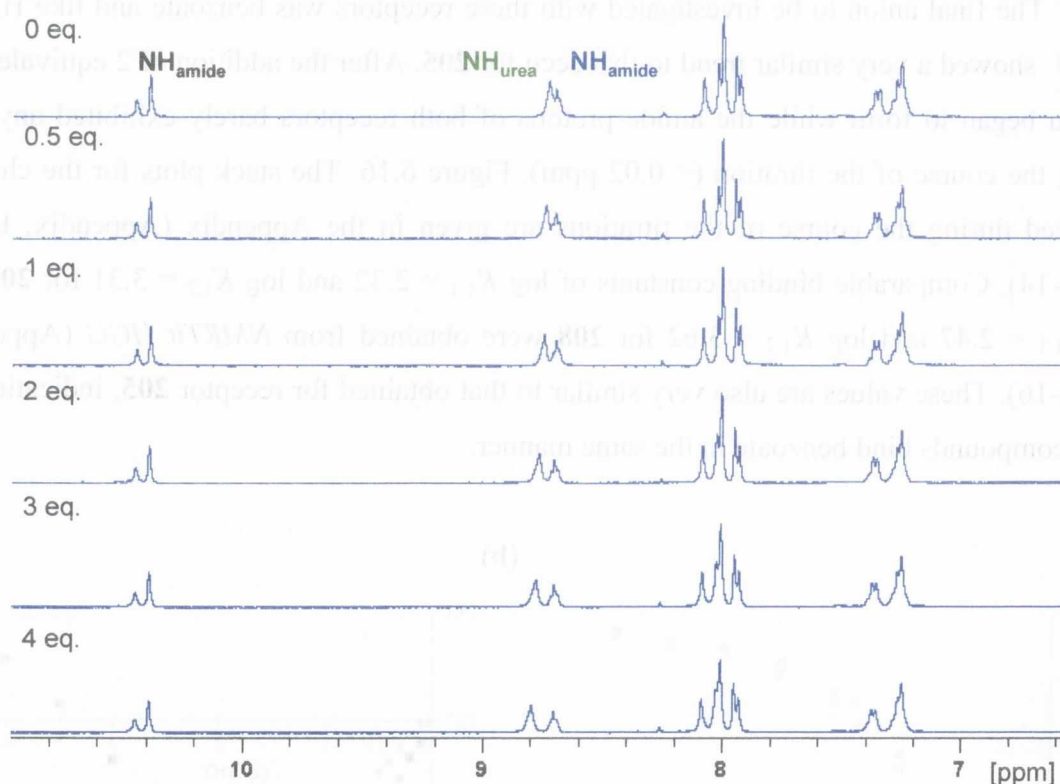


Figure 6.17: Stack plot of ^1H NMR spectra (400 MHz, $\text{DMSO}-d_6$) of **211** (7×10^{-3} M) upon addition of 0, 0.5, 1, 2, 3, and 4 equivalents of SO_4^{2-} .

The titrations with Cl^- and benzoate resulted in binding profiles not unlike those seen for the other receptors in the series. Again, the urea protons only experienced a very minor shift upon addition of Cl^- , Figure 6.18 (a) with the amide proton experiencing no shift at all during the course of the titration (Appendix, Figure A6.17). In contrast, the addition of benzoate resulted in a large downfield shift of the urea protons, Figure 6.18 (b) but no effect

on the amide protons were observed (Appendix, Figure A6.18). It was possible to fit the data for the titration of **211** with benzoate to a 1:2 (host:guest) stoichiometry using *NMRTit HGG* (Appendix, Figure A6.19). Binding constants of $\log K_{1:1} = 2.04$ and $\log K_{1:2} = 2.60$ were obtained and when compared to that of the previous receptors **205**, **207** and **208** were the lowest observed in the series. It may be possible the receptor is forming a π - π stacking network coupling with intermolecular H-bonds, which are more favourable than the interaction with anions such as SO_4^{2-} or benzoate.

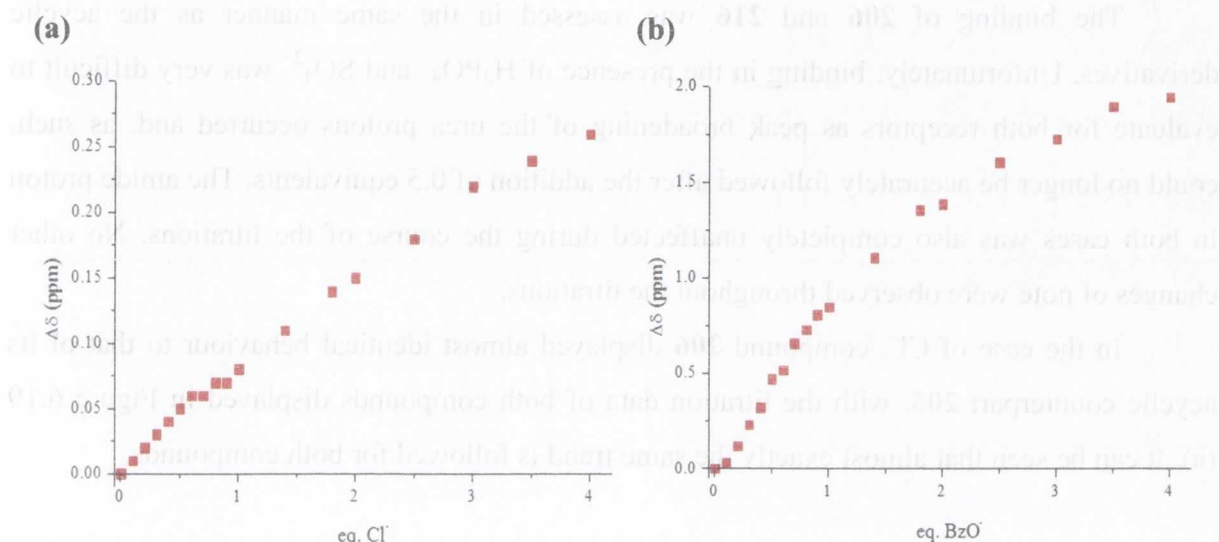


Figure 6.18: Changes in the urea protons of **211** (as $\Delta\delta$) upon titration with (a) Cl^- and (b) BzO^- .

Unfortunately, irrespective of the pendant attachments to the core di-aryl urea framework, receptors **205**, **207**, **208** and **211** did not display large differences upon titration with the various anions. The interaction between receptor **205** with H_2PO_4^- and benzoate were almost identical with very small differences in the binding constants determined. The biggest difference observed was the interaction of **205** with SO_4^{2-} in comparison to the other receptors, where a 1:1 binding interaction was observed and rapid formation of a stable host:guest species between **205** and SO_4^{2-} . Receptors **207** and **208** exhibited a less favourable interaction with a plateau starting to occur at *ca.* 2 equivalents of SO_4^{2-} and a second 1:2 (host:guest) species being observed upon fitting the data. In the case of **208** and H_2PO_4^- again the binding constants were almost identical to that seen previously as the behaviour of the shorter chain derivatives followed the same trend as that of **205**. With the exception of H_2PO_4^- , the amide proton did not appear to participate in the binding process.

The next stage was to investigate the effect of RCM on the anion binding ability of **205** and **211**, *i.e.* macrocycles **206** and **216**. As mentioned previously extension of this method to the shorter chain derivatives, **207** and **208**, was met with severe problems as separation of the desired macrocycle from the acyclic starting material impossible. Therefore, the following section details the studies conducted on macrocycles **206** and **216**.

6.2.4 Anion Binding Studies of Macrocycles **206** and **216**

The binding of **206** and **216** was assessed in the same manner as the acyclic derivatives. Unfortunately, binding in the presence of H_2PO_4^- and SO_4^{2-} was very difficult to evaluate for both receptors as peak broadening of the urea protons occurred and, as such, could no longer be accurately followed after the addition of 0.5 equivalents. The amide proton in both cases was also completely unaffected during the course of the titrations. No other changes of note were observed throughout the titrations.

In the case of Cl^- , compound **206** displayed almost identical behaviour to that of its acyclic counterpart **205**, with the titration data of both compounds displayed in Figure 6.19 (a). It can be seen that almost exactly the same trend is followed for both compounds.

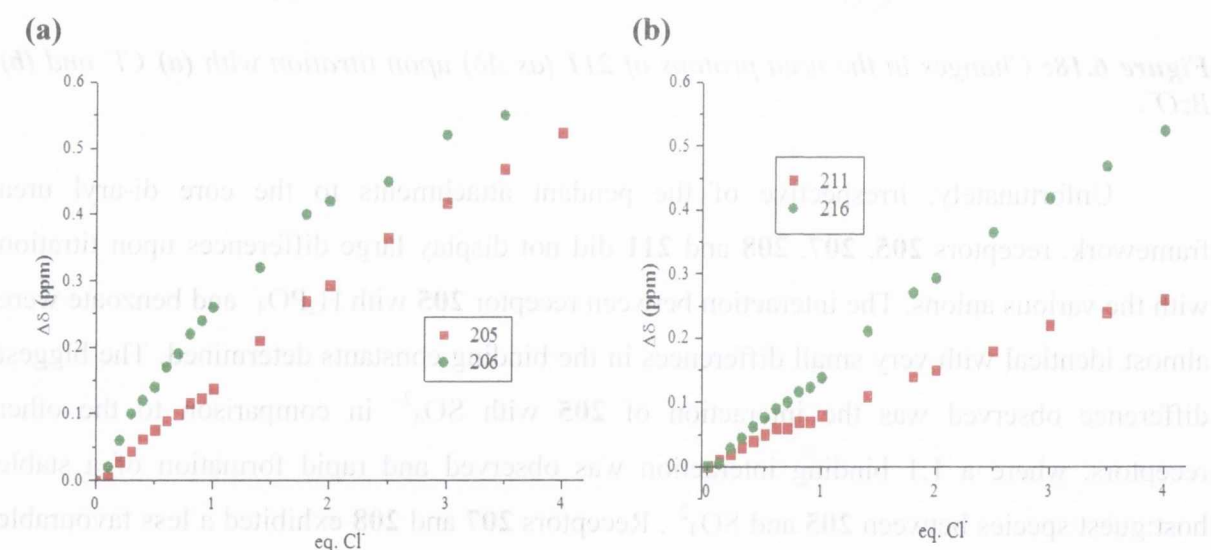


Figure 6.19: Changes in the urea protons of (a) **205** vs. **206** and (b) **211** vs. **216** (as $\Delta\delta$) upon titration with Cl^- .

Figure 6.19 (b) shows the data for the titration of the acyclic compound **211** alongside its macrocyclic counterpart **216** with Cl^- and, again, it can be seen that there is hardly any difference in the binding profile of these compounds. It was already determined that the Cl^- did not interact strongly with compounds **205**, **207**, **208** or **211** and it was, therefore, not surprising that the macrocycle analogues displayed the same weak interaction.

In direct contrast, successive additions of benzoate to compound **206** showed a more stable binding profile to that of its acyclic equivalent, **205**, with a plateau forming at *ca.* 1 equivalent, Figure 6.20 (a). The ^1H NMR data was indeed best fit to a 1:1 binding model and a binding constant of $\log K_{1:1} = 3.04$ determined (Appendix, Figure A6.20). This illustrates the more rigid macrocycle interacts differently than the acyclic derivative, however the amide proton did not experience any shift in both cases.

In the case of **216** although the magnitude of the shift was larger compared to **211**, the overall slope of the binding curve followed the same trend indicating the binding process was the same for both acyclic and macrocycle compounds, Figure 6.20 (b).

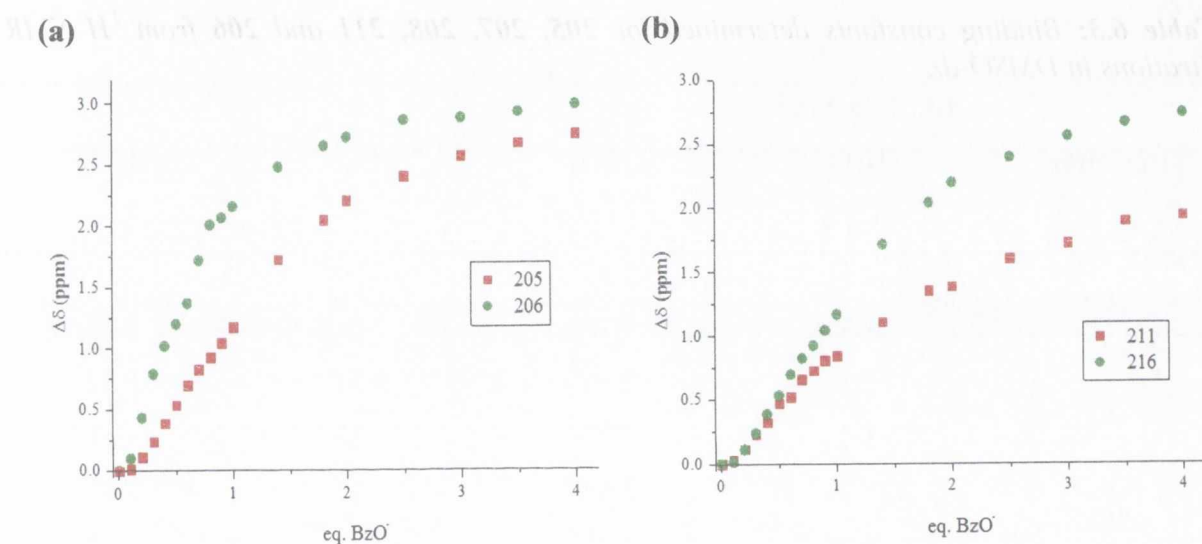


Figure 6.20: Changes in the urea protons of (a) **205** vs. **206** and (b) **211** vs. **216** (as $\Delta\delta$) upon titration with BzO^- .

In summary, a library of four urea-based compounds with terminal olefin groups, **205**, **207**, **208** and **211**, were successfully synthesised. Due to their very low solubility, they spontaneously separate from the reaction mixture – a phenomenon seen with other similar urea-based compounds.¹⁵⁴ RCM was also successfully carried out on compounds **205** and **211** to give macrocycles **206** and **216**, however in the case of **207** and **208**, the reaction never went to completion and the macrocycles could never be isolated from the acyclic starting materials. The anion binding abilities of these compounds were investigated and it was found that there was very little difference between the various acyclic compounds themselves and also very little difference between the acyclic and macrocyclic derivatives. The binding constants are summarised in Table 6.3. There were two notable exceptions, *i.e.* compound **205** preferentially bound SO_4^{2-} in a 1:1 stoichiometry while **207** and **208** exhibited a very similar pattern with a 2:1 (guest:host) stoichiometry seen upon fitting of the ^1H NMR data. The

binding constants determined for both receptors were also of similar value. Receptor **211**, in contrast, did not show any change in chemical shift upon addition of SO_4^{2-} . The other main difference seen between the receptors was the binding interaction of **205** and **206** (*i.e.* acyclic vs. cyclic) and benzoate where the more rigid macrocycle **206** showed the formation of a 1:1 species while in the case of compound **205** the binding interaction appeared weaker with a plateau beginning to form at *ca.* 2 equivalents of anion. Again, fitting of the data revealed two different binding stoichiometries for the open and closed forms of the receptor. Thus, preorganisation and complementarity are pivotal concepts for the correct design for anion receptors.

Table 6.3: Binding constants determined for **205**, **207**, **208**, **211** and **206** from ^1H NMR titrations in $\text{DMSO}-d_6$.

Receptor	Binding Mode			
	(H:G)	H_2PO_4^-	SO_4^{2-}	BzO^-
	Log <i>K</i>			
205	1:1	2.32	3.90	2.39
	1:2	3.75	-	3.70
207	1:1	2.59	2.57	2.32
	1:2	3.27	3.25	3.31
208	1:1	2.52	2.15	2.47
	1:2	3.78	2.42	3.62
211	1:1	-	-	2.04
	1:2	-	-	2.60
206	1:1	-	-	3.04

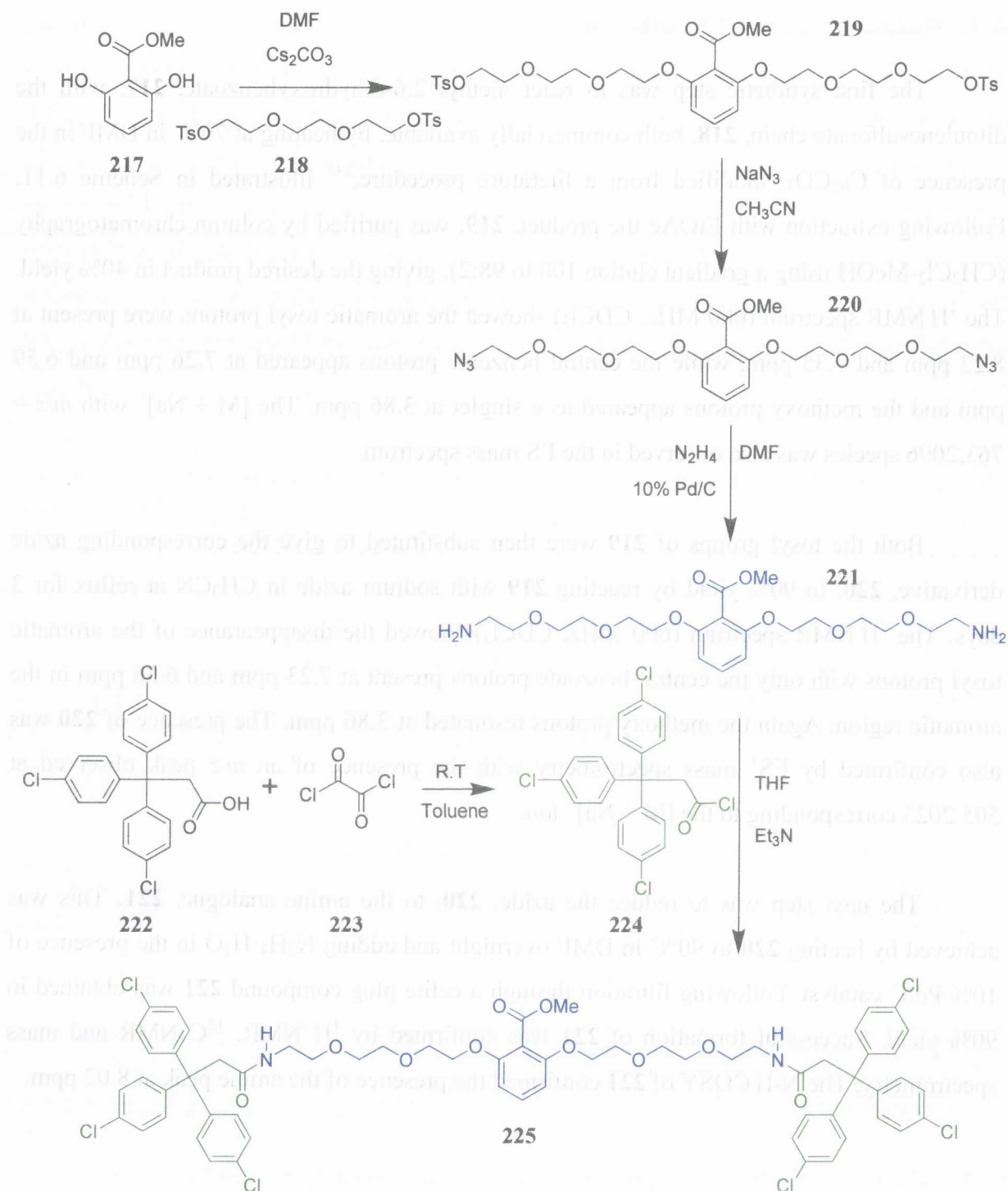
Although these compounds were designed to be employed in the assembly of an anion templated rotaxane, the poor solubility properties coupled with the extremely harsh reaction conditions of RCM did not make them ideal candidates. However, the interesting properties of the acyclic compound **205** and the macrocycle **206** compound with the benzoate anion may still lead to the possible formation of an interlocked molecule. Therefore the following sections detail the synthesis of a rotaxane thread component that contains a central benzoate core, which offers the possibility of H-bonding to the urea macrocycle.

6.3 Rotaxane Thread Synthesis

The first synthetic step was to react methyl 2,6-dihydroxybenzoate, **217**, with the ditoulenesulfonate chain, **218**, both commercially available, by heating at 70°C in DMF in the presence of Cs_2CO_3 , modified from a literature procedure,²⁴³ illustrated in Scheme 6.11. Following extraction with EtOAc the product, **219**, was purified by column chromatography (CH_2Cl_2 -MeOH using a gradient elution 100 to 98:2), giving the desired product in 40% yield. The ^1H NMR spectrum (600 MHz, CDCl_3) showed the aromatic tosyl protons were present at 8.22 ppm and 7.35 ppm, while the central benzoate protons appeared at 7.26 ppm and 6.59 ppm and the methoxy protons appeared as a singlet at 3.86 ppm. The $[\text{M} + \text{Na}]^+$ with $m/z = 763.2096$ species was also observed in the ES mass spectrum.

Both the tosyl groups of **219** were then substituted to give the corresponding azide derivative, **220**, in 90% yield by reacting **219** with sodium azide in CH_3CN at reflux for 3 days. The ^1H NMR spectrum (600 MHz, CDCl_3) showed the disappearance of the aromatic tosyl protons with only the central benzoate protons present at 7.23 ppm and 6.56 ppm in the aromatic region. Again the methoxy protons resonated at 3.86 ppm. The presence of **220** was also confirmed by ES^+ mass spectrometry with the presence of an m/z peak observed at 505.2023 corresponding to the $[\text{M} + \text{Na}]^+$ ion.

The next step was to reduce the azide, **220**, to the amine analogue, **221**. This was achieved by heating **220** to 90°C in DMF overnight and adding $\text{N}_2\text{H}_4 \cdot \text{H}_2\text{O}$ in the presence of 10% Pd/C catalyst. Following filtration through a celite plug compound **221** was obtained in 90% yield. Successful formation of **221** was confirmed by ^1H NMR, ^{13}C NMR and mass spectrometry. The N-H COSY of **221** confirmed the presence of the amine peak at 8.02 ppm.



Scheme 6.11: Synthetic pathway for the synthesis of rotaxane thread 225.

Stopper **224** was synthesised by reacting the commercially available 3,3,3-tris(4-chlorophenyl)propanoic acid, **222** with oxalyl chloride, **223** in toluene at room temperature overnight.²⁴⁴ Stopper **224** was obtained in 85% yield following recrystallisation from hexane- CH_2Cl_2 (50:50). The presence of the acid chloride functionality was confirmed by IR spectrometry with a characteristic stretch at *ca.* 1816 cm^{-1} and the disappearance of the broad $-\text{OH}$ stretch at *ca.* 2800 cm^{-1} of the acid starting material (Appendix, Figure A6.21-22).

The penultimate step in the target thread synthesis was to react stopper **224** with the amine **221** to give compound **225**. This was achieved by dissolving **221** and Et₃N in dry THF and cooling to 0°C. Stopper **224** was dissolved in THF and added dropwise to the solution and the reaction stirred overnight. The solvent was then removed under reduced pressure, diluted with CH₂Cl₂ (15 mL) and washed with water (4 × 20 mL). The organic layer was dried over MgSO₄ and solvent removed under reduced pressure. A yellow oil was obtained in 77% yield. The ¹H NMR spectrum (600 MHz, DMSO-*d*₆), Figure 6.21, showed the presence of two doublets at 7.34 ppm and 7.16 ppm, corresponding to the aromatic protons of the three phenyl rings. The amide proton appeared at 7.70 ppm, while the CH₂'s of the ethoxy chain ranged from 2.94 ppm to 4.09 ppm. The central benzoate protons appeared at 7.29 ppm and 6.70 ppm, respectively.

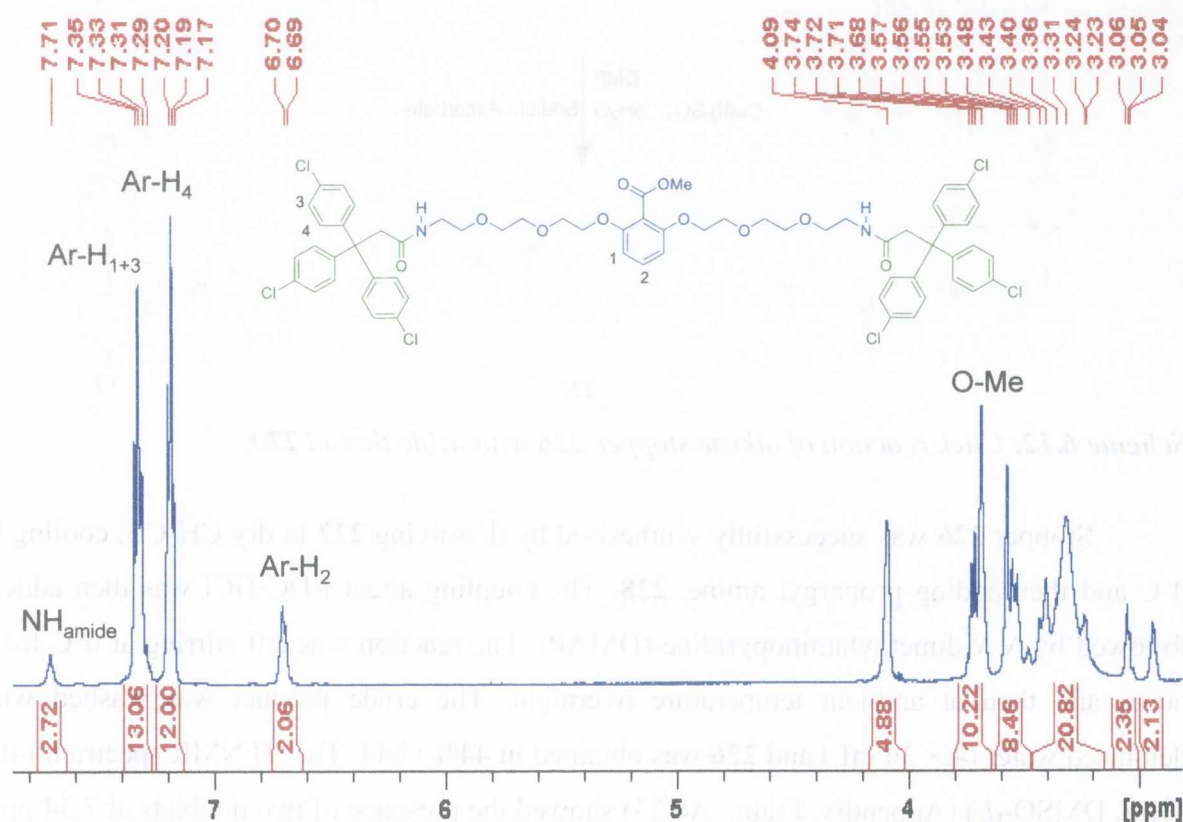
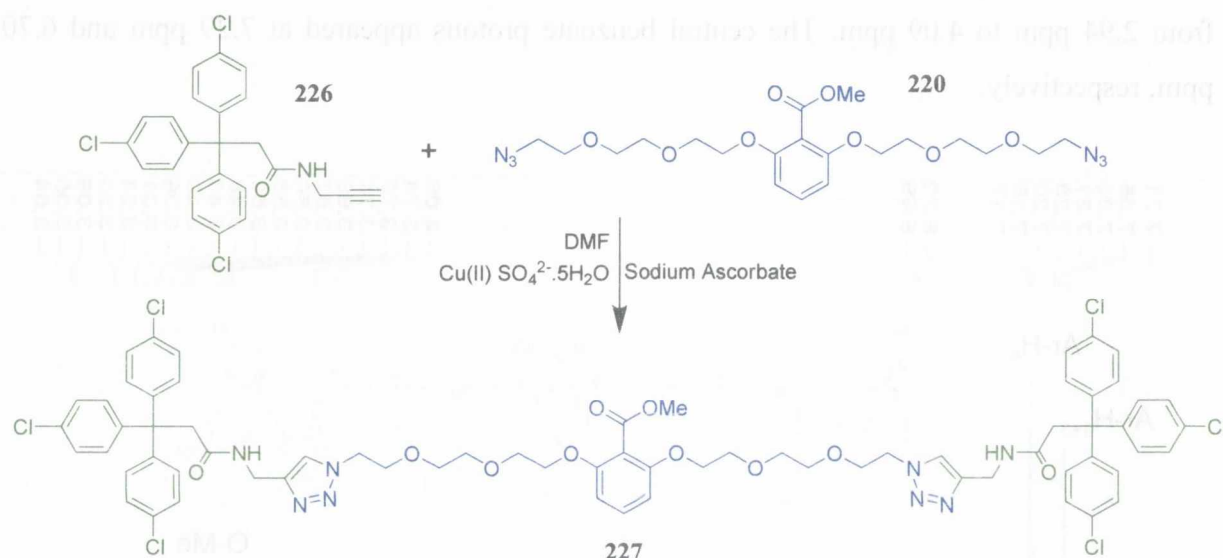


Figure 6.21: ¹H NMR spectrum (600 MHz, DMSO-*d*₆) of **225**.

¹³C NMR was also employed to determine successful formation of **225** with MALDI-ToF analysis also confirming the successful formation of **225** with the presence of a peak at *m/z* = 1225.2316, corresponding to the [M + Na]⁺ species in solution.

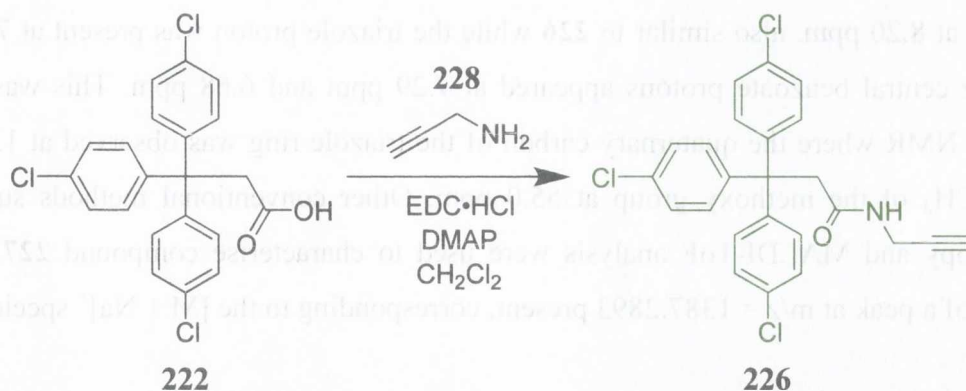
The terminal azide functionality of **220** could also be reacted with a stopper containing an alkyne group in a “click reaction”, *i.e.* by using the the Huisgen-Meldal-Fokin copper(I)-

catalysed terminal alkyne-azide cycloaddition (the CuAAC reaction), providing a second thread for the rotaxane, **227**. The unique structural features of the 1,2,3-triazole ring with its large dipole moment, aromatic stability, and free electron pairs on nitrogen render it a versatile building block in its own right,²⁴⁵ while the mild reaction conditions and high yields of ‘click chemistry’ offered a promising synthetic approach, as illustrated in Scheme 6.12. However this involved the synthesis of compound **226**. Scheme 6.13 illustrates the synthesis undertaken to develop alkyne stopper **226** that was suitable for the click reaction conditions, using the commercially available carboxylic acid, **222** employed in the synthesis of stopper **224**.



Scheme 6.12: Click reaction of alkyne stopper **226** with azide thread **220**.

Stopper **226** was successfully synthesised by dissolving **222** in dry CH₂Cl₂, cooling to 0°C and then adding propargyl amine, **228**. The coupling agent EDC·HCl was then added, followed by *N,N*-dimethylaminopyridine (DMAP). The reaction was left stirring at 0°C for 2 hours and then at ambient temperature overnight. The crude product was washed with deionised water (4 × 30 mL) and **226** was obtained in 44% yield. The ¹H NMR spectrum (400 MHz, DMSO-*d*₆) (Appendix, Figure A6.23) showed the presence of two doublets at 7.34 ppm and 7.16 ppm, corresponding to the aromatic protons of the three phenyl rings. The amide proton appeared as a triplet at 8.10 ppm, while the terminal alkyne proton was a broad singlet at 3.02 ppm.



Scheme 6.13: Synthetic scheme of alkyne stopper **226**.

Stopper **226** and the azide thread **220** were then used in the CuAAC reaction, shown previously in Scheme 6.12. This was achieved by dissolving **220**, **226** and sodium ascorbate in dry DMF, followed by the addition of $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ dissolved in water. The reaction was left stirring at 25°C overnight. The crude product was then washed with water ($2 \times 60\text{ mL}$) and extracted with CH_2Cl_2 ($2 \times 60\text{ mL}$). Solvents were removed under reduced pressure and **227** was obtained as a green oil in 91% yield.

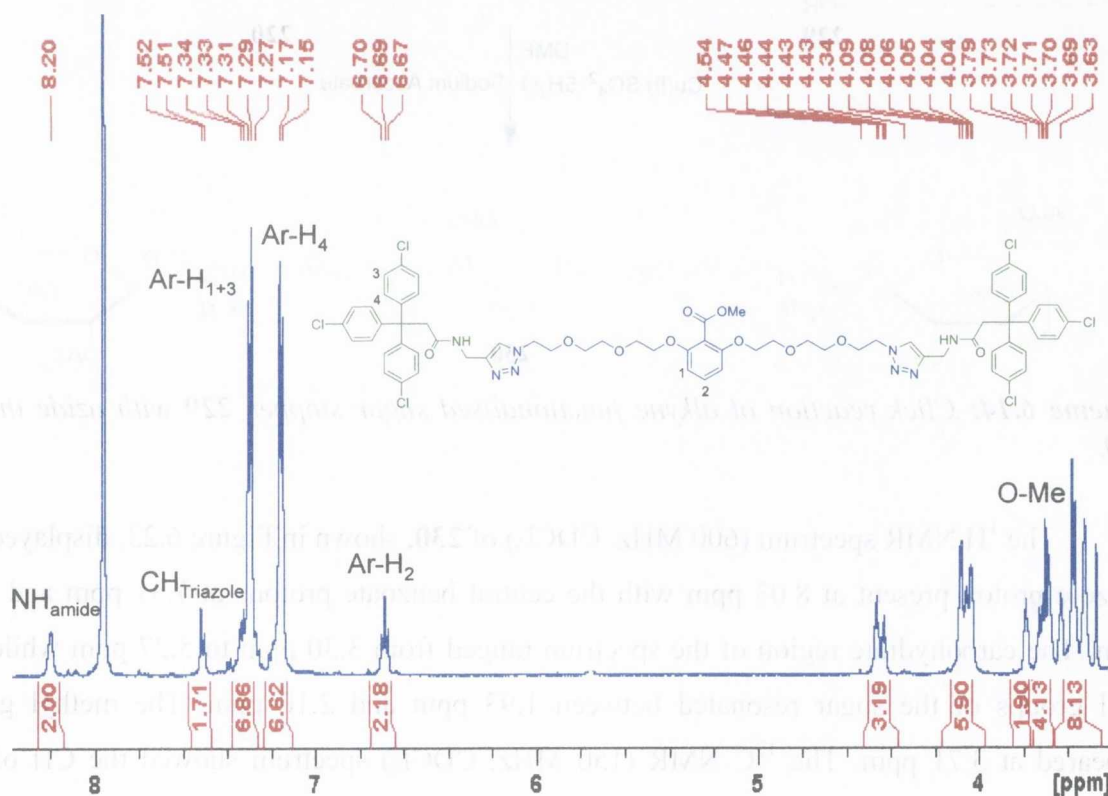
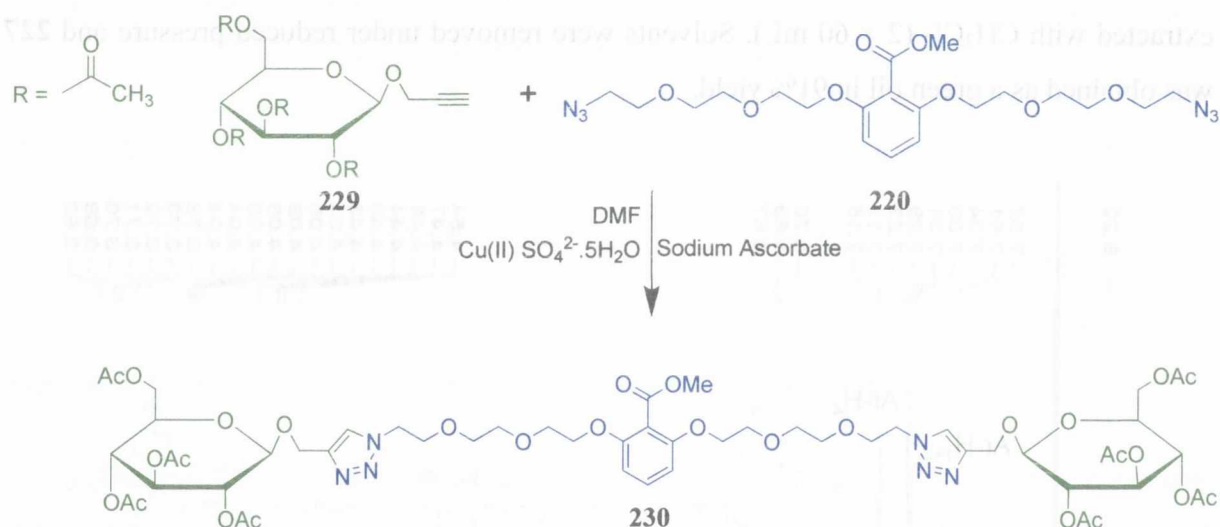


Figure 6.22: ^1H NMR spectrum (600 MHz, $\text{DMSO}-d_6$) of **227**.

The ^1H NMR spectrum (600 MHz, $\text{DMSO}-d_6$) of **227**, Figure 6.22, displayed two doublets at 7.34 ppm and 7.16 ppm corresponding to the aromatic protons of the three phenyl rings, previously seen in the ^1H NMR spectrum of **226** alone. The characteristic amide protons

resonated at 8.20 ppm, also similar to **226** while the triazole proton was present at 7.52 ppm. Again the central benzoate protons appeared at 7.29 ppm and 6.68 ppm. This was verified using ^{13}C NMR where the quaternary carbon of the triazole ring was observed at 131.4 ppm and the CH_3 of the methoxy group at 55.0 ppm. Other conventional methods such as IR spectroscopy and MALDI-ToF analysis were used to characterise compound **227** with the presence of a peak at $m/z = 1387.2893$ present, corresponding to the $[\text{M} + \text{Na}]^+$ species.

Using the same methodology, the sugar clicked compound **230** was also successfully synthesised by reacting **220** with the alkyne functionalised sugar **229**. In this case, however, the reaction was microwave irradiated at 80°C for 40 minutes and **230** was obtained in 75% yield. These unique stoppers provide an alternative to the triphenyl groups conventionally employed in rotaxane synthesis.



Scheme 6.14: Click reaction of alkyne functionalised sugar stopper **229** with azide thread **220**.

The ^1H NMR spectrum (600 MHz, CDCl_3) of **230**, shown in Figure 6.23, displayed the triazole proton present at 8.03 ppm with the central benzoate protons at 7.31 ppm and 6.71 ppm. The carbohydrate region of the spectrum ranged from 3.30 ppm to 5.27 ppm while the acyl groups of the sugar resonated between 1.93 ppm and 2.10 ppm. The methyl group appeared at 3.71 ppm. The ^{13}C NMR (150 MHz, CDCl_3) spectrum showed the CH of the triazole ring at 124.4 ppm while the quaternary carbon of this functionality resonated at 143.0 ppm. The methoxy group was found at 51.7 ppm. MALDI-ToF analysis confirmed formation of the sugar functionalised product with the presence of a peak at $m/z = 1277.4408$ for the $[\text{M} + \text{Na}]^+$ species.

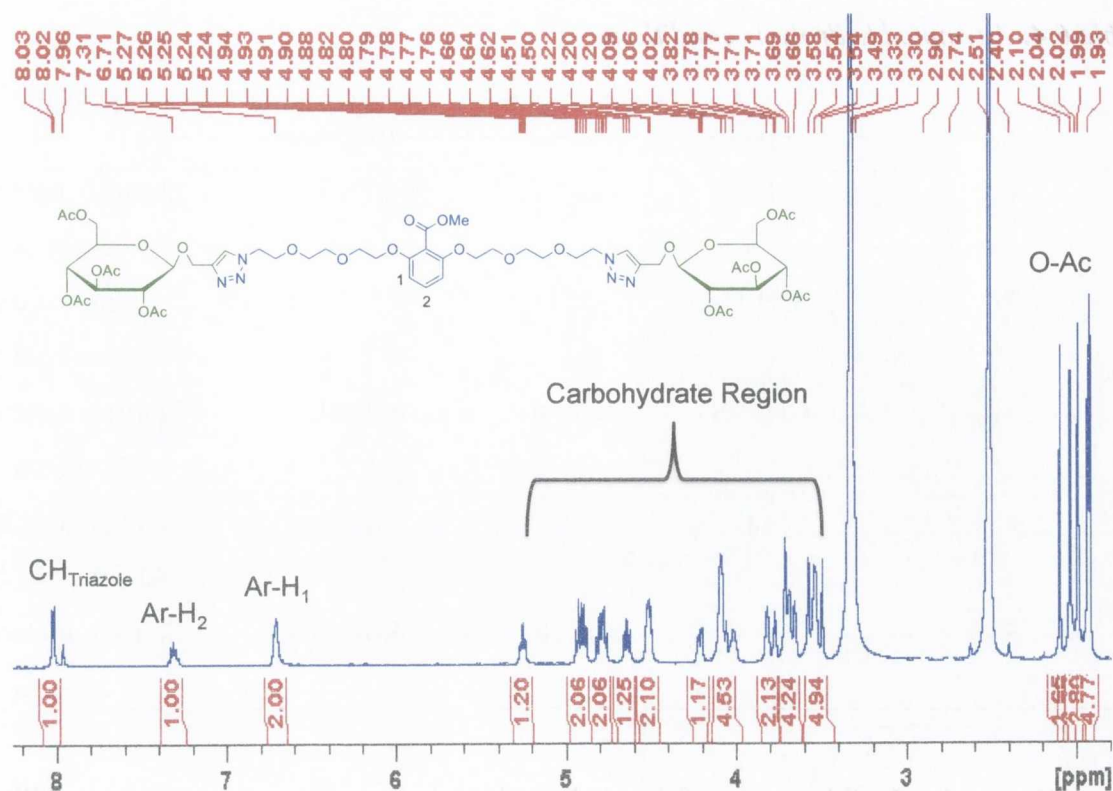
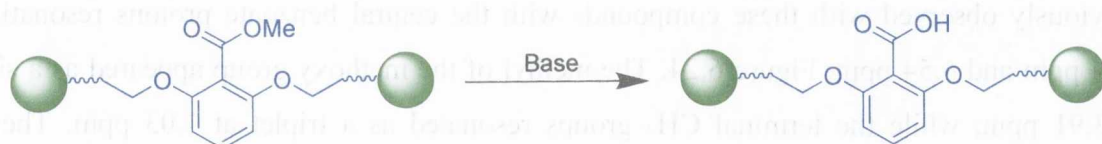


Figure 6.23: ^1H NMR spectrum (600 MHz, $\text{DMSO}-d_6$) of **230**.

The final stage in the synthetic pathway was hydrolysis of the methyl ester group of threads **225**, **227**, **230** to generate the benzoate anion. The reaction was attempted multiple times to obtain the benzoate salt or the free acid, illustrated in Scheme 6.15 and in each case either starting material was recovered or the acid formed in too low a yield to be isolated. The conditions attempted are summarised in Table 6.4.



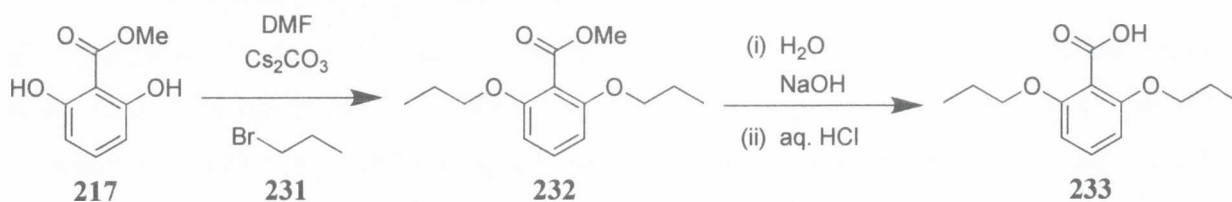
Scheme 6.15: Hydrolysis of the methyl ester group of **225**, **227** and **230**.

Table 6.4: Attempted hydrolysis conditions.

Attempt	Conditions			Result
	Solvent	Base	Temperature	
1	H ₂ O	NaOH	μW/Reflux	Starting material recovered
2	MeOH/H ₂ O	NaOH	μW/Reflux	Starting material recovered
3	CH ₃ CN	TBA OH	μW/Reflux	Starting material recovered
4	CH ₃ CN	KOH	μW/Reflux	Acid present but could not be isolated
5	-	conc. HCl	μW/Reflux	Starting material recovered

Due to the flexible nature of the chain and the bulky stopper groups, a possibility for the problems encountered with the hydrolysis step is steric hindrance coupled with the stability of the methyl ester. Therefore a model compound, **232**, with short three carbon alkyl arms was synthesised in order to optimise the hydrolysis conditions of the methyl ester. Using compound **217** and 1-bromopropane, **231**, compound **232** was successfully synthesised using the same reaction conditions as those used for **219**, Scheme 6.16. No further purification was required and **232** was obtained in 80% yield.

The ¹H NMR spectrum (400 MHz, CDCl₃) displayed features similar to that previously observed with these compounds with the central benzoate protons resonating at 7.24 ppm and 6.54 ppm, Figure 6.24. The methyl of the methoxy group appeared as a singlet at 3.91 ppm, while the terminal CH₃ groups resonated as a triplet at 1.03 ppm. The CH₂ groups were found as multiplets at 3.97 ppm and 1.79 ppm. ¹³C NMR (150 MHz, CDCl₃) analysis revealed the carbon of the methyl group at 51.8 ppm.

**Scheme 6.16:** Synthesis and base catalysed hydrolysis of model compound **232**.

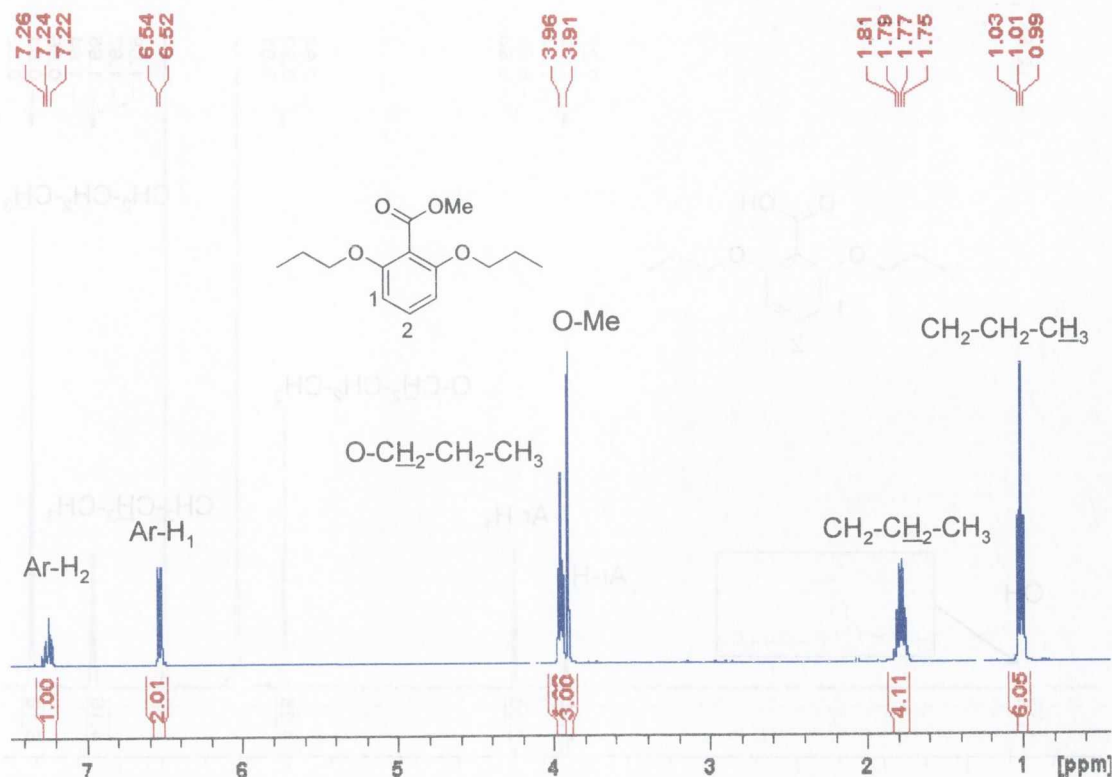


Figure 6.24: ^1H NMR spectrum (400 MHz, CDCl_3) of **232**.

The next step was to hydrolyse the methyl ester group of **232**, Scheme 6.16, and the first attempt in H_2O with NaOH under microwave irradiation for 10 minutes resulted in successful formation of the Na salt. After dropwise addition of 2 M HCl a white precipitate developed in solution, which was subsequently collected by centrifugation to give **233** in 75% yield.

The ^1H NMR spectrum (400 MHz, $\text{DMSO}-d_6$) of **233** revealed the disappearance of the CH_3 group at 3.91 ppm and a broad singlet at 12.56 ppm corresponding to the OH group. Confirmation of successful hydrolysis to the acid analogue was also achieved by ^{13}C NMR (150 MHz, $\text{DMSO}-d_6$), whereby the signal at 51.8 ppm corresponding to the carbon of the methyl group had also disappeared. HRMS analysis verified the presence of **233** with an m/z peak = 239.1285 corresponding to the $[\text{M} + \text{H}]^+$ species.

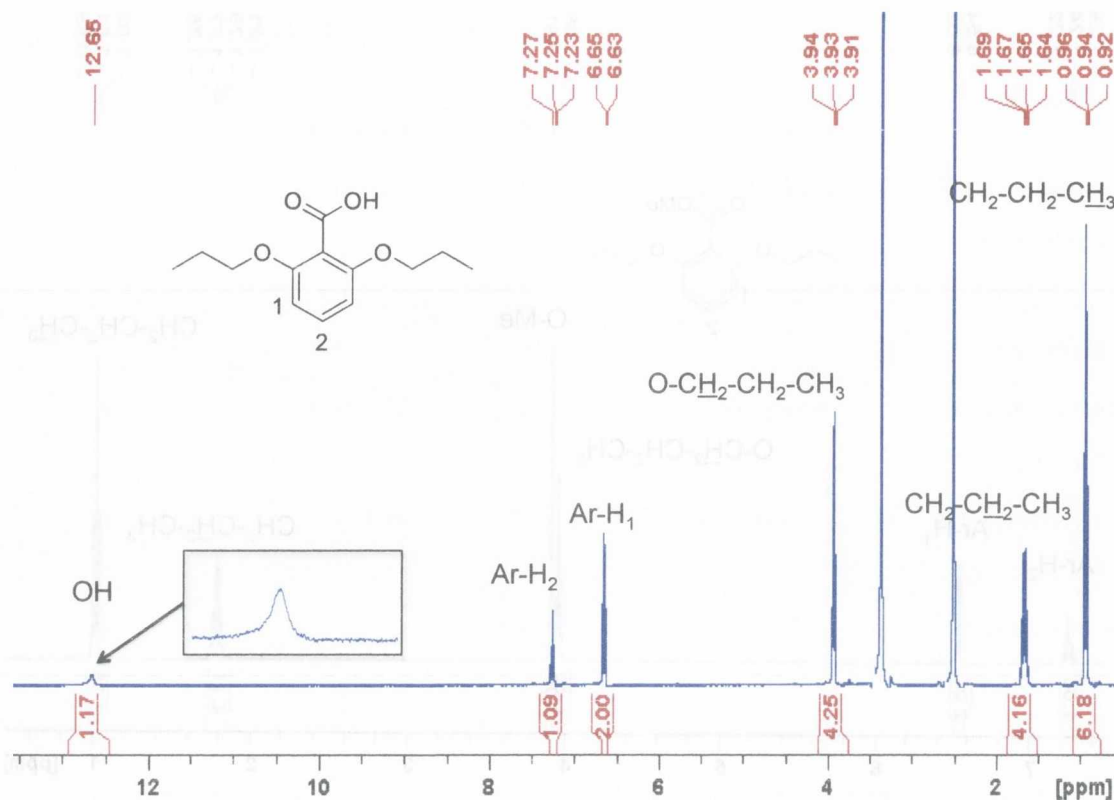
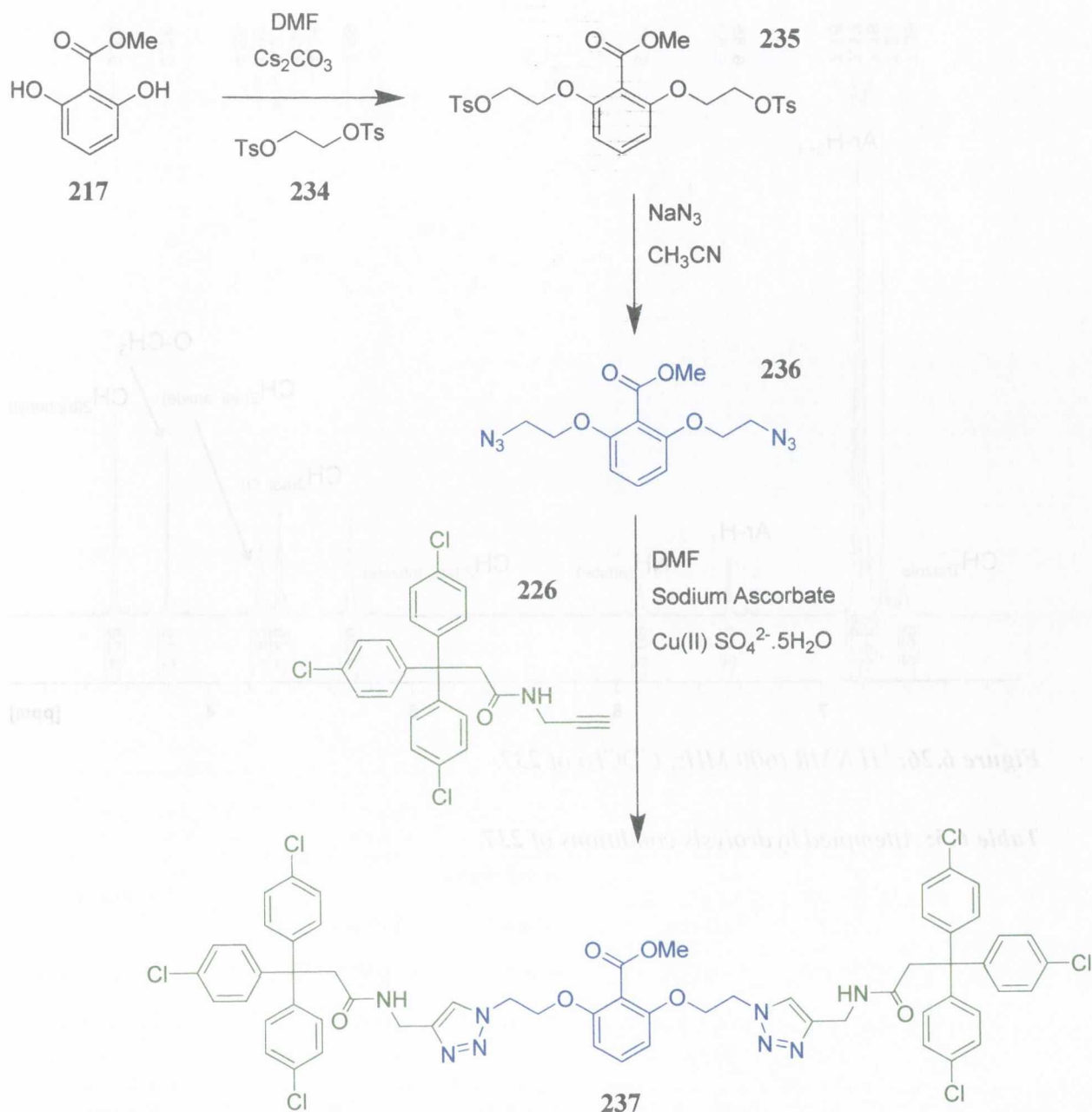


Figure 6.25: ¹H NMR spectrum (400 MHz, DMSO-*d*₆) of **233**.

Following the immediate success of the hydrolysis reaction of compound **232**, the other reaction conditions outlined in Table 6.4 were also attempted with **232** to investigate optimum reaction conditions. All attempts resulted in the free acid being readily formed; indicating the bulky stopper groups of threads **225**, **227** and **230** may play a crucial role in preventing hydrolysis of these compounds. Therefore, the chain of the original threads was shortened to a two carbon linker and compound **237** synthesised under the same conditions used for the clicked thread **227**, as these conditions proved the most synthetically straightforward, Scheme 6.17. Compound **237** was obtained in 20% yield following column chromatography (CHCl₃-MeOH using a gradient elution 100 to 96:4).

The ¹H NMR spectrum (600 MHz, CDCl₃) of **237**, Figure 6.26, revealed the characteristic triphenyl protons of the stopper groups at 7.21 ppm and 7.19 ppm and the central benzoate protons at 6.11 ppm and 6.55 ppm. The CH of the triazole group was the most downfield signal at 7.39 ppm while the methoxy proton resonated at 3.78 ppm. The presence of the [M + H]⁺ species at *m/z* = 1189.2007 in the MALDI-ToF spectrum also confirmed successful formation of compound **237**.



Scheme 6.17: Synthetic pathway for the synthesis of rotaxane thread **237**.

Again, the hydrolysis step was attempted using various conditions outlined in Table 6.5, however the acid analogue of **237** could never be obtained. Despite multiple attempts and multiple variations of the reaction conditions, including room temperature, reflux or microwave irradiation, neither the salt nor the free acid could be isolated.

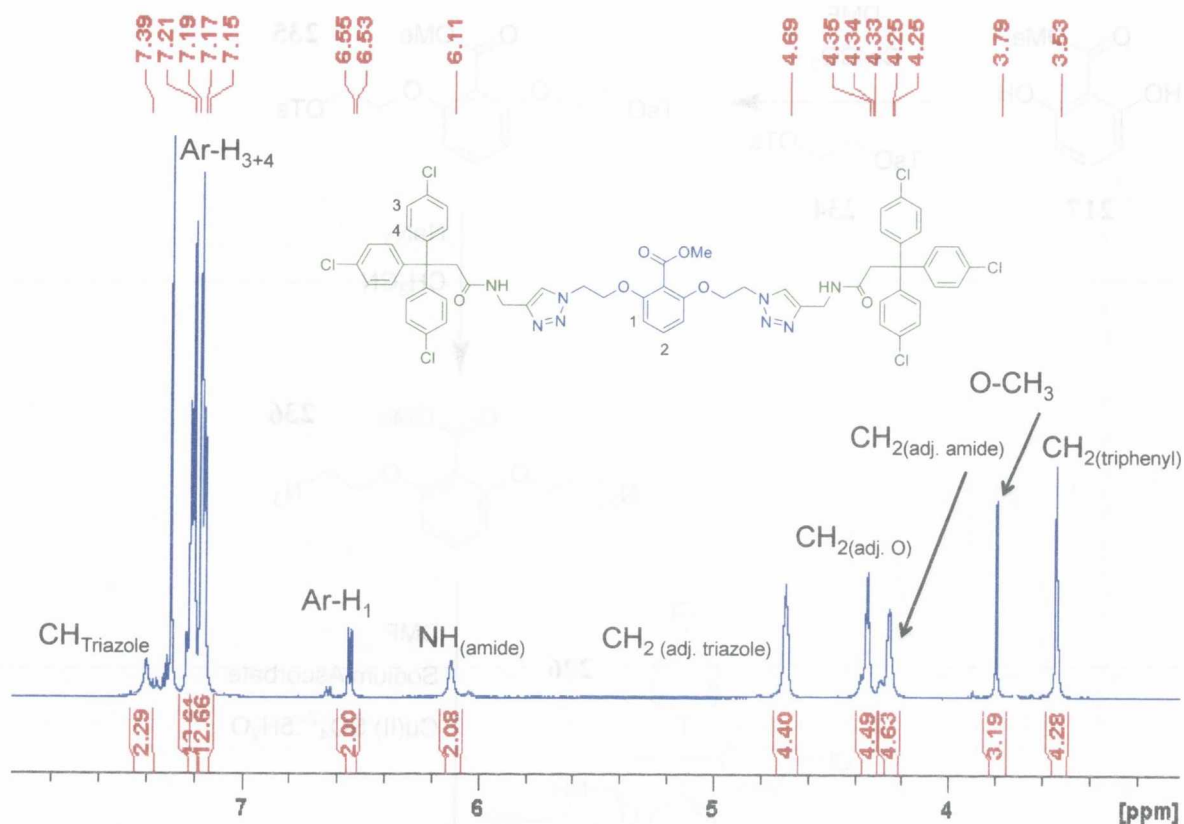
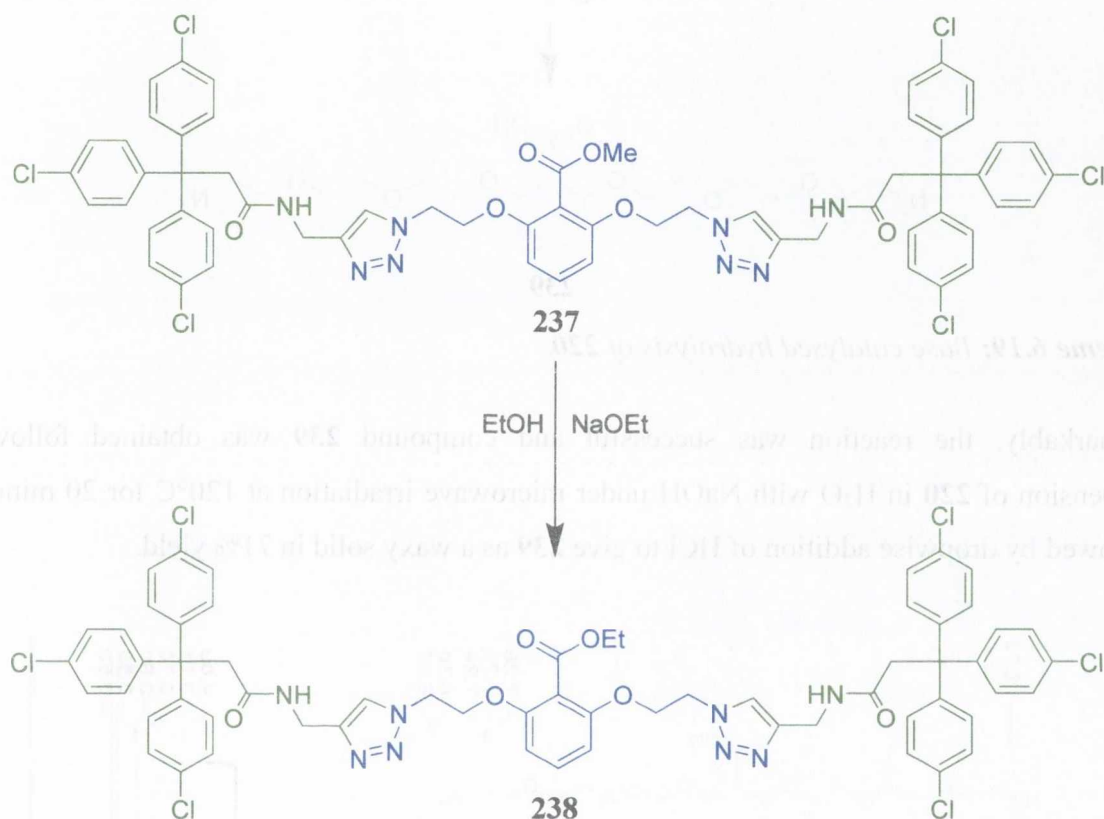


Figure 6.26: ^1H NMR (600 MHz, CDCl_3) of **237**.

Table 6.5: Attempted hydrolysis conditions of **237**.

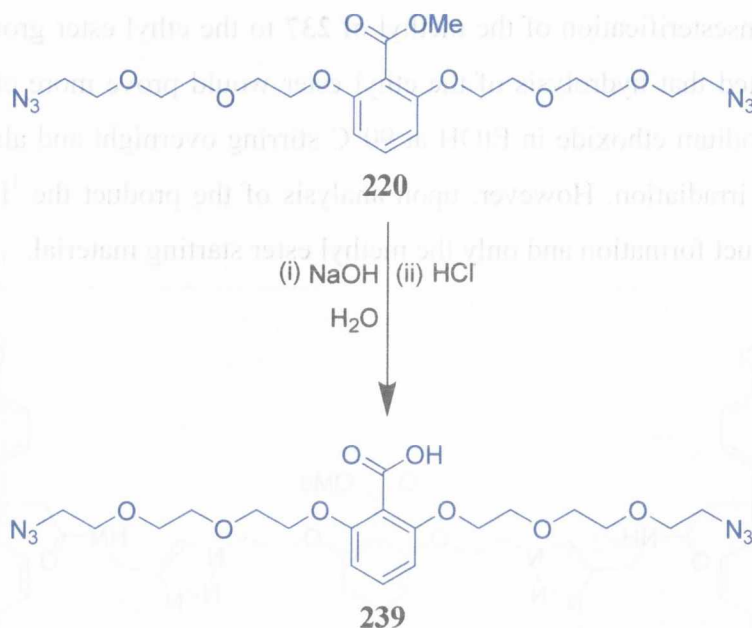
Attempt	Conditions			Result
	Solvent	Base	Temperature	
1	H_2O	NaOH	$\mu\text{W/Reflux}$	No reaction
2	$\text{MeOH/H}_2\text{O}$ (1:1)	NaOH	$\mu\text{W/Reflux}$	No reaction
3	CH_3CN	TBA OH	$\mu\text{W/Reflux}$	No reaction
4	CH_3CN	KOH	$\mu\text{W/Reflux}$	No reaction
5 ²⁴⁶	MeOH	KOH	R.T	No reaction
6	EtOAc	LiOH	Reflux	No reaction
7 ²⁴⁷	EtOAc	LiI	Reflux	No reaction
8 ²⁴⁸	THF	LiOH	Reflux	No reaction
9	<i>i</i> -propanol	KOH (20%)	70°C	No reaction
10 ²⁴⁹	1,2-dichloroethane	$\text{Sn}(\text{CH}_3)_3\text{OH}$	70°C	No reaction
11 ²⁵⁰	-	conc. HCl	$\mu\text{W/Reflux}$	No reaction

Finally transesterification of the methyl of **237** to the ethyl ester group was attempted as it was anticipated that hydrolysis of the ethyl ester would prove more efficient. This was attempted using sodium ethoxide in EtOH at 90°C stirring overnight and also for 40 minutes under microwave irradiation. However, upon analysis of the product the ^1H NMR spectrum did not show product formation and only the methyl ester starting material.



Scheme 6.18: Attempted trans transesterification of **237**.

Although the synthesis of multiple threads as suitable components for the construction of a rotaxane were synthesised, the final step to generate the benzoate anion could not be completed as the methyl ester group of each thread molecule could not be hydrolysed to the desired acid. Repeated attempts only resulted in starting material being recovered despite the fact that a model compound, **232**, was synthesised and could be successfully hydrolysed. Modification of the original design of the thread to shorten the carbon chain linker between the core benzoate group and the bulky stopper groups failed to yield the desired the acid analogue; while attempts to transesterify the methyl group to the ethyl ester also failed. The final attempt to obtain the hydrolysed rotaxane thread was to attempt the hydrolysis reaction on the azide thread precursor **220**, illustrated in Scheme 6.19.



Scheme 6.19: Base catalysed hydrolysis of **220**.

Remarkably, the reaction was successful and compound **239** was obtained following suspension of **220** in H_2O with NaOH under microwave irradiation at 120°C for 20 minutes, followed by dropwise addition of HCl to give **239** as a waxy solid in 71% yield.

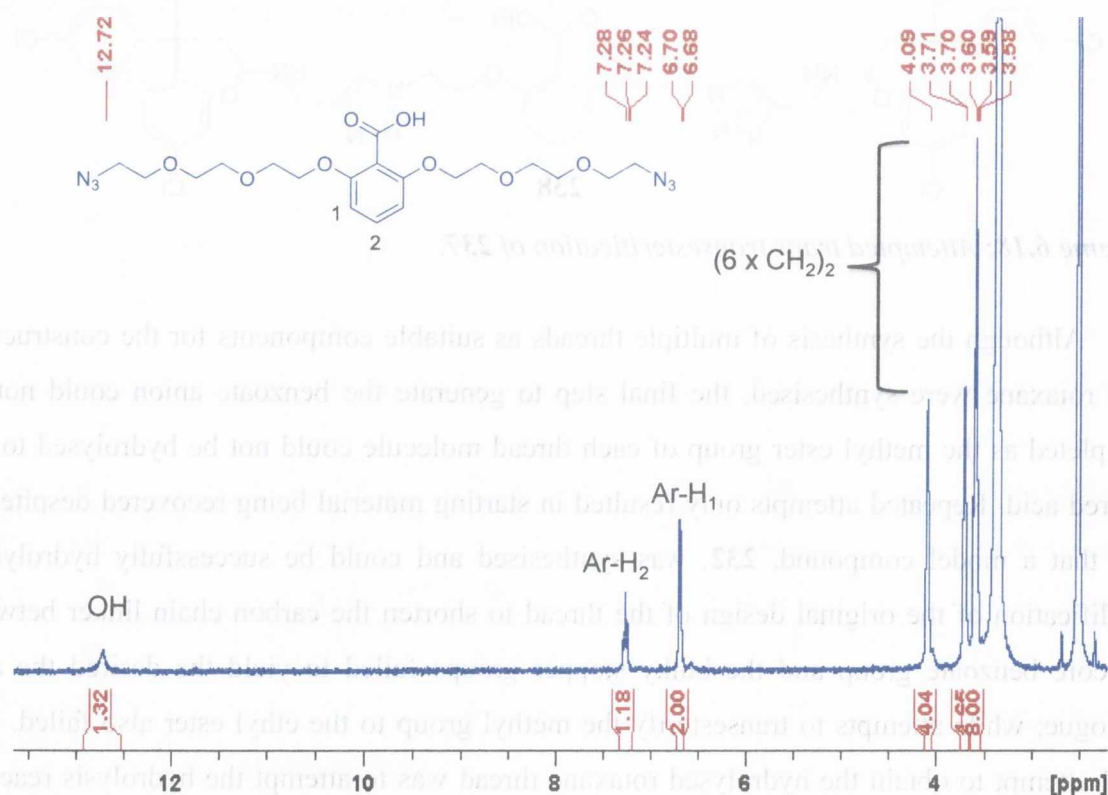
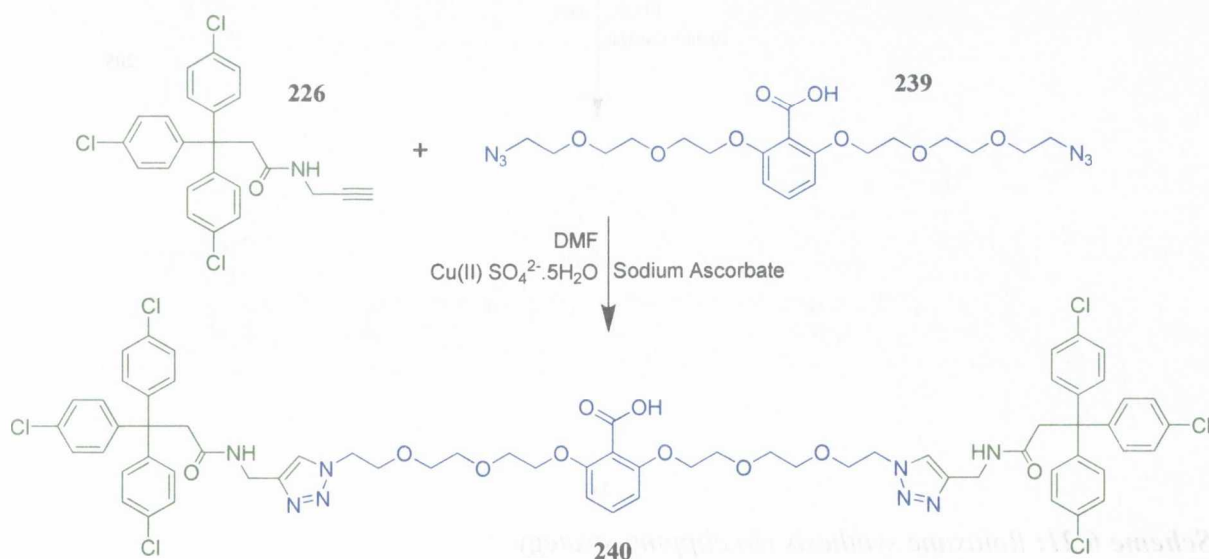


Figure 6.27: ^1H NMR (400 MHz, $\text{DMSO}-d_6$) spectrum of **239**.

The ^1H NMR spectrum (400 MHz, $\text{DMSO-}d_6$) shows the characteristic broad singlet at 12.72 ppm for the OH proton, Figure 6.27, while compared to the ^1H NMR spectrum (400 MHz, $\text{DMSO-}d_6$) of **220** (Appendix, Figure A6.24) the methyl signal at 3.73 ppm was no longer present. The ^{13}C NMR spectrum (150 MHz, $\text{DMSO-}d_6$) showed the expected number of signals and HRMS also confirmed successful hydrolysis with an $m/z = 491.1857$ in the ES^+ mass spectrum, corresponding to the $[\text{M} + \text{Na}]^+$.

Having successfully hydrolysed the azide derivative **220**, the next step was to complete the thread synthesis by clicking the bulky stopper groups, Scheme 6.20. This was done using the same conditions as previously described for the click reaction of compounds **226** and **220** to give the ester analogue **227**. The reaction was followed by mass spectrometry and the formation of the clicked acid analogue **240** was observed in the MALDI-ToF mass spectrum ($m/z = 1349.2937$ for the $[\text{M} - \text{H}]^-$ species) after 24 hours stirring at room temperature. Isolation and purification of the product, however, was never achieved despite numerous attempts including column chromatography, acid-base extraction and recrystallisation.

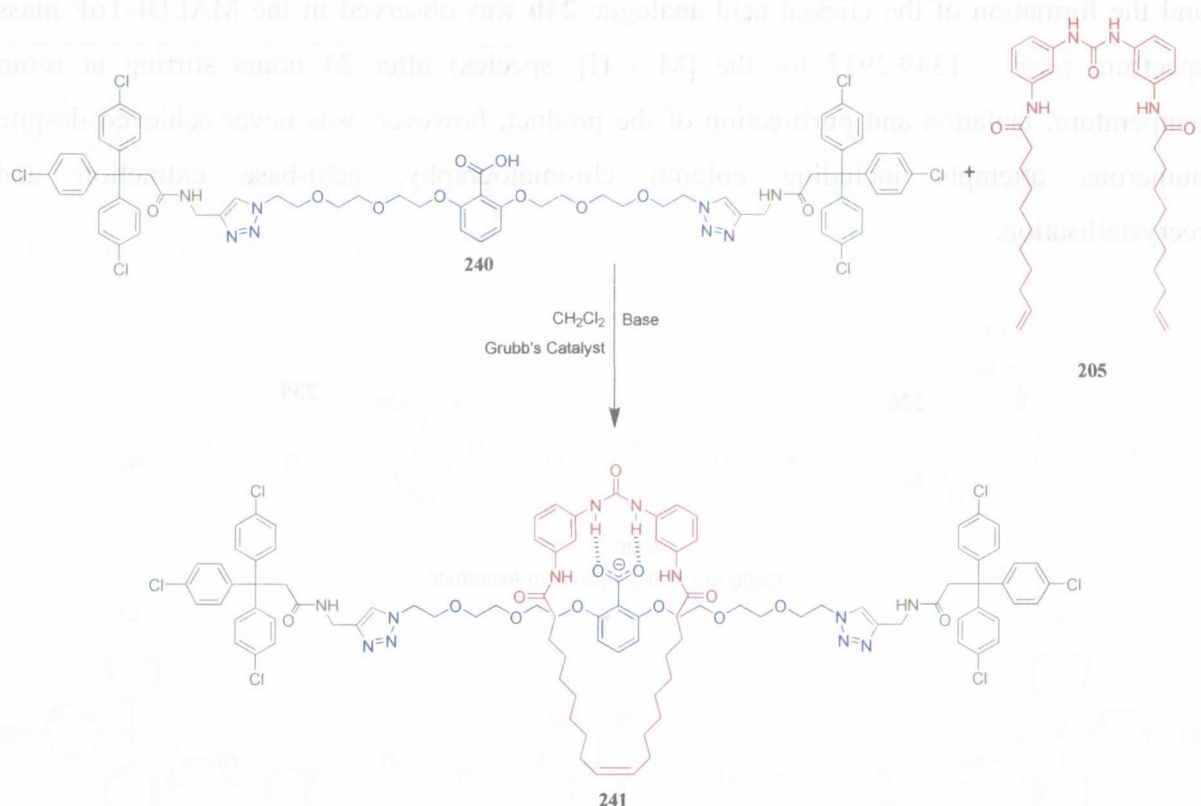


Scheme 6.20: Click reaction of alkyne stopper **226** with azide thread **239**.

Although compound **240** could not be isolated, product formation was still achieved and so it was decided to continue the synthesis with the crude product. The next stage was to attempt rotaxane formation *via* the clipping method using thread **240** and acyclic compound **205** or the capping strategy using compound **239**, stopper **226** and the macrocyclic component **206** and will be discussed in the following section.

6.4 Attempted Rotaxane Formation

As stated earlier, compound **240** could not be isolated and so the crude product was stirred first with Cs_2CO_3 in dry CH_2Cl_2 for 30 minutes to allow the deprotonation of the benzoic acid moiety, Scheme 6.21. Following this, excess base was filtered off and compound **205** was added to the reaction mixture. This was also allowed to stir for 30 minutes to allow equilibration of the H-bonding interaction between **240** and **205**. Although RCM of **205** was unsuccessful in CH_2Cl_2 at room temperature previously it was anticipated that if H-bonding occurred between the two components, compound **205** may solubilise in CH_2Cl_2 and allow RCM under these conditions. Following addition of the catalyst, the reaction was allowed to stir at room temperature and monitored continuously by TLC and mass spectrometry.



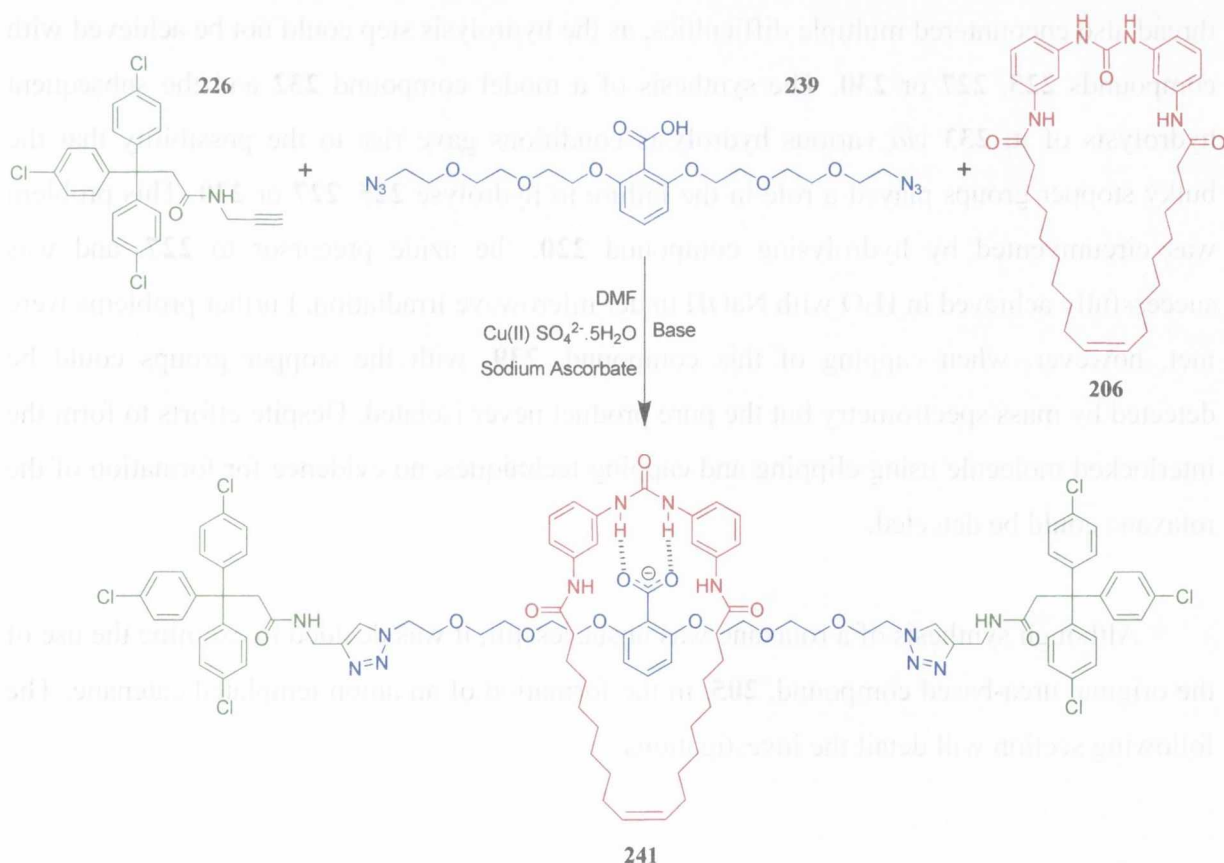
Scheme 6.21: Rotaxane synthesis via clipping strategy.

Despite allowing the reaction to stir for over 24 hours, compound **205** never solubilised and only compound **240** (and impurities) was visible on TLC. Compound **241** was never observed by mass spectrometry, however compounds **205** and **240** could be found. Following this unsuccessful attempt, the base was changed to TBAOH, as was stated earlier if it were possible to complete the reaction in CH_2Cl_2 this solvent would provide the least competitive conditions for the H-bonding interaction and also be optimal for RCM.

The same conditions were employed as above, with compound **240** stirring with TBAOH in dry CH_2Cl_2 for 30 minutes followed by the addition of **205**. Again, however compound **205** never solubilised and no rotaxane was observed by mass spectrometry. The reaction was then heated at reflux and again continuously monitored but no solubilisation of **205** occurred and no evidence of the formation of rotaxane **241** found.

As compound **205** was only soluble in DMF (or DMSO) it was decided to attempt rotaxane formation in this solvent (dry). The conditions outlined above were employed and although solubilisation of **205** occurred, no RCM was achieved as evidenced by mass spectrometry with only compound **205** observed and no trace of **206**. No rotaxane formation occurred even with gentle heating of the reaction mixture and also at reflux, although at reflux it was not anticipated that the H-bonding interaction would survive.

Following these unsuccessful attempts, the last method to achieve rotaxane formation was the capping method, Scheme 6.22. As the click reaction was carried out in DMF and solubility of **206** could only be achieved in this solvent, it was envisaged that the conditions might prove suitable.



Scheme 6.22: Rotaxane synthesis via capping strategy.

Therefore compound **239** was again allowed to stir with Cs_2CO_3 in dry DMF for 30 minutes, which was then filtered off before compound **206** was slowly added. The reaction mixture was again allowed to equilibrate further before finally stopper **226** and the other reagents were added. The reaction was allowed to stir at room temperature and monitored by mass spectrometry. Unfortunately, over the course of a 48 hour period no evidence of rotaxane formation was found. No evidence of the click reaction occurring could be found by mass spectrometry either, possibly due to the copper coordinating to the carboxylate group, thus rendering it inactive as a catalyst for the click reaction. The reaction was repeated using K_2CO_3 , TBAOH and Et_3N however the outcome remained the same with no indication of rotaxane formation found.

Unfortunately, despite a challenging synthetic process the synthesis of a rotaxane *via* H-bonding interactions between an anionic thread species and a urea-based macrocycle was never achieved. Numerous problems were encountered throughout the course of the synthetic preparation beginning with the solubility of the urea compounds **205**, **207**, **208** and **211**. The harsh reaction conditions associated with their RCM diminished the suitability of the compounds in their use as a component of an interlocked molecule. The synthesis of the thread also encountered multiple difficulties, as the hydrolysis step could not be achieved with compounds **225**, **227** or **230**. The synthesis of a model compound **232** and the subsequent hydrolysis of it, **233** *via* various hydrolysis conditions gave rise to the possibility that the bulky stopper groups played a role in the failure to hydrolyse **225**, **227** or **230**. This problem was circumvented by hydrolysing compound **220**, the azide precursor to **227**, and was successfully achieved in H_2O with NaOH under microwave irradiation. Further problems were met, however, when capping of this compound, **239**, with the stopper groups could be detected by mass spectrometry but the pure product never isolated. Despite efforts to form the interlocked molecule using clipping and capping techniques, no evidence for formation of the rotaxane could be detected.

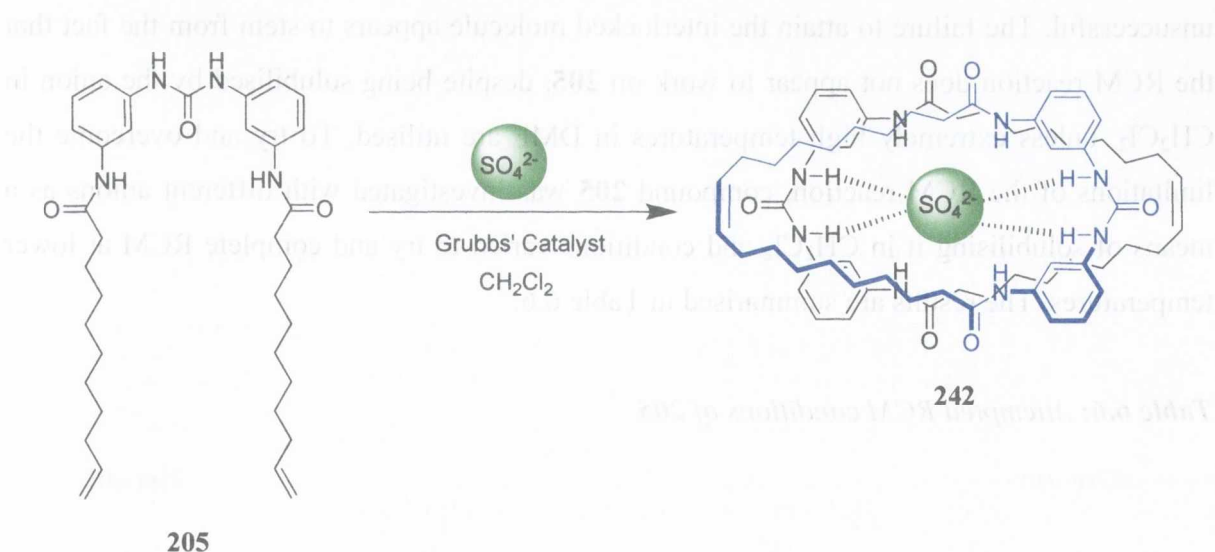
Although synthesis of a rotaxane was unsuccessful, it was decided to examine the use of the original urea-based compound, **205**, in the formation of an anion templated catenane. The following section will detail the investigations.

6.5 Attempted Catenane Synthesis

A fundamental requirement for an interweaving template is the ability to direct two components in an orthogonal manner. A suitable method of trapping assemblies to access the anion-templated interlocked structures is also of major importance. As outlined earlier, the primary method utilised is olefin RCM mediated by Grubbs' catalyst.

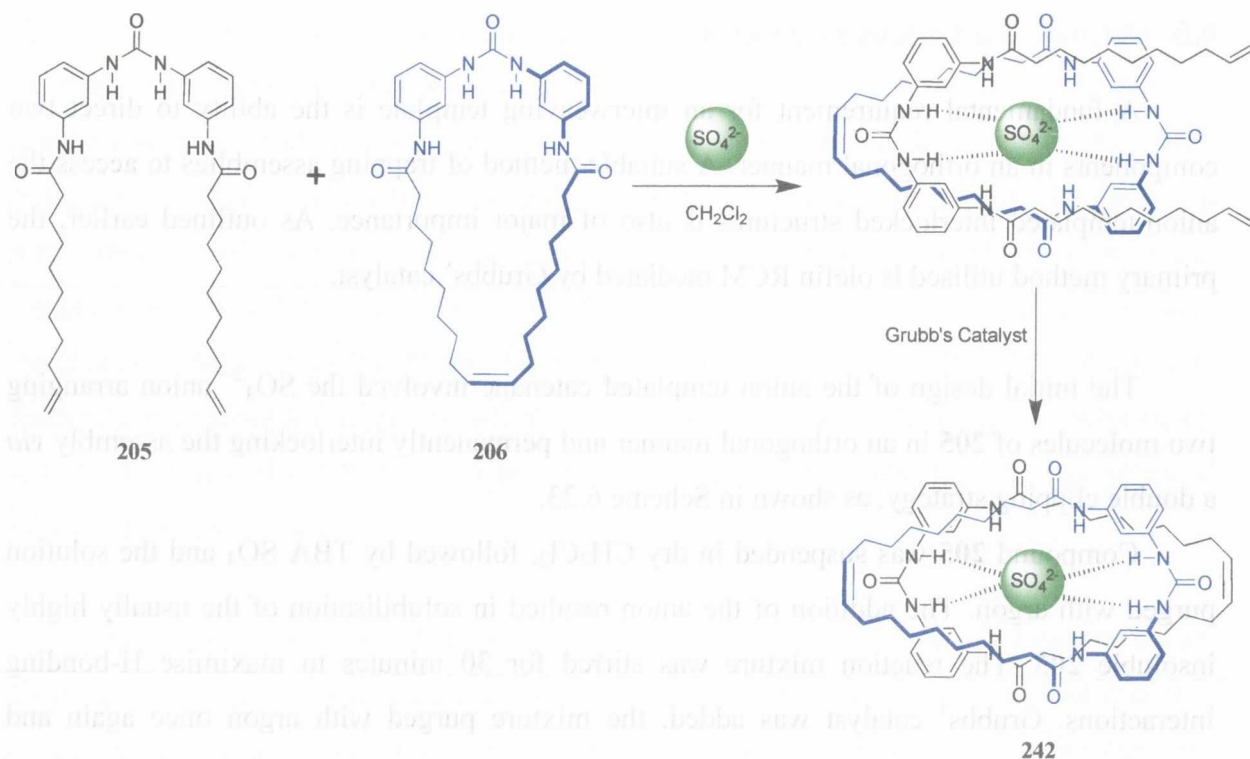
The initial design of the anion templated catenane involved the SO_4^{2-} anion arranging two molecules of **205** in an orthogonal manner and permanently interlocking the assembly *via* a double clipping strategy, as shown in Scheme 6.23.

Compound **205** was suspended in dry CH_2Cl_2 , followed by TBA SO_4 and the solution purged with argon. The addition of the anion resulted in solubilisation of the usually highly insoluble **205**. The reaction mixture was stirred for 30 minutes to maximise H-bonding interactions. Grubbs' catalyst was added, the mixture purged with argon once again and monitored by mass spectrometry. Unfortunately, sequential analysis revealed no indication of the catenane; and as had been previously observed when carrying out the RCM reaction at room temperature, only the open starting material could be detected.



Scheme 6.23: Double clipping of **205** approach to give SO_4^{2-} templated catenane **242**.

The second approach involved suspending both the acyclic compound **205** and macrocycle **206** in dry CH_2Cl_2 together with the anion, Scheme 6.24, as having one component already closed would result in the open form being arranged, *via* anion templation, in the orthogonal manner required that RCM would result in the catenane. Again, however repeated analysis by mass spectrometry never yielded the desired catenane.



Scheme 6.24: RCM of **205** around **206** to give SO_4^{2-} templated catenane **242**

Repeated attempts to successfully synthesise the anion-templated catenane were all unsuccessful. The failure to attain the interlocked molecule appears to stem from the fact that the RCM reaction does not appear to work on **205**, despite being solubilised by the anion in CH_2Cl_2 , unless extremely high temperatures in DMF are utilised. To try and overcome the limitations of the RCM reaction, compound **205** was investigated with different anions as a means of solubilising it in CH_2Cl_2 and conditions varied to try and complete RCM at lower temperatures. The results are summarised in Table 6.6.

Table 6.6: Attempted RCM conditions of **205**.

Attempt	Conditions			Result
	Solvent	Anion	Temperature	
1	CH_2Cl_2	SO_4^{2-}	RT	No RCM
2	CH_2Cl_2	Cl^-	RT	No RCM
3	CH_2Cl_2	AcO^-	RT	No RCM
4	DMF	SO_4^{2-}	RT	No RCM
5	DMF	Cl^-	RT	No RCM
6	DMF	AcO^-	RT	No RCM

Unfortunately it was not possible to optimise RCM conditions of **205** using Grubbs' catalyst at lower temperatures in CH_2Cl_2 . Although addition of various anions resulted in solubilisation of **205**, the closed form **206** was never detected by mass spectrometry unless the reaction was carried out at 160°C in DMF under microwave irradiation (without the anion present). These conditions are highly unsuitable for the synthesis of an anion-templated catenane, in which the template utilises H-bonds to arrange the two components.

6.6 Conclusion

The assembly of mechanically bonded molecules such as rotaxanes and catenanes is of great interest in the field of supramolecular chemistry, not only for the challenge of their synthesis but also for the potential uses these systems may have such as molecular switches, sensors, and machines.^{251,252} Their synthesis is usually based on some kind of template assistance such as the preorganisation of building blocks by metal coordination, hydrophobic and donor-acceptor interactions, or hydrogen bonding.

Due to their ability to act as strong Y-shaped H-bond donors, urea and its derivatives play key roles in the design of receptors for anions, including both spherical halide anions and Y-shaped carboxylate anions in solution, and offer a novel way of forming mechanically interlocked structures. Based on these properties, rotaxane **196** was designed with an anionic thread component containing a benzoate moiety available to H-bond to a urea-based macrocycle. It was anticipated that after anion recognition between the urea moiety and the benzoate anion occurred, RCM could be employed to form the [2]-rotaxane by clipping. Alternatively, the macrocycle could undergo RCM first, followed by capping of stopper groups to form the interlocked molecule.

The development of the macrocycle began with the synthesis of a diaryl urea core. Attachment of an ethoxy chain containing alkene groups, however, proved unsuccessful and was replaced by a long alkyl chain functionalised to the diaryl urea core *via* a peptide coupling reaction. Unfortunately, although the product obtained, **205**, was highly pure and the reaction high yielding, the solubility of **205** was less than ideal with DMF or DMSO being the only solvents capable of solubilisation. Nonetheless, the terminal alkene groups of **205** are particularly suitable for RCM using Grubbs' catalyst with the Ru-based catalyst known to tolerate a variety of functional groups and the scope of the reaction widely reported in the literature.^{253,254} Normally, however, the molecule must have polar side chains that are able to build a template for the catalyst. As stated previously, the solvent of choice for alkene

metastasis using Grubbs' catalyst is CH_2Cl_2 , as the stability of the catalyst is optimal and provides maximum activity of the metathesis (pre)catalysts.²⁵⁵ The RCM reaction with **205** was attempted multiple times in CH_2Cl_2 with all three generations of Grubbs' catalyst, however starting material was only ever recovered. The reaction was attempted in other non-polar solvents, however the macrocycle product **206** was only obtained when the reaction was carried out in DMF at 160°C under microwave irradiation. As compound **205** was readily synthesised, the method was expanded to include compounds **207**, **208** and **211** with the expectation that the solubility properties of these compounds may be varied based on shorter chain lengths (**207** and **208**) and incorporation of phenyl rings (**211**). This, unfortunately, was not the case and all additional compounds synthesised retained similar solubility properties as the original compound **205**. The reaction conditions used for the RCM of **205** were attempted on compounds **207**, **208** and **211** with the reaction being unsuccessful on **207** and **208**, most likely due to steric demands or divergent orientation of the precursor arms. Compound **211** was successfully cyclised to give **216**, however the severe conditions of the reaction remained problematic.

Anion binding studies of acyclic compounds **205**, **207**, **208** and **211** and macrocycles **206** and **211** were investigated by ^1H NMR spectroscopy in $\text{DMSO}-d_6$. It was anticipated that differences between acyclic vs. cyclic would be observed or even amongst the two classes of molecules themselves, however in the majority of cases very few variations were seen. Compounds **205** and **206** showed a different binding profile upon titration with SO_4^{2-} , with **205** forming a rapid and stable 1:1 species in solution while the more rigid **206** did not show a plateau until *ca.* 2 equivalents of the anion. The reverse phenomenon was seen upon addition of benzoate with the macrocycle **206** showing a more stable binding profile than the flexible precursor **205**.

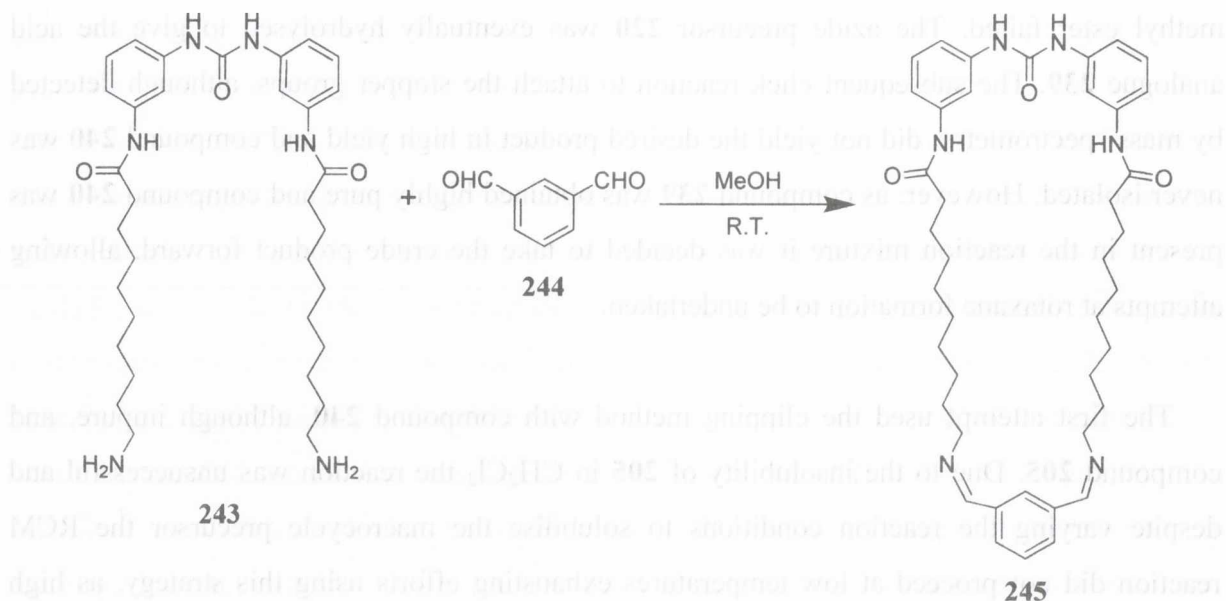
Having successfully synthesised a macrocycle component and expanded the library to include three other derivatives, the development of a potential rotaxane thread containing a central benzoate moiety was undertaken. The synthetic methods employed to develop this thread were largely successful. A thread containing an amide functionality, **225**, and also a "clicked" thread, **227**, were synthesised, with the click methodology extended to include a sugar functionalised thread, **230**. The hydrolysis step of the synthesis, however, proved extremely problematic with multiple attempts to obtain the acid analogues of the threads all failing. A model compound, **232**, with short alkyl arms was synthesised with hydrolysis of the methyl ester readily occurring using various reaction conditions. As a result, a smaller analogue of compound **227** was synthesised but again numerous attempts in hydrolysing the

methyl ester failed. The azide precursor **220** was eventually hydrolysed to give the acid analogue **239**. The subsequent click reaction to attach the stopper groups, although detected by mass spectrometry, did not yield the desired product in high yield and compound **240** was never isolated. However, as compound **239** was obtained highly pure and compound **240** was present in the reaction mixture it was decided to take the crude product forward, allowing attempts at rotaxane formation to be undertaken.

The first attempt used the clipping method with compound **240**, although impure, and compound **205**. Due to the insolubility of **205** in CH_2Cl_2 the reaction was unsuccessful and despite varying the reaction conditions to solubilise the macrocycle precursor the RCM reaction did not proceed at low temperatures exhausting efforts using this strategy, as high temperatures destroyed any H-bonding interactions. The next attempt was to form the pseudorotaxane and then to cap the stopper groups *in situ* using the click methodology. Unfortunately the click reaction did not proceed, as the desired thread was not detected using HRMS and as a result the rotaxane did not assemble as anticipated.

Another effort to synthesise an interlocked molecule was attempted by using compounds **205** and **206** to form an anion templated catenane. Again, however solubility of the compounds proved very problematic, despite addition of various anions to a solution of either compound resulting in solubilisation in CH_2Cl_2 , the RCM using Grubbs' catalyst did not proceed at low temperatures.

Future work of this project could still generate a rotaxane. The current design of the urea macrocycle needs to be altered, as the main issue that needs to be addressed is the solubility of compounds **205**, **207**, **208** and **211**. Although the focus of this thesis was urea-based molecules other H-bond donors, *e.g.* simple amides or a squaramide unit may be a more suitable component in a rotaxane. Another modification would be to vary the terminal groups of the chain on the macrocycle to allow easier access to a closed system than that experienced with the RCM reaction using Grubbs' catalyst in this case, *e.g.* *bis*-Schiff base formation could provide a facile and efficient method to obtain a macrocycle, as illustrated in Scheme 6.25 or alternatively using the click approach, as both reactions are carried out at room temperature which would preserve any H-bonding interaction between components. Therefore, minor modifications or redesign of the synthetic pathway and target molecules may be a future project within the Gunnlaugsson group.



Scheme 6.25: Proposed alternative macrocycle synthesis.

HRMS and as a result the message did not translate as anticipated.

Another effort to synthesise an interlocked molecule was interrupted by using compounds **205** and **206** to form an aryl tetraphenyl calcium. Again, however, solubility of the compounds proved very problematic, despite addition of various salts to a solution of either compound resulting in solubilisation in CHCl_3 . The RCM using Grubbs' catalyst did not proceed at low temperatures.

Future work of this project could still generate a rotaxane. The current design of the new macrocycle needs to be altered as the main issue that needs to be addressed is the solubility of compounds **205**, **207**, **208** and **211**. Although the focus of this thesis was macrocyclic molecules rather than rotaxanes, a simple amide or a squaramide unit may be a more suitable component in a rotaxane. Another modification would be to vary the terminal groups of the chain on the macrocycle to allow easier access to a closed system than that experienced with the RCM reaction using Grubbs' catalyst in this case, e.g. the Schotten-Baumann reaction could provide a faster and efficient method to obtain a macrocycle, as illustrated in Scheme 6.25 or alternatively using the click approach as both reactions are carried out at room temperature which would preserve any H-bonding interaction between components. Therefore, minor modifications or redesign of the synthetic pathway and target molecules may be a future project within the Cunningham group.

Chapter 7

Experimental

7. General Experimental Techniques

All starting materials were obtained from Sigma-Aldrich, Acros Organics or TCI Ltd. ^1H NMR spectra were recorded at 400.13 MHz or 600.13 MHz using Bruker Spectrospin DPX-400 instrument and Bruker AV600 instrument respectively. Chemical shifts are expressed in parts per million (ppm or δ) downfield from the standard, followed by the splitting pattern, number of protons, assignment of proton and coupling constant (if applicable). ^{13}C NMR spectra were recorded at 100.61 MHz and 150.9 MHz using a Bruker Spectrospin DPX-400 instrument and Bruker AV600 instrument respectively. Infrared spectra were recorded on a Perkin Elmer Spectrum One FR-IR spectrometer equipped with a Universal ATR Sampling Accessory. Electro mass spectra was recorded on a Mass Lynx NT V 3.4 on a Waters 600 controller connected to a 996 photodiode array detector with HPLC-grade methanol as carrier solvents. Accurate molecular weights were determined by a peak-matching method, using leucine enkephaline (H-Tyr-Gly-Gly-Phe-Leu-OH) as the standard reference ($m/z = 556.2771$); all accurate mass were reported within ± 5 ppm of the expected mass. Melting points were determined using an Electrothermal IA9000 digital melting point apparatus. Elemental analysis was carried out at the Microanalysis Laboratory, School of Chemistry and Chemical Biology, University College Dublin.

7.1 Ultraviolet-Visible and Fluorescence Spectroscopy

UV-visible absorption spectra were recorded using a Varian Cary 50 spectrophotometer and Varian Cary Eclipse spectrophotometer. The solvents used were of spectroscopic grade. The wavelength range was 200 nm to 600 nm with a scan rate of 600 nm min^{-1} . The blank used was a sample of the solvent system the titration was undertaken in. Baseline correction measurements were used in all spectra. All stock solutions were prepared freshly before measurement. Data analysis was conducted using Origin 7.5[®] and SPECFIT[™]. Fluorescence measurements were made with a Varian Carey Eclipse Fluorimeter in a 3 cm quartz cuvette with a 1.0 cm path length. All titrations were repeated to ensure reproducibility.

7.1.1 Preparation of Solutions for UV-Vis Titrations with Anions

The TBA salts of the anions used in the titrations were of spectroscopic grade and were purchased from Sigma Aldrich. All TBA salts were dried over P_2O_5 at 40°C under vacuum, except for $\text{TBAF} \cdot 3\text{H}_2\text{O}$, which was dried under vacuum at room temperature. Solutions of these salts were prepared at varying concentrations of *ca.* 0.1 M, 5×10^{-2} M, 1×10^{-2} M, and 1

$\times 10^{-3}$ M. Host solutions of 1×10^{-3} M were prepared and then diluted to the desired concentration before titration (*ca.* 1×10^{-5} M).

7.2 ^1H NMR Titrations

^1H NMR titrations were carried out on a Bruker Spectrospin DPX-400 instrument at 25°C. Data analysis was conducted using Origin 7.5[®], TopSpin, and NMRtit.¹⁹⁵ The TBA salts of the anions used in the titrations were of spectroscopic grade and were purchased from Sigma Aldrich. All TBA salts were dried over P_2O_5 at 40°C under vacuum. All titrations were repeated to ensure reproducibility. The concentrations of these solutions were prepared such that 2 μL would give *ca.* 0.1 molar equivalents of the anion. Host solutions of *ca.* 7×10^{-3} M were prepared by dissolving a known amount of host in 0.8 mL of solvent.

7.3 General Synthetic Procedures

Procedure 2.1: General Experimental Procedure for Compounds 118-120¹⁴⁵

The relevant nitroaniline was placed into a RBF and acetic anhydride, **117**, was added. The solution was then stirred at room temperature overnight. The resulting precipitate was then filtered and washed twice with cold diethyl ether. The solid was collected and dried under high vacuum.

Procedure 2.2: General Experimental Procedure for Compounds 121-123¹⁴⁵

The relevant nitro acetamide was placed into a RBF with the catalyst, 10% Pd/C and ethanol was added. $\text{N}_2\text{H}_4 \cdot \text{H}_2\text{O}$ was subsequently added and the reaction mixture stirred at 95°C overnight under an atmosphere of argon. The mixture was filtered, while hot, through celite and the solvent removed under reduced pressure. The resulting solid was washed with diethyl ether, collected and dried under vacuum.

Procedure 2.3: General Experimental Procedure for Receptors 111-113

The relevant amino acetamide was placed in RBF and dissolved with chloroform. Trifluoro-*p*-tolyl isothiocyanate, **124** (1.1 equiv.) was added and the solution was then stirred at room temperature overnight under an argon atmosphere. The resulting precipitate was filtered and washed with cold CHCl_3 . The solid obtained was then dried under vacuum.

Procedure 4.1: General Experimental Procedure for Compounds 154 and 155

The relevant nitroaniline, **114** or **115** or *N*-methyl nitroaniline, **165**, was dissolved in CH_3CN and 1,3,5-benzenetricarbonyl trichloride **153**, was added. The reaction mixture was then stirred under reflux overnight. The resulting precipitate was then filtered and washed with cold CH_3CN .

Procedure 4.2: General Experimental Procedure for Compounds 156 and 157

The relevant nitro derivative, **154** or **155**, was suspended in DMF. To the obtained suspension was added EtOH and the catalyst, 10% Pd/C. Following this $\text{N}_2\text{H}_4 \cdot \text{H}_2\text{O}$ (9 equiv.) was subsequently added and the reaction mixture stirred at 95°C overnight under an argon atmosphere. The reaction mixture was filtered, through celite while hot, and washed with hot EtOH. The solvent was then removed under reduced pressure to yield a brown oil, EtOH was added and a precipitate was observed within minutes, which was filtered and washed with EtOH to yield the desired product.

Procedure 4.3: General Experimental Procedure for Tripodal Urea Receptors 147-152

The relevant amine, **156**, **157** or **168**, was suspended in CH_3CN and stirred at 85°C for 10 mins. The desired isocyanate, **158-161** or **169**, was added, and the reaction mixture stirred under reflux overnight, or for 48 hrs in the case of **162-164**, under an argon atmosphere. The resulting precipitate was then filtered and washed with cold CH_3CN . Any unreacted amine was removed by recrystallisation in CH_3CN .

Procedure 5.1: General Experimental Procedure for Chalcones 176 and 177²⁵⁶

The appropriate nitro-benzaldehyde (**174** or **175**) (1 equiv.) was added to EtOH and the mixture heated to 70°C until the solid dissolved. Sodium pyruvate (1.1 equiv.) dissolved in H_2O was added, and the mixture cooled to 0°C in an ice bath. NaOH solution (2 M, 30 mL) was added dropwise and the resulting mixture stirred at 0°C for 3 hrs. The mixture was subsequently neutralised with 2 M HCl, filtered, the solid washed with EtOH (2×10 mL) and dried.

Procedure 5.2: General Experimental Procedure for Formation of 4-(nitrophenyl)-2,2'-bipyridine Compounds 184 and 185²⁵⁶

The appropriate chalcone (**176** or **177**) (1 equiv.), 2-pyridacetyl pyridinium iodide (**179**) (1 equiv.) and ammonium acetate (8 equiv.) were added to H_2O and the mixture heated at reflux for 5 hrs. The solid was filtered, and washed with H_2O (2×10 mL) and acetone (2×5

mL). The ammonium salt was heated under high vacuum with a heat gun until evolution of CO₂ ceased. The resulting black solid was dissolved in EtOAc (150 mL), activated charcoal added and the mixture refluxed for 15 mins. The mixture was filtered through a pad of celite and the solvent removed under reduced pressure.

Procedure 5.3: General Experimental Procedure for Reduction of 4-(nitrophenyl)-2,2'-bipyridine Compounds **184 and **185****²⁵⁶

The appropriate 4-(nitrophenyl)-2,2'-bipyridine derivative (**184** or **185**) (1 equiv.) and 10% Pd/C (0.2 g) were added to EtOH (20 mL), followed by hydrazine monohydrate (98%, 20 equiv.) and the mixture microwave irradiated at 100°C for 40 mins. The mixture was filtered through a pad of celite and the solid washed with CH₂Cl₂ (40 mL). The filtrate was washed with water, dried over MgSO₄, and the solvent removed under reduced pressure.

Procedure 5.4: General Experimental Procedure for Formation of Urea-based Compounds **189-192**

The appropriate 4-(aminophenyl)-2,2'-bipyridine derivative (**186** or **187**) (1 equiv.) and the relevant isocyanate (**158** or **188**) (1.1 equiv.) were added to CH₃CN (20 mL) and the mixture microwave irradiated at 100°C for 40 mins. The reaction mixture was filtered and the solid washed with CHCl₃ (40 mL).

Procedure 5.5: General Experimental Procedure for Complexation of Urea-based Compounds **189-192**

The appropriate ligand (**189-192**) and solid *cis-bis*-(bpy)Ru(II), **194**, was suspended in 4 mL EtOH/H₂O (1:1) and the resulting dark mixture microwave irradiated at 120°C for 45 mins. The resulting clear deep red solution was added to an aqueous solution of excess ammonium hexafluorophosphate resulting in the formation of a bright orange precipitate, which was collected by filtration. Purification was achieved by column chromatography on silica eluting with 40:4:1 CH₃CN:H₂O:NaNO₃(sat.aq.) to yield a red solid.

Procedure 6.1: General Experimental Procedure for Tosyl Threads **219 and **235****²⁴³

A solution of methyl 2,6-dihydroxybenzoate (**217**) (1.00 g, 5.95 mmol) in dry DMF (40 mL) was treated with Cs₂CO₃ (5.81 g, 17.84 mmol). After stirring for 30 mins, a solution of **218** or **234**, (4.36 g, 11.89 mmol) in dry DMF (10 mL) was added, and the resulting mixture stirred overnight at 70°C, then diluted with EtOAc (250 mL) and washed with saturated aq. NH₄Cl solution (4 × 100 mL). The combined organic extracts were dried over

MgSO₄, evaporated and purified by manual column chromatography (CH₂Cl₂-MeOH using a gradient elution 100 to 98:2).

Procedure 6.2: General Experimental Procedure for Azide Threads 220 and 236

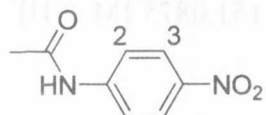
Compound **219** or **235** (0.540 g, 0.73 mmol) and sodium azide (0.570 g, 8.75 mmol) were heated at reflux in CH₃CN for 3 days. The solution was filtered by suction filtration and the organic extract dried over MgSO₄ and evaporated without any further purification.

Procedure 6.3: General Experimental Procedure for “Clicked” Threads 225 and 237

Compound **220** or **236** (0.540 g, 0.73 mmol), **226** (0.190 g, 0.44 mmol) and sodium ascorbate (0.320 g, 1.6 mmol) were dissolved in dry DMF (6 mL). CuSO₄·5H₂O (0.135 g, 0.54 mmol) was dissolved in water (2 mL) and added to the solution. This was stirred as a yellow solution at 25°C overnight under argon. The resulting green solution was diluted with 60 mL water and extracted with 60 mL CH₂Cl₂. The organic extracts were dried over MgSO₄, evaporated and purified by column chromatography (CH₂Cl₂-MeOH using a gradient elution 100 to 98:2).

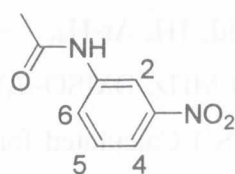
7.4 Experimental Details for Chapter 2

N-(4-Nitrophenyl)-acetamide (**118**)



Compound **118** was synthesised according to Procedure 2.1 using 4-nitroaniline, **114** (0.500 g, 3.62 mmol). The product was isolated as an off-white solid in 67% yield (0.440 g). m.p. 209-211°C (lit. m.p. 208-210°C); ¹H NMR (400 MHz, DMSO-*d*₆) δ_H: 10.56 (broad s, 1H, NH), 8.22 (d, 2H, Ar-H₃, *J* = 9.2 Hz), 7.83 (d, 2H, Ar-H₂, *J* = 9.2 Hz), 2.12 (s, 3H, CH₃); ¹³C{¹H} NMR (100 MHz, DMSO-*d*₆) δ_C: 169.8, 145.9, 142.4, 125.4, 118.9, 24.7; HRMS (*m/z*) (EI⁺) Calculated for C₈H₈N₂O₃ *m/z* = 180.0535 [M]⁺. Found *m/z* = 180.0537.

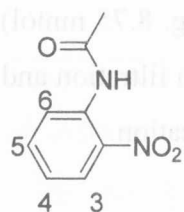
N-(3-Nitrophenyl)-acetamide (**119**)



Compound **119** was synthesised according to Procedure 2.1 using 3-nitroaniline, **115** (0.350 g, 2.53 mmol). The product was isolated as an off-white solid in 71% yield (0.213 g). m.p. 89-91°C (lit. 89-91°C)¹⁴⁵; ¹H NMR (400 MHz, DMSO-*d*₆) δ_H: 10.46 (broad s, 1H, NH), 8.63 (dd, 1H, Ar-H₂, *J* = 2.0 Hz, 2.0 Hz), 7.91 (ddd, 1H, Ar-H₄, *J* = 1.0 Hz, 2.0 Hz, 8.2 Hz), 7.89 (ddd, 1H, Ar-H₆, *J* = 1.0 Hz, 2.0 Hz, 8.2 Hz), 7.60 (app. t, 1H, Ar-H₅), 2.10 (s, 3H, CH₃); ¹³C{¹H} NMR

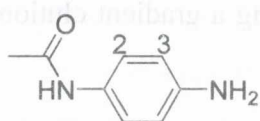
(100 MHz, DMSO- d_6) δ_C : 169.5, 148.4, 140.8, 130.6, 125.3, 118.0, 113.4, 24.5; HRMS (m/z) (ES^+) Calculated for $C_8H_8N_2O_3Na$ m/z = 203.0428 $[M + Na]^+$. Found m/z = 203.0433.

N-(2-Nitrophenyl)-acetamide (**120**)



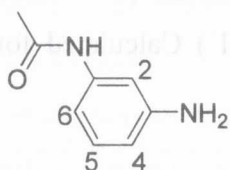
Compound **120** was synthesised according to Procedure 2.1 using 2-nitroaniline, **116** (0.500 g, 3.62 mmol). The product was isolated as a bright yellow solid in 57% yield (0.370 g). m.p. 147-149°C (lit. 148-150°C)¹⁴⁵; 1H NMR (400 MHz, DMSO- d_6) δ_H : 10.29 (broad s, 1H, NH), 7.93 (d, 1H, Ar-H₃, J = 8.2 Hz), 7.69 (app. t, 1H, Ar-H₅), 7.60 (d, 1H, Ar-H₆, J = 8.1 Hz), 7.35 (app. t, 1H, Ar-H₄), 2.06 (s, 3H, CH₃); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO- d_6) δ_C : 168.4, 142.6, 133.8, 131.1, 125.2, 125.1, 124.8, 23.3; HRMS (m/z) (ES^+) Calculated for $C_8H_8N_2O_3Na$ m/z = 203.0433 $[M + Na]^+$. Found m/z = 203.0433.

N-(4-Aminophenyl)-acetamide (**121**)

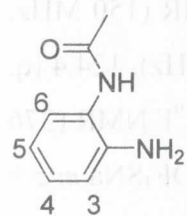


Compound **121** was synthesised according to Procedure 2.2, using *N*-(4-nitrophenyl)-acetamide, **118** (0.440 g, 2.43 mmol) and $N_2H_4 \cdot H_2O$ (0.94 mL, 0.970 g, 19.44 mmol). The product was isolated as a pale yellow solid in 73% yield (0.270 g). m.p. 86-89°C (lit. 86-89°C)¹⁴⁵; 1H NMR (400 MHz, DMSO- d_6) δ_H : 9.47 (s, 1H, NH), 7.19 (d, 2H, Ar-H₂, J = 8.5 Hz), 6.48 (d, 2H, Ar-H₃, J = 8.5 Hz), 4.81 (s, 2H, NH₂), 1.94 (s, 3H, CH₃); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO- d_6) δ_C : 167.6, 145.0, 129.0, 121.2, 114.2, 24.1; HRMS (m/z) (ES^+) Calculated for $C_8H_{11}N_2O$ m/z = 151.0875 $[M + H]^+$. Found m/z = 151.0871.

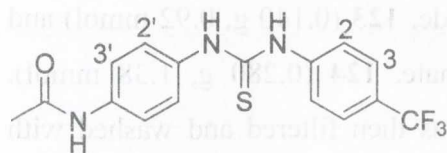
N-(3-Aminophenyl)-acetamide (**122**)



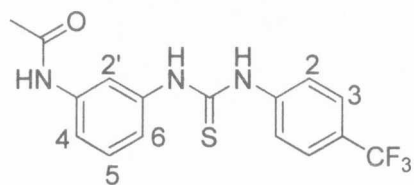
Compound **122** was synthesised according to Procedure 2, using *N*-(4-nitrophenyl)-acetamide, **119** (0.240 g, 1.35 mmol) and $N_2H_4 \cdot H_2O$ (0.52 mL, 0.540 g, 10.78 mmol). The product was isolated as a pale yellow solid in 80% yield (0.160 g). m.p. 126-129°C (lit. 126-128°C)¹⁴⁵; 1H NMR (400 MHz, DMSO- d_6) δ_H : 9.58 (s, 1H, NH), 6.91 (dd, 1H, Ar-H₂ J = 2.0 Hz, 2.0 Hz), 6.88 (app. t, 1H, Ar-H₅), 6.65 (dd, 1H, Ar-H₆, J = 8.0 Hz, 2.0 Hz), 6.62 (dd, 1H, Ar-H₄, J = 8.0 Hz, 2.0 Hz), 5.01 (s, 2H, NH₂), 1.96 (s, 3H, CH₃); $^{13}C\{^1H\}$ NMR (100 MHz, DMSO- d_6) δ_C : 168.4, 149.4, 140.4, 129.3, 109.5, 107.4, 105.1, 24.5; HRMS (m/z) (ES^+) Calculated for $C_8H_{11}N_2O$ m/z = 151.0869 $[M + H]^+$. Found m/z = 151.0871.

***N*-(2-Aminophenyl)-acetamide (123)**

Compound **123** was synthesised according to Procedure 2.2, using *N*-(4-nitrophenyl)-acetamide, **120** (0.200 g, 1.11 mmol) and $\text{N}_2\text{H}_4 \cdot \text{H}_2\text{O}$ (0.43 mL, 0.440 g, 8.88 mmol). The product was isolated as an off-white solid in 84% yield (0.140 g). m.p. 147-149°C (lit. 148-150°C)¹⁴⁵; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ_{H} : 9.13 (s, 1H, NH), 7.15 (d, 1H, Ar-H₆, $J = 7.5$ Hz), 6.88 (app. t, 1H, Ar-H₅), 6.71 (d, 1H, Ar-H₃, $J = 7.5$ Hz), 6.52 (app. t, 1H, Ar-H₄), 4.84 (s, 2H, NH₂), 2.03 (s, 3H, CH₃); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ_{C} : 170.3, 141.5, 126.4, 125.3, 123.1, 117.5, 116.5, 21.1; HRMS (m/z) (CI^+) Calculated for $\text{C}_8\text{H}_{11}\text{N}_2\text{O}$ $m/z = 151.0874$ [$\text{M} + \text{H}^+$]. Found $m/z = 151.0871$.

***N*-(4-(3-(4-(Trifluoromethyl)phenyl)thioureido)phenyl)acetamide (111)**

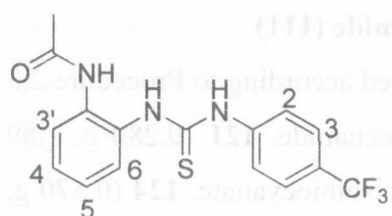
Receptor **111** was synthesised according to Procedure 2.3 using *N*-(4-aminophenyl)-acetamide, **121** (0.280 g, 1.89 mmol) and trifluoro-*p*-tolyl isothiocyanate, **124** (0.570 g, 2.83 mmol). The resulting precipitate was then filtered and washed with cold CHCl_3 to give the pure compound as an off white solid in 89% yield (0.590 g). m.p. 209-211°C; ^1H NMR (600 MHz, $\text{DMSO}-d_6$) δ_{H} : 9.98 (broad s, 1H, NH_{thiourea}), 9.94 (broad s, 2H, NH_{thiourea} + amide), 7.76 (d, 2H, Ar-H₃, $J = 8.5$ Hz), 7.68 (d, 2H, Ar-H_{3'}, $J = 8.5$ Hz), 7.56 (d, 2H, Ar-H₂, $J = 8.5$ Hz), 7.37 (d, 2H, Ar-H_{2'}, $J = 8.5$ Hz), 2.04 (s, 3H, CH₃); $^{13}\text{C}\{^1\text{H}\}$ NMR (150 MHz, $\text{DMSO}-d_6$) δ_{C} : 179.5, 168.0, 143.4, 136.3, 133.9, 125.5 (q, $J_{13\text{C}-19\text{F}} = 4$ Hz), 125.3 (q, $J_{13\text{C}-19\text{F}} = 26$ Hz), 125.2, 124.5, 124.3 (q, $J_{13\text{C}-19\text{F}} = 270$ Hz), 122.7, 119.0, 23.8; ^{19}F NMR (376 MHz, $\text{DMSO}-d_6$) δ_{F} : -60.84 (CF_3); HRMS (m/z) (ES^+) calculated for $\text{C}_{16}\text{H}_{13}\text{N}_3\text{OF}_3\text{S}$ $m/z = 352.0731$ [$\text{M} - \text{H}]^-$. Found $m/z = 352.0731$. Calculated for $\text{C}_{16}\text{H}_{14}\text{N}_3\text{OF}_3\text{S} \cdot 0.05\text{CHCl}_3$: C, 53.50; H, 3.93; N, 11.65 %. Found C, 53.34; H, 3.79; N, 11.64 %; IR ν_{max} (cm^{-1}) 3302, 3206, 3094, 1669, 1618, 1599, 1567, 1521, 1330, 1304, 1158, 1130, 1112, 1072, 1014, 839, 404.

***N*-(3-(3-(4-(Trifluoromethyl)phenyl)thioureido)phenyl)acetamide (112)**

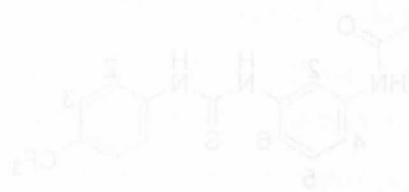
Receptor **112** was synthesised according to Procedure 2.3 using *N*-(3-aminophenyl)-acetamide, **122** (0.160 g, 1.08 mmol) and trifluoro-*p*-tolyl isothiocyanate, **124** (0.330 g, 1.63 mmol). The resulting precipitate was then filtered and washed with cold CHCl_3 to give the pure compound as an off white solid in 89% yield (0.340 g). m.p. 169-171°C; ^1H NMR (600 MHz, $\text{DMSO}-d_6$) δ_{H} : 10.06 (s, 2H, NH_{thiourea}), 9.97 (s, 1H, NH_{acetamide}), 7.77 (d, 2H, Ar-H₃, $J = 8.2$ Hz), 7.76 (dd, 1H, Ar-H_{2'}, $J = 2.0$ Hz, 2.0 Hz), 7.68

(d, 2H, Ar-H₂, $J = 8.2$ Hz), 7.37 (dd, 1H, Ar-H₄, $J = 8.0$ Hz, 2 Hz), 7.25 (t, 1H, Ar-H₅, $J = 8.0$ Hz), 7.20 (dd, 1H, Ar-H₆, $J = 8.0$ Hz, 2.0 Hz), 2.04 (s, 3H, CH₃); $^{13}\text{C}\{^1\text{H}\}$ NMR (150 MHz, d_6 -(CD₃)₂SO) δ_{C} : 179.4, 168.3, 143.4, 139.6, 139.3, 128.7, 125.5 (q, $J_{13\text{C}-19\text{F}} = 4$ Hz), 124.4 (q, $J_{13\text{C}-19\text{F}} = 272$ Hz), 123.8 (q, $J_{13\text{C}-19\text{F}} = 32$ Hz), 122.8, 118.2, 115.4, 114.1, 23.9; ^{19}F NMR (376 MHz, DMSO- d_6) δ_{F} : -60.84 (CF₃); HRMS (m/z) (ES⁺) Calculated for C₁₆H₁₄N₃OF₃SNa m/z = 376.0731 [M + Na]⁺. Found m/z = 352.0707; Calculated for C₁₆H₁₄N₃OF₃S·0.05CHCl₃: C, 53.64; H, 3.94; N, 11.69 %. Found C, 53.76; H, 3.87; N, 11.59 %; IR ν_{max} (cm⁻¹) 3320, 3232, 3180, 3126, 3064, 1654, 1597, 1573, 1545, 1453, 1417, 1320, 1305, 1288, 1254, 1161, 1104, 1063, 1016, 840, 785, 713, 680.

N-(2-(3-(4-(Trifluoromethyl)phenyl)thioureido)phenyl)acetamide (113)

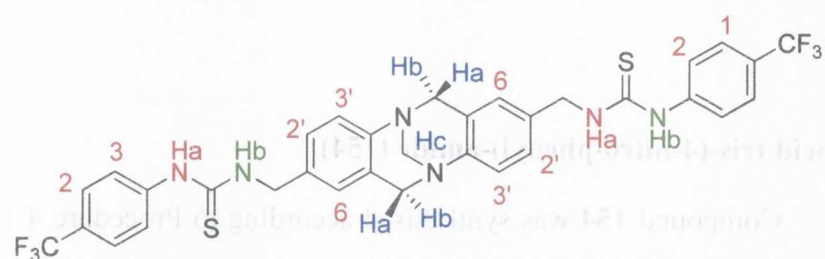


Receptor **113** was synthesised according to Procedure 3 using *N*-(2-aminophenyl)-acetamide, **123** (0.140 g, 0.92 mmol) and trifluoro-*p*-tolyl isothiocyanate, **124** (0.280 g, 1.38 mmol). The resulting precipitate was then filtered and washed with cold CHCl₃ to give the pure compound as an off white solid in 42% yield (0.140 g). m.p. 179-182°C; ^1H NMR (600 MHz, DMSO- d_6) δ_{H} : 10.41 (broad s, 1H, NH_{thiourea}), 9.74 (s, 1H, NH_{amide}), 9.20 (broad s, 1H, NH_{thiourea}), 7.82 (d, 2H, Ar-H₃, $J = 8.5$ Hz), 7.69 (d, 2H, Ar-H₂, $J = 8.5$ Hz), 7.55 (d, 1H, Ar-H₂, $J = 7.1$ Hz), 7.47 (d, 1H, Ar-H₃, $J = 7.1$ Hz), 7.21 (t, 1H, Ar-H₆, $J = 7.1$ Hz), 7.18 (t, 2H, Ar-H₄₊₅, $J = 7.1$ Hz), 2.08 (s, 3H, CH₃); $^{13}\text{C}\{^1\text{H}\}$ NMR (150 MHz, DMSO- d_6) δ_{C} : 180.1, 169.1, 143.3, 132.6, 132.0, 128.2, 126.1 (q, $J_{13\text{C}-19\text{F}} = 4$ Hz), 125.7, 125.6, 125.5 (q, $J_{13\text{C}-19\text{F}} = 272$ Hz), 124.8, 124.4 (q, $J_{13\text{C}-19\text{F}} = 272$ Hz), 122.7, 23.4; ^{19}F NMR (376 MHz, DMSO- d_6) δ_{F} : -60.86 (CF₃); HRMS (m/z) (ES⁺) Calculated for C₁₆H₁₄N₃OF₃SNa m/z = 376.0700 [M + Na]⁺. Found m/z = 352.0707; Calculated for C₁₆H₁₄N₃OF₃S·0.04CHCl₃: C, 53.79; H, 3.95; N, 11.73 %. Found C, 53.81; H, 3.99; N, 11.60 %; IR ν_{max} (cm⁻¹) 3197, 3110, 3012, 1642, 1598, 1537, 1500, 1481, 1442, 1319, 1296, 1260, 1239, 1166, 1156, 1106, 1064, 1016, 845, 762, 736, 700.



7.5 Experimental Details for Chapter 3

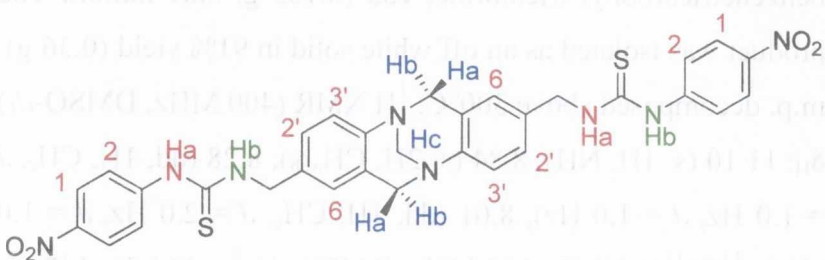
Bis-1-Benzyl-3-(4-(trifluoromethyl)phenyl)thiourea-[1,5]diazocene (138)¹³⁹



Compound **145** (0.246 g, 0.88 mmol) was dissolved in CHCl_3 with Et_3N and stirred vigorously while trifluoro-*p*-toyl isothiocyanate, **124**

(0.358 g, 1.76 mmol) was added dropwise in CHCl_3 over one hr. The solution was heated at reflux overnight, after which the product was isolated by suction filtration to give a white solid in 43% yield (0.260 g). ^1H -NMR (400 MHz, $\text{DMSO}-d_6$) δ_{H} : 9.84 (s, 2H, NHa), 8.35 (s, 2H, NHb), 7.72 (d, 2H, Ar- H_1 , $J = 5.6$ Hz), 7.65 (d, 2H, Ar- H_2 , $J = 5.7$ Hz), 7.12 (m, 4H, Ar- $\text{H}_{2'+3'}$), 6.91 (s, 2H, Ar- H_6), 4.64 (d, 2H, Ha, $J = 11.0$ Hz), 4.59 (d, 4H, CH_2 , $J = 11.0$ Hz), 4.22 (s, 2H, Hc), 4.11 (d, 2H, Hc, $J = 11.0$ Hz); $^{13}\text{C}\{^1\text{H}\}$ NMR (150 MHz, $\text{DMSO}-d_6$) δ_{C} : 180.3, 147.1, 143.3, 133.4, 127.8, 126.6, 125.9, 125.6, 125.2, 124.7, 123.5, 121.9, 66.3, 58.3, 46.8; ^{19}F NMR (376 MHz, $\text{DMSO}-d_6$) δ_{F} : -60.8 (CF_3); HRMS (m/z) (MALDI-ToF) Calculated for $\text{C}_{33}\text{H}_{29}\text{N}_6\text{F}_6\text{S}_2$ $m/z = 687.1799$ $[\text{M} + \text{H}]^+$. Found $m/z = 687.1801$; Calculated for $\text{C}_{33}\text{H}_{28}\text{F}_6\text{N}_6\text{S}_2 \cdot 0.2\text{H}_2\text{O}$: C, 57.41; H, 4.15; N, 12.17 %. Found C, 57.02; H, 4.03; N, 12.44 %; IR ν_{max} (cm^{-1}) 3250, 1616, 1543, 1493, 1462, 1422, 1321, 1266, 1209, 1166, 1121, 1066, 1016, 978, 962, 942, 888, 836, 744, 670.

Bis-1-Benzyl-3-(4-nitrophenyl)thiourea-[1,5]diazocene (139)¹³⁹



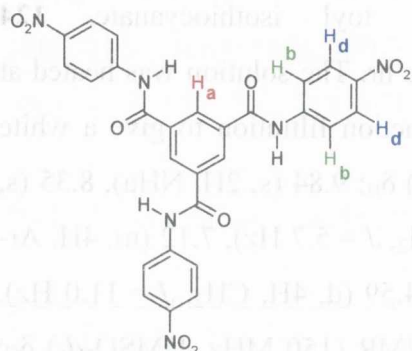
Compound **145** (0.19 g, 0.68 mmol) was dissolved in CHCl_3 with Et_3N and stirred vigorously while 4-nitrophenyl isothiocyanate

146 (0.26 g, 1.43 mmol) was added dropwise in CHCl_3 over one hr. The solution was heated at reflux overnight at 65°C , after which the product was isolated by suction filtration to give an orange solid in 40% yield (0.17 g). ^1H -NMR (400 MHz, $\text{DMSO}-d_6$) δ_{H} : 10.15 (s, 2H, NHa), 8.58 (s, 2H, NHb), 8.18 (d, 2H, Ar- H_1 , $J = 5.6$ Hz), 7.84 (d, 2H, Ar- H_2 , $J = 5.7$ Hz), 7.13 (m, 4H, Ar- $\text{H}_{2'+3'}$), 6.92 (s, 2H, Ar- H_6), 4.64 (M, 2H, Ha+ CH_2), 4.22 (s, 2H, Hc), 4.11 (d, 2H, Hc, $J = 11.0$ Hz); $^{13}\text{C}\{^1\text{H}\}$ NMR (150 MHz, $\text{DMSO}-d_6$) δ_{C} : 179.8, 147.0, 145.8, 141.7, 133.0, 127.8, 126.5, 125.9, 124.6, 124.5, 123.2, 120.2, 66.09, 58.2, 46.7. HRMS (m/z) (ES^+) Calculated for $\text{C}_{31}\text{H}_{29}\text{N}_8\text{O}_4\text{S}_2$ $m/z = 641.1753$ $[\text{M} + \text{H}]^+$. Found $m/z = 641.1740$; Calculated for $\text{C}_{31}\text{H}_{28}\text{N}_8\text{O}_4\text{S}_2 \cdot 0.2\text{H}_2\text{O} \cdot 0.2\text{CHCl}_3$: C, 56.08; H, 4.31; N, 16.77 %. Found C, 56.27; H, 4.53; N,

17.01 %; IR $\nu_{\max}$ (cm^{-1}) 3295, 3082, 2979, 1597, 1495, 1453, 1327, 1319, 1257, 1231, 1171, 1111, 969, 875, 849, 751, 725, 721.

7.6 Experimental Details for Chapter 4

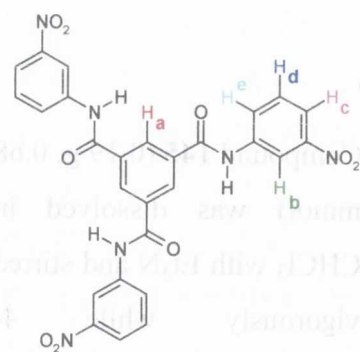
Benzene-1,3,5-tricarboxylic acid tris-(4-nitro-phenyl)-amide (**154**)



Compound **154** was synthesised according to Procedure 4.1 using 4-nitroaniline, **114** (0.80 g, 5.79 mmol) and 1,3,5-benzenetricarbonyl trichloride, **153** (0.465 g, 1.75 mmol). The product was isolated as an off white solid in 84% yield (0.84 g). m.p. decomposed above 300°C; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ_{H} : 11.18 (s, 1H, NH), 8.81 (s, 1H, CH_a), 8.31 (d, 2H, CH_d , $J = 9.0$ Hz), 8.12 (d, 2H, CH_b , $J = 9.0$ Hz);

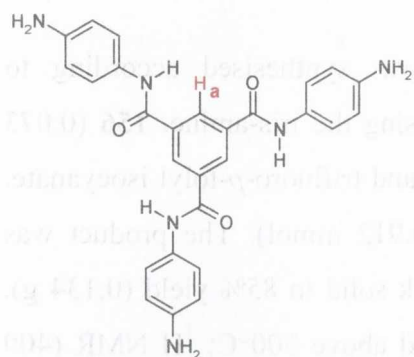
$^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, $\text{DMSO}-d_6$) δ_{C} : 165.4, 145.5, 143.2, 135.3, 131.2, 125.3, 120.5; HRMS (m/z) (ES^-) Calculated for $\text{C}_{27}\text{H}_{17}\text{N}_6\text{O}_9$ $m/z = 569.1057$ [$\text{M} - \text{H}$]. Found $m/z = 569.1050$; IR $\nu_{\max}$ (cm^{-1}) 3393, 3358, 3120, 1696, 1613, 1597, 1544, 1503, 1327, 1305, 1228, 1181, 1110, 849, 737.

Benzene-1,3,5-tricarboxylic acid tris-(3-nitro-phenyl)-amide (**155**)

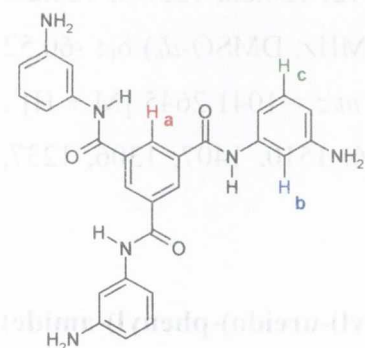


Compound **155** was synthesised according to Procedure 4.1 using 3-nitroaniline, **115** (0.314 g, 2.27 mmol) and 1,3,5-benzenetricarbonyl trichloride, **153** (0.183 g, 0.69 mmol). The product was isolated as an off white solid in 91% yield (0.36 g). m.p. decomposed above 300°C; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ_{H} : 11.10 (s, 1H, NH), 8.84 (s, 2H, CH_{a+b}), 8.28 (dd, 1H, CH_c , $J = 1.0$ Hz, $J = 1.0$ Hz), 8.01 (dd, 1H, CH_e , $J = 2.0$ Hz, $J = 1.0$ Hz), 7.70 (t, 1H, CH_d , $J = 8.0$ Hz);

$^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, $\text{DMSO}-d_6$) δ_{C} : 164.76, 147.92, 140.07, 134.90, 130.39, 130.23, 126.24, 118.53, 114.48; HRMS (m/z) (ES^-) Calculated for $\text{C}_{27}\text{H}_{17}\text{N}_6\text{O}_9$ $m/z = 569.1057$ [$\text{M} - \text{H}$]. Found $m/z = 569.1047$; IR $\nu_{\max}$ (cm^{-1}) 3264, 3087, 1650, 1597, 1523, 1421, 1347, 1325, 1299, 1260, 733.

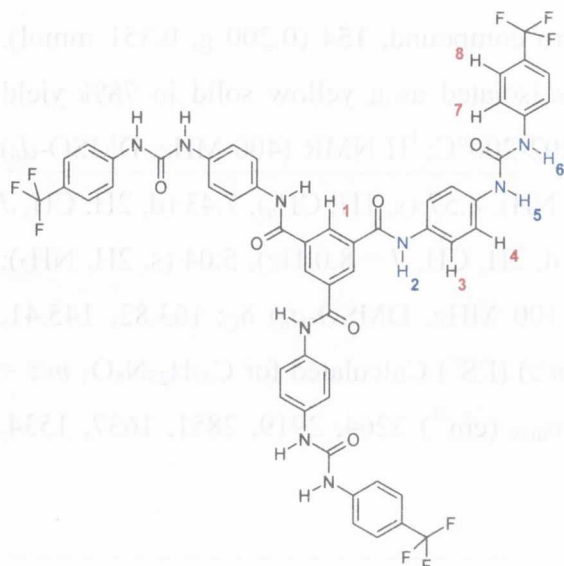
Benzene-1,3,5-tricarboxylic acid tris-(4-amino-phenyl)-amide (156)

Compound **156** was synthesised according to Procedure 4.2 using the tris-nitro compound, **154** (0.200 g, 0.351 mmol). The product was isolated as a yellow solid in 78% yield (0.131 g). m.p. 202-206°C; ^1H NMR (400 MHz, DMSO- d_6) δ_{H} : 10.17 (s, 1H, NH), 8.57 (s, 1H, CH_a), 7.43 (d, 2H, CH, J = 8.0 Hz), 6.57 (d, 2H, CH, J = 8.0 Hz), 5.04 (s, 2H, NH₂); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, DMSO- d_6) δ_{C} : 163.82, 145.41, 135.72, 128.98, 127.91, 122.11, 113.72. HRMS (m/z) (ES^+) Calculated for $\text{C}_{27}\text{H}_{25}\text{N}_6\text{O}_3$ m/z = 481.1988 [$\text{M} + \text{H}$] $^+$. Found m/z = 481.1986; IR ν_{max} (cm^{-1}) 3264, 2919, 2851, 1637, 1534, 1511, 1421, 1321, 1255, 1173, 1128, 823.

Benzene-1,3,5-tricarboxylic acid tris-(3-amino-phenyl)-amide (157)

Compound **157** was synthesised according to Procedure 4.2 using the tris-nitro compound, **155** (0.500 g, 0.876 mmol). The product was isolated as a white solid in 91% yield (0.383 g). m.p. decomposed above 300°C; ^1H NMR (400 MHz, DMSO- d_6) δ_{H} : 10.26 (s, 1H, NH), 8.59 (s, 1H, CH_a), 7.14 (s, 1H, CH_b), 7.00 (t, 1H, CH_c, J = 8.0 Hz), 6.91 (d, 1H, CH, J = 8.0 Hz), 6.34 (d, 1H, CH, J = 8.0 Hz), 5.17 (s, 2H, NH₂); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, DMSO- d_6) δ_{C} : 164.8, 149.5, 140.0, 136.1, 129.9, 129.3, 110.4, 108.7, 106.4; HRMS (m/z) (ES^+) Calculated for $\text{C}_{27}\text{H}_{25}\text{N}_6\text{O}_3$ m/z = 481.1988 [$\text{M} + \text{H}$] $^+$. Found m/z = 481.1981; IR ν_{max} (cm^{-1}) 3323, 1671, 1641, 1611, 1598, 1543, 1493, 1451, 1311, 1252, 681.

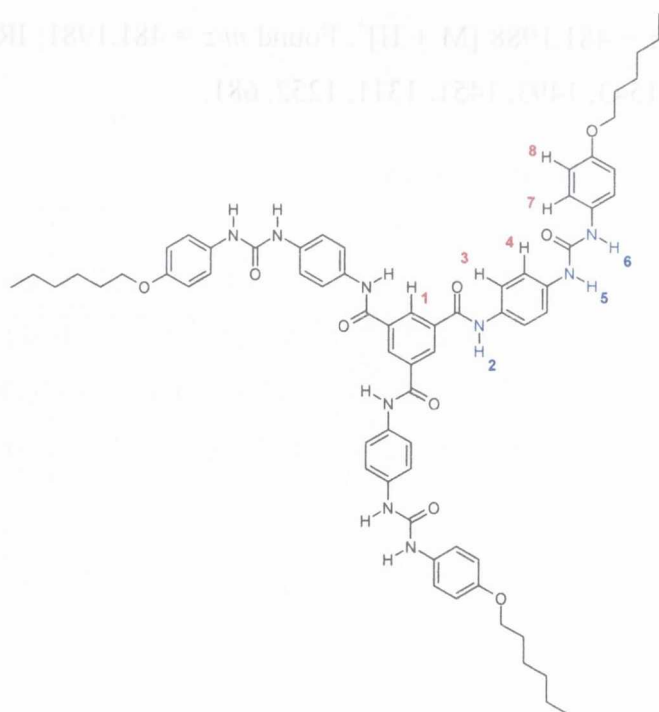
Benzene-1,3,5-tricarboxylic acid tris-((4-(3-(4-trifluoromethyl-phenyl)-ureido)-phenyl)-amide) (147)



Receptor **147** was synthesised according to Procedure 4.3 using the tris-amine, **156** (0.073 g, 0.152 mmol) and trifluoro-*p*-tolyl isocyanate, **158** (0.171 g, 0.912 mmol). The product was isolated as a pink solid in 85% yield (0.134 g). m.p. decomposed above 300°C; ^1H NMR (400 MHz, DMSO- d_6) δ_{H} : 10.55 (s, 1H, NH), 9.11 (s, 1H, NH), 8.83 (s, 1H, NH), 8.70 (s, 1H, CH), 7.76 (d, 2H, CH, $J = 8.52$ Hz), 7.65 (d + d, 4H, CH, $J = 8.52$ Hz, 9.04 Hz), 7.50 (d, 2H, CH, $J = 9.04$ Hz); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, DMSO- d_6)

δ_{C} : 164.26, 152.33, 143.54, 135.53, 135.40, 133.56, 129.58, 126.12, 126.08, 125.93, 123.23, 121.83, 121.52, 121.20, 121.12, 118.84, 117.80; ^{19}F NMR (376 MHz, DMSO- d_6) δ_{F} : -60.52 (CF₃); HRMS (m/z) (MALDI-ToF) Calculated for C₅₁H₃₆N₉O₆F₉ $m/z = 1041.2645$ [M + H]⁺. Found $m/z = 1041.2686$; IR ν_{max} (cm⁻¹) 3290, 1641, 1602, 1546, 1510, 1407, 1306, 1237, 1161, 1111, 1067, 1015, 831.

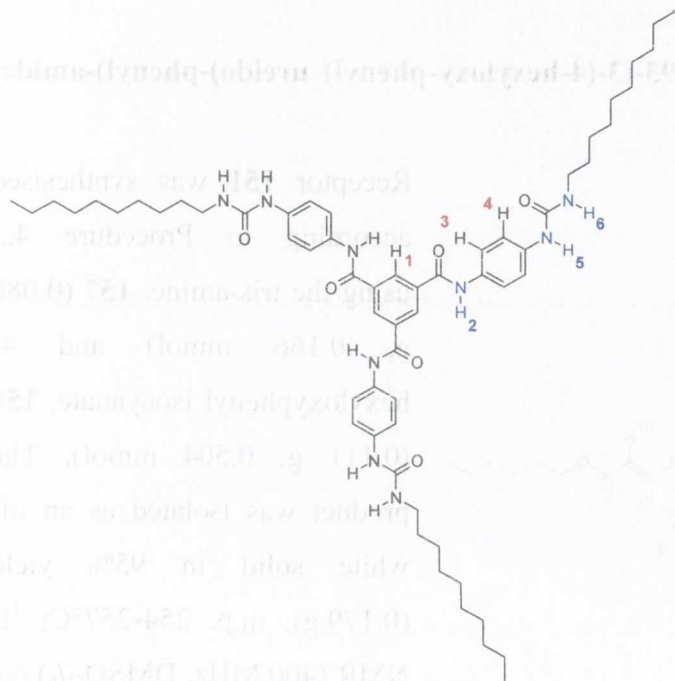
Benzene-1,3,5-tricarboxylic acid tris-((4-[3-(4-hexyloxy-phenyl)-ureido)-phenyl]-amide) (148)



Receptor **148** was synthesised according to Procedure 4.3 using the tris-amine, **156** (0.080 g, 0.166 mmol) and 4-hexyloxyphenyl isocyanate, **159** (0.111 g, 0.504 mmol). The product was isolated as a white solid in 89% yield (0.168 g). m.p. decomposed above 300°C; ^1H NMR (400 MHz, DMSO- d_6) δ_{H} : 10.51 (s, 1H, NH), 8.69 (s, 1H, CH), 8.59 (s, 1H, NH), 8.46 (s, 1H, NH), 7.72 (d, 2H, CH, $J = 8.0$ Hz), 7.46 (d, 2H, CH, $J = 8.0$ Hz), 7.35 (d, 2H, CH, $J = 9.0$ Hz), 6.86 (d, 2H, CH, $J = 9.0$ Hz), 3.91 (t, 2H, OCH₂, $J = 6.0$ Hz), 1.69 (m,

2H, CH₂), 1.41 (t, 2H, CH₂, $J = 6.0$ Hz), 1.31 (t, 2H, CH₂, $J = 4.0$ Hz), 0.88 (t, 3H, CH₃, $J = 6.0$ Hz); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, DMSO- d_6) δ_{C} : 164.19, 153.84, 152.77, 136.08, 135.56, 133.02, 132.67, 129.50, 121.11, 119.96, 118.36, 114.58, 67.56, 31.05, 28.75, 25.24, 22.11, 13.95; IR ν_{max} (cm⁻¹) 3280, 3044, 2929, 2858, 1638, 1603, 1554, 1507, 1405, 1308, 1211, 1171, 826.

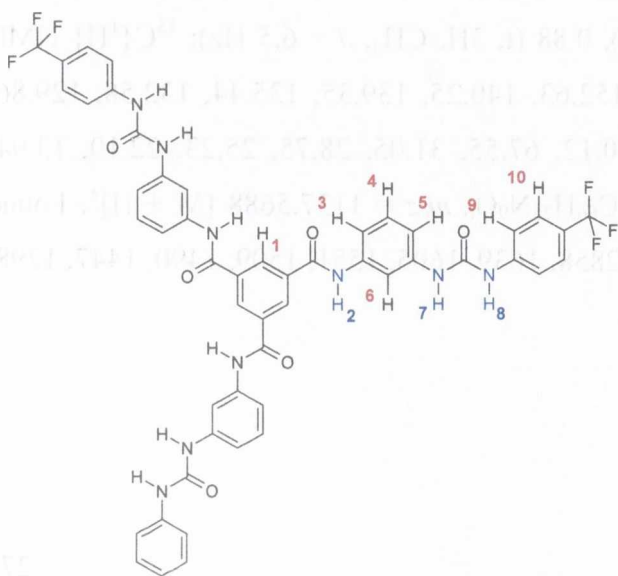
Benzene-1,3,5-tricarboxylic acid tris-((4-[3-decyl-ureido)-phenyl]-amide) (149)



Receptor **149** was synthesised according to Procedure 4.3 using the tris-amine, **156** (0.080 g, 0.166 mmol) and dodecyl isocyanate, **160** (0.107 g, 0.504 mmol). The product was isolated as a white solid in 67% yield (0.123 g). m.p. decomposed above 300°C; ^1H NMR (400 MHz, DMSO- d_6) δ_{H} : 10.44 (s, 1H, NH), 8.65 (s, 1H, CH), 8.39 (s, 1H, NH), 7.66 (d, 2H, CH, $J = 9.0$ Hz), 7.39 (d, 2H, CH, $J = 9.0$ Hz), 6.10 (s, 1H, NH-CH₂), 3.08 (2H, CH₂-NH), 1.42 (2H, CH₂), 1.25 (18H, CH₂), 0.85

(t, 3H, CH₃, $J = 3.0$ Hz); $^{13}\text{C}\{^1\text{H}\}$ NMR (150 MHz, DMSO- d_6) δ_{C} : 164.43, 155.56, 137.18, 135.88, 132.71, 129.70, 121.38, 118.10, 39.52, 31.61, 30.10, 29.36, 29.33, 29.10, 29.03, 26.71, 22.41, 14.27; IR ν_{max} (cm⁻¹) 3326, 2921, 2851, 1638, 1607, 1598, 1510, 1405, 1305, 1231, 832, 720.

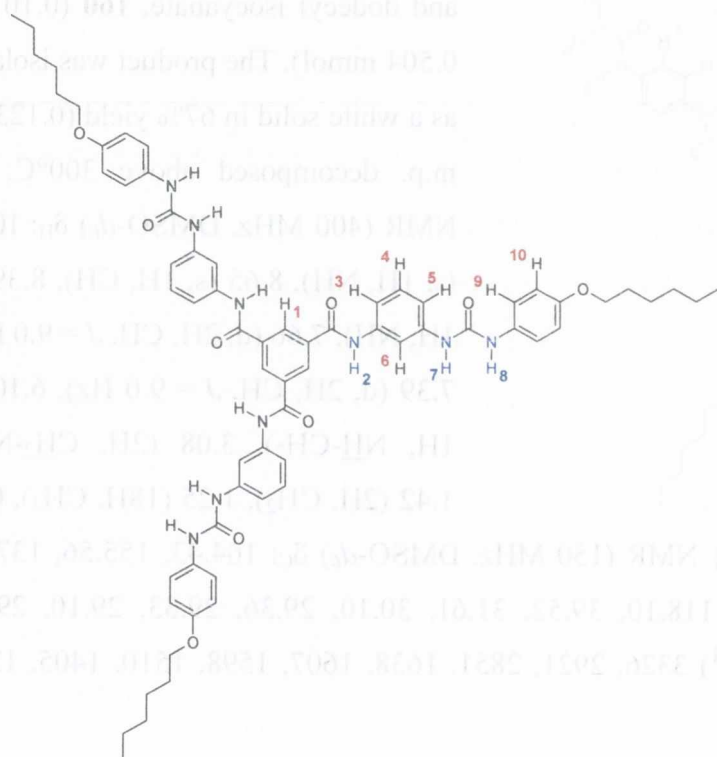
Benzene-1,3,5-tricarboxylic acid tris-((3-(4-trifluoromethyl-phenyl)-ureido)-phenyl)-amide (150)



Receptor **150** was synthesised according to Procedure 4.3 using the tris-amine, **157** (0.080 g, 0.166 mmol) and trifluoro-*p*-tolyl isocyanate, **158** (0.094 g, 0.504 mmol). The product was isolated as an off white solid in 91% yield (0.157 g). m.p. decomposed above 300°C; ^1H NMR (400 MHz, DMSO-

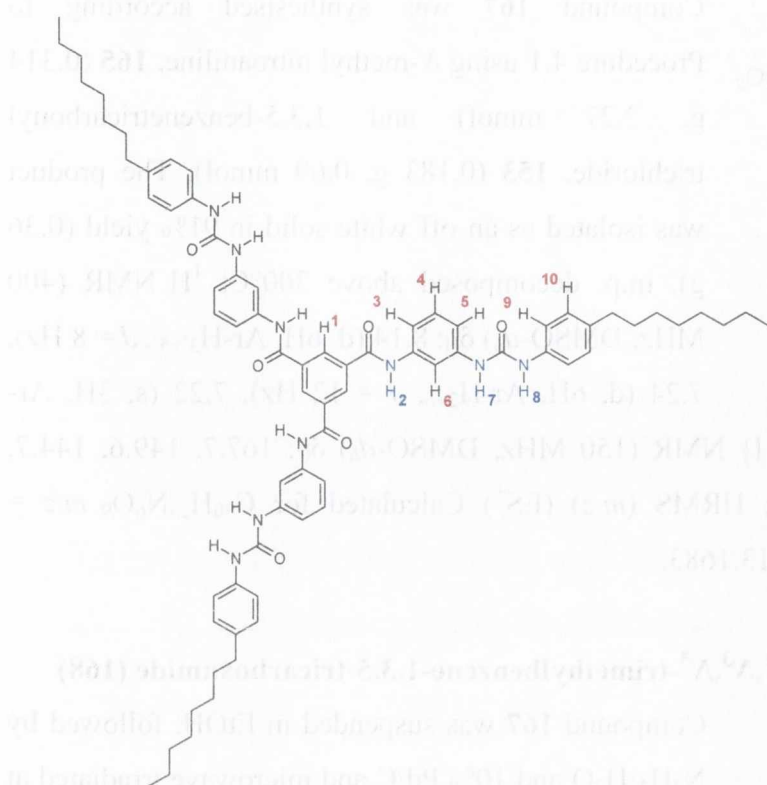
d_6) δ_H : 10.62 (s, 1H, NH), 9.08 (s, 1H, NH), 8.94 (s, 1H, NH), 8.72 (s, 1H, CH), 8.09 (s, 1H, CH), 7.65 (d,d, 4H, CH, $J = 8.5$ Hz, $J = 9.0$ Hz), 7.49 (d, 1H, CH, $J = 8.0$ Hz), 7.30 (m, 2H, CH); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, DMSO- d_6) δ_C : 164.60, 152.20, 143.44, 139.64, 139.42, 135.42, 129.90, 129.08, 128.04, 126.09, 125.90, 121.59, 117.80, 114.40, 114.07, 110.47; ^{19}F -NMR (376 MHz, DMSO- d_6) δ_F : -60.54 (CF_3); HRMS (m/z) (MALDI-ToF) Calculated for $\text{C}_{51}\text{H}_{36}\text{N}_9\text{O}_6\text{F}_9$ $m/z = 1040.2567$ $[\text{M} + \text{H}]^+$. Found $m/z = 1040.2522$; IR ν_{max} (cm^{-1}) 3303, 1654, 1602, 1534, 1482, 1414, 1318, 1245, 1209, 1164, 1109, 1068, 840, 773.

Benzene-1,3,5-tricarboxylic acid tris-(93-(3-(4-hexyloxy-phenyl) ureido)-phenyl)-amide) (151)

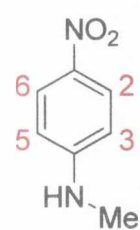


Receptor **151** was synthesised according to Procedure 4.3 using the tris-amine, **157** (0.080 g, 0.166 mmol) and 4-hexyloxyphenyl isocyanate, **159** (0.111 g, 0.504 mmol). The product was isolated as an off white solid in 95% yield (0.179 g). m.p. 254-257°C; ^1H NMR (400 MHz, DMSO- d_6) δ_H : 10.58 (s, 1H, NH), 8.71 (s, 1H, NH), 8.70 (s, 1H, CH), 8.44 (s, 1H, NH), 8.03 (s, 1H, CH), 7.45 (d, 1H, CH, $J = 7.5$ Hz), 7.35 (d, 2H, CH, $J = 8.5$ Hz), 7.26 (m,

2H, CH), 6.85 (d, 2H, CH, $J = 9.0$ Hz), 3.90 (t, 2H, CH_2 , $J = 6.0$ Hz), 1.68 (m, 2H, CH_2), 1.40 (t, 2H, CH_2 , $J = 6.0$ Hz), 1.30 (m, 4H, CH_2), 0.88 (t, 3H, CH_3 , $J = 6.5$ Hz); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, DMSO- d_6) δ_C : 164.57, 153.88, 152.63, 140.25, 139.35, 135.44, 132.58, 129.86, 128.97, 119.91, 114.59, 113.85, 113.76, 110.12, 67.55, 31.05, 28.75, 25.23, 22.10, 13.94; HRMS (m/z) (MALDI-ToF) Calculated for $\text{C}_{66}\text{H}_{75}\text{N}_9\text{O}_6$ $m/z = 1137.5688$ $[\text{M} + \text{H}]^+$. Found $m/z = 1137.5670$; IR ν_{max} (cm^{-1}) 3288, 2932, 2858, 1639, 1605, 1551, 1509, 1490, 1447, 1298, 1240, 1034, 831.

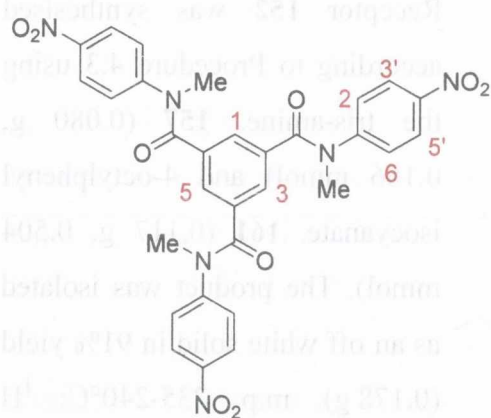
Benzene-1,3,5-tricarboxylic acid tris-((3-[3-(4-octyl-phenyl) ureido)-phenyl)-amide) (152)

Receptor **152** was synthesised according to Procedure 4.3 using the tris-amine, **157** (0.080 g, 0.166 mmol) and 4-octylphenyl isocyanate, **161** (0.117 g, 0.504 mmol). The product was isolated as an off white solid in 91% yield (0.178 g). m.p. 235-240°C; ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ_{H} : 10.59 (s, 1H, NH), 8.75 (s, 1H, NH), 8.71 (s, 1H, CH), 8.55 (s, 1H, NH), 8.05 (s, 1H, CH), 7.46 (d, 1H, CH, $J = 8$ Hz), 7.36 (d, 2H, CH, $J = 8$ Hz), 7.27 (m, 2H, CH), 7.08 (d, 2H, CH, $J = 8.5$ Hz), 1.53 (s, 2H, CH_2), 1.26 (m, 12H, CH_2), 0.85 (t, 3H, CH_3 , $J = 6.5$ Hz); $^{13}\text{C}\{^1\text{H}\}$ NMR (150 MHz, $\text{DMSO}-d_6$) δ_{C} : 164.58, 152.47, 148.96, 140.15, 139.37, 138.25, 137.28, 135.75, 135.43, 129.87, 128.99, 128.52, 118.21, 117.99, 113.94, 113.78, 110.15, 34.50, 31.30, 31.14, 28.87, 28.71, 28.65, 22.10, 13.97; HRMS (m/z) (MALDI-ToF) Calculated for $\text{C}_{72}\text{H}_{88}\text{N}_9\text{O}_6$ $m/z = 1174.6858$ $[\text{M} + \text{H}]^+$. Found $m/z = 1174.6799$; IR ν_{max} (cm^{-1}) 3294, 2922, 2851, 1642, 1604, 1551, 1490, 1447, 1411, 1301, 1241, 781, 686.

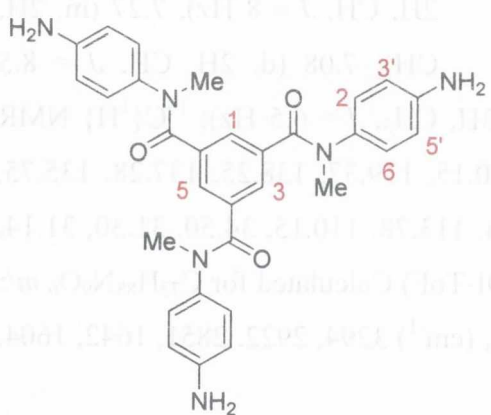
N-methyl nitroaniline (165)

1-Iodo-4-nitrobenzene, **166** (3g, 12mmol) was dissolved in 5ml of 40% aqueous methyl amine solution with copper powder (0.45g, 5.8mmol) in a pressure tube and heated to 100°C for 24 hrs, after which it was allowed to cool. The solution was extracted with EtOAc (5×50 mL) and the organic layer dried over MgSO_4 .

The solvent was removed under reduced pressure and the resulting solid purified by column chromatography eluting CHCl_3 :EtOAc (85:15%) to give **165** as a yellow powder in 55% yield (0.5 g). ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ_{H} : 8.00 (d, 2H, Ar- H_{2+6} , $J = 12$ Hz), 7.33 (s, 1H, NH), 6.60 (d, 2H, Ar- H_{3+5} , $J = \text{Hz}$), 2.50 (s, 3H, CH_3); $^{13}\text{C}\{^1\text{H}\}$ NMR (150 MHz, $\text{DMSO}-d_6$) δ_{C} : 156.1, 136.3, 127.5, 114.4, 29.6; HRMS (m/z) (ES^+) Calculated for $\text{C}_7\text{H}_9\text{N}_2\text{O}_2$ $m/z = 153.0644$ $[\text{M} + \text{H}]^+$. Found $m/z = 153.0664$; IR ν_{max} (cm^{-1}) 3360, 1593, 1541, 1106.

***N*¹,*N*³,*N*⁵-Trimethyl-*N*¹,*N*³,*N*⁵-tris(4-nitrophenyl)benzene-1,3,5-tricarboxamide (167)**

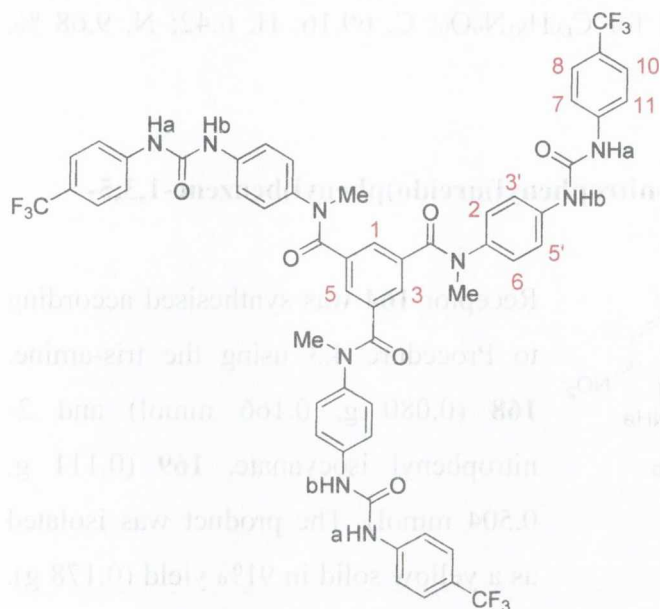
Compound **167** was synthesised according to Procedure 4.1 using *N*-methyl nitroaniline, **165** (0.314 g, 2.27 mmol) and 1,3,5-benzenetricarbonyl trichloride, **153** (0.183 g, 0.69 mmol). The product was isolated as an off white solid in 91% yield (0.36 g). m.p. decomposed above 300°C; ¹H NMR (400 MHz, DMSO-*d*₆) δ_H: 8.14 (d, 6H, Ar-H_{3'+5'}, *J* = 8 Hz), 7.24 (d, 6H, Ar-H₂₊₆, *J* = 12 Hz), 7.22 (s, 3H, Ar-H₁₊₃₊₅), 3.27 (s, 9H, CH₃); ¹³C{¹H} NMR (150 MHz, DMSO-*d*₆) δ_C: 167.7, 149.6, 144.7, 135.7, 128.5, 127.4, 124.2, 37.3; HRMS (*m/z*) (ES⁺) Calculated for C₃₀H₂₅N₆O₉ *m/z* = 613.1683 [M + H]⁺. Found *m/z* = 613.1683.

***N*¹,*N*³,*N*⁵-Tris(4-aminophenyl)-*N*¹,*N*³,*N*⁵-trimethylbenzene-1,3,5-tricarboxamide (168)**

Compound **167** was suspended in EtOH, followed by N₂H₄·H₂O and 10% Pd/C and microwave irradiated at 90°C for 40 mins. The reaction mixture was filtered through a pad of celite and the solvent reduced under pressure to give **168** as a white solid in 60% yield. (0.36 g). m.p. decomposed above 300°C; ¹H NMR (400 MHz, DMSO-*d*₆) δ_H: 6.83 (s, 3H, Ar-H₁₊₃₊₅), 6.50 (s, 6H, Ar-H₂₊₆), 6.37 (s, 6H, Ar-H_{3'+5'}), 5.09 (s, 6H, NH₂), 3.18 (s, 9H, CH₃); ¹³C{¹H} NMR (150 MHz, DMSO-*d*₆) δ_C: 168.3, 147.0, 135.9, 132.4, 128.0, 127.5, 114.0, 37.6; HRMS (*m/z*) (ES⁺) Calculated for C₃₀H₃₁N₆O₃ *m/z* = 523.6055 [M + H]⁺. Found *m/z* = 523.2458.



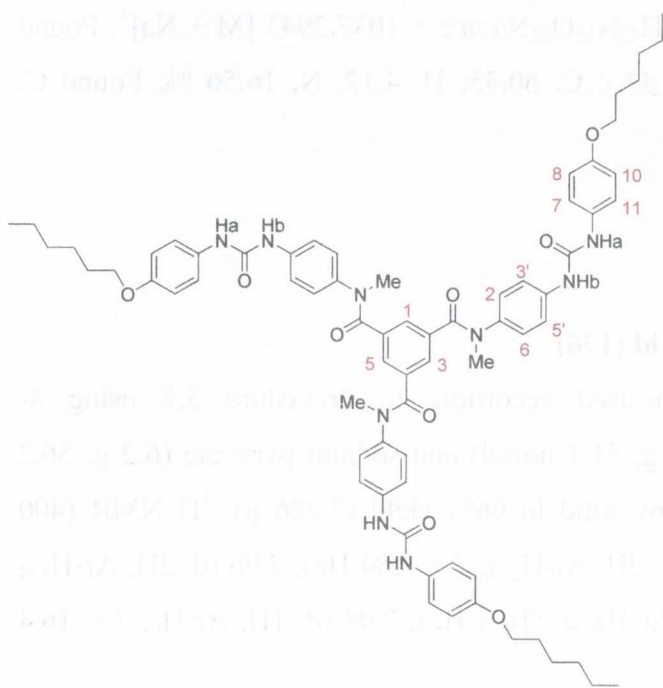
***N*¹,*N*³,*N*⁵-Trimethyl-*N*¹,*N*³,*N*⁵-tris(4-(3-(4-(trifluoromethyl)phenyl)ureido)phenyl)benzene-1,3,5-tricarboxamide (162)**



Receptor **162** was synthesised according to Procedure 4.3 using the tris-amine, **168** (0.080 g, 0.166 mmol) and trifluoro-*p*-tolyl isocyanate, **158** (0.171 g, 0.912 mmol). The product was isolated as a yellow solid in 91% yield (0.178 g). ¹H NMR (400 MHz, DMSO-*d*₆) δ_H: 9.10 (s, 3H, NHa), 8.84 (s, 3H, NHb), 7.64 (d, 6H, Ar-H₈₊₁₀, *J* = 8 Hz), 7.50 (d, 6H, Ar-H₇₊₁₁, *J* = 8 Hz), 7.45 (d, 6H, Ar-H_{3'+5'}, *J* = 8 Hz), 7.01 (br s, 3H, Ar-H₁₊₃₊₅), 6.79 (br s, 6H, Ar-H₂₊₆), 3.24 (br s, 9H, N-

Me); ¹³C{¹H} NMR (150 MHz, DMSO-*d*₆) δ_C: 168.3, 152.4, 143.5, 138.3, 137.8, 127.5, 126.0, 125.7, 123.8, 119.5, 118.4, 38.1; HRMS (*m/z*) (ES⁺) Calculated for C₅₄H₄₁N₉O₆F₉ *m/z* = 1082.3036 [M - H]⁺. Found *m/z* = 1082.302; Calculated for C₅₄H₄₂F₉N₉O₆: C, 59.83; H, 3.91; N, 11.63 %. Found C, 59.58; H, 3.67; N, 11.47 %.

***N*¹,*N*³,*N*⁵-Tris(4-(3-(4-(hexyloxy)phenyl)ureido)phenyl)-*N*¹,*N*³,*N*⁵-trimethylbenzene-1,3,5-tricarboxamide (163)**

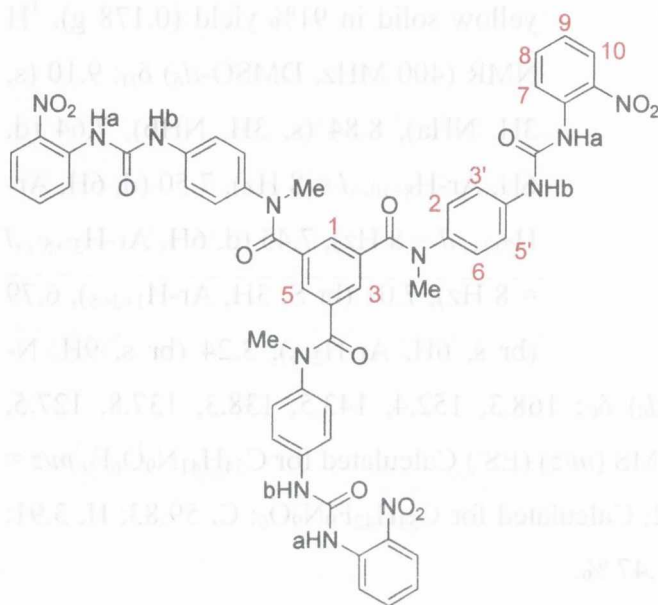


Receptor **163** was synthesised according to Procedure 4.3 using the tris-amine, **168** (0.080 g, 0.166 mmol) and 4-hexyloxyphenyl isocyanate, **159** (0.111 g, 0.504 mmol). The product was isolated as a yellow solid in 91% yield (0.178 g). ¹H NMR (400 MHz, DMSO-*d*₆) δ_H: 8.39 (s, 3H, NHa), 8.25 (s, 3H, NHb), 7.15 (d, 6H, Ar-H_{3'+5'}, *J* = 8 Hz), 7.02 (d, 6H, Ar-H₇₊₁₁, *J* = 8 Hz), 6.70 (br s, 3H, Ar-H₁₊₃₊₅), 6.42 (d, 12H, Ar-H₂₊₆₊₈₊₁₀), 3.47 (s, 6H, O-CH₂), 2.96 (br s, 9H, N-Me), 1.36 (t, 6H, O-CH₂-CH₂, *J* = 8 Hz), 1.10

(s, 18H, (CH₂)₆), 0.61 (s, 9H, CH₂-CH₃); ¹³C{¹H} NMR (150 MHz, DMSO-*d*₆) δ_C: 168.0,

153.9, 152.7, 138.1, 137.5, 135.9, 132.1, 127.2, 120.4, 118.6, 114.3, 67.4, 37.5, 31.1, 28.7, 25.4, 22.0, 13.9; HRMS (m/z) (ES^+) Calculated for $C_{69}H_{81}N_9O_9Na$ $m/z = 1202.6055$ [$M + Na$] $^+$. Found $m/z = 1202.5997$; Calculated for $C_{69}H_{81}N_9O_9$: C, 69.16; H, 6.42; N, 9.68 %. Found C, 69.52; H, 6.39; N, 9.90 %.

N^1, N^3, N^5 -Trimethyl- N^1, N^3, N^5 -tris(4-(3-(2-nitrophenyl)ureido)phenyl)benzene-1,3,5-tricarboxamide (164)

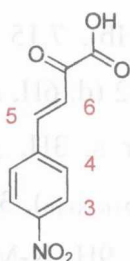


Receptor **164** was synthesised according to Procedure 4.3 using the tris-amine, **168** (0.080 g, 0.166 mmol) and 2-nitrophenyl isocyanate, **169** (0.111 g, 0.504 mmol). The product was isolated as a yellow solid in 91% yield (0.178 g). 1H NMR (400 MHz, $DMSO-d_6$) δ_H : 9.90 (s, 3H, NHa), 9.58 (s, 3H, NHb), 8.30 (d, 3H, Ar- H_{10} , $J = 12$ Hz), 8.05 (d, 3H, Ar- H_7 , $J = 8$ Hz), 7.56 (t, 3H, Ar- H_9 , $J = 8$ Hz), 7.44 (d, 6H, Ar- H_{3+5} , $J = 8$ Hz), 7.13 (t, 3H, Ar- H_8 , $J = 8$ Hz), 7.02 (br s,

3H, Ar- H_{1+3+5}), 6.86 (br s, 6H, Ar- H_{2+6}), 3.23 (br s, 9H, N-Me); $^{13}C\{^1H\}$ NMR (150 MHz, $DMSO-d_6$) δ_C : 168.0, 152.0, 138.6, 137.9, 137.6, 135.1, 127.1, 125.6, 122.8, 122.4, 119.6, 38.0; HRMS (m/z) (ES^+) Calculated for $C_{51}H_{42}N_{12}O_{12}Na$ $m/z = 1037.2943$ [$M + Na$] $^+$. Found $m/z = 1037.2891$; Calculated for $C_{51}H_{42}N_{12}O_{12}$: C, 60.35; H, 4.17; N, 16.56 %. Found C, 59.85; H, 3.93; N, 16.43 %.

7.7 Experimental Details for Chapter 5

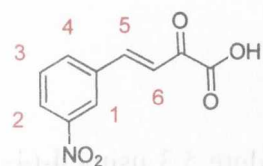
(*E*)-4-(4-Nitrophenyl)-2-oxo-3-butenic acid (176)



Compound **176** was synthesised according to Procedure 5.1 using 4-nitrobenzaldehyde, **174** (7.7 g, 51.1 mmol) and sodium pyruvate (6.2 g, 56.2 mmol) giving a bright yellow solid in 66% yield (7.486 g). 1H NMR (400 MHz, $DMSO-d_6$) δ_H : 8.24 (d, 2H, Ar- H_{2+3} , $J = 8.84$ Hz), 7.96 (d, 2H, Ar- H_{1+4} , $J = 8.76$ Hz), 7.55 (d, 1H, Ar- H_5 , $J = 16.4$ Hz), 7.05 (d, 1H, Ar- H_6 , $J = 16.4$

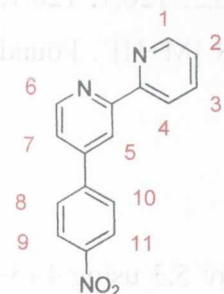
Hz); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, DMSO- d_6) δ_{C} : 196.9, 168.8, 148.2, 141.8, 140.8, 129.6, 129.3, 124.4; HRMS (m/z) (ES^-) Calculated for $\text{C}_{10}\text{H}_6\text{NO}_5$ m/z = 220.0246 $[\text{M}-\text{H}]^-$. Found m/z = 220.0255; IR ν_{max} (cm^{-1}) 3461, 1677, 1514, 1346.

(E)-4-(3-Nitrophenyl)-2-oxo-3-butenic acid (177)



Compound **177** was synthesised according to Procedure 5.1 using 3-nitrobenzaldehyde, **175** (7.7 g, 51.1 mmol) and sodium pyruvate (6.2 g, 56.2 mmol), giving the product as a bright yellow solid in 54% yield (6.19 g). ^1H NMR (400 MHz, DMSO- d_6) δ_{H} : 8.45 (s, 1H, Ar-H₁), 8.22 (dd, 1H, Ar-H₂, J = 2.0 Hz, J = 8.0 Hz), 8.15 (d, 1H, Ar-H₄, J = 8.0 Hz), 7.70 (t, 1H, Ar-H₃, J = 8.0 Hz), 7.54 (d, 1H, Ar-H₅, J = 16.6 Hz), 7.05 (d, 1H, Ar-H₆, J = 16.6 Hz); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, DMSO- d_6) δ_{C} : 196.8, 169.1, 148.8, 141.3, 137.0, 134.5, 130.9, 127.8, 124.8, 123.0; HRMS (m/z) (ES^-) Calculated for $\text{C}_{10}\text{H}_6\text{NO}_5$ m/z = 220.0246 $[\text{M}-\text{H}]^-$. Found m/z = 220.0252; IR ν_{max} (cm^{-1}) 3502, 1688, 1535, 1346.

4-(4-Nitrophenyl)-2,2'-bipyridine (184)



Compound **184** was synthesised according to Procedure 5.2 using compound **176** (2.13 g, 9.63 mmol), 2-pyridacetyl pyridinium iodide, **179** (3.14 g, 9.63 mmol) and ammonium acetate (5.95 g, 77.21 mmol) to yield a pale yellow solid in 50% yield (1.34 g). ^1H NMR (400 MHz, CDCl_3) δ_{H} : 8.82 (d, 1H, Ar-H₆, J = 5.04 Hz), 8.74 (m, 2H, Ar-H₁₊₅), 8.50 (d, 1H, Ar-H₄, J = 7.96 Hz), 8.39 (d, 2H, Ar-H₉₊₁₁, J = 8.84 Hz), 7.94 (d, 2H, Ar-H₈₊₁₀, J = 8.88 Hz), 7.89 (dt, 1H, Ar-H_{2/3}, J = 7.68 Hz, J = 1.64 Hz), 7.58 (dd, 1H, Ar-H₇, J = 5.12 Hz, J = 1.8 Hz), 7.39 (m, 1H, Ar-H_{2/3}); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ_{C} : 154.8, 149.5, 148.5, 147.7, 146.5, 144.1, 136.9, 127.7, 123.87, 123.8, 121.2, 121.0, 118.8; HRMS (m/z) (ES^+): Calculated for $\text{C}_{16}\text{H}_{12}\text{N}_3\text{O}_2$ m/z = 278.0930 $[\text{M}+\text{H}]^+$. Found m/z = 278.0919; IR ν_{max} (cm^{-1}) 1516, 1360.

4-(3-Nitrophenyl)-2,2'-bipyridine (185)



Compound **185** was synthesised according to Procedure 5.2 using compound **177** (2.13 g, 9.63 mmol), 2-pyridacetyl pyridinium iodide, **179** (3.14 g, 9.63 mmol) and ammonium acetate (5.95 g, 77.21 mmol) giving the product as a pale yellow solid in 51% yield (2.67 g). ^1H NMR (400 MHz, CDCl_3) δ_{H} : 8.83 (d, 1H, Ar-H₇, J = 5.04 Hz), 8.75 (m, 2H, Ar-H₅₊₁), 8.65 (app d, 1H, Ar-H₈), 8.50 (d, 1H, Ar-H₄, J = 8.0 Hz), 8.35 (dd, 1H, Ar-

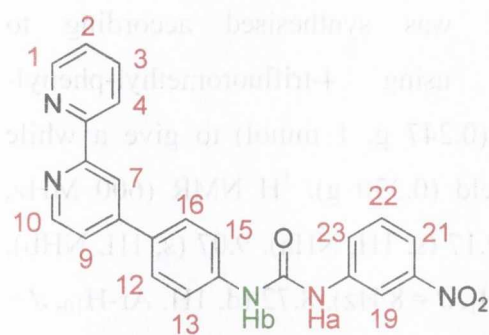
H₉, $J = 2.0$ Hz, $J = 8.0$ Hz), 8.13 (d, 1H, Ar-H₁₁, $J = 7.52$), 7.89 (dt, 1H, Ar-H₃, $J = 7.52$ Hz, $J = 2.0$ Hz), 7.72 (t, 1H, Ar-H₁₀, $J = 7.52$ Hz), 7.60 (dd, 1H, Ar-H₆, $J = 2.0$, $J = 5.0$ Hz), 7.41 (dt, 1H, Ar-H₂, $J = 1.52$ Hz, $J = 6.04$ Hz); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl₃) δ_{C} : 156.7, 155.1, 149.6, 148.7, 148.3, 146.3, 139.7, 136.6, 132.6, 129.6, 123.7, 123.3, 121.6, 121.0, 120.8, 118.5; HRMS (m/z) (ES⁺): Calculated for C₁₆H₁₂N₃O₂ $m/z = 278.0930$ [M+H]⁺ Found $m/z = 278.0923$; IR ν_{max} (cm⁻¹) 1529, 1349.

4-(4-Aminophenyl)-2,2'-bipyridine (186)

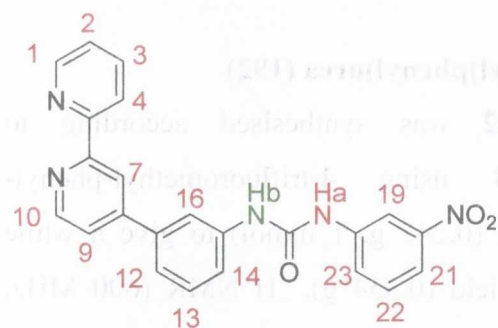
Compound **186** was synthesised according to Procedure 5.3 using 4-(4-nitrophenyl)-2,2'-bipyridine, **184** (1.00 g, 3.61 mmol) and 10% Pd/C (0.2 g) yielding the product as an off white solid in 83% yield (0.745 g). ^1H NMR (400 MHz, CDCl₃) δ_{H} : 8.73 (d, 1H, Ar-H₁, $J = 4.24$ Hz), 8.67 (d, 1H, Ar-H₆), 8.63 (d, 1H, Ar-H₅, $J = 1.6$ Hz), 8.45 (d, 1H, Ar-H₄, $J = 8.0$ Hz), 7.85 (dt, 1H, Ar-H_{2/3}, $J = 7.76$ Hz, $J = 1.76$ Hz), 7.66 (d, 2H, Ar-H₈₊₁₀, $J = 8.52$ Hz), 7.51 (dd, 1H, Ar-H₇, $J = 5.2$ Hz, $J = 1.8$ Hz), 7.34 (dt, 1H, Ar-H_{2/3}, $J = 7.44$ Hz, $J = 0.84$ Hz), 6.81 (d, 2H, Ar-H₉₊₁₁, $J = 8$ Hz), 3.90 (s, 2H, NH₂); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl₃) δ_{C} : 155.9, 149.0, 148.5, 147.1, 136.4, 127.7, 127.4, 123.2, 120.7, 120.1, 117.4, 114.8; HRMS (m/z) (ES⁺): Calculated for C₁₆H₁₄N₃ $m/z = 248.1188$ [M+H]⁺. Found $m/z = 248.1175$; IR ν_{max} (cm⁻¹) 3319, 1582.

4-(3-Aminophenyl)-2,2'-bipyridine (187)

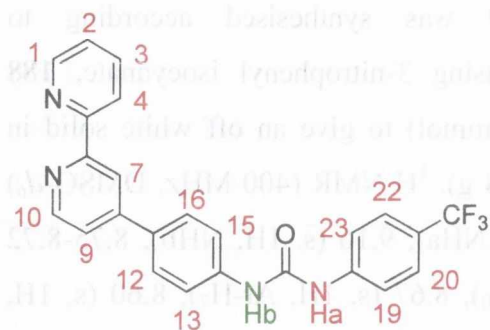
Compound **187** was synthesised according to Procedure 5.3 using 4-(3-nitrophenyl)-2,2'-bipyridine, **185** (0.87 g, 3.14 mmol) and 10% Pd/C (0.2 g) yielding the product as an off white solid in 94% yield (0.73 g). ^1H NMR (400 MHz, CDCl₃) δ_{H} : 8.75 (m, 2H, Ar-H₁₊₇), 8.65 (d, 1H, Ar-H₅, $J = 1.24$ Hz), 8.47 (d, 1H, Ar-H₄, $J = 8.0$ Hz), 7.86 (dt, 1H, Ar-H₃, $J = 7.76$ Hz, $J = 1.52$ Hz), 7.53 (dd, 1H, Ar-H₆, $J = 5.0$ Hz, $J = 1.76$ Hz), 7.33 (m, 2H, Ar-H₂₊₁₀), 7.17 (d, 1H, Ar-H₁₁, $J = 7.76$ Hz), 7.11 (s, 1H, Ar-H₈), 6.79 (dd, 1H, Ar-H₉, $J = 8.04$ Hz, $J = 1.76$ Hz), 3.85 (s, 1H, NH₂); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl₃) δ_{C} : 156.53, 156.23, 149.59, 149.21, 147.04, 139.44, 136.99, 129.99, 123.80, 121.67, 121.30, 119.03, 117.48, 115.74, 113.63; HRMS (m/z) (ES⁺): Calculated for C₁₆H₁₄N₃ $m/z = 248.1188$ [M+H]⁺. Found $m/z = 248.1198$; IR ν_{max} (cm⁻¹) 3429, 1632.

1-(4-(2,2'-Bipyridin-4-yl)phenyl)-3-(3-nitrophenyl)urea (189)

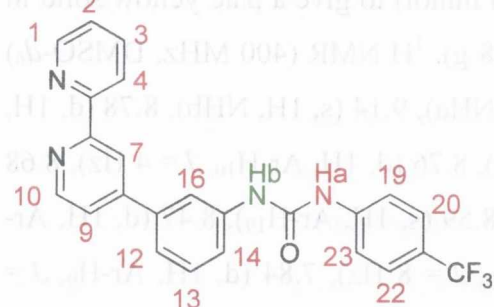
Compound **189** was synthesised according to Procedure 5.4 using 3-nitrophenyl isocyanate, **188** (0.066 g, 0.404 mmol) to give an off white solid in 59% yield (0.098 g). ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ_{H} : 9.32 (s, 1H, NHa), 9.16 (s, 1H, NHb), 8.75-8.72 (m, 2H, Ar- H_{1+10}), 8.67 (s, 1H, Ar- H_7), 8.60 (s, 1H, Ar- H_{19}), 8.44 (d, 1H, Ar- H_4), 7.98 (t, 1H, Ar- H_3 , J = Hz) 7.86 (d, 3H, Ar- $\text{H}_{12+16+23}$), 7.50 (dd, 1H, Ar- H_9), 7.74 (d, 1H, Ar- H_{21}), 7.69 (d, 2H, Ar- H_{13+15}), 7.59 (t, 1H, Ar- H_{22} , J = Hz), 7.50 (dd, 1H, Ar- H_2); $^{13}\text{C}\{^1\text{H}\}$ NMR (150 MHz, $\text{DMSO-}d_6$) δ_{C} : 155.9, 155.2, 152.3, 149.9, 149.3, 148.1, 147.7, 140.9, 140.7, 137.4, 130.7, 130.1, 127.4, 124.5, 124.3, 120.9, 120.6, 118.9, 116.9, 116.5, 112.2; HRMS (m/z) (ES^+) Calculated for $\text{C}_{23}\text{H}_{17}\text{N}_5\text{O}_3$ m/z = 412.1410 $[\text{M} + \text{H}]^+$. Found m/z = 412.1411; Anal. calc. for $\text{C}_{23}\text{H}_{17}\text{N}_5\text{O}_3$: C, 67.15; H, 4.16; N, 17.07 %. Found C, 67.05; H, 4.22; N, 16.85 %; IR ν_{max} (cm^{-1}) 3060, 1723, 1590, 1550, 1521, 1461, 1417, 1390, 1342, 1317, 1240, 1184, 1167, 1097, 1074, 998, 820, 789, 739, 726, 678.

1-(3-(2,2'-Bipyridin-4-yl)phenyl)-3-(3-nitrophenyl)urea (190)

Compound **190** was synthesised according to Procedure 5.4 using 3-nitro phenyl isocyanate, **188** (0.0358 g, 0.218 mmol) to give a pale yellow solid in 76% yield (0.068 g). ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ_{H} : 9.33 (s, 1H, NHa), 9.14 (s, 1H, NHb), 8.78 (d, 1H, Ar- H_1 , J = 4 Hz), 8.76 (d, 1H, Ar- H_{10} , J = 4 Hz), 8.68 (s, 1H, Ar- H_7), 8.59 (s, 1H, Ar- H_{19}), 8.47 (d, 1H, Ar- H_4 , J = 4 Hz), 8.06 (s, 1H, Ar- H_{16}), 8.00 (t, 1H, Ar- H_3 , J = 8 Hz), 7.84 (d, 1H, Ar- H_9 , J = 8 Hz) 7.78 (d, 2H, Ar- H_{14+21} , J = 8 Hz), 7.58 (m, 2H, Ar- H_{13+22}), 7.52 (m, 3H, Ar- $\text{H}_{2+12+23}$); $^{13}\text{C}\{^1\text{H}\}$ NMR (150 MHz, $\text{DMSO-}d_6$) δ_{C} : 155.9, 155.0, 152.5, 150.1, 149.3, 148.2, 148.1, 140.2, 137.9, 137.8, 130.0, 129.8, 124.8, 124.3, 121.5, 120.7, 120.6, 119.5, 117.4, 116.6, 116.3, 112.2; HRMS (m/z) (ES^+) Calculated for $\text{C}_{23}\text{H}_{17}\text{N}_5\text{O}_3$ m/z = 412.1410 $[\text{M} + \text{H}]^+$. Found m/z = 412.1413; IR ν_{max} (cm^{-1}) 3060, 1723, 1590, 1550, 1521, 1461, 1417, 1390, 1342, 1317, 1240, 1184, 1167, 1097, 1074, 998, 820, 789, 739, 726, 678.

1-(4-(2,2'-Bipyridin-4-yl)phenyl)-3-(4-(trifluoromethyl)phenyl)urea (191)

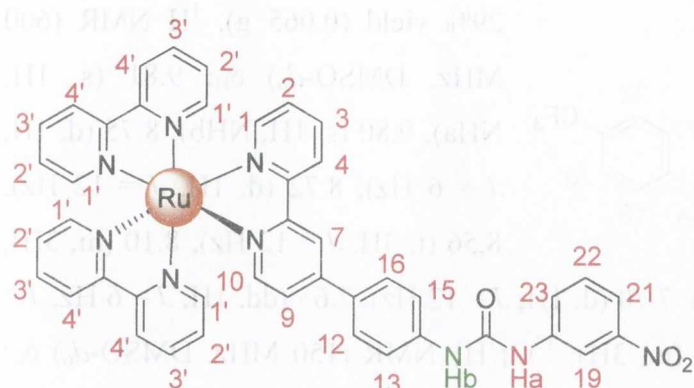
Compound **191** was synthesised according to Procedure 5.4 using 4-trifluoromethyl-phenyl-isocyanate, **158** (0.247 g, 1 mmol) to give a white solid in 76% yield (0.330 g). ^1H NMR (600 MHz, $\text{DMSO}-d_6$), δ_{H} : 9.17 (s, 1H, NHa), 9.07 (s, 1H, NHb), 8.74 (d, 1H, Ar-H₁, $J = 8$ Hz), 8.72 (d, 1H, Ar-H₁₀, $J = 8$ Hz), 8.67 (s, 1H, Ar-H₇), 8.44 (d, 1H, Ar-H₄, $J = 4$ Hz), 7.98 (td, 1H, Ar-H₃), 7.86 (d, 2H, Ar-H₂₀₊₂₂, $J = 8$ Hz), 7.76 (dd, 1H, Ar-H₉), 7.71 (d, 2H, Ar-H₁₉₊₂₃), 7.68 (d, 2H, Ar-H₁₃₊₁₅, $J = 8$ Hz), 7.66 (d, 2H, Ar-H₁₂₊₁₆, $J = 8$ Hz), 7.49 (dd, 1H, Ar-H₂, $J = 4$ Hz, $J = 4$ Hz); $^{13}\text{C}\{^1\text{H}\}$ NMR (150 MHz, $\text{DMSO}-d_6$) δ_{C} : 155.9, 155.2, 152.1, 149.9, 149.2, 147.7, 143.1, 140.7, 137.3, 130.5, 127.4, 126.0 ($J_{19\text{F}-13\text{C}} = 3.6$ Hz), 124.5 ($J_{19\text{F}13\text{C}} = 270$ Hz), 124.3, 122.0 ($J_{19\text{F}-13\text{C}} = 32$ Hz), 120.9, 120.6, 118.8, 118.0, 116.9; ^{19}F NMR (376 MHz, $\text{DMSO}-d_6$) δ_{F} : -60.6 (CF_3); HRMS (m/z) (ES^+) Calculated for $\text{C}_{24}\text{H}_{18}\text{N}_4\text{OF}_3$ $m/z = 435.1442$ $[\text{M} + \text{H}]^+$. Found $m/z = 435.1433$; Anal. calcd. for $\text{C}_{24}\text{H}_{17}\text{N}_4\text{OF}_3 \cdot \text{H}_2\text{O}$: C 63.69, H 4.23, N 12.39, F 12.60. Found: C 63.55, H 4.21, N 12.54, F 12.58 %; IR ν_{max} (cm^{-1}) 3329, 1687, 1598, 1553, 1535, 1464, 1415, 1389, 1337, 1318, 1246, 1215, 1185, 1158, 1101, 1072, 837, 816, 791, 722.

1-(3-(2,2'-Bipyridin-4-yl)phenyl)-3-(4-(trifluoromethyl)phenyl)urea (192)

Compound **192** was synthesised according to Procedure 5.4 using 4-trifluoromethyl-phenyl-isocyanate, **158** (0.247 g, 1 mmol) to give a white solid in 81% yield (0.354 g). ^1H NMR (600 MHz, $\text{DMSO}-d_6$), δ_{H} : 9.17 (s, 1H, NHa), 9.07 (s, 1H, NHb), 8.78 (d, 1H, Ar-H₁, $J = 8$ Hz), 8.76 (d, 1H, Ar-H₁₀, $J = 8$ Hz), 8.68 (s, 1H, Ar-H₇), 8.47 (d, 1H, Ar-H₄, $J = 4$ Hz), 8.06 (s, 1H, Ar-H₁₆), 8.02 (td, 1H, Ar-H₃), 7.84 (d, 1H, Ar-H₉, $J = 8$ Hz), 7.78 (d, 2H, Ar-H₁₄₊₂₁, $J = 8$ Hz), 7.61 (m, 2H, Ar-H₁₃₊₂₂), 7.52 (m, 3H, Ar-H₂₊₁₂₊₂₃); $^{13}\text{C}\{^1\text{H}\}$ NMR (150 MHz, $\text{DMSO}-d_6$) δ_{C} : 155.9, 155.0, 152.3, 150.1, 149.3, 148.2, 143.3, 140.2, 137.9, 137.3, 129.8, 126.0 ($J_{19\text{F}-13\text{C}} = 4$ Hz), 124.3, 122.8 ($J_{19\text{F}-13\text{C}} = 270$ Hz), 121.8 ($J_{19\text{F}-13\text{C}} = 30$ Hz), 121.5, 120.6, 119.3, 118.0, 117.4, 116.5; ^{19}F NMR (376 MHz, $\text{DMSO}-d_6$) δ_{F} : -60.5 (CF_3); HRMS (m/z) (ES^+) Calculated for $\text{C}_{24}\text{H}_{18}\text{N}_4\text{OF}_3$ $m/z = 435.1442$ $[\text{M} + \text{H}]^+$. Found $m/z = 435.1433$; Anal. calcd. for $\text{C}_{24}\text{H}_{17}\text{N}_4\text{OF}_3 \cdot \text{H}_2\text{O}$: C 63.69, H 4.23, N 12.39, F 12.60. Found: C

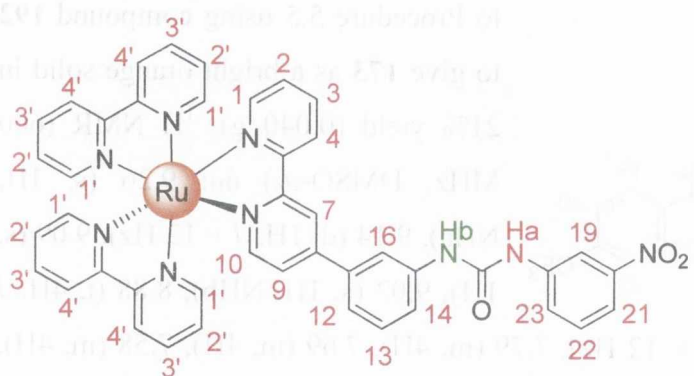
63.55, H 4.21, N 12.54, F 12.58 %; IR $\nu_{\max}$ (cm^{-1}) 3329, 1687, 1598, 1553, 1535, 1464, 1415, 1389, 1337, 1318, 1246, 1215, 1185, 1158, 1101, 1072, 837, 816, 791, 722.

[Ru(*bpy*)₂(189)](PF₆)₂ (170)

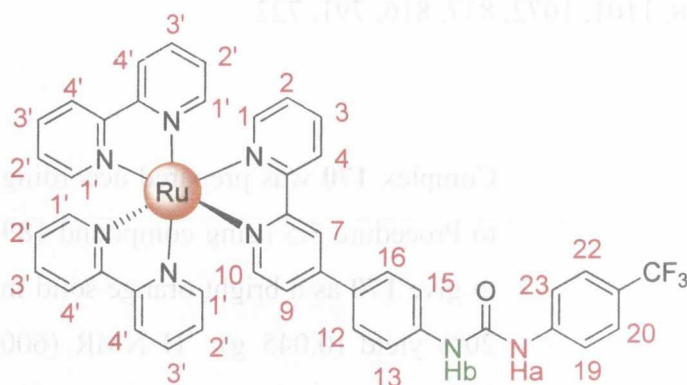


Complex **170** was prepared according to Procedure 5.5 using compound **189** to give **170** as a bright orange solid in 20% yield (0.045 g). ¹H NMR (600 MHz, CD₃CN) δ_{H} : 8.75 (d, 1H, H), 8.71 (d, 1H, Ar-H₂, J = Hz), 8.60 (t, 1H, Ar-H, J = Hz), 8.54 (dd, 4H, H), 8.11-8.07 (m, 4H, H), 8.01 (s, 1H, NHa), 7.94 (s, 1H, NHb) 7.89 (m, 3H, H), 7.85 (d, 1H, H), 7.79-7.71 (m, 8H, H), 7.65 (dd, 1H, H), 7.57 (t, 1H, H), 7.45-7.42 (m, 6H, H); HRMS (m/z) (MALDI-ToF) Calculated for C₄₃H₃₃N₉O₃RuPF₆ m/z = 970.1404 [M - PF₆]⁺. Found m/z = 970.1414; Anal. calc. for C₄₃H₃₃N₉O₃F₁₂P₂Ru: C 63.69, H 4.23, N 12.39, F 12.60. Found: C 63.55, H 4.21, N 12.54, F 12.58%; IR $\nu_{\max}$ (cm^{-1}) 3094, 1711, 1594, 1520, 1466, 1426, 1347, 1320, 1239, 1190, 824, 761, 730, 658.

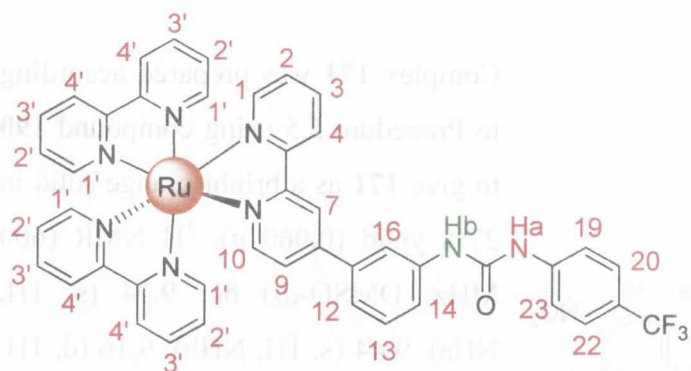
[Ru(*bpy*)₂(190)](PF₆)₂ (171)



Complex **171** was prepared according to Procedure 5.5 using compound **190** to give **171** as a bright orange solid in 27% yield (0.060 g). ¹H NMR (600 MHz, DMSO-*d*₆) δ_{H} : 9.74 (s, 1H, NHa), 9.44 (s, 1H, NHb), 9.16 (d, 1H, J = 12 Hz), 9.10 (s, 1H), 8.88 (t, 2H, J = 12 Hz), 8.66 (t, 1H, J = 12 Hz), 8.25 (s, 1H), 8.20 (m, 3H, J = 6 Hz), 7.89 (d, 1H, J = 12 Hz), 7.85 (dd, 1H, J = 12 Hz), 7.79 (m, 3H, J = 12 Hz), 7.73 (d, 1H, J = 12 Hz), 7.67 (d, 1H, J = 12 Hz), 7.60 (m, 4H); ¹³C {¹H} NMR (150 MHz, DMSO-*d*₆) δ_{C} : 157.0, 156.69, 156.57, 156.55, 156.53, 156.50, 152.6, 151.4, 151.3, 151.2, 151.19, 151.14, 148.6, 148.1, 141.0, 140.3, 137.92, 137.90, 137.83, 135.96, 130.0, 129.8, 127.93, 127.91, 127.88, 124.9, 127.8, 124.9, 124.8, 124.5, 124.48, 124.45, 124.43, 124.34, 121.6, 121.3, 120.5, 117.3, 116.3, 112.0; HRMS (m/z) (MALDI-ToF) Calculated for C₄₃H₃₃N₉O₃RuPF₆ m/z = 970.1392 [M - PF₆]⁺. Found m/z = 970.1385.

[Ru(*bpy*)₂(191)](PF₆)₂ (172)

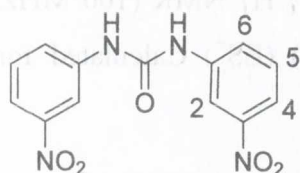
Complex **172** was prepared according to Procedure 5.5 using compound **191** to give **172** as a bright orange solid in 29% yield (0.065 g). ¹H NMR (600 MHz, DMSO-*d*₆) δ_H: 9.81 (s, 1H, NHa), 9.80 (s, 1H, NHb), 8.75 (d, 1H, *J* = 6 Hz), 8.72 (d, 1H, *J* = 12 Hz), 8.56 (t, 3H, *J* = 12 Hz), 8.10 (m, 3H), 7.88 (s, 1H), 7.87 (m, 1H), 7.81 (m, 4H), 7.70 (d, 1H, *J* = 12 Hz), 7.65 (dd, 1H, *J* = 6 Hz, *J* = 12 Hz), 7.61 (d, 1H, *J* = 12 Hz), 7.45 (m, 3H); ¹³C{¹H} NMR (150 MHz, DMSO-*d*₆) δ_C: 158.2, 158.9, 158.0, 157.9, 153.7, 152.6, 152.3, 150.1, 144.9, 143.8, 138.7, 129.4, 128.6, 128.5, 128.4, 126.9, 125.2, 124.8, 121.9, 119.8, 118.9; ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ_F: -62.7 (CF₃); HRMS (*m/z*) (MALDI-ToF) Calculated for C₄₄H₃₃N₈ORuF₉ *m/z* = 993.1415 [M - PF₆]⁺. Found *m/z* = 993.1393; Anal. calc. for C₄₄H₃₃N₈OF₁₅P₂Ru: C 47.49, H 3.11, N 13.69. Found: C 46.45, H 2.92, N 9.85%; IR ν_{max} (cm⁻¹) 3277, 3075, 1709, 1518, 1316, 1183, 1013, 898, 827, 729, 658.

[Ru(*bpy*)₂(192)](PF₆)₂ (173)

Complex **173** was prepared according to Procedure 5.5 using compound **192** to give **173** as a bright orange solid in 21% yield (0.040 g). ¹H NMR (600 MHz, DMSO-*d*₆) δ_H: 9.26 (s, 1H, NHa), 9.14 (d, 1H, *J* = 12 Hz), 9.09 (s, 1H), 9.02 (s, 1H, NHb), 8.88 (t, 4H, *J* = 12 Hz), 8.21 (m, 5H), 7.88 (d, 1H, *J* = 12 Hz), 7.79 (m, 4H), 7.69 (m, 4H), 7.58 (m, 4H), 7.47 (d, 2H, *J* = 6 Hz); ¹³C{¹H} NMR (150 MHz, DMSO-*d*₆) δ_C: 157.3, 157.0, 152.5, 151.7, 151.6, 149.6, 140.3, 137.8, 137.7, 136.6, 130.0, 127.6, 126.1, 126.0, 125.0, 124.4, 124.2, 122.0, 121.7, 120.9; ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ_F: -60.5 (CF₃); HRMS (*m/z*) (MALDI-ToF) Calculated for C₄₄H₃₃N₈ORuPF₉ *m/z* = 993.1415 [M - PF₆]⁺. Found *m/z* = 993.1512.

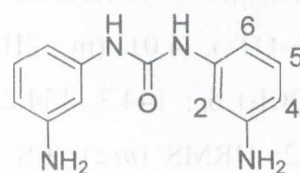
7.8 Experimental Details for Chapter 6

1,3-Bis(3-Nitrophenyl)urea (**198**)



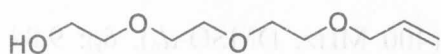
3-nitroisocyanate, **188** (1.00 g, 6.09 mmol) was dissolved in CH_3CN . 3-nitroaniline, **115** (0.561 g, 4.06 mmol) was then added and the reaction microwave irradiated at 90°C for 40 mins. The solvent was removed under reduced pressure leaving a yellow solid. This was triturated with CHCl_3 and then filtered to give a light yellow solid in 85% yield (0.850 g). m.p. $242\text{--}244^\circ\text{C}$; ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ_{H} : 9.45 (s, 2H, NH_{urea}), 8.57 (dd, 2H, Ar- H_2 , $J = 2$ Hz), 7.87 (dd, 2H, Ar- H_4 , $J = 8.2$, Hz, $J = 2$ Hz), 7.78 (dd, 2H, Ar- H_6 , $J = 8$ Hz, 2 Hz), 7.59 (t, 2H, Ar- H_5 , $J = 8.2$ Hz); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, $\text{DMSO-}d_6$) δ_{C} : 152.4, 148.1, 140.6, 130.0, 124.6, 116.6, 112.5; HRMS (m/z) (ES^+) Calculated for $\text{C}_{13}\text{H}_{10}\text{N}_4\text{O}_5\text{Na}$ m/z = 325.0543 $[\text{M} + \text{Na}]^+$. Found m/z = 325.0549; IR ν_{max} (cm^{-1}) 3355, 3092, 1738, 1683, 1598, 1543, 1520, 1431, 1345, 1320, 1238, 1209, 1090, 800, 732.

1,3-Bis(3-Aminophenyl)urea (**199**)



Compound **198** (0.200 g, 0.66 mmol) was dissolved in MeOH (10 mL). 10% Pd/C was added, followed by $\text{N}_2\text{H}_4 \cdot \text{H}_2\text{O}$ and the reaction microwave irradiated at 100°C for 40 mins. After filtering through celite, the solvent was removed under reduced pressure leaving a beige solid in 45% yield (0.070 g). m.p. $104\text{--}106^\circ\text{C}$; ^1H NMR (600 MHz, $\text{DMSO-}d_6$) δ_{H} : 8.23 (s, 2H, NH_{urea}), 6.88 (t, 2H, Ar- H_5 , $J = 8.0$ Hz), 6.75 (dd, 2H, Ar- H_2 , $J = 2.0$ Hz), 6.55 (d, 2H, Ar- H_6 , $J = 8.0$ Hz), 6.18 (d, 2H, Ar- H_4 , $J = 8.0$ Hz), 4.98 (s, 4H, NH_{amine}); $^{13}\text{C}\{^1\text{H}\}$ NMR (150 MHz, $\text{DMSO-}d_6$) δ_{C} : 152.2, 149.0, 140.3, 128.9, 107.8, 105.9, 103.5; HRMS (m/z) (ES^+) Calculated for m/z = 243.1238 $[\text{M} + \text{H}]^+$. Found m/z = 243.1246; IR ν_{max} (cm^{-1}) 3406, 3269, 2922, 2854, 1633, 1592, 1544, 1455, 1315, 1287, 1210, 1158, 767, 685.

2-(2-(2-(Allyloxy)ethoxy)ethoxy)ethanol (**202**)²⁴⁰



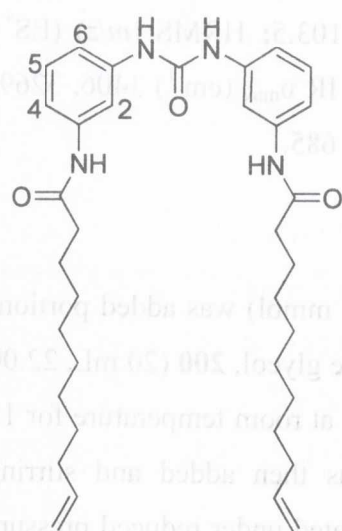
Sodium hydride (3.00 g, 79.5 mmol) was added portion-wise to a solution of triethylene glycol, **200** (20 mL, 22.00 g, 149.05 mmol) in dry THF (20 mL) and the solution was stirred at room temperature for 15 mins. Allyl bromide, **201** (4.3 mL, 6.00 g, 49.69 mmol) was then added and stirring maintained at room temperature for 1 hr. The solvent was evaporated under reduced pressure and the residue was dissolved in CH_2Cl_2 . The solution was then filtered and washed with brine (40 mL). The aqueous phase was extracted with CH_2Cl_2 (2×100 mL). The organic phase was dried over MgSO_4 and the solvent was evaporated under reduced pressure. The resulting

yellowish oil was purified by chromatography (*n*-hexane-EtOAc 70:30 and then 50:50) to give **202** in 73% yield (6.93 g). ^1H NMR (400 MHz, CDCl_3) δ_{H} : 5.95 (m, 1H, $\text{CH}=\text{CH}_2$), 5.28 (m, 2H, $\text{CH}=\text{CH}_2$), 4.06 (m, 2H, $\text{CH}_2\text{CH}=\text{CH}_2$), 3.63 (m, 12H, CH_2); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ_{C} : 134.6, 117.1, 72.5, 72.2, 70.2-70.5, 61.6; HRMS (m/z) (ES^+) Calculated for $\text{C}_9\text{H}_{19}\text{O}_4$ m/z = 191.1286 $[\text{M} + \text{H}]^+$. Found m/z = 191.1286.

2-(2-(2-(Allyloxy)ethoxy)ethoxy)ethyl 4-methylbenzenesulfonate (**203**)

Compound **202** (0.5 g, 2.6 mmol) and TsCl (2.5 g, 13 mmol) were dissolved in CH_2Cl_2 and the reaction mixture stirred for 15 mins. To the solution, pyridine (2.13 mL, 26 mmol) was added drop wise and the reaction stirred at room temperature for 48 hr. The pyridine was quenched with 1 M (1 mL) before the solvents were removed under reduced pressure. The resulting mixture was diluted with CHCl_3 (50 mL) and the organic layer extracted with water (4×50 mL) and then dried over MgSO_4 . Compound **203** was isolated as a yellow oil in 45% yield (0.404 g) following purification by column chromatography (CH_2Cl_2 - CH_3OH 90:10). ^1H NMR (400 MHz, CDCl_3) δ_{H} : 7.79 (d, 2H, $\text{Ar-H}_{\text{Tosyl}}$, J = 8.0 Hz), 7.33 (d, 2H, $\text{Ar-H}_{\text{Tosyl}}$, J = 8.0 Hz), 5.89 (m, 1H, $\text{CH}=\text{CH}_2$), 5.28 (m, 2H, $\text{CH}=\text{CH}_2$), 4.16 (m, 2H, $\text{CH}_2\text{-OTs}$), 4.01 (m, 2H, $\text{CH}_2\text{CH}=\text{CH}_2$), 3.63 (m, 12H, CH_2); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3) δ_{C} : 144.3, 134.2, 132.5, 129.3, 127.5, 117.1, 71.8, 70.3, 70.2, 68.9, 68.8, 68.2, 21.2; HRMS (m/z) (ES^+) Calculated for $\text{C}_{16}\text{H}_{24}\text{O}_6\text{S}$ m/z = 367.1191 $[\text{M} + \text{Na}]^+$. Found m/z = 367.1132.

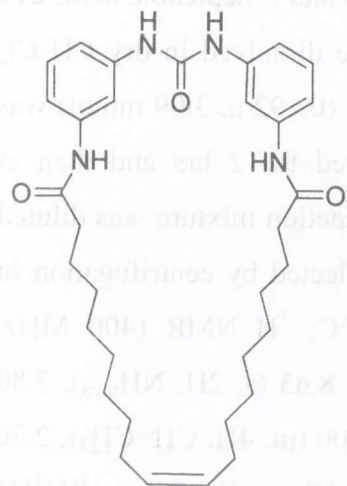
N,N'-(3,3'-Carboxylbis(azanediyl)bis(3,1-phenylene))diundec-10-enamide (**205**)



Compound **199** (0.5 g, 2.06 mmol) and 1,10-undecenoic acid, **204** (0.84 g, 4.54 mmol) were dissolved in dry CH_2Cl_2 (40 mL) and cooled to 0°C . EDC·HCl (1.98 g, 10.32 mmol) was added and the reaction mixture stirred for 2 hrs and then at ambient temperature overnight. The reaction mixture was diluted with water and an off-white solid collected by centrifugation in 79% yield (0.93 g). m.p. $209\text{--}211^\circ\text{C}$; ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ_{H} : 9.84 (s, 2H, NH_{amide}), 8.62 (s, 2H, NH_{urea}), 7.81 (s, 2H, Ar-H_2), 7.15 (m, 6H, $\text{Ar-H}_{4,5,6}$), 5.78 (m, 2H, $\text{CH}=\text{CH}_2$), 5.01 (m, 4H, $\text{CH}=\text{CH}_2$), 2.29 (t, 4H, CH_2 , J = 7.4 Hz), 2.00 (m, 4H, CH_2), 1.58 (t, 4H, CH_2 , J = 6.8 Hz), 1.28 (s, 20H, CH_2); $^{13}\text{C}\{^1\text{H}\}$ NMR (150 MHz, $\text{DMSO-}d_6$) δ_{C} : 171.3, 152.2, 139.9, 139.7, 138.8, 128.8, 114.6, 112.7, 108.8, 36.4, 33.1, 28.7, 28.6, 28.4, 28.2, 25.1; HRMS (m/z) (ES^+) Calculated for $\text{C}_{35}\text{H}_{50}\text{N}_4\text{O}_3\text{Na}$ m/z = 597.3781 $[\text{M} + \text{Na}]^+$. Found m/z = 597.3770;

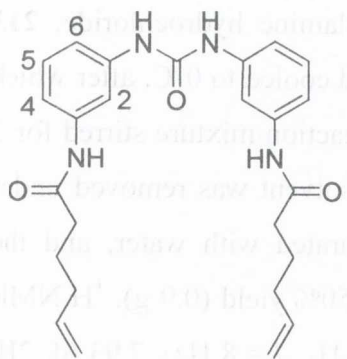
IR $\nu_{\max}$ (cm^{-1}) 3300, 2920, 2850, 1647, 1608, 1580, 1530, 1489, 1297, 1189, 911, 871, 766, 687.

***N,N*-(3,3'-Carbonylbis(azanediyl)bis(3,1-phenylene))diundec-10-ene**



Compound **205** (0.1 g, 0.174 mmol) was dissolved in dry DMF (10 mL). Grubb's 2nd Generation catalyst (0.0073 g, 10 mol%) was added and the reaction mixture microwave irradiated at 160°C for 90 mins. Solvent was removed under reduced pressure and the product triturated with CH_2Cl_2 . A grey solid was collected by suction filtration 89% yield (0.084g). m.p. 229–231°C; ^1H NMR (400 MHz, $\text{DMSO}-d_6$), δ_{H} : 9.85 (s, 2H, NH_{amide}), 8.64 (s, 2H, NH_{urea}), 7.81 (s, 2H, Ar- H_2), 7.16 (m, 6H, Ar- $\text{H}_{4,5,6}$), 5.39 (s, 2H, $\text{CH}=\text{CH}$), 2.28 (t, 4H, CH_2 , $J = 6.8$ Hz), 1.99 (m, 4H, CH_2), 1.58 (m, 8H, CH_2), 1.28 (s, 16H, CH_2); $^{13}\text{C}\{^1\text{H}\}$ NMR (150 MHz, $\text{DMSO}-d_6$) δ_{C} : 171.5, 152.4, 139.9, 139.7, 131.3, 129.0, 112.7, 108.8, 36.4, 31.9, 31.8, 25.0, 17.7; HRMS (m/z) (ES^+) Calculated for $\text{C}_{35}\text{H}_{50}\text{N}_4\text{O}_3\text{Na}$ $m/z = 569.3468$ [$\text{M} + \text{Na}$] $^+$. Found $m/z = 569.3469$; Anal. calc. for $\text{C}_{33}\text{H}_{46}\text{N}_4\text{O}_3 \cdot 0.2\text{CH}_2\text{Cl}_2 \cdot 2\text{H}_2\text{O}$: C 68.40, H 8.71, N 9.61. Found: C 68.80, H 8.42, N 9.47%; IR $\nu_{\max}$ (cm^{-1}) 3274, 2921, 2850, 1653, 1605, 1539, 1489, 1297, 1214, 964, 883, 781, 693.

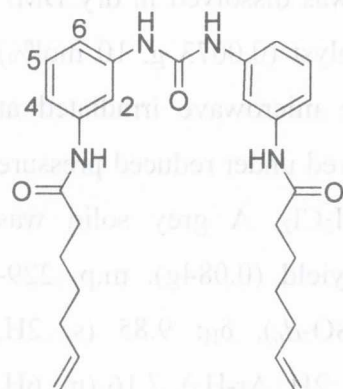
***N,N'*-(3,3'-Carbonylbis(azanediyl)bis(3,1-phenylene))dihex-5-enamide (207)**



Compound **199** (0.150 g, 0.062 mmol) and 5-hexenoic acid, **209** (0.154 mL, 0.148 g, 1.30 mmol) were dissolved in dry CH_2Cl_2 (30 mL) and cooled to 0°C. EDC·HCl (0.197 g, 1.03 mmol) was added and the reaction mixture stirred for 2 hrs and then at ambient temperature overnight. The reaction mixture was diluted with water, which resulted in the formation of an off-white solid that was collected by centrifugation in 74% yield (0.202 g). m.p. 249–251°C; ^1H NMR (400 MHz, $\text{DMSO}-d_6$), δ_{H} : 9.85 (s, 2H, NH_{amide}), 8.61 (s, 2H, NH_{urea}), 7.80 (s, 2H, Ar- H_2), 7.17 (m, 6H, Ar- $\text{H}_{4,5,6}$), 5.83 (m, 2H, $\text{CH}=\text{CH}_2$), 5.01 (m, 4H, $\text{CH}=\text{CH}_2$), 2.31 (t, 4H, CH_2 , $J = 7.2$ Hz), 2.07 (m, 4H, CH_2), 1.69 (m, 4H, CH_2); $^{13}\text{C}\{^1\text{H}\}$ NMR (150 MHz, $\text{DMSO}-d_6$) δ_{C} : 171.3, 152.5, 140.2, 140.1, 138.5, 129.2, 115.4, 113.0, 109.1, 36.1, 33.0, 24.6; HRMS (m/z) (MALDI-MS) Calculated for $\text{C}_{25}\text{H}_{30}\text{N}_4\text{O}_3\text{Na}$ $m/z = 457.2216$ [$\text{M} + \text{Na}$] $^+$. Found $m/z = 457.2231$; Anal. calc. for $\text{C}_{25}\text{H}_{30}\text{N}_4\text{O}_3 \cdot 0.1\text{DMF}$ C 68.77, H 7.00, N 12.99. Found:

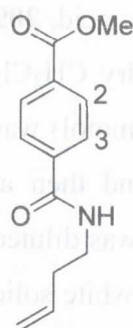
C 68.24, H 6.99, N 13.16%; IR $\nu_{\max}$ (cm^{-1}) 3280, 1654, 1636, 1603, 1570, 1541, 1490, 1404, 1297, 1203, 989, 911, 873, 787, 691.

N,N'-(3,3'-Carbonylbis(azanediyl)bis(3,1-phenylene))dihept-6-enamide (**208**)

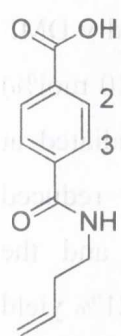


Compound **199** (0.150 g, 0.062 mmol) and 6-heptenoic acid, **210** (0.176 mL, 0.166 g, 1.30 mmol) were dissolved in dry CH_2Cl_2 (30 mL) and cooled to 0°C . EDC·HCl (0.192 g, 3.09 mmol) was added and the reaction mixture stirred for 2 hrs and then at ambient temperature overnight. The reaction mixture was diluted with water and an off-white solid collected by centrifugation in 80% yield (0.230 g). m.p. $239\text{--}241^\circ\text{C}$; ^1H NMR (400 MHz, $\text{DMSO-}d_6$), δ_{H} : 9.86 (s, 2H, NH_{amide}), 8.63 (s, 2H, NH_{urea}), 7.80 (s, 2H, Ar- H_2), 7.16 (m, 6H, Ar- $\text{H}_{4,5,6}$), 5.80 (m, 2H, $\text{CH}=\text{CH}_2$), 5.00 (m, 4H, $\text{CH}=\text{CH}_2$), 2.30 (t, 4H, CH_2 , $J = 7.4$ Hz), 2.04 (m, 4H, CH_2), 1.59 (m, 4H, CH_2), 1.39 (m, 4H, CH_2); $^{13}\text{C}\{^1\text{H}\}$ NMR (150 MHz, $\text{DMSO-}d_6$) δ_{C} : 171.1, 152.2, 139.9, 139.7, 138.6, 128.9, 114.8, 112.6, 108.7, 36.2, 32.9, 27.8, 24.6; HRMS (m/z) (MALDI-MS) Calculated for $\text{C}_{27}\text{H}_{34}\text{N}_4\text{O}_3\text{Na}$ $m/z = 485.2529$ [$\text{M} + \text{Na}$] $^+$. Found $m/z = 485.2546$; Anal. calc. for $\text{C}_{27}\text{H}_{34}\text{N}_4\text{O}_3 \cdot 0.5\text{DMF}$ C 68.58, H 7.57, N 12.62. Found: C 68.48, H 7.47, N 12.19%; IR $\nu_{\max}$ (cm^{-1}) 3275, 2930, 1655, 1635, 1603, 1540, 1570, 1491, 1404, 1294, 1199, 989, 911, 874, 795, 691.

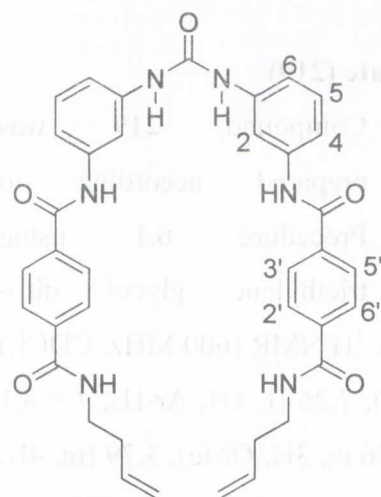
Methyl 4-(but-3-enylcarbamoyl)benzoate (**214**)



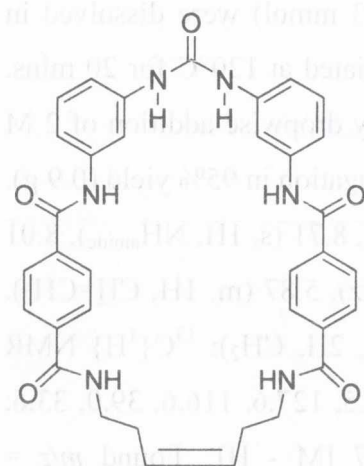
Compound **212**, (1.38 g, 7.67 mmol) and 3-butenylamine hydrochloride, **213** (0.64 g, 8.43 mmol), were dissolved in dry CH_2Cl_2 and cooled to 0°C , after which EDC·HCl (3.67 g, 11.97 mmol) was added and the reaction mixture stirred for 2 hrs and then at ambient temperature overnight. The solvent was removed under reduced pressure and the resulting white solid triturated with water, and the product collected by suction filtration to give **214** in 50% yield (0.9 g). ^1H NMR (400 MHz, $\text{DMSO-}d_6$), δ_{H} : 8.70 (s, 2H, NH_{amide}), 8.02 (d, 2H, Ar- H_2 , $J = 8$ Hz), 7.93 (d, 2H, Ar- H_3 , $J = 8$ Hz), 5.82 (m, 1H, $\text{CH}=\text{CH}_2$), 5.03 (m, 2H, $\text{CH}=\text{CH}_2$), 3.87 (s, 3H, CH_3), 3.33 (m, 2H, CH_2), 2.30 (m, 2H, CH_2); $^{13}\text{C}\{^1\text{H}\}$ NMR (150 MHz, $\text{DMSO-}d_6$) δ_{C} : 166.0, 165.6, 139.0, 136.3, 131.9, 129.4, 127.8, 116.6, 52.6, 39.0, 33.6; HRMS (m/z) (ES^+) Calculated for $\text{C}_{13}\text{H}_{16}\text{NO}_3$ $m/z = 234.1130$ [$\text{M} + \text{H}$] $^+$. Found $m/z = 234.1132$; IR $\nu_{\max}$ (cm^{-1}) 3307, 2960, 1720, 1632, 1537, 1434, 1277, 1107, 1019, 951, 915, 867, 822, 736, 716, 695, 668.

4-(But-3-enylcarbamoyl)benzoic acid (215)

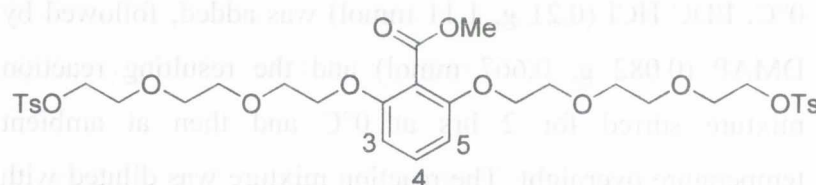
Compound **214** (0.1 g, mmol) and NaOH (0.1 g, 0.43 mmol) were dissolved in H₂O (5 mL) and the reaction mixture microwave irradiated at 120°C for 20 mins. The pH of the solution was then lowered to pH = 2 by dropwise addition of 2 M HCl. The resulting white solid was collected by centrifugation in 95% yield (0.9 g). ¹H NMR (400 MHz, DMSO-*d*₆) δ_H: 13.22 (s, 1H, OH), 8.71 (s, 1H, NH_{amide}), 8.01 (d, 2H, Ar-H₂, *J* = 4 Hz), 7.94 (d, 2H, Ar-H₃, *J* = 8 Hz), 5.87 (m, 1H, CH=CH₂), 5.11 (m, 2H, CH=CH₂), 3.35 (m, 2H, CH₂), 2.32 (m, 2H, CH₂); ¹³C{¹H} NMR (150 MHz, DMSO-*d*₆) δ_C: 167.1, 165.7, 138.6, 136.3, 133.2, 129.5, 127.6, 116.6, 39.0, 33.6; HRMS (*m/z*) (ES⁻) Calculated for C₁₂H₁₂NO₃ *m/z* = 218.0817 [M - H]⁻. Found *m/z* = 218.0808; IR ν_{max} (cm⁻¹) 3304, 3066, 2846, 2667, 2553, 1684, 1631, 1536, 1426, 1284, 1113, 912, 875, 729, 695.

***N*¹,*N*^{1'}-(3,3'-Carbonylbis(azanediyl))bis(3,1-phenylene))bis(N4-(but-3-enyl)terephthalamide) (211)**

Compounds **199** (0.054 g, 0.22 mmol) and **215** (0.1 g, 0.456 mmol) were dissolved in dry CH₂Cl₂ (30 mL) and cooled to 0°C. EDC·HCl (0.21 g, 1.11 mmol) was added, followed by DMAP (0.082 g, 0.667 mmol) and the resulting reaction mixture stirred for 2 hrs at 0°C and then at ambient temperature overnight. The reaction mixture was diluted with water and an off-white solid collected by centrifugation. This was then triturated in hot MeOH overnight to give **211** in 56% yield (0.8 g). m.p. decomposed over 250°C. ¹H NMR (400 MHz, DMSO-*d*₆) δ_H: 10.34 (s, 2H, NH_{amide}), 8.73 (s, 2H, NH_{urea}), 8.65 (s, 2H, NH_{amide}), 8.11 (s, 2H, Ar-H₂), 8.04 (d, 4H, Ar-H₃' + H₅'), 8.02 (d, 2H, Ar-H₆), 7.97 (d, 4H, Ar-H₂' + H₆'), 7.40 (d, 2H, Ar-H₄), 7.28 (d, 2H, Ar-H₅), 5.85 (m, 2H, CH=CH₂), 5.02 (m, 4H, CH=CH₂), 3.35 (t, 4H, CH₂-CH₂, *J* = 7.4 Hz), 2.33 (t, 4H, CH₂-CH₂, *J* = 6.8 Hz); ¹³C{¹H} NMR (150 MHz, DMSO-*d*₆) δ_C: 165.5, 164.8, 152.3, 139.9, 139.4, 137.0, 136.0, 127.6, 127.0, 116.3, 114.1, 113.6, 110.2, 38.6, 33.3; HRMS (*m/z*) (ES⁺) Calculated for C₃₇H₃₆N₆O₅Na *m/z* = 667.2645 [M + Na]⁺. Found *m/z* = 667.265; IR ν_{max} (cm⁻¹) 3302, 2867, 2549, 1685, 1631, 1535, 1426, 1284, 1114, 1017, 912, 782, 730.

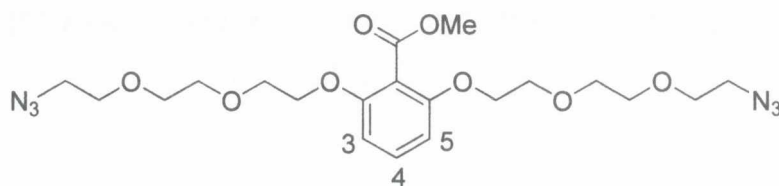
***N*¹,*N*^{1'}-(3,3'-carbonylbis(azanediy))bis(3,1-phenylene))bis(*N*⁴-(but-3-enyl)terephthalene)**

Compound **216** (0.1 g, 0.174 mmol) was dissolved in dry DMF (10 mL). Grubb's 2nd Generation catalyst (0.0073 g, 10 mol%) was added and the reaction mixture microwave irradiated at 160°C for 90 mins. Solvent was removed under reduced pressure and the product triturated with CH₂Cl₂ and the resulting grey solid collected by suction filtration in 21% yield (0.044g). m.p. decomposed over 250°C. ¹H NMR (400 MHz, DMSO-*d*₆), δ_H: 10.34 (s, 2H, NH_{amide}), 8.73 (s, 2H, NH_{urea}), 8.65 (s, 2H, NH_{amide}), 8.11 (s, 2H, Ar-H₂), 8.04 (d, 4H, Ar-H_{3'}+H_{5'}), 8.02 (d, 2H, Ar-H₆), 7.97 (d, 4H, Ar-H_{2'}+H_{6'}), 7.40 (d, 2H, Ar-H₄), 7.28 (d, 2H, Ar-H₅), 5.39 (s, 2H, CH=CH), 3.35 (t, 4H, CH₂-CH₂, *J* = 7.4 Hz), 2.33 (t, 4H, CH₂-CH₂, *J* = 6.8 Hz); ¹³C{¹H} NMR (150 MHz, DMSO-*d*₆) δ_C: 167.9, 165.2, 152.2, 137.6, 136.1, 134.2, 129.1, 127.6, 117.2, 113.3, 43.6, 28.7; HRMS (*m/z*) (ES⁺) Calculated for C₃₅H₃₂N₆O₅Na *m/z* = 616.2434 [M + Na]⁺. Found *m/z* = 616.2689;

Methyl 2,6-bis(2-(2-(2-(tosyloxy)ethoxy)ethoxy)ethoxy)ethoxy)benzoate (219**)**

Compound **219** was prepared according to Procedure 6.1 using triethylene glycol di(*p*-

toluenesulfonate giving **219** as a brown oil in 40% yield (1.71 g). ¹H NMR (600 MHz, CDCl₃) δ_H: 7.82 (d, 4H, Ar-H_{Tosyl}, *J* = 8.2 Hz), 7.35 (m, 4H, Ar-H_{Tosyl}), 7.26 (t, 1H, Ar-H₄, *J* = 8.1 Hz), 6.59 (m, 2H, Ar-H_{3,5}), 4.14 (m, 8H, O-CH₂-CH₂-O-Ar), 3.86 (s, 3H, OMe), 3.79 (m, 4H, Tosyl-CH₂-CH₂-O), 3.59 (m, 12H, Tosyl-CH₂-CH₂-O-CH₂-CH₂-O), 2.47 (s, 3H, CH₃_{Tosyl}), 2.45 (s, 3H, CH₃_{Tosyl}); ¹³C{¹H} NMR (150 MHz, CDCl₃) δ_C: 166.5, 156.4, 144.6, 132.9, 130.8, 129.6, 127.8, 114.0, 105.4, 70.8, 70.7, 70.6, 70.5, 69.3, 69.0, 69.0, 68.6, 68.6, 68.5, 51.9, 21.4; HRMS (*m/z*) (ES⁺) Calculated for C₃₄H₄₄O₁₄S₂Na *m/z* = 763.2096 [M + Na]⁺. Found *m/z* = 763.2070; IR ν_{max} (cm⁻¹) 2874, 1731, 1596, 1470, 1449, 1352, 1297, 1254, 1188, 1174, 1095, 1073, 1010, 916, 816, 775, 759, 661.

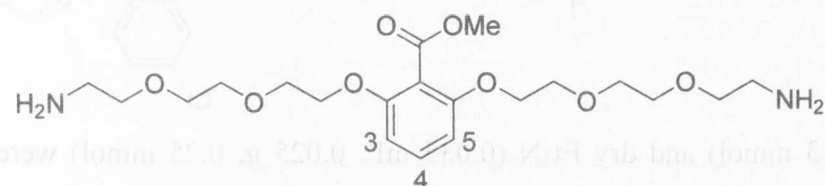
Methyl 2,6-bis(2-(2-(2-(azidoethoxy)ethoxy)ethoxy)ethoxy)benzoate (220**)**

Compound **220** was prepared according to Procedure 6.2 using **219** (0.540 g, 0.73

mmol) to giving **220** as a dark orange oil in 90% yield (0.310 g). ^1H NMR (600 MHz, CDCl_3) δ_{H} : 7.29 (m, 1H, Ar- H_4), 6.59 (m, 2H, Ar- $\text{H}_{3,5}$), 4.15 (d, 4H, O- CH_2 - CH_2 -O-Ar, $J = 3.1$ Hz), 3.86 (s, 3H, OCH₃), 3.85 (s, 4H, O- CH_2 - CH_2 -O-Ar), 3.66 (m, 12H, N₃- CH_2 - CH_2 -O- CH_2 - CH_2 -O), 3.41 (m, 4H, N₃- CH_2 - CH_2 -O); $^{13}\text{C}\{^1\text{H}\}$ NMR (150 MHz, CDCl_3) δ_{C} : 166.5, 148.0, 130.8, 114.0, 105.4, 70.8, 70.6, 69.8, 69.6, 69.4, 52.1, 50.5; HRMS (m/z) (ES^+) Calculated for $\text{C}_{20}\text{H}_{30}\text{N}_6\text{O}_8\text{Na}$ $m/z = 505.2002$ [$\text{M} + \text{Na}$] $^+$. Found $m/z = 505.2023$; IR ν_{max} (cm^{-1}) 2870, 2097, 1731, 1596, 1470, 1449, 1297, 1253, 1099, 1073, 937, 851, 826, 782, 759, 728, 665.

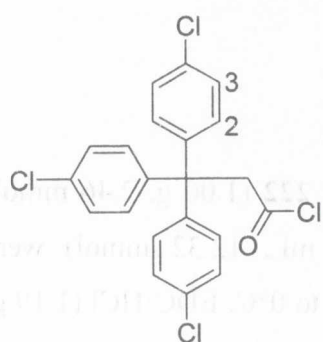
Methyl 2,6-bis(2-(2-(2-aminoethoxy)ethoxy)ethoxy)benzoate (**221**)

Compound **220** (0.100 g, 0.207 mmol) was dissolved in DMF (5 mL). To this solution 10% Pd/C was added, followed by



$\text{N}_2\text{H}_4 \cdot \text{H}_2\text{O}$ (0.08 mL, 0.080 g, 1.65 mmol) and the reaction mixture stirred at 90°C overnight under an atmosphere of argon. The mixture was filtered, while hot, through celite and the solvent removed under reduced pressure, giving a dark orange oil in 90% yield (0.080 g). ^1H NMR (600 MHz, $\text{DMSO}-d_6$) δ_{H} : 8.00 (m, 4H, NH), 7.31 (m, 1H, Ar- H_4), 6.71 (m, 2H, Ar- $\text{H}_{3,5}$), 4.10 (m, 4H, O- CH_2 - CH_2 -O-Ar), 3.74 (s, 3H, OMe), 3.69 (m, 4H, O- CH_2 - CH_2 -O-Ar), 3.58 (m, 4H, O- CH_2 - CH_2 -O), 3.52 (m, 4H, O- CH_2 - CH_2 -O), 3.43 (m, 4H, NH_2 - CH_2 - CH_2 -O), 3.38 (m, 4H, NH_2 - CH_2 - CH_2 -O); $^{13}\text{C}\{^1\text{H}\}$ NMR (150 MHz, $\text{DMSO}-d_6$) δ_{C} : 166.0, 155.9, 131.5, 114.0, 106.1, 70.5, 70.29, 69.5, 69.2, 69.0, 51.8, 37.5; HRMS (m/z) (ES^+) Calculated for $m/z = 431.2390$ [$\text{M} + \text{H}$] $^+$. Found $m/z = 431.2393$; IR ν_{max} (cm^{-1}) 3357, 2870, 1729, 1669, 1596, 1470, 1450, 1298, 1255, 1103, 952, 827.

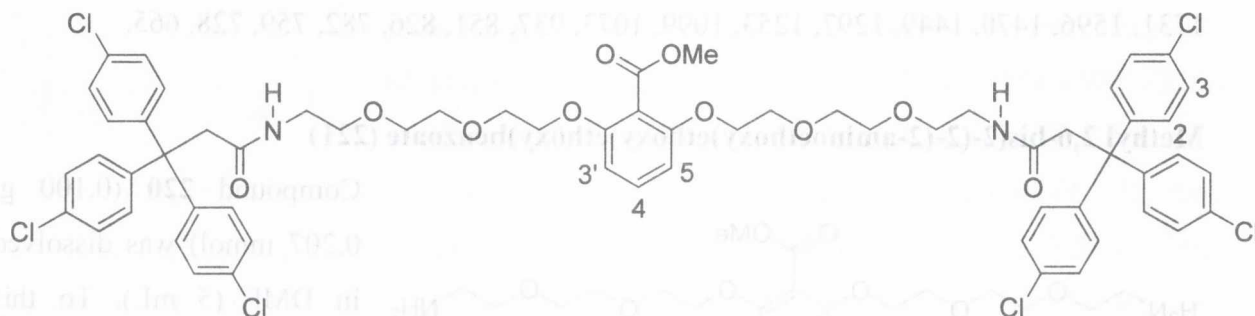
3,3,3-Tris(4-chlorophenyl)propanoyl chloride (**224**)²⁴⁴



Tris(4-chlorophenyl)propionic acid, **222** (5.00 g, 12.3 mmol) and oxalyl dichloride, **223** (2.34 mL, 3.12 g, 24.7 mmol) were stirred in toluene (35 mL) at room temperature for 24 hr. The reaction mixture was then reduced to dryness and recrystallised from CH_2Cl_2 -hexane (50:50) to give **224** as an off-white solid in 85% yield (4.44 g). m.p. $227\text{--}229^\circ\text{C}$ (lit. $227\text{--}229^\circ\text{C}$); ^1H NMR (400 MHz, CDCl_3) δ_{H} : 7.28 (d, 6H, Ar- H_3 , $J = 5.7$ Hz), 7.05 (d, 6H, Ar-

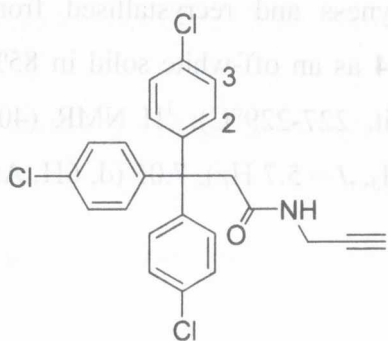
H_2 , $J = 5.7$ Hz), 3.48 (s, 2H, CH_2); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ_C : 164.4, 143.3, 133.0, 130.1, 128.4, 53.3, 46.5; IR ν_{max} (cm^{-1}) 1816, 1736, 1489, 1400, 1208, 1093, 1028, 1011, 995, 975, 810.

Methyl 2,6-bis(2-(2-(2-(3,3,3-tris(4-chlorophenyl)propanamido)ethoxy)ethoxy)ethoxy)benzoate (225)



Compound **221** (0.100 g, 0.23 mmol) and dry Et_3N (0.035 mL, 0.025 g, 0.25 mmol) were dissolved in dry THF (6 mL) and the solution cooled to $0^\circ C$. Compound **224** (0.098 g, 0.23 mmol) was dissolved in dry THF (2 mL) and added dropwise to this solution. The resulting reaction mixture was stirred overnight at ambient temperature. The solvent was removed under reduced pressure and the resulting oil diluted with 15 mL CH_2Cl_2 and extracted with water (4×20 mL). The organic layer was dried over $MgSO_4$ and solvents removed under reduced pressure leaving a yellow oil in 77% yield (0.220 g). 1H NMR (600 MHz, $DMSO-d_6$) δ_H : 7.70 (s, 2H, NH), 7.33 (m, 12H, Ar- H_3), 7.18 (m, 12H, Ar- H_2), 7.29 (m, 1H, Ar- H_4), 6.70 (m, 2H, Ar- $H_{3',5}$), 4.08 (m, 4H, O- CH_2-CH_2 -O-Ar), 3.72 (s, 3H, OMe), 3.69 (m, 4H, O- CH_2-CH_2 -O-Ar), 3.54 (m, 4H, Triphenyl- CH_2 -Amide), 3.58 (m, 4H, O- CH_2-CH_2 -O), 3.54 (m, 4H, O- CH_2-CH_2 -O), 3.06 (m, 4H, Amide- CH_2-CH_2), 2.94 (m, 4H, Amide- CH_2-CH_2); $^{13}C\{^1H\}$ NMR (150 MHz, $DMSO-d_6$) δ_C : 169.1, 165.8, 145.2, 131.0, 130.8, 127.6, 113.5, 105.4, 70.0, 69.9, 69.8, 69.5, 68.8, 54.7, 51.7, 45.8, 45.6, 38.7; HRMS (m/z) (MALDI) Calculated for $C_{62}H_{60}Cl_6N_2O_{10}$ $m/z = 1225.2316$ $[M + Na]^+$. Found $m/z = 1225.2277$; IR ν_{max} (cm^{-1}) 3329, 2918, 1729, 1669, 1596, 1490, 1257, 1092, 1011, 805.

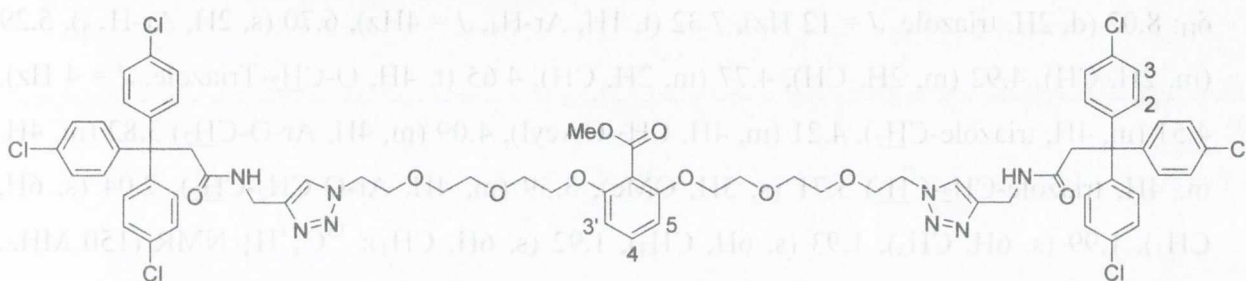
3,3,3-Tris(4-chlorophenyl)-N-(prop-2ynyl)propanamide (226)



Tris(4-chlorophenyl)propionic acid, **222** (1.00 g, 2.46 mmol) and propargyl amine, **228** (0.84 mL, 12.32 mmol) were dissolved in dry CH_2Cl_2 and cooled to $0^\circ C$. EDC·HCl (1.19 g, 6.16 mmol) and DMAP (0.300 g, 2.46 mmol) were added to the mixture and stirred for 2 hrs. The reaction was then brought to ambient temperature and stirred overnight. The

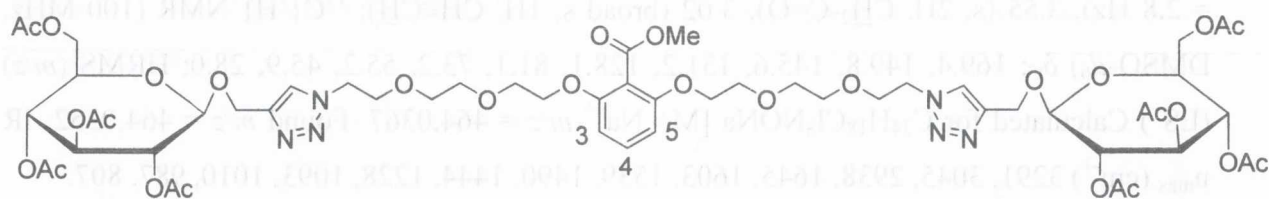
crude product was washed with deionised water ($6 \times 30\text{mL}$). The CH_2Cl_2 layer was dried over MgSO_4 and solvents removed under reduced pressure to give **226** as a beige solid in 44% yield (0.480 g). m.p. $104\text{--}106^\circ\text{C}$; ^1H NMR (400 MHz, $\text{DMSO-}d_6$) δ_{H} : 8.10 (t, 1H, NH $J = 5.2$ Hz), 7.34 (d, 6H, Ar- H_3 , $J = 8.4$ Hz), 7.16 (d, 6H, Ar- H_2 , $J = 8.4$ Hz), 3.60 (d, 2H, $\text{CH}\equiv\text{CH}$, $J = 2.8$ Hz), 3.55 (s, 2H, $\text{CH}_2\text{-C=O}$), 3.02 (broad s, 1H, $\text{CH}\equiv\text{CH}$); $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, $\text{DMSO-}d_6$) δ_{C} : 169.4, 149.8, 145.6, 131.2, 128.1, 81.1, 73.2, 55.2, 45.9, 28.0; HRMS (m/z) (ES^+) Calculated for $\text{C}_{24}\text{H}_{18}\text{Cl}_3\text{NONa}$ [$\text{M}^+ \text{Na}^+$] $m/z = 464.0367$. Found $m/z = 464.0352$; IR ν_{max} (cm^{-1}) 3291, 3045, 2938, 1645, 1603, 1539, 1490, 1444, 1228, 1093, 1010, 987, 807.

Methyl 2,6-bis(2-(2-(2-(4-((3,3,3-tris(4-chlorophenyl)propanamido)methyl)-1H-1,2,3-triazol-1-yl)ethoxy)ethoxy)ethoxy)benzoate (227)



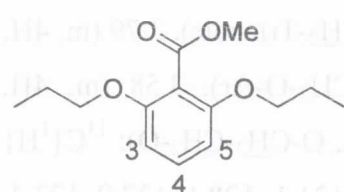
Compound **227** was prepared according to Procedure 6.3 using compound **220** (0.100 g, 0.207 mmol) to give **226** as a dark green oil in 91% yield (0.260 g). ^1H NMR (600 MHz, $\text{DMSO-}d_6$) δ_{H} : 8.19 (s, 2H, NH), 7.52 (d, 2H, triazole, $J = 12$ Hz), 7.30 (d, 12H, Ar- H_3 , $J = 6$ Hz), 7.16 (d, 12H, Ar- H_2 , $J = 6$ Hz), 7.29 (m, 1H, Ar- H_4), 6.68 (m, 2H, Ar- H_3 , $J = 5$), 4.46 (m, 4H, triazole- $\text{CH}_2\text{-CH}_2$), 4.07 (m, 4H, O- $\text{CH}_2\text{-CH}_2\text{-O-Ar}$), 4.03 (m, 4H, Amide- $\text{CH}_2\text{-Triazole}$), 3.79 (m, 4H, triazole- $\text{CH}_2\text{-CH}_2$), 3.70 (s, 3H, OMe), 3.68 (m, 4H, O- $\text{CH}_2\text{-CH}_2\text{-O-Ar}$), 3.58 (m, 4H, Triphenyl- $\text{CH}_2\text{-Amide}$), 3.53 (m, 4H, O- $\text{CH}_2\text{-CH}_2\text{-O}$), 3.52 (m, 4H, O- $\text{CH}_2\text{-CH}_2\text{-O}$); $^{13}\text{C}\{^1\text{H}\}$ NMR (150 MHz, $\text{DMSO-}d_6$) δ_{C} : 169.6, 162.6, 156.4, 145.6, 131.4, 131.1, 128.1, 127.9, 123.4, 121.4, 113.9, 105.8, 70.4, 70.2, 69.9, 69.7, 68.7, 55.0, 52.1, 49.5, 45.9, 34.2; HRMS (m/z) (MALDI-ToF) Calculated for $\text{C}_{68}\text{H}_{66}\text{N}_8\text{O}_{10}\text{Cl}_6\text{Na}$ $m/z = 1387.2893$ [$\text{M} + \text{Na}^+$]. Found $m/z = 1387.2931$; IR ν_{max} (cm^{-1}) 3285, 3063, 2872, 1731, 1664, 1597, 1490, 1402, 1255, 1093, 1011, 807, 731.

(2S,3S,4R,5S,6S)-2-(acetoxymethyl)-6-(((1-(2-(2-(2-(2-(methoxycarbonyl)-3-(2-(2-(2-(4-(((2R,3R,4S,5R,6R)-3,4,5-triacetoxy-6-(acetoxymethyl)tetrahydro-2H-pyran-2-yloxy)methyl)-1H-1,2,3-triazol-1-yl)ethoxy)ethoxy)ethoxy)phenoxy)ethoxy)ethoxy)ethyl)-1H-1,2,3-triazol-4-yl)methoxy)tetrahydro-2H-pyran-3,4,5-triyl triacetate (**230**)



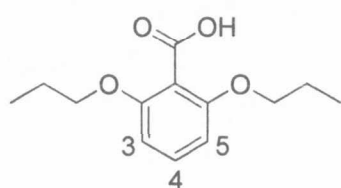
Compound **230** was prepared according to Procedure 6.3 using compound **229** (0.088 g, 0.228 mmol) to give **230** as a dark green oil in 75% yield (0.216 g). ^1H NMR (600 MHz, $\text{DMSO}-d_6$) δ_{H} : 8.02 (d, 2H, triazole, $J = 12$ Hz), 7.32 (t, 1H, Ar- H_4 , $J = 4$ Hz), 6.70 (s, 2H, Ar- $\text{H}_{3,5}$), 5.29 (m, 2H, CH), 4.92 (m, 2H, CH), 4.77 (m, 2H, CH), 4.65 (t, 4H, O- CH_2 -Triazole, $J = 4$ Hz), 4.51 (m, 4H, triazole- CH_2), 4.21 (m, 4H, CH_2 -OAcyl), 4.09 (m, 4H, Ar-O- CH_2), 3.82 (m, 4H, m, 4H, triazole- CH_2 - CH_2), 3.71 (s, 3H, OMe), 3.59 (m, 4H, Ar-O- CH_2 - CH_2), 2.04 (s, 6H, CH_3), 1.99 (s, 6H, CH_3), 1.93 (s, 6H, CH_3), 1.92 (s, 6H, CH_3); $^{13}\text{C}\{^1\text{H}\}$ NMR (150 MHz, $\text{DMSO}-d_6$) δ_{C} : 170.0, 169.5, 169.3, 165.8, 155.9, 143.0, 131.1, 124.4, 113.6, 98.6, 72.0, 70.8, 70.6, 69.0, 68.1, 62.2, 61.6, 51.7, 49.6, 36.0, 31.1, 20.8, HRMS (m/z) (MALDI-ToF) Calculated for $\text{C}_{54}\text{H}_{74}\text{N}_6\text{O}_{28}\text{Na}$ $m/z = 1277.4449$ $[\text{M} + \text{Na}]^+$. Found $m/z = 1277.4408$.

Methyl 2,6-dipropoxybenzoate (**232**)



Compound **232** was prepared according to Procedure 6.1 using 1-bromopropane, **231**, to give **232** as a dark red oil in 80% yield (1.2 g). ^1H NMR (400 MHz, CDCl_3) δ_{H} : 7.24 (t, 1H, Ar- H_4 , $J = 8.1$ Hz), 6.54 (m, 2H, Ar- $\text{H}_{3,5}$), 3.96 (m, 4H, O- CH_2 - CH_2 - CH_3), 3.91 (s, 3H, OMe), 1.79 (m, 4H, O- CH_2 - CH_2 - CH_3), 1.01 (t, 6H, O- CH_2 - CH_2 - CH_3); $^{13}\text{C}\{^1\text{H}\}$ NMR (150 MHz, CDCl_3) δ_{C} : 166.9, 156.7, 130.6, 113.7, 104.7, 70.1, 51.8, 22.3, 10.2; HRMS (m/z) (ES^+) Calculated for $\text{C}_{14}\text{H}_{20}\text{O}_4\text{Na}$ $m/z = 275.1259$ $[\text{M} + \text{Na}]^+$. Found $m/z = 275.1248$; IR ν_{max} (cm^{-1}) 2965, 1734, 1595, 1459, 1251, 1108, 827, 725.

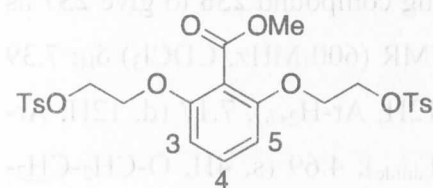
2,6-dipropoxybenzoic acid (**233**)



Compound **233** (0.350 g, 1.39 mmol) was suspended in an aqueous solution of excess NaOH and microwave irradiated at 120°C for 40 mins. The pH of the solution was then lowered to $\text{pH} = 2$ by dropwise addition of 2 M HCl. The resulting white

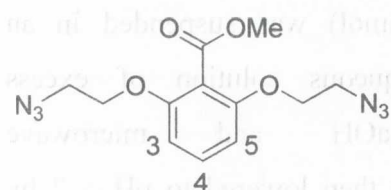
solid was collected by centrifugation in 75% yield (0.250 g). m.p. decomposed above 50°C; ^1H NMR (400 MHz, CDCl_3) δ_{H} : 12.65 (s, 1H, OH), 7.31 (t, 1H, Ar-H₄, $J = 8.1$ Hz), 6.60 (m, 2H, Ar-H_{3,5}), 4.03 (m, 4H, O-CH₂-CH₂-CH₃), 1.84 (m, 4H, O-CH₂-CH₂-CH₃), 1.06 (t, 6H, O-CH₂-CH₂-CH₃); $^{13}\text{C}\{^1\text{H}\}$ NMR (150 MHz, CDCl_3) δ_{C} : 168.5, 157.1, 131.3, 111.3, 104.8, 70.2, 22.0, 9.9; HRMS (m/z) (ES^+) Calculated for $\text{C}_{13}\text{H}_{19}\text{O}_4$ $m/z = 239.1283$ [$\text{M} + \text{H}$] $^+$. Found $m/z = 239.1285$; IR ν_{max} (cm^{-1}) 2966, 2936, 2878, 2666, 1595, 1459, 1303, 1252, 1111, 738.

Methyl 2,6-bis(2-(2-(tosyloxy)benzoate (235)



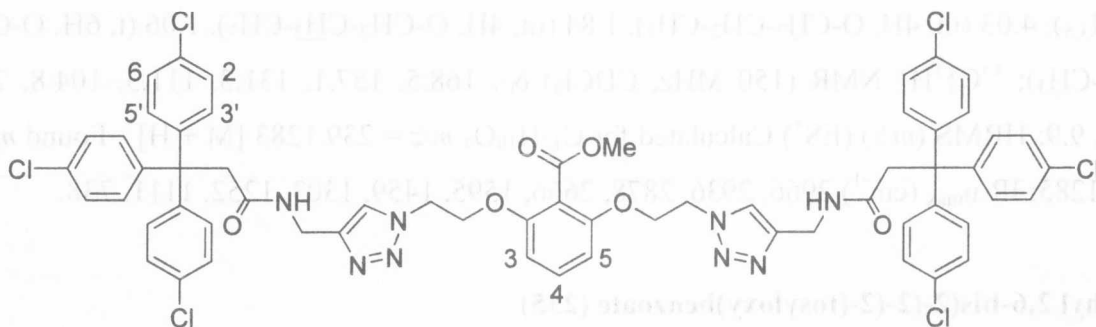
Compound **235** was prepared according to Procedure 6.1 using ethylene glycol di(*p*-toluenesulfonate, **234** (4.36 g, 11.89 mmol) to give **70** as a clear oil that solidifies upon standing in 40% yield (1.71 g). ^1H NMR (400 MHz, CDCl_3) δ_{H} : 7.79 (d, 4H, Ar-H_{Tosyl}, $J = 8.2$ Hz), 7.33 (d, 4H, Ar-H_{Tosyl}), 7.20 (t, 1H, Ar-H₄, $J = 8.1$ Hz), 6.49 (d, 2H, Ar-H_{3,5}), 4.31 (d, 4H, O-CH₂-CH₂-OTs), 4.17 (d, 4H, O-CH₂-CH₂-OTs), 3.81 (s, 3H, O-Me), 2.43 (s, 6H, CH₃_{Tosyl}); $^{13}\text{C}\{^1\text{H}\}$ NMR (150 MHz, CDCl_3) δ_{C} : 165.5, 155.3, 144.5, 132.1, 130.6, 129.4, 127.4, 114.1, 105.7, 67.2, 66.0, 51.8, 21.1; HRMS (m/z) (ES^+) Calculated for $\text{C}_{26}\text{H}_{28}\text{O}_{10}\text{S}_2\text{Na}$ $m/z = 587.1022$ [$\text{M} + \text{Na}$] $^+$. Found $m/z = 587.1022$; IR ν_{max} (cm^{-1}) 2874, 1731, 1596, 1470, 1449, 1352, 1297, 1254, 1188, 1174, 1095, 1073, 1010, 916, 816, 775, 759, 661.

Methyl 2,6-bis(2-azidoethoxy)benzoate (236)



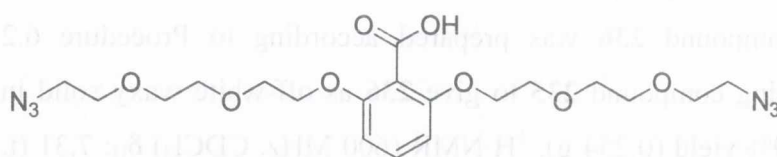
Compound **236** was prepared according to Procedure 6.2 using compound **235** to give **236** as off-white waxy solid in 99% yield (0.254 g). ^1H NMR (600 MHz, CDCl_3) δ_{H} : 7.31 (t, 1H, Ar-H₄, $J = 12$ Hz), 6.60 (d, 2H, Ar-H_{3,5}, $J = 6$ Hz), 4.19 (t, 4H, O-CH₂-CH₂-N₃, $J = 6$ Hz), 3.92 (s, 3H, O-Me), 3.58 (t, 4H, O-CH₂-CH₂-N₃, $J = 6$ Hz); $^{13}\text{C}\{^1\text{H}\}$ NMR (150 MHz, CDCl_3) δ_{C} : 166.1, 156.1, 131.1, 114.3, 105.6, 68.8, 52.6, 50.1; HRMS (m/z) (ES^+) Calculated for $\text{C}_{12}\text{H}_{14}\text{O}_4\text{N}_6\text{Na}$ $m/z = 329.0974$ [$\text{M} + \text{Na}$] $^+$. Found $m/z = 329.0967$; IR ν_{max} (cm^{-1}) 2955, 2107, 1735, 1597, 1450, 1356, 1256, 1173, 1075, 921, 815, 775, 664.

Methyl 2,6-bis(2-(4-((3,3,3-tris(4-chlorophenyl)propanamido)methyl)-1H-1,2,3-triazol-1-yl)ethoxy)benzoate (237)



Compound **237** was prepared according to Procedure 6.3 using compound **236** to give **237** as a white solid in 20% yield (0.110 g). m.p. 149-151°C; ^1H NMR (600 MHz, CDCl_3) δ_{H} : 7.39 (s, 2H, $\text{CH}_{\text{triazole}}$), 7.31 (t, 1H, Ar- H_4 , $J = 8.1$ Hz), 7.21 (d, 12H, Ar- H_{2+6}), 7.17 (d, 12H, Ar- $\text{H}_{3'+5'}$), 6.55 (d, 2H, Ar- H_{3+5} , $J = 12$ Hz), 6.11 (s, 2H, NH_{amide}), 4.69 (s, 4H, O- CH_2 - CH_2 -triazole), 4.34 (t, 4H, O- CH_2 - CH_2 -triazole, $J = 6$ Hz), 4.25 (s, 4H, $\text{CH}_{2\text{adj. Amide}}$), 3.79 (s, 3H, O- Me), 3.53 (s, 4H, $\text{CH}_{2\text{adj. Triphenyl}}$); $^{13}\text{C}\{^1\text{H}\}$ NMR (150 MHz, CDCl_3) δ_{C} : 169.4, 166.1, 155.6, 144.3, 132.5, 131.7, 130.4, 128.2, 113.8, 105.9, 67.0, 55.2, 52.6, 49.6, 47.7, 34.6; HRMS (m/z) (MALDI-ToF) Calculated for $\text{C}_{60}\text{H}_{51}\text{O}_6\text{N}_8\text{Cl}_6$ $m/z = 1189.2063$ $[\text{M} + \text{H}]^+$. Found $m/z = 1189.2007$; IR ν_{max} (cm^{-1}) 2955, 1735, 1597, 1449, 1357, 1257, 1188, 1095, 1021, 921, 815, 774, 664.

2,6-bis(2-(2-(2-azidoethoxy)ethoxy)ethoxy)benzoic acid (239)



Compound **220** (0.305 g, 0.632 mmol) was suspended in an aqueous solution of excess NaOH and microwave

irradiated at 120°C for 40 mins. The pH of the solution was then lowered to pH = 2 by dropwise addition of 2 M HCl. The resulting white solid was collected by centrifugation in 71% yield (0.211 g). m.p. decomposed above 200°C; ^1H NMR (400 MHz, CDCl_3) δ_{H} : 12.72 (s, 1H, OH), 7.28 (t, 1H, Ar- H_2 , $J = 8$ Hz), 6.70 (d, 2H, Ar- H_1 , $J = 8$ Hz), 4.09 (s, 4H, Ar-O- CH_2), 3.71 (m, 8H, CH_2), 3.60 (m, 8H, CH_2), 3.41 (m, 4H, CH_2); $^{13}\text{C}\{^1\text{H}\}$ NMR (150 MHz, CDCl_3) δ_{C} : 169.8, 159.2, 134.8, 104.4, 101.8, 70.4, 70.1, 70.0, 69.7, 52.2; HRMS (m/z) (ES^+) Calculated for $\text{C}_{13}\text{H}_{19}\text{O}_4$ $m/z = 491.1866$ $[\text{M} + \text{Na}]^+$. Found $m/z = 491.1857$; IR ν_{max} (cm^{-1}) 2875, 2104, 1730, 1596, 1450, 1253, 1071, 941, 785, 729.

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Appendices

Appendix 2:

Figure A2.1: Crystallographic Data for Receptor 113.

Identification code:	EMB24
Empirical formula:	C ₆₄ H ₅₆ F ₁₂ N ₁₂ O ₄ S ₄
Formula weight:	357.00
Temperature:	108(2) K
Wavelength:	0.71075 Å
Crystal System:	Monoclinic
Space Group:	P21/c
Unit Cell Dimensions:	a = 12.254(3) Å α = b = 15.675(4) Å β = 103.627(3)° c = 8.889(2) Å γ = 1659.3(7)°
Volume:	1659.3(7) Å ³
Z:	1
Density (calculated):	1.358 Mg/m ³
Absorption Coefficient:	0.232 mm ⁻¹
F(000):	672
Crystal Size:	0.40 x 0.40 x 0.15 mm ³
Theta Range for Data Collected:	1.71 to 25.00°
Index Ranges:	-14 ≤ h ≤ 14, -18 ≤ k ≤ 18, -10 ≤ l ≤ 10
Reflections Collected:	10253
Independent Reflections:	2894 [R(int) = 0.0185]
Completeness to Theta = 25.00°	98.8%
Max. and Min. Transmission:	1.0000 and 0.7206
Refinement Method:	Full-matrix least-squares on F ²
Data/Restraints/Parameters:	2894 / 0 / 218
Goodness-of-Fit on F ² :	1.099
Final R Indices [I>2sigma(I)]:	R1 = 0.0445, wR2 = 0.1218
R Indices (All Data):	R1 = 0.0505, wR2 = 0.1341
Largest Diff. Peak and Hole:	0.731 and -0.677 e.Å ⁻³

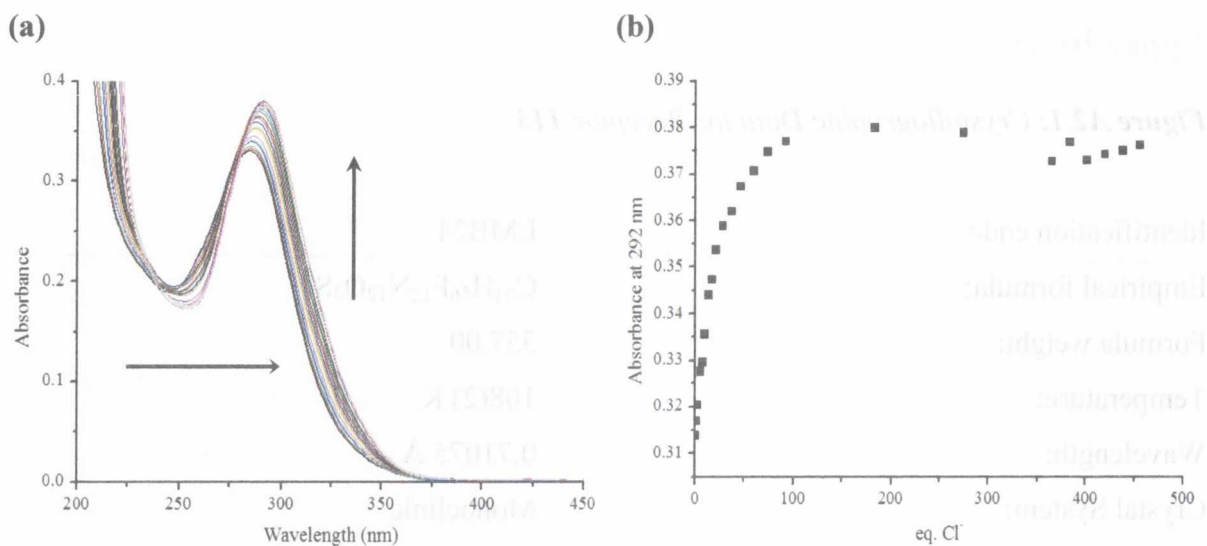


Figure A2.2: (a) Changes observed in the absorption spectra of receptor **111** ($1.1 \times 10^{-5} \text{ M}$) upon titration with Cl^- ($0 \rightarrow 4.5 \text{ mM}$) in CH_3CN . (b) The changes in the absorbance at 292 nm as a function of equivalents of Cl^- .

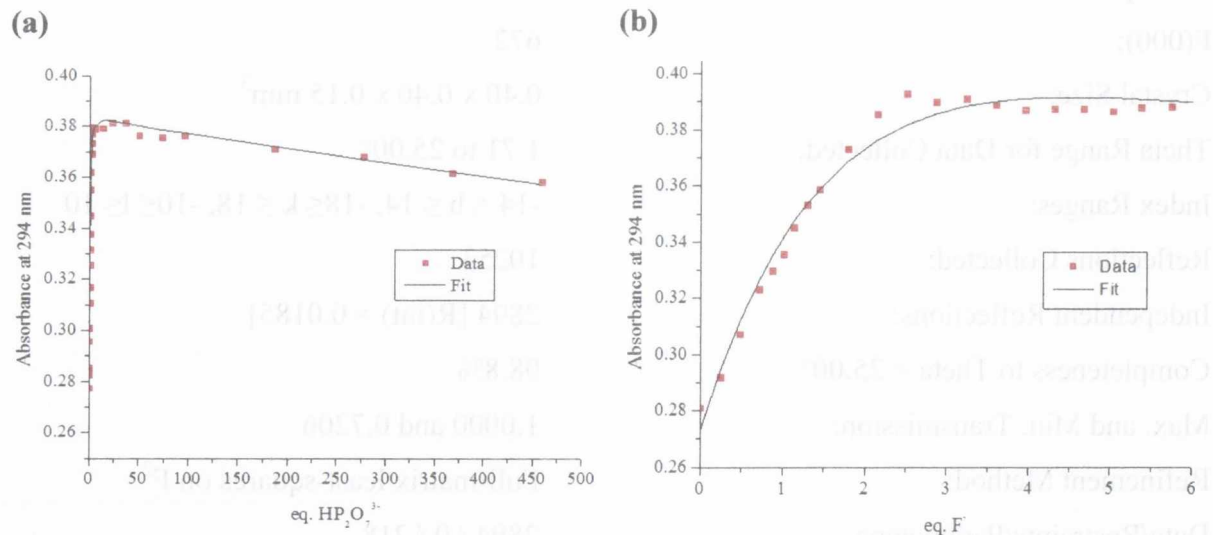


Figure A2.3: (a) Experimental binding isotherm for the titration of **111** ($1.05 \times 10^{-5} \text{ M}$) and $\text{HP}_2\text{O}_7^{3-}$ and the corresponding fit from SPECFIT™. (b) Experimental binding isotherm for the titration of **111** ($1.04 \times 10^{-5} \text{ M}$) and F^- the corresponding fit from SPECFIT™.

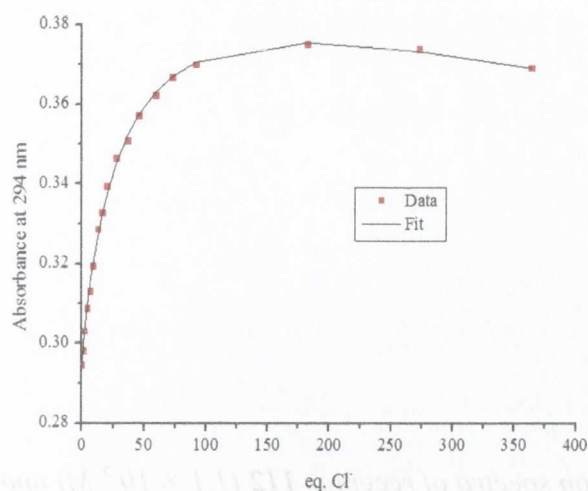


Figure A2.4: Experimental binding isotherm for the titration of **111** (1.1×10^{-5} M) and CT^- and the corresponding fit from SPECFITTM.

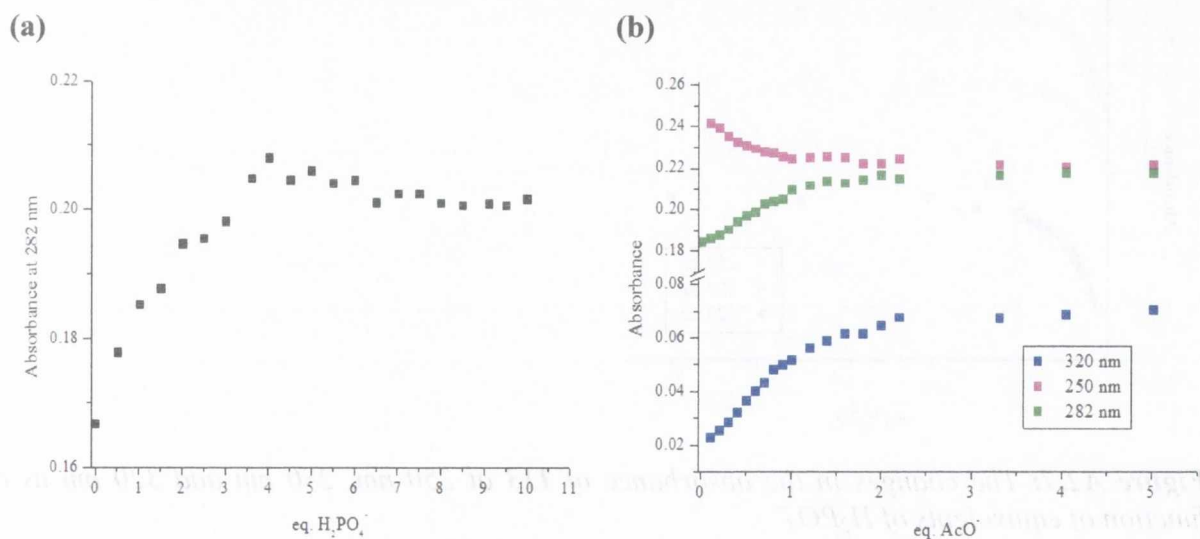


Figure A2.5: (a) The changes in the absorbance of **112** at 282 nm as a function of equivalents of H_2PO_4^- . (b) The changes in the absorbance of **112** at 250 nm, 282 nm and 320 nm as a function of equivalents of AcO^- .

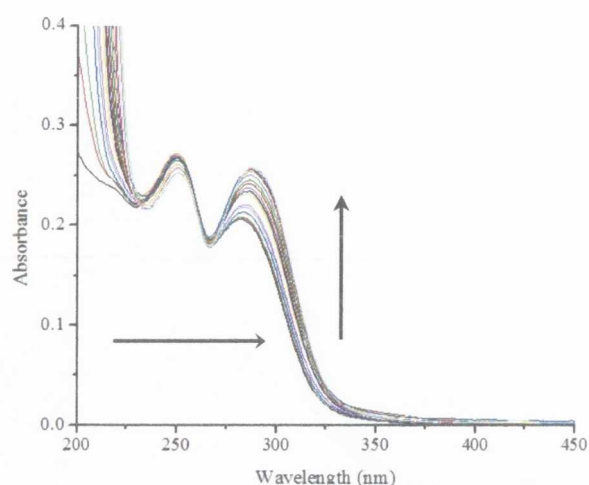


Figure A2.6: Changes observed in the absorption spectra of receptor **112** (1.1×10^{-5} M) upon titration with Cl^- ($0 \rightarrow 5.5$ mM) in CH_3CN .

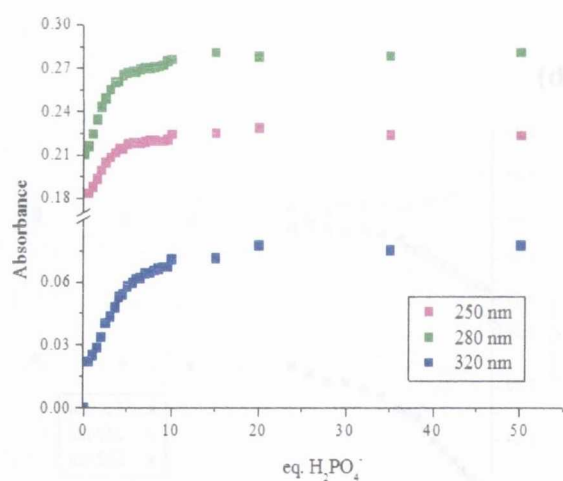


Figure A2.7: The changes in the absorbance of **113** at 250 nm, 280 nm and 320 nm as a function of equivalents of H_2PO_4^-

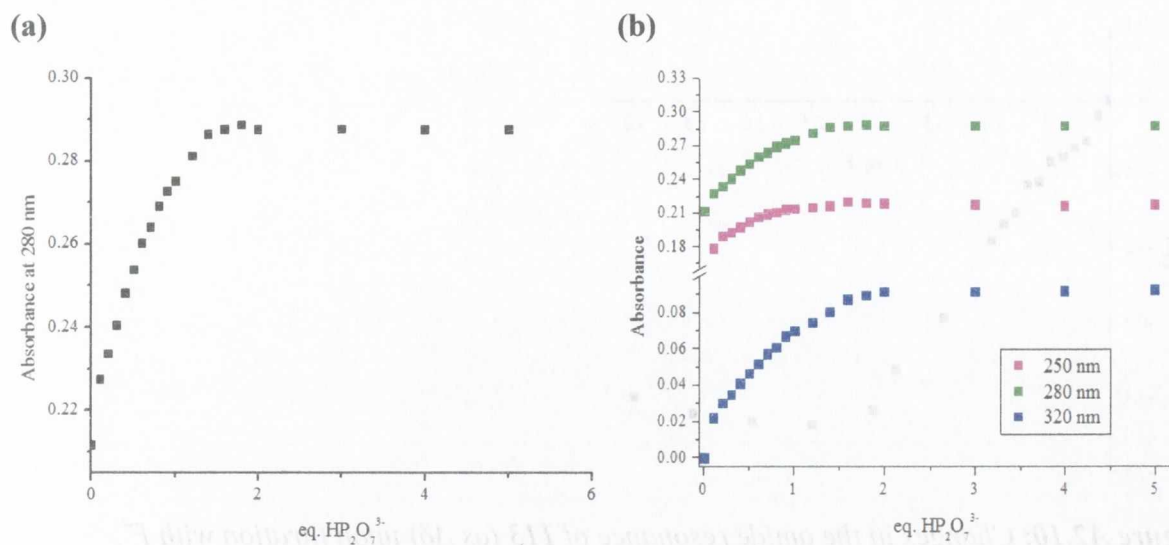


Figure A2.8: (a) The changes in the absorbance of **113** ($1.09 \times 10^{-5} \text{ M}$) at 294 nm as a function of equivalents of $\text{HP}_2\text{O}_7^{3-}$. (b) The changes in the absorbance of **113** at 250 nm, 280 nm and 320 nm as a function of equivalents of $\text{HP}_2\text{O}_7^{3-}$.

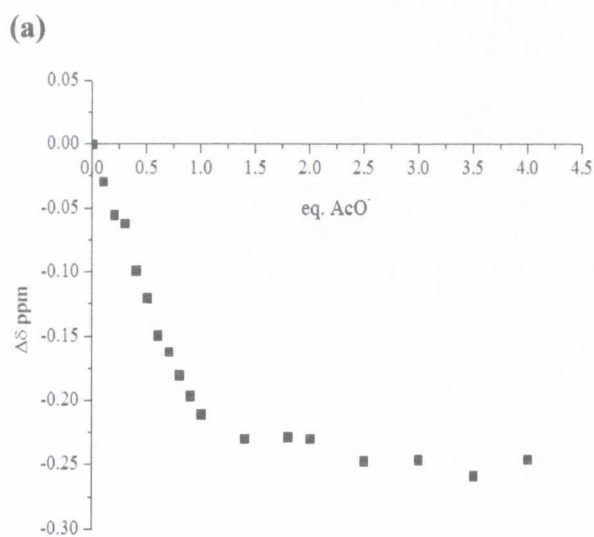


Figure A2.9: (a) Changes in the amide resonance of **113** (as $\Delta\delta$) upon titration with AcO^- .

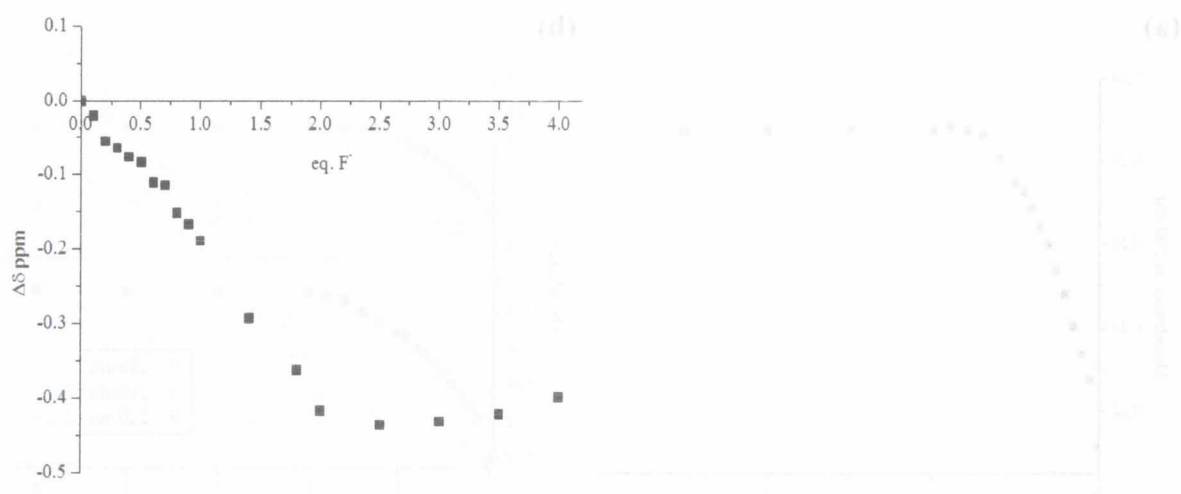


Figure A2.10: Changes in the amide resonance of 113 (as $\Delta\delta$) upon titration with F^- .

(a)

100% DMSO- d_6
50% DMSO- d_6

Figure A2.9: (a) Changes in the amide resonance of 113 (as $\Delta\delta$) upon titration with $2Cl^-$.

Appendix 3:

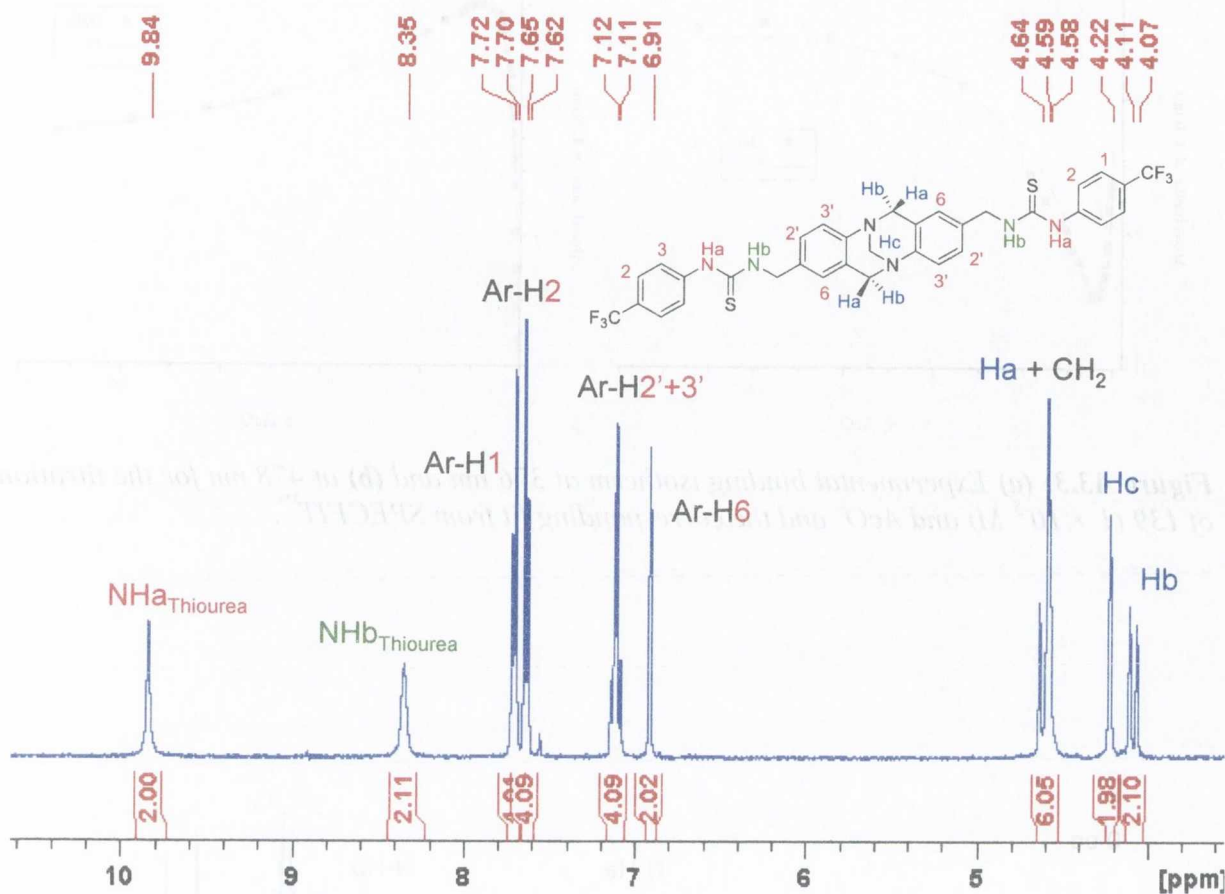


Figure A3.1: ¹H NMR spectrum (400 MHz, DMSO-d₆) of 139.

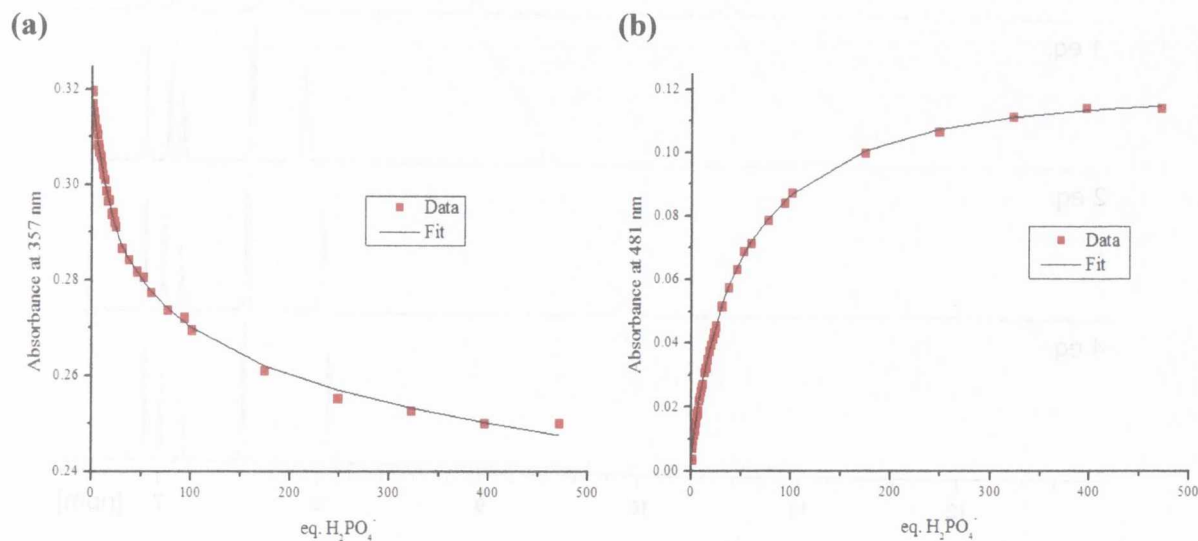


Figure A3.2: (a) Experimental binding isotherm at 357 nm and (b) at 481 nm for the titration of 139 (1×10^{-5} M) and H₂PO₄⁻ and the corresponding fit from SPECFIT™.

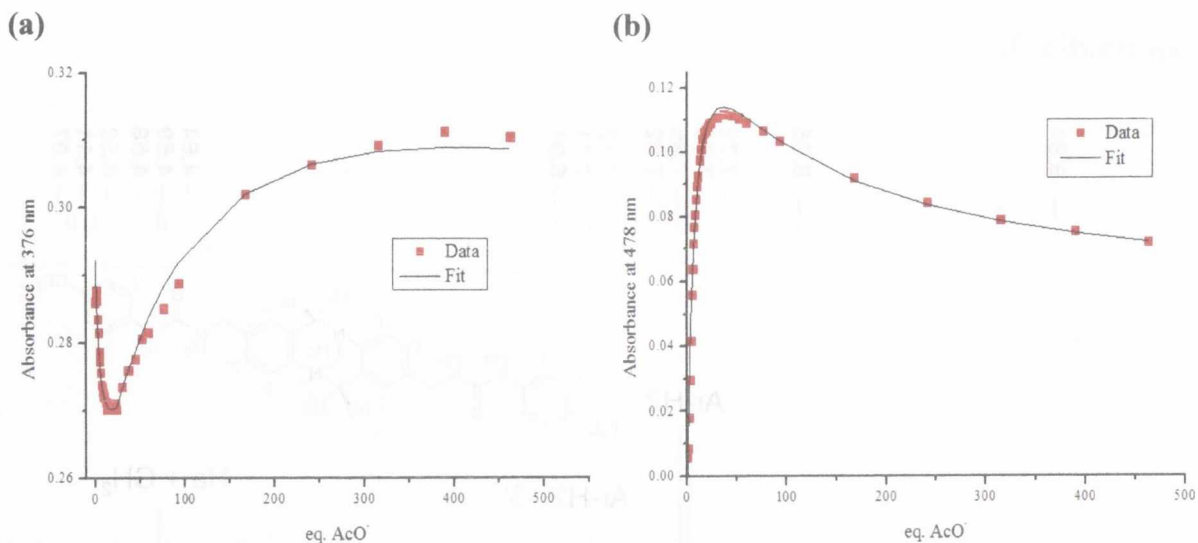


Figure A3.3: (a) Experimental binding isotherm at 376 nm and (b) at 478 nm for the titration of **139** ($1 \times 10^{-5} \text{ M}$) and AcO^- and the corresponding fit from SPECFITTM.

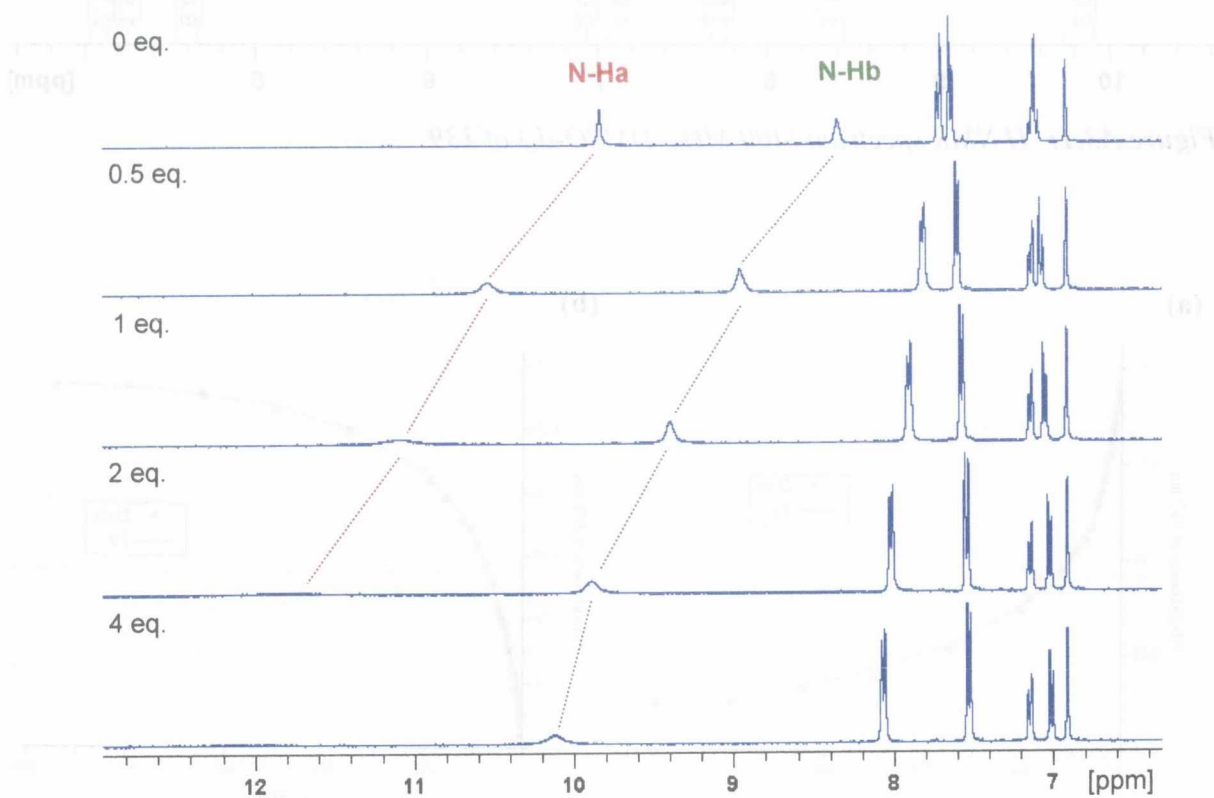


Figure A3.4: Stack plot of the ^1H NMR (400 MHz, DMSO-d_6) spectra of **138** upon addition of 0.5, 1, 2 and 4 equivalents of H_2PO_4^- .

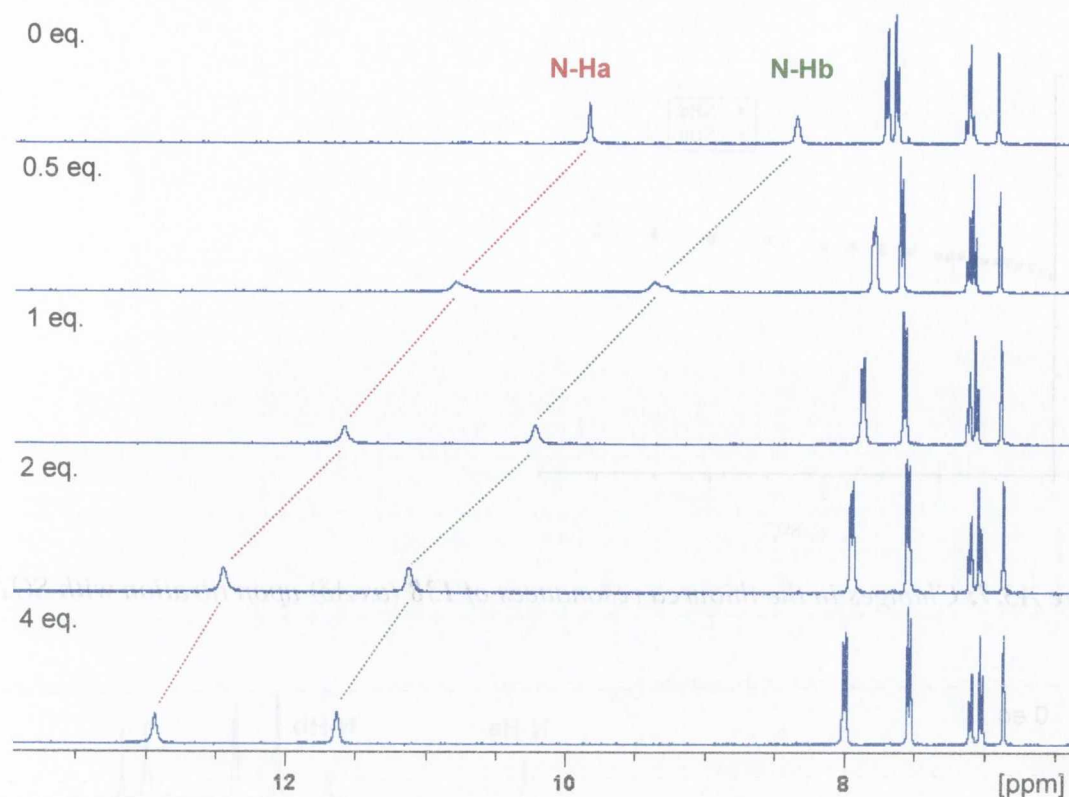


Figure A3.5: Stack plot of the ^1H NMR (400 MHz, DMSO-d_6) spectra of **138** upon addition of 0.5, 1, 2 and 4 equivalents of AcO^- .

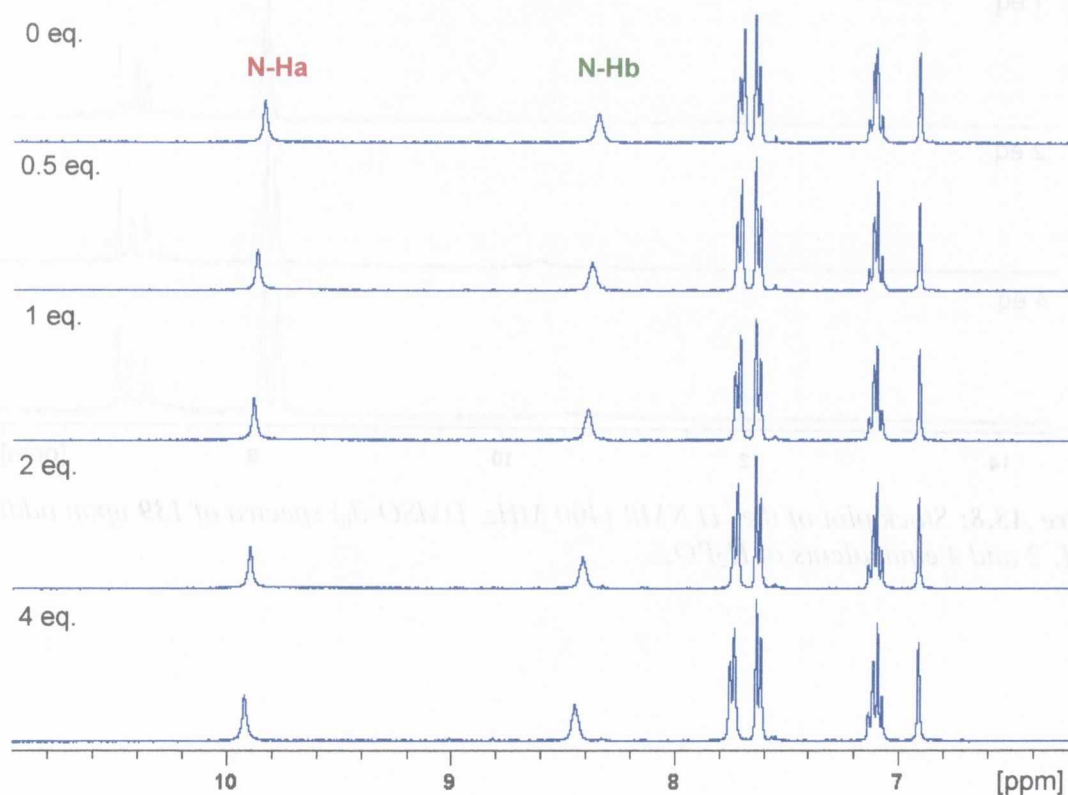


Figure A3.6: Stack plot of the ^1H NMR (400 MHz, DMSO-d_6) spectra of **138** upon addition of 0.5, 1, 2 and 4 equivalents of SO_4^{2-} .

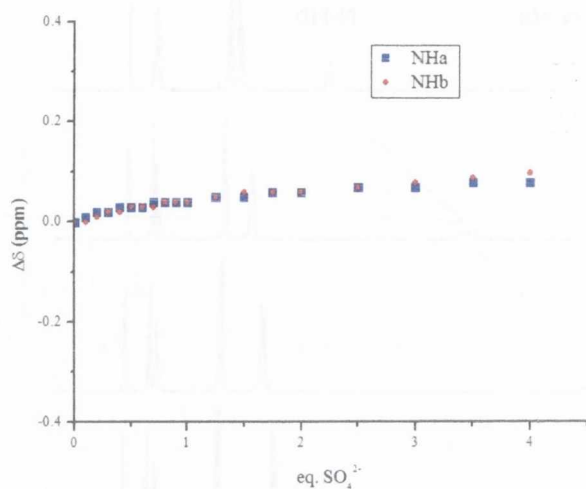


Figure A3.7: Changes in the thiourea resonances of **138** (as $\Delta\delta$) upon titration with SO_4^{2-} .

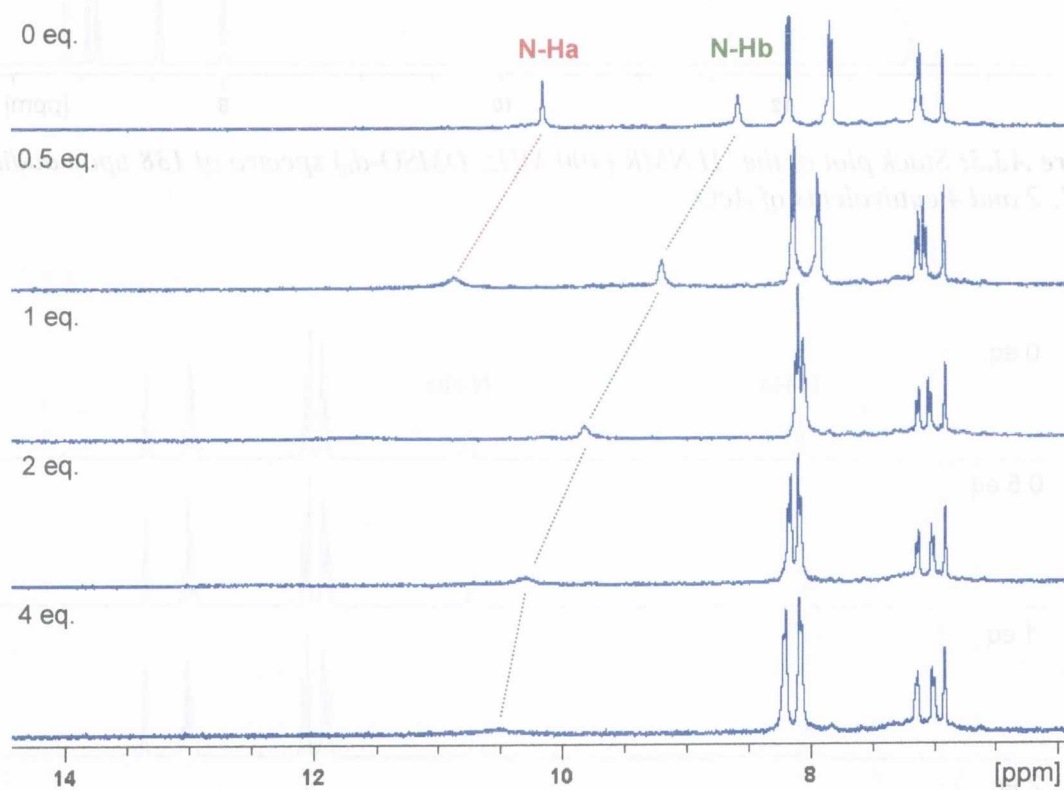


Figure A3.8: Stack plot of the ^1H NMR (400 MHz, DMSO-d_6) spectra of **139** upon addition of 0.5, 1, 2 and 4 equivalents of H_2PO_4^- .

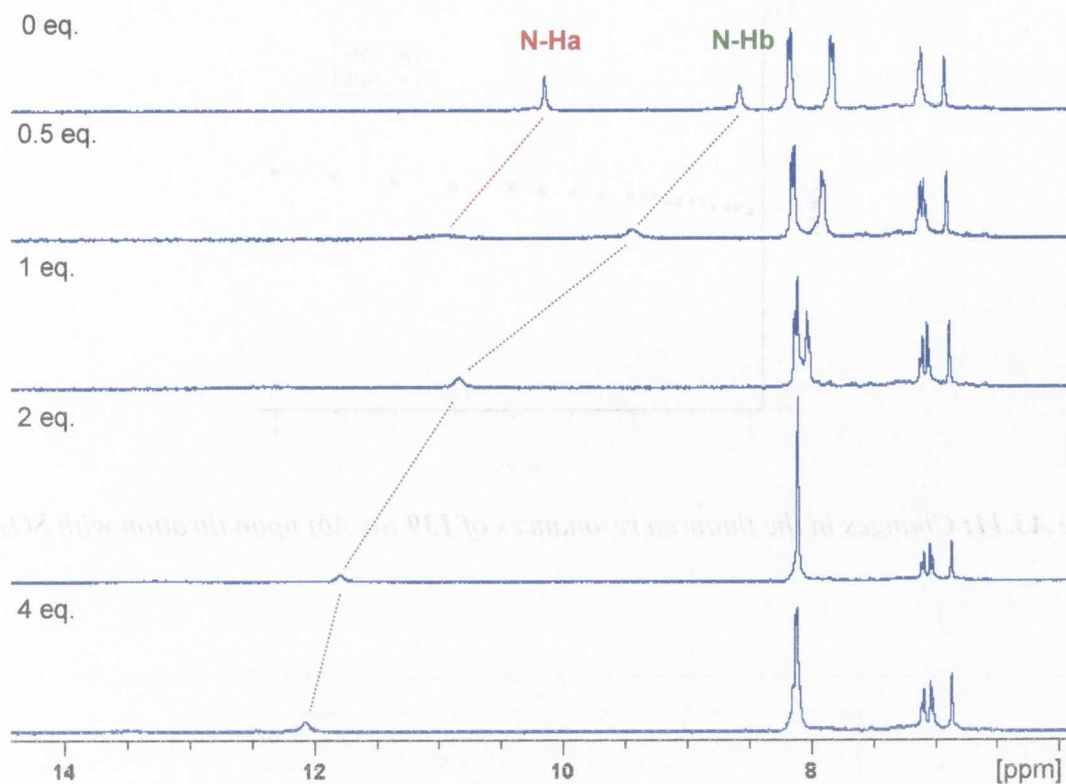


Figure A3.9: Stack plot of the ^1H NMR (400 MHz, DMSO-d_6) spectra of **139** upon addition of 0.5, 1, 2 and 4 equivalents of AcO^- .

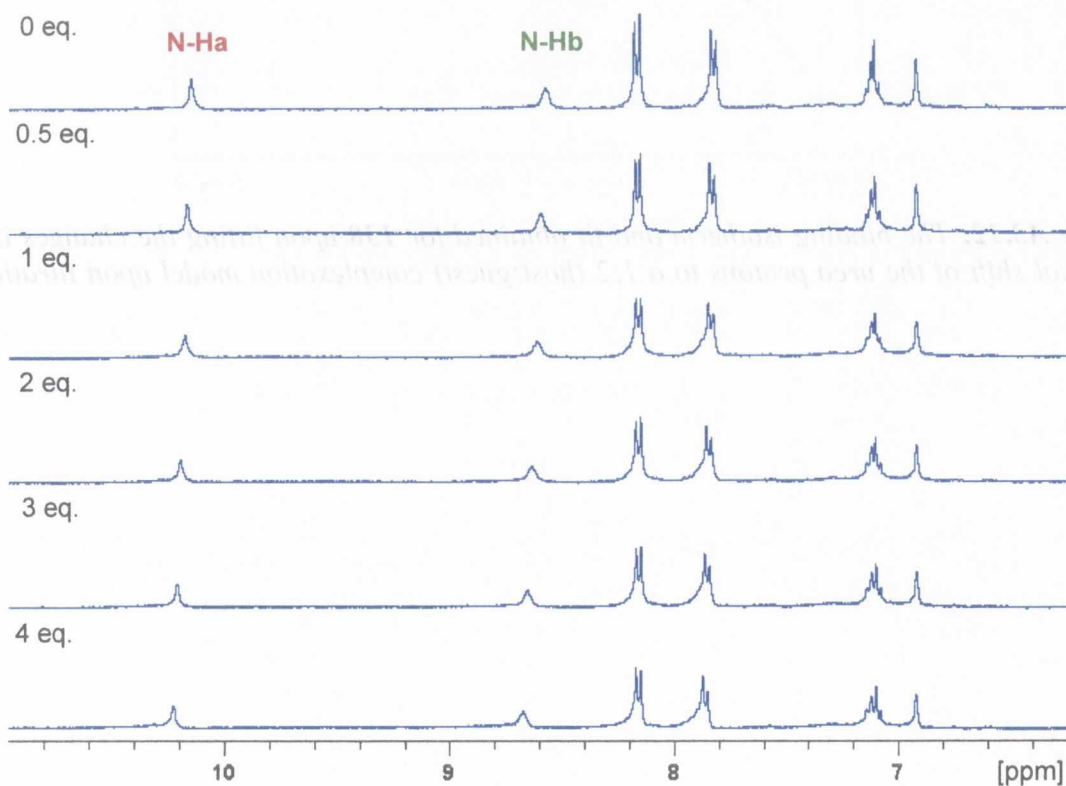


Figure A3.10: Stack plot of the ^1H NMR (400 MHz, DMSO-d_6) spectra of **139** upon addition of 0.5, 1, 2 and 4 equivalents of SO_4^{2-} .

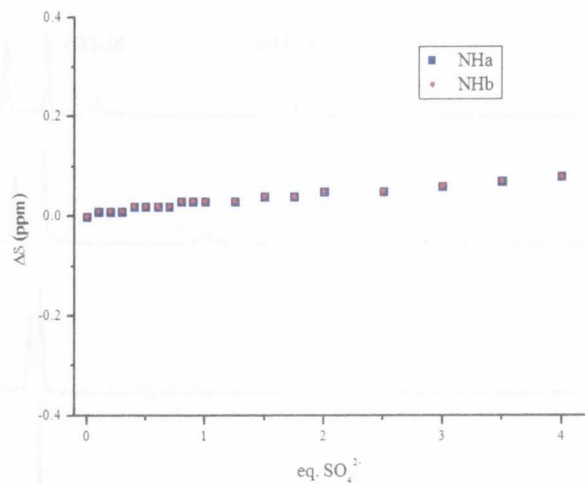


Figure A3.11: Changes in the thiourea resonances of **139** (as $\Delta\delta$) upon titration with SO_4^{2-} .

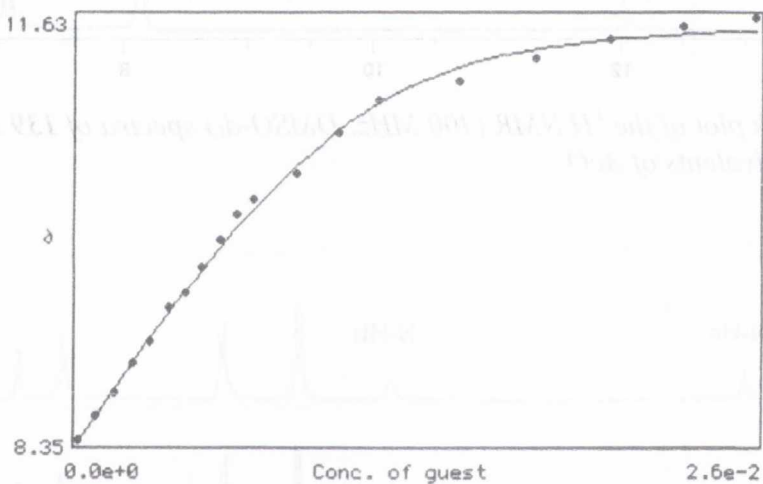


Figure A3.12: The binding isotherm and fit obtained for **138** upon fitting the changes in the chemical shift of the urea protons to a 1:2 (host:guest) complexation model upon titration of AcO^- .

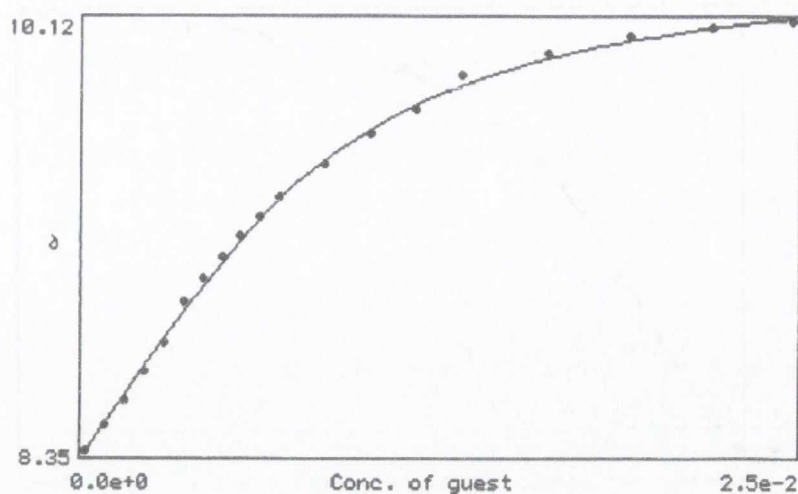


Figure A3.13: The binding isotherm and fit obtained for **138** upon fitting the changes in the chemical shift of the urea protons to a 1:2 (host:guest) complexation model upon titration of H_2PO_4^- .

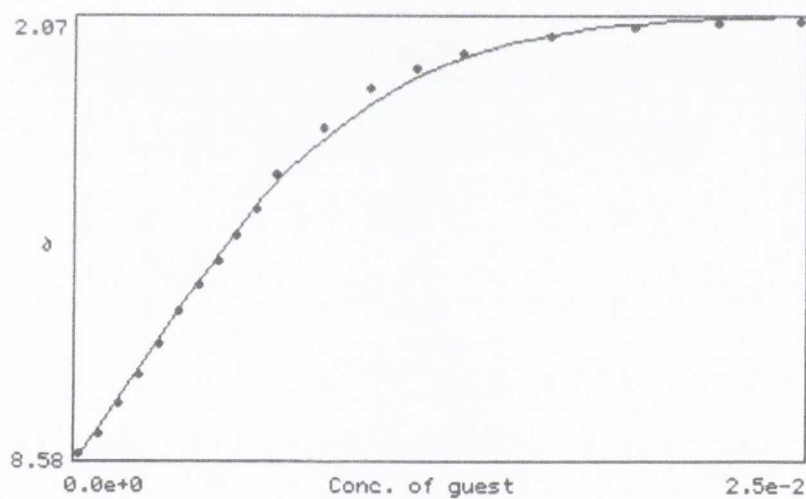


Figure A3.14: The binding isotherm and fit obtained for **139** upon fitting the changes in the chemical shift of the urea protons to a 1:2 (host:guest) complexation model upon titration of AcO^- .

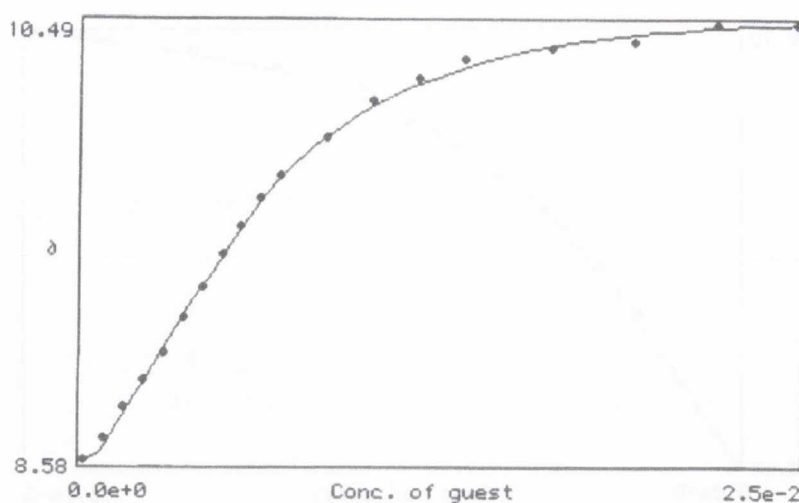


Figure A3.15: The binding isotherm and fit obtained for **139** upon fitting the changes in the chemical shift of the urea protons to a 1:2 (host:guest) complexation model upon titration of H_2PO_4^- .

Figure A3.14 The binding isotherm and fit obtained for **139** upon fitting the changes in the chemical shift of the urea protons to a 1:2 (host:guest) complexation model upon titration of H_2PO_4^- .

Appendix 4:

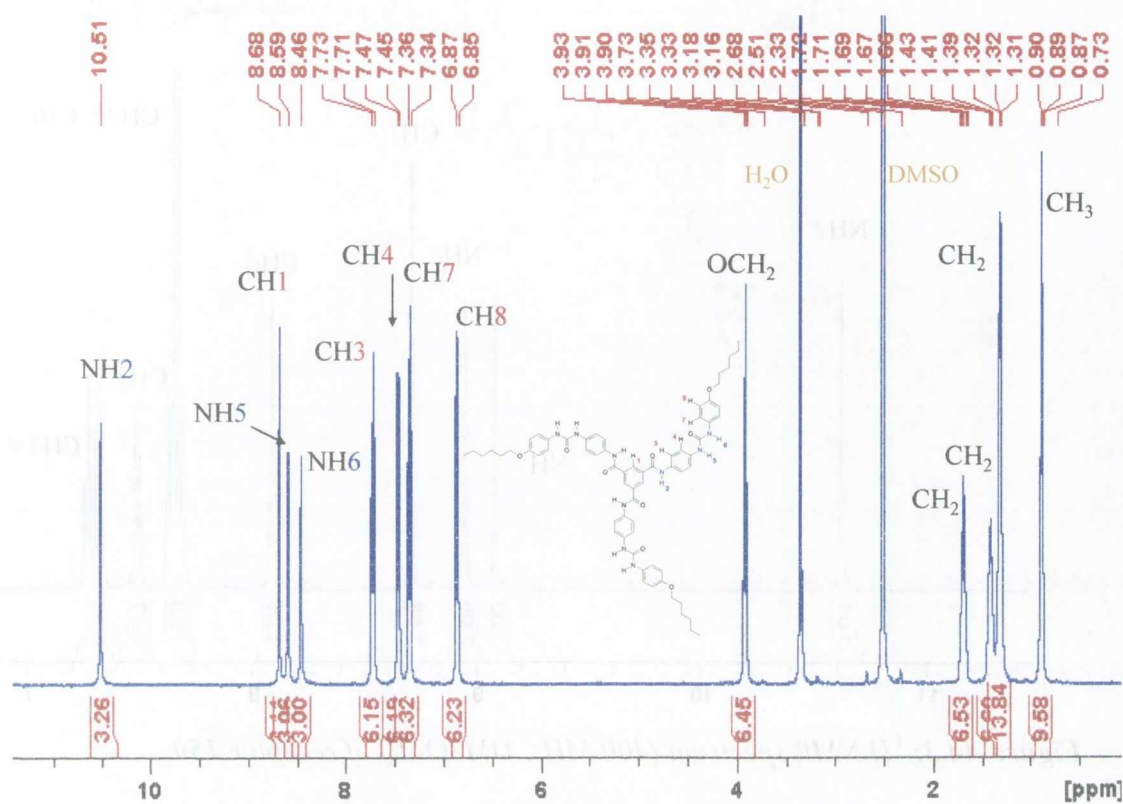


Figure A4.1: ^1H NMR spectrum (400 MHz, DMSO-d_6) of receptor 148.

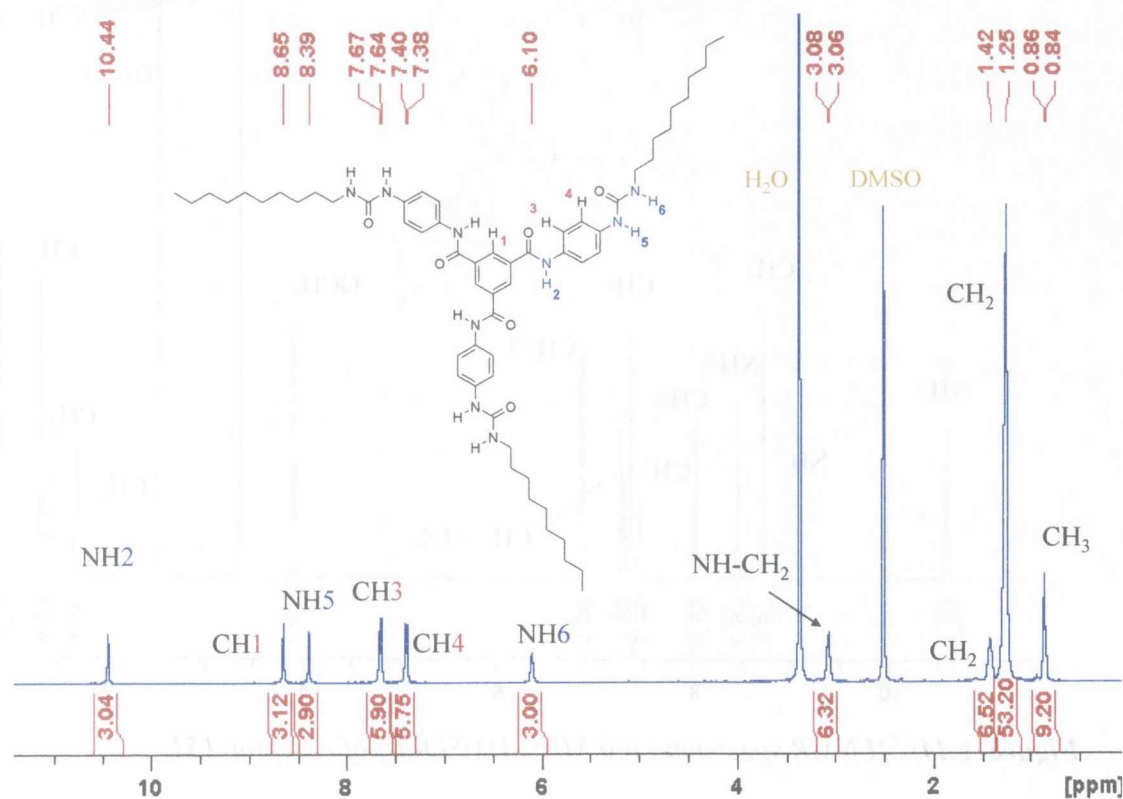


Figure A4.2: ^1H NMR spectrum (400 MHz, DMSO-d_6) of receptor 149.

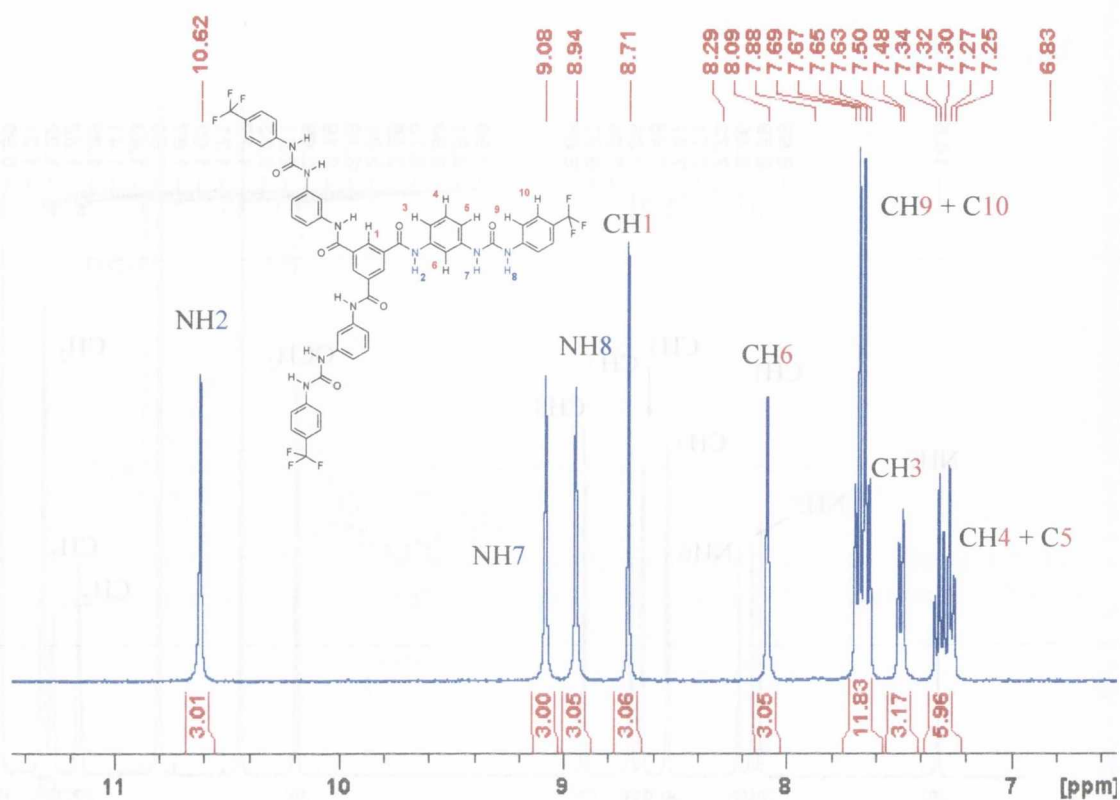


Figure A4.3: ^1H NMR spectrum (400 MHz, $\text{DMSO}-d_6$) of receptor 150.

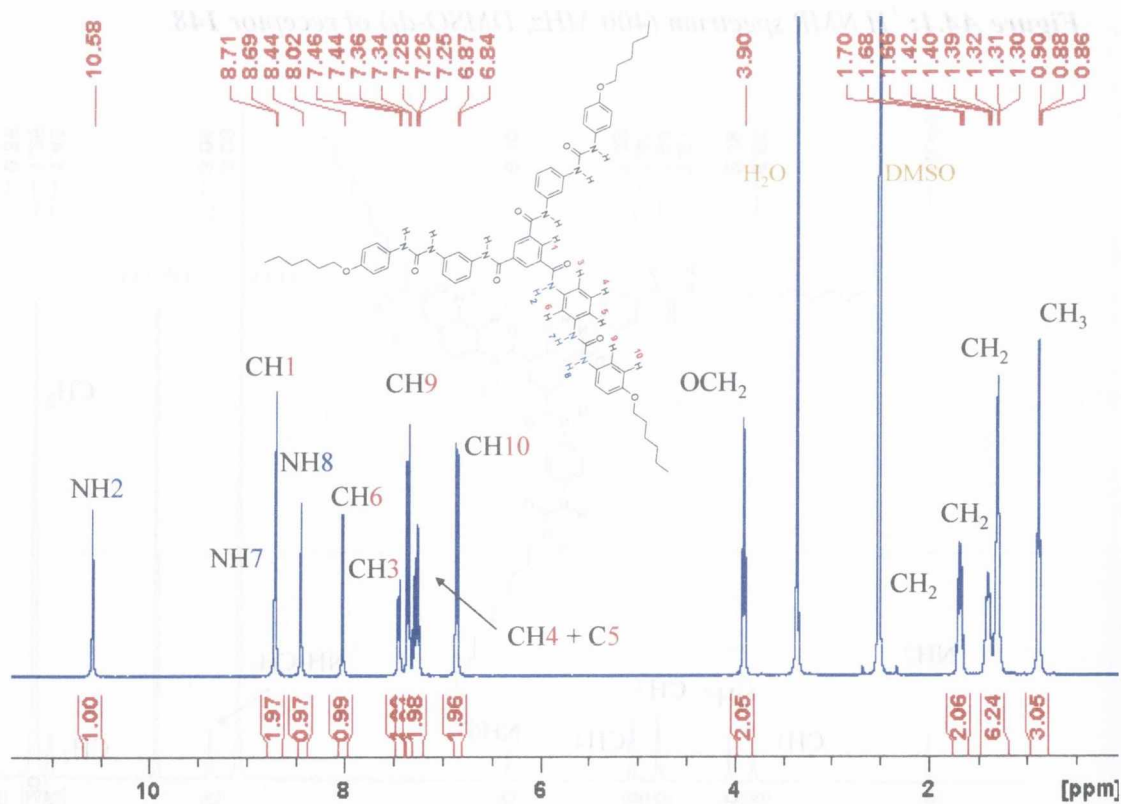


Figure A.44: ^1H NMR spectrum (400 MHz, $\text{DMSO}-d_6$) of receptor 151.

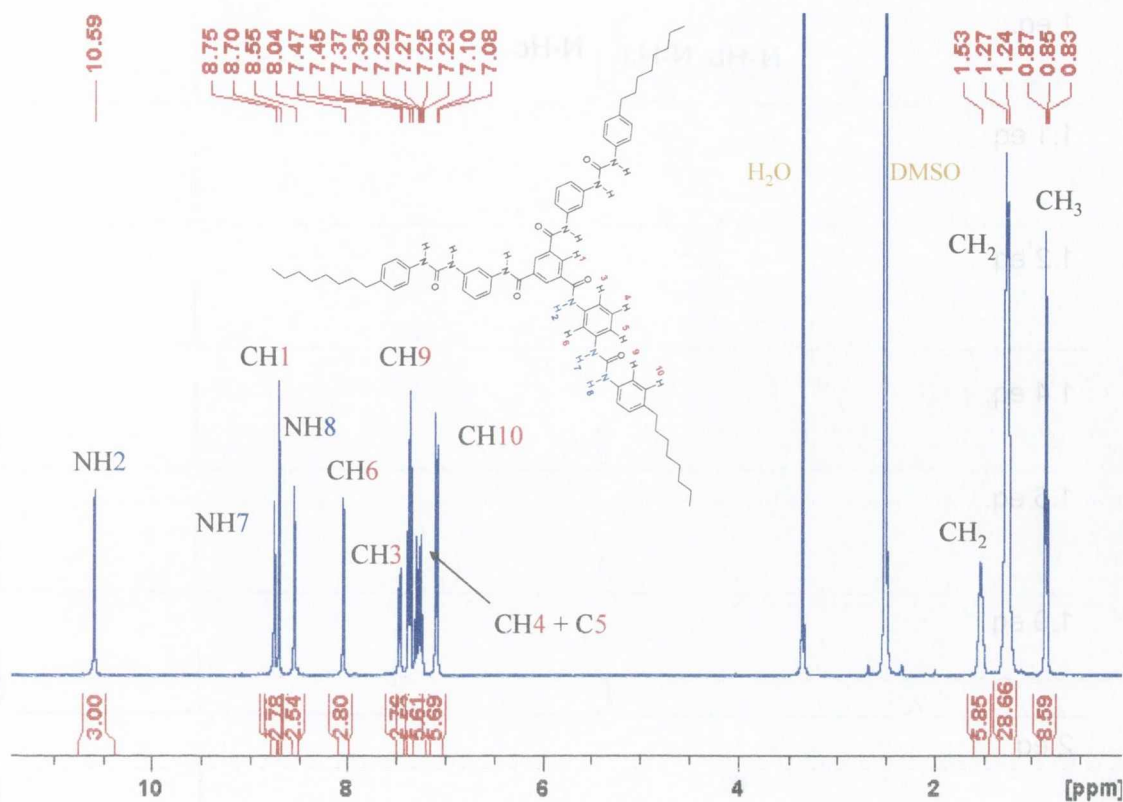


Figure A4.5: ^1H NMR spectrum (400 MHz, DMSO-d_6) of receptor 152.

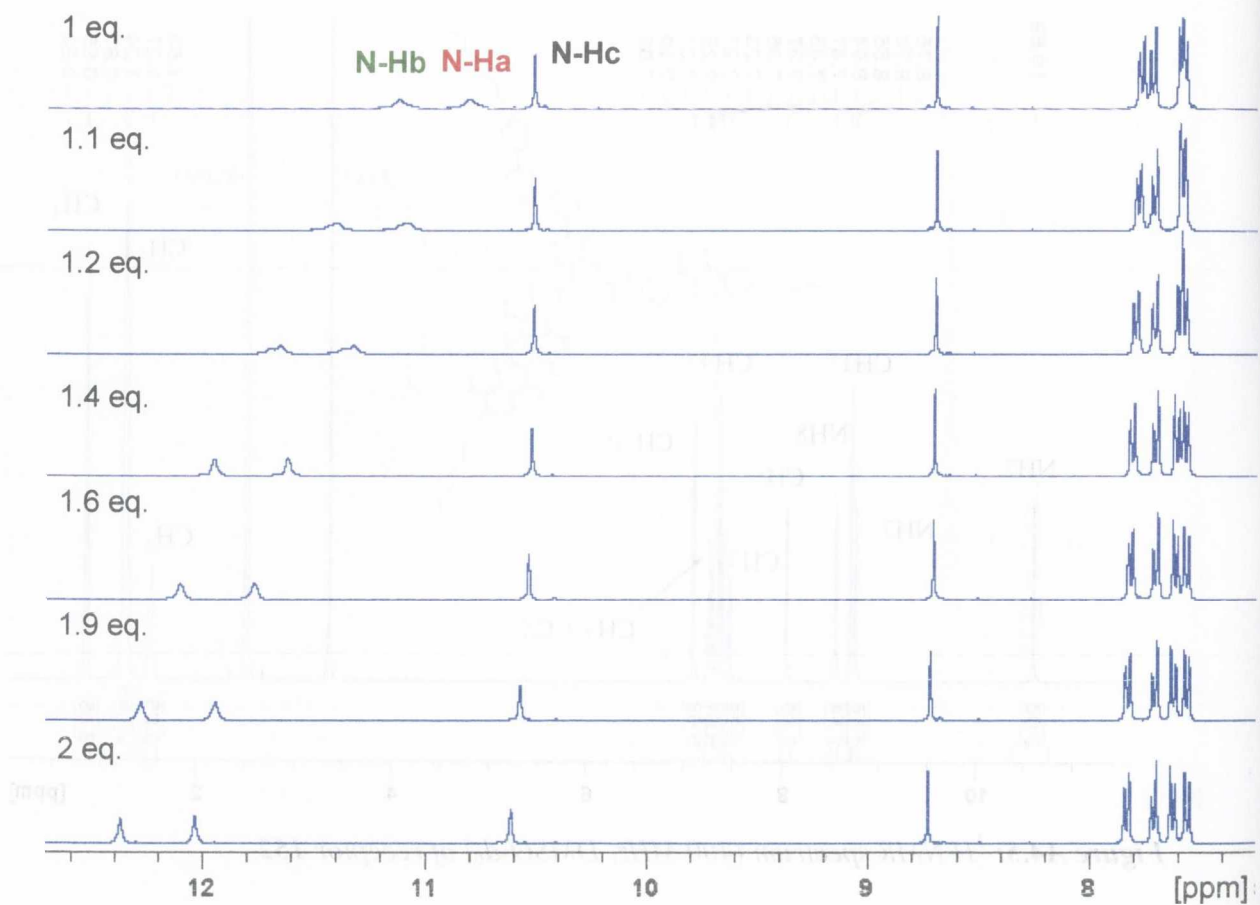


Figure A4.6: Stack plot of ^1H NMR spectra (400 MHz, DMSO-d_6) of **147** (7×10^{-3} M) upon addition of 1, 1.1, 1.2, 1.4, 1.6, 1.9 and 2 equivalents of AcO^- . N-Ha and N-Hb are the urea protons, while N-Hc is the amide proton.

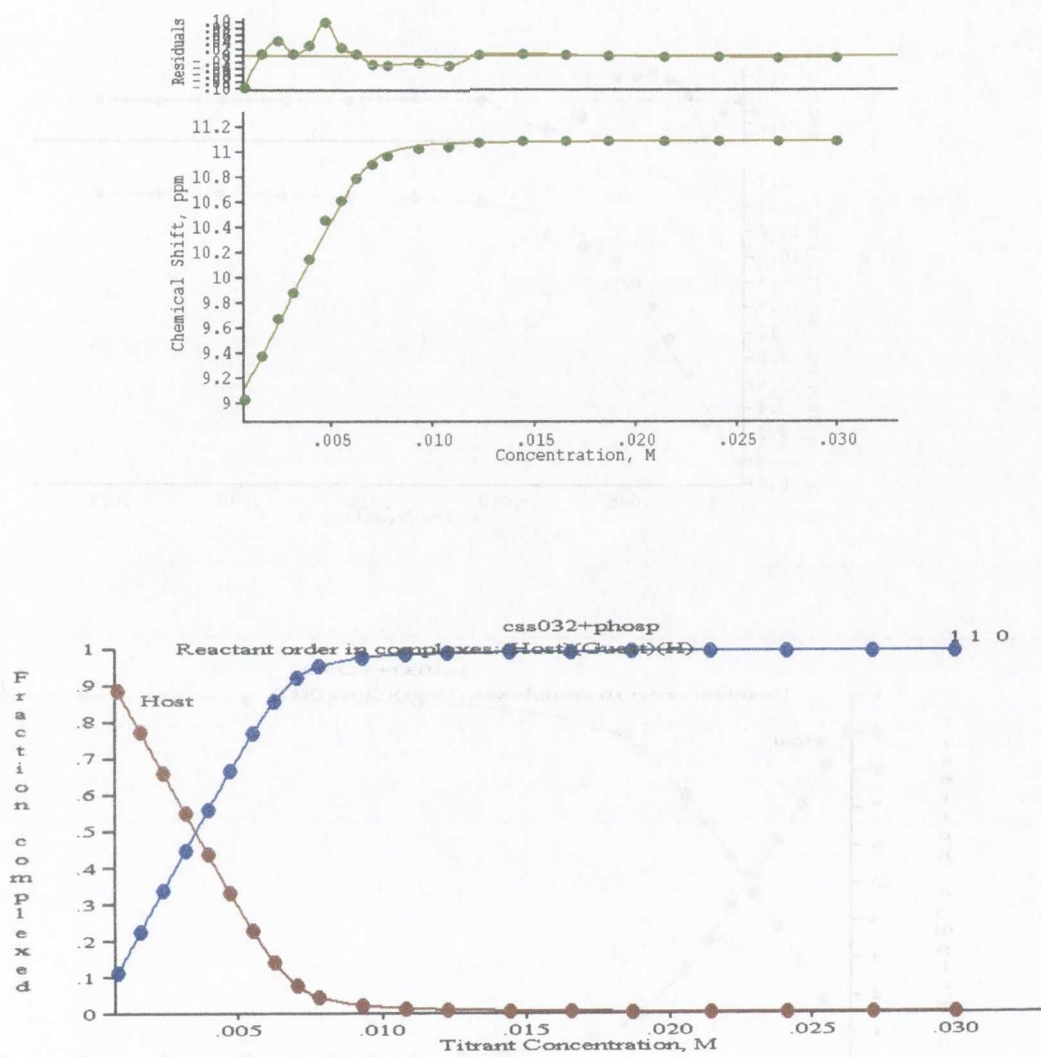


Figure A4.7: The experimental binding isotherms for the 1H NMR titration receptor **147** with $H_2PO_4^-$ in $DMSO-d_6$ and the corresponding fit using Win-Eq NMR.

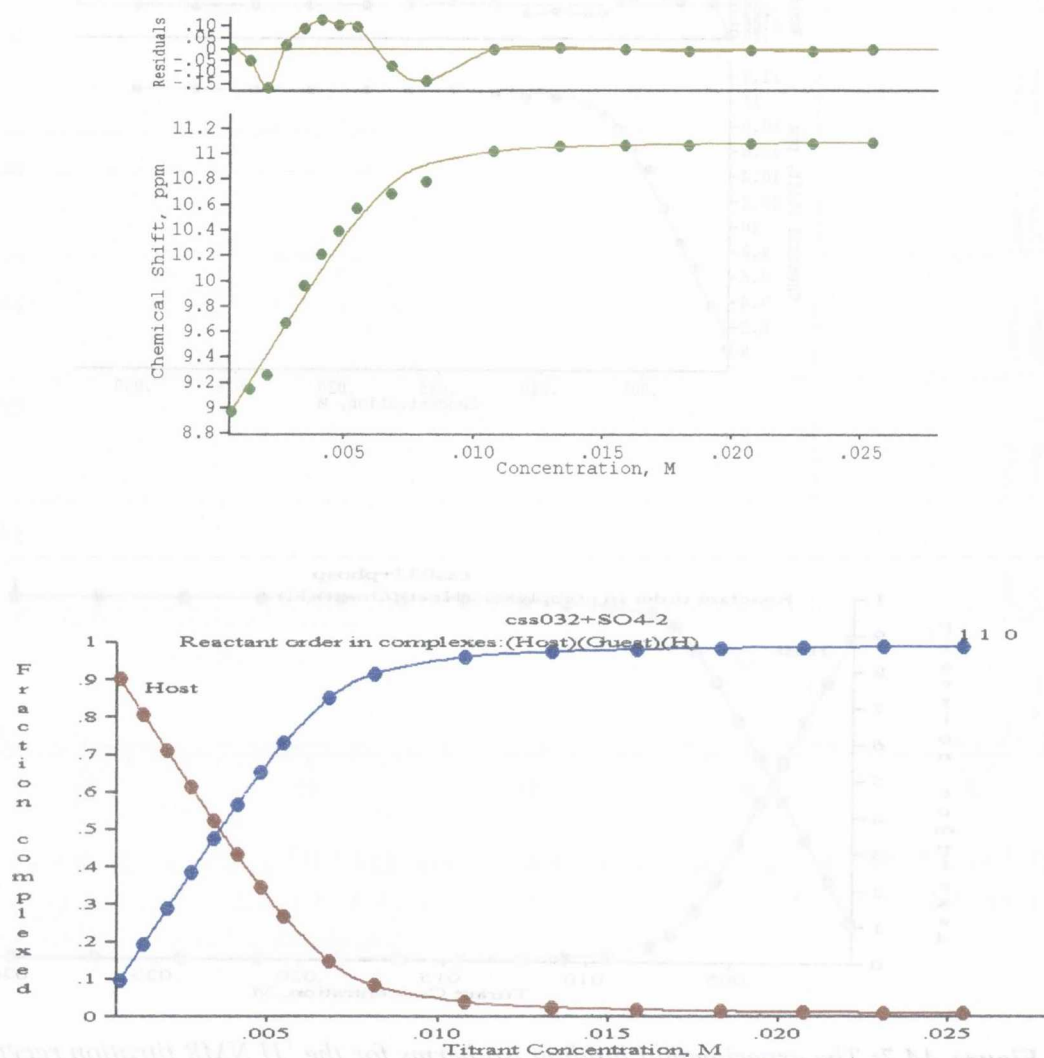


Figure A4.8: The experimental binding isotherms for the ^1H NMR titration receptor **147** with SO_4^{2-} in DMSO-d_6 and the corresponding fit using Win-Eq NMR.

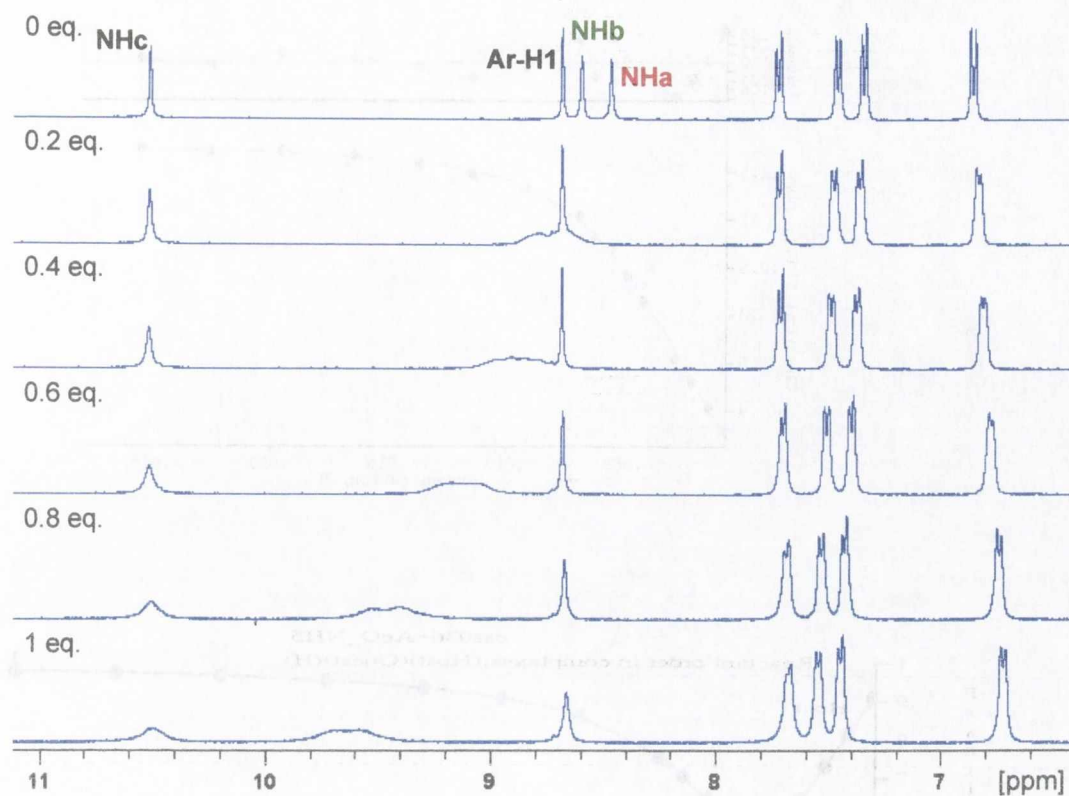


Figure A4.9: Stack plot of ^1H NMR spectra (400 MHz, $\text{DMSO}-d_6$) of **148** (7×10^{-3} M) upon addition of 0.2, 0.4, 0.6, 0.8, and 1 equivalents of SO_4^{2-} . *N-Ha* and *N-Hb* are the urea protons, while *N-Hc* is the amide proton.

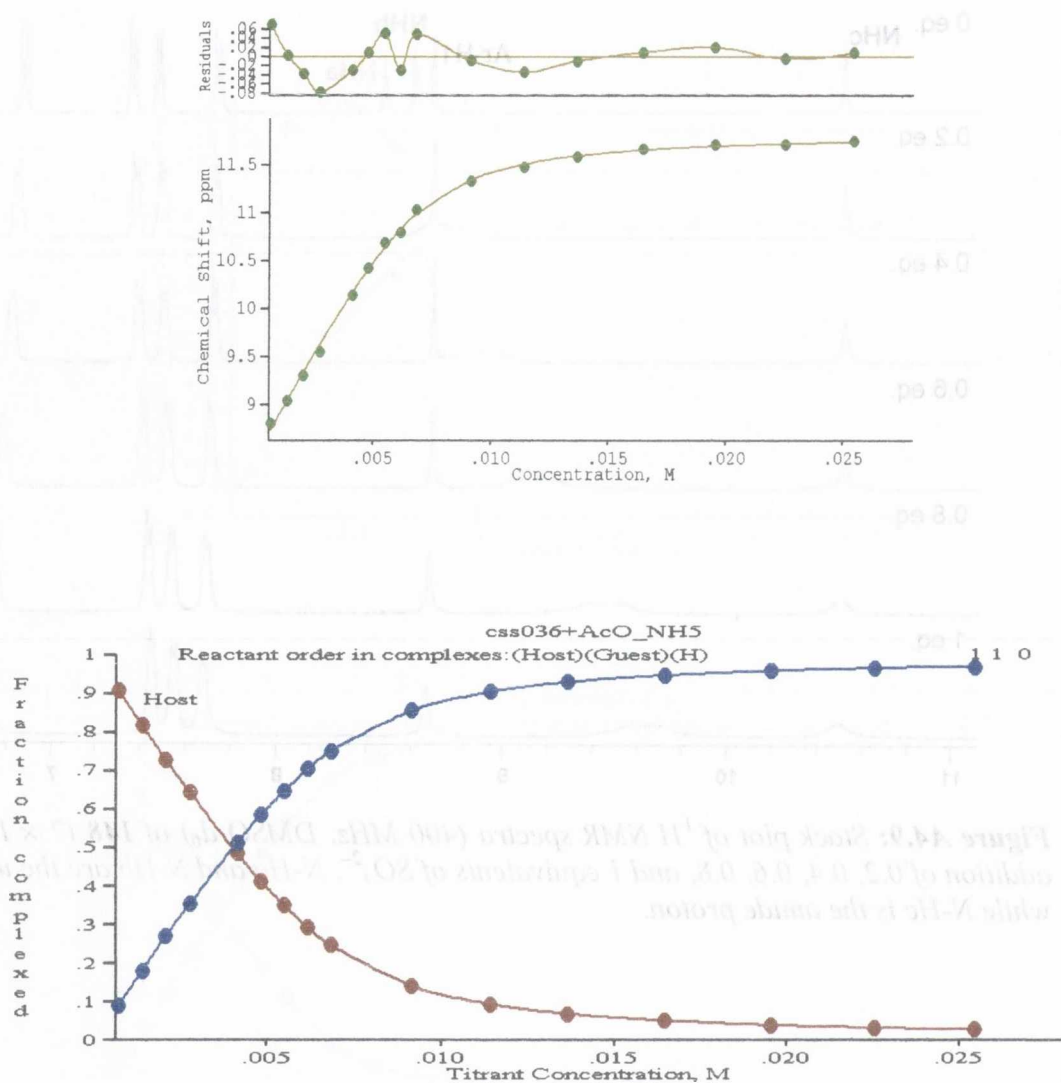


Figure A4.10: The experimental binding isotherms for the ^1H NMR titration receptor **148** with AcO^- in DMSO-d_6 and the corresponding fit using Win-Eq NMR.

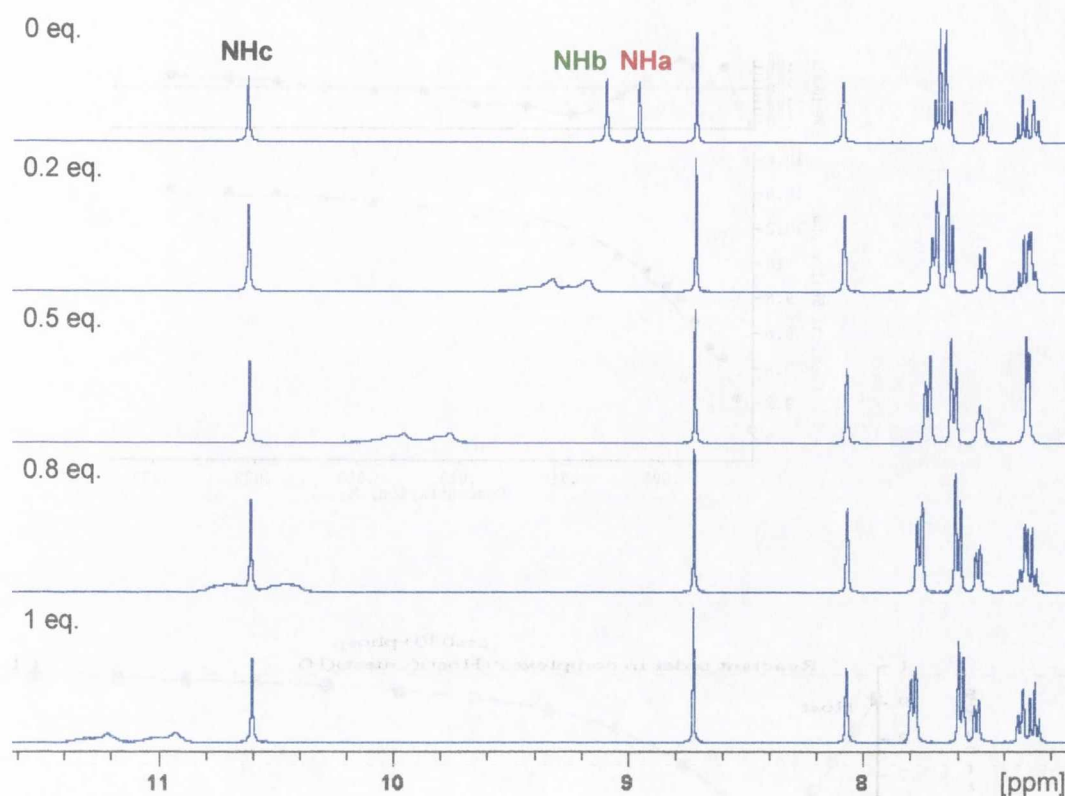


Figure A4.11: Stack plot of ^1H NMR spectra (400 MHz, $\text{DMSO-}d_6$) of **150** (7×10^{-3} M) upon addition of 0.2, 0.5, 0.8, and 1 equivalents of AcO^- . *N-Ha* and *N-Hb* are the urea protons, while *N-Hc* is the amide proton.

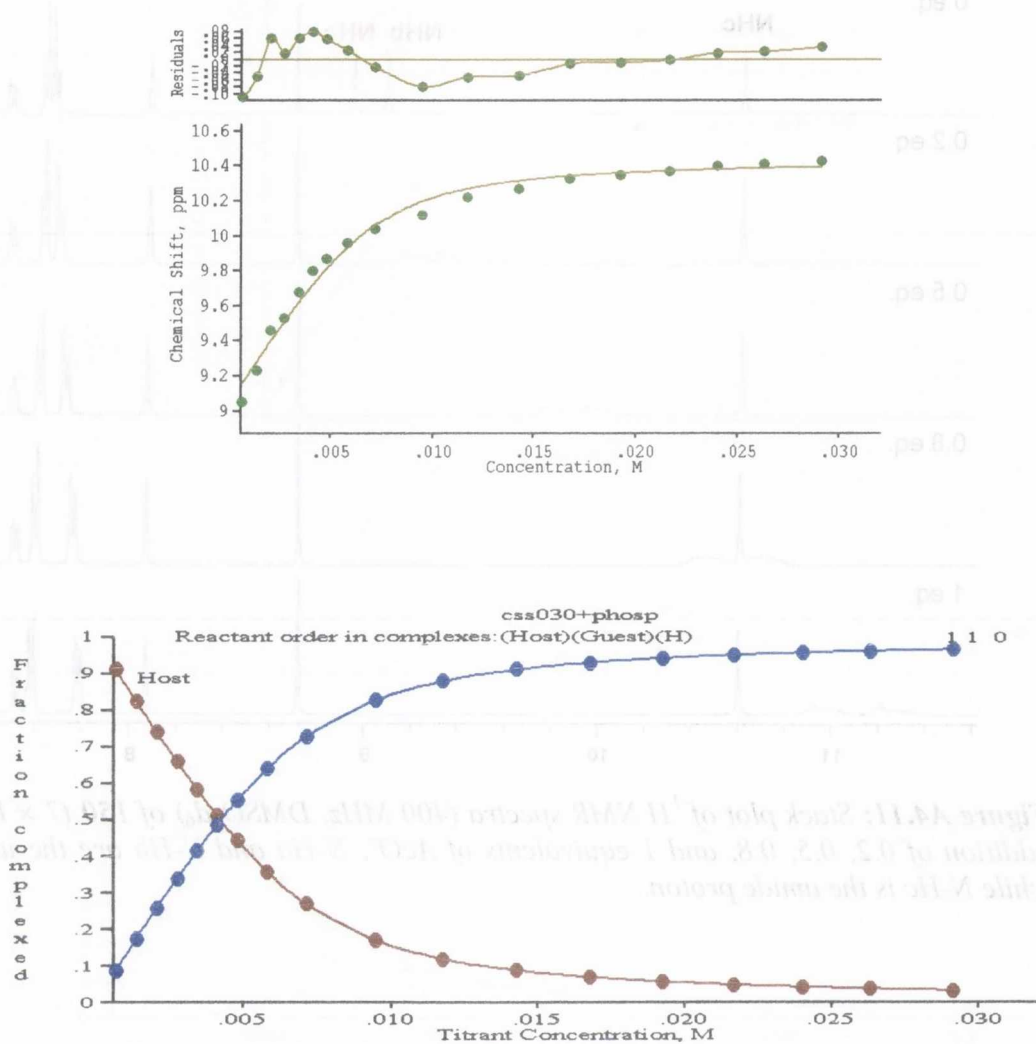


Figure A4.12: The experimental binding isotherms for the ^1H NMR titration receptor **150** with H_2PO_4^- in $\text{DMSO}-d_6$ and the corresponding fit using Win-Eq NMR.

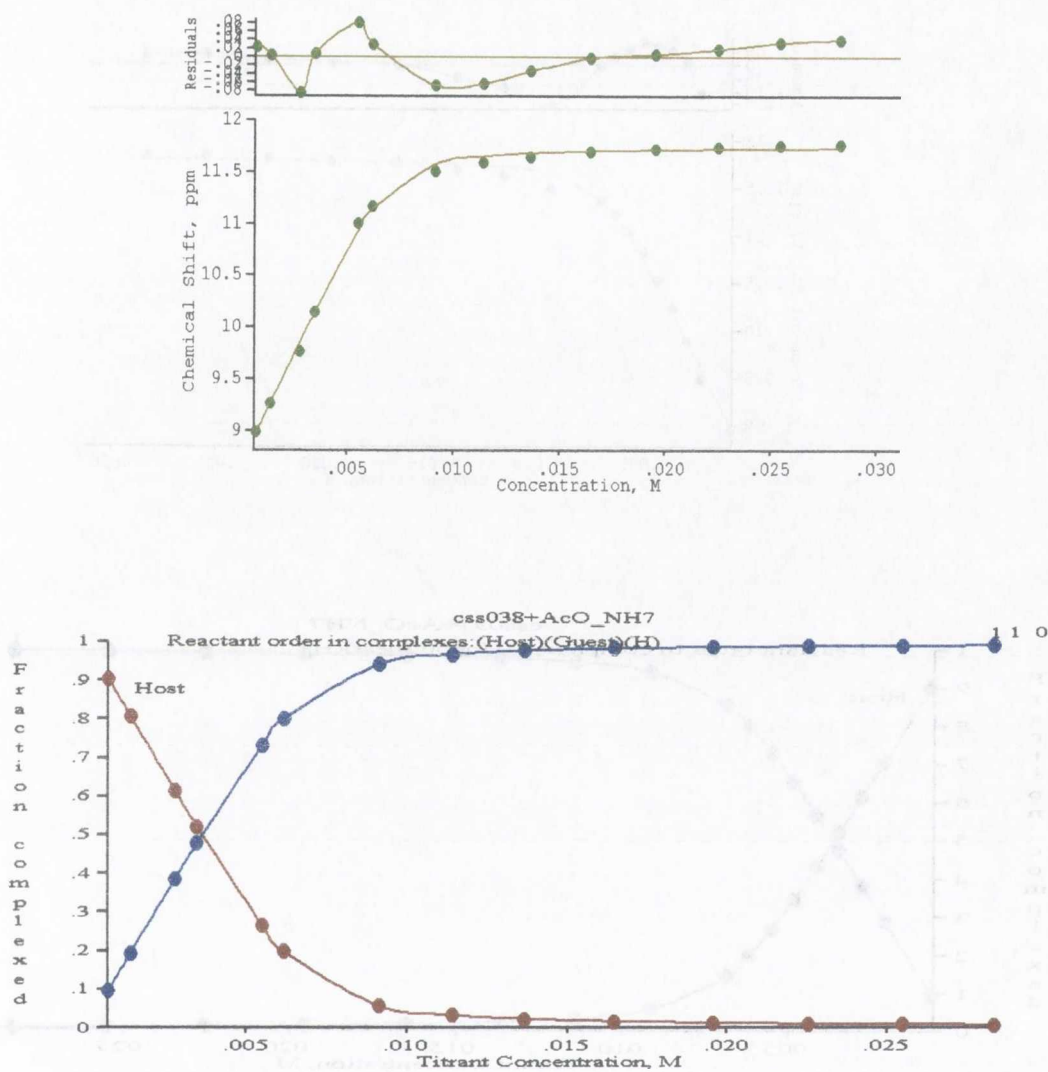


Figure A4.13: The experimental binding isotherms for the ^1H NMR titration receptor 151 with AcO^- in DMSO-d_6 and the corresponding fit using Win-Eq NMR.

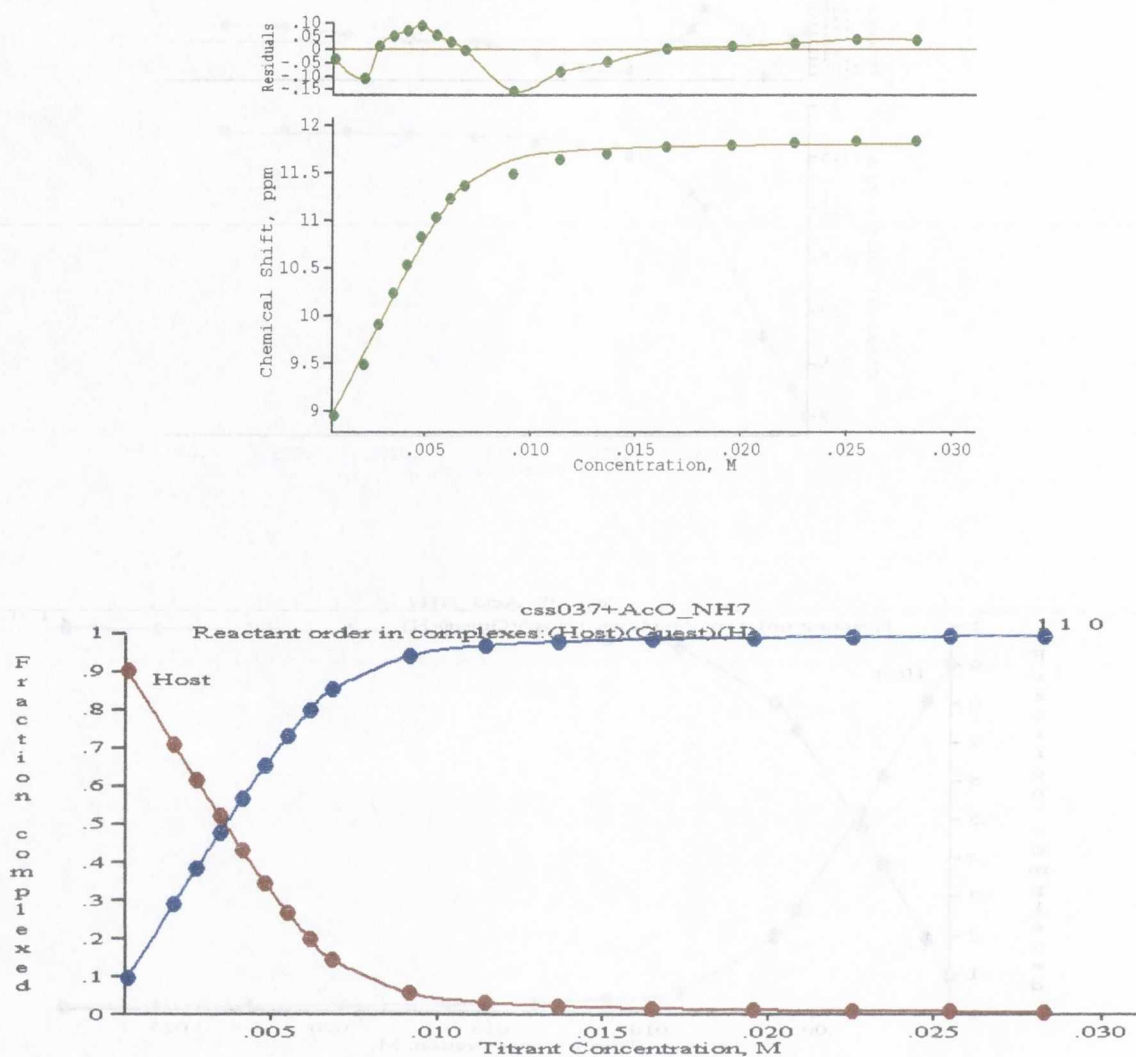


Figure A4.14: The experimental binding isotherms for the ^1H NMR titration receptor 152 with AcO^- in DMSO-d_6 and the corresponding fit using Win-Eq NMR.

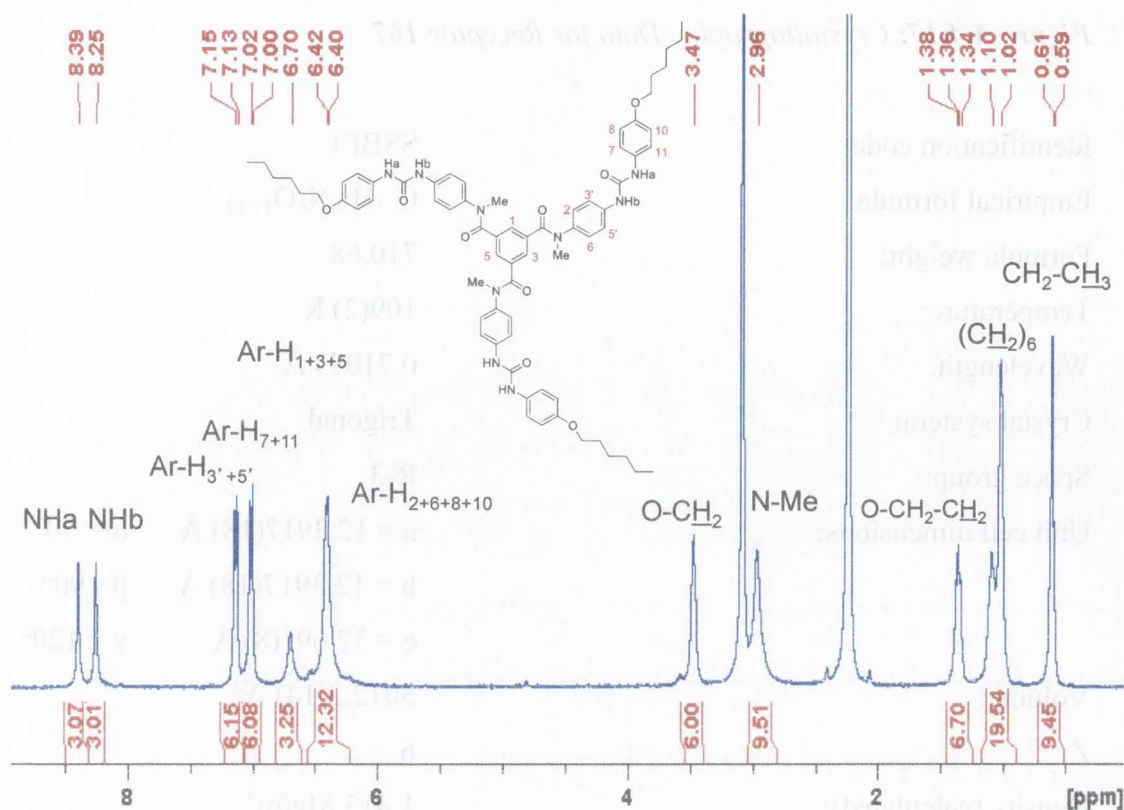


Figure A4.15: ¹H NMR spectrum (400 MHz, DMSO-d₆) of receptor 163.

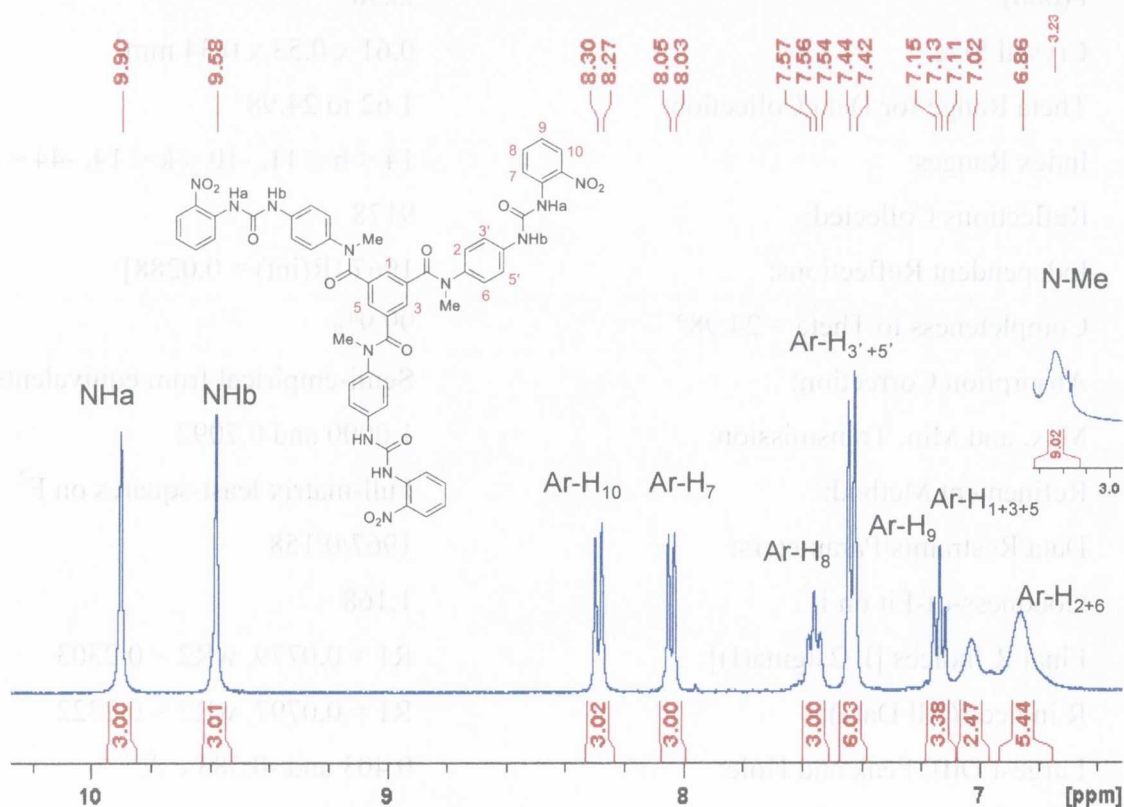


Figure A4.16: ¹H NMR spectrum (400 MHz, DMSO-d₆) of receptor 164.

Figure A.4.17: Crystallographic Data for Receptor 167.

Identification code:	SSBF1
Empirical formula:	$C_{33}H_{36}N_6O_{12.13}$
Formula weight:	710.68
Temperature:	109(2) K
Wavelength:	0.71073 Å
Crystal system:	Trigonal
Space group:	R-3
Unit cell dimensions:	$a = 12.3917(18) \text{ Å} \quad \alpha = 90^\circ$ $b = 12.3917(18) \text{ Å} \quad \beta = 90^\circ$ $c = 37.691(8) \text{ Å} \quad \gamma = 120^\circ$
Volume:	$5012.2(14) \text{ Å}^3$
Z:	6
Density (calculated):	1.413 Mg/m^3
Absorption Coefficient:	0.109 mm^{-1}
F(000):	2238
Crystal Size:	$0.61 \times 0.53 \times 0.34 \text{ mm}^3$
Theta Range for Data Collection:	$1.62 \text{ to } 24.98^\circ$
Index Ranges:	$14 < h < 11, -10 < k < 14, -44 < l < 32$
Reflections Collected:	9178
Independent Reflections:	1967 [R(int) = 0.0288]
Completeness to Theta = 24.98°	99.9%
Absorption Correction:	Semi-empirical from equivalents
Max. and Min. Transmission:	1.0000 and 0.7092
Refinement Method:	Full-matrix least-squares on F^2
Data/Restraints/Parameters:	1967/0/158
Goodness-of-Fit on F^2 :	1.168
Final R Indices [$I > 2\sigma(I)$]:	$R1 = 0.0779, wR2 = 0.2303$
R indices (All Data):	$R1 = 0.0797, wR2 = 0.2322$
Largest Diff. Peak and Hole:	$0.403 \text{ and } -0.583 \text{ e.Å}^{-3}$

Figure A4.18: Crystal data and structure refinement for 163.

Identification code	kp83	
Empirical formula	$C_{73}H_{93}N_9O_{11}S_2$	
Formula weight	1336.68	
Temperature	123(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	$a = 33.454(7)$ Å	$\alpha = 90^\circ$
	$b = 10.009(2)$ Å	$\beta = 95.31(3)^\circ$
	$c = 25.229(5)$ Å	$\gamma = 90^\circ$
Volume	$8412(3)$ Å ³	
Z	4	
Density (calculated)	1.055 Mg/m ³	
Absorption coefficient	0.119 mm ⁻¹	
F(000)	2856	
Crystal size	0.46 x 0.26 x 0.13 mm ³	
Theta range for data collection	1.62 to 25.00°	
Index ranges	-39 < h < 35, -9 < k < 11, -29 < l < 30	
Reflections collected	54086	
Independent reflections	14109 [R(int) = 0.0292]	
Completeness to theta = 25.00°	95.3%	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.0000 and 0.7714	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	14109/0/872	
Goodness-of-fit on F ²	1.072	
Final R indices [I > 2sigma(I)]	R1 = 0.0569, wR2 = 0.1486	
R indices (all data)	R1 = 0.0663, wR2 = 0.1545	
Largest diff. peak and hole	0.342 and -0.345 e.Å ⁻³	

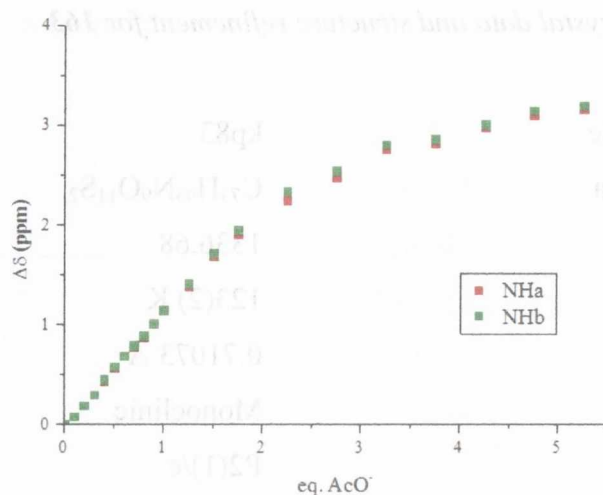


Figure A4.19: Changes in the urea resonances of **162** (as $\Delta\delta$) upon titration with AcO^- .

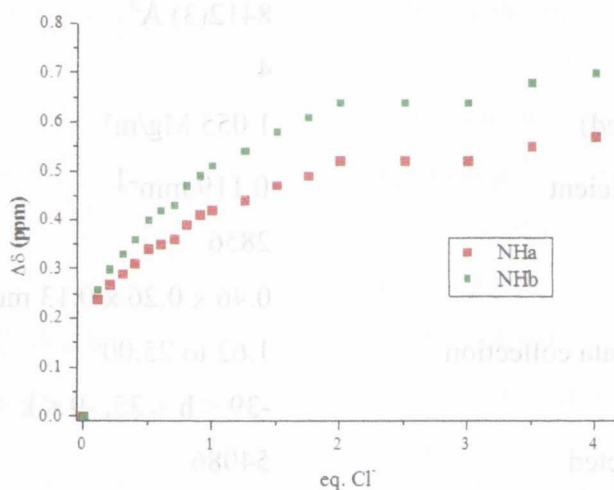


Figure A4.20: Changes in the urea resonances of **163** (as $\Delta\delta$) upon titration with Cl^- .

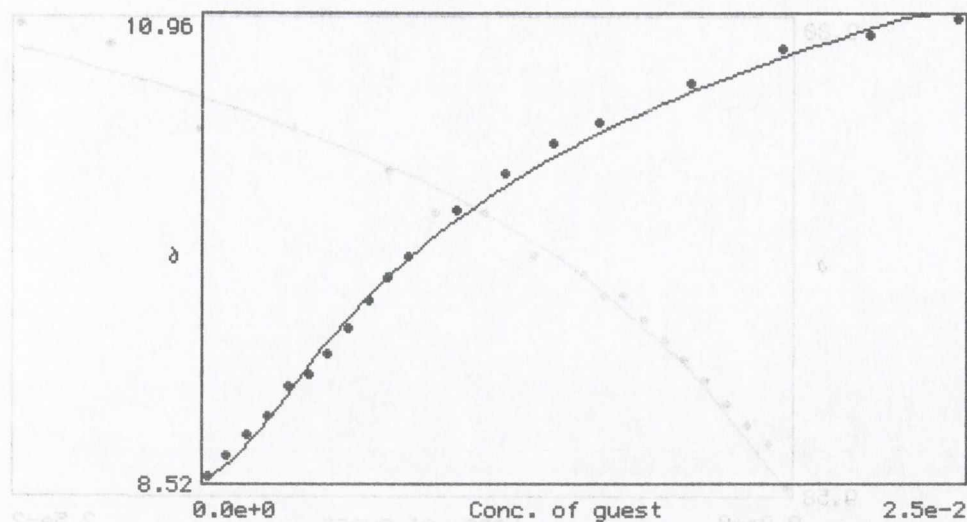


Figure A4.21: The binding isotherm and fit obtained for **163** upon fitting the changes in the chemical shift of the urea protons to a 2:1 (host:guest) complexation model upon titration of AcO^- .

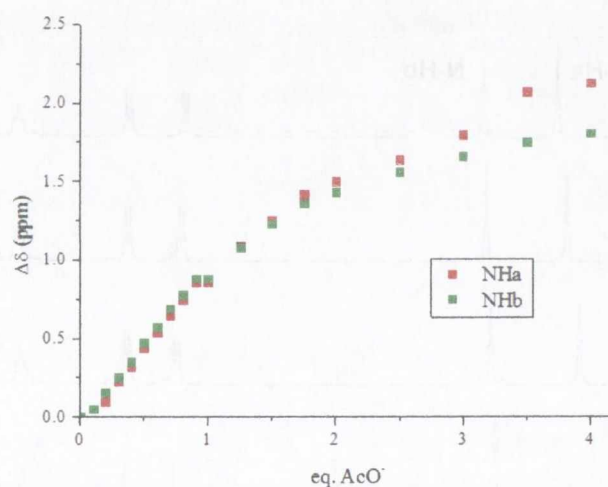


Figure A4.22: Changes in the urea resonances of **164** (as $\Delta\delta$) upon titration with AcO^- .

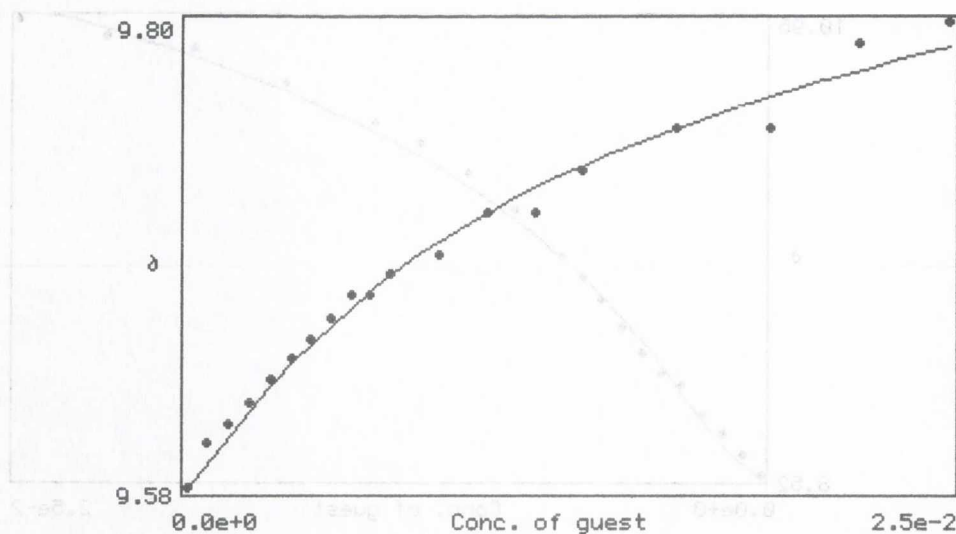


Figure A4.23: The binding isotherm and fit obtained for **164** upon fitting the changes in the chemical shift of the urea protons to a 2:1 (host:guest) complexation model upon titration of SO_4^{2-} .

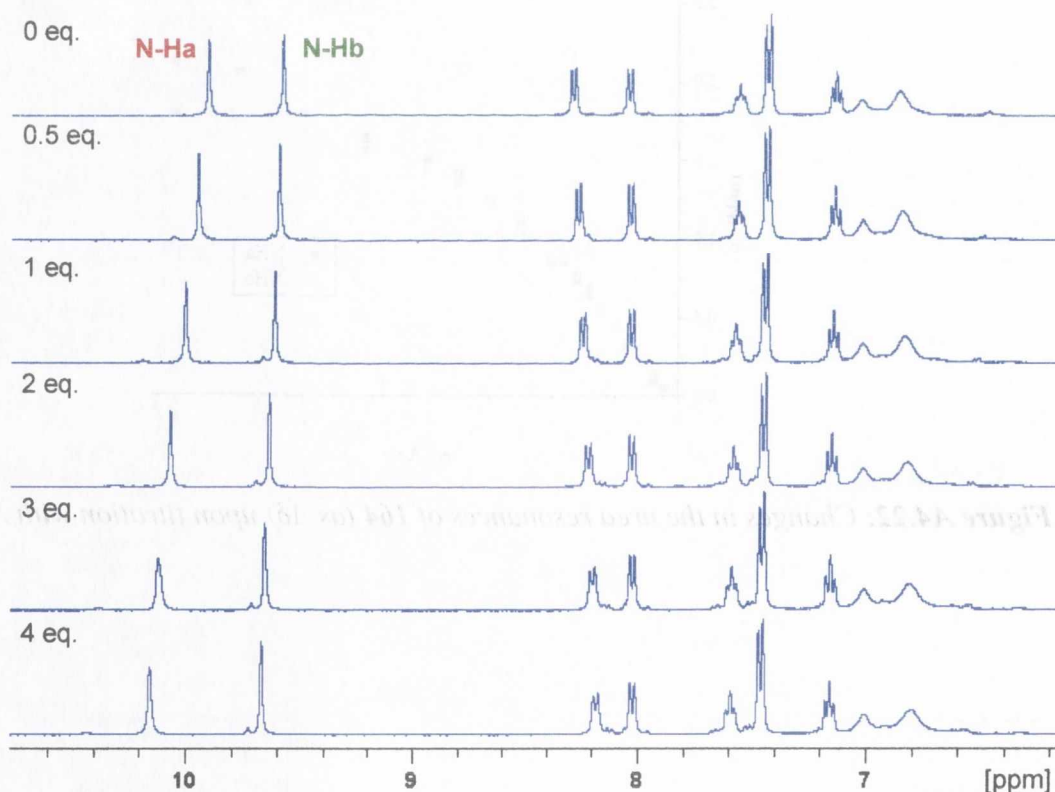


Figure A4.24: Stack plot of ^1H NMR spectra (400 MHz, DMSO-d_6) of **164** (ca. 7×10^{-3} M) upon addition of 0.5, 1, 2, 3 and 4 equivalents of CT. N-Ha and N-Hb are the urea protons.

Appendix 5:

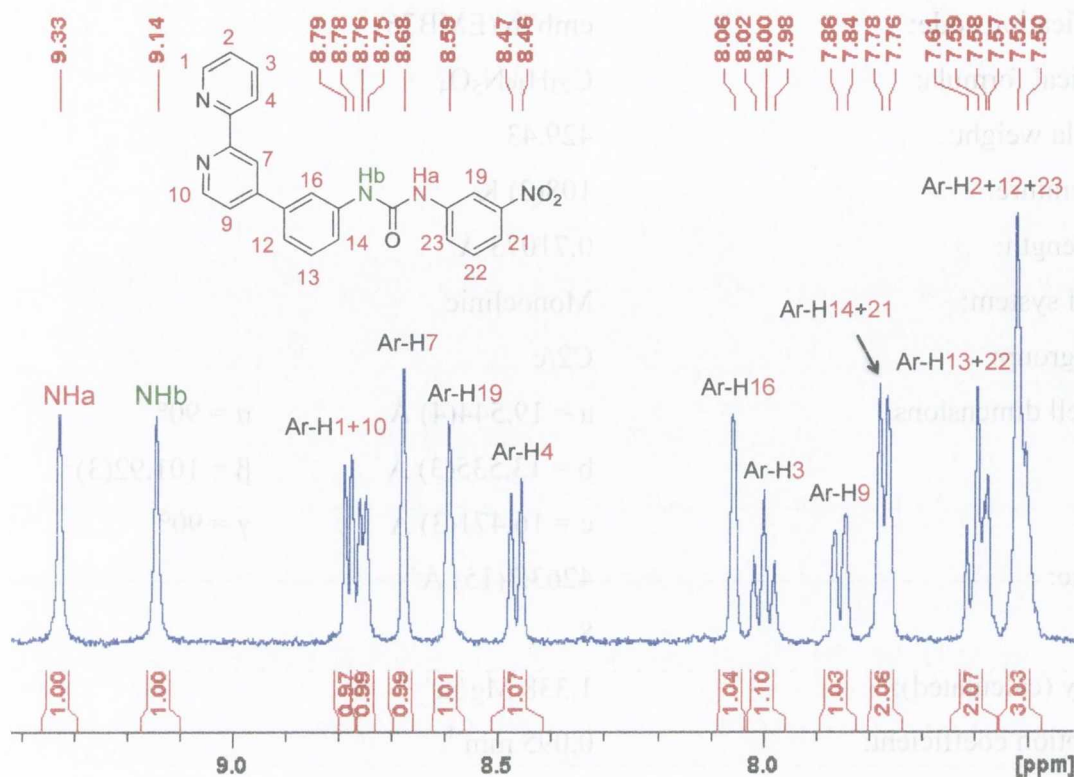
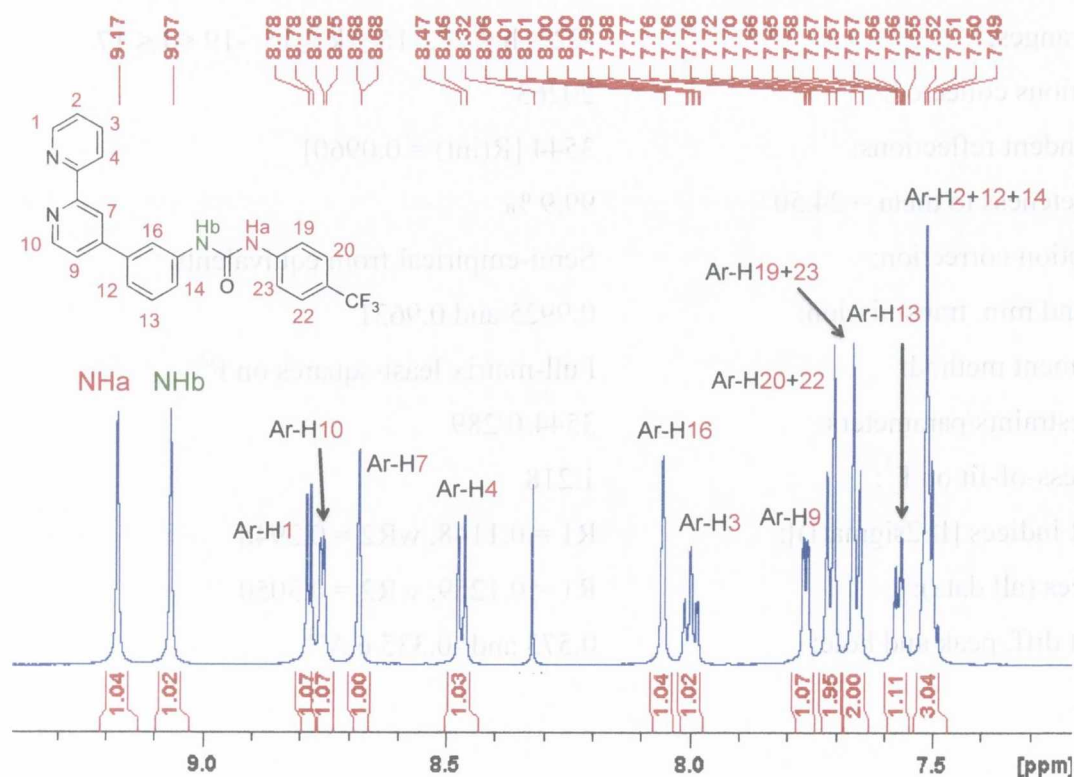
Figure A5.1: ^1H NMR spectrum (600 MHz, DMSO-d_6) of **190**.Figure A5.2: ^1H NMR spectrum (600 MHz, DMSO-d_6) of **192**.

Figure A5.3: Crystal data and structure refinement for 189.

Identification code:	emb7b (EMB76)
Empirical formula:	C ₂₃ H ₁₉ N ₅ O ₄
Formula weight:	429.43
Temperature:	108(2) K
Wavelength:	0.71073 Å
Crystal system:	Monoclinic
Space group:	C2/c
Unit cell dimensions	a = 19.544(4) Å α = 90° b = 13.535(3) Å β = 101.92(3)° c = 16.471(3) Å γ = 90°
Volume:	4263.3(15) Å ³
Z:	8
Density (calculated):	1.338 Mg/m ³
Absorption coefficient:	0.095 mm ⁻¹
F(000):	1792
Crystal size:	0.40 x 0.13 x 0.08 mm ³
Theta range for data collection:	2.36 to 24.50°.
Index ranges:	-22 ≤ h ≤ 22, -15 ≤ k ≤ 15, -19 ≤ l ≤ 17
Reflections collected:	20263
Independent reflections:	3544 [R(int) = 0.0960]
Completeness to theta = 24.50°	99.9 %
Absorption correction:	Semi-empirical from equivalents
Max. and min. transmission:	0.9925 and 0.9631
Refinement method:	Full-matrix least-squares on F ²
Data/restraints/parameters:	3544/0/289
Goodness-of-fit on F ² :	1.218
Final R indices [I > 2sigma(I)]:	R1 = 0.1148, wR2 = 0.2948
R indices (all data):	R1 = 0.1259, wR2 = 0.3050
Largest diff. peak and hole:	0.573 and -0.335 e.Å ⁻³

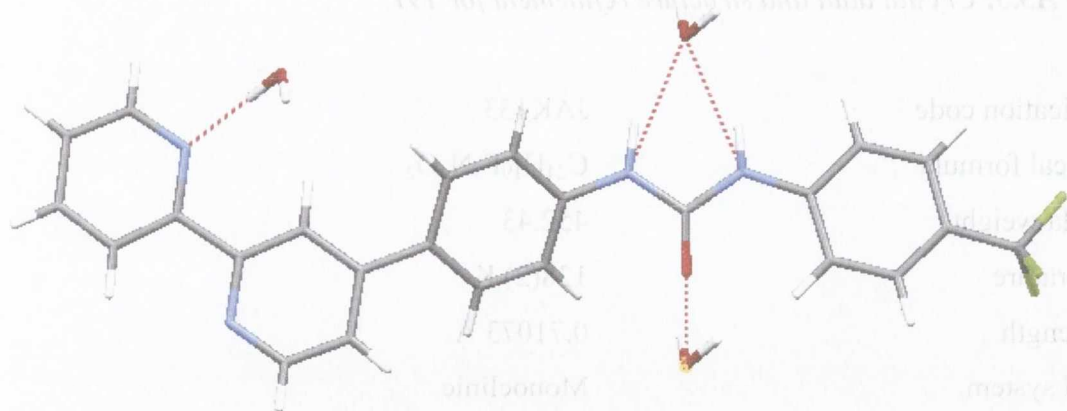


Figure A5.4: The X-ray crystal structure of ligand 191.

Figure A5.5: *Crystal data and structure refinement for 191.*

Identification code	JAK133
Empirical formula	C ₂₄ H ₁₉ F ₃ N ₄ O ₂
Formula weight	452.43
Temperature	128(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	P2(1)/c
Unit cell dimensions	a = 22.640(5) Å α = 90° b = 13.625(3) Å β = 97.26(3)° c = 6.8307(14) Å γ = 90°
Volume	2090.2(7) Å ³
Z	4
Density (calculated)	1.438 Mg/m ³
Absorption coefficient	0.112 mm ⁻¹
F(000)	936
Crystal size	0.40 x 0.40 x 0.05 mm ³
Theta range for data collection	0.91 to 24.00°.
Index ranges	-25 ≤ h ≤ 25, -15 ≤ k ≤ 15, -7 ≤ l ≤ 7
Reflections collected	15065
Independent reflections	3239 [R(int) = 0.0488]
Completeness to theta = 24.00°	99.0 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	1.0000 and 0.5720
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	3239/0/298
Goodness-of-fit on F ²	1.590
Final R indices [I>2sigma(I)]	R1 = 0.0909, wR2 = 0.3088
R indices (all data)	R1 = 0.1137, wR2 = 0.3591
Largest diff. peak and hole	0.770 and -0.576 e.Å ⁻³

Figure A5.6: Crystal data and structure refinement for 192.

Identification code	JAK153	
Empirical formula	C ₄₅ H ₃₃ F ₁₂ N ₁₀ O ₃ P ₂ Ru	
Formula weight	1152.82	
Temperature	108(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 9.793(2) Å	α = 82.70(3)°
	b = 11.327(2) Å	β = 89.85(3)°
	c = 24.609(5) Å	γ = 73.52(3)°
Volume	2594.8(9) Å ³	
Z	2	
Density (calculated)	1.475 Mg/m ³	
Absorption coefficient	0.455 mm ⁻¹	
F(000)	1158	
Crystal size	0.35 x 0.27 x 0.24 mm ³	
Theta range for data collection	0.83 to 24.00°	
Index ranges	-11 ≤ h ≤ 9, -12 ≤ k ≤ 12, -26 ≤ l ≤ 28	
Reflections collected	24989	
Independent reflections	7856 [R(int) = 0.0593]	
Completeness to theta = 24.00°	96.6 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.8992 and 0.8578	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	7856 / 383 / 667	
Goodness-of-fit on F ²	1.857	
Final R indices [I > 2sigma(I)]	R1 = 0.1558, wR2 = 0.4118	
R indices (all data)	R1 = 0.1929, wR2 = 0.4589	
Largest diff. peak and hole	1.740 and -1.393 e.Å ⁻³	



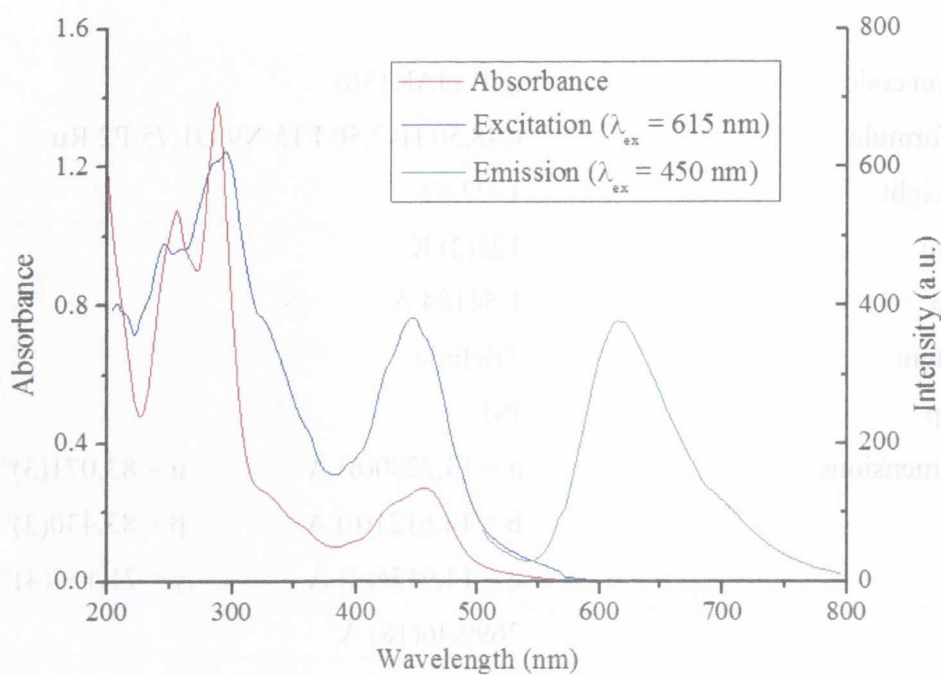
Figure A5.10: Crystal data and structure refinement for 172.

Identification code	squeezed (JAK134)	
Empirical formula	$C_{48}H_{39}F_3N_{11}O_4Ru$	
Formula weight	991.97	
Temperature	108(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	$a = 14.838(3)$	$\alpha = 90^\circ$
	$b = 32.275(7)$	$\beta = 104.87(3)^\circ$
	$c = 10.968(2)$	$\gamma = 90^\circ$
Volume	$5076.4(18) \text{ Å}^3$	
Z	4	
Density (calculated)	1.298 Mg/m^3	
Absorption coefficient	0.372 mm^{-1}	
F(000)	2028	
Crystal size	$0.39 \times 0.24 \times 0.19 \text{ mm}^3$	
Theta range for data collection	1.26 to 25.00° .	
Index ranges	$-17 \leq h \leq 17, -38 \leq k \leq 38, -12 \leq l \leq 10$	
Reflections collected	34461	
Independent reflections	8539 [R(int) = 0.0418]	
Completeness to $\theta = 25.00^\circ$	95.6 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9276 and 0.8591	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	8539 / 0 / 606	
Goodness-of-fit on F^2	1.278	
Final R indices [I>2sigma(I)]	$R1 = 0.0863, wR2 = 0.2739$	
R indices (all data)	$R1 = 0.0966, wR2 = 0.2929$	
Largest diff. peak and hole	1.151 and -1.766 e.Å^{-3}	

Figure A5.11: Crystal data and structure refinement for 173.

Identification code	tg01 (JAK136)	
Empirical formula	C48.50 H42.50 F15 N9 O1.75 P2 Ru	
Formula weight	1227.42	
Temperature	123(2) K	
Wavelength	1.54184 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 13.2280(6) Å	$\alpha = 83.071(3)^\circ$
	b = 14.6121(6) Å	$\beta = 83.430(3)^\circ$
	c = 14.9136(4) Å	$\gamma = 71.157(4)^\circ$
Volume	2699.46(18) Å ³	
Z	2	
Density (calculated)	1.510 Mg/m ³	
Absorption coefficient	3.794 mm ⁻¹	
F(000)	1239	
Crystal size	0.21 x 0.12 x 0.10 mm ³	
Theta range for data collection	2.99 to 73.90°.	
Index ranges	-14 ≤ h ≤ 16, -18 ≤ k ≤ 18, -12 ≤ l ≤ 18	
Reflections collected	20961	
Independent reflections	10581 [R(int) = 0.0470]	
Completeness to theta = 73.90°	96.5 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	1.00000 and 0.70895	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	10581 / 0 / 736	
Goodness-of-fit on F ²	1.071	
Final R indices [I>2sigma(I)]	R1 = 0.0468, wR2 = 0.1350	
R indices (all data)	R1 = 0.0533, wR2 = 0.1413	
Largest diff. peak and hole	1.668 and -0.895 e.Å ⁻³	

(a)



(b)

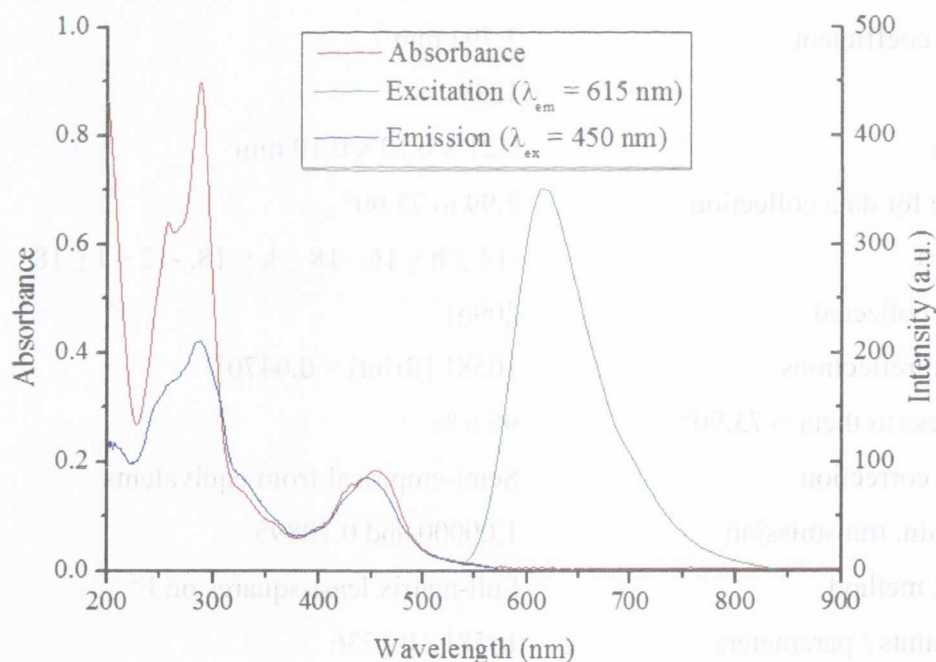


Figure A5.12: The UV-Vis, excitation and emission spectra of (a) 171 and (b) 173 in CH_3CN .

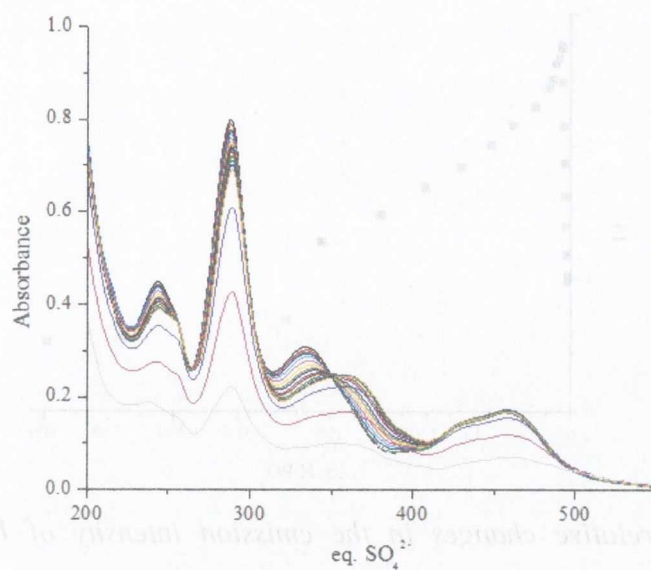


Figure A5.13: The changes observed in the absorption spectrum of **170** in CH_3CN upon titration with SO_4^{2-} (before precipitation of the complex occurred).

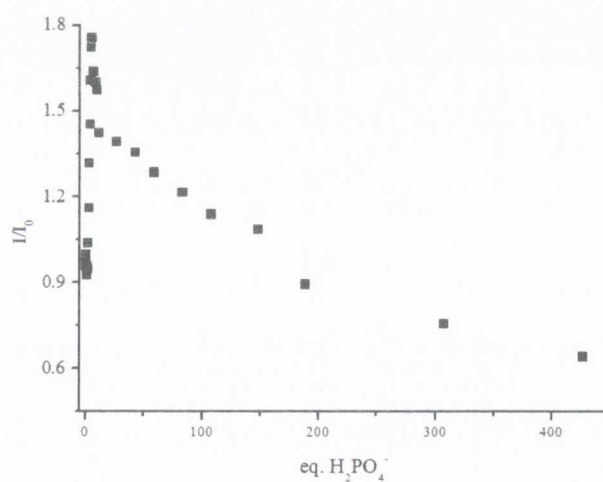


Figure A5.14: The relative changes in the emission intensity of **171** as a function of equivalents of H_2PO_4^- .

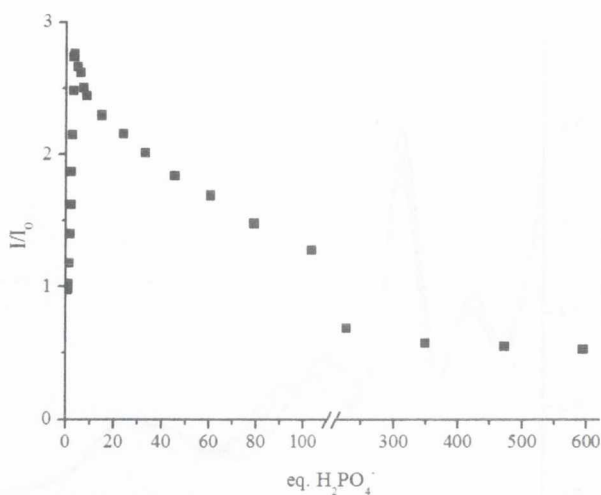


Figure A5.15: The relative changes in the emission intensity of 173 as a function of equivalents of H_2PO_4^- .



Figure A5.16: The relative changes in the emission intensity of 171 as a function of equivalents of H_2PO_4^- .

Appendix 6:

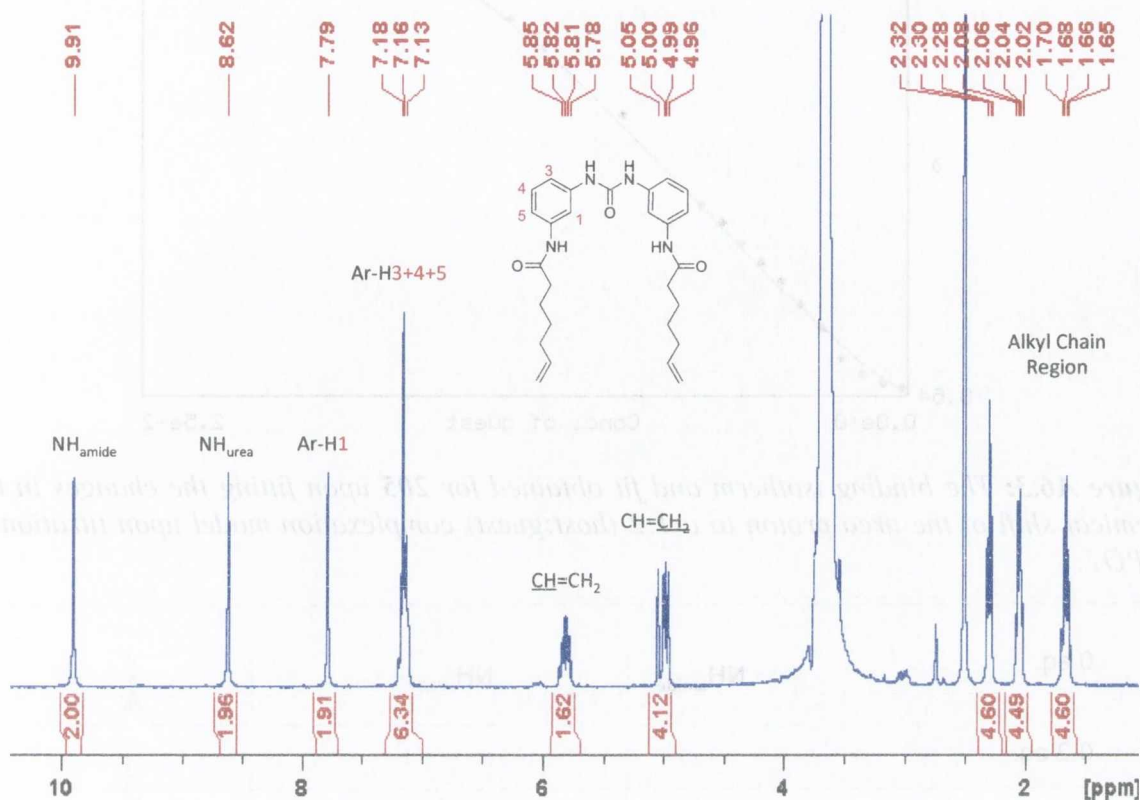


Figure A6.1: ^1H NMR spectrum (400 MHz, DMSO-d_6) of **208**.

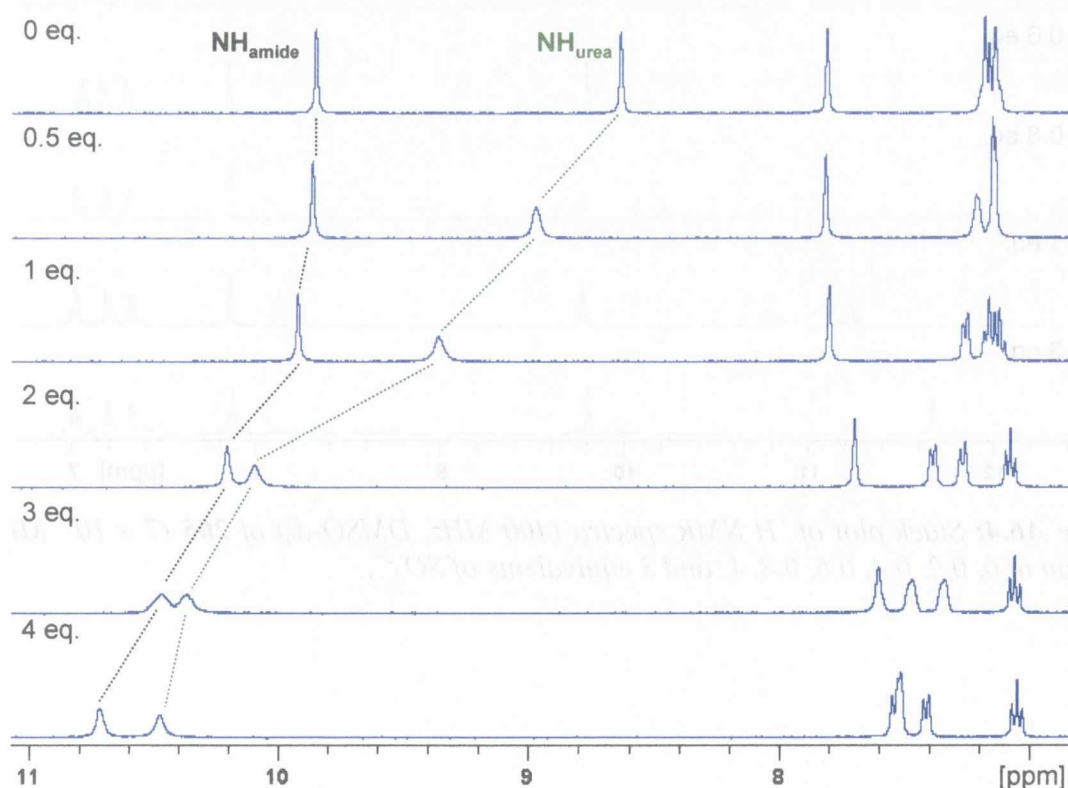


Figure A6.2: Stack plot of ^1H NMR spectra (400 MHz, DMSO-d_6) of **205** ($7 \times 10^{-3} \text{ M}$) upon addition of 0, 0.5, 1, 2, 3, and 4 equivalents of H_2PO_4^- .

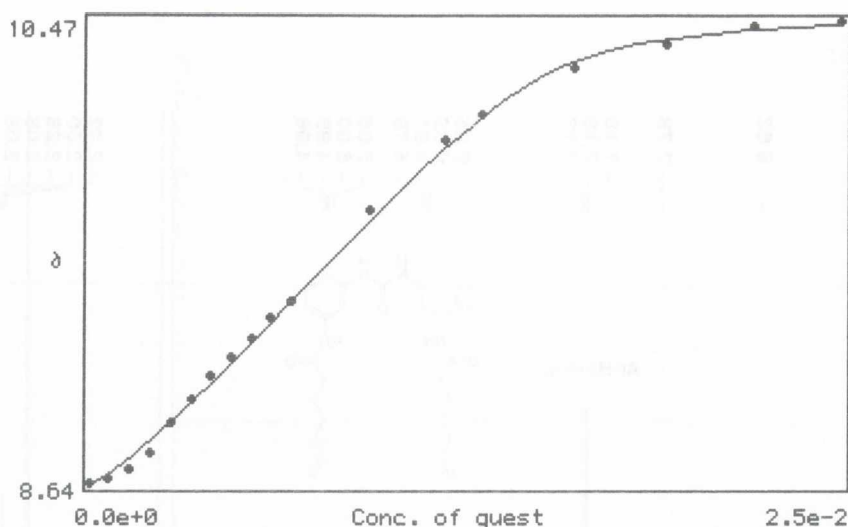


Figure A6.3: The binding isotherm and fit obtained for **205** upon fitting the changes in the chemical shift of the urea proton to a 1:2 (host:guest) complexation model upon titration of H_2PO_4^- .

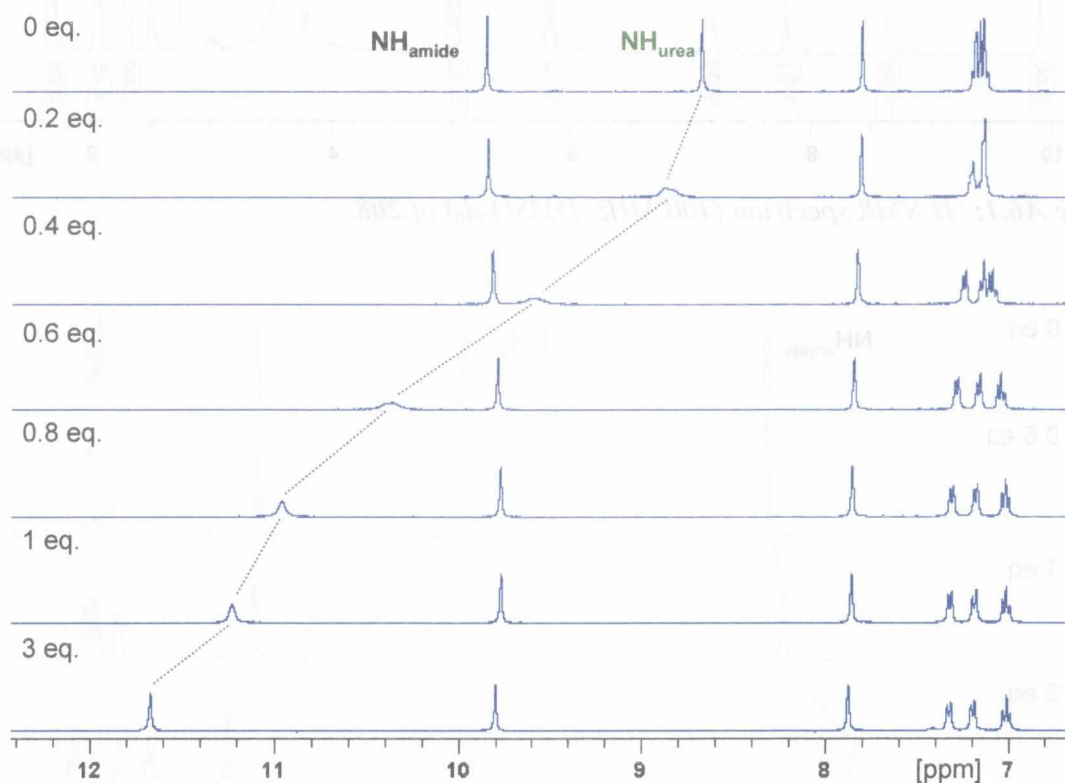


Figure A6.4: Stack plot of ^1H NMR spectra (400 MHz, $\text{DMSO}-d_6$) of **205** (7×10^{-3} M) upon addition of 0, 0.2, 0.4, 0.6, 0.8, 1, and 3 equivalents of SO_4^{2-} .

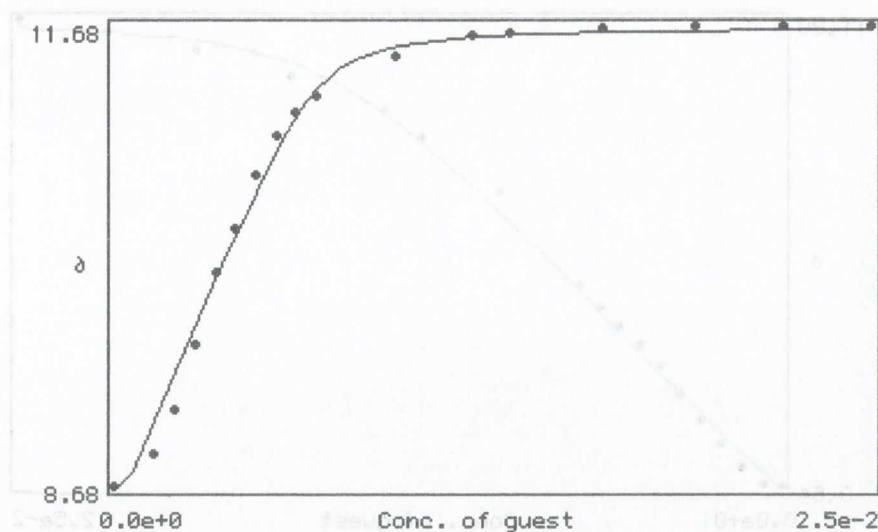


Figure A6.5: The binding isotherm and fit obtained for **205** upon fitting the changes in the chemical shift of the urea proton to a 1:1 (host:guest) complexation model upon titration of SO_4^{2-} .

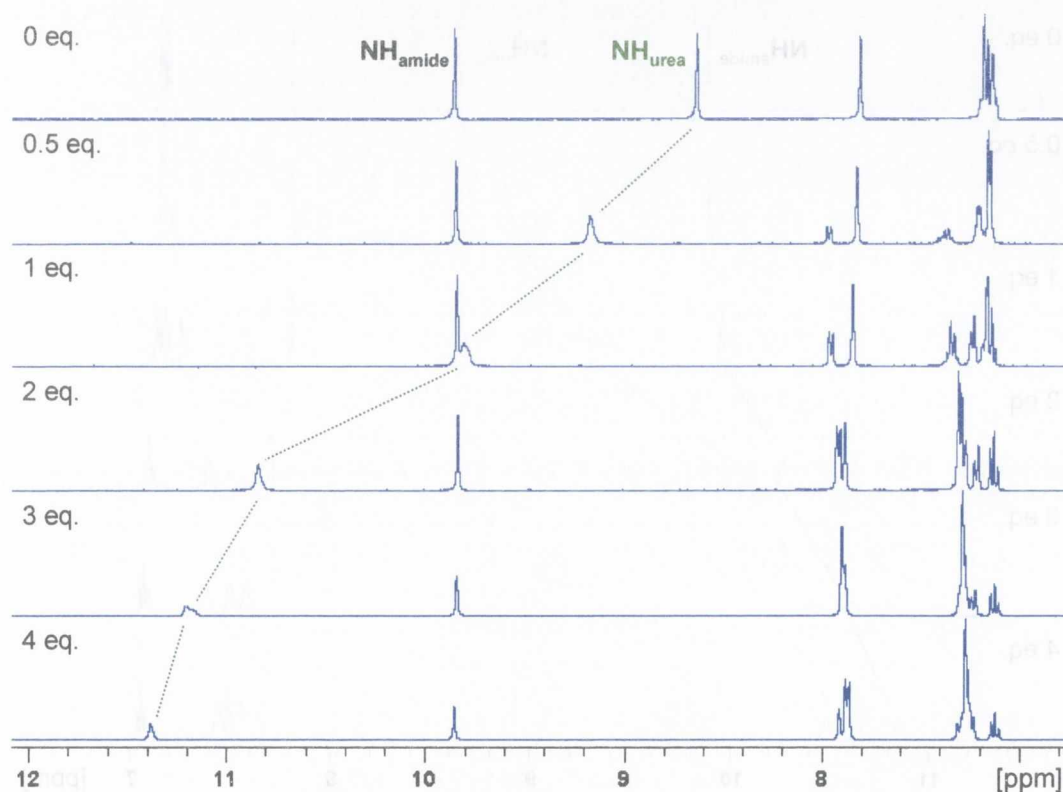


Figure A6.6: Stack plot of ^1H NMR spectra (400 MHz, $\text{DMSO}-d_6$) of **205** (7×10^{-3} M) upon addition of 0, 0.5, 1, 2, 3, and 4 equivalents of $\text{C}_6\text{H}_5\text{O}^-$.

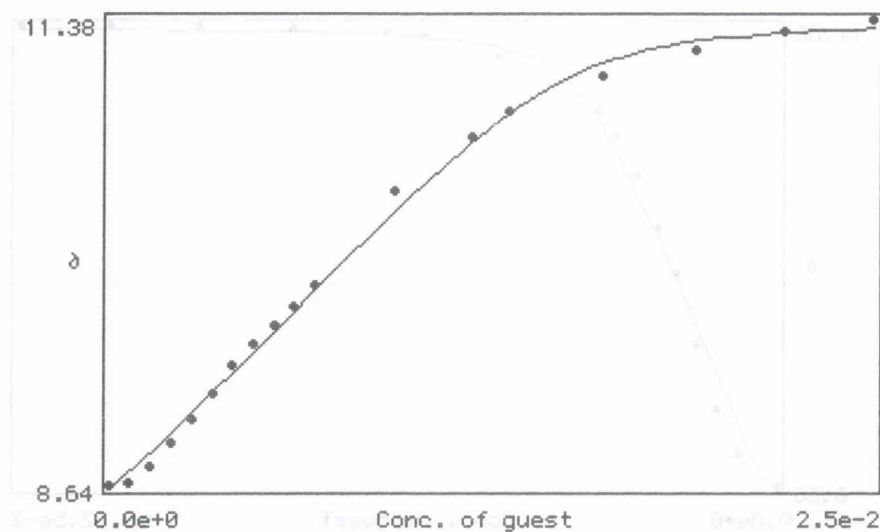


Figure A6.7: The binding isotherm and fit obtained for **205** upon fitting the changes in the chemical shift of the urea proton to a 1:2 (host:guest) complexation model upon titration of $C_6H_5O^-$.

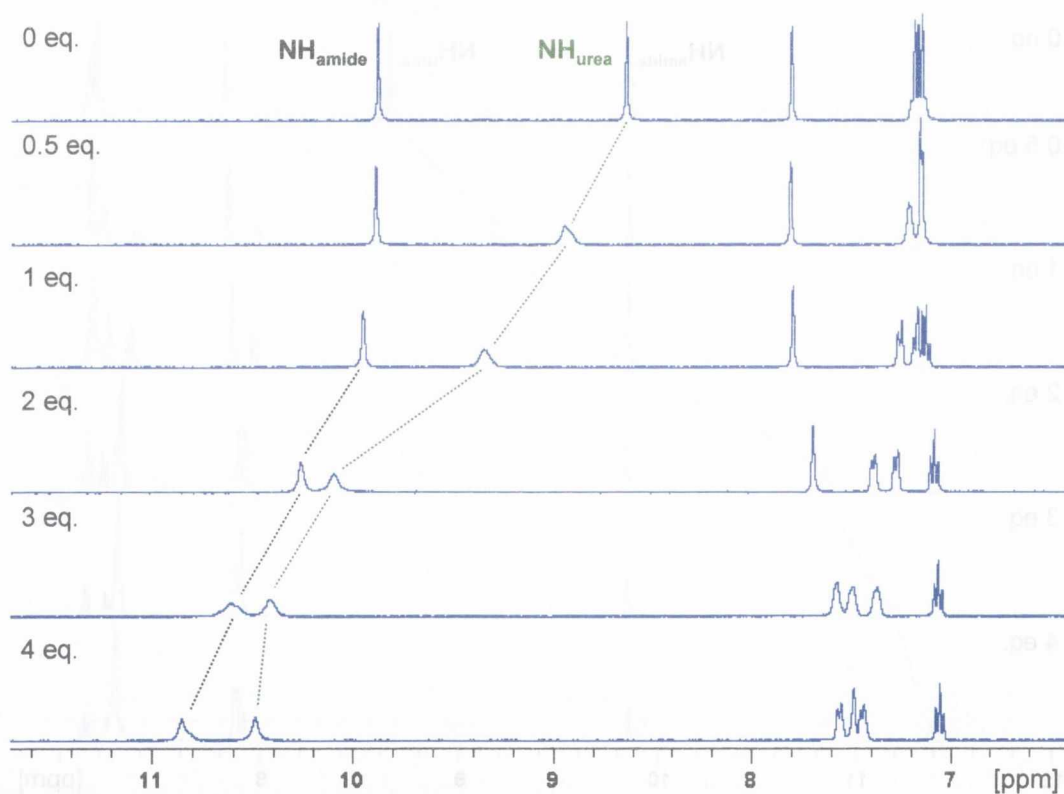


Figure A6.8: Stack plot of 1H NMR spectra (400 MHz, $DMSO-d_6$) of **208** ($7 \times 10^{-3} M$) upon addition of 0, 0.5, 1, 2, 3, and 4 equivalents of $H_2PO_4^-$.

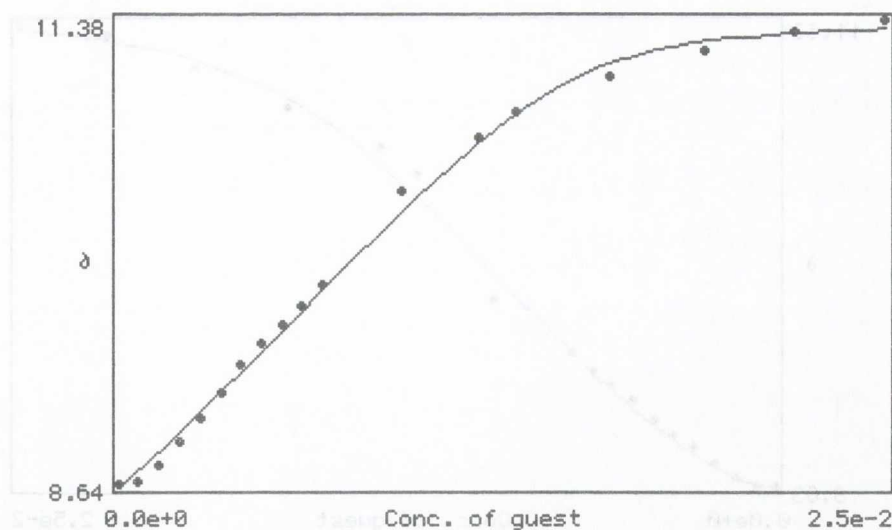


Figure A6.9: The binding isotherm and fit obtained for **208** upon fitting the changes in the chemical shift of the urea proton to a 1:2 (host:guest) complexation model upon titration of H_2PO_4^- .

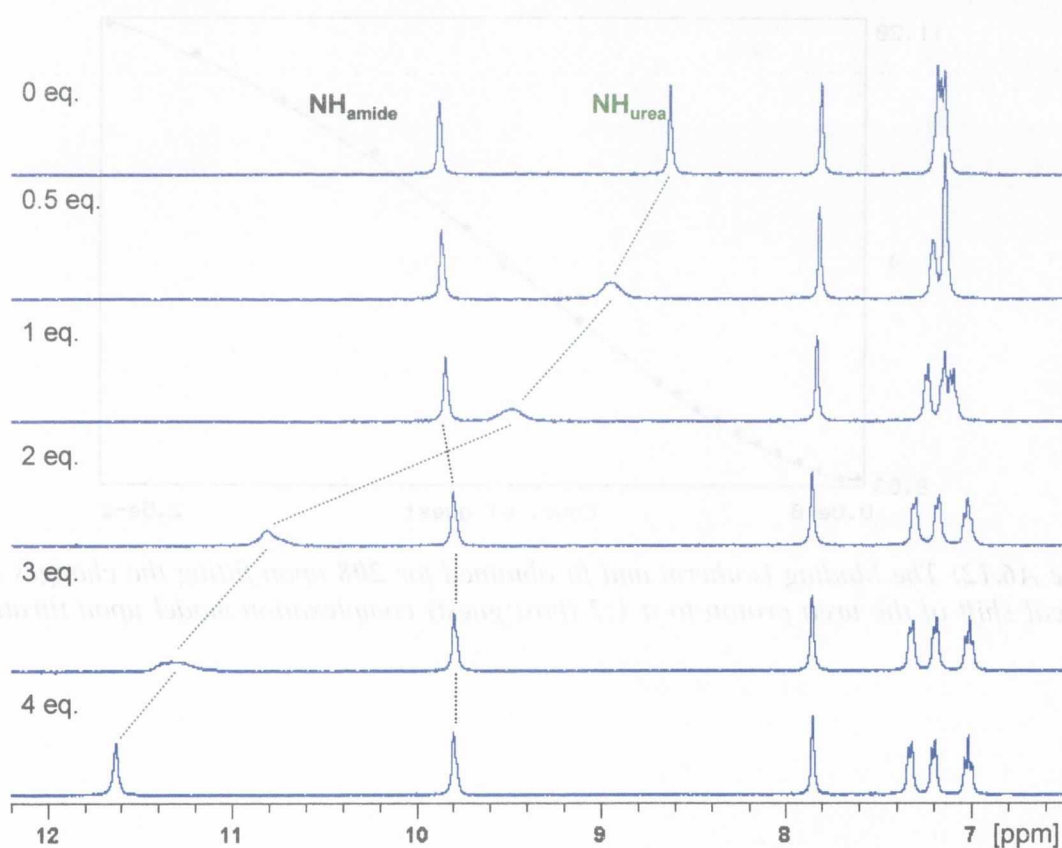


Figure A6.10: Stack plot of ^1H NMR spectra (400 MHz, DMSO-d_6) of **207** (7×10^{-3} M) upon addition of 0, 0.5, 1, 2, 3, and 4 equivalents of SO_4^{2-} .

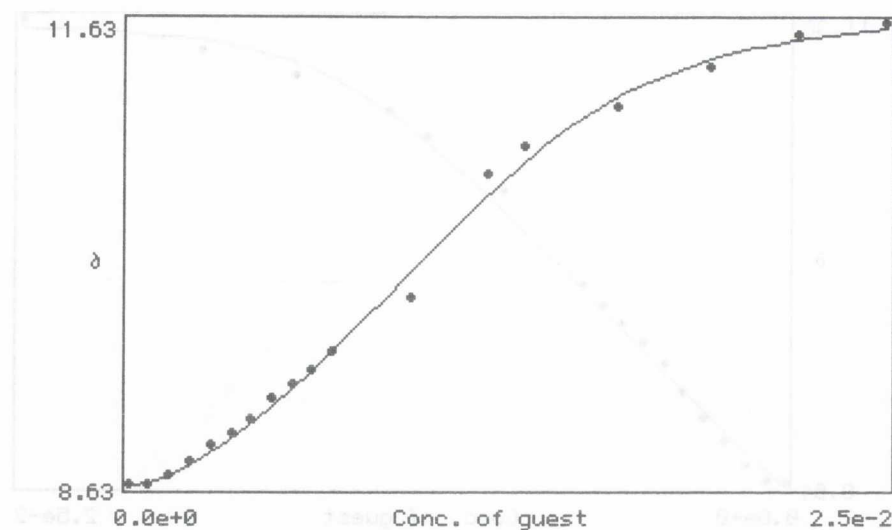


Figure A6.11: The binding isotherm and fit obtained for **207** upon fitting the changes in the chemical shift of the urea proton to a 1:2 (host:guest) complexation model upon titration of SO_4^{2-} .

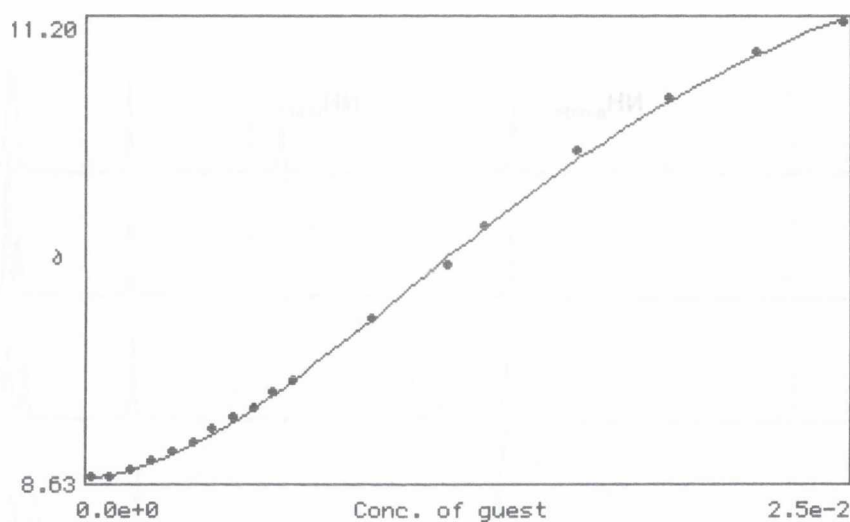


Figure A6.12: The binding isotherm and fit obtained for **208** upon fitting the changes in the chemical shift of the urea proton to a 1:2 (host:guest) complexation model upon titration of SO_4^{2-} .

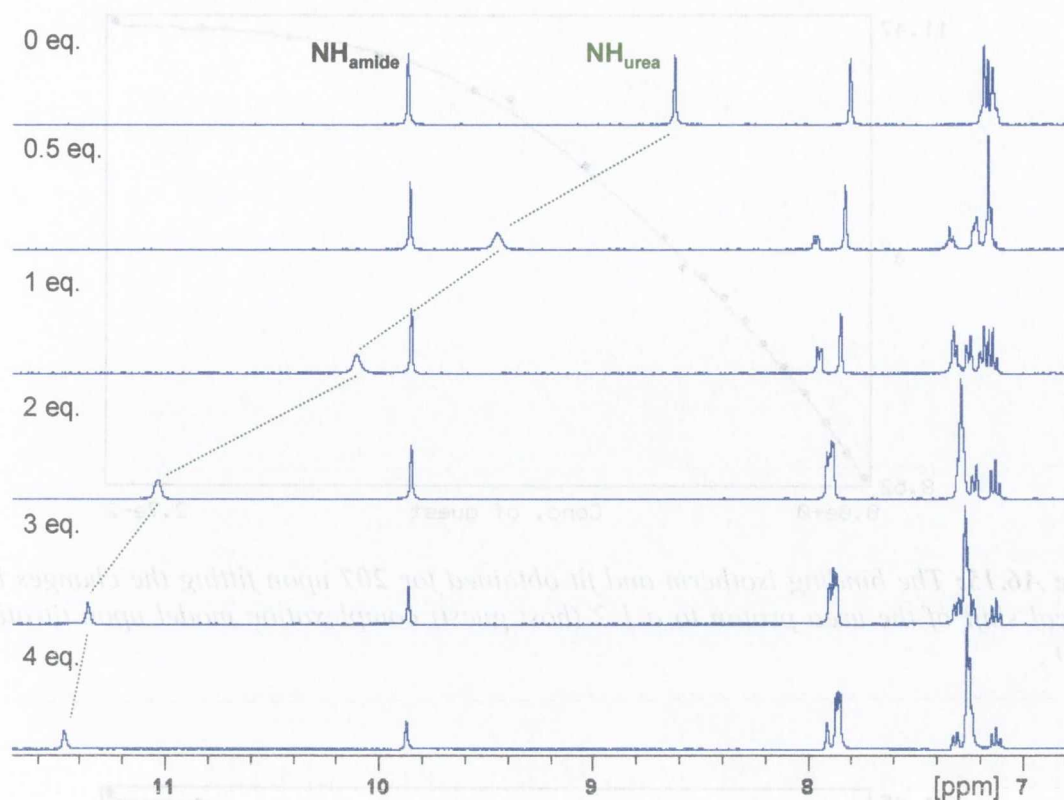


Figure A6.13: Stack plot of ^1H NMR spectra (400 MHz, $\text{DMSO-}d_6$) of **207** (7×10^{-3} M) upon addition of 0, 0.5, 1, 2, 3, and 4 equivalents of $\text{C}_6\text{H}_5\text{O}^-$.

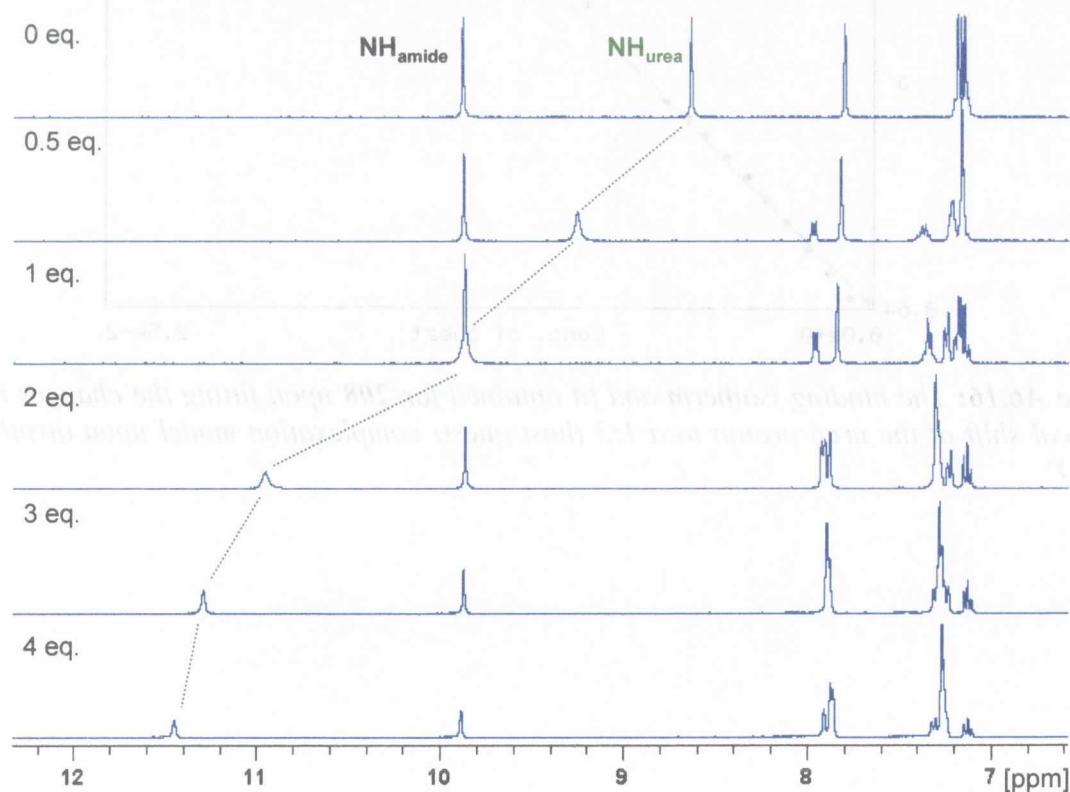


Figure A6.14: Stack plot of ^1H NMR spectra (400 MHz, $\text{DMSO-}d_6$) of **208** (7×10^{-3} M) upon addition of 0, 0.5, 1, 2, 3, and 4 equivalents of $\text{C}_6\text{H}_5\text{O}^-$.

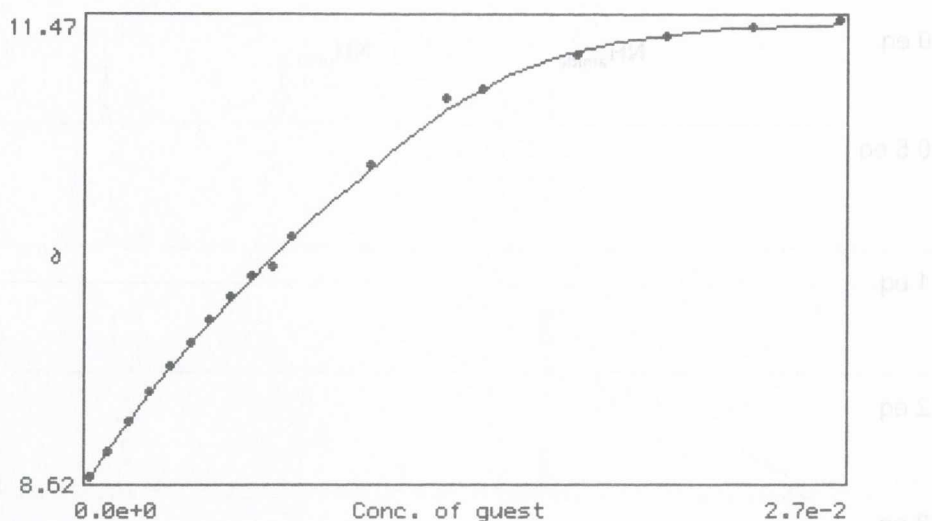


Figure A6.15: The binding isotherm and fit obtained for **207** upon fitting the changes in the chemical shift of the urea proton to a 1:2 (host:guest) complexation model upon titration of $C_6H_5O^-$.

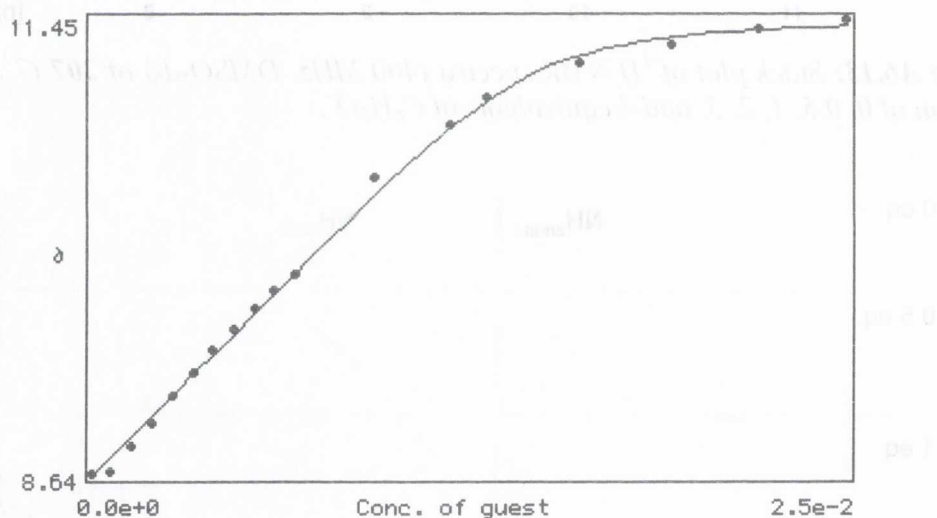


Figure A6.16: The binding isotherm and fit obtained for **208** upon fitting the changes in the chemical shift of the urea proton to a 1:2 (host:guest) complexation model upon titration of $C_6H_5O^-$.

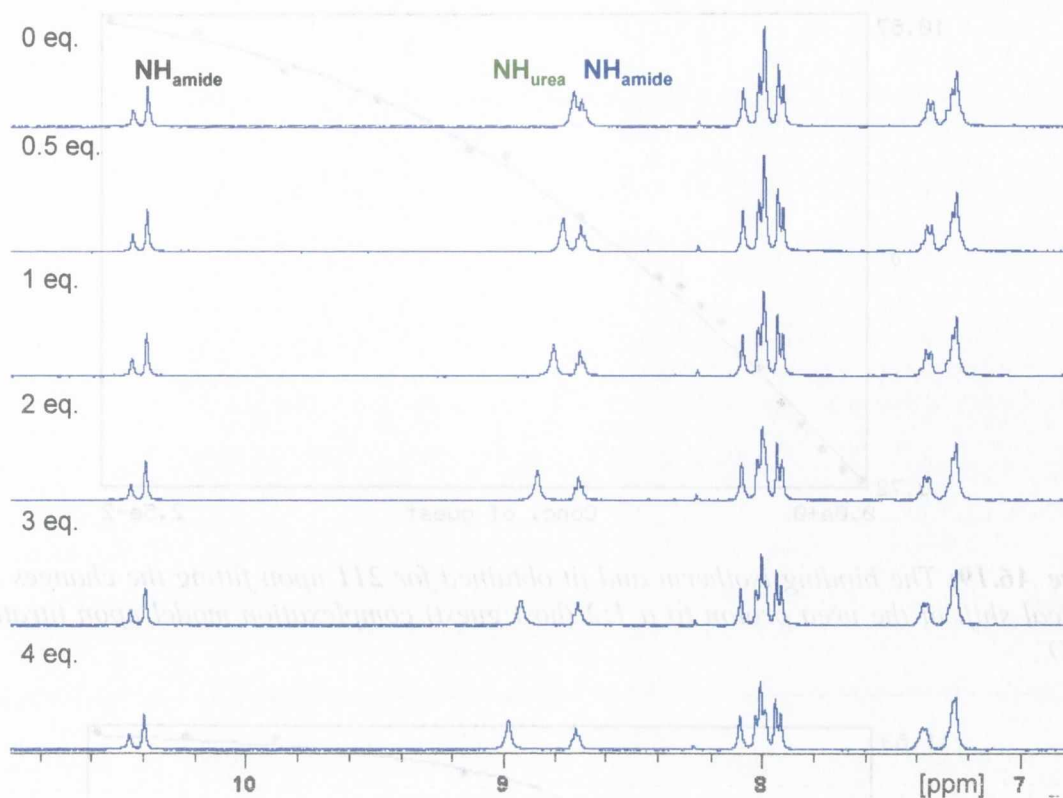


Figure A6.17: Stack plot of ^1H NMR spectra (400 MHz, DMSO-d_6) of **211** (7×10^{-3} M) upon addition of 0, 0.5, 1, 2, 3, and 4 equivalents of CF^- .

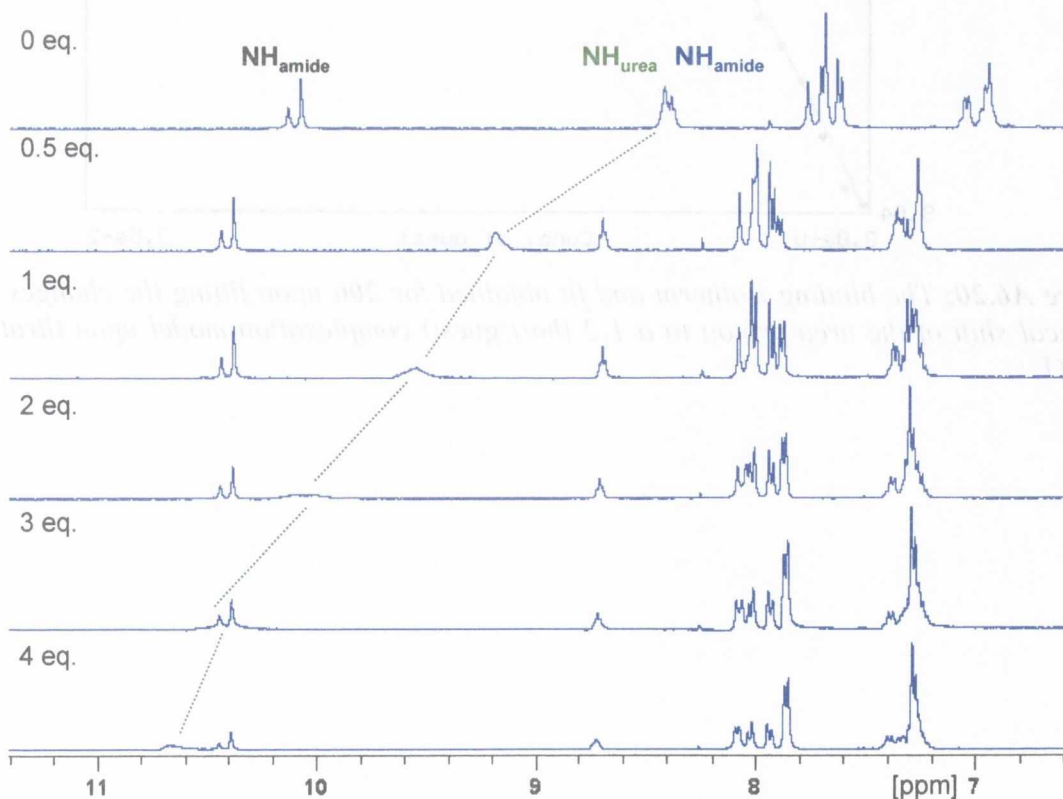


Figure A6.18: Stack plot of ^1H NMR spectra (400 MHz, DMSO-d_6) of **211** (7×10^{-3} M) upon addition of 0, 0.5, 1, 2, 3, and 4 equivalents of $\text{C}_6\text{H}_5\text{O}^-$.

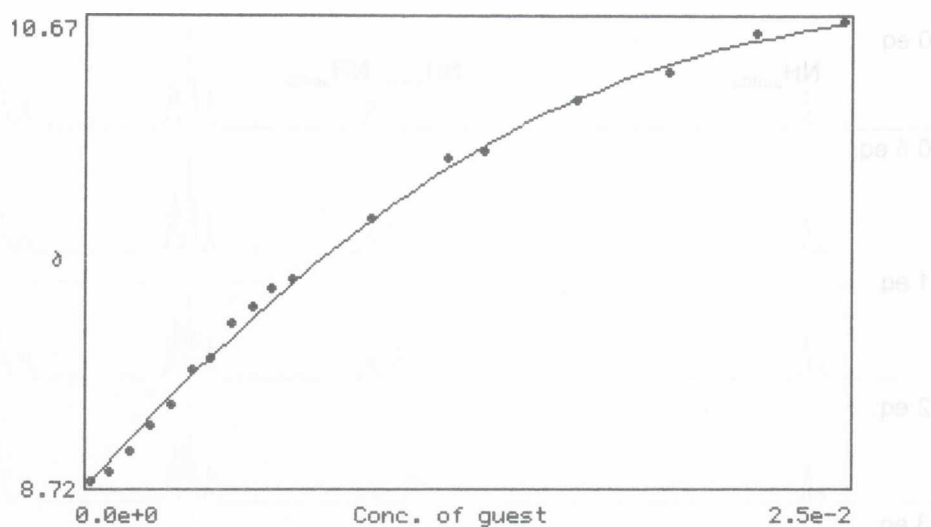


Figure A6.19: The binding isotherm and fit obtained for **211** upon fitting the changes in the chemical shift of the urea proton to a 1:2 (host:guest) complexation model upon titration of $C_6H_5O^-$.

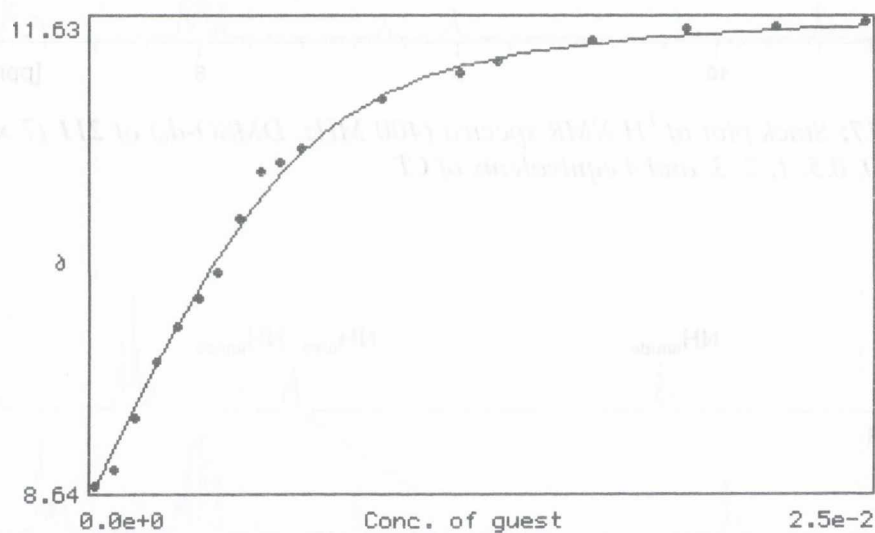


Figure A6.20: The binding isotherm and fit obtained for **206** upon fitting the changes in the chemical shift of the urea proton to a 1:2 (host:guest) complexation model upon titration of $C_6H_5O^-$.

δ (ppm)

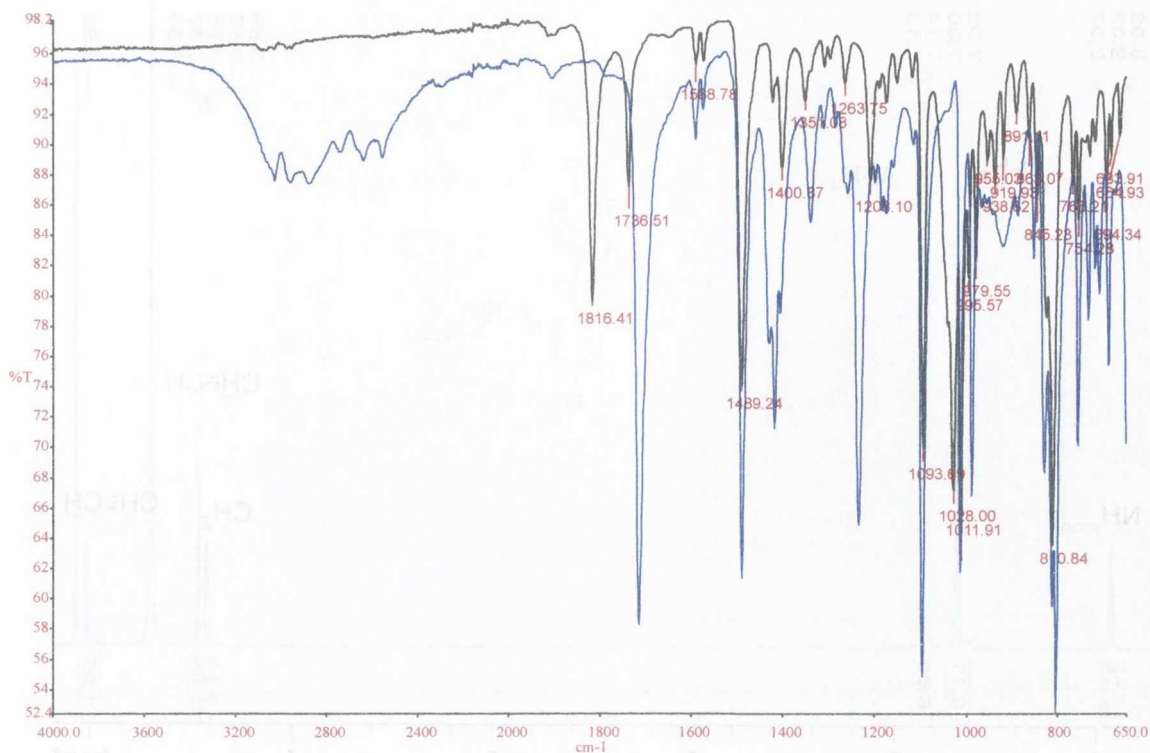


Figure A6.21: IR spectra overlay of acid starting material 222 (blue) and acid chloride product 224 (black).

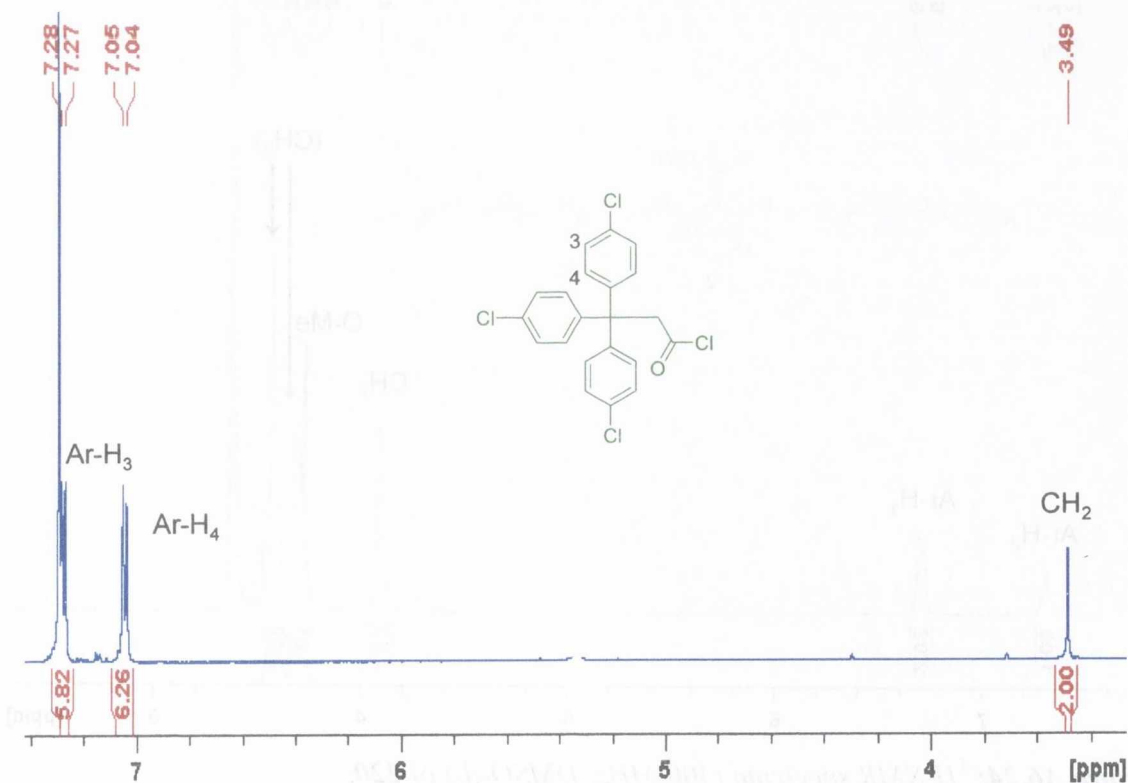


Figure A6.22: ^1H NMR spectrum (400 MHz, CDCl_3) of 224.

Publications