THE USE OF ARRAYS OF ORIENTED HYDROGEN BONDS TO FORM SUPRAMOLECULAR DEVICES

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The use of arrays of oriented hydrogen bonds to form supramolecular devices

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This work has not been submitted for any other award, except that entailed by research training as declared when the project was initially approved; and it is the work of the student alone. The student has also completed the required training programme.

For My Parents

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Abstract

A group of simple amide receptors were synthesised to investigate the effect varying the number/type of hydrogen bond donors or in preorganisation has on host/guest binding abilities. Proton NMR titrations revealed preorganised nitrogen atoms could reduce the size of the binding cleft increasing the selectivity for the smaller anions and binding affinities were increased by the addition of additional hydrogen bond donors, increasing the size of the binding cleft and the presence of sulphonamide groups. A number of receptors were also investigated as colorimetric sensors and visual colour changes were observed with the addition of guest, however further investigations revealed these could be due to deprotonation of the receptor. A fluorescent cation was also synthesised which proton NMR titrations proved had increasing binding affinities. Fluorescence titrations showed the addition of guest increased the fluorescence intensity suggesting it could possibility be used for calculating the concentration of chloride in serum samples.

Cyclotrimeric receptors containing three urea/thiourea moieties were successfully synthesised by a one-pot cyclotrimerisation. However they proved to be very insoluble preventing purification and investigations of their binding ability. The presence of TBA nitrate proved to have a templating effect in the synthesis of the thiourea cyclotrimer but not the urea cyclotrimer. A step-wise cyclotrimerisation was not possible due to the lack of solubility of the products from step-one for the urea receptor and step-two for the thiourea. However Proton NMR titrations of these receptors revealed the urea/thiourea hydrogen bond donors formed stronger interactions with anionic guests than the previous amide receptors.

Finally a number of substrates containing alkene moieties and bis-urea/thiourea receptors were synthesised in the hope of templating cycloaddition photochemical reactions forcing the formation of head-to-head photodimers. Unfortunately cycloaddition photochemical reactions were unsuccessful due to the lack of solubility of both the receptors and substrates preventing any investigations being carried out.

Contents

Abbreviations

Boc	t-butoxycarbonyl
CPK	Corey-Pauling-Koltun
DAPNE	1-(p-dimethylaminophenyl)-2-nitroethylene
DCM	dichloromethane
DHB	5,5-dihexylbarbituric acid
DMAP	4-dimethylaminopyridine
DMF	dimethyl formamide
DMSO	dimethylsulphoxide
E.S.M.S.	electro spray mass spectrometry
G.C.M.S.	gas column mass spectrometry
HOMO	highest occupied molecular orbital
LUMO	lowest unoccupied molecular orbital
MMFF	Merck Molecular Force Field
NMR	nuclear magnetic resonance
ppm	parts per million
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy
TBA	tetrabutylammonium
TBAA	tetrabutylammonium actetate
TBATos	tetrabutylammonium tosylate
TFA	trifluoroacetic acid
TLC	thin layer chromatography
tren	tris(2-aminomethyl)amine
UHP	urea-hydrogen peroxide
UV-Vis	ultra violet - visible

Chapter 1

1. Introduction

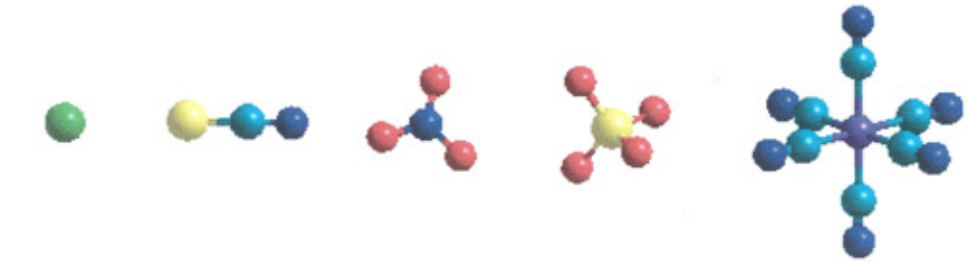
1.1 Preamble

Supramolecular chemistry is the study of components being held together by intermolecular bonding. It is chemistry beyond the molecule[1]. Supramolecular assemblies rely on weaker intermolecular bonding interactions not covalent interactions e.g. electrostatic interactions, π-π stacking interactions, dispersion and induction forces, hydrophobic effects and hydrogen bonding. The coming together of these components in this way is an example of host/guest binding, in which one component, the host, recognises and binds another component, the guest. It is imperative that the hosts are complimentary to the guest. This is best described by Emil Fisher's 'Lock and Key' principle[2] in which the binding sites of the host are of ideal size, shape and position to recognise the guest.

The following sections of this introduction will focus on the research done towards designing receptors effective for anion binding which is the target guests dealt with in this thesis.

Anions play essential roles in many processes both chemically and biologically and this makes their strong, selective recognition an area of intense interest[1]. Environmentally, pollution problems can be caused by anions. For example aquatic life cycles are disrupted by excessive plant /algal growth which are caused by nitrate anions[3, 4] from fertilisers running off agricultural land. Biologically, there are a large number of processes in the human body that involves anion recognition and cells must distinguish between a number of very similar anions. For example ATP and DNA are also both anions. Medically, many diseases have anion involvements for example a misregulation of chloride channels causes cystic fibrosis[5, 6]. Chemically, anions can have many functions for example complex chemical mixtures separation can be assisted by anions. The study of anion recognition with synthetic receptors, therefore, can be used either to get further insight into the role of anions in biochemical and pharmaceutical research and highlights the importance of identifying what receptor design qualities give strong selective recognition.

A number of anion properties need to be taken into account when designing host receptors to ensure the binding site is complementary. The negative charge is the defining feature of an anion therefore electrostatic interactions can play a significant part in anion coordination and are utilised by many anion receptors. The binding cavities must be larger than the previous cation receptors, which is where most research has focussed on to date, as anions can vary in size and are generally larger than cations. Anions can also exhibit a range of geometries as shown in **Figure 1.1,** which can prove challenging for the supramolecular designer to create a complementary binding site. Finally anions can only exist over a limited pH range e.g. carboxylates, phosphates, sulfates become protonated at low pH and consequently lose their negative charge.



Spherical	Linear	Planar	Tetrahedral	Octahedral
Cl^-	SCN^-	NO_3^-	SO_4^{2-}	$Fe(CN)_6^{4-}$

Figure 1.1 – Possible geometries of anionic guests

However it is not only the operating pH of the anion that causes problems in anion recognition. These receptors are highly protonated and only operate at low to moderate pH. There is therefore only a narrow pH zone in which recognition of anions can take place between deprotonation of the receptor and protonation of the anion guest.

1.2 Intermolecular forces

There are a number of different types of intermolecular interactions. As already stated they form weaker bonds than covalent bonds. The typical bond energy of a covalent bond is 350 KJ mol^{-1} rising up to 942 KJ mol^{-1} for the NN triple bond[1]. The bond energy of bonds formed by intermolecular forces range from 2 KJ mol^{-1} for dispersion forces through to 20 KJ mol^{-1} for a hydrogen bond to 250 KJ mol^{-1} for an ion-ion

interaction[1]. All intermolecular forces are essentially electrostatic in character though specific functionality properties allow them to be classed separately.

Electrostatic interactions are based on the Coulombic attraction between opposite charges. There are three types of electrostatic interactions. Ion-ion interactions are of the strongest and involve the attraction of a positive ion to a negative ion. However assembling positively charged groups into a receptor can cause problems. Positive charges repel each other and the counter anion can act as a competitor for the binding site. Electrostatic anion recognition can also use dipolar bonds. Ion-dipole interactions can be formed or dipole-dipole interactions. However both of these interactions are directional and must align for optimal binding and are much weaker than ion-ion interactions.

π-π Stacking[7-9] occurs between molecules containing aromatic rings. It is the attraction of the π cloud of one aromatic for another. Two different geometries can form. A face to face geometry and a face to edge geometry as shown in **Figure 1.2**.

Face to Face Face to edge

Figure 1.2 – Possible geometries of π-π stacking interactions

Dispersion and induction forces are also know as van der Waal forces. They occur as molecules approach each other. As they approach the electron cloud is distorted causing a temporary dipole moment which is aligned for attraction. On collision molecules rebound and the distortion diminishes and the molecules separate as normal. It is difficult to design receptors using this type of interaction due to their general nature.

Hydrophobic or solvatophobic effects occur when water molecules align in a structured array around the surface of a hydrophobic cavity. These water molecules are released and become disordered upon guest complexation resulting in a favourable increase in entropy.

A hydrogen bond[10] is an electrostatic attraction of opposite charges between a hydrogen covalently bonded to a donor which is an electronegative atom, usually oxygen or nitrogen, and a acceptor bearing an electron pair as shown in **Figure 1.3.** This acceptor atom can again be oxygen, nitrogen or sulphur, a halogen or π-bond containing moieties.

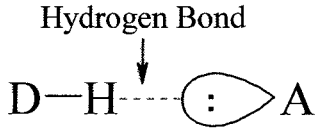


Figure 1.3 – Formation of a hydrogen bond

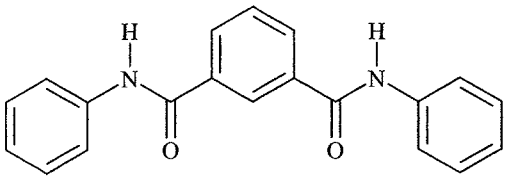
The strength of a hydrogen bond is variable depending on the combination of the donor and the acceptor but the upper limit of the range is on par with a weak covalent bond if one of the components is ionic. The length of hydrogen bonds ranges between 2.5-3.5 Å[11]. Again this depends on the donor atom, acceptor atom and charges on the atoms. Most importantly hydrogen bonds are directional and must be suitably aligned for optimal binding. The optimum angel of the A-H-D complex is about 180^0 allowing alignment with the lone pair. Coordinated arrays of hydrogen bonds can be built into receptor design with specific shape cavities due to their directionality.

Receptors can be designed to achieve the desired interaction. A combination of interactions can also be used to enhance the binding strength and selectivities. There are many known receptors based on hydrogen bonding, ion-ion attractions, ion-dipole, or a mixture of the three.

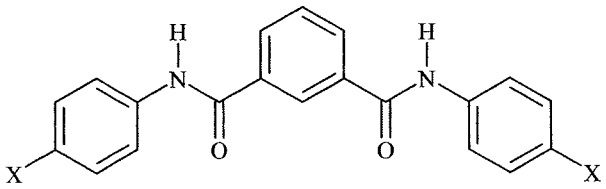
1.3 Synthetic anion receptors

Considerable research has been carried out in this field by a number of people. The main areas associated with this project are highlighted below.

The research studies of Crabtree *et al* [12-14] focuses on hydrogen bonding acyclic anion receptors. Previously reported neutral acyclic synthetic anion receptors that bind exclusively through hydrogen bonding via pyrrole, urea or amide groups have the disadvantage of limited synthetic flexibility for optimising binding selectivity. He discovered however simple non-preorganised acyclic receptors, **1.1** and **1.2**, can bind halides through strong hydrogen bonds.



1.1



1.2 X = p-n-BuC_6H_4

His research suggests the two hydrogen bonds formed between receptor **1.1** and the bromide guest forces the receptor to adopt the unfavourable syn-syn confirmation instead of the syn-anti or anti-anti as shown below in **Figure 1.4**. This forces the two amide bonds out of the central ring plane, presumably due to the large size of the bromide ion. Proton NMR data for the complexes formed with $[PPh_4]Br$ in chloroform showed significant downfield shifts for the N-H with a maximum $\Delta\delta$ of 2.8ppm consistent with strong N-H ----Br hydrogen bonding. The data also showed significant downfield shifts for the aromatic 2 C-H resonances with a maximum $\Delta\delta$ of 0.74ppm suggesting that these protons are close to the bromide anion in the complex.

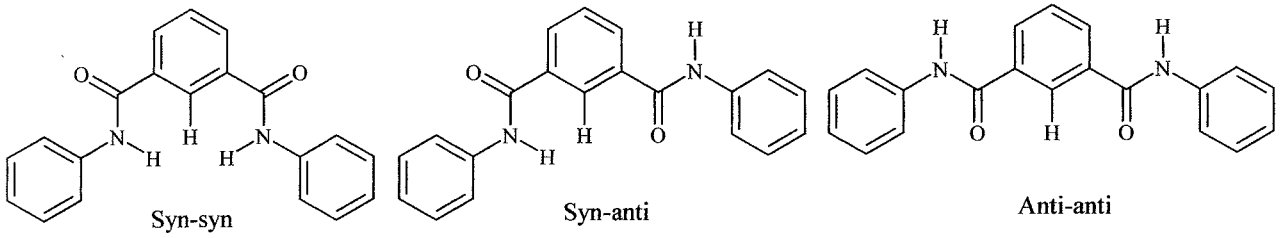
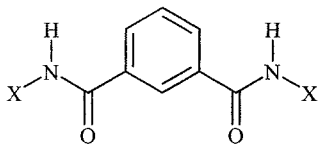
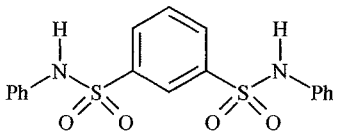


Figure 1.4 – Possible structural confirmations of receptor **1.1**

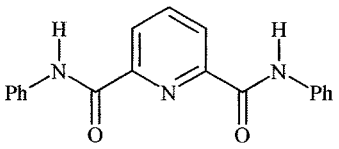
He advanced these findings further by the synthesis of receptors **1.3-1.5** and fully testing these receptors with **1.1** and **1.2**[15, 16]. All of these receptors have a minimally preorganised *meta* arrangement of two hydrogen bonding groups but they differ slightly by the nature of the pendant groups, in the skeletons' rigidity and some are heterocyclic. These slightly different structures allowed Crabtree to demonstrate the importance of hydrogen bonding for anion recognition and the relationship between certain receptor structural features, such as the presence of electron-withdrawing or donating groups or the flexibility of the receptor, and the strength and selectivity of anion binding by studying the interactions of these receptors with a range of anions.



1.3 X = 2,4,6 -$Me_3C_6H_2$



1.4



1.5

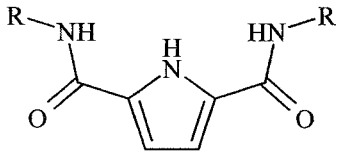
Proton NMR binding studies of receptors **1.1-1.5** with a range of anions in dichloromethane showed a 1:1 stoichiometry for all cases except for receptor **1.4** with fluoride and acetate. These results were confirmed by Job plots. The results showed unusually high association constants for both the smaller and harder anions and the larger and softer anions.

The binding studies also showed the less rigid and simple receptor **1.4** binds iodide with a quite impressive association constant of 1200 M^{-1} compared with receptors **1.2** or **1.3** which have association constant of 460 M^{-1} and 220 M^{-1} respectively. This is due to the nature of the two hydrogen bonds allows formation of two almost linear hydrogen bonds. This is because the host skeleton is flexible, as it has free rotation about the carbon-sulphur bond, and there are no bulky groups present which together allows adjustment of conformation depending on the size of the guest which is more important for the bulkier and softer anions. The acidity of the N-H hydrogen could also have a significant influence. Sulphonamides are about 5 pKa units more acidic than amides with a pKa of about 14-15[15] which may also be a factor in explaining the very high association constants of receptor **1.4**.

Receptor **1.5** had the highest selectivity for the smaller anions. This is probably due to the nitrogen being close to the binding site. The lone pair on the nitrogen is sterically more bulky than the aromatic carbon-hydrogen bond preventing the larger anions getting into the cavity to bind. There will also be electrostatic repulsion between the lone pair and the negatively charged anion reducing the strength of the hydrogen bonds formed. Again this will be more pronounced for the larger anions.

Crabtree concluded the most important factors in halide binding were the cavity size of the receptor, their flexibility and the receptors ability to form two linear hydrogen bonds.

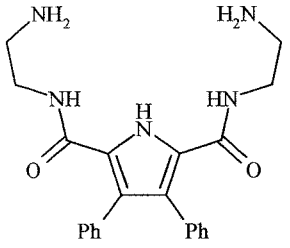
The research carried out by Gale *et al.*[17-20] also involved the synthesis of amide cleft anion receptors. His initial investigations revealed simple 2,5-diamidopyrroles **1.6** and **1.7** were successful oxo-anion receptors.



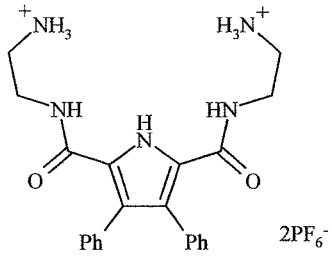
1.6 R = n-Bu
1.7 R = Ph

He hoped modified pendent arm receptors would adapt this unit to bind anions with a higher affinity and synthesised receptors **1.8-1.10**. Proton NMR titrations were carried out in deuterated dimethylsulphoxide (DMSO)-0.5% water and the association constants of receptors **1.8-1.10** were calculated with a range of anions. The results are shown in **Table 1.1**. Receptor **1.8** proved to bind strongly to dihydrogenphosphate and hydrogensulfate. However Gale approached the calculated association constant for dihydrogenphosphate with caution because the least squares non-linear fit of the titration curve had large errors present. This titration was carried out in the presence of 5% water to try and weaken the interaction giving an association constant of 2,050 M^{-1} but the errors were non-random in the data set.

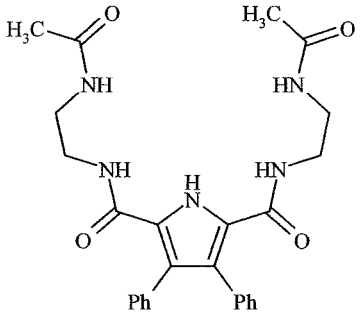
It was likely the hydrogensulfate anion protonated the receptor, adding an electrostatic component and strengthening the interactions resulting in the formation of this very strong complex with an association constant greater than 10^4 M^{-1}.



1.8



1.9



1.10

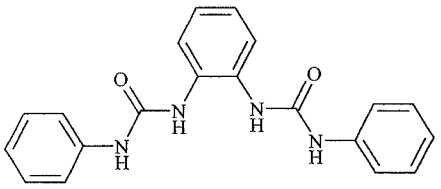
The data found for receptor **1.10** supported this theory. Receptor **1.10** failed to interact with hydrogensulfate and the interaction was greatly reduced for dihydrogenphosphate with an association constant of just 525 M^{-1} for the amide closest to the pyrrole unit. This was as expected since it is not possible to protonate this receptor providing evidence for the above mechanism. The association constants of receptor **1.10** with dihydrogenphosphate and benzoate were calculated following both the amide closest to the pyrrole (1) and the amide on the pendent arm (2) resulting in a higher association constant for the amide directly attached to the pyrrole indicating these protons interact more strongly.

Anion	K_a /M^{-1}		
	Compound **1.8**	Compound **1.9**	Compound **1.10**
Cl^-	<20	(1) 110, (2) 39, (3) 140	<20
Br^-	No binding	35	No binding
$H_2PO_4^-$	2050	44	(1) 525, (2) 190
HSO_4^-	$>10^4$	125	No binding
$C_6H_5CO_2^-$	47.6	<20	(1) 152, (2) 19.5

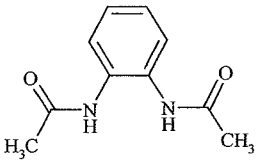
Table 1.1 – Associations constants of receptors **1.8-1.10** with TBA salts in 0.5% water /DMSO

The association constants calculated for receptor **1.9** showed the extra electrostatic component enhanced binding of halide anions. Again the association constants were determined following the shift of the pyrrole (3), the amide (1) and the ammonium protons (2) resulting in the same conclusion that the pyrrole NH and the close amide NH interact more strongly.

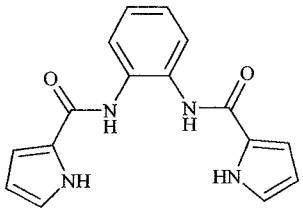
Gale[21, 22] went on to investigate an anion receptor that utilises a bis-urea as the hydrogen bond donor. He synthesised 1,1-(1,2-phenylene)bis(3-phenylurea) **1.11** and two structurally related compound **1.12-1.13**. Proton NMR titrations were carried out in deuterated DMSO-0.5% water to investigate the anion complexation properties of **1.11-1.13**.



1.11



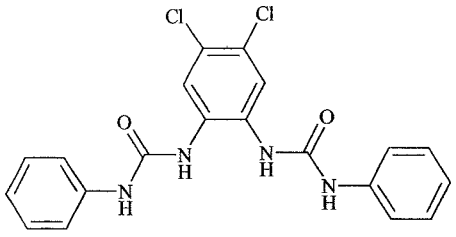
1.12



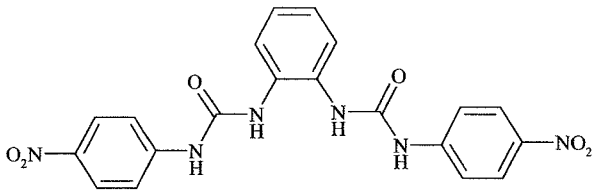
1.13

The calculated association constants revealed receptor **1.11** was capable of selectively binding carboxylate anions with association constants of 3,210 M^{-1} and 1330 M^{-1} for acetate and benzoate respectively. Much lower association constants of 43 M^{-1} and less than 10 M^{-1} were observed for chloride and bromide. Receptors **1.12** and **1.13** bound acetate and benzoate with a much lower affinity with association constants of 98 M^{-1} and 251 M^{-1} for acetate and 43 M^{-1} and 113 M^{-1} for benzoate respectively. Gale presumed the higher affinities of receptor **1.11** was because receptor **1.11** was capable of forming four hydrogen bonds to the anion due to the more open binding site. Crystallography revealed that the molecules of receptor **1.11** were capable of binding to benzoate via four hydrogen bonds while molecules of receptor **1.13** were only capable of binding to acetate via three hydrogen bonds, two from the amide NH groups and one from a pyrrole group. The other pyrrole NH group formed an intermolecular hydrogen bond to an adjacent complex because it was orientated out of the cavity.

Receptors **1.14** and **1.15** were also synthesised to investigate the effect electron-withdrawing substituents have on the observed anion association constants[23].



1.14



1.15

The chloro substituents on the central ring of compound **1.14** increases the acidity of the central urea hydrogen atoms resulting in strong interactions with anions. This is consistent with the calculated association constants for compound **1.14** being significantly enhanced for dihydrogenphosphate and acetate at 8,079 M^{-1} and 4,724 M^{-1} respectively. However the calculated association constants for compound **1.15** were only slightly higher than those observed for **1.11** which suggested the urea protons increasing acidity does not always result in higher association constants.

The proton NMR data suggested receptor **1.14** is capable of forming stabilising intramolecular CH---O hydrogen bonds with the urea carbonyl oxygen as shown in **Figure 1.5** resulting in a higher affinity from a more preorganised confirmation.

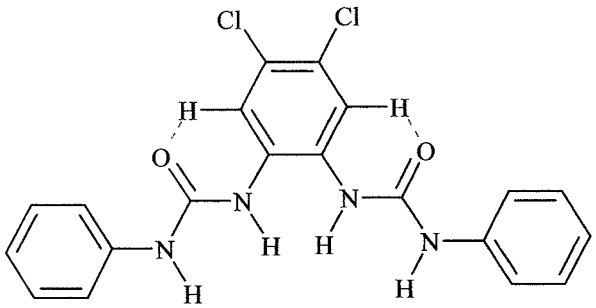
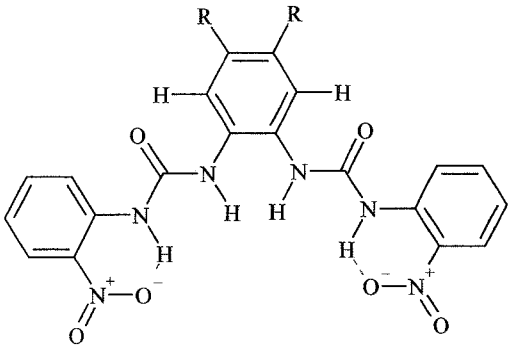


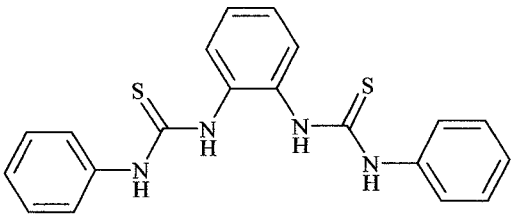
Figure 1.5 – Stabilising intramolecular hydrogen bonds of receptor **1.14**

Compound **1.16** was synthesised with the nitro groups in the 2 position which will involve the outer urea NH groups in intramolecular hydrogen bonding reducing its hydrogen bonding ability. A steric constraint may have also been introduced on the binding site. As expected lower but fairly constant association constants were observed with 1,739 M^{-1} for acetate and 349 M^{-1} for dihydrogenphosphate indicating the selectivity of the bis-urea skeleton is not altered by the presence of the nitro group.

Compound **1.17** was synthesised which combines both electron withdrawing substituents. This again showed dihydrogenphosphate interacts strongly with the inner urea hydrogens by an increase in the association constant to 1,637 M^{-1}.



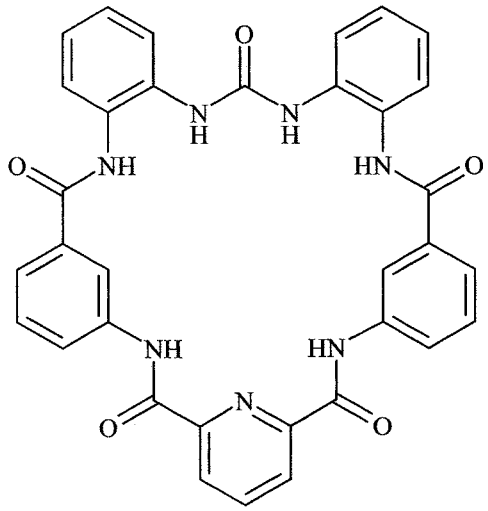
1.16 R = H
1.17 R = Cl



1.18

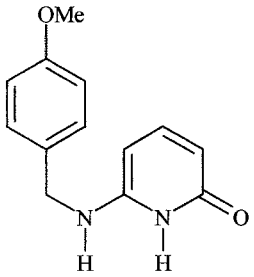
Bis-thiourea **1.18** was also synthesis to see if it would exhibit similar behaviour as **1.14** since thioureas also increase the acidity of the NH protons. However the calculated association constants were even lower than its urea analogue **1.11** suggesting the shape of the binding site is distorted by the large sulphur atom preventing the outer thiourea NH groups from coordinating to the anion.

Finally Gale[24] also synthesised macrocycle **1.19** which combines a 2,6-dicarboxamidopyridine and a urea. Proton NMR titrations were carried out and the association constants calculated. They showed macrocycle **1.19** had high affinity for carboxylates with the association constant for acetate approximately 100 times higher than the association constant of dihydrogenphosphate at 16,500 M^{-1} and 115 M^{-1} respectively. The proton NMR data revealed the two urea NH groups bind to one carboxylate oxygen while the 2,6-dicarboxamidopyridine groups bind to the other. However only a single atom of the dihydrogenphosphate anion is bound to the amide groups adjacent to the pyridine ring therefore it is les strongly bound resulting in the reduced association constant.

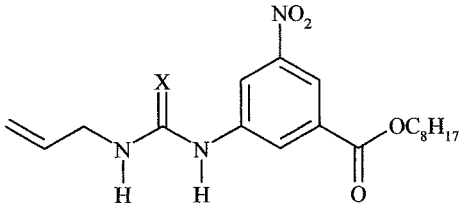


1.19

The research undertaken by Wilcox *et al.*[25] also utilised the approach of using ureas as hydrogen bond donors to bind anions. Initially he looked at compounds like 6-alkylamino-2-pyridone **1.20** which is capable of forming a pair of hydrogen bonds but it only binds moderately to tetrabutylammonium tosylate (TBATos). Receptors **1.21** and **1.22** where synthesised in a hope of increasing the strength of sulfonate anion binding with more potent hydrogen bond donors.



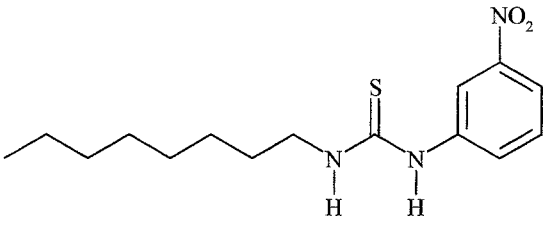
1.20



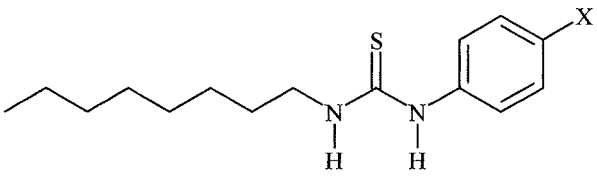
1.21 X = O
1.22 X = S

Receptor **1.21** was found to be an excellent host for ion pairs containing sulfonates, phosphates and carboxylates in chloroform. Receptor **1.22** with the thiourea was found to be an even better host but he focussed his investigations on receptor **1.21** as thioureas are more susceptible to nucleophilic attack and might result in undesirable side reactions when applied in catalytic schemes, his final goal.

Wilcox[26, 27] went on to investigate the effect substituents have on association constants in host-guest systems involving hydrogen-bond formation. He prepared a *meta*-substituted thiourea **1.23** and a series of *para*-substituted thioureas **1.24-1.31**.

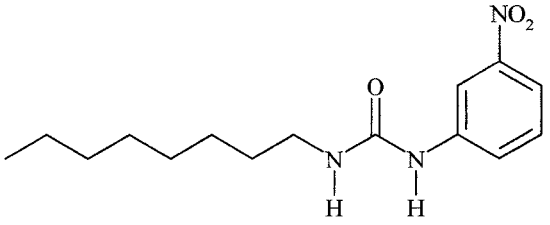


1.23

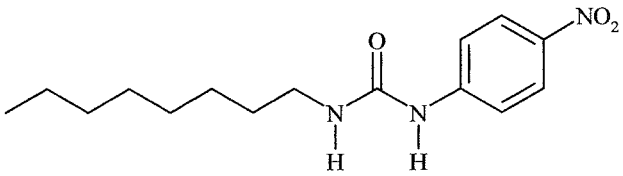


1.24 X = H **1.28** X = $COOC_2H_5$
1.25 X = NO_2 **1.29** X = C_6H_5
1.26 X = CN **1.30** X = OC_2H_5
1.27 X = CF_3 **1.31** X = $N(CH_3)_2$

Investigations with zwitterion 4-(tri-1-butylammonium) butane-1-sulfonate showed the *meta*-nitro to the thiourea increased the binding constant however not as effective as the *para*-nitro thiourea although the difference was not large. The related ureas, receptors **1.32** and **1.33**, were also prepared and investigated, and the association constants were calculated to be about three times larger than the corresponding thioureas. For example the association constant of **1.23** was 2.1 x 10^3 M^{-1} compared to **1.32** with an association constant of 6.3 x 10^3 M^{-1}.



1.32



1.33

Wilcox found the overall trend was receptors with electron withdrawing substituents lead to stronger binding while receptors with strong donating substituents reduce binding relative to receptor **1.24** which has no substituents. It was found that the introduction of nitro or cyano substituents, strong electron withdrawing groups, resulted in a number of changes. Firstly the geometry would be changed slightly, the nitro containing molecules were more planar than the unsubstituted molecules, and secondly

the direction and magnitude of the dipole moment changed as the charge distribution in the molecules were affected. These changes in the local electric field resulted in the electric potential at the molecular surface adjacent to the N-H bonds becoming more positive. This increased positive potential in the vicinity of the N-H bonds led to increased affinity for the charged sulfonate region of the guest, a region that has a substantial negative electric potential.

The research carried out by Moran *et al.*[28-30] investigated optimising ureas to form complexes with carboxylates by increasing the number of hydrogen bonding donors. He did this by combining an amino chromenone fragment with a urea function forming receptor **1.34** which can make three hydrogen bonds as shown in **Figure 1.6**.

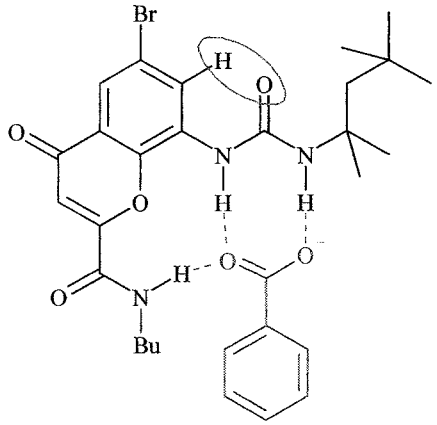


Figure 1.6 – Receptor **1.34** / benzoate complex

However the associating constant of this receptor was surprisingly small with TBA benzoate in DMSO at only 20 M^{-1} compared with other known urea associates. This was explained by CPK models which showed the urea function was twisted due to the hindrance between the urea carbonyl and the neighbouring *ortho* hydrogen of the chromenone unit as shown in **Figure 1.6**. CPK models also showed steric interference between the receptors butyl substituent and the benzoate aromatic ring. Together these movements widen the cleft and prevent the formation of any linear hydrogen bonds. Receptor **1.35** was prepared to overcome this. The tetrahedral geometry of the sulphur atom prevents this twisting as the hydrogen can sit between the two sulfuryl oxygen's as shown in **Figure 1.7**. The better geometry and higher acidity of the sulfuryl amide

hydrogen atom should provide better binding properties and as expected the association constant of this receptor with TBA benzoate in DMSO was much higher at 3.3 x 10^2 M^{-1}.

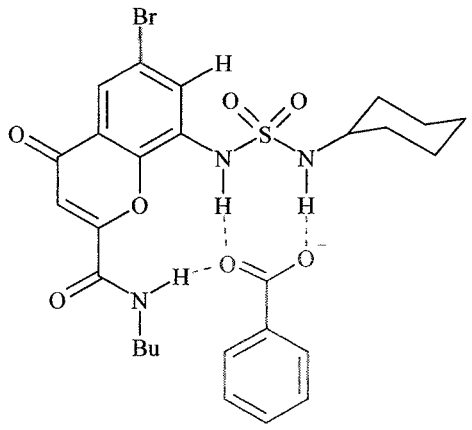


Figure 1.7 – Receptor **1.35** / benzoate complex

Receptors **1.36** and **1.37** were also synthesised which combines two chromenone fragments with a urea function which is capable of making four linear hydrogen bonds with a carboxylate guest as shown in **Figure 1.8**. Again receptor **1.37** with the symmetric sulfuryl amide would prevent the twisted geometry of the urea.

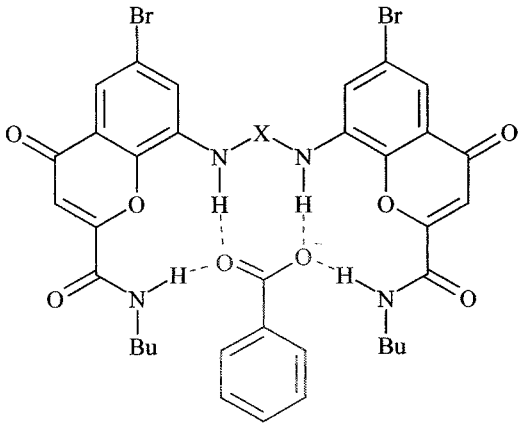
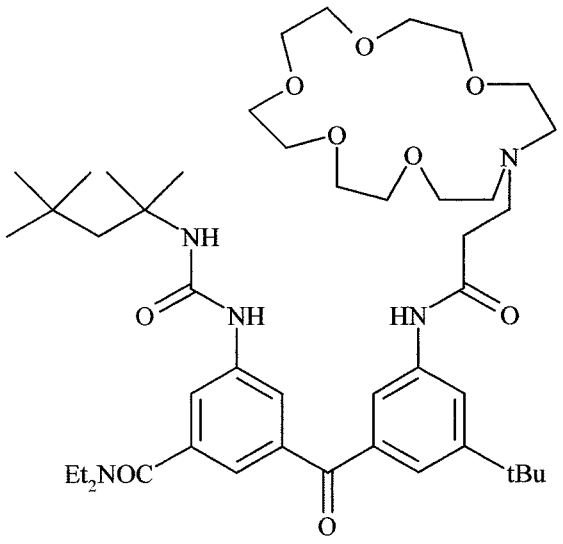


Figure 1.8 – Receptor **1.36** (X = CO) or **1.37** (X = SO_2) / benzoate complex

With the additional hydrogen bond donor the association constants for receptor **1.36** and **1.37** should be higher. The association constant of receptor **1.36** with the benzoate guest in DMSO is 1.5 x 10^4 M^{-1} and the association constant for receptor **1.37** was at least 10 times higher at over 10^5 M^{-1}.

Moran[31] also synthesised receptor **1.38** which he hoped would selectively extract amino acid systems. Modelling studies suggested the xanthane based hydrogen bonds and the crown ether would allow association with the carboxylate and ammonium group of the amino acid. Significant shifts in the proton NMR spectra of the receptor was seen upon addition of an amino acid however the amino acid signals were not easily identified due to the complex spectra. Using phenylalanine as the substrate was the exception due to the strong shielding of the aromatic ring and the integration of the proton NMR signals showed 70 % of this amino acid was extracted.



1.38

Hamilton *et al.*[32, 33] designed a series of carboxylate receptors to investigate the effect increasing the number of hydrogen bonding groups has on binding affinity. Originally Hamilton showed receptors with two 2-aminopyridine derivatives linked by an isophthalic acid spacer are capable of binding urea's or carboxylic acids as shown in **Figure 1.9**. However by changing the isophthalic acid spacer to 3-aminobenzoic acid Hamilton managed to redirect the second amide N-H to 120^0 instead of the previous 60^0 providing a cavity capable of forming hydrogen bonds with both the amide and acid groups of a terminal peptide carboxylate as shown in **Figure 1.10**.

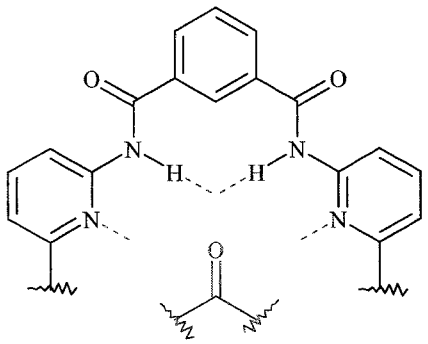


Figure 1.9 – Receptor **1.39** / carboxylic acid

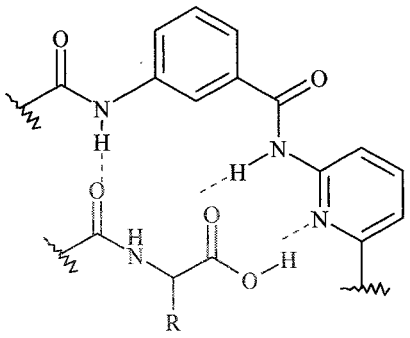


Figure 1.10 – Receptor **1.40** / peptide carboxylate

Receptors **1.41** and **1.42** were synthesised and proton NMR binding studies were used to investigate the peptide recognition properties in chloroform. Receptor **1.41** is capable of forming three hydrogen bonds with the substrate while **1.42** is capable of forming four hydrogen bonds as shown in **Figures 1.11** and **1.12** respectively, which should allow receptor **1.42** to bind with a higher affinity.

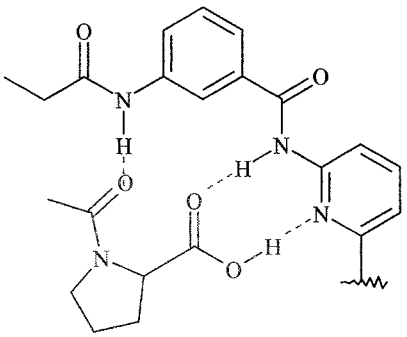


Figure 1.11 – Receptor **1.41** / peptide carboxylate

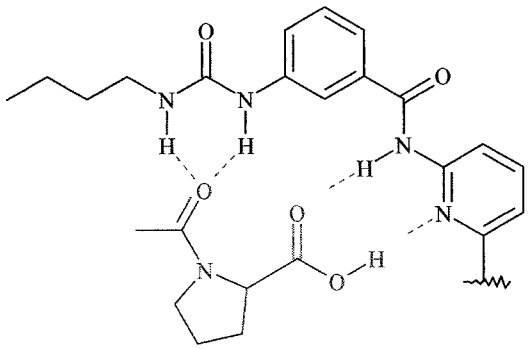


Figure 1.12 – Receptor **1.42** / peptide carboxylate

This was confirmed by the results which showed receptor **1.42** binds n-butyl-L-proline very strongly with an association constant of 2,600 M^{-1} compared to receptor **1.41** with an association constant of 410 M^{-1}.

Hamilton[34] went on to synthesis receptors that utilise urea moieties as the hydrogen bond donor atoms. He synthesised bis-urea receptor **1.43** which was capable of interacting with both oxygen's of the carboxylate group through four specially positioned hydrogen bond donors as shown in **Figure 1.13**.

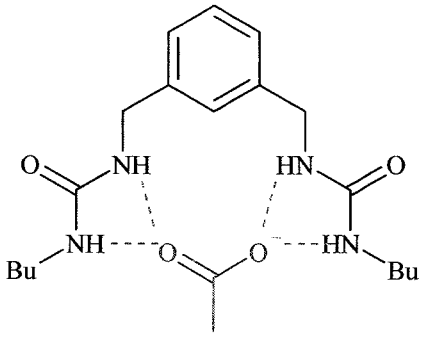
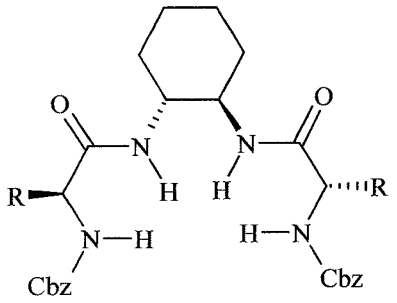


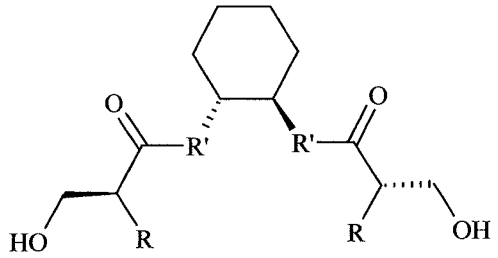
Figure 1.13 – Receptor **1.43** / carboxylate anion

Proton NMR binding studies showed receptor **1.43** binds strongly with tetrabutylammonium acetate (TBAA) in acetonitrile with a association constant of 2,240 M^{-1}. A 1:1 stoichiometry was confirmed by a Job's plot. It also showed both ureas are involved in binding. However further investigations with 1,3-dimethyl urea indicated only a ten-fold advantage of the bis-urea over the mono-urea. The downfield shift of the saturated urea-NH resonance is larger in the weaker mono-urea complex than the complex that is formed with receptor **1.43,** at 3.3 ppm and 1.8 ppm respectively. This suggests two different geometries for the two different complexes. Also the basicity of the oxygen's will be distributed through both N-H bonds in receptor **1.43** giving the hydrogen bonds different electrostatic character compared to the hydrogen bonds formed with the mono-urea complex. Together these factors account for the small ten-fold difference in the binding affinity of the two receptors.

Hamilton decided to alter his approach and again prepared a number of receptors **1.44-1.46** with four amide N-H groups positioned to bind carboxylate anions but this time they were separated by two carbon atoms. Unfortunately though proton NMR binding studies of receptor **1.44** and **1.46** with TBAA in acetonitrile showed this arrangement of the binding sites is not the best as only weak association constant of 210 M^{-1} and 340 M^{-1} was found. However the associate constant calculated for TBAA with receptor **1.45**, which has the two hydroxyl groups incorporated into the binding site, showed a dramatic increase of 270,000 M^{-1}.



1.44 - R = H
1.45 - R = CH_2OH
1.46 - R = CH_3



1.47 - R = NPhth, R' = NH
1.48 - R = NHCbz, R' = O

The proton NMR data for receptor **1.45** shows there was a large downfield shift seen from the urethane-NH of 2.03 ppm but there was very little shift seen for the amide-NH of 0.44 ppm. This suggests there is only a small interaction from the amide-NH group and it is the urethane-NH and the hydroxyl that predominantly hydrogen bond to the acetate as shown in **Figure 1.14**.

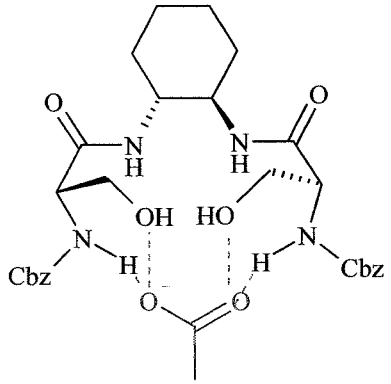


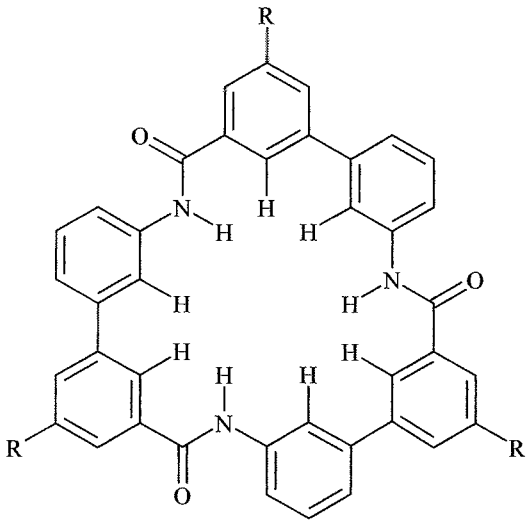
Figure 1.14 – Receptor **1.45** / acetate complex

This was confirmed further by investigation of receptors **1.46-1.48** which are systematically missing one of the three binding sites of receptor **1.45**. The calculated association constants were 340 M^{-1}, 1,400 M^{-1} and 10,000 M^{-1} respectively confirming the important role of the urethane-NH and the hydroxyl groups in providing high binding affinity.

However, high binding affinity is not the only objective to consider when designing receptors. It is also important to develop shape-selective anion receptors due to the

diverse geometries of the different anions. With this in mind Hamilton[35-37] went on to synthesise novel macrocyclic receptors **1.49-1.50**, which are capable of selectively binding anions. They were synthesised by a four step process to give the receptors in 40-60% yield.

Their structures contrast drastically to previous examples. This receptor has a rigid disposition with three amide groups in the centre of the cavity, serving as hydrogen bonding donors, which allows the receptor to surround the periphery of the guest with the maximum amount of hydrogen bonds. The steric constraints and the positioning of the amide groups results in anion selectivity because the size and shape of the cavities are a close match to that of tetrahedral oxyanions.



1.49 R= CO_2Et
1.50 R = NH Boc

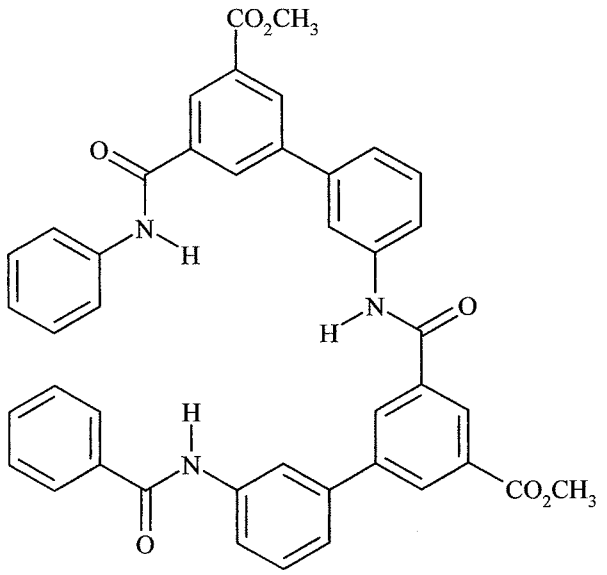
Proton NMR binding studies of receptors **1.49** and **1.50** with TBATos in 2% DMSO/chloroform resulted in chemical shift changes for the protons projecting into the cavity indicating binding. A small upfield shift was also seen for the externally directed protons however this will be due to the ring current effect. A 1:1 binding stoichiometry was seen for both receptors and the association constants were calculated to be 260,000 M^{-1} and 210,000 M^{-1} indicating strong binding. The functional groups outside the cavity have little effect on the anion binding properties of the receptor as shown by the similar association constants of the two receptors.

Proton NMR binding studies of the other shaped anions, such as spherical halide and planar nitrate showed more complex binding properties with both 2:1 and 1:1 binding stoichiometries seen for the complexes. This means these anions were capable of binding two equivalents of macrocycle in a sandwich formation. This is possible due to the even distribution of charge on these anions. The association constant are shown below in **Table 1.2** and confirm these receptors are selective towards tetrahedral oxyanions however nitrate was the preferred anion but this is a 2:1 complex.

Anion	Stoichiometry	Ka of 1.49 (M^{-1})	Ka of 1.50 (M^{-1})
I^-	1:1	130,000	120,000
	2:1	11,000	9,000
Cl^-	1:1	8,800	7,600
	2:1	1,700	1,900
NO_3^-	1:1	460,000	Not determined
	2:1	2,100	Not determined

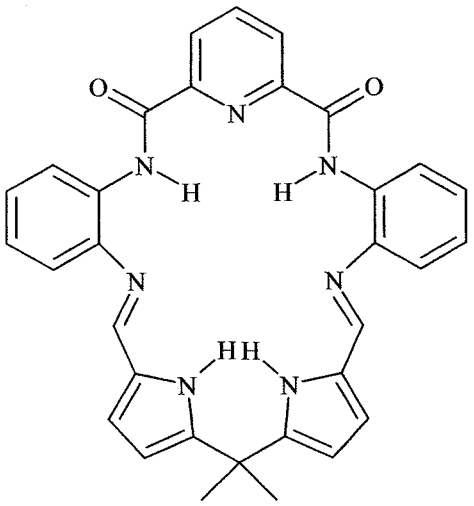
Table 1.2 – Associations constants of receptors **1.49** and **1.50** with TBA salts in 2% DMSO/chloroform

A linear analogue **1.51** was tested to confirm the importance of the rigid deposition of the receptor. The results showed much weaker binding for all anions. For example the association constant with TBATos is only 780 M^{-1} which is almost a 600-fold decrease.



1.51

This macrocyclic approach was also investigated by Sessler *et al.*[38] to prepare a receptor that shows a high sulfate/nitrate selectivity that could be used in radioactive waste remediation systems. Macrocyclic receptor **1.52** was synthesised which contains both a pyridine-2,6-dicarboxamide moiety and a dipyrromethane fragment. Both have previously shown potential in anion binding so together they should prove effective as an anion receptor[38].



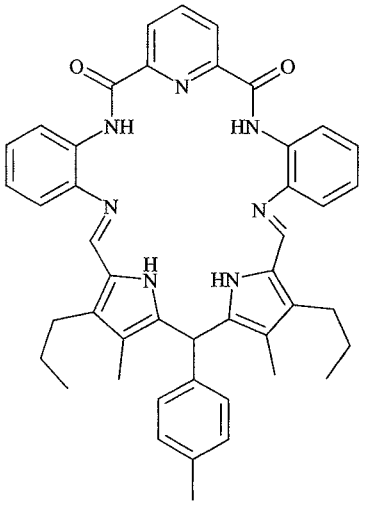
1.52

UV-Vis spectroscopy binding studies of receptor **1.52** with hydrogensulfate in acetonitrile showed strong 1:1 binding affinity with an association constant of 64,000 M^{-1}. Investigations with other anions showed receptor **1.52** exhibits no affinity for both the nitrate and bromide anions and very weak binding interactions with chloride and cyanide with association constants of 2,000 M^{-1} and 12,000 M^{-1} respectively. This suggests the cavity of receptor **1.52** favours the size and geometry of the sulfate anion giving it this selectivity. This selectivity was even seen in the presence of nitrate, bromide, chloride and cyanide which can be very beneficial in applications requiring the selective removal of hydrogensulfate from nitrate-rich waste mixtures such as the radioactive waste remediation systems.

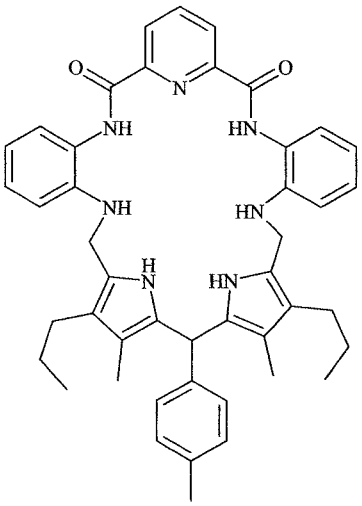
UV-Vis spectroscopy binding studies of receptor **1.52** with acetate and phosphate confirmed the receptor is best suited to this geometry as they are bound with moderate affinities. The association constants were 38,000 M^{-1} and 342,000 M^{-1} respectively however this large affinity for phosphate is undermined by the formation of both 1:1

and 2:1 (anion-receptor) complexes with an association constant of 26,000 M^{-1} for the 2:1 complex. Further competition experiments confirmed this binding pattern reflects the presence of a second binding site that is external to the macrocyclic cavity and therefore is not directly involved in sulfate recognition.

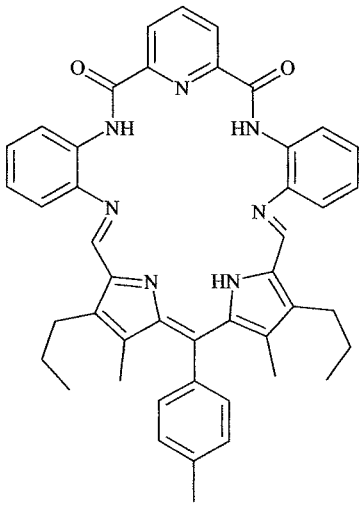
Sessler[39] also synthesised other pyridine-2,6-dicarboxamide dipyrromethane macrocycles **1.53-1.55**. Sessler hoped the substituted β-position of the pyrrole and the toyl group would prevent the flexibility of these macrocycles.



1.53



1.54

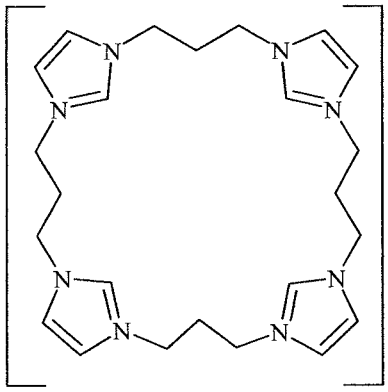


1.55

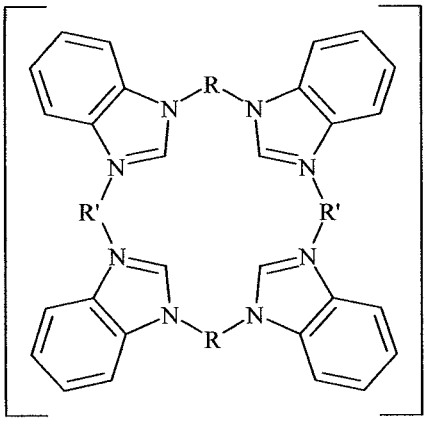
DFT calculations revealed the presence of two binding sites for macrocycle **1.50** was due to the flexibility of the dipyrromethane fragment. However this was unlikely to be observed for macrocycle **1.53** since it was not as flexible. The first equivalent of dihydrogenphosphate also did not bind as strongly due to steric considerations. Together this should result in macrocycles **1.53-1.55** exhibiting greater selectivity for hydrogen sulphate rather than dihydrogenphosphate.

The research carried out by Beer *et al.*[40] also involved the synthesis of macrocyclic receptors with imidazolium moieties which allow the complexation of anions via electrostatic interactions in addition to the hydrogen bonds. He synthesised and tested a series of novel tetrakis(imidazolium) and benzimidazolium macrocyclic receptor

systems **1.56-1.59** to investigate their differences in host-guest binding properties with a range of anions.



1.56



1.57 - R = $(CH_2)_3$, R' = $(CH_2)_3$
1.58 - R = $(CH_2)_4$, R' = $(CH_2)_4$
1.59 - R = $(CH_2)_4$, R' = $(CH_2)_3$

Proton NMR binding studies were carried out for all receptors in a mixture of acetonitrile and water (9:1). This highly competitive solvent mixture was used due to solubility characteristics. The data revealed receptor **1.56** was capable of binding anions by significant downfield shifts of the methine $(C\text{-}H)^+$ imidazolium proton. Both 1:1 and 1:2 binding stoichiometries were observed for receptor **1.56** with fluoride, chloride and bromide. This mixed host-guest binding stoichiometry prevented Beer from determining association constants for these complexes.

The proton NMR data for receptors **1.57** and **1.59** again showed both receptors were capable of binding fluoride, chloride and bromide but only a 1:1 binding stoichiometry was observed. Both receptor **1.57** and **1.59** revealed strong and selective binding towards fluoride with association constants greater than 10^4 M^{-1}. Merck Molecular Force Field (MMFF) was used to calculate the equilibrium geometry of **1.57** with a fluoride anion revealing the fluoride anion was bound to each of the benzimidazolium moieties within the macrocyclic cavity. However, this selectivity for fluoride was found to have little to do with complementarities of the receptors cavity to anion size due to calculated geometries of the larger chloride and bromide anions being very similar. This suggested the observed selectivity is dictated by the basic character of the fluoride anion.

A degree of complementarities of the receptors cavity to anion size can be seen for receptor **1.58** though. The proton NMR binding studies reveals receptor **1.53** binds iodide ions most strongly with an association constant of 900 M^{-1}. This compared to association constants of receptors **1.56**, **1.57** and **1.59** of 370 M^{-1}, 560 M^{-1} and 470 M^{-1} respectively.

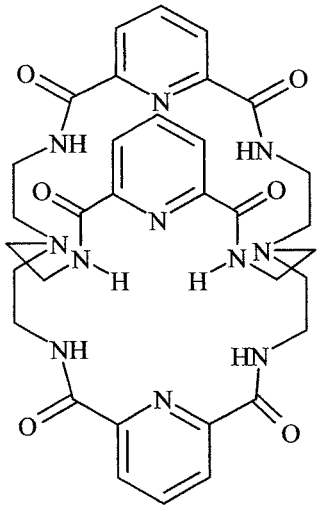
The proton NMR binding studies for the benzoate anion with receptors **1.56-1.58** revealed 1:2 binding stoichiometries. The larger and planar size and shape of the benzoate anion means it can only partially reside within the cavity allowing a benzoate anion to bind to each side of the receptor at independent binding sites.

Beer concluded the preorganisation of his cyclic (tetrakis)imidazolium receptor design is important for anion recognition efficacy.

The research carried out by Bowman-James *et al.*[41, 42] involves the synthesis and testing of a three dimensional macrocyclic receptor **1.60** which compares with the two dimensional receptors in the previous examples. Receptor **1.60** is made up of tren-based cryptands which act as the hydrogen bond donors.

The crystal structure of receptor **1.60** with a chloride anion showed the receptor was monoprotonated, it encapsulated the chloride anion and the anion was bound in the cavity by six hydrogen bonds of varying length so it is not quite in the centre of the cavity but is placed to one side. The crystal structure of receptor **1.60** with a fluoride anion illustrated again the anion was bound by six hydrogen bonds but this time the fluoride was in the centre of the cavity and all of the hydrogen bonds are slightly longer but all of the same length. This crystal structure also revealed the receptor has a symmetrical but twisted coordination pattern when bound to fluoride.

The calculated association constants from proton NMR binding studies of receptor **1.60** with a range of anions in chloroform or acetonitrile exceeded the 10^5 limit. The small amounts of hydrochloric acid present in the chloroform solution were immediately scavenged because the affinity of receptor **1.60** was so high.

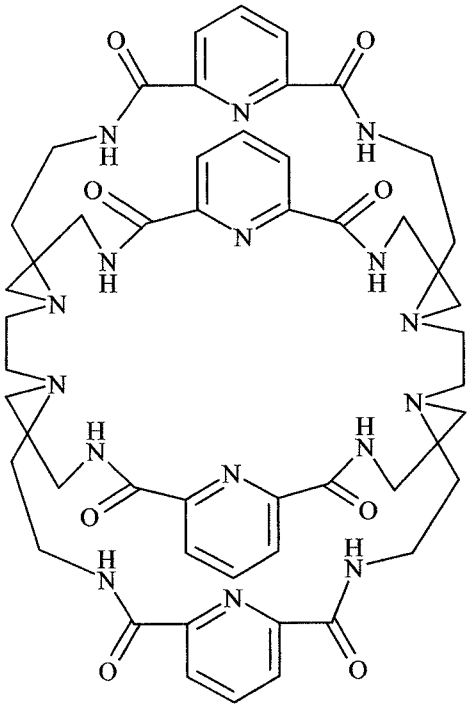


1.60

Instead proton NMR binding studies were carried out in the more polar DMSO solvent. The data revealed receptor **1.60** has a strong affinity and selectivity for fluoride with an association constant of 100,000 M^{-1}. There was a moderate association seen for chloride of 2951 M^{-1} and very weak association observed for bromide of 40 M^{-1}. This was due to both the increasing size and the decreasing hydrogen bonding capabilities of the anions.

This difference in the hydrogen bonding capabilities can also be seen in the comparison of anion with the same geometries. The proton NMR data showed a 30-fold decrease between the trigonal anions acetate and nitrate and a 30-fold decrease between the tetrahedral anions hydrogen phosphate and hydrogensulfate. The hydrogen bonding capabilities of both nitrate and hydrogen sulfate are fairly weak. It was concluded this tren-based amide cryptands receptor has a strong affinity and selectivity for fluoride anions and could represent a new class of receptor for anion binding.

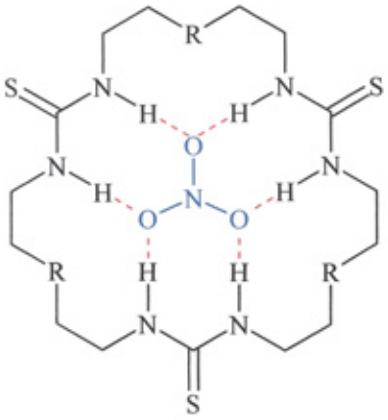
Bowman-James[43] also synthesised tricyclic receptor **1.61** which contained two monocyclic macrocycles joined by two ethylene linkages that each provide a binding site for anions which meant this receptor could be used as a receptor for ditopic anions. This receptor proved to be capable of encapsulating a bifluoride ion as seen in the crystal structure of the expected fluoride complex.



1.61

Proton NMR titrations were carried out in DMSO with a range of anions. The calculated association constants revealed receptor **1.61** bound the ditopic bifluoride with high affinity and selectivity with an association constant of 5,500 M^{-1}. This was 7-fold higher than the dihydrogenphosphate anion which was next strongly bound with an association constant of 740 M^{-1}. The proton NMR titrations carried out with the fluoride guest resulted in the formation of both multiple stoichiometries and the generation of bifluoride producing a complicated titration curve. It was concluded this receptor has a stable complementary structure for ditopic anions.

The research carried out by Herges *et al.*[44] also utilises the approach of neutral macrocyclic receptors but he focused on designing receptors capable of recognition of the weakly basic anions such as nitrate. He started with a chicken wire patterned molecular frame with three thiourea units that can provide the six hydrogen bond donors required to bind to the six hydrogen bond acceptor sites on the nitrate anion as shown in **Figure 1.15**.



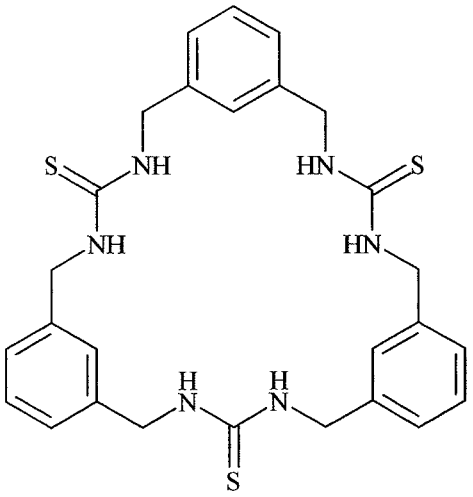
R = O, S, NH, CH_2

Figure 1.15 – Chicken wire designed receptor for the nitrate anion

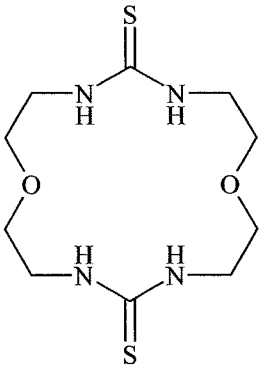
The R groups on the receptor allowed the geometry and size of the cavity to be varied to find the optimum position of the thiourea units. Density functional theory calculations revealed the optimum cavity size required for the nitrate anion is 2.799 Å. Further investigations predicted the optimum geometry comes when the R group was oxygen with a cavity size of 2.727 Å.

Receptor **1.62** (R = O) was synthesised and proton NMR titrations were carried out to investigate its anion-binding properties. The association constant of receptor **1.62** with TBA nitrate was 17.1 M^{-1}. When sodium nitrate was used as the guest the association constant increased to 23.2 M^{-1}. This is likely to be due to the sodium counter-ion coordinating to the ether oxygen atom giving the ionophore greater affinity for the nitrate anion. However correlations of the pKa values of the anions and their association constants revealed receptor **1.62** does not exhibit great binding selectivity for nitrate.

To investigate how important it is to have the exact geometry of the binding site for the anions Herges carried out further NMR titrations using receptor **1.63** (R = S) and **1.64** which had slightly different structures to **1.62**. Receptor **1.65** with only two thiourea units was also investigated for comparison.



1.64



1.65

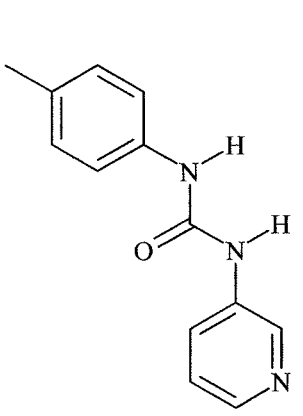
The proton NMR titrations revealed these small structural variations of receptors **1.63** and **1.64** resulted in the binding activity being practically lost with association constants less than 1 M^{-1} for both. Very weak binding was also seen for receptor **1.65**.

In conclusion Herges successfully designed a macrocyclic receptor with affinity for nitrate but no selectivity. He also demonstrated the importance the size and geometry of the binding cavity has on the binding affinity.

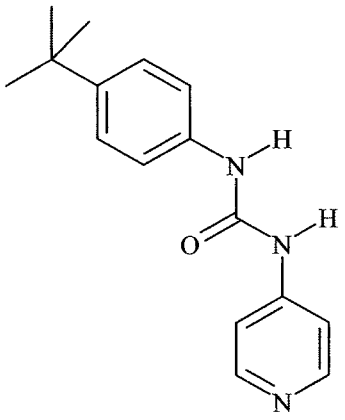
Steed *et al.*[45, 46] has synthesised two receptors that show remarkable shape selectivity for nitrate. Hosts **1.66** and **1.67** are simple urea-substituted receptors which can assemble together using a metal atom. Crystallography reveals these assemblies had the exact size and shape fit for the nitrate anion in the solid-state.

Proton NMR titrations were carried out with a range of TBA oxoanions in acetone to see if this assembly persisted in solution. The free receptors were investigated first and the calculated association constants revealed they hydrogen bond strongly with both nitrate and acetate before they assemble. The association constants were 956 M^{-1} and 3,500 M^{-1} for receptors **1.66** and **1.67** respectively for nitrate. The stronger binding of receptor **1.67** compared to receptor **1.66** may be due to the urea acidity being effected by the inductive effect of the pyridyl atom. The association constants of both receptors with acetate were also very high of over 10^5 M^{-1}. This can be explained by the high

basicity of the acetate anion. The NMR data for the receptors with acetate also revealed the presence of two separate binding modes by the splitting into two of the urea NH proton signal.



1.66



1.67

Proton NMR titrations of $[Ag(\mathbf{1.66})_2]CF_3SO_3$ with TBA nitrate showed the complex bound nitrate with even more selectivity. However the pyridyl resonance showed a change of binding mode after the addition of one equivalent of guest. A Job plot confirmed the first binding mode to be a 1:1 host-guest stoichiometry while the second was the result of a 1:2 stoichiometry. The complex adapted a tweezer-like conformation corresponding to the solid-state structure with a 1:1 stoichiometry. The structure gradually changed after the addition of one equivalent of guest allowing the two nitrate anions to bind separately. The two different structural conformations are shown in **Figure 1.16**.

The association constants of the 1:1 and 1:2 host-guest complexes were 30,200 M^{-1} and 2,900 M^{-1} respectively showing this assembly structure shows great affinity for nitrate. The much higher value of the 1:1 complexes supports the observed geometry shown by crystallography.

The NMR data also showed a third binding mode present when an excess of guest is present. This correlates to a direct coordination of the nitrate anion to the silver atom. However this correlation was very weak compared to the other binding modes with an association constant of 550 M^{-1}.

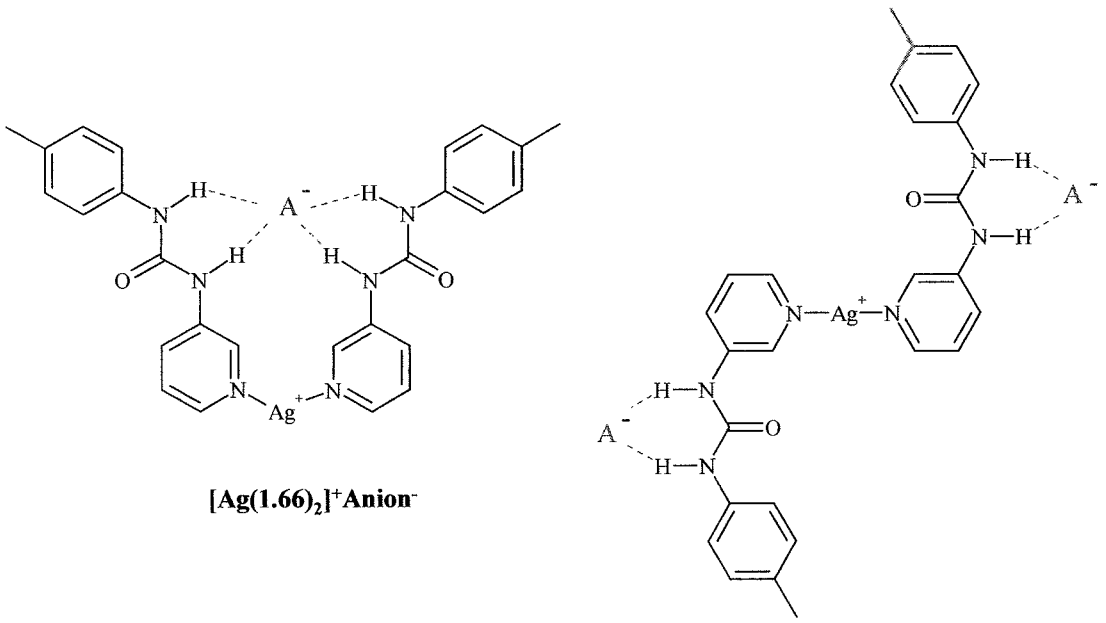


Figure 1.16 – Structural confirmations for the 1:1 and 1:2 host-guest complexes

A different response was seen when $[Ag(\mathbf{1.66})_2]CF_3SO_3$ was titrated with TBA acetate. Changes in the chemical shift values of the NH protons were only really noticeable after one equivalent of acetate was added. This was due to the first acetate equivalent ligating to the silver atom. Significant binding was seen upon addition of further equivalents of acetate with a binding mode modelled as a 1:3 host-guest stoichiometry. The association constants were 4.97 x 10^5 M^{-1} and 5.31 x 10^6 M^{-1} for the 1:1 and the 1:3 complexes showing great affinity, which again can be explained by the high basicity of the acetate anion. However little selectivity was shown because the acetate anion can not template the formation of the tweezer geometry of the complex since it is not the correct shape.

Steed was unable to carryout any binding studies on the receptor **1.67**/metal assembly complex due to its lack of solubility. He concluded the binding affinity can be enhanced when the host is assembled with the correct geometry for a specific guest giving it great selectivity.

Smith *et al*[47] research has also focused on the synthesis of receptors for trigonal oxyanions. Macrobicyclic receptor **1.68** has adjacent anion and cation binding sites and

is capable of extracting alkali halides as shown in **Figure 1.17**. Smith went on to consider if receptor **1.68** is capable of binding oxyanions in particular nitrate.

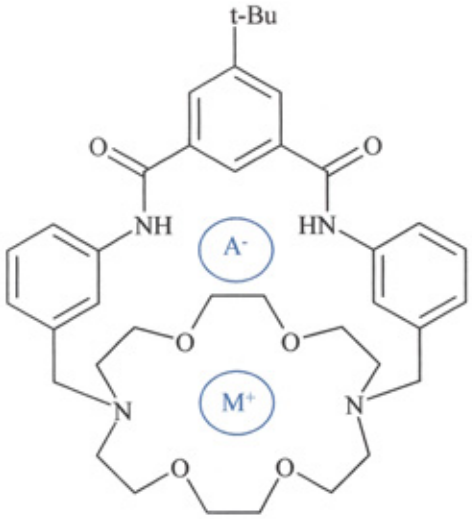


Figure 1.17 – Receptor **1.68** / salt complex

The X-ray structures of the solid-state receptor/salt complexes showed the salts where encapsulated by the receptor and the shapes of the various oxyanions leads to a number of different complexation geometries. They revealed steric factors, hydrogen bonding to the receptor and metal cation coordination bonding control the anions orientation. The X-ray structures revealed the anion and the counter metal cation are directly chelated twisting the receptor/anion orientation. This resulted in directing one or both of the NH protons at the anion π-surface consequently forming weaker hydrogen bonds. Hydrogen bonds formed with lone pair electrons are ~8.37 KJ/mol stronger than the π-electrons.

NMR titrations of receptor **1.68** were carried out with a range of oxyanions in chloroform. The data showed downfield chemical shifts of the NH proton signals when sodium chloride, sodium acetate and potassium acetate were used as the guests, which is consistent with binding. The most noteworthy results shown by the data though comes from the data where nitrate or nitrile salts were used as the guest. The data showed quite different and unusual upfield chemical shifts movements for the hydrogen pointing into the cavity between the two binding sites upon complexation. These unusual changes suggest the nitrate anion has a magnetic shielding surface and was shielded in the region above the central nitrogen. The orientation formed by the encapsulated anion can be

determined by the direction and magnitude of the shielding calculated by quantitative mapping. This revealed the probe was shielded only immediately above the nitrogen ($\pm 20^0$). Although deshielding once again presumes as it advances less than ~1.85 Å towards the nitrogen.

Smith concluded ditopic salt receptor **1.68** was capable of molecular recognition of trigonal oxyanions and provided evidence the nitrate anion has a shielding surface.

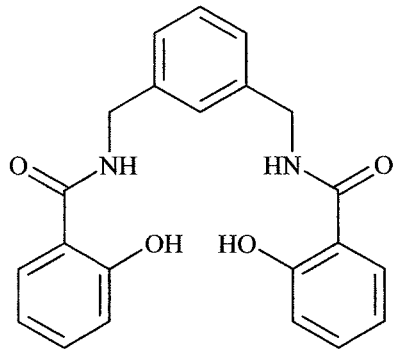
In conclusion receptors can be designed and analysed to detect the stoichiometry, strength and selectivity of binding. More effective and selective second-generation receptors can be synthesised from this insight and eventually tuned receptors suitable for application can be synthesised.

1.4 The Aim of the project

As discussed, receptors capable of binding anions are very important. The basic ideas and concepts above can be combined and expanded to investigate the properties of host/guest binding to develop new receptors with greater affinity, selectivity and efficacy. Our project plan was to synthesis a range of receptors with an array of preorganised hydrogen bond donors that could be analysed to investigate their anion binding affinity and selectivities if any. This was divided into two main areas.

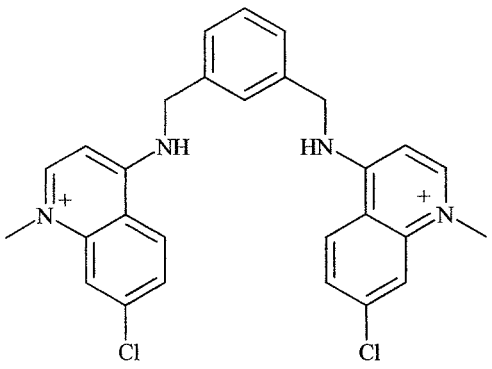
- **The synthesis and testing of supramolecular hosts for halide anions.**

  Initially synthetically trivial hosts such as bis salicylamide **1.69** and its derivatives would be synthesised. This would allow the assessment of the effects increased preorganisation or the number of hydrogen bond donors had on guest binding efficacy and selectivity.



1.69

Secondly charged host such as the bisquinolinium salt **1.70** would be synthesised. The doubly positive charge would aid the effectiveness of the hydrogen bonding.



1.70

- **The synthesis and testing of a cyclotrimeric supramolecular host for nitrate and carbonate anions.**

This compound was designed to have a trigonal array with urea (X=O), thiourea (X=S) and guanidinium ($X=NH^+$) moieties and could hydrogen bond to all six of the lone pairs of the nitrate or carbonate anion exhibiting great affinity and selectivity as shown in **Figure 1.18**.

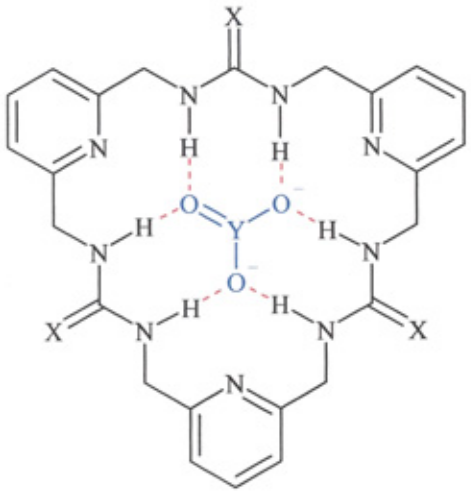


Figure 1.18

Chapter 2

2. Simple receptors for halide anions

2.1 Introduction

Initial investigations focused on the synthesis of a group of simple, synthetically trivial, receptors for halide anions which vary in preorganisation and in the number and type of hydrogen bond donors. This allowed the effect these factors have on guest binding efficacy and selectivity to be analysed by ultraviolet or proton NMR titrations. However a number of these receptors were also highly coloured or fluorescent which allowed them to be investigated as supramolecular chemosensors. If these receptors proved to be successful chemosensors they would allow visual detection of binding of specific anions.

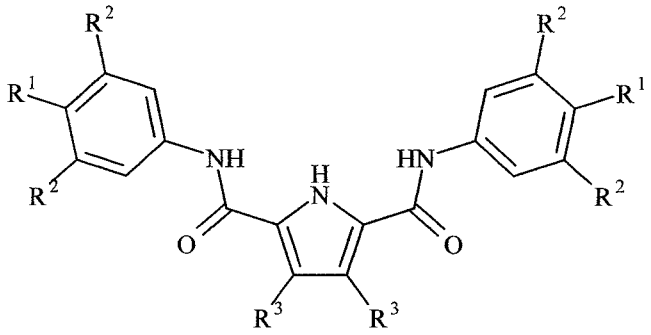
The term chemosensor has been defined as a molecule of abiotic origins that signals the presence of matter or energy[48]. The optical properties of the chemosensor are changed producing a visual response when it binds an analyte by noncovalent intermolecular interactions; hence it is a supramolecular chemosensor.

A number of chemists have designed artificial receptors that proved to be capable of binding analytes with optical responses by changes in their absorption properties. This type of receptor is known as a colorimetric sensor. Fluorimetric sensors will be discussed later in this chapter.

Gale *et al*[22, 49] found receptor **2.1**, a diamine-substituted pyrrole, was a simple receptor that showed selectivity towards oxo-anions. However attempts to increase affinity of the receptor by the introduction of two electron withdrawing chloride substituents producing receptor **2.2** resulted in the deprotonation of the pyrrole NH's by the more basic anions. To try and prevent this, receptors **2.3-2.4** were synthesised with electron withdrawing groups introduced to the phenyl ring to enhance affinity without increasing the pyrrole NH proton acidity. These receptors were not deprotonated in most cases.

Proton NMR titrations of receptor **2.3** in DMSO/ 0.5% water showed this receptor bound strongly with fluoride and benzoate with association constants of 1,245 M^{-1} and 4,150 M^{-1} respectively but only weakly with chloride with an association constant of

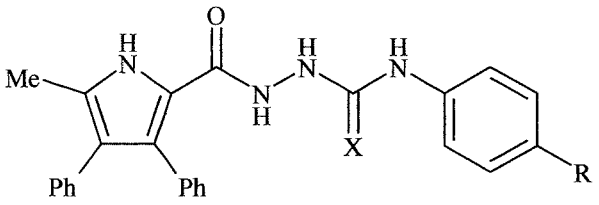
just 39 M^{-1}. Proton NMR titrations of receptor **2.4** under the same conditions resulted in very similar association constants with benzoate and chloride with association constants of 4,200 M^{-1} and 53 M^{-1} respectively. However no shift in the NH resonance was seen with the addition of fluoride. Instead the CH protons of the nitro-aromatic ring move downfield in a three stage process. This was consistent with coordination of the first equivalent to the receptor, deprotonation by the second equivalent and coordination of the third equivalent to the deprotonated receptor. The deprotonated receptor was confirmed by X-ray crystallography.



2.1 $R^1 = R^2 = H$, $R^3 = Ph$
2.2 $R^1 = R^2 = H$, $R^3 = Cl$
2.3 $R^1 = NO_2$, $R^2 = H$, $R^3 = Ph$
2.4 $R^1 = H$, $R^2 = NO_2$, $R^3 = Ph$

Gale also investigated using these receptors as colorimetric sensors. A yellow colour appeared with receptor **2.3** in acetonitrile with fluoride, benzoate and dihydrogenphosphate, the anions that were bound most strongly. An intense blue colour was observed with receptor **2.4** in acetonitrile upon addition of fluoride. Gale believes this is due to fluoride acting as a base, deprotonating the receptor resulting in charge transfer interactions.

Gale *et al*[22, 50] went on to investigate anion binding versus deprotonation in colorimetric anion sensors. The deprotonation process is controlled by the basicity of the anion, the stability of the conjugate base and the acidity of the receptor. Compounds **2.5-2.8** were synthesised which have increasing acidity and their interactions with anions were investigated by UV-Vis and proton NMR titrations in DMSO to identify which process, deprotonation or binding, occurred.



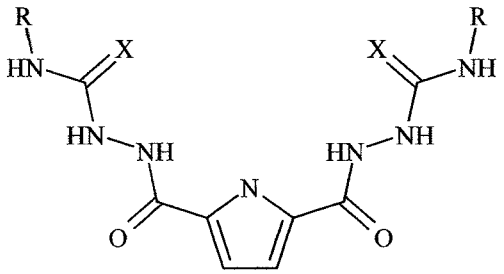
2.5 X = O, R = H
2.6 X = O, R = NO_2
2.7 X = S, R = H
2.8 X = S, R = NO_2

No significant changes were observed in the spectra from both the UV-Vis and proton NMR titrations for compound **2.5** upon addition of anions indicating no significant interactions were taken place. However the more acidic **2.6** proton NMR spectra indicated a hydrogen bonding interaction taken place with TBA fluoride, acetate, benzoate and dihydrogenphosphate by the broadening of all the amide signals. This was accompanied by a colour change visible to the naked eye from almost colourless to dark yellow so UV-Vis titrations were carried out. Association constants were calculated for the more basic anions fluoride, acetate, benzoate and dihydrogenphosphate of 3,010 M^{-1}, 5,580 M^{-1}, 1,440 M^{-1} and 1,060 M^{-1} respectively in DMSO.

UV-Vis titrations of receptors **2.7** and **2.8** with these anions resulted in dramatic changes but the resultant binding curves were too steep to allow calculation of association constants. The changes observed with receptor **2.8** were again accompanied by a distinct colour change from yellow to red. Proton NMR titrations revealed these four anions deprotonate compound **2.8**. This was indicated by the appearance of three new sharp amide signals instead of broadening of the signals. Similar behaviour was observed for the less acidic **2.7** but complete deprotonation only occurred upon addition of excess anionic guest.

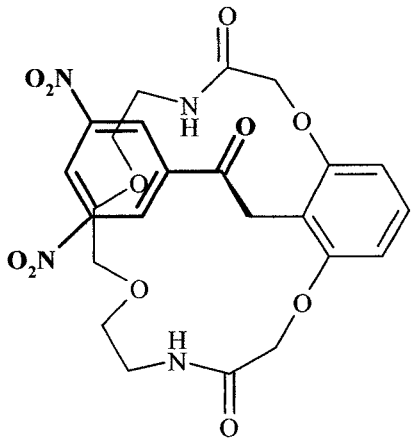
Gale[51] also synthesised disubstituted pyrrole derivatives **2.9-2.11** which resulted in the more favourable cheft-like binding mode in the hope of increasing affinity. To avoid deprotonation only the urea derivatives were synthesised. Although the NH signals in the proton NMR spectrum broadened upon addition of TBA fluoride, acetate, benzoate and dihydrogenphosphate this broadening prevented any association constants being calculated. Instead the association constants were calculated by carrying out UV/Vis

titrations. The results showed the disubstituted pyrrole receptors had increased affinity for anions compared to the mono-substituted receptor **2.6**. For example the association constant for receptor **2.10** with fluoride is 8,590 M^{-1} compared to 3,010 M^{-1} for receptor **2.6**. However the previous selectivity shown with the mono-substituted receptors had been lost.



2.9 X = O, R = Ph
2.10 X = O, R = 4-nitrophenyl
2.11 X = O, R = 3,5-dinitrophenyl

Jurczak *et al*[52, 53] also developed a colorimetric anion sensor **2.12** which allowed visual detection for anions with similar basicity. Proton NMR titrations were carried out with a range of anionic guests in DMSO and acetonitrile and the association constants were calculated.



2.12

The results showed receptor **2.12** had greater binding affinities for the more basic anions, for example fluoride and acetate, in DMSO. However crucial changes were

observed when the solvent was changed to acetonitrile. In most cases the association constants increased as shown in **Table 2.1**. The most notice change was for that of dihydrogenphosphate which increased from 142 M^{-1} to 4,271 M^{-1}. Jurczak believed the interaction between the ethereal oxygen atoms of receptor **2.12** and the hydroxyl group of dihydrogenphosphate was enhanced in acetonitrile and suppressed by DMSO.

Anion	H:G	Ka (DMSO)	Ka (CD_3CN)	pKa
F^-	1:2	7.8×10^6	7.5×10^6	3.18
AcO^-	1:1	337	503	4.76
$H_2PO_4^-$	1:1	142	4,271	2.15
HSO_4^-	1:1	32	138	-3.1
Cl^-	1:1	5	164	-6.1

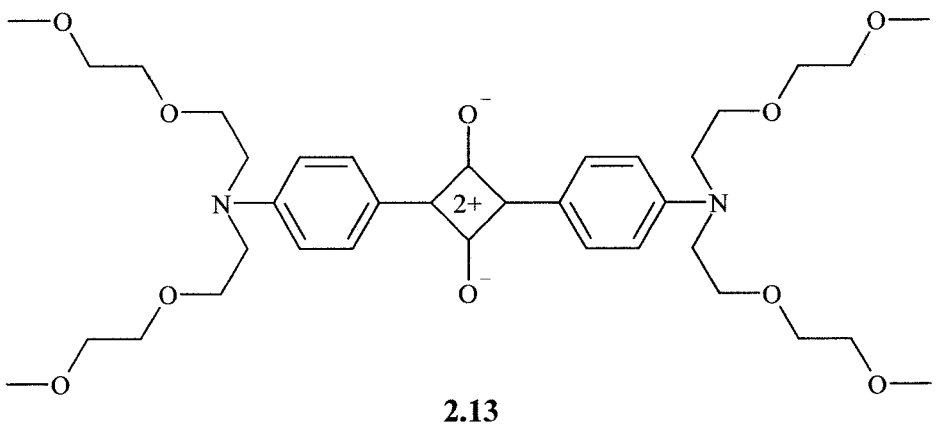
Table 2.1 – Association constants (M^{-1}) of receptor **2.12** from proton NMR titrations

Dramatic colour changes were also observed in both solvents allowing visual detection. Solutions of receptor **2.12** changed from a colourless solution to dark blue, yellow and yellow upon addition of fluoride, acetate and dihydrogenphosphate in DMSO. Solutions of receptor **2.12** changed from a colourless solution to turquoise, yellow and purple upon addition of fluoride, acetate and dihydrogenphosphate in acetonitrile.

Martinez-Manez *et al*[54] reported a chromogenic reagent **2.13** which can determine the presence of cyanide which was of great interest since cyanide is one of the most toxic anions. However this selective decolouration was observed due to nucleophilic attack of the cyanide anion to the electron deficient squaraine. The ether chains improve the solubility of the squaraine.

Initial studies of **2.13** were carried out in acetonitrile with a range of anions but only cyanide could induce a change from a blue solution to colourless. Proton NMR showed this change was due to the loss of the acceptor character of the squaraine ring and prevention of electron delocalisation when the cyanide attacks a carbon next to the phenyl group on the squaraine ring. This decolouration process was found to be

proportional to the cyanide concentration and increased with time. Further studies revealed **2.13** could act as a selective chromogenic reagent for cyanide in water.



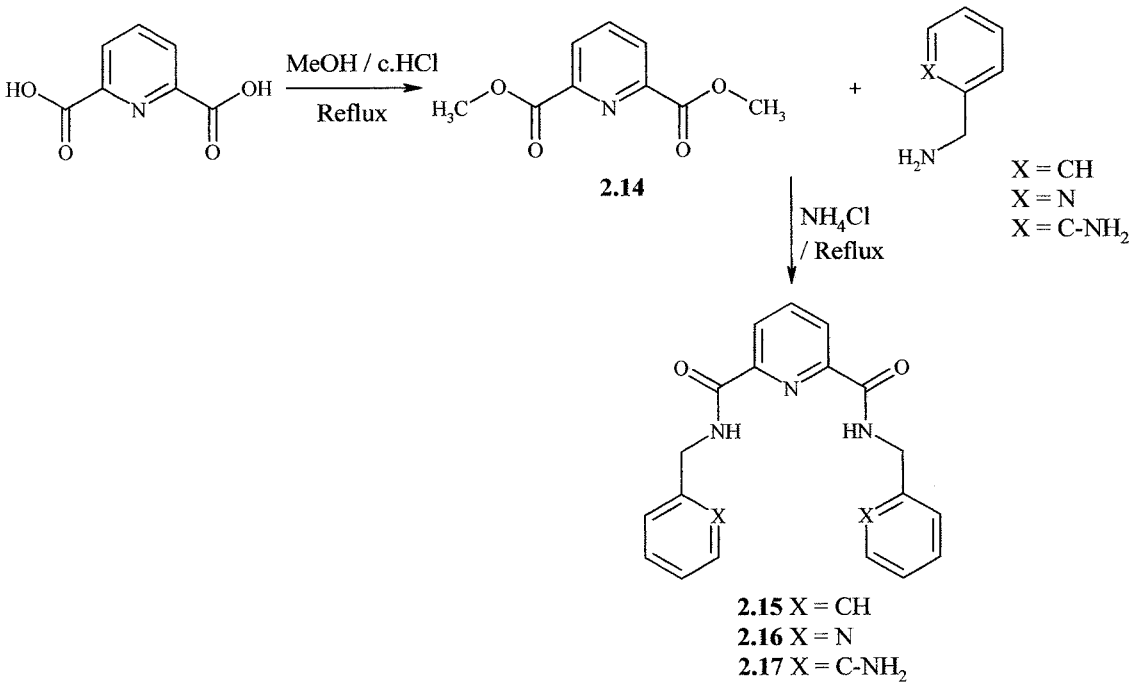
2.13

It was hoped a number of our synthesised receptors would act as chemosensors by the visual appearance of a colour change upon hydrogen bonding to an anionic guest.

2.2 Synthesis of simple receptors

The initial designs of receptors developed the work by Crabtree in creating a cleft with correctly oriented arrays of two amides that can form a binding motif for anions[12, 15]. 2,6-dimethylpyridinoate **2.14** was synthesised first that would act as the starting material for the first set of receptors as shown in **Scheme 2.1**. 2,6-pyridinedicarboxylic acid underwent esterification by refluxing the acid in methanol in the presence of concentrated hydrochloric acid, which acts as a catalyst[55]. Proton NMR and TLC confirmed the precipitated crystals were diester **2.14** in 80 % yield and showed no further purification was needed.

Compound **2.14** was then refluxed with either benzylamine or 2-(aminomethyl) pyridine in the presence of ammonium chloride[56] to obtain receptors **2.15** and **2.16** respectively. The formation of **2.15** and **2.16** was confirmed by proton NMR in 92% and 89% yield and again the resulting crystals that precipitated from the reaction mixture needed no further purification.



Scheme 2.1

The proton NMR for receptor **2.15** also revealed the amide signal was at 9.92 ppm higher than expected and very sharp as shown in **Figure 2.1**.

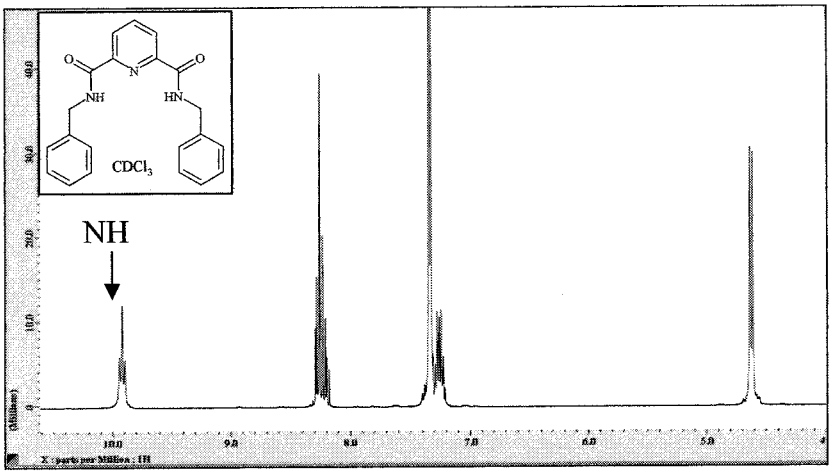
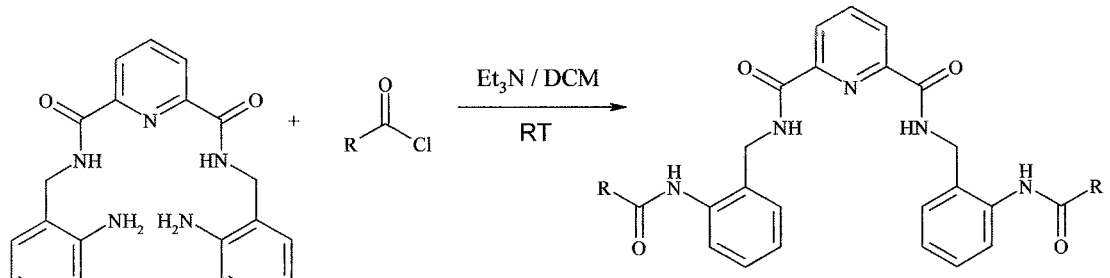


Figure 2.1 – Proton NMR of receptor **2.15** in chloroform

This can be explained by intra-molecular hydrogen bonding taking place between the hydrogen on the amide group and the lone pair of electrons on the nitrogen atom. This will prevent rotation and pre-organise the receptor for anion binding. This is just as

pronounced for receptor **2.16** with the amide signal at 9.37 ppm. This time the hydrogen on the amide group could also bind to the nitrogen atoms on both pyridine rings.

Synthesis of receptor **2.13** was also attempted by refluxing **2.14** with 2-aminobenzylamine but TLC and proton NMR showed the reaction did not go to completion with starting material still present. Attempts to purify the required product by recrystallisation were unsuccessful. Instead receptor **2.17** was reacted with two equivalents of acetyl chloride, benzoyl chloride or 3,5-dinitrobenzoyl chloride to form receptors **2.18**, **2.19** and **2.20** respectively as shown in **Scheme 2.2** which may have been easier to purify. Purification by flash column chromatography gave receptors **2.18** and **2.19** which were confirmed to be the desired products by proton NMR and E.S.M.S. Even though E.S.M.S. confirmed the formation of receptor **2.20** the proton NMR showed starting material was still present.

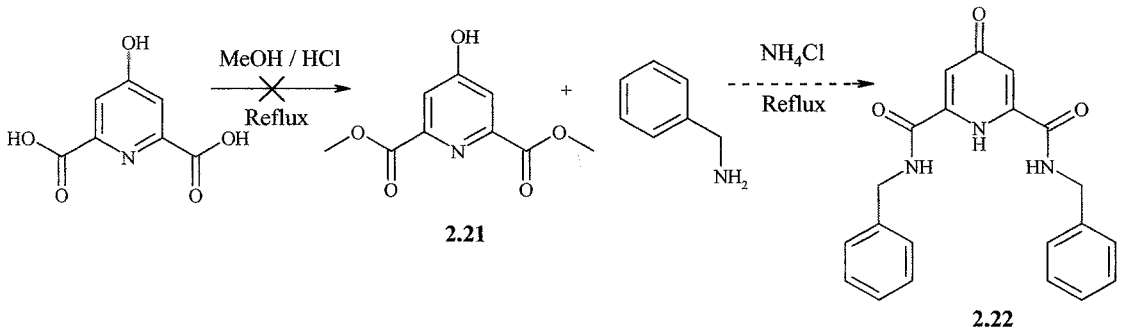


2.13

2.18 R = H
2.19 R = Ph
2.20 R = 3,5-dinitro Ph

Scheme 2.2

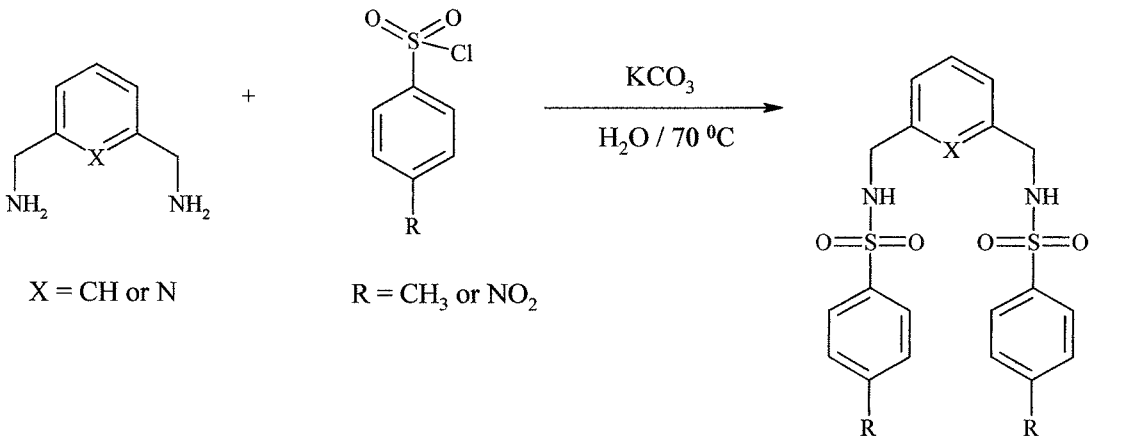
Attempts were made to take this group of receptors one step further with the introduction of a pyridinone functional group by the synthesis of receptor **2.22** as shown in **Scheme 2.3**. This was attempted by an analogous two-step process used in the synthesis of receptors **2.14-2.17** substituting pyridine-2,6-dicarboxylic acid for chelidamic acid hydrate in the first step to form **2.21**. Unfortunately proton NMR showed the reaction was unsuccessful with only starting material present. This meant the synthesis of **2.22** could not be carried out.



Scheme 2.3

Research focussed next on the synthesis of a set of similar receptors but these receptors have two sulphoxide groups present. The sulphoxide group alters the pKa of these receptors which alters the binding affinity or selectivity[15, 28] and allowed a comparison of binding between the two sets of receptors. Receptors **2.23-2.25** were synthesised by the nucleophilic substitution of the relevant sulfonyl chloride by heating with 3-(aminomethyl) benzylamine or compound **2.27** in the presence of potassium carbonate as shown in **Scheme 2.4** with 78 %, 71 % and 22 % yields respectively.

Proton NMR and E.S.M.S confirmed receptor **2.23** which precipitated out the reaction mixture needed no further purification but receptor **2.24** was recrystallised from ethanol.



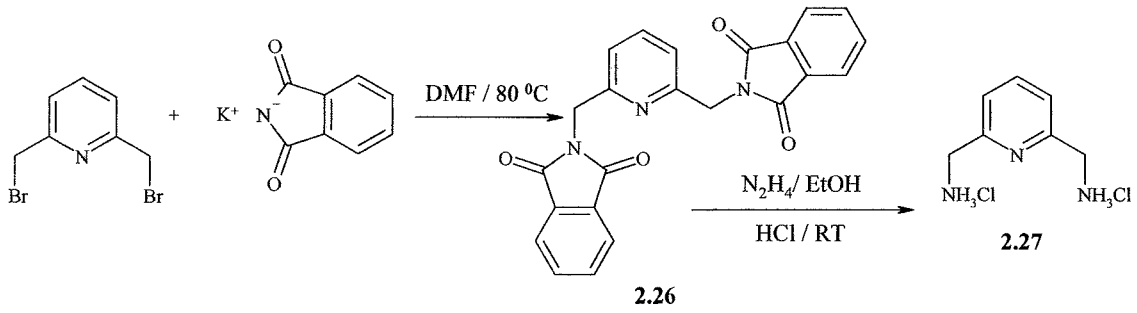
X = CH or N

R = CH_3 or NO_2

2.23 X = CH, R = CH_3
2.24 X = CH, R = NO_2
2.25 X = N, R = NO_2

Scheme 2.4

Receptor **2.25** was also synthesised in the same way but the starting material is not readily available and had to be synthesised first using the two-step Gabriel synthesis as shown in **Scheme 2.5**. In the first step compound **2.26** was synthesised by the alkylation of phthalimide by heating with the appropriate dibrominated compound[57]. The precipitated crystals were not soluble enough to get a proton NMR or a carbon NMR spectrum but the presence of **2.26** was confirmed by E.S.M.S. This was then reacted with hydrazine hydrate and hydrochloric acid to form the hydrochloride salt **2.27**[57]. This was used directly in the synthesis of receptor **2.25**, with no need to remove the hydrochloride salt, since the reaction was carried out under basic conditions.



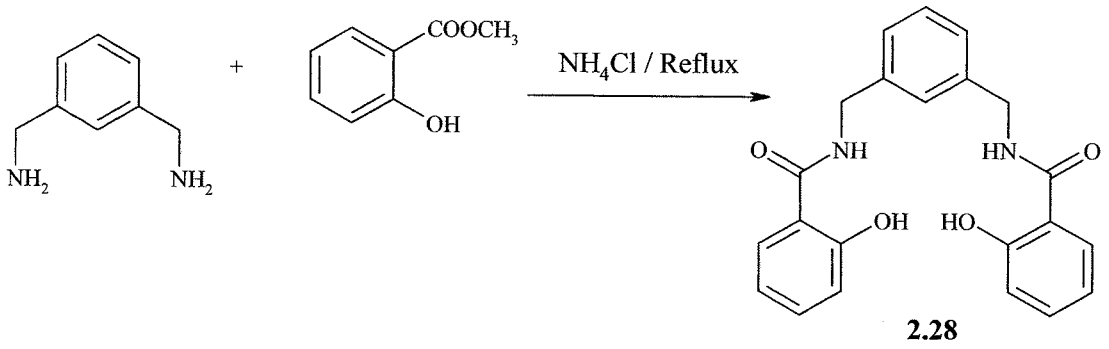
2.26 **2.27**

Scheme 2.5

Again receptor **2.25** was recrystallised from ethanol and proton NMR confirmed the recrystallised precipitate was receptor **2.25**.

Studies focussed next on the preparation of bis salicylamide **2.28** another receptor that exhibits a Crabtree-like cleft but has a phenol group present that increases the number and type of hydrogen bonding moieties. This phenol group would also allow utilization of classic azo dye chemistry to produce compounds that could indicate the binding of an anion by a colour change.

Preparation was carried out by the nucleophilic substitution of methyl salicylate by refluxing with 3-(aminomethyl) benzylamine in the presence of a catalytic amount of ammonium chloride as shown in **Scheme 2.6**.

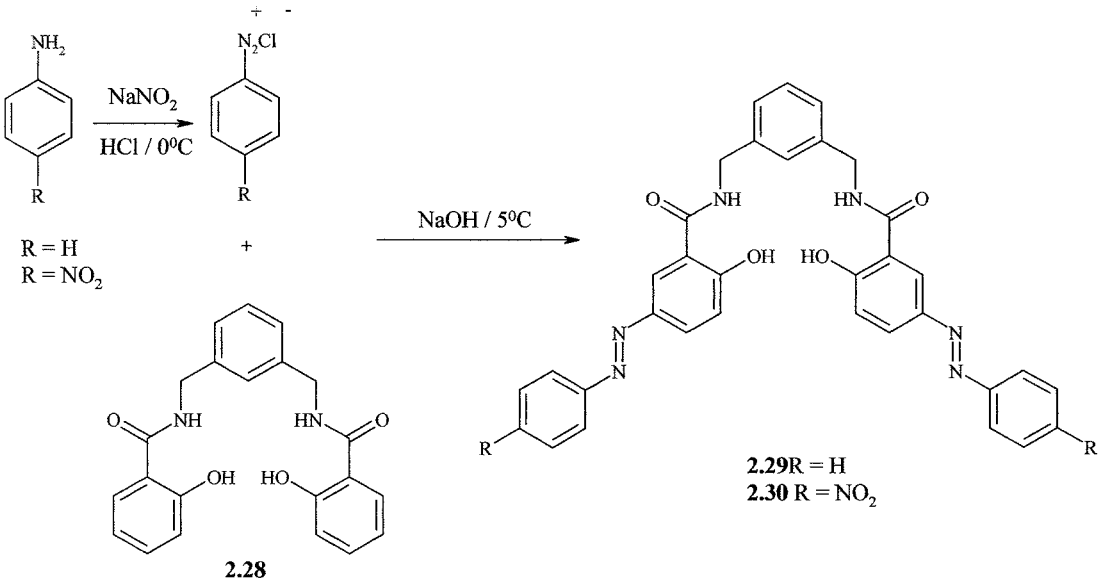


2.28

Scheme 2.6

TLC and proton NMR showed a mixture of receptor **2.28** and starting material. This was purified by recrystallisation in aqueous ethanol to obtain receptor **2.28** in 23 % yield. The proton NMR showed the amide peak is broad compared to the sharp peak seen for receptor **2.15** but on addition of a tetrabutylammonium salt of an anion the amide peak moves to a higher ppm indicating receptor **2.28** is capable of anion binding. When a proton is hydrogen bonded the electron density of the proton is spread onto the hydrogen bond acceptor and therefore there is less density on the hydrogen atom making the proton more deshielded resulting in a higher chemical shift. The more hydrogen bonding there is the higher the chemical shift. The proton NMR also showed the amide peak becomes more coupled, from a broad signal to a sharp triplet, upon addition of a tetrabutylammonium salt of an anion. Normally there is an exchange between the amide group and water molecules preventing the effect of the neighbouring hydrogens being seen during the NMR time scale therefore no coupling is seen. However when hydrogen bonding takes place no exchange can take place so the effect of the neighbouring hydrogens can now be seen. The full capabilities of receptor **2.28** to bind anions will be explained later in this chapter.

Bis-salicylamide **2.28** was then used as a basis for the synthesis of the next two receptors. Firstly bis-salicylamide was reacted with the aniline diazo salt[55] to yield receptor **2.29** that exhibits the same qualities but is a larger more conjugated receptor resulting in a yellow compound (λ_{max} 345 nm) instead of the colourless bis salicylamide. This was carried out as a two-step process as shown in **Scheme 2.7**.



Scheme 2.7

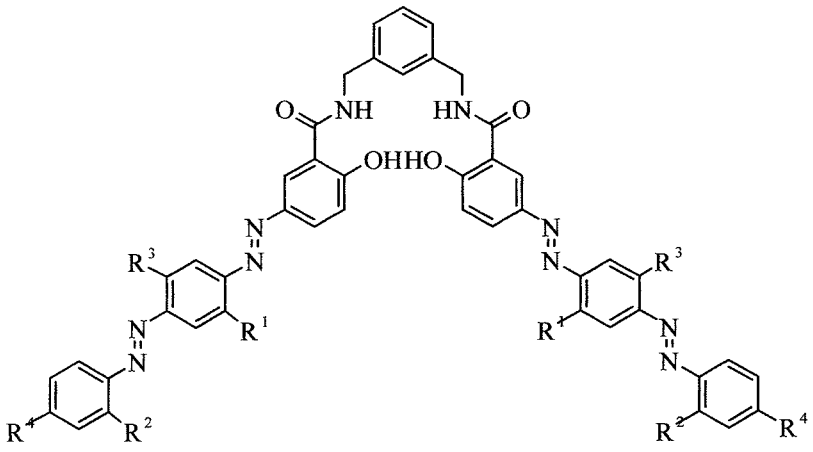
In the first step aniline was diazotised by dissolving in concentrated hydrochloric acid and water (1:1) and adding a solution of sodium nitrite maintaining the temperature below 0 ^{0}C. In the second step this cold diazo salt was added to a solution of bis salicylamide dissolved in sodium hydroxide maintaining the temperature below 5 ^{0}C to yield receptor **2.29**.

TLC and proton NMR showed the precipitated crystals were a mixture of starting material, mono substituted product and receptor **2.29**. This was purified by recrystallisation from ethanol to obtain receptor **2.29** in 36 % yield. The NMR showed only the desired product was present with no additional baseline material.

Receptor **2.30** was synthesised by an analogous method using p-nitroaniline instead of aniline and a small amount of urea was also added at the beginning of the second step to remove any remaining nitrous acid[58]. This resulted in receptor **2.30**, which had an additional nitro functionality giving a red compound (λ_{max} = 525 nm) instead of the previous yellow. Again TLC showed purification was needed and recrystallisation from ethanol gave a 3 % yield of the desired receptor. The proton NMR confirmed the presence of pure receptor **2.30**.

Since both receptors were highly coloured they could have be used to show visual characteristic colour changes with the addition of tetrabutylammonium salts of different anions through azo dye chemistry.

Attempts were made to extend these molecules further by the aromatic electrophilic substitution of bis salicylamide **2.28** with both Fast Garnet Salt and Fast Black Potassium Salt by repeating the second step of **Scheme 2.7**. This would have resulted in receptors **2.31** and **2.32** which are even more conjugated and have an additional range of electron withdrawing or electron donating groups present resulting in more highly coloured receptors that could be used for visual detection.

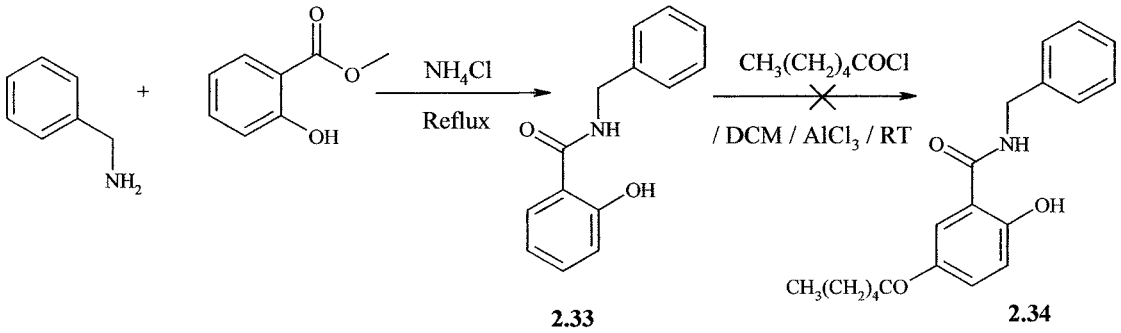


2.31 $R^1 = CH_3$, $R^2 = CH_3$ $R^3 = CH$, $R^4 = CH$
2.32 $R^1 = OCH_3$, $R^2 = H$, $R^3 = OCH_3$, $R^4 = NO_2$

Unfortunately proton NMR and E.S.M.S showed the reaction was unsuccessful with only starting material present. TLC revealed a number of impurities in the commercially available diazo salts which could be preventing the reaction from working.

Since this was not possible we moved on instead of trying to extend these receptors further. Initial solubility tests proved receptors **2.29** and **2.30** are only soluble in selected organic solvents so research focussed next on trying to add additional chains which should help overcome this. Adding branches allows easier solvation of the molecules with solvent, increasing the degrees of freedom which increases entropy making it more energetically favourable hence more soluble.

This was first attempted by trying to add the side chains onto receptor **2.28**, which also has poor solubility, resulting in the receptor having two additional side chains in the four positions of the pendant phenyl rings. This was attempted as a two step process as shown in **Scheme 2.8**. In the first step receptor **2.33** was synthesised in 66 % yield by the nucleophilic substitution of methyl salicylate by benzylamine in the presence of ammonium chloride to be used as a starting material which if successful can be repeated with receptor **2.28**. Proton NMR showed the precipitated crystals of receptor **2.33** needed no further purification. This was then stirred with hexanoyl chloride in the presence of aluminium chloride to try and yield the acylated receptor **2.34**[59]. Unfortunately proton NMR showed the reaction was unsuccessful with only starting material present in the sample.



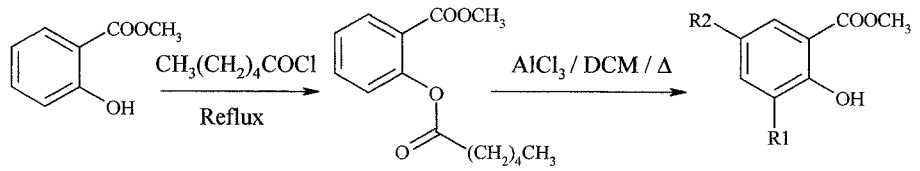
2.33 **2.34**

Scheme 2.8

Next we attempted to add the chain to methyl salicylate (the starting material for receptor **2.28**). This was attempted by the Friedel Craft acylation of methyl salicylate using the procedure described above, the second step of **Scheme 2.8**. Proton NMR showed the desired product was possibly present but in a small yield and the rest of the sample was starting material. This experiment was repeated using acetyl chloride instead of hexanoyl chloride, the original conditions. Proton NMR showed the desired product was not present in the sample instead it was a mixture of methyl salicylate and di-ester.

It was decided another approach was required. This time attempts were made to add the chain to methyl salicylate using the Fries Rearrangement[60]. This again was a two-step process as shown in **Scheme 2.9**. The first step involved the esterification of methyl salicylate by refluxing with hexanoyl chloride to yield compound **2.35** in 66 % yield.

Proton NMR and G.C.M.S. showed product **2.35** needed no further purification. This was added to a mixture of aluminium chloride in dichloromethane and heated at 40 ^{0}C to try and yield the rearranged product **2.36**.



2.35

2.36 = R1 = H, R2 = $CO(CH_2)_4CH_3$
2.37 = R1= $CO(CH)_4CH_3$, R2 = H

Scheme 2.9

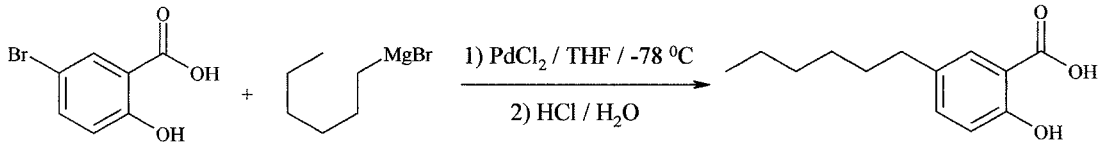
Unfortunately proton NMR and G.C.M.S. showed the reaction did not work and there was no desired product in the sample. Instead the sample was a mixture of methyl salicylate and starting material. The presence of methyl salicylate indicates compound **2.35** must be broken down during the second step. The second step was repeated using nitrobenzene as the solvent instead of dichloromethane. TLC showed a mixture of three compounds and the proton NMR spectrum revealed the resultant crystals were mainly methyl salicylate and *ortho* substituted product with trace amounts of desired product. This was expected since the principal position is the *ortho* position for the Fries Rearrangement[61]. Separation was still attempted by flash column chromatography. Unfortunately TLC showed there was nothing in the eluant no matter what solvent ratio was used. The compounds must have crystallised on the column.

The second step was repeated again without any solvent present[62]. Again TLC showed a mixture of compounds. Purification by flash column chromatography resulted in the isolation of **2.36** which was confirmed by proton NMR and G.C.M.S. Unfortunately though the desired product was only isolated in a 14 % yield which is unsuitable since this compound was to be used as a starting material.

It was decided the Fries Rearrangement was not a suitable approach to extend the synthesised hosts. The electron withdrawing ester group on the starting materials were probably preventing the above reactions from occurring. The function of the aluminium chloride in these reactions is to withdraw electron density by coordinating to the acyl-

oxygen allowing the rearrangement to take place[61]. Unfortunately this coordination can take place with the oxygen on the ester group preventing the reaction.

The next approach was to try and add a chain to methyl salicylate using a Grignard reagent[63] as shown in **Scheme 2.10**. 5-Bromosalicylate acid underwent a palladium coupling reaction by slowly adding hexylmagnesium bromide at -78 ^{0}C in an inert atmosphere in the presence of palladium dichloride to form **2.38**.

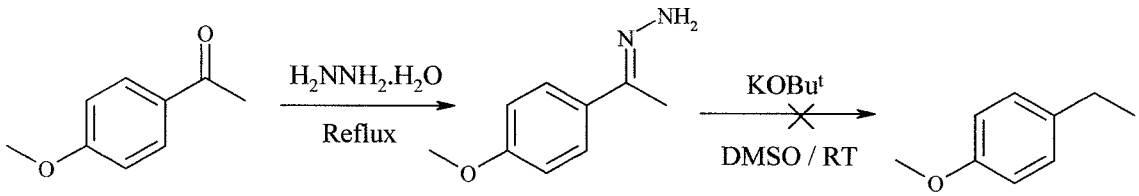


2.38

Scheme 2.10

Proton NMR and E.S.M.S confirmed the formation of the desired product with only slight baseline impurities present by proton NMR. However the reaction had a very low yield at only 5 %. This was not good enough since receptor **2.38** would be the starting material at the beginning of the receptor synthesis process and we decided another approach was needed.

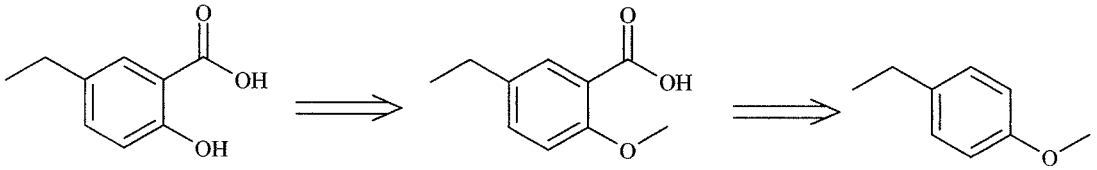
The next approach was to try and add a chain via the formation of a hydrazone[64] as shown in **Scheme 2.11**. Methoxyacetophenone was refluxed with hydrazine hydrate to give **2.39** in 45 % yield. Proton NMR showed the extracted product needed no further purification and was used directly in the attempted synthesis of **2.40**. A Wolff-Kishner Reduction was attempted by stirring with potassium tert-butoxide[65] to form **2.40**. Proton NMR showed the desired product was not present with the absence of the CH_2 group instead only starting material was present but E.S.M.S suggested the desired product was present. This was only seen as a trace amount on the proton NMR baseline so purification was not attempted.



2.39 **2.40**

Scheme 2.11

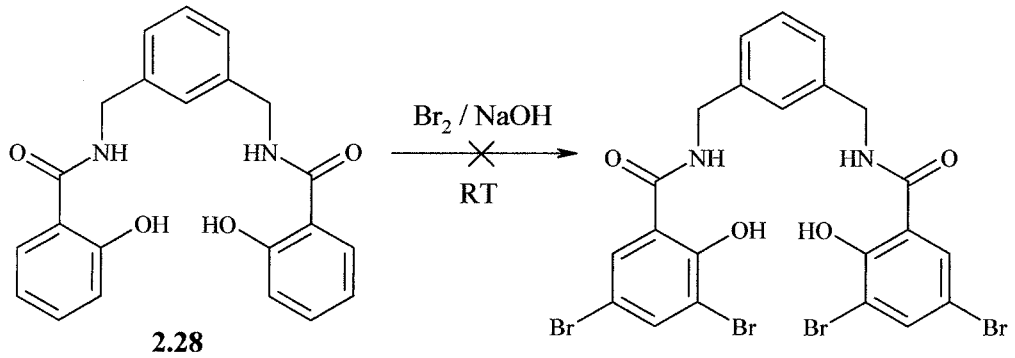
It was hoped compound **2.40** would undergo a Vilsmeier reaction followed by oxidation to add the carboxylic acid group followed by cleavage of the ether linkage by hydrogen iodide or hydrogen bromide to produce compound **2.41** as shown in **Scheme 2.12**. This could have then been used as the starting material for the synthesis of the receptors.



2.41 **2.40**

Scheme 2.12

It was decided that it was not possible to increase the host's solubility by adding a side chain. The last attempt at increasing solubility was by bromination. Receptor **2.28** was stirred with bromine under basic conditions to hopefully give receptor **2.42** as shown in **Scheme 2.13**.



2.28 **2.42**

Scheme 2.13

The precipitated crystals were not very soluble and the solution proved too weak to get a proton NMR. However E.S.M.S showed the desired product was not present only starting material.

Since it was proving impossible to increase the solubility of these receptors further analysis was carried out in the organic solvents that these receptors were soluble in.

2.3 Visual analysis of binding by colour changes

Computer based molecular mechanics experiments using 'Hyperchem' showed how receptor **2.28** is designed to have a correctly oriented array to hydrogen bond to specific anions as shown in **Figure 2.2** below. This was obtained by model building receptor **2.28** using molecular mechanics MM+ force field followed by geometrically optimisation using semi empirical PM3. A chloride anion was then strategically placing in position showing the receptor cleft and anion size ratio.

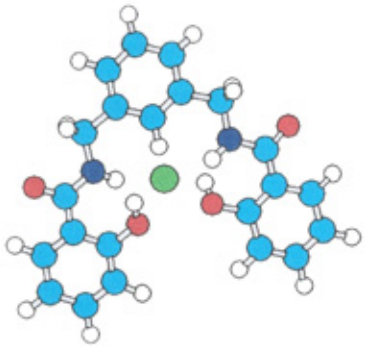
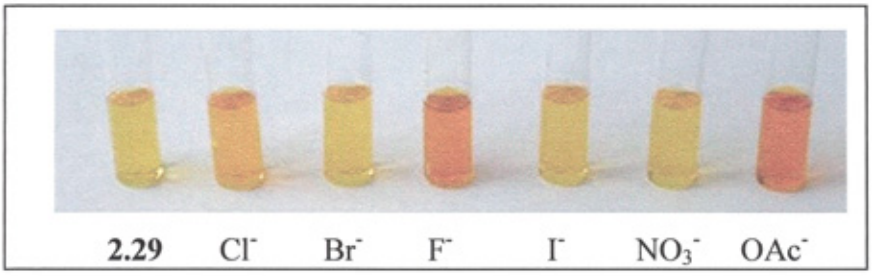


Figure 2.2 – Receptor **2.28** with a bound chloride anion

Receptor **2.28** is a colourless solid that dissolved in chloroform to form a colourless solution but no visual detection of binding could be seen with the addition of anions. However receptors **2.29** and **2.30** both dissolved to form highly coloured solutions that showed characteristic colour changes with the addition of tetrabutylammonium salts of different anions.

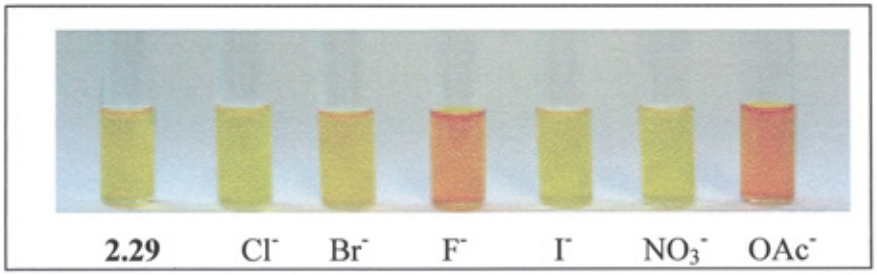
A solution of receptor **2.29** (0.002 M) was made up in chloroform and 1 ml of solution was placed into seven different glass tubes. A different tetrabutylammonium salt (0.05

g) of an anion was added into each tube and any observations recorded. **Photograph 2.1** below shows the resulting colours. The solutions containing receptor **2.29** with chloride, fluoride and acetate showed colour changes indicating complexes forming.



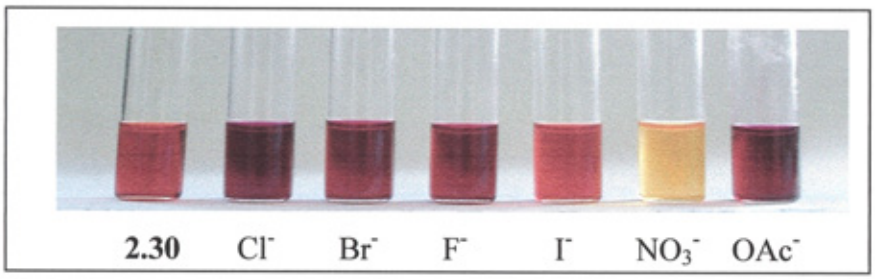
Photograph 2.1 – Receptor **2.29** with a range of anions in chloroform

The above procedure was repeated for receptor **2.30** but unfortunately receptor **2.30** would not dissolve in chloroform so the solvent was changed to acetone. **Photograph 2.3** below shows the various colour changes observed for receptor **2.29** (0.004 M) in acetone indicating complexes forming with fluoride, acetate and very slightly with bromide.



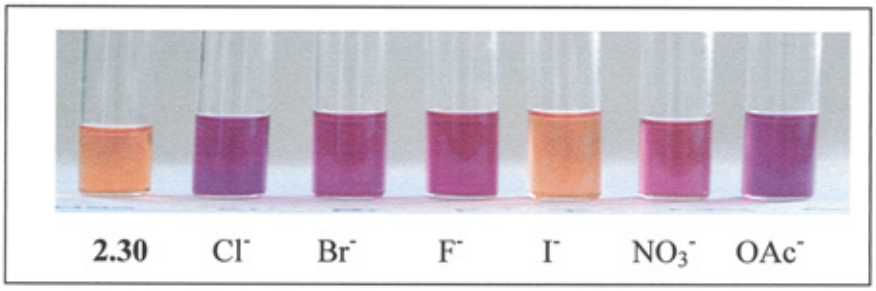
Photograph 2.2 – Receptor **2.29** with a range of anions in acetone

Photograph 2.3 shows the various colour changes observed for receptor **2.30** (0.001 M) in acetone indicating complexes forming between receptor **2.30** with all anions except iodide. This proved the addition of the nitro group on receptor **2.30** makes it capable of binding to more anions. This is because the charge can be delocalised further on to the nitro group strengthening the attraction to the hydroxyl group.



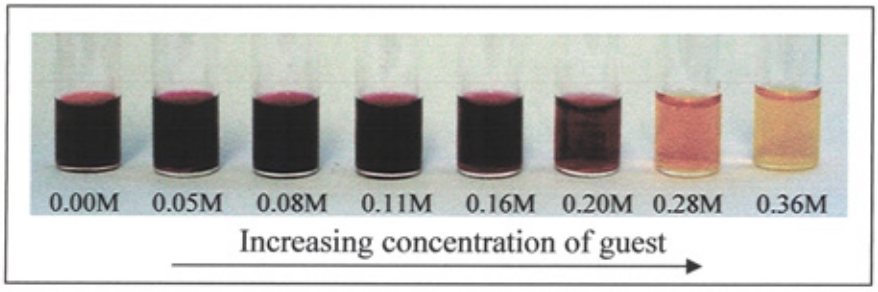
Photograph 2.3 – Receptor **2.30** with a range of anions in acetone

Photograph 2.3 also shows that a very individual response is seen for nitrate. This is not due to a chemical reaction taking place because it was reversible and did not occur at a lower concentration. This was shown when all of the solutions were diluted by a factor of ten, a purple/pink colour is observed for all the binding solutions including nitrate as shown in **photograph 2.4**



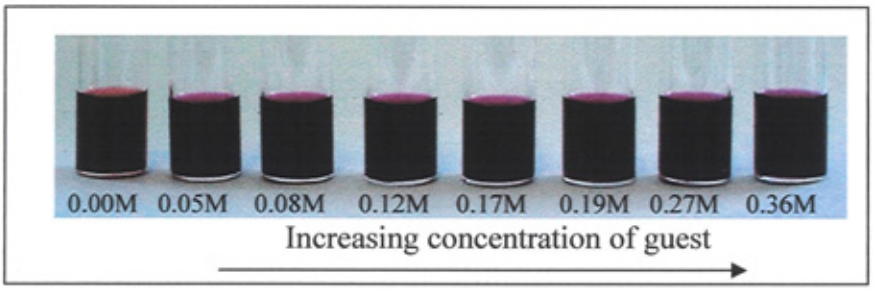
Photograph 2.4 – Dilute receptor **2.30** with a range of anions in acetone

This response was proven to be a concentration issue by slowly increasing the concentration of the TBA nitrate guest in each host solution of receptor **2.30** (0.0005 M) until this unusual colour change was observed as shown in **photograph 2.5**. The results showed this response is only observed at high concentrations.



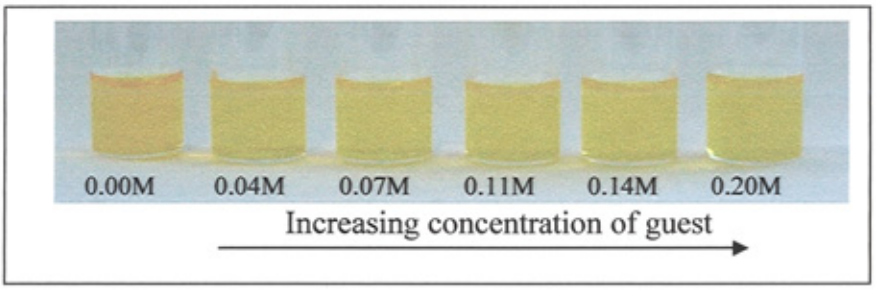
Photograph 2.5 – Receptor **2.30** with in an increasing concentration of TBA NO_3^-

This was also shown to be unique to the nitrate guest by repeating the above procedure with chloride as the guest. **Photograph 2.6** shows there is no unusual change seen with an increasing TBA chloride concentration.



Photograph 2.6– Receptor **2.30** with in an increasing concentration of TBA Cl^-

Finally to show that this response was unique for this receptor this was repeated using receptor **2.29** (0.002 M) and an increasing concentration of TBA nitrate. **Photograph 2.30** shows no response is seen. Since the only different between the two receptors is an additional nitro group on receptor **2.30** this nitro group must have something to do with the observation. The likely conclusion for this observation is the anion guest is deprotonating the receptor at high concentrations. The presence of the nitro group increases the acidity of the receptor[50] making deprotonation more likely.



Photograph 2.7 – Receptor **2.29** with an increasing concentration of TBA NO_3^-

None of the colour changes observed in the photographs necessarily proved the hosts are binding the guest anions. All of these colour changes could simply be down to the deprotonation of the host receptor. Fluoride and acetate are the most basic anions therefore they are more likely to bond or possibility deprotonate the hydroxyl group of the receptor which is what could be giving rise to these results especially in the case of

receptor **2.29** in acetone. To investigate this, a pH titration experiment was carried out on both hosts to track at what pH deprotonation occurred.

A host solution of receptor **2.29** (0.68 mM) was made up in a mixture of sodium hydroxide (10 ml, 0.01 M) and sodium chloride (10 ml, 0.01 M) (to ensure the ionic strength was approximately constant). Dilute hydrochloric acid (0.01 M) was added to make the solution acidic. Aliquots of sodium hydroxide (0.01 M) were then added to change the pH whilst following the absorbance at 400 nm. A pH range between 6 and 10 was utilised. These results were plotted to calculate the pKa as shown in **Figure 2.3**.

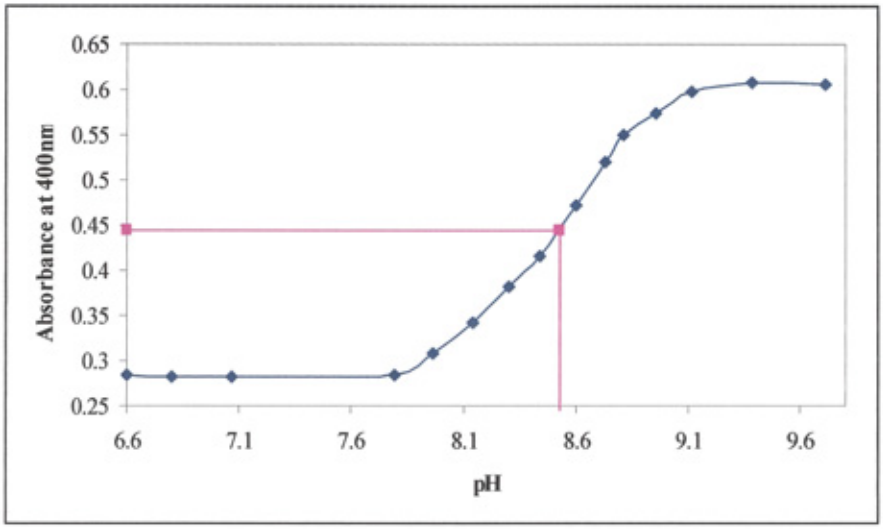


Figure 2.3 – pKa determination of receptor **2.29**

The graph showed that receptor **2.29** had a pKa at approximately 8.5. This is more acidic than the literature value of 9.98[66] for phenol suggesting receptor **2.29** was easier to deprotonate. This is likely since the added conjugation of receptor **2.29** allows further delocalisation of the negative charge increasing its stability. Also the surrounding hydrogens could help stabilise the negative charge on the oxygen.

The above procedure was repeated for receptor **2.30** following the absorbance at 500 nm as shown in **Figure 2.4.** The graph showed receptor **2.30** had a pKa at approximately 8.99 which is more basic than the literature value of 7.15[66] for *para* nitrophenol suggesting receptor **2.30** is harder to deprotonate. This was not as expected. The added conjugation should have again resulted in more favourable deprotonation.

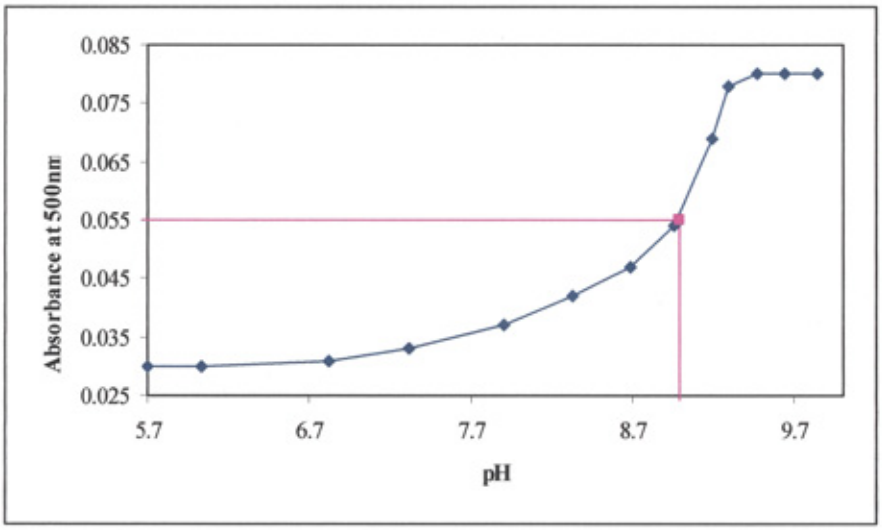


Figure 2.4 - pKa determination of receptor **2.30**

These results indicated the colour changes seen for receptor **2.29** are due to deprotonation not binding which explains why colour changes are only visible with the most basic anions, fluoride and acetate.

The results for receptor **2.30** indicated the colour changes are due to binding occurring not deprotonation. This would be consistent with the further colour change with high concentrations of nitrate suggesting binding was occurring first until very high concentration resulted in deprotonation. However this does not explain why this happens with nitrate and not the more basic fluoride or acetate anions. It is possible for deprotonation of the same receptor by different anions to result in the appearance of different colours as seen by Jurczak *et al*[52] which suggests it may be possible the most basic anions, fluoride and acetate, deprotonated the receptor straight away without any binding occurring. Gale *et al*[50] found less acidic receptors would only result in complete deprotonation once an excess of anionic guest was added but since the deprotonation is controlled by the basicity of the anion as well as the acidity of the receptor[50] it is possible that deprotonation only occurred with an excess of the slightly less basic nitrate anion. Nevertheless since all of the other colour changes observed resulted in the same change, from red to purple, and only a difference was seen with the nitrate anion it suggested something else was at play in this case. However nitrate does exhibit the same colour change as the other anions at a low concentration as indicated by

Photograph 2.4 which suggested this receptor did follow the same pattern with a change at high concentrations.

2.4 Binding studies

2.4.1 UV-Vis titrations

The association of the host guest complexes was further investigated by UV-Vis titrations to give more insight into the nature of binding that was occurring.

The UV spectroscopy titrations were carried out by titrating a dilute solution of the host receptor with a dilute solution of a TBA salt of an anion guest in chloroform. A wavelength was chosen that showed a large change and the absorbance was plotted against the guest concentration divided by the host concentration to produce a binding curve.

The first binding study carried out was the titration of receptor **2.29** (0.01 M) with TBA chloride (0.0005 M) as the guest in chloroform. Unfortunately there was only a small change in the absorbance which was too small to give accurate results. This was proven by the binding curve that shows no distinct pattern instead the points were very scattered. Attempts were made to home in closer on the binding area by repeating the titration by adding smaller aliquots of TBA chloride guest (0.048 M) into the host solution (0.0025 M) but again there was only a small change in the absorbance values. The binding curve produced from this titration is shown in **Figure 2.5**.

This showed two distinct modes of binding taking place. In the first instance the absorbance is steadily reduced until a third of an equivalent is added in which case the absorbance gradually increasing again but does not tail off. It is likely the first mode is the result of a 1:1 interaction between the chloride guest and receptor **2.29**. The second mode is probably the result of a 2:1 interaction between the chloride guest and receptor **2.29** which becomes the dominant mode once a portion of the free receptor is used up.

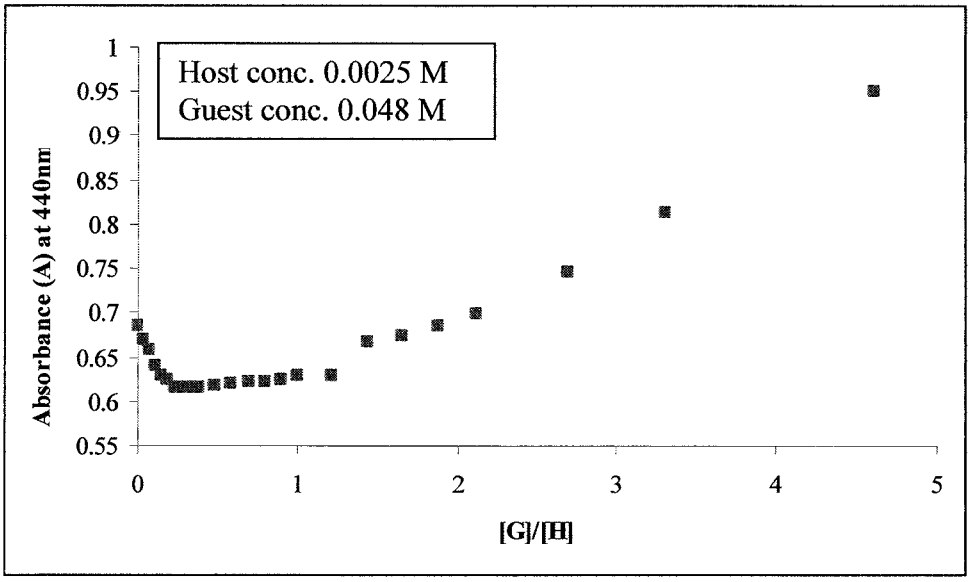


Figure 2.5 – Binding curve of receptor **2.29** with TBA chloride in chloroform at 440nm.

The binding of receptor **2.29** with TBA acetate was next investigated. This time there was a much greater change in the absorbance value which is as expected since there was such a distinct colour change as shown in **Photograph 2.1**. Again the binding curve was homed in on by adding smaller aliquots of guest. This resulted in a very steep binding curve with a 1:2 host/guest stoichiometry as shown in **Figure 2.6**. This is more consistent with deprotonation rather than binding suggesting the colour change observed is the result of receptor **2.29** being deprotonated by the acetate anion.

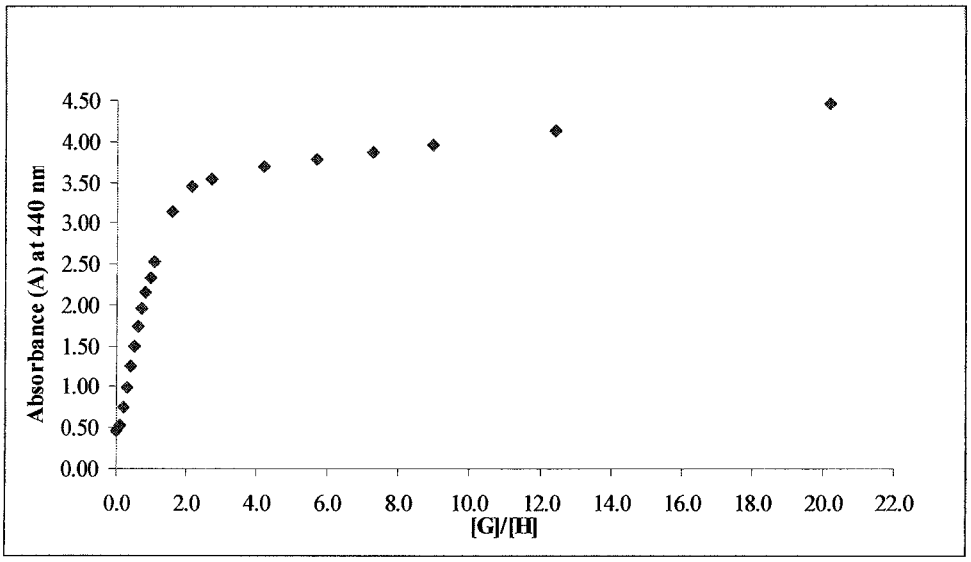


Figure 2.6 – Binding curve of receptor **2.29** with TBA acetate in chloroform at 440nm.

Since there was also a distinct colour change visible with receptor **2.29** and fluoride this interaction was also investigated by a UV-Vis titration. Again the initial procedure was carried out, followed by the second procedure where a smaller volume of guest was added and a binding curve produced as shown in **Figure 2.7**.

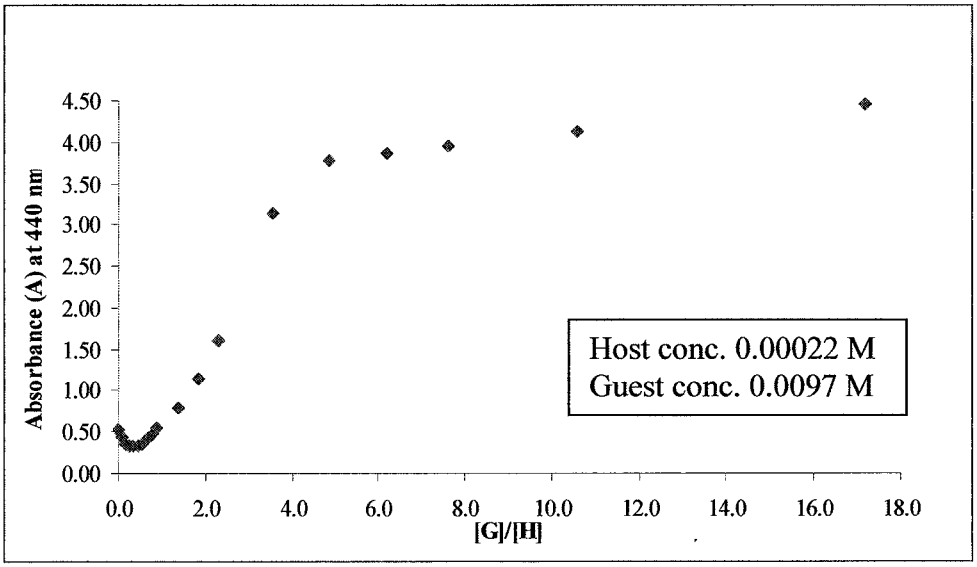


Figure 2.7 – Binding curve of receptor **2.29** with TBA fluoride in chloroform at 440nm.

Again this binding curve indicated a number of binding modes taken place which is consistent with Gale *et al*[49] observations with this anion. This suggested the first mode is the result of a binding interaction between the receptor and the first equivalent of guest followed by the deprotonation of the receptor by the second equivalent. This suggests the colour changes observed for receptor **2.29** are consistent with deprotonation as previous thought.

Finally the binding ability of receptor **2.30** was investigated by UV-Vis titrations with chloride and nitrate. These titrations were carried out in acetone since receptor **2.30** was not soluble in chloroform. Unfortunately the titration of receptor **2.30** with TBA chloride only resulted in a small change in the absorbance observed suggesting very little interaction is taken place. This resulted in a scattered binding curve preventing any accurate conclusions. The difference in the absorbance observed over the measured wavelength range at the start and end of the titration and the correlating binding curve at 520 nm are shown in **Figure 2.8**.

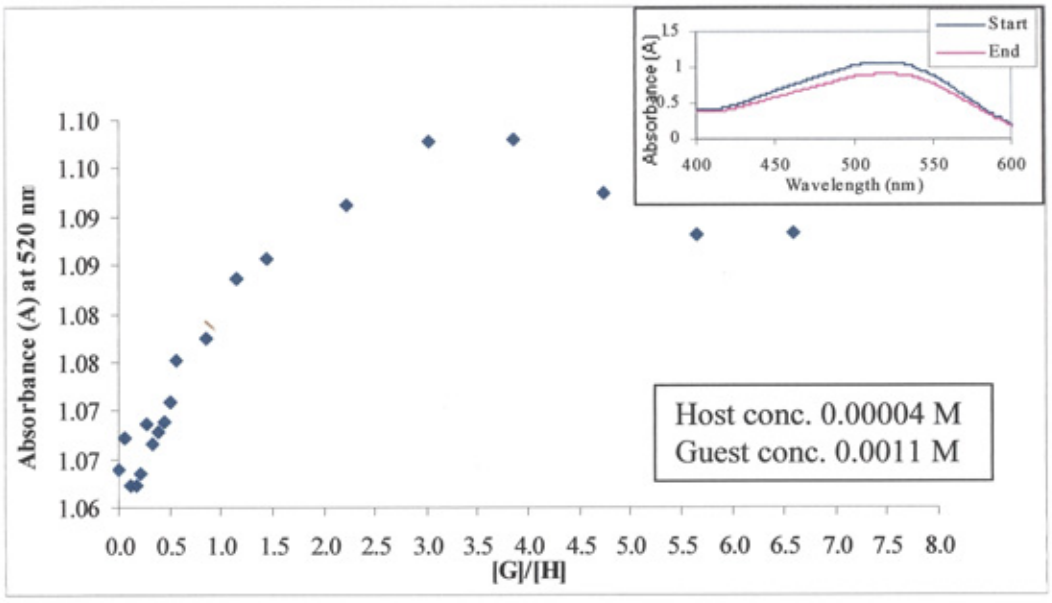


Figure 2.8 – Titration of receptor **2.30** with TBA chloride in acetone.

The titration of receptor **2.30** with TBA nitrate however did result in a larger change in the absorbance observed. The difference in the absorbance observed over the measured wavelength range at the start and end of the titration and the correlating binding curve at 375 nm are shown in **Figure 2.9**.

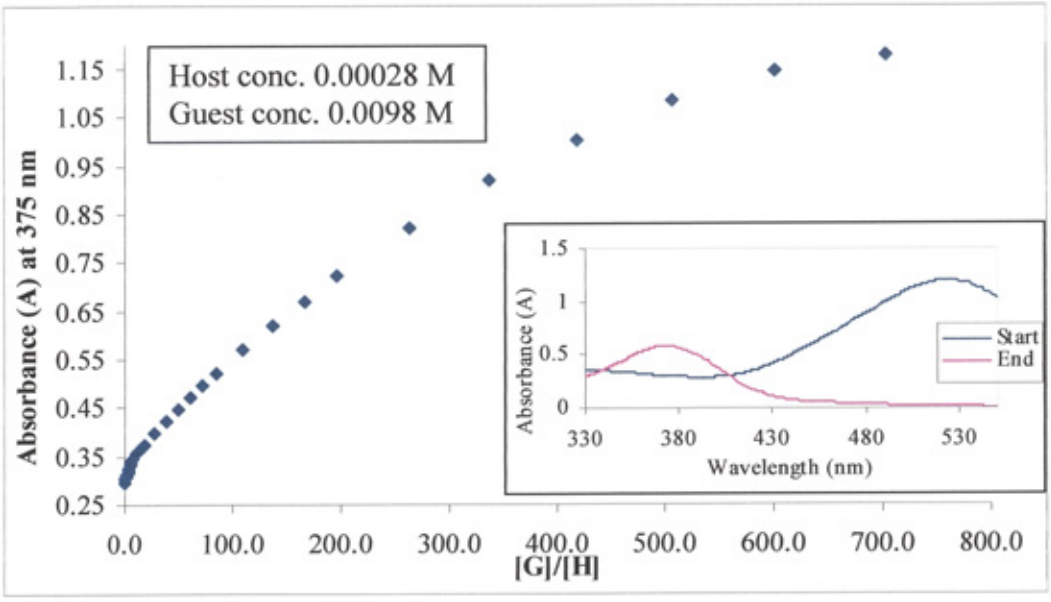


Figure 2.9 – Titration of receptor **2.30** with TBA nitrate in acetone.

This time a smooth binding curve was obtained but it indicated only a weak interaction is taken place between receptor **2.30** and the nitrate anion. The curve also revealed only one binding mode appeared to be in operation however the concentration required to obtain the unusual colour change was not reached.

2.4.2 Proton NMR titrations

To get a better insight into the spatial binding characteristics of these receptors we moved onto binding studies carried out by proton NMR. The proton signal of the hydrogen's involved in binding to the anion guest move. This is due to a change of electron density on the proton. When the proton is hydrogen bonded the electron density is more spread out therefore there is less density on the hydrogen atom which results in a shift to a higher ppm. **Figure 2.10** shows the proton NMR spectrum from the start and end of the titration of receptor **2.15** with TBA chloride in chloroform which clearly indicates this movement in chemical shift throughout a titration.

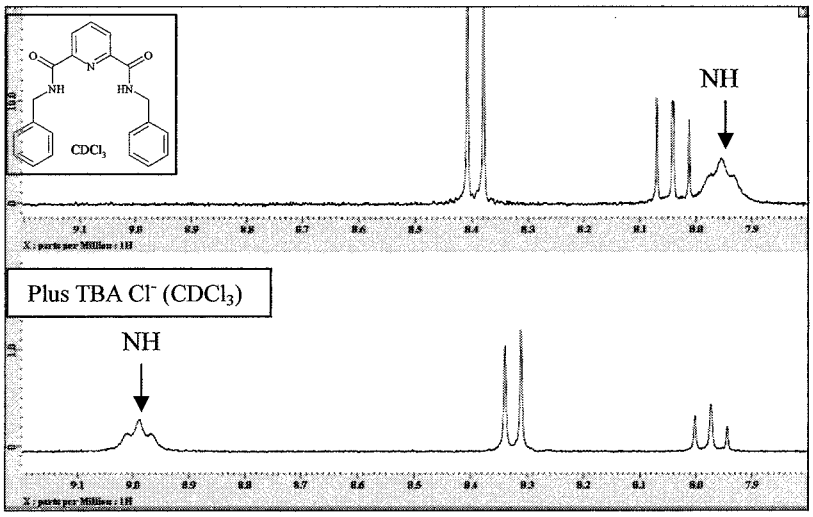


Figure 2.10 – Spectrum from the start and end of a titration of receptor **2.15** with TBA chloride in deuterated chloroform.

The change in proton chemical shift after each aliquot of guest can be used to calculate the binding constant of the receptor using non-linear least square fitting. **Tables 2.3-2.5** show the calculated binding constants for the different receptors.

A number of the proton NMR titrations were repeated to give an indication of the error involved. The calculated binding constants for each titration were used to calculate the average and error for each titration as summarised in **Table 2.2**. These errors were then used to give an indication of the overall error involved in the titration process.

Receptor	**Guest**	**Solvent**	**Binding Constants (M^{-1})**	**Average (M^{-1})**	**Error**
2.16	Cl^-	Chloroform	11 22	16.5	± 33 %
2.16	Cl^-	Acetone	353 315	334	± 6 %
2.28	Cl^-	Acetonitrile	60 60	60	± 0 %
2.23	NO_3^-	Chloroform	136 126	131	± 4 %

Table 2.2 – Average calculated binding constants from repeat titrations

The results showed percentage errors ranging from 0 % to 33 %. This calculated to an overall average experimental error of 11 % for all titrations. This will be taken into account when drawing any conclusions from all proton NMR titrations.

The calculated binding constants for receptors **2.15** and **2.16,** as shown in **Table 2.3,** were very small in chloroform and acetonitrile so it is difficult to draw any accurate conclusions from them however the acetone results were significantly larger and allowed analysis to be made. This indicated the solvent has an effect on the selectivity of the receptor. It is well know that interactions takes place between the receptor and the solvent molecules reducing any interaction that is taken place with the guest and resulting in lower binding constants. However it is also possible the solvent molecules are binding to the guest and the receptor has to compete.

Receptor	Guest	Binding Constants (M^{-1})		
		Chloroform	Acetone	Acetonitrile
2.15	Cl^-	19 ± 10 %	566 ± 10 %	92 ± 10 %
	NO_3^-	10 ± 20 %	36 ± 15 %	21 ± 10 %
2.16	Cl^-	16.5 ± 33 %	334 ± 6 %	58 ± 15 %
	NO_3^-	9 ± 20 %	34 ±10 %	13 ± 15 %

Table 2.3 – Calculated binding constants for receptors **2.15** and **2.16**

It was expected that receptors **2.15** and **2.16** should have shown selectivity towards the smaller anions due to the preorganised nitrogen atom. The nitrogen atom is sterically more bulky than the normal CH group due to its lone pairs reducing the size of the binding cleft[15]. There will also be electrostatic repulsion between the anion and the lone pair which will get more pronounced as the anion gets larger hence the selectivity towards smaller anions. This is indeed what was seen for receptors **2.15** and **2.16** in acetone with very high binding constants observed for chloride but very small for nitrate. The addition two nitrogen atoms on receptor **2.16** compared to receptor **2.15** should have pronounced these effects more giving receptor **2.16** even greater selectivity for smaller anions. Unfortunately this was not the case and the binding constant of receptor **2.16** for chloride was 1.5 fold lower than receptor **2.15**. It is likely the addition of the bulky lone pairs of the extra nitrogen atoms made the binding cavity too small even for chloride.

The additional hydrogen bond donor of receptor **2.28** should have greatly improve the binding constants since there are now four moieties available for hydrogen bonding. The binding constants of receptor **2.28** are shown in **Table 2.4**. They showed there is a significant increase in the binding constants of receptor **2.28** especially for chloride in chloroform with a value of 240 M^{-1} compared to the binding constant of receptor **2.15** of just 19 M^{-1}. Unfortunately the selectivity that was previous seen in acetone has now been removed. This is probably because the receptor is strong enough to compete with the solvent molecule for the guest in all solvents.

Increasing the size of the binding cleft of receptor **2.28** should produce even higher binding constants because the additional conjugation allows more opportunity to delocalize the charge strengthening any hydrogen bond formed from the hydroxyl

group[26]. This was proven by the increased binding constant of receptor **2.29** in acetone. The calculated binding constants of receptors **2.28-2.30** are summarised in **Table 2.4**.

Receptor	Guest	Binding Constants (M^{-1})		
		Chloroform	Acetone	Acetonitrile
2.28	Cl^-	240 ± 20 %	210 ± 10 %	60 ± 0 %
	NO_3^-	120 ± 30 %	105 ± 10 %	13 ± 10 %
2.29	Cl^-	Not soluble	355 ± 5 %	Not soluble
	NO_3^-	"	200 ± 5 %	"
2.30	Cl^-	Not soluble	190 ± 15 %	Not soluble
	NO_3^-	"	300 ± 10 %	"

Table 2.4 – Calculated binding constants for receptors **2.28-2.30**

The additional nitro group on receptor **2.30** should made this receptor a stronger donor again since the delocalised charge can be stabilised further onto the nitro group and hence give an even stronger hydrogen bond donor. However this was not the case for chloride and the binding constant were about even at 200 M^{-1} for receptor **2.29** and 190 M^{-1} for receptor **2.30**. Another unexpected result for receptor **2.30** was the larger binding constant for nitrate. It is generally expected to get higher binding constants for chloride compared to nitrate for this type of receptor because chloride is traditionally a better hydrogen bond acceptor as indicated by the Hofmeister Series[1, 11] as shown in **Figure 2.11**. These receptors are also preorganised to have the correct shape for spherical anions.

$$SO_4^{2-} > PO_4^{2-} > F^- > Cl^- > Br^- > I^- > NO_3^-$$

Figure 2.11 – The Hofmeister Series

Receptor **2.24** also has an additional nitro group compared to receptor **2.19**. The calculated binding constants for the two receptors are shown in **Table 2.5**. This time the expected increase in the binding constant was seen for chloride in acetone with the binding constant increasing from 91 M^{-1} for receptor **2.23** to 153 M^{-1} for receptor **2.24**. However this is not a very significant change. The results also showed there is no unusual increase of the nitrate value compared to chloride with the additional nitro

group seen with these receptors. The binding constant decreased significantly from 153 M^{-1} for chloride to 57 M^{-1} for nitrate in acetone as expected.

Receptor	Guest	Binding Constants (M^{-1})		
		Chloroform	Acetone	Acetonitrile
2.23	Cl^-	129 ± 5 %	91 ± 10 %	34 ±20 %
	NO_3^-	131 ± 4 %	43 ± 10 %	8 ± 10 %
2.24	Cl^-		153 ± 20 %	46 ± 15 %
	NO_3^-		57 ± 10 %	59 ± 20 %

Table 2.5 – Calculated binding constants for receptors **2.23** and **2.24**

The sulphonamide groups present in receptors **2.23** and **2.24** should have resulted in increased binding constants since they are more acidic than the amide groups[15]. This was the case for receptor **2.23** in chloroform. The binding constants calculated in chloroform were significantly higher than the binding constants for receptor **2.15** and **2.16**.

2.5 Charged receptor with potentially fluorescent properties

2.5.1 Introduction

Fluorimetric sensors are very similar to colorimetric but contain a fluorophore instead of a chromophore making the receptor fluorescent. It is the changes of the fluorescent properties of a receptor that are used to give an optical response to binding.

When a molecule absorbs light it is excited from the lowest vibration level in its ground state, S_0, to a range of vibration levels in the excited state, S_1. Energy undergoes internal conversion from the higher vibration levels during this time the molecule spends in the excited state and the lowest vibration level is reached. Fluorescence occurs if the molecule then emits light as it reverts from this level to various vibration levels in the ground state. This is summarised by the Jablonski Diagram which is shown below in **Figure 2.12**. The energy is lower due to the energy internal conversion therefore of longer wavelength.

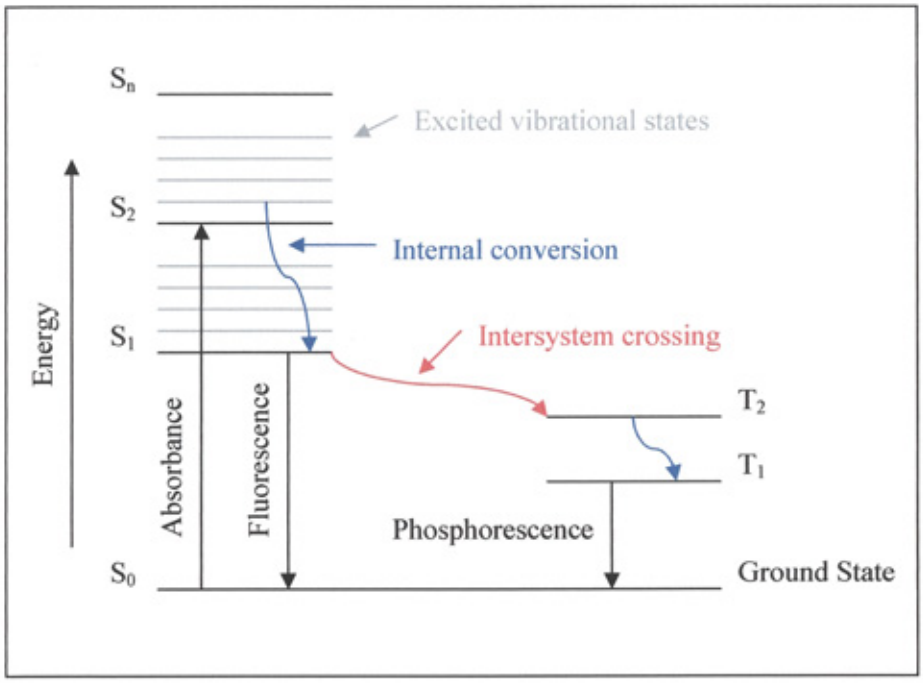
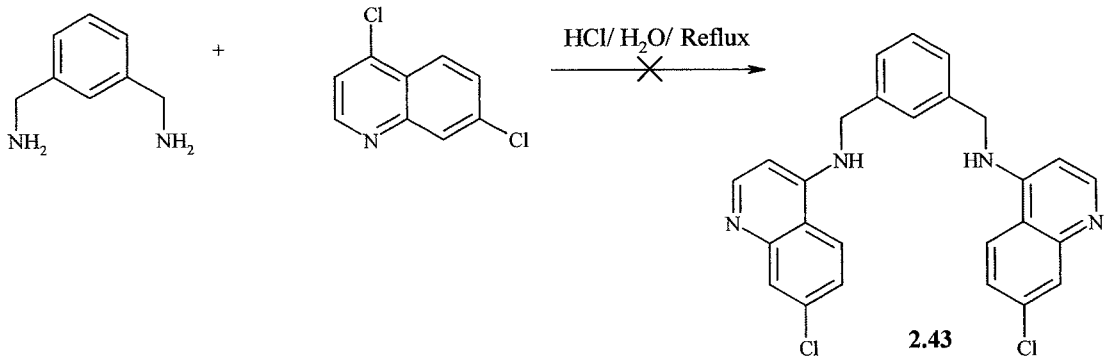


Figure 2.12 – The Jablonski Diagram

The most visual response that can be seen by a fluorimetric sensor is when fluorescence quenching occurs. This happens when energy is transferred to another molecule during the life-time of the excited state of the species returning it to ground state resulting in reduced or no fluorescence intensity. We hoped the binding interaction between our receptor and anions would result in fluorescence quenching allowing visual detection.

2.5.2 Synthesis of a charged receptor

Studies focussed next on the synthesis of a charged receptor **2.43** that should aid the effectiveness of the hydrogen bonding and could have fluorescent properties allowing analysis by fluorescent quenching. This was first attempted by the nucleophilic substitution of 4,7-dichloroquinoline by refluxing with 3-(aminomethyl)-benzylamine in the presence of hydrochloric acid[67] as shown in **Scheme 2.14**. It was reported that a precipitate should form after a short length of time. After refluxing for twenty four hours a precipitate had not formed so a sample was removed and submitted for proton NMR. TLC and proton NMR showed only starting material was present.

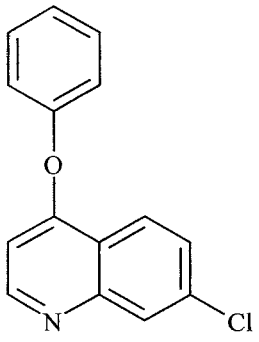


2.43

Scheme 2.14

In the original paper 4,7-dichloroquinoline was refluxed with aniline not 2-aminobenzylamine to yield the mono substituted product. This experiment was repeated using the exact conditions of the paper to check if it was just this change that resulted in the unsuccessful reaction. Proton NMR showed this reaction was also unsuccessful in our hands with only dichloroquinoline starting material present so a different approach was needed.

The next approach investigated was the same as above but this time the solvent was changed to phenol[68]. TLC showed only one spot but the proton NMR revealed a 70/30 mixture was present. The spectrum, shown in **Figure 2.13**, revealed baseline peaks (highlighted in red) which were consistent with the desired product however the major component was identified to be compound **2.44**.



2.44

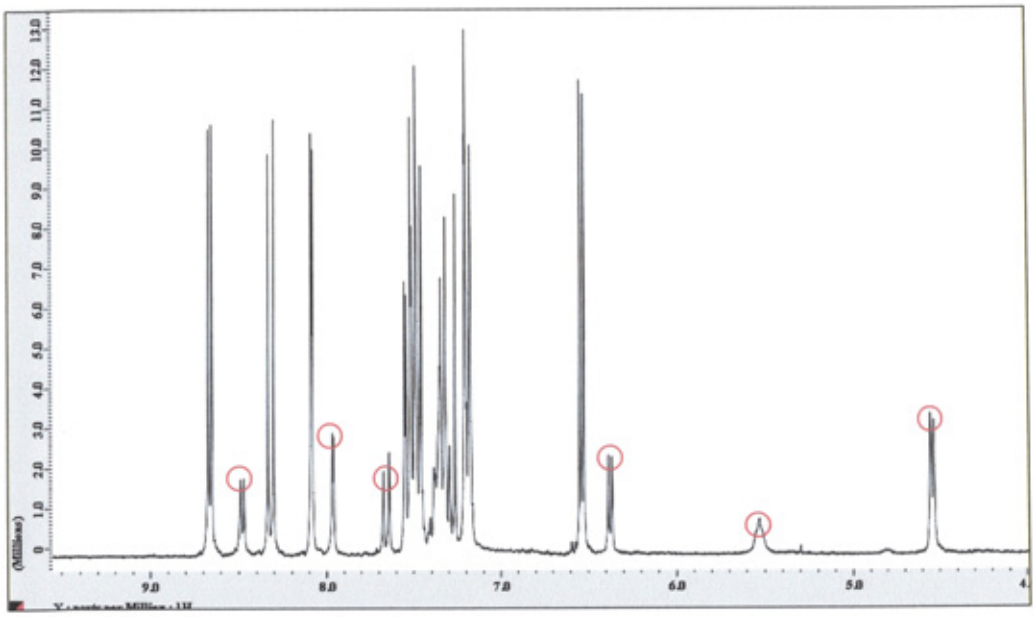
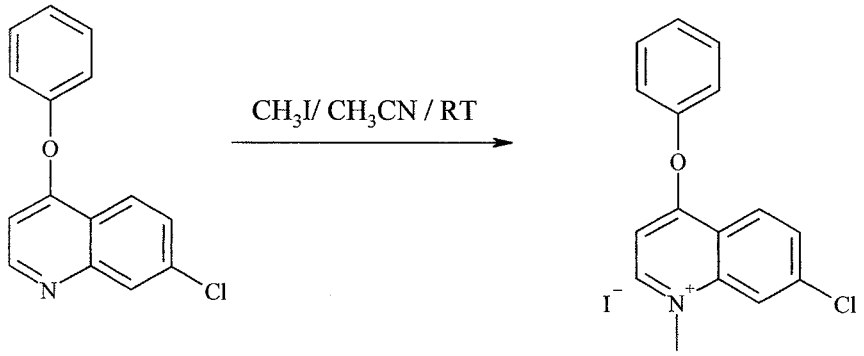


Figure 2.13

Purification was carried out by flash column chromatography using 2% methanol/dichloromethane. Proton NMR and E.S.M.S revealed the desired product had been lost during purification and confirmed the resultant crystals were compound **2.44** in 50 % yield.

It is likely that the hydrochloric acid condition in the first attempt was protonating the amine group destroying its ability to act as a nucleophile and preventing nucleophilic attack. Since phenol is not acidic these condition were much more favourable allowing the reaction to work. However heating at these temperatures in the presence of phenol allowed the solvent molecule to act as a nucleophile resulting in the formation of **2.44**. Receptor **2.44** was then methylated to yield the charged compound **2.45** as shown in **Scheme 2.15** to see if this compound had any fluorescent properties. This compound would have also allowed investigations into cation-anion binding. Receptor **2.44** was dissolved in acetonitrile and stirred with methyl iodide resulting in receptor **2.45**.



2.45

Scheme 2.15

Although the TLC showed only one spot the proton NMR again showed an impurity present so the product was recrystallised from petroleum ether to yield visually bright suggesting fluorescent yellow crystals in 40 % yield. This time the proton NMR was much cleaner and suggested the methylated product was present which was confirmed by E.S.M.S.

2.5.3 Analysis of charged receptor

2.5.3.1 NMR titrations

The positive charge on the nitrogen atoms of compound **2.45** makes this compound a cation which can bind to anions via an ion-ion interaction. As already stated, an ion-ion interaction is a stronger interaction than a hydrogen bond which means we should see the strongest and most effective binding with this compound. However the titrations carried out with this receptor were competition titrations due to the presence of the iodide counterion. The binding constants for receptor **2.45** are summarised in **Table 2.6**. Stronger binding with this receptor was proven to be the case for chloride in chloroform with a binding constant of 601 M^{-1}. The highest binding constant seen in chloroform for the other receptors was 240 M^{-1} for receptor **2.28** with chloride which is 2.4 fold lower. However the binding constants in acetone were surprisingly low suggesting again the solvent was having an effect on selectivity. The bind constant for nitrate was very similar to that of receptor **2.28** indicating very little attraction between compound **2.45**

and the nitrate anion. It is likely the δ^+ nitrogen atom on the nitrate repels the cation preventing a strong interaction forming.

Receptor	Guest	Binding Constants (M^{-1})	
		Chloroform	Acetone
2.44	Cl^-	601 ± 10 %	51 ± 15 %
	NO_3^-	123 ± 5 %	67 ± 10 %

Table 2.6 – Calculated binding constants for receptor **2.45**

2.5.3.2 Fluorescence experiments

Since receptor **2.45** seemed to exhibit fluorescent qualities the fluorescence spectrum was produced using a spectrofluorometer which confirmed receptor **2.45** does fluoresce at 400 nm. A fluorescence titration was then carried out to identify any effect binding has on fluorescence. A host solution of receptor **2.45** (0.0003 M) and a guest solution of TBA chloride (0.0094 M) were made up in water. Aliquots of guest were added to the host solution and the fluorescence intensity recorded keeping the parameters constant. The change in fluorescence intensity after each aliquot of guest was used to calculate the binding constant of the receptor using non-linear least square fitting. The binding curve is shown in **Figure 2.14**. This procedure was repeated to ensure consistent results. The estimated binding constant was less than 100 M^{-1}.

The titration showed the fluorescence intensity of the receptor increased as the concentration of the guest increased. This was not as expected. As already stated, we hoped the binding of a guest anion would quench the fluorescence allowing visual detection. Rurack *et al*[69] also experienced enhanced output signals which were caused by the conversion of weak hydrogen bonds into strong hydrogen bonds. This suggests the increased fluorescence intensity seen with receptor **2.45** is a result of the increasing strength of the ion-ion interaction as more guest becomes available.

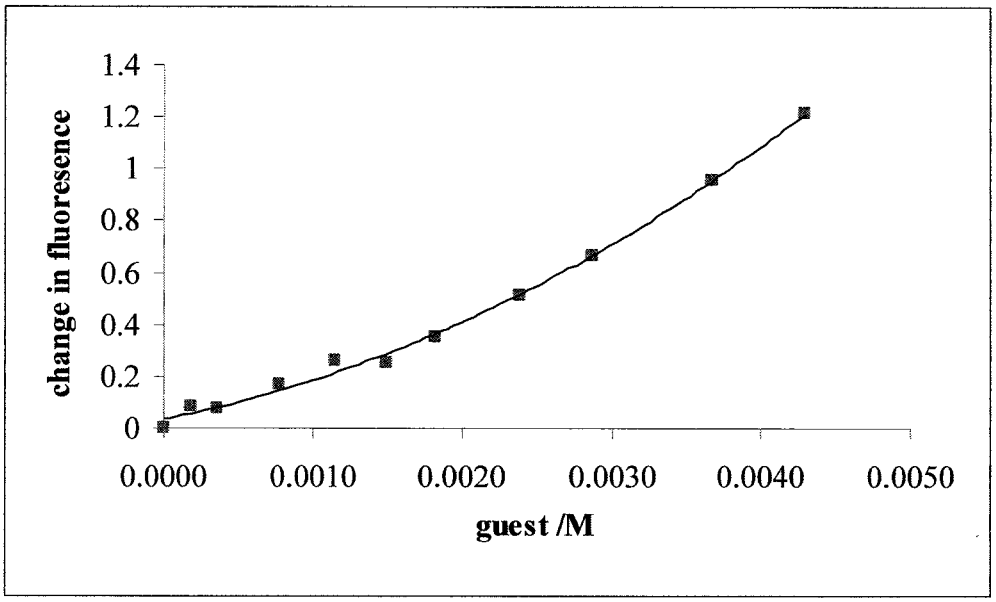


Figure 2.14 – fluorescence binding curve of **2.45** with TBA chloride in water

Since the fluorescence of receptor **2.45** increases with an increasing concentration of chloride guest in water it is possible this receptor could be used as a way of calculating the concentration of chloride in serum samples. Unfortunately these experiments were only carried out up to a chloride concentration of 4.3 mmol which falls below the normal serum chloride concentration of 300 mmol[70]. However this is easily rectified by repeating at higher concentrations.

2.6 Conclusion

A group of simple, synthetically trivial, amide receptors were synthesised which varied in the number and type of hydrogen bond donors or in preorganisation to investigate these effects on guest binding ability. A number were investigated as possible colorimetric sensors and testing showed visual colour changes were observed upon addition of anions. The calculated pKa and UV-Vis binding studies of receptor **2.29** revealed these visible changes, with only the basis anions, were consistent with deprotonation. However the calculated pKa and UV-Vis binding studies of receptor **2.30** showed this receptor was not as easily deprotonated and suggested the colour changes were a result of an interaction with the guests. The most pronounced observation was an unusual colour change that was seen between receptor **2.30** upon addition of a large excess of nitrate guest. This suggested a different binding mode pattern was observed during this interaction.

Proton NMR binding studies revealed a preorganised nitrogen atom within the cleft reduced the size of the binding cleft and increased selectivity for the smaller chloride anion however the introduction of two more additional nitrogen atoms made the binding cavity too small even for chloride. The results also showed the addition of extra hydrogen bond donors in the form of hydroxyl groups increased the binding affinity. Increasing the size of the binding cleft and the presence of sulphonamide groups also resulted in increased binding affinities. Finally the proton NMR titrations revealed the solvent had an effect on the selectivity of the receptors suggesting the solvent molecules were capable of interacting with the guest molecules and the receptor had to compete.

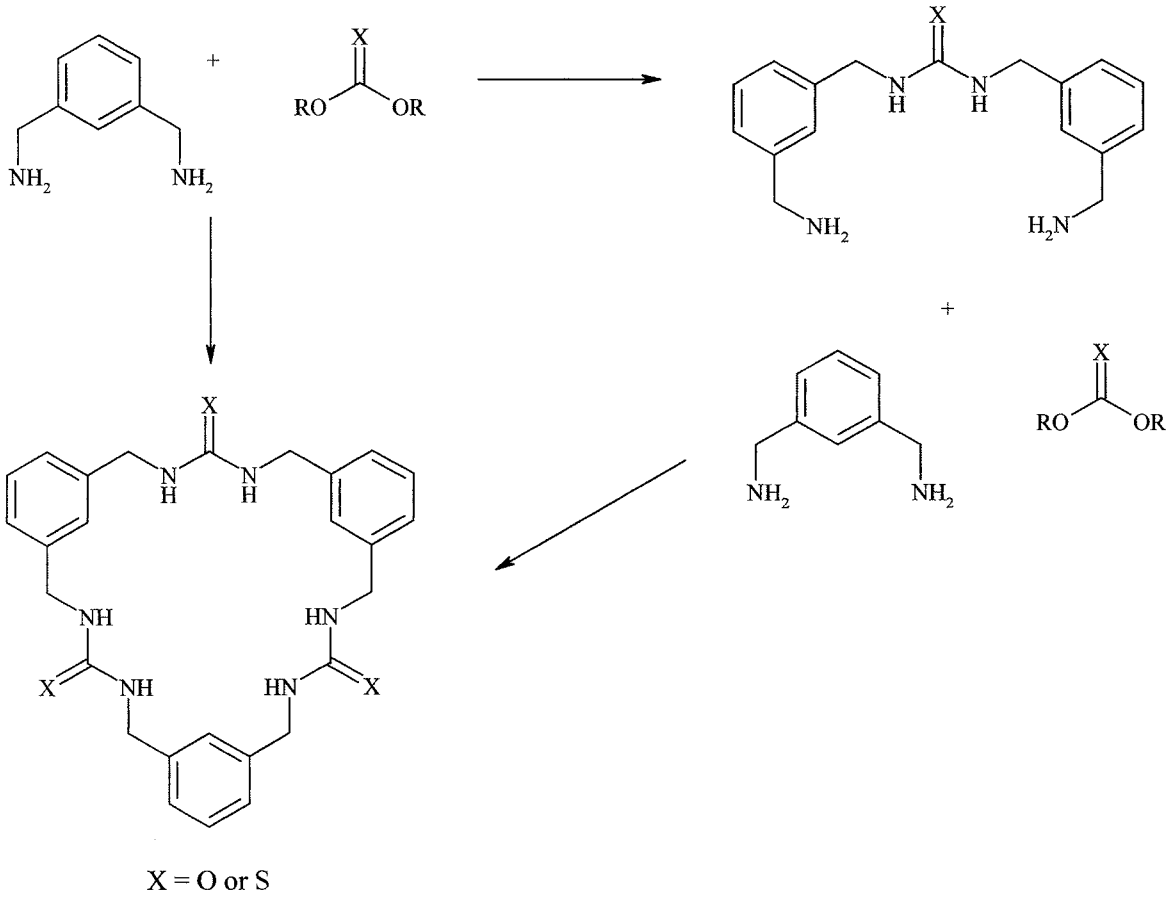
Finally a charged receptor was synthesised. Unfortunately the synthesis of the target receptor was unsuccessful and resulted in the formation of a cation **2.45** with no hydrogen bonding moieties. Proton NMR titrations were still carried out and revealed the cation formed much stronger interactions with the chloride anion than the previously examined receptors as expected. Fluorescence experiments were also performed in water which revealed the addition of guest increased the fluorescence intensity of the receptor. This could allow this receptor to possibility be used for calculating the concentration of chloride in serum samples.

Chapter 3

3. Cyclotrimeric receptors for nitrate anions

3.1 Introduction

Investigations focused next on the synthesis of a cyclotrimeric receptor which was designed to have a trigonal array with urea/thiourea moieties which can hydrogen bond to all six of the lone pairs of the nitrate or carbonate anion exhibiting great affinity and selectivity. We planned to do this in two ways as shown in **Scheme 3.1**.

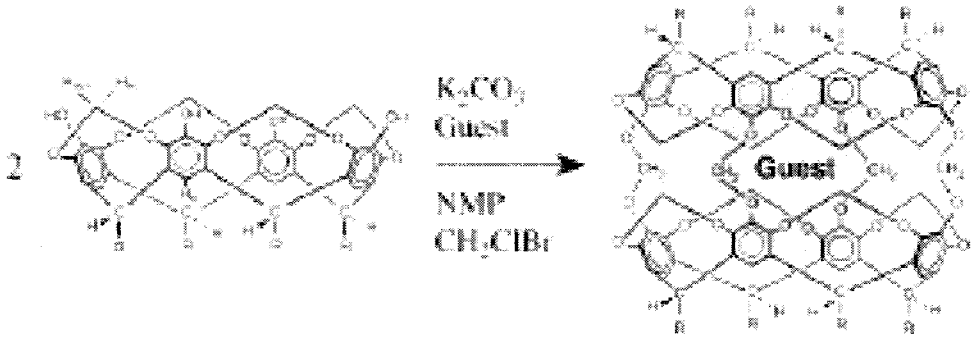


Scheme 3.1

Firstly, by a stepwise synthesis that would result in a group of receptors with an extra urea/thiourea moiety present at each step. This would have allowed the effect this factor has on guest binding efficacy and selectivity to be analysed by proton NMR titrations. Secondly, by a one step trimerisation of monomers that would result in the formation of the cyclotrimer directly. However this method could have given rise to a number of side products and impurities by the formation of polymers. To overcome this we planned to investigate using a nitrate anion to template and catalyse the reaction. Since this

receptor was designed to bind to the nitrate anion its presence should have helped position the amide groups of the monomers into the correct orientation for the formation of the cyclotrimer.

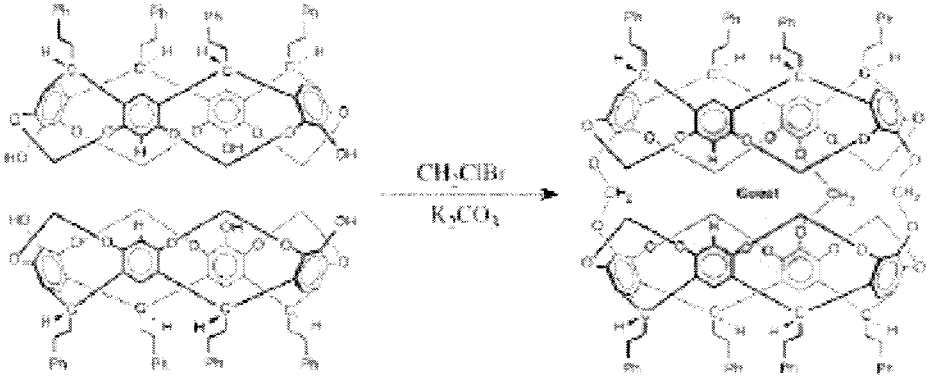
Templating techniques have been researched by a number of people. Sherman[71, 72] reported a number of compounds that were synthesised in the presence of an external template. For example tetrol **3.1** underwent a bridging reaction to incorporate linkages to produce **3.2**·guest as shown in **Scheme 3.2** which is copied from Sherman's publication[71].



3.1 **3.2·Guest**

Scheme 3.2

Sherman found a template was needed to obtain carceplex **3.2**·guest or carcerand **3.2**. He investigated a range of solvents as templates by carrying out competitive experiments and examining the integration of the proton NMR signals of the resulting mixture. He found pyrazine was the best template which resulted in a 75 % yield however only when it was present in stoichiometric amounts. Hexicarceplex **3.4**·guest was also formed from **3.3** as shown in **Scheme 3.3** which is copied from Sherman's publication[71] to explore the template effect that occurs during the assembly process. The templating ratios of the guest showed the formation of **3.4**·guest mirrored the template effect of **3.2**·guest.



3.3 **3.4·Guest**

Scheme 3.3

Sherman next investigated the transition state formed during the formation of **3.2**·guest and **3.4**·guest. He characterised the reversible complexes formed in solution by proton NMR spectroscopy. This revealed two tetrol **3.1** molecules had collectively lost four protons and charged hydrogen bonds formed linking them together surrounding one guest molecule. The thermodynamic guest binding selectivities mirrored the kinetic template ratios of **3.2** and **3.4** showing these complexes serves as transition state in their formation. Sherman concluded the guests preorganise the hosts for appropriate bridge formation.

Cuccia *et al*[73] synthesised a number of naphthyridine and pyridazine containing macrocycles with high yields from one-step reversible reactions. However he took advantage of intramolecular hydrogen bonding instead of using an external template.

He synthesised macrocycles **3.5** and **3.6** by the condensation reaction of 2,7-diamino-1,8-napthyridine with 1,1-carbonyldiimidazole and triethyl orthoformate respectively. A series of *N*-substituted 3,6-diaminopyridazines where reacted with tolylene-2,6-diisocyanate to produce **3.7-3.9** or 1,3-phenylenediisocyanate to produce **3.10**. The respective yields are shown in **Table 3.1**.

Macrocycle	% Yield
3.5	64
3.6	75
3.7	64
3.8	67
3.9	64
3.10	46

Table 3.1 – Percentage yields of macrocycles **3.5-3.10**

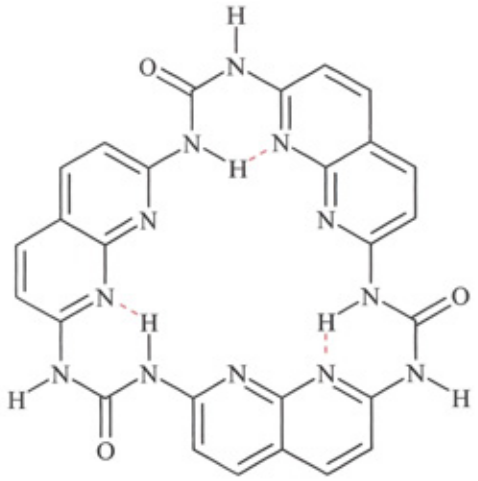
The crystal structure of macrocycle **3.6** revealed the compound adopted a near planar structure with the formamidine N-H hydrogen atoms pointing out over and the C-H hydrogen atoms pointing into the interior of the cavity. The bond distances suggested these C-H hydrogen atoms participated in intramolecular hydrogen bonding with the naphthyridyl nitrogens and Cuccia believes these intramolecular hydrogen bonds form during the transition state directing irreversible macrocyclic ring closure as shown in **Figure 3.1**.

The crystal structures of macrocycles **3.9** and **3.10** also revealed the urea hydrogen atoms are pointing into the interior of the cavity and again they form intramolecular hydrogen bonds with the pyridazine nitrogen atoms as shown in **Figure 3.1**.

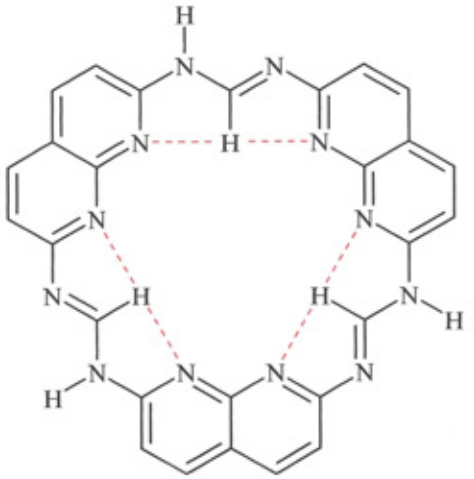
Cuccia also exploited the steric repulsion between the tolyl methyl groups and the adjacent urea carbonyl that are present in macrocycles **3.7-3.9** to direct macrocyclisation. The percentage yields between macrocycles **3.7-3.9** and **3.10** supported this. The only difference between macrocycle **3.10** and **3.7-3.9** was the presence of the phenyl group in macrocycle **3.10** versus the tolyl group in macrocycles **3.7-3.9**. The macrocycle without the tolyl group, **3.10**, resulted in a much lower percentage yield.

Single crystals suitable for X-ray analysis could not be produced for macrocycle **3.5**. Instead Cuccia used proton NMR analysis to confirm the structure of this macrocycle. A singlet at 12 ppm was seen in the proton NMR spectra for all macrocycles including

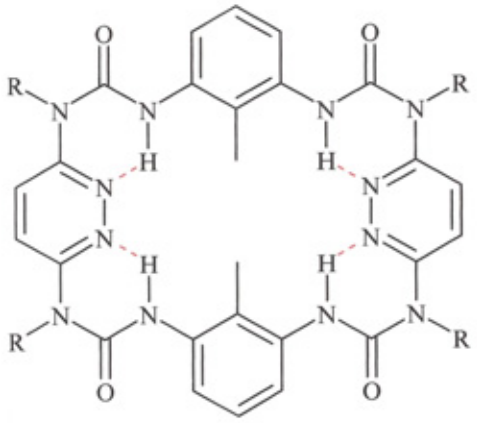
macrocycle **3.5** which is characteristic of an intramolecularly hydrogen bonded proton. Deuterium exchange suggested a structure consistent with that shown in **Figure 3.1**.



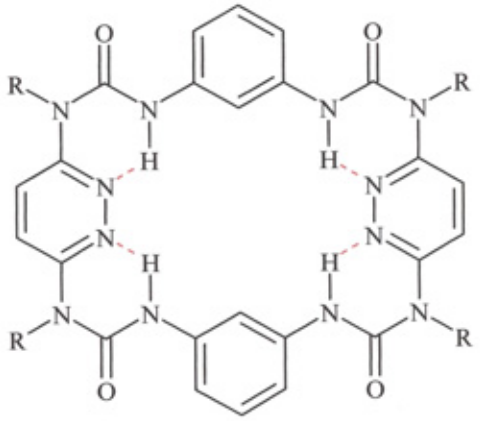
3.5



3.6



3.7 R = Ph-$C_{10}H_{21}$
3.8 R = n-$C_{12}H_{25}$
3.9 R = i-C_4H_9



3.10 R = i-C_4H_9

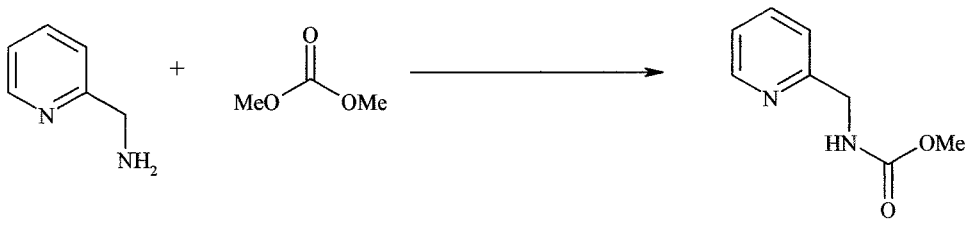
Figure 3.1

In conclusion, Cuccia *et al* have demonstrated an efficient one-step synthesis of self-templating macrocycles. This was due to the formation of intramolecular hydrogen bonds that inclined the starting material to form closed cyclic structures.

3.2 Synthesis of receptors

3.2.1 Urea receptors

Preliminary studies focused on determining green synthetic methods for the synthesis of the cyclotrimeric receptor by a stepwise trimerisation of monomers. Model reactions were first attempted by the nucleophilic substitution of dimethyl carbonate by 2-(aminomethyl) pyridine as shown in **Scheme 3.4**. A number of different catalysts were investigated to identify the favoured conditions for the formation of **3.11**. The different conditions attempted are summarised in **Table 3.2**.



3.11

Scheme 3.4

Initial investigations were carried out in the presence of alumina[74] which acts as a Lewis Acid catalyst. Two identical reactions were set up using two different kinds of alumina, Laboratory Reagents BDH Ltd aluminium oxide active basic Brockmann grade 1 for chromatographic analysis and Aldrich aluminium oxide, activated, neutral, Brockmann I, Std grade, CA 150 mesh. Proton NMR revealed the resultant crystals from experiment one was mainly starting material with a small amount of product, its presence was confirmed by E.S.M.S. Proton NMR and E.S.M.S. also showed the resultant crystals from experiment two were mainly starting material with only trace amounts of product.

The next catalyst investigated was silica gel[75] which is reported to operate under similar conditions. Merck silica gel 60 was used. However E.S.M.S. and proton NMR revealed the resultant crystals were again mainly starting material with only trace amounts of the desired product.

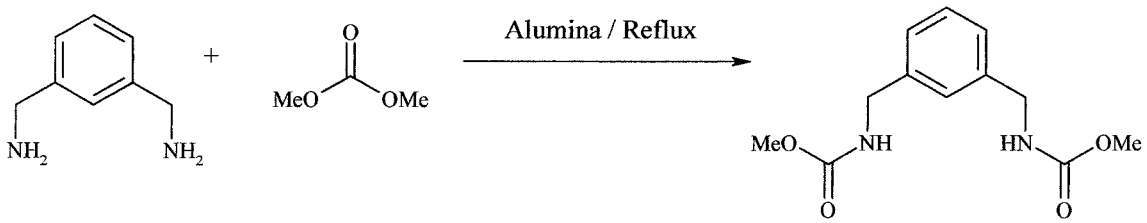
The use of an acid catalyst was investigated next using toluenesulfonic acid monohydrate. Unfortunately again proton NMR revealed the resultant crystals were starting material with only trace amounts of the desired product visible by E.S.M.S.

The final catalyst investigated was ytterbium (III) trifluoromethanesulfonate hydrate[76]. Unfortunately there was not enough sample present in the proton NMR but again a mixture of starting material and mono-substituted product were identified by E.S.M.S. and TLC.

Attempt	Reaction conditions
1	Aluminium oxide active / Reflux
2	Neutral aluminium / Reflux
3	Silica / 100 ^{0}C / N_2
4	Toluenesulfonic acid monohydrate / 100 ^{0}C / N_2
5	$Yb(OTF)_3$ / 80 ^{0}C

Table 3.2 – Conditions used in the formation of **3.11**

Since these investigations revealed the optimum conditions were in the presence of aluminium oxide active these conditions were used in the nucleophilic substitution of dimethyl carbonate by 2-amino benzylamine as shown in **Scheme 3.5.** However although E.S.M.S and the proton NMR confirmed the resultant liquid contained **3.12** they also revealed the presence of side products in the form of the cyclotrimer and other oligomers.

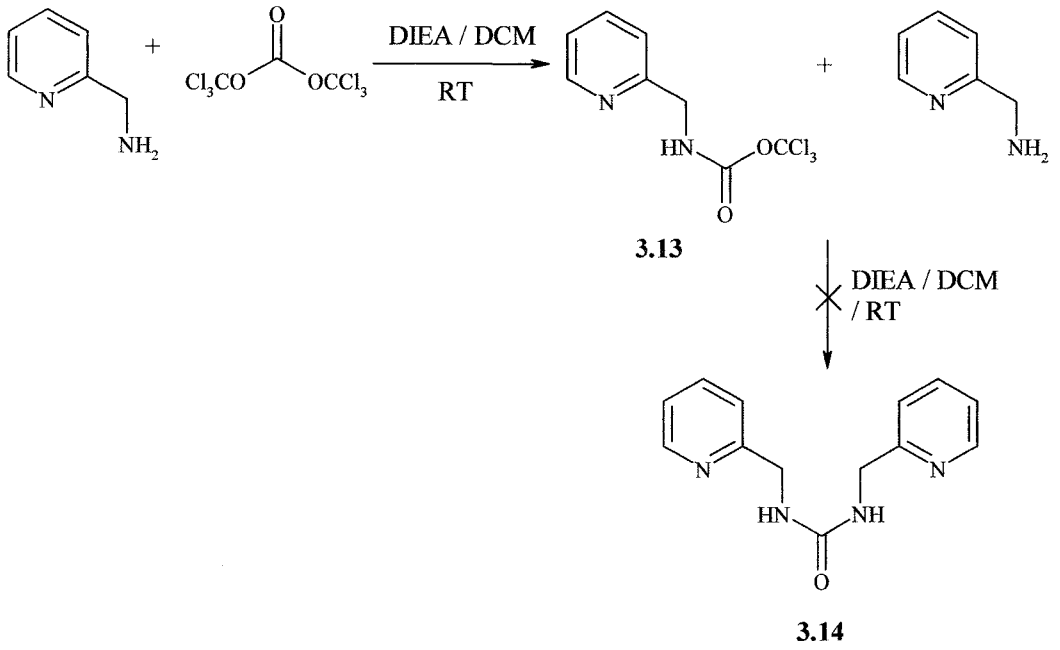


3.12

Scheme 3.5

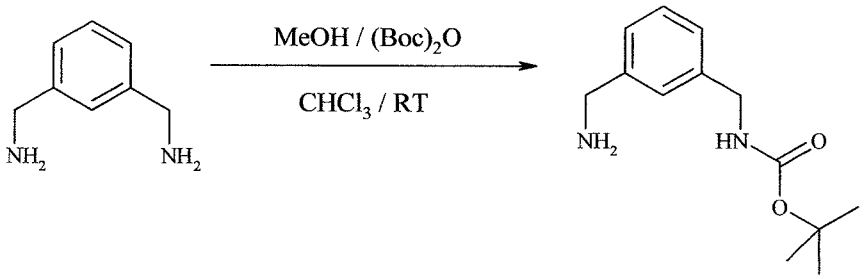
Another approach to the formation of ureas is the reaction of an appropriate amine with a carbonyl dichloride equivalent[77]. A model reaction is the nucleophilic substitution of triphosgene by adding one equivalent of 2-(aminomethyl) pyridine to obtain the reactive carbonate **3.13**. Another equivalent of 2-(aminomethyl) pyridine was then added to hopefully yield the urea product **3.14** as shown in **Scheme 3.6**. This was carried out as a one pot method without the carbonate being isolated.

E.S.M.S revealed the resultant liquid did not contain **3.14** and proton NMR showed that this reaction was not clean as reported in our hands. Instead there were a number of compounds present which were identified by the number of CH_2 signals present in the methine region.



Scheme 3.6

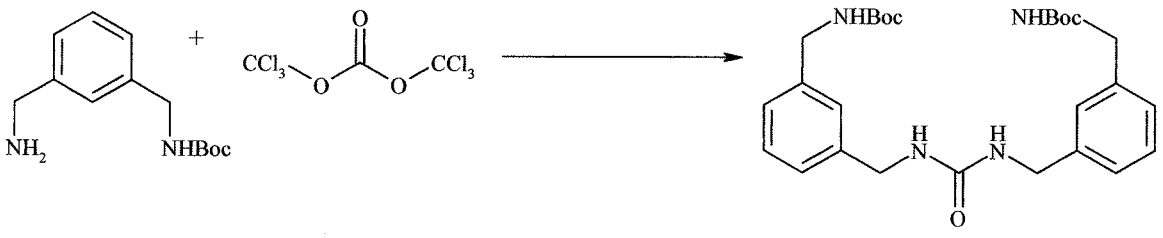
To try and minimise the presence of side products a Boc protecting group was introduced on to one of the amide groups of 3-(aminomethyl)-benzylamine resulting in compound **3.15**[44] as shown in **Scheme 3.7**. This limited the compound to only one amide group capable of performing nucleophilic substitution preventing the formation of monomer chains. The proton NMR and E.S.M.S. following flash column chromatography confirmed the resultant liquid was mono-Boc **3.15** in 29 % yield and showed no further purification was needed.



3.15

Scheme 3.7

This was then reacted with triphosgene to give receptor **3.16** as shown in **Scheme 3.8**. Again a number of reactions were set up to identify the optimum conditions. The different conditions attempted are summarised in **Table 3.3**.



3.16

Scheme 3.8

The first attempt was carried out in dry chloroform in the presence of a catalytic amount of 4-dimethylaminopyridine (DMAP)[44] under basic conditions. E.S.M.S confirmed the resultant crystals were urea **3.16** however proton NMR and TLC revealed starting material was still present. Unfortunately attempts of purification by flash column chromatography were unsuccessful due to its lack of solubility in non polar solvents.

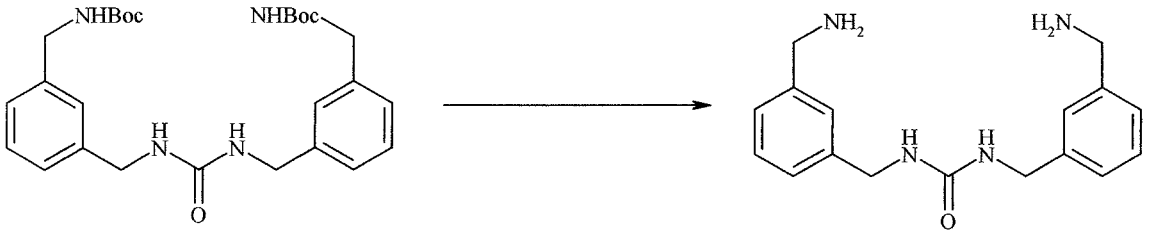
The next experiment was set up using very similar condition but this time the mixture was heated to try and aid the reaction. E.S.M.S confirmed the resultant crystals were urea **3.16** but again proton NMR revealed a small amount of starting material was still present as a baseline impurity.

Finally the experiment was carried out without the presence of any catalyst or base to identify their importance. Unfortunately the resultant crystals were not soluble enough to get a proton NMR but E.S.M.S. revealed a mixture of receptor **3.16**, the mono Boc urea and the urea with no Boc groups present indicating the Boc groups were removed under these conditions. This could be due to the absence of base. Boc groups are removed under acidic conditions and a slight presence of acid in the solvent could have facilitating Boc removal.

Attempt	Reaction conditions
1	Et_3N / DMAP / $CHCl_3$ / RT
2	Et_3N / DMAP / $CHCl_3$ / Reflux
3	$CHCl_3$ / RT

Table 3.3 - Conditions used in the formation of **3.16**

These investigations revealed the best conditions for the formation of **3.16** was nucleophilic substitution of triphosgene by compound **3.15** in the presence of DMAP in dry chloroform under basic conditions since only a small amount of starting material was still present. The resultant crystals from this reaction was then treated with acid to try and remove the Boc groups resulting in receptor **3.17** as shown in **Scheme 3.9** to allow the next step in the formation of the cyclotrimer to be carried out.



3.16 **3.17**

Scheme 3.9

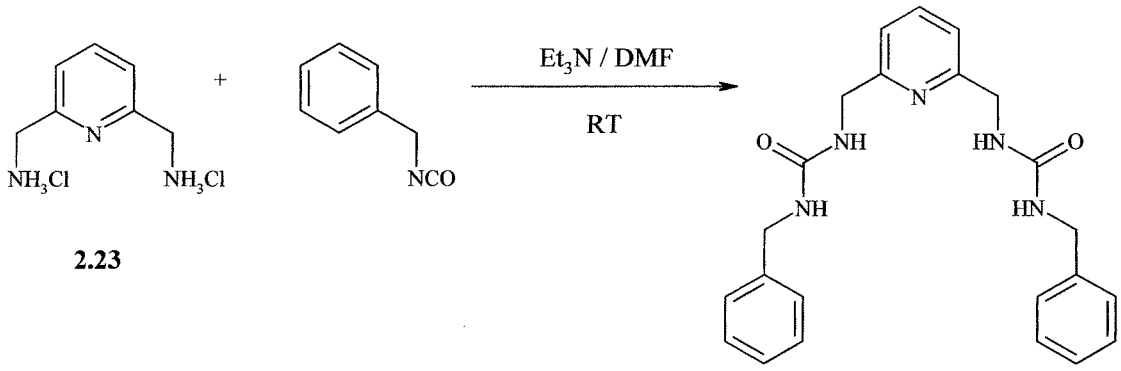
Initial attempts to remove the Boc groups were carried out using hydrochloric acid[44] in dichloromethane as shown in **Table 3.4**. Unfortunately TLC suggested a slow reaction was occurring so the reaction was left for three days. After this time a small sample was removed and proton NMR showed only diamine present indicating receptor **3.16** was

broken down. Instead TFA was used but the reaction was only left for a few minutes. E.S.M.S. and proton NMR confirmed the resultant oil was receptor **3.17**. This was noticeable on the proton NMR spectrum by the disappearance of the CH_3 peak however the spectrum did reveal baseline impurities were present.

Attempt	Reaction conditions
1	HCl / CH_2Cl_2 / RT
2	TFA / RT

Table 3.4 - Conditions used in the formation of **3.17**

Unfortunately initial solubility tested proved receptor **3.17** was not very soluble preventing it being used in the next step in the formation of the cyclotrimer. Instead attempts were made to synthesis a bis-urea receptor directly to provide a comparison. Receptor **2.23** was reacted with benzyl isocyanate under basic conditions resulting in receptor **3.18** as shown in **Scheme 3.10**. Proton NMR confirmed the precipitated crystals were bis-urea **3.18** in 19 % yield and showed no further purification was needed.



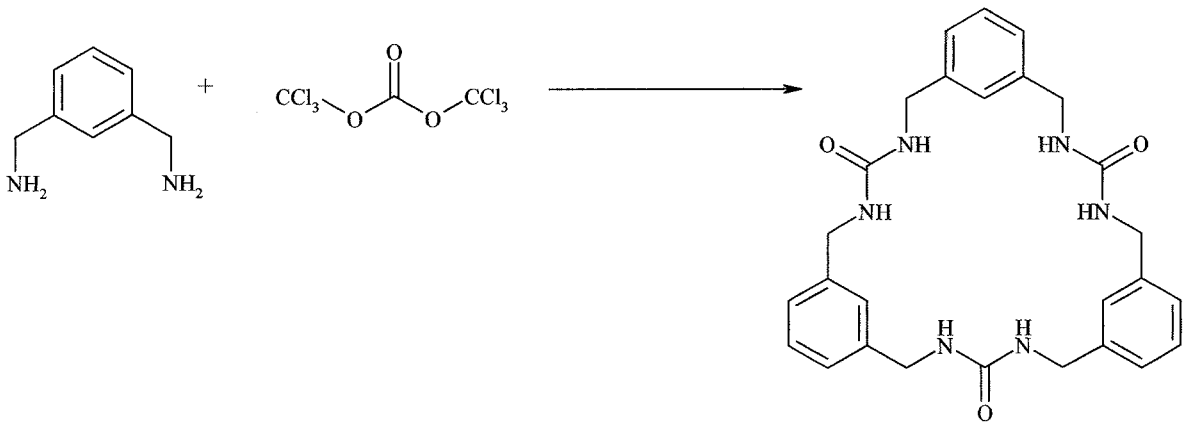
2.23 **3.18**

Scheme 3.10

The final approach investigated the formation of the cyclotrimer in a one-step synthesis. Triphosgene was reacted with 3-(aminomethyl)-benzylamine in both dry DCM and dry chloroform to try and yield **3.19** as shown in **Scheme 3.11**. The different conditions used are summarised in **Table 3.5**. Unfortunately the resultant crystals from attempt one were not soluble enough to get a proton NMR however E.S.M.S. confirmed the desired

product was present but also revealed the presence of starting material and the bis-urea product.

The resultant crystals from attempt two again were not soluble enough to get a proton NMR spectrum. E.S.M.S. again revealed a mixture of starting material, bis-urea product and the desired product **3.19**.



3.19

Scheme 3.11

Attempts were also made to template the reaction with TBA nitrate. As already explained the nitrate should have orientated the monomers into position favourable to cyclic structure formation and hopefully result in improved yield. Again this was carried out in both dry chloroform and dry dichloromethane. However E.S.M.S. revealed the reaction was unsuccessful in both cases with only starting material, mono-urea and bis-urea present.

Attempt	**Reaction conditions**
1	Dry CH_2Cl_2 / RT
2	Dry $CHCl_3$ / RT
3	Dry CH_2Cl_3 / TBA NO_3^- / RT
4	Dry $CHCl_3$ / TBA NO_3^- / RT

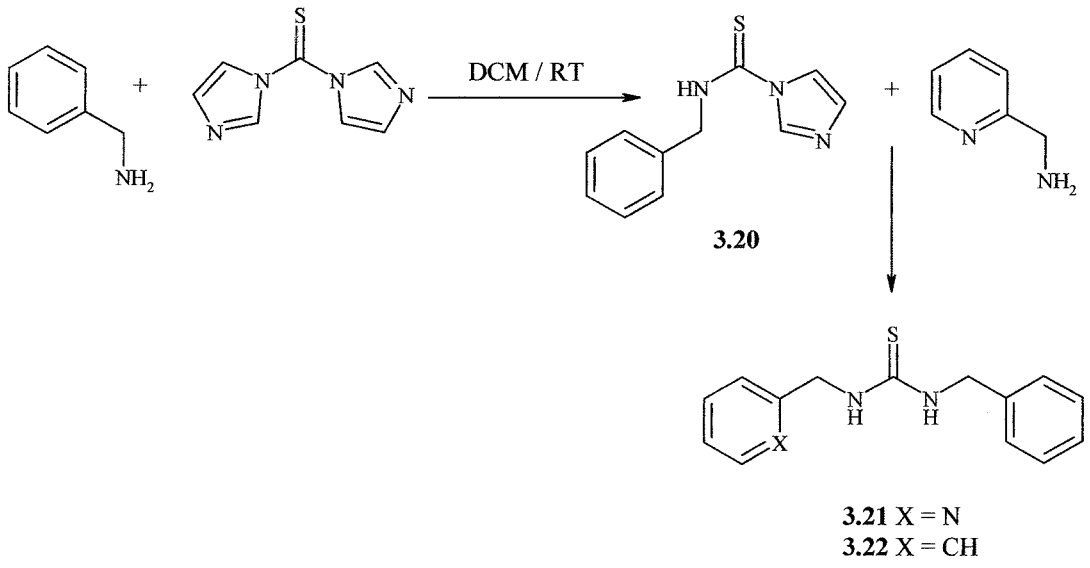
Table 3.5 – Conditions used in the formation of **3.19**

Unfortunately these receptors proved to be very insoluble preventing any attempt of purification. The solubility tests also showed receptors **3.18** and **3.19** were not soluble in the solvent used to carryout proton NMR binding studies preventing any investigation into the binding capabilities of the urea containing receptors with anions. Instead attempts were made to increase the solubility of the receptors.

3.2.2 Thiourea receptors

Studies focussed next on the synthesis of a group of receptors containing thiourea moieties instead of urea. The presence of the sulphur atom should have helped make these receptors more soluble allowing further progression in the stepwise synthesis of the cylcotrimer.

Model reactions were first attempted as a two-step process. Intermediate **3.20** was synthesised by the nucleophilic substitution of 1,1-thiocarbonyldiimidazole by benzylamine then after sufficient time an equivalent of 2-(aminomethyl) pyridine was added to obtain **3.21** as shown in **Scheme 3.12.**

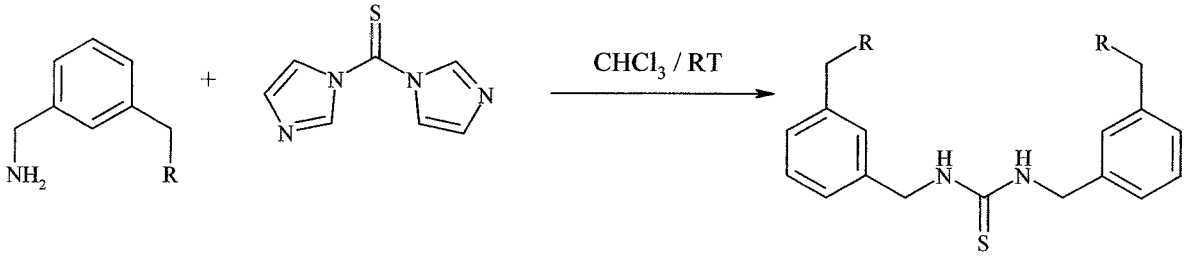


Scheme 3.12

Proton NMR and E.S.M.S revealed the resultant crystals were a mixture of desired compound **3.21** and **3.22**. Purification by flash column chromatography resulted in the isolation of compound **3.21** in 53 % yield. Proton NMR revealed the resultant liquid

needed no further purification. This suggested this was a good method for the stepwise addition of amines to a carbonyl group.

These reagents were then used to try and synthesis the first receptor in the stepwise cyclotrimerisation process by the nucleophilic substitution of 1,1-thiocarbonyldiimidazole by 3-(aminomethyl) benzylamine as shown in **Scheme 3.13**. Proton NMR and E.S.M.S. revealed the resultant crystals were not receptor **3.23** instead they showed the formation of the cyclotrimer however the proton NMR also revealed starting material was still present.

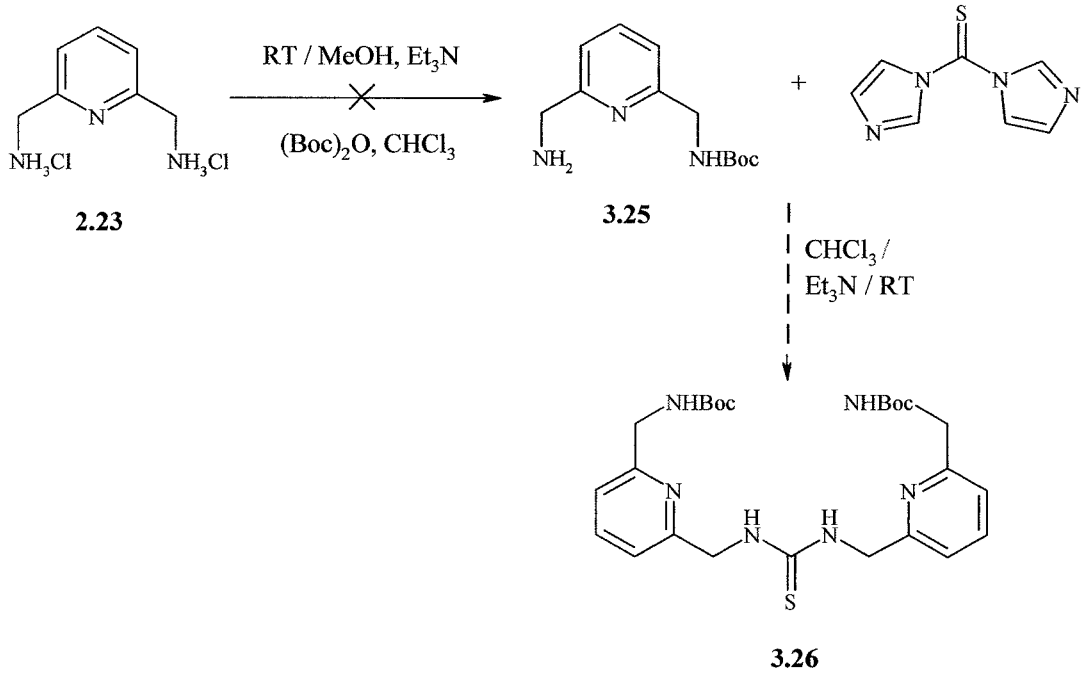


3.23 R = NH_2
3.24 R = NHBoc

Scheme 3.13

To overcome this mono protected **3.15** was used instead of 3-(aminomethyl) benzylamine. Purification by flash column chromatography obtained receptor **3.24** which was confirmed to be the desired products by proton NMR and E.S.M.S in 33 % yield.

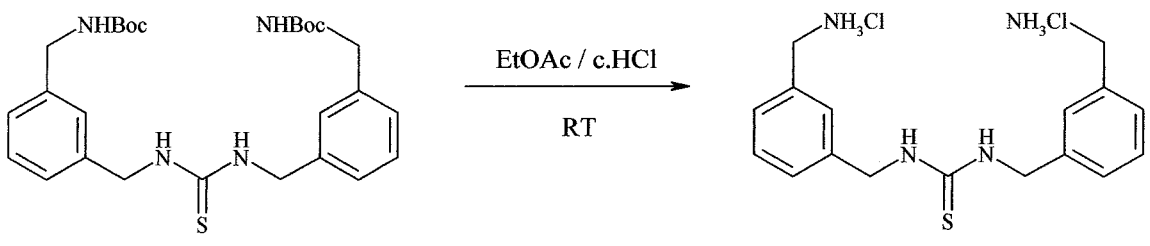
Attempts were also made to synthesis the thiourea containing pyridyl receptor as shown in **Scheme 3.14**. Firstly, the synthesis of the mono-Boc pyridyl receptor **3.25** was attempted by the nucleophilic substitution of di-tert-butyl dicarbonate[44] by compound **2.23** under basic conditions. Unfortunately proton NMR and E.S.M.S. showed the desired product was not present. Instead only starting material was present in the proton NMR spectrum. This prevented the second step from being carried out. It was hoped compound **3.25** would react with 1,1-thiocarbonyldiimidazole to give receptor **3.26**.



2.23 **3.25** **3.26**

Scheme 3.14

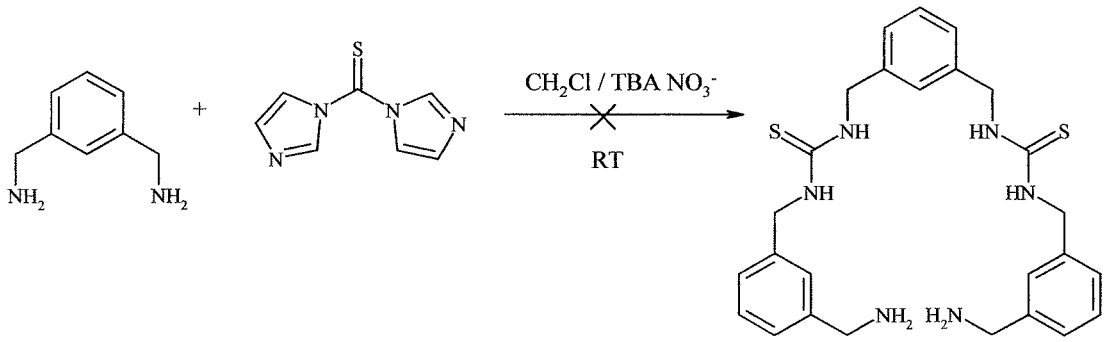
Research focused next on the second stage of the cyclotrimerisation process. Solubility tests showed the mono thiourea receptor was much more soluble than its urea analogue. First, the Boc protecting groups needed to be removed from receptor **3.24**. Compound **3.24** was dissolved in hydrochloric acid saturated ethyl acetate[59] to give receptor **3.27** as shown in **Scheme 3.15**. E.S.M.S. showed the desired compound was present without the hydrochloride salt. The formation of receptor **3.27** was confirmed by proton NMR which showed slight impurities. However the 133 % yield suggested some inorganic material, not visible by proton NMR, was present but the small overall mass of product prevented any purification being carried out.



3.27

Scheme 3.15

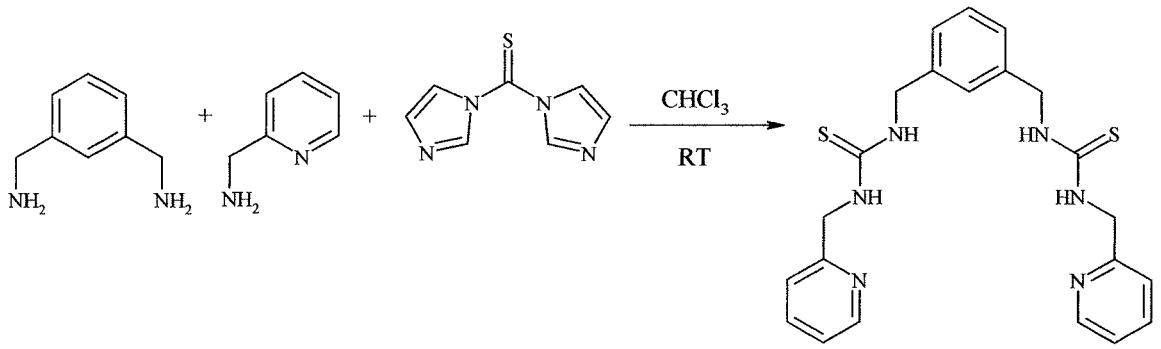
Instead attempts were made to make the bis-thiourea receptor **3.28** in a one-pot synthesis as shown in **Scheme 3.16**. This was attempted by reacting 3-(aminomethyl) benzylamine with 1,1-thiocarbonyldiimidazole in the presence of TBA nitrate. It was hope the presence of the nitrate anion would prevent polymerisation. Unfortunately the resultant crystals were not soluble enough to get a proton NMR or E.S.M.S. spectrum. Attempts to dissolve the crystals in acid were also unsuccessful which suggested the formation of a polymer.



3.28

Scheme 3.16

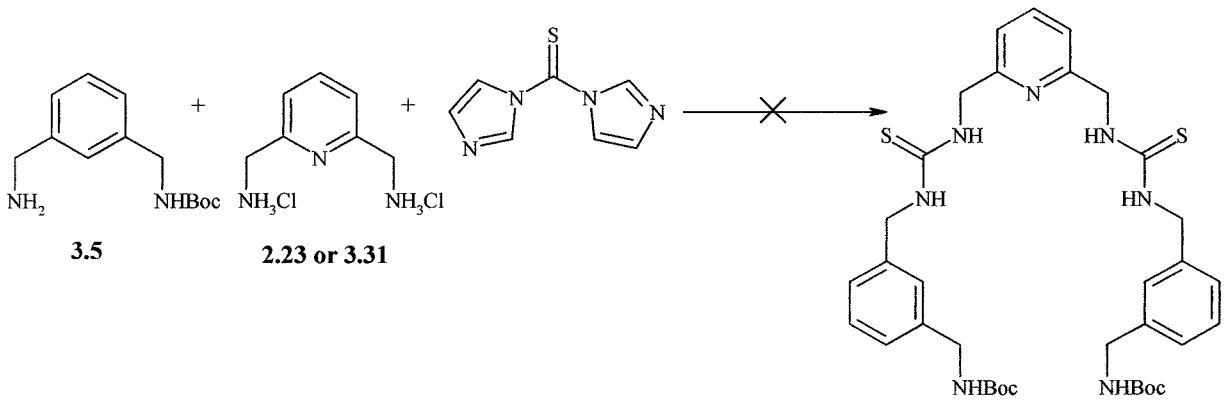
To try and prevent this polymerisation 2-(aminomethyl) pyridine was used as shown in **Scheme 3.17**. Again this was carried out as a one-pot method but this time adequate time was allowed between each addition to allow time for the reaction to occur. 1,1-thiocarbonyldiimidazole first underwent nucleophilic substitution by two equivalents of 3-(aminomethyl) benzylamine. Two equivalents of 2-(aminomethyl) pyridine were then added to form bis-urea **3.29** after adequate time had elapsed for the reaction to take place. Although E.S.M.S. confirmed the resultant crystals contained the desired product the proton NMR spectrum revealed mainly starting material was present with only trace amount of the desired product possibility visible on the baseline.



3.29

Scheme 3.17

The final attempt to make the bis-thiourea utilised a similar approach with mono-Boc **3.15** as shown in **Scheme 3.18**. Two different conditions were attempted as summarised in **Table 3.6** but in both cases methanol was used as the solvent to ensure the reactants dissolved properly. Again this was carried out as a stepped one-pot method. Unfortunately proton NMR and E.S.M.S. showed the reaction was unsuccessful with mainly starting material present. The proton NMR also revealed the mono-thiourea side product was present resulting from the coming together of two mono-Boc monomers **3.15**.



3.5 **2.23 or 3.31** **3.30**

Scheme 3.18

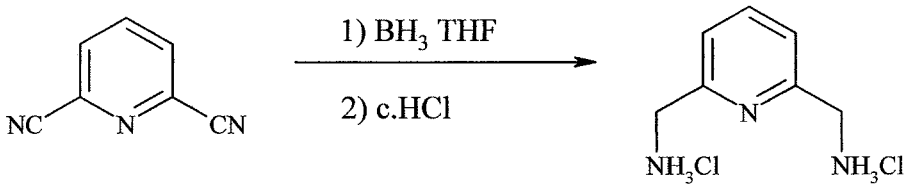
Since this was unsuccessful the reaction was preformed again under slightly different conditions. Firstly, compound **2.23** was synthesised again using a different approach. Pyridine-2,6-dinitrile was reacted with borane tetrahydrafuran complex[78] as shown in **Scheme 3.19** resulting in the newly named compound **3.31.** Proton NMR confirmed the

recrystallised crystals were pure **3.31** in 69 % yield. This was then used in the above reaction instead of **2.23**. Also the mixture was refluxed throughout this time in the hope the heat would aid the reaction.

Attempt	Pyridyl receptor	Reaction conditions
1	2.23	Et_3N / MeOH / RT
2	3.31	Et_3N / MeOH / 75 ^0C

Table 3.6 – Conditions used in the formation of **3.30**

Unfortunately the resultant crystals were not soluble enough to get a proton NMR but E.S.M.S. showed the desired product was not present. This lack of solubility suggested the presence of multiple thiourea moieties as a result of polymerisation of compound **3.31**.

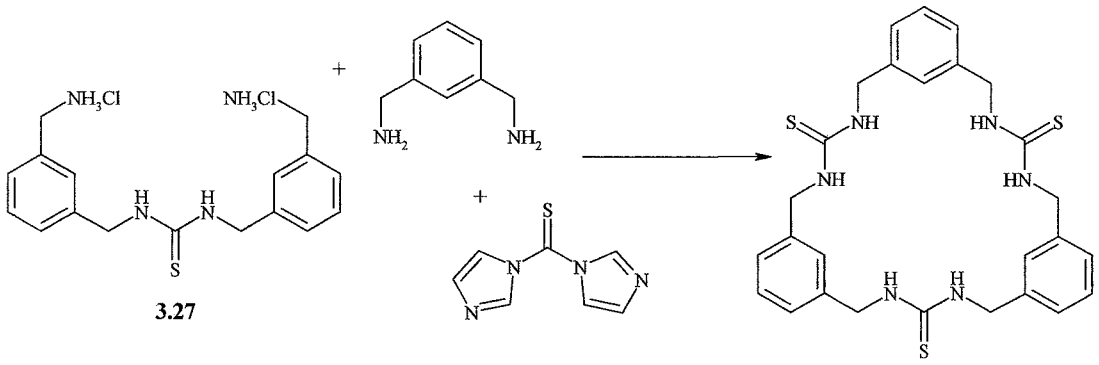


3.31

Scheme 3.19

Since attempts were proven difficult to complete step-two of the stepwise cyclotrimerisation process we decided to focus final investigations on the one-pot formation of the cyclotrimer.

Initially the successfully synthesised mono-thiourea **3.27** was stirred with a mixture of two equivalents of 1,1-thiocarbonyldiimidazole and one equivalent of 3-(aminomethyl) benzylamine monomer in the presence of base to try and produce cyclotrimer **3.32** as shown in **Scheme 3.20**. Again the reaction was stepped and methanol was used as the solvent to try and prevent precipitation of the not very soluble bis-thiourea before cyclotrimer production.



3.27

3.32

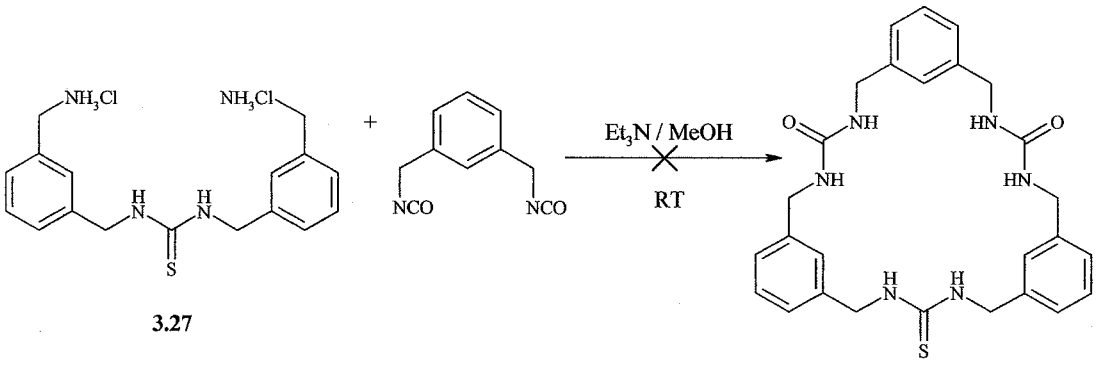
Scheme 3.20

With and without the presence of a template was investigated as summarised in **Table 3.7**. E.S.M.S. clearly indicated the formation of cyclotrimer **3.32** from both reactions. However the proton NMR spectra of the resultant liquid from attempt one showed a mixture was present which is reflected in the yield produced. Again purification was not possible due to the poor solubility of this compound. Although the proton NMR looked a lot cleaner for attempt two with only slight baseline impurities this reaction resulted in a very low yield of only 14 %.

Attempt	Reaction conditions
1	Et_3N / MeOH / RT
2	Et_3N / MeOH / TBA NO_3^- / RT

Table 3.7 – Conditions used in the formation of **3.32**

Attempts where also made to synthesis receptor **3.33** which contained both urea and thiourea moieties. This was attempted by reacting xylylene diisocyanate with thiourea **3.27** as shown in **Scheme 3.21**. Unfortunately E.S.M.S. and proton NMR showed the reaction was unsuccessful with only starting material still present.

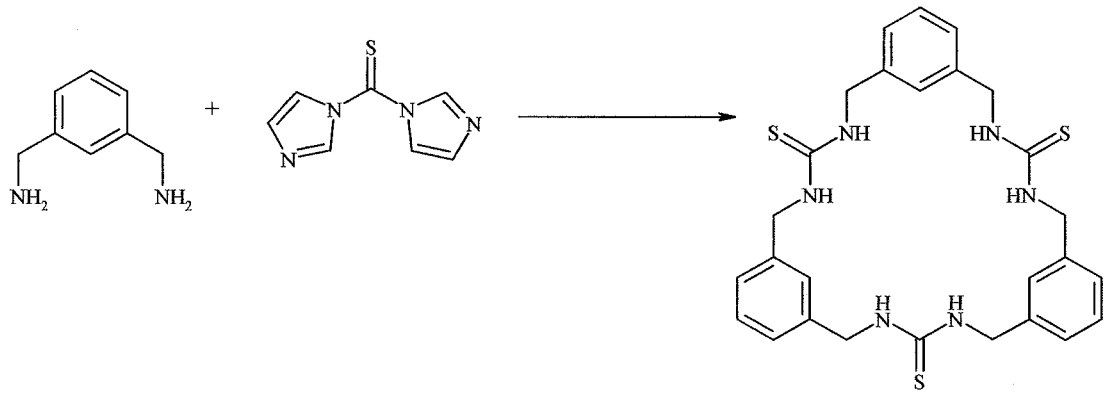


3.27

3.33

Scheme 3.21

A one-pot cyclotrimerisation of monomers to form the cyclotrimer **3.32** directly was also investigated by reacting 1,1-thiocarbonyldiimidazole with 3-(aminomethyl) benzylamine as shown in **Scheme 3.22**.



3.32

Scheme 3.22

Again a number of different experiments where set up and carried out under slightly different conditions. These conditions are summarised in **Table 3.8**. Firstly, the reaction was carried out in methanol and base and templated by TBA nitrate. Unfortunately E.S.M.S. confirmed only the bis-thiourea product **3.28** was present and the proton NMR also revealed a mixture was present. These conditions were repeated but the reaction was stepped again allowing more time for the reaction to occur before the next equivalent of reactant was added. Once the procedure got to the formation of the bis-thiourea a small precipitate started to form but the reaction was continued. The E.S.M.S.

confirmed the reaction did not go to completion with only the bis-thiourea **3.28** present and no cyclotrimer. This was expected since the bis-urea precipitated out of solution preventing it from being used in the final step. The proton NMR again showed a mixture was present.

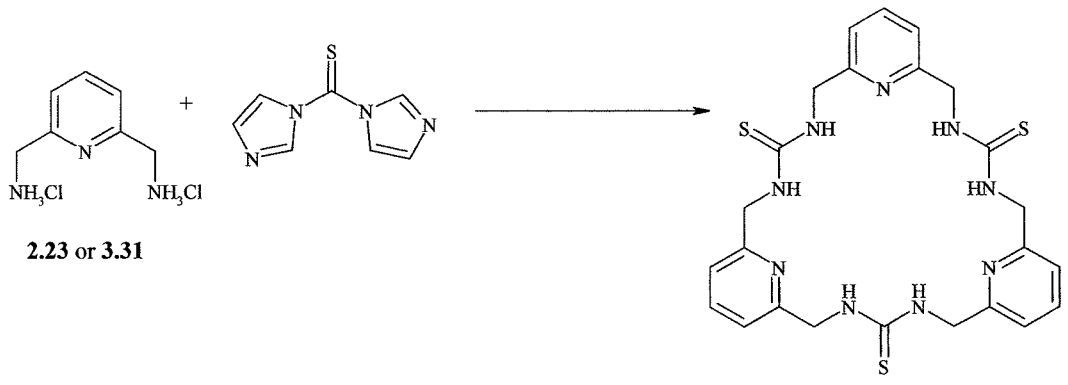
Attempt	Reaction conditions
1	Et_3N / MeOH / TBA NO_3^- / RT
2	Et_3N / MeOH / TBA NO_3^- / RT
3	CH_2Cl_3 / TBA NO_3^- / RT
4	$CHCl_3$ / TBA Cl^- / RT
5	CH_2Cl_3 / MeOH / RT

Table 3.8 – Conditions used in the formation of **3.32**

The monomer cyclotrimerisation was carried out next in dichloromethane since these conditions seem to be more favourable. Again TBA nitrate was added to try and template the reaction. The formation of **3.32** was confirmed by E.S.M.S. The spectrum also revealed the nitrate anion could still be bound in the middle. The proton NMR spectrum however showed there were some slight impurities present but its lack of solubility prevented any purification attempt. Again the yield was low at only 23 %. These conditions were repeated but this time TBA chloride was used as the template since the initial proton NMR titrations revealed mono-urea **3.16** had greater binding affinity for TBA chloride (see section 3.3) in the hope of improving the yield. Unfortunately the E.S.M.S. spectrum showed no cyclotrimeric product was present instead the bis-thiourea **3.28** was formed again. Very little could be seen in the proton NMR spectrum against the TBA salt.

The last conditions investigated was a stepped reaction starting off using dichloromethane as the solvent then changing to methanol once solubility became an issue. E.S.M.S. confirmed the precipitated crystals were cyclotrimer **3.32**. However the proton NMR showed trace amounts of impurities were present but solubility prevented any purification attempt. Again the yield was very low at only 17 %. However this did suggest the presence of TBA nitrate did template the reaction slightly since the yield from the successful templated reaction, attempt three, was slightly higher at 23 %.

Finally attempts were made to synthesis the pyridyl containing cyclotrimer **3.34**. We hoped the presence of the nitrogen atoms would allow the reactants to self-template via intramolecular hydrogen bonding taking place similar to the macrocyclic receptors synthesis by Cuccia *et al*[73]. 1,1-Thiocarbonyldiimidazole was reacted with the pyridyl hydrochloride salt as shown in **Scheme 3.23**.

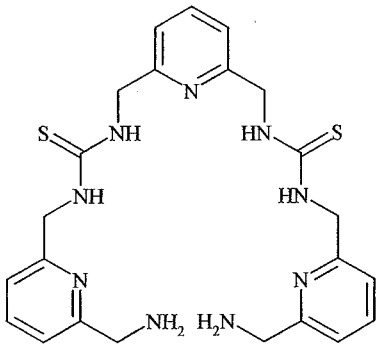


2.23 or **3.31**

3.34

Scheme 3.23

Again a number of different reaction conditions were investigated. The different conditions are summarised in **Table 3.9**. Firstly, the reaction was carried out in methanol and base. Unfortunately E.S.M.S. showed no cyclotrimer product was present only bis-thiourea **3.35** but the resultant crystals were not soluble enough to get a proton NMR.



3.35

These conditions were repeated with TBA nitrate present to template the reaction. E.S.M.S. and proton NMR confirmed the formation of **3.34**. The E.S.M.S. spectrum

was complicated with a number of chloride ions and the imidazole ion present as shown in **Figure 3.2**.

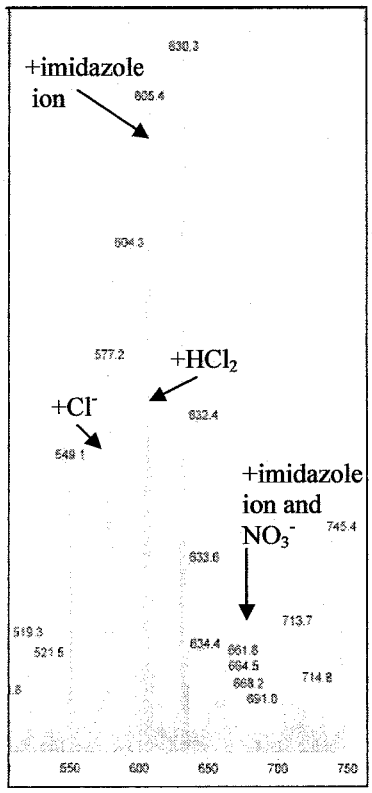


Figure 3.2

The next reaction conditions attempted used methanol as the solvent and the reaction mixture was refluxed throughout in the hope the heat would help aid the reaction. Unfortunately the resultant crystals were not soluble enough to get a proton NMR however E.S.M.S. revealed the reaction was unsuccessful with only starting material still present. This was repeated using DMF as the solvent. Again the resultant crystals proved to insoluble to get a proton NMR but E.S.M.S. showed the reaction was unsuccessful. These conditions were repeated adding TBA nitrate to template the reaction but again the resultant crystals proved to insoluble to get a proton NMR and E.S.M.S. confirmed cyclotrimer **3.34** was not present.

Attempt	Pyridine receptor	Reaction conditions
1	3.31	Et_3N / MeOH / RT
2	2.23	Et_3N / MeOH / TBA NO_3^- / RT
3	3.31	MeOH / Reflux
4	3.31	DMF / Reflux
5	3.31	DMF / TBA NO_3^- / Reflux

Table 3.9 – Conditions used in the formation of **3.34**

Sadly the lack of solubility of these urea/thiourea based receptors prevented their successful synthesis and purification and we decided these issues where to great to overcome.

3.3 NMR binding studies

The lack of purity and solubility of these receptors also meant their binding capabilities could not be fully investigated by proton NMR as planned. We had hoped to investigate the binding capabilities at each stepwise stage identifying an increase in binding affinity with the addition of each urea or thiourea hydrogen bond donor ending with the cyclotrimer exhibiting great affinity and selectivity for nitrate. Computer based molecular mechanics experiments using 'Hyperchem', procedure previously described, shows how receptor **3.34** is designed to have a correctly oriented array to hydrogen bond all six lone pairs of the nitrate anion as shown in **Figure 3.3**.

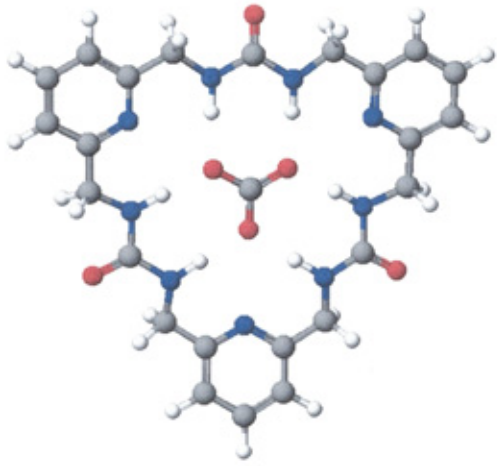


Figure 3.3 – Receptor **3.34** with a bound nitrate anion

It was possible to dissolve receptor **3.16** in acetone so a proton NMR binding study was carried out with TBA chloride guest and the binding constants were calculated using the change in chemical shift of both the amide and urea protons. The binding curves are shown in **Figures 3.4-3.5** and the results are shown in **Table 3.10**.

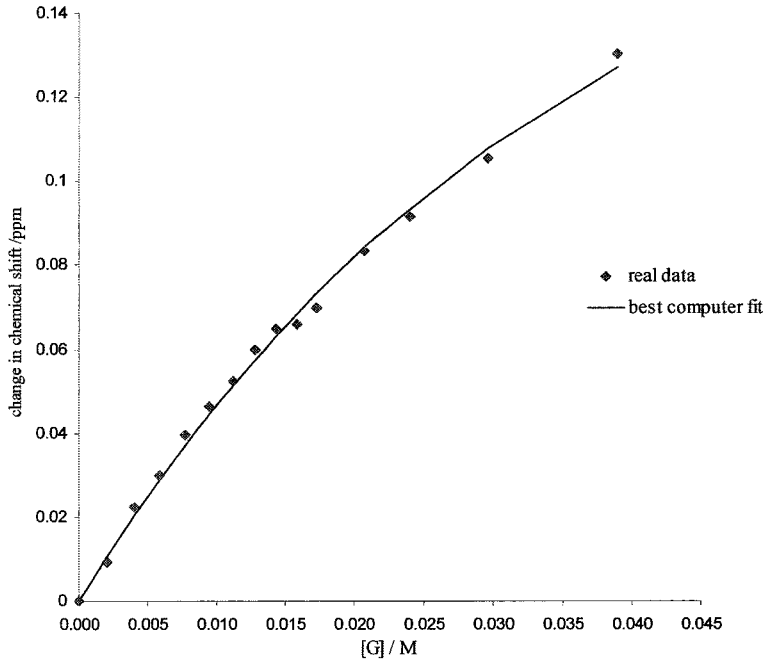


Figure 3.4 – Binding curve of receptor **3.16** with chloride in acetone following NH 1

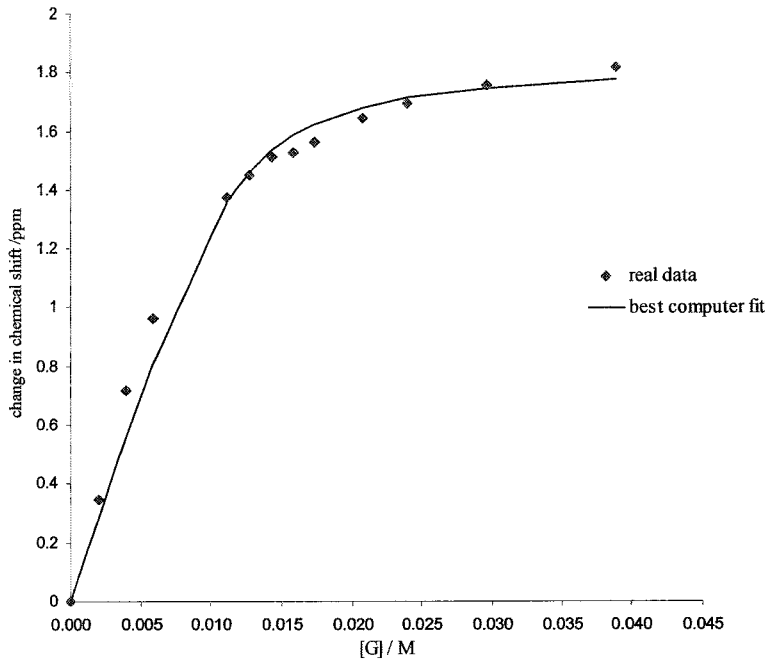


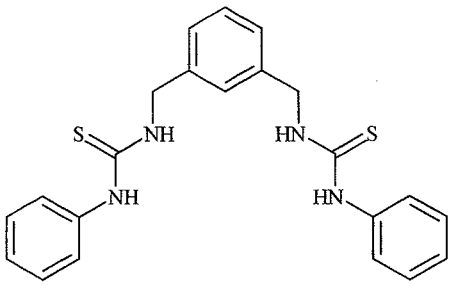
Figure 3.5 – Binding curve of receptor **3.16** with chloride in acetone following NH 2

The two calculated binding constants were very different indicating one of the NH protons followed played a larger part in a 1:1 binding interaction with the chloride anion than the other. There was only a very small chemical shift change of 0.13 ppm for the first NH followed compared to a much larger shift of 1.8 ppm for the other. This was consistent with the anion sitting in the cleft and forming two hydrogen bonds to the urea protons resulting in a strong interaction and a higher binding constant. This position only allows weak interactions to form with the amide protons resulting in a much lower binding constant. There would also be repulsion between the chloride anion and the Boc groups weakening any hydrogen bond formed with the amide protons.

Receptor	Guest	Binding Constants (M^{-1})
3.16	Cl^-	NH 1 – 27 ± 10 % NH 2 – 881 ± 5 %

Table 3.10 – Calculated binding constants for receptor **3.16** in acetone

For a comparison receptor **3.36** containing two thiourea moieties was supplied by Dr Justin Perry.



3.36

Proton NMR binding study were carried out with both TBA chloride and TBA nitrate guests and the binding constants were calculated. The titration with TBA chloride was repeated as before to allow an indication of the error involved in the calculation. The binding curves are shown in **Figure 3.6-3.8** and the results are shown in **Table 3.11**.

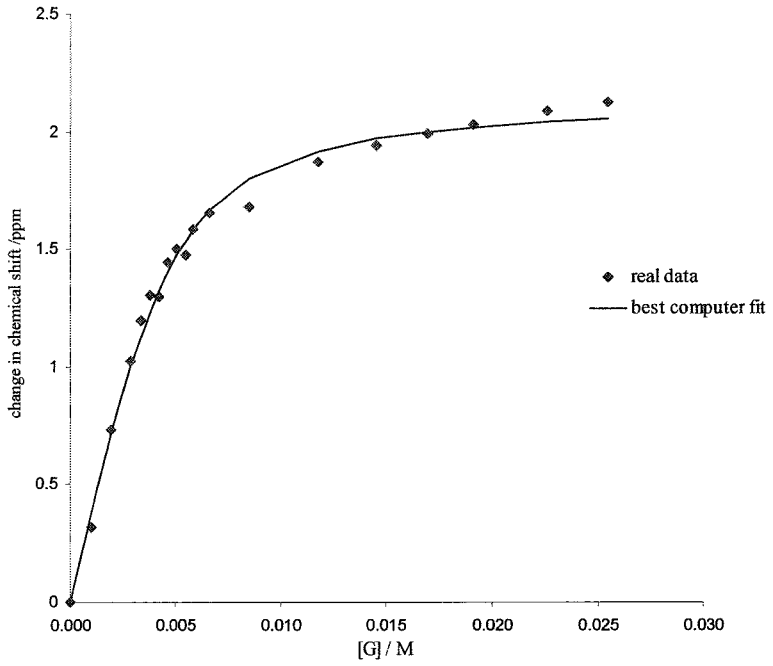


Figure 3.6 – Binding curve of receptor **3.36** with chloride in acetonitrile following NH 1

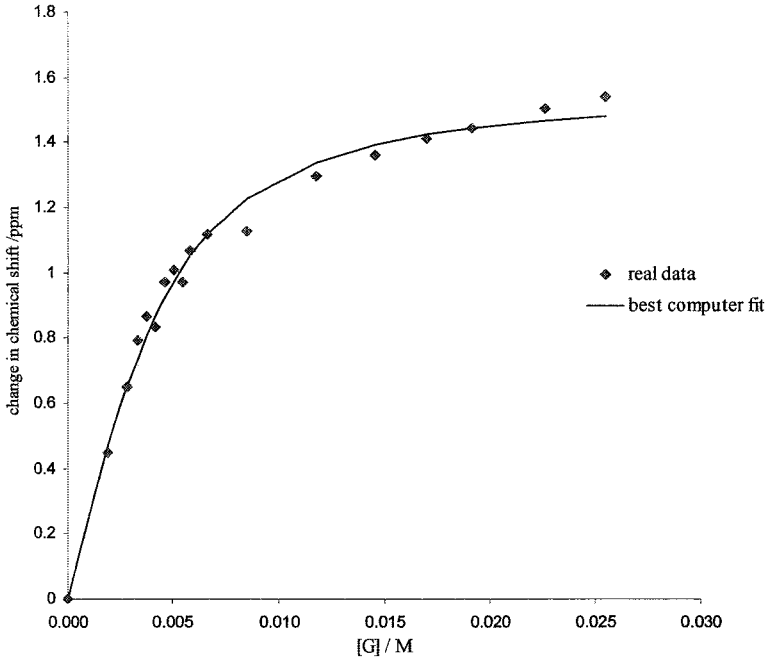


Figure 3.7 – Binding curve of receptor **3.36** with chloride in acetonitrile following NH 2

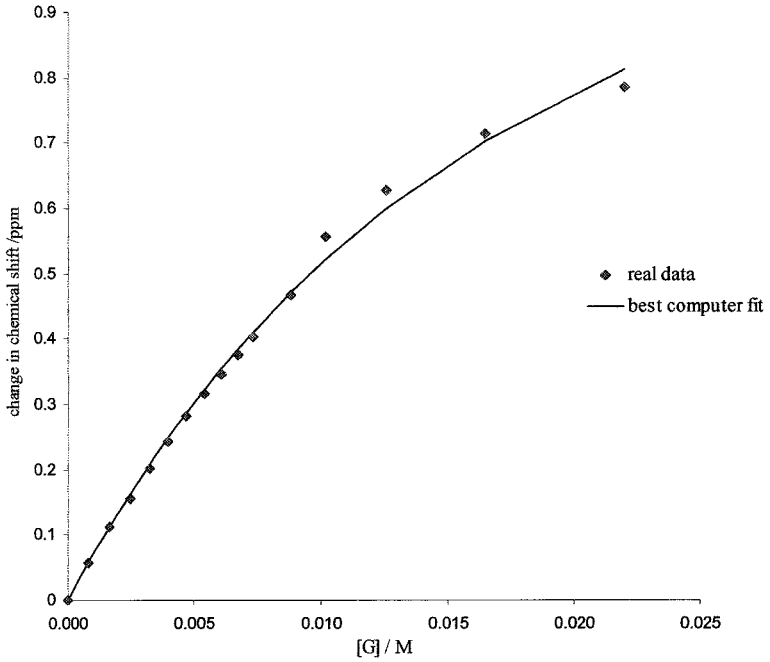


Figure 3.8 – Binding curve of receptor **3.36** with nitrate in acetonitrile

It was expected the binding affinity would increase with the addition of another hydrogen binding moiety and the presence of the more acidic thioureas. However this was not the case. The results were about even for the urea proton from receptor **3.16** and the first of the thiourea proton followed from receptor **3.36** with binding constants of 881 M^{-1} and 865 M^{-1} respectively. However these were carried out in different solvents.

Receptor	**Guest**	**Binding Constants (M^{-1})**	
		Actual	**Average**
3.36	Cl^-	NH 1 – 970 NH 2 – 625 NH 1 – 760 NH 2 - 565	NH 1 – 865 ± 12 % NH 2 – 595 ± 5 %
	NO_3^-	75 ± 25 %	

Table 3.11 – Calculated binding constants for receptor **3.36** in acetonitrile

The results for receptor **3.36** also revealed this receptor has little binding affinity for the nitrate guest. This was disappointing since this was our target guest and indicates the receptors cleft is not the correct shape and size as hoped. This suggested the cyclotrimer receptor would not have exhibited the correct geometry to selectively bind the nitrate anion. As already explained Herges *et al*[44] published his findings of our target tris thiourea cyclotrimer **3.34** after our research began. He found receptor **1.64** exhibited virtually no binding affinity for nitrate with a binding constant of less than 1 M^{-1} confirming our suspicions.

The results shown in **Table 3.10-3.11** also revealed how the use of ureas or thioureas instead of amide groups as the hydrogen bond donors does increase the binding affinity. Previous titrations for the simple receptors with two amide groups present, as explained in chapter 2, showed receptor **2.11** exhibited the largest affinity for chloride in acetonitrile with a binding constant of 92 M^{-1}. This is significantly smaller than the binding constant of 865 M^{-1} calculated for receptor **3.36**. This is as expected since the two thiourea moieties provide two additional hydrogen bonding donors.

3.4 Conclusion

The stepwise synthesis of the cyclotrimer containing urea moieties was unsuccessful after the mono-urea product **3.16** from step one proved to be insoluble in the solvents required for the reaction and prevented any further stepwise synthesis. However the mono-urea receptor was soluble in acetone which enabled proton NMR titrations to be carried out. Instead, the one-pot method was used to successfully synthesise a bis-urea **3.18**. Unfortunately though the one-pot method of the cyclotrimer **3.19** resulted in a mixture and purification was not possible due to the insolubility of the resultant crystals. The presence of TBA nitrate did not prove to have a templating effect in fact the cyclotrimer **3.19** was not synthesised in its presence. The bis-urea **3.18** also proved to be very insoluble preventing any analysis of binding ability being carried out.

To try and overcome this, receptors containing thiourea moieties were attempted in the hope of increasing solubility. Again the step-wise process resulted in the successful synthesis of the mono-thiourea **3.27** however the yield suggested impurities were present. Despite this the receptor was successfully used in the formation of the cyclotrimer **3.32**. Unfortunately a mixture was present and again the lack of solubility of the resultant crystals prevented purification. Both the benzyl and pyridyl cyclotrimer **3.32** and **3.34** were successfully synthesised from the one-pot method with only a small amount of impurities present but again the lack of solubility prevented any investigation into their binding abilities. This time the presence of TBA nitrate resulted in a cleaner reaction and an improved yield in the synthesis of the benzyl cyclotrimer **3.32**. The synthesis of the pyridyl cyclotrimer **3.34** was only possible in the presence of TBA nitrate which showed it had a templating effect.

Proton NMR titrations were carried out on the synthesised mono-urea **3.16** and a bis-thiourea **3.36** provided by Dr. Justin Perry. The results showed the urea/thiourea receptors were capable of forming strong interactions with the anion guest, much stronger than those formed with the previous discussed amide receptors.

Chapter 4

4. Experimental

4.1 Experimental directions

Proton NMR and carbon NMR spectra were recorded on a Jeol EX270 instrument (270 MHz). All chemical shifts are quoted in ppm relative to tetramethylsilane (TMS) as an internal standard in either deterio-trichloromethane ($CDCl_3$) or deterio-dimethylsulphoxide (DMSO). All chemical shifts are reported as follows: δ value in ppm (multiplicity, number of protons, coupling constants in Hz, and assignments). The multiplicity of signals is expressed as follows: s, singlet; d, doublet; dd, double doublet; ddd, double doublet of doublets; t, triplet; td, triplet of doublets; dt, double triplet; m, multiplet and br, broad.

G.C.M.S. were recorded using a Hewlett Packard 5890 series II instrument in conjunction with a Hewlet Packard 5971A mass detector. E.S.M.S. were recorded using a Thermo Finnigan LCQ Advantage on Electro Spray Ionisation.

Infra-red spectra were obtained using a diamond anvil on a Perkin Elmer 1000 spectrophotometer. Melting points are reported uncorrected as determined on a Stuart SMP1 melting point apparatus.

Elemental analysis was performed by the Department of Chemistry at the University of Newcastle. High-Resolution mass spectra were performed by the EPSRC's mass spectrometry service.

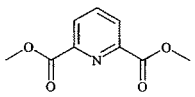
Thin layer chromatography was performed on Merck foil plates pre-coated with silica gel $60F_{254}$. Silica gel used for column chromatography was Merck silica gel 60.

Experimental Details for Chapter 2

4.2 Chapter 2

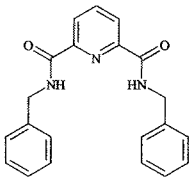
4.2.1 Synthesis of receptors

Pyridine-2,6-dicarboxylic acid dimethyl ester 2.14



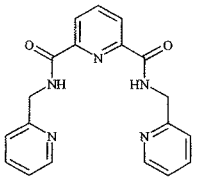
Concentrated hydrochloric acid (0.5 ml) was added to a stirring solution of 2,6-pyridinecarboxylic acid (5.0 g, 30 mmol) in methanol (100 ml) and the mixture was heated under reflux (2 hr). After cooling in ice the resultant solid was filtered under suction to give 2,6-dimethylpyridinoate **2.14** as white crystals (4.65 g, 80 %) m. p. 114-118 ^{0}C (Lit., 117-119 ^{0}C)[79]. δ_H ($CDCl_3$) 8.33 (d, 2H, J=7 Hz, *meta* Ph-*H*), 8.05 (t, 1H, J=7 Hz, *para* Ph-*H*), 4.04 (s, 6H, -*CH*$_3$) ppm. δ_C ($CDCl_3$) 165.0 (CO), 148.2 (C), 138.5 (C), 128.1 (C), 53.2 (CH_3) ppm. ν_{max} / cm^{-1} 1730 (C=O), 1247 (C-O). E.S.M.S. for $C_9H_9N_1O_4$. Calculated mass of molecular ion: 196 $(M+H)^+$; Measured mass: 196 $(M+H)^+$. The melting point and proton NMR spectral data is consistent with that found in the literature[79].

Pyridine-2,6-dicarboxylic acid bis-benzylamide 2.15



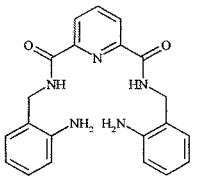
Ammonium chloride (0.1 g, 2 mmol) was added to 2,6-dimethylpyridinoate **2.14** (1.0 g, 5 mmol) and benzylamine (3 ml, 28 mmol) and the mixture heated under reflux (1 hr). After cooling and washing with water to remove excess benzylamine the solid n-benzylamide **2.15** was filtered under suction as white crystals (1.63 g, 92 %) m. p. 178-180 ^{0}C (Lit., 180 ^{0}C)[80] and washed with cold petroleum ether (100-120 ^{0}C). δ_H (DMSO) 9.94 (t, 2H, J=6 Hz, -*NH*) 8.25 (m, 3H, Py-*H*) 7.28 (m, 10H, Ph-*H*), 4.62 (d, 4H, J=6 Hz, -*CH*$_2$-) ppm. Partial δ_C ($CDCl_3$) 163.5 (CO), 148.8 (C), 139.1 (C), 138.1 (C), 128.9 (C), 127.8 (C), 127.7 (C), 125.5 (C), 43.6 (CH_2) ppm. ν_{max} / cm^{-1} 3341 (NH), 1652 (C=O), 1526 (C=O). E.S.M.S. for $C_{21}H_{19}N_3O_2$. Calculated mass of molecular ion: 344 $(M-H)^-$; Measured mass: 344 $(M-H)^-$. Anal. for $C_{21}H_{19}N_3O_2$: calc, N 12.17, C 73.03, H 5.54; found N 12.18, C 72.83, H 5.62. The melting point and proton NMR spectral data is consistent with that found in the literature[80].

Pyridine-2,6-dicarboxylic acid bis-[(pyridin-2-ylmethyl)-amide] 2.16



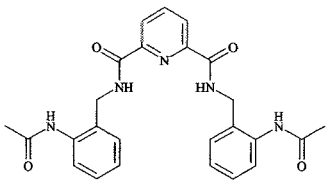
Ammonium chloride (0.1 g, 2 mmol) was added to 2,6-dimethylpyridinoate **2.14** (1.0 g, 5 mmol) and 2-(aminomethyl)pyridine (3 ml, 28 mmol) and the mixture heated under reflux (1 hr). After cooling and washing with water the solid was filtered under suction to gave **2.16** as pale yellow crystals (1.58 g, 89 %) m. p. 128-130 ^{0}C and washed with cold petroleum ether (100-120 ^{0}C). δ_H ($CDCl_3$) 9.38 (br, 2H, *-NH*), 8.52 (d, J=5 Hz, 2H, *ortho*-Py2-*H*), 8.34 (d, J=7 Hz, 2H, *meta*-Py1-*H*), 8.01 (t, J=7 Hz, 1H, *para*-Py1-*H*), 7.69 (td, J=6 and 1 Hz, 2H, *para*-Py2-*H*), 7.40 (d, J=7 Hz, 2H, Py2-*H*), 7.21 (td, J=6 and 1 Hz, 2H, *meta*-Py2-*H*), 4.80 (d, J=6 Hz, 4H, -CH_2-) ppm. δ_C ($CDCl_3$) 163.8 (CO), 157.2 (C), 149.2 (C), 148.7 (C), 138.9 (C), 137.1 (C), 128.1 (C), 124.9 (C), 122.5 (C), 44.6 (CH_2) ppm. ν_{max} / cm^{-1} 3347 (NH), 1658 (C=O), 1532 (C=O). E.S.M.S. for $C_{19}H_{17}N_5O_2$. Calculated mass of molecular ion: 348 $(M+H)^+$; Measured mass: 348 $(M+H)^+$. The proton NMR spectral data is consistent with that found in the literature[81].

Pyridine-2,6-dicarboxylic acid bis-(2-amino-benzylamide) 2.17



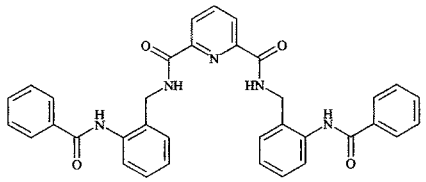
Ammonium chloride (0.2 g, 4 mmol) was added to 2,6-dimethylpyridinoate **2.14** (2.0 g, 10 mmol) and 2-aminobenzylamine (6 ml, 49 mmol) and the mixture was heated under reflux (1 hr). After cooling to room temperature chloroform was added and the mixture was washed with water. The organic layer was separated, dried ($MgSO_4$) and the solvent removed under reduced pressure to gave **2.17** as a sticky yellow solid (1.70 g, 44 %). δ_H ($CDCl_3$) 8.58 (br t, J=6 Hz, 2H, *-NH*), 8.30 (d, J=8 Hz, 2H, *meta*-Py-*H*), 7.94 (t, J=7 Hz, 1H, *para*-Py-*H*), 6.98 (m, 4H, *ortho* and *para*-amine-Ph-*H*), 6.58 (m, 4H, Ph-*H*), 4.49 (d, J=6 Hz, 4H, -CH_2-) ppm. There is no data reported in the literature for this compound.

Pyridine-2,6-dicarboxylic acid bis-(2-acetylamino-benzylamide) 2.18



Acetyl chloride (0.89 g, 11.3 mmol) was slowly added to a stirring solution of **2.17** (1.0 g, 5.1 mmol) in dichloromethane (100 ml) and triethylamine (1.14 g, 11.3 mmol) and stirring continued (12 hrs). The mixture was washed with sodium hydrogen carbonate (10%) and water. The organic layer was dried ($MgSO_4$) and the solvent removed under reduced pressure. Purification by flash column chromatography using methanol/ dichloromethane (2.5/97.5) gave **2.18** as a white solid (0.3 g, 25 %) m. p. 222-224 ^{0}C. δ_H ($CDCl_3$) 9.27 (br t, 2H, -*NH*), 9.02 (s, 2H, methyl-*NH*), 8.32 (d, J=7 Hz, 2H, *meta*-Py-*H*), 8.01 (t, J=8 Hz, 1H, *para*-Py-*H*), 7.79 (d, J=7 Hz, 2H, *ortho*-amide-Ph-*H*), 7.32 (m, 4H, Ph-*H*), 7.14 (t, J=8 Hz, 2H, *meta*-amide-Ph-*H*), 4.55 (d, J=6 Hz, 4H, -CH_2-), 2.23 (s, 6H, -CH_3) ppm. δ_C ($CDCl_3$) 170.8 (CO), 164.2 (CO), 148.4 (C), 136.4 (C), 131.3 (C), 130.5 (C), 129.2 (C), 125.8 (C), 125.1 (C), 124.9 (C), 40.8 (CH_2), 24.2 (CH_3) ppm. ν_{max} / cm^{-1} 3186 (NH), 3011 (NH), 1652 (C=O), 1523 (C=O). E.S.M.S. for $C_{25}H_{25}N_5O_4$. Calculated mass of molecular ion: 460 $(M+H)^+$; Measured mass: 460 $(M+H)^+$. There is no data reported in the literature for this compound.

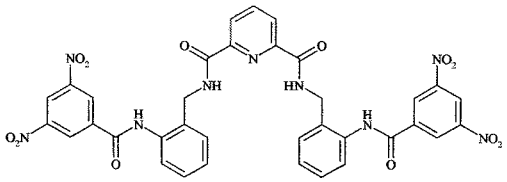
Pyridine-2,6-dicarboxylic acid bis-(2-benzoylamino-benzylamide) 2.19



Benzoyl chloride (0.82 g, 5.9 mmol) was slowly added to a stirring solution of **2.17** (1.0 g, 5.1 mmol) in dichloromethane (100 ml) and triethylamine (0.59 g, 5.9 mmol) and stirring continued (12 hrs). The mixture was washed with sodium hydrogen carbonate (10%) and water. The organic layer was dried ($MgSO_4$) and the solvent removed under reduced pressure. Purification by flash column chromatography using methanol/ dichloromethane (1.5/98.5) gave **2.19** as a white solid (0.1 g, 6 %) m. p. 264-266 ^{0}C. δ_H (DMSO) 10.41(s, 2H, -*NH*), 9.92 (br t, 2H, Py-*NH*), 8.23 (m, 3H, Py-*H*), 8.04 (d, 4H, J=8 Hz, *ortho*-amide-Ph2-*H*), 7.54 (m, 8H, *ortho*-amide-Ph1-*H* and Ph2-*H*), 7.32 (m, 6H, Ph1-*H*), 4.61 (d, J=6 Hz, 4H, -CH_2-) ppm. ν_{max} / cm^{-1} 3312 (NH), 3055 (NH), 1650 (C=O), 1520 (C=O). E.S.M.S. for $C_{35}H_{29}N_5O_4$. Calculated mass of molecular ion: 582

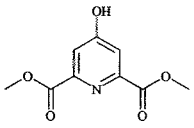
$(M-H)^-$; Measured mass: 582 $(M-H)^-$. There is no data reported in the literature for this compound.

Pyridine-2,6-dicarboxylic acid bis-[2-(3,5-dinitro-benzoylamino)-benzylamide] 2.20

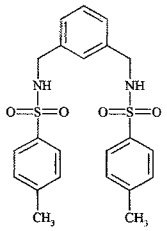


3,5-Dinitrobenzoyl chloride (1.84 g, 8.0 mmol) was slowly added to a stirring solution of **2.17** (0.5 g, 1.3 mmol) in dichloromethane (100 ml) and triethylamine (0.30 g, 8.0 mmol) and stirring continued (12 hrs). The mixture was washed with sodium hydrogen carbonate (10%) and water. The organic layer was dried ($MgSO_4$) and the solvent removed under reduced pressure to give an orange solid (0.51 g, 50 %) m. p. 198-200 ^{0}C. The proton NMR spectral data suggested a mixture of compound **2.20** and starting material. δ_H (compound **2.20**) (DMSO) 10.14 (br m, 2H, -*NH*-), 8.22 (m, 5H, Py-*H* and Ph-*H*), 7.13 (m, 11H, Ph-*H*), 4.54 (d, 4H, J=6 Hz, -CH_2-) ppm. E.S.M.S. for $C_{35}H_{25}N_9O_{12}$. Calculated mass of molecular ion: 762 $(M-H)^-$; Measured mass: 762 $(M-H)^-$. There is no data reported in the literature for this compound.

Attempted synthesis of 4-hydroxypyridine-2,6-dicarboxylic acid dimethyl ester 2.21

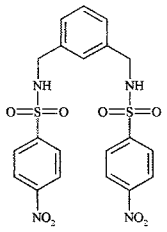


Concentrated hydrochloric acid (0.09 ml) was added to a stirring solution of chelidamic acid hydrate (1.0 g, 5.5 mmol) in methanol (18 ml) and the mixture was heated under reflux (2 hr). After cooling in ice the resultant solid was filtered under suction to give cream crystals (0.53 g). Proton NMR and carbon NMR spectroscopy does not show evidence of the desired product and was not consistent with that found in the literature[82]. The proton NMR spectral data of the product showed this to be starting material.



N,N'-1,3-Xylylene-bis-toluene-4-sulfonamide 2.23

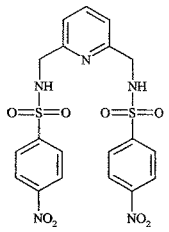
Potassium carbonate (1.61 g, 11.7 mmol) was carefully added to a solution of 3-(aminomethyl)-benzylamine (0.27 g, 2.0 mmol) in water (10 ml) and the mixture was heated to 70 ^{0}C. 4-Methylbenzene sulfonyl chloride (0.95 g, 5.0 mmol) was added in small portions under intense stirring. After 4 hrs the first oily precipitate was filtered under suction and washed with water and diethyl ether. 4-Methylbenzene sulfonyl chloride (0.1 g, 0.5 mmol) was added to the filtrate and the mixture was again heated to 70 ^{0}C to complete the reaction. The solids were combined to give **2.23** as a white solid (0.69 g, 78 %) m. p. 144-146 ^{0}C (Lit., 151-153 ^{0}C)[83]. δ_H ($CDCl_3$) 7.74 (d, J=8 Hz, 4H, *meta*-Ph2-*H*), 7.31 (d, J=8 Hz, 4H, *ortho*-Ph2-*H*), 7.19 (t, J=6 Hz, 1H, *meta*-Ph1-*H*), 7.10 (d, J=8 Hz, 2H, *ortho*-Ph1-*H*) 7.03 (s, 1H, *ortho*-Ph1-*H*), 4.78 (br t, 2H, -*NH*), 4.04 (d, J=6 Hz, 4H, -CH_2-), 2.44 (s, 6H, -CH_3) ppm. δ_C (DMSO) 143.2 (C), 138.3 (C), 138.2 (C), 130.2 (C), 128.8 (C), 127.3 (C), 127.1 (C), 127.0 (C), 46.6 (CH_2) 21.5 (CH_3) ppm. ν_{max} / cm^{-1} 3267 (NH), 1324 (SO_2), 1153 (SO_2). High-resolution M.S.E.I. for $C_{22}H_{24}N_2O_4S_2$. Calculated mass of molecular ion: 445.1250 $(M+H)^+$; Measured mass: 445.1252 $(M+H)^+$. The spectral data is consistent with that found in the literature[83].



N,N'-1,3-Xylylene-bis-(4-nitrobenzenesulfonamide) 2.24

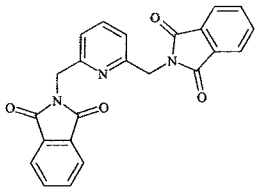
Potassium carbonate (1.61 g, 11.7 mmol) was carefully added to a solution of 3-(aminomethyl)-benzylamine (0.27 g, 2.0 mmol) in water (10 ml) and the mixture was heated to 70 ^{0}C. 4-Nitrobenzene sulfonyl chloride (1.11 g, 5.0 mmol) was added in small portions under intense stirring. After 4 hrs the first oily precipitate was filtered under suction and washed with water and diethyl ether. 4-Nitrobenzene sulfonyl chloride (0.1 g, 0.5 mmol) was added to the filtrate and the mixture was again heated to 70 ^{0}C to complete the reaction. The combined solids were recrystallised from ethanol to give **2.24** as a cream solid (0.72 g, 71 %) m. p. 156-158 ^{0}C. δ_H ($CDCl_3$) 8.55 (br, 2H, -*NH*), 8.37 (d, J=7 Hz, 4H, *ortho*-nitro-Ph2-*H*), 7.99 (d, J=9 Hz, 4H, *meta*-nitro-Ph2-*H*),

7.07 (m, 4H, Ph1-*H*), 3.99 (s, 4H, -*CH2*-) ppm. δ_C ($CDCl_3$) 150.0 (C), 146.9 (C), 137.8 (C), 128.6 (C), 127.5 (C), 127.2 (C), 125.1 (C), 123.9 (C), 40.6 (CH_2) ppm. ν_{max} / cm^{-1} 3265 (NH), 1533 (NO_2), 1345 (NO_2), 1310 (SO_2), 1157 (SO_2). E.S.M.S. for $C_{20}H_{18}N_4O_8S_2$. Calculated mass of molecular ion: 505 $(M-H)^-$; Measured mass: 505 $(M-H)^-$. There is no data reported in the literature for this compound.



_N,N'_-Pyridine-2,6-diyldimethyl-bis-(4-nitrobenzenesulfonamide) 2.25

Potassium carbonate (0.7 g, 5.1 mmol) was carefully added to a solution of 2,6-diaminomethylpyridine **2.27** (0.18 g, 0.9 mmol) in water (4.35 ml) and the mixture was heated to 70 ^{0}C. 4-Nitrobenzene sulfonyl chloride (0.48 g, 2.1 mmol) was added in small portions under intense stirring. After 4 hrs the first oily precipitate was filtered under suction and washed with water and diethyl ether. 4-Nitrobenzene sulfonyl chloride (0.1 g, 0.5 mmol) was added to the filtrate and the mixture was again heated to 70 ^{0}C to complete the reaction. The combined solids were recrystallised from ethanol to give **2.25** as a tan solid (0.10 g, 22 %) m. p. >350 ^{0}C. δ_H (DMSO) 8.60 (t, J=6 Hz, 2H, -*NH*), 8.30 (d, J=9 Hz, 4H, *ortho*-nitro-Ph-*H*), 7.96 (d, J=9 Hz, 4H, *meta*-nitro-Ph-*H*), 7.57 (t, J=8 Hz, 1H, *para*-Py-*H*), 7.09 (d, J=8 Hz, 2H, *meta*-Py-*H*), 4.05 (d, J=6 Hz, 4H, -CH_2-) ppm. ν_{max} / cm^{-1} 3265 (NH), 1528 (NO_2), 1346 (NO_2), 1308 (SO_2), 1159 (SO_2). E.S.M.S. $C_{19}H_{17}N_5O_8S_2$. Calculated mass of molecular ion: 508 $(M+H)^+$; Measured mass: 508 $(M+H)^+$. There is no data reported in the literature for this compound.

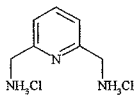


_N,N'_-Pyridine-2,6-diyldimethyl-bis-phthalimide 2.26

Potassium phthalimide (4.0 g, 22 mmol) was added to a solution of 2,6-dibromomethylpyridine (2.65 g, 100 mmol) in DMF (40 ml) and the mixture was heated to 80 ^{0}C and stirred (2 hr) with a condenser and a calcium chloride tube attached. The mixture was poured into water (100 ml) and the resultant precipitate was filtered under suction and washed with water, methanol and ethyl ether to give **2.26** as a cream solid (2.71 g, 31 %) m. p. 158-160 ^{0}C (Lit., 298-299 ^{0}C)[84]. ν_{max} / cm^{-1} 1697 (C=O). E.S.M.S.

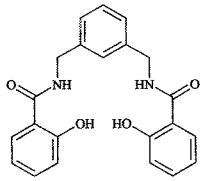
for $C_{23}H_{15}N_3O_4$. Calculated mass of molecular ion: 398 $(M+H)^+$; Measured mass: 398 $(M+H)^+$.

2,6-bis-Aminomethyl-pyridine 2.27



85 % Hydrazine hydrate (0.7 ml, 17 mmol) was added to a suspension of diphthalimide **2.26** (2.0 g, 5.0 mmol) in ethanol (30 ml) and the stirring mixture was heated under reflux (3 hrs). The excess hydrazine was removed under reduced pressure and the residue was dissolved in water (40 ml). Hydrochloric acid (3 ml, 6N) was added resulting in the precipitation of the phthalic hydrazide which was filtered under suction. The water was removed by dean stark distillation with benzene to give the dihydrochloride **2.27** as a brown solid (1.11 g, 106 %) m. p. 210-212 ^{0}C. δ_H (DMSO) 8.76 (s, 6H, *-NH$_3$*), 7.89 (t, J= 8Hz, 1H, *para*-Py-*H*) 7.46 (d, J=8Hz, 2H, *meta*-Py-*H*), 4.20 (d, J=6 Hz, 4H, *-CH$_2$-*) ppm. δ_C (DMSO) 153.0 (C), 138.9 (C), 122.2 (C), 42.8 (CH_2) ppm. ν_{max} / cm^{-1} 2886 (NH_3). E.S.M.S. for $C_7H_{13}N_3Cl_2$. Calculated mass of molecular ion: 210 $(M+H)^+$; Measured mass: 210 $(M+H)^+$. There is no data reported in the literature for this compound.

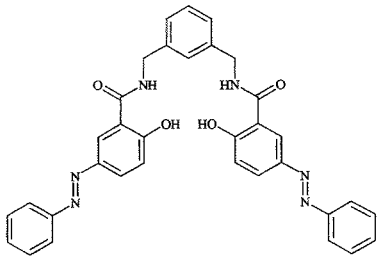
N,N'-1,3-Xylylene-bis-(2-hydroxybenzamide) 2.28



A mixture of methyl salicylate (22.0 g, 144.7 mmol), 3-(aminomethyl)-benzylamine (10.0 g, 73.5 mmol) and ammonium chloride (0.5 g) was heated under reflux (3 hrs). The hot solution was poured into water (100 ml) which solidifies into a plastic spiral. Dissolution of the plastic mass was done by adding sodium hydroxide (200 ml, 1M) which was re-acidified by adding hydrochloric acid (200 ml, 1M) which turned the solution a milky white colour. The aqueous layer was decanted off and hydrochloric acid (200 ml, 1M) was added. Again the aqueous layer was decanted off to leave an oily precipitate. Aqueous ethanol (200 ml, 50/50) was added to each aqueous fraction and the precipitate and after trituration a white precipitate formed in each which was filtered under suction and recrystallised from aqueous ethanol (50/50) to give **2.28** as a white powder (5.2 g, 19 %) m. p. 174-178 ^{0}C. δ_H (DMSO) 9.41 (br t, 2H, *-NH*), 7.87 (dd, J=6 and 1 Hz, 2H, *ortho*-Ph2-*H*), 7.40 (td, J=7 Hz, 2H, *para*-Ph2-*H*), 7.32 (t, J=6 Hz, 1H,

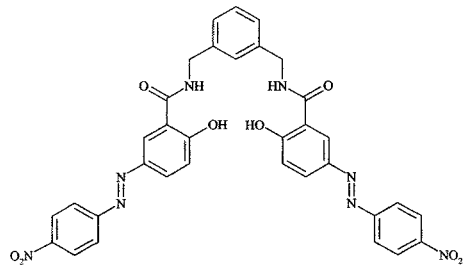
meta-Ph1-*H*), 7.29 (s, 1H, *ortho*-Ph1-*H*), 7.22 (d, J=8 Hz, 2H, *ortho*-Ph1-*H*), 6.89 (m, 4H, Ph2-*H*), 4.50 (d, J=6 Hz, 4H, -CH_2-) ppm. δ_C (DMSO) 169.5 (CO), 160.8 (C), 139.8 (C), 134.3 (C), 129.0 (C), 128.3 (C), 126.7 (C), 126.4 (C), 119.0 (C), 118.0 (C), 115.8 (C), 42.9 (CH_2) ppm. ν_{max} / cm^{-1} 3314 (OH), 2930 (NH), 1550 (C=O), 1097 (C-O). High-resolution M.S.E.I. for $C_{22}H_{20}N_2O_4$. Calculated mass of molecular ion: 377.1496 $(M+H)^+$; Measured mass: 375.1496 $(M+H)^+$. There is no spectral data reported in the literature for this compound.

_N,N'_-1,3-Xylylene-bis-(2-hydroxy-5-phenylazobenzamide) 2.29



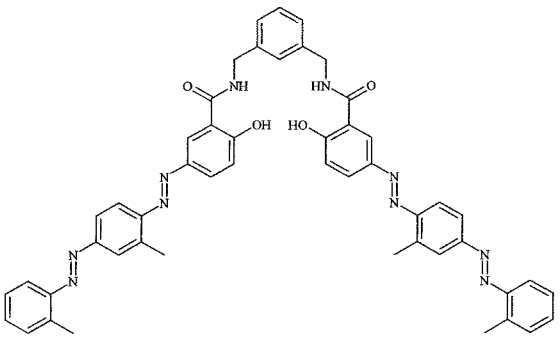
A stirred solution of aniline (0.43 g, 4 mmol) in concentrated hydrochloric acid (0.8 ml) and water (0.8 ml) was immersed in an ice bath and cooled below 5 ^{0}C. A chilled solution of sodium nitrite (0.2 g, 29 mmol) in water (1.0 ml) was added slowly preventing the temperature from rising above 10 ^{0}C and the mixture was left stirring (4 min). A solution of **2.28** (0.43 g, 1 mmol) in sodium hydroxide solution (0.9 ml, 10%) was cooled to 5 ^{0}C by immersion in the ice bath and stirred. The cold diazonium salt solution was added very slowly and left to stand with occasional stirring. The resultant crystals were filtered under suction, washed with water and recrystallised from ethanol to give **2.29** as yellow/orange solid (0.24 g , 38 %) m. p. 258-260 ^{0}C. δ_H (DMSO) 9.70 (br, 2H, -*NH*), 8.53 (d, J=2 Hz, 2H, *ortho*-Ph2-*H*), 7.91 (dd, J=7 and 2 Hz, 2H, *para*-Ph2-*H*), 7.79 (dd, J=7 and 2 Hz, 4H, *meta*-Ph3-*H*), 7.54 (m, 6H, Ph3-*H*), 7.31 (m, 4H, Ph1-*H*), 7.03 (d, J=9 Hz, 2H, *meta*-Ph2-*H*), 4.54 (d, J=6 Hz, 4H, -CH_2-) ppm. Partial δ_C (DMSO) 168.9 (CO), 163.7 (C), 152.5 (C), 144.9 (C), 139.6 (C), 131.5 (C), 129.9 (C), 129.1 (C), 126.7 (C), 126.6 (C), 125.8 (C), 122.8 (C), 119.2 (C), 116.1 (C), 40.4 (CH_2) ppm. ν_{max} / cm^{-1} 3399 (OH), 3067 (NH), 1648 (C=O), 1579 (C=O). High-resolution M.S.E.I. for $C_{34}H_{28}N_6O_4$. Calculated mass of molecular ion: 585.2245 $(M+H)^+$; Measured mass: 585.2245 $(M+H)^+$. There is no data reported in the literature for this compound.

_N,N'_-1,3-Xylylene-bis-2-hydroxy-5-(4-nitrophenylazobenzamide) 2.30



A stirring solution of p-nitroaniline (0.59 g, 4.3 mmol) in concentrated hydrochloric acid (5 ml) and water (20 ml) was immersed in an ice bath and cooled below 5 ^{0}C. A chilled solution of sodium nitrite (0.29 g, 4.2 mmol) in water (20 ml) and a few crystals of urea to remove any remaining nitrous acid, was added slowly preventing the temperature rising above 10 ^{0}C. A solution of **2.28** (1.61 g, 4.3 mmol) in sodium hydroxide solution (40.0 ml, 10%) was cooled to 5 ^{0}C by immersion in the ice bath and stirred vigoursly. The cold diazonium salt solution was added very slowly and left to stand with occasional stirring (30 min). The resultant crystals were filtered under suction, dissolved in salt water and extracted with dichloromethane. The resulting precipitate was filtered under suction to give **2.30** as dark red crystals (0.20 g , 3 %) m. p. >350 ^{0}C. δ_H (DMSO) 11.58 (br t, 2H, *-NH*), 8.43 (d, J=3 Hz, 2H, *ortho*-Ph2-*H*) 8.28 (dd, J=9 Hz, 4H, *ortho*-Ph3-*H*), 7.83 (dd, J=9 Hz, 4H, *meta*-Ph3-*H*), 7.70 (dd, J=6 Hz, 2H, *para*-Ph2-*H*), 7.30 (t, J=6 Hz, 1H, *meta*-Ph1-*H*), 7.27 (s, 1H, Ph1-*H*) 7.20 (d, J=8 Hz, 2H, *ortho*-Ph1-*H*), 6.38 (d, J=9 Hz, 2H, *ortho*-hydroxyl-Ph2-*H*), 4.52 (d, J=6 Hz, 4H, *-CH_2-*) ppm. Partial δ_C (DMSO) 167.7 (CO), 157.9 (C), 146.0 (C), 140.7 (C), 140.2 (C), 129.0 (C), 127.0 (C),126.2 (C), 125.5 (C), 122.2 (C), 119.5 (C), 42.6 (CH_2) ppm. ν_{max} / cm^{-1} 3202 (OH) and (NH), 1557 (C=O), 1490 (C=O), 1083 (C-O). High-resolution M.S.E.I. for $C_{34}H_{26}N_8O_8$. Calculated mass of molecular ion: 675.1946 $(M+H)^+$; Measured mass: 673.1941 $(M+H)^+$. There is no data reported in the literature for this compound.

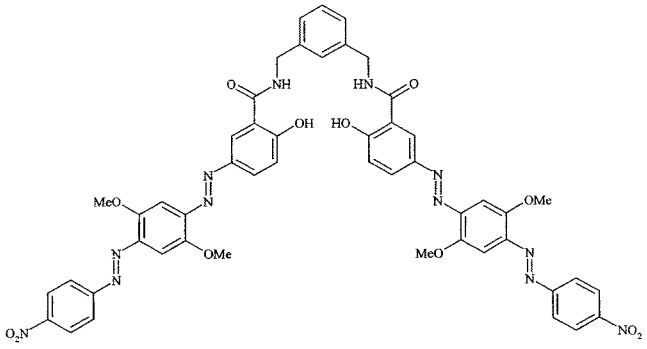
Attempted synthesis of _N,N'_-1,3-xylylene-bis-2-hydroxy-5-(2-methyl-4-2-tolylazo-phenylazo)-benzamide 2.31



Compound **2.28** (0.28 g, 0.7 mmol) was dissolved in ethanol (20 ml) containing sodium hydroxide (0.12 g, 1.5 mmol) by heating. Fast garnet (0.50 g, 1.5 mmol) was suspended

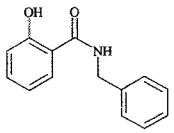
in ethanol (20 ml) and both flasks were cooled to 0 ^{0}C by immersion in an ice bath. The fast garnet solution was slowly added to the stirring **2.28** solution. Removing the solvent under reduced pressure gave brown crystals (0.76 g). Proton NMR and E.S.M.S. spectroscopy does not show evidence of the desired product. Instead they showed the product to be starting material.

Attempted synthesis of *N,N'*-1,3-xylylene-bis-2-hydroxy-(2,5-dimethoxy-4-4-nitrophenylazo-phenylazo)-benzamide 2.32



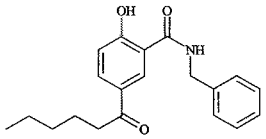
Compound **2.28** (0.23 g, 1.0 mmol) was dissolved in ethanol (20 ml) containing sodium hydroxide (0.10 g, 2.0 mmol) by heating. Fast black potassium salt (0.50 g, 2.0 mmol) was suspended in ethanol (20 ml) and both flasks were cooled to 0 ^{0}C by immersion in an ice bath. The fast black solution was slowly added to the stirring **2.28** solution and the resultant solid filtered under suction and purified by flash column chromatography using dichloromethane to give brown/red crystals (0.18 g). Proton NMR and E.S.M.S. spectroscopy does not show evidence of the desired product. Instead they showed the product to be starting material.

***N*-Benzyl-2-hydroxy-benzamide 2.33**



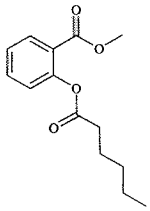
Ammonium chloride (0.1 g, 2.0 mmol) was added to methyl salicylate (4.26 g, 28.0 mmol) and benzylamine (3 ml, 28.0 mmol) and the mixture was heated under reflux (1 hr). After cooling and washing with water to remove excess benzylamine the solid was filtered under suction and washed with cold petroleum ether (100-120 ^{0}C) to give **2.33** as cream crystals (4.21 g, 66 %) m. p. 120-122 ^{0}C (Lit., 132 ^{0}C)[85]. δ_H (DMSO) 9.42 (br, 1H, -*NH*), 7.89 (dd, J=6 and 1 Hz, 1H, *ortho*-Ph2-*H*), 7.37 (m, 6H, Ph1-*H* and *para*-Ph2-*H*), 6.92 (m, 2H, Ph2-*H*), 4.51 (d, J=5 Hz, 2H, -CH_2-) ppm. δ_C (DMSO) 169.5 (CO), 160.7 (C), 139.6 (C), 134.3 (C), 128.9 (C), 128.4 (C), 127.8 (C), 127.5 (C), 119.1 (C), 118.0 (C), 115.8 (C), 53.0 (CH_2) ppm. ν_{max} / cm^{-1} 3352 (OH), 3064 (NH) 1589

(C=O). E.S.M.S. for $C_{14}H_{13}N_1O_2$. Calculated mass of molecular ion: 226 $(M-H)^-$; Measured mass: 226 $(M-H)^-$. The proton NMR spectral data are consistent with that found in the literature[85].



Attempted synthesis of *N*-benzyl-5-hexanoyl-2-hydroxy-benzamide 2.34

Hexanoyl chloride (0.60 g, 100 mmol) was cautiously added in portions and with swirling to a solution of aluminium trichloride (0.59 g) in dichloromethane (1.32 ml). Once most of the solid had dissolved the solution was decanted into a flask with a condenser attached and **2.33** (1.0 g, 4.4 mmol) was slowly added over a 15 minute period with thorough mixing. The mixture was gently warmed in hot water for 10 minutes, cooled to room temperature, poured onto stirring ice and extracted several times with dichloromethane. The organic extracts were combined, washed with water and dilute sodium hydroxide, dried (K_2CO_3) and the solvent removed under reduced pressure to give an orange solid (0.07 g). Proton NMR spectroscopy does not show evidence of the desired product. Instead it showed the product to be starting material.

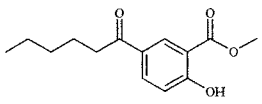


2-Hexanoyloxy-benzoic acid methyl ester 2.35

A solution of methyl salicylate (7.61 g, 50 mmol) and hexanoyl chloride (6.73 g, 50 mmol) was heated under reflux (3 hr) at the boiling point of the acid chloride (150 ^{0}C). The solution was treated with dilute sodium bicarbonate solution and the water layer was decanted. Dichloromethane (250 ml) was added to the white oily layer and the solution was washed with sodium hydroxide (4 x 150 ml, 2M), dried ($MgSO_4$) and the solvent removed under reduced pressure to give **2.35** as a pale yellow liquid (8.27 g, 66 %). δ_H ($CDCl_3$) 8.00 (dd, J=6 and 2 Hz, 1H, *ortho*-ethanoate-Ph-*H*), 7.54 (td, J=6 and 1 Hz, 1H, *para*-ethanoate-Ph-*H*), 7.29 (td, J=7 and 1 Hz, 1H, *meta*-ethanoate-Ph-*H*), 7.08 (dd, J=7 and 1 Hz, 1H, *ortho*-ester-Ph-*H*), 3.85 (s, 3H, ethanoate-CH_3), 2.63 (t, J= Hz, 2H, C=O-CH_2-), 1.78 (m, 2H, pentyl-CH_2-), 1.40 (m, 4H, pentyl-CH_2-), 0.92 (m, 3H, pentyl-CH_3) ppm. δ_C ($CHCl_3$) 172.4 (CO), 165.0 (CO), 150.8 (C), 133.8 (C), 131.7 (C), 125.9 (C), 123.9 (C), 123.4 (C), 52.2 (CH_3), 34.2 (CH_2), 31.4 (CH_2), 24.3 (CH_2), 22.4

(CH_2), 14.0 (CH_3) ppm. ν_{max} / cm^{-1} 1762 (C=O), 1723 (C=O), 1135 (C-O), 1080 (C-O). E.I.M.S., m/z (relative abundance): 250 (100) [M]. The data is consistent with that found in the literature[86].

5-Hexanoyl-2-hydroxy-benzoic acid methyl ester 2.36



Attempt 1

Compound **2.35** (3.0 g, 12.0 mmol) was added to a heated (40 ^{0}C) and stirring solution of aluminium chloride (2.5 g) in dichloromethane (5 ml) and heating continued (3 hr). The solvent was removed under reduced pressure, a few anti bumping granules were added and the residue heated to 100 ^{0}C (1 hr). Water was added to form an oily layer and washed with dichloromethane at which point an emulsion formed. The dichloromethane was removed under reduced pressure and the residue left overnight to form a creamy, oily liquid. This was dissolved in dichloromethane (50 ml), dried ($MgSO_4$) and the solvent removed under reduced pressure to give a pale yellow liquid (2.31 g). Proton NMR and G.C.M.S. spectroscopy does not show evidence of the desired product and was not consistent with that found in the literature[87]. The proton NMR data of the product showed this to be a mixture of starting material and methyl salicylate.

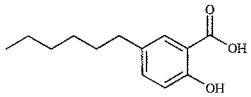
Attempt 2

Compound **2.35** (1.5 g, 6.0 mmol) was added to a stirring solution of ground aluminium chloride (1.5 g) in nitrobenzene (2 ml) and the mixture was heated to 110 ^{0}C (3 hr). Dichloromethane was added to the mixture after cooling to room temperature and the solution was washed with sodium hydroxide (1M). The aqueous layer was acidified by dilute hydrochloric acid and washed with dichloromethane. The organic layer was dried ($MgSO_4$) and the solvent removed under reduced pressure resulting in a mixture of methyl salicylate and ortho substituted product containing trace amounts of the desired product. δ_H (Compound **2.36**) ($CDCl_3$) 11.22 (s, 1H, -*OH*), 8.50 (d, J=2 Hz, 1H, *ortho*-ester-Ph-*H*), 8.10 (dd, J=2 and 6 Hz, 1H, *para*-ester-Ph-*H*), 7.03 (d, J=4 Hz, 1H, *meta*-ester-Ph-*H*) 4.01 (s, 3H, ester-CH_3), 2.89 (t, J=7 Hz, 2H, carbonyl-CH_2-), 1.72 (t, J=8 Hz, 2H, -CH_2-), 1.34 (m, 4H, -CH_2-), 0.91 (t, J=7 Hz, 3H, pentyl-CH_3) ppm. The proton NMR spectral data is consistent with that found in the literature[87].

Attempt 3

Compound **2.35** (3.0 g, 12 mmol) was added to a solution of aluminium chloride (2.5 g) and the mixture heated to 110 ^{0}C (3 hr) with a calcium chloride tube attached. Dichloromethane was added to the solution after cooling to room temperature and washed with sodium hydroxide (1M). The aqueous layer was acidified by dilute hydrochloric acid and washed with dichloromethane. The organic layer was dried ($MgSO_4$) and the solvent removed under reduced pressure. Purification by flash column chromatography using petroleum ether/dichloromethane (75/25) gave **2.36** as yellow crystals (0.42 g, 14 %). δ_H ($CDCl_3$) 11.20 (s, 1H, -*OH*), 8.49 (d, J=2 Hz, 1H, *ortho*-ester-Ph-*H*), 8.10 (dd, J=6 and 2 Hz, 1H, *para*-ester-Ph-*H*), 7.03 (d, J=8, 1H, *meta*-ester-Ph-*H*), 4.00 (s, 3H, ester-C*H*$_3$), 2.90 (t, J=7 Hz, 2H, carbonyl-*CH*$_2$-), 1.72 (t, J=8 Hz, 2H, -*CH*$_2$-), 1.34 (m, 4H, -*CH*$_2$-), 0.90 (t, J=7 Hz, 3H, pentyl-*CH*$_3$) ppm. δ_C ($CDCl_3$) 198.5 (C=O), 170.2 (C=O), 165.2 (C), 135.4 (C), 131.1 (C), 129.0 (C), 118.0 (C), 112.0 (C), 52.8 (CH_3), 38.3 (CH_2), 31.6 (CH_2), 24.2 (CH_2), 22.6 (CH_2), 14.1 (CH_3) ppm. ν_{max} / cm^{-1} 2955 (OH), 1706 (C=O), 1675 (C=O), 1209 (C-O). E.I.M.S., m/z (relative abundance): 250 (100) [M]. The proton NMR spectral data is consistent with that found in the literature[87].

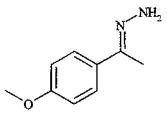
5-Hexyl-2-hydroxy-benzoic acid 2.38



A suspension of $PdCl_2$ (dppf) (0.16g, 0.2 mmol) and 5-bromosalicyclic acid (4.34 g, 20 mmol) in THF (50 ml) was cooled to -78 ^{0}C with an inert environment. Hexylmagnesium bromide (33 ml, 66 mmol) was slowly and carefully syringed in through the septum and the mixture was left stirring at -78 ^{0}C (10 mins). The cooling was removed and the mixture was left stirring at 20 ^{0}C (3 hr). Aqueous hydrochloric acid (5 %) was added to quench the react and the mixture was extracted with ethyl ether. The organic extracts were washed with water, dried ($MgSO_4$) and the solvent removed under reduced pressure. Purification by flash column chromatography using petroleum ether/dichloromethane (75/25) gave **2.38** as a yellow solid (0.21 g, 5 %). δ_H ($CDCl_3$) 7.86 (d, J=2 Hz, 1H, *ortho*-carboxylic acid-Ph-*H*), 7.53 (dd, J=2 and 6 Hz, 1H, *meta*-hydroxy-Ph-*H*), 6.89 (d, J=9 Hz, 1H, *ortho*-hydroxy-Ph-*H*), 2.96 (t, J=7 Hz, 2H, -*CH*$_2$-), 1.75 (t, J=7 Hz, 2H, -*CH*$_2$-), 1.35 (m, 6H, -*CH*$_2$-), 0.91 (t, J=7 Hz, 3H, -*CH*$_3$)

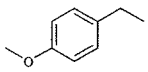
ppm. E.S.M.S. for $C_{13}H_{18}O_3$. Calculated mass of molecular ion: 221 $(M-H)^-$; Measured mass: 221 $(M-H)^-$. There is no spectral data reported in the literature for this compound.

[1-(4-Methoxy-phenyl)-ethylidene]-hydrazine 2.39



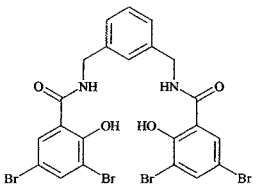
A mixture of 85 % hydrazine hydrate (4.0 g, 106 mmol) and p-methoxyacetophenone (2.0 g, 13.3 mmol) was vigorously heated under reflux (overnight). The cooled solution was extracted with diethyl ether, dried ($MgSO_4$) and the solvent removed under reduced pressure to give **2.39** as a yellow solid (0.98 g, 45 %) m. p. 108-110 ^0C (Lit., 114-116 ^0C)[88]. δ_H ($CDCl_3$) 7.60 (d, J=9 Hz, 2H, *ortho*-ether-Ph-*H*), 6.88 (d, J=9 Hz, 2H, *meta*-ether-Ph-*H*), 5.25 (br, 2H, -NH_2), 3.81 (s, 3H, ether-CH_3), 2.12 (s, 3H, -CH_3) ppm. E.S.M.S. for $C_9H_{13}N_2O_1$. Calculated mass of molecular ion: 165 $(M+H)^+$; Measured mass: 165 $(M+H)^+$.

Attempted synthesis of 1-ethyl-4-methoxy-benzene 2.40



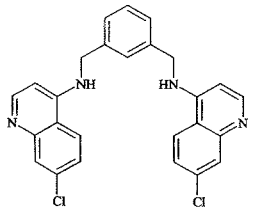
Compound **2.39** (0.41 g, 2.5 mmol) was slowly added to a rapidly stirring mixture of potassium tert-butoxide (1.0 g) and anhydrous dimethyl sulfoxide (2.5 ml) over an 8 hour period. The mixture was shaken with a mixture of dichloromethane and water (50:50). The organic layer was washed with water, dried ($MgSO_4$) and the solvent removed under reduced pressure to give a red solid (0.22 g). Proton NMR does not show evidence of the desired product and was not consistent with that found in the literature[89]. Instead it showed the product to be starting material.

Attempted synthesis of *N,N'*-1,3-xylylene-bis-(2-hydroxy-3,5-bromobenzamide) 2.42



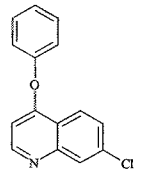
Bromine (0.17 g, 1.1 mmol) was carefully added to a stirring solution of **2.28** (0.1 g, 0.3 mmol) in sodium hydroxide (5 ml, 1M) and the mixture was left stirring (2 hr). The solution was poured into hydrochloric acid (5 ml, 1M) and the precipitate was collected

under suction to give an orange solid (0.26g). E.S.M.S. spectroscopy does not show evidence of the desired product. Instead it showed the product to be starting material.



Attempted synthesis of *N,N'*-1,3-xylylene-bis-(7-chloro-quinolin-4-yl)-amine 2.43

A few drops of concentrated hydrochloric acid was added to a solution of 4,7-dichloroquinoline (2.0 g, 10.2 mmol) and 3-(aminomethyl)-benzylamine (0.72 g, 5.3 mmol) in water (100 ml) and the mixture was heated under reflux. A solid should have precipitated but did not so the reaction was stopped. Proton NMR spectroscopy of the residue does not show evidence of the desired product. Instead they showed the product to be starting material.

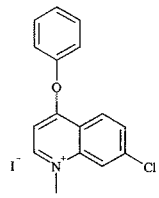


7-Chloro-4-phenoxy-quinoline 2.44

3-(Aminomethyl) benzylamine (0.14 g, 1.05 mmol) was added to a mixture of 4,7-dichloroquinoline (0.62 g, 3.15 mmol) in phenol (1.50 g) and heated at 120 ^{0}C (24 hr). The mixture was cooled to room temperature, diluted with aqueous sodium hydroxide (150 ml, 5M) and extracted with ethyl ether (3 x 225 ml). The combined organics were extracted with aqueous hydrochloric acid (3 x 225 ml, 10%) and the pooled aqueous layers were made alkaline with potassium hydroxide (10%). The aqueous phase was extracted with ethyl ether (3 x 225 ml) and the pooled organics were dried ($MgSO_4$). The solvent was removed under reduced pressure and the residue purified by flash column chromatography using methanol/dichloromethane (2/98) to give **2.44** as a pale yellow liquid (0.08 g, 30 %). δ_H ($CDCl_3$) 8.66 (br d, 1H, *ortho*-Py-*H*) 8.31 (d, J=9 Hz, 1H, *meta*-chloro-Ph2-*H*) 8.08 (d, J=2 Hz, 1H, *ortho*-chloro-Ph2-*H*), 7.54 (d, J=2 Hz, 1H, *ortho*-chloro-Ph2-*H*), 7.48 (tt, J=8 and 2 Hz, 2H, *meta*-Ph1-*H*), 7.31 (tt, J=7 and 1 Hz, 1H, *para*-Ph1-*H*), 7.18 (dt, J=7 and 2 Hz, 2H, *ortho*-Ph1-*H*) 6.53 (d, J=5 Hz, 1H, *meta*-Py-*H*) ppm. δ_C ($CDCl_3$) 162.2 (C), 154.0 (C), 152.3 (C), 150.1 (C), 136.4 (C), 130.5 (C), 129.7 (C), 128.0 (C), 127.3 (C), 126.0 (C), 123.5 (C), 121.2 (C), 115.5 (C), 104.4 (C) ppm. ν_{max} / cm^{-1} 2923 (Ph-H), 1563 (C=N), 1486 (C-O), 1205 (C-O), 857 (C-Cl). E.S.M.S for $C_{15}H_{10}Cl_1N_1O_1$. Calculated mass of molecular ion: 256 $(M+H)^+$;

Measured mass: 256 $(M+H)^+$. The proton NMR spectral data is consistent with that found in the literature[90].

7-Chloro-1-methyl-4-phenoxy-quinolinium iodide 2.45



Methyl iodide (0.09 g, 0.6 mmol) was added to a solution of **2.44** (0.14g, 0.3 mmol) in acetonitrile (10 ml) and the mixture was left stirring until TLC showed the reaction was complete. The solvent was removed under reduced pressure and the residue recrystallised from petroleum ether (2 ml, 60-80 ^{0}C) to give **2.45** as bright yellow crystals (0.06 g, 40 %) m. p. 234-236 ^{0}C. δ_H ($CDCl_3$) 10.31 (d, J=7 Hz, 1H, *ortho*-Py-*H*), 8.65 (d, J=9 Hz, 1H, *meta*-chloro-Ph2-*H*), 8.18 (d, J=2 Hz, 1H *ortho*-chloro-Ph2-*H*), 7.92 (dd, J=2 and 7 Hz, 1H, *ortho*-chloro-Ph2-*H*), , 7.60 (t, J=7 Hz, 2H, *meta*-Ph1-*H*), 7.49 (tt, J=7 and 1 Hz, 1H, *para*-Ph1-*H*), 7.24 (m, 2H, *ortho*-Ph1-*H*), 7.00 (d, J=7 Hz, 1H, *meta*-Py-*H*), 4.71 (s, 3H, -CH_3) ppm. δ_C ($CDCl_3$) 168.2 (C), 153.5 (C), 151.9 (C), 143.4 (C), 140.6 (C), 131.4 (C), 130.7 (C), 128.3 (C), 126.2 (C), 120.8 (C), 120.0 (C), 118.0 (C), 104.7 (C), 45.1 (CH_3) ppm. ν_{max} / cm^{-1} 2974 (Ph-H), 1190 (C-O), 823 (C-Cl). E.S.M.S for $C_{16}H_{13}Cl_1N_1O_1$. Calculated mass of molecular ion: 270 $(M+H)^+$; Measured mass: 271 $(M+H)^+$. There is no data reported in the literature for this compound.

4.2.2 Titrations experiments

All pH titrations were preformed using a Cecil Spectrophotometer 1011 at 298K. In all experiments, the tetrabutylammonium salts were used as received from Alfa Aesar.

All UV-Vis titration studies were performed using a Shimadzu UV-1601 UV-Vis Spectrophometer at 298K.

All NMR titration studies were preformed using a Jeol EX270 instrument (270 MHz) at 298K. Association constants were calculated by non-linear least squares analysis using a Microsoft Excel spreadsheet obtained from Dr Justin Perry which calculated the best fit for δ_{HG} and K_a, utilising the value for δ_H from the host solution. Errors were calculated by two different methods: by calculating the average from repetitive titrations or examining the extend of best fit of the binding curve.

All fluorescence titrations studies were performed using a Thermo Spectronic Aminco Bowman Series 2 Luminescence Spectrometer at 298K. Association constants were estimated by non-linear least squares analysis. λ_{max} values were obtained using a Thermo Nicolet Evolution 300.

Figure 4.1 – pH titration of 2.25

Stock solutions - [H] = 0.068 mM
[HCl] = 0.01 M
[NaOH] = 0.01 M

pKa = 8.5

pH	Absorbance (A) at 400 nm
6.60	0.284
6.80	0.282
7.07	0.283
7.79	0.285
7.96	0.309
8.14	0.341
8.30	0.383
8.44	0.416
8.60	0.473
8.73	0.521
8.81	0.550
8.96	0.575
9.12	0.598
9.39	0.608
9.71	0.606

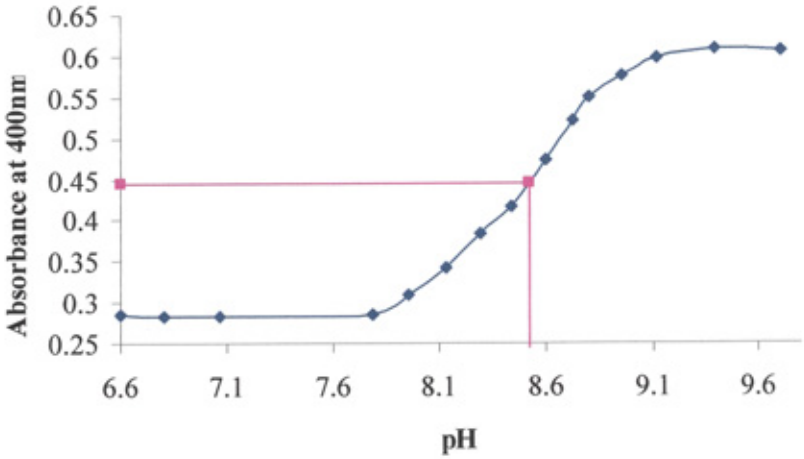


Figure 4.2 – pH titration of 2.26

Stock solutions - [H] = 0.068 mM
[HCl] = 0.01 M
[NaOH] = 0.01 M

pKa = 8.99

pH	Absorbance (A) at 500 nm
5.70	0.030
6.04	0.030
6.82	0.031
7.32	0.033
7.90	0.037
8.33	0.042
8.69	0.047
8.96	0.054
9.19	0.069
9.29	0.078
9.47	0.080
9.64	0.080
9.84	0.080

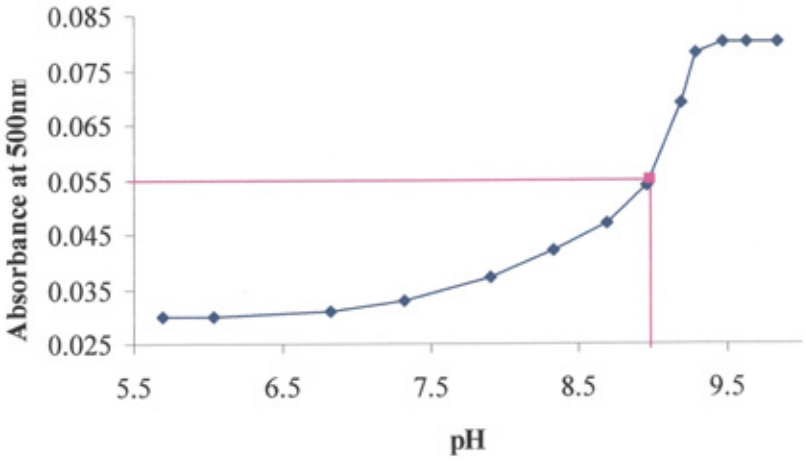


Figure 4.3 - UV Binding Study of Association between 2.25 and TBA chloride

Solvent = Chloroform
Stock solutions – [H] = 0.00025 M [G] = 0.048 M
Initial volume of host = 10 mL

mL of guest added	[G] added /M	[G]/[H]	Observed absorbance /A at 440 nm	Absorbance corrected for dilution /A
0.00	0.000000	0.000000	0.686	0.686000
0.02	0.000096	0.038477	0.668	0.669336
0.04	0.000192	0.077107	0.655	0.657620
0.06	0.000288	0.115891	0.636	0.639816
0.08	0.000384	0.154829	0.624	0.628992
0.10	0.000480	0.193920	0.617	0.623170
0.12	0.000576	0.233165	0.608	0.615296
0.14	0.000672	0.272563	0.607	0.615498
0.16	0.000768	0.312115	0.606	0.615696
0.18	0.000864	0.351821	0.604	0.614872
0.20	0.000960	0.391680	0.604	0.616080
0.25	0.001200	0.492000	0.602	0.617050
0.30	0.001440	0.593280	0.601	0.619030
0.35	0.001680	0.695520	0.602	0.623070
0.40	0.001920	0.798720	0.599	0.622960
0.45	0.002160	0.902880	0.598	0.624910
0.50	0.002400	1.008000	0.598	0.627900
0.60	0.002880	1.221120	0.594	0.629640
0.70	0.003360	1.438080	0.624	0.667680
0.80	0.003840	1.658880	0.623	0.672840
0.90	0.004320	1.883520	0.629	0.685610
1.00	0.004800	2.112000	0.636	0.699600
1.25	0.006000	2.700000	0.663	0.745875
1.50	0.007200	3.312000	0.707	0.813050
2.00	0.009600	4.608000	0.792	0.950400

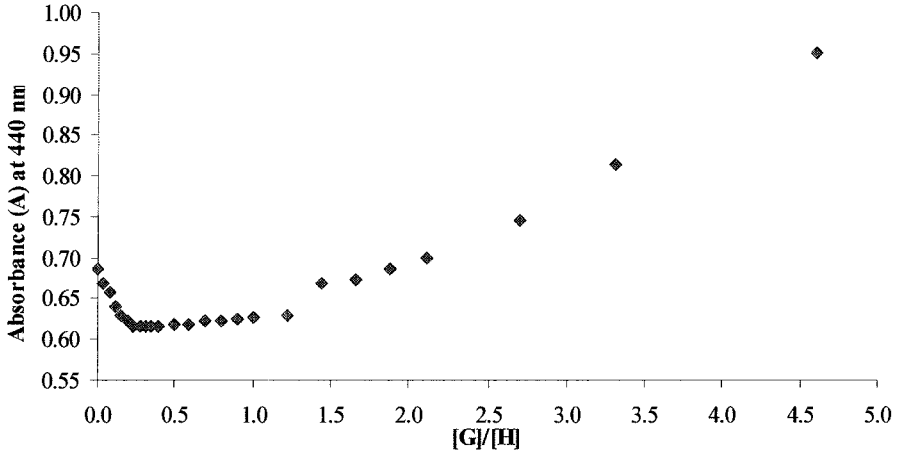


Figure 4.4 - UV Binding Study of Association between 2.25 and TBA acetate

Solvent = Chloroform
Stock solutions – [H] = 0.00022 M [G] = 0.0114 M
Initial volume of host = 10 mL

mL of guest added	[G] added /M	[G]/[H]	Observed absorbance /A at 440 nm	Absorbance corrected for dilution /A
0.00	0.000000	0.000000	0.451	0.451000
0.02	0.000023	0.103844	0.521	0.522042
0.04	0.000046	0.208102	0.741	0.743964
0.06	0.000068	0.312775	0.991	0.996946
0.08	0.000091	0.417862	1.241	1.250928
0.10	0.000114	0.523364	1.485	1.499850
0.12	0.000137	0.629280	1.717	1.737604
0.14	0.000160	0.735611	1.927	1.953978
0.16	0.000182	0.842356	2.128	2.162048
0.18	0.000205	0.949516	2.296	2.337328
0.20	0.000228	1.057091	2.466	2.515320
0.30	0.000342	1.601182	30.39	3.130170
0.40	0.000456	2.155636	3.311	3.443440
0.50	0.000570	2.720455	3.374	3.542700
0.75	0.000855	4.177841	3.436	3.693700
1.00	0.001140	5.700000	3.436	3.779600
1.25	0.001425	7.286932	3.436	3.865500
1.50	0.001710	8.938636	3.436	3.951400
2.00	0.002280	12.436360	3.436	4.123200
3.00	0.003420	20.209090	3.436	4.466800

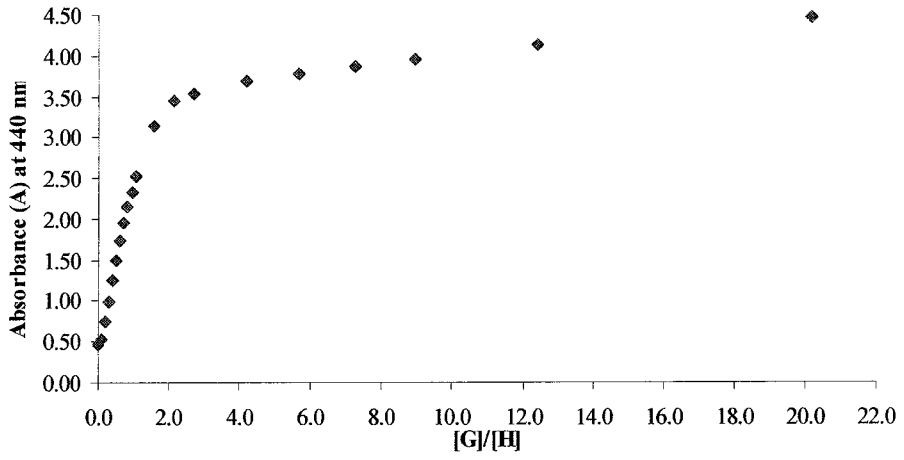


Figure 4.5 - UV Binding Study of Association between 2.25 and TBA fluoride hydrate

Solvent = Chloroform
Stock solutions – [H] = 0.00022 M [G] = 0.0097 M
Initial volume of host = 10 mL

mL of guest added	[G] added /M	[G]/[H]	Observed absorbance /A at 440 nm	Absorbance corrected for dilution /A
0.00	0.000000	0.000000	0.529	0.529000
0.02	0.000019	0.088358	0.435	0.435870
0.04	0.000039	0.177069	0.349	0.350396
0.06	0.000582	0.266133	0.334	0.336004
0.08	0.000078	0.355549	0.332	0.334656
0.10	0.000097	0.445318	0.333	0.336330
0.12	0.000116	0.535440	0.345	0.349140
0.14	0.000136	0.625915	0.379	0.384306
0.16	0.000155	0.716742	0.423	0.429768
0.18	0.000175	0.807922	0.471	0.479478
0.20	0.000194	0.899455	0.529	0.539580
0.30	0.000291	1.362409	0.775	0.798250
0.40	0.000388	1.834182	1.091	1.134640
0.50	0.000485	2.314773	1.518	1.593900
0.75	0.000728	3.554830	2.914	3.132550
1.00	0.000970	4.850000	3.436	3.779600
1.25	0.001213	6.200284	3.436	3.865500
1.50	0.001455	7.605682	3.436	3.951400
2.00	0.001940	10.581820	3.436	4.123200
3.00	0.002910	17.195450	3.436	4.466800

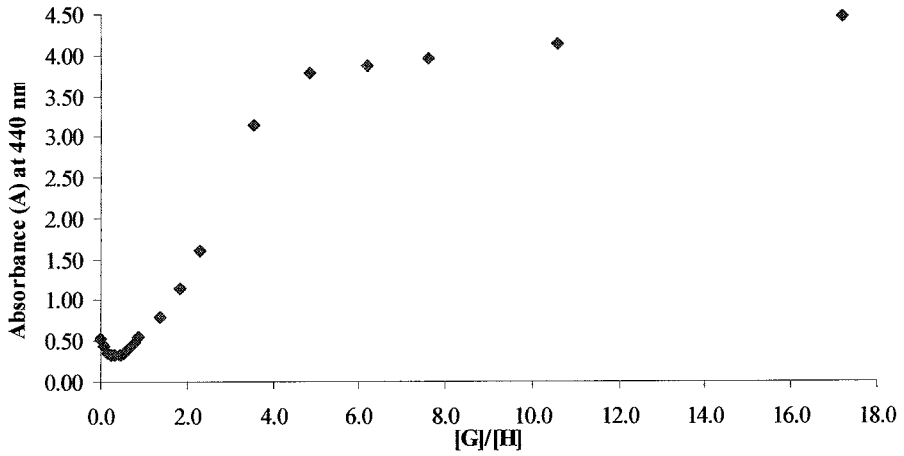


Figure 4.6- UV Binding Study of Association between 2.26 and TBA chloride

Solvent = Acetone
Stock solutions – [H] = 0.00004 M [G] = 0.0011 M
Initial volume of host = 10 mL

mL of guest added	[G] added /M	[G]/[H]	Observed absorbance /A at 520 nm	Absorbance corrected for dilution /A
0.00	0.000000	0.000000	1.064	1.064000
0.02	0.000002	0.055110	1.065	1.067130
0.04	0.000004	0.110440	1.058	1.062232
0.06	0.000007	0.165990	1.056	1.062336
0.08	0.000009	0.221760	1.055	1.063440
0.10	0.000011	0.277750	1.058	1.068580
0.12	0.000013	0.333960	1.054	1.066648
0.14	0.000015	0.390390	1.053	1.067742
0.16	0.000176	0.447040	1.052	1.068832
0.18	0.000020	0.503910	1.052	1.070936
0.20	0.000022	0.561000	1.054	1.075080
0.30	0.000033	0.849750	1.046	1.077380
0.40	0.000044	1.144000	1.042	1.083680
0.50	0.000055	1.443750	1.034	1.085700
0.75	0.000083	2.217188	1.015	1.091125
1.00	0.000110	3.025000	0.998	1.097800
1.25	0.000138	3.867188	0.976	1.098000
1.50	0.000165	4.743750	0.95	1.092500
1.75	0.000193	5.654688	0.926	1.088050
2.00	0.000220	6.600000	0.907	1.088400

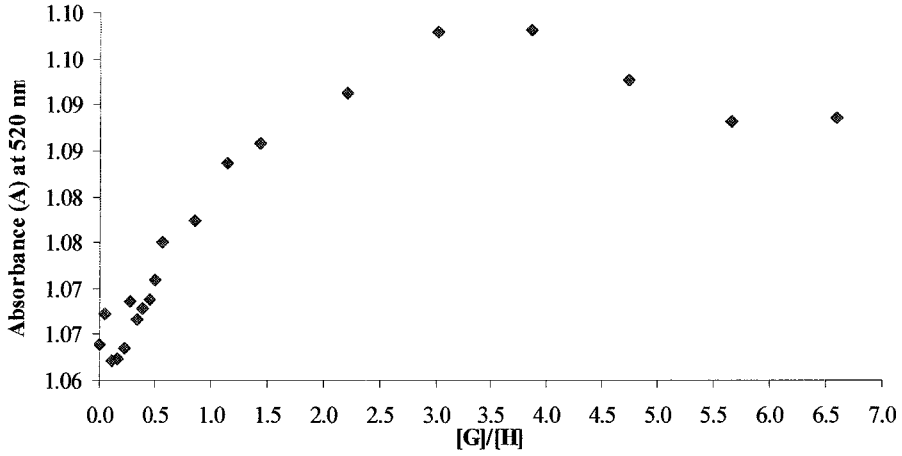


Figure 4.7 - UV Binding Study of Association between 2.26 and TBA nitrate

Solvent = Acetone
Stock solutions – [H] = 0.00028 M [G] = 0.00985 M
Initial volume of host = 10 mL

mL of guest added	[G] added /M	[G]/[H]	Observed absorbance /A at 375 nm	Absorbance corrected for dilution /A
0.00	0.000000	0.000000	0.297	0.297000
0.02	0.000020	0.704979	0.301	0.301602
0.04	0.000039	1.412771	0.306	0.307224
0.06	0.000059	2.123379	0.31	0.311860
0.08	0.000079	2.836800	0.313	0.315504
0.10	0.000099	3.553036	0.317	0.320170
0.12	0.000118	4.272086	0.32	0.323840
0.14	0.000138	4.993950	0.326	0.330564
0.16	0.000158	5.718629	0.33	0.335280
0.18	0.000177	6.446120	0.334	0.340012
0.20	0.000197	7.176429	0.336	0.342720
0.30	0.000296	10.870180	0.345	0.355350
0.40	0.000394	14.634290	0.351	0.365040
0.50	0.000493	18.468750	0.357	0.374850
0.75	0.000739	28.362720	0.372	0.399900
1.00	0.000985	38.696430	0.385	0.423500
1.25	0.001231	49.469870	0.398	0.447750
1.50	0.001478	60.683040	0.41	0.471500
1.75	0.001724	72.335940	0.422	0.495850
2.00	0.001970	84.428570	0.433	0.519600
2.50	0.002463	109.933000	0.458	0.572500
3.00	0.002955	137.196400	0.477	0.620100
3.50	0.003448	166.218800	0.496	0.669600
4.00	0.003940	197.000000	0.515	0.721000
5.00	0.004925	263.839300	0.547	0.820500
6.00	0.005910	337.714300	0.576	0.921600
7.00	0.006895	418.625000	0.59	1.003000
8.00	0.007880	506.571400	0.602	1.083600
9.00	0.008865	601.553600	0.604	1.147600
10.00	0.009850	703.571400	0.589	1.178000

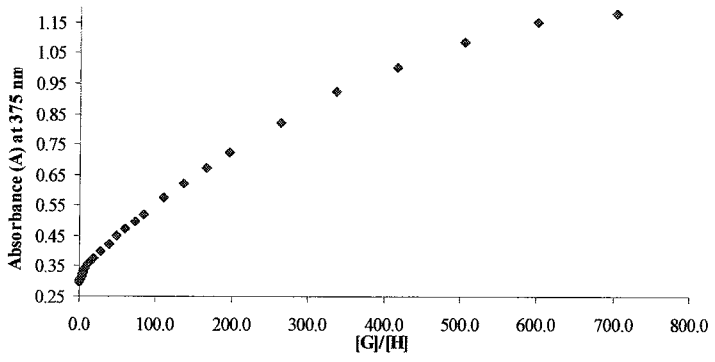


Figure 4.8 - NMR Binding Study of Association between 2.11 and TBA chloride

Solvent = Chloroform
Stock solutions – [H] = 0.011 M [G] = 0.099 M
Initial volume of host = 500μL δH = 7.9744 ppm

μL of guest added	[G] added /M	Observed shift of NH /ppm	Change in shift relative to δH /ppm	Computer fit for change in shift /ppm
20	0.003808	8.1457	0.1713	0.1775
30	0.005604	8.2405	0.2661	0.2560
40	0.007333	8.2977	0.3233	0.3287
60	0.010607	8.4378	0.4634	0.4586
70	0.012158	8.5019	0.5275	0.5168
80	0.013655	8.5404	0.5660	0.5711
90	0.015102	8.5917	0.6173	0.6218
100	0.016500	8.6393	0.6649	0.6693
125	0.019800	8.7473	0.7729	0.7757
150	0.022846	8.8472	0.8728	0.8671
200	0.028286	8.9888	1.0144	1.0159

51 % saturation at end of titration
K_a = 19 M^{-1} ±10 % δHG = 9.7968 ppm

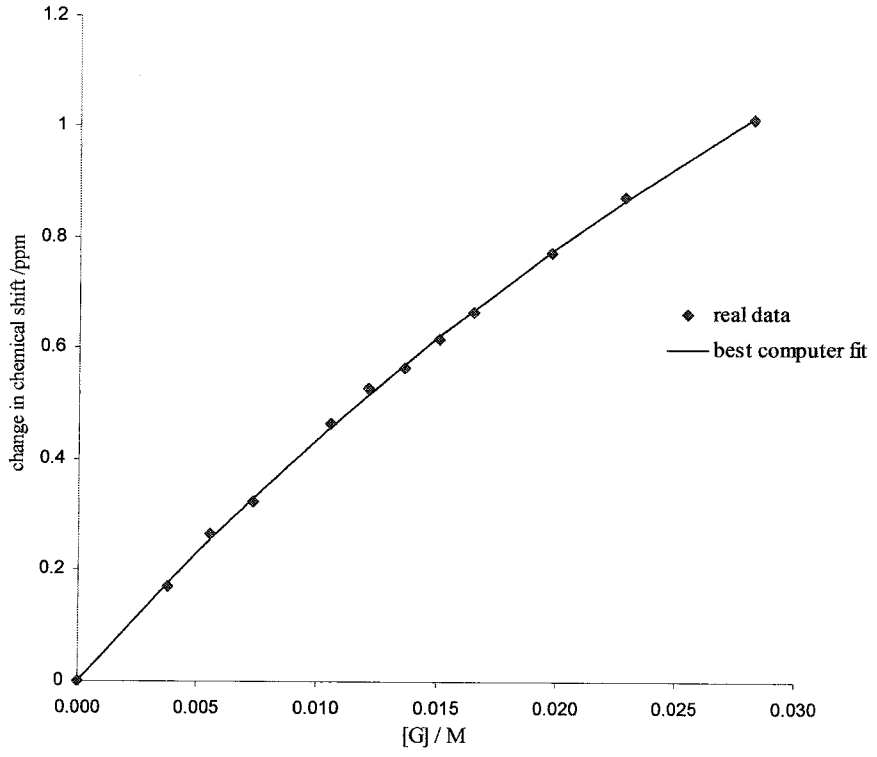


Figure 4.9 - NMR Binding Study of Association between 2.11 and TBA nitrate

Solvent = Chloroform
Stock solutions – [H] = 0.011 M [G] = 0.101 M
Initial volume of host = 500μL δH = 8.0092 ppm

μL of guest added	[G] added /M	Observed shift of NH /ppm	Change in shift relative to δH /ppm	Computer fit for change in shift /ppm
20	0.003885	8.0706	0.0614	0.0791
30	0.005717	8.1091	0.0999	0.1149
40	0.007481	8.1603	0.1511	0.1485
50	0.009182	8.1823	0.1731	0.1801
60	0.010821	8.2144	0.2052	0.2099
70	0.012404	8.2437	0.2345	0.2379
80	0.013931	8.2730	0.2638	0.2645
90	0.015407	8.3087	0.2995	0.2896
100	0.016833	8.3343	0.3251	0.3134
150	0.023308	8.4200	0.4202	0.4156
200	0.028857	8.5074	0.4982	0.4963
300	0.037875	8.6191	0.6099	0.6154

24 % saturation at end of titration
Ka = 10 M^{-1} ± 20 % δHG = 10.3317 ppm

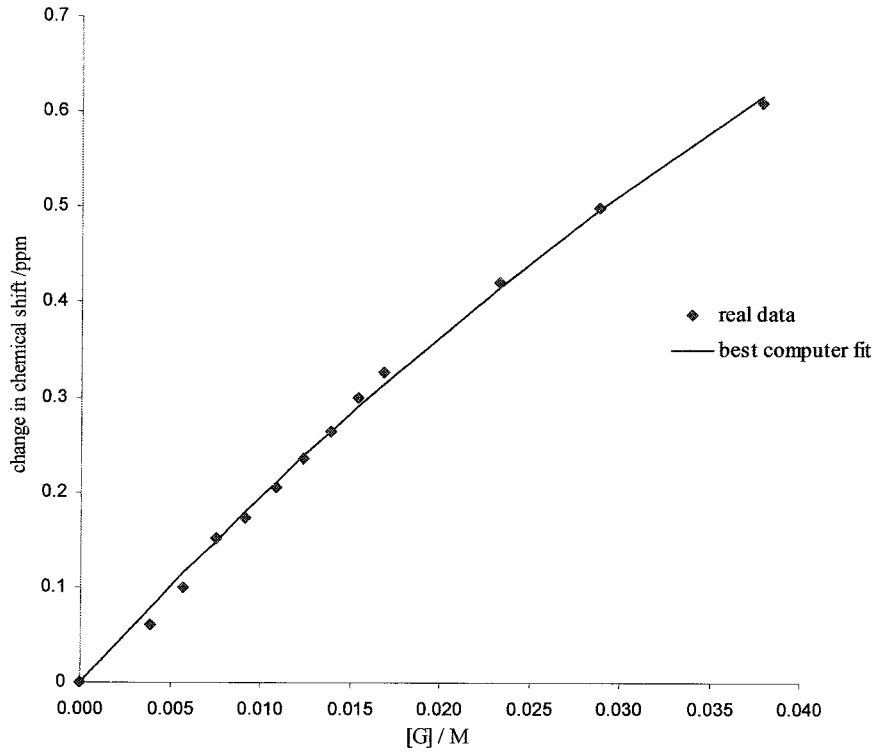


Figure 4.10 - NMR Binding Study of Association between 2.11 and TBA chloride

Solvent = Acetone
Stock solutions – [H] = 0.01 M [G] = 0.100 M
Initial volume of host = 500μL δH = 9.1565 ppm

μL of guest added	[G] added /M	Observed shift of NH /ppm	Change in shift relative to δH /ppm	Computer fit for change in shift /ppm
10	0.001961	9.5120	0.0355	0.3726
20	0.003846	9.9261	0.7695	0.7143
30	0.005660	10.1947	1.0382	1.0148
40	0.007407	10.4337	1.2772	1.2652
50	0.009091	10.6233	1.4668	1.4626
60	0.010714	10.7668	1.6103	1.6119
70	0.012281	10.8399	1.6834	1.7225
80	0.013793	10.9111	1.7545	1.8046
90	0.015254	11.0379	1.8814	1.8664
100	0.016667	11.0917	1.9352	1.9138
125	0.020000	11.1725	2.0160	1.9933
150	0.023077	11.1875	2.0310	2.0416
200	0.028571	11.2481	2.0916	2.0964

91 % saturation at end of titration
K_a = 566 M^{-1} ± 10 % δHG = 11.4216 ppm

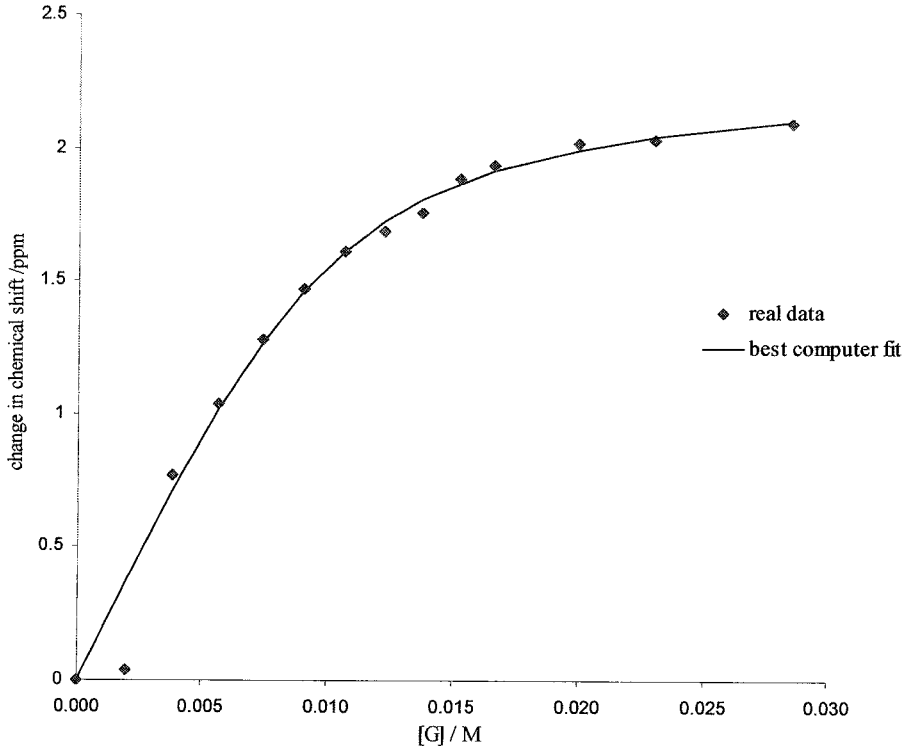


Figure 4.11 - NMR Binding Study of Association between 2.11 and TBA nitrate

Solvent = Acetone
Stock solutions – [H] = 0.01 M [G] = 0.099 M
Initial volume of host = 500μL δH = 9.2081 ppm

μL of guest added	[G] added /M	Observed shift of NH /ppm	Change in shift relative to δH /ppm	Computer fit for change in shift /ppm
10	0.001941	9.2553	0.0472	0.0696
20	0.003808	9.3212	0.1131	0.1323
30	0.005604	9.3825	0.1744	0.1888
40	0.007333	9.4347	0.2266	0.2399
50	0.009000	9.4822	0.2741	0.2862
60	0.010607	9.5576	0.3495	0.3283
70	0.012158	9.5949	0.3868	0.3666
80	0.013655	9.6286	0.4205	0.4016
90	0.015102	9.6239	0.4159	0.4337
100	0.016500	9.6873	0.4792	0.4632
125	0.019800	9.7456	0.5375	0.5272
150	0.022846	9.7607	0.5529	0.5800
200	0.028286	9.8730	0.6649	0.6616

46 % saturation at end of titration
K_a = 36 M^{-1} ± 15 % δHG = 10.6075 ppm

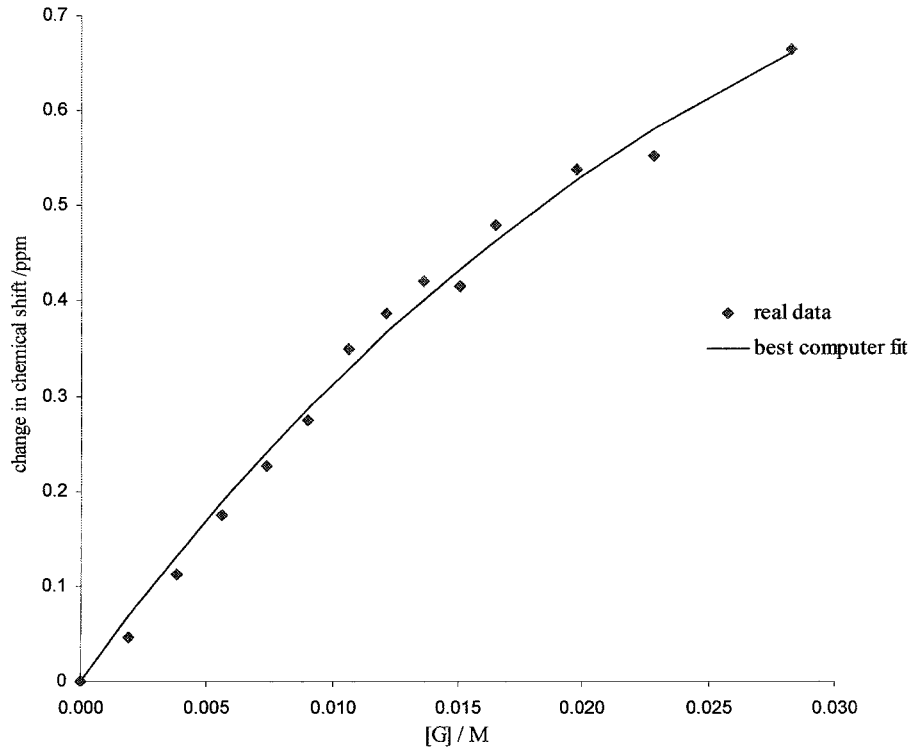


Figure 4.12 - NMR Binding Study of Association between 2.11 and TBA chloride

Solvent = Acetonitrile
Stock solutions – [H] = 0.01 M [G] = 0.098 M
Initial volume of host = 500μL δH = 8.8617 ppm

μL of guest added	[G] added /M	Observed shift of NH /ppm	Change in shift relative to δH /ppm	Computer fit for change in shift /ppm
10	0.001922	9.0551	0.1934	0.1643
20	0.003769	9.1859	0.3242	0.3106
30	0.005547	9.3065	0.4448	0.4399
40	0.007259	9.4171	0.5554	0.5538
50	0.008909	9.5104	0.6486	0.6540
60	0.010500	9.5934	0.7317	0.7419
70	0.012035	9.6660	0.8043	0.8192
80	0.013517	9.7270	0.8653	0.8872
90	0.014949	9.7892	0.9275	0.9473
100	0.016333	9.8999	1.0374	1.0006
125	0.019600	9.9879	1.1262	1.1098
150	0.022615	10.0593	1.1498	1.1931
200	0.028000	10.1679	1.3062	1.3104
300	0.036750	10.3005	1.4388	1.4425

71 % saturation at end of titration
$K_a = 92\ M^{-1} \pm 10\ \%$ δHG = 10.7999 ppm

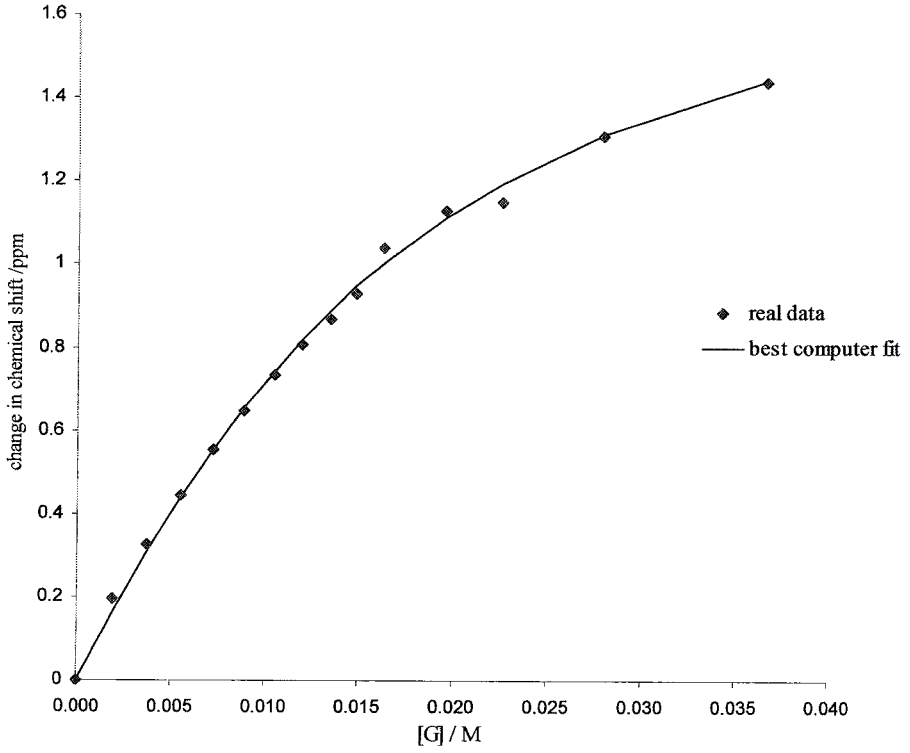


Figure 4.13 - NMR Binding Study of Association between 2.11 and TBA nitrate

Solvent = Acetonitrile
Stock solutions – [H] = 0.010 M [G] = 0.112 M
Initial volume of host = 500μL δH = 8.8618 ppm

μL of guest added	[G] added /M	Observed shift of NH /ppm	Change in shift relative to δH /ppm	Computer fit for change in shift /ppm
10	0.002196	8.8837	0.0219	0.0246
20	0.004308	8.9046	0.0428	0.0469
30	0.006340	8.9242	0.0624	0.0673
40	0.008296	8.9544	0.0926	0.0860
50	0.010182	8.9701	0.1083	0.1031
60	0.012000	8.9858	0.1240	0.1188
70	0.013754	9.0014	0.1397	0.1333
80	0.015448	9.0134	0.1517	0.1467
90	0.017085	9.0277	0.1659	0.1592
100	0.018667	9.0380	0.1762	0.1707
125	0.022400	9.0398	0.1780	0.1963
150	0.025846	9.0650	0.2032	0.2179
200	0.032000	9.1079	0.2461	0.2524
300	0.042000	9.1730	0.3113	0.2992

45 % saturation at end of titration
$K_a = 21\ M^{-1} \pm 10\ \%$ δHG = 9.5246 ppm

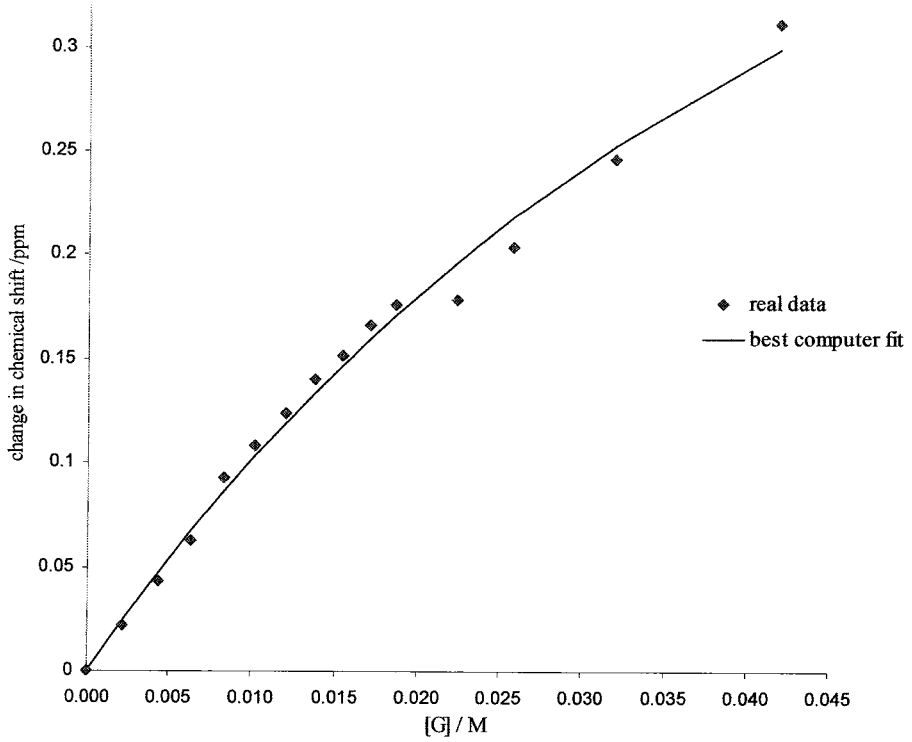


Figure 4.14 - NMR Binding Study of Association between 2.12 and TBA chloride

Solvent = Chloroform
Stock solutions – [H] = 0.01 M [G] = 0.107 M
Initial volume of host = 500μL δH = 9.0431 ppm

μL of guest added	[G] added /M	Observed shift of NH /ppm	Change in shift relative to δH /ppm	Computer fit for change in shift /ppm
10	0.002098	9.0743	0.0312	0.0287
20	0.004115	9.1014	0.0583	0.0555
30	0.006057	9.1255	0.0824	0.0804
40	0.007926	9.1439	0.1008	0.1037
50	0.009727	9.1690	0.1259	0.1255
60	0.011464	9.1892	0.1461	0.1460
70	0.013140	9.2070	0.1639	0.1652
80	0.014759	9.2220	0.1791	0.1833
90	0.016322	9.2418	0.1987	0.2003
100	0.017833	9.2592	0.2161	0.2164
125	0.021400	9.3104	0.2673	0.2530
150	0.024692	9.3282	0.2851	0.2851
200	0.030571	9.3778	0.3347	0.3385
300	0.040125	9.4527	0.4096	0.4164
500	0.053500	9.5558	0.5127	0.5094

35 % saturation at end of titration
K_a = 16.5 M^{-1} ± 33 % δHG = 10.4484 ppm

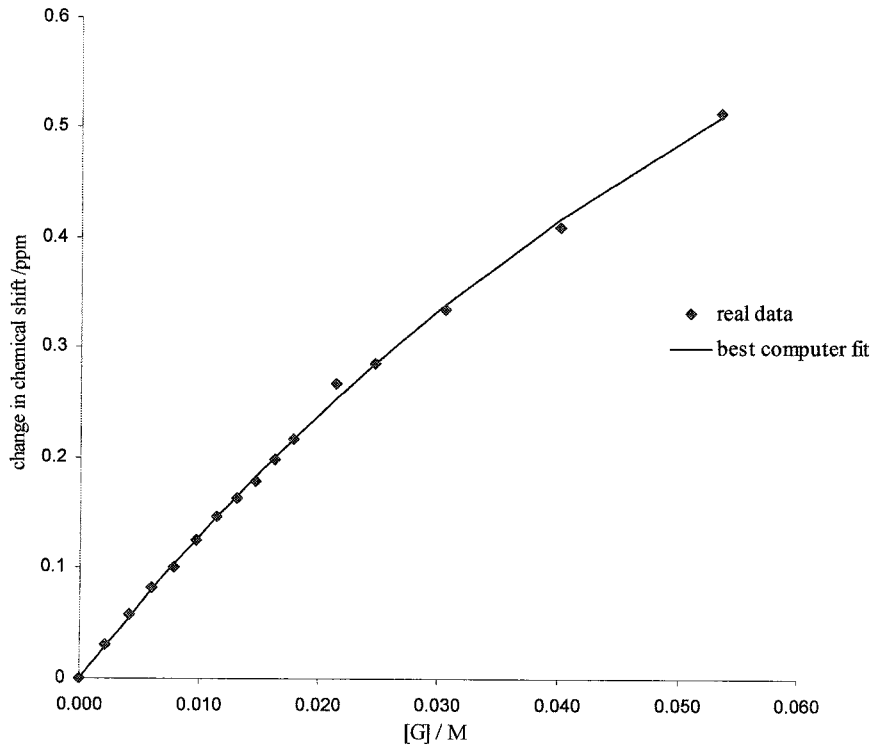


Figure 4.15 - NMR Binding Study of Association between 2.12 and TBA chloride

Solvent = Chloroform
Stock solutions – [H] = 0.01 M [G] = 0.102 M
Initial volume of host = 500μL δH = 9.0884 ppm

μL of guest added	[G] added /M	Observed shift of NH /ppm	Change in shift relative to δH /ppm	Computer fit for change in shift /ppm
10	0.002000	9.1228	0.0344	0.0312
20	0.003923	9.1493	0.0609	0.0597
30	0.005774	9.1745	0.0861	0.0858
40	0.007556	9.1965	0.1081	0.1098
50	0.009273	9.2226	0.1342	0.1318
60	0.010929	9.2381	0.1497	0.1521
70	0.012526	9.2597	0.1713	0.1709
80	0.014069	9.2768	0.1885	0.1884
90	0.015559	9.2968	0.2085	0.2046
100	0.017000	9.3095	0.2211	0.2196
125	0.020400	9.3401	0.2517	0.2531
150	0.023538	9.3693	0.2809	0.2815
200	0.029143	9.4117	0.3234	0.3271
300	0.038250	9.4793	0.3909	0.3894

42 % saturation at end of titration
K_a = 16.5 M^{-1} ± 33 % δHG = 9.9763 ppm

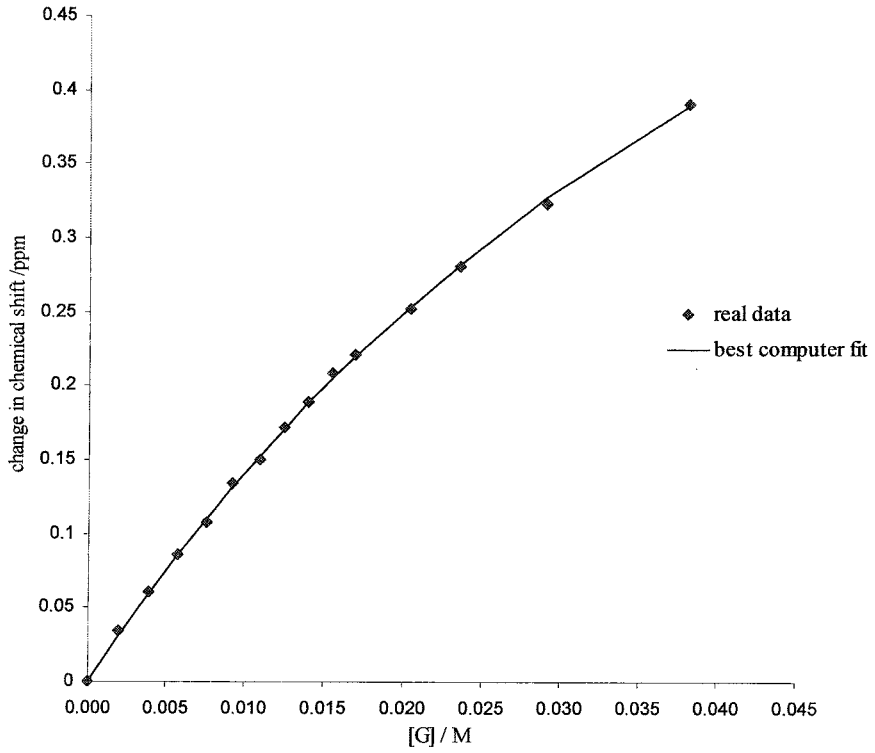


Figure 4.16 - NMR Binding Study of Association between 2.12 and TBA nitrate

Solvent = Chloroform
Stock solutions – [H] = 0.01 M [G] = 0.108 M
Initial volume of host = 500μL δH = 9.0489 ppm

μL of guest added	[G] added /M	Observed shift of NH /ppm	Change in shift relative to δH /ppm	Computer fit for change in shift /ppm
10	0.002118	9.0571	0.0083	0.0057
20	0.004154	0.0599	0.0111	0.0109
30	0.006113	9.0654	0.0166	0.0159
40	0.008000	9.0688	0.0199	0.0206
50	0.009818	9.0739	0.0250	0.0249
60	0.011571	9.0779	0.0290	0.0290
70	0.013263	9.0787	0.0298	0.0329
80	0.014897	9.0833	0.0345	0.0366
90	0.016475	9.0917	0.0429	0.0401
100	0.018000	9.0930	0.0442	0.0433
125	0.021600	9.1007	0.0519	0.0509
150	0.024923	9.1065	0.0576	0.0575
200	0.030857	9.1165	0.0681	0.0686

19 % saturation at end of titration
$K_a = 9\ M^{-1} \pm 20\ \%$ δHG = 9.3772 ppm

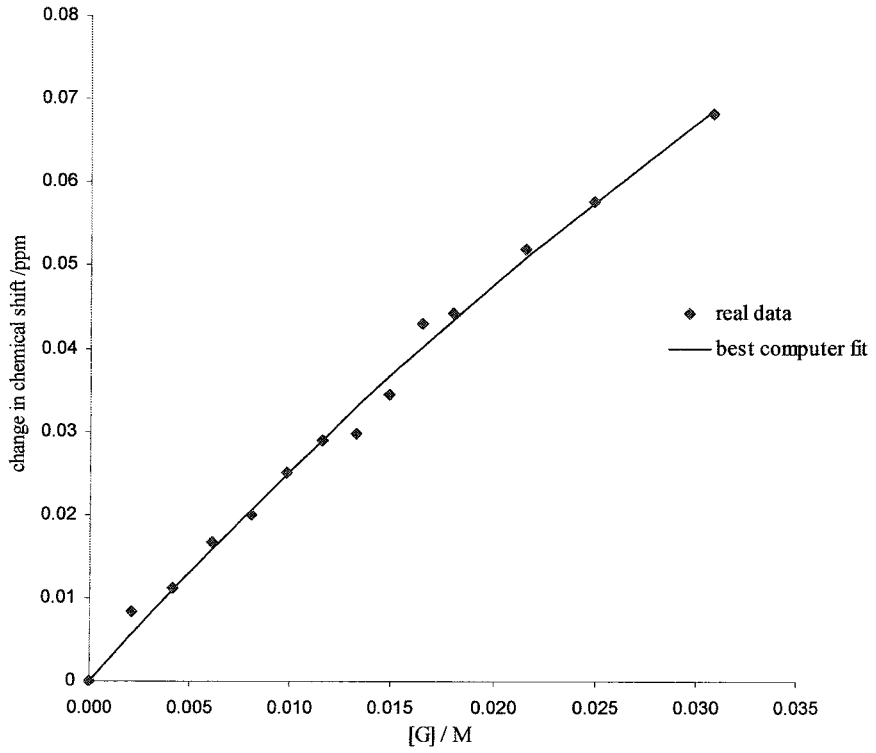


Figure 4.17 - NMR Binding Study of Association between 2.12 and TBA chloride

Solvent = Acetone
Stock solutions – [H] = 0.01 M [G] = 0.099 M
Initial volume of host = 500μL δH = 9.4025 ppm

μL of guest added	[G] added /M	Observed shift of NH /ppm	Change in shift relative to δH /ppm	Computer fit for change in shift /ppm
10	0.001941	9.7603	0.3578	0.3247
20	0.003808	9.9928	0.5904	0.6168
30	0.005604	10.2638	0.8614	0.8709
40	0.007333	10.5088	1.1063	1.0840
50	0.009000	10.6836	1.2811	1.2572
60	0.010607	10.7731	1.3706	1.3950
70	0.012158	10.8207	1.5182	1.5034
80	0.013655	10.9982	1.5957	1.5889
90	0.015102	11.0201	1.6176	1.6568
100	0.016500	11.1150	1.7126	1.7112
125	0.019800	11.2269	1.8245	1.8081
150	0.022846	11.2698	1.8673	1.8705
200	0.028286	11.3415	1.9390	1.9449
300	0.037125	11.4108	2.0084	2.0140
500	0.049500	11.4784	2.0760	2.0652

93 % saturation at end of titration
K_a = 334 M^{-1} ± 6 % δHG = 11.5982 ppm

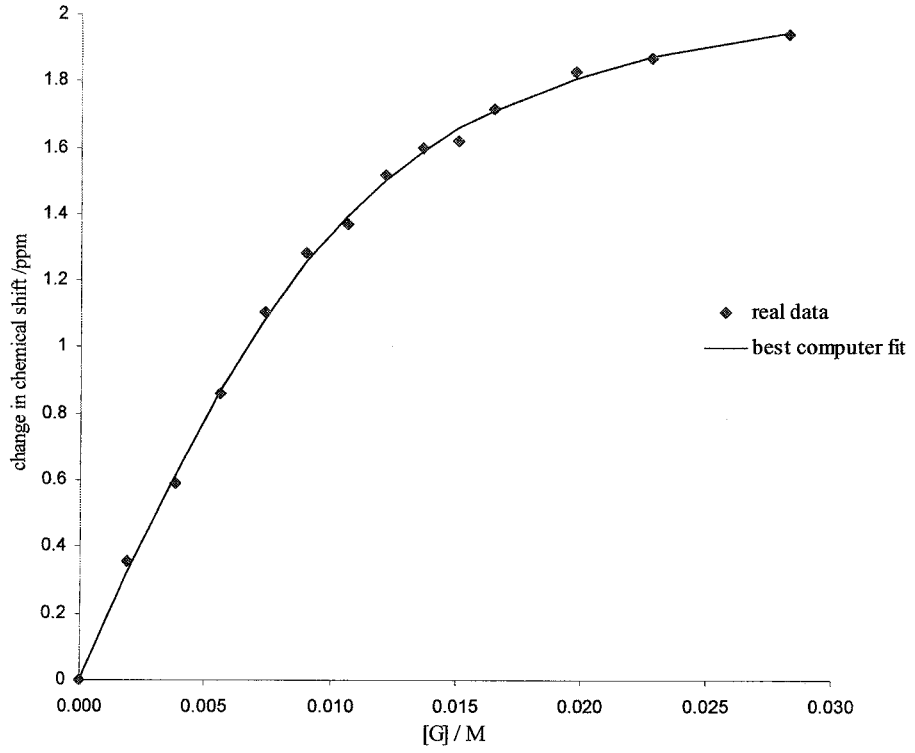


Figure 4.18 - NMR Binding Study of Association between 2.12 and TBA chloride

Solvent = Acetone
Stock solutions – [H] = 0.01 M [G] = 0.100 M
Initial volume of host = 500μL δH = 9.4156 ppm

μL of guest added	[G] added /M	Observed shift of NH /ppm	Change in shift relative to δH /ppm	Computer fit for change in shift /ppm
10	0.001961	9.7277	0.3121	0.3088
20	0.003846	9.9981	0.5825	0.5852
30	0.005660	10.2368	0.8212	0.8246
40	0.007407	10.4393	1.0237	1.0253
50	0.009091	10.6102	1.1946	1.1889
60	0.010714	10.7386	1.3233	1.3200
70	0.012281	10.8433	1.4276	1.4241
80	0.013793	10.9224	1.5068	1.5071
90	0.015254	10.9870	1.5714	1.5735
100	0.016667	11.0404	1.6248	1.6274
125	0.020000	11.1345	1.7189	1.7243
150	0.023077	11.2022	1.7865	1.7876
200	0.028571	11.2789	1.8633	1.8640
300	0.037500	11.3564	1.9408	1.9359

90 % saturation at end of titration
K_a = 334 M^{-1} ± 6 % δHG = 11.5447 ppm

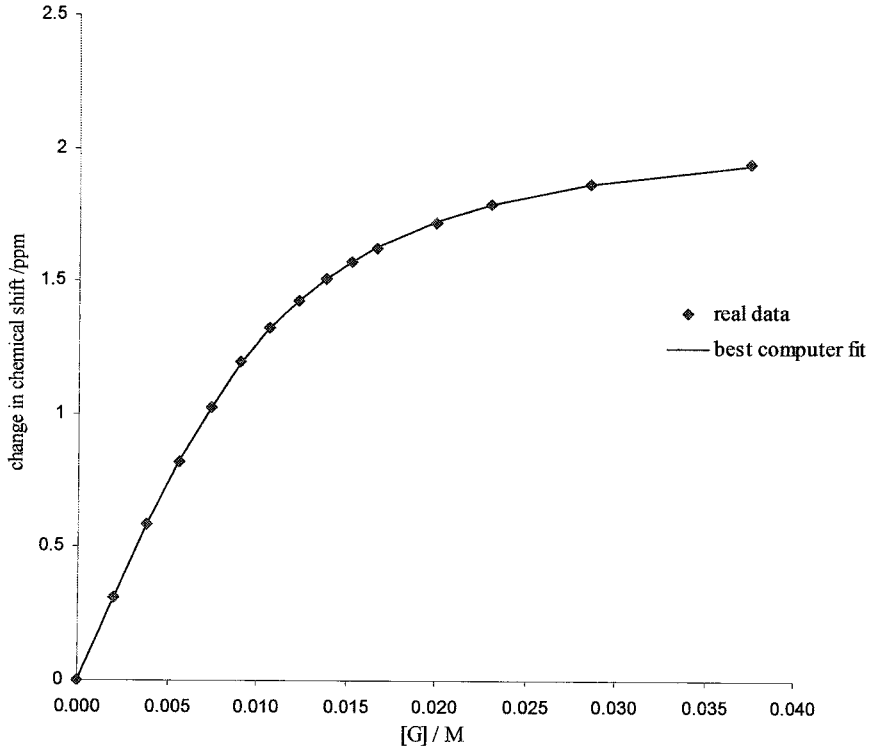


Figure 4.19 - NMR Binding Study of Association between 2.12 and TBA nitrate

Solvent = Acetone
Stock solutions – [H] = 0.012 M [G] = 0.103 M
Initial volume of host = 500μL δH = 9.4196 ppm

μL of guest added	[G] added /M	Observed shift of NH /ppm	Change in shift relative to δH /ppm	Computer fit for change in shift /ppm
10	0.002020	9.4628	0.0423	0.0385
20	0.003962	9.4987	0.0791	0.0734
30	0.005830	9.5291	0.1095	0.1050
40	0.007630	9.5577	0.1381	0.1338
50	0.009364	9.5831	0.1636	0.1600
60	0.011036	9.6048	0.1852	0.1840
70	0.012649	9.6263	0.2067	0.2059
80	0.014207	9.6447	0.2251	0.2259
90	0.015712	9.6639	0.2443	0.2444
100	0.017167	9.6781	0.2585	0.2614
125	0.020600	9.7126	0.2930	0.2984
150	0.023769	9.7428	0.3233	0.3292
200	0.029429	9.7939	0.3744	0.3769
300	0.038625	9.8651	0.4456	0.4390

52 % saturation at end of titration
$K_a = 34\ M^{-1} \pm 10\ \%$ δHG = 10.2321 ppm

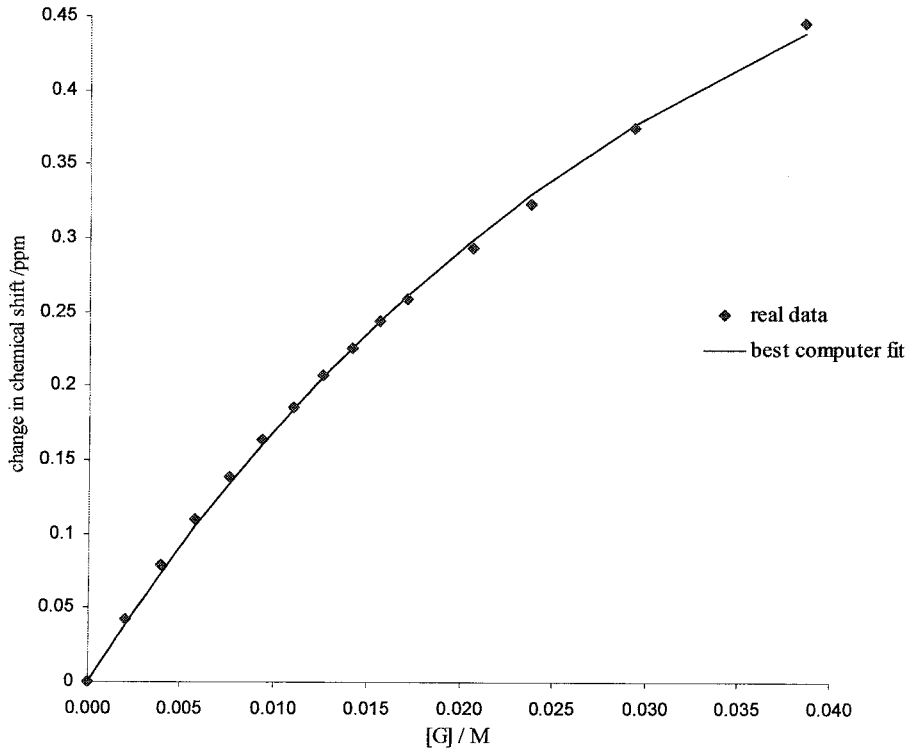


Figure 4.20 - NMR Binding Study of Association between 2.12 and TBA chloride

Solvent = Acetonitrile
Stock solutions – [H] = 0.011 M [G] = 0.111 M
Initial volume of host = 500μL δH = 9.0405 ppm

μL of guest added	[G] added /M	Observed shift of NH /ppm	Change in shift relative to δH /ppm	Computer fit for change in shift /ppm
10	0.002176	9.1827	0.1422	0.1428
20	0.004269	9.3130	0.2725	0.2691
30	0.006283	9.4252	0.3847	0.3806
40	0.008222	9.5222	0.4817	0.4791
50	0.010091	9.6113	0.5708	0.5661
60	0.011893	9.6853	0.6449	0.6432
70	0.013632	9.7561	0.7156	0.7117
80	0.015310	9.8112	0.7707	0.7727
90	0.016932	9.8687	0.8282	0.8272
100	0.018500	9.9139	0.8735	0.8762
125	0.022200	10.0108	0.9703	0.9786
150	0.025615	10.0910	1.0505	1.0591
200	0.031714	10.2197	1.1792	1.1764
300	0.041625	10.2197	1.3208	1.3156

58 % saturation at end of titration
K_a = 58 M^{-1} ± 15 % δHG = 10.9702 ppm

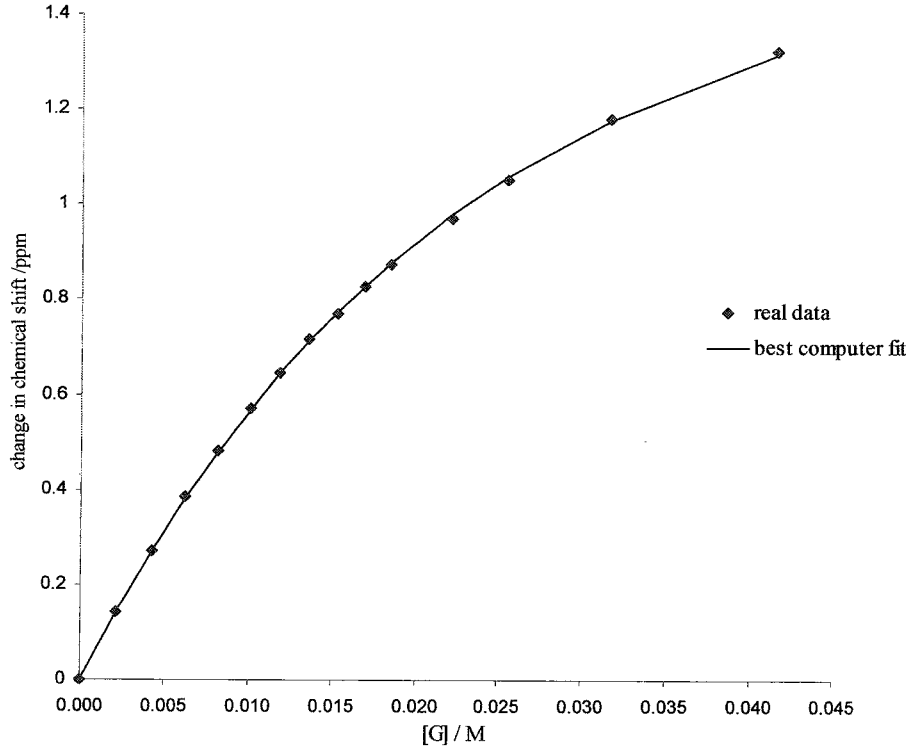


Figure 4.21 - NMR Binding Study of Association between 2.12 and TBA nitrate

Solvent = Acetonitrile
Stock solutions – [H] = 0.011 M [G] = 0.106 M
Initial volume of host = 500μL δH = 9.0387 ppm

μL of guest added	[G] added /M	Observed shift of NH /ppm	Change in shift relative to δH /ppm	Computer fit for change in shift /ppm
10	0.002078	9.0503	0.0166	0.0117
20	0.004077	9.0599	0.0212	0.0226
30	0.006000	9.0686	0.0299	0.0328
40	0.007852	9.0799	0.0412	0.0422
50	0.009636	9.0880	0.0493	0.0510
60	0.011357	9.0969	0.0582	0.0592
70	0.013018	9.1059	0.0672	0.0669
80	0.014621	9.1101	0.0714	0.0742
90	0.016169	9.1195	0.0808	0.0810
100	0.017667	9.1282	0.0895	0.0874
125	0.021200	9.1415	0.1028	0.1019
150	0.024462	9.1562	0.1175	0.1146
200	0.030286	9.1793	0.1406	0.1356
300	0.039750	9.1997	0.1610	0.1657

30 % saturation at end of titration
K_a = 13 M^{-1} ± 15 % δHG = 9.5443 ppm

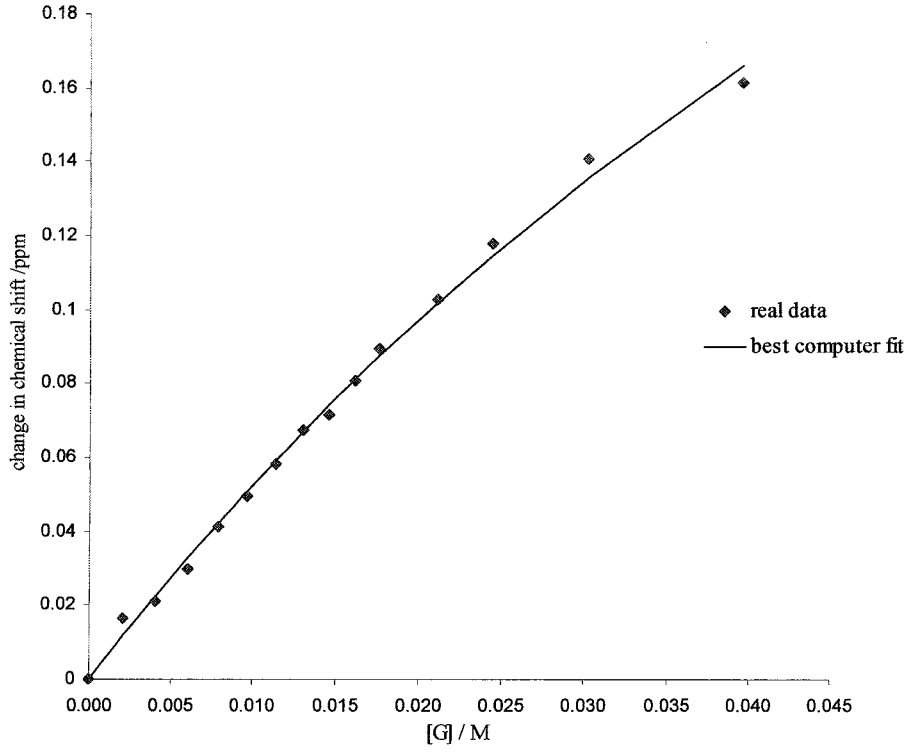


Figure 4.22 - NMR Binding Study of Association between 2.24 and TBA chloride

Solvent = Chloroform
Stock solutions – [H] = 0.0009 M [G] = 0.0076 M
Initial volume of host = 500μL δH = 6.6005 ppm

μL of guest added	[G] added /M	Observed shift of NH /ppm	Change in shift relative to δH /ppm	Computer fit for change in shift /ppm
25	0.000362	6.6821	0.0816	0.0877
50	0.000691	6.7529	0.1524	0.1600
125	0.001520	6.9173	0.3168	0.3150
150	0.001754	6.9607	0.3602	0.3525
250	0.002533	7.0672	0.4667	0.4616
300	0.002850	7.0927	0.4922	0.4999

34 % saturation at end of titration
K_a = 240 M^{-1} ± 20 % δHG = 7.8916 ppm

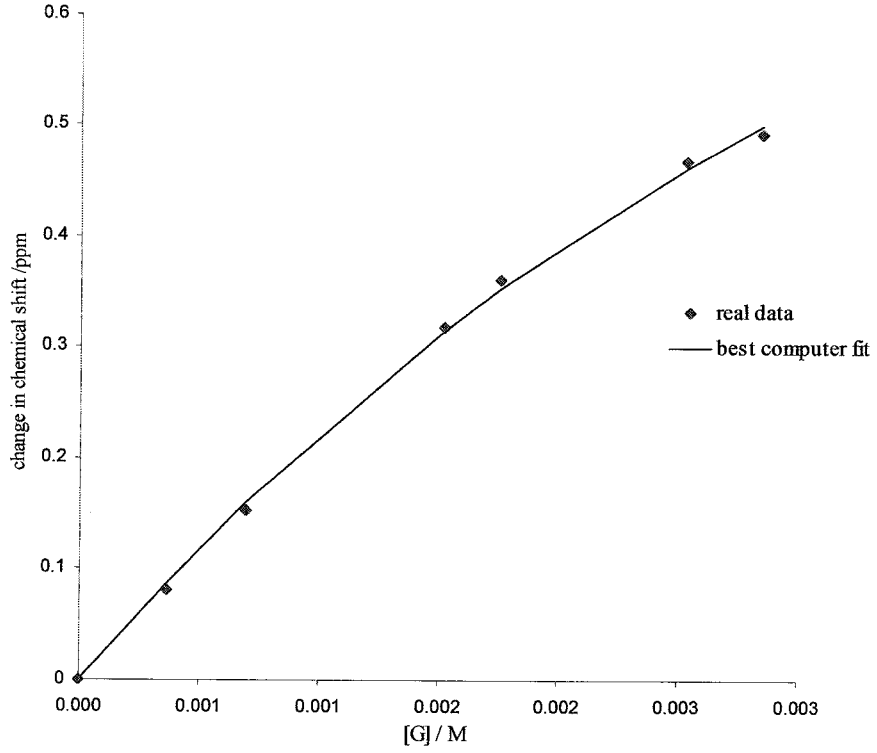


Figure 4.23 - NMR Binding Study of Association between 2.24 and TBA nitrate

Solvent = Chloroform
Stock solutions – [H] = 0.0011 M [G] = 0.0108 M
Initial volume of host = 500μL δH = 6.6065 ppm

μL of guest added	[G] added /M	Observed shift of NH /ppm	Change in shift relative to δH /ppm	Computer fit for change in shift /ppm
25	0.000514	6.6933	0.0868	0.0906
50	0.000982	6.7672	0.1607	0.1665
125	0.002160	6.9332	0.3267	0.3340
200	0.003086	7.0520	0.4455	0.4454
250	0.003600	7.1092	0.5027	0.5008
300	0.004050	7.1575	0.5510	0.5459

28 % saturation at end of titration
K_a = 120 M^{-1} ± 30 % δHG = 8.3391 ppm

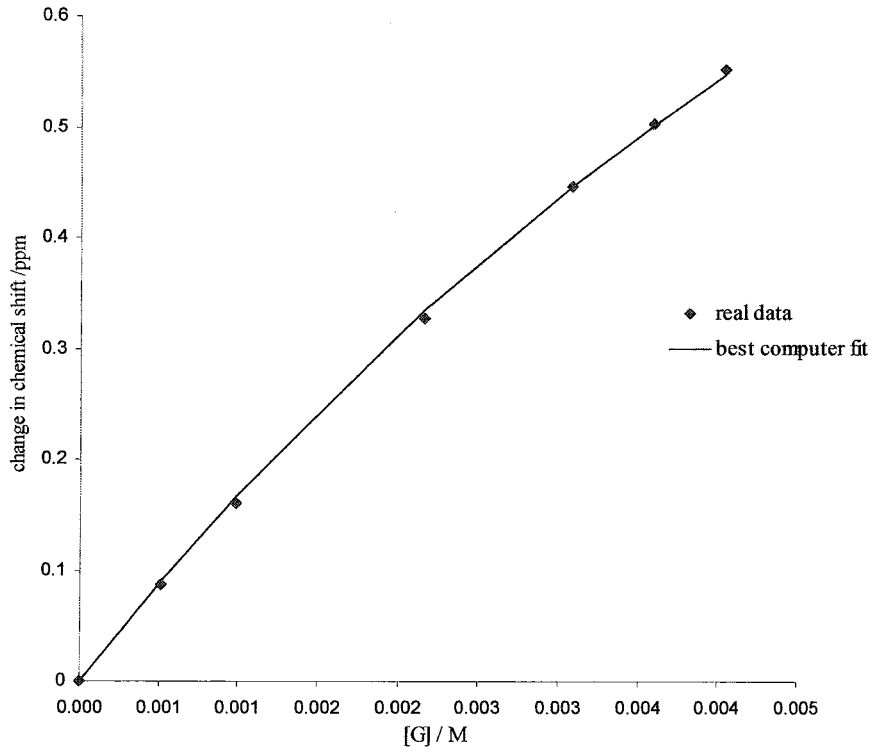


Figure 4.24 - NMR Binding Study of Association between 2.24 and TBA chloride

Solvent = Acetone
Stock solutions – [H] = 0.0053 M [G] = 0.0522 M
Initial volume of host = 500μL δH = 8.6947 ppm

μL of guest added	[G] added /M	Observed shift of NH /ppm	Change in shift relative to δH /ppm	Computer fit for change in shift /ppm
10	0.001024	8.8510	0.1563	0.1547
20	0.002008	8.9934	0.2987	0.2908
30	0.002955	9.1192	0.4245	0.4095
40	0.003867	9.1777	0.4830	0.5124
50	0.004745	9.2790	0.5843	0.6013
60	0.005593	9.3596	0.6649	0.6780
70	0.006411	9.4101	0.7154	0.7444
80	0.007200	9.4801	0.7854	0.8019
90	0.007963	9.5850	0.8903	0.8519
100	0.008700	9.5698	0.8751	0.8956
125	0.010440	9.7112	1.0165	0.9834
150	0.012046	9.7690	1.0743	1.0489
200	0.014914	9.8555	1.1608	1.1386
300	0.019575	9.9152	1.2205	1.2367
500	0.026100	10.0009	1.3062	1.3202

81 % saturation at end of titration
K_a = 210 M^{-1} ± 10 % δHG = 10.2780 ppm

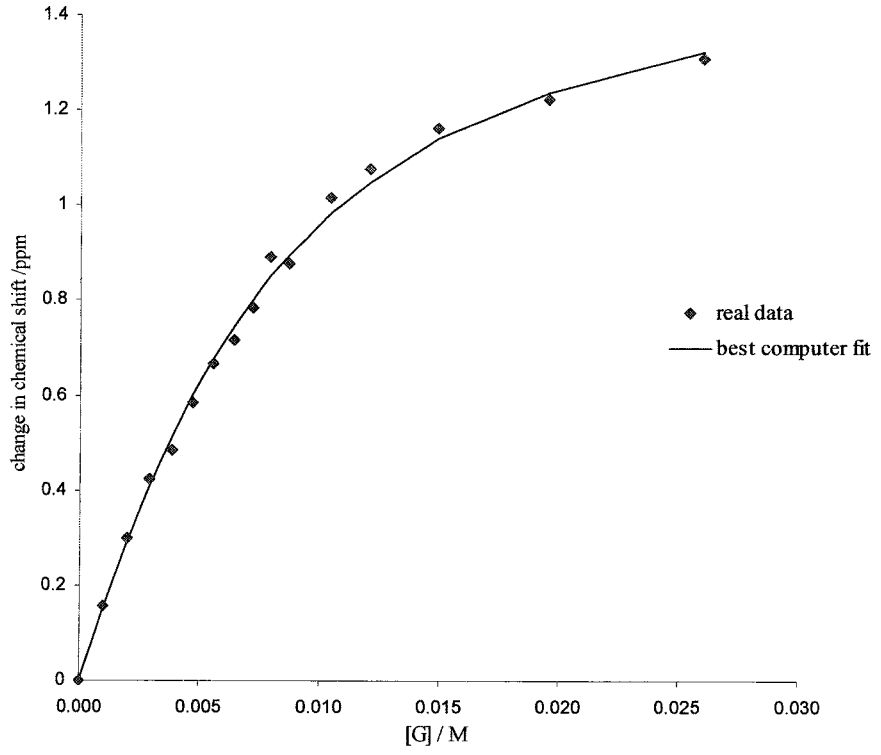


Figure 4.25 - NMR Binding Study of Association between 2.24 and TBA nitrate

Solvent = Acetone
Stock solutions – [H] = 0.0061 M [G] = 0.045 M
Initial volume of host = 500μL δH = 6.61 ppm

μL of guest added	[G] added /M	Observed shift of NH /ppm	Change in shift relative to δH /ppm	Computer fit for change in shift /ppm
10	0.000882	6.6500	0.0400	0.0314
20	0.001731	6.6700	0.0600	0.0599
30	0.002547	6.7000	0.0900	0.0857
40	0.003333	6.7200	0.1100	0.1092
50	0.004091	6.7500	0.1400	0.1305
60	0.004821	6.7600	0.1500	0.1499
70	0.005526	6.7800	0.1700	0.1675
80	0.006207	6.7900	0.1800	0.1836
90	0.006864	6.8100	0.2000	0.1983
100	0.007500	6.8200	0.2100	0.2117
125	0.009000	6.8400	0.2300	0.2406
150	0.010385	6.8700	0.2600	0.2643
200	0.012857	6.9000	0.2900	0.3002
300	0.016875	6.9800	0.3700	0.3451
500	0.022500	6.9900	0.3800	0.3892

64 % saturation at end of titration
K_a = 105 M^{-1} ± 10 % δHG = 7.1807 ppm

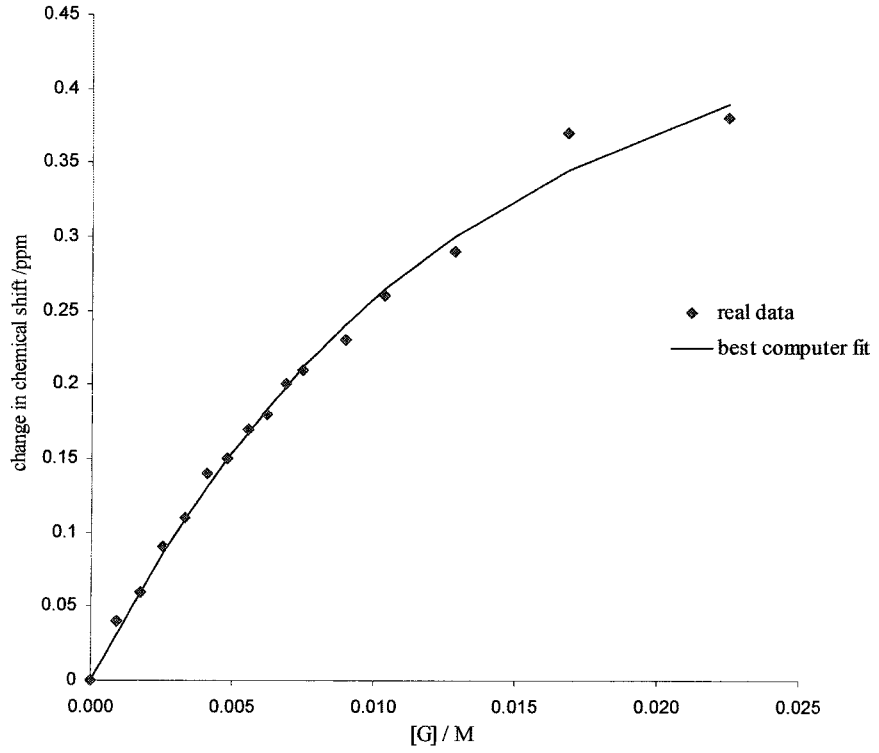


Figure 4.26 - NMR Binding Study of Association between 2.24 and TBA chloride

Solvent = Acetonitrile
Stock solutions – [H] = 0.0029 M [G] = 0.0554 M
Initial volume of host = 500μL δH = 7.8852 ppm

μL of guest added	[G] added /M	Observed shift of NH /ppm	Change in shift relative to δH /ppm	Computer fit for change in shift /ppm
10	0.001086	7.9702	0.0850	0.0872
20	0.002131	8.0461	0.1609	0.1641
30	0.003136	8.1156	0.2304	0.2323
40	0.004104	8.1795	0.2943	0.2931
50	0.005036	8.2375	0.3523	0.3475
60	0.005936	8.2795	0.3943	0.3965
70	0.006804	8.3280	0.4428	0.4407
80	0.007641	8.3665	0.4812	0.4809
90	0.008451	8.4025	0.5173	0.5174
100	0.009233	8.4384	0.5532	0.5509
125	0.011080	8.5108	0.6255	0.6230
150	0.012785	8.5690	0.6838	0.6822
200	0.015829	8.6580	0.7728	0.7733
300	0.020775	8.7774	0.8922	0.8908
500	0.027700	8.8914	1.0062	1.0119

59 % saturation at end of titration
K_a = 60 M^{-1} ± 0 % δHG = 9.5262 ppm

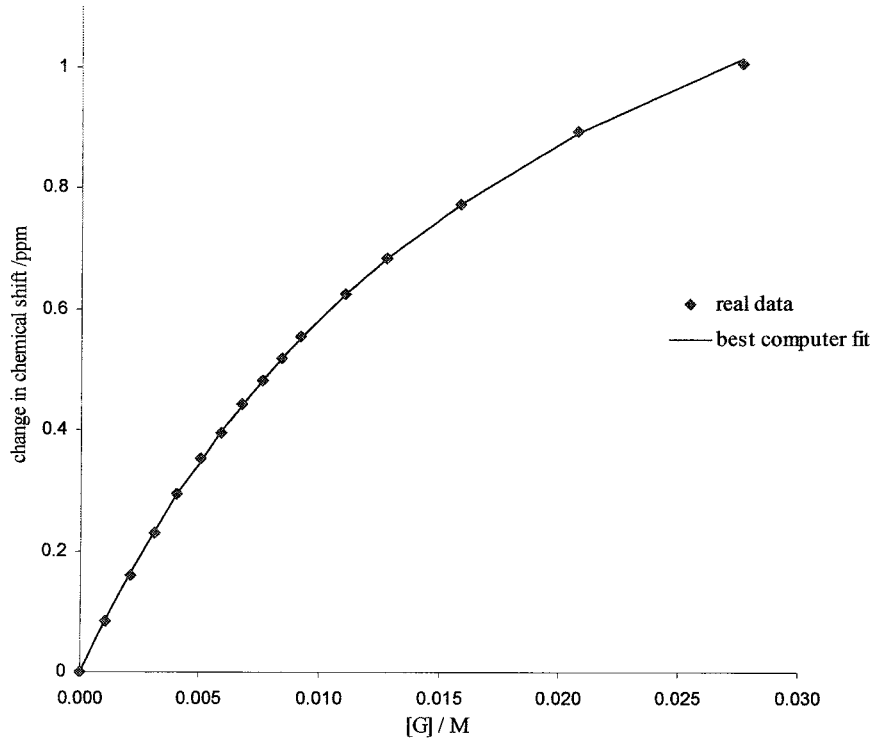


Figure 4.27 - NMR Binding Study of Association between 2.24 and TBA chloride

Solvent = Acetonitrile
Stock solutions – [H] = 0.004 M [G] = 0.104 M
Initial volume of host = 500μL δH = 7.8824 ppm

μL of guest added	[G] added /M	Observed shift of NH /ppm	Change in shift relative to δH /ppm	Computer fit for change in shift /ppm
10	0.002039	8.0520	0.1696	0.1604
20	0.004000	8.1812	0.2988	0.2935
30	0.005887	8.3005	0.4181	0.4050
40	0.007704	8.3949	0.5125	0.4993
50	0.009455	8.4748	0.5924	0.5798
60	0.011143	8.5378	0.6555	0.6492
70	0.012772	8.5895	0.7071	0.7094
80	0.014345	8.6387	0.7563	0.7622
90	0.015864	8.6814	0.7990	0.8086
100	0.017333	8.7191	0.8367	0.8499
150	0.024000	8.8555	0.9731	1.0010
200	0.029714	8.9632	1.0808	1.0966
300	0.039000	9.1290	1.2466	1.2100

68 % saturation at end of titration
K_a = 60 M^{-1} ± 0 % δHG = 9.6335ppm

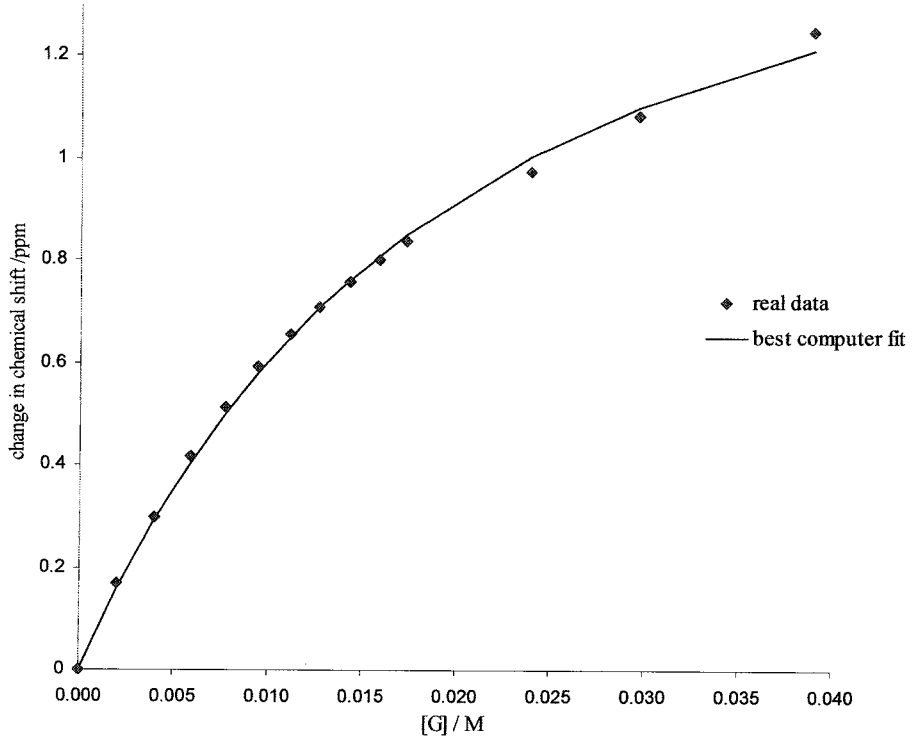


Figure 4.28 - NMR Binding Study of Association between 2.24 and TBA nitrate

Solvent = Acetonitrile
Stock solutions – [H] = 0.004 M [G] = 0.102 M
Initial volume of host = 500μL δH = 7.8655 ppm

μL of guest added	[G] added /M	Observed shift of NH /ppm	Change in shift relative to δH /ppm	Computer fit for change in shift /ppm
10	0.002000	7.8891	0.0236	0.0259
20	0.003923	7.9129	0.0474	0.0497
30	0.005774	7.9341	0.0686	0.0717
40	0.007556	7.9545	0.0890	0.0920
50	0.009273	7.9834	0.1179	0.1110
60	0.010929	8.0005	0.1350	0.1286
70	0.012526	8.0067	0.1412	0.1450
80	0.014069	8.0203	0.1548	0.1603
90	0.015559	8.0463	0.1808	0.1747
100	0.017000	8.0604	0.1949	0.1882
125	0.020400	8.0764	0.2109	0.2186
150	0.023538	8.1103	0.2448	0.2450
200	0.029143	8.1542	0.2886	0.2884
300	0.038250	8.2156	0.3501	0.3504

31 % saturation at end of titration
K_a = 13 M^{-1} ± 10 % δHG = 8.9359 ppm

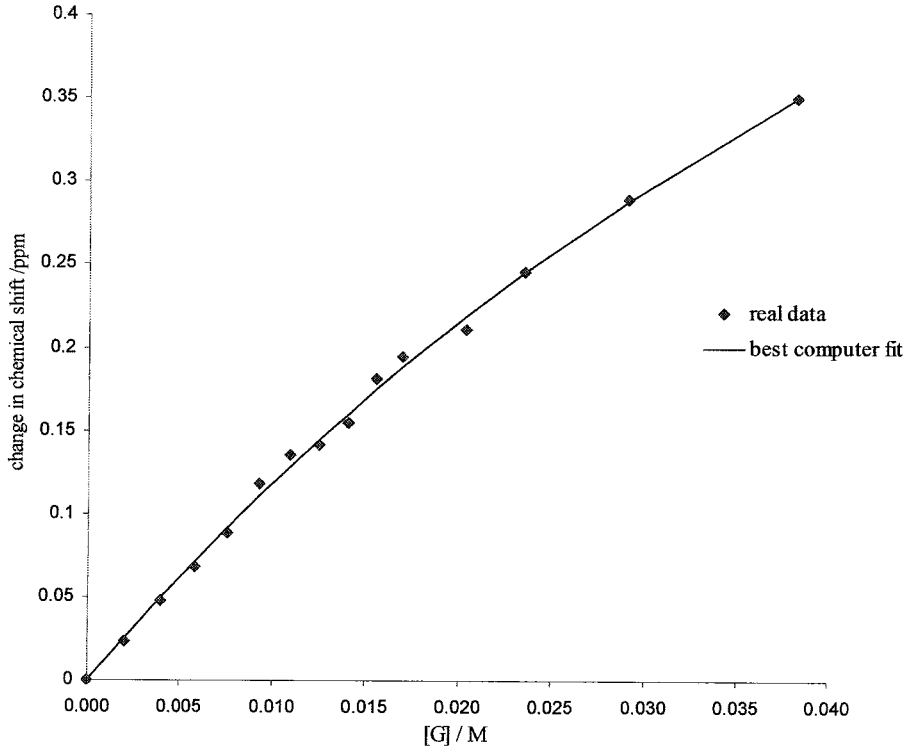


Figure 4.29 - NMR Binding Study of Association between 2.25 and TBA chloride

Solvent = Acetone
Stock solutions – [H] = 0.0022 M [G] = 0.0191 M
Initial volume of host = 500μL δH = 9.1272 ppm

μL of guest added	[G] added /M	Observed shift of NH /ppm	Change in shift relative to δH /ppm	Computer fit for change in shift /ppm
10	0.000375	9.1751	0.0479	0.0534
20	0.000735	9.2236	0.0964	0.1012
30	0.001081	9.2664	0.1391	0.1438
40	0.001415	9.2964	0.1692	0.1817
50	0.001736	9.3436	0.2164	0.2154
60	0.002046	9.3778	0.2506	0.2455
70	0.002346	9.4026	0.2754	0.2722
80	0.002634	9.4248	0.2975	0.2962
90	0.002914	9.4466	0.3194	0.3176
100	0.003183	9.4656	0.3384	0.3369
125	0.003820	9.5040	0.3768	0.3773
150	0.004408	9.5365	0.4093	0.4091
200	0.005457	9.5834	0.4562	0.4553
300	0.007163	9.6383	0.5111	0.5098
500	0.009550	9.6853	0.5581	0.5599

74 % saturation at end of titration
K_a = 355 M^{-1} ± 5 % δHG = 9.8681 ppm

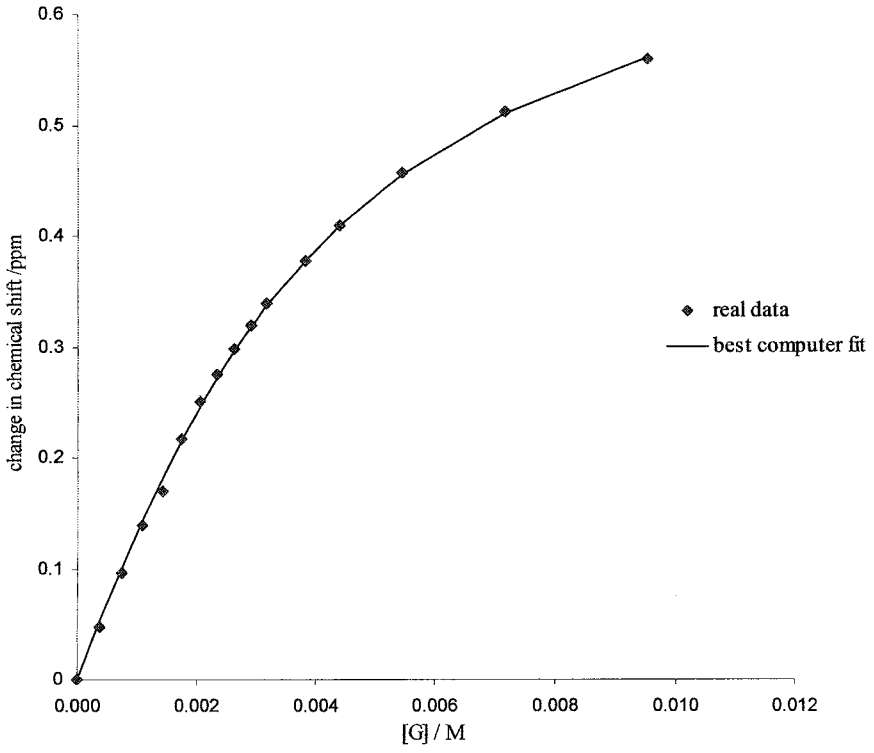


Figure 4.30 - NMR Binding Study of Association between 2.25 and TBA nitrate

Solvent = Acetone
Stock solutions – [H] = 0.0021 M [G] = 0.0190 M
Initial volume of host = 500μL δH = 7.05 ppm

μL of guest added	[G] added /M	Observed shift of NH /ppm	Change in shift relative to δH /ppm	Computer fit for change in shift /ppm
10	0.000375	7.0700	0.0200	0.0137
20	0.000731	7.0900	0.0400	0.0261
30	0.001075	7.0900	0.0400	0.0373
40	0.001407	7.1000	0.0500	0.0474
50	0.001727	7.1100	0.0600	0.0566
60	0.002036	7.1200	0.0700	0.0649
70	0.002333	7.1200	0.0700	0.0725
80	0.002621	7.1300	0.0800	0.0795
90	0.002898	7.1400	0.0900	0.0858
100	0.003167	7.1400	0.0900	0.0916
125	0.003800	7.1500	0.1000	0.1043
150	0.004385	7.1600	0.1100	0.1147
200	0.005429	7.1700	0.1200	0.1308
300	0.007125	7.2000	0.1500	0.1513
500	0.009500	7.2300	0.1800	0.1723

64 % saturation at end of titration
K_a = 200 M^{-1} ± 5 % δHG = 7.3198 ppm

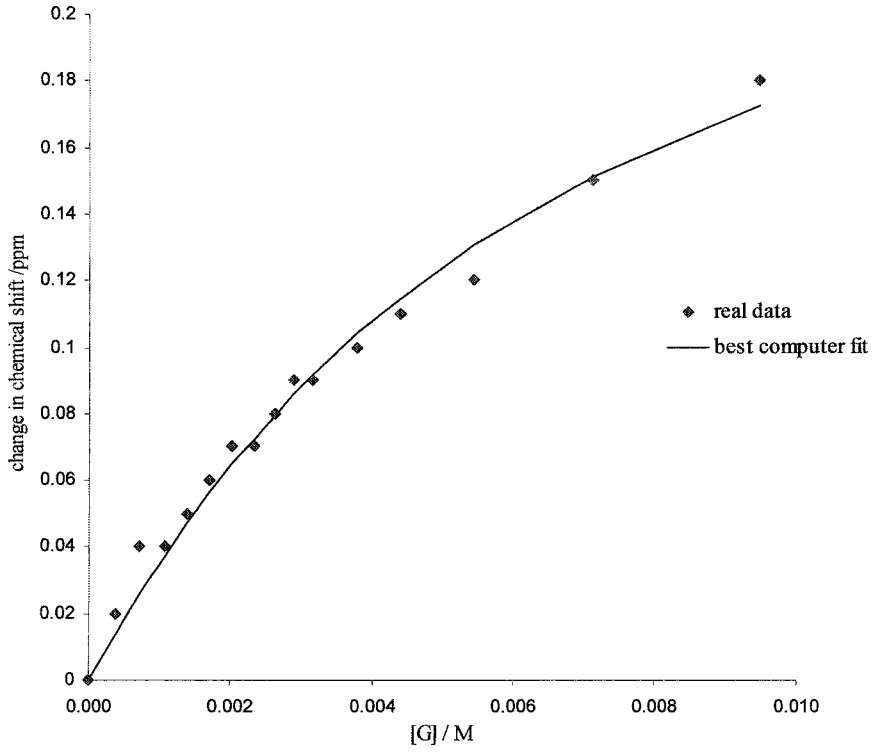


Figure 4.31 - NMR Binding Study of Association between 2.26 and TBA chloride

Solvent = Acetone
Stock solutions – [H] = 0.0018 M [G] = 0.0201 M
Initial volume of host = 500μL δH = 8.6371 ppm

μL of guest added	[G] added /M	Observed shift of NH /ppm	Change in shift relative to δH /ppm	Computer fit for change in shift /ppm
10	0.000394	8.6411	0.0039	0.0049
20	0.000773	8.6434	0.0063	0.0093
30	0.001138	8.6474	0.0102	0.0132
40	0.001489	8.6514	0.0143	0.0168
50	0.001827	8.6562	0.0191	0.0199
60	0.002154	8.6604	0.0233	0.0228
70	0.002468	8.6642	0.0271	0.0254
80	0.002772	8.6664	0.0293	0.0278
90	0.003066	8.6683	0.0312	0.0299
100	0.003350	8.6697	0.0326	0.0319
125	0.004020	8.6736	0.0365	0.0361
150	0.004638	8.6774	0.0402	0.0396
200	0.005743	8.6817	0.0446	0.0450
300	0.007538	8.6885	0.0514	0.0518
500	0.010050	8.6954	0.0583	0.0587

62 % saturation at end of titration
K_a = 190 M^{-1} ± 15 % δHG = 8.7284 ppm

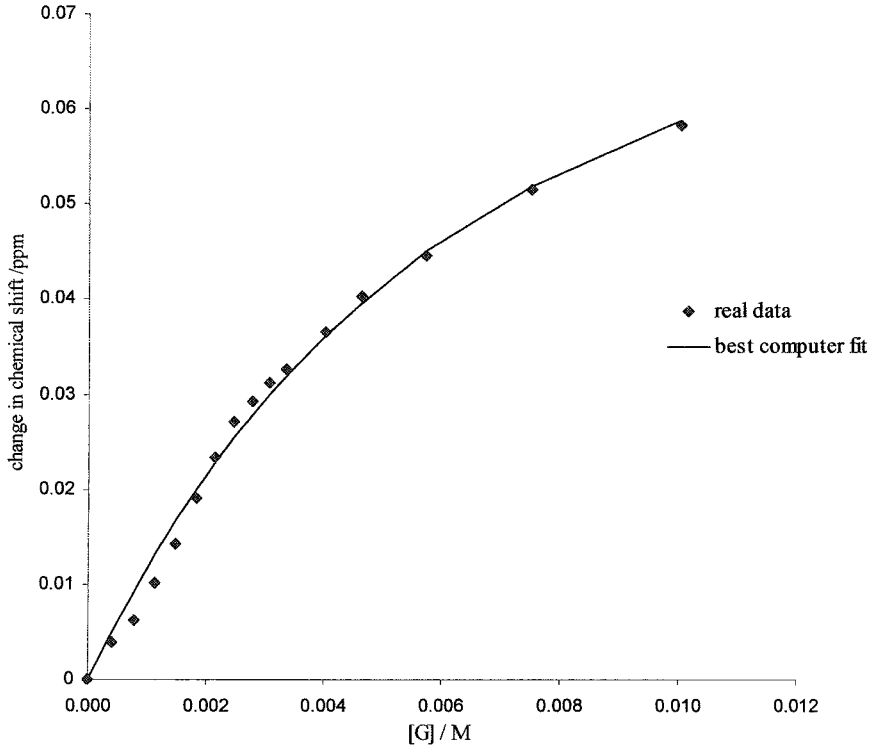


Figure 4.32 - NMR Binding Study of Association between 2.26 and TBA nitrate

Solvent = Acetone
Stock solutions – [H] = 0.0018 M [G] = 0.0204 M
Initial volume of host = 500μL δH = 8.6362 ppm

μL of guest added	[G] added /M	Observed shift of NH /ppm	Change in shift relative to δH /ppm	Computer fit for change in shift /ppm
10	0.000400	8.6392	0.0030	0.0023
20	0.000785	8.6399	0.0037	0.0043
30	0.001155	8.6420	0.0058	0.0061
40	0.001511	8.6433	0.0071	0.0077
50	0.001855	8.6443	0.0081	0.0091
60	0.002186	8.6467	0.0106	0.0103
70	0.002505	8.6475	0.0113	0.0114
80	0.002814	8.6481	0.0119	0.0123
90	0.003112	8.6494	0.0132	0.0132
100	0.003400	8.6511	0.0149	0.0139
125	0.004080	8.6521	0.0159	0.0156
150	0.004708	8.6535	0.0173	0.0168
200	0.005829	8.6549	0.0187	0.0187
300	0.007650	8.6574	0.0212	0.0209
500	0.010200	8.6585	0.0223	0.0230

67 % saturation at end of titration
K_a = 300 M^{-1} ± 10 % δHG = 8.6672 ppm

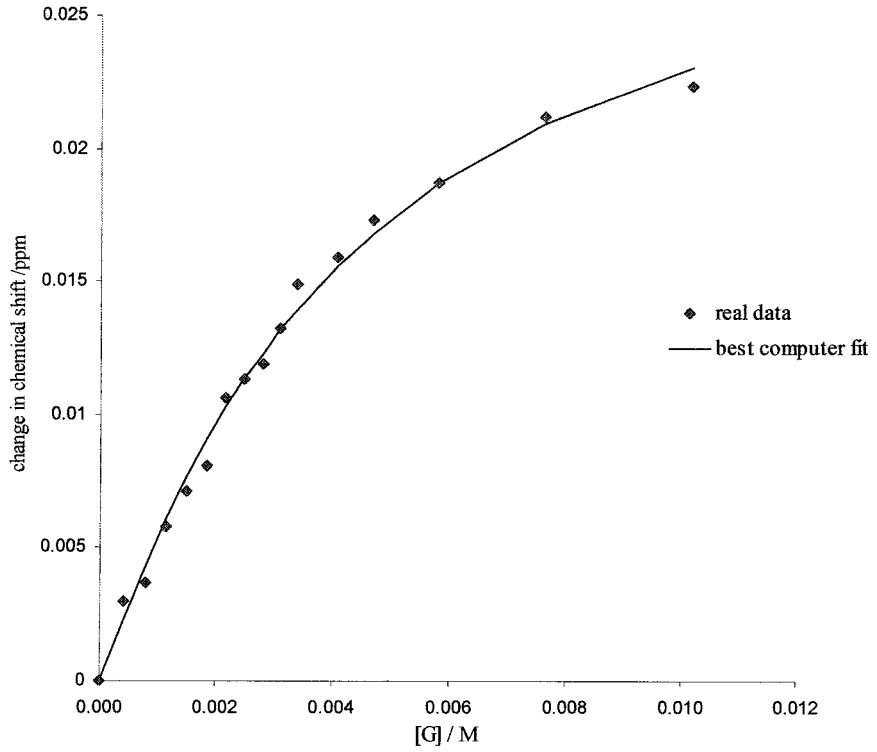


Figure 4.33 - NMR Binding Study of Association between 2.19 and TBA chloride

Solvent = Chloroform
Stock solutions – [H] = 0.0105 M [G] = 0.1133 M
Initial volume of host = 500μL δH = 4.6475 ppm

μL of guest added	[G] added /M	Observed shift of NH /ppm	Change in shift relative to δH /ppm	Computer fit for change in shift /ppm
10	0.002222	4.9407	0.2932	0.2964
20	0.004358	5.2070	0.5595	0.5541
30	0.006413	5.4270	0.7795	0.7749
40	0.008393	5.6113	0.9638	0.9622
50	0.010300	5.7702	1.1227	1.1200
60	0.012139	5.9012	1.2537	1.2528
70	0.013914	6.0065	1.3590	1.3648
80	0.015628	6.1045	1.4570	1.4595
90	0.017283	6.1915	1.5440	1.5402
100	0.018883	6.2647	1.6172	1.6093
125	0.022660	6.3838	1.7363	1.7440
150	0.026146	6.4763	1.8288	1.8409
200	0.032371	6.6132	1.9657	1.9692
300	0.042488	6.7629	2.1154	2.1038

81 % saturation at end of titration
K_a = 129 M^{-1} ± 5 % δHG = 7.1914 ppm

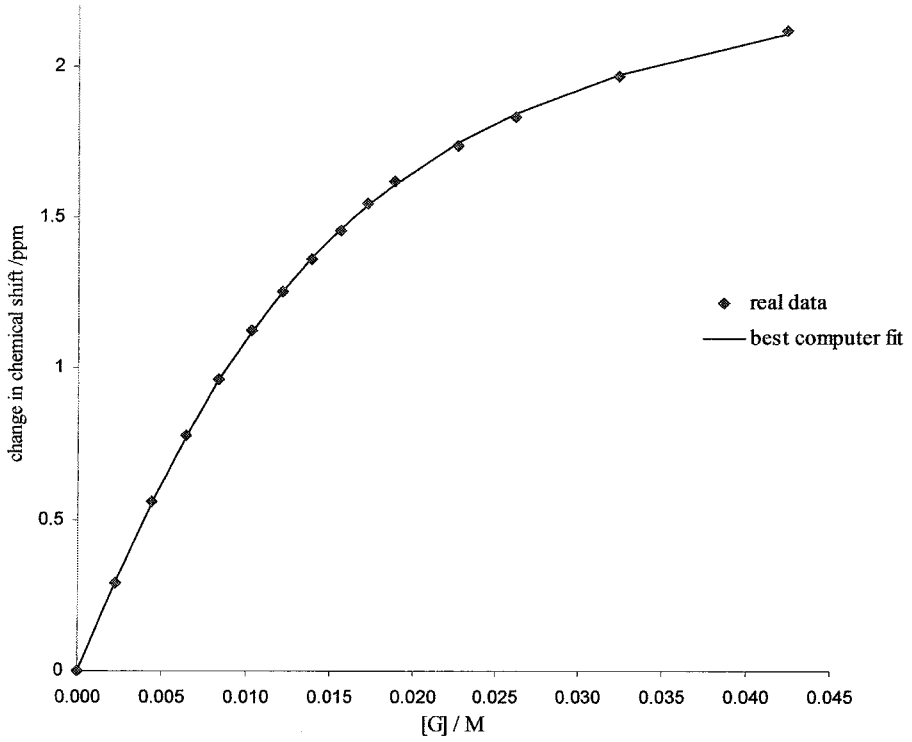


Figure 4.34 - NMR Binding Study of Association between 2.19 and TBA nitrate

Solvent = Chloroform
Stock solutions – [H] = 0.0105 M [G] = 0.1035 M
Initial volume of host = 500μL δH = 4.6521 ppm

μL of guest added	[G] added /M	Observed shift of NH /ppm	Change in shift relative to δH /ppm	Computer fit for change in shift /ppm
10	0.002029	4.8352	0.1831	0.1866
20	0.003981	5.0074	0.3553	0.3509
30	0.005858	5.1502	0.4981	0.4935
40	0.007667	5.2748	0.6227	0.6161
50	0.009409	5.3783	0.7262	0.7206
60	0.011089	5.4643	0.8122	0.8096
70	0.012711	5.5394	0.8873	0.8853
80	0.014276	5.5990	0.9469	0.9499
90	0.015788	5.6512	0.9991	1.0052
100	0.017250	5.7002	1.0481	1.0528
125	0.020700	5.7922	1.1401	1.1463
150	0.023885	5.8654	1.2133	1.2139
200	0.029571	5.9511	1.2990	1.3039
300	0.038813	6.0599	1.4078	1.3985

80 % saturation at end of titration
K_a = 131 M^{-1} ± 4 % δHG = 6.3582 ppm

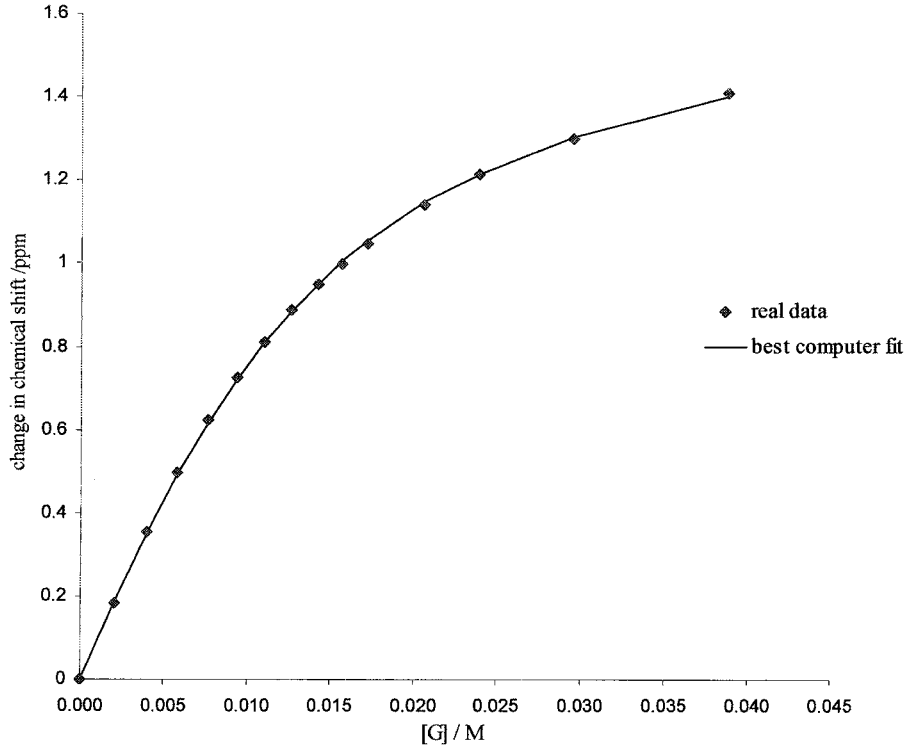


Figure 4.35 - NMR Binding Study of Association between 2.19 and TBA nitrate

Solvent = Chloroform
Stock solutions – [H] = 0.010 M [G] = 0.102M
Initial volume of host = 500μL δH = 4.6878 ppm

μL of guest added	[G] added /M	Observed shift of NH /ppm	Change in shift relative to δH /ppm	Computer fit for change in shift /ppm
10	0.002000	4.8764	0.1886	0.1890
20	0.003923	5.0400	0.3522	0.3545
30	0.005774	5.1923	0.5045	0.4978
40	0.007556	5.3160	0.6282	0.6207
50	0.009273	5.4185	0.7307	0.7258
60	0.010929	5.5042	0.8164	0.8154
70	0.012526	5.5779	0.8901	0.8919
80	0.014069	5.6420	0.9542	0.9574
900	0.015559	5.6978	1.0100	1.0138
100	0.017000	5.7510	1.0632	1.0625
125	0.020400	5.8425	1.1547	1.1590
150	0.023538	5.9094	1.2216	1.2295
200	0.029143	6.0097	1.3219	1.3242
300	0.038250	6.1230	1.4352	1.4254

79 % saturation at end of titration
K_a = 131 M^{-1} ± 4 % δHG = 6.4539 ppm

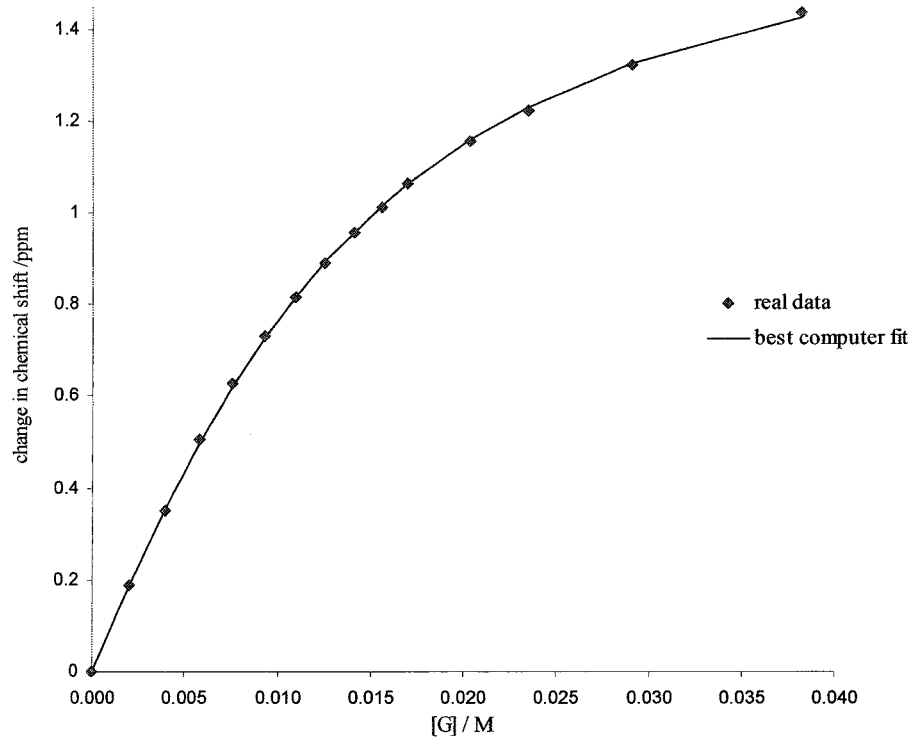


Figure 4.36 - NMR Binding Study of Association between 2.19 and TBA chloride

Solvent = Acetone
Stock solutions – [H] = 0.010 M [G] = 0.109 M
Initial volume of host = 500μL δH = 6.8602 ppm

μL of guest added	[G] added /M	Observed shift of NH /ppm	Change in shift relative to δH /ppm	Computer fit for change in shift /ppm
10	0.002137	7.0388	0.1786	0.1927
40	0.008074	7.4968	0.6367	0.6305
50	0.009909	7.6054	0.7452	0.7381
60	0.011679	7.6971	0.8369	0.8309
70	0.013386	7.7749	0.9147	0.9111
100	0.018167	7.9513	1.0912	1.0947
125	0.021800	8.0559	1.1957	1.2021
150	0.025154	8.1345	1.2743	1.2828
200	0.031143	8.2505	1.3903	1.3947
300	0.040875	8.3882	1.5280	1.5190

75 % saturation at end of titration
K_a = 91 M^{-1} ± 10 % δHG = 8.8417 ppm

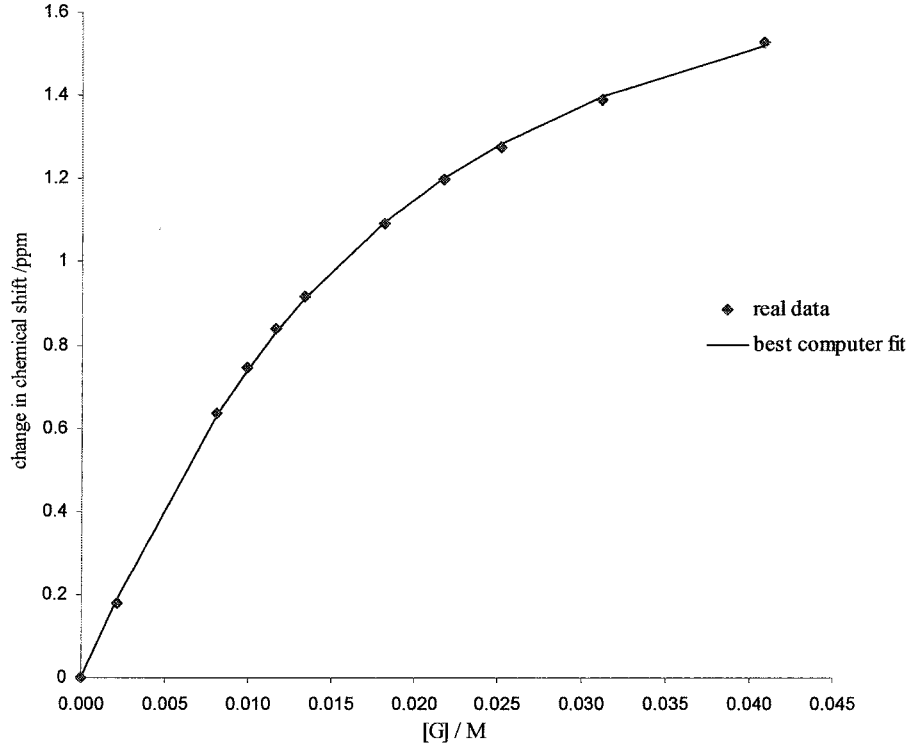


Figure 4.37 - NMR Binding Study of Association between 2.19 and TBA nitrate

Solvent = Acetone
Stock solutions – [H] = 0.010 M [G] = 0.100 M
Initial volume of host = 500μL δH = 6.8582 ppm

μL of guest added	[G] added /M	Observed shift of NH /ppm	Change in shift relative to δH /ppm	Computer fit for change in shift /ppm
10	0.001961	6.8973	0.0391	0.0302
20	0.003846	6.9201	0.0619	0.0572
30	0.005660	6.9423	0.0841	0.0815
40	0.007407	6.9609	0.1027	0.1032
50	0.009091	6.9792	0.1210	0.1223
60	0.010714	6.9978	0.1396	0.1404
70	0.012281	7.0128	0.1546	0.1563
80	0.013793	7.0266	0.1684	0.1708
90	0.015254	7.0412	0.1830	0.1839
100	0.016667	7.0535	0.1953	0.1959
125	0.020000	7.0792	0.2210	0.2217
150	0.023077	7.1038	0.2456	0.2426

42 % saturation at end of titration
K_a = 43 M^{-1} ± 10 % δHG = 7.3893 ppm

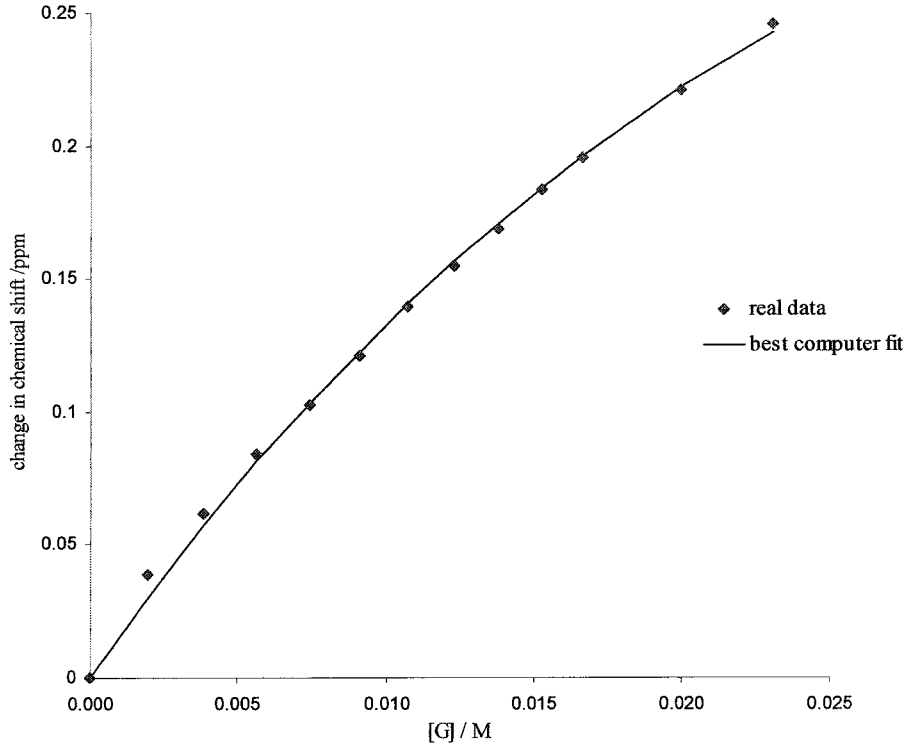


Figure 4.38 - NMR Binding Study of Association between 2.19 and TBA chloride

Solvent = Acetonitrile
Stock solutions – [H] = 0.011 M [G] = 0.105 M
Initial volume of host = 500μL δH = 5.9425 ppm

μL of guest added	[G] added /M	Observed shift of NH /ppm	Change in shift relative to δH /ppm	Computer fit for change in shift /ppm
10	0.002059	6.0384	0.0958	0.1079
20	0.004038	6.1378	0.1952	0.2053
30	0.005943	6.2257	0.2831	0.2932
40	0.007778	6.3102	0.3677	0.3727
50	0.009545	6.3881	0.4456	0.4449
60	0.011250	6.4602	0.5176	0.5106
70	0.012895	6.5219	0.5794	0.5705
80	0.014483	6.5679	0.6254	0.6252
90	0.016017	6.6241	0.6816	0.6754
100	0.017500	6.6644	0.7218	0.7214
125	0.021000	6.7627	0.8201	0.8216
150	0.024231	6.8421	0.8996	0.9043
200	0.030000	6.9749	1.0324	1.0323

45 % saturation at end of titration
K_a = 34 M^{-1} ± 20 % δHG = 8.1297 ppm

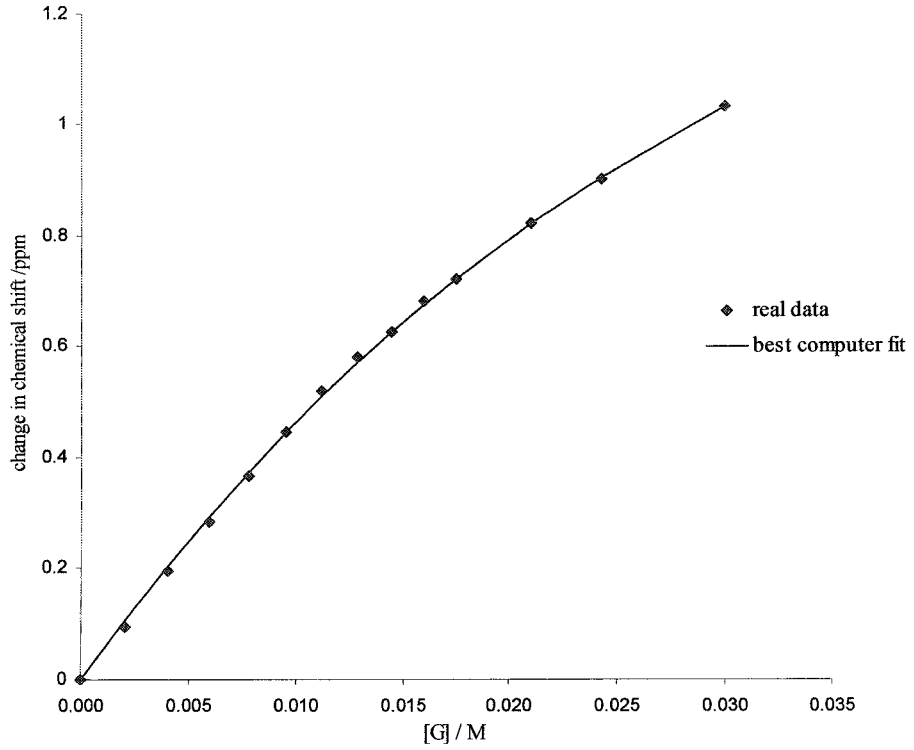


Figure 4.39 - NMR Binding Study of Association between 2.19 and TBA nitrate

Solvent = Acetonitrile
Stock solutions – [H] = 0.011 M [G] = 0.102 M
Initial volume of host = 500μL δH = 5.9568 ppm

μL of guest added	[G] added /M	Observed shift of NH /ppm	Change in shift relative to δH /ppm	Computer fit for change in shift /ppm
10	0.002000	5.9738	0.0169	0.0182
20	0.003923	5.9917	0.0349	0.0352
30	0.005774	6.0076	0.0508	0.0513
40	0.007556	6.0229	0.0661	0.0664
50	0.009273	6.0374	0.0805	0.0807
60	0.010929	6.0504	0.0935	0.0942
70	0.012260	6.0654	0.1086	0.1070
80	0.014069	6.0761	0.1193	0.1191
90	0.015559	6.0889	0.1321	0.1306
100	0.017000	6.0999	0.1431	0.1416
125	0.020400	6.1246	0.1678	0.1667
150	0.023538	6.1443	0.1875	0.1890
200	0.029143	6.1828	0.2260	0.2269
300	0.038250	6.2400	0.2832	0.2837

22 % saturation at end of titration
$K_a = 8\ M^{-1} \pm 10\ \%$ δHG = 7.2070 ppm

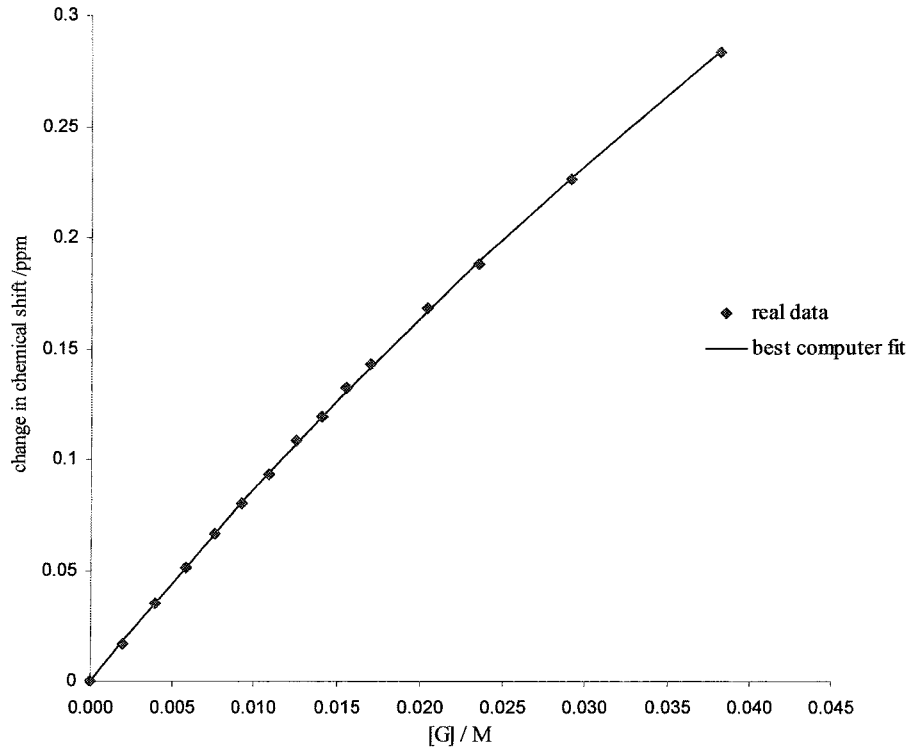


Figure 4.40 - NMR Binding Study of Association between 2.20 and TBA chloride

Solvent = Acetone
Stock solutions – [H] = 0.011 M [G] = 0.119 M
Initial volume of host = 500μL δH = 7.3821 ppm

μL of guest added	[G] added /M	Observed shift of NH /ppm	Change in shift relative to δH /ppm	Computer fit for change in shift /ppm
10	0.002333	7.7009	0.3188	0.3289
20	0.004577	7.9119	0.5298	0.6154
40	0.008815	8.5085	1.1264	1.0650
50	0.010818	8.6198	1.2377	1.2356
60	0.012750	8.8315	1.4494	1.3769
70	0.014614	8.8494	1.4673	1.4940
80	0.016414	8.9486	1.5665	1.5913
90	0.018153	9.0121	1.6300	1.6729
100	0.019833	9.1974	1.8152	1.7418
125	0.023800	9.1860	1.8039	1.8731
150	0.027462	9.3061	1.9240	1.9652
200	0.034000	9.5241	2.1420	2.0839
300	0.044625	9.5872	2.2051	2.2046

84 % saturation at end of titration
K_a = 153 M^{-1} ± 20 % δHG = 9.9587 ppm

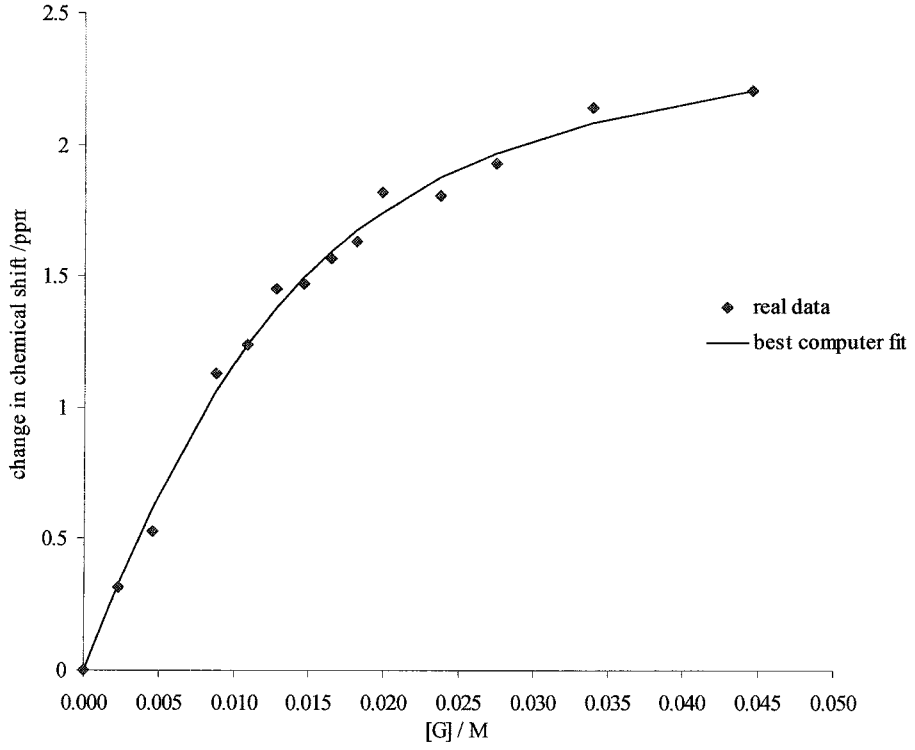


Figure 4.41 - NMR Binding Study of Association between 2.20 and TBA nitrate

Solvent = Acetone
Stock solutions – [H] = 0.011 M [G] = 0.102 M
Initial volume of host = 500μL δH = 7.4205 ppm

μL of guest added	[G] added /M	Observed shift of NH /ppm	Change in shift relative to δH /ppm	Computer fit for change in shift /ppm
10	0.002000	7.4880	0.0676	0.0724
20	0.003923	7.5548	0.1344	0.1369
30	0.005774	7.6137	0.1932	0.1944
40	0.007556	7.6645	0.2441	0.2456
50	0.009273	7.7133	0.2928	0.2913
60	0.010929	7.7525	0.3320	0.3321
70	0.012526	7.7900	0.3695	0.3686
80	0.014069	7.8235	0.4030	0.4014
90	0.015559	7.8525	0.4320	0.4310
100	0.017000	7.8788	0.4584	0.4576
125	0.020400	7.9349	0.5144	0.5139
150	0.023538	7.9772	0.5567	0.5587

49 % saturation at end of titration
$K_a = 57\ M^{-1} \pm 10\ \%$ δHG = 8.4917 ppm

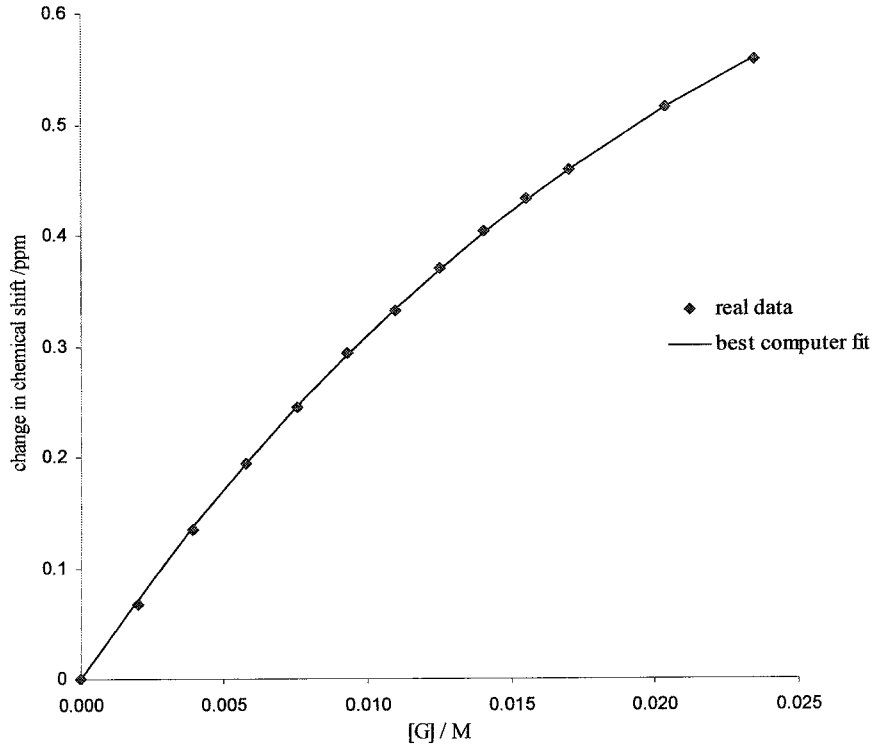


Figure 4.42 - NMR Binding Study of Association between 2.20 and TBA chloride

Solvent = Acetonitrile
Stock solutions – [H] = 0.012 M [G] = 0.117 M
Initial volume of host = 500μL δH = 6.3732 ppm

μL of guest added	[G] added /M	Observed shift of NH /ppm	Change in shift relative to δH /ppm	Computer fit for change in shift /ppm
10	0.002294	6.3696	-0.0036	0.2248
20	0.004500	6.6196	0.2464	0.4249
30	0.006623	6.8274	0.4542	0.6031
50	0.010636	7.3219	0.9488	0.9034
60	0.012536	7.3529	0.9798	1.0300
70	0.014368	7.5992	1.2260	1.1436
80	0.016138	7.6057	1.2326	1.2457
90	0.017847	7.8057	1.4325	1.3378
100	0.019500	7.8465	1.4733	1.4211
125	0.023400	8.0246	1.6514	1.5977
300	0.043875	8.5162	2.1430	2.2051

62 % saturation at end of titration
K_a = 46 M^{-1} ± 15 % δHG = 9.8056 ppm

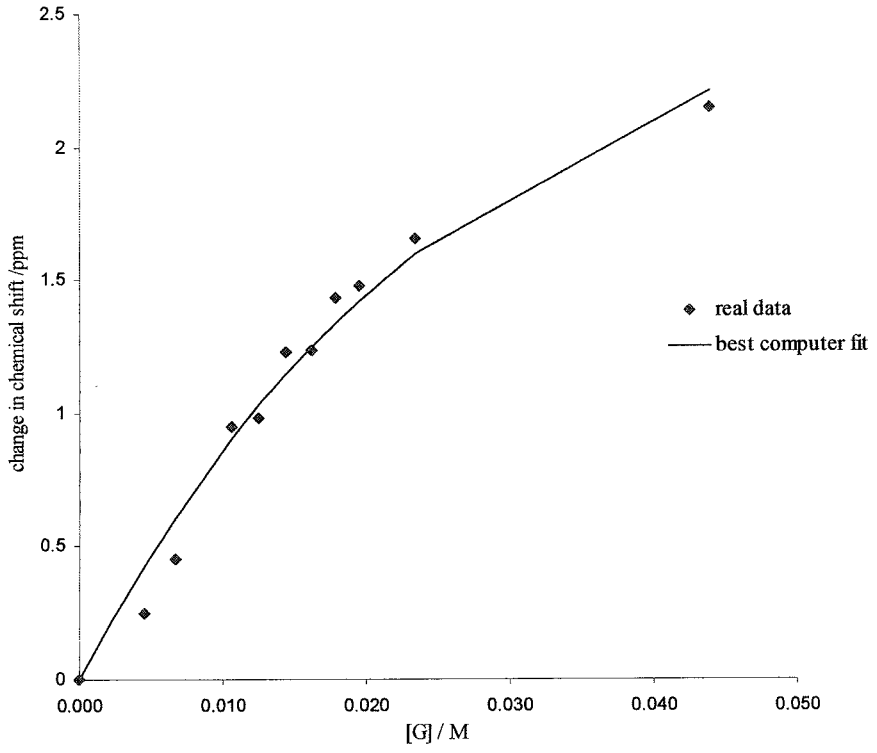


Figure 4.43 - NMR Binding Study of Association between 2.20 and TBA nitrate

Solvent = Acetonitrile
Stock solutions – [H] = 0.012 M [G] = 0.101 M
Initial volume of host = 500μL δH = 6.3768 ppm

μL of guest added	[G] added /M	Observed shift of NH /ppm	Change in shift relative to δH /ppm	Computer fit for change in shift /ppm
10	0.001980	6.3654	-0.0114	0.0484
20	0.003885	6.4638	0.0870	0.0918
30	0.005717	6.4860	0.1093	0.1307
40	0.007481	6.5675	0.1908	0.1655
50	0.009182	6.5583	0.1816	0.1967
60	0.010821	6.6329	0.2562	0.2247
90	0.015407	6.6698	0.2931	0.2928
100	0.016833	6.6862	0.3094	0.3112
125	0.020200	6.7369	0.3602	0.3502
150	0.023308	6.7384	0.3617	0.3812
200	0.028857	6.8092	0.4324	0.4271

60 % saturation at end of titration
K_a = 59 M^{-1} ± 20 % δHG = 7.1074 ppm

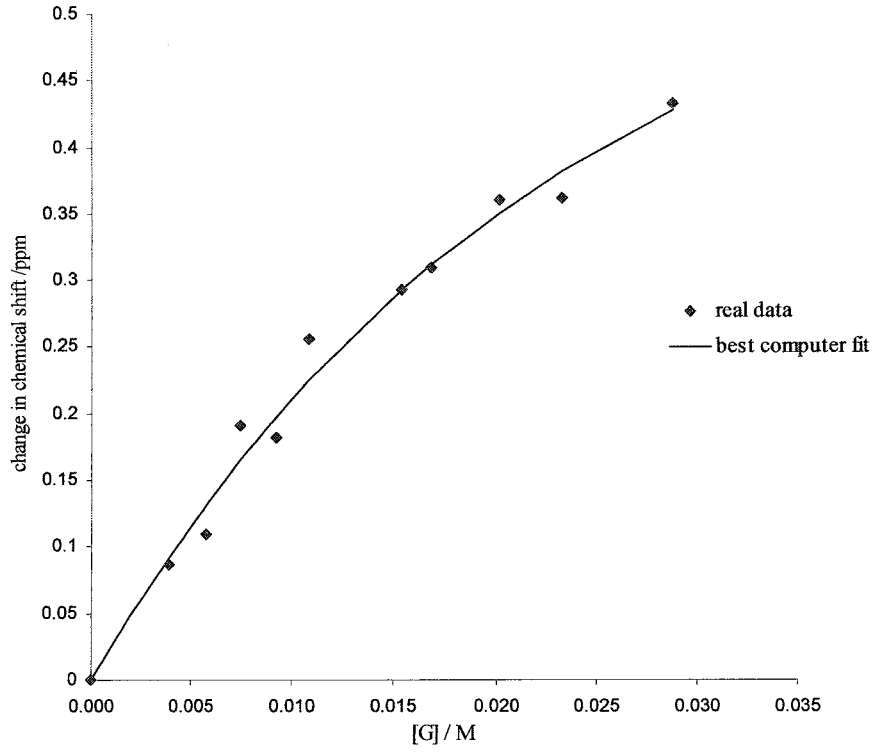


Figure 4.44 - NMR Binding Study of Association between 2.41 and TBA chloride

Solvent = Chloroform
Stock solutions – [H] = 0.099 M [G] = 0.0957 M
Initial volume of host = 500μL δH = 10.3279 ppm

μL of guest added	[G] added /M	Observed shift of NH /ppm	Change in shift relative to δH /ppm	Computer fit for change in shift /ppm
10	0.001876	10.4168	0.0889	0.0852
20	0.003681	10.4873	0.1594	0.1638
30	0.005417	10.5633	0.2354	0.2335
40	0.007089	10.6219	0.2940	0.2923
50	0.008700	10.6668	0.3389	0.3393
60	0.010254	10.7016	0.3737	0.3750
70	0.011753	10.7281	0.4002	0.4017
80	0.013200	10.7492	0.4213	0.4215
90	0.014598	10.7647	0.4368	0.4364
100	0.015950	10.7767	0.4488	0.4479
125	0.019140	10.7959	0.4680	0.4669
150	0.022085	10.8069	0.4790	0.4785
200	0.027343	10.8206	0.4927	0.4914
300	0.035888	10.8286	0.5007	0.5029

93 % saturation at end of titration
K_a = 601 M^{-1} ± 10 % δHG = 10.8587 ppm

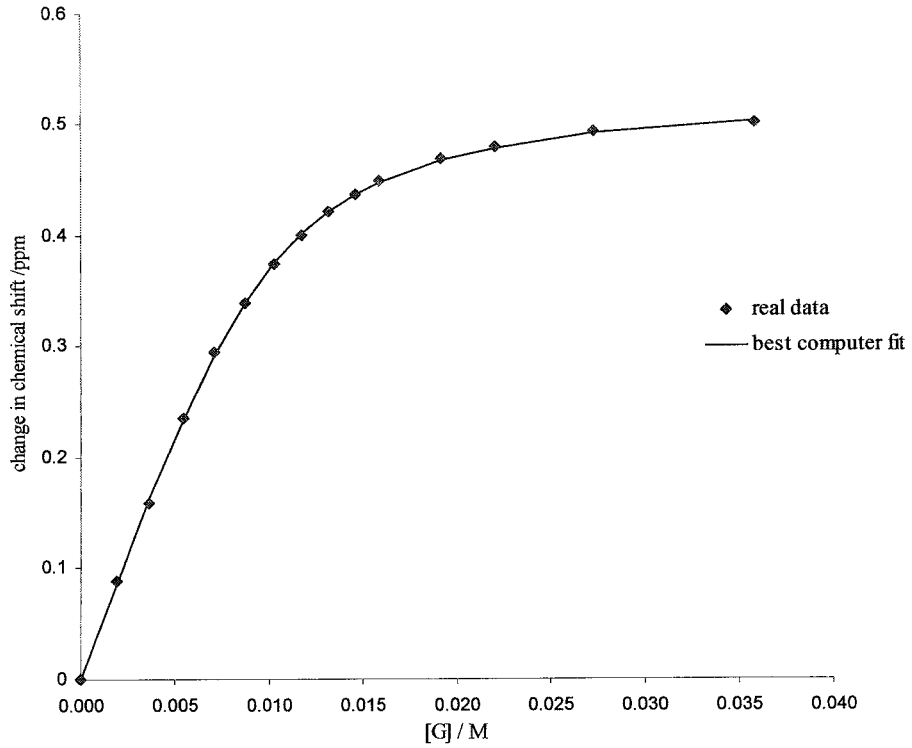


Figure 4.45 - NMR Binding Study of Association between 2.41 and TBA nitrate

Solvent = Chloroform
Stock solutions – [H] = 0.0099 M [G] = 0.0982 M
Initial volume of host = 500μL δH = 10.3298 ppm

μL of guest added	[G] added /M	Observed shift of NH /ppm	Change in shift relative to δH /ppm	Computer fit for change in shift /ppm
10	0.001925	10.2657	-0.0641	-0.0525
20	0.003777	10.2180	-0.1118	-0.0987
30	0.005558	10.1842	-0.1456	-0.1389
40	0.007274	10.1393	-0.1905	-0.1736
50	0.008927	10.1265	-0.2033	-0.2033
60	0.010521	10.1027	-0.2271	-0.2289
70	0.012060	10.0688	-0.2610	-0.2508
80	0.013545	10.0633	-0.2665	-0.2698
90	0.014980	10.0486	-0.2812	-0.2861
100	0.016367	10.0358	-0.2940	-0.3003
125	0.019640	10.0111	-0.3187	-0.3286
150	0.022662	9.9928	-0.3370	-0.3494
200	0.028057	9.9644	-0.3654	-0.3777
300	0.036825	9.9143	-0.4156	-0.4081
400	0.043644	9.8929	-0.4369	-0.4239

83 % saturation at end of titration
K_a = 123 M^{-1} ± 5 % δHG = 9.8177 ppm

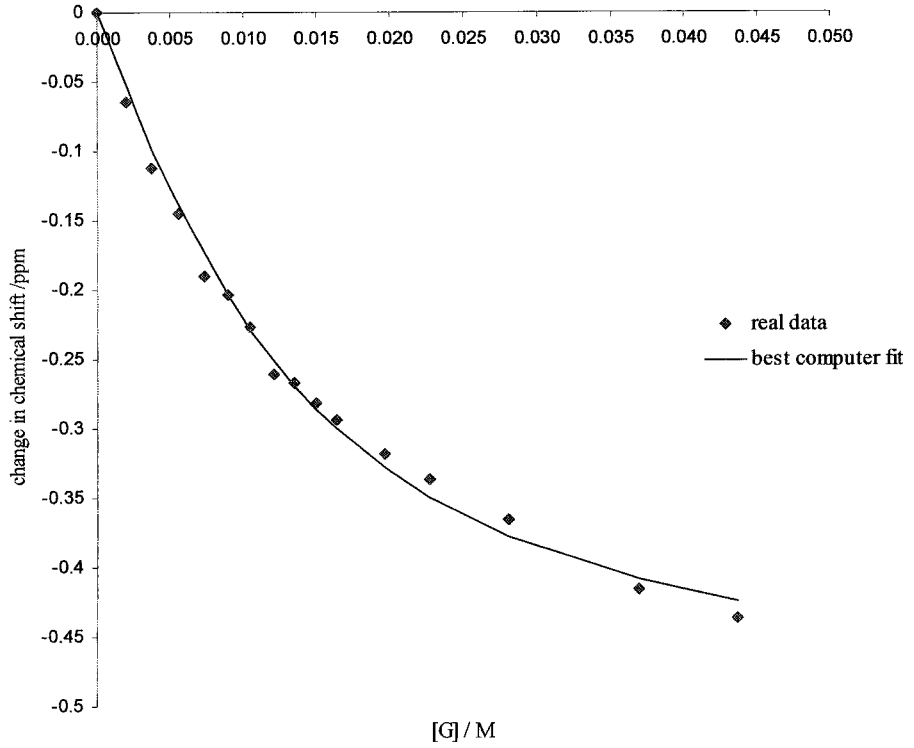


Figure 4.46 - NMR Binding Study of Association between 2.41 and TBA chloride

Solvent = Acetone
Stock solutions – [H] = 0.0098 M [G] = 0.1029 M
Initial volume of host = 500μL δH = 8.0414 ppm

μL of guest added	[G] added /M	Observed shift of NH /ppm	Change in shift relative to δH /ppm	Computer fit for change in shift /ppm
10	0.002018	8.5932	0.1918	0.2112
30	0.003958	8.8109	0.4095	0.3985
40	0.005825	9.0013	0.5999	0.5646
50	0.007622	9.1523	0.7509	0.7122
60	0.009355	9.1942	0.7927	0.8435
70	0.011025	9.3337	0.9323	0.9608
80	0.012637	9.4616	1.0601	1.0658
90	0.014193	9.5697	1.1683	1.1602

32 % saturation at end of titration
K_a = 51 M^{-1} ± 15 % δHG = 11.6049 ppm

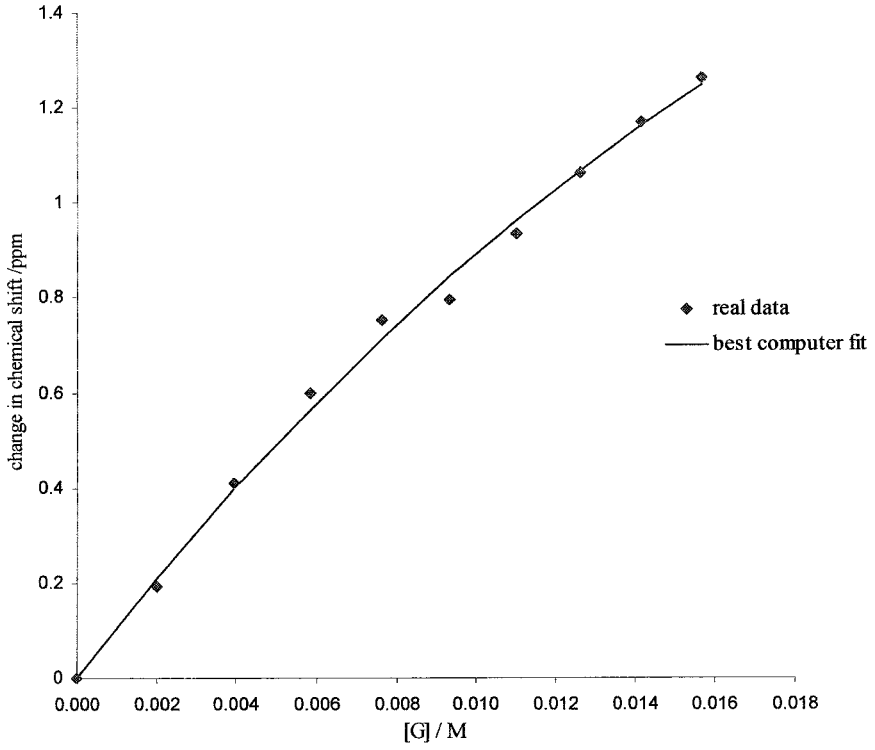


Figure 4.47 - NMR Binding Study of Association between 2.41 and TBA nitrate

Solvent = Acetone
Stock solutions – [H] = 0.010 M [G] = 0.099 M
Initial volume of host = 500μL δH = 9.4466 ppm

μL of guest added	[G] added /M	Observed shift of NH /ppm	Change in shift relative to δH /ppm	Computer fit for change in shift /ppm
10	0.001941	9.4681	0.0215	0.0191
30	0.005604	9.5012	0.0546	0.0509
40	0.007333	9.5138	0.0672	0.0641
50	0.009000	9.5252	0.0787	0.0757
60	0.010600	9.5343	0.0877	0.0860
70	0.012158	9.5425	0.0959	0.0952
80	0.013655	9.5500	0.1035	0.1033
90	0.015102	9.5575	0.1110	0.1106
100	0.018512	9.5698	0.1232	0.1257
125	0.019800	9.5743	0.1277	0.1308
150	0.022846	9.5839	0.1373	0.1415
200	0.028286	9.6005	0.1539	0.1570
300	0.037125	9.6224	0.1758	0.1754
400	0.044000	9.6367	0.1901	0.1857

72 % saturation at end of titration
K_a = 67 M^{-1} ± 10 % δHG = 9.7017 ppm

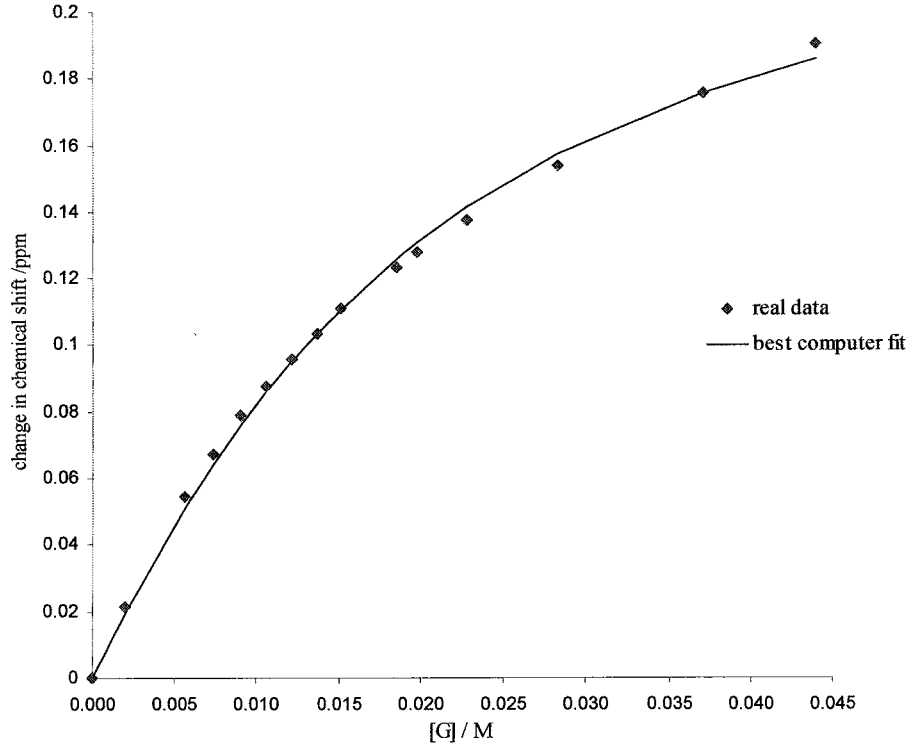


Figure 4.48 - Fluorescence Binding Study of Association between 2.41 and TBA chloride

Solvent = Water
Stock solutions – [H] = 0.0003 M [G] = 0.0094 M
Initial volume of host = 500μL Initial H fluorescence = 2.1983 ppm

Parameters - Excitation = 315 nm Emission = 500 nm Volts = 700
16 nm 16 nm

λ_{max} = 315 nm

μL of guest added	[G] added /M	Observed Fluorescence	Change in fluorescence relative to initial
10	0.000184	2.2795	0.0812
20	0.000362	2.2765	0.0782
45	0.000776	2.3663	0.1680
70	0.001154	2.4566	0.2584
95	0.001501	2.4482	0.2499
120	0.001819	2.5499	0.3516
170	0.002385	2.7108	0.5125
220	0.002872	2.8658	0.6675
320	0.003668	3.1572	0.9589
420	0.004291	3.4119	1.2136

K_a = ~ 100 M^{-1}

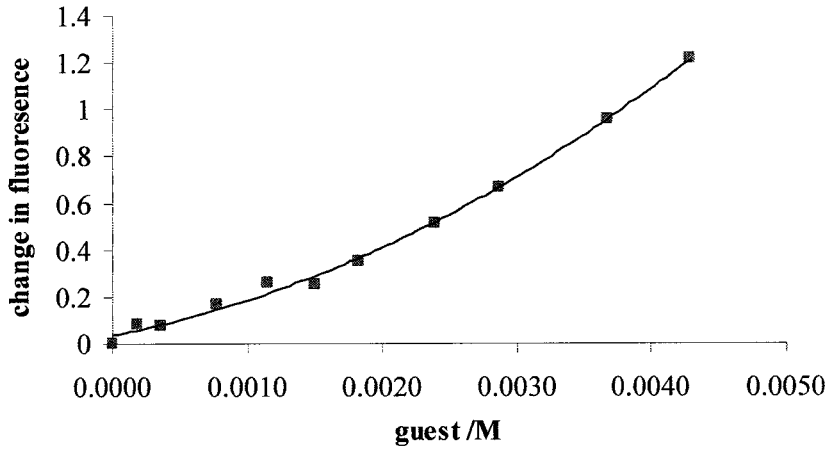


Figure 4.49 - Fluorescence Binding Study of Association between 2.41 and TBA chloride

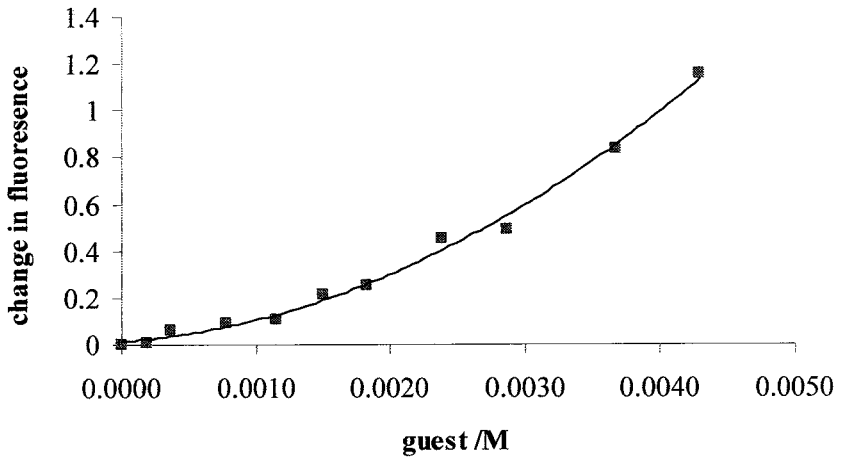
Solvent = Water
Stock solutions – [H] = 0.0003 M [G] = 0.0094 M
Initial volume of host = 500μL Initial H fluorescence = 2.2073 ppm

Parameters - Excitation = 315 nm Emission = 500 nm Volts = 700
16 nm 16 nm

λ_{max} = 315 nm

μL of guest added	[G] added /M	Observed Fluorescence	Change in fluorescence relative to initial
10	0.000184	2.2183	0.0109
20	0.000362	2.2652	0.0579
45	0.000776	2.2987	0.0914
70	0.001154	2.3108	0.1035
95	0.001501	2.4224	0.2151
120	0.001819	2.4614	0.2541
170	0.002385	2.6605	0.4531
220	0.002872	2.6979	0.4906
320	0.003668	3.0406	0.8333
420	0.004291	3.3618	1.1544

K_a = ~ 100 M^{-1}



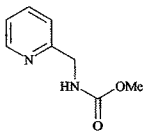
Experimental Details for Chapter 3

4.3 Chapter 3

4.3.1 Synthesis of receptors

4.3.1.1 Urea receptors

Pyridin-2-ylmethyl-carbamic acid methyl ester 3.11



Attempt 1

Aluminium oxide active (0.45 g, 4.41 mmol) was added to a stirring mixture of 2-(aminomethyl) pyridine (0.45 g, 4.16 mmol) and dimethyl carbonate (0.28M, 15 mls) and the mixture was heated under reflux (16 hrs). The mixture was filtered through celite under suction and the DMC removed under reduced pressure to give a thick dark brown liquid (1.06 g, 154 %). The proton NMR spectral data suggested a mixture of starting material and compound **3.11.** δ_H (compound **3.11**) ($CDCl_3$) 8.76 (m, 1H, Py-*H*), 8.15 (m, 1H, Py-*H*), 7.87 (m, 2H, Py-*H*), 5.96 (br, 1H, -*NH*-) 4.60 (m, 2H, -CH_2-), 3.75 (s, 3H, -CH_3) ppm. E.S.M.S. for $C_8H_{10}N_2O_2$. Calculated mass of molecular ion: 167 $(M+H)^+$; Measured mass: 167 $(M+H)^+$. There is no data reported in the literature for this compound.

Attempt 2

Neutral aluminium (0.45 g, 4.41 mmol) was added to a stirring mixture of 2-(aminomethyl) pyridine (0.45 g, 4.16 mmol) and dimethyl carbonate (0.28M, 15 mls) and the mixture was heated under reflux (16 hrs). The mixture was filtered through celite under suction and the DMC removed under reduced pressure to give a thick dark brown liquid (0.82 g, 119 %). The proton NMR spectral data suggested a mixture of starting material and compound **3.11.** δ_H (compound **3.11**) ($CDCl_3$) 8.75 (m, 1H, Py-*H*), 8.15 (m, 1H, Py-*H*), 7.86 (m, 2H, Py-*H*), 5.98 (br, 1H, -*NH*-), 4.60 (m, 2H, -CH_2-), 3.76 (s, 3H, -CH_3) ppm. E.S.M.S. for $C_8H_{10}N_2O_2$. Calculated mass of molecular ion: 167 $(M+H)^+$; Measured mass: 167 $(M+H)^+$. There is no data reported in the literature for this compound.

Attempt 3

Silica gel (0.20 g, 3.33 mmol) was added to a stirring mixture of 2-(aminomethyl) pyridine (0.34 g, 3.16 mmol) and dimethyl carbonate (14.02 g, 155.6 mmol) and the mixture was heated to 100 ^{0}C (16 hrs) with an inert environment. The reaction mixture was cooled to room temperature, acetone was added and the catalyst filtered under suction. The solvent was removed under reduced pressure to give a thick dark red liquid (0.31 g). Proton NMR spectroscopy does not show evidence of the desired product. Instead it showed the product to be starting material.

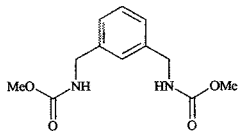
Attempt 4

Toluenesulfonic acid monohydrate (0.20 g, 1.05 mmol) was added to a stirring mixture of 2-(aminomethyl) pyridine (0.34 g, 3.16 mmol) and dimethyl carbonate (14.02 g, 155.6 mmol) and the mixture was heated to 100 ^{0}C (16 hrs) with an inert environment. The reaction mixture was cooled to room temperature, washed with sodium hydroxide and the precipitate filtered under suction. The solvent was removed under reduced pressure to give **3.11** as a thick dark red liquid (0.10 g, 19 %). E.S.M.S. for $C_8H_{10}N_2O_2$. Calculated mass of molecular ion: 167 $(M+H)^+$; Measured mass: 167 $(M+H)^+$. There is no data reported in the literature for this compound.

Attempt 5

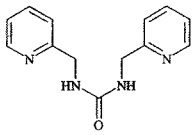
Ytterbium (III) trifluoromethanesulfonate hydrate (0.03 g, 0.05 mmol) was added to a stirring mixture of 2-(aminomethyl) pyridine (0.11 g, 1.00 mmol) and dimethyl carbonate (0.45 g, 5.00 mmol) and heated to 80 ^{0}C (8 hrs). The reaction mixture was cooled to room temperature, dichloromethane (2 ml) was added and the catalyst filtered under suction. The filtrate was diluted with dichloromethane (20 ml), washed with water, dried (Na_2SO_4) and the solvent was removed under reduced pressure to give **3.11** as red crystals (0.08 g, 48 %). E.S.M.S. for $C_8H_{10}N_2O_2$. Calculated mass of molecular ion: 167 $(M+H)^+$; Measured mass: 167 $(M+H)^+$. There is no data reported in the literature for this compound.

_N,N'_-m-Xylylene-bis-carbamic acid dimethyl ester 3.12

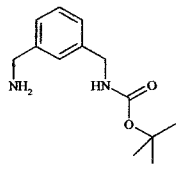


Aluminium oxide active (0.45 g) was added to a stirring mixture of 3-(aminomethyl)-benzylamine (0.57 g, 4.16 mmol) and dimethyl carbonate (0.28M, 15 mls) and heated under reflux (60 hrs). 3-(aminomethyl)-benzylamine (0.57 g, 4.16 mmol) was added and heating under reflux continued (16 hrs). 3-(aminomethyl)-benzylamine (0.57 g, 4.16 mmol) and aluminium oxide active (0.45 g) was added and again heating under reflux continued (16 hrs).The mixture was filtered through celite under suction and the DMC removed under reduced pressure to give a yellow liquid (3.05 g, 97 %). The proton NMR spectral data suggested a mixture of compound **3.12**, the cyclotrimer and other oligomers. δ_H (compound **3.12**) (DMSO) 7.71 (t, 2H, J=6 Hz, -*NH*-), 7.26 (t, 1H, J=7 Hz, Ph-*H*), 7.12 (m, 3H, Ph-*H*), 4.16 (d, 4H, J=6 Hz, -CH_2-), 3.54 (s, 6H, -CH_3) ppm. E.S.M.S. for $C_{12}H_{16}N_2O_4$. Calculated mass of molecular ion: 251 $(M-H)^-$; Measured mass: 251 $(M-H)^-$. The proton NMR spectral data is consistent with that found in the literature[91].

Attempted synthesis of 1,3-bis-pyridin-2-ylmethyl-urea 3.14

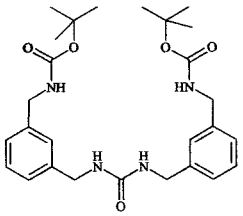


A mixture of 2-(aminomethyl) pyridine (0.11 g, 1 mmol) and diisoproylethylamine (DIEA, 0.28 g, 2.2 mmol) in dichloromethane (3.5 ml) was slowly added over a 30 minute period to a stirring solution of triphosgene (0.11 g, 0.37 mmol) in dichloromethane (2 ml) and the mixture was left stirring (5 mins). A solution of 2-(aminomethyl) pyridine (0.11 g, 1 mmol) and DIEA (0.28 g, 2.2 mmol) in dichloromethane (2 ml) was added in one portion and stirring continued (10 mins). The mixture was diluted with ethyl acetate, washed with 5% aqueous sodium hydrogen carbonate, brine and water. The organic layer was dried ($MgSO_4$) and the solvent removed under reduced pressure to give a brown/orange liquid (0.04 g). Proton NMR and E.S.M.S. spectroscopy does not show evidence of the desired product.



Mono-Boc-1,3-bis(aminomethyl) benzene 3.15

A solution of di-tert-butyl dicarbonate (1.55 g, 7.14 mmol) in chloroform (4 ml) was added dropwise to a stirring solution of 3-(aminomethyl)-benzylamine (2.44 g, 17.9 mmol) in methanol (100 ml) and the mixture was left stirring (24 hrs). The solvent was removed under reduced pressure. Water (50 ml) was added to the residue and extracted with dichloromethane (2 x 100 ml). The organic extracts were combined, dried (Na_2SO_4) and the solvent removed under reduced pressure. Purification by flash column chromatography using ethyl acetate/methanol (80/20) gave **3.15** as a pale yellow liquid (1.24g, 29 %). δ_H ($CDCl_3$) 7.21 (m, 4H, Ph-*H*), 5.30 (br, 1H, -*NH*-), 4.29 (d, 2H, J=6 Hz, amide -CH_2-), 3.82 (s, 2H, amine -CH_2-), 1.45 (s, 9H, -CH_3) ppm. δ_C ($CDCl_3$) 156.2 (CO), 143.5 (C), 139.5 (C), 128.6 (C), 126.0 (C), 125.8 (C), 125.7 (C), 79.0 (C), 53.6 (C), 46.2 (CH_2), 44.4 (CH_2), 28.4 (CH_3) ppm. ν_{max} / cm^{-1}3352 (N-H), 2975 (Ph-H), 1687 (C=O), 1161 (C-O). E.S.M.S. for $C_{13}H_{20}N_2O_2$. Calculated mass of molecular ion: 237 $(M+H)^+$; Measured mass: 237 $(M+H)^+$. The proton NMR spectral data is consistent with that found in the literature[92].



(3-{3-[3-(tert-Butoxycarbonylamino-methyl)-benzyl]-ureidomethyl}-benzyl)-carbamic acid tert-butyl ester 3.16

Attempt 1

A solution of triphosgene (0.15g, 0.51 mmol) in chloroform (1.5 ml) was added dropwise to a stirring solution of **3.15** (0.24 g, 1.02 mmol) in dry chloroform (13 ml) and triethylamine (0.44 g) and the mixture was left stirring (16 hrs) with a small amount of DMAP (0.02 g) with a calcium chloride tube attached. The mixture was washed with acetic acid (4M, 3 x 15 ml), saturated sodium hydrogen carbonate solution and brine. The organic layer was dried ($MgSO_4$) and the solvent removed under reduced pressure to give yellow crystals (0.24 g, 47 %). The proton NMR spectral data suggested a mixture of compound **3.16** and starting material. δ_H (compound **3.16**) (DMSO) 7.40 (br t, 2H, -*NH*-), 7.19 (m, 8H, Ph-*H*), 6.43 (t, 2H, J=6 Hz, -*NH*-), 4.21 (m, 4H, -CH_2-), 4.10

(d, 4H, J=6 Hz, -*CH*$_2$-), 1.39 (s, 18H, -*CH*$_3$) ppm. E.S.M.S. for $C_{12}H_{16}N_2O_4$. Calculated mass of molecular ion: 251 $(M-H)^-$; Measured mass: 251 $(M-H)^-$. There is no data reported in the literature for this compound.

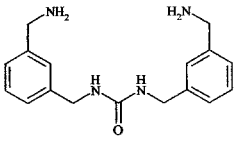
Attempt 2

A solution of triphosgene (0.2 g, 0.68 mmol) in chloroform (2 ml) was added dropwise to a stirring solution of **3.15** (0.32 g, 1.36 mmol) in dry chloroform (18 ml). A catalytic amount of DMAP (0.01 g) was added and the mixture heated under reflux (16 hr) with a calcium chloride tube attached. The reaction mixture was washed with acetic acid (4M, 3 x 15 ml), saturated sodium hydrogen carbonate solution and brine. The organic layer was dried ($MgSO_4$) and the solvent removed under reduced pressure to give **3.16** as orange crystals (0.27 g, 40 %) m. p. 156-158 ^{0}C. δ_H (DMSO) 7.40 (br t, 2H, -*NH*-), 7.20 (m, 8H, Ph-*H*), 6.42 (br t, 2H, -*NH*-), 4.21 (d, 4H, J=5 Hz, -*CH*$_2$-), 4.10 (d, 4H, J=6 Hz, -*CH*$_2$-), 1.39 (s, 18H, -*CH*$_3$) ppm. δ_C (DMSO) 158.9 (CO), 156.2 (CO), 140.1 (C), 139.2 (C), 129.0 (C), 126.7 (C), 126.3 (C), 126.0 (C), 79.5 (C), 44.3 (C), 44.0 (CH_2), 43.5 (CH_2), 28.3 (CH_3) ppm. ν_{max} / cm^{-1} 3339 (NH), 1687 (C=O), 1161 (C-O). E.S.M.S. for $C_{27}H_{38}N_4O_5$. Calculated mass of molecular ion: 521 $(M+Na)^+$; Measured mass: 521 $(M+Na)^+$. There is no data reported in the literature for this compound.

Attempt 3

Triphosgene (0.21g, 0.69 mmol) was added to a stirring solution of **3.15** (0.15 g, 0.69 mmol) in dichloromethane (5 ml) and was left stirring (64 hrs). **3.15** (0.15 g, 0.69 mmol) was added and the mixture was again left stirring (16 hrs). The solvent was removed under reduced pressure to give **3.16** as a yellow solid (0.01 g, 1 %). E.S.M.S. for $C_{27}H_{38}N_4O_5$. Calculated mass of molecular ion: 521 $(M+Na)^+$; Measured mass: 521 $(M+Na)^+$. There is no data reported in the literature for this compound.

1,3-Bis-(3-aminomethyl-benzyl)-urea 3.17



Attempt 1

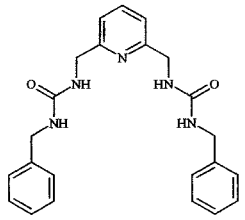
Acetic acid (2M, 20 ml) and hydrochloric acid (1M, 20 ml) were added to a solution of **3.16** (0.32 g, 0.64 mmol) in dichloromethane (10 ml) and the mixture was stirred

vigorously (9 days). After 2 days TLC showed a slow reaction so conc. HCl (1 ml) was added and stirring continued. The mixture was washed with water and the combined aqueous layer was made basic using sodium hydroxide (2M, 50 ml). This was washed with dichloromethane and the combined organic extracts were washed, dried ($MgSO_4$) and the solvent removed under reduced pressure. Proton NMR and E.S.M.S. spectroscopy does not show evidence of the desired product. Instead the proton NMR data was consistent with that of 3-(aminomethyl)-benzylamine.

Attempt 2

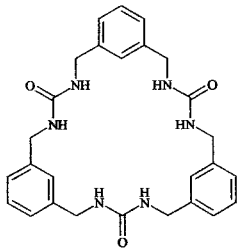
Compound **3.16** (0.24 g, 0.48 mmol) was dissolved in trifluoroacetic acid (TFA, 5 ml) and the mixture left stirring (16 hrs). Methanol (30 ml) was added and the TFA was removed by distillation and the solvent removed under reduced pressure to give **3.17** as a brown oil (0.19 g, 133 %). δ_H (DMSO) 8.33 (br, 4H, -*NH*$_2$), 7.32 (m, 8H, Ph-*H*), 6.68 (br, 2H, -*NH*-), 4.23 (s, 4H, -*CH*$_2$-), 4.00 (m, 4H, -*CH*$_2$-) ppm. E.S.M.S. for $C_{17}H_{22}N_4O_1$. Calculated mass of molecular ion: 299 $(M+H)^+$; Measured mass: 299 $(M+H)^+$. There is no data reported in the literature for this compound.

1-Benzyl-3-[6-(3-benzyl-ureidomethyl)-pyridin-2-ylmethyl]-urea 3.18



Benzyl isocyanate (0.32 g, 2.39 mmol) was added to a mixture of **2.27** (0.25 g, 1.20 mmol) and triethylamine (0.36 g, 3.59 mmol) in methanol (25 ml) and the mixture was stirred (16 hrs) with a calcium chloride tube attached. The precipitate was filtered under suction and oven dried to give **3.18** as a grey solid (0.28 g, 19 %) m. p. 236-238 ^{0}C. δ_H (DMSO) 7.70 (t, 1H, J=8 Hz, Py-*H*), 7.25 (m, 12H, Ph-*H*), 6.64 (br, 4H, -*NH*-), 4.28 (d, 4H, J=6 Hz, -*CH*$_2$-), 4.21 (d, 4H, J=6 Hz, -*CH*$_2$-) ppm. δ_C 159.65 (CO), 158.64 (C), 141.42 (C), 137.73 (C), 128.78 (C), 127.57 (C), 127.12 (C), 119.26 (C), 43.05 (CH_2), 45.56 (CH_2) ppm. ν_{max} / cm^{-1} 3294 (N-H), 2926 (Ph-H), 1573 (C=O), 1247 (C-N). E.S.M.S. for $C_{23}H_{25}N_5O_2$. Calculated mass of molecular ion: 404 $(M+H)^+$; Measured mass: 404 $(M+H)^+$. There is no data reported in the literature for this compound.

Xylylene cyclic tris(urea) 3.19



Attempt 1

Triphosgene (0.31 g, 1 mmol) was added to a stirring solution of 3-(aminomethyl)-benzylamine (0.14 g, 1 mmol) in dry dichloromethane (3 ml) and the mixture was left stirring (16 hrs). The resultant precipitate was filtered under suction to give yellow crystals (0.28 g, 58 %). The E.S.M.S. data suggested a mixture of compound **3.19**, starting material and the bis-urea product. E.S.M.S. for $C_{27}H_{30}N_6O_3$. Calculated mass of molecular ion: 487 $(M+H)^+$; Measured mass: 487 $(M+H)^+$. There is no data reported in the literature for this compound.

Attempt 2

Triphosgene (0.31 g, 1 mmol) was added to a stirring solution of 3-(aminomethyl)-benzylamine (0.14 g, 1 mmol) in dry chloroform (3 ml) and the mixture was left stirring (16 hrs). The precipitate was filtered under suction to give white crystals (0.33 g, 68 %). The E.S.M.S. data suggested a mixture of compound **3.19**, starting material and the bis-urea product. E.S.M.S. for $C_{27}H_{30}N_6O_3$. Calculated mass of molecular ion: 487 $(M+H)^+$; Measured mass: 487 $(M+H)^+$. There is no data reported in the literature for this compound.

Attempt 3

Triphosgene (0.31 g, 1 mmol) was added to a stirring mixture of 3-(aminomethyl)-benzylamine (0.14 g, 1 mmol) and tetrabutylammonium nitrate (0.31 g, 1 mmol) in dry dichloromethane (3 ml) and the mixture was left stirring (16 hrs). The resultant precipitate was filtered under suction to give yellow crystals (0.55 g). E.S.M.S. spectroscopy does not show evidence of the desired product. Instead it showed the product to be a mixture of starting material, the mono-urea product and the bis-urea product.

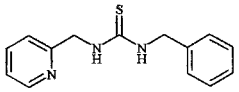
Attempt 4

Triphosgene (0.31 g, 1 mmol) was added to a stirring mixture of 3-(aminomethyl)-benzylamine (0.14 g, 1 mmol) and tetrabutylammonium nitrate (0.31 g, 1 mmol) in dry

chloroform (3 ml) and the mixture was left stirring (16 hrs). The resultant precipitate was filtered under suction to give white crystals (0.54 g). E.S.M.S. spectroscopy does not show evidence of the desired product. Instead it showed the product to be a mixture of starting material, the mono-urea product and the bis-urea product.

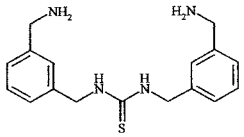
4.3.1.2 Thiourea receptors

1-Benzyl-3-pyridin-2-ylmethyl-thiourea 3.21



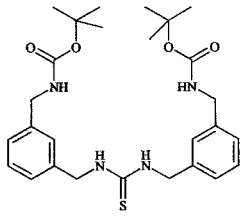
Benzylamine (0.15 g, 1.40 mmol) was added to a solution of 1,1-thiocarbonylimidazole (0.25 g, 1.40 mmol) in dichloromethane (25 ml) and the mixture was stirred (2 hrs). 2-(aminomethyl) pyridine (0.15 g, 1.40 mmol) was added and stirring continued (16 hrs) with a calcium chloride tube attached. The reaction mixture was poured into water and extracted with dichloromethane. The organic layer was washed with water, dried ($MgSO_4$) and the solvent removed under reduced pressure. Purification by flash column chromatography using dichloromethane gave **3.21** as a green solid (0.19 g, 53 %) m. p. 84-86 ^{0}C (Lit., 118 ^{0}C)[93]. δ_H ($CDCl_3$) 8.38 (d, 1H, J=4 Hz, Py-*H*), 7.68 (td, 1H, J=2 and 6 Hz, Py-*H*), 7.28 (m, 9H, -*NH*-, Py-*H* and Ph-*H*), 4.70 (s, 4H, -CH_2-) ppm. ν_{max} / cm^{-1} 2920 (N-H). E.S.M.S. for $C_{14}H_{15}N_3S_1$. Calculated mass of molecular ion: 256 $(M-H)^-$; Measured mass: 256 $(M-H)^-$. The proton NMR spectral data is consistent with that found in the literature[93].

Attempted synthesis of 1,3-bis-(3-aminomethyl-benzyl)-thiourea 3.23



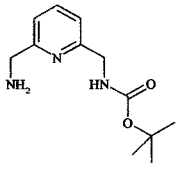
A solution of 1,1-thiocarbonylimidazole (0.33 g, 1.84 mmol) in chloroform (5 ml) was slowly added to a stirring solution of 3-(aminomethyl) benzylamine (0.25 g, 1.84 mmol) in chloroform (5 ml) and the mixture was left stirring (16 hr) with a calcium chloride tube attached. A solution of 3-(aminomethyl) benzylamine (0.25 g, 1.84 mmol) in chloroform (5 ml) was added and stirring continued (16 hrs). The mixture was washed with dilute HCl, dried ($MgSO_4$) and the solvent removed under reduced pressure to give

yellow crystals (0.83 g). Proton NMR and E.S.M.S. spectroscopy does not show evidence of the desired product. Instead it showed the product to be a mixture of starting material and the cyclotrimer product.



(3-{3-[3-(tert-Butoxycarbonylamino-methyl)-benzyl]-thioureidomethyl}-benzyl)-carbamic acid tert-butyl ester 3.24

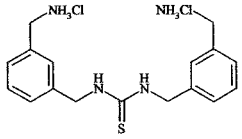
Compound **3.15** (0.25 g, 1.06 mmol) was dissolved in dichloromethane (10 ml). Half the solution was added to a stirring solution of 1,1-thiocarbonylimidazole (0.09 g, 0.53 mmol) and the mixture was left stirring (3 hrs). The remaining **3.15** solution was added and stirring continued (16 hrs). The reaction mixture was washed with water, dried ($MgSO_4$) and the solvent removed under reduced pressure. Purification by flash column chromatography using dichloromethane/methanol (97.5/2.5) gave **3.24** as yellow crystals (0.18 g, 33 %) m. p. 158-160 ^{0}C (Lit., 137-138 ^{0}C)[94]. δ_H ($CDCl_3$) 7.27 (t, 2H, J=6 Hz, *meta* Ph-*H*), 7.15 (d, 4H, J=7 Hz, *ortho* Ph-*H*), 7.07 (s, 2H, *ortho* Ph-*H*), 6.62 (br, 2H, -*NH*-), 5.08 (br, 2H, -*NH*-), 4.61 (d, 4H, J=4 Hz, -CH_2-), 4.15 (d, 4H, J=6 Hz, -CH_2-), 1.40 (s, 18H, -CH_3) ppm. ν_{max} / cm^{-1} 3322 (N-H), 2920 (Ph-H), 1684 (C=O), 1524 (C=O), 1160 (C-O). E.S.M.S. for $C_{27}H_{38}N_4O_4S$. Calculated mass of molecular ion: 515 $(M+H)^+$; Measured mass: 515 $(M+H)^+$. The proton NMR spectral data are consistent with that found in the literature[94].



Attempted synthesis of (6-aminomethyl-pyridin-2-ylmethyl)-carbamic acid tert-butyl ester 3.25

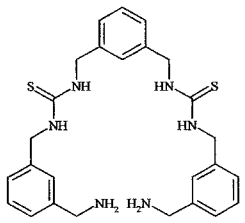
A solution of di-tert-butyl dicarbonate (0.50 g, 2.29 mmol) in chloroform (2 ml) was added dropwise to a stirring solution of **2.27** (1.20 g, 5.74 mmol) in methanol (50 ml) and the mixture was left stirring (16 hrs). The solvent was removed under reduced pressure. Water (50 ml) was added to the residue and extracted with dichloromethane (2 x 100 ml). The organic extracts were combined, dried (Na_2SO_4) and the solvent removed under reduced pressure to give an orange liquid (0.22 g). Proton NMR spectroscopy does not show evidence of the desired product. Instead it showed the product to be starting material.

1,3-Bis-(3-aminomethyl-benzyl)-thiourea hydrochloride salt 3.27



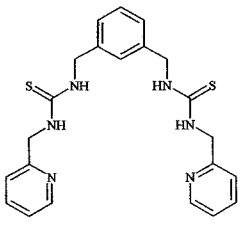
Compound **3.24** (0.05 g, 0.10 mmol) was dissolved in c.HCl saturated ethyl acetate (5 ml) and the solution was left stirring (10 mins). The solvent was removed under reduced pressure to give **3.27** as white crystals (0.05 g, 130 %) m. p. 238-240 ^{0}C. δ_H (DMSO) 8.50 (br, 6H, -*NH*-), 7.31 (m, 10H, Ph-*H*), 4.70 (br s, 4H, -CH_2-), 3.97 (d, 4H, J=5 Hz, -CH_2-) ppm. E.S.M.S. for $C_{17}H_{22}N_4S$ (without salt). Calculated mass of molecular ion: 315 $(M+H)^+$; Measured mass: 315 $(M+H)^+$. There is no data reported in the literature for this compound.

Attempted synthesis of 1-(3-aminomethyl-benzyl)-3-{3-[3-(3-aminomethyl-benzyl)-thioureidomethyl]-benzyl}-thiourea 3.28



A solution of 1,1-thiocarbonylimidazole (1.31 g, 7.34 mmol) in dichloromethane (10 ml) was slowly added to a stirring solution of 3-(aminomethyl) benzylamine (0.50 g, 3.67 mmol) in dichloromethane (5 ml) and the mixture was left stirring (16 hr) with a calcium chloride tube attached. 3-(aminomethyl) benzylamine (1.0 g, 7.34 mmol) was added and stirring continued (48 hrs). The mixture was washed with dilute HCl, dried ($MgSO_4$) and the solvent removed under reduced pressure to give cream crystals (1.40 g). Proton NMR and E.S.M.S. spectroscopy does not show evidence of the desired product.

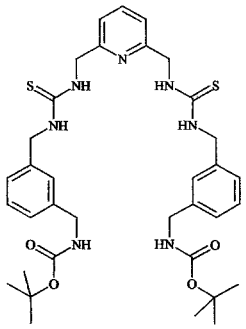
Attempted synthesis of 1-pyridin-2-ylmethyl-3-[3-(3-pyridin-2-ylmethyl-thioureidomethyl)-benzyl]-thiourea 3.29



A solution of 1,1-thioarbonylimidazole (0.66g, 3.84 mmol) in chloroform (5 ml) was added to a stirring solution of 3-(aminomethyl) benzylamine (0.25 g, 1.84 mmol) in chloroform (5 ml) and the mixture was left stirring (16 hrs) with a calcium chloride tube attached. 2-(aminomethyl) pyridine (0.50 g, 4.63 mmol) was added and stirring continued (16 hrs). The solvent was removed under reduced pressure and the residue

dried under suction (0.12 g). Proton NMR spectroscopy does not show evidence of the desired product.

Attempted synthesis of (3-{3-[6-(3-{3-[(2-hydroxy-3,3-dimethyl-butyrylamino)-methyl]-benzyl}-thioureidomethyl)-pyridin-2-ylmethyl]-thioureidomethyl}-benzyl)-carbamic acid tert-butyl ester 3.30



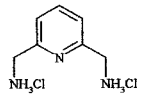
Attempt 1

Compound **2.27** (0.25 g, 1.20 mmol) was dissolved in methanol (100 ml) and left stirring (16 hrs) with a calcium chloride tube attached. Triethylamine (0.24 g, 2.40 mmol) was added and stirring continued (1 hr). 1,1-thiocarbonylimidazole (0.43 g, 2.40 mmol) was added and again stirring continued (1 hr). **3.15** (0.60 g, 2.40 mmol) was added to the mixture and stirring continued (16 hrs). The solvent was removed under reduced pressure. Dichloromethane was added and the precipitate was filtered under suction. The filtrate was washed with water, dried ($MgSO_4$) and the solvent removed under reduced pressure (0.32 g). Proton NMR spectroscopy does not show evidence of the desired product. Instead it showed the product to be a mixture of starting material and the mono-thiourea product.

Attempt 2

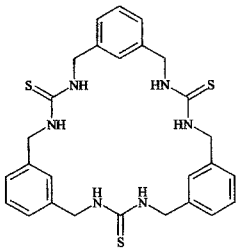
Compound **3.31** (0.10 g, 0.48 mmol) was dissolved in methanol (5 ml) and left stirring (1 hrs) with a calcium chloride tube attached. Triethylamine (0.10 g) was added and the stirring solution was heated to 75 ^{0}C (1 hr). 1,1-thiocarbonylimidazole (0.17 g, 0.99 mmol) in methanol (3 ml) was added and heating continued (2 hr). **3.15** (0.24 g, 1.02 mmol) in methanol (2 ml) was added and again heating continued (16 hrs). The solvent was removed under reduced pressure (0.48 g). E.S.M.S. spectroscopy does not show evidence of the desired product.

2,6-Diethyl-pyridine hydrochloride salt 3.31



Borane tetrahydrofuran complex (25 ml, 1M, 25 mmol) was added to a solution of pyridine-2,6-dinitrile (0.26 g, 2.0 mmol) in dry THF (10 ml) and the mixture was stirred (16 hrs) with an inert environment. Methanol was carefully added to destroy the excess borane and the solvent was removed under reduced pressure. Recrystallisation from ethanoic HCl (30 ml) gave **3.31** as white crystals (0.29 g, 69 %) m. p. >300 ^{0}C. δ_H (DMSO) 8.77 (br s, 6H, -*NH*$_3$-), 7.90 (t, 1H, J=8 Hz, Py-*H*), 7.47 (d, 2H, Py-*H*), 4.20 (d, 4H, -*CH*$_2$-) ppm. δ_C (DMSO) 165.9 (C),149.6 (C), 139.7 (C), 128.5 (C), 124.7 (C), 62.1 (CH_2) ppm. ν_{max} / cm^{-1} 3045 (NH_3). E.S.M.S. for $C_7H_{13}N_3Cl_2$. Calculated mass of molecular ion: 210 $(M+H)^+$; Measured mass: 210 $(M+H)^+$. There is no data reported in the literature for this compound

Xylylene cyclic tris(thiourea) 3.32



Attempt 1

Triethylamine (0.05 ml, 0.52 mmol) was added to a solution of **3.27** (0.10 g, 0.26 mmol) in methanol (5 ml) and the mixture was stirred (30 mins). A solution of 1,1-thiocarbonylimidazole (0.09 g, 0.52 mmol) in methanol (3 ml) and a solution of 3-(aminomethyl) benzylamine (0.04 g, 0.26 mmol) in methanol (3 ml) were added and stirring continued (112 hrs) with a calcium chloride tube attached. The solvent was removed under reduced pressure to give a red liquid (0.26 g, 187 %). The E.S.M.S data suggested a mixture containing compound **3.32**. E.S.M.S. for $C_{27}H_{30}N_6S_3$. Calculated mass of molecular ion: 533 $(M-H)^-$; Measured mass: 533 $(M-H)^-$.

Attempt 2

Triethylamine (0.05 ml, 0.52 mmol) was added to a solution of **3.27** (0.10 g, 0.26 mmol) in methanol (5 ml) and the mixture was stirred (30 mins). A solution of 1,1-thiocarbonylimidazole (0.09 g, 0.52 mmol) in methanol (3 ml), a solution of 3-(aminomethyl) benzylamine (0.04 g, 0.26 mmol) in methanol (3 ml) and tetrabutylammonium nitrate (0.03 g, 0.10 mmol) were added and stirring continued (112 hrs) with a calcium chloride tube attached. The solvent was removed under reduced

pressure to give **3.32** as a thick red liquid (0.02 g, 14 %). E.S.M.S. for $C_{27}H_{30}N_6S_3$. Calculated mass of molecular ion: 533 $(M-H)^-$; Measured mass: 533 $(M-H)^-$.

Attempt 3

A solution of 1,1-thiocarbonylimidazole (0.33 g, 1.83 mmol) in methanol (5 ml) was added to a solution of 3-(aminomethyl) benzylamine (0.25 g, 1.83 mmol) and tetrabutylammonium nitrate (0.56 g, 1.83 mmol) and a couple of drops of triethylamine in methanol (3 ml) and the mixture was stirred (88 hrs) with a calcium chloride tube attached. The solvent was removed under reduced pressure to give **3.32** as a thick orange liquid (1.10 g). Proton NMR and E.S.M.S. spectroscopy does not show evidence of the desired product. Instead they showed the product to be a mixture of the bis-thiourea product and starting material.

Attempt 4

A solution of 1,1-thiocarbonylimidazole (0.66 g, 3.66 mmol) in methanol (5 ml) was added to a solution of 3-(aminomethyl) benzylamine (0.25 g, 1.83 mmol) and a couple of drops of triethylamine in methanol (3 ml) and the mixture was stirred (2 hrs) with a calcium chloride tube attached. 3-(aminomethyl) benzylamine (0.50 g, 3.66 mmol) was added and stirring continued (2 hrs). A solution of tetrabutylammonium nitrate (0.56 g, 1.83 mmol) in methanol (2 ml) was added and stirring continued (30 mins). A solution of 1,1-thiocarbonylimidazole (0.33 g, 1.83 mmol) in methanol (5 ml) was added and again stirring continued (16 hrs). The solvent was removed under reduced pressure to give a thick yellow liquid (2.34 g). Proton NMR and E.S.M.S. spectroscopy does not show evidence of the desired product. Instead they showed the product to be a mixture of the bis-thiourea product and starting material.

Attempt 5

A solution of 1,1-thiocarbenylimidazole (0.65 g, 3.67 mmol) in dichloromethane (15 ml) was added to a stirring solution of 3-(aminomethyl)-benzylamine (0.50 g, 3.67 mmol) and TBA nitrate (0.45 g, 3.67 mmol) in dichloromethane (10 ml) and the mixture was left stirring (16 hrs) with a calcium chloride tube attached. The precipitate was filtered under suction and washed with water to give **3.32** as white crystals (0.46 g, 23 %) m. p. >300 ^{0}C (Lit., 250 ^{0}C)[94]. δ_H (DMSO) 7.97 (br s, 6H, -*NH*-), 7.27 (m, 12H, Ph-*H*), 4.67 (br s, 12H, -CH_2-) ppm. ν_{max} / cm^{-1} 3225 (N-H), 3068 (Ph-H). E.S.M.S. for

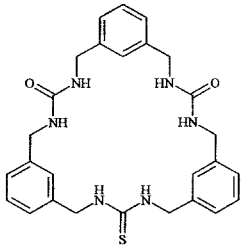
$C_{27}H_{30}N_7O_3S_3$. Calculated mass of molecular ion: 596 $(M+NO_3)^-$; Measured mass: 596 $(M+NO_3)^-$.

Attempt 6

A solution of 1,1-thiocarbonylimidazole (0.33 g, 1.84 mmol) in chloroform (5 ml) was slowly added to a stirring solution of 3-(aminomethyl) benzylamine (0.25 g, 1.84 mmol) and tetrabutylammonium chloride (0.51 g, 1.84 mmol) in chloroform (5 ml) and the mixture was left stirring (184 hr) with a calcium chloride tube attached. The solvent was removed under reduced pressure to give a thick yellow liquid (1.03 g). Proton NMR and E.S.M.S. spectroscopy does not show evidence of the desired product. Instead they showed the product to be the bis-thiourea product.

Attempt 7

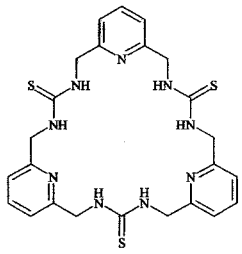
A solution of 1,1-thiocarbonylimidazole (0.39 g, 2.20 mmol) in dichloromethane (10 ml) was added to a stirring solution of 3-(aminomethyl)-benzylamine (0.15 g, 1.10 mmol) in dichloromethane (5 ml) and the mixture was stirred (2 hrs). A solution of 3-(aminomethyl)-benzylamine (0.30 g, 2.20 mmol) in dichloromethane (5 ml) was added to the mixture and stirring continued (2 hrs). Methanol (50 ml) was added to dissolve the precipitate and a solution of 1,1-thiocarbonylimidazole (0.20 g, 1.10 mmol) in methanol (5 ml) was added and the mixture was stirred (16 hrs). The precipitate was filtered under suction to give **3.32** as white crystals (0.30 g, 17 %) m. p. >300 ^{0}C (Lit., 250 ^{0}C)[94]. δ_H (DMSO) 8.01 (br s, 6H, -*NH*-), 7.18 (m, 12H, Ph-*H*), 4.66 (br s, 12H, -*CH*$_2$-) ppm. ν_{max} / cm^{-1} 3045 (N-H). E.S.M.S. for $C_{27}H_{30}N_7O_3S_3$. Calculated mass of molecular ion: 569 $(M+Cl)^-$ and 596 $(M+NO_3)^-$; Measured mass: 569 $(M+Cl)^-$ and 596 $(M+NO_3)^-$.



Attempted synthesis of xylylene cyclic mono(thiourea) bis(urea) 3.33

Triethylamine (0.05 ml, 0.52 mmol) was added to a solution of **3.23** (0.10 g, 0.26 mmol) in methanol (5 ml) and the mixture was stirred (30 mins). A solution of xylylene diisocyanate (0.05 g, 0.26 mmol) in methanol (3 ml) was added and stirring continued

(112 hrs) with a calcium chloride tube attached. The solvent was removed under reduced pressure to give orange crystals (0.16 g). Proton NMR and E.S.M.S. spectroscopy does not show evidence of the desired product. Instead they showed the product to be starting material.



Pyridine cyclic tris(thiourea) 3.34

Attempt 1

A solution of 1,1-thiocarbonylimidazole (0.09 g, 0.48 mmol) in methanol (3 ml) was added to a solution of **3.31** (0.10 g, 0.48 mmol) and triethylamine (0.10 ml, 0.96mmol) in methanol (2 ml) and the mixture was stirred (160 hrs) with a calcium chloride tube attached. The solvent was removed under reduced pressure to give a dark red liquid (0.22 g). E.S.M.S. spectroscopy does not show evidence of the desired product. Instead they showed the product to be the bis-thiourea product.

Attempt 2

A solution of 1,1-thiocarbonylimidazole (0.21 g, 1.20 mmol) in methanol (10 ml) was added to a solution of **2.27** (0.25 g, 1.20 mmol), triethylamine (0.24 g, 2.40 mmol) and tetrabutylammonium nitrate (0.15 g, 0.48 mmol) in methanol (100 ml) and the mixture was stirred (16 hrs) with a calcium chloride tube attached. The solvent was removed under reduced pressure. Dichloromethane was added and the precipitate was filtered under suction to give **3.34** as a brown solid (0.03 g, 5 %) m. p. >300 ^{0}C. δ_H (DMSO) 8.58 (br, 6H, -*NH*-), 7.91 (t, 3H, J=8 Hz, Py-*H*), 7.46 (d, 6H, J=8 Hz, Py-*H*), 4.22 (s, 12H, -CH_2-) ppm. ν_{max} / cm^{-1} 2870 (N-H), 1515 (C=N), 1119 (C-N). E.S.M.S. for $C_{14}H_{15}N_3S_1$. Calculated mass of molecular ion: 281 $(M+3H)^+$; Measured mass: 281 $(M+3H)^+$. There is no data reported in the literature for this compound

Attempt 3

A solution of 1,1-thiocarbonylimidazole (0.17 g, 0.96 mmol) in methanol (3 ml) was added to a solution of **3.31** (0.10g, 0.48 mmol) in methanol (2 ml) and the mixture was heated under reflux (60 hrs). A solution of **3.31** (0.20 g, 0.96 mmol) in methanol (2 ml) was added to the mixture and heating under reflux continued (60 hrs). A solution of 1,1-thiocarbonylimidazole (0.09 g, 0.48 mmol) in methanol (2 ml) was added and again the

mixture was heated under reflux (60 hrs). The solvent was removed under reduced pressure to give a dark red liquid (0.30 g). E.S.M.S. spectroscopy does not show evidence of the desired product. Instead it showed the product to be starting material.

Attempt 4

A solution of 1,1-thiocarbonylimidazole (0.17 g, 0.96 mmol) in DMF (3 ml) was added to a solution of **3.31** (0.10g, 0.48 mmol) in DMF (5 ml) and the mixture was left stirring (40 hrs). **3.31** (0.20 g, 0.96 mmol) was added to the mixture and stirring continued (16 hrs). **3.31** (0.10 g, 0.48 mmol) was added and the mixture was heated under reflux (2 hrs) then stirred (16 hrs). A solution of 1,1-thiocarbonylimidazole (0.09 g, 0.48 mmol) in DMF (1 ml) was added and again the mixture was heated under reflux (16 hrs). The solvent was removed under reduced pressure to give black crystals (0.06 g). E.S.M.S. spectroscopy does not show evidence of the desired product. Instead it showed the product to be starting material.

Attempt 5

A solution of 1,1-thiocarbonylimidazole (0.17 g, 0.96 mmol) in DMF (3 ml) was added to a solution of **3.31** (0.10g, 0.48 mmol) in DMF (5 ml) and the mixture was heated under reflux (16 hrs). A solution of tetrabutylammonium nitrate (0.15 g, 0.48 mmol) in DMF (2 ml) and a solution of **3.31** (0.20 g, 0.96 mmol) in DMF (10 ml) was added to the mixture and heating continued (16 hrs). A solution of 1,1-thiocarbonylimidazole (0.09 g, 0.48 mmol) in DMF (2 ml) was added and again the mixture was heated under reflux (16 hrs). The solvent was removed under reduced pressure to give dark brown crystals (0.06 g). E.S.M.S. spectroscopy does not show evidence of the desired product. Instead it showed the product to be starting material.

Figure 4.50 - NMR Binding Study of Association between 3.16 and TBA chloride following NH-1

Solvent = Acetone
Stock solutions – [H] = 0.012 M [G] = 0.104 M
Initial volume of host = 500μL δH = 6.4939 ppm

μL of guest added	[G] added /M	Observed shift of NH /ppm	Change in shift relative to δH /ppm	Computer fit for change in shift /ppm
10	0.002039	6.5031	0.0092	0.0106
20	0.004000	6.5164	0.0225	0.0202
30	0.005887	6.5240	0.0301	0.0290
40	0.007704	6.5333	0.0394	0.0370
50	0.009455	6.5403	0.0464	0.0444
60	0.011143	6.5463	0.0524	0.0512
70	0.012772	6.5539	0.0600	0.0574
80	0.014345	6.5589	0.0650	0.0632
90	0.015864	6.5597	0.0658	0.0685
100	0.017333	6.5636	0.0697	0.0734
125	0.020800	6.5774	0.0835	0.0843
150	0.024000	6.5855	0.0916	0.0935
200	0.029714	6.5995	0.1056	0.1080
300	0.039000	6.6243	0.1304	0.1273

48 % saturation at end of titration
$K_a = 27\ M^{-1} \pm 10\ \%$ δHG = 6.7547 ppm

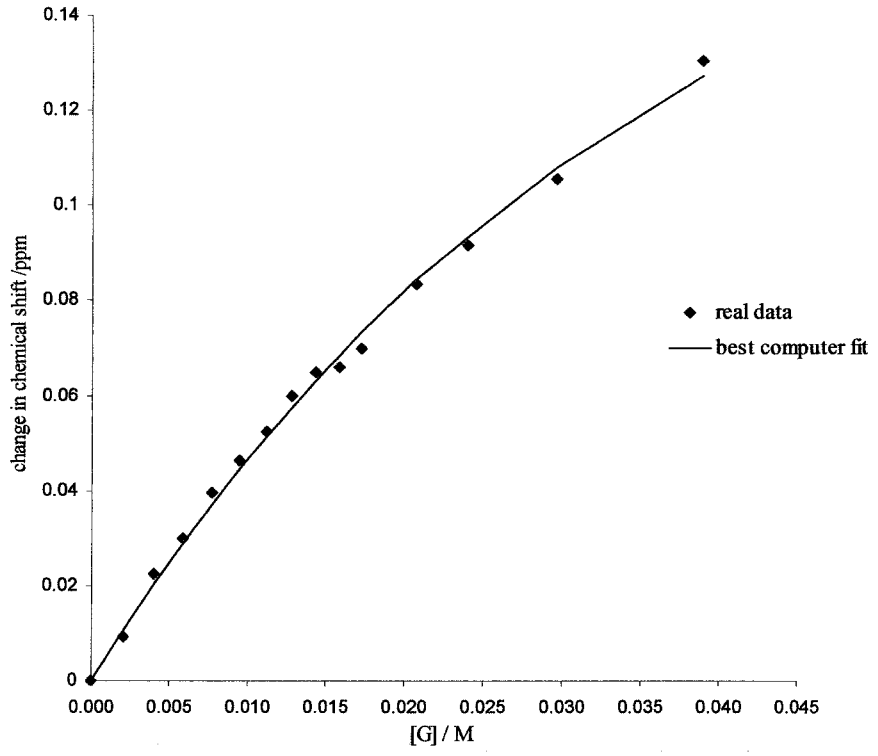


Figure 4.51 - NMR Binding Study of Association between 3.16 and TBA chloride following NH-2

Solvent = Acetone
Stock solutions – [H] = 0.012 M [G] = 0.104 M
Initial volume of host = 500μL δH = 6.0100 ppm

μL of guest added	[G] added /M	Observed shift of NH /ppm	Change in shift relative to δH /ppm	Computer fit for change in shift /ppm
10	0.002039	6.3551	0.3451	0.2862
20	0.004000	6.7296	0.7196	0.5588
30	0.005887	6.9700	0.9600	0.8111
60	0.011143	7.3829	1.3729	1.3602
70	0.012772	7.4617	1.4518	1.4625
80	0.014345	7.5231	1.5131	1.5347
90	0.015864	7.5383	1.5283	1.5859
100	0.017333	7.5737	1.5638	1.6231
125	0.020800	7.6559	1.6459	1.6809
150	0.024000	7.7049	1.6949	1.7133
200	0.029714	7.7650	1.7550	1.7476
300	0.039000	7.8249	1.8149	1.7761

98 % saturation at end of titration
K_a = 881 M^{-1} ± 5 % δHG = 7.8495 ppm

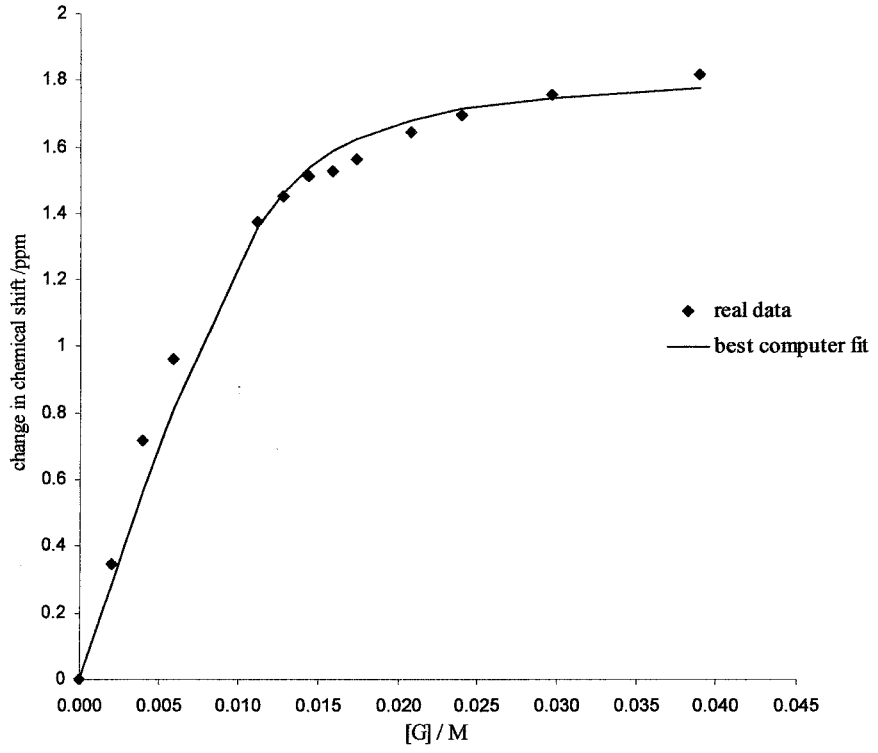


Figure 4.52 - NMR Binding Study of Association between 3.36 and TBA chloride following NH-1

Solvent = Acetonitrile
Stock solutions – [H] = 0.0045 M [G] = 0.051 M
Initial volume of host = 500μL δH = 8.3447 ppm

μL of guest added	[G] added /M	Observed shift of NH /ppm	Change in shift relative to δH /ppm	Computer fit for change in shift /ppm
10	0.001000	8.6604	0.3157	0.3787
20	0.001962	9.0761	0.7314	0.7162
30	0.002887	9.3702	1.0254	1.0020
35	0.003336	9.5403	1.1956	1.1235
40	0.003778	9.6514	1.3066	1.2306
45	0.004211	9.6404	1.2960	1.3240
50	0.004636	9.7899	1.4452	1.4049
55	0.005054	9.8451	1.5003	1.4745
60	0.005464	9.8211	1.4764	1.5343
65	0.005867	9.9300	1.5852	1.5858
75	0.006652	9.9988	1.6540	1.6684
100	0.008500	10.0261	1.6814	1.7987
150	0.011769	10.2139	1.8692	1.9172
200	0.014571	10.2839	1.9391	1.9702
250	0.017000	10.3368	1.9920	1.9999
300	0.019125	10.3726	2.0278	2.0187
400	0.022667	10.4309	2.0862	2.0413
500	0.025500	10.4681	2.1233	2.0543

99 % saturation at end of titration
K_a = 865 M^{-1} ± 12 % δHG = 10.4898 ppm

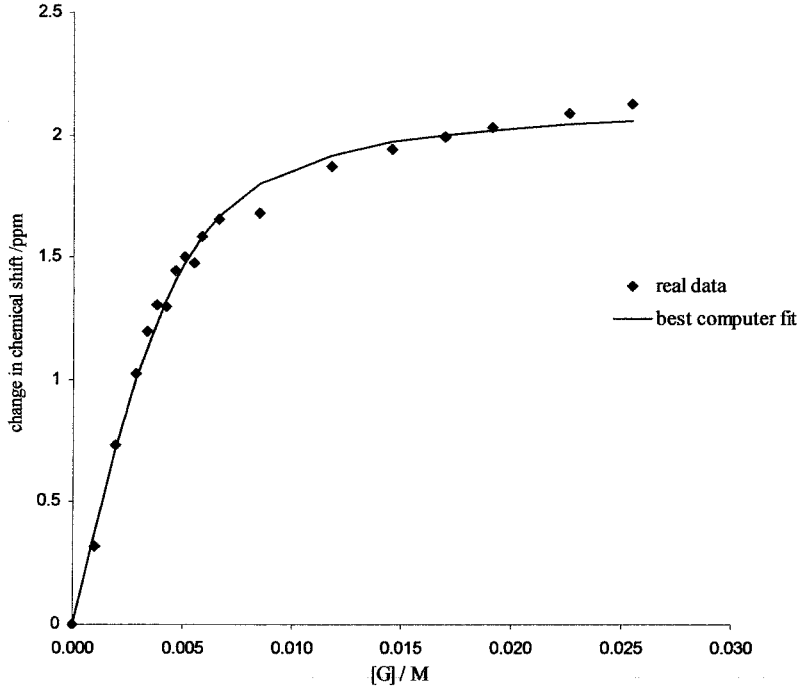


Figure 4.53 - NMR Binding Study of Association between 3.36 and TBA chloride following NH-2

Solvent = Acetonitrile
Stock solutions – [H] = 0.0045 M [G] = 0.051 M
Initial volume of host = 500μL δH = 7.1258 ppm

μL of guest added	[G] added /M	Observed shift of NH /ppm	Change in shift relative to δH /ppm	Computer fit for change in shift /ppm
20	0.001962	7.5764	0.4506	0.4698
30	0.002887	7.7776	0.6519	0.6545
35	0.003336	7.9191	0.7933	0.7338
40	0.003778	7.9936	0.8678	0.8047
45	0.004211	7.9598	0.8340	0.8678
50	0.004636	8.0957	0.9699	0.9237
55	0.005054	8.1336	1.0078	0.9731
60	0.005464	8.0989	0.9731	1.0167
65	0.005867	8.1944	1.0686	1.0553
75	0.006652	8.2454	1.1196	1.1198
100	0.008500	8.2541	1.1283	1.2292
150	0.011769	8.4220	1.2962	1.3390
200	0.014571	8.4864	1.3606	1.3917
250	0.017000	8.5364	1.4106	1.4223
300	0.019125	8.5690	1.4432	1.4420
400	0.022667	8.6274	1.5016	1.4661
500	0.025500	8.6646	1.5388	1.4801

96 % saturation at end of titration
K_a = 865 M^{-1} ± 5 % δHG = 8.7072 ppm

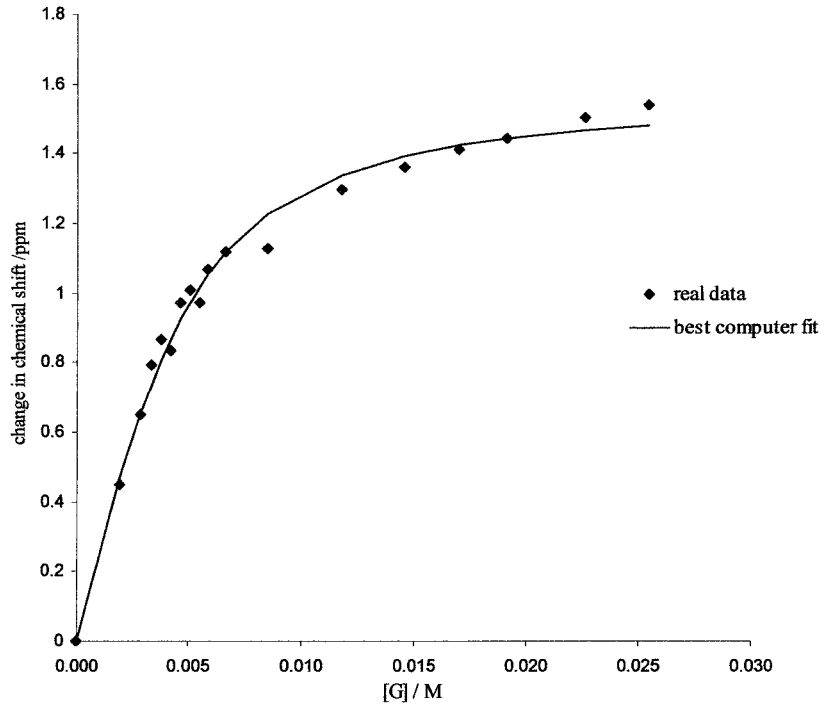


Figure 4.54 - NMR Binding Study of Association between 3.36 and TBA chloride following NH-1

Solvent = Acetonitrile
Stock solutions – [H] = 0.0052 M [G] = 0.0504 M
Initial volume of host = 500μL δH = 8.2687 ppm

μL of guest added	[G] added /M	Observed shift of NH /ppm	Change in shift relative to δH /ppm	Computer fit for change in shift /ppm
10	0.000988	8.6301	0.3614	0.3380
20	0.001938	8.9326	0.6639	0.6443
30	0.002853	9.2003	0.9316	0.9125
40	0.003733	9.4341	1.1654	1.1385
45	0.004161	9.5664	1.2977	1.2355
50	0.004582	9.6169	1.3482	1.3223
65	0.005798	9.7321	1.4634	1.5284
100	0.008400	9.9990	1.7303	1.7970
150	0.011631	10.2158	1.9471	1.9577
250	0.016800	10.3155	2.0468	2.0724
400	0.022400	10.4519	2.1832	2.1301

95 % saturation at end of titration
K_a = 595 M^{-1} ± 5 % δHG = 10.5411 ppm

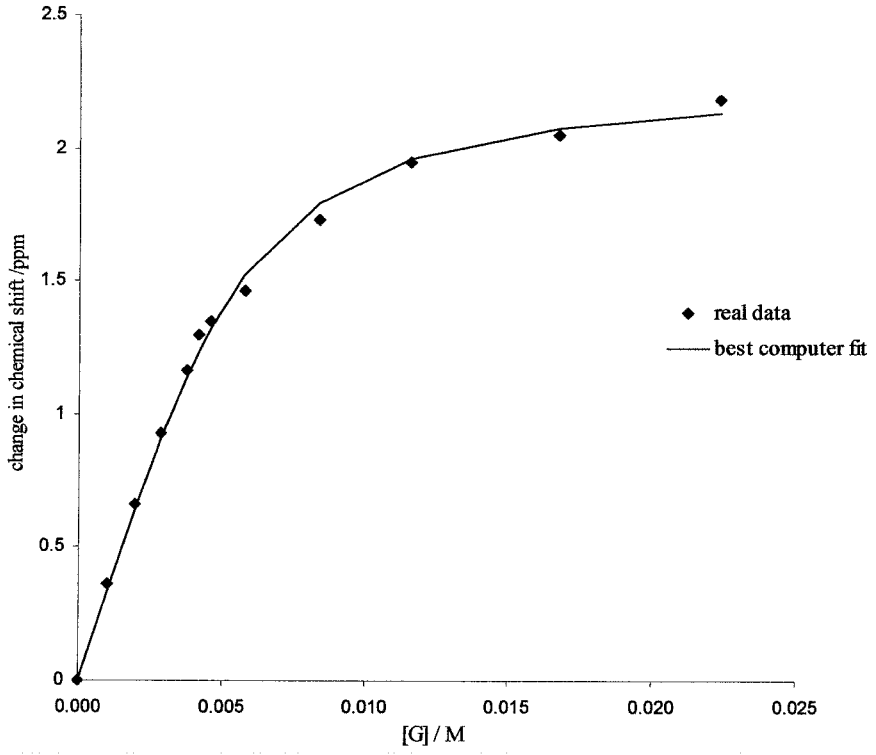


Figure 4.55 - NMR Binding Study of Association between 3.36 and TBA chloride following NH-2

Solvent = Acetonitrile
Stock solutions – [H] = 0.0052 M [G] = 0.0504 M
Initial volume of host = 500μL δH = 7.0462 ppm

μL of guest added	[G] added /M	Observed shift of NH /ppm	Change in shift relative to δH /ppm	Computer fit for change in shift /ppm
30	0.002887	7.6793	0.6332	0.6210
40	0.003778	7.8446	0.7984	0.7742
45	0.004211	7.9328	0.8866	0.8406
50	0.004636	7.9686	0.9224	0.9006
65	0.005867	8.0641	1.0180	1.0469
100	0.008500	8.2397	1.1935	1.2511
150	0.011769	8.4211	1.3749	1.3852
200	0.014571	8.5036	1.4574	1.4876
250	0.017000	8.6373	1.5911	1.5412

92 % saturation at end of titration
K_a = 595 M^{-1} ± 5 % δHG = 8.7255 ppm

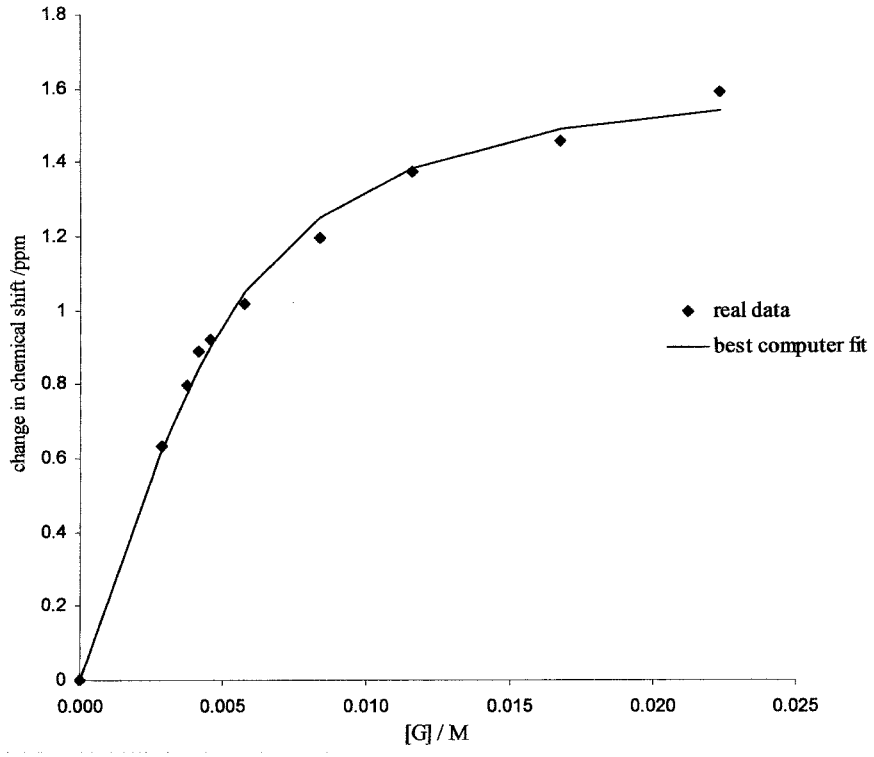
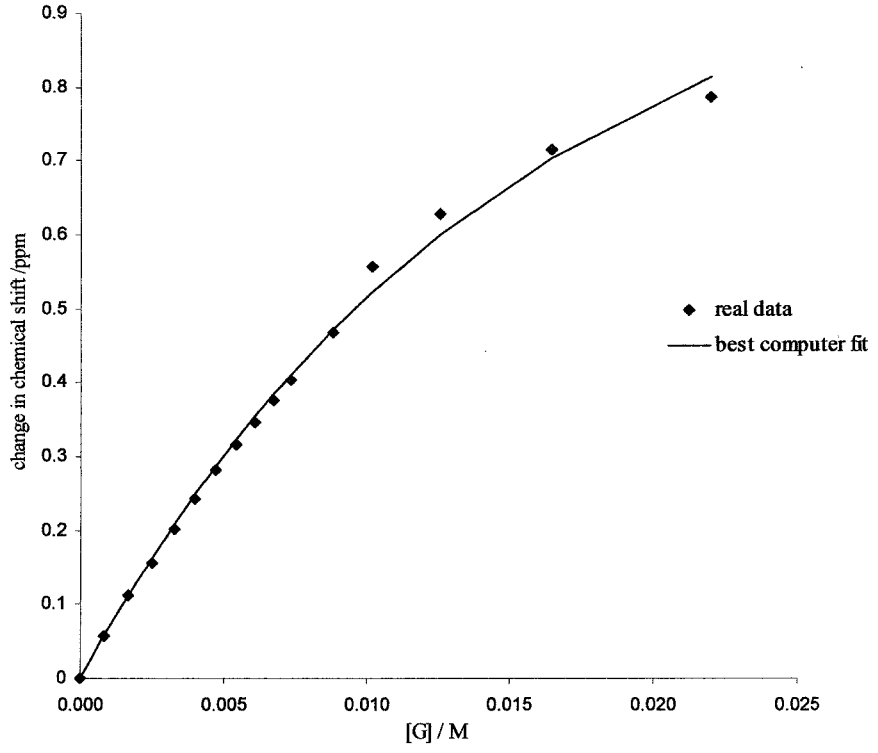


Figure 4.56 - NMR Binding Study of Association between 3.36 and TBA nitrate

Solvent = Acetonitrile
Stock solutions – [H] = 0.0058 M [G] = 0.044 M
Initial volume of host = 500μL δH = 8.2282 ppm

μL of guest added	[G] added /M	Observed shift of NH /ppm	Change in shift relative to δH /ppm	Computer fit for change in shift /ppm
10	0.000863	8.2849	0.0567	0.0592
20	0.001692	8.3400	0.1118	0.1132
30	0.002491	8.3840	0.1559	0.1625
40	0.003259	8.4292	0.2011	0.2076
50	0.004000	8.4699	0.2417	0.2490
60	0.004714	8.5088	0.2806	0.2869
70	0.005404	8.5430	0.3149	0.3218
80	0.006069	8.5745	0.3463	0.3539
90	0.006712	8.6047	0.3766	0.3836
100	0.007333	8.6301	0.4020	0.4110
125	0.008800	8.6943	0.4662	0.4711
150	0.010154	8.7841	0.5559	0.5214
200	0.012571	8.8545	0.6264	0.6002
300	0.016500	8.9428	0.7147	0.7039
500	0.022000	9.0138	0.7857	0.8119

57 % saturation at end of titration
$K_a = 75\ M^{-1} \pm 25\ \%$ δHG = 9.5746 ppm



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