UNIVERSITY OF SOUTHAMPTON

The Use of Supramolecular Chemistry in Dye Delivery Systems

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ABSTRACT

FACULTY OF SCIENCE

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Doctor of Philosophy

The Use of Supramolecular Chemistry in Dye Delivery Systems

by Daniel Andrew Sturton Merckel

This thesis reports an investigation into supramolecular recognition of the sulfate/ sulfonate oxoanionic group, a moiety present in the majority of reactive dyes. In the first section the problems associated with the use of reactive dyes in dyeing cotton fabrics together with a literature review of supramolecular approaches to anion recognition are discussed. Drawing on the current literature concerning anion recognition (in particular the recognition of phosphates), the main body of the thesis concerns the design and synthesis of several series of C-shaped (tweezer) and tripodal potential sulfate/ sulfonate receptors. These receptors incorporate the H-bond donor groups guanidine and thiourea and to a lesser extent urea and amide functionalities. In addition the behaviour of potential tweezer-like receptor molecules based on *s*-triazine (derived from cyanuric chloride) has also been investigated.

The sulfate/ sulfonate and related phosphonate association properties of these potential receptors have been studied. Particular emphasis has been placed on the solid-state supramolecular structures formed by these complexes as determined by single crystal X-ray structural studies, and several novel and revealing examples have been analysed in detail. NMR titration binding studies have also been undertaken in order to investigate the complexation behaviour of several receptors with "model dye" phosphonates and sulfonates in solution.

In addition a number of single crystal X-ray crystallographic studies were undertaken for other members of the Grossel research group during the course of this work, and the results of these structural studies are also reported.

Contents

Appendix A: NMR Titration data

Appendix B: Crystallographic Data on attached floppy disc

Acknowledgements

As anyone who has undertaken one knows, a PhD can sometimes be a daunting and disheartening affair and it is at these moments that one feels particularly grateful for others' help and empathy. Since I began my PhD in 1998 many people have contributed in different ways, and it is these people who have helped make the experience ultimately an incredibly rewarding and enjoyable one. It is with a huge amount of gratitude that I mention the following:

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The Southampton University Hartley Library staff for their help and their maintenance of literature essential to research.

And finally Marigold, Henry and Nola Merckel for their encouragement and unerring support.

Abbreviations and Nomenclature

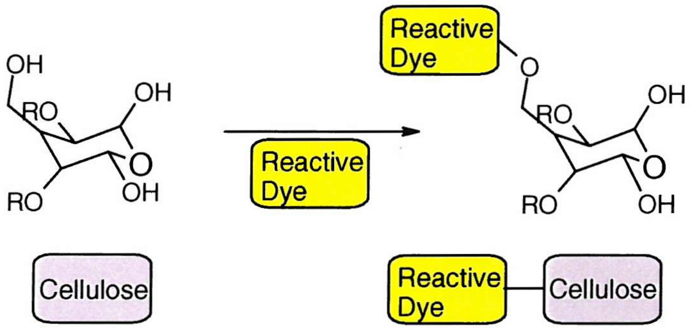
Bn	Benzyl [$PhCH_2$-]
BOC	*tert*-Butoxycarbonyl
CBZ	Carboxybenzoyl
DCM	Dichloromethane
DMF	*N,N'*-Dimethyl formamide
DMSO	Dimethyl sulfoxide
ES	Electrospray (Mass Spectroscopy)
Et	Ethyl
H-bond	Hydrogen bond
lit.	Literature
Me	Methyl
mp	Melting point
NMR	Nuclear Magnetic Resonance
Ph	Phenyl
TBME	*tert*-Butyl Methyl Ether
TFA	Trifluoroacetic acid [CF_3CO_2H]

1 Introduction

1.1 Reactive Dyestuffs

Cotton-based fabrics are commonly dyed in aqueous solution using Reactive Dyes. The process is carried out in aqueous solution as opposed to organic solvent for several reasons: cost, environmental factors, and hazards associated with organic solvents (including possible degradation of the fabric).

The surface of cotton fabric at a molecular level consists of a mesh of cellulose fibres, and it is the hydroxyl groups of cellulose that form bonds with the Reactive Dye molecules. A possible reaction scheme for the attachment of a dye molecule to a cellulose moiety is shown below (scheme 1).

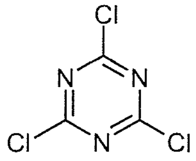


Scheme 1. Attachment of a Reactive Dye to cellulose.

The class of dyestuffs used to dye cotton fabrics, Reactive Dyes, are so-called because they possess reactive sites that are susceptible to nucleophilic substitution. It is this property that enables physical bonds to form between dye and fabric, as shown above.

1.1.1 Cyanuric Chloride

Reactive Dyes first appeared on the market in 1924 and to this day have almost exclusively been derived from cyanuric chloride (**1**) and closely related *s*-triazines (including cyanuric fluoride).



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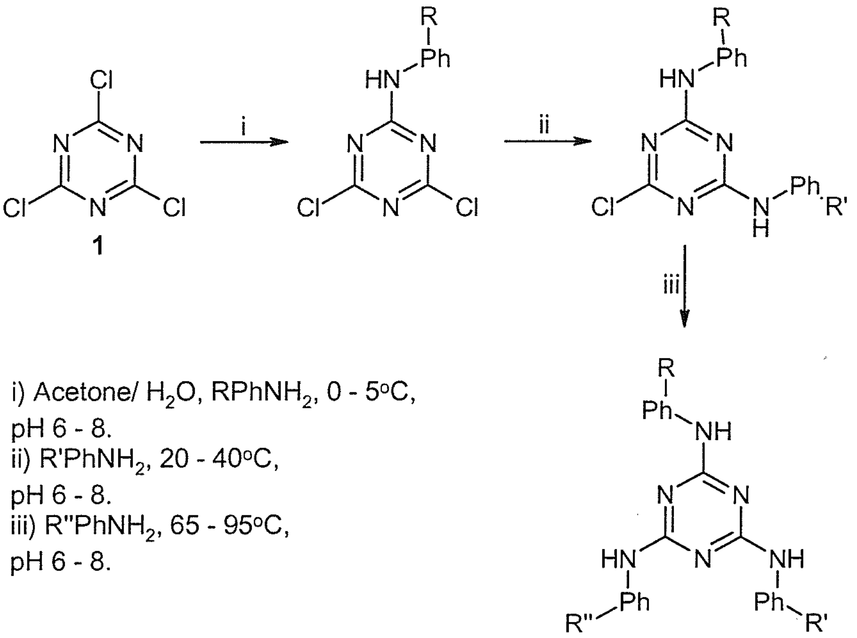
Cyanuric chloride is synthesised industrially in several ways. Two of the methods first developed are as follows: a) gaseous hydrogen cyanide is passed into chloroform which contains 1% alcohol, the solution is cooled and saturated with chlorine. After a few days the residue is recrystallised from ether after removal of chloroform[1], b) chlorine is passed through methyl thiocyanate and cyanuric chloride is produced directly[2].

Cyanuric chloride is very reactive and can be considered as three acid chloride functionalities in a ring. However, cyanuric chloride remains unhydrolysed in pure water at 0°C even after twelve hours[3].

1.1.2 Substitutions of Cyanuric Chloride

It is possible to substitute each chlorine atom in cyanuric chloride sequentially so long as the correct conditions are employed. These reactions can be carried out in organic or aqueous solution, depending on the nature of the nucleophile. The sequential substitution of cyanuric chloride requires increasingly severe conditions since the molecule's reactivity decreases with each substitution. If substitution is carried out in aqueous solution, it is quite possible to afford the totally unsymmetrical tri-substituted product with careful control of the temperature and pH. For example, tri-substitution with three different aqueous soluble arylamines could proceed under the following conditions (scheme 2).



i) Acetone/ H_2O, $RPhNH_2$, 0 - 5°C, pH 6 - 8.
ii) $R'PhNH_2$, 20 - 40°C, pH 6 - 8.
iii) $R''PhNH_2$, 65 - 95°C, pH 6 - 8.

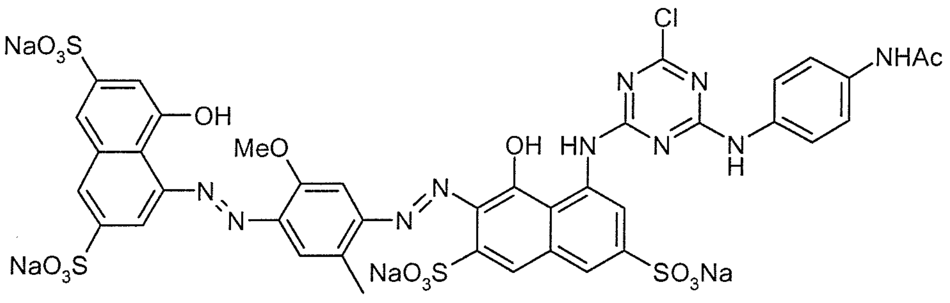
Scheme 2. Sequential Substitution of Cyanuric Chloride.

Inorganic bases (*eg*. sodium carbonate, sodium hydroxide) are commonly used to maintain the pH as HCl is evolved in the reactions.

Substitutions in organic solvents are controlled by stoichiometry and temperature.

1.1.3 Reactive Dye Synthesis

Reactive dyes are synthesised using similar conditions as shown in scheme 2.



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For example, Chlorantine Fast Blue 10 GL (**2**) is synthesised by the slow addition of an aqueous solution of one mole of the diazo dye containing one mole sodium carbonate to one mole of cyanuric chloride suspended in water at 0 – 5°C. The pH is maintained at about 6 by the addition of sodium carbonate solution. Next, a neutral solution of the arylamine is added at 40°C followed by sodium carbonate solution in order to maintain the pH at about 6. The reactive dye is isolated as the sodium salt by the addition of sodium chloride to the solution to “salt” the product out of solution.

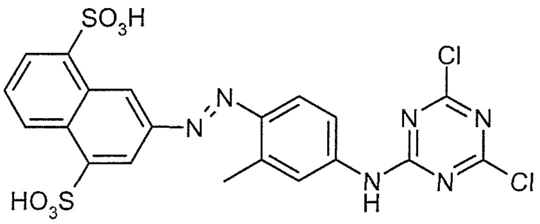
Using similar syntheses many series of commercial reactive dyes have been and are still synthesised by companies such as Ciba, ICI and BASF.

Thus cyanuric chloride provides not only the reactive site for the reactive dyestuff, but also the linker for introducing chromophores (*eg.* azo dyes) and other groups desirable in dyestuffs. More than one chromophore can be introduced so that new shades are produced. For example, Chlorantine Fast Green BLL contains two chromophores in the form of two azo dyes, one blue and one yellow.

1.1.4 Dichloro-triazine-based Reactive Dyes

Two main classes of reactive dye exist which are differentiated by the number of unsubstituted chlorine atoms in the molecule; dichloro-triazines (in which there are two unsubstituted chlorine atoms) and monochloro-triazines (in which there is only one unsubstituted chlorine atom).

Dichloro-triazines have two chlorine atoms (*ie.* two reactive sites), the third chlorine atom having been substituted with a group containing the molecule's chromophore. Some of the chromophores commonly used are azo dyes, as is the case for Procion Yellow M-RS (**3**)[4], and anthraquinone dyes, for example Procion Blue M-3GS (**4**)[5].



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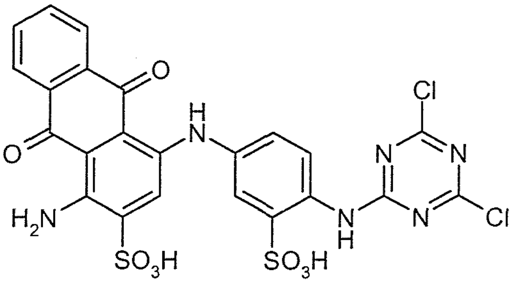

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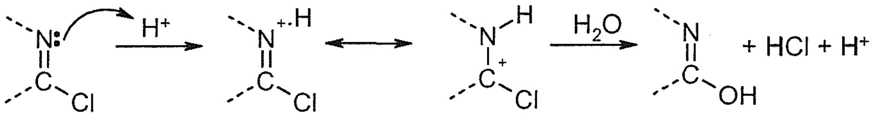
The action of dichloro-triazines was first recognised in 1954 at ICI, and dyeing processes were greatly influenced by this discovery resulting in a significant improvement in wet – fastness properties. Fabrics are dyed from warm (~30°C) alkaline solution containing sodium chloride, which helps transport of the dye into the fabric. Urea, alginate thickening and sodium bicarbonate are used as additives in the dye solution.

However, the high reactivity of dichloro-triazines which accounts for low dyeing temperatures also has a disadvantage; during storage HCl from hydrolysis through protonation of the triazine leads to the autocatalytic acceleration of further hydrolysis (scheme 3).



Scheme 3. Chloro-triazine acid hydrolysis.

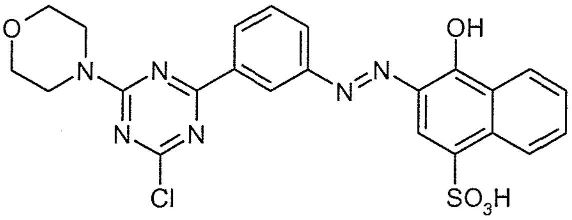
To avoid this, phosphate buffers (Na_2HPO_4 and KH_2PO_4) are added to dichloro-triazine reactive dyes before storage.

1.1.5 Monochloro-triazine-based Reactive Dyes

Monochloro-triazine reactive dyes have one chlorine atom available for nucleophilic substitution, and are easily formed from dichloro-triazines as described above. This process allows the incorporation of two different chromophores into the reactive dye.

The introduction of a second substituent has a far greater impact on the molecule's reactivity in comparison with dichloro-triazines. For example an alkylamino substituent produces a stronger deactivating effect on the reactive centre than amino ($-NH_2$) or arylamino groups, whilst the deactivating effect of a dialkylamino group can be so great that substitution of the remaining chlorine becomes very difficult.

A number of other groups are commonly used as well as amino functionalities to construct reactive dyes. These include: methoxy; thio; hydrazino; alkyl and aryl groups. Hydrazine is introduced easily but greatly deactivates the triazine's remaining substitution centre. Substitution with a phenyl group using the Friedel-Crafts reaction has been developed by BASF to give dyes such as **5**[6].



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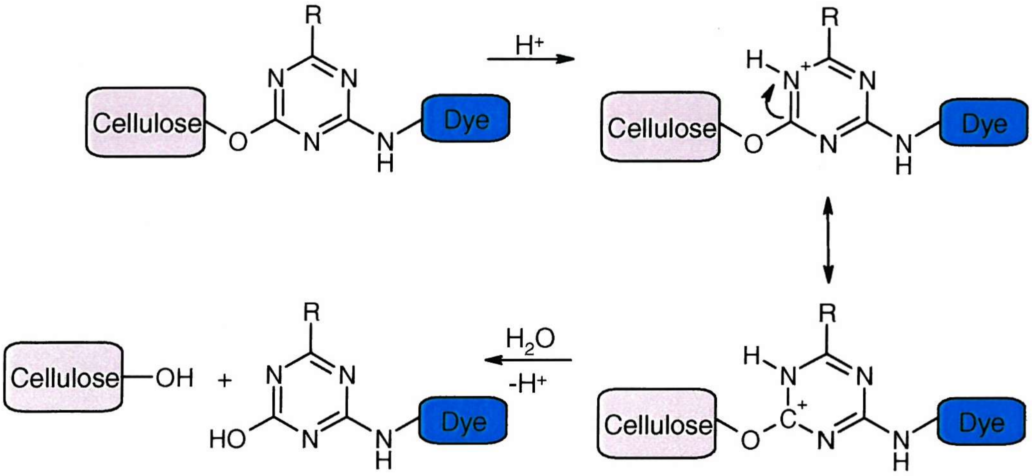
In addition to controlling reactivity, the two substituents present in monochloro-triazines are used to influence properties such as solubility and affinity so that a series of reactive dyes behaves similarly under dyeing conditions.

The conditions used to dye fabrics with monochloro-triazines have to be harsher than those employed for dichloro-triazines. Higher temperatures (70 – 90°C) and higher pHs (~11) are usual for dye application from the salt-containing alkaline solution.

1.1.6 Disadvantages of Reactive Dyes

Dyeing cotton fabrics with reactive dyes has a number of disadvantages that detract from the efficiency of the process and can cause environmental problems.

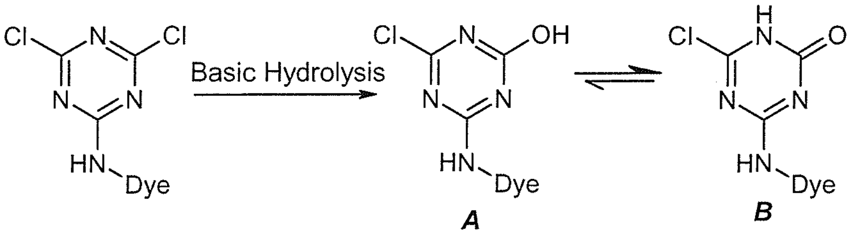
Even after a fabric has been dyed it is susceptible to hydrolysis in an acidic industrial atmosphere, or simply by the action of atmospheric carbonic acid. This hydrolysis process is summarised below (scheme 4).



Scheme 4. Hydrolysis of fixed Reactive Dye.

If the R group is not bonded to the fabric then the dye becomes dislodged and "colour bleeding" results.

However, more serious disadvantages are experienced in the actual dyeing process. Irreversible hydrolysis of the reactive dye molecule can occur in the basic solution before attachment of the dye to the fabric. Monochloro-triazine reactive dyes, which require much greater temperatures and pHs for dyeing to occur, are particularly susceptible to this problem. In the case of the hydrolysis of dichloro-triazines during the dyeing process, one reactive site can be hydrolysed under the conditions employed. However, even though one substitutable chlorine remains, the remaining reactive centre is often too deactivated by the hydroxy substituent from hydrolysis for reaction to occur; the triazine preferentially exists in the tautomeric lactam form ***B*** (scheme 5).



Scheme 5. Tautomeric structures of hydrolysed dichloro-triazine.

Both hydrolysed dye products are not only useless but also cause the added complication of adhering electrostatically to the fabric's surface. This interaction is weak so that the efficiency of the dyeing process is further lowered by the necessity of having to wash the dyed cotton to remove the hydrolysed by-product before the cloth can be used. If this is not carried out, "colour bleed" occurs. There is also an environmental implication; the hydrolysed dye product is difficult to remove from the dye effluent and so causes colouration of water effluent. The presence of common salt, which is used as an electrolyte, is also undesirable for environmental reasons. It is not removed easily by water treatment plants and so dye effluent that enters freshwater can have an undesirable environmental impact, in the worst cases causing mortality in freshwater aquatic organisms.

1.1.7 The Sulfonate Group in Reactive Dyes

One substituent that is almost always present in all kinds of reactive dye is the tetrahedral oxoanionic sulfonate group. The main effect of the sulfonate group is to increase the aqueous solubility of the reactive dye. Sulfonates are ideal because they do not exert a very large electron withdrawing effect (as is the case for groups such as phosphate or nitrate) so that this effect on the chromophoric and reactive properties of the reactive dye is minimal.

1.1.8 Improving the Dyeing Process – A Supramolecular Approach

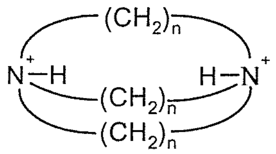
We hoped to address some of the problems associated with reactive dyes using a supramolecular approach, involving recognition of the sulfonate group. Recognition of the sulfonate group in a reactive dye molecule by a suitably designed receptor could facilitate transport of the dye molecule to the fabric's surface. This could be achieved by appropriate functionalisation of the receptor so that the complex's solubility is "fine-tunable". This approach might lower the concentration of salt needed in the dyeing process.

Alternatively, the receptor molecule could be designed to greatly lower the reactive dye's aqueous solubility upon recognition of the sulfonate group, thus precipitating it from solution or aiding extraction of the host – dye complex from aqueous solution. This approach could be used to remove the hydrolysed reactive dye by-product from the dye effluent, ultimately decreasing colouration in rivers.

1.2 Supramolecular Chemistry: Anion Recognition

Ever since Pedersen's discovery of crown ethers in the late 1960s[7], the recognition of cations has received much attention. As well as being a particularly attractive guest species for reasons of commercial and academic interest, cations (for example the alkali metals) are electropositive and "hard" (reflecting high charge density) because of their inherent small size, and they therefore constitute "easy" targets for supramolecular recognition.

At about the same time as Pedersen's discoveries, Simmons and Park synthesised several new cage-like macrocycles (**6**) that were found to noncovalently encapsulate spherical anionic guests such as chloride by H-bonding and electrostatic interactions[8].



6 n = 9 or 10

Anions are generally larger and so more diffuse in terms of charge ("softer") than cations as well as exhibiting a far greater array of polyatomic geometries, as for example in the tetrahedral oxoanions. These factors make anions more complex targets for supramolecular recognition, and may explain why the field of 'Anion Recognition' has only really gathered momentum in the last decade or so. At the same time our knowledge of natural anion hosts has increased. Phosphate and sulfate recognition has been shown to be essential in nature for active transport in cells[9], while prokaryotic and periplasmic proteins bind phosphate and sulfate exclusively through H-bonds, the former binding phosphate $>10^5$ more selectively than sulfate and the latter binding sulfate $>10^5$ more selectively than phosphate[10]. Both these discoveries occurred in the early 1990s. Now many detailed and interesting review articles[11] exist on the subject of anion recognition as well as many excellent supramolecular texts published with sections devoted to anion recognition by authors including Lehn, Gokel, Schneider, Cram and Steed[12].

1.2.1 Form and Function

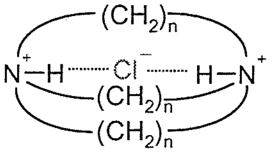
The two accepted essential features of any molecular host required to achieve selective recognition of a specific host are its shape/size and functionality. The host molecule must have some form of cavity or cleft that is similar in shape and size to the host it is designed to recognise, with functional groups complimentary to the guest positioned in propitious areas of the cavity to achieve selective complexation.

The kinds of shapes used for the recognition of anions differ little from those used for cations; rings (macrocycles, macrobicycles and -tricycles), buckets (eg. calixarenes) and clefts (C-shaped and tripodal molecules) have all been used as host molecules for anions. Functionalities commonly used for anion recognition contain H-bond donors, and/or a (partial) positive charge, or an empty outer electronic orbital (which can accept a pair of electrons as is the case for Lewis acids). Suitable functionalities include: amines, amides, Lewis acids/ metal centres, (thio)ureas, guanidines, and perfluorinated alcohols. Anion receptors are most easily categorised by the functionality they contain. The following sections describe a series of examples drawn from the literature, grouped by functionality, to highlight some of the strategies used to date to recognise anions.

1.2.2 Polyammonium-containing Receptors

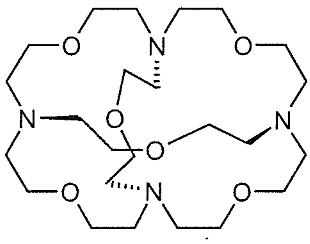
Host molecules containing multiple amine functionalities were one of the first types of anionic guest receptors synthesised. The amine group can be protonated and so bind an anion through one H-bond as well as through the inherent electrostatic charge.

The earliest example of such a strategy, as mentioned above, was devised by Park and Simmons in a series of molecules they called "katapinates"[8]. These host molecules were macrobicycles containing two tertiary amines at the two bridging points (**6**). Under the correct conditions the two tertiary amines could be protonated, and a spherical anionic guest (chloride) was found to fit inside the molecule's cavity after systematic variation of the host's size. The proposed host – guest complex was later proven by a crystal structure[13]. This revealed that the guest was bound by two H-bonds and electrostatics from the two ammonium groups.



6 n = 9 or 10

In the mid 1970s, the polyammonium macrocyclic approach to spherical anion recognition was developed by Lehn *et al* using pseudo spherical macrotricyclic cryptate ligands[14] such as 7.



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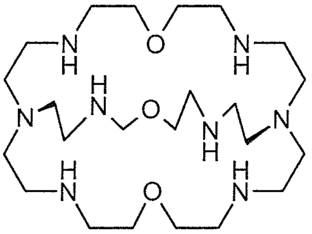
Lehn found by carbon NMR in d$_4$-methanol that addition of one equivalent of HCl resulted in the formation of the diprotonated ligand, **7**.H_2^{2+}, in which two of the bridging amines were protonated. Once three equivalents of HCl had been added the tetraprotonated ligand, **7**.H_4^{4+}, was formed (in a ratio of 1:1 with the diprotonated form) in which all four bridging amines were protonated. A crystal structure of **7**.$H_4^{4+}Cl^-$ was solved and showed the expected encapsulation of the guest in the host's cavity via four N-H···Cl^- H-bonds. **7** was also found to bind fluoride and bromide ions.

In the late 1970s Lehn and co-workers developed a similar strategy for binding a linear triatomic species[15]. They designed and synthesised a polyammonium macrobicycle **8** with an ellipsoidal cavity for anionic species such as azide.



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This ligand demonstrates not only the careful design of size but also shape for a specific guest. In addition the amine functionalities are all positioned at either end of the ligand, so that upon guest encapsulation they are in closest proximity to the guest's negatively charged H-bond acceptors. Ligand **8** was dissolved in water and the solution was acidified. By pH 5.7, six protons had been added to the ligand. It was proposed that the remaining two unprotonated amine functionalities were the two tertiary bridging amines, as these are much harder to protonate ($pK_a < 3.0$). Investigation of the binding properties of multi-protonated **8** was undertaken, and the ligand was shown to bind azide in a 1:1 stoichiometry by infrared and Raman spectroscopy in water at pH 5. The proton NMR spectrum of the complex also showed three-fold symmetry, consistent with the assignment of the six protonations. This ligand was found to bind other linear anions such as NCO^- and FHF^- as well as spherical anions and carboxylates, although these latter showed far weaker affinity. A crystal structure of the **8**.H_6^{6+}.N_3^- complex was solved and is shown below (figure 1). It confirms that the guest resides inside the host with a 1:1 stoichiometry.

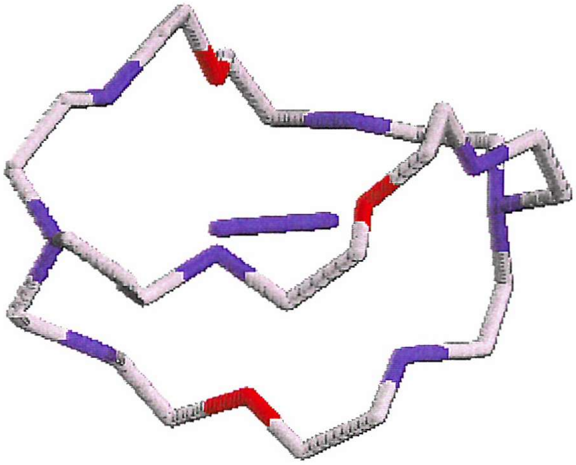
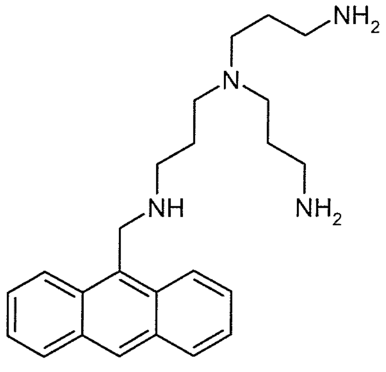


Figure 1. Crystal structure of **8**.H_6^{6+}.N_3^- (hydrogens omitted for clarity).

In addition to polyammonium ligands that recognise anions, polyammonium ligands that can also potentially give an optical response upon anion complexation have been investigated; tripodal ligands have been designed and synthesised which give a fluorescence response upon chelation[16]. A benzylic anthracenyl group is incorporated in ligands **9** and **10** which is attached to the tris (2-aminopropyl) amine groups by a terminal secondary amine in both cases. Changes in the electronic character of this benzylic nitrogen influence the fluorescence properties of the anthracene ring. Therefore the authors postulated that upon recognition of a phosphate guest, protonation of the benzylic nitrogen would occur and so elicit a change in the fluorescence properties of the anthracene ring.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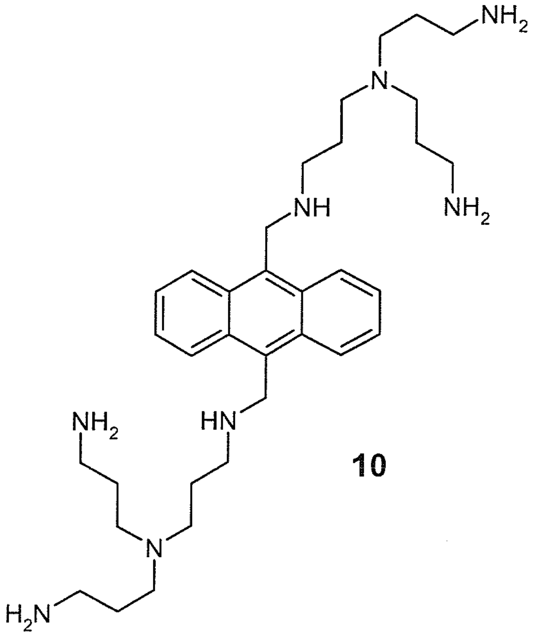
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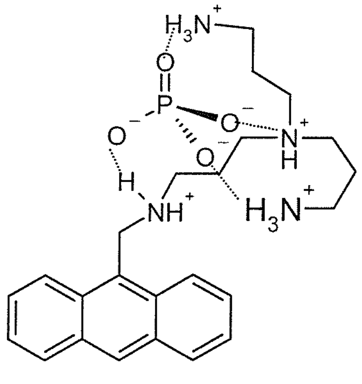
Addition of HPO_4^{2-} in aqueous solution at pH 6 did indeed increase the fluorescence of the ligand. It was suggested that the complex **11** was formed, which prevented intramolecular quenching by the favourable transfer of a proton to the benzylic nitrogen.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A similar but smaller effect was observed with sulfate and acetate guests. Both these species are totally dissociated at pH 6 so that no proton transfer could occur; this explains the far weaker increase in fluorescence observed with these guests.

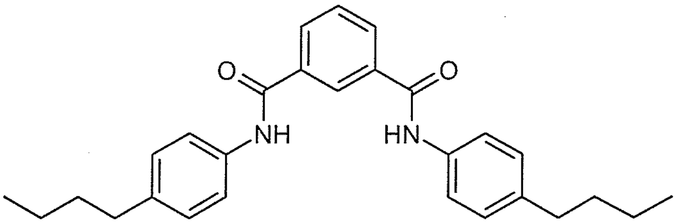
Polyammonium ligands have been shown to be effective receptors for anionic guests. The ammonium group's proton is acidic and is therefore a good H-bond donor.

The size of the cationic ammonium group is small (for instance when compared with the cationic guanidinium group) and so it has a high charge density causing it to form strong electrostatic interactions with anions. However as well as giving the ammonium group strong binding characteristics, the cationic charge has the detrimental effect of reducing this functionality's anion selectivity. This means that the ammonium group works best in rigid preorganised structures, ideally macrocycles, in which anion selectivity is chiefly governed by the host's cavity size.

1.2.3 Amide- and Sulfonamide-containing Receptors

Amides and sulfonamides are neutral under most conditions but have the ability to form H-bonds with negatively charged ions. Because of this property, amides, and to a lesser extent sulfonamides, have been widely used in anion receptors.

Crabtree and co-workers have synthesised a series of simple C-shaped receptors including amide or sulfonamide functionalities for the recognition of halide and acetate anions[17,18]. They had observed that receptors with a high degree of preorganisation (such as macrocycles) are usually synthetically inaccessible, and so concentrated on producing simple, effective receptors in one or two steps. Any preorganisation would be instilled in the receptors by virtue of rigidity and sterics. The effectiveness of these receptors was evaluated by proton NMR titrations in deuterated DCM with fluoride, chloride, bromide, iodide and acetate anionic guests (all added as their tetraphenylphosphate salts). 1:1 complexes were formed in most cases, and the receptors generally achieved the strongest association constants with chloride. $K_a = 6.1 \times 10^4\ M^{-1}$ was the highest observed for chloride using receptor **12**.



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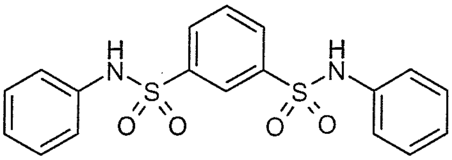
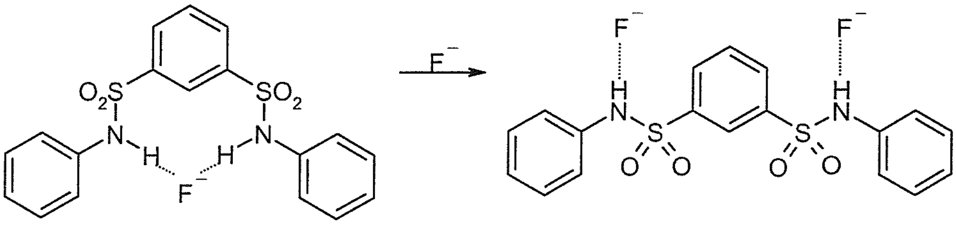
The exception to the 1:1 solution phase binding stoichiometry observed was the sulfonamide receptor **13**.



13

This formed both 1:1 and 1:2 complexes with fluoride and acetate anions during NMR titrations. The experimenters postulated that this binding preference was the result of the various conformations adopted by this receptor, the least rigid of the series synthesised. With no guest present, the receptor adopts an *anti-anti* conformation. Up to an equimolar guest concentration a 1:1 complex is formed, the host adopting a *syn-syn* conformation. As more guest is added, a 1:2 complex starts to dominate in which the receptor reverts to the *anti-anti* conformation via an intermediate *syn-anti* conformation (figure 2).



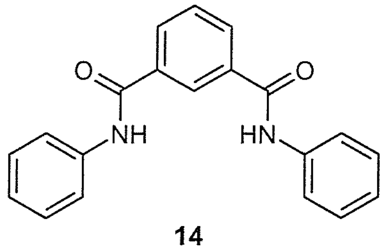
a) 1:1 binding, *syn-syn*

b) 1:2 binding, *anti-anti*

Figure 2. Changing conformation of **13** with fluoride concentration.

Overall, it was found that increased receptor rigidity led to enhanced binding of the smaller halides whilst receptor **13**, the least rigid of the series, exhibited the lowest anion selectivity.

Receptor **14** was crystallised with a bromide guest as $(PPh_4)_2(Bu(Br).CH_2Cl_2$. The crystal structure showed that 1:1 binding occurred with a twisted *syn-syn* host conformation so that two N-H···Br H-bonds were formed.



14

The second bromide was not involved in any H-bonds with the host molecule. The structure constitutes quite a rare solid-state phenomenon, namely the complexation by H-bonding of a negatively charged guest by a neutral host.

An interesting example of crystal engineering involving a C-shaped amide receptor has been published by Hamilton and co-workers[19], elaborating on earlier solution phase work[20]. The *para* substituted ligand **15** had been synthesised to recognise glutaric acid, an association constant of 6.4×10^2 M^{-1} was observed in 5% THF/ $CDCl_3$ (figure 3).

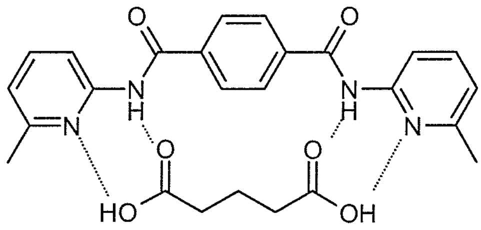


Figure 3. Complex of host **15** and glutaric acid

The *meta* homologue **16** was also synthesised and crystallised with glutaric acid. Receptor **16**'s cleft is too small to accommodate the alkyl dicarboxylic acid guest in an exclusive 1:1 complex, and so forms an H-bonded helix in the solid-state in which receptor molecules are stacked in rows held together by glutaric acid with **16** adopting a *syn-anti* geometry (figure 4).

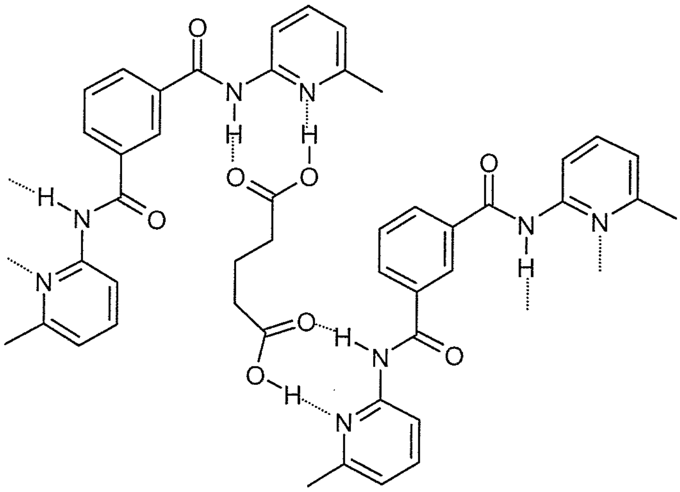
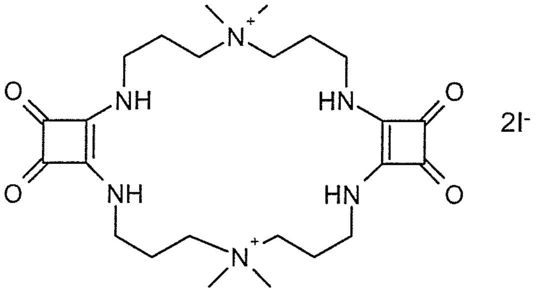


Figure 4. Representation of H-bonding in **16**.glutaric acid crystal structure

This work demonstrates that small adjustments in molecular structure can have a marked effect on solid-state architectures.

An extended amide function called squaramide has been used recently in a macrocycle that demonstrates selectivity for sulfate over phenyl phosphate and carboxylate in methanol[21]. Squaramides can form H-bonds with anionic guests and in so doing elicit a fluorescent response, making the group well suited for sensing applications.



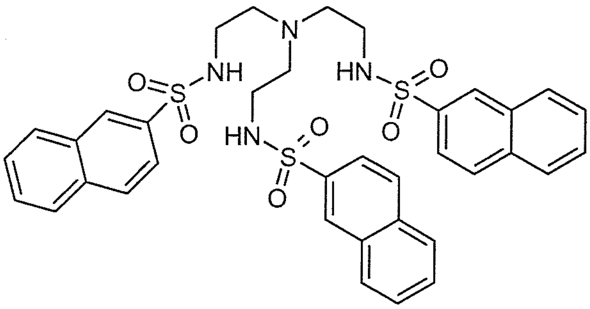
17

The squaramide functionality has previously been shown to bind carboxylates tightly in an extended conformation[22]. In **17** the experimenters have included two positively charged quaternary ammonium groups and have spatially arranged four amides from two squaramide groups to favour tetrahedral oxodianionic guests. The receptor's cavity is held open by the rigid squaramide functions and a charge repulsion between the cationic quaternary nitrogens.

The association constants proved to be too great to be measured by proton NMR titrations (> 10^5 M^{-1}), and so **17** was evaluated by Isothermal Titration Calorimetry (ITC) in methanol. 1:1 binding was observed for all guests and was endothermically and entropically driven. Upon binding, both receptor and guest break their bonds with the methanol solvent which is released to the bulk, outweighing the entropic cost of association[23]. $PhOPO_3^{2-}$ was bound with an association constant of 1.5×10^4 M^{-1}, $C_2O_4^{2-}$ with 3.2×10^5 M^{-1} and SO_4^{2-} with 4.6×10^6 M^{-1}. The binding of monoanions (eg. the halides, nitrate and acetate) was negligible due to the electroselectivity of the two tetraalkyl ammonium groups.

Fluorescence experiments with **17** in aqueous solution at pH ≥ 10 were carried out, and it was found that with increasing concentration of sulfate increased receptor fluorescence was observed.

Reinhoudt and co-workers have synthesised a series of neutral, acyclic tripodal receptors incorporating amide or sulfonamide groups to bind anions[24]. The receptors are all derivatives of tris (2-aminoethyl) amine with differing alkyl or aryl sidearm groups. The receptors' binding properties with phosphate, sulfate and chloride guests were explored by proton NMR titrations in deuterated chloroform; N-H proton shifts were recorded between 1.5 and 2 ppm downfield (Δδ). In all cases 1:1 complexes were reported, except for phosphate in high concentration when 1:2 complexes were recorded. Phosphate was bound most strongly by all the receptors, association constants ranging between 510 and 14200 M^{-1}, the latter value found for **18**. It was postulated that **18** was the best receptor for phosphate due to the increased electrophilicity of the sulfonamide N-Hs and probable π-stacking of the naphthyl rings. The association constants for sulfate were much lower, ranging from 31 M^{-1} to the highest value of 170 M^{-1} for ligand **19**.



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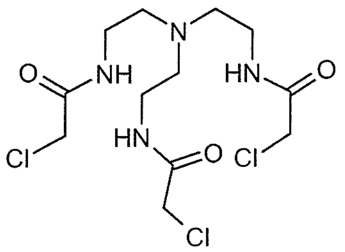
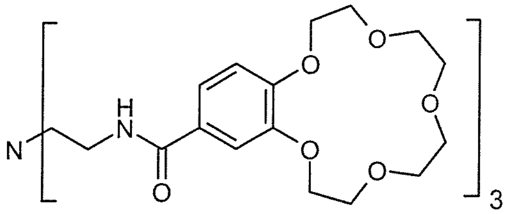


19

Receptors **18** and **19** also bound chloride most strongly, with association constants of 1600 M^{-1} and 1740 M^{-1} respectively (the remaining receptors had association constants of ≤ 540 M^{-1}).

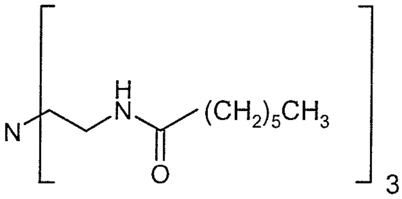
Both ligands **18** and **19** have the same selectivity for the three anions tested ($H_2PO_4^{2-} > Cl^- > HSO_4^-$). Binding was accomplished exclusively through H-bonding, explaining the receptors' preferences for an oxoanion. Sulfate was the weakest bound guest, probably because sulfur is "soft" and so its oxygen atoms have a lower charge density than those in phosphate.

Beer and co-workers have published an elegant piece of work in which a neutral tripodal receptor was produced for ion pair recognition (the simultaneous complexation of cationic and anionic species) of sodium pertechnetate salts[25]. Ion pair recognition is of great environmental importance as the technique could be used to extract undesirable waste products from effluent, such as $Na^+TcO_4^-$ from nuclear fuel reprocessing plants. Receptor **20** incorporates both anion recognition groups (three amides) and cation recognition groups (three 15-crown-5 rings).



20

Upon complexation of the first guest, electrostatic and conformational changes in the host molecule can influence the subsequent co-ordination of the counter ion. Receptors 21 and 22, both of which only have amide H-bonding donor sites, were also evaluated as reference comparisons for 20.



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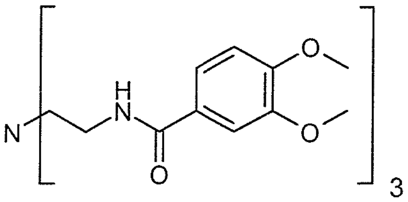
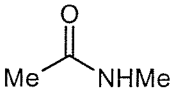


22

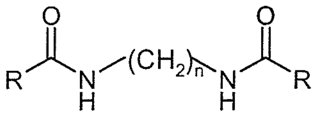
Initial NMR titration anion binding studies were carried out in deuterated chloroform with chloride, iodide and perrhenate; iodide was chosen as it has a similar charge density and size to TcO_4^- and ReO_4^- was chosen as it is isostructural with TcO_4^-. 1:1 complexes were formed with all three ligands. Each receptor bound chloride tightest, 22 having the greatest association constant ($K_a = 75\ M^{-1}$). Association constants for iodide and perrhenate fell between 20 and 40 M^{-1}, and 30 and 40 M^{-1} respectively.
UV/ Vis binding studies on **20** using sodium picrate to evaluate the cation binding properties of the receptor suggested that at low guest concentrations a 1:1 "sandwich" complex was formed involving one sodium cation. At higher concentrations of guest, each of **20**'s three crowns was associated with a sodium cation.
However a more interesting result was obtained from NMR titration experiments on **20** in the presence of one equivalent of sodium picrate. Under these conditions the association constants for all three of the anion guests were increased by a factor of 20, the receptor selective for ReO_4^- ($K_a = 840\ M^{-1}$) in the presence of chloride ($K_a = 520\ M^{-1}$), (as had been the case when sodium picrate was not present).
The increase in binding of all anions was attributed to an electrostatic attraction between the pairing ions in the complex. It was suggested that the sodium cation preorganised the ligand for tetrahedral anion binding, altering the anion guest preference of **20** (ReO_4^- instead of Cl^-).

Extraction experiments with **20**, **21** and **22** also gave encouraging results. Receptor **20** extracted ca. 70% TcO_4^- from basic aqueous solution into DCM, whereas the figure was less than 10% even after 24 hours for receptors **21** and **22**.

A particularly thorough investigation of neutral C-shaped and tripodal receptors incorporating amide binding sites (as well as ureas in some cases) for anion recognition has been published fairly recently[26]. The receptors' association constants with halides, phosphate and carboxylate were systematically evaluated as were the Free Energy changes of each receptor associated with binding different anions.



23



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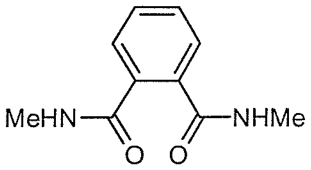
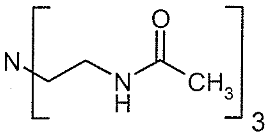


25

Receptors **23**, **24** and **25** represent the series of amide "chain" receptors synthesised and evaluated, and **26** and **27** the two amide tripodal receptors investigated.



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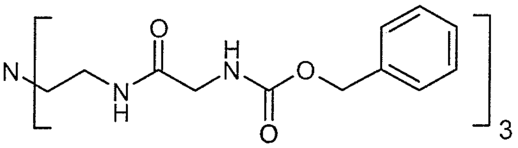


27

Proton NMR titrations of C-shaped receptors **23**, **24** and **25** with various anions gave 1:1 complexes. Phosphate and chloride were bound tightest, and the more preorganised receptors (**25** and **24** with a short CH_2 chain and a bulky R group) showed increased affinity for all anions. The tripodal receptors **26** and **27** bound anionic guests tighter than the C-shaped ligands, and **27** showed only a small increase in binding affinity over **26**. The analogous urea receptors of the C-shaped and tripodal amide receptors showed increased binding with all anions.

1.2.4 (Thio)urea-containing Receptors

Along with guanidines, thioureas and ureas have been very widely used as H-bond donor functions in anion receptor molecules. Unlike amides, (thio)ureas are capable of forming two H-bonds with a guest. This pairwise interaction is particularly favoured in the case of geometrically complimentary oxoanion guests (phosphates, carboxylates and sulfates) as the (thio)urea donates both hydrogens (AA-DD H-bonds), such a pattern resulting in positive secondary H-bond interactions (figure 5).

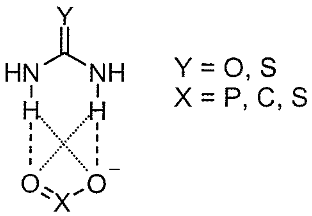
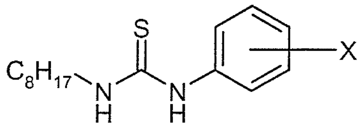


Figure 5. Bidentate Pairwise H-bonds.

Developing the work of Etter in which N,N'-di-*m*-nitrophenylurea was co-crystallised with moderate H-bond acceptors[27], Wilcox and co-workers have investigated the aryl substituent effect on an unsymmetrical disubstituted thiourea's ability to bind a zwitterion[28]. They synthesised several receptors based on **28** and evaluated their affinity for association with zwitterion **29** both experimentally (in solution) and theoretically.



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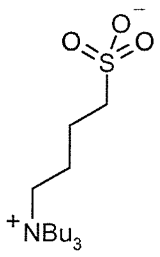
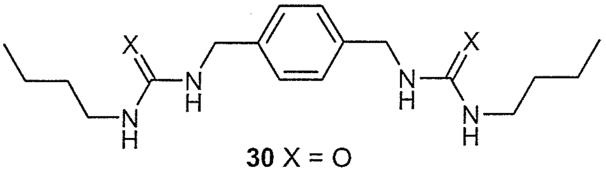


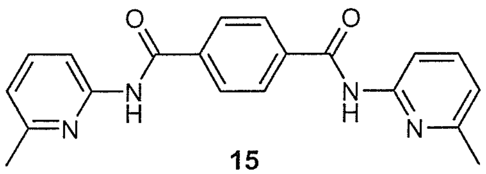
29

The presence of an aryl *meta* nitro substituent increased the association constant over that of the unsubstituted ligand and, in contrast to Etter's work, introduction of a *para* nitro group gave a slight increase in association constant over that for the *meta* substituent. These experiments demonstrated that by increasing the acidity of an aryl thiourea NH through the addition of an electron withdrawing group, increased binding ability was achieved.

Far greater solution association constants can be achieved when more than one thiourea or urea group is present in the receptor. The *para* xylylene di-urea type ligands **30** and **31** have been synthesised by Hamilton *et al* to recognise glutaric acid[29].



30 X = O
31 X = S



15

These receptors are derived from the amide analogue **15** used for the same purpose and discussed earlier (section 1.2.3), and avoid the unfavourable AD-DA H-bonding pattern associated with **15**.

30 and **31** are easily synthesised from *p*-xylylene diamine and butyliso(thio)cyanate, and bind glutaric acid in d_6-DMSO with association constants of 6.4×10^2 M^{-1} and 1×10^4 M^{-1} respectively (NMR titration). The difference in binding strengths can be explained in terms of the increased acidity of thiourea ($pK_a = 21.0$) over urea ($pK_a = 26.9$), as previously calculated[30]. All four NH signals shift in the spectrum, indicating that all NH groups form H-bonds with the guest in the complex supporting the proposed structure (figure 6).

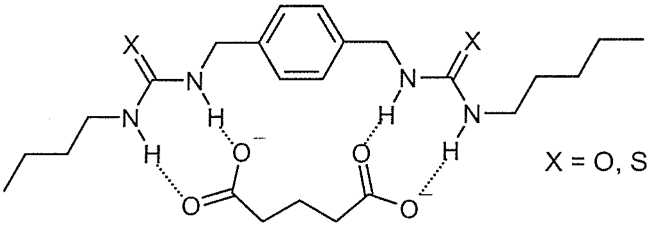
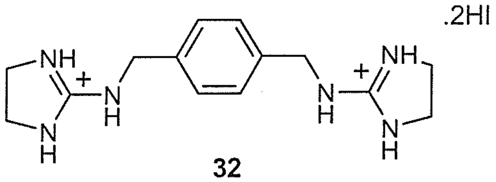


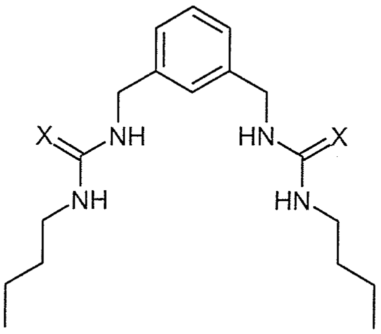
Figure 6. Proposed H-bond structure for hosts **30** and **31** with glutaric acid.

The related bis-guanidinium compound, **32**, was synthesised and found to have an association constant > 5×10^4 M^{-1}. Addition of D_2O lowered the binding strength, but at 25% D_2O/ d_6-DMSO binding was still appreciable ($K_a = 4.8 \times 10^2$ M^{-1}).



32

meta-Xylylene “cores” have been used commonly for C-shaped ligands containing (thio)urea binding sites. Two *meta* analogues (**33** and **34**) of **30** and **31** have been prepared and shown to bind phosphate in solution selectively over acetate, chloride, sulfate, nitrate and perchlorate[31].



33 X = O
34 X = S

Using NMR titrations, binding stoichiometry was determined as 1:1 and association constants with phosphate in d_6-DMSO were 110 M^{-1} for **33** and 820 M^{-1} for **34**. The association constants for N,N'-dimethylurea (28 M^{-1}) and N,N'-dimethylthiourea (120 M^{-1}) were measured for comparison. All four NH moieties of the two receptors **33** and **34** were involved in H-bonds, and led to the postulated complex geometry shown below (figure 7).

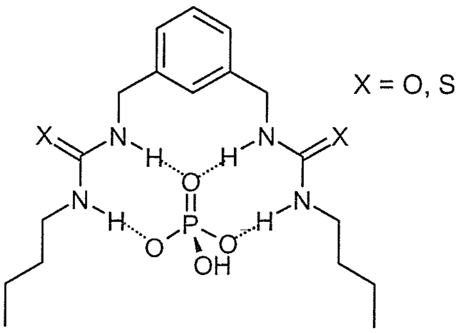
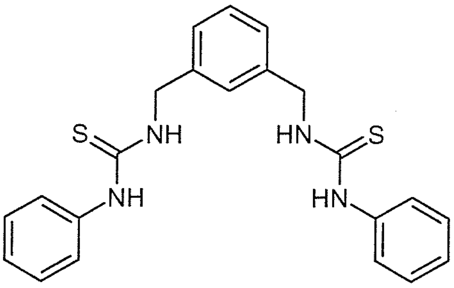


Figure 7. Postulated complex structure of hosts **33** and **34** with phosphate

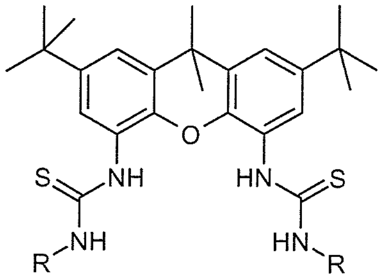
However co-crystals of either **33**.$H_2PO_4N(C_4H_9)_4$ or **34**.$H_2PO_4N(C_4H_9)_4$ could not be grown to give substance to this hypothesis. Sulfate recognition by the two receptors was weak (K_a = 1 or 2 M^{-1}). In addition to its vastly improved binding, **34** was also more soluble than **33**. A variable concentration NMR experiment in $CDCl_3$ showed no evidence for the self-association of **34**.

In a follow-up paper the experimenters found that **35**, the phenyl substituted bis-thiourea, bound phosphate nearly six times better than **34** (K_a = 4600 M^{-1}) using the same method[32].



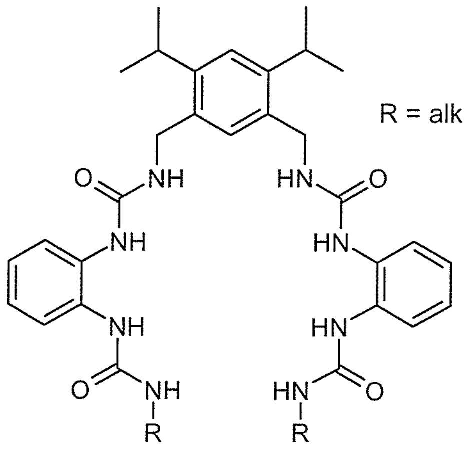
35

A more rigid xanthene spacer unit, or "core", employed in two related thiourea receptors (**36** and **37**) had the effect of increasing binding constants at least 12-fold.

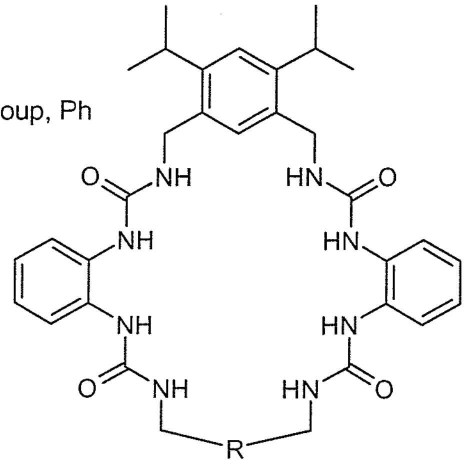


36 R = Bu
37 R = Ph

Echoing the results found with receptors **34** and **35**, **37** bound phosphate more tightly than **36** ($K_a = 195000\ M^{-1}$ and $K_a = 55000\ M^{-1}$ respectively). This led to the conclusion that electron withdrawing thiourea substituents increase binding (**34** → **35** and **36** → **37**) and the reiteration that increasing core rigidity (receptor preorganisation) greatly increases binding strengths **34** → **36** and **35** → **37**).



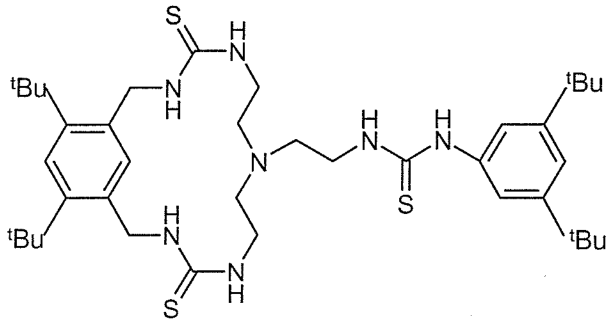
R = alkyl group, Ph



38 **39**

The inclusion of four urea groups in C-shaped and macrocyclic receptors has been shown to further increase anion binding strengths, as demonstrated by Reinhoudt *et al*[33]. The tetrakisurea-type receptors **38** and **39** were evaluated with a number of anions by NMR titrations in d_6-DMSO. The binding strengths were similar for both the acyclic and cyclic receptors (ca. $10^3\ M^{-1}$ for 1:1 stoichiometric association with phosphate), but the macrocyclic receptors **39** showed 100-fold selectivity for phosphate over chloride unlike the acyclic receptors **38**. All four urea groups were involved in H-bonds. Macrocycles showed 1:1 binding, whereas binding stoichiometries of 1:1 and 2:1 were observed for the acyclic receptors. The mode of binding for receptors **38** depended largely on the nature of the R group; phenylic R groups favoured 2:1 guest – host binding stoichiometry. Sulfate binding was weak in all cases.

Macrocyclic receptors incorporating thiourea groups have received little attention compared to other receptor architectures involving these groups. Recently an in-depth investigation of thiouryl macrocycle receptors has been completed by Tobe and co-workers[34]. A range of dithiouryl macrocycles was synthesised and binding affinities with phosphate, acetate, sulfate, chloride and bromide were measured by NMR titration in d_6-DMSO. All receptors that exhibited binding were selective for phosphate, and a lariat-type (pendant) macrocycle **40** bound all anions more tightly than the standard macrocyles such as **41** (K_a (phosphate) > 10^4 M^{-1}). All receptors bound guests in a 1:1 stoichiometry, and for each receptor the order of selectivity was $H_2PO_4^- > AcO^- > Cl^- > HSO_4^- > Br^-$. No crystals could be grown, but molecular modelling suggested that each receptor favoured a *trans-trans* thiourea geometry and that the anionic guest bridged the two thiourea groups. In the case of the oxoanions, the guest was predicted to sit on top of the receptor's cavity so that H-bonds were formed between two oxygens and the two thiourea groups.



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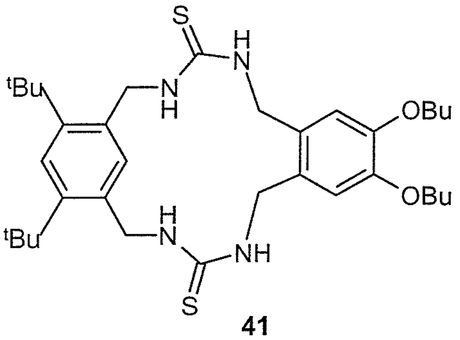
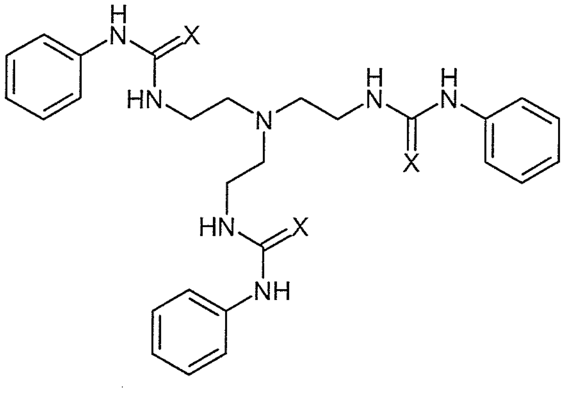


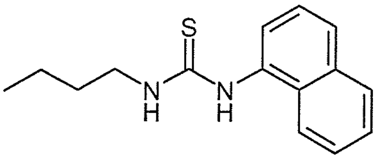
41

Tripodal receptors have been designed that incorporate (thio)urea donor sites: Receptors **42** and **43** both bind phosphate in d_6-DMSO with association constants of 1.1×10^4 M^{-1} and 1.6×10^3 M^{-1} respectively[35]. In this case the urea derivative binds phosphate more tightly than the thiourea **43**. Interestingly, receptor **42** was found to appreciably bind sulfate in d_6-DMSO (K_a = 3000 M^{-1}).



42 X = O
43 X = S

A comparison of the anion complexation behaviour of the mono-, bis-, and tris-*N*-ethyl-*N'*-naphthyl thioureas using UV/ Vis spectroscopy in DMF has been published[36]. Ligands **44** and **45** showed no change in their UV/ Vis absorption spectra upon addition of phosphate, sulfate, bromide, iodide, or acetate. However receptor **46**, the tris adduct, was found to complex phosphate and, to a lesser extent, sulfate.



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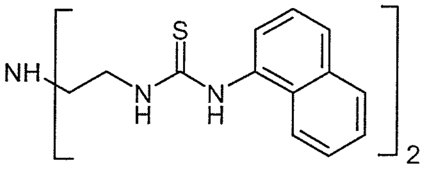

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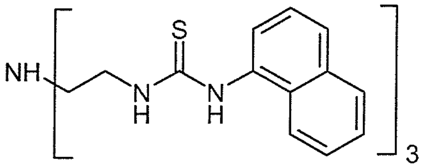
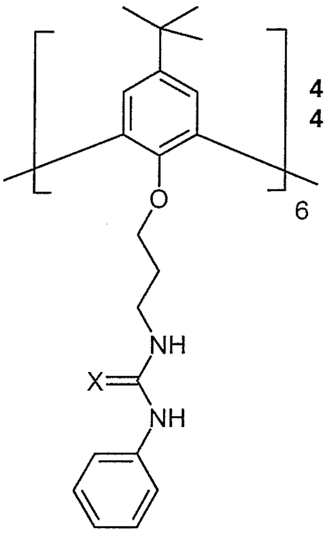


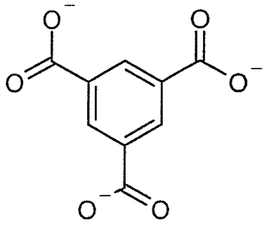
46

NMR titration experiments were also carried out with **46** and the same range of anionic guests. The results obtained for the absorption experiments were replicated, namely that this receptor showed binding with phosphate and sulfate but not with bromide, iodide and acetate.

Calix-6-arenes with (thio)ureas attached at the lower rim phenolic positions have been synthesised by Reinhoudt and co-workers[37], and their anion receptor properties evaluated by NMR titrations in $CDCl_3$. For the halides, bromide was bound preferentially over chloride. The best association constant found was for the urea derivative **47** with bromide ($K_a = 1.4 \times 10^3$ M^{-1}). Various carboxylates were also used as guests, the C_3 symmetric tricarboxylate **49** being bound most strongly by the thiourea receptor **48** ($K_a = 2.9 \times 10^5$ M^{-1}). An NOE NMR experiment showed that the three thiourea groups in **48** bound guest **49** symmetrically through six H-bonds.



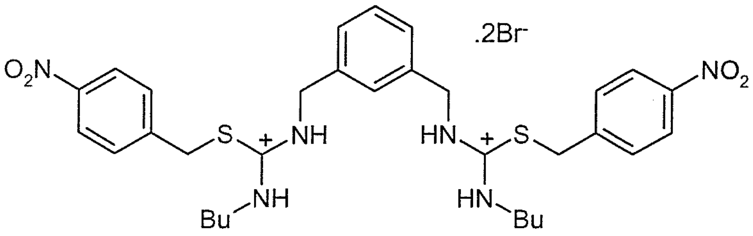
47 X = O
48 X = S



49

Thiouronium groups, generated by S-alkylation of a thiourea to give a cationic moiety, have been used in C-shaped receptors[38,39]. The thiouronium group has a larger dipole moment and more acidic hydrogens than the thiourea group, inaddition to the positive charge. It was hoped these factors would increase binding affinities.

Phosphate, acetate, phenyl sulfonate and various phenyl phosphates and phosphonates were bound by receptor **50**. It was postulated that the best correlation of anion binding affinity is the Bronsted basicity of the anion; phenyl sulfonate, which has the lowest Bronsted basicity, being bound most weakly. However the author stated that although thiouronium salts have stronger association constants with anionic guests than thioureas, guanidines have even higher association constants, probably due to increased charge density (nitrogen being smaller than sulfur).

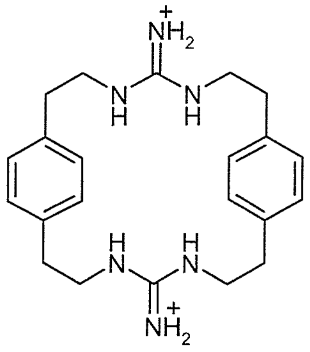


50

1.2.5 Guanidine-containing Receptors

To date, guanidines have probably been more widely used in anion receptors than any other single type of anionic recognition functionality. There is one overriding reason for this: The guanidinium group remains protonated over a far greater pH range than the ammonium group because of its much higher pK_a (13.5 for guanidine). This means that the guanidinium ion readily forms zwitterionic $N\text{-}H\cdots X^-$ H-bond pairs with anions of the form shown in figure 5, but with the additional charge-pairing which greatly increases the strength of the interaction. The propensity for guanidinium salts to exhibit this interaction, especially with oxoanions, is illustrated by many of the published crystal structures of guanidinium salts[40,41,42,43].

Lehn and co-workers synthesised a series of guanidinium-containing macrocycles in the late 1970s[44]. The work involved a new approach to guanidinium synthesis; S-alkylation of a thiourea followed by reaction with an amine (in this case ammonia) to give the guanidinium salt. Macrocycles **51**, **52** and **53** were prepared in this way as either their chloride or bromide salts. All were soluble in water, methanol and ethanol, and were evaluated for their PO_4^{3-} binding ability by comparison of the pH titration curves of PO_4^{3-} in absence of macrocycle and in the presence of macrocycle. The resulting complexes all had a 1:1 stoichiometry.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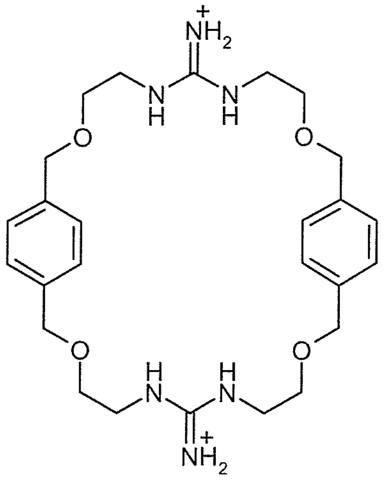
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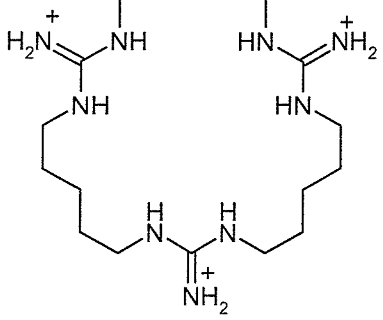
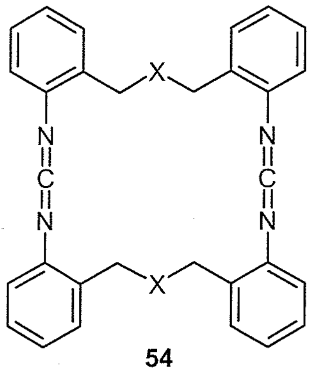

53

The macrocyclic guanidinium salts were found to form stronger complexes with PO_4^{3-} than their acyclic analogues, which were also prepared. This result was purported to arise from chelate and macrocyclic (preorganisation) effects.

A more recent method of macrocyclic guanidinium preparation has been reported by Sanchez-Andrada and co-workers[45]. Reaction of bis-(carbodiimides) **54** with various amines in DCM at room temperature produced a novel class of guanidinium-based macrocycles **55** which were selective for phosphate in solution.



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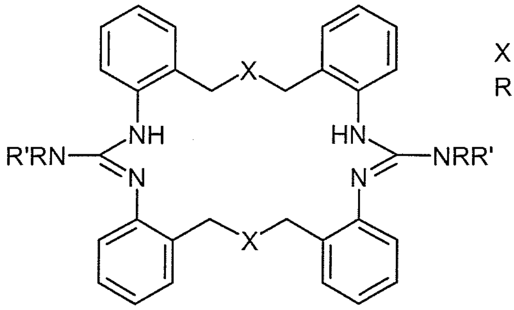
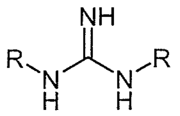


55

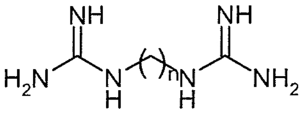
X = O, CH_2
R, R' = H, alkyl, aryl

A series of acyclic polyguanidinium receptors was synthesised by Lehn, Dietrich and co-workers and evaluated by pH titrations for anion binding with phosphate and carboxylates[46]. They investigated several methods of substituted guanidine synthesis. Reaction of an amine with either a substituted *S*-methylisothiourea or with *O*-methylisourea was high yielding but required harsh conditions for introduction of multiple guanidine groups. The method of choice was reaction of an amine with *O*-methyl-*N*-nitro-isourea to give the substituted *N*-nitro guanidine, which was converted to the guanidine by acidic hydrogenolysis. **56**, **57**, **58** and **59** were each prepared by one of these two methods as their hydrochloride salts.



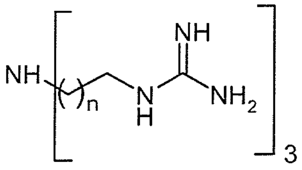
R = H, phenyl, benzyl

56



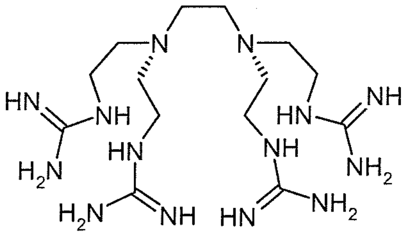
n = 2, 3, 4

57



n =1, 2

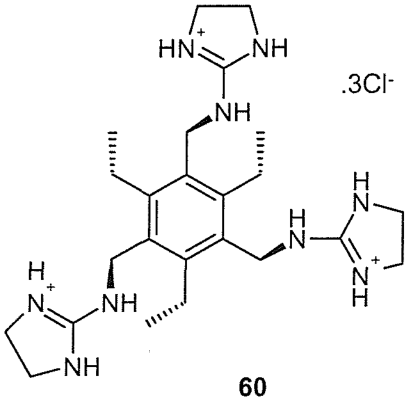
58



59

The pH-metric titration experiments indicated that binding was predominantly electrostatic for phosphate and carboxylate. Thus the strongest complexes were formed between receptors and guests with the highest charge density; tris-(ethylguanidine) **58** gave the highest stability constant with $P_2O_7^{4-}$, stability constants decreasing in the order $P_2O_7^{4-} > HP_2O_7^{3-} > H_2P_2O_7^{2-}$. The polyammonium ligands formed complexes an order of magnitude more strongly than their guanidinium analogues. The delocalisation effect in guanidinium, which lowers charge density, was considered to be the cause of the observed difference in stability constants between polyammonium and polyguanidinium derivatives, even though the guanidinium unit can form an additional H-bond with a guest.

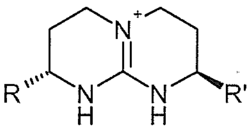
A novel tripodal tris-cyclicguanidinium receptor selective for citrate (tricarboxylic acid) has been prepared by Anslyn *et al*[47]. The receptor **60**, built around a benzene core with three alternating ethyl and methylene guanidinium substituents, is sterically preorganised.



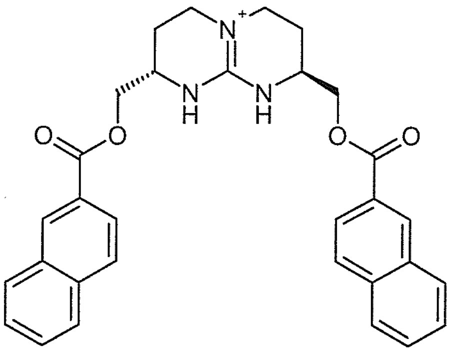
60

A crystal structure with tricarballate (1,2,3-propanetricarboxylate, a citrate analogue) demonstrated that all three guanidinium groups are situated on one side of the benzene ring. NMR titrations showed that **60** bound citrate with an association constant of 7 × 10^3 M^{-1} in pure water, very strong association for such an unfavourable medium. An analogue of **60**, which did not have the three ethyl groups, gave an association constant of just under half that value as did the trisammonium analogue of **60** showing the importance of both preorganisation and guanidium's bidentate H-bond donor ability. Receptor **60** also bound citrate with good selectivity in a crude extract of orange juice at pH 7.4 ($K_a = 4.6 \times 10^3$ M^{-1}).

Two research groups, one comprised of de Mendoza, Echavarren, Lehn *et al*[48,49] and the other Schmidtchen and co-workers[50,51,52,53], have extensively investigated receptors based on the optically active bicyclic guanidinium core **61**. **61** imparts chirality to the receptor molecule aiding enantioselectivity, and the rigid bicyclic nature of the guanidinium group enhances its anion binding ability.



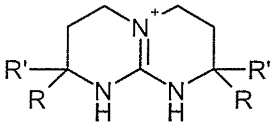
61



62

The laboratory of Echavarren *et al* produced a C_2 symmetric receptor derived from **61** incorporating naphthyl ester-linked R and R' groups. This receptor, **62**, extracted *p*-nitrobenzoate quantitatively from aqueous solution into chloroform. The host – guest complex involved the double recognition of the guest through zwitterionic H-bonds from the guanidinium and π-stacking of the naphthyl groups with the electron deficient guest. Free amino acids in zwitterionic form were not extracted from water by **62**, however *N*-acetyl and *N-tert*-butoxycarbonyl derivatives of sodium tryptophan were. NMR titrations of **62** with the *L* and *D* enantiomers of *N*-acetyl tryptophan in chloroform gave association constants of 1051 M^{-1} and 534 M^{-1} respectively, demonstrating the host's enantioselectivity.

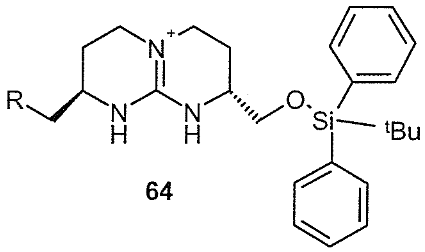
Schmidtchen's group have synthesised a series of receptors derived from **63**. In the achiral receptors when both R and R' groups are the same (R, R' = CH_3 or $(CH_2)_3OH$), this receptor binds *para*-nitrobenzoate, and to a lesser extent phosphate and chloride, strongly in acetonitrile with 1:1 stoichiometry. A crystal structure of the tetra-alcohol (R, R' = $(CH_2)_3OH$) with acetate showed the bidentate pairwise H-bonding pattern expected, as well as two additional H-bonds to the acetate from both alcohol groups of a second host molecule. This additional interaction had the effect of weakening the bidentate guanidinium···oxygen H-bonds.



63

By imparting chirality to the receptor molecule **63** through the inclusion of bulky sidearm groups (R = H, R' = $-(CH_2)OSi(Ph)_2{}^tBu$), Schmidtchen was able to demonstrate this derivative's appreciable enantioselectivity by NMR. An X-ray crystal structure with nitrate showed bidentate H-bonding, and illustrated the asymmetric receptor cleft formed by two phenyl groups which appeared to be large enough to accommodate larger guests. NMR titrations in acetonitrile with *N*-acetyl *D, L*-alanine showed 1:1 binding.

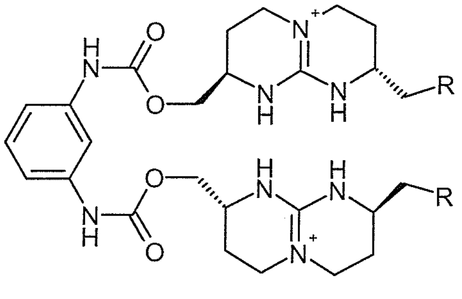
Schmidtchen then extended work with the core receptor **63** by the introduction of asymmetry in the R groups as in the generic receptor precursor **64**.



64

The R groups employed comprised leaving groups such as halides and azide. Upon nucleophilic substitution of these leaving groups no scrambling of regioselectivity was observed. A crystal structure of **64** (R = I) as the perchlorate salt was obtained which showed that the pairwise bidentate N-H···O H-bonding motif is retained even though perchlorate is a poor H-bond acceptor.

Schmidtchen also used guanidinium bicycle **63** in a different context; as a C-shaped receptor side arm.[54,55,56]



a) R = CH_2OH
b) R = $CH_2OSi(Ph)_2{}^tBu$

$.2ClO_4^-$

65

65 bound both dicarboxylates and organophosphate species in water (R = CH_2OH) and in chloroform (R = $(CH_2)OSi(Ph)_2{}^tBu$). **65b** also extracted *di*carboxylates from aqueous solution, but not *mono*carboxylates. The four NH groups of the two guanidinium moieties point to the corners of a distorted tetrahedron and so are well suited for association with tetrahedral anions. NMR titrations also showed significant binding in d_6-DMSO.

The binding thermodynamics in d_6-DMSO of sulfate by receptor **65**, with a linker group at the 5-position of the benzene ring, have been reported by Schmidtchen in an intriguing study[56]. The receptor binds sulfate strongly in methanol, and binding is even observed in d_6-DMSO (by NMR). Isothermal Titration Calorimetry (ITC), a technique used to measure the evolution/ absorption of heat upon addition of guest to host solution, was used to give the thermodynamic parameters for association, enthalpy (ΔH_a) and entropy (ΔS_a), in methanol. Sulfate was bound strongly ($K_a = 6.8 \times 10^6\ M^{-1}$) with 1:1 stoichiometry. However the enthalpy of association was strongly endothermic ($\Delta H_a = +7.7$ kcal mol^{-1}). The strongly positive change in entropy upon association showed that this was entropy driven, $T\Delta S_a$ far outweighing the unfavourable enthalpy term. ΔH_a reflected the endothermic reorganisation of the host's and guest's solvent shells upon complexation; the complex was less solvated than the sum of its free components, and so release of solvent to the bulk led to entropic over-compensation of the unfavourable positive enthalpy of desolvation.

In a more recent study again using ITC, Hamilton found similar results for association of carboxylate guests with simple monoguanidinium receptors with varying degrees of substitution in methanol, but contrasting behaviour in DMSO[57]. In this latter system association was enthalpically exothermic, heat being evolved upon complexation resulting in a negative ΔH_a term. Systematic blocking of H-bonding sites on the guanidinium receptor by alkylation allowed Hamilton to establish the importance of the bidentate H-bond between guanidinium ions and carboxylate. Upon mono-*N*-methylation of bicyclic guanidinium, the enthalpy of association became neutral suggesting either no association or enthalpically-neutral association (figure 8).

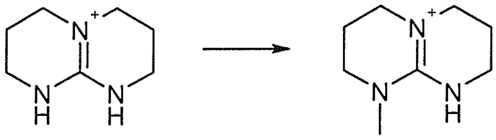
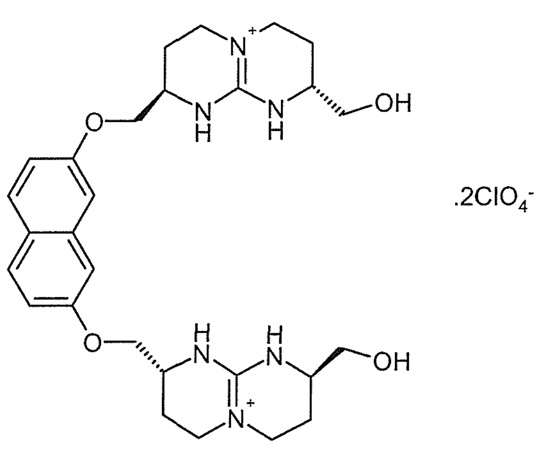


Figure 8. Methylation of a bicyclic guanidinium.

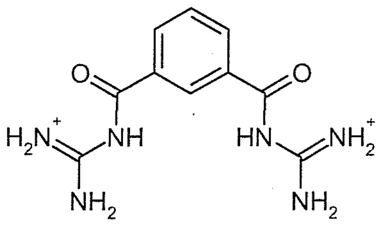
An NMR titration showed only weak binding of carboxylate guests by the *N*-methylated guanidinium moiety. This study proved that binding of carboxylate guests by guanidinium ions in DMSO is highly dependent upon bidentate H-bonding, and *not* upon electrostatics.



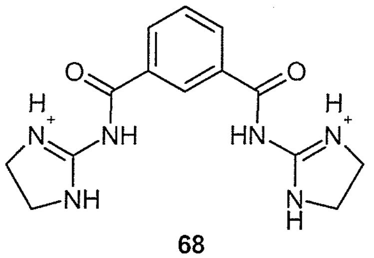
66

The C-shaped receptor **66** of Schmidtchen, which has a wider core spacer than receptor **65**, binds a range of alkyl dicarboxylate guests in MeOH. Molecular modelling showed that **66** most likely adopts an extended conformation because of cation-cation repulsion. However, upon interaction with a dianionic guest, a secondary conformation was observed in which the guest is pinched between the two guanidinium ions. Most guests were predicted to bind strongly regardless of dicarboxylate alkyl chain length and geometry, demonstrating the flexibility of the host **66**.

In the early 1990s the three research groups of Hamilton, Anslyn and Gobel all synthesised bis-(guanidinium) receptors in an attempt to electrostatically activate phosphodiesters and so enhance transesterification of these phosphates, emulating the active site of staphylococcal nuclease (SNase). Hamilton synthesised receptors **67** and **68** each in one step[58]. Both receptors are preorganised by an intramolecular H-bond between the carbonyl group and a guanidinium NH on the exterior of the cleft, forming a five-membered ring.



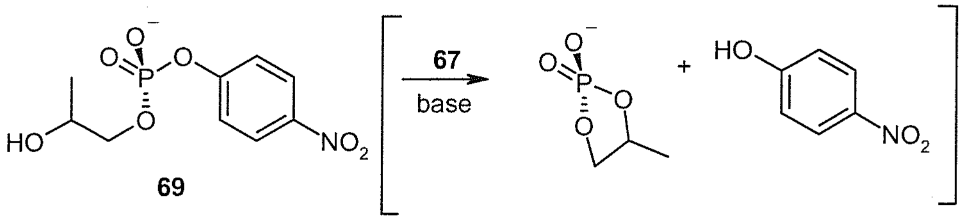
67



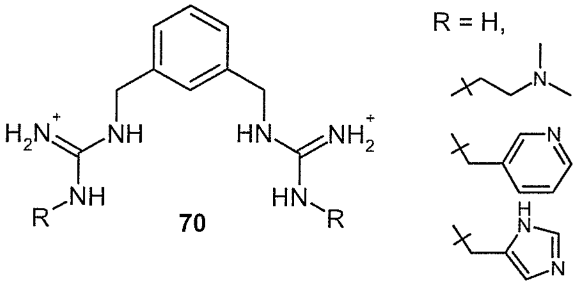
68

Initial NMR titrations in acetonitrile with diphenylphosphate showed appreciable 1:1 association with both receptors. However, upon increasing addition of one to three equivalents of guest to **67**, 3:1 (guest:host) association predominated as shown by the downfield NH shifts of the protons on the exterior of the cleft.

The rate of transesterification of **69** (HPNPP) by receptor **67** was followed spectrophotometrically by the release of 4-nitrophenol. Hamilton found a 700-fold rate increase over the uncatalysed reaction[59].



Next Hamilton synthesised receptors which incorporated the base needed for reaction in the receptor sidearm derived from the simple receptor **70**[60].

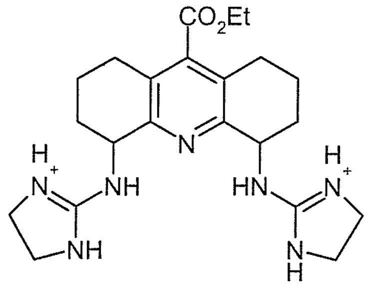


The same substrate (**69**) and conditions were employed, and it was found that the derivative of **70** with R = ethyl(*N*-dimethyl) gave a 290-fold rate enhancement over **70**.

Similar work and results, again focussing on the cleavage of HPNPP (**69**) by a number of bis-(guanidinium) receptors with varying cores and internal bases, has been published more recently by Kalesse and co-workers[61].

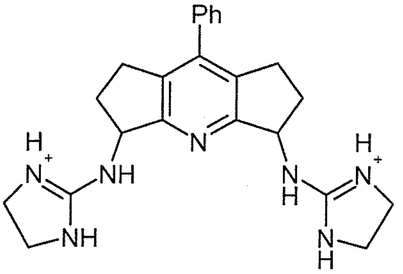
Interestingly the presence of further substitution on structures based on **70** (an R group on each terminal guanidinium nitrogen, *ie.* four R groups in total) leads not to catalysis, but to anticatalysis of the transesterification reaction, as reported by Benner[62].

Anslyn's first RNA cleavage enzyme mimic **71** was built around a more rigid but synthetically less accessible core[63]. Impressively, under physiological conditions with imidazole as base **71** enhances cleavage of a phosphodiester substrate 8 – 20-fold over imidazole alone.

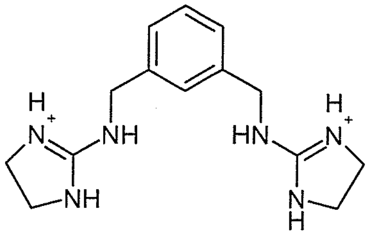


71

Anslyn then studied effects such as receptor flexibility, cavity size and counterion on complexation of phosphodiesters[64]. These experiments were carried out on receptors **67**, **71**, **72** and **73** in water/ DMSO mixtures.



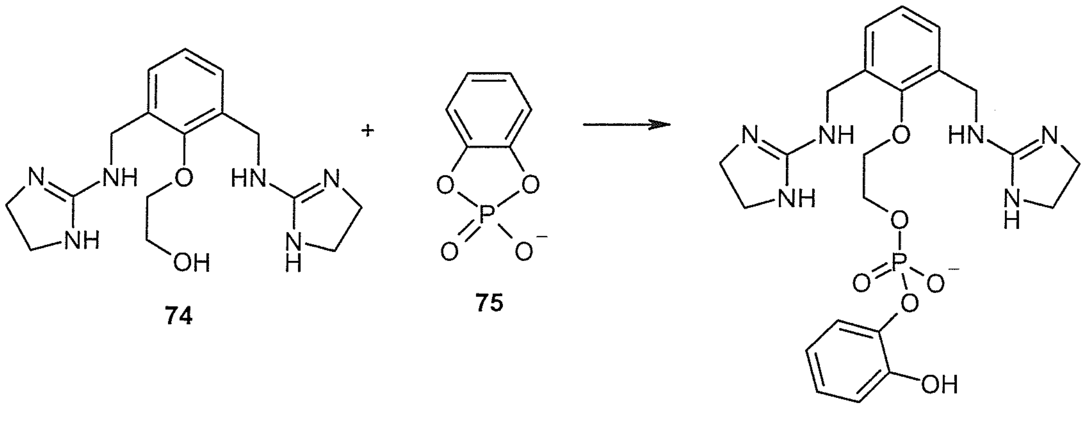
72



73

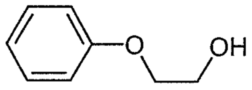
In low concentrations of water in DMSO, both 1:1 and 2:1 binding was observed but as the water concentration was increased, only 1:1 binding was observed. **71** showed stronger binding than **72**; **71** is more flexible and so can adjust to accommodate the phosphodiester more readily. Two crystal structures of **72** with dibenzyl phosphate and **72** with phenyl phosphate were collected. The former, with the more sterically hindered guest, presents only one bidentate NH···O H-bond, whereas the latter demonstrates 1:1 recognition with the "wedge" motif involving four NH to three oxygen H-bonds (as shown in figure 7).

The third research group that conducted work in this area, that of Gobel, found that both the *m*-xylylene and 1,2-ethylene core spacer units for bis-(guanidinium) receptors gave large rate enhancement effects in substitution reactions of phosphoric acid diesters[65]. Further rate enhancements were achieved by using imidazole groups instead of guanidine, with receptor **73** returning the best rate enhancement (4800-fold over the uncatalysed reaction). Investigations of dihexane cores were also undertaken[66]. Gobel extrapolated this area of research by combining receptor and reactive site by the inclusion of an alcohol function in the receptor (**74**) that could reversibly react with the phosphodiester **75**.



74 **75**

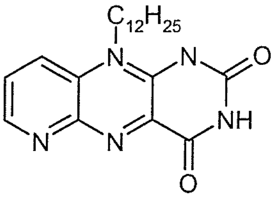
74 was phosphorylated 800 times faster than the mono-guanidine analogue and 380,000 times faster than **76** because of i) stabilisation of the transition state, and ii) enhanced protonation of the leaving group during elimination.



76

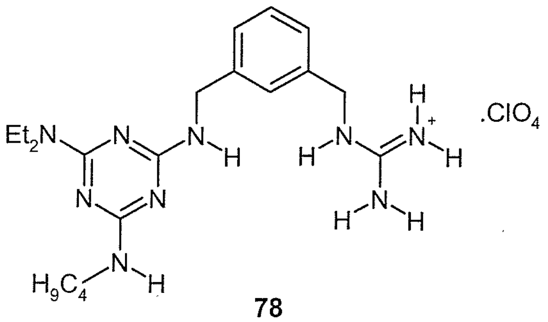
Again using the same building block, receptor **73**, Gobel has attached an arginine amino acid residue at the 5-position to create a receptor that efficiently binds and cleaves the TAR amino acid sequence of HIV-1, mimicking the protein tat[67].

Recently asymmetric, non-chiral guanidinium receptors have been synthesised that include extra functionality to selectively recognise structurally more demanding guests that are not always charged.



77

A receptor capable of recognising 6-Azaflavin (77) through five H-bonds has been synthesised[68]. Receptor **78** has a substituted triazine sidearm and a guanidinium sidearm spaced by an *m*-xylyene core. 1:1 complexation was confirmed by NMR titration (in $CDCl_3$), all host NH resonances being shifted downfield.



78

An analogue of 6-azaflavin (77) with one less aromatic nitrogen was bound less tightly by receptor **78** than the former guest, suggesting the importance of H-bonding in the complex. The anticipated binding motif is shown below (figure 9).

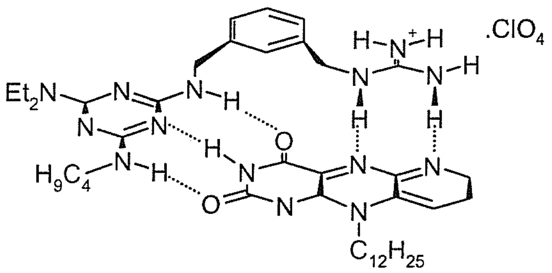
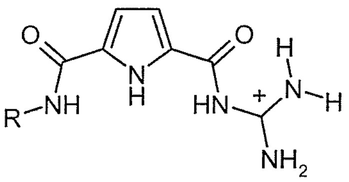


Figure 9. Anticipated binding motif between host **78** and guest **77**.

Schmuck has designed a series of asymmetric guanidinium receptors with a pyrrole core based on **79** that recognise *N*-acetyl-α-amino acid carboxylates in aqueous solvents[69,70].



79

In 40% water/ DMSO receptor **79** with R = ethyl showed appreciable 1:1 binding of *N*-acetyl-phenylalanine. Molecular modelling studies suggested that the amide and pyrrole nitrogen of **79** forms two H-bonds with the guest carboxylate, in addition to the two H-bonds from the guanidinium. Other *N*-acetyl-α-amino acid carboxylates were also bound, molecular modelling studies indicating that association strengths depend largely on the host-guest geometry, as influenced by guest steric hindrance. *N*-Acetyl-phenylalanine shows the strongest association constant; the carboxylate group lies nearly co-planar with the host and a π-stacking interaction between the guest's phenyl ring and the host's acyl group contributes to a better binding interaction. The addition of larger R groups to host **79** has the result of dropping the association constants reflecting increased steric hindrance.

1.2.6 Guanidinium – Sulfonate Solid–state Crystal Engineering

In the last five years or so Ward *et al* have reported a substantial body of work on solid-state lattices built around puckered guanidinium – sulfonate H-bonded sheets[71,72,73,74]. This work is important because as well as demonstrating the guanidinium and sulfonate ions' innate propensity for forming 2-dimensional sheets through multiple bidentate H-bonding (figure 10), it constitutes marked progress in the field of Crystal Engineering[75].

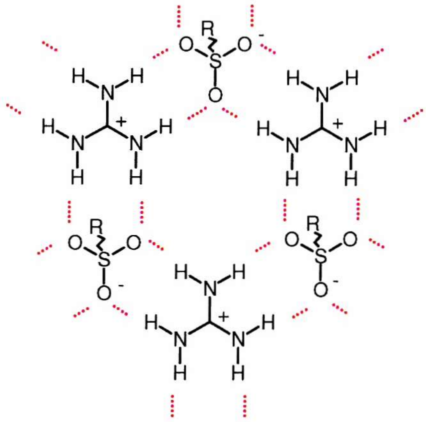


Figure 10. 2-dimensional sheet of guanidinium and sulfonate ions (H-bonds in red).

In the case of simple monosulfonates such as methane-, ethane-, butane- and benzenesulfonate, puckered 2-dimensional H-bonded sheets are observed with guanidinium counterions. In the third dimension two arrangements exist depending on the size of the sulfonate R group: smaller R groups adopt a "bilayer" architecture whereas large R groups favour a "single layer" structure. The former consists of repeating bilayers in which R groups in each sheet are all oriented on the same side, with interpenetrating R groups with the bilayer directed towards each other and Coulombic interactions between opposing sheets (figure 11).

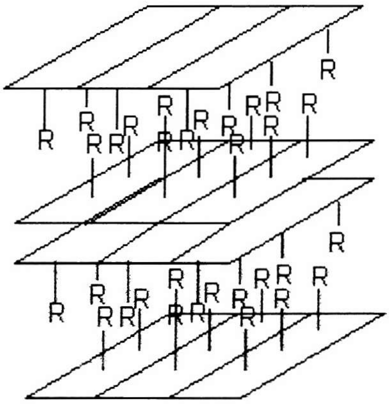


Figure 11. "Bilayer"

The former, the "single layer", consists of sheets of ribbons with R groups lying on alternate sides of each ribbon. The sheets stack with R groups interpenetrating (figure 12).

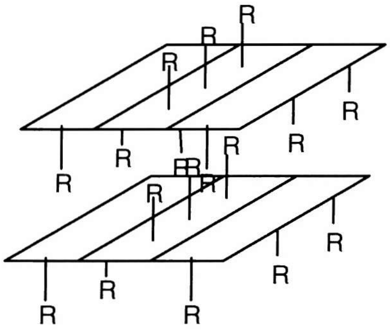
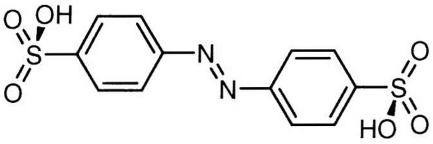


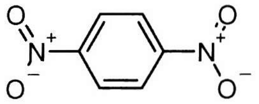
Figure 12. “Single Layer”

When terminal di-sulfonates, for example **80**, are used more complex and interesting solid-state structures result.

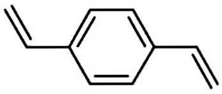


80

Ward found that crystals only form if elongated organic molecules like **81** and **82** were included in the guanidinium – disulfonate mixtures.



81



82

The reason for this observation is that these molecules act as “spacers”, filling the voids between the disulfonates in the two discreet guanidinium – disulfonate sheets. These crystal structures bear striking architectural similarilties to the Parthenon with their pillar-like disulfonates, guanidinium - sulfonate floors and ceilings, and guests between the pillars (figure 13).

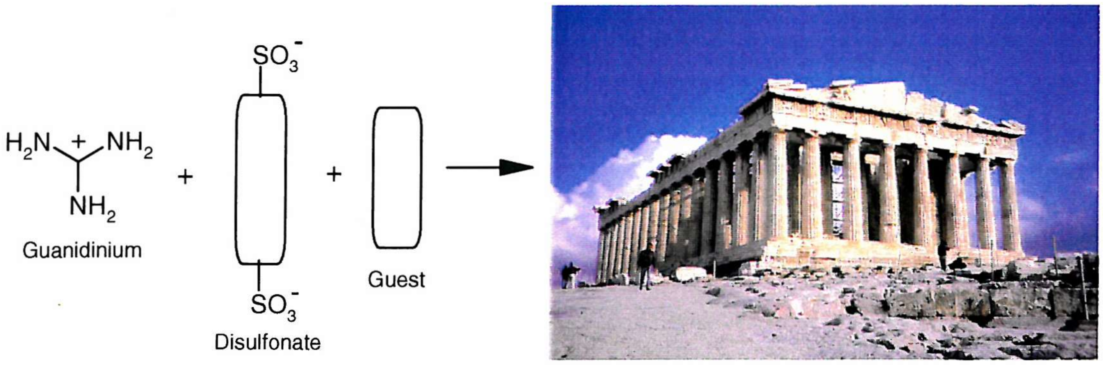


Figure 13. Ward’s Parthenon structures.

1.2.7 Aims of the Project

- To systematically produce a series of synthetically accessible "simple" C-shaped receptors incorporating *N*-substituted (thio)urea or preferably guanidinium groups for the recognition of sulfate and sulfonate anions.

The literature has demonstrated that the guanidinium ion can form very strong interactions with oxoanions. Building on work carried out in the research group, we chose the *m*-xylylene and 2,6-disubstituted pyridine spacer cores for the series of receptors. 2,6-Diamido pyridines have been shown to preferentially adopt a rigid planar conformation enforced by two intramolecular NH···N(pyridine) H-bond-like interactions both in solution and the solid state (figure 14)[76].

This interaction should contribute to receptor preorganisation.

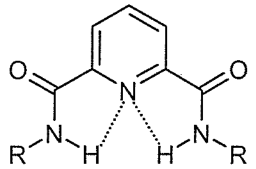


Figure 14. H-bond-like contact in pyridine-2,6-dicarboxylates.

- To then extend the series of C-shaped receptors to include more complex *N,N'*-disubstituted (thio)urea and guanidinium receptors.

- To synthesise tripodal analogues of the two C-shaped receptor series.

- To undertake an investigation of the synthesis of C-shaped receptors for sulfates with a *s*-triazine cores, derived from cyanuric chloride (**1**), a study which has not previously been explored to the best of our knowledge.

Cyanuric chloride is a cheap starting material and incorporates three sequentially substitutable positions. After the addition of the two sidearms to give the C-shaped receptor, the third position could be used to anchor the receptor to a support or be used to incorporate additional functionality.

- To evaluate the receptors' sulfate/ sulfonate (and phosphate) recognition characteristics.

Particular emphasis was to be placed upon solid-state studies of both the receptors' "unbound" geometrical behaviour and the complexes formed with sulfate guests, as well as solution binding studies.

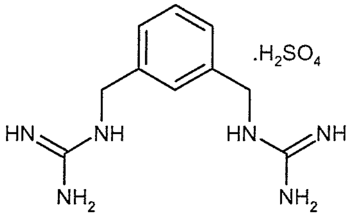
2 Results and Discussion

2.1 "Simple" Archetypal Ligands

C-shaped ligands that can potentially recognise and bind oxoanions have, as previously detailed, been a subject of considerable literature interest. However sulfate and sulfonates have received far less attention than other anionic guest species, and so a series of simple known and novel ligands was synthesised to target sulfate and sulfonate anions. These ligands consist of an aromatic "**core**" (benzene or pyridine) with a functional "**side-arm**" containing H-bonding sites (guanidine, thiourea or urea) linked by a "**bridge**" (a methylene or carbonyl group). The synthesis and, where applicable, solid-state behaviour of these compounds is now discussed starting with the methylene-bridged compounds followed by the carbonyl-bridged compounds.

2.1.1 i) Methylene-bridged Receptors: *m*-Xylylene Di(guanidinium) Sulfate

The starting point for this series (and indeed the project) was identified as the benzene-cored guanidinium side-armed sulfate ligand **70**, previously synthesised by Gobel *et al*[65], Hamilton *et al*[57] and partially investigated by Kenworthy[77] in an earlier study relating to sulphate recognition.



70

Two synthetic approaches to **70** were investigated. The first, based on the Erlenmeyer synthesis[78], in which *m*-xylylene diamine was reacted with cyanamide in water at pH 6.5 and 50°C, gave the desired product in 32% yield. The second method was based on the Rathke synthesis[79], as previously followed by Kenworthy. In this, reaction of *m*-xylylene diamine with excess *O*-methylisourea sulfate in water afforded the product in a more reasonable yield (41%).

In the previous study carried out by Kenworthy[77], a complex X-ray powder diffraction pattern of **70** indicated a highly ordered solid-state structure. Unfortunately the compound's solid-state structure could not be deduced from these data; this would require single crystal X-ray diffraction data. In the present work, recrystallisation of the sparingly soluble microcrystalline powder from a large volume of slowly cooled water gave small needle crystals suitable for such a study. The single crystal X-ray diffraction data was solved by standard methods and, along with a description of the crystal's structure, was published in a communication[80]. The data are summarised below (table 1).

Empirical Formula	$C_{10} H_{18} N_6 O_4 S_1$
Mass	318.36
Collection Temperature/ K	150 (2)
Crystal System	Orthorhombic
Space Group	Pbca
Unit Cell (a,b,c in Å, α,β,χ in °.)	a = 11.057 (2), b = 13.059 (3), c = 19.496 (4), α = 90.00, β = 90.00, χ = 90.00
Volume	2815.1(10)
Z	8
R1	0.0425
wR2	0.1059

Table 1. Crystallographic data for **70**.

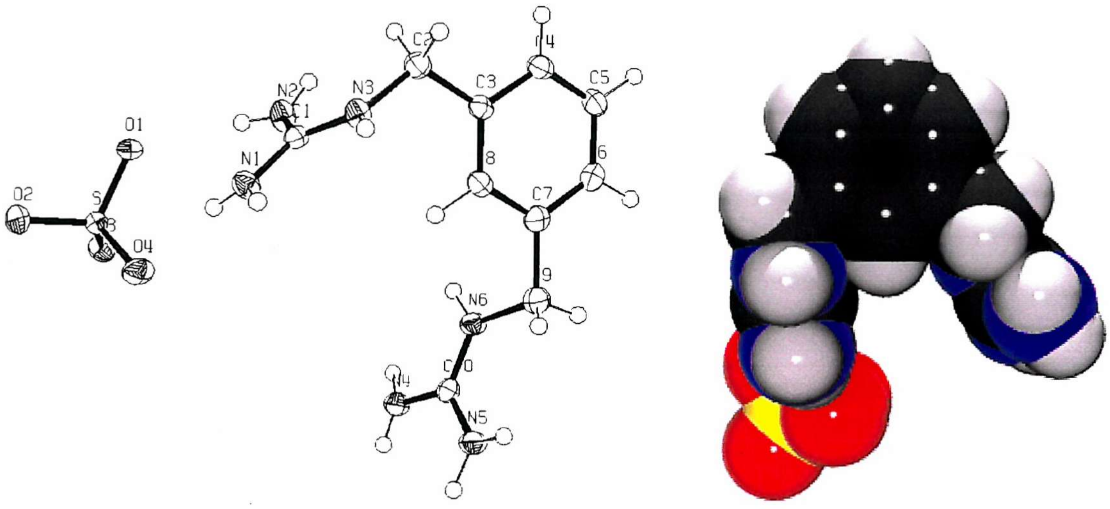


Figure 15. Asymmetric unit of **70** in ORTEP ellipsoids (left) and van der Waal radii (right).

The dication **70** is clearly not planar in the solid state (figure 15) and most significantly does not exhibit tweezer-like host – guest association.

Each guanidinium CN_3^+ unit is planar and is oriented out of the *m*-xylylene plane being disposed in a *trans* manner with respect to the aromatic core.

The non-planar geometry of **70** appears to be inevitable because of hydrogen-hydrogen clashes between the *m*-xylylene C8 hydrogen and the hydrogen atoms attached to N3 and N6 (figure 15). This limits the ability of **70** to accommodate an isolated internal sulfonate guest and consequently encourages external H-bonding contacts as observed in the present structure (Figure 15).

One CH_2-guanidinium group is rotated about a C-(aryl)-CH_2 bond so that the guanidinium N (N3) attached to the CH_2 group is wholly out of the aromatic plane. In the case of the corresponding nitrogen atom (N6) the same is true (although to a lesser extent), but this group is rotated in the opposite direction giving the arms their *transoid* disposition about the aromatic core.

Both guanidinium units are profuse H-bond donors to surrounding sulfate counter ions within the crystal rather than co-ordinating to a single sulfate anion, and hence are components of a complex inter-ion H-bonded array. The dominant packing feature is a sheet in which each sulfate anion is H-bonded to six guanidinium hydrogens from three separate cationic "host" molecules based on a common guanidinium – oxoanion H-bonding motif[81] (figure 16).

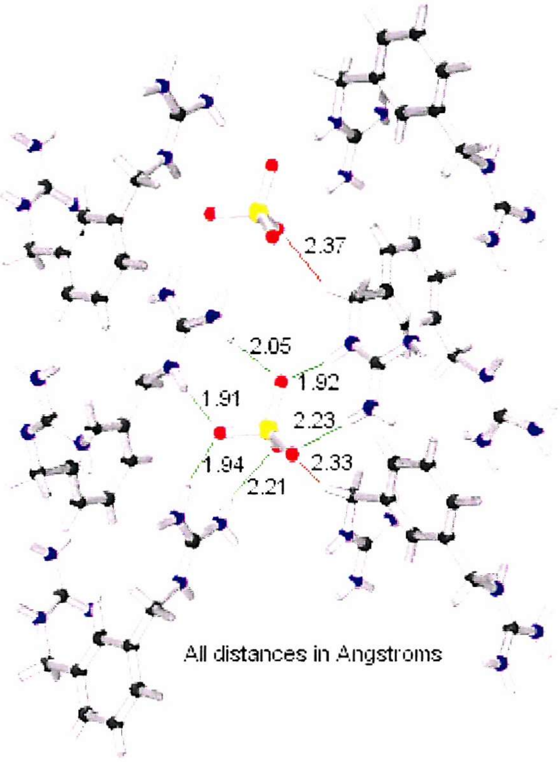


Figure 16. Sheet showing multiple H-bonds between guanidinium units and sulfate.

For these contacts the (N)-H···O distances lie between 1.91 and 2.23 Å. While one of the H-bonded units is essentially fully planar, two are twisted away from co-planarity by about 30°C (figure 15). Sheets are held together by four additional H-bonds to each sulfate anion, two of which comprise the bidentate motif shown below (figure 17), whereas the other two are single N-H···O-SO_3^{2-} interactions.

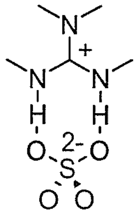


Figure 17. Bidentate H-bonding motif.

In addition, there are two C-H···O close contacts in the sheet ((C)-H···O distance = 2.33 and 2.37 Å) involving *m*-xylylene methylene hydrogens (figure 16 in red). In one case, the oxygen atom contact is already involved in trifurcated H-bonding, and in the other a bifurcated contact.

The solid-state structure of **70** thus forms a highly interconnected H-bonded array in which each sulfate anion is involved in ten N-H···O H-bonds and two C-H···O close contacts. A Cambridge Structural Database[82] search has yielded no other example of a guanidinium-oxoanion crystal with such a high degree of H-bonding about one oxo-anion unit. The four sulfate oxygens are co-ordinated in four different modes: one oxygen is bonded to two N–H groups; a second to two N–H groups plus one C–H; a third to three N–H groups; and the fourth to three N–H groups plus one C–H moiety. All ten guanidinium NH units of each dication are involved in H-bonding to a sulfate anion. The overall conclusion from this structure was that **70** is not an ideal host for sulfate inclusion in the solid state.

As a result of this crystal structure, two avenues for improving the tweezer-like inclusion behaviour of a related molecule presented themselves. These were the replacement of the C8 atom with a heteroatom such as nitrogen to alleviate the hydrogen clash discussed earlier, and/ or substitution of some of the H-bond donor sites to discourage "external" binding (figure 18).

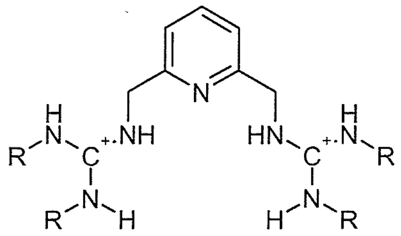
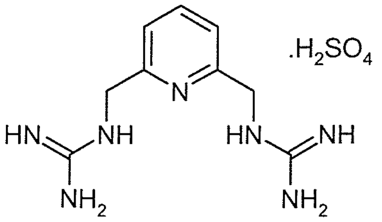


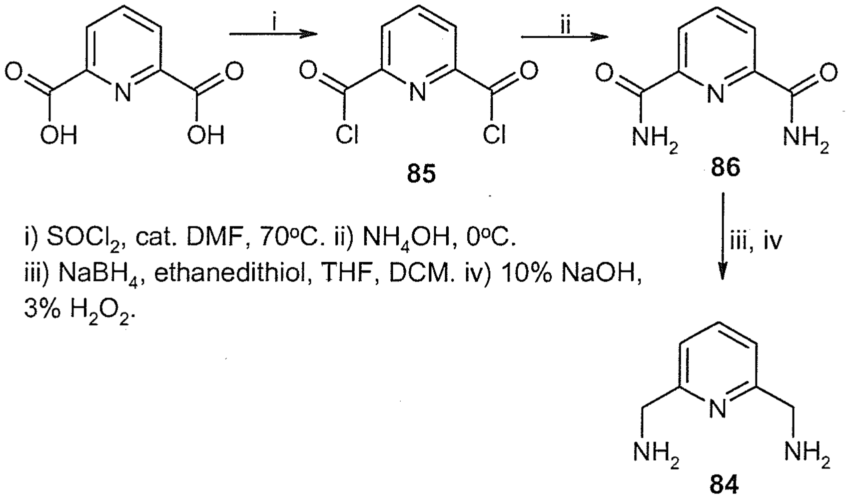
Figure 18. Ligand core modification and guanidinium substitution.

2.1.2 2,6-Bis-(Aminomethyl) Pyridine Synthesis

The simplest route to **83**, as with the benzene analogue **70**, seemed to be reaction of the core diamine with a guanidinium precursor electrophile. However the synthesis of **83** was not as straightforward as the synthesis of **70**, in which both starting materials were commercially available. 2,6-Bis-(aminomethyl) pyridine (**84**) is not commercially available and therefore had to be synthesised. Scheme 6 below shows the first method attempted in the synthesis of **84**.



83

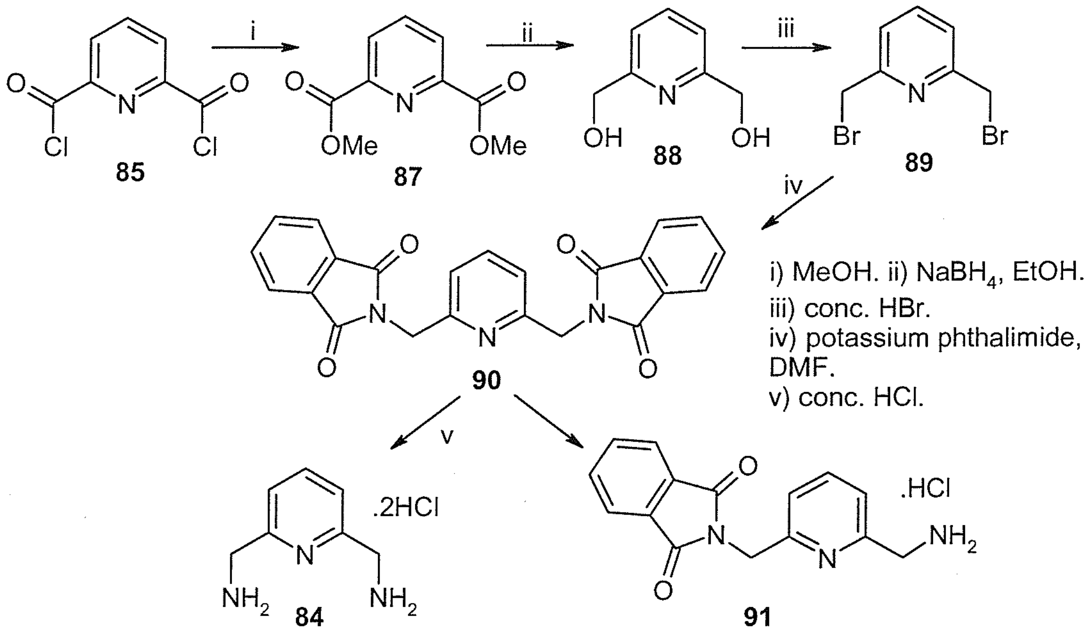


i) $SOCl_2$, cat. DMF, 70ºC. ii) NH_4OH, 0ºC.
iii) $NaBH_4$, ethanedithiol, THF, DCM. iv) 10% NaOH, 3% H_2O_2.

Scheme 6. 2,6-Bis-(aminomethyl) pyridine via diamide reduction.

The pyridine diacid chloride **85** was prepared from commercially available pyridine-2,6-dicarboxylic acid in high yield (92%). The second step also progressed in high yield to afford the pyridine diamide **86** (83%)[83]. However, the reduction of the diamide **86** did not proceed as expected according to the adapted literature method[84]. After basic work up the isolated solid did not correspond to either the diamine **84**, the diamide starting material or the mono-reduced product (by mass spectroscopy and proton NMR). The route was repeated but the reduction of diamide **86** was attempted with a borane/ THF complex instead of sodium borohydride. This also proved fruitless. The reduction was not attempted with lithium aluminium hydride as it was thought that this harsh reducing agent would degrade the pyridine ring. It was decided to abandon routes to 2,6-bis-(aminomethyl) pyridine (**84**) that relied upon the reduction of diamide **86**.

The literature furnished the next method which was attempted, which used the Gabriel synthesis (scheme 7).

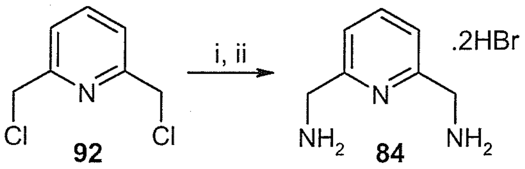


i) MeOH. ii) $NaBH_4$, EtOH.
iii) conc. HBr.
iv) potassium phthalimide, DMF.
v) conc. HCl.

Scheme 7. 2,6-Bis-(aminomethyl) pyridine via diphthalimide (**90**).

Diacid chloride **85** was synthesised as previously, converted to the dimethyl ester **87** in high yield (96%) and then reduced to 2,6-pyridine dimethanol (**88**) again in high yield (96%). However reaction of 2,6-pyridine dimethanol with hydrobromic acid solution to give dibromo **89** was never accomplished in satisfactory yield (16% highest yield achieved). The next step, preparation of diphthalimide **90** from **89**, was also disappointing (24% yield). The final step in the synthesis did not afford 2,6-bis-(aminomethyl) pyridine **84** as its dihydrochloride salt as hoped. Instead, the half-cleavage of the diphthalimide **90** seemed to have occurred (by proton and carbon NMR) to give **91**.

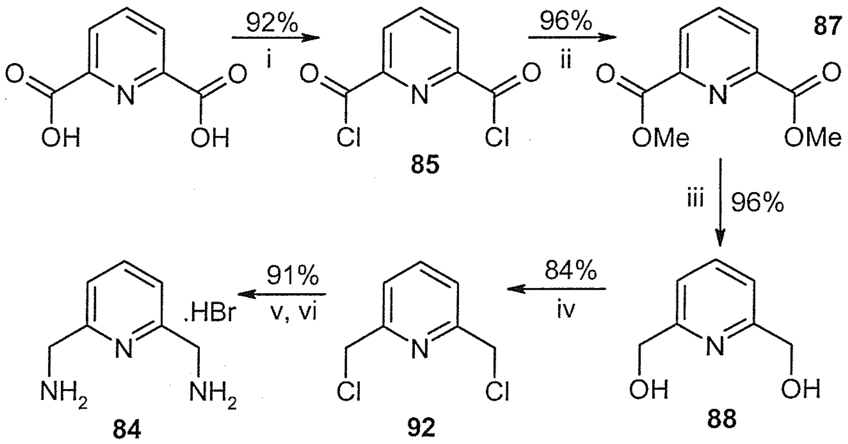
A paper detailing the conversion of 2,6-bis-(chloromethyl) pyridine (**92**) to the dihydrobromide salt of 2,6-bis-(aminomethyl) pyridine (**84**) via diphthalimide **90** in good yield (80%) was published about this time[62] (scheme 8).



i) potassium phthalimide, DMF, 140°C.
ii) 50% HBr.

Scheme 8. 2,6-Bis-(aminomethyl) pyridine via diphthalimide (**90**).

This method, again derived from the Gabriel synthesis, used concentrated hydrobromic acid to convert diphthalimide **90** to diamine **84**.2HBr. The procedure was followed and found to give 2,6-bis-(aminomethyl) pyridine as its dihydrobromide salt (**84**.2HBr) in high yield (91%). However, 2,6-bis-(chloromethyl) pyridine (**92**) is expensive and so the method of Bailey *et al*[85] for the conversion of 2,6-pyridine dimethanol (**88**) to 2,6-bis-(chloromethyl) pyridine (**92**) was followed. This gave **92** in good yield (84%). The route to 2,6-bis-(aminomethyl) pyridine had been established and was optimised to give an overall yield (starting from pyridine-2,6-dicarboxylic acid) of 65%. The route is summarised with yields for each step below (scheme 9).



i) $SOCl_2$, cat. DMF. ii) MeOH. iii) $NaBH_4$, EtOH. iv) $SOCl_2$, toluene.
v) potassium phthalimide, DMF vi) conc. HBr.

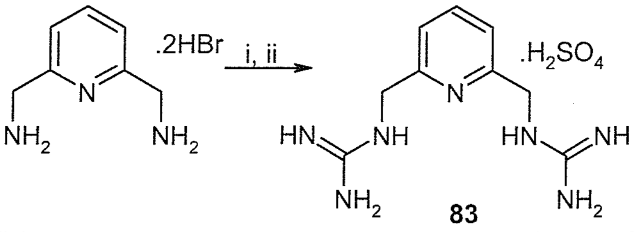
Scheme 9. Optimised route to 2,6-bis-(aminomethyl) pyridine.

2.1.3 2,6-Bis-(Methylguanidinium) Pyridine Sulfate

2,6-Bis-(methylguanidinium) pyridine sulfate (**83**) was synthesised according to a literature procedure[62]. This involved reaction of the dihydrobromide diamine salt **84**.2HBr with excess *S*-methylisothiourea sulfate in the presence of *N,N*-diisopropylethylamine in methanol in a sealed heated ampule to give 2,6-bis-(methylguanidinium) pyridine sulfate (**83**) in relatively low yield (31%). This method was followed and gave the title compound in similar yield (36%). However this synthesis leads to the evolution of methyl mercaptan as an undesirable by-product as well as having low efficiency. Two alternative routes were investigated, both relying on the formation of the neutral ("free") form of diamine **84** before reaction.

The extraction with DCM of an aqueous solution of **84**.2HBr dissolved in basic solution (sodium hydroxide, pH 11) was not very successful, yielding only 11% of neutral diamine **84** after repeated extractions. It was assumed that the neutral diamine preferred to remain in aqueous solution rather than in the organic layer. Instead an anion exchange resin was used. Dowex®-1-chloride (1 × 8 –100) ion-exchange resin was treated with aqueous sodium hydroxide solution to give the hydroxide-charged resin form. Passing an aqueous solution of **84**.2HBr through this gave the neutral diamine **84** in quantitative yield. (It is interesting to note the effect different NMR solvents had on the chemical shifts of 2,6-bis-(aminomethyl) pyridine (**84**). The proton NMR shifts in D_2O and in $CDCl_3$ did not vary much, but the carbon spectrum showed a large downfield shift (124.16 ppm to 161.48 ppm, $\Delta\delta \approx 37$ ppm) for the most downfield resonance on changing solvent from D_2O to $CDCl_3$, reflecting a deshielding effect).

Once neutral diamine **84** had been obtained, the same method as that used for the synthesis of **70**, the benzene cored analogue, was employed to produce **83** (Scheme 10).



i) Dowex-1-hydroxide. ii) *O*-methylisourea sulfate, H_2O, pH 11.

Scheme 10. Synthesis of 2,6-bis-(methylguanidinium) pyridine sulfate (**83**).

2,6-Bis-(methylguanidinium) pyridine sulfate (**83**) was afforded in good yield (84%) and without the formation of undesirable by-products. It is worth noting that application of the Erlenmeyer synthesis also gave **83**. This involved reaction of the neutral diamine with cyanamide in aqueous solution in the presence of sulfuric acid. However reaction time was much greater (4 days) and the yield was lower for this latter route.

83 was recrystallised from water/ ethanol to give needle crystals suitable for an X-ray crystallographic study. The data is summarised below (table 2).

Empirical Formula	$C_9 H_{17} N_7 O_4 S_1$
Mass	319.36
Collection Temperature/ K	150 (2)
Crystal System	Monoclinic
Space Group	P2(1)/c
Unit Cell (a,b,c in Å, α,β,χ in °.)	a = 7.202 (10), b = 11.180 (2), c = 18.192 (4), α = 90.00, β = 100.48 (3), χ = 90.00
Volume	1440.4(5)
Z	4
R1	0.0442
wR2	0.1091

Table 2. Crystallographic data for **83**.

The asymmetric unit is shown in figure 19.

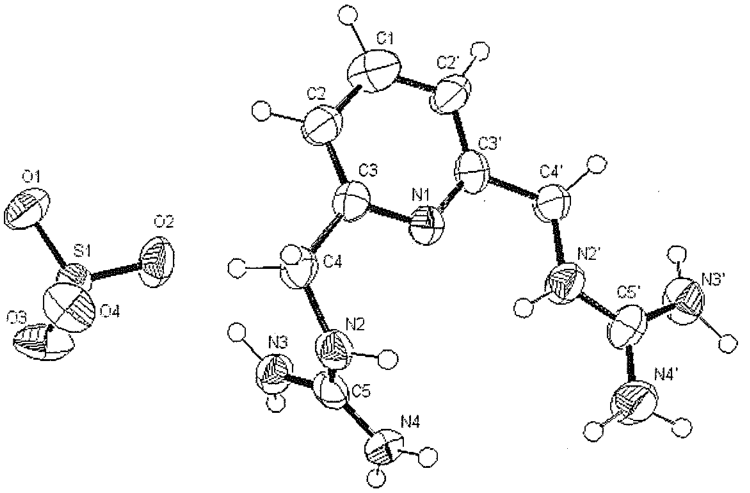


Figure 19. An ORTEP plot of the asymmetric unit of **83**.

It is immediately apparent that once again the sulfate counter ion does not sit within the cavity of the host molecule (as previously observed for **70**). The dication has an unsymmetrical geometry in which one guanidinium arm lies co-planar with the aromatic core whilst the other is twisted out of the pyridine plane by about 90°. The co-planar arm seems to be involved in an internal H-bond-like contact between the pyridine nitrogen N1 and the hydrogen of N2' forming a 5-membered ring (distance N-H...N (pyridine) = 2.11 Å) (figure 19).

Packing of the structure reveals the presence of a complex 3-D lattice in which each bis-guanidinium ligand forms a series H-bonds to more than one sulfate counter ion, behaviour reminiscent of the benzene analogue **70**. However unlike the benzene-cored analogue **70**, the current structure assembles itself into a series of infinite columns (stacked along the b axis) two ligand molecules wide, each column being separated at the corners by sulfate counter ions (figure 20).

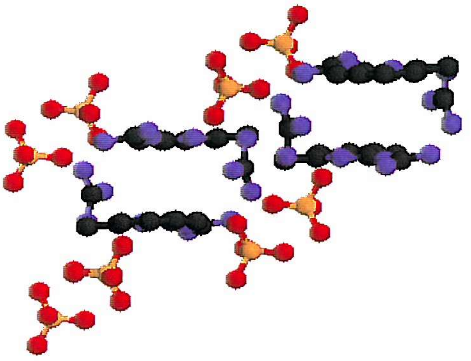


Figure 20. Columns of **83** and sulfate (hydrogens omitted for clarity).

Elucidation of the packed structure shows that four different sulfate orientations occur about each dication **83** (figure 21).

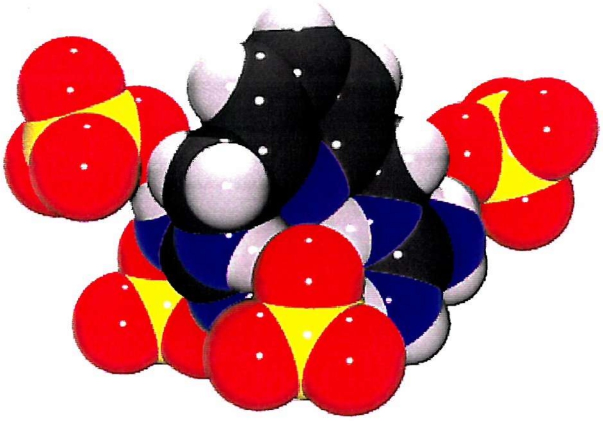


Figure 21. View showing the four sulfate anions in contact with dication **83**.

Each of these sulfate counterions is involved in ten O···H-N H-bonding contacts with multiple donors. For each sulfate anion, two of the oxygen atoms are each involved in two O···H-N H-bonds, while the remaining two oxygen atoms are each involved in three O···H-N H-bonds. All H-bond distances are in the range 1.93 – 2.23 Å.

Whilst the solid-state structure of *m*-xylylene bis-(guanidinium) sulfate **70** involved a maximum of two H-bonds between a single sulfate anion and a single ligand in a bidentate pairwise motif, in **83** two oxygen atoms of a sulfate anion are H-bonded to three N-H donor sites of one ligand so that the sulfate anion sits on top of the ligand cavity (figure 22).

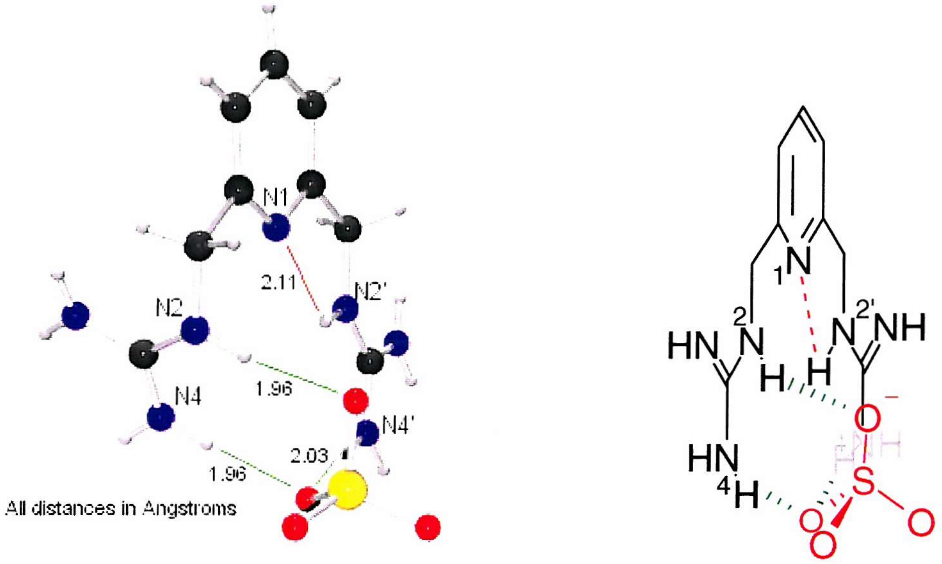


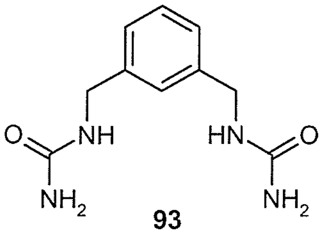
Figure 22. Sulfate counterion sitting on the ligand cavity.

A bidentate N-H···O interaction (in green in figure 22) from the guanidinium arm (comprising N2 and N4) which is twisted out of the plane of the ligand's aromatic core accounts for two of the three H-bonds to the sulfate anion (N-H···O distances both of 1.96 Å). The third H-bond (in green in figure 22) involves the bottom-most nitrogen of the other (co-planar) guanidinium arm (N4'), which H-bonds to the lower of the two oxygens involved in the pairwise interaction with the non-co-planar guanidinium arm (N-H···O distance of 2.03 Å). The intramolecular N-H···N (pyridine) H-bond-like interaction discussed above is shown in red in figure 22.

The solid-state structure of 2,6-bis-(methyl guanidinium) pyridine sulfate **83** does demonstrate an increased preference for 1:1 host – guest recognition not seen in the solid-state structure of its benzene-cored analogue *m*-xylylene bis-(guanidinium) sulfate **70**.

2.1.4 1,3-Bis-(Methylurea) Benzene

Bisurea **93** was synthesised in high yield by the reaction of commercially available 1,3-bis-(isocyanatomethyl) benzene with concentrated aqueous ammonia solution.



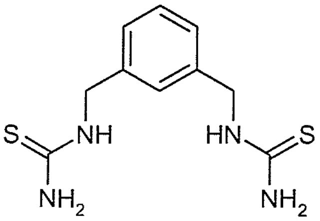
93

93 has previously been prepared by Benner *et al*[62] by reaction of the bis-isocyanate dissolved in MeCN with ammonia gas.

Attempts to co-crystallise **93** with sulfate, sulfonate and phosphonate guests failed.

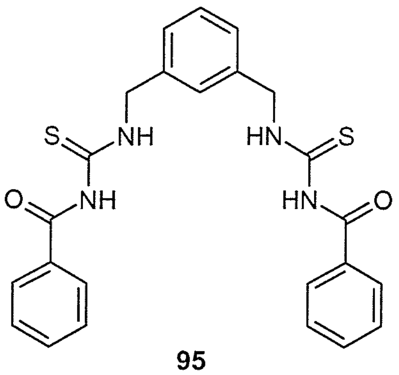
2.1.5 1,3-Bis-(Methylthiourea) Benzene

The thiourea analogue of **93** has been prepared by Hamilton *et al*[60] as an intermediate in their synthesis of ligand **70**.



94

The route Hamilton used involved preparation of the benzene-cored-*N'*-benzoyl-thiourea **95** from ammonium isothiocyanate and benzoyl chloride, followed by aqueous sodium hydroxide hydrolysis to give **94**.



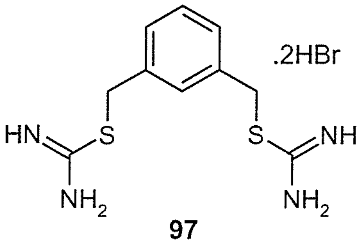
95

Reproduction of Hamilton's method gave **94** in poor yield. The final reduction step accounted for the low efficiency of the synthesis (5% yield). Rather than repeating the procedure a different method was attempted. 1,3-Bis-(isothiocyanato) benzene (**96**) was prepared in good yield (70%) from *m*-xylylene diamine according to the method of Zepik and Benner[62]. Reaction of this in concentrated aqueous ammonia solution gave **94** in a more acceptable yield (88%).

However, as was the case for **93**, attempts to co-crystallise **94** with sulfate, sulfonate and phosphonate guests failed.

2.1.6 *m*-Xylylene Bis-isothiouronium Dibromide

m-Xylylene bis-isothiouronium dibromide (**97**) was synthesised in good yield from reaction of thiourea with *m*-xylylene dibromide in alcohol, similar to the literature procedure[86].



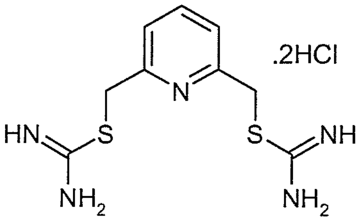
97

Unlike **94**, **97** is a salt and forms a guanidinium-like delocalised cation as is the case for **70** and **83**. The bidentate H-bonding pattern with an oxoanionic guest inside the cavity of **97** is not possible due to the thiouronium bridge. However it was hoped that dication **97** would favour co-crystallisation with a sulfate guest due to zwitterionic charge pairing so that X-ray crystallographic studies could be undertaken.

Unfortunately attempts to crystallise the ligand as its sulfate salt and with sulfonate guests from water/ alcohol mixtures all failed.

2.1.7 Pyridine-2,6-Bis-(methylisothiouronium) Chloride

Synthesis of novel pyridine-2,6-bis-(methylisothiouronium) chloride (**98**) was carried out in reasonable yield (67% after recrystallisation) in the same manner as for **97**, except that the dichloride salt was used instead of the dibromide.

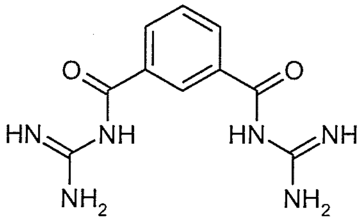


98

Attempted co-crystallisation of this novel compound with sulfate and sulfonate guests once again failed to produce material suitable for X-ray crystallographic studies.

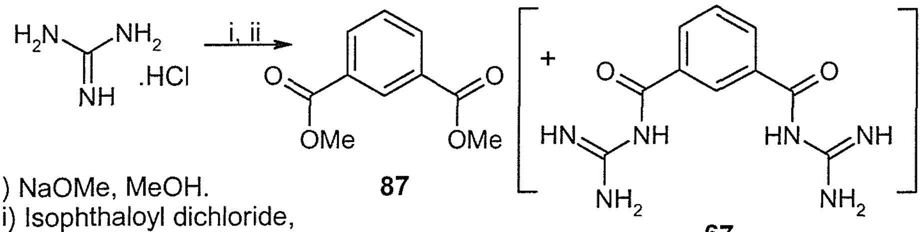
2.1.8 ii) Carbonyl-bridged Receptors: *N,N'*-Bis-(aminoiminomethyl)-1,3-benzenedicarboxamide

The carbonyl-bridged analogue of **70**, *N,N'*-bis-(aminoiminomethyl)-1,3-benzenedicarboxamide (**67**), has previously been prepared by Hamilton and co-workers[58,59] and also by Kenworthy[77] (using a different method). Both these syntheses and a third approach were attempted in the preparation of this compound.



67

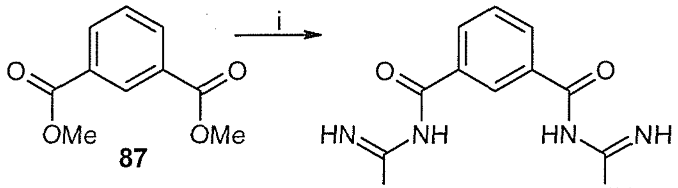
The method of Kenworthy involved reaction of excess guanidine with isophthaloyl dichloride. Guanidine hydrochloride was deprotected with stoichiometric sodium methoxide in methanol and the common salt produced was removed. Isophthaloyl dichloride dissolved in THF in the presence of triethylamine was then added to this solution at room temperature. However in the present work, this method failed to produce **67**. This result was attributed to the presence of methanol as solvent. This could act as a "competitive nucleophile" in the reaction so that dimethyl isophthalate was produced (scheme 11). As methanol is a good nucleophile with respect to acid chlorides and was in a great excess in the reaction, the dimethyl ester **87** was indeed the major product under the conditions employed.



i) NaOMe, MeOH.
ii) Isophthaloyl dichloride,
THF, Et$_3$N, *room temperature.*

Scheme 11. Unsuccessful preparation of **67**.

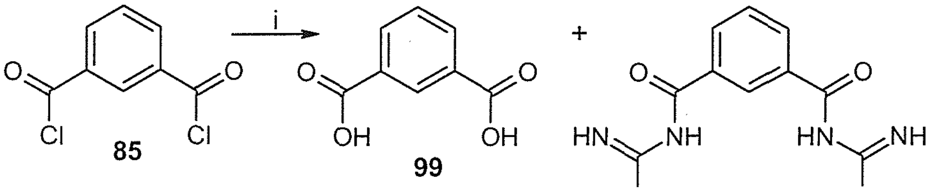
Hamilton and co-workers[58] prepared **67** by reacting guanidine directly with dimethyl isophthalate in methanol at reflux (scheme 12). These harsher reaction conditions seemed sufficient to enable substitution of the poor methoxy leaving group with guanidine and thus **67** was obtained in relatively low yield after recrystallisation from water (19%).



i) Guanidine, methanol, ⥮

Scheme 12. Hamilton's preparation of **67**.

The third synthesis of **67** was attempted using a "mixed phase" methodology. Guanidine hydrochloride was added to a vigourously stirred mixture of basic aqueous solution and DCM at 0°C, isophthaloyl dichloride dissolved in DCM was then added (scheme 13).



i) Guanidine.HCl, aq. NaOH
solution, DCM, 0°C.

Scheme 13. "Mixed phase" preparation of **67**.

This reaction produced largely the hydrolysed starting material, isophthalic diacid (**99**), which remained suspended in the organic layer (this was identified by comparison of its proton and carbon NMR with that of commercially available isophthalic diacid). However, once the aqueous layer had been neutralised and evaporated to dryness and the residue had been recrystallised from water, **67** was produced albeit in very poor yield (5%) but with higher purity than the two previous methods.

2.1.9 *N,N'*-Bis-(Aminoiminomethyl)-1,3-benzenedicarboxamide Sulfate

67 was converted to its sulfate salt (**67**.H_2SO_4) by dissolution in hydrochloric acid solution followed by addition of sodium sulfate, as reported by Kenworthy[77]. Slow recrystallisation of the salt from boiling water/ DMSO gave tiny needle crystals suitable for X-ray crystallographic study and the structure of these was solved from the data collected. Table 3 shows a summary of the crystal data and the asymmetric unit is displayed below (figure 23).

Empirical Formula	$C_{10}\ H_{18}\ N_6\ O_8\ S_1$
Mass	382.36
Collection Temperature/ K	150 (2)
Crystal System	Triclinic
Space Group	P-1
Unit Cell (a,b,c in Å, α,β,χ in °.)	a = 7.0598 (4), b = 9.4365 (5), c = 12.7661 (9), α = 68.312 (2), β = 88.648 (3), χ = 86.344 (4)
Volume	788.66 (8)
Z	2
R1	0.0492
wR2	0.1055

Table 3. Crystallographic data for **67**.H_2SO_4

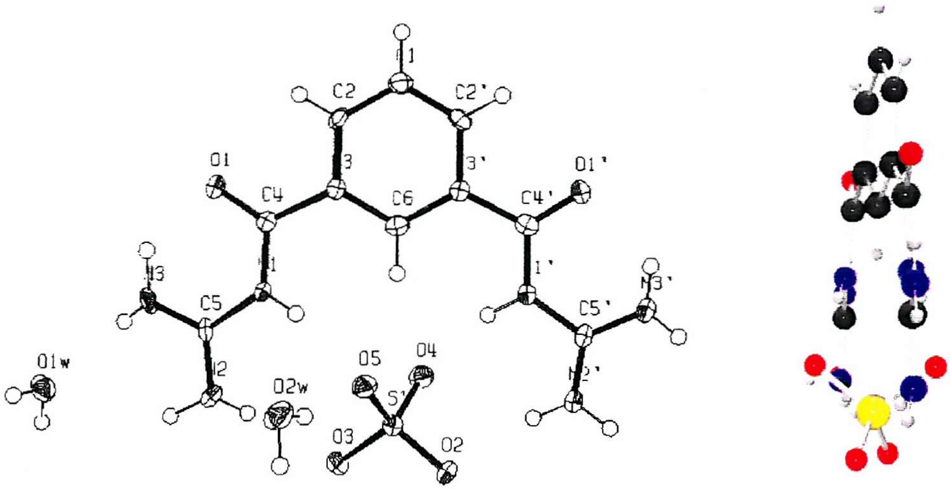


Figure 23. Asymmetric unit of **67**.H_2SO_4.

It is immediately apparent that the sulfate guest is located in the host molecule's cavity. It seems that the *cis-cis* near planar geometry responsible for the cavity in the ligand is brought about by an intramolecular H-bond between the N3 hydrogens and O1 oxygens (figure 25), as proposed by Hamilton *et al*[58]. These H-bonds cause the guanidine arms to lie almost co-planar with the aromatic core. Somewhat surprisingly despite the sp^2 character of C4 and C4', the N-H bond distances for N1 and N1' differ little compared to those in the structures of **70** and **83**, the methylene-bridged pincers discussed previously (in which the analogous carbon atoms are sp^3 hybridised) (see table 4). More interestingly the distances from the hydrogens bonded to N1 and N1' to the C6 hydrogen are much smaller than the analogous distances found in **70** (see table 4).

	Secondary N-H Bond Lengths (Å)	N1(')-H...H-C6 distances (Å)
70	0.95 ± 0.03 and 0.85 ± 0.04	2.73 ± 0.04 and 2.95 ± 0.03
83	0.84 ± 0.04 and 0.77 ± 0.05	-
67	0.95 ± 0.04 and 0.90 ± 0.05	2.04 ± 0.06 and 2.10 ± 0.05

Table 4. Selected non-bonded distances and bond lengths in the crystal structures of **70, 83** and **67**.H_2SO_4.

In **70** these distances are close to van der Waals' contacts[87], whereas in **67**.H_2SO_4 the distances are markedly shorter; presumably the latter is brought about by a combination of the intramolecular H-bonding within the host and maximisation of H-bonding to the sulfate ion. Distances between O4 and O5 of the sulfate ion and the C6 hydrogen are too great to imply any close contact (> 2.55 Å).

In **67**.H_2SO_4 the sulfate anion forms four H-bonds to the host molecule which involve all four sulfate oxygen atoms. These H-bonds have effective C_2 symmetry about a rotation axis through C1 and C6 of the benzene ring. The key contacts are summarised in figure 24. They consist of two twisted pairwise bidentate H-bond interactions between host and guest. O2 is H-bonded to a hydrogen from N2' and O4 is H-bonded to the hydrogen of N1' to form one pairwise bidentate H-bond interaction; O3 is H-bonded to a hydrogen from N2 and O5 is H-bonded to the hydrogen of N1 to form the other pairwise bidentate H-bond interaction. H-bond distances are in the range 1.91 – 1.96 Å. Two water molecules are also present in the asymmetric unit which H-bond to 'external' N-H groups.

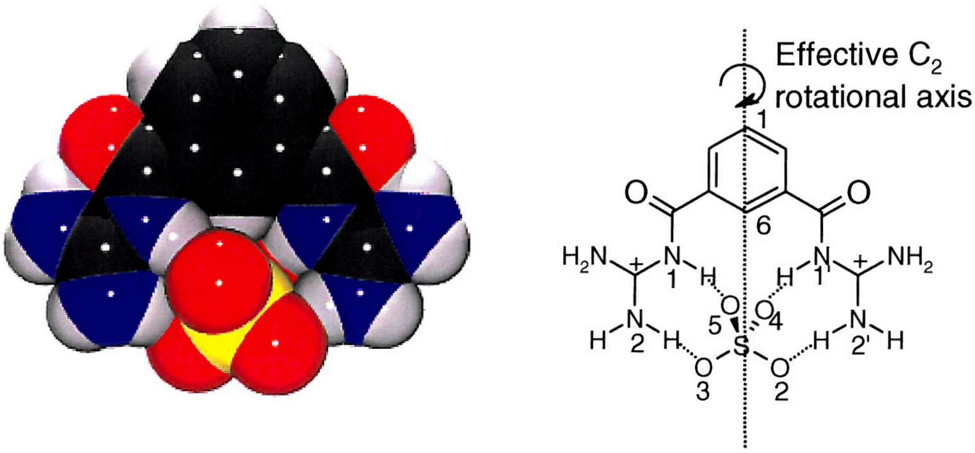


Figure 24. van der Waals representation (left) and sketch (right) of the H-bonding pattern in **67**.H_2SO_4.

The structure packs in a series of rows (figure 25) in which lateral ligand neighbours are packed "head-to-toe" with H-bonded water filling the gaps between adjacent molecules. A pairwise N-H...O H-bonding interaction (similar to that observed for carboxylic acids in the solid state) is also apparent.

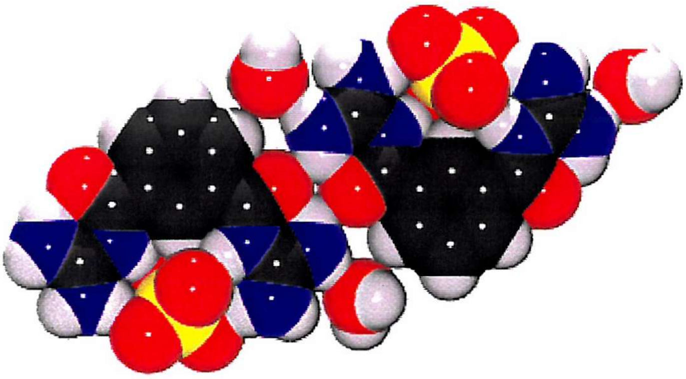


Figure 25. Part of a row in the crystal structure of **67**.H_2SO_4.

These rows pack together in stacks, in which rows are staggered with respect to one another with a face-to-face separation of about 3.4 Å (figure 26).

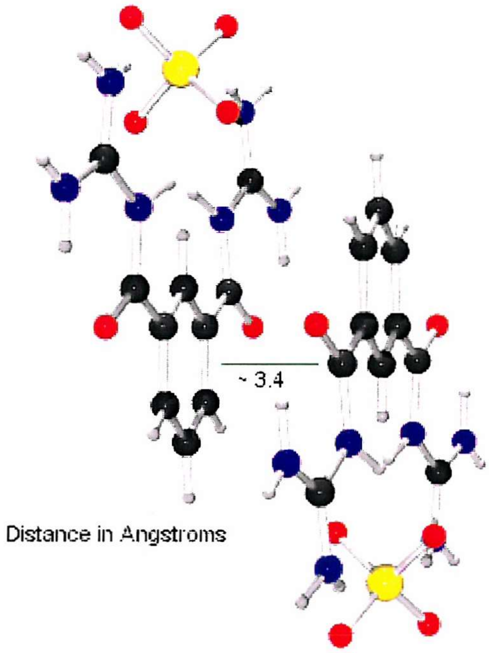


Figure 26. Part of a stack in the crystal structure of **67**.H_2SO_4.

The structure of *N,N'*-bis-(aminoiminomethyl)-1,3-benzenedicarboxamide sulfate (**67**.H_2SO_4) is an example of exclusive 1:1 host – guest recognition in the solid-state, in which each ligand forms four H-bonds to one sulfate anion situated within its cavity. All four sulfate oxygens are involved in the H-bond pattern. It is interesting to compare this solid-state structure with that reported by Anslyn[64] for phenyl phosphate co-crystallised with a bis-(guanidinium) tricyclic-cored receptor **72** (figure 27).

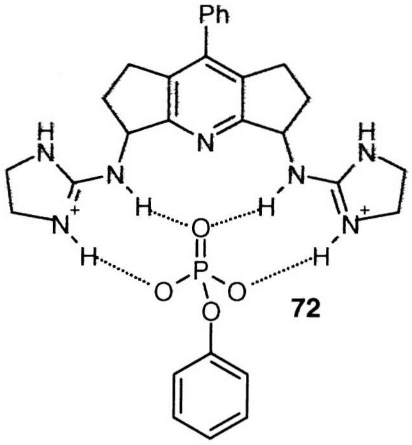

72

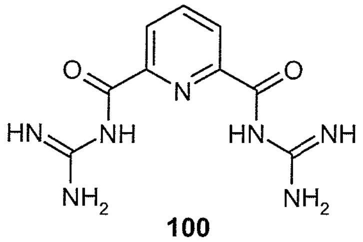
Figure 27. Representation of the crystal structure reported by Anslyn.

That structure includes four NH H-bonds to three of the phosphate oxygen atoms in a "wedge" mode.

In a recent publication involving a related benzene-cored C-shaped thiouronium receptor[88], $H_2PO_4^-$ ($K_a = 1080\ M^{-1}$) was found to bind more strongly in d_6-DMSO solution than $PhP(OH)O_2^-$ ($K_a = 150\ M^{-1}$) (by ^1H NMR titration). The author states that "It is not clear why phenyl was deleterious, but we might argue the diminished binding strength of $PhP(OH)O_2^-$ could be rationalized by the different number of oxygens which could interact with the receptor." A possible explanation for the observed solution association constants is that complexes with simple sterically unhindered unsubstituted sulphates and phosphates could adopt the binding mode observed for **67**.H_2SO_4 in the solid-state, where all four oxygen atoms are involved in H-bonds, instead of the "wedge" mode observed for the substituted tetrahedral oxoanion as in **72**.

2.1.10 *N,N'*-Bis-(Aminoiminomethyl)-2,6-pyridinedicarboxamide

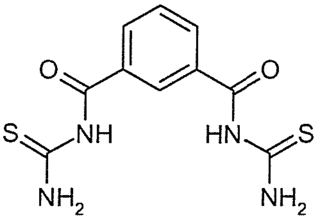
The novel pyridine analogue of **67**, N,N'-bis-(aminoiminomethyl)-2,6-pyridinedicarboxamide (**100**), was successfully synthesised by the application of Hamiton and co-workers' method[58] in reasonable yield after recrystallisation (43%).


100

Adaptation of Kenworthy's method[77], involving reaction of pyridine-2,6-diacid chloride (**85**) and guanidine in THF, was low yielding (8% after recrystallisation). Both of these yields are improvements on those obtained for **67**, the benzene-cored analogue of **100**, and are presumably brought about due to the slightly increased reactivity of the electrophilic centre in the pyridine-cored precursors over their benzene-cored analogues. The proton NMR spectrum of **100** was interesting because in d_6-DMSO each aromatic proton environment gave a distinct signal, whereas in D_2O all three aromatic proton signals showed up as a singlet at the same chemical shift ($\delta = 7.8$ ppm).

2.1.11 *N,N'*-Bis-(Aminothiocarbonylmethyl)-1,3-benzenedicarboxamide

Adaptation of Kenworthy's methodology was used to synthesise **101**, the thiourea dicarboxamide, from thiourea and isophthaloyl dichloride though once again in low yield (15%).



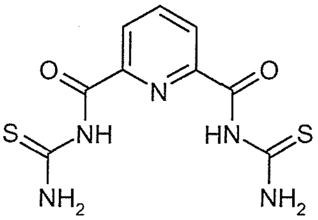
101

Comparison of the chemical shifts (from carbon NMR) with those for **67** confirmed that **101** exists as the structural isomer shown (C=S at 181.87 ppm and C=O at 166.87). Purification of the thiourea was more difficult than for the two aminoimino dicarboxamides **67** and **100**, mainly due to the similar solubilities of thiourea and the product. Most of the excess thiourea was filtered off before removal of solvents, but some thiourea remained in solution and so several recrystallisations of the residue were required to remove it.

Attempts to produce **101** by the reaction of thiourea with dimethyl isophthalate failed.

2.1.12 *N,N'*-Bis-(Aminothiocarbonylmethyl)-2,6-pyridinedicarboxamide

102 was prepared in the same manner as *N,N'*-bis-(aminothiocarbonylmethyl)-1,3-benzenedicarboxamide (**101**), the dimethyl ester route again proving unsuccessful. However, perhaps due to the increased solubility of **102**, purification proved more difficult and *N,N'*-bis-(aminothiocarbonylmethyl)-2,6-pyridinedicarboxamide could not be isolated in its pure form after numerous recrystallisations. Comparison of the chemical shifts (from carbon NMR) with those from **100** confirmed that **102** exists as the structural isomer shown (C=S at 181.44 ppm and C=O at 163.92 ppm).



102

2.1.13 Benzene-1,3-Dicarboxylic Acid Dihydrazide

In addition to the pincer ligands in which the H-bond donor group is bonded to the core unit via a carbonyl bridge, pincer ligands that included an additional "spacer" atom between these two regions of the molecule were investigated. The "spacer" atom used was nitrogen, thus giving two hydrazide functionalities (figure 28). It was hoped this arrangement would increase the effective width of the host's cavity, thus modifying its solid-state behaviour towards an oxoanionic guest.

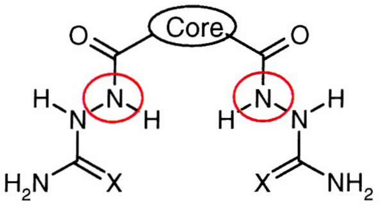
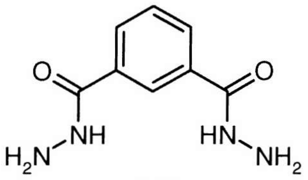


Figure 28. Additional sidearm "spacer" atom derived from the hydrazide group.

Benzene-1,3-dicarboxylic acid dihydrazide (**103**) was synthesised in moderate yield (46%) from the reaction of dimethyl isophthalate with excess hydrazine in methanol.



103

Recrystallisation of the product from water gave colourless needle crystals suitable for X-ray crystallographic study. The data was collected and solved (table 5).

Empirical Formula	$C_8 H_{10} N_4 O_2$
Mass	194.20
Collection Temperature/ K	150 (2)
Crystal System	Triclinic
Space Group	P-1
Unit Cell (a,b,c in Å, α,β,χ in °.)	a = 3.856 (10), b = 9.811 (2), c = 12.158 (2), α = 109.61 (3), β = 92.29 (3), χ = 101.12 (3)
Volume	422.40 (16)
Z	2
R1	0.0483
wR2	0.1144

Table 5. Crystallographic data for **103**.

These data revealed that a *syn-anti* geometry exists for **103** in the solid-state (figure 29).

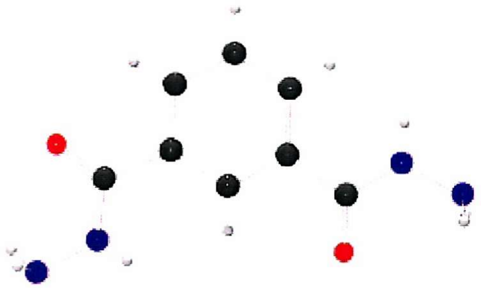
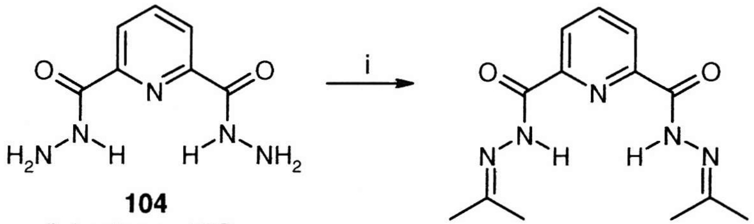


Figure 29. *Syn-anti* geometry in **103**.

2.1.14 Pyridine-2,6-Dicarboxylic Acid Dihydrazide

The analogous pyridine-cored compound **104** was also prepared, however application of the conditions used for the synthesis of benzene-1,3-dicarboxylic acid dihydrazide (**103**) did not afford the desired product. Instead, pyridine-2,6-dimethyl ester (**87**) was reacted in neat hydrazine hydrate to give **104**. Crystals of suitable size for solid-state studies could not be grown from water or aqueous alcohol mixtures, but when **104** was dissolved in acetone and the solution was chilled, colourless needle crystals of the reversibly-formed imine product (**105**) were obtained. These were studied instead (scheme 14). Although a different compound, it was felt that this bis-imine would possess a geometry similar to that of **104**.



104

i) Acetone, -5°C.

105

Scheme 14. Preparation of diimine **105**.

The data for the solid-state structure of **105** are displayed below (table 6).

Empirical Formula	$C_{13}H_{17}N_5O_2$
Mass	275.32
Collection Temperature/ K	150 (2)
Crystal System	Monoclinic
Space Group	P2(1)/c
Unit Cell (a,b,c in Å, α,β,χ in °.)	a = 8.6507 (3), b = 12.3418 (6), c = 12.8189 (7), α = 90.00, β = 97.967 (2), χ = 90.00
Volume	13355.40 (11)
Z	4
R1	0.0445
wR2	0.0983

Table 6. Crystallographic data for **105**.

The unit cell of **105** revealed that a *syn-syn* geometry exists, as expected for a pyridine diamide-related compound of this type (figure 30). N-H···N distances are 2.34 and 2.31 Å.

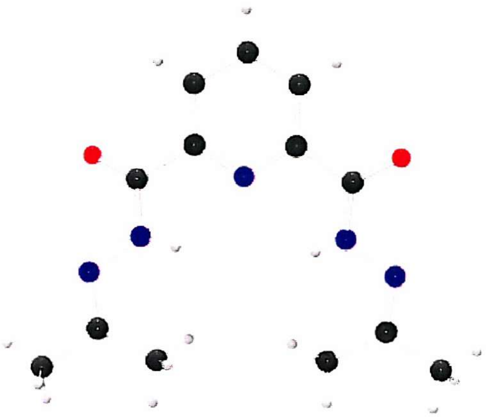
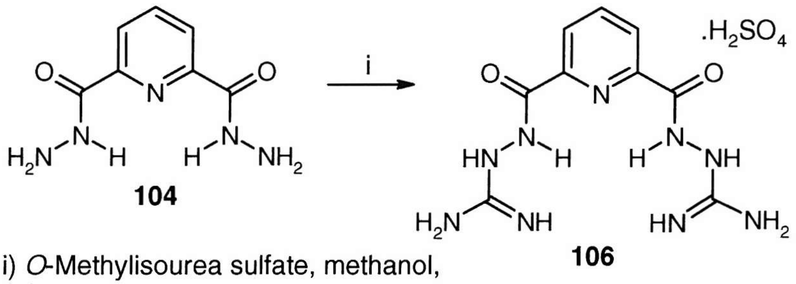


Figure 30. Asymmetric unit of **105**.

2.1.15 *N,N'*-Bis-(Guanidinium)-2,6-pyridinedicarboxamide Sulfate

104 was reacted with excess *O*-methylisourea sulfate in methanol containing a small amount of DMSO at reflux (scheme 15).



i) *O*-Methylisourea sulfate, methanol, reflux.

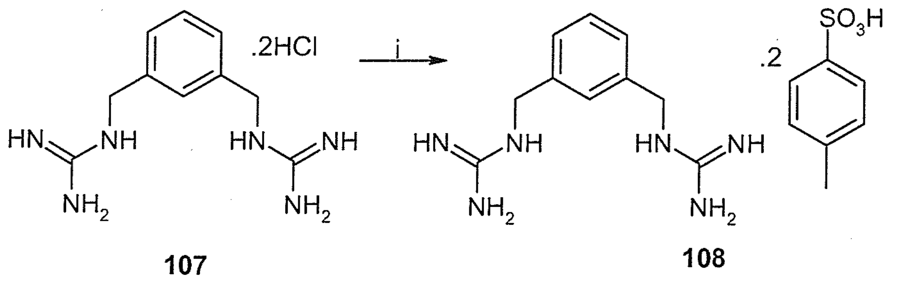
Scheme 15. Attempted preparation of **106**.

The product of the reaction was recrystallised from water/ DMSO to give colourless plate crystals too small for crystallographic study. Although the proton NMR suggested the desired product had been formed, the guanidine carbon was not represented in the carbon NMR spectrum. The mass spectrum showed a peak consistent with the dihydrazide starting material. Together with the elemental analysis, these data showed that the sulfate salt of pyridine-2,6-dicarboxylic acid dihydrazide (**104**.H_2SO_4) had been formed rather than **106**.

2.1.16 Sulfonate Salts i) *m*-Xylylene Di(guanidinium) Di(Toluene Sulfonate) Salt

As well as attempting to make and determine the structures of sulfate complexes of the synthesised ligands, efforts were made to co-crystallise the various host molecules prepared in this study with "model" dye molecules. Reactive dye molecules have numerous phenyl sulfonate groups, so toluene sulfonic acid was selected as one "model" dye molecule because of its structure, aqueous solubility, availability and low cost.

m-Xylylene di(guanidinium) sulfate (**70**) was converted to the corresponding dihydrochloride salt **107** which is both water and alcohol soluble. (A similar procedure was used for compounds **67** and **83**, however neither of these produced crystalline salts with any sulfonate guests). Slow crystallisation of *m*-Xylylene di(guanidinium) dihydrochloride (**107**) with two equivalents of toluene sulfonic acid from water gave large colourless crystals of the di(toluene sulfonate) salt **108** after several weeks (scheme 16).



i) $TsOH.H_2O$, H_2O.

Scheme 16. Preparation of ditosylate salt **108**.

The crystal structure was solved conventionally and the relevant summary data are displayed below (table 7).

Empirical Formula	$C_{24}H_{34}N_6O_7S_2$
Mass	567.04
Collection Temperature/ K	150 (2)
Crystal System	Triclinic
Space Group	P-1
Unit Cell (a,b,c in Å, α,β,χ in °.)	a = 12.974 (3), b = 13.048 (3), c = 18.094 (4), α = 106.18 (3), β = 105.26 (3), χ = 103.99 (3)
Volume	2668.8 (11)
Z	4
R1	0.1138
wR2	0.2626

Table 7. Crystallographic data for **108**.

The unit cell of the structure consisted of two bis-guanidinium molecules and four sulfonates and also included one water molecule (figure 31).

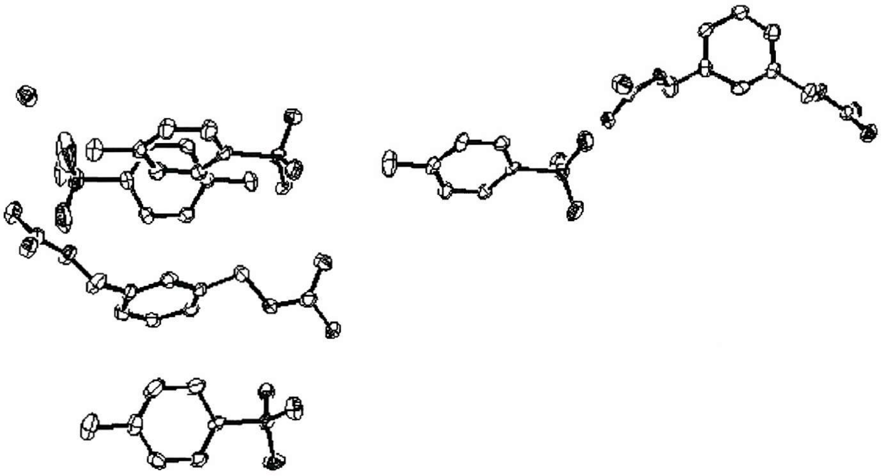


Figure 31. Asymmetric unit of **108** (hydrogen atoms and labels omitted for clarity).

Packing of the structure revealed that no host – guest inclusion recognition occurs in the solid-state architecture of this salt; rather the di(guanidinium) and toluene sulfonate counter ions are arranged in alternating rows (figures 32 and 33).

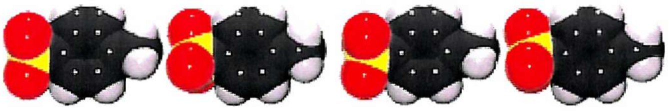


Figure 32. Toluene sulfonate row.

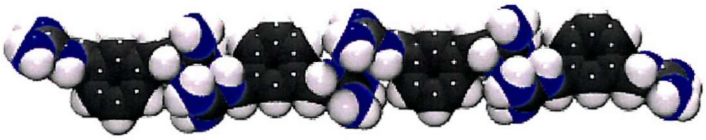


Figure 33. *m*-Xylylene di(guanidinium) row.

These two types of rows are held together by N-H···O H-bonds between di(guanidinium) ligands and sulfonate counter ions (figure 34). The two twisted guanidinium moieties from one ligand form H-bonds to sulfonate counter ions in *separate* rows.

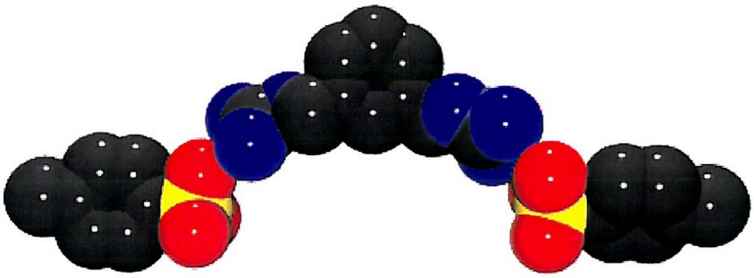
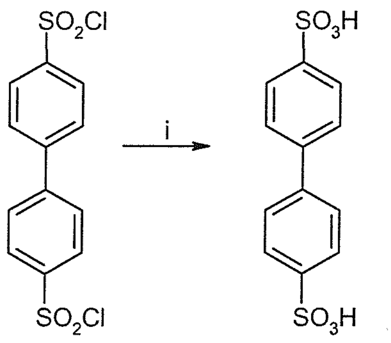


Figure 34. A di(guanidinium) ligand and two tosyl counterions.

2.1.17 ii) *m*-Xylylene Di(guanidinium) 4,4'-Biphenyldisulfonate Salt

The second "model" dye sulfonate used was 4,4'-biphenyldisulfonate (**109**). This was easily synthesised from the sulfonyl precursor (scheme 17) and has been used by Ward *et al*[72] as a building block in their guanidinium – sulfonate architectures.



i) NaOH solution, 50°C.

Scheme 17. Preparation of **109**.

Crystals of *m*-xylylene di(guanidinium) 4,4'-biphenyldisulfonate (**110**) were grown from water solution and solved conventionally. Table 8 summarises the data.

Empirical Formula	$C_{22} H_{27} N_6 O_7 S_2$
Mass	543.62
Collection Temperature/ K	150 (2)
Crystal System	Orthorhombic
Space Group	Pbca
Unit Cell (a,b,c in Å, α,β,χ in °.)	a = 10.949 (2), b = 15.328 (3), c = 29.703 (6), α = 90.00, β = 90.00, χ = 90.00
Volume	4984.9 (17)
Z	8
R1	0.0451
wR2	0.1109

Table 8. Crystallographic data for **110**.

The unit cell contains one ligand and one disulfonate unit. A molecule of water (O1W) is also present (figure 35).

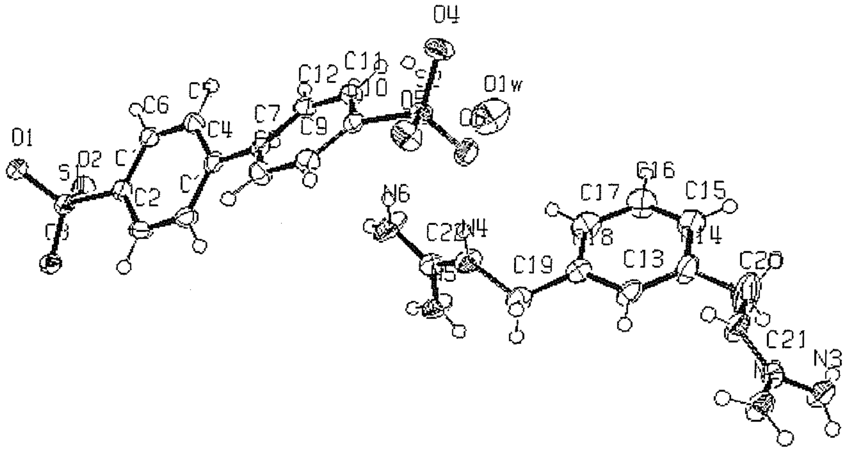


Figure 35. Asymmetric unit of **110**.

The packed structure exists as a complex 3-D array of twisting and zigzaging H-bonded bis-guanidinium and disulfonate molecules, a section of which is shown below (figure 36). Single and bidentate N-H···OSO_2^- H-bonding interactions exist in the structure.

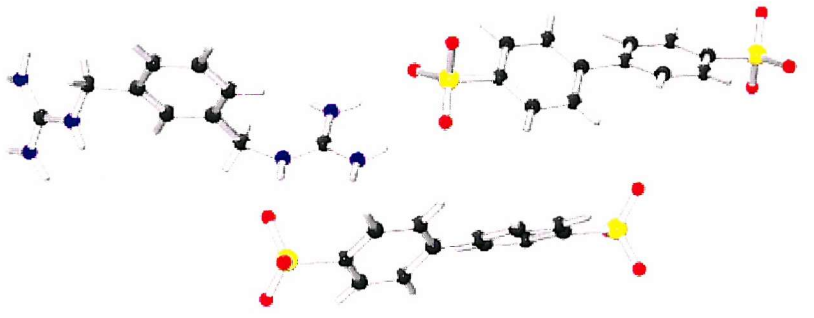


Figure 36. The two H-bonding motifs found in **110**.

Again, no host – guest inclusion recognition occurs in the solid-state architecture of this salt.

2.1.18 Summary

All of the "simple" C-shaped ligands prepared as part of the work described in this chapter are displayed below in the order in which they appear (figures 37 and 38).

Methylene-Bridged Ligands

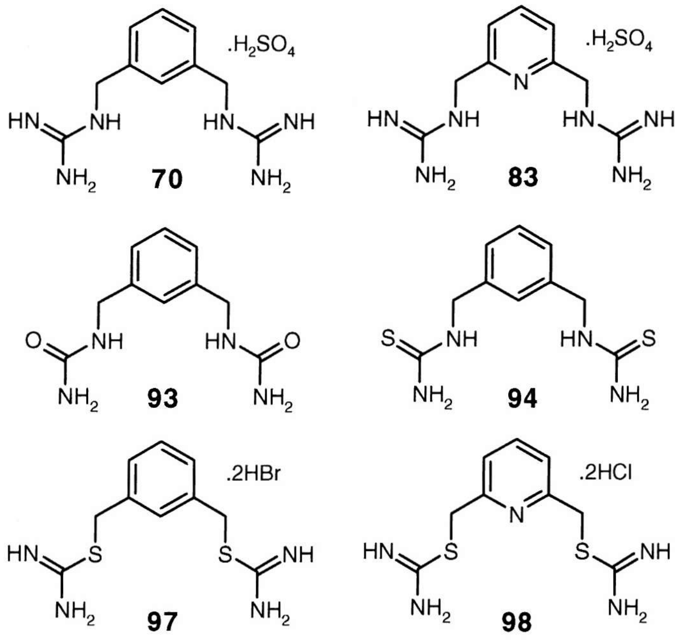


Figure 37. Methylene-bridged ligands.

Carbonyl-Bridged LIgands

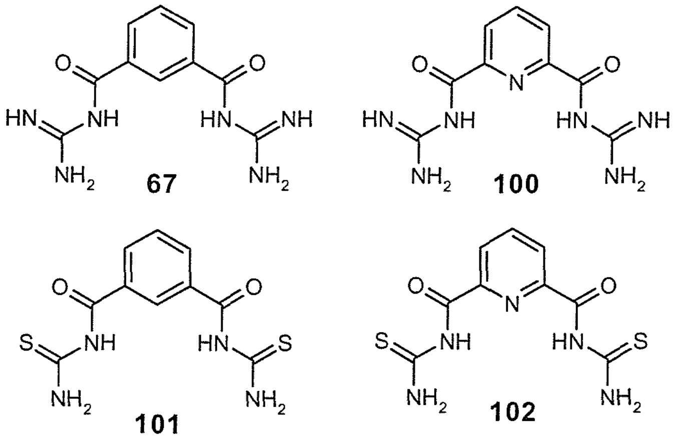


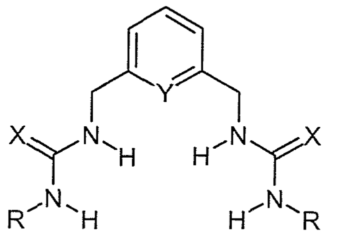
Figure 38. Carbonyl-bridged ligands.

The synthesis of a series of simple potential tweezer receptors including some novel materials has been successfully completed. The crystal structures of three of these compounds as their sulfate salts, **70**, **83** and **67**.H_2SO_4, have shown that a relationship between increasing receptor preorganisation (planarity) and an increased preference for 1:1 host – guest recognition exists in the solid state for molecules of this type.

A cheap and efficient route to the important intermediate 2,6-bis-(aminomethyl) pyridine **84** has been optimised.

2.2 Substituted Urea-type C-shaped Ligands

The next series of C-shaped ligands investigated were those which contained substitution at the *N'* (and *N''*) position of the receptor urea-like moiety (scheme 18). It was hoped that substitution at this position would sterically preorganise the receptor so that the majority of the host's H-bonding sites were situated inside its cavity, thus increasing the likelihood of internal guest recognition in the solid-state.

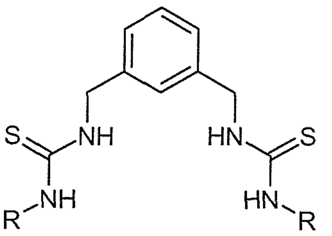


X = S, O, NH, NR'
Y = CH, N
R = Alkyl, aryl

Scheme 18. "Di-substituted" C-shaped receptor.

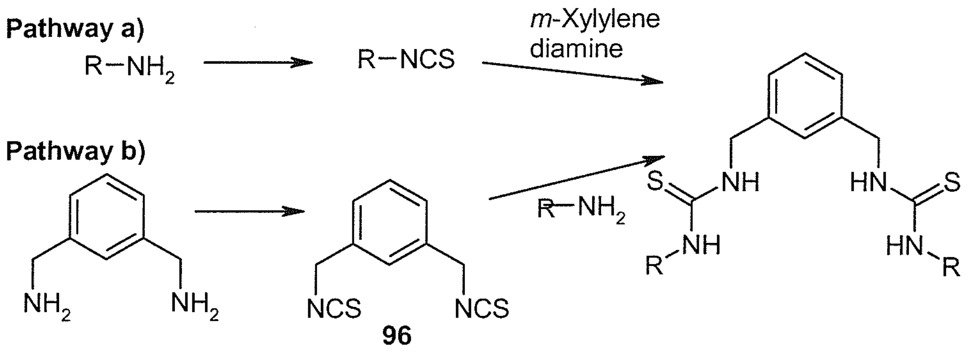
2.2.1 *N'*-Substituted Benzene-cored Thiourea Ligands

Compounds **111**, **112**, **35** and **95** were all synthesised in one step by the reaction of *m*-xylylene diamine with the corresponding isothiocyanate in DCM.



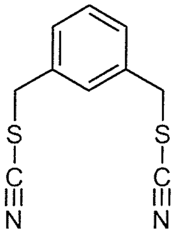
111 R = Me
112 R = Et
35 R = Ph
95 R = COPh

This straightforward approach gave **111**, **112**, **35** and **95** in high yields but the R group is limited to commercially available isothiocyanates, unless a preceding step in each synthesis is included to prepare particular isothiocyanates. Rather than synthesising each R-isothiocyanate precursor individually, a more logical approach undertaken was to prepare 1,3-bis-(isothiocyanato) benzene (**96**) and react this with the far larger number of commercially available amines (scheme 19, pathway b).



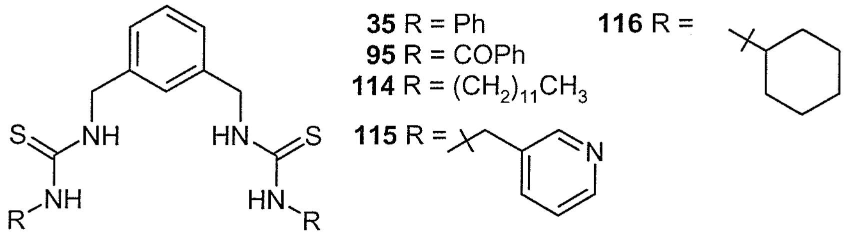
Scheme 19. Two approaches to di-substituted thiourea ligands.

The reaction of both sodium thiocyanate and ammonium thiocyanate with 1,3-bis-(chloromethyl) benzene (**92**) gave the corresponding bis-thiocyanate (**113**) instead of isothiocyanate **96** (by IR spectroscopy). However, **96** was successfully synthesised by reaction of the diamine with thiophosgene in chloroform in the presence of triethylamine[62].



113

Reaction of **96** with the appropriate amine gave **114**, **115** and **116** all in high yields (> 66%).



The dodecyl derivative, **114**, was particularly insoluble in all solvents tried except for very low solubility in DMSO.

The crystal structures of the phenyl **35** and benzoyl **95** derivatives were solved by standard methods. The table below summarises the data for the phenyl derivative **35** (Table 9).

Empirical Formula	$C_{48}\ H_{33}\ N_8\ O_2\ S_4$
Mass	451.11
Collection Temperature/ K	150 (2)
Crystal System	Monoclinic
Space Group	C2/c
Unit Cell (a,b,c in Å, α,β,χ in °.)	a = 21.245 (2), b = 11.4132 (11), c = 9.8443 (6), α = 90.00, β = 101.497 (5), χ = 90.00
Volume	2339.1(3)
Z	4
R1	0.0413
wR2	0.1087

Table 9. Crystallographic data for **35**.

Ethanol, disordered about the mirror plane above and below the benzene core over two sites, is present in the crystal as shown in the asymmetric unit which contains half the molecule (figure 39).

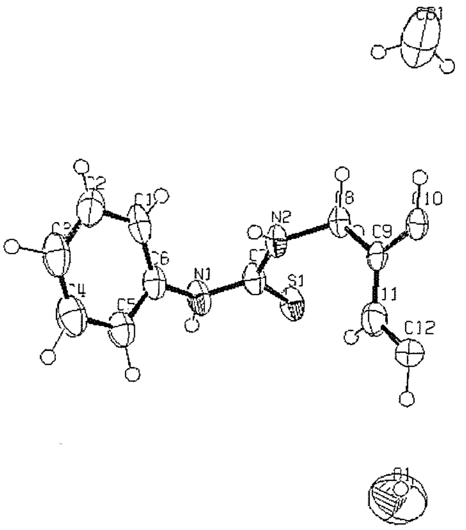


Figure 39. ORTEP representation of the asymmetric unit of **35**.

In the solid-state **35** has an "open wing" (*anti-anti*) conformation with each phenyl sidearm twisted ca. 90° out of planarity with the benzene core (figure 40). The structure organises itself into staggered benzene core stacks with a pair of off-centred N-H···S H-bonds (N-H···S distances 2.71 Å) and a pair of methylene C-H···π (benzene core) edge-to-face interactions (C-H···π distance 2.88 Å) (figure 40). Both thiourea groups have a *cis-trans* geometry and are *trans* with respect to one another.

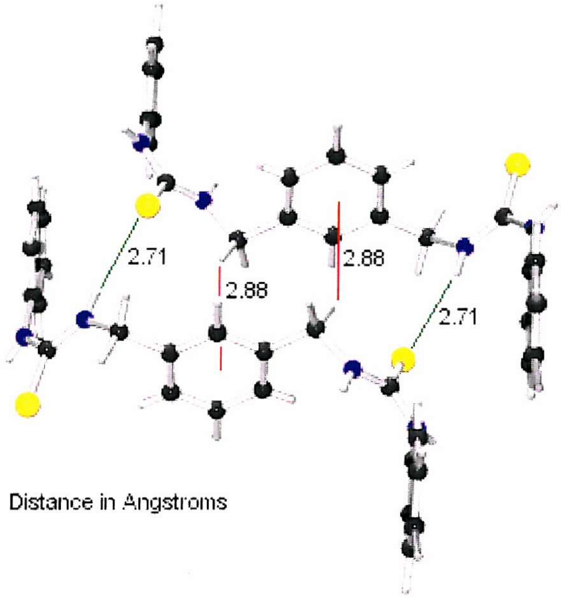


Figure 40. Staggered stack of **35** showing H-bonding (in green) and C-H···π (in red) interactions.

The benzoyl derivative **95** displays a more cleft-like (*syn-syn*) geometry. Both thiourea groups again have a *cis-trans* conformation as shown in the asymmetric unit (figure 41).

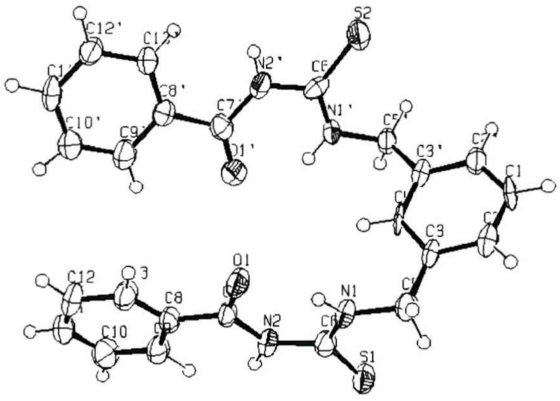


Figure 41. Asymmetric unit of **95**.

The data for the crystal structure of **95** is summarised below (table 10).

Empirical Formula	$C_{24}H_{22}N_4O_2S_2$
Mass	462.58
Collection Temperature/ K	150 (2)
Crystal System	Monoclinic
Space Group	P2(1)/c
Unit Cell (a,b,c in Å, α,β,χ in °.)	a = 4.6870 (10), b = 22.931 (5), c = 20.414 (4), α = 90.00, β = 91.22 (3), χ = 90.00
Volume	2193.6(8)
Z	4
R1	0.0631
wR2	0.1117

Table 10. Crystallographic data for **95**.

There is an intramolecular H-bond between the *m*-xylylene N-H (N1) and benzoyl oxygen (O1) in each sidearm (N-H···O distances 1.97 and 1.93 Å). This accounts for the *cis-trans* thiourea geometry observed in this structure.

The crystal structure of **95** forms 2-dimensional sheets composed of rows of molecules oriented alternately (figure 42). Rows are held together by a twisted pairwise intermolecular H-bonding interaction between the N-H group nearest the benzoyl group and thiourea sulfur (N-H···S distances 2.89 and 2.96 Å) (figure 42).

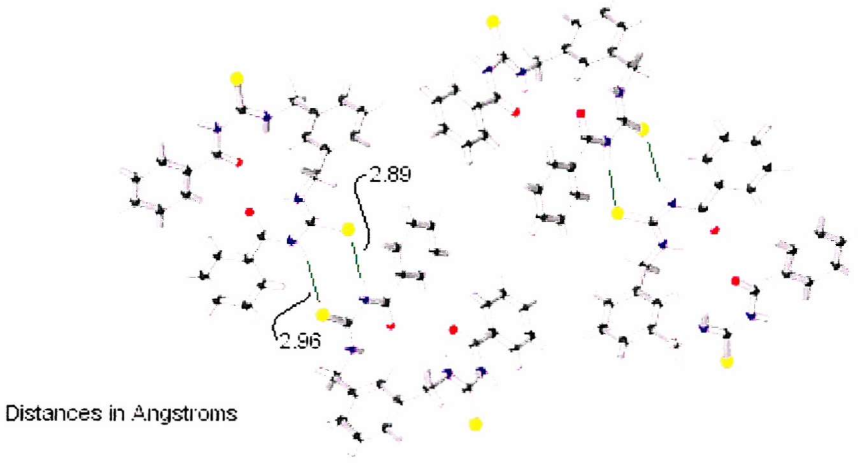


Figure 42. Sections of two rows in the crystal structure of **95**, H-bonds in green.

These sheets form staggered stacked levels, with one methylene C-H···π (benzene core) interaction (C-H···π distance ca. 2.86 Å) between each molecule (figure 43).

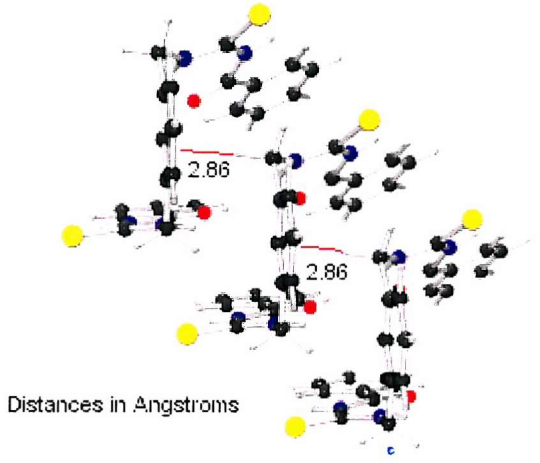
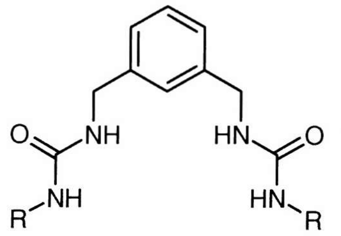


Figure 43. Staggered rows in the crystal structure of **95**, C-H···π interactions in red.

2.2.2 *N'*-Substituted Benzene-cored Urea Ligands

Commercially available 1,3-bis-(methylisocyanato) benzene was used to prepare compounds **117**, **118**, **119** and **120** in one step with the appropriate amine in high yield (≥ 80%).

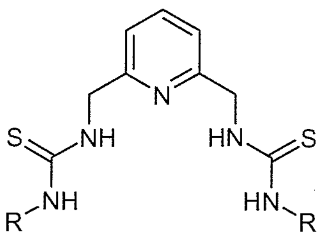


117 R = Ph
118 R = Bz
119 R = cC_6H_{11}
120 R = $(CH_2)_{11}CH_3$

The bis-(ureas) all had lower solubility than their thiourea counterparts described above. Derivative **119** had such low solubility that a very weak proton NMR spectrum was only recorded after 256 scans and **120** was the least soluble of these ureas; NMR and mass spectroscopic data could not be collected for this compound.
Attempts to crystallise these compounds failed, as did attempts to co-crystallise the bis-(ureas) with sulfate guests.

2.2.3 *N'*-Substituted Pyridine-cored Thiourea Ligands

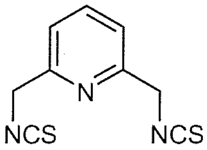
The synthesis of **121** and **122** was attempted using similar methodology. 2,6-bis-(aminomethyl) pyridine dihydrobromide (**84**.2HBr) was converted to the neutral amine using an anion exchange resin as described previously, dried, and reacted with either ethyl isothiocyanate or phenyl isothiocyanate in DCM. However the corresponding pyridine bis-(thioureas) were not produced. The reactions yielded only decomposed isothiocyanate starting materials. This was because water was still present in **84** even after drying at high vacuum. Vacuum distillation was therefore attempted, but caused the neutral diamine **84** to degrade.



121 R = Et
122 R = Ph

The thiourea **122** was eventually obtained by reaction of **84**.2HBr with phenyl isothiocyanate in DCM at reflux in the presence of excess sodium carbonate under anhydrous conditions. However the ethyl derivative **121** could not be synthesised under the same conditions.

Attempts to synthesise 2,6-bis-(isothiocyanato) pyridine (**123**), a precursor analogous to **96**, were not successful.



123

Crystals of the *N'*-phenyl bis-thiourea **122** suitable for X-ray study were produced by slow crystallisation from ethanol/acetone. The details of the structure are shown below (table 11).

Empirical Formula	$C_{21} H_{21} N_5 S_2$
Mass	407.55
Collection Temperature/ K	150 (2)
Crystal System	Triclinic
Space Group	P-1
Unit Cell (a,b,c in Å, α,β,χ in °.)	a = 9.429 (2), b = 9.907 (2), c = 12.351 (2), α =73.92 (3), β = 84.79 (3), χ = 65.65 (3)
Volume	1009.6(3)
Z	2
R1	0.0319
wR2	0.0857

Table 11. Crystallographic data for **122**.

The asymmetric unit is displayed in figure 44, and shows that **122** adopts a *syn-anti* conformation in the solid-state. There is an N-H···N (pyridine) H-bond-like interaction (N-H···N distance 2.27 Å) present in one sidearm between N1 and the hydrogen bonded to N2', bringing about the *syn* sidearm conformation. Once again both thiourea groups have a *cis-trans* geometry.

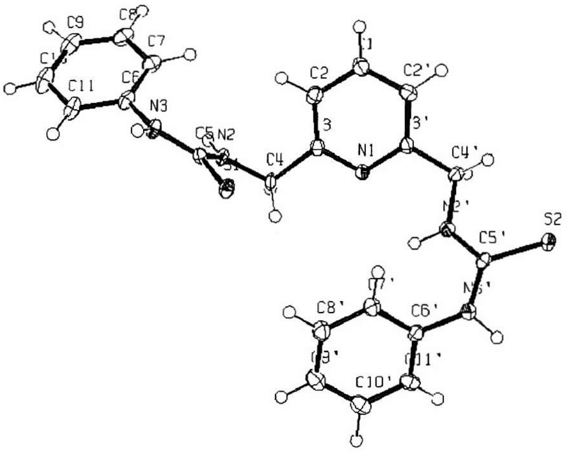


Figure 44. Asymmetric unit of **122**.

Unravelling the complicated packed architecture reveals a pairwise intermolecular H-bonding motif between two N-H groups and two thiourea sulfurs, as seen in the structure of **95** (both N-H···S distances 2.58 Å) (figure 45).

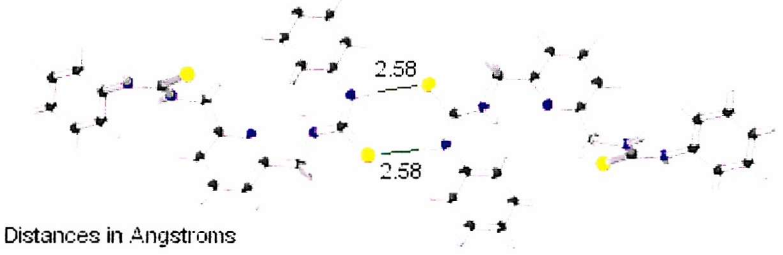
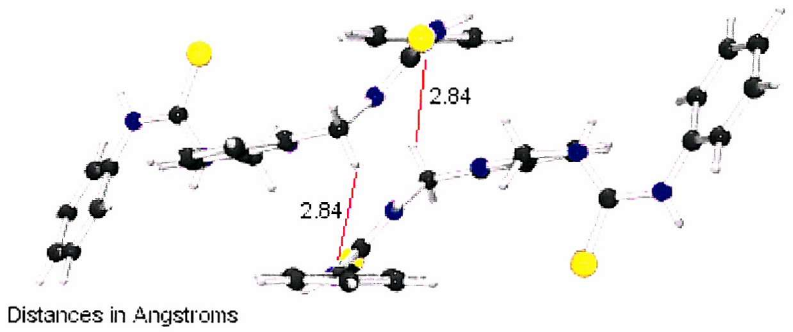


Figure 45. Pairwise H-bonding motif (in green) between molecules.

C-H···π edge-to-face interactions between molecules are also present: a pairwise methylene C-H···π (phenyl) interaction (ca. 2.84 Å) (figure 46) and a single phenyl C-H···π (pyridine) interaction (ca. 2.97 Å).



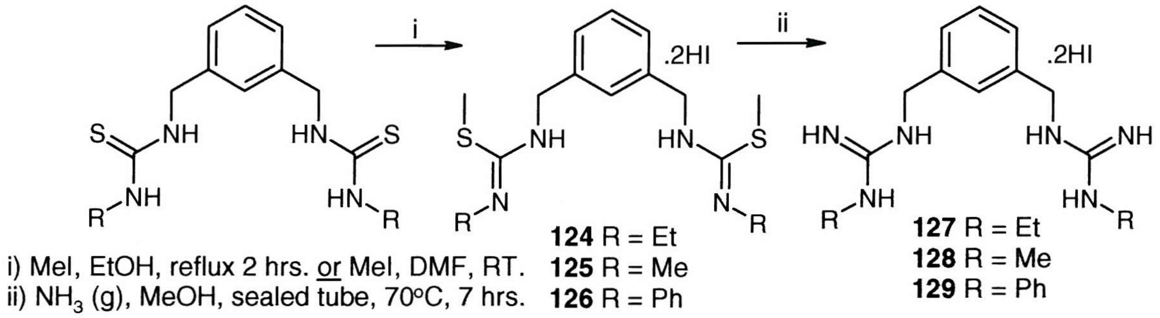
Distances in Angstroms

Figure 46. C-H···π interactions (in red) between molecules.

Attempts to co-crystallise **122** with sulfate guests failed.

2.2.4 *N'*-Substituted Guanidinium Ligands

Three methods for the synthesis of these disubstituted receptors were explored. The first method, as described in the literature, involves the *S*-alkylation of a bis-(thiourea) and subsequent displacement of the *S*-alkyl group with ammonia (scheme 20).



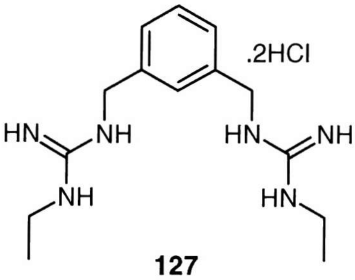
124 R = Et
125 R = Me
126 R = Ph

127 R = Et
128 R = Me
129 R = Ph

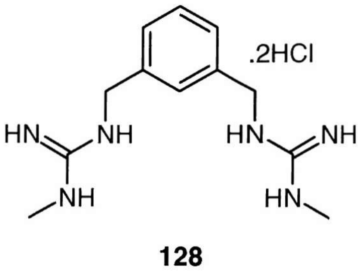
i) MeI, EtOH, reflux 2 hrs. or MeI, DMF, RT.
ii) NH_3 (g), MeOH, sealed tube, 70°C, 7 hrs.

Scheme 20. *S*-Alkylation route to substituted guanidinium ligands.

Compounds **127**, **128** and **129** prepared in this way were impure (by NMR) sticky solids, which could not be further purified by recrystallisation. However, use of Dowex followed by Amberlite aqueous anion exchange columns to give the pure dichloride salts proved successful in the cases of **127** and **128**.



127



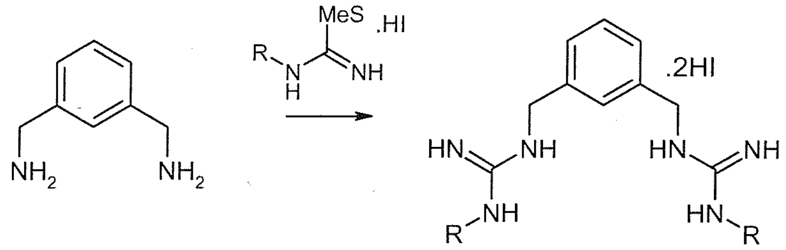
128

This purification method could not be used for the phenyl derivative **129** due to its low water solubility. Passing a methanol/water solution of **129** down the anion exchange columns did not work.

Handling of the dihydrochloride salts **127** and **128** (and all dihydroiodide salts) was troublesome due to the extremely hygroscopic nature of these solids. Attempts to crystallise **127** and **128** as their sulfate salts and with organic sulfonate guests failed, the solutions in all cases turning a deep brown colour over a short period of time.

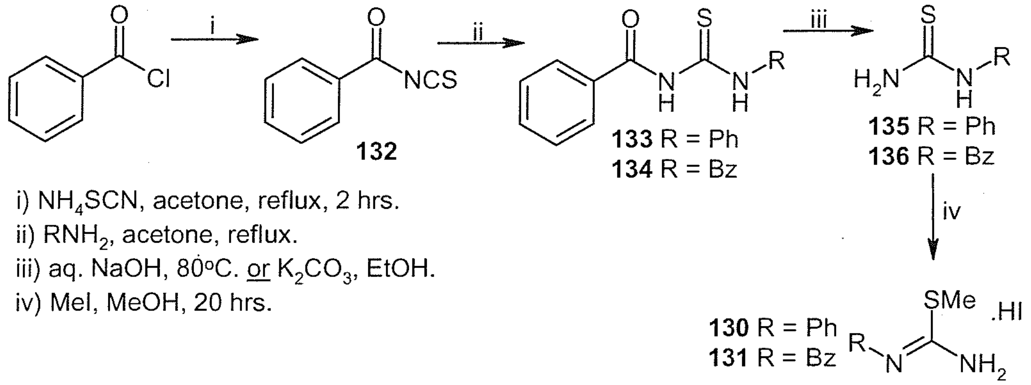
Using the same synthetic method for the pyridine-cored bis-(thiourea) analogue **122** was unsuccessful; *S*-methylation of **122** always gave a very impure product that did not produce the desired *N'*-substituted bis-(guanidinium) salt upon further reaction with ammonia. It was postulated that the pyridine nitrogen was also methylated to an extent in the reaction.

The second route used similar methodology but reversed the functionality present in the reactants (scheme 21).



Scheme 21. Second route attempted for substituted guanidinium ligands.

m-Xylylene diamine was reacted with an excess of an *N*-substituted *S*-methyl-thiouronium hydroiodide under similar conditions to those above in scheme 20. Two *N*-substituted *S*-methyl-thiouronium hydroiodides (**130** and **131**) were prepared using a method adapted from the literature[89] (scheme 22).

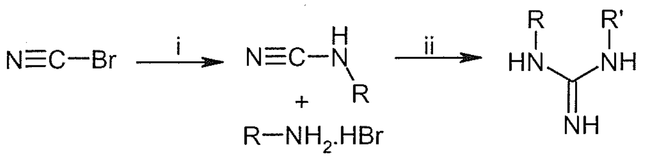


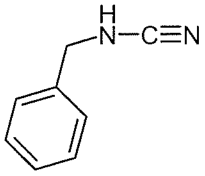
i) NH_4SCN, acetone, reflux, 2 hrs.
ii) RNH_2, acetone, reflux.
iii) aq. NaOH, 80°C. <u>or</u> K_2CO_3, EtOH.
iv) MeI, MeOH, 20 hrs.

Scheme 22. Preparation of *N*-substituted *S*-methyl thiouronium salts.

Whilst this route successfully produced the *N'*-substituted bis-(guanidinium) derivatives, removal of the excess *S*-methyl hydroiodide reactants **130** and **131** in the final step (scheme 21) could not be achieved.

The third route to these disubstituted bis-(guanidine) derivatives investigated is outlined below (scheme 23).





137

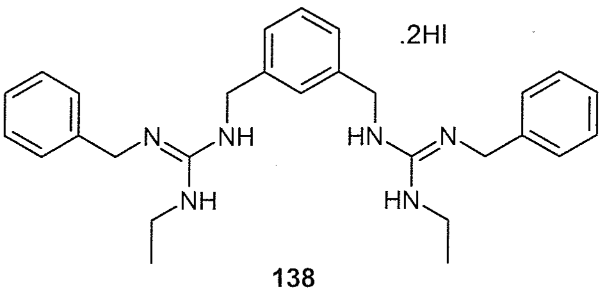
i) 2 eq. RNH_2, TBME.
ii) excess $R'NH_2$, H_2SO_4, pH 10, 80°C.

Scheme 23. The third route to substituted guanidinium ligands investigated.

In order to evaluate the effectiveness of this path, benzylamine ($R-NH_2$) and n-propylamine ($R'-NH_2$) were used as reactants. **137** was produced in high yield after the first step, but no reaction occurred in the second step of the synthesis with n-propylamine. Repetition of the second step with harsher conditions (heating at reflux, greater excess of n-propylamine) surprisingly still gave no reaction. The route was therefore abandoned.

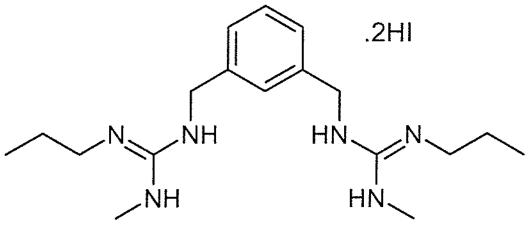
2.2.5 *N', N''*-Trisubstituted Guanidinium Ligands

The first reaction pathway shown in the previous section (scheme 20) using primary amines instead of ammonia gas was used for the attempted synthesis of trisubstituted bis-(guanidinium) receptors. **138** was prepared from the *N'*-ethyl substituted thiouronium salt **124** in a sealed tube using excess benzylamine.



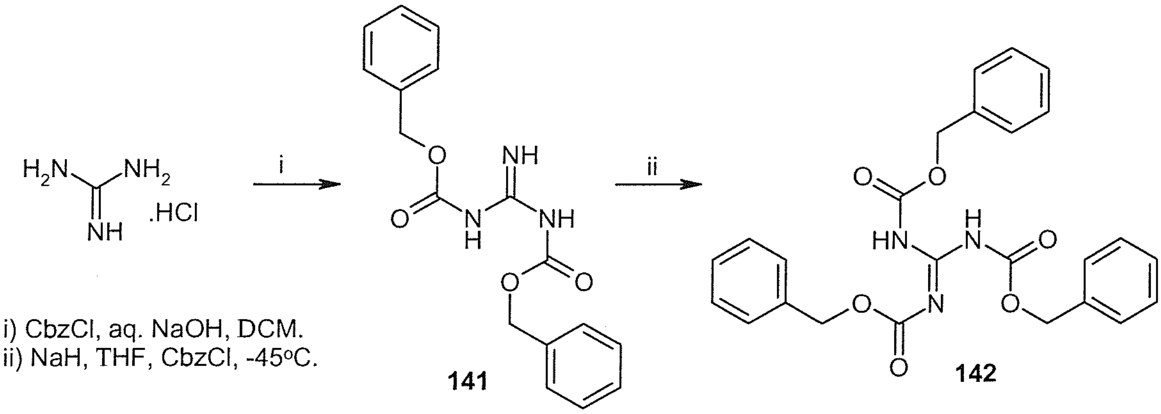
138

Unfortunately **138** could not be purified by anion exchange column due to its low water solubility and the presence of the excess unreacted benzylamine. Purification of the *N'*-methyl, *N''*-butyl bis-(guanidine), **139**, failed for the same reasons.

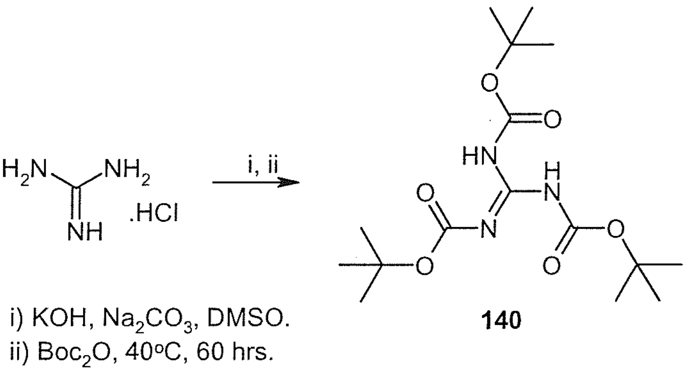


139

A second attempt to synthesise these trisubstituted compounds using the Mitsunobu reaction was undertaken. Using a synthetic route adapted from the literature[90], guanidine was tri-protected with either the CBZ or BOC protecting group in one or two steps (see schemes 24 and 25 respectively).



Scheme 24. Tri-CBZ protection of guanidine.

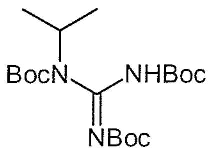


Scheme 25. Tri-BOC protection of guanidine.

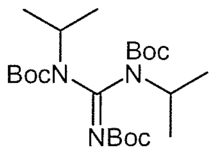
Compounds **140** and **142** were produced cleanly and in high yield.

The crystal structure of **140** was solved by single crystal X-ray diffraction (see Chapter 2.6).

The tri-BOC-protected guanidine **140** was reacted with propan-2-ol under Mitsunobu conditions to give **143** as an oil after purification by column chromatography.

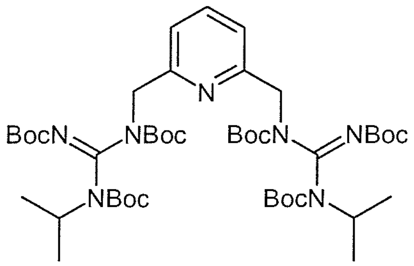


143



144

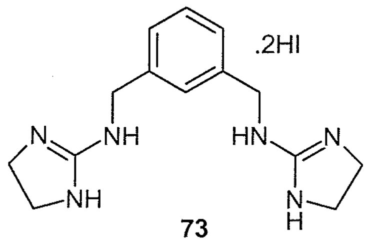
However it appeared that the over-substituted tri-BOC-protected guanidine **144** had also been produced (by mass spectroscopy), and separation of these two compounds by column chromatography proved unsuccessful. Even so the final step in the synthesis was carried out, the attempted preparation of **145** from **143** and 2,6-pyridine dimethanol under Mitsunobu conditions.



145

Mass spectroscopy did not suggest the presence of **145** after reaction, and separation of the many components was not achieved satisfactorily by column chromatography. Consequently the reaction was abandoned without attempting deprotection of the final product. The publication from which this method was adapted only dealt with mono-guanidine products, so it was thought that steric hindrance might have prevented the bis adduct **145** from being formed.

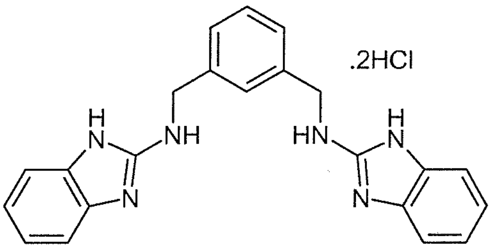
A literature-known compound, **73**, was prepared in one step and in high yield from reaction of *m*-xylylene diamine and 2-methylthio-2-imidazoline hydroiodide.



73

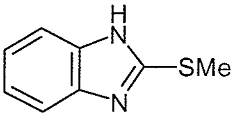
Attempted crystallisation of **73** as its sulfate salt and with model dye sulfonates from aqueous solution failed.

Synthesis of the related compound **146** was attempted by a similar method.



146

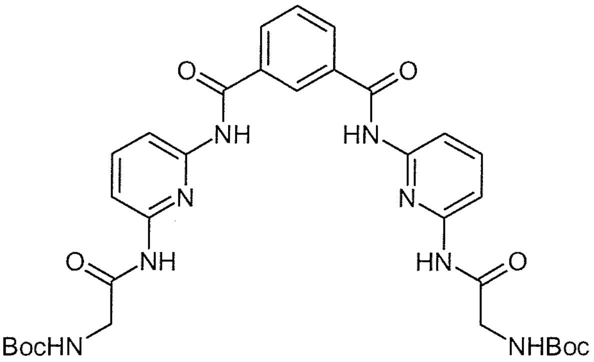
However the novel hydrochloride salt of commercially available neutral 2-methylthiobenzimidazole **147** was not afforded after passing HCl gas through a solution of **147** in warm ethanol, and no reaction occurred between *m*-xylylene diamine and the unactivated neutral compound **147**.



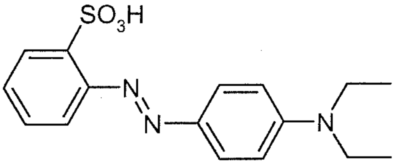
147

2.2.6 Tetraamido C-shaped Ligands

In addition to the disubstituted bis-(guanidine) ligands, organic-soluble receptors with four amide functionalities were investigated briefly. Kenworthy had found previously that **148** strongly extracted the sulfonated azo dye **149** into DCM from aqueous solution[77].

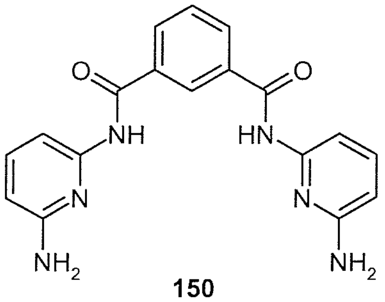


148

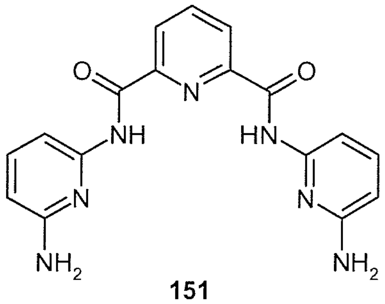


149

This observation required further investigation to try to establish the nature of any interaction that occurred between **148** and **149**. To this end the receptor precursors **150** and **151** were synthesised from the relevant diacid chlorides and 2,6-diamino pyridine.

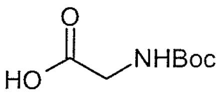


150



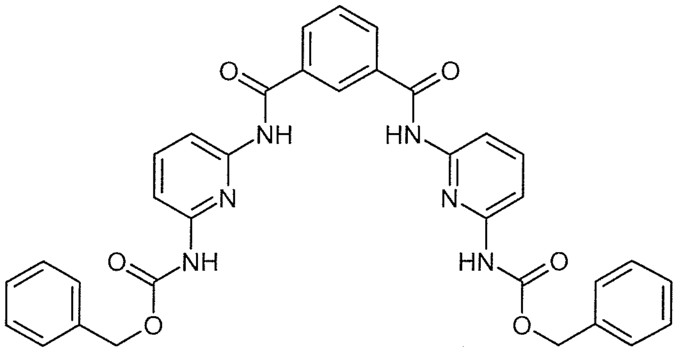
151

Synthesis of **148** from **150** required the preparation of the N-Boc compound **152**; the tertiary Boc groups impart organic solubility to **148**. As time was short at this stage, it was decided that a commercially available reactant (benzyl chloroformate), which would give organic solubility to the molecule, would be used in stead of **152**, so shortening the receptor's synthesis.



152

153 was synthesised from **150** and benzyl chloroformate.



153

The tetra-amide **153** was organic-soluble, and extracted azo dye **149** from water into DCM to a greater extent than the organic-soluble bis-(benzoylthiourea) **95**. An NMR titration binding study was carried out with ligand **153** and guest **149** in deuterated chloroform, and is discussed in Chapter 2.5 (pages 117-118).

Neither crystals of **153** nor co-crystals of **153** with azo dye **149** could be grown.

2.2.7 Summary

The *N'*-substituted benzene-cored bis-(thio)ureas were easily synthesised in one step and high yield. The pyridine-cored analogues were more difficult to prepare due to inherent problems isolating dry 2,6-bis-(aminomethyl) pyridine (**84**) starting material.

The bis-thioureas were more soluble than the corresponding bis-ureas, concurring with the literature[29]. In the solid state, all three of the bis-thioureas exhibited a *cis-trans* thiourea geometry, presumably because of steric effects (compounds **35** and **122**) and in the benzoyl case (compound **95**) as a result of an intramolecular H-bond between the carbonyl oxygen and thiourea N'-H. No self-recognition was observed in these crystal structures in contrast to similar structures studied in a recent publication, which describes the self-assembly of related 4-*tert*-butyl bis-(thio)ureas in solution and the solid state[91].

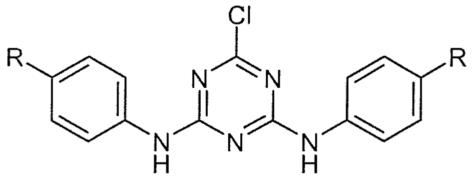
The *N'*-substituted bis-guanidines were considerably more difficult to synthesise than the bis-(thio)ureas, involving several steps and tricky purification. The best method attempted was via the methylation of the analogous bis-thiourea. Purification by anion exchange resin was only possible for the alkyl *N'*-substituted water-soluble compounds (**127** and **128**). These products were highly hygroscopic and sulfate salt crystals could not be grown.

2.3 Triazine Cored Receptors

The versatile and cheap electrophilic starting material cyanuric chloride (**1**) seems an ideal receptor precursor as it allows the straightforward consecutive introduction of three similar or different sidearm groups. Two sidearms with relevant functionality could form a C-shape and serve as the receptor's complexation cleft, while the third sidearm could be used as an additional 'scorpion' recognition moiety or as an attachment linker point to a solid support.

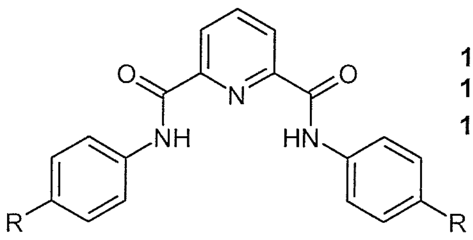
2.3.1 Arylamino- Disubstituted Triazines

Simple arylamino disubstituted triazines have been widely synthesised[92,93,94,95,96], and seemed a good starting point for this investigation.



154 R = H
155 R = NO_2
156 R = OMe

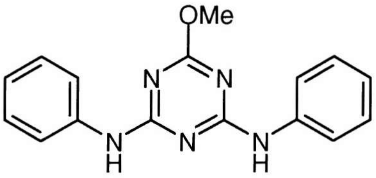
In all three cases (**154**, **155** and **156**) reaction conditions involved addition of two equivalents of amine to cyanuric chloride at 0°C followed by heating (for the second substitution to occur) and addition of an aqueous solution of an inorganic base, as discussed in the Introduction. (Reaction of the same nucleophiles with pyridine-2,6-diacid chloride (**85**) to give **157**, **158** and **159** required far less harsh reaction conditions for both substitutions to proceed than those needed for the second substitution of cyanuric chloride, reflecting the versatility of cyanuric chloride with respect to the introduction of different substituents).



157 R = H
158 R = NO_2
159 R = OMe

2.3.2 Trisubstituted Triazine

The parent triazine **154** was heated at reflux in methanol to give **160**, the tri-substituted triazine.



160

Crystals of **160** were grown and solved by X-ray diffraction (table 12).

Empirical Formula	$C_{16} H_{15} N_5 O_1$
Mass	293.33
Collection Temperature/ K	150 (2)
Crystal System	Monoclinic
Space Group	P2(1)/c
Unit Cell (a,b,c in Å, α,β,χ in °.)	a = 17.043 (3), b = 11.854 (2), c = 7.229 (10), α = 90, β = 100.41 (3), χ = 90
Volume	1436.4 (4)
Z	4
R1	0.0527
wR2	0.1011

Table 12. Crystallographic data for **160**.

The asymmetric unit of **160** shows a twisted *syn-syn* geometry including two intramolecular H-bond-like contacts between two aromatic C-H groups and a central triazine nitrogen (C-H···N distances of 2.36 and 2.31 Å) (figure 47). There is no possibility of forming an N-H···N (triazine) close contact as this would involve a geometrically disfavoured four membered ring.

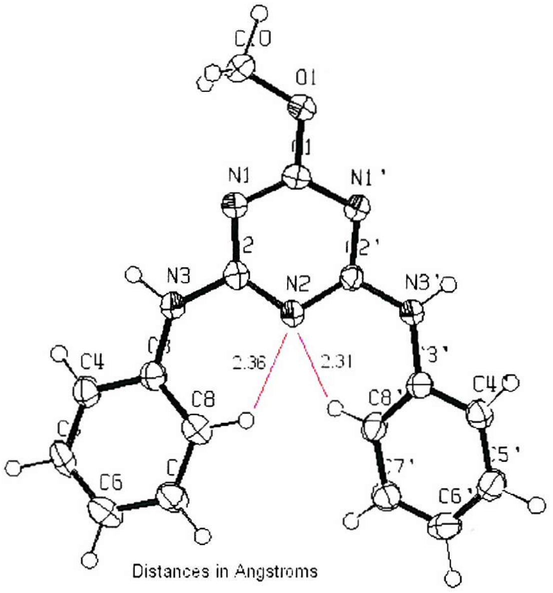


Figure 47. Asymmetric unit of **160**, close contacts in red.

As observed for previous cleft-like structures, the packed structure forms rows and stacks. The rows are held together by intermolecular bidentate N-H···N (triazine) H-bonds (N-H···N distances of 2.23 Å) and bidentate methoxy(C)-H···N (triazine) contacts (both distances 2.76 Å) (figure 48).

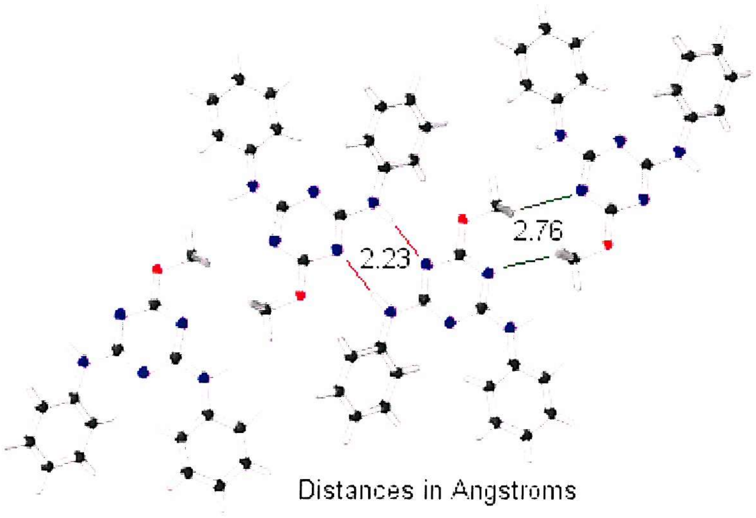


Figure 48. Sheets of **160** with intermolecular interactions in red and green.

Each molecule is oriented in a tilted and staggered stack in which the triazine rings are between 3.32 and 4.13 Å apart. The opposing phenyl rings form edge-to-face interactions with C-H···π distances of ca. 2.81 and 3.00 Å and angles of ca. 74° (figure 49).

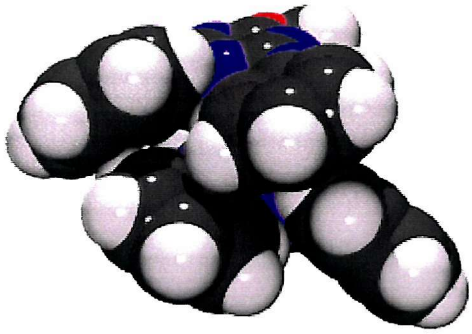


Figure 49. Two molecules of **160** showing C-H···π interactions.

2.3.3 Hydrazino-containing Triazines

Although this last structure has a *syn-syn* geometry through weak preorganisation, it is unlikely that this will be the case for all disubstituted triazines. Therefore we hoped to introduce a 'spacer' into the sidearms of these compounds so that a favourable N-H···N (triazine) intramolecular H-bond-like interaction might preorganise the molecule, as seen in 2,6-pyridine diamido compounds. Hydrazino-nucleophiles were chosen as the reactive functions to introduce this 'spacer'; several examples in the literature exist of hydrazino-triazine compounds synthesised from cyanuric chloride derivatives[97,98]. In addition, the inclusion of a bulky substituent at the 5-position might help promote the desired *syn-syn* geometry over an *anti-anti* or *syn-anti* geometry (figure 50).

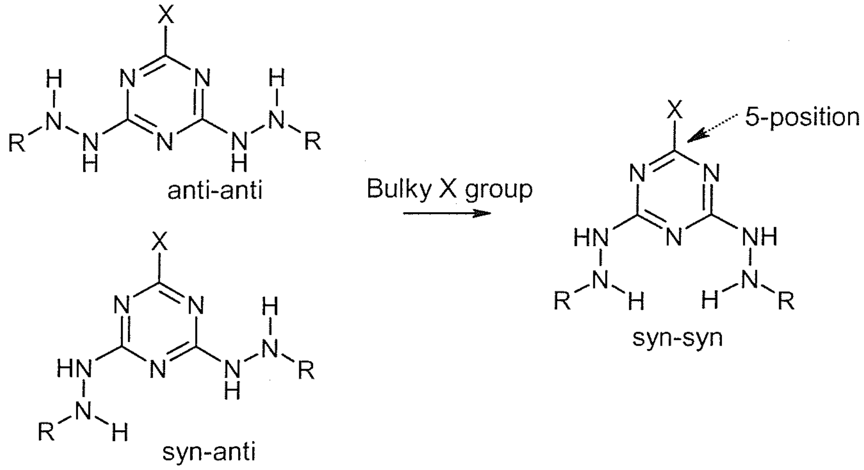


Figure 50. Possible conformations of dihydrazine-substituted triazine.

A Cambridge Crystallographic Database[82] search for triazine crystal structures yielded the crystal structure of 1,3,5-trihydrazino-*s*-triazine (**161**). This structure shows a *syn-syn* geometry through two intramolecular H-bond-like interactions even without a bulky group at the 5-position (figure 51)[99].

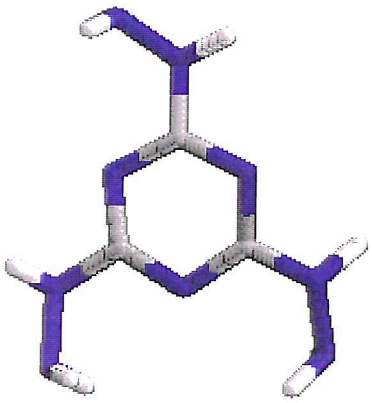


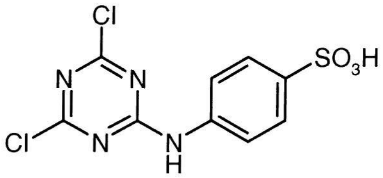
Figure 51. Representation of the solid-state conformation of **161**.

The solid state conformation of **161** lent creditability to our approach to preorganised triazine receptors.

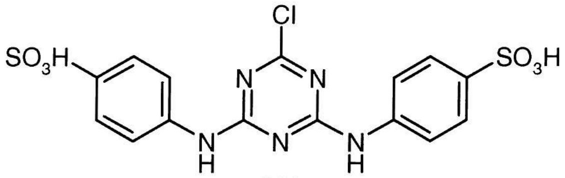
2.3.4 Aqueous Chemistry Approach to Hydrazino-substituted Triazines

The investigation into hydrazino triazines was started using aqueous solution chemistry while on placement at BASF; hence many of the prepared compounds were sulfonated to increase aqueous solubility.

The mono- and di-substituted compounds **162** and **163** were prepared as aqueous soluble starting materials from cyanuric chloride and one or two equivalents of *p*-sulfanilinic acid.

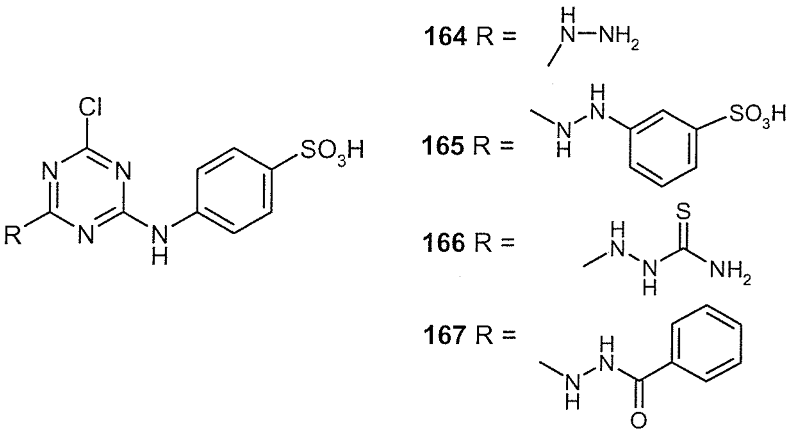


162



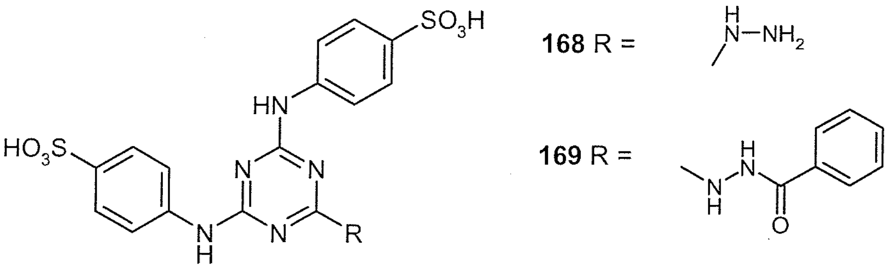
163

First of all, **162** was reacted with one equivalent of several hydrazino-nucleophiles to produce compounds **164**, **165**, **166**, and **167**.



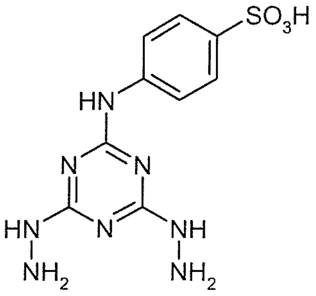
The unsymmetrically substituted triazines **165**, **166** and **167** were all prepared in reasonable yield under similar conditions (at about pH 6 and a temperature of 40°C). However **164** was not produced under these conditions, as hydrazine was considerably more reactive than the other nucleophiles. Instead **164** was obtained by reaction of hydrazine with **162** at pH 9 and a temperature of < 5°C. No crystals of any of these compounds could be grown.

Next, substitution of the one remaining reactive site in **163** with the same series of hydrazino- nucleophiles was attempted; in terms of reactivity the third substitution of cyanuric chloride is the most difficult. The synthesis of compounds **168** and **169** was attempted.



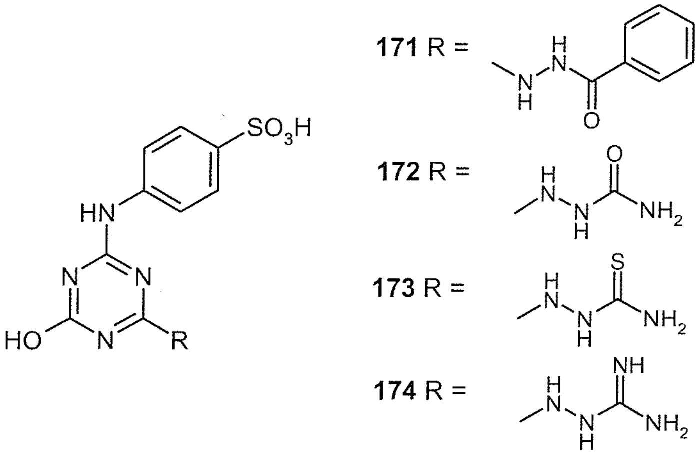
Conditions for preparation of **168** were pH 6 and a temperature of 60°C. Reaction appeared to occur; however the desired product could not be separated from hydrolysed starting material (R = OH). In the case of **169**, similar conditions did not promote reaction, and a further increase in temperature seemed only to produce hydrolysed starting material (R = OH).

Next, reaction of two equivalents of hydrazino nucleophile with electrophilic starting material **162** was attempted. Compound **170** was afforded after **162** was heated in undiluted hydrazine monohydrate at 100°C for two hours.

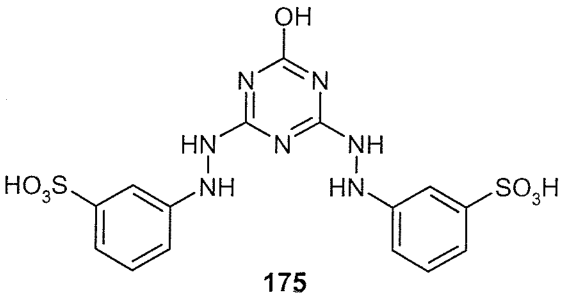


170

The other compounds in this series could not be prepared satisfactorily. In each case, the third substitution did not proceed. Instead, the third substitutable position appeared to hydrolyse under the harsh conditions employed, to give compounds **171**, **172**, **173** and **174**. Reaction of **170** with *O*-methylisourea sulfate and isothiocyanates proved fruitless.

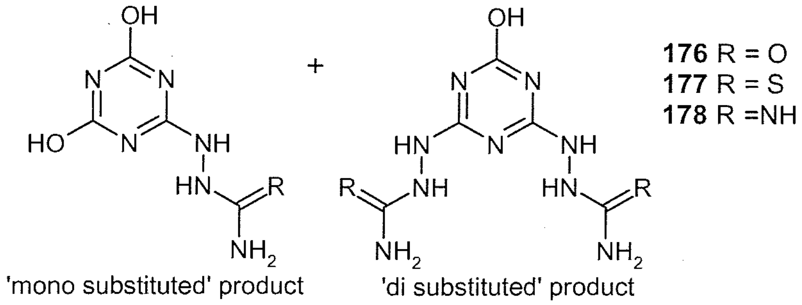


Finally, cyanuric chloride was reacted directly with two equivalents of hydrazino- nucleophile at pH6 and temperatures varying from 0°C to 40°C. In most cases isolation of the product proved troublesome, and it appeared that mixed hydrolysis products were common. **175** was successfully synthesised, although the 5-position had been hydrolysed during the reaction (by mass spectroscopy).



175

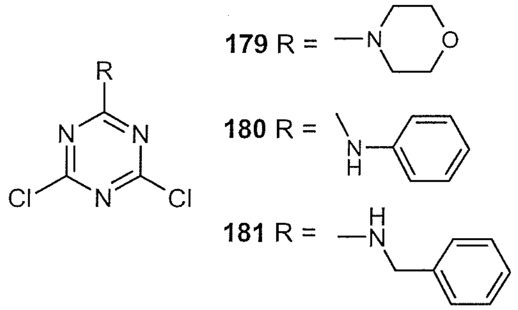
The exact nature of the remaining compounds in this series, synthesised by reaction of cyanuric chloride with semicarbazide, thiosemicarbazide and aminoguanidine, was not easy to identify; all have N-H protons only (not easily assigned in proton NMR spectra), the carbon NMRs were ambiguous, mass spectroscopy showed no chlorine splitting patterns and the compounds were too polar for tlc. From the spectra collected, it seemed likely that inseparable mixtures of the hydrolysed mono- and di-substituted products had been produced, as shown below (scheme 26).



Scheme 26. Inseparable triazine products obtained.

2.3.5 Organic Chemistry Approach to Hydrazino-substituted Triazines

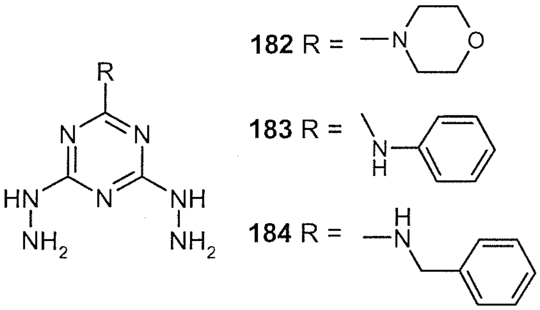
Hydrazino-triazine derivatives were also prepared in organic solvents. Several precursors were synthesised by literature methods from cyanuric chloride in either acetone or THF.



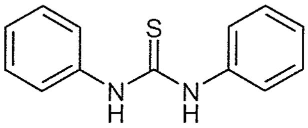
According to the method of Whitesides *et al*[95], reactions carried out in THF used triethylamine as base. This method never gave pure products and so dichloro-triazines produced in this manner had to be purified by column chromatography, which they surprisingly seemed to survive without hydrolysis; the crystal structure of **181** was obtained after the compound had been purified by column chromatography (see Chapter 2.6, pages 121-122).

The method of preference for the preparation of **179** – **181** was that of Krymova *et al*[92], involving reaction in acetone and the addition of aqueous inorganic base. This method allowed for the simple separation of the product (by filtration) followed by facile purification (recrystallisation).

The dichloro-triazines **179** – **181** were reacted with hydrazine to give the dihydrazino-triazines **182** – **184**.

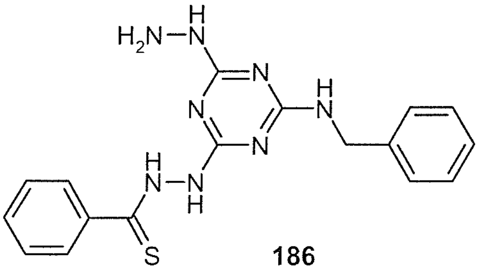


Reaction of **182** – **184** to produce either a substituted thiosemicarbazide or an amino guanidine was next attempted. **184** was reacted with excess phenyl isothiocyanate in DMF. Two products were isolated from the reaction; one turned out to be *N,N'*-diphenyl thiourea, **185**, presumably from phenyl isothiocyanate self-condensation. The crystal structure of **185** was solved, and the molecule was found to have a *trans-trans* geometry (as shown schematically below).

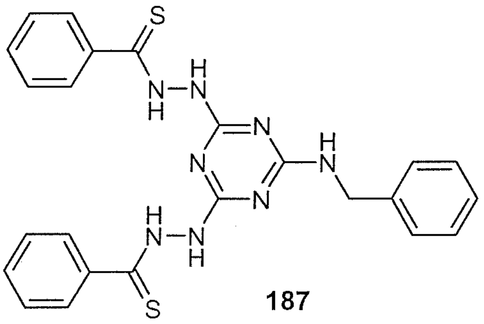


185

The other very polar and sparingly soluble product appeared to be a mixture of the mono- and di-substituted thiosemicarbazido-triazines, **186** and **187** (by NMR and mass spectroscopy). Attempts to separate these products failed, as did attempts to fractionally crystallise the mixture.

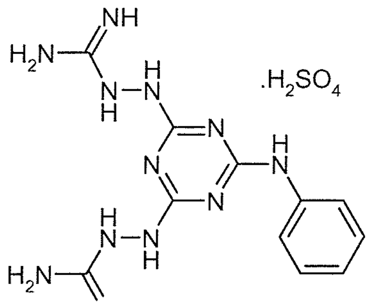


186



187

Di-hydrazine **183** was reacted with *O*-methyl-isourea sulfate to give **188**, albeit in low yield (13%).



188

Again attempts to crystallise this compound were not successful.

2.3.6 Summary

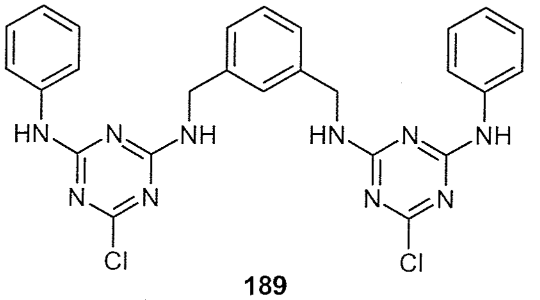
The synthesis and identification of triazine-cored hydrazino receptors was not easy, due in part to the high number of N-H groups. However several novel compounds were produced during this investigation.

Aqueous solution preparations of hydrazino-triazines were particularly difficult because of competitive hydrolysis; hydrazino groups attached to chloro-triazines are known to have a large deactivating effect on the remaining substitutable position(s).

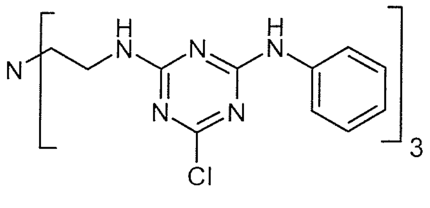
2.3.7 Receptors with Triazine Sidearms

In addition to using triazine as a receptor core unit, a short investigation of potential receptor molecules including triazine-containing sidearms was undertaken. It was hoped that compounds of this type might recognise triazine rings via π - π stacking interactions, particularly in the solid state.

Dichloro-triazine **183** was reacted with *m*-xylylene diamine and tris-(2-aminoethyl) amine to give compounds **189** and **190** respectively.

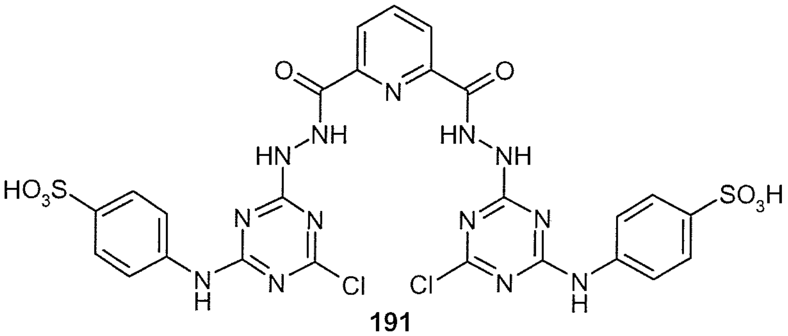


189



190

The dihydrazido compound **105**, discussed on page 71, was reacted with dichloro-triazine **168** to give **191**.



191

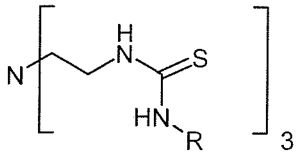
Recrystallisation of these three compounds (**189 – 191**) was attempted from THF, aqueous mixtures containing THF and aqueous/alcohol mixtures. However in each case no crystalline material could be obtained and so the solid-state structures of these compounds were not determined.

2.4 Tripodal Receptor Ligands

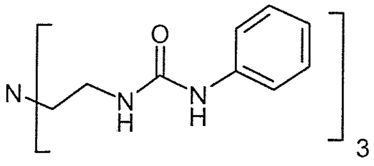
The preparation of tripodal receptors analogous to the C-shaped receptors discussed in the preceding chapters has also been investigated. Similar methodology was applied to synthesise these compounds, although in general they were not prepared as easily as their C-shaped relations.

2.4.1 Ethyl Tripodal (Thio)ureas

Reaction of commercially available tris-(2-aminoethyl) amine with substituted iso(thio)cyanates, as employed previously, produced compounds **192**, **193** and **194** in high yield.



192 R = Et
193 R = Ph



194

The thioureas **192** and **193** were soluble in chlorinated solvents whereas the urea **194** was not, reflecting the trend observed for these compounds' C-shaped cousins. Thioureas **192** and **193** were hygroscopic and seemed to decompose over time, unlike the urea **194**.

Crystals of thiourea **193** were grown and characterised by a single crystal X-ray structural study. A summary of the data obtained is shown below (table 13).

Empirical Formula	$C_{54}\,H_{66}\,N_{14}\,O_2\,S_6$
Mass	575.78
Collection Temperature/ K	150 (2)
Crystal System	Orthorhombic
Space Group	Pca2(1)
Unit Cell (a,b,c in Å, α,β,χ in °.)	a = 25.806 (5), b = 9.785 (2), c = 26.026 (5), $\alpha = 90$, $\beta = 90$, $\chi = 90$
Volume	6572 (2)
Z	8
R1	0.0929
wR2	0.2424

Table 13. Crystallographic data for **193**

The asymmetric unit contains two molecules with very similar conformations, related to each other by a 180° rotation; three disordered water molecules are also present (figure 52).

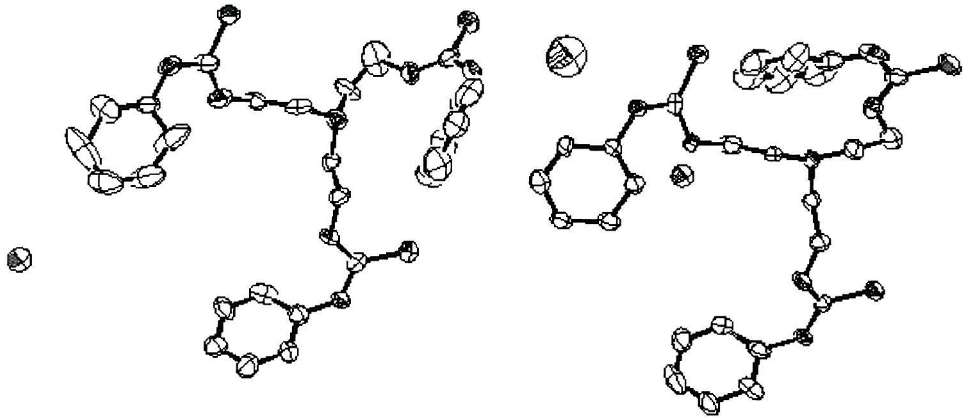


Figure 52. Asymmetric unit of **193** (hydrogens omitted for clarity).

Each thiourea group in the molecule has a *syn-anti* geometry (figure 52) and no intramolecular H-bonding occurs. In the packed structure (figure 53), molecules of **193** form tapes in which one sulfur atom of one thiourea group of each molecule occupies the cavity formed by two arms of the adjacent molecule. Two H-bonds between the 'included' sulfur atom and the two inward-facing N-H groups of the cavity wall exist (distances 2.89 and 2.76 Å) (figure 53 in green).

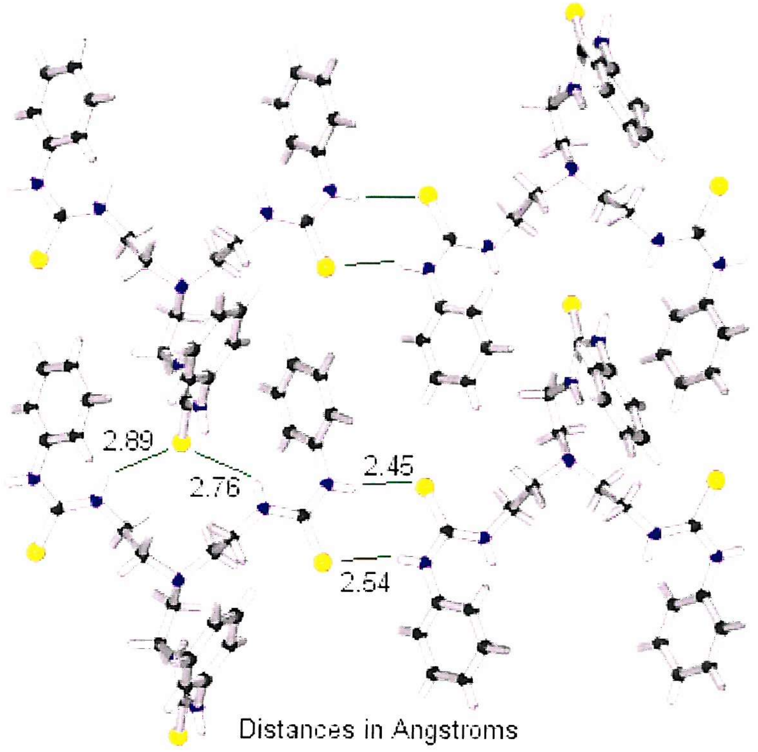
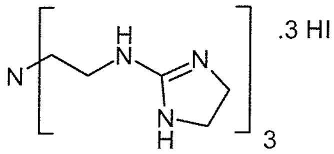


Figure 53. Adjacent tapes of **193** with H-bonds in green.

Adjacent tapes run in opposite directions, and are held together by a thiourea pairwise bidentate H-bond interaction (N-H···S distances 2.45 and 2.54 Å) (figure 53 in green). Disordered water molecules spacefill and form single H-bonds with many remaining thiourea N-H groups, though not all of the N-H groups are involved in H-bonding. Attempts to co-crystallise each of these three ligands with sulfate guests failed to produce any complexes.

2.4.2 Ethyl Tripodal Guanidines

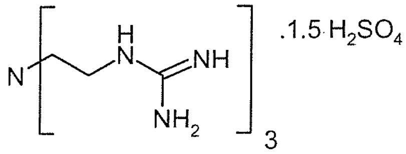
Triguanidine **195** was synthesised in high yield from the facile reaction between tris-(2-aminoethyl) amine and 2-methylthio-2-imidazoline hydroiodide in methanol.



195

However crystals of **195** suitable for a solid-state structural study could not be obtained, and co-crystallisation of this ligand with sulfate guests did not proceed.

Preparation of trisguanidinium salt **196** proved to be more difficult than **195**. Tris-(2-aminoethyl) amine was reacted with *O*-methylisourea sulfate in ammonia solution in a sealed vessel, according to the method of Lehn *et al*[46], since methods analogous to the preparation of **195** were not successful.



196

Colourless needle crystals of **196** were grown from a D_2O NMR solution and the structure was solved by a single crystal X-ray structural study. Table 14 displays a summary of the data.

Empirical Formula	$C_{18}H_{54}N_{20}O_{17}S_3$
Mass	459.50
Collection Temperature/ K	150 (2)
Crystal System	Monoclinic
Space Group	P2(1)
Unit Cell (a,b,c in Å, α,β,χ in °.)	a = 11.089 (2), b = 11.832 (2), c = 17.840 (4), α = 90, β = 105.00 (3), χ = 90
Volume	2260.9 (8)
Z	4
R1	0.0805
wR2	0.1801

Table 14. Crystallographic data for **196**.

Once again the asymmetric unit contains two ligand molecules having slightly different conformations, three sulfate counterions and a disordered layer of water molecules which H-bond to 'free' N-H groups. Figure 54 below shows the asymmetric unit with the disordered water molecule omitted.

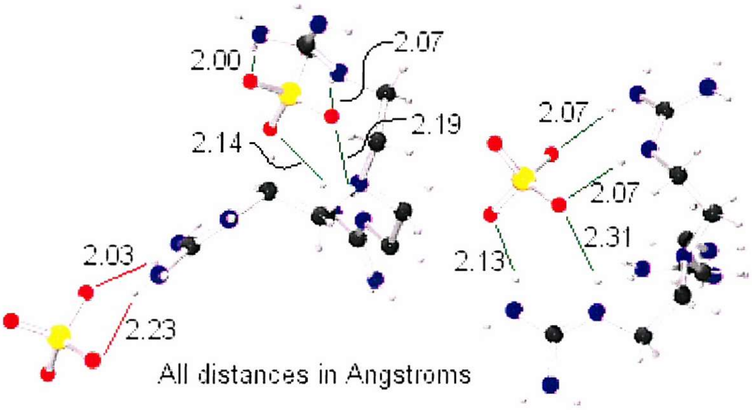


Figure 54. Asymmetric unit of **196**.

One sulfate counterion forms a twisted pairwise bidentate H-bond with two NH groups from one ligand (shown in red in figure 54). The remaining two sulfate anions are both involved in four H-bonds from two NH groups forming twisted 'wedge' motifs as described in the introduction and Chapter 2.1 (shown in green in figure 54).

Packing of the structure and subsequent analysis reveals a number of H-bond interactions between sulfate counterions and multiple ligands. Between two ligands of the same conformation (the left-hand ligand as displayed in figure 54 above) a sulfate anion is H-bonded in a 'wedge' motif between two N-H groups from two different ligands (H-bonds in green in figure 55 below). Sulfate anions H-bonded in the twisted pairwise bidentate motif associated with "external" N-H groups of the ligands (shown in red in figure 55 below).

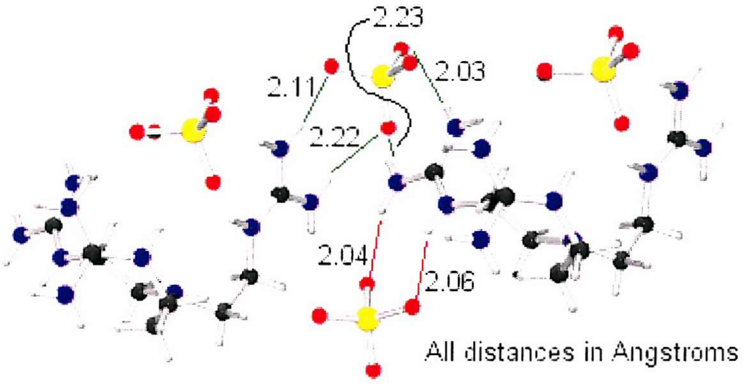
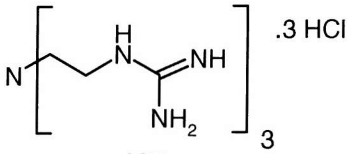


Figure 55. H-bonding interactions between **196** and sulfate counterions in the packed structure.

Sulfate anions involved in 'wedge' motifs from one ligand are also involved in two pairwise bidentate interactions from two other ligands, giving a total of eight N-H···O H-bonds about one sulfate in this orientation (H-bond distances 2.00 to 2.31 Å). H-bond interactions formed with either sulfate or water satisfy all N-H H-bond donors in the structure.

The conversion of **196** to the hydrochloride salt **197** was attempted by a method analogous to that for **107** discussed in Chapter 2.1.



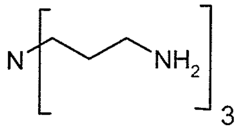
197

Dissolution of **196** in strong basic solution and precipitation of barium sulfate with barium hydroxide was accomplished, followed by neutralisation with hydrochloric acid. However **197** could not be extracted from the residue of the reaction. The second method attempted involved passing a weak solution of **196** down a Dowex®-1-chloride (1 × 8 –100) ion-exchange column as described by Lehn[46]. Neither product nor starting material were recovered from the column even after elution with very large volumes of water, deeming this method also unsuccessful. For this reason crystallisation experiments with sulfonate guests were not undertaken.

Adaptation of the successful method used in Chapter 2.2 for the synthesis of *N'*-substituted bis-guanidines was applied to the thioureas **192** and **193** discussed above. However a similar result to that found with the pyridine-cored bis-(phenylthiourea) **122** was seen here; methylation of the thioureas **192** and **193** gave very impure products and it was supposed that limited competitive methylation of the tertiary core nitrogen atom had occurred.

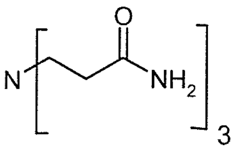
2.4.3 Propyl Tripodal Receptors

Tripodal molecules with propylamino cores are known in the literature[46,100,101,102]. Tris-(propylamino) amine **198**, unlike the analogous starting material discussed in the previous section, is not commercially available and therefore synthesis of this precursor was attempted.



198

The method of Hahn[101] was followed and involved reaction of acrylamide with ammonium hydroxide in water. Tris-amide **199** was produced in almost quantitative yield (94%).



199

The next step involved reduction of **199** with lithium aluminium hydride to produce tris-amine **198**. However each attempt at this reduction proved unsuccessful, producing what appeared to be mainly starting material and only a very small amount of tris-amine **198**. The reduction was also undertaken using a borane/ THF complex, again with no success. Lack of time prevented further pursuit of this area.

2.5 NMR Titration Binding Studies

2.5.1 Overview

A brief investigation of the ability of a selection of the synthesised C-shaped and tripodal receptors to bind sulfonate and phosphonate guests in solution was undertaken. The author carried out the practical NMR experiments, however all of the data treatment and subsequent calculations were carried out by Salvatore Camiolo whom the author thanks.

All of the experiments bar one that showed binding in solution had too large error margins for the association constants to be calculated, even after numerous repetitions of the experiments. This was partly due to the relatively small changes in chemical shift observed.

2.5.2 Guests

Several guests were chosen for these experiments. Simple aromatic sulfonates were selected for their structural similarities to reactive dyes. Simple phosphonic acid analogues of two of the sulfonates were also investigated. Figure 56 shows the guests used. These were used as either the neutral acid or the sodium salt for reasons of solubility, depending on the solvent system required for the particular experiment.

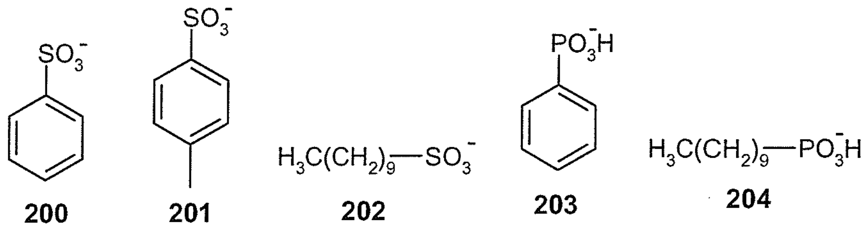


Figure 56. Phosphonate and sulfonate guests.

2.5.3 Hosts

Three categories of potential host ligand were investigated: i) those soluble in chlorinated solvent (tripodal thiourea receptors **192** and **193**) which were matched with guests in their neutral acid form for solubility reasons; ii) those only soluble in DMSO (C-shaped receptors **35**, **67**.2HCl, **94**, **98** and **101**) matched with both neutral and sodium salt guests; iii) those soluble in DMSO, alcohol and water (C-shaped guanidiniums **70** and **83**) matched with sodium salt guest (see figure 57).

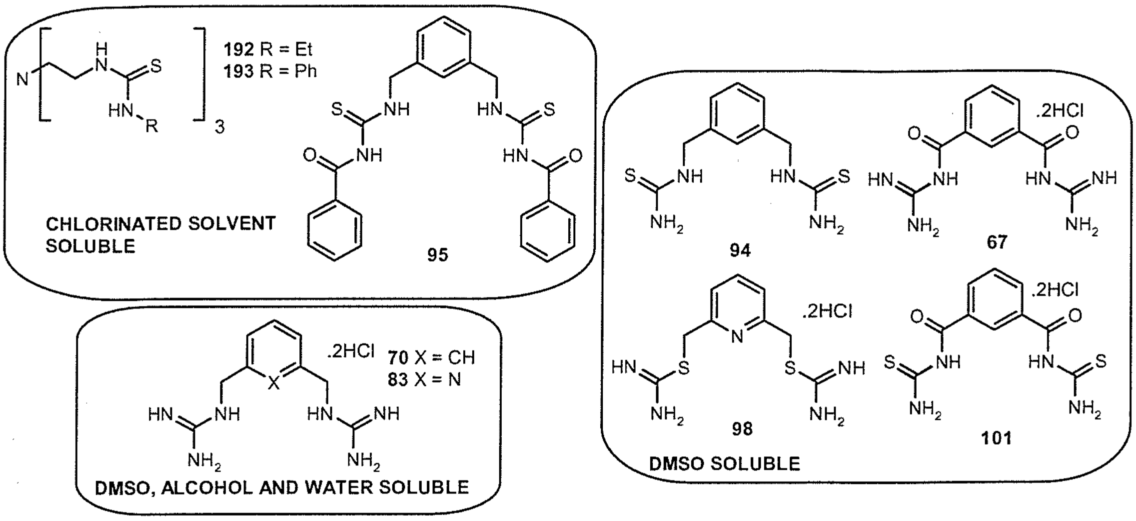


Figure 57. Hosts investigated by NMR titration.

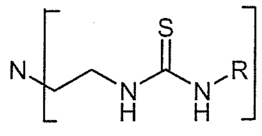
2.5.4 NMR Titration Experiment Overview

Each titration experiment was carried out using a similar protocol. Host (5×10^{-6} M) was dissolved in 0.5 ml of the chosen NMR solvent and guest (1×10^{-4} M) was dissolved in 1 ml of the same NMR solvent and stored in a sealed vial. A proton NMR spectrum of the host solution was collected. An aliquot of guest solution was then added to the host solution, and another proton NMR spectrum was collected. This process was repeated stepwise until a great excess of guest solution had been added to the host solution. In most cases for the aprotic solvent systems the downfield shifts of host N-H peaks were monitored, although in some cases line broadening of these peaks rendered error margins too great and so downfield shifts of C-H resonances were monitored instead. Aliquot volumes of guest solution varied depending upon the sensitivity of the host – guest system.

Salvatore Camiolo used the program EQNMR[103] to calculate binding association constants from plots of guest concentration versus chemical shift of the host signal under study. The curve was also used to estimate binding stoichiometries.

2.5.5 Chloroform NMR Titration Experiments

Both **192** and **193** formed 1:1 association complexes with *n*-decyl phosphonic acid (**204**) (in its protonated neutral form) in chloroform.



192 R = Et
193 R = Ph

$H_3C(CH_2)_9-PO_3H_2$

204

N-H group downfield shifts were followed in the case of **193**, and both N-H group downfield shifts and C-H group downfield shifts were monitored for **192**. In both cases the signals for both N-H environments shifted downfield by between 0.5 and 0.8 ppm, suggesting that both N-H groups of each thiourea were involved in the association. Despite numerous experiments the error margin in the curve obtained for the **192** system, the ethyl derivative, was too great to give an association constant. However, an association constant for the **193** – *n*-decyl phosphonic acid system was calculated as 261 (± 27) M^{-1}. The relevant data is displayed in Table 15. Figure 58 shows plots of guest concentration versus host chemical shift for the experiments involving **192** and **193**.

Spectrum number	Volume of Guest Solution (µl)	'Host' concentration	'Guest' concentration	N-H Chemical Shift (ppm)	equivalents of guest added
0	0	0.01	0	2.7216	0
1	10	0.009804	0.001961	2.8770	0.2
2	20	0.009615	0.003846	2.8638	0.4
3	30	0.009434	0.00566	3.1093	0.6
4	40	0.009259	0.007407	3.2069	0.8
5	50	0.009091	0.009091	3.2986	1
6	60	0.008929	0.010714	3.3664	1.2
7	70	0.008772	0.012281	3.4193	1.4
8	80	0.008621	0.013793	3.4524	1.6
9	90	0.008475	0.015254	3.4755	1.8
10	100	0.008333	0.016667	3.4995	2
11	150	0.007692	0.023077	3.5607	3
12	200	0.007143	0.028571	3.5876	4
13	250	0.006667	0.033333	3.6152	5
14	300	0.00625	0.0375	3.6152	6

Table 15. Titration data collected for **193** + **204** in $CDCl_3$.

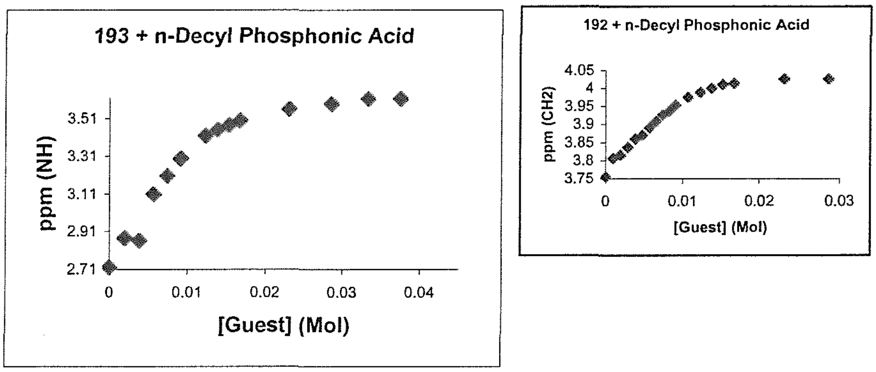
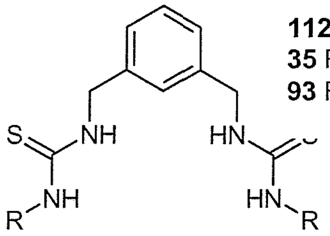


Figure 58. Plots of chemical shift vs. guest concentration for hosts **192** (left) and **193** (right) with guest **204** in d-chloroform.

The C-shaped analogues of **192** and **193**, **112** and **35** respectively, could not be studied in a similar system due to their low solubility in chloroform.



112 R = Et
35 R = Ph
93 R = COPh

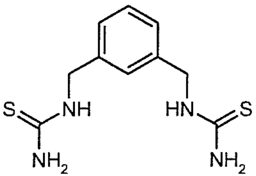
$H_3C(CH_2)_9—PO_3H_2$

204

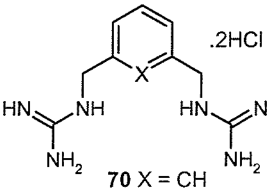
The titration of **95** with *n*-decyl phosphonic acid (**204**) (again in its neutral form) in chloroform showed no association whatsoever. No shifting was observed for either of the signals corresponding to the thiourea N-H groups or the CH_2 resonance. It was postulated that a combination of the likely presence of intramolecular H-bonds, which give both thiourea groups a *cis-trans* geometry in the solid state (involving an N-H group and carbonyl group in both sidearms as discussed in Chapter 2.2), and the steric bulk of the benzoyl groups prevented any intermolecular association.

2.5.6 DMSO NMR Titration Experiments

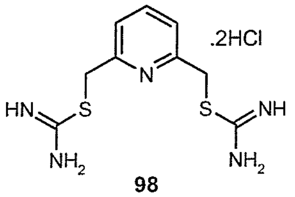
In general any association observed in DMSO, a highly competitive solvent, was small. A very small downfield N-H group signal shift was observed for **94** with phenyl phosphonic acid (**203**) in its neutral form, but the error was large enough to render the data useless. In the case of the dihydrochloride salts of hosts **70, 83** and **98,** small upfield shifts were observed for the CH_2 and N-H signals in experiments carried out with sodium benzene sulfonate (**200**$^-$.Na$^+$) and toluene sulfonic acid (**201**) as guests. Figure 59 shows plots for three of these titrations. These shifts were very small (typically <0.1 ppm) and continued to high concentration of guest (up to seven equivalents), and so unfortunately little can be inferred from these results.



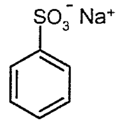
94



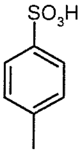
70 X = CH
83 X = N



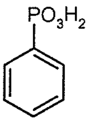
98



200$^-$.Na$^+$



201



203

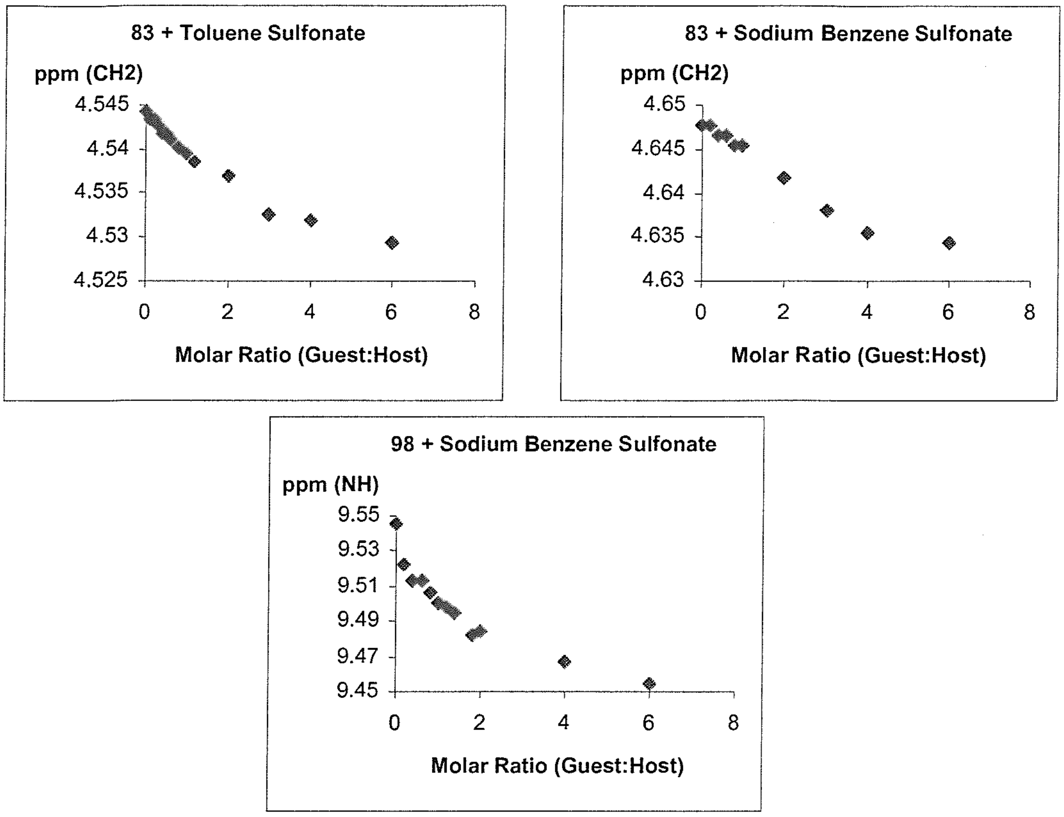
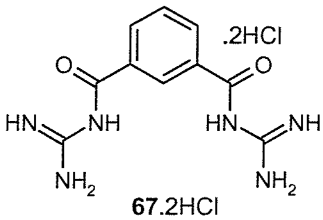
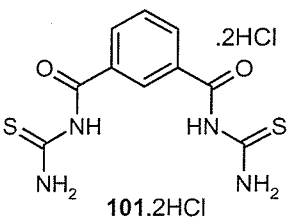


Figure 59. Plots of chemical shift vs. molar ratio (guest:host) for host **83** with guest **201** (top left), **83** with **200**$^-$.Na$^+$ (top right), and **98** with **200**$^-$.Na$^+$ (bottom middle) in d$_6$-DMSO.

Titration experiments involving **67**.2HCl and **101**.2HCl gave very poor data for two reasons; sufficiently pure hydrochloride salts of these hosts for the experiments could not be prepared, and error margins in the experiments were again large.



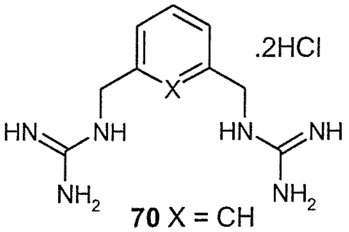
67.2HCl



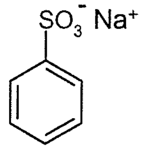
101.2HCl

2.5.7 D$_2$O NMR Titration Experiments

As was the case for the dihydrochloride salt hosts in DMSO, very small upfield shifts were observed for CH$_2$ signals in D$_2$O solvent experiments for both **70** and **83** with sodium benzene sulfonate (**200**$^-$.Na$^+$) as guest. Figure 60 shows a rough plot of chemical shift vs. molar ratio (guest:host) of the methylene signal. Again these shifts are far too small to draw any conclusions about the solution association behaviour of these compounds.



70 X = CH
83 X = N



200$^-$.Na$^+$

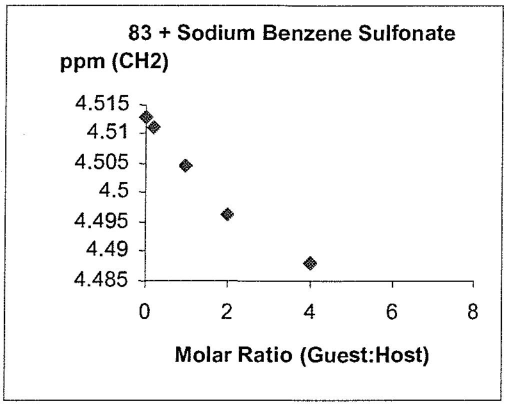
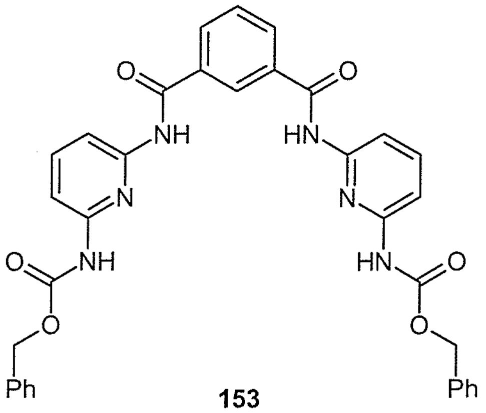


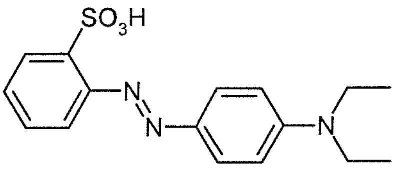
Figure 60. Plot of chemical shift vs. molar ratio (guest:host) for host **83** with guest **200**$^-$.Na$^+$ in D_2O.

2.5.8 NMR Titration of Tetraamide host 153 with Azo Dye guest 149

An NMR titration binding study of tetraamide host **153** (discussed in Chapter 2.2, page 93) with azo dye **149** was carried out in deuterated chloroform (it was presumed that azo dye **149** was in its protonated neutral form as it dissolved in this solvent).



153



149

N-H resonances were observed to move downfield, consistent with host – guest recognition.

However, neither a binding constant nor an association stoichiometry could be measured because of the large error present in the data. The shape of the chemical shift (NH) vs. molar ratio (guest:host) curve suggests that simple 1:1 association *does not* dominate (figure 61).

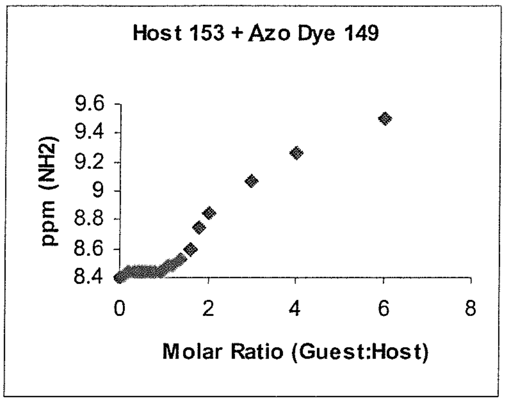


Figure 61. Plot of chemical shift vs. molar ratio (guest:host) for host **153** with guest **149** in chloroform.

2.5.9 Summary

Numerous NMR titration experiments were carried out with 'model' dye sulfonates and phosphonates, but gave little information as to the solution association behaviour of many of the host molecules synthesised. Ideally the experiments would have been carried out using the tetrabutylammonium salt of the guest molecules (Guest$^-$ ^{t}BuNH$_4^+$) and the hexafluorophosphate salt of the bis-guanidium host molecules (bis-guandinium^{2+} (PF$_6^-$)$_2$), however due to time restrictions these salts were not prepared.

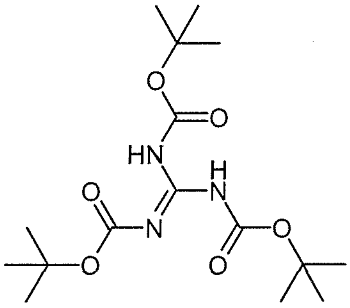
The tripodal receptors **192** and **193** gave the best results and clearest indication of 1:1 solution phase host – guest recognition.

2.6 Related Additional Crystal Structures

The crystal structures related to work discussed earlier in this thesis are summarised in this section.

2.6.1 Tri-*t*-BOC-guanidine (140, Chapter 2.1)

The crystal structure of **140** was solved by conventional methods. **140** is planar in the solid state, and its crystallographic C_3 rotation axis results from three intramolecular H-bonds between each N-H group and the adjacent carbonyl moiety (N-H···O=C distance 2.06 Å) (figure 62).



140

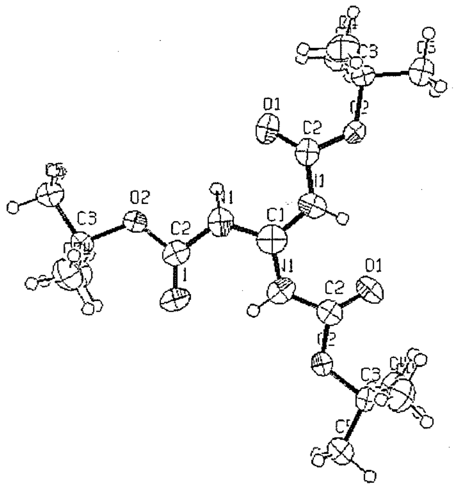


Figure 62. Asymmetric unit of **140**.

No intermolecular H-bonding is apparent in the packed structure.

Empirical Formula	$C_{16} H_{31} N_3 O_6$
Mass	361.44
Collection Temperature/ K	150 (2)
Crystal System	Hexagonal
Space Group	P6(3)/m
Unit Cell (a,b,c in Å, α,β,χ in °.)	a = 11.201 (2), b = 11.201 (2), c = 8.783 (2), α =90.00, β = 90.00, χ = 120.00
Volume	954.3 (3)
Z	2
R1	0.0485
wR2	0.1272

Table 16. Crystallographic data for **140**.

2.6.2 1,3-Dichloro-5-benzlamino-*s*-triazine (181, Chapter 2.3)

In **181** the phenyl ring is twisted 90° away from the triazine ring plane (figure 63).

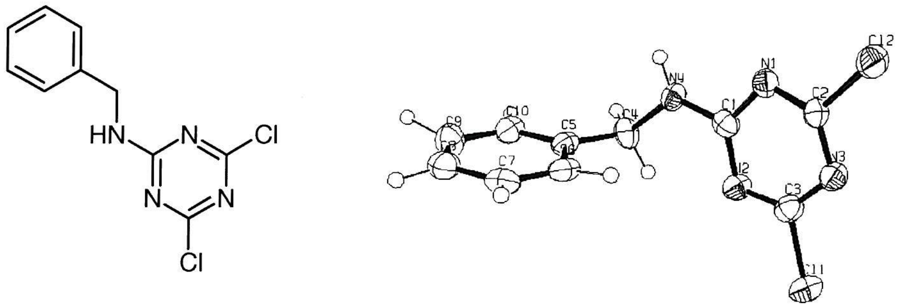


Figure 63. Asymmetric unit of **181**.

A pairwise H-bonding interaction exists in the packed structure between the N-H group and the β-nitrogen atom of the triazine ring of another molecule (figure 64).

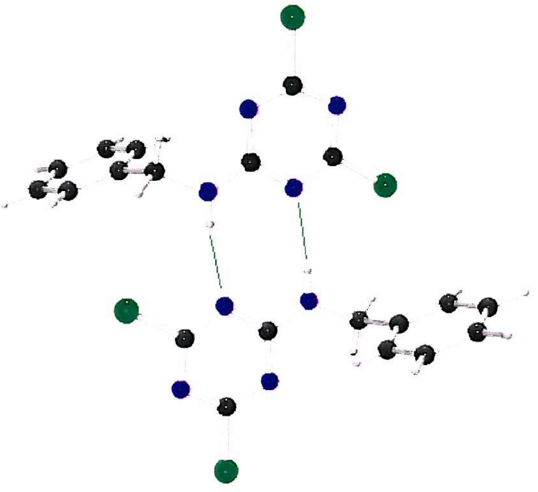


Figure 64. Pairwise H-bonding interaction in the solid-state structure of **181**.

Empirical Formula	$C_{10} H_8 N_4 Cl_2$
Mass	255.10
Collection Temperature/ K	150 (2)
Crystal System	Monoclinic
Space Group	P2(1)/c
Unit Cell (a,b,c in Å, α,β,χ in °.)	a = 11.559 (2), b = 4.874 (10), c = 19.604 (4), α =90.00, β = 91.82 (3), χ = 90.00
Volume	1103.9 (4)
Z	4
R1	0.0512
wR2	0.1191

Table 17. Crystallographic data for **181**.

2.6.3 *N,N'*-Diphenyl Thiourea (185, Chapter 2.3)

185 adopts the sterically-favoured *trans-trans* solid-state geometry expected for a simple di-substituted thiourea. The phenyl rings are both rotated through 90° with respect to the thiocarbonyl bond (figure 65).

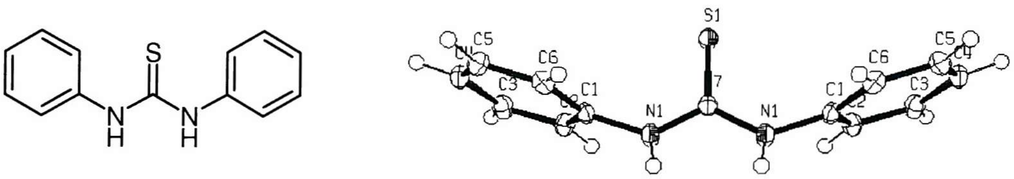


Figure 65. Sketch and asymmetric unit of **185**.

In the packed structure two intermolecular H-bond-like interactions are apparent between molecules, involving both N-H groups and the thiourea sulfur atom of another molecule (figure 66). Molecules are twisted by 90° away from one another, and N-H···S distances are both 2.65 Å.

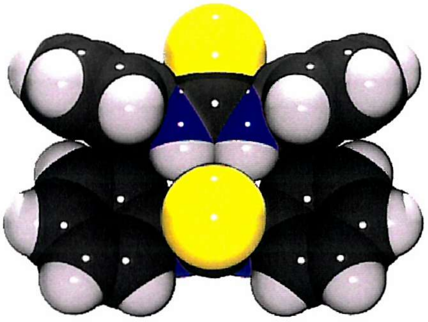


Figure 66. N-H···S contacts in the solid-state structure of **185**.

Empirical Formula	$C_{26} H_{24} N_4 S_2$
Mass	456.61
Collection Temperature/ K	150 (2)
Crystal System	Orthorhombic
Space Group	Pnma
Unit Cell (a,b,c in Å, α,β,χ in °.)	a = 7.792 (2), b = 25.464 (5), c = 5.679 (10), α =90.00, β = 90.00, χ = 90.00
Volume	1126.8 (4)
Z	2
R1	0.0353
wR2	0.0907

Table 18. Crystallographic data for **185**.

2.7 Unrelated Additional Crystal Structures

During the course of the present work, a number of crystal structures were also collected and solved for other members of the Grossel research group. This section lists the structures that were solved successfully and briefly discusses any interesting features observed. Full characterisation data for the compounds can be found in the theses of those who prepared the compounds (names given in the title to each compound), together with a detailed analysis of their solid-state behaviour. In each case the asymmetric unit and a table summarising the crystallographic data is displayed.

2.7.1 Pyridine Dicarboxamides

Ten pyridine dicarboxamide structures were successfully solved, a number of which were co-crystallised with cationic counter ions.

2,6-Pyridine-(*p*-bromo-benzyl)-dicarboxamide (205) (Robert Parker)

The structure has a C-shaped geometry brought about by an intramolecular N-H···N (pyridine) close contact (N-H···N distances between 2.30 and 2.34 Å). Two conformations exist in the asymmetric unit (figure 67).

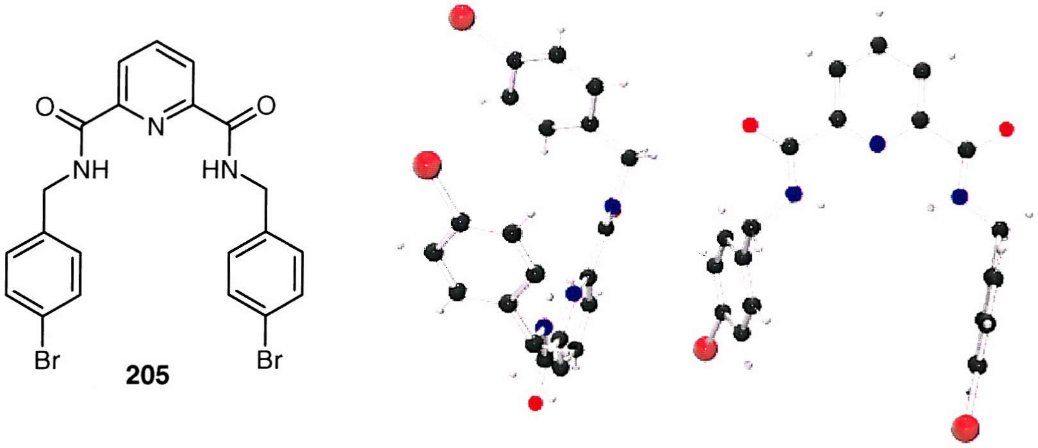


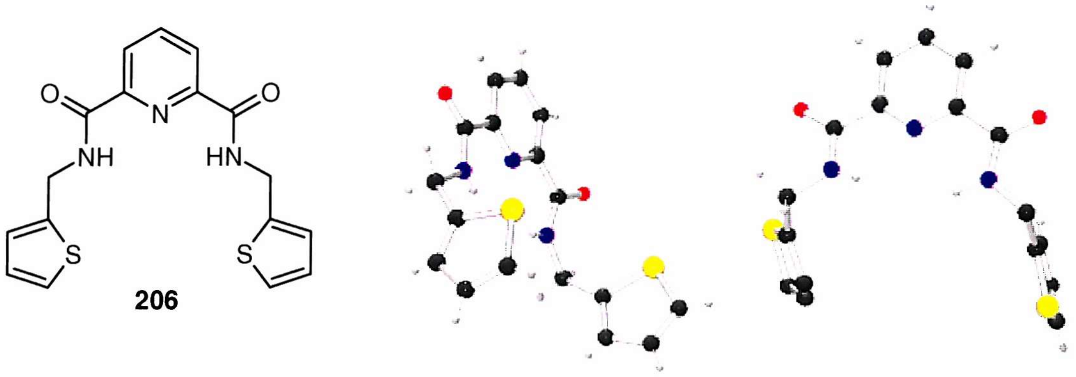
Figure 67. Sketch and asymmetric unit of **205**.

Empirical Formula	C21 H17 Br2 N3 O2
Mass	503.20
Collection Temperature/ K	293 (2)
Crystal System	Monoclinic
Space Group	P2(1)/c
Unit Cell (a,b,c in Å, α,β,χ in °.)	a = 10.529 (2), b = 19.544 (4), c = 19.686 (4), α =90.00, β = 101.53 (3), χ = 90.00
Volume	3969.2 (14)
Z	8
R1	0.0626
wR2	0.1364

Table 19. Crystallographic data for **205**.

2,6-Pyridine-(methyl-2’-thiophenyl)-dicarboxamide (206) (John Gomm)

Similar to the previous structure, a C-shaped geometry brought about by an intramolecular N-H···N(pyridine) close contact exists (N-H···N distances between 2.20 and 2.46 Å). Again two conformations of the molecule are present in the asymmetric unit (figure 68).



206

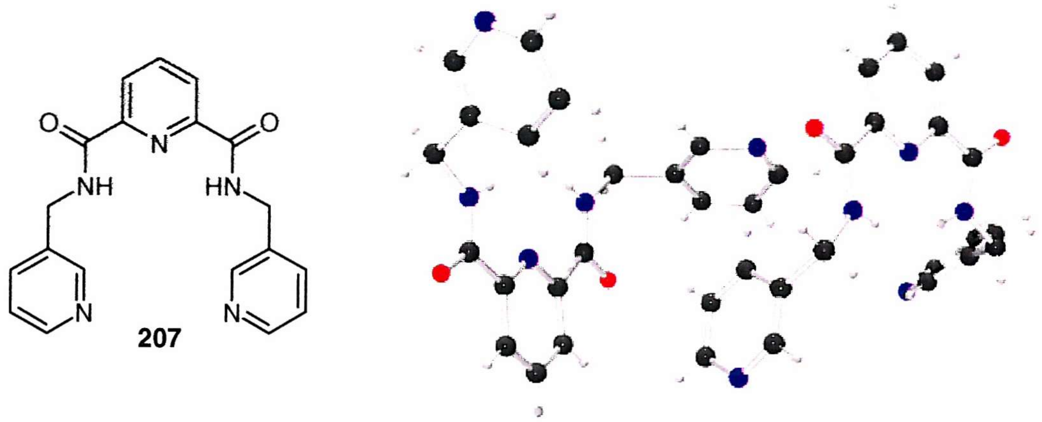
Figure 68. Sketch and asymmetric unit of **206**.

Empirical Formula	$C_{34}H_{27}N_6O_4S_4$
Mass	355.93
Collection Temperature/ K	150 (2)
Crystal System	Monoclinic
Space Group	P2(1)/c
Unit Cell (a,b,c in Å, α,β,χ in °.)	a = 9.566 (2), b = 22.116 (4), c = 16.400 (3), α =90.00, β = 103.71 (3), χ = 90.00
Volume	3370.8 (11)
Z	8
R1	0.0708
wR2	0.1851

Table 20. Crystallographic data for **206**.

2,6-Pyridine-(methyl-*m*-pyridyl)-dicarboxamide (207) (John Gomm)

Again a C-shaped geometry brought about by an intramolecular N-H···N(pyridine) close contact dominates (N-H···N distances between 2.21 and 2.42 Å). Once again two conformations are present in the asymmetric unit (figure 69).



207

Figure 69. Sketch and asymmetric unit of **207**.

Empirical Formula	$C_{19}H_{17}N_5O_2$
Mass	347.38
Collection Temperature/ K	150 (2)
Crystal System	Monoclinic
Space Group	P-1
Unit Cell (a,b,c in Å, α,β,χ in °.)	a = 9.635 (2), b = 12.987 (3), c = 14.835 (3), α =89.33 (3), β = 71.94 (3), χ = 88.58 (3)
Volume	1764.3 (7)
Z	4
R1	0.1462
wR2	0.3212

Table 21. Crystallographic data for **207**.

Packing of the structure reveals an interesting discreet dimeric self-recognition pattern in which the nitrogen atom of one pyridyl sidearm of a tweezer is H-bonded to the two amide N-H groups of another tweezer molecule, and vice versa (figure 70). Intermolecular N-H···N distances lie between 2.24 and 2.36 Å.

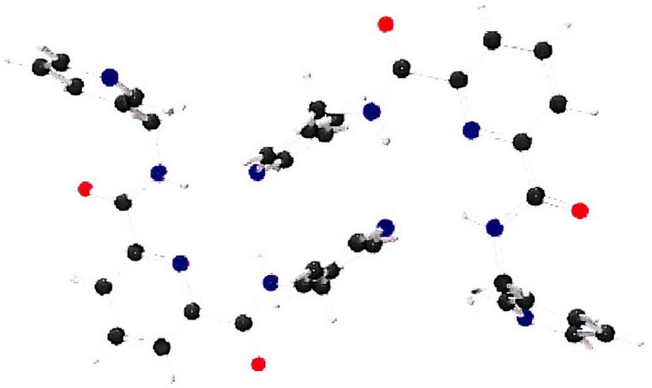


Figure 70. Self-recognition in the crystal structure of **207**.

2,6-Pyridine-benzyl-dicarboxamide (208) (John Gomm)

Only one molecular conformation is presnt in this crystal. The usual C-shaped preorganisation is displayed (N-H···N distances both 2.29 Å) (figure 71).

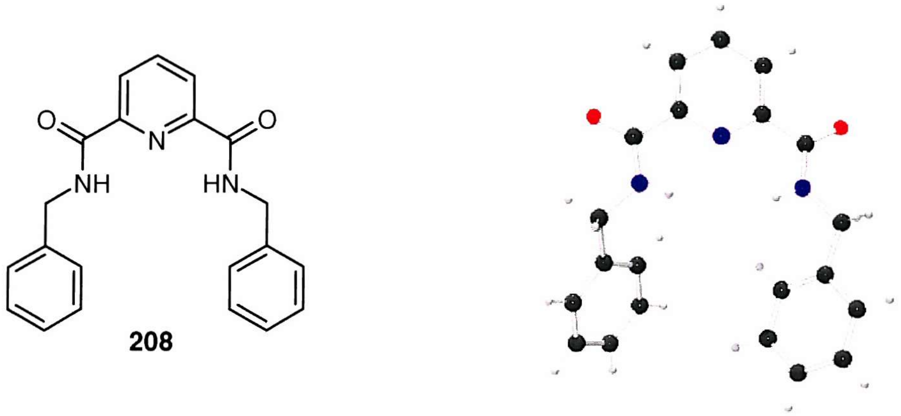


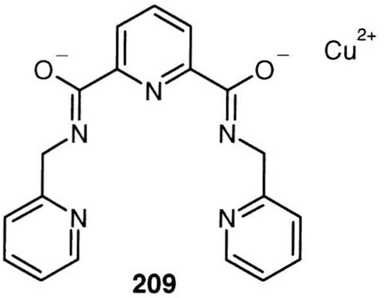
Figure 71. Sketch and asymmetric unit of **208**.

Empirical Formula	$C_{21} H_{19} N_3 O_2$
Mass	345.39
Collection Temperature/ K	150 (2)
Crystal System	Monoclinic
Space Group	P2(1)/c
Unit Cell (a,b,c in Å, α,β,χ in °.)	a = 15.879 (3), b = 11.030 (2), c = 9.863 (2), α = 90.00, β = 97.54 (3), χ = 90.00
Volume	1712.5 (6)
Z	4
R1	0.0406
wR2	0.1038

Table 22. Crystallographic data for **208**.

2,6-Pyridine-(methyl-*o*-pyridyl)-dicarboxamide co-crystallised with Copper (209) (Andrew Dwyer)

This structure, rather than forming discreet zwitterionic copper-ligand complexes, organises itself into a helical architecture in which each copper dication forms four close contacts with surrounding nitrogen atoms from two C-shaped ligands. Two such units are present in the asymmetric unit (figure 72). Disordered water is also present in the structure, but has been omitted from figure 72 for clarity. (This disordered water accounts for the non-integer value of oxygen in the structure's empirical formula). All nitrogen atoms in the structure are involved in bonds to copper cations.



209

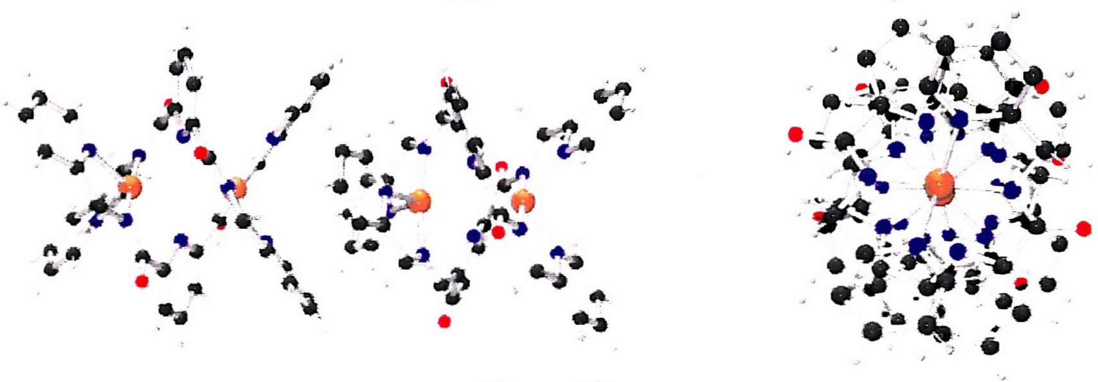


Figure 72.

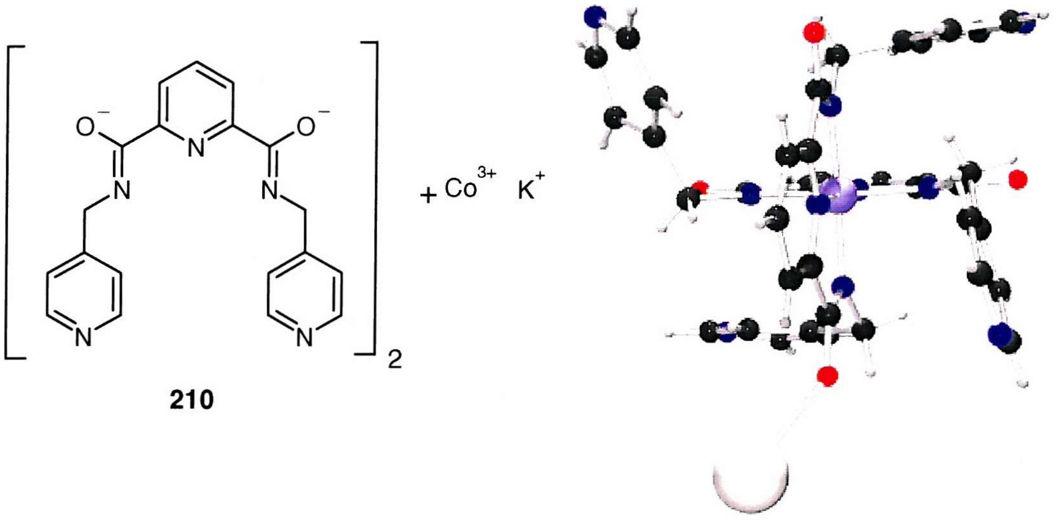
Helical structure of **209**.

Empirical Formula	$C_{19}\,H_{15}\,Cu_1\,N_5\,O_{3.90}$
Mass	439.29
Collection Temperature/ K	150 (2)
Crystal System	Monoclinic
Space Group	P2(1)/c
Unit Cell (a,b,c in Å, α,β,χ in °.)	a = 20.486 (4), b = 19.271 (4), c = 19.351 (4), α = 90.00, β = 90.37 (3), χ = 90.00
Volume	7639 (3)
Z	16
R1	0.0754
wR2	0.1722

Table 23. Crystallographic data for **209**.

2,6-Pyridine-(methyl-*p*-pyridyl)-dicarboxamide co-crystallised with Cobalt (III) and Potassium (210) (Andrew Dwyer)

Discreet 'paddles' involving two interlocking ligands, one cobalt cation and one potassium cation (to balance charge) are formed in the solid state structure of this salt (figure 73). The cobalt (III) cation sits in the cavity created by the two interlocking ligands. Both sidearm pyridyl nitrogen atoms are not involved in cobalt binding in each ligand. The asymmetric unit encompasses two conformations of this 'paddle' motif, however only one conformation is shown below as both conformations differ little.



210

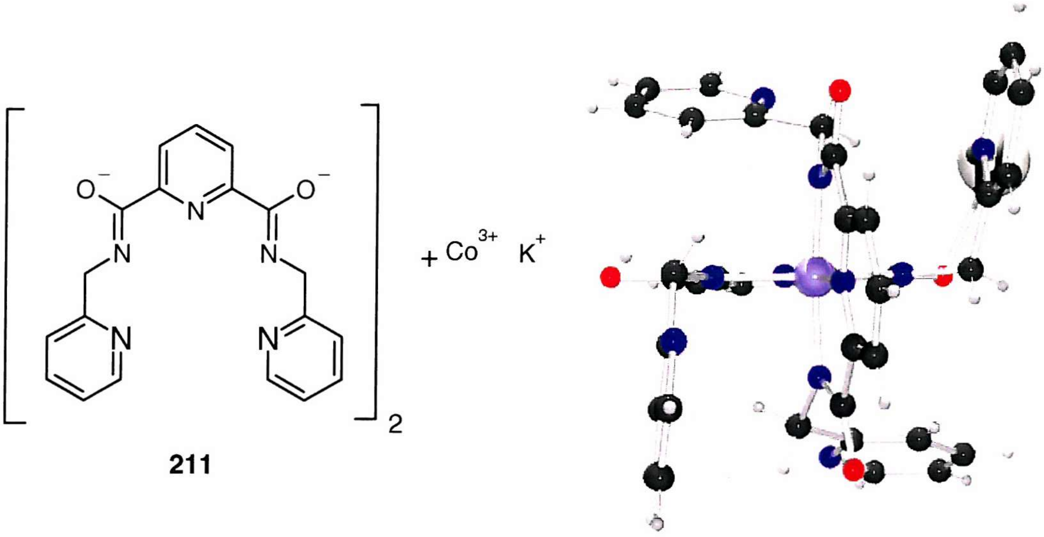
Figure 73. "Paddle" motif of **210**.

Empirical Formula	$C_{76} H_{59} Co_{16} K_8 N_2 O_2$
Mass	450.43
Collection Temperature/ K	150 (2)
Crystal System	Orthorhombic
Space Group	Pna2(1)
Unit Cell (a,b,c in Å, α,β,χ in °.)	a = 17.086 (3), b = 23.633 (5), c = 17.765 (4), α = 90.00, β = 90.00, χ = 90.00
Volume	7173 (3)
Z	14
R1	0.0834
wR2	0.2176

Table 24. Crystallographic data for **210**.

2,6-Pyridine-(methyl-*o*-pyridyl)-dicarboxamide co-crystallised with Cobalt (III) and Potassium (211) (Andrew Dwyer)

Again discreet 'paddles' involving two interlocking ligands, one cobalt (III) cation and one potassium cation (to balance charge) are formed in the solid state structure of this salt (figure 74). The cobalt cation sits in the cavity created by the two interlocking ligands. Both sidearm pyridyl nitrogen atoms are not involved in cobalt binding in each ligand. Unlike the previous structure, only one discreet 'paddle' is present in the asymmetric unit along with disordered water molecules (figure 74). These water molecules have been omitted from figure 74.



211

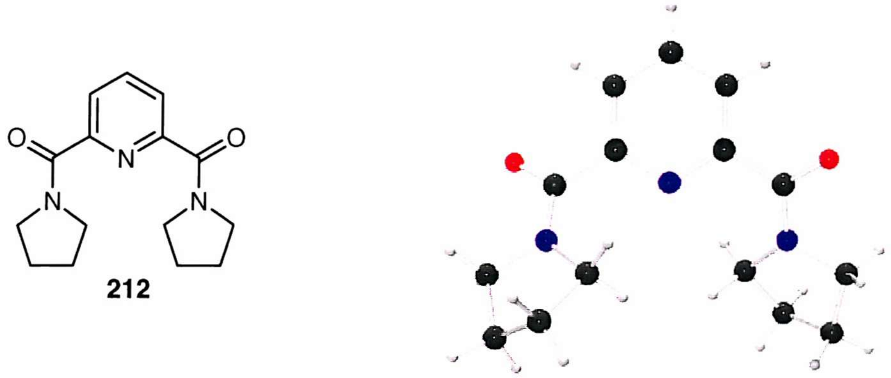
Figure 74. "Paddle" motif in **211**.

Empirical Formula	$C_{39} H_{29} Co_1 K_1 N_{10} O_9$
Mass	439.88
Collection Temperature/ K	150 (2)
Crystal System	Triclinic
Space Group	P-1
Unit Cell (a,b,c in Å, α,β,χ in °.)	a = 10.918 (2), b = 10.942 (2), c = 17.992 (4), α = 101.26 (3), β = 90.84 (3), χ = 109.83 (3)
Volume	1975.4 (7)
Z	4
R1	0.0902
wR2	0.2543

Table 25. Crystallographic data for **211**.

N,N'-Bis-pyrrolidyl Pyridine-2,6-dicarboxamide (212) (John Gomm)

As the nitrogen atoms of the amide functions in this compound are both tertiary, the prominent intramolecular N-H···N(pyridine) close contact seen above cannot therefore be present in this structure (figure 75). However the solid state conformation still exhibits a pseudo C-shape, due more to steric arguments from the two pyrrolidine rings rather than as a result of two possible intramolecular C-H···N(pyridine) contacts, which are rather long (C-H···N distances both 2.65 Å).



212

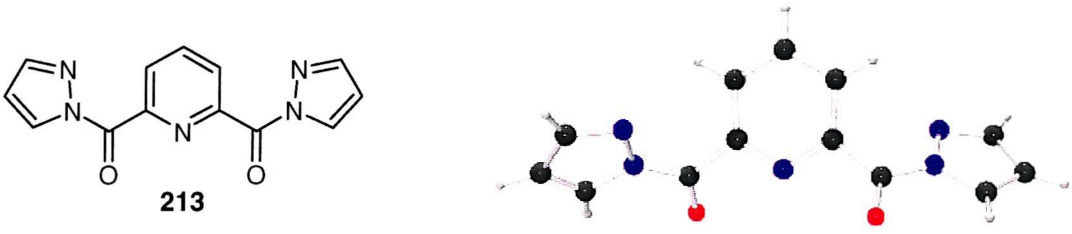
Figure 75. Sketch (left) and asymmetric unit (right) of **212**.

Empirical Formula	$C_{15} H_{19} N_3 O_2$
Mass	273.33
Collection Temperature/ K	150 (2)
Crystal System	Monoclinic
Space Group	C2/c
Unit Cell (a,b,c in Å, α,β,χ in °.)	a = 12.095 (2), b = 10.012 (2), c = 11.808 (2), α = 90.00, β = 94.06 (3), χ = 90.00
Volume	1426.3 (4)
Z	4
R1	0.0444
wR2	0.1217

Table 26. Crystallographic data for **212**.

N,N'-Bis-diimidazole Pyridine-2,6-dicarboxamide (213) (John Gomm)

This compound does not exhibit the characteristic C-shaped geometry of other diamides as there is no true intramolecular H-bonding possible, all the nitrogen atoms being part of aromatic ring systems. Instead a twisted *anti-anti* ('open wing') geometry is adopted in which both sidearms are twisted out of the plane of the aromatic core by ca. 40° (figure 76).



213

Figure 76. Sketch (left) and asymmetric unit (right) of **213**.

Empirical Formula	$C_{13}H_9N_5O_2$
Mass	267.25
Collection Temperature/ K	150 (2)
Crystal System	Monoclinic
Space Group	C2/c
Unit Cell (a,b,c in Å, α,β,χ in °.)	a = 14.038 (3), b = 12.376 (2), c = 7.047 (10), α = 90.00, β = 103.67 (3), χ = 90.00
Volume	1189.6 (4)
Z	4
R1	0.0420
wR2	0.1080

Table 27. Crystallographic data for **213**.

N,N'-Bis-(α-methylbenzyl) Pyridine-2,6-dicarboxamide co-crystallised with Palladium (II) (214) (Andrew Dwyer)

This chiral C_2-symmetric ligand forms 1:1 complexes with palladium (II) in the solid state (figure 77). Three nitrogen-palladium close contacts exist; in addition one molecule of acetonitrile is bound to the vacant co-ordination site on the palladium guest through its nitrogen atom.

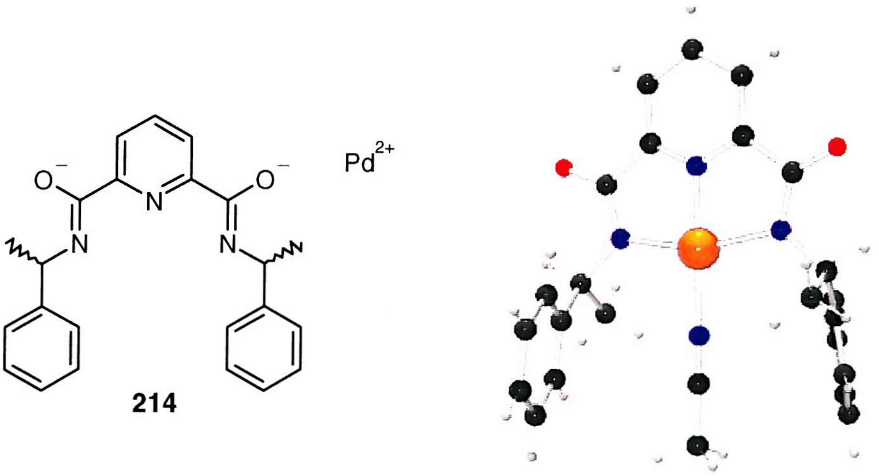


Figure 77. Sketch (left) and asymmetric unit (right) of **214**.

Empirical Formula	$C_{25}\,H_{24}\,N_4\,O_2\,Pd_1$
Mass	518.88
Collection Temperature/ K	150 (2)
Crystal System	Monoclinic
Space Group	C2/c
Unit Cell (a,b,c in Å, α,β,χ in °.)	a = 11.316 (2), b = 13.267 (3), c = 15.156 (3), α = 90.00, β = 90.00, χ = 90.00
Volume	2275.4 (8)
Z	4
R1	0.0353
wR2	0.0798

Table 28. Crystallographic data for **214**.

N,N'-Bis-(α-methyl-1'-naphthyl) Pyridine-2,6-dicarboxamide co-crystallised with Palladium (II) (215) (Andrew Dwyer)

This chiral C_2-symmetric ligand again forms 1:1 inclusion complexes with palladium (II) in the solid state (figure 78). As with the previous structure, three nitrogen-palladium close contacts exist; in addition one molecule of acetonitrile is also co-ordinated to the palladium atom (as seen for **214**).

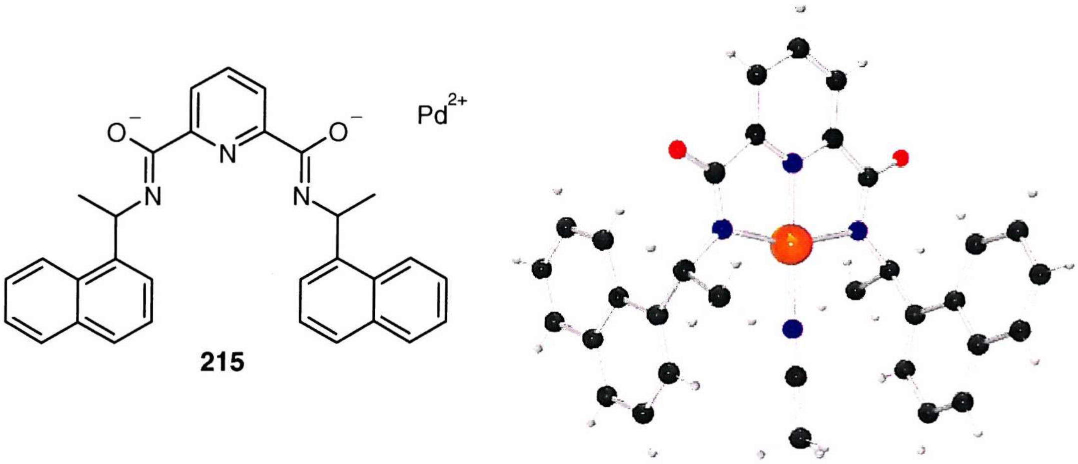


Figure 78. Sketch (left) and asymmetric unit (right) of **215**.

Empirical Formula	C_{33} H_{28} N_4 O_2 Pd_1
Mass	618.99
Collection Temperature/ K	150 (2)
Crystal System	Hexagonal
Space Group	P3(2)
Unit Cell (a,b,c in Å, α,β,χ in °.)	a = 14.435 (2), b = 14.435 (2), c = 11.221 (2), α = 90.00, β = 90.00, χ = 120.00
Volume	2024.9 (5)
Z	3
R1	0.0205
wR2	0.0567

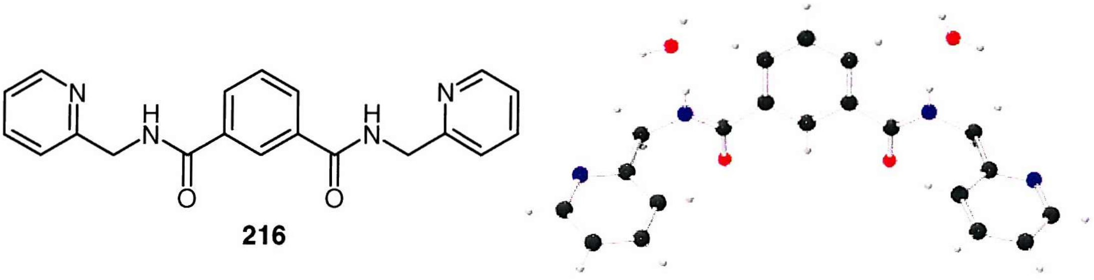
Table 29. Crystallographic data for **215**.

2.7.2 Other Aromatic-cored Dicarboxamides

A number of dicarboxamides with aromatic cores other than pyridine were also studied.

N,N'-Bis-(2-pyridyl)methyl Benzene-1,3-dicarboxamide (216) (John Gomm)

An 'open wing' (*cis-cis*) geometry is adopted by this compound in the solid-state (in contrast with the C-shaped geometry favoured by its pyridine-cored analogue **207** – see page 124) (figure 79). Two water molecules are present in the asymmetric unit, and are H-bonded to the two N-H groups.



216

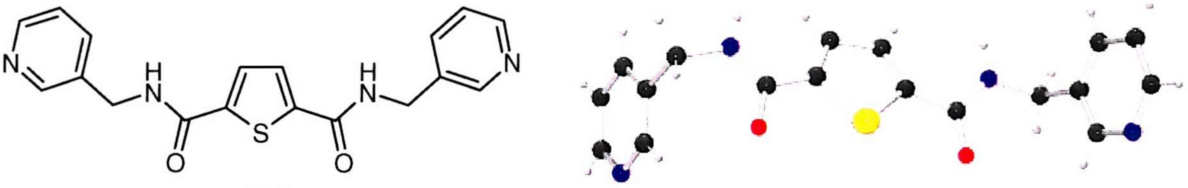
Figure 79. Sketch (left) and asymmetric unit (right) of **216**.

Empirical Formula	$C_{20}H_{22}N_4O_4$
Mass	382.42
Collection Temperature/ K	150 (2)
Crystal System	Triclinic
Space Group	P-1
Unit Cell (a,b,c in Å, α,β,χ in °.)	a = 6.978 (10), b = 11.089 (2), c = 13.293 (3), α = 88.29 (3), β = 75.15 (3), χ = 71.69 (3)
Volume	942.5 (3)
Z	2
R1	0.0432
wR2	0.1104

Table 30. Crystallographic data for **216**.

N,N'-Bis-(*m*-pyridyl) Thiophene-2,5-dicarboxamide (217) (John Gomm)

This structure adopts an *anti-anti* conformation in the solid-state, with sidearms disposed *trans* to one another behind and in front of the plane of the thiophene core (figure 80).



217

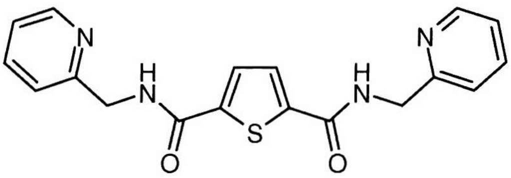
Figure 80. Sketch (left) and asymmetric unit (roght) of **217**.

Empirical Formula	$C_{18} H_{16} N_4 O_2 S_1$
Mass	352.41
Collection Temperature/ K	150 (2)
Crystal System	Triclinic
Space Group	P1
Unit Cell (a,b,c in Å, α,β,χ in °.)	a = 6.083 (10), b = 7.356 (10), c = 9.795 (2), α = 102.29 (3), β = 91.91 (3), χ = 109.62 (3)
Volume	400.62 (12)
Z	1
R1	0.0454
wR2	0.1163

Table 31. Crystallographic data for **217**.

N,N'-Bis-(*o*-pyridyl) Thiophene-2,5-dicarboxamide (218) (John Gomm)

This structure, a homologue of the preceding compound, again has an *anti-anti* conformation with sidearms disposed *trans* to one another and at 90° to the plane of the thiophene core (figure 81).



218

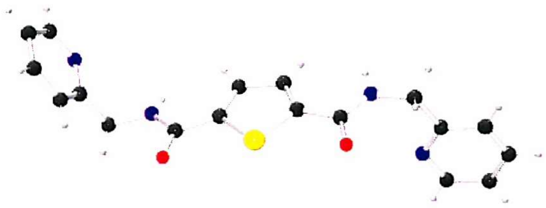


Figure 81.

Empirical Formula	$C_{18} H_{16} N_4 O_2 S_1$
Mass	352.41
Collection Temperature/ K	150 (2)
Crystal System	Orthorhombic
Space Group	P2(1)2(1)2(1)
Unit Cell (a,b,c in Å, α,β,χ in °.)	a = 7.815 (2), b = 10.747 (2), c = 20.026 (4), α = 90.00, β = 90.00, χ = 90.00
Volume	1681.9 (6)
Z	4
R1	0.0310
wR2	0.0725

Table 32. Crystallographic data for **218**.

2.7.3 Pyridine-2,6-dicarboxylate esters

These compounds are interesting because the great majority studied in the solid state in the research group formed ribbons via a novel three-pronged ('trident-like') motif, consisting of two Ar-H···O=C H-bonds and one central Ar-H···N (pyridine) contact (figure 82).

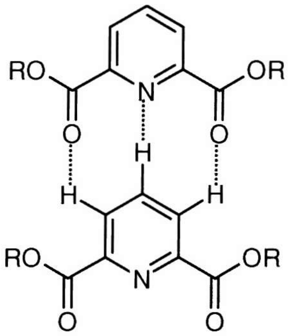


Figure 82. Trident-like motif between pyridine-2,6-dicarboxylate esters.

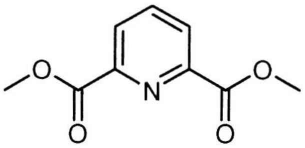
Three pyridine-2,6-dicarboxylate esters are discussed below, two of which display the trident motif. Table 33 below shows the distances for these close contacts.

	C-H···O distance (Å)	C-H···N distance (Å)	C-H···O distance (Å)
Dimethyl (**219**)	2.88 ± 0.02	3.02 ± 0.02	2.88 ± 0.02
di(*p*-chlorobenzyl) (**220**)	2.65 ± 0.03	2.62 ± 0.05	2.65 ± 0.03

Table 33. Trident-like motif distances in **219** and **220**.

Dimethyl Pyridine-2,6-dicarboxylate (219) (John Gomm)

This compound displays the trident motif discussed above (figure 83).



219

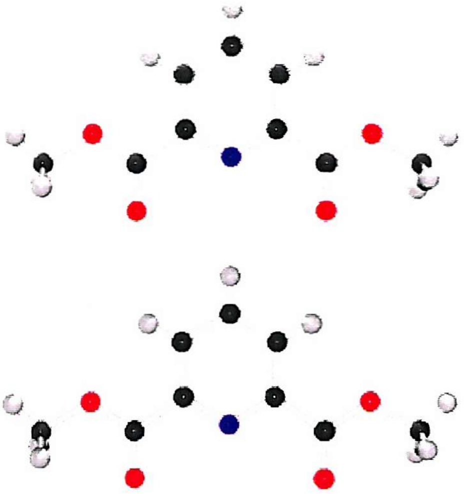


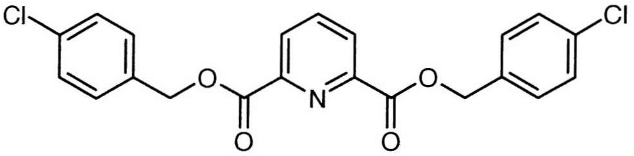
Figure 83. Sketch (left) and trident-like motif of **219**.

Empirical Formula	$C_9 H_9 N_1 O_4$
Mass	195.17
Collection Temperature/ K	150 (2)
Crystal System	Monoclinic
Space Group	C2/c
Unit Cell (a,b,c in Å, α,β,χ in °.)	a = 13.008 (3), b = 6.760 (10), c = 11.039 (2), α = 90.00, β = 118.47 (3), χ = 90.00
Volume	853.3 (3)
Z	4
R1	0.0425
wR2	0.1174

Table 34. Crystallographic data for **219**.

Bis-(4-chlorophenyl) methyl Pyridine-2,6-dicarboxylate (220) (John Gomm)

The trident motif is represented again in this structure (figure 84).



220

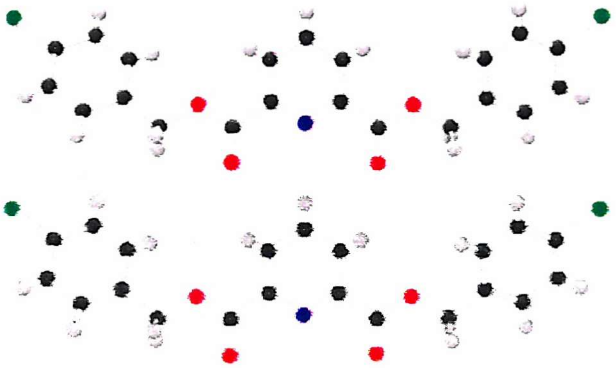


Figure 84. Sketch and asymmetric unit of **220**.

Empirical Formula	$C_{21}H_{15}N_1O_4Cl_2$
Mass	416.24
Collection Temperature/ K	150 (2)
Crystal System	Orthorhombic
Space Group	P2(1)2(1)2
Unit Cell (a,b,c in Å, α,β,χ in °.)	a = 31.705 (6), b = 4.655 (10), c = 6.262 (10), α = 90.00, β = 90.00, χ = 90.00
Volume	924.2 (3)
Z	2
R1	0.0540
wR2	0.1277

Table 35. Crystallographic data for **220**.

Bis-(*m*-trifluorophenyl) methyl Pyridine-2,6-dicarboxylate (221) (John Gomm)

This molecule does not adopt the 'open wing' (*trans-trans*) conformation seen previously but instead favours a *cis-trans* geometry (figure 85).

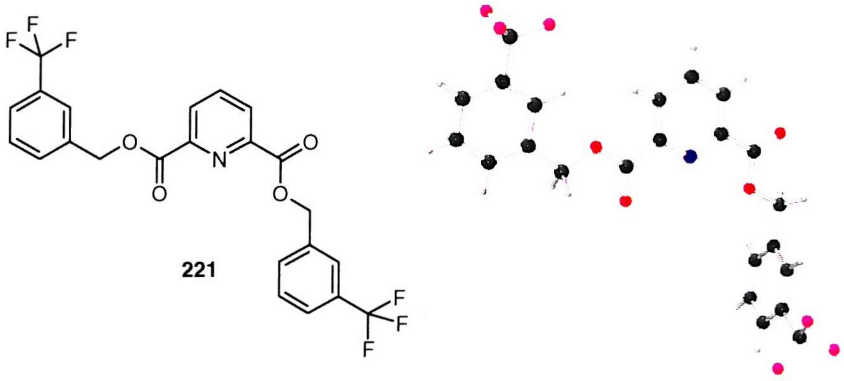


Figure 85. Sketch (left) and asymmetric unit (right) of **221**.

The structure does not therefore show the trident-like association. Instead undulating sheets of molecules held together by (phenyl) C-H···O contacts are observed (in green in figure 86). Two contacts between fluorine atoms and pyridyl hydrogen atoms are also present ((pyridyl) C-H···F distances 2.67 and 2.95 Å) (in red in figure 86).

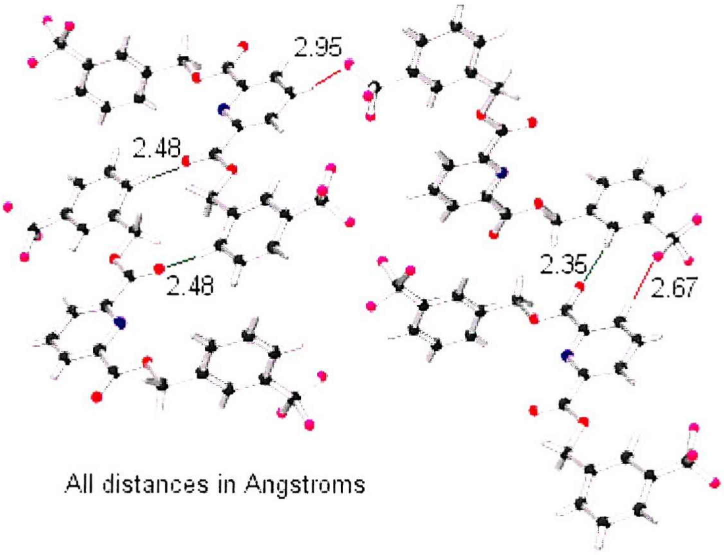


Figure 86. Section of an undulated sheet in the strucutre of **221**. Contacts shown in red and green.

Empirical Formula	$C_{23}H_{15}F_6N_1O_4$
Mass	483.36
Collection Temperature/ K	150 (2)
Crystal System	Triclinic
Space Group	P-1
Unit Cell (a,b,c in Å, α,β,χ in °.)	a = 4.908 (10), b = 16.474 (3), c = 25.092 (5), α = 89.56 (3), β = 89.86 (3), χ = 89.76 (3)
Volume	2028.7 (7)
Z	4
R1	0.0672
wR2	0.1563

Table 36. Crystallographic data for **221**.

2.7.4 Other Aromatic-cored Diesters

In addition to the 2,6-pyridine-cored diesters above, a number of other aromatic-cored diester compounds were studied.

Dimethyl Pyridine-3,5-dicarboxylate (222) (John Gomm)

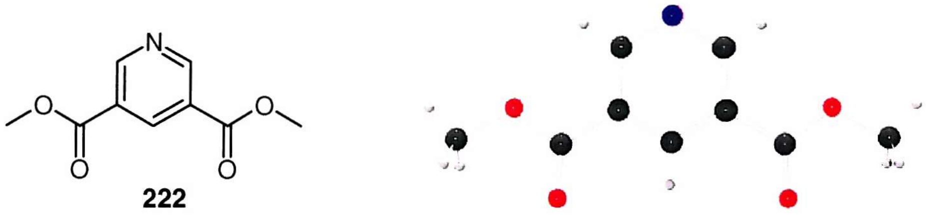


Figure 87. Sketch (left) and asymmetric unit (right) of **222**.

Empirical Formula	$C_9 H_9 N_1 O_4$
Mass	195.17
Collection Temperature/ K	150 (2)
Crystal System	Monoclinic
Space Group	P2(1)/c
Unit Cell (a,b,c in Å, α,β,χ in °.)	a = 3.809 (10), b = 24.542 (5), c = 9.501 (2), α = 90.00, β = 95.07 (3), χ = 90.00
Volume	884.7 (3)
Z	4
R1	0.0506
wR2	0.1149

Table 37. Crystallographic data for **222**.

Bis-(2,2-Dimethylpropyl) Pyrazine-2,5-dicarboxylate (223) (John Gomm)

Due to the high symmetry of this structure, it is difficult to differentiate the pyrazine core carbon and nitrogen atoms, therefore both have been designated as carbon atoms both with attached hydrogens (figure 88). This similarity results in an unsatisfactorily high R number.

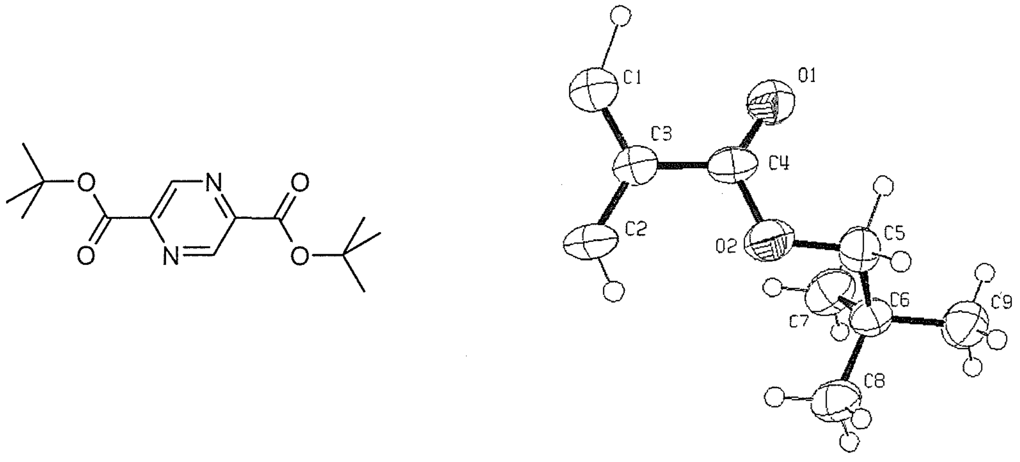


Figure 88. Sketch (left) and asymmetric unit (right) of **223**.

Empirical Formula	$C_{17} H_{26} N_1 O_4$
Mass	308.39
Collection Temperature/ K	150 (2)
Crystal System	Triclinic
Space Group	P-1
Unit Cell (a,b,c in Å, α,β,χ in °.)	a = 5.916 (10), b = 6.145 (10), c = 13.348 (3), α = 90.36 (3), β = 100.39 (3), χ = 118.73 (3)
Volume	416.10 (14)
Z	1
R1	0.0946
wR2	0.2363

Table 38. Crystallographic data for **223**.

Dimethyl Thiophene-2,5-dicarboxylate (224) (John Gomm)

This structure adopts an 'open-wing' conformation (figure 89).

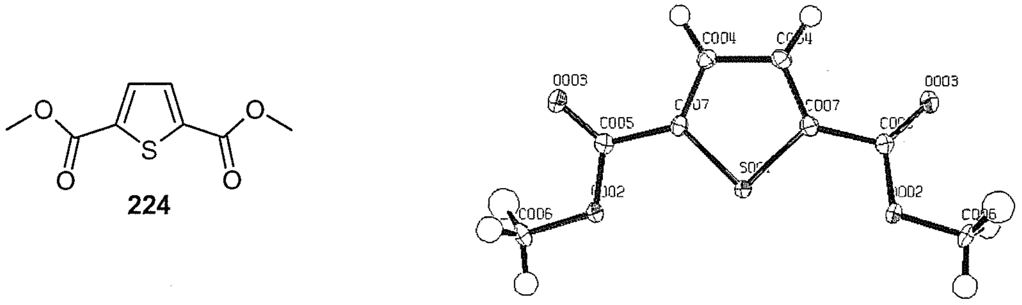

224

Figure 89. Sketch (left) and asymmetric unit (right) of **224**.

Empirical Formula	$C_8 H_8 O_4 S_1$
Mass	200.20
Collection Temperature/ K	150 (2)
Crystal System	Monoclinic
Space Group	C2/c
Unit Cell (a,b,c in Å, α,β,χ in °.)	a = 20.358 (4), b = 5.982 (10), c = 7.288 (10), α = 90.00, β = 105.12 (3), χ = 90.00
Volume	856.8 (3)
Z	4
R1	0.0290
wR2	0.0736

Table 39. Crystallographic data for **224**.

Diethyl Thiophene-2,5-dicarboxylate (225) (John Gomm)

Again the structure has an 'open-wing' conformation, and is very similar to the preceding compound **224** with the addition of the two methyl groups.

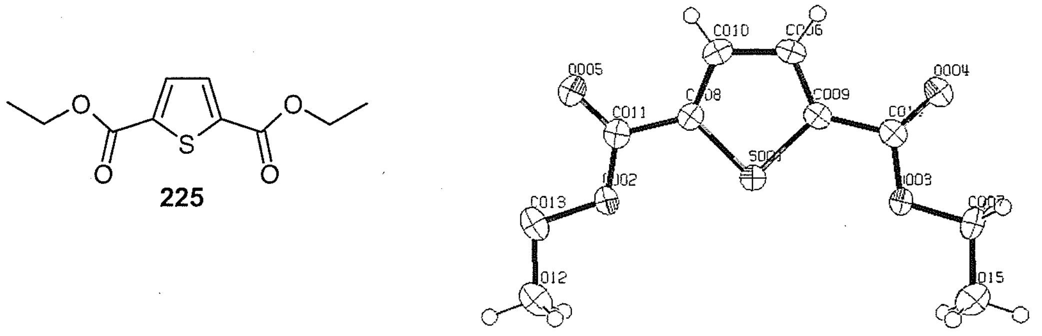

225

Figure 90. Sketch (left) and asymmetric unit (right) of **225**.

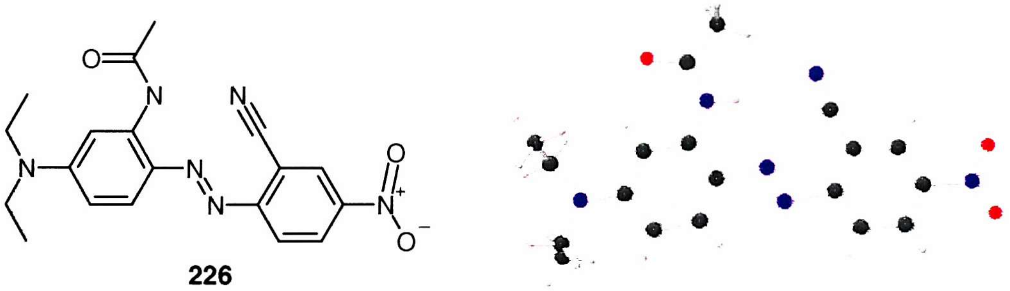
Empirical Formula	$C_{10}\,H_{12}\,O_4\,S_1$
Mass	228.26
Collection Temperature/ K	150 (2)
Crystal System	Monoclinic
Space Group	C2/m
Unit Cell (a,b,c in Å, α,β,χ in °.)	a = 16.289 (3), b = 6.8102 (14), c = 10.672 (2), α = 90.00, β = 107.09 (3), χ = 90.00
Volume	1131.6 (4)
Z	4
R1	0.0426
wR2	0.0937

Table 40. Crystallographic data for **225**.

2.7.5 Miscellaneous Structures

N-[2-(2-Cyano-4-nitro-phenylazo)-5-diethylamino-phenyl]-acetamide (226)

No intermolecular H-bonds are apparent in this azo dye structure, but an intramolecular H-bond between the NH group of the amide and the adjacent nitrogen atom of the azo function is present (N-H···N 2.26 Å) which locks the geometry in the solid-state (figure 91).



226

Figure 91. Sketch (left) and asymmetric unit (right) of **226**.

Empirical Formula	$C_{38}\,H_{44}\,N_{12}\,O_7$
Mass	780.85
Collection Temperature/ K	150 (2)
Crystal System	Monoclinic
Space Group	Cc
Unit Cell (a,b,c in Å, α,β,χ in °.)	a = 21.785 (2), b = 12.6486 (15), c = 14.189 (10), α = 90.00, β = 103.391 (4), χ = 90.00
Volume	3803.4 (7)
Z	4
R1	0.0667
wR2	0.1493

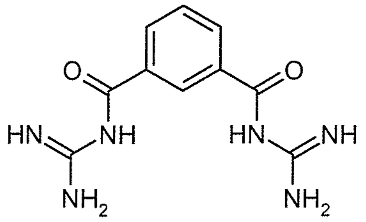
Table 41. Crystallographic data for **226**.

3 Conclusions

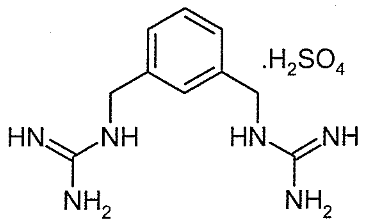
Simple C-shaped Ligands

The synthesis of eleven simple C-shaped ligands, including four novel compounds, has been successfully completed.

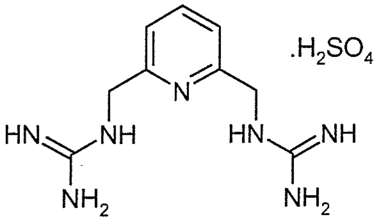
The crystal structures of three of the sulphate salts of these ligands incorporating guanidinium units (**67**, **70** and **83**) have been solved. These showed that with increasing receptor preorganisation the complexes favour 1:1 host – guest recognition.



67



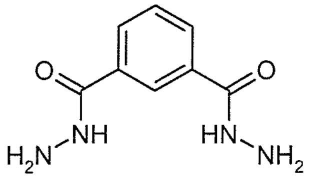
70



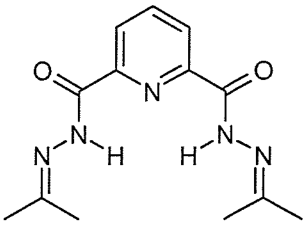
83

Two crystal structures of the least preorganised guanidinium-based receptor (**70**) with two "model dye" sulfonates, one as the ditosylate salt and the other as the disulfonate 4,4'-biphenyl bisulfonate salt, show no 1:1 host – guest recognition.

The crystal structures of benzene-1,3-dicarboxylic acid dihydrazide (**103**) and the related 2,6-pyridine-cored molecule (**105**) have been solved.



103



105

Whilst the former shows a *syn-anti* geometry in the solid-state, the latter displays a *syn-syn* geometry including a favourable (pyridine) N···HN (dihydrazide) close contact, reminiscent of the solid-state geometry found in most pyridine-2,6-dicarboxamides.

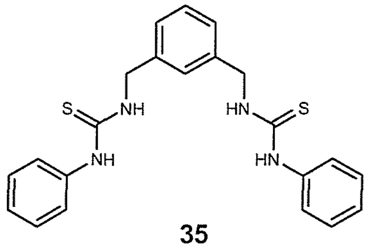
Finally the synthetic route to the useful intermediate 2,6-bis-(aminomethyl) pyridine (**84**) has been improved.

N'-Substituted C-shaped Ligands

Synthesis of benzene-cored *N'*-substituted urea and thiourea-based ligands has proved facile and has been achieved in two general ways: i) by reaction of the benzene-core diamine with the appropriately substituted iso(thio)cyanate, ii) by reaction of the benzene-core diiso(thio)cyanate with the appropriately substituted amine.
However, synthesis of pyridine-cored *N'*-substituted (thio)urea ligands has proved less easy because of the inherent hygroscopic nature of the synthesised 2,6-bis-(aminomethyl) pyridine starting material.

N'-Substituted guanidinium ligand synthesis has been hampered by difficulties with purification of these products. Of the three synthetic approaches explored, the most widely used literature route to disubstituted guanidiniums (involving reaction of an *S*-alkylated thiourea with ammonia) has proved to be the most successful. Synthesis of trisubstituted *N,N',N''*-guanidinium salts has proved unsuccessful for similar reasons.

Three crystal structures of *N'*-substituted thioureas have been solved (**35**, **95** and **122**).



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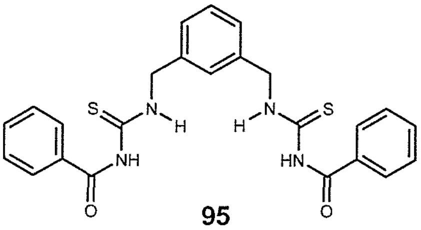
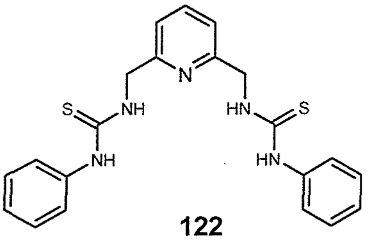


95



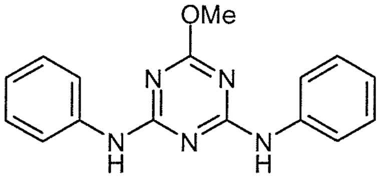
122

All show a *cis-trans* thiourea geometry. Only one of these (**95**) exhibits a C-shape *syn-syn* conformation, and this is brought about by an intramolecular H-bond between one of the thiourea NH groups and the adjacent C=O carbonyl group of each sidearm.

Triazine-cored Receptors

Approaches to triazine-cored receptors using hydrazino nucleophiles were hampered by the reduced reactivity of the partially-substituted intermediates. Consequently the third (and final) and in some cases second substitution of the triazine core with the hydrazine nucleophile did not proceed satisfactorily.

The crystal structure of one trisubstituted "C_2" symmetric triazine (**160**) was solved.

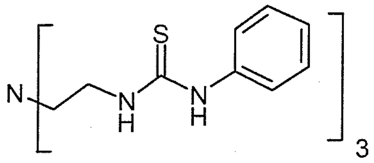


160

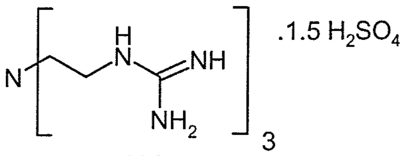
Tripodal Receptors

Several tripodal analogues of the "simple" and *N'*-substituted C-shaped receptors have been synthesised successfully.

Crystal structures of two of these tripods have been solved.



193



196

The *N'*-phenyl thiourea **193** adopts a *cis-trans* thiourea geometry (as observed for all of the C-shaped thioureas) and a self-recognition pattern involving the close contact of one sulphur atom of one molecule with two NH groups in the cavity of another molecule. In the second crystal structure which has been solved, the tris-guanidinium sulphate **196**, each ligand binds sulfate anions in a characteristic "wedge" motif from two guanidinium sidearms.

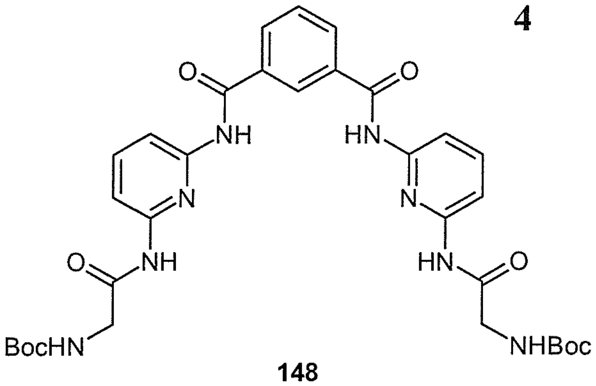
Complexation Studies

NMR titration experiments were used to assess the complexation behaviour of a number of the receptors prepared in this study. In general the results obtained were disappointing due to large error margins even after many experiment repetitions. As a consequence the association constant of only one tripodal receptor (**193**) with a "model dye" phosphonate guest (**204**) in chloroform has been measured, although again the error was large; 2.61×10^2 M^{-1} (± 27.23). Binding stoichiometry was 1:1.

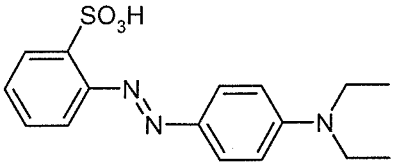
$$H_3C(CH_2)_{11}\text{—}PO_3^-H$$

204

The association behaviour of tetraamide **153** with sulfonated azo dye **149** has also been investigated in chloroform. Again large error margins have prevented the calculation of a binding constant, but binding seemed to occur with the chemical shift of one NH group varying by ca. 1 ppm, most of this change being observed at higher guest concentrations, pointing to an association more complex than simple 1:1 stoichiometry.



148



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Experimental

4.1 General Experimental

4.1.1 Instrumentation

^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AC 300 spectrometer. Chemical Shifts (δ) are quoted relative to tetramethylsilane at 0 ppm or to residual solvent peaks. DEPT experiments were carried out for ^{13}C assignments when required.

Infra-red spectra were obtained using a Golden Gate sampling attachment on a Mattson Satellite 3000 FTIR instrument.

Electrospray Mass spectra were recorded on a Micromass Platform, recorded with a quadrupole mass analyser.

Elemental Analyses were performed by the Microanalytical Service, Department of Chemistry, University College London or by MEDAC Ltd., Brunel Science Centre, Cooper's Hill Lane, Englefield Green, Egham, Surrey.

Melting points were measured on an Electrothermal melting point apparatus and are uncorrected.

Thin layer chromatography was carried out on Machery-Nagel Alugram® Sil G/UV$_{254}$. Preparative scale flash column chromatography was carried out on Sorbsil C60 40/60 H.

Single Crystal X-ray Diffraction experiments were carried out on a Nonius Kappa CCD diffractometer at either 150(2) K or 293(2) K with graphite-monochromated Mo-Kα 0.71073 Å radiation and corrected for Lorentz and polarization effects, and for absorption. Structures were solved by direct methods and refined on F^2 by full-matrix least-squares methods anisotropically for non-hydrogen atoms. Data was solved using WinGX[104] solftware and refined by SHELX-97[105]. The programs

Cameron[106], Rasmol[107], Ortep-3[108] and POV-Ray[109] were used to investigate crystal architecture and produce the figures found in this thesis.

4.1.2 Chemicals and Solvents

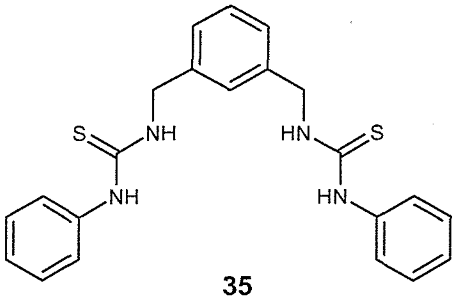
All chemicals were reagent grade and were used as supplied by Aldrich Chemical Company, Lancaster, Avacado or Acros unless stated otherwise.

Anhydrous methanol and ethanol were obtained by distillation from magnesium and iodine. Anhydrous DCM was obtained by distillation from calcium hydride. Anhydrous tetrahydrofuran was obtained by distillation from sodium wire using benzophenone indicator. Anhydrous *N,N'*-dimethyl formamide was dried over molecular sieves.

4.2 Methods of Synthesis

It is worth noting that *s*-triazine compounds containing sulfonate groups that are synthesised from aqueous solution are renowned for their unsatisfactory combustion analytical data. This arises from both the sulfonate group's high hygroscopic properties and common salt impurities that are effectively inseparable from these products. In Industry these factors lead to the use of a "Strength" measure calculated from the combustion analysis for sulfonated intermediates, which gives an effective molecular mass of the compound.

4.2.1 (1-Phenyl-3[3-(3-phenyl-thioureidomethyl)-benzyl]-thiourea)[32] (35)



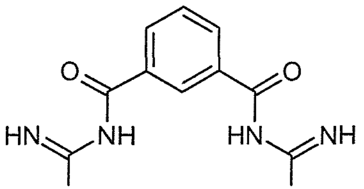
35

Phenyl isothiocyanate (2.39 ml, 0.02 mol) was dissolved in DCM (10 ml) and a solution of *m*-xylylene diamine (1.32 ml, 0.01 mol) dissolved in DCM (10 ml) was added dropwise under nitrogen. The mixture was stirred for 2 hours and monitored by tlc. The white precipitate that formed was filtered off and recrystallised from ethanol/ acetone to give white crystals (3.25 g, 80%). mp 171 - 173°C. (lit.[32] 170°C) NMR δ_H (300 MHz, d_6-DMSO) 9.6 (s, 2H, N<u>H</u>) 8.2 (s, 2H, N<u>H</u>) 7.4 (d, 4H, J = 8.1 Hz, Ar<u>H</u>) 7.4 (s, 1H, Ar<u>H</u>) 7.3 (m, 6H, Ar<u>H</u>) 7.2 (d, 2H, J = 7.7 Hz, Ar<u>H</u>) 7.1 (t, 2H, J = 7.7 Hz, Ar<u>H</u>) 4.8 (s, 4H, C<u>H</u>$_2$). δ_C (75MHz, d_6-DMSO) 180.8 (<u>C</u>=S), 139.2 (Ar<u>C</u>), 128.8 (Ar<u>C</u>), 128.4 (Ar<u>C</u>), 126.5

(Ar<u>C</u>), 126.1 (Ar<u>C</u>), 124.4 (Ar<u>C</u>), 123.5 (2 x Ar<u>C</u>), 47.3 ($\underline{C}H_2$). *m/z* (ES+, MeCN) 407.3, 75% $(M + H)^+$, 429.3, 55% $(M + Na)^+$, 813.3, 60% $(2M + H)^+$, 835.4, 100% $(2M + Na)^+$. ν_{max} Golden Gate (cm^{-1}) 3273 (w), 2922 (s), 2852 (s). Single crystal X-ray diffraction study monoclinic system, space group C2/c, R1 = 4.1%.

4.2.2 *N,N'*-Bis-(Aminoiminomethyl)-1,3-benzenedicarboxamide[58] (67)

Method a)



67

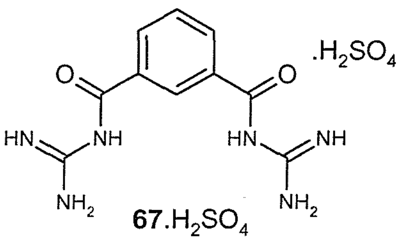
Sodium metal (1.15 g, 0.05 mol) was added to dry methanol (20 ml) over 30 minutes. Guanidinium hydrochloride (4.78 g, 0.05 mol) was added to the solution in one portion. The suspension was stirred at room temperature for 1 hour. The sodium chloride was filtered off and the filtrate was placed in a flask and stirred. To this was added dropwise dimethyl isophthalate (1 g, 5 mmol) in methanol (50 ml). The reaction was heated at reflux overnight. The solution was allowed to cool to room temperature and evaporated to dryness. The residue was recrystallised from water to give a white solid (0.23 g, 19%). mp 231 – 234°C. (lit.[58] mp not quoted). NMR δ_H (300 MHz, d_6-DMSO) 8.7 (s, 1H, Ar<u>H</u>), 8.1 (d, 2H, J = 7.7 Hz, Ar<u>H</u>), 7.4 (t, 1H, J = 7.7 Hz, Ar<u>H</u>), 6.8 (bs, 2H, N<u>H</u>). δ_C (75MHz, d_6-DMSO) 176.0 (<u>C</u>=O), 163.2 (<u>C</u>=N), 138.8 (Ar<u>C</u>), 130.7 (Ar<u>C</u>), 128.9 (Ar<u>C</u>), 127.0 (Ar<u>C</u>). m/z (ES+, H_2O, formic acid) No peak consistent with product or starting materials. ν_{max}(Golden Gate)/cm^{-1} 3329 (m), 3124 (m), 1648 (s), 1602 (s).

Method b)

DCM (80 ml) was added to a solution of guanidine hydrochloride (3.82 g, 40 mmol) and sodium hydroxide (8 g, 0.2 mol) in water (40 ml). The resulting mixture was cooled to 5°C and stirred vigourously. Isophthaloyl chloride (4.06 g, 20 mmol) in DCM (10 ml) was added dropwise to the solution over about 45 minutes. The reaction was stirred at 5°C for two hours, then allowed to warm to room temperature. Stirring was continued overnight. DCM (100 ml) was added, and the layers were separated. The aqueous layer was extracted with DCM (100ml) and the organic layers were combined and washed with water. The aqueous layer was neutralised with aqueous HCl solution (2N) and the white precipitate that appeared was removed by filtration.

The white solid was recrystallised from water and dried *in vacuo* to give the product as a white solid (0.25 g, 5%). mp 233 – 236°C. (lit.[58] mp not quoted). NMR δ_H (300 MHz, d_6-DMSO) 8.7 (s, 1H, ArH), 8.1 (dd, 2H, J = 7.7 Hz, ArH), 8.0 (bs, 2H, NH), 7.4 (t, 1H, J = 7.7 Hz, ArH), 6.8 (bs, 2H, NH). δ_C (75MHz, d_6-DMSO) 176.0 (C=O), 163.2 (C=N), 138.8 (ArC), 130.7 (ArC), 129.0 (ArC), 127.0 (ArC). m/z (ES+, H_2O, formic acid) No peaks consistent with product. ν_{max}(Golden Gate)/cm^{-1} 3325 (m), 3095 (m), 1648 (s), 1603 (s).

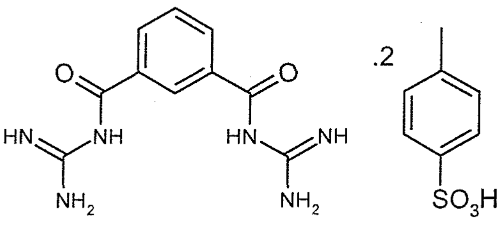
4.2.3 *N,N'*-Bis-(Aminoiminomethyl)-1,3-benzenedicarboxamide sulfate ($67.H_2SO_4$)



67.H_2SO_4

N,N'-Bis-(Aminoiminomethyl)-1,3-benzenedicarboxamide (0.05 g, 0.2 mmol) was suspended in water (10 ml). HCl solution (2N) was added until the pH was 2.8. The white precipitate dissolved. Sodium sulfate (0.034 g, 0.25 mmol) was added in one portion and the solution was stirred for 30 mins. The white precipitate was filtered off, washed with water and dried *in vacuo*. Recrystallisation from a large volume of water and 2 drops of DMSO gave the product as colourless needle crystals (0.07 g, 98%). mp > 240°C. NMR δ_H (300 MHz, 256 scans, D_2O, 10% w/v Na_2CO_3) 8.5 (s, 1H, ArH), 8.1 (d, 2H, J = 7.7 Hz, ArH), 7.5 (t, 1H, J = 7.7 Hz, ArH). Found: C, 33.87; H, 4.41; N, 22.92; S, 8.80. Calculated: C, 32.97; H, 4.43; N, 23.07; S, 8.80. Single crystal X-ray diffraction study, triclinic system, space group P-1, R1 = 4.9%. ν_{max}(Golden Gate)/cm^{-1} 3355 (m), 3329 (m), 3080 (bs), 1714 (m), 1687 (s). Compound too insoluble to give 256 scan ^{1}H NMR spectrum (d_6-DMSO).

4.2.4 *N,N'*-Bis-(Aminoiminomethyl)-1,3-benzenedicarboxamide Ditosylate (67.2 TsOH)



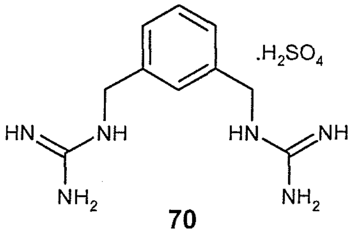
67.2 TsOH

N,N'-Bis-(Aminoiminomethyl)-1,3-benzenedicarboxamide (0.05 g, 0.2 mmol) was suspended in water (10 ml). HCl solution (2N) was added until the pH was

2.8. The white precipitate dissolved. Toluene sulfonic acid monohydrate (0.09 g, 0.45 mmol) was added in one portion and the solution was stirred for 30 mins. The white precipitate was filtered off, washed with water and dried *in vacuo*. Recrystallisation from a large volume of water and 1 drop of DMSO gave the product as colourless needle crystals (0.09 g, 76%). mp > 240°C. NMR δ_H (300 MHz, d_6-DMSO) 11.4 (bs, 2H, N$\underline{H}$), 8.5 (s, 1H, Ar$\underline{H}$), 8.4 (bs, 4H, N$\underline{H}$), 8.3 (bs, 4H, N$\underline{H}$), 8.2 (d, 2H, J = 7.7 Hz, Ar$\underline{H}$), 7.8 (t, 1H, J = 7.7 Hz, Ar$\underline{H}$), 7.5 (d, 4H, J = 7.9 Hz, Ar$\underline{H}$), 7.1 (d, 4H, J = 7.9 Hz, Ar$\underline{H}$), 2.3 (s, 6H, $C\underline{H}_3$). δ_C (75MHz, 29000 scans, d_6-DMSO) 137.8 (Ar$\underline{C}$), 132.8 (Ar$\underline{C}$), 129.5 (Ar$\underline{C}$), 128.1 (Ar$\underline{C}$), 128.0 (Ar$\underline{C}$), 125.4 (Ar$\underline{C}$), 20.7 ($\underline{C}H_3$). Sample concentration too low to show the three quarternary ^{13}C signals and one Ar$\underline{C}$ signal. ν_{max}(Golden Gate)/cm^{-1} 3357 (w), 3081 (bs), 1707 (s), 1693 (s), 1670 (m).

4.2.5 *m*-Xylylene di(guanidinium) sulfate[60,66,77] (70)

Method a)



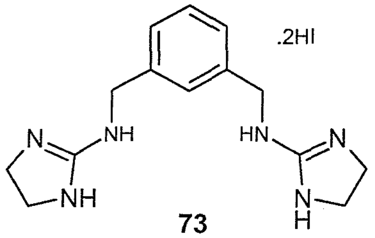
70

m-Xylylene diamine (1.97 g, 0.0145 mol) was suspended in water (25 ml) and *O*-methylisourea hydrogen sulphate (5.2 g, 0.029 mol) was added in portions. The resulting mixture was stirred at room temperature at pH 11 (aq. sodium hydroxide was added, doubling volume) for 24 hours. After about twenty minutes a white precipitate appeared. The white precipitate was filtered off, washed with water until the washings were about pH 7, and dried *in vacuo* to give a white powder (1.89 g, 41%). mp 335°C (decomp.). (lit.[77] 337°C (decomp.)). NMR δ_H (300 MHz, 256 scans, D_2O, 10% w/v Na_2CO_3) 7.4 (t, 1H, J = 7.7 Hz, Ar$\underline{H}$), 7.4 (s, 1H, Ar$\underline{H}$), 7.3 (d, 2H, J = 7.7 Hz, Ar$\underline{H}$), 4.4 (s, 4H, $C\underline{H}_2$). m/z (ES+, H_2O, MeCN) 221.1, 100% $(M + H)^+$. ν_{max}(Golden Gate)/cm^{-1} 3348 (w), 3154 (m), 3016 (w), 2898 (w), 1662 (m), 1644 (m), 1629 (m). Found: C, 38.00; H, 5.59; N, 25.96; S, 9.97. Calculated: C, 37.73; H, 5.70; N, 26.40; S, 10.07. Crystals were grown from water/ EtOH. Crystal structure data collected and solved, orthorhombic system, space group Pbca, R1 = 4.3%. Compound too insoluble to give 256 scan ^{1}H NMR spectrum (d_6-DMSO).

Method b)

m-Xylylene diamine (2 ml, 15.15 mmol) was dissolved in water (15 ml) and aq. sulphuric acid (4N, about 7 ml) was added until the pH was about 6.5. Cyanamide (1.27 g, 30.3 mmol) was dissolved in water (5 ml) and added dropwise to the solution. The pH remained fairly stable. The reaction was then warmed to 50°C and stirred overnight. The reaction was allowed to cool to room temperature and the pH was adjusted from 8.8 to 7 (2N HCl). The precipitate was filtered off, washed with water and dried *in vacuo* to give the product as a white solid (1.54 g, 32%). mp > 300°C. (lit.[77] 337°C (decomp.)). ν_{max}(Golden Gate)/cm^{-1} 3348 (w), 3152 (m), 3015 (m), 1663 (s), 1643 (s), 1630 (s). Found: C, 37.47; H, 5.56; N, 25.76; S, 9.83. Calculated: C, 37.73; H, 5.70; N, 26.40; S, 10.07. Data in good agreement with that from the previous synthesis by method a).

4.2.6 2,2'-(1,3-Phenylenebis-(methyleneimino)) bis-(4,5-dihydro-1H-imidazolium) Diiodide[65] (73)

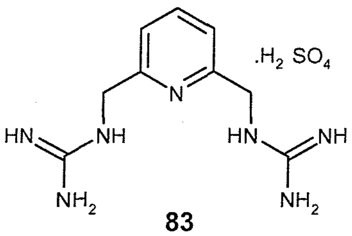


73

2-Methylthio-2-imidazoline hydroiodide (4.88 g, 0.02 mol) was dissolved in ethanol (50 ml) and stirred at room temperature. *m*-Xylylene diamine (1 g, 7.5 mmol) was added and the solution was stirred and heated at a gentle reflux overnight. The solution was concentrated *in vacuo* to about 20 ml volume and chilled in a fridge. The white precipitate that formed was removed by filtration (1.98g, 50%). mp 228 - 231°C. (lit.[65] 233 - 235°C). NMR δ_H (300 MHz, d_6-DMSO) 8.6 (bs, 2H, N$\underline{H}$), 7.4 (t, 1H, J = 7.7 Hz, Ar$\underline{H}$), 7.2 (d, 3H, J = 7.7 Hz, Ar$\underline{H}$), 4.4 (d, 4H, J = 5.2 Hz, C$\underline{H}_2$), 3.6 (s, 8H, C$\underline{H}_2$). δ_C (75MHz, d_6-DMSO) 159.4 ($\underline{C}$=N), 137.5 (Ar$\underline{C}$), 129.0 (Ar$\underline{C}$), 126.6 (Ar$\underline{C}$), 126.2 (Ar$\underline{C}$), 45.4 ($\underline{C}H_2$), 42.7 ($\underline{C}H_2$). m/z (ES+, MeOH) 137.2, 90% $(M + 2H)^{2+}$, 273.3, 20% $(M + H)^+$. ν_{max}(Golden Gate)/cm^{-1} 3206 (w), 3028 (w), 2970 (w), 2358 (m), 1739 (s), 1664 (s). Found: C, 31.79; H, 4.25; N, 15.64; I, 48.06. Calculated: C, 31.84; H, 4.20; N, 15.91; I, 48.05.

4.2.7 2,6-Bis-(*N*-Methyl guanidinium) pyridine sulfate[62] (83)

Method a)



83

2,6-Bis-(Aminomethyl) pyridine dihydrobromide (6 g, 20.08 mmol), 2-methyl-2-thiopseudourea sulfate (2.3 g, 44.18 mmol) and *N,N*-diisopropylethylamine (14 ml, 80.32 mmol) were mixed in dry methanol (60 ml) in a glass ampule. The ampule was sealed with a teflon cap and heated at 70°C for seven hours. After allowing to cool to room temperature, the ampule was opened slowly and the white precipitate was filtered off and dried *in vacuo*. The residue was recrystallised from H_2O/ ethanol to give a white solid (2.32 g, 36%). mp > 300°C. (lit.[62] not quoted). NMR δ_H (300 MHz, D_2O) 7.8 (t, 1H, J = 7.7 Hz, Ar<u>H</u>), 7.3 (d, 2H, J = 7.7 Hz, Ar<u>H</u>), 4.4 (s, 4H, C<u>H</u>$_2$). δ_C (75MHz, D_2O) 154.0 (Ar<u>C</u>), 141.7 (Ar<u>C</u>), 124.8 (Ar<u>C</u>), 45.3 (<u>C</u>H$_2$). *m/z* (ES+, H_2O) 221.1, 100% $(M + H)^+$, 244.2, 15% $(M + Na)^+$. ν_{max}(Golden Gate)/cm^{-1} 3310 (w), 3125 (m), 3040 (m), 1692 (w), 1656 (m), 1625 (s). Found: C, 33.36; H, 5.32; N, 30.40; S, 10.30. Calculated: C, 33.85; H, 5.37; N, 30.70; S, 10.04.

Colourless needle crystals were grown by slow evaporation of a solution of a small amount of the product from an H_2O/ ethanol mix. Single crystal structure data collected and solved by standard methods, monoclinic system, space group P2(1)/c, R1 = 4.4%.

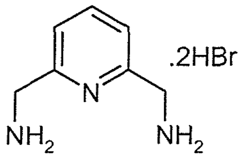
Method b)

2,6-Bis-(Aminomethyl) pyridine dihydrobromide (1 g, 3.35 mmol) was dissolved in water (2 ml). Sodium hydroxide solution (20%, w/ v) was added until the pH of the solution was 11. The aqueous layer was then extracted with DCM (8 × 10ml), the organic layers were combined, dried ($NaSO_4$) and evaporated to dryness *in vacuo* to leave a clear yellow oil which solidified on standing (0.05g, 11%). The free diamine was dissolved in water (2 ml) and acidified to about pH 6.5 with sulfuric acid (4N). Cyanamide (46 mg, 1.09 mmol) was added in one portion, and the reaction was heated at 50°C with stirring for 2 days, then for 2 days more at 60°C. Upon cooling to room temperature and standing, the needle crystals that precipitated were filtered off and dried *in vacuo* (0.04g, 38%). mp >250°C. (lit.[62] not quoted). NMR δ_H (300 MHz, $D_2O + Na_2CO_3$) 7.7 (t, 1H, J = 7.3 Hz, Ar<u>H</u>), 7.2 (d, 2H, J = 8.1 Hz, Ar<u>H</u>), 4.3 (s, 4H, C<u>H</u>$_2$). ν_{max}(Golden Gate)/cm^{-1} 3310 (w), 3133 (bs), 3038 (bs), 1696 (w), 1655 (m), 1626 (s). Crystal structure collected and solved by standard methods, monoclinic system, space group P2(1)/c, R1 = 4.9%. Spectral data in good agreement with that from method a).

Method c)

2,6-Bis-(Aminomethyl) pyridine dihydrobromide (1 g, 3.35 mmol) was dissolved in water (10 ml) and passed through a Dowex 1 × 8 –100 $^{-}$OH column (6 g dry mass). The column was washed with water until the washings were pH 7. The combined washings were concentrated *in vacuo* to leave a yellowish oil, which was dissolved in water (10 ml) and *O*-methylisourea sulfate (1.72g, 10 mmol) was added. The pH was adjusted to 11 with aqueous sodium hydroxide solution (2N) and the solution was stirred overnight. The white precipitate was filtered off and washed with a little methanol. The filtrate was concentrated *in vacuo* to about half its volume and methanol (25 ml) was added. The apparent white precipitate was filtered off and washed with a little methanol. Both crops were recrystallised from water/ ethanol to give the product as a white crystalline solid (0.9 g, 84%). mp > 250°C. (lit.[62] not quoted). NMR δ_H (300 MHz, D_2O) 7.7 (t, 1H, J = 7.7 Hz, Ar<u>H</u>), 7.2 (d, 2H, J = 7.7 Hz, Ar<u>H</u>), 4.4 (s, 4H, C<u>H</u>$_2$). m/z (ES+, H_2O) 221.1, 100% $(M + H)^+$, 244.2, 15% $(M + Na)^+$. Data in good agreement with methods a) and b).

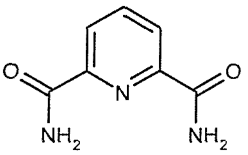
4.2.8 2,6-Bis-(Aminomethyl) pyridine Dihydrobromide[62] (84.2HBr)



84.2HBr

2,6-Bis-(Chloromethyl) pyridine (5.50 g, 31.25 mmol) and potassium phthalimide (11.58 g, 62.50 mmol) were suspended in dry DMF (100 ml) and heated at 140°C for 5 hours. After cooling to room temperature and removal of solvent, the residue was treated with water, the mixture was filtered and the solid was washed with a little more water. The residue was then heated with aqueous HBr (48%, 200 ml) for 3 hours at reflux. After allowing to cool to room temperature, the white precipitate was filtered off, washed with water and the washings were combined with the hydrobromic acid solution. This was concentrated to about half its volume *in vacuo.* A white precipitate formed which was filtered off, washed with ethanol and dried *in vacuo* (8.51 g, 91%). mp 304°C (decomp.). (lit.[62] not quoted). NMR δ_H (300 MHz, d_6-DMSO) 8.5 (bs, 6H, N$\underline{H}$), 7.9 (t, 1H, J =7.7 Hz, Ar$\underline{H}$), 7.5 (d, 2H, J = 7.7 Hz, Ar$\underline{H}$), 4.2 (d, 4H, J = 5.5 Hz, C$\underline{H}_2$). NMR δ_H (300 MHz, D_2O) 7.8 (t, 1H, J = 7.7 Hz, Ar$\underline{H}$), 7.3 (d, 2H, J = 7.7 Hz, Ar$\underline{H}$), 4.3 (s, 4H, C$\underline{H}_2$). δ_C (75MHz, D_2O) 153.9 (Ar$\underline{C}$), 142 (Ar$\underline{C}$), 124.9 (Ar$\underline{C}$), 45.3 $\underline{C}H_2$). m/z (ES+, H_2O) 137.9, 100% $(M + H)^+$. ν_{max}(Golden Gate)/cm^{-1} 2991 (s), 2643 (m), 2622 (m), 1737 (s).

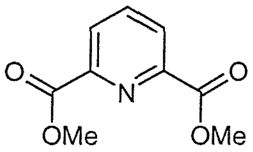
4.2.9 Pyridine-2,6-dicarboxamide[110] (86)



86

To aqueous 8/80 ammonia solution (50 ml) was added pyridine-2,6-dicarbonyl dichloride (2.5 g, 0.012 mol) slowly with stirring at 0°C. An exothermic reaction occurred. The reaction mixture was stirred for 1 hour and allowed to warm to room temperature. The white precipitate that formed was filtered off and washed with water. The solid was recrystallised from glacial acetic acid, washed with water and dried *in vacuo* (1.64 g, 83%). mp >250°C (lit.[110] 321 – 322°C). NMR δ_H (300 MHz, d_6-DMSO) 8.9 (s, 2H, N$\underline{H}$), 8.2 (m, 3H, Ar$\underline{H}$), 7.7 (s, 2H, N$\underline{H}$). δ_C (75MHz, d_6-DMSO) 165.5 ($\underline{C}$=O), 149.1 (Ar$\underline{C}$), 139.3 (Ar$\underline{C}$), 124.3 (Ar$\underline{C}$). m/z (ES+, MeCN) No peak consistent with product or starting material. ν_{max}(Golden Gate)/cm^{-1} 3399 (m), 3228 (m), 3173 (m), 1662 (s), 1585 (s).

4.2.10 Dimethyl pyridine-2,6-dicarboxylate[111] (87)

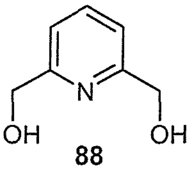


87

Pyridine-2,6-dicarbonyl dichloride (12.90 g, 0.06 mol) was suspended in methanol (200 ml) at 0°C, allowed to warm to room temperature and then the mixture was heated gently for one hour. The solution was allowed to cool and the white precipitate was removed by filtration. The filtrate was concentrated *in vacuo*, chilled to 5°C, and a second crop was removed by filtration. Both crops were recrystallised from methanol to give colourless crystals (11.74g, 96%). mp 121°C. (lit.[111] 118 – 121°C). NMR δ_H (300 MHz, $CDCl_3$) 8.3 (d, 2H, J = 8.1 Hz, Ar$\underline{H}$), 8.0 (t, 1H, J = 8.1 Hz, Ar$\underline{H}$), 4.0 (s, 6H, C$\underline{H}_3$). δ_C (75MHz, $CDCl_3$) 165.2 ($\underline{C}$=O), 148.3 (Ar$\underline{C}$), 138.6 (Ar$\underline{C}$), 128.2 (Ar$\underline{C}$), 53.4 ($\underline{C}H_3$). m/z (ES+, MeOH) 195.9, 100% (M +

H)$^+$, 217.9, 45% (M + Na)$^+$, 412.9, 95% (2M + Na)$^+$. ν_{max}(Golden Gate)/cm^{-1} 3062 (w), 2973 (w), 1729 (s).

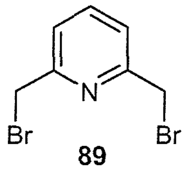
4.2.11 Pyridine-2,6-dimethanol[112] (88)



88

Dimethyl pyridine-2,6-dicarboxylate (11.7 g, 0.06 mol) was suspended in ethanol (200 ml) and the mixture was stirred over ice. Sodium borohydride (11.34 g, 0.3 mol) was added in portions over fifteen minutes, and the mixture was then stirred at 0°C for one hour. The white suspension turned creamy brown. The ice bath was removed and the reaction warmed as an exothermic reaction occurred. The solution was stirred at room temperature for two hours after which time it was heated at reflux for two days. The solvent was removed *in vacuo* and the residue was mixed with acetone (50 ml) and heated at reflux for one hour. The solvent was removed *in vacuo* and the residue was stirred with hot saturated aqueous potassium carbonate solution (150 ml). The solution was allowed to cool, and then it was extracted with chloroform (6 x 100 ml), dried ($MgSO_4$) and the solvent was removed to give a white solid (8.02g, 96%). mp 114 - 116°C. (lit.[112] 112 – 114°C). NMR δ_H (300 MHz, $CDCl_3$) 7.6 (t, 1H, J = 7.7 Hz, Ar$\underline{H}$), 7.1 (d, 2H, J = 7.7 Hz, Ar$\underline{H}$), 4.7 (s, 4H, C$\underline{H_2}$). No OH peak evident. δ_C (75MHz, $CDCl_3$) 160.9 (Ar$\underline{C}$), 137.1 (Ar$\underline{C}$), 118.3 (Ar$\underline{C}$), 64.3 ($\underline{C}H_2$). m/z (ES+, MeCN) 140.0, 100% (M + H)$^+$. ν_{max}(Golden Gate)/cm^{-1} 3345 (s), 3052 (w), 2942 (w), 2895 (w), 2764 (w), 2622 (w), 1599 (s).

4.2.12 2,6-Bis-(Bromomethyl) pyridine[113] (89)

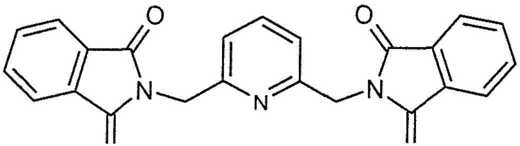


89

Cocentrated hydrobromic acid (100 ml) was added to pyridine-2,6-dimethanol (7.9 g, 0.057 mol) and the mixture was heated at reflux for two hours. The resulting solution was cooled to 0°C and neutralised by careful addition of 20% sodium hydroxide solution. The resultant aqueous solution was extracted with DCM (4 x 50 ml), dried ($MgSO_4$) and concentrated *in vacuo* to leave a brown solid. This was purified by column chromatography (chloroform). The relevant fractions were combined and the solvent was removed *in vacuo* to give an off-white solid (2.37g, 16%). mp 84 - 87°C. (lit[113]. 85 - 88°C). NMR δ_H (300 MHz, $CDCl_3$) 7.6 (t, 1H, J = 7.7 Hz, Ar$\underline{H}$), 7.3 (d, 2H, J =

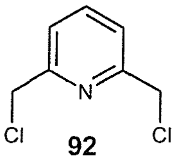
7.7 Hz, ArH), 4.5 (s, 4H, CH$_2$). δ$_C$ (75MHz, CDCl$_3$) 156.9 (ArC), 138.3 (ArC), 123.0 (ArC), 33.7 (CH$_2$). m/z (ES+, MeCN) 144.0, 100% $(M + Na + H)^{2+}$, 531.4, 5% $(2M + H)^+$. ν$_{max}$(Golden Gate)/cm^{-1} 3008 (w), 2964 (w), 1591 (s), 1576 (s).

4.2.13 2,6-Bis-(Methylphthalimide) pyridine[114] (90)


90

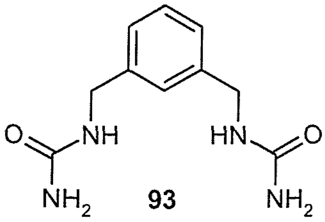
2,6-Bis-(Bromomethyl) pyridine (2.37 g, 8.9 mmol) and potassium phthalimide (3.30 g, 0.018 mol) were suspended in DMF (20 ml) and heated at 70°C for 12 hours. The solvent was removed *in vacuo* and the resultant solid was suspended in 20% MeOH/ DCM. The organic layer was washed with sodium hydroxide solution (3 x 30 ml, 0.2N), dried (MgSO$_4$) and the solvent was removed to give an off-white solid (0.84g, 24%). mp 229 - 232°C. (lit.[114] 237°C). NMR δ$_H$ (300 MHz, CDCl$_3$) 7.8 – 7.5 (m, 7H, ArH), 7.2 (d, 2H, J = 7.7 Hz, ArH), 7.1 (d, 2H, J = 7.7 Hz, ArH), 4.9 (s, 4H, CH$_2$). δ$_C$ (75MHz, CDCl$_3$) 168.3 (C=O), 137.6 (ArC), 134.3 (ArC), 134.0 (ArC), 132.2 (ArC), 123.7 (ArC), 120.1 (ArC), 42.8 (CH$_2$). m/z (ES+, MeCN) 398.1, 20% $(M + H)^+$, 420.1, 100% $(M + Na)^+$, 816.9, 40% $(2M + Na)^+$. ν$_{max}$(Golden Gate)/cm^{-1} 2962 (w), 2931 (w), 1766 (m), 1698 (s), 1588 (m).

4.2.14 2,6-Bis-(chloromethyl) pyridine[115] (92)


92

Thionyl chloride (120 ml) was added dropwise over two hours to solid pyridine-2,6-dimethanol (24 g, 0.173 mol) with stirring, and then warmed gently for four hours (until gas evolution had ceased). The solution was allowed to cool to room temperature, and toluene (120 ml) was added. The hydrochloride salt of the product was filtered off, washed with toluene followed by ether, and then dried *in vacuo*. The salt was slurried in water (120 ml) and neutralised with aqueous sodium hydroxide (2N). The precipitate was filtered off and dried *in vacuo*. The white solid was then recrystallised from petroleum ether (40 – 60) to give the product as off white needle crystals which were filtered off and dried *in vacuo* (25.67g, 84%). mp 68 - 71°C. (lit.[115] 74 – 75°C). NMR δ$_H$ (300 MHz, CDCl$_3$) 7.7 (t, 1H, J = 7.7 Hz, CH), 7.4 (d, 2H, J = 7.7 Hz, CH), 4.6 (s, 4H, CH$_2$). δ$_C$ (75MHz, CDCl$_3$) 156.5 (ArC), 138.3 (CH), 122.3 (CH), 46.6 (CH$_2$). *m/z* (ES+, MeCN) 176, 100% $(M + H)^+$, 178, 70% $(M + H)^+$, 180, 10% $(M + H)^+$. ν_{max}(Golden Gate)/cm^{-1} 3067 (w), 3007 (w), 2964 (w), 1591 (m).

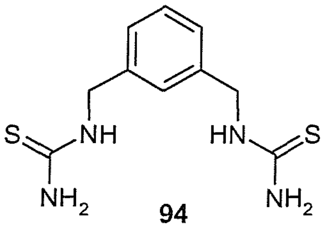
4.2.15 1,3-Bis-(Methylurea) benzene[116] (93)


93

1,3-Bis-(Isocyanatomethyl) benzene (1 ml, 6.39 mmol) was added dropwise to 8/80 ammonia solution (20 ml) at 5°C. The reaction was stirred and allowed to warm to room temperature. The white precipitate was filtered off, washed with water and dried *in vacuo* to give the product (1.26 g, 89%). mp 202 – 204°C. (lit.[116] 203°C) NMR δ_H (300 MHz, d_6-DMSO) 7.3 (t, 1H, J = 7.7 Hz, Ar<u>H</u>), 7.1 (s, 1H, Ar<u>H</u> covered by doublet), 7.1 (d, 2H, J = 7.7 Hz, Ar<u>H</u>), 6.43 (t, 2H, J = 5.5 Hz, N<u>H</u>), 5.6 (s, 4H, N<u>H</u>$_2$), 4.2 (d, 4H, J = 5.9 C<u>H</u>$_2$). δ_C (75MHz, d_6-DMSO) 158.8 (<u>C</u>=O), 140.9 (Ar<u>C</u>), 128.2 (Ar<u>C</u>), 125.9 (Ar<u>C</u>), 125.4 (Ar<u>C</u>), 42.9 (<u>C</u>H$_2$). m/z (ES+, MeCN/ H_2O) 222.9, 50 % $(M + H)^+$. ν_{max}(Golden Gate)/cm^{-1} 3497 (w), 3414 (w), 3339 (m), 3212 (w), 2915 (w), 1645 (s), 1619 (m), 1596 (s).

4.2.16 1,3-Bis-(Methylthiourea) benzene[60] (94)

Method a)

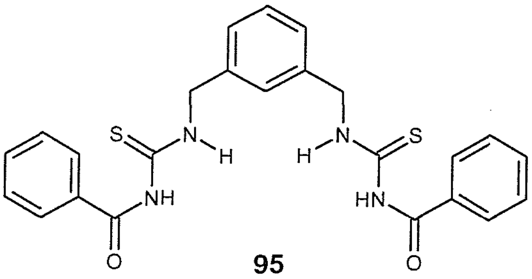

94

m-Xylylene bis-(*N'*-benzoyl-thiourea) (2.31 g, 0.005 mol) was suspended in 5% sodium hydroxide solution (100ml) and heated at 80°C with stirring for one hour. A yellow solid was filtered off and dried *in vacuo* (0.06 g, 5%). mp 212 – 215°C. (lit.[60] mp not quoted). NMR δ_H (300 MHz, d_6-DMSO) 8.0 (bs, 2H, N<u>H</u>), 7.3 (t, 1H, J = 7.7 Hz, Ar<u>H</u>), 7.2 (d, 2H, J = 7.7 Hz, Ar<u>H</u>), 7.0 (bs, 1H, Ar<u>H</u>, covered by NH peak), 4.6 (bs, 4H, C<u>H</u>$_2$). δ_C (75MHz, d_6-DMSO) 183.5 (<u>C</u>=S), 139.4 (Ar<u>C</u>), 128.4 (Ar<u>C</u>), 126.4 (Ar<u>C</u>), 125.1 (Ar<u>C</u>), 47.5 (<u>C</u>H$_2$). m/z (ES+, MeCN) 127.0, 100% $(M + H)^{2+}$, 255.1, 40% $(M + H)^+$. ν_{max}(Golden Gate)/cm^{-1} 3161 (bs), 2963 (w), 1648 (w), 1604 (s).

Method b)

1,3-Bis-(Isothiocyanatomethyl) benzene (1 g, 4.55 mmol) was added dropwise to 8/ 80 ammonia solution at 5°C with stirring. The solution was allowed to warm to room temperature. It was then heated at 40°C for 10 minutes, allowed to cool to room temperature and stirred overnight. The precipitate was filtered off, washed with water (20 ml) and dried *in vacuo* to give a white solid (1.22 g, 88%). mp 212 – 214°C. (lit.[60] mp not quoted). NMR δ_H (300 MHz, d_6-DMSO) 8.0 (bs, 2H, N$\underline{H}$), 7.3 (t, 1H, J = 7.0 Hz, Ar$\underline{H}$), 7.2 (d, 2H, J = 7.0 Hz, Ar$\underline{H}$), 7.0 (bs, 1H, Ar$\underline{H}$, covered by NH peak), 4.6 (bs, 4H, C$\underline{H}_2$). δ_C (75MHz, d_6-DMSO) 183.4 ($\underline{C}$=S), 139.2 (Ar$\underline{C}$), 128.3 (Ar$\underline{C}$), 126.3 (Ar$\underline{C}$), 126.0 (Ar$\underline{C}$), 47.4 ($\underline{C}H_2$). m/z (ES+, MeCN) 254.8, 100% $(M + H)^+$, 276.8, 20% $(M + Na)^+$, 508.8, 20% $(2M + H)^+$. ν_{max}(Golden Gate)/cm^{-1} 3379 (m), 3256 (bs), 3175 (m), 3071 (w), 1602 (s).

4.2.17 *m*-Xylylene bis-(*N'*-benzoyl-thiourea)[60] (95)

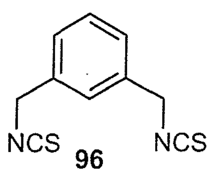


95

Benzoyl chloride (0.87 ml, 0.013 mol) was dissolved in dry acetone (50 ml). Ammonium thiocyanate (1 g, 0.013 mol) was suspended in dry acetone (20 ml) and added to the benzoyl chloride solution. The mixture was heated at reflux for 24 hours, after which time tlc (eluent = 5% MeOH/DCM) showed that the reaction was complete. The solution was allowed to cool to room temperature. The apparent white precipitate was filtered off to leave a clear yellow filtrate. *m*-Xylylene diamine (0.87 ml, 0.0066 mol) was added slowly to the filtrate solution with stirring. The mixture was heated at reflux for 24 hours and monitored by tlc (eluent = 5% MeOH/DCM). After this time, the yellow solution had turned a deep brown. The solvent was removed to leave a black/ brown gum. This was purified by column chromatography (60:40 petroleum ether (40 - 60): ethyl acetate) and the solvent was removed *in vacuo* from the relevant fractions to leave an off-white crystalline solid (0.22 g, 7%). mp 161 - 163°C. (lit.[60] mp not quoted). NMR δ_H (300 MHz, $CDCl_3$) 11.1 (s, 2H, N$\underline{H}$), 9.1 (s, 2H, N$\underline{H}$), 7.9 - 7.3 (m, 14H, Ar$\underline{H}$), 4.9 (apparent d, 4H, J = 5.2 Hz, C$\underline{H}_2$). δ_C (75MHz, $CDCl_3$) 180.4 ($\underline{C}$=S), 174.0 ($\underline{C}$=O), 167.0 (Ar$\underline{C}$), 137.1

(ArC), 133.7 (ArC), 131.9 (ArC), 129.6 (ArC), 129.3 (ArC), 127.6 (ArC), 127.6 (ArC), 49.7 (CH_2). m/z (ES+, MeCN) 485.3, 10% $(M + Na)^+$, 501.2, 5% $(M + K)^+$, 947.3, 100% $(2M + Na)^+$. ν_{max}(Golden Gate)/cm^{-1} 3199 (w), 2921 (s), 2862 (s), 1665 (s). Crystal structure solved by standard methods, monoclinic system, space group P2(1)/c, R1 = 6.3%.

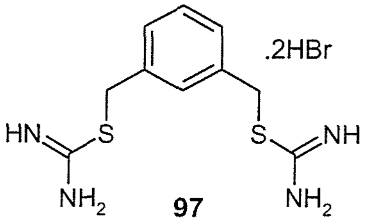
4.2.18 1,3-Bis-(Isothiocyanatomethyl)-benzene[62] (96)



96

To a solution of *m*-xylylene diamine (5 ml, 37.9 mmol) and triethylamine (20.17 ml, 83 mmol) in chloroform (200 ml) was added thiophosgene (6.33 ml, 83 mmol) in chloroform (100 ml) dropwise at 0°C over 40 mins with stirring. The solution was allowed to warm to room temperature and stirred for 30 mins then heated at reflux for 1 hour. After allowing the solution to cool to room temperature the solvent was removed *in vacuo* and the residue was purified by column chromatography (10 – 20% EtOAc/ petroleum ether (40 – 60)). After removal of solvents a yellow oil remained that solidified in the freezer (5.85 g, 70%). NMR δ_H (300 MHz, $CDCl_3$) 7.5 (t, 1H, J = 8.5 Hz, ArH), 7.3 (d, 2H, J = 8.5 Hz, ArH), 7.3 (s, 1H, ArH), 4.8 (s, 4H, CH_2). δ_C (75MHz, $CDCl_3$) 135.4 (ArC), 129.9 (ArC), 127.0 (ArC), 125.4 (ArC), 48.6 (CH_2). m/z (ES+, MeCN) 239.1, 80%, 317.1, 100%. ν_{max}(Golden Gate)/cm^{-1} 2169 (w), 2073 (m), 1729 (w). Spectra consistent with lit.[62]

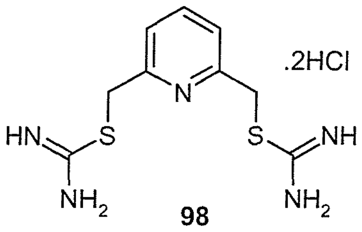
4.2.19 *m*-Xylylene di(*S*-thiouronium) dihydrobromide[117] (97)



97

Thiourea (1.15 g, 15.2 mmol) was dissolved in ethanol (20ml) and stirred. α,α'-Dibromo-*m*-xylene (2 g, 7.6 mmol) was dissolved in ethanol (20ml) and added in portions to the first solution. The reaction mixture was heated at a gentle reflux. After about an hour the reaction was cooled, the solvent was removed *in vacuo* and the resulting white solid was recrystallised from ethanol and dried *in vacuo* (3.16 g, 99%). mp 210 - 214°C. (lit.[117] 215 – 217°C). NMR δ_H (300 MHz, d_6-DMSO) 9.3 (bs, 4H, NH), 9.1 (bs, 4H, NH), 7.5 (bs, 1H, ArH), 7.4 (bs, 3H, ArH), 4.6 (bs, 4H, CH_2). δ_C (75MHz, d_6-DMSO) 169.1 (C=N), 135.7 (ArC), 129.6 (ArC), 129.4 (ArC), 128.8 (Ar<u>C</u>), 34.2 (<u>C</u>H_2). m/z (ES+, MeOH) 128.1, 15% $(M + 2H)^{2+}$, 262.0, 5% $(M + H)^{+}$. (146.0, 100%, contamination). ν_{max}(Golden Gate)/cm^{-1} 3175 (bs), 3086 (bs), 2706 (w), 1637 (s). Found: C, 28.62; H, 3.70; N, 13.78; Br, 38.45; S, 15.03. Calculated: C, 28.86; H, 3.87; N, 13.46; Br, 38.40; S, 15.41.

4.2.20 2,6-Pyridine Bisisothiouronium dihydrochloride (98)

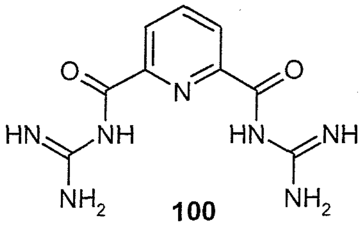


98

Thiourea (1.3 g, 17.05 mmol) was dissolved in dry methanol (40 ml) and stirred. 2,6-Bis-(chloromethyl) pyridine (1.5 g, 8.52 mmol) dissolved in methanol (10 ml) was added dropwise. The solution was stirred for 30 mins at room temperature, then heated gently and stirred overnight. The solution was allowed to cool to room temperature and the solvent was removed *in vacuo*. The residue was recrystallised from ethanol/ acetone and dried *in vacuo* to give the product as an off-white solid (1.88 g, 67%). mp 184°C. NMR δ_H (300 MHz, d_6-DMSO) 9.5 (bs, 8H, N<u>H</u>), 7.9 (t, 1H, J = 7.7 Hz, Ar<u>H</u>), 7.5 (d, 2H, J = 7.7 Hz, Ar<u>H</u>), 4.7 (s, 4H, C<u>H</u>$_2$). δ_C (75MHz, d_6-DMSO) 169.9 (<u>C</u>=N), 155.3 (Ar<u>C</u>), 139.1 (Ar<u>C</u>), 122.8 (Ar<u>C</u>), 35.6 (<u>C</u>H_2). m/z (ES+, MeOH) 256.0, 98% $(M + H)^{+}$. High Resolution m/z (ES+, MeOH) $C_9H_{13}N_5S_2$ (M) Calculated 255.3552. Found 256.0687 $(M + H)^{+}$. ν_{max}(Golden Gate)/cm^{-1} 3457 (m), 3265 (bs), 2972 (bs), 1654 (s), 1636 (s).

4.2.21 *N,N'*-Bis-(Aminoiminomethyl)-2,6-pyridinedicarboxamide (100)

Method a)



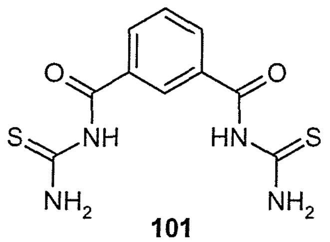
100

Sodium metal (1.15 g, 0.05 mol) was added to dry methanol (20 ml) over 30 minutes. Guanidinium hydrochloride (4.78 g, 0.05 mol) was added to the solution in one portion. The suspension was stirred at room temperature for 1 hour. The sodium chloride was filtered off and the filtrate was placed in a flask and stirred. To this was added dropwise pyridine-2,6-diacid chloride (1.02 g, 5 mmol) in dry THF (20 ml). Triethylamine (1.67 ml, 12 mmol) was added in one portion and the solution was stirred for 2 hours at room temperature. The white precipitate that formed was removed by filtration, washed with cold methanol and dried *in vacuo*. The solid was recrystallised from water/ ethanol to give the product as a white powder (0.10 g, 8%). mp 256 – 259°C. NMR δ_H (300 MHz, d_6-DMSO) 8.2 (apparent d, 4H, J = 8.1 Hz, N<u>H</u>), 8.1 (d, 2H, J = 8.5 Hz, Ar<u>H</u>), 8.0 (t, 1H, J = 8.5 Hz, Ar<u>H</u>), impurities around 8.1 ppm. δ_C (75MHz, d_6-DMSO) 173.8 (<u>C</u>=O), 163.8 (<u>C</u>=N), 153.3 (Ar<u>C</u>), 138.7 (Ar<u>C</u>), 124.9 (Ar<u>C</u>), trace impurities at 158.6 and 138.3. m/z (ES+, H_2O, formic acid) No peaks consistent with product or starting materials. ν_{max}(Golden Gate)/cm^{-1} 3417 (w), 3155 (w), 3016 (w), 2970 (w), 2359 (m), 2342 (m), 1739 (s), 1653 (m), 1601 (m).

Method b)

Sodium metal (1.15 g, 0.05 mol) was added to dry methanol (20 ml) over 30 minutes. Guanidinium hydrochloride (4.78 g, 0.05 mol) was added to the solution in one portion. The suspension was stirred at room temperature for 1 hour. The sodium chloride was filtered off and the filtrate was placed in a flask and stirred. To this was added dropwise pyridine-2,6-dimethanol (0.98 g, 5 mmol) dissolved in warm methanol (50 ml). The solution was heated at reflux for 2 hours. A white precipitate was filtered off, washed with cold methanol and dried *in vacuo*. The solid was recrystallised from water/ acetone to give a white solid (0.54 g, 43%). mp >250°C. NMR δ_H (300 MHz, d_6-DMSO) 8.1 (bs, 4H, N<u>H</u>), 8.0 (d, 2H, J = 8.5 Hz, Ar<u>H</u>), 7.9 (dd, 1H, J = 8.5 Hz, Ar<u>H</u>). δ_C (75MHz, d_6-DMSO) 169.49 (<u>C</u>=O), 159.07 (<u>C</u>=N), 153.98 (Ar<u>C</u>), 137.45 (Ar<u>C</u>), 124.00 (Ar<u>C</u>). NMR δ_H (300 MHz, D_2O) 7.8 (s, 3H, Ar<u>H</u>). δ_C (75MHz, D_2O) 175.7 (<u>C</u>=O), 155.3 (Ar<u>C</u>), 141.2 (Ar<u>C</u>), 127.7 (Ar<u>C</u>). m/z (ES+, H_2O, formic acid) No peaks consistent with product or starting materials. ν_{max}(Golden Gate)/cm^{-1} 3436 (w), 3016 (w), 2970 (w), 2360 (m), 1738 (s), 1670 (m), 1627 (m). Combustion data unsatisfactory (Found: C, 36.86; H, 4.27; N, 24.57. Calculated: C, 43.37; H, 4.45; N, 39.32). Further attempts to purify this compound by recrystallisation were not successful.

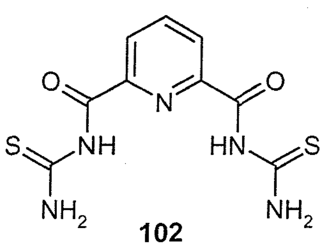
4.2.22 *N,N'*-Bis-(Aminothiocarbonylmethyl)-1,3-benzenedicarboxamide (101)



101

Isophthaloyl chloride (2.03 g, 0.01 mol) was dissolved in THF (30 ml) and triethylamine (3.1 ml, 22 mmol) was added. Thiourea (1.9 g, 25 mmol) suspended in THF (40 ml) was added to the solution over 1 hour. The reaction was stirred at room temperature for 1 hour, and then heated at reflux for 48 hours. The reaction was allowed to cool to room temperature and the insoluble excess thiourea was removed by filtration. The filtrate was concentrated *in vacuo* and the precipitate that appeared was filtered off. A second crop was recovered in the same manner by further concentration of the filtrate. Both crops were recrystallised from THF/ water to give the product as a yellow solid (0.42 g, 15%). mp >250°C. NMR δ_H (300 MHz, d_6-DMSO) 9.8 (bs, 2H, N$\underline{H}$), 9.7 (bs, 2H, N$\underline{H}$), 8.4 (s, 1H, Ar$\underline{H}$), 8.1 (d, 2H, J = 7.7 Hz, Ar$\underline{H}$), 7.6 (t, 1H, J = 7.7 Hz, Ar$\underline{H}$), trace impurity at 11.2 ppm. δ_C (75MHz, d_6-DMSO) 181.9 ($\underline{C}$=S), 166.9 ($\underline{C}$=O), 133.2 (Ar$\underline{C}$), 132.0 (Ar$\underline{C}$), 129.2 (Ar$\underline{C}$), 128.6 (Ar$\underline{C}$). m/z (ES+, H_2O, formic acid) no peaks consistent with starting materials or product. ν_{max}(Golden Gate)/cm^{-1} 3374 (m), 3246 (m), 3198 (m), 1735 (w), 1679 (s), 1616 (s). Combustion data unsatisfactory (Found: C, 44.21; H, 3.50; N, 18.29; S, 18.69. Calculated: C, 42.54; H, 3.57; N, 19.83; S, 22.71). Further attempts to purify this compound by recrystallisation were not successful.

4.2.23 *N,N'*-Bis-(Aminothiocarbonylmethyl)-2,6-pyridinedicarboxamide (102)

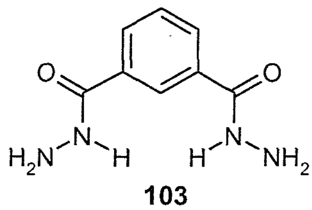


102

Pyridine-2,6-dicarbonyl dichloride (2.04 g, 0.01 mol) was dissolved in THF (30 ml) and triethylamine (3.1 ml, 22 mmol) was added. Thiourea (1.9 g, 25 mmol) suspended in THF (40 ml) was added to the solution over 1 hour. The reaction was stirred at room temperature for 1 hour, then heated at reflux for 48 hours. The reaction was allowed to cool to room temperature and the insoluble excess thiourea was removed by filtration. The filtrate was concentrated *in vacuo* and the precipitate that appeared was filtered off and washed with a little water. A second crop was recovered in the same manner by further concentration of the filtrate. Both crops were recrystallised from THF/

water twice to give the product as a brown/ yellowish solid (0.07 g, 2%). mp 180°C (Decomp). NMR δ_H (300 MHz, d_6-DMSO) 11.8 (bs, 2H, N$\underline{H}$), 9.8 (bs, 4H, N$\underline{H}$), 8.3 (m, 3H, Ar$\underline{H}$), trace impurities at 13.9, 11.3 & 8.6 ppm. δ_C (75MHz, d_6-DMSO) 181.4 ($\underline{C}$=S), 163.9 ($\underline{C}$=O), 147.6 (Ar$\underline{C}$), 140.2 (Ar$\underline{C}$), 127.7 (Ar$\underline{C}$), trace impurities at 162.6 & 147.3 ppm. m/z (ES+, H_2O, formic acid) no peaks consistent with starting materials or product. ν_{max}(Golden Gate)/cm^{-1} 3375 (m), 3247 (m), 1728 (w), 1687 (s), 1597 (s). Combustion data unsatisfactory (Found: C, 42.89; H, 3.63; N, 20.00; S, 16.11. Calculated: C, 38.15; H, 3.20; N, 24.71; S, 22.63). Further attempts to purify this compound by recrystallisation were not successful.

4.2.24 Benzene-1,3-dicarboxylic acid dihydrazide[118] (103)

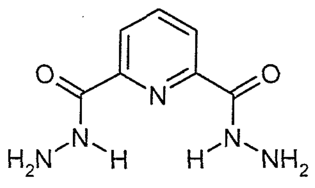


103

Dimethyl isophthalate (3 g, 0.015 mol) was suspended in methanol (50ml) and hydrazine monohydrate (5 ml, 0.09 mol) was added in one portion. The reaction vessel was sealed and the reaction was stirred for two hours. The white solid that appeared was filtered off and washed with a small amount of cold methanol. The filtrate was concentrated *in vacuo* and then cooled to yield a second crop and subsequent third crop. The three crops were combined and recrystallised from water/ ethanol (20/ 80) to give white crystals (1.33g, 46%). mp 216 - 218°C. (lit.[118] 220°C (EtOH)). NMR δ_H (300 MHz, d_6-DMSO) 9.9 (s, 2H, N$\underline{H}$), 8.4 (s, 1H, Ar$\underline{H}$), 7.9 (d, 2H, J = 7.7 Hz, Ar$\underline{H}$), 7.5 (t, 1H, J = 7.7 Hz, Ar$\underline{H}$). δ_C (75MHz, d_6-DMSO) 165.6 ($\underline{C}$=O), 133.6 (Ar$\underline{C}$), 129.4 (Ar$\underline{C}$), 128.5 (Ar$\underline{C}$), 126.1 (Ar$\underline{C}$). m/z (ES+, MeCN) 194.9, 10% $(M + H)^+$. ν_{max}(Golden Gate)/cm^{-1} 3287 (m), 3056 (w), 1664 (w), 1620 (s).

4.2.25 Pyridine-2,6-dicarboxylic acid dihydrazide[119] (104)

Method a)



104

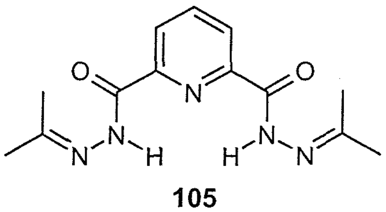
Hydrazine monohydrate (10 ml) was added with stirring to dimethyl-2,6-pyridine ester (1.4g, 7.2 mmol). A pink solution with a white precipitate resulted. The suspension was heated at reflux for 1 hour then allowed to cool to room temperature. The precipitate was filtered off, washed with water and dried *in vacuo* to give a white solid (1.24 g, 88%). mp >250°C. (lit.[119] 280°C). NMR δ_H (300 MHz, d_6-DMSO) 10.6 (s, 2H, N$\underline{H}$), 8.1 (s, 3H, Ar$\underline{H}$), 4.6 (bs, 4H, N$\underline{H}_2$). δ_C (75MHz, d_6-DMSO) 162.0 ($\underline{C}$=O), 148.5 (Ar$\underline{C}$), 139.4 (Ar$\underline{C}$), 123.8 (Ar$\underline{C}$). m/z (ES+, H_2O, Formic acid) 195.8, 55% $(M + H)^+$, 217.8, 30% $(M + Na)^+$. ν_{max}(Golden Gate)/cm^{-1} 3261 (s), 3180 (m), 1687 (m), 1629 (s).

Method b)

Dimethyl pyridine-2,6-dicarboxylate (3 g, 0.015 mol) was suspended in methanol (30 ml) and hydrazine acetate (1.66 g, 0.018 mol) was added in one portion. The reaction was heated at reflux under nitrogen and monitored by tlc (1% MeOH/ DCM). Reaction was complete after about 2 hours. The solution was cooled causing a white precipitate to appear which was removed by filtration. The filtrate was then chilled and a second crop was recovered in a similar manner. Both crops were recrystallised from water and dried *in vacuo* to give the product as colourless needle crystals (0.50 g, 32%). mp 175 - 179°C. (lit.[119] 280°C (H_2O)) NMR δ_H (300 MHz, d_6-DMSO) 10.7 (s, 1H, N$\underline{H}$), 9.7 (s, 2H, N$\underline{H}_2$), 8.3 – 8.1 (m, 3H, Ar$\underline{H}$). δ_C (75MHz, d_6-DMSO) 162.0 ($\underline{C}$=O), 148.5 (Ar$\underline{C}$), 139.4 (Ar$\underline{C}$), 123.8 (Ar$\underline{C}$) NMR spectra contain impurities. m/z (ES+, MeCN) 196.0, 90% $(M + H)^+$, 218.0, 35% $(M + Na)^+$, 413.0, 100% $(2M + Na)^+$. ν_{max}(Golden Gate)/cm^{-1} 3332 (w), 3270 (w), 1745 (s).

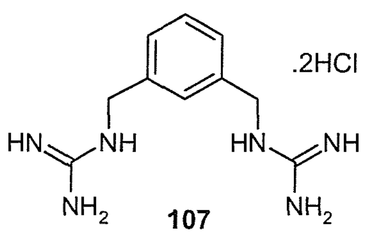
4.2.26 Pyridine-2,6-dicarboxylic acid dihydrazide-bis-acetanide (105)

Pyridine-2,6-dicarboxylic acid dihydrazide (0.25 g, 1.28 mmol) was suspended in acetone (5 ml) and warmed until the precipitate dissolved. The solution was then placed in the fridge overnight. The resultant colourless needle crystals were removed by filtration and dried *in vacuo* (0.19 g, 55%). mp = 176°C. Crystal structure solved by standard methods, monoclinic system, space group P2(1)/c, R1 = 4.5%.



105

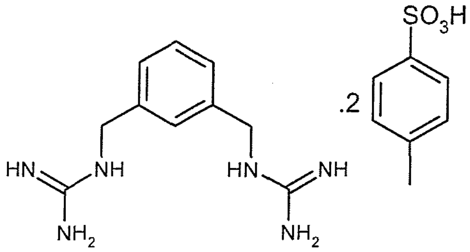
4.2.27 *m*-Xylyene bis-(guanidinium) dihydrochloride[77] (107)



107

m-Xylyene bis-(guanidinium) sulfate (2 g, 6.29 mmol) was suspended in water (100 ml) and aqueous sodium hydroxide (2M) was added until the pH was about 13.7. Saturated barium hydroxide solution was added to the former solution in small amounts until no more precipitate formed. The barium sulphate was then filtered off, the filtrate was neutralised with aqueous hydrochloric acid (2N) and evaporated to dryness to leave a white solid. The residue was suspended in dry ethanol (20 ml), stirred, and then filtered. The solvent was removed *in vacuo* to leave a white gummy hygroscopic solid (1.29g, 70%). NMR δ_H (300 MHz, d_4-MeOD) 6.7 (m, 4H, Ar$\underline{H}$), 3.8 (s, 4H, C$\underline{H}_2$). δ_C (75MHz, d_6-DMSO) 158.7 ($\underline{C}$=N), 138.4 (Ar$\underline{C}$), 130.4 (Ar$\underline{C}$), 127.9 (Ar$\underline{C}$), 127.3 (Ar$\underline{C}$), 45.7 ($\underline{C}H_2$). ν_{max}(Golden Gate)/cm^{-1} 3277 (m), 3136 (bs), 1672 (s), 1641 (s), 1608 (s).

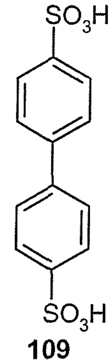
4.2.28 *m*-Xylylene bis-(guanidinium) di-p-toluene sulfonate (108)



108

m-Xylylene bis-(guanidinium) dihydrochloride (0.32 g, 0.0011 mol) was dissolved in water (10 ml) and toluene sulfonic acid monohydrate (0.45 g, 0.0022 mol) dissolved in water (10 ml) was added. The solution was stirred, and then allowed to stand and slowly evaporate. After several weeks large crystals had formed. These were filtered off and washed with a little water. mp 197 – 199°C. NMR δ_H (300 MHz, D_2O) 7.5 (d, 4H, J = 8.1 Hz, Ar$\underline{H}$), 7.3 (t, 1H, J = 7.0 Hz, Ar$\underline{H}$), 7.2 (d, 4H, J = 8.1 Hz, Ar$\underline{H}$), 7.2 (d, 2H, J = 7.0 Hz, Ar$\underline{H}$), 7.1 (s, 1H, Ar$\underline{H}$). δ_C (75MHz, D_2O) 155.8 ($\underline{C}$=N), 141.3 (Ar$\underline{C}$), 138.3 (Ar$\underline{C}$), 135.7 (Ar$\underline{C}$), 128.3 (Ar$\underline{C}$), 128.3 (Ar$\underline{C}$), 125.2 (Ar$\underline{C}$), 124.2 (Ar$\underline{C}$), 123.9 (Ar$\underline{C}$), 43.1 ($\underline{C}H_2$), 19.3 ($\underline{C}H_3$). Found: C, 50.88; H, 5.53; N, 14.81; S, 11.07. Calculated: C, 51.05; H, 5.71; N, 14.88; S, 11.36. Crystal structure solved by standard methods, triclinic system, space group P-1, R1 = 11.4%.

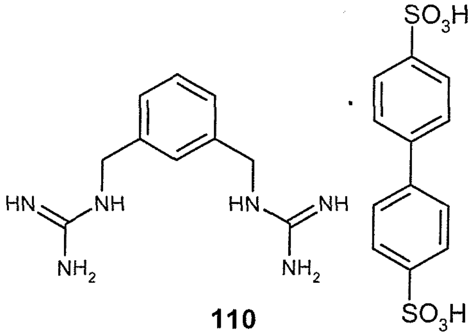
4.2.29 4,4'-Diphenyldisulfonic acid[120] (109)



109

4,4'-Diphenyldisulfonyl chloride (5 g, 0.014 mol) was suspended in water (50 ml). The pH was adjusted to 9 with sodium hydroxide (2N), and then to pH 13. The suspension was warmed to 50°C, at which temperature the pH started to drop, stabilising at pH 11. The reaction was stirred overnight at room temperature. The solution was neutralised to pH 7 with hydrochloric acid (2N), cooled to about 5°C and the apparent white precipitate was filtered off and washed with cold water. The filtrate was concentrated *in vacuo* to yield a second crop. Both crops were dried *in vacuo* (4.22 g, 96%). mp >350°C. (lit.[120] mp not quoted). NMR δ_H (300 MHz, D_2O) 7.8 (d, 4H, J = 8.8 Hz, ArH), 7.6 (d, 4H, J = 8.8 Hz, ArH). δ_C (75MHz, D_2O) 144.7 (ArC), 144.4 (ArC), 130.2 (ArC), 128.6 (ArC). m/z (ES+, MeCN) 156.0, 100% $(M-2H)^{2-}$, 313.1, 10% $(M-H)^-$. ν_{max}(Golden Gate)/cm^{-1} 3065 (w), 1597 (w).

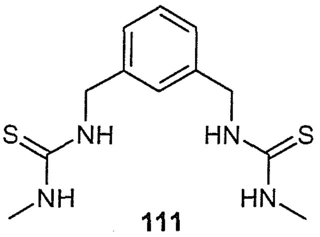
4.2.30 *m*-Xylylene bis-(guanidinium) di-phenyl-di-p-sulfonate (110)



110

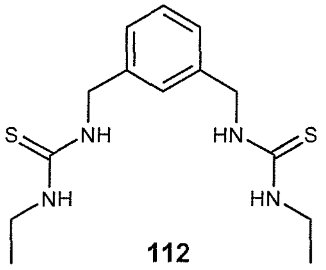
m-Xylylene bis-(guanidinium) dihydrochloride (0.93 g, 0.0032 mol) was dissolved in water (30 ml) and 4,4'-diphenylsulfonic acid (1 g, 0.0032 mol) dissolved in water (50 ml) was added. The solution was heated to 60°C with stirring, at which temperature the solution became clear. Needle crystals were produced by slow evaporation after about a month. These were filtered off and washed with a little water. mp 290 - 293°C. NMR δ_H (300 MHz, D_2O) 7.8 (d, 4H, J = 8.8 Hz, ArH), 7.7 (d, 4H, J = 8.8 Hz, ArH) 7.3 (t, 1H, J = 7.7 Hz, ArH), 7.1 (d, 2H, J = 7.7 Hz, ArH), 7.1 (s, 1H, ArH), 4.2 (s, 4H, CH_2). δ_C (75MHz, D_2O) 142.4 (ArC), 142.0 (ArC), 136.9 (ArC), 129.6 (ArC), 127.8 (ArC), 126.5 (ArC), 126.5 (ArC), 126.2 (ArC), 125.2 (ArC), 44.4 (CH_2). Found: C, 49.17; H, 4.85; N, 15.74; S, 11.91. Calculated: C, 49.43; H, 4.90; N, 15.72; S, 11.99. Crystal structure solved by standard methods, orthorhombic system, space group Pbca, R1 = 4.5%.

4.2.31 *m*-Xylylene di(*N'*-methyl-thiourea)[121] (111)


111

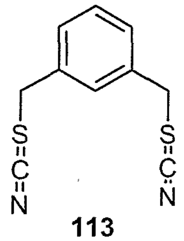
Methyl isothiocyanate (1.46 g, 20 mmol) dissolved in DCM (10 ml) was added dropwise to *m*-xylylene diamine (1.32 ml, 10 mmol) dissolved in DCM (15 ml) under nitrogen. The reaction was stirred and heated at reflux for 2 hours. The reaction was allowed to cool to room temperature and the white precipitate was filtered off, recrystallised from methanol and dried *in vacuo* to give a white solid (2.45 g, 87%). mp 135°C. (lit.[121] 134.5 – 137°C). NMR δ_H (300 MHz, d_6-DMSO) 7.9 (bs, 2H, N$\underline{H}$), 7.5 (bs, 2H, N$\underline{H}$), 7.3 (t, 1H, J = 7.7 Hz, Ar$\underline{H}$), 7.2 (s, 1H, Ar$\underline{H}$), 7.1 (d, 2H, J = 7.7 Hz, Ar$\underline{H}$), 4.6 (bs, 4H, C$\underline{H}_2$), 2.8 (bs, 6H, C$\underline{H}_3$). δ_C (75MHz, d_6-DMSO) 139.5 (Ar$\underline{C}$), 128.2 (Ar$\underline{C}$), 126.2 (Ar$\underline{C}$), 125.8 (Ar$\underline{C}$), 47.1 ($\underline{C}H_2$). m/z (ES+, MeCN) 283.3, 100% $(M + H)^+$, 565.4, 35%, $(2M + H)^+$. ν_{max}(Golden Gate)/cm^{-1} 3216 (s), 3018 (w), 2941 (w), 1556 (s).

4.2.32 1-ethyl-3[3-(3-ethyl-thioureidomethyl)-benzyl]-thiourea)[62] (112)


112

Ethyl isothiocyanate (1.75 ml, 0.02 mol) was dissolved in DCM (10 ml) and stirred under nitrogen. *m*-Xylylene diamine (1.32 ml, 0.01 mol) was dissolved in DCM (10 ml) and added dropwise to the solution. The solution was stirred and heated at reflux for one hour, after which time a white precipitate had appeared. The reaction was monitored by tlc (eluent = ethyl acetate). This showed the reaction to be incomplete, so the reaction was refluxed for a further 2 hours. The white precipitate was filtered off and recrystallised from ethanol. A second crop was collected from the mother liquour (2.67g, 90%). mp 154 - 156°C. (lit.[62] 163 - 165°C) NMR δ_H (300 MHz, d_6-DMSO) 7.8 (s, 2H, N$\underline{H}$) 7.5 (s, 2H, N$\underline{H}$) 7.3 (t, 1H, J = 7.7 Hz, Ar$\underline{H}$), 7.2 (d, 2H, J = 7.7 Hz, Ar$\underline{H}$) 7.1 (s, 1H, Ar$\underline{H}$) 4.6 (bs, 4H, C$\underline{H}_2$) 3.4 (bs, 4H, C$\underline{H}_2$) 1.1 (t, 6H, J = 7.4 Hz, C$\underline{H}_3$). δ_C (75MHz, d_6-DMSO) 182.1 ($\underline{C}$=S), 139.5 (Ar$\underline{C}$), 128.3 (Ar$\underline{C}$), 126.2 (Ar$\underline{C}$), 125.8 (Ar$\underline{C}$), 47.0 ($\underline{C}H_2$), 39.3 ($\underline{C}H_2$), 14.5 ($\underline{C}H_3$). m/z (ES+, MeCN) 311.2, 5% $(M + H)^+$, 333.2, 5% $(M + Na)^+$. ν_{max} (nujol) 3208 (s), 2923 (s), 2862 (s).

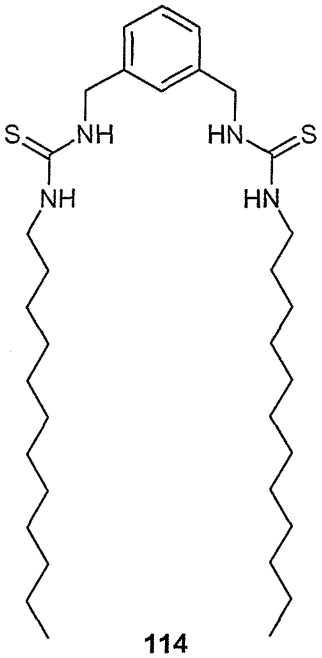
4.2.33 1,3-Bis-(Methyl thiocyanate) benzene (113)



113

Potassium thiocyanate (1.47 g, 15.2 mmol) was dissolved in dry acetone (10 ml) and stirred. α, α'-Dibromo-*m*-xylene (2 g, 7.58 mmol) dissolved in acetone (10 ml) was added dropwise. The reaction was heated at reflux for 2 hours. The precipitate was filtered off and the filtrate was evaporated to dryness *in vacuo* to leave an off-white solid (1.16 g, 70%). mp 60 – 63°C. NMR δ_H (300 MHz, d_6-DMSO) 7.5 (m, 4H, Ar$\underline{H}$), 4.4 (s, 4H, C$\underline{H}_2$). δ_C (75MHz, d_6-DMSO) 136.9 (Ar$\underline{C}$), 129.6 (Ar$\underline{C}$), 129.3 (Ar$\underline{C}$), 129.2 (Ar$\underline{C}$), 113.0 (S$\underline{C}$N), 36.9 ($\underline{C}H_2$).m/z (ES+, MeCN) 220.8, 10% $(M + H)^+$. ν_{max}(Golden Gate)/cm^{-1} 3416 (w), 2146 (s).

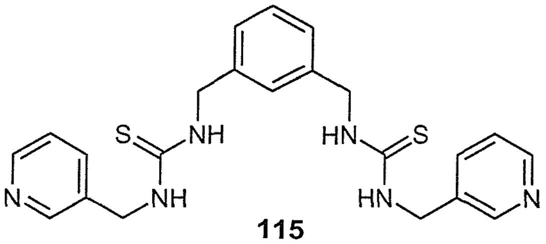
4.2.34 1-Dodecyl-3-(3-[(3-dodecyl-thioureido)-methyl]-benzyl)-thiourea (114)



114

1,3-Bis-(Methylthiocyanato) benzene (1 g , 4.55 mmol) was dissolved in dry DCM (10 ml) and was added dropwise to dodecylamine (1.69 g, 9.10 mmol) dissolved in dry DCM (10 ml). The reaction was stirred at room temperature overnight. The precipitate was removed by filtration, washed with DCM and dried *in vacuo* to give a white solid (1.78 g, 66%). mp 145 - 146°C. NMR δ_H (300 MHz, 256 scans, d_6-DMSO) 7.4 (t, 1H, J = 7.5 Hz, Ar$\underline{H}$), 7.3 (s, 1H, Ar$\underline{H}$), 7.2 (d, 2H, J = 7.5 Hz, Ar$\underline{H}$), 4.7 (s, 4H, C$\underline{H}_2$), 1.3 (bs, 44H, C$\underline{H}_2$), 1.0 (t, 6H, J = 7.0 Hz, C$\underline{H}_3$). m/z (ES+, MeCN) Too insoluble. ν_{max}(Golden Gate)/cm^{-1} 3309 (w), 3242 (m), 3073 (w), 2956 (w), 2917 (s), 2870 (m), 2849 (s), 1610 (w), 1561 (s). Found: C, 68.87; H, 10.72; N, 9.36. Calculated: C, 69.10; H, 10.57; N, 9.48.

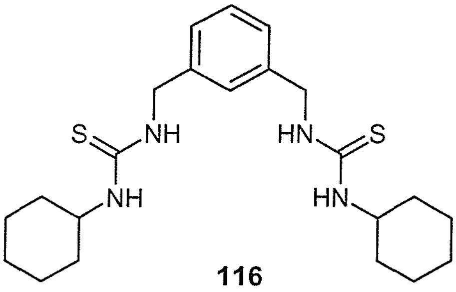
4.2.35 1-Pyridin-3-ylmethyl-3-[3-(3-pyridin-3-ylmethyl-thioureidomethyl)-benzyl]-thiourea (115)



115

1,3-Bis-(Isothiocyanatomethyl) benzene (1 g, 4.55 mmol) was dissolved in MeCN (5 ml) and added dropwise to a solution of 3-aminomethyl pyridine (1 ml, 10 mmol) in MeCN (5 ml). The solution was stirred at room temperature overnight. The white precipitate was filtered off, washed with MeCN and dried *in vacuo* to give a white powder (1.65 g, 83%). mp 113 – 114°C. NMR δ_H (300 MHz, d_6-DMSO) 8.5 (s, 2H, N$\underline{\mathrm{H}}$), 8.5 (d, 2H, J = 4.8 Hz, N$\underline{\mathrm{H}}$), 8.1 (bs, 4H, Ar$\underline{\mathrm{H}}$), 7.7 (d, 2H, J = 7.5 Hz, Ar$\underline{\mathrm{H}}$), 7.4 (t, 2H, J = 7.8 Hz, Ar$\underline{\mathrm{H}}$), 7.3 (t, 1H, J = 7.5 Hz, Ar$\underline{\mathrm{H}}$), 7.2 (s, 1H, Ar$\underline{\mathrm{H}}$ covered by doublet), 7.2 (d, 2H, J = 7.8 Hz, Ar$\underline{\mathrm{H}}$), 4.7 (d, 4H, J = 4.8 Hz, C$\underline{\mathrm{H}}_2$), 4.7 (s, 4H, C$\underline{\mathrm{H}}_2$). δ_C (75MHz, d_6-DMSO) 183.1 (C=S), 148.8 (Ar$\underline{\mathrm{C}}$), 148.1 (Ar$\underline{\mathrm{C}}$), 139.3 (Ar$\underline{\mathrm{C}}$), 135.1 (Ar$\underline{\mathrm{C}}$), 135.0 (Ar$\underline{\mathrm{C}}$), 128.4 (Ar$\underline{\mathrm{C}}$), 126.2 (Ar$\underline{\mathrm{C}}$), 125.9 (Ar$\underline{\mathrm{C}}$), 123.5 (Ar$\underline{\mathrm{C}}$), 47.2 ($\underline{\mathrm{C}}\mathrm{H}_2$), 44.7 ($\underline{\mathrm{C}}\mathrm{H}_2$). m/z (ES+, MeCN) 458.9, 10% $(M + Na)^+$, 872.8, 25% $(2M + H)^+$. ν_{max}(Golden Gate)/cm^{-1} 3182 (bs), 3009 (m), 2927 (m), 1605 (w), 1546 (s).

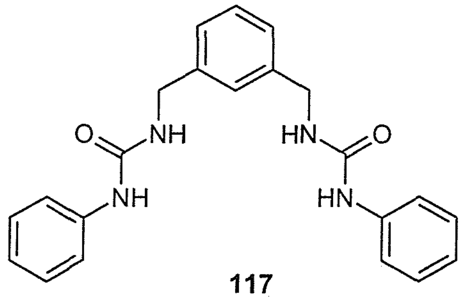
4.2.36 1,3-Bis-((*N'*-Cyclohexyl)-methylthiourea) benzene (116)



116

1,3-Bis-(Methylthiocyanato) benzene (1.30 g , 6 mmol) was dissolved in dry DCM (10 ml) and was added dropwise to cyclohexylamine (1.40 ml, 12 mmol) dissolved in dry DCM (10 ml) over 30 mins. The reaction was stirred at room temperature overnight. The precipitate was removed by filtration, washed with DCM and dried *in vacuo* to give a white solid (2.47 g, 98%). mp 214 - 217°C. NMR δ_H (300 MHz, d_6-DMSO) 7.6 (bs, 2H, N$\underline{\mathrm{H}}$), 7.4 (bs, 2H, N$\underline{\mathrm{H}}$), 7.3 (t, 1H J = 7.5 Hz, Ar$\underline{\mathrm{H}}$), 7.2 (s, 1H, Ar$\underline{\mathrm{H}}$), 7.2 (d, 2H, J = 7.5 Hz, Ar$\underline{\mathrm{H}}$), 4.6 (s, 4H, C$\underline{\mathrm{H}}_2$), 4.0 (s, 2H, C$\underline{\mathrm{H}}$), 1.9 (apparent d, 4H, J = 10.7 Hz, C$\underline{\mathrm{H}}$), 1.7 (m, 4H, C$\underline{\mathrm{H}}$), 1.6 (m, 2H, C$\underline{\mathrm{H}}$), 1.2 (m, 10H, C$\underline{\mathrm{H}}$). m/z (ES+, MeCN) 419, 40% $(M + H)^+$, 441, 85% $(M + Na)^+$, 584, 100%, $(M + H + TPA)^+$. High Resolution m/z (ES+, MeCN) $C_{22}H_{34}N_4S_2$ (M) Calculated 418.4374. Found 419.2296 $(M + H)^+$. ν_{max}(Golden Gate)/cm^{-1} 3236 (m), 3063 (m), 2928 (s), 2852 (m), 1551 (s), 1534 (s).

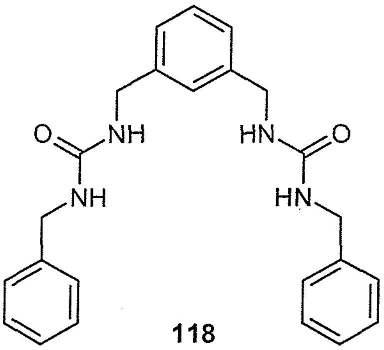
4.2.37 1,3-Bis-((*N*'-Phenyl)-methylurea) benzene (117)



117

Phenyl isocyanate (1.65 ml, 15.16 mmol) was dissolved in DCM (15 ml) and stirred under nitrogen. *m*-Xylylene diamine (1 ml, 7.58 mmol) was dissolved in DCM (5 ml) and added dropwise over 10 mins. The reaction was stirred for 2 hours after which time the precipitate was removed by filtration, washed with DCM (20 ml) and dried *in vacuo* to give a white solid (2.78 g, 98%). mp >240°C. NMR δ_H (300 MHz, d_6-DMSO) 8.6 (s, 2H, N$\underline{H}$), 7.4 (d, 4H, J = 7.6 Hz, Ar$\underline{H}$), 7.2 (m, 7H, Ar$\underline{H}$), 6.9 (t, 2H, J = 7.6 Hz, Ar$\underline{H}$), 6.6 (t, 2H, J = 5.9 Hz, N$\underline{H}$), 4.3 (d, 4H, J = 5.9 Hz, C$\underline{H}_2$). δ_C (75MHz, d_6-DMSO) 155.3 ($\underline{C}$=O), 140.5 (Ar$\underline{C}$), 128.7 (Ar$\underline{C}$), 128.4 (Ar$\underline{C}$), 126.0 (Ar$\underline{C}$), 125.7 (Ar$\underline{C}$), 121.2 (Ar$\underline{C}$), 117.8 (Ar$\underline{C}$), 42.8 ($\underline{C}H_2$). m/z (ES+, MeCN) 375, 70% $(M + H)^+$, 397, 100% $(M + Na)^+$, 749, 20% $(2M + H)^+$, 771, 25% $(2M + H)^+$. ν_{max}(Golden Gate)/cm^{-1} 3305 (bs), 2860 (w), 1629 (s), 1594 (s), 1561 (s). Found: C, 70.37; H, 5.91; N, 14.94. Calculated: C, 70.57; H, 5.92; N, 14.96.

4.2.38 *m*-Xylylene bis-(*N*'-benzylurea) (118)

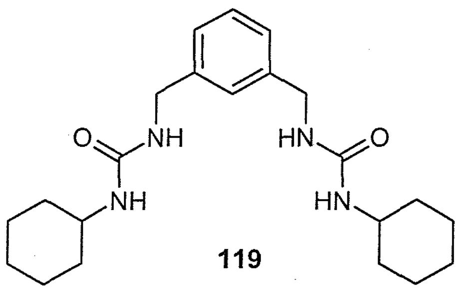


118

Benzylamine (3.5 ml, 32 mmol) was dissolved in acetonitrile (20 ml) and stirred under nitrogen. 1,3-Bis-(Isocyanatomethyl) benzene (2 ml, 12.77 mmol) dissolved in acetonitrile (15 ml) was added dropwise. The reaction was stirred at room temperature for 2 hours then the white precipitate which had formed was filtered off, recrystallised from acetonitrile and dried *in vacuo* to give a white solid (4.61 g, 90%). mp 230 – 232°C. NMR δ_H (300 MHz, d_6-DMSO) 7.3 (m, 10H, Ar$\underline{H}$), 7.1 (d, 4H, J = 7.7 Hz, Ar$\underline{H}$), 6.4 (t, 4H, J = 6.0 Hz, N$\underline{H}$), 4.2 (t, 8H, J = 6.0 Hz, C$\underline{H}_2$). δ_C (75MHz, d_6-DMSO) 158.2 ($\underline{C}$=O), 141.0 (Ar$\underline{C}$), 140.9 (Ar$\underline{C}$), 128.3 (Ar$\underline{C}$), 127.1 (Ar$\underline{C}$), 126.7

(ArC), 125.8 (ArC), 125.4 (ArC), 43.1 (CH_2), 43.1 (CH_2). m/z (ES+, MeCN) 403.2, 100% $(M + H)^+$, 425.2, 70% $(M + Na)^+$. High Resolution m/z (ES+, MeCN) $C_{24}H_{26}N_4O_2$ (M) Calculated 402.495. Found 425.1943 $(M + Na)^+$, 441.1680 $(M + K)^+$. ν_{max}(Golden Gate)/cm^{-1} 3307 (m), 3031 (w), 2909 (w), 1620 (s), 1562 (s).

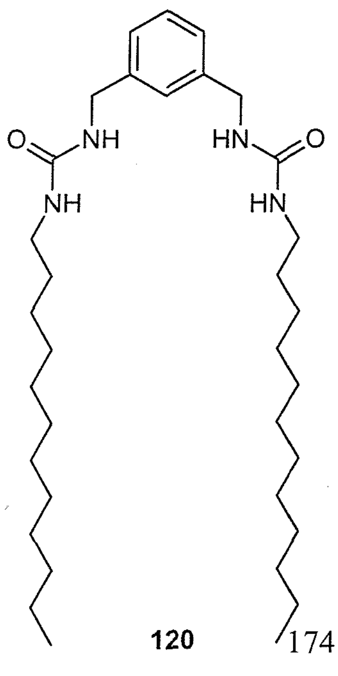
4.2.39 1,3-Bis-((*N'*-Cyclohexyl)-methylurea) benzene (119)



119

1,3-Bis-(Methylcyanato) benzene (1 ml, 6.39 mmol) was dissolved in dry DCM (10 ml) and was added dropwise to cyclohexylamine (1.47 ml, 12.77 mmol) dissolved in dry DCM (10 ml) over 30 mins. The reaction was stirred at room temperature overnight. The precipitate was removed by filtration, washed with DCM and dried *in vacuo* to give a white solid (2.69 g, 100%). mp >240°C. NMR δ_H (300 MHz, 256 scans, d_6-DMSO) 7.3 (m, 1H, ArH), 7.2 (s, 1H, ArH), 7.1 (d, 2H, J = 7.0 Hz, ArH), 6.1 (t, 2H, J = 5.9 Hz, NH), 5.8 (d, 2H, J = 8.1 Hz, NH), 4.2 (d, 4H, J = 5.9 Hz, CH_2), 1.6 (m, 11H, CH_2 & CH), 1.2 (m, 11H, CH_2). m/z (ES+, MeCN) 387, 30% $(M + H)^+$, 409, 100% $(M + Na)^+$. High Resolution m/z (ES+, MeCN) $C_{22}H_{34}N_4O_2$ (M) Calculated 386.3166. Found 387.2756 $(M + H)^+$, 409.2577 $(M + Na)^+$. ν_{max}(Golden Gate)/cm^{-1} 3310 (m), 2924 (bs), 2851 (s), 1624 (s), 1561 (s). Compound too insoluble to collect extended scans ^{13}C NMR spectrum.

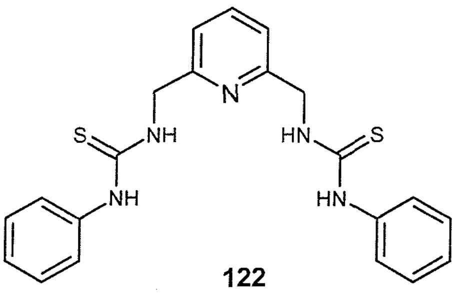
4.2.40 1-Dodecyl-3-(3-[(3-dodecyl-ureido)-methyl]-benzyl)-urea (120)



120

1,3-Bis-(Methylcyanato) benzene (1 ml, 6.39 mmol) was dissolved in dry DCM (10 ml) and was added dropwise to dodecylamine (2.37 g, 12.78 mmol) dissolved in dry DCM (10 ml) over 30 mins. The reaction was stirred at room temperature for 2 hours. The precipitate was removed by filtration, washed with DCM and dried *in vacuo* to give a white solid (3.60 g, 100%). mp 174 - 177°C. NMR δ_H (300 MHz, 256 scans, d_6-DMSO) no signal, material too insoluble. m/z (ES+, MeCN) material too insoluble. ν_{max}(Golden Gate)/cm^{-1} 3318 (m), 2955 (w), 2920 (s), 2849 (s), 1618 (s), 1562 (s). Found: C, 72.89; H, 11.18; N, 10.01. Calculated: C, 73.07; H, 11.18; N, 10.02.

4.2.41 (1-Phenyl-3[3-(3-phenyl-thioureidomethyl)-pyridyl]-thiourea) (122)

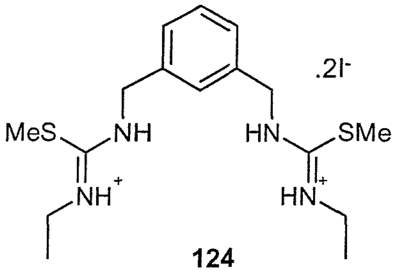


122

Phenyl isothiocyanate (0.8 ml, 6.69 mmol) was dissolved in dry DCM (20 ml) and sodium carbonate (0.71 g, 6.69 mmol) was added. 2,6-Bis-(Aminomethyl) pyridine dihydrobromide (1 g, 3.35 mmol) was added in portions under nitrogen. The reaction was then heated at reflux with stirring for 1 day, after which time sodium carbonate (0.3 g, 2.83 mmol) was added. The reaction was heated at reflux for a further 2 days. After allowing to cool to room temperature, the precipitate was removed by filtration and washed with DCM (10 ml) followed by water (70 ml) to leave an off-white solid which was recrystallised from ethanol/ acetone (0.75 g, 55%). mp 210°C (decomp.). NMR δ_H (300 MHz, d_6-DMSO) 10.3 (bs, 2H, N$\underline{H}$), 8.7 (bs, 2H, N$\underline{H}$), 7.7 (t, 1H, J = 7.7 Hz, Ar$\underline{H}$), 7.5 (d, 4H, J = 7.4 Hz, Ar$\underline{H}$), 7.3 (t, 4H, J = 7.4 Hz, Ar$\underline{H}$), 7.2 (d, 2H, J = 7.7 Hz, Ar$\underline{H}$), 7.1 (t, 2H, J = 7.4 Hz, Ar$\underline{H}$), 4.8 (s, 4H, C$\underline{H}_2$). δ_C (75MHz, d_6-DMSO) 180.9 ($\underline{C}$=S), 157.1 (Ar$\underline{C}$), 139.5 (Ar$\underline{C}$), 137.4 (Ar$\underline{C}$), 128.6 (Ar$\underline{C}$), 124.2 (Ar$\underline{C}$), 123.1 (Ar$\underline{C}$), 119.6 (Ar$\underline{C}$), 48.8 ($\underline{C}H_2$). m/z (ES+, MeCN) 408.1, 100% (M + H)$^+$. High Resolution m/z (ES+, MeCN) $C_{21}H_{21}N_5S_2$ (M) Calculated 407.5504. Found 408.1314 (M + H)$^+$. ν_{max}(Golden Gate)/cm^{-1} 3331 (w), 3246 (m), 3186 (m), 3005 (w), 1595 (s). A sample of the compound was recrystallised from EtOH/ acetone and allowed to slowly cool producing transparent yellow block crystals. The crystal structure was solved using standard methods, triclinic system, space group P-1, R1 = 3.4%.

4.2.42 α, α'-Bis-(*N*'-Ethyl-*S*-methyl-thiouronium hydroiodide)-*m*-xylene[62] (124)

Method a)



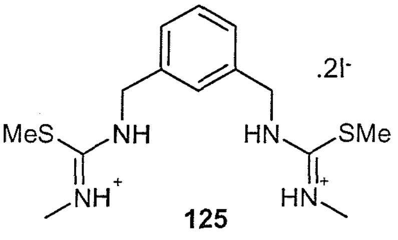
124

m-Xylyene bis-(*N'*-ethyl-thiourea) (0.5 g, 1.61 mmol) was dissolved in dry methanol (10 ml) and methyl iodide (2 ml, 32 mmol) was added. The reaction was heated at reflux for 2 hours. The solution was allowed to cool and the solvents were removed *in vacuo* to leave a yellowish gum (0.85 g, 99%). NMR δ_H (300 MHz, d$_6$-DMSO) 8.8 (bs, 1H, N$\underline{H}$), 7.4 (t, 1H, J = 7.7 Hz, Ar$\underline{H}$), 7.2 (m, 3H, Ar$\underline{H}$), 4.6 (bs, 4H, C$\underline{H}_2$), 2.6 (s, 4H, C$\underline{H}_2$), 2.5 (s, 6H, C$\underline{H}_3$), 1.2 (m, 6H, C$\underline{H}_3$).δ_C (75MHz, d$_6$-DMSO) 167.6 ($\underline{C}$-S), 137.1 (Ar$\underline{C}$), 129.2 (Ar$\underline{C}$), 126.5 (Ar$\underline{C}$), 125.5 (Ar$\underline{C}$), 47.3 ($\underline{C}$H$_2$), 38.8 ($\underline{C}$H$_2$), 14.2 ($\underline{C}$H$_3$), 13.5 ($\underline{C}$H$_3$). m/z (ES+, MeOH) 170.1, 100% $(M + 2H)^{2+}$, 339.2, 10% $(M + H)^+$.

Method b)

Methyl iodide (0.45g, 3.4 mmol) was added to a solution of *m*-xylylene bis-(*N'*-ethyl thiourea) (0.5g, 1.6 mmol) in DMF (10 ml) and the mixture was sealed in a Schlenk tube and stirred at room temperature for 48 hours. The resultant yellow solution was concentrated *in vacuo* to give a brown oil. The oil was concentrated on a vacuum line for 8 hours, to leave a thick brown oil (1.01 g, >100%). NMR δ_H (300 MHz, d$_6$-DMSO) 9.7 (s, 2H, N$\underline{H}$) 8.8 (s, 2H, N$\underline{H}$) 7.4 (t, 1H, J = 7.4 Hz, Ar$\underline{H}$) 7.3 (m, 3H, Ar$\underline{H}$) 4.6 (bs, 4H, C$\underline{H}_2$) 3.4 (s, 4H, C$\underline{H}_2$) 2.7 (s, 6H, C$\underline{H}_3$) 1.2 (t, 6H, J = 6.8 Hz, C$\underline{H}_3$). δ_C (75MHz, d$_6$-DMSO) 167.6 ($\underline{C}$=S), 137.0 (Ar$\underline{C}$), 129.2 (Ar$\underline{C}$), 126.6 (Ar$\underline{C}$), 125.5 (Ar$\underline{C}$), 47.3 ($\underline{C}$H$_2$), 46.3 ($\underline{C}$H$_2$), 35.9 ($\underline{C}$H$_3$), 14.2 ($\underline{C}$H$_3$), also DMF impurities in aliphatic region. *m/z* (ES+, MeOH) 170.2, 100%, $(M + 2H)^{2+}$, 339.3, 10% $(M + H)^+$.

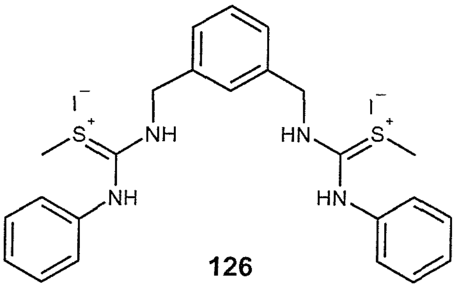
4.2.43 α, α'-Bis-(*N*'-Methyl-*S*-methyl-thiouronium hydroiodide)-*m*-xylene (125)



125

m-Xylyene bis-(*N'*-methyl-thiourea) (0.45 g, 1.61 mmol) was dissolved in dry methanol (10 ml) and methyl iodide (2 ml, 32 mmol) was added. The reaction was heated at reflux for 2 hours. The solution was allowed to cool and the solvents were removed *in* *vacuo* to leave a yellowish gum (0.91 g, 99%). NMR δ_H (300 MHz, d$_6$-DMSO) 6.8 (m, 2H, Ar$\underline{H}$), 6.6 (m, 2H, Ar$\underline{H}$), 4.0 (bs, 4H, C$\underline{H}_2$), 2.5 (bs, 6H, C$\underline{H}_3$), 1.9 (bs, 6H, C$\underline{H}_3$). δ_C (75MHz, d$_6$-DMSO) 170.8 ($\underline{C}$-S), 138.0 (Ar$\underline{C}$), 130.5 (Ar$\underline{C}$), 128.1 (Ar$\underline{C}$), 127.6 (Ar$\underline{C}$), 48.7 ($\underline{C}H_2$), 31.8 ($\underline{C}H_3$), 14.3 ($\underline{C}H_3$). *m/z* (ES+, MeOH) 156.0, 85%, $(M + 2H)^{2+}$, 311.1, 35% $(M + H)^+$. ν_{max}(Golden Gate)/cm^{-1} 3136 (bs), 1656 (m), 1603 (s).

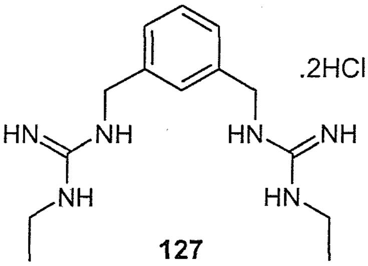
4.2.44 α, α'-Bis-(*N*'-Phenyl-*S*-methyl-thiouronium hydroiodide)-*m*-xylene (126)



126

m-Xylyene di(*N'*-phenylthiourea) (4.07 g, 10 mmol) was suspended in dry methanol (50 ml) and methyl iodide (12 ml, 0.192 mol) was added. The reaction was heated at reflux for 2 hours. The solution was allowed to cool and the solvents were removed *in vacuo* to leave a yellowish gum (6.90 g, 99%). Both NMR spectra poorly resolved. NMR δ_H (300 MHz, d$_6$-DMSO) 6.8 (bs, 14H, Ar$\underline{H}$), 4.2 (s, 4H, C$\underline{H}_2$ under water peak), 2.1 (bs, 3H, C$\underline{H}_3$), 2.0 (bs, 3H, C$\underline{H}_3$). δ_C (75MHz, d$_6$-DMSO) 130.7 (Ar$\underline{C}$), 130.4 (Ar$\underline{C}$), 128.4 (Ar$\underline{C}$), 127.7 (Ar$\underline{C}$), 15.2 ($\underline{C}H_3$). m/z (ES+, MeOH) 435.3, 100% $(M + H)^+$. ν_{max}(Golden Gate)/cm^{-1} 2963 (bs), 1602 (m), 1573 (s).

4.2.45 α, α'-Bis-(*N*'-Ethylguanidinium hydrochloride)-*m*-xylene[62] (127)

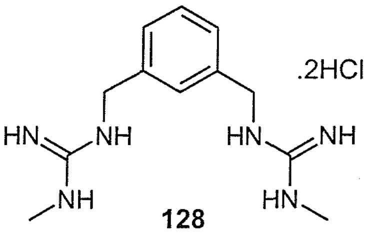


127

α, α'-Bis-(*N'*-Ethyl-*S*-methyl-thiouronium hydroiodide)-*m*-xylene (1.91g, 3.2 mmol) was dissolved in dry methanol (20ml) and placed in a glass ampule. Ammonia gas was bubbled through this solution for ten minutes at 0°C. The clear yellow solution turned colourless. The ampule was then sealed (teflon cap) and heated at 70°C for 7 hours behind a blast shield. After this time the ampule was carefully opened and the pressure was released. Nitrogen gas was bubbled through the solution with gentle heating to drive off the MeSH gas. The solvent was removed *in vacuo* and the white gummy foam was dissolved in water (10ml) and passed through a Dowex 1 x 8 –100 $^{-}$OH anion exchange resin column.

The column was eluted with water until the pH of the washings was near pH 7. The solvent was removed *in vacuo* and the clear oil was passed through an Amberlite column (dry mass = 6 g) eluted with HCl solution (0.001 M, 100 ml). The solvent was removed *in vacuo* to give a hygroscopic foam (0.81 g, 86%). NMR δ_H (300 MHz, D_2O) 7.3 (dd, 1H, J = 7.7 Hz, Ar<u>H</u>), 7.2 (d, 2H, J = 7.7 Hz, Ar<u>H</u>), 7.1 (s, 1H, Ar<u>H</u>), 4.3 (s, 4H, C<u>H</u>$_2$), 3.1 (dd, 4H, J = 7.4 Hz, C<u>H</u>$_2$), 1.0 (t, 6H, J = 7.4 Hz, C<u>H</u>$_3$). δ_C (75MHz, D_2O) 159.1 (<u>C</u>=N), 140.3 (Ar<u>C</u>), 131.9 (Ar<u>C</u>), 128.7 (Ar<u>C</u>), 127.0 (Ar<u>C</u>), 46.8 (<u>C</u>H$_2$), 38.9 (<u>C</u>H$_2$), 16.0 (<u>C</u>H$_3$). m/z (ES+, MeOH) 277.3, 100% $(M + H)^+$. High Resolution m/z (ES+, MeOH) $C_{14}H_{24}N_6$ (M) Calculated 276.3838. Found 277.2145, $(M + H)^+$, 553.4230 $(2M + H)^+$. ν_{max}(Golden Gate)/cm^{-1} 3256 (bs), 3145 (bs), 1625 (bs).

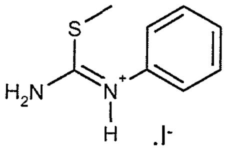
4.2.46 *m*-Xylyene di(*N*'-methyl guanidinium) dihydrochloride (128)



128

m-Xylyene di(*S*-methyl-*N*'-methylthiouronium) dihydroiodide (3.61 g, 6.35 mmol) was dissolved in dry methanol (50 ml) in a glass ampule. Ammonia gas was bubbled through the solution at 0°C for 10 mins after which time the ampule was sealed with a teflon tap and heated with stirring at 70°C behind a blast shield. The ampule was allowed to cool to room temperature and was carefully opened. The solution was flushed with nitrogen gas for 30 mins, then evaporated to dryness to leave a clear foam. This was dissolved in water (10 ml) and passed through a Dowex 1 × 8 $^-$OH column (10 g dry mass). The column was eluted until the washings were pH 7. The washings were combined and concentrated *in vacuo*. The remaining clear oil was dissolved in water (10 ml) and passed through an Amberlite column (5 g dry mass) and eluted with HCl solution (0.001 N, 500 ml). The combined fractions were evaporated to dryness *in vacuo* to leave a clear hygroscopic foam (0.30 g, 15%). NMR δ_H (300 MHz, D_2O) 7.2 (t, 1H, J = 7.7 Hz, Ar<u>H</u>), 7.1 (d, 2H, J = 7.7 Hz, Ar<u>H</u>), 7.0 (s, 1H, Ar<u>H</u>), 4.2 (s, 4H, C<u>H</u>$_2$), 2.6 (s, 6H, C<u>H</u>$_3$). δ_C (75MHz, D_2O) 161.2 (<u>C</u>=N), 141.0 (Ar<u>C</u>), 131.7 (Ar<u>C</u>), 128.4 (Ar<u>C</u>), 127.3 (Ar<u>C</u>), 47.0 (<u>C</u>H$_2$), 30.2 (<u>C</u>H$_3$). m/z (ES+, MeOH) 125.0, 80% $(M + 2H)^{2+}$, 249.1, 35% $(M + H)^+$. High Resolution m/z (ES+, MeCN) $C_{12}H_{20}N_6$ (M) Calculated 249.332. Found 250.1660 $(M + H)^+$. ν_{max}(Golden Gate)/cm^{-1} 3262 (bs), 3156 (bs), 1630 (bs).

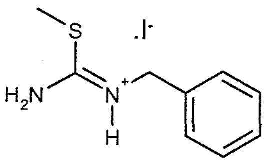
4.2.47 *N'*-Phenyl Methyl Carbamimidothioate Hydroiodide[90] (130)



130

N-Phenyl thiourea (1g, 6.6 mmol) was dissolved in methanol (100ml) and methyl iodide (0.93g, 6.6 mmol) was added in one portion. The reaction was sealed in a glass ampule and stirred at room temperature for one day. The solvent was removed *in vacuo* to give a yellow solid (1.9g, 98%). mp 139 - 142°C. (lit.[90] 145 - 147°C). NMR δ_H (300 MHz, d_6-DMSO) 9.4 (bs, 1H, N<u>H</u>), 7.5 (t, 2H, J = 7.7 Hz, Ar<u>H</u>), 7.4 (t, 1H, J = 7.7 Hz, Ar<u>H</u>), 7.3 (d, 2H, J = 7.7 Hz, Ar<u>H</u>), 2.7 (bs, 3H, C<u>H</u>$_3$). δ_C (75MHz, d_6-DMSO) 170.3 (<u>C</u>=S), 135.8 (Ar<u>C</u>), 130.8 (Ar<u>C</u>), 129.1 (Ar<u>C</u>), 126.4 (Ar<u>C</u>), 14.1 (<u>C</u>H$_3$). m/z (ES+, MeOH) 167.0,100% $(M + H)^+$. ν_{max}(Golden Gate)/cm^{-1} 3252 (m), 2973 (m), 2682 (m), 1619 (s), 1591 (s).

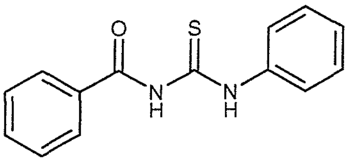
4.2.48 *N'*-Benzyl Methyl Carbamimidothioate Hydroiodide[122] (131)



131

N-Benzyl thiourea (1.5 g, 9 mmol) was dissolved in methanol (100 ml) and methyl iodide (1.92 g, 13.5 mmol) was added in one portion. The reaction was stirred in a sealed ampule overnight. The solvent was removed *in vacuo* to leave a yellow solid (2.48 g, 90%). mp 95 - 97°C. (lit.[122] 103 – 104°C (EtOH)). NMR δ_H (300 MHz, d_6-DMSO) 9.4 (bs, 1H, N<u>H</u>), 7.4 (t, 2H, J = 6.3 Hz, Ar<u>H</u>), 7.3 (d, 2H, J = 6.3 Hz, Ar<u>H</u>), 7.3 (t, 1H, Ar<u>H</u> covered by 2H doublet), 4.6 (bs, 2H, C<u>H</u>$_2$), 2.7 (s, 3H, C<u>H</u>$_3$). δ_C (75MHz, d_6-DMSO) 168.9 (<u>C</u>=S), 136.1 (Ar<u>C</u>), 129.5 (Ar<u>C</u>), 128.2 (Ar<u>C</u>), 128.1 (Ar<u>C</u>), 46.8 (<u>C</u>H$_2$), 13.9 (<u>C</u>H$_3$). m/z (ES+, MeOH) 181.0, 100% $(M + H)^+$. ν_{max}(Golden Gate)/cm^{-1} 3275 (m), 3176 (w), 3115 (m), 3088 (m), 3026 (s), 1633 (s).

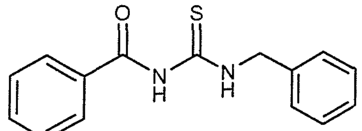
4.2.49 *N*-Phenyl-*N'*-benzoyl-thiourea[90] (133)



133

Benzoyl chloride (4.92 g, 0.035 mol) was dissolved in dry acetone (60ml). Ammonium thiocyanate (2.66 g, 0.035 mol) was suspended in dry acetone (40 ml) and added to the benzoyl chloride solution. The mixture was heated at reflux for two hours, after which time tlc (eluent = 5% MeOH/DCM) showed that the reaction had gone to completion. Upon cooling to room temperature, a white precipitate appeared and was filtered off. Aniline (3.26 g, 0.035 mol) was added quickly to the filtrate, a solution of benzoylisothiocyanate. The mixture was heated at reflux and monitored by tlc (eluent = 5% MeOH/DCM). The reaction was complete after about thirty minutes. The solution was filtered warm, then the filtrate was cooled to give the product as needle crystals. These were filtered off, and a second crop was collected in the same manner. Both crops were washed with a small amount of water/ acetone (50/ 50) (7.35 g, 82%). mp 143 - 144°C. (lit.[90] 147.5 – 148.5°C (IPA)). NMR δ_H (300 MHz, CDCl$_3$) 12.6 (bs, 1H, NH), 9.1 (bs, 1H, NH), 7.9 (d, 2H, J = 7.0 Hz, ArH), 7.7 (d, 2H, J = 8.5 Hz, ArH), 7.7 (t, 1H, J = 7.0 Hz, ArH), 7.6 (t, 2H, J = 8.5 Hz, ArH), 7.4 (t, 2H, J = 7.0 Hz, ArH), 7.3 (t, 1H J = 8.5 Hz, ArH). δ_C (75MHz, CDCl$_3$) 178.5 (C=O), 167.1 (C=S), 137.8 (ArC), 133.9 (ArC), 131.8 (ArC), 129.4 (ArC), 129.1 (ArC), 127.7 (ArC), 127.1 (ArC), 124.3 (ArC). m/z (ES+, MeCN) 153.0, 100% (M + 2Na)$^{2+}$, 257.1, 15 % (M + H)$^+$, 512.9, 10% (2M + H)$^+$. ν_{max}(Golden Gate)/cm^{-1} 3244 (w), 2983 (m), 1670 (m), 1599 (s).

4.2.50 *N*-Benzyl-*N*'-benzoyl-thiourea[123] (134)

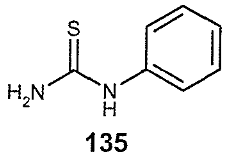


134

Benzylamine (3.75 g, 0.035 mol) was dissolved in acetone (20 ml) and added quickly to a solution of benzoyl isothiocyanate (5.29 g 0.035 mol) in acetone (100 ml). The yellow solution was heated at reflux for two hours, after which time the reaction was complete. The solution was hot filtered, then cooled to produce the product as colourless needle crystals. These were filtered off, and a second crop was recovered in the same manner (5.51 g, 63%). mp 118 - 121°C. (lit.[123] 124 – 124.5°C (IPA)). NMR δ_H (300 MHz, CDCl$_3$) 11.1 (bs, 1H, NH), 9.1 (apparent bs, 1H, NH), 7.8 (d, 2H, J = 7.0 Hz, ArH), 7.6 (t, 1H, J = 7.7 Hz, ArH), 7.5 (t, 2H, J = 7.7 Hz, ArH), 7.4 (m, 5H, ArH), 4.9 (d, 2H, J = 5.5 Hz, CH$_2$). δ_C (75MHz, CDCl$_3$) 180.2 (C=O), 167.0 (C=S), 136.3 (ArC), 133.8 (ArC), 131.9 (ArC), 129.3 (ArC), 129.1 (ArC), 128.1 (ArC), 128.1 (ArC), 127.6 (ArC), 50.0 (CH$_2$). m/z

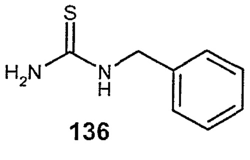
(ES+, MeCN) 271.2, 20% $(M + H)^+$, 541.3, 15% $(2M + H)^+$. ν_{max}(Golden Gate)/cm^{-1} 3257 (m), 3167 (w), 3052 (w), 1672 (s), 1636 (w), 1602 (w).

4.2.51 *N*'-Phenylthiourea[90] (135)


135

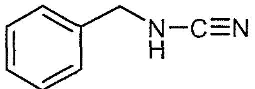
Sodium hydroxide solution (100 ml, 10% w/v) was heated to 80°C with stirring. *N*-benzoyl-*N'*-phenyl thiourea (3.84 g, 0.015 mol) was added in one portion. After stirring for thirty minutes the solution was allowed to cool to room temperature. Hydrochloric acid (2N) was added with stirring until the pH was about 2. The pH was then raised to 8 with sodium bicarbonate solution, and the white solid which formed was filtered off, washed with water and dried *in vacuo* (1.34 g, 59%). mp 147 - 149°C. (lit.[90] 152.5 - 153°C). NMR δ_H (300 MHz, d_6-DMSO) 9.7 (s, 1H, N<u>H</u>), 7.4 (d, 2H, J = 7.4 Hz, Ar<u>H</u>), 7.3 (t, 2H, J = 7.4 Hz, Ar<u>H</u>), 7.1 (t, 1H, J = 7.4 Hz, Ar<u>H</u>). δ_C (75MHz, d_6-DMSO) 181.0 (<u>C</u>=S), 139.1 (Ar<u>C</u>), 128.8 (Ar<u>C</u>), 124.5 (Ar<u>C</u>), 123.1 (Ar<u>C</u>). m/z (ES+, MeCN) 153.0, 100% $(M + H)^+$, 305.2, 10% $(2M + H)^+$. ν_{max}(Golden Gate)/cm^{-1} 3420 (s), 3267 (w), 3167 (m), 3002 (w), 1608 (s).

4.2.52 *N*'-Benzylthiourea[124] (136)


136

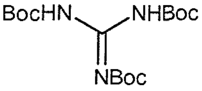
Potassium carbonate (2 g) was suspended in ethanol (100 ml) and *N*-benzoyl-*N'*-benzyl thiourea (4.05 g, 0.015 mol) was added in one portion. The solution was heated at a leisurely reflux for one hour after which time the reaction was complete. The white precipitate was filtered off and washed with cold water, then dried *in vacuo*. A second crop was collected which had crystallised from the filtrate (2.17 g, 87%). mp 164 - 166°C (lit.[124] 164°C (EtOH)). NMR δ_H (300 MHz, d_6-DMSO) 8.0 (bs, 1H, N<u>H</u>), 7.3 (bs, 4H, Ar<u>H</u>), 7.1 (bs, 1H, Ar<u>H</u>), 4.6 (bs, 2H, C<u>H</u>$_2$), 4.3 (bs, 1H, N<u>H</u>). δ_C (75MHz, d_6-DMSO) 183.5 (<u>C</u>=S), 139.4 (Ar<u>C</u>), 128.4 (Ar<u>C</u>), 127.4 (Ar<u>C</u>), 127.0 (Ar<u>C</u>), 47.5 (<u>C</u>H$_2$). m/z (ES+, MeCN) 166.9, 100%, $(M + H)^+$. ν_{max}(Golden Gate)/cm^{-1} 3390 (m), 3242 (m), 3173 (bs), 3027 (w), 1625 (s).

4.2.53 Benzyl cyanamide[125] (137)


137

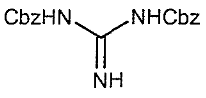
Benzylamine (2.18 ml, 20 mmol) was dissolved in TBME (10 ml) and added dropwise to cyanogen bromide (1.06 g, 10 mmol) dissolved in TBME (10 ml) at 0°C over 10 mins. The reaction was stirred and allowed to warm to room temperature. The white precipitate was filtered off and the solvent was removed from the filtrate *in vacuo*. *n*-Propylamine (0.82 ml, 10 mmol) was dissolved in degassed water (20 ml) and sulfuric acid (2M) was added until pH 3 was reached. Excess n-propylamine was added until the pH was about 10. This solution was then added to the filtrate residue, and the mixture was heated at 80°C under nitrogen with stirring overnight. The precipitate was filtered off after the reaction had been allowed to cool to room temperature and was dried *in vacuo*. mp 128 – 130°C. NMR δ_H (300 MHz, d_6-DMSO) 7.3 (m, 5H, Ar$\underline{H}$), 6.5 (bs, 1H, N$\underline{H}$), 5.3 (bs, 2H, C$\underline{H}_2$).δ_C (75MHz, d_6-DMSO) 145.9 (Ar$\underline{C}$), 137.1 (N$\underline{C}$N), 128.5 (Ar$\underline{C}$), 126.9 (Ar$\underline{C}$), 126.5 (Ar$\underline{C}$), 46.5 ($\underline{C}H_2$). m/z (ES+, MeCN) 397.2, 100% $(3M + H)^+$. ν_{max}(Golden Gate)/cm^{-1} 3381 (w), 3032 (w), 2918 (w), 2164 (w), 1655 (w), 1597 (s).

4.2.54 *N*, *N*', *N*''-Tri-BOC guanidine[126] (140)


140

Potassium hydroxide pellets (2.81 g, 50 mmol) and sodium carbonate (5.3 g, 50 mmol) were finely ground in a pestle and mortar and then placed in a three-neck round bottomed flask equipped with a stirrer and condenser. DMSO (50 ml) was added, and the solution was stirred for five minutes at room temperature. Guanidine hydrochloride (4.78 g, 50 mmol) was added, and the reaction was stirred for five minutes. Di-*tert*-butyl dicarbonate (51.7 g, 225 mmol) was added and the mixture was stirred at 40°C for sixty hours. The reaction was allowed to cool to room temperature and was then poured onto water (1 L). The white precipitate was filtered off, washed with water, and dried *in vacuo*. The resultant dry white solid was recrystallised from acetonitrile to give the product as colourless needles (7.28 g, 41%). mp >250°C. (lit.[126] 147 - 150°C). NMR δ_H (300 MHz, $CDCl_3$) 1.46 (s, 27H, C$\underline{H}_3$). NMR δ_H (300 MHz, $CDCl_3$) 152.6 ($\underline{C}$=O), 28.0 ($\underline{C}H_3$). m/z (ES+, MeCN) 360.3, 50% $(M + H)^+$, 382.2, 20% $(M + Na)^+$, 398.2, 10% $(M + K)^+$, 719.5, 10% $(2M + H)^+$, 741.5, 100% $(2M + Na)^+$, 757.4, 10% $(2M + K)^+$. ν_{max}(Golden Gate)/cm^{-1} 3288 (w), 2982 (m), 2936 (w), 1779 (s), 1716 (s), 1638 (s). Crystal structure collected and solved by standard methods, hexagonal system, space group P6(3)/m, R1 = 4.9%.

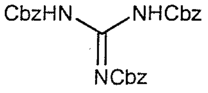
4.2.55 *N, N'*-Di-CBZ guanidine[126] (141)



141

DCM (80 ml) was added to a solution of guanidine hydrochloride (3.82 g, 40 mmol) and sodium hydroxide (8 g, 0.2 mol) in water (40 ml). The resulting mixture was cooled to 0°C. Benzyl chloroformate (17.1 ml, 120 mmol) was added dropwise with vigourous stirring over 45 minutes. After completion of the addition stirring was continued at 0°C for twenty hours, and the reaction was then allowed to warm to room temperature. The mixture was diluted with DCM (100 ml), the layers were separated, and the aqueous layer was extracted with DCM (100 ml). The extracts were combined, washed with water, and dried with $MgSO_4$. Concentration *in vacuo* yielded a crude product that was recrystallised from methanol to give the product as white plate crystals (7.86 g, 60%). mp 156 – 158°C. (lit.[126] 149 - 150°C). NMR δ_H (300 MHz, d_6-DMSO) 10.9 (bs, 1H, N$\underline{H}$), 8.7 (bs, 2H, N$\underline{H}$), 7.4 – 7.3 (m, 10H, C$\underline{H}$), 5.1 (s, 4H, C$\underline{H}_2$). δ_C (75MHz, d_6-DMSO) 160.0 ($\underline{C}$=N), 158.9 ($\underline{C}$=O), 136.5 ($\underline{C}$H), 128.5 ($\underline{C}$H), 128.1 ($\underline{C}$H), 127.9 ($\underline{C}$H), 66.3 ($\underline{C}H_2$). m/z (ES+, MeCN) 328.2, 50% $(M + H)^+$, 350.2, 20% $(M + Na)^+$, 655.5, 80% $(2M + H)^+$, 677.4, 100% $(2M + Na)^+$. ν_{max}(Golden Gate)/cm^{-1} 3396 (m), 3229 (m), 3032 (w), 2953 (w), 1733 (m), 1680 (w), 1654 (m), 1618 (s).

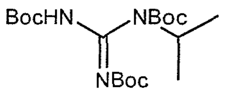
4.2.56 *N, N', N''*-Tri-CBZ-guanidine[126] (142)



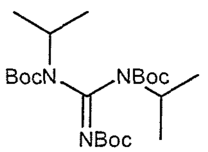
142

Sodium hydride (400 mg, in mineral oil) was added in small portions to a suspension of *N, N'*-Di-CBZ guanidine (1.65 g, 5 mmol) in dry and oxygen-free THF (20 ml) at -45°C under nitrogen. After complete addition, the reaction was stirred for one hour at -45°C. Benzyl chloroformate (0.82 ml, 5 mmol) was added, and the reaction was allowed to warm to room temperature and was stirred overnight. The solvent was removed *in vacuo* and the residue was dissolved in a mixture of DCM (50 ml) and water (25 ml). The phases were separated and the aqueous layer was extracted with DCM (2 × 50 ml). The extracts were combined, washed with aq. hydrochloric acid (1N) and water, and dried ($MgSO_4$). The solvent was removed *in vacuo* to leave the crude product which was purified by column chromatography (eluent = DCM/ Diethyl ether, 98:2). The product was obtained as a white solid (2.14 g, 93%). mp 99 - 102°C (lit.[126] 111 - 112°C). NMR δ_H (300 MHz, $CDCl_3$) 10.9 (bs, 2H, N$\underline{H}$), 7.3 (s, 10H, Ar$\underline{H}$), 5.1 (s, 6H, C$\underline{H}_2$). δ_C (75MHz, $CDCl_3$) 152.5 ($\underline{C}$=O), 128.8 (Ar$\underline{C}$), 128.5 (Ar$\underline{C}$), 68.6 ($\underline{C}H_2$). m/z (ES+, MeCN) 462.1, 20% $(M + H)^+$. ν_{max}(Golden Gate)/cm^{-1} 3256 (w), 3037 (w), 1788 (s), 1729 (s), 1637 (s), 1626 (s).

4.2.57 *N, N'*-DiBOC-*N''*-BOC-(*s*-propyl) guanidine[126] (143/ 144)



143

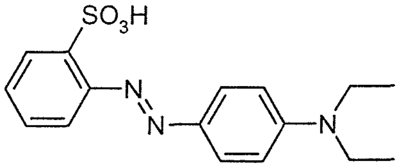


144

A solution of isopropylalcohol (0.14 ml, 1.84 mmol), phenyl phosphine (0.73 g, 2.8 mmol) and *N, N', N''*-tri-BOC guanidine (1 g, 2.8 mmol) in dry THF (40 ml) was cooled to -5°C under nitrogen. Diethylazodicarboxylate (0.44 ml, 2.8 mmol) was added dropwise at a rate such that the reaction mixture was completely colourless before each addition. The mixture was heated at reflux overnight. The reaction was allowed to cool to room temperature and then concentrated *in vacuo*. The clear oil that remained was purified by column chromatography (eluent = 1 part EtOAc: 4 parts petroleum ether) to give the product as a colourless oil (1.01 g, 90%). Spectroscopic studies (mass spectroscopy) indicated that the product was a mixture of **143** and **144**. NMR δ_H (300 MHz, $CDCl_3$) 10.5 (bs, 1H, N$\underline{H}$), 1.4 (m, 29H, C$\underline{H}_3$ & C$\underline{H}$), 1.3 (d, 6H, J = 6.7 Hz, C$\underline{H}_3$). δ_C (75MHz, $CDCl_3$) 171.2 ($\underline{C}$=O), 154.5 ($\underline{C}$=N), 152.4 ($\underline{C}$=N), 60.4 ($\underline{C}$H), 28.3 ($\underline{C}H_3$), 28.1 ($\underline{C}H_3$). m/z (ES+, MeCN) 402.2, 30% $(M + H)^+$, 545.3, 100% $(M + TPA + H)^+$, 803.2, 15% $(2M + H)^+$. Also peaks at: 444.3, 15% $(M_1 + H)^+$, 587.3, 80% $(M_1 + TPA + H)^+$ consistent with disubstituted product. ν_{max}(Golden Gate)/cm^{-1} 2977 (m), 2933 (w), 1759 (m), 1720 (s), 1654 (m), 1606 (s).

4.2.58 2-(*p*-(Diethylamino) phenylazo) benzenesulfonic acid[127] (149)

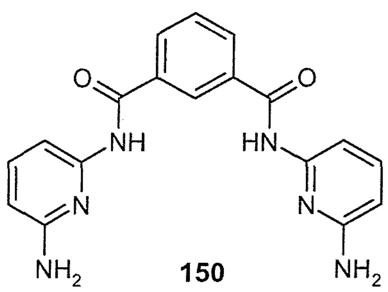
2-Aminobenzenesulfonic acid (10 g, 57.7 mmol) was slurried in water and added to ice (100 ml).



149

Sodium nitrite (4.37 g, 63.4 mmol) was dissolved in water (50 ml) and added dropwise to the suspension, the pH being maintained at 2 and temperature at <5°C. Excess sodium nitrite was added after 2 hours and the reaction was stirred for a further 2 hours. Sulfanilic acid (10% w/v) was added until no HNO_2 remained in solution. The 2-diazonium benzenesulfonic acid solution was added dropwise to *N,N*-diethylaniline (8.25 ml, 51.93 mmol) dissolved in ethanol (50 ml) and water (50 ml) at <5°C. The pH was maintained at 4.5. After addition was complete, the temperature was allowed to rise to room temperature and the solution was concentrated *in vacuo* to about half its volume. The blackish precipitate was filtered off and dried *in vacuo* to give the product (0.54 g, 3%). mp 220 – 222°C (Decomp.) (lit.[127] mp not quoted). NMR δ_H (300 MHz, D_2O) 7.8 (m, 4H, Ar$\underline{H}$), 7.7 (d, 1H, J = 8.1 Hz, Ar$\underline{H}$), 7.5 (t, 1H, J = 8.1 Hz, Ar$\underline{H}$), 7.4 (t, 1H, J = 8.1 Hz, Ar$\underline{H}$), 7.2 (d, 1H, J = 9.2 Hz, Ar$\underline{H}$), 2.0 (bs, 4H, C$\underline{H}_2$), 1.2 (t, 6H, J = 7.4 Hz, C$\underline{H}_3$). m/z (ES+, MeOH) 332.0, 100% $(M - H)^-$. ν_{max}(Golden Gate)/cm^{-1} 3538 (w), 3456 (w), 2947 (w), 1616 (m).

4.2.59 2,6-Bis-(6'-Amino-2'-carboxamidopyridyl) benzene[128] (150)

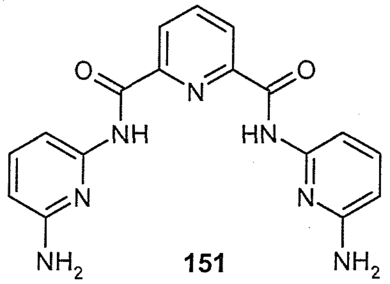


150

2,6-Diaminopyridine (5.46 g, 0.05 mol) was dissolved in dry THF (100 ml), triethylamine (3.48 ml, 0.025 mol) was added and the solution was stirred under nitrogen. Isophthaloyl dichloride (2.03 g, 0.01 mol) dissolved in DCM (50 ml) was added dropwise and the solution was stirred overnight at room temperature. The solvent was removed *in vacuo* and water (50 ml) was added. The resultant suspension was stirred for 1 hour then the precipitate was filtered off, washed with water and dried *in vacuo*. The solid was recrystallised from THF/ petroleum ether (40 – 60) to give a brown solid (2.94 g, 85%). mp 178 – 179°C (lit.[128] 201 – 202°C). NMR δ_H (300 MHz, d_6-DMSO) 10.3 (s, 2H, N$\underline{H}$), 8.5 (s, 1H, Ar$\underline{H}$), 8.1 (t, 2H, J = 7.7 Hz, Ar$\underline{H}$), 7.6 (t, 1H, J = 7.7 Hz, Ar$\underline{H}$), 7.4 (d, 4H, J = 6.6 Hz, Ar$\underline{H}$), 6.3 (t, 2H, J = 7.0 Hz, Ar$\underline{H}$), 5.8 (s, 4H, N$\underline{H}$). δ_C (75MHz, d_6-DMSO) 165.0 ($\underline{C}$=O), 158.7 (Ar$\underline{C}$), 150.4 (Ar$\underline{C}$), 139.1 (Ar$\underline{C}$), 134.3 (Ar$\underline{C}$), 131.3 (Ar$\underline{C}$), 128.9 (Ar$\underline{C}$), 126.7 (Ar$\underline{C}$), 104.3 (Ar$\underline{C}$), 101.9 (Ar$\underline{C}$). m/z (ES+, MeCN) 349.1, 100% (M +

H)$^+$, 697.1, 20% (2M + H)$^+$. ν_{max}(Golden Gate)/cm^{-1} 3452 (w), 3403 (w), 3347 (w), 3220 (w), 1669 (m), 1613 (s).

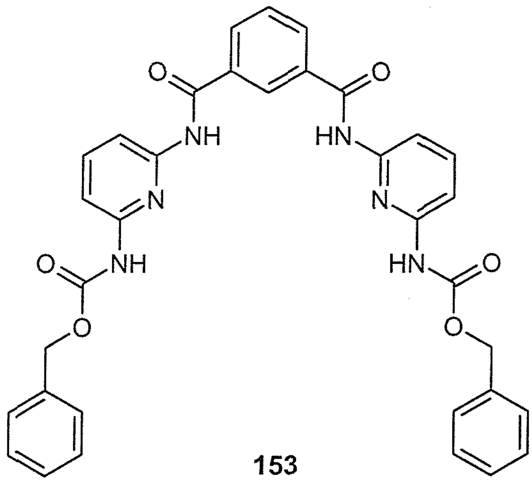
4.2.60 2,6-Bis-(6'-Amino-2'-carboxamidopyridyl) pyridine (151)



151

2,6-Diaminopyridine (5.46 g, 0.05 mol) was dissolved in dry THF (100 ml), triethylamine (3.48 ml, 0.025 mol) was added and the solution was stirred under nitrogen. 2,6-Pyridine diacid dichloride (2.04 g, 0.01 mol) dissolved in DCM (50 ml) was added dropwise and the solution was stirred overnight at room temperature. The solvent was removed *in vacuo* and water (50 ml) was added. The resultant suspension was stirred for 1 hour then the precipitate was filtered off, washed with water and dried *in vacuo*. The solid was recrystallised from THF/ petroleum ether (40 – 60) to give a greenish solid (1.49 g, 43%). mp 224°C. NMR δ_H (300 MHz, d_6-DMSO) 11.0 (s, 2H, N$\underline{H}$), 8.4 (d, 2H, J = 6.6 Hz, Ar$\underline{H}$), 8.2 (t, 1H, J = 6.3 Hz, Ar$\underline{H}$), 7.4 (d, 4H, J = 7.7 Hz, Ar$\underline{H}$), 6.3 (d, 2H, J = 7.7 Hz, Ar$\underline{H}$), 5.9 (s, 4H, N$\underline{H}$). δ_C (75MHz, d_6-DMSO) 162.1 ($\underline{C}$=O), 158.8 (Ar$\underline{C}$), 149.7 (Ar$\underline{C}$), 149.1 (Ar$\underline{C}$), 139.9 (Ar$\underline{C}$), 139.2 (Ar$\underline{C}$), 125.5 (Ar$\underline{C}$), 104.5 (Ar$\underline{C}$), 102.1 (Ar$\underline{C}$). m/z (ES+, MeCN) 350.2, 100% (M + H)$^+$, 699.3, 10% (2M + H)$^+$. High Resolution m/z (ES+, MeCN) $C_{17}H_{15}N_7O_2$ (M) Calculated 349.3516. Found 350.1356 (M + H)$^+$. ν_{max}(Golden Gate)/cm^{-1} 3483 (w), 3363 (w), 3185 (w), 1687 (s), 1623 (s).

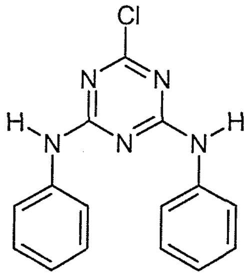
4.2.61 1,3-Bis-(6-[Pyridine-2-carbonyl)-amino]-pyridin-2-yl)-carbamic acid benzyl ester (153)



153

2,6-Bis-(6'Amino-2'-carboxamido pyridyl) benzene (0.52 g, 1.5 mmol) was dissolved in THF (20 ml) and DCM (20 ml). Triethylamine (0.42 ml, 3 mmol) was added followed by benzyl chloroformate (0.43 ml, 3 mmol) at 0°C. The reaction was stirred for 1 hour and allowed to warm to room temperature then heated at reflux overnight. The solvent was removed *in vacuo* and water (10 ml) was added to the residue. The resultant suspension was stirred and sodium hydroxide (2N, 20 ml) was added and stirring was continued for about 1 hour. The solution was extracted with DCM (100ml × 2), the organic layers were combined, dried and evaporated to dryness to leave a white solid. The solid was purified by column chromatography (4% MeOH/ DCM) to give starting material and a less polar product (0.14 g, 15%). mp 83 – 86°C. NMR δ_H (300 MHz, $CDCl_3$) 8.6 (bs, 4H, N$\underline{H}$), 8.4 (s, 1H, Ar$\underline{H}$), 8.0 (t, 4H, J = 6.7 Hz, Ar$\underline{H}$), 7.7 (t, 2H, J = 7.9 Hz, Ar$\underline{H}$), 7.6 (t, 2H, J = 7.9 Hz, Ar$\underline{H}$), 7.5 (t, 4H, J = 7.9 Hz, Ar$\underline{H}$), 7.2 (m, 17H, Ar$\underline{H}$), 6.2 (t, 4H, J = 7.9 Hz, Ar$\underline{H}$), 5.0 (apparent d, 4H, J = 5.5 Hz, C$\underline{H}_2$). δ_C (75MHz, $CDCl_3$) 164.6 ($\underline{C}$=O), 140.6 ($\underline{C}$=O), 140.3 (Ar$\underline{C}$), 135.0 (Ar$\underline{C}$), 131.1 (Ar$\underline{C}$), 131.0 (Ar$\underline{C}$), 129.6 (Ar$\underline{C}$), 128.8 (Ar$\underline{C}$), 127.5 (Ar$\underline{C}$), 127.2 (Ar$\underline{C}$), 125.8 (Ar$\underline{C}$), 105.0 (Ar$\underline{C}$), 103.7 (Ar$\underline{C}$), 103.5 (Ar$\underline{C}$), 102.9 (Ar$\underline{C}$), 46. 3 ($\underline{C}H_2$). m/z (ES+, MeCN) 439.2, 100%. Not consistent with product. ν_{max}(Golden Gate)/cm^{-1} 3353 (w), 1666 (m), 1608 (s). Elemental analysis not satisfactory (Found: C, 67.70; H, 5.08; N, 16.55. Calculated: C, 66.23; H, 4.50; N, 13.62).

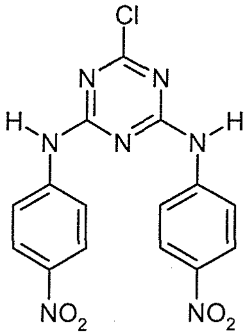
4.2.62 2-Chloro-4,6-dianilino-*s*-triazine[92] (154)



154

To a solution of cyanuric chloride (4.61 g, 0.025 mol) in acetone (50 ml) was added aniline (4.66 g, 0.05 mol) slowly with stirring at a temperature of 0 – 5°C. Stirring was continued for 2 hours while the temperature was allowed to rise to room temperature. Aqueous sodium hydroxide (2 g, 0.05 mol in 20 ml) was then added gradually, and the temperature was raised to 40 – 45°C. The mixture was stirred for a further 2 hours during which time a precipitate formed. This was filtered off, washed with water and then dried to give a white powder (6.5 g, 87%). mp 198 - 201°C (lit.[92] 199 - 201°C). NMR δ_H (300 MHz, d_6-DMSO) 10.3 (s, 2H, N$\underline{H}$), 7.6 (apparent bs, 4H, Ar$\underline{H}$), 7.3 (t, 4H, J = 7.5 Hz, Ar$\underline{H}$), 7.1 (t, 2H, J = 7.4 Hz, Ar$\underline{H}$). δ_C (75MHz, d_6-DMSO) 168.3 ($\underline{C}$=N), 164.0 ($\underline{C}$=N), 138.3 ($\underline{C}$=N), 128.6 (Ar$\underline{C}$), 123.7 (Ar$\underline{C}$), 121.2 (Ar$\underline{C}$). *m/z* (ES+, MeCN) 298.3, 100% (^{35}Cl M + H)$^+$, 300.4, 33% (^{37}Cl M + H)$^+$. ν_{max}(Golden Gate)/cm^{-1} 3254 (w), 3062 (w), 1686 (w), 1613 (m), 1600 (m).

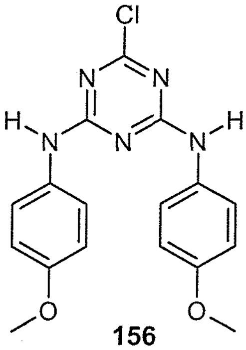
4.2.63 2-Chloro-4,6-di-*p*-nitroanilino-*s*-triazine[92] (155)



155

To a solution of *p*-nitroaniline (13.91 g, 0.1 mol) in acetone (50 ml) was added cyanuric chloride (4.61 g, 0.025 mol) in acetone (25 ml). The mixture was stirred at 40°C for 16 hours, left to cool, and then water (150 ml) was added. The resultant precipitate was filtered off. This precipitate was washed with aqueous acetic acid (50% v/v) until the filtrate was colourless, allowed to dry, and then recrystallised from acetone. The product was a bright yellow powder (8.42 g, 86%). mp > 360°C (lit.[92] 304°C decomp.). NMR δ_H (300 MHz, d_6-DMSO) 10.3 (s, 2H, N$\underline{H}$), 8.2 (d, 4H, J = 9.3 Hz, Ar$\underline{H}$), 8.1 (d, 4H, J = 9.3 Hz, Ar$\underline{H}$). m/z (ES+, MeCN) 127.1, 98%, 140.1, 60%, 153.1, (100%) No peaks consistent with product or starting materials. ν_{max}(Golden Gate)/cm^{-1} 3317 (m), 1624 (s), 1588 (m).

4.2.64 2-Chloro-4,6-di-*p*-anisidino-*s*-triazine [129] (156)

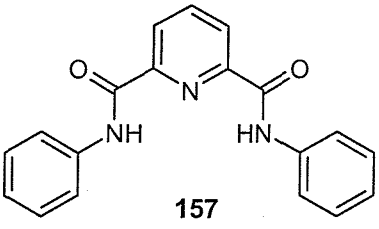


156

To a solution of cyanuric chloride (5 g, 0.027 mol) in acetone (50 ml) was added *p*-anisidine (6.67 g, 0.054 mol) in acetone (50 ml) dropwise over 20 minutes at 0 - 5°C. The mixture was allowed to reach room temperature, then aqueous sodium carbonate (3.7 g, 0.03 mol) was added, and the resulting mixture was heated at 40 - 45°C with stirring for 2 hours. The resulting precipitate was filtered off, washed with water (100 ml) and methanol (100 ml) and recrystallised from toluene. A creamy brown solid resulted (5.18 g, 54%). mp 197 - 198°C (toluene) (lit.[129] 202 - 203°C (benzene)). NMR δ_H (300 MHz, d_6-DMSO) 10.1 (s, 2H, N$\underline{H}$), 7.5 (d, 4H, J = 8.5 Hz, Ar$\underline{H}$), 6.9 (d, 4H, J = 8.5 Hz, Ar$\underline{H}$), 3.7 (s, 6H, C$\underline{H}_3$). δ_C (75MHz, d_6-DMSO) 163.8 ($\underline{C}$=N), 155.7 ($\underline{C}$=N), 131.3 (Ar$\underline{C}$), 122.8 (Ar$\underline{C}$), 122.2 (Ar$\underline{C}$), 113.8 (Ar$\underline{C}$), 55.3 ($\underline{C}H_2$). *m/z* (ES+, MeCN) 358.3, 100% (^{35}Cl M + H)$^+$, 360.3, 33% (^{37}Cl M + H)$^+$. ν_{max}(Golden Gate)/cm^{-1} 3248 (w), 3005 (w), 2834 (w), 1607 (m), 1574 (s).

A sample of the product was recrystallised from toluene a second time to give a pure white solid. The analytical data for this sample matched that of the bulk product.

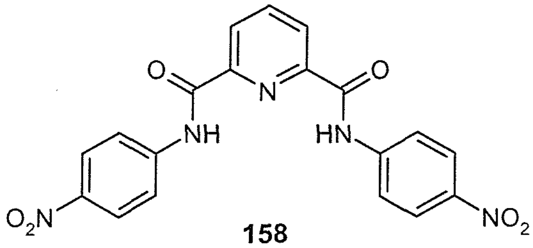
4.2.65 *N,N'*-Diphenyl Pyridine-2,6-dicarboxamide[130] (157)



157

To pyridine-2,6-dicarbonyl dichloride (4 g, 0.02 mol) dissolved in acetonitrile (75 ml) was added aniline (3.75 g, 0.042 mol) in acetonitrile (75 ml). The mixture was heated at reflux for 1 hour. The resultant precipitate was filtered off and suspended in DCM (100 ml). This mixture was washed with aqueous 10% potassium hydroxide (100 ml), and the white solid which remained suspended in the DCM was filtered off and dried (5.17 g, 91%). mp 281 - 283°C (lit.[130] 274°C). NMR δ_H (300 MHz, d_6-DMSO) 11.1 (s, 2H, N$\underline{H}$), 8.4 (d, 2H, J = 6.6 Hz, Ar$\underline{H}$), 8.3 (t, 1H, J = 6.6 Hz, Ar$\underline{H}$), 7.9 (d, 4H, J = 8.5 Hz, Ar$\underline{H}$), 7.4 (t, 4H, J = 8.5 Hz, Ar$\underline{H}$), 7.2 (t, 2H, J = 8.5 Hz, Ar$\underline{H}$). δ_C (75MHz, d_6-DMSO) 161.7 ($\underline{C}$=O), 148.9 (Ar$\underline{C}$), 140.1 (Ar$\underline{C}$), 138.1 (Ar$\underline{C}$), 128.9 (Ar$\underline{C}$), 125.4 (Ar$\underline{C}$), 124.5 (Ar$\underline{C}$), 121.2 (Ar$\underline{C}$). m/z (ES+, MeCN) 317.9, 25% $(M + H)^+$, 339.8, 10% $(M + Na)^+$, 656.6, 60% $(2M + Na)^+$. ν_{max}(Golden Gate)/cm^{-1} 3264 (w), 1672 (m), 1655 (m).

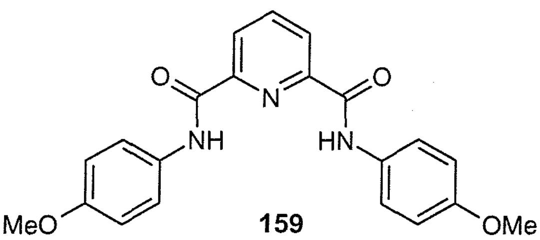
4.2.66 *N,N'*-Di(*p*-Nitro-phenyl)-Pyridine-2,6-dicarboxamide[131] (158)



158

p-Nitroaniline (1.38 g, 0.01 mol) was dissolved in DCM (25 ml) and to the resulting solution triethylamine (1.21 g, 0.01 mol) was added. Pyridine-2,6-dicarbonyl dichloride (1 g, 0.005 mol) was added dropwise, and the mixture was heated at reflux with stirring for 48 hours. The resulting cream/ brown precipitate was filtered off and washed with DCM (50 ml) and dried *in vacuo* to give a cream/brown solid. The residue was recrystallised from acetone to give a fluffy cream solid (0.11 g, 5.4%). mp 245°C decomp. (lit.[131] mp not quoted) NMR δ_H (300 MHz, d_6-DMSO) 11.5 (s, 2H, N$\underline{H}$), 8.5 (d, 2H, J = 7.0 Hz, Ar$\underline{H}$), 8.4 (d, 4H, J = 9.2 Hz, Ar$\underline{H}$), 8.4 covered by doublet (t, 1H, J = 7.0 Hz, Ar$\underline{H}$), 8.3 (d, 4H, J = 9.2 Hz, Ar$\underline{H}$). δ_C (75MHz, d_6-DMSO) 162.7 ($\underline{C}$=O), 148.6 (Ar$\underline{C}$), 144.7 (Ar$\underline{C}$), 142.9 (Ar$\underline{C}$), 140.2 (Ar$\underline{C}$), 126.3 (Ar$\underline{C}$), 124.8 (Ar$\underline{C}$), 120.7 (Ar$\underline{C}$). m/z (ES+, MeCN) 150.1, 100% No peak consistent with starting materials or product. ν_{max}(Golden Gate)/cm^{-1} 3135 (w), 1687 (m), 1609 (m), 1595 (s).

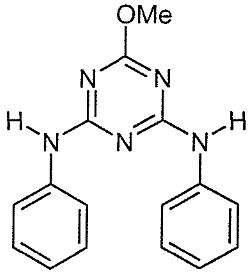
4.2.67 *N,N'*-Di(*p*-methoxy-phenyl)-Pyridine-2,6-dicarboxamide[132] (159)



159

To a solution of *p*-anisidine (1.21 g, 0.01 mol) in DCM (25 ml) was added triethylamine (1.01 g, 0.01 mol). A solution of pyridine-2,6-dicarbonyl dichloride (1 g, 0.005 mol) in DCM (25 ml) was added to the mixture dropwise over fifteen minutes. The resulting mixture was stirred for 8 hours and the resulting precipitate was filtered off to leave a white solid (1.68 g, 89%). mp 290 - 293°C. (lit.[132] 281°C). NMR δ_H (300 MHz, d_6-DMSO) 10.9 (s, 2H, NH), 8.4 (d, 2H, J = 6.6 Hz, ArH), 8.3 (t, 1H, J = 6.6 Hz, ArH), 7.8 (d, 4H, J = 8.8 Hz, ArH), 7.0 (d, 4H, J = 8.8 Hz, ArH), 3.8 (s, 6H, CH_3). δ_C (75MHz, d_6-DMSO) 161.4 (C=O), 156.2 (C=N), 149.0 (C=N), 140.0 (ArC), 131.1 (ArC), 125.1 (ArC), 123.0 (ArC), 114.0 (ArC), 55.3 (CH_3). *m/z* (ES+, MeCN) 378.3, 30% $(M + H)^+$, 399.8, 10% $(M + Na)^+$, 777.1, 35% $(2M + Na)^+$. ν_{max}(Golden Gate)/cm^{-1} 3277 (w), 1666 (m), 1650 (s), 1597 (m).

4.2.68 2-Methoxy-4,6-dianilino-*s*-triazine[133] (160)



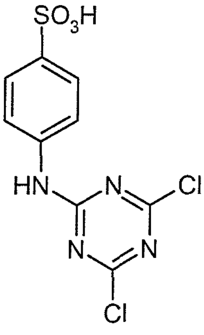
160

2-Chloro-4,6-dianilino-s-triazine (1 g, 0.003 mol) was suspended in methanol (25 ml) and the mixture was heated at reflux for 24 hours. The solvent was then evaporated, the residue was suspended in DCM (25 ml) and the mixture was washed with aqueous potassium hydroxide solution (10%) twice. The white suspension in the DCM layer was then filtered off and dried *in vacuo* to give the product as a white solid (0.7g, 71%). mp 148 - 151°C. (lit.[133] 166°C (ethanol)). NMR δ_H (300 MHz, d_6-DMSO) 9.7 (bs, 2H, NH), 7.8 (bs, 2H, ArH), 7.7 (bs, 2H, ArH), 7.3 (t, 4H, J = 8.5 Hz, ArH), 7.1 (t, 1H, J = 7.4 Hz, ArH), 7.0 (t, 1H, J = 7.4 Hz, ArH), 3.4 (s, 3H, CH_3). δ_C (75MHz, d_6-DMSO) 170.7 (C=N), 165.3 (C=N), 128.7 (ArC), 128.5 (ArC), 122.6 (ArC), 120.5 (ArC), 54.0

(<u>C</u>H_3). m/z (ES+, MeCN) 294.2, 100% $(M + H)^+$. ν_{max}(Golden Gate)/cm^{-1} 3252 (w), 3057 (w), 1613 (m), 1602 (m).

Single crystal X-ray structure solved, Monoclinic system, space group P2 (1)/c, R1 = 5.7%.

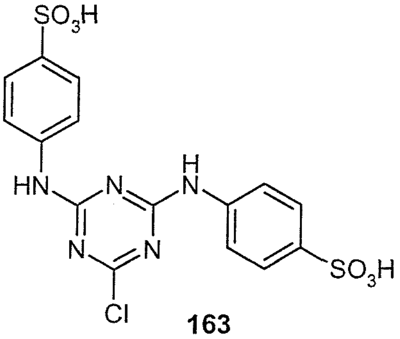
4.2.69 1,3-Dichloro-5-sulfanilino-*s*-triazine (162)



162

Sulfanilic acid (8.42 g, 48.6 mmol) was dissolved in water (100 ml) and concentrated aqueous sodium hydroxide was added until pH 6 was reached. Cyanuric chloride (10 g, 54 mmol) was dissolved in acetone (100 ml) and added to vigourously stirred ice (100 ml). The sulfanilic acid solution was added dropwise to the cyanuric chloride solution , the pH maintained between 5.5 and 6.5 and the temperature kept below 5°C. After all the sulfanilic acid solution had been added, the reaction was stirred and the pH raised to 7.5 when the solution reached room temperature. A grey/ white precipitate had appeared. The pH was then adjusted to pH 6. About half the solution was filtered and the precipitate was washed with methylated spirit and dried *in vacuo* (7.4 g, 80%). mp >250°C. NMR δ_H (300 MHz, d$_6$-DMSO) 11.2 (s, 1H, N<u>H</u>), 7.6 (d, 2H, J = 8.8 Hz, Ar<u>H</u>), 7.5 (d, 2H, J = 8.8 Hz, Ar<u>H</u>). δ_C (75MHz, d$_6$-DMSO) 169.8 (<u>C</u>=N), 168.9 (<u>C</u>=N), 163.8 (<u>C</u>=N), 144.2 (Ar<u>C</u>), 137.6 (Ar<u>C</u>), 126.3 (Ar<u>C</u>), 120.8 (Ar<u>C</u>). m/z (ES-, H_2O) 159.0, 70% $(M – 2H)^{2-}$, 319.1, 100% $(M - H)^-$, 321.1, 67% $(M – H)^-$, 323.1, 13% $(M – H)^-$. ν_{max}(Golden Gate)/cm^{-1} 3467.99 (bm), 3399 (bm), 3269 (w), 3134 (w), 1649 (w), 1618 (s), 1560 (s).

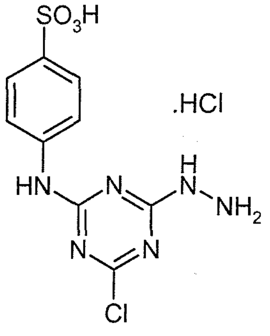
4.2.70 1,3-Dichloro-5-sulfanilino-*s*-triazine (163)



163

1,3-Dichloro-5-sulfanilino-s-triazine (10 g, 0.029 mol) was suspended in water, adjusted to pH 6 (NaOH, 2N) and gently heated whilst sulfanilic acid (4.21g, 0.024mol) dissolved in water (100 ml) at pH 6 was added dropwise. The suspension disappeared to leave a dark blue solution. The reaction was stirred at room temperature overnight at pH 6. HPLC and TLC showed reaction had occurred but some starting material was still present, so excess sulfanilic acid was added. After about one hour at 40°C, HPLC showed ~96% product so the solution was salted with sodium chloride until a blue/ grey precipitate appeared. This was filtered off, washed with methylated spirit and dried *in vacuo* to give a grey solid (11.8 g, 81%). mp >250°C. NMR δ_H (300 MHz, d_6-DMSO) 10.4 (bs, 2H, N<u>H</u>), 7.6 (apparent bs, 8H, Ar<u>H</u>). δ_C (75MHz, d_6-DMSO) 168.0 (<u>C</u>=N), 163.9 (<u>C</u>=N), 142.9 (Ar<u>C</u>), 138.8 (Ar<u>C</u>), 126.1 (Ar<u>C</u>), 120.0 (Ar<u>C</u>). m/z (ES-, H_2O) 227.5, 50% $(M - 2H)^{2-}$, 228.6, 15% $(M – 2H)^{2-}$. ν_{max}(Golden Gate)/cm^{-1} 3461 (bm), 3269 (m), 1610 (m), 1567 (s). Found: C, 28.23; H, 3.42; N, 11.21; S, 10.28. Calculated: C, 39.35; H, 2.64; N, 15.30; S, 14.00.

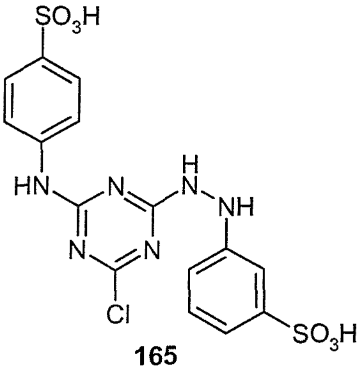
4.2.71 1-Chloro-3-hydrazino-5-sulfanilino-*s*-triazine (164)



164

1,3-Dichloro-5-sulfanilino-s-triazine (2 g, 4.5 mmol) was suspended in water (100 ml), cooled to 0°C and adjusted to pH 9. Hydrazine monohydrate (0.22 g, 4.5 mmol) was dissolved in water (20ml) and added dropwise to the former solution. The pH was maintained at 9. Reaction was fast, and after twenty minutes the dark grey solution was adjusted to pH 1.5 and a precipitate appeared. The mixture was stirred for about one hour, and then the precipitate was filtered off and dried *in vacuo* (0.75 g, 53%). mp >250°C. NMR δ_H (300 MHz, d_6-DMSO) 10.6 (bs, 1H N<u>H</u>), 7.7 (m, 2H, Ar<u>H</u>), 7.5 (d, 2H, J = 8.5 Hz, Ar<u>H</u>). δ_C (75MHz, d_6-DMSO) 165.6 (<u>C</u>=N), 163.3 (<u>C</u>=N), 150.0 (<u>C</u>=N), 142.8 (Ar<u>C</u>), 126.2 (Ar<u>C</u>), 123.0 (Ar<u>C</u>), 120.3 (Ar<u>C</u>). m/z (ES+, H_2O, 2 drops 2N HCl) 315.1, 100% $(M – H)^{-}$, 317.1, 40% $(M – H)^{-}$. ν_{max}(Golden Gate)/cm^{-1} 2364 (w), 1754 (m), 1614 (s), 1556 (s). Found: C, 31.06; H, 3.40; N, 23.72. Calculated: C, 28.81; H, 2.42; N, 22.39.

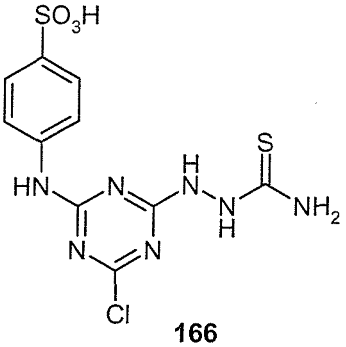
4.2.72 1-Chloro-3-(phenylhydrazino-*m*-sulfonic acid)-5-sulfanilino-*s*-triazine (165)



165

1,3-Dichloro-5-sulfanilino-s-triazine (2 g, 4.5 mmol) was suspended in water and adjusted to pH 6. Phenyl hydrazine-*m*-sulfonic acid (0.84 g, 4.5 mmol) was dissolved in water (10 ml) and adjusted to pH 6 then added dropwise at 40°C to the former solution. The solution was stirred for 2 hours. Sodium chloride (5% w/ v) was added to the solution. A grey/ white precipitate was filtered off. Tlc indicated that this was unreacted starting material. Sodium chloride (10% w/ v) was added to the solution. The white/ brown precipitate that formed was filtered off and dried *in vacuo*. TLC suggested that this was a mixture of product and starting material. Sodium chloride (10% w/ v) was added to the solution and it was stirred for 1 hour. A precipitate was removed by filtration. TLC suggested this was the product. The grey/ blue solid was dried *in vacuo* (1.81 g, 85%). mp >250°C. NMR δ_H (300 MHz, d_6-DMSO) 10.3 (bs, 1H, N$\underline{H}$), 9.9 (bs, 1H, N$\underline{H}$), 7.5 (m, 6H, Ar$\underline{H}$), 7.1 (m, 2H, Ar$\underline{H}$), 6.7 (apparent m, 1H, N$\underline{H}$). δ_C (75MHz, d_6-DMSO) 168.9 ($\underline{C}$=N), 168.1 ($\underline{C}$=N), 167.6 ($\underline{C}$=N), 148.4 (Ar$\underline{C}$), 148.2 (Ar$\underline{C}$), 141.9 (Ar$\underline{C}$), 138.9 (Ar$\underline{C}$), 128.3 (Ar$\underline{C}$), 126.1 (Ar$\underline{C}$), 119.0 (Ar$\underline{C}$), 109.4 (Ar$\underline{C}$), impurities at 163.6 ppm, 148.7 ppm, 116.4 ppm. m/z (ES-, H_2O) 156.0, 95% $(M-3H)^{3-}$, 471.0, 10% $(M-H)^-$, 473.1, 5% $(M-H)^-$. ν_{max}(Golden Gate)/cm^{-1} 3287 (bs), 1752 (w), 1604 (s), 1571 (s). Found: C, 19.53; H, 1.51; N, 9.51. Calculated: C, 34.86; H, 2.15; N, 16.25.

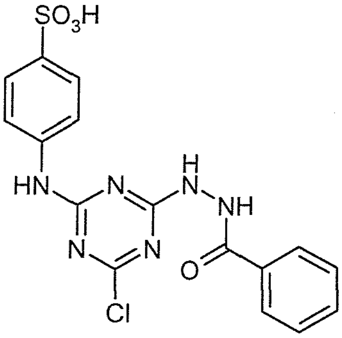
4.2.73 1-Chloro-3-thiosemicarbazido-5-sulfanilino-*s*-triazine (166)



166

1,3-Dichloro-5-sulfanilino-s-triazine (2 g, 4.5 mmol) was suspended in water (25 ml) and stirred at room temperature. Thiosemicarbazide (0.41 g, 4.5 mmol) was added in portions to this and the pH was kept between 5.5 and 6.5. The suspension was heated at 40°C for about one hour. Excess thiosemicarbazide was added and the reaction was stirred at pH 6 and 40°C for a further hour. Sodium chloride was added and the reaction was stirred at RT until a grey/ white precipitate appeared. This was filtered off, washed with methylated spirit and dried *in vacuo* (1.02 g, 60%). mp >250°C. NMR δ_H (300 MHz, d_6-DMSO) 10.4 (bs, 1H, N<u>H</u>), 10.0 (bs, 1H, N<u>H</u>), 9.5 (apparent d, 1H, J = 19.5 Hz, N<u>H</u>), 7.9 (d, 2H, J = 7.9 Hz, N<u>H</u>$_2$), 7.6 (bs, 2H, Ar<u>H</u>), 7.5 (d, 2H, J = 7.9 Hz, Ar<u>H</u>). δ_C (75MHz, d_6-DMSO) 181.9 (<u>C</u>=S), 168.0 (<u>C</u>=N), 163.7 (<u>C</u>=N), 142.1 (Ar<u>C</u>), 139.1 (Ar<u>C</u>), 126.1 (Ar<u>C</u>), 118.9 (Ar<u>C</u>). m/z (ES-, H_2O) 374, 100% $(M - H)^-$. Second spectrum 375, 100% $(M – H)^-$. ν_{max}(Golden Gate)/cm^{-1} 3267 (bs), 1618 (s), 1561 (s). Found: C, 19.34; H, 1.88; N, 15.77. Calculated: C, 30.19; H, 2.28; N, 24.64.

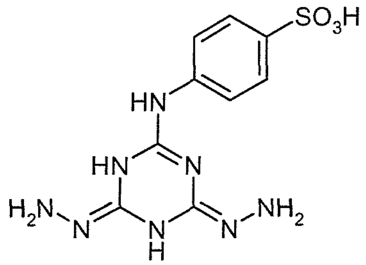
4.2.74 1-Chloro-3-benzoichydrazido-5-sulfanilino-*s*-triazine (167)



167

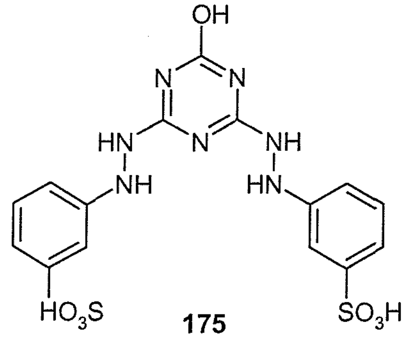
1,3-Dichloro-5-sulfanilino-s-triazine (2 g, 4.5 mmol) was suspended in water, adjusted to pH 6 and heated to 40°C. Benzoic hydrazide (0.61 g, 4.5 mmol) was dissolved in a 1:1 ethanol/ water mixture (20 ml) and added dropwise to the former solution. The solution was stirred for 2 hours. The solution was allowed to cool to RT and sodium chloride (6% w/ v) was added with stirring. A blue/ white precipitate appeared and was filtered off. The precipitate was washed with methylated spirit and dried *in vacuo*. A second crop was recovered in a similar manner (1.53 g, 81%). mp >250°C. NMR δ_H (300 MHz, d_6-DMSO) 10.7 (bs, 1H N<u>H</u>), 10.4 (bs, 1H, N<u>H</u>), 10.1 (bs, 1H, N<u>H</u>), 7.9 (d, 2H, J = 7.4 Hz, Ar<u>H</u>), 7.7 (bs, 1H, Ar<u>H</u>), 7.5 (m, 4H, Ar<u>H</u>), 7.2 (d, 2H, J = 7.4 Hz, Ar<u>H</u>). δ_C (75MHz, d_6-DMSO) 168.2 (<u>C</u>=N), 167.6 (<u>C</u>=N), 167.5 (<u>C</u>=N), 163.8 (<u>C</u>=O), 142.5 (Ar<u>C</u>), 132.2 (Ar<u>C</u>), 128.7 (Ar<u>C</u>), 127.6 (Ar<u>C</u>), 127.6 (Ar<u>C</u>), 126.2 (Ar<u>C</u>), 126.0 (Ar<u>C</u>), 118.9 (Ar<u>C</u>). m/z (ES-, H_2O) 419.1, 100% $(M – H)^-$, 421.1, 40% $(M – H)^-$, 838.6, 5% $(2M – H)^-$. ν_{max}(Golden Gate)/cm^{-1} 3205 (bs), 1671 (w), 1648 (m), 1619 (m), 1605 (m), 1571 (s). Found: C, 35.29; H, 2.81; N, 15.16. Calculated: C, 41.82; H, 2.81; N, 19.50.

4.2.75 1,3-dihydrazino-5-sulfanilo-*s*-triazine (170)


170

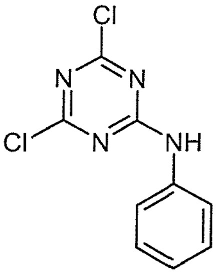
1,3-dichloro-5-sulfanilo-s-triazine (5 g, 11 mmol) was added to hydrazine hydrate (20 ml) with stirring at RT. After about 10 minutes the mixture was heated at 100°C (oil bath) and stirred for 2 hours. The mixture was allowed to cool, and diluted with water (30 ml). Overnight a white precipitate appeared. This was filtered off, washed with a small amount of water and then a small amount of methylated spirit, then dried *in vacuo* (2.83 g, 77%). mp 305 – 310°C (decomp.). NMR δ_H (300 MHz, d_6-DMSO) 9.1 (bs, 2H, N$\underline{H}$), 8.0 (bs, 1H, N$\underline{H}$), 7.4 (d, 2H, J = 8.3 Hz, Ar$\underline{H}$), 7.2 (d, 2H, J = 8.3 Hz, Ar$\underline{H}$), 3.2 (bs, 4H, N$\underline{H}_2$). m/z (ES+, H_2O, 2N HCl) 313, 100% $(M + H)^+$. m/z (ES-, H_2O) 311, 100% $(M - H)^-$. ν_{max}(Golden Gate)/cm^{-1} 3293 (w), 2971 (w), 2351 (w), 2331 (w), 1747 (w), 1634 (m). Found C, 30.32; H, 5.20; N, 40.59; S, 9.02. Calculated C, 32.33; H, 3.30; N, 33.52; S, 9.58.

4.2.76 1,3-Di(phenyl hydrazine-*m*-sulfonic acid)-5-hydroxy-*s*-triazine (175)


175

Phenyl hydrazine-*m*-sulphonic acid (2.5 g, 12 mmol) was dissolved in water (50 ml) and concentrated sodium hydroxide solution was added until the pH was 6. Cyanuric chloride (2.21 g, 12 mmol) was dissolved in acetone (20 ml) and added to well stirred ice (20 ml). The phenyl hydrazine solution was added dropwise to the cyanuric chloride suspension, the pH maintained between 5.5 and 6.5 and the temperature below 5°C (ice bath) until all the phenyl hydrazine was added. The reaction was then allowed to warm to RT, and phenyl hydrazine-*m*-sulphonic acid (2.5 g, 12 mmol) dissolved in water at pH 6 was added dropwise. The pH was again kept between 5.5 and 6.5 and the solution was gently heated to about 40°C. After allowing the reaction to cool to RT, the clear brown solution was concentrated *in vacuo* to about 20 ml, and methylated spirits was added to produce a brown gum. The mother liquor was decanted and the gum was triturated in clean meths. The brown solid was filtered off and dried *in vacuo* (5.31 g, 91%). mp >340°C. NMR δ_H (300 MHz, d_6-DMSO) 7.2 (m, 8H, ArH). m/z (ES+, H_2O) 470, 100% $(M + H)^+$. m/z (ES-, H_2O) 468, 100% $(M - H)^-$. ν_{max}(Golden Gate)/cm^{-1} 2363 (w), 2163 (w), 1752 (w), 1600 (s). Found C, 29.79; H, 3.70; N, 15.00; S, 10.17. Calculated C, 38.38; H, 3.20; N, 20.89; S, 13.65.

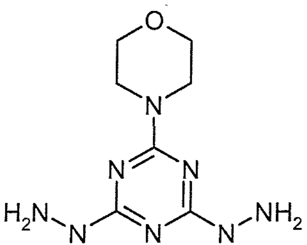
4.2.77 2-Anilino-4,6-dichloro-*s*-triazine[92] (180)



180

Cyanuric chloride (18.44 g, 0.1 mol) was dissolved in dry acetone (100 ml) and cooled to 0°C. Aniline (9.11 ml, 0.1 mol) dissolved in acetone (50 ml) was added dropwise over 30 mins to the solution. The reaction was stirred at 0°C for 1 hour. Aqueous sodium carbonate solution (5.3 g, 0.05 mol in 50 ml water) was added at 0°C over 10 mins. As no precipitate appeared, ice water (100 ml) was added and the solution stirred. The off-white precipitate was filtered off, washed with cold water and dried *in vacuo* overnight. The solid was recrystallised from toluene to give the product was off-white needle crystals (14.01 g, 58%). mp 138°C (lit.[92] 138°C). NMR δ_H (300 MHz, $CDCl_3$) 7.9 (s, 1H, NH), 7.6 (d, 2H, J = 7.4 Hz, ArH), 7.4 (t, 2H, J = 7.4 Hz, ArH), 7.2 (t, 1H, J = 7.4 Hz, ArH). δ_C (75MHz, $CDCl_3$) 170.7 (C=N), 169.1 (C=N), 164.1 (C=N), 135.7 (ArC), 129.3 (ArC), 125.9 (ArC), 121.6 (ArC). ν_{max}(Golden Gate)/cm^{-1} 3366 (m), 1619 (m), 1604 (s).

4.2.78 1,3-Dihydrazino-5-morpholino-*s*-triazine[134] (182)

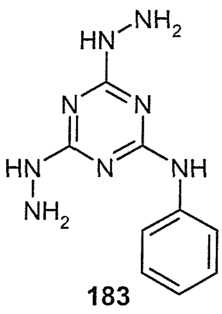


182

Cyanuric chloride (1 g, 5.42 mmol) was dissolved in dry THF (10 ml) and cooled to 0°C. *N,N'*-Diisopropylethylamine (0.94 ml, 5.42 mmol) was added. Morpholine (0.48 ml, 5.42 mmol) dissolved in THF (10 ml) was added dropwise over 30 mins. The solution was allowed to warm to room temperature and stirred overnight. The precipitate was removed by filtration to leave a clear yellowish solution which was purified by column chromatography (DCM) to give a white solid. Hydrazine monohydrate (25 ml) was added to the solid dropwise with stirring at 0°C.

The resultant suspension was allowed to warm to room temperature and stirred for 30 mins, then was heated at 60°C with stirring for 2 hours. The reaction was allowed to cool to room temperature, water (10 ml) was added and the white solid was removed by filtration, washed with water and dried *in vacuo* to give a white solid (0.54 g, 44%). mp 223 - 225°C. (lit.[134] 156 – 157°C). NMR δ_H (300 MHz, d_6-DMSO) 7.9 (bs, 2H, N$\underline{H}$), 4.1 (bs, 4H, N$\underline{H}_2$), 3.7 (apparent s, 4H, C$\underline{H}_2$), 3.6 (apparent s, 4H, C$\underline{H}_2$). δ_C (75MHz, d_6-DMSO) 167.6 ($\underline{C}$=N), 164.5 ($\underline{C}$=N), 66.2 ($\underline{C}H_2$), 43.3 ($\underline{C}H_2$). m/z (ES+, H_2O, 2 drops 2N HCl) 135.8, 25% $(M + Na + Na)^{2+}$, 151.8, 65% $(M + K + K)^{2+}$. ν_{max}(Golden Gate)/cm^{-1} 3292 (m), 3194 (w), 2984 (w), 2960 (w), 2866 (w), 1573 (s).

4.2.79 2-Anilino-4,6-dihydrazino-*s*-triazine [135] (183)

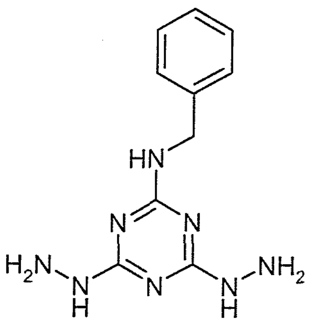


183

2-Anilino-4,6-dichloro-s-triazine (6 g, 25 mmol) was stirred at 0°C. Hydrazine monohydrate (25 ml, 0.5 mol) was added dropwise and the suspension was stirred for 1 hour. Excess hydrazine (20 ml) was added, and the temperature was allowed to rise to room temperature. The suspension was heated at 100°C for 2 hours and then allowed to cool to room temperature. Water (40 ml) was added and the white precipitate was filtered off, washed with water and dried *in vacuo* (5.62 g, 97%). mp 248 – 250°C. (lit.[135] 239°C) NMR δ_H (300 MHz, d_6-DMSO) 9.1 (bs, 1H, N$\underline{H}$), 8.1 (bs, 2H, N$\underline{H}$), 7.8 (d, 2H, J = 7.7 Hz, Ar$\underline{H}$), 7.2 (t, 2H, J = 7.7 Hz, Ar$\underline{H}$), 6.9 (t, 1H, J = 7.7 Hz, Ar$\underline{H}$), 4.2 (bs, 4H, N$\underline{H}_2$). δ_C (75MHz, d_6-DMSO) 167.6 ($\underline{C}$=N), 163.8 ($\underline{C}$=N), 140.6 (Ar$\underline{C}$), 128.4 (Ar$\underline{C}$), 121.3 (Ar$\underline{C}$), 119.6 (Ar$\underline{C}$). m/z (ES+, H_2O, Formic acid) 233.0, 100% $(M + H)^+$. ν_{max}(Golden Gate)/cm^{-1} 3312 (w), 1625 (m), 1583 (s).

4.2.80 1,3-Dihydrazino-5-benzylamino-*s*-triazine[136] (184)

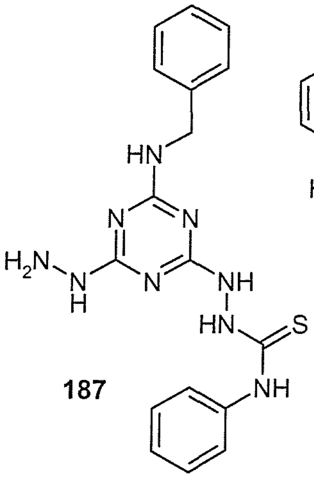
Cyanuric chloride (2 g, 10.85 mmol) was dissolved in dry THF (10 ml) and cooled to 0°C. *N,N'*-Diisopropylethylamine (1.89 ml, 10.85 mmol) was added. Benzylamine (1.18 ml, 10.85 mmol) dissolved in THF (10 ml) was added dropwise over 30 mins. The solution was



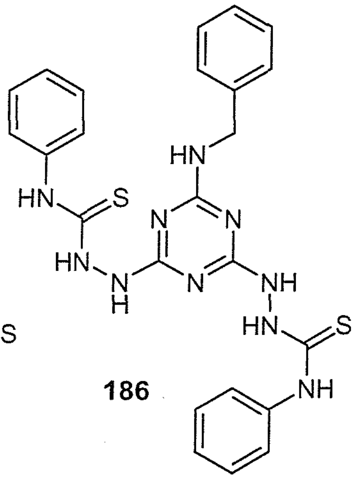
184

allowed to warm to room temperature and stirred for 1 hour. The precipitate was removed by filtration to leave a clear yellowish solution which was purified by column chromatography (DCM) to give a white solid. Hydrazine monohydrate (20 ml) was added to the solid dropwise with stirring at 0°C. The resultant suspension was heated at 100°C with stirring for 2 hours. The reaction was allowed to cool to room temperature and stirred overnight. Water (30 ml) was added and the white solid was removed by filtration, washed with water and dried *in vacuo* to give a white solid (1.86 g, 76%). mp 192 – 194°C (lit.[136] 116 – 118°C). NMR δ_H (300 MHz, d_6-DMSO) 7.9 (bs, 2H, $\mathrm{N\underline{H}}$), 7.3 (apparent d, 4H, J = 4.77 Hz, $\mathrm{Ar\underline{H}}$), 7.2 (m, 1H, $\mathrm{Ar\underline{H}}$), 4.5 (d, 2H, J = 5.2 Hz, $\mathrm{C\underline{H}_2}$), 4.1 (bs, 4H, $\mathrm{N\underline{H}_2}$). δ_C (75MHz, d_6-DMSO) 169.2 ($\mathrm{\underline{C}{=}N}$), 167.6 ($\mathrm{\underline{C}{=}N}$), 165.5 ($\mathrm{\underline{C}{=}N}$), 140.7 ($\mathrm{Ar\underline{C}}$), 128.1 ($\mathrm{Ar\underline{C}}$), 127.2 ($\mathrm{Ar\underline{C}}$), 126.4 ($\mathrm{Ar\underline{C}}$), 43.2 ($\mathrm{\underline{C}H_2}$). m/z (ES+, H_2O, 2 drops 2N HCl) 134.9, 100% $(M + H + Na)^{2+}$, 142.9, 45% $(M + H + K)^{2+}$. High Resolution m/z (ES+, H_2O) $C_{10}H_{14}N_8$ (M) Calculated 246.1742. Found 247.1411 $(M + H)^+$. ν_{max}(Golden Gate)/cm^{-1} 3216 (m), 3181 (w), 2925 (w), 1613 (m), 1519 (s).

4.2.81 1-Hydrazino-3-*N*'-phenylthiosemicarbazido-5-benzylamino-*s*-triazine (186/ 187)



187

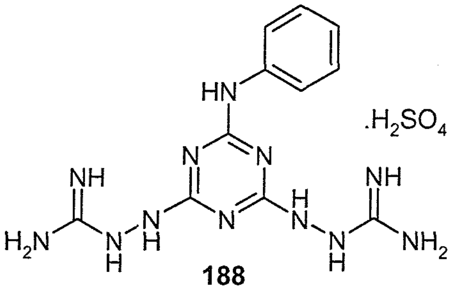


186

1,3-Dihydrazino-5-benzylamino-*s*-triazine (0.5 g, 2.03 mmol) was dissolved in dry DMF (15 ml) under nitrogen. The solution was stirred and phenyl isothiocyanate (0.5 ml, 4.07 mmol) was added. The reaction was heated at 100°C for a total of 2 hours. The solvent was removed *in vacuo* to leave an orange gum. (The filtrate was chilled in a fridge to produce needle crystals consistent with *N,N'*-diphenyl thiourea). The orange gum was recrystallised from warm ethanol to give an off-white precipitate which was removed by filtration and dried *in vacuo* (0.11 g, 14%). mp >250°C. NMR δ_H (300 MHz, d_6-

DMSO) 13.7 (s, 1H, N$\underline{\text{H}}$), 10.7 (t, 1H, J = 5.9 Hz, N$\underline{\text{H}}$), 7.3 (m, 10H, Ar$\underline{\text{H}}$), 4.7 (d, 2H, J = 5.9 Hz, C$\underline{\text{H}}_2$). ν_{max}(Golden Gate)/cm^{-1} 3605 (w), 3489 (w), 3031 (m), 2931 (m), 2767 (m), 1675 (s), 1618 (s).

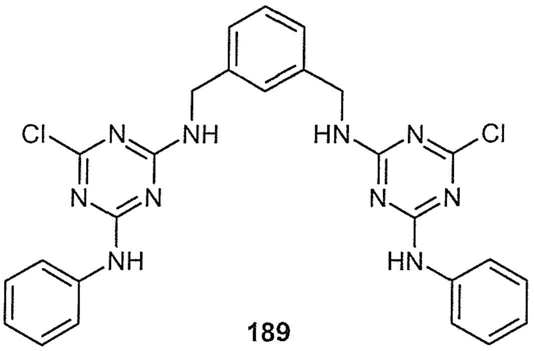
4.2.82 1,3-Aminoguanidinium-5-anilino-*s*-triazine sulfate (188)



188

1-Anilino-3,5-dihydrazino-s-triazine (2 g, 8.62 mmol) was suspended in dry methanol (30 ml). *O*-Methylisourea sulfate (3.18 g, 25.86 mmol) was added and the reaction was heated at reflux for 4 hours. Tlc showed no reaction, so DMSO (2 ml) was added and the reaction was heated at reflux overnight. Upon cooling, a white precipitate appeared in the clear red solution. The precipitate was removed by filtration and dried *in vacuo* then recrystallised from water to give a white solid (0.47 g, 13%). mp > 250°C. NMR δ_H (300 MHz, d_6-DMSO) 9.8 (bs, 1H, N$\underline{\text{H}}$), 7.6 (m, 2H, Ar$\underline{\text{H}}$), 7.5 (apparent d, 3H, J = 8.5 Hz, Ar$\underline{\text{H}}$), 7.3 (t, 1H, J = 8.5 Hz, N$\underline{\text{H}}$), 6.0 (vbs, integration unclear, N$\underline{\text{H}}$). δ_C (75MHz, d_6-DMSO) 143.0 (Ar$\underline{\text{C}}$), 139.0 (Ar$\underline{\text{C}}$), 126.0 (Ar$\underline{\text{C}}$), 119.9 (Ar$\underline{\text{C}}$). m/z (ES+, H_2O) 143.0, 100% (TPA), 170.1, 65% $(M + Na + H)^{2+}$, 159.0, 5% $(M + 2H)^{2+}$, 317.1, 30% $(M + H)^+$. ν_{max}(Golden Gate)/cm^{-1} 3182 (m), 1678 (m), 1612 (s), 1587 (s). Found: C, 36.45; H, 4.34; N, 32.83. Calculated: C, 31.88; H, 4.38; N, 40.54.

4.2.83 *m*-Xylylene Bis-(1'-amino-(3'-chloro-5'anilino)-*s*-triazine) (189)

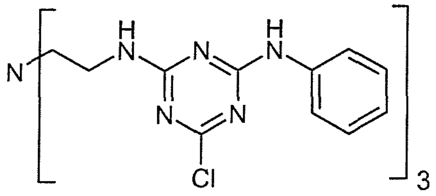


189

m-Xylylene diamine (0.55 ml, 4.15 mmol) dissolved in dry acetone (10 ml) was added dropwise to a solution of 1,3-dichloro-5-anilino-s-triazine (2g, 8.3 mmol) dissolved in dry acetone (40 ml) with stirring. The reaction was stirred at room temperature for 2 hours, after which time aqueous sodium hydroxide solution (0.33g, 8.3 mmol in 10 ml water) was added slowly. The temperature was raised to 40°C and the reaction was stirred for 2 hours.

The reaction was allowed to cool to room temperature and the white precipitate was filtered off, washed with water and dried *in vacuo* overnight to give the product as a white solid (1.91 g, 84%). mp 216°C (decomp.) NMR δ_H (300 MHz, d_6-DMSO) 10.0 (bs, 2H, N$\underline{H}$), 8.7 (bs, 2H, N$\underline{H}$), 7.7 (bs, 1H, Ar$\underline{H}$), 7.5 (d, 2H, J = 7.4 Hz, Ar$\underline{H}$), 7.3 (d, 4H, J = 7.4 Hz, Ar$\underline{H}$), 7.2 (bs, 4H, Ar$\underline{H}$), 7.0 (m, 3H, Ar$\underline{H}$), 4.5 (bs, 4H, C$\underline{H}_2$). δ_C (75MHz, d_6-DMSO) 168.0 ($\underline{C}$=N), 165.7 ($\underline{C}$=N), 163.7 ($\underline{C}$=N), 139.2 (Ar$\underline{C}$), 138.8 (Ar$\underline{C}$), 128.6 (Ar$\underline{C}$), 128.5 (Ar$\underline{C}$), 125.6 (Ar$\underline{C}$), 125.3 (Ar$\underline{C}$), 123.0 (Ar$\underline{C}$), 120.2 (Ar$\underline{C}$), 43.6 ($\underline{C}H_2$). m/z (ES+, MeCN) 182.1, 30% $(M + 3H)^+$, 545.0, 10% $(M + H)^+$. ν_{max}(Golden Gate)/cm^{-1} 3253 (w), 3110 (w), 1634 (m), 1603 (m). Found: C, 57.05; H, 3.85; N, 24.97. Calculated: C, 57.47; H, 3.71; N, 25.76.

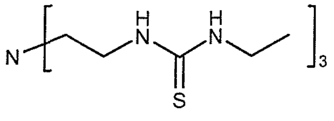
4.2.84 Tris (2-Aminoethyl-(3'-chloro-5'anilino)-*s*-triazine) amine (190)



190

Tris (2-Aminoethyl) amine (0.41 ml, 2.7 mmol) dissolved in dry acetone (10 ml) was added dropwise to a solution of 1,3-Dichloro-5-anilino-s-triazine (2 g, 8.3 mmol) dissolved in dry acetone (40 ml) with stirring. The reaction was stirred at room temperature for 2 hours, after which time aqueous sodium hydroxide solution (0.33 g, 8.3 mmol in 10 ml water) was added slowly. The temperature was raised to 40°C and the reaction was stirred for 2 hours. The reaction was allowed to cool to room temperature and the white precipitate was filtered off, washed with water and dried *in vacuo* overnight to give the product as a white solid (1.26 g, 62%). mp 139°C (decomp.). NMR δ_H (300 MHz, d_6-DMSO) 10.0 (bs, 3H, N$\underline{H}$), 8.1 (bs, 3H, N$\underline{H}$), 7.6 (apparent bs, 6H, Ar$\underline{H}$), 7.2 (m, Ar$\underline{H}$), 7.0 (t, 1H, J = 7.4 Hz, Ar$\underline{H}$), 6.9 (apparent bs, 2H, Ar$\underline{H}$), 3.4 (s, 6H, C$\underline{H}_2$ covered by water peak), 2.7 (d, 6H, J = 5.9 Hz, C$\underline{H}_2$). δ_C (75MHz, d_6-DMSO) 167.9 ($\underline{C}$=N), 165.6 ($\underline{C}$=N), 163.7 ($\underline{C}$=N), 138.9 (Ar$\underline{C}$), 128.5 (Ar$\underline{C}$), 122.8 (Ar$\underline{C}$), 120.1 (Ar$\underline{C}$), 52.9 ($\underline{C}H_2$), 30.8 ($\underline{C}H_2$). *m/z* (ES+, MeCN) 758.8, 100% $(M+H)^+$. ν_{max}(Golden Gate)/cm^{-1} 3399 (w), 3255 (w), 1709 (w), 1610 (m). Found: C, 52.00; H, 4.54; N, 28.52. Calculated: C, 52.15; H, 4.38; N, 29.47.

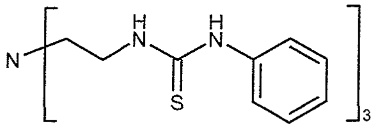
4.2.85 Tris (2-Ethyl-*N*'-ethyl-thiourea) amine (192)



192

Ethyl isothiocyanate (1.92 ml, 22 mmol) was dissolved in dry DCM (15 ml) and stirred at 0°C under nitrogen. Tris (2-Aminoethyl) amine (1 ml, 6.68 mmol) was dissolved in dry DCM (5 ml) and added dropwise to the above solution. The reaction was stirred at 0°C for about thirty minutes and then allowed to warm to room temperature. TLC (50:50 EtOAc: petroleum ether) indicated complete reaction. The solution was concentrated *in vacuo* to leave an off-white foam. This was triturated with ether (40 ml) twice, and the resultant gummy white solid was dried *in vacuo* to give the product as a white powder (1.12 g, 82%). mp 59 - 63°C. NMR δ_H (300 MHz, $CDCl_3$) 6.7 (bs, 1H, N<u>H</u>), 3.6 (bs, 2H, C<u>H</u>$_2$), 3.4 (quintet, 2H, J = 7.1 Hz, C<u>H</u>$_2$), 2.6 (bs, 2H, C<u>H</u>$_2$), 1.1 (t, 3H, J = 7.1 Hz, C<u>H</u>$_3$). δ_C (75MHz, $CDCl_3$) 181.6 (<u>C</u>=S), 53.2 (<u>C</u>H$_2$), 42.8 (<u>C</u>H$_2$), 39.5 (<u>C</u>H$_2$), 14.7 (<u>C</u>H$_3$). *m/z* (ES+, MeCN) 408.2, 60% $(M + H)^+$. High Resolution m/z (ES+, MeCN) $C_{15}H_{33}N_7S_3$ (M) Calculated 407.6526. Found 408.2025, $(M + H)^+$. ν_{max}(Golden Gate)/cm^{-1} 3223 (bs), 3061 (w), 2968 (w), 2821 (w), 1548 (s). Found: C, 44.09; H, 8.12; N, 23.96; S, 23.78. Calculated: C, 44.20; H, 8.20; N, 24.05; S, 23.59.

4.2.86 Tris (2-Ethyl-*N*'-phenyl-thiourea) amine[35] (193)

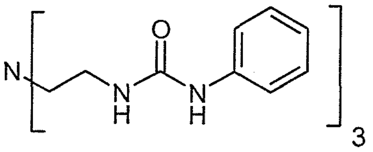


193

Phenyl isothiocyanate (2.4 ml, 20 mmol) was dissolved in dry DCM (15 ml) and stirred at 0°C under nitrogen. Tris (2-Ethylamino) amine (1 ml, 6.68 mmol) was dissolved in dry DCM (5 ml) and added dropwise to the above solution. The reaction was allowed to warm to room temperature, and then was stirred overnight. TLC (5% MeOH, DCM) indicated complete reaction. The product was purified by column chromatography (5% MeOH, DCM) and concentrated *in vacuo* to leave an off-white foam. This was recrystallised from DCM/ ether to give the product as an off-white solid (2.95 g, 80%). mp 92 - 94°C (lit.[35] 94 - 98°C). δ_H (300 MHz, $CDCl_3$) 8.7 (bs, 3H, N<u>H</u>), 7.3 (m, 9H, Ar<u>H</u>), 7.1 (d, 6H, J = 7.0 Hz, Ar<u>H</u>), 6.8 (bs, 3H, N<u>H</u>), 3.7 (d, 6H, J = 5.2 Hz, C<u>H</u>$_2$), 2.7 (apparent bs, 6H, C<u>H</u>$_2$). δ_C (75MHz, $CDCl_3$) 180.5 (<u>C</u>=S), 137.3 (Ar<u>C</u>), 129.7 (Ar<u>C</u>), 126.5 (Ar<u>C</u>), 124.8 (Ar<u>C</u>), 53.1 (<u>C</u>H$_2$), 43.0 (<u>C</u>H$_2$). *m/z* (ES+, MeCN) 552.6, 40% $(M + H)^+$.

ν_{max}(Golden Gate)/cm^{-1} 3167 (m), 1593 (m), 1523 (s). Crystals were grown by slow addition of ether to a solution of tris (2-ethyl-*N'*-phenyl-thiourea) amine in DCM. Single crystal structure data collected and solved using standard methods, orthorhombic system, space group Pca2(1), R1 = 10.4%.

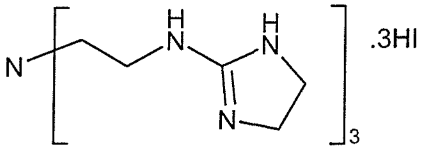
4.2.87 Tris (2-(*N'*Phenyl)-urea-ethyl) amine[35] (194)



194

Phenylisocyanate (2.39 ml, 22 mmol) was dissolved in DCM (15 ml) and stirred under nitrogen at 0°C. Tris (2-Aminoethyl) amine (1 ml, 6.68 mmol) dissolved in DCM (5 ml) was added dropwise over 10 mins. The solution was allowed to warm to room temperature and stirred overnight. The precipitate was filtered off, washed with DCM (50 ml) and dried *in vacuo* to give a white powder (3.40 g, 100%). mp 202 – 204°C (lit.[35] 184 – 186°C). NMR δ_H (300 MHz, d$_6$-DMSO) 8.5 (bs, 3H, N$\underline{H}$), 7.4 (d, 6H, J = 7.4 Hz, Ar$\underline{H}$), 7.2 (t, 6H, J = 7.4 Hz, Ar$\underline{H}$), 6.9 (t, 3H, J = 7.4 Hz, Ar$\underline{H}$), 6.2 (t, 3H, J = 5.8 Hz, N$\underline{H}$), 3.2 (t, 6H, J = 5.8 Hz, C$\underline{H}_2$), 2.6 (t, 6H, J = 5.8 Hz, C$\underline{H}_2$). δ_C (75MHz, d$_6$-DMSO) 155.4 ($\underline{C}$=O), 140.5 (Ar$\underline{C}$), 128.7 (Ar$\underline{C}$), 121.1 (Ar$\underline{C}$), 117.8 (Ar$\underline{C}$), 54.0 ($\underline{C}H_2$), 37.6 ($\underline{C}H_2$). m/z (ES+, MeCN) 504.1, 100% (M + H)$^+$, 526.0, 5% (M + Na)$^+$, 1006.8, 5% (2M + H)$^+$. ν_{max}(Golden Gate)/cm^{-1} 3308 (m), 2928 (w), 2857 (w), 2819 (m), 1683 (m), 1643 (s), 1594 (s).

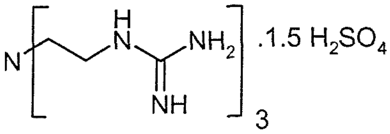
4.2.88 *N*1-(4,5-Dihydro-1*H*-2-imidazolyl)-*N*2,*N*2-di[2-(4,5-dihydro-1*H*-2-imidazolylamino)ethyl]-1,2-ethanediamine trihydroiodide (195)



195

2-Methylthio-2-imidazoline hydroiodide (4.89 g, 0.02 mol) was dissolved in ethanol (10 ml) and stirred under nitrogen at room temperature. Tris (2-Aminoethyl) amine (1 ml, 6.68 mmol) was dissolved in ethanol (5 ml) and added dropwise to the former solution. The reaction was heated at a gentle reflux for two hours, then allowed to cool to room temperature. The solvent was removed *in vacuo* to leave an off-white foam. This was recrystallised from ethanol/ ether. The mother liquor was decanted, and the remaining sticky residue was triturated with ether to give an off-white solid. The mother liquor was concentrated *in vacuo* to give a second crop which was triturated with neat ether to give an off-white solid. Both solids were recrystallised from the minimum amount of ethanol to give the product as a white solid (4.76g, 95%). mp 159 - 162°C. NMR δ_H (300 MHz, d_6-DMSO) 6.9 (bs, $N\underline{H}$), 3.6 (bs, 4H, $C\underline{H}_2$), 3.2 (apparent bs, 2H, $C\underline{H}_2$), 2.6 (apparent bs, 2H, $C\underline{H}_2$). δ_C (75MHz, d_6-DMSO) 159.3 ($\underline{C}$=N), 51.8 ($\underline{C}H_2$), 42.6 ($\underline{C}H_2$), 40.4 ($\underline{C}H_2$). m/z (ES+, MeOH) 139.9, 10% $(M + 3Na)^{3+}$, 145.9, 100% $(M + Na + Na + K)^{3+}$, 176.0, 20% $(M + 2H)^{2+}$. ν_{max}(Golden Gate)/cm^{-1} 3215 (w), 3172 (w), 1659 (s), 1588 (w). Found: C, 24.81; H, 4.64; N, 19.04; I, 51.73. Calculated: C, 24.54; H, 4.53; N, 19.08; I, 51.85.

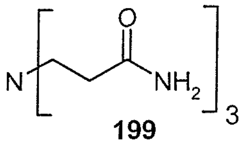
4.2.89 Tris (2-Guanidinium-ethyl) amine sulfate[46] (196)



196

Tris (2-Aminoethyl) amine (0.45 ml, 2.98 mmol), *O*-methylisourea hydrogen sulfate (3.08 g, 17.89 mmol) and conc. NH_4OH solution (10 ml) were placed in a glass ampule and sealed with a teflon tap at room temperature. The vessel was heated at 60°C for 8 hours, after which time it was allowed to cool to room temperature. The vessel was carefully opened, and the white precipitate was removed by filtration and dried *in vacuo*. The solid was recrystallised from water to give the product as white needle crystals (0.54 g, 43%). mp >240°C (lit.[46] >260°C). NMR δ_H (300 MHz, D_2O) 3.2 (apparent t, 6H, J = 5.4 Hz, $C\underline{H}_2$), 2.5 (apparent t, 6H, J = 5.4 Hz, $C\underline{H}_2$). δ_C (75MHz, D_2O) 160.7 ($\underline{C}$=N), 55.3 ($\underline{C}H_2$), 41.8 ($\underline{C}H_2$). m/z (ES+, H_2O) No peak consistent with product. ν_{max}(Golden Gate)/cm^{-1} 3147 (bs), 1660 (s), 1620 (s). Single crystal X-ray structure solved by standard methods, monoclinic system, space group P2(1), R1 = 8.1%.

4.2.90 Tris (3-Amidopropyl) amine[102] (199)

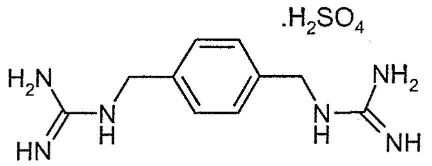


199

Acrylamide (43 g, 0.6 mol) was suspended in water (20 ml). 30% Ammonia solution (26 g, 0.22 mol) was added dropwise with stirring. The reaction was stirred at room temperature overnight. After a further 2 days stirring at room temperature a white precipitate appeared. This was filtered off, washed with water (3 × 10 ml) and dried *in vacuo* to give a white solid (39.02 g, 94%). mp 191 – 193°C. (lit.[102] mp not quoted). NMR δ_H

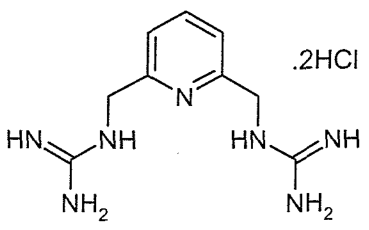
(300 MHz, d_6-DMSO) 7.3 (s, 1H, N<u>H</u>), 6.7 (s, 1H, N<u>H</u>), 2.6 (t, 2H, J = 7.0 Hz, C<u>H</u>$_2$), 2.1 (t, 2H, J = 7.0 Hz, C<u>H</u>$_2$). δ_C (75MHz, d_6-DMSO) 173.8 (<u>C</u>=O), 49.1 (<u>C</u>H$_2$), 32.9 (<u>C</u>H$_2$). m/z (ES+, MeCN) 137.9, 100% $(M + Na + Na)^{2+}$, 230.9, 55% $(M + H)^+$, 253.0, 40% $(M + Na)^+$. ν_{max}(Golden Gate)/cm^{-1} 3326 (m), 3163 (bs), 2989 (w), 2968 (w), 2822 (m), 2741 (w), 1664 (s), 1633 (s).

4.2.91 *p*-Xylylene Bis-(methylguanidinium) sulfate[65] (227)



p-Xylylene diamine (1 g, 7.34 mmol) was dissolved in water (3 ml). Aqueous sulfuric acid solution (1N) was added until the pH reached 6.5, then cyanamide (0.7 g, 16.65 mmol) was added in one portion. The solution was heated at 60°C under nitrogen with stirring overnight. Excess sulfuric acid was added until the pH was 6.5, and the reaction was stirred under the same conditions for 12 hours more. After allowing the reaction to cool the white precipitate that had formed was removed by filtration, washed with water (15 ml) followed by methanol (15ml) and recrystallised from water to give the product as a white powder which was dried *in vacuo* (0.52 g, 22%). mp >250°C. (lit.[65] 278 – 280°C). NMR δ_H (300 MHz, D_2O, 10% w/ v Na_2CO_3) 7.1 (s, 4H, Ar<u>H</u>), 4.2 (s, 4H, C<u>H</u>$_2$). NH groups not evident. δ_C (75MHz, D_2O, 10% w/ v NaOH) 162.7 (<u>C</u>=N), 140.4 (Ar<u>C</u>), 129.8 (Ar<u>C</u>), 47.5 (<u>C</u>H$_2$). m/z (ES+, H_2O) 221.0, 60% $(M + H)^+$, 243.1, 100% $(M + Na)^+$. ν_{max}(Golden Gate)/cm^{-1} 3320 (bs), 3126 (bs), 1656 (s), 1629 (s).

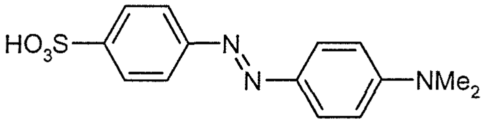
4.2.92 2,6-Bis-(Methylguanidinium) pyridine dihydrochloride (83.2HCl)



2,6-Bis-(Methylguanidinium) pyridine sulfate (1 g, 3.13 mmol) was suspended in water (50 ml) and aqueous sodium hydroxide (2M) was added until the pH was about 13.7. Saturated barium hydroxide solution was added to the former solution in small amounts until no more precipitate formed. The barium sulphate was filtered off, the filtrate was neutralised with aqueous hydrochloric acid (2N) and evaporated to dryness to leave a white solid. The residue was suspended in dry ethanol (20 ml), stirred, and then filtered. The solvent was removed *in vacuo* to leave a white solid

(0.51 g, 55%). mp 188 – 190°C. NMR δ_H (300 MHz, d_4-MeOD) 6.1 (t, 1H, J = 7.7 Hz, Ar<u>H</u>), 5.6 (d, 2H, J = 7.7 Hz, Ar<u>H</u>), 2.9 (s, 4H, C<u>H</u>$_2$). δ_C (75MHz, d_6-DMSO) 159.1 (<u>C</u>=N), 156.2 (Ar<u>C</u>), 139.6 (Ar<u>C</u>), 122.1 (Ar<u>C</u>), 46.8 (<u>C</u>H$_2$). m/z (ES+, MeOH) 222.0, 50% $(M + H)^+$. ν_{max}(Golden Gate)/cm^{-1} 3279 (bs), 3142 (bs), 1648 (s), 1609 (s). Found: C, 35.37; H, 5.82; N, 31.81. Calculated: C, 36.75; H, 5.82; N, 33.31.

4.2.93 Methyl Orange[137] (228)



Sulfanilic acid (10 g, 57.7 mmol) was slurried in water and added to ice (100 ml). The pH was 2.6. Sodium nitrite (4.37 g, 63.4 mmol) was dissolved in water (50 ml) and added dropwise to the sulfanilic acid solution. The pH was kept around 2 and the temperature was kept below 5°C. The sulfone indicator was employed to test for HNO_2 and Elulich's reagent was used to test for aromatic amines. After 1 hour all the sulfanilic acid had reacted but HNO_2 was still present, so 10% sulfonic acid was added until no more HNO_2 was detected. The sulfanilic diazonium salt thus prepared was stored at <5°C. *N,N'*-dimethyl aniline (6.29 g, 51.9 mmol) was dissolved in methylated spirit (50 ml) and added to water (50 ml). The solution was stirred over ice. The sulfanilic diazonium salt prepared above was added dropwise at 0°C. The pH was maintained at 4.5. The clear solution turned yellow, then orange, then red/ brown when full addition had been completed. After stirring at 0 – 10°C over lunch, the reaction was allowed to warm to room temperature. The purple/ brown precipitate was filtered off and washed with methylated spirit then filtered and dried *in vacuo* (14.4 g, 85%). mp >250°C. NMR δ_H (300 MHz, d_6-DMSO) 7.8 (d, 2H, J = 9.2 Hz, Ar<u>H</u>), 7.7 (s, 4H, Ar<u>H</u>), 6.8 (d, 2H, J = 9.2 Hz, Ar<u>H</u>), 3.1 (s, 6H, C<u>H</u>$_3$). δ_C (75MHz, d_6-DMSO) 152.7 (Ar<u>C</u>), 152.2 (Ar<u>C</u>), 149.0 (Ar<u>C</u>), 142.6 (Ar<u>C</u>), 126.6 (Ar<u>C</u>), 124.9 (Ar<u>C</u>), 121.3 (Ar<u>C</u>), 111.7 (Ar<u>C</u>). m/z (AP+, H_2O) 306.2, 100% $(M + H)^+$. ν_{max}(Golden Gate)/cm^{-1} 2817 (bw), 1620 (m), 1598 (m).

4.2.94 Dye Extraction Experiment with Compounds 95 and 153

2-(*p*-(Diethylamino) phenylazo) benzenesulfonic acid (0.07 g, 0.216 mmol) was dissolved in water (2 ml) in a glass vial. DCM (2 ml) was added and the vial was shaken. Some dye remained dissolved in the water while some was suspended in the organic layer. 1,3-Bis-(Methyl-*N*-methyl-*N'*-benzoyl-thiourea) benzene (**95**) (0.10g, 0.216 mmol) was added and the vial was shaken. The organic layer was clear and coloured brown, indicating that extraction of the dye by the ligand from the aqueous layer to the organic layer had occurred.

2-(*p*-(Diethylamino) phenylazo) benzenesulfonic acid (0.07 g, 0.216 mmol) was dissolved in water (2 ml) in a glass vial. DCM (2 ml) was added and the vial was shaken. Some dye remained dissolved in the water while some was suspended in the organic layer. 1,3-Bis-(6-[Pyridine-2-carbonyl)-amino]-pyridin-2-yl)-carbamic acid benzyl ester (**153**) (0.13g, 0.216 mmol) was added and the vial was shaken. The organic layer was clear and coloured brown to a greater extent than with host **95** above, indicating that again extraction of the dye by the ligand from the aqueous layer to the organic layer had occurred.

4.2.95 NMR Titration Experiment with Host 193 and Guest 204

Tris (2-Ethyl-*N*'-phenyl-thiourea) amine (2.75 mg, 5 μmol) was dissolved in dry deuterated chloroform (0.5 ml) (Solution A). *n*-Decylphosphonic acid (22.23 mg, 0.1 mmol) was dissolved in deuterated chloroform (1 ml) (Solution B). 16 scan proton NMR spectra were collected of the following samples made up of aliquots of Solution B added to all of Solution A as follows:

Spectrum number	Solution B added to A (μl)	'Host' concentration	'Guest' concentration	N-H Chemical Shift (ppm)	equivalents of guest added	total sample volume/ ml
0	0	0.01	0	2.7216	0	0.5
1	10	0.009804	0.001961	2.8770	0.2	0.51
2	20	0.009615	0.003846	2.8638	0.4	0.52
3	30	0.009434	0.00566	3.1093	0.6	0.53
4	40	0.009259	0.007407	3.2069	0.8	0.54
5	50	0.009091	0.009091	3.2986	1	0.55
6	60	0.008929	0.010714	3.3664	1.2	0.56
7	70	0.008772	0.012281	3.4193	1.4	0.57
8	80	0.008621	0.013793	3.4524	1.6	0.58
9	90	0.008475	0.015254	3.4755	1.8	0.59
10	100	0.008333	0.016667	3.4995	2	0.6
11	150	0.007692	0.023077	3.5607	3	0.65
12	200	0.007143	0.028571	3.5876	4	0.7
13	250	0.006667	0.033333	3.6152	5	0.75
14	300	0.00625	0.0375	3.6152	6	0.8

These data were analysed by Salvatore Camiolo. A plot of chemical shift versus concentration of guest **204** was produced and from the curve a 1:1 binding stoichiometry was estimated and an association constant of 2.61×10^2 M^{-1} (± 27.23) was calculated using EQNMR software[103].

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Appendix A: NMR Titration Data

Deuterated Chloroform Experiments

Host **192** + Guest **204**:

no.	ul guest	Δδ CH_2 (ppm)	[host]	[guest]	eq. Guest	volume/ ml
0	0	3.7549	0.01	0	0	0.5
1	5	3.8062	9.90E-03	9.90E-04	0.1	0.505
2	10	3.8161	0.009804	0.001961	0.2	0.51
3	15	3.8368	9.71E-03	2.91E-03	0.3	0.515
4	20	3.8607	0.009615	0.003846	0.4	0.52
5	25	3.8707	9.52E-03	4.76E-03	0.5	0.525
6	30	3.8913	0.009434	0.00566	0.6	0.53
7	35	3.9087	9.35E-03	6.54E-03	0.7	0.535
8	40	3.926	0.009259	0.007407	0.8	0.54
9	45	3.9368	9.17E-03	8.26E-03	0.9	0.545
10	50	3.9542	0.009091	0.009091	1	0.55
11	60	3.9765	0.008929	0.010714	1.2	0.56
12	70	3.9897	0.008772	0.012281	1.4	0.57
13	80	4.0013	0.008621	0.013793	1.6	0.58
14	90	4.0104	0.008475	0.015254	1.8	0.59
15	100	4.0137	0.008333	0.016667	2	0.6
16	150	4.0261	0.007692	0.023077	3	0.65
17	200	4.0261	0.007143	0.028571	4	0.7

Host **193** + Guest **204**:

no.	ul guest	Δδ NH (ppm)	[host]	[guest]	eq. Guest	volume/ ml
0	0	2.7216	0.01	0	0	0.5
1	10	2.8770	0.009804	0.001961	0.2	0.51
2	20	2.8638	0.009615	0.003846	0.4	0.52
3	30	3.1093	0.009434	0.00566	0.6	0.53
4	40	3.2069	0.009259	0.007407	0.8	0.54
5	50	3.2986	0.009091	0.009091	1	0.55
6	60	3.3664	0.008929	0.010714	1.2	0.56
7	70	3.4193	0.008772	0.012281	1.4	0.57
8	80	3.4524	0.008621	0.013793	1.6	0.58
9	90	3.4755	0.008475	0.015254	1.8	0.59
10	100	3.4995	0.008333	0.016667	2	0.6
11	150	3.5607	0.007692	0.023077	3	0.65
12	200	3.5876	0.007143	0.028571	4	0.7
13	250	3.6152	0.006667	0.033333	5	0.75
14	300	3.6152	0.00625	0.0375	6	0.8

Host **95** + Guest **203**:

no.	ul guest	Δδ NH (ppm)	[host]	[guest]	eq. Guest	volume/ ml
0	0	11.0642	0.01	0	0	0.5
1	5	11.0642	9.90E-03	9.90E-04	0.1	0.505
2	10	11.0618	0.009804	0.001961	0.2	0.51
3	15	11.0618	9.71E-03	2.91E-03	0.3	0.515
4	20	11.0630	0.009615	0.003846	0.4	0.52
5	30	11.0642	0.009434	0.00566	0.6	0.53
6	40	11.0642	0.009259	0.007407	0.8	0.54
7	50	11.0642	0.009091	0.009091	1	0.55
8	60	11.0618	0.008929	0.010714	1.2	0.56
9	160	11.0609	0.007578	0.024242	3.2	0.66

DMSO Experiments

Host **94** + Guest **203**:

no.	ul guest	Δδ NH (ppm)	[host]	[guest]	eq. Guest	volume/ ml
0	0	8.0706	0.01	0	0	0.5
1	10	8.0767	0.009804	0.001961	0.2	0.51
2	20	8.0743	0.009615	0.003846	0.4	0.52
3	30	8.0743	0.009434	0.00566	0.6	0.53
4	40	8.0718	0.009259	0.007407	0.8	0.54
5	50	8.0718	0.009091	0.009091	1	0.55
6	100	8.0767	0.008333	0.016667	2	0.6
7	200	8.0779	0.007143	0.028571	4	0.7
8	300	8.0841	0.00625	0.0375	6	0.8
9	400	8.0804	0.00556	0.044444	8	0.9

Host **83** + Guest **200**:

no.	ul guest	Δδ CH_2 (ppm)	[host]	[guest]	eq. Guest	volume/ ml
0	0	4.6478	0.01	0	0	0.5
1	10	4.6478	0.009804	0.001961	0.2	0.51
2	20	4.6466	0.009615	0.003846	0.4	0.52
3	30	4.6466	0.009434	0.00566	0.6	0.53
4	40	4.6454	0.009259	0.007407	0.8	0.54
5	50	4.6454	0.009091	0.009091	1	0.55
6	100	4.6417	0.008333	0.016667	2	0.6
7	150	4.638	0.007692	0.023077	3	0.65
8	200	4.6356	0.007143	0.028571	4	0.7
9	300	4.6344	0.00625	0.0375	6	0.8

Host **98** + Guest **200**:

no.	ul guest	Δδ NH (ppm)	[host]	[guest]	eq. Guest	volume/ ml
0	0	9.5455	0.01	0	0	0.5
1	10	9.5223	0.009804	0.001961	0.2	0.51
2	20	9.5137	0.009615	0.003846	0.4	0.52
3	30	9.5137	0.009434	0.00566	0.6	0.53
4	40	9.5063	0.009259	0.007407	0.8	0.54
5	50	9.5002	0.009091	0.009091	1	0.55
6	60	9.4978	0.008929	0.010714	1.2	0.56
7	70	9.4953	0.008772	0.012281	1.4	0.57
8	90	9.4818	0.008475	0.015254	1.8	0.59
9	100	9.4842	0.008333	0.016667	2	0.6
10	200	9.4671	0.007143	0.028571	4	0.7
11	300	9.4549	0.00625	0.0375	6	0.8

Host **83** + Guest **201**:

no.	ul guest	Δδ CH_2 (ppm)	[host]	[guest]	eq. Guest	volume/ ml
0	0	4.5443	0.01	0	0	0.5
1	5	4.5435	9.90E-03	9.90E-04	0.1	0.505
2	10	4.5435	0.009804	0.001961	0.2	0.51
3	15	4.5427	9.71E-03	2.91E-03	0.3	0.515
4	20	4.5418	0.009615	0.003846	0.4	0.52
5	25	4.5418	9.52E-03	4.76E-03	0.5	0.525
6	30	4.541	0.009434	0.00566	0.6	0.53
7	40	4.5402	0.009259	0.007407	0.8	0.54
8	50	4.5394	0.009091	0.009091	1	0.55
9	60	4.5385	0.008929	0.010714	1.2	0.56
10	100	4.5369	0.008333	0.016667	2	0.6
11	150	4.5327	0.007692	0.023077	3	0.65
12	200	4.5319	0.007143	0.028571	4	0.7
13	300	4.5294	6.25E-03	0.0375	6	0.8

Host **98** + Guest **201**:

no.	ul guest	Δδ CH (ppm)	[host]	[guest]	eq. Guest	volume/ ml
0	0	7.2748	0.01	0	0	0.5
1	5	7.2723	9.90E-03	9.90E-04	0.1	0.505
2	10	7.2566	0.009804	0.001961	0.2	0.51
3	15	7.2599	9.71E-03	2.91E-03	0.3	0.515
4	20	7.2591	0.009615	0.003846	0.4	0.52
6	30	7.2558	0.009434	0.00566	0.6	0.53
7	40	7.2599	0.009259	0.007407	0.8	0.54
8	50	7.3269	0.009091	0.009091	1	0.55
9	70	7.3277	0.008772	0.012281	1.4	0.57
10	90	7.3326	0.008475	0.015254	1.8	0.59
11	110	7.3359	0.008197	0.018033	2.2	0.61
12	150	7.3492	0.007692	0.023077	3	0.65
13	200	7.3558	0.007143	0.028571	4	0.7
14	250	7.3707	0.006667	0.033333	5	0.75
15	300	7.3641	6.25E-03	0.0375	6	0.8
16	350	7.3649	0.005882	0.041176	7	0.85

Host **67** + Guest **203**:

no.	ul guest	Δδ CH (ppm)	[host]	[guest]	eq. Guest	volume/ ml
0	0	8.2298	0.01	0	0	0.5
1	5	8.2335	9.90E-03	9.90E-04	0.1	0.505
2	10	8.2397	0.009804	0.001961	0.2	0.51
3	15	8.2507	9.71E-03	2.91E-03	0.3	0.515
4	20	8.2531	0.009615	0.003846	0.4	0.52
5	25	8.2593	9.52E-03	4.76E-03	0.5	0.525
6	30	8.2678	0.009434	0.00566	0.6	0.53
7	35	8.274	9.35E-03	6.54E-03	0.7	0.535
8	40	8.2752	0.009259	0.007407	0.8	0.54
9	45	8.2801	9.17E-03	8.26E-03	0.9	0.545
10	50	8.285	0.009091	0.009091	1	0.55
11	60	8.2899	0.008929	0.010714	1.2	0.56
12	70	8.2997	0.008772	0.012281	1.4	0.57
13	80	8.2997	0.008621	0.013793	1.6	0.58
14	90	8.3046	0.008475	0.015254	1.8	0.59
15	100	8.307	0.008333	0.016667	2	0.6
16	110	8.3107	0.008197	0.018633	2.2	0.61
17	120	8.3107	0.008065	0.019355	2.4	0.62
18	130	8.3083	0.007937	0.020635	2.6	0.63
19	140	8.3144	0.007813	0.021875	2.8	0.64
20	150	8.3181	0.007692	0.023077	3	0.65
21	160	8.3193	7.58E-03	0.024242	3.2	0.66
22	170	8.3193	7.46E-03	0.025373	3.4	0.67
23	180	8.3193	7.35E-03	0.026471	3.6	0.68
24	190	8.3205	7.25E-03	0.027536	3.8	0.69
25	200	8.3217	0.007143	0.028571	4	0.7
26	220	8.3217	6.94E-03	3.06E-02	4.4	0.72
27	250	8.3217	6.67E-03	0.033333	5	0.75

28	300	8.3242	6.25E-03	0.0375	6	0.8

Host **101** + Guest **201**:

no.	ul guest	Δδ NH (ppm)	[host]	[guest]	eq. Guest	volume/ ml
0	0	11.3427	0.01	0	0	0.5
1	5	11.3427	9.90E-03	9.90E-04	0.1	0.505
2	10	11.3402	0.009804	0.001961	0.2	0.51
3	15	11.3402	9.71E-03	2.91E-03	0.3	0.515
4	20	11.3427	0.009615	0.003846	0.4	0.52
5	30	11.3427	0.009434	0.00566	0.6	0.53
6	40	11.3451	0.009259	0.007407	0.8	0.54
7	50	11.3414	0.009091	0.009091	1	0.55
8	60	11.3390	0.008929	0.010714	1.2	0.56
9	100	11.3402	0.008333	0.016667	2	0.6
10	200	11.3378	0.007143	0.028571	4	0.7

Host **67** + Guest **201**:

no.	ul guest	Δδ CH (ppm)	[host]	[guest]	eq. Guest	volume/ ml
0	0	7.4581	0.01	0	0	0.5
1	10	7.4777	0.009804	0.001961	0.2	0.51
2	20	7.5	0.009615	0.003846	0.4	0.52
3	30	7.7227	0.009434	0.00566	0.6	0.53
4	40	7.7717	0.009259	0.007407	0.8	0.54
5	50	7.9456	0.009091	0.009091	1	0.55
6	60	7.9603	0.008929	0.010714	1.2	0.56
7	70	7.9603	0.008772	0.012281	1.4	0.57
8	80	7.9542	0.008621	0.013793	1.6	0.58
9	90	7.9787	0.008475	0.015254	1.8	0.59
10	100	7.9775	0.008333	0.016667	2	0.6
11	150	7.9469	0.007692	0.023077	3	0.65
12	300	7.9505	0.00625	0.0375	6	0.8

D_2O Experiments

Host **83** + Guest **200**:

no.	ul guest	Δδ CH_2 (ppm)	[host]	[guest]	eq. Guest	volume/ ml
0	0	4.513	0.01	0	0	0.5
1	10	4.5113	0.009804	0.001961	0.2	0.51
2	50	4.5047	0.009091	0.009091	1	0.55
3	100	4.4965	0.008333	0.016667	2	0.6
4	200	4.4882	0.007143	0.028571	4	0.7

Host 153 + Azo Dye 149 in Deuterated Chloroform:

no.	ul guest	Δδ NH (ppm)	[host]	[guest]	eq. Guest	volume/ ml
0	0	8.4069	0.01	0	0	0.5
1	5	8.4081	9.90E-03	9.90E-04	0.1	0.505
2	10	8.4388	0.009804	0.001961	0.2	0.51
3	15	8.4388	9.71E-03	2.91E-03	0.3	0.515
4	20	8.44	0.009615	0.003846	0.4	0.52
5	25	8.44	9.52E-03	4.76E-03	0.5	0.525
6	30	8.4412	0.009434	0.00566	0.6	0.53
7	35	8.4412	9.35E-03	6.54E-03	0.7	0.535
8	40	8.4473	0.009259	0.007407	0.8	0.54
9	45	8.4473	9.17E-03	8.26E-03	0.9	0.545
10	50	8.4535	0.009091	0.009091	1	0.55
11	60	8.489	0.008929	0.010714	1.2	0.56
12	70	8.5245	0.008772	0.012281	1.4	0.57
13	80	8.598	0.008621	0.013793	1.6	0.58
14	90	8.745	0.008475	0.015254	1.8	0.59
15	100	8.8516	0.008333	0.016667	2	0.6
16	150	9.0746	0.007692	0.023077	3	0.65
17	200	9.2693	0.007143	0.028571	4	0.7
18	300	9.5	0.00625	0.0375	6	0.8